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Streamlined Synthesis of Diaminopyridines *via* Pd-Catalyzed Ammonia Coupling with Deactivated Amino-Chloropyridines

Florian Bourriquen, Antoine Bruneau-Voisine, Aliénor Jeandin, Etienne Stihle, and Serena Fantasia*

Abstract: An efficient and cost-effective two-step synthesis of diaminopyridines, fundamental building blocks of biologically active compounds, is reported. The advantages over previously reported routes include cost and wider availability of the bromo-chloropyridine starting materials and the straightforward accessibility to an extended array of diaminopyridine regioisomers. The key enabler of this synthetic strategy is the development of an unprecedented palladium-catalyzed coupling of ammonia with chloropyridines deactivated by the presence of an alkylamino substituent. The coupling was accomplished with very low catalyst loadings under remarkably mild reaction conditions, making the system particularly suitable for both academic and industrial applications. The utility of the methodology is exemplified by the application to the synthesis of highly relevant scaffolds, including the synthetic intermediates of marketed drugs Ribociclib and Palbociclib.

Diaminopyridines have long been recognized as biologically active compounds.[1] As such, their inclusion in structures of increasing molecular complexity has led to the discovery of a number of potent medicines in the fields of oncology, autoimmune disorder and infection treatment (Figure 1).[2],[3]

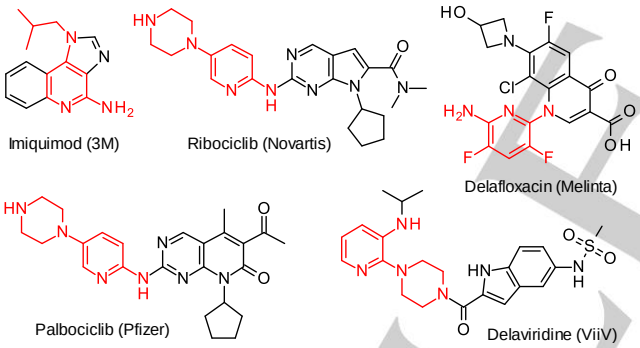
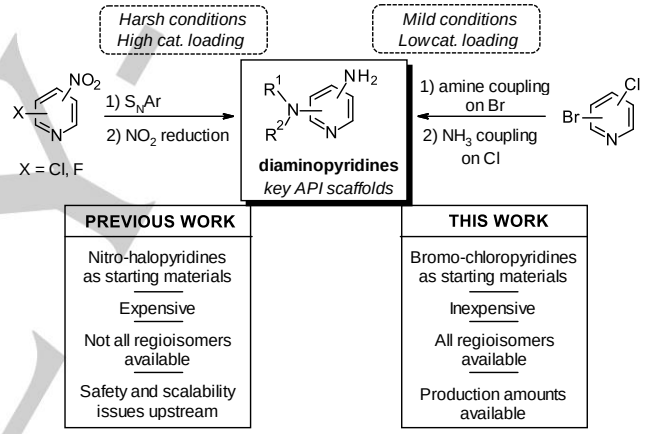


Figure 1. Examples of marketed drugs containing the diaminopyridine motif.

The most widely used synthetic approach to the diaminopyridine moiety features a S_NAr on a halo-nitro-pyridine to install the amine substituent, followed by reduction of the nitro group to afford the free $-NH_2$ that can be further functionalized (Scheme 1, left).[2a-c],[3],[4] Besides the well-known issues of this route (harsh reaction conditions leading to low functional group tolerance, high Pd/C loadings), a major limitation lies within the availability of the starting materials. Indeed, only 3-NO_2-pyridines are directly accessible via ring nitration,[5] while laborious synthetic sequences are required for the corresponding 2- and 4-regioisomers. In fact, nitration in 4-position is possible only *via* pyridine N-oxides,[3g],[6] while in the case of 2-NO_2-halopyridines the NO_2 functionality is obtained by oxidation of the corresponding NH_2 group[7],[8] –i.e. the final target– in redox sequences of overall very poor economy.[9] This chemistry also pose considerable safety and scalability issues, making its application in industrial setting extremely problematic.[10] Hence, the development of novel synthesis routes to diaminopyridines is of paramount importance in both industrial and academic settings.



Scheme 1. Synthetic approaches to diaminopyridines

In this context, bromo-chloropyridines represent very attractive building blocks thanks to their broad availability and competitive prices.[11] Given the well-documented reactivity difference between bromo and chloro substituents on the pyridine core towards Pd-catalyzed cross-coupling reactions,[12] we decided to investigate the potential of a bromo-selective Buchwald-Hartwig amination,[13] followed by the coupling of the resulting amino-chloro-pyridine with ammonia (Scheme 1, right).[14] Although arylation of ammonia has witnessed tremendous progress in recent times, its coupling with chloropyridines is still clearly underdeveloped,[15] with a scope mainly limited to simple 3-Cl-pyridines and reaction conditions typically requiring high catalyst loadings and/or high temperatures.[16] In particular, when considering substrates deactivated by strong electron-donating groups, reports of successful ammonia coupling are extremely scarce.[17] In fact, the presence of electron-donating groups on the aromatic core enhances the well-known problems associated with the reaction,[18] namely: 1) the intrinsically poor reactivity of the C–Cl bond; 2) the increased nucleophilicity of the aminopyridine product leading to undesired diarylamine and 3) the coordinating ability of the pyridine nitrogen. Herein we report the development

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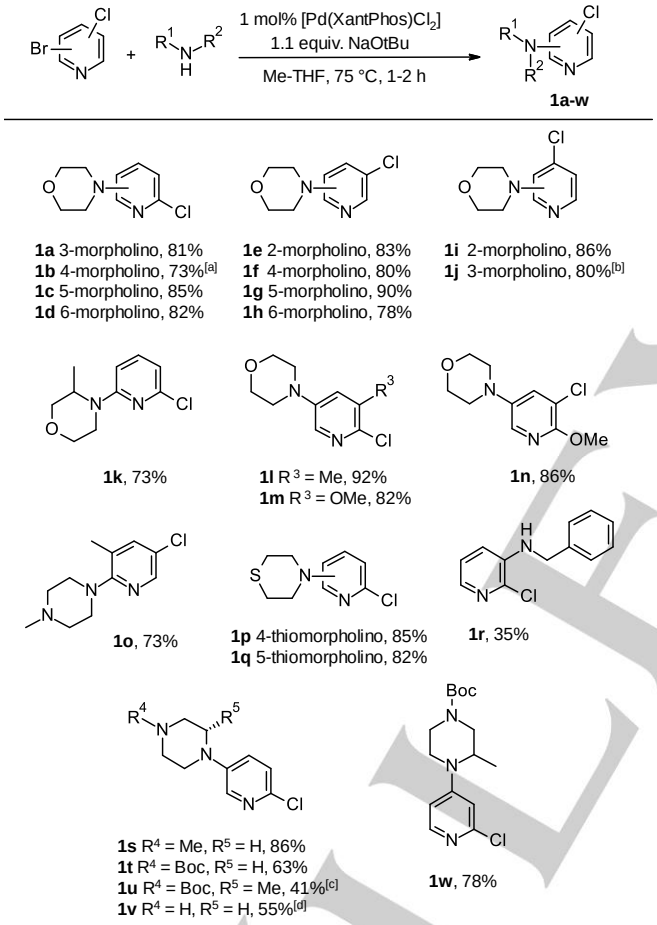
of a highly active and selective catalytic system that enabled the streamlined synthesis of diaminopyridines.

Our research effort started with the synthesis of the amino-chloropyridine substrates. Expanding on the report of Ji and co-workers[19] all Br-Cl-pyridine regioisomers were coupled with 1 mol% [Pd(XantPhos)Cl_2] in Me-THF at 75 °C in generally good to excellent yields (Scheme 2). With respect to the amine coupling partner, we focused on nitrogen-containing six-membered heterocycles, as this motif is one of the most represented in biologically active compounds and hence of particular relevance to the field of drug design and development.[20] Overall, the synthesis of 23 different amino-chloropyridines was realized, offering a working platform for our next endeavor: the ammonia coupling.



Bromo-chloropyridine (1.0 g), [C] = 13 mL/g, amine (1.0 equiv.). [a] Reaction time: 4h. [b] [Pd(XantPhos)Cl_2] (2 mol%). [c] [Pd(XantPhos)Cl_2] (2 mol%), 3 h, 2.0 g scale. [d] Piperazine: 5 equiv.

Scheme 2. Substrates synthesis.

Turning to the second step of our strategy, we focused our screening effort on 5-morpholino-2-Cl-pyridine **1c**. For the initial investigation we decided to avoid the use of commercially available ammonia stock solutions as they carry several intrinsic limitations, namely 1) limited choice of suitable solvent and 2) low molarity, resulting in high dilution of the reaction mixture. In fact, not only has the reaction concentration been recognized as a key parameter in ammonia arylation,[16d] but also reducing the volume factor is extremely important in industrial settings, where a value ≤10 L/kg is typically targeted for production campaigns. Ammonia gas (6 bar)[21] was therefore considered the best choice. A screening of nine phosphine ligands (2 mol%) in combination with [Pd(cinnamyl)Cl]$_2$ (1 mol%) in four different solvents at 110 °C revealed that tBuBrettPhos **L7** was the most active and selective ligand in 1,4-dioxane (Chart 1). Of note, amongst the most efficient ligands in ammonia arylation reported in literature, MorDalPhos[16c] **L1** and JosiPhos[16b] **L4** displayed very low selectivity with considerable amount of secondary amine **2c'** formed while CataCXiumPIntBu[16a] **L3** gave systematically poor conversions. Additional examination of different palladium sources identified Pd_2dba_3 as the optimal one, providing full conversion and the highest selectivity of primary *vs* secondary amine (**2c**/**2c'** = 200:1) at 30 °C with as little as 1 mol% of both ligand and palladium.[21] Well-defined palladium complexes have proven in several cases to be a superior option compared to the analogous *in-situ* generated catalytic systems, generally displaying higher activity and selectivity.[22] In particular, allylpalladium scaffolds have emerged as one of the most promising pre-catalysts in cross-coupling chemistry due to their exceptional performance and ease of preparation. In an effort to further reduce the catalyst loading, we prepared and tested [(tBuBrettPhos)Pd(allyl)]OTf[23] **C1** (Scheme 3) and found that full conversion was reached with 0.5 mol% of catalyst after 3 h at 30 °C, allowing for isolation of **2c** in 91% yield with a **2c**/**2c'** selectivity >200:1. Noteworthy, thanks to the mild temperature, the pressure during the reaction remained below 6 atm. Being aware that not every laboratory might be equipped for handling gaseous ammonia, we performed the reaction employing a commercially available ammonia solution (0.5 M in 1,4-dioxane) and found that full conversion and comparable **2c**/**2c'** selectivity could be achieved by using 10 equivalent of ammonia, though at the expense of higher dilutions.[24]

Next, we examined the reactivity of the different morpholino substituted chloropyridines (Scheme 3). 2-NH_2-pyridines **2a**-**d** were obtained in excellent yields, regardless of the morpholine position. More challenging 3- and 4-Cl-pyridines proved to be more sensitive to the steric and electronic effects dictated by the amine substituent. Thus, very good reactivity was observed when the morpholine substituent occupied the *meta* position relative to the chloride, with **2g** and **2i** being obtained in 90% yield. The deactivating effect of the electron-donating amine substituent became evident in substrate **1h** where both 1 mol% of **C1** and a temperature of 80 °C were needed to isolate **2h** in moderate yield. Finally, the combination of unfavorable electronic and steric environment suppressed the reactivity and no product **2e**, **2f** and **2j** was observed despite high catalyst loading and elevated temperature.

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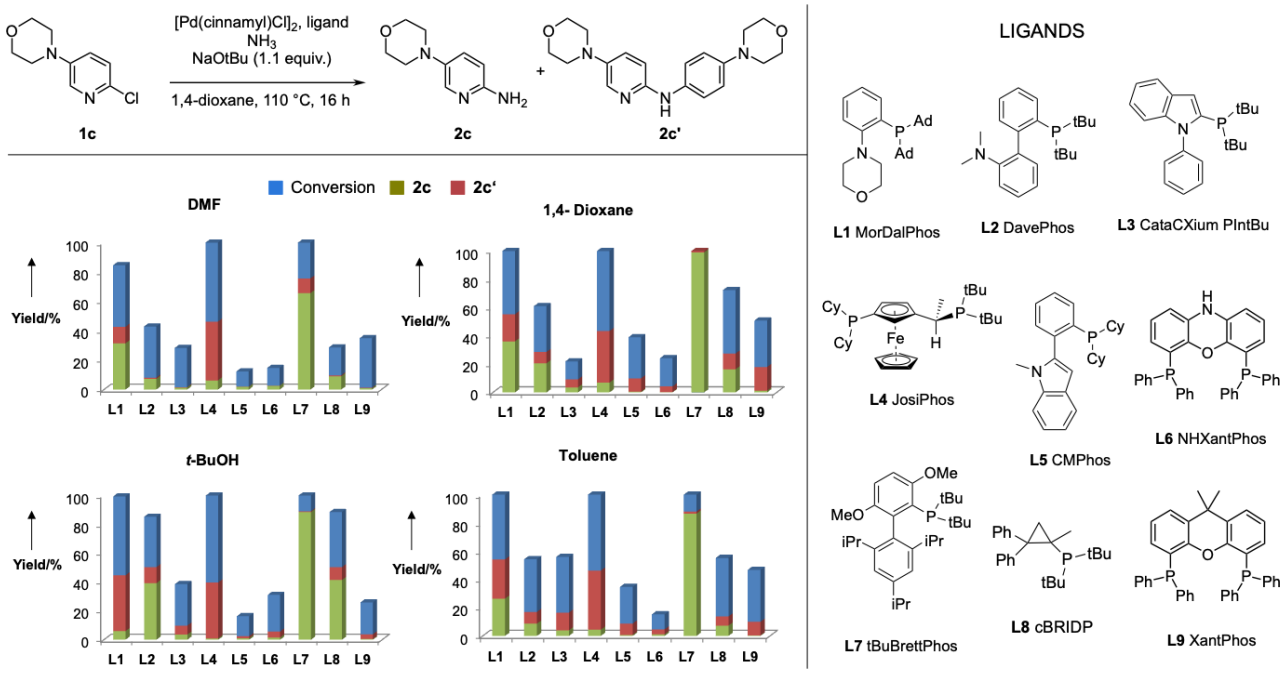
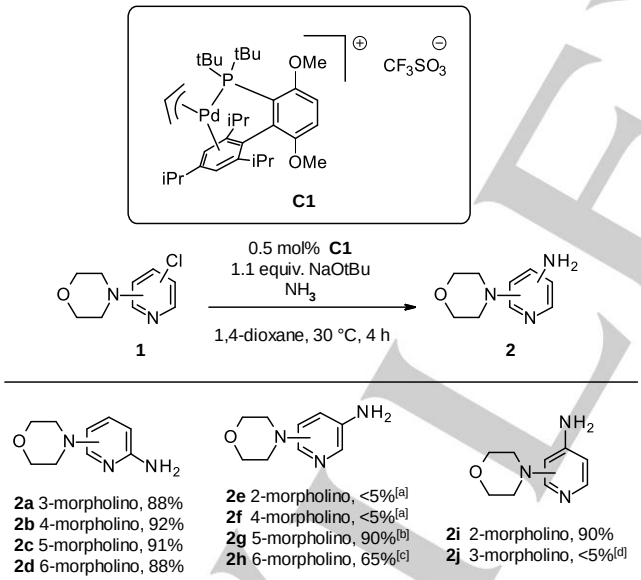


Chart 1. Activity and selectivity of various ligands in the ammonia coupling.



1 (1 mmol), NH_3 (20 equiv.), [**1**] = 0.2 M, isolated yields, conversion >95%. [a] GC yield, 2 mol % **C1**, 110 °C, 15 h. [b] 80 °C. [c] 1 mol% **C1**, 80 °C, conv. =78%. [d] GC yield, 1 mol% **C1**, 110 °C.

Scheme 3. Reactivity of the morpholino-Cl-pyridine regioisomers.

Widening our study of the substrate scope, another 14 strongly deactivated chloropyridines were coupled with ammonia (Scheme 4). It should be emphasized that a particular attention was paid to 2-Cl-pyridines as the corresponding amination products are of highest relevance in the synthesis of biologically active compounds as proven by marketed drug Ribociclib, Palbociclib, Imiquimod and Delafloxacin (Figure 1).[25] Hence, compound **2k** was obtained in 96% yield. Pleasingly, the catalytic system remained extremely active in the presence of an additional electron-donating group on the pyridine ring with 2-Cl-pyridines **1l** and **1m,** bearing a methyl and methoxy group *ortho* to the chlorine, undergoing ammonia coupling to afford **2l** and **2m** in exceptionally high yields. By increasing the temperature to 110 °C, even the more challenging 3-NH_2-pyridines **2n** and **2o** were obtained in 73% and 75% yield, respectively. Noteworthy, the present catalytic system is not poisoned by the presence of sulfur-based substituents, as exemplified by thiomorpholine containing products **2p** and **2q** that were isolated in >90% yields. Aminopyridine **2r**, bearing a secondary benzyl amine substituent was also synthesized in excellent yield. The latter example is especially remarkable as previous attempts to selectively couple a similar substrate with ammonia led to a high amount of undesired secondary amine and the use of benzophenone imine as ammonia surrogate was needed to overcome the selectivity issue.[26]

Of particular interest to the present study were piperazines, one of the top three nitrogen-containing heterocycles present in US FDA approved drugs.[20a] Hence, N-methylpiperazine containing substrate **1s** was efficiently coupled with ammonia to afford **2s** in 89% yield. Importantly, the isolation of **2t**, **2u** and **2w** in high yield highlights the tolerance of the Boc-protecting group to the reaction conditions, an extremely useful feature in the synthesis of complex molecules. Free amino groups are also very well tolerated as showed by the efficient coupling of **1v** containing an unprotected piperazine to afford **2v** in 86% yield. To highlight the importance of piperazines, it is worth pointing out that aminopyridine **2t** is an intermediate in the synthesis of Ribociclib[2a] and Palbociclib[2b] and can be synthesized with the

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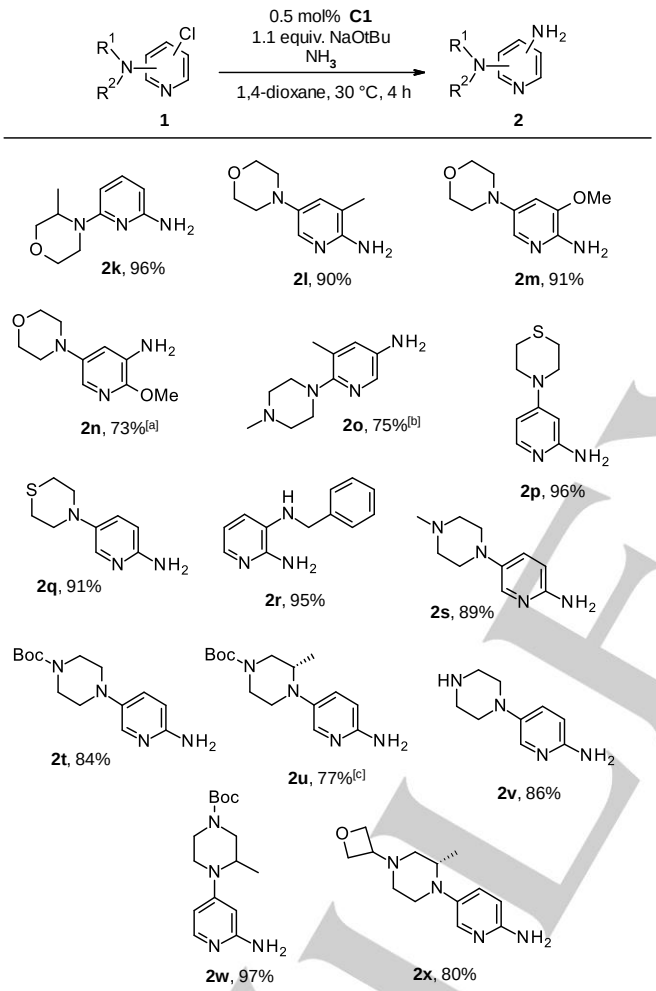
present methodology in 84% yield. As outlined in the introduction, the reported route to this building block relies on a S_NAr on the 5-bromo-2-nitropyridine, followed by nitro group reduction (Scheme 1). Drawbacks besides the ones previously described are long reaction times required for the S_NAr (typically above 24 h) and the formation of potential genotoxic impurities during the nitro group reduction, the latter being an issue of particular concern to the pharmaceutical industry.[27] Thus, the advantages brought by the 2-step route herein described are evident. As an additional example, aminopyridine **2x**, a building block of clinical development compound Fenebrutinib[3d] can also be synthesized *via* ammonia coupling on the parent chloride in 80% yield.[28]



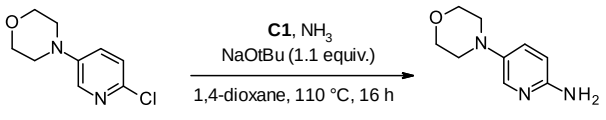
1 (1 mmol), NH_3 (20 equiv.), [**1**] = 0.2 M, isolated yields, conversion >95%. [a] 110 °C, 5 h. [b] 110 °C, conv. = 80%. [c] 6 h.

Scheme 4. Scope of the ammonia coupling.

To the best of our knowledge, only three articles describing the ammonia coupling with deactivated chloropyridines have appeared in literature. Buchwald and co-workers reported the palladium catalyzed coupling of 2-Cl-6-MeO-pyridine and 2-Cl-3-NH_2-6-Me-pyridine with 2 mol% catalyst loading at 50 °C.[16e] Recently, Stradiotto[16f] and Ma[16g] with their co-workers reported the coupling 2-Cl-6-MeO-pyridine with nickel and copper-based catalytic system, though at higher catalyst loadings (10 mol% and 5 mol%, respectively) and temperatures (65 °C and 110 °C, respectively). In order to compare our methodology with the state-of-the-art, we applied our reaction conditions to 2-Cl-6-MeO-pyridine and found that employing 0.5 mol% of **C1** at 30 °C delivered the amination product in 91% isolated yield after 4 hours. This result shows that the catalytic system presented in this work is the most efficient one, operating at the lowest temperature and with the lowest catalyst loading – four to twenty times less than previously reported procedures. Noteworthy, it is also the system that requires the least amount of ligand with remarkable advantages in terms of cost and purification effort.[29]

Finally, having such an active catalytic system in our hands, we explored the limit of the catalyst loading on model substrate **1c** (Table 1). Pleasingly, the amount of **C1** could be lowered to 0.06 mol% maintaining mild reaction conditions (30 °C, 4 h) and employing only 7 equivalents of ammonia with no impact on the conversion, the product being isolated in 97% yield (Table 1, entry 3). To our knowledge, this is the lowest catalyst loading achieved so far in transition-metal catalyzed ammonia arylation and represents a 15-fold reduction when compared with available system for the coupling of chloropyridine substrates. The reaction was performed on a 8 mmol scale with the volume factor reduced to 5 L/kg demonstrating the scalability of the present catalytic system. Attempts to further lower the catalyst loading led to incomplete conversion. Still, using 0.03 mol% of **C1** the reaction attained 55% conversion after 4 hour at 30 °C (Table 1, entry 4).[30] Further optimization was not performed but this results clearly highlight the high activity of this catalytic system even at low loadings.

Table 1. Optimization of the catalyst loading, ammonia equivalents and concentration.



Entry	**C1** (mol%)	NH_3 (equiv.)	Scale	[**1c**] (mol/L)	Conv.(yield)[a]
1	0.50	20	0.2 g	0.2	100% (91%)[b]
2	0.12	13	0.8 g	0.8	100% (99%)
3	0.06	7	1.6 g	1.0	100% (97%)[b]
4	0.03	7	4.0 g	1.0	55% (54%)

[a] Determined by GC. [b] Isolated yield.

In summary, we report an extremely active and selective catalytic system for the coupling of deactivated chloropyridines

with ammonia. Under very mild conditions, monoarylated products are obtained in high yields with the lowest catalyst loading reported so far. For the first time, chloropyridines bearing a strongly deactivating amino group have been successfully employed as substrates, with the scope not limited to the more reactive 2-chloropyridines but remarkably also including the challenging 3- and 4-chloro regioisomers. Noteworthy features of this catalytic system include tolerance of functional groups such as Boc, free amines and sulfur-containing heterocycles and the use of a well-defined pre-catalyst with the valuable 1:1 ligand to palladium ratio. The herein presented methodology is the key enabler of the efficient and cost effective two-step access to diaminopyridine building blocks, a synthetic strategy that not only offers significant advantages compared to classical routes, but also provides access to an extended array of these highly relevant structures.

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Keywords: Amination • Heterocycles • Homogeneous catalysis • Palladium • Synthetic methods

[1] a) W. E. Glover, *Gen. Pharmac.* **1982**, *13*, 259; b) M. M. Vohra, S. N. Pradhan, P. C. Jain, S. K. Chatterjee, N. Anand, *J. Med. Chem.* **1965**, *8*, 296.

[2] a) J. V. Calienni, G.-P. Chen, B. Gong, P. K. Kapa, V. Saxena US 2012/0115878, **2012**; b) D. T. Erdman, C. M. Flamme, J. D. Nelson (Pfizer Products Inc.), WO 2008/032157 A2, **2008**; c) J. F. Gerster et al. *J. Med. Chem.* **2005**, *48*, 3481; d) D. L. Romero et al. *J. Med. Chem.* **1993**, *36*, 1505; e) A. Haight, D. Barnes, G. Zhang (Abbott Laboratories), WO 2006/015194 A2, **2006**.

[3] For selected examples of clinical development compounds, see: a) D. L. Romero et al., *J. Med. Chem.* **1994**, *37*, 999; b) X. Zhao et al., *Bioorg. Med. Chem.* **2015**, *23*, 348; c) S. Tadesse et al., *J. Med. Chem.* **2017**, *60*, 1892; d) H. Zhang et al., *Org. Process Res. Dev.* **2018**, *22*, 978; e) Y. Imaeda, T. Kawamoto, M. Tobisu, N. Konishi, K. Hiroe, M. Kawamura, T. Tanaka, K. Kubo, *Bioorg. Med. Chem.* **2008**, *16*, 3125; f) A. H. Miah, R. C. B. Copleay, D. O'Flynn, J. M. Percy, P. A. Procopiu, *Org. Biomol. Chem.* **2014**, *12*, 1779; g) F. Julemont, X. de Leval, C. Michaux, J.-F. Renard, J.-Y. Winum, J.-L. Montero, J. Damas, J.-M. Dogné, B. Pirotte, *J. Med. Chem.* **2004**, *47*, 6749.

[4] a) G. W. Gribble, L. Fu, Q.-X. Lin in *Pyridines: From Lab to Production* (Ed.: Eric F. V. Scriven), Academic Press, Waltham, **2013**, pp. 153-373; b) *Comprehensive Heterocyclic Chemistry III* (Eds: A. Katritzky, C. Ramsden, E. Scriven, R. Taylor), Elsevier Science, **2008**; c) M. Orlandi, D. Brenna, R. Harms, S. Jost, M. Benaglia, *Org. Process Res. Dev.* **2018**, *22*, 430. For specific examples, see [4d-q] in the SI.

[5] J. M. Bakke, *Pure App. Chem.* **2003**, *75*, 1403.

[6] a) F. E. Cislak, *Ind. Eng. Chem.* **1955**, *47*, 800; b) C. Riemer, E. Borroni, B. Levet-Trafit, J. R. Martin, S. Poli, R. H. P. Porter, M. Bös, *J. Med. Chem.* **2003**, *46*, 1273.

[7] a) O. A. Rakitin, O. G. Vlasova, L. I. Khmel'nitskii, I. F. Falyakhov, T. N. Sobachkina, *Chem. Heterocycl. Compd.* **1990**, *11*, 1536; b) L. Dolci, F. Dolle, H. Valette, F. Vaufrey, C. Fuseau, M. Bottlaender, C. Crouzel, *Bioorg. Med. Chem* **1999**, *7*, 467; c) S. J. Nara, M. Jha, J. Brinkhorst, T. J. Zemanek, D. A. Pratt, *J. Org. Chem.* **2008**, *73*, 9326.

[8] As a shortcut, the direct use of 2-NH_2-halo-pyridines for the coupling with an amine has been reported but the need for harsh reaction conditions renders this methodology incompatible with sensitive functional groups and drastically limits its application. See ref. [3f] and a) K. W. Anderson, R. E. Tundel, T. Ikawa, R. A. Altman, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 6523; *Angew. Chem.* **2006**, *118*, 6673; b) F. Perez, A. Minatti, *Org. Lett.* **2011**, *13*, 1984; c) H. Tian, Q.-W. Liu, H. Xu, W.-B. Huang, J. Lin, S.-Q. Zhang, *Synth. Commun.* **2012**, *42*, 2707; d) B. Büttelmann, A. Alanine, A. Bourson, R. Gill, M.-P. Heitz, V. Mutel, E. Pinard, G. Trube, R. Wyler, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1759.

[9] N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 2854; *Angew. Chem.* **2009**, *121*, 2896.

[10] a) A. Agosti, G. Bertolini, G. Bruno, C. Lautz, T. Glarner, W. Deichtmann, *Org. Process Res. Dev.* **2017**, *21*, 451; b) M. Hua, M. Qi, X. Pan, W. Yu, L. Zhang, J. Jiang, *Process Saf. Prog.* **2018**, *37*, 355; c) H. S. Mosher, L. Turner, A. Carlsmith, *Org. Synth.* **1953**, *33*, 79.

[11] For example: 5-bromo-2-X-pyridine X=Cl at 4 Euro/g, X = NO_2 at 19 Euro/g; 5-bromo-3-X-pyridine X=Cl at 44 Euro/g, X = NO_2 not available (prices from Sigma-Aldrich); 4-bromo-3-X-pyridine X=Cl at 6 Euro/g, X = NO_2 at 160 Euro/g (prices from Fluorochem). Prices as per March 2019.

[12] a) J. Almond-Thynne, D. C. Blakemore, D. C. Pryde, A. C. Spivey, *Chem. Sci.* **2017**, *8*, 40; b) I. J. S. Fairlamb, *Chem. Soc. Rev.* **2007**, *36*, 1036.

[13] P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564.

[14] An analogous strategy employing benzophenone imine as ammonia surrogate has been recently reported. It displays limited pyridine scope at high catalyst loadings and an additional step to liberate the free NH_2 is required with impact on cost, waste generation and purification effort. See: A. A. Mikhailine, G. A. Grasa Mannino, T. J. Colacot, *Org. Lett.* **2018**, *20*, 2301.

[15] For a recent review on ammonia coupling, see: a) J. Schrank, A. Tlili, *ACS Catal.* **2018**, *8*, 405. For seminal work see: b) Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 10028; c) D. S. Surry, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 10354.

[16] a) T. Schulz, C. Torborg, S. Enthaler, B. Schäffner, A. Dumrath, A. Spannenberg, H. Neumann, A. Börner, M. Beller, *Chem. Eur. J.* **2009**, *15*, 4528; b) G. D. Vo, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 11049; c) R. J. Lundgren, B. D. Peters, P. G. Alsabeh, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 4071; *Angew. Chem.* **2010**, *122*, 4165; d) C. Lombardi, J. Day, N. Chandrasoma, D. Mitchell, M. J. Rodriguez, J. L. Farmer, M. G. Organ, *Organometallics* **2017**, *36*, 251; e) C. W. Cheung, D. S. Surry, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 3734; f) A. Borzenko, N. L. Rotta-Loria, P. M. MacQueen, C. M. Lavoie, R. McDonald, M. Stradiotto, *Angew. Chem. Int. Ed.* **2015**, *54*, 3773; *Angew. Chem.* **2015**, *127*, 3844; g) M. Fan, W. Zhou, Y. Jiang, D. Ma, *Org. Lett.* **2015**, *17*, 5934.

[17] For the coupling of 2-Cl-6-MeO-pyridine see references [16e-g]; for the coupling of 2-Cl-3-NH_2-6-Me-pyridine see reference [16e].

[18] a) J. L. Klinkenberg, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2011**, *50*, 86; *Angew. Chem.* **2011**, *123*, 88; b) J.I. van der Vlugt, *Chem. Soc. Rev.* **2010**, *39*, 2302; c) A. F. Littke, G. C. Fu, *Angew. Chem. In. Ed.* **2002**, *41*, 4176; *Angew. Chem.* **2002**, *114*, 4350 d) V. V. Grushin, H. Alper, *Chem. Rev.* **1994**, *94*, 1047.

[19] J. Ji, T. Li, W. H. Bunnelle, *Org. Lett.* **2003**, *5*, 4611.

[20] a) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257; b) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845.

[21] For more details, see SI.

[22] H. Li, C. C. C. Johansson Seechurn, T. J. Colacot, *ACS Catal.* **2012**, *2*, 1147, and references therein.

[23] A. J. DeAngelis, P. G. Gildner, R. Chow, T. J. Colacot, *J. Org. Chem.* **2015**, *80*, 6794.

[24] When only 3 equivalent were employed, a slightly lower conversion and **2c**/**2c'** selectivity were observed, pointing to the importance of controlling

10.1002/chem.201902147

both the reaction concentration and the ammonia equivalents. See SI for details.
[25] For additional examples, see references [3b-e] and [4d-j].
[26] D. K. Leahy, L. V. Desai, R. P. Deshpande, A. V. Mariadass, S. Rangaswamy, S. K. Rajagopal, L. Madhavan, S. Illendula, *Org. Process Res. Dev.* **2012**, *16*, 244.
[27] a) G. Szekely, M. C. Amores de Sousa, M. Gil, F. Castelo Ferreira, W. Heggie, *Chem. Rev.* **2015**, *115*, 8182; b) D. J. Snodin, *Org. Process Res. Dev.* **2010**, *14*, 960.
[28] For the synthesis of **1x**, see SI.
[29] See SI for a comparison table.
[30] No conversion in absence of catalyst.

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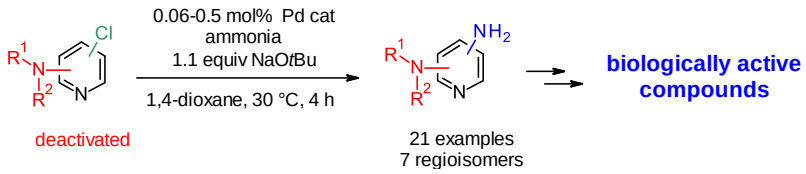

deactivated

21 examples
7 regioisomers

*Florian Bourriquen, Antoine Bruneau-Voisine, Aliénor Jeandin, Etienne Stihle, and Serena Fantasia**

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Streamlined Synthesis of Diaminopyridines *via* Pd-Catalyzed Ammonia Coupling with Deactivated Amino-Chloropyridines

All with one: the synthesis of a broad range of diaminopyridines regioisomers is achieved by the development of an efficient catalytic system able to couple ammonia with deactivated chloropyridines. This methodology enables the cost effective access to building blocks of utmost relevance to the field of drug design and development.