ChemInform Abstract: Alkyl 4-Chlorobenzoyloxycarbamates as Highly Effective Nitrogen Source Reagents for the Base-Free, Intermolecular Aminohydroxylation Reaction.

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Alkyl 4-Chlorobenzoyloxycarbamates as Highly Effective Nitrogen Source Reagents for the Base-Free, Intermolecular Aminohydroxylation Reaction

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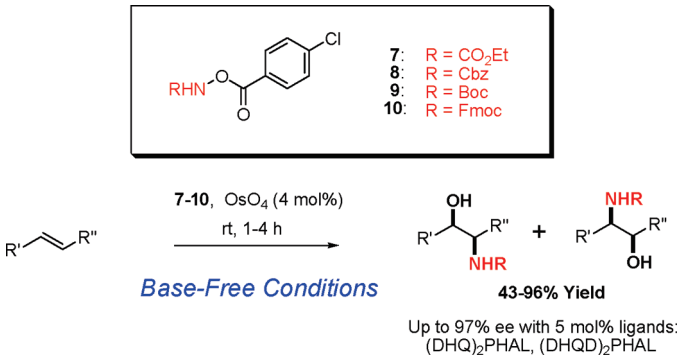

Ethyl- (**7**), benzyl- (**8**), *tert*-butyl- (**9**), and fluorenylmethyl-4-chlorobenzoyloxycarbamates (**10**) have been prepared as storable and easy-to-prepare nitrogen sources for use in the intermolecular Sharpless aminohydroxylation reaction and its asymmetric variant. These reagents were found to be effective under *base-free* reaction conditions. The scope and limitations of these methods have been explored using a variety of alkenes, among which, *trans*-cinnamates, in particular, proved to be good substrates.

1. Introduction

The catalytic Sharpless aminohydroxylation and asymmetric aminohydroxylation (AA) are effective, one-step procedures for preparing pharmacologically important[1] vicinal amino alcohols by treating alkenes with salts of *N*-halosulfonamides,[2,3] -amides,[4] and -carbamates[5] in the presence of an osmium catalyst. Since publication of a comprehensive study on the AA method by Sharpless and co-workers in 1996,[2−5] it has been used in countless syntheses, and there have been numerous reports of improvements to the procedure.[6] In particular, carbamates as nitrogen sources have found a wide range of applications because of their potential use as orthogonal protecting groups and relative ease of deprotection under acidic (Boc), nucleophilic (Teoc), and reductive (Cbz) conditions.[7] The typical procedure developed by Sharpless et al. uses *tert*-butyl hypochlorite in the presence of sodium hydroxide to generate the *N*-halocarbamate reoxidant in situ, but this method is not without drawbacks. Donohoe et al. reported that the use of *tert*-butyl hypochlorite led in some cases to chlorination of the alkene moiety in the tethered aminohydroxylation (TA) reaction and that this problem was even more pronounced with homoallylic carbamates.[8] Furthermore, the general instabilities of *N*-halocarbamate reagents[8]

(1) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561–2576.
(2) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 451–453.
(3) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2810–2812.
(4) Brunko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1997**, *36*, 1483–1486.
(5) (a) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2813–2817. (b) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207–1217. (c) O'Brien, P. O.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2519–2526. (d) Reddy, K. L.; Dress, K. R.; Sharpless, K. B. *Terahedron Lett.* **1998**, *39*, 3667–3670.
(6) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733–2746.
(7) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons Inc.: New York, 1991.
(8) Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514–2515.

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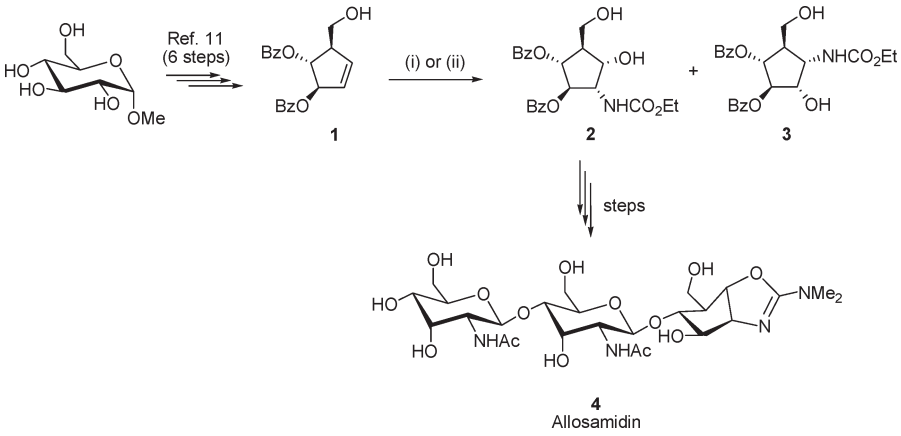
SCHEME 1. Aminohydroxylation Reaction in the Synthesis of Allosamidin[a]



[a]Reagents and conditions: (i) EtO_2CNH_2, OsO_4, DABCO, *i*-PrOH, H_2O, *t*-BuOCl, NaOH, **2**: 0−40%, **3**: 0−40% (ii) ethyl 4-chlorobenzoyloxycarbamate (**7**), OsO_4, *t*-BuOH, water, **2**: 40%, **3**: 44%.

and of *tert*-butyl hypochlorite contribute to these shortcomings, thereby limiting the general applicability of the methodology.

Commercially available *N*-bromoacetamides and a range of other *N*-bromocarboxamides, readily prepared by treating carboxamides with dibromoisocyanuric acid, have been used by Sharpless et al.[9] to generate in situ the corresponding *N*-bromo, *N*-lithio salts which are effective reagents for the AA. However, certain *N*-bromocarboxamides need to be stored under vacuum, and critical control of the temperature and concentration of the reaction mixture, as well as the amount of base used, is needed. Lower temperatures were also required to avoid decomposition, and excess base was shown to shut down the catalytic cycle completely.[9,10] In addition, base-sensitive substrates may be incompatible under such basic conditions.

During resynthesis of the natural product allosamidin (**4**),[11] the Sharpless aminohydroxylation reaction was employed in the preparation of intermediate **2** with varying degrees of success (Scheme 1, i). The reaction proved to be capricious, frequently failing to proceed to completion on scales larger than 2 g or sometimes no desired products were formed at all.

As the total synthesis of allosamidin (**4**) comprises more than 30 synthetic steps and the crucial aminohydroxylation reaction is required at a very early stage in the synthesis, we were highly motivated to improve this transformation. We reasoned that the presence of base-sensitive benzoate protecting groups in olefin **1** might be the cause for the apparent unreliability using the standard Sharpless conditions. In search of new methodology, we were inspired by certain features of Donohoe et al.'s recent modifications to the tethered aminohydroxylation reaction[12] which use *N*-sulfonyloxy carbamates[13] or *O*-derivatized hydroxycarbamates[14] as the nitrogen source under base-free conditions. Although the base-free conditions were desirable for our purpose, the TA method would give the undesired regio- and stereoisomer of product derived from olefin **1**. Furthermore, the TA reaction introduces the nitrogen source as a cyclized carbamate and not a protected carbamate with a relatively easy deprotection protocol.

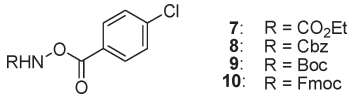


FIGURE 1. Alkyl 4-chlorobenzoyloxycarbamate reagents.

We sought to implement some of the beneficial features found in the TA reaction to the *base-free intermolecular* aminohydroxylation reaction. We report herein our efforts to exemplify the great potential of a class of alkyl 4-chlorobenzoyloxycarbamate reagents (**7**−**10**)[15] (Figure 1) for the aminohydroxylation reaction and its asymmetric variant and further expand the capabilities of these widely used reactions.

2. Results and Discussion

At the outset, we elected to start with the synthesis of ethyl 4-chlorobenzoyloxycarbamate (**7**) as the nitrogen source reagent of choice (Scheme 2) for the intermolecular aminohydroxylation reaction. This was prepared by treating ethyl chloroformate (**5**) with hydroxylamine to give the known *N*-hydroxycarbamate **6**,[16] which was subsequently reacted

(9) Demko, Z. P.; Bartsch, M.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 2221–2223.

(10) Goossen, L. J.; Liu, H.; Dress, K. R.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1080–1083.

(11) Blattner, R.; Furneaux, R. H.; Kemmitt, T.; Tyler, P. C.; Ferrier, R. J.; Tiden, A.-K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3411–3421.

(12) Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934–12935.

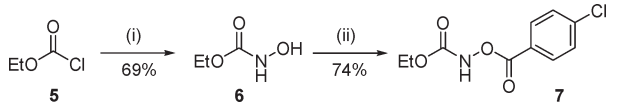
(13) See ref 8.

(14) (a) Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett.* **2007**, *9*, 1725–1728. (b) Oesper, R. E.; Cook, W. A. *J. Am. Chem. Soc.* **1925**, *47*, 422–428.

(15) During the course of this work, a poster by Klauber et al. described the reaction of 2-vinylnaphthalene with *tert*-butyl and 2-(trimethyl)silylethyl 2,4,6-trichlorobenzoyloxycarbamate in the presence of 4 mol % of potassium osmate and 1.3 equiv of lithium hydroxide. To the best of our knowledge, this is the only example cited in the literature in which *N*-aroyloxycarbamates have been used in an intermolecular aminohydroxylation reaction, but it takes place under basic conditions: Klauber, D. J.; Donohoe, T. J.; Chughtai, M. J.; Griffin, D.; Campbell, A. D. *N*-Sulfonyloxy carbamates as reoxidants for aminohydroxylation reactions. Presented at the 232nd ACS National Meeting, San Fransisco, CA, Sep 10−14, 2006; University of Oxford, http://donohoe.chem.ox.ac.uk/News/Images/DaveACS.pdf.

(16) (a) Fuller, A. T.; King, H. *J. Chem. Soc.* **1947**, 963–969. (b) Bhat, J. I.; Clegg, W.; Maskill, H.; Elsegood, M. R. J.; Menneer, I, D.; Miatt, P. C. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1435–1446. (c) Major, R. T.; Dürsch, F.; Hess, H.-J. *J. Org. Chem.* **1959**, *24*, 431–433.

SCHEME 2.[a] **Synthesis of Ethyl 4-Chlorobenzoyloxycarbamate (7)**



[a]Reagents and conditions: (i) $NH_2OH \cdot HCl$, Na_2CO_3, H_2O; (ii) 4-chlorobenzoyl chloride, Et_3N, Et_2O.[14,16]

with 4-chlorobenzoyl chloride to furnish the stable and crystalline ethyl 4-chlorobenzoyloxycarbamate (**7**) in an overall yield of 51% (Scheme 2).

When alkene **1**, the allosamidin precursor, was treated with **7** in the presence of 4 mol % of osmium tetraoxide in the absence of base, we were greatly encouraged to recover the two possible regioisomeric products **2** and **3** (Scheme 1, ii) in an almost 1:1 ratio and a total yield of 84%. The reaction proved to be reliable and reproducible on scales up to 20 g.

We then explored the possibility of extending the methodology to other alkyl 4-chlorobenzoyloxycarbamates which would allow subsequent deprotection of the newly established carbamate to take place under a variety of different reaction conditions. Due to the *base-free* nature of our intermolecular aminohydroxylation method, base-sensitive substituents should be tolerated as well. Therefore, the benzyl (**8**), *tert*-butyl (**9**), and fluorenylmethyl (**10**) carbamate analogues of **7** (Figure 1) were prepared in a fashion analogous to that which furnished **7**.

Cinnamates have been commonly used in aminohydroxylation studies[4] and upon treatment of *trans*-isopropyl cinnamate with reagents **7**−**10** in the presence of osmium tetraoxide racemic products were isolated in excellent yield with low catalyst loading (4 mol%) and relatively short reaction times (3−4 h) at room temperature (Table 1). Varying the solvent had an apparent effect on the regioselectivity but it was found to be beneficial to use an 8:1 mixture of acetonitrile and water to ensure the reaction remained homogeneous. As a result of this observation, we selected acetonitrile as the standard cosolvent for all further reactions. Furthermore, when comparing the observed product ratios shown in entries 3−5 (Table 1) it became obvious that the different protecting groups of the reagents **8**−**10** had a certain influence on the regioselectivity of the reaction. The Fmoc derivative **10** favored the formation of the isomer **14b** over **14a** in a ratio of almost 2:1, while no such preference was observed when using the Boc reagent **9**.

Compounds **11a** and **12a** were distinguished from their respective regioisomers **11b** and **12b** by HMBC NMR experiments. For **11a** and **12a** a strong $^3J_{CH}$ coupling was observed between the *o*-PhC*H* and the carbon atom, *C*(3) adjacent to the phenyl ring, at ca. 56.3 and 56.4 ppm, respectively, while the *o*-PhC*H* in **11b** and **12b** coupled to *C*(3) ca. 74.1 and 73.8 ppm. On this basis, the range of ^{1}H and ^{13}C chemical shifts for all products **11**−**14a** and **11**−**14b** are shown in Figure 2. Confirmation of the assignment of regiochemistry of **12a** was provided by X-ray crystallographic analysis of subsequent reaction products (vide infra).

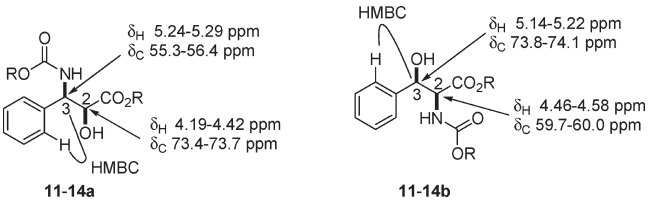


FIGURE 2. Assignment of regiochemistry by ^{1}H and ^{13}C NMR relationships.

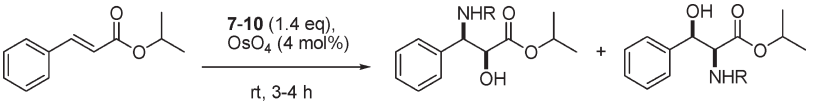
As further evidence of the effectiveness of these reagents, we found that the benzyl carbamate **8** also reacted under the same oxyamination conditions with a range of other alkenes to afford racemic products in excellent yield (Table 2).

Reactions involving the simple unsymmetrical alkenes (entries 1 and 2, Table 2) were regioselective with product ratios (a:b) of 9.5:1 and 5.5:1, respectively, as determined by HPLC analysis. In both cases, the carbamate moiety was established preferentially at the least sterically hindered end of the alkene.

Next, we studied the impact of the addition of chiral phthalazine (PHAL) ligands,[17] $(DHQ)_2$PHAL and $(DHQD)_2$PHAL, as well as the chiral anthraquinone (AQN) ligand,[17] $(DHQ)_2$AQN, on the product distribution in the asymmetric version of the aminohydroxylation of *trans*-isopropyl cinnamate with benzyl reagent **8** (Table 3).

While ligand $(DHQ)_2$AQN (entry 3, Table 3), had little effect on the regioselectivity (1:1.6) and gave only a moderate enantiomeric excess of 71%, addition of catalytic $(DHQ)_2$PHAL or $(DHQD)_2$PHAL, as expected,[4,5,18] dramatically

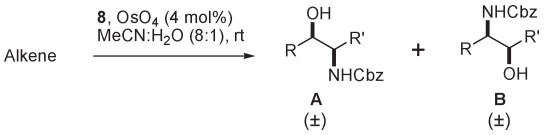
TABLE 1. Results of Aminohydroxylation of *trans*-Isopropyl Cinnamate with Reagents 7−9

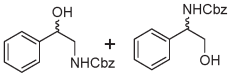
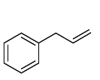
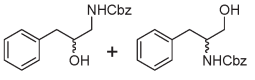
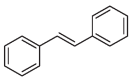
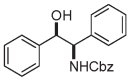
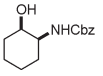
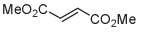
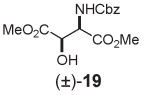
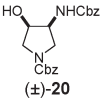


entry	reagent (R =)	solvent	yield[a] (%)	regioisomeric ratio[b] (**a**:**b**)
1	**7** (EtO_2C)	*t*-BuOH/water 3:1	96	1:1.4
2	**8** (Cbz)	*t*-BuOH/water 6:1	95	1:1
3	**8** (Cbz)	MeCN/water 8:1	96	1:1.3
4	**9** (Boc)	MeCN/water 8:1	93	1:1
5	**10** (Fmoc)	MeCN/water 8:1	96	1:1.9

[a]Yield of both regioisomers after chromatography. [b]Measured by HPLC.

TABLE 2. Reaction of Benzyl Carbamate 8 with Various Alkenes



Entry	Alkene	Products	Time [h]	Total yield [%][a]	Regioisomeric ratio[b] (a:b)
1		 (±)-**15a** (±)-**15b**	3	96	9.5:1
2		 (±)-**16a** (±)-**16b**	15	91	5.5:1
3		 (±)-**17**	3	96	-
4		 (±)-**18**	3	96	-
5		 (±)-**19**	15	93	-
6		 (±)-**20**	3	96	-

[a]Yield after chromatography. [b]Determined by HPLC.

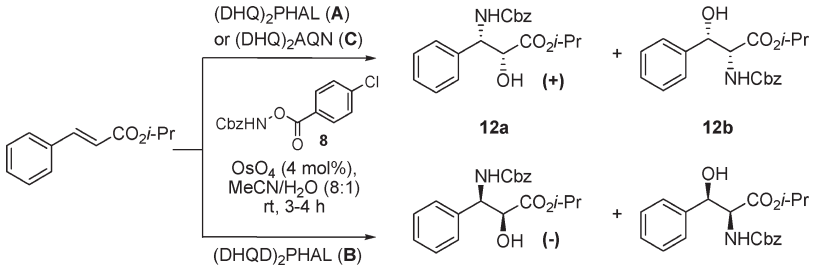
reversed the regioselectivity from 1:1.4 (entry 3, Table 1) to 12.7:1 and 13.4:1, respectively (entries 1 and 2, Table 3), with excellent overall yields (84−96%) and enantiomeric excesses of 97% for the major products. Nesterenko et al. have demonstrated that the pH can have an influence on the regioselectivity of the AA;[19] however, the choice of ligand/substrate combination appears to be of great importance here.

To further exemplify the general applicability of our methodology and for comparison purposes with data already published,[5a] we also sought to deploy *trans*-methyl cinnamate as a substrate in the *base-free* intermolecular asymmetric aminohydroxylation reaction (Table 4). Ligands $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ provided the major products in acceptable yields with enantiomeric excesses of 94−97%. The moderate yields obtained for products (+)-**23a** and (−)-**23a** from the reactions with the Boc reagent **9** were balanced with a notable increase in the formation of the corresponding diol byproduct (25%), a side reaction noted previously by others.[5b] The presence of larger groups on the carbamate or sulfamate nitrogen atoms of reagents used in the AA reactions have been correlated with greater levels of diol formation.[2−6] Furthermore, it has been suggested that Os(VI) should be used to minimize diol byproduct, but where the use of Os(VIII) is advantageous,[18] catalyst loading should be kept low. It can be speculated that, when osmium is coordinated to cinchona ligands, the size of the nitrogen protecting group influences the rate of initial addition to the corresponding alkene to the point that when it becomes slow enough, the asymmetric dihydroxylation is faster. In contrast to this, we observed only negligible amounts of diol byproduct, in the achiral reactions (Table 2). In light of this mechanistic consideration, one might expect a larger nitrogen protecting group to retard the rate of initial addition of the active osmium species to alkene in the catalytic cycle. The trend of decreasing yields of major products, that we observed during our experiments, where the *N*-carbamate = CO_2Et; (+) 81% and (−) 68% > Cbz; (+) 59% and (−) 61% > Boc; (+) 46% and (−) 43%, supports this argument. In the case of the Fmoc reagent **10**, however, the yields of reaction product **24a** turned out to be higher than with Cbz reagent **8** at 75% and 80%.

(17) $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether, $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether, $(DHQ)_2AQN$ = hydroquinine anthraquinone-1,4-diyl diether.

(18) Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949–1952.
(19) Nesterenko, V.; Byers, J. T.; Hergenrother, P. J. *Org. Lett.* **2003**, *5*, 281–284.

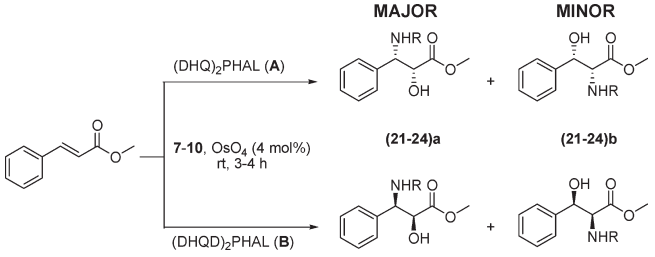
TABLE 3. Reaction of Benzyl Carbamate 8 with *trans*-Isopropyl Cinnamate in the Presence of Chiral Ligands



entry	major product	ligand	yield[a] (%)	optical purity (% ee)[b]	$[\alpha]_D$[c]	regioisomeric ratio (**a**:**b**)
1	(+)-**12a**	A	84−96	97	+15.1	12.7:1[d]
2	(−)-**12a**	B	96	97	−14.7	13.4:1[d]
3	(+)-**12b**	C	90	71		1:1.6

[a]Combined yield. [b]Determined by chiral-phase HPLC. [c]Major product at quoted ee. [d]Determined by achiral phase HPLC.

TABLE 4. Chiral Reaction of *trans*-Methyl Cinnamate and Reagents 7−10



major product	reagent (R =)	ligand	yield[a] (%)	optical purity (% ee)[b]	$[\alpha]_D$	regioisomeric ratio (**a**:**b**)[b]
21a	**7** (CO_2Et)	A	81	97	+4.3	13:1
		B	68	96	−4.9	15:1
22a	**8** (Cbz)	A	61	95	−1.3	5.9:1
		B	59	95	+1.1	6.8:1
23a	**9** (Boc)	A	43[c,d]	95	−6.7	6.1:1
		B	46[c,d]	96	+6.6	4.9:1
24a	**10** (Fmoc)	A	75	94	+8.0	6.6:1
		B	80	96	−8.3	5.6:1

[a]Yield of major product. [b]Determined by chiral-phase HPLC. [c]Lower yield due to enhanced yield of diol. [d]Although Boc reagent **9** produced the lowest yields in Table 4, remarkably the ee's of 95% and 96% are far superior to the reported value of 78% in a footnote by Sharpless[5a] when *tert*-BuOCONClNa was used as the oxidant in the analogous reaction with methyl *trans*-cinnamate. It is also noteworthy that the diol byproduct isolated from these reactions had ee's of greater than 95%.

The absolute configurations of the two major reaction products (+)-**12a** and (−)-**12a** (Table 3) were established by converting them into the corresponding oxazolidinone methyl ester derivatives (−)-**25** and (+)-**25**, respectively (Scheme 3). X-ray crystallographic analysis of oxazolidinone (−)-**25** using copper K-α X-radiation determined it to have the (2*R*,3*S*)-configuration with a degree of uncertainty of less than 0.4%. Oxazolidinone (+)-**25** derived by subjecting (+)-**22a** to the same reaction conditions was found, by coelution experiments in chiral phase HPLC analysis, to have an identical retention time to that derived from (−)-**12a**.

In a parallel approach, amino alcohol (+)-**26** and its Boc-protected analogue (+)-**23a** were prepared as shown in Scheme 3. In both cases, the analytical data were congruent with those reported in the literature, and the specific rotation of $[\alpha]^{22}_D$ +6.5 (*c* 0.9, $CHCl_3$) for Boc derivative (+)-**23a** was also in good agreement with the value obtained in Table 4 supporting our structural assignments.[20]

We observed a discrepancy between our specific rotation value of −1.3 (*c* 0.85, EtOH) [and −2.7 (*c* 1.15, $CHCl_3$)] for (−)-**22a** (Table 4) and that of +4.4 (*c* 0.32, EtOH) reported by Sharpless et al.[5a] On the other hand, our result was in closer agreement with the value of −3.79 (*c* 1.0, $CHCl_3$) obtained by Barycki et al.[21] To corroborate our assignments, we obtained crystal structures of (−)-**22a** and (−)-**23a** using copper K-α X-radiation. The expected absolute configurations are apparent with probabilities of incorrect assignment of less than 0.4% and 0.01%, respectively. Extensive chiral-phase HPLC analysis (Supporting Information) of these compounds also supports the assignments.

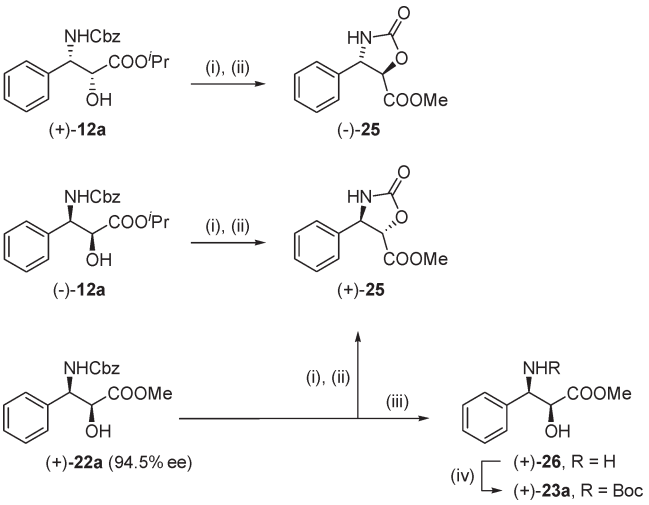
From these results, it is anticipated that the ethoxycarbonyl and Fmoc derivatives **21a** and **24a**, respectively, have been formed with the same facial selectivity by using the same chiral ligand.

Next, the AA reaction was explored using cyclohexene and benzyl 2,5-dihydro-1*H*-pyrrolo-1-carboxylate[22] as substrates and $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$, respectively, as the

(20) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron* **1998**, *54*, 12301–12322.

(21) Barycki, R.; Gumulka, M.; Masnyk, M.; Daniewski, W. M.; Kobus, M.; Luczak, M. *Collect. Czech. Chem. Commun.* **2002**, *67*, 75–82.

SCHEME 3. Determination of Absolute Configuration of Oxazolidinones (−)-25 and (+)-25[a]

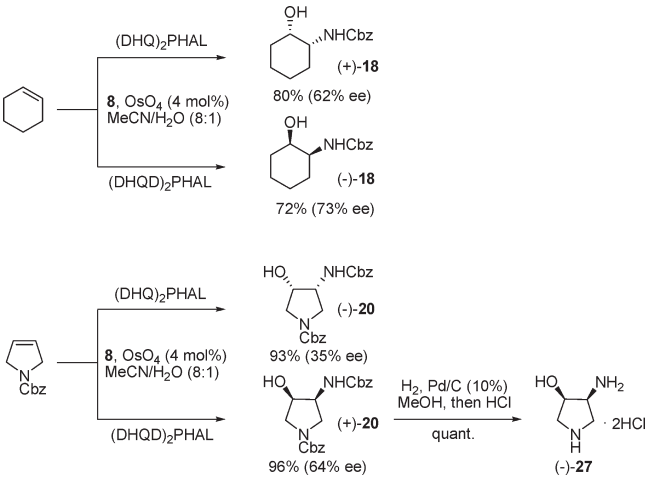


[a]Reagents and conditions: (i) LiOH, MeOH, H_2O, rt, 4 h, (ii) CH_2N_2, THF, (−)-**25**: 50%, (+)-**25**: 55% [from (−)-**12a**], (+)-**25**: 19% [from (+)-**22a**], (iii) H_2, Pd/C, MeOH, (iv) Boc_2O, MeOH, (+)-**23a**: 70% (over two steps).

chiral ligands (Scheme 4). In all events, the aminohydroxylation products were isolated in good yields but with reduced enantiomeric purities. While the reactions carried out in the presence of $(DHQD)_2PHAL$ gave the best results with ee's of 73 and 64% for products (−)-**18** and (+)-**20**, respectively, the reactions conducted in the presence of $(DHQ)_2PHAL$ gave rise to 62% ee for (+)-**18** but only 35% ee in the case of (−)-**20**. Since the asymmetric aminohydroxylation of *Z*-alkenes has already been reported to be less effective,[5,6] the lower enantiomeric excesses obtained in our experiments are in agreement with this observation.[5,6] The absolute configurations of (+) and (-)-**18** were assigned by matching optical rotations with previously published data,[5a] and that of (+)-**20** was achieved by comparison of the analytical data of its hydrogenolysis product (−)-**27** with literature data.[23]

Previously, the AA reaction was successfully applied (with chloramine-T hydrate as a nitrogen source) to an unsubstituted vinyl phosphonate ester by Cravotto et al. but the enantiomeric purity achieved with chiral ligands was found to be as low as 15%.[24] On the other hand, Thomas et al. reported the failure of allylic phosphonate esters to undergo reaction by using various *N*-chloro-*N*-sodioamides in the AA reaction, even upon prolonged heating.[25] Here, we report the reaction of Cbz and Fmoc reagents **8** and **10**, with diethyl allyl phosphonate[26] to give products in good yields (Table 5). Once again the regioselectivity favors addition of the amino functionality at the terminus of the alkene. In line with the findings of Cravotto et al.[24] (for the vinylic

SCHEME 4. Chiral Reactions of Symmetric *Z*-Alkenes



unsaturated phosphonate ester), we also found the enantiomeric excesses of regioisomer **28a** to be very low at 15% and 23% with Cbz reagent **8** and $(DHQ)_2PHAL$ or $(DHQD)_2$-PHAL ligands, respectively. However, in the achiral version, the Fmoc derivatives were isolated in a very good combined yield of 80%. Both of the major products **28a** and **29a** could be deprotected to the common primary amine product by hydrogenation and base-mediated removal of Fmoc (20% piperidine in DMF), respectively, in excellent yields.

3. Conclusion

In summary, we have described a *base-free* intermolecular aminohydroxylation procedure employing a range of alkyl 4-chlorobenzoyloxycarbamates (**7**-**10**) as highly effective nitrogen source reagents. The method is robust, high yielding and compatible with base-sensitive protecting groups such as *N*-Fmoc, thereby providing greater flexibility in the choice of protecting group used. These stable reagents are easy to prepare in two steps from commercially available starting materials and are crystalline with no special storage requirements. The method further allowed us to significantly improve a capricious, low-yielding key step in the synthesis of allosamidin. We are continuing to investigate the scope and utility of these reagents and will report our results in due course.

4. Experimental Section

General Experimental Procedures. Melting points were determined either on a standard melting point apparatus and are uncorrected, or by differential scanning calorimetry (DSC) with a heating rate of 10 $K \cdot min^{-1}$. Infrared spectra were recorded on FTIR (ATR) spectrometer. Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on 500 or 300 MHz spectrometers. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a QTOF Premier mass spectrometer under normal conditions. Sodium formate solution was used as calibrant for HRMS measurements.

All reactions were monitored by thin-layer chromatography (TLC) using 0.2 μm silica gel (60 F_{254}) precoated plates,

(22) Benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate was prepared following the literature procedure: Kamal, A.; Shaik, A. A.; Sandbhor, M.; Malik, M. S.; Azeeza, S. *Tetrahedron: Asymmetry* **2006**, *17*, 2876–2883.

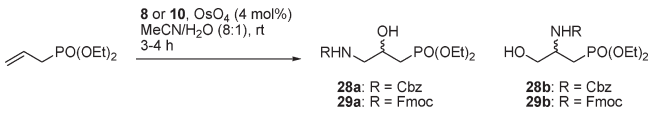
(23) Limberg, G.; Lundt, I.; Zavilla, J. *Synthesis* **1999**, *1*, 178–183.

(24) Cravotto, G.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron: Asymmetry* **1998**, *9*, 745–748.

(25) Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379–8385.

(26) Diethyl allylphosphonate was prepared following the literature procedure: Dappen, M. S.; Pelliciari, R.; Natalini, B.; Monahan, J. B.; Chiorri, C.; Cordi, A. A. *J. Med. Chem.* **1991**, *34*, 161–168.

TABLE 5. Reactions of Diethyl Allylphosphonate



entry	major product	reagent (R =)	ligand[a]	yield[b] (%)	optical purity (% ee)[c]	regioisomeric ratio (**a**:**b**)[d]
1	**28a**	**8** (Cbz)	A	55	15	6.1:1
2	**28a**	**8** (Cbz)	B	59	23	8.9:1
3	**29a**	**10** (Fmoc)		80		10.1:1

[a]Ligand A = $(DHQ)_2PHAL$, ligand B = $(DHQD)_2PHAL$. [b]Combined yield of both regioisomers. [c]Determined by chiral-phase HPLC. [d]Calculated from the corresponding ^1H NMR spectra.

using UV light, ammonium molybdate or potassium permanganate to visualize. Flash column chromatography was performed on silica gel 60 with a particle size of 0.040−0.063 mm, or using an automated flash system. Solvents for reactions and chromatography were analytical grade and were used as supplied unless otherwise stated. Benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate and diethyl allylphosphonate were prepared following literature procedures.[22,26]

Product ratios and enantiomeric excesses (ee) were determined, if not otherwise indicated, by HPLC analysis employing columns as indicated in the Supporting Information using an quaternary pump HPLC system with a diode array detector (200−400 nm). Injection volumes were typically 10 μL (1−2 mg·mL^{-1}) and data was processed with the supplied software.

General Procedure for Asymmetric Aminohydroxylation (AA) Reactions. Osmium tetraoxide (8 mg, 32 μmol) was added to a solution (or suspension) of ligand [$(DHQ)_2PHAL$ (**A**), $(DHQD)_2PHAL$) (**B**), or $(DHQ)_2AQN$ (**C**)] (39 μmol) and 4-chlorobenzoyloxycarbamate reagent (**7**−**10**) (1.10 mmol) in acetonitrile (3.5 mL). This mixture was allowed to stir for 10 min before a solution of alkene (0.79 mmol) in acetonitrile (3.5 mL) was added followed immediately by the addition of water (0.85 mL). The reaction mixture was stirred at room temperature and monitored by TLC analysis and deemed to be complete when the alkene starting material had been completely consumed (1−24 h; typically reactions were complete in 3−4 h). The reaction mixture was quenched with saturated aqueous $K_2S_2O_5$ solution (2 mL) followed by adding water (30−50 mL) and ethyl acetate (30−50 mL). The separated aqueous layer was extracted with ethyl acetate (2 × 30 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (2 × 50 mL) and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography on silica gel eluting with solvent mixtures outlined below. In all cases, except for Fmoc reagent **10**, the reactions were initially homogeneous with a colorless precipitate typically appearing within 2 h.

Reactions without Chiral Ligands. For achiral reactions unless indicated an identical procedure was followed as above (AA) but without the addition of chiral ligands.

(1*R*,2*R*,3*S*,4*S*,5*S*)-3-(Ethoxycarbonylamino)-4-hydroxy-5-(hydroxymethyl)cyclo-pentane-1,2-diyl Dibenzoate (2)[11,27] and (1*R*,2*R*,3*S*,4*S*,5*R*)-4-(Ethoxycarbonylamino)-3-hydroxy-5-(hydroxymethyl)cyclopentane-1,2-diyl Dibenzoate (3).[11,27] Osmium tetraoxide (150 mg, 592 μmol) was added to a solution of ethyl 4-chlorobenzoyloxycarbamate **7** (7.22 g, 29.6 mmol) in *tert*-butyl alcohol (70 mL) and stirred at room temperature for 10 min. (1*R*,2*R*,5*R*)-5-(Hydroxymethyl)cyclopent-3-ene-1,2-diyl dibenzoate[11,27] (5.00 g, 14.8 mmol) dissolved in *tert*-butyl alcohol (80 mL) was added to the carbamate solution followed by the addition of water (50 mL). After being stirred at room temperature for 3 h, the reaction was quenched with saturated $K_2S_2O_5$ (50 mL) solution and stirred for another 15 min. Ethyl acetate (100 mL) was added, the separated organic layer was washed with water (100 mL) and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, petroleum spirit/ethyl acetate 4:1 then 1:1 then 3:7) to yield 2.91 g of a 10:1 mixture of **2** (40%) and the corresponding triol resulting from dihydroxylation along with 2.93 g (44%) of **3** as an off-white foam. The NMR data of **2** were consistent with those previously reported.[11]

3: mp 95−97 °C; $[\alpha]^{21}_D$ −56.2 (*c* 1.37, $CHCl_3$) [lit.[11] $[\alpha]_D$ −36 (*c* 0.2−1.6, $CHCl_3$)]; FTIR (KBr, cm^{-1}) 3422, 2981, 1722, 1602, 1524, 1452, 1273, 1178, 1112, 1070, 1027, 712, 419; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05−8.01 (m, 4H), 7.57−7.51 (m, 2H), 7.43−7.38 (m, 4H), 5.73 (d, J = 7.6 Hz, 1H), 5.59 (dd, J = 1.0, 9.4 Hz, 1H), 5.22 (d, J = 4.5 Hz, 1H), 4.26−4.17 (m, 2H), 4.14 (q, J = 7.0 Hz, 2H), 4.02 (br s, 1H), 3.84−3.75 (m, 2H), 3.61 (m, 1H), 2.48−2.41 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 166.1, 157.4, 133.5, 133.3, 129.9, 129.8, 129.4, 129.0, 128.4, 128.3, 84.6, 74.8, 74.1, 61.5, 58.3, 50.8, 49.4, 14.5; HRMS (ESI) calcd for $C_{23}H_{25}NO_8Na^+$ 466.1472, found 466.1475. Anal. Calcd for $C_{23}H_{25}NO_8$: C, 62.30; H, 5.68; N, 3.16. Found: C, 62.06; H, 5.75; N, 3.12.

Ethyl Hydroxycarbamate (6).[16] Ethyl chloroformate (13.4 mL, 140 mmol) was added dropwise to a suspension of hydroxylamine hydrochloride (10.0 g, 145 mmol) and sodium carbonate (22.4 g, 211 mmol) in water (66 mL) maintaining the internal temperature below 30 °C. After being stirred at room temperature for 2 h, the reaction was quenched by the dropwise addition of concd hydrochloric acid until pH 1 and then extracted with diethyl ether (2 × 100 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield 5.40 g of **6** as a colorless gum. Another 150 mL of diethyl ether were added to the aqueous portion and the mixture stirred vigorously for 1 d. The organic layer was separated, dried over $MgSO_4$, and concentrated to give an additional 2.50 g of **6**. This procedure was repeated one more time to afford another 2.20 g of the desired product **6**. In total 10.1 g (69%) of **6** were isolated: ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (br s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz,

(27) (a) Blattner, R.; Gerard, P. J.; Spindler-Barth, M. *Pestic. Sci.* **1997**, *50*, 312–318. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9526–9538. and literature cited therein. (c) Blattner, R.; Furneaux, R. H.; Lynch, G. P. *Carbohydr. Res.* **1996**, *294*, 29–40.

3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 62.1, 14.3. The spectroscopic data were consistent with those reported in the literature.[16]

Ethyl 4-Chlorobenzoyloxycarbamate (7).[14] 4-Chlorobenzoyl chloride (1.10 mL, 8.57 mmol) was added dropwise to a solution of ethyl hydroxycarbamate **6** (1.00 g, 9.52 mmol) and triethylamine (1.19 mL, 8.57 mmol) in diethyl ether (30 mL) at 0 °C. The reaction was stirred at room temperature for 30 min after which time it was quenched with 1 M hydrochloric acid (10 mL), water (100 mL) was added, and the mixture was extracted with diethyl ether (1 × 100 mL). The organic layer was washed with saturated $NaHCO_3$ (50 mL) and water (50 mL), dried with $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (silica gel, petroleum spirit/ethyl acetate 9:1 then 4:1) to yield 1.54 g (74%) of **7** as an off-white solid: mp 79 °C (DSC, sharp onset); FTIR (neat, cm^{-1}) 3210, 3094, 2990, 1765, 1708, 1588, 1495, 1487, 1473, 1443, 1401, 1368, 1298, 1283, 1249, 1235, 1177, 1121, 1107, 1090, 1054, 1016, 996, 876, 852, 771, 747, 728, 681; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.02 (dt, J = 2.1, 8.7 Hz, 2H), 7.46 (dt, J = 2.1, 8.7 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 156.5, 140.9, 131.3, 129.1, 125.2, 63.1, 14.3; HRMS (ESI) calcd for $C_{10}H_{10}ClNO_4Na^+$ 266.0191, found 266.0199.

Benzyl Hydroxycarbamate and Benzyl Benzyloxycarbonyloxycarbamate.[28,29] Benzyl chloroformate (46.0 mL, 321 mmol) was added dropwise to a solution of hydroxylamine hydrochloride (22.2 g, 321 mmol) and sodium carbonate (51.1 g, 482 mmol) in water (146 mL) maintaining the internal temperature below 30 °C with ice-bath cooling. The ice bath was removed and the reaction left to warm to room temperature. After 10 min, however, the reaction temperature had risen to 45 °C with considerable gas evolution. A water bath was used to reduce the reaction temperature, and it was stirred for an additional 1 h. The reaction was quenched by the addition of concd hydrochloric acid until pH 1 then extracted with CH_2Cl_2 (2 × 500 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a residue that was purified by flash column chromatography (silica gel, petroleum spirit/ethyl acetate 4:1 then 7:3) to yield 19.0 g (35%) of benzyl hydroxycarbamate as an off-white solid and 34.9 g (36%) of the benzyl benzyloxycarbonyloxycarbamate. The analytical data for benzyl hydroxycarbamate and benzyl benzyloxycarbonyloxycarbamate were consistent with that reported previously.[28,29]

Benzyl hydroxycarbamate: mp 62−63 °C (lit.[28] mp 62−64 °C); ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.81 (br s, 2H), 7.26 (s, 5H), 5.06 (s, 2H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 159.4, 135.5, 128.6, 128.4, 128.3, 67.8; HRMS (ESI) calcd for $C_8H_9NO_3Na^+$ 190.0475, found 190.0487.

Benzyl benzyloxycarbonyloxycarbamate:[28] mp 57.5−59 °C (lit.[28] mp 72−74 °C); ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.99 (s, 1H), 7.30−7.40 (m, 5H), 7.35 (s, 5H), 5.26 (s, 2H), 5.22 (s, 2H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 156.3, 155.3, 134.9, 134.0, 129.0, 128.7, 128.7, 128.6, 128.5, 128.3, 71.6, 68.5; HRMS (ESI) calcd for $C_{16}H_{15}NO_5Na^+$ 324.0837, found 324.0850.

Benzyl 4-Chlorobenzoyloxycarbamate (8). 4-Chlorobenzoyl chloride (13.1 mL, 102 mmol) was added dropwise to a solution of benzyl hydroxycarbamate (19.0 g, 114 mmol) and triethylamine (14.4 mL, 104 mmol) in diethyl ether (500 mL) at 0 °C. The reaction was stirred at room temperature for 1 h before it was quenched with 1 M hydrochloric acid (100 mL). The separated organic layer was washed with water (2 × 400 mL) and saturated $NaHCO_3$ solution (100 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 32.4 g (93%) of **8** as a colorless crystalline solid which was used without further purification. An analytical sample (5 g) was obtained by flash column chromatography (silica gel, petroleum spirit/ethyl acetate 9:1 and 4:1): mp 97 °C (DSC, sharp onset); FTIR (neat, cm^{-1}) 3231, 2917, 1772, 1734, 1701, 1593, 1489, 1472, 1454, 1405, 1388, 1288, 1267, 1233, 1179, 1119, 1108, 1089, 1045, 1027, 1020, 1009, 975, 946, 911, 883, 848, 785, 772, 753, 730, 697, 682, 668, 655; ^{1}H NMR (500 MHz, $CHCl_3$) δ 8.38 (s, 1H), 8.04−8.01 (m, 2H), 7.48−7.45 (m, 2H), 7.39−7.32 (m, 5H), 5.25 (s, 2H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 165.0, 156.3, 141.0, 134.9, 131.3, 129.2, 128.7, 128.3, 125.1, 68.5; HRMS (ESI) calcd for $C_{15}H_{12}NO_4ClNa^+$ 328.0347, found 328.0359.

***tert*-Butyl Hydroxycarbamate.**[29] To a biphasic mixture of hydroxylamine hydrochloride (3.00 g, 43.2 mmol) in water (39 mL) and CH_2Cl_2 (40 mL) at 0 °C was added solid $NaHCO_3$ (6.60 g, 79.0 mmol) portionwise. After 10 min, di-*tert*-butyl dicarbonate (7.50 g, 34.4 mmol) was introduced portionwise. The reaction mixture was allowed to warm to room temperature overnight. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL), and brine (30 mL), dried over $MgSO_4$, and concentrated to yield 3.90 g (85%) of the title compound as a colorless oil which was used without further purification. The spectroscopic data were consistent with those reported in the literature.[29]

***tert*-Butyl 4-Chlorobenzoyloxycarbamate (9).**[30] To a solution of *tert*-butyl hydroxycarbamate (3.90 g, 29.3 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added 4-chlorobenzoyl chloride (3.25 mL, 29.3 mmol) followed by the dropwise addition of triethylamine (4.12 mL, 29.3 mmol). The reaction was allowed to stir at room temperature for 1 h before 1 M hydrochloric acid (20 mL) was added. The organic layer was separated, washed with saturated $NaHCO_3$ solution (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (silica gel, petroleum spirit/ethyl acetate 19:1 then 93:7) to afford **8** (3.00 g, 38%) as a colorless solid: mp 45 °C (DSC, slow onset); FTIR (neat, cm^{-1}) 3250, 2982, 2935, 1763, 1720, 1596, 1485, 1401, 1369, 1328, 1284, 1243, 1187, 1159, 1117, 1106, 1089, 1050, 1029, 1000, 956, 940, 925, 868, 842, 784, 745, 730, 679; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.05−8.00 (m, 2H), 7.49−7.42 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 155.4, 140.7, 131.2, 129.1, 125.4, 83.5, 28.0; HRMS (ESI) calcd for $C_{12}H_{14}ClNO_4Na^+$ 294.0504, found 294.0507.

(28) (a) Darbeau, R. W.; Alvarez, N. T.; Trahan, G. A.; Fronczek, F. R. *J. Org. Chem.* **2005**, *70*, 9599–9602. (b) Darbeau, R. W.; Trahan, G. A.; Siso, L. M. *Org. Biomol. Chem.* **2004**, *2*, 695–700.

(29) Bollans, L.; Bacsa, J.; Iggo, J. A.; Morris, G. A.; Stachulski, A. V. *Org. Biomol. Chem.* **2009**, *7*, 4531–4538.

(30) Yousef, A.-A. WO 145888 (A2), 2007.

(9*H*-Fluoren-9-yl)methyl Hydroxycarbamate.[31] To a biphasic mixture of hydroxylamine hydrochloride (3.00 g, 43.2 mmol) in CH_2Cl_2 (200 mL) and water (50 mL) at 0 °C was added solid $NaHCO_3$ (7.30 g, 87.0 mmol) portionwise. After 10 min, FmocCl (12.0 g, 46.4 mmol) was added portionwise to the vigorously stirred suspension which was then allowed to stir for 1 h at room temperature. The colorless precipitate that formed was filtered and washed with CH_2Cl_2 (50 mL) and water (100 mL). The filter cake was then dissolved in ethyl acetate (200 mL) and the organic solution washed with brine, dried over $MgSO_4$, and concentrated to give 5.20 g (47%) of the title compound as a colorless solid which was used without further purification; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.75 (br s, 1H), 8.78 (s, 1H), 7.89 (d, J = 7.5 Hz, 2H), 7.70 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 4.35 (d, J = 7.0 Hz, 2H), 4.24 (t, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.5, 143.7, 140.7, 127.6, 127.0, 125.1, 120.0, 65.5, 46.6; HRMS (ESI) calcd for $C_{15}H_{13}NO_3Na^+$ 278.0788, found 278.0793.

(9*H*-Fluoren-9-yl)methyl 4-Chlorobenzoyloxycarbamate (10). To a solution of (9*H*-fluoren-9-yl)methyl hydroxycarbamate (5.20 g, 20.4 mmol) in ethyl acetate (300 mL) at −10 °C was added 4-chlorobenzoyl chloride (3.56 g, 20.3 mmol). Triethylamine (3.0 mL, 21.3 mmol) was added dropwise keeping the internal temperature below −5 °C. After 10 min, water (100 mL) was added, and the separated aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated to give 7.90 g (98%) of **10** as a colorless solid which required no purification prior to further use. An analytical sample was prepared by flash column chromatography (silica gel, petroleum spirits/CH_2Cl_2 1:1 then CH_2Cl_2): mp 156 °C (DSC, sharp onset); FTIR (neat, cm^{-1}) 3238, 3018, 2982, 2890, 1767, 1741, 1717, 1595, 1486, 1452, 1403, 1373, 1320, 1275, 1231, 1173, 1118, 1092, 1040, 1011, 962, 935, 880, 847, 792, 783, 755, 736, 682; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.01−7.96 (m, 2H), 7.71 (d, J = 7.5 Hz, 2H), 7.55 (dd, J = 0.9, 7.5 Hz, 2H), 7.47−7.44 (m, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.25 (td, J = 1.1, 7.5 Hz, 2H), 4.54 (d, J = 6.9 Hz, 2H), 4.24 (t, J = 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 156.3, 143.1, 141.3, 141.0, 131.3, 129.2, 127.9, 127.1, 125.0, 120.0, 68.5, 46.8; HRMS (ESI) calcd for $C_{22}H_{16}ClNO_4Na^+$ 416.0660, found 416.0660.

(±)-(2*S*,3*R*)-Isopropyl 3-(Ethoxycarbonylamino)-2-hydroxy-3-phenylpropanoate (11a) and (±)-(2*S*,3*R*)-Isopropyl 2-(Ethoxycarbonylamino)-3-hydroxy-3-phenylpropanoate (11b). Osmium tetraoxide (53.0 mg, 211 μmol) was added to a solution of ethyl reagent **7** (1.80 g, 7.37 mmol) in *tert*-butyl alcohol (18 mL) and stirred at room temperature for 10 min. *trans*-Isopropyl cinnamate (1.00 g, 5.26 mmol) as a solution in *tert*-butyl alcohol (18 mL) was added to the carbamate solution followed by the addition of water (12 mL), and the reaction was stirred at room temperature for 3 h. The reaction was quenched with saturated $K_2S_2O_5$ solution (5 mL) and stirred for another 5 min. Water (100 mL) was added, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The organic layers were combined, washed with saturated $NaHCO_3$ solution (2 × 100 mL) and brine, and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, petroleum spirit/ethyl acetate 4:1) to yield 171 mg (11%) of **11a** and 171 mg (11%) of **11b** as colorless gums and 1.14 g (74%) of a 1:1.4 mixture of **11a** and **11b**.

11a: FTIR (neat, cm^{-1}) 3377, 3050, 3035, 3000, 2983, 2947, 1712, 1690, 1526, 1500, 1472, 1458, 1449, 1437, 1420, 1373, 1353, 1329, 1311, 1291, 1257, 1232, 1218, 1183, 1171, 1145, 1115, 1093, 1042, 1033, 992, 948, 938, 917, 880, 848, 821, 807, 775, 742, 702, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.31 (m, 4H), 7.29−7.24 (m, 1H), 5.68 (br d, J = 8.5 Hz, 1H), 5.26 (br d, J = 8.5 Hz, 1H), 5.16−5.07 (m, 1H), 4.42 (s, 1H), 4.12−4.01 (m, 2H), 3.44 (br, 1H), 1.29 (d, J = 6.3 Hz, 3H), 1.27 (d, J = 6.3 Hz, 3H), 1.20 (br t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 155.8, 139.2, 128.6, 127.6, 126.7, 73.6, 70.5, 61.0, 56.3, 21.6, 21.4, 14.4; HRMS (ESI) calcd for $C_{15}H_{21}NO_5Na^+$ 318.1312, found 318.1324.

11b: FTIR (neat, cm^{-1}) 3404, 3067, 3032, 2982, 2938, 1701, 1513, 1504, 1477, 1469, 1455, 1437, 1419, 1375, 1331, 1271, 1209, 1147, 1105, 1057, 977, 935, 916, 870, 836, 821, 776, 700, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.24 (m, 5H), 5.44 (br m, 1H), 5.17 (d, J = 3.2 Hz, 1H), 5.07−4.96 (m, 1H), 4.55−4.49 (br m, 1H), 4.05−3.90 (br m, 2H), 2.85 (br s, 1H), 1.26 (d, J = 6.2 Hz, 3H), 1.18−1.11 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 156.5, 139.7, 128.4, 128.1, 126.1, 74.1, 69.6, 61.2, 59.9, 21.7, 21.5, 14.4; HRMS (ESI) calcd for $C_{15}H_{21}NO_5Na^+$, 318.1312, found 318.1320.

(±)-(2*S*,3*R*)-Isopropyl 3-(Benzyloxycarbonylamino)-2-hydroxy-3-phenylpropanoate (12a) and (±)-(2*S*,3*R*)-Isopropyl 2-(Benzyloxycarbonylamino)-3-hydroxy-3-phenylpropanoate (12b). Method A. *trans*-Isopropyl cinnamate (1.00 g, 5.26 mmol) was treated with osmium tetraoxide (53.0 mg, 211 μmol) and benzyl reagent **8** (2.25 g, 7.37 mmol) in *tert*-butyl alcohol (72 mL) and water (12 mL) following the procedure outlined for the preparation of **11a** and **11b** to yield 175 mg (9%) of **12a** and 175 mg (9%) of **12b** as off-white solids and 1.45 g (77%) of a 1:1 mixture of **12a** and **12b**.

Method B. Osmium tetraoxide (8.00 mg, 31.6 μmol) was added to a solution of benzyl reagent **8** (338 mg, 1.11 mmol) in acetonitrile (3.5 mL) and stirred at room temperature for 10 min. *trans*-Isopropyl cinnamate (150 mg, 789 μmol) as a solution in acetonitrile (3.5 mL) was added to the carbamate solution followed by the addition of water (0.85 mL) and the reaction was stirred at room temperature for 3 h. The reaction was quenched with saturated $K_2S_2O_5$ solution (2 mL) and stirred for a further 5 min. Water (50 mL) was added to the reaction solution, and it was extracted with ethyl acetate (2 × 50 mL). The organic layers were combined and washed with saturated $NaHCO_3$ solution (2 × 50 mL), followed by brine, and then dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum spirit/ethyl acetate 4:1) to yield 270 mg (96%) of a 1:1.4 mixture of **12a** and **12b**.

12a: mp 96−97 °C; FTIR (neat, cm^{-1}) 3359, 3041, 2980, 2935, 1715, 1696, 1533, 1497, 1469, 1454, 1437, 1419, 1387, 1374, 1351, 1326, 1309, 1287, 1256, 1233, 1218, 1183, 1147, 1115, 1100, 1052, 1029, 979, 954, 915, 906, 853, 839, 821, 774, 750, 739, 721, 703, 697, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.23 (m, 10H), 5.79 (br d, 9.2 J = Hz, 1H), 5.27 (br d, J = 9.2 Hz, 1H), 5.11−4.99 (m, 3H), 4.40 (s, 1H), 3.37 (br s, 1H), 1.26 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.1 Hz, 3H); ^{13}C

(31) Mellor, S. L.; McGuire, C.; Chan, W. C. *Tetrahedron Lett.* **1997**, *38*, 3311–3314.

NMR (125 MHz, $CDCl_3$) δ 172.2, 155.6, 139.0, 136.3, 128.5, 128.5, 128.4, 128.0, 127.6, 126.7, 73.5, 70.6, 66.8, 56.4, 21.6, 21.3; HRMS (ESI) calcd for $C_{20}H_{23}NO_5Na^+$ 380.1468, found 380.1469.

12b: mp 92−93 °C; FTIR (neat, cm^{-1}) 3499, 3366, 3036, 2983, 2939, 1725, 1691, 1522, 1498, 1454, 1438, 1400, 1376, 1356, 1316, 1292, 1239, 1211, 1195, 1160, 1105, 1055, 1029, 1015, 1002, 980, 956, 916, 903, 863, 836, 795, 778, 737, 712, 703, 694, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.19 (m, 10H), 5.66 (br d, J = 8.4 Hz, 1H), 5.17 (s, 1H), 5.05−4.93 (m, 3H), 4.54 (br d, J = 7.2 Hz, 1H), 3.13 (br s, 1H), 1.22 (d, J = 6.2 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 156.3, 139.7, 136.2, 128.4, 128.3, 128.3, 128.0, 127.8, 126.0, 73.8, 69.6, 66.9, 60.0, 21.6, 21.5; HRMS (ESI) calcd for $C_{20}H_{23}NO_5Na^+$ 380.1468, found 380.1468.

Chiral Methods [Table 3, (+)-12a, (−)-12a, (+)-12b]. **(+)-12a.** Following the general AA procedure above, *trans*-isopropyl cinnamate (150 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol), $(DHQ)_2PHAL$ (31.0 mg, 39.5 μmol), and benzyl reagent **8** (338 mg, 1.11 mmol). (Note: The solution changed from a yellow color to dark green very quickly after addition of the *trans*-isopropyl cinnamate and a colorless precipitate formed during the course of the reaction.) Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 4:1) afforded 270 mg (96%) of **(+)-12a** and **12b** as a 12.7:1 mixture of regioisomers: **(+)-12a**, 97% ee; **12b**, 33% ee; **(+)-12a**, $[\alpha]^{21}_D$ = +15.1 (*c* 1.26, $CHCl_3$); spectroscopic data was identical to **(±)-12a** above.

(−)-12a. Following the general AA procedure above, *trans*-isopropyl cinnamate (150 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol), $(DHQD)_2PHAL$ (31.0 mg, 39.5 μmol), and benzyl reagent **8** (338 mg, 1.11 mmol). (Note: The solution changed from a yellow color to dark green very quickly after addition of the *trans*-isopropyl cinnamate and a colorless precipitate formed during the course of the reaction.) Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 4:1) afforded 269 mg (96%) of the products **(−)-12a** and **12b** in a 13.4:1 ratio of regioisomers: **(−)-12a**, 97% ee; **12b**, 28% ee. **(−)-12a**: $[\alpha]^{21}_D$ −14.7 (*c* 1.07, $CHCl_3$); spectroscopic data were identical to **(±)-12a** above.

(+)-12b. Following the general AA procedure above, *trans*-isopropyl cinnamate (150 mg, 0.79 mmol) was treated with osmium tetraoxide (8 mg, 32 μmol), $(DHQ)_2AQN$ (31.0 mg, 39.5 μmol), and benzyl reagent **8** (338 mg, 1.11 mmol). (Note: The solution changed from a yellow color to dark green within a minute after addition of the *trans*-isopropyl cinnamate and no precipitate formed during the course of the reaction.) Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 4:1) afforded 253 mg (90%) of **12a** and **12b** in a 1:1.6 ratio of regioisomers: **12a**, 71% ee; **12b**, 71% ee.

(±)-(2*S*,3*R*)-Isopropyl 3-(*tert*-Butoxycarbonylamino)-2-hydroxy-3-phenylpropanoate (13a) and (±)-(2*S*,3*R*)-Isopropyl 2-(*tert*-Butoxycarbonylamino)-3-hydroxy-3-phenylpropanoate (13b). Following the general procedure above, *trans*-isopropyl cinnamate (150 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol) and Boc reagent **9** (300 mg, 1.10 mmol). Subsequent flash column chromatography (silica gel, ethyl acetate/petroleum spirit 15:85) gave 238 mg (93%) of **13a** and **13b** in a 1:1.8 ratio of regioisomers. Further column chromatography yielded analytical samples of **13a** and **13b**.

13a: mp 136−137 °C (DSC, sharp onset); FTIR (neat, cm^{-1}) 3392, 2978, 2943, 1713, 1685, 1517, 1473, 1578, 1422, 1389, 1355, 1327, 1313, 1293, 1234, 1218, 1170, 1146, 1116, 1100, 1055, 1039, 1022, 952, 917, 877, 848, 822, 790, 775, 755, 729, 703; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.26 (m, 5H), 5.38 (br d, J = 8.3 Hz, 1H), 5.23 (br d, J = 8.3 Hz, 1H), 5.12 (sept, J = 6.4 Hz, 1H), 4.43 (br s, 1H), 3.14 (br s, 1H), 1.40 (s, 9H), 1.33−1.28 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 155.0, 139.5, 128.5, 127.6, 126.7, 79.7, 73.6, 70.7, 55.8, 28.3, 21.7, 21.5; HRMS (ESI) calcd for $C_{17}H_{25}NO_5Na^+$ 346.1625, found 346.1634.

13b: FTIR (neat, cm^{-1}) 3432, 2981, 2935, 1695, 1498, 1454, 1392, 1367, 1334, 1267, 1162, 1106, 1054, 1027, 982, 936, 916, 861, 836, 823, 776, 736, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.20 (m, 5H), 5.34 (br s, 1H), 5.14 (br s, 1H), 5.02 (sept, J = 6.1 Hz, 1H), 4.46 (br s, 1H), 3.17 (br s, 1H), 1.42−1.26 (br m, 9H), 1.25 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 155.7, 140.0, 128.2, 127.8, 126.1, 79.9, 74.1, 69.4, 59.6, 28.1, 21.7, 21.5; HRMS (ESI) calcd for $C_{17}H_{25}NO_5Na^+$ 346.1625, found 346.1625.

(±)-(2*S*,3*R*)-Isopropyl 2-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-3-hydroxy-3-phenylpropanoate (14a) and (±)-(2*S*,3*R*)-Isopropyl 3-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-2-hydroxy-3-phenylpropanoate (14b). Following the general procedure above, *trans*-isopropyl cinnamate (150 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol) and Fmoc reagent **10** (434 mg, 1.10 mmol). The crude product was purified by flash column chromatography (silica gel, ethyl acetate/petroleum spirit 1:4 and 3:7) to afford 338 mg (96%) of a 1:1.9 mixture of regioisomers **14a** and **14b**. Further column chromatography yielded analytical samples of **14a** and **14b** as colorless solids.

14a: mp 118 °C (DSC, sharp onset); FTIR (neat, cm^{-1}) 3384, 2976, 1721, 1695, 1519, 1449, 1355, 1324, 1287, 1250, 1217, 1182, 1112, 1026, 978, 914, 823, 776, 757, 732, 740, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 7.7 Hz, 2H), 7.59−7.50 (m, 2H), 7.42−7.25 (m, 9H), 5.70 (d, J = 9.4 Hz, 1H), 5.29 (d, J = 9.4 Hz, 1H), 5.11 (sept, J = 6.2 Hz, 1H), 4.46 (s, 1H), 4.41−4.29 (2H, m), 4.19 (t, J = 6.3 Hz, 1H), 3.23 (br s, 1H), 1.29 (d, J = 6.2 Hz, 3H), 1.24 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 155.6, 143.8, 141.3, 139.0, 128.7, 127.8, 127.7, 127.1, 126.7, 125.0, 120.0, 73.4, 70.9, 67.0, 56.3, 47.2, 21.7, 21.5; HRMS (ESI) calcd for $C_{27}H_{27}NO_5Na^+$ 468.1781, found 468.1782.

14b: mp 133 °C (DSC, slow onset); FTIR (neat, cm^{-1}) 3502, 3385, 2981, 1720, 1691, 1524, 1449, 1374, 1315, 1288, 1247, 1232, 1163, 1105, 1088, 1065, 1039, 992, 960, 836, 759, 742, 728, 713, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 7.5 Hz, 2H), 7.55−7.47 (m, 2H), 7.41−7.25 (m, 9H), 5.60 (br d, J = 8.4 Hz, 1H), 5.24 (br s, 1H), 5.07 (sept, J = 6.5 Hz, 1H), 4.58 (br d, J = 6.7 Hz, 1H), 4.32−4.18 (m, 2H), 4.15−4.08 (m, 1H), 2.68 (br s, 1H), 1.26 (d, J = 6.5 Hz, 3H), 1.19 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 156.2, 143.8, 141.3, 139.6, 128.5, 128.2, 127.7, 127.0, 126.1, 125.1, 119.9, 74.0, 69.7, 67.2, 59.9, 47.1, 21.7, 21.6; HRMS (ESI) calcd for $C_{27}H_{27}NO_5Na^+$ 468.1781, found 468.1781.

(±)-Benzyl 2-Hydroxy-2-phenylethylcarbamate (15a)[32] and (±)-Benzyl 2-Hydroxy-1-phenylethylcarbamate (15b).[32] Following the general procedure above, styrene (250 μL, 2.18 mmol) was reacted with osmium tetraoxide (22.1 mg, 87.1 μmol) and benzyl reagent **8** (933 mg, 3.05 mmol). The crude

product was purified by flash column chromatography (silica gel, ethyl acetate/petroleum spirit 3:7) to afford 570 mg (96%) of a mixture of regioisomers **15a** and **15b** in a 9.5:1 ratio. Further column chromatography yielded analytical samples of **15a** and **15b** as off-white solids.

15a: mp 114−115 °C [lit.[32] mp 113 °C (petroleum spirit/ethyl acetate)]; FTIR (neat, cm^{-1}) 3368, 3272, 3063, 3025, 2936, 2887, 1693, 1605, 1586, 1549, 1497, 1453, 1431, 1369, 1345, 1318, 1271, 1240, 1210, 1162, 1098, 1066, 1024, 993, 948, 918, 890, 834, 822, 781, 755, 741, 718, 705, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.22 (m, 10H), 5.32 (br s, 1H), 5.08−5.01 (m, 2H), 4.81−4.67 (br m, 1H), 3.54−3.44 (br m, 1H), 3.29−3.11 (br m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 141.5, 136.3, 128.5, 128.5, 128.1, 128.1, 127.9, 125.8, 73.5, 66.9, 48.5; HRMS (ESI) cslcd for $C_{16}H_{17}NO_3Na^+$ 294.1101, found 294.1104.

15b: mp 83−85 °C [lit.[32] mp 85 °C (petroleum spirit/ethyl acetate)]; FTIR (neat, cm^{-1}) 3350, 3036, 2930, 2879, 1683, 1587, 1531, 1496, 1451, 1348, 1326, 1277, 1246, 1219, 1193, 1147, 1099, 1076, 1057, 1027, 915, 841, 778, 762, 734, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.24 (m, 10H), 5.54 (br s, 1H), 5.13−5.05 (m, 2H), 4.83 (br s, 1H), 3.90−3.77 (br m, 2H), 2.19 (br m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 139.1, 136.3, 128.8, 128.5, 128.2, 127.9, 126.6, 67.0, 66.5, 57.2; HRMS (ESI) calcd for $C_{16}H_{17}NO_3Na^+$ 294.1101, found 294.1100.

(±)-Benzyl 2-Hydroxy-3-phenylpropylcarbamate (16a) and (±)-Benzyl 1-Hydroxy-3-phenylpropan-2-ylcarbamate (16b).[33] Allyl benzene (288 μL, 2.18 mmol) was reacted with osmium tetraoxide (22.1 mg, 87.1 μmol) and benzyl reagent **8** (933 mg, 3.05 mmol) for 15 h, using the general procedure as described above. The crude product was purified by flash column chromatography (silica gel, ethyl acetate/petroleum spirit 3:7) to afford a 565 mg (91%) of a mixture of regioisomers **16a** and **16b** in a 5.5:1 ratio. Further column chromatography yielded analytical samples of **16a** and **16b** as off-white solids.

16a: mp 150 °C (petroleum spirit/ethyl acetate); FTIR (neat, cm^{-1}) 3352, 3034, 2943, 1688, 1537, 1494, 1466, 1454, 1432, 1352, 1319, 1286, 1251, 1221, 1150, 1083, 1070, 1042, 1028, 1001, 962, 911, 839, 768, 749, 725, 701, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.12 (m, 10H), 5.40−5.34 (m, 1H), 5.09−5.05 (m, 2H), 3.91−3.84 (m, 1H), 3.41−3.33 (m, 1H), 3.12−3.02 (m, 1H), 2.77−2.62 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 137.5, 136.4, 129.2, 128.5, 128.4, 128.0, 128.0, 126.5, 71.9, 66.8, 46.2, 41.1; HRMS (ESI) calcd for $C_{17}H_{19}NO_3Na^+$ 308.1257, found 308.1256.

16b: mp 78 °C (petroleum spirit/ethyl acetate); FTIR (neat, cm^{-1}) 3320, 3064, 3031, 2954, 2876, 1688, 1602, 1543, 1498, 1466, 1454, 1446, 1379, 1312, 1260, 1190, 1146, 1085, 1069, 1053, 1015, 967, 918, 907, 866, 842, 776, 746, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.16 (m, 10H), 5.07 (s, 2H), 5.01 (d, J = 6.8 Hz, 1H), 3.94 (br s, 1H), 3.70−3.52 (m, 2H), 2.85 (d, J = 6.8 Hz, 2H), 2.29−2.15 (br m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 137.5, 136.4, 129.2, 128.6, 128.5, 128.1, 128.0, 126.6, 66.8, 64.0, 54.1, 37.4; HRMS (ESI) calcd for $C_{17}H_{19}NO_3Na^+$ 308.1257, found 308.1260.

(±)-Benzyl (1*R*,2*R*)-2-Hydroxy-1,2-diphenylethylcarbamate (17).[5] *trans*-Stilbene (392 mg, 2.18 mmol) was reacted with osmium tetraoxide (22.1 mg, 87.1 μmol) and benzyl reagent **8** (933 mg, 3.05 mmol) for 3 h using the general procedure described above. The crude product was purified by flash column chromatography (silica gel, ethyl acetate/petroleum spirit 1:4) to afford 725 mg (96%) of **17** as an off-white solid: mp 149−151 °C (methanol) [lit.[5] mp 152 °C (methanol)]; FTIR (neat, cm^{-1}) 3353, 3034, 2943, 2889, 2488, 1687, 1603, 1533, 1493, 1467, 1454, 1431, 1350, 1318, 1286, 1250, 1220, 1198, 1164, 1150, 1069, 1042, 1027, 1001, 961, 910, 839, 768, 749, 725, 701, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.23 (m, 15H), 5.71−5.61 (m, 1H), 5.05−4.91 (m, 4H), 2.43 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 140.5, 136.4, 128.6, 128.4, 128.3, 128.0, 127.9, 127.7, 126.8, 126.2, 66.8, 61.0; HRMS (ESI) calcd for $C_{22}H_{21}NO_3Na^+$ 370.1414, found 370.1413.

(±)-Benzyl (1*S*,2*R*)-2-Hydroxycyclohexylcarbamate (18).[5] Cyclohexene (220 μL, 2.18 mmol) was reacted with osmium tetraoxide (22.1 mg, 87.1 μmol) and benzyl reagent **8** (933 mg, 3.05 mmol) for 3 h following the general procedure described above. The crude product was purified by flash column chromatography (silica gel, ethyl acetate/petroleum spirit 1:4) to afford 523 mg (96%) of **18** as an off-white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 5.39 (br d, 8.5 Hz, 1H), 5.11−5.01 (m, 2H), 3.90 (br s, 1H), 3.62 (br s, 1H), 2.67 (br s, 1H), 1.74−1.66 (m, 1H), 1.64−1.46 (m, 5H), 1.39−1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 136.4, 128.4, 127.9, 68.8, 66.6, 52.5, 31.5, 27.2, 23.6, 19.6; HRMS (ESI) calcd for $C_{14}H_{19}NO_3Na^+$ 272.1257, found 272.1260.

(+)-18. Following the general procedure described above, cyclohexene (45 μL, 0.45 mmol) was reacted with osmium tetraoxide (4.5 mg, 18 μmol), $(DHQ)_2PHAL$ (17 mg, 22 μmol) and benzyl reagent **8** (191 mg, 0.62 mmol). Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 19:1 and 7:3) afforded 90 mg (80%, 62% ee) of (+)-**18** as an off-white solid the spectroscopic data of which was identical to that recorded for (±)-**18**.

(−)-18. Following the general AA procedure above, cyclohexene (45 μL, 0.45 mmol) was reacted with osmium tetraoxide (4.5 mg, 18 μmol), $(DHQD)_2PHAL$ (17 mg, 22 μmol), and benzyl reagent **8** (191 mg, 0.62 mmol). Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 19:1 and 7:3) yielded 81 mg (72%, 73% ee) of (−)-**18** as an off-white solid the spectroscopic data of which were identical to that reported for (±)-**18**.

(±)-(2*R*,3*R*)-Dimethyl 2-(Benzyloxycarbonylamino)-3-hydroxysuccinate (19).[5] Dimethyl fumarate (157 mg, 1.09 mmol) was reacted with osmium tetraoxide (11.1 mg, 43.6 μmol) and benzyl reagent **8** (467 mg, 1.53 mmol) for 15 h, using the general procedure described above. The crude product was purified by flash column chromatography (silica gel, ethyl acetate/petroleum spirit 1:4) to afford 315 mg (93%) of **19** as an off-white solid: mp 129−130 °C (benzene) [lit.[34] 129−130 °C (chloroform)]; FTIR (neat, cm^{-1}) 3358, 3312, 3034, 2957, 2890, 2854, 1749, 1687, 1529, 1439, 1391, 1341, 1265, 1215, 1186, 1173, 1126, 1063, 1031, 984, 971, 952, 927, 910, 860, 802, 779, 762, 740, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H), 5.66 (d, J = 9.1 Hz, 1H), 5.09 (s, 2H), 4.85 (d, J = 9.1 Hz, 1H),

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4.71 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.43 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 169.6, 156.0, 136.0, 128.4, 128.1, 127.9, 70.9, 67.2, 56.5, 53.1, 52.9; HRMS (ESI) calcd for $C_{14}H_{17}NO_7Na^+$ 334.0897, found 334.0899.

(±)-(3*S*,4*R*)-Benzyl 3-(Benzyloxycarbonylamino)-4-hydroxypyrrolidine-1-carboxylate (20). Benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate[22] (200 mg, 985 μmol) was treated with osmium tetraoxide (10.0 mg, 39.4 μmol) and benzyl benzyl reagent **8** (422 mg, 1.38 mmol) for 3 h using the general procedure described above. The crude product was purified by flash column chromatography (silica gel, ethyl acetate/petroleum spirit 1:4) to afford 350 mg (96%) of **20** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.25 (m, 10H), 5.58−5.52 (m, 1H), 5.12−5.02 (m, 4H), 4.26−4.13 (m, 2H), 3.81−3.73 (m, 1H), 3.52−3.41 (m, 2H), 3.29−3.15 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) rotameric signals observed: δ 156.1, 155.1, 154.9, 136.4, 136.3, 136.1, 128.5, 128.4, 128.2, 128.0, 128.0, 127.8, 70.1, 69.3, 67.1, 67.0, 53.2, 52.9, 52.5, 47.8; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.45−7.28 (m, 10H), 6.64 (br s, 1H), 5.12 (s, 2H), 5.11 (s, 2H), 5.01 (d, J = 4.3 Hz, 1H), 4.23−4.19 (m, 1H), 4.10−4.02 (m, 1H), 3.65 (dd, J = 7.8, 10.1 Hz, 1H), 3.54 (dd, J = 4.3, 11.6 Hz, 1H), 3.38 (dd, J = 2.2, 11.6 Hz, 1H), 3.25 (dd, J = 9.0, 10.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 155.3, 153.7, 136.7, 136.6, 127.8, 127.8, 127.2, 127.1, 127.1, 126.9, 68.1, 65.4, 65.2, 52.8, 52.1, 47.4; HRMS (ESI) calcd for $C_{20}H_{22}N_2O_5Na^+$ 393.1421, found 393.1421.

(−)-(3*R*,4*S*)-Benzyl 3-(Benzyloxycarbonylamino)-4-hydroxypyrrolidine-1-carboxylate ((−)-20). Following the general AA procedure above, a solution of benzyl 4-chlorobenzoyloxycarbamate **8** (211 mg, 0.69 mmol), osmium tetraoxide (5 mg, 0.02 mmol) and $(DHQ)_2PHAL$ (19.0 mg, 0.024 mmol) in acetonitrile (2 mL) and water (0.5 mL) was reacted with a solution of benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate[22] (100 mg, 0.492 mmol) in acetonitrile (2 mL) at room temperature for 3 h. Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 7:3 and 3:7) afforded 169 mg (93%) of (−)-**20** (35% ee) as a colorless oil: $[\alpha]^{16}_D$ −1.65 (*c* 1.4, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{22}N_2O_5Na^+$ 393.1421, found 393.1422. The spectroscopic data were consistent with those reported for the racemic compound (±)-**20** above.

(+)-(3*S*,4*R*)-Benzyl 3-(Benzyloxycarbonylamino)-4-hydroxypyrrolidine-1-carboxylate ((+)-20). Following the general AA procedure above, a solution of benzyl reagent **8** (211 mg, 0.69 mmol), osmium tetraoxide (5 mg, 0.02 mmol), and $(DHQD)_2PHAL$ (19.0 mg, 0.024 mmol) in acetonitrile (2 mL) and water (0.5 mL) was treated with a solution of benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate[22] (100 mg, 0.492 mmol) in acetonitrile (2 mL) at room temperature for 3 h. Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 7:3 and 3:7) afforded 168 mg (92%) of (+)-**20** (64% ee) as a colorless oil: $[\alpha]^{16}_D$ +2.68 (*c* 1.12, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{22}N_2O_5Na^+$ 393.1421, found 393.1424. The spectroscopic data were consistent with those reported for the racemic compound (±)-**20** above.

(+)-(2*R*,3*S*)-Methyl 3-(Ethoxycarbonylamino)-2-hydroxy-3-phenylpropanoate ((+)-21a).[5] Following the general AA procedure above, *trans*-methyl cinnamate (128 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol), $(DHQ)_2PHAL$ (31 mg, 0.039 mmol) and ethyl reagent **7** (269 mg, 1.10 mmol). Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 6:1 and 3:1) afforded (+)-**21a** as a colorless crystalline solid (85 mg, 40%) and a mixture of **21a** and **21b** (99 mg, 47%). The ratio of **21a**:**21b** was determined to be 13:1. (+)-**21a**: mp 89 °C (DSC, sharp onset); $[\alpha]^{23}_D$ +4.3 (*c* 1.85, $CHCl_3$) [lit.[5] +2.78; (*c* 0.9, EtOH)]; FTIR (neat, cm^{-1}) 3491, 3362, 2984, 1739, 1695, 1522, 1288, 1236, 1143, 1236, 1143, 1101, 1052, 1030, 766, 704, 682; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.26 (m, 5H), 5.56 (d, J = 8.1 Hz, 1H), 5.23 (d, J = 9.0 Hz, 1H), 4.48 (br s, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.84 (s, 3H), 3.20 (br s, 1H), 1.21 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 155.9, 139.0, 128.6, 127.9, 126.7, 73.5, 61.2, 56.4, 53.1, 14.5; HRMS (ESI) calcd for $C_{13}H_{17}NO_5Na^+$ 290.0999, found 290.1005. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.68; H, 6.46; N, 5.18.

(−)-(2*S*,3*R*)-Methyl 3-(Ethoxycarbonylamino)-2-hydroxy-3-phenylpropanoate ((-)-21a).[5] Following the general AA procedure above, *trans*-methyl cinnamate (159 mg, 0.98 mmol) was treated with osmium tetraoxide (10 mg, 39 μmol), $(DHQD)_2PHAL$ (38 mg, 49 mmol), and ethyl reagent **7** (335 mg, 1.38 mmol). Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 6:1 and 3:1) afforded (−)-**21a** as a colorless crystalline solid (97 mg, 37%) and a mixture of **21a** and **21b** (94 mg, 36%). The ratio of **21a**:**21b** was determined to be 15:1: mp 90 °C (DSC, sharp onset); $[\alpha]^{23}_D$ −4.9 (*c* 0.9, $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{17}NO_5Na^+$ 290.0999, found 290.1001; ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported for (+)-**21a** above.

(−)-(2*R*,3*S*)-Methyl 3-(Benzyloxycarbonylamino)-2-hydroxy-3-phenylpropanoate ((-)-22a).[5] Following the general AA procedure above, *trans*-methyl cinnamate (128 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol), $(DHQ)_2PHAL$ (31 mg, 0.039 mmol), and benzyl reagent **8** (337 mg, 1.10 mmol) at 0 °C. Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 6:1 and 3:1) afforded (−)-**22a** as a colorless crystalline solid (159 mg, 61%): mp 120−121 °C (DSC, sharp onset; lit.[21] 120−121 °C); $[\alpha]^{24}_D$ −1.29 (*c* 0.85, EtOH), $[\alpha]^{24}_D$ −2.7 (*c* 1.15, $CHCl_3$) {lit.[5] $[\alpha]^{20}_D$ +4.4; (*c* 0.32, EtOH), lit.[21] $[\alpha]^{20}_D$ −3.79; (*c* 1.0, $CHCl_3$)}; FTIR (neat, cm^{-1}) 3391, 1744, 1689, 1510, 1498, 1341, 1275, 1260, 1209, 1145, 1110, 1041, 1030, 987, 759, 749; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.05 (m, 10H), 5.65 (br d, J = 8.8 Hz, 1H), 5.27 (d, J = 8.8 Hz, 1H), 5.13−5.02 (m, 2H), 4.48 (br s, 1H), 3.80 (s, 3H), 3.13 (d, J = 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 155.7, 138.8, 136.3, 128.7, 128.5, 128.2, 128.1, 127.9, 126.7, 73.4, 67.0, 56.5, 53.1; LRMS (ESI) [M + Na]$^+$ 352 (100). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found C, 65.56; H, 5.90; N, 4.21.

(+)-(2*S*,3*R*)-Methyl 3-(Benzyloxycarbonylamino)-2-hydroxy-3-phenylpropanoate ((+)-22a).[5] Following the general AA procedure above, *trans*-methyl cinnamate (128 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol), $(DHQD)_2PHAL$ (31 mg, 0.039 mmol) and benzyl reagent **8** (337 mg, 1.10 mmol). Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 6:1 and 3:1) afforded 152 mg (59%) of (+)-**22a** as a colorless crystalline solid: mp 120−121 °C (DSC, sharp onset); $[\alpha]^{21}_D$ +1.1 (*c* 1, EtOH); ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported for (−)-**22a** above.

(−)-(2*R*,3*S*)-Methyl 3-(*tert*-Butoxycarbonylamino)-2-hydroxy-3-phenylpropanoate ((−)-23a).[35,36] Following the general AA procedure above, *trans*-methyl cinnamate (128 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol), $(DHQ)_2PHAL$ (31 mg, 0.039 mmol) and Boc-reagent **9** (300 mg, 1.10 mmol). Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 9:1 and 4:1) afforded 100 mg (43%) of **(-)-23a** as a colorless crystalline solid: mp 126 °C (DSC, sharp onset; lit.[36] mp 129 °C); $[\alpha]^{23}_D$ −6.7 (*c* 0.85, $CHCl_3$) {lit.[20] $[\alpha]^{20}_D$ −7.3 (*c* 1.00, $CHCl_3$)}; HRMS (ESI) calcd for $C_{15}H_{21}NO_5Na^+$ 318.1312, found 318.1314. The spectroscopic data were consistent with those reported in the literature.[36]

(+)-(2*S*,3*R*)-Methyl 3-(*tert*-Butoxycarbonylamino)-2-hydroxy-3-phenylpropanoate ((+)-23a). Method A. Following the general AA procedure above, *trans*-methyl cinnamate (128 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol), $(DHQD)_2PHAL$ (31 mg, 39 μmol) and Boc reagent **9** (300 mg, 1.10 mmol). Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 9:1 and 4:1) afforded 107 mg (46%) of **(+)-23a** as a colorless crystalline solid: mp 129 °C (DSC, sharp onset); $[\alpha]^{23}_D$ +6.6 (*c* 0.8, $CHCl_3$) {lit.[20] $[\alpha]^{20}_D$ +7.2 (*c* 0.22, $CHCl_3$)}; HRMS (ESI) calcd for $C_{15}H_{21}NO_5Na^+$ 318.1312, found 318.1318. Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found C, 61.13; H, 7.39; N, 4.61. The spectroscopic data of **(+)-23a** were consistent with those recorded for **(−)-23a** above.

Furthermore, 16 mg (7%) of the regioisomer and 38 mg (25%) diol byproduct were isolated: HRMS (ESI) calcd for $C_{10}H_{12}O_4Na^+$ 219.0628, found 219.0632. The spectroscopic data of the diol [(2*S*,3*R*)-methyl 2,3-dihydroxy-3-phenylpropanoate] matched the data given in the literature.[37]

Method B. To a solution of **(+)-26** (90 mg, 0.46 mmol) in methanol (5 mL) was added di-*tert*-butyl dicarbonate (121 mg, 0.55 mmol). The mixture was stirred at room temperature overnight and concentrated. Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 4:1) afforded 95 mg (70%) of **(+)-23a** as a colorless solid: $[\alpha]^{22}_D$ +6.5 (*c* 0.9, $CHCl_3$).

(+)-(2*R*,3*S*)-Methyl 3-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-2-hydroxy-3-phenylpropanoate ((+)-24a). Following the general AA procedure above, *trans*-methyl cinnamate (128 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol), $(DHQ)_2PHAL$ (31 mg, 39 μmol), and Fmoc reagent **10** (434 mg, 1.10 mmol). Subsequent flash column chromatography (silica gel, CH_2Cl_2 then petroleum spirit/ethyl acetate 4:1) afforded 58 mg (18%) of **(+)-24a** as a colorless solid and 224 mg (68%) of a mixture of **(+)-24a** and **24b**. HPLC analysis reveals that the overall ratio **(+)-24a**:**b** is 6.6:1: mp 173 °C (DSC, sharp onset); $[\alpha]^{21}_D$ +8.0 (*c* 0.75, $CHCl_3$); FTIR (neat, cm^{-1}) 3371, 3342, 1724, 1693, 1542, 1310, 1289, 1263, 1219, 1176, 1143, 1104, 1085, 1030, 991, 976, 777, 755, 738, 702, 667; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 6.9 Hz, 2H), 7.55 (d, *J* = 6.9 Hz, 2H), 7.42−7.11 (m, 9H), 5.68 (d, *J* = 9.1 Hz, 1H), 5.28 (d, *J* = 9.1 Hz, 1H), 4.51 (s, 1H), 4.45−4.26 (m, 2H), 4.23−4.16 (m, 1H), 3.82 (s, 3H), 3.20 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 155.7, 143.7, 141.3, 138.8, 128.7, 127.9, 127.7, 127.1, 126.7, 125.0, 120.0, 73.3, 67.0, 56.4, 53.2, 47.2; HRMS (ESI) calcd for $C_{25}H_{23}NO_5Na^+$ 440.1468, found 440.1477.

(−)-(2*S*,3*R*)-Methyl 3-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-2-hydroxy-3-phenylpropanoate ((−)-24a). Following the general AA procedure above, *trans*-methyl cinnamate (128 mg, 0.79 mmol) was reacted with osmium tetraoxide (8 mg, 32 μmol), $(DHQD)_2PHAL$ (31 mg, 39 μmol), and Fmoc reagent **10** (434 mg, 1.10 mmol). Subsequent flash column chromatography (silica gel, CH_2Cl_2 then petroleum spirit/ethyl acetate 4:1) afforded 58 mg (18%) of **(−)-24a** as a colorless solid and 255 mg (76%) of a mixture of **(−)-24a** and **24b**. HPLC analysis reveals that the overall ratio **(−)-24a**:**b** is 5.6:1: mp 161 °C (DSC, sharp onset); $[\alpha]^{21}_D$ −8.3 (*c* 1.16, $CHCl_3$); ^1H and ^{13}C NMR data were consistent with those for **(+)-24a** above; HRMS (ESI) calcd for $C_{25}H_{23}NO_5Na^+$ 440.1468, found 440.1474.

(+)-(4*R*,5*S*)-Methyl 2-Oxo-4-phenyloxazolidine-5-carboxylate ((+)-25).[38] **Method A.** A mixture of **(−)-12a** (111 mg, 0.31 mmol) and lithium hydroxide monohydrate (64 mg, 1.55 mmol) in methanol (3.5 mL) was stirred for 10 min at room temperature. Water (1.5 mL) was added, the reaction mixture was stirred at room temperature for another 4 h before it was concentrated, and ethyl acetate (5 mL) and water (5 mL) were added. The aqueous layer was separated and washed with ethyl acetate (5 mL). The organic phases were then discarded. Ethyl acetate (5 mL) was added to the aqueous layer, and the biphasic mixture was stirred before 1 M aqueous hydrochloric acid (5 mL, 5 mmol) was added. The organic phase was separated and the aqueous was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine and dried over $MgSO_4$ before being concentrated to dryness. The residue was taken up in THF (5 mL) and freshly prepared excess diazomethane was distilled directly into the solution. The excess diazomethane was quenched by the dropwise addition of acetic acid and the mixture was concentrated. The crude reaction product was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether 4:1 and 1:1) to yield 38 mg (55%) of **(+)-25** as a colorless crystalline solid: $[\alpha]^{23}_D$ +74.8 (*c* 0.85, EtOH); FTIR (neat, cm^{-1}) 3264, 3168, 2922, 2852, 1761, 1722, 1458, 1435, 1385, 1376, 1318, 1301, 1279, 1228, 1211, 1190, 1155, 1093, 1076, 969, 933, 921, 914, 855, 821, 776, 760, 721, 700; ^1H and ^{13}C NMR data were consistent with those reported for the racemic compound reported in the literature;[38] HRMS (ESI) calcd for $C_{11}H_{11}NO_4Na^+$ 244.0580, found 244.0581.

Method B. A mixture of **(+)-22a** (110 mg, 0.33 mmol) and lithium hydroxide monohydrate (64 mg, 1.55 mmol) in methanol (3.5 mL) was stirred for 10 min at room temperature. Water (1.5 mL) was added, and the reaction was stirred at room temperature for 16 h. Following the remainder of method A (above), 14 mg (19%) of **(+)-25** was isolated as a colorless crystalline solid: $[\alpha]^{16}_D$ +82.3 (*c* 0.6, EtOH); ^1H and ^{13}C NMR data were consistent with those reported for the racemic compound reported in the literature.[38]

(−)-(4*S*,5*R*)-Methyl 2-Oxo-4-phenyloxazolidine-5-carboxylate ((−)-25). Method A. **(+)-12a** (109 mg, 0.310 mmol) was

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subjected to the same reaction conditions used for the preparation of (+)-**25** to give 34 mg (50%) of (-)-**25** as a colorless crystalline solid: mp 152−153 °C (DSC, slow onset); $[\alpha]^{21}_D$ −68.8 (*c* 0.9, EtOH); ^{1}H and ^{13}C NMR data were identical to those found for (+)-**25** above; HRMS calcd for $C_{11}H_{11}NO_4Na^+$ 244.0580, found 244.0585.

(+)-(2*S*,3*R*)-Methyl 3-Amino-2-hydroxy-3-phenylpropanoate ((+)-26).[39] To a degassed solution of (+)-**22a** (152 mg, 0.461 mmol) in methanol (5 mL) was added 30 mg of Pd/C (10%). The solution was stirred under an atmosphere of hydrogen at atmospheric pressure at room temperature for 16 h. The solution was filtered through Celite with ethyl acetate and concentrated to give 90 mg (quant) of (+)-**26** as a colorless solid: $[\alpha]^{20}_D$ +22.1 (*c* 1.0, MeOH) {lit.[39] $[\alpha]^{20}_D$ +30 (*c* 1.0, MeOH)}. The ^{1}H and ^{13}C NMR spectroscopic data were consistent with those reported in the literature.[39] The enantiomer [(−)-**26**] was also synthesized from (−)-**22a** by the same method: $[\alpha]^{20}_D$ = −22.1 (*c* 1.0, MeOH) {lit.[39] $[\alpha]^{20}_D$ −22 (*c* 1.0, MeOH)}; HRMS calcd for $C_{10}H_{14}NO_3^+$ 196.0968, found 196.0970.

(3*R*,4*S*)-4-Aminopyrrolidin-3-ol Dihydrochloride Salt (27).[23] To a degassed solution of (+)-**20** (64% ee, 155 mg, 0.418 mmol) in methanol (5 mL) was added 21 mg of Pd/C (10%). The solution was stirred under an atmosphere of hydrogen at room temperature and atmospheric pressure for 16 h. The solution was filtered through Celite with ethyl acetate and concentrated. The residue was dissolved in methanol (2 mL), and two drops of concd hydrochloric acid were added. The solution was concentrated to yield the title compound as a colorless solid (quant): $[\alpha]^{21}_D$ −12.2 (*c* 0.58, H_2O) {lit.[23] $[\alpha]^{20}_D$ −23.9 (*c* 1.12, H_2O)}. The ^{1}H and ^{13}C spectroscopic data were consistent with those reported in the literature.[23]

Benzyl 3-(Diethoxyphosphoryl)-2-hydroxypropylcarbamate (28a) and Benzyl 1-(Diethoxyphosphoryl)-3-hydroxypropan-2-ylcarbamate (28b).[40] **Method A.** Following the general AA procedure above, diethyl allylphosphonate[26] (300 mg, 1.64 mmol) was reacted with osmium tetraoxide (17 mg, 67 μmol), $(DHQ)_2PHAL$ (66 mg, 84 mmol), and benzyl reagent **8** (721 mg, 2.36 mmol). Subsequent flash column chromatography (silica gel, petroleum spirit/ethyl acetate 3:7 then ethyl acetate) gave 275 mg (47%) of **28a** as a light brown oil, 20 mg (3%) of **28b** as a light brown oil, and 30 mg (5%) as a mixture of **28a** and **28b** in a 1:1 ratio (determined by ^{1}H NMR).

Method B. Following the general AA procedure, diethyl allylphosphonate[26] (300 mg, 1.64 mmol) was reacted with osmium tetraoxide (17 mg, 67 μmol), $(DHQD)_2PHAL$ (66 mg, 84 mmol), and benzyl reagent **8** (721 mg, 2.36 mmol). Purification of the crude residue by flash column chromatography (silica gel, petroleum spirit/ethyl acetate 3:7 then ethyl acetate) gave 284 mg (49%) of **28a** as a light brown oil, 3 mg (< 1%) of **28b** as a light brown oil, and 55 mg (9%) as a mixture of **28a** and **28b** in a 1:1 ratio (determined by ^{1}H NMR).

28a: FTIR (neat, cm^{-1}) 3323, 2983, 2932, 1702, 1536, 1456, 1393, 1216, 1162, 1144, 1096, 1021, 962, 878, 835, 775, 738, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 5.52 (br m, 1H, N*H*), 5.10 (s, 2H), 4.19−4.00 (m, 6H), 3.48−3.33 (m, 1H), 3.27−3.14 (m, 1H), 1.93 (dd, *J* = 6.5, 17.9 Hz, 2H), 1.36−1.22 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 136.4, 128.4, 128.0, 128.0, 66.8, 65.9, 62.0 (br), 47.3, 47.0, 30.8 (d, *J* = 139.9 Hz), 16.3, 16.3; HRMS (ESI) calcd for $C_{15}H_{24}NO_6PNa^+$ 368.1233, found 368.1234.

28b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 5.73 (d, *J* = 6.0 Hz), 5.09 (s, 2H), 4.14−3.96 (m, 5H), 3.85−3.76 (m br, 1H), 3.75−3.64 (m, 2H), 2.24−1.97 (m, 2H), 1.33−1.24 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 136.4, 128.5, 128.1, 128.0, 66.7, 64.4, 64.4, 62.0 (br), 48.7, 27.7 (d, *J* = 138.6 Hz), 16.3, 16.3; HRMS (ESI) calcd for $C_{15}H_{24}NO_6PNa^+$ 368.1233, found 368.1235.

(9*H*-Fluoren-9-yl)methyl 3-(Diethoxyphosphoryl)-2-hydroxypropylcarbamate (29a) and (9*H*-Fluoren-9-yl)methyl 1-(Diethoxyphosphoryl)-3-hydroxypropan-2-ylcarbamate (29b). Following the general procedure, diethyl allylphosphonate[26] (500 mg, 2.81 mmol) was reacted with osmium tetraoxide (25 mg, 98 μmol) and Fmoc reagent **10** (1.49 g, 3.79 mmol). Subsequent flash column chromatography (silica gel, ethyl acetate/petroleum ether 1:1 then ethyl acetate) gave 520 mg (43%) of **29a**, 32 mg (3%) of **29b**, and 420 mg (34%) of a 1:1 mixture of **29a** and **29b** (determined by ^{1}H NMR) as light yellow viscous oils.

29a: FTIR (neat, cm^{-1}) 3327, 3066, 2982, 2931, 2907, 1704, 1535, 1478, 1450, 1393, 1368, 1320, 1243, 1151, 1097, 1022, 962, 885, 834, 815, 759, 740; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (td, *J* = 1.0, 7.5 Hz, 2H), 5.43 (t, *J* = 5.3, 1H, N*H*), 4.39 (d, *J* = 7.0 Hz, 2H), 4.21 (t, *J* = 7.0 Hz, 1H), 4.18−4.07 (m, 5H), 4.06 (br s, 1H, O*H*), 3.50−3.40 (m, 1H), 3.30−3.18 (m, 1H), 1.94 (dd, *J* = 6.2, 17.6 Hz, 2H), 1.36−1.33 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 143.9, 141.3, 127.7, 127.0, 125.0, 119.9, 66.9, 66.0, 62.1, 62.1, 47.2, 47.2, 47.0, 30.8 (d, *J* = 140.0 Hz), 16.4 (t, *J* = 5.7 Hz); HRMS (ESI) calcd for $C_{22}H_{28}NO_6PNa^+$ 456.1546, found 456.1548.

29b: FTIR (neat, cm^{-1}) 3322, 3068, 2982, 2930, 1702, 1537, 1478, 1450, 1394, 1369, 1320, 1223, 1163, 1139, 1020, 965, 910, 837, 759, 738; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 5.77 (d, *J* = 6.9 Hz, 1H), 4.42−4.34 (m, 2H), 4.20 (t, *J* = 6.8 Hz, 1H) 4.14−3.95 (m, 6H), 3.83 (d, *J* = 10.4 Hz, 1H), 3.71 (d, *J* = 10.4 Hz, 1H), 2.25−2.05 (m, 2H), 1.33−1.25 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 143.8, 143.8, 141.3, 127.7, 127.0, 125.0, 119.9, 66.8, 64.3, 62.1, 62.1, 48.7, 47.2, 27.6 (d, *J* = 138.6 Hz), 16.3 (d, *J* = 5.9 Hz); HRMS (ESI) calcd for $C_{22}H_{28}NO_6PNa^+$ 456.1546, found 456.1547.

Diethyl 3-Amino-2-hydroxypropylphosphonate. Method A. A mixture of **28a** (284 mg, 0.82 mmol) and 10% Pd/C (43 mg, 0.4 mmol) in ethanol (10 mL) was stirred under an atmosphere of hydrogen (1 atm) at room temperature for 16 h. The mixture was filtered through Celite and concentrated to yield 174 mg (quant) of the title compound as a colorless oil. NMR data were consistent with those reported in the literature.[41]

Method B. To a solution of **29a** (102 mg, 0.24 mmol) in DMF (5 mL) was added piperidine (1.33 mL). The mixture was left to stir at room temperature for 72 h before being poured into water (20 mL), and washed with diethyl ether

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(6 × 20 mL) before a further 5 mL of water was added. The aqueous phase was allowed to stand and after 1 h was filtered through cotton wool and concentrated under high vacuum to yield 48 mg (97%) of the title compound as a colorless oil, the spectroscopic data of which were identical to those observed for the product obtained by method A above.

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Supporting Information Available: ^{1}H and ^{13}C spectra, HPLC and DSC traces for compounds as well as crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.