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Development of a Scalable Route for a Key Thiadiazole Building Block via Sequential Sandmeyer Bromination and Room-Temperature Suzuki–Miyaura Coupling

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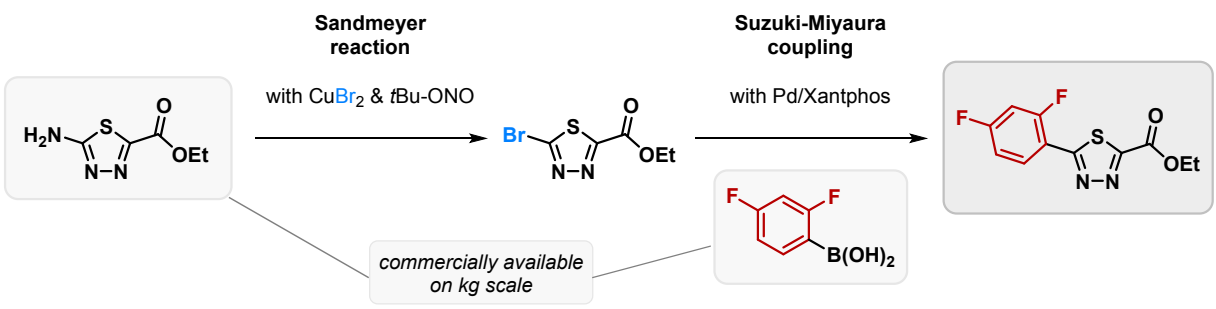
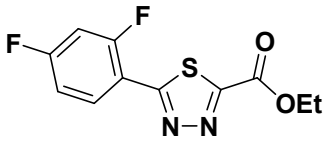


ABSTRACT. To avoid the use and handling of Lawesson's reagent or other thiation agents in the in-house kilolab, a new scalable route to ethyl 5-(2,4-difluorophenyl)-1,3,4-thiadiazole-2-carboxylate (**1**) was developed. The key to success was the use of a commercially available amino-thiadiazole building block, which was converted into the desired product via a sequence of Sandmeyer bromination and Suzuki-Miyaura coupling. The different parameters of the Pd-catalyzed coupling have been studied in detail and

allowed the reaction to be performed under mild conditions at room temperature and with low catalyst loading. The inconsistencies of the initial scale-up runs with regards to the sluggish conversion of the Suzuki-Miyaura coupling due to Cu contaminations were addressed, and the learnings directly implemented in the subsequent batches, which finally led to an improved overall understanding and robustness of the process.

KEYWORDS: thiadiazole, heterocycles, Suzuki-Miyaura coupling, Sandmeyer reaction, Xantphos.

INTRODUCTION. For a recent project at Idorsia Pharmaceuticals, a robust and scalable route to ethyl 5-(2,4-difluorophenyl)-1,3,4-thiadiazole-2-carboxylate (**1**) needed to be developed (Figure 1).[1]



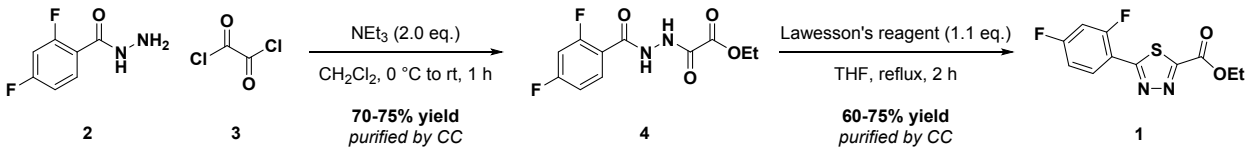
1,3,4-thiadiazole building block (**1**)

Figure 1: Structure of desired building block **1**.

In our medicinal chemistry laboratories, **1** was synthesized via acylation of commercially available 2,4-difluorobenzoic acid hydrazide **2** with ethyl chlorooxoacetate **3**, followed by cyclization of **4** with Lawesson's reagent (Scheme 1). The overall yield and throughput of this early route was high and delivered **1** in multigram amounts to prepare an array of different thiadiazole-containing compounds for biological testing. However, the route also suffered from certain drawbacks with regards to scale up: a) the use of malodorous

Lawesson's reagent was assessed to be very challenging to handle in our kilolab;[2] b) the lipophilic Lawesson's reagent byproducts were challenging to remove by crystallization and the final product had to be purified by column chromatography (CC); c) the use of high volumes of undesired CH_2Cl_2 (15−20 vol.) in the first acylation step. For these reasons, we wanted to develop a new synthetic route from a commercially available thiadiazole starting material, which would supersede the use of Lawesson's reagent in our laboratories.

Scheme 1: First Generation Synthesis of **1** using Lawesson's reagent

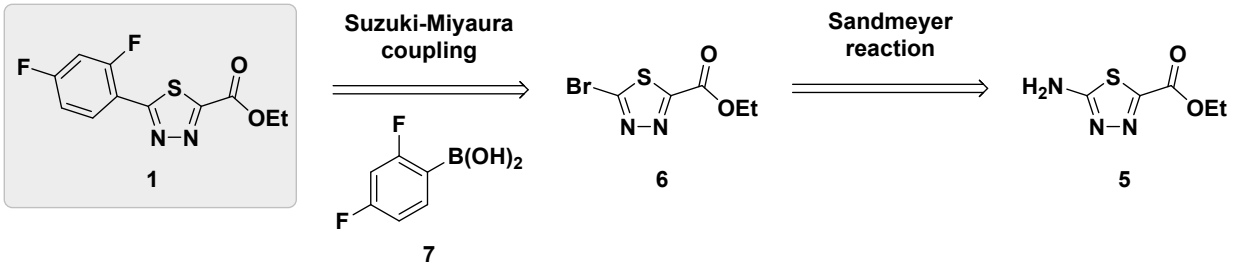


2 3 4 1

INITIAL EXPERIMENTS. After considering many different potential starting materials, we found ethyl 5-amino-1,3,4-thiadiazole-2-carboxylate (**5**) to be a suitable candidate due

to its commercial availability on kg-scale and its ease of handling as a bench-stable solid.[3] We envisioned that the starting material could be converted into the desired building block **1** by a sequence of Sandmeyer bromination and subsequent Suzuki-Miyaura coupling with 2,4-difluorophenyl boronic acid (**7**)[4] (Scheme 2).

Scheme 2: Retrosynthetic Analysis of **1** starting from commercially available **5**



Perfluorophenyl boronic acids are known to undergo rapid protodeboronation under the traditional basic aqueous conditions of Suzuki-Miyaura couplings.[5] Therefore, the stability of 2,4-difluorophenyl boronic acid (**7**) under basic conditions was assessed at the start of the project. The boronic acid was found to be stable in a 1:1 v/v-mixture of THF and 1 M aq. NaOH at room temperature and no protodeboronation could be observed after 24 h. However, in the same solvent system, protodeboronated product **8** started to be observed

by LC/MS after gradual heating to 55 °C (Figure 2). Therefore, it was apparent that room-temperature Suzuki-Miyaura coupling conditions needed to be developed, preferably employing a mild base to further reduce the risk of protodeboronation. In addition, it was known that the free carboxylic acid of **1** is highly unstable and instantaneously decarboxylates,[6] further highlighting the necessity to use a mild base in the Suzuki-Miyaura coupling to avoid saponification of the ethyl ester.

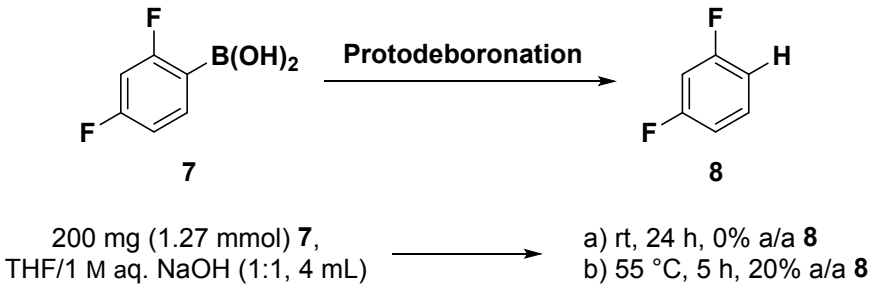


Figure 2: Protodeboronation of **7** to **8** (ratio determined by LC/MS).

PROCESS DEVELOPMENT. After establishing the stability of the fluorinated boronic acid at room temperature, we started with the development of the Sandmeyer bromination of **5**.[7] After initial screenings with different bromide and nitrite sources,[8] the dosing of *tert*-butyl nitrite to a mixture of $CuBr_2$ and the starting material in MeCN at room temperature

was found to be optimal with regards to reaction conversion and impurity profile. With regards to process safety, differential scanning calorimetry (DSC) analysis of *tert*-butyl nitrite showed a highly energetic, autocatalytic decomposition (2175 KJ/kg) at 180 °C. Therefore, the Sandmeyer bromination was studied in a Systag reaction calorimeter (10 g scale, addition time of *tert*-butyl nitrite: 30 min). The reaction with *tert*-butyl nitrite was found to be dose-controlled at 23 °C with release of an exotherm of 92.9 kJ/kg and a heat production per unit mass of ca. 45 W/Kg, leading to a MTSR (*maximum temperature of the synthesis reaction*) of 65 °C. The intermediate diazonium species was never detected by LC/MS, and after complete addition of *tert*-butyl nitrite, the starting material was normally fully converted (>98% conversion). In addition, analysis of the reaction mixture after addition of *tert*-butyl nitrite by thermal screening unit (TSU) showed no sudden gas-release or exothermic event below 120 °C. Taking all these experiments into consideration, we deemed the reaction safe to be run on 1-2 kg scale.[9] The excess nitrite was destroyed by quenching the reaction mixture with aqueous sulfamic acid (H_3NSO_3) solution,[10] followed by addition of iPrOAc and phase-split. The resulting green organic phase was repeatedly washed with 20% aq. NH_4Cl and brine to remove excess copper

(Figure 3). After removal of the organic solvent under reduced pressure, a dark yellow crude solid with good chemical purity (ca. 95% a/a) was obtained.

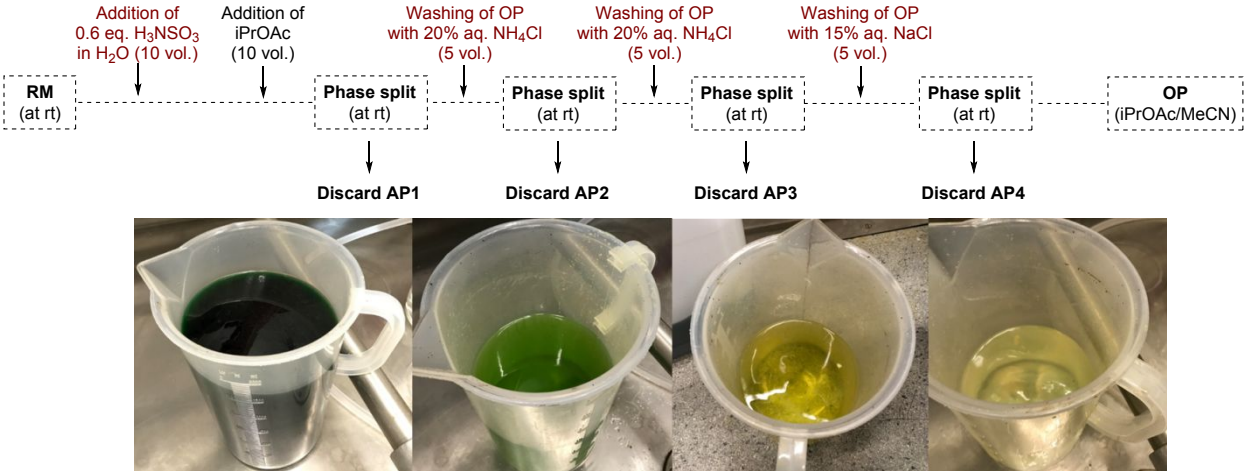
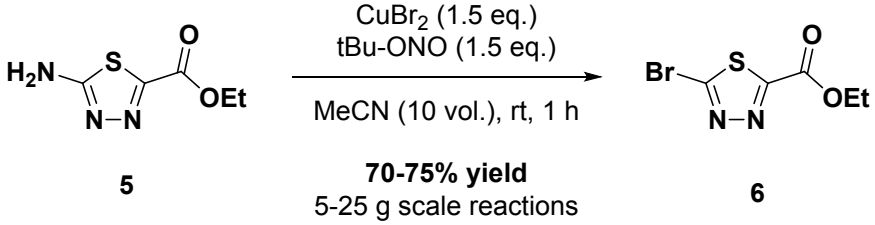


Figure 3: Flow diagram of aqueous workup and aspect of aqueous phases after each phase split. RM = reaction mixture; rt = room temperature; OP = organic phase; AP = aqueous phase.

However, ICP/MS analysis showed that the crude product was contaminated with high levels of residual copper (> 1000 ppm). Recrystallization of the crude product proved to be challenging due to its high solubility in a wide range of organic solvents (TBME, EtOH, iPrOH, iPrOAc, toluene). The low-melting solid (mp: 81 °C by DSC) also showed the tendency to oil-out from highly nonpolar solvents such as heptane or methylcyclohexane.

On the other hand, the crude product was completely insoluble in H_2O. After many crystallization attempts, it was found that the crude product could be successfully recrystallized from a 2:1-mixture of H_2O and EtOH to isolate the product as an off-white solid. In order to avoid concentration of the organic phase to dryness to isolate the crude product, a solvent swap from iPrOAc/MeCN to EtOH was introduced after the aqueous workup, followed by addition of H_2O to induce crystallization of the product. This solvent swap-crystallization procedure was demonstrated on 5-25 g scale and led to the isolation of bromo thiadiazole **6** in good yield (70-75%) and purity (97% a/a) (Scheme 3). The residual copper content was found to be 50-100 ppm for these batches and hence drastically reduced compared to the crude material.

Scheme 3: Gram-Scale Sandmeyer reaction



For the screening of the Suzuki-Miyaura coupling, we decided that it was best to additionally purify the bromo thiadiazole **6** by column chromatography to exclude any possible interference of residual Cu with the Pd-catalyst system. Many of our initial efforts were fruitless, and using $Pd(PPh_3)_4$, $Pd(OAc)_2$/SPhos or $Pd(OAc)_2$/XPhos in combination with different bases (K_3PO_4, K_2CO_3, Cs_2CO_3, NEt_3) in THF/H_2O at room temperature did not provide any trace of coupling product **1**, and mainly unreacted and/or hydrolyzed bromo thiadiazole **6** was observed. More promising was the use of bidentate phosphine ligands such as dppf or Xantphos. In particular, $Pd(OAc)_2$/Xantphos proved to be a highly active catalyst system, and full conversion of **6** was achieved with different bases and solvent combinations (entries 4-9). The major difference between the individual reactions was the degree at which the starting material **6** was hydrolyzed over the course of the reaction. Conditions that enhance the saponification of the ethyl ester in the starting material, e.g. water-miscible THF with strong inorganic bases (K_3PO_4 or Cs_2CO_3, entries 4-5), led to a diminished overall purity of the final IPC (*in-process control*), as **6** was mainly converted into its corresponding carboxylate salt. On the other hand, a biphasic system of toluene and H_2O protected the starting material **6** from hydrolysis (entries 7-9). By

employing a mild organic base such as *N*-methylmorpholine (NMM, entry 9), the hydrolysis was almost completely suppressed, and a clean reaction profile was obtained after stirring overnight at room temperature.

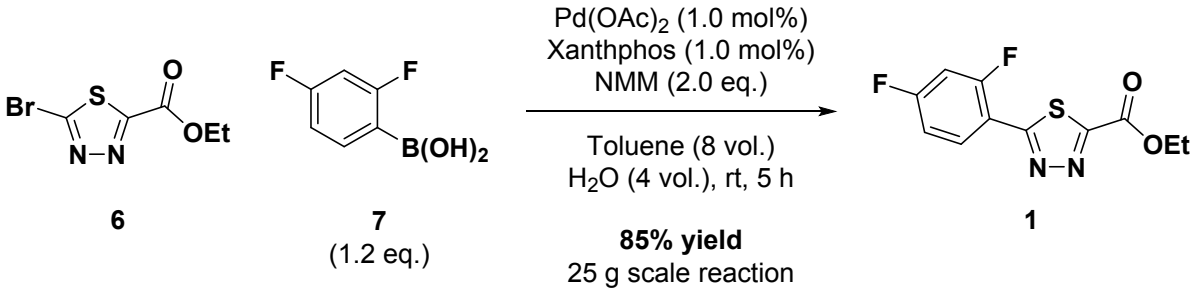
Table 1. Suzuki-Miyaura Coupling Screening at Room Temperature

Entry	Pd/L	Solvent	Base	Conversion[a]	Overall Purity[b]
1	$Pd(dppf)Cl_2$	THF/H_2O	K_3PO_4	66%	28% a/a
2	$Pd(dppf)Cl_2$	THF/H_2O	K_2CO_3	25%	16% a/a
3	$Pd(dppf)Cl_2$	THF/H_2O	Cs_2CO_3	18%	8% a/a
4	$Pd(OAc)_2$/ Xantphos	THF/H_2O	K_3PO_4	>98%	19% a/a
5	$Pd(OAc)_2$/ Xantphos	THF/H_2O	Cs_2CO_3	>98%	47% a/a
6	$Pd(OAc)_2$/ Xantphos	$MeTHF/H_2O$	Cs_2CO_3	>98%	57% a/a
7	$Pd(OAc)_2$/ Xantphos	$toluene/H_2O$	Cs_2CO_3	>98%	77% a/a
8	$Pd(OAc)_2$/ Xantphos	$Toluene/H_2O$	NEt_3	>98%	73% a/a
9	$Pd(OAc)_2$/ Xantphos	$Toluene/H_2O$	NMM	>98%	90% a/a

Conditions: 100 mg **6** (0.42 mmol, 1.0 eq.), **7** (1.2 eq.), base (2.0 eq.), Pd/L (3.0 mol%), organic solvent/H_2O (2:1, 12 vol.), 23 °C. [a]Conversion was judged by consumption of **6** relative to the formation of **1** by LC/MS at 230 nm. [b]Overall purity refers to area/area (a/a)-percentage of **1** in final IPC by LC/MS at 230 nm.

On 25 g scale, the catalyst loading could be further reduced to 1.0 mol% and full conversion was achieved after 5 h at room temperature. After phase split and solvent swap to iPrOH, the product crystallized as off-white crystalline needles. The isolated yield (85%) and purity of the product (99% a/a) were both excellent (Scheme 4).

Scheme 4: Gram-Scale Suzuki Coupling



6

7 (1.2 eq.)

85% yield
25 g scale reaction

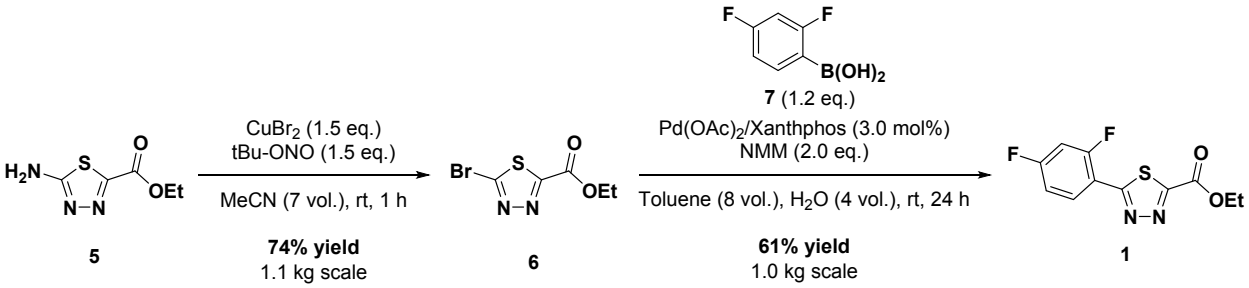
1

SCALE UP. The Sandmeyer reaction performed well on 1.1 kg scale from a conversion and impurity profile point-of-view (Scheme 5). The isolated yield (74%) and purity (96% a/a, 96% w/w) were also in line with the results from small scale trials. However, the aqueous washings proved to be much less effective in removing the excess copper, and

the crystallized product was still intensely yellow and contained 820 ppm Cu. The differences between the copper content of the gram-scale batches and the kg-batch can most likely be explained by different O_2 contents during the aqueous workup when using laboratory or scale up equipment, respectively. On laboratory scale, the presence of oxygen during the workup was most likely sufficient to convert all Cu(I) species into Cu(II). However, in the 30 L reactor in our kilolab the O_2 level is consistently lower - especially during the aqueous workup - and a higher concentration of Cu(I) species are present, which are known to be more challenging to remove by aqueous washings.[11] A Suzuki-Miyaura coupling use test of the material obtained from the kg-run revealed that the conversion was sluggish and additional portions of $Pd(OAc)_2$/Xantphos needed to be added to reach full conversion of **6**. We concluded that interference of residual Cu with the Pd-catalyst system was the most likely reason for the sluggish conversion. Due to the high time pressure on the project, we decided to move on with the scale up, without additional purification of the batch. In addition, by extrapolating the yield from the Suzuki-Miyaura coupling use test, we estimated that we will get more than sufficient material for the production of the preclinical candidate. Not surprisingly, the Suzuki-Miyaura coupling

was very slow on 1.0 kg scale, and we added a total of 3.0 mol% of catalyst to reach full conversion at 20-25 °C after 24 h (Scheme 5). The extended reaction time also led to partial hydrolysis of **6**, and the isolated product yield dropped to 61%. Nevertheless, the amount (0.70 kg) and quality (95% a/a, 96% w/w. Main contaminant was Xantphos: 3.6% a/a) of **1** were sufficient and allowed for the timely production of the final compound.

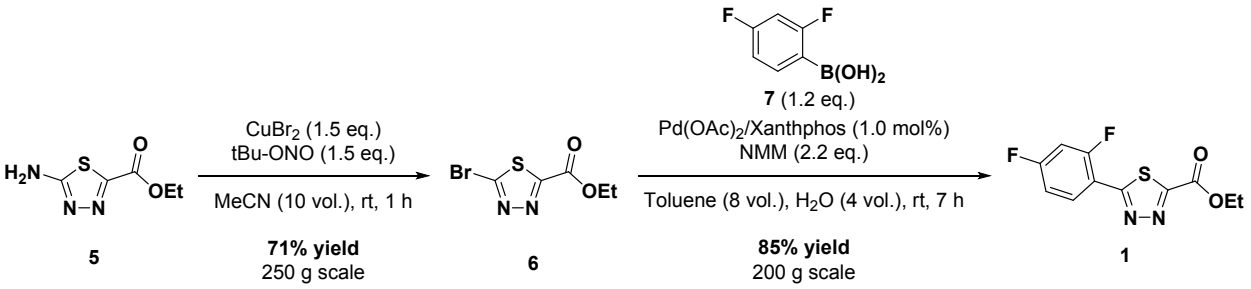
Scheme 5: Kg-Scale Synthesis of **1**



After successful production of the final compound, we went back and improved the isolation and purification procedure of the Sandmeyer reaction. We realized that a simple charcoal treatment dramatically lowered the residual Cu content of the isolated product. Therefore, after completed aqueous workup (an additional brine washing was also implemented), the dark yellow organic phase was circulated through an inline charcoal

cartridge system until the solution was light yellow, followed by crystallization from EtOH/H_2O. Using this procedure on 250 g scale, the isolated product (72% yield, 99% a/a purity, >98% w/w) was now light off-white and residual Cu was found to be 16 ppm. This material performed very well in the Suzuki reaction, and on 200 g scale full conversion could be achieved with 1.0 mol% catalyst after 7 h at room temperature, and the product was isolated as light-yellow needles in high yield (85%) and purity (99% a/a, >98% w/w) (Scheme 6).

Scheme 6: Improved Synthesis of 1 with Charcoal Treatment of 6



CATALYST SYSTEM. We were curious why the $Pd(OAc)_2$/Xantphos catalyst system showed such a remarkable high reactivity in the Suzuki-Miyaura coupling. A recent report by Eastgate and Blackmond on a Pd/Xantphos-catalyzed C–H arylation reaction

suggested that under their reaction conditions, the active ligand was not Xantphos or Xantphos bisphosphine oxide, but the bisphosphine monoxide form of Xantphos (Figure 4).[12] This previously unknown hemilabile, bidentate ligand for palladium was identified by several experiments to be responsible for the catalytic activity. They also proved that addition of excess free Xantphos relative to the Pd-source significantly inhibited the coupling. It was concluded that non-oxidized Xantphos has a higher binding strength to Pd as the bisphosphine monoxide form (and the bisphosphine oxide) and therefore the Pd-centre would be saturated with free Xantphos, resulting in the formation of an inactive catalyst. We observed the same phenomenon: when a 3-fold excess of Xantphos relative to $Pd(OAc)_2$ was used, the reaction basically shut down and only 7% conversion of bromo thiadiazole **6** was obtained after 2 h at room temperature (ca. 20% after 18 h).[13] In addition, analyzing an equimolar mixture of **6**, Xantphos and $Pd(OAc)_2$ in d8-toluene/D_2O/NMM by ^{31}P-NMR showed two phosphorus resonances at 15.7 and 26.7 ppm, which is most likely in accordance with the formation of a highly active Xantphos mono-oxide complex of Pd (X = Br or NMM) in our Suzuki-coupling (signal at 26.5 ppm corresponds to Xantphos bis-oxide).[14]

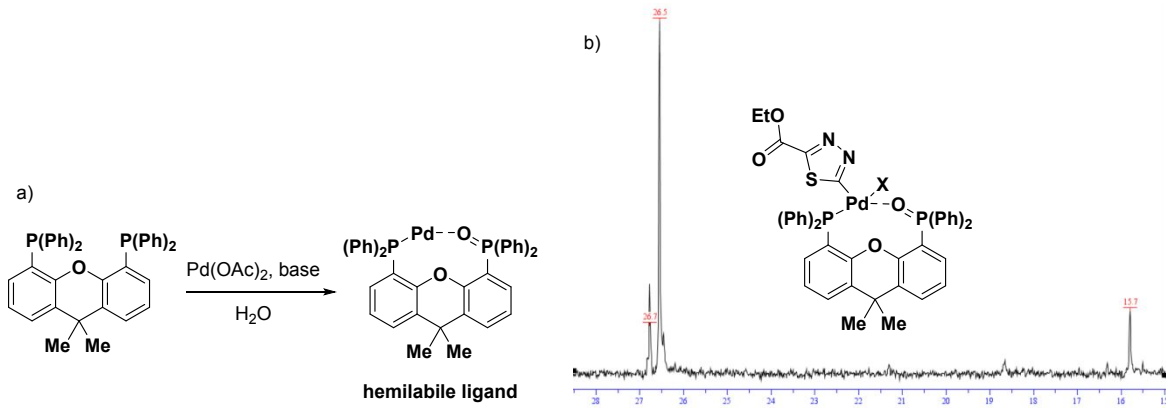


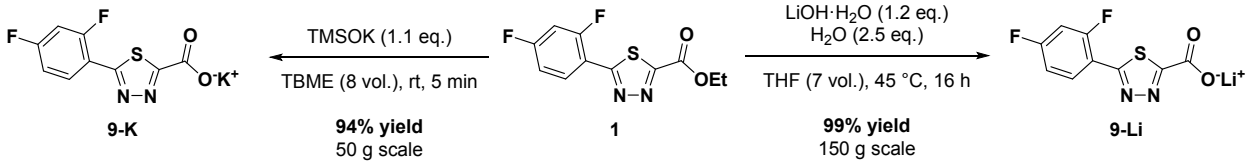
Figure 4: a) Schematic representation of Xantphos mono-oxide as hemilabile ligand. b) ^{31}P-NMR spectrum of proposed Pd-Xantphos mono-oxide complex in Suzuki coupling of **6**.

FORMATION OF CARBOXYLATE SALT. The next synthetic step towards our final compound was an amide coupling on the carboxyl moiety of **1**. As mentioned before, the free acid of **1** was found to be completely unstable and decarboxylated in minutes at room temperature. Therefore, we envisioned two strategies for this key amide bond formation: a) Direct amidation of the ethyl ester, or b) finding a stable carboxylate salt and employ it in the amide coupling. Our medicinal chemistry colleagues found an initial solution by

mixing **1** in THF/aq. NaOH and then removal of the organic solvent and water under reduced pressure to give the stable sodium salt **9-Na**. With regards to a potential scale up, this procedure was not optimal, as the **9-Na** did not crystallize from THF. Therefore, large amounts (> 20 vol.) of an aqueous organic solvent mixture would have needed to be removed to isolate the product. In order to circumvent this problem, we initially found that potassium salt **9-K** was conveniently formed when **1** was treated with potassium trimethylsilanolate (KOTMS) in TBME/THF. The reaction with a THF-solution of KOTMS was dose-controlled and **9-K** crystallized directly from the reaction mixture. However, **9-K** showed poor filterability and was also completely insoluble in any organic solvent and H_2O, and even recording a standard NMR was difficult. Therefore, we turned our attention to the synthesis of lithium salt **9-Li**. After many screenings, we found that the lithium salt could be prepared by heating a THF mixture of **1**, LiOH monohydrate (1.2 eq.) and H_2O (2.5 eq.) to 45 °C. **9-Li** nicely crystallized over the course of the reaction and could be collected by filtration in quantitative yield and excellent purity (>99% a/a) (Scheme 7). This salt form had much better physicochemical properties and nicely dissolved in DMF to successfully perform the subsequent amide coupling. Finally, heavy metal content was

measured for **9-Li**, and without the use of any expensive scavengers during the whole reaction sequence, both residual Pd and Cu were found to be below 10 ppm.

Scheme 7: Formation of **9-K** and **9-Li** Carboxylate Salts.



In summary, a robust and scalable route towards key thiadiazole building block **1** has been developed. In order to avoid the use of Lawesson's reagent on scale in the in-house kilolab, commercially available **5** was converted into the desired product via a sequence of Sandmeyer bromination and Suzuki-Miyaura coupling. Due to the hydrolytic instability of bromo thiadiazole **6** and the propensity of the fluorinated phenylboronic acid **7** to protodeboronate at higher temperature, mild Suzuki-Miyaura coupling conditions needed to be found. Identifying $Pd(OA)_2$/Xantphos as highly active catalyst system, in combination with NMM as mild base, allowed us to perform the key Suzuki-Miyaura coupling at room temperature and to isolate the product in high yield and excellent quality. The residual Cu content in the starting material was crucial for the success of the Suzuki-

Miyaura coupling, as severe catalyst poisoning was observed when the content was too high. Inline charcoal treatment during the workup of the Sandmeyer reaction solved the problem, and the Suzuki-Miyaura coupling reliably worked with this “purified” material, using only 1.0 mol% of catalyst. Finally, due to the instantaneous decarboxylation of free acid **9**, a stable carboxylate salt needed to be found. Lithium carboxylate **9-Li** is a bench-stable solid, which was formed from **1** in THF and LiOH monohydrate and crystallized directly from the reaction mixture.

EXPERIMENTAL SECTION. General information.

All commercially available materials and solvents were used as received. All small scale reaction screenings were performed in 4 mL screw-cap vials under nitrogen atmosphere. All other reactions were run in double-jacketed glass reactors flushed with nitrogen. Reaction temperatures are expressed as ET = external temperature (e.g. reactor jacket) or IT = internal temperature (temperature of reaction mixture). In-process control (IPC) analyses by LC/MS for intermediates and final product were conducted on a Waters

Acquity UPLC instrument using an Agilent Zorbax RRHD SB-aq column (2.1 x 50 mm, 1.8 µm). The mobile phase consisted of two eluents: A:Water/TFA 100:0.04 (v/v) and eluent B: Acetonitrile. For the formation of the carboxylate salt **9-Li**, a basic eluent system was used: Waters BEH C18 column (2.1 x 50 mm, 2.5 µm). The mobile phase consisted of two eluents: A: Water/NH_3 [c(NH_3) = 13 mmol/l] and eluent B: Acetonitrile. ^{1}H NMR and ^{13}C NMR were measured on a Bruker Ultrashield 400 MHz, 101 MHz. ^{19}F NMR spectra were recorded with ^{1}H decoupling in $CDCl_3$ or D_2O referenced to TFA (-76.53 ppm). Chemical shifts are expressed in parts per million (ppm) downfield from residual solvent peaks and coupling constants are reported in Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet. Melting points were determined by differential scanning calorimetry (DSC).

Ethyl 5-bromo-1,3,4-thiadiazole-2-carboxylate (6). A 30 L double-jacketed glass-lined reactor was charged with ethyl 5-amino-1,3,4-thiadiazole-2-carboxylate (**5**) (1.12 kg, 6.47 mol, 1.0 eq.) and $CuBr_2$ (2.20 kg, 9.70 mol, 1.5 eq.). MeCN (7.7 L, 7.0 vol.) was added at IT = 20−25 °C. Then, *tert*-butyl nitrite (1.15 L, 9.70 mol, 1.5 eq.) was added dropwise over

60−90 minutes, keeping IT between 20−33 °C during addition. The reaction mixture was stirred at IT = 20−25 °C for 30 min. A solution of H_3NSO_3 (314 g, 3.23 mol, 0.50 eq.) in H_2O (8.8 L, 8.0 vol.) was added slowly while maintaining IT between 20−30 °C. After complete addition, iPrOAc (9.9 L, 9.0 vol.) was added and the phases were separated. The organic phase was washed twice with 20% aq. NH_4Cl solution (2 x 5.5 L) and once with 15% aq. NaCl (1 x 5.5 L). A slight vacuum was applied to the reactor and the organic phase was concentrated at ET = 75 °C until a minimal stirring volume was reached. Then, EtOH (total amount used for solvent switch: 12.5 L) was continuously added and the distillation continued. Final EtOH content in the reactor after distillation: ca. 5.5 L (5.0 vol.). The mixture was kept at IT = 60−70 °C and H_2O (11 L, 10 vol.) was added over 15 min. The resulting suspension was cooled to IT = 20−25 °C over 1 h and then aged at IT = 20−25 °C for 1 h. The solid was collected by filtration, washed with H_2O (3 x 2 L) and then dried at 65 °C under vacuum for 5 h to give **6** (1.13 kg, 4.76 mol, 74% yield) as a dark yellow crystalline solid. LC/MS purity: 96% a/a. m.p. 81 ºC (DSC); ^{1}H NMR (400 MHz, d6-DMSO) 4.43 (q, *J* = 7.0 Hz, 2H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz,

d6-DMSO) 163.6, 157.1, 144.7, 63.2, 39.5, 13.9. HRMS (ESI) m/z calcd for $C_5H_6N_2O_2BrS$ ($[M+H]^+$): 236.9328. Found: 236.9333.

Ethyl 5-(2,4-difluorophenyl)-1,3,4-thiadiazole-2-carboxylate (1). A 30 L double-jacketed glass-lined reactor was charged with ethyl 5-bromo-1,3,4-thiadiazole-2-carboxylate (**6**) (1.0 kg, 4.22 mol, 1.0 eq.), 2,4-difluorophenylboronic acid (0.80 kg, 5.06 mol, 1.2 eq.), $Pd(OAc)_2$ (18.9 g, 84.4 mmol, 2.0 mol%) and Xantphos (48.8 g, 84.4 mmol, 2.0 mol%). A solution of NMM (0.94 L, 8.44 mol, 2.0 eq.) in toluene (8 L, 8.0 vol.) was added at IT = 20−25 °C, followed by addition of H_2O (4 L, 4.0 vol.). The reaction mixture was strongly stirred (250 rpm) at IT = 20−25 °C for 10 h, after which a second portion of $Pd(OAc)_2$ (9.47 g, 42.2 mmol, 1.0 mol%) and Xantphos (24.4 g, 42.2 mmol, 1.0 mol%) was added. The reaction mixture was continued to be stirred (250 rpm) at IT = 20−25 °C for 14 h. Then, iPrOAc (2.5 L, 2.5 vol.) was added and the phases were separated. The aqueous phase was extracted once with iPrOAc (5.0 L, 5.0 vol.). The combined organic phases were recharged to the reactor, a slight vacuum was applied and the organic phase concentrated at ET = 80 °C until a minimal stirring volume was reached. Then, iPrOH

(total amount used for solvent switch: 15 L) was continuously added and the distillation continued. Final iPrOH content in the reactor after distillation: ca. 7 L (7.0 vol.). The mixture was kept at IT = 65−75 °C and then slowly cooled to IT = 20−25 °C over 2 h. The resulting suspension was aged for an additional hour at IT = 20−25 °C. The solid was collected by filtration, washed with iPrOH (3 x 1 L) and dried at 65 °C under vacuum for 3 h to give **1** (0.70 kg, 2.59 mol, 61% yield) as yellow crystalline needles. LC/MS purity: 96% a/a. m.p. 122 ºC (DSC); ^{1}H NMR (400 MHz, d6-DMSO) 8.42 (q, *J* = 7.8 Hz, 1H), 7.66 (m, 1H), 7.39 (m, 1H), 4.45 (q, *J* = 7.0 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 165.1 (dd, *J* = 257, 12 Hz), 163.5 (dd, *J* = 8, 1 Hz), 160.6 (d, *J* = 5 Hz), 160.6 (dd, *J* = 256, 12 Hz), 158.8, 130.9 (dd, *J* = 10, 3 Hz), 114.3 (dd, *J* = 12, 4 Hz), 113.0 (dd, *J* = 22, 3 Hz), 104.8 (t, *J* = 26 Hz), 63.4, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) -102.60 (d, *J* = 11.1 Hz), -106.03 (d, *J* = 11.1 Hz). HRMS (ESI) m/z calcd for $C_{11}H_9F_2N_2O_2S$ ($[M+H]^+$): 271.0347. Found: 271.0350.

Ethyl 5-bromo-1,3,4-thiadiazole-2-carboxylate (6). Procedure with charcoal treatment: a 10 L double-jacketed glass reactor was charged with ethyl 5-amino-1,3,4-thiadiazole-

2-carboxylate (**5**) (250 g, 1.44 mol, 1.0 eq.) and $CuBr_2$ (484 g, 2.17 mol, 1.5 eq.). MeCN (2.5 L, 10 vol.) was added at IT = 20−25 °C. Then, *tert*-butyl nitrite (260 mL, 2.17 mol, 1.5 eq.) was added dropwise over 45−60 minutes, keeping IT between 20−33 °C during addition. The reaction mixture was stirred at IT = 20−25 °C for 60 min. A solution of H_3NSO_3 (86.1 g, 0.866 mol, 0.60 eq.) in H_2O (2.5 L, 10 vol.) was added slowly while maintaining IT between 20−30 °C. After complete addition, iPrOAc (2.5 L, 10 vol.) was added and the phases were separated. The organic phase was washed twice with 20% aq. NH_4Cl solution (2 x 1.25 L) and twice with 15% aq. NaCl (2 x 1.25 L). The organic phase was circulated through an inline charcoal filter system from 3M (ZetaCarbon R55SP) until the aspect was light yellow (ca. 30 min circulation time). A slight vacuum was applied to the reactor and the organic phase was concentrated at ET = 75 °C until a minimal stirring volume was reached. Then, EtOH (total amount used for solvent switch: 3.0 L) was continuously added and the distillation continued. Final EtOH content in the reactor after distillation: ca. 1.25 L (5.0 vol.). The mixture was kept at IT = 60−70 °C and H_2O (2.5 L, 10 vol.) was added over 15 min. The resulting suspension was cooled to IT = 20−25 °C over 1 h and then aged at IT = 20−25 °C for 1 h. The solid was collected by

filtration, washed with H_2O (3 x 0.5 L) and dried at 65 °C under vacuum for 3 h to give **6** (247 g, 1.04 mol, 72% yield) as a light off-white crystalline solid. LC/MS purity: 99% a/a.

Ethyl 5-(2,4-difluorophenyl)-1,3,4-thiadiazole-2-carboxylate (1). A 10 L double-jacketed glass reactor was charged with ethyl 5-bromo-1,3,4-thiadiazole-2-carboxylate (**6**) (200 g, 0.844 mol, 1.0 eq.), 2,4-difluorophenylboronic acid (160 g, 1.01 mol, 1.2 eq.), $Pd(OAc)_2$ (1.89 g, 8.44 mmol, 1.0 mol%) and Xantphos (4.88 g, 8.44 mmol, 1.0 mol%). A solution of NMM (204 mL, 1.86 mol, 2.2 eq.) in toluene (1.6 L, 8.0 vol.) was added at IT = 20−25 °C, followed by addition of H_2O (0.8 L, 4.0 vol.). The reaction mixture was strongly stirred (300 rpm) at IT = 20−25 °C for 7 h. Then, iPrOAc (0.6 L, 3.0 vol.) was added and the phases were separated. The aqueous phase was extracted once with iPrOAc (1.0 L, 5.0 vol.). The combined organic phases were recharged to the reactor, a slight vacuum was applied and the organic phase concentrated at ET = 80 °C until a minimal stirring volume was reached. Then, iPrOH (total amount used for solvent switch: 4 L) was continuously added and the distillation continued. Final iPrOH content in the reactor after distillation: ca. 1.2 L (6.0 vol.). The mixture was kept at IT = 65−75 °C and then slowly cooled to IT =

20−25 °C over 2 h. The resulting suspension was aged for an additional hour at IT = 20−25 °C. The solid was collected by filtration, washed with iPrOH (2 x 0.4 L) and dried at 65 °C under vacuum for 3 h to give **1** (193 g, 0.714 mol, 85% yield) as light-yellow crystalline needles. LC/MS purity: 99% a/a.

Lithium 5-(2,4-difluorophenyl)-1,3,4-thiadiazole-2-carboxylate (9-Li). A 4 L double-jacketed glass reactor was charged with ethyl 5-(2,4-difluorophenyl)-1,3,4-thiadiazole-2-carboxylate (**1**) (150 g, 0.555 mol, 1.0 eq.) and THF (1.05 L, 7.0 vol.). LiOH monohydrate (27.9 g, 0.666 mol, 1.2 eq.) and H_2O (25 mL, 1.39 mol, 2.5 eq.) were added and the reaction mixture heated to IT = 43−45 °C and stirred for 24 h. The reaction mixture turned from a clear solution into a suspension over the course of the reaction. The resulting suspension was cooled to IT = 20−25 °C and was aged for 1 h at this temperature. The solid was collected by filtration, washed with THF (2 x 0.25 L) and dried at 65 °C under vacuum for 3 h to give **9-Li** (138 g, 0.555 mol, quantitative yield) as an off-white crystalline solid. LC/MS purity: >99% a/a. m.p. 155 ºC (DSC); ^{1}H NMR (400 MHz, D_2O) 7.74 (m, 1 H), 6.89 (m, 2H); ^{13}C NMR (101 MHz, D_2O) 168.0 (d, J = 5 Hz), 164.6 (dd, J = 254, 13

Hz), 163.7 (d, J = 8 Hz), 162.9, 159.4 (dd, J = 254, 13 Hz), 129.7 (dd, J = 10, 3 Hz), 113.0 (m), 112.8 (m), 104.8 (t, J = 26 Hz). ^{19}F NMR (376 MHz, D_2O) -103.27 (d, J = 11.1 Hz), -105.95 (d, J = 11.1 Hz). HRMS (ESI) m/z calcd for $C_9H_5F_2N_2O_2S$ ($[M+H]^+$): 243.0034. Found: 243.0038. Mass of carboxylic acid detected, together with decarboxylated fragment.

ASSOCIATED CONTENT

Supporting Information. Analytical data for compounds **1**, **6** and **9-Li** (NMR and DSC).

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