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The first tandem double palladium-catalyzed aminations: synthesis of dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo- and aza-analogues

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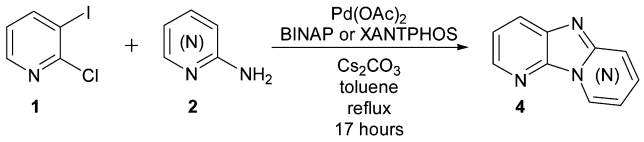
A new strategy for the synthesis of the title compounds *via* a regio- and chemoselective one-pot inter- and intramolecular Buchwald–Hartwig amination of 2-chloro-3-iodopyridine with aminoazines and -diazines is reported.

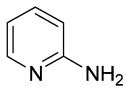
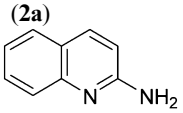
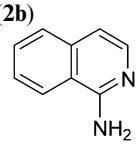
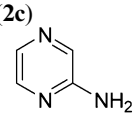
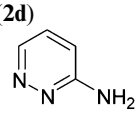
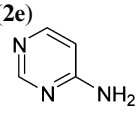
In the last decade major advances have been made in the field of carbon-heteroatom bond formation *via* palladium-catalyzed cross-coupling. Among these tin-free palladium catalyzed C–N bond formation, independently discovered by Buchwald and Hartwig, has established itself as one of the most important methods to create arylamines.[1] Since its discovery in 1995 the synthesis of several heterocyclic skeletons making use of an intramolecular Buchwald–Hartwig amination has been described in the literature.[2] The interest of our laboratory in (aza)-carbolines[3] and regio- and chemoselective Pd-catalyzed amination of chloro-iodopyridines,[4] prompted us to develop a new synthetic route for the dipyrido[1,2-*a*:3′,2′-*d*]imidazole skeleton and its benzo- and aza-analogues *via* the regio- and chemoselective one-pot double Buchwald–Hartwig amination of 2-chloro-3-iodopyridine (**1**) with aminoazines and -diazines. Hitherto, tandem (one pot consecutive inter- and intramolecular) Pd-catalyzed aminations are unprecedented in the literature.

In 2002, our laboratory described the regio- and chemoselective arylamination of **1** using Pd(BINAP) (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)[5] as the catalyst in combination with a large excess of caesium carbonate.[4a] The large excess of base, although almost completely insoluble in the solvent used (toluene), was essential to obtain high cross-coupling rates. Recently, we gained experimental evidence that an interphase deprotonation of the palladium(II)-amine intermediate formed in the catalytic cycle is the basis for this remarkable 'base effect'.[4b] Consequently, controlling the shape and size of the carbonate particles and/or the molar excess used, is important for Buchwald–Hartwig aminations with a rate-limiting deprotonation of the palladium(II)-amine complex. As a consequence of these earlier obtained results, we investigated the synthesis of dipyrido[1,2-*a*:3′,2′-*d*]imidazole (**4a**), *via* the coupling of **1** with 2-aminopyridine (**2a**), using a Pd(BINAP) catalyst in combination with an excess of carbonate base. We chose a 4 mol% catalyst loading and 4 equivalents of caesium carbonate as starting conditions; 2 mol% catalyst and 2 equivalents of base per amination reaction. Gratifyingly, we observed that in an overnight reaction 97% of **4a** could be obtained after column chromatography. Work-up of a reaction performed in a limited reaction time of 8 h yielded 0% **1**, 55% *N*-(2-chloropyridin-3-yl)pyridin-2-amine (**3a**) and 44% **4a**. This result clearly indicates that **3a** is the intermediate formed in the tandem amination process and the mechanism of the reaction can be rationalized as presented in Scheme 1. Reducing the catalyst loading from 4 mol% to 3 mol% gave **4a** in an overnight reaction in essentially the same yield (96%). A further decrease to 2 mol% gave an incomplete reaction in the same reaction time since **3a** was still present in the crude reaction mixture. Application of the optimized conditions for the double amination of **1** with 2-aminoquinoline (**2b**) gave a mixture of intermediate *N*-(2-chloropyridin-3-yl)-quinolin-2-amine (**3b**) and pyrido[3′,2′:4,5]imidazo[1,2-*a*]quinoline (**4b**). No remaining starting material **1** was observed. Using 4 mol% of catalyst gave complete conversion of **1** to **4b** in 17 hours of reflux and yielded 98% of **4b**. Under the same conditions **1** could be smoothly transformed into pyrido[3′,2′:4,5]imidazo[2,1-*a*]isoquinoline (**4c**) using 1-aminoisoquinoline (**2c**) as the amination partner. This is summarized in Table 1.

Table 1 Synthesis of dipyrido[1,2-*a*:3′,2′-*d*]imidazole and analogues[a]



1 **2** **4**

Compound number	Amidine	Pd loading (mol%)	Ligand	Pd:Ligand ratio	Yield (%)
4a	 (**2a**)	3	1	1	96[b]
4b	 (**2b**)	4	1	1	98[b]
4c	 (**2c**)	4	1	1	98[b]
4d	 (**2d**)	4	1	1	93[b]
4e	 (**2e**)	4	2	1	94[b]
4f	 (**2f**)	6	2	1:2	82[c]

[a] $Pd(OAc)_2$, BINAP or XANTPHOS, **1** (1.5 mmol), **2** (1.5 or 1.8 mmol), Cs_2CO_3 (6 mmol), toluene (17 mL), reflux [b] 1.8 mmol amidine was used [c] 1.5 mmol amidine was used

Secondly, we turned our attention to aminodiazines containing an amidine functionality. Tandem Buchwald–Hartwig amination of **1** with 2-aminopyrazine (**2d**), using 4 mol% catalyst in combination with 4 equivalents caesium carbonate, gave 93% of pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyrazine (**4d**). Unfortunately, double amination of **1** with 3-aminopyridazine (**2e**) yielded predominantly starting material since 56% of **1** could be recovered after working up the reaction mixture. Therefore, we turned our attention to other second generation catalysts. We chose XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene)[6] since we previously

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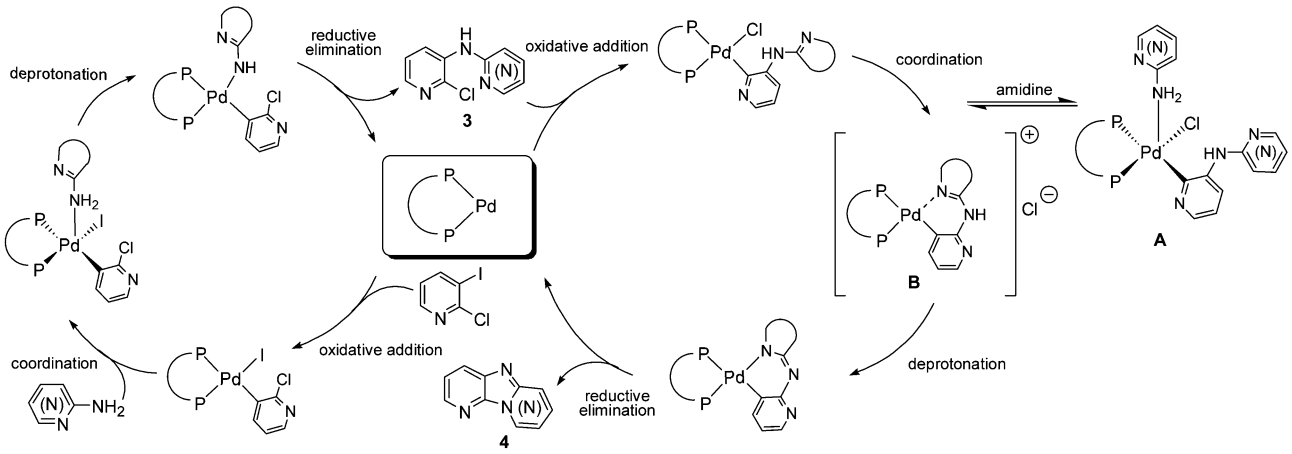

Scheme 1 Probable catalytic pathway.

reported that for the selective amination of **1** with *p*-toluidine, Pd(XANTPHOS) gave a similar result as Pd(BINAP).[4a] Gratifyingly, we observed that the use of 4 mol% Pd(XANTPHOS) gave 94% of pyrido[3′,2′:4,5]imidazo[1,2-*b*]pyridazine (**4e**) in an overnight reaction. Also for the tandem amination of **1** with 4-aminopyrimidine (**2f**) starting material was predominantly recovered (80% recovered) after 17 h reflux using 4 mol% Pd(BINAP) catalyst. Disappointingly, the use of 4 mol% Pd(XANTPHOS) gave 73% of *N*-(2-chloropyridin-3-yl)pyrimidin-4-amine (**3f**) and only 3% pyrido [3′,2′:4,5]imidazo[1,2-*c*]pyrimidine (**4f**) in the same reaction time. While in the former case using Pd(BINAP) the major compound was the starting material, the latter experiment gave 0% **1** and the intermediate **3f** was the major reaction product. Increasing the palladium:XANTPHOS ratio from 1:1 to 1:2 shifted the outcome of the reaction towards the desired tricyclic compound **4f** (17%). An additional decrease of the amount of amidine **2f** from 1.2 equivalents to 1 equivalent further increased the amount of **4f** (49%). The latter might be rationalized *via* the competitive formation of palladium(II)–amine complex **A** over palladacycle **B** which slows down the desired intramolecular amination reaction. Finally, combining the use of a 1:2 ratio of palladium:XANTPHOS and the use of only 1 equivalent of aminopyrimidine **2f** with a higher loading of catalyst (6 mol%) gave a complete conversion of **3f** and an isolated yield of **4f** of 82%.

Interestingly, the new methodology starts from commercially available products and gives access to relatively complex polycyclic compounds in only one step.[7] Only the synthesis of **4e** is an exception since 3-aminopyridazine was prepared form 3-amino-6-chloropyridazine *via* hydrogenolysis.[8]

The prepared polycyclic azaheteroaromatics are relevant basic skeletons in the search for new antitumour drugs due to their potential to strongly intercalate with DNA. The dipyrido[1,2-*a*:3′,2′-*d*]imidazole nucleus for instance is the tricyclic azaheteroaromatic basic skeleton of Glu-P's (2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazoles), which are formed in the pyrolysis of L-glutamic acid.[9] Glu-P's have been identified as muta-carcinogens (Human exposure may occur by ingestion of cooked food.). DNA adducts are presumably formed from the metabolically activated Glu-P's; (2-hydroxyamino)dipyrido[1,2-*a*:3′,2′-*d*]imidazoles.[9] Prior to covalent bond formation intercalation into DNA base pairs occurs. Benzo-analogues 10-aminopyrido[3′,2′:4,5]imidazo[1,2-*a*]quinoline and 8-aminopyrido[3′,2′:4,5]imidazo[2,1-*a*]isoquinoline have subsequently been prepared and tested on their DNA intercalator properties and mutagenicity.[10a] In addition monomeric and dimeric dipyrido[1,2-*a*:3′,2′-*d*]imidazole, covalently bound to a spermine chain, have been described in the literature and identified as strong DNA intercalators.[10b] The strong interaction of 2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazoles with DNA also led to the development of new porphyrin(Fe)-intercalators with a strong DNA-cleaving ability.[10c] To the best of our knowledge, the aza-analogue **4f** of the dipyrido[1,2-*a*:3′,2′-*d*]imidazole nucleus is a new polycyclic skeleton which has hitherto never been described in the literature.

In summary, we have shown that dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo- and aza-analogues can be prepared by a novel, tandem inter- and intramolecular Buchwald–Hartwig amination in excellent yields. Currently, we are investigating the extension of this new methodology towards the synthesis of other heterocyclic systems.

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