JOC The Journal of Organic Chemistry Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX Article pubs.acs.org/joc

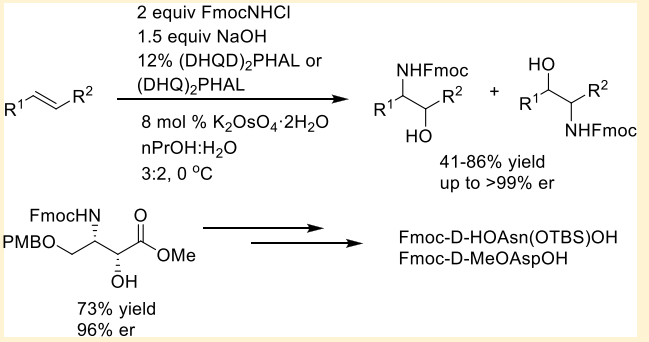
Synthesis of Fmoc-Protected Amino Alcohols via the Sharpless Asymmetric Aminohydroxylation Reaction Using FmocNHCl as the Nitrogen Source

Ryan Moreira, Matthew Diamandas, and Scott D. Taylor*

Department of Chemistry, University of Waterloo, 200 University Avenue West, Waterloo, Ontario, Canada, N2L 3G1

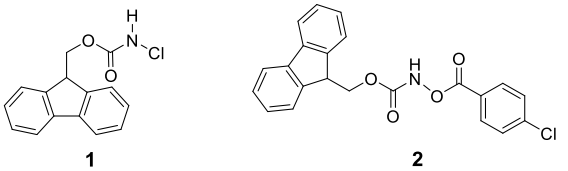
Supporting Information

ABSTRACT: The aminohydroxylation of various alkenes using FmocNHCl as a nitrogen source is reported. In general, in the absence of a ligand, the reaction provided racemic Fmoc-protected amino alcohols with excellent regioselectivity but in low to moderate yields. However, in some instances, the yield of an amino alcohol product and the regioselectivity could be altered by the addition of a catalytic amount of triethylamine (TEA). The Sharpless asymmetric variant of this reaction (Sharpless asymmetric aminohydroxylation (SAAH)), using $(DHQD)_2PHAL$ (DHQD) or $(DHQ)_2PHAL$ (DHQ) as chiral ligands, proceeded more readily and in higher yield compared to the same reaction in the absence of a chiral ligand. The enantiomeric ratios (er) of all but two examples exceeded 90:10 with many examples giving er values of 95:5 or higher, making FmocNHCl a highly practical reagent for preparing chiral amino alcohols. The SAAH reaction using FmocNHCl was used for the preparation of D-*threo*-*β*-hydroxyasparagine and D-*threo*-*β*-methoxyaspartate, suitably protected for Fmoc solid phase peptide synthesis.



INTRODUCTION

The Sharpless asymmetric aminohydroxylation (SAAH) reaction is perhaps the most powerful and direct approach for preparing vicinal amino alcohols in an enantioselective manner.[1] *N*-Chlorinated derivatives of benzyl (CbzNHCl) and *tert*-butyl carbamates (BocNHCl), which are usually generated *in situ* from the corresponding carbamates and *tert*-butylhypochlorite, have been widely used as the nitrogen source in the SAAH reaction.[1] In contrast, until very recently, fluorenylmethyl (Fmoc) carbamates, such as FmocNHCl (**1**, Figure 1),



1 **2**

Figure 1. Reagents used for introducing Fmoc-protected amines in the SAAH reaction.

had never been used as a nitrogen source in SAAH reactions. The reason for this is probably because it had been assumed that the Fmoc group was too bulky to allow for high enantioselectivity[2] and too base labile to survive the basic conditions normally employed in the SAAH reaction. The latter problem was circumvented in 2011 by Harris et al., who reported that fluorenylmethylcarbamate **2** (Figure 1) could be used as a nitrogen source for the SAAH reaction under base-free conditions.[3]

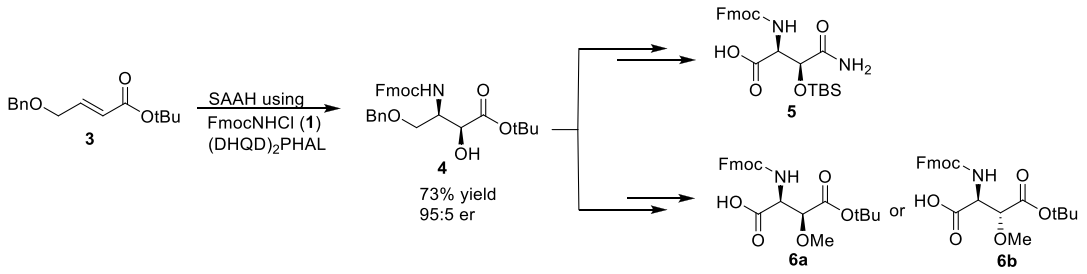
Recently, we reported that Fmoc-protected amino alcohol **4** could be prepared in good yield and enantioselectivity from alkene **3** via a SAAH reaction under classic (i.e., basic) SAAH reaction conditions using **1** as the nitrogen source (Scheme 1).[4] We showed that the reaction proceeded much better when **1** was introduced into the reaction mixture as a reagent rather than being generated *in situ* from $FmocNH_2$ and *tert*-butylhypochlorite. Multigram quantities of reagent **1** were prepared in a single step and in high yield by reacting $FmocNH_2$ with trichloroisocyanuric acid, an inexpensive chlorinating agent, and **1** is a stable, easily handled solid and is storable at room temperature.[4a] Compound **4** was used to achieve concise syntheses of L-*threo*-*β*-hydroxyasparagine, L-*threo*-*β*-methoxyaspartate, and L-*erythro*-*β*-methoxyaspartate, suitably protected for Fmoc solid phase peptide synthesis (**5**, **6a**, and **6b**, respectively in Scheme 1).[4a,b] Amino acids **5** and **6b** were used to achieve the total synthesis of A54145 factor D, a complex cyclic lipodepsipeptide antibiotic.[4b] Overall, these studies suggested that reagent **1** could be a very useful and general reagent for SAAH reactions and natural product synthesis.

Here we report the results of our investigations on the scope of the SAAH reaction using reagent **1** as the nitrogen source

Received: September 13, 2019
Published: October 31, 2019

   DOI: 10.1021/acs.joc.9b02491
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of Fmoc-Protected Amino Alcohol 4 Using Reagent 1

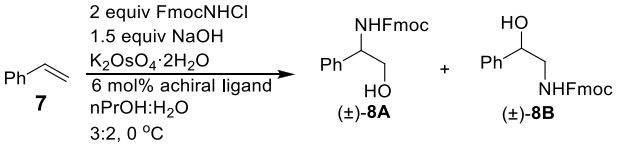


both in the absence of a chiral ligand and in the presence of the chiral ligands $(DHQD)_2PHAL$ (DHQD) and $(DHQ)_2PHAL$ (DHQ). These studies enabled us to develop an efficient synthesis of highly enantiomerically enriched **ent-5** and **ent-6a** (D-*threo*-*β*-hydroxyasparagine and D-*threo*-*β*-methoxyaspartate, respectively), which could not be achieved starting from **3**.

RESULTS AND DISCUSSION

We first explored the effectiveness of FmocNHCl as a nitrogen source for the amino hydroxylation on some common olefins in the absence of chiral ligands. We began this study by subjecting styrene (**7**) to **1**/NaOH/8% osmate in *n*PrOH/H_2O (Table 1, entry 1). Although the regioselectivity was excellent in that the ratio of the resulting amino alcohols, (±)-**8A**:(±)-**8B**, was 1:19, the isolated yield of the major product, (±)-**8B**, was only a moderate 45%. We noticed that this reaction produced significant amounts of $FmocNH_2$, suggesting that competing hydrolysis of the *in situ* formed $FmocNOsO_3$ was having a deleterious effect on reaction efficiency.[5] This prompted us to investigate the stability of FmocNHCl which we found to spontaneously convert to $FmocNH_2$ in *n*PrOH/H_2O at 0 °C; however, the conversion is much faster in the presence of osmate and an alkene (see Scheme S1). The hydrolysis could be suppressed to an extent by lowering the catalyst loading to 4% (Scheme S5), which gave (±)-**8B** in an isolated yield of 56% (entry 2). Further reduction of the catalyst loading to 2% did not result in an increase in the yield of (±)-**8B** even if the reaction time was doubled (entry 3).

Table 1. Effect of a Catalytic Amount of an Achiral Ligand on the Yield and Regioselectivity of the Aminohydroxylation Reaction Using Styrene as a Substrate



entry	achiral ligand (6 mol %)	mol % $K_2OsO_4 \cdot 2H_2O$	time (h)	% yield (±)-**8B**[a]	regioselectivity[b]
1	none	8	3	45	1:19
2	none	4	3	56	1:19
3	none	2	6	56	1:10
4	pyridine	4	4	18	1:10
5	NMM	4	4	30	1:7
6	DABCO	4	1	36	1:7
7	TEA	4	6	69	1:10
8	DIPEA	4	4	61	1:6.2
9	DBU	4	6	62	1:7

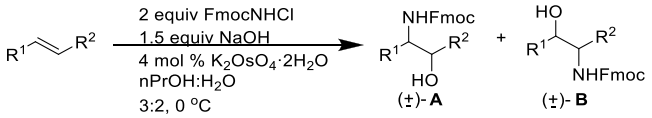
[a]Isolated yield of (±)-**8B**. [b](±)-**8A**:(±)-**8B** determined by ^{1}H NMR of mixture of (±)-**8A** and (±)-**8B**.

It is well-known that some simple, achiral tertiary amine base ligands accelerate the osmium catalyzed dihydroxylation process.[6] Therefore, we considered that the addition of a catalytic amount of achiral amine base ligand could suppress unwanted hydrolysis by accelerating the osmylation step in the aminohydroxylation process.[6] Only a few reports have appeared describing the effects of simple, achiral tertiary amine base ligands on the aminohydroxylation process. The most notable examples were described by Angelaud et al.[7] and Donohoe et al.[8] Angelaud et al.[7] reported that the addition of quinuclidine or DIPEA greatly affected the regioselectivity of the aminohydroxylation process. Unfortunately, no data on reaction yield was provided. Donohoe et al. explored the effects of quinuclidine and DIPEA on the tethered amino-hydroxylation reaction and found that DIPEA enhanced the rate of the reaction substantially and increased the yield.[8] Interestingly, quinuclidine was found to slow the reaction down and greatly decreased the reaction yield. The mixed results observed by Donohoe et al. may be explained by the fact that the ligand can accelerate the osmylation step but hinder the rate-controlling hydrolysis step.[6] With this in mind, we screened a series of tertiary amine bases to determine if any were capable of improving the efficiency of the amino-hydroxylation reaction on styrene (Table 1).

For its historical significance,[6] we first tried pyridine which we found to inhibit catalytic turnover almost immediately (the solution quickly turned from green to bright yellow, indicating that the dioxo osmium(VI) monoazaglycolate species was no longer present).[9] After 4 h, the reaction was worked-up and the small amount of product that was recovered had a regioselectivity of 1:10 (entry 4). The same turnover-inhibiting effect was observed when pyridyl acrylates were subjected to SAAH with *in situ* generated CbzNHCl.[10] We found that the *N*-methylmorpholine (NMM) decreased the reaction yield and altered the regioselectivity to 1:7 (entry 5). Similar results were observed with 1,4-diazabicyclo[2.2.2]octane (DABCO), although the regioselectivity was 1:10 (entry 6). It should be noted that turnover with DABCO was quickly inhibited, which may be explained by the formation of an unreactive bridged DABCO−imidoosmium complex.[11] The results observed with triethylamine (TEA) as a ligand are perplexing (entry 7). We found TEA to substantially increase the overall yield (76%) and isolated reaction yield (69%) even though the regioselectivity decreased to 1:10 and the reaction took twice as long to reach completion.We initially thought that TEA was stabilizing the imidoosmium complex, decreasing the reaction rate and preventing hydrolysis of the imidoosomium complex. However, closer analysis of the FmocNHCl, $FmocNH_2$, and

DOI: 10.1021/acs.joc.9b02491
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Aminohydroxylation Reactions Using FmocNHCl



entry	alkene	mol % TEA	time (h)	major product	product ratio[a]	yield (%)[b]
1	**7** (R^1 = Ph, R^2=H)	0	3	(±)-**8B**	1:19	56
2	**7**	6	6	(±)-**8B**	1:19	69
3	**9** (R^1 = $PhCH_2$, R^2 = H)	0	15	(±)-**10B**	1:20	55
4	**9**	6	15	(±)-**10B**	1:20	43, 46[g]
5[e]	**11** (R^1=R^2=Ph)	0	18	(±)-**12**	NA[c]	47
6[e]	**11**	6	18	(±)-**12**	NA[c]	84
7	**13** (R^1 = 4-MeOPh, R^2 = CO_2Me)	0	36	(±)-**14B**	1:2	18[f]
8	**13**	6	36	(±)-**14B**	1:2.4	33[f]
9	**15** (R^1 = Ph, R^2 = CO_2iPr)	0	60	(±)-**16B**	1:1.9	46[f]
10	**15**	6	48	(±)-**16B**	1:2	55[f]
11	cyclohexene (**17**)	0	24	(±)-**18**	NA[c]	18
12	**17**	6	24	(±)-**18**	NA[c]	0
13	 **19**	0/6	24	NR[d]	NR[d]	NR[d]

[a]Ratio of **A**:**B** determined using ^{1}H NMR. [b]Isolated yield of major product. [c]NA = not applicable. [d]NR = no reaction. [e]3:2 MeCN/H_2O was used as a solvent. [f]Yield of major product estimated using ^{1}H NMR. [g]6 mol % DIPEA in place of TEA.

(±)-**8B** produced under ligand and ligand-free conditions (see Table S5) suggests that TEA selectively accelerates the osmylation process and has little effect on the amount of carbamate produced. Therefore, the extended reaction time observed with TEA does not reflect a decrease in reaction rate but demonstrates that catalytic turnover is still possible at much lower concentrations of FmocNHCl, compared to the ligand-free conditions. In addition, this analysis revealed that TEA seems to have a similar, although less dramatic, effect on the reaction rate compared to DHQD. Similar effects are observed with *N*,*N*-diisopropylethylamine (DIPEA), although the observed regioselectivity is lower (1:6.2, entry 8). These results show that the observed effects on regioselectivity are not due to small changes in pH since TEA and DIPEA have the same pK_a, and thus the two ligands must be forming a complex with $FmocNOsO_3$ in solution.[12] 1,8-Diazabicyclo-(5.4.0)undec-7-ene (DBU) gave results that are almost identical to those observed with DIPEA.

Using 4 mol % osmate catalyst, we examined several other common alkenes as substrates (Table 2). Like styrene, the regioselectivity of the reaction with alkene **9** was very high and the yield of the major product, (±)-**10B**, was a moderate 55% (entry 3). To our surprise, we found that the addition of TEA reduced the yield of (±)-**10B** to 43% (entry 4). Adding DIPEA in place of TEA gave (±)-**10B** in a 46% yield and caused no change in regioselectivity, suggesting that this effect is not due to sterics alone.

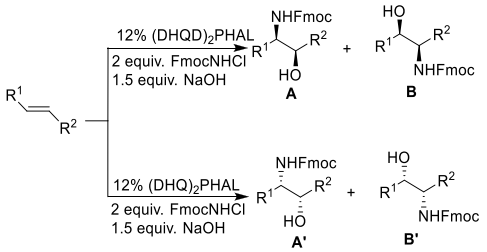
Initial attempts at converting alkene **11** to (±)-**12** were unsuccessful due to the alkene's poor solubility in the aqueous alcohol solvent system. When aqueous acetonitrile was used, **11** was converted to (±)-**12** in a 47% yield (entry 5). Under these conditions, the addition of catalytic TEA dramatically improved the yield of (±)-**12** to 84% (entry 6).

The reaction using alkene **13** produced amino alcohols (±)-**14A** and (±)-**14B**, which were difficult to separate by column chromatography and so were characterized as a 1:2 mixture ((±)-**14A**:(±)-**14B**). The yield of the major product, (±)-**14B**, was estimated using ^{1}H NMR on the isolated mixture to be only 18% (entry 7). In the presence of catalytic TEA, the yield of (±)-**14B** was improved to 33% (entry 8) although the regioselectivity was not substantially affected (1:2.4).

The reaction using isopropylcinnamate (**15**) produced products (±)-**16A** and (±)-**16B** as a 1:1.9 mixture ((±)-**16A**:(±)-**16B**), entry 9). The regioselectivity of this entry matched that reported by Harris et al. under base-free conditions using reagent **2**.[3,13] These two amino alcohols were also difficult to separate by column chromatography and so were characterized as a 1:1.9 mixture. The yield of the major product, (±)-**16B**, was estimated using ^{1}H NMR on the isolated mixture to be 46% (entry 9), which is quite high compared to the previous entries despite the reaction having to proceed for 60 h. The yield of (±)-**16B** was improved to 55% by the addition of catalytic TEA while the regioselectivity was

DOI: 10.1021/acs.joc.9b02491
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 3. Asymmetric Aminohydroxylation Reactions Using FmocNHCl



entry	alkene	solvent[a]	ligand[b]	time (h)	major product	product ratio[c]	yield (%)[d]	er[e]
1	**7** (R^1 = Ph, R^2 = H)	*n*PrOH/H_2O	DHQD	3	**8B**	47:53	45	93:7
2	**7**	*n*PrOH/H_2O	DHQ	18	**8B′**	49:51	41	89:11
3[f,g]	cyclohexene (**17**)	*n*PrOH/H_2O	DHQD	20	**18A** (1*R*,2*S*)	–	62	98:2
4[f,g]	**17**	*n*PrOH/H_2O	DHQ	36	**18A′** (1*S*,2*R*)	–	73	84:16
5	**15** (R^1 = Ph, R^2 = CO_2iPr)	*n*PrOH/H_2O	DHQD	3	**16A**	>20:1	81	98:2
6	**15**	*n*PrOH/H_2O	DHQ	3	**16A′**	>20.1	71	99.5:0.5
7	**20** (R^1 = Ph, R^2 = CO_2Me)	*n*PrOH/H_2O	DHQD	2	**21A**	15:1	67	97:3
8	**20**	*n*PrOH/H_2O	DHQ	2	**21A′**	15:1	86	94:6
9	**13** (R^1 = 4-MeOPh, R^2 = CO_2Me)	*n*PrOH/H_2O	DHQD	2.5	**14A**	>20:1	67	95:5
10	**13**	*n*PrOH/H_2O	DHQ	3	**14A′**	>20.1	46	98:2
11	**22** (R^1 = *N*-*t*Boc-3-indol, R^2 = CO_2Me)	*n*PrOH/H_2O	DHQD	4	**23A**	20:1	65	98:2
12	**22**	*n*PrOH/H_2O	DHQ	23	**23A′**	8.4:1	59	>99
13	**3** (R^1 = $BnOCH_2$, R^2 = CO_2tBu)	*n*PrOH/H_2O	DHQD	3	**4A**	12:1	70	95:5
14	**3**	MeCN/H_2O	DHQD	5	**4A**	4:1	56	96:4
15	**3**	*n*PrOH/H_2O	DHQ	8	**4A′**	ND	51	92:8
16	**3**	MeCN/H_2O	DHQ	18	**4A′**	ND	25	92.5:7.5
17	**24** (R^1 = 4-MeOBnOCH_2, R^2 = CO_2Me)	*n*PrOH/H_2O	DHQD	3	**25A**	15:1	73	89:11
18	**24**	MeCN/H_2O	DHQD	4	**25A′**	5:1	45	93:7
19	**24**	*n*PrOH/H_2O	DHQ	2	**25A′**	15:1	73	96:4

[a]Ratio of *n*PrOH/H_2O or MeCN/H_2O was 3:2. [b]12 mol % ligand used, 8 mol % K_2OsO_4·$2H_2O$ used in all reactions. [c]Product ratio = **A**:**B** or **A′**:**B′** determined by ^{1}H NMR. [d]Isolated yield of major product. [e]er = enantiomeric ratio of major product as determined by chiral HPLC. [f]The general scheme does not apply to this cis alkene. [g]The configuration of the product is indicated under the major product column. Carbon 1 bears the installed alcohol. Carbon 2 bears the installed carbamate.

almost unaffected (1:2) (entry 10). In this case, TEA also reduced the reaction time to 48 h.

The reaction with cyclohexene (**17**) gave amino alcohol (±)-**18** in a meager 18% yield after 24 h (entry 11). The addition of catalytic TEA was found to almost completely inhibit conversion of this starting material (entry 12). Attempts to convert **19** to its amino alcohol proved unfruitful (entry 13) even in the presence of achiral bases (TEA) and even chiral ligands $(DHQ)_2$PHAL or $(DHQD)_2$PHAL.

Next, we explored the reaction in the presence of chiral ligands $(DHQD)_2$PHAL (DHQD) and $(DHQ)_2$PHAL (DHQ) (Table 3). With styrene (**7**), we found that the presence of either ligand significantly increased the overall reaction yield, but since little regioselectivity was observed, the isolated yields of the major products, **8B** and **8B′**, were moderate (entries 1 and 2). Poor regioselectivity is often observed when using styrene and *in situ* generated CbzNHCl[14] or BocNHCl[15] in the SAAH reaction. The er values using reagent **1** are slightly less than those reported for the same reaction and ligands using *in situ* generated CbzNHCl[14] or BocNHCl.[15]

The presence of a chiral ligand dramatically increased the rate of the reaction with cyclohexene (**17**) (entries 3 and 4).[6] Using DHQD, amino alcohol **18A** was obtained in a reasonable yield and with excellent enantioselectivity (entry 3). The er values using reagent **1** are considerably superior, while the yield of the major product is similar to those reported for the same reaction and ligand but using other nitrogen sources.[3,5,16] The reaction was slower with DHQ, but the yield of the major product, **18A′**, was higher while the er was lower (entry 4) compared to the corresponding DHQD reaction. The er values using DHQ and reagent **1** are slightly better than those reported for the same reaction and ligand using other nitrogen sources.[3,5,16]

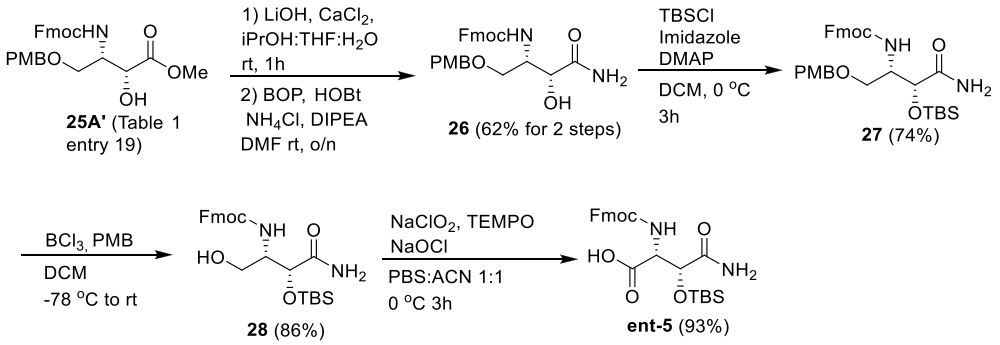
The reaction with alkene ester **15** also proceeded much faster in the presence of the ligands, and in good yield, with very high regioselectivity and enantioselectivity with either ligand (entries 5 and 6). The reaction in the presence of a ligand favored the formation of **16A** and **16A′**, while in the absence of an alkaloid ligand **16B** was favored (entries 9 and 10, Table 2).

Substituting the isopropyl group in **15** with a methyl group (**20**, entries 7 and 8) resulted in only a small decrease in regioselectivity, and the enantioselectivity was still excellent. Ester **20** has been examined by Harris et al. as a substrate in the SAAH reaction using reagent **2** under base-free conditions using both DHQD and DHQ as ligands.[3] They obtained the same regioisomers (**21A** and **21A′**) as the major products and in similar yields and enantioselectivities to those reported here; however, their regioisomeric ratios were significantly less (approximately 6:1 for both ligands).[3,17]

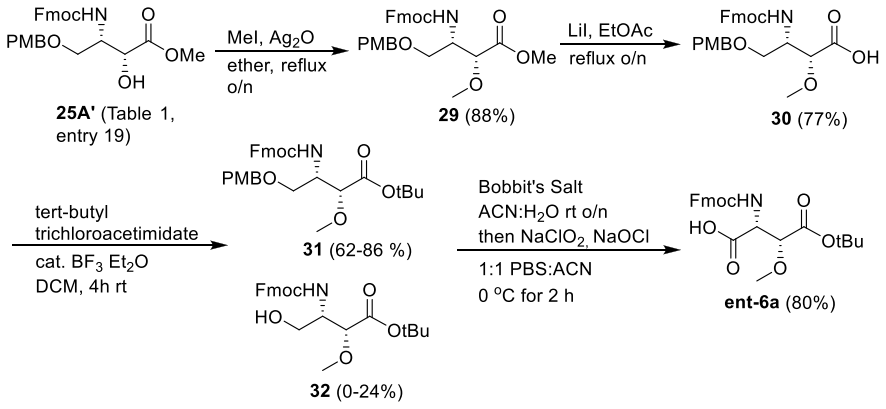
The reaction using the *p*-methoxyphenyl derivative of **20**, compound **13**, and the DHQD ligand proceeded with excellent regioselectivity and provided amino alcohol **14A** as the major

DOI: 10.1021/acs.joc.9b02491
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. Synthesis of ent-5



Scheme 3. Synthesis of ent-6a



product in good yield and enantioselectivity (entry 9). The er obtained with reagent **1** is slightly lower than those reported for the same reaction using the DHQD ligand and *in situ*-generated CbzNHCl.[18,19] The reaction using the DHQ ligand also proceeded with excellent regioselectivity and enantioselectivity; however, the yield of the major regioisomer, **14A′**, was moderate (entry 10).

Using the DHQD ligand, indole alkene **22** afforded **23A** as the major regioisomer in a good yield with excellent regioselectivity and enantioselectivity (entry 11). Likewise, the reaction with the DHQ ligand proceeded with high regioselectivity and excellent enantioselectivity providing **23A′** in a similar yield (entry 12). Although the regioselectivity using the DHQ ligand is poorer than that previously reported with a very similar substrate and *in situ* generated CbzNHCl, the enantioselectivity using either the DHQD or DHQ ligand and **1** as a nitrogen source is superior.[10]

We previously reported that the SAAH reaction of alkene **3** with the DHQD ligand proceeded with very good regioselectivity and provided amino alcohol **4A** (compound **4** in Scheme 1) in good yield and enantioselectivity (entry 13).[4] Changing the solvent to MeCN/H_2O resulted in a decrease in regioselectivity and yield of **4A**, but with almost identical enantioselectivity (entry 14). To our surprise, the reaction was slower with the DHQ ligand, and the major product, **4A′**, was produced in lower yield and er compared to the reaction using DHQD regardless of whether the solvent was *n*PrOH/H_2O or MeCN/H_2O (entries 15 and 16).

Previous work by Janda and McLeod showed that *p*-methoxy phenyl ethers are strong directing groups for the SAAH reaction.[20−22] The reaction on the *p*-OMe analog (**24**[23]) of compound **3** proceeded with better regioselectivity compared to the reaction using alkene **3**, and the yield of the major products, **25A** or **25A′**, was also better, regardless of the ligand used (entries 17 and 19). However, with the DHQD ligand, the er of **25A** was less than that of compound **4A**, while with the DHQ ligand, the er of amino alcohol **25A′** was greater than that of **4A′**. Performing this reaction with the DHQD ligand in MeCN/H_2O resulted in a decrease in regioselectivity and yield of the major product, though the er did not change significantly (entry 18).

As part of our work on the synthesis of lipopeptide antibiotics,[4a,b] we wished to prepare the enantiomers of protected amino acids **5** and **6a**. For these syntheses, it would have been preferable to start with compound **4A′** (entry 15, Table 2), which is the enantiomer of **4A** (compound **4** in Scheme 1), as this would have allowed us to use the identical route that we developed for the syntheses of **5** and **6a** (**ent-5** and **ent-6a**, respectively).[4] Unfortunately, the er of **4A′** was not quite high enough for this purpose. Since the er of **25A′** (entry 19, Table 2) was high enough, we decided to develop a synthesis of **ent-5** and **ent-6a** starting with **25A′**.

To prepare **ent-5**, we first hydrolyzed the methyl ester of **25A′** with aqueous lithium hydroxide in the presence of a high concentration of calcium chloride (Scheme 2).[24] After aqueous workup, the crude material was amidated using BOP/DIPEA/NH_4Cl[25] yielding **26** in a 62% yield over two steps. Silylation of **26** using TBSCl/imidazole and catalytic DMAP gave **27** in a 74% yield. Attempts to remove the PMB group in **27** using Bobbitt's salt were unsuccessful.[4] We also tried to remove the PMB group in **27** using DDQ in aqueous DCM; however, these conditions provided **28** in low yield due to concomitant removal of the TBS group.[26] However, **28** could be obtained in an 86% yield using BCl_3 with pentamethylbenzene as a

DOI: 10.1021/acs.joc.9b02491
J. Org. Chem. XXXX, XXX, XXX−XXX

scavenger.[27] Oxidation of **28** using TEMPO/$NaClO_2$/NaOCl provided **ent-5** in very high yield, although a stoichiometric amount of TEMPO was required to prevent chlorination of the amide nitrogen. The NMR data of **ent-5** were identical to those reported for **5** and possessed an optical rotation equal and opposite to that reported for **5**.[4]

To prepare **ent-6a**, **25A′** was methylated with MeI/Ag_2O to give **29** in an 88% yield (Scheme 3). We found that the hydrolysis of the ester in **29** was too slow using aqueous lithium hydroxide to allow for selective deprotection of the acid in the presence of the Fmoc group, even at high calcium concentrations. After trying trimethyl tin hydroxide[28] and $AlCl_3$/DMA,[29] we found that efficient deprotection of **29** could be achieved in good yield using LiI in ethyl acetate at 80 °C.[30] The free acid **30** was converted to *tert*-butyl ester **31** in excellent yield using *tert*-butyltrichloroacetimidate catalyzed by $BF_3{\cdot}Et_2O$. However, we found that these results were difficult to reproduce at larger scales (>1 g) due to concomitant removal of the PMB group, which yielded a mixture of **31** and **32**.[34] We saw this as potentially advantageous since **32** could simply be added to the subsequent oxidation, after the cleavage was complete, reducing that amount of Bobbit's salt needed to afford **ent-6a**. As suspected, the PMB group of **31** was easily removed and the resulting *in situ* generated primary alcohol was oxidized via a two-stage, one-pot reaction employing 1.1 equiv of Bobbit's salt followed by treatment with TEMPO/$NaClO_2$/NaOCl.[4] This provided **ent-6a** in 80% yield. The NMR data of **ent-6a** were identical to those reported for **6a** and possessed an optical rotation equal and opposite to that reported for **6a**.[4]

SUMMARY AND CONCLUSIONS

In summary, we have shown that FmocNHCl (**1**) is an effective nitrogen source for the SAAH reaction. In the absence of a ligand, the reaction usually provided Fmoc-protected amino alcohols in moderate yields but with excellent regioselectivity. However, in some instances, both the yields and regioselectivities could be altered by the addition of a catalytic amount of TEA. In the presence of a chiral ligand, the reactions proceeded more readily. In general, yields as well as regio- and enantioselectivities were similar to those reported using other carbamate nitrogen sources. Remarkably, the enantioselectivity of all but two examples exceed an er of 90:10 with many examples giving an er of 95:5 or higher. A practical application of this chemistry was demonstrated by the synthesis of D-*threo*-β-hydroxyasparagine and D-*threo*-β-methoxyaspartate, suitably protected for Fmoc solid phase peptide synthesis.

EXPERIMENTAL SECTION

General Experimental Information. All reagents were purchased from commercial suppliers. ACS grade *n*-propanol (*n*PrOH) and toluene were used without further purification. Methylene chloride (CH_2Cl_2) and acetonitrile (ACN) were dried by distillation over calcium hydride under nitrogen. Pyridine was dried by refluxing over potassium hydroxide followed by fractional distillation. Tetrahydrofuran (THF) was distilled from sodium metal in the presence of benzophenone under N_2. Chromatography was performed using 60 Å silica gel. All reported enantiomeric ratios (er's) were determined by chiral HPLC. Reversed-phase analytical chiral HPLC was performed using a CHIRAL PAK AS-RH 5 μm 4.6 mm × 150 mm column with a flow rate of 0.5 mL/min. Normal-phase analytical chiral HPLC was performed using a CHIRAL PAK OD-H 5 μm 4.6 mm × 250 mm column with a flow rate of 0.4 mL/min. Analytical samples were prepared by dissolving a small amount of pure sample in 1 mL of mobile phase. For some samples run on the normal phase column which were not very soluble in the mobile phase, the solid was first dissolved in MeCN (50 μL) before being diluted with 90:10 *i*PrOH/hexanes. High resolution positive electrospray (ESI) mass spectra were obtained using an orbitrap mass spectrometer. Samples were sprayed from MeOH/1% formic acid in H_2O. All spectra were collected in the positive mode. ^1H and ^{13}C NMR were collected using a Bruker Avance-300 spectrophotometer. ^1H NMR chemical shifts (δ) are reported in ppm relative to an internal standard (trimethylsilane, 0 ppm). $^{13}C\{^1H\}$ NMR chemical shifts are reported relative to the residual solvent peak (77.0 ppm for $CDCl_3$, 49.2 ppm for CD_3OD, 39.5 ppm for DMSO-d_6). The configurations of **8B**, **14A**, **18A**, and **23A′** were determined using Mosher's ester.[31]

Improved Procedure for Preparing FmocNHCl. $FmocNH_2$ (12 g, 50.15 mmol, 1 equiv) was dissolved with heating in MeOH (750 mL). When the reaction mixture had cooled to 35 °C, pulverized trichloroisocyanuric acid (3.86 g, 16.72 mmol, 1/3 equiv) was added in a single portion. The reaction was stirred for 14 h at room temperature in a dark fumehood and then reheated to 35 °C, and another portion of pulverized trichloroisocyanuric (386 mg, 1.66 mmol, 0.03 equiv) was added. After stirring at room temperature for an additional 4 h, the reaction mixture was concentrated and the resulting solid was suspended in hot toluene and then filtered while hot. Crystals form in the filtrate as the filtrate cools. Pure FmocNHCl (13.0 g, 95%) was obtained by heating the filtrate until the crystals redissolved and then allowing the filtrate to cool slowly at which point pure FmocNHCl crystallized out of solution. The resulting crystals (FmocNHCl) were obtained by filtration and then dried under high vacuum. .

General Procedure for Sharpless Aminohydroxylation Reactions Using FmocNHCl. To a suspension of FmocNHCl (221 mg, 0.804 mmol, 2.00 equiv) in *n*PrOH (1.75 mL) cooled in an ice−water bath was added NaOH (24 mg, 0.60 mmol, 1.5 equiv) in H_2O (3 mL). This was followed by the addition of a solution of $(DHQD)_2PHAL$, $(DHQ)_2PHAL$ (38 mg, 0.048 mmol, 12 mol %), or triethylamine (6 mol %) fully dissolved in *n*PrOH (3 mL) and a solution of alkene (0.402 mmol) in *n*PrOH (1.5 mL). $K_2[OsO_2(OH)_4]$ (12 mg, 0.032 mmol, 8 mol %) dissolved in H_2O (1.25 mL, a couple drops of the NaOH solution were added to the solution of $K_2[OsO_2(OH)_4]$ in H_2O) was added to the reaction mixture, and at this point, the reaction solution was deep-green and homogeneous. The cooled (ice−water bath) reaction mixture was stirred until the green color had dissipated or until TLC had indicated complete conversion of the alkene. The reaction was extracted with EtOAc (20 mL) twice, and this organic layer was washed with aqueous sat. $NaHCO_3$ (30 mL) and brine. The organic layer was dried with Na_2SO_4 and concentrated. The crude residue was purified by silica-gel column chromatography.

(9*H*-Fluoren-9-yl)methyl (*R*)-(2-Hydroxy-2-phenylethyl)-carbamate (8B) and (9*H*-Fluoren-9-yl)methyl (*S*)-(2-Hydroxy-2-phenylethyl)carbamate (8B′). **8B** was prepared from **7** following the general procedure using $(DHQD)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (5% EtOAc/95% CH_2Cl_2) which yielded **8B** as a colorless, crystalline solid (65 mg, 45%). $[\alpha]^{22}_D = -18.2°$ (*c* 0.560, CH_2Cl_2). Er = 94:6 (see Figure S1). **8B′** was prepared from **7** following the general procedure using $(DHQ)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (5% EtOAc/95% CH_2Cl_2) which yielded **8B′** as a colorless, crystalline solid (54 mg, 37%). $[\alpha]^{22}_D = 15.9°$ (*c* 0.324, CH_2Cl_2). Er = 88:11 (see Figure S1). NMR data matched those previously reported.[32] The ^1H NMR spectra of (±)-**8B**, **8B**, and **8B′** were identical. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (2H, d, J = 7.5 Hz), 7.49 (2H, m), 7.34−7.16 (9H, m), 5.14 (1H, m), 4.73 (1H, d, J = 9.3 Hz), 4.34−4.32 (2H, m), 4.12 (1H, dd, J = 6.9, 6.9 Hz), 3.48−3.44 (1H, m), 3.25−3.16 (1H, m), 2.78 (1H, br. s). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 157.1, 143.8, 141.5, 141.3, 128.5, 127.9, 127.7, 127.0, 125.9, 125.0, 120.0, 73.6, 66.8, 48.5, 47.2. HRMS-ESI+ (*m*/*z*): $[M + H]^+$ calculated for $C_{23}H_{22}O_3N$, 360.1594; found, 360.1594.

DOI: 10.1021/acs.joc.9b02491
J. Org. Chem. XXXX, XXX, XXX−XXX

(9*H*-Fluoren-9-yl)methyl (2-hydroxy-3-phenylpropyl)-carbamate ((±)-10B). (±)-**10B** was prepared from **9** following the general procedure (no ligand was added). It was isolated by silica gel column chromatography (5% EtOAc/95% CH_2Cl_2) which yielded (±)-**10B** as a colorless, crystalline solid (83 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (2H, d, J = 7.8 Hz), 7.51 (2H, m), 7.34−7.11 (9H, m), 4.35 (1H, m), 4.12 (1H, dd, J = 6.3, 6.3 Hz), 3.85 (1H, m), 3.36 (1H, m), 3.03 (1H, m), 2.74−2.57 (2H, m), 2.15 (1H, br. s). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 157.0, 143.8, 141.3, 137.4, 129.3, 128.7, 127.7, 127.0, 126.7, 125.0, 120.0, 72.0, 66.7, 50.7, 47.2, 46.2, 41.2. HRMS-ESI+ (m/z): [M + H]$^+$ calculated for $C_{24}H_{24}O_3N$, 374.1751; found, 374.1746.

(9*H*-Fluoren-9-yl)methyl (2-Hydroxy-1,2-diphenylethyl)-carbamate ((±)-12). (±)-**12** was prepared from **11** following the general procedure using MeCN in place of *n*PrOH and triethylamine as a ligand. It was isolated by silica gel column chromatography (2.5% EtOAc/97.5% CH_2Cl_2 to 5% EtOAc/95% CH_2Cl_2) which yielded (±)-**12** as a colorless, crystalline solid (147 mg, 84% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ7.89−7.66 (5H, m) 7.41−7.17 (14H, m) 5.52 (1H, d, J = 4.8 Hz), 4.79−4.74 (2H, m), 4.20−4.12 (3H, m). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): 155.7, 143.9, 143.7, 143.0, 141.5, 140.6, 127.7, 127.6, 127.3, 127.0, 127.0, 126.8, 126.6, 126.6, 125.3, 125.2, 120.0, 75.5, 65.5, 61.3, 46.6. HRMS-ESI+ (m/z): [M + H]$^+$ calculated for $C_{29}H_{26}O_3N$, 436.1907; found, 436.1910.

Methyl (2*S*,3*R*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)-amino)-2-hydroxy-3-(4-methoxyphenyl)propanoate (14A) and Methyl (2*R*,3*S*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)-amino)-2-hydroxy-3-(4-methoxyphenyl)propanoate (14A′). **14A** was prepared from **13** following the general procedure using $(DHQD)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (25% EtOAc/75% hexanes to 20% EtOAc/80% hexanes) which yielded **14A** as a colorless, crystalline solid (119 mg, 67%). $[\alpha]^{22}_D$ = −19.5° (c 0.868, CH_2Cl_2). Er = 97:3 (see Figure S2). **14A′** was prepared from **13** following the general procedure using $(DHQ)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (25% EtOAc/75% hexanes) which yielded **14A′** as a colorless, crystalline solid (83 mg, 46%). $[\alpha]^{22}_D$ = 21.3° (c 0.952, CH_2Cl_2). Er = 99:1 (see Figure S2). The ^{1}H NMR spectra of **14A** and **14A′** were identical. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (2H, d, J = 7.2 Hz), 7.47 (2H, m), 7.33−7.16 (6H, m), 6.79 (2H, d, J = 8.7 Hz), 5.63 (1H, d, J = 9.3 Hz), 5.13 (1H, d, J = 9.6 Hz), 4.39−4.08 (4H, m), 3.73−3.70 (6H, m), 3.22 (1H, d, J = 4.2 Hz). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 173.3, 159.2, 155.7, 143.7, 141.2, 130.9, 127.9, 127.7, 127.0, 120.0, 114.0, 73.4, 66.9, 55.9, 55.3, 53.1, 47.1. HRMS-ESI+ (m/z): [M + H]$^+$ calculated for $C_{26}H_{26}O_6N$, 448.1755; found, 448.1746.

Isopropyl (2*S*,3*R*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)-amino)-2-hydroxy-3-phenylpropanoate (16A) and Isopropyl (2*R*,3*S*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-hydroxy-3-phenylpropanoate (16A′). **16A** was prepared from **15** following the general procedure using $(DHQD)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (10% EtOAc/90% hexanes to 20% EtOAc/80% hexanes) which yielded **16A** as a colorless, crystalline solid (145 mg, 81%). $[\alpha]^{22}_D$ = −17.2° (c 0.744, CH_2Cl_2). Er = 98:2 (see Figure S3). **16A′** was prepared from **15** following the general procedure using $(DHQ)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (10% EtOAc/90% hexanes to 20% EtOAc/80% hexanes) which yielded **16A′** as a colorless, crystalline solid (128 mg, 71%). $[\alpha]^{22}_D$ = 21.2° (c 0.712, CH_2Cl_2). Er = 99:1 (see Figure S3). NMR data matched those previously reported.[2] The ^{1}H NMR spectra of **16A** and **16A′** were identical. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (2H, d, J = 7.2 Hz), 7.48 (2H, m), 7.34−7.22 (9H, m), 5.64 (1H, d, J = 9.3 Hz), 5.22 (1H, d, J = 9.0 Hz), 5.07 (1H, sept, J = 6.0 Hz), 4.40−4.09 (4H, m), 3.18 (1H, br. s), 1.23−1.16 (6H, m). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 172.3, 155.6, 143.9, 143.8, 141.3, 139.0, 128.6, 127.8, 127.7, 127.1, 126.7, 125.0, 120.0, 73.5, 70.9, 67.0, 56.3, 47.2, 21.7, 21.6. HRMS-ESI + (m/z): [M + H]$^+$ calculated for $C_{27}H_{28}O_5N$, 446.1962; found, 446.1951.

(9*H*-Fluoren-9-yl)methyl ((1*S*,2*R*)-2-Hydroxycyclohexyl)-carbamate (18A) and (9*H*-Fluoren-9-yl)methyl ((1*R*,2*S*)-2-Hydroxycyclohexyl)carbamate (18A′). **18A** was prepared from **17** following the general procedure using $(DHQD)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (5% EtOAc/95% CH_2Cl_2) which yielded **18A** as a colorless, crystalline solid (113 mg, 75%). $[\alpha]^{22}_D$ = −17.4° (c 0.800, CH_2Cl_2). Er = 98.5:1.5 (see Figure S4). **18A′** was prepared from **17** following the general procedure using $(DHQ)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (5% EtOAc/95% CH_2Cl_2) which yielded **18A′** as a colorless, crystalline solid (102 mg, 68%). $[\alpha]^{22}_D$ = 15.6° (c 0.904, CH_2Cl_2). Er = 84:16 (see Figure S4). The ^{1}H NMR spectra of **18A** and **18A′** were identical. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (2H, d, J = 7.5 Hz), 7.49 (2H, d, J = 7.5 Hz), 7.30 (2H, dd, J = 7.2, 7.2 Hz), 7.21 (2H, dd, J = 7.2, 7.2 Hz), 5.18 (1H, d, J = 7.5 Hz), 4.30 (2H, m), 4.11 (1H, dd, J = 6.9, 6.9 Hz), 3.55 (1H, m), 2.11 (1H, br. s), 1.65−1.18 (8H, m). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 156.1, 143.9, 141.2, 127.6, 127.0, 125.0, 119.9, 68.8, 66.5, 52.5, 47.2, 31.7, 27.2, 23.7, 19.6. HRMS-ESI+ (m/z): [M + H]$^+$ calculated for $C_{21}H_{24}O_3N$, 338.1751; found, 338.1748.

Methyl (2*S*,3*R*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)-amino)-2-hydroxy-3-phenylpropanoate (21A) and Methyl (2*R*,3*S*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-hydroxy-3-phenylpropanoate (21A′). **21A** was prepared from **19** following the general procedure using $(DHQD)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (5% EtOAc/95% CH_2Cl_2) which yielded **21A** as a colorless, crystalline solid (113 mg, 67%). $[\alpha]^{22}_D$ = −9.9° (c 0.728, $CHCl_3$). Er = 97:3 (see Figure S5). **21A′** was prepared from **19** following the general procedure using $(DHQ)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (5% EtOAc/95% CH_2Cl_2) which yielded **21A′** as a colorless, crystalline solid (145 mg, 86%). $[\alpha]^{22}_D$ = 10.5° (c 0.852, $CHCl_3$). Er = 94:6 (see Figure S5). NMR spectra matched those previously reported.[2] The ^{1}H NMR spectra of **21A** and **21A′** were identical. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (2H, d, J = 6.7 Hz), 7.48 (2H, d, J = 7.2 Hz), 7.31−7.10 (9H, m), 5.65 (1H, d, J = 9.0 Hz), 5.19 (1H, d, J = 9.6 Hz), 4.43−4.12 (4H, m), 3.74 (3H, s), 3.18 (1H, br. s). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ173.1, 155.6, 143.6, 143.6, 141.2, 138.7, 128.6, 127.8, 127.6, 127.0, 124.9, 118.9, 73.3, 66.9, 56.3, 53.1, 47.0. HRMS-ESI+ (m/z): [M + H]$^+$ calculated for $C_{25}H_{24}O_5N$, 418.1649; found, 418.1639.

(2*R*,3*S*)-*tert*-Butyl 3-(1-((((9*H*-Fluoren-9-yl)methoxy)-carbonyl)amino)-2-hydroxy-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate (23A) and (2*R*,3*S*)-*tert*-Butyl 3-(1-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-hydroxy-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate (23A′). **23A** was prepared from **22**[33] following the general procedure using $(DHQD)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (20% EtOAc/80% hexanes) which yielded **23A** as a colorless, crystalline solid (148 mg, 65%). $[\alpha]^{22}_D$ = −17.3° (c 0.808, CH_2Cl_2). Er = 98:2 (see Figure S6). **23A′** was prepared from **22**[33] following the general procedure using $(DHQ)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (20% EtOAc/80% hexanes) which yielded **23A′** as a colorless, crystalline solid (134 mg, 59%). $[\alpha]^{22}_D$ = 20.8 (c 0.903, CH_2Cl_2). Er = >99.5:0.5 (see Figure S6). The ^{1}H NMR spectra of **23A** and **23A′** were identical. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (1H, d, J = 6.5 Hz), δ 7.80−7.49 (6H, m), δ 7.43−7.21 (6H, m), δ 5.83−5.40 (2H, m), δ 5.66 (1H, br s), δ 4.50−4.10 (3H, m), δ 3.86 (3H, s), δ 3.52 (1H, br s), δ 1.67 (9H, s). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 176.2, 158.6, 152.5, 146.7, 146.6, 144.1, 138.4, 131.6, 130.6, 130.0, 128.0, 127.7, 126.9, 125.8, 122.9, 122.2, 121.6, 118.3, 86.9, 75.1, 70.1, 56.2, 52.8, 50.0, 31.1. HRMS-ESI + (m/z): [M + H]$^+$ calculated for $C_{32}H_{33}O_7N_2$, 557.2282; found, 557.2301.

Methyl (2*S*,3*R*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)-amino)-2-hydroxy-4-((4-methoxybenzyl)oxy)butanoate (25A). **25A** was prepared from **24**[23] following the general procedure using $(DHQD)_2PHAL$ as a ligand. It was isolated by silica gel column chromatography (30% EtOAc/70% hexanes to 40% EtOAc/70% hexanes) which yielded **25A** as a colorless, crystalline solid (144 mg, 73%). $[\alpha]^{22}_D$ = +2.4° (c 0.704, CH_2Cl_2). Er = 91:9 (see Figure S7). The ^{1}H NMR spectrum was identical to that of **25A′**.

DOI: 10.1021/acs.joc.9b02491
J. Org. Chem. XXXX, XXX, XXX−XXX

Methyl (2*R*,3*S*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)-amino)-2-hydroxy-4-((4-methoxybenzyl)oxy)butanoate (25A′). To a cooled (ice bath) slurry of FmocNHCl (8.9 g, 32.5 mmol, 2.0 equiv) in *n*PrOH (71 mL) was added a solution of sodium hydroxide (975 mg, 24.4 mmol, 1.5 equiv) in water (121 mL). A solution of $(DHQ)_2PHAL$ (1.52 g, 1.95 mmol, 12 mol %) in *n*PrOH (121 mL) and a solution of alkene **24**[23] (3.84 g, 16.3 mmol, 1.0 equiv) in *n*PrOH (61 mL) were added immediately afterward. The reaction mixture was cooled (ice bath), and at this point it was homogeneous. Then, a solution of potassium osmate (479 mg, 1.30 mmol, 8 mol %) and sodium hydroxide (61 mg, 1.525 mmol, 0.09 equiv) in water (51 mL) was added. The cooled reaction was stirred for 3 h, at which point TLC had indicated that the reaction was complete. The mixture was neutralized with 1 N HCl, and the resulting slurry was filtered. The filter cake was washed several times with 3:2 *n*PrOH/H_2O. The filtrate was concentrated and then partitioned between ethyl acetate (EtOAc, 100 mL) and water (100 mL). The aqueous layer was extracted twice, and the combined organic layer was washed with 1 N HCl (300 mL), sat. $NaHCO_3$ (300 mL), and brine (300 mL). The resulting organic layer was dried with $MgSO_4$, filtered, and concentrated. The crude oil was suspended in CH_2Cl_2, filtered, and concentrated. This process was repeated three times, and then the crude oil was purified by silica gel column chromatography (30% EtOAc/70% hexanes to 40% EtOAc/60% hexanes) yielding **25A′** as a colorless foam (5.53 g, 73% yield). $[\alpha]^{22}_D$ = −3.0° (*c* 0.801, CH_2Cl_2). Er = 96:4 (see Figure S7). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (2H, d, *J* = 7.2 Hz), 7.61 (2H, m), 7.43−7.28 (6H, m), 6.88 (2H, d, *J* = 8.1 Hz), 5.66 (1H, d, *J* = 9.6 Hz), 4.53−4.20 (7H, m), 3.89−3.55 (9H, m). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): 173.5, 158.9, 155.8, 143.6, 143.4, 140.9, 129.4, 129.1, 127.3, 126.7, 124.8, 124.7, 119.6, 113.4, 72.5, 69.3, 52.4, 46.7. HRMS-ESI+ (*m*/*z*): $[M + H]^+$ calculated for $C_{28}H_{30}O_7N$, 492.2017; found, 492.2011.

(9*H*-Fluoren-9-yl)methyl((2*S*,3*R*)-4-amino-3-hydroxy-1-((4-methoxybenzyl)oxy)-4-oxobutan-2-yl)carbamate (26). To a solution of **25A′** (2.88 g, 5.86 mmol, 1 equiv) in THF (40 mL) and isopropanol (133 mL) was added pulverized $CaCl_2$ (10.66 g, 96.08 mmol, 16.4 equiv). The resulting suspension was cooled (ice−water bath), and ice-cold LiOH (0.28 N, 41.8 mL, 2.0 equiv) was added dropwise. After stirring for 15 min more ice cold LiOH (0.28 N, 33.5 mL, 1.6 equiv) was added dropwise to the suspension. Cooling was removed, and once it had reached room temperature, the reaction mixture was stirred for 45 min, at which point it was extracted with diethyl ether (100 mL). The aqueous layer was acidified with 1 N HCl (pH ca. 2) and extracted with EtOAc (100 mL) three times. The combined organic layer was washed with 0.1 N HCl (300 mL) twice, dried over $MgSO_4$, filtered, and concentrated. The crude residue was dissolved in DMF (117 mL) and reacted with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP; 3.89 g, 8.79 mmol, 1.5 equiv) for 5 min at room temperature. NH_4Cl (627 mg, 11.7 mmol, 2.0 equiv) and DIPEA (3.06 mL, 17.58 mmol, 3 equiv) were then added, and the resulting suspension was stirred at room temperature for 2 h. The reaction mixture was then diluted with EtOAc (1200 mL) and washed with 1 N HCl (800 mL), sat. $NaHCO_3$ (800 mL), and brine (800 mL) twice. The organic layer was dried with Na_2SO_4, concentrated, and subjected to silica gel flash column chromatography (80% EtOAc/19% hexanes/1% AcOH then 98% EtOAc/2% AcOH) yielding **26** as a colorless oil (1.73 g, 62% for two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (2H, d, *J* = 7.5 Hz), 7.44−7.40 (2H, m), 7.27−7.22 (2H, m), 7.17−7.12 (2H, m), 7.05 (2H, d, *J* = 8.4 Hz), 6.70 (2H, d, *J* = 8.7 Hz), 6.66 (1H, br. s), 6.13 (1H, br. s), 5.81 (1H, d, *J* = 9.0 Hz), 4.35−3.99 (8H, m), 3.70−3.50 (5H, m). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 175.3, 159.3, 156.6, 143.8, 143.6, 141.2, 129.4, 129.2, 127.6, 127.0, 125.0, 125.0, 119.9, 113.8, 73.1, 72.3, 70.3, 66.9, 55.1, 52.0, 46.9. HRMS-ESI+ (*m*/*z*): $[M + H]^+$ calculated for $C_{27}H_{29}O_6N_2$, 477.2020; found, 477.2005.

(9*H*-Fluoren-9-yl)methyl((2*S*,3*R*)-4-amino-3-((*tert*-butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-4-oxobutan-2-yl)carbamate (27). To a cool (ice bath) solution of **26** (1.069 g, 2.244 mmol, 1.00 equiv) in dry CH_2Cl_2 (22.5 mL) was added Imidazole (764 mg, 11.2 mmol, 5 equiv) and TBSCl (1.69 g, 11.2 mmol, 5 equiv). After 5 min of stirring, DMAP (27 mg, 0.22 mmol, 0.1 equiv) was added and the suspension was stirred for 3 h. After this time, the reaction was quenched with 0.2 N HCl (22 mL) while cold. The aqueous layer was then extracted with CH_2Cl_2 (22 mL) three times, and the combined organic layer was washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated. The crude residue was subjected to silica gel flash column chromatography (30% EtOAc/70% hexanes then 50% EtOAc/50% hexanes) yielding **27** as a colorless oil (979 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (2H, d, *J* = 8.4 Hz), 7.53−7.50 (2H, m), 7.29 (2H, t, *J* = 7.5 Hz), 7.22−7.12 (6H, m), 6.75 (2H, d, *J* = 8.4 Hz), 6.32 (1H, br. s), 6.04 (1H, br. s), 5.56 (1H, d, *J* = 9.3 Hz), 4.36−4.11 (7H, m), 3.68 (3H, s), 3.50−3.23 (2H, m), 0.830 (9H, s), 0.049−0.031 (6H, m). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ175.1, 159.1, 155.8, 143.9, 143.9, 141.2, 129.9, 129.2, 127.6, 127.0, 125.1, 119.9, 113.6, 72.6, 71.3, 67.3, 66.8, 55.2, 53.4, 47.1, 25.6, 17.9, −5.1, −5.4. HRMS-ESI+ (*m*/*z*): $[M + H]^+$ calculated for $C_{33}H_{43}O_6N_2Si$, 591.2885; found, 591.2891.

(9*H*-Fluoren-9-yl)methyl((2*S*,3*R*)-4-amino-3-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-4-oxobutan-2-yl)carbamate (28). **27** (1.1 g, 1.9 mmol, 1.0 equiv) and pentamethylbenzene (306 mg, 2.06 mmol, 1.10 equiv) were dissolved in dry CH_2Cl_2 (20 mL) under an inert atmosphere. The reaction mixture was cooled to −78 °C, and BCl_3 (1 M in CH_2Cl_2, 5.62 mL, 5.62 mmol, 3.00 equiv) was added dropwise over 10 min. After the addition, the reaction mixture was warmed in an ice−water bath. The resulting mixture was stirred for 1 h and then quenched by the dropwise addition of sat. $NaHCO_3$ (40 mL). After 10 min of stirring, the reaction mixture was brought to room temperature and the aqueous layer was extracted with EtOAc (40 mL) twice. The organic layers were combined, washed with brine, dried with $MgSO_4$, and concentrated. The crude oil was purified by silica gel column chromatography (50% EtOAc/49% hexanes/1% AcOH to 60% EtOAc/39% hexanes/1% AcOH) yielding **28** (759 mg, 86%) as a colorless foam. Characterization data matched those previously reported.[3] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (2H, d, *J* = 7.5 Hz), 7.59 (2H, m), 7.40−7.26 (4H, m), 6.06 (2H, m), 5.86 (1H, d, *J* = 9.3 Hz), 4.37−4.35 (2H, m), 4.29 (1H, d, *J* = 3.6 Hz), 4.20 (1H, dd, *J* = 6.9, 6.9 Hz), 4.00 (1H, m), 3.79−3.62 (2H, m), 0.93 (9H, s), 0.16−0.12 (6H, m). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 175.9, 156.3, 143.8, 143.8, 141.2, 141.2, 127.6, 126.6, 125.1, 119.8, 71.5, 66.9, 61.0, 55.7, 47.1, 25.6, 17.9, −5.2, −5.4. HRMS-ESI+ (*m*/*z*): $[M + H]^+$ calculated for $C_{25}H_{35}O_5N_2Si$, 471.2310; found, 471.2309.

(2*R*,3*R*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-4-amino-3-((*tert*-butyldimethylsilyl)oxy)-4-oxobutanoic Acid (ent-5). **28** (786 mg, 1.67 mmol, 1 equiv) was dissolved in ACN (23.4 mL) and cooled in an ice−water bath. TEMPO (392 mg, 2.88 mmol, 1.50 equiv) was added to the stirring reaction mixture. $NaClO_2$ (80% w/w; 529 mg, 4.68 mmol, 2.80 equiv) was dissolved in cold phosphate buffer (0.67 N, pH = 7; 15.8 mL) and added dropwise to the stirring reaction mixture. NaOCl (6% bleach; 1.44 mL, 1.17 mmol, 0.70 equiv) was added dropwise over 30 min. Once the addition was complete, the reaction was stirred for 3 h and then quenched with sat. Na_2SO_3 (10 mL) and brought to room temperature. The reaction mixture was acidified with 12 N HCl (pH ca. 2), and the aqueous layer was extracted with CH_2Cl_2 (75 mL) three times. The combined organic layer was dried with $MgSO_4$ and filtered. After concentrating, the residue was subjected to silica gel column chromatography (40% EtOAc/60% hexanes/1% AcOH) allowing for the isolation of **ent-5** (721 mg, 92% yield) as a colorless solid. (635 mg, 92%). NMR data matched those previously reported for its enantiomer.[3] $[\alpha]^{22}_D$ = 16.3° (*c* 0.744, CH_3OH) ^{1}H NMR (300 MHz, CD_3OD): δ 7.62−7.40 (4H, m), 7.24−7.12 (4H, m), 6.73 (1H, d, *J* = 8.7 Hz), 4.61−4.55 (2H, m), 4.23−4.04 (3H, m), 0.81 (9H, s), 0.00 (6H, m). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD): δ 175.9, 172.9, 158.6, 145.3, 142.6, 128.9, 128.3, 126.4, 121.0, 75.4, 68.4, 58.9, 26.4, 19.2, −4.7, −5.0. HRMS-ESI+ (*m*/*z*): $[M + H]^+$ calculated for $C_{25}H_{33}O_6N_2Si$, 485.2102; found, 485.2105.

DOI: 10.1021/acs.joc.9b02491
J. Org. Chem. XXXX, XXX, XXX−XXX

(2*R*,3*S*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-methoxy-4-((4-methoxybenzyl)oxy)butanoate (29). 25A′ (1.70 g, 3.46 mmol, 1.00 equiv) was dissolved in ether (69 mL) at room temperature. Freshly prepared, dry Ag_2O (2.40 g, 10.4 mmol, 3 equiv), followed by MeI (4.31 mL, 69.2 mmol, 20.0 equiv), was added to the flask. The reaction mixture was vortexed briefly until a suspension was formed. The reaction mixture was then brought to reflux and allowed to react for 18 h, with vigorous stirring, under an inert atmosphere. The reaction mixture was cooled to room temperature, filtered, and concentrated. The residue was purified by silica gel column chromatography (20% EtOAc/80% hexanes) allowing for the isolation of **29** (1.54 g, 88% yield) as a colorless, vicious oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (2H, d, J = 7.2 Hz), 7.59 (2H, m), 7.41−7.28 (6H, m), 6.88 (2H, d, J = 8.1 Hz), 5.40 (1H, d, J = 9.6 Hz), 4.53−4.13 (7H, m), 3.76−3.71 (6H, m), 3.55−3.45 (5H, m). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 171.0, 159.0, 155.6, 143.7, 143.5, 141.0, 129.6, 129.1, 127.4, 126.8, 124.9, 124.8, 119.7, 113.5, 77.6, 72.5, 67.3, 66.7, 58.6, 54.9, 52.1, 51.8, 46.8. HRMS-ESI+ (m/z): $[M + H]^+$ calculated for $C_{29}H_{32}O_7N$, 506.2173; found, 506.2172.

Preparation of (2*R*,3*S*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-methoxy-4-((4-methoxybenzyl)oxy)butanoic Acid (30). To a solution of **29** (1.03 g, 2.04 mmol, 1.00 equiv) in degassed ethyl acetate (14.6 mL) was added LiI (1.36g, 10.2 mmol, 5.00 equiv) at room temperature. The reaction vessel was then sealed, brought to 80 °C, and stirred for 18 h. Once the reaction mixture had cooled to room temperature, it was diluted with ethyl acetate (50 mL) and washed with 0.1 N HCl (50 mL), dried over $MgSO_4$, and concentrated. The crude residue was subjected to silica gel column chromatography (40% EtOAc/59% hexanes/1% AcOH) yielding **30** as a colorless oil (800 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.0 (1H, br. s), 7.73 (2H, d, J = 7.5 Hz), 7.58 (2H, m), 7.40−7.22 (6H, m), 6.85 (2H, d, J = 8.4 Hz), 4.53−4.26 (5H, m), 4.21−4.12 (2H, m), 3.78 (3H, s), 3.52−3.38 (5H, m). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 174.5, 159.1, 156.3, 143.9, 143.5, 141.2, 141.1, 129.7, 129.3, 127.6, 127.0, 125.2, 125.1, 119.8, 113.7, 72.6, 67.5, 67.2, 59.0, 55.1, 52.1, 52.1, 46.9. HRMS-ESI+ (m/z): $[M + H]^+$ calculated for $C_{28}H_{30}O_7N$, 492.2017; found, 492.2027.

(2*R*,3*S*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-methoxy-4-((4-methoxybenzyl)oxy)butanoic Acid (31). To a solution of **30** (1.00 g, 2.05 mmol, 1.00 equiv) in CH_2Cl_2 (26 mL) cooled in an ice−water bath were added *tert*-butyl 2,2,2-trichloroacetimidate (1.83 mL, 10.25 mmol, 5.00 equiv) and $BF_3{\cdot}Et_2O$ (29 μL, 0.21 mmol, 0.10 equiv). The resulting suspension was stirred for 1 h at room temperature and then concentrated. The crude residue was dissolved in CH_2Cl_2 (50 mL) and washed with 1 N NaOH (50 mL), H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated. The crude residue was purified by silica gel column chromatography (20% EtOAc/80% hexanes then 40% EtOAc/59% Hexanes/1% AcOH) yielding **31** as a colorless oil (966 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (2H, d, J = 7.5 Hz), 7.57 (2H, d, J = 7.2 Hz), 7.39 (2H, dd, J = 7.2, 7.2 Hz), 7.32−7.28 (2H, m), 6.91 (2H, d, J = 6.9 Hz), 5.19 (1H, d, J = 9.3 Hz), 4.54−4.16 (6H, m), 3.99 (1H, br. s), 3.79 (3H, m), 3.50−3.44 (5H, m), 1.44 (9H, s). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.8, 159.2, 155.8, 143.9, 143.7, 141.2, 141.2, 130.0, 129.4, 127.6, 127.0, 125.1, 125.1, 119.9, 113.7, 82.1, 78.0, 72.7, 67.9, 66.9, 58.9, 55.2, 52.3, 47.1, 27.9. HRMS-ESI+ (m/z): $[M + H]^+$ calculated for $C_{32}H_{38}O_7N$, 548.2643; found, 548.2650.

***tert*-Butyl (2*R*,3*S*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-4-hydroxy-2-methoxybutanoate (32).** **32** was recovered from the silica gel column used to purify **31**. This yielded **32** as a colorless foam (0−24% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (2H, d, J = 7.2 Hz), 7.28, (2H, d, J = 6.9 Hz), 7.28 (2H, t, J = 6.9 Hz), 7.20 (2H, t, J = 7.5 Hz), 5.36 (1H, d, J = 9.0 Hz), 4.31−4.08 (4H, m), 3.92 (1H, m) 3.71−3.53 (2H, m), 3.37 (3H, s), 1.35 (9H, s). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.6, 156.2, 143.7, 143.6, 141.1, 141.1, 127.6, 126.9, 125.0, 119.8, 82.3, 79.1, 67.0, 62.2, 58.7, 54.2, 47.0, 27.8. HRMS-ESI+ (m/z): $[M + H]^+$ calculated for $C_{24}H_{30}NO_6$, 428.2073; found, 428.2080.

(2*R*,3*R*)-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-4-(*tert*-butoxy)-3-methoxy-4-oxobutanoic Acid (ent-6a). **31** (883 mg, 1.61 mmol, 1.00 equiv) was dissolved in freshly prepared 9:1 ACN/H_2O (6.5 mL), and Bobbit's Salt (532 mg, 1.77 mmol, 1.10 equiv) was added to the stirring solution. The reaction mixture was sealed and allowed to stir for 18 h at room temperature. The resulting solution was cooled in an ice−water bath (any recovered **32** was added at this point, and the amount of primary oxidant was scaled accordingly) and diluted with a solution of $NaClO_2$ (80% w/w; 547 mg, 4.84 mmol, 3.00 equiv) in phosphate buffer (0.67 M, pH ca. 7; 10.75 mL), and then the mixture was neutralized with 1 N NaOH. The neutralized mixture was diluted with ACN (9.65 mL) followed by a dropwise addition of NaOCl (6% bleach; 1.40 mL, 1.13 mmol, 0.70 equiv) over 30 min. Once the addition was complete, the reaction proceeded to completion in 4 h at which point it was quenched with saturated aqueous Na_2SO_3. The organic layer was separated, and the aqueous layer was acidified slowly with 12 N HCl (pH ca. 2). The aqueous layer was extracted with CH_2Cl_2 (50 mL) three times, and the combined organic layer was dried with $MgSO_4$. The residue was purified by silica gel column chromatography (40% EtOAc/59% hexanes/1% AcOH), allowing for the isolation of **ent-6a** as a colorless solid (569 mg, 80%). NMR data matched those previously reported for its enantiomer.[3] $[\alpha]^{22}_D$ = 14.3° (c 0.628, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.11 (1H, br. s), 7.73 (2H, d, J = 7.2 Hz), 7.61−7.56 (2H, m), 7.40−7.26 (4H, m), 5.76 (1H, d, J = 10.2 Hz), 4.96 (1H, d, J = 9.9 Hz), 4.35−4.32 (3H, m), 4.20 (1H, dd, J = 7.2 Hz), 3.48 (3H, s), 1.45 (9H, s). ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$): δ174.5, 168.0, 156.4, 143.7, 143.6, 141.2, 127.7, 127.1, 125.2, 125.2, 119.9, 83.2, 79.6, 77.4, 67.6, 59.3, 56.4, 46.9, 27.9. HRMS-ESI+ (m/z): $[M + H]^+$ calculated for $C_{24}H_{28}O_7N$, 442.1860; found, 442.1852.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b02491.

NMR spectra for all Fmoc-protected amino alcohols; chiral HPLC chromatograms for all chiral Fmoc-protected amino alcohols (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: s5taylor@uwaterloo.ca.

ORCID

Scott D. Taylor: 0000-0001-5449-5940

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant to S.D.T. (RGPIN-2017-04233). R.M. thanks NSERC for a postgraduate scholarship.

■ REFERENCES

(1) For a review of the SAAH reaction, see: Bodkin, J. A.; McLeod, M. D. The Sharpless asymmetric aminohydroxylation. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2733−2746.

(2) Reddy, K. L.; Dress, K. R.; Sharpless, K. B. N-Chloro-N-Sodio-2-Trimethylsilyl Ethyl Carbamate: A New Nitrogen Source for the Catalytic Asymmetric Aminohydroxylation. *Tetrahedron Lett.* **1998**, *39*, 3667−3670.

(3) Harris, L.; Mee, S. P. H.; Furneaux, R. H.; Gainsford, G. J.; Luxenburger, A. Alkyl 4-Chlorobenzoyloxycarbamates as Highly Effective Nitrogen Source Reagents for the Base-Free, Intermolecular Aminohydroxylation Reaction. *J. Org. Chem.* **2011**, *76*, 358−372.

DOI: 10.1021/acs.joc.9b02491
J. Org. Chem. XXXX, XXX, XXX−XXX

(4) (a) Moreira, R.; Taylor, S. D. Asymmetric Synthesis of Fmoc-Protected β-Hydroxy and β-Methoxy Amino Acids via a Sharpless Aminohydroxylation Reaction Using FmocNHCl. *Org. Lett.* **2018**, *20*, 7717−7720. (b) Kralt, B.; Moreira, R.; Palmer, M.; Taylor, S. D. Total Synthesis of A5145 Factor D. *J. Org. Chem.* **2019**, *84*, 12021−12030.
(5) Li, G.; Chang, H.; Sharpless, K. B. Catalytic Asymmetric Aminohydroxylation (AA) of Olefins. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−453.
(6) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. Ligand-Accelerated Catalysis. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.
(7) Angelaud, R.; Babot, O.; Charvat, T.; Landais, Y. Desymmetrization of Cyclohexadienylsilanes. Regio-, Diastereo-, and Enantioselective Access to Sugar Mimics. *J. Org. Chem.* **1999**, *64*, 9613−9624.
(8) (a) Donohoe, T. J.; Johnson, P. D.; Keenan, M. The Regioselective Aminohydroxylation of Allylic Carbamates. *Chem. Commun.* **2001**, 2078−2079. (b) Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. The Tethered Aminohydroxylation (TA) of Cyclic Allylic Carbamates. *J. Am. Chem. Soc.* **2002**, *124*, 12934−12935.
(9) Demko, Z. P.; Bartsch, M.; Sharpless, K. B. Primary Amides. A General Nitrogen Source for Catalytic Asymmetric Aminohydroxylation of Olefins. *Org. Lett.* **2000**, *2*, 2221−2223.
(10) Raatz, D.; Innertsberger, C.; Reiser, O. Asymmetric Aminohydroxylation of Heteroaromatic Acrylates. *Synlett* **1999**, *1999* (12), 1907−1910.
(11) Griffith, W. P.; McManus, N. T.; Skapski, A. C.; White, A. D. Partial Coordination in an Adduct of an Osmium Imido Complex: X-ray Molecular Structure of $[OsO_3(NOctt)]_2{\cdot}N_2C_6H_{12}$. *Inorg. Chim. Acta* **1985**, *105*, L11.
(12) Nesterenko, V.; Byers, J. T.; Hergenrother, P. J. The Use of PH to Influence Regio- and Chemoselectivity in the Asymmetric Aminohydroxylation of Styrenes. *Org. Lett.* **2003**, *5* (3), 281−284.
(13) The reaction reported by Harris was much faster, being completed in about 4 h. See ref 2.
(14) Reddy, K. L.; Sharpless, K. B. From Styrenes to Enantiopure α-Arylglycines in Two Steps. *J. Am. Chem. Soc.* **1998**, *120*, 1207−1217.
(15) O'Brien, P.; Osborne, S. A.; Parker, D. D. Asymmetric Aminohydroxylation of Substituted Styrenes: Applications in the Synthesis of Enantiomerically Enriched Arylglycinols and a Diamine. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2519−2526.
(16) Li, G.; Angert, H.; Sharpless, K. B. *N*-Halocarbarnate Salts Lead to More Efficient Catalytic Asymmetric Aminohydroxylation. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813.
(17) Harris used less catalyst (4 mol %) and ligand (5 mol %) than used in this report. See ref 2.
(18) Boger, D. L.; Lee, R. J.; Bounaud, P. Y.; Meier, P. Asymmetric Synthesis of Orthogonally Protected L-*threo*-β-Hydroxyasparagine. *J. Org. Chem.* **2000**, *65*, 6770−6772.
(19) Jiang, W.; Wanner, J.; Lee, R. J.; Bounaud, P.-Y.; Boger, D. L. Total Synthesis of the Ramoplanin A2 and Ramoplanose Aglycone. *J. Am. Chem. Soc.* **2003**, *125*, 1877.
(20) Han, H.; Cho, C.-W.; Janda, K. D. A Substrate-Based Methodology That Allows the Regioselective Control of the Catalytic Aminohydroxylation Reaction. *Chem. - Eur. J.* **1999**, *5*, 1565−1569.
(21) Shuter, E. C.; Duong, H.; Hutton, C. A.; McLeod, M. D. The Enantioselective Synthesis of APTO and AETD: Polyhydroxylated β-amino acid Constituents of the Microsclerodermin Cyclic Peptides. *Org. Biomol. Chem.* **2007**, *5*, 3183−3189.
(22) Bodkin, J. A.; Bacskay, G. B.; McLeod, M. D. The Sharpless Asymmetric Aminohydroxylation Reaction: Optimising Ligand/Substrate Control of Regioselectivity for the Synthesis of 3- and 4-Aminosugars. *Org. Biomol. Chem.* **2008**, *6*, 2544−2553.
(23) **24** was prepared following the procedure outlined by Ito et al. replacing BnOH with PMBOH. Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. Biogenetically Inspired Approach to the Strychnos Alkaloids. Concise Syntheses of (±)-Akuammicine and (±)-Strychnine. *J. Am. Chem. Soc.* **2001**, *123*, 8003−8010.
(24) Duttagupta, I.; Bhadra, J.; Das, S. K.; Sinha, S. Proteolytic stability of cyclic α-hydrazino acid containing peptides: a qualitative study. *Tetrahedron Lett.* **2016**, *57*, 3858−3861.
(25) Wang, W.; McMurray, J. S. A Selective Method for the Preparation of Primary Amides: Synthesis of Fmoc-L-4-Carboxamidophenylalanine and other Compounds. *Tetrahedron Lett.* **1999**, *40*, 2501−2504.
(26) Tanemura, K.; Suzuki, S. T.; Horaguchi, T. Deprotection of Silyl Ethers using 2,3-Dichloro-5,6-dicyano-p-benzoquinone. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2997−2998.
(27) Okano, K.; Okuyama, K. I.; Fukuyama, T.; Tokuyama, H. Mild Debenzylation of Aryl Benzyl Ether with BCl_3 in the Presence of Pentamethylbenzene as a Non-Lewis-Basic Cation Scavenge. *Synlett* **2008**, *2008* (13), 1977−1980.
(28) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. A Mild and Selective Method for the Hydrolysis of Esters with Trimethyltin Hydroxide. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378−1382.
(29) Di Gioia, M. L.; Gioia, D.; Leggio, A.; Le Pera, L.; Liguori, A.; Perri, F.; Siciliano, C. Alternative and Chemoselective Deprotection of the α-Amino and Carboxy Functions of *N*-Fmoc-Amino Acid and *N*-Fmoc-Dipeptide Methyl Esters by Modulation of the Molar Ratio in the $AlCl_3$/N,N-Dimethylaniline Reagent System. *Eur. J. Org. Chem.* **2004**, *2004*, 4437−4441.
(30) Fisher, J. W.; Trinkle, K. L. Iodide Dealkylation of Benzyl, PMB, PNB, and t-Butyl *N*-acyl Amino Acid Esters via Lithium Ion Coordination. *Tetrahedron Lett.* **1994**, *35*, 2505−2508.
(31) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. High-field FT NMR Application of Mosher's Method. The Absolute Configurations of Marine Terpenoids. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.
(32) Kuroda, Y.; Harada, S.; Oonishi, A.; Kiyama, H.; Yamaoka, Y.; Yamada, K. I.; Takasu, K. Use of a Catalytic Chiral Leaving Group for Asymmetric Substitutions at Sp3-Hybridized Carbon Atoms: Kinetic Resolution of β-Amino Alcohols by p-Methoxybenzylation. *Angew. Chem., Int. Ed.* **2016**, *55* (42), 13137−13141.
(33) **22** was prepared following the procedure outlined by Zaimoku et al. utilizing Boc-indole-3-carbaldehyde. Zaimoku, H.; Taniguchi, T.; Ishibashi, H. Synthesis of the Core of Actinophyllic Acid Using a Transannular Acyl Radical Cyclization. *Org. Lett.* **2012**, *14*, 1656−1658.
(34) In all cases, we found that the combined yield of **31** and **32** exceeded 85%.

DOI: 10.1021/acs.joc.9b02491
J. Org. Chem. XXXX, XXX, XXX−XXX