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Copper bis(oxazolines) as catalysts for stereoselective aziridination of styrenes with *N*-tosyloxycarbamates

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ABSTRACT

A Cu(I)-catalyzed asymmetric aziridination of styrenes with a chiral *N*-tosyloxycarbamate has been developed. Double stereodifferentiation was observed and both the *N*-tosyloxycarbamate substituent and the bis(oxazoline) ligand have a significant effect on the yields and diastereoselectivities. The best results for the aziridination were obtained with electron-deficient styrenes. Subsequent ring-opening reactions of styrene-derived aziridines at the benzylic position were observed with various oxygen and nitrogen nucleophiles under Lewis acid catalysis affording the corresponding products with complete inversion of stereochemistry. The strategy was used to synthesize the β-blocker, (*R*)-nifenalol.

1. Introduction

Aziridines are one of the smallest nitrogen-containing heterocycles and display important biological activities.[1] While other three-membered rings, such as cyclopropanes and epoxides, are readily found in natural products, the aziridine moiety is present in only a few.[2] These include the antitumor and antibiotic mitomycin C,[3] as well as the antibacterials madurastatin A1[4] and azicemicin A[5] (Fig. 1).

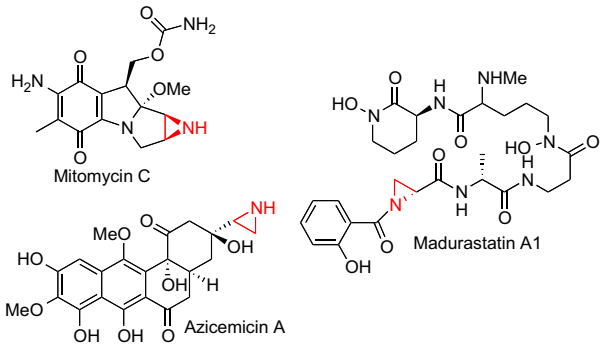

Fig. 1. Aziridine natural products.

Many synthetic and semi-synthetic aziridine alkaloids have anticancer, antibacterial, and/or antimicrobial activity against selected cancer cell lines, pathogenic bacteria, and/or micro-organisms.[6] The powerful mutagenic and toxic activities of aziridines are generally associated with their electrophilic properties to act as alkylating agents. As a result, aziridines are highly valuable heterocyclic compounds in medicinal chemistry and have been introduced in a variety of structures to create novel cancer chemotherapeutic agents.[7] Furthermore, aziridines have been used as the key structural element to create novel selective inhibitors of bacterial enzymes, potentially leading to a new class of antibiotics.[8]

Aziridines are valuable building blocks in organic chemistry due to their ability to undergo ring-opening reactions with a variety of nucleophiles.[9] Consequently, strategies involving ring-opening reactions have been used in process chemistry for the commercial preparation of pharmaceutical intermediates.[10] Aziridines have also been identified as key intermediates in diversity-oriented syntheses of alkaloids,[11] and in the asymmetric total syntheses of (−)-renieramycins M and G and (−)-jorumycin.[12] Recently, aziridines were reported as masked 1,3-dipoles that react with alkenes, alkynes, nitriles, and carbonyl compounds to produce various [3+2] cycloadducts.[13]

In comparison with the number of methods that have been reported to perform epoxidation reactions, synthetic approaches to prepare aziridines remain limited particularly in the enantioselective manifold.[1,2,14] The methods can be divided into three classes: 1. intramolecular substitutions; 2. addition to imines; and 3. aziridination of alkenes (Scheme 1). Intramolecular substitutions via the cyclization of 1,2-aminoalcohols were historically the first

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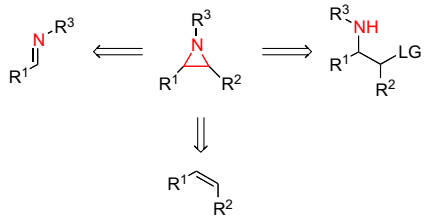
method reported for the synthesis of aziridines.[15] Since then, novel precursors have been exploited and many are available as single stereoisomers.[16] The approach remains attractive despite the lengthy synthetic sequence.



Scheme 1. Synthetic methods to aziridines.

Another approach to synthesize aziridines involves an initial addition to an imine, followed by a cyclization reaction. For example, the addition of stabilized anions bearing α-leaving groups to imines is known as the aza-Darzens reaction.[17] Stoichiometric chiral substrates or reagents have been successfully used to perform such a reaction with high levels of stereoselectivity.[18] A catalytic version of the methodology using chiral sulfoniums was described by Aggarwal.[19,20] Wulff has recently reported the addition of diazocarbonyl compounds to imines catalyzed by the chiral boron Lewis acids VANOL and VAPOL, that proceeded in excellent yields and enantioselectivities.[21,22]

The previously described approaches to aziridines involve the use of nitrogen-containing substrates and the formation of a single C–N bond to construct the three-membered ring. The aziridination of alkenes is a more efficient chemical transformation in that it leads to the formation of two new C–N bonds. Electron-deficient alkenes have been used in aza-Michael-initiated-ring-closing reactions with *N*-alkoxycarbamates.[23] Among them, successful organocatalytic enantioselective aziridinations of conjugated aldehydes and enones have been reported.[22d,24] Nitrene transfer by means of transition metal complexes is possible with unactivated alkenes using iminoiodinane reagents.[25] The seminal work of Jacobsen[26] and Evans[27] reported that chiral salen- and bis(oxazoline)–copper complexes, respectively, could be used to induce stereocontrol in the presence of PhI=NTs or PhI=NNs as nitrene precursors. Other chiral diimine ligands were studied and produced aziridines in high yields and enantioselectivities, notably as shown by Ding[28] for cinnamate derivatives and Xu[29] for chalcone derivatives.[30] Other transition metal complexes were reported for nitrene transfer to alkenes using iminoiodinanes, although with less efficiency.[31] To extend the scope of the reaction and to avoid the tedious isolation of the iminoiodinane reagent, novel in situ procedures in which the amine is oxidized with a hypervalent iodine reagent have emerged.[32] Less than a handful of asymmetric catalysts derived from copper[28,33] and rhodium[34] have been devised to perform aziridination reactions under these reaction conditions, with limited substrate scope and selectivities. Conversely highly efficient enantioselective aziridinations using azides as nitrene precursors have recently been reported.[35,36] Notably the chiral ruthenium catalyst developed by Katsuki[35] and the chiral porphyrin cobalt complex developed by Zhang[36] provided excellent results. However, the lengthy synthesis of the chiral ligands associated with these catalytic systems remains a significant drawback to the method. Another limitation associated with the method is the production of notoriously stable *N*-sulfonyl aziridines.[37] Although alternative sulfonyl groups have been introduced, cleavage of the *N*-sulfonyl aziridines has not always been reported[38] or proceeded in moderate yields and with the use of excess of expensive reagents.[39]

A few years ago, our group introduced *N*-tosyloxycarbamates as alternative metal nitrene precursors to perform C–H amination and aziridination reactions.[40] The ease of preparation and the stability of *N*-tosyloxycarbamates, as well as the mild reaction conditions are among the advantages of the method.[41] Both copper and rhodium complexes catalyzed the aziridination of styrene derivatives with *N*-tosyloxycarbamates. We observed that good stereocontrol could be obtained for the reaction using more sterically hindered or chiral *N*-tosyloxycarbamates in the presence of chiral metal complexes.[42] Herein, we report the complete details of our studies and the use of a chiral bis(oxazoline) copper complex with a chiral *N*-tosyloxycarbamate to produce enantioenriched aziridines with high selectivities. Furthermore, one of the aziridines was used as a chiral building block to synthesize the β-blocker, (*R*)-nifenalol.[43]

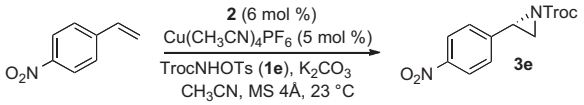
2. Results and discussion

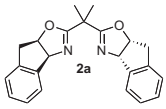
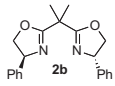
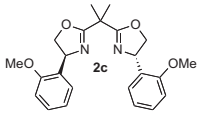
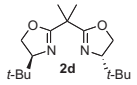
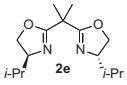
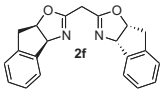
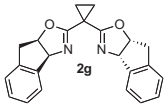
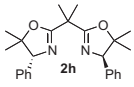
2.1. Copper-catalyzed enantioselective aziridination

We began our studies by examining the aziridination of 4-nitrostyrene with TrocNHOTs using catalytic amounts of $Cu(MeCN)_4PF_6$ and a variety of chiral ligands **2**, in the presence of potassium carbonate and molecular sieves in acetonitrile (Table 1). The carbamate TrocNHOTs was initially selected, as it was previously shown to display good reactivity in aziridination reactions with achiral catalysts.[40b] Indenyl-substituted ligand **2a**[44] initially provided the best result in terms of yield (85%) although the enantiomeric ratio (73:27) was modest (entry 1). When the reaction was performed at 0 °C, the enantiomeric ratio was slightly increased, but the yield dropped quite significantly (entry 2). The less rigid phenyl-substituted ligand **2b**[45] resulted in similar yield and enantioselectivity, whereas a more sterically hindered aryl substituent (**2c**)[46] afforded essentially no product (entries 3 and 4). Bis(oxazolines) with bulky alkyl groups (**2d** and **2e**)[47] resulted in enantiomeric ratios similar to those obtained with **2b** (entries 5 and 6 vs entry 3). The bridging substituents of the ligand were then modified to examine the effect of the metal–ligand chelation angle (entries 7 and 8). Small substituents or a cyclopropane ring increase the N=C–C–C=N angle and the bite angle of the ligand. The effect seems deleterious in the aziridination reaction as shown with ligands **2f** and **2g**,[48] which both afforded lower enantioselectivities. Conversely, substitutions at other positions of the ligand improved the reaction. When a *gem*-dimethyl substituent was added at the alpha position relative to oxygen (ligand **2h**),[49] higher yield and enantioselectivity were observed (entry 9).

As ligand **2h** was identified as the most promising ligand, it was tested with other *N*-tosyloxycarbamates (Table 2). *N*-Tosyloxycarbamates were designed to bear a side chain that could not undergo intramolecular reaction with the in situ generated metal nitrene. Furthermore, electron-deficient side chains were chosen, as they favored metal nitrenes reactive toward both aziridination and C–H insertion versus decomposition reactions.[50] The aromatic *N*-tosyloxycarbamates, in particular the most electron poor reagent **1c**, was the most reactive of the series, although overall poor yields and selectivities were obtained (entries 1–3). Chloro-substituted alkyl *N*-tosyloxycarbamates were then examined and the best results were obtained with trichloroethyl-substituted reagents (entries 4–8). Whereas the best yields were obtained with TrocNHOTs (**1e**), the best enantioselectivities were observed with the *gem*-dimethyl analog **1f**, illustrating that a more sterically hindered reagent provided better stereochemical discrimination (entries 5 and 6). The enantioselectivities did not change during the course of the reaction, as the same enantiomeric ratio was measured at partial conversion (34%) (entry 7). The yield with **1f** was only slightly increased when using 10 mol % of catalyst (entry 8). Other variables were examined, including additives and solvents, but none of them

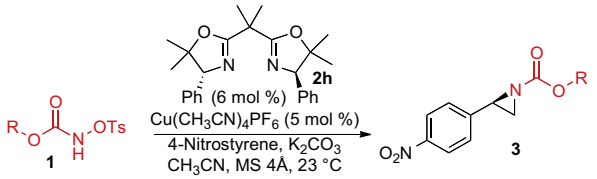
Table 1
Screening of bis(oxazoline) ligands **2** in the copper-catalyzed aziridination of 4-nitrostyrene with TrocNHOTs (**1e**)[a]

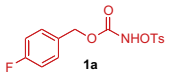
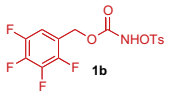
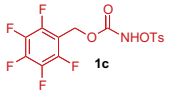
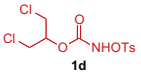
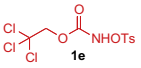
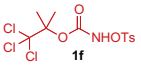
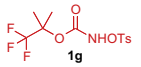
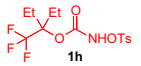


Entry	Ligand	Yield[b] (%)	Enantiomeric ratio[c]
1	 **2a**	85	73:27
2		56[d]	76:24[d]
3	 **2b**	65	75:25
4	 **2c**	<10	nd
5	 **2d**	62	72:28
6	 **2e**	~10[d]	73:27[d]
7	 **2f**	54	58:42
8	 **2g**	nd[c]	69:31[c]
9	 **2h**	*82*[e]	*15:85*[e]

[a] 4-Nitrostyrene (3 equiv), K_2CO_3 (1.5 equiv).
[b] Isolated yield.
[c] Ratio *S*/*R* determined by HPLC on chiral stationary phase.
[d] The reaction was performed at 0 °C.
[e] The antipode of the product shown (**3e**) was obtained.

Table 2
Copper-catalyzed enantioselective aziridination of 4-nitrostyrene with various *N*-tosyloxycarbamates[a]



Entry	*N*-tosyloxycarbamate	Yield[b] (%)	Enantiomeric ratio[c]
1	 **1a**	17	57:43
2	 **1b**	31	58:42
3	 **1c**	46	60:40
4	 **1d**	16	80:20
5	 **1e**	82	86:14
6		*52*	*93:7*
7	 **1f**	34[d]	*93:7*[d]
8		60[e]	*93:7*[e]
9	 **1g**	81	86:14
10		44[f]	91:9[f]
11	 **1h**	Decomp.[g]	—

[a] 4-Nitrostyrene (3 equiv), K_2CO_3 (1.5 equiv).
[b] Isolated yield.
[c] Ratio *R*/*S*, determined by HPLC on chiral stationary phase.
[d] Reaction was stopped at partial conversion after 3 h.
[e] Using 10 mol % of $Cu(CH_3CN)_4PF_6$ and 11 mol % of **2a**.
[f] Reaction was run at 0 °C.
[g] Decomposition of the *N*-tosyloxycarbamate reagent was observed.

proved advantageous. Trifluoro-substituted reagent **1g** was then prepared, with the hope that such a reagent would provide better yields, while keeping the same level of enantioselectivity (entries 9 and 10). Although the yield was better, the enantiomeric ratio was decreased compared to **1f** (entry 9). The ratio could be increased by performing the reaction at 0 °C, but to the detriment of the yield (entry 10). When a more sterically hindered carbamate reagent was used (**1h**), only decomposition of the *N*-tosyloxycarbamate reagent was observed.

Furthermore, a series of cyclic *N*-tosyloxycarbamates were prepared (Fig. 2), but were found to be unstable under the aziridination reaction conditions.

Having identified *N*-tosyloxycarbamate reagent **1f** as the optimal reagent, it was tested in the aziridination reaction with another substrate, 2-chlorostyrene (Table 3). As observed for the aziridination of 4-nitrostyrene, bis(oxazoline) **2h**[49] possessing a *gem*-dimethyl substituent at the alpha position relative to oxygen proved to be superior to the unsubstituted ligand **2b** (entries 1 and 2). However, the enantiomeric ratio dropped quite significantly for the aziridination of 2-chlorostyrene compared to 4-nitrostyrene (Table 2, entry 6 vs Table 3, entry 2). Other ligands **2** possessing different bridging substituents were then synthesized and tested in the aziridination of 2-chlorostyrene with reagent **1f**. Unfortunately, the use of ligands with both a more hindered substituent (ligand **2i**) and a cyclic substituent (ligand **2j**), which, respectively, decreases

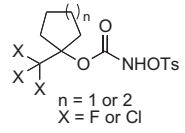
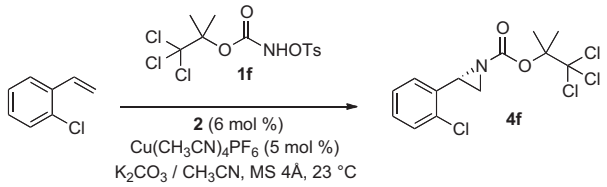
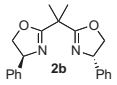
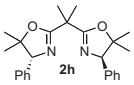
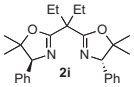
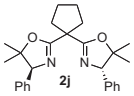


Fig. 2. Cyclic *N*-tosyloxycarbamates.

Table 3
Screening of bis(oxazoline) ligands **2** in the copper-catalyzed aziridination of 2-chlorostyrene with dimethyl-TrocNHOTs (**1f**)[a]



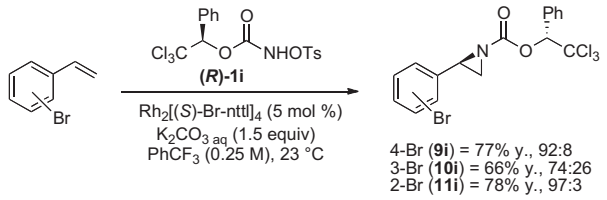
Entry	Ligand	Yield[b] (%)	Enantiomeric ratio[c]
1	 **2b**	37	67:33
2	 **2h**	71	22:78[d]
3	 **2i**	48	78:22
4	 **2j**	53	79:21

[a] 2-Chlorostyrene (3 equiv), K_2CO_3 (1.5 equiv).
[b] Isolated yield.
[c] Ratio *S*/*R* determined by HPLC on chiral stationary phase.
[d] The antipode of the product shown (**4f**) was obtained.

or increases the bite angle, did not affect the enantioselectivity of the reaction. Although good results were obtained for the enantioselective aziridination of 4-nitrostyrene, the problematic enantioselective aziridination of 2-chlorostyrene suggested that the scope of the reaction would be limited. We then decided to investigate chiral *N*-tosyloxycarbamate reagents to perform diastereoselective aziridination reactions.

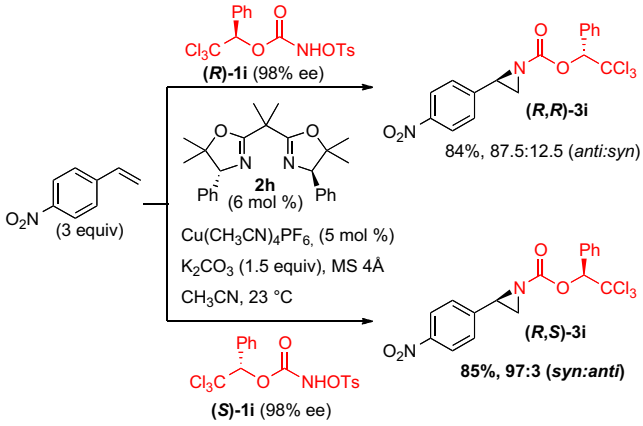
2.2. Copper-catalyzed diastereoselective aziridination

We have recently reported a stereoselective rhodium-catalyzed amination of alkenes using readily available chiral *N*-tosyloxycarbamate reagent **1i**.[42b] Excellent yields and diastereoselectivities were obtained for a large variety of diversely substituted styrene derivatives with the exception of mono 3-substituted styrenes. For example, >90:10 diastereoselectivity was obtained with 2- and 4-bromostyrene, whereas 3-bromostyrene led to a 73:26 dr (Scheme 2). In addition, it is necessary to use 5 mol % of expensive rhodium dimer catalyst (thus a total of 10 mol % of rhodium). These limitations prompted us to examine the reaction using a cheaper option such as copper catalysts and bis(oxazoline) ligands **2**.



Scheme 2. Rhodium-catalyzed aziridination of styrenes using *N*-tosyloxycarbamate **1i**.[42b]

The stereoselective aziridination of 4-nitrostyrene was performed under the best reaction conditions found previously (see Table 3) with both enantiomers of chiral *N*-tosyloxycarbamate reagent **1i** (Scheme 3). In contrast to what was observed in rhodium-catalyzed aziridination reactions, the chiral catalyst (as opposed to the chiral *N*-tosyloxycarbamate reagent) dictated the facial selectivity. Furthermore, both enantiomers of chiral *N*-tosyloxycarbamate reagent **1i** reacted at roughly the same rate to produce aziridine **3i** in similar yields. However, a match and mismatch pair effect was still observed as enantiomer (*S*)-**1i** led to higher enantioselectivities and produced aziridine (*R*,*S*)-**3i** with 97:3 diastereoselectivity.

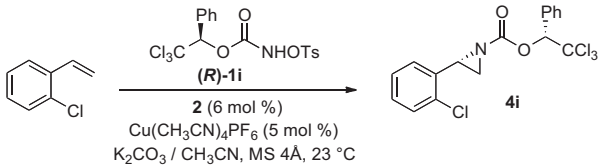


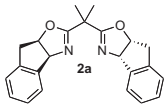
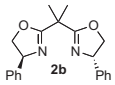
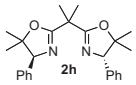
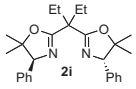
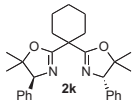
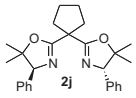
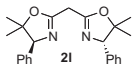
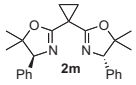
Scheme 3. Double stereodifferentiation with *N*-tosyloxycarbamate **1i**.

We then tested the same reaction conditions with 2-chlorostyrene and chiral *N*-tosyloxycarbamate reagent **1i** (Table 4, entry 3). The desired aziridine was produced in good yield and stereoselectivity, although the diastereomeric ratio was somewhat lower to what was obtained with 4-nitrostyrene. To insure we had the optimal catalyst system, we then investigated other bis(oxazoline) ligands **2**. As previously observed, the phenyl substituted ligand **2h** proved to be better than the more rigid bis(oxazoline) ligand **2a** derived from an aminoindanol (entry 1 vs 3). Furthermore having a *gem*-dimethyl substituent at the alpha position relative to oxygen was also beneficial, as ligand **2b** provided a lower diastereomeric ratio than ligand **2h**. The bridging substituents of the ligand were then examined, but did not lead to any significant improvement (entries 4–8). Whereas larger substituents (ligand **2i**) produced the same ratio (entry 4 vs 3), smaller substituents (ligands **2j**, **2k**, and **2m**) or no substituent (ligand **2l**[51]), which increases the ligand bite angle, proved to be deleterious for the stereoselectivity (entries 5–8).

The copper-catalyzed diastereoselective aziridination with chiral *N*-tosyloxycarbamate **1i** and ligand **2h** was then conducted with a variety of styrene derivatives (Table 5). Aziridines were produced from nitro-substituted styrenes in moderate to good yields and excellent diastereomeric ratios (entries 1 and 2). Slightly lower diastereomeric ratios were observed with 3- and 4-halo substituted styrenes (entries 3–6), whereas aziridine **11i** derived from 2-bromostyrene was obtained in excellent diastereoselectivity (entry 7). In contrast to what was observed in rhodium-catalyzed aziridination reactions, *meta*-substituted styrenes were not problematic substrates with the

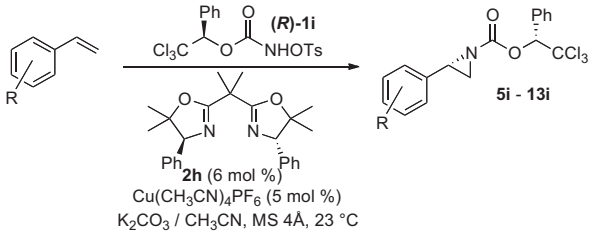
Table 4
Screening of bis(oxazoline) ligands **2** in the copper-catalyzed aziridination of 2-chlorostyrene with Ph–TrocNHOTs (*R*)-**1i**[a]

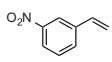
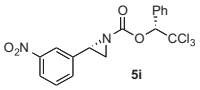
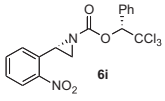
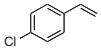
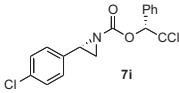
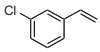
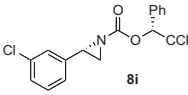
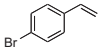
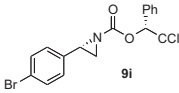
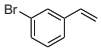
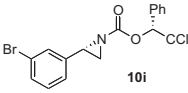
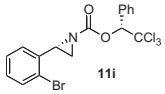
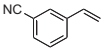
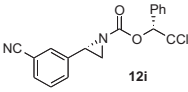


Entry	Ligand	Yield[b] (%)	Diastereomeric ratio[c]
1	 **2a**	81	75:25
2	 **2b**	85	80:20
3	 **2h**	*76*	*92:8*
4	 **2i**	76	92:8
5	 **2k**	74	88:11
6	 **2j**	66	81:9
7	 **2l**	69	80:20
8	 **2m**	76	81:9

[a] 2-Chlorostyrene (3 equiv), K_2CO_3 (1.5 equiv).
[b] Isolated yield.
[c] Ratio *SR*/*RR* (*syn*/*anti*) determined by ^{1}H NMR on the crude mixture.

Table 5
Scope of the copper-catalyzed diastereoselective aziridination with chiral *N*-tosyloxycarbamate **1i**[a]

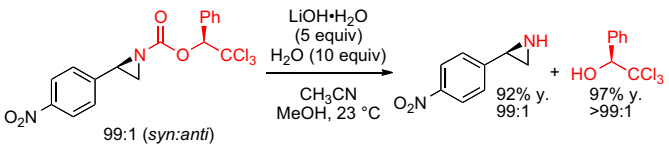


Entry	Styrene	Aziridine	Yield[b] (%)	Diastereomeric ratio[c]
1		 **5i**	84	89:11
2		 **6i**	50	93:7
3		 **7i**	70	81:19
4		 **8i**	47	84:16
5		 **9i**	80	81:19
6		 **10i**	71	81:19
7		 **11i**	73	89:11
8		 **12i**	44	82:18

[a] Styrene (3 equiv); K_2CO_3 (1.5 equiv).
[b] Isolated yield.
[c] Ratio *SR*:*RR* (*syn*:*anti*), determined by ^{1}H NMR on the crude mixture.

copper–bis(oxazoline) system. Overall the diastereomeric ratios for the copper-catalyzed aziridination of 3- and 4-halo substituted styrenes were similar (entries 3,4 and 5,6). Whereas the rhodium-catalyzed aziridination of 3-nitro- and 3-bromostyrene proceeded in 80:20 and 74:26 diastereomeric ratio (Scheme 2),[52] aziridines **5i** and **10i** were produced in 89:11 and 82:18 diastereomeric ratio, respectively, using the copper–bis(oxazoline) **2h** catalytic system (entries 1 and 6). Furthermore, the copper catalyst was compatible with a nitrile functional group (which inhibits rhodium dimer catalysts) and aziridine **12i** was isolated in moderate yield, but good diastereoselectivity (entry 8).

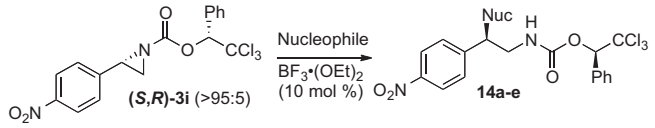
An advantage of the *N*-tosyloxycarbamate reagents is the facile cleavage in the resulting aziridines under mild basic reaction conditions.[42b] As such, both the chiral aziridine and alcohol were recovered in excellent yields and enantioselectivities (Scheme 4).

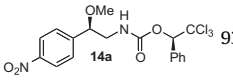
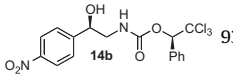
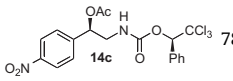
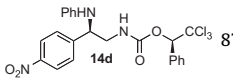


Scheme 4. Cleavage of the protecting group and recovery of the chiral alcohol.

It is also possible to perform ring-opening reactions of aziridine **3i** with a variety of nucleophiles using a catalytic amount of a Lewis acid, $BF_3{\cdot}OEt_2$ (Table 6).[9] In all cases, the nucleophilic attack occurred at the activated benzylic position and the reaction typically proceeded with complete inversion of stereochemistry. When an alcohol or water was used as nucleophile, the corresponding amino ether or alcohol was recovered in excellent yields and

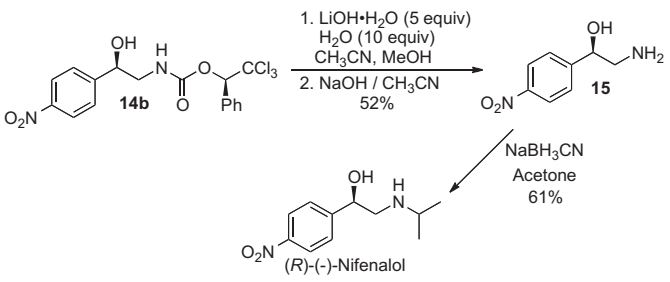
Table 6
Ring-opening reactions of aziridines **3i** with various nucleophiles



Entry	Conditions	Product	Yield[a] (%); diastereomeric ratio[b]
1	MeOH (0.1 M), rt, 1 h		93; >95:5
2	H_2O/MeCN 1:1 (0.1 M), rt, 1 h		93; >95:5[c]
3	AcOH (3 equiv), DCM (0.1 M), rt, 1 h		78; 89:11
4	$PhNH_2$ (6 equiv),[d] MeCN (0.1 M), rt, 24 h		87; >95:5[c]

[a] Isolated yield.
[b] Ratio *RR*/*SR*, determined by HPLC on chiral stationary phase.
[c] One diastereomer by ^{1}H NMR.
[d] $BF_3{\cdot}(OEt)_2$ of 20 mol % was used.

diastereomeric ratios (entries 1 and 2). When acetic acid was used, the desired product was produced in good yields, although with some erosion of the diastereoselectivity (entry 3). In the latter case, it is believed that a carbocation pathway (i.e., S_N1) is probably competitive with the predominant S_N2 reaction, due to the increased acidity of the reaction mixture. Conversely, using aniline as a nucleophile led to the ring-opened product in an excellent yield and conservation of the diastereomeric ratio (entry 4). Ring opened-product **14b**, resulting from the attack of water to aziridine **3i** is an advanced chiral building block to access (*R*)-(−)-nifenalol, an important β-adrenergic receptor blocking drug.[43,53] Cleavage of the chiral alcohol using lithium hydroxide produced the corresponding oxazolidinone, which was then hydrolyzed using stronger basic reaction conditions to lead to aminoalcohol **15** (Scheme 5). Reductive amination using sodium cyanoborohydride in acetone smoothly produced the desired (*R*)-(−)-nifenalol in 61% yield.



Scheme 5. Total synthesis of (*R*)-(−)-nifenalol.

Other aziridines were tested in the ring-opening reactions with water under the same reaction conditions described previously (Table 7). Nucleophilic addition to nitro-substituted aziridine **5i** proceeded well with complete inversion of configuration to produce **16** in excellent yield and diastereomeric ratio (entry 1). Conversely, partial isomerization was observed with halo-substituted aziridines, indicating that the formation of the benzylic carbocation was competitive (entries 2 and 3). Aminoalcohols **17** and **18** were recovered in excellent yields, but with moderate diastereomeric ratios. Neither changing the Lewis acid nor the reaction conditions improved the stereochemical outcome of the reaction with these substrates.

3. Conclusions

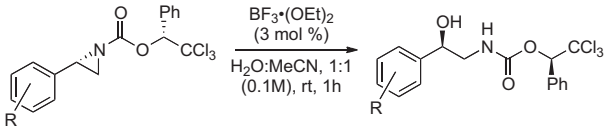
In summary, the aziridination of styrenes with a chiral *N*-tosyloxycarbamate and a chiral copper complex afforded carbamate-protected aziridines in good yields with good to excellent diastereoselectivities. The selectivity of the system is complementary to the previously reported system using a chiral rhodium catalyst, as good results were obtained with *meta*-substituted styrene substrates. Excellent results were produced for the aziridination of nitro-substituted styrenes. Ring-opening reactions were performed with these aziridines to produce a variety of chiral derivatives typically with complete stereochemical inversion. One of these intermediates was converted in a few steps into (*R*)-(−)-nifenalol.

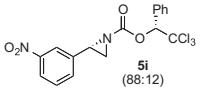
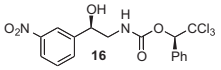
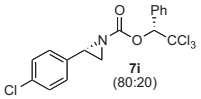
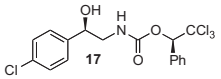
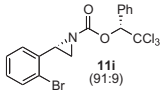
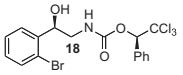
4. Experimental section

4.1. General details

All non-aqueous reactions were run under an inert atmosphere (argon) with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds. All glassware was stored in the oven and/or was flame dried prior to use under an inert atmosphere of gas. Anhydrous solvents were obtained either by filtration through drying columns (CH_2Cl_2, CH_3CN, methanol) on a GlassContour system (Irvine, CA) or by distillation over calcium hydride (ethanol). Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel (Merck 60 F_{254}). Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, iodine or aqueous potassium permanganate. Flash column chromatography was performed using 230–400 mesh silica (Silicycle) of the indicated solvent system according to standard technique. Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum One FTIR spectrometer equipped with a Golden Gate Diamond ATR and are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were recorded either on a Bruker AV-700, Bruker AV-400, a Bruker ARX-400, a Bruker AMX-300 or a Bruker AV-300 spectrometer (700, 400, 400, 300 or 300 MHz, respectively). Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ=7.27 ppm). Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ 77.00 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. Chemical shifts for ^{19}F NMR spectra are recorded in parts per million from trichlorofluoromethane using the resonance of α,α,α-trifluorotoluene (δ −63.7 ppm) as standard. Optical rotations were determined with a Perkin–Elmer 341 polarimeter at 589 or 546 nm. Data are reported as follows: $[\alpha]_{temp}$, concentration (*c* in g/100 mL), and solvent. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. High performance liquid chromatography (HPLC) analyses were performed on a Hewlett Packard 1100 Series quaternary gradient pump with diode-array detector interfaced with HP

Table 7
Ring-opening reactions of aziridines with water



Entry	Aziridine	Product	Yield[a] (%); diastereomeric ratio[b]
1	 **5i** (88:12)	 **16**	87; 88:12
2	 **7i** (80:20)	 **17**	84; 72:28
3	 **11i** (91:9)	 **18**	88; 87:13

[a] Isolated yield.
[b] Ratio *RR*/*SR*, determined by HPLC on chiral stationary phase.

Chemstation software. Values for enantiomeric excess were determined using a chiral column. Data are reported as follows: column type, flow, solvent used, and retention time (t_R). Analytical supercritical fluid chromatography (SFC) were performed at Laboratoire d'Analyse et de Séparation Chirale par SFC de l'Université de Montréal. Data are reported as follows: column type, eluent, flow rate, and retention time (t_R).

Unless otherwise stated, commercial reagents were used without purification. K_2CO_3 was purchased from Aldrich Chemical Company and finely powdered before use. $Cu(MeCN)_4PF_6$ was purchased from Aldrich Chemical Company and stored in a glove box under an argon atmosphere at room temperature. $BF_3{\cdot}(OEt_2)$ was purchased from Aldrich Chemical Company and used without purification. Molecular sieves were dried under reduced pressure at 120 °C for 16 h and stored in dessicator. 1,1,1-Trichloro-2-methylpropan-2-ol[54] and *N*-tosyloxycarbamates **1a**[50], **1e**,[50] and **1i**[42b] were prepared according to known published procedures.

4.2. Preparation of *N*-tosyloxycarbamates 1b, 1c, 1d, 1f, and 1g

*4.2.1. 1,2,3,4-Tetrafluorobenzyl N-tosyloxycarbamate (**1b**).* To a solution of 1,1′-carbonyldiimidazole (1.72 g, 10.6 mmol) in MeCN (50 mL) was added 1,2,3,4-tetrafluorobenzyl alcohol (1.74 g, 9.68 mmol). The resulting mixture was stirred at room temperature for 3 h. Hydroxylamine hydrochloride (2.70 g, 39.7 mmol) was then added followed by imidazole (1.98 g, 29.0 mmol) and the resulting mixture was stirred for 16 h. The suspension was concentrated under reduced pressure. The white residue was dissolved in a 1:1 mixture of ethyl acetate and HCl_{aq} 10% (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting *N*-hydroxycarbamate used without further purification. To a solution of *N*-hydroxycarbamate (2.28 g, 9.55 mmol) in ether (90 mL) at 0 °C was added tosyl chloride (1.91 g, 10.0 mmol). Triethylamine (1.39 mL, 10.0 mmol) was then slowly added to the solution. The resulting white suspension was stirred at room temperature for 2 h. Water (25 mL) was added to the solution and the two layers were separated. The aqueous layer was washed with ether (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and the solvent was removed under reduced. The desired *N*-tosyloxycarbamate **1b** (2.78 g, 72% yield) was obtained as a white solid after flash chromatography (20% EtOAc/hexanes). R_f 0.22 (20% EtOAc/hexanes); mp 61–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.83 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 6.91–6.80 (m, 1H), 5.07 (s, 3H), 2.45 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −139.64 to −139.84 (m, 1F), −143.71 to −143.90 (m, 1F), −155.37 to −155.58 (m, 1F), −156.11 to −156.30 (m, 1F); IR (neat) 3200, 2948, 1774, 1743, 1525, 1490, 1384, 1363, 1228, 1194, 1181, 1120, 1084, 983, 936, 859, 817, 691 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{15}H_{11}NO_5F_4SNa$ $[M+Na]^+$: 416.01863; found: 416.01817.

*4.2.2. Pentafluorobenzyl N-tosyloxycarbamate (**1c**).* To a solution of 1,1′-carbonyldiimidazole (1.78 g, 11.0 mmol) in MeCN (50 mL) was added pentafluorobenzyl alcohol (1.99 g, 10.0 mmol). The resulting mixture was stirred at room temperature for 1 h. Hydroxylamine hydrochloride (2.78 g, 40.0 mmol) was then added followed by imidazole (2.04 g, 30.0 mmol) and the resulting mixture was stirred for 4 h. The suspension was concentrated under reduced pressure. The white residue was dissolved in a 1:1 mixture of ethyl acetate and HCl_{aq} 10% (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting *N*-hydroxycarbamate used without further purification. To a solution of *N*-hydroxycarbamate (~10 mmol) in ether (100 mL) at 0 °C was added tosyl chloride (2.09 g, 11.0 mmol). Triethylamine (1.53 mL, 11.0 mmol) was then slowly added to the solution. The resulting white suspension was stirred at room temperature for 2 h. Water (25 mL) was added to the solution and the two layers were separated. The aqueous layer was washed with ether (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The desired *N*-tosyloxycarbamate **1c** (1.88 g, 46% yield) was obtained as a white solid after recrystallization from a 1:1 mixture of hexanes and chloroform. R_f 0.38 (30% EtOAc/hexanes); mp 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.83 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 5.13 (t, J=1.4 Hz, 2H), 2.46 (s, 3H, CH_3); ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.5, 146.49–144.74 (m, 1C), 143.01–141.23 (m, 1C), 138.33–136.59 (m, 1C), 129.9, 129.7, 129.5, 108.39–108.11 (m, 1C),

55.2, 21.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −142.68 (dd, J=23.1, 7.9 Hz, 2F), −152.60 (tt, J=20.8, 2.5 Hz, 1F), −162.6 to −162.4 (m, 2F); IR (neat) 3200, 1781, 1748, 1517, 1488, 1366, 1233, 1196, 1130, 1060, 934, 817, 725, 693 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{15}H_{10}NO_5F_5SNa$ $[M+Na]^+$: 434.00921; found: 434.00861.

*4.2.3. 1,3-Dichloropropan-2-yl N-tosyloxycarbamate (**1d**).* To a solution of 1,1′-carbonyldiimidazole (3.57 g, 22.0 mmol) in MeCN (100 mL) was added 1,3-dichloropropan-2-ol (1.91 mL, 20.0 mmol). The resulting mixture was stirred at room temperature for 3 h. Hydroxylamine hydrochloride (5.56 g, 80.0 mmol) was then added followed by imidazole (4.08 g, 60.0 mmol) and the resulting mixture was stirred for 16 h. The suspension was concentrated under reduced pressure. The white residue was dissolved in a 1:1 mixture of ethyl acetate and HCl_{aq} 10% (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting *N*-hydroxycarbamate used without further purification. To a solution of *N*-hydroxycarbamate (~20 mmol) in ether (200 mL) at 0 °C was added tosyl chloride (4.20 g, 22.0 mmol). Triethylamine (3.07 mL, 12.0 mmol) was then slowly added to the solution. The resulting white suspension was stirred at room temperature for 2 h. Water (50 mL) was added to the solution and the two layers were separated. The aqueous layer was washed with ether (2×40 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The desired *N*-tosyloxycarbamate **1d** (3.99 g, 59% yield) was obtained as a colorless oil after flash chromatography (20% EtOAc/hexanes). R_f 0.42 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.88 (d, J=8.2 Hz, 2H), 7.38 (d, J=8.1 Hz, 2H), 5.03–4.93 (quint, J=5.2 Hz, 1H), 3.60 (d, J=5.2 Hz, 4H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 146.4, 129.8, 129.6, 129.1, 74.3, 41.8, 21.7; IR (neat) 3204, 2964, 1761, 1734, 1597, 1493, 1383, 1245, 1191, 1185, 1086, 813, 730, 702, 657 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{11}H_{13}NO_5Cl_2SNa$ $[M+Na]^+$: 363.97837; found: 363.97837.

4.2.4. N-(2,2,2-Trichloro-1,1-dimethyl-1-ethyloxycarbonyl)-imidazolium tosylate. To a solution of 1,1′-carbonyldiimidazole (3.56 g, 22.0 mmol) and potassium hydroxide (0.078 g, 1.4 mmol) in MeCN (100 mL) at 0 °C was added dropwise 1,1,1-trichloro-2-methylpropan-2-ol (3.52 g, 20.0 mmol). The mixture was stirred at room temperature for 5 h. The solvent was then removed under reduced pressure. The residue was dissolved in Et_2O, washed with saturated NH_4Cl_{aq}, brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure. The desired 1,1,1-trichloro-2-methylpropyl imidazole carboxylate was isolated as a white solid (4.22 g, 78% yield) and used without further purification. The residue (3.30 g, 12.1 mmol) was dissolved in acetone (12 mL) and *p*-toluenesulfonic acid (2.42 g, 12.7 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. Et_2O was added to the solution and the precipitated salt was filtered and dried under vacuum for 30 min. The desired product was isolated as a white solid (4.98 g, 93% yield). R_f 0.22 (20% EtOAc/hexanes); mp 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.76 (d, J=8 Hz, 2H), 7.61 (d, J=6 Hz, 2H), 7.16 (d, J=8 Hz, 2H), 2.34 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 141.7, 140.3, 136.8, 128.8, 125.9, 122.6, 118.7, 103.7, 95.2, 21; IR (neat) 3105, 1810, 1570, 1320, 1235, 1210, 1125, 1110, 1005, 980, 800, 790, 675 cm^{-1}; HMRS (ESI$^+$) calcd for $C_8H_{10}N_2Cl_3O_2$ $[M+H]^+$: 270.9797; found: 270.9802.

*4.2.5. 2,2,2-Trichloro-1,1-dimethylethyl N-tosyloxycarbamate (**1f**).* *O*-Benzylhydroxylamine (878 mg, 5.50 mmol) and imidazole (374 mg, 5.50 mmol) were stirred in MeCN (50 mL) at room temperature for 1 h. *N*-(2,2,2-Trichloro-1,1-dimethyl-1-ethyloxycarbonyl)-imidazolium tosylate (2.21 g, 5.00 mmol) was then added to the mixture and the resulting mixture was stirred at 60 °C for 2 h. After cooling to room temperature, Et_2O (50 mL) was added to precipitate the salts, which were filtered off. The solvent of the filtrate was then removed under reduced pressure to afford the corresponding *N*-benzyloxycarbamate. *N*-Benzyloxycarbamate (~5 mmol) was dissolved in MeOH (20 mL) and DCM (10 mL). Pd/C 10 wt % (160 mg) was added to the solution. The resulting mixture was stirred under a hydrogen atmosphere (balloon) for 16 h. The mixture was filtered through a Celite pad and the solvent was removed under reduced pressure to afford the corresponding *N*-hydroxycarbamate, which was used without further purification. To a solution of *N*-hydroxycarbamate (~5.00 mmol) in ether (50 mL) at 0 °C was added tosyl chloride (1.04 g, 5.50 mmol). Triethylamine (0.77 mL, 5.50 mmol) was then slowly added to the solution. The resulting white suspension was stirred at room temperature for 2 h. Water (25 mL) was added to the solution and the two layers were separated. The aqueous layer was washed with ether (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The desired *N*-tosyloxycarbamate **1f** was obtained as a white solid (1.28 g, 66% yield) after flash chromatography (15% EtOAc/hexanes). R_f 0.37 (20% EtOAc/hexanes); mp 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J=8 Hz, 2H), 7.87 (br s, 1H), 7.38 (d, J=8 Hz, 2H), 2.47 (s, 3H), 1.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 146.0, 129.8, 129.4, 129.3, 104.7, 90.5, 21.5, 21.0; IR (neat) 3240, 2925, 1745, 1600, 1470, 1390, 1375, 1265, 1195, 1175, 1085, 785, 730, 660 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{12}H_{14}Cl_3NO_5SNa$ $[M+Na]^+$: 411.95505; found: 411.95571.

*4.2.6. 2,2,2-Trifluoro-1,1-dimethylethyl N-tosyloxycarbamate (**1g**).* The title compound was prepared from 1,1,1-trifluoro-2-methylpropan-2-ol (1.64 mL, 15.0 mmol) following the typical procedure to prepare **1f**. The desired *N*-tosyloxycarbamate **1g** was obtained as a white solid (2.59 g, 51% yield) after flash chromatography (20% EtOAc/hexanes). R_f 0.33 (20% EtOAc/hexanes); mp 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.88 (d, J=8 Hz, 2H), 7.37 (d, J=8 Hz, 2H), 2.46 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 146.3, 129.9, 129.7, 129.6, 124.2 (q, J=283 Hz, 1C), 82.1 (q, J=30 Hz, 1C), 21.7, 19.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −84.9; IR (neat) 3215, 2950, 1740, 1485, 1395, 1270, 1175, 1160, 1135, 730, 650 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{12}H_{14}NF_3O_5SNa$ $[M+Na]^+$: 364.0437; found: 364.0438.

4.3. Preparation of bis(oxazoline) derivatives 2i, 2j, 2k, and 2m[55]

*4.3.1. (4S,4′S)-2,2′-(Pentane-3,3-diyl)bis(5,5-dimethyl-4-phenyl-4,5-dihydrooxazole) (**2i**).* To a solution of bis(oxazoline) **2l**[51] (0.200 g, 0.560 mmol) in THF (10 mL) were added TMEDA (0.150 mL, 1.12 mmol) and *i*-Pr_2NH (78 μL, 0.56 mmol). The resulting mixture was then cooled at −78 °C. *n*-BuLi (0.450 mL of a 2.5 M solution in hexanes, 1.12 mmol) was added via syringe to the cold mixture. The reaction mixture was warmed to −20 °C and stirred for 20 min. The solution was cooled to −70 °C and ethyliodide (90.0 μL, 1.12 mmol) was added. After the addition, the cooling bath was removed and the mixture was allowed to stir at room temperature for 16 h. The mixture was quenched with saturated aqueous NH_4Cl solution (2 mL) and diluted with water (3 mL). The resulting mixture was extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford a dark orange oil. The desired bis(oxazoline) **2i** was obtained as a white solid (180 mg, 76% yield) after flash chromatography (50% EtOAc/hexanes). R_f 0.62 (50% EtOAc/hexanes); $[\alpha]_D^{25}$ −137.0 (*c* 1.00, $CHCl_3$); mp 109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J=8.7 Hz, 2H), 7.40 (dd, J=7.2,

2.1 Hz, 2H), 7.08–7.01 (m, 3H), 6.67 (d, *J*=8.7 Hz, 2H), 6.50 (s, 1H), 2.99 (dd, *J*=6.4, 3.6 Hz), 2.17 (d, *J*=6.3 Hz, 1H), 1.64 (d, *J*=3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 147.7, 143.6, 132.3, 129.9, 129.5, 128.0, 127.1, 123.9, 99.0, 84.4, 38.7, 35.7; IR (neat) 2955, 2924, 2856, 1741, 1603, 1515, 1346, 1323, 1305, 1288, 1222, 1181, 1136, 1019, 948, 787, 748, 698 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{14}N_2O_4Cl_3$ $[M+H]^+$: 415.00137; found: 415.00161.

*4.3.2. (4S,4′S)-2,2′-(Cyclopentane-1,1-diyl)bis(5,5-dimethyl-4-phenyl-4,5-dihydrooxazole) (**2j**).* To a solution of bis(oxazoline) **2l**[51] (0.100 g, 0.280 mmol) in THF (5 mL) were added TMEDA (73 μL, 0.56 mmol) and *i*-Pr_2NH (39 μL, 0.28 mmol). The resulting mixture was then cooled at −78 °C. *n*-BuLi (0.370 mL of a 2.5 M solution in hexanes, 0.56 mmol) was added via syringe to the cold mixture. The reaction mixture was warmed to −20 °C and stirred for 20 min. The solution was cooled to −78 °C and freshly distilled 1,4-diiodobutane (50 μL, 0.38 mmol) was added. After the addition, the cooling bath was removed and the mixture was allowed to stir at room temperature for 16 h. The mixture was quenched with saturated aqueous NH_4Cl solution (1 mL) and diluted with water (1 mL). The resulting mixture was extracted with Et_2O (2×5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford a dark orange oil. The desired bis(oxazoline) **2j** was obtained as a white solid (87 mg, 75% yield) after flash chromatography (50% EtOAc/hexanes). R_f 0.58 (50% EtOAc/hexanes); $[\alpha]_D^{25}$ −108.8 (*c* 0.50, $CHCl_3$); mp 79–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.7 Hz, 2H), 7.40 (dd, *J*=7.2, 2.1 Hz, 2H), 7.08–7.01 (m, 3H), 6.67 (d, *J*=8.7 Hz, 2H), 6.50 (s, 1H), 2.99 (dd, *J*=6.4, 3.6 Hz, 1H), 2.17 (d, *J*=6.3 Hz, 1H), 1.64 (d, *J*=3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 147.7, 143.6, 132.3, 129.9, 129.5, 128.0, 127.1, 123.9, 99.0, 84.4, 38.7, 35.7; IR (neat) 2955, 2924, 2856, 1741, 1603, 1515, 1346, 1323, 1305, 1288, 1222, 1181, 1136, 1019, 948, 787, 748, 698 cm^{-1}; HMRS (ESI) calcd for $C_{27}H_{33}N_2O_2$ $[M+H]^+$: 417.25365; found: 417.25428.

*4.3.3. (4S,4′S)-2,2′-(Cyclohexane-1,1-diyl)bis(5,5-dimethyl-4-phenyl-4,5-dihydrooxazole) (**2k**).* To a solution of bis(oxazoline) **2l**[51] (0.190 g, 0.520 mmol) in THF (10 mL) were added TMEDA (135 μL, 1.04 mmol) and *i*-Pr_2NH (72 μL, 0.52 mmol). The resulting mixture was then cooled at −78 °C. *n*-BuLi (0.415 mL of a 2.5 M solution in hexanes, 1.04 mmol) was added via syringe to the cold mixture. The reaction mixture was warmed to −20 °C and stirred for 20 min. The solution was cooled to −70 °C and freshly distilled 1,5-diiodopentane (78 μL, 0.52 mmol) was added. After the addition, the cooling bath was removed and the mixture was allowed to stir at room temperature for 16 h. The mixture was quenched with saturated aqueous NH_4Cl solution (2 mL) and diluted with water (3 mL). The resulting mixture was extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford a dark orange oil. The desired bis(oxazoline) **2k** was obtained as a white solid (183 mg, 81% yield) after flash chromatography (50% EtOAc/hexanes). R_f 0.64 (50% EtOAc/hexanes); $[\alpha]_D^{25}$ −90.6 (*c* 0.50, C_6H_6); mp 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.7 Hz, 2H), 7.40 (dd, *J*=7.2, 2.1 Hz, 2H), 7.08–7.01 (m, 3H), 6.67 (d, *J*=8.7 Hz, 2H), 6.50 (s, 1H), 2.99 (dd, *J*=6.4, 3.6 Hz, 1H), 2.17 (d, *J*=6.3 Hz, 1H), 1.64 (d, *J*=3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 147.7, 143.6, 132.3, 129.9, 129.5, 128.0, 127.1, 123.9, 99.0, 84.4, 38.7, 35.7; IR (neat) 2955, 2924, 2856, 1741, 1603, 1515, 1346, 1323, 1305, 1288, 1222, 1181, 1136, 1019, 948, 787, 748, 698 cm^{-1}; HMRS (ESI) calcd for $C_{28}H_{35}N_2O_2$ $[M+H]^+$: 431.26984; found: 431.2693.

*4.3.4. (4S,4′S)-2,2′-(Cyclopropane-1,1-diyl)bis(5,5-dimethyl-4-phenyl-4,5-dihydrooxazole) (**2m**).* To a solution of bis(oxazoline) **2l**[51] (0.200 g, 0.560 mmol) in THF (10 mL) were added TMEDA (0.150 mL, 1.12 mmol) and *i*-Pr_2NH (78 μL, 0.56 mmol). The resulting mixture was then cooled at −78 °C. *n*-BuLi (0.450 mL of a 2.5 M solution in hexanes, 1.12 mmol) was added via syringe to the cold mixture. The reaction mixture was warmed to −20 °C and stirred for 20 min. The solution was cooled to −70 °C and 1,2-dibromoethane (48 μL, 0.56 mmol) was added. After the addition, the cooling bath was removed and the mixture was allowed to stir at room temperature for 16 h. The mixture was quenched with saturated aqueous NH_4Cl solution (2 mL) and diluted with water (3 mL). The resulting mixture was extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford a dark orange oil. The desired bis(oxazoline) **2m** was obtained as a white solid (172 mg, 72% yield) after flash chromatography (50% EtOAc/hexanes). R_f 0.68 (50% EtOAc/hexanes); $[\alpha]_D^{25}$ −116.0 (*c* 0.50, C_6H_6); mp 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.7 Hz, 2H), 7.40 (dd, *J*=7.2, 2.1 Hz, 2H), 7.08–7.01 (m, 3H), 6.67 (d, *J*=8.7 Hz, 2H), 6.50 (s, 1H), 2.99 (dd, *J*=6.4, 3.6 Hz, 1H), 2.17 (d, *J*=6.3 Hz, 1H), 1.64 (d, *J*=3.5 Hz, 1H); HMRS (ESI) calcd for $C_{25}H_{29}N_2O_2$ $[M+H]^+$: 389.22277; found: 389.22235.

4.4. Enantioselective aziridination with *N*-tosyloxycarbamates 1f and 1g

*4.4.1. (R)-1,1,1-Trichloro-2-methylpropan-2-yl 2-(4-nitrophenyl)aziridine-1-carboxylate (**3f**).* A suspension of $Cu(CH_3CN)_4PF_6$ (9.0 mg, 0.025 mmol), bis(oxazoline) (*S*,*S*)-**2h** (12 mg, 0.030 mmol), and 4 Å molecular sieves (200 mg) in MeCN (3 mL) was stirred at room temperature for 30 min. Potassium carbonate (104 mg, 0.750 mmol), then 4-nitrostyrene (223 mg, 1.50 mmol) were successively added. The heterogeneous solution was stirred for 15 min. A solution of 2,2,2-trichloro-1,1-dimethylethyl *N*-tosyloxycarbamate (**1f**) (195 mg, 0.500 mmol) in MeCN (2 mL) was slowly added over 2 h with a syringe pump. The resulting mixture was then stirred at room temperature for 12 h. The solution was filtered and rinsed with Et_2O (5 mL), and then the solvent was removed under reduced pressure. The desired aziridine **3f** was obtained as a yellow oil (95 mg, 52% yield) after flash chromatography (15% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The enantiomeric ratio was determined by HPLC analysis using Chiracel-OD column (2% *i*-PrOH/hexanes at 1.0 mL/min), retention time: t_R (major)=17.2 min and t_R (minor)=16.7 min (97:3 er). R_f 0.55 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ −80.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.74 (d, *J*=8.8 Hz, 2H), 6.76 (d, *J*=8.7 Hz, 2H), 2.96 (dd, *J*=6.3, 3.5 Hz, 1H), 2.20 (d, *J*=6.3 Hz, 1H), 1.78 (s, 3H), 1.76 (s, 3H), 1.65 (d, *J*=3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 147.4, 143.1, 126.4, 123.1, 105.9, 88.9, 38.0, 34.7, 20.6; IR (neat) 3084, 3010, 2905, 1718, 1599, 1518, 1365, 1307, 1291, 1186, 1147, 1106, 856, 790, 750, 699 cm^{-1}; HMRS (ESI) calcd for. $C_{13}H_{13}N_2O_4Cl_3Na$ $[M+Na]^+$: 388.9822; found: 388.9833.

*4.4.2. (R)-1,1,1-Trifluoro-2-methylpropan-2-yl 2-(4-nitrophenyl)aziridine-1-carboxylate (**3g**).* A suspension of $Cu(CH_3CN)_4PF_6$ (9.0 mg, 0.025 mmol), bis(oxazoline) (*S*,*S*)-**2h** (12 mg, 0.030 mmol), and 4 Å molecular sieves (200 mg) in MeCN (3 mL) was stirred at room temperature for 30 min. Potassium carbonate (104 mg, 0.750 mmol), then 4-nitrostyrene (223 mg, 1.50 mmol) were successively added. The heterogeneous solution was stirred for 15 min. A solution of 2,2,2-trifluoro-1,1-dimethylethyl *N*-tosyloxycarbamate (**1g**) (170 mg, 0.500 mmol) in MeCN (2 mL) was slowly added over 2 h with a syringe pump. The resulting mixture was then stirred at room temperature for 12 h. The solution was filtered and rinsed with Et_2O (5 mL), and then the solvent was removed under reduced pressure. The desired aziridine **3g** was obtained as a yellow oil (129 mg, 81% yield) after flash chromatography (15% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The enantiomeric ratio was determined by HPLC analysis using

Chiracel-OD column (2% *i*-PrOH/hexanes at 1.0 mL/min), retention time: t_R (major)=15.0 min and t_R (minor)=16.7 min (86:14 er). R_f 0.38 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ −71.8 (*c* 1.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J*=8.8 Hz, 2H), 6.65 (d, *J*=8.8 Hz, 2H), 2.84 (dd, *J*=6.3, 3.4 Hz, 1H), 2.07 (d, *J*=6.3 Hz, 1H), 1.54 (d, *J*=3.5 Hz, 1H), 1.49 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 147.6, 144.0, 127.1, 124.6 (q, *J*=283 Hz, 1C), 123.7, 81.1 (q, *J*=29.8 Hz, 1C), 77.2, 38.5, 35.6, 19.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −84.8; IR (neat) 3002, 1733, 1604, 1522, 1346, 1309, 1162, 1133, 855 cm^{-1}; HMRS (ESI) calcd for. $C_{13}H_{14}N_2O_4F_3$ $[M+H]^+$: 319.09002; found: 319.09012.

*4.4.3. (R)-1,1,1-Trichloro-2-methylpropan-2-yl 2-(2-chlorophenyl) aziridine-1-carboxylate (**4f**).* A suspension of $Cu(CH_3CN)_4PF_6$ (9.0 mg, 0.025 mmol), bis(oxazoline) (*S*,*S*)-**2h** (12 mg, 0.030 mmol), and 4 Å molecular sieves (200 mg) in MeCN (3 mL) was stirred at room temperature for 30 min. Potassium carbonate (104 mg, 0.750 mmol), then 2-chlorostyrene (208 mg, 1.50 mmol) were successively added. The heterogeneous solution was stirred for 15 min. A solution of 2,2,2-trichloro-1,1-dimethylethyl *N*-tosyloxycarbamate (**1f**) (195 mg, 0.500 mmol) in MeCN (2 mL) was slowly added over 2 h with a syringe pump. The resulting mixture was then stirred at room temperature for 12 h. The solution was filtered and rinsed with Et_2O (5 mL), and then the solvent was removed under reduced pressure. The desired aziridine **4f** was obtained as a colorless oil (137 mg, 77% yield) after flash chromatography (15% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The enantiomeric ratio was determined by HPLC analysis using Chiracel-AD column (1% *i*-PrOH/hexanes at 1.0 mL/min), retention time: t_R (major)=5.0 min and t_R (minor)=6.9 min (78:22 er). R_f 0.66 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ −96.7 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 1H), 7.40–7.35 (m, 1H), 7.30–7.23 (m, 2H), 3.82 (dd, *J*=6.4, 3.6 Hz, 1H), 2.83 (d, *J*=6.7 Hz, 1H), 2.24 (d, *J*=3.6 Hz, 1H), 1.97 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 134.6, 133.6, 129.0, 128.9, 127.6, 126.9, 105.9, 89.3, 37.7, 34.7, 21.3, 21.2; IR (neat) 3005, 2953, 2306, 1730, 1462, 1386, 1303, 1153, 194, 152 cm^{-1}; HMRS (ESI) calcd for. $C_{13}H_{14}NO_2Cl_4$ $[M+H]^+$: 355.97732; found: 355.97626.

4.5. Diastereoselective aziridination with *N*-tosyloxycarbamate 1i

*4.5.1. (2S)-(R)-2,2,2-Trichloro-1-phenylethyl 2-(4-nitrophenyl)aziridine-1-carboxylate (**3i**).* A suspension of $Cu(CH_3CN)_4PF_6$ (9.0 mg, 0.025 mmol), bis(oxazoline) (*S*,*S*)-**2h** (12 mg, 0.030 mmol), and 4 Å molecular sieves (200 mg) in MeCN (3 mL) was stirred at room temperature for 30 min. Potassium carbonate (104 mg, 0.750 mmol), then 4-nitrostyrene (223 mg, 1.50 mmol) were successively added. The heterogeneous solution was stirred for 15 min. A solution of (1*R*)-2,2,2-trichloro-1-phenylethyl *N*-tosyloxycarbamate (**1i**) (195 mg, 0.500 mmol) in MeCN (2 mL) was slowly added over 2 h with a syringe pump. The resulting mixture was then stirred at room temperature for 12 h. The solution was filtered and rinsed with Et_2O (5 mL), and then the solvent was removed under reduced pressure. The desired aziridine **3i** was obtained as a white solid (174 mg, 85% yield) after flash chromatography (15% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The diastereomeric ratio was determined by SFC analysis using Chiracel-AD-H Chiralpak column (25 cm, 35 °C, 7% MeOH at 150 bar), retention time: t_R (minor)=13.4 min and t_R (major)=17.0 min (97:3 dr). R_f 0.36 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ −116.0 (*c* 0.50, C_6H_6); mp 128–130 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.7 Hz, 2H), 7.40 (dd, *J*=7.2, 2.1 Hz, 2H), 7.08–7.01 (m, 3H), 6.67 (d, *J*=8.7 Hz, 2H), 6.50 (s, 1H), 2.99 (dd, *J*=6.4, 3.6 Hz, 1H), 2.17 (d, *J*=6.3 Hz, 1H), 1.64 (d, *J*=3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 147.7, 143.6, 132.3, 129.9, 129.5, 128.0, 127.1, 123.9, 99.0, 84.4, 38.7, 35.7; IR (neat) 2955, 2924, 2856, 1741, 1603, 1515, 1346, 1323, 1305, 1288, 1222, 1181, 1136, 1019, 948, 787, 748, 698 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{14}N_2O_4Cl_3$ $[M+H]^+$: 415.00137; found: 415.00161.

*4.5.2. (2S)-(R)-1,1,1-Trichloropropan-2-yl 2-(2-chlorophenyl)aziridine-1-carboxylate (**4i**).* The title compound was prepared from 2-chlorostyrene (208 mg, 1.50 mmol) according to the typical procedure described to synthesize aziridine **3i**. The desired aziridine **4i** was obtained as a colorless oil (155 mg, 76% yield) after flash chromatography (10% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The diastereomeric ratio was determined by ^1H NMR on the crude mixture (92:8 dr). R_f 0.74 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ −87.3 (*c* 0.50, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 7.63 (dd, *J*=7.6, 1.7 Hz, 2H), 7.46–7.37 (m, 5H), 7.29–7.26 (m, 2H), 6.34 (s, 1H), 3.93 (dd, *J*=6.4, 3.7 Hz, 1H), 2.86 (d, *J*=6.5 Hz, 1H), 2.32 (d, *J*=3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 134.4, 133.8, 132.6, 129.9, 129.6, 129.2, 129.1, 128.0, 127.4, 127.1, 99.2, 84.3, 37.8, 35.0; IR (neat) 2953, 1735, 1321, 1172, 1139, 1017, 754 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{14}NO_2Cl_4$ $[M+H]^+$: 403.97732; found: 403.97806.

*4.5.3. (2S)-(R)-2,2,2-Trichloro-1-phenylethyl 2-(3-nitrophenyl)aziridine-1-carboxylate (**5i**).* The title compound was prepared from 3-nitrostyrene (90 mg, 0.60 mmol) according to the typical procedure described to synthesize aziridine **3i**. The desired aziridine **5i** was obtained as a yellow oil (70 mg, 84% yield) after flash chromatography (15% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The diastereomeric ratio was determined by ^1H NMR on the crude mixture (89:11 dr). R_f 0.67 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ −101.2 (*c* 0.51, C_6H_6); ^1H NMR (400 MHz, C_6D_6) δ 7.82 (t, *J*=1.8 Hz, 1H), 7.70–7.66 (m, 1H), 7.52–7.47 (m, 2H), 7.08–7.04 (m, 3H), 6.96 (d, *J*=7.7 Hz, 1H), 6.62 (t, *J*=7.9 Hz, 1H), 6.52 (s, 1H), 2.94 (dd, *J*=6.4, 3.5 Hz, 1H), 2.30 (d, *J*=6.4 Hz, 1H), 1.64 (d, *J*=3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 148.4, 138.7, 132.3, 130.0, 129.6, 129.5, 128.0, 123.1, 123.0, 121.3, 99.0, 84.4, 38.5, 35.7; IR (neat) 3001, 2970, 1740, 1605, 1515, 1351, 1274, 1228, 1181, 1138, 948, 787, 751, 699 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{14}N_2O_4Cl_3$ $[M+H]^+$: 415.00137; found: 415.00159.

*4.5.4. (2S)-(R)-2,2,2-Trichloro-1-phenylethyl 2-(2-nitrophenyl)aziridine-1-carboxylate (**6i**).* The title compound was prepared from 2-nitrostyrene (90 mg, 0.60 mmol) according to the typical procedure described to synthesize aziridine **3i**. The desired aziridine **6i** was obtained as a colorless oil (42 mg, 50% yield) after flash chromatography (15% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The diastereomeric ratio was determined by ^1H NMR on the crude mixture (93:7 dr). R_f 0.70 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ −121.0 (*c* 0.5, C_6H_6); ^1H NMR (400 MHz, C_6D_6) δ 7.62 (dd, *J*=8.2, 1.3 Hz, 1H), 7.53–7.44 (m, 3H), 7.08–7.03 (m, 3H), 6.85 (dt, *J*=7.6, 1.3 Hz, 1H), 6.62 (dt, *J*=7.7, 1.4 Hz, 1H), 6.52 (s, 1H), 3.97 (dd, *J*=6.7, 3.7 Hz, 1H), 2.50 (d, *J*=6.8 Hz, 1H), 1.65 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 147.7, 133.9, 132.4, 132.1, 129.6, 129.2, 129.0, 128.6, 127.7, 124.5, 99.1, 84.1, 38.2, 34.7; IR (neat) 3040, 1738, 1525, 1394, 1345, 1173, 805, 743, 701 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{14}N_2O_4Cl_3$ $[M+H]^+$: 415.00137; found: 415.00168.

*4.5.5. (2S)-(R)-2,2,2-Trichloro-1-phenylethyl 2-(4-chlorophenyl)aziridine-1-carboxylate (**7i**).* The title compound was prepared from 4-chlorostyrene (208 mg, 1.50 mmol) according to the typical procedure described to synthesize aziridine **3i**. The desired aziridine **7i** was obtained as a white solid (142 mg, 70% yield) after flash chromatography (15% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The diastereomeric ratio was determined by ^1H NMR on the crude mixture (81:19 dr). R_f 0.71 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ −85.2 (*c* 0.55, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6)

δ 7.52–7.46 (m, 2H), 7.08–7.03 (m, 2H), 7.03–6.99 (m, 2H), 6.79 (d, *J*=8.6 Hz, 2H), 6.53 (s, 1H), 3.04 (dd, *J*=6.3, 3.6 Hz, 1H), 2.32 (d, *J*=6.4 Hz, 1H), 1.75 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 134.9, 133.9, 132.5, 129.8, 129.5, 128.7, 128.0, 127.6, 99.1, 84.3, 39.1, 35.3; IR (neat) 3036, 1736, 1321, 1168, 825, 735 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{14}NO_2Cl_4$ $[M+H]^+$: 403.97732; found: 403.97749.

*4.5.6. (2S)-(R)-2,2,2-Trichloro-1-phenylethyl 2-(3-chlorophenyl)aziridine-1-carboxylate (**8i**).* The title compound was prepared from 3-chlorostyrene (83 mg, 1.50 mmol) according to the typical procedure described to synthesize aziridine **3i**. The desired aziridine **8i** was obtained as a white solid (38 mg, 47% yield) after flash chromatography (15% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The diastereomeric ratio was determined by ^{1}H NMR on the crude mixture (84:16 dr). R_f 0.78 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ −97.1 (*c* 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.48 (m, 2H), 7.13 (t, *J*=1.7 Hz, 1H), 7.08–7.01 (m, 3H), 6.99 (d, *J*=7.9 Hz, 1H), 6.84 (d, *J*=7.7 Hz, 1H), 6.73 (t, *J*=7.83 Hz, 1H), 6.52 (s, 1H), 3.02 (dd, *J*=6.3, 3.6 Hz, 1H), 2.29 (d, *J*=6.4 Hz, 1H), 1.71 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 160.8, 138.7, 134.8, 132.7, 130.1, 130.0, 129.8, 128.4, 128.2, 126.6, 124.7, 99.3, 84.6, 39.2, 35.6; IR (neat) 2955, 1735, 1290, 1166, 787 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{14}NO_2Cl_4$ $[M+H]^+$: 403.97732; found: 403.97743.

*4.5.7. (2S)-(R)-2,2,2-Trichloro-1-phenylethyl 2-(4-bromophenyl) aziridine-1-carboxylate (**9i**).* The title compound was prepared from 4-bromostyrene (208 mg, 1.50 mmol) according to the typical procedure described to synthesize aziridine **3i**. The desired aziridine **9i** was obtained as a pale yellow oil (180 mg, 80% yield) after flash chromatography (5% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The diastereomeric ratio was determined by ^{1}H NMR on the crude mixture (81:19 dr). R_f 0.70 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ −95.7 (*c* 0.56, C_6H_6); ^{1}H NMR (400 MHz, C_6D_6) δ 7.48–7.42 (m, 2H), 7.15–7.09 (m, 2H), 7.04–6.99 (m, 3H), 6.68 (d, *J*=8.3 Hz, 2H), 6.48 (s, 1H), 2.98 (dd, *J*=6.4, 3.6 Hz, 1H), 2.27 (dd, *J*=6.4, 0.6 Hz, 1H), 1.70 (dd, *J*=3.6, 0.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 135.2, 132.2, 131.4, 129.6, 129.3, 127.7, 127.6, 121.7, 98.8, 84.0, 38.8, 35.0; IR (neat) 2955, 1734, 1491, 1320, 1288, 1167, 1071, 822, 747, 699 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{14}NO_2BrCl_3$ $[M+H]^+$: 447.92680; found: 447.92695.

*4.5.8. (2S)-(R)-2,2,2-Trichloro-1-phenylethyl 2-(3-bromophenyl) aziridine-1-carboxylate (**10i**).* The title compound was prepared from 3-bromostyrene (275 mg, 1.50 mmol) according to the typical procedure described to synthesize aziridine **3i**. The desired aziridine **10i** was obtained as a colorless oil (160 mg, 71% yield) after flash chromatography (10% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The diastereomeric ratio was determined by ^{1}H NMR on the crude mixture (81:19 dr). R_f 0.57 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ −82.3 (*c* 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.48 (dd, *J*=6.7, 2.7 Hz, 2H), 7.30 (t, *J*=1.8 Hz, 1H), 7.08–7.02 (m, 3H), 6.90–6.84 (m, 1H), 6.65 (t, *J*=7.8 Hz, 1H), 6.52 (s, 1H), 3.00 (dd, *J*=6.3, 3.6 Hz, 1H), 2.28 (d, *J*=6.4 Hz, 1H), 1.69 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 138.7, 132.5, 131.1, 130.1, 129.9, 129.5, 129.2, 128.0, 125.0, 122.6, 99.1, 84.3, 38.9, 35.4; IR (neat) 3066, 2957, 1735, 1395, 1292, 1167, 786, 698 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{14}NO_2Cl_3Br$ $[M+H]^+$: 447.92680; found: 447.92721.

*4.5.9. (2S)-(R)-2,2,2-Trichloro-1-phenylethyl 2-(2-bromophenyl) aziridine-1-carboxylate (**11i**).* The title compound was prepared from 2-bromostyrene (275 mg, 1.50 mmol) according to the typical procedure described to synthesize aziridine **3i**. The desired aziridine **11i** was obtained as a colorless oil (165 mg, 73% yield) after flash chromatography (10% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The diastereomeric ratio was determined by ^{1}H NMR on the crude mixture (89:11 dr). R_f 0.81 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ −100.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.67 (d, *J*=6.7 Hz, 2H), 7.57 (d, *J*=7.8 Hz, 1H), 7.48–7.39 (m, 4H), 7.33 (t, *J*=7.4 Hz, 1H), 7.20 (t, *J*=7.2 Hz, 1H), 6.36 (s, 1H), 3.81 (dd, *J*=6.2, 3.7 Hz, 1H), 2.92 (d, *J*=6.5 Hz, 1H), 2.30 (d, *J*=3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 135.9, 132.5, 132.2, 129.8, 129.6, 129.4, 128.0, 127.9, 127.6, 123.1, 99.1, 84.3, 40.1, 35.1; IR (neat) 3065, 2955, 1736, 1395, 1319, 1294, 1268, 1171, 749, 698 cm^{-1}; HMRS (ESI) calcd for $C_{17}H_{14}NO_2Cl_3Br$ $[M+H]^+$: 447.92680; found: 447.92676.

*4.5.10. (2S)-(R)-2,2,2-Trichloro-1-phenylethyl 2-(3-cyanophenyl) aziridine-1-carboxylate (**12i**).* The title compound was prepared from 3-cyanostyrene (78 mg, 0.6 mmol) according to the typical procedure described to synthesize aziridine **3i**. The desired aziridine **12i** was obtained as a pale yellow oil (35 mg, 44% yield) after flash chromatography (10% EtOAc/hexanes) on silica gel (pre-treated with 1% Et_3N/hexanes). The diastereomeric ratio was determined by ^{1}H NMR on the crude mixture (82:18 dr). R_f 0.40 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ −43.5 (*c* 0.5, C_6H_6); ^{1}H NMR (400 MHz, C_6D_6) δ 7.53–7.47 (m, 1H), 7.09–7.05 (m, 1H), 6.97 (s, 1H), 6.88 (dd, *J*=15.54, 7.77 Hz, 1H), 6.57 (t, *J*=7.78, 7.78 Hz, 1H), 6.51 (s, 1H), 2.91 (dd, *J*=6.39, 3.55 Hz, 1H), 2.27 (d, *J*=6.46 Hz, 1H), 1.59 (d, *J*=3.52 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 137.8, 132.0, 131.4, 130.4, 129.7, 129.6, 129.2, 129.1, 127.07, 118.1, 112.5, 98.7 84.1, 38.2, 35.3; IR (neat) 2957, 1736, 1485, 1383, 1320, 1277, 1185, 1139, 794 cm^{-1}; HMRS (ESI) calcd for $C_{18}H_{14}N_2O_2Cl_3$ $[M+H]^+$: 395.01154; found: 395.01192.

4.6. Ring-opening reactions of aziridines

*4.6.1. (R)-2,2,2-Trichloro-1-phenylethyl (R)-2-methoxy-2-(4-nitrophenyl)ethylcarbamate (**14a**).* Methanol (5 mL, 0.1 M) was added to aziridine **3i** (208 mg, 0.500 mmol) and the mixture was stirred. $BF_3{\cdot}OEt_2$ (7 μL, 0.05 mmol) was added and the mixture was stirred at room temperature for 1 h. Upon completion of the reaction, the solvent was evaporated and the crude product was purified by flash chromatography (100% CH_2Cl_2). The desired product **14a** was obtained as a gummy yellow solid (209 mg, 93% yield). The diastereomeric ratio was determined by HPLC analysis Chiralpak-AD column (7% *i*-PrOH/hexanes at 1 mL/min), retention time: t_R (major)=24.1 min and t_R (minor)=16.0 min (dr >95:5). R_f 0.30 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J*=9 Hz, 2H), 7.58 (d, *J*=9 Hz, 2H), 7.46–7.40 (m, 5H), 6.24 (s, 1H), 5.46 (s, 1H), 4.45–4.41 (m, 1H), 3.49–3.52 (m, 1H), 3.27–3.22 (m, 1H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 147.7, 146.1, 133.1, 129.6, 129.4, 127.8, 127.3, 123.7, 99.4, 83.3, 81.3, 57.3, 46.9; IR (neat) 3341, 1736, 1522, 1346, 737 cm^{-1}; HMRS calcd for $C_{18}H_{18}Cl_3N_2O_5$ $[M+H]^+$ 447.0289; found: 447.0276.

*4.6.2. (R)-2,2,2-Trichloro-1-phenylethyl (R)-2-hydroxy-2-(4-nitrophenyl)ethylcarbamate (**14b**).* A mixture of water (2.5 mL) and acetonitrile (2.5 mL) was added to aziridine **3i** (208 mg, 0.500 mmol) and the mixture was stirred. $BF_3{\cdot}OEt_2$ (7 μL, 0.05 mmol) was added and the mixture was stirred at room temperature for 1 h. EtOAc (3 mL) was added and the layers were separated. The aqueous layer was washed with EtOAc (2×3 mL). The combined organic layers were washed with brine (1×3 mL), then dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (100% CH_2Cl_2). The desired product **14b** was obtained as a yellow solid (201 mg, 93% yield) and as one diastereomer by ^{1}H NMR. R_f 0.06 (20% EtOAc/hexanes); mp 57–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J*=9 Hz, 2H), 7.63 (d, *J*=9 Hz, 2H), 7.46–7.37 (m, 5H), 6.25 (s, 1H), 5.52 (s, 1H), 5.01–4.99 (m, 1H), 3.63–3.57 (m, 1H), 3.38–3.31 (m, 1H), 3.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 147.7, 146.1,

132.9, 129.7, 129.4, 127.8, 126.6, 123.6, 83.5, 72.5, 48.2; IR (neat) 3423, 2945, 1723, 1522, 1348, 909 cm^{-1}; HMRS calcd for $C_{17}H_{19}Cl_3N_3O_5$ $[M+NH_4]^+$ 450.0392; found: 450.0385.

*4.6.3. (R)-1-(4-Nitrophenyl)-2-(((R)-2,2,2-trichloro-1-phenylethoxy) carbonylamino)ethyl acetate (**14c**).* Dichloromethane (5 mL) was added to aziridine **3i** (208 mg, 0.500 mmol) and the mixture was stirred. Acetic acid (90 μL, 1.50 mmol), then $BF_3 \cdot OEt_2$ (7 μL, 0.05 mmol) were added and the mixture was stirred at room temperature for 1 h. Water (3 mL) was added and the layers were separated. The aqueous layer was washed with dichloromethane (2×3 mL). The combined organic layers were washed with brine (1×3 mL), then dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (20% EtOAc/hexanes). The desired product **14c** was obtained as a yellow solid (185 mg, 78% yield). The diastereomeric ratio was determined by SFC analysis Chiralpak-AD-H column (25 cm, 40 °C, 10% MeOH at 150 bar), retention time: t_R (major)=11.0 min and t_R (minor)=9.9 min (dr 89:11). R_f 0.31 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J=9 Hz, 2H), 7.56 (d, J=9 Hz, 2H), 7.47–7.39 (m, 5H), 6.21 (s, 1H), 5.93–5.91 (m, 1H), 5.25 (s, 1H), 3.63–3.58 (m, 2H), 3.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 154.0, 147.6, 144.2, 132.9, 129.7, 129.3, 127.8, 127.1, 123.7, 99.3, 83.4, 73.3, 45.5, 20.8; IR (neat) 3377, 2923, 1721, 1519, 1346, 1236 cm^{-1}, HMRS calcd for $C_{19}H_{17}Cl_3N_2NaO_6$ $[M+Na]^+$ 497.0062; found: 497.0044.

*4.6.4. (R)-2,2,2-Trichloro-1-phenylethyl-(R)-2-(4-nitrophenyl)-2-(phenylamino)ethylcarbamate (**14d**).* Acetonitrile (5 mL) was added to aziridine **3i** (208 mg, 0.500 mmol) and the mixture was stirred. Aniline (280 μL, 3.00 mmol), then $BF_3 \cdot OEt_2$ (14 μL, 0.10 mmol) were added and the mixture was stirred at room temperature for 16 h. EtOAc (3 mL) was added and the layers were separated. The aqueous layer was washed with EtOAc (2×3 mL). The combined organic layers were washed with brine (1×3 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (100% CH_2Cl_2). The desired product **14d** was obtained as a yellow solid (220 mg, 87% yield) and as one diastereomer by ^1H NMR. R_f 0.29 (20% EtOAc/hexanes); mp 81–86 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J=9 Hz, 2H), 7.59 (d, J=9 Hz, 2H), 7.54 (d, J=9 Hz, 2H), 7.47–7.38 (m, 3H), 7.09–7.04 (m, 2H), 6.71–6.67 (m, 1H), 6.36 (d, J=8 Hz, 3H), 6.31 (s, 1H), 5.30 (s, 1H), 4.74 (s, 1H), 4.63–4.61 (m, 1H), 3.70–3.64 (m, 1H), 3.57–3.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 148.2, 147.5, 146.0, 132.8, 129.7, 129.4, 129.1, 127.9, 127.4, 124.1, 118.2, 113.3, 99.3, 83.9, 58.9, 47.1; IR (neat) 3383, 3053, 1728, 1521, 1346, 737 cm^{-1}, HMRS calcd for $C_{23}H_{20}Cl_3N_3NaO_4$ $[M+Na]^+$ 530.0405; found: 530.0412.

*4.6.5. (R)-2,2,2-Trichloro-1-phenylethyl (R)-2-hydroxy-2-(3-nitrophenyl)ethylcarbamate (**16**).* A mixture of water (1.5 mL) and acetonitrile (1.5 mL) was added to aziridine **5i** (140 mg, 0.340 mmol) and the mixture was stirred. $BF_3 \cdot OEt_2$ (13 μL of a 10% solution in ether, 0.01 mmol) was added and the mixture was stirred at room temperature for 5 h. EtOAc (3 mL) was added and the layers were separated. The aqueous layer was washed with EtOAc (2×3 mL), brine (1×3 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (100% $CHCl_3$). The desired product **16** was obtained as a yellow solid (128 mg, 87% yield). The diastereomeric ratio was determined by HPLC analysis Chiralpak-AD column (7% *i*-PrOH/hexanes at 1 mL/min), retention time: t_R (major)=23.8 min and t_R (minor)=34.2 min (dr 88:12). R_f 0.02 (20% EtOAc/hexanes); mp 43–49 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25–8.12 (m, 2H), 7.69–7.26 (m, 7H), 6.26 (s, 1H), 5.54 (s, 1H), 5.01–4.99 (m, 1H), 3.6–3.58 (m, 1H), 3.39–3.30 (m, 1H), 3.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 148.1, 143.3, 132.9, 132.0, 129.7, 129.4, 127.8, 122.8, 120.8, 99.4, 83.5, 72.2, 48.2; IR (neat) 3351, 1716, 1528, 1350, 739 cm^{-1}, HMRS calcd for $C_{17}H_{14}Cl_3N_2O_5$ $[M+H]^+$ 430.9985; found: 430.9974.

*4.6.6. (R)-2,2,2-Trichloro-1-phenylethyl (R)-2-(4-chlorophenyl)-2-hydroxyethylcarbamate (**17**).* A mixture of water (1.25 mL) and acetonitrile (1.25 mL) was added to aziridine **7i** (97 mg, 0.24 mmol) and the mixture was stirred. $BF_3 \cdot OEt_2$ (9 μL of a 10% solution in ether, 0.007 mmol) was added and the mixture was stirred at room temperature for 15 min. EtOAc (3 mL) was added and the layers were separated. The aqueous layer was washed with EtOAc (2×3 mL), brine (1×3 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (100% $CHCl_3$). The desired product **17** was obtained as a white solid (86 mg, 84% yield). The diastereomeric ratio was determined by SFC analysis Chiralcel-OJ-H column (25 cm, 40 °C, 20% MeOH at 150 bar), retention time: t_R (major)=4.4 min and t_R (minor)=6.3 min (dr 72:28). R_f 0.35 (20% EtOAc/hexanes); mp 54–60 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J=9 Hz, 2H), 7.44–7.25 (m, 7H), 6.29 (s, 1H), 5.49 (s, 1H), 4.88–4.85 (m, 1H), 3.49–3.61 (m, 1H), 3.24–3.36 (m, 1H), 2.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 139.5, 133.7, 133.0, 129.6, 129.4, 128.6, 127.8, 127.1, 99.5, 83.3, 72.6, 48.3; IR (neat) 3438, 1733, 1515, 1265, 739 cm^{-1}, HMRS calcd for $C_{17}H_{15}Cl_4NNaO_3$ $[M+Na]^+$ 443.9708; found: 443.9698.

*4.6.7. (R)-2,2,2-Trichloro-1-phenylethyl (R)-2-(2-bromophenyl)-2-hydroxyethylcarbamate (**18**).* A mixture of water (1.5 mL) and acetonitrile (1.5 mL) was added to aziridine **11i** (145 mg, 0.32 mmol) and the mixture was stirred. $BF_3 \cdot OEt_2$ (12 μL of a 10% solution in ether, 0.01 mmol) was added and the mixture was stirred at room temperature for 1 h. EtOAc (3 mL) was added and the layers were separated. The aqueous layer was washed with EtOAc (2×3 mL), brine (1×3 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (100% $CHCl_3$). The desired product **18** was obtained as a white solid (132 mg, 88% yield). The diastereomeric ratio was determined by SFC analysis Chiralcel-OJ-H column (25 cm, 40 °C, 20% MeOH at 150 bar), retention time: t_R (major)=6.0 min and t_R (minor)=7.6 min (dr 87:13). R_f 0.33 (20% EtOAc/hexanes); mp 56–59 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61–7.50 (m, 4H), 7.45–7.33 (m, 4H), 7.19–7.11 (m, 1H), 6.28 (s, 1H), 5.45 (s, 1H), 5.22–5.19 (m, 1H), 3.72–3.64 (m, 1H), 3.43–3.34 (m, 1H), 3.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 139.8, 133.0, 132.6, 129.6, 129.3, 127.8, 127.7, 127.5, 121.6, 99.5, 83.3, 72.5, 46.6; IR (neat) 3423, 1715, 1515, 1243, 747 cm^{-1}, HMRS calcd for $C_{17}H_{16}BrCl_3NO_3$ $[M+H]^+$ 465.9377; found: 465.9374.

4.7. Total synthesis of (*R*)-(−)-nifenalol

*4.7.1. (R)-2-Amino-1-(4-nitrophenyl)ethanol (**15**).* To a solution of **14b** (335 mg, 0.770 mmol) in a mixture of acetonitrile (7.5 mL) and methanol (3 mL) were added $LiOH \cdot H_2O$ (162 mg, 3.86 mmol) and water (139 μL, 7.72 mmol). After 2 h of stirring at 23 °C, water (10 mL) and EtOAc (20 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude compound as a yellow oil. Purification by flash chromatography (from 50% EtOAc/Hexanes to 100% EtOAc) yields the corresponding oxazolidinone as a pale-yellow solid (118 mg, 74% yield). To a solution of this oxazolidinone (78 mg, 0.37 mmol) in acetonitrile (2 mL) was added a 1 M solution of NaOH (1.87 mL, 1.87 mmol) and the solution was stirred at 23 °C for 20 h. Then, another portion of a 1 M solution of NaOH (1.87 mL, 1.87 mmol,

5.0 equiv) was added and the solution was stirred at 50 °C for 16 h. After evaporation under reduced pressure, purification by flash chromatography (20% MeOH/EtOAc) yields the aminoalcohol **15** as a pale-yellow solid (48 mg, 71% yield). R_f 0.08 (20% MeOH/EtOAc), ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (d, J=8.5, Hz, 2H), 7.69 (d, J=8.5 Hz, 2H), 5.02 (dd, J=9.4, 3.2 Hz, 1H), 3.21 (dd, J=9.4, 3.2 Hz, 1H), 2.99 (dd, J=9.4, 9.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 150.3, 149.2, 128.2, 124.7, 70.9, 47.3; HMRS (ESI$^+$) calcd for $C_8H_{11}N_2O_3$ $[M+H]^+$: 183.07642; found: 183.07674.

4.7.2. (R)-(−)-Nifenalol. To a solution of the aminoalcohol **15** (40 mg, 0.22 mmol) in acetone (2 mL) was added $NaBH_3CN$ (28 mg, 0.44 mmol) at 0 °C and the mixture was stirred at 23 °C for 1 h. Water (5 mL) and DCM (10 mL) were added and the two layers were separated. The aqueous layer was extracted with DCM (3×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude compound as a pale-yellow solid. Purification by flash chromatography (15% MeOH/CH_2Cl_2) yielded the title compound as a pale-yellow solid (30 mg, 61% yield). R_f 0.16 (15% MeOH/CH_2Cl_2); mp 111–113 °C (lit.[53e] 113.2 °C); $[\alpha]_D^{25}$ −37.7 (c 0.7, $CHCl_3$); $[\alpha]_D^{25}$ −12.1 (c 0.7, EtOH) {lit.[53e] $[\alpha]_D^{25}$ −11.3 (c 1.0, EtOH)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J=8.3 Hz, 2H), 7.55 (d, J=8.3 Hz, 2H), 4.80 (dd, J=9.0, 3.6 Hz, 1H), 3.27 (s large, 1H), 3.02 (dd, J=12.2, 3.6 Hz, 1H), 2.93–2.87 (m, 1H), 2.63 (dd, J=12.2, 9.0 Hz, 1H), 1.13 (d, J=3.7 Hz, 3H), 1.10 (d, J=3.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ 150.1, 147.5, 126.7, 123.8, 70.8, 54.0, 49.2, 22.9, 22.6; HMRS (ESI$^+$) calcd for $C_{11}H_{17}N_2O_3$ $[M+H]^+$: 225.12337; found: 225.12369.

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