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Development of an Alternate Synthesis for a Key JAK2 Inhibitor Intermediate via Sequential C−H Bond Functionalization

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Supporting Information

ABSTRACT: The development of an alternative synthetic route to a functionalized imidazopyridazine which strategically streamlines the synthesis and avoids a number of problematic reagents is described. Key to the success of this alternative route is the use of two C−H functionalization reactions: a Pd-catalyzed direct benzylation reaction to functionalize a C−H bond with a substituted benzyl group and a V-catalyzed NMO addition reaction to install a benzylic morpholine moiety.

INTRODUCTION

Myeloproliferative disorders are a group of blood cell cancers in which the bone marrow cells that produce the body's blood cells develop and function abnormally; these chronic disorders are associated with splenomegaly and the development of leukemia.[1] LY2784544 (**1**) has been identified as a highly selective inhibitor of JAK2-V617F, the most common molecular abnormality found in BCR/ABL-negative myeloid proliferative neoplasms,[2] and is currently undergoing clinical trials for the treatment of several myeloproliferative disorders.[3] A practical synthesis of **1** has been previously reported and is shown in Scheme 1.[4] Several liabilities were identified in this synthesis, particularly en route to the key late-stage intermediate **2**. First, the amino acetal used to form the pyridazine framework (step 1) was not readily available. Long lead times were required to secure the desired amounts for active pharmaceutical ingredient (API) synthesis campaigns, and a wide range of purity profiles were observed due to residual methanol.[5] Second, the ketone deoxygenation step, which utilized trifluoroacetic acid (TFA) and triethylsilane, was a liability from a waste disposal perspective. Incineration of fluoride-containing waste is known to corrode waste incinerators and reduces the useful life of incinerator refractory brick.[6,7] Silicon dioxide which results from triethylsilane incineration leads to particulate agglomeration on the heat transfer media of regenerative thermal oxidizers.[8] The challenges associated with the route shown in Scheme 1 led us to pursue a diverse, alternative synthesis to access **2** which avoids the use of the undesirable TFA and silane reagents and shares no common intermediates with the previous route. We report herein our efforts directed toward the development of a new synthetic route to **2**.

RESULTS AND DISCUSSION

Overview of Targeted Route. The route selection and development described in this report were focused on the following two key retrosynthetic disconnections of **2**: at the benzylic morpholine substituent and at the benzyl moiety (Scheme 2). Installation of the benzylic morpholine moiety onto the 8-position of the imidazopyridazine core had been a historically challenging component of the synthesis. A vanadium-catalyzed NMO addition reaction was previously developed to install this functionality (Scheme 1, step 4),[4] and in our current synthesis, we sought to implement a similar set of conditions.

We envisioned installing the benzyl group of **2** in one of two ways: either via a direct C−H benzylation reaction or by a decarboxylative benzylation. The efficiency and high-atom economy of these metal-catalyzed transformations made them attractive approaches. While both direct[9] and decarboxylative couplings[10] have received considerable attention in the literature as atom-economical means of achieving sp^2−sp^2 bond formation (e.g., direct arylation), sp^2−sp^3 coupling reactions are notably more scarce.[11,12] However, we believed that one of these methods could serve as a viable and efficient means of installing the benzylic functionality, and the development of this approach is discussed herein.

As exemplified in Scheme 2, there are several possible orders in which the key steps can be performed. The final order of the steps was the result of analyzing several possible substrates for each reaction with a focus on maximizing the yield, product quality, and manufacturability of **2**. The development of each step is discussed in turn, and considerations related to route selection (e.g., yield, impurity control, scalability) are detailed.

Imidazopyridazine Formation. Construction of the 6-chloro-2-methyl-imidazopyridazine core can be accomplished through the coupling of 3-amino-6-chloropyridazine (**3**) with either chloroacetone (*CAUTION: highly irritating and a strong lachrymator*) or ethyl 2-chloroacetoacetate to give **4** or **5**, respectively (Scheme 3).[13] The literature reports on formation of these imidazopyridazines are plagued by low yields and poor conversion of the starting materials.[14] A broad screen of solvents revealed that DMF, MeCN, and EtOH each gave the desired product in ∼50% yield.[15] Further improvement to the yield was realized by the addition of substoichiometric NaBr and several equivalents of H_2O to reactions run in DMF (Table 1).[16] The use of such additives in MeCN or EtOH did not

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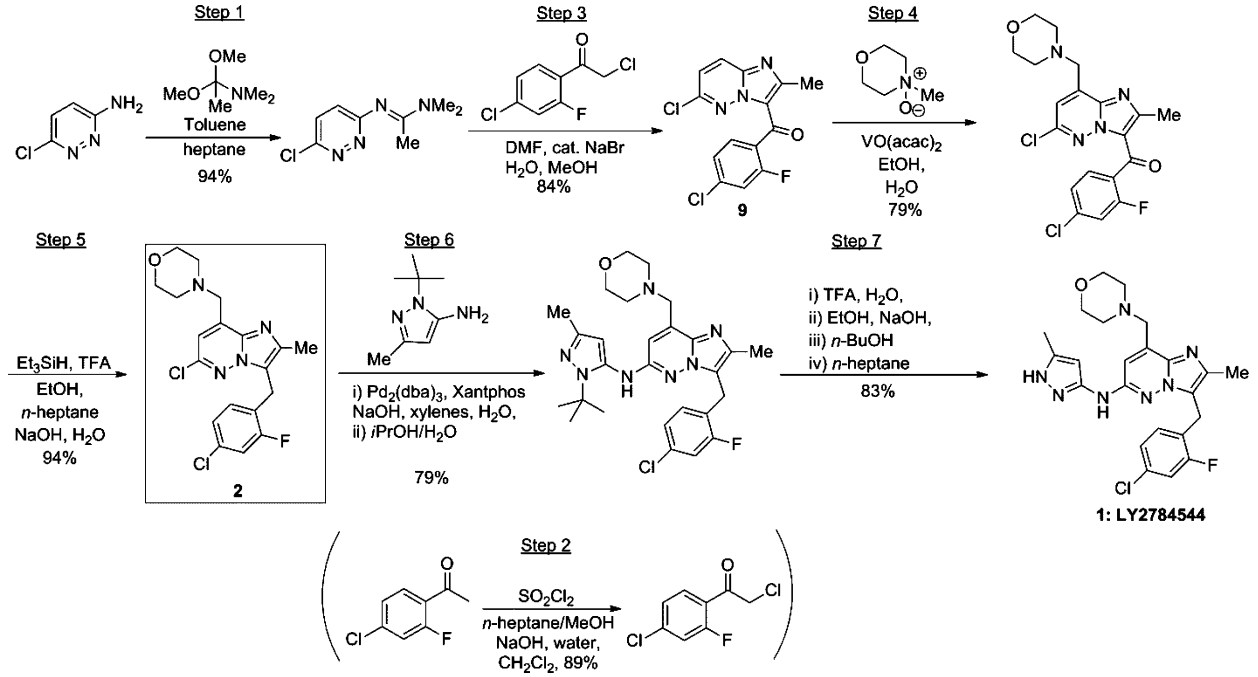
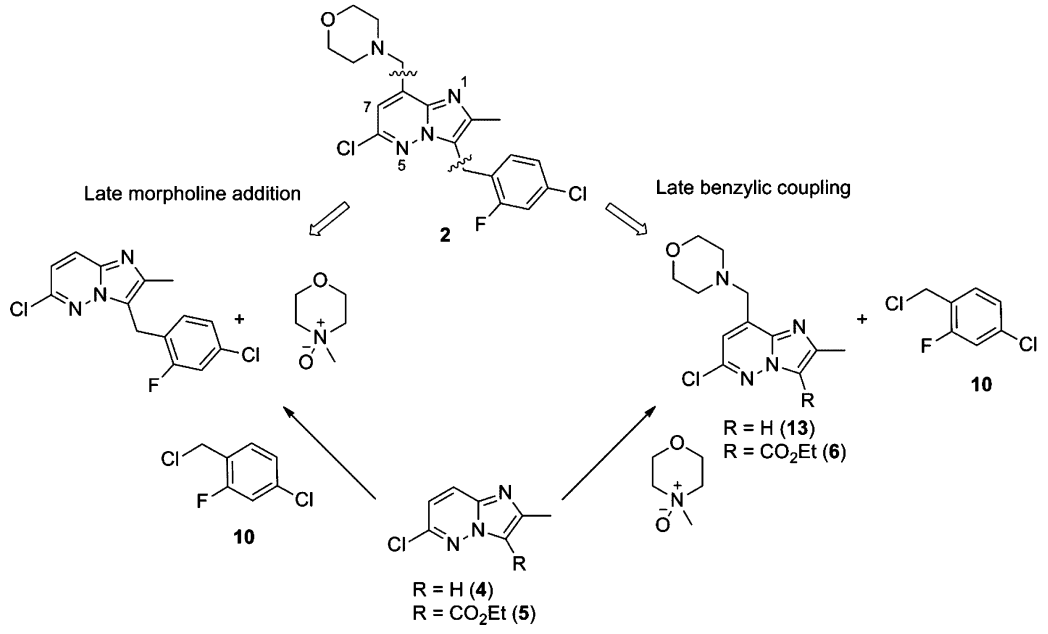
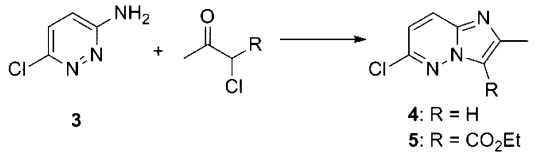
Scheme 1. Route to LY2784544



Scheme 2. Key retrosynthetic disconnections of 2



Scheme 3. Synthesis of imidazopyridazine



result in similar improvements to the reaction yield (Table 1, entries 1−2).

Optimized conditions employed 0.7 equiv NaBr and 4 equiv H_2O in DMF and achieved 91% conversion of **3** (Table 1, entry 7). Addition of water to the crude reaction mixture, isolation of

Table 1. Additive effects on the synthesis of 5 from 3 and ethyl 2-chloroacetoacetate

entry	solvent	NaBr (equiv)	H_2O (equiv)	5[a] (%)
1	MeCN	1.2	1.7	52
2	EtOH	1.2	3.4	51
3	DMF	–	–	52
4	DMF	1.2	–	66
5	DMF	–	4	73
6	DMF	1.2	4	84
7	**DMF**	**0.7**	**4**	**91**

[a]HPLC area %.

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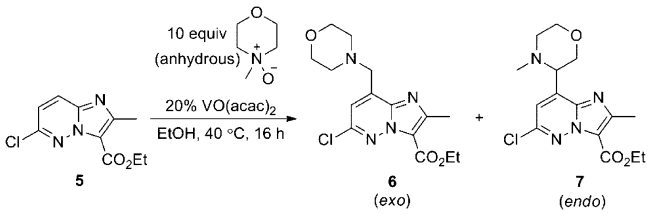
the resulting solids, and crystallization from ethyl acetate/*n*-heptane resulted in isolation of **5** in 62% yield and with 99.3% relative HPLC area. Similar conditions were applied to the synthesis of **4**, but the reaction was not clean with only 60% formation of the desired product and only a 41% isolated yield. Although the use of **4** eliminates a decarboxylation step downstream, **5** was the preferred intermediate since the yield was higher and chloroacetone was eliminated. Additionally, the presence of the electron-withdrawing ester group improved reactivity in downstream chemistry (vide infra).

Installation of Benzylic Morpholine. Installation of the benzylic morpholine functionality had been historically challenging, and the development of a $VO(acac)_2$-catalyzed NMO addition reaction in the previous route to **2** greatly facilitated this functionalization (Scheme 1, step 4).[4] On the basis of previous success with the $VO(acac)_2$-catalyzed process, we sought to develop a similar process for functionalization of **5**. Starting with analogous conditions, treatment of **5** with 10 equiv anhydrous NMO and 20 mol % $VO(acac)_2$ in EtOH at 40 °C led to 73% conversion of the starting material but surprisingly gave a 3:1 mixture of the *exo* and *endo* addition products (respectively **6** and **7**, Scheme 4).[17] In an effort to

Scheme 4. Vanadium-catalyzed NMO addition reaction



improve both reaction yield and selectivity for the desired *exo* product **6**, various reaction parameters were screened. Incremental improvements in selectivity could be made by altering the reaction concentration in ethanol (15 vol EtOH, 3:1; 20 vol EtOH, 4.1:1 ratio of **6**:**7**), but changes to reaction time, temperature, solvent, catalyst, and additives failed to improve the reaction conversion or selectivity.[18] Success in affecting the *exo*:*endo* selectivity toward the desired product could be achieved by slow addition of the NMO. Maximum selectivity for the *exo* product (5.9:1) was achieved by addition of 15 equiv NMO over 18 h, but the reaction was sluggish, requiring 43 h to reach 93% conversion of starting material.[19]

While these conditions provided a small-scale solution to install the benzylic morpholine, the continued use of anhydrous solid NMO was not viewed as an acceptable long-term approach. Due to its large-scale commercial use in the Lyocell process,[20] the 50 wt % aqueous solution of NMO is more readily available and less expensive than anhydrous NMO. The high stoichiometry of NMO required in the transformation led to efforts to develop a system which used NMO as a 50 wt % aqueous solution. In EtOH, the reaction was poor when aqueous NMO was used, stalling at 40% conversion. During a solvent screen with anhydrous NMO, a particularly fast transformation in dimethylacetamide (DMAc) had been previously noted. Replacing anhydrous NMO with aqueous NMO in a DMAc solvent led to 55% conversion in 16 h; however, the selectivity for the desired isomer was poor (1.9:1 of **6**:**7**). Adding 1,2-propanediol as a cosolvent and implementing the NMO slow addition protocol used in the EtOH system (vide supra), the selectivity of the reaction could be improved to 9:1 using a 9 h addition time. Although the reaction times were long (48 h) and conversion reached only 88%, **6** with 96% relative HPLC area could be crystallized from the crude reaction mixture by addition of water, albeit in ∼45% yield. Unfortunately, DMAc appears to be uniquely successful in facilitating the transformation in the presence of aqueous NMO. While DMAc has been historically considered an undesirable but acceptable solvent, there is now growing concerns associated with its use, particularly in the European Union (EU) where it has been identified as a substance of very high concern (SVHC) and is now a candidate on the REACH list.[21] Given the incomplete conversion, very long reaction time, and concerns associated with the use of DMAc, we turned our attention to developing an alternative, cost-efficient source of anhydrous NMO.

In order to utilize the inexpensive and widely available 50% aqueous solution of NMO, a dehydration method was necessary to satisfy the requirements of the chemistry. Azeotropic water removal from a refluxing biphasic mixture of NMO and toluene under reduced pressure (130 mmHg) was effective in removing the water level near that of the monohydrate, but the resultant monohydrate crystallized as a solid mass (mp 76−78 °C) during the reflux, and removal of the water below the monohydrate level proved to be impossible with this technique.[22] Azeotropic water removal using alcoholic solvents (EtOH, *i*-PrOH, *n*-PrOH, *n*-BuOH) was an improvement over toluene because the polar solvent was able to keep the *N*-oxide in solution; however, these solvents were similarly unable to remove water below the monohydrate level.

Subsequent investigation focused on the direct distillation of water after addition of a cosolvent with a very high boiling point that would be able to provide ample hydrogen bonding for the strongly polar *N*-oxide. Preliminary studies utilized one equivalent of ethylene glycol relative to NMO and were simply performed on a rotary evaporator at full house vacuum (∼20 mbar) and 80 °C. These studies showed great promise, but a switch to propylene glycol (PG) solvent was made due to toxicity concerns over the large-scale use of ethylene glycol. Larger-scale batch distillations of water showed the tendency for the NMO solution to become darker in color upon prolonged heating, and there was some concern over the large-scale high-temperature distillation for safety reasons, despite a measured decomposition onset temperature of >140 °C. This prompted us to investigate a continuous method for the dehydration, which could utilize a short contact time of the hydrated solution to a high temperature.

Wiped-film evaporation (WFE) was identified as a suitable technology for this application. Initial studies were highly successful, and it was rapidly determined that house vacuum (∼20 mbar), a WFE jacket temperature of 100−110 °C, and a flow rate of ∼1600 mL/h were suitable conditions for the dehydration of aqueous NMO to which one equivalent of PG (relative to NMO) had been added.[23] This method of distillation minimized color formation while producing a very consistent water level (2−4% by KF). The NMO in PG produced in this manner was found to perform in the reaction as well as or better than solid "anhydrous" NMO (in EtOH, 97% conversion, 3.1:1 ratio of **6**:**7**).[24] This was viewed as an easily scalable operation with minimal engineering requirements and was used to prepare >75 kg of the NMO in PG solution, which assayed at 59−62 wt % NMO by Q-NMR. We believe that both the hydrogen bond-donating ability of the PG

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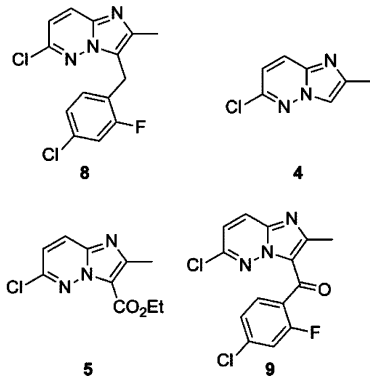
and the high temperature during the WFE are responsible for the successful dehydration of NMO.

Again taking advantage of the improvement in selectivity when NMO is added slowly to the reaction, an 18 h addition of 13 equiv of 60 wt % NMO in PG to a solution of **5** and 20 mol % $VO(acac)_2$ in EtOH resulted in installation of the benzylic morpholine functionality with >95% conversion of SM and an 11:1 ratio of **6**:**7** in 48 h. Addition of water to the crude reaction mixture led to an efficient crystallization of the desired product which could be isolated with good purity (97.5%). The major impurities were starting material (**5**) and the *endo* isomer (**7**), which were rejected in downstream isolations. Vanadium was well rejected (<10 ppm). This reaction was successfully carried out on a 400 g scale with 55% yield and 97.2% relative HPLC area of the isolated material. The main impurities were **5** (0.4%) and **7** (0.6%).

It should be noted that two other substrates were considered in the development of this step as a means of ultimately accessing **2**. However, functionalization of either **8** or **4** (Chart 1) gave incomplete conversion of starting material and required

Chart 1. Substrates for the V-catalyzed NMO addition reaction

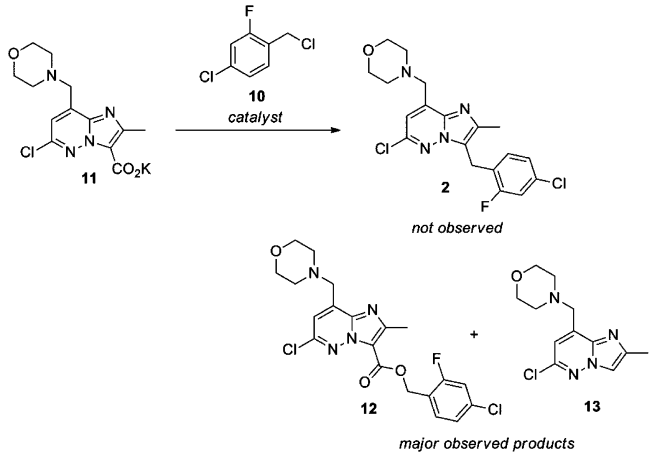


longer reaction times and higher stoichiometry of NMO. The data at hand suggest that substrates with electron-withdrawing groups in the 3-position (e.g., **5** and **9**) are more reactive in the V-catalyzed NMO addition reaction than substrates without electron-withdrawing groups in the same position (**8** and **4**). Given the improved reactivity of **5** as well as the benefits of having an ester group present in the synthesis of the imidazopyridazine core (**4** vs **5**), we chose to pursue development of **5** and **6**.

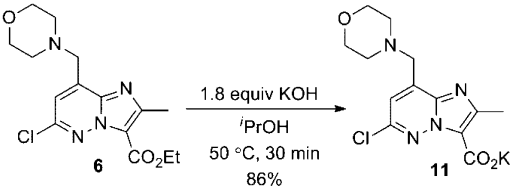
Decarboxylation. Early efforts to complete the synthesis of **2** focused on a decarboxylative coupling between the potassium salt of **6** (**11**) and benzyl chloride **10** (Scheme 5). Although successful decarboxylative aryl (sp^2–sp^2) couplings have been reported in the literature,[10] there are no reported examples of intermolecular decarboxylative benzylations of heteroarenes.[12] However, because of the high efficiency such a transformation would afford to our process, we explored the reactivity of our imizadopyridazine under decarboxylative conditions.

Saponification of **6** under basic conditions readily afforded the potassium salt **11** (Scheme 6). Treatment of **11** with benzyl chloride **10** in the presence of monometallic Pd-catalyst systems[25] led to exclusive formation of the benzyl ester (**12**, Scheme 5). Even under harsh conditions (150–200 °C), the benzyl ester did not decarboxylate. Bimetallic systems containing a Pd-catalyst together with catalytic or stoichio-

Scheme 5. Attempted decarboxylative coupling to form 2



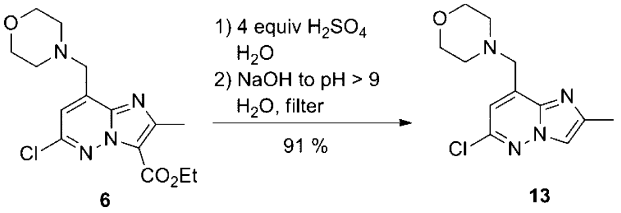
Scheme 6. Saponification of 6



metric Cu or Ag have been more commonly reported in the decarboxylative coupling literature.[26] Unfortunately, in this case, the bimetallic systems led to mixtures which largely contained decarboxylated starting material (**13**) and benzyl ester, **12**, and only traces of **2**.

In order to pursue direct C–H benzylation as an alternate way of accessing **2**, acid hydrolysis and decarboxylation of the ester group of **6** were carried out. This transformation was quite straightforward and involved treatment of an aqueous suspension of **6** with 4 equiv H_2SO_4 for 24 h at reflux followed by neutralization and isolation of the resulting precipitate which afforded **13**. The reaction was carried out on a 165 g scale to give **13** in 91% yield with 99% relative HPLC area. (Scheme 7).

Scheme 7. Decarboxylation of 6



Palladium-Catalyzed Direct Benzylation. Key to the design of the aforementioned route was the use of a Pd-catalyzed direct benzylation to install the benzylic functionality at the C-3 position on the imidazopyridazine. While direct arylation of C–H bonds has received extensive attention in the recent literature as an efficient, atom-economical method of cross-coupling,[9] direct benzylation reactions are notably more scarce.[11] However, the success of direct benzylation reactions, particularly on heterocyclic substrates, suggested that the desired transformation may be obtainable under the right conditions. An additional challenge in designing any C–H activation process is the presence of multiple C–H bonds in

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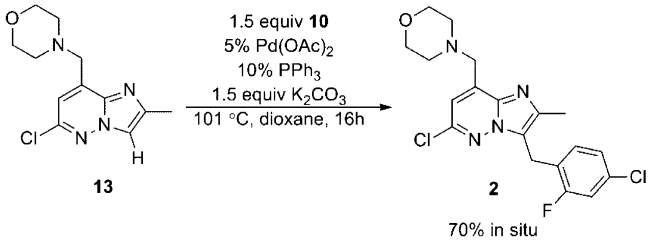
the substrate. In the case of **13**, we hypothesized that the more nucleophilic C-3 position would preferentially undergo the desired activation and reaction.[27]

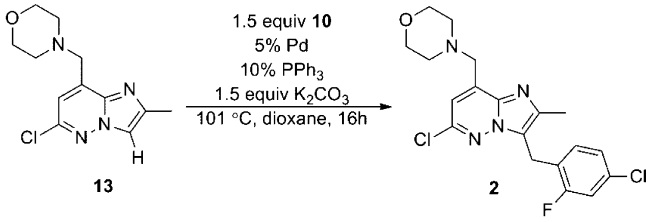
Preliminary screening of reaction conditions in 1,4-dioxane indicated that C−H activation of **13** did occur and was exclusive to the C-3 position. A wide range of ligands and bases were screened,[28] and results indicated that PPh_3 was the optimal ligand and that K_2CO_3 was a superior choice of base for the reaction (Scheme 8).

Scheme 8. Palladium-catalyzed direct benzylation



A broader screen of Pd sources led to insight into the mechanism of C−H activation (Table 2) which in this case can

Table 2. Palladium source screening for the synthesis of 2

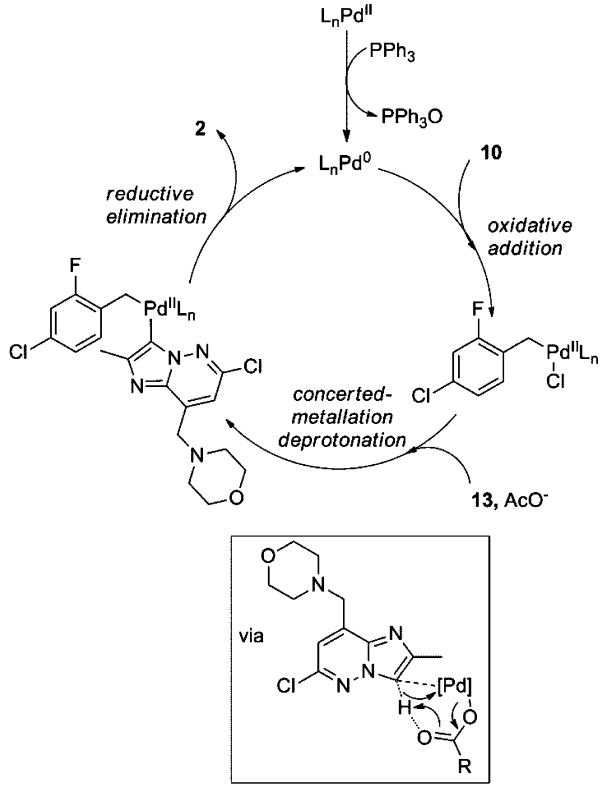


entry	Pd source	additive	2[a] (%)
1	$Pd(OAc)_2$	none	70
2	$Pd(TFA)_2$	none	33
3	$Pd(OPiv)_2$	none	51
4	$PdCl_2$	none	19
5	$PdCl_2$	10% NaOAc	70
6	Pd_2dba_3	none	4
7	Pd_2dba_3	10% NaOAc	60
8	$(PPh_3)_4Pd$[b]	none	24
9	$(PPh_3)_4Pd$[b]	10% NaOAc	56

[a]Based on HPLC wt % of **2**. [b]No additional PPh_3 was added. Separate control experiments indicated that, after 16 h, up to a 6-fold excess of PPh_3 relative to Pd had no effect on the reaction.

be well-rationalized within the context of a concerted metalation deprotonation (CMD) mechanism (Scheme 9).[29] CMD is commonly proposed in the recent C−H activation literature and requires the presence of a basic, anionic ligand on the palladium center capable of assisting in the deprotonation of the C−H bond. Examining the present data (Table 2), $Pd(TFA)_2$ was clearly inferior to $Pd(OAc)_2$, likely because the TFA anion is less basic. $Pd(OPiv)_2$ performed moderately well and led to only a slightly lower yield than $Pd(OAc)_2$. Palladium sources which did not contain a basic anionic ligand (Table 2, entries 4, 6, and 8) gave low yields of **2**. However, when these catalysts were used in combination with 10% NaOAc (2 equiv relative to Pd), the reactions performed nearly as well as when $Pd(OAc)_2$ was used as the catalyst, emphasizing the importance of the basic, anionic ligand.[30] Interestingly, replacement of the

Scheme 9. Proposed mechanism for the formation of 2 from 10 and 13



stoichiometric base, K_2CO_3, with NaOAc led to almost no product formation (4% as compared to 70%), likely due to poisoning of the Pd center with excess acetate. In fact, even the addition of catalytic PivOH (10 or 30 mol %), which has been shown to be beneficial in promoting some CMD reactions,[31] was detrimental in this case, resulting in a decrease in the in situ yield from 70% to 38%. Clearly, the reaction is highly sensitive to the stoichiometry of carboxylate ligands.

Although the $Pd(OAc)_2/PPh_3/K_2CO_3$/dioxane system identified through the screening reaction detailed above did provide an appreciable amount of desired product, the reaction stalled at 70% yield and 85% conversion of **13** and did not proceed further with longer reaction times (up to 72 h) even though both starting materials remained; such a scenario suggested catalyst decomposition. Increasing the catalyst loading to 10 mol % led to complete consumption of **13**, but the in situ yield of **2** remained 70% due to increased formation of a number of byproducts. The mechanism of the catalyst deactivation remains unclear at this point. Experiments in which product and impurity-rich filtrate were spiked into a catalytic reaction showed no difference in the reaction performance (Figure 1), suggesting that catalyst poisoning does not occur by simple coordination of a reaction product or byproduct to the Pd center.

Another notable concern with the process was the use of dioxane, a suspect carcinogen,[32] as the solvent. In an effort to both replace dioxane and improve the overall yield of the reaction, a number of alternative reaction solvents (toluene, CPME, *t*-AmOH, THF, 2-MeTHF, anisole, MTBE, 2-BuOH, DME, diglyme; see Table S6 in Supporting Information) were screened. Unfortunately, no improvement in yield was

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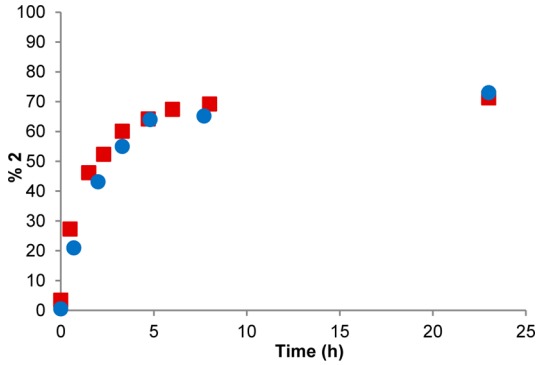

Figure 1. Reaction time course for the conversion of **13** to **2** for a reaction run under standard conditions (red ■) or with impurity-rich filtrate added (blue ●).

achieved, although anisole, with 61% yield, showed promise as a suitable replacement for dioxane.

Product Isolation. We next turned our attention to isolation of **2** from the crude reaction mixture. Addition of toluene and water to the crude reaction followed by addition of concentrated HCl to pH <0.5 led to a scenario in which compounds containing the imidazopyridazine core were protonated and in the aqueous phase, whereas nonbasic impurities (**10**, PPh_3O, etc.) were readily removed by separation of the organic layer and repeated washing of the acidic aqueous layer with toluene. Subsequent adjustment of the pH of the aqueous solution to ∼1.0 allowed for direct crystallization of **2** as the HCl salt with good rejection of remaining **13**. Freebasing of the HCl salt in 2-MeTHF/H_2O followed by a toluene/heptane crystallization allowed for isolation of **2** in 50% yield with 96.9% relative HPLC area when the reaction was carried out on a 235 g scale (Scheme 8). This material was carried on to prepare **1** with quality comparable to that of material prepared via the route in Scheme 1.

■ CONCLUSIONS

In summary, a synthesis for **2** was developed (Scheme 10) which avoids the major challenges associated with the previous route, namely fluoride and silane waste incineration (Scheme 1). Furthermore, using the route described in this report, the synthesis of the imidazopyridazine core is accomplished in a single step and circumvents the use of the amino acetal (Scheme 1, step 1) which had required long lead times to secure. The Pd-catalyzed direct benzylation is one of the most complex examples of this type of reaction reported to date and exemplifies the potential of this powerful but underdeveloped methodology as well as its scalability. The route described in this report shares no common intermediates with the previous route and is one step shorter. However, while there are several key advantages to the route described in this report, because several of the steps have only moderate yields, the overall yield is lower than that of the previous route (16% vs 35%).[4] The demonstrated synthesis offers future suppliers of our key building block an alternative for manufacture, and continued reaction optimization and development, particularly to the vanadium- and palladium-catalyzed steps, may help to realize a more competitive route.

■ EXPERIMENTAL SECTION

General Considerations. Reactions were monitored by reverse-phase HPLC using a Zorbax SB-C18 4.6 mm × 75 mm column with 3.5 μm particle size. Solvent A was a 0.1% solution of TFA in water, and solvent B was a 0.1% solution of TFA in CH_3CN. The flow rate was 1.0 mL/min with a column temperature of 40 °C. The gradient method is given in Table 3. HPLC retention times for the given conditions are given in Table 4.

Table 3. HPLC gradient elution conditions

time (min)	% A	% B
0	95	5
15	20	80
16	20	80
20	95	5

6-Chloro-2-methylimidazo[1,2-*b*]pyridazine (4). A slurry of **3** (10.1 g, 78.0 mmol), NaBr (5.56 g, 1.73 mmol), DMF (60 mL), water (5.6 mL, 311 mmol), and chloroacetone[33] (3.75 mL, 46.2 mmol) was heated to 100 °C. After 4 h, additional chloroacetone (3.75 mL, 46.2 mmol) was added over 10 min, and the reaction was then stirred at 100 °C for an additional 10 h. The reaction was cooled to 20 °C, and water

Scheme 10. Alternative route to 2

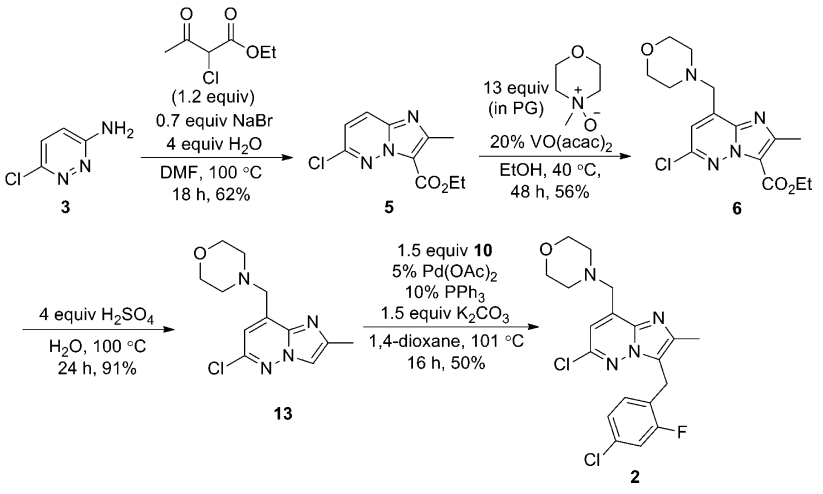

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Table 4. Relevant HPLC retention times

cmpd	HPLC retention time (min)
2	9.95
3	1.67
4	3.59
5	8.25
6	6.40
7	6.67
10	12.74
11	3.36
13	4.81

(210 mL) was charged over 60 min. After stirring for 12 h at 20 °C, the solids were isolated by filtration and dried to afford **4** as a tan solid (5.39 g, 41% yield). ^{1}H and ^{13}C NMR match previously reported data.[14c] HPLC t_R = 3.59 min (220 nm).

Ethyl 6-Chloro-2-methylimidazo[1,2-*b*]pyridazine-3-carboxylate (5). A slurry of **3** (1.20 kg, 9.26 mol), NaBr (672 g, 6.53 mol), DMF (7.2 L), water (672 mL, 37.3 mol), and ethyl 2-chloroacetoacetate (762 mL, 5.6 mol) was heated to 100 °C. After 4 h, additional ethyl 2-chloroacetoacetate (762 mL, 5.6 mol) was added over 1 h, and the reaction was then stirred at 100 °C for an additional 10 h. The reaction was cooled to 20 °C, and water (25 L) was charged over 2 h. After stirring for 1 h at 20 °C, the slurry was filtered. The resulting wet cake was dissolved in ethyl acetate (21.6 L) at 60 °C. The organic solution was washed with water (2 × 6 L) and then concentrated to 3.6 L. *n*-Heptane (6 L) was then charged to the reactor. The solids were isolated by filtration and dried to afford **5** as a tan solid (1.38 kg, 61% yield). ^{1}H and ^{13}C NMR match previously reported data.[14b] HPLC t_R = 8.25 min (254 nm).

Ethyl 6-Chloro-2-methyl-8-(morpholinomethyl)-imidazo[1,2-*b*]pyridazine-3-carboxylate (6). A solution of **5** (400 g, 1.67 mol), $VO(acac)_2$ (88.5 g, 0.33 mol), and EtOH (4.0 L) was heated to 40 °C with stirring. A 60 wt % solution of NMO in 1,2-propanediol (4.6 kg, 23.5 mol) was added over 18 h, and the reaction mixture was then stirred for an additional 24 h at 40 °C. Addition of water (3.2 L) over 2 h, cooling to 20 °C, seeding with **6** (4.0 g, 16.7 mmol), and then cooling to 0−5 °C resulted in crystallization of **6**. The solids were isolated via filtration and washed with water (4 × 800 mL) to afford **6** as a tan powder in 56% yield (315 g) after drying under vacuum; mp = 285 °C dec; ^{1}H NMR ($CDCl_3$): δ 7.38 (s, 1H), 4.43 (q, 2H, J = 7.2 Hz), 3.96 (d, 2H, J = 1.2 Hz), 3.76 (t, 4H, J = 4.8 Hz), 2.70 (s, 3H), 2.58 (t, 4H, J = 4.8 Hz), 1.42 (t, 3H, J = 7.2). ^{13}C NMR ($CDCl_3$): δ 159.5, 151.2, 147.9, 139.0, 138.6, 118.7, 67.0, 61.0, 56.0, 53.9, 16.8, 14.5. HPLC t_R = 6.40 min (254 nm); ESI-HRMS calc'd for $C_{15}H_{20}O_3N_4Cl$ $(M + H)^+$ 399.1218, found 399.1217.

Potassium 6-Chloro-2-methyl-8-(morpholinomethyl)-imidazo[1,2-*b*]pyridazine-3-carboxylate (11). A slurry of **6** (1.08 g, 3.19 mmol) in isopropanol (12.5 mL) was heated to 50 °C at which point a solution formed. Powdered KOH (322 mg, 5.74 mmol) was added, and the resulting slurry was stirred for 30 min after which time the reaction was cooled to rt. The solids were isolated by filtration, washed with isopropanol (3 × 5 mL), and dried under vacuum to afford **12** in 86% yield (955 mg); mp = 111−113 °C; ^{1}H NMR (CD_3OD): δ 7.36 (s, 1H), 3.92 (d, 2H, J = 0.8 Hz), 3.74 (t, 4H, J = 4.4 Hz), 2.66 (s, 3H), 2.59 (t, 4H, J = 4.4 Hz). ^{13}C NMR (CD_3OD): δ 166.8, 148.1, 147.3, 138.8, 138.1, 118.8, 111.6, 68.0, 56.9, 55.0, 15.5. HPLC t_R = 3.36 min (254 nm); ESI-HRMS calc'd for $C_{13}H_{16}ClN_4O_3$ $(M + 2H - K)^+$ 311.0905, found 311.0903.

4-((6-Chloro-2-methylimidazo[1,2-*b*]pyridazin-8-yl)-methyl)morpholine (13). A solution of water (400 mL), sulfuric acid (203.6 g, 1.95 mol), and **6** (165 g, 0.49 mol) was heated to 100 °C and stirred for 24 h after which time it was cooled to rt and water added (3.2 L). Sodium hydroxide (50 wt %, 314 g, 3.9 mol) was added slowly to bring the pH to >9. The resulting solids were isolated via filtration and washed with water (3 × 200 mL) to afford **11** as a beige powder in 91% yield (119 g) after drying under vacuum; mp = 136−137 °C; ^{1}H NMR ($CDCl_3$): δ 7.68 (s, 1H), 7.19 (s, 1H), 3.96 (d, 2H, J = 1.2 Hz), 3.77 (t, 4H, J = 4.4 Hz), 2.59 (t, 4H, J = 4.4 Hz), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 146.6, 144.0, 138.1, 115.7, 114.9, 67.1, 56.1, 54.0, 15.0. HPLC t_R = 4.81 min (235 nm); ESI-HRMS calc'd for $C_{12}H_{16}ClN_4O$ $(M + H)^+$ 267.1007, found 267.1004.

4-((6-Chloro-3-(4-chloro-2-fluorobenzyl)-2-methylimidazo[1,2-*b*]pyridazin-8-yl)methyl)morpholine (2). To a mixture of $Pd(OAc)_2$ (10.0 g, 44.5 mmol), PPh_3 (23.4 g, 89.5 mmol), K_2CO_3 (185 g, 1.35 mol), and **13** (237 g, 0.889 mol) was added anhydrous dioxane (1.90 L) and **10** (241 g, 1.35 mol). The reaction mixture was thoroughly inerted with a nitrogen atmosphere and then heated to reflux (101 °C) for 16 h. The mixture was cooled to rt, and toluene (1 L) and water (1 L) were added. Concentrated HCl (435 mL) was added over 30 min to adjust the pH to <0.5. The layers were separated, and the acidic aqueous layer was subsequently washed with toluene (3 × 500 mL). The pH of the resulting aqueous solution was adjusted to 1.0 by addition of 50% NaOH (178 mL) and the resulting slurry stirred at rt overnight. Filtration of the solids, washing with water, and drying under vacuum afforded **2·HCl**. 2-MeTHF (3.0 L) and water (1.0 L) were added to **2·HCl**. To reach a pH of 10−12, 50% NaOH (35 mL) was added. The layers were separated, and the aqueous layer was extracted with 2-MeTHF (500 mL). The combined organics were dried over Na_2SO_4 and filtered, and the 2-MeTHF was removed by rotary evaporation. The resulting residue was dissolved in PhMe (1.0 L) at 60 °C, *n*-heptane (3.0 L) was added over 5 h, and the resulting slurry was slowly cooled to rt. After stirring at rt overnight, the slurry was cooled to 5 °C and stirred for 3 h. Filtration of the solids and washing with *n*-heptane (2 × 300 mL) afforded **2** (199 g, 50% yield) as an off-white powder after drying. ^{1}H and ^{13}C NMR match previously reported data.[4] HPLC t_R = 9.95 min (220 nm).

Wiped-Film Evaporation to Prepare NMO in 1,2-Propanediol. The distillation was carried out in a Sambay WFE. The material feed was performed with a Telab 2500 pump set to 1625 mL/h. The jacket temperature was set to 130 °C. The heating device for the glass bridge to the distillate vessel was set to 110 °C to ensure that the water would not condense and flow back into the product. The distillate was condensed at 2 °C and the distillation performed at 20 mbar. The wiper rotation speed was set to 590 rpm. In a typical distillation, 50 wt % aqueous NMO (6.41 kg, 27.3 mol NMO) and 1,2-propanediol (2.14 kg, 27.6 mol) were combined, and the water was distilled to afford a ∼60 wt % solution of NMO in 1,2-propanediol (5.12 kg, 26.1 mol NMO, 96% recovery of NMO) as determined by quantitative ^{1}H NMR. The water content in this solution was 2% which met the specification of <5% (by KF).

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra and additional experimental data (Tables S1−S6). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Dameshek, W. *Blood* **1951**, *6*, 372−375.

(2) Kralovics, R.; Passamonti, F.; Buser, A. S.; Teo, S. S.; Tiedt, R.; Passweg, J. R.; Tichelli, A.; Cazzola, M.; Skoda, R. C. *N. Engl. J. Med.* **2005**, *352*, 1779−1790.

(3) Burkholder, T. P.; Clayton, J. R.; Ma, L. Amino pyrazole compounds. U.S. Pat. Appl. Publ. US/0152181, 2010; A1 20100617; CAN 153:97762, CAN 21010:753991.2010.

(4) Mitchell, D.; Cole, K. P.; Pollock, P. M.; Coppert, D. M.; Burkholder, T. P.; Clayton, J. R. *Org. Process Res. Dev.* **2012**, *16*, 70−81.

(5) Acetal with high levels of residual methanol led to longer reaction times.

(6) The cost of shut-down and relining the incinerator must be considered as a contributor to the cost of manufacturing.

(7) Wilson, J. D. Incineration Design Limitations. In *Proceedings of the International Conference on Thermal Treatment Technologies and Hazardous Waste Combustors (IT3/HWC)*; University of Maryland, Air and Waste Management Association: College Park, 2004.

(8) Plugging/fouling of thermal media in regenerative thermal oxidizers due to particulate SiO_2 formation can lead to additional manufacturing costs associated with incineration shutdown and thermal media replacement. See: Hickstein, B.; Meynhardt, B.; Niemeier, O.; Weber, D. *Chem. Eng. Technol.* **2012**, *35*, 2023−2029.

(9) For recent reviews on direct arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35−41. (c) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200−205. (d) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949−957. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826. (f) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269−10310. (g) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447−2464. (h) Lei, A.; Liu, W.; Liu, C.; Chen, M. *Dalton Trans.* **2010**, *39*, 10352−10361.

(10) For recent reviews on decarboxylative cross-coupling, see: (a) Gooßen, L. J.; Rodriguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100−3120. (b) Rodriguez, N.; Gooßen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030−5048. (c) Cornella, J.; Larrosa, I. *Synthesis* **2012**, *44*, 653−676.

(11) For examples of direct benzylation reactions, see: (a) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160−4163. (b) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647−650. (c) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866−4877. (d) Ackermann, L.; Barfuesser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724−726. (e) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360−1363. (f) Ackermann, L.; Barfuesser, S.; Kornhaass, C.; Kapdi, A. R. *Org. Lett.* **2011**, *13*, 3082−3085. (g) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *ChemCatChem* **2011**, *3*, 893−897. (h) Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2011**, *134*, 111−114. (i) Mai, W.; Yuan, J.; Li, Z.; Yang, L.; Xiao, Y.; Mao, P.; Qu, L. *Synlett* **2012**, *23*, 938−942.

(12) There are no reported examples of (hetero)arene decarboxylative benzylation. For other examples of decarboxylative benzylation, see: (a) Torregrosa, R. R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 9280−9282. (b) Zhang, W.-W.; Zhang, X.-G.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 5259−5264. (c) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846−1913. (d) Recio, A., III; Heinzman, J. D.; Tunge, J. A. *Chem. Commun.* **2012**, *48*, 142−144.

(13) Both chloroacetone and ethyl 2-chloroacetoactate are commercially available in bulk quantities, whereas the chloroacetophenone used in the previous route to prepare the imidazopyridazine necessitates an additional synthetic step (Scheme 1, step 2).

(14) (a) Stanovnik, B.; Tisler, M. *Tetrahedron* **1967**, *23*, 2739−46. (b) Abignente, E.; Arena, F.; Luraschi, E.; Saturnino, C.; Rossi, F.; Berrino, L.; Cenicola, M. L. *Farmaco* **1992**, *47*, 931−944. (c) Pevarello, P.; Garcia, C. A. M.; Rodriguez, H. A.; Saluste, C.-G. P.; Ramos, L. F. J.; Gonzalez, C. E.; Oyarzabal, S. J. Preparation of imidazo[1,2-*b*] pyridazines as protein kinase inhibitors. U.S. Pat. Appl. Publ. US/0046127, 2011; A1 741765, 2010. (d) Banno, H.; Hirose, M.; Kurasawa, O.; Langston, S. P.; Mizutani, H.; Shi, Z.; Visiers, I.; Vos, T. J.; Vyskocil, S. Heteroaryls as PI3K and/or mTOR inhibitors and their preparation and use in the treatment of diseases. U.S. Pat. Appl. Publ. US/0256172, 2010; A1 657801, 2010.

(15) See Table S1 in Supporting Information for more details

(16) See Table S2 in Supporting Information for more details

(17) When **9** is used as the substrate (Scheme 1), the *endo*-isomer forms in only trace quantities.[4]

(18) Up to 5 equiv trifluoroacetic acid or 10% H_3PO_4 had no effect on the outcome of the reaction. For additional details on catalyst and solvent screening, see Tables S3 and S4 in Supporting Information.

(19) Generally, only 1−2 equiv of the excess NMO remained at the end of the reaction with the remainder largely decomposed in a competing V-catalyzed reaction to *N*-methylmorpholine. See reference 20 for details on the decomposition of NMO in the presence of transition metals.

(20) Rosenau, T.; Potthast, A.; Sixta, H.; Kosma, P. *Prog. Polym. Sci.* **2001**, *26*, 1763−1837.

(21) *N*,*N*-Dimethylacetamide (DMAC). Proposed Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) list item and Substance of Very High Concern (SVHC) by the EU, European Chemicals Agency (ECHA), *Annex XV Dossier: IDENTIFICATION OF N,N-DIMETHYLACETAMIDE (DMAC) AS SVHC*; 2011; http://echa.europa.eu/documents/10162/13640/svhc_axvrep_echa_cmr_dmac_20110829_en.pdf.

(22) We were hesitant to perform the distillation at ambient pressure due to safety concerns over heating the neat NMO (as very little toluene was present in the lower NMO phase), but use of a higher temperature may have allowed further water removal and the ability to maintain a liquid NMO phase. Crystallization of NMO from this solution upon cooling likely would have further complicated this method.

(23) The WFE used for development was glass (Pope Scientific) and used a Teflon 2 in. × 13 in. distillation column with surface area of 0.033 m^3.

(24) The manufacturer COA for "anhydrous" NMO states 2.4% water by KF, but it is believed to rapidly pick up atmospheric moisture upon opening of the container; NMO·H_2O is 13.3% water by mass.

(25) For examples of palladium-catalyzed decarboxylative cross-coupling of (hetero)arenes, see: (a) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350−11351. (b) Bilodeau, F.; Brochu, M.-C.; Guimond, N.; Thesen, K. H.; Forgione, P. *J. Org. Chem.* **2010**, *75*, 1550−1560. (c) Rodriguez, N.; Gooßen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030−5048. (d) Mitchell, D.; Coppert, D. M.; Moynihan, H. A.; Lorenz, K. T.; Kissane, M.; McNamara, O. A.; Maguire, A. R. *Org. Process Res. Dev.* **2011**, *15*, 981−985. (e) Kissane, M.; McNamara, O. A.; Mitchell, D.;

Coppert, D. M.; Moynihan, H. A.; Lorenz, K. T.; Maguire, A. R. *Tetrahedron Lett.* **2012**, *53*, 403−405.
(26) For recent examples of bimetallic systems for decarboxylative cross-coupling of (hetero)arenes, see: (a) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662−664. (b) Gooßen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824−4833. (c) Gooßen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248−15249. (d) Gooßen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103−7106. (e) Gooßen, L. J.; Lange, P. P.; Rodriguez, N.; Linder, C. *Chem.—Eur. J.* **2010**, *16*, 3906−3909. (f) Gooßen, L. J.; Rodriguez, N.; Lange, P. P.; Linder, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111−1114. (g) Zhang, F.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 4745−4747. (h) Messaoudi, S.; Brion, J.-D.; Alami, M. *Org. Lett.* **2012**, *14*, 1496−1499.
(27) Fu, H. Y.; Chen, L.; Doucet, H. *J. Org. Chem.* **2012**, *77*, 4473−4478.
(28) See Table S5 in Supporting Information for additional details
(29) (a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754−13755. (b) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066−1067. (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848−10849. (d) Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749−823. (e) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315−1345.
(30) The use of 10% AcOH resulted in a similar effect, presumably by in situ generation of 10% KOAc.
(31) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496−16497.
(32) Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL): 100 ppm: Surprenant, K. S. *Ullmann's Encyclopedia of Industrial Chemicals*; Wiley-VCH Verlag: Weinheim,Germany, 2002; pp 309−314; 10.1002/14356007.a08_545.
(33) Chloroacetone is highly irritating and a strong lachrymator and should be used with caution.