Highly regioselective Buchwald-Hartwig amination at C-2 of 2,4-dichloropyridine enabling a novel approach to 2,4-bisanilinopyridine (BAPyd) libraries

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PII: S0040-4039(13)01770-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.10.035
Reference: TETL 43673

To appear in: *Tetrahedron Letters*

Received Date: 29 July 2013
Revised Date: 10 September 2013
Accepted Date: 8 October 2013

Please cite this article as: Burton, R.J., Crowther, M.L., Fazakerley, N.M., Fillery, S.M., Hayter, B.M., Kettle, J.G., McMillan, C.A., Perkins, P., Robins, P., Smith, P.M., Williams, E.J., Wrigley, G.L., Highly regioselective Buchwald-Hartwig amination at C-2 of 2,4-dichloropyridine enabling a novel approach to 2,4-bisanilinopyridine (BAPyd) libraries, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.10.035

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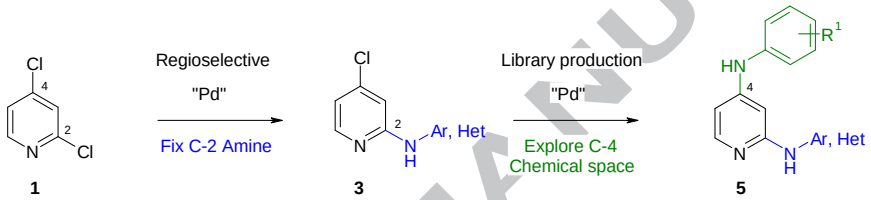

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TETRAHEDRON LETTERS

Highly regioselective Buchwald-Hartwig amination at C-2 of 2,4-dichloropyridine enabling a novel approach to 2,4-bisanilinopyridine (BAPyd) libraries

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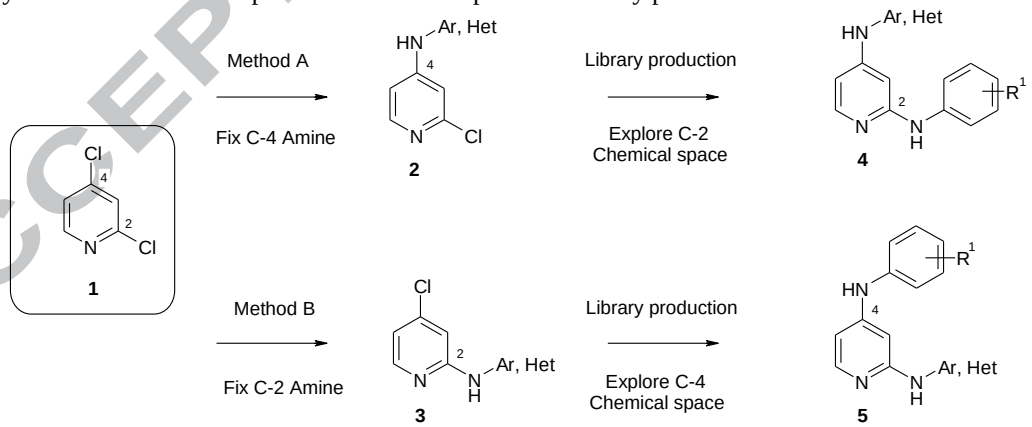
Abstract - The highly regioselective Buchwald-Hartwig amination at C-2 of the cheap and readily accessible reagent, 2,4-dichloropyridine with a range of anilines and heterocyclic amines is described. This new methodology is robust and provides facile access to 4-chloro-*N*-phenylpyridin-2-amines on 0.25 mol scale. These intermediates undergo a further Buchwald-Hartwig amination at higher temperature to enable rapid exploration of the chemical space at C-4 and to provide a library of 2,4-bisaminopyridines.

Following on from our investigations into the structure-activity relationship (SAR) around a series of 2,4-bisanilinopyrimidines (BAPs),[1] we decided to specifically target an expansion of chemical diversity at the C-4 position of 2,4-bisanilinopyridines (BAPyds) **5**. We postulated that two approaches to BAPyds **4** and **5** were possible from the cheap and readily accessible reagent 2,4-dichloropyridine (**1**)[2] (Scheme 1). Method A would allow specific C-4 amines of interest to be introduced first and a subsequent expansion of chemical space at C-2. However, method B was of most interest to us as it would allow introduction of specific C-2 amines first and therefore provide the most efficient and flexible intermediates, 4-chloro-*N*-arylpyridin-2-amines **3** to explore C-4 chemical space in a library production.



Scheme 1. Strategy for regioselective substitution of 2,4-dichloropyridine and subsequent synthesis of 2,4-bisanilinopyridines

Many procedures are exemplified for method A in the literature using 2,4-dichloropyridine directly to generate 2-chloro-*N*-phenylpyridin-4-amines **2** using neutral,[3] basic[4] and acidic[5] methods. A complimentary procedure utilizing Buchwald-Hartwig[6,7] methodology on more expensive mixed halogen substrates, e.g 2-fluoro-4-iodopyridine[8] and 2-chloro-4-bromopyridine[9] guarantees either 2-fluoro-*N*-phenylpyridin-4-amines or 2-chloro-*N*-phenylpyridin-4-amines can also be made, and subsequently used to expand the chemical space at C-2 and synthesise 2,4-bisanilinopyridines (BAPyds) **4**. However, a general procedure (method B) for the synthesis of a diverse set of 4-chloro-*N*-arylpyridin-2-amines **3** directly from 2,4-dichloropyridine has not been reported (Scheme 1). The literature has detailed various alternative methods;

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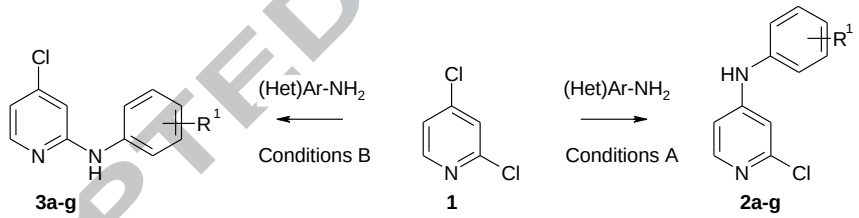
Keywords: Buchwald-Hartwig amination, regioselective substitution, 2-chloro-*N*-phenylpyridin-4-amines, 4-chloro-*N*-phenylpyridin-2-amines

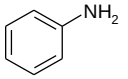
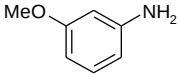
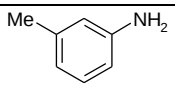
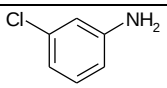
additional substitution on the pyridine ring, e.g., trimethylsilyl groups to block C-4 substitution,[10] electron-withdrawing groups *para* to C-2 and aniline protecting group strategies, e.g., *N*-arylacetamides[11] to enhance the C-2 regioselectivity and more expensive, mixed halogenated pyridines.[12] However, the disadvantage of these is the requirement for extra synthetic steps or the use of more expensive, less accessible starting materials compared to 2,4-dichloropyridine. More recently, Schnüch *et al.* highlighted that direct amination of 2,4-dichloropyridine with *p*-anisidine using palladium was possible but gave an equimolar ratio of regioisomers in less than 10% yield when subjected to a relatively high temperature of 180 °C in a microwave reactor.[8] Miyata *et al.* also provide one example of the direct amination of 2,4-dichloropyridine with aniline in 19% yield, but with no evidence provided of regioselectivity.[13] Focused studies on the coupling of substituted 2-amino-1,3-oxazoles with chloroheterocycles by Noonan *et al*. showed that 2,4-dichloropyridine could be displaced regioselectively at C-2 using palladium, and that the results could be optimised through the use of electron-rich and electron-poor substituents on the oxazole.[14] However, to date, there is no general procedure described for C-2 substitution of 2,4-dichloropyridine with commonly used aryl and heterocyclic amines. Based on these observations, and recognising the gap, we felt compelled to disclose our own work in this area. We have successfully utilised Buchwald-Hartwig methodology directly on cheap and readily accessible 2,4-dichloropyridine utilising simple, unprotected anilines and heterocyclic amines to provide a highly regioselective synthesis of 4-chloro-*N*-phenylpyridin-2-amines **3**. Herein, we report our findings in synthesising key intermediates **3** and the utilization of these to expand the chemical space at C-4 directly and deliver a library of 2,4-bisaminopyridines **5**.

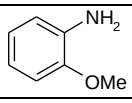
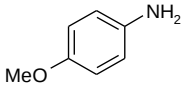
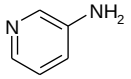
The synthesis of 2-chloro-*N*-phenylpyridin-4-amines **2** (Scheme 2) was attained using conditions A. Subsequent isolation and structural analysis confirmed regioisomers, with ^{1}H NMR (nOe) being employed to determine that indeed the 4-regioisomer was the major product. Investigations into the syntheses of 4-chloro-*N*-phenylpyridin-2-amines, **3** were first carried out using conditions B. Gratifyingly, the crude reaction profile on LCMS showed the C-2 regioisomers were formed almost exclusively, in >95:5 ratio, as initially confirmed by comparing with the crude reaction LCMS profiles for the C-4 regioisomers. Typically, the C-4 regioisomer eluted around 0.5 minutes later than its C-2 counterpart. Subsequent isolation allowed structural confirmation of the C-2 regioisomers by ^{1}H NMR (nOe). The preferential substitution at C-2 is assumed to be as a result of the neighbouring pyridine nitrogen stabilising the developing radical during oxidative addition of palladium.[15] It is noteworthy that product ratios were not affected by the nature of the substituent on the anilines, i.e., by electron-withdrawing or -donating groups. There was no obvious trend identified at this stage to explain some of the observed modest yields other than these were initial unoptimised results (Table 1).



Scheme 2. Regioselective synthesis of either 2-chloro-*N*-phenylpyridin-4-amines **2** or 4-chloro-*N*-phenylpyridin-2-amines **3**. Conditions A: NaH (60% dispersion in mineral oil), 1:1 ratio of heterocyclic amine or aniline:2,4-dichloropyridine, DMA, 22 °C, 24 h; Conditions B: $Pd(OAc)_2$, Cs_2CO_3, Xantphos, 1:1 ratio of heterocyclic amine or aniline:2,4-dichloropyridine, 1,4-dioxane, 30 min, 100 °C, microwave.

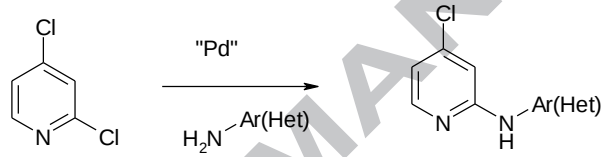
Table 1. Summary of 2- / 4- regioselectivity in reactions of anilines with 2,4-dichloropyridine under either Buchwald-Hartwig or NaH/DMA conditions

Entry	(Het)Ar-NH_2	Conditions A			Conditions B		
		Product	Ratio[a] **2**:**3**	Yield[b] (%)	Product	Ratio[a] **2**:**3**	Yield[b] (%)
1		**2a**	85:15	36	**3a**	5:95	23
2		**2b**	90:10	39	**3b**	2:98	64
3		**2c**	90:10	45	**3c**	5:95	37
4		**2d**	85:15	43	**3d**	5:95	64

5		**2e**	85:15	65	**3e**	3:97	44
6		**2f**	85:15	83	**3f**	2:98	37
7		**2g**	85:15	51	**3g**	2:98	47

[a] Product ratios taken from LCMS of crude reaction mixtures prior to work-up
[b] Isolated yield after reverse phase HPLC on Phenomenex Gemini 5 μ silica, C18 30 mm diameter, 100 mm length using decreasingly polar mixtures of H_2O (containing 0.5% NH_3) and MeCN as eluents.

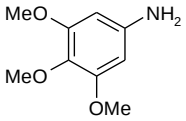
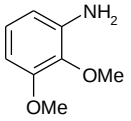
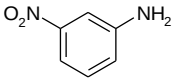
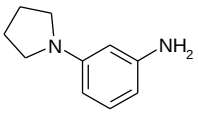
Recognising the potential of this early success, we subsequently discovered the methodology could be transferred to more diverse anilines and some six-membered aminoheterocycles. However, the reaction was less successful with electron-deficient five-membered aminoheterocycles, e.g., 1,3-thiazol-2-amine and 1,3-oxazol-2-amine. Lower reaction temperatures tended to give cleaner results by crude LCMS, and higher yields for those anilines that contained electron-donating groups (Scheme 3, Table 2). The chemistry was subsequently scaled up to 0.25 mol to provide many of the intermediates listed (Table 2) on 20-30 gram scale. This demonstrates how effective and robust this chemistry is to execute.

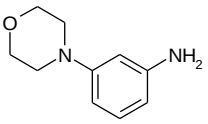
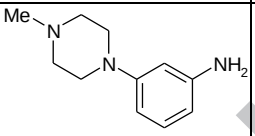
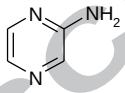
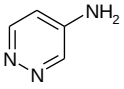
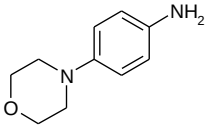
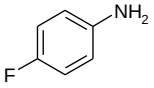
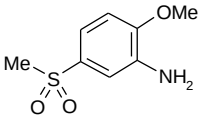
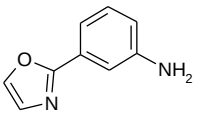
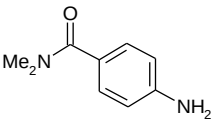


1 **3h-t**

Scheme 3. Further expansion of the regioselective synthesis of 4-chloro-*N*-phenylpyridin-2-amines **3** with anilines and amino heterocycles

Table 2. Expansion of the Buchwald-Hartwig methodology to reactions of more diverse substrates with 2,4-dichloropyridine

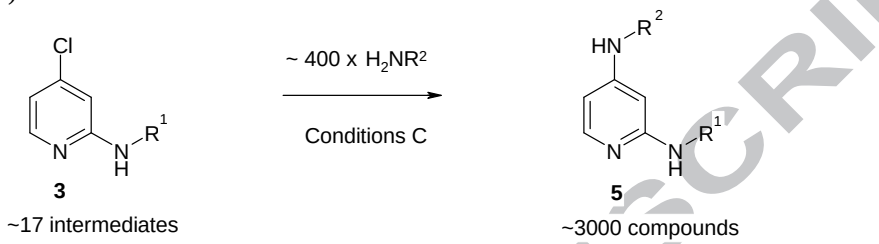
Entry	Product	Temp (°C)	Time (h)	(Het)Ar-NH_2	Yield (%)[a,b]
1	**3h**	80	16		68[a]
2	**3i**	50	4		83[a]
3	**3j**	100	1.5		48[a]
4	**3k**	50	21		59[b]

5	**3l**	50	21		57[b]
6	**3m**	50	21		63[b]
7	**3n**	100	2		73[b]
8	**3o**	100	6		24[c]
9	**3p**	80	18		30[e]
10	**3q**	100	48		40[d]
11	**3r**	80	18		58[e]
12	**3s**	80	18		62[d]
13	**3t**	80	18		56[d]

[a] Isolated yield after reverse phase HPLC on Phenomenex Gemini 5 μ silica, C18 30 mm diameter, 100 mm length using decreasingly polar mixtures of H_2O (containing 0.5% NH_3) and MeCN as eluents.
[b] Isolated yield after flash silica chromatography, eluting gradient 0-50% EtOAc/iHex
[c] Crude reaction yield from LCMS of reaction mixtures prior to work-up
[d] Purified by trituration of the crude material using IPA
[e] Purified by trituration of the crude material using CH_2Cl_2:Et_2O (1:1)

Previous diversification of the pyridine core, in our hands, had been limited to variations at C-2 once the C-4 aniline had been set through the S_NAr reaction. We recognized there was a real opportunity for us to exploit the new methodology by introducing a C-2 substituent first through the described Buchwald-Hartwig protocol and then diversify the C-4 position

using a further higher temperature coupling protocol to generate new libraries from the less activated 4-chloro-*N*-phenylpyridin-2-amine intermediates **3** (Scheme 4). This second coupling reaction was optimized (150 °C for 1 h) to provide a practically simple, robust, high throughput reaction process. Key to the successful outcome was the use of polymer-supported MP-TMT (2,4,6-trimercaptotriazine) resin[16] to scavenge palladium from the reaction mixture. This resin is a highly cross-linked macroporous polystyrene and was effective in our DMA:water reaction solvent at removing residual palladium, which was thought to be causing rapid deterioration and blockages within the reverse phase columns used for our trial reactions. Consequently, we believe we saved in the region of £64000 on column expenditure through direct application of this resin technology. Altogether >4000 reactions were purified by reverse phase preparative HPLC resulting in ~3000 isolated compounds (Figure 1).



Scheme 4. Use of Buchwald-Hartwig methodology to deliver 2,4-bisaminopyridines. Conditions C: $Pd(OAc)_2$, Xantphos, Cs_2CO_3, H_2NR^2, DMA:H_2O, 150 °C, 1 h, then MP-TMT resin, DMA:H_2O, 22 °C, 18 h

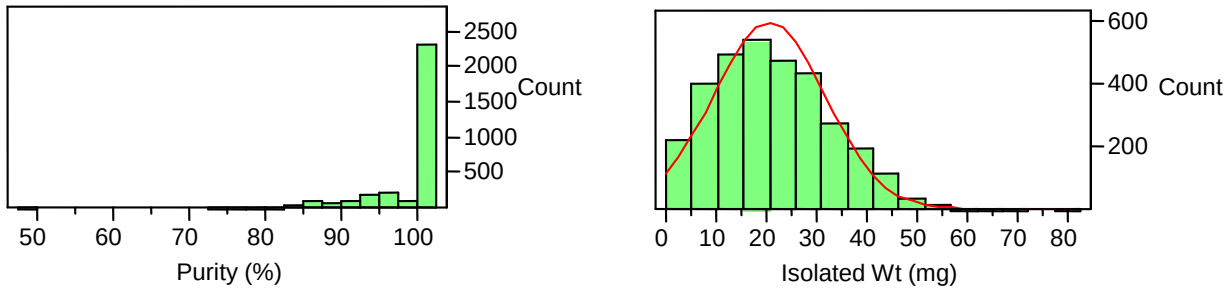


Figure 1 Graphical representations summarising the purity and weight of the compounds isolated: The purity was high with 72% of samples showing 100% purity by LC with a UV-Vis detector. The isolated weight of samples registered into the AstraZeneca compound database showed 50% >20 mg, 80% >10 mg.

In conclusion, we have described a highly selective approach to the regioselective substitution of cheap and readily accessible 2,4-dichloropyridine with anilines and heterocyclic amines using Buchwald-Hartwig methodology to provide almost exclusively 2-amino-4-chloropyridines. We believe the preferential substitution at C-2 is as a result of the neighbouring pyridine nitrogen stabilising the developing radical during oxidative addition of palladium. Subsequently, we have demonstrated that these intermediates can be diversified rapidly at C-4 by introduction of other anilines and heterocyclic amines using a robust practical procedure at a higher temperature to afford libraries of 2,4-bisaminopyridines.

Acknowledgements
We would like to acknowledge Mr. Howard Beeley, Mr. Paul Davey, Mr. Scott Boyd and Mr. David Whittaker for their analytical support.

Supplementary Data
Full experimental procedures and supporting LCMS, ^1H, ^{13}C, nOe and HRMS characterisation data are available *via* the on line version. Included are representative examples from the library production run.

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2. 2,4-Dichloropyridine (£2.32/g), 2-fluoro-4-iodopyridine (£102/g), 2-chloro-4-iodopyridine (£8.80/g), 4-bromo-2-fluoropyridine (£42/g), 4-bromo-2-chloropyridine (£4.80/g), 4-chloro-2-iodopyridine ($2000/g), 2-bromo-4-chloropyridine (price on request), 2-bromo-4-fluoropyridine ($119/g), 2-chloro-4-fluoropyridine (£3.40/g). Prices sourced April 2013 from available ACD suppliers.

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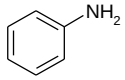
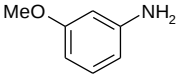
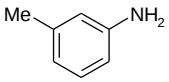
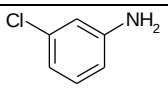
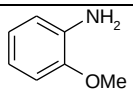
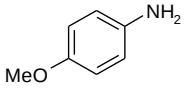
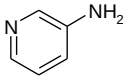
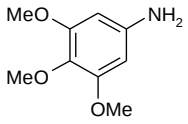
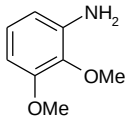
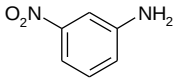
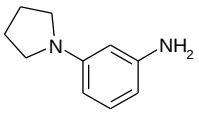
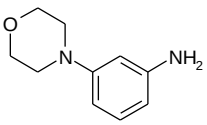
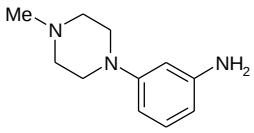
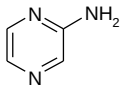
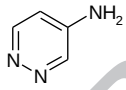
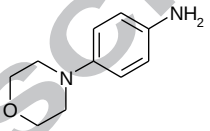
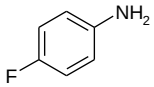
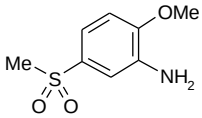
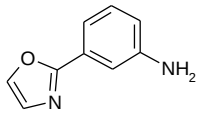
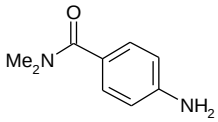
Table 1. Summary of 2- / 4- regioselectivity in reactions of anilines with 2,4-dichloropyridine under either Buchwald-Hartwig or NaH/DMA conditions

Entry	(Het)Ar-NH_2	Conditions A			Conditions B		
		Product	Ratio[a] **2**:**3**	Yield[b] (%)	Product	Ratio[a] **2**:**3**	Yield[b] (%)
1		**2a**	85:15	36	**3a**	5:95	23
2		**2b**	90:10	39	**3b**	2:98	64
3		**2c**	90:10	45	**3c**	5:95	37
4		**2d**	85:15	43	**3d**	5:95	64
5		**2e**	85:15	65	**3e**	3:97	44
6		**2f**	85:15	83	**3f**	2:98	37
7		**2g**	85:15	51	**3g**	2:98	47

[a] Product ratios taken from LCMS of crude reaction mixtures prior to work-up
[b] Isolated yield after reverse phase HPLC on Phenomenex Gemini 5 μ silica, C18 30 mm diameter, 100 mm length using decreasingly polar mixtures of H_2O (containing 0.5% NH_3) and MeCN as eluents.

Table 2. Expansion of Buchwald-Hartwig methodology to reactions of more diverse substrates with 2,4-dichloropyridine

Entry	Product	Temp (°C)	Time (h)	(Het)Ar-NH_2	Yield (%)[a,b]
8	**3h**	80	16		68[a]
9	**3i**	50	4		83[a]
10	**3j**	100	1.5		48[a]
11	**3k**	50	21		59[b]
12	**3l**	50	21		57[b]

13	**3m**	50	21		63[b]
14	**3n**	100	2		73[b]
15	**3o**	100	6		24[c]
16	**3p**	80	18		30[e]
17	**3q**	100	48		40[d]
18	**3r**	80	18		58[e]
19	**3s**	80	18		62[d]
20	**3t**	80	18		56[d]

[a] Isolated yield after reverse phase HPLC on Phenomenex Gemini 5 μ silica, C18 30 mm diameter, 100 mm length using decreasingly polar mixtures of H_2O (containing 0.5% NH_3) and MeCN as eluents.
[b] Isolated yield after flash silica chromatography, eluting gradient 0-50% EtOAc/iHex
[c] Crude reaction yield from LCMS of reaction mixtures prior to work-up
[d] Purified by trituration of the crude material using IPA
[e] Purified by trituration of the crude material using CH_2Cl_2:Et_2O (1:1)