DOI: 10.1002/chem.201102468

Synthesis of 4-Aminoquinazolines by Palladium-Catalyzed Intramolecular Imidoylation of *N*-(2-Bromoaryl)amidines

Gitte Van Baelen,[a] Sander Kuijer,[a] Lukáš Rýček,[a] Sergey Sergeyev,[b] Elwin Janssen,[a] Frans J. J. de Kanter,[a] Bert U. W. Maes,*[b] Eelco Ruijter,*[a] and Romano V. A. Orru*[a]

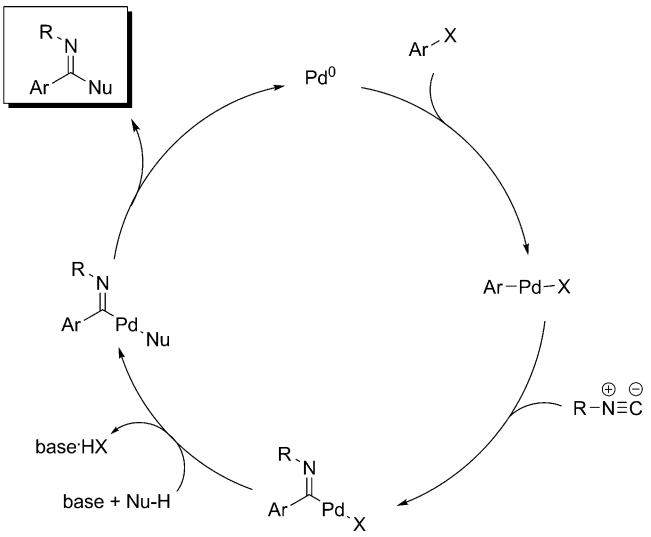
Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday

Abstract: Compared with the widespread use of carbonylative Pd-catalyzed cross-coupling reactions, similar reactions involving isocyanide insertion are almost virgin territory. We investigated the intramolecular imidoylative cross-coupling of *N*-(2-bromoaryl)amidines, leading to 4-aminoquinazolines. After thorough optimization of the reaction with respect to palladium source and loading, ligand, base, temperature, and solvent, a small library of 4-aminoquinazolines was prepared to determine the scope of this method. Various substituents are tolerated on the amidine and the isocyanide, providing efficient access to a broad range of diversely substituted 4-aminoquinazolines of significant pharmaceutical interest.

Keywords: homogeneous catalysis · isocyanides · insertion · nitrogen heterocycles · palladium · synthetic methods

Introduction

Pd-catalyzed cross-coupling reactions have made an enormous impact on organic synthesis over the past few decades, as shown by the award of the 2010 Nobel Prize in Chemistry to Heck, Suzuki, and Negishi. Moreover, the synthetic potential of these reactions has been considerably expanded by the development of carbonylative cross-coupling reactions, in which carbon monoxide is inserted between the two coupling partners.[1] Although isocyanides are isoelectronic with carbon monoxide, synthetic applications of Pd-catalyzed isocyanide insertion are extremely scarce.[2] These reactions would provide interesting opportunities for Pd-catalyzed cascade reactions.[3] On the other hand, isocyanide insertion into Pd–C bonds is a well-known phenomenon in coordination chemistry.[4] In light of our experience with the use of isocyanides in multicomponent reactions and our continuing interest in the efficient synthesis of nitrogen heterocycles, we decided to investigate the potential of Pd-catalyzed imidoylative cross-coupling reactions in the synthesis of nitrogen heterocycles. The general mechanism of Pd-catalyzed imidoylative cross-coupling reactions is depicted in Scheme 1. We reasoned that intramolecular cross-coupling reactions involving an isocyanide insertion that leads to the formation of five- or six-membered rings would be most favorable because it would plausibly suppress multiple isocyanide insertion, which is the most likely side reaction. In addition, we assumed that reaction sequences that are termi-



Scheme 1. Proposed general mechanism for Pd-catalyzed imidoylative cross-coupling reactions.

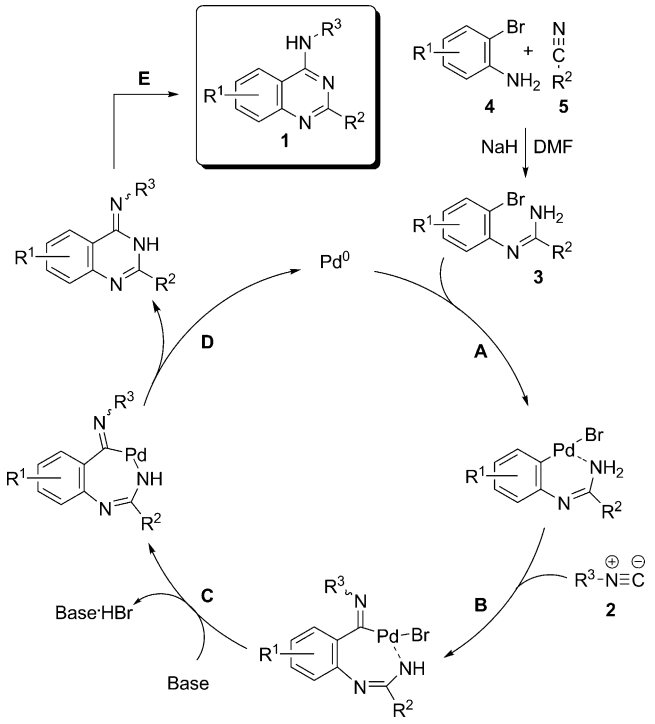
[a] Dr. G. Van Baelen, S. Kuijer, L. Rýček, E. Janssen, Dr. F. J. J. de Kanter, Dr. E. Ruijter, Prof. Dr. R. V. A. Orru
Department of Chemistry & Pharmaceutical Sciences
Amsterdam Institute for Molecules, Medicines & Systems
VU University Amsterdam, De Boelelaan 1083
1081 HV Amsterdam (The Netherlands)
Fax: (+31) 20-5987488
E-mail: e.ruijter@vu.nl
r.v.a.orru@vu.nl

[b] Dr. S. Sergeyev, Prof. Dr. B. U. W. Maes
Organic Synthesis, Department of Chemistry
University of Antwerp, Groenenborgerlaan 171
B-2020 Antwerp (Belgium)
Fax: (+32) 32653233
E-mail: bert.maes@ua.ac.be

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102468.

nated by an irreversible step, such as tautomerization/aromatization, would have a favorable effect on the reaction.

In light of these considerations, we envisioned the synthesis of 4-aminoquinazolines **1** by Pd-catalyzed intramolecular imidoylative cross-coupling of *N*-(2-bromoaryl)amidines **3**, which in turn can be derived from 2-bromoanilines **4** and nitriles **5**. A plausible reaction mechanism is presented in Scheme 2. First, palladium oxidatively inserts into the C–Br



Scheme 2. Proposed mechanism for the Pd-catalyzed synthesis of **1**, involving an isocyanide insertion (**A**: oxidative addition, **B**: isocyanide insertion, **C**: deprotonation, **D**: reductive elimination, **E**: tautomerization/aromatization).

bond in **3** (**A**) and then coordinates to the amidine moiety. Alternatively, a directed oxidative addition involving pre-coordination of amidine could occur.[5] Next, the isocyanide inserts into the oxidative addition complex (**B**). Subsequent deprotonation of the amidine results in a seven-membered palladacycle (**C**). Reductive elimination (**D**) followed by tautomerization/aromatization (**E**) affords the desired 4-aminoquinazoline **1**. At the same time, this benchmark reaction also poses a challenge, that is, to avoid the competing direct intramolecular amination leading to 1*H*-benzimidazole formation.[6] For the selective formation of the desired 4-aminoquinazolines, isocyanide insertion into the aryl–palladium bond must be fast with respect to the amination reaction with the amidine. However, our comparison with the corresponding carbonylative reactions suggests that this is a realistic assumption.[1]

The products resulting from this approach are interesting from a medicinal chemistry perspective. 4-Amino-2-arylquinazolines display diverse biological activities, including the inhibition of kinases[7] and the modulation of cannabinoid receptor 2,[8] glutamate receptors,[9] and ion channels.[10] Very recently, 4-amino-2-phenylquinazolines were also identified as potent topoisomerase I inhibitors.[11] Representative examples of pharmaceutically relevant 4-amino-2-arylquinazolines are shown in Figure 1.

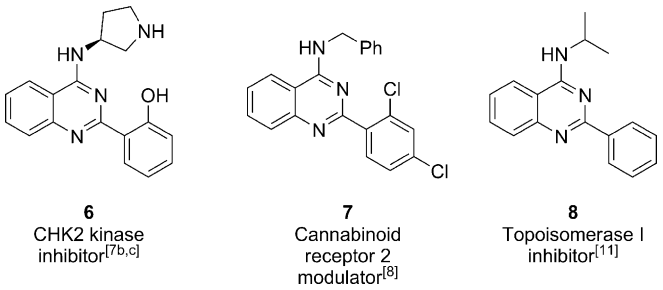


Figure 1. Examples of biologically active 4-amino-2-arylquinazolines.

Results and Discussion

We set out to investigate the potential of Pd-catalyzed isocyanide insertion in the synthesis of 4-aminoquinazolines by using the reaction between the known amidine **3a** (R^1 = H, R^2 = Ph) and *tert*-butyl isocyanide (**2a**) as a benchmark. To our delight, the use of [Pd(dba)$_2$] (5 mol%; dba = dibenzylideneacetone), XPhos (10 mol%; XPhos = 2-dicyclohexylphosphino-2′,5′,6′-trisisopropylbiphenyl), isocyanide (1.5 equiv), and KOAc (3.0 equiv) led to full conversion of the amidine starting material and, moreover, furnished the desired 4-aminoquinazoline **1a** in 95% isolated yield (Table 1, entry 1).[12] Nevertheless, we decided to optimize this model reaction further in terms of catalyst loading, ligand, solvent, and temperature to achieve an optimal procedure.

Reduction of the Pd loading to 3 mol% still led to full conversion of **3a**, but the isolated yield dropped to 75% (Table 1, entry 2). Further reduction of the catalyst loading to 2 mol% led to incomplete conversion (Table 1, entry 3). Evaluation of various monodentate dialkylbiaryl phosphine ligands[13] (Figure 2) showed that the use of DCPB and JohnPhos led to incomplete conversion of **3a**, whereas SPhos performed similarly to XPhos (Table 1, entries 4–6).

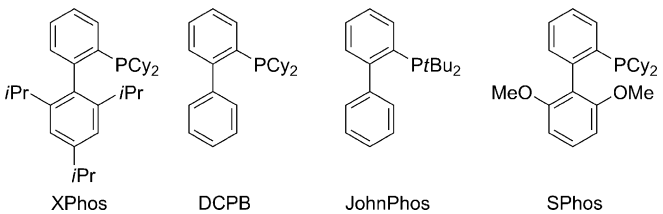
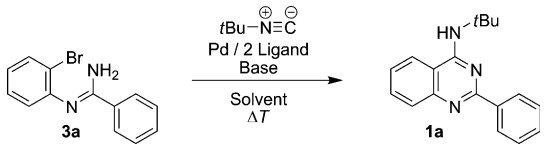


Figure 2. Structures of the biphenyl-based phosphine ligands used.

Interestingly, when we changed the palladium source to Pd(OAc)$_2$ (Ac = acetyl) in combination with the relatively

Table 1. Screening of the reaction conditions for the Pd-catalyzed synthesis of **1a** from **3a** and *tert*-butyl isocyanide (**2**, $R^3 = t$Bu).



Entry[a]	Base	Solvent	Pd source	Ligand	Pd [mol%]	T [°C]	t [h]	Remaining **3a**	Yield of **1a** [%][b]
1	KOAc	DMF	$[Pd(dba)_2]$	XPhos	5	120	5	no	95
2	KOAc	DMF	$[Pd(dba)_2]$	XPhos	3	120	7	no	75
3	KOAc	DMF	$[Pd(dba)_2]$	XPhos	2	120	7	yes	50
4	KOAc	DMF	$[Pd(dba)_2]$	DCPB	3	120	7	yes	67
5	KOAc	DMF	$[Pd(dba)_2]$	JohnPhos	3	120	7	yes	77
6	KOAc	DMF	$[Pd(dba)_2]$	SPhos	3	120	7	no	87
7	KOAc	DMF	$Pd(OAc)_2$	DCPB	3	120	7	no	89
8[c]	KOAc	DMF	$Pd(OAc)_2$	DCPB	3	120	7	yes	76
9	K_2CO_3	DMF	$Pd(OAc)_2$	DCPB	3	120	7	yes	59
10	KOAc	1,4-dioxane	$Pd(OAc)_2$	DCPB	3	110	7	no	79
11	K_2CO_3	1,4-dioxane	$Pd(OAc)_2$	DCPB	3	110	7	yes	9
12	KOAc	DMF	$Pd(OAc)_2$	DCPB	3	100	7	yes	54
13	KOAc	DMF	$Pd(OAc)_2$	DCPB	3	160	3	no	87
14	KOAc	1,4-dioxane	$Pd(OAc)_2$	SPhos	3	110	7	yes	74

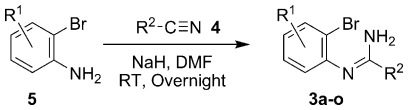
[a] Reactions were performed in a preheated oil bath on a 1 mmol scale in the indicated solvent (5 mL). 1.5 equivalents of isocyanide and 3 equivalents of the base were used. [b] Isolated yield. [c] 1.5 equivalents of KOAc were used.

inexpensive ligand DCPB, amidine **3a** was fully converted and **1a** was isolated in 89% yield (Table 1, entry 7). Since these conditions led to a similarly high isolated yield to the original conditions (Table 1, entry 1), but have the additional advantages of easier handling of a Pd^{II} versus a Pd^0 source and the lower cost of DCPB versus XPhos, we decided to continue the optimization with the $Pd(OAc)_2$/DCPB system. Changes in solvent, temperature, and the amount and type of base did not lead to further improvements in the isolated yield (Table 1, entries 8–13). The use of the more expensive ligand SPhos did not offer an advantage with respect to DCPB in combination with $Pd(OAc)_2$ (compare Table 1, entries 10 and 14). Thus, we decided to continue our investigation by using $Pd(OAc)_2$ (3 mol%) and DCPB (6 mol%) as the catalyst system, with KOAc (1.5 equiv) as the base and DMF as the solvent (Table 1, entry 7).

Having optimized the reaction conditions, we focused our attention on the determination of the scope of our methodology. To this end, we synthesized a range of *N*-(2-bromoaryl)amidines (**3a–l**, Table 2) by using a previously published procedure.[14] We found that a range of electron-rich and electron-deficient aromatic and heteroaromatic nitriles react with 2-bromoanilines in the presence of sodium hydride to afford the corresponding amidines **3** in reasonable to excellent yield after chromatography (Table 2, entries 1–11). We experienced some problems when applying the same procedure to aliphatic nitriles because the expected amidines were not isolated after chromatography. However, MS analysis of the reaction mixture indicated that the desired amidines were formed quantitatively. It appears that the amidines derived from aliphatic nitriles are generally not stable to chromatography on silica. However, the use of a slight excess of a volatile aliphatic nitrile (acetonitrile) followed by aqueous work-up without subsequent chromatographic purification led to the isolation of the desired amidine **3l** (Table 2, entry 12).

With a highly diverse set of *N*-(2-bromoaryl)amidines (**3a–l**) in hand, we turned our attention to the investigation of the scope of the Pd-catalyzed imidoylative cross-coupling reaction. To our delight, we found that all of the synthesized amidines react with various aliphatic isocyanides to afford the desired 4-aminoquinazolines in moderate to excellent yield (Scheme 3). The optimized conditions for the formation of **3a** ($Pd(OAc)_2$ (3 mol%), DCPB (6 mol%), KOAc (3 equiv), DMF, 120°C; method A in Scheme 3) did not prove optimal for all combinations of amidines **3** and isocyanides **2** and the target 4-aminoquinazolines **1** were sometimes isolated in disappointing yields. Fortunately, simply increasing the catalyst loading to 5 mol% Pd (methods B and D in Scheme 3), optionally combined with increasing the reaction temperature to 160°C (method C) led to significant improvements in yield in many

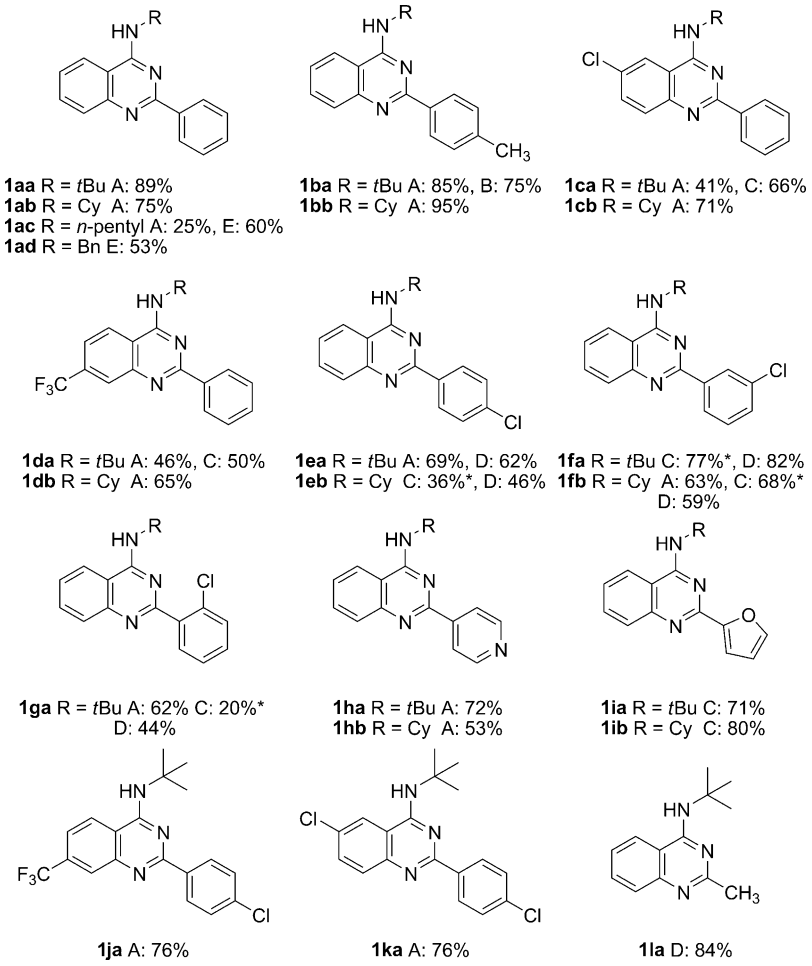
Table 2. Synthesis of *N*-(2-bromophenyl)imidamides (**3**).



5 **3a-o**

Entry[a]	R^1	R^2	Product	Yield [%][b]
1	H	Ph	**3a**	90
2	H	4-MeC_6H_4	**3b**	80
3	4-Cl	Ph	**3c**	75
4	5-CF_3	Ph	**3d**	77
5	H	4-ClC_6H_4	**3e**	97
6	H	3-ClC_6H_4	**3f**	82
7	H	2-ClC_6H_4	**3g**	97
8	H	4-pyridyl	**3h**	53
9	H	2-furyl	**3i**	60
10	5-CF_3	4-ClC_6H_4	**3j**	53
11	4-Cl	4-ClC_6H_4	**3k**	49
12	H	Me	**3l**	n.d.[c]

[a] Reaction conditions: nitrile **4** (1 equiv), 2-bromoaniline **5** (1.2 equiv), NaH (1.5 equiv), DMF, RT, overnight. [b] Isolated yield. [c] The reaction was performed in THF with nitrile **4** (1.2 equiv) and 2-bromoaniline **5** (1 equiv). The yield was not determined (n.d.) because the reaction product was not purified, but was taken straight on to the subsequent reaction.



Scheme 3. Study of the scope of our Pd-catalyzed isocyanide insertion reaction: synthesis of 4-aminoquinazolines **1aa**–**1la**. All reactions were performed by using amidines **3** (1 equiv), the appropriate isocyanide (1.5 equiv), and KOAc (3 equiv) in DMF. Method A: $Pd(OAc)_2$ (3 mol%), DCPB (6 mol%), 120°C, 7 h; method B: $Pd(OAc)_2$ (5 mol%), DCPB (10 mol%), 120°C, 3 h; method C: $Pd(OAc)_2$ (5 mol%), DCPB (10 mol%), 160°C, 7 h; method D: $Pd(OAc)_2$ (5 mol%), DCPB (10 mol%), 120°C, 7 h; method E: $Pd(OAc)_2$ (3 mol%), XPhos (6 mol%), 120°C, 7 h. A * indicates reactions for which the dehalogenated product was formed. Cy = cyclohexyl.

cases. Interestingly, a catalyst loading of 3 mol% Pd proved sufficient for reactions involving primary isocyanides, but the use of XPhos instead of DCPB as the ligand proved essential to achieve a satisfactory isolated yield (**1ac** and **1ad**, Scheme 3). Another remarkable observation is that halogen-substituted amidines **3c**, **3e**–**g**, **3j**, and **3k** are also converted into the corresponding 4-aminoquinazolines **4**. In some cases, dehalogenation was observed (by MS analysis) as a side reaction. Two interesting observations were made concerning this side reaction. First, dehalogenation proved more pronounced at elevated temperature (i.e., method C) and could typically be fully suppressed by limiting the reaction temperature to 120°C (method D). Second, although dehalogenated 4-aminoquinazolines were observed during MS analysis, the corresponding dehalogenated amidines were not observed. This implies that the dehalogenation side reaction only takes place after the desired reaction has been completed. Careful monitoring of the conversion of the amidine starting material combined with maintaining a lower reaction temperature can therefore completely suppress the dehalogenation reaction.

Interestingly, 4-aminoquinazolines substituted on both the quinazoline core and the C2 phenyl ring (**1ja** and **1ka**) were also obtained in good yield, even under the standard reaction conditions. Not only phenyl, but also heteroaryl C2 substituents are tolerated in this reaction, as exemplified by the synthesis of 2-(4-pyridyl)- and 2-(2-furyl)-substituted 4-aminoquinazolines **1ha**, **1hb**, **1ia**, and **1ib** (Scheme 3). These compounds were isolated in reasonable to good yield, although an elevated temperature was required to achieve full conversion in the case of substrate **3i**.

Although the reactions with aliphatic isocyanides proved very efficient, we were thus far unsuccessful in employing aromatic isocyanides (phenyl isocyanide and 2,6-dimethylphenyl isocyanide) in our synthesis of 4-aminoquinazolines. This is somewhat surprising in light of a recent study by Chatani and co-workers, who reported a direct intramolecular arylation reaction involving isonitrile insertion.[2f] However, they could only use 2,6-dimethylphenyl isocyanide (and similar sterically hindered aromatic isocyanides), whereas phenyl isocyanide and aliphatic isocyanides were unreactive.[15] A possible rationalization for this observation is catalyst deactivation by multiple coordination of the isonitrile to Pd[16] and/or decomposition of the reactants, for example, through polymerization of the aromatic isonitriles under our catalytic conditions.[17] On the other hand, the Pd-catalyzed isocyanide-insertion reactions recently reported by the groups of Jiang[2g] and Murakami[2h] proceed with both aromatic and aliphatic isocyanides. It appears that a very subtle combination of steric and electronic effects of the isocyanide, substrate, and catalyst used determine the final outcome of the reaction.

Several of the products shown in Scheme 3 display pharmaceutically important biological activities. For example, compound **1ad** inhibits phosphodiesterase V (PDE 5) with an IC_{50} of 320 nM.[18] Furthermore, compound **1ab** was recently reported to display topoisomerase I inhibitory activity

equal to camptothecin.[11] All of the compounds reported in Scheme 3 can therefore be considered to be potential topoisomerase I inhibitors. In addition, these compounds have potential as, for example, kinase inhibitors.[7] Therefore, the constructed library of 4-aminoquinazolines could serve as a valuable source of new leads in various fields of medicinal chemistry. Biological activities of compounds **1** will be reported in due course.

Conclusion

We have developed an efficient Pd-catalyzed intramolecular imidoylative cross-coupling reaction of readily available *N*-(2-bromoaryl)amidines, yielding 4-aminoquinazolines that are of considerable interest in medicinal and agricultural chemistry. We have optimized the reaction with respect to the ligand, catalyst loading, base, temperature, and solvent. Easier to handle $Pd(OAc)_2$, in comparison with $[Pd(dba)_2]$, proved to be equally suited as the Pd source and generally allowed the use of the relatively inexpensive (compared with XPhos) ligand DCPB. An array of diversely substituted amidines can be combined with various aliphatic isocyanides to afford the target 4-aminoquinazolines in good to excellent yield, although fine-tuning of the reaction conditions was required for the more challenging substrates. The synthesized 4-aminoquinazolines include known potent topoisomerase I inhibitors, as well as phosphodiesterase inhibitors. The high modularity and mild reaction conditions make this methodology very attractive for future applications in medicinal chemistry.

Experimental Section

General procedure for the synthesis of 4-aminoquinazolines (1) by Pd-catalyzed intramolecular imidoylation of *N*-(2-bromoaryl)amidines (3): A round-bottomed flask was charged with $Pd(OAc)_2$ (7 mg, 0.03 mmol) and DCPB (21 mg, 0.06 mmol), followed by dry DMF (3 mL). The mixture was flushed with N_2 for 10 min. Meanwhile, amidine **3** (1.0 mmol), KOAc (3.0 mmol, 3 equiv), and isocyanide **2** (1.5 mmol, 1.5 equiv) were added to another round-bottomed flask. The Pd catalyst solution was then added to this mixture, and the flask was subsequently flushed with N_2 for 5 min. The resulting mixture was heated at the indicated temperature in a pre-heated oil bath for 7 h under magnetic stirring. After cooling to room temperature, EtOAc was added and the suspension was filtered over a pad of Celite and rinsed with EtOAc (125 mL). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford 4-aminoquinazolines **1** in high purity.

Acknowledgements

This work was financially supported by the Netherlands Organization for Scientific Research (NWO) by means of a Rubicon grant to Dr. Gitte van Baelen and by the Hercules Foundation. We thank Dr. M. T. Smoluch (VU University) for (HR)MS measurements.

[1] For recent reviews of palladium-catalyzed carbonylation reactions, see: a) C. F. J. Barnard, *Organometallics* **2008**, *27*, 5402–5422; b) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176–4196; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133.

[2] For examples of transition metal-catalyzed cyclization reactions incorporating isocyanides, see: a) M. Zhang, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 4498–4499; b) S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 11940–11945; c) T. Shibata, K. Yamashita, E. Katayama, K. Takagi, *Tetrahedron* **2002**, *58*, 8661–8667; d) K. Onitsuka, S. Suzuki, S. Takahashi, *Tetrahedron Lett.* **2002**, *43*, 6197–6199; e) S. Park, R. Shintani, T. Hayashi, *Chem. Lett.* **2009**, *38*, 204–205; f) M. Tobisu, S. Imoto, S. Ito, N. Chatani, *J. Org. Chem.* **2010**, *75*, 4835–4840; g) H. Jiang, B. Liu, Y. Li, A. Wang, H. Huang, *Org Lett.* **2011**, *13*, 1028–1031; h) T. Miura, Y. Nishida, M. Morimoto, M. Yamauchi, M. Murakami, *Org Lett.* **2011**, *13*, 1429; i) S. Zhang, W.-X. Zhang, Z. Xi, *Chem. Eur. J.* **2010**, *16*, 8419–8426.

[3] For a recent review of palladium-catalyzed cascade cyclizations, see: T. Vlaar, E. Ruijter, R. V. A. Orru, *Adv. Synth. Catal.* **2011**, *353*, 809–841.

[4] a) B. Crociani, F. Dibianca, R. Bertani, C. B. Castellani, *Inorg. Chim. Acta* **1985**, *101*, 161–169; b) R. Bertani, A. Berton, F. Di Bianca, B. Crociani, *J. Organomet. Chem.* **1986**, *303*, 283–299; c) O. Schuster, L. Yang, H. G. Raubenheimer, M. Albrecht, *Chem. Rev.* **2009**, *109*, 3445–3478; d) J. G. P. Delis, P. G. Aubel, K. Vrieze, P. W. N. M. van Leeuwen, N. Veldman, A. L. Spek, F. J. R. van Neer, *Organometallics* **1997**, *16*, 2948–2957; e) J. Vicente, M. T. Chicote, A. J. Martínez-Martínez, P. G. Jones, D. Bautista, *Organometallics* **2008**, *27*, 3254–3271; f) J. Dupont, C. S. Consorti, J. Spencer, *Chem. Rev.* **2005**, *105*, 2527–2572; g) V. K. Jain, L. Jain, *Coord. Chem. Rev.* **2005**, *249*, 3075–3197.

[5] K. S. Masters, T. R. M. Rauws, A. K. Yadav, W. A. Herrebout, B. Van der Veken, B. U. W. Maes, *Chem. Eur. J.* **2011**, *17*, 6315–6320.

[6] For 1*H*-benzimidazole synthesis involving Pd-catalyzed intramolecular N-arylation, see: a) C. T. Brain, S. A. Brunton, *Tetrahedron Lett.* **2002**, *43*, 1893–1895; b) C. T. Brain, J. T. Steer, *J. Org. Chem.* **2003**, *68*, 6814–6816; c) J. M. Travins, R. C. Bernotas, D. H. Kaufman, E. Quinet, P. Nambi, I. Feingold, C. Huselton, A. Wilhelmsson, A. Goos-Nilsson, J. Wrobel, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 526–530.

[7] Rho kinase inhibitors: a) P. Sweetnam, A. Bartolozzi, A. Campbell, B. Cole, H. Foudoulakis, B. Kirk, H. Seshadri, S. Ram (Surfacelogix, Brighton, MA, USA), WO2010/104851A1, **2010**. CHK2 kinase inhibitors: b) I. Collins, A. W. Oliver, T. M. Raynham, C. A. J. Matijssen, E. J. Welsh, J. J. Caldwell, (Cancer Research Technology, London, UK), WO2009/53694A1, **2009**; c) J. J. Caldwell, E. J. Welsh, C. Matijssen, V. E. Anderson, L. Antoni, K. Boxall, F. Urban, A. Hayes, F. I. Raynaud, L. J. M. Rigoreau, T. Raynham, G. W. Aherne, L. H. Pearl, A. W. Oliver, M. D. Garrett, I. Collins, *J. Med. Chem.* **2011**, *54*, 580–590.

[8] T. C. Gahman, D. J. Thomas, M. E. Massari, H. Lang (Kalypsis, San Diego, CA, USA), WO2008/157500A1, **2008**.

[9] M. Reich, S. Kuehnert, S. Oberboersch, M. Haurand, K. Schiene (Gruenenthal, Aachen, DE), US2009/69320A1, **2009**.

[10] D. Wilson, L. T. D. Fanning, P. Krenitsky, A. Termin, P. Joshi, U. Sheth (Vertex Pharmaceuticals Incorporated, Cambridge, MA, USA), US2008/167305A1, **2008**.

[11] T. N. Le, S. H. Yang, D. B. Khadka, H. T. M. Van, S. H. Cho, Y. Kwon, E.-S. Lee, K.-T. Lee, W.-J. Cho, *Bioorg. Med. Chem.* **2011**, *19*, 4399–4404.

[12] These conditions proved to be successful for domino condensation/Heck cyclization reactions on 3-amino-4-bromoquinoline and 3-amino-4-bromoisoquinoline with acetaldehyde, see: G. Van Baelen, G. L. F. Lemière, R. A. Dommisse, B. U. W. Maes, *ARKIVOC* **2009**, *vi*, 174–182.

[13] For a recent review of the use of dialkylbiaryl phosphines in Pd-catalyzed aminations, see: D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50.

[14] G. Brasche, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 1958–1960; *Angew. Chem. Int. Ed.* **2008**, *47*, 1932–1934.
[15] We performed the reactions with aromatic isocyanides not only under the optimized conditions from Table 1, but also under the reaction conditions used by Chatani and co-workers in ref. [2f].
[16] Y. Yamamoto, *Coord. Chem. Rev.* **1980**, *32*, 193–233.
[17] a) F. Millich, *Chem. Rev.* **1972**, *72*, 101–113; b) F. Millich, *J. Polym. Sci., Macromol. Rev.* **1980**, *15*, 207–253; c) M. Suginome, Y. Ito, *Adv. Polym. Sci.* **2004**, *171*, 77–136.
[18] S. J. Lee, Y. Konishi, D. T. Yu, T. A. Miskowski, C. M. Riviello, O. T. Macina, M. R. Frierson, K. Kondo, M. Sugitani, J. C. Sircar, K. M. Blazejewski, *J. Med. Chem.* **1995**, *38*, 3547–3557.

Received: August 9, 2011
Published online: November 28, 2011

