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Atropo- and Diastereoselective Construction of Tetracyclic Biphenylazepinium Salts Derived from Aminoalcohols: Use as Catalysts in Enantioselective Asymmetric Epoxidation

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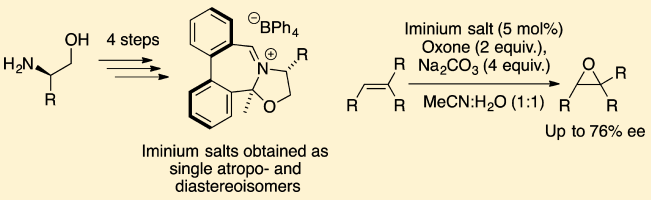
Supporting Information

ABSTRACT: A range of new biphenylazepinium salt organocatalysts effective for asymmetric epoxidation has been developed incorporating an additional substituted oxazolidine ring, and providing improved enantiocontrol in alkene epoxidation over the parent structure. Starting from enantiomerically pure aminoalcohols, tetracyclic iminium salts were obtained as single diastereoisomers through an atroposelective oxazolidine formation.



INTRODUCTION

Epoxides are versatile building blocks widely used in synthesis.[1] The past 30 years have seen the development of many methodologies capable of efficient asymmetric epoxidation of various types of alkene.[2] Dioxiranes[3] and oxaziridinium salts, first reported by Lusinchi,[4] and generated *in situ* from the corresponding iminium salts[5] or amines,[6] have proven to be two of the most effective types of organocatalyst for asymmetric oxygen transfer to weakly nucleophilic substrates such as unfunctionalized alkenes. Over the past 10 years we have developed a range of enantiopure iminium salts effective as organocatalysts for highly enantioselective asymmetric epoxidation in the presence of Oxone as a stoichiometric oxidant. We have reported that the most reactive and selective iminium salt catalysts discovered to date are based on (*S*,*S*)-acetonamine derivative **1** and a biphenyl backbone such as **2**, **3**, and **4**, or a binaphthyl backbone such as **5** (Figure 1). For example, iminium species **2a** catalyzes the oxidation of 1-phenylcyclohexene to its corresponding epoxide in less than 4 min inducing up to 60% enantioselectivity,[7] while catalyst **5a** affords the same epoxide in 91% ee after 15 min.[8] The use of alternative oxidants, such as bleach or hydrogen peroxide, has also been explored,[9] and the successful development of nonaqueous conditions using tetraphenylphosphonium monoperoxysulfate[10] (TPPP) has allowed us to access highly enantioenriched epoxides (up to 99% ee).[11]

A potential issue concerning cyclic biaryl structures is their ability to rotate through the aryl/aryl bond generating two interconverting atropoisomers.[12] Using biaryl azepine **6** as a model substrate, Wallace showed that asymmetric introduction of an alkyl group at C(7) could induce a strong conformational preference for one atropoisomer.[13] Lacour has used derivatization at the 3,3′-positions on the aromatic rings to prevent such interconversion, as in **3a**/**3b**.[14] We have shown that the introduction of an axial substituent at the C(7) position by nucleophilic addition to **2a** to create a new chiral center adjacent to the iminium nitrogen, followed by reoxidation, generates "second generation" iminium salt catalysts such as **2b**, **3b**, **4b**, and **5b**, which provide increased enantiocontrol in the epoxidation of alkene substrates.[15]

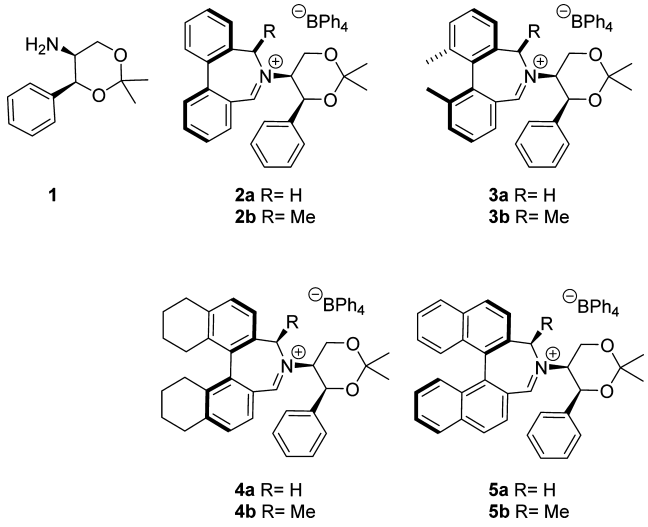


Figure 1. Iminium salt catalysts for asymmetric epoxidation.

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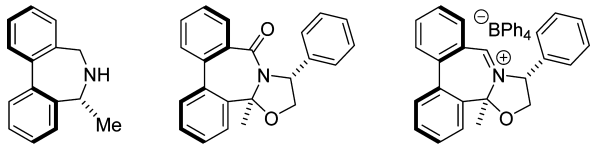


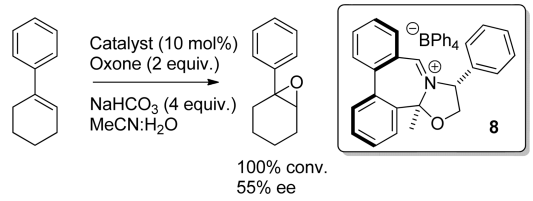
6 7 8

Meyers' bicyclic lactam methodology has been widely used in the stereoselective construction of five-, six-, and seven-membered ring nitrogen heterocycles from enantiopure amino alcohols.[16] Particularly of interest to us, the methodology has been applied to prepare a range of axially chiral biaryl lactams such as **7**.[17] We postulated that structurally related iminium salts such as **8** might impart increased levels of enantioselectivity when used as an asymmetric epoxidation catalyst by imparting additional rigidity and structural elements in the transition state compared to catalysts such as **4**.

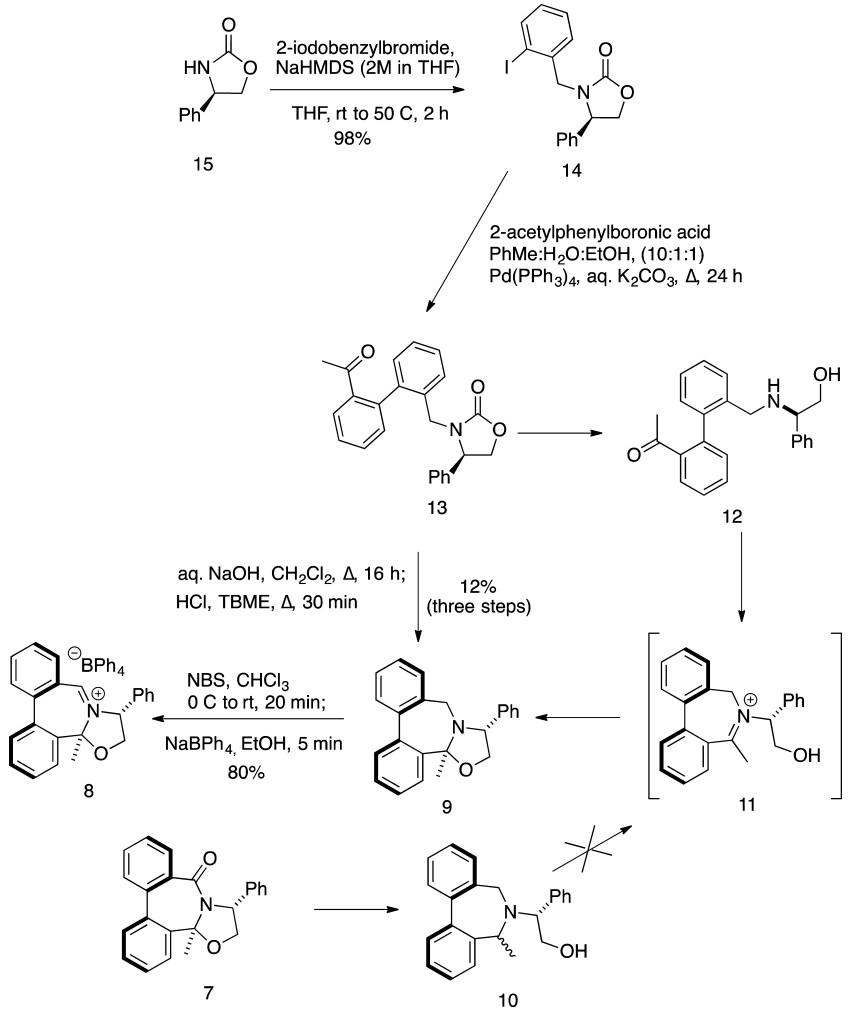
RESULTS AND DISCUSSION

Our initial hypothesis was that the 7,5-fused bicyclic lactam substructure **7** could be used to generate amine **9**, a suitable precursor to iminium species **8**, by reduction of the lactam unit (Scheme 1). However, reduction of compound **7** is known to lead to aminoalcohol **10** using literature procedures.[18] We have previously shown that oxidation of such azepines occurs preferentially at the least substituted adjacent position, ruling out the possibility to use this pathway, because **10** would not be oxidized to **11**.[15] We therefore devised an alternative pathway based upon a biaryl coupling of a suitably functionalized oxazolidinone using an adaptation of Fagnou's methodology[19] by Wallace (Scheme 1).[20] Synthesis of the cyclization precursor **12** would be achieved by Suzuki–Miyaura coupling of a suitably functionalized aminoalcohol **14** with 2-acetylphenylboronic acid to give **13** and subsequent hydrolysis of the oxazolidinone protecting group. Cyclocondensation of **12** to form the iminium species **11** would result in concomitant cyclization to the oxazolidine **9** by intramolecular attack of the hydroxyl group. We have previously observed diastereoselective formation of oxazolidines in a related binaphthyl system when generating iminium species bearing an alcohol moiety.[21]

Scheme 2



Scheme 1



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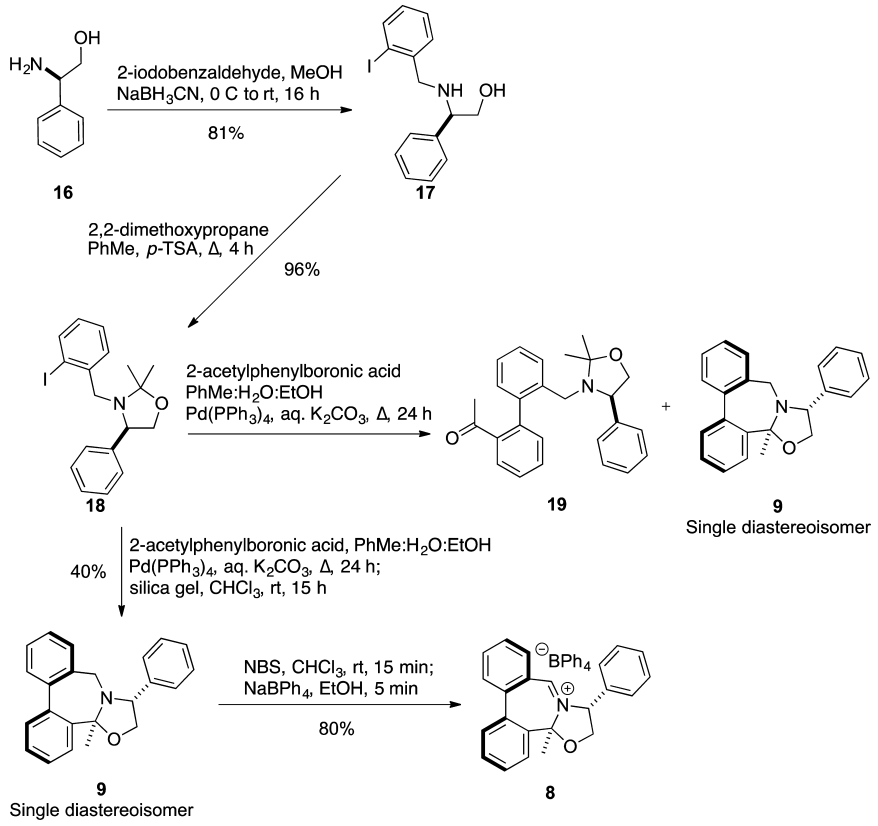
Scheme 3



Scheme 4

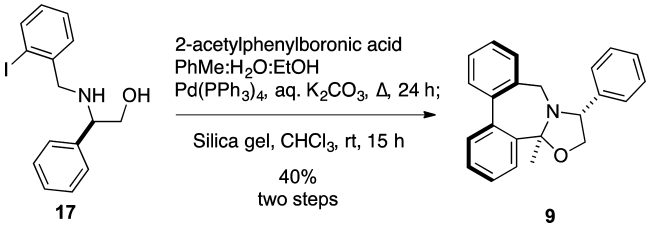


Table 1. Isolated Yields of the Key Intermediates in Generating Six Tetracyclic Iminium Salt Catalysts

R = (*S*)-Me	83% (**20**)	22% (**24**)	74% (**28**)
R = (*S*)-^{i}Pr	16% (**21**)	47% (**25**)	81% (**29**)
R = (*R*)-Ph	81% (**17**)	40% (**9**)	80% (**8**)
R = (*R*)-Bn	90% (**22**)	60% (**26**)	82% (**30**)
R = (*S*)-Bn	86% (**23**)	30% (**27**)	75% (**31**)

Finally, oxidation of **9** under our standard conditions would give iminium salt catalyst **8**.

This methodology would allow the use of a wide variety of enantiomerically pure aminoalcohol precursors. Accordingly, alkylation of (*R*)-phenyl oxazolidinone **15** with 2-iodobenzyl bromide afforded *N*-substituted oxazolidinone **14** in 98% yield.

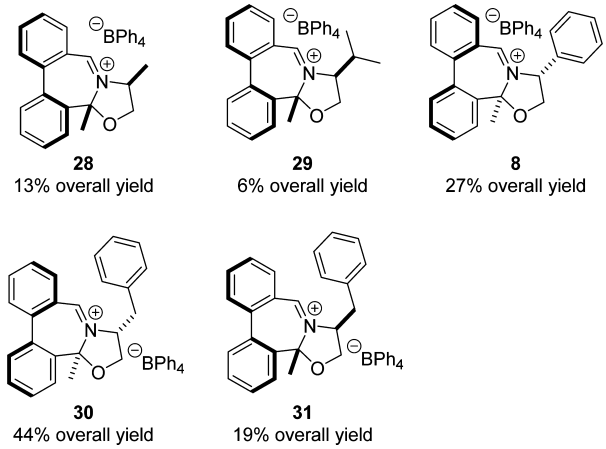


Figure 2. New iminium salts.

N-Benzyl oxazolidinone **14** was coupled with 2-acetylphenyl boronic acid under conditions used by Levacher.[17a] Hydrolysis of the crude oxazolidinone **13** was completed with aqueous sodium hydroxide in dichloromethane; the solvent was removed and *tert*-butylmethyl ether (TBME) added. The resulting solution of aminoalcohol **12** was treated with aqueous HCl to generate the desired tetracyclic amine **9** via **11** as a single diastereoisomer in 12% yield over the three steps. Finally, the iminium salt **8** was generated by oxidation of the amine using NBS in chloroform in 80% yield.

We tested iminium salt **8** for its efficacy as an epoxidation catalyst, using 1-phenylcyclohexene as our test substrate under our standard Oxone oxidative conditions. Catalyst **8** gave 100%

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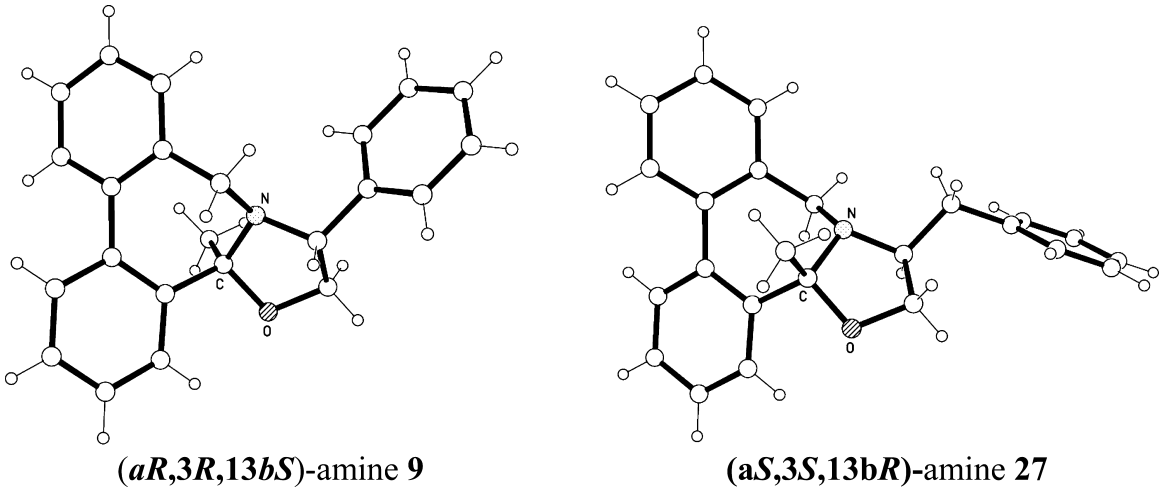
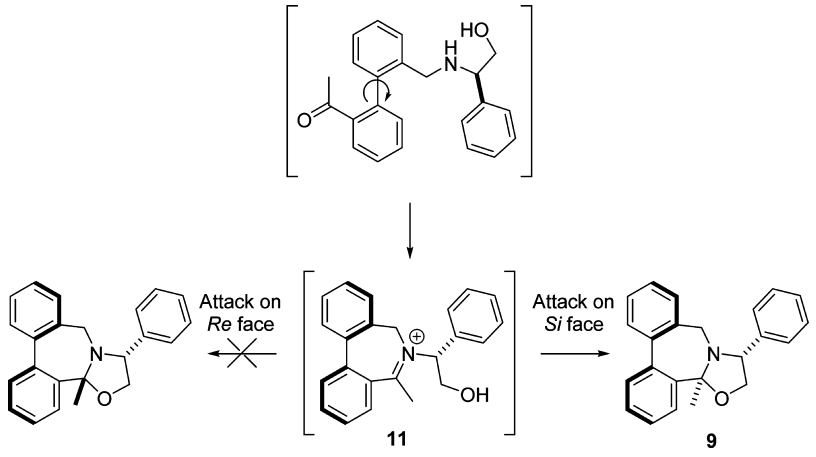


Figure 3. Single crystal X-ray structural determination of **9** and **27**.

Scheme 5



conversion within 30 min, imparting a fair 55% ee for 1-phenylcyclohexene oxide (Scheme 2).

While this result established a new substructure of iminium salts active for the catalytic asymmetric epoxidation of alkenes, the overall yield of this synthetic route, particularly in the conversion of **14** into **9**, coupled with the problematic purification of the unstable oxazolidinone **13** led us to seek an alternative.

We reasoned that a change of aminoalcohol protecting group from oxazolidinone to a much more readily hydrolyzed oxaminal might improve the process and so targeted dimethyloxazolidine **18** (Scheme 3). Reductive amination of 2-iodobenzaldehyde with (*R*)-phenyl glycinol **16** gave the *N*-benzyl amino alcohol **17** in 81% yield. Protection of the aminoalcohol functionality with dimethoxypropane gave the oxazolidine **18** in 96% yield.

Oxazolidine **18** was coupled with 2-acetylphenylboronic acid under the conditions described above. Attempted purification using column chromatography on silica gel of the crude coupled product led to the isolation of a mixture of two inseparable compounds. Upon inspection of the ^{1}H NMR spectrum of the mixture, the two products were identified as the desired Suzuki adduct **19** and the target tetracyclic 6,6,7,5 material **9** as a single diastereoisomer.

Following our conjecture that silica gel had effected a deprotection to expose the aminoalcohol, which then condensed *in situ* with the pendent ketone generating the desired tetracycle, we subjected the crude reaction mixture from the Suzuki coupling to silica gel in chloroform over 15 h (Scheme 3), so generating tetracycle **9** as a single diastereoisomer in a somewhat improved 40% yield. The absolute configuration of **9** was confirmed by single crystal X-ray analysis. The tetracylic tertiary amine **9** was readily converted into iminium salt **8** in 80% yield. To test the need for the protection/deprotection steps, a Suzuki coupling between unprotected aminoalcohol **17** and 2-acetylphenylboronic acid was attempted.

Anticipating the deactivation of the palladium−phosphine catalyst by the aminoalcohol, we expected to observe poor conversion. To our delight, however, we observed the Suzuki coupling followed by *in situ* intramolecular cyclization, generating the 6,6,7,5-tetracyclic core **9** as a single diastereoisomer in 40% yield (Scheme 4).

The phenyl substituted azepinium bromide salt **8** was thus obtained in just four steps in 26% overall yield from (*R*)-phenyl glycinol **16**. A number of aminoalcohols—(*S*)-alaninol, (*S*)-valinol, and (*R*)- and (*S*)-phenylalaninol—were subjected to the same reaction sequence to prepare a selection of potential catalysts with different substituents at the oxazolidine ring, to give the cyclized products **8** and **28**−**31**, each again generated as single diastereoisomers (Table 1; Figure 2).

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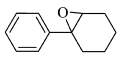
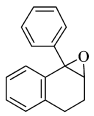
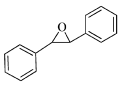
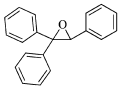
Table 2. Asymmetric Epoxidation of a Range of Alkenes by Catalysts 8 and 28−31[a]

Epoxide	Catalyst	Conversion/%[c-e]	ee/%[b, c]	Major enantiomer[f]
	**2a**	100	60	(−)-1*S*,2*S*
	8	100	55	(+)1*R*,2*R*
	28	100	30	(−)-1*S*,2*S*
	29	100	30	(−)-1*S*,2*S*
	30	100	64	(+)1*R*,2*R*
	31	100	64	(−)-1*S*,2*S*
	**2a**	100	32	(+)1*S*,2*R*
	8	100	76	(−)1*R*,2*S*
	30	100	46	(−)1*R*,2*S*
	31	100	47	(+)1*S*,2*R*
	**2a**	34	41	(−)1*R*,2*S*
	8	20	64	(+)1*S*,2*R*
	30	47	52	(+)1*S*,2*R*
	31	39	55	(−)1*R*,2*S*
	**2a**	90	15	(−)1*S*,2*S*
	8	100	22	(+)1*R*,2*R*
	30	98	18	(+)1*R*,2*R*
	31	95	13	(−)1*S*,2*S*
	**2a**	90	24	(−)1*S*
	8	100	30	(+1*R*
	30	100	23	(+)1*R*
	31	100	19	(−)1*S*

[a]Epoxidation conditions: Iminium salt catalyst (5 mol %), Oxone (2 equiv), Na_2CO_3 (4 equiv), MeCN/H_2O 1:1 (5 mL), 0 °C, 1−6 h. [b]Enantiomeric excesses were determined by chiral GC chromatography on a Chiraldex B-DM column by comparison of the two epoxide peak areas. [c]Conversions were evaluated from the chiral GC−FID spectra by comparison of the alkene and epoxide peak areas. [d]Enantiomeric excess determined by Chiral HPLC on a Chiracel OD-H column. [e]Conversions were evaluated from the ^{1}H NMR spectra by integration of alkene and epoxide signals. [f]Absolute configurations of the major enantiomers were determined by comparison of both optical rotation and GC-FID of samples of known configuration.

Single crystal X-ray structure determination carried out on the (*R*)-phenyl **9** and (*S*)-benzyl **27** derivatives (Figure 3) shows the *cis*-relationship between the methyl groups and the oxazolidine ring phenyl and benzyl substituents derived from the parent aminoalcohols, the pseudoequatorial placement of these phenyl and benzyl substituents, the axial orientation of the methyl groups, and the chirality of the atropoisomeric biaryl units.

The stereoselectivity of the cyclization of the aminoalcohol functionality in the intermediate iminium species **11** may be driven by preferred placement of the smaller methyl substituent in the pseudoaxial orientation (Scheme 5), perhaps through an equilibrium process.[17a]

Catalysts **8** and **28−31** were tested for catalytic activity under our standard conditions, using oxone as the oxidant, and compared to the simple biphenyl azepinium catalyst **2a** (Table 2).

Catalysts **8**, **30**, and **31** provide greater enantioselectivity in the oxidation of 1-phenylcyclohexene than catalysts **28** and **29**, and this pattern is repeated for the other alkene substrates tested. Observed enantioselectivities are comparable with or superior to that of the simple azepinium catalyst **3a**. Highest enantioselectivities were observed with the cyclic *cis*-alkene dihydronaphthalene substrates, where catalysts **8**, **30**, and **31** outperformed catalyst **2a** by a considerable margin.

CONCLUSION

To conclude, we have successfully developed a new substructure of an iminium salt catalyst containing a 6,6,7,5-ring tetracyclic core. The synthesis of these novel iminium salts can be completed within four steps in good yields from the corresponding aminoalcohols. We have postulated that the cyclization occurs through one favored atropoisomer, giving rise to a favored diastereoisomer in all the iminium salt catalysts generated, where the methyl group is pseudoaxial. Catalysts **8**, **30**, and **31** generally provide enantioselectivities better than or equal to that of the parent azepinium catalyst **2a**.

EXPERIMENTAL SECTION

General Experimental Details. All infrared spectra were obtained using thin films on sodium chloride plates. All ^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.62 MHz, respectively, or at 500.21 and 125.79 MHz, respectively, in deuteriochloroform solution unless otherwise stated, using TMS (tetramethylsilane) as the internal reference. Mass spectra were recorded utilizing electron-impact (EI), fast atom bombardment (FAB) or electrospray (ESI) techniques and an ion trap mass analyzer. Optical rotation values were measured at λ = 589 nm, corresponding to the sodium D line, at the temperatures indicated. All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored using thin layer chromatography (TLC) on aluminum-backed plates coated with F254 silica gel. TLC plates were visualized by UV irradiation at a wavelength of 254 nm or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid), followed by charring where appropriate. Reactions requiring anhydrous conditions were carried out using glassware dried overnight at 150 °C, under a nitrogen atmosphere unless otherwise stated. Reaction solvents were used as obtained commercially unless otherwise stated. Light petroleum (bp 40−60 °C) was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium chloride. Dichloromethane was distilled over calcium hydride. Tetrahydrofuran and diethyl ether were distilled under a nitrogen atmosphere from the sodium/benzophenone ketyl radical. Acetone was dried over 4 Å Linde molecular sieve and distilled under a nitrogen atmosphere. Enantiomeric excesses were determined by chiral HPLC using Chiracel OD and OD-H columns with an ultraviolet absorption detector set at 254 nm, by chiral GC using a Chiraldex B-DM column and a flame ionization detector, or by proton nuclear magnetic resonance spectroscopy in the presence of europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] as the chiral shift reagent.

General Procedure A: Reductive Amination Using 2-Iodobenzaldehyde and Aminoalcohols. The aminoalcohol and 2-iodobenzaldehyde (1.1 equiv) were dissolved in methanol (10 mL per g of aminoalcohol) and agitated over 5 to 16 h. The mixture was cooled to 0 °C, sodium cyanoborohydride (1.1 equiv) added, and the mixture stirred at ambient temperature for 16 h. Saturated aqueous ammonium chloride (1 mL per g of aminoalcohol) was added, and the solvent removed under reduced pressure. The residue was dissolved in *tert*-butyl methyl ether (10 mL per g of aminoalcohol), and the solution washed with saturated brine and dried over magnesium sulfate. The solvents were removed, and the crude oil purified by column chromatography using CH_2Cl_2/MeOH (100:0−95:5) as eluent to yield the desired secondary amine.

General Procedure B: Suzuki Coupling between 2-Iodobenzyl Aminoalcohols and 2-Acetyl Phenylboronic Acid. The aminoalcohol and 2-acetyl phenylboronic acid (3 equiv) were

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dissolved in toluene (10 mL per g of aminoalcohol) and ethanol (1 mL per g of aminoalcohol), and saturated aqueous potassium carbonate (1 mL per g of aminoalcohol) was added. The mixture was degassed with nitrogen over 30 min. $Pd(PPh_3)_4$ (10 mol %) was added, and the mixture degassed for a further 15 min. The mixture was stirred at reflux under a nitrogen atmosphere with monitoring by HPLC; once complete consumption of the starting material was observed, the mixture was allowed to cool to ambient temperature and filtered through a plug of Celite. The organic layer was separated, washed with water, and dried over magnesium sulfate, and the solvents were removed under reduced pressure. The residue was dissolved in chloroform (10 mL per g of aminoalcohol), and silica gel (0.5 g per g of aminoalcohol) added. The mixture was stirred for 15 h at room temperature to achieve cyclization. The suspension was filtered through a plug of Celite, and the solvent removed under reduced pressure. The residue was purified using flash chromatography on silica gel using ethyl acetate/heptane (1−5%) as eluent.

General Procedure C: Oxidation of Tertiary Cyclic Amines Using *N*-Bromosuccinimide. The amine was dissolved in chloroform (5 mL per g of amine), and the mixture cooled to 0 °C. *N*-Bromosuccinimide (2 equiv) was added. The reaction mixture was removed from the ice bath and stirred for 15−20 min with monitoring by HPLC/TLC. Upon completion, water (10 mL per g of amine) was added, and the organic layer separated and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield the corresponding bromide salt. The residue was dissolved in ethanol (50 mL per g of bromide salt), and a solution of sodium tetraphenylborate (1 equiv) in the minimum amount of acetonitrile to enable dissolution was added. The solvents were removed under reduced pressure, and the residue was recrystallized from ethanol to yield the desired tetracyclic imnium tetraphenylborate salts.

General Procedure for the Formation of Racemic Epoxides for ee Determinations. The alkene was dissolved in dichloromethane (10 mL per g of alkene) and cooled to 0 °C. *m*-CPBA (2 equiv) was added as a solution in dichloromethane (10 mL per g of alkene). The mixture was allowed to attain ambient temperature and stirred until complete consumption of the substrate was observed by TLC. Saturated aqueous $NaHCO_3$ (20 mL per g of alkene) was added, and the layers were separated. The organic layer was washed with NaOH (1.0 M, 20 mL per g of alkene) and dried ($MgSO_4$). The solvents were removed under reduced pressure and the product was purified by column chromatography, eluting with ethyl acetate/light petroleum (1:99).

General Procedure for Catalytic Asymmetric Epoxidation of Simple Alkenes Mediated by Iminium Salts Using Oxone. Oxone (2 equiv) was added to an ice cooled solution of Na_2CO_3, (4 equiv) in water (8 mL per g of Na_2CO_3), and the resulting foaming solution stirred for 5−10 min. The iminium salt (10 mol %) was added as a solution in acetonitrile (4 mL per g of Na_2CO_3 used), followed by the alkene substrate, also as a solution in acetonitrile (4 mL per g of Na_2CO_3 used). The mixture was stirred at 0 °C until the alkene substrate was completely consumed as observed by TLC. The mixture was dissolved in ice-cooled diethyl ether (20 mL per 100 mg substrate), and the same volume of water was added. The aqueous phase was washed four times with diethyl ether, and the combined organic layers were washed with saturated brine and dried over magnesium sulfate. Filtration and evaporation of the solvents gave a yellow/brown residue, which was purified by column chromatography, eluting with ethyl acetate/light petroleum (1:99).

3-(2′-Iodobenzyl)-4*R*-phenyloxazolidin-2-one 14. (*R*)-(−)-4-phenyl-2-oxazolidinone (0.20 g, 1.23 mmol, 1.0 equiv) was dissolved in THF (2 mL) at room temperature under a nitrogen atmosphere. NaHMDS (2 M in THF, 0.68 mL, 1.35 mmol, 1.1 equiv) was added, and the reaction mixture stirred for 30 min. A solution of 2-iodobenzyl bromide (0.40 g, 1.35 mmol, 1.1 equiv) in THF (2 mL) was added, and the reaction was monitored by HPLC. On complete consumption of the starting material, saturated aqueous potassium carbonate (10 mL per g of oxazolidinone) and *tert*-butyl methyl ether (20 mL per g of oxazolidinone) were added. The organic layer was separated, washed with brine (10 mL per g of oxazolidinone), and dried over anhydrous magnesium sulfate and the solvents were removed under reduced pressure to yield the desired alkylated oxazolidinone (0.46 g, 1.21 mmol, 98%); ν_{max}(film) /cm^{-1} 2960, 1749, 1428, 1240, 1081, 1012, 751, 668. $[\alpha]^{20}_D$ −7.8° (*c* 1.0, CH_2Cl_2), ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.00 (1 H, d, *J* 15.6 Hz), 4.17 (1 H, dd. *J* 5.6, 8.4 Hz), 4.56 (1 H, dd, *J* 5.2, 9.2 Hz), 4.63 (1 H, t, *J* 8.3 Hz), 4.80 (1 H, d, *J* 15.4 Hz), 6.97 (1 H, td, *J* 1.5, 7.5 Hz), 7.14−7.20 (3 H, m), 7.29 (1 H, td, *J* 1.2, 7.5 Hz), 7.35−7.40 (3 H, m), 7.79 (1 H, dd, *J* 1.2, 7.9 Hz). ^{13}C NMR (100 MHz; $CHCl_3$) δ_C 50.7, 59.3, 70.1, 99.0, 127.2, 128.6, 129.2, 129.4, 129.7, 130.0, 137.8, 137.9, 140.0, 158.4; *m*/*z* found for $[M + H]^+$ 380.0145; $[C_{16}H_{14}NO_2I + H]^+$ requires 380.0142.

2-(2′-Iodobenzylamino)-2(*R*)-phenylethanol 17. (*R*)-Phenylglycinol (1.32 g, 9.60 mmol, 1.1 equiv) in MeOH (25 mL), 2-iodobenzaldehyde (2.20 g, 9.50 mmol, 1.0 equiv), and $NaBH_3CN$ (0.60 g, 9.60 mmol, 1.1 equiv) were treated using general procedure A to yield the desired product (2.77 g, 7.80 mmol, 81%); $[\alpha]^{20}_D$ −49.7° (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.58 (1 H, dd, *J* 8.6, 10.8 Hz), 3.66 (1 H, d, *J* 13.2 Hz), 3.73 (1 H, dd, *J* 4.4, 10.8 Hz), 3.78 (1 H, d, *J* 13.2 Hz), 3.81 (1 H, dd, *J* 4.4, 8.4 Hz), 6.93−6.98 (1 H, m), 7.26−7.40 (7 H, m), 7.80−7.83 (1 H, m); ^{13}C NMR (100 MHz; $CHCl_3$) δ_C 55.8, 64.0, 67.0, 100.0, 127.5, 127.9, 128.4, 128.8, 129.1, 130.2, 139.8, 140.3, 142.2; *m*/*z* found for $[M + H]^+$: 354.0363; $[C_{15}H_{16}INO + H]^+$ requires 354.0355.

3-(2′-Iodobenzyl)-2,2-dimethyl-(4*R*)-phenyloxazolidine 18. (2*R*)-2-(2′-Iodo-benzylamino)-2-phenyl-ethanol **17** (650 mg, 1.84 mmol, 1 equiv) was dissolved in toluene (10 mL). Dimethoxypropane (2.25 mL, 18.40 mmol, 10 equiv) and *p*-TSA (70.0 mg, 0.37 mmol, 0.2 equiv) were added, and the mixture was heated under reflux using a Dean−Stark apparatus. The reaction was monitored by TLC and the azeotropic removal of solvents. Upon completion, the mixture was allowed to reach ambient temperature. Saturated brine (3 × 20 mL) was added, the organic phase was separated and dried over $MgSO_4$, and the solvents were removed under reduced pressure. Purification using column chromatography on silica gel (washed with 4% TEA) using ethyl acetate/light petroleum (10%) as eluent yielded the desired acetal as a yellow low-melting solid (694 mg, 1.76 mmol, 96%); ν_{max}(film)/cm^{-1} 3420, 2972, 1455, 1362, 1255, 1187, 1054, 1011, 753, 700; $[\alpha]^{20}_D$ −60.2° (*c* 1.19, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.34 (3 H, s), 1.37 (3 H, s), 3.67 (1 H,d, *J* 14.4 Hz), 3.75 (1 H, t, *J* 8.0 Hz), 3.88 (1 H, d, *J* 14.8 Hz), 4.08 (1 H, t, *J* 7.6 Hz), 4.21 (1 H, t, *J* 7.2 Hz), 6.75 (1 H, dt, *J* 1.6, 7.6 Hz), 7.09−7.14 (2 H, m), 7.15−7.20 (2 H, m), 7.32−7.36 (2 H, m), 7.43 (1 H, dd, *J* 1.6, 7.6 Hz), 7.61 (1 H, dd, *J* 1.2, 8.0 Hz); ^{13}C NMR (100 MHz; $CHCl_3$) δ_C 21.6, 28.7, 56.8, 67.8, 72.1, 96.4, 99.6, 127.5, 127.7, 128.1, 128.2, 128.5, 131.3, 139.1, 140.5, 141.2; *m*/*z* found for M^+: 393.0583; $[C_{18}H_{20}INO]^+$ requires 393.0590.

(*aR*,3*R*,13*bS*)-13b-Methyl-3-phenyl-2,3-dihydro-13bH-dibenz[*c*,*e*]oxazolo[3,2-*a*]azepine 9. *First Method: From Oxazolidinone **14**.* (4*R*)-3-(2′-Iodo-benzyl)-4-phenyl-oxazolidin-2-one **14** (0.46 g, 1.21 mmol) was dissolved in toluene (5 mL) and ethanol (7.5 mL). 2-Acetyl phenylboronic acid (0.20 g, 1.21 mmol, 1 equiv) and saturated aqueous potassium carbonate (5 mL) were added. The mixture was degassed with nitrogen over 30 min. $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol, 5 mol %) was added, and the mixture was degassed with nitrogen for a further 15 min. The mixture was stirred under reflux under a nitrogen atmosphere with monitoring by HPLC. Once complete consumption of the starting material was observed, the mixture was allowed to cool to ambient temperature. The mixture was filtered through a plug of Celite, and the solvents were removed under reduced pressure. *tert*-Butyl methyl ether (10 mL) and water (5 mL) were added to the residue. The organic layer was separated, washed with water (5 mL), and dried over $MgSO_4$. The solvents were removed under reduced pressure, and the residue was dissolved in ethanol (5 mL) and aqueous NaOH (2M, 5 mL) added. The mixture was heated under reflux for 16 h to remove the protecting group and then allowed to cool to ambient temperature. The organic solvent was removed under reduced pressure, the residue was dissolved in *tert*-butyl methyl ether (5 mL), and aqueous HCl (5M, 1 mL) was added. The mixture was stirred for 30 min to achieve cyclization, the organic layer was separated and dried over magnesium sulfate, and the solvents

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were removed under reduced pressure. The residue was purified using flash chromatography on silica gel using ethyl acetate/heptane (1−5%) as eluent to give the desired product (0.049 g, 0.15 mmol, 12%).

Second Method: From Oxazolidine ***18.*** (4*R*)-3-(2-Iodo-benzyl)-2,2-dimethyl-4-phenyl-oxazolidine **18** (0.69 g, 1.76 mmol) was dissolved in toluene (10 mL) and ethanol (15 mL). 2-Acetyl phenylboronic acid (0.29 g, 1.76 mmol, 1 equiv) and saturated aqueous potassium carbonate (10 mL) were added. The mixture was degassed with nitrogen over 30 min. $Pd(PPh_3)_4$ (0.10 g, 0.09 mmol, 5 mol %) was added, and the mixture degassed with nitrogen for a further 15 min. The mixture was stirred under reflux under a nitrogen atmosphere for 4 h. The mixture was allowed to cool to ambient temperature and filtered through a plug of Celite, and the solvents were removed under reduced pressure. *tert*-Butyl methyl ether (10 mL) and water (5 mL) were added to the residue. The organic layer was separated, washed with water (5 mL), and dried over $MgSO_4$. The solvents were removed under reduced pressure, the residue was dissolved in chloroform (10 mL), and silica gel was added. The mixture was stirred at room temperature for 30 min, and the suspension was filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue was purified using flash chromatography on silica gel using ethyl acetate/heptane (1−5%) as eluent to give the desired product (0.23 g, 0.70 mmol, 40%).

Third Method: From Amino Alcohol ***17.*** (2*R*)-(2′-Iodobenzyl-amino)-2-phenylethanol **17** (2.29 g, 6.50 mmol) and 2-acetyl phenylboronic acid (3.20 g, 19.5 mmol, 3 equiv) were treated using general procedure B to yield the desired product (0.85 g, 2.60 mmol, 40%); ν_{max}(film)/cm^{-1} 2963, 1449, 1260, 1153, 1038, 897, 802, 758, 740, 701. $[\alpha]^{20}_D$ −15.6° (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.11 (3 H, s), 3.09 (1 H, d, *J* 10.8 Hz), 3.58 (1 H, d, *J* 10.8 Hz), 3.86 (1 H, dd, *J* 7.6, 9.2 Hz), 3.94 (1 H, dd, *J* 6.0, 9.6 Hz), 4.37 (1 H, t, *J* 6.8 Hz), 7.25 (1 H, d, *J* 6.8 Hz), 7.30−7.37 (2 H, m), 7.38−7.45 (3 H, m), 7.46−7.53 (6 H, m), 7.86−7.92 (1 H, m); ^{13}C NMR (100 MHz; $CHCl_3$) δ_C 30.6, 52.5, 69.3, 72.8, 97.3, 125.8, 127.6, 127.8, 127.9, 128.00, 128.04, 128.1, 128.5, 128.8, 129.1, 128.2, 135.3, 137.0, 139.1, 140.4, 142.1; *m*/*z* found for M^+ 327.1626; $[C_{23}H_{21}NO]^+$ requires 327.1623.

2S-(2′-Iodobenzylamino)-propan-1-ol ***20.*** (*S*)-Alaninol (1.3 mL, 16.38 mmol) and 2-iodobenzaldehyde (3.8 g, 16.38 mmol, 1 equiv) were dissolved in toluene (100 mL) in a round-bottomed flask fitted with a Dean−Stark apparatus. Acetic acid (0.5 mL) was added, and the solution was heated under reflux for 16 h. The reaction mixture was allowed to reach room temperature, and the solvents were removed under reduced pressure. The residue was dissolved in methanol (50 mL), $NaBH_3CN$ (1.23 g, 19.66 mmol, 1.2 equiv) and acetic acid (1 mL) were added, and the solution was stirred for 16 h. Saturated aqueous NH_4Cl (20 mL) was added, and the aqueous layer was washed with Et_2O (3 × 20 mL). The combined organic layers were washed with a saturated solution of aqueous NH_4Cl (20 mL). The aqueous layers were combined, and the pH of the solution was brought to 8−9 using a saturated solution of Na_2CO_3. The resulting solution was extracted using dichloromethane (3 × 20 mL); the combined organic layers were washed with water and brine, dried over $MgSO_4$, and filtered; and the solvents removed to yield the product (4.0 g, 13.75 mmol, 83%); ν_{max}(film)/cm^{-1} 3324, 2956, 1563, 1435, 1045, 1011, 750, 648. $[\alpha]^{20}_D$ +10.8° (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 1.08 (3 H, d, *J* 6.0 Hz), 2.78−2.85 (1 H, m), 3.29 (1 H, dd, *J* 7.0, 11.0 Hz), 3.58 (1 H, dd, *J* 4.0, 11.0 Hz), 3.74 (1 H, d, *J* 13.5 Hz), 3.87 (1 H, d, *J* 13.5 Hz), 6.94 (1 H, dt, *J* 1.5, 7.5 Hz), 7.30 (1 H, dt, *J* 1.0, 7.5 Hz), 7.35 (1 H, dd, *J* 1.5, 7.5 Hz), 7.81 (1 H, dd, *J* 1.2, 8.0 Hz). ^{13}C NMR (125 MHz; $CHCl_3$) δ_C 17.1, 53.9, 55.6, 65.6, 99.8, 128.4, 129.0, 129.8, 139.6, 142.2; *m*/*z* found for $[M + H]^+$: 292.0204; $[C_{10}H_{14}NOI+H]^+$ requires 292.0198.

2S-(2′-Iodobenzylamino)-3-methyl-butan-1-ol ***21.*** (*S*)-Valinol (2.56 g, 24.8 mmol) in MeOH (50 mL), 2-iodobenzaldehyde (6.33 g, 27.3 mmol, 1.1 equiv), and $NaBH_3CN$ (1.71 g, 27.3 mmol, 1.1 equiv) were treated using general procedure A to yield the product (1.30 g, 4.09 mmol, 16%); ν_{max}(film)/cm^{-1} 3321, 2956, 1563, 1464, 1435, 1045, 1011, 750, 648. $[\alpha]^{20}_D$ −16.7° (*c* 1.5, $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.93 (3 H, d, *J* 6.8 Hz), 0.99 (3 H, d, *J* 6.8 Hz), 1.81 (1 H, sextet, *J* 6.8 Hz), 2.41 (1 H, dt, *J* 4.0, 6.4 Hz), 3.40 (1 H, dd *J* 6.8, 10.8 Hz), 3.68 (1 H, dd, *J* 4.0, 10.8 Hz), 3.78 (1 H, d, *J* 13.2 Hz), 3.88 (1 H, d, *J* 13.2 Hz), 6.97 (1 H, dt, *J* 2.0, 7.6 Hz), 7.32 (1 H, dt, *J* 1.2, 7.2 Hz), 7.36 (1 H, dd, *J* 1.6, 7.6 Hz), 7.83 (1 H, dd, *J* 0.8, 8.0 Hz); ^{13}C NMR (100 MHz; $CHCl_3$) δ_C 18.7, 19.8, 29.1, 56.0, 60.6, 64.1, 100.0, 128.6, 129.2, 130.1, 139.7, 142.5; *m*/*z* found for $[M + H]^+$ 320.0511; $[C_{12}H_{18}INO + H]^+$ requires 320.0511.

2R-(2′-Iodobenzylamino)-3-phenyl-propan-1-ol ***22.*** (2*R*)-2-Amino-3-phenylpropan-1-ol (2.92 g, 19.6 mmol) in MeOH (50 mL), 2-iodobenzaldehyde (3.00 g, 21.5 mmol, 1.1 equiv), and $NaBH_3CN$ (1.35 g, 21.5 mmol, 1.1 equiv) were treated using general procedure A to yield the product (6.47 g, 17.6 mmol, 90%); ν_{max}(film)/cm^{-1} 3441, 2359, 1652, 1635, 1113, 743, 699, 668. $[\alpha]^{20}_D$ +20.0° (*c* 1.5, $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.81 (2 H, qd, *J* 7.2, 14.0 Hz), 2.93−3.00 (1 H, m), 3.38 (1 H, dd, *J* 5.2, 10.8 Hz), 3.71 (1 H, dd, *J* 4.0, 10.8 Hz), 3.80 (2 H, s), 6.95 (1 H, dt, *J* 1.6, 7.6 Hz), 7.14−7.18 (2 H, m), 7.19−7.24 (2 H, m), 7.25−7.31 (3 H, m), 7.79 (1 H, dd, *J* 1.2, 8.0 Hz); ^{13}C NMR (100 MHz; $CHCl_3$) δ_C 38.4, 55.7, 59.5, 62.6, 100.0, 126.7, 128.5, 128.8, 129.2, 129.4, 129.9, 138.4, 139.7, 142.0; *m*/*z* found for $[M + H]^+$ 368.0506; $[C_{16}H_{18}NOI+H]^+$ requires 368.0510.

2S-(2′-Iodobenzylamino)-3-phenyl-propan-1-ol ***23.*** (2*S*)-2-Amino-3-phenylpropan-1-ol (2.92 g, 19.6 mmol) in MeOH (50 mL), 2-iodobenzaldehyde (3.00 g, 21.5 mmol, 1.1 equiv), and $NaBH_3CN$ (1.35 g, 21.5 mmol, 1.1 equiv) were treated using general procedure A to yield the product (6.19 g, 16.9 mmol, 86%); ν_{max}(film)/cm^{-1} 3450, 2358, 1645, 1112, 745, 670, 668. $[\alpha]^{20}_D$ −22.8° (*c* 1.3, $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.81 (2 H, qd, *J* 7.2, 14.0 Hz), 2.93−3.00 (1 H, m), 3.38 (1 H, dd, *J* 5.2, 10.8 Hz), 3.70 (1 H, dd, *J* 3.6, 10.8 Hz), 3.80 (2 H, s), 6.95 (1 H, dt, *J* 2.0, 8.0 Hz), 7.14−7.18 (2 H, m), 7.19−7.24 (2 H, m), 7.26−7.31 (3 H, m), 7.79 (1 H, dd, *J* 1.2, 8.0 Hz); ^{13}C NMR (100 MHz; $CHCl_3$) δ_C 38.4, 55.7, 59.5, 62.7, 100.0, 126.7, 128.5, 128.8, 129.1, 129.4, 129.9, 138.4, 139.7, 142.0; *m*/*z* found for $[M + H]^+$ 368.0506; $[C_{16}H_{18}INO + H]^+$ requires 368.0510.

(a*S*,3*S*,13b*R*)-3,13b-Dimethyl-2,3-dihydro-13bH-dibenz[*c*,*e*]-oxazolo[3,2-*a*]azepine 24. (2*S*)-2-(2′-Iodo-benzylamino)-propan-1-ol **20** (1.05 g, 3.60 mmol) and 2-acetyl phenylboronic acid (1.77 g, 10.8 mmol, 3 equiv) were treated using general procedure B to yield the product (0.21 g, 0.80 mmol, 22%); ν_{max}(film)/cm^{-1} 3377, 2966, 1448, 1365, 1217, 1161, 1097, 1046, 756, 738. $[\alpha]^{20}_D$ −69.2° (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.98 (3 H, s), 1.22 (3 H, d, *J* 6.0 Hz), 2.85−2.94 (1 H, m), 3.01 (1 H, d, *J* 10.8 Hz), 3.68 (1 H, dd, *J* 7.6, 9.6 Hz), 3.86 (1 H, d, *J* 11.2 Hz), 4.20 (1 H, dd, *J* 6.4, 7.6 Hz), 7.32−7.46 (7 H, m), 7.74−7.79 (1 H, m); ^{13}C NMR (100 MHz; $CHCl_3$) δ_C 15.9, 30.5, 52.9, 59.7, 71.7, 97.5, 121.8, 125.9, 127.6, 127.7, 128.1, 128.7, 129.0, 129.3, 134.9, 136.9, 142.4; *m*/*z* found for $[M + H]^+$ 266.1542; $[C_{18}H_{19}NO + H]^+$ requires 266.1539.

(a*S*,3*S*,13b*R*)-13b-Methyl-3-isopropyl-2,3-dihydro-13bH-dibenz[*c*,*e*]oxazolo[3,2-*a*]azepine 25. (2*S*)-2-(2′-Iodobenzylamino)-3-methyl-butan-1-ol **21** (1.30 g, 4.09 mmol) and 2-acetyl phenylboronic acid (2.01 g, 12.3 mmol, 3 equiv) were treated using general procedure B to yield the product (0.54 g, 1.90 mmol, 47%); ν_{max}(film)/cm^{-1} 3419, 2954, 2871, 1459, 1365, 1213, 1160, 1043, 756, 730. $[\alpha]^{20}_D$ −98.8° (*c* 1.21, $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 0.96 (3 H,s), 0.99 (6 H, d, *J* 6.8 Hz), 1.88 (1 H, octet, *J* 6.8 Hz), 2.82 (1 H, q, *J* 6.0 Hz), 3.24 (1 H, d, *J* 11.2 Hz), 3.74 (1 H, d, *J* 11.2 Hz), 3.86 (1 H, dd, *J* 6.0, 8.0 Hz), 4.02 (1 H, dd, *J* 7.0, 8.0 Hz), 7.34−7.37 (2 H, m), 7.38−7.43 (3 H, m), 7.44−7.48 (2 H, m), 7.69−7.74 (1 H, m); ^{13}C NMR (100 MHz; $CHCl_3$) δ_C 17.1, 19.6, 30.2, 30.5, 54.3, 65.8, 70.1, 98.2, 125.2, 127.6, 127.90, 127.91, 128.0, 128.3, 129.1, 135.8, 137.4, 140.5, 142.1; *m*/*z* found for $[M + H]^+$: 294.1857 $[C_{20}H_{23}NO + H]^+$ requires 294.1852.

(a*R*,3*R*,13b*S*)-13b-Methyl-3-benzyl-2,3-dihydro-13bH-dibenz[*c*,*e*]oxazolo[3,2-*a*]azepine 26. (2*R*)-2-(2′-Iodobenzyl-amino)-3-phenyl-propan-1-ol **22** (1.00 g, 2.70 mmol) and 2-acetyl phenylboronic acid (1.34 g, 8.20 mmol, 3 equiv) were treated using general procedure B to yield the product (0.51 g, 1.60 mmol, 60%); ν_{max}(film)/cm^{-1} 2926, 1493, 1452, 1365, 1215, 1158, 1069, 1043, 761, 738, 700. $[\alpha]^{20}_D$ −130.1° (*c* 0.99, $CHCl_3$); ^{1}H NMR (500 MHz;

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$CDCl_3$) δ_H 0.93 (3 H, s), 2.60−2.67 (1 H, m), 2.99−3.06 (2 H, m), 3.09 (1 H, d, *J* 11 Hz), 3.66 (1 H, d, *J* 11 Hz), 3.75 (1 H, t, *J* 7.5 Hz), 3.93 (1 H, dd, *J* 6.5, 8.0 Hz), 7.11−7.16 (3 H, m), 7.18−7.24 (3 H, m), 7.24−7.27 (1 H, m), 7.27- 7.32 (2 H, m), 7.32−7.39 (3 H, m), 7.63 (1 H, dd, *J* 1.5, 7.5 Hz); ^{13}C NMR (125 MHz; $CHCl_3$) δ_C 30.6, 39.7, 53.5, 66.2, 69.9, 98.1, 125.4, 126.4, 127.5, 127.8, 128.0, 128.5, 129.0, 129.1, 129.2, 135.0, 137.1, 138.8, 140.1, 142.0; *m*/*z* found for $[M + H]^+$: 342.1853; $[C_{24}H_{23}NO + H]^+$ requires 342.1858.

(a*S*,3*S*,13b*R*)-13b-Methyl-3-benzyl-2,3-dihydro-13bH-dibenz[*c*,*e*]oxazolo[3,2-*a*]azepine 27. (2*S*)-2-(2′-Iodobenzylamino)-3-phenylpropan-1-ol **23** (1.00 g, 2.70 mmol) and 2-acetyl phenylboronic acid (1.34 g, 8.20 mmol, 3 equiv) were treated using general procedure B to yield the product (0.27 g, 0.80 mmol, 30%); ν_{max}(film)/cm^{-1} 2926, 1493, 1452, 1365, 1215, 1158, 1069, 1043, 761, 738, 700. $[\alpha]^{20}_D$ +130.9° (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.01 (3 H, s), 2.68−2.76 (1 H, m), 3.07−3.19 (3 H, m), 3.75 (1 H, d, *J* 10.8 Hz), 3.83 (1 H, t, *J* 7.6 Hz), 4.02 (1 H, dd, *J* 6.2, 7.6 Hz), 7.20−7.26 (3 H, m), 7.27−7.33 (3 H, m), 7.34−7.41 (3 H, m), 7.42−7.48 (3 H, m), 7.68−7.72 (1 H, m); ^{13}C NMR (100 MHz; $CHCl_3$) δ_C 30.7, 39.7, 53.6, 66.3, 70.0, 98.2, 125.5, 126.5, 127.6, 127.9, 128.0, 128.6, 129.1, 129.2, 129.3, 135.0, 137.1, 138.9, 140.1, 142.1; *m*/*z* $[M + H]^+$: 342.1853; $[C_{24}H_{23}NO + H]^+$ requires 342.1858.

(a*S*,3*S*,13b*R*)-3,13b-Dimethyl-2,3-dihydro-13bH-dibenz[*c*,*e*]-oxazolo[3,2-*a*]azepin-5-ium Tetraphenylborate Salt 28. Compound **24** (0.21 g, 0.80 mmol) in dichloromethane (2 mL) and *N*-bromosuccinimide (0.29 g, 1.60 mmol, 2 equiv) were treated using general procedure C to yield the product (0.20 g, 0.59 mmol, 74%); ν_{max}(film)/cm^{-1} 2965, 1704, 1652, 1558, 1259, 1184, 1102, 1017, 763, 615. $[\alpha]^{20}_D$ 107.6° (*c* 10.3, $CHCl_3$); ^{1}H NMR (500 MHz; *d*6-acetone) δ_H 1.56 (3 H, s), 1.90 (3 H, d, *J* 6.8 Hz), 4.48 (1 H, dd, *J* 2.9, 9.5 Hz), 4.54 (1 H, dd, *J* 5.3 and 9.5 Hz), 4.96−5.03 (1 H, m), 6.74−6.78 (4 H, m), 6.91 (8 H, t, *J* 7.4 Hz), 7.31−7.35 (8 H, m), 7.71 (1 H, dt, *J* 1.5, 7.5 Hz), 7.76 (1 H, dt, *J* 1.4, 7.5 Hz), 7.84−7.89 (2 H, m), 7.91 (1 H, dd, *J* 1.1, 7.6 Hz), 8.10 (1 H, dt, *J* 1.2, 7.4 Hz), 8.16−8.20 (2 H, m), 9.67 (1 H, s); ^{13}C NMR (125 MHz; *d*6-acetone) δ_C 19.7, 23.4, 65.8, 71.5, 100.4, 122.3, 124.6, 126.0 (q, 3 Hz), 129.9, 131.4, 131.5, 131.7, 132.6, 134.6, 136.0, 137.0, 137.9, 139.3, 143.1, 164.4, 164.8, 165.1, 165.5, 165.7; *m*/*z* found for iminium cation: 264.1385; $C_{18}H_{18}NO^+$ requires 264.1383.

(a*S*,3*S*,13b*R*)-13b-Methyl-3-isopropyl-2,3-dihydro-13bH-dibenz[*c*,*e*]oxazolo[3,2-*a*]azepin-5-ium Tetraphenylborate Salt 29. Compound **25** (0.54 g, 1.90 mmol) in dichloromethane (2 mL) and *N*-bromosuccinimide (0.68 g, 3.80 mmol, 2 equiv) were treated using general procedure C to yield the product (0.57 g, 1.50 mmol, 81%); ν_{max}(film)/cm^{-1} 3055, 2998, 1639, 1596, 1579, 1559, 1479, 1425, 1377, 1184, 1031, 734. $[\alpha]^{20}_D$ +236.8° (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz; *d*6-acetone) δ_H 1.24 (3 H, d, *J* 7.0 Hz), 1.26 (3 H, d, *J* 7.0 Hz), 1.54 (3 H, s), 2.64 (1 H, sextet, *J* 7.0 Hz), 4.47 (1 H, dd, *J* 5.0, 10.0 Hz), 4.60 (1 H, tt, *J* 1.5, 6.5 Hz), 4.72 (1 H, dd, *J* 2.0, 10.0 Hz), 6.79 (4 H, t, *J* 7.2 Hz), 6.93 (8 H, t, *J* 7.5 Hz), 7.33−7.37 (8 H, m), 7.73 (1 H, td, *J* 1.5, 7.5 Hz), 7.77 (1 H, td, *J* 1.5, 7.5 Hz), 7.83−7.87 (2 H, m), 7.92 (1 H, dd, *J* 1.5, 7.5 Hz), 8.09 (1 H, td, *J* 1.5, 7.5 Hz), 8.14 (1 H, dd, *J* 1.5, 7.5 Hz), 8.18 (1 H, d, 7.5 Hz), 9.50 (1 H, s); ^{13}C NMR (125 MHz; *d*6-acetone) δ_C 17.8, 19.2, 22.2, 31.9, 67.4, 73.6, 100.3, 122.0, 124.3, 125.6, 125.73, 125.75, 125.77, 125.80, 129.7, 131.0, 131.2, 131.4, 132.4, 134.4, 135.6, 136.75, 136.76, 137.6, 139.2, 142.7, 164.1, 164.5, 164.9, 165.3, 166.2; *m*/*z* found for M^+ (iminium cation) 292.1704; $[C_{20}H_{22}NO]^+$ requires 292.1701.

(a*R*,3*R*,13b*S*)-13b-Methyl-3-phenyl-2,3-dihydro-13bH-dibenz[*c*,*e*]oxazolo[3,2-*a*]azepin-5-ium Tetraphenylborate Salt 8. Compound **9** (0.43 g, 1.32 mmol) in dichloromethane (2 mL) and *N*-bromosuccinimide (0.47 g, 2.64 mmol, 2 equiv) were treated using general procedure C to yield the product as a pair of diastereoisomers (0.27 g, 0.66 mmol, 50%); ν_{max}(film)/cm^{-1} 3055, 1709, 1641, 1596, 1579, 1557, 1479, 1426, 1361, 1222, 731, 703. $[\alpha]^{20}_D$ −9.2° (*c* 1.3, acetone). ^{1}H NMR (500 MHz; *d*6-acetone) δ_H 1.65 (3 H, s), 4.85 (1 H, dd, *J* 5.0, 10.0 Hz), 4.89 (1 H, dd, *J* 6.5, 10.0 Hz), 5.79 (1 H, dt, *J* 1.0, 5.8 Hz), 6.72−6.77 (4 H, m), 6.88 (8 H, t, *J* 7.5 Hz), 7.28−7.34 (8 H, m), 7.57−7.60 (3 H, m), 7.68−7.72 (2 H, m), 7.72−7.75 (2 H, m), 7.80 (1 H, dt, *J* 1.5, 7.5 Hz), 7.90 (2 H, dt, *J* 1.5, 7.5 Hz), 7.95 (1 H, dd, *J* 1.0, 8.0 Hz), 8.05 (1 H, dt, *J* 1.5, 8.0 Hz), 8.16 (1 H, d, *J* 7.5 Hz), 9.27 (1 H, d, *J* 1.5 Hz); ^{13}C NMR (125 MHz; *d*6-acetone) δ_C 21.4, 71.08, 71.15, 99.8, 121.4, 124.0, 125.1 (q, *J* 3 Hz), 128.6, 128.8, 129.1, 129.9, 130.4, 130.6, 130.7, 130.9, 131.8, 135.6, 136.2 (q, *J* 1 Hz), 137.4, 142.5, 163.5, 163.9, 164.3, 164.7, 165.7. *m*/*z* found for M^+ (iminium cation) 326.1549; $[C_{23}H_{20}NO]^+$ requires 326.1545.

(a*R*,3*R*,13b*S*)-13b-Methyl-3-benzyl-2,3-dihydro-13bHdibenz[*c*,*e*]oxazolo[3,2-*a*]azepin-5-ium Tetraphenylborate Salt 30. Compound **26** (0.26 g, 0.80 mmol) in dichloromethane (2 mL) and *N*-bromosuccinimide (0.29 g, 1.60 mmol, 2 equiv) were treated using general procedure C to yield the product (0.28 g, 0.66 mmol, 82%); ν_{max}(film)/cm^{-1} 3051, 3013, 1642, 1598, 1581, 1557, 1481, 1426, 1381, 1183, 1031, 1016, 767, 755, 716, 714. $[\alpha]^{20}_D$ −30.3° (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz; *d*6-acetone) δ_H 1.59 (3 H, s), 3.61 (2 H, dq, *J* 7.5, 13.5 Hz), 4.49 (1 H, dd, *J* 5.0, 10.0 Hz), 4.66 (1 H, dd, *J* 1.5, 10.0 Hz), 5.06−5.13 (1 H, m), 6.76 (4 H, t, *J* 7.0 Hz), 6.91 (8 H, t, *J* 7.0 Hz), 7.30−7.35 (8 H, m), 7.44−7.52 (5 H, m), 7.70 (1 H, td, *J* 1.5, 7.5 Hz), 7.71 (1 H, dd, *J* 1.5, 8.0 Hz), 7.75 (1 H, td, *J* 1.5, 7.5 Hz), 7.82 (1 H, td, *J* 1.0, 8.0 Hz), 7.85 (1 H, td, *J* 1.5, 7.5 Hz), 7.89 (1 H, dd, *J* 1.5, 8.0 Hz), 8.08 (1 H, td, *J* 1.5, 7.5 Hz), 8.16 (1 H, d, *J* 7.5 Hz), 8.91 (1 H, s); ^{13}C NMR (125 MHz; *d*6-acetone) δ_C 23.3, 40.2, 70.1, 70.5, 100.9, 122.2, 124.4, 125.5, 125.98, 126.00, 126.02, 126.04, 128.9, 130.0, 130.3, 130.9, 131.4, 131.5, 131.7, 132.7, 134.6, 135.3, 136.0, 137.04, 137.05, 138.0, 139.2, 143.0, 134.4, 164.8, 165.2, 165.5, 165.8; *m*/*z* found for M^+ (iminium cation) 340.1707; $[C_{24}H_{22}NO]^+$ requires 340.17014.

(a*S*,3*S*,13b*R*)-13b-Methyl-3-benzyl-2,3-dihydro-13bHdibenz-[*c*,*e*]oxazolo[3,2-*a*]azepin-5-ium Tetraphenylborate Salt 31. Compound **27** (0.51 g, 1.60 mmol) in dichloromethane (5 mL) and *N*-bromosuccinimide (0.57 g, 3.20 mmol, 2 equiv) were treated using general procedure C to yield the product (0.62 g, 1.20 mmol, 75%); ν_{max}(film)/cm^{-1} 3445, 2358, 1714, 1654, 1616, 1558, 1454, 1404, 1257, 1182, 1104, 744, 701, 668; $[\alpha]^{20}_D$ +15.0° (*c* 1.07, $CHCl_3$); ^{1}H NMR (400 MHz; *d*6-acetone) δ_H 1.58 (3 H, s), 3.58 (2 H, dq, *J* 7.6, 13.6 Hz), 4.45 (1 H, dd, *J* 5.2, 10.0 Hz), 4.62 (1 H, dd, *J* 1.2, 10.0 Hz), 4.98−5.06 (1 H, m), 6.76 (4 H, t, *J* 7.2 Hz), 6.90 (8 H, t, *J* 7.6 Hz), 7.30−7.36 (8 H, m), 7.43−7.52 (5 H, m), 7.67 (1 H, dd, *J* 1.2, 7.6 Hz), 7.70 (1 H, td, *J* 1.6, 7.6 Hz), 7.75 (1 H, td, *J* 1.6, 7.6 Hz), 7.80 (1 H, td, *J* 1.2, 7.6 Hz), 7.85 (1 H, td, *J* 1.6, 8.0 Hz), 7.88 (1 H, dd, *J* 1.6, 7.6 Hz), 8.06 (1 H, td, *J* 1.2, 8.0 Hz), 8.14 (1 H, d, *J* 7.2 Hz), 8.84 (1 H, s); ^{13}C NMR (125 MHz; *d*6-acetone) δ_C 23.4, 40.3, 70.1, 70.5, 101.0, 122.4, 124.5, 125.5, 126.10, 126.12, 126.15, 126.18, 129.0, 130.1, 130.4, 131.0, 131.5, 131.6, 131.8, 132.8, 134.7, 135.5, 137.13, 137.15, 139.3, 143.1, 164.3, 164.8, 165.8, 165.9; *m*/*z* found for M^+ (iminium cation) 340.1701; $[C_{24}H_{22}NO]^+$ requires 340.1701.

1-Phenylcyclohexene Oxide.[24] Isolated as a colorless oil: ν_{max}(neat)/cm^{-1} 3083, 1602, 1495, 1445, 1359, 1248, 1174, 1133, 1078, 1030, 993, 974; ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 1.20−1.33 (1 H, m), 1.51−1.62 (3 H, m), 1.97−2.05 (2 H, m), 2.16−2.18 (1 H, m), 2.24−2.31 (1 H, m), 3.10 (1 H, t, *J* = 2.0 Hz), 7.26−7.41 (5 H, m).

1-Phenyldihydronaphthalene Oxide.[24] Isolated as a colorless crystalline solid: ν_{max}(neat)/cm^{-1} 3087, 1601, 1493, 1284, 1176, 1158, 1094, 1072, 1028; ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 2.10 (1 H, td, *J* = 15.5 Hz, 5.6 Hz) 2.48−2.59 (1 H, m), 2.76 (1 H, dd, *J* = 15.5 Hz, 5.5 Hz) 2.96−3.07 (1 H, m), 3.70 (1 H, d, *J* = 3.0 Hz), 7.09−3.29 (4 H, m), 7.45−7.60 (5 H, m). HPLC conditions: hexane/2-propanol (90:10), oven temp 20 °C, column Chiracel OD-H 01 250 mm × 4.6 mm, 5 μm particle size, flow rate 1 mL/min, 254 nm, t_r 4.51 min (−)-(1*S*,2*R*) and 5.94 min (+)-(1*R*,2*S*).

(E)-Stilbene Oxide.[24] Isolated as a colorless crystalline solid: ν_{max}(neat)/cm^{-1} 3081, 1776, 1602, 1485, 1336, 1155, 1074, 1042, 953; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.87 (2 H, s), 7.29−7.39 (10 H, m); δ_C (75 MHz; $CDCl_3$) 63.3, 126.0, 128.6, 129.3, 137.6. HPLC conditions: hexane/2-propanol (80:20), oven temp 20 °C, column Chiracel OD-H 01 250 mm × 4.6 mm, 5 μm particle size, flow rate 1 mL/min, 254 nm, t_r 4.98 min (−)-(1*S*,2*S*) and 6.54 min (+)-(1*R*,2*R*).

Dihydronaphthalene Oxide.[8] Isolated as a colorless oil: ν_{max}(neat)/cm^{-1} 3058, 3028, 2931, 2850, 1602, 1492, 1314, 1129, 1088, 1031, 965; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.65−1.84 (1 H, m), 2.33−2.42 (1 H, m), 2.52 (1 H, dd, *J* = 15.5 Hz, 5.5 Hz), 2.67−

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2.85 (1 H, m), 3.71−3.80 (1 H, m), 3.81−3.89 (1 H, m), 7.05 (1 H, d, J = 7.2 Hz), 7.18−7.35 (2 H, m), 7.40 (1 H, d, J = 7.1 Hz).

Triphenylethylene Oxide.[8] Isolated as a colorless crystalline solid: ν_{max}(neat)/cm^{-1} 3061, 3031, 2956, 2924, 2857, 1604, 1595, 1498, 1471, 1448, 1262, 1220, 741, 699; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.42 (1 H, s), 7.13- 5.50 (15H, m). HPLC conditions: hexane/2-propanol (90:10), oven temp 20 °C, column Chiracel OD-H 01 250 mm × 4.6 mm, 5 μm particle size, flow rate 1 mL/min, 254 nm, t_r 4.26 min (+)-(*S*), 7.47 min (−)-(*R*).

Crystallography. For **9** and **27** diffraction data were collected at 150(2) K, and corrections were made for absorption, Lorentz, and polarization factors. Both structures were solved by direct methods and were routine in nature. The absolute structures could not be determined reliably from the diffraction data and so were set from unchanging chiral centers. For **9**: $C_{23}H_{21}NO$, M = 327.41, monoclinic, $P2_1$, a = 8.4016(5) Å, b = 9.9253(6) Å, c = 10.5431(7) Å, β = 97.2928(9)°, V = 872.06(9) Å^3, Z = 2, colorless crystal, 0.32 × 0.29 × 0.10 mm^3, D_{calc} = 1.247 g/cm^3, μ(Mo Kα) = 0.076 mm^{-1}, 9089 data measured, R_{int} = 0.020, wR_2 = 0.090 for all 4258 unique data, $R1$ = 0.037 for 3932 data with $F^2 \geq 2\sigma(F^2)$. For **27**: $C_{24}H_{23}NO$, M = 341.43, monoclinic, $P2_1$, a = 8.5648(4) Å, b = 9.8551(5) Å, c = 11.1777(5) Å, β = 98.4207(7)°, V = 933.30(8) Å^3, Z = 2, colorless crystal, 0.52 × 0.38 × 0.36 mm^3, D_{calc} = 1.247 g/cm^3, μ(Mo Kα) = 0.073 mm^{-1}, 11 151 data measured, R_{int} = 0.022, wR_2 = 0.119 for all 5541 unique data, $R1$ = 0.044 for 4987 data with $F^2 \geq 2\sigma(F^2)$. CCDC 1400420−1400421 contain supplementary crystallographic data in cif format. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk.).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01157.

^{1}H and ^{13}C NMR spectra; displacement ellipsoid plots of **9** and **27** (PDF)

Crystallographic data for **9** and **27** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67. (b) Gorzynski Smith, J. *Synthesis* **1984**, *1984*, 629. (c) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189. (d) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543. (e) Amano, S.; Ogawa, N.; Ohtsuka, M.; Chida, N. *Tetrahedron* **1999**, *55*, 2205. (f) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.

(2) See for example: (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (b) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 621. (c) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 649. (d) Julia, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929. (e) Allen, J. V.; Bergeron, S.; Griffiths, M. J.; Mukherjee, S.; Roberts, S. M.; Williamson, N. M.; Wu, L. E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3171. (f) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (g) Michaelson, R. C.; Palermo, R. E.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 1990. (h) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032. (i) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791. (j) Cavallo, L.; Jacobsen, H. *Inorg. Chem.* **2004**, *43*, 2175. (k) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345. (l) Kawai, H.; Okusu, S.; Yuan, Z.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2221.

(3) See for example: (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328. (c) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099. (d) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622. (e) Cao, G. A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425. (f) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. (g) Tu, Y.; Wang, Z. X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475. (h) Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675. (i) Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718. (j) Shu, L.; Shi, Y. *Tetrahedron Lett.* **1999**, *40*, 8721. (k) Shu, L.; Shi, Y. *J. Org. Chem.* **2000**, *65*, 8807. (l) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929. (m) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435. (n) Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792. (o) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (p) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391. (q) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479. (r) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (s) Yang, D.; Wang, X. C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (t) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X. C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (u) Yang, D.; Yip, M. C.; Tang, M. M.; Wong, M. K.; Cheung, K. K. *J. Org. Chem.* **1998**, *63*, 9888. (v) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621. (w) Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B. R.; Wailes, J. S. *J. Org. Chem.* **2002**, *67*, 8610. (x) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155.

(4) Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, *17*, 1573. Picot, A.; Milliet, P.; Lusinchi, X. *Tetrahedron Lett.* **1976**, *17*, 1577.

(5) (a) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1987**, *28*, 6061. (b) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29*, 3941. (c) Bohé, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 7271. (d) Bohé, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141. (e) Lacour, J.; Monchaud, D.; Marsol, C. *Tetrahedron Lett.* **2002**, *43*, 8257. (f) Bohé, L.; Kammoun, M. *Tetrahedron Lett.* **2002**, *43*, 803. (g) Bohé, L.; Kammoun, M. *Tetrahedron Lett.* **2004**, *45*, 747. (h) Aggarwal, V. K.; Wang, M. F. *Chem. Commun.* **1996**, 191. (i) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K. *Synlett* **1997**, *1997*, 1075. (j) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J. S. *Tetrahedron* **1999**, *55*, 2341. (k) Gluszynska, A.; Mackowska, I.; Rozwadowska, M. D.; Sienniak, W. *Tetrahedron: Asymmetry* **2004**, *15*, 2499. (l) Biscoe, M. R.; Breslow, R. *J. Am. Chem. Soc.* **2005**, *127*, 10812. (m) Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* **2000**, 1810. (n) Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587. (o) Crosthwaite, J. M.; Farmer, V. A.; Hallett, J. P.; Welton, T. *J. Mol. Catal. A: Chem.* **2008**, *279*, 148. (p) Novikov, R.; Lacour, J. *Tetrahedron: Asymmetry* **2010**, *21*, 1611. (q) Novikov, R.; Vachon, J.; Lacour, J. *Chimia* **2007**, *61*, 236. (r) Vachon, J.; Lauper, C.; Ditrich, K.; Lacour, J. *Tetrahedron: Asymmetry* **2006**, *17*, 2334. (s) Vachon, J.; Rentsch, S.; Martinez, A.; Marsol, C.; Lacour, J. *Org. Biomol. Chem.* **2007**, *5*, 501. (t) Novikov, R.; Bernardinelli, G.; Lacour, J. *Adv. Synth. Catal.* **2009**, *351*, 596.

DOI: 10.1021/acs.joc.5b01157
J. Org. Chem. 2015, 80, 8036−8045

(6) (a) Gonçalves, M.-H.; Martinez, A.; Grass, S.; Bulman Page, P. C.; Lacour, J. *Tetrahedron Lett.* **2006**, *47*, 5297. (b) Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317. (c) Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 11223. (d) Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596. (e) Ho, C.-Y.; Chen, Y.-C.; Wong, M.-K.; Yang, D. *J. Org. Chem.* **2005**, *70*, 898.

(7) Farah, M. M.; Page, P. C. B.; Buckley, B. R.; Blacker, A. J.; Elsegood, M. R. J. *Tetrahedron* **2013**, *69*, 758.

(8) (a) Page, P. C. B.; Buckley, B. R.; Farah, M. M.; Blacker, A. J. *Eur. J. Org. Chem.* **2009**, *2009*, 3413. (b) Bulman Page, P. C.; Bartlett, C. J.; Chan, Y.; Day, D. P.; Parker, P.; Buckley, B. R.; Rassias, G. A.; Slawin, A. M. Z.; Allin, S. M.; Lacour, J.; Pinto, A. *J. Org. Chem.* **2012**, *77*, 6128.

(9) (a) Bulman Page, P. C.; Parker, P.; Buckley, B. R.; Rassias, G. A.; Bethell, D. *Tetrahedron* **2009**, *65*, 2910. (b) Buckley, B. R.; Chan, Y.; Dreyfus, N.; Elliott, C. E.; Marken, F.; Bulman Page, P. C. *Green Chem.* **2012**, *14*, 2221 and references therein. (c) Buckley, B. R.; Elliott, C. E.; Chan, Y.; Dreyfus, N.; Bulman Page, P. C. *Synlett* **2013**, *24*, 2266 and references therein.

(10) Campestrini, S.; Di Furia, F.; Labat, G.; Novello, F. *J. Chem. Soc., Perkin Trans. 2* **1994**, *10*, 2175.

(11) (a) Page, P. C. B.; Buckley, B. R.; Barros, D.; Blacker, J. A.; Marples, B. A.; Elsegood, M. R. J. *Tetrahedron* **2007**, *63*, 5386. (b) Bartlett, C. J.; Day, D. P.; Chan, Y.; Allin, S. M.; McKenzie, M. J.; Slawin, A. M. Z.; Bulman Page, P. C. *J. Org. Chem.* **2012**, *77*, 772. (c) Bulman Page, P. C.; Appleby, L. F.; Chan, Y.; Day, D.; Buckley, B. R.; Slawin, A. M. Z.; Allin, S. M.; McKenzie, M. J. *J. Org. Chem.* **2013**, *78*, 8074. (d) Bulman Page, P. C.; Chan, Y.; Day, D. P. *Eur. J. Org. Chem.* **2014**, *2014*, 8029.

(12) (a) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (b) Baudoin, O. *Eur. J. Org. Chem.* **2005**, *2005*, 4223. (c) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197.

(13) Pira, S. L.; Wallace, T. W.; Graham, J. P. *Org. Lett.* **2009**, *11*, 1663.

(14) Novikov, R.; Bernardinelli, G.; Lacour, J. *Adv. Synth. Catal.* **2008**, *350*, 1113.

(15) Bulman Page, P. C.; Bartlett, C. J.; Chan, Y.; Day, D.; Parker, P.; Buckley, B. R.; Rassias, G. A.; Slawin, A. M. Z.; Allin, S. M.; Lacour, J.; Pinto, A. *J. Org. Chem.* **2012**, *77*, 6128.

(16) (a) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1. (b) Amat, M.; Canto, M.; Llor, N.; Ponzo, V.; Perez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335. (c) Amat, M.; Canto, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343. (d) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. (e) Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813. (f) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464. (g) Houpis, J. N.; Molina, A.; Reamer, R. A.; Lynch, J. E.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1993**, *34*, 2593. (h) Penhoat, M.; Leleu, S.; Dupas, G.; Papamicaël, C.; Marsais, F.; Levacher, V. *Tetrahedron Lett.* **2005**, *46*, 8385. (i) Husain, S. M.; Heim, M. T.; Schepmann, D.; Wünsch, B. *Tetrahedron: Asymmetry* **2009**, *20*, 1383. (j) Penhoat, M.; Bohn, P.; Dupas, G.; Papamicaël, C.; Marsais, F.; Levacher, V. *Tetrahedron: Asymmetry* **2006**, *17*, 281. (k) Husain, S. M.; Fröhlich, R.; Wünsch, B. *Tetrahedron: Asymmetry* **2008**, *19*, 1613. (l) Bouet, A.; Oudeyer, S.; Dupas, G.; Marsais, F.; Levacher, V. *Tetrahedron: Asymmetry* **2008**, *19*, 2396.

(17) (a) Penhoat, M.; Levacher, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517. (b) Ried, W.; Conte, R. *Chem. Ber.* **1971**, *104*, 1573. (c) Edwards, D. J.; Pritchard, R. G.; Wallace, T. W. *Tetrahedron Lett.* **2003**, *44*, 4665. (d) Edwards, D. J.; House, D.; Sheldrake, H. M.; Stone, S. J.; Wallace, T. W. *Org. Biomol. Chem.* **2007**, *5*, 2658. (e) Postikova, S.; Sabbah, M.; Wightman, D.; Nguyen, I. T.; Sanselme, M.; Besson, T.; Brière, J.-F.; Oudeyer, S.; Levacher, V. *J. Org. Chem.* **2013**, *78*, 8191.

(18) (a) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656. (b) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413. (c) Husain, S. M.; Fröhlich, R.; Schepmann, D.; Wünsch, B. *J. Org. Chem.* **2009**, *74*, 2788. (d) Pira, S. L.; Wallace, T. W.; Graham, J. P. *Org. Lett.* **2009**, *11*, 1663.

(19) (a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (b) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849. (c) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015.

(20) Cheetham, C. A.; Massey, R. S.; Pira, S. L.; Pritchard, R. G.; Wallace, T. W. *Org. Biomol. Chem.* **2011**, *9*, 1831.

(21) Bulman Page, P. C.; Farah, M. M.; Buckley, B. R.; Blacker, A. J.; Lacour, J. *Synlett* **2008**, *2008*, 1381.

(22) APEX 2 and SAINT (2006), software for CCD diffractometers; Bruker AXS Inc.: Madison, WI, USA.

(23) (a) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Adv.* **2015**, *71*, 3. (b) Sheldrick, G. M. SHELXTL user manual, version 6.12; Bruker AXS Inc.: Madison, WI, USA, 2001.

(24) Bulman Page, P. C.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, *63*, 2774.

DOI: 10.1021/acs.joc.5b01157
J. Org. Chem. 2015, 80, 8036−8045