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Organocatalytic, Diastereo- and Enantioselective Synthesis of Nonsymmetric *cis*-Stilbene Diamines: A Platform for the Preparation of Single-Enantiomer *cis*-Imidazolines for Protein−Protein Inhibition

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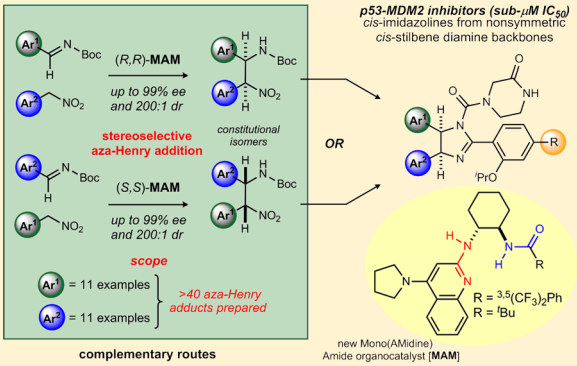
Supporting Information

ABSTRACT: The finding by scientists at Hoffmann-La Roche that *cis*-imidazolines could disrupt the protein−protein interaction between p53 and MDM2, thereby inducing apoptosis in cancer cells, raised considerable interest in this scaffold over the past decade. Initial routes to these small molecules (i.e., Nutlin-3) provided only the racemic form, with enantiomers being enriched by chromatographic separation using high-pressure liquid chromatography (HPLC) and a chiral stationary phase. Reported here is the first application of an enantioselective aza-Henry approach to *nonsymmetric cis*-stilbene diamines and *cis*-imidazolines. Two novel mono(amidine) organocatalysts (MAM) were discovered to provide high levels of enantioselection (>95% ee) across a broad range of substrate combinations. Furthermore, the versatility of the aza-Henry strategy for preparing nonsymmetric *cis*-imidazolines is illustrated by a comparison of the roles of aryl nitromethane and aryl aldimine in the key step, which revealed unique substrate electronic effects providing direction for aza-Henry substrate−catalyst matching. This method was used to prepare highly substituted *cis*-4,5-diaryl imidazolines that project unique aromatic rings, and these were evaluated for MDM2-p53 inhibition in a fluorescence polarization assay. The diversification of access to *cis*-stilbene diamine-derived imidazolines provided by this platform should streamline their further development as chemical tools for disrupting protein−protein interactions.



INTRODUCTION

Initially discovered by high-throughput screening at Hoffman-La Roche (HLR) in 2004, the Nutlins are *cis*-imidazoline small molecules that inhibit the MDM2-p53 protein−protein interaction (PPI).[1] The Nutlins have been widely used to study the consequences of inducing the activity of the tumor suppressor p53 when it is suppressed by MDM2 in cancer cells.[2] To date, HLR has continued to pursue cancer drug development with the series.[3] The most potent member (and enantiomer) in the original Nutlin family, (−)-Nutlin-3 (**1**, Chart 1), or Nutlin-3a, is able to selectively disrupt the binding of MDM2 and p53 by mimicking the side chains of key hydrophobic p53 amino acid residues in the MDM2 binding motif.[1] This orthosteric binding releases p53 from its heterodimer complex with MDM2, leading to cell cycle arrest and apoptosis. Since the initial discovery of the Nutlins, a host of structurally different MDM2-p53 inhibitors that function as p53 mimetics have been reported.[4] These small molecules have received much attention from academia and industry in the past decade, since the function of wild-type (WT) p53 is inactivated by overexpression[5] or amplification[6] of MDM2, even though the p53 gene is either deleted or mutated in approximately 50% of all human cancers.[7−9] Additionally, since MDM2 is overexpressed in many types of cancer and functions as a key negative regulator of wild-type p53, the Nutlins have shown promise as anticancer therapeutics. Hoffmann-La Roche (HLR) was the first to advance a Nutlin analogue (RG7112) into clinical trials for solid and hematological tumors.[10,11] An MDM2 homologue—MDMX or MDM4—is similarly overexpressed in nearly one-fifth of lung cancers, breast cancers, and retinoblastomas[12,13] and was most recently found to be overexpressed in ∼65% of human melanomas.[14] Recent reports have since validated MDMX as an additional and valuable therapeutic target.[15−17] The chemistry discussed hereafter has enabled the facile synthesis of a number of enantioenriched *cis*-imidazolines modeled after (−)-Nutlin that were evaluated for MDM2-p53 inhibition using a previously reported fluorescence polarization competition assay for p53 peptide binding to MDM2.[18]

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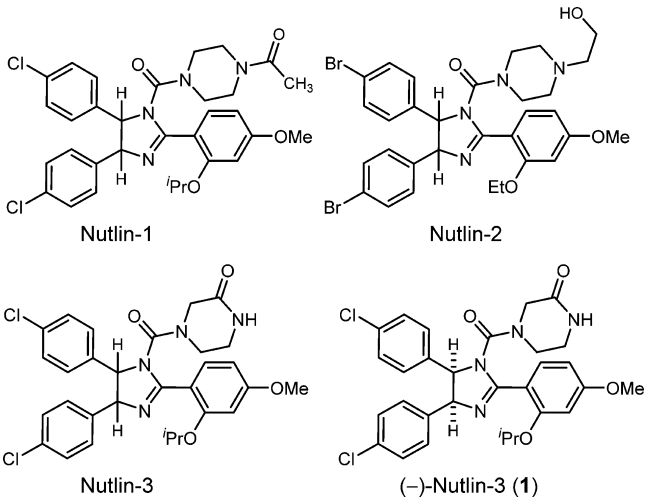
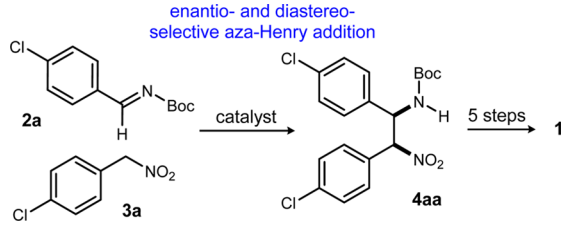
Chart 1. Nutlin Family of p53/MDM2 Inhibitors



Scheme 1. Overview of the Enantioselective Aza-Henry Approach to *cis*-Imidazolines



We recently reported the first asymmetric synthesis of (−)-Nutlin-3 (**1**, Scheme 1).[19,20] This required the development of a diastereo- and enantioselective aza-Henry reaction with an aryl nitromethane (**3a**),[21] a pronucleophile used on only two prior occasions but with low levels of selectivity in this context.[22] The *β*-amino nitroalkane product (**4aa**) was transformed in five linear steps to (−)-Nutlin-3. Alternatives to prepare Nutlin-3 remain limited to (1) the HLR synthesis of (±)-Nutlin-3[12] followed by chromatographic separation of the enantiomers[23,24] and (2) a promising enantioselective acylation of symmetric *cis*-stilbene diamines reported recently by Seidel.[25] Further modifications to our preparation have reduced chromatographic purification of intermediates to one, enabling the preparation of (−)-Nutlin 3 on a multigram scale (>17 g/batch).[20]

The use of a diaza-Cope reaction by HLR provided access to a large number of symmetrical *cis*-stilbene diamines.[26] The diaza-Cope reaction is less amenable to the preparation of *cis*-imidazolines bearing unique aromatic rings at C4 and C5, and yet access to these small molecules may eventually lead to selective and potent inhibitors of protein−protein interactions. Application of the aza-Henry approach to this problem was not without potential complication. While convergence in the imidazoline synthesis would be well-served (top equation in Figure 1), the levels of enantioselectivity can be attenuated by electronic effects. These challenges are often overcome by reagent (catalyst) modification while maintaining a high level of catalyst activity. When successful, this typically provides the most general solution.

Separately, the aza-Henry construction of unsymmetrical *cis*-stilbene diamines offered a strategic question to be examined in conjunction with tactical catalyst development. As outlined in Figure 1, a single enantiomer of imidazoline **6** bearing unique aromatic substituents can be prepared in two ways using this strategy, on the basis of catalyst antipodes and the roles of the nitroalkane and imine (cf. top and bottom equations in Figure 1). The studies reported here detail our work to (1) the identification of a new class of mono(amidine) organocatalyst (MAM) that provides high levels of enantioselection in the aza-Henry addition involving diverse combinations of aryl nitromethane donors and imine acceptors, (2) the implementation and evaluation of parallel pathways to *cis*-imidazolines **6**, and (3) the synthesis and biological evaluation of novel *cis*-imidazoline MDM2 inhibitors rationally designed from (−)-Nutlin-3. As a result, highly enantioenriched *cis*-imidazolines bearing either identical or differentiated aryl substituents at C4 and C5 are now more generally accessible and can be applied to therapeutically valuable small molecules.

RESULTS AND DISCUSSION

We elected to first study the use of an electron-deficient aldimine (**2b**) paired with a relatively unbiased aryl nitromethane (**3a**) using a standard set of conditions (24 h at −20 °C). The Boc-imine of 3-(trifluoromethoxy) benzaldehyde was prepared in good yield using a standard procedure.[27] Two of our most reactive and selective catalysts were evaluated,[19,20] and as in previous studies, we hypothesized that the combination of a Brønsted basic catalyst with a Brønsted acidic aryl nitromethane would form a salt (e.g., **7**·$H^+{}^-$CH(Ar)NO_2) that can, in turn, function as a bifunctional Brønsted acid/Brønsted base in the reaction. First-generation Brønsted basic catalysts (*S*,*S*)-PBAM (**7**) and (*R*,*R*)-[8](MeO)PBAM (**8**) afforded the aza-Henry adduct (*ent*-**4ab** and **4ab**) in −52% and 61% ee, respectively. Although the reactivity and diastereoselectivity were generally comparable to those of past pyrrolidine bis(amidine) (PBAM) catalysts, the enantioselectivity was diminished. In theory, this may be due to

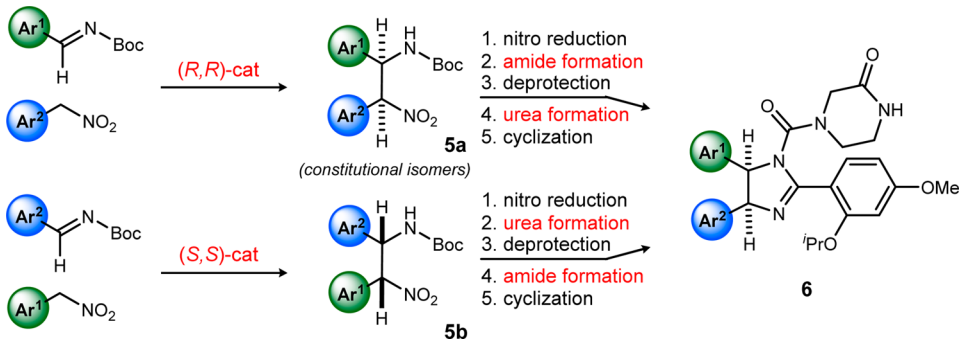


Figure 1. Parallel pathways to the same enantiomer of *cis*-imidazolines derived from nonsymmetric *cis*-stilbene diamines.

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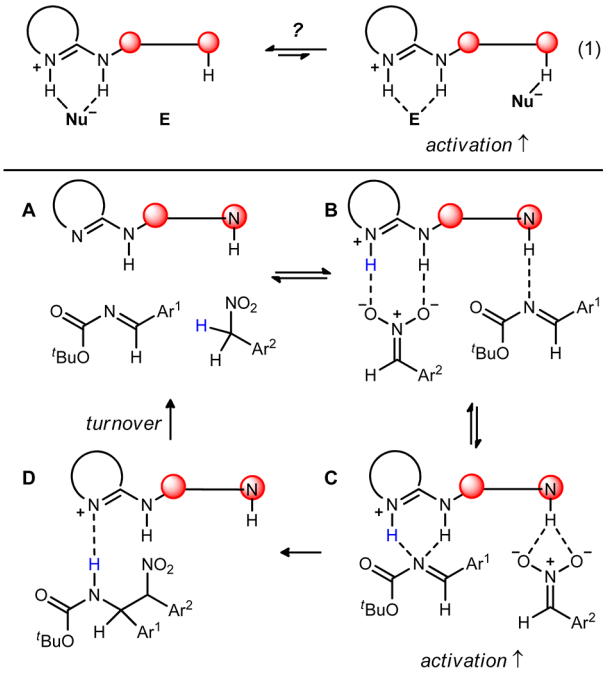


Figure 2. Outline for activation of aryl nitromethane (nucleophile, **Nu**) and imine (electrophile, **E**) by a bifunctional catalyst.

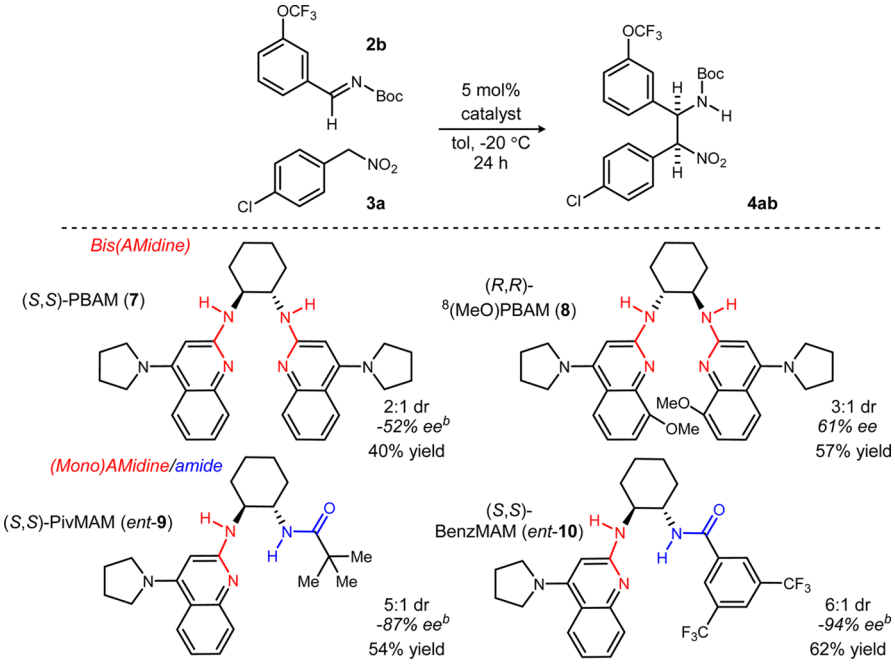
the elevated temperature of the reaction (−20 °C in contrast with −78 °C of past reactions) and/or intolerable steric interactions with the catalyst.

As an alternative to an extensive exploration of the impact of quinoline substituents on enantioselection,[19] an effort that afforded little improvement in this case, we reasoned that the insensitivity of aryl nitromethane additions to added strong acid (e.g., TfOH) might offer the opportunity to explore combinations of amidine and *amide* functionalities projected from the diamine backbone. The conceptual framework for this modification was also rather different by comparison to previous bis(amidine) modifications. Beginning from its free base form, the catalyst would be expected to form a salt with the aryl nitromethane at the amidine (eq 1, Figure 2), but the greatest level of *dual activation* is expected to involve electrophile binding to the polar ionic hydrogen bond concomitant with nitronate counterion binding to the (amide) polar covalent hydrogen bond. Figure 2 illustrates this conceptually, progressing from substrates and catalyst in **A** to catalyst-bound product in **D**. The initial activation event is catalyst deprotonation of the nitroalkane, but in this arrangement (**B**), the nitronate reactivity may be attenuated by a strong ion pair and imine activation by an amide N−H may be relatively weak. Exchange of the hydrogen bond acceptors (Figure 2, **C**), however, leads to a more reactive nitronate due to charge separation and increased activation of the imine. An arrangement such as this might maximize the benefit of drawing the counterion away from the electrophile binding site while providing discrete directional control. Elements of this approach overlap with developments in the field of anion binding catalysis, particularly when the catalyst involves two polar covalent hydrogen bond donors.[28] Other catalyst systems use not only a Brønsted basic catalyst but also a Brønsted base additive (e.g., Et_3N).[29]

The Mono(AMidine) (MAM) catalysts in Scheme 2 were prepared in five steps using an approach that mirrored our preparation of unsymmetrical bis(amidine) ligands in prior studies.[30] Under reaction conditions identical with those used for **7** and **8**, (*S*,*S*)-PivMAM (*ent*-**9**) afforded the addition adduct in an improved −87% ee and 5:1 dr (54% yield), while (*S*,*S*)-BenzMAM (*ent*-**10**) afforded the adduct in −94% ee and 6:1 dr (62% yield).

A similar comparative analysis was made using aldimine **2a** in combination with a range of electronically diverse aryl nitromethanes **3x**, yielding adducts **4xa** (Table 1). The aryl

Scheme 2. Catalyzed Aza-Henry Addition of *p*-Chloro Aryl Nitromethane to Aryl Boc-imines[a]



[a]Conditions: 1.1 equiv of nitroalkane in toluene (0.1 M). The diastereomeric ratio (dr) and enantiomeric excess (ee) were determined by chiral HPLC. [b]Using this enantiomeric diamine backbone, *ent*-**4ab** is formed, as expected.

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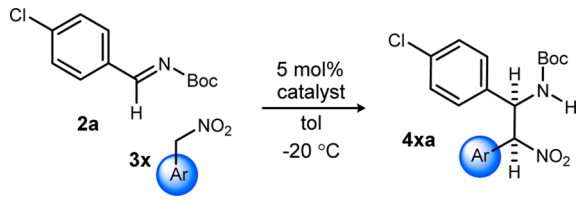
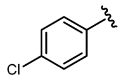
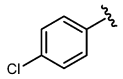
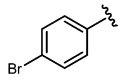
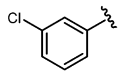
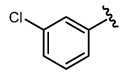
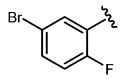
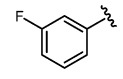
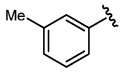
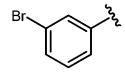
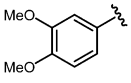
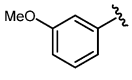
Table 1. Aza-Henry Additions of Aryl Nitromethanes to *p*-Chlorophenyl Boc-imine[a]



entry	aryl	x	catalyst[b]	ee (%)[c]	dr	yield (%)[d]
1		**a**	**10**	96	53:1	72
2		**a**	**8**[e]	91	13:1	97
3		**b**	**10**	94	>200:1	75
4		**c**	**9**	93	>200:1	81
5		**c**	**10**	89	>50:1	74
6		**d**	**8**[e]	92	3:1	65
7		**e**	**10**	92	35:1	54
8		**f**	**9**	93	21:1	65
9		**g**	**9**	91	24:1	57
10		**h**	**10**	76	18:1	76
11		**i**	**9**	95	23:1	87

[a]All reactions employed 1.1 equiv of nitroalkane in toluene (0.1 M) at −20 °C with 24−36 h reaction time. [b]Catalyst prepared from (*R*,*R*)-cyclohexanediamine or (*S*,*S*)-cyclohexanediamine (denoted *ent*). [c]Diastereomeric ratio (dr) and enantiomeric excess (ee) determined by chiral HPLC following vacuum filtration or silica column chromatogaphy (see the Supporting Information). [d]Isolated yields. [e]Reaction temperature: −78 °C.

nitromethanes were prepared from their corresponding and commercially available benzaldehyde derivatives, and all were successful feedstock for the aza-Henry reaction using representative conditions (5 mol % catalyst loading, −20 °C, toluene; Table 1). We first examined MAM catalyst **10** efficacy with 4-chlorophenyl nitromethane and 4-chlorophenyl Boc-imine (Table 1, entry 1), to compare the new catalyst directly to **8**; the resulting aza-Henry adduct **4aa** can lead to (−)-Nutlin-3 (**1**). BenzMAM (**10**) provided the adduct in 96% ee and 53:1 dr at −20 °C, in comparison to 91% ee and 13:1 dr at −78 °C when using **8** (Table 1, entries 1 and 2, respectively). High levels of selectivity continued during the evaluation of a range of electronically deficient (Table 1, entries 3−7) and electronically neutral (Table 1, entry 8) aryl nitromethanes, providing the aza-Henry adducts with excellent enantioselection (92−94% ee). 2-Fluoro-5-bromoaryl nitromethane (Table 1, entry 6) provided an exception to the trend, however, as the bis(amidine) free base of [8](MeO)PBAM (**8**) provided the aza-Henry adduct in the highest ee in comparison to PivMAM (**9**) and BenzMAM (**10**). The most electron rich case, 3,4-dimethoxyaryl nitromethane (Table 1, entry 10), converted with lower enantioselectivity and reaction rate, perhaps due to its diminished Brønsted acidity. Dialing back the electronic effects to (mono)methoxyaryl nitromethane **3i** (Table 1, entry 11), however, reestablishes good levels of stereocontrol (95% ee and >20:1 dr). Interestingly, PivMAM (**9**) enhanced enantioselectivity for *meta*-substituted arenes (Table 1, entries 4, 5, 8, and 9). For example, the adduct of 3-chloroaryl nitroalkane (Table 1, entry 5) was formed in 89% ee with BenzMAM (**10**), in comparison to 93% ee when PivMAM (**9**) (Table 1, entry 4) was employed.

The substrate scope for aryl Boc-imines (**2x**) was investigated next (Table 2). The synthesis of aryl Boc-aldimines from α-amido sulfones[31] is well established, and a wide array of aldimine substrates can be prepared.[32] A range of aryl Boc-imines was prepared for analysis, leading to β-amino nitroalkanes (**4ax**) in very high enantio- and diastereoselectivity (up to 99% ee and >200:1 dr; Table 2). Haloaryl (Table 2, entries 1−5, 7, 8, and 10), electron-deficient imines (Table 2, entries 7−10), and electron-neutral (Table 2, entry 6) and electron-rich imines (Table 2, entries 11 and 12) were transformed to β-amino nitroalkanes in uniformly good to excellent dr/ee and isolated yield.

The behaviors outlined in Table 2 suggest that electronic variations to the aldimine affected stereoselection to a lesser degree than that observed with aryl nitromethane donors. This was more carefully investigated by examining each pairing of aldimine (**2**) and aryl nitromethane (**3**) substrates to explore and better gauge reactivity trends (Table 3). The arenes selected in Table 3 contain a wide range of functionalities with the purpose of maximizing diversity to a reasonable extent. Using a standard set of reaction conditions, aryl Boc-imines **2** and aryl nitromethanes **3** were combined. Aryl Boc-imines **2j,k** and their nitroalkane counterparts **3d,h** are notable challenges, as they represent highly electron poor and rich substrates, respectively, in the aza-Henry reaction. As was expected, the ee and dr values observed for neutral and moderately electron deficient aryl nitromethanes are uniformly high (Table 3, entries 1−4, **3a,b,f,c**). The comparison of *ent*-**4fh** with **4cg**, however, is an exception to this trend. Under identical reaction conditions with BenzMAM (**10**), 3-chloro nitroalkane (**3c**) behaves remarkably better than its imine counterpart (**2h**) on reaction with the 3-methyl arene partner (99% ee, >20:1 dr by ^{1}H NMR and 85% ee, 8:1 dr, respectively). A few generalizations can be made from the data generated as well. aza-Henry adducts where the electron-poor 2-fluoro-5-bromo arene is employed as the nitroalkane (**3d**) consistently resulted in low dr—presumably due to the increased α-hydrogen acidity in the product (up to 5:1 dr, **4dg**). Fortunately, the 2-fluoro-5-bromoaryl imine (**2j**) delivers adducts with improved diastereoselectivity and enantioselectivity in specific cases (**4fj**, 85% ee/40:1 dr, in comparison to **4dg**, 68% ee/5:1 dr). In the case of the 3,4-dimethoxyaryl substrate, employing this electron-rich arene as the nitroalkane (**3h**) proved unsatisfactory (up to 78% ee/20:1 dr, **4hg**) in almost every case. Gratifyingly, significantly higher ee and dr was

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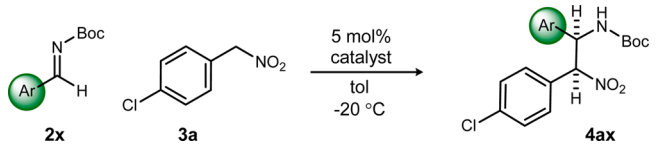
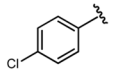
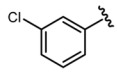
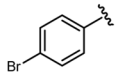
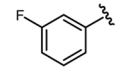
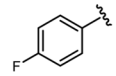
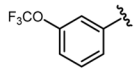
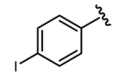
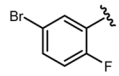
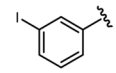
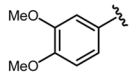
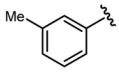
Table 2. Catalyzed Aza-Henry Addition of *p*-Chlorophenyl Nitromethane to Aryl Boc-imines: Scope using Catalysts 9 and 10[a,b]



entry	Ar	x	catalyst	ee (%)[c]	dr	yield (%)[d]	entry	Ar	x	catalyst	ee (%)[c]	dr	yield (%)[d]
1		a	**10**	96	53:1	72	7		h	**10**	97	9:1	71
2		c	**10**	93	>200:1	88	8		i	**10**	88	60:1	98
3		d	**10**	94	18:1	82	9		b	*ent*-**10**	-94	6:1	62
4		e	*ent*-**10**	-99	>200:1	77	10		j	**10**	84	35:1	53
5		f	*ent*-**9**	-99	>200:1	80	11		k	**10**	92	25:1	54
6		g	**10**	88	50:1	98							

[a]All reactions employed 1.1 equiv of nitroalkane in toluene (0.1 M) at −20 °C with 24−36 h reaction time. [b]Catalyst prepared from (*R*,*R*)-cyclohexanediamine or (*S*,*S*)-cyclohexanediamine (denoted *ent*). [c]Diastereomeric ratio (dr) and enantiomeric excess (ee) were determined by chiral HPLC following vacuum filtration or silica column chromatography (see the Supporting Information). [d]Isolated yields.

observed when this arene was employed as the *imine* (up to 93% ee/56:1 dr, **2k**). To further illustrate the value of this observation, entries **4hh** and **4ck** should be compared. In cases where the adducts were generated in suboptimal ee and dr, switching catalyst antipode and arene pairings proved beneficial in almost all cases, using the tactic outlined in Figure 1. The 36 compounds outlined in Table 3 represent a wide range of possibilities when targeting symmetrical or unsymmetrical *cis*-stilbene diamines. These experiments further demonstrate synthetic flexibility using a pair of mono(amidine) (MAM) amide catalysts (**9** and **10**) to access highly diastereo- and enantiomerically enriched aza-Henry adducts.

Table 3 gives adducts that contain either an underlying *symmetric* *cis*-stilbene diamine backbone (results along the diagonal from top left to bottom right), or a *nonsymmetric* *cis*-stilbene diamine backbone. The latter are constitutional isomers paired on either side of the diagonal. This relationship was considered when converting these intermediates to their derived *cis*-imidazolines (cf. **5a**,**b** → **6**, Figure 1). If the two constitutional isomers in Figure 1 are transformed into their derived *cis*-imidazolines using *identical* procedures and reagents, the final imidazolines would be *enantiomeric* at their C4 and C5 carbon centers (although overall constitutionally isomeric *cis*-imidazolines). However, if the constitutional isomers are formed using *enantiomeric* catalysts, and the order of steps 2 (amide formation) and 4 (urea formation) is reversed, then the same enantiomer of the *cis*-imidazoline will be formed, as outlined in Figure 1. Additionally, the benefits of this method allow for direct and predictable functionalization at a given nitrogen due to their protected nature. Previous attempts at monoderivatization from symmetric (*meso*) or nonsymmetrical stilbene diamines are notorious for generating a mixture of mono- and disubstituted products.[33] This strategy was reduced to practice using the example in Scheme 3.

In the first case, *p*-chloro aldimine **2a** was converted to **4ba** using (*R*,*R*)-BenzMAM (**10**) and *p*-bromoaryl nitromethane **3b**. This adduct was then converted to *cis*-imidazoline **11** using the five steps outlined in Scheme 3. In the second case, the identities of the aldimine and aryl nitromethane were reversed (to **2c** and **3a**, respectively), and (*S*,*S*)-BenzMAM (*ent*-**10**) was deployed to promote a similarly highly diastereo- and enantioselective addition. The adduct **4ac** was converted to the corresponding *cis*-imidazoline, but the amine produced by nitro reduction was subjected to urea—as opposed to amide—formation. Deprotection, amide formation, and dehydrative cyclization then furnished the identical *cis*-imidazoline **11**. Hence, by using an enantiomeric catalyst and reversing the order of amide and urea formation in the finishing sequence, the same enantiomer of *cis*-imidazoline was formed by straightforward permutation of aldimine and aryl nitromethane substrates.

Each case illustrated in Scheme 3 works equally well such that less obvious factors might lead one to choose one route over the other. However, we have identified situations where only one of the two options may be optimal, or even available. For example, we targeted the *cis*-imidazoline **15** (Scheme 4) bearing *p*-chloroaryl and *m*-(trifluoromethoxy)aryl substituents. Attempts to prepare the aryl nitromethane **3i** bearing a *m*-trifluoromethoxy substituent were unsuccessful. Although aldoximine **13** was isolated in 53% yield, a range of oxidants uniformly failed to yield the nitroalkane, presumably due to the electron-withdrawing nature of the substituent (Scheme 4). Conversely, α-amido sulfone formation and its conversion to the corresponding aldimine **2b** was successful. Since *p*-chloroaryl

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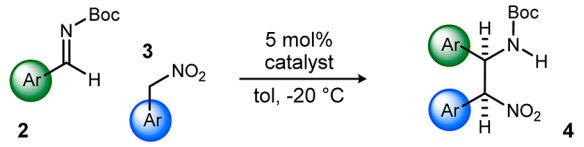
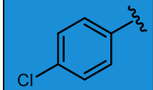
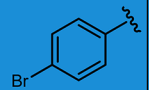
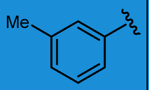
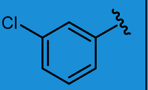
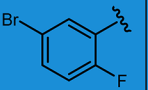
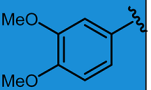
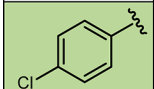
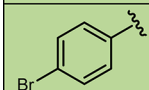
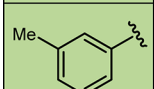
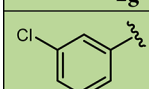
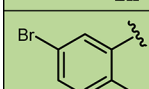
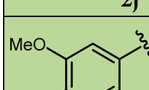
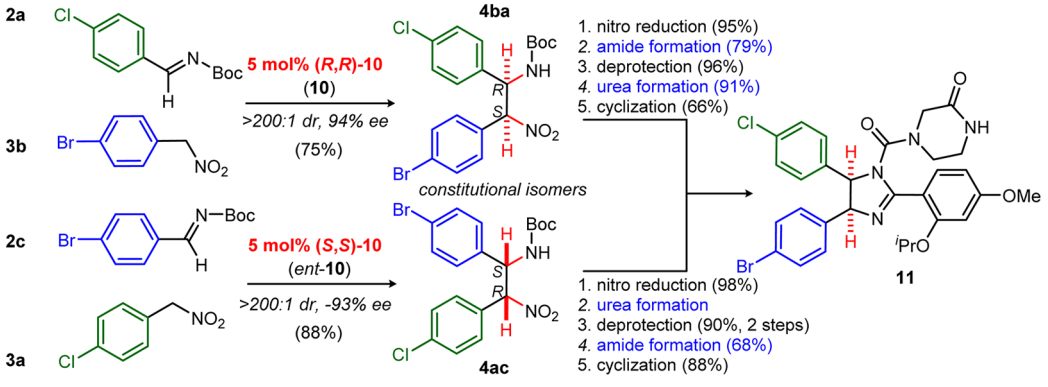
Table 3. Comparative Analysis of Aldimine–Aryl Nitromethane Reactant Pairs in the Catalyzed Aza-Henry Reaction[a,b]



Aryl nitromethane / Aryl Boc-aldimine	 3a	 3b	 3f	 3c	 3d	 3h
 2a	**10** **96% ee** 53:1 dr 72% yield	**10** **94% ee** >200:1 dr 75% yield	**9** **93% ee** >200:1 dr 65% yield	**9** **93% ee** >200:1 dr 81% yield	**8** **92% ee** 3:1 dr 65% yield	**10** **76% ee** 37:1 dr 76% yield
 2c	**10** **93% ee** >200:1 dr 88% yield	**10** **84% ee** 9:1 dr 75% yield	**10** **87% ee** 7:1 dr 92% yield	**10** **95% ee** 5:1 dr 80% yield	**10** **93% ee** 3:1 dr 80% yield	**10** **73% ee** 31:1 dr 51% yield
 2g	**10** **88% ee** 50:1 dr 98% yield	**10** **85% ee** 68:1 dr 88% yield	**10** **86% ee** 50:1 dr 95% yield	**10** **99% ee** >20:1 dr 97% yield	**9** **68% ee** 5:1 dr 91% yield	**10** **78% ee** 20:1 dr 70% yield
 2h	**10** **97% ee** 9:1 dr 71% yield	**10** **90% ee** 70:1 dr 78% yield	*ent*-**10** **-85% ee** 8:1 dr 74% yield	**9** **93% ee** 30:1 dr 90% yield	**10** **76% ee** 1:1 dr 66% yield	**10** **70% ee** 23:1 dr 68% yield
 2j	**10** **84% ee** 25:1 dr 53% yield	**10** **86% ee** 60:1 dr 87% yield	**10** **85% ee** 40:1 dr 42% yield	**9** **88% ee** 8:1 dr 90% yield	**10** **79% ee** 2:1 dr 56% yield	**10** **56% ee** 4:1 dr 70% yield
 2k	**10** **92% ee** 25:1 dr 54% yield	**10** **85% ee** 9:1 dr 60% yield	**10** **70% ee** 10:1 dr 70% yield	**10** **93% ee** 56:1 dr 64% yield	**9** **42% ee** 3:1 dr 67% yield	**10** **50% ee** 5:1 dr 72% yield

[a]All reactions employed 1.1 equiv of nitroalkane in toluene (0.1 M) at −20 °C with 24–36 h reaction time. [b]Catalyst prepared from (*R*,*R*)-cyclohexanediamine or (*S*,*S*)-cyclohexanediamine (denoted *ent*). Diastereomeric ratio (dr) and enantiomeric excess (ee) were determined by chiral HPLC following vacuum filtration or silica column chromatography (see the Supporting Information). All yields presented are isolated yields.

Scheme 3. Adaptable Synthesis Arriving at the Same (4*S*,5*R*)-Nutlin Derivative but Originating from Constitutional Isomeric Aza-Henry Adducts



nitromethane **3a** is readily available, this combination could be transformed into the desired *cis*-imidazoline **15** (Scheme 4). By employment of (*S*,*S*)-BenzMAM (*ent*-**10**), the desired *β*-amino nitroalkane enantiomer *ent*-**4ab** was generated in −94% ee and 6:1 dr (Scheme 5).[34] Nitro group reduction with $CoCl_2$ and $NaBH_4$ produced the free amine. Subsequent isocyanate

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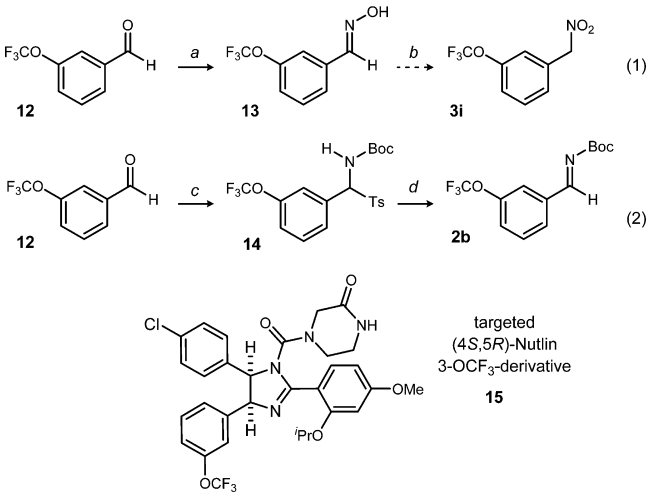
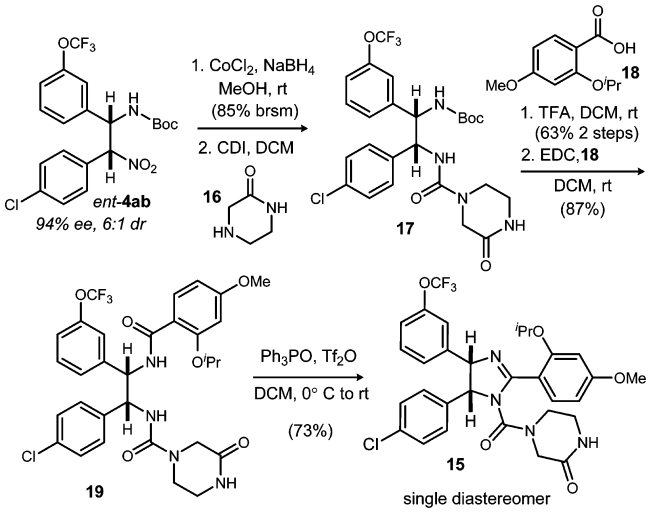
Scheme 4. Comparative Analysis: Unsuccessful and Successful Preparations of 3-Trifluoromethoxy Aryl Nitromethane and *N*-Boc Imine, Respectively



[a]Conditions: $H_2NOH{\cdot}HCl$, pyr, EtOH, room temperature, 53%. [b]Conditions: MCPBA, DCM. [c]Conditions: $^{p}TolSO_2H$, $BocNH_2$, Et_2O, room temperature, 27%. [d]Conditions: Cs_2CO_3, Na_2SO_4, THF, room temperature, 98%.

Scheme 5. Strategy To Access the Desired (4*S*,5*R*)-Nutlin Derivative, Calling for the (1*S*,2*R*)-Aza-Henry Adduct To Be Employed



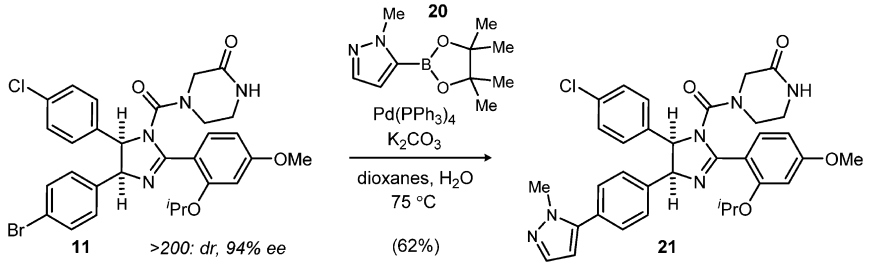
formation using carbonyl diimidazole and its reaction with oxopiperazine **16** led to urea **17**. Straightforward Boc deprotection with TFA afforded the free amine, which underwent an acylation with acid **18** using EDC coupling conditions to generate benzamide urea **19**. Triphenylphosphine oxide and triflic acid generated a phosphonium anhydride in situ (Hendrickson's reagent),[35] promoting regioselective dehydrative cyclization to provide the imidazoline **15** as a single diastereomer in 94% ee.

This ability to generate nonsymmetrical *cis*-imidazolines from a host of halogenated arenes could provide a platform for further derivatization using common metal-catalyzed transformations. For example, we postulated that the bromoaryl derivative **11** (Scheme 6) might be functionalized selectively, as oxidative addition should be accelerated in comparison to the neighboring chloroarene. Traditional palladium cross couplings under various conditions to generate new sp^2–sp^2 C–C bonds or sp^2 carbon–heteroatom bonds should be substrate compatible.[36] We decided to employ traditional Suzuki cross-coupling conditions with Pd(0)–tetrakis(triphenylphosphine) and an aryl boronic ester (**20**) to test this hypothesis (Scheme 6).[37] After the mixtue was stirred for 24 h at 75 °C, formation of the desired pyrazole adduct **21** was confirmed by its isolation in 62% yield. The aryl chloride subunit was clearly intact (confirmed by HRMS), and oxidation to imidazole was not observed. This example establishes the feasibility of late-stage, site-selective functionalization from differentiated haloarenes leading to novel heterocyclic derivatives within this family.

Medicinal Chemistry and SAR. The synthetic studies detailed above were driven in part by a parallel program in the detailed exploration of *cis*-imidazolines as inhibitors of protein–protein interactions. We investigated the binding sites of MDM2 reported from its cocrystal structure complexed with (−)-Nutlin-3 (PDB 4HG7) to improve the MDM2-p53 (WT) binding inhibitory activity. These compounds are uniformly more potent in their binding to MDM2 as the 4*S*,5*R*-configured *cis*-imidazolines; therefore, their preparation in high ee was considered paramount. As a part of the effort not only to explore MDM2 affinity but also to access structural novelty, our focus was on three hydrophobic side chains that exist within the p53 binding pocket (Phe19, Trp23, and Leu26) and structural modifications were made to both *cis*-arenes (Ar_1 and Ar_2, Table 4) employing the optimal synthetic pathway (cf. top and bottom equations in Figure 1). We also addressed optimization of *para* substituents of ring A by replacing the electron-donating group (methoxy) with electron-withdrawing groups, including halogens and a nitrile, to explore electrostatic effects. A total of 12 *cis*-imidazoline analogues were designed and prepared to probe structure–activity relationships (SAR; Table 4).

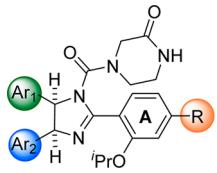
According to recent literature,[38,39] affinity for MDM2 can be improved by varying the aromatic substituents on the phenyl ring that occupy the Leu26 pocket and by enhancing a π–π stacking

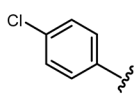
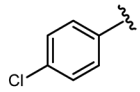
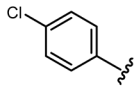
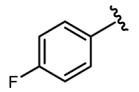
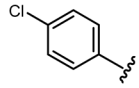
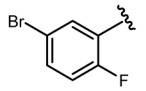
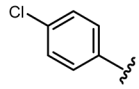
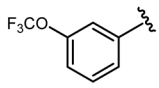
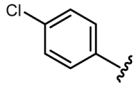
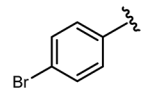
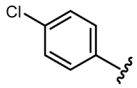
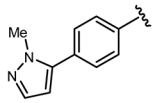
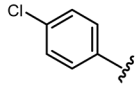
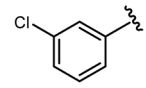
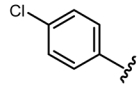
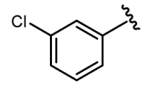
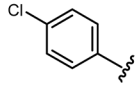
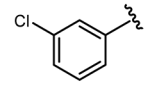
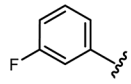
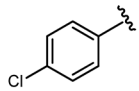
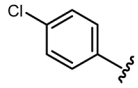
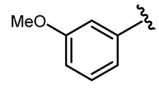
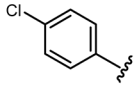
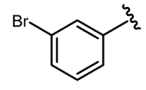
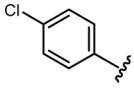
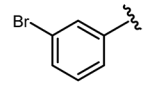
Scheme 6. Nonsymmetrical Halogenated Nutlin Analogues Allowing for Regioselective Cross-Coupling Reaction



dx.doi.org/10.1021/jo501003r | J. Org. Chem. 2014, 79, 6913–6938

Table 4. MDM2 Inhibition Activity of *cis*-Imidazoline Derivatives



Entry	SJNUM	ID/ (compound)	Ar_1	Ar_2	R	MDM2 FP IC_{50} (μM) [95% CI[a]]
1	(-)-Nutlin-3	1			OCH_3	0.3 [0.3, 0.4]
2	SJ000773209-5	22			OCH_3	0.7 [0.6, 0.8]
3	SJ000773212-2	23			OCH_3	1.6 [1.1, 2.2]
4	SJ000792939-1	15			OCH_3	2.1 [1.5, 2.9]
5	SJ000773211-3	11			OCH_3	0.5 [0.4, 0.6]
6	SJ000803773-1	21			OCH_3	1.0 [0.6, 1.6]
7	SJ000801055-1	28			Cl	0.7 [0.5, 0.9]
8	SJ000801056-1	24			Br	0.9 [0.7, 1.1]
9	SJ000801057-1	25			CN	0.7 [0.5, 0.9]
10	SJ000558306-5	26			OCH_3	1.0 [0.7, 1.4]
11	SJ000558298-7	29			OCH_3	3.3 [1.4, 8.0]
12	SJ000804143-1	27			OCH_3	1.4 [1.1, 1.9]
13	SJ000821716-1	30			CN	0.7 [0.4 to 1.2]

interaction with the His96 residue on MDM2. In an attempt to occupy the Leu26 pocket, several analogues were designed and synthesized by introducing different halogens and other functional groups at either the *para* or *meta* position on the Ar_2 ring. From the outset, it was clear that any substituents larger than Cl at the *meta* position slightly decreased the affinity (**15**, **23**, and **27**). However, the only slightly larger *p*-Br-substituted compound **11** showed potency equivalent with that of **1**. An exception to this trend was the *N*-methylpyrazole **21**, which was surprisingly well tolerated given its size. In order to explore possible secondary interactions with a loop of MDM2 crossing the binding site, substituents (halogen, nitrile) were introduced on the *para* position of the A ring to replace the methoxy group (R group in Table 4); no dramatic improvement was observed, but these analogues still exhibited submicromolar affinities (**24**, **25**, **28**, and **30**).

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CONCLUSION

Generalization of the first highly selective aza-Henry addition reaction between aryl nitromethanes and aryl Boc-imines has been achieved, leading to orthogonally protected, *cis*-stilbene diamine precursors (up to 99% ee as a single diastereomer). The unprecedented selectivity reported for this transformation lies in the discovery of novel mono(amidine) (MAM) bifunctional catalysts that not only afford aza-Henry adducts in high levels of stereocontrol but can achieve this at noncryogenic temperature (−20 °C). The goal to generalize these additions to include an array of aryl nitromethanes and aryl Boc-imine substrates was achieved. In cases where a nitroalkane/imine pair led to an addition product with low stereoselection, a strategy-level solution was postulated and reduced to practice, involving a straightforward exchange of nitroalkane/imine identity. By utilization of this methodology, a number of biologically active *cis*-imidazoline small molecules reminiscent of the Nutlin family were accessed from enantioenriched aza-Henry adducts in subsequent transformations. The realization that constitutionally isomeric products could be transformed to the same *cis*-imidazoline small molecule (see Scheme 3) further improved access, and this was demonstrated in cases where exchange of electrophile and pronucleophile identity in the aza-Henry step led to a combination with markedly higher stereoselection. Operationally, synthetic points of variation for this strategy when pursuing a target synthesis are (1) the sense of the chiral catalyst employed (*R,R* vs *S,S* diamine) and (2) the sequence of amine coupling reactions—both of which are easily manipulated. More broadly, the ability to access enantioenriched, protected *cis*-stilbene diamines now allows for direct and predictable functionalization at each nitrogen—an unsolved problem associated with approaches based on *meso*-stilbene diamine intermediates. Furthermore, unsymmetrical Nutlin-3 analogues bearing differentiated haloarenes can be selectively functionalized via late-stage cross-coupling reactions, allowing for more direct access to analogues for screening aimed at PPI drug discovery efforts.

Among the designed Nutlin analogues, four new compounds (SJ000773209-5, SJ000773211-3, SJ000801055-1, and SJ000801057-1) showed levels of MDM2-p53 inhibition activity similar to that of (−)-Nutlin-3 (**1**), measured by a fluorescence-polarization assay. These findings provide a robust framework together with a streamlined, enantioselective synthesis in which to develop an in vivo candidate for MDM2-p53 inhibition, as well as pursue *cis*-imidazoline-class MDMX-p53 inhibitors.

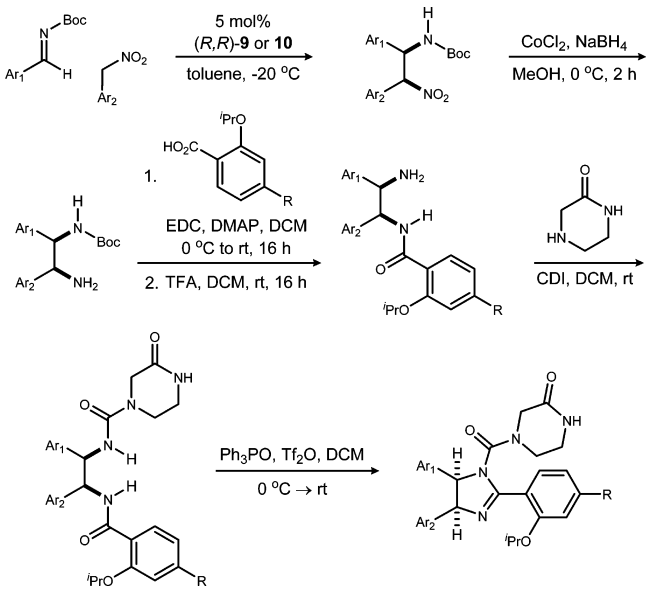
EXPERIMENTAL SECTION

All reagents and solvents were commercial grade and were purified prior to use when necessary. Toluene (tol) and dichloromethane (CH_2Cl_2) were dried by passage through a column of activated alumina as described by Grubbs.[40] Aldimines not included were prepared as reported in the literature.[41] Thin-layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates, and flash chromatography utilized 230−400 mesh silica gel. UV light and/or the use of potassium iodoplatinate and potassium permanganate solutions were used to visualize products. IRA-900-NO_2 resin was prepared by washing IRA900-Cl resin with aqueous $NaNO_2$ until the wash no longer tested positive for chloride by an $AgNO_3$ test.

Nuclear magnetic resonance spectra (NMR) were acquired at 400, 500, or 600 MHz, and chemical shifts were measured relative to residual solvent peaks as an internal standard set to δ 7.26 and 77.0 ($CDCl_3$). IR spectra were recorded as neat films on a NaCl plate (transmission) and are reported in wavenumbers (cm^{-1}). Mass spectra were recorded on a high-resolution spectrometer by use of the ionization method noted (APCI or ESI) and used TOF mass analysis. Melting points were measured and are not corrected. Optical rotations were measured using a polarimeter. Absolute and relative configuration of the aza-Henry adducts (**4aa**−**4hk**) were assigned by analogy to previously synthesized adducts, for which a crystal structure was obtained.[19]

Scheme 7 gives the general scheme to access *cis*-imidazoline/Nutlin derivatives.

Scheme 7. General Scheme To Access *cis*-Imidazoline/Nutlin Derivatives[a]



Protein Expression and Purification. GST-MDM2 (1-188) was cloned, expressed, and purified as described previously.[18]

Fluorescence Polarization (FP) Assay. The fluorescence polarization (FP) assay was performed with 1 μM GST-MDM2 (1-188) in 10 mM Tris (pH 8.0), 42.5 mM NaCl, and 0.0125% Tween-20 assay buffer. For testing, a dilution series of small molecules (spanning 10 mM to 0.5 μM in DMSO, in 3-fold steps) was added by direct addition to protein using pin transfer (100ss pins, V&P Scientific), giving a test dilution series spanning 65 μM to 3.2 nM with a final concentration of 0.65% DMSO. The increasing concentrations of small molecules dissolved in DMSO were preincubated with protein for 30 min in black 384-well plates and then treated with Texas Red labeled wild-type p53 peptide (15 nM, amino acids 15−29: GSGSSQETFSDLWKLLPEN) and incubated for an additional 45 min. After incubation the FP signal was measured on a multilabel plate reader fitted with a 555 nm excitation filter, 632 nm static and polarized filters, and a Texas Red FP dichroic mirror. Unlabeled WT-p53 peptide was used as a positive control, and DMSO was used as a negative control.

Technical triplicate data were normalized to the positive (100% inhibition) and negative (0% inhibition) controls on the corresponding row of the 384-well plate (percentage inhibition = 100 × ((sample result) − (negative control))/((positive control mean) − (negative control))). Two to seven independent experiments of normalized data were combined into a data set and then fit using a nonlinear regression in GraphPad Prism with the formula log (inhibitor) vs response − variable slope (four parameters). Additionally the residuals of the curve fit were plotted to determine the fit of the theoretical curve. IC50 and 95% confidence intervals (CI) were determined from these graphs.

(*E*)-*tert*-Butyl 3-(Trifluoromethoxy)benzylidenecarbamate (2b). In a flame-dried flask equipped with a magnetic stir bar were placed Na_2SO_4 (384 mg, 2.69 mmol), Cs_2CO_3 (293 mg, 8.98 μmol), and *tert*-butyl (tosyl(3-(trifluoromethoxy)phenyl)methyl)carbamate (200 mg, 449 μmol). The solids were suspended in THF (2.2 mL) at room temperature. The mixture was monitored by ^{1}H NMR and vigorously stirred for 75 min. The solution was filtered through a plug of Celite with excess dichloromethane and concentrated to a white oil

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which was 90% pure by ^{1}H NMR (128 mg, about 98%). This material was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.80 (d, J = 6.8 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.40 (m, 1H), 1.58 (s, 9H). The extent to which this compound was prone to decomposition precluded acquisition of the remaining analytical data.

(*E*)-*tert*-Butyl 4-Iodobenzylidenecarbamate (2e). In a flame-dried round-bottom flask equipped with a magnetic stir bar were placed $MgSO_4$ (888 mg, 7.4 mmol), Cs_2CO_3 (240 mg, 0.74 mmol), and then *tert*-butyl ((4-iodophenyl)(tosyl)methyl)carbamate (175 mg, 0.37 mmol). The solids were suspended in THF (2.8 mL), and the mixture was stirred for 4.5 h at room temperature and then filtered through a bed of Celite on an oven-dried frit and washed with dichloromethane. Concentration of the filtrate revealed a white oil (106 mg, 87%) that solidified after sitting in a freezer at −20 °C overnight to give a white waxy solid: mp 46 °C; R_f = 0.40 (20% EtOAc/hexanes); IR (film) 2978, 2931, 1715, 1629, 1584, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.6, 162.3, 138.2, 133.4, 131.2, 101.2, 82.5, 27.8; HRMS (ESI) exact mass calcd for $C_{12}H_{14}INNaO_2$ $[M + Na]^+$ 353.9961, found 353.9955.

(*E*)-*tert*-Butyl 3-Iodobenzylidenecarbamate (2f). In a flame-dried flask equipped with a magnetic stir bar were placed Cs_2CO_3 (488 mg, 1.50 mmol), Na_2SO_4 (850 mg, 5.99 mmol), and then *tert*-butyl ((3-iodophenyl)(tosyl)methyl)carbamate (355 mg, 749 μmol) and toluene (7.7 mL). The mixture was vigorously stirred for 2.5 h and monitored by ^{1}H NMR. The reaction mixture was filtered through a plug of Celite with excess dichloromethane and concentrated to a clear oil containing analytically pure aldimine: IR (film) 2978, 2930, 1719, 1631, 1367, 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.31 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.8, 162.1, 142.1, 138.2, 136.0, 130.5, 129.7, 94.5, 82.7, 27.9 (3C); HRMS (ESI) exact mass calcd for $C_{12}H_{14}INNaO_2$ $[M + Na]^+$ 353.9967, found 353.9961.

(*E*)-*tert*-Butyl 5-Bromo-2-fluorobenzylidenecarbamate (2j). In a flame-dried flask equipped with a magnetic stir bar were placed sodium sulfate (7.95 g, 56 mmol), potassium carbonate (6.77 g, 49 mmol), and *tert*-butyl ((5-bromo-2-fluorophenyl)(tosyl)methyl)carbamate (3.11 g, 7.0 mmol). The solids were suspended in THF (70 mL), and the mixture was refluxed for 7 h, cooled, filtered through an oven-dried frit, and concentrated in vacuo to reveal a white oil (1.881 g, 89%) which solidified to a white waxy solid after being stored at −20 °C: mp 39−40 °C; R_f = 0.47 (30% EtOAc/hexanes); IR (film) 2982, 2930, 1728, 1621, 1584 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.27 (d, J = 6.0 Hz, 1H), 7.63 (m, 1H), 7.05 (dd, J = 9.2, 9.2 Hz, 1H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 162.7 (d, $^1J_{CF}$ = 256 Hz), 161.1 (d, $^4J_{CF}$ = 5 Hz), 137.7 (d, $^4J_{CF}$ = 8 Hz), 130.8 (d, $^3J_{CF}$ = 15 Hz), 123.6 (d, $^3J_{CF}$ = 10 Hz), 117.8 (d, $^2J_{CF}$ = 22 Hz), 117.5 (d, $^4J_{CF}$ = 3 Hz), 82.9, 27.8; HRMS (ESI) exact mass calcd for $C_{12}H_{14}BrFNO_2$ $[M + H]^+$ 302.0192, found 302.0193.

General Procedure for the Preparation of Nitroalkanes 3a−h via Aldoxime.[42] Aldehyde (1.00 mmol), pyridine (1.80 mmol), hydroxylamine hydrochloride (1.20 mmol), and ethanol (333 μL) were combined (in order) in a flask at room temperature. The mixture was stirred for 1−20 h, and ethanol was evaporated under reduced pressure. The mixture was diluted with EtOAc, washed twice with 1 M aqueous HCl, once with saturated aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to a white crystalline solid. Flash column chromatography was used if needed.

The aldoxime (1.00 mmol), MCPBA (2.0−3.0 mmol), and dichloromethane (1.0 mL) were combined in a flask at room temperature. The reaction was monitored by TLC or ^{1}H NMR, and after 1−3 days the mixture was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, MeOH/dichloromethane) of the residue provided the title compound.

5-Bromo-2-fluoro-4-(nitromethyl)benzene (3d). (*E*)-5-Bromo-2-fluorobenzaldehyde oxime (1.01 g, 4.63 mmol), MCPBA (1.60 g, 9.27 mmol), and dichloromethane were combined in a flask at room temperature. After 48 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0−2% methanol in dichloromethane) of the residue provided the compound as a bronze oil (502 mg, 46%): R_f = 0.85 (CH_2Cl_2); IR (film) 3074, 2915, 2369, 1761, 1560, 1491 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.06 (t, J = 8.8 Hz, 1H), 5.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 161.6 (d, $^1J_{CF}$ = 251 Hz), 135.2, 134.8 (d, $^3J_{CF}$ = 3 Hz), 119.0 (d, $^2J_{CF}$ = 16 Hz), 117.7 (d, $^2J_{CF}$ = 23 Hz), 116.9 (d, $^3J_{CF}$ = 4 Hz), 72.2 (d, $^3J_{CF}$ = 3 Hz); HRMS (APCI) exact mass calcd for $C_7H_5BrFNO_2$ $[M]^+$ 232.9482, found 232.9476.

1,2-Dimethoxy-4-(nitromethyl)benzene (3h). 3,4-Dimethoxybenzaldehyde (3.0 g, 18.0 mmol), hydroxylamine hydrochloride (1.50 g, 21.7 mmol), pyridine (2.62 mL, 32.5 mmol), and ethanol (6.0 mL) were combined in a flask at room temperature. The mixture was stirred for 15 h, and ethanol was evaporated under reduced pressure. The mixture was diluted with EtOAc and washed twice with 1 M aqueous HCl and once with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to a white crystalline solid. This material was carried on without further purification. The resulting aldoxime (3.3 g, 18.2 mmol), MCPBA (6.29 g, 36.4 mmol), and dichloromethane (18 mL) were combined in a flask at room temperature. After 18 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, dichloromethane) of the residue provided the compound as a yellow solid (1.26 g, 36%): mp 66−67 °C; R_f = 0.9 (CH_2Cl_2); IR (film) 3016, 2948, 2838, 1554, 1506, 1376 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (dd, J = 2.0, 1.6 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 5.36 (s, 2H), 3.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 150.3, 149.2, 123.0, 122.1, 112.6, 111.1, 79.9, 55.9 (2C); HRMS (CI) exact mass calcd for $C_9H_{11}NO_4$ $[M]^+$ 197.0604, found 197.0602.

1-Methoxy-3-(nitromethyl)benzene (3i). In a 200 mL flask were placed silver nitrite (1.68 g, 10.94 mmol) and 1-methoxy-3-benzyl bromide (2.0 g, 9.95 mmol). The flask was purged with N_2 and covered with aluminum foil. At room temperature, THF (80 mL) was added via syringe. The reaction mixture was stirred at room temperature in the dark for 46 h and then filtered and concentrated. The crude product was purified on a column (SiO_2, 0−20% ethyl acetate in hexanes) to give the desired product as a pale yellow solid (0.60 g, 36%): R_f = 0.9 (CH_2Cl_2); IR (film) 3069, 2916, 2365, 1760, 1558, 1310 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (m, 1H), 7.03 (dt, J = 7.6, 1.3 Hz, 1H), 7.01−6.95 (m, 2H), 5.41 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 130.9, 130.1, 122.1, 115.6, 115.3, 80.0, 55.4; HRMS (ESI) exact mass calcd for $C_8H_{10}NO_3$ $[M + H]^+$ 168.0661, found 168.0662.

General Procedure for Amidine−Amide Catalyst Preparation (9, 10). The synthesis was derived from the previously reported assembly of chiral bis(amidine) catalysts.[43]

2-((1*R*,2*R*)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-isoindoline-1,3-dione (S1). A flame-dried flask equipped with a stir bar was charged with $Pd(dba)_2$ (208 mg, 362 μmol), *rac*-BINAP (225 mg, μmol), cesium carbonate (8.84 g, 27.1 mmol), the amine (2.21 g, 9.05 mmol), and 2,4-dichloroquinoline (1.79 g, 9.05 mmol). An oven-dried condenser was attached, and the apparatus was purged twice with argon. Toluene (45 mL) was added, and the resulting solution was stirred under reflux for 27 h. The reaction mixture was then cooled to room temperature, filtered through a Celite pad with CH_2Cl_2 and EtOAc, and concentrated. Flash column chromatography of the residue afforded the desired product as a light yellow foam (1.53 g, 42%): $[\alpha]_D^{20}$ = +96° (*c* 0.68, $CHCl_3$); R_f = 0.31 (20% EtOAc/hexanes); IR (film) 3381, 3060, 2935, 2858, 1767, 1705, 1606, 1567, 1531 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.6 Hz, 1H), 7.49 (m, 3H), 7.38 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.31 (dd, J = 5.6, 3.2 Hz, 2H), 7.06 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H), 6.59 (s, 1H), 4.84 (dddd, J = 10.8, 10.8, 10.8, 4.0 Hz, 1H), 4.74 (d, J = 10.0 Hz, 1H), 4.08 (ddd, J = 10.8, 10.8, 4.0 Hz, 1H), 2.66 (dddd, J = 12.8, 12.8, 12.8, 3.6 Hz, 1H), 2.23 (br m, 1H), 1.85 (m, 3H), 1.66 (ddddd, J = 13.2, 13.2, 13.2, 3.2, 3.2 Hz, 1H), 1.42−1.30 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) ppm 168.8, 156.0, 148.1, 142.3, 133.1, 131.3, 129.9,

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126.3, 123.3, 122.4, 122.3, 120.9, 111.0, 56.1, 51.3, 33.4, 28.7, 25.5, 24.8; HRMS (ESI) exact mass calcd for $C_{23}H_{21}ClN_3O_2$ $[M + H]^+$ 406.1322, found 406.1308.

(1*R*,2*R*)-*N*1-(4-Chloroquinolin-2-yl)cyclohexane-1,2-diamine (S2). In a flask equipped with a stir bar were placed the quinoline (596 mg, 1.47 mmol) and ethanol (3 mL), and the resulting solution was stirred at room temperature for 5 min. Hydrazine monohydrate (264 μL, 5.43 mmol) was added, and the reaction mixture was stirred under reflux for 3 h, whereupon a white solid precipitated out of solution. After the reaction mixture was cooled to room temperature, the solid was washed with ether and filtered. The remaining solid was triturated with ether, the suspension was filtered once more, and the filtrate was concentrated to an orange foam (401 mg, 99%): $[\alpha]_D^{20} = -3.3°$ (*c* 0.61, $CHCl_3$); R_f = 0.25 (10% MeOH/1%AcOH/CH_2Cl_2); IR (film) 3268, 2930, 2857, 1609, 1538 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.49 (ddd, *J* = 8.4, 8.4, 1.2 Hz, 1H), 7.20 (ddd, *J* = 8.0, 8.0, 0.8 Hz, 1H), 6.75 (s, 1H), 5.19 (d, *J* = 8.4 Hz, 1H), 3.64 (m, 1H), 2.44 (ddd *J* = 10.0, 10.0, 4.0 Hz, 1H), 2.07 (br m, 1H), 1.90 (br m, 1H), 1.69−1.64 (br m, 4H), 1.39−1.14 (m, 3H), 1.07 (ddd, *J* = 12.8, 12.8, 3.2 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) ppm 156.7, 148.5, 142.4, 130.2, 126.1, 123.7, 122.3, 121.3, 111.0, 57.4, 55.8, 35.2, 32.5, 24.9, 24.8; HRMS (ESI) exact mass calcd for $C_{15}H_{19}ClN_3$ $[M + H]^+$ 276.1268, found 276.1260.

***N*-((1*R*,2*R*)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-3,5-bis(trifluoromethyl)benzamide (S3).** In a flame-dried flask equipped with a stir bar were placed the amine (200 mg, 725 μmol), the carboxylic acid (187 mg, 725 μmol), and dichloromethane (4 mL). The resulting solution was chilled to 0 °C, and EDC (181 mg, 943 μmol) and DMAP (9.00 mg, 72.5 μmol) were added. The reaction mixture was stirred and gradually warmed to room temperature. After 20 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed once with water, dried over $MgSO_4$, and concentrated. Flash column chromatography of the residue (SiO_2, 5−40% ethyl acetate in hexanes) afforded the desired amide as a white amorphous solid (291 mg, 78%): $[\alpha]_D^{20} = +291°$ (*c* 1.11, $CHCl_3$); R_f = 0.43 (30% EtOAc/hexanes); IR (film) 3335, 2937, 2861, 1654, 1608, 1536 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$) δ 8.60 (br d, *J* = 5.4 Hz, 1H), 7.94 (s, 2H), 7.93 (dd, *J* = 9.0, 0.6 Hz, 1H), 7.74 (s, 1H), 7.61 (d, 7.8 Hz, 1H), 7.55 (ddd, *J* = 7.8, 7.8, 0.6 Hz, 1H), 7.29 (ddd, *J* = 7.8, 7.8, 0.6 Hz, 1H), 6.71 (s, 1H), 4.70 (d, *J* = 7.2 Hz, 1H), 4.26 (m, 1H), 3.86 (m, 1H), 2.46 (m, 1H), 2.12 (m, 1H), 1.90 (br dd, *J* = 5.4, 1.8 Hz, 1H), 1.83 (br s, 1H), 1.47 (m, 4H); ^{13}C NMR (150.9 MHz, $CDCl_3$) ppm 164.9, 156.8, 147.6, 143.3, 137.0, 131.7 (q, J_{FC} = 34.0 Hz, 1C), 131.2, 127.1, 125.7, 124.5 (q, J_{FC} = 3.5 Hz, 1C), 124.1, 123.4, 122.7 (q, J_{FC} = 273.0 Hz, 1C), 121.7, 112.1, 58.9, 53.4, 33.2, 32.1, 25.3, 24.3; HRMS (ESI) exact mass calcd for $C_{24}H_{21}ClF_6N_3O$ $[M + H]^+$ 516.1278, found 516.1254.

***N*-((1*R*,2*R*)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-pivalamide (S4).** In a flame-dried flask equipped with a stir bar were placed the amine (60.0 mg, 218 μmol) and dichloromethane (3 mL), immediately followed by the addition of *N*,*N*-diisopropylethylamine (46.0 μL, 261 μmol), the acid chloride (32.0 μL, 261 μmol), and DMAP (2.70 mg, 22.0 μmol). The reaction mixture was stirred at room temperature for 24 h, quenched with 1 M HCl, and extracted with dichloromethane. The organic extracts were then washed with saturated aqueous $NaHCO_3$, extracted with dichloromethane, dried ($MgSO_4$), filtered and concentrated. Flash column chromatography of the residue (SiO_2, 20−50% ethyl acetate in hexanes) afforded the desired amide as a white solid (57.9 mg, 74%): mp 213-216 °C; $[\alpha]_D^{20} = +281°$ (*c* 0.45, $CHCl_3$); R_f = 0.38 (40% EtOAc/hexanes); IR (film) 3313, 2932, 2858, 1607, 1576, 1535 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.56 (ddd, *J* = 8.4, 6.6, 1.2 Hz, 1H), 7.27 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1H), 6.84 (d, *J* = 6.0 Hz, 1H), 6.71 (s, 1H), 5.03 (br d, *J* = 7.8 Hz, 1H), 4.18 (m, 1H), 3.71 (m, 1H), 2.16 (m, 2H), 1.82 (m, 1H), 1.78 (d, *J* = 10.8 Hz, 1H), 1.47−1.28 (m, 4H), 0.87 (s, 9H); ^{13}C NMR (150.9 MHz, $CDCl_3$) ppm 179.1, 156.7, 148.3, 142.6, 130.5, 126.2, 124.0, 122.6, 121.6, 112.2, 56.1, 53.5, 38.4, 33.1, 32.5, 27.3, 25.1, 24.7; HRMS (ESI) exact mass calcd for $C_{20}H_{26}ClN_3NaO$ $[M + Na]^+$ 382.1662, found 382.1658.

***N*-((1*R*,2*R*)-2-((4-(Pyrrolidin-1-yl)quinolin-2-yl)amino)-cyclohexyl)pivalamide (9).** A 0.5−2 mL microwave vial was charged with *N*-((1*R*,2*R*)-2-((4-chloroquinolin-2-yl)amino)cyclohexyl)-pivalamide (40.0 mg, 111 μmol), pyrrolidine (37.0 μL, 445 μmol), and trifluorotoluene (800 μL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction mixture was concentrated and purified by flash column chromatography (1−10% methanol in dichloromethane w/1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aqueous NaOH. The organic layers were combined and washed three times more with 3 M aqueous NaOH. The combined organic layers were dried ($MgSO_4$) and concentrated to afford a tan amorphous solid (23.5 mg, 54%): mp 251−256 °C; $[\alpha]_D^{20} = +143°$ (*c* 0.69, $CHCl_3$); R_f = 0.35 (5% MeOH/1% AcOH/CH_2Cl_2); IR (film) 3299, 2929, 2856, 2361, 1630, 1588, 1534 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.58 (br d, *J* = 7.8 Hz, 1H), 7.47 (br s, 1H), 7.42 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.06 (dd, *J* = 7.8, 7.8 Hz, 1H), 5.64 (s, 1H), 4.34 (br s, 1H), 4.21 (m, 1H), 3.60−3.54 (m, 5H), 2.22 (br d, *J* = 11.4 Hz, 1H), 2.06 (br m, 1H), 1.99 (m, 4H), 1.80 (br d, *J* = 10.8 Hz, 1H), 1.73 (br d, *J* = 12.0 Hz, 1H), 1.46−1.28 (m, 4H), 0.84 (s, 9H); ^{13}C NMR (150.9 MHz, $CDCl_3$) ppm 178.9, 158.1, 153.9, 149.6, 128.7, 126.6, 124.9, 119.8, 118.8, 92.0, 57.5, 52.3, 52.0, 38.3, 33.5, 32.4, 27.3, 25.8, 25.4, 24.6; HRMS (ESI) exact mass calcd for $C_{24}H_{34}N_4NaO$ $[M + Na]^+$ 417.2630, found 417.2630.

***N*-((1*R*,2*R*)-2-((4-(pyrrolidin-1-yl)quinolin-2-yl)amino)-cyclohexyl)-3,5-bis(trifluoromethyl)benzamide (10).** A 2−5 mL microwave vial was charged with *N*-((1*R*,2*R*)-2-((4-chloroquinolin-2-yl)amino)cyclohexyl)-3,5-bis(trifluoromethyl)benzamide (291 mg, 564 μmol), pyrrolidine (185 μL, 2.26 mmol), and trifluorotoluene (3.52 mL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction mixture was concentrated and purified by flash column chromatography (1−10% methanol in dichloromethane w/1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aqueous NaOH. The organic layers were combined and washed twice more with 3 M aqueous NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a white amorphous solid (215 mg, 69%): $[\alpha]_D^{20} = +184°$ (*c* 0.93, $CHCl_3$); R_f = 0.15 (5% MeOH/1% AcOH/CH_2Cl_2); IR (film) 3343, 2935, 2861, 1655, 1589, 1531 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.52 (d, *J* = 4.2 Hz, 1H), 7.98 (s, 2H), 7.96 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.73 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.39 (ddd, *J* = 8.4, 8.4, 1.2 Hz, 1H), 7.07 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 5.65 (s, 1H), 4.34 (br s, 1H), 4.21 (m, 1H), 3.73 (m, 1H), 3.55 (m, 4H), 2.51 (d, *J* = 12.0 Hz, 1H), 2.07 (m, 1H), 1.98 (m, 4H), 1.87 (d, *J* = 4.8 Hz, 1H), 1.81 (d, *J* = 6.0 Hz, 1H), 1.44 (m, 4H); ^{13}C NMR (150.9 MHz, $CDCl_3$) ppm 165.2, 158.3, 154.0, 149.0, 137.6, 131.5 (q, J_{FC} = 33.7 Hz, 1C), 129.3, 127.3, 126.1, 124.9, 124.2, 122.8 (q, *J* = 273.1 Hz, 1C), 120.3, 118.6, 91.2, 59.6, 53.1, 51.9, 33.3, 31.9, 25.8, 25.5, 24.4; HRMS (ESI) exact mass calcd for $C_{28}H_{29}F_6N_4O$ $[M + H]^+$ 551.2246, found 551.2237.

***(E)*-5-Bromo-2-fluorobenzaldehyde Oxime (S5).** Aldehyde (2.0 mL, 16.8 mmol), hydroxylamine hydrochloride (1.40 g, 20.2 mmol), pyridine (2.45 mL, 30.3 mmol), and ethanol (5.6 mL) were combined in a flask at room temperature. The mixture was stirred for 10 h, and ethanol was evaporated under reduced pressure. The mixture was diluted with EtOAc and washed twice with 1 M aqueous HCl and once with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a white crystalline solid (3.6 g, 98%): mp 76−77 °C; R_f = 0.6 (CH_2Cl_2); IR (film) 3285 (br), 3079, 3017, 1904, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 8.30 (s, 1H), 7.89 (dd, *J* = 8.8, 4.0 Hz, 1H). 7.46 (m, 1H), 6.97 (t, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 161.0 (d, $^1J_{CF}$ = 255 Hz), 143.1 (d, $^3J_{CF}$ = 3 Hz), 134.2, 129.6 (d, $^3J_{CF}$ = 3 Hz), 121.8, 117.7 (d, $^2J_{CF}$ = 22 Hz), 117.1 (d, $^3J_{CF}$ = 3 Hz); HRMS (APCI): exact mass calcd for C_7H_5BrFNO $[M]^+$ 216.9533, found 216.9539.

General Procedure for Enantioselective Aza-Henry Additions (4aa−hk). Aryl Boc-imine (**4a**−**k**; 100 μmol) and BenzMAM (**10**; 2.8 mg, 5.0 μmol) or PivMAM (**9**; 2.0 mg, 5.0 μmol) were dispensed into a flame-dried vial with a stir bar. Toluene (1.0 mL) was added, and the reaction was stirred at room temperature until homogeneous. The reaction mixture was chilled to −78 °C before the aryl nitroalkane **3a**−**i** (110 μmol) was added. The reaction mixture was warmed to −20 °C and stirred for 18−60 h. The chilled mixture was either diluted with

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CH_2Cl_2 to dissolve precipitate and quickly flushed through a pad of silica gel or diluted with cold hexanes and filtered through a Buchner funnel with filter paper (scale ≥0.2 mmol). Vacuum filtration with cold hexanes resulted in analytically pure material. If the product was added to silica, the pad was flushed with CH_2Cl_2, the filtrate was concentrated, and the residue was purified by column chromatography (SiO_2, ethyl acetate in hexanes), if needed.

***tert*-Butyl ((1*R*,2*S*)-2-(4-Chlorophenyl)-2-nitro-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (4ab).** Imine **2b** (163 mg, 564 μmol) and (*S*,*S*)-**10** (15.4 mg, 28 μmol) were placed in a flask in toluene (5.6 mL) under argon. The mixture was cooled to −20 °C, and nitroalkane **3a** (106 mg, 620 μmol) was added. After 48 h the reaction mixture was filtered through a plug of silica gel and concentrated. Column chromatography (SiO_2, 0−15% ethyl acetate in hexanes) afforded the product as a white crystalline solid (160 mg, 62%). The major diastereomer was determined to be 94% ee and the minor to be 92% ee, with 6:1 dr determined by chiral HPLC (Chiralcel AD: 6% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_2$ minor/minor) = 11.5 min, $t_r(d_1e_1$ major/major) = 13.4 min, $t_r(d_1e_2$ major/minor) = 15.4 min, $t_r(d_2e_1$ minor/major) = 20.3 min): mp 145 °C; R_f = 0.58 (20% EtOAc/hexanes); IR (film) 3372, 2981, 2927, 1686, 1558, 1498 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 1H), 7.39 (m, 4H), 7.29 (m, 2H), 7.20 (m, 1H), 5.78 (br dd, 1H), 5.61 (br d, 2H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.7, 154.3, 139.5, 136.6, 130.5, 130.0, 129.6, 129.3, 129.2 (2C), 125.7, 125.4, 124.7, 121.2, 120.4 (q, $^1J_{CF}$ = 249 Hz), 119.9, 93.0, 28.3, 28.0; HRMS (APCI): exact mass calcd for $C_{20}H_{20}ClF_3N_2NaO_5$ $[M + Na]^+$ 483.0911, found 483.0907.

***tert*-Butyl ((1*R*,2*S*)-2-(4-Bromophenyl)-1-(4-chlorophenyl)-2-nitroethyl)carbamate (4ba).** Imine **2a** (348 mg, 1.45 mmol) and (*R*,*R*)-**10** (40.0 mg, 73.0 μmol) were placed in a flask in toluene (14.5 mL) under argon. The mixture was cooled to −78 °C and nitroalkane **3b** (377 mg, 1.61 mmol) added. After 36 h the white precipitate was vacuum-filtered and washed with hexanes to afford the title compound as a white crystalline solid (493 mg, 75%). The major diastereomer was determined to be 94% ee with >200:1 dr determined by chiral HPLC (Chiralcel IA: 15% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 10.2 min, $t_r(d_2e_1$ minor/major) = 11.8 min, $t_r(d_1e_1$ major/major) = 24.2 min, $t_r(d_2e_2$ minor/minor) = 33.4 min): $[\alpha]_D^{20}$ = −23° (*c* 0.27, $CHCl_3$); mp 183−184 °C; R_f = 0.40 (20% EtOAc/hexanes); IR (film) 3375, 2980, 1683, 1544, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.74 (d, *J* = 8.8 Hz, 1H), 5.57 (dd, *J* = 9.2, 8.8 Hz, 1H), 4.82 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 134.8, 132.1, 130.3, 129.3, 129.0, 128.6, 128.2, 124.8, 93.2, 30.9, 28.0; HRMS (ESI) exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M + Na]^+$ 477.0193, found 477.0211.

***tert*-Butyl ((1*R*,2*S*)-2-(3-Chlorophenyl)-1-(4-chlorophenyl)-2-nitroethyl)carbamate (4ca).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**9** (5 mol %) with a 48 h reaction time. The reaction precipitate was added to the filter paper a Buchner funnel and washed with cold hexanes to afford the product as a white crystalline solid (35 mg, 81%) that was found to be 93% ee and >200:1 dr by chiral HPLC (Chiralcel IA: 9% ^{i}PrOH/hexanes, 0.6 mL/min: $t_r(d_1e_1$ major/major) = 12.6 min, $t_r(d_2e_1$ minor/major) = 15.0 min, $t_r(d_1e_2$ major/minor) = 17.1 min, $t_r(d_2e_2$ minor/minor) = 18.6 min): $[\alpha]_D^{20}$ = −37° (*c* 0.44, $CHCl_3$); mp 182−183 °C; R_f = 0.55 (25% EtOAc/hexanes); IR (film) 3389, 3056, 2980, 1683, 1490 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 1H), 7.44 (m, 2H), 7.37−7.28 (m, 5H), 5.76 (br d, 1H), 5.56 (br dd, 1H), 4.86 (br d, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz. $CDCl_3$) ppm 154.2, 134.9, 134.8, 133.1, 130.5, 130.3, 130.2, 130.1, 129.3, 129.1, 128.9, 128.6, 128.3, 128.0, 126.8, 93.2, 28.1; HRMS (ESI) exact mass calcd for $C_{19}H_{20}Cl_2N_2NaO_4$ $[M + Na]^+$ 433.0698; found 433.0715.

***tert*-Butyl ((1*R*,2*S*)-2-(5-Bromo-2-fluorophenyl)-1-(4-chlorophenyl)-2-nitroethyl)carbamate (4da).** The reaction was run with catalyst (*R*,*R*)-**8** (2 mol %) at −78 °C for 8 h and the mixture was then warmed to −20 °C for an additional 24 h. Following silica plug removal of the catalyst, column chromatography (SiO_2, 0−10% ethyl acetate in hexanes) afforded the product as a white crystalline solid (422 mg, 65%). The major diastereomer was determined to be 92% ee and the minor to be 90% ee, with 3:1 dr determined by chiral HPLC (Chiralcel IA: 10% ^{i}PrOH/hexanes, 0.8 mL/min: $t_r(d_1e_1$ minor/major) = 17.6 min, $t_r(d_1e_2$ minor/minor) = 18.6 min, $t_r(d_2e_1$ major/major) = 20.9 min, $t_r(d_1e_2$ major/minor) = 44.6 min): mp 184−185 °C; R_f = 0.30 (25% EtOAc/hexanes); IR (film) 3505, 3374 (br), 2976, 2935, 1698, 1561, 1492 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 2.4, 2.4 Hz, 1H), 7.52 (m, 1H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 8.8 Hz, 1H), 6.10 (d, *J* = 10.4 Hz, 1H), 5.64 (br d, 1H), 4.84 (d, *J* = 9.6 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 161.0 (d, $^1J_{CF}$ = 259 Hz), 154.6, 135.3, 135.0, 134.9, 130.9, 129.4, 129.2, 128.5, 128.2 (d, $^3J_{CF}$ = 4 Hz), 127.9 (d, $^3J_{CF}$ = 4 Hz), 120.8 (d, $^2J_{CF}$ = 24 Hz), 117.3, 85.4, 28.0; HRMS (APCI) exact mass calcd for $C_{19}H_{19}BrClFN_2NaO_4$ $[M + Na]^+$ 495.0098, found 495.0107.

***tert*-Butyl ((1*S*,2*R*)-1-(4-Chlorophenyl)-2-(3-fluorophenyl)-2-nitroethyl)carbamate (4ea).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the adduct as a white crystalline solid (42 mg, 54%), which was found to be 35:1 dr and 92% ee by chiral HPLC analysis (Chiralpak AD-H, 8% *i*PrOH/hexanes, 1 mL/min, $t_r(d_1e_1$, major/major) = 21.6 min, $t_r(d_2e_2$, minor/minor) = 23.8 min, $t_r(d_2e_2$, minor/minor) = 30.9 min, $t_r(d_1e_2$, major/minor) = 40.2 min): mp 162−164 °C; R_f = 0.53 (33% EtOAc/hexanes); IR (film) 3379, 2977, 1680, 1553, 1523, 1289, 1252, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 6 H), 7.18 (m, 2 H), 5.80 (s, 1 H), 5.59 (s, 1 H), 4.92 (s, 1 H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 163.8, 161.3, 154.2, 135.6, 134.8, 133.4, 133.3, 131.2, 130.5, 130.4, 129.2, 129.1, 129.0, 128.6, 128.3, 128.2, 125.2, 124.5, 117.5, 117.3, 115.9, 115.6, 93.2, 93.1, 80.8, 28.2, 28.1, 28.0, 27.8; HRMS exact mass calcd for $C_{19}H_{20}ClFN_2NaO_4$ $[M + Na]^+$ 417.0993, found 417.1101.

***tert*-Butyl ((1*R*,2*S*)-1-(4-Chlorophenyl)-2-nitro-2-(*m*-tolyl)-ethyl)carbamate (4fa).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**9** (5 mol %) with a 60 h reaction time. Column chromatography (SiO_2, 0−5% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (22 mg, 65%), which was found to be 21:1 dr and 93% ee by chiral HPLC analysis (Chiralpak AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$, minor/major) =17.9 min, $t_r(d_1e_2$, major/minor) = 22.0 min, $t_r(d_2e_2$, minor/minor) = 26.3, $t_r(d_1e_1$, major/major) = 32.0 min). The 79% ee and 34:1 dr material was used for optical rotation: $[\alpha]_D^{20}$ −25.8° (*c* 1.13, $CHCl_3$); mp 127−130 °C; R_f = 0.56 (33% EtOAc/hexanes); IR (film) 3385, 1681, 1548, 1521, 1365, 1161 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.22 (m, 8 H), 5.72 (d, *J* = 8.8 Hz, 1 H), 5.61 (dd, *J* = 8.8, 8.8 Hz, 1 H), 4.74 (d, *J* = 7.6 Hz, 1 H), 2.39 (s, 3 H), 1.28 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 138.8, 134.5, 131.4, 131.1, 130.8, 129.1, 128.8, 128.6, 125.6, 94.0, 68.1, 38.7, 28.9, 28.2, 28.0, 23.7, 22.9, 21.3; HRMS (ESI) exact mass calcd for $C_{20}H_{23}ClN_2NaO_4$ $[M + Na]^+$ 413.1244, found 413.1252.

***tert*-Butyl ((1*R*,2*S*)-2-(3-Bromophenyl)-1-(4-chlorophenyl)-2-nitroethyl)carbamate (4ga).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**9** (5 mol %) with a 48 h reaction time. The crude product that precipitated out was filtered and washed with cold hexanes to give a off-white crystalline solid (740 mg, 78%) that was found to be 92% ee and 25:1 dr by chiral HPLC (Chiralcel AD-H: 8% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 11.5 min, $t_r(d_2e_1$ minor/major) = 14.0 min, $t_r(d_1e_1$ minor/minor) = 18.6 min, $t_r(d_2e_2$ major/major) = 21.3 min): $[\alpha]_D^{20}$ = −26.7° (*c* 0.26, CH_3OH); mp 172−173 °C; IR (film) 3388, 2982, 1681, 1549, 1519, 1493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (t, *J* = 1.8 Hz, 1H), 7.62−7.55 (m, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.38−7.33 (m, 2H), 7.33−7.27 (m, 3H), 5.75 (s, 1H), 5.56 (t, *J* = 9.7 Hz, 1H), 4.83 (s, 1H), 1.28 (s, 9H); ^{13}C NMR (126 MHz, CD_3OD) δ 156.8, 138.2, 135.9, 135.5, 134.4, 133.0, 131.7, 130.3, 130.0, 128.6, 123.5, 94.5, 80.9, 57.1, 28.4; HRMS (ESI) exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M + Na]^+$ 477.0193, found 477.0218.

***tert*-Butyl ((1*R*,2*S*)-1-(4-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (4ha).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 10−25% ethyl acetate in hexanes) afforded the adduct as an

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off-white solid (56.0 mg, 76%) that was found to be 76% ee and 37:1 dr by chiral HPLC (Chiralcel IA: 12% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 16.9 min, $t_r(d_1e_1$ major/major) = 19.2 min, $t_r(d_1e_2$ major/minor) = 20.1 min, $t_r(d_2e_2$ minor/minor) = 25.5 min): $[\alpha]_D^{20}$ = −4.5° (*c* 0.40, $CHCl_3$); mp 148−149 °C; R_f = 0.25 (CH_2Cl_2); IR (film) 3367, 2975, 2837, 1703, 1557, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 2H), 7.29, (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 4.0 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.70 (d, *J* = 10.0 Hz, 1H), 5.64 (d, *J* = 8.4 Hz, 1H), 4.82 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 150.7, 149.2, 136.2, 134.6, 129.2, 128.6, 123.5, 122.1, 110.9, 93.9, 80.6, 56.0 (2C), 28.1; HRMS (ESI) exact mass calcd for $C_{21}H_{25}ClN_2NaO_6$ $[M + Na]^+$ 459.1299, found 459.1309.

***tert*-Butyl ((1*R*,2*S*)-1-(4-Chlorophenyl)-2-(3-methoxyphenyl)-2-nitroethyl)carbamate (4ia).** The reaction employed catalyst (*R*,*R*)-**9** (5 mol %) with a 48 h reaction time. The crude precipitated product was filtered and washed with cold hexanes to give a white solid (1.05 g, 87%) that was found to be 95% ee and 23:1 dr by chiral HPLC (Chiralcel AD: 10% EtOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 9.1 min, $t_r(d_1e_1$ major/major) = 11.3 min, $t_r(d_2e_2$ minor/minor) = 13.0 min, $t_r(d_1e_2$ major/minor) = 32.1 min): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 7.09 (dd, *J* = 5.1, 2.8 Hz, 2H), 7.00−6.94 (m, 1H), 5.73 (d, *J* = 9.8 Hz, 1H), 5.62 (d, *J* = 9.8 Hz, 1H), 4.89 (s, 1H), 3.82 (s, 3H), 1.27 (s, 9H); LRMS (ESI) $C_{20}H_{24}ClN_2O_5$ $[M + H]^+$ 406.86, found 407.58.

***tert*-Butyl ((1*S*,2*R*)-1-(4-Bromophenyl)-2-(4-chlorophenyl)-2-nitroethyl)carbamate (*ent*-4ac).** This compound was prepared according to the general procedure employing catalyst (*S*,*S*)-**10** (5 mol %)with a 36 h reaction time. The reaction precipitate was added to the filter paper in a Buchner funnel and washed with cold hexanes to afford the adduct as a white crystalline solid (310 mg, 88%) that was found to be 93% ee with >200:1 dr determined by chiral HPLC (Chiralcel AD-H: 15% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$ major/major) = 10.5 min, $t_r(d_2e_1$ minor/minor) = 12.4 min, $t_r(d_1e_2$ major/minor) = 22.0 min, $t_r(d_2e_1$ minor/minor) = 36.7 min): $[\alpha]_D^{20}$ = +28° (*c* 0.24, $CHCl_3$); mp 185−186 °C; R_f = 0.42 (20% EtOAc/hexanes); IR (film) 3389, 2976, 1681, 1552, 1519, 1498 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 4H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.75 (br d, 1H), 5.56 (br dd, 1H), 4.84 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 136.6, 132.2, 130.1, 129.7, 129.1, 128.9, 123.0, 93.1, 20.0; HRMS (ESI) exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M + Na]^+$ 477.0193, found 477.0216.

***tert*-Butyl ((1*R*,2*S*)-2-(4-Chlorophenyl)-1-(4-fluorophenyl)-2-nitroethyl)carbamate (4ad).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 1−10% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (21 mg, 82%) that was found to be 94% ee and 9:1 dr by chiral HPLC (Chiralcel AD-H: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 11.7 min, $t_r(d_2e_1$ major/minor) = 19.6 min, $t_r(d_1e_1$ major/major) = 25.7 min, $t_r(d_2e_2$ minor/minor) = 40.2 min): mp 179−181 °C; R_f = 0.49 (20% EtOAc/hexanes); IR (film) 3378, 2977, 2922, 1678, 1560, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.32 (dd, *J* = 8.4, 8.4 Hz, 2H), 7.05 (dd, *J* = 8.4, 8.4 Hz, 2H), 5.75 (br d, 1H), 5.59 (br dd, 1H), 4.80 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 162.4 (d, $^1J_{CF}$ = 249 Hz), 154.2, 136.5, 133.0, 130.1, 129.8, 129.1, 129.0 (d, $^4J_{CF}$ = 7.5 Hz), 116.1 (d, $^2J_{CF}$ = 23 Hz), 93.4, 80.8, 28.0; HRMS (ESI) exact mass calcd for $C_{19}H_{20}ClFN_2NaO_4$ $[M + Na]^+$ 417.0993, found 417.1010.

***tert*-Butyl ((1*S*,2*R*)-2-(4-Chlorophenyl)-1-(4-iodophenyl)-2-nitroethyl)carbamate (*ent*-4ae).** This compound was prepared according to the general procedure employing catalyst (*S*,*S*)-**10** (5 mol %) with a 24 h reaction time. Column chromatography (SiO_2, 0−5% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (27 mg, 84%) that was found to be a 99% ee and >100:1 dr by chiral HPLC; (ChiralPak AD-H, 15% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$, major/major) = 11.8 min, t_r (d_2e_1, minor/major) = 14.1 min, t_r (d_1e_1, major/major) = 22.8 min, t_r (d_2e_2, minor/minor = 42.4 min): $[\alpha]_D^{20}$ + 22° (*c* 0.16, $CHCl_3$); mp 189−190 °C; R_f = 0.50 (20% EtOAc in hexanes); IR (film) 3380, 2979, 1679, 1548, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.75 (d, *J* = 8.8 Hz, 1H), 5.55 (dd, *J* = 9.4, 8.8 Hz, 1H), 4.76 (d, *J* = 9.2 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR (100.6 MHz, $(CD_3)_2SO$) ppm 154.7, 138.4, 137.9, 135.4, 131.1, 130.9, 130.3, 129.2, 95.3, 92.9, 79.2, 55.9, 28.2; HRMS (ESI) exact mass calcd for $C_{19}H_{20}ClIN_2NaO_4$ $[M + Na]^+$ 525.0054, found 525.0082.

***tert*-Butyl ((1*S*,2*R*)-2-(4-Chlorophenyl)-1-(3-iodophenyl)-2-nitroethyl)carbamate (*ent*-4af).** This compound was prepared according to the general procedure employing catalyst (*S*,*S*)-**9** (5 mol %) with a 72 h reaction time. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the adduct as a white crystalline solid (360 mg, 80%). The major diastereomer was determined to be 99% ee with >200:1 dr determined by chiral HPLC (Chiralcel AD-H: 15% ^{i}PrOH/hexanes, 0.6 mL/min: $t_r(d_1e_1$ major/major) = 14.3 min, $t_r(d_2e_2$ minor/minor) = 15.2 min, $t_r(d_1e_2$ major/minor) = 29.5 min, $t_r(d_2e_1$ minor/minor) = 32.4 min): $[\alpha]_D^{20}$ = +220° (*c* 0.20, $CHCl_3$); mp 170−172 °C; R_f = 0.45 (20% EtOAc/hexanes); IR (film) 3393, 2981, 2360, 1679, 1545, 1518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.09 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.72 (br d, *J* = 9.2 Hz, 1H), 5.55 (br dd, 1H), 4.82 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.1, 139.4, 138.0, 136.6, 136.1, 130.7, 130.1, 129.7, 129.4, 129.1, 126.6, 94.8, 93.1, 28.0; HRMS (ESI) exact mass calcd for $C_{19}H_{20}ClIN_2NaO_4$ $[M + Na]^+$ 525.0054, found 525.0071.

***tert*-Butyl ((1*R*,2*S*)-2-(4-Chlorophenyl)-2-nitro-1-(*m*-tolyl)-ethyl)carbamate (4ag).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time, and following silica filtration the product was isolated as a white crystalline solid (48 mg, 98% overall) that was found to be 88% ee and 50:1 dr by chiral HPLC (Chiralpak IA, 10% ^{i}PrOH/hexanes, 1 mL/min, $t_r(d_1e_1$ major/major) = 9.6 min, $t_r(d_2e_2$ minor/minor) = 12.4 min, $t_r(d_1e_2$ minor/major) = 14.9, $t_r(d_1e_2$ major/minor) = 32.7 min): $[\alpha]_D^{20}$ = −38° (*c* 0.11, $CHCl_3$, recrystallized material, 96% ee, 200:1 dr); mp 186−188 °C; R_f = 0.56 (33% EtOAc/hexanes); IR (film) 3399, 2984, 2921, 2359, 1688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.28 (m, 2 H), 7.15 (m, 3 H), 5.76 (d, *J* = 10.0 Hz, 1 H), 5.64 (m, 1 H), 4.71 (d, *J* = 9.6 Hz, 1 H), 2.48 (s, 3 H), 1.3 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 138.9, 137.0, 136.3, 130.2, 130.0, 129.7, 129.0, 128.9, 127.9, 124.0, 94.6, 80.4, 56.5, 28.0, 21.4; HRMS (ESI) exact mass calcd for $C_{20}H_{23}ClN_2NaO_4$ $[M + Na]^+$ 413.1243, found 413.1262.

***tert*-Butyl ((1*R*,2*S*)-1-(3-Chlorophenyl)-2-(4-chlorophenyl)-2-nitroethyl)carbamate (4ah).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 24 h reaction time. Column chromatography (SiO_2, 0−5% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (23 mg, 71%) that was found to be 97% ee and 9:1 dr determined by chiral HPLC (Chiralcel IA: 5% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_2$ minor/minor) = 18.4 min, $t_r(d_2e_1$ minor/major) = 21.3 min, $t_r(d_1e_1$ major/major) = 31.3 min, $t_r(d_1e_1$ major/minor) = 47.8 min): mp 174−175 °C; R_f = 0.58 (20% EtOAc/hexanes); IR (film) 3385, 2977, 1685, 1553, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.34−7.22 (m, 4H), 5.73 (br d, 1H), 5.60 (br m, 1H), 4.71 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 139.2, 136.6, 135.0, 130.4, 130.1, 129.7, 129.1, 127.4, 125.5, 93.1, 28.0; HRMS (ESI) exact mass calcd for $C_{19}H_{20}Cl_2N_2NaO_4$ $[M + Na]^+$ 433.0698, found 433.0713.

***tert*-Butyl ((1*R*,2*S*)-2-(4-Chlorophenyl)-1-(3-fluorophenyl)-2-nitroethyl)carbamate (4ai).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with an 18 h reaction time, and following silica gel filtration, the product was isolated as a white crystalline solid (37 mg, 98%), which was found to be 60:1 dr and 88% ee by chiral HPLC analysis (Chiralpak AD-H, 5% *i*PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$, minor/major) =28.7 min, $t_r(d_1e_2$, major/minor) = 34.8 min, $t_r(d_1e_1$, major/major) = 48.5, $t_r(d_2e_2$, minor/minor) = 70 min): $[\alpha]_D^{20}$ = −11° (*c* 0.11, $CHCl_3$, 40% ee); mp 169−171 °C; R_f = 0.58 (33% EtOAc/hexanes); IR (film) 3383, 2983, 1681, 1551, 1524, 1366, 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2 H),

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7.42 (d, J = 8.4 Hz, 2 H), 7.37 (m, 1 H), 7.15 (d, J = 8.0 Hz, 1 H), 7.08 (m, 2 H), 5.77 (br d, 1 H), 5.64 (br dd, 1 H), 4.86 (br d, 1 H), 1.30 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.1, 161.6, 136.6, 130.74, 130.66, 130.0, 129.6, 129.1, 122.8, 116.0, 115.8, 114.4, 114.2, 93.1, 27.9; HRMS (ESI) exact mass calcd for $C_{19}H_{20}ClFN_2NaO_4$ $[M + Na]^+$ 417.0993, found 417.1080.

***tert*-Butyl ((1*R*,2*S*)-1-(5-Bromo-2-fluorophenyl)-2-(4-chlorophenyl)-2-nitroethyl)carbamate (4aj).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 0−5% ethyl acetate in hexanes) afforded an off-white crystalline solid (29.0 mg, 53%) that was found to be 84% ee and 25:1 dr by chiral HPLC (Chiralcel AD: 6% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ minor/major) = 12.9 min, $t_r(d_2e_1$ minor/major) = 14.6 min, $t_r(d_2e_2$ minor/minor) = 29.6 min, $t_r(d_1e_1$ major/major) = 32.8 min): $[\alpha]_D^{20} = -11°$ (c 0.40, $CHCl_3$); mp 165 °C (dec.); R_f = 0.60 (20% EtOAc/hexanes); IR (film) 3327, 2980, 2924, 1704, 1565, 1489 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H), 7.44 (m, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.28 (m, 1H), 7.00 (dd, J = 8.8, 8.8 Hz, 1H), 5.80 (br d, 1H), 5.64 (br d, 1H), 5.07 (br d, 1H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.0 (d, $^1J_{CF}$ = 246 Hz), 154.1, 136.6, 133.7 (d, $^3J_{CF}$ = 8.0 Hz), 132.5, 130.1, 129.5, 129.3, 129.1, 126.0 (d, $^3J_{CF}$ = 13 Hz), 117.9 (d, $^2J_{CF}$ = 23 Hz), 117.3, 92.1, 28.1, 27.9; HRMS (ESI) exact mass calcd for $C_{19}H_{19}BrClFN_2NaO_4$ $[M + Na]^+$ 495.0109, found 495.0098.

***tert*-Butyl ((1*R*,2*S*)-1,2-bis(4-Bromophenyl)-2-nitroethyl)carbamate (4bc).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 0−10% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (19 mg, 75%) that was found to be 84% ee and 9:1 dr by chiral HPLC (Chiralcel IA: 6% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$ major/major) = 15.9 min, $t_r(d_1e_2$ major/minor) = 17.4 min, $t_r(d_2e_1$ minor/major) = 20.1 min, $t_r(d_2e_2$ minor/minor) = 50.5 min): mp 178−179 °C dec; R_f = 0.54 (20% EtOAc/hexanes); IR (film) 3370, 2980, 2918, 1679, 1549, 1529 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 5.73 (d, J = 6.8 Hz, 1H), 5.56 (dd, J = 9.6, 8.8 Hz, 1H), 4.85 (br d, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 136.1, 132.3, 132.1, 130.3, 128.9, 128.6, 124.8, 123.0, 93.2, 28.2, 28.0; HRMS (ESI) exact mass calcd for $C_{19}H_{20}Br_2N_2NaO_4$ $[M + Na]^+$ 520.9687, found 520.9703.

***tert*-Butyl ((1*R*,2*S*)-1-(4-Bromophenyl)-2-(3-chlorophenyl)-2-nitroethyl)carbamate (4cc).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 0−10% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (23 mg, 80%) that was found to be 95% ee and 5:1 dr by chiral HPLC (Chiralcel IA: 10% ^{i}PrOH/hexanes, 0.6 mL/min: $t_r(d_1e_1$ major/major) = 21.0 min, $t_r(d_1e_2$ major/minor) = 25.1 min, $t_r(d_2e_1$ minor/major) = 29.6 min, $t_r(d_2e_2$ major/major) = 30.8 min): mp 184 °C; R_f = 0.49 (25% EtOAc/hexanes); IR (film) 3368, 2976, 2914, 1677, 1554, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.42 (m, 2H), 7.35 (m, 1H), 7.23 (d, J = 8.4 Hz, 2H), 5.76 (br d, 1H), 5.56 (br dd, J = 8.0 Hz, 1H), 4.85 (br d, 1H) 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 136.1, 134.8, 133.1, 132.2, 130.5, 130.2, 128.9, 128.6, 126.8, 123.0, 93.1, 28.0; HRMS (ESI) exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M + Na]^+$ 477.0193, found 477.0208.

***tert*-Butyl ((1*R*,2*S*)-2-(5-Bromo-2-fluorophenyl)-1-(4-bromophenyl)-2-nitroethyl)carbamate (4dc).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 36 h reaction time. Column chromatography (SiO_2, 0−30% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (15.0 mg, 80%) that was found to be 93% ee and 3:1 dr by chiral HPLC (Chiralcel AD-H: 3% EtOH/hexanes, 0.8 mL/min: $t_r(d_2e_2$ minor/minor) = 22.8 min, $t_r(d_2e_1$ minor/major) = 25.6 min, $t_r(d_1e_1$ major/major) = 31.0 min, $t_r(d_1e_2$ major/minor) = 43.5 min): mp 170−171 °C; R_f = 0.6 (20% EtOAc/hexanes); IR (film) 3335, 2975, 2926, 1708, 1563, 1486 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 6.0, 2.0 Hz, 1H), 7.48 (m, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.94 (dd, J = 9.2, 8.4 Hz, 1H), 6.22 (d, J = 6.0 Hz, 1H), 5.58 (d, J = 6.0 Hz, 1H), 5.52 (d, J = 7.6 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.6 (d, $^1J_{CF}$ = 249 Hz), 154.6, 147.9, 135.3, 134.8 (d, $^3J_{CF}$ = 7.5 Hz), 132.2 (2C), 131.0, 128.4 (2C), 122.7, 120.9 (d, $^3J_{CF}$ = 13.5 Hz), 117.7, 117.6, 85.5 (d, $^3J_{CF}$ = 3 Hz), 28.1; HRMS (ESI) exact mass calcd for $C_{19}H_{19}Br_2FN_2NaO_4$ $[M + Na]^+$ 538.9593, found 538.9606.

***tert*-Butyl ((1*R*,2*S*)-1-(4-Bromophenyl)-2-nitro-2-(*m*-tolyl)ethyl)carbamate (4fc).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**9** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 0−10% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (29 mg, 92%) that was found to be 87% ee and 7:1 dr by chiral HPLC (Chiralcel AD-H: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 25.9 min, $t_r(d_2e_2$ minor/minor) = 30.8 min, $t_r(d_1e_2$ major/minor) = 38.3 min, $t_r(d_1e_1$ major/major) = 43.8 min): mp 165−166 °C; R_f = 0.53 (25% EtOAc/hexanes); IR (film) 3379, 2965, 2924, 2848, 1689, 1551, 1517 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.40 (m, 1H), 7.35 (s, 1H), 7.31 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 5.71 (br d, 1H), 5.58 (br dd, 1H), 5.44 (br d, 1H), 2.37 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 138.8, 136.8, 131.1, 129.2, 129.0, 128.8, 128.7, 127.5, 125.6, 122.7, 93.9, 29.7, 28.2, 28.0; HRMS (ESI) exact mass calcd for $C_{20}H_{23}BrN_2NaO_4$ $[M + Na]^+$ 457.0689, found 457.0696.

***tert*-Butyl ((1*R*,2*S*)-1-(4-Bromophenyl)-2-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (4hc).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 72 h reaction time. Column chromatography (SiO_2, 0−5% ethyl acetate in hexanes) afforded the adduct as a white solid (27 mg, 51%) that was found to be 73% ee and 31:1 dr by chiral HPLC (ChiralPak IA, 7% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 16.1 min, $t_r(d_1e_1$ major/major) = 18.4 min, $t_r(d_2e_2$ minor/minor) = 21.0 min, $t_r(d_2e_1$ minor/major) = 28.8 min): $[\alpha]_D^{20} = -5.4°$ (c 0.37, $CHCl_3$); mp 183−184 °C; R_f = 0.24 (20% EtOAc in hexanes); IR (film) 3376, 2975, 2926, 1687, 1556, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.09−7.05 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 5.70 (d, J = 10.0 Hz, 1H), 5.62 (br dd, 1H), 4.86 (d, J = 8.8 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 143.3, 150.7, 149.2, 136.7, 132.1, 129.0 (2C), 128.2, 125.3, 123.5, 122.8, 122.1, 110.9, 93.8, 56.0, 28.1; HRMS (ESI) exact mass calcd for $C_{21}H_{25}BrN_2NaO_6$ $[M + Na]^+$ 503.0794; found 503.0777.

***tert*-Butyl ((1*R*,2*S*)-2-(4-Bromophenyl)-2-nitro-1-(*m*-tolyl)ethyl)carbamate (4bg).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Following silica plug filtration, the adduct was isolated as an off-white solid (35 mg, 88%) that was found to be 85% ee and 68:1 dr by chiral HPLC (Chiralcel IA: 7% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 15.6 min, $t_r(d_1e_2$ major/minor) = 17.5 min, $t_r(d_1e_1$ major/major) = 21.1 min, $t_r(d_2e_2$ minor/minor) = 49.1 min): $[\alpha]_D^{20} = -33°$ (c 0.54, $CHCl_3$); mp 184−185 °C; R_f = 0.57 (25% EtOAc/hexanes); IR (film) 3379, 2972, 2917, 1696, 1551, 1517 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H), 7.46 (J = 8.0 Hz, 2H), 7.25 (m, 1H), 7.13 (m, 3H), 5.73 (d, J = 9.6 Hz, 1H), 5.6 (br dd, 1H), 4.82 (br d, 1H), 2.35 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 138.9, 137.0, 132.3, 131.9, 131.6, 130.5, 129.7, 129.0, 127.9, 124.6, 124.0, 93.6, 28.0, 21.4; HRMS (ESI) exact mass calcd for $C_{20}H_{23}BrN_2NaO_4$ $[M + Na]^+$, 457.0739, found 457.0720.

***tert*-Butyl ((1*R*,2*S*)-2-(3-Chlorophenyl)-2-nitro-1-(*m*-tolyl)ethyl)carbamate (4cg).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Following silica plug filtration, the adduct was isolated as an off-white crystalline solid (22 mg, 97%) that was found to be 99% ee and 20:1 dr by chiral HPLC (Chiralcel IA: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_2$ minor/minor) = 10.5 min, $t_r(d_1e_1$ major/major) = 14.1 min, $t_r(d_1e_2$ major/minor) = 15.5 min, $t_r(d_2e_1$ minor/major) = 23.7 min): mp 151−152 °C; R_f = 0.45 (25% EtOAc/hexanes); IR (film) 3391, 2977, 2922, 1692, 1553, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.28−7.24 (m, 1H), 7.14 (m, 3H), 5.73 (d, J = 9.2 Hz, 1H), 5.60 (br d, 1H), 4.77 (d, J = 9.2 Hz, 1H), 2.36 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 154.1, 139.0, 136.9, 133.4, 130.3, 130.0,

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129.7, 129.0, 127.9, 126.9, 124.0, 93.6, 28.0, 21.4; HRMS (ESI) exact mass calcd for $C_{20}H_{23}ClN_2NaO_4$ $[M + Na]^+$, 413.1244, found 413.1247.

***tert*-Butyl ((1*R*,2*S*)-2-(5-bromo-2-fluorophenyl)-2-nitro-1-(*m*-tolyl)ethyl)carbamate (4dg).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**9** (5 mol %) with a 42 h reaction time. Column chromatography (SiO_2, 0−10% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (34 mg, 80%) that was found to be 68% ee and 5:1 dr by chiral HPLC (Chiralcel AD: 7% EtOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 9.5 min, $t_r(d_1e_1$ major/major) = 10.5 min, $t_r(d_2e_2$ minor/minor) = 12.2 min, $t_r(d_1e_2$ major/minor) = 34.6 min): mp 150−151 °C; R_f = 0.60 (25% EtOAc/hexanes); IR (film) 3297, 2974, 2919, 1707, 1563, 1487 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 4.0 Hz, 1H), 7.51 (m, 1H), 7.25 (m, 1H), 7.16 (m, 2H), 7.00 (m, 2H), 6.12 (d, J = 10.4 Hz, 1H), 5.61 (d, J = 10.0 Hz, 1H), 4.88 (br d, 1H), 2.36 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.9 (d, $^1J_{CF}$ = 248 Hz), 154.1, 139.0, 136.7, 134.7 (d, $^3J_{CF}$ = 8 Hz), 129.8, 129.1, 127.8, 127.3, 124.0, 121.2 (d, $^3J_{CF}$ = 13 Hz), 117.4 (d, $^2J_{CF}$ = 23 Hz), 117.1 (d, $^4J_{CF}$ = 3 Hz), 85.9 (d, $^3J_{CF}$ = 13 Hz), 28.1, 21.4; HRMS (ESI) exact mass calcd for $C_{20}H_{22}BrFN_2NaO_4$ $[M + Na]^+$, 475.0645, found 475.0663.

***tert*-Butyl ((1*R*,2*S*)-2-Nitro-1,2-bis(*m*-tolyl)ethyl)carbamate (4fg).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. The filtrate was analytically pure, and the adduct was isolated as a white crystalline solid (40.0 mg, 95%) that was found to be 86% ee and 50:1 dr by chiral HPLC (Chiralcel AD-H: 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 9.8 min, $t_r(d_2e_2$ minor/minor) = 15.2 min, $t_r(d_1e_1$ major/major) = 16.4 min, $t_r(d_1e_2$ major/minor) = 18.1 min): $[\alpha]_D^{20}$ = −35° (*c* 0.29, $CHCl_3$); mp 179−180 °C; R_f = 0.38 (25% EtOAc/hexanes); IR (film) 3384, 2911, 2857, 1686, 1549, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.36 (m, 2H), 7.29 (dd, J = 7.2, 7.2 Hz, 1H), 7.16−7.23 (m, 2H), 7.15−7.13 (m, 3H), 5.72 (d, J = 9.6 Hz, 1H), 5.64 (br dd, 1H), 4.82 (d, J = 8.0 Hz, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 138.7, 138.6, 137.6, 131.5, 130.9, 129.4, 129.3, 128.9, 128.7, 127.9, 125.8, 124.0, 94.4, 80.2, 28.0, 21.4, 21.3; HRMS (ESI) exact mass calcd for $C_{21}H_{26}N_2NaO_4$ $[M + Na]^+$ 393.1790, found 393.1794.

***tert*-Butyl ((1*R*,2*S*)-2-(4-Bromophenyl)-1-(3-chlorophenyl)-2-nitroethyl)carbamate (4bh).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 20 h reaction time. Following silica plug filtration, the product was isolated as an an off-white crystalline solid (27 mg, 78%) that was found to be 90% ee and 70:1 dr by chiral HPLC (Chiralcel AD-H: 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 13.4 min, $t_r(d_1e_2$ major/minor) = 14.9 min, $t_r(d_1e_1$ major/major) = 20.9 min, $t_r(d_2e_2$ minor/minor) = 35.9 min): $[\alpha]_D^{20}$ = −30° (*c* 0.25, $CHCl_3$); mp 175−176 °C; R_f = 0.54 (25% EtOAc/hexanes); IR (film) 3391 (s), 2991, 2928, 1692, 1560, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 2H), 7.43 (J = 8.0 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.29−7.22 (m, 2H), 5.73 (br d, J = 10.0 Hz, 1H), 5.95 (br d, 1H), 4.85 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 139.1, 135.0, 132.1, 130.4, 130.3, 130.2, 129.1, 127.4, 125.5, 124.8, 93.2, 28.1; HRMS (ESI) exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M + Na]^+$, 477.0193, found 477.0190.

***tert*-Butyl ((1*R*,2*S*)-1,2-Bis(3-chlorophenyl)-2-nitroethyl)carbamate (4ch).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**9** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 5−10% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (27.0 mg, 90%) that was found to be 93% ee and 30:1 dr by chiral HPLC; (Chiralcel IA: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 10.6 min, $t_r(d_1e_2$ major/minor) = 12.9 min, $t_r(d_1e_1$ major/major) = 14.3 min, $t_r(d_2e_2$ minor/minor) = 17.5 min): $[\alpha]_D^{20}$ = −44° (*c* 0.29, $CHCl_3$); mp 170−171 °C; R_f = 0.63 (20% EtOAc/hexanes); IR (film) 3372, 2986, 2924, 1682, 1558, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.47−7.43 (m, 2H), 7.38−7.31 (m, 3H), 7.30−7.24 (m, 2H), 5.75 (br d, 1H), 5.59 (br dd, 1H), 4.98 (br d, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 139.1, 135.0, 134.8, 133.0, 130.5, 130.4, 130.2, 129.2, 128.9, 127.4, 126.8, 125.5, 93.1, 28.2; HRMS (ESI) exact mass calcd for $C_{19}H_{20}Cl_2N_2NaO_4$ $[M + Na]^+$ 433.0698, found 433.0715.

***tert*-Butyl ((1*R*,2*S*)-2-(5-Bromo-2-fluorophenyl)-1-(3-chlorophenyl)-2-nitroethyl)carbamate (4dh).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 24 h reaction time. Following silica plug filtration, ^1H NMR showed 3:1 dr. Column chromatography (SiO_2, 0−10% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (24 mg, 66%) that was found to be 76% ee and 1:1 dr by chiral HPLC (Chiralcel OJ-H: 3% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 20.2 min, $t_r(d_1e_1$ major/major) = 22.8 min, $t_r(d_2e_2$ minor/minor) = 25.3 min, $t_r(d_2e_2$ minor/minor) = 27.5 min): mp 158−159 °C; R_f = 0.55 (20% EtOAc/hexanes); IR (film) 3372, 2986, 2924, 1682, 1558, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 6.0, 2.4, 1H), 7.54 (m, 1H), 7.34 (m, 2H), 7.25 (m, 2H), 7.04 (dd, J = 9.2, 9.2 Hz, 1H), 6.10 (d, J = 9.6 Hz, 1H), 5.66 (br d, J = 9.4 Hz, 1H), 4.90 (br d, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.9 (d, $^1J_{CF}$ = 249 Hz), 154.0, 138.3, 134.9 (d, $^2J_{CF}$ = 23 Hz), 134.8 (d, $^3J_{CF}$ = 8 Hz), 130.5, 129.3, 127.4, 124.9, 120.8 (d, $^3J_{CF}$ = 12 Hz), 117.6 (d, $^2J_{CF}$ = 24 Hz), 117.3 (d, $^4J_{CF}$ = 3 Hz), 85.6 (d, $^4J_{CF}$ = 4 Hz), 28.0; HRMS (ESI) exact mass calcd for $C_{19}H_{19}BrClFN_2NaO_4$ $[M + Na]^+$, 495.0098, found 495.0115.

***tert*-Butyl ((1*R*,2*S*)-1-(3-Chlorophenyl)-2-nitro-2-(*m*-tolyl)ethyl)carbamate (4fh).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 0−5% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (25 mg, 74%) that was found to be 85% ee and 8:1 dr by chiral HPLC (Chiralcel AD: 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 9.1 min, $t_r(d_1e_2$ major/minor) = 12.8 min, $t_r(d_2e_2$ minor/minor) = 14.8 min, $t_r(d_1e_1$ major/major) = 15.9 min): mp 153−154 °C; R_f = 0.50 (20% EtOAc/hexanes); IR (film) 3390, 2980, 1687, 1548, 1515, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.23 (m, 8H), 5.71 (d, J = 9.6 Hz, 1H), 5.62 (dd, J = 9.6, 8.0 Hz, 1H), 4.79 (d, J = 8.8 Hz, 1H), 2.38 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (150 MHz. $CDCl_3$) ppm 154.2, 139.7, 138.8, 134.8, 131.2, 131.1, 130.2, 129.2, 128.9 (2C), 127.4, 125.7, 125.5, 94.0, 28.0, 21.3; HRMS (ESI) exact mass calcd for $C_{20}H_{23}ClN_2NaO_4$ $[M + Na]^+$ 413.1241; found 413.1245.

***tert*-Butyl ((1*R*,2*S*)-1-(3-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (4hh).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 72 h reaction time. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the product as a light brown crystalline solid (38 mg, 68%) that was found to be 70% ee and 23:1 dr determined by chiral HPLC (Chiralcel IA: 7% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 8.5 min, $t_r(d_1e_1$ major/major) = 9.3 min, $t_r(d_2e_1$ minor/major) = 10.6 min, $t_r(d_2e_2$ minor/minor) = 12.8 min): mp 161−162 °C; R_f = 0.4 (20% EtOAc/hexanes); IR (film) 3342, 2975, 2940, 1701, 1563, 1521, 1376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 1H), 7.30−7.28 (m, 2H), 7.25−7.22 (m, 1H), 7.09−7.05 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 5.70 (m, 2H), 4.88 (br d, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 150.7, 149.2, 139.7, 134.8, 130.2, 128.9, 127.4, 125.5, 123.5, 122.1, 93.8, 56.0, 28.6; HRMS (ESI) exact mass calcd for $C_{21}H_{25}ClN_2NaO_6$ $[M + Na]^+$ 459.1299, found 459.1301.

***tert*-Butyl ((1*R*,2*S*)-1-(5-Bromo-2-fluorophenyl)-2-(4-bromophenyl)-2-nitroethyl)carbamate (4bj).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 0−10% ethyl acetate in hexanes) afforded the product as an off-white crystalline solid (95 mg, 87%) that was found to be 86% ee and 60:1 dr by chiral HPLC (Chiralcel AD-H: 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 9.8 min, $t_r(d_2e_1$ minor/major) = 11.0 min, $t_r(d_1e_1$ major/major) = 21.9 min, $t_r(d_2e_2$ minor/minor) = 25.9 min): $[\alpha]_D^{20}$ = −14° (*c* 0.43, $CHCl_3$); mp 160−161 °C; R_f = 0.53 (20% EtOAc/hexanes); IR (film) 3397, 2982, 2926, 1708, 1563, 1500, 1376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 2H), 7.51 (m, 1H), 7.49−7.43 (m, 3H), 7.00 (dd, J = 8.8, 8.8 Hz, 1H), 5.79 (m, 2H), 5.04 (br d, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 160.1 (, $^1J_{CF}$ = 241 Hz), 154.1, 133.7 (d, $^3J_{CF}$ = 9 Hz), 132.3, 132.1, 130.3, 130.0, 126.0 (d, $^3J_{CF}$ = 15 Hz), 124.9, 117.9 (d, $^2J_{CF}$ = 23 Hz), 117.4,

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92.3, 28.0; HRMS (ESI) exact mass calcd for $C_{19}H_{19}Br_2FN_2NaO_4$ [M + Na]$^+$, 538.9593, found 538.9596.

***tert*-Butyl ((1*S*,2*R*)-1-(4-Bromophenyl)-2-(4-chlorophenyl)-2-nitroethyl)carbamate (4cj).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**9** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 0−5% ethyl acetate in hexanes) afforded the adduct as a white solid (28 mg, 90%) that was found to be 88% ee and 8:1 dr determined by chiral HPLC (Chiralcel AD-H: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 10.6 min, $t_r(d_2e_1$ minor/major) = 13.8 min, $t_r(d_2e_2$ minor/minor) = 19.1 min, $t_r(d_1e_1$ major/major) = 22.2 min): mp 185−186 °C; R_f = 0.45 (20% EtOAc/hexanes); IR (film) 3361, 2973, 2924, 1710, 1565, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.54−7.51 (m, 2H), 7.48−7.42 (m, 2H), 7.40−7.33 (m, 1H), 7.01 (dd, *J* = 8.8, 8.8 Hz, 1H), 5.80 (m, 2H), 5.03 (d, *J* = 9.6 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 160.2 (d, $^1J_{CF}$ = 244 Hz), 133.8, 133.7, 132.8, 130.9 (2C), 130.6, 130.2, 129.1, 128.8 (2C), 126.7, 125.9, 118.0 (d, $^2J_{CF}$ = 23 Hz), 117.4, 92.2, 28.1; HRMS (ESI) exact mass calcd for $C_{19}H_{19}BrClFN_2NaO_4$ [M + Na]$^+$ 495.0095, found 495.0100.

***tert*-Butyl ((1*R*,2*S*)-1,2-Bis(5-bromo-2-fluorophenyl)-2-nitroethyl)carbamate (4dj).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 0−5% ethyl acetate in hexanes) afforded the product as a white crystalline solid (22 mg, 56%) that was found to be 78% ee and 2:1 dr by chiral HPLC; (ChiralPak IA, 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$ major/major) = 5.9 min, $t_r(d_2e_1$ minor/major) = 6.5 min, $t_r(d_2e_2$ minor/minor) = 7.1 min, $t_r(d_1e_2$ major/minor) = 8.9 min): mp 156−157 °C; R_f = 0.78 (20% EtOAc in hexanes); IR (film) 3324, 2965, 2924, 1710, 1565, 1489 cm^{-1}; ^{1}H NMR for both diastereomers reported (600 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.72 (dd, *J* = 4.8 Hz, 1H), 7.53−7.37 (m, 4H), 7.03 (m, 2H), 6.94 (m, 2H), 6.28 (br d, 1H), 6.21 (d, *J* = 10.8 Hz, 1H), 5.79−5.71 (m, 2H), 5.10 (d, *J* = 9.6 Hz, 1H), 1.39 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 159.8 (d, $^1J_{CF}$ = 249 Hz), 159.4 (d, $^1J_{CF}$ = 249 Hz), 154.5, 154.1, 135.0 (2C), 133.9 (2C), 133.7, 133.5, 133.4, 132.1, 131.9, 130.1, 125.6, 120.7, 118.2, 118.0, 117.8, 117.6, 117.4 (2C), 117.2, 84.7, 84.4, 81.2, 81.0, 29.7, 28.3, 28.1; HRMS (ESI) exact mass calcd for $C_{19}H_{18}Br_2F_2N_2NaO_4$ [M + Na]$^+$ 556.9499; found 556.9482.

***tert*-Butyl ((1*R*,2*S*)-1-(5-Bromo-2-fluorophenyl)-2-nitro-2-(*m*-tolyl)ethyl)carbamate (4fj).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**9** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 5−10% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (23 mg, 42%) that was found to be 82% ee and 40:1 dr by chiral HPLC (Chiralcel IA: 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 7.4 min, $t_r(d_1e_1$ major/major) = 14.9 min, $t_r(d_1e_2$ major/minor) = 6.6 min, $t_r(d_2e_2$ minor/minor) = 9.2 min): $[\alpha]_D^{20}$ = −13° (*c* 0.31, $CHCl_3$, 76% ee, 20:1 dr); mp 159−165 °C; R_f = 0.48 (20% EtOAc in hexanes); IR (film) 3450, 3000, 2950, 2410, 1710, 1590, 1490, 1260 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (br s, 1H), 7.44 (ddd, *J* = 8.8, 4.8, 2.8 Hz, 1H), 7.38 (s, 1H), 7.36 (s, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.25 (s, 1H), 7.00 (dd, *J* = 10.8, 9.2 Hz, 1H), 5.80 (m, 2H), 4.98 (br d, 1H), 2.38 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.4 (d, $^1J_{CF}$ = 249 Hz), 154.5, 138.7, 133.4, 131.1 (d, $^3J_{CF}$ = 8 Hz), 130.9, 129.1, 128.8, 125.6, 118.0, 117.5 (d, $^2J_{CF}$ = 23 Hz), 92.8, 27.9, 21.3; HRMS (ESI) exact mass calcd for $C_{20}H_{22}{}^{81}BrFN_2NaO_4$ [M + Na]$^+$ 477.0646, found 477.0660.

***tert*-Butyl ((1*R*,2*S*)-1-(5-Bromo-2-fluorophenyl)-2-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (4hj).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 72 h reaction time. Following silica plug filtration, ^{1}H NMR showed >20:1 dr. Column chromatography (SiO_2, 10−40% ethyl acetate in hexanes) afforded the adduct as an off-white solid (31.0 mg, 70%) that was found to be 56% ee and 4:1 dr (racemized on silica) by chiral HPLC (Chiralcel IA: 12% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 9.5 min, $t_r(d_2e_1$ minor/major) = 10.3 min, $t_r(d_2e_2$ minor/minor) = 16.8 min, $t_r(d_1e_1$ major/major) = 23.4 min): mp 131−132 °C; R_f = 0.66 (50% EtOAc/hexanes); IR (film) 3368, 2974, 2928, 1703, 1556, 1518, 1279 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 4.8 Hz, 1H), 7.44 (m, 1H), 7.15 (br s, 1H), 7.09 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.00 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.88 (dd, *J* = 8.0, 8.0 Hz, 1H), 5.77 (m, 2H), 5.00 (d, *J* = 8.8 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 150.1 (d, $^1J_{CF}$ = 253 Hz), 133.5 (d, $^3J_{CF}$ = 9 Hz), 126.5 (d, $^3J_{CF}$ = 9 Hz), 123.2 (d, $^2J_{CF}$ = 27 Hz), 122.3, 122.1, 117.9 (d, $^2J_{CF}$ = 23 Hz), 117.3, 112.6, 111.1, 110.8, 110.7, 92.8 (d, $^4J_{CF}$ = 5 Hz), 80.5, 56.0 (2C), 28.1; HRMS (ESI) exact mass calcd for $C_{21}H_{24}BrFN_2NaO_6$ [M + Na]$^+$ 521.0699, found 521.0701.

***tert*-Butyl ((1*R*,2*S*)-2-(4-Bromophenyl)-1-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (4bk).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 44 h reaction time. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the product as an off-white crystalline solid (33 mg, 60%) that was found to be 85% ee and 9:1 dr by chiral HPLC (Chiralcel AD-H: 9% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 16.3 min, $t_r(d_2e_1$ minor/major) = 19.5 min, $t_r(d_1e_1$ major/major) = 22.4 min, $t_r(d_2e_2$ major/major) = 53.5 min): mp 153−154 °C; R_f = 0.19 (25% EtOAc/hexanes); IR (film) 3368, 2973, 2938, 1697, 1551, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 6.86 (m, 3H), 5.76 (d, *J* = 9.2 Hz, 1H), 5.54 (dd, *J* = 9.6, 9.2 Hz, 1H), 4.83 (br d, 1H), 3.87 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 149.4, 149.2, 131.9, 130.6, 130.5, 129.5, 124.6, 119.2, 111.3, 110.6, 93.5, 56.0, 55.9, 28.0; HRMS (ESI) exact mass calcd for $C_{21}H_{25}BrN_2NaO_6$ [M + Na]$^+$, 503.0790, found 503.0794.

***tert*-Butyl ((1*R*,2*S*)-2-(3-Chlorophenyl)-1-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (4ck).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 60 h reaction time. Following the silica plug filtration, the resulting white solid was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the pure compound as an off-white solid (15.3 mg, 64%) that was found to be 93% ee and 56:1 dr by chiral HPLC (Chiralcel AD-H: 6% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 19.9 min, $t_r(d_2e_1$ minor/major) = 23.3 min, $t_r(d_1e_1$ major/major) = 25.5 min, $t_r(d_2e_2$ minor/minor) = 35.2 min): $[\alpha]_D^{20}$ = −8.8° (*c* 0.25, $CHCl_3$); mp 185 °C (dec.); R_f = 0.17 (25% EtOAc/hexanes); IR (film) 3351, 2979, 2937, 1703, 1565, 1517 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.35 (m, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 2H), 5.77 (d, *J* = 9.2 Hz, 1H), 5.54 (dd, *J* = 9.6, 9.2 Hz, 1H), 4.80 (d, *J* = 9.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 149.4, 149.3, 134.6, 133.4, 130.3, 130.0, 129.5, 129.1, 126.9, 119.2, 111.4, 110.6, 93.5, 56.0, 55.9, 28.0; HRMS (ESI) exact mass calcd for $C_{21}H_{25}ClN_2NaO_6$ [M + Na]$^+$ 459.1299, found 459.1322.

***tert*-Butyl ((1*R*,2*S*)-2-(5-Bromo-2-fluorophenyl)-1-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (4dk).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**9** (5 mol %) with a 46 h reaction time. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the adduct as a white crystalline solid (22 mg, 45%) that was found to be 86% ee and 1.5:1 dr by chiral HPLC (Chiralcel IC: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 15.1 min, $t_r(d_1e_1$ major/major) = 16.8 min, $t_r(d_2e_2$ minor/minor) = 20.0 min, $t_r(d_1e_2$ major/minor) = 38.3 min): mp 135−136 °C; R_f = 0.27 (25% EtOAc/hexanes); IR (film) 3391, 2991, 2928, 1692, 1560, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 6.0, 2.0 Hz, 1H), 7.51 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.90 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.85 (m, 2H), 6.12 (d, *J* = 10.0 Hz, 1H), 5.60 (br d, 1H), 4.82 (d, *J* = 9.6 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.9 (d, $^1J_{CF}$ = 240 Hz), 149.5, 149.4, 134.7 (d, $^3J_{CF}$ =11 Hz), 132.4 (d, $^3J_{CF}$ = 9 Hz), 129.2, 126.9, 121.2, 121.1, 119.0, 117.2 (d, $^4J_{CF}$ = 3 Hz), 111.5, 85.5 (d, $^4J_{CF}$ = 2 Hz), 56.0, 55.9, 28.2, 28.0; HRMS (ESI) exact mass calcd for $C_{21}H_{24}BrFN_2NaO_6$ [M + Na]$^+$, 521.0699, found 521.0684.

***tert*-Butyl ((1*R*,2*S*)-1-(3,4-Dimethoxyphenyl)-2-nitro-2-(*m*-tolyl)ethyl)carbamate (4fk).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**9** (5 mol %) with a 36 h reaction time. Column chromatography (SiO_2, 0−20% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (18 mg, 65%) that was found to be 72% ee and 60:1 dr by chiral HPLC

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(Chiralcel IA: 12% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 13.4 min, $t_r(d_1e_2$ major/minor) = 18.3 min, $t_r(d_1e_1$ major/major) = 22.2 min, $t_r(d_2e_2$ minor/minor) = 28.8 min): $[\alpha]_D^{20} = -16°$ (c 0.25, $CHCl_3$); mp 146−148 °C; R_f = 0.31 (25% EtOAc/hexanes); IR (film) 3377, 2987, 2925, 1686, 1549, 1522 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.31−7.22 (m, 2H), 6.90 (d, J = 8.0 Hz, 1H), 6.83 (m, 2H), 5.74 (d, J = 9.2 Hz, 1H), 5.58 (dd, J = 9.2, 8.8 Hz, 1H), 4.78 (d, J = 8.8 Hz, 1H), 3.87 (s, 6H), 2.37 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 149.2, 149.1, 138.6, 131.5, 130.9, 130.2, 129.3, 128.7, 125.8, 119.2, 111.3, 110.6, 94.3, 55.9 (2C), 29.7, 28.0, 21.3; HRMS (ESI) exact mass calcd for $C_{22}H_{28}N_2NaO_6$ [M + Na]$^+$, 439.1845, found 439.1862.

***tert*-Butyl ((1*S*,2*R*)-2-(4-Chlorophenyl)-1-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (4ak).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Column chromatography (SiO_2, 0−5% ethyl acetate in hexanes) afforded the product as a tan crystalline solid (28.3 mg, 54%) that was found to be 92% ee and 25:1 dr by chiral HPLC (ChiralPak AD-H, 10% EtOH/hexanes, 1.0 mL/min: t_r (*anti*, minor) = 13.2 min, t_r (*syn*, major) = 15.8 min, t_r (*anti*, major) = 17.2 min, t_r (*syn*, minor) = 36.8 min): $[\alpha]_D^{20} = -21°$ (c 0.36, $CHCl_3$); mp 150−151 °C; R_f = 0.11 (20% EtOAc in hexanes); IR (film) 3383, 2989, 1676, 1595, 1519, 1463, 1423, 1367 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 6.82−6.89 (m, 3H), 5.77 (d, J = 9.2 Hz, 1H), 5.54 (dd, J = 9.4, 9.2 Hz, 1H), 3.87 (br d, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 149.3, 149.2, 136.3, 130.2, 130.0, 129.5, 128.9, 119.1, 111.3, 110.5, 93.4, 80.5, 55.9, 55.8, 29.6, 28.0; HRMS (ESI) exact mass calcd for $C_{21}H_{25}ClN_2NaO_6$ [M + Na]$^+$ 459.1299; found 459.1305.

***tert*-Butyl ((1*R*,2*S*)-1,2-Bis(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (4hk).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 48 h reaction time. Following silica plug filtration, ^{1}H NMR showed >20:1 dr. Column chromatography (SiO_2, 10−40% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (23.0 mg, 72%) that was found to be 50% ee and 5:1 dr (epimerized on silica) by chiral HPLC (Chiralcel IA: 12% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_2$ minor/minor) = 15.4 min, $t_r(d_1e_2$ major/minor) = 17.8 min, $t_r(d_1e_1$ major/major) = 24.8 min, $t_r(d_2e_2$ minor/minor) = 34.5 min): mp 171 °C dec; R_f = 0.75 (50% EtOAc/hexanes); IR (film) 3369, 2969, 2930, 2838, 1699, 1553, 1523, 1253 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.08 (dd, J = 8.4, 2.0 Hz, 1H), 6.91−6.83 (m, 4H), 5.73 (d, J = 10.0 Hz, 1H), 5.63 (dd, J = 10.0, 8.4 Hz, 1H), 4.78 (d, J = 9.2 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.4, 150.5, 149.2, 149.1 (2C), 130.1, 123.9, 122.2, 119.1, 111.3, 122.2, 119.1, 111.1, 111.0, 110.7, 110.6, 94.2, 80.3, 55.9 (4C), 28.1; HRMS (ESI) exact mass calcd for $C_{23}H_{30}N_2NaO_8$ [M + Na]$^+$ 485.1933, found 485.1958.

***tert*-Butyl ((1*R*,2*S*)-2-(3,4-Dimethoxyphenyl)-2-nitro-1-(*m*-tolyl)ethyl)carbamate (4hg).** This compound was prepared according to the general procedure employing catalyst (*R*,*R*)-**10** (5 mol %) with a 72 h reaction time. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the product as a light brown crystalline solid (30 mg, 70%) that was found to be 78% ee and 1:1 dr (epimerized from 20:1 dr (^{1}H NMR) shortly after Buchner filtration) determined by chiral HPLC (Chiralcel AD: 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$ major/major) = 15.2 min, $t_r(d_1e_2$ major/minor) = 22.4 min, $t_r(d_2e_1$ minor/major) = 24.8 min, $t_r(d_2e_2$ minor/minor) = 39.0 min): mp 175−177 °C; R_f = 0.31 (20% EtOAc/hexanes); IR (film) 3344, 2972, 2931, 1703, 1558, 1524, 1468 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.2 Hz, 1H), 7.15−7.08 (m, 5H), 6.85 (d, J = 8.4 Hz, 1H), 5.70 (m, 2H), 4.81 (d, J = 8.4 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.34 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.4, 150.5, 149.0, 138.7, 137.0, 129.5, 128.9, 127.7, 124.0, 122.2, 121.4, 111.1, 111.0, 94.3, 56.0, 28.2, 21.2; HRMS (ESI) exact mass calcd for $C_{22}H_{28}N_2NaO_6$ [M + Na]$^+$, 439.1845, found 439.1862.

***tert*-Butyl ((1*R*,2*S*)-2-Amino-2-(4-bromophenyl)-1-(4-chlorophenyl)ethyl)carbamate (S6).** β-Nitro Boc-amine **4ba** (470 mg, 1.03 mmol) and $CoCl_2$ (134 mg, 1.03 mmol) were added to methanol (4.1 mL) in a flask and chilled to 0 °C before $NaBH_4$ (194 mg, 5.15 mmol) was added in three portions over 2 h. The reaction mixture was stirred at 0 °C for an additional 15 min before the mixture was quenched with saturated aqueous NH_4Cl. The reaction mixture was adjusted to pH 10 with concentrated aqueous NH_4OH, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a white foam (416 mg, 95%): $[\alpha]_D^{20} = +44°$ (c 0.80, $CHCl_3$); R_f = 0.40 (50% EtOAc/hexanes); IR (film) 3378, 3274, 2977, 1698, 1526, 1491 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 7.2 Hz, 2H), 6.94 (d, J = 7.2 Hz, 2H), 5.46 (d, J = 6.8 Hz, 1H), 4.79 (br t, 1H), 4.22 (br d, 1H), 1.56 (br s, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.1, 140.8, 133.4, 132.6, 128.7 (2C), 128.3, 121.41, 120.3, 79.8, 59.3, 28.3 (3C); HRMS (ESI) exact mass calcd for $C_{19}H_{23}BrClN_2O_2$ [M + H]$^+$ 425.0631, found 425.0643.

***tert*-Butyl ((1*R*,2*S*)-2-(4-Bromophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)carbamate (S7).** Amine **S6** (383 mg, 900 μmol) and carboxylic acid (189 mg, 900 μmol) were dissolved in CH_2Cl_2 (4.5 mL), chilled to 0 °C, and treated with EDC·HCl (224 mg, 1.17 mmol) and DMAP (10 mg, 90 μmol). The reaction mixture was stirred and gradually warmed to room temperature over 2 h. After 16 h, the mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$, and once more with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was washed with a 3/7 dichloromethane/hexanes mixture and decanted to afford a white solid (438 mg, 79%) that was >95% pure by ^{1}H NMR: $[\alpha]_D^{20} = -17°$ (c 0.39, $CHCl_3$); mp =223−225 °C; R_f = 0.9 (10% MeOH/CH_2Cl_2); IR (film) 3350, 2978, 1685, 1631, 1611, 1530, 1496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 6.8 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.94 (m, 4H), 6.59 (dd, J = 8.8, 2.4 Hz, 1H), 6.46 (d, J = 1.2 Hz, 1H), 5.87 (d, J = 4.8 Hz, 1H), 5.75 (d, J = 5.6 Hz, 1H), 5.08 (d, J = 3.6 Hz, 1H), 4.68 (qq, J = 6.0, 6.0 Hz, 1H), 3.84 (s, 3H), 1.38 (s, 9H), 1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.6, 163.7, 157.2, 155.1, 137.3, 134.4, 133.4, 131.5, 128.9, 128.7, 128.4, 121.7, 114.2, 105.3, 100.3, 80.0, 71.5, 59.5, 56.7, 55.5, 31.6, 28.3, 22.6, 22.0, 21.6, 14.1; HRMS (ESI) exact mass calcd for $C_{30}H_{34}BrClN_2NaO_5$ [M + Na]$^+$ 639.1237, found 639.1248.

***N*-((1*S*,2*R*)-2-Amino-1-(4-bromophenyl)-2-(4-chlorophenyl)ethyl)-2-isopropoxy-4-methoxybenzamide (S8).** Amide **S7** (374 mg, 605 μmol) was dissolved in dichloromethane (6.0 mL), and the solution was treated with TFA (1.8 mL, 24 mmol) and stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane, poured into saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a white foam (300 mg, 96%): $[\alpha]_D^{20} = -103°$ (c 1.07, $CHCl_3$); R_f = 0.6 (10% MeOH/CH_2Cl_2); IR (film) 3371, 2991, 2929, 1643, 1609, 1519, 1498 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.89 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.55 (dd, J = 8.8, 2.0 Hz, 1H), 6.48 (d, J = 2.0 Hz, 1H), 5.40 (dd, J = 8.0, 8.0 Hz, 1H), 4.75 (qq, J = 6.0, 6.0 Hz, 1H), 4.40 (d, J = 8.8 Hz, 1H), 3.83 (s, 3H), 1.70 (br, 2H), 1.44 (d, J = 6.0 Hz, 3H), 1.43 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 164.6, 163.3, 157.2, 140.7, 137.3, 134.1, 133.1, 131.1, 129.5, 128.4, 128.3, 121.4, 114.9, 105.1, 100.3, 71.5, 58.9, 58.6, 55.5, 22.2, 22.0; HRMS (ESI) exact mass calcd for $C_{25}H_{26}BrClN_2NaO_3$ [M + Na]$^+$ 539.0713, found 539.0696.

***N*-((1*R*,2*S*)-2-(4-Bromophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S9).** Amine **S8** (267 mg, 516 μmol) was added to carbonyl diimidazole (109 mg, 671 μmol) in dichloromethane (1.8 mL). The mixture was stirred at room temperature for 90 min (or until no starting material remained by TLC), at which point the oxopiperazine (103 mg, 1.03 μmol) was added. The mixture was stirred for 16 h and then diluted with dichloromethane and water. The aqueous layer was extracted with dichloromethane, and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to an off-white oil. Column chromatography (SiO_2, 0−3% methanol in dichloromethane) afforded

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the urea as a white solid (301 mg, 91%): $[\alpha]_D^{20}$ = +90° (*c* 0.54, $CHCl_3$); mp =170 °C (dec.); R_f = 0.36 (10% MeOH/CH_2Cl_2); IR (film) 3375, 3236, 2980, 1669, 1634, 1606, 1537, 1495 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.6 Hz, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.89 (m, 4H), 6.70 (br s, 1H), 6.60 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.75 (dd, *J* = 8.0, 2.4 Hz, 1H), 5.10 (dd, *J* = 2.8, 2.4 Hz, 1H), 4.65 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.13 (d, *J* = 2.4 Hz, 2H), 3.85 (s, 3H), 3.71 (m, 1H), 3.59 (m, 1H), 3.38 (m, 2H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 167.8, 167.2, 164.0, 157.3, 155.0, 137.0, 136.4, 134.4, 133.3, 131.6, 129.4, 128.7, 128.1, 122.0, 113.4, 105.4, 100.3, 71.5, 61.8, 57.7, 55.6, 47.5, 41.1, 40.0, 22.0, 21.5; HRMS (ESI) exact mass calcd for $C_{30}H_{32}BrClN_4NaO_5$ $[M + Na]^+$ 665.1142, found 665.1149.

***tert*-Butyl ((1*S*,2*R*)-2-Amino-1-(4-bromophenyl)-2-(4-chlorophenyl)ethyl)carbamate (S10).** *β*-Nitro Boc-amine **4ac** (265 mg, 581 *μ*mol) and $CoCl_2$ (75.4 mg, 581 *μ*mol) were added to methanol (3 mL) in a flask and chilled to 0 °C before $NaBH_4$ (110 mg, 2.91 mmol) was added in three portions over 45 min. The reaction mixture was stirred at 0 °C for an additional 15 min before the mixture was quenched with saturated aqueous NH_4Cl. The reaction mixture was adjusted to pH 10 with concentrated aqueous NH_4OH, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a white foam (260 mg, 99%): $[\alpha]_D^{20}$ = +40° (*c* 0.27, $CHCl_3$); R_f = 0.31 (50% EtOAc/hexanes); IR (film) 3371, 2976, 2982, 2859, 1697, 1489, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.45 (br s, 1H), 4.77 (br s, 1H), 4.23 (s, 1H), 1.36 (s, 9H), 1.25 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.0, 140.3, 133.3, 131.5, 131.2, 129.1, 128.4, 128.3, 121.5, 59.1, 28.3 (3C); HRMS (ESI) exact mass calcd for $C_{19}H_{23}BrClN_2O_2$ $[M + H]^+$ 425.0631, found 425.0641.

***N*-((1*R*,2*S*)-2-Amino-2-(4-bromophenyl)-1-(4-chlorophenyl)-ethyl)-3-oxopiperazine-1-carboxamide (S11).** Amine **S10** (241 mg, 566 *μ*mol) was added to carbonyl diimidazole (119 mg, 736 *μ*mol) in dichloromethane (2.0 mL). The mixture was stirred at room temperature for 3 h (or until no starting material remained by TLC), at which point the oxopiperazine (113 mg, 1.13 mmol) was added. The mixture was stirred for 16 h and then diluted with dichloromethane and water. The aqueous layer was extracted with dichloromethane, and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to an off-white solid. The solid was washed with 1/1 dichloromethane/hexanes (6 mL), and the wash layer was decanted to afford the desired product as a 1/1 mixture with imidazole. This was used without further purification. The urea (230 mg, 417 *μ*mol) was dissolved in dichloromethane (5.0 mL), and the solution was treated with TFA (1.26 mL, 16.0 mmol) and stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane, poured into saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a brown oil (170 mg, 67% over two steps): $[\alpha]_D^{20}$ = +32° (*c* 0.24, $CHCl_3$); R_f = 0.23 (10% MeOH/CH_2Cl_2); IR (film) 3344, 3262, 3069, 2924, 2848, 1675, 1537, 1496 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.84 (br s, 1H), 5.89 (d, *J* = 7.2 Hz, 1H), 5.00 (t, *J* = 6.4 Hz, 1H), 4.26 (d, *J* = 4.8 Hz, 1H), 4.05 (s, 2H), 3.60 (d, *J* = 2.8 Hz, 2H), 3.33 (br d, 2H), 1.85 (br s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 167.3, 155.7, 140.8, 136.7, 133.4, 131.4, 128.8, 128.5 (2C), 128.3, 121.5 (2C), 59.3, 59.1, 47.6, 40.9, 39.7, 29.7; HRMS (ESI) exact mass calcd for $C_{19}H_{21}BrClN_4O_2$ $[M + H]^+$ 451.0536, found 451.0536.

***N*-((1*R*,2*S*)-2-(4-Bromophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S12).** Amine **S11** (116 mg, 257 *μ*mol) and carboxylic acid (54.0 mg, 257 *μ*mol) were dissolved in dichloromethane (1.3 mL), chilled to 0 °C, and treated with EDC·HCl (64.0 mg, 334 *μ*mol) and DMAP (3.1 mg, 26 *μ*mol). The reaction mixture was stirred and gradually warmed to room temperature over 2 h. After 5 h, the mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$, and once more with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0−6% methanol in dichloromethane) afforded the amide as a white solid (112 mg, 68%): $[\alpha]_D^{20}$ = +32° (*c* 0.65, $CHCl_3$); mp =169 °C; R_f = 0.60 (10% MeOH/CH_2Cl_2); IR (film) 3367, 2978, 2934, 1638, 1604, 1532, 1492, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 4.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.85 (br s, 1H), 6.60 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 5.76 (dd, *J* = 8.0, 2.8 Hz, 1H), 5.10 (dd, *J* = 2.8, 2.0 Hz, 1H), 4.65 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.10 (d, *J* = 3.2 Hz, 2H), 3.84 (s, 3H), 3.70 (m, 1H), 3.58 (m, 1H), 3.37 (m, 2H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.9, 167.2, 164.0, 157.2, 156.0, 137.1, 136.5, 134.4, 133.3, 131.6, 129.4, 128.7, 128.1, 121.9, 113.5, 105.4, 100.3, 71.5, 61.7, 60.4, 57.7, 55.6, 47.5, 41.1, 40.0, 22.0, 21.5, 21.0, 14.2; HRMS (ESI) exact mass calcd for $C_{30}H_{32}BrClN_4NaO_5$ $[M + Na]^+$ 665.1142, found 665.1165.

***cis*-Imidazoline 11.** Tf_2O (143 *μ*L, 845 *μ*mol) was added to a stirred solution of Ph_3PO (470 mg, 1.69 mmol) in dichloromethane (1.0 mL) at 0 °C, and this mixture was stirred for 10 min and then treated with the *cis*-amide urea **S11** or **S8** (272 mg, 422 *μ*mol) as a solution in dichloromethane (2.0 mL). The mixture was stirred at 0 °C for 1 h prior to stirring at room temperature for 4 h. The reaction mixture was quenched with $NaHCO_3$, the aqueous layer was extracted with dichloromethane, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0−2% methanol in dichloromethane) of the residue provided the product as a white solid (173 mg, 66%): $[\alpha]_D^{20}$ = −69° (*c* 0.70, $CHCl_3$); mp 118−120 °C; R_f = 0.39 (10% MeOH/CH_2Cl_2); IR (film) 3223, 3077, 2980, 2931, 1676, 1613, 1495, 1419 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.55 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.00 (br s, 1H), 5.56 (d, *J* = 9.6 Hz, 1H), 5.46 (d, *J* = 9.6 Hz, 1H), 4.61 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.85 (s, 3H), 3.77 (d, *J* = 18.0 Hz, 1H), 3.65 (d, *J* = 18.0 Hz, 1H), 3.88 (m, 1H), 3.22 (m, 1H), 3.01 (m, 2H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.34 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.9, 163.0, 160.2, 157.0, 154.7, 136.5, 135.0, 133.1, 132.1, 130.9, 129.6, 128.4,128.1, 121.0, 113.4, 104.6, 100.1, 71.8, 70.9, 69.1, 55.5, 49.4, 41.8, 40.3, 22.0 (2C); HRMS (ESI) exact mass calcd for $C_{30}H_{31}BrClN_4O_4$ $[MH]^+$ 625.1217, found 625.1207.

***tert*-Butyl ((1*R*,2*S*)-2-Amino-2-(4-chlorophenyl)-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (S17).** *β*-Nitro Boc-amine *ent*-**4ab** (140 mg, 304 *μ*mol) and $CoCl_2$ (46.0 mg, 304 *μ*mol) were added to methanol (1.2 mL) in a flask and chilled to 0 °C before $NaBH_4$ (57 mg, 1.5 mmol) was added in three portions over 5 h. The reaction mixture was stirred at 0 °C for an additional 15 min before the mixture was quenched with saturated aqueous NH_4Cl. The reaction mixture was adjusted to pH 10 with concentrated aqueous NH_4OH, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 40−60% ethyl acetate in hexanes) afforded the product as a white foam (60 mg, 46%) in about 15:1 dr (by ^1H NMR): R_f = 0.40 (50% EtOAc/hexanes); IR (film) 3378, 3302, 2977, 2929, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.94 (m, 1H), 6.86 (s, 1H), 5.56 (d, *J* = 8.0 Hz, 1H), 4.84 (br dd, 1H), 4.26 (br d, 1H), 1.50 (br m, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.1, 149.0, 140.1, 133.4, 130.6, 129.4, 128.4, 128.2, 125.9, 121.6, 120.3 (q, $^1J_{CF}$ = 251 Hz), 120.0, 119.9, 119.1 79.9, 59.1, 28.2; HRMS (ESI) exact mass calcd for $C_{20}H_{23}ClF_3N_2O_3$ $[M + H]^+$ 431.1349, found 431.1366.

***tert*-Butyl ((1*R*,2*S*)-2-(4-Chlorophenyl)-2-(3-oxopiperazine-1-carboxamido)-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (S18).** Amine **S17** (60 mg, 139 *μ*mol) was added to carbonyl diimidazole (29.4 mg, 181 *μ*mol) in dichloromethane (0.5 mL). The mixture was stirred at room temperature for 90 min (or until no starting material remained by TLC), at which point the oxopiperazine (27.8 mg, 278 *μ*mol) was added. The mixture was stirred for 16 h and then diluted with dichloromethane and water. The aqueous layer was extracted with dichloromethane, and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to an off-white oil. The

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residue was washed with hexanes (4 mL) and the wash layer was decanted to afford the desired product as a 1:1 mixture with imidazole. This was used without further purification. The urea (47 mg, 84 μmol) was dissolved in dichloromethane (2.0 mL), and the solution was treated with TFA (180 μL, 3.3 mmol) and stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane, poured into saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to an oil. The residue was washed with hexanes, and the wash layer was decanted to afford the desired product as a yellow foam (40 mg, 63% over two steps) in about 20:1 dr (by ^1H NMR): R_f = 0.1 (5% MeOH/CH_2Cl_2); IR (film) 3344, 3262, 2924, 1668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, J = 7.8 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 7.8 Hz, 1H), 7.04 (m, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.88 (s, 1H), 6.00 (d, J = 7.2 Hz, 1H), 5.03 (dd, J = 12.6, 1.8 Hz, 1H), 4.33 (d, J = 4.8 Hz, 1H), 4.07 (dd, J = 17.4, 12.6 Hz, 2H), 3.60 (m, 2H), 3.31 (m, 2H), 1.24 (br m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 167.5, 155.7, 149.1, 144.5, 136.6, 133.4, 129.8, 128.8 (2C), 128.3 (2C), 125.2, 120.1, 119.5, 59.4, 59.0, 47.5, 40.9, 39.6, 14.1; HRMS (ESI) exact mass calcd for $C_{20}H_{21}ClF_3N_4O_3$ $[M + H]^+$ 457.1254, found 457.1268.

***cis*-Imidazoline 15.** Tf_2O (16 μL, 96 μmol) was added to a stirred solution of Ph_3PO (53 mg, 191 μmol) in dichloromethane (300 μL) at 0 °C, and this mixture was stirred for 10 min and then treated with *cis*-amide urea **19** (30.2 mg, 48.8 μmol) as a solution in dichloromethane (800 μL). The mixture was stirred at 0 °C for 1 h prior to stirring at room temperature for 4 h. The reaction mixture was quenched with $NaHCO_3$, the aqueous layer was extracted with dichloromethane, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0–4% methanol in dichloromethane) of the residue provided the product as a white solid (21.0 mg, 73%): $[\alpha]_D^{20}$ = −1.7° (*c* 0.21, $CHCl_3$); mp 125–126 °C; R_f = 0.26 (5% MeOH/CH_2Cl_2); IR (film) 3216, 2980, 2932, 1683, 1614, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.8 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 2H), 6.94 (t, J = 8.0 Hz, 2H), 6.87 (s, 1H), 6.84 (d, J = 8.4 Hz, 2H), 6.56 (dd, J = 8.4, 2.0 Hz, 1H), 6.49 (d, J = 2.0 Hz, 1H), 6.40 (s, 1H), 5.59 (d. J = 10.0 Hz, 1H), 5.52 (d, J = 10.0 Hz, 1H), 4.61 (qq, J = 6.0, 6.0 Hz, 1H), 3.83 (s, 3H), 3.83 (d, J = 18.0 Hz, 1H), 3.62 (d, J = 18.0 Hz, 1H), 3.42 (m, 1H), 3.18 (m, 1H), 3.00 (m, 2H), 1.38 (d, J = 6.0 Hz, 3H), 1.33 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.8, 163.0, 160.6, 157.1, 154.7, 148.9, 134.8, 133.3, 132.1, 129.2, 128.2, 128.1, 126.4, 121.6, 120.6, 120.4 (q, $^1J_{CF}$ = 256 Hz), 119.9, 133.4, 104.6, 104.1, 100.2, 71.8, 71.1, 69.1, 63.9, 55.5, 49.3, 42.0, 40.5, 22.0 (2C), 18.0, 15.3; HRMS (ESI) exact mass calcd for $C_{31}H_{31}ClF_3N_4O_5$ $[M + H]^+$ 631.1935, found 631.1917.

***N*-((1*S*,2*R*)-1-(4-Chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-2-(3-(trifluoromethoxy)phenyl)ethyl)-3-oxopiperazine-1-carboxamide (19).** *N*-((1*R*,2*S*)-2-Amino-1-(4-chlorophenyl)-2-(3-(trifluoromethoxy)phenyl)ethyl)-3-oxopiperazine-1-carboxamide (35 mg, 76 μmol) and carboxylic acid **18** (16 mg, 77 μmol) were dissolved in dichloromethane (385 μL), and the solution was chilled to 0 °C and treated with EDC·HCl (19 mg, 99 μmol) and DMAP (1 mg, 7.7 μmol). The reaction mixture was stirred and gradually warmed to room temperature over 2 h. After 17 h, the mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$, and once more with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0–4% methanol in dichloromethane) afforded a single diastereomer of the amide as a yellow oil (42 mg, 87%): $[\alpha]_D^{20}$ = +84° (*c* 1.01, $CHCl_3$); R_f = 0.2 (5% MeOH/CH_2Cl_2); IR (film) 3368, 3257, 2980, 2931, 1676, 1641, 1537, 1503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 5.2 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.17 (m, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 2H), 6.87 (m, 1H), 6.83 (br d, 1H), 6.60 (dd, J = 8.8, 2.0 Hz, 1H), 6.45 (d, J = 2.0 Hz, 1H), 5.85 (dd, J = 8.0, 2.4 Hz, 1H), 5.14 (dd, J = 2.4, 2.4 Hz, 1H), (qq, J = 6.0, 6.0 Hz, 1H), 4.12 (br m, 2H), 3.85 (s, 3H), 3.70 (m, 1H), 3.58 (m, 1H), 3.38 (br m, 2H), 1.19 (d, J = 6.0 Hz, 3H), 1.16 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.9, 167.2, 157.3, 155.9, 149.2, 140.5, 136.3, 134.5, 133.4, 130.0, 129.2, 128.1, 125.8, 121.0 (q, $^1J_{CF}$ = 254 Hz), 120.5, 119.8, 113.4, 105.4, 100.3, 71.6, 61.8, 57.7, 55.6, 47.5, 41.1, 40.0, 21.8, 21.4; HRMS (ESI) exact mass calcd for $C_{31}H_{33}ClF_3N_4O_6$ $[M + H]^+$ 649.2041, found 649.2023.

***cis*-Imidazoline 21.**[44] In a microwave vial under an inert atmosphere was placed $Pd(PPh_3)_4$ (4.7 mg, 4.1 μmol). The vial was charged with K_2CO_3 (13.3 mg, 96.0 μmol), boronic ester **20** (10.0 mg, 48.0 μmol), and *cis*-imidazoline **11** (20.0 mg, 32.0 μmol). The vial was sealed, evacuated, and back-filled with argon. This process was repeated three times. A 5/1 mixture of dioxanes in water (865 μL) was then added via syringe under argon. The mixture was stirred for 20 h at 80 °C (conventional heating), and the solvent was then evaporated after cooling. Column chromatography (SiO_2, 0–5% methanol in dichloromethane) of the residue afforded the adduct as an off-white foam (13 mg, 62%): $[\alpha]_D^{20}$ = −37° (*c* 0.27, $CHCl_3$); R_f = 0.68 (10% MeOH/CH_2Cl_2); IR (film) 3259, 2923, 2852, 1674, 1607, 1423 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.57 (dd, J = 8.4, 2.0 Hz, 1H), 6.49 (d, J = 2.0 Hz, 1H), 6.24 (d, J = 2.0 Hz, 1H), 5.86 (br s, 1H), 5.62 (d, J = 9.6 Hz, 1H), 5.58 (d, J = 9.6 Hz, 1H), 4.61 (qq, J = 6.0, 6.0 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.73 (m, 2H), 3.38 (m, 1H), 3.28 (m, 1H), 3.04 (m, 2H), 1.40 (d, J = 6.0 Hz, 3H), 1.62 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.5, 163.0, 160.3, 157.1, 154.9, 143.2, 138.4, 138.0, 135.3, 133.1, 132.2, 129.5, 128.4, 128.2 (2C), 127.9, 105.8, 104.6, 100.2, 72.2, 71.1, 69.3, 68.4, 63.7, 55.6, 49.8, 41.7, 40.5, 37.3, 29.7, 22.1; HRMS (ESI) exact mass calcd for $C_{34}H_{36}ClN_6O_4$ $[M + H]^+$ 627.2487, found 627.2466.

***tert*-Butyl ((1*S*,2*R*)-2-Amino-2-(4-chlorophenyl)-1-(4-fluorophenyl)ethyl)carbamate (S19).** β-Nitro Boc-amine **4ad** (301 mg, 760 μmol), methanol (2.9 mL), and cobalt(II) chloride (49.3 mg, 379 μmol) were combined and stirred. The solution was cooled to 0 °C, and sodium borohydride (431 mg, 11.2 mmol) was added in five portions over 1 h. The reaction mixture was stirred at 0 °C for an additional 30 min before the mixture was quenched with saturated aqueous NH_4Cl. The reaction mixture was adjusted to pH 10 with concentrated aqueous NH_4OH. The mixture was placed on a glass frit and washed with water, and the aqueous layer was collected. The remaining solid was thoroughly washed with CH_2Cl_2 and collected in a separate flask. The organic layers were dried ($MgSO_4$), filtered, and concentrated to afford a white solid (221 mg, 75%): $[\alpha]_D^{20}$ = −45° (*c* 0.84, $CHCl_3$); mp 144–146 °C; R_f = 0.36 (50% EtOAc in hexanes); IR (film) 3371, 2970, 2922, 2355, 1692, 1602, 1512 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ7.58 (d, J = 8.4 Hz, 2H), 7.02–6.92 (m, 6H), 4.81 (br m, 1H), 4.24 (br d, 1H), 1.48–1.38 (m, 12H); ^{13}C NMR (100 MHz, CD_3OD) ppm 163.7 (d, $^1J_{CF}$ = 244 Hz), 157.2, 142.2, 137.6, 134.2, 130.7 (d, $^3J_{CF}$ = 8.0 Hz), 130.4, 129.3, 116.2 (d, $^2J_{CF}$ = 22.0 Hz), 80.2, 61.5, 60.9, 28.6; LRMS (ESI) exact mass calcd for $C_{19}H_{22}ClFN_2O_2$ $[M + H]^+$ 365.135, found 365.57,

***tert*-Butyl ((1*S*,2*R*)-2-(4-Chlorophenyl)-1-(4-fluorophenyl)-2-(3-oxopiperazine-1-carboxamido)ethyl)carbamate (S20).** Amine **S19** (210 mg, 575 μmol), dichloromethane (2.9 mL), and carbonyl diimidazole (112 mg, 689 μmol) were combined, and the mixture was stirred at room temperature for 1 h before adding oxopiperazine (115 mg, 1.15 mmol). The resulting mixture was stirred for 5 h before quenching with water and extracting with dichloromethane. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to afford a white solid (166 mg, 54%): $[\alpha]_D^{20}$ = +16° (*c* 0.09, CH_3COCH_3); Mp: 216–218 °C; R_f = 0.54 (10% MeOH in CH_2Cl_2); IR (film) 3379 (br), 2981, 1505, 1682, 1608 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.68 (s, 1H), 7.45–7.40 (m, 4H), 7.32 (d, J = 8.4 Hz, 2H), 7.05 (dd, J = 8.8 Hz, 8.0 Hz, 4H), 5.06 (d, J = 10.8 Hz, 1H), 4.97 (d, J = 10.8 Hz, 1H), 3.90 (d, J = 17.6 Hz, 1H), 3.72 (d, J = 17.6 Hz, 1H), 3.62–3.42 (m, 1H), 3.37–3.36 (m, 1H), 3.10 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) ppm 169.9, 163.5 (d, $^1J_{CF}$ = 243 Hz), 157.9, 157.3, 140.9, 138.2, 136.2, 134.2, 130.7, 130.6 (d, $^3J_{CF}$ = 8.0 Hz), 129.2, 116.0 (d, $^2J_{CF}$ = 21 Hz), 80.3, 59.5, 58.5, 48.2, 41.33, 41.26, 28.6; HRMS (ESI) exact mass cald for $C_{24}H_{28}ClFN_4NaO_4$ $[M + Na]^+$ 513.1681, found 513.1704.

***N*-((1*R*,2*S*)-2-Amino-1-(4-chlorophenyl)-2-(4-fluorophenyl)-ethyl)-3-oxopiperazine-1-carboxamide (S21).** Boc-protected urea **S20** (150 mg, 306 μmol) was dissolved in dichloromethane (3.0 mL),

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and the solution was treated with TFA (702 μL, 9.80 mmol) and stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with dichloromethane, and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to an off-white oil (100 mg, 84%): $[\alpha]_D^{20} = -1.8°$ (*c* 0.61, MeOH); $R_f = 0.36$ (10% MeOH in CH_2Cl_2); IR (film) 3352 br, 3067, 2936, 2890, 1664, 1518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.4 Hz, 2H), 7.03 (m, 6H), 5.97 (d, *J* = 7.2 Hz, 1H), 4.99 (dd, *J* = 7.2, 6.0 Hz, 1H), 4.28 (d, *J* = 5.6 Hz, 1H), 4.01 (d, *J* = 5.6 Hz, 2H), 3.60−3.56 (m, 2H), 3.29 (br m, 2H), 1.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.5, 162.1 (d, $^1J_{CF}$ = 243 Hz), 155.7, 137.5 (d, $^4J_{CF}$ = 3 Hz), 137.0, 133.3, 128.9, 128.4, 128.3 (d, $^3J_{CF}$ = 9 Hz), 115.1 (d, $^2J_{CF}$ = 21 Hz), 59.4, 58.9, 47.5, 40.8, 39.6; HRMS (ESI) exact mass cald for $C_{19}H_{20}ClFN_4NaO_2$ $[M + Na]^+$ 413.1157, found 413.1145.

***N*-((1*R*,2*S*)-1-(4-Chlorophenyl)-2-(4-fluorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S22).** Amine **S21** (80.0 mg, 205 μmol) and 2-isopropoxy-4-methoxybenzoic acid (43.1 mg, 205 μmol) were combined in dichloromethane (1.0 mL). The solution was chilled to 0 °C, and DMAP (2.5 mg, 21 μmol) and EDC·HCl (51.0 mg, 266 μmol) were added. The mixture was gradually warmed to room temperature and stirred for 24 h before it was diluted with dichloromethane and water. The aqueous layer was extracted with dichloromethane three times. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified via column chromatography (0−6% methanol in dichloromethane) to afford an off-white oil (74 mg, 62%). $[\alpha]_D^{20} = +61°$ (*c* 0.36, $CHCl_3$); $R_f = 0.56$ (10% MeOH in CH_2Cl_2); IR (film) 3369, 3259, 2975, 2926, 1666, 1646, 1542, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.6 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 5.2 Hz, 1H), 7.27 (br m, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.00 (m, 4H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.58 (dd, *J* = 9.2, 8.8 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 5.77 (dd, *J* = 8.0, 7.6 Hz, 1H), 5.08 (dd, *J* = 3.2, 3.2 Hz, 1H), 4.64 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.10 (s, 2H), 3.83 (s, 3H), 3.66 (m, 1H), 3.56 (m, 1H), 3.35 (br m, 2H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.1, 167.0, 163.9, 162.3 (d, $^1J_{CF}$ = 244 Hz), 157.2, 155.9, 136.7, 134.2 (d, $^2J_{CF}$ = 27 Hz), 134.0, 133.2, 129.4, 128.8, 128.0, 115.3 (d, $^2J_{CF}$ = 21 Hz), 113.5, 105.4, 100.3, 71.4, 61.7, 57.5, 55.0, 47.4, 40.9, 40.0, 21.9, 21.5; HRMS (ESI) exact mass calcd for $C_{30}H_{33}ClFN_4O_5[M + H]^+$ 583.2124, found 583.2134.

***cis*-Imidazoline 22.** Triphenylphosphine oxide (136 mg, 488 μmol) and dichloromethane (200 μL) were placed in a flame-dried flask. The solution was chilled to 0 °C, treated with triflic anhydride (41 μL, 244 μmol), and stirred for 10 min. *cis*-Amide urea **S22** (71 mg, 122 μmol) as a solution in dichloromethane (800 μL) was placed in the reaction flask and stirred for 1 h at 0 °C. The mixture was warmed to room temperature and stirred for 3 h more. The solution was diluted with dichloromethane and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via column chromatography (0−5% methanol in dichloromethane) yielded an off-white foam (60 mg, 88%): $[\alpha]_D^{20} = +137°$ (*c* 0.28, $CHCl_3$); $R_f = 0.33$ (5% MeOH in CH_2Cl_2); IR (film) 3217, 1982, 1926, 1680, 1611, 1514, 1424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.95−6.92 (m, 2H), 6.88−6.84 (m, 3H), 6.78 (dd, *J* = 8.8, 8.4 Hz, 2H), 6.53 (dd, *J* = 8.4, 8.4 Hz, 1H), 6.46 (dd, *J* = 2.0 Hz, 1H), 5.53 (d, *J* = 10.0 Hz, 1H), 5.48 (d, *J* = 10.0 Hz, 1H), 4.59 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.82 (s, 3H), 3.73 (d, *J* = 18.4 Hz, 1H), 3.62 (d, *J* = 18.4 Hz, 1H), 3.35 (m, 1H), 3.18 (m, 1H), 2.95 (br m, 2H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 167.0, 163.9, 161.9 (d, $^1J_{CF}$ = 244 Hz ppm), 160.0, 156.9, 154.8, 135.1, 133.1 (d, $^4J_{CF}$ = 3 Hz), 133.0, 132.2, 129.3 (d, $^3J_{CF}$ = 8 Hz), 128.3, 128.0, 114.6 (d, $^2J_{CF}$ = 21 Hz), 113.5, 104.5, 100.1, 71.7, 70.9, 69.2, 55.5, 49.4, 41.8, 40.3, 22.0 (2C); HRMS (ESI) exact mass calcd for $C_{30}H_{31}ClFN_4O_4$ $[M + H]^+$ 565.2018, found 565.1992.

***tert*-Butyl ((1*R*,2*S*)-2-Amino-2-(5-bromo-2-fluorophenyl)-1-(4-chlorophenyl)ethyl)carbamate (S13).** β-Nitro Boc-amine **4da** (430 mg, 0.908 μmol) and $CoCl_2$ (118 mg, 0.908 μmol) were added to methanol (3.7 mL) in a flask and chilled to 0 °C before $NaBH_4$ (343 mg, 9.08 mmol) was added in two portions over 1 h. The reaction mixture was stirred at 0 °C for an additional 15 min before the mixture was quenched with saturated aqueous NH_4Cl. The reaction mixture was adjusted to pH 10 with concentrated aqueous NH_4OH, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 20−40% ethyl acetate in hexanes) afforded the product as a white oil (172 mg, 43%) in 6:1 dr (by ^1H NMR): R_f = 0.71 (50% EtOAc/hexanes); IR (film) 3378, 2975, 2920, 1691, 1527, 1486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 4.0, 4.0 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 4.8 Hz, 1H), 7.03, (d, *J* = 7.6 Hz, 2H), 6.92 (t, *J* = 8.8 Hz, 1H), 5.50 (d, *J* = 6.4 Hz, 1H), 4.79 (br d, 1H), 4.46 (d, *J* = 6.4 Hz, 1H), 1.40 (br m, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 160.6 (d, $^1J_{CF}$ = 255 Hz), 133.6, 131.9, 131.8, 131.1 (d, $^3J_{CF}$ = 4 Hz), 128.6, 128.5, 128.2, 117.2 (d, $^2J_{CF}$ = 24 Hz), 116.8 (d, $^3J_{CF}$ = 4 Hz), 79.0, 58.6, 53.4, 28.2; HRMS (ESI) exact mass calcd for $C_{19}H_{22}BrClFN_2O_2$ $[M + H]^+$ 443.0537, found 443.0547.

***tert*-Butyl ((1*R*,2*S*)-2-(5-Bromo-2-fluorophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)carbamate (S14).** Amine **S13** (172 mg, 388 μmol) and carboxylic acid (81.6 mg, 388 μmol) were dissolved in dichloromethane (1.75 mL) at room temperature. The solution was chilled to 0 °C, and EDC·HCl (96.6 mg, 504 μmol) and DMAP (4.8 mg, 39 μmol) were added. The reaction mixture was stirred and gradually warmed to room temperature over 2 h. After 17 h, the reaction mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$, and once more with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 20−30% ethyl acetate in hexanes) afforded the amide as a clear foam (213 mg, 87%): R_f = 0.77 (50% EtOAc/hexanes); IR (film) 3373, 3318, 2980, 2925, 2247, 1714, 1645, 1604, 1536 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 9.2 Hz, 1H), 8.13 (d, *J* = 9.2 Hz, 1H), 7.37 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 8.8 Hz, 1H), 6.54 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.44 (s, 1H), 5.97 (dd, *J* = 9.2, 9.2 Hz, 1H), 5.74 (m, 1H), 5.08 (m, 1H), 4.69 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.82 (s, 3H), 1.32 (br s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.3, 163.7, 157.2 (d, $^1J_{CF}$ = 244 Hz), 134.4, 133.6, 132.3 (2C), 132.2, 128.7, 128.6, 128.5 (d, $^3J_{CF}$ = 4 Hz), 117.6 (d, $^2J_{CF}$ = 22 Hz), 116.5 (d, $^3J_{CF}$ = 4 Hz), 114.0, 105.5, 100.1, 77.2, 71.5, 55.5, 28.1, 21.8, 21.7; HRMS (ESI) exact mass calcd for $C_{30}H_{33}BrClFN_2NaO_5$ $[M + Na]^+$ 657.1143, found 657.1113.

***N*-((1*S*,2*R*)-2-Amino-1-(5-bromo-2-fluorophenyl)-2-(4-chlorophenyl)ethyl)-2-isopropoxy-4-methoxybenzamide (S15).** Amide **S14** (210 mg, 330 μmol) was dissolved in dichloromethane (3.0 mL) and treated with TFA (758 μL, 9.91 mmol). The mixture was stirred at room temperature for 3 h and then diluted with dichloromethane, poured into saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a yellow oil. Column chromatography (SiO_2, 30−50% ethyl acetate in hexanes) afforded the product as a foam (153 mg, 87%) and >20:1 dr by ^1H NMR: R_f = 0.15 (50% EtOAc/hexanes); IR (film) 3382, 2980, 2945, 1648, 1606, 1495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.41, (dd, *J* = 6.4, 2.0 Hz, 1H), 7.34 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.88 (t, *J* = 8.8 Hz, 1H), 6.53 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.71 (dd, *J* = 9.2, 1.6 Hz, 1H), 4.73 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.43 (d, *J* = 6.4 Hz, 1H), 3.82 (s, 3H), 1.42 (d, *J* = 6.0 Hz, 3H), 1.41 (d, *J* = 6.0 Hz, 3H), 1.36 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.8, 163.4, 160.8 (d, $^1J_{CF}$ = 245 Hz), 157.2, 139.9, 134.2, 133.4, 132.5 (d, $^3J_{CF}$ = 4 Hz), 132.0 (2C), 128.9, 128.8, 128.5, 128.4, 117.5 (d, $^2J_{CF}$ = 24 Hz), 116.6 (d, $^3J_{CF}$ = 4 Hz), 114.6, 105.8, 104.1, 100.2, 77.2, 71.4, 63.8, 58.4, 55.5, 54.0, 21.9 (2C); HRMS (ESI) exact mass calcd for $C_{25}H_{26}BrClFN_2O_3$ $[M + H]^+$ 535.0799, found 535.0790.

***N*-((1*R*,2*S*)-2-(5-Bromo-2-fluorophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S16).** Amine **S15** (150 mg, 277 μmol) was added to carbonyl diimidazole (53.0 mg, 332 μmol) in dichloromethane (6.5 mL). The mixture was stirred at room temperature for 3 h, or until no starting material remained by TLC, at which point oxopiperazine

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(55.0 mg, 554 μmol) was added. The mixture was stirred for 16 h. The reaction mixture was concentrated and purified by column chromatography (SiO_2, 40−100% ethyl acetate in hexanes) to afford the product as a white solid (68 mg, 40%): $[\alpha]_D^{20}$ = +90° (*c* 0.20, $CHCl_3$); mp 150−152 °C (dec.); R_f = 0.61 (10% MeOH/CH_2Cl_2); IR (film) 3371, 3260, 3074, 2977, 2928, 1650, 1602, 1533 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.8 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.39 (m, 1H), 7.31 (d, *J* = 9.6 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.97 (m 3H), 6.55 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.44 (d, *J* = 1.6 Hz, 1H), 6.07 (dd, *J* = 9.2, 9.2 Hz, 1H), 5.13 (m, 1H), 4.67 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.10 (d, *J* = 1.6 Hz, 2H), 3.83 (s, 3H), 3.68 (m, 1H), 3.56 (m, 1H), 3.38 (br m, 2H), 1.26 (dd, *J* = 6.0, 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.9, 166.6, 163.9, 159.1 (d, $^1J_{CF}$ = 246 Hz), 157.3, 155.8, 137.0, 134.4, 133.5, 132.4 (2C), 131.1 (d, $^3J_{CF}$ = 4 Hz), 129.2, 128.3, 128.1, 117.7 (d, $^2J_{CF}$ = 24 Hz), 116.4 (d, $^3J_{CF}$ = 4 Hz), 113.4, 105.2, 100.2, 71.6, 60.1, 55.5, 52.2, 47.4, 41.1, 39.9, 21.9, 21.6; HRMS (ESI) exact mass calcd for $C_{30}H_{31}BrClFN_4NaO_5$ $[M + Na]^+$ 683.1048, found 683.1021.

***cis*-Imidazoline 23.** Tf_2O (35.8 μL, 212 μmol) was added to a stirred solution of Ph_3PO (118 mg, 424 μmol) in dichloromethane (300 μL) at 0 °C. The mixture was stirred for 10 min before *cis*-amide urea **S16** (70 mg, 106 μmol) was added as a solution in dichloromethane (800 μL), and the mixture was stirred at 0 °C and warmed to room temperature over 3 h. The reaction mixture was quenched with $NaHCO_3$ at room temperature, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0−4% methanol in dichloromethane) of the residue provided the product as a white solid (52.0 mg, 78%): $[\alpha]_D^{20}$ = −57° (*c* 0.71, $CHCl_3$); mp 123−124 °C; R_f = 0.57 (10% MeOH/CH_2Cl_2); IR (film) 3229, 2981, 2933, 2361, 1680, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 6.8 Hz, 1H), 7.16 (m, 1H), 7.02 (s, 4H), 6.64 (s, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.47 (s, 1H), 5.76 (d, *J* = 10.0 Hz, 1H), 5.55 (d, *J* = 10.0 Hz, 1H), 4.59 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.84 (s, 3H), 3.80 (d, *J* = 18.0 Hz, 1H), 3.58 (d, *J* = 18.0 Hz, 1H), 3.42 (m, 1H), 3.12 (m 1H), 3.02 (br m, 2H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.27 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.9, 163.1, 160.6, 158.7 (d, $^1J_{CF}$ = 244 Hz), 156.9, 154.9, 153.3, 133.4, 132.4, 132.1 (2C), 131.9, 131.7 (2C), 128.5, 128.4, 128.3, 128.1, 127.9, 116.5 (d, $^3J_{CF}$ = 4 Hz), 116.1 (d, $^2J_{CF}$ = 24 Hz), 113.4, 104.6, 100.0, 70.8, 68.1, 66.6, 55.5, 49.7, 42.1, 40.3, 22.1, 22.0; HRMS (ESI) exact mass calcd for $C_{30}H_{30}BrClFN_4O_4$ $[M + H]^+$ 643.1123, found 643.1127.

***N*-((1*S*,2*R*)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)-ethyl)-4-bromo-2-isopropoxybenzamide (S30).** To amine **S27** (298 mg, 782 μmol) and 4-bromo-2-isopropoxybenzoic acid (202 mg, 782 μmol) in dichloromethane (4.0 mL) were added EDC·HCl (195 mg, 1.02 mmol) and DMAP (9.55 mg, 78 μmol) at 0 °C, and the reaction mixture was gradually warmed to room temperature over 16 h. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a white solid. The crude product was triturated with dichloromethane and hexanes, filtered, and dried under vacuum to give a white solid (438 mg, 90%) which was used for the next step directly. To *tert*-butyl ((1*R*,2*S*)-2-(4-bromo-2-isopropoxybenzamido)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-ethyl)carbamate (240 mg, 386 μmol) in dichloromethane (3.8 mL) was added TFA (1.191 mL, 15.46 mmol), and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (SiO_2, 0−7% methanol in dichloromethane) to give a white foam (151 mg, 75%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.26−7.21 (m, 3H), 7.21−7.15 (m, 2H), 7.14 (d, *J* = 2.0 Hz, 3H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 7.6 Hz, 1H), 5.42 (dd, *J* = 8.2, 4.9 Hz, 1H), 4.87−4.73 (m, 1H), 4.40 (d, *J* = 4.9 Hz, 1H), 1.52−1.41 (m, 7H); HRMS (ESI) exact mass calcd for $C_{24}H_{24}BrCl_2N_2O_2$ $[M + H]^+$ 521.0400, found 521.0392.

***N*-((1*R*,2*S*)-2-(4-Bromo-2-isopropoxybenzamido)-2-(3-chlorophenyl)-1-(4-chlorophenyl)ethyl)-3- oxopiperazine-1-carboxamide (S31).** To amine **S30** (221 mg, 423 μmol) in dichloromethane (2.1 mL) was added CDI (103 mg, 635 μmol) at room temperature under nitrogen, the reaction mixture was stirred for 1 h, piperazin-2-one (85 mg, 846 μmol) was then added, and this mixture was stirred for 15 h at room temperature. The solvent was removed, and the crude product was purified by column chromatography (SiO_2, 0−10% methanol in dichloromethane) to give a white solid (160 mg, 58%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.9 Hz, 1H), 8.18 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.54 (d, *J* = 5.2 Hz, 1H), 7.33−7.28 (m, 2H), 7.25−7.22 (m, 1H), 7.21−7.17 (m, 2H), 7.11 (dt, *J* = 1.9, 0.9 Hz, 1H), 7.06−7.00 (m, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.90−6.84 (m, 2H), 6.13 (s, 1H), 5.82−5.72 (m, 1H), 5.17 (dd, *J* = 5.4, 2.4 Hz, 1H), 4.79−4.62 (m, *J* = 6.2, 5.8 Hz, 1H), 4.14 (t, *J* = 1.4 Hz, 2H), 3.74 (dt, *J* = 13.6, 4.8 Hz, 1H), 3.60 (ddd, *J* = 13.5, 6.1, 4.7 Hz, 1H), 3.48−3.35 (m, 2H), 1.25−1.16 (m, 6H); HRMS (ESI) exact mass calcd for $C_{29}H_{30}BrCl_2N_4O_4$ $[M + H]^+$ 647.0829, found 647.0826.

***cis*-Imidazoline 24.** To triphenylphosphine oxide (251 mg, 0.901 mmol) in dichloromethane (2.5 mL) was added trifluoromethanesulfonic anhydride (0.076 mL, 0.450 mmol)) at 0 °C, the reaction mixture was stirred for 10 min, amide-urea **S31** (146 mg, 0.225 mmol) in dichloromethane (2 mL) was then added, and the reaction mixture was stirred at 0 °C for 1 h and warmed to room temperature before the addition of saturated aqueous $NaHCO_3$. The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, 0−7% methanol in dichloromethane) to give a white solid (98 mg, 69%): $[\alpha]^{23}_D$ = −81.9° (*c* 0.5, CH_3OH); IR (film) 3263, 2979, 1680, 1589, 1488,1406 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1 Hz, 1H), 7.19 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.11 (d, *J* = 1.5 Hz, 1H), 7.09−7.01 (m, 4H), 6.98 (s, 1H), 6.87 (dd, *J* = 7.7, 6.1 Hz, 3H), 6.03 (s, 1H), 5.68−5.50 (m, 2H), 4.74−4.56 (m, 1H), 3.92−3.65 (m, 3H), 3.35 (s, 1H), 3.25 (ddd, *J* = 13.5, 7.2, 4.2 Hz, 1H), 3.14−2.95 (m, 2H), 1.41 (d, *J* = 6.1 Hz, 3H), 1.37 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 160.1, 156.2, 154.7, 139.4, 134.7, 133.9, 133.5, 132.0, 129.1, 128.4, 128.2, 127.9, 127.4, 126.0, 125.9, 123.7, 120.1, 116.3, 72.4, 71.6, 69.0, 49.5, 41.7, 40.3, 36.7, 24.7, 22.0 (2C); HRMS (ESI) exact mass calcd for $C_{29}H_{28}BrCl_2N_4O_3$ $[M + H]^+$ 629.0722, found 629.0716.

***N*-((1*S*,2*R*)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)-ethyl)-4-cyano-2-isopropoxybenzamide (S32).** To amine **S27** (186 mg, 905 μmol) in dichloromethane (4.0 mL) were added EDC·HCl (225 mg, 1.18 mmol) and DMAP (11.05 mg, 90 μmol) at 0 °C, and the reaction mixture was gradually warmed to room temperature over 16 h. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a white solid. The crude product was triturated with dichloromethane and hexanes, filtered, and dried under vacuum to give a white solid (428 mg, 83%), which was used for the next step directly. To *tert*-butyl ((1*R*,2*S*)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-(4-cyano-2-isopropoxybenzamido)-ethyl)carbamate (390 mg, 686 μmol) in dichloromethane (6.5 mL) was added TFA (2.12 mL, 27.5 mmol), and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (SiO_2, 0−7% methanol in dichloromethane) to give a white solid (290 mg, 90%): $[\alpha]_D^{23.3}$ = −21.0° (*c* 0.275, CH_3OH); mp =165−166 °C; IR (film) 3378, 2980, 2935, 2231, 1655, 1603, 1573, 1557, 1515, 1489, 1411 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 8.0 Hz, 1H), 8.24 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.32 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.28−7.19 (m, 4H), 7.18−7.11 (m, 2H), 7.04−6.97 (m, 2H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.39 (dd, *J* = 8.0, 4.9 Hz, 1H), 4.83 (p, *J* = 6.1 Hz, 1H), 4.39 (d, *J* = 4.7 Hz, 1H), 1.55−1.50 (m, 6H), 1.45 (d, *J* = 11.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 155.8, 140.3, 139.6, 134.2, 133.6, 133.4, 129.3, 128.5, 128.2, 127.9, 127.5, 126.4, 126.2, 124.5, 118.1, 116.7, 115.8, 72.6, 58.9, 58.9, 22.03, 21.96; HRMS (ESI) exact mass calcd for $C_{25}H_{24}Cl_2N_3O_2$ $[M + H]^+$ 468.1247, found 468.1239.

***N*-((1*R*,2*S*)-2-(3-Chlorophenyl)-1-(4-chlorophenyl)-2-(4-cyano-2-isopropoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S33).** To amine **S32** (252 mg, 538 μmol) in dichloromethane

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(3.0 mL) was added CDI (131 mg, 807 μmol) at room temperature under N_2. The reaction mixture was stirred for 1 h, piperazin-2-one (108 mg, 1.08 mmol) was then added, and this mixture was stirred for 15 h at room temperature. The solvent was removed, and the crude product was purified by column chromatography (SiO_2, 0−10% methanol in dichloromethane) to give a white solid (292 mg, 91%). $[\alpha]_D^{23.5} = 16.4°$ (*c* 0.30, CH_3OH); mp 196−197 °C; IR (film) 3314, 2981, 2231, 1637, 1538, 1492, 1413 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 12.2, 8.0 Hz, 2H), 7.38 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.30 (dt, *J* = 9.1, 5.3 Hz, 3H), 7.21 (d, *J* = 8.1 Hz, 3H), 7.05 (d, *J* = 6.3 Hz, 1H), 6.95 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.28 (s,1H), 5.76 (dd, *J* = 8.0, 2.5 Hz, 1H), 5.21 (dd, *J* = 5.3, 2.6 Hz, 1H), 4.74 (p, *J* = 6.0 Hz, 1H), 4.12 (s, 2H), 3.73(dt, *J* = 13.0, 4.9 Hz, 1H), 3.68−3.51 (m, 1H), 3.41 (s, 2H), 1.35−1.13 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 165.5, 155.8, 139.5, 136.0, 134.7, 133.9, 133.7, 130.1, 129.2, 128.5, 128.3, 126.9, 125.4, 124.6, 124.5, 117.8, 116.7, 116.7, 72.8, 61.5, 58.4, 47.6, 41.2, 39.9, 21.8, 21.4; HRMS (ESI) exact mass calcd for $C_{30}H_{30}Cl_2N_5O_4$ $[M + H]^+$ 594.1677, found 594.1674.

***cis*-Imidazoline 25.** To triphenylphosphine oxide (324 mg, 1.164 mmol) in dichloromethane (2.5 mL) was added trifluoromethanesulfonic anhydride (0.099 mL, 0.586 mmol) at 0 °C, the reaction mixture was stirred for 10 min, amide-urea **S33** (170 mg, 0.286 mmol) in dichloromethane (1.5 mL) was then added, and the reaction mixture was stirred at 0 °C for 1 h and then warmed to room temperature before the addition of saturated aqueous $NaHCO_3$. The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO2, 0−7% MeOH in dichloromethane) to give a white solid (135 mg, 82%): $[\alpha]_D^{23} = -85.1°$ (*c* 0.5, CH_3OH); IR (film) 3231, 2981, 2230, 1676, 1599, 1573, 1541, 1493, 1414 $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.35 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.20 (s, 1H), 7.11−6.96 (m, 5H), 6.94−6.81 (m, 3H), 6.75 (d, *J* = 3.4 Hz, 1H), 5.75−5.53 (m, 2H), 4.69 (hept, *J* = 6.2 Hz, 1H), 3.81 (q, *J* = 17.7 Hz, 2H), 3.29 (q, *J* = 5.8 Hz, 2H), 3.10 (dq, *J* = 12.3, 4.7, 4.0 Hz, 1H), 3.06−2.95 (m, 1H), 1.45−1.35 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 159.9, 155.6, 154.7, 139.2, 134.4, 134.0, 133.8, 131.7, 129.2, 128.4, 128.3, 127.9, 127.5, 126.3, 125.9, 124.2, 118.2, 115.8, 115.1, 73.0, 71.9, 69.0, 49.6, 41.4, 40.4, 21.9 (2C); HRMS (ESI) exact mass calcd for $C_{30}H_{28}Cl_2N_5O_3$ $[M + H]^+$ 576.1569, found 576.1572.

***tert*-Butyl ((1*S*,2*R*)-2-Amino-1-(4-chlorophenyl)-2-(3-fluorophenyl)ethyl)carbamate (S23).** β-Nitro Boc-amine *ent*-**4ea** (500 mg, 1.27 mmol) and $CoCl_2$ (165 mg, 1.27 mmol) were dissolved in methanol (16.7 mL) at room temperature and then cooled to 0 °C with stirring. $NaBH_4$ (716 mg, 19.0 mmol) was added in three portions over 1 h. The reaction mixture was then stirred for 1 h and acidified to pH 2 with 1 M HCl. The solution was readjusted to pH 10 with 1 M aqueous NH_4OH and filtered through a glass frit, washing with deionized water. The solid on the filter was washed heavily with dichloromethane, and the filtrate was collected, dried ($MgSO_4$), filtered, and concentrated to yield the product as a white solid (355 mg, 77%): mp 141−143 °C; R_f = 0.51 (10% MeOH/CH_2Cl_2); IR (film) 3380, 2981, 2935, 1682, 1523, 1490, 1249, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 6.5 Hz, 1 H), 7.23 (d, *J* = 8.3 Hz, 3 H), 6.95 (m, 3 H), 6.99 (d, *J* = 7.7 Hz, 1 H), 6.83 (d, *J* = 9.5 Hz), 5.55 (br d, *J* = 6.5 Hz, 1 H), 4.84 (br dd, 1 H), 4.27 (br d, 1 H), 1.39 (br s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 162.6 (d, $^1J_{CF}$ = 244 Hz), 155.0, 144.7, 144.6, 133.3, 129.8, 129.7, 128.6, 128.2, 127.7, 122.5, 114.5, 114.3, 113.9, 113.7, 79.7, 59.3, 28.2; HRMS (ESI) exact mass calcd for $C_{19}H_{23}ClFN_2O_2$ $[M + H]^+$ 365.1432, found 365.1448.

***tert*-Butyl ((1*S*,2*R*)-1-(4-Chlorophenyl)-2-(3-fluorophenyl)-2-(3-oxopiperazine-1-carboxamido)ethyl)carbamate (S24).** Amine **S23** (300 mg, 0.82 mmol) was dissolved in dichloromethane (9.7 mL) at room temperature. To the solution was added CDI (174 mg, 1.07 mmol) with stirring under argon. Oxopiperazine (164 mg, 1.64 mmol) was delivered after 1 h, and the reaction mixture was stirred for 18 h. The reaction mixture was then concentrated by rotary evaporation, triturated with dichloromethane, and filtered through qualitative filter paper, washing with a small amount of dichloromethane. The product was removed from the filter paper and dried under high vacuum to yield the title compound as a light yellow solid (217 mg, 54%): mp 181−184 °C; R_f = 0.36 (10% MeOH/CH_2Cl_2); IR (film) 3366, 2980, 2930, 1678, 1632, 1526, 1250, 1168; ^1H NMR (400 MHz, DMSO-d_6) δ 7.88 (br d, 1 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.44−7.27 (m, 6 H), 7.03 (br m, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 4.93 (m, 2 H), 3.76 (d, *J* = 16.8 Hz, 1 H), 3.53 (d, *J* = 18 Hz, 1 H), 3.27 (m, 2 H), 2.92 (br m, 2 H), 1.15 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm 166.9, 155.8, 154.9, 145.5, 141.4, 131.9, 129.9, 129.8, 128.2, 124.7, 118.4, 115.0, 114.8, 113.7, 78.2, 58.0, 56.6, 55.3, 47.6, 28.4; HRMS (ESI) exact mass calcd for $C_{24}H_{28}ClFN_4NaO_4$ $[M + Na]^+$ 513.1681, found 513.1704.

***tert*-Butyl ((1*S*,2*R*)-2-Amino-1-(4-chlorophenyl)-2-(3-fluorophenyl)ethyl)carbamate (S25).** The urea **S24** (178 mg, 0.36 mmol) was dissolved in methanol (16 mL) at room temperature and the solution then cooled to 0 °C. Acetyl chloride (206 μL, 2.90 mmol) was added via syringe to the cold solution, and the reaction mixture was stirred under an Ar atmosphere for 15 h, at which point the solvent was removed by rotary evaporation and high vacuum. The solid was redissolved in dichloromethane and $NaHCO_3$ and extracted once. The aqueous layer was back-extracted 10 times with dichloromethane to afford the deprotected amine as a light yellow solid (84 mg, 60%): mp 139−142 °C; R_f = 0.21 (10% MeOH/CH_2Cl_2); IR (film) 3329, 3054, 2926, 1669, 1636, 1542, 1343, 1245 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.93 (br s, 1 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.34 (m, 3 H), 7.25 (d, *J* = 10.8 Hz, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 7.05 (m, 3 H), 6.75 (d, *J* = 8.8 Hz, 1 H), 4.73 (dd, *J* = 9.2, 9.2 Hz, 1 H), 4.10 (d, *J* = 9.6 Hz, 1 H), 3.85 (m, 1 H), 3.61 (m, 1 H), 2.99 (br m, 2 H), 1.93 (br m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm 166.7, 161.2, 156.0, 145.6, 144.1, 131.4, 129.9, 129.6, 128.0, 124.7, 115.0, 114.8, 114.0, 113.8, 60.8, 58.9, 47.7; HRMS (ESI) exact mass calcd for $C_{19}H_{21}ClFN_4O_2$ $[M + H]^+$ 391.1337, found 391.1342.

***N*-((1*R*,2*S*)-2-(4-Chlorophenyl)-1-(3-fluorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S26).** In a glass vial equipped with a magnetic stir bar and argon balloon were placed amine **S25** (49 mg, 0125 mmol), carboxylic acid (26.3 mg, 0.125 mmol), and dichloromethane (1.0 mL). The mixture was cooled to 0 °C with stirring before addition of EDC·HCl (31 mg, 0.163 mmol) and DMAP (1.6 mg, 13 μmol). The reaction mixture was stirred for 18 h before dilution with dichloromethane and aqueous extraction. The combined organic layers were dried with $MgSO_4$ and concentrated to a light yellow solid (62 mg, 85%). The solid was redissolved in CH_2Cl_2 and purified by column chromatography (2−10% MeOH/CH_2Cl_2, 55%): mp 123−136 °C; R_f = 0.27 (10% MeOH/CH_2Cl_2), IR (film) 3369, 2933, 1639, 1605, 1533, 1493, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.4 Hz, 1 H), 8.27 (d, *J* = 9.2 Hz, 1 H), 7.71 (d, *J* = 4.8 Hz), 7.28 (s, 1 H), 7.15 (m, 1 H), 6.55 (d, *J* = 8.4 Hz, 2 H), 6.77 (d, *J* = 10.0 Hz, 1 H), 6.66 (d, *J* = 7.2 Hz, 1 H), 6.62 (dd, *J* = 9.2, 2.4 Hz, 1 H), 6.46 (d, *J* = 2.0 Hz, 1 H), 6.43 (s, 1 H), 5.80 (dd, *J* = 8.0, 2.4 Hz, 1 H), 5.13 (dd, *J* = 4.8, 2.8 Hz, 1 H), 4.67 (qq, *J* = 6.0, 6.0 Hz, 1 H), 4.14 (s, 2 H), 3.85 (s, 3 H), 3.70 (m, 1 H), 3.60 (m, 1 H), 3.41 (br m, 2 H), 1.22 (d, *J* = 6.0 Hz, 3 H), 1.15 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.0, 167.1, 163.9, 162.1 (d, $^1J_{CF}$ = 243 Hz), 157.2, 156.0, 140.8, 140.7, 136.6, 134.4, 133.8, 129.3, 129.2, 128.6, 128.4, 124.1, 114.9, 114.6, 114.5, 114.3, 113.5, 105.3, 100.3, 71.4, 61.8, 57.5, 55.5, 47.4, 41.0, 40.0, 22.0, 21.3; HRMS (ESI) exact mass calcd for $C_{30}H_{33}ClFN_4O_5$ $[M + H]^+$ 583.2124, found 583.2126.

***cis*-Imidazoline 26.** Triphenylphosphine oxide (92 mg, 0.330 mmol) was dissolved in dichloromethane (0.65 mL) at room temperature. Triflic anhydride (27.8 μL, 0.165 mmol) was delivered via syringe, and the solution was stirred for 30 min. The *cis*-amide urea (48 mg, 0.082 mmol) was delivered as a solution in dichloromethane (0.65 mL, 1.30 mL total), and the reaction mixture was stirred for 18 h. The reaction mixture was diluted with dichloromethane, quenched with saturated aqueous $NaHCO_3$, and extracted once. The aqueous layer was back-extracted with dichloromethane, and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to a yellow-orange foam. This material was redissolved in dichloromethane and purified by column chromatography (SiO_2, 0−4% methanol in dichloromethane) to afford the desired product as a light yellow solid (30 mg, 65%) in 9:1 dr: mp 112−114 °C; R_f = 0.40 (10% MeOH/CH_2Cl_2); IR (film) 3223, 2979, 2929, 1676, 1607, 1424, 1340, 1280; ^1H NMR (400 MHz, $CDCl_3$)

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δ 7.62 (d, J = 8.4 Hz, 1 H), 7.06 (d, J = 8.4 Hz, 2 H), 6.99 (m, 1 H), 6.94 (d, J = 8.0 Hz), 6.76 (m, 2 H), 6.62 (d, J = 8.0 Hz), 6.58 (s, 1 H), 6.55 (dd, J = 8.4, 2.0 Hz, 1 H), 6.48 (d, J = 2.0 Hz, 1 H), 5.55 (d, J = 9.6 Hz, 1 H), 5.49 (d, J = 9.6 Hz, 1 H), 4.61 (qq, J = 6.0, 6.0 Hz, 1 H), 3.84 (s, 3 H), 3.80 (d, J = 18.4 Hz, 1 H), 3.60 (d, J = 18.0 Hz, 1 H), 3.44 (m, 1 H), 3.15 (m, 1 H), 2.99 (m, 2 H), 1.39 (d, J = 6.0 Hz, 3 H), 1.33 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.9, 163.0, 162.5 (d, $^1J_{CF}$ = 244 Hz), 160.2, 157.0, 154.8, 139.2, 139.1, 135.9, 132.8, 132.3, 129.5, 129.4, 129.1, 128.4, 127.8, 122.7, 114.4, 114.2, 114.1, 113.8, 113.3, 104.5, 100.0, 71.9, 70.9, 69.3, 55.5, 53.4, 49.5, 42.0, 40.4, 29.6, 22.0, 21.7; HRMS (ESI) exact mass calcd for $C_{30}H_{31}ClFN_4O_4$ $[M + H]^+$ 565.2018, found 565.2023.

***tert*-Butyl ((1*R*,2*S*)-2-Amino-2-(3-bromophenyl)-1-(4-chlorophenyl)ethyl)carbamate (S37).** In a 100 mL flask was placed β-nitro Boc-amine **4ga** (700 mg, 1.54 mmol) in MeOH (15 mL), the reaction mixture was stirred at room temperature, and then cobalt(II) chloride (199 mg, 1.54 mmol) was added. The purple solution was cooled to 0 °C, and then sodium borohydride (872 mg, 23.0 mmol) was added in three portions over 45 min. The reaction mixture was stirred at 0 °C for 75 min and then quenched with saturated aqueous NH_4Cl. The solution pH was adjusted to 10 with concentrated NH_4OH. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a white solid (615 mg, 94%): $[\alpha]_D^{22.8}$ = −5.4° (*c* 0.36, CH_3OH); mp 158−159 °C; IR (film) 3373, 2981, 1683, 1594, 1570, 1524, 1493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dt, J = 8.1, 1.3 Hz, 1H), 7.27 (s, 1H), 7.25−7.20 (m, 2H), 7.14 (t, J = 7.8 Hz, 1H), 6.99 (dt, J = 7.8, 1.3 Hz, 1H), 6.94 (d, J = 8.1 Hz, 2H), 5.47 (s, 1H), 4.80 (s, 1H), 4.21 (d, J = 5.6 Hz, 1H), 1.37 (s, 11H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 144.4, 136.7, 133.4, 130.7, 130.1, 129.9, 128.8, 128.3, 125.5, 122.5, 79.9, 59.4, 28.3; HRMS (ESI) exact mass calcd for $C_{19}H_{23}BrClN_2O_2$ $[M + H]^+$ 425.0633, found 425.0634.

***N*-((1*S*,2*R*)-2-Amino-1-(3-bromophenyl)-2-(4-chlorophenyl)-ethyl)-2-isopropoxy-4-methoxybenzamide (S38).** To amine S37 (350 mg, 0.822 mmol) and 2-isopropoxy-4-methoxybenzoic acid (173 mg, 822 μmol) in dichloromethane (4.1 mL) were added EDC·HCl (205 mg, 1.07 mmol) and DMAP (10.0 mg, 820 μmol) at 0 °C, and the reaction mixture was gradually warmed to room temperature over 16 h. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a white solid. The crude product was triturated with dichloromethane and hexanes, filtered, and dried under vacuum to give a white solid (500 mg, 98%), which was used for the next step directly. To *tert*-butyl ((1*R*,2*S*)-2-(3-bromophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)carbamate (330 mg, 534 μmol) in dichloromethane (5.0 mL) was added TFA (1.65 mL, 21.4 mmol) at room temperature, and the reaction mixture was stirred under N_2 for 16 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil. This oil was purified by column chromatography (SiO_2, 0−10% methanol in dichloromethane) to give a white solid (202 mg, 73%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.36 (ddd, J = 7.9, 2.0, 1.0 Hz, 1H), 7.31 (t, J = 1.8 Hz, 1H), 7.26−7.22 (m, 2H), 7.08 (t, J = 7.8 Hz, 1H), 7.06−7.00 (m, 2H), 6.96−6.89 (m, 1H), 6.56 (dd, J = 8.8, 2.3 Hz, 1H), 6.49 (d, J = 2.3 Hz, 1H), 5.45 (dd, J = 8.3, 5.0 Hz, 1H), 4.76 (p, J = 6.1 Hz, 1H), 4.40 (d, J = 5.0 Hz, 1H), 3.84 (s, 3H), 1.57−1.38 (m, 8H); HRMS (ESI) exact mass calcd for $C_{25}H_{27}BrClN_2O_3$ $[M + H]^+$ 517.0895, found 517.0882.

***N*-((1*R*,2*S*)-2-(3-Bromophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S39).** To amine S38 (190 mg, 367 μmol) in dichloromethane (2 mL) was added CDI (95 mg, 59 μmol) at room temperature under N_2. The reaction mixture was stirred for 1 h, piperazin-2-one (77 mg, 0.771 mmol) was then added, and this mixture was warmed to room temperature over 4 h. The solvent was removed, and the crude product was purified by column chromatography (SiO_2, 0−10% methanol in dichloromethane) to give a white solid (137 mg, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.0 Hz, 1H), 8.27 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 5.0 Hz, 1H), 7.45 (dt, J = 8.2, 1.4 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.21−7.16 (m, 2H), 7.08 (dd, J = 6.9, 1.3 Hz, 2H), 6.90−6.85 (m, 2H), 6.62 (dd, J = 8.9, 2.3 Hz, 1H), 6.50−6.40 (m, 2H), 5.79 (dd, J = 8.1, 2.5 Hz, 1H), 5.13 (dd, J = 5.0, 2.5 Hz, 1H), 4.66 (hept, J = 6.0 Hz, 1H), 4.15 (d, J = 1.7 Hz, 2H), 3.86 (s, 3H), 3.73 (ddd, J = 13.3, 5.9, 4.1 Hz, 1H), 3.60 (ddd, J = 13.3, 6.4, 4.6 Hz, 1H), 3.44−3.38 (m, 2H), 1.22−1.18 (m, 6H); HRMS (ESI) exact mass calcd for $C_{30}H_{33}BrClN_4O_5$ $[M + H]^+$ 643.1325, found 643.1309.

***cis*-Imidazoline 27.** To triphenylphosphine oxide (185 mg, 0.665 mmol) in dichloromethane (1.3 mL) was added trifluoromethanesulfonic anhydride (0.056 mL, 0.332 mmol) at 0 °C, the reaction mixture was stirred at 0 °C for 10 min, amide-urea **S39** (107 mg, 0.166 mmol) in dichloromethane (1 mL) was then added, and the reaction mixture was stirred at 0 °C for 1 h and then allowed to warmed to room temperature before the addition of aqueous $NaHCO_3$. The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane. The combined dichloromethane layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, 0−7% methanol in dichloromethane) to give a white solid (95 mg, 91%): $[\alpha]_D^{23.3}$ = −110.2° (*c* 0.575, CH_3OH); IR (film) 3224, 2979, 2936,1675, 1608, 1493,1424 cm$^{-1;}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.5 Hz, 1H), 7.21 (dt, J = 7.7, 1.7 Hz, 1H), 7.11 (t, J = 1.8 Hz, 1H), 7.07−7.00 (m, 2H), 7.01−6.86 (m, 4H), 6.56 (dd, J = 8.5, 2.3 Hz, 1H), 6.48 (d, J = 2.3 Hz, 1H), 6.43 (d, J = 2.7 Hz, 1H), 5.61−5.43 (m, 2H), 4.61 (hept, J = 6.1 Hz, 1H), 3.85 (s, 3H), 3.78 (d, J = 18.0 Hz, 1H), 3.63 (d, J = 18.1 Hz, 1H), 3.40 (dt, J = 13.6, 4.8 Hz, 1H), 3.27−3.13 (m, 1H), 3.08−2.94 (m, 2H), 1.39 (d, J = 6.0 Hz, 3H), 1.33 (d, J = 6.0 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 163.1, 160.4, 157.0, 154.9, 139.9, 135.1, 133.3, 132.4, 131.0, 130.2, 129.3, 128.4, 128.0, 126.5, 122.0, 113.5, 104.6, 100.2, 72.0, 71.0, 69.3, 55.6, 50.0, 42.0, 40.5, 22.1 (2C). HRMS (ESI) exact mass calcd for $C_{30}H_{31}BrClN_4O_4$ $[M + H]^+$ 625.1217, found 625.1218.

***tert*-Butyl ((1*R*,2*S*)-2-Amino-2-(3-chlorophenyl)-1-(4-chlorophenyl)ethyl)carbamate (S27).** In a 100 mL flask was placed β-Nitro Boc-amine **4ca** (1.10 g, 2.67 mmol) in MeOH (25 mL), the reaction mixture was stirred at room temperature, and then cobalt(II) chloride (347 mg, 2.67 mmol) was added. The purple solution was cooled to 0 °C, and sodium borohydride (1.51 g, 40.1 mmol) was added in three portions over 45 min. Stirring was continued at 0 °C for 2 h, and the reaction mixture was quenched with saturated aqueous NH_4Cl and adjusted to pH 10 with concentrated NH_4OH. The aqueous layer was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a white solid. The crude product was purified on a silica gel column using a hexane/ethyl acetate (0−45%) gradient (670 mg, 66%): $[\alpha]_D^{22.1}$ = −11.9° (*c* 0.29, CH_3OH); mp 162−163 °C; IR (film) 3361, 2983, 1682, 1525, 1492 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.19 (m, 4H), 7.11 (s, 1H), 6.99−6.91 (m, 3H), 5.47 (s, 1H), 4.80 (s, 1H), 4.23 (s, 1H), 1.36 (s, 11H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 144.1, 136.8, 134.3, 133.4, 129.5, 128.7, 128.3, 127.7, 127.2, 125.1, 79.8, 59.4, 28.3; HRMS (ESI) exact mass calcd for $C_{19}H_{23}Cl_2N_2O_2$ $[M + H]^+$ 381.1138, found 381.1131.

***N*-((1*S*,2*R*)-2-Amino-1-(3-chlorophenyl)-2-(4-chlorophenyl)-ethyl)-4-chloro-2-isopropoxybenzamide (S28).** To amine S27 (300 mg, 787 μmol) and 4-chloro-2-isopropoxybenzoic acid (169 mg, 787 μmol) in dichloromethane (4.0 mL) were added EDC·HCl (196 mg, 1.02 mmol) and DMAP (9.61 mg, 79 μmol) at 0 °C, and the reaction mixture was gradually warmed to room temperature. After 16 h the reaction mixture was diluted with water and extracted with dichloromethane. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a white solid. The crude product was triturated with dichloromethane and then hexanes and dried under vacuum to give a white solid (420 mg, 92%), which was used in the next step directly. To *tert*-butyl ((1*R*,2*S*)-2-(4-chloro-2-isopropoxybenzamido)-2-(3-chlorophenyl)-1-(4-chlorophenyl)ethyl)carbamate (370 mg, 640 μmol) in dichloromethane (6 mL) was added TFA (1.98 mL, 25.7 mmol), and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured into aqueous $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4),

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filtered, and concentrated. The residue was purified by column chromatography (SiO_2, methanol in dichloromethane 0−7%) to give a white foam (290 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.28−7.18 (m, 4H), 7.17−7.11 (m, 2H), 7.05−6.96 (m, 4H), 6.84 (d, J = 7.7 Hz, 1H), 5.42 (dd, J = 8.2, 4.9 Hz, 1H), 4.79 (p, J = 6.0 Hz, 1H), 4.40 (d, J = 4.8 Hz, 1H), 1.53−1.40 (m, 8H); HRMS (ESI) exact mass calcd for $C_{24}H_{24}Cl_3N_2O_2$ $[M + H]^+$ 477.0905, found 477.0897.

***N*-((1*R*,2*S*)-2-(4-Chloro-2-isopropoxybenzamido)-2-(3-chlorophenyl)-1-(4-chlorophenyl)ethyl)-3-oxopiperazine-1-carboxamide (S29).** To amine **S28** (260 mg, 544 μmol) in dichloromethane (3.0 mL) was added CDI (105 mg, 652 μmol) at 23 °C under a nitrogen atmosphere; the reaction mixture was stirred for 1 h before piperazin-2-one (109 mg, 1.088 mmol) was added, and the resulting mixture was stirred for 15 h at room temperature. The solvent was removed, and the crude product was purified by column chromatography (SiO_2, 0−10% methanol in dichloromethane) to give a white solid (250 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 7.9 Hz, 1H), 8.24 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 5.3 Hz, 1H), 7.33−7.28 (m, 2H), 7.22−7.17 (m, 2H), 7.12−7.09 (m, 2H), 6.97−6.92 (m, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.45 (s, 1H), 5.77 (dd, J = 7.9, 2.5 Hz, 1H), 5.17 (dd, J = 5.2, 2.6 Hz, 1H), 4.75−4.64 (m, 1H), 4.14 (d, J = 1.2 Hz, 2H), 3.77−3.68 (m, 1H), 3.60 (dt, J = 13.3, 5.3 Hz, 1H), 3.42−3.37 (m, 2H), 1.26−1.17 (m, 6H); HRMS (ESI) exact mass calcd for $C_{29}H_{30}Cl_3N_4O_4$ $[M + H]^+$ 603.1334, found 603.1329.

***cis*-Imidazoline 28.** To triphenylphosphine oxide (276 mg, 0.994 mmol) in dichloromethane (2 mL) was added trifluoromethanesulfonic anhydride (0.084 mL, 0.497 mmol) at 0 °C, the reaction mixture was stirred for 10 min, amide-urea **S29** (150 mg, 0.248 mmol) in dichloromethane (1.6 mL) was then added, and the reaction mixture was stirred at 0 °C for 1 h and then warmed to room temperature before the addition of saturated aqueous $NaHCO_3$. The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, 0−7% methanol in dichloromethane) to give a white solid (125 mg, 86%): $[\alpha]_D^{22}$ = −95.2° (c 0.5, CH_3OH); IR (film) 3226, 2980, 1678, 1595, 1490, 1409 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.2 Hz, 1H), 7.03 (ddt, J = 8.3, 5.6, 3.4 Hz, 5H), 7.00−6.93 (m, 2H), 6.87 (t, J = 7.9 Hz, 3H), 6.82 (s, 1H), 5.65−5.49 (m, 2H), 4.64 (p, J = 6.1 Hz, 1H), 3.81 (d, J = 17.9 Hz, 1H), 3.68 (d, J = 17.9 Hz, 1H), 3.35 (dt, J = 12.9, 4.6 Hz, 1H), 3.28−3.14 (m, 1H), 3.10−2.93 (m, 2H), 1.40 (d, J = 6.0 Hz, 3H), 1.36 (d, J = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 160.0, 156.2, 154.7, 139.4, 137.8, 134.7, 133.9, 133.5, 131.8, 129.1, 128.4, 128.2, 127.9, 127.4, 126.0, 120.7, 119.6, 113.4, 72.4, 71.6, 69.1, 49.5, 41.7, 40.3, 22.0 (2C); HRMS (ESI) exact mass calcd for $C_{29}H_{28}Cl_3N_4O_3$ $[M + H]^+$ 585.1227, found 585.1226.

***cis*-Imidazoline 29.** To triphenylphosphine oxide (673 mg, 2.420 mmol) in dichloromethane (5 mL) was added trifluoromethanesulfonic anhydride (0.204 mL, 1.210 mmol) at 0 °C, the reaction mixture was stirred at 0 °C for 10 min, *N*-((1*R*,2*S*)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-2-(3-methoxyphenyl)ethyl)-3-oxopiperazine-1-carboxamide (360 mg, 0.605 mmol) in dichloromethane (3 mL) was then added, and the reaction mixture was stirred at 0 °C for 1 h and then warmed to room temperature before the addition of saturated aqueous $NaHCO_3$. The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane. The combined dichloromethane layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, 0−7% methanol in dichloromethane) to give a white solid (264 mg, 76%): $[\alpha]_D^{22}$ = −134.1° (c 0.4, CH_3OH); IR (film) 3215, 2979, 2937, 2837, 1674,1607,1492,1431 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.5 Hz, 1H), 7.02 (dd, J = 15.7, 8.1 Hz, 3H), 6.89 (d, J = 8.5 Hz, 3H), 6.63 (dd, J = 8.1, 2.1 Hz, 2H), 6.55 (dd, J = 8.5, 2.2 Hz, 1H), 6.47 (d, J = 2.1 Hz, 1H), 6.45−6.40 (m, 1H), 5.54 (d, J = 9.7 Hz, 1H), 5.46 (d, J = 9.6 Hz, 1H), 4.59 (p, J = 6.0 Hz, 1H), 3.83 (s, 3H), 3.79−3.57 (m, 5H), 3.35 (dd, J = 8.5, 5.0 Hz, 1H), 3.18 (dt, J = 12.8, 5.3 Hz, 1H), 2.96 (t, J = 7.0 Hz, 2H), 1.37 (d, J = 6.0 Hz, 3H), 1.32 (d, J = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 163.0, 160.1, 159.2, 157.0, 154.9, 138.9, 135.4, 132.9, 132.4, 128.8, 128.5, 127.8, 120.3, 113.8, 113.6, 112.9, 104.6, 100.1, 72.4, 71.0, 69.4, 55.5, 55.1, 49.4, 42.0, 40.34, 22.1, 22.0; HRMS (ESI) exact mass calcd for $C_{31}H_{34}ClN_4O_5$ $[M + H]^+$ 577.2218, found 577.2221.

***N*-((1*S*,2*R*)-2-Amino-1-(3-bromophenyl)-2-(4-chlorophenyl)-ethyl)-4-cyano-2-isopropoxybenzamide (S40).** To amine **S37** (221 mg, 519 μmol) and 4-cyano-2-isopropoxybenzoic acid (107 mg, 519 μmol) in dichloromethane (2.6 mL) were added EDC·HCl (129 mg, 675 μmol) and DMAP (6.3 mg, 52 μmol) at 0 °C, and the reaction mixture was gradually warmed to room temperature over 16 h. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a white solid. The crude product was triturated with dichloromethane and hexanes, filtered, and dried under vacuum to give a white solid (500 mg, 98%), which was used for the next step directly. To *tert*-butyl ((1*R*,2*S*)-2-(3-bromophenyl)-1-(4- chlorophenyl)-2-(4-cyano-2-isopropoxybenzamido)ethyl)-carbamate (225 mg, 367 μmol) in dichloromethane (4 mL) was added TFA (1.13 mL, 14.7 mmol) at room temperature, and the reaction mixture was stirred under N_2 for 16 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford an oil. This crude oil was purified by column chromatography (SiO_2, 0−10% methanol in dichloromethane) to give a white solid (183 mg, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, J = 8.0 Hz, 1H), 8.31−8.20 (m, 1H), 7.41−7.35 (m, 1H), 7.32 (dd, J = 8.1, 1.5 Hz, 1H), 7.29−7.20 (m, 4H), 7.08 (td, J = 7.8, 1.2 Hz, 1H), 7.03−6.97 (m, 2H), 6.86 (d, J = 7.1 Hz, 1H), 5.56−5.28 (m, 1H), 4.84 (hept, J = 6.1 Hz, 1H), 4.39 (d, J = 4.9 Hz, 1H), 1.63−1.44 (m, 8H); HRMS (ESI) exact mass calcd for $C_{25}H_{24}BrClN_3O_2$ $[M + H]^+$ 512.0742, found 512.0735.

***N*-((1*R*,2*S*)-2-(3-Bromophenyl)-1-(4-chlorophenyl)-2-(4-cyano-2-isopropoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S41).** To amine **S40** (105 mg, 205 μmol) in dichloromethane (1.2 mL) was added CDI (49.8 mg, 307 μmol) at room temperature, and the reaction mixture was stirred for 1 h. Piperazin-2-one (41.0 mg, 409 μmol) was added, and stirring was continued for 4 h at room temperature. The reaction mixture was concentrated and purified by column chromatography (SiO_2, 0−10% methanol in dichloromethane) to give a white solid (97 mg, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53−8.34 (m, 2H), 7.53−7.42 (m, 1H), 7.37 (dd, J = 8.1, 1.4 Hz, 1H), 7.30−7.15 (m, 5H), 7.15−7.06 (m, 2H), 6.94−6.87 (m, 2H), 6.44 (d, J = 3.2 Hz, 1H), 5.75 (dd, J = 8.1, 3.1 Hz, 1H), 5.20 (dd, J = 5.7, 3.0 Hz, 1H), 4.74 (hept, J = 6.0 Hz, 1H), 4.17−4.08 (m, 2H), 3.78−3.67 (m, 1H), 3.66−3.55 (m, 1H), 3.40 (td, J = 5.5, 4.8, 2.0 Hz, 2H), 1.29−1.23 (m, 6H); HRMS (ESI) exact mass calcd for $C_{30}H_{30}BrClN_5O_4$ $[M + H]^+$ 638.1171, found 638.1158.

***cis*-Imidazoline 30.** To triphenylphosphine oxide (139 mg, 0.501 mmol) in dichloromethane (1 mL) was added trifluoromethanesulfonic anhydride (0.042 mL, 0.250 mmol) at 0 °C, the reaction mixture was stirred at 0 °C for 10 min, amide-urea **S41** (80 mg, 0.125 mmol) in dichloromethane (1 mL) was then added, and the reaction mixture was stirred at 0 °C for 1 h and then warmed to room temperature before the addition of aqueous $NaHCO_3$. The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane. The combined dichloromethane layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, 0−7% methanol in dichloromethane) to give a white solid (64 mg, 82%): $[\alpha]_D^{23.7}$ = −75.0° (c 0.22, CH_3OH); IR (film) 3214, 2980, 2923, 2230, 1678, 1598, 1566, 1493, 1413 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.8 Hz, 1H), 7.35 (dd, J = 7.9, 1.4 Hz, 1H), 7.25−7.17 (m, 2H), 7.12 (d, J = 1.9 Hz, 1H), 7.10−7.04 (m, 2H), 6.98 (t, J = 7.7 Hz, 1H), 6.95−6.84 (m, 3H), 6.46 (d, J = 3.0 Hz, 1H), 5.69−5.55 (m, 2H), 4.69 (hept, J = 6.1 Hz, 1H), 3.93−3.73 (m, 2H), 3.30 (t, J = 5.4 Hz, 2H), 3.20−3.08 (m, 1H), 3.02 (dtd, J = 12.0, 7.9, 6.7, 4.0 Hz, 1H), 1.42 (d, J = 6.0 Hz, 3H), 1.39 (d, J = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 160.0, 155.5, 154.7, 139.4, 134.3, 133.9, 131.7, 130.8, 130.4, 129.4, 128.4, 128.3, 126.3, 124.2, 122.2, 118.2, 115.8, 115.2, 73.0, 71.9, 69.0,

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49.7, 41.4, 40.4, 29.7, 21.9; HRMS (ESI) exact mass calcd for $C_{30}H_{28}BrClN_5O_3$ $[M + H]^+$ 620.1064, found 620.1071.

***tert*-Butyl ((1*R*,2*S*)-2-Amino-1-(4-chlorophenyl)-2-(3-methoxyphenyl)ethyl)carbamate (S34).** In a 100 mL flask was placed β-nitro Boc-amine **4ia** (1.00 g, 2.46 mmol) in MeOH (24 mL), the reaction mixture was stirred at room temperature, and then cobalt(II) chloride (319 mg, 2.46 mmol) was added. The purple solution was cooled to 0 °C, and then sodium borohydride (1.40 g, 36.9 mmol) was added in three portions over 45 min. Stirring was continued at 0 °C for 75 min, and then the reaction mixture was treated with saturated aqueous NH_4Cl and its pH adjusted to 10 with concentrated NH_4OH. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, 0−45% ethyl acetate in hexanes) to afford an oil (440 mg, 48%): $[\alpha]_D^{22.5} = -6.7°$ (*c* 0.45, CH_3OH); IR (film) 3383, 2977, 2836, 1699, 1600, 1491, 1436, 1412 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.15 (m, 3H), 6.94 (d, J = 8.0 Hz, 2H), 6.79 (ddd, J = 8.2, 2.7, 1.0 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.59 (t, J = 2.0 Hz, 1H), 5.54 (s, 1H), 4.82 (s, 1H), 4.28−4.12 (m, 1H), 3.73 (s, 3H), 1.53−1.23 (m, 11H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 155.1, 143.5, 137.4, 133.1, 129.3, 128.8, 128.1, 119.2, 113.2, 112.3, 79.7, 59.7, 55.2, 28.3; HRMS (ESI) exact mass calcd for $C_{20}H_{26}ClN_2O_3$ $[M + H]^+$ 377.1634, found 377.1635.

***N*-((1*S*,2*R*)-2-Amino-2-(4-chlorophenyl)-1-(3-methoxyphenyl)ethyl)-2-isopropoxy-4-methoxybenzamide (S35).** To amine **S34** (403 mg, 1.07 mmol) and 2-isopropoxy-4-methoxybenzoic acid (225 mg, 1.07 mmol) in dichloromethane (5.4 mL) were added EDC·HCl (266 mg, 1.39 mmol) and DMAP (13.1 mg, 107 μmol) at 0 °C, and the reaction mixture was gradually warmed to room temperature over 16 h. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a white solid. The crude product was triturated with dichloromethane and hexanes, filtered, and dried under vacuum to give a white solid (580 mg, 95%), which was used for the next step directly. To *tert*-butyl ((1*R*,2*S*)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-2-(3-methoxyphenyl)ethyl)carbamate (560 mg, 0.984 mmol) in dichloromethane (9 mL) was added TFA (3.04 mL, 39.5 mmol), and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layers were combined and washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (SiO_2, 0−7% methanol in dichloromethane) to give a white foam (459 mg, 99%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 8.3 Hz, 2H), 7.16 (t, J = 7.9 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.76 (dd, J = 8.2, 2.5 Hz, 1H), 6.70 (d, J = 7.7 Hz, 1H), 6.60 (s, 1H), 6.55 (dd, J = 8.8, 2.2 Hz, 1H), 6.48 (d, J = 2.2 Hz, 1H), 5.45 (dd, J = 8.3, 5.2 Hz, 1H), 4.74 (p, J = 6.1 Hz, 1H), 4.40 (d, J = 5.2 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 1.64−1.36 (m, 8H); HRMS (ESI) exact mass calcd for $C_{26}H_{30}ClN_2O_4$ $[M + H]^+$ 469.1896, found 469.1902.

***N*-((1*R*,2*S*)-1-(4-Chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-2-(3-methoxyphenyl)ethyl)-3-oxopiperazine-1-carboxamide (S36).** To amine **S35** (290 mg, 618 μmol) in dichloromethane (3.0 mL) was added CDI (150 mg, 928 μmol) at room temperature under N_2. The reaction mixture was stirred for 1 h, piperazin-2-one (124 mg, 1.24 mmol) was then added, and the reaction mixture was stirred for 15 h at room temperature. The solvent was removed, and the crude product was purified by column chromatography (SiO_2, 0−10% methanol in dichloromethane) to give a white solid (360 mg, 98%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 7.7 Hz, 1H), 8.28 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 5.0 Hz, 1H), 7.18−7.13 (m, 2H), 7.10 (d, J = 1.1 Hz, 1H), 6.95−6.86 (m, 2H), 6.87−6.80 (m, 1H), 6.66−6.58 (m, 2H), 6.55 (dd, J = 8.0, 1.5 Hz, 1H), 6.46 (d, J = 2.2 Hz, 1H), 6.27 (d, J = 3.2 Hz, 1H), 5.74 (dd, J = 7.7, 2.2 Hz, 1H), 5.14 (dd, J = 5.0, 2.3 Hz, 1H), 4.65 (hept, J = 6.1 Hz, 1H), 4.16 (d, J = 1.3 Hz, 2H), 3.86 (s, 3H), 3.81−3.70 (m, 4H), 3.60 (ddd, J = 13.4, 6.5, 4.4 Hz, 1H), 3.41 (tdd, J = 9.3, 5.9, 3.6 Hz, 2H), 1.19 (d, J = 6.0 Hz, 3H), 1.15 (d, J = 6.1 Hz, 3H); HRMS (ESI) exact mass calcd for $C_{31}H_{36}ClN_4O_6$ $[M + H]^+$ 595.2325, found 595.2313.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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