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Asymmetric Synthesis of Chiral 1,2-Amino Alcohols and Morpholin-2-ones from Arylglyoxals

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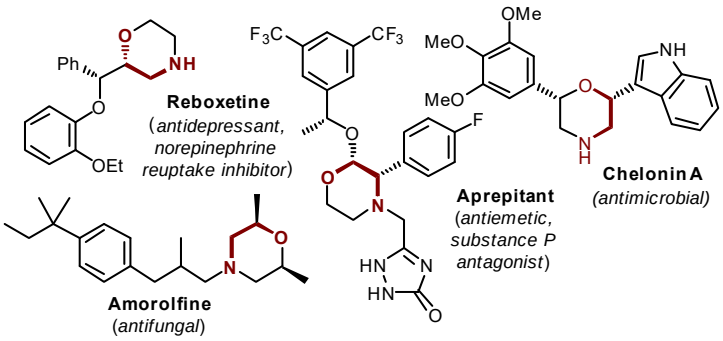
ABSTRACT: Chiral 1,2-amino alcohols are privileged scaffolds with important applications as drug candidates and chiral ligands. Although various methods for the preparation of this structural motif have been reported, these methods are limited because of the use of precious metals and ligands. Here, we report a practical and high yielding synthesis of chiral 1,2-amino alcohols using arylglyoxals and pseudoephedrine auxiliary. This reaction is catalyzed by a Brønsted acid and provides morpholinone products in high yields and selectivities. The morpholine ring was converted into 1,2-amino alcohols in a two-step protocol.

INTRODUCTION

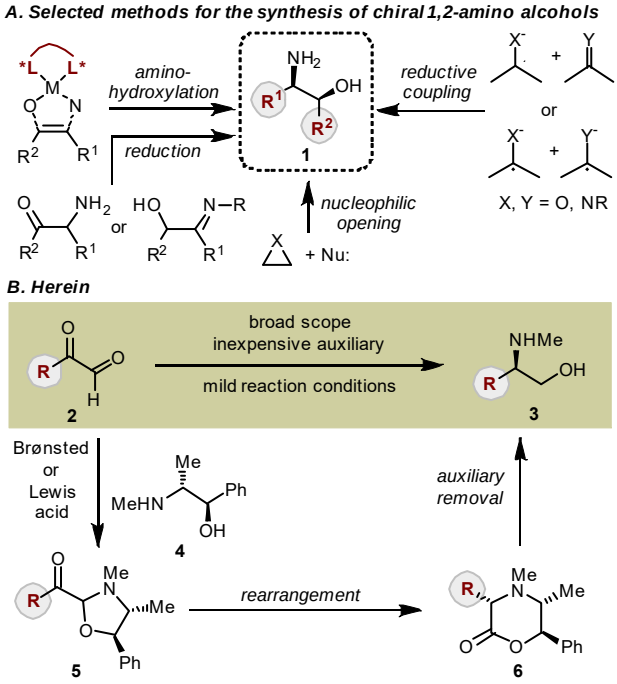
Chiral 1,2-amino alcohols are privileged compounds in organic chemistry due to their versatility as building blocks in the synthesis of natural products, commercial drugs, and ligands.[1-5] Although methods to access vicinal 1,2-amino alcohols often focus on catalytic transformations of C=C and C=X (X = N, O) groups, approaches that use inexpensive and readily available starting materials and also meet the current sustainability criteria are in demand. Here, we report a practical and high-yielding conversion of aryl glyoxals into chiral aryl 1,2-amino alcohols and morpholinones using pseudoephedrine as a dispensable auxiliary. This method offers a viable alternative to other technologies because of its generality, mildness and cost-efficiency, and can be applied in a gram-scale preparation of value-added chemicals.

Figure 1. Selected bioactive morpholines.



Vicinal amino alcohols are found in commercial drugs that display antifungal,[6-7] antiemetic,[8] and anti-depressant[9] properties (Figure 1). One of the most prevalent applications of chiral amino alcohols is in the preparation of chiral ligands for metal-catalyzed reactions and organocatalysis.[1] Because of the importance of the 1,2-amino alcohol functionality, methods that focus on aminohydroxylation,[10-11] opening of aziridines[12] and epoxides,[13] reductions of α-amino ketones,[14] reductive cross-coupling,[15-16] and enantioselective redox couplings with a ruthenium photoredox sensitizer[17-18] have been reported (Scheme 1A).

Scheme 1. Synthesis of chiral 1,2-amino alcohols.



A majority of these technologies are applicable to the synthesis of amino alcohols with the aryl or alkyl groups located at the oxygen-bearing carbon. However, there is a knowledge gap in the preparation of isomeric structures, i.e., those with a chiral nitrogen-substituted carbon. In search of a practical method for the synthesis of aryl amino alcohols we were inspired by the work of Polyak who reported a transformation of arylglyoxals into morpholinones.[19] This method is characterized by unusual mildness and utilizes 1,2-amino alcohols that, when exposed to aryl glyoxals and a Brønsted acid, undergo a rearrangement into morpholinones. We proposed that inexpensive 1,2-amino alcohol auxiliaries could be used to introduce a chiral center into aryl glyoxals and effectively lead to a transfer of two heteroatoms from the auxiliary to the glyoxal substrate.[20] The chiral auxiliary would be removed from the final product unmasking the chiral amino alcohol scaffold (Scheme 1B). Arylglyoxals are convenient reagents to prepare nitrogen-containing heterocycles[21] and well-established methods are known to access substrates with a broad range of modifications,[22-25] including oxidation of aryl methyl ketones.[26-29] This novel method complements recent developments in the synthesis of morpholines using bifunctional reagents and aldehydes.[30-35]

RESULTS AND DISCUSSION

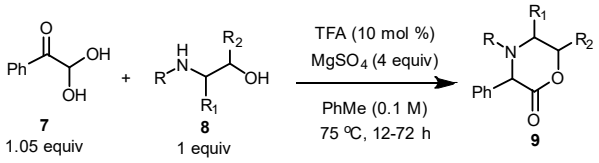
In order to identify an optimal chiral auxiliary, we tested a series of commercial chiral 1,2-amino alcohols (Table 1). As the model system, we used phenylglyoxal hydrate **7** that exists predominantly in the form of a hydrate. The presence of the hydrate has no bearing on the efficiency and selectivity of the rearrangement reactions and this "protected" form is more stable and easier to handle than the glyoxals. However, when the reaction was attempted with dimethyl acetal of **7**, only poor conversions were recorded regardless of the conditions tested.

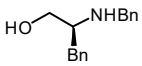
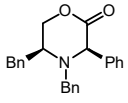
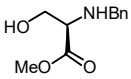
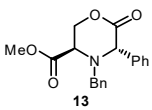
We first wondered if the nature of the catalyst impacts the formation of the putative oxazolidine intermediate and the subsequent shift of the aryl group. We established that oxophilic Lewis acids such as those based on zinc ($ZnCl_2$, $ZnBr_2$), Brønsted acids (TfOH, TFA, $PhPO_3H_2$; 10 mol %), but not boron-

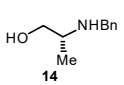
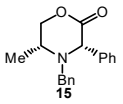
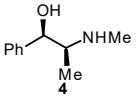
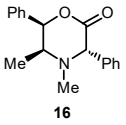
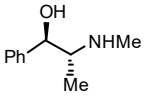
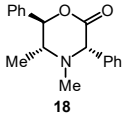
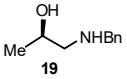
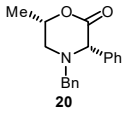
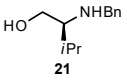
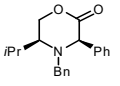
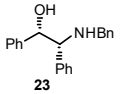
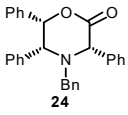
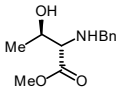
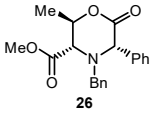
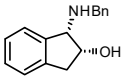
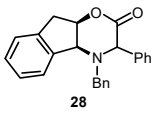
derived Lewis acid catalysts ($BF_3 \cdot Et_2O$) were competent in catalyzing the transformation into morpholinones (40-90%). For practical reasons, TFA was selected as the optimal catalyst, and loadings as low as 2% could be used. We found that an acid is required for the reaction to occur, and attempts to induce thermal migration of the aryl group under neutral or slightly basic conditions resulted in <10% of the products (24 h at 110 ºC).

Next, we tested various amino alcohol ligands and a few general observations regarding the diastereoselectivity are noteworthy – amino alcohols with only one chiral center gave poor *dr* and, in some cases, the yields were also unsatisfactory (e.g., **21**). Similar results were recorded for bicyclic amino alcohol **27**. From the optimization studies, pseudoephedrine **17** emerged as the amino alcohol resulting in the best isolated yield (entry 5). Pseudoephedrine is an inexpensive and abundant source of chirality that found use in organic synthesis as an auxiliary in aldol reactions.[36-42] The relative stereochemistry for the products reported in Table 1 was established based on 1D/2D NMR, NOESY analysis, and single crystal X-ray data for **11** and **31j** (*vide supra*).

Table 1. Identification and optimization of rearrangement conditions.



Entry	Amino alcohol	Product	Yield [%][a]	*dr*[b]
1	 **10**	 **11**	64	87:13
2	 **12**	 **13**	79	87:13

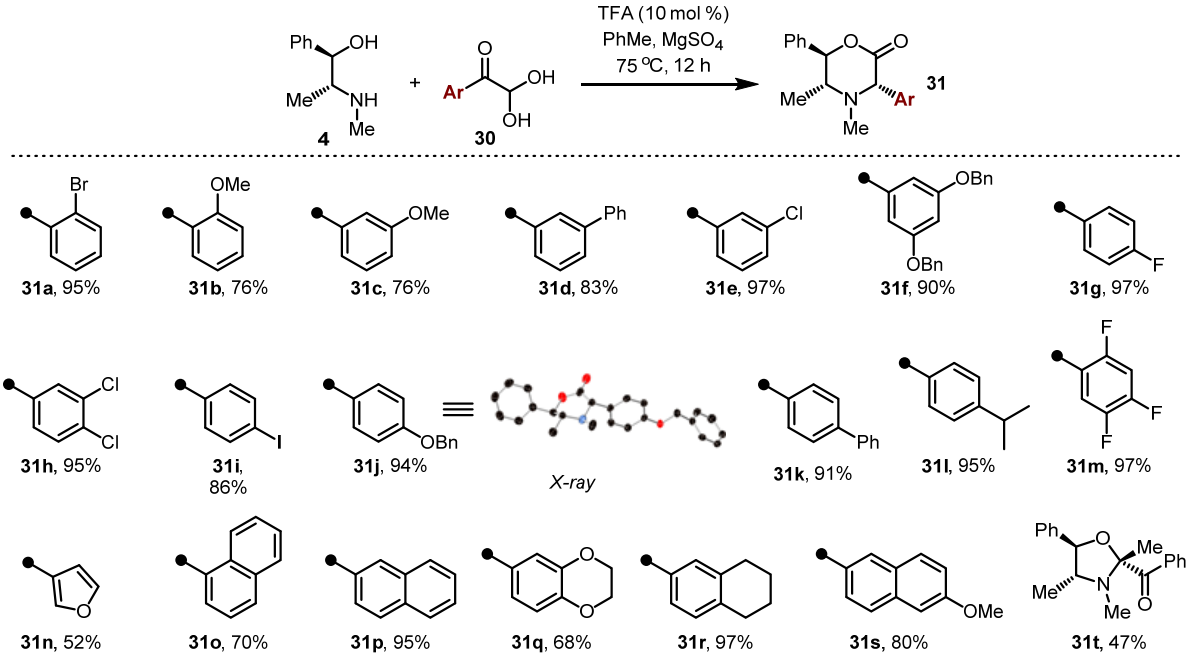
3	 14	 15	84	63:37
4	 4	 16	88	61:39
5	 17	 18	95	87:14
6	 19	 20	78	82:18
7[c]	 21	 22	24	73:27
8	 23	 24	46	60:40
9	 25	 26	96	57:43
10	 27	 28	32	65:35

[a]Combined yield of two diastereoisomers. [b]Determined by ^{1}H NMR using unpurified reaction mixtures. [c]Relative stereochemistry of the major isomer not established.

Further optimization of reaction conditions with pseudoephedrine **17** revealed that the rearrangement reactions can be carried out using azeotropic removal of water but also using heterogeneous desiccants such as 4 Å molecular sieves, $MgSO_4$, or Na_2SO_4. These reagents have no impact on the *dr* or the yield, and allow for the reaction to reach completion within 12 h at 75 ºC. The initial formation of oxazolidine is complete within 2 h whereas the transformation into morpholinone takes an additional 10 h at the same

temperature. Decreasing the reaction temperature to 50 ºC significantly retarded the conversion into **9** (36 h) but without any impact on *dr*. Chlorinated solvents ($CHCl_3$, CH_2Cl_2) and strongly coordinating solvents (DMSO, MeCN) resulted in significantly lower *dr* (3.3-4.1:1) and yields for **18**. The rearrangement reaction with **17** is also scalable and the conversion of **7** into **18** could be accomplished on a gram scale without erosion of the yield and selectivity.

Scheme 2. Scope of arylglyoxal rearrangement.[a]



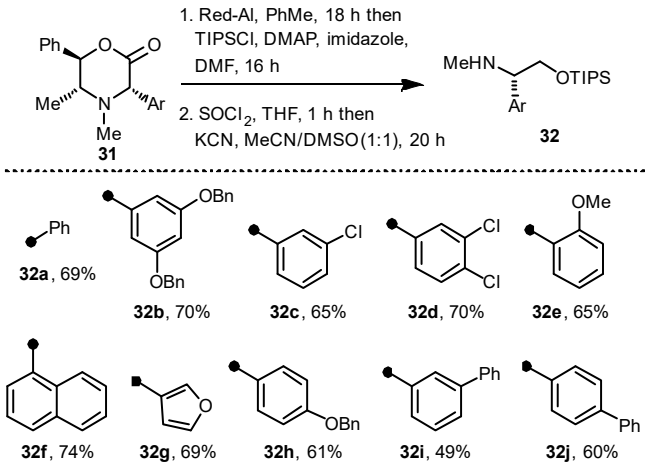
[a]Compounds **31a**,**p**-**r**,**t** were formed as a 9:1 mixture of diasteromers. All other compounds were formed as a 4:1 mixture of diasteroisomers.

With the optimized conditions in hand, we explored the substrate scope (Scheme 2). A series of arylglyoxals was prepared by oxidation of aryl methyl ketones using HBr and DMSO at 60 ºC for 9 h (60-99% yield) and the corresponding hydrates were converted into morpholinones **9**. The rearrangement reaction provides access to morpholinone products for aryl substrates with modifications located at the *ortho*- (**31a-b**), *meta*- (**31c-f**), and *para*- positions (**31g-m**) around the aryl ring. Heteroaromatic groups (**31n**) and polycyclic systems (**31o-s**) were also tolerated and afforded the products in excellent yields (70-97%). As expected, when 1-phenylpropane-1,2-dione was exposed to the optimized conditions, oxazolidine **31t**

was formed as the only product; similar behavior was observed for benzil (PhCOCOPh). Amino alcohol auxiliaries that contain primary amines gave a complex mixture of products. Reactions with 1,2-diamines resulted in the synthesis of dihydropyridines whereas 1,2-amino thiols were unreactive under these conditions.

Following the reaction scope studies, we next investigated methods for the removal of the pseudoephedrine auxiliary (Scheme 3). We initially focused on reactions that could convert the morpholinone group into an amino alcohol. To this end, the lactone was reduced with RedAl® (>98%) and the primary alcohol was protected with a bulky silyl group (TIPSCl or TIPSOTf). In the subsequent steps the removal of the amino alcohol functionality was attempted - direct oxidative cleavage with $NaIO_4$, oxidation of the secondary alcohol to a ketone followed by α-oxidation,[43] or demethylation (NIS)[44] were ineffective in providing the desired chiral vicinal amino alcohol. We eventually found that the conversion of the benzylic alcohol into a chloride with $SOCl_2$ followed by a reaction with KCN (10 equiv) in a 1:1 mixture of acetonitrile and DMSO at room temperature cleanly afforded amino alcohols **32** without erosion of enantiomeric purity (>98% *ee*).[45] Further studies on the generality of this method revealed that a series of aryl substituted 1,2-amino alcohols could be prepared in excellent yields using the major diastereoisomers **31**, including electron-rich (**32a**, **32b**), electron-poor (**32c**, **32d**), heteroaromatic (**32g**) groups, and polycyclic products (**32f**, **32i-j**).

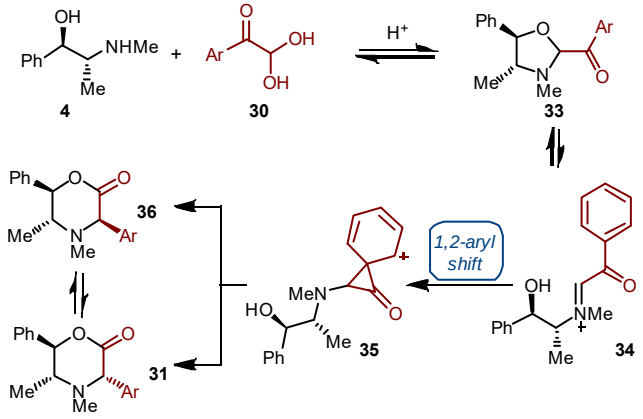
Scheme 3. Removal of pseudoephedrine auxiliary.



To better understand the mechanism of the glyoxal rearrangement and the origin of diastereoselectivity, we performed preliminary mechanistic studies. Firstly, exposure of pure diastereoisomers of **18** to TFA (10 mol%) in PhMe (70 ºC) resulted in equilibration to a 7:1 mixture of **18**, regardless of the configuration of the starting oxazolidine. This observation is consistent with the thermodynamic preference of the product **18** - DFT calculations (B3LYP/6-311++G**//B3LYP/6-31G*, for details, see the SI) revealed that the major product **18** is 2.77 kcal/mol (ΔG_{298}) more stable than the minor diastereoisomer (gas phase). The origin of its increased stability is easy to understand based on the steric argument – all substituents are located in the equatorial positions around the morpholinone ring. Secondly, the migration of the aryl group is correlated with the nature of the substituent attached to the aryl group, and the overall rate of the reaction depends on the shift of the Ar moiety. Electron-donating substituents (OR, aryl) significantly facilitated the rearrangement step (complete in 4 h) from the oxazolidine intermediate whereas deactivating groups such as halogen resulted in ~1.5 times slower transformation at the identical reaction conditions.

Based on the collected data, we propose that the glyoxal rearrangement is initiated by the formation of an acid labile oxazolidine intermediate **33** (typically in 6:1 – 9:1 *dr*) (Scheme 4). An equilibrium is established between the iminium alcohol **34** and **33**, followed by a 1,2-aryl shift through cyclopropanone **35**.[46-52] A collapse of **35** and nucleophilic opening of the strained ring leads to two morpholinones **36** and **31** that channel into the more stable isomer **31**. The configuration of chiral center in **33** and **35** has no bearing on the stereochemical outcome of the morpholinone product as the labile lactone subsequently converts into thermodynamic morpholinone **31**.

Scheme 4. Proposed mechanism of acid-catalyzed rearrangement of arylglyoxals.



CONCLUSIONS

In summary, we have described a practical and scalable synthesis of chiral vicinal amino alcohols via rearrangement of aryl glyoxals into morpholinones. This novel method affords a series of value-added chiral building blocks and represents a prime example of an application of abundant auxiliaries in the synthesis of valuable building blocks. Because of the mildness of the conditions, reaction scope, and generality, this method represents a viable alternative to other approaches that are limited in scope. Future work on the applications of the arylglyoxal rearrangement in target oriented-synthesis and expanding the scope are currently undergoing.

EXPERIMENTAL SECTION

General Procedures

All chemicals were purchased as reagent grade and used without further purification, unless otherwise noted. Solvents were CaH_2 prior to use. All reactions were carried out under dry N_2 in oven-dried glass-ware. TLC analyses were performed on Merck TLC plates and visualizations were performed with UV light and/or the Hanessian stain. Column chromatography was performed on silica gel (230-400 mesh). Melting points were recorded in open capillaries and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz instruments are reported as follows: chemical shift (δ), multiplicity (s = singlet, d =

doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. The residual solvent reference peaks were used from published literature.[1] 2D NMR experiments were performed using standard parameters (*200 and More NMR Experiments,* S. Berger, S. Braun, Wiley-VCH, **2004**). IR measurements were performed on Agilent Cary 630 FT/IR instrument and optical rotations were measured on JASCO P-1030. All HRMS measurements were recorded on a Waters Synapt G2 HDMS instrument with a Quadrupole/ToF mass analyzer.

Rearrangement Protocol for Amino-Alcohols and Phenylglyoxal Hydrate (Protocol A)

A stirring suspension of amino alcohol (1 equiv), phenylglyoxal hydrate (1.05 equiv), $MgSO_4$ (4 equiv), and dry toluene (0.1M) was treated with TFA (0.1 equiv) via microliter syringe. The reaction mixture was placed in an oil bath heated to 75 °C under a constant stream of N_2 for 12 - 72 hr. After cooling to rt, quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried over Na_2SO_4, and concentrated. ^{1}H NMR of the crude mixture was used to determine diastereoselectivity. The residue was purified with column chromatography over SiO_2.

(3R,5S)-4,5-Dibenzyl-3-phenylmorpholin-2-one (11). According to the general protocol A, a suspension of **10** (241 mg, 0.999 mmol), phenylglyoxal hydrate (160 mg, 1.05 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 24 h and afforded **11** (230 mg, 64%, 83:17 *dr*) after chromatographic purification on SiO_2 (2-10% EtOAc/Hex) and recrystallization from EtOAc/Hex.

Major isomer: Colorless shards (230 mg); m.p. = 84.0-85.1 °C; $[\alpha]_D^{25} = -6.03$ (c = 4.62, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3082, 3055, 3032, 2932, 2849, 2818, 1747, 1490, 1447, 1263, 1170, 1133, 1050, 746, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dt, *J* = 8.2, 1.2 Hz, 2H), 7.44 – 7.20 (m, 11H), 7.09 – 7.01 (m, 2H), 4.58 (s, 1H), 4.13 (dd, *J* = 11.8, 4.2 Hz, 1H), 3.93 (dd, *J* = 11.8, 8.5 Hz, 1H), 3.84 (d, *J* = 2.1 Hz, 2H), 3.24 (dddd, *J* = 9.4, 8.5, 5.2, 4.2 Hz, 1H), 2.92 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.68 (dd, *J* = 13.6, 9.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 137.7, 136.6 (2), 129.5, 129.2, 128.9, 128.8, 128.7, 128.2, 127.9,

127.2, 126.9, 67.3, 65.1, 60.6, 60.2, 39.5; FT-HRMS (ESI) *m/z* calc for $C_{24}H_{23}NO_2Na$ $[M+Na]^+$ 380.1621, found 380.1644.

Methyl (3R,5S)-4-benzyl-6-oxo-5-phenyl-morpholine-3-carboxylate (13). According to the general protocol A, a suspension of **12**[53] (210 mg, 1.00 mmol), phenylglyoxal hydrate (163 mg, 1.07 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 °C under N_2 for 24 h and afforded **13** (257 mg, 79%, 87:13 *dr)* after chromatographic purification on SiO_2 (2 - 12% EtOAc/Hex).

Major isomer: yellow oil (227 mg); $[\alpha]_D^{24} =$ -2.71 (c = 5.28, $CHCl_3$); IR (FTIR) ṽ = 3080, 3056, 3030, 3003, 2950, 2920, 2847, 2810, 1756, 1450, 1380, 1204, 1157, 1064, 752, 695cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (ddd, *J* = 8.2, 1.8, 0.9 Hz, 2H), 7.41 – 7.24 (m, 8H), 4.65 (s, 1H), 4.42 (dd, *J* = 11.8, 4.5 Hz, 1H), 4.27 (dd, *J* = 11.8, 8.7 Hz, 1H), 3.95 (s, 2H), 3.83 (dd, *J* = 8.7, 4.5 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.8, 136.8, 136.5, 129.3, 128.8, 128.6, 128.2, 128.0, 127.3, 65.6, 64.6, 60.4, 60.3, 52.6; FT-HRMS (ESI) *m/z* calc for $C_{19}H_{20}NO_4$ $[M+H]^+$ 326.1387, found 326.1393.

Minor isomer: yellow oil (30.0 mg); $[\alpha]_D^{24} =$ +10.5 (c = 3.01, $CHCl_3$); IR (FTIR) ṽ = 3082, 3055, 3022, 2952, 2919, 2853, 1740, 1458, 1392, 1209, 1189, 1159, 1070, 751, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 2H), 7.47 – 7.27 (m, 6H), 7.19 (dd, *J* = 7.5, 2.0 Hz, 2H), 5.13 (s, 1H), 4.71 (dd, *J* = 11.1, 3.3 Hz, 1H), 4.59 (dd, *J* = 11.0, 1.9 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 3.64 (dd, *J* = 3.3, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 168.2, 138.4, 136.7, 129.1, 129.0, 128.8, 128.7, 128.7, 128.0, 69.9, 67.1, 55.3, 54.7, 52.3; FT-HRMS (ESI) *m/z* calc for $C_{19}H_{20}NO_4$ $[M+H]^+$ 326.1387, found 326.1393.

(3S,5R)-4-Benzyl-5-methyl-3-phenyl-morpholin-2-one (15). According to the general protocol A, a suspension of **14** (165 mg, 0.999 mmol), phenylglyoxal hydrate (160 mg, 1.05 mmol), $MgSO_4$ (485 mg, 4.03 mmol), and dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture

was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **15** (236 mg, 84%, 63:37 *dr*) as an inseparable mixture of diastereomers after chromatographic purification on SiO_2 (4-12% EtOAc/Hex).

Yellow oil; (236 mg); $[\alpha]_D^{23}$ = -0.08 (c = 6.25, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3085, 3060, 3025, 2965, 2933, 2896, 2842, 2820, 1741, 1495, 1451, 1259, 1212, 1177, 1066, 1044, 757, 726, 701 cm^{-1}; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{19}NO_2Na$ $[M+Na]^+$ 304.1308, found 304.1318.

Major isomer: ^1H NMR(300 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 2H), 7.48 – 7.21 (m, 8H), 4.57 (s, 1H), 4.15 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.01 (dd, *J* = 11.4, 9.9 Hz, 1H), 3.93 – 3.79 (m, 2H), 3.17 (m, 1H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 138.0, 137.5, 128.9, 128.5, 128.5, 128.3, 127.9, 127.3, 70.7, 65.9, 58.2, 53.2, 17.0.

Minor isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.47 – 7.29 (m, 8H), 4.67 (dd, *J* = 10.6, 3.1 Hz, 1H), 4.51 (s, 1H), 4.24 – 4.18 (m, 1H), 3.64 (d, *J* = 13.4 Hz, 1H), 3.46 (dd, *J* = 13.4, 0.8 Hz, 1H), 3.15 – 3.11 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 138.1, 137.4, 128.6, 128.6, 128.5, 128.4, 128.3, 127.4, 74.0, 66.1, 53.5, 45.7, 7.9.

(3*S*,5*S*,6*R*)-4,5-Dimethyl-3,6-diphenyl-morpholin-2-one (16). According to the general protocol A, a suspension of (1*R*,2*S*)-(-)-ephedrine (165 mg, 0.999 mmol), phenylglyoxal hydrate (165 mg, 1.08 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 °C under N_2 for 12 h and afforded **16** (248 mg, 88%, 61:39 *dr*) after chromatographic purification on SiO_2 (4 - 10% EtOAc/Hex).

Major isomer: yellow oil (138 mg); 90% NMR purity; $[\alpha]_D^{24}$ = +10.6 (c =1.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2977, 2922, 2844, 2792, 1739, 1231, 1140, 1004, 729, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.45 – 7.31 (m, 8H), 6.02 (d, *J* = 2.8 Hz, 1H), 4.24 (s, 1H), 3.40 (qd, *J* = 6.8, 2.8 Hz, 1H), 2.28 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 138.2, 136.9, 128.8 (2),

128.6, 128.5, 128.2, 125.6, 83.7, 66.8, 58.0, 39.9, 3.4; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{19}NO_2Na$ $[M+Na]^+$ 304.1308, found 304.1318.

Minor isomer: pale yellow amorphous solid (110 mg); $[\alpha]_D^{24}$ = -4.76 (c = 5.25, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2877, 2931, 2862, 2793, 2766, 1734, 1454, 1177, 1042, 755, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.32 (m, 10H), 5.50 (d, *J* = 3.5 Hz, 1H), 4.12 (s, 1H), 3.17 (qd, *J* = 6.7, 3.5 Hz, 1H), 2.23 (s, 3H), 1.02 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 137.4, 136.2, 129.2, 128.7, 128.5, 128.4, 128.3, 127.7, 82.0, 71.0, 59.1, 41.2, 15.8; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{19}NO_2Na$ $[M+Na]^+$ 304.1308, found 304.1318.

(3*S*,5*R*,6*R*)-4,5-Dimethyl-3,6-diphenyl-morpholin-2-one (18). According to the general protocol A, a suspension of (1*R*,2*R*)-(-)-pseudoephedrine (1.33 g, 8.04 mmol), phenylglyoxal hydrate (1.22 g, 8.04 mmol), $MgSO_4$ (3.872 g, 32.169 mmol) in dry toluene (75 mL) was treated with TFA (62 µL, 0.804 mmol). The reaction mixture was heated in an oil bath at 75 °C under N_2 for 12 h and afforded **18** (2.16 g, 95%, 86:14 *dr*) after chromatographic purification on SiO_2 (4 - 10% EtOAc/Hex).

Major isomer: off-white amorphous solid (1.89 g); $[\alpha]_D^{23}$ = +8.4 (c = 4.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3057, 3028, 2984, 2917, 2844, 2790, 1744, 1494, 1450, 1234, 1187, 1022, 752, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 2H), 7.38 (tt, *J* = 6.9, 4.8 Hz, 8H), 5.18 (d, *J* = 9.5 Hz, 1H), 4.21 (s, 1H), 2.81 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.27 (s, 3H), 1.02 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 138.5, 137.1, 129.2, 128.8, 128.7, 128.6, 128.4, 127.9, 86.6, 71.7, 60.2, 40.2, 15.6; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{19}NO_2Na$ $[M+Na]^+$ 304.1308, found 304.1313.

Minor isomer: pale yellow oil (0.270 g); $[\alpha]_D^{22}$ = -9.70 (c = 1.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3056, 3032, 2970, 2917, 2848, 2799, 1737, 1451, 1371, 1204, 1152, 1015, 732, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 10H), 5.38 (d, *J* = 5.8 Hz, 1H), 4.49 (s, 1H), 3.39 (dq, *J* = 6.9, 5.9 Hz, 1H), 2.35 (s, 3H), 1.18 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 138.6, 136.4, 128.6, 128.6, 128.5, 128.4,

128.2, 126.5, 84.5, 67.6, 54.3, 38.2, 12.0; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{19}NO_2Na$ $[M+Na]^+$ 304.1308, found 304.1318.

(3S,6S)-4-Benzyl-6-methyl-3-phenylmorpholin-2-one (20). According to the general protocol A, a suspension of **19** (165 mg, 0.999 mmol), phenylglyoxal hydrate (160 mg, 1.05 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 μL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 °C under N_2 for 12 h and afforded **20** (218 mg, 78%, 82:18 *dr*) after chromatographic purification on 25 g Silicycle SiO_2 cartridge (0-40% EtOAc/Hex).

Major isomer: yellow oil (188 mg); $[\alpha]_D^{24} =$ -15.2 (c = 2.94, $CHCl_3$); IR (FTIR) ṽ = 3060, 3027, 2984, 2924, 2809, 1741, 1446, 1286, 1261, 1213, 1164, 1137, 758, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.57 (m, 2H), 7.48 – 7.22 (m, 8H), 4.88 – 4.66 (m, 1H), 4.20 (s, 1H), 3.80 (d, *J* = 13.4 Hz, 1H), 3.14 (d, *J* = 13.4 Hz, 1H), 3.03 (dd, *J* = 12.6, 2.8 Hz, 1H), 2.34 (dd, *J* = 12.6, 10.4 Hz, 1H), 1.32 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 137.8, 136.9, 128.9, 128.8, 128.7, 128.4, 128.4, 127.5, 75.9, 69.7, 58.6, 53.7, 18.9; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{19}NO_2Na$ $[M+Na]^+$ 304.1308, found 304.1318.

Minor isomer: yellow oil (30.0 mg); 93% NMR purity; $[\alpha]_D^{24} =$ +13.4 (c = 3.00, $CHCl_3$); IR (FTIR) ṽ = 3080, 3057, 3028, 2982, 2926, 2847, 2807, 1733, 1490, 1451, 1372, 1198, 1148, 757, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.46 – 7.24 (m, 8H), 4.69 (tt, *J* = 6.5, 3.0 Hz, 1H), 4.27 (s, 1H), 3.76 (d, *J* = 13.4 Hz, 1H), 3.24 (d, *J* = 13.4 Hz, 1H), 2.89 – 2.63 (m, 2H), 1.56 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 137.3, 136.9, 129.0, 128.8, 128.7, 128.6, 128.5, 127.6, 75.0, 69.9, 58.4, 50.9, 20.2; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{19}NO_2Na$ $[M+Na]^+$ 304.1308, found 304.1318.

(3R,5S)-4-Benzyl-5-isopropyl-3-phenylmorpholin-2-one (22). According to the general protocol A, a suspension of **21** (287 mg, 1.48 mmol), phenylglyoxal hydrate (230 mg, 1.51 mmol), $MgSO_4$ (750 mg, 6.23 mmol) in dry toluene (15 mL) was treated with TFA (12 μL, 0.156 mmol). The reaction mixture was

heated in an oil bath at 75 ºC under N_2 for 24 h and afforded **22** (108 mg, 24%, 73:27 *dr*) after chromatographic purification on SiO_2 (4-10% EtOAc/Hex).

Major isomer: yellow oil (108 mg); $[\alpha]_D^{24}$ = -4.10 (c = 2.00, $CHCl_3$); IR (FTIR) ṽ = 3063, 3026, 2957, 2921, 2865, 1752, 1458, 1444, 1154, 1061, 1018, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.34 (qd, *J* = 7.7, 1.5 Hz, 8H), 4.54 (s, 1H), 4.27 (dd, *J* = 11.8, 4.5 Hz, 1H), 3.98 (dd, *J* = 11.9, 9.0 Hz, 1H), 3.90 (d, *J* = 13.5 Hz, 1H), 3.78 (d, *J* = 13.5 Hz, 1H), 2.73 (ddd, *J* = 9.0, 7.8, 4.5 Hz, 1H), 1.78 (dq, *J* = 13.9, 6.9 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 137.5 (2), 129.6, 128.8, 128.7, 128.0, 127.9, 127.1, 66.8, 64.5, 61.5, 31.1, 20.2, 18.8; FT-HRMS (ESI) *m/z* calc for $C_{20}H_{23}NO_2Na$ $[M+Na]^+$ 332.1621, found 332.1648.

(3*R*,5*R*,6S)-4-Benzyl-3,5,6-triphenyl-morpholin-2-one (24). According to the general protocol A, a suspension of (1*S*,2*R*)-*N*-benzyl-2-amino-1,2-diphenylethanol[54] (305 mg, 1.01 mmol), phenylglyoxal hydrate (160 mg, 1.05 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 μL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 °C under N_2 for 12 h and afforded **24** (198 mg, 46%, 60:40 *dr*) after chromatographic purification on SiO_2 (0 - 10% EtOAc/Hex).

Major isomer: white amorphous solid (109 mg); $[\alpha]_D^{23}$ = -5.97 (c = 3.94, $CHCl_3$); IR (FTIR) ṽ = 3085, 3062, 3030, 2917, 2856, 2778, 1739, 1497, 1455, 1206, 1180, 1116, 1051, 1029, 754, 735, 719, 699 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.66 (m, 2H), 7.62 – 7.40 (m, 2H), 7.32 – 7.06 (m, 12H), 6.98 – 6.79 (m, 4H), 5.73 (d, *J* = 3.5 Hz, 1H), 4.98 (s, 1H), 4.40 (d, *J* = 3.5 Hz, 1H), 3.99 (d, *J* = 14.2 Hz, 1H), 3.80 (d, *J* = 14.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 137.7, 136.5, 135.5, 135.1, 129.6, 129.4, 129.0, 128.9, 128.7, 128.3, 128.1, 127.9, 127.7, 127.6, 127.4, 126.8, 79.9, 65.7, 65.4, 57.1; FT-HRMS (ESI) *m/z* calc for $C_{29}H_{26}NO_2$ $[M+H]^+$ 420.1958, found 420.1970.

Minor isomer: white amorphous solid (88 mg); $[\alpha]_D^{23}$ = -5.41 (c = 3.82, $CHCl_3$); IR (FTIR) ṽ = 3029, 2924, 2823, 2345, 2091, 1757, 1696, 1598, 1494, 1451, 1226, 1154, 1076, 1002, 918, 753, 698 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.15 (m, 2H), 7.64 – 7.56 (m, 1H), 7.52 – 7.43 (m, 3H), 7.40 – 7.29 (m, 2H), 7.19 (m, 3H), 7.13 – 7.02 (m, 11H), 7.01 – 6.96 (m, 2H), 5.43 (s, 1H), 5.38 (d, *J* = 7.9 Hz, 1H), 4.43 (d, *J* = 8.0 Hz, 1H), 4.13 (d, *J* = 14.0 Hz, 1H), 3.88 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 138.2, 136.9, 135.9, 135.1, 133.4, 130.2, 129.5, 129.0, 128.7, 128.5, 128.2, 127.8, 127.5, 127.3, 127.3 (2), 93.1, 84.2, 69.9, 53.60; FT-HRMS (ESI) *m/z* calc for $C_{29}H_{25}NO_2Na$ $[M+Na]^+$ 442.1778, found 442.1783.

Methyl (2*R*,3*S*,5*S*)-4-benzyl-2-methyl-6-oxo-5-phenyl-morpholine-3-carboxylate (26). According to the general protocol A, a suspension of **25**[55] (223 mg, 1.01 mmol), phenylglyoxal hydrate (165 mg, 1.08 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 °C under N_2 for 24 h and afforded **26** (327 mg, 96%, 57:43 *dr*) after chromatographic purification on SiO_2 (4 - 16% EtOAc/Hex).

Major isomer: orange oil (186 mg); $[\alpha]_D^{25} =$ -16.6 (c = 3.68, $CHCl_3$); IR (FTIR) ṽ = 3081, 3058, 3031, 2988, 2951, 2928, 2841, 1735, 1455, 1379, 1199, 1165, 1025, 746, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 2H), 7.48 – 7.22 (m, 8H), 5.15 (s, 1H), 4.88 (qd, *J* = 6.5, 1.4 Hz, 1H), 3.80 (m, 4H), 3.66 (dd, *J* = 13.2, 0.9 Hz, 1H), 3.44 (d, *J* = 1.4 Hz, 1H), 1.66 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 168.4, 137.6, 136.8, 128.9, 128.9, 128.7, 128.6, 127.9, 76.0, 66.3, 58.3, 54.7, 52.1, 20.9; FT-HRMS (ESI) *m/z* calc for $C_{20}H_{21}NO_4Na$ $[M+Na]^+$ 362.1363, found 362.1390.

Minor isomer: yellow oil (141 mg); $[\alpha]_D^{25} =$ +8.74 (c = 4.17, $CHCl_3$); IR (FTIR) ṽ = 3080, 3059, 3028, 2980, 2949, 2835, 1740, 1454, 1257, 1202, 1171, 1071, 744, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dt, *J* = 8.3, 1.3 Hz, 2H), 7.41 – 7.22 (m, 8H), 4.70 (s, 1H), 4.47 (dq, *J* = 9.8, 6.2 Hz, 1H), 4.04 – 3.88 (m, 2H), 3.66 (s, 3H), 3.44 (d, *J* = 9.8 Hz, 1H), 1.27 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 169.6, 136.7, 136.2, 129.4, 128.7, 128.5, 128.1, 127.9, 126.8, 73.0, 67.7, 64.5, 61.0, 52.4, 18.1; FT-HRMS (ESI) *m/z* calc for $C_{20}H_{21}NO_4Na$ $[M+Na]^+$ 362.1363, found 362.1390.

(3S,4aS,9aR)-4-Benzyl-3-phenyl-4,4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-2(3H)-one (28). According to the general protocol A, **27**[56] (230 mg, 0.961 mmol), phenylglyoxal hydrate (160 mg, 1.05 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 36 h and afforded **28** (115 mg, 34%, 64:36 *dr*) after chromatographic purification on SiO_2 (4-15% EtOAc/Hex).

Major isomer: yellow oil (115 mg); $[\alpha]_D^{25} = +1.34$ (c = 3.59, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3067, 3033, 2951, 2913, 2849, 1747, 1450, 1378, 1358, 1221, 1170, 1047, 754, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (q, *J* = 3.3, 2.2 Hz, 11H), 7.17 (d, *J* = 4.7 Hz, 1H), 7.02 (d, *J* = 3.7 Hz, 2H), 5.35 (td, *J* = 4.9, 2.8 Hz, 1H), 4.56 (s, 1H), 4.51 (d, *J* = 4.7 Hz, 1H), 4.06 (d, *J* = 13.6 Hz, 1H), 3.88 (d, *J* = 13.6 Hz, 1H), 3.36 (dd, *J* = 16.4, 2.8 Hz, 1H), 3.19 (dd, *J* = 16.4, 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 140.9, 138.4, 137.7, 137.5, 129.3, 129.0, 128.6, 128.3, 128.1, 128.1, 127.7, 126.9, 125.7, 125.1, 80.3, 65.4, 63.4, 59.5, 38.3; FT-HRMS (ESI) *m/z* calc for $C_{24}H_{22}NO_2$ $[M+H]^+$ 356.1645, found 356.1674.

Rearrangement Protocol for (1R,2R)-(-)-pseudoephedrine and Aryl Glyoxal (Protocol B)

A stirring suspension of (1*R*,2*R*)-(-)-pseudoephedrine (1 equiv), aryl glyoxal (1.05 equiv), $MgSO_4$ (4 equiv), and dry toluene (0.1M) was treated with TFA (0.1 equiv) via microliter syringe. The reaction mixture was placed in an oil bath heated to 75 °C under a constant stream of N_2 for 12 - 48 hr. After cooling to rt, quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried over Na_2SO_4, and concentrated. ^1H NMR of the crude mixture was used to determine diastereoselectivity. The residue was purified with column chromatography over SiO_2.

(3S,5R,6R)-3-(2-Bromophenyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31a). According to the general protocol B, a suspension of (1*R*,2*R*)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S1** (280 mg, 1.21 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31a** (342 mg, 95%,

9:1 *dr*) as an inseparable mixture of diasteromers after chromatographic purification on SiO_2 (4% EtOAc/Hex).

Colorless oil; $[\alpha]_D^{24} = +6.79$ (c = 5.51, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2921, 2790, 2338, 2092,1920, 1734, 1468, 1361, 1306, 1214, 1179, 1136, 1023, 940, 745, 670, 565, 522, 448 cm^{-1}; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{18}BrNO_2Na$ $[M + Na]^+$ 382.0413, found 382.0388.

Major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (ddd, *J* = 20.7, 7.9, 1.6 Hz, 2H), 7.44 – 7.30 (m, 6H), 7.27 – 7.16 (m, 1H), 5.31 (d, *J* = 9.4 Hz, 1H), 4.67 (s, 1H), 2.83 (dq, *J* = 9.4, 6.3 Hz, 1H), 2.16 (s, 3H), 1.01 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 138.0, 137.0, 133.3, 131.1, 129.8, 129.1, 128.7, 127.9, 126.3, 125.1, 86.9, 71.0, 60.0, 39.1, 15.1.

Minor isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (ddd, *J* = 23.8, 7.9, 1.6 Hz, 2H), 7.42 – 7.33 (m, 6H), 7.20 (td, *J* = 7.7, 1.8 Hz, 1H), 5.29 (d, *J* = 9.4 Hz, 1H), 4.65 (s, 1H), 2.82 (dq, *J* = 9.4, 6.3 Hz, 1H), 2.16 (s, 3H), 1.02 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 138.1, 137.2, 133.5, 131.1, 129.9, 129.3, 128.8, 128.0, 126.6, 125.4, 87.0, 71.1, 60.3, 39.2, 15.3.

(3S,5R,6R)-3-(2-Methoxyphenyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31b). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S2** (200 mg, 1.10 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 48 h and afforded **31b** (237 mg, 76%, 4:1 *dr*) after chromatographic purification on SiO_2 (5-20% EtOAc/Hex).

Major isomer: yellow oil (178 mg); $[\alpha]_D^{25} = +6.92$ (c = 3.71, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3060, 3024, 3001, 2926, 2847, 2778, 1729, 1595, 1491, 1458, 1357, 1236, 1190, 1046, 1027, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 2.1 Hz, 5H), 7.36 – 7.30 (m, 2H), 6.98 (dd, *J* = 7.8, 6.9 Hz, 2H), 5.30 (d, *J* = 9.2 Hz, 1H), 4.21 (s, 1H), 3.88 (s, 3H), 2.73 (dq, *J* = 9.2, 6.4 Hz, 1H), 2.22 (s, 3H), 0.97 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 157.2, 137.3, 131.6, 129.7, 128.9, 128.6, 127.8, 127.4, 120.7, 112.2,

86.3, 68.0, 60.2, 55.9, 39.2, 15.1; FT-HRMS (ESI) *m/z* calc for $C_{19}H_{21}NO_3Na$ $[M + Na]^+$ 334.1414, found 334.1403.

Minor isomer: yellow oil (59.0 mg); $[\alpha]_D^{24} =$ -1.20 (c = 27.0, $CHCl_3$); IR (FTIR) ṽ = 3064, 3025, 2965, 2926, 2850, 2794, 1740, 1591, 1489, 1463, 1248, 1192, 1033, 766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.35 (m, 5H), 7.33 – 7.20 (m, 2H), 6.98 – 6.88 (m, 2H), 5.32 (d, *J* = 5.6 Hz, 1H), 4.90 (s, 1H), 3.78 (s, 3H), 3.50 (qd, *J* = 6.7, 5.6 Hz, 1H), 2.28 (s, 3H), 1.17 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 157.9, 138.8, 130.5, 129.6, 128.6, 128.5, 127.1, 125.7, 120.7, 111.7, 84.8, 61.7, 55.9, 54.3, 38.2, 12.3; FT-HRMS (ESI) *m/z* calc for $C_{19}H_{21}NO_3Na$ $[M + Na]^+$ 334.1414, found 334.1403.

(3S,5R,6R)-3-(3-Methoxyphenyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31c). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S3** (200 mg, 1.10 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31c** (236 mg, 76%, 4:1 *dr*) after chromatographic purification on SiO_2 (4-12% EtOAc/Hex).

Major isomer: off-white amorphous solid (236 mg); $[\alpha]_D^{23} =$ +6.40 (c = 8.50, $CHCl_3$); IR (FTIR) ṽ = 3063, 3028, 2989, 2931, 2841, 2783, 1740, 1598, 1485, 1456, 1314, 1269, 1233, 1175, 1026, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 6H), 7.14 (dd, *J* = 7.5, 1.5 Hz, 2H), 6.89 (ddd, *J* = 8.2, 2.4, 1.2 Hz, 1H), 5.16 (d, *J* = 9.5 Hz, 1H), 4.19 (s, 1H), 3.83 (s, 3H), 2.80 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.27 (s, 3H), 1.01 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 159.7, 139.8, 136.8, 129.6, 128.9, 128.5, 127.6, 120.7, 113.9, 113.5, 86.2, 71.4, 60.0, 55.1, 40.1, 15.4; FT-HRMS (ESI) *m/z* calc for $C_{19}H_{21}NO_3Na$ $[M + Na]^+$ 334.1414, found 334.1403.

(3S,5R,6R)-4,5-Dimethyl-6-phenyl-3-(3-phenylphenyl)morpholin-2-one (31d). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S4** (300 mg, 1.04 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol).

The reaction mixture was heated in an oil bath at 75 °C under N_2 for 12 h and afforded **31d** (295 mg, 83%, 4:1 *dr*) after chromatographic purification on SiO_2 (4-15% EtOAc/Hex).

Major isomer: off-white foam (229 mg); $[\alpha]_D^{25} = +9.00$ (c = 10.5, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3060, 3030, 2987, 2918, 2852, 2793, 1731, 1474, 1454, 1279, 1230, 1184, 1035, 752, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (t, *J* = 1.8 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.60 (ddt, *J* = 11.1, 7.7, 1.6 Hz, 2H), 7.54 – 7.46 (m, 3H), 7.44 – 7.34 (m, 6H), 5.24 (d, *J* = 9.5 Hz, 1H), 4.30 (s, 1H), 2.86 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.31 (s, 3H), 1.05 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 141.7, 141.0, 139.0, 137.0, 129.2, 129.1, 128.8, 128.7, 127.8, 127.6, 127.5, 127.3 (2), 127.2, 86.6, 71.8, 60.2, 40.2, 15.5; FT-HRMS (ESI) *m/z* calc for $C_{24}H_{23}NO_2Na$ $[M + Na]^+$ 380.1621, found 380.1644.

Minor isomer: yellow oil (66 mg); $[\alpha]_D^{25} = -6.40$ (c = 31.0, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3062, 3028, 2968, 2921, 2849, 2792, 1736, 1479, 1450, 1372, 1193, 1152, 1017, 753, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (q, *J* = 1.3 Hz, 1H), 7.60 – 7.53 (m, 3H), 7.48 – 7.34 (m, 10H), 5.43 (d, *J* = 5.2 Hz, 1H), 4.53 (s, 1H), 3.48 (qd, *J* = 6.7, 5.1 Hz, 1H), 2.37 (s, 3H), 1.25 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 141.5, 140.8, 138.9, 137.1, 129.0, 128.8, 128.6, 128.3, 127.7, 127.5, 127.2, 127.2, 126.9, 126.5, 84.5, 67.5, 54.5, 38.5, 11.7; FT-HRMS (ESI) *m/z* calc for $C_{24}H_{23}NO_2Na$ $[M + Na]^+$ 380.1621, found 380.1644.

(3S,5R,6R)-3-(3-Chlorophenyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31e). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S5** (190 mg, 1.02 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 °C under N_2 for 12 h and afforded **31e** (305 mg, 97%, 4:1 *dr*) after chromatographic purification on SiO_2 (6% EtOAc/Hex).

Major isomer: colorless oil (260 mg); $[\alpha]_D^{24} = +3.80$ (c = 20.5, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3062, 3031, 2987, 2915, 2852, 2792, 1739, 1595, 1576, 1469, 1453, 1296, 1277, 1233, 1183, 1083, 1035, 762, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.54 (m, 1H), 7.47 – 7.30 (m, 8H), 5.16 (d, *J* = 9.5 Hz, 1H), 4.18 (s,

1H), 2.81 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.25 (s, 3H), 1.01 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 140.5, 136.8, 134.7, 130.0, 129.3, 128.8, 128.6, 128.5, 127.9, 127.0, 86.7, 71.1, 60.0, 40.2, 15.5; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{18}ClNO_2Na$ $[M + Na]^+$ 338.0918, found 338.0930.

Minor isomer: colorless oil (45.0 mg); $[\alpha]_D^{24} = -5.60$ (c = 20.0, $CHCl_3$); IR (FTIR) ṽ = 3066, 3028, 2970, 2918, 2845, 2793, 1737, 1595, 1576, 1473, 1454, 1367, 1204, 1146, 1072, 1027, 992, 773, 741, 690 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.46 – 7.33 (m, 4H), 7.27 (m, 5H), 5.40 (d, *J* = 5.1 Hz, 1H), 4.40 (s, 1H), 3.39 (qd, *J* = 6.8, 5.1 Hz, 1H), 2.32 (s, 3H), 1.23 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 138.7, 138.7, 134.6, 129.9, 128.7, 128.6, 128.5, 126.8, 126.3, 84.4, 67.0, 54.8, 38.5, 11.8; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{18}ClNO_2Na$ $[M + Na]^+$ 338.0918, found 338.0930.

(3*S*,5*R*,6*R*)-3-(3,5-Dibenzyloxyphenyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31f). According to the general protocol B, a suspension (1*R*,2*R*)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S6** (380 mg, 1.04 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 μL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 24 h and afforded **31f** (446 mg, 90%, 4:1 *dr*) after chromatographic purification on SiO_2 (4-15% EtOAc/Hex).

Major isomer: pale yellow foam (372 mg); $[\alpha]_D^{23} = +4.00$ (c = 7.50, $CHCl_3$); IR (FTIR) ṽ = 3057, 3032, 2978, 2920, 2869, 2782, 1736, 1589, 1461, 1375, 1295, 1234, 1186, 1160, 1055, 1023, 834, 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.29 (m, 15H), 6.90 – 6.83 (m, 2H), 6.61 (t, *J* = 2.3 Hz, 1H), 5.11 (d, *J* = 9.5 Hz, 1H), 5.06 (d, *J* = 1.4 Hz, 4H), 4.16 (s, 1H), 2.78 (dq, *J* = 9.6, 6.3 Hz, 1H), 2.29 (s, 3H), 0.98 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 160.3, 140.8, 137.0, 136.9, 129.2, 128.7, 128.2, 127.9, 127.8, 107.7, 101.9, 86.3, 71.5, 70.3, 60.3, 40.6, 15.7; FT-HRMS (ESI) *m/z* calc for $C_{32}H_{31}NO_4Na$ $[M + Na]^+$ 516.2145, found 516.2173.

Minor isomer: orange oil (74.0 mg); $[\alpha]_D^{23} = -4.70$ (c = 18.0, $CHCl_3$); IR (FTIR) ṽ = 2961, 2922, 2868, 2847, 2796, 1734, 1593, 1452, 1380, 1347, 1284, 1209, 1158, 1053, 1029, 846, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 15H), 6.66 (d, *J* = 2.3 Hz, 2H), 6.56 (t, *J* = 2.3 Hz, 1H), 5.39 (d, J = 5.0

Hz, 1H), 4.93 (s, 4H), 4.35 (s, 1H), 3.45 (qd, *J* = 6.7, 5.0 Hz, 1H), 2.29 (s, 3H), 1.23 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 160.1, 139.1, 139.0, 136.9, 128.7, 128.3, 128.1, 127.7, 126.5, 107.5, 102.4, 84.3, 70.1, 67.5, 54.5, 38.4, 11.7; FT-HRMS (ESI) *m/z* calc for $C_{32}H_{31}NO_4Na$ $[M + Na]^+$ 516.2145, found 516.2173.

(3S,5R,6R)-3-(4-Fluorophenyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31g). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S7** (170 mg, 0.999 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 μL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31g** (290 mg, 97%, 4:1 *dr*) after chromatographic purification on SiO_2 (2-10% EtOAc/Hex).

Major isomer: off-white amorphous solid (239 mg); $[\alpha]_D^{22} = +10.8$ (c = 6.5, $CHCl_3$); IR (FTIR) ṽ = 2986, 2921, 2853, 2791, 2110, 1738, 1603, 1508, 1455, 1220, 1181, 1031, 828, 768, 700, 525, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.43 – 7.31 (m, 5H), 7.08 (t, *J* = 8.7 Hz, 2H), 5.18 (d, *J* = 9.5 Hz, 1H), 4.18 (s, 1H), 2.81 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.22 (s, 3H), 1.00 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (2), 164.2, 160.9, 136.9, 134.2 (2), 130.2 (2), 129.1, 128.2 (2), 115.5 (2), 86.6, 70.9, 59.9, 39.9, 15.3; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{18}FNO_2Na$ $[M + Na]^+$ 322.1214, found 322.1219.

Minor isomer: yellow oil (51.0 mg); $[\alpha]_D^{22} = -2.90$ (c = 35.0, $CHCl_3$); IR (FTIR) ṽ = 2923, 2853, 2796, 2359, 2103, 1734, 1601, 1505, 1452, 1199, 1152, 1013, 828, 730, 698, 529 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.26 (m, 7H), 7.01 (t, *J* = 8.7 Hz, 2H), 5.38 (d, *J* = 5.2 Hz, 1H), 4.42 (s, 1H), 3.39 (qd, *J* = 6.7, 5.2 Hz, 1H), 2.32 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 164.3, 161.0, 138.8, 132.3 (2), 130.2 (2), 128.4, 127.5(2), 115.5(2), 84.4, 66.7, 54.7, 38.4, 11.8; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{18}FNO_2Na$ $[M + Na]^+$ 322.1214, found 322.1241.

(3S,5R,6R)-3-(3,4-Dichlorophenyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31h). According to the general protocol B, a suspension of (1*R*,2*R*)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S8** (230 mg,

1.04 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31h** (334 mg, 95%, 4:1 *dr*) after chromatographic purification on SiO_2 (2-10% EtOAc/Hex).

Major isomer: yellow oil (272 mg); $[\alpha]_D^{24} = +14.3$ (c = 7.00, $CHCl_3$); IR (FTIR) ṽ = 3065, 3026, 2982, 2925, 2645, 2791, 1740, 1473, 1375, 1298, 1282, 1238, 1178, 1136, 1035, 761, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.9 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.41 – 7.31 (m, 5H), 5.16 (d, *J* = 9.5 Hz, 1H), 4.16 (s, 1H), 2.81 (dq, *J* = 9.4, 6.3 Hz, 1H), 2.21 (s, 3H), 1.00 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 138.7, 136.6, 132.7, 132.3, 130.6, 130.3, 129.2, 128.7, 128.1, 127.7, 86.6, 70.4, 59.7, 40.0, 15.3; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{17}Cl_2NO_2Na$ $[M + Na]^+$ 372.0529, found 372.0560.

Minor isomer: yellow oil (62.0 mg); $[\alpha]_D^{24} = -6.30$ (c = 28.5, $CHCl_3$); IR (FTIR) ṽ = 3086, 3064, 3031, 2973, 2924, 2850, 2798, 1735, 1466, 1371, 1206, 1154, 1031, 755, 697 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 7.48 – 7.33 (m, 5H), 7.30 – 7.18 (m, 3H), 5.41 (d, *J* = 4.7 Hz, 1H), 4.35 (s, 1H), 3.40 (qd, *J* = 6.8, 4.7 Hz, 1H), 2.30 (s, 3H), 1.25 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 138.7, 136.9, 132.8, 132.3, 130.5, 130.4, 128.7, 128.5, 127.9, 126.1, 84.2, 66.2, 55.0, 38.6, 11.5; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{17}Cl_2NO_2Na$ $[M + Na]^+$ 372.0529, found 372.0560.

(3S,5R,6R)-3-(4-Bromophenyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31i). According to the general protocol B, a suspension of (1*R*,2*R*)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S9** (300 mg, 1.08 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31i** (309 mg, 76%, 4:1 *dr*) after chromatographic purification on SiO_2 (0-8% EtOAc/Hex).

Major isomer: pale yellow amorphous solid (239 mg); $[\alpha]_D^{22} = +7.60$ (c = 6.50, $CHCl_3$); IR (FTIR) ṽ = 2984, 2921, 2851, 2789, 1739, 1586, 1481, 1234, 1181, 1030, 768, 700, 517 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.69 (m, 2H), 7.44 – 7.28 (m, 7H), 5.14 (d, *J* = 9.5 Hz, 1H), 4.14 (s, 1H), 2.80 (dq, *J* = 9.4, 6.3 Hz, 1H), 2.24 (s, 3H), 1.01 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 138.2, 138.,

136.9, 130.5, 129.3, 128.8, 127.9, 94.2, 86.7, 71.2, 60.2, 40.3, 15.6; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{18}INO_2Na$ $[M + Na]^+$ 430.0274, found 430.0254.

Minor isomer: yellow oil (70.0 mg); $[\alpha]_D^{22} =$ -5.90 (c = 35.0, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2922, 2852, 2795, 2292, 1733, 1583, 1452, 1200, 1059, 1004, 751, 696, 511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.42 – 7.33 (m, 3H), 7.27 (dd, *J* = 5.7, 2.2 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 5.38 (d, *J* = 5.2 Hz, 1H), 4.38 (s, 1H), 3.43 – 3.32 (m, 1H), 2.32 (s, 3H), 1.21 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 138.7, 137.7, 136.4, 130.5, 128.7, 128.5, 126.3, 94.0, 84.3, 67.0, 54.7, 38.4, 11.78 ; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{18}INO_2Na$ $[M + Na]^+$ 430.2407, found 430.0254.

(3S,5R,6R)-3-(4-Benzyloxyphenyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31j). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S10** (260 mg, 1.01 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 24 h and afforded **31j** (366 mg, 94%, 4:1 *dr*) after chromatographic purification on SiO_2 (2-10% EtOAc/Hex). The major isomer was crystalized by slow evaporation from EtOAc/Hex for X-ray analysis.

Major isomer: amorphous off-white solid (319 mg); m.p. 136.1-138.2°C; $[\alpha]_D^{22} =$ +5.70 (c = 5.50, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3033, 2923, 2790, 2360, 1739, 1607, 1509, 1454, 1380, 1235, 1176, 1028, 824, 699, 609, 413 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.31 (m, 11H), 7.03 (d, *J* = 8.7 Hz, 2H), 5.19 (d, *J* = 9.5 Hz, 1H), 5.09 (s, 2H), 4.16 (s, 1H), 2.81 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.26 (s, 3H), 1.02 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 158.8, 137.1, 137.0, 130.8, 129.7, 129.1, 128.6, 128.0, 127.8, 127.6, 115.1, 86.6, 71.1, 70.1, 60.2, 40.0, 15.5; FT-HRMS (ESI) *m/z* calc for $C_{25}H_{26}NO_3$ $[M + H]^+$ 388.1907, found 388.1882.

Minor isomer: yellow oil (47.0 mg); $[\alpha]_D^{22} =$ -4.60 (c = 22.5, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3032, 2923, 2793, 2331, 1734, 1604, 1508, 1453, 1375, 1202, 1170, 1020, 827, 736, 698, 536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.29 (m, 12H), 6.96 (d, *J* = 8.7 Hz, 2H), 5.36 (d, *J* = 5.8 Hz, 1H), 5.07 (s, 2H), 4.44 (s,

1H), 3.39 (p, *J* = 6.6 Hz, 1H), 2.34 (s, 3H), 1.18 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 158.8, 138.8, 137.0, 129.7, 128.7, 128.6, 128.4, 128.1, 127.6, 126.6, 114.9, 84.6, 70.1, 67.0, 54.3, 38.2, 12.1; FT-HRMS (ESI) *m/z* calc for $C_{25}H_{26}NO_3$ $[M + H]^+$ 388.1907, found 388.1882.

(3S,5R,6R)-4,5-Dimethyl-6-phenyl-3-(4-phenylphenyl)morpholin-2-one (31k). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S11** (250 mg, 1.10 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 μL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31k** (325 mg, 91%, 4:1 *dr*) after chromatographic purification on SiO_2 (4-8% EtOAc/Hex).

Major isomer: pale yellow amorphous solid (259 mg); $[\alpha]_D^{23} = +5.30$ (c = 8.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3056, 3026, 2974, 2919, 2842, 2778, 1734, 1231, 1179, 1035, 944, 833, 754, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 6H), 7.49 – 7.34 (m, 8H), 5.21 (d, *J* = 9.5 Hz, 1H), 4.25 (s, 1H), 2.83 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.31 (s, 3H), 1.04 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 141.4, 140.9, 137.5, 137.1, 129.3, 129.0, 128.9, 128.8, 127.9, 127.7, 127.5, 127.3, 86.7, 71.6, 60.3, 40.3, 15.6; FT-HRMS (ESI) *m/z* calc for $C_{24}H_{23}NO_2Na$ $[M + Na]^+$ 380.1621, found 380.1644.

Minor isomer: yellow oil (66.0 mg); $[\alpha]_D^{23} = -9.00$ (c = 31.0, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3058, 3029, 2967, 2924, 2853, 2797, 1741, 1487, 1449, 1371, 1205, 1156, 1016, 762, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.7, 5.1 Hz, 4H), 7.52 – 7.32 (m, 10H), 5.41 (d, *J* = 5.6 Hz, 1H), 4.54 (s, 1H), 3.44 (p, *J* = 6.5 Hz, 1H), 2.40 (s, 3H), 1.23 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 141.1, 140.7, 138.7, 135.5, 129.0, 128.9, 128.6, 128.4, 127.5, 127.4, 127.2, 126.5, 84.6, 67.4, 54.4, 38.3, 12.0; FT-HRMS (ESI) *m/z* calc for $C_{24}H_{23}NO_2Na$ $[M + Na]^+$ 380.1621, found 380.1644.

(3S,5R,6R)-3-(4-Isopropylphenyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31l). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S12** (200 mg, 1.03 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 μL, 0.104

mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31l** (301 mg, 93%, 80:20 *dr*) after chromatographic purification on SiO_2 (2-12% EtOAc/Hex).

Major isomer: yellow oil (241 mg); $[\alpha]_D^{24} = +6.91$ (c = 3.71, $CHCl_3$); IR (FTIR) ṽ = 3086, 3055, 3024, 2959, 2922, 2870, 2792, 1734, 1457, 1385, 1361, 1303, 1176, 1026, 817, 772, 748, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.34 (m, 5H), 7.28 (s, 1H), 7.25 (s, 1H), 4.18 (s, 1H), 2.94 (hept, *J* = 7.1 Hz, 1H), 2.80 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.26 (s, 3H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.01 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 148.9, 137.1, 135.8, 129.1, 128.7, 128.4, 127.9, 126.9, 86.5, 71.5, 60.2, 40.1, 33.9, 24.1, 24.0, 15.6; FT-HRMS (ESI) *m/z* calc for $C_{21}H_{26}NO_2$ $[M + H]^+$ 324.1958, found 324.1954.

Minor isomer: yellow oil (60.0 mg); $[\alpha]_D^{24} = -2.80$ (c = 22.0, $CHCl_3$); IR (FTIR) ṽ = 3084, 3053, 3034, 2960, 2925, 2879, 2795, 1735, 1455, 1371, 1269, 1204, 1176, 1145, 1011, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 7H), 7.20 (d, *J* = 8.2 Hz, 2H), 5.36 (d, *J* = 5.9 Hz, 1H), 4.46 (s, 1H), 3.44 – 3.32 (m, 1H), 2.90 (hept, *J* = 6.9 Hz, 1H), 2.35 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 6H), 1.17 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 148.9, 138.7, 133.7, 128.6, 128.5, 128.5, 126.7, 126.7, 84.7, 67.5, 54.2, 38.3, 33.9, 24.1, 12.2; FT-HRMS (ESI) *m/z* calc for $C_{21}H_{26}NO_2$ $[M + H]^+$ 324.1958, found 324.1954.

(3S,5R,6R)-4,5-Dimethyl-6-phenyl-3-(2,4,5-trifluorophenyl)morpholin-2-one (31m). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S13** (210 mg, 1.02 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 μL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31m** (326 mg, 97%, 4:1 *dr*) after chromatographic purification on SiO_2 (4-8% EtOAc/Hex).

Major isomer: yellow oil (272 mg); $[\alpha]_D^{25} = +18.3$ (c = 3.71, $CHCl_3$); IR (FTIR) ṽ = 3071, 3024, 2984, 2926, 2842, 2798, 1957, 1888, 1728, 1626, 1502, 1448, 1426, 1018, 876, 836, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 6H), 6.99 (ddd, *J* = 10.0, 9.2, 6.5 Hz, 1H), 5.21 (d, *J* = 9.4 Hz, 1H), 4.40 (s, 1H), 2.80 (dq, *J* = 9.4, 6.3 Hz, 1H), 2.18 (s, 3H), 1.00 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 167.3 (2), 158.1 (4), 154.8 (4), 151.6 (4), 149.2 – 147.4 (m), 145.3 (4), 136.7, 129.3, 128.7, 127.8, 122.5 (6), 118.7 – 117.2 (m), 106.0 (4), 87.0, 64.7, 59.8, 39.4, 15.1; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{16}F_3NO_2Na$ $[M + Na]^+$ 358.1025, found 358.0974.

Minor isomer: yellow oil (54.0 mg); $[\alpha]_D^{25} =$ -6.60 (c = 24.5, $CHCl_3$); IR (FTIR) ṽ = 3057, 3027, 2972, 2927, 2855, 2800, 1746, 1625, 1522, 1466, 1428, 1369, 1340, 1275, 1204, 1191, 1155, 1006, 876, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.31 (m, 5H), 7.04 – 6.87 (m, 2H), 5.40 (s, 1H), 4.69 (d, *J* = 1.0 Hz, 1H), 3.47 (qd, *J* = 6.7, 3.7 Hz, 1H), 2.19 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 167.7, 158.4 (2), 155.1 (2), 152.5 – 151.0 (m), 149.1 – 147.8 (m), 145.3 (4), 138.9, 128.8, 128.5, 126.1, 120.9 (6), 117.5 (6), 106.0 (4), 84.6, 59.5, 55.7, 39.0, 10.9; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{16}F_3NO_2Na$ $[M + Na]^+$ 358.1025, found 358.1056.

(3S,5R,6R)-3-(3-Furyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31n). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (115 mg, 0.700 mmol), **S14** (100 mg, 0.703 mmol), $MgSO_4$ (300 mg, 2.49 mmol) in dry toluene (6 mL) was treated with TFA (5 µL, 0.0649 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 36 h and afforded **31n** (79 mg, 52%, 4:1 *dr*) after chromatographic purification on SiO_2 (4-12% EtOAc/Hex).

Major isomer: off-white amorphous solid (57 mg); $[\alpha]_D^{22} =$ +2.40 (c = 5.50, $CHCl_3$); IR (FTIR) ṽ = 2982, 2922, 2852, 2788, 1736, 1500, 1454, 1136, 1027, 933, 873, 766, 700, 600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.57 (m, 1H), 7.44 (t, *J* = 1.8 Hz, 1H), 7.40 – 7.29 (m, 5H), 6.51 (d, *J* = 1.1 Hz, 1H), 5.12 (d, *J* = 9.5 Hz, 1H), 4.21 (s, 1H), 2.75 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.33 (s, 3H), 0.98 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 143.7, 141.8, 137.0, 129.2, 128.7, 127.8, 123.1, 109.8, 86.3, 63.4, 60.4, 40.2, 15.7; FT-HRMS (ESI) *m/z* calc for $C_{16}H_{17}NO_3Na$ $[M + Na]^+$ 294.1101, found 294.1082.

Minor isomer: pale yellow solid (22.0 mg); $[\alpha]_D^{22} =$ -3.00 (c = 4.00, $CHCl_3$); IR (FTIR) ṽ = 2964, 2923, 2852, 2794, 1741, 1673, 1507, 1455, 1158, 1073, 933, 700, 600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51

– 7.49 (m, 1H), 7.43 (t, *J* = 1.7 Hz, 1H), 7.38 – 7.33 (m, 3H), 7.26 (dd, *J* = 5.4, 2.4 Hz, 2H), 6.45 (d, *J* = 1.1 Hz, 1H), 5.27 (d, *J* = 8.0 Hz, 1H), 4.54 (s, 1H), 3.26 (dt, *J* = 7.8, 6.6 Hz, 1H), 2.43 (s, 3H), 1.07 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 143.5, 141.5, 137.9, 128.8, 128.7, 127.0, 120.9, 110.5, 85.0, 60.5, 54.1, 37.7, 13.5; FT-HRMS (ESI) *m/z* calc for $C_{16}H_{17}NO_3Na$ $[M + Na]^+$ 294.1101, found 294.1082.

(3S,5R,6R)-4,5-Dimethyl-3-(1-naphthyl)-6-phenyl-morpholin-2-one (31o). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S15** (220 mg, 1.09 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31o** (232 mg, 70%, 84:16 *dr*) after chromatographic purification on SiO_2 (2-10% EtOAc/Hex).

Major isomer: orange foam (232 mg); $[\alpha]_D^{23} = +11.5$ (c = 5.00, $CHCl_3$); IR (FTIR) ṽ = 3066, 3034, 2979, 2929, 2853, 2785, 1736, 1269, 1226, 1180, 1123, 1026, 777, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 – 8.35 (m, 1H), 7.91 – 7.85 (m, 2H), 7.67 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.61 – 7.39 (m, 8H), 5.45 (d, *J* = 9.5 Hz, 1H), 4.66 (s, 1H), 2.86 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.14 (s, 3H), 1.09 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 137.4, 134.5, 134.0, 131.5, 129.5, 129.3, 129.0, 128.9, 128.8, 128.0, 126.4, 126.0, 125.3, 124.6, 87.3, 71.4, 61.0, 39.6, 15.4; FT-HRMS (ESI) *m/z* calc for $C_{22}H_{21}NO_2Na$ $[M + Na]^+$ 354.1465, found 354.1441.

(3S,5R,6R)-4,5-Dimethyl-3-(2-naphthyl)-6-phenyl-morpholin-2-one (31p). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S16** (250 mg, 1.10 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31p** (314 mg, 95%, 82:18 *dr*) after chromatographic purification on SiO_2 (2-8% EtOAc/Hex).

Major isomer: pale yellow amorphous solid (255 mg); $[\alpha]_D^{22} = +16.5$ (c = 7.50, $CHCl_3$); IR (FTIR) ṽ = 2982, 2922, 2852, 2787, 2339, 1736, 1454, 1271, 1179, 1031, 817, 762, 700, 479 cm^{-1}; ^{1}H NMR (300

MHz, $CDCl_3$) δ 8.05 (d, *J* = 1.7 Hz, 1H), 7.97 – 7.84 (m, 3H), 7.72 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.41 (s, 5H), 5.28 (d, *J* = 9.5 Hz, 1H), 4.39 (s, 1H), 2.88 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.30 (s, 3H), 1.06 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 137.0, 135.9, 133.4 (2), 129.1, 128.7 (2), 128.1, 127.8 (2), 126.3 (2), 125.9, 86.6, 71.9, 60.2, 40.2, 15.5; FT-HRMS (ESI) *m/z* calc for $C_{22}H_{21}NO_2Na$ $[M + Na]^+$ 354.1465, found 354.1441.

Minor isomer: green oil (59.0 mg); $[\alpha]_D^{22}$ = -7.90 (c = 27.5, $CHCl_3$); IR (FTIR) ṽ = 3057, 2923, 2853, 2796, 2359, 1736, 1453, 1370, 1202, 1152, 1019, 747, 699, 634, 479 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.73 (m, 5H), 7.52 (ddd, *J* = 13.2, 7.4, 2.5 Hz, 3H), 7.43 – 7.30 (m, 5H), 5.44 (d, *J* = 5.6 Hz, 1H), 4.64 (s, 1H), 3.47 (q, *J* = 6.4 Hz, 1H), 2.41 (s, 3H), 1.23 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 138.8, 134.1, 133.3 (2), 128.6, 128.5 (2), 128.2, 127.7 (2), 126.6, 126.3 (2), 126.2, 84.5, 67.8, 54.4, 38.4, 12.0; FT-HRMS (ESI) *m/z* calc for $C_{22}H_{21}NO_2Na$ $[M + Na]^+$ 354.1465, found 354.1441.

(3S,5R,6R)-3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31q). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S17** (215 mg, 1.02 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31q** (231 mg, 68%, 9:1 *dr*) after chromatographic purification on SiO_2 (4-15% EtOAc/Hex).

Major isomer: yellow oil (231 mg); $[\alpha]_D^{25}$ = +11.4 (c = 7.00, $CHCl_3$); IR (FTIR) ṽ = 3059, 3034, 2983, 2927, 2879, 2787, 1736, 1508, 1287, 1189, 1062, 1037, 771, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (q, *J* = 4.5, 3.4 Hz, 4H), 7.09 (d, *J* = 2.1 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.15 (d, *J* = 9.5 Hz, 1H), 4.21 (s, 4H), 4.08 (s, 1H), 2.77 (dq, *J* = 9.4, 6.3 Hz, 1H), 2.23 (s, 3H), 0.98 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 143.5, 136.9, 131.5, 129.0, 128.5, 127.7, 121.4, 117.3, 117.2, 86.4, 70.9, 64.2 (2), 59.9, 39.9, 15.4; FT-HRMS (ESI) *m/z* calc for $C_{20}H_{21}NO_4Na$ $[M + Na]^+$ 362.1363, found 362.1390.

(3S,5R,6R)-4,5-Dimethyl-6-phenyl-3-tetralin-6-yl-morpholin-2-one (31r). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S18** (220 mg, 1.07 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31r** (345 mg, 97%, 9:1 *dr*) after chromatographic purification on SiO_2 (2-10% EtOAc/Hex).

Major isomer: orange oil (304 mg); $[\alpha]_D^{25} = +6.34$ (c = 3.78, $CHCl_3$); IR (FTIR) ṽ = 3068, 3007, 2942, 2856, 2778, 2660, 2443, 2398, 1949, 1887, 1740, 1495, 1454, 1364, 1225, 1025, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, *J* = 3.0 Hz, 5H), 7.26 (td, *J* = 7.2, 6.5, 1.9 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 5.21 (d, *J* = 9.4 Hz, 1H), 4.13 (s, 1H), 2.86 – 2.74 (m, 5H), 2.27 (s, 3H), 1.83 (dq, *J* = 6.7, 3.0 Hz, 4H), 1.03 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 137.5, 137.3, 137.1, 135.4, 129.5, 129.1, 129.0, 128.6, 127.8, 125.6, 86.5, 71.7, 60.2, 40.0, 29.5, 29.2, 23.2 (2), 15.5; FT-HRMS (ESI) *m/z* calc for $C_{22}H_{25}NO_2Na$ $[M + Na]^+$ 358.1778, found 358.1800.

Minor isomer: yellow oil (41.0 mg); $[\alpha]_D^{24} =$ -4.30 (c = 10.0, $CHCl_3$); IR (FTIR) ṽ = 3060, 3029, 2928, 2855, 2794, 1733, 1714, 1363, 1272, 1205, 1162, 1016, 765, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H), 7.15 – 6.97 (m, 3H), 5.35 (d, *J* = 5.8 Hz, 1H), 4.41 (s, 1H), 3.44 – 3.35 (m, 1H), 2.74 (d, *J* = 6.0 Hz, 4H), 2.35 (s, 3H), 1.86 – 1.68 (m, 4H), 1.17 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 138.8, 137.4, 137.3, 133.4, 129.4, 129.3, 128.6, 128.4, 126.7, 125.7, 84.7, 67.6, 54.2, 38.3, 29.6, 29.3, 23.3 (2), 12.2; FT-HRMS (ESI) *m/z* calc for $C_{22}H_{25}NO_3Na$ $[M + Na]^+$ 358.1778, found 358.1800.

(3S,5R,6R)-3-(6-Methoxy-2-naphthyl)-4,5-dimethyl-6-phenyl-morpholin-2-one (31s). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), **S19** (240 mg, 1.03 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31s** (288

mg, 80%, 84:16 *dr*) after chromatographic purification on SiO_2 (4-10% EtOAc/10% DCM/Hex) and re-crystallization from EtOAc/Hex.

Major isomer: white fibrous needles (245 mg); m.p. 189.5-189.9°C; $[\alpha]_D^{23} = +10.3$ (c = 6.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3058, 3032, 2996, 2935, 2841, 2789, 1736, 1719, 1267, 1227, 1178, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.77 (dd, *J* = 8.5, 4.5 Hz, 2H), 7.62 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.42 – 7.34 (m, 5H), 7.20 – 7.13 (m, 2H), 5.23 (d, *J* = 9.5 Hz, 1H), 4.32 (s, 1H), 3.93 (s, 3H), 2.85 (dq, *J* = 9.5, 6.3 Hz, 1H), 2.30 (s, 3H), 1.05 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 158.1, 137.1, 134.7, 133.6, 129.7, 129.2, 128.9, 128.8, 128.0, 127.9, 127.6, 126.5, 119.2, 105.9, 86.7, 71.9, 60.4, 55.5, 40.3, 15.7; FT-HRMS (ESI) *m/z* calc for $C_{23}H_{23}NO_3Na$ $[M + Na]^+$ 384.1570, found 384.1573.

Minor isomer: yellow oil (43.0 mg); $[\alpha]_D^{23} = -9.70$ (c = 12.5, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3056, 3028, 2960, 2925, 2847, 2791, 1731, 1606, 1391, 1372, 1275, 1203, 1169, 1025, 853, 759, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.65 (m, 3H), 7.48 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.42 – 7.31 (m, 5H), 7.19 – 7.09 (m, 2H), 5.41 (d, *J* = 5.7 Hz, 1H), 4.61 (s, 1H), 3.92 (s, 3H), 3.45 (qd, *J* = 6.7, 5.7 Hz, 1H), 2.40 (s, 3H), 1.21 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 158.1, 138.8, 134.5, 131.7, 129.7, 128.8, 128.7, 128.5, 127.6, 127.3, 126.8, 126.6, 119.2, 105.7, 84.5, 67.7, 55.5, 54.4, 38.3, 12.1; FT-HRMS (ESI) *m/z* calc for $C_{23}H_{23}NO_3Na$ $[M + Na]^+$ 384.1570, found 384.1573.

Phenyl-[(2R,4R,5R)-2,3,4-trimethyl-5-phenyl-oxazolidin-2-yl]methanone (31t). According to the general protocol B, a suspension of (1R,2R)-(-)-pseudoephedrine (165 mg, 0.999 mmol), 1-phenylpropane-1,2-dione (0.151 mL, 1.12 mmol), $MgSO_4$ (485 mg, 4.03 mmol) in dry toluene (10 mL) was treated with TFA (8 µL, 0.104 mmol). The reaction mixture was heated in an oil bath at 75 ºC under N_2 for 12 h and afforded **31t** (139 mg, 47%, 9:1 *dr*) after chromatographic purification on SiO_2 (0-6% EtOAc/Hex).

Major isomer: yellow oil (139 mg); $[\alpha]_D^{24} = -5.83$ (c = 2.57, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3062, 3031, 2972, 2886, 2799, 1957, 1895, 1816, 1687, 1601, 1497, 1445, 1369, 1023, 964, 915, 884, 752 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.0 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.45 – 7.32 (m, 7H), 4.59 (d, *J* = 8.8 Hz, 1H), 2.70 (dq, *J* = 8.9, 6.0 Hz, 1H), 2.43 (s, 3H), 1.67 (s, 3H), 1.18 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 139.2, 137.0, 131.7, 129.5, 128.5, 128.2, 127.9, 126.6, 98.6, 86.4, 65.2, 32.8, 17.7, 14.7; FT-HRMS (ESI) *m/z* calc for $C_{19}H_{21}NO_2Na$ $[M + Na]^+$ 318.1465, found 318.1495.

Morpholine Reduction (Protocol C). A solution of Morpholine (1 equiv) in dry toluene (0.1 M) was treated with Red-Al 70% in toluene (6 equiv) while stirring in an ice bath under N_2, and slowly warmed to room temperature overnight. After 18 h the reaction was cooled to 0 °C in an ice bath and quenched with 6 mL H_2O. After warming to room temperature, the solution was poured into 50 mL of 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated.

TIPS Protection (Protocol D1). A solution of crude diol (1 equiv), 4-DMAP (0.1 equiv), imidazole (3 equiv) in anhydrous DMF (0.1M) was treated with TIPSCl (1.2 equiv) at room temperature under N_2. After 18 h the reaction was quenched with 6 mL H_2O, extracted with 1:1 EtOAc/Hex (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated.

TIPS Protection (Protocol D2). A solution of crude diol (1 equiv), 2,6-lutidine (2 equiv) in dry DCM (0.1M) was treated with TIPSOTf (1.05 equiv) at -78 °C under N_2. After 4 h the reaction was quenched with saturated aqueous $NaHCO_3$ and allowed to warm to room temperature. The mixture was extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. The residue was co-evaporated with toluene three times and dried under vacuum.

Chlorination and Cyanation (Protocol E)

A solution of crude silyl ether (1 equiv) in dry THF (0.1M) was treated with $SOCl_2$ (2 equiv) at room temperature under N_2. After 1 h the reaction was concentrated, co-evaporated with PhMe, taken up in 1:1

MeCN/DMSO (0.1M), and treated with KCN (10 eq). After 24 h the reaction was quenched with H_2O (3.00 mL), poured into saturated aqueous $NaHCO_3$, extracted EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified with column chromatography over SiO_2.[45]

(*S*)-*N*-Methyl-1-phenyl-2-((triisopropylsilyl)oxy)ethan-1-amine (32a). According to the general protocol C, a solution of **18** (2.80 g, 9.52 mmol) in dry toluene (73 mL) was treated with Red-Al 70% in toluene (14.0 mL, 59.7 mmol) while stirring in an ice bath under N_2 and slowly warming to room temperature overnight. After 16 h the reaction was cooled to 0 °C in an ice bath and quenched with 6 mL H_2O. After warming to room temperature the solution was poured into 200 mL 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated to afford diol (2.73 g, 96%). According to the general protocol D2, a solution of diol (74.0 mg, 0.259 mmol), 2,6-lutidine (60 µL, 0.518 mmol) in dry DCM (2.6 mL) was treated with TIPSOTf (73.4 µL, 0.272 mmol) at -78 °C under N_2. After 2 h the reaction was quenched with saturated aqueous $NaHCO_3$ and allowed to warm to room temperature, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. The residue was coevaporated with toluene three times and dried under vacuum. According to the general protocol E, the crude silyl ether in dry THF (2.6 mL) was treated with $SOCl_2$ (60 µL, 0.524 mmol) at room temperature under N_2. After 1 h the reaction was concentrated, coevaporated with PhMe, taken up in 1:1 MeCN/DMSO (2.6 mL), and treated with KCN (194 mg, 2.98 mmol). After 20 h under N_2 the reaction was quenched with 3.0 mL H_2O, poured into saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and afforded **32a** (58 mg, 70% over 3 steps) after chromatographic purification on SiO_2 (0-25% MeCN/5% EtOAc/DCM).

Amber oil; $[\alpha]_D^{23} = +5.55$ (c = 2.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2943, 2866, 2790, 1463, 1094, 1069, 882, 700, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 5H), 3.85 – 3.52 (m, 3H), 2.33 (s, 4H), 1.07

(q, J = 4.0 Hz, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 128.4, 127.9, 127.5, 68.8, 67.7, 34.7, 18.1, 12.1; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{34}NOSi$ $[M + H]^+$ 308.2404, found 308.2404.

(*S*)-1-(3,5-Bis(benzyloxy)phenyl)-N-methyl-2-((triisopropylsilyl)oxy)ethan-1-amine (32b). According to the general protocol C, a solution of **31f** (140 mg, 0.284 mmol) in dry toluene (3 mL) was treated with Red-Al 70% in toluene (0.57 mL, 1.70 mmol) while stirring in an ice bath under N_2 and slowly warming to room temperature overnight. After 18 h the reaction was cooled to 0 °C in an ice bath and quenched with H_2O (3.00 mL). After warming to room temperature, the solution was poured into 50 mL 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated to afford crude diol. According to the general protocol D1, a solution of crude diol, 4-DMAP (4.0 mg, 0.0322 mmol), imidazole (68.0 mg, 0.999 mmol) in anhydrous DMF (2.80 mL) was treated with TIPSCl (91.0 μL, 0.426 mmol) at room temperature under N_2. After 26 h the reaction was quenched with 50 mL H_2O, extracted with 1:1 EtOAc/Hex (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. According to the general protocol E, the crude silyl ether in dry THF (2.80 mL) was treated with $SOCl_2$ (41.0 μL, 0.568 mmol) at room temperature under N_2. After 1 h the reaction was concentrated, coevaporated with PhMe, taken up in 1:1 MeCN/DMSO (2.80 mL), and treated with KCN (210 mg, 3.23 mmol). After 21 h under N_2 the reaction was quenched with 3.00 mL H_2O, poured into saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and afforded **32b** (103 mg, 70% over 3 steps) after chromatographic purification on SiO_2 (0-20% MeCN/10% EtOAc/DCM).

Amber oil; $[\alpha]_D^{24} = +2.40$ (c = 1.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2941, 2865, 2782, 1595, 1446, 1152, 1091, 1054, 882 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.27 (m, 10H), 6.66 (d, *J* = 2.3 Hz, 2H), 6.56 (d, *J* = 2.3 Hz, 1H), 5.05 (s, 4H), 3.85 – 3.58 (m, 3H), 3.27 (s, 1H), 2.35 (s, 3H), 1.63 (d, *J* = 1.1 Hz, 3H), 1.15 – 0.86 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 142.9, 137.1, 128.7, 128.1, 127.7, 107.0, 101.4,

70.2, 68.5, 67.8, 34.5, 29.6 (2), 18.1, 12.1; FT-HRMS (ESI) *m/z* calc for $C_{32}H_{46}NO_3Si$ $[M + H]^+$ 520.3241, found 520.3207.

(S)-1-(3-Chlorophenyl)-*N*-methyl-2-((triisopropylsilyl)oxy)ethan-1-amine (32c). According to the general protocol C, a solution of **31e** (169 mg, 0.535 mmol) in dry toluene (5.40 mL) was treated with Red-Al 70% in toluene (1.10 mL, 3.21 mmol) while stirring in an ice bath under N_2 and slowly warming to room temperature overnight. After 18 h the reaction was cooled to 0 °C in an ice bath and quenched with 6 mL H_2O. After warming to room temperature, the solution was poured into 50 mL 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. According to the general protocol D1, a solution of diol (171 mg, 0.535 mmol), 4-DMAP (7 mg, 0.0573 mmol), imidazole (111 mg, 1.63 mmol) in anhydrous DMF (5.4 mL) was treated with TIPSCl (137 µL, 0.642 mmol) at room temperature under N_2. After 26 h the reaction was quenched with 50 mL H_2O, extracted with 1:1 EtOAc/Hex (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. According to the general protocol E, the crude silyl ether in dry THF (5.40 mL) was treated with $SOCl_2$ (77.0 µL, 1.07 mmol) at room temperature under N_2. After 1 h the reaction was concentrated, coevaporated with PhMe, taken up in 1:1 MeCN/DMSO (5.4 mL), and treated with KCN (354 mg, 5.44 mmol). After 20 h under N_2 the reaction was quenched with H_2O (3.00 mL), poured into saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and afforded **32c** (115 mg, 63% over 3 steps) after chromatographic purification on SiO_2 (0-20% MeCN/5% EtOAc/DCM).

Red oil; $[\alpha]_D^{24} = +4.90$ (c = 1.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2943, 2866, 1464, 1381, 1340, 1095, 882, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (dt, *J* = 2.4, 1.1 Hz, 1H), 7.24 (t, *J* = 2.1 Hz, 3H), 3.80 – 3.57 (m, 3H), 2.31 (s, 3H), 2.30 – 2.25 (m, 1H), 1.17 – 0.89 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 134.4, 129.7, 128.0, 127.7, 126.1, 68.5, 67.3, 34.7, 18.1, 12.1; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{33}ClNOSi$ $[M + H]^+$ 342.2014, found 342.1980.

(*S*)-1-(3,4-Dichlorophenyl)-*N*-methyl-2-((triisopropylsilyl)oxy)ethan-1-amine (32d). According to the general protocol C, a solution of **31h** (180 mg, 0.514 mmol) in dry toluene (5.1 mL) was treated with Red-Al 70% in toluene (1 mL, 3.08 mmol) while stirring in an ice bath under N_2 and slowly warming to room temperature overnight. After 18 h the reaction was cooled to 0 °C in an ice bath and quenched with H_2O (3.00 mL). After warming to room temperature, the solution was poured into 50 mL 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated to afford crude diol. According to the general protocol D1, a solution of crude diol, 4-DMAP (7 mg, 0.0573 mmol), imidazole (104 mg, 1.53 mmol) in anhydrous DMF (5.1 mL) was treated with TIPSCl (132 μL, 0.617 mmol) at room temperature under N_2. After 26 h the reaction was quenched with 50 mL H_2O, extracted with 1:1 EtOAc/Hex (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. According to the general protocol E, the crude silyl ether in dry THF (5.1 mL) was treated with $SOCl_2$ (74 μL, 1.03 mmol) at room temperature under N_2. After 1 h the reaction was concentrated, coevaporated with PhMe, taken up in 1:1 MeCN/DMSO (5.1 mL), and treated with KCN (340 mg, 5.22 mmol). After 20 h under N_2 the reaction was quenched with H_2O (3.00 mL), poured into saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and afforded **32d** (135 mg, 70% over 3 steps) after chromatographic purification on SiO_2 (0-20% MeCN/5% EtOAc/DCM).

Amber oil; $[\alpha]_D^{24} = +2.45$ (c = 2.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2943, 2866, 2782, 1465, 1391, 1098, 1030, 882, 792 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.19 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.77 – 3.49 (m, 3H), 2.29 (s, 3H), 2.12 (s, 1H), 1.13 – 0.96 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 132.6, 131.2, 130.4, 129.8, 127.3, 68.4, 66.7, 34.7, 18.1, 12.0; FT-HRMS (ESI) *m/z* calc for $C_{18}H_{32}Cl_2NOSi$ $[M + H]^+$ 376.1625, found 376.1631.

(*S*)-1-(2-Methoxyphenyl)-*N*-methyl-2-((triisopropylsilyl)oxy)ethan-1-amine (32e). According to the general protocol C, a solution of **31b** (140 mg, 0.450 mmol) in dry toluene (4.5 mL) was treated with Red-Al 70% in toluene (0.90 mL, 2.70 mmol) while stirring in an ice bath under N_2 and slowly warming to room temperature overnight. After 18 h the reaction was cooled to 0 °C in an ice bath and quenched with 6 mL H_2O. After warming to room temperature, the solution was poured into 200 mL 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated to afford crude diol (108 mg, 76%). According to the general protocol D2, a solution of diol, 2,6-lutidine (79 μL, 0.684 mmol) in dry DCM (3.4 mL) was treated with TIPSOTf (97 μL, 0.360 mmol) at -78 °C under N_2. After 4 h the reaction was quenched with saturated aqueous $NaHCO_3$ and allowed to warm to room temperature, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. The residue was coevaporated with toluene three times and dried under vacuum. According to the general protocol E, the crude silyl ether in dry THF (3.4 mL) was treated with $SOCl_2$ (50 μL, 0.684 mmol) at room temperature under N_2. After 1 h the reaction was concentrated, coevaporated with PhMe, taken up in 1:1 MeCN/DMSO (3.4 mL), and treated with KCN (303 mg, 4.65 mmol). After 48 h under N_2 the reaction was quenched with H_2O (3.00 mL), poured into saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and afforded **32e** (99 mg, 65% over 3 steps) after chromatographic purification on SiO_2 (0-20% MeCN/3% EtOAc/DCM).

Amber oil; $[\alpha]_D^{25} = +2.80$ (c = 1.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2942, 2866, 2795, 1489, 1463, 1238, 1099, 878, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.22 (td, *J* = 7.8, 1.8 Hz, 1H), 6.96 (td, *J* = 7.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.16 (dd, *J* = 8.4, 3.8 Hz, 1H), 3.88 (dd, *J* = 9.7, 3.9 Hz, 1H), 3.81 (s, 3H), 3.56 (dd, *J* = 9.7, 8.4 Hz, 2H), 2.35 (s, 3H), 1.05 (q, *J* = 2.6, 2.0 Hz, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 128.2, 128.1, 127.9, 120.7, 110.4, 66.8, 60.7, 55.3, 34.6, 18.1 (2), 12.1; FT-HRMS (ESI) *m/z* calc for $C_{19}H_{35}NO_2SiNa$ $[M + Na]^+$ 360.2329, found 360.2313.

(*S*)-*N*-Methyl-1-(naphthalen-2-yl)-2-((triisopropylsilyl)oxy)ethan-1-amine (32f). According to the general protocol C, a solution of **31p** (80 mg, 0.238 mmol) in dry toluene (2.4 mL) was treated with Red-Al 70% in toluene (0.48 mL, 1.45 mmol) while stirring in an ice bath under N_2 and slowly warming to room temperature overnight. After 18 h the reaction was cooled to 0 °C in an ice bath and quenched with 6 mL H_2O. After warming to room temperature, the solution was poured into 200 mL 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated to afford crude diol. According to the general protocol D2, a solution of diol, 2,6-lutidine (55 µL, 0.477 mmol) in dry DCM (3.1 mL) was treated with TIPSOTf (67 µL, 0.250 mmol) at -78 °C under N_2. After 4 h the reaction was quenched with saturated aqueous $NaHCO_3$ and allowed to warm to room temperature, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. The residue was coevaporated with toluene three times and dried under vacuum. According to the general protocol E, the crude silyl ether in dry THF (3.1 mL) was treated with $SOCl_2$ (44 µL, 0.602 mmol) at room temperature under N_2. After 1 h the reaction was concentrated, coevaporated with PhMe, taken up in 1:1 MeCN/DMSO (3.1 mL), and treated with KCN (306 mg, 4.70 mmol). After 48 h under N_2 the reaction was quenched with H_2O (3.00 mL), poured into saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and afforded **32f** (64 mg, 75% over 3 steps) after chromatographic purification on SiO_2 (0-25% MeCN/3% EtOAc/DCM).

Amber oil; $[\alpha]_D^{21} = +3.70$ (c = 2.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 3048, 2942, 2865, 2782, 1463, 1093, 883, 821, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 – 7.72 (m, 4H), 7.49 (dtd, *J* = 14.4, 7.7, 7.0, 3.3 Hz, 3H), 3.94 – 3.69 (m, 3H), 2.87 (s, 1H), 2.39 (s, 3H), 1.19 – 0.98 (m, 21H); ^{13}C NMR 138.1, 133.6, 133.2, 128.1, 127.9, 127.8, 126.8, 126.04 (2), 125.7, 68.7, 67.8, 34.7, 18.1, 12.1; FT-HRMS (ESI) *m/z* calc for $C_{22}H_{35}NOSiNa$ $[M + Na]^+$ 380.2380, found 380.2410.

(*S*)-1-(Furan-3-yl)-*N*-methyl-2-((triisopropylsilyl)oxy)ethan-1-amine (32g). According to the general protocol C, a solution of **31n** (70 mg, 0.322 mmol) in dry toluene (3.2 mL) was treated with Red-Al 70%

in toluene (0.64 mL, 1.93 mmol) while stirring in an ice bath under N_2 and slowly warming to room temperature overnight. After 18 h the reaction was cooled to 0 °C in an ice bath and quenched with 6 mL H_2O. After warming to room temperature, the solution was poured into 200 mL 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated to afford crude diol (71 mg, 99%). According to the general protocol D2, a solution of diol, 2,6-lutidine (74 µL, 0.642 mmol) in dry DCM (3.2 mL) was treated with TIPSOTf (91 µL, 0.337 mmol) at -78 °C under N_2. After 4 h the reaction was quenched with saturated aqueous $NaHCO_3$ and allowed to warm to room temperature, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. The residue was coevaporated with toluene three times and dried under vacuum. According to the general protocol E, the crude silyl ether in dry THF (3.2 mL) was treated with $SOCl_2$ (47 µL, 0.642 mmol) at room temperature under N_2. After 1 h the reaction was concentrated, coevaporated with PhMe, taken up in 1:1 MeCN/DMSO (3.2 mL), and treated with KCN (321 mg, 4.93 mmol). After 48 h under N_2 the reaction was quenched with H_2O (3.00 mL), poured into saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and afforded **32g** (54 mg, 69% over 3 steps) after chromatographic purification on SiO_2 (0-25% MeCN/3% EtOAc/DCM).

Amber oil; $[\alpha]_D^{22} = +4.20$ (c = 1.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2943, 2866, 2791, 1499, 1467, 1389, 1095, 878, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H), 6.40 (dd, *J* = 1.8, 0.9 Hz, 1H), 4.54 (s, 1H), 3.87 – 3.60 (m, 3H), 2.37 (s, 3H), 1.14 – 0.95 (m, 21H); ^{13}C NMR 143.2, 140.6, 124.2, 109.7, 67.3, 58.4, 34.0, 18.1, 12.1; FT-HRMS (ESI) *m/z* calc for $C_{16}H_{31}NO_2SiNa$ $[M + Na]^+$ 320.2016, found 320.2001.

(*S*)-1-(4-(Benzyloxy)phenyl)-*N*-methyl-2-((triisopropylsilyl)oxy)ethan-1-amine (32h). According to the general protocol C, a solution of **31j** (110 mg, 0.284 mmol) in dry toluene (2.8 mL) was treated with Red-Al 70% in toluene (0.57 mL, 1.70 mmol) while stirring in an ice bath under N_2 and slowly warming to room temperature overnight. After 18 h the reaction was cooled to 0 °C in an ice bath and quenched

with 6 mL H_2O. After warming to room temperature, the solution was poured into 200 mL 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated to afford crude diol (95 mg, 85%). According to the general protocol D2, a solution of diol, 2,6-lutidine (56 μL, 0.486 mmol) in dry DCM (2.4 mL) was treated with TIPSOTf (69 μL, 0.255 mmol) at -78 °C under N_2. After 4 h the reaction was quenched with saturated aqueous $NaHCO_3$ and allowed to warm to room temperature, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. The residue was coevaporated with toluene three times and dried under vacuum. According to the general protocol E, the crude silyl ether in dry THF (2.4 mL) was treated with $SOCl_2$ (35 μL, 0.486 mmol) at room temperature under N_2. After 1 h the reaction was concentrated, coevaporated with PhMe, taken up in 1:1 MeCN/DMSO (2.4 mL), and treated with KCN (194 mg, 2.98 mmol). After 48 h under N_2 the reaction was quenched with H_2O (3.00 mL), poured into saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and afforded **32h** (72 mg, 61% over 3 steps) after chromatographic purification on SiO_2 (0-20% MeCN/2% EtOAc/DCM).

Amber oil; $[\alpha]_D^{25} = +3.60$ (c = 1.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2942, 2865, 2791, 1610, 1510, 1463, 1240, 1092, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.26 (m, 7H), 7.01 – 6.91 (m, 2H), 5.06 (s, 2H), 3.81 – 3.58 (m, 3H), 2.94 (s, 1H), 2.32 (s, 3H), 1.13 – 1.01 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 137.3, 132.8, 128.9, 128.7, 128.0, 127.6, 114.8, 70.2, 68.8, 67.00, 34.5, 18.1, 12.1; FT-HRMS (ESI) *m/z* calc for $C_{25}H_{39}NO_2SiNa$ $[M + Na]^+$ 436.2642, found 436.2654.

(S)-1-([1,1'-Biphenyl]-3-yl)-*N*-methyl-2-((triisopropylsilyl)oxy)ethan-1-amine (32i). According to the general protocol C, a solution of **X** (189 mg, 0.529 mmol) in dry toluene (5.3 mL) was treated with Red-Al 70% in toluene (1.06 mL, 3.17 mmol) while stirring in an ice bath under N_2 and slowly warming to room temperature overnight. After 18 h the reaction was cooled to 0 °C in an ice bath and quenched with 5 mL H_2O. After warming to room temperature, the solution was poured into 50 mL 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated

to afford diol (171 mg, 89%). According to the general protocol D1, a solution of diol (171 mg, 0.473 mmol), 4-DMAP (6 mg, 0.0491 mmol), imidazole (99 mg, 1.45 mmol) in anhydrous DMF (4.7 mL) was treated with TIPSCl (121 μL, 0.568 mmol) at room temperature under N_2. After 26 h the reaction was quenched with 50 mL H_2O, extracted with 1:1 EtOAc/Hex (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. According to the general protocol E, the crude silyl ether in dry THF (4.7 mL) was treated with $SOCl_2$ (69 μL, 0.946 mmol) at room temperature under N_2. After 1 h the reaction was concentrated, coevaporated with PhMe, taken up in 1:1 MeCN/DMSO (4.7 mL), and treated with KCN (440 mg, 6.76 mmol). After 21 h under N_2 the reaction was quenched with 5 mL H_2O, poured into saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and afforded **32i** (99 mg, 49% over 3 steps) after chromatographic purification on SiO_2 (5-20% MeCN/5% EtOAc/DCM).

Amber oil; $[\alpha]_D^{23} = +3.90$ (c = 2.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2942, 2865, 2790, 1463, 1093, 882, 787, 756, 665cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dt, J = 6.2, 1.4 Hz, 3H), 7.56 – 7.31 (m, 6H), 3.90 – 3.67 (m, 3H), 2.67 (s, 1H), 2.39 (s, 3H), 1.21 – 0.97 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 141.3, 141.2, 128.9, 128.8, 127.3, 126.9, 126.7, 126.4, 68.8, 67.8, 34.8, 18.1, 12.1; FT-HRMS (ESI) *m/z* calc for $C_{24}H_{37}NOSiNa$ $[M + Na]^+$ 406.2537, found 406.2533.

(*S*)-1-([1,1'-Biphenyl]-4-yl)-N-methyl-2-((triisopropylsilyl)oxy)ethan-1-amine (32j). According to the general protocol C, a solution of **31k** (182 mg, 0.509 mmol) in dry toluene (5 mL) was treated with Red-Al 70% in toluene (1.0 mL, 3.06 mmol) while stirring in an ice bath under N_2 and slowly warming to room temperature overnight. After 18 h the reaction was cooled to 0 °C in an ice bath and quenched with H_2O (3.00 mL). After warming to room temperature, the solution was poured into 50 mL 30% potassium tartrate (w/v), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated to afford crude diol (172 mg, 93%). According to the general protocol D1, a solution of crude diol, 4-DMAP (6 mg, 0.0491 mmol), imidazole (108 mg, 1.586 mmol) in anhydrous DMF (4.7 mL) was treated

with TIPSCl (153 μL, 0.714 mmol) at room temperature under N_2. After 20 h the reaction was quenched with 50 mL H_2O, extracted with 1:1 EtOAc/Hex (3 x 30 mL), washed with brine, dried over Na_2SO_4, and concentrated. According to the general protocol E, the crude silyl ether in dry THF (4.7 mL) was treated with $SOCl_2$ (69 μL, 0.952 mmol) at room temperature under N_2. After 1 h the reaction was concentrated, coevaporated with PhMe, taken up in 1:1 MeCN/DMSO (4.7 mL), and treated with KCN (368 mg, 5.65 mmol). After 20 h under N_2 the reaction was quenched with H_2O (3.00 mL), poured into saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and afforded **32j** (116 mg, 59% over 3 steps) after chromatographic purification on SiO_2 (0-20% MeCN/5% EtOAc/DCM).

Amber oil; $[\alpha]_D^{24} = +5.45$ (c = 2.00, $CHCl_3$); IR (FTIR) $\tilde{\nu}$ = 2942, 2865, 2790, 1462, 1092, 878, 756, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.55 (m, 4H), 7.50 – 7.40 (m, 4H), 7.38 – 7.30 (m, 1H), 3.98 – 3.58 (m, 3H), 2.63 (d, *J* = 9.7 Hz, 1H), 2.39 (s, 3H), 1.22 – 0.96 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 140.5, 139.8, 128.8, 128.3, 127.3, 127.2 (2), 68.7, 67.4, 34.7, 18.1, 12.1; FT-HRMS (ESI) *m/z* calc for $C_{24}H_{37}NOSiNa$ $[M + Na]^+$ 406.2537, found 406.2533.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystallography data, computational details, and copies of NMR spectra for all new compounds (PDF)

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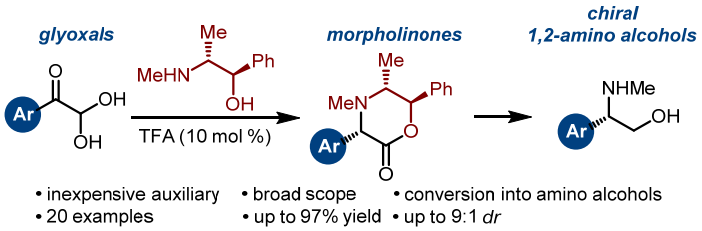
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OH
OH
O
Me
MeHN
Ph
OH
TFA (10 mol %)
Me
MeN
Ph
O
O
Ar
NHMe
OH
Ar
• inexpensive auxiliary
• 20 examples
• broad scope
• up to 97% yield
• conversion into amino alcohols
• up to 9:1 dr