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# Cobalt catalyzed formation of 2-pyridylzinc reagents and their subsequent coupling.

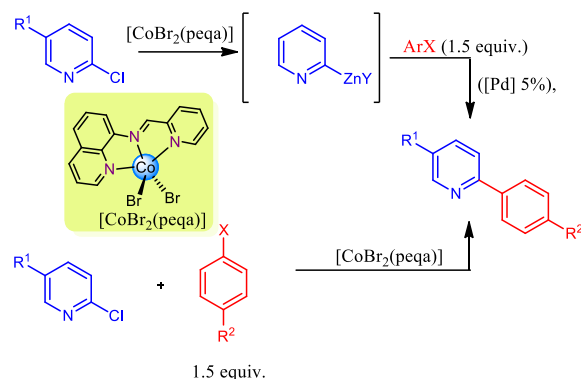
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**Abstract** The preparation of pyridinyl zinc compounds from the corresponding halides using a cobalt catalyst is described. The complex employed features a polydentate N-heterocyclic ligand and allows the reaction to be carried out in absence of pyridine as co-solvent and also in THF in place of acetonitrile. First cross coupling attempts are also presented. Satisfactory yields were obtained via a one-pot protocol without the addition of another catalyst.

**Key words** Cobalt catalysis. N-heterocyclic ligand. Zinc. Cross-coupling. Pyridine

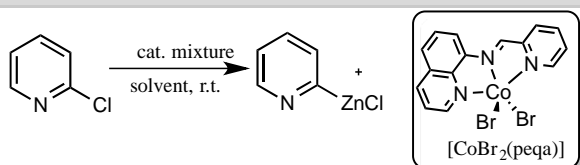
The pyridyl group is an important motif, which can be found in a variety of molecules ranging from pharmaceuticals,<sup>1</sup> natural products,<sup>2</sup> to metal-complexing-ligands<sup>3</sup> or materials.<sup>4</sup> Therefore, the synthesis of pyridyl organometallic reagents has been much investigated. However, the preparation of pyridyl-metal compounds by direct deprotonative metalation gave numerous side reactions that can be circumvented by working at low temperatures with hindered lithium bases.<sup>5</sup> The use of additives such as aminoalkoxide, or metal salts forming bimetallic bases offers other alternatives.<sup>5b, 5d</sup> Nevertheless, those pyridinyl-metal species are rather unstable. Since Suzuki-Miyaura coupling reactions allow an efficient introduction of heteroaryles,<sup>6</sup> the stabilization of pyridyl boronates using N-methyliminoacetic acid (MIDA) proposed by Burke et coll. in 2012 represents an important progress.<sup>7</sup> However all these protocols involved at some point lithium species which impose some limitations in terms of functional group tolerance. In that sense, the development of 2-pyridylzinc halides is promising; they can be prepared under Rieke conditions.<sup>8</sup> Most interestingly Buchwald and Knochel reported the synthesis of solid 2-pyridyl zinc reagents which presents moderate air-stability.<sup>9</sup> Some years ago, we developed a convenient cobalt-catalyzed methodology to prepare organozinc reagents that

does not require inert atmosphere and distilled solvents.<sup>10</sup> However it does not work with pyridyl halides, therefore we were interested in extending it to such motifs. This is the subject of this paper that presents an easy preparation of pyridinyl zinc reagents thanks to cobalt catalysis and our first attempt to further couple them with arylhalides. In the course of these investigations, we developed an unprecedented cobalt(II) complex featuring a N-(1-pyridin-2-yl)ethylidene)quinolin-8-amine ligand, which proved very useful.

In order to prepare 2-pyridyl-zinc halide from 2-pyridyl halide by a cobalt catalyzed procedure, we decided to use the catalytic conditions which were effective with aryl and thienyl chlorides to start the optimization study however a poor yield was obtained (Table 1, entry 1).<sup>10b</sup> Better results were obtained when associating CoBr<sub>2</sub> salt and zinc dibromide; the 2-pyridyl zinc derivative was formed in 61% yield after 24 h (Table 1, entry 2). Adding more cobalt (20 %) during the course of the reaction increased the proportion of side products leading to a lower yield (Table 1, entry 3). Cobalt complexes featuring nitrogen based ligands were then used; preformed [CoBr<sub>2</sub>(phen)] afforded 66 % of zinc compound (Table 1, entry 4) which is quite similar to that obtained with only CoBr<sub>2</sub>. Reaction with [CoBr<sub>2</sub>(bipy)], was more efficient since 84 % of pyridyl zinc formed (Table 1, entry 5). Finally two bidentate phosphine ligands were tested, the reactions were conducted by adding cobalt salt and the free ligand. The outcome of the reaction highly depends on the carbon linker between the phosphorus atoms: with diphenylphosphinopropane (dppp) the zinc compound forms in 42 % (Table 1, entry 6) compared to 86 % with diphenylphosphinoethane (dppe) (Table 1, entry 7). As the results of entry 5 and 7 were similar, we compared the cost of the ligand, the phosphorous one being approximatively 5 times more expensive than the bipyridine, we decided to continue with the latter, and the use of preformed complex can also be considered as an advantage. With these reaction conditions in hand, we were interested in reducing the amount

of pyridine, replacing it or even suppressing it, as we thought that a ligand should be sufficient to stabilize the formed cobalt intermediate. However, no reaction was observed when suppressing pyridine or substituting it by bipyridine, triethylamine, quinoline, isoquinoline. When decreasing the quantity of pyridine from 4, to 1, and 0.5 mL, the GC yield for the zinc derivative after 5 h was 68, 74, and 61 % respectively. With 0.25 mL of pyridine no organozinc was detected.

**Table 1** Optimization of the catalytic system



cat. mixture : Co cat. (13 mol %), Zn (3.3 equiv.), ZnBr<sub>2</sub> (0.13 equiv), AllylCl (0.3 equiv.), CF<sub>3</sub>CO<sub>2</sub>H (traces)

	Cat. syst.	Solvent	ArZnX <sup>a</sup>
1	CoBr <sub>2</sub> <sup>b</sup>	CH <sub>3</sub> CN/pyr	5
2	CoBr <sub>2</sub>	CH <sub>3</sub> CN/pyr	61
3	CoBr <sub>2</sub> + CoBr <sub>2</sub>	CH <sub>3</sub> CN/pyr	40 <sup>c</sup>
4	[CoBr <sub>2</sub> (phen)]	CH <sub>3</sub> CN/pyr	66
5	[CoBr <sub>2</sub> (bipy)(CH <sub>3</sub> CN) <sub>2</sub> ]	CH <sub>3</sub> CN/pyr	84
6	CoBr <sub>2</sub> + dppp	CH <sub>3</sub> CN/pyr	42
7	CoBr <sub>2</sub> +dppe	CH <sub>3</sub> CN/pyr	86
8	[CoBr <sub>2</sub> (peqa)]	CH <sub>3</sub> CN/pyr	88 <sup>d</sup>
9	[CoBr <sub>2</sub> (peqa)]	CH <sub>3</sub> CN	88 <sup>e</sup>
10	[CoBr <sub>2</sub> (peqa)] <sup>f</sup>	CH <sub>3</sub> CN	74
11	[CoBr <sub>2</sub> (peqa)] <sup>g</sup>	CH <sub>3</sub> CN	42
12	[CoBr <sub>2</sub> (peqa)] <sup>f,g</sup>	CH <sub>3</sub> CN	76
13	[CoBr <sub>2</sub> (peqa)] <sup>f,g</sup>	THF	74

<sup>a</sup> GC yield (%) determined after iodolysis after 24 h using dodecane as internal reference. <sup>b</sup> Reaction conducted without ZnBr<sub>2</sub>. <sup>c</sup> The reaction was stopped after 5h (no more starting material). <sup>d</sup> Reaction stopped after 8h (no more starting material). <sup>e</sup> Reaction stopped after 20h (no more starting material). <sup>f</sup> at 50°C. <sup>g</sup> with 5% catalyst

As many equivalents of pyridine relative to the cobalt center were necessary to ensure an efficient catalysis, we thought to develop a polydentate ligand incorporating N-heterocyclic donors. In order to maintain a good balance between activity and stability, we focused on tridentate ligands and were interested in incorporating a quinoline motif which was demonstrated to have an accelerating effect in Co- and Fe-catalyzed cross-coupling reactions.<sup>11</sup> Inspired by the work of W.-H. Sun et al. with nickel,<sup>12</sup> we synthesized a cobalt(II) complex featuring a N-(1-pyridin-2-yl)ethylidene)quinolin-8-amine ligand (abbreviated as peqa in the rest of the text). The synthesis was realized as reported for nickel by refluxing 2-aminoquinoline, 2-pyridyl-carboxaldehyde and CoBr<sub>2</sub> in acetic

acid. The highly insoluble complex was isolated in 88 % yield after filtrations. Unfortunately, all our crystallization attempts failed precluding a structural determination by X-ray analysis. Nevertheless a satisfying elemental analysis was obtained, and the magnetic moment in solution was measured at 3.9(1) μ<sub>B</sub> by the Evans method<sup>13</sup> in agreement with a high spin complex (S=3/2) for which we propose the structure depicted in scheme above table 1.

With [CoBr<sub>2</sub>(peqa)] in the previously mentioned conditions the 2-pyridylzinc derivative was formed in 88 % yield (Table 1, entry 8). When performing the same reaction in the absence of pyridine, this catalyst was able to generate the zinc compound as efficiently after 15 h (Table 1, entry 9). This evidences the interest of this tridentate ligand. In order to decrease the reaction time, the reaction medium was heated at 50 °C, but the yield was lower (Table 1, entry 10). To further test the ability of [CoBr<sub>2</sub>(peqa)], reactions were conducted at a lower catalyst loading. With 5 % of cobalt catalyst, the organozinc compound was formed in only 42 % yield (Table 1, entry 11), but increasing the temperature to 50 °C allowed to increase the yield to 76 % yield (Table 1, entry 12). Finally, reasoning that acetonitrile may not be necessary to stabilize cobalt intermediates with this ligand, the reaction was attempted in THF and we were pleased to observe the formation of the organozinc in 74 % at 50°C (Table 1, entry 13). This nicely illustrated that the use of an appropriate ligand for the cobalt center allows the employ of less coordinating solvent such as THF. This is the first time we were able to form the organozinc compound in this solvent via a cobalt-catalyzed procedure.

**Table 2** Catalytic reactions with 5% mol of [CoBr<sub>2</sub>(peqa)]<sup>a</sup>

Entry	Substrate	ArZnX <sup>b</sup>	
		CH <sub>3</sub> CN <sup>c</sup>	THF <sup>c</sup>
1	2-Br-pyridine	80	73
2	3-Br-pyridine	90	86
3	2-F-pyridine	81	39
4	2-Cl-5-CF <sub>3</sub> -pyridine	42 <sup>d</sup>	70 <sup>d</sup>
5	2-Cl-5-NO <sub>2</sub> -pyridine	70	65
6	2-Cl-3-CN-pyridine	60	84
7	2-Cl-5-CF <sub>3</sub> -pyridine	57	58
8	2-Cl-6-CN-pyridine	80	84

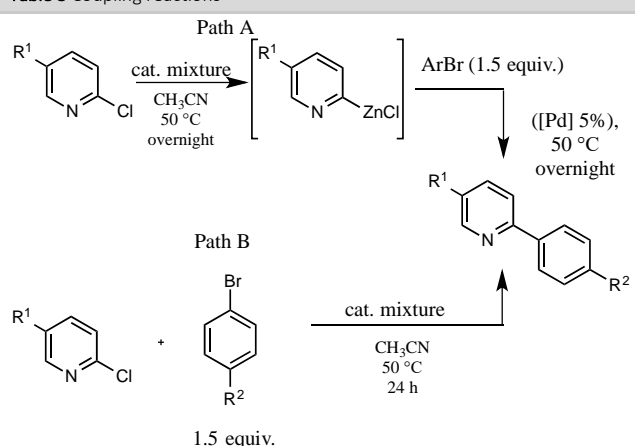
<sup>a</sup> Reaction conducted in presence of Zn (3.3 equiv.), ZnBr<sub>2</sub> (0.13 equiv.), AllylCl (0.3 equiv.), CF<sub>3</sub>O<sub>2</sub>H as traces. <sup>b</sup> GC yield (%) determined after iodolysis using dodecane as internal reference. <sup>c</sup> performed at 50 °C. <sup>d</sup> performed at 60 °C

With these conditions in hand we explored the scope of this cobalt-catalyzed methodology (Table 2). From 2-bromopyridine the organozinc species formed in 80% at 50°C. At this temperature the metalation is almost as efficient in THF (73 %) (Table 2, entry 1). For 3-bromopyridine, the reaction worked well in both solvents (Table 2, entry 2). On the contrary for 2-fluoropyridine only the metalation in acetonitrile was satisfactory (Table 2, entry 3). **The formation of 2-pyridylzinc from the corresponding fluoride seems rather unusual although, some Co-catalyzed biaryl coupling through C-F cleavage were described.<sup>14</sup>**

For some other halides, surprisingly, the reaction worked better in THF (Table 2, entry 6), the organozinc derivative forming in 84 % for 2-chloro-3-cyano-pyridine. For 2-chloro-5-(trifluoromethyl)-pyridine and 2-chloro-6-cyanopyridine, there was almost no solvent effect.

Even if it was interesting to probe that the organozinc can form quite efficiently with 5 % catalyst, when examining the possibility to further couple it with another arylhalide, we decided to use 13 % of cobalt catalyst. Indeed performing the zincation in pure acetonitrile at room temperature, full conversion to the organozinc compound (70-80 % GC yield) was observed starting from 2-chloro-5-trifluoromethylpyridine or 2-chloropyridine. Thus these were chosen as substrates to evaluate the following coupling reactions, results are gathered in Table 3.

**Table 3** Coupling reactions



Cat. mixture [CoBr<sub>2</sub>(peqa)] (5 mol %), Zn (3.3 equiv.), ZnBr<sub>2</sub> (0.13 equiv), AllylCl (0.3 equiv.), CF<sub>3</sub>CO<sub>2</sub>H.

Entry	R <sup>1</sup>	R <sup>2</sup>	Path	Cat.2	Yield (%)
1	CF <sub>3</sub>	OMe	A	-	48
2	CF <sub>3</sub>	OMe	A	Pd(dppf)Cl <sub>2</sub> (5%)	58
3	CF <sub>3</sub>	OMe	A	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> (5%)	56
4	CF <sub>3</sub>	OMe	A	CrCl <sub>2</sub> (5%)	4
5	H	OMe	A	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> (5%)	65
6	CF <sub>3</sub>	OMe	B	-	66 <sup>b</sup>
7	CF <sub>3</sub>	SMe	B	-	62
8	CF <sub>3</sub>	Me	B	-	41
9	CF <sub>3</sub>	CO <sub>2</sub> Et	B	-	46
10	H	OMe	B	-	31

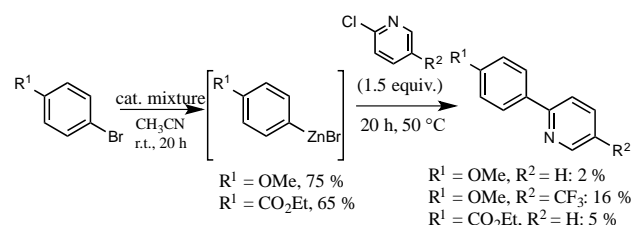
<sup>a</sup> GC yield (%) using dodecane as reference. <sup>b</sup> 4% yield when the reaction was conducted in an acetonitrile/pyridine (6/1) mixture.

For the first attempts, the 2-pyridylzinc compound was formed in a first step, then the coupling partner (p-bromoanisole) was added without any additional catalyst and the reaction mixture was heated at 50 °C for 8 h, the corresponding coupling product was isolated in 48 % yield (Table 3, entry 1). The introduction of a palladium catalyst (5 %) to perform a classical Negishi reaction gave slightly better yields; 58 and 56 % using respectively 5 % of [Pd(dppf)Cl<sub>2</sub>] and [Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] (Table 3, entries 2 and 3). The use of chromium catalyst<sup>15</sup> was disappointing, no product could be detected by adding [Cr(acac)<sub>3</sub>] (5 %), whereas CrCl<sub>2</sub> (5%) only led to 4 % product. Starting from 2-chloropyridine, via the intermediate formation of the corresponding zinc species, 65 % yield was obtained (Table 3, entry 5). Having observed that the filtration of the reaction mixture before the eventual addition of a second

catalyst almost inhibits the coupling reaction, we wondered if the zincation and the coupling reactions could not be conducted in the same pot without any additional catalyst as we previously reported using a nickel catalyst.<sup>16</sup>

Heating 2-chloro-5-trifluoromethylpyridine and p-bromoanisole in presence of the cobalt catalytic system at 50 °C in acetonitrile (path B) gave the coupling product in 66 % yield after 24 h. Adding pyridine (acetonitrile/ pyridine : 6/1) nearly annihilated the catalytic ability since only 4 % product was observed by GC analysis (Table 3, entry 6). Comparable coupling yield was obtained from 4-bromothioanisole (Table 3, entry 7). Using arylbromides with less electron rich substituents led to lower yield: the coupling yield decreased to 41 and 46 % using p-bromotoluene and p-bromo-ethylbenzoate respectively (Table 3, entries 8, 9). Starting from 2-chloropyridine, the coupling product with p-bromoanisole was isolated in 31 % yield (Table 3, entry 10).

In order to prove that these one-pot reactions do involve the formation of a pyridyl zinc compound, we tested the reverse reaction i.e. those involving the coupling of cobalt-catalyzed formed arylzinc derivative with chloropyridine (scheme 1).



Cat. mixture [CoBr<sub>2</sub>(peqa)] cat. (13 mol %), Zn (3.3 equiv.), ZnBr<sub>2</sub> (0.13 equiv), AllylCl (0.3 equiv.), CF<sub>3</sub>CO<sub>2</sub>H.

**Scheme 1:** Coupling from arylzinc compounds and pyridinyl chloride.

The arylzinc derivative forms with [CoBr<sub>2</sub>(peqa)] in a satisfactory yield from bromo and p-trifluoromethylbromobenzene (Scheme 1). These yields are lower than those obtained with CoBr<sub>2</sub> salt<sup>10a</sup>. Nevertheless, the addition of chloropyridine followed by heating at 50 °C only led to traces of coupling product. Best result was obtained with 4-methoxyphenyl zinc bromide and 2-Cl-5-CF<sub>3</sub>-pyridine yielding 16 % of coupling product. Therefore the observed 66 % yield obtained with the one-pot methodology (path B) previously discussed should involve a pyridylzinc adduct.

As a conclusion, we developed an efficient cobalt methodology for the preparation of pyridylzinc compound. Interestingly only [CoBr<sub>2</sub>(peqa)] allows the reaction to be conducted without pyridine. Quite unprecedentedly, the reaction with this catalyst allowed the zincation in THF with a comparable efficiency. First attempts for subsequent coupling with arylbromides led to average to good yields (40-60 % for 2 steps). Best results with a two-step were obtained with an additional palladium catalyst. Nevertheless, the one-pot cobalt catalyzed procedure could in some cases exhibit similar performances. This first study shows that cobalt catalyst featuring polydentate N-heterocyclic ligand may offer an interesting alternative. Ligand tuning would be necessary to improve the coupling efficiency. Developing bidentate ligands may be an option to facilitate the interaction between substrates and catalyst.

**Synthesis of [CoBr<sub>2</sub>(peqa)]:** 8-aminoquinoline (1.8 g, 12.5 mmol) 2-acetylpyridine (1.40 mL, 12.5 mmol) and CoBr<sub>2</sub> (2.72 g, 12.5 mmol) were

refluxed at 130°C in glacial acetic acid (60 mL, 0.21 M) for 5h. After cooling back to room temperature, the suspension was filtered and the obtained black solid was washed with diethyl ether (3 x 50 mL). This solid was dissolved in hot ethanol (100 mL). The solution is concentrated under vacuum (roughly half of the volume of solvent is evacuated) and diethyl ether (80 mL) is added to induce precipitation. The obtained solid is washed with diethyl ether (3 x 20 mL) and dried in vacuo to give [CoBr<sub>2</sub>(peqa)] (5.2 g 82%).

M.p. : 128.9 °C

$\mu$  : 3.9(1)  $\mu_B$

Anal. Calcd. for C<sub>16</sub>H<sub>13</sub>Br<sub>2</sub>CoN<sub>3</sub> : C, 41.24; H, 2.81; N, 9.02. Found: C, 41.35; H, 2.77; N, 8.95.

### Preparation of the Arylzinc Reagents Followed by Cross-Coupling with Aryl Halides (GP 1)

Preparation of the Arylzinc Reagents:

An oven dried flask was equipped with a stirring bar and closed with a septum. Zinc dust (1.08 g, 16.5 mmol, 3.33 equiv.), ZnBr<sub>2</sub> (146 mg, 0.65 mmol, 0.13 equiv.) and Co<sup>II</sup> catalyst were added and stirred in MeCN (4 mL). TFA (0.1 mL, 1.3 mmol, 0.26 equiv.) and allyl chloride (0.17 mL, 2.05 mmol, 0.41 equiv.) were added subsequently which caused a rise in temperature and gas evolution. Pyridine was added if necessary. Once the mixture reached room temperature again the aryl halide (5.0 mmol) was added and the reaction was stirred at the indicated temperature until iodolyzed aliquots of the reaction showed full conversion of the starting material via GC analysis. The yield was determined by addition of an internal standard (*n*-decane or *n*-dodecane, 100  $\mu$ L).

Cross-Coupling with Aryl Halides

The crude arylzinc reagent was used unless indicated otherwise. (In these cases the reagent was filtered with a syringe filter and/or additives were added). The corresponding aryl halide was added neat and the reaction was stirred at the indicated temperature until iodolyzed aliquots of the reaction showed full conversion of the arylzinc reagent via GC analysis. The reaction was quenched by addition of saturated aqueous NH<sub>4</sub>Cl solution (20 mL) followed by extraction with DCM (3 x 50 mL). The combined organic layers were dried over MgSO<sub>4</sub> and after filtration the solvents were evaporated in vacuo. Purification by flash column chromatography furnished the desired biaryls.

### One-Pot Synthesis of Biaryls (GP2)

An oven dried flask was equipped with a stirring bar and closed with a septum. Zinc dust (1.08 g, 16.5 mmol, 3.33 equiv.), ZnBr<sub>2</sub> (146 mg, 0.65 mmol, 0.13 equiv.) and Co(II)-catalyst were added and stirred in MeCN (4 mL). TFA (0.1 mL, 1.3 mmol, 0.26 equiv.) and allyl chloride (0.17 mL, 2.05 mmol, 0.41 equiv.) were added subsequently which caused a rise in temperature and gas evolution. Pyridine was added if necessary. Once the mixture reached room temperature again the two aryl halides were added and the reaction was stirred at the indicated temperature until iodolyzed aliquots of the reaction showed full conversion of the starting material via GC analysis. The reaction was quenched by addition of saturated aqueous NH<sub>4</sub>Cl solution (20 mL) followed by extraction with DCM (3 x 50 mL). The combined organic layers were dried over MgSO<sub>4</sub> and after filtration the solvents were evaporated in vacuo. Purification by flash column chromatography furnished the desired biaryls.

### Synthesis of 2-(4-Methoxyphenyl)pyridine<sup>16</sup>

According to GP 2 using 2-chloropyridine (0.47 mL, 5.0 mmol) and 4-bromoanisole (0.94 mL, 7.5 mmol). Flash column chromatography (SiO<sub>2</sub>, petrol ether : Et<sub>2</sub>O = 4 : 1) afforded the desired product in 31% (287 mg, 1.55 mmol) overall yield.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  / ppm = 8.67 (d, *J* = 4.7 Hz, 1H), 7.98 (d, *J* = 8.9 Hz, 2H), 7.74 - 7.63 (m, 2H), 7.16 (ddd, *J* = 6.7, 4.8, 1.5 Hz, 1H), 7.01 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H)

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 160.60, 157.20, 149.59, 136.80, 132.08, 128.28, 121.51, 119.92, 114.25, 55.46.

HRMS for C<sub>12</sub>H<sub>11</sub>NO (185.0841): found: 185.0834.

### Synthesis of 2-(4-methoxyphenyl)-5-(trifluoromethyl)pyridine<sup>16</sup>

According to GP 2 using 2-chloro-5-(trifluoromethyl)pyridine (0.64 mL, 5.0 mmol) and 4-bromoanisole (0.94 mL, 7.5 mmol). Flash column chromatography (SiO<sub>2</sub>, petrol ether : DCM = 2 : 1) afforded the desired product in 66% (822 mg, 3.25 mmol) overall yield.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  / ppm = 8.89 (s, 1H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 2H), 3.87 (s, 3H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 161.50, 160.38, 146.62 (q, *J* = 4.0 Hz), 133.93 (q, *J* = 3.5 Hz), 130.62, 128.82, 124.18 (q, *J* = 33 Hz), 124.02 (q, *J* = 270 Hz), 119.18, 114.50, 55.55.

HRMS for C<sub>13</sub>H<sub>10</sub>F<sub>3</sub>NO (253.0714): found: 253.0724.

### Synthesis of 2-(4-(methylthio)phenyl)-5-(trifluoromethyl)pyridine<sup>17</sup>

According to GP 2 using 2-chloro-5-(trifluoromethyl)pyridine (0.64 mL, 5.0 mmol) and 4-bromothioanisole (1.52 g, 7.5 mmol). Flash column chromatography (SiO<sub>2</sub>, pentane : DCM = 4 : 1) afforded the desired product in 62% (874 mg, 3.24 mmol) overall yield.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  / ppm = 8.91 (s, 1H), 8.02 - 7.90 (m, 3H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 2.54 (s, 3H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  / ppm = 160.12, 146.72 (q, *J* = 4.0 Hz), 141.74, 134.49, 134.01 (q, *J* = 3.5 Hz), 127.63, 126.34, 124.68 (q, *J* = 33 Hz), 123.91 (q, *J* = 270 Hz), 119.47, 15.43.

HRMS for C<sub>13</sub>H<sub>10</sub>F<sub>3</sub>NS (269.0486): found: 269.0482.

### Synthesis of 2-(*p*-Tolyl)-5-(trifluoromethyl)pyridine<sup>16</sup>

According to GP 2 using 2-chloro-5-(trifluoromethyl)pyridine (0.32 mL, 2.5 mmol) and *p*-bromotoluene (1.22 mL, 7.5 mmol). Flash column chromatography (SiO<sub>2</sub>, pentane : Et<sub>2</sub>O = 20 : 1) afforded the desired product in 41% (604 mg, 2.05 mmol) overall yield.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  / ppm = 8.98 (s, 1H), 8.31 - 8.07 (m, 4H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  / ppm = 160.80, 146.67 (q, *J* = 4.0 Hz), 140.45, 135.31, 134.45 (q, *J* = 3.5 Hz), 129.83, 127.28, 124.62 (q, *J* = 32 Hz), 123.69 (q, *J* = 270 Hz), 119.69, 21.46.

### Synthesis of Ethyl 4-(5-(trifluoromethyl)pyridin-2-yl)benzoate.<sup>18</sup>

According to GP 2 using 2-chloro-5-(trifluoromethyl)pyridine (0.64 mL, 5.0 mmol) and ethyl 4-bromobenzoate (0.46 g, 7.5 mmol). Flash column chromatography (SiO<sub>2</sub>, pentane : DCM = 4 : 1) afforded the desired product in 46% (275 mg, 1.16 mmol) overall yield.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  / ppm = 8.92 (s, 1H), 8.01 - 7.89 (m, 3H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  / ppm = 166.28, 159.61, 146.91 (q, *J* = 4.0 Hz), 141.92, 134.22 (q, *J* = 3.5 Hz), 131.89, 130.27, 127.31, 125.65 (q, *J* = 33 Hz), 123.74 (q, *J* = 270 Hz), 120.54, 61.35, 14.46.

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### Supporting Information

NO (this text will be deleted prior to publication)

### Primary Data

Is there **Primary Data** to be associated with this manuscript? [Click here](#), then the arrow, and choose YES or NO.

### References

1. (a) DeGoey, D. A.; Grampovnik, D. J.; Flentge, C. A.; Flosi, W. J.; Chen, H.-j.; Yeung, C. M.; Randolph, J. T.; Klein, L. L.; Dekhtyar, T.; Colletti, L.; Marsh, K. C.; Stoll, V.; Mamo, M.; Morfitt, D. C.; Nguyen, B.; Schmidt, J. M.; Swanson, S. J.; Mo, H.; Kati, W. M.; Molla, A.; Kempf, D. J., *J. Med. Chem.* **2009**, *52*, 2571-2586; (b) Pilon, J. L.; Clausen, D. J.; Hansen, R. J.; Lunghofer, P. J.; Charles, B.; Rose, B. J.; Thamm, D. H.; Gustafson, D. L.; Bradner, J. E.; Williams, R. M., *Cancer Chemother. Pharmacol.* **2015**, *75*, 671-682.
2. (a) Jakubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J., *J. Am. Chem. Soc.* **2012**, *134*, 17482-17485; (b) Goetz, A. E.; Shah, T. K.; Garg, N. K., *Chem. Commun.* **2015**, *51*, 34-45; (c) White, J. D.; Li, Y.; Kim, J.; Terinek, M., *J. Org. Chem.* **2015**, *80*, 11806-11817.
3. (a) Glasson, C. R. K.; Lindoy, L. F.; Meehan, G. V., *Coord. Chem. Rev.* **2008**, *252*, 940-963; (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C., *Chem. Rev.* **2013**, *113*, 5322-5363; (c) Han, Y.-F.; Jin, G.-X., *Acc. Chem. Res.* **2014**, *47*, 3571-3579; (d) Veliks, J.; Tseng, J.-C.; Arias, K. I.; Weissnar, F.; Linden, A.; Siegel, J. S., *Chem. Sci.* **2014**, *5*, 4317-4327; (e) Liu, C.-C.; Chan, M. C. W., *Acc. Chem. Res.* **2015**, *48*, 1580-1590.
4. (a) Chi, C.-C.; Chiang, C.-L.; Liu, S.-W.; Yueh, H.; Chen, C.-T.; Chen, C.-T., *J. Mater. Chem.* **2009**, *19*, 5561-5571; (b) Wild, A.; Winter, A.; Schluetter, F.; Schubert, U. S., *Chem. Soc. Rev.* **2011**, *40*, 1459-1511; (c) Chatterjee, S.; Karuso, P.; Boulange, A.; Franck, X.; Datta, A., *J. Phys. Chem. B* **2015**, *119*, 6295-6303.
5. (a) Chau, N. T. T.; Meyer, M.; Komagawa, S.; Chevallier, F.; Fort, Y.; Uchiyama, M.; Mongin, F.; Gros, P. C., *Chem. Eur. J.* **2010**, *16*, 12425-12433; (b) Khartabil, H. K.; Gros, P. C.; Fort, Y.; Ruiz-Lopez, M. F., *J. Am. Chem. Soc.* **2010**, *132*, 2410-2416; (c) Gros, P. C.; Fort, Y., *Curr. Org. Chem.* **2011**, *15*, 2329-2339; (d) Snegaroff, K.; Tan Tai, N.; Marquise, N.; Halauko, Y. S.; Harford, P. J.; Roisnel, T.; Matulis, V. E.; Ivashkevich, O. A.; Chevallier, F.; Wheatley, A. E. H.; Gros, P. C.; Mongin, F., *Chem. Eur. J.* **2011**, *17*, 13284-13297; (e) Marquise, N.; Bretel, G.; Lassagne, F.; Chevallier, F.; Roisnel, T.; Dorcet, V.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Gros, P. C.; Mongin, F., *Rsc Adv.* **2014**, *4*, 19602-19612.
6. Billingsley, K. L.; Buchwald, S. L., *Angew. Chem. Int. Ed.* **2008**, *47*, 4695-4698.
7. Dick, G. R.; Woerly, E. M.; Burke, M. D., *Angew. Chem. Int. Ed.* **2012**, *51*, 2667-2672.
8. Coleridge, B. M.; Bello, C. S.; Ellenberger, D. H.; Leitner, A., *Tetrahedron Lett.* **2010**, *51*, 357-359.
9. (a) Colombe, J. R.; Bernhardt, S.; Stathakis, C.; Buchwald, S. L.; Knochel, P., *Org. Lett.* **2013**, *15*, 5754-5757; (b) Manolikakes, S. M.; Ellwart, M.; Stathakis, C. I.; Knochel, P., *Chem. Eur. J.* **2014**, *20*, 12289-12297.
10. (a) Fillon, H.; Gosmini, C.; Perichon, J., *J. Am. Chem. Soc.* **2003**, *125*, 3867-3870; (b) Gosmini, C.; Amatore, M.; Claudel, S.; Perichon, J., *Synlett* **2005**, 2171-2174.
11. Kuzmina, O. M.; Steib, A. K.; Markiewicz, J. T.; Flubacher, D.; Knochel, P., *Angew. Chem. Int. Ed.* **2013**, *52*, 4945-4949.
12. Sun, W.-H.; Wang, K.; Wedeking, K.; Zhang, D.; Zhang, S.; Cai, J.; Li, Y., *Organometallics* **2007**, *26*, 4781-4790.
13. (a) Evans, D. F., *J. Chem. Soc.* **1959**, 2003-2005; (b) Deutsch, J. L.; Poling, S. M., *J. Chem. Educ.* **1969**, *46*, 167-168; (c) Grant, D. H., *J. Chem. Educ.* **1995**, *72*, 39-40.
14. (a) Korn, T. J.; Schade, M. A.; Wirth, S.; Knochel, P., *Org. Lett.* **2006**, *8*, 725-728; (b) Wei, J.; Liu, K.-M.; Duan, X.-F., *J. Org. Chem.* **2017**, *82*, 1291-+.
15. Steib, A. K.; Kuzmina, O. M.; Fernandez, S.; Flubacher, D.; Knochel, P., *J. Am. Chem. Soc.* **2013**, *135*, 15346-15349.
16. Gosmini, C.; Bassene-Ernst, C.; Durandetti, M., *Tetrahedron* **2009**, *65*, 6141-6146.
17. Tellis, J. C.; Primer, D. N.; Molander, G. A., *Science* **2014**, *345*, 433-436.
18. Chen, S. M.; Tan, G. P.; Wong, W. Y.; Kwok, H. S., *Adv. Funct. Mater.* **2011**, *21*, 3785-3793.