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Green Chemistry

A Highly Efficient Suzuki-Miyaura Methylation of Pyridines Leading to the Drug Pirfenidone and to its CD_3 Version (SD-560)

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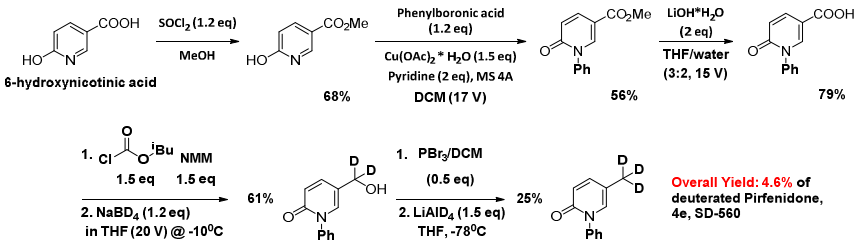
Abstract: Efficient introduction of methyl or methyl-d_3 into aromatic and heteroaromatic systems still presents a synthetic challenge. In particular, we were in search of a non-cryogenic synthesis of the 5-CD_3 version of pirfenidone (**4d**, also known as Pirespa®, Esbriet® or Pirfenex®), one of the two drugs approved to date for retarding idiopathic pulmonary fibrosis (IPF), a serious, rare and fatal lung disease, with life expectancy of 3-5 years. The methyl-deuterated version of pirfenidone (**4e,** also known as **SD-560**) was designed with the objective of attenuating the rate of drug metabolism, and our goal was to find a green methylation route to avoid the environmental and economic impact of employing alkyllithium at cryogenic temperatures. Examination of several cross-coupling strategies for introduction of methyl or methyl-d_3 into methoxypyridine and pyridone systems culminated in two green and nearly quantitative Suzuki-Miyaura cross-coupling routes in the presence of RuPhos ligand: the first, using commercially available methyl boronic acid or its CD_3 analog; and the second, employing potassium methyl trifluoborate or CD_3BF_3K, the latter obtained by a new route in 88% yield. This led, on a scale of tens of grams, to pirfenidone (**4d**) and its d_3 analog, SD-560 (**4e**), at 99% isotopic purity.

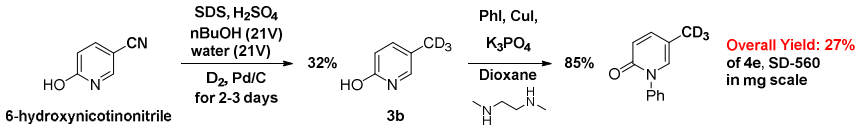
Introduction:

Pyridines are a ubiquitous class of compounds important in biological applications and human medicine[1]. Pirfenidone (5-methyl-1-phenyl-2-pyridone), **4d**[2], is an important drug approved for treatment of idiopathic pulmonary fibrosis (IPF), a serious, rare and fatal lung disease, and its methyl deuterated form, **4e**, has been shown in nonclinical and clinical studies to have a higher peak and total exposure compared to non-deuterated pirfenidone at equal doses. With both **4d** and **4e** as effective, robust, controlled and green synthetic targets, we examined known and new routes toward this goal. Two major approaches come to mind: one involves introduction of deuterium into an existing 5-substituted pyridone, while the second option is introduction of deuterated methyl (CD_3) into pyridine systems. The second approach has the advantage of providing an efficient synthesis of both pirfenidone **4d** and its CD_3 analog, **4e**. Extensive synthetic work by Auspex Pharmaceuticals and Concert Pharmaceuticals in recent years has focused on interconversion of a 5-substituent on a pyridine into a 5-CD_3 group leading to SD-560 (**4e**) as an example of the first approach (Schemes 1 and 2).



Scheme 1: WO 2015/112701, WO 2012/122165 A2, WO 2008/157786 A1 Route[3]

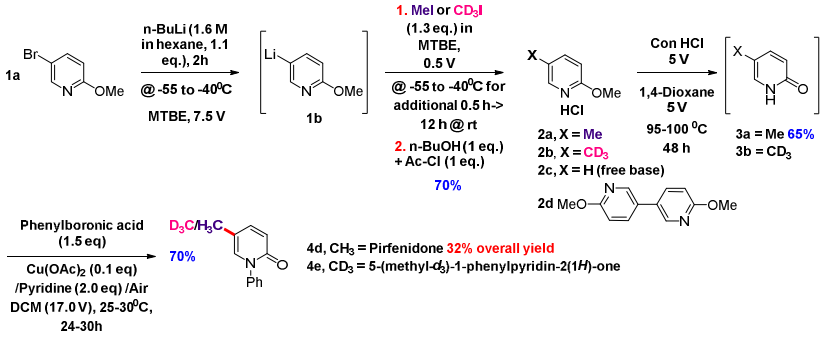
The atom economy of using heavy atom reagents such as thionyl chloride, isobutyl chloroformate and phosphorus tribromide to enable the introduction of the three deuterium atoms is low for Scheme 1. Furthermore, the use of expensive and dangerous $LiAlD_4$ under cryogenic conditions and quenching of the reaction intermediates with D_2O are additional complications in large scale synthesis where convergence, brevity, safety, efficiency, robustness, and economics are critical parameters to optimise.



Scheme 2: WO 2009/035598 A1Route[4]

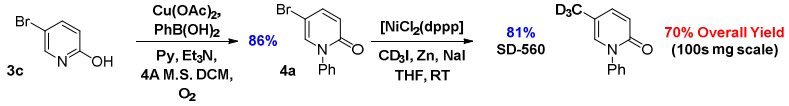
Similarly, in Scheme 2, reduction of the nitrile found in 6-hydroxynicotinonitrile with highly flammable deuterium gas for a long period of time is not practical and does not meet the safety requirements to allow process development to **4e.**

An example of the second approach to **4e**[4,5] involves methylation of **1a** to **2b** with methyl-d3 iodide (CD_3I). It requires cryogenic metalation with BuLi and is therefore not energy-efficient. Moreover, the free bases **2a** and **2b** are viscous liquids and volatile and therefore must be derived and isolated as HCl salts. While examining this scheme we found **1b** to be very reactive, giving rise to des-methyl **2c,** which is very difficult to separate from **2a**, and to bipyridine **2d**. Consequently, the atom economy of reaction of **1a** with CH_3I/CD_3I *via* lithiation with hazardous BuLi is low and the whole process does not meet most of the principles of green chemistry[6].



Scheme 3: WO 2009/035598 A1[4] and WO 2015/171345 A1[5] Route

A recent report by Liao[7] *et al* describes an effective Negishi[8] procedure for the methylation of aryl halides with CD_3I, including the synthesis of **SD-560** from **3c** at 70% overall yield; this approach required a special Ni catalyst *in a glove box,* a large excess of THF and volatile CD_3I on a scale of 100s of mg (Scheme 4):

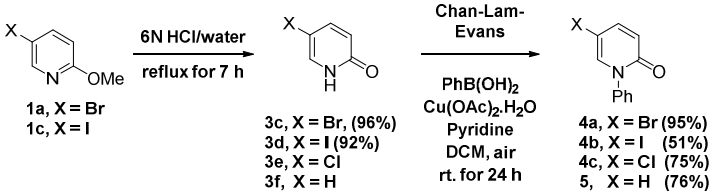


Scheme 4: L. Hu, X. Liu and X. Liao, *Angew. Chem.*, 2016, **128**, 9895-9899

It is clear that efficient functionalization of pyridines, such as methylation and deuteriomethylation under non-cryogenic conditions still represents a major challenge. Herein, we report our efforts involving methyl cross-coupling of 5-bromo-2-methoxy pyridine (**1a**) or of N-phenyl pyridone (**4a**) which ultimately led to a high yielding, simple, fast and green process that is amenable to plant manufacturing of pirfenidone (**4d**) and its deuterated analog (**4e**), with 99% isotopic purity.

Results and Discussion:

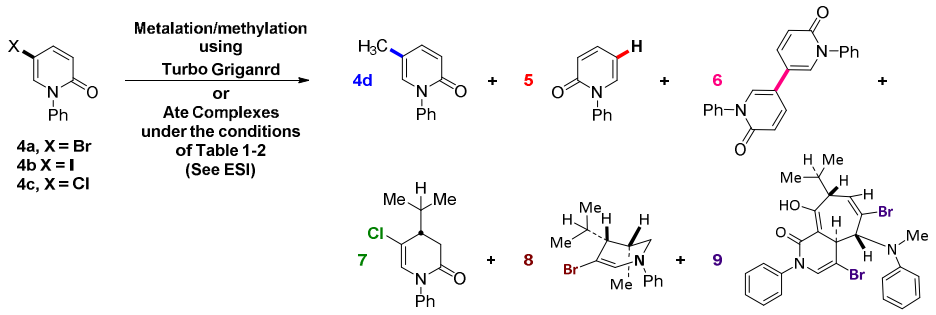
The synthesis of **4d** and **4e** *via* "methylation-first" (Scheme 3) of **1a-1c** through low molecular weight intermediates **2a** and **2b** and their unstable/hygroscopic HCl salts has some operational and environmental drawbacks; **2a** and **2b** sublime on drying, and therefore, they are difficult to isolate and store, and the pyrophoric nature of the BuLi used in the halogen exchange to give **1b** enhances the accident potential of the process. Furthermore, in the sequence **1a**->**2b**->**3b**->**4e** methylation with an expensive deuterated reagent in the first step of the process is much less economically efficient than a "methylation-last" process. Hence, we examined a new route to **4d-e** (Schemes 5, 6 and 7), taking advantage of heavy halogen and crystallinity of **3c**[9]-**3e**[10,11], obtained in nearly quantitative yield by hydrolysis of the methyl ether of **1a** and **1c**, simply by heating in aqueous HCl followed by neutralization and filtration. Next, pyridones, **3c**-**3e**, underwent N-phenylation *via* the Chan-Lam-Evans conditions to furnish **4a**[12]-**4c**[13,14] in high yields. With the latter in hand, we addressed the challenge of introducing the CH_3 and CD_3 groups, respectively, into position 5 in compounds **4d** and **4e.**



Scheme 5: Preparation of halo-N-phenylpyridones, **4a-c**

We employed two methodologies for "methylation last": **1)** introducing a methyl *via* metalation with organometallic reagents, **under non-cryogenic conditions**, followed by trapping the C-metal active species of **4a-c** with electrophilic methyl; **2)** transition metal catalyzed cross coupling between **4a-c** and a methyl partner. The first methodology has the advantage of **side-stepping the cryogenic lithiation**; however, it still produces unnecessary derivatization and waste. Cross-coupling under transition metal catalysis is much greener, but despite of numerous protocols utilizing boronic acids/esters that have been disclosed for alkenylation and alkynylation, there are only limited examples for sp^3-hybridized electrophiles, and even fewer for CH_3 electrophile, and coupling often proceeds with unsatisfactory yields due to sluggish reaction rates and/or generation of undesired side products.

Methylation of **4a-c** with Turbo Grignard[15] or Ate complexes[16] in the presence or absence of CuCN•2LiCl using different methylation reagents and addition regimens as well as different concentrations of the metalating agents, did not enable us to meet our goal. The reaction of **4a** with Turbo Grignard, followed by methylation, resulted mostly in dehalogenation to **5**, with substantial dimerization to **6** and only minor amounts of the desired **4d** (Table 1-2, see the ESI). Moreover, 1,4 *i*PrMg addition to **4c** gave 21% of **7**, while addition to **4a** followed by methylation gave 6% **8**, and 4% of a unique rearrangement product **9**[17] (Scheme 6). Therefore, the lack of selectivity and high susceptibility (Table 1-2, ESI) and the overall low atom economy calls into question the efficiency of these organometallic agents in a green route to **4d-e**.



Scheme 6: Products in reaction between halo-N-phenylpyridones (**4a-c**) and Turbo-Grignard or Ate complexes followed by methylation

In spite of the problems encountered with the Turbo Grignard and Ate complexes in obtaining pirfenidone, **4d**, in high yield and without side products, *via* methylation of **4a-c** (methodology 1 of halogen-metal exchange), we also examined methyl cross-coupling of **1a** and **1c** under Pd catalysis, as well as **Stille** coupling[18] with the Bu_3Sn derivative of **1a** and **Negishi** coupling[8,19], using CH_3ZnI[20]. In all cases **2a** was accompanied by **2c** and by homo-coupling product **2d.** In the best case, 44% of **2a** and 55% of **2d** were obtained using the InterMune patent[21] conditions employed on a different pyridone system.

Finally, we turned to **Suzuki-Miyaura cross-coupling** (SMC)[22] with **4a-c**, as one of the mildest and most appealing methods for the introduction of an alkyl group into various functionalized arenes. This is true also from the perspective of green chemistry since the nontoxic inorganic byproducts can be readily removed by simple workup, after the coupling of the organoboron reagent. We examined methyl coupling of **4a-c**, in which Me-$B(OH)_2$, the pinacol ester of methylboronic acid or trimethylboroxine (TMB)[23] serve as the boron coupling partner, using either $PdCl_2(dppf)$[24] or $Pd(PPh_3)_4$ catalysis, in THF or 1,2-dimethoxyethane (DME) or DME/water mixtures and K_2CO_3 or Na_2CO_3 or KF as the base, under inert atmosphere at reflux temperature. Reactions were monitored by TLC and HPLC, and the most promising ones were worked up, purified and the structures confirmed by NMR. Again, as with **1a** and **1c**, cross-coupling presented a major challenge with "dimerization" of the halo-(phenyl)pyridones into **6** and dehalogenation to **5** concomitant to the desired "methylation". With **4a** and $Pd(PPh_3)_4$ and $MeB(OH)_2$[21], phenyl ring transfer occurred to generate **10**[25], in addition to **5** and **6**. **10** was isolated and characterized, **5** was independently synthesized from pyridin-2-ol, **3f**, as shown in Scheme 5 and was found to be identical to **5** isolated from SMC. In addition, oxidation of the catalyst to triphenyl phosphine oxide and its subsequent adhesion to the highly conjugated aromatic products resulted in complex mixtures of **4d**, **5**, **6** and **10** (Scheme 7), which were difficult to purify and impractical to pursue further.

Scheme 7: Phenyl ring transfer from Pd catalyst into the skeleton of N-Ph-5-bromopyridone (**4a**)

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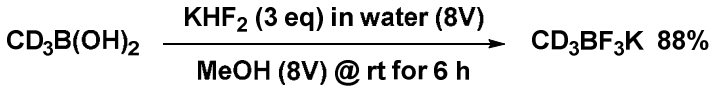
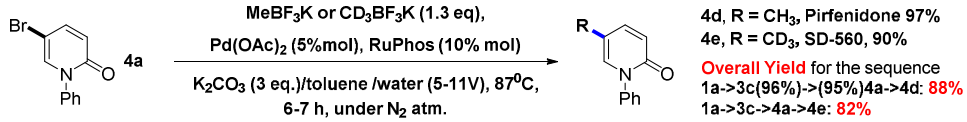
In his recent instructive review[26], Molander highlighted the importance of **organotrifluoroborates** ($R\text{-}BF_3K$) for increasing the chemical diversity in transition-metal-catalyzed cross-couplings, also with sp^3 carbon. Apparently, $R\text{-}BF_3K$ serve as stable, slow release reservoirs for boronic acids, which tune their release to match the rate of the trans-metalation, hence minimising protodeboronation, **2c** and **5** in our case, and other side reactions, such as homo-couplings, e.g., compounds **2d** and **6**. Molander's group did not ignore simple methylation. In fact, preparation of $MeBF_3K$ was reported in 2003[27] and it was used for methylation with various halo-aryl/heteroaryl substances[28], but **not with pyridone systems**. $MeBF_3K$ is air-stable, more atom-economical than most organo-borons and water-soluble, thereby minimizing the amount of organic solvent, enabling higher throughput and non-toxic waste of boron salts. For the synthesis of **4d** we used commercially available $MeBF_3K$; however, for its deuterated form, CD_3BF_3K, commercial supply is limited to sporadic availability of small quantities at a premium cost; hence, we prepared it from deuterated boronic acid ($CD_3B(OH)_2$) by reaction with commercially available, inexpensive, potassium hydrogen fluoride (KHF_2) at 88% yield and excellent purity as determined by ^1H, ^{13}C, ^{11}B (δ (D_2O) 5.91 ppm, q, J = 65 Hz) and ^{19}F (δ (D_2O) -132.39 ppm, q, J = 65 Hz) NMR and HRMS[29].



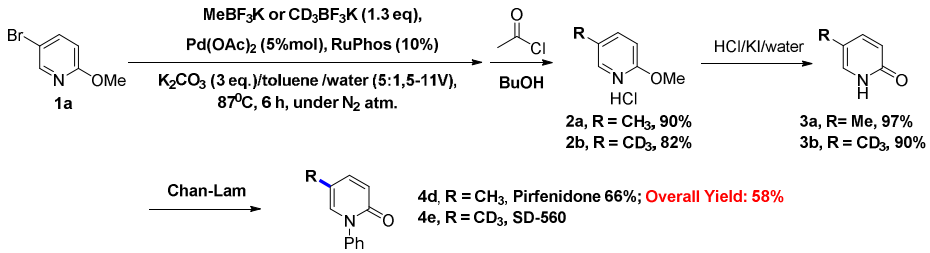
Scheme 8: Facile preparation of deuterated version of Molander's potassium methyltrifluoroborate reagent

With the two reagents in hand, we applied Molander's set of conditions on **4a**. The reaction, monitored by HPLC, showed complete disappearance of the starting material and formation of **4d**, with less than 0.5% of **5** and **6**, each, within 6-7 hours. To our delight, *for the first time near quantitative methylation of **4a** to furnish **4d** and **4e**, at 97% and 90%* (Scheme 9) *respective isolated yields, was achieved and without the loss of deuterium for **4e***; the latter was obtained at more than *99% isotopic purity* (based on mass spectra and NMR data; see ESI).



Scheme 9: Suzuki-Miyaura cross-coupling (SMC) in a "methylation-last" route to pirfenidone (**4d**) and **SD-560 (4e)**

Alternatively, **4d** was also obtained by the "methylation-first" route (Scheme 3 *vs.* Scheme 10) but instead of introducing the CH_3/CD_3 *via* cryogenic lithiation (Scheme 3, overall yield of 32%) **1a** was coupled under SMC conditions *via* **2a** and **2b**, isolated as the HCl salts, followed by OMe cleavage to **3a** and **3b**, and Chan-Lam phenylation to provide **4d** in overall yield of 58%.

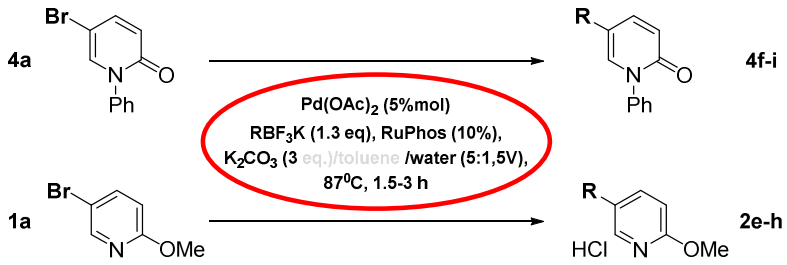


Scheme 10: SMC and "methylation-first" route to pirfenidone and **SD-560**

It should be pointed out that there is only one report by Blum[30] *et al* on Pd-catalyzed methylation of **1a** which led to **2a** in 68% yield, but it was carried out with bis[μ-[2-(dimethylamino)ethanolato-N,*O:O*]] tetramethyldiindium. The latter is not commercially available or easy to prepare[31], mainly because it requires trimethylindium, which is pyrophoric and needs to be handled with the utmost care and caution. Most other reported routes[32] leading to 2-methoxy-5-methylpyridine (**2a**) or to 5-methyl-2-pyridone (**3a**) involves a pyridine which already incorporates the 5-methyl substituent, and are thus not suitable for effective introduction of a 5-CD_3 group.

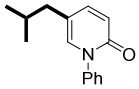
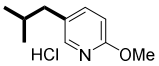
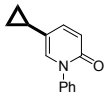
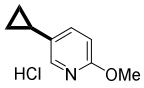
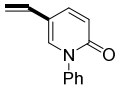
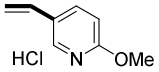
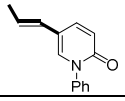
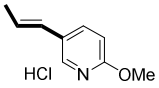
We showed that these SMC conditions (5% of Pd $(OAc)_2$ and 10% of 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (RuPhos))[33] ligand are general for alkylation of bromomethoxypyridine **1a** as well as of bromopyridone **4a**. Using *i*-

butyl[34]-, cyclopropyl[35]-, vinyl[36]- and trans-1-propenyl[37]-trifluoroborates K salts resulted in moderate to high yield of alkylated products **2e**-**2h**[38] and **4f**[39], **4g**[40], **4h**[41], **4i**[42], as shown in Scheme 11 and Table 1.

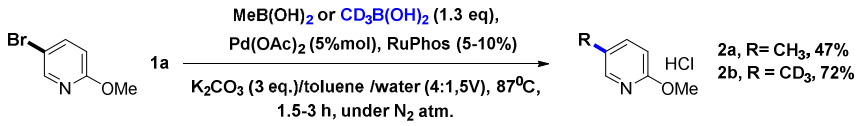


Scheme 11: SMC route for alkylated and alkenylated N-phenylpyridones and pyridines

Table 1: Synthesis of N-phenylpyridones and pyridines *via* Scheme 11

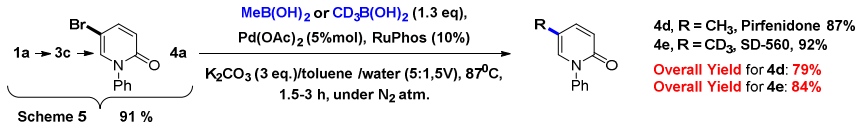
Cpd. No.	Structure	% Conversion (in HPLC)	Yield	Cpd. No.	Structure	% Conversion (in HPLC for the free base)	Isolated Yield
4f		81.5%	66%	**2e**		99.71%	65%
4g		100%	98%	**2f**		80.27%	60%
4h		100%	98%	**2g**		100%	38%
4i		100%	85%	**2h**		95.5%	44%

Finally, to our pleasant surprise, when the Suzuki-Miyaura methyl cross-coupling conditions (5% mol $Pd(OAc)_2$ catalysis and K_2CO_3, but also requiring 5-10% mol Buchwald's RuPhos ligand), were used with greener and less expensive Me-$B(OH)_2$ or with its deuterated version ($CD_3B(OH)_2$, Scheme 12), **2a** and **2b**, were obtained in moderate to good yields and within ca. 3 h. The lower yields in the route starting with **1a** may be attributed to the volatility of intermediates 2.



Scheme 12: SMC with Me/$CD_3B(OH)_2$ and **1a** in presence of Buchwald's RuPhos ligand

By using the "methyl last" route, these new coupling conditions, provided even higher overall yields in the synthesis of pirfenidone **4d** and its deuterated form **4e** (scheme 13) than *via* the "methyl first" route.



Scheme 13: SMC with Me/$CD_3B(OH)_2$ and **4a** in presence of Buchwald's RuPhos Ligand

We followed the progress of methylation of **4a** *via* SMC with $CH_3/CD_3B(OH)_2$ by HPLC (Fig. 1 and 2, ESI), which clearly showed the consumption of **4a** and formation of **4d** and **4e** in high yield and essentially devoid of side products, within 2 hours, unlike the poor results obtained by Scheme 7. The bromo pyridine **4a** was found to be the most effective substrate for SMC under the conditions of scheme 13, even with 1% mol of $Pd(OAc)_2$, leading to almost full conversion to **4d**, while **4b** and **4c** gave only 67% and 7.8% respective conversion. **4a** was fully consumed under catalysis of 5% mol $Pd_2(dba)_3$/5% mol RuPhos (instead of $Pd(OAc)_2$/RuPhos) to give 90% of isolated **4d** (see Table 3 in ESI).

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Schemes 3, 10 and 13, which are the most practical for further process development for plant production (excluding Schemes 1, 2 and 4), were examined based on a set of green chemistry parameters (Table 2) to enable a more calculated/quantitative/objective discrimination between the three routes before commencing the next stage of process development, including avoiding chromatographic purification and improving the crystallization procedure[43]. While most of the calculations are based on accepted and known methods in the pharmaceutical industry, some are our own internal methods.

Table 2: Quantitative green evaluation of the operational routes to **pirfenidone** and its deuterated analog **SD-560**

Green Index	**Scheme 3*** **Methylation 1st *via* lithiation**	**Scheme 10*** **Methylation 1st *via* SMC**	**Scheme 13^** **Methylation last *via* SMC**
Overall Yield	32%!	58%	84%
PMI [g/g]	257	130	56
Atom Economy	38%	23%	41%
E-Factor	147	104	28
Total Solvents	273	95	44
Class 4 (Dioxane)	9.5	0	0
Class 3 (DCM, Pyridine, n-Hexane)	41	46	15
Class 2 (Toluene, MTBE)	130	21	6
Class 1 (Butanol)	1.5	1	0
Water	91	27	23
5-Bromo-2-Methoxy pyridine input for 1kg DS	3.17	1.74	1.21
Methylation reaction volume [L/kgDS]	55	26	8
Methylation reaction Temperature	-50	87	87
Duration of methylation	14.5h	6h	3h

!Based on 70% of volataile **2a** after its filtration and before complete drying; *Each calculation contains all the stages required to synthesise pirfenidone from **1a**; ^calculated for **SD-560**, **4e** from **1a**; **PMI** (Process Mass index) - All input materials required for one gram of product; **Atomic Efficiency** - ratio between MW of the product to MWs of all raw materials and reagents x 100; **E-factor** - ratio between input material mass without product mass to product mass[44]; **Class 4** - forbidden; **Class 3** - undesirable; **Class 2** - usable; **Class 1** - preferable - according to our internal classification[45]

The SMC procedures show significant reduction of the environmental footprint. Thus, in Scheme 10, still with the "methylation-first" strategy, replacing the cryogenic step (BuLi/MTBE/-55°C protocol) with Molander's $MeBF_3K$, there is a marked improvement in almost all the green parameters. Moreover, in Scheme 13, employing the "methylation-last" strategy, with $CD_3B(OH)_2$ and Buchwald's RuPhos ligand, all the green parameters are **reduced**, mainly due to **higher yield** and ca. **6 fold reduction of solvent volume**, especially class 3 solvents, which **saves waste treatment**. The fact that the methylation with an expensive deuterated reagent is done at the end of the process with **significant energy conservation** *reduces both environmental footprint as well as production costs*. From the operational point of view an important benefit in Scheme 13 is its **higher throughput in less manufacturing time**, which yields more active pharmaceutical ingredient (API) in a **reduced number of batches** under the **same construction costs with fewer human working hours and release analysis**, in the plant environment.

In summary, our vision of a highly efficient introduction of methyl or methyl-d_3 at position 5 on the 1-phenylpyridine-2(1H)-one skeleton of pirfenidone (**4d**) and its d_3-analog (**4e**) in ca. 90% yield and >99% isotopic purity became reality, avoiding cryogenic lithiation of 5-bromo-2-methoxypyridine (**1a**, Scheme 3) or dangerous and complex reduction strategies of introducing deuterated methyl into the pirfenidone framework (Schemes 1 and 2). This was best accomplished *via* Suzuki-Miyaura cross-coupling (SMC) by a "methylation-last" strategy, which proceeded in 90% isolated yield and with high isotopic purity, taking advantage of heavy bromo-N-phenyl pyridone systems **4a** as crystalline, easy-to-store and handle substrate for the cross-coupling using Molander's alkyltrifluoroborate methodology and requiring only 1.3 eq. of the trifluoroborate reagent. Furthermore, the latter methodology led us to identify a simple, nearly quantitative methylation of **4a** with commercially available, d_3-methylboronic acid in the presence of Buchwald's RuPhos ligand, which we found essential for methylation of pyridine and N-phenyl pyridone systems, *via* SMC. This green and essentially quantitative cross-coupling with solid Me/CD_3-$B(OH)_2$ or Me/CD_3-BF_3K and cheap $Pd(OAc)_2$ using small solvent volumes (5-6 V) of **wet** toluene, applicable to both lab

and plant preparation of pirfenidone **4d** and its deuterated version, **4e**, **SD-560**, has several advantages over the Li route (Scheme 3), as well as over the Negishi procedure reported recently (Scheme 4)[7]; in the latter case, it avoids the preparation of special Ni catalyst in a glove box, and the use of a large excess of solvent (40 V) and volatile MeI, and hence offers a state-of-the art, high-yield, flexible, practical, scalable and simple methylation/alkylation procedure for pyridine and pyridone systems.

In conclusion, our studies of introducing a methyl and methyl d_3 into N-phenylated halo-pyridones or halo-pyridines by several non-cryogenic methodologies, e.g. *via* "Turbo-Grignard" and *via* "Ate complexes" and *via* Suzuki-Miyaura cross-methylation under Pd catalysis have demonstrated that the 12 principles of green chemistry are indeed an integral part of the development of a robust, efficient, and easy to operate process for the manufacturing of an API with control of impurities.

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boron isotopes; m/z 85.0512 and 86.0475 in relative abundance of 25% and 100%, for the CD_3-BF_3 anion (compared to m/z 82.0322 and 83.0286 for $CH_3BF_3^-$), in a perfect match for the calculated exact mass 85.0510 and 86.0474.

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38 **2e-h** were isolated as HCl salts because of the volatility of the free bases.

39 **4f** is a new chemical entity.

40 **4g** was prepared earlier from **2f** in 25% yield as reported in WO2009/149188A1 for example 132.

41 **4h** is a new chemical entity.

42 **4i** was prepared earlier from **2h** in 15% yield as reported in WO2009/149188A1 for example 326.

43 Our route scouting campaign was focused on finding a green methylation route with complete conversion to a high quality crude pirfenidone (**4d**) and its deuterated version (SD-560, **4e**), the crude material was purified by Combi-Flash chromatography to allow characterization and comparison of isolated yields with the understanding that the current crystallization procedure demands more development and will be addressed as a part of the next step in the process development and before pilot plant production.

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A Highly Efficient Suzuki-Miyaura Methylation of Pyridines Leading to the Drug Pirfenidone and to its CD_3 Version (SD-560)

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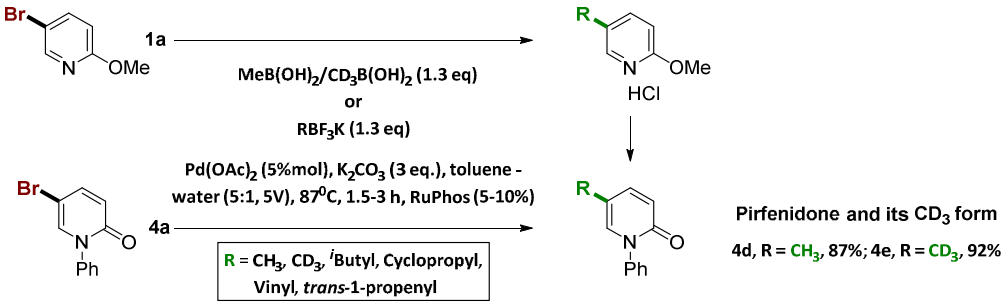

The first methylation/deuteromethylation in green and nearly quantitative Suzuki-Miyaura routes to **Pirfenidone** and its **d_3 analog SD-560**, at 99% isotopic purity.