JOC Article

Study of a New Rate Increasing “Base Effect” in the Palladium-Catalyzed Amination of Aryl Iodides

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Evidence for an interphase deprotonation of Pd(II)−amine complexes with weak carbonate base has been gained for the first time. When a rate-limiting deprotonation step is involved in the catalytic cycle, controlling the structure (shape and size of the particles) and/or molar excess of the carbonate base used can significantly increase the reaction rate of Buchwald−Hartwig aminations. By taking such a “base effect” into account a general protocol for the intermolecular amination of aryl iodides with all types of amines has been developed based on a standard Pd−BINAP catalyst, using cesium carbonate as the base.

Introduction

Arylamines are very important structural entities in modern organic chemistry. These subunits can be found in natural products, pharmaceuticals, and agrochemicals, as well as new materials (small molecules, oligomers, and polymers) with interesting optical and electronic properties.[1] Traditional routes for their synthesis involve electrophilic nitration followed by reduction and subsequent reductive amination, Ullmann-type reaction, and nucleophilic aromatic substitution of the addition−elimination (S_NAr) or elimination−addition (via aryne) type.[2] All these traditional methods suffer from a limited substrate scope due to the requirement of (relatively) harsh reaction conditions or the presence of activating electron withdrawing groups. Interestingly, in the mid nineties Buchwald and Hartwig independently discovered the tin free Pd-catalyzed amination of aryl bromides showing a wide scope.[3] This new procedure has established itself as the most important method for C−N bond formation on aromatics currently available.[4] Since 1995, major advances have been made in this field mainly by developing new palladium catalysts (aryl dialkylphosphine ligands, trialkylphoshine ligands, palladacycles) that allow the use of bases weaker than the traditional “MO*t*Bu” (in order to have a large functional group compatibility) and by tackling industrially relevant aryl chloride substrates by using only a low loading of catalyst.[5] If weak bases are used in Buchwald−Hartwig aminations, rate-limiting deprotonation of the Pd(II)−amine intermediate formed in the catalytic cycle (complex **2**, Scheme 1) is most likely and consequently often observed. In the present work we clearly show that in such cases the reaction rate can be seriously increased by carefully controlling the structure (particle size and shape) and/or molar excess of the base used (“base effect”). We selected the intermolecular amination of aryl iodides as a case study for this base effect since in amination reactions, in contrast to C−C bond forming processes, the aryl iodides have been shown to be less effective substrates than aryl bromides or chlorides. Hitherto, only two studies have been published that describe a general protocol for the intermolecular amination of aryl iodides with use of a weak base (Cs_2CO_3).[6,7] In 2001, Buchwald reported that 2-(dicyclohexylphosphanyl)-2′-dimethylaminobiphenyl (DCPDMAB) is effective for the coupling of aliphatic amines while 9,9-dimethyl-4,5-bis-(diphenylphosphanyl)xanthene (XANTPHOS) is a more

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(1) (a) Buckingham, J. *Dictionary of Natural Products*; University Press: Cambridge, MA, 1994. (b) Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112. (c) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 3rd ed.; Thieme: Stuttgart, Germany, 1999. (d) *CRC Handbook of Pesticides*; Milne, G. W. A., Ed.; CRC Press: Boca Raton, FL, 1994. (e) Waring, D. R.; Hallas, G. *The Chemistry and Application of Dyes*; Plenum: New York, 1990. (f) *Polymers for Lightwave and Integrated Optics*; Hornak, L. A., Ed.; Marcel Dekker: New York, 1992. (g) D'Aprano, G.; Leclerc, M.; Zotti, G.; Schiavon, G. *Chem. Mater.* **1995**, *7*, 33. (h) Skotheim, T. A.; Elsenbaumer, R. L.; Reynolds, J. R. *Handbook of Conducting Polymers*, 2nd ed.; Marcel Dekker: New York, 1997.

(2) (a) Belfield, A. J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, *55*, 11399. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (c) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502. (d) March, *J. Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992.

(3) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

(4) For reviews and accounts on the Buchwald−Hartwig reaction see: (a) Barañano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Frost, C. G.; Mendonça, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615. (d) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046. (e) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (f) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000. (g) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (h) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041.

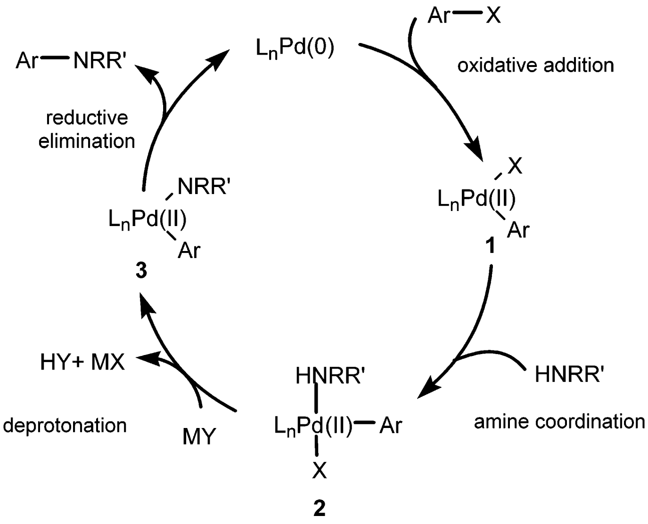
(5) For a review partly dealing with palladium-catalyzed aminations of aryl chlorides see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(6) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560.

(7) Urgaonkar, S.; Xu, J. H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416.

10.1021/jo049774e CCC: $27.50

SCHEME 1. General Catalytic Cycle for the Buchwald−Hartwig Amination with Weak Base.



suitable ligand for C−N bond formation with anilines.[6] For both catalysts special cosolvents (EtN_3 or *t*BuOH) were needed to obtain rate enhancements, and a high loading of catalyst is required to couple acyclic secondary aliphatic amines. Recently, while our work was in progress, Verkade published an alternative for Buchwald's protocol. By using a bicyclic triaminophosphine ligand, aryl iodides could be efficiently coupled with aromatic as well as aliphatic amines under mild reaction conditions.[7] A limitation of this protocol is that the use of primary aliphatic amines gives only poor results. We present here our finding that, in contrast to what is hitherto generally accepted, the use of a standard second generation catalyst, based on air-stable and commercially available racemic 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) ligand, in combination with a weak cesium carbonate base can be used as a general catalytic system for the efficient amination of aryl iodides with all types of amines if the base effect is taken into account.[8,9]

Results and Discussion

Recently, our laboratory reported regioselective palladium-catalyzed aminations of 2-chloro-3-iodopyridine and 2-chloro-5-iodopyridine with anilines in the 3- and 5-position, respectively.[10] In this preliminary study we found that a Pd−BINAP catalyst, used in combination with a large excess of mild carbonate base (Cs_2CO_3), gave selective aminations in excellent yields.[11] Surprisingly, we observed that a large excess of base (5 equiv), although almost completely insoluble in toluene, was essential to obtain sufficiently fast reactions and full conversions.[10] This and our earlier qualitative observation that larger excesses of carbonate bases also speed up Buchwald−Hartwig aminations of chloropyridazin-3(2*H*)-ones and dichloropyridines with use of Pd−BINAP catalyst in toluene, as well as a similar observation made by Watanabe's group when performing aminations of aryl bromides using Pd−P(*t*Bu)$_3$ in xylene, indicate that this base effect might be quite general.[12,13]

The first goal of the present work was to investigate if the combination of a Pd−BINAP catalyst with 5 equiv of Cs_2CO_3 is indeed a general protocol for the efficient amination of aryl iodides with all types of amines. To have an idea about the potential of our protocol in comparison with Buchwald's method, using a Pd−DCP-DMAB (aliphatic amines) or Pd−XANTPHOS (anilines) catalyst in combination with a small excess of Cs_2CO_3 (1.4 equiv), we first investigated the same seven substrate combinations (Table 1, entries 1, 2, 3, 4a, 10, 11, and 12) Buchwald reported in 2001, but under the reaction conditions we reported for the regioselective amination of chloro-iodopyridines with anilines.[6,10] Interestingly, similar yields were obtained by using the same loading of palladium in an overnight reaction. For the coupling of 2-iodoanisole with morpholine some starting material remained after an overnight reaction under our conditions (Table 1, entry 4a). Therefore we increased the catalyst loading with 1 mol % and subsequently obtained a similar yield as under Buchwald's conditions (Table 1, entry 4b). To further investigate the applicability of our new protocol, we studied an additional set of five different substrate combinations involving the coupling of different aliphatic amines (primary as well as acyclic and cyclic secondary amines) (Table 1, entries 5−9). As a starting point a 1 mol % loading of Pd−BINAP catalyst was always used. A higher catalyst loading was taken if no full conversion of starting material was obtained after an overnight reaction. Clearly, secondary cyclic amines are coupled more easily than secondary acyclic ones and the primary aliphatic amines can be situated between (compare Table 1, entries 7, 8a, and 9a). In all the cases studied, secondary cyclic aliphatic amines seem to work

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(8) No successful report on intermolecular aminations on aryl iodides with use of mild bases such as Cs_2CO_3 in combination with Pd−BINAP has been published yet. Only the use of strong NaO*t*Bu in combination with Pd−BINAP has been reported as a useful general protocol. In this case also toxic additives were required: Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066. There is only one exception reported in the literature. For the specific case of the palladium-catalyzed *N*-arylation of sulfoximines, the use of aryl iodides with Pd−BINAP as catalyst in combination with Cs_2CO_3 has been reported. However, to ensure product formation in acceptable yields the use of additives (LiBr, AgOTf) was essential: Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169.

(9) For the Pd-catalyzed amination of aryl iodides with strong MO*t*Bu base see: (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (c) See ref 8. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (e) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617. (f) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (g) See ref 6. (h) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452.

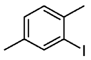
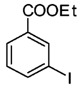
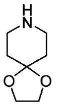
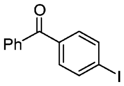
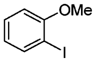
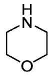
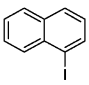
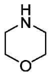
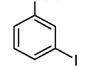
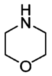
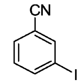
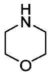
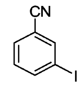
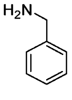
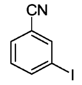
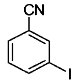
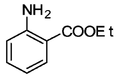
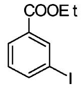
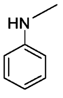
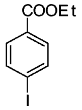
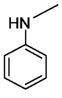
(10) For a preliminary communication see: Maes, B. U. W.; Loones, K. T. J.; Jonckers, T. H. M.; Lemière, G. L. F.; Dommisse, R. A.; Haemers, A. *Synlett* **2002**, 1995.

(11) For the Pd-catalyzed amination of azaheteroaryl iodides with strong MO*t*Bu base see: (a) Cheng, J.; Trudell, M. L. *Org. Lett.* **2001**, *3*, 1371. Interestingly, a completely opposite regioselectivity has been observed by Cheng and Trudell when they studied the coupling of 2-chloro-5-iodopyridine with 7-azabicyclo[2.2.1]heptane using a Pd−carbene complex. (b) Parrot, I.; Ritter, G.; Wermuth, C. G.; Hibert, M. *Synlett* **2002**, 1123.

(12) Pd−BINAP catalyst in combination with a large excess (5−20 equiv) of K_2CO_3 accelerated the amination of azaheteroaryl chloride substrates with anilines: (a) Chloropyridazin-3(2*H*)-ones: Košmrlj, J.; Maes, B. U. W.; Lemière, G. L. F.; Haemers, A. *Synlett* **2000**, 1581. (b) Dichloropyridines: Jonckers, T. H. M.; Maes, B. U. W.; Lemière, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027.

(13) Pd−P(*t*-Bu)$_3$ catalyst in combination with an excess of K_2CO_3 or Rb_2CO_3 (3 equiv) accelerated the amination of aryl bromide substrates with carbazole, indole, and pyrrole: Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481.

TABLE 1. Pd-Catalyzed Amination of Aryl Iodides with 5 equiv of Cesium Carbonate Type 1

Entry	ArI	Amine	mol% Pd	Yield (%)^a	Buchwald's catalytic system (%)^b
1		n-HexNH$_2$	3	81	74^c
2			1	75	81^c
3		NH(C$_3$H$_7$)$_2$	5	89	70^c
4a 4b			2 3	41 56	62^c /
5			1	91	/
6			1	99	/
7			1	98	/
8a 8b			1 2	43 80	/ /
9a 9b		NH(C$_3$H$_7$)$_2$	1 5	34 60	/ /
10			1	95	91^d
11			1	98	84^d
12			1	98	86^d

[a] All reactions were run overnight (17 h); reaction times were not minimized; yields refer to the average of several runs; x mol % of Pd(OAc)$_2$, x mol % of BINAP, aryl iodide (1.5 mmol), amine (1.8 mmol), Cs$_2$CO$_3$ "type 1" (7.5 mmol), toluene (15 mL), oil bath (120 °C). [b] 0.5x mol % of Pd$_2$(dba)$_3$, 2x mol % of XANTPHOS or DCHPDMAB, aryl iodide (1.5 mmol), amine (1.8 mmol), Cs$_2$CO$_3$ (1.4 equiv), mixture of dioxane/NEt$_3$ (2:1) or dioxane/tBuOH (2:1 or 1:1), Δ. [c] DCHPDMAB was used as the ligand for the Pd catalyst. [d] XANTPHOS was used as the ligand for the Pd catalyst.

very well with a low catalyst loading (Table 1, entries 5, 6, and 7; see also Table 1, entry 2). Table 1 indicates that the general profile of our catalytic system is equal to the Pd−DCPDMAB (aliphatic amines) and Pd−XANTPHOS (anilines) system reported by Buchwald. The use of a large excess of base (5 equiv of cesium carbonate), when Pd−BINAP is used, is essential to obtain sufficiently high reaction rates in the coupling of amines with aryl iodides as exemplified by the study of the coupling of 3-iodobenzonitrile with morpholine and ethyl 3-iodobenzoate with N-methylaniline in a limited reaction time. When 5 equiv of cesium carbonate was used in the former coupling 50% of 3-(morpholin-4-yl)benzonitrile was obtained after refluxing for only 4 h, whereas the use of 2 equiv of the same base gave a lower isolated yield of 35% in the same reaction time. Similarly, the coupling of ethyl 3-iodobenzoate with N-methylaniline gave 79% of ethyl 3-[methyl-(phenyl)amino]benzoate in 3 h of reflux with use of 5 equiv of cesium carbonate, whereas the use of 2 equiv of the same base in 3 h yielded only 51% reaction product. Interestingly, in 1997 and 2000 a Pd−BINAP catalyst, using only a small excess of Cs$_2$CO$_3$ (1.4 equiv), has already been described as a general system for the Buchwald−Hartwig amination of aryl bromides.[14] In contrast, aryl iodides have hitherto only been successfully aminated with use of a Pd−BINAP catalyst in combination with a strong base (NaOtBu).[8] Clearly, the large excess of carbonate base makes the difference. Consequently, a further investigation of this new base effect was our second goal in order to understand its nature.

The observation that the use of 5 equiv in comparison with 2 equiv of cesium carbonate significantly speeds up the coupling reactions of amines with aryl iodides is quite odd since also 2 equiv of this base scarecely dissolve in solvents commenly used in Buchwald−Hartwig aminations.[14] The well-known low solubility of cesium carbonate in toluene and the obtained experimental evidence that larger excesses increase the reaction rates suggest that an interphase mechanism is operating. There seems to be a direct solid−liquid phase interaction between the solid carbonate and the five-coordinated Pd(II)−amine intermediate in the toluene phase. If the deprotonation of such a Pd(II)−amine intermediate is the rate-limiting step of the catalytic cycle, one can indeed imagine that by supplying a larger excess of base a substantial effect on the reaction rate of the coupling will be observed. Such an interphase mechanism has hitherto never been taken into consideration in Buchwald−Hartwig aminations and might be a generally useful parameter for the further optimization of aminations with a rate-limiting deprotonation once a catalyst giving a significant conversion of starting material has been selected.[15] To gain further evidence for an interphase process we investigated the influence of the shape and size of the cesium carbonate particles on the coupling rate. We selected two batches

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(14) For Pd−BINAP-catalyzed aminations of aryl bromides with a small excess of Cs$_2$CO$_3$ (1.4 equiv) as base see: (a) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. In the description of the general experimental procedure of both manuscripts it is indicated that the Cs$_2$CO$_3$ used was standardly ground prior to its use. The authors gave no specific reason for this grinding and no effect on the reaction rate was reported. The supplier and quality of the base were not specified.

(15) Interestingly, Hartwig and co-workers investigated the effect of phase-transfer catalysts, in palladium-catalyzed aminations of aryl bromides and chlorides using Pd[P(tBu)$_3$]$_2$ as the catalyst, to increase the solubility of base in toluene. The phase-transfer catalyst should assist in the rate of deprotonation of the intermediate Pd(II)−amine complex. Potassium hydroxide in combination with water and a catalytic amount of cetyltrimethylammonium bromide was found to be superior: Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479. In 2003, Buchwald reported that phase-transfer catalysts had no effect when solid potassium hydroxide without added water was used with Pd(OAc)$_2$/2-(di-*tert*-butylphosphanyl)biphenyl (DTBPB) as precatalyst for the amination of aryl chlorides in toluene: Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413.

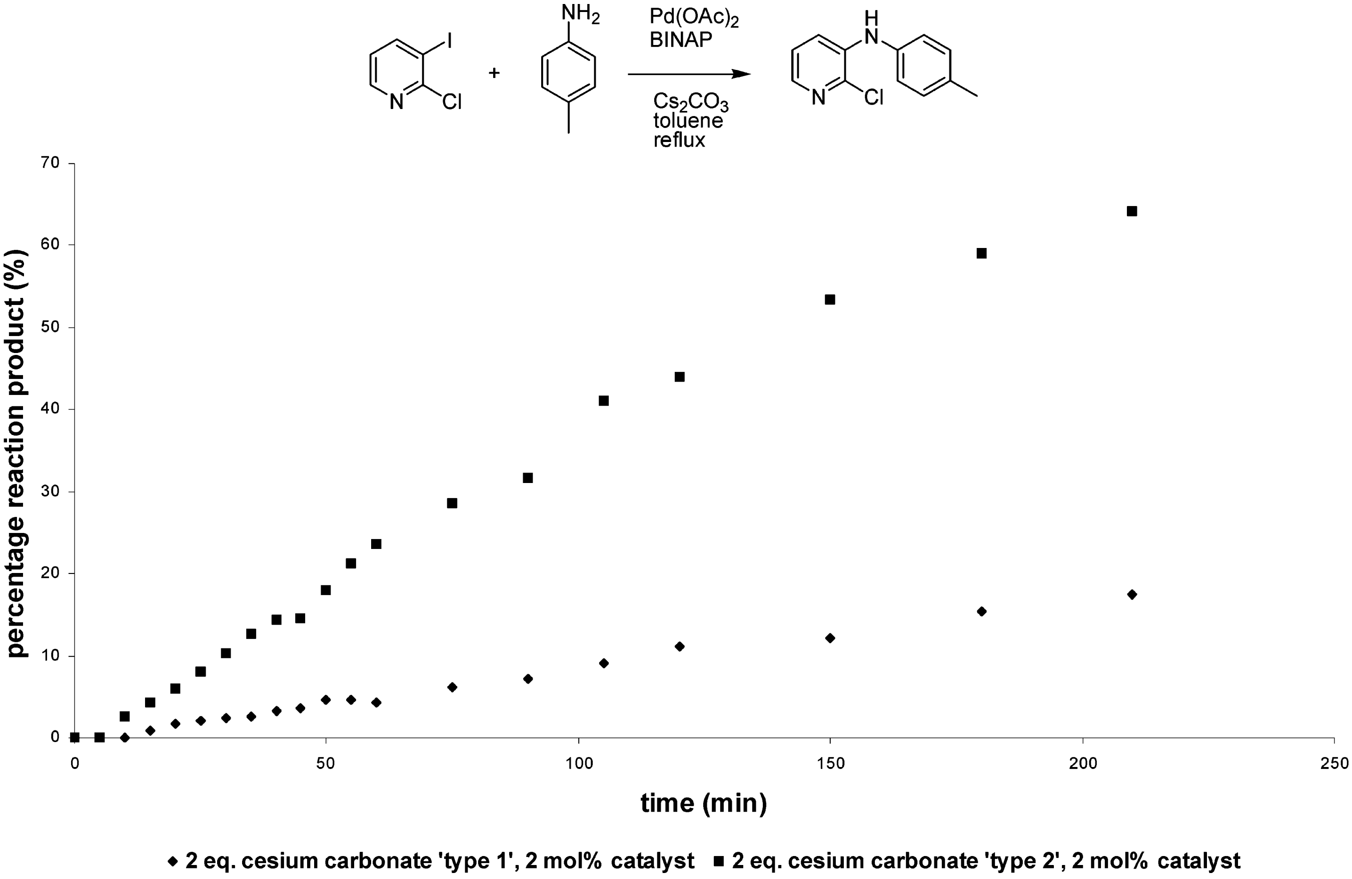

FIGURE 1. Study of the effect of the structure (particle size and shape) of the base on the coupling rate of 2-chloro-3-iodopyridine with *p*-toluidine.

of cesium carbonate from different suppliers and investigated their structure with electron microscopy (SEM) (see Supporting Information). The electron microscopic image of the cesium carbonate of Acros (99.5%) ("type 1"), which we used in all the experiments summarized in Table 1, revealed uniformely bulbed particles with a smooth surface and narrow size distribution while the image of the cesium carbonate of Aldrich (99%) ("type 2") showed rough irregularly shaped particles with a broad size distribution (containing many small particles).[16] If an interphase mechanism is indeed involved in the rate-limiting step one expects that running two identical reactions only differing in the structure of the cesium carbonate particles used should give a different reaction rate. To get a good idea about the magnitude of this particle effect on the reaction rate, we decided to select a specific amination reaction and followed the appearance rate of reaction product with an HPLC-UV system. We chose the coupling of 2-chloro-3-iodopyridine with *p*-toluidine since our first discovery of the base effect in the amination of aryl iodides was done with this specific substrate combination.[10] The percentage of reaction product is plotted versus the reaction time in Figure 1 for this amination reaction, using a 2 mol % loading of Pd−BINAP catalyst. Two equivalents of cesium carbonate were used for both reactions, only the type differed. Figure 1 clearly shows that cesium carbonate type 2 gives the fastest reaction. The observed effect is quite large since the reaction rate in the linear area shown increases with a factor 5.5 changing from cesium carbonate type 1 to type 2. This observed difference in rate is in agreement with the isolated yields after a limited reaction time of 8 h since the coupling of 2-chloro-3-iodopyridine with *p*-toluidine yielded 91% of 2-chloro-3-(4-methylphenylamino)pyridine with use of 2 equiv of cesium carbonate type 2 while the same excess of type 1 gave an incomplete reaction and an isolated yield of only 68% in the same reaction time. We decided to follow also the coupling of 2-chloro-3-iodopyridine with an aliphatic amine using an HPLC-UV system. The intermediate Pd(II)−amine complex containing an aliphatic amine is expected to be less acidic, which must be reflected in a decrease of the observed reaction rate. In Figure 2 the obtained result for the amination of 2-chloro-3-iodopyridine with benzylamine using a 2 mol % loading of Pd−BINAP catalyst and 2 equiv of cesium carbonate type 1 is shown. When we compare the rate of this coupling with that previously discussed for the amination with *p*-toluidine using the same type and excess of base, a rate decrease is indeed observed (factor 1.5). We decided to double the catalyst loading from 2 mol % to 4 mol % to speed up the coupling rate since after 3.5 h reaction time the amination of 2-chloro-3-iodopyridine with benzylamine yielded less

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[16] Unfortunately, attempts to obtain the specific surface area (m^2/g) of the cesium carbonate of Acros (99.5%) (type 1) and Aldrich (99%) (type 2) via classical adsorption experiments with liquid N_2 were unsuccessful since the contact surface area was too small: Rouquerol, F.; Rouquerol, J.; Sing, K. *Adsorption by powders & porous solids*; Academic Press: London, UK, 1999. Consequently, only the difference in particle shape and size of the cesium carbonate particles, observed by recording SEM images, could be taken into account.

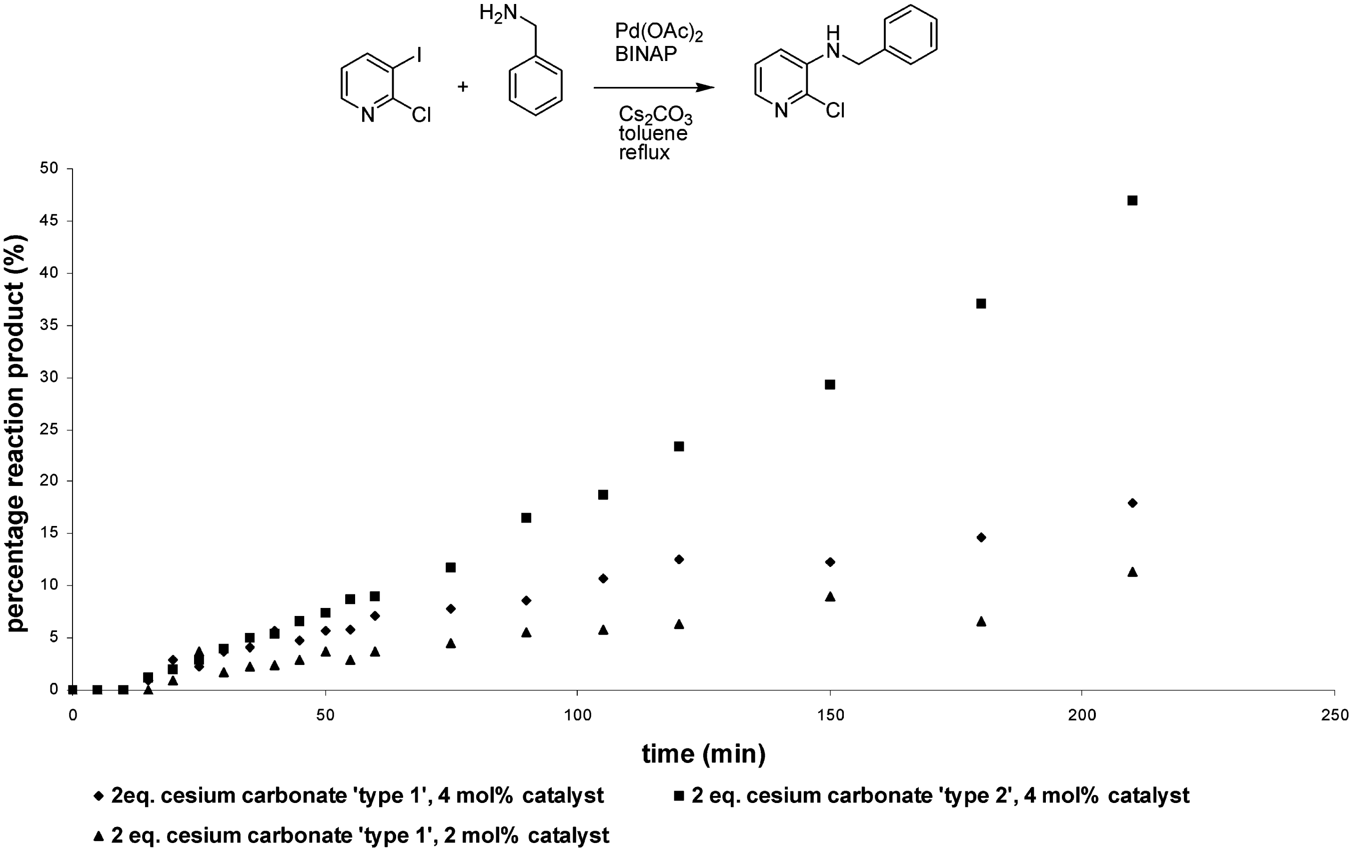

FIGURE 2. Study of the effect of the structure (particle size and shape) of the base on the coupling rate of 2-chloro-3-iodopyridine with benzylamine.

than 15% conversion of starting material to reaction product. As expected, doubling the catalyst loading significantly improved the reaction rate. When we subsequently changed the type of cesium carbonate from 2 equiv of type 1 to 2 equiv of type 2 the rate in the linear area shown increased with a factor 1.5. This rate increase is less pronounced for the coupling of benzylamine than for the reaction with *p*-toluidine and can be rationalized by taking into account that the pK_a value of the Pd(II)−benzylamine complex is much higher than the pK_a value of the Pd(II)−*p*-toluidine complex. The observed difference for the coupling of 2-chloro-3-iodopyridine with benzylamine using type 1 and type 2 base respectively is also reflected in the isolated yields after a limited reaction time of 8 h with 4 mol % of Pd−BINAP. The amination with 2 equiv of type 1 yielded 52% of 3-benzylamino-2-chloropyridine while the same excess of type 2 carbonate base gave a higher yield (76%) in the same reaction time.[17] Not surprisingly, on the basis of the rate difference observed in the linear area (factor 2.2) between the coupling of *p*-toluidine (2 mol % Pd−BINAP) and benzylamine (4 mol % of Pd−BINAP) with 2-chloro-3-iodopyridine using 2 equiv of cesium carbonate type 2, in this case both couplings gave an incomplete reaction.

Since cesium carbonate is very hygroscopic and since we always weighed it in the air it most probably took up some water during handling. Thermogravimetric analysis (TGA) of the batches cesium carbonate type 1 and type 2 used revealed a different water content. The weight loss on heating to 188 °C was 0.38% for type 1 and 1.63% for type 2 base. When type 1 and type 2 bases were exposed to the air for 1 h the weight loss on heating at the same temperature was 1.65% for the former and 3.15% for the latter. These data confirm that the base has indeed taken up water from the air and therefore we investigated the influence of the amount of water on the amination rate. For the amination of 2-chloro-3-iodopyridine with *p*-toluidine we compared the yields of the reactions using 2 equiv of cesium carbonate of both types that had been exposed to the air for 1 h with those previously obtained under standard conditions (see previous paragraph). These standard conditions involve the use of cesium carbonate rapidly weighed in air as all other reagents. For the coupling of cesium carbonate type 1 a yield of 64% and an incomplete reaction was obtained in 8 h of reflux, which is similar to the result obtained under standard conditions (68%) in the same reaction time. Similarly, the use of base type 2 exposed to the air for 1 h yielded 85% of 2-chloro-3-(4-methylphenylamino)-pyridine and 91% under standard conditions both performed in a reaction time of 8 h. These results indicate that the water content, in the studied range, does not have a significant influence on the coupling rate.

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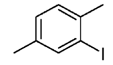
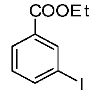
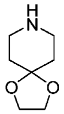
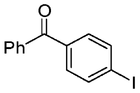
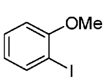
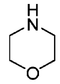
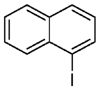
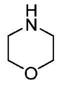
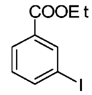
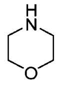
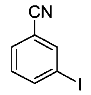
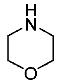
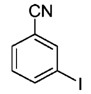
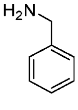
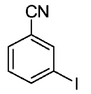
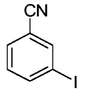
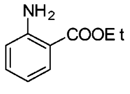
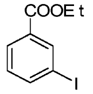
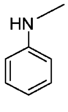
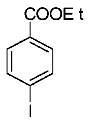
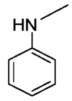
(17) The regioselective amination of 2-chloro-3-iodopyridine with aliphatic amines is not restricted to primary amines. Amination of 2-chloro-3-iodopyridine with morpholine, under the standard conditions, using 4 mol % of Pd-BINAP and 5 equiv of Cs_2CO_3 of Acros (99.5%) (“type 1”) gave 84% isolated yield of 2-chloro-3-(morpholin-4-yl)pyridine in a reaction time of 17 h.

TABLE 2. Pd-Catalyzed Amination of Aryl Iodides with Cesium Carbonate Type 2 and Comparison with the Yields Obtained with 5 equiv of Cesium Carbonate Type 1

Entry	ArI	Amine	mol% Pd	Equivalents Cs_2CO_3 'type 2'	Yield using Cs_2CO_3 'type 2' (%)[a]	Equivalents Cs_2CO_3 'type 1'	Yield using Cs_2CO_3 'type1' (%)[a]
1a		*n*-HexNH$_2$	3	2	51	5	81
1b				4	71		
2a			1	2	41	5	75
2b			1	4	70		
3a		NH(C$_3$H$_7$)$_2$	5	2	43	5	89
3b			5	4	82		
4a			3	2	28	5	56
4b			3	4	50		
5a			1	2	45	5	91
5b			1	4	90		
6			1	2	96	5	99
7			1	2	93	5	98
8			2	2	73	5	80
9		NH(C$_3$H$_7$)$_2$	5	2	50	5	60
10			1	2	91	5	95
11			1	2	91	5	98
12a			1	2	82	5	98
12b			1	4	96		

[a] All reactions were run overnight (17 h); reaction times were not minimized; yields refer to the average of several runs; *x* mol % of Pd(OAc)$_2$, *x* mol % of BINAP, aryl iodide (1.5 mmol), amine (1.8 mmol), Cs_2CO_3, toluene (15 mL), oil bath (120 °C).

With the knowledge of the importance of the particle size and shape, resulting from the kinetic studies, we reinvestigated all the coupling reactions summarized in Table 1 using base type 2 (Table 2). The same loading of catalyst that gave optimal results for the aminations with 5 equiv of base type 1 was used. We started with only 2 equiv of cesium carbonate type 2 since we knew that this type gives faster reactions. As can be seen in Table 2, in general, only anilines can be coupled efficiently with aryl iodides under these reaction conditions in an overnight reaction (Table 2, entries 10–12). For aliphatic amines no general trend could be observed. Sometimes they give low yields and in these cases large amounts of starting material remained after an overnight reflux (Table 2, entries 1a–5a). However, for the coupling of morpholine with ethyl 3-iodobenzoate (Table 2, entry 6) and morpholine, benzylamine, and diethylamine with 3-iodobenzonitrile (Table 2, entries 7, 8, and 9) the aminations worked very well with only 2 equiv of base type 2. To rationalize this, one has to realize that the acidity of the hydrogen atom on the complexed nitrogen is determined by the structure of the whole Pd(II)–amine complex: the

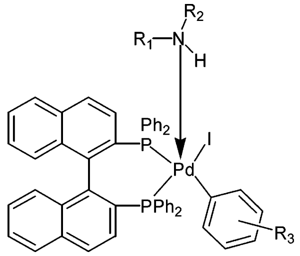


FIGURE 3. Proposed structure of the Pd(II)−amine complex formed in the catalytic cycle.

ligand (kept constant in this study), the halide (kept constant in this study), and the amine, as well as the aryl group from the aryl iodide substrate used (Figure 3).[4b]

The main factor determining the Brönsted acidity of the complexed amine is the Lewis acidity of the Pd(II) center in the oxidative addition complex to which the amine (Lewis base) is coordinated. If an electron poor aryl iodide is used as a substrate the Lewis acidity of the Pd(II) metal will increase and consequently also the acidity of the hydrogen atom on the nitrogen atom that complexes with the oxidative addition complex. Therefore good results with aliphatic amines can be obtained by using only 2 equiv of base type 2 depending on the specific aliphatic amine used and the position and electron withdrawing effect of the substituents located on the aryl iodide. Using this model one can also understand why all anilines react very well with use of only 2 equiv of cesium carbonate type 2 since the aryl group of the aniline will significantly contribute to the Brönsted acidity, resulting in a lower pK_a value. As expected, doubling the amount of cesium carbonate type 2 in the coupling reactions with aliphatic amines, giving only poor yields and no full conversions of aryl iodide (Table 2, entries 1a−5a), improved the yields to a level similar to that obtained earlier with 5 equiv of base type 1 (compare entries 1a−5a with entries 1b−5b in Table 2). No attempts were made to search for the optimal amount of base type 2 for these specific coupling reactions. The optimal excess for these aminations will be situated between 2 and 4 equiv depending on the acidity of the specific Pd(II)−amine complex formed. Since the structure (particle size and shape) of a specific type of cesium carbonate might differ from batch to batch this optimal excess is also of no real practical use. It has to be emphasized that the producers do not guarantee that the structure of the cesium carbonate particles of Acros (99.5%) and Aldrich (99%) will be equal in different batches. Consequently, for all the aminations published in this study cesium carbonate from the same batches was used.

In principle, grinding should also have an effect on the coupling rate if an interphase mechanism is operating.[14] Unfortunately, simple grinding in a mortar cannot be reproducibly performed and this is a serious problem when larger quantities of base with the same particle profile are required in order to be able to quantitatively compare different reactions. To investigate the effect of grinding we performed only one test experiment and compared the yield of the amination of ethyl 3-iodobenzoate with *N*-methylaniline using 2 equiv of ground cesium carbonate type 1 with the yield previously obtained using 2 equiv of unground base of the same type under otherwise identical conditions (see higher). Ground cesium carbonate yielded 85% of ethyl 3-[methyl(phenyl)amino]benzoate in 3 h of reflux while unground base yielded only 51% in the same reaction time. This observation also supports an interphase deprotonation mechanism.

In conclusion, based on kinetic data, we have proven for the first time that an interphase deprotonation of Pd(II)−amine complexes with weak bases is possible. Controlling the structure (shape and size of the particles) and/or molar excess of the base used can significantly speed up Buchwald−Hartwig aminations of aryl halides with rate-limiting deprotonation. In the last years, the research in palladium-catalyzed aminations was mainly focused on the development of new ligands that allow the tackling of industrially relevant aryl chlorides by using a weak base and a low catalyst loading. Taking into account a possible base effect might further improve some of these existing protocols. Our successful application of the base effect for the intermolecular amination of aryl iodides (using a standard second generation Pd−BINAP catalyst in combination with weak cesium carbonate base), which historically have been shown to be less effective substrates, clearly demonstrates the power of this base effect.

Experimental Section

General Procedure for the Pd-Catalyzed Aminations of Aryl Iodides. A round-bottom flask was charged with Pd$(OAc)_2$, (±)-BINAP, and toluene (5 mL). The mixture was flushed with nitrogen for 10 min under magnetic stirring. In another round-bottom flask aryl iodide (1.5 mmol), amine (1.8 mmol), and Cs_2CO_3 were weighed. Then, the Pd$(OAc)_2$/BINAP solution was added, and the flask was rinsed well with an additional amount of toluene (10 mL). The resulting mixture was flushed with nitrogen for 5 min under magnetic stirring and subsequently heated in a preheated oil bath under vigorous magnetic stirring (oil bath temperature 120 °C) (N_2 atmosphere). After reflux overnight the mixture was cooled to room temperature. The solid material was filtered off and washed well with CH_2Cl_2 (200 mL). The filtrate was evaporated and the resulting crude product was purified by flash column chromatography.

The characterization data of (2,5-dimethylphenyl)hexylamine, ethyl 3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)benzoate, [4-(dipropylamino)phenyl](phenyl)methanone, 4-(2-methoxyphenyl)morpholine, ethyl 2-[(3-cyanophenyl)amino]benzoate, ethyl 3-[methyl(phenyl)amino]benzoate, and ethyl 4-[methyl(phenyl)amino]benzoate were identical with those reported in the literature.[6]

4-(1-Naphthyl)morpholine (1): Eluent CH_2Cl_2; mp 82 °C; δ_H ($CDCl_3$) 8.22−8.17 (m, 1H, H-5 or H-8), 7.82−7.77 (m, 1H, H-5 or H-8), 7.54 (br d, $J = 8.2$ Hz, 1H, H-4), 7.48−7.41 (m, 2H, H-6,7), 7.37 (dd, $J = 8.2$, 7.5 Hz, 1H, H-3), 7.04 (dd, $J = 7.5$, 1.1 Hz, 1H, H-2), 3.86 (br t, 4H, H-2′), 3.18 (br t, 4H, H-3′); δ_C ($CDCl_3$) 149.4, 134.8, 128.8, 128.4, 125.8, 125.8, 125.3, 123.7, 123.3, 114.6, 67.4, 53.5; ν_{max} (KBr) 2853, 1453, 1397, 1258, 1113, 1011, 918, 801, 776; MS (ESI) 214, 170, 168, 167, 141; HRMS (ESI) for $C_{14}H_{16}NO$ [M + H$^+$] calcd 214.1232, found 214.1226.

Ethyl 3-(morpholin-4-yl)benzoate (2): Eluent CH_2Cl_2/EtOAc 95:5; δ_H ($CDCl_3$) 7.58 (br s, 1H, H-2), 7.54 (d, $J = 7.6$ Hz, 1H, H-6), 7.31 (dd, $J = 8.1$, 7.6 Hz, 1H, H-5), 7.07 (d, $J = 8.1$ Hz, 1H, H-4), 4.37 (q, $J = 7.2$ Hz, 2H, CH_2), 3.84 (br t, 4H, H-2′), 3.19 (br t, 4H, H-3′), 1.38 (t, $J = 7.2$ Hz, 3H, CH_3); δ_C ($CDCl_3$) 166.6, 151.1, 131.3, 128.9, 120.7, 119.7, 116.2, 66.6, 60.7, 49.0, 14.2; ν_{max} (liquid film) 1715, 1601, 1581, 1445, 1367, 1302, 1265, 1228, 1122, 959, 757; MS (ESI) 236, 208, 190, 164, 120; HRMS (ESI) for $C_{13}H_{18}NO_3$ [M + H^+] calcd 236.1287, found 236.1275.

3-(Morpholin-4-yl)benzonitrile (3): Eluent CH_2Cl_2/EtOAc 98:2; mp 105 °C; δ_H ($CDCl_3$) 7.34 (dd, *J* = 9.3, 7.6 Hz, 1H, H-5), 7.13 (dt, *J* = 7.8, 1.2 Hz, 1H, H-4 or H-6), 7.12−7.09 (m, 2H, H-2, H-4 or H-6), 3.86 (br t, 4H, H-2′), 3.18 (br t, 4H, H-3′); δ_C ($CDCl_3$) 151.1, 129.7, 122.5, 119.2, 119.0, 117.8, 112.8, 66.3, 48.2; ν_{max} (KBr) 2226, 1600, 1573, 1293, 1270, 1244, 1116, 994, 960, 864, 776, 679; MS (ESI) 189, 145, 143; HRMS (ESI) for $C_{11}H_{13}N_2O$ [M + H^+] calcd 189.1028, found 189.1026.

3-(Benzylamino)benzonitrile (4): Eluent CH_2Cl_2/hexane 70:30; mp 68−69 °C; δ_H ($CDCl_3$) 7.35−7.23 (m, 5H, H-2′, H-3′, H-4′), 7.15 (td, *J* = 7.6, 0.9 Hz, H-5), 6.88 (dt, *J* = 7.6, 1.2 Hz, 1H, H-4 or H-6), 6.77 (dd, *J* = 2.4, 0.9 Hz, 1H, H-4 or H-6), 6.74 (br s, 1H, H-2), 4.33 (d, *J* = 5.2 Hz, 2H, CH_2), 4.31 (br s, 1H, NH); δ_C ($CDCl_3$) 148.3, 138.2, 129.8, 128.7, 127.5, 127.3, 120.7, 119.4, 117.2, 115.0, 112.8, 47.7; ν_{max} (KBr) 3387, 2229, 1601, 1583, 1531, 1340, 777; MS(ESI) 209, 91; HRMS (ESI) for $C_{14}H_{13}N_2$ [M + H^+] calcd 209.1079, found 209.1084.

3-(Dipropylamino)benzonitrile (5): Eluent heptane/ether 90:10; δ_H ($CDCl_3$) 7.22 (dd, *J* = 9.4, 7.4 Hz, 1H, H-5), 6.85 (dt, 1H, *J* = 7.4, 1.2 Hz, H-4 or H-6), 6.81−6.77 (m, 2H, H-2, H-4 or H-6), 3.23 (t, *J* = 7.7 Hz, 4H, H-1′, H-1″), 1.59 (h, *J* = 7.5 Hz, 4H, H-2′, H-2″), 0.94 (t, *J* = 7.5 Hz, 6H, H-3′, H-3″); δ_C ($CDCl_3$) 148.2, 129.8, 119.9, 118.3, 115.7, 114.3, 112.9, 52.7, 20.1, 11.3; MS (ESI) 203, 161, 119; ν_{max} (liquid film) 2961, 2874, 2227, 1596, 1497, 1467, 1367, 1245, 1194, 1009, 772, 682; MS-(ESI) 203, 161, 119; HRMS (ESI) for $C_{13}H_{19}N_2$ [M + H^+] calcd 203.1548, found 203.1540.

General Procedure for the Kinetic Experiments. A two-necked round-bottom flask was charged with $Pd(OAc)_2$, (±)-BINAP, and toluene (5 mL). The mixture was flushed with nitrogen for 10 min under magnetic stirring. In another round-bottom flask 2-chloro-3-iodopyridine (1.5 mmol, 0.356 g), amine (1.8 mmol), and Cs_2CO_3 were weighed. Then, the $Pd(OAc)_2$/BINAP solution was added, and the flask was rinsed well with an additional amount of toluene (10 mL). The resulting mixture was flushed with nitrogen under magnetic stirring. At that time the first sample was taken. After flushing with nitrogen for 5 min the second sample was taken from the reaction mixture. Next the reaction mixture was heated in a preheated oil bath under vigorous magnetic stirring (oil bath temperature 120 °C) (N_2 atmosphere). During the first hour a sample was taken every 5 min, during the second hour every 15 min, and then every 30 min. The samples were taken with a GC-syringe. Herewith 50 μL of fluid was taken from the flask via a septum, brought into a 25 mL volumetric flask, and immediately diluted with a 50:50 H_2O/MeOH solution (HPLC grade solvents). The solutions were filtered (0.2 mm; Nylon) and subsequently analyzed with HPLC-UV. The percentage reaction product is determined by dividing the HPLC peak area of the reaction product by the sum of the peak areas of the starting material and reaction product after a correction factor on the peak areas, based on the difference in extinction coefficient of the starting material and reaction product at the used wavelength (254 nm), has been taken into account.

Chromatographic Conditions. The analytical column (Lichrospher RP-select B, C8, 5-μm particles, 120 mm × 4 mm) was purchased from Merck (Darmstadt, Germany). For the amination of 2-chloro-3-iodopyridine with *p*-toluidine the HPLC analysis was executed with a gradient elution at 1 mL/min starting at 50:50 (v/v) NH_4OAc (0.1 M)−MeOH. The composition of the mobile phase was altered to 17:83 (v/v) NH_4OAc (0.1 M)−MeOH in 10 min. For the amination of 2-chloro-3-iodopyridine with benzylamine the HPLC analysis was executed with a gradient elution at 1 mL/min starting at 70:30 (v/v) NH_4OAc (0.1 M)−MeOH. The composition of the mobile phase was altered to 38:62 (v/v) NH_4OAc (0.1 M)−MeOH in 20 min.

2-Chloro-3-(4-methylphenylamino)pyridine (6): Eluent CH_2Cl_2/heptane/EtOAc 70:25:5; δ_H ($CDCl_3$) 7.78 (dd, *J* = 4.6, 1.7 Hz, 1H, H-6), 7.34 (dd, *J* = 8.1, 1.7 Hz, 1H, H-4), 7.14 (d, *J* = 8.1 Hz, 2H, H-3′, H-5′), 7.03 (d, *J* = 8.1 Hz, 2H, H-2′, H-6′), 7.00 (dd, *J* = 8.1, 4.6 Hz, 1H, H-5), 6.08 (br s, 1H, NH), 2.32 (s, 3H, CH_3); δ_C ($CDCl_3$) 138.5, 138.3, 138.0, 137.6, 133.7, 130.0, 122.9, 121.9, 120.4, 20.6; ν_{max} (liquid film) 3405, 1589, 1516, 1486, 1322, 810; MS(ESI) 219, 184, 183, 168; HRMS (ESI) for $C_{12}H_{12}N_2Cl$ [M + H^+] calcd 219.0689, found 219.0682.

2-Chloro-3-(benzylamino)pyridine (7): Eluent CH_2Cl_2; δ_H ($CDCl_3$) 7.70 (dd, *J* = 4.6, 1.7 Hz, 1H, H-6), 7.40−7.28 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 7.01 (ddd, *J* = 8.1, 4.6, 0.6 Hz, 1H, H-5), 6.82 (dd, *J* = 8.1, 1.7 Hz, 1H, H-4), 4.84 (br s, 1H, NH), 4.38 (br d, *J* = 5.7 Hz, 2H, CH_2); δ_C ($CDCl_3$) 140.6, 137.7, 137.1, 136.6, 128.8, 127.6, 127.1, 123.3, 117.8, 47.4); ν_{max} (liquid film) 3408, 1582, 1559, 1494, 1447, 1380, 1357, 1050, 795, 732; MS(ESI) 219, 183, 128, 91; HRMS (ESI) for $C_{12}H_{12}N_2Cl$ [M + H^+] calcd 219.0689, found 219.0679.

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Supporting Information Available: General experimental considerations, SEM images of cesium carbonate “type 1”, “type 2”, and ground “type 1” as well as ^{1}H NMR spectra for compounds **1**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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