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Application of C−H Functionalization in the Development of a Concise and Convergent Route to the Phosphatidylinositol-3-kinase Delta Inhibitor Nemiralisib

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Cite This: *Org. Process Res. Dev.* 2021, 25, 529−540 Read Online

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ABSTRACT: This paper describes the development of an improved and scalable method for the manufacture of nemiralisib, a phosphatidylinositol-3-kinase delta inhibitor. Incorporation of three consecutive catalytic reactions, including a palladium-catalyzed C−H functionalization and an iridium-catalyzed borylation, significantly simplified and shortened the synthetic sequence. The revised route was successfully implemented in a pilot plant on a multikilogram scale to deliver >100 kg of product.

KEYWORDS: *catalysis, C−H functionalization, iridium, borylation*

The selective insertion of transition metals into unfunctionalized carbon−hydrogen bonds without prior activation with a stoichiometric reagent and their subsequent application to coupling reactions offer huge potential in the simplification of complex small-molecule synthesis, especially at process scale.[1] In particular, coupling of such organometallic species in catalytic fashion with aryl and heteroaryl halides offers an attractive alternative to standard cross-coupling procedures such as Suzuki−Miyaura,[2] Stille,[3] Negishi,[4] Kumada−Corriu,[5] and Hiyama[6] reactions. In each of those procedures, an aryl halide is reacted with an organometallic species under transition metal catalysis. Both coupling partners must be preformed and thus synthetically tractable; in many cases, the organometallic coupling partner is prepared from an aryl halide itself. In turn, each aryl halide must be made by functionalization of an aryl ring, a process that requires stoichiometric reagents and is often unselective,[7] potentially necessitating painstaking purification procedures and generating halogenated waste streams that can be difficult to dispose. Considering these factors, it is obvious that C−H functionalization processes have the potential to shorten and improve the economic viability of manufacturing routes to fine chemicals and pharmaceuticals and significantly reduce the associated environmental burden. We report herein the incorporation of two of these reactions into the synthetic route to a molecule in development for the treatment of respiratory disease.

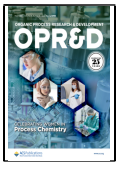
Nemiralisib (**13**) is currently in development as a treatment for chronic obstructive pulmonary disease (COPD). It is a selective inhibitor of the delta isoform of the phosphatidylinositol-3-kinase enzyme, which has been implicated in potentiating the inflammatory response to allergens in the airways.[8] The initial supply route was used to generate 5 kg of material to fund safety assessment studies and Phase I clinical trials (Scheme 1).[9]

Despite the extensive development work done on the initial supply route, numerous issues remained with the route itself and associated processes. First, the mixture of esters **3** and **4** produced in the first step necessitated a three-step telescope that took approximately a week to complete in a pilot-plant setting. Furthermore, polymeric material was produced in the synthesis of esters **3** and **4** that was carried through the sequence, resulting in low intermediate purity. We also demonstrated that these polymers were responsible for stalling of the Suzuki−Miyaura reaction in the lab, forcing us to rely on recrystallization and hot filtration of aryl chloride **11** to ensure that stalling did not occur in the plant. Finally, the synthesis of 4-iodo-6-chloroindazole (**5**) required seven synthetic steps, causing this intermediate to account for over 60% of the cost of materials for the route and to have a long production lead time (Scheme 2).[10] We therefore set about looking for shorter, cheaper, and more convergent routes to **13**.

We considered many synthetic approaches; however, central to the development of an efficient synthesis of **13** is the application of methods for orthogonal functionalization of the 4- and 6-positions of indazole to allow sequential formation of the two biaryl bonds. Application of selective C−H functionalization protocols would drastically simplify the starting materials since 4-haloindazoles can easily be accessed from readily available 3-halo-2-methylanilines[11] and precedent exists in the literature for selective insertion into C−H bonds

Special Issue: Celebrating Women in Process Chemistry

Received: October 30, 2020
Published: February 9, 2021



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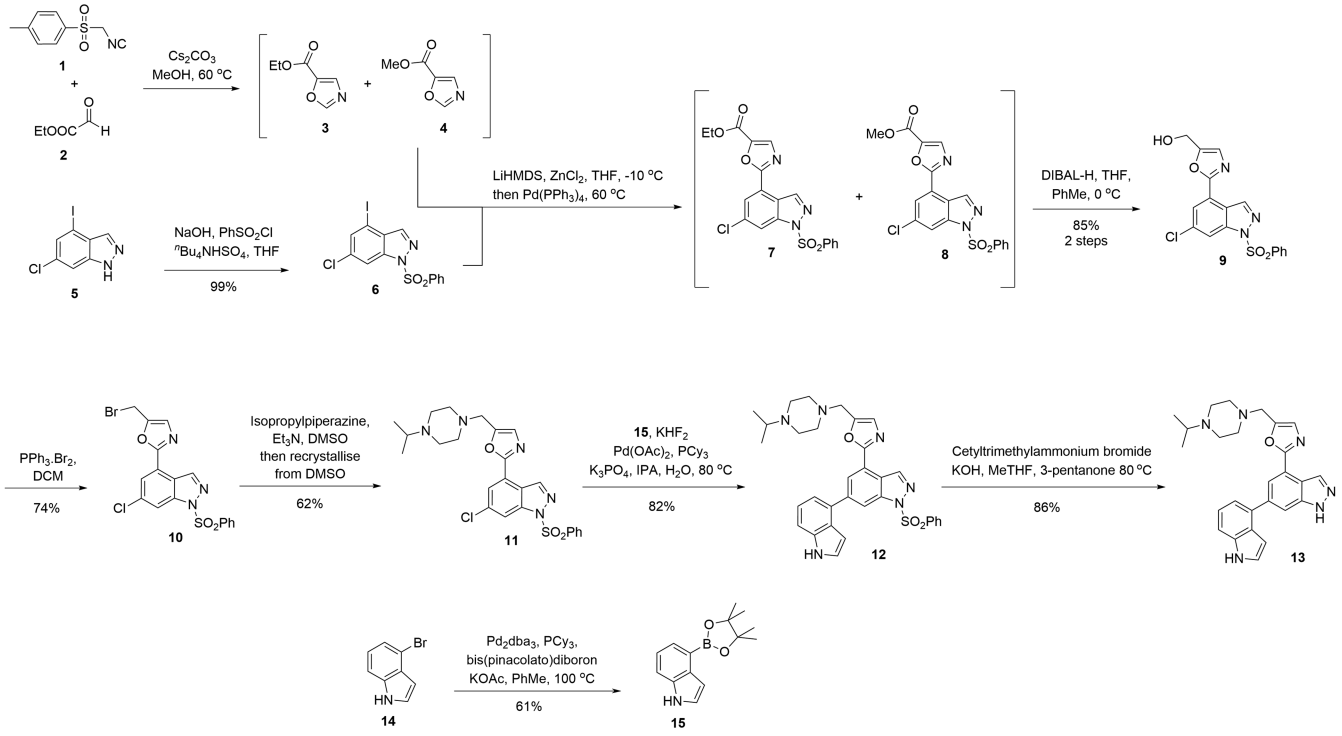
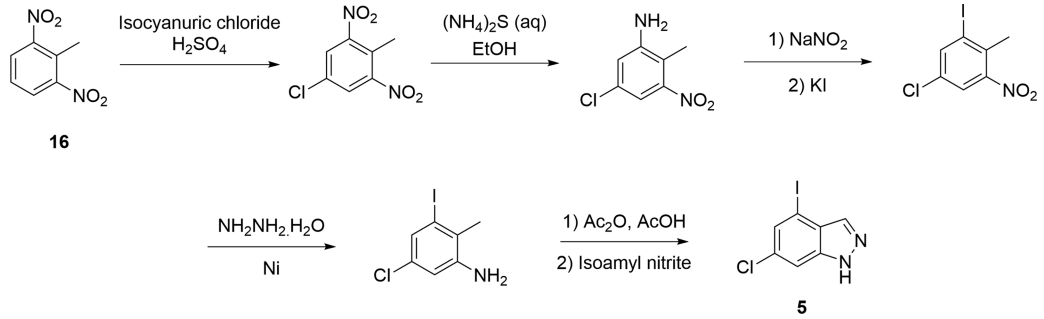
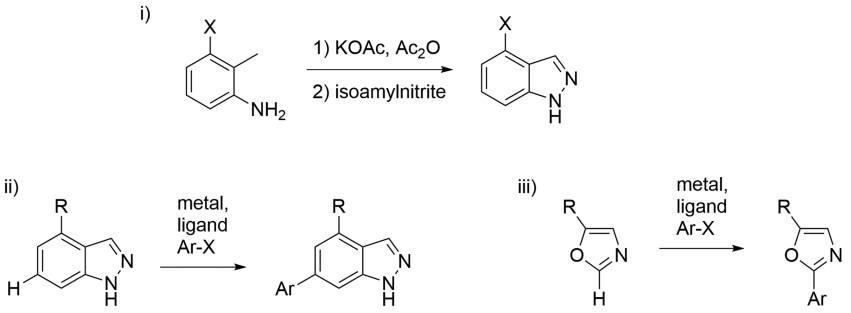
Scheme 1. Initial Enabling Supply Route to Nemiralisib



Scheme 2. Synthesis of 4-Iodo-6-chloroindazole (5) from 2,6-Dinitrotoluene (16)



Scheme 3. Approaches to Selective C−H Functionalization of the Indazole and Oxazole Rings



at the 2-position of oxazoles[12] and the 5-position of 1,2,3-trisubstituted benzenes (Scheme 3).[13,14]

We began by investigating the selective insertion of palladium at the 2-position of the oxazole ring in **3**. Others have demonstrated that the reactivity can be modulated by judicious choices of the ligand and solvent.[12d] A key issue with our strategy was the potential for insertion into multiple carbon−hydrogen bonds in both oxazole and indazole substrates, especially those adjacent to heteroatoms.

Initial investigations coupled oxazole ester **3** with iodo- or bromobenzene, guided by literature precedent, and confirmed that conversion to product with the required selectivity could be achieved using a combination of $Pd(OAc)_2$, RuPhos, pivalic acid, and cesium carbonate as the base in toluene.

https://dx.doi.org/10.1021/acs.oprd.0c00486
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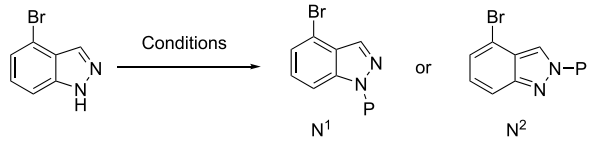
Following this positive indication that we could access the desired reactivity, we attempted the coupling of 4-bromoindazole with oxazole ester **3** under the same conditions; however, no reaction to give the desired product was observed. This is perhaps unsurprising in light of Buchwald's observation that unprotected indazoles and pyrazoles inhibit cross-coupling reactions unless very specific conditions are used.[15] To explore further whether it was indeed the free N−H that caused the observed lack of reactivity, we set about synthesizing a range of model 4-bromoindazole substrates (Table 1). Protection of indazoles is often unselective,[9,16] although under strongly acidic or basic conditions selectivity for N^1 was achieved. In the case of mixtures, the N^1 and N^2 isomers were separated by chromatography.

Table 1. Synthesis of Various N^1- and N^2-Protected Indazoles



protecting group	conditions	N^1:N^2 ratio	combined yield (%)
THP	TFA, 3,4-Dihydro-2*H*-pyran, EtOAc, 77 °C	1:0	86
Boc	Boc_2O, DMAP, MeCN, 20 °C	2:1	88
$PhSO_2$	$PhSO_2Cl$, NaOH, Bu_4NHSO_4, THF, 20 °C	1:0	99
Me_2NSO_2	Me_2NSO_2Cl, NaOH, Bu_4NHSO_4, THF, 20 °C	1:1	57
Piv	PivCl, DMAP, DIPEA, THF, 70 °C	1:0	89
PMB	PMBCl, NaOH, Bu_4NHSO_4, THF, 20 °C	3:1	79
TIPS	N/A	N/A	unstable
TBS	N/A	N/A	unstable

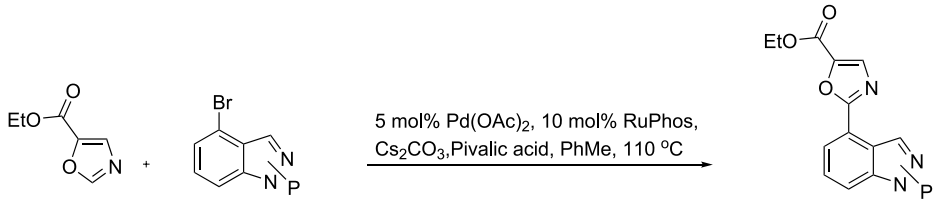
We next assessed the performance of these 4-haloindazoles in a direct coupling reaction with oxazole ester **3** in a 1:1 molar ratio using the same RuPhos conditions (Table 2). As was observed for the attempted reaction in the absence of a protecting group, coupling was inhibited in cases where the indazole protecting group was labile under the basic reaction conditions (Piv, Boc). When a more robust protecting group was used (THP, PMB, N^1-Me_2NSO_2), the desired product was formed readily and isolated in good yield.

In the case of THP-protected 4-bromo-6-chloroindazole **31**, a mixture of products from competitive addition into both the C−Br bond and the C−Cl bond was observed (Scheme 4). Following this observation, an alternative approach was evaluated whereby the 6-position could be functionalized after coupling to the oxazole ring.

Iridium-catalyzed C−H borylation has been the subject of significant advances in recent years.[17] In the case of 1,2,3-trisubstituted benzenes, borylation is favored at the least hindered 5-position.[18] However, less is known about the relative ease of borylation of heteroaryl C−H bonds. Borylation of indazole **24** could potentially occur at H^1, H^2, or H^3, giving rise to a mixture of mono-, di-, and triborylated products (Scheme 5).

We subjected indazole **24** to a mixture of $[Ir(OMe)COD]_2$ (0.02 equiv), di-*tert*-butylbipyridine (0.04 equiv), and bis(pinacolato)diboron (1.2 equiv) in refluxing THF. Analysis of the reaction mixture by HPLC revealed a number of peaks corresponding to a small amount of residual indazole **24** and a mixture of mono- and diborylated products, identified by LC−MS as consisting of pinacol ester and boronic acid species. The crude mixture was purified by flash column chromatography, and the products were analyzed by ^{1}H NMR spectroscopy, which revealed that the products were in fact the pinacol

Table 2. Direct C−H Coupling of Oxazole Ester 3 with a Range of Protected 4-Bromoindazoles



3

17 - P = N^1 THP
18 - P = N^1 PMB
19 - P = N^2 PMB
20 - P = N^1 Boc
21 - P = N^1 Piv
22 - P = N^1 Me_2NSO_2
23 - P = N^2 Me_2NSO_2

24 - P = N^1 THP
25 - P = N^1 PMB
26 - P = N^2 PMB
27 - P = N^1 Boc
28 - P = N^1 Piv
29 - P = N^1 Me_2NSO_2
30 - P = N^2 Me_2NSO_2

		crude HPLC area % at 220 nm after 3 h		
substrate	product	SM	product	isolated yield (%)[a]
17	**24**	0	78	89
18	**25**	0	88	92
19	**26**	0	79	84
20	**27**	43	3	–
21	**28**	44	0	–
22	**29**	0	87	85
23	**30**	0	54	–

[a]Isolated yields after chromatography.

https://dx.doi.org/10.1021/acs.oprd.0c00486
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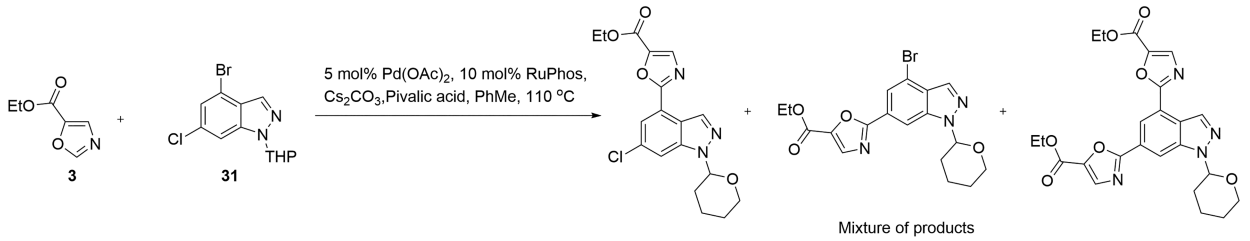
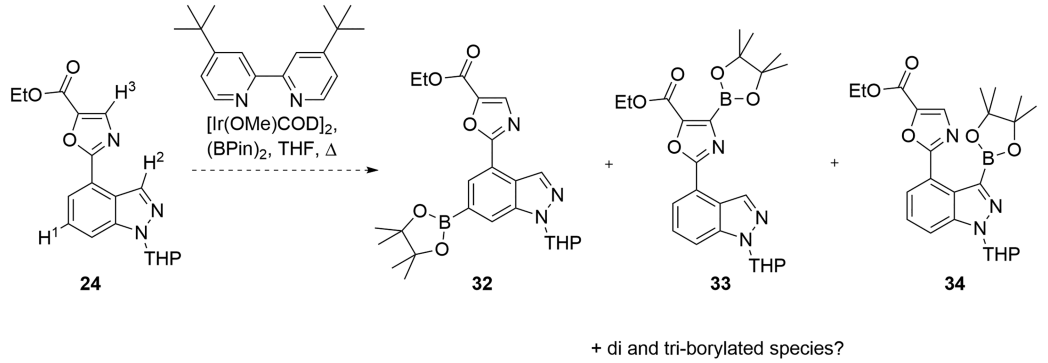
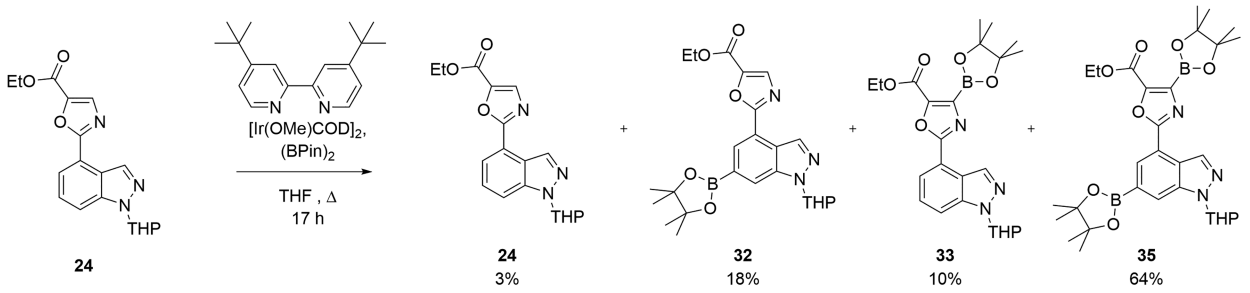
Scheme 4. Mixture of Products Arising from the Attempt to Couple Oxazole Ester 3 with THP-Protected 4-Bromo-6-chloroindazole 31



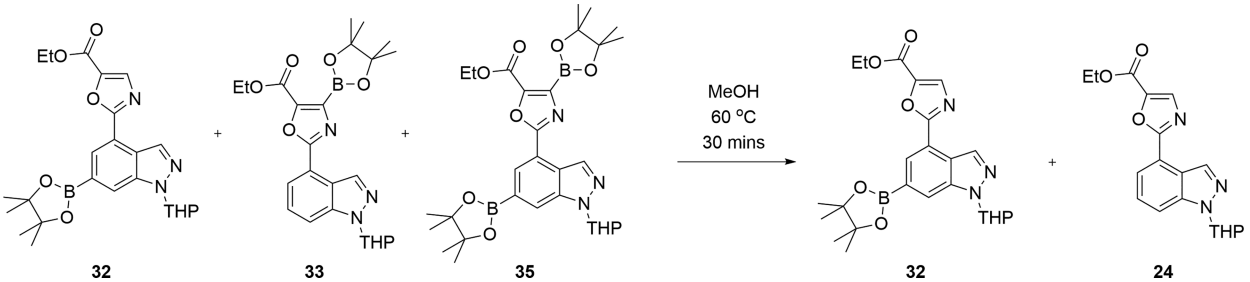
Scheme 5. Potential Selectivity Issues in C−H Borylation of Indazole 24



Scheme 6. Product Distribution from Borylation of Indazole 24, Reported as the Sum of HPLC Area % of Boronic Ester and Acid Peaks Corresponding to Each Species



Scheme 7. Selective Cleavage of the Undesired C−B bond in 35 upon Heating in Methanol



boronate ester derivatives rather than the boronic acids (i.e., partial hydrolysis occurred during HPLC analysis). Products arising from borylation at the desired position (H^1) (**32**) and on the oxazole ring (H^3) (**33**) as well as both positions H^1 and H^3 (**35**) were identified by ^{1}H NMR analysis; however, no borylation adjacent to the indazole nitrogen (H^2) (**34**) was detected (Scheme 6).

Given the tendency of heteroarylboron species to protodeboronate during Suzuki−Miyaura reactions, we speculated that the oxazole C−B bond might be more labile than the indazole C−B bond.[19] Treatment with a range of aqueous acids and bases, including KHF_2 in an attempt to generate potassium trifluoroborates, failed to selectively cleave the unwanted C−B bond.[20,21] However, we were delighted to discover that simply heating diboronate **35** gently in alcoholic solvents rapidly and selectively cleaved the oxazole C−B bond, delivering highly pure mono(pinacol boronate) **32** after crystallization (Scheme 7).

We next optimized the conditions to selectively produce bisborylated material. Increasing the charge of the boron

https://dx.doi.org/10.1021/acs.oprd.0c00486
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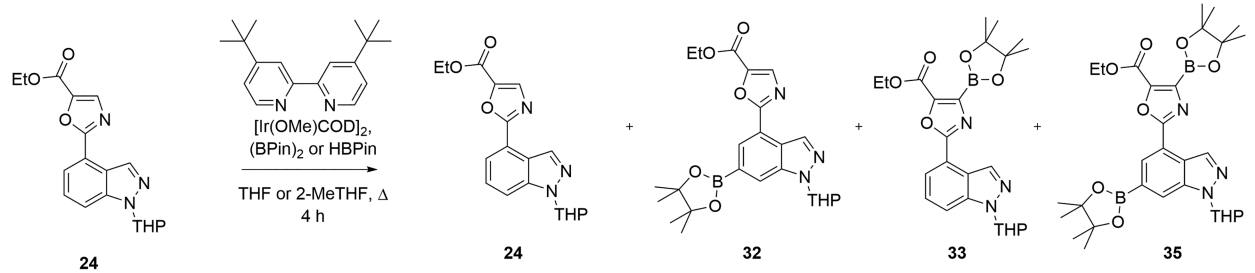
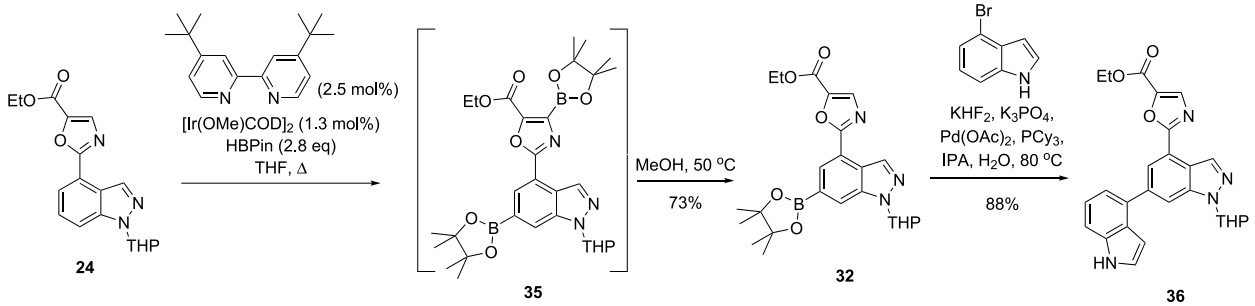
Scheme 8. Evaluation of Alternative Borylating Reagents and Solvents for Borylation of Indazole 24[a]



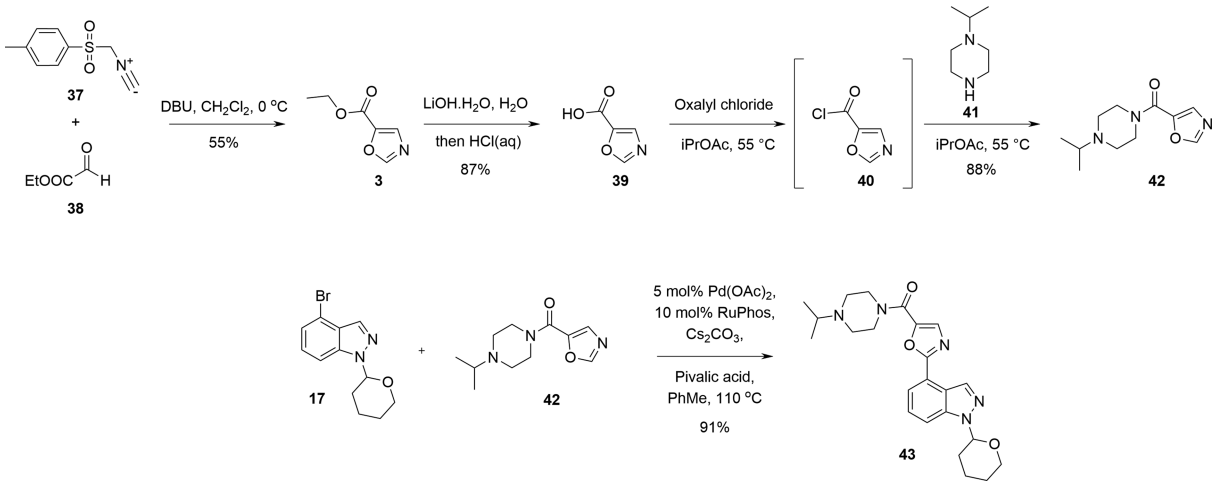
	24	32	33	35
Run 1: $(BPin)_2$, 2-MeTHF	1%	5%	18%	68%
Run 2: HBPin, 2-MeTHF	0.3%	6%	5%	83%
Run 3: $(BPin)_2$, THF	0%	6%	2%	87%
Run 4: HBPin, THF	0%	5%	0%	88%

[a]The product distributions are represented as sums of HPLC area % of boronic ester and acid peaks corresponding to the indicated species.

Scheme 9. Borylation of 24, Selective Cleavage of the Unwanted Oxazole C−B Bond, and Suzuki−Miyaura Coupling with 4-Bromoindole



Scheme 10. New Process to Synthesize Oxazole Ester 3, Conversion to Amide 42, and Subsequent Demonstration of C−H Functionalization with THP-Protected 4-Bromoindazole 17



reactant to 2.8 equiv led to essentially complete consumption of starting material **24** within 4 h, with pinacol borane in THF giving the best selectivity for the desired products in a very focused screen of borylating reagents and solvents (Scheme 8).

This combination was successfully demonstrated on a 2 g scale, with cooling of the reaction mixture to 50 °C upon reaction completion before addition of methanol and aging for 30 min to effect selective cleavage of the undesired C−B bond. The mixture was then cooled to 20 °C and aged for 18 h, after which filtration provided the desired product **32** in 73% yield with excellent purity. Suzuki−Miyaura coupling of this species with 4-bromoindole using the previously developed conditions afforded product **36** in 88% yield (Scheme 9).[9]

All that remained to complete the synthesis of nemiralisib was to introduce the isopropylpiperazine ring in place of the ester and remove the THP protecting group. However, we saw an opportunity to further shorten the synthetic route by introducing the piperazine ring in a more convergent fashion. The process for generating oxazole ester **3** was improved by switching the base to DBU and running the reaction in CH_2Cl_2

https://dx.doi.org/10.1021/acs.oprd.0c00486
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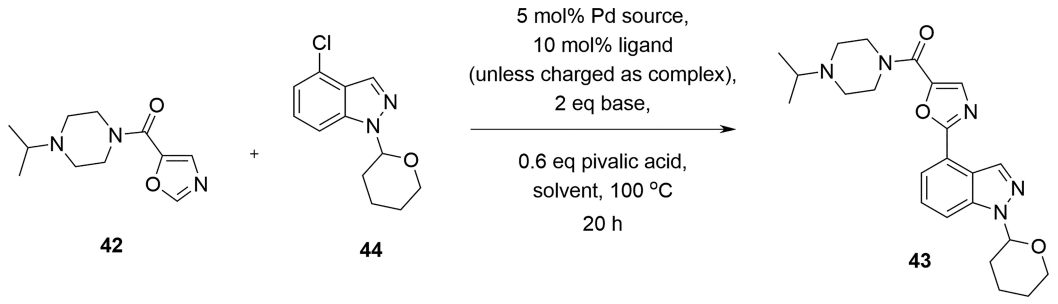


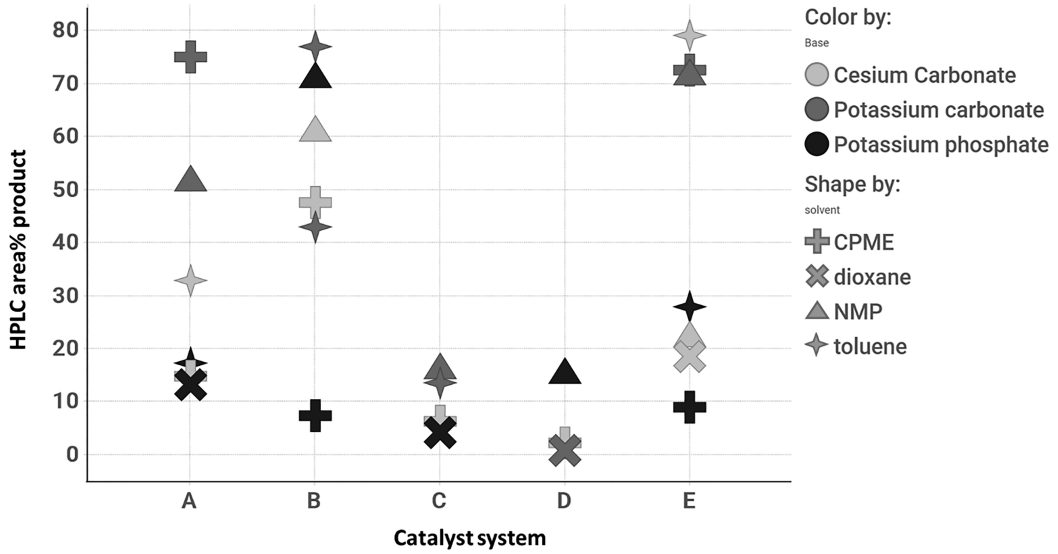
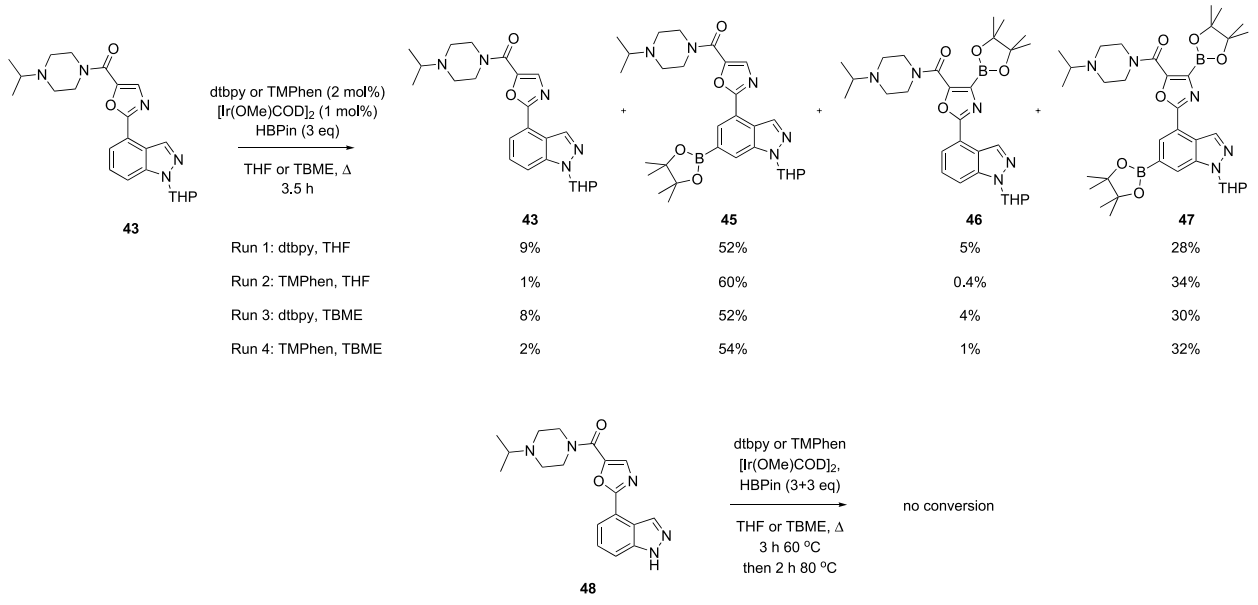


Figure 1. Solvent/base/ligand screening for Pd-catalyzed C−H fuctionalization. All of the experiments were performed with 5 mol % Pd source, 10 mol % ligand (where this was not part of the precatalyst charged), 0.6 equiv of pivalic acid, and 2 equiv of base at 100 °C for 20 h. Catalyst systems: (A) [1,2-bis(dicyclohexylphosphino)ethane]$PdCl_2$; (B) CataCXium A/$Pd(OAc)_2$; (C) CyJohnPhos/$Pd(OAc)_2$; (D) dichlorobis(chlorodi-*tert*-butylphosphine)palladium(II); (E) XPhos PdG2.

Scheme 11. Evaluation of the Borylation Conditions for Indazole Amide Substrate 43 and Free N−H Analogue 48[a]



	43	45	46	47
Run 1: dtbpy, THF	9%	52%	5%	28%
Run 2: TMPhen, THF	1%	60%	0.4%	34%
Run 3: dtbpy, TBME	8%	52%	4%	30%
Run 4: TMPhen, TBME	2%	54%	1%	32%

[a]The product distributions are expressed as sums of HPLC area % of boronic ester and acid peaks corresponding to the indicated components.

at 0 °C, which avoided transesterification.[22] Distillation under high vacuum gave the product in 55% yield with high purity on a 70 kg scale (Scheme 10). The distilled product was free from the polymeric impurities that caused issues in the previous

https://dx.doi.org/10.1021/acs.oprd.0c00486
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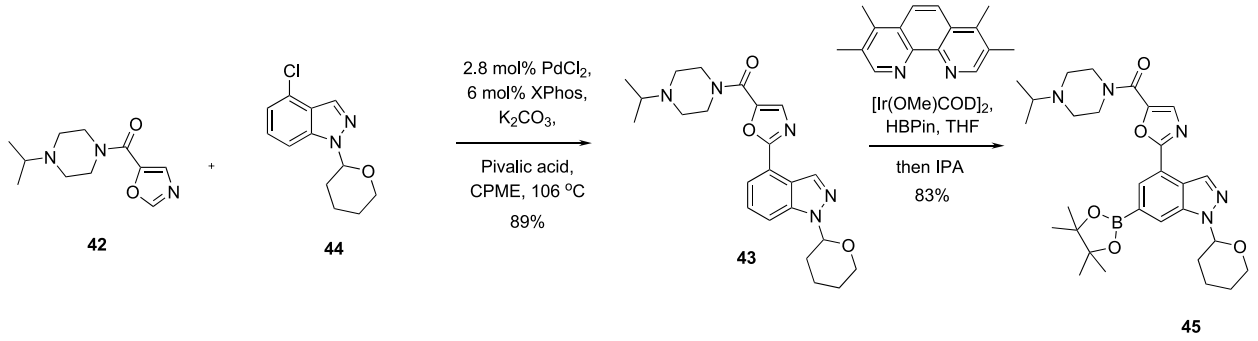
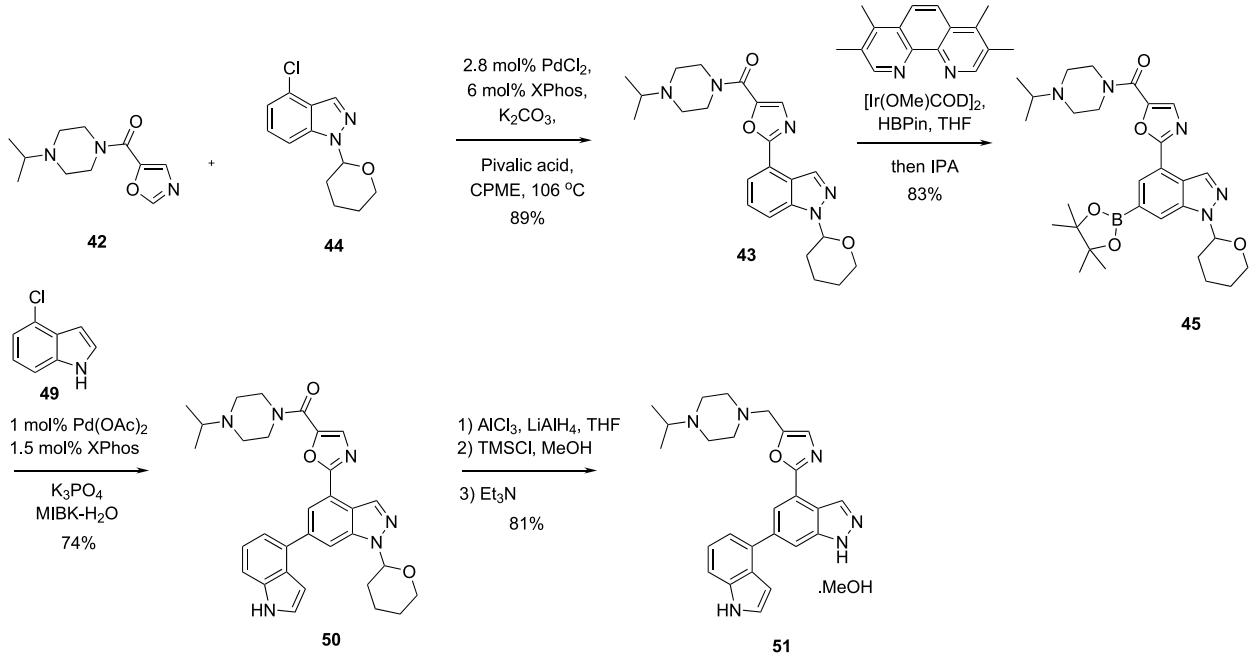
Scheme 12. Scaled-Up Process from Oxazole Amide 42 to Pinacol Boronate Ester 45



Scheme 13. Final Scaled-up Synthesis of Nemiralisib (13)



route, but the isolated yield was moderate because of degradation to a range of impurities during the distillation; an assay of the organic phases during the workup suggested >80% solution yield of the desired product, with a small amount also being lost with the toluene fraction in the distillation. Although CH_2Cl_2 is an undesirable solvent from a sustainability perspective, the cleaner reaction profile and lack of transesterification justified making the change from methanol; nonetheless, further work has continued to evaluate suitable alternatives that give clean conversion to the desired ethyl ester product, with ethyl acetate showing promise, albeit resulting in a lower isolated yield to date. Ester hydrolysis[23] was performed on a 54 kg scale with LiOH in 87% yield, with the isolation facilitated by simple adjustment of the pH. Amide **42** was produced via acid chloride **40** and subsequent addition to isopropylpiperazine in isopropyl acetate, and an isolated yield of 88% was achieved on a 33 kg scale.

The C−H insertion proceeded in excellent yield under the conditions developed for the oxazole ester; however, by this point we had identified an opportunity to improve the cost and sustainability of the process by switching to the corresponding indazole chloride **44**. This coupling was subjected to optimization (Figure 1). The switch from RuPhos to XPhos was attempted because the latter was quoted at a significantly lower price at the time. The hit with XPhos and potassium carbonate in cyclopentyl methyl ether (CPME) was the most favorable from a sustainability perspective as well as from subsequent work on the isolation demonstrating the potential to perform the reaction, workup, and isolation in the same solvent rather than necessitating a lengthy solvent switch. Further work on related nonproprietary ligands led us to pursue dicyclohexylphenylphosphine as a potential alternative to XPhos; however, this gave a significantly higher degree of bis-C−H functionalization and less reproducible results. Ultimately, optimization of the XPhos process, including the use of palladium chloride rather than palladium acetate, enabled a reduction in the loadings of both the palladium source and the ligand that was deemed viable for this system and was successfully implemented on multikilogram scale in the plant (see Scheme 12).

The borylation was revisited to confirm the optimal conditions for diborylation of this substrate, with a brief evaluation of the ligand (3,4,7,8-tetramethylphenanthroline or 4,4′-di-*tert*-butyl-2,2′-bipyridine), solvent, and performance on free N−H indazole **48** (Scheme 11). This work demonstrated 3,4,7,8-tetramethylphenanthroline in THF to be optimal and also showed that free N−H indazole **48** was a poor substrate, further confirming the need for the THP protecting group in

https://dx.doi.org/10.1021/acs.oprd.0c00486
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this synthetic sequence despite the potential improvement in green metrics had we been able to avoid the use of protecting groups.

Further optimization of the selective oxazole monodeborylation and isolation of **45** resulted in a process whereby a solvent swap to 2-propanol is carried out at 50 °C under reduced pressure, conditions that not only cleave the undesired C−B bond but also allow isolation of highly pure pinacol boronate **45** in 83% yield. Controlling the temperature during this process avoids cleavage of the indazole C−B bond; performing the solvent swap at atmospheric pressure (70−80 °C) on a 10 g scale led to >15% indazole deborylation. Although it was possible to reduce the dimeric iridium catalyst charge to 0.5 mol % or below while still ensuring complete borylation at C−H[1] when very pure input **43** was used, residual amide **42** was found to inhibit the reaction. In the interests of achieving a robust process, a compromise was reached on 1 mol % [Ir] with 5 mol % ligand, as this enabled a greater tolerance to carried-over amide **42**. Very low Ir levels (<150 ppm) were retained in the crystallized product, with the rest being purged to the liquors; this presented options for future recovery. This borylation process was successfully scaled up to deliver the required product in 83% yield on a 54 kg scale (Scheme 12).

The next step in the synthesis was to perform a Suzuki−Miyaura coupling to complete the carbon skeleton of nemiralisib. 4-Chloroindole (**49**) represented a more sustainable alternative to 4-bromoindole, and a small, focused screen was performed in order to select the best catalyst/ligand/solvent/base combination. XPhos/palladium acetate was identified as the best catalyst system. Methyl isobutyl ketone (MIBK) was chosen as the solvent because the solubility profile enabled reaction, workup and crystallization in a single solvent. The reaction was worked up with basic aqueous *N*-acetylcysteine to extract most of the residual palladium from the product, allowing facile control of the palladium content in the active pharmaceutical ingredient.[24] Distillation of the MIBK at atmospheric pressure azeotropically dried the solvent, which significantly reduced the solubility of **50**, allowing direct crystallization. The reaction was successfully performed on a 50 kg scale, and the product was isolated in 74% yield with no processing issues (Scheme 13).

Finally, the reduction and deprotection of the advanced intermediate **50** was investigated. Many reducing agents were assessed, but even with subsequent stoichiometric addition of the reducing agent, the reduction typically did not reach completion. Our initial enabling conditions were to add a solution of **50** in THF to a solution of DIBAL-H in THF. Interestingly, the reduction selectivity with respect to aldehyde, alcohol, and other byproducts was significantly better when the reaction was performed in this addition mode. This process still had issues due to the high dilution required and large quantities of isobutane/isobutene produced upon quenching, which represented a significant safety concern. Following the hypothesis that a Lewis acid may improve the reaction profile, the optimal conditions were found to be the addition of lithium aluminum hydride (10% w/w in THF) to a solution of the starting material **50** and aluminum chloride. The reaction was carefully quenched with the addition of EtOAc to reduce gas production, followed by addition of triethanolamine and sodium hydroxide. The high ionic strength of the workup allowed the aluminum salts to be effectively removed in the aqueous phase to give a THF solution of the product. The deprotection could be telescoped by exchange of the solvent for MeOH by distillation and addition of chlorotrimethylsilane, generating anhydrous HCl. Acetyl chloride could not be used in this instance, as it resulted in acetylated impurities that were challenging to purge. The reaction was quenched with triethylamine at the end of the deprotection to enable direct crystallization of the product as the methanol solvate (**51**) in 81% yield on a 35 kg scale. The final overall process is depicted in Scheme 13.[25]

In summary, we have developed a new synthetic route to an investigational drug for the treatment of COPD, taking advantage of the power of successive selective C−H functionalization processes in the context of complex heterocyclic intermediates. The route is shorter and higher-yielding than the previous sequence (44% from 4-chloroindazole starting material compared with 25% from 6-chloro-4-iodoindazole), and the starting materials are cheaper and more readily available (see above). The route represents the basis of a potential long-term manufacturing route for nemiralisib.

EXPERIMENTAL SECTION

General Methods. All commercially sourced chemicals and solvents were used as received without further purification. ^{1}H NMR spectra were acquired on a Bruker AV-400 NMR spectrometer, and chemical shifts are reported in parts per million relative to tetramethylsilane.

Oxazole-5-carboxylic Acid (39). An aqueous solution of lithium hydroxide monohydrate (124.5 kg of a solution prepared from 49.44 kg of lithium hydroxide monohydrate dissolved in 319 kg of water, 398 mol) was added to a solution of ethyl oxazole-5-carboxylate (**3**) (54 kg, 382.7 mol) in water (54 kg) while the temperature was maintained below 25 °C. The reaction mixture was stirred for 6.5 h and then concentrated aqueous HCl (64.8 kg) was added while the temperature was maintained below 25 °C. The crystallization mixture was cooled to 5 °C and held for 1 h. The product was filtered off, washed with cold water (88 kg) and then isopropanol (171.1 kg), and dried under vacuum at 50 °C to afford the title compound (37.88 kg, 87.4%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H 13.68 (br s, 1H), 8.59 (s, 1H), 7.88 (s, 1H).

(4-Isopropylpiperazin-1-yl)(oxazol-5-yl)methanone (42). Oxalyl chloride (47.7 kg, 375.8 mol) was added to a solution of oxazole-5-carboxylic acid (**39**) (32.88 kg, 290.8 mol) in isopropyl acetate (144 kg) while the temperature was maintained at 52−58 °C. The temperature was increased to 58.5 °C, and the mixture was stirred for 5 h and then cooled to 20 °C. The reaction mixture was added to a solution of 1-(isopropyl)piperazine (**41**) (41 kg, 319.8 mol) and potassium carbonate (118.4 kg) in isopropyl acetate (348 kg) and water (103 kg), while the temperature was maintained below 25 °C. The reaction mixture was stirred for 15 min, and the temperature was increased to 33 °C. The organic phase washed with water (191 kg), concentrated under reduced pressure to 95 L, and cooled to 20 °C. *n*-Heptane (157 kg) was added, and the crystallization mixture was stirred for 2 h. The product was filtered off, washed with *n*-heptane (157 kg), and dried under vacuum at 40 °C to give the title compound (57.14 kg, 88.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.94 (s, 1H), 7.56 (s, 1H), 3.91−3.73 (m, 4H), 2.75 (spt, J = 6.5 Hz, 1H), 2.63−2.52 (m, 4H), 1.06 (d, J = 6.6 Hz, 6H).

(4-Isopropylpiperazin-1-yl)(2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)oxazol-5-yl)methanone

https://dx.doi.org/10.1021/acs.oprd.0c00486
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(43). Palladium chloride (0.74 kg, 4.2 mol) and XPhos (4.36 kg, 9.1 mol) were suspended in CPME (372 L). 4-Chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (**44**) (36 kg, 152.1 mol), (4-isopropylpiperazin-1-yl)(oxazol-5-yl)methanone (**42**) (34.78 kg, 155.8 mol), and potassium carbonate (325 mesh, 35.64 kg, 257.9 mol) were added and rinsed in with CPME (2.58 kg). A solution of pivalic acid (9.294 kg, 91.0 mol) in CPME (10 L) was added, followed by a rinse with CPME (10 L). The reaction mixture was vacuum-degassed and backfilled with nitrogen three times and then heated to reflux for 5 h, and the contents were cooled back to 40 °C. The reaction mixture was washed with water (144 L) and then 5% w/v aqueous sodium chloride solution (151.2 kg), and the organic phase was concentrated to 288 L under atmospheric pressure. The reaction mixture was filtered into another vessel, and the filter was washed with CPME (36 L). Then the filtrate was distilled down to 108 L under atmospheric pressure. Methylcyclohexane (162 L) was added to the vessel while the temperature was maintained at 75 °C. The contents were then cooled to 62−65 °C, and the crystallization mixture was seeded with the title compound (90 g) slurried in chilled methylcyclohexane (0.52 L). The crystallization mixture was held at 62 °C for 30 min, cooled to 7 °C, and then held at 7 °C overnight. The product was filtered off, washed with methylcyclohexane (2 × 72 L), and dried in a vacuum oven at 50 °C to give the title compound (57.2 kg, 88.9%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H 8.59 (s, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.95 (s, 1H), 7.91 (d, J = 7.3 Hz, 1H), 7.62 (dd, J = 7.3, 8.3 Hz, 1H), 5.97 (dd, J = 2.0, 9.5 Hz, 1H), 4.03−3.85 (m, 1H), 3.84−3.70 (m, 1H), 3.66 (br s, 4H), 2.72 (spt, J = 6.5 Hz, 1H), 2.57−2.40 (m, 5H), 2.11−1.96 (m, 2H), 1.85−1.68 (m, 1H), 1.68−1.47 (m, 2H), 0.99 (d, J = 6.4 Hz, 6H).

(4-Isopropylpiperazin-1-yl)(2-(1-(tetrahydro-2*H*-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-4-yl)oxazol-5-yl)methanone (45). Pinacolborane (40.80 kg, 318.8 mol) was added to a stirred solution of (4-isopropylpiperazin-1-yl)(2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)oxazol-5-yl)methanone (**43**) (54.00 kg, 127.5 mol), (1,5-cyclooctadiene)(methoxy)iridium-(I) dimer (0.864 kg, 1.30 mol), and 3,4,7,8-tetramethyl-1,10-phenanthroline (1.51 kg, 6.39 mol) in THF (243.2 kg) at 20 °C. The reaction mixture was heated to reflux for 8 h, cooled to 20 °C, and transferred into a vessel containing isopropanol (253.8 kg), washing through with THF (23.8 kg). The contents of the vessel were distilled down to 270 L at 200 mbar, and isopropanol (253.8 kg) was added, after which the mixture was redistilled down to 324 L at 100 mbar. ***CAUTION:*** *to avoid peroxide formation, THF distillate should be treated with a stabilizer*. The crystallization mixture was heated to 40 °C for 4 h, cooled to 20 °C, and stirred overnight, and then the product was filtered off, washed with isopropanol (84.8 kg), and dried in a vacuum oven at 50 °C to give the title compound (57.35 g, 82.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.70 (s, 1H), 8.40 (s, 1H), 8.17 (s, 1H), 7.74 (s, 1H), 5.85 (dd, J = 2.4, 9.5 Hz, 1H), 4.11−4.03 (m, 1H), 3.97−3.77 (m, 5H), 2.78 (spt, J = 6.4 Hz, 1H), 2.70−2.59 (m, 5H), 2.24−2.14 (m, 1H), 2.14−2.03 (m, 1H), 1.86−1.72 (m, 2H), 1.72−1.62 (m, 1H), 1.40 (s, 12H), 1.08 (d, J = 6.4 Hz, 6H).

(2-(6-(1*H*-Indol-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)oxazol-5-yl)(4-isopropylpiperazin-1-yl)-methanone (50). 4-Chloroindole (**49**) (13.8 kg, 91.04 mol) was added to a stirred solution of (4-isopropylpiperazin-1-yl)(2-(1-(tetrahydro-2*H*-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazol-4-yl)oxazol-5-yl)-methanone (**45**) (50 kg, 91.00 mol), palladium acetate (0.2 kg, 0.89 mol), XPhos (0.65 kg, 1.36 mol), and potassium phosphate (46.4 kg, 218.6 mol) in MIBK (176 kg) and water (250 kg). The reaction mixture was vacuum-degassed and backfilled with nitrogen three times and then heated to 82 °C for 78 min prior to addition of further MIBK (300 L). The phases were mixed for 30 min and then separated. The organic phase washed sequentially with an aqueous solution made up from potassium carbonate (2.75 kg), *N*-acetylcysteine (5.2 kg), and water (250 kg) and then with water (250 kg) before it was concentrated to 300 L at atmospheric pressure. The crystallization mixture was cooled to 20 °C and stirred for 5 h, and then the product was filtered off, washed with MIBK (80 kg), and dried under vacuum at 50 °C to give the title compound (36.15 kg, 73.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.72 (s, 1H), 8.38 (br s, 1H), 8.35 (d, J = 1.0 Hz, 1H), 8.06 (s, 1H), 7.81 (s, 1H), 7.52−7.46 (m, 1H), 7.36−7.30 (m, 3H), 6.79−6.75 (m, 1H), 5.84 (dd, J = 9.17, 2.32 Hz, 1H), 4.10−4.04 (m, 1H), 3.88 (br s, 4H), 3.84−3.72 (m, 1H), 2.76 (spt, J = 6.5 Hz, 1H), 2.68−2.59 (m, 5H), 2.30−2.12 (m, 2H), 1.86−1.73 (m, 2H), 1.73−1.64 (m, 1H), 1.07 (d, J = 6.60 Hz, 6H).

2-(6-(1*H*-Indol-4-yl)-1*H*-indazol-4-yl)-5-((4-isopropyl-piperazin-1-yl)methyl)oxazole Methanol Solvate (51). Aluminum chloride (2.94 kg, 22 mol) was added to THF (216 kg) with stirring until dissolved. (2-(6-(1*H*-Indol-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)oxazol-5-yl)(4-isopropylpiperazin-1-yl)methanone (34.75 kg, 64.5 mol) (**50**) was added to the vessel, washed in with THF (0.5 kg), and the contents were cooled to 0 °C. A solution of lithium aluminum hydride in THF (10% w/w, 22.6 kg, 59.6 mol) was added while the temperature was maintained at less than 20 °C, followed by a THF (0.9 kg) line wash. The reaction mixture was stirred for 30 min, and then EtOAc (15.6 kg) was added, followed by 1 h of stirring. A solution of triethanolamine (2.36 kg) in THF (2.1 L) was added, followed by triethanolamine (36.8 kg) and then aqueous NaOH (15% w/w, 121 kg). The phases were separated, and the organic phase washed with aqueous NaOH (15% w/w, 121 kg). THF (17 kg) was added, and the solvent was distilled down to 104 L at atmospheric pressure. A constant-volume distillation (104 L) was performed by adding MeOH (174 L). ***CAUTION:*** *to avoid peroxide formation, THF distillate should be treated with a stabilizer*. MeOH (193.3 kg) was added, followed by chlorotrimethylsilane (35.8 kg, 329.5 mol), and the reaction mixture was heated to 50 °C for 3 h, after which time triethylamine (35.8 kg, 353.8 mol) was added and the crystallization mixture was cooled to 20 °C. The product was filtered off, washed with MeOH (2 × 55 kg), and dried under vacuum at 50 °C to give the title compound (24.80 kg, 81%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H 13.43 (br s, 1H), 11.36 (br s, 1H), 8.61 (s, 1H), 8.09 (d, J = 1.2 Hz, 1H), 7.92 (m, 1H), 7.51−7.46 (m, 2H), 7.32 (s, 1H), 7.28−7.22 (m, 2H), 6.61 (m, 1H), 4.09 (q, J = 5.3 Hz, 1H), 3.73 (s, 2H), 3.18 (d, J = 4.9 Hz, 3H), 2.60 (br s, 1H), 2.56−2.40 (m, 4H), 0.94 (d, J = 6.4 Hz, 6H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00486.

https://dx.doi.org/10.1021/acs.oprd.0c00486
Org. Process Res. Dev. 2021, 25, 529−540

Synthetic methods and characterization data for compounds **3**, **17**−**26**, **29**, **32**, **36**, 4-chloro-1*H*-indazole, and **44** (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All of the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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