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Enantioselective Synthesis of a γ-Secretase Modulator via Vinylogous Dynamic Kinetic Resolution

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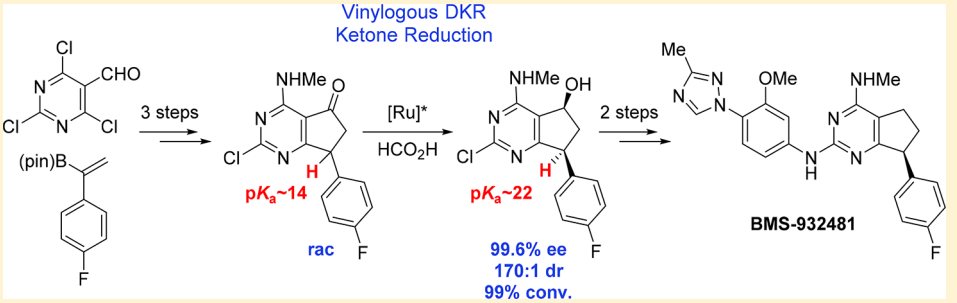
Supporting Information



ABSTRACT: Two efficient asymmetric routes to γ-secretase modulator BMS-932481, under investigation for Alzheimer's disease, have been developed. The key step for the first route involves a challenging enantioselective hydrogenation of an unfunctionalized trisubstituted alkene to establish the benzylic stereocenter, representing a very rare case of achieving high selectivity on a complex substrate. The second route demonstrates the first example of a vinylogous dynamic kinetic resolution (VDKR) ketone reduction, where the carbonyl and the racemizable stereocenter are not contiguous, but are conjugated through a pyrimidine ring. Not only did this transformation require both catalyst and substrate control to correctly establish the two stereocenters, but it also necessitated that the nonadjacent benzylic center of the ketone substrate be more acidic than that of the alcohol product to make the process dynamic. DFT computations aided the design of this novel VDKR pathway by reliably predicting the relative acidities of the intermediates involved.

INTRODUCTION

γ-Secretase modulator BMS-932481 ((*S*)-**1**) is a drug candidate for the treatment of Alzheimer's disease, a degenerative brain disorder that represents the most common cause of dementia (Scheme 1).[1,2] The highly nitrogenated compound is composed of a cyclopenta[*d*]pyrimidine core (**A**), a bis-benzylic stereocenter in the (*S*) configuration, and two different amine substituents at the C2 and C4 positions of the pyrimidine ring. The initial process from our discovery team involved a synthesis of racemic product **1** followed by chromatographic separation on a chiral phase, and was capable of delivering small quantities of (*S*)-**1** in high enantiopurity.[3] However, a sustainable, long-term solution would be required to support the high demand of (*S*)-**1** anticipated for commercialization.

To efficiently synthesize (*S*)-**1**, we envisioned a convergent strategy that established the C7 stereocenter of the cyclopenta-[*d*]pyrimidine core **A** and selectively connected the triazol-1-yl-phenylamino group with fragment **A** through the C_2−N bond in a later stage (Scheme 1). Herein we describe three approaches to the preparation of cyclopenta[*d*]pyrimidine core **A**, which explored (a) an enantioselective intramolecular hydroacylation of unactivated alkene **B**, (b) an enantioselective hydrogenation of trisubstituted cyclopentenes **C**, and (c) a dynamic kinetic resolution of β-aryl ketones **D**. This work enabled the development of robust, sustainable, and scalable approach toward (*S*)-**1**.

RESULTS AND DISCUSSION

Synthesis of (*S*)-1 by Enantioselective Hydroacylation. Although (*S*)-**1** could be obtained in high enantiomeric purity using the chromatographic separation approach, focus was shifted to evaluating asymmetric options which could provide a streamlined route with improved yields and greater synthetic efficiency. Accordingly, a new route was devised that exploited the use of commercially available trichloropyrimidine **3**[4] as a highly functionalized precursor (Scheme 2). Adaptation of an established procedure[5] facilitated the regioselective installation of the methylamine substituent at C4 to prepare methylamino pyrimidine **4**. Suzuki coupling of **4** with α-vinyl boronate **5**[6] afforded pyrimidin-5-carbaldehyde derivative **6**. The key transformation in this sequence was envisioned as an asymmetric hydroacylation[7] of **6** to construct the C_2−C_6 bond

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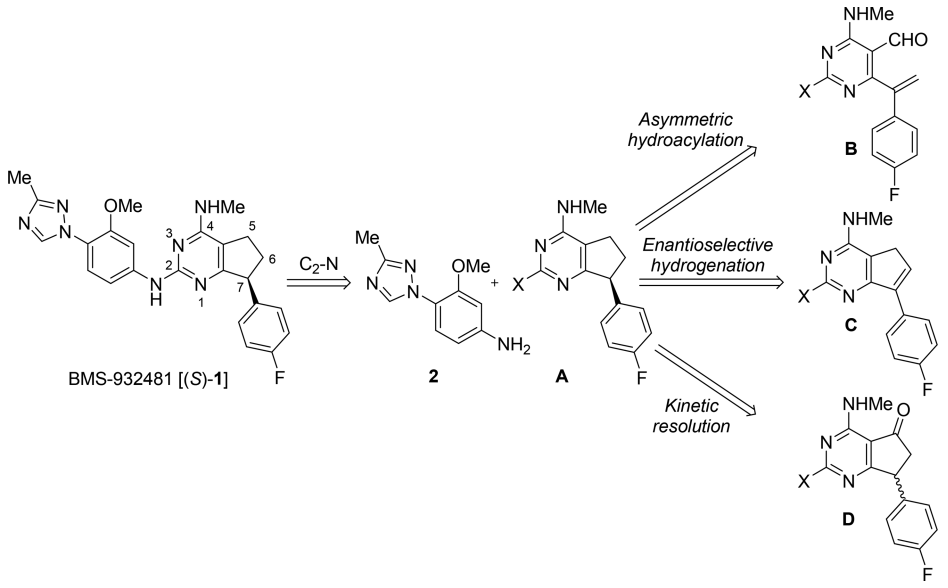
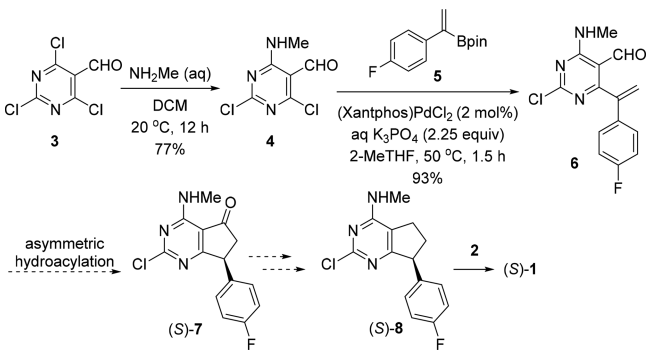
Scheme 1. Retrosynthetic Analysis for (*S*)-1



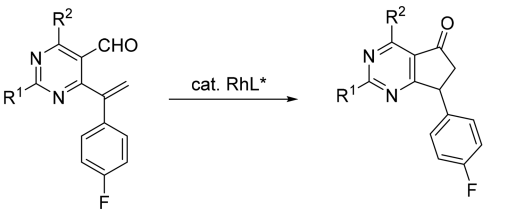
Scheme 2. Potential Route to (*S*)-1 through Enantioselective Hydroacylation



and install the C7 stereogenic center of ketone **7**. Reduction of **7** to intermediate **8** would be followed by the substitution at the chloropyrimidine moiety to form (*S*)-**1**.[8]

A promising precedent for the enantioselective cyclization was reported by Morehead and co-workers using cationic Rh(I)BINAP catalysts for the hydroacylation of 2-vinyl benzaldehydes.[9] Inspired by this work, we conducted an extensive screen of chiral Rh(I) complexes for the hydroacylation of **6** (Table 1).[10] Unfortunately, using analogous conditions to those reported by Morehead gave poor conversions and selectivities (entries 1 and 2). On the basis of the beneficial effect of Brønsted acid additives observed for related transformations,[11] HBF_4 was explored as an additive and was found to greatly improve the rate of hydroacylation, but still gave racemic **7** (entries 3 and 4).[12,13] Interestingly, the 2,4-dimethoxy analog **9** underwent hydroacylation without the

Table 1. Enantioselective Hydroacylation of 6 and 9



6 R^1=Cl, R^2=NHMe
9 R^1=OMe, R^2=OMe

7 R^1=Cl, R^2=NHMe
10 R^1=OMe, R^2=OMe

entry[a]	substrate	ligand	time (h)	additive (mol %)	conv. (%)[b]	ee (%)[b]
1	**6**	*R*-BINAP	21		18	0
2	**6**	*R*-TolBINAP	21		0	
3	**6**	*R*-BINAP	21	HBF_4	78	0
4	**6**	*R*-TolBINAP	21	HBF_4	60	3
5	**9**	*R*-BINAP	16		85	3
6	**9**	*R*-TolBINAP	16		100	95
7	**9**	*R*-Xyl-SDP	16		90	94
8	**9**	*R*-DuanPhos	16		99	95

[a]Substrate (0.1 M in 1,2-dichloroethane), ([$Rh(nbd)_2$]BF_4 (18 mol %), and ligand (20 mol %) at 80 °C, 16−24 h. [b]Determined by HPLC analysis of the crude reaction mixture.

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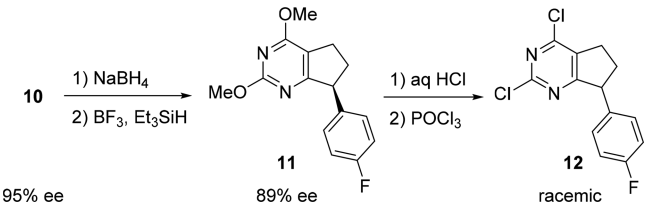
requirement of acidic additives to afford cyclopenta[*d*]-pyrimidin-5-one **10** with excellent yields and enantioselectivities (e.g., entries 6−8) revealing that the steric and electronic properties of the substituents on the pyrimidine ring play a critical role in the success of the annulative process. A two-step reduction of ketone **10** afforded cyclopenta[*d*]pyrimidine **11** with limited epimerization (Scheme 3). However, under the

Scheme 3. Attempt to Prepare Enantiopure 2,4-Dichloropyrimidine 12 from 10



conditions to prepare 2,4-dichloropyrimidine **12**, racemization of the C7 stereocenter occurred giving racemic product. DFT calculations predicted a pK_a of 14 for the benzylic proton of **12**, explaining the configurational lability, and halting further investigation of the enantioselective hydroacylation approach.[14−16]

Despite this setback, we envisioned that racemic ketone **7** could be a valuable intermediate for other asymmetric routes. To obtain **7** via acid-catalyzed cycloisomerization of **6**, we evaluated 120 Brønsted and Lewis acids, and various other catalysts (Table 2).[17] Although Brønsted acids performed

Table 2. Acid-Catalyzed Cyclization of Pyrimidine-5-carbaldehyde 6

entry[a]	acid	product (%)[b]	conv. (%)[b]
1[c]	HCl	3	30
2	MsOH	6	9
3	$ZnCl_2$	2	3
4	BF_3−AcOH	60	78
5	$AlCl_3$	55	79
6	$HfCl_4$	30	36
7	$GaCl_3$	23	27
8[d]	$TiCl_4$	21	98
9	$SnCl_4$	81	98
10	$ZrCl_4$	80	88

[a]Reaction conditions: 0.5 equiv catalyst, 25 vol DCE, 40 °C, 16 h. [b]Determined by HPLC analysis of the crude reaction mixture. On the basis of mol % of product or remaining SM vs an internal standard. [c]Anhydrous HCl in dioxane. [d]Decomposed to several unidentified byproducts.

poorly, giving only trace cyclized product (entries 1 and 2), metal chloride Lewis acids were effective for the cyclization of **6**. Among the Lewis acids, weakly electrophilic species such as $ZnCl_2$ showed almost no reactivity (entry 3) while strongly electrophilic species such as $SnCl_4$ were the most effective (entry 9). Due to the toxicity and environmental impact of Sn, we chose to proceed with $ZrCl_4$ (entry 10) and conditions were optimized to provide cyclopenta[*d*]pyrimidin-5-one **7** in 90% yield using 10 mol % $ZrCl_4$ in DCM at 40 °C. Reduction of **7** with DIBAL-H gave a mixture of diastereomeric alcohols **13**, which upon dehydration with Eaton's reagent (MSA/P_2O_5) selectively afforded cyclopentene **14** (Scheme 4). This trisubstituted alkene, if reduced enantioselectively, could lead to the desired cyclopenta[*d*]pyrimidine core (*S*)-**8**.

Synthesis of (*S*)-1 by Enantioselective Hydrogenation. While introducing the C7 stereocenter via an enantioselective hydrogenation of **14** was conceptually feasible, highly selective asymmetric hydrogenations of minimally functionalized cyclic alkenes remain an unmet challenge in asymmetric catalysis.[18] The search for an effective enantioselective hydrogenation of cyclopentene **14** started with a series of high-throughput screening experiments using Ir and Rh catalysts (Table 3). Although Ir catalysts have found the most success in the hydrogenation of unfunctionalized alkenes,[19] the chiral Ir catalysts examined for the hydrogenation of **14** gave poor conversion and enantioselectivity (entry 1).[20] In contrast, chiral Rh catalysts such as cat*A*Sium M complex **Rh-1** provided higher conversion, albeit with modest enantioselectivity (entry 2).[21] This promising reactivity prompted the study of a series of Rh(I) catalysts generated in situ from $[Rh(nbd)_2]BF_4$ and chiral bisphosphine ligands.[22] Among the numerous ligands examined, bulky, electron-rich axially chiral bisphosphine ligands such as BIPHEP and SEGPHOS offered the most encouraging results (entries 3−8). In particular, a combination of $[Rh(nbd)_2]BF_4$ with DTBM-SEGPHOS-*R* (**L6**) gave (*S*)-**8** in 82% conversion and 76% ee (entry 8). Along with the desired (*S*)-**8**, significant amounts of dechlorinated byproduct **15** were also observed.[23]

With a functional catalyst system in hand (i.e., Rh/**L6**), further optimization focused on minimizing the formation of byproduct **15**, as well as lowering the Rh loading and improving the reaction performance. Numerous Rh(I) catalyst precursors,[24] solvents,[25] additives,[26] and hydrogen pressures were evaluated (Figure 1). For the hydrogenation using Rh-**L6**, ethereal and ester solvents were found to be optimal, with MeOAc providing the best conversion and selectivity (entries 10−12). Optimization of the solvent enabled a 9-fold reduction in catalyst loading and minimized the levels of dechlorinated byproduct **15**. Since negligible difference in performance was observed among different Rh sources (Table S6), $[Rh(cod)Cl]_2$ was chosen to conduct subsequent studies due to its lower cost and greater air stability (entry 13). A survey of Brønsted and Lewis acid additives (Table S7) indicated that reactions conducted in the presence of KOTf under high H_2 pressures (≥1000 psi) provided better conversion and selectivities, giving full conversion to (*S*)-**8** in 90% ee after 24 h (entries 14−15).[27] The optimized conditions using Rh-**L6** were performed on a multigram scale to prepare (*S*)-**8** in 69% yield and >99% ee.

Nucleophilic aromatic substitution of final intermediate (*S*)-**8** with triazol-1-yl-aniline **2** under acidic conditions (H_2SO_4, NMP, 100 °C) led to substitution at the 2-chloro position to give (*S*)-**1** in 86% yield and >99% ee.[28,29] Importantly, there was no loss of enantiopurity, demonstrating a viable enantioselective route that provided (*S*)-**1** in >99% ee and 16.3% overall yield over 7 steps.[30]

Synthesis of (*S*)-1 by Dynamic Kinetic Resolution. Despite the development of a successful synthesis through alkene hydrogenation, our team investigated if a shorter synthesis, which would not require Rh, an expensive ligand, or high-pressure (1000 psi) capabilities could be developed. A potential route would involve kinetic resolution of racemic **7** through ketone reduction (Scheme 5). A variety of bio- or chemocatalysts could affect this transformation, but as with any kinetic resolution, the yield would be capped at 50%.[31]

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Scheme 4. Route to (*S*)-1 via Enantioselective Hydrogenation

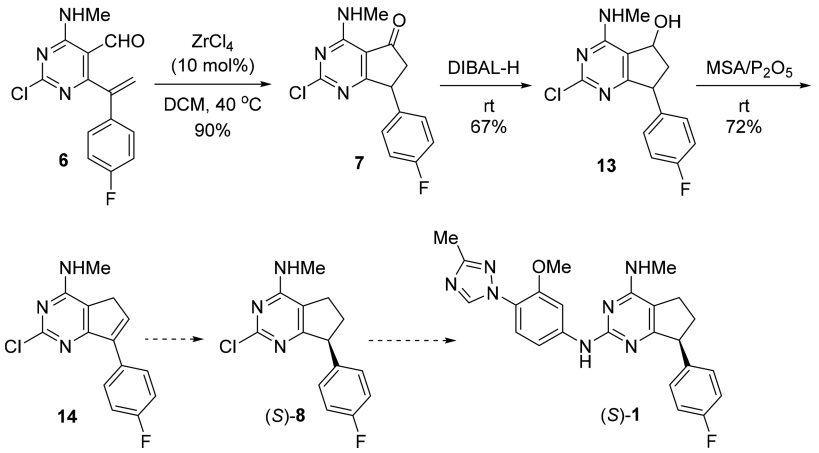
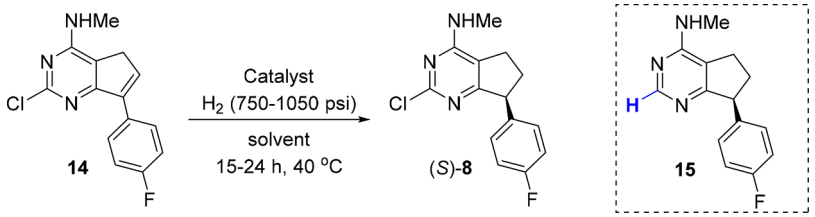


Table 3. Optimization of Enantioselective Hydrogenation of Alkene 14



entry[a]	metal precursor	metal (mol %)	ligand	solvent	H_2 (psi)	additive (mol %)	conv. (%)[b]	ee (%)[b]	15 (%)[b]
1	**Ir-1**	5.0		DCE	750		17	+18	
2	**Rh-1**	5.0		MeOH	750		55	−26	2.8
3	$[Rh(nbd)_2]BF_4$	4.5	**L1**	MeOH	750		35	+40	4.8
4	$[Rh(nbd)_2]BF_4$	4.5	**L2**	MeOH	750		40	−49	6.3
5	$[Rh(nbd)_2]BF_4$	4.5	**L3**	toluene	750		32	−23	8.4
6	$[Rh(nbd)_2]BF_4$	4.5	**L4**	toluene	750		36	+60	4.3
7	$[Rh(nbd)_2]BF_4$	4.5	**L5**	toluene	750		53	+66	5.6
8	$[Rh(nbd)_2]BF_4$	4.5	**L6**	toluene	750		82	+76	5.7
9[c]	$[Rh(nbd)_2]BF_4$	0.8	**L6**	DMAc	750		6		
10[c]	$[Rh(nbd)_2]BF_4$	0.8	**L6**	DME	750		93	+89	0.9
11[c]	$[Rh(nbd)_2]BF_4$	0.8	**L6**	EtOAc	750		89	+87	0.9
12[d]	$[Rh(nbd)_2]BF_4$	0.5	**L6**	MeOAc	750		>99	+86	0.7
13[d]	$[Rh(cod)Cl]_2$	0.5	**L6**	MeOAc	750		97	+85	<0.1
14	$[Rh(cod)Cl]_2$	0.75	**L6**	MeOAc	1050	KOTf (2.3)	>99	+90	2.1
15	$[Rh(cod)Cl]_2$	0.50	**L6**	MeOAc	1000	KOTf (0.7)	>99	+90	0.8

[a]Reaction conditions: **14** (10−100 μmol), metal precursor, ligand (1.1 ligand:metal ratio), solvent (125−500 μL), 40 °C, 750−1050 psi H_2, 15−24 h. [b]Determined by HPLC analysis of the crude reaction mixture. [c]30 °C. [d]50 °C.

Alternatively, we hypothesized that a *dynamic* kinetic resolution (DKR) via ketone reduction could be effective, allowing for both enantiomers of ketone **7** to be converted to chiral alcohol **13**, and offering the potential for higher yield and selectivity.[32] Rather than trying to avoid epimerization of the benzylic stereocenter of **7** as in the asymmetric hydroacylation approach, we could embrace this reactivity and possibly use it to our advantage. Typically, DKR of ketones via reduction involves epimerization of an alpha stereocenter, which is more acidic in the ketone substrate than in the alcohol product (e.g., Scheme 6).[33] The selective epimerization of the substrate is driven by a large ΔpK_a, allowing for the product to be configurationally stable. This type of process is well established for contiguous centers, but no such 1,2 relationship existed between the ketone and the C7 benzylic center of **7**. We considered that the 1,4 relationship of the two centers through the pyrimidine ring would allow for epimerization of C7 via a dienolate intermediate (Scheme 7). This type of reactivity would be consistent with the principle of *vinylogy* introduced by Ludwig Claisen in 1926, involving the transmission of electronic effects through a conjugated organic bonding system.[34] However, a *vinylogous* DKR process (VDKR) would only be possible if there were a significant difference in pK_a between ketone **7** and alcohol **13**, as well as a steric bias imparted by the 4-fluorophenyl substituent.

At the outset, we employed computational predictions to assess the viability of the VDKR. DFT calculations predicted a pK_a of 14 for the benzylic proton of ketone **7**, a pK_a of 21 for the benzylic proton of the *trans*-alcohol (5*S*,7*R*)-**13**, and a pK_a of 22 for the *cis*-alcohol (5*S*,7*S*)-**13**.[14] Importantly, the carbonyl bond length increased considerably going from the ketone (1.229 Å) to the ketone enolate (1.251 Å), consistent with dienolate character leading to anion stability. With the hope that a pK_a difference of approximately 7−8 units could be

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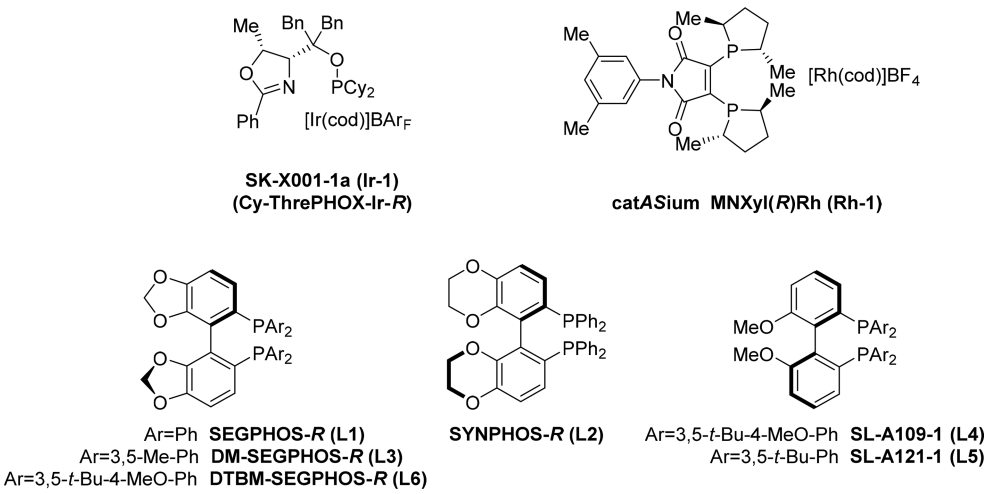
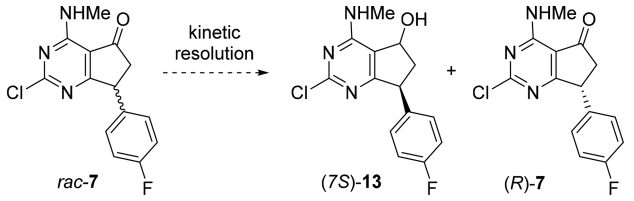
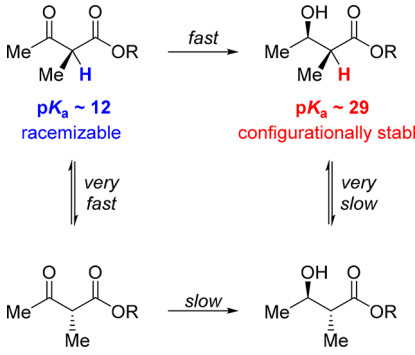


Figure 1. Selected Complexes and Ligands Evaluated for the Enantioselective Hydrogenation of **14**.

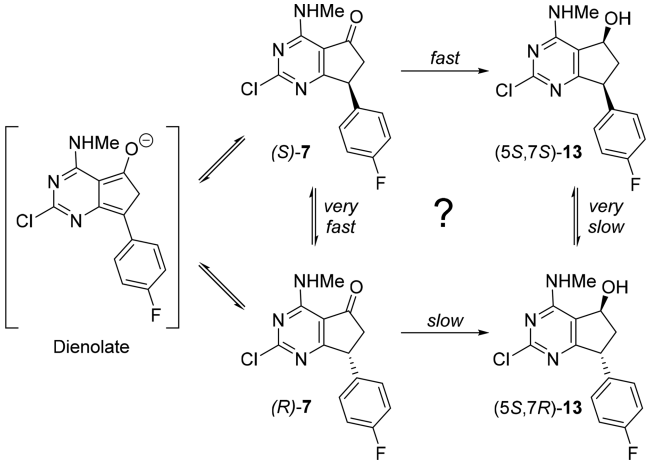
Scheme 5. Kinetic Resolution of Racemic Ketone 7



Scheme 6. DKR of a Representative α-Keto ester



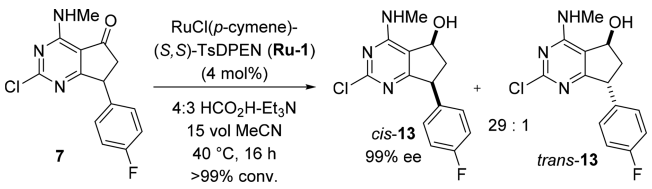
Scheme 7. Potential Vinylogous DKR with a 1,4-Relationship between Ketone and the Benzylic Center



sufficient for a successful VDKR process, we began experimental investigations into this approach. The correct choice of catalyst system would be necessary to allow for epimerization of the starting material ketone **7**, but not the product alcohols **13**.

The Noyori transfer hydrogenation catalyst RuCl(*p*-cymene)(*S*,*S*)-TsDPEN (**Ru-1**)[35] was selected in the initial attempt at this novel transformation. This catalyst can function with mixtures of formic acid and triethylamine under either acidic or basic conditions, allowing the pH of the medium to be tuned.[36] A promising result under mildly acidic conditions showed high conversion and a 29:1 isomer ratio by ^{1}H NMR analysis (Scheme 8). The cis configuration was established

Scheme 8. VDKR of Ketone 7 with a Transfer Hydrogenation Catalyst



through detection of NOE interaction between the protons at C5 and C7. The high cis-selectivity is indicative of inherent substrate control where the catalyst approaches the face opposite to the 4-fluorophenyl substituent at C7. Additionally, chiral HPLC analysis showed 99% ee for this transformation, consistent with high facial selectivity associated with the transfer hydrogenation catalyst for acetophenone-type substrates. With a successful proof of concept for the VDKR, we directed our efforts to further optimize this transformation.

A screen of solvents, amines, and acid−base ratios was undertaken to determine if the selectivity and reactivity could be further improved (Table 4).[37] Except for *i*-PrOH (entry 2), which offered poor solubility, all of the other solvents gave high conversion and high levels of enantio- and diastereoselectivity. However, dechlorinated species **15** was observed as a prominent byproduct and varied greatly with solvent choice. Alcohol solvents such as MeOH provided the highest levels of dechlorination (entry 5) while polar aprotic solvents such as DMAc provided the lowest amounts (i.e., 0.2%, entry 6). While dehalogenation is common for Ru hydrogenation

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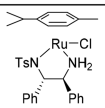
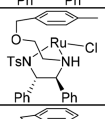
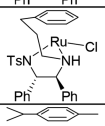
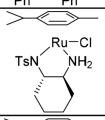
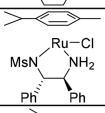
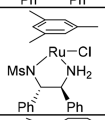
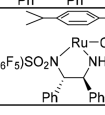
Table 4. Screen of Ru-Catalyzed Transfer Hydrogenation Conditions

entry[a]	solvent	amine	HCO_2H:amine	conv. (%)[c]	dr[c]	ee (%)[c]	15 (%)[c]
1	MeCN	TEA	4:3	97	42	>99	5
2	*i*-PrOH	TEA	4:3	33			15
3	DCM	TEA	4:3	97	112	>99	14
4	THF	TEA	4:3	98	134	>99	26
5	MeOH	TEA	4:3	80	31	93	60
6	DMAc	TEA	4:3	98	67	>99	0.2
7	EtOAc	TEA	4:3	85	85	>99	25
8	PhOMe	TEA	4:3	91	98	>99	31
9	DMAc	TEA	5:3	97	56	>99	0.3
10	DMAc	TEA	3:5	98	57	>99	0.2
11	DMAc	*N*,*N*-dimethyl-*p*-toluidine	3:5	21			5
12	DMAc	*N*,*N*-dimethyl-*p*-toluidine	5:3	27			5
13[b]	DMAc	pyridine	3:5	94			11

[a][7] = 0.19 M, 18 vol solvent, 40 °C, 16 h, 4% RuCl(*p*-cymene)(*S*,*S*)-TsDPEN (**Ru-1**). [b]Although all other reactions showed >90% mass balance, the reaction with pyridine gave <1% product and several unidentified impurities. [c]Determined by HPLC analysis of the crude reaction mixture.

Table 5. Screen of Ru-Catalyzed Transfer Hydrogenation Conditions for Reaction Optimization

Entry[a]	Catalyst	Catalyst Loading (mol %)	Conv. (%)[b]	ee (%)[b]	dr[b]	15 (%)[b]
1	 **Ru-1**	4	100	97.7	29	0.4
2		2	100	99.3	31	0.4
3		1	93	99.5	32	0.3
4		0.5	76	99.6	33	0.1
5		0.5	90	99.6	111	0.2
6		0.5	66	99.5	178	0.1
7		0.5	42	94.3	35	0
8		0.5	14	99.4	17	0.1
9		0.5	80	99.3	48	0.2
10		0.5	99	99.8	57	0.3
11		0.5	41	99.6	26	0

[a][7] = 0.26, 12 vol DMAc, 2:1 HCO_2H-Et_3N, 40 °C, 16 h. [b]Determined by HPLC analysis of the crude reaction mixture.

catalysts, it has not been previously reported with Noyori-type transfer hydrogenation catalysts.[38] The highly electrophilic nature of the chloropyrimidine moiety may be responsible for this unusual behavior of the nucleophilic Ru-hydride. The effect of the relative pH on the system was evaluated by varying the formic acid-triethylamine proportion. Reversal of the acid−base ratio showed no impact on selectivity (cf. entries 9 and 7) demonstrating that, across this range, racemization of substrate **7** is sufficiently fast and epimerization of product **13** sufficiently slow to obtain a high dr. Weaker amine bases like *N*,*N*-dimethyl-*p*-toluidine or pyridine gave either very low conversion or undesired side reactions (entries 11−13). Although the ee was quite high with most catalysts, the dr was critical to consider since, upon removal of the hydroxyl group at C5, both diastereomers with the *R* configuration at C7 would converge to the undesired (*R*)-**8** enantiomer.

Using the optimized conditions, we evaluated other Ru transfer hydrogenation catalysts (Table 5). In general, reducing

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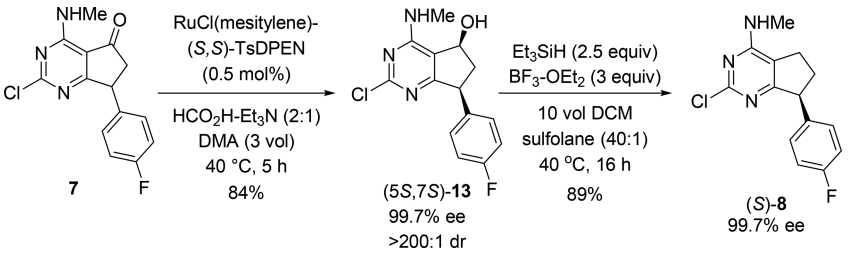
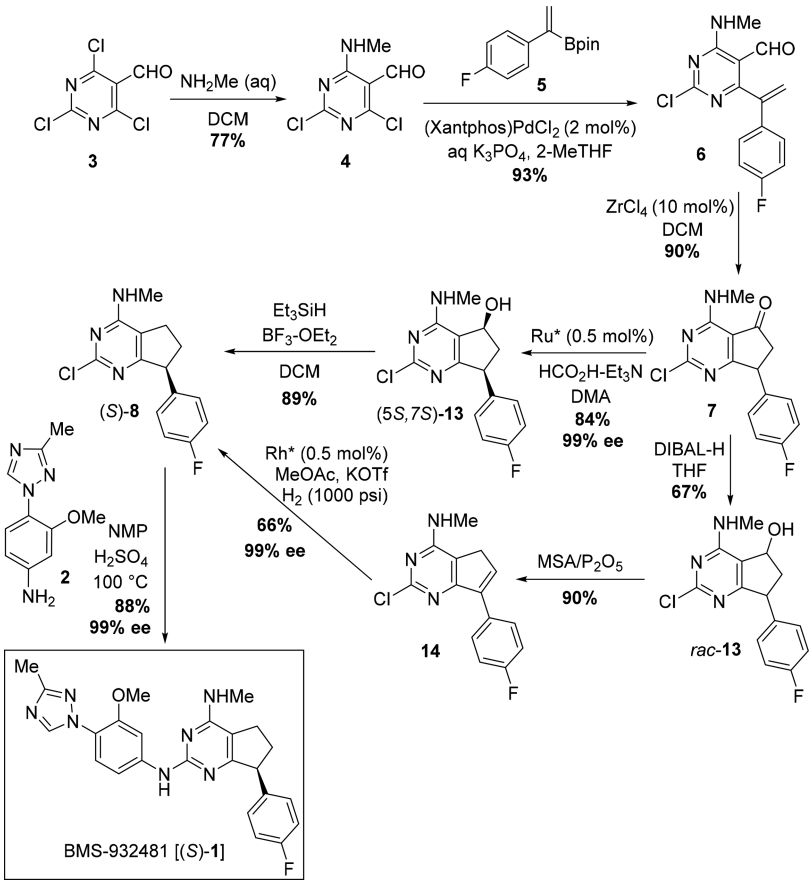
Scheme 9. Optimized Conditions for the VDKR of Ketone 7 and Deoxygenation of 13



Scheme 10. Two Asymmetric Routes to BMS-932481 ((*S*)-1)



the catalyst loading offered improved enantio- and diastereoselectivity, but resulted in a decrease in reaction conversion (entries 1 and 4). Among the catalysts tested, RuCl(mesityl)-(*S*,*S*)-TsDPEN was selected for further development based on its high reactivity and stereoselectivity, and for its wide commercial availability (entry 5). Further optimization reduced the catalyst loading to 0.5% Ru and allowed for the reaction to be run at high concentrations.[39] On a 400 g scale, a high selectivity of 99.4% ee and 146:1 dr was observed for the reaction. After workup and isolation, (5*S*,7*S*)-**13** was obtained in 84% yield, with 99.7% ee and >200:1 dr (Scheme 9).

With the conditions for the VDKR optimized, only a deoxygenation of (5*S*,7*S*)-**13** remained to provide (*S*)-**8**. Due to the importance of maintaining the stereochemical integrity at the C7 benzylic position, we tested a series of acids and silanes.[40] Although most acids were capable of mediating the deoxygenation, the highest yield was obtained using a combination of BF_3−OEt_2 and Et_3SiH, accompanied by no epimerization at the C7 stereocenter (>99% ee). Additional optimization led to a reaction in 40:1 DCM-sulfolane at 40 °C that gave 89% yield without erosion in enantioselectivity. The final coupling of (*S*)-**8** and **2** under acidic conditions provided (*S*)-**1** in 88% yield, > 99% purity, and >99% ee (Scheme 10). The synthetic route using the VDKR gave (*S*)-**1** in 38.2% overall yield over six steps.[41]

■ CONCLUSIONS

We have developed two efficient asymmetric routes to γ-secretase modulator BMS-932481 [(*S*)-**1**]. Some important elements of both routes were the regioselective amination of trichloropyrimidine **3**, the regioselective Suzuki coupling of dichloropyrimidine **4**, and a Lewis acid mediated intramolecular hydroacylation to generate the cyclopentanone fragment of **7**. The key asymmetric step for each of the two routes was capable of setting the C7 benzylic center with high enantioselectivity. First, through a combination of high-throughput experimentation and process optimization, a challenging asymmetric hydrogenation of unfunctionalized

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trisubstituted alkene **14** was accomplished. While this reaction is known for substrates with directing groups, the transformation represents a very rare case of achieving high selectivity on a complex substrate with only aryl and alkyl substituents. Second, a unique vinylogous dynamic kinetic resolution of ketone **7** was developed, where the carbonyl and the epimerizable chiral center were not contiguous but conjugated through a pyrimidine fragment. This process, which allowed for both the alcohol and benzylic stereocenters to be set in a single operation, required catalyst control to add to the desired face of the carbonyl, as well as substrate control to add to the face opposite to the aryl substituent. It also required that the nonadjacent benzylic center of the ketone substrate be more acidic than that of the alcohol product. DFT computations aided in the design of the VDKR by predicting the fulfillment of the relative acidity requirement, despite attenuation of the electron-withdrawing character of the ketone in a vinylogous system. This novel application of a DKR to establish a remote chiral center led to a highly efficient route to BMS-932481, which was suitable for long-term implementation.

EXPERIMENTAL SECTION

General Materials and Methods. All reactions were carried out using dry glassware under a nitrogen atmosphere unless otherwise noted. All reagents and solvents were purchased from commercial vendors and employed without further purification. ^{1}H NMR chemical shifts are given in ppm with respect to the residual $CDCl_3$ peak (δ 7.26 ppm), residual DMSO-d_6 (δ 2.50 ppm), or an internal TMS standard (δ 0.00 ppm), ^{13}C{^{1}H} NMR shifts are given in ppm with respect to $CDCl_3$ (δ 77.16 ppm), or DMSO-d_6 (δ 39.52 ppm). Coupling constants are reported as *J*-values in Hz. Mass spectral data were obtained using an Orbitrap mass spectrometer. High-resolution mass spectra were collected on an Agilent 6200 series TOF/6500 series Q-TOF B.06.01 (B6172 SP1). Melting points were measured with a capillary melting Stuart SMP10 instrument and are uncorrected. Moisture determinations were performed with a Karl Fischer titrator. Infrared spectra were recorded on an FT instrument at 4.00 cm^{-1} resolution. Optical rotation values were measured were recorded on a PerkinElmer Model 341 polarimeter (1 mL cell, 1 dm path length); concentration (*c*) is in g/100 mL and [α]D values are in degrees. HPLC analyses were performed using reversed-phase techniques. Chiral and achiral analysis was performed on a Shimadzu LC-20 AT liquid chromatograph with conditions as noted for individual compounds. Area percent (AP) refers to HPLC area percent purity.

Catalyst and ligand screenings were carried out in a nitrogen-filled glovebox. A 96-well block was loaded with 1 mL glass vials containing the appropriate preformed catalyst (0.5 μmol) or ligand (0.5 μmol for bidentate ligands, 1.0 μmol for monodentate ligands). To each vial containing ligand only was added 45 μL (0.45 μmol) of a solution of the appropriate metal precursor, and the resulting mixture was aged at room temperature for 20 min. A solution of the substrate was then added (10 μmol per vial), and the resulting mixtures were concentrated to dryness using a Genevac vacuum centrifuge. A micro stir bar was charged to each vial, followed by solvent (125−150 μL). For the enantioselective hydrogenation screening, the 96-well block was placed inside an aluminum hydrogenation block, which was then sealed under nitrogen and removed from the glovebox. The hydrogenation block was set on a shaker plate and placed under a hydrogen atmosphere. The pressurized block was then heated to target temperature with orbital shaking for 15−20 h. Upon cooling to room temperature and venting the hydrogen atmosphere, the reaction mixtures were concentrated to dryness using a Genevac vacuum centrifuge, redissolved in MeCN and analyzed by chiral HPLC.

Preparation of 2,4-Dichloro-6-(methylamino)pyrimidine-5-carbaldehyde (4). To a 20 L reactor were charged DCM (12 L), 2,4,6-trichloropyrimidine-5-carbaldehyde (**3**) (1.20 kg, 5.45 mol), and a solution of $KHCO_3$ (0.64 kg, 6.41 mol) in water (3 L). After cooling the solution to 15 °C, a solution of methylamine (40 wt % in water, 0.44 kg, 5.71 mol, 1.05 equiv) was charged slowly while maintaining the temperature below 20 °C. After stirring for an additional 12 h, the DCM layer was set aside and the aqueous layer was extracted with DCM (2 L). The combined DCM layer was swapped to IPA through a vacuum distillation. The product crystallized, was collected by filtration, and was dried under vacuum to give **4** (CAS: 1007197−30−9)[5] as a pale yellow crystalline solid (905 g, 77% yield). MP: 127 °C (DSC). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.31 (s, 1H), 9.28 (br s, 1H), 3.15 (d, *J* = 5.0 Hz, 3H). ^{13}C NMR (125.75 MHz, $CDCl_3$) δ: 190.5, 165.9, 162.8, 162.3, 106.9, 28.2. IR (cm^{-1}) 3293, 1664, 1606, 1553, 1415, 1370, 1290, 1112, 956, 836.

Preparation of 2-Chloro-4-(1-(4-fluorophenyl)vinyl)-6-(methylamino)pyrimidine-5-carbaldehyde (6). To a 5 L reactor were charged 2-MeTHF (1.13 L, 17 vol), 2-(1-(4-fluorophenyl)-vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5**, CAS:850567−55−4, 455.5 mmol, 113 g), 2,4-dichloro-6-(methylamino)pyrimidine-5-carbaldehyde (**4**, 114 g, 546.5 mmol, 1.2 equiv) and (Xantphos)$PdCl_2$ (7.03 g, 9.11 mmol, 2 mol %). The suspension was degassed through three evacuation/nitrogen backfill cycles and warmed to 50 °C. An aqueous solution of K_3PO_4 (4.0 M, 256 mL, 1025 mmol, 2.25 equiv) was added in one portion via addition funnel, and the mixture was allowed to stir until the consumption of the vinylboronate was confirmed by HPLC (approximately 1.5 h). The reaction mixture was cooled to rt, water (1.1 L) was added and the biphasic system was stirred for 30 min. The aqueous phase was separated and discarded, and the organic layer was stirred with an aqueous solution of 2-(dimethylamino)ethanethiol hydrochloride (10% w/w, 550 mL) for 12 h to remove residual Pd. The aqueous layer was separated and discarded, and the organic layer was washed with 10% w/w brine (2 × 550 mL). The 2-MeTHF solvent was swapped to MeCN (1.1 L), and water (1.1 L) was added to induce crystallization. Isolation of the solids by Büchner filtration followed by drying overnightin a vacuum oven at 50 °C provided pyrimidin-5-carbaldehyde derivative **6** (131 g, 82% yield). MP: 152−153 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: ppm 9.97 (s, 1H), 9.13 (br s, 1H), 7.37−7.28 (m, 2H), 7.08−6.97 (m, 2H), 6.03 (s, 1H), 5.46 (s, 1H), 3.15 (d, *J* = 5.0 Hz, 3H). ^{13}C NMR (125.75 MHz, $CDCl_3$) δ: 191.7, 174.6, 164.0, 162.9 (d, *J* = 232), 162.3, 142.5, 134.0 (d, *J* = 3.4 Hz), 128.4 (d, *J* = 8.3 Hz), 120.2, 115.9 (d, *J* = 21.8 Hz), 109.06, 27.8. IR (cm^{-1}) 3310, 1655, 1610, 1437, 1303, 1228, 1170, 965, 809, 711. HRMS (ESI-TOF)*m*/*z*: [M + H]$^+$ calcd for $C_{14}H_{11}ClFN_3O$ 292.0647; found 292.0662.

Preparation of 2-Chloro-7-(4-fluorophenyl)-4-(methylamino)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-5-one (7). To a 250 mL reactor were charged DCM (120 mL, 6 vol) and pyrimidin-5-carbaldehyde derivative **6** (18 g, 62 mmol). Once fully dissolved, $ZrCl_4$ (1.6 g, 6.9 mmol, 0.10 equiv) was added in a single portion, and the reaction mixture was heated at reflux for 16 h. While still near reflux, IPA (120 mL, 6 vol) was added dropwise over 1 h, and then aged for 1 h. The resulting suspension was cooled to 5 °C and filtered, washed with IPA (2 × 60 mL), and dried under vacuum to give pyrimidin-5-one **7** as a pale yellow crystalline solid (16.6 g, 92% yield). MP: 230 °C (dec). ^{1}H NMR (500 MHz, $CDCl_3$) δ: ppm 7.35 (d, *J* = 7.3 Hz, 1H), 7.15−7.05 (m, 2H), 7.05−6.96 (m, 2H), 4.41 (dd, *J* = 8.0, 3.1 Hz, 1H), 3.21 (dd, *J* = 19.2, 8.0 Hz, 1H), 3.17 (d, *J* = 5.1 Hz, 3H), 2.66 (dd, *J* = 19.2, 3.1 Hz, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$) δ: 202.6, 186.3, 166.5, 162.1 (d, *J* = 246 Hz), 159.8, 135.5 (d, *J* = 3.4 Hz), 129.2 (d, *J* = 8.2 Hz), 116.0 (d, *J* = 21.3 Hz), 110.8, 45.6, 45.3, 27.5. IR (cm^{-1}) 3350, 1686, 1628, 1570, 1424, 1317, 1228, 1116, 912, 809. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{14}H_{11}ClFN_3O$ 292.0647; found 292.0659.

Preparation of 4-(1-(4-Fluorophenyl)vinyl)-2,6-dimethoxypyrimidine-5-carbaldehyde (9). To a 50 mL three-necked flask were charged 2-MeTHF (22 mL), 2-(1-(4-fluorophenyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5**, 8.60 mmol, 2.13 g), 4-chloro-2,6-dimethoxypyrimidine-5-carbaldehyde (CAS:134221−52−6, 2.09 g, 10.3 mmol, 1.2 equiv) and (Xantphos)$PdCl_2$ (133 mg, 0.172 mmol, 2 mol %). The suspension was degassed and warmed to 50 °C.

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An aqueous solution of K_3PO_4 (4.0 M, 4.8 mL) was added and the reaction mixture was stirred for 4 h. After allowing to cool to 20 °C, the organic phase was washed with water (20 mL) and then stirred with an aqueous solution of 2-(dimethylamino)ethanethiol hydrochloride (10% w/w, 10 mL) for 18 h. After removing the aqueous layer, the organic layer was washed with 10% w/w brine (2 × 10 mL) and was concentrated by rotary evaporation. The residue was dissolved in MeCN (20 mL), and water (20 mL) was added to induce crystallization. The crystals were isolated as an off-white powder of pyrimidin-5-carbaldehyde derivative **9** (2.20 g, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: ppm 7.28−7.32 (m, 2H), 7.01 (t, J = 10.0 Hz, 2H), 5.92 (bs, 1H), 5.42 (bs, 1H), 4.15 (s, 3H), 4.08 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 186.9, 174.2, 171.3, 165.0 (d, J_{C-F} = 194 Hz), 161.5, 144.4, 134.3, 128.3 (d, J_{C-F} = 8.0 Hz), 118.9, 115.5 (d, J_{C-F} = 21.1 Hz), 110.8, 55.6, 55.0. LC-MS (ESI-MS) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}FN_2O_3$ 289.10; found 289.10.

Preparation of 7-(4-Fluorophenyl)-2,4-dimethoxy-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-5-one (10). *Step 1: Catalyst Preparation.* To a 40 mL scintillation vial were charged $[Rh(nbd)_2]BF_4$ (380 mg, 1.0 mmol), *R*-TolBINAP (700 mg, 1.3 mmol), and 1,2-dichloroethane (10 mL) in a nitrogen-filled glovebox to form a deep red solution that was reduced at rt under 2 atm H_2 for 30 min.

Step 2: Hydroacylation. The catalyst mixture was added under nitrogen to a vial containing aldehyde **9** (1.5 g, 5.2 mmol) in 1,2-dichloroethane (10 mL). The resulting solution was heated to 75 °C and allowed to stir at the same temperature for 16 h. The crude reaction was filtered through a silica plug and purified by flash chromatography (hexanes-AcOEt gradient) to afford ketone **10** as a yellow solid (1.26 g, 84% yield, 95% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ: ppm 7.01−7.08 (m, 2H), 6.93 (t, J = 10.0 Hz, 2H), 4.34 (dd, J = 4.5, 4.0 Hz, 1H), 4.09 (s, 3H), 3.94 (s, 3H), 3.14 (dd, J = 18.0, 8.0 Hz, 1H), 2.64 (dd, J = 18.0, 4.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 198.5, 189.6, 169.0, 167.9, 163.2, 160.7, 136.1, 129.1, 115.9, 115.7, 110.9, 55.8, 54.9, 45.4, 45.4. LC-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}FN_2O_3$ 289.0988; found 289.0966.

Preparation of 2,4-Dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (12). *Step 1: Ketone to Alcohol Reduction.* $NaBH_4$ (570 mg, 15 mmol) was added to a solution of ketone **10** (1.2 g, 4.2 mmol) in MeOH (40 mL), and the resulting slurry was stirred for 30 min at rt. The reaction was analyzed by HPLC to confirm consumption of the ketone and formation of the alcohol intermediate as a 6:1 mixture of diastereomers. The reaction mixture was concentrated by rotary evaporation to give a crude oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (m, 2H, major), 7.08 (m, 2H, minor), 6.96 (m, 2H, major), 5.35 (m, 1H, major), 4.48 (m, 1H, minor), 4.11 (m, 1H, major), 4.04 (s, 3H, major), 3.89 (s, 3H, major), 2.98 (m, 1H, major), 2.56 (m, 1H, minor), 2.38 (m, 1H, minor), 2.06 (m, 1H, major).

Step 2: Deoxygenation of the Alcohol Intermediate. To a 40 mL scintillation vial containing a solution of alcohol intermediate in DCM (20 mL) were added Et_3SiH (2.0 mL, 12 mmol) and $BF_3{\cdot}Et_2O$ (1.6 mL, 13 mmol) at rt. The vial was capped and stirred over 24 h, at the end of which time the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, extracted with AcOEt and purified by flash chromatography (hexanes-AcOEt 80:20) to afford **11** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.02−7.09 (m, 2H), 6.85−6.94 (m, 2H), 4.15 (t, J = 8.0 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 2.82 (m, 1H), 2.70 (m, 1H), 2.55 (m, 1H), 2.00 (m, 1H).

Step 3: Methyl Cleavage and Dichlorination. To a 40 mL scintillation vial containing the crude product of step 2 was added 1 M HCl (10 mL), and the reaction mixture was stirred at 60 °C for 16 h. The mixture was extracted with EtOAc, and the organic stream was washed with aq $NaHCO_3$. The organic layer was concentrated by rotary evaporation to give a crude oil. This material was dissolved in $POCl_3$ (7 mL) and heated to 100 °C for 7 h. The $POCl_3$ was removed by rotary evaporation, and MTBE (10 mL) was charged to the residue. This mixture was poured over ice and aged overnight. The organic layer was separated, and the aqueous was extracted with MTBE (10 mL). The combined organic layers were dried over sodium sulfate, and concentrated by rotary evaporation, at which point 2,4-dichloropyrimidine **12** crystallized as a red solid (502 mg, 43% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: ppm 7.29 (m, 1H), 7.16 (m, 1H), 4.57 (t, J = 8.0 Hz, 1H), 2.90−3.10 (m, 2H), 2.66 (m, 1H), 2.11 (m, 1H); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ: 180.4, 162.4, 160.0, 157.5, 156.9, 137.6, 133.8, 130.3, 130.2, 115.4, 115.2, 50.8, 32.2, 26.86. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_9Cl_2FN_2$ 283.0200; found 283.0192.

Preparation of 2-Chloro-7-(4-fluorophenyl)-*N*-methyl-5*H*-cyclopenta[*d*]pyrimidin-4-amine (14). *Step 1. Preparation of 2-Chloro-7-(4-fluorophenyl)-4-(methylamino)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-ol (**rac-13**).* . A 100 mL three-necked flask equipped with a thermocouple was charged with pyrimidin-5-one **7** (4 g, 13.75 mmol) and DCM (50 mL). The flask was cooled to 0 °C, evacuated-nitrogen filled, and 16.5 mL of 1 M DIBAL-H incyclohexane (16.5 mmol, 1.2 equiv) was added via syringe while maintaining the internal temperature below 10 °C. Upon complete addition, a reddish orange slurry formed that was aged at the same temperature for 2 h. Then, a solution of citric acid (65 mL, 20 wt %/vol in water, 68.75 mmol, 5 equiv) was added via addition funnel (CAUTION!: Vigorous reaction! Gas evolution!), and the mixture was transferred to a separatory funnel. Extraction of the phases with DCM (2 × 40 mL) followed by concentration under vacuum afforded a solid residue that was slurried in 5 vol MTBE, filtered and dried (50 °C, 20 mmHg) to give crude pyrimidin-5-ol **13** as a 9:1 mixture of diastereomers (2.7 g, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: ppm 7.15 (m, 2H, major), 7.09 (m, minor) 7.00 (m, 2H, major), 6.96 (m, minor), 5.77 (br s, 1H, major), 5.67 (br s, minor), 5.44 (q, J = 6.0 Hz, minor), 5.25 (q, J = 6.0 Hz, 1H, major), 5.40 (m, minor), 4.08 (t, J = 8.0 Hz, 1H, major), 3.13 (m, 3H, minor), 3.26 (m, 3H, major), 1.88 (m, 2H).

*Step 2. Preparation of Pyrimidin-4-amine (**14**).* The crude **13** from the previous step was dissolved in 1,2-DCE (200 mL) and Eaton's reagent (67.5 g, 18.4 mmol, 2 equiv) was added under nitrogen at rt. The resulting mixture was stirred overnight at rt and quenched with aqueous K_2CO_3 (20% w/v) to adjust the pH to 7−8. Extraction with DCM (2 × 100 mL) and evaporation under vacuum afforded a solid that was slurried in MTBE (10 mL) and stirred at rt for 3 h. The product was then isolated by filtration and dried in a vacuum oven at 40 °C overnight to (2.28 g, 90% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ: ppm 8.07 (m, 2H), 7.29 (s, 1H), 7.27 (t, J = 10.0 Hz, 2H), 5.22 (br s, 1H), 3.38 (br s, 2H), 2.90 (s, 3H). ^{13}C NMR (125.75 MHz, $CDCl_3$) δ: 167.2, 162.8, 160.9, 159.1, 158.2, 139.6, 137.0, 129.6, 129.2, 116.0, 115.3, 115.1, 33.4, 27.2 HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}ClFN_3$ 276.0698; found 276.0710.

Preparation of (S)-2-Chloro-7-(4-fluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[d]pyrimidin-4-amine [(*S*)-8] through enantioselective alkene hydrogenation. *Catalyst Preparation.* In a nitrogen-filled glovebox, a 40 mL vial was charged with $[Rh(cod)Cl]_2$ (178 mg, 361 mmol, 0.50 mol % Rh), DTBM-SEGPHOS-*R* (942 mg, 799 mmol, 0.55 mol %) and 30 mL MeOAc. The vial was gently agitated to dissolve the solids, and the mixture was aged for 10 min to give a dark red solution that was added to a separate 40 mL vial containing KOTf (163 mg, 866 mmol, 0.6 mol %). The vial containing the original Rh-ligand solution was rinsed with 4 mL MeOAc and the rinse was transferred to the vial containing the Rh-L-KOTf mixture, which was aged for 5 min to give a dark orange solution.

Hydrogenation. A 17 mL aliquot of the catalyst solution was added to each of 2 × 350 mL stainless-steel autoclaves each charged with 20.0 g (72.5 mmol) alkene **14** and 163 mL MeOAc. The autoclaves were sealed with a lid containing a suspended magnetic stir bar, then removed from the glovebox and placed in an HEL polyblock inside a fume hood. Using the HEL WinISO software program, stirring was begun at 600 rpm and the autoclaves were pressurized with 1000 psi of H_2. The pressurized autoclaves were heated to 40 °C for 20 h, then allowed to cool to RT and carefully vented. *Isolation at rt:* The mother liquor from the first autoclave was removed via pipet to leave a fine white solid. The solid was transferred to a 60 mL fritted funnel and washed with heptane (200 mL). The cake was dried under

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vacuum for 5 min to give 12.8 g (63% yield) of (*S*)-**8** as a white solid (99.4 AP, 99.6% ee, 0.15 AP dechlorinated byproduct **15**). Prior to isolation, the second autoclave was cooled to 0 °C for 1.5 h with 450 rpm stirring. The mother liquor was removed via pipet to leave a fine white solid, which was transferred to a 60 mL fritted funnel, reslurried in heptane (3 × 20 mL) and then washed with heptane (140 mL). The cake was dried under vacuum for 5 min to give 14.0 g (69% yield) of (*S*)-**8** as a white solid (98.9 AP, 99.1% ee, 0.26 AP dechlorinated byproduct **15**). ^{1}H NMR (400 MHz, $CDCl_3$) δ: ppm 7.08 (m, 2H), 6.69 (m, 2H), 4.76 (br s, 1H), 4.24 (t, J = 8.0 Hz, 1H), 3.09 (d, J = 4.0 Hz, 3H), 2.60−2.76 (m, 3H), 2.08 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$) δ: 172.6, 162.6, 160.9, 159.8, 138.4, 129.2, 115.4, 115.2, 50.7, 32.7, 27.8, 25.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}ClFN_3$ 278.0855; found 278.0847. $[\alpha]^{20}_D$ +1.12 (c 1.16, DMSO). Chiral HPLC method: ChiralPak OJ-Rh, 5 um, 4.6 × 150 mm, 0.8 mL/min, 254 nm, solvent A: 0.01 M NH_4OAc in MeOH-water (20:80), solvent B: 0.01 M NH_4OAc in MeOH-water-MeCN (20:5:75), 52% to 100% B over 4 min, hold 6 min, RT = 5.366 min (undesired (*R*)-**8**), 7.003 min (desired (*S*)-**8**).

Preparation of (5*S*,7*S*)-2-Chloro-7-(4-fluorophenyl)-4-(methylamino)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-5-ol ((5*S*,7*S*)-13). A 20 L reactor was charged with DMAc (12.3 L, 3.00 L/kg), ketone **4** (410 g, 99.0 wt %, 1.41 mol), RuCl(mesityl)(*S*,*S*)-TsDPEN (4.37 g, 7.03 mmol, 0.005 equiv), and DIPEA (245 mL, 182g, 1.41 mmol, 1 equiv). The reaction mixture was heated to 40 °C and degassed by sparging with nitrogen for 20 min. Over a period of 2 h, formic acid (129 g, 2.81 mmol, 2 equiv) was added dropwise. After completion of the addition, the reaction mixture was aged for an additional 3 h until it showed <1% of starting ketone. At this point, the end of reaction mixture contained 98.8 AP of 5*S*,7*S*)-**13** in 99.4% ee and 146:1 dr. 2-MeTHF (2.05 L, 5 L/kg) was added to the reaction mixture, which was subsequently cooled to 20 °C. A solution of citric acid (148 g citric acid, 1.03 L brine, 1.03 L water) was added over 20 min and the stirred mixture was warmed to 20 °C. The aqueous layer was removed, and the organic layer was extracted with a saturated $NaHCO_3$ solution (2.05 L), a half brine solution (2.05 L), and water (2.05 L) to fully remove the DMAc. 2-MeTHF was swapped for toluene (5.0 L) under reduced pressure, maintaining the temperature below 40 °C. After cooling to 20 °C and aging for 3 h, the product slurry was filtered and the cake was washed with toluene (2.05 L). Overnight drying in a vacuum oven gave (5*S*,7*S*)-**13** (346 g, 84% yield) in 99.37% HPLC purity, > 200 dr, 99.7% ee, and >99.5% potency. MP: 181−183 °C. ^{1}H NMR (500 MHz, CD_3CN) δ: 7.31−7.19 (m, 2H), 7.14−7.02 (m, 2H), 6.19 (br s, 1H), 5.15 (q, J = 4.9 Hz, 1H), 4.06 (t, J = 8.2 Hz, 1H), 3.66 (d, J = 6.1 Hz, 1H), 3.05−3.00 (m, 1H), 2.99 (d, J = 4.9 Hz, 3H), 1.84 (ddd, J = 13.5, 7.8, 5.8 Hz, 1H). ^{13}C NMR (125.75 MHz, CD_3CN) δ: 172.4, 162.6 (d, J = 242 Hz), 162.5, 161.7, 139.8 (d, J = 3.1 Hz), 131.1 (d, J = 8.1 Hz), 117.67, 116.1 (d, J = 21.4 Hz), 71.3, 49.6, 44.9, 27.8. IR: 3435, 3257, 3061, 2945, 1619, 1521. 1513, 1388, 1263, 1165, 1108, 1041, 987. 849, 814. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{14}ClFN_3O$ 294.0809; found 294.0815. $[\alpha]^{20}_D$ +2.00 (c 1.08, DMSO). Chiral HPLC method: Phenomenex Lux Cellulose-1, 3 um, 4.6 × 150 mm, 1 mL/min, 220 nm, solvent A: 0.01 M NH_4OAc in MeCN-water (5:95), solvent B: 0.01 M NH_4OAc in MeCN-water (95:5), 25 to 100% B over 30 min, RT = 8.20 min (major trans), 9.22 min (minor trans), 11.69 min (major cis (5*S*, 7*S*)-**13**), 13.72 min (minor cis), 19.73 min (**7**), 24.24 min (**7**).

Preparation of (*S*)-8 through Deoxygenation. To a 5 L reactor was charged alcohol (5*S*,7*S*)-**13** (150 g, 97.0 wt %, 495 mmol), DCM (1.5 L), sulfolane (37.5 mL), and Et_3SiH (200 mL, 1.24 mol, 2.5 equiv). The resulting suspension was warmed to 42 °C and $BF_3{\cdot}OEt_2$ was added (190 mL, 1.49 mol, 3.0 equiv). The reaction mixture became homogeneous and was allowed to stir for 21 h, at which point the consumption of starting material was confirmed by HPLC. The reaction mixture was cooled to 0 °C and isobutyraldehyde (110 mL, 1.24 mol, 2.5 equiv) was added (exotherm = 20 °C). After stirring for 30 min, the solvent was swapped from DCM to THF (3.0 L). To the resulting solution was added 20% w/w brine (750 mL) and 20% w/w aqueous $KHCO_3$. The phases were allowed to stir for 1 h, and then the aqueous layer was separated and discarded. The organic phase was washed with brine (2 × 1.5 L). The THF solvent was swapped for MeCN (1.5 L) by distillation, and water (1.5 L) was added to induce crystallization. Isolation of the product was achieved through Büchner filtration, washing with 1:1 MeCN-water (750 mL) and *tert*-butylmethyl ether (200 mL) at 0 °C. The product was dried in a vacuum oven overnight to afford (*S*)-**8** (123.0 g, 89% yield) with 99.74% HPLC purity and >99.5% potency. MP: 250−252 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: ppm 7.51 (q, J = 4.7 Hz, 1H), 7.18 (dd, J = 8.6, 5.6 Hz, 2H), 7.11 (t, J = 8.8 Hz, 2H), 4.21 (t, J = 8.0 Hz, 1H), 2.87 (d, J = 4.7 Hz, 3H), 2.78 (td, J = 9.8, 8.8, 4.7 Hz, 1H), 2.58 (dddd, J = 27.3, 18.6, 14.8, 8.8 Hz, 2H), 1.95 (dq, J = 16.1, 6.6 Hz, 1H). ^{13}C NMR (125.75 MHz, DMSO-d_6) δ: 171.9, 160.9 (d, J = 242 Hz), 160.6, 158.6, 139.4 (d, J = 3.0 Hz), 129.7 (d, J = 8.0 Hz), 115.6, 115.1 (d, J = 21 Hz), 49.9, 32.1, 27.3, 25.2. IR: 3279, 2941, 2896, 1584, 1508, 1401, 1317, 1268, 1112, 916. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}ClFN_3$ 278.0855; found 278.0847.

Preparation of (*S*)-1. To a 5 L reactor were charged NMP (83 mL, 3 L/kg), chloropyrimidine (*S*)-**8** (27.7 g, 100 mmol), aniline **2** (22.1 g, 108 mmol, 1.08 equiv), and sulfuric acid (7.36 g, 75.0 mmol, 0.75 equiv). The reaction mixture was heated to 100 °C. After 30 min, a slurry was formed and aging at 90−100 °C was continued for 4 h. The slurry was cooled to 60 °C and water (125 mL, 4.5 L/kg), brine (33 mL, 1.5 L/kg), and 2 M NaOH (100 mL, 200 mmol, 2 equiv) were added. Seed of BMS-932481 (0.1 g, 0.5%) was charged, followed by THF (13.9 mL, 0.5 L/kg). After stirring for 30 h, the reaction mixture was cooled to 20 °C. BMT-932481 [(*S*)-**1**] was isolated as off-white crystals (39.2 g, 88% yield) in >98.9% purity and >99% ee.[3a] ^{1}H NMR (400 MHz, DMSO-d_6) δ: ppm 9.20 (br s, 1H), 8.57 (br s, 1H), 8.17 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.22 (m, 2H), 7.15 (m, 2H), 6.93 (dd, J = 8.0, 4.0 Hz, 1H), 4.16 (br s, 1H), 3.63 (s, 3H), 2.98 (br s, 3H), 2.76 (m, 1H), 2.61 (m, 2H), 2.31 (s, 3H), 1.90 (m, 1H). ^{13}C NMR (125.75 MHz, DMSO-d_6) δ: 171.2, 160.3, 160.1, 159.7, 151.9, 145.6, 143.5, 141.0, 130.4, 130.3, 125.1, 118.6, 115.5, 115.3, 110.2, 108.7, 102.2, 55.8, 51.0, 33.2, 27.9, 26.0, 14.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{25}FN_7O$ 446.2099; found 446.2084. $[\alpha]^{20}_D$ −69.13 (c 1.08, $CHCl_3$). Chiral HPLC method: Phenomenex Lux Cellulose-3, 3 um, 4.6 × 150 mm^2, 0.8 mL/min, 220 nm, solvent A: 0.01 M NH_4OAc in MeOH-water (20:80), solvent B: 0.01 M NH_4OAc in MeOH-water-MeCN (20:5:75), 75% B isocratic, 15 min, RT = 3.17 min (desired *S*), 4.08 min (undesired *R*).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01734.

NMR spectra for all new compounds, computational details, chiral HPLC chromatograms, reaction screening results, and PMI and process greenness comparison of routes (PDF)

X-ray data for (*S*)-**1** (CIF)

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Notes

The authors declare no competing financial interest.

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(28) When a 0.6 M solution of (*S*)-**1** in NMP was treated with 1 equiv H_2SO_4 at 100 °C, < 1% (*R*)-**1** formed in 24 h.

(29) (S)-**1** racemized under strongly basic conditions and elevated temperatures (2.5 equiv *t*-BuONa in *n*-PrOH at 96 °C, 12 h). DFT

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