DOI: 10.1002/adsc.200700328

Auto-Tandem Catalysis: Synthesis of Substituted 11*H*-Indolo [3,2-*c*]quinolines *via* Palladium-Catalyzed Intermolecular C–N and Intramolecular C–C Bond Formation

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Received: July 5, 2007; Revised: December 1, 2007; Published online: February 11, 2008

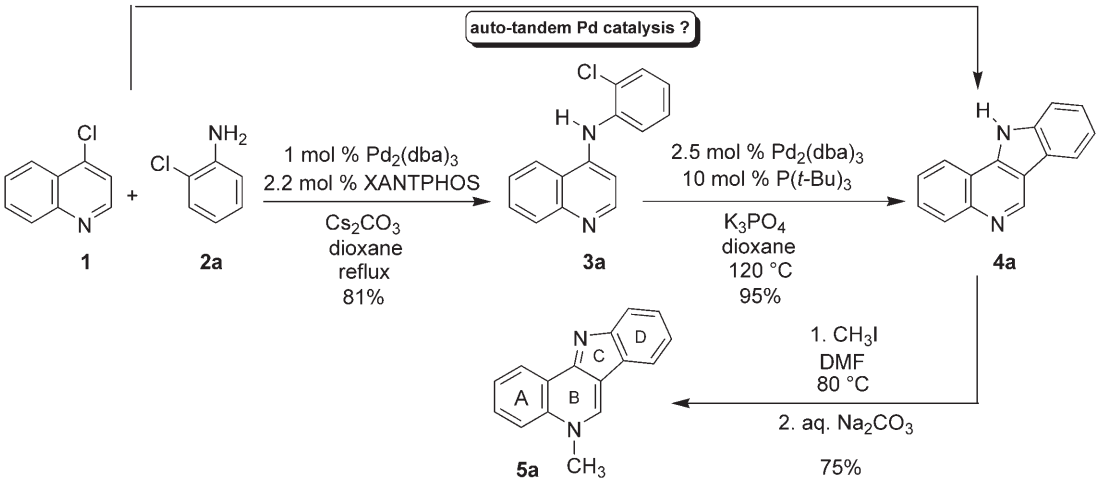
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: D-Ring substituted 11*H*-indolo[3,2-*c*]quinolines (**4**) have been prepared *via* auto-tandem consecutive intermolecular Buchwald-Hartwig reaction and intramolecular palladium-catalyzed arylation on 4-chloroquinoline (**1**) with *N*-unsubstituted 2-chloroanilines (**2**). The reported 11*H*-indolo[3,2-*c*]quinolines (**4**) represent the first examples in which tandem catalysis has been used to construct *N*-unsubstituted carbolines.

Keywords: amination; C–H activation; malaria; palladium; tandem catalysis

Introduction

In 2003 our research group published a communication which described a new method for the synthesis of 11*H*-indolo[3,2-*c*]quinoline (**4a**) starting from commercially available 4-chloroquinoline (**1**) and 2-chloroaniline (**2a**) (Scheme 1).[1] The methodology consists of two consecutive palladium-catalyzed reactions: a selective Buchwald–Hartwig reaction (chemoselective oxidative addition) followed by an intramolecular arylation involving C–H activation.[2,3] The latter reaction is interesting in itself as published examples on intramolecular Pd-catalyzed arylations of electron-deficient heteroaromatics are scarce in comparison with electron-rich heteroarenes.[3c] Selective *N*-5 methylation of the obtained 11*H*-indolo[3,2-*c*]quinoline (**4a**) yielded the antiplasmodial natural product isocryptolepine (5-methyl-5*H*-indolo[3,2-*c*]quinoline) (**5a**) (Scheme 1).[4] The increasing resistance of parasites of the genus *Plasmodium* to well known drugs like chloroquine and mefloquine prompted us to investigate more closely the biological



Scheme 1. Synthesis of **4a** *via* consecutive palladium-catalyzed reactions.

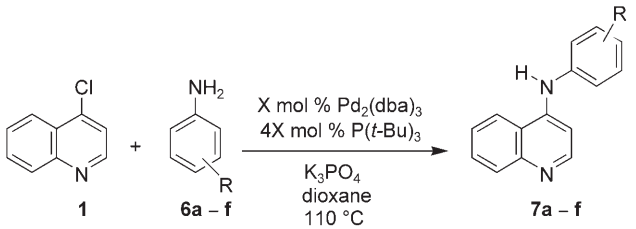
profile of isocryptolepine. For this purpose we decided to prepare a set of D-ring substituted derivatives in order to be able to look at the effect of these substituents on the selectivity index (cytotoxicity/antiplasmodial activity). The initial choice for the D-ring is based on the presumed mechanism of action of isocryptolepine, namely inhibition of the heme detoxification process, which is similar to that of chloroquine.[5] D-Ring modified isocryptolepine analogues are rational from a medicinal chemistry point of view since the quinoline part in chloroquine and analogues is known to be very important in the heme complexation process and only limited substitutions are tolerated.

Instead of simply using the earlier developed three-step methodology to prepare D-ring substituted isocryptolepines, starting from 4-chloroquinoline (**1**) and substituted 2-chloroanilines (**2**), we wondered if it would be possible to perform the two palladium-catalyzed reactions in an auto-tandem fashion (Scheme 1).[6] This would give access to a very powerful method to prepare 11*H*-indolo[3,2-*c*]quinolines (**4**) in a single reaction step using only one catalyst starting from commercially available reagents. Consequently, the target 5-methyl-5*H*-indolo[3,2-*c*]quinolines (**5**) can be synthesized in just two reaction steps. Currently, tandem catalysis is at the forefront of scientific research in organic synthesis since it permits one to create complexity from easily accessible building blocks in only one reaction step.[7] This makes it a preferred tool for the generation of libraries in pharmaceutical and agrochemical companies. While the synthesis of carbolines and carbazoles *via* a stepwise approach involving an intramolecular Pd-catalyzed arylation reaction is already very attractive,[8] the development of tandem protocols starting from commercially available building blocks certainly poses an additional chemical challenge. Hitherto no methods based on tandem catalysis have been reported for the construction of *N*-unsubstituted carbolines. For *N*-substituted carbazole synthesis two general auto-tandem protocols (involving an intramolecular arylation step) have appeared.[9a,10] Recently, two independent papers were published describing the use of *N*-unsubstituted anilines allowing the synthesis of *N*-unsubstituted carbazoles.[9b,10] Besides the usefulness of a library of isocryptolepine derivatives, the absence of tandem protocols for the synthesis of *N*-unsubstituted carbolines stimulated us to study the auto-tandem palladium-catalyzed coupling of 4-chloroquinoline (**1**) and 2-chloroanilines (**2**).[10]

Results and Discussion

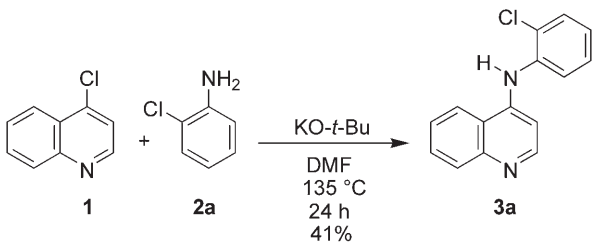
For the intramolecular C–C bond formation on *N*-(2-chlorophenyl)quinolin-4-amine (**3a**) we previously described that P(*t*-Bu)$_3$ is a suitable ligand for the palladium catalyst (Scheme 1).[1] Based on the fact that the cyclodehydrochlorination is the most sensitive reaction of the desired auto-tandem protocol, we consequently decided to investigate if the catalyst [Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$] and excess base (K$_3$PO$_4$) combination used for the cyclodehydrochlorination reaction of **3a** is also suitable to perform Buchwald–Hartwig aminations on 4-chloroquinoline (**1**). Ethyl 4-aminobenzoate (**6a**) was chosen as a test amine. Interestingly, when 1 mol% Pd$_2$(dba)$_3$/4 mol% P(*t*-Bu)$_3$ was used in dioxane as solvent in combination with 1.2 equivalents of **6a** and 5 equivalents of K$_3$PO$_4$, we observed a complete conversion of **1** in 17 h at 110 °C. The desired *N*-(4-ethoxycarbonylphenyl)quinolin-4-amine could be isolated in 95% yield after purification by column chromatography (Table 1). When we used the conditions for the reaction of **1** with **6a** for the coupling of other anilines with an electron-withdrawing group [ethyl 2-aminobenzoate (**6b**), 4-aminobenzonitrile (**6c**) and 4-fluoroaniline (**6d**)] excellent results were also obtained (Table 1). For electron-releasing substituents a slower reaction was observed. When 4-*tert*-butylaniline (**6e**) and 4-methoxyaniline (**6f**) were used an increase of the catalyst loading to 5 mol% was required to get complete conversion of **1** in an overnight protocol (Table 1). The slower conversion observed with electron-releasing substituents on the aniline was confirmed when comparing the conversion of the reaction of **1** with **6a** and **6f**, respectively, using an HPLC-UV system.[11] The amination reactions studied are completely Pd-catalyzed since under our reaction conditions no trace of amination product could be observed when the catalyst was omitted in

Table 1. Pd-Catalyzed amination of 4-chloroquinoline (**1**) with substituted anilines (**6**).[a]



Product	R	Catalyst loading [mol% Pd]	K_3PO_4 [equivs.]	Yield [%]
7a	4-COOEt (**6a**)	2	5	95
7b	2-COOEt (**6b**)	2	5	81
7c	4-CN (**6c**)	2	5	86
7d	4-F (**6d**)	2	5	88
7e	4-*t*-Bu (**6e**)	5	5	97
7f	4-MeO (**6f**)	5	5	80

[a] *General conditions:* X mol % Pd$_2$(dba)$_3$, 4X mol % P(*t*-Bu)$_3$, 2 mmol **1**, 2.4 mmol **6**, 10 mmol K$_3$PO$_4$, dioxane, 110 °C (oil bath temperature), pressure tube, 17 h.

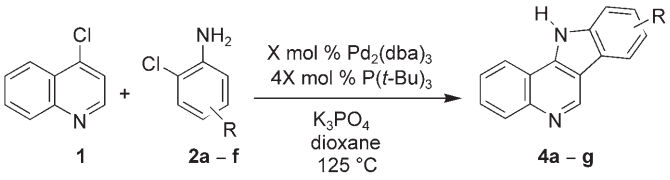


Scheme 2. Synthesis of *N*-(2-chlorophenyl)quinolin-4-amine (**3a**) *via* nucleophilic aromatic substitution.

the coupling reactions of **1** with **6**. In itself the results obtained for the Buchwald–Hartwig amination of **1** with a wide variety of anilines (**6a–f**) under mild reaction conditions are already of interest since there is only one other report in the literature that describes the arylamination of 4-chloroquinolines.[12] In this report Wolf and Lerebours describe one example of arylamination, namely the coupling of 4-chloro-2-phenylquinoline with aniline using di-*tert*-butylphosphinous acid as ligand for the catalyst. However, in their protocol strong *t*-BuOK base in DMF at 135 °C was used. These rather harsh reaction conditions in a very polar medium even allowed a direct nucleophilic aromatic substitution of aniline on 4-chloro-2-phenylquinoline. A similar yield of *N*,2-diphenylquinolin-4-amine could be obtained omitting the catalyst. When we reacted **1** with **2a** using *t*-BuOK in DMF at 135 °C for 24 h a dirty reaction mixture was obtained out of which only 41% of **3a** could be isolated after flash column chromatography (Scheme 2). This is 40% lower than the yield obtained using the $Pd_2(dba)_3$/XANTPHOS system (Scheme 1).[1]

Based on the knowledge that 4-chloroquinoline (**1**) can be arylaminated using the same catalyst, base and solvent as used for the cyclodehydrochlorination of **3a**, we attempted an auto-tandem reaction of **1** with 2-chloroaniline (**2a**). For this experiment we used exactly the same reaction conditions (2.5 mol % $Pd_2(dba)_3$, 10 mol % P(*t*-Bu)$_3$, 2 mmol **1**, 2.4 mmol **2a**, 20 mmol K_3PO_4, dioxane, pressure tube, oil bath temperature 125 °C) as previously described in our communication for the intramolecular Pd-catalyzed arylation reaction of *N*-(2-chlorophenyl)quinolin-4-amine (**3a**). We were very delighted to observe that with the same loading of catalyst as used for the ring closure of **3a**, a complete conversion of **1** to **4a** was observed in a reaction time of 24 h (Table 2). 11*H*-Indolo[3,2-*c*]quinoline (**4a**) could be isolated in 82% yield which is similar to the overall yield of the two-step approach (77%). The reaction occurs *via* auto-tandem catalysis: Pd-catalyzed C–N bond formation (based on a chemoselective oxidative addition) followed by a Pd-catalyzed arylation. Amine **3a** is certainly an intermediate since TLC and MS analysis clearly revealed its presence during the course of the reaction. Both reactions require Pd catalysis since omitting the catalyst under otherwise similar conditions gave no **3a** and **4a**. With the same auto-tandem protocol 2-chloroanilines with electron-withdrawing [4-F (**2b**), 6-F (**2c**), 4-COOMe (**2d**), 4-CN (**2e**)] as well as electron-releasing substituents [4-*t*-Bu (**2f**), 4-MeO (**2g**)] yielded the corresponding substituted 11*H*-indolo[3,2-*c*]quinolines in a good yield (Table 2). Only for the auto-tandem reaction with 4-aminobenzonitrile (**2e**) a higher catalyst loading was required to drive the reaction to completion in 24 h (Table 2).

Table 2. Synthesis of D-ring substituted 11*H*-indolo[3,2-*c*]-quinolines *via* auto-tandem Pd-catalyzed intermolecular C–N and intramolecular C–C bond formation.[a]

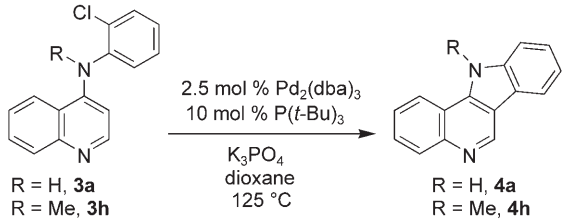


Product	2-Chloroaniline (**2**)	Catalyst loading [mol% Pd]	Yield [%]
4a	H (**2a**)	5	82
4b	4-F (**2b**)	5	55
4c	6-F (**2c**)	5	80
4d	4-COOMe (**2d**)	5	50
4e	4-CN (**2e**)	7	80
4f	4-*t*Bu (**2f**)	5	76
4g	4-MeO (**2g**)	5	52

[a] *General conditions:* X mol % $Pd_2(dba)_3$, 4X mol % P(*t*-Bu)$_3$, 2 mmol **1**, 2.4 mmol **2**, 20 mmol K_3PO_4, dioxane, 125 °C (oil bath temperature), pressure tube, 24 h.

Next we further investigated if the large excess of base (10 equivalents) used in the auto-tandem reactions (Table 2) is really required (Table 3). In our communication dealing with the synthesis of isocryptolepine we noticed a beneficial effect of a large excess of K_3PO_4 on the cyclization of **3a**. To quantitatively determine if such a "*base effect*"[13] is really present in the second catalytic cycle of our auto-tandem protocol, namely the palladium-catalyzed arylation of **3**, we determined the conversion of **3a** to **4a** using different amounts of K_3PO_4 (Table 3). Limited reaction times of 15 and 30 min were selected and the conversions were determined by recording ^{1}H NMR spectra of the crude reaction mixtures. When 2 equivalents of K_3PO_4 were used 16% conversion to **4a** occurred in 15 min, while a similar experiment with 10 equivalents base gave 39%. With 2 equivalents of K_3PO_4 in 30 min 35% conversion to **4a** occurred and upon using 10 equivalents of base 55% conversion was achieved. These observations clearly confirm that, although 2 equivalents of base do already not completely dissolve in the reaction mixture, the use of

Table 3. Effect of base and excess of base on the Pd-catalyzed cyclodehydrochlorination of **3a** and **3h**.

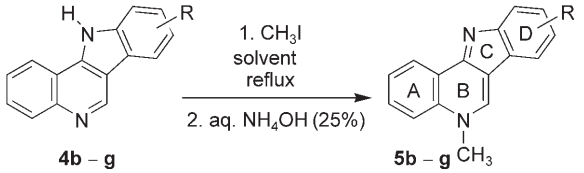


Substrate	Base	Equivalents	Time (min)	% **4a**[a]
3a	K_3PO_4	2	15	16
3a	K_3PO_4	2	30	35
3a	K_3PO_4	10	15	39
3a	K_3PO_4	10	30	55
3a	K_3PO_4	5	30	46
3a	*t*-BuONa	5	30	5
3a	*t*-BuOK	5	30	11
3a	*t*-BuOK	5	120	88
3h	*t*-BuOK	5	30	11
3h	*t*-BuOK	5	120	78
3h	K_3PO_4	5	120	11

[a] Average conversion of two reactions. Conversion determined using ^{1}H NMR.

a larger excess speeds up the reaction to some extent. The effect of the strength of the base was also checked (Table 3). When 5 equivalents of K_3PO_4, *t*-BuONa and *t*-BuOK were used, respectively, 46%, 5% and 11% conversion occurred in 30 min reaction time. In 2 h 88% conversion was obtained for the latter base. We wondered if the increased acidity of the NH of **3a** in comparison to the NH of *N*-aryl-2-chloroanilines in the reported carbazole synthesis is responsible for our observation.[9b] Therefore we prepared *N*-(2-chlorophenyl)-*N*-methylquinolin-4-amine (**3h**) and subjected the molecule to the same ring-closure conditions. With 5 equivalents of *t*-BuOK we observed 11% conversion to **4h** in a limited reaction time of 30 min and 78% conversion for the same reaction in 2 h. When we compare the conversion value of **3a** using *t*-BuOK with the one of the N-Me analogue (**3h**), there is slightly better conversion for **3a**. This is an indication that the increased acidity of **3a** (deprotonation) is not responsible for the slower intramolecular C–C bond formation with stronger base on this substrate. More experiments would be required to fully prove this as a change in rate-limiting step or mechanism cannot be excluded at this moment. Interestingly, 5 equivalents K_3PO_4 gave a substantially slower reaction on **3h** than on **3a** as only 11% conversion was obtained in 2 h. In conclusion, the use of milder bases (K_3PO_4 *versus* *t*-BuOM) is not only beneficial for the general functional group compatibility of the protocol but in some cases, as exemplified by substrate **3a**, also advantageous for the rate of the ring-closure reaction involving C–H activation.

Table 4. *N*-5 Methylation of 11*H*-indolo[3,2-*c*]quinolines.[a]



Product	R	Solvent	Yield [%]
5b	8-F	BTF	90
5c	10-F	toluene	78
5d	8-COOMe	toluene	89
5e	8-CN	toluene	60
5f	8-*t*-Bu	toluene	82
5g	8-MeO	toluene	82

[a] *General conditions:* a) 0.25 mmol **4**, 3 mL MeI, 3.75 mL solvent, reflux, 20 h; b) 40 mL aqueous NH_4OH, 40 mL CH_2Cl_2.

Finally, selective *N*-5 methylation of the synthesized D-ring substituted 11*H*-indolo[3,2-*c*]quinolines (**4b–g**) could be smoothly performed under conditions recently reported for the selective *N*-5 methylation of 7*H*-indolo[2,3-*c*]quinoline (Table 4).[14] This yielded the target compounds in moderate to good yields.

Conclusions

We have developed the first auto-tandem Pd-catalyzed consecutive C–N and C–C bond forming process for *N*-unsubstituted carboline synthesis. 11*H*-Indolo[3,2-*c*]quinolines have been obtained in one step from 4-chloroquinoline and 2-chloroanilines. Electron-releasing as well as electron-withdrawing substituents are tolerated on the 2-chloroaniline. The protocol is based on a weak base which is beneficial from the point of view of functional group compatibility.

Experimental Section

General Procedure for the Pd-Catalyzed Amination of 4-Chloroquinoline (1) with Substituted Anilines (6)

A 50-mL, round-bottomed flask was charged with $Pd_2(dba)_3$ (0.02 mmol, 0.018 g), followed by dry freshly distilled dioxane (20 mL). To this solution P(*t*-Bu)$_3$ (0.08 mmol, 0.2 mL of 0.4 M solution in toluene) was added *via* a syringe. The obtained mixture was flushed with Ar for 10 min under magnetic stirring. Meanwhile an 80-mL pressure tube was charged with 4-chloroquinoline (2.0 mmol, 0.324 g), aniline (2.4 mmol) and finely ground K_3PO_4 (10.0 mmol, 2.12 g). To this mixture, the preformed Pd catalyst was added under an

argon flow. The 50-mL flask was subsequently rinsed with freshly distilled dioxane (2×10 mL). Then the resulting mixture was flushed with argon for 5 min, closed and heated at 110 °C (oil bath temperature) under vigorous magnetic stirring for 17 h. After cooling down to room temperature the crude reaction mixture was filtered through a pad of Celite which was rinsed with CH_2Cl_2 (100 mL) and CH_2Cl_2/MeOH (98/2) (50 mL). The filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

General Procedure for the Auto-Tandem Pd-Catalyzed Coupling of 4-Chloroquinoline (1) with 2-Chloroanilines (2)

A 50-mL, round-bottomed flask was charged with $Pd_2(dba)_3$ (0.05 mmol, 0.046 g), followed by dry freshly distilled dioxane (20 mL). To this solution P(*t*-Bu)$_3$ (0.2 mmol, 0.2 mL of 1 M solution in toluene) was added *via* a syringe. The obtained mixture was flushed with argon for 15 min under magnetic stirring. Meanwhile an 80-mL pressure tube was charged with 4-chloroquinoline (2.0 mmol, 0.327 g), aniline (2.4 mmol) and finely ground K_3PO_4 (20.0 mmol, 4.25 g). To this mixture, the preformed Pd catalyst was added under an argon flow. The 50-mL flask was subsequently rinsed with freshly distilled dioxane (2×10 mL). Then the resulting mixture was flushed with argon for 5 min, closed and heated at 125 °C (oil bath temperature) under vigorous magnetic stirring for 24 h. After cooling down to room temperature the crude reaction mixture was filtered through a pad of Celite which was rinsed with CH_2Cl_2/MeOH or CH_2Cl_2. The filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

General Procedure for the Methylation of 7*H*-Indolo[2,3-*c*]quinolines (4)

In a round-bottomed flask 7*H*-indolo[2,3-*c*]quinoline (**4**) (0.25 mmol), toluene (3.75 mL) and CH_3I (3 mL) were heated at reflux under an argon atmosphere for 20 h under magnetic stirring. Then the reaction mixture was evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: dichloromethane/methanol, 9/1) giving the isocryptolepine hydroiodide (**5**·HI). To obtain the free base, **5**·HI was brought in a mixture of dichloromethane (40 mL) and 28–30% ammonia in water (40 mL). The organic phase was separated and the aqueous phase subsequently extracted with dichloromethane (2×40 mL). The combined organic phase was dried over $MgSO_4$, filtered and evaporated to dryness to yield **5**.

Acknowledgements

The authors acknowledge financial support from the University of Antwerp (GOA BOF UA, NOI BOF UA) and the Flemish Government enabling the purchase of NMR equipment (Impulsfinanciering van de Vlaamse Overheid voor Strategisch Basisonderzoek PFEU 2003) as well as the technical assistance of P. Franck. C. Meyers thanks the Fund for Scientific Research – Flanders (Belgium) for a PhD scholarship.

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[11] Compound **6a** as aniline and 2 mol % catalyst: with 5 equivalents K_3PO_4 84% conversion in 1 hour and 90% in 2 h was observed. Compound **6f** as aniline and 2 mol % catalyst: with 5 equivalents K_3PO_4 42% conversion in 2 h and 50% in 4 h was observed. When 2 equivalents of K_3PO_4 were used a similar conversion was observed. This indicates that there is no "base effect" in the Pd-catalyzed amination reactions on **1** with a Pd/P-(*t*-Bu)$_3$ catalyst-K_3PO_4 base combination.

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[13] For examples of "base effects" in Pd-catalyzed amination reactions, see: a) J. Košmrlj, B. U. W. Maes, G. L. F. Lemière, A. Haemers, *Synlett* **2000**, 1581–1584; b) M. Watanabe, M. Nishiyama, T. Yamamoto, Y. Koie, *Tetrahedron Lett.* **2000**, *41*, 481–483; c) B. U. W. Maes, K. T. J. Loones, T. H. M. Jonckers, G. L. F. Lemière, R. A. Dommisse, A. Haemers, *Synlett* **2002**, 1995–1998; d) C. Meyers, B. U. W. Maes, K. T. J. Loones, G. Bal, G. L. F. Lemière, R. A. Dommisse, *J. Org. Chem.* **2004**, *69*, 6010–6017; e) S. Hostyn, B. U. W. Maes, G. Van Baelen, A. Gulevskaya, C. Meyers, K. Smits, *Tetrahedron* **2006**, *62*, 4676–4684; f) G. Rombouts, B. U. W. Maes, T. H. M. Jonckers, K. T. J. Loones, *Org. Synth.* **2007**, *84*, 215–221. Important general remarks should be made about '*base effects*' in Pd-catalyzed reactions involving deprotonations in the rate-determining step of the catalytic cycle. If one wants to compare absolute amounts of base used for different bond forming reactions (e.g., C–N), described in separate publications, one has to be sure that the base particle size distribution/total contact surface area was the same. Even if two teams buy the same quality of base from the same chemical supplier, it is highly doubtful that this requirement is fulfilled as they most probably received base from another lot. The stirring speed of the reaction should also be similar and therefore controlled as an interphase deprotonation mechanism will be seriously influenced by this factor. When no fundamental comparisons of different reactions are aimed, the base can be used as such if the total contact surface area is large. If not, a simple grinding of base in a mortar can be performed or a larger excess can be used. For an example of a study dealing with a fundamental comparison of Pd-catalyzed amination reactions on aryl iodides: see ref.[13d]

[14] S. Hostyn, B. U. W. Maes, L. Pieters, G. L. F. Lemière, P. Mátyus, G. Hajós, R. Dommisse, *Tetrahedron* **2005**, *61*, 1571–1577.

