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Development of an Asymmetric Synthesis of a Chiral Quaternary FLAP Inhibitor

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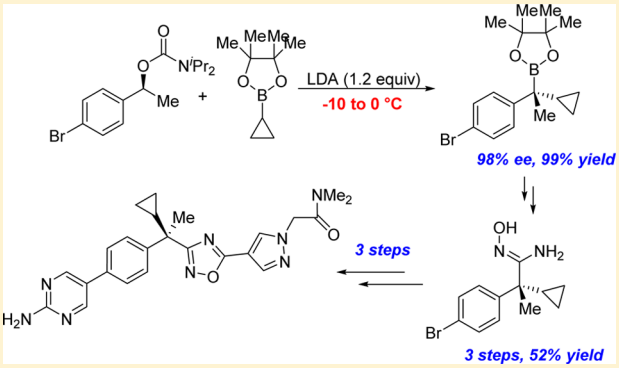
Supporting Information

ABSTRACT: A practical sequence involving a noncryogenic stereospecific boronate rearrangement followed by a robust formylation with an in situ generated DCM anion has been developed for the asymmetric construction of an all-carbon quaternary stereogenic center of a FLAP inhibitor. The key boronate rearrangement was rendered noncryogenic and robust by using LDA as the base and instituting an in situ trapping of the unstable lithiated benzylic carbamate with the boronic ester. A similar strategy was implemented for the DCM formylation reaction. It was found that the 1,2-boronate rearrangement for the formylation reaction could be temperature-controlled, thus preventing overaddition of the DCM anion and rendering the process reproducible. The robust stereospecific boronate rearrangement and formylation were utilized for the practical asymmetric synthesis of a chiral quaternary FLAP inhibitor.



INTRODUCTION

Cardiovascular disease is a significant health issue and is expected to become a greater public health threat with the aging population;[1] therefore, the development of effective new treatments for atherosclerosis is required. Inhibitors of the leukotriene (LT) biosynthesis pathway are effective treatments for inflammatory-based diseases,[2] and recently the LT pathway became the focus of atherosclerosis treatments. In particular, 5-lipoxygenase-activating protein (FLAP) inhibitors have been shown to affect biomarkers of atherosclerosis[3] and reduce plaque growth.[4] Compound **1**[5] (Figure 1) is under development as a FLAP inhibitor, and in order to continue the advancement of the molecule in development, an efficient and reproducible synthesis is required.

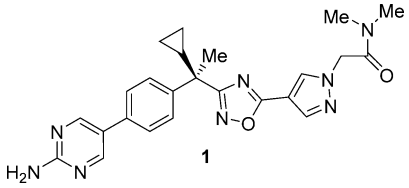


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Figure 1. Structure of FLAP inhibitor **1**.

Compound **1** represents a significant challenge for development,[6,7] as it contains diverse functionalities and at its core is an all-carbon quaternary stereogenic center. Retrosynthetically the target can be reduced to the chiral quaternary aryl aldehyde **5** (Scheme 1). A classical approach involves the construction of the benzylic quaternary center via ionization of the tertiary alcohol followed by trapping with a suitable soft nucleophile.[5a] Due to the formation of the benzylic carbocation the route is racemic and a chiral separation is required to produce the enantiopure FLAP inhibitor while also sacrificing at least half of the overall yield. As highlighted in a recent review article,[8] the stereoselective construction of all-carbon quaternary centers embedded in acyclic systems has proved to be particularly challenging. Although there are several asymmetric methodologies for the synthesis of acyclic all-carbon stereocenters in the literature,[9,10] these methods require cryogenic temperatures and/or have limited substrate scopes. Thus, the development of a new practical synthesis is required.

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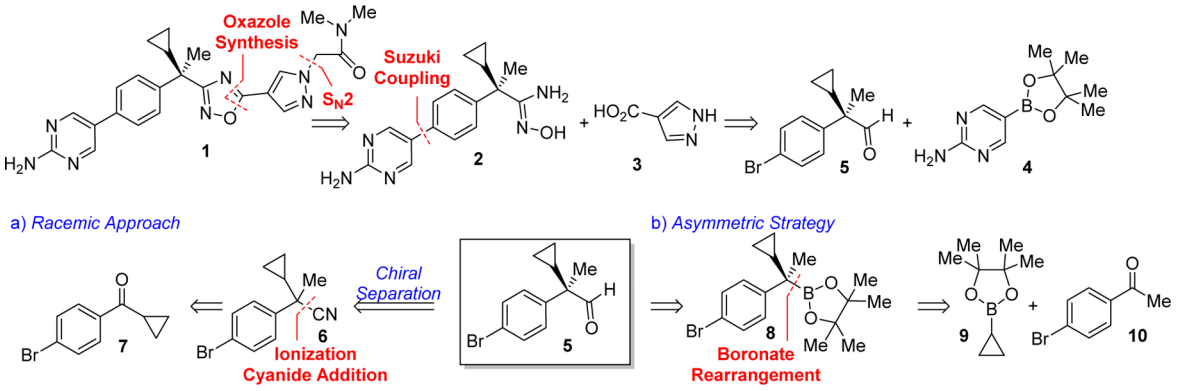
Scheme 1. Retrosynthetic Strategy for 1



RESULTS AND DISCUSSION

After evaluating several synthetic strategies for the construction of the key all-carbon stereocenter, Aggarwal's approach is particularly attractive with respect to the availability of the key starting materials and overall cost. Aggarwal and co-workers reported a direct stereoretentive conversion of secondary carbonates to tertiary boronates.[11] Furthermore, the authors demonstrated that the resulting boronic esters could then be utilized as a handle for the introduction of a carbon unit to complete the all-carbon quaternary stereocenter.[12] This methodology offers an attractive synthetic strategy in which the stereochemistry of the process is ultimately generated from a well-known asymmetric reduction of a prochiral ketone (Figure 2).[13] However, the two-step process required cryogenic

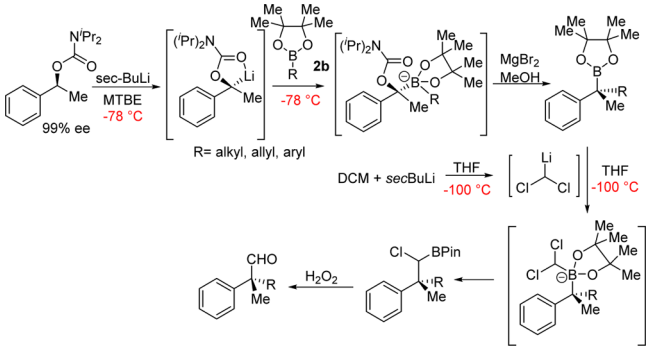


Figure 2. Aggarwal's approach for the construction of chiral quaternary stereocenters from secondary chiral carbamates.

temperatures (−78 and −100 °C) due to the accumulation of configurationally and thermally unstable intermediates. The accumulation of these unstable intermediates precluded the use of the process on a large scale, as these intermediates would be formed and held for extended periods (1 h or more). Furthermore, the use of alkyllithium bases prevented the use of the more versatile aryl bromide substrates which was required for the planned Suzuki cross-coupling.[14] In order to implement this elegant methodology in the synthesis of the chiral quaternary FLAP inhibitor **1**, we needed to render the process practical for large scale by eliminating the accumulation of the unstable intermediates and also eliminating the required extreme cryogenic temperatures. Herein we wish to report the development of a practical and robust boronate rearrangement and formylation process and its implementation in the practical asymmetric synthesis of the FLAP inhibitor **1**.

The required chiral secondary alcohol **11** was prepared by a Noyori asymmetric transfer hydrogenation[15] of bromoacetophenone **10** (91% ee, Figure 3). Purging of the reaction with dry nitrogen[16] allowed the catalyst loading to be reduced to 0.1 mol %. The crude intermediate alcohol **11** was treated with carbamyl chloride to form the solid carbamate **12a**, which after crystallization increased the ee to 99.9%. The two-step synthesis of carbamate **12a** proceeded in 80% overall isolated yield and 99.9% ee.

The reported Aggarwal boronate rearrangement process[11,12] is performed in three separate stages (Figure 4a); the first is the deprotonation of the benzylic carbamate with an alkyllithium base[17] and then the trapping of the lithiated carbamate with the boronic ester followed by a Lewis acid and/or thermally promoted 1,2-alkyl rearrangement. This process was shown to be quite general with regard to both the nature of the borane substitution and the migratory group. However, due to the accumulation of both the lithiated carbamate and the boronate complex the process required cryogenic temperatures to minimize racemization. However, if the deprotonation is conducted in the presence of the boronic ester substrate, the in situ formed lithiated carbamate would be quickly trapped by the boronic ester to form the boronate complex (Figure 4b). This in turn would bypass the accumulation of the configurationally unstable lithiated carbamate and would allow the process to be conducted at noncryogenic temperatures. In order to accomplish the in situ deprotonation and render the process inherently robust, a suitable base that is compatible with the electrophilic boronic ester needed to be found.

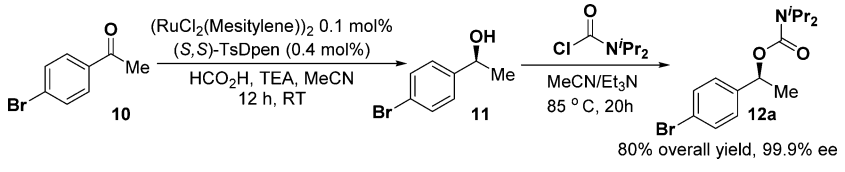


Figure 3. Synthesis of chiral benzylic carbamate **12a**.

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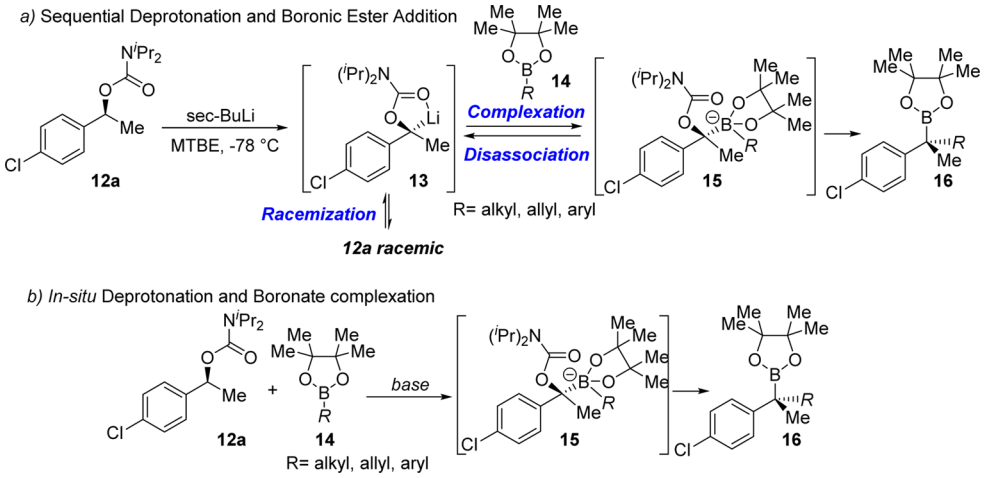
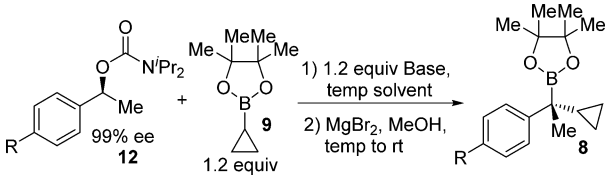


Figure 4. Boronate rearrangement mechanisms.

Table 1. Initial Development of the LDA in Situ Deprotonation and Boronate Rearrangement



entry	R	base	solvent	temp (°C)	conversion (%)[a]	ee erosion (%)[b]
1	Cl (**12a**)	*sec*-BuLi (1.2 equiv)	Et_2O	−30	0	NA
2	Br (**12b**)	LDA (2 M THF/Hept/EtPh)	CpOMe	−78	90	−4
3	Br (**12b**)	LDA (2 M THF/Hept/EtPh)	CpOMe	−30	80	−4
4	Br (**12b**)	LDA (2 M THF/Hept/EtPh)	CpOMe	−10	50	−10
5	Br (**12b**)	LDA (1 M CpOMe	CpOMe	−25	91	−0.8
6	Br (**12b**)	LDA (1 M CpOMe)	CpOMe	−10	96	−1.0
7	Br (**12b**)	LDA (1 M CpOMe)	CpOMe	4	92	−2.2

[a]Molar conversion determined by HPLC analysis. [b]Measured by ee erosion = (ee of product) − (ee of carbamate). Enantiomeric excess determined by chiral HPLC analysis.

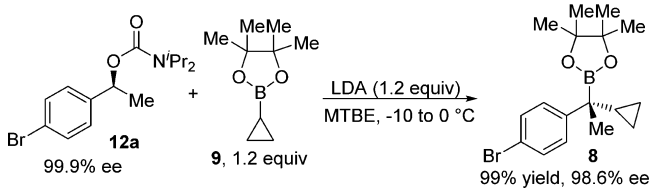
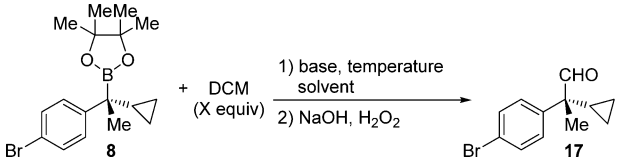


Table 2. Survey of Bases and Conditions for the in Situ DCM Anion Trapping



entry	base[a] (amt (equiv))	amt of DCM (equiv)	solvent	addition time (min)[b]	temp (°C)	conversion (%)[c]
1	*n*-BuLi (3)	5	THF/CPME (4/1)	<1	−30	85
2	LDA (4)	5	THF/CPME (4/1)	<1	−30	90
3	LDA (4)	5	THF/CPME (4/1)	<1	−10	90
4	LDA (4)	5	THF/CPME (4/1)	<1	0	93
5	LDA (4)	5	THF/CPME (4/1)	35	−15	25

[a]Base: *n*-BuLi 2.5 M in hexanes; LDA 2.0 M in THF/heptane/ethylbenzene. [b]Addition time of the base to the DCM/boronate solution. [c]Molar conversion as determined by HPLC analysis.

Attempts to perform the in situ deprotonation of the benzylic carbamate in the presence of the boronic ester with *n*-butyllithium provided no observable product. As was suspected, the alkyllithium base kinetically traps the boronic ester faster than

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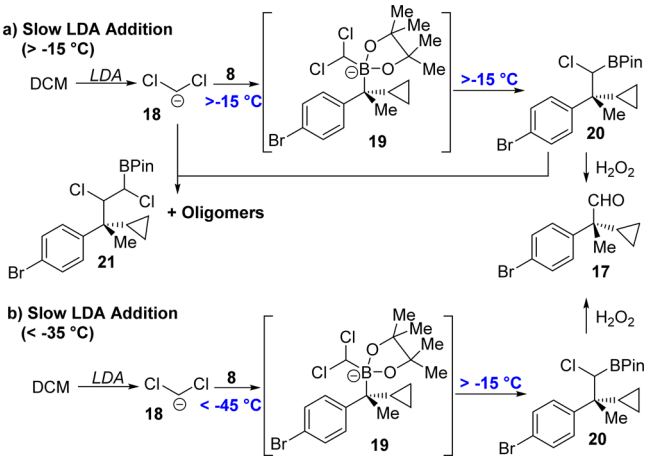

Figure 5. Proposed mechanism and effects of temperature for the DCM homologation.

it deprotonates the benzylic carbamate. However, the use of LDA[18] was found to be compatible with the boronic ester in the in situ deprotonation and boronate formation (Table 1), as high conversion and low ee erosion were obtained for the model system.[19,20] Furthermore, it was found that the reaction could be conducted under noncryogenic conditions (4 °C) if coordinating ethereal solvents (tetrahydrofuran) were removed from the system (92% conversion and 97% ee, entry 7). It was subsequently discovered that the use of methanolic magnesium bromide was not needed, as the requisite tertiary boronic ester **8** was formed with this LDA process in near-perfect yield (99%, Table 1) and with excellent stereoretention (98.6% ee) without this additive.

To convert the optically enriched boronate **8** into chiral aldehyde **17** containing the requisite all-carbon stereocenter, a subsequent in situ deprotonation of DCM[21] was implemented to trap the highly unstable lithated DCM species upon its formation.[22] Initial attempts at the in situ deprotonation of DCM at −30 °C with *n*-BuLi (2 M in hexanes) provided the desired chloromethylene addition intermediate **20** (Table 2), indicating that the deprotonation of DCM is faster than trapping of the alkyllithium base with the boronic ester intermediate or the competitive lithium halogen exchange. However, the reaction is highly exothermic upon the addition of the alkyllithium base to the reaction solution. The in situ deprotonation with LDA was found to be far less exothermic and controllable by the rate of LDA addition to the reaction. Our original investigation suggested that the process required the use of a large excess of DCM (6 equiv) and LDA (4 equiv) to drive the reaction to high conversion (>80%). The reaction could be conducted at 0 °C with a short LDA addition time (entry 4). However, this process was found to be irreproducible, with wide variations of reaction yields and byproduct formation. Therefore, we investigated the long addition time of LDA, as this was suspected to be a defining factor for the reaction irreproducibility. Indeed, the longer addition times provided for significantly lower yields (20−40%, −15 °C, entry 5) and the formation of several major byproducts. We hypothesized that side reactions involved the overaddition of DCM anion to product **20** due to the premature rearrangement of intermediate **19** at higher reaction temperatures (Figure 5).

The boronate rearrangement of the DCM anion process was monitored by ReactIR[23] to determine the relative temperature at which the 1,2-rearrangement of compound **19** to **20** occurs at an appreciable rate to compete with the LDA addition time (Figure 6). After the boronate complex was formed at −45 °C, the system was slowly warmed. At approximately −25 °C the rearrangement was observed to form the chloromethylene insertion product **20**. Thus, when the reaction temperature is maintained below −45 °C, the premature boronate rearrangement to **20** can be effectively suppressed and the borate complex is shielded from overaddition of the DCM anion during the LDA addition. The 1,2-migration process was also studied computationally utilizing density functional theory (DFT) with the B3LYP level of theory[24] and 6-311G basis set[25] employing the Gaussian 09 software package[26] (Figure 7). The 1,2-migration of the benzylic fragment was found to be a smooth process with concurrent displacement of the antiperiplanar chloride leaving group. The calculated transition state was found to be 17.9 kcal/mol higher

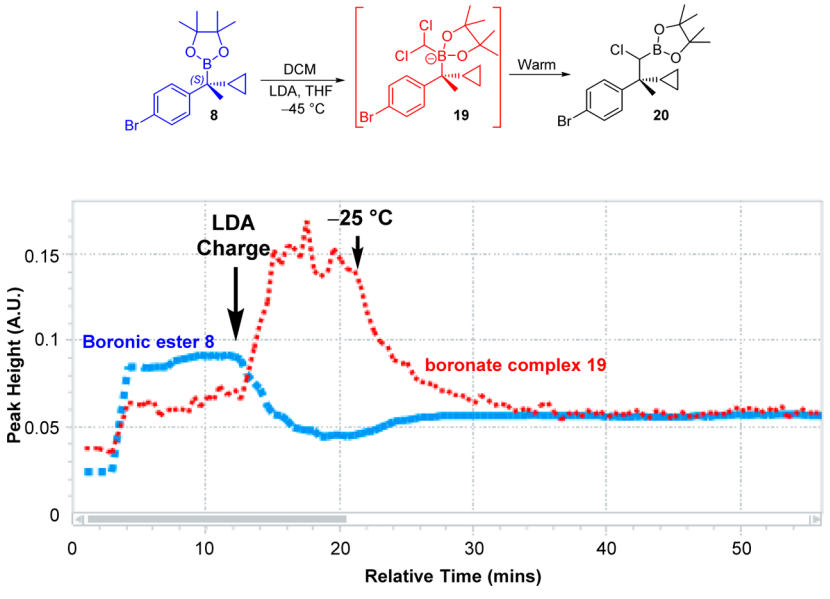

Figure 6. ReactIR monitoring of the LDA DCM formylation process.

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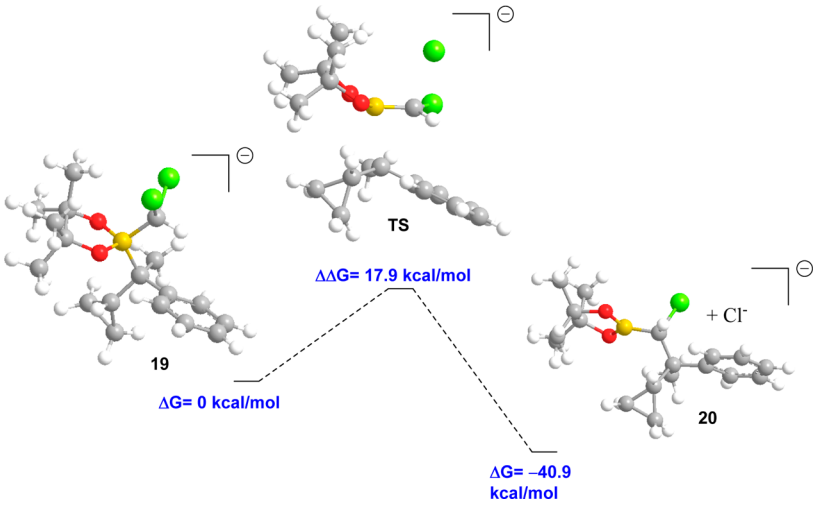
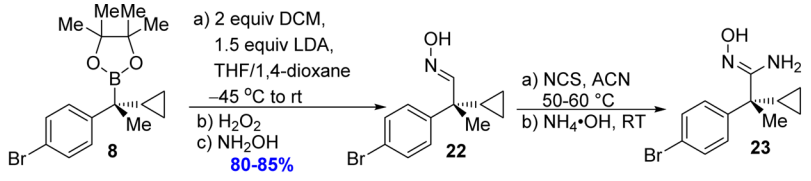


Figure 7. Computational results for the 1,2-migration (B3LYP/6-311G).



a) Quality of **22** for the thermal NCS Chlorination

Substrate	Temp.	Conversion[a]
Purified **22**	20 °C	0%
Purified **22**	60 °C	>95%
Crude **22**	60 °C	<10% Decomposition

[a]Molar conversion as determined by HPLC analysis

b) Heat flow monitoring of the NCS induction period for the chlorination of purified oxime **22**

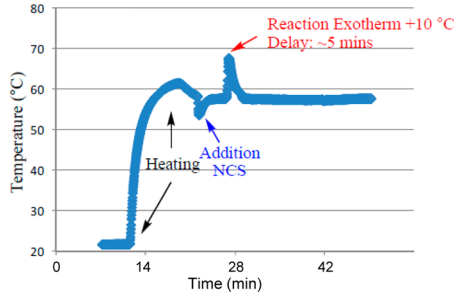


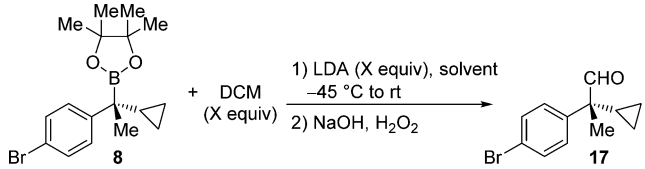
Figure 8. Initial investigation of the NCS chlorination of oxime **22**.

in energy from the corresponding dichloromethylene boronate complex **19**.

Given this understanding of the stability of the DCM anion and the key intermediate behavior with respect to temperature and side product formation, we turned our attention to reducing the amount of LDA in the process (Table 3) in order to render the process efficient. The amount of LDA could be lowered to 1.5 equiv by using a more polar solvent system (4/1 THF/dioxane, entry 3) to provide high conversions to the desired addition product. The crude chloromethylene intermediate **20** was subsequently oxidized in the same pot to the aldehyde **17** in 85−93% molar conversion. Oxime **22** (Figure 8) was formed directly from the aldehyde in near-quantitative yield.

Attempts to use the crude oxime **22** in the subsequent *N*-chlorosuccinimide oxidation[27] and amido-oxime formation[28] led to significant decomposition. With purified oxime **22** the chlorination reaction was found to require elevated temperatures (Figure 8). Calorimetric monitoring of the reaction (Figure 8b) found that the reaction had an unpredictable induction period, which was found to be marked by a sharp exothermic event. Furthermore, the crude oxime **22** from the formylation process failed to thermally induce. It was suspected that the reaction is autocatalytic with the formation of trace HCl[29] during the heating cycle. As the formylation of the tertiary boronic ester **8** does not reach complete conversion (>90%), trace amounts of

Table 3. Survey of Solvents for the in Situ DCM Anion Formylation



entry	amt of LDA[a] (equiv)	amt of DCM (equiv)	solvent	conversion (%)[b]
1	3.8	5	THF/CPME (4/1)	94
2	2.0	3	THF	93
3	1.5	2	THF/1,4-dioxane (4/1)	95

[a]The base was added portionwise until the conversion was recorded as >90% via HPLC analysis. [b]Molar conversion as determined by HPLC analysis.

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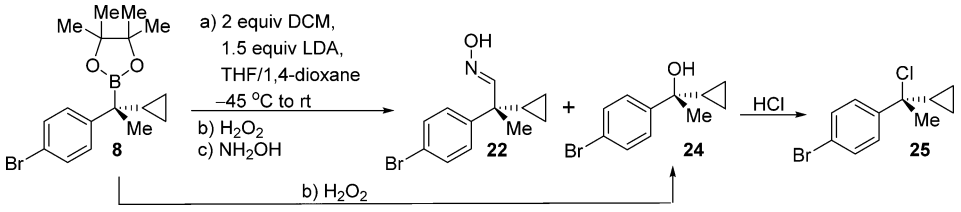


Figure 9. Formation of tertiary alcohol **24** from the incomplete formylation of boronic ester **8**.

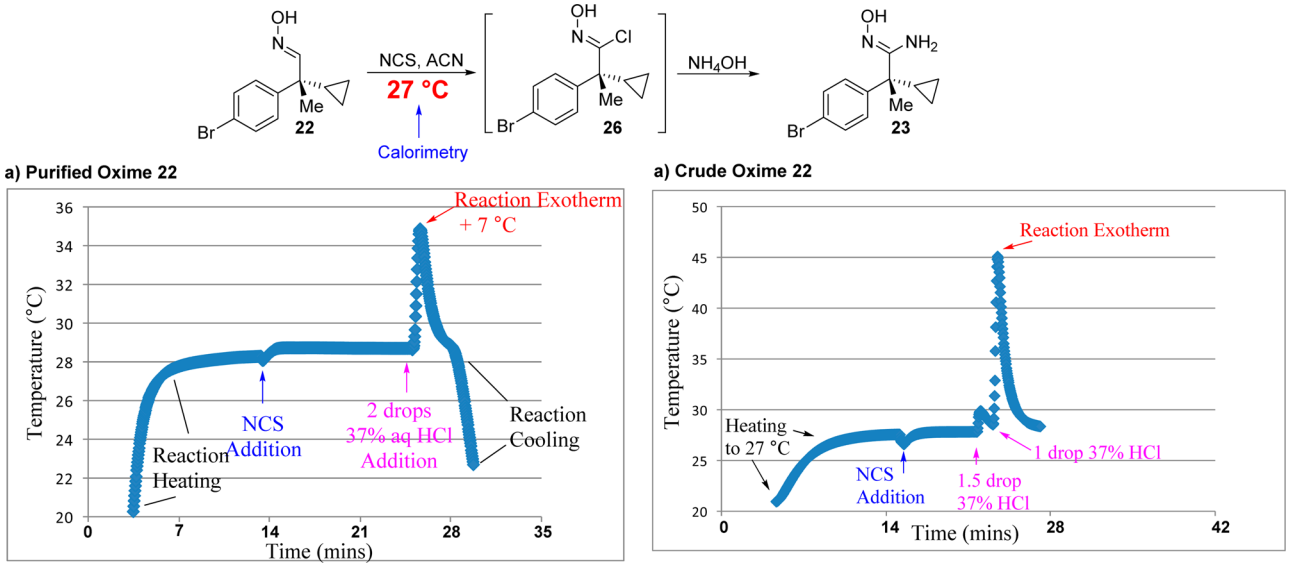


Figure 10. HCl-promoted chlorination of oxime **22**.

boronic ester **8** would be converted to the tertiary alcohol **24** (Figure 9) during the hydrogen peroxide treatment. The trace tertiary alcohol **24** could serve as an acid scavenger, thus impeding the acid-promoted chlorination of the oxime. To test this hypothesis, both crude and purified oxime **22** were treated with NCS at 27–28 °C (Figure 10). HPLC and calorimetric analysis indicated no reaction when the batch was held at this temperature. However, upon the addition of catalytic HCl (37% aqueous) an instant exothermic event that corresponded to the formation of the chlorinated product by HPLC analysis was observed. Furthermore, with the addition of catalytic amounts of HCl at the onset of the reaction, the process was rendered reproducible while eliminating the unpredictable exothermic induction period and allowing the chemistry to be conducted at ambient or subambient temperatures. The formylation process was demonstrated with crude boronic ester **8**, whereas a 90% molar conversion was obtained for the intermediate aldehyde **17**. The crude aldehyde product (an oil) was directly processed to the solid amido-oxime intermediate **23** in 99% ee and 52% overall yield for the entire sequence from the boronic ester **8** (Figure 11).

With the key quaternary stereocenter established in >99% ee as the amido-oxime **23**, the substrate was in position for the

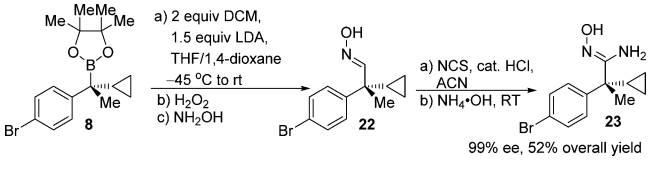
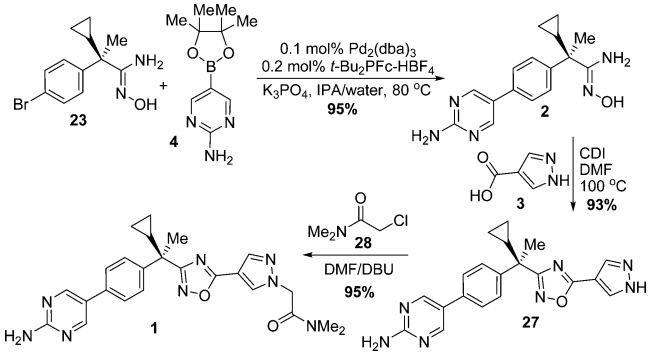


Figure 11. Synthesis of amido-oxime **23** from tertiary boronate **8**.

Suzuki cross-coupling[30] with the pinacol boronic ester **4** (Scheme 2). Although the cross-coupling could be performed

Scheme 2. Synthesis of 1 from Amido-Oxime 15



with $Pd_2(dba)_3$ and the tetrafluoroborate salt of P(*t*-Bu)$_3$ (1 mol % of Pd), it was found that the catalyst loading could be reduced to 0.2 mol % (Pd) with the di-*tert*-butylphosphinoferrocene (*t*-Bu_2PFc-HBF_4)[31] ligand. The Suzuki product **2** was found to precipitate directly from the reaction mixture in high yield and purity. Following the synthesis of the oxadiazole[32] from the CDI-activated carboxylic acid **3**, a final alkylation of the pyrazole completed the synthesis. This sequence was employed to produce multikilogram quantities of the target compound **1** to support preclinical development.

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CONCLUSION

In conclusion, a short and efficient asymmetric synthesis of a structurally challenging FLAP inhibitor has been developed. The asymmetric synthesis proceeded in nine steps and 35% overall yield. The requirements for large-scale synthesis served as the impetus for the development of a robust asymmetric synthesis of the all-carbon quaternary carbon stereocenter of the target molecule. By replacing *sec*-BuLi with LDA and instituting an in situ trapping of the unstable lithiated carbamate, the key boronate rearrangement was rendered noncyrogenic while the substrate scope was also increased to include the requisite aryl bromide substrate. Furthermore, a similar strategy was implemented to convert the chiral tertiary boronate to the key all-carbon quaternary aldehyde with excellent optical purity. ReactIR and DFT molecular modeling studies were conducted to study the key 1,2-migration process for the formylation reaction. It was found that the 1,2-boronate rearrangement could be temperature-controlled, thus preventing overaddition of the DCM anion and rendering the reaction reproducible. We believe that these new methods would provide the chemists with valuable tools for the practical and stereoselective construction of acyclic all-carbon quaternary chiral centers and the production of complex bioactive compounds.

EXPERIMENTAL SECTION

(*S*)-1-(4-Bromophenyl)ethyl Diisopropylcarbamate (12a). In a Schlenk flask was placed dichloro(mesitylene)ruthenium(II) dimer (307.5 mg, 0.5 mmol, 0.001 equiv) and (1*S*,2*S*)-*N*-*p*-Tosyl-1,2-diphenylethylenediamine (748 mg, 2.0 mmol, 0.004 equiv). The mixture was purged with argon three times, and degassed acetonitrile (75 mL) followed by triethylamine (20 mL, 0.15 mol, 0.37 equiv) were added to the flask. The mixture was stirred at 20 °C for 30 min. In a separate flask was placed 1-(4-bromophenyl)ethan-1-one (**10**; 99%, 99.52 g, 0.5 mol, 1.00 equiv), the flask was purged with nitrogen three times, and acetonitrile (375 mL) was added to the reactor, followed by triethylamine (85 mL, 0.6 mol, 1.13 equiv) and formic acid (65 mL, 1.5 mol, 3.00 equiv) at 0−3 °C. After nitrogen sparging, the catalyst solution was added and the mixture was stirred for 15 h with slow nitrogen sparging. The mixture was concentrated to ∼30% volume, diluted with ethyl acetate (150 mL), and then concentrated to ∼25% volume and diluted again with ethyl acetate (700 mL). The organics were washed with water (200 mL) and 5% aqueous sodium bicarbonate solution (200 mL). The organics were concentrated to a thick liquid via reduced pressure (∼45 °C), acetonitrile (200 mL) was added, and the batch was concentrated again to yield the crude product **11**, which was used directly in the next step.

In a 1 L 3-neck flask were placed diisopropylcarbamic chloride (94.1 g, 0.575 mol, 1.15 equiv), acetonitrile (400 mL), an acetonitrile solution of (*S*)-1-(4-bromophenyl)ethan-1-ol (**11**), and finally triethylamine (83.6 mL, 0.6 mol, 1.2 equiv). The mixture was heated at a mild reflux (∼83 °C) for ∼15 h and was then concentrated via reduced pressure (∼55 °C), and the concentrate was diluted with ethyl acetate (200 mL) and reconcentrated to minimum volume (350 mL). At 20 °C ethyl acetate (700 mL) was added and the organics were washed with water (2 × 200 mL). The organic layer was cut and passed through a pad of Celite, and the flask and pad were rinsed with ethyl acetate (50 mL). The combined filtrates were concentrated via reduced pressure (∼50 °C). Methanol (200 mL) was added, and the mixture was concentrated. Methanol (270 mL) was added, and the mixture was cooled to −5 °C, seeded, and stirred at ∼0 °C for 1 h, after which an off-white slurry was formed. A precooled (∼0 °C) solution of methanol−water (960 mL) was added to the slurry over 2 h while the reaction temperature was kept between −5 and 0 °C, then the slurry was held at −5 °C for 12 h. The product was collected by filtration and was rinsed with a precooled (0 °C) 1:1 mixture of methanol and water (150 mL). The solids were dried on the filter and then under vacuum with no heating (the melting point of the product carbamate is 39−40 °C) for 20 h with a nitrogen stream to afford 141 g of a beige crystalline solid (**12a**). Yield: 84%, 99.7% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 5.78 (q, J = 7.0 Hz, 1H), 4.2−3.6 (m, 2H), 1.53−1.51 (d, J = 7.0 Hz, 3H), 1.4−1.1 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.8, 141.9, 131.5, 127.8, 121.2, 72.0, 46.3−45.3 (br), 22.6, 21.5−20.7 (br). HRMS (TOF MS): [$C_{15}H_{22}BrNO_2$ + H^+] calculated 328.0907; found 328.0904.

(*S*)-2-(1-(4-Bromophenyl)-1-cyclopropylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8). In a dry, inert flask were placed (*S*)-1-(4-bromophenyl)ethyl diisopropylcarbamate (**12a**; 100 g, 0.302 mol), MTBE (600 mL), and cyclopropylboronic acid pinacol ester (**9**; 67.2 mL, 0.40 mol, 1.3 equiv) at 20 °C. The mixture was cooled to −15 °C. In a second flask were placed diisopropylamine (38.15 g, 0.377 mol, 1.25 equiv) and MTBE (100 mL), and the mixture was cooled to 0 °C. *n*-Butyllithium (2.5 M hexanes) (144.7 mL, 0.362 mol, 1.20 equiv) was added over 30 min to the diisopropylamine solution, with the temperature maintained at ∼0 °C. After it was stirred for 15 min at 0 °C, the LDA solution was added to the solution of carbamate/pinacol ester, wih the temperature maintained below −10 °C. After complete addition of the LDA solution, the mixture was warmed to +10 °C and was stirred for 1 h. Upon completion the mixture was quenched by addition of a solution of aqueous citric acid (20 g, 104 mmol in 380 mL of water), with the temperature maintained below 30 °C. The bottom layer was removed, and the organics were washed with water (400 mL) and then concentrated by vacuum distillation (∼50 °C) to afford **8** as an oily liquid: 295 g (31 wt %), 99% assay yield, 97.3% ee. The resulting solution was used directly in the following step. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 1.2−1.19 (d, J = 5 Hz, 12H), 1.78 (s, 3H), 1.10−1.02 (m, 1H), 0.51−0.44 (m, 3H), 0.33−0.27 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.3, 128.7, 126.8, 116.7, 81.2, 65.4, 22.3, 22.3, 19.4, 16.4, 0.00, −0.70. HRMS (TOF MS): [$C_{17}H_{24}BBrO_2$ + H^+] calculated 351.1125; found 351.1110.

(*R*)-2-(4-Bromophenyl)-2-cyclopropyl-*N*′-hydroxypropanimidamide (23). In a clean, dry flask were placed a solution of (*S*)-2-(1-(4-bromophenyl)-1-cyclopropylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**8**) in MTBE (50 g at 47 wt %, 68.2 mmol, 1.0 equiv) and anhydrous THF (60 mL). The mixture was concentrated to remove MTBE. The water content, as determined by Karl Fisher analysis, of the resulting solution was targeted to be less than 350 ppm. If the water content exceeded 350 ppm, iterative distillation was used to lower the water content to the targeted level. To the mixture were added THF (100 mL), 1,4-dioxane (25 mL), and dichloromethane (8.75 mL, 136.4 mmol, 2.0 equiv). The mixture was cooled to −50 °C, and lithium diisopropylamide (2 M in THF/heptane/ethylbenzene; 51.2 mL, 102.3 mmol, 1.50 equiv) was added over a period of 30 min while the reaction temperature was maintained at −50 to −45 °C and then held at −50 °C for 16 h (overnight). After completion of the reaction (to α-chloromethyl boronoester intermediate) was confirmed (monitored by HPLC), methanol (24 mL) was added while the reaction temperature was maintained below −20 °C. Following complete addition, the mixture was warmed to ∼10 °C and was stirred for 20 min. Afterward, aqueous hydrogen peroxide (30 wt %, 8.1 g, 71.6 mmol, 1.05 equiv) was added over a period of 30 min. After completion of the reaction (aldehyde was confirmed by HPLC), 4 N aqueous hydrochloric acid (37 wt %, 65 mL) and MTBE (25 mL) were added. The aqueous phase was discarded, and the organics were washed with a 20 wt % aqueous solution of sodium sulfite (30 mL). The organics were concentrated, giving 49.7 g (31 wt %, 90% assay yield) of the crude aldehyde **17**. To an organic solution of (*R*)-2-(4-bromophenyl)-2-cyclopropylpropanal (**17**) was added ethanol (60 mL), and the mixture was concentrated to a volume of ∼45 mL. After further addition of ethanol (60 mL) and cooling of the mixture to 10 °C, an aqueous hydroxylamine hydrochloride solution (50 wt %, 6.28 mL, 102.3 mmol, 1.5 equiv) was added to the mixture, while the temperature was maintained below 20 °C. The mixture was stirred at 20 °C for 3.5 h, and then isopropyl acetate (141 mL) was added. The mixture was washed with 5 wt % aqueous sodium chloride (2 × 59 mL) and concentrated to a volume of ∼50 mL. To the concentrate was added acetonitrile (48 mL), and the mixture was concentrated again to ∼50 mL. The material was transferred from the flask, and acetonitrile (24 mL) was used to rinse the

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flask; the rinse was combined with the product and concentrated under reduced pressure to provide 21.6 g of crude **22** (74.4 wt %; 98.2% assay yield for oxime step, 88% combined yield for two steps). HRMS (TOF MS) for compound **22**: $[C_{12}H_{14}BrNO + H^+]$: calculated 268.0332; found 268.0339. The concentrate was used in the next step directly. The solution of (*R*)-2-(4-bromophenyl)-2-cyclopropylpropanal oxime (**22**) in acetonitrile from the previous step was cooled to 15 °C, and aqueous hydrochloric acid (37 wt %, 1.93 mL, 22.2 mmol, 0.2 equiv) was added. A solution of *N*-chlorosuccinimide (18.1 g, 132.9 mmol, 1.2 equiv) in acetonitrile (110 mL) was then added while the temperature was maintained at ∼15 °C. The resulting mixture was stirred at this temperature for 5 h. After reaction completion (chlorinated oxime intermediate) was confirmed (monitored by HPLC), the mixture was cooled to 0 °C and aqueous ammonia (28−30 wt %, 29.7 mL, 221.5 mmol, 2.0 equiv) was added while the reaction temperature was maintained at <20 °C. The mixture was warmed to ∼20 °C and stirred for 3.5 h. The mixture was cooled to ∼10 °C, and 11.5 M HCl (65 mL) and water (75 mL) were added slowly to maintain the temperature between 20 and 25 °C. Heptane (100 mL) and MTBE (50 mL) were added to the mixture. The top layer (heptane/MTBE) was removed, and the bottom layer (ACN/water/product) was retained. To this product layer were added isopropyl acetate (195 mL) and 4 N aqueous sodium hydroxide (169 mL). After mixing and settling, the bottom aqueous layer was removed and the top organic layer was washed with water (75 mL). The final organic layer was concentrated to ∼50 mL volume, and 2-propanol (250 mL) was added. The mixture was concentrated to remove 250 mL of solvents to reach a final volume of 50 mL. Heptane (25 mL) was added, and the mixture was heated to ∼55 °C, cooled to ∼48 °C, seeded, and then cooled to 30 °C over 2 h. Heptane (120 mL) was then added to the mixture over 2 h. The mixture was concentrated at 30 °C under reduced pressure to reach a batch volume of ∼90 mL, and then the resulting slurry was further cooled to to −3 °C over 2 h and stirred for an additional 1 h at −3 °C. The product was collected by filtration, and the solid was rinsed with a cold mixture of 1:4 IPA−heptane (20 mL) and air-dried for 2 h, followed by vacuum drying at 50 °C for 12 h, to afford 23.51 g of **23** as an off-white solid (75% yield for the amidoxime step, 99.1% ee). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.89 (s, 1H), 7.45 (d, J = 8.5, 2H), 7.32 (d, J = 8.5, 2H), 4.39 (s, 1H), 1.37−1.32 (m, 1H), 1.31 (s, 3H), 0.60−0.49 (m, 2H), 0.38−0.33 (m, 1H), 0.30−0.26 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.6, 141.3, 129.2, 127.1, 118.9, 43.8, 20.0, 16.7, 0.00, −0.92. HRMS (TOF MS): $[C_{12}H_{15}BrN_2O + H^+]$ calculated 283.0441; found 283.0441.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (4). In a clean, dry, nitrogen-inerted flask (#1) were placed 2-amino-5-bromopyrimidine (30 g, 172 mmol, 1.0 equiv), bis-(pinacolato)diboron (48.16 g, 190 mmol, 1.1 equiv), di-*tert*-butylphosphinoferrocene tetrafluoroborate (0.144 g, 0.35 mmol, 0.2 mol %), tris(dibenzylidineacetone)palladium (0.158 g, 0.17 mmol, 0.1 mol %), and potassium acetate (33.84 g, 345 mmol, 2.0 equiv). Flask #1 was evacuated and purged with nitrogen. In flask #2, 2-methyltetrahydrofuran (120 mL) was sparged with nitrogen and then placed in flask #1. The mixture was heated to 82 °C over 0.5 h and then held at 82 °C for 4.5 h (a slurry forms). The mixture was cooled to ∼60 °C (suspension), and tetrahydrofuran (390 mL) was added to make a solution. The solution was filtered at 60 °C to remove solids, ensuring both filter and the receiver were heated to 60 °C. Tetrahydrofuran (150 mL) heated to 60 °C was used to rinse the flask and filtered solids. The combined filtrates were distilled at ∼55 °C under vacuum to the minimum stirrable volume. Ethanol (150 mL) was added, and the mixture was again concentrated to minimum volume. Ethanol (390 mL) was added, and the mixture was heated to 65 °C and held for 1 h. The ethanol solution was then filtered through a heated (65 °C) filter containing CUNO type 5 carbon. The reactor and filter were rinsed with preheated (60 °C) ethanol (60 mL). The combined filtrates were placed in a clean flask and were concentrated at 60 °C under vacuum. The resulting slurry was cooled to 20 °C over 2 h and then held at 20 °C for 2 h. The solids were collected by filtration and were rinsed with ethanol (90 mL). The solid was dried on the funnel for 1 h and then in a vacuum oven at 45 °C for 8 h, giving 28.4 g of **4** as a white crystalline solid (75% yield, 97.8 wt %, Pd 2 ppm). Mp: 212 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.59 (s, 1H), 5.69 (s, 2H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.9, 164.4, 84.1, 25.0. HRMS (TOF MS): $[C_{10}H_{16}BN_3O_2 + H^+]$ calculated 222.1408; found 222.1399.

(*R*,*Z*)-2-(4-(2-Aminopyrimidin-5-yl)phenyl)-2-cyclopropyl-*N*′-hydroxypropanimidamide (2). In a clean, dry, nitrogen-inerted flask were placed **23** (50 g, 170 mmol, 1.0 equiv), **4** (49.5 g, 222 mmol, 1.3 equiv), $FcPtBu_2HBF_4$ (0.162 g, 0.22 mol %), and $Pd(OCOCF_3)_2$ (0.117 g, 0.20 mol %). The flask was evacuated and purged with nitrogen. A solution of potassium phosphate hydrate (78 g, 341 mmol, 2 equiv) in water (200 mL) was placed in the flask, followed by isopropyl alcohol (250 mL) (both liquids were previously sparged with nitrogen). The mixture was heated to 80 °C over 0.5 h with good agitation (biphasic mixture) and then held at 80 °C for 4 h. A solution of *N*-acetyl-L-cysteine (7.0 g) in water (300 mL) was added at a constant rate over 1 h, at a temperature of 80 °C. The slurry was held at 80 °C for 4 h, cooled to 20 °C over 4 h, and then held at 20 °C for 30 min. The solids were collected by filtration and were rinsed with water (150 mL) followed by isopropyl acetate (150 mL). The product was dried on the filter at 20 °C for 1 h and then in a vacuum oven at 40 °C for 30 h, giving 50.5 g of **2** as an off-white crystalline solid (95% yield, 99.7% ee, Pd 180 ppm). Mp: 201 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.18 (s, 1H), 8.55 (s, 2H), 7.55 (d, J = 8.48 Hz, 2H), 7.43 (d, J = 8.48 Hz, 2H), 6.73 (s, 2H), 5.06 (s, 2H), 1.50 (m, 1H), 1.11 (s, 3H), 0.51 (m, 1H), 0.33−0.42 (m, 2H),), 0.20 (m, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 162.9, 157.1, 155.8, 145.4, 133.1, 127.6, 124.8, 122.1, 45.1, 21.2, 18.4, 2.2, 0.9. HRMS (TOF MS): $[C_{16}H_{19}N_5O + H^+]$ calculated 298.1662, found 298.1651.

(*R*)-5-(4-(1-(5-(1*H*-Pyrazol-4-yl)-1,2,4-oxadiazol-3-yl)-1-cyclopropylethyl)phenyl)pyrimidin-2-amine (27). In a clean, dry, nitrogen-inerted flask were placed carbonydimidazole (CDI) (35.4 g, 218 mmol, 1.2 equiv) and tetrahydrofuran (378 mL). To the CDI slurry was added a solution of 1*H*-pyrazole-4-carboxylic acid (**3**; 26.5 g, 236 mmol, 1.3 equiv) in dimethylformamide (135 mL) slowly at 20 °C, and the flask was rinsed with tetrahydrofuran (60 mL) into the CDI solution. The mixture was heated to 50 °C over 0.5 h and held at 50 °C for 0.5 h (gas evolution was observed). A slurry of **2** (60.0 g, 90.0 wt %, 182 mmol, 1 equiv) in THF (358 mL) was added to the activated acid, and the mixture was heated to 105 °C (removing the THF by distillation) and then held at 105 °C for 17 h. The mixture was cooled to 20 °C over 1 h, and then ethyl acetate (757 mL) and water (378 mL) were added. The layers were separated, and the organic layer was washed with water (378 mL). The organic layers were then heated to 50 °C and passed through a filter containing CUNO type 3 carbon. The filter was rinsed with ethyl acetate (216 mL), and the combined filtrates were added to a clean flask (no Pd) and were concentrated under vacuum at 55−60 °C to 150−200 mL total volume. At 55−60 °C the solution was seeded and stirred for 0.5 h. At 55−60 °C isopropyl acetate (324 mL) was added and the slurry was concentrated to 150−200 mL total volume. Heptane (108 mL) was added at 55−60 °C, and the slurry was stirred at 57 °C for 1 h and then cooled to 20 °C over 4 h and held at 20 °C for 8 h. The product was collected by filtration, and the solids were rinsed with isopropyl acetate (54 mL) and then heptane (162 mL). The solids were dried on the funnel for 1 h at 20 °C and then for 24 h at 60 °C under vacuum, yielding 58.9 g of **27** as an off-white crystalline solid (85.9% yield, 99.7% ee, Pd <2 ppm). Mp: 190 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.54 (s, 2H), 8.19 (s, 1H), 7.56 (d, J = 8.71 Hz, 2H), 7.37 (d, J = 8.71 Hz, 2H), 6.75 (s, 2H), 1.67 (m, 1H), 0.64 (m, 1H), 0.31−0.51 (m, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 175.7, 170.8, 162.9, 155.9, 143.8, 133.6, 127.4, 125.2, 121.8, 106.1, 42.8, 22.0, 19.4, 2.1, 1.1. HRMS (TOF MS): $[C_{20}H_{19}N_7O + H^+]$ calculated 374.1724; found 374.1721.

(*R*)-2-(4-(3-(1-(4-(2-Aminopyrimidin-5-yl)phenyl)-1-cyclopropylethyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*,*N*-dimethylacetamide (1). In a clean, dry, nitrogen-inerted flask were placed **27** (50.0 g, 99.1 wt %, 132.7 mmol, 1.0 equiv), DMF (150 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 27.8 mL, 185.8 mmol, 1.4 equiv). To the mixture was added 2-chloro-*N*,*N*-dimethylacetamide (**28**; 17.74 mL, 172.5 mmol, 1.3 equiv) over 10 min with cooling to maintain an internal temperature of <50 °C. The mixture was heated to 50 °C and held for 1 h. At 50 °C isopropyl acetate (200 mL) was added, and the solution was seeded at 52 °C. Water (150 mL) was added at 52 °C slowly over 1 h, and the slurry was agitated at this temperature for 0.5

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h (creates initial seed bed). Water (150 mL) was added to the flask at 52 °C slowly over 1 h, and the slurry was agitated at this temperature for 1 h. Water (300 mL) was added to the reaction mixture at 52 °C slowly over 1 h, the mixture was agitated at 52 °C for 2 h, and the slurry was cooled to 20 °C linearly over 4 h and stirred at 20 °C for 9 h. The product was collected by filtration, and the solid was rinsed consecutively with water (150 mL), isopropyl acetate (150 mL), and heptane (150 mL). The solid was dried for 1 h at 20 °C on the funnel and then for 24 h at 55 °C under vacuum, giving 58.3 g of **1** as an off-white crystalline solid (94.4% yield, 98.5 wt %, 99.8% ee). Crude **1** could be further purified by recrystallization from ethanol/water. Mp: 196 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.55 (s, 2H), 8.49 (s, 1H), 8.06 (s, 1H), 7.56 (d, J = 8.48 Hz, 2H), 7.38 (d, J = 8.48 Hz, 2H), 6.75 (s, 2H), 5.22 (s, 2H), 3.03 (s, 3H), 2.85 (s, 3H), 1.67 (m, 1H), 0.64 (m, 1H), 0.31−0.52 (m, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 175.7, 170.4, 165.9, 162.9, 155.9, 143.8, 138.6, 134.0, 133.6, 127.4, 125.2, 121.8, 106.7, 53.2, 42.8, 35.90, 35.3, 22.1, 19.4, 2.1, 1.1. HRMS (TOF MS): [$C_{24}H_{26}N_8O_2$ + H^+] calculated 459.2251, found 459.2241.

■ ASSOCIATED CONTENT

Supporting Information

Figures, tables, and a CIF file giving crystallographic data for compound **23**, ^{1}H NMR, ^{13}C NMR, and chiral HPLC spectra, and computational data. 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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