Peptide-Catalyzed Kinetic Resolution of Formamides and Thioformamides as an Entry to Nonracemic Amines

Brandon S. Fowler, Peter J. Mikochik and Scott J. Miller*

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, CT 06520-8107

Supporting Information

I. General Procedures.

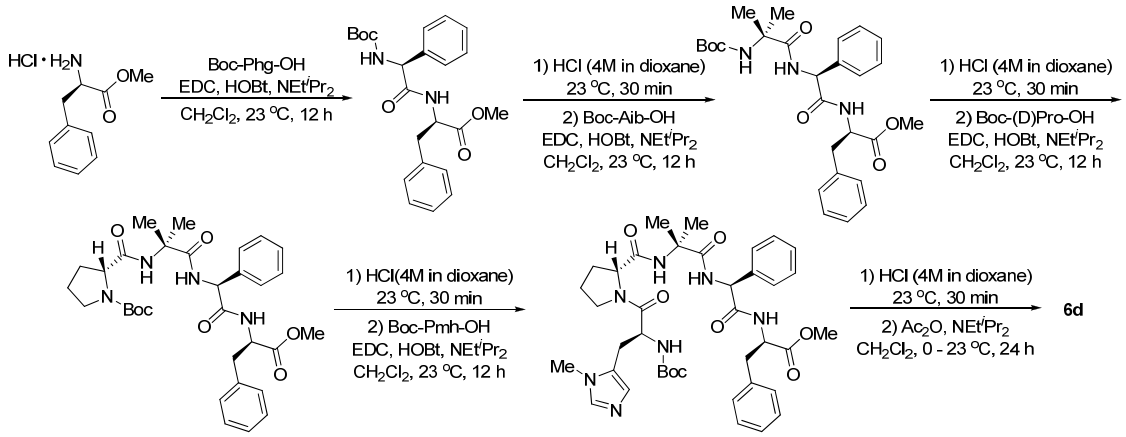
Proton NMR spectra were recorded on a Bruker 400 or 500 MHz spectrometer. Proton chemical shifts were reported in ppm (δ) with the residual protium in the NMR solvent as a reference ($CHCl_3$, δ 7.26 relative to tetramethylsilane, TMS).[1] Spectral data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants (Hz), integration). Carbon NMR spectra were recorded on a Bruker 100 or 125 MHz spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to the solvent signal ($CDCl_3$, δ 77.0). NMR data were collected at 25 °C. Infrared spectra were obtained on a Nicolet 6700 ATR/FT-IR spectrometer and ν_{max} are partially reported (cm^{-1}). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 pre-coated plates (0.25 mm thickness). TLC R_f values are reported, and visualization was accomplished by irradiation with a UV lamp and/or staining with ceric ammonium molybdate (CAM) solution. Flash column chromatography was performed using Silica Gel 60 Å (32-62 micron). Optical rotations were recorded on a Perkin-Elmer Polarimeter 341 at the sodium D line (1.0 dm path length). High resolution mass spectra (HRMS) were acquired from the Keck Center of Yale University or the Mass Spectrometry Laboratory at the University of Illinois (Urbana-Champaign, IL). In place of HRMS for some samples, ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters UPLC/MS instrument equipped with a reverse-phase C_{18} column (1.7 μm particle size, 2.1 × 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Samples were eluted with a liner gradient of 20% acetonitrile-water to 100% acetonitrile containing 0.1% formic acid over 3 min at a flow rate of 0.8 mL/min. The method of ionization is given in parentheses. Enantiomeric ratios (e.r.) were determined by analytical HPLC on a Hewlett-Packard or Agilent 1100 Series chromatograph equipped with a diode array detector (210 nm or 230 nm) and columns (chiral supports) from Daicel Chemical Industries (Chiralcel OD and Chiralcel OJ-H).

Commercially available Lawesson's reagent was purified by recrystallization from toluene and was stored under vacuum. Tetrahydrofuran and dichloromethane were purified by a Seca Solvent Purification System from GlassContour. Chloroform was

purified by washing with water to remove ethanol, drying over potassium carbonate, and distilling from phosphorus (V) oxide. Di-*tert*-butyldicarbonate (Boc_2O) was purchased from Advanced ChemTech and was used without further purification. Chloroform-*d* ($CDCl_3$) for the catalyst screening and competition reactions was purchased from Cambridge Isotope Laboratories without TMS internal standard and was used without further purification. Molecular sieves (4 Å, powder) were activated by flame-drying, and were oven-stored. All other chemicals were commercially available and used as received.

Selectivity factors (s-factors or k_{rel}) were calculated using the method of Kagan.[2]

II. Solution Phase Synthesis of Peptide Catalyst 6d



Peptide Coupling 1. Catalyst **6d** was synthesized by solution phase peptide synthesis using the Boc protection strategy. A dry roundbottom flask was charged with D-phenylalanine methyl ester hydrochloride (602 mg, 2.80 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) (591 mg, 3.10 mmol), 1-hydroxybenzotriazole (HOBt) (472 mg, 3.10 mmol), and *N*-Boc-phenylglycine (Boc-Phg-OH) (704 mg, 2.80 mmol). Dichloromethane (28 mL) and Hünig's base (555 μL, 3.40 mmol) were added, and the reaction mixture was stirred at ambient temperature for 12 hr. The reaction mixture was transferred to separatory funnel, diluted with 30 mL dichloromethane, and washed with saturated sodium bicarbonate (1 × 50 mL), 10% citric acid (1 × 50 mL), and saturated sodium chloride (1 × 30 mL). The organic layer was then dried with sodium sulfate and concentrated to give 1.1 g (2.70 mmol, 96%) of crude dipeptide Boc-Phg-D-Phe-OMe.

Deprotection 1. To the flask containing crude dipeptide Boc-Phg-D-Phe-OMe was added 5 mL of 4M HCl in dioxane at ambient temperature. The reaction was stirred for 30 min, and dry nitrogen was passed through the headspace of the flask and into an aqueous solution of sodium bicarbonate for 3 hr to remove excess HCl and dioxane. The resulting residue was dried under vacuum for 1 hr before proceeding to the next peptide coupling.

Peptide Coupling 2. The second peptide coupling was carried out in the same manner as Peptide Coupling 1 using EDC (576 mg, 3.00 mmol), HOBt (460 mg, 3.00 mmol), *N*-Boc-α-aminoisobutyric acid (Boc-Aib-OH) (549 mg, 2.70 mmol), dichloromethane (27 mL), and Hünig's base (535 μL, 3.20 mmol). The workup was carried out as described previously to yield 1.34 g (2.70 mmol, quant.) of the crude trimer Boc-Aib-Phg-D-Phe-OMe.

Deprotection 2. Deprotection of the crude tripeptide Boc-Aib-Phg-D-Phe-OMe was carried out in the same manner as Deprotection 1 above.

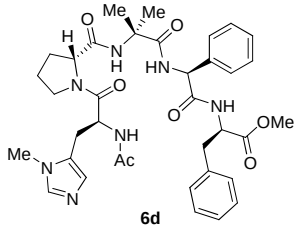
Peptide Coupling 3. The third peptide coupling was carried out in the same manner as Peptide Coupling 1 using EDC (576 mg, 3.00 mmol), HOBt (460 mg, 3.00 mmol), *N*-Boc-D-proline (Boc-D-Pro-OH) (577 mg, 2.70 mmol), dichloromethane (27 mL), and Hünig's base (535 μL, 3.20 mmol). The workup was carried out as described previously. The workup was carried out as described previously to yield 1.44 g (2.40 mmol, 89%) of the crude tetramer Boc-D-Pro-Aib-Phg-D-Phe-OMe.

Deprotection 3. Deprotection of a portion of the crude tetrapeptide Boc-D-Pro-Aib-Phg-D-Phe-OMe (550 mg, 0.93 mmol) was carried out in the same manner as Deprotection 1 above.

Peptide Coupling 4. The fourth peptide coupling was carried out in the same manner as Peptide Coupling 1 using EDC (196 mg, 1.02 mmol), HOBt (156 mg, 1.02 mmol), α-*N*-Boc-π-methylhistidine (Boc-Pmh-OH) (275 mg, 0.93 mmol), dichloromethane (9.5 mL), and Hünig's base (184 μL, 1.11 mmol). The workup was modified from previous couplings to exclude the citric acid wash and yielded 528 mg (0.71 mmol, 77%) of the crude pentamer Boc-Pmh-D-Pro-Aib-Phg-D-Phe-OMe.

Deprotection 4. Deprotection of a portion of the crude pentapeptide Boc-Pmh-D-Pro-Aib-Phg-D-Phe-OMe (207 mg, 0.28 mmol) was carried out in the same manner as Deprotection 1 above except that 3 mL of 4M HCl was used.

***N*-terminus Capping.** To the deprotected pentamer (0.28 mmol) were added dichloromethane (3 mL) and Hünig's base (161 μL, 0.97 mmol). The solid pentamer dissolved with the addition of base, and the reaction mixture was cooled to 0 °C. Acetic anhydride (53 μL, 0.56 mmol) was added slowly with vigorous stirring. The reaction mixture was allowed to warm to ambient temperature while stirring for 24 hr, after which it was transferred to a separatory funnel, diluted with 10 mL CH_2Cl_2, and washed with saturated sodium bicarbonate (1 × 10 mL) and saturated sodium chloride (1 × 10 mL). The organic layer was dried with sodium sulfate and concentrated. The crude peptide was purified by reverse phase column chromatography using a Biotage SP4 system with a C18HS 25-S column (40% methanol/water to 90% methanol/water over 40 min; flow rate = 25 mL/min; t_r = 12 min). The fractions were concentrated and residual water removed by azeotrope with toluene (3 × 10 mL) to yield purified peptide **6d** (Ac-Pmh-D-Pro-Aib-Phg-D-Phe-OMe) (119 mg, 0.17 mmol, 62%).

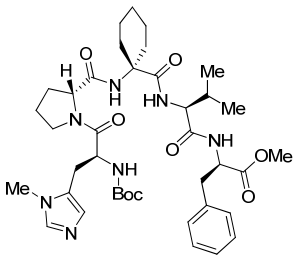


6d

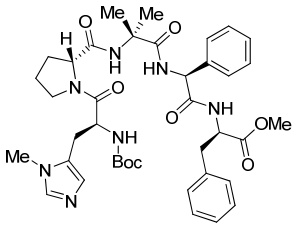
Peptide 6d. White amorphous solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3, 1H), 7.51 (d, *J* = 7.2, 2H), 7.36 (s, 1H), 7.35 – 7.27 (m, 4H), 7.19 – 7.17 (m, 3H), 7.09 (d, *J* = 7.9, 1H), 7.00 – 6.98 (m, 2H), 6.75 (s, 1H), 6.70 (s, 1H), 5.58 (d, *J* = 8.3, 1H), 4.82 (dt, *J* = 5.4, 8.9, 1H), 4.70 (dt, *J* = 7.1, 7.1, 1H), 4.13 (t, *J* = 6.6, 1H), 3.65 – 3.57 (m, 7H), 3.09 – 3.00 (m, 3H), 2.98 – 2.81 (m, 2H), 2.10 – 1.99 (m, 3H), 1.83 (s, 3H), 1.82 – 1.76 (m, 1H), 1.57 (s, 3H), 1.44 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.62, 172.63, 171.84, 170.35, 170.17, 170.14, 137.98, 137.13, 135.89, 129.10, 128.59, 128.43, 128.25, 128.00, 127.86, 127.21, 126.91, 61.48, 57.29, 57.08, 54.15, 52.24, 50.91, 47.42, 37.66, 31.37, 28.75, 27.17, 26.37, 25.11, 24.04, 22.54. **IR** (film, cm^{-1}) 3298, 2952, 1745, 1660,

1499, 1445, 1371, 1215, 1110, 1032, 751, 699. **Exact mass** calculated for $[C_{36}H_{45}N_7O_7 H]^+$ requires *m/z* 688.3453 Found 688.3442 (ESI+). $\mathbf{[\alpha]_D^{20}} = -11.7$(*c* 1.0, $CHCl_3$).

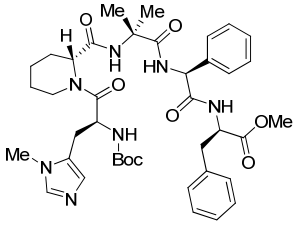
HRMS analysis for peptides 6a-c, 6e from Table 1.



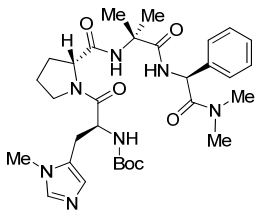
6a, HRMS: $[C_{39}H_{57}N_7O_8 H]^+$
requires *m/z* 752.4341; found 742.4317.



6b, HRMS: $[C_{39}H_{51}N_7O_8 H]^+$
requires *m/z* 746.3872; found 746.3861.

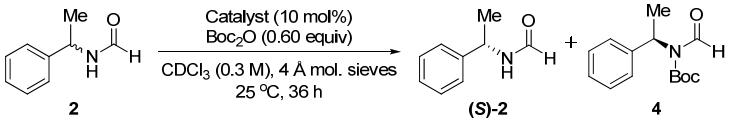


6c, HRMS: $[C_{40}H_{53}N_7O_8 H]^+$
requires *m/z* 760.4028; found 760.4015.



6e, HRMS: $[C_{31}H_{45}N_7O_6 H]^+$
requires *m/z* 612.3504; found 612.3493.

III. Peptide-Catalyzed KR of Formamide 2 (eq 2 & Table 1)

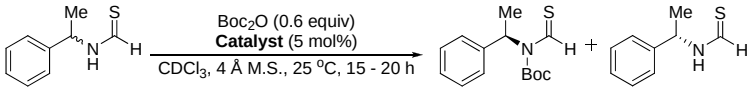


2 **(*S*)-2** **4**

Typical Procedure A. An oven-dried vial charged with 10 mg of activated 4 Å molecular sieves was allowed to cool to room temperature in a desiccator. The reagents were added to the vial as stock solutions in $CDCl_3$: formamide **7** (20.0 mg, 0.134 mmol in 200 μL), Boc_2O (17.6 mg, 0.080 mmol in 100 μL), NMR standard $(TMS)_2O$ (1.2 mg, 0.007 mmol in 100μL), and, finally, catalyst (0.013 mmol in 50 μL). The vial was capped, sealed with Parafilm, and agitated on a platform shaker for 36 h at 25 °C, after which the conversion was determined by ^1H NMR. The remaining Boc_2O was quenched with 250 μL 1:1 concentrated NH_4OH:methanol, stirred for 10 minutes, and concentrated in vacuo. The concentrate was passed through a short silica plug into a single fraction using 10% 2-propanol/hexanes as the eluent. An aliquot of the fraction was analyzed by

chiral-phase HPLC to determine substrate and product enantiopurity. Characterization of formamide **2** and *N*-Boc-formamide **4** can be found in sections **XI** and **VI**, respectively.

IV. Catalyst Profile for the KR of Thioformamide 7 (Analogous to Table 1)

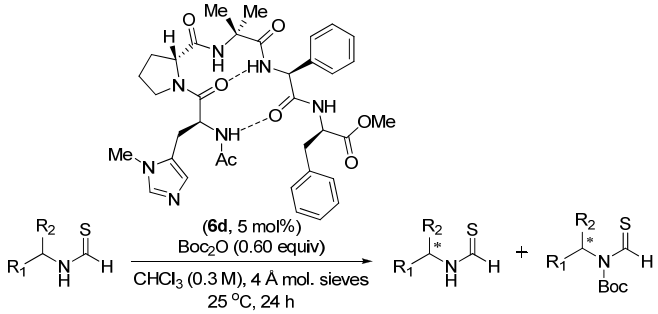


7 **8** **(*S*)-7**

Entry	Catalyst	*i-1*	*i+1*	*i+2*	*i+3*	*i+4*	s-factor
1	**6a**	Boc	D-Pro	Sp6	L-Val	D-Phe-OMe	5.1
2	**6b**	Boc	D-Pro	Aib	L-Phg	D-Phe-OMe	7.5
3	**6d**	Ac	D-Pro	Aib	L-Phg	D-Phe-OMe	12.8
4	**6e**	Boc	D-Pro	Aib	L-Phg	$-NMe_2$	3.3

Typical Procedure B. An oven-dried vial with 10 mg of activated 4 Å molecular sieves was allowed to cool to room temperature in a desiccator. The reagents were added to the vial as stock solutions in $CDCl_3$: thioformamide **7** (22.0 mg, 0.134 mmol in 200 μL), Boc_2O (17.6 mg, 0.080 mmol in 100 μL), NMR standard $(TMS)_2O$ (1.2 mg, 0.007 mmol in 100μL), and, finally, catalyst (0.007 mmol in 50 μL). The vial was capped, sealed with Parafilm, and agitated on a platform shaker for 15–20 h at 25 °C, after which the conversion was determined by ^{1}H NMR. The reaction mixture was loaded onto a silica column; the visible bright yellow product (**8**) was eluted with 10% ethyl acetate/hexanes, and the resolved substrate (**(*S*)-7**) was eluted with 50% ethyl acetate/hexanes. The resolved substrate was converted to the corresponding formamide for determination of enantiopurity as described in section **XI** (Typical Procedure H).

V. Peptide-Catalyzed KR of Thioformamides 7 & 9 – 17 (Table 2)

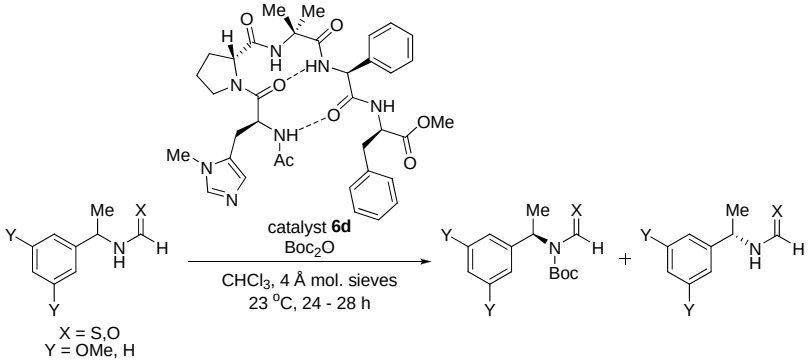


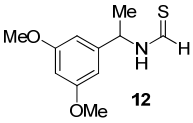
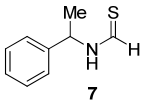
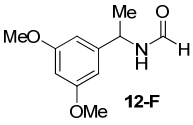
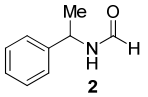
Typical Procedure C. An oven-dried vial charged with 10 mg of activated 4 Å molecular sieves was allowed to cool to room temperature in a desiccator. The reagents

were added to the vial as stock solutions in chloroform: thioformamide (0.134 mmol in 200 μL), Boc_2O (17.6 mg, 0.080 mmol in 100 μL), NMR standard $(TMS)_2O$ (1.2 mg, 0.007 mmol in 100μL), and, finally, catalyst (4.6 mg, 0.007 mmol in 50 μL). The vial was capped, sealed with Parafilm, and agitated on a platform shaker for 24 h at 25 °C, after which the conversion was determined by ^1H NMR. The reaction mixture was loaded onto a silica column; the visible bright yellow product was eluted with 10 to 20% ethyl acetate/hexanes, and the resolved substrate was eluted with 50% ethyl acetate/hexanes. The *N*-Boc-thioamide products are characterized in section **X**. The recovered thioformamide substrate was converted to the corresponding formamide for optical rotation and determination of enantiopurity as described in detail in section **XI** (Typical Procedure H).

For entries 3 and 10 in Table 2 (substrates **10** and **17**, respectively), slightly more Boc_2O (19.0 mg, 0.087 mmol in 100 μL) was used for the kinetic resolution.

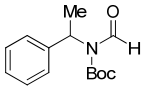
VI. 0.5 mmol-Scale KR of Formamides and Thioformamides



Entry	Substrate	e.r. (Recovered SM)	NMR Conversion	Yield (Recovered SM)	s-factor
1	 **12**	94.2 : 5.8	50%	0.235 mmol (47%)	45.6
2	 **7**	93.4 : 6.6	59%	0.203 mmol (41%)	10.9
3	 **12-F**	94.2 : 5.8	58%	0.211 mmol (42%)	12.9
4	 **2**	89.1 : 10.9	56%	0.201 mmol (40%)	9.6

Typical Procedure D: 0.5 mmol-Scale Formamide KR. A 1-dram vial was charged with 37 mg of oven-dried 4 Å molecular sieves (powder) and a magnetic stirbar. The vial and sieves were then flame-dried and allowed to cool under vacuum. Chloroform (0.6 mL) was added to the sieves and was allowed to stir for 5 minutes to give a homogeneous suspension. In a separate oven-dried vial, the formamide substrate (0.500 mmol) was dissolved in chloroform (0.3 mL) and transferred to the reaction mixture by pipette. To ensure complete transfer, the vial was rinsed again with chloroform (0.3 mL), which was also added to the reaction mixture. Catalyst **6d** (34 mg, 50.0 μmol) and Boc_2O (65 mg, 0.300 mmol) were added directly to the reaction mixture, and the sides of the reaction vial were rinsed with chloroform (0.4 mL), the vial was capped tightly, and the reaction was allowed to stir vigorously for 12 hours at 23 °C. Additional catalyst (34 mg, 50.0

μmol) and Boc_2O (65 mg, 0.300 mmol) were added directly to the reaction mixture, the vial was re-capped, and the reaction was stirred another 12 hours at 23 °C. At this point, an aliquot (25 μL) of the reaction mixture was removed, dissolved in $CDCl_3$ (0.5 mL) and the final conversion was determined by ^1H NMR using the ratio of *N*-Boc-formamide to formamide. The NMR sample and the reaction mixture were loaded onto a silica column; the product was eluted with 10 – 20 % ethyl acetate/hexanes, and the remaining formamide was eluted with 50 – 75 % ethyl acetate/hexanes. The enantiomeric ratio of the recovered formamide was determined by chiral-phase HPLC, and characterization of the formamides can be found in section **XI**. The *N*-Boc-formamide products for entries 3 and 4 in the table above are as follows:



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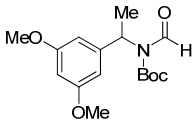
***N*-Boc-formamide 4.** Following Typical Procedure D, *N*-Boc-formamide **4** was isolated from the kinetic resolution as a clear oil (69 mg, 0.277 mmol, 55%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.28 – 7.13 (m, 5H), 5.70 (q, *J* = 7.1, 1H), 1.64 (d, *J* = 7.1, 3H), 1.24 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.39, 152.63, 140.67, 128.11, 126.94, 126.49, 83.94, 48.71, 27.76, 16.77. **IR** (film, cm^{-1}) 2983, 2930, 1727, 1692, 1500, 1406, 1366, 1289, 1247, 1149, 1099, 860, 779, 754, 708. **R_f** (1:4 ethyl acetate:hexanes, UV) = 0.59. **UPLC/MS** monoisotopic mass calculated for $[C_{14}H_{19}NO_3 H]^+$ requires *m/z* 250.1443. Found 250.03 (ES+), t_r = 1.79 min.



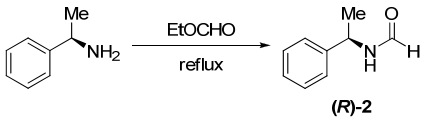
Boc-12-F

***N*-Boc-formamide Boc-12-F.** Following Typical Procedure D, *N*-Boc-formamide **Boc-12-F** was isolated from the kinetic resolution as a clear oil (74.3 mg, 0.240 mmol, 48%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 6.42 (d, *J* = 2.1, 2H), 6.35 (t, *J* = 2.2, 1H), 5.67 (q, *J* = 7.0, 1H), 3.76 (s, 6H), 1.67 (d, *J* = 7.1, 3H), 1.34 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.34, 160.65, 152.60, 143.21, 104.83, 98.59, 83.98, 55.30, 48.78, 27.81, 16.95. **IR** (film, cm^{-1}) 2977, 2839, 1729, 1692, 1596, 1457, 1368, 1324, 1240,

1147, 1096, 1043, 926, 848, 775, 698. **R_f** (1:4 ethyl acetate:hexanes, UV) = 0.44. **UPLC/MS** monoisotopic mass calculated for $[C_{16}H_{23}NO_5\ H]^+$ requires *m/z* 310.1655 Found 310.12 (ES+), t_r = 1.72 min.

Typical Procedure E: 0.5 mmol-Scale Thioformamide KR. A 1-dram vial was charged with 37 mg of oven-dried 4 Å molecular sieves (powder) and a magnetic stirbar. The vial and sieves were then flame-dried and allowed to cool. Chloroform (0.6 mL) was added to the sieves and was allowed to stir for 5 minutes to give a homogeneous suspension. In a separate oven-dried vial, the thioformamide substrate (0.500 mmol) was dissolved in chloroform (0.3 mL) and transferred to the reaction mixture by pipette. To ensure complete transfer, the vial was rinsed again with chloroform (0.3 mL), which was also added to the reaction mixture. Catalyst **6d** (17 mg, 25.0 μmol) and Boc_2O (65 mg, 0.300 mmol) were added directly to the reaction mixture, and the sides of the reaction vial were rinsed with chloroform (0.4 mL), the vial was capped tightly, and the reaction was allowed to stir vigorously for 24 – 28 hours at 23 °C. At this point, an aliquot (25 μL) of the reaction mixture was removed, dissolved in $CDCl_3$ (0.5 mL) and the final conversion was determined by ^{1}H NMR using the ratio of *N*-Boc-thioformamide to thioformamide. The NMR sample and the reaction mixture were loaded onto a silica column; the product (bright yellow) was eluted with 10 – 20 % ethyl acetate/hexanes, and the remaining thioformamide was eluted with 50 % ethyl acetate/hexanes. A portion of the recovered thioformamide was converted to the formamide (see Typical Procedure H in section **XI**) for determination of enantiomeric ratio by chiral-phase HPLC. Characterization of thioformamides and *N*-Boc-thioformamides can be found in sections **IX** and **X**, respectively.

VII. Determination of Absolute Stereochemistry



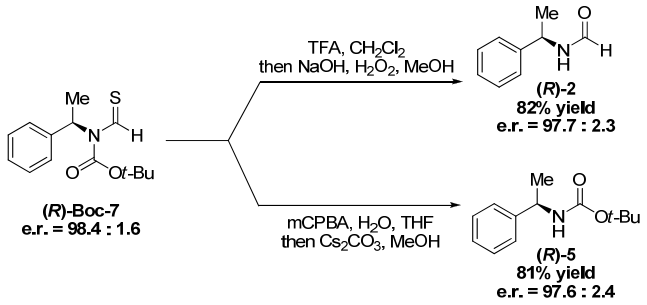
(*R*)-2

(*R*)-(+)-α-Methylbenzylamine (Sigma Aldrich, 96% e.e., 209 mg, 1.73 mmol) was stirred with ethyl formate (6 mL) at reflux for 8 hr. The reaction mixture was

concentrated by rotary evaporation to quantitatively yield formamide **(*R*)-2**. $[\alpha]_D^{20}$ = +161.4 (*c* 0.5, $CHCl_3$, 98.4:1.6 e.r.). **HPLC** Chiralcel OD; 3.0% 2-propanol/hexanes; flow rate = 0.75 mL/min; t_r = 56.6 min. (major enantiomer),t_r = 76.7 min. (minor enantiomer).

Compared to the recovered formamide product of the kinetic resolution (**7-F**), formamide **(*R*)-2** provides the opposite optical rotation and the opposite major enantiomer by chiral HPLC. It is, therefore, concluded that the major enantiomer of the recovered starting material for the kinetic resolution is **(*S*)-2**, and that the (*R*)-enantiomer is the more reactive.

VIII. Reactivity of *N*-Boc-thioformamides



Formamide 2 from Boc-7. An oven-dried vial with magnetic stirbar was charged with **(*R*)-Boc-7** (17 mg, 0.0641 mmol) (prepared from **(*R*)-2** of section **VII**) and dichloromethane (1.3 mL) and the mixture was cooled to 0 °C. Trifluoroacetic acid (TFA) (257 μL, 3.46 mmol) was added slowly to the reaction mixture with vigorous stirring. The vial was capped, and, after 30 min, the ice bath was removed. The mixture was stirred for another 2.5 hr at which time the yellow color of the starting material was no longer visible. TLC (1:9 ethyl acetate:hexanes) confirmed that no starting material remained, and the reaction mixture was concentrated to dryness by vacuum. Methanol (804 μL) was added to the resulting crude oil, and the solution was cooled to 0 °C. An aqueous solution of sodium hydroxide (2 M, 199 μL) was added and was quickly followed by 30% aqueous hydrogen peroxide (319 μL). The reaction was stirred vigorously at 0 °C for 5 min and then removed from the ice bath. The reaction was allowed to stir at ambient temperature for 15 min before the reaction was diluted with 1 mL of water, cooled to 0 °C, and acidified with 1M HCl (300 μL). Excess peroxide was

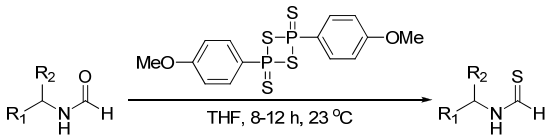
carefully quenched with saturated aqueous sodium thiosulfate (540 μL). The reaction mixture was transferred to a separatory funnel, diluted again with 2 mL water, and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried with sodium sulfate and concentrated. The crude product was passed through a short silica plug (50% to 75% ethyl acetate/hexanes) to provide formamide **(*R*)-2** as a colorless solid (7.8 mg, 0.0523 mmol, 82%). Characterization of **2** can be found in section **XI**.

Carbamate 5 from Boc-7. An oven-dried vial with magnetic stir bar was charged with **(*R*)-Boc-7** (17 mg, 0.0641 mmol) (prepared from **(*R*)-2** of section **VII**), THF (1.3 mL), and water (115 μL, 6.41 mmol), and the mixture was cooled to 0 °C. *meta*-Chloroperoxybenzoic acid (*m*CPBA, < 77%) (16 mg, 0.0705 mmol) was added to the reaction mixture, and the yellow color faded dramatically within 1 min. After 40 min at 0 °C, another portion of *m*CPBA (16 mg, 0.0705 mmol) was added, and the yellow color quickly disappeared altogether. The reaction was stirred an additional 90 min at 0 °C, methanol (2.6 mL) and cesium carbonate (209 mg, 0.641 mmol) were added, and the reaction was stirred for 3 hr while gradually warming to ambient temperature. The reaction mixture was concentrated in vacuo to approximately 2 mL, diluted with water (4 mL), carefully quenched with saturated aqueous sodium thiosulfate (300 μL), and extracted with ether (3 × 6 mL). The combined organic layers were dried over sodium sulfate, concentrated, and passed through a short silica plug (10% to 30% ethyl acetate/hexanes) to provide clean carbamate **(*R*)-5** as a white solid (11.5 mg, 0.0520 mmol, 81%). Spectroscopic data for **5** were consistent with literature values,[3] and the details for chiral-phase HPLC analysis are as follows: Chiralcel OD; 1.0% to 2.5% 2-propanol/hexanes (0 – 30 min); flow rate = 0.75 mL/min; t_r = 10.6 min. (minor enantiomer), t_r = 12.4 min. (major enantiomer).

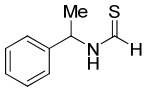
IX. Preparation of Thioformamide Substrates from Formamides.

A typical procedure for the thionation of formamides to the corresponding thioformamides with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent) is described below.[4] The formamide starting material was synthesized as described in section **XI** (Typical Procedure G). In general, the formamide was purified before thionation; however, it may sometimes be convenient to forgo

purification until after thionation. The yields reported in this section are for thionation reactions starting from the purified formamide.

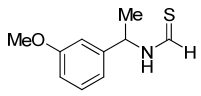


Typical Procedure F. In a roundbottom flask equipped with a magnetic stirbar, the formamide was dissolved in THF (0.1 M). To this was added Lawesson's reagent (0.51 equiv), and the reaction mixture was stirred at ambient temperature for 8–12 h. The solvent was removed by evaporation, and the remaining residue was loaded onto a silica column. The product was isolated by flash column chromatography (dichloromethane or ethyl acetate/hexanes). The pure product typically provided two spots by TLC (detectable by CAM stain and/or UV) representing the *cis*- and *trans*- rotational isomers. After several minutes, two-dimensional TLC may be applied to confirm that each spot can isomerize to yield both isomers.



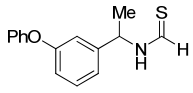
7

Thioformamide 7. Following Typical Procedure F, thioformamide **7** was prepared from the corresponding formamide (300 mg, 2.01 mmol) and Lawesson's reagent (415 mg, 1.03 mmol) in THF (20 mL). The crude product was purified by flash column chromatography (CH_2Cl_2) to yield a slightly yellow oil (210 mg, 1.27 mmol, 63%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (1.5:1 major:minor): δ 9.38 (d, *J* = 6.3, 1H), 7.69 (br s, 1H), 7.41 – 7.24 (m, 5H), 5.86 (dq, *J* = 7.0, 7.0, 1H), 1.62 (d, *J* = 5.9, 3H). Distinguishable Peaks for Minor Rotamer: δ 9.18 (d, *J* = 15.0, 1H), 8.27 (br s, 1H), 4.78 (dq, *J* = 6.7, 6.7, 1H), 1.63 (d, *J* = 5.6, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.34, 187.63, 140.76, 140.56, 129.11, 128.83, 128.33, 127.92, 126.52, 126.15, 58.96, 51.87, 22.25, 19.87. **IR** (film, cm^{-1}) 3185, 3060, 3027, 2971, 2931, 1529, 1493, 1453, 1377, 1325, 1269, 1203, 1122, 1087, 1016, 943, 923, 844, 758, 696. **R_f** (3:7 ethyl acetate:hexanes, CAM) = 0.43 and 0.57 (two rotamers). **Exact mass** calculated for $[C_9H_{11}NS\ H]^+$ requires *m/z* 166.0685 Found 166.0683 (ESI+).



9

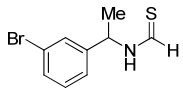
Thioformamide 9. Following Typical Procedure F, thioformamide **9** was prepared from the corresponding formamide (1.0 g, 5.58 mmol) and Lawesson's reagent (1.15 g, 2.84 mmol) in THF (56 mL). The crude product was purified by flash column chromatography (30% ethyl acetate/hexanes) to yield an off-white solid (422 mg, 2.16 mmol, 39%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (2.5:1 major:minor): δ 9.38 (d, *J* = 6.4, 1H), 7.63 (br s, 1H), 7.29 (d, *J* = 8.1, 1H), 6.93 (d, *J* = 7.6, 1H), 6.89 (s, 1H), 6.84 (m, 1H), 5.82 (dq, *J* = 7.1, 7.1, 1H), 3.80 (s, 3H), 1.60 (d, *J* = 6.9 3H). Distinguishable Peaks for Minor Rotamer: δ 9.18 (d, *J* = 15.1, 1H), 8.11 (br s, 1H), 6.78 (s, 1H), 4.74 (dq, *J* = 6.9, 6.9, 1H), 3.80 (s, 3H), 1.61 (d, *J* = 6.6, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.41, 187.67, 160.09, 159.91, 142.39, 142.18, 130.23, 129.92, 118.65, 118.34, 113.42, 113.11, 112.59, 112.16, 58.89, 55.29, 55.25, 51.85, 22.24, 19.85. **IR** (film, cm^{-1}) 3188, 3001, 2968, 2834, 1601, 1585, 1530, 1488, 1434, 1320, 1253, 1162, 1042, 948, 930, 827, 781, 670. **R_f** (3:7 ethyl acetate:hexanes, CAM) = 0.32 and 0.43 (two rotamers). **Exact mass** calculated for $[C_{10}H_{13}NOS\ H]^+$ requires *m/z* 196.0791 Found 196.0788 (ESI+).



10

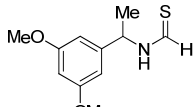
Thioformamide 10. Following Typical Procedure F, thioformamide **10** was prepared from the corresponding formamide (322 mg, 1.34 mmol) and Lawesson's reagent (275 mg, 0.68 mmol) in THF (13 mL). The crude product was purified by flash column chromatography (CH_2Cl_2) to yield a colorless oil (286 mg, 1.11 mmol, 83%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (2.8:1 major:minor): δ 9.29 (d, *J* = 6.4, 1H), 7.56 (br s, 1H), 7.32 – 7.16 (m, 3H), 7.08 – 6.80 (m, 6H), 5.73 (dq, *J* = 7.1, 7.1, 1H), 1.51 (d, *J* = 6.9, 3H). Distinguishable Peaks for Minor Rotamer: δ 9.10 (d, *J* = 15.1, 1H), 8.04 (br s, 1H), 4.66 (dq, *J* = 6.9, 6.9, 1H), 1.53 (d, *J* = 7.0, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$ δ 190.44, 187.80, 158.03, 157.65, 156.74, 156.47, 142.90, 142.67, 130.48, 130.14, 129.87, 129.80, 123.74, 123.49, 121.30, 120.63, 119.16, 118.93, 118.14, 117.93, 116.82, 116.40,

58.67, 51.66, 22.20, 20.10. **IR** (film, cm^{-1}) 3189, 3010, 2971, 1582, 1529, 1503, 1434, 1236, 1210, 1162, 939, 757, 691. $\mathbf{R_f}$ (3:7 ethyl acetate:hexanes, CAM) = 0.38 and 0.52 (two rotamers). **Exact mass** calculated for $[C_{15}H_{15}NOS\ H]^+$ requires *m/z* 258.0947 Found 258.0941 (ESI+).



11

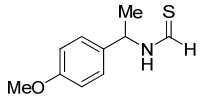
Thioformamide 11. Following Typical Procedure F, thioformamide **11** was prepared from the corresponding formamide (250 mg, 1.10 mmol) and Lawesson's reagent (226 mg, 0.56 mmol) in THF (11 mL). The crude product was purified by flash column chromatography (CH_2Cl_2) to yield a slightly yellow oil (206 mg, 0.84 mmol, 77%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (2.9:1 major:minor): δ 9.39 (d, *J* = 6.3, 1H), 7.72 (br s, 1H), 7.50 – 7.39 (m, 2H), 7.30 – 7.18 (m, 2H), 5.80 (dq, *J* = 7.1, 7.1, 1H), 1.59 (d, *J* = 6.9, 3H). Distinguishable Peaks for Minor Rotamer: δ 9.17 (d, *J* = 15.0, 1H), 8.23 (br s, 1H), 4.75 (dq, *J* = 6.9, 6.9, 1H), 1.61 (d, *J* = 6.9, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.57, 188.02, 143.12, 142.94, 131.46, 130.94, 130.71, 130.37, 129.50, 129.32, 125.31, 124.78, 123.13, 122.82, 58.39, 51.31, 22.17, 20.19. **IR** (film, cm^{-1}) 3173, 2970, 2931, 2812, 1524, 1433, 1267, 1199, 1070, 943, 924, 857, 779, 692, 675. $\mathbf{R_f}$ (3:7 ethyl acetate:hexanes, CAM) = 0.35 and 0.49 (two rotamers). **Exact mass** calculated for $[C_9H_{10}BrNS\ H]^+$ requires *m/z* 245.9769 Found 245.9764 (ESI+).



12

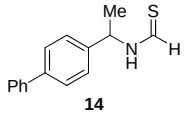
Thioformamide 12. Following Typical Procedure F, thioformamide **12** was prepared from the corresponding formamide (300 mg, 1.43 mmol) and Lawesson's reagent (296 mg, 0.73 mmol) in THF (14 mL). The crude product was purified by flash column chromatography (30% to 50% ethyl acetate/hexanes) to yield an orange oil (201 mg, 0.89 mmol, 62%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (2.2:1 major:minor): δ 9.37 (d, *J* = 6.4, 1H), 7.70 (br s, 1H), 6.49 – 6.37 (m, 3H), 5.76 (dq, *J* = 7.0, 7.0, 1H), 3.77 (s, 6H), 1.58 (d, *J* = 7.0, 3H). Distinguishable Peaks for Minor Rotamer: δ 9.16 (d, *J* = 15.1,

1H), 8.21 (br s, 1H), 4.68 (dq, *J* = 6.8, 6.8, 1H), 3.78 (s, 6H), 1.59 (d, *J* = 7.3, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.38, 187.65, 161.29, 161.09, 143.18, 142.98, 104.72, 104.34, 99.72, 99.49, 59.04, 55.37, 55.34, 51.97, 22.16, 19.79. **IR** (film, cm^{-1}) 3243, 3202, 2999, 2966, 2936, 2836, 1594, 1530, 1427, 1342, 1291, 1202, 1150, 1052, 1026, 938, 831, 694. **R_f** (3:7 ethyl acetate:hexanes, CAM) = 0.24 and 0.35 (two rotamers). **Exact mass** calculated for $[C_{11}H_{15}NO_2S\ H]^+$ requires *m/z* 226.0896 Found 226.0895 (ESI+).



13

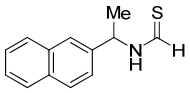
Thioformamide 13. Following Typical Procedure F, thioformamide **13** was prepared from the corresponding formamide (200 mg, 1.12 mmol) and Lawesson's reagent (230 mg, 0.57 mmol) in THF (11 mL). The crude product was purified by flash column chromatography (30% ethyl acetate/hexanes) to yield a colorless oil (155 mg, 0.86 mmol, 77%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (2.3:1 major:minor): δ 9.34 (d, *J* = 6.5, 1H), 7.69 (br s, 1H), 7.28 (d, *J* = 8.5, 2H), 6.92 – 6.85 (m, 2H), 5.80 (dq, *J* = 7.1, 7.1, 1H), 3.79 (s, 3H), 1.59 (d, *J* = 6.9, 3H). Distinguishable Peaks for Minor Rotamer: δ 9.13 (d, *J* = 15.2, 1H), 8.17 (br s, 1H), 7.18 (d, *J* = 8.5, 2H), 4.72 (dq, *J* = 6.8,. 6.8, 1H), 3.80 (s, 3H), 1.60 (d, *J* = 6.9, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.00, 187.31, 159.48, 159.17, 132.86, 132.42, 127.79, 127.46, 114.40, 114.13, 58.43, 55.30, 55.26, 51.30, 22.17, 19.69. **IR** (film, cm^{-1}) 3187, 2967, 2933, 2834, 1611, 1510, 1435, 1336, 1304, 1242, 1177, 1103, 1024, 943, 922, 829, 808, 702. **R_f** (3:7 ethyl acetate:hexanes, CAM) = 0.30 and 0.40 (two rotamers). **Exact mass** calculated for $[C_{10}H_{13}NOS\ Na]^+$ requires *m/z* 218.0610 Found 218.0608 (ESI+).



14

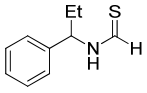
Thioformamide 14. Following Typical Procedure F, thioformamide **14** was prepared from the corresponding formamide (175 mg, 0.78 mmol) and Lawesson's reagent (164 mg, 0.40 mmol) in THF (8 mL). The crude product was purified by flash column

chromatography (CH_2Cl_2) to yield a colorless solid (175 mg, 0.73 mmol, 93%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (4.4:1 major:minor): δ 9.42 (d, *J* = 6.4, 1H), 7.65 – 7.55 (m, 5H), 7.49 – 7.31 (m, 5H), 5.92 (dq, *J* = 7.0, 7.0, 1H), 1.66 (d, *J* = 6.9, 3H). Distinguishable Peaks for Minor Rotamer: δ 9.23 (d, *J* = 15.1, 1H), 8.02 (br s, 1H), 4.83 (dq, *J* = 6.8, 6.8, 1H), 1.67 (d, *J* = 6.8, 3H). **^{13}C NMR** (125 MHz, CDCl3) δ 190.47, 187.72, 141.37, 140.90, 140.42, 140.20, 139.74, 139.49, 128.84, 128.80, 127.82, 127.60, 127.54, 127.46, 127.05, 127.03, 126.98, 126.62, 58.63, 51.57, 22.28, 19.91. **IR** (film, cm^{-1}) 3341, 3175, 3052, 3026, 2970, 2929, 1527, 1485, 1435, 1331, 1273, 1105, 1007, 944, 921, 836, 763, 731, 696. **R_f** (3:7 ethyl acetate:hexanes, CAM) = 0.38 and 0.53 (two rotamers). **Exact mass** calculated for $[C_{15}H_{15}NS\ H]^+$ requires *m/z* 242.0998 Found 242.0998 (ESI+).



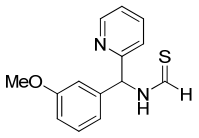
15

Thioformamide 15. Following Typical Procedure F, thioformamide **15** was prepared from the corresponding formamide (200 mg, 1.00 mmol) and Lawesson's reagent (207 mg, 0.51 mmol) in THF (10 mL). The crude product was purified by flash column chromatography (30% ethyl acetate/hexanes) to yield a colorless solid (179 mg, 0.83 mmol, 83%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (2.1:1 major:minor): δ 9.40 (d, *J* = 6.4, 1H), 7.90 – 7.60 (m, 5H), 7.55 – 7.46 (m, 2H), 7.44 (d, *J* = 8.5, 1H), 6.02 (dq, *J* = 7.1, 7.1, 1H), 1.69 (d, *J* = 6.8, 3H). Distinguishable Peaks for Minor Rotamer: δ 9.20 (d, *J* = 15.1, 1H), 8.24 (br s, 1H), 7.33 (d, *J* = 8.5, 1H), 4.88 (dq, *J* = 6.8, 6.8, 1H), 1.68 (d, *J* = 6.6, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.49, 187.74, 138.08, 137.85, 133.20, 133.17, 132.95, 132.84, 129.16, 128.72, 127.92, 127.90, 127.68, 127.62, 126.69, 126.52, 126.43, 126.22, 125.20, 125.14, 124.65, 123.79, 59.01, 51.88, 22.17, 19.84. **IR** (film, cm^{-1}) 3346, 3176, 3050, 3011, 2969, 2930, 1526, 1504, 1432, 1377, 1269, 1176, 1128, 950, 857, 815, 747, 728. **R_f** (3:7 ethyl acetate:hexanes, CAM) = 0.32 and 0.46 (two rotamers). **Exact mass** calculated for $[C_{13}H_{13}NS\ Na]^+$ requires *m/z* 238.0661 Found 238.0661 (ESI+).



16

Thioformamide 16. Following Typical Procedure F, thioformamide **16** was prepared from the corresponding formamide (200 mg, 1.23 mmol) and Lawesson's reagent (273 mg, 0.55 mmol) in THF (12 mL). The crude product was purified by flash column chromatography (CH_2Cl_2) to yield a slightly yellow oil (164 mg, 0.92 mmol, 75%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (2.2:1 major:minor): δ 9.40 (d, *J* = 6.2, 1H), 7.79 (br s, 1H), 7.42 – 7.19 (m, 5H), 5.62 (dt, *J* = 7.6, 7.6, 1H), 2.10 – 1.87 (m, 2H), 0.97 – 0.89 (m, 3H). Distinguishable Peaks for Minor Rotamer: δ 9.16 (d, *J* = 15.0, 1H), 8.24 (br s, 1H), 4.47 (dt, *J* = 7.3, 7.3, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 190.74, 187.98, 139.65, 139.44, 129.07, 128.77, 128.30, 127.84, 127.03, 126.57, 65.73, 57.95, 29.33, 27.82, 10.62, 10.46. **IR** (film, cm^{-1}) 3186, 3027, 2964, 2932, 2874, 1529, 1438, 1342, 1300, 958, 901, 872, 836, 747, 697. **R_f** (3:7 ethyl acetate:hexanes, CAM) = 0.40 and 0.58 (two rotamers). **Exact mass** calculated for $[C_{10}H_{13}NS\ H]^+$ requires *m/z* 180.0841 Found 180.0839 (ESI+).

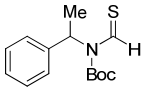


17

Thioformamide 17. Following Typical Procedure F, thioformamide **17** was prepared from the corresponding formamide (374 mg, 1.54 mmol) and Lawesson's reagent (318 mg, 0.79 mmol) in THF (15 mL). The crude product was purified by flash column chromatography (30% to 100% ethyl acetate/hexanes) to yield a yellow oil (136 mg, 0.53 mmol, 34%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (7.3:1 major:minor): δ 9.66 (br s, 1H), 9.56 (d, *J* = 6.2, 1H), 8.54 (d, *J* = 4.9, 1H), 7.66 (dd, *J* = 7.7, 7.7, 1H), 7.29 (d, *J* = 7.9, 1H), 7.25 – 7.18 (m, 2H), 6.95 (s, 1H), 6.94 (d, *J* = 2.1, 2H), 6.78 (d, *J* = 8.4, 1H), 6.74 (d, *J* = 7.1, 1H), 3.75 (s, 3H). Distinguishable Peaks for Minor Rotamer: δ 9.30 (d, *J* = 15.3, 1H), 8.60 (d, *J* = 4.9, 1H), 7.14 (d, *J* = 7.9, 1H), 6.87 (d, *J* = 7.1, 1H), 6.84 (d, *J* = 8.3, 1H), 5.79 (d, *J* = 5.8, 1H), 3.76 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 191.10, 187.63, 160.18, 159.74, 157.31, 156.47, 149.00, 148.74, 141.28, 141.27, 137.23,

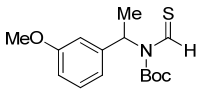
130.31, 129.67, 123.07, 122.96, 122.87, 122.22, 120.11, 119.81, 113.85, 113.72, 113.33, 113.10, 65.79, 59.66, 55.28, 55.18. **IR** (film, cm^{-1}) 3234, 3154, 3050, 2999, 2958, 2937, 2833, 1589, 1488, 1434, 1260, 1147, 1038, 996, 906, 867, 779, 729, 699. $\mathbf{R_f}$ (3:7 ethyl acetate:hexanes, CAM) = 0.15 (single spot). **Exact mass** calculated for $[C_{14}H_{14}N_2OS\ H]^+$ requires *m/z* 259.0900 Found 259.0894 (ESI+).

X. Characterization of *N*-Boc-thioformamides



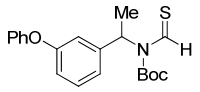
Boc-7

***N*-Boc-thioformamide Boc-7.** Following Typical Procedure C, **Boc-7** was isolated from the kinetic resolution reaction as a yellow oil (14.3 mg, 0.054 mmol, 40%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 7.36 – 7.29 (m, 2H), 7.26 – 7.24 (m, 3H), 6.78 (q, *J* = 6.9, 1H), 1.73 (d, *J* = 7.0, 3H), 1.24 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.28, 150.93, 140.37, 128.23, 126.97, 125.93, 85.06, 52.14, 27.51, 15.72. **IR** (film, cm^{-1}) 2976, 1735, 1405, 1370, 1242, 1150, 1015, 845, 805, 773, 742, 697. $\mathbf{R_f}$ (1:9 ethyl acetate:hexanes, UV) = 0.45. **Exact mass** calculated for $[C_{14}H_{19}NO_2S\ Na]^+$ requires *m/z* 288.1029 Found 288.1031 (ESI+).



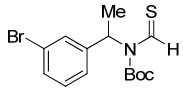
Boc-9

***N*-Boc-thioformamide Boc-9.** Following Typical Procedure C, **Boc-9** was isolated from the kinetic resolution reaction as a yellow oil (18.4 mg, 0.062 mmol, 46%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.52 (s, 1H), 7.23 (dd, *J* = 7.8, 7.8, 1H), 6.85 – 6.77 (m, 3H), 6.74 (q, *J* = 7.0, 1H), 3.78 (s, 3H), 1.71 (d, *J* = 7.0, 3H), 1.27 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.21, 159.62, 150.91, 142.05, 129.25, 118.31, 112.08, 111.97, 85.10, 55.24, 52.08, 27.55, 15.81. **IR** (film, cm^{-1}) 2978, 2938, 2837, 1736, 1597, 1460, 1407, 1370, 1330, 1242, 1205, 1152, 1097, 1041, 1018, 847, 773. $\mathbf{R_f}$ (1:9 ethyl acetate:hexanes, UV) = 0.39. **Exact mass** calculated for $[C_{15}H_{21}NO_3S\ Na]^+$ requires *m/z* 318.1134 Found 318.1140 (ESI+).



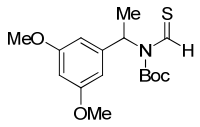
Boc-10

***N*-Boc-thioformamide Boc-10.** Following Typical Procedure C, **Boc-10** was isolated from the kinetic resolution reaction as a yellow solid (24.5 mg, 0.069 mmol, 51%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.32 – 7.27 (m, 2H), 7.24 (d, *J* = 7.8, 1H), 7.07 (dd, *J* = 7.4, 7.4, 1H), 6.98 – 6.91 (m, 4H), 6.84 (d, *J* = 8.1, 1H), 6.73 (q, *J* = 6.9, 1H), 1.67 (d, *J* = 7.0, 3H), 1.28 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.19, 157.16, 157.07, 150.72, 142.60, 129.72, 129.50, 123.26, 120.89, 118.61, 117.24, 116.94, 85.19, 51.86, 27.61, 15.82. **IR** (film, cm^{-1}) 2979, 2936, 1737, 1583, 1486, 1405, 1370, 1326, 1239, 1149, 1018, 928, 845, 771, 756, 693. **R_f** (1:9 ethyl acetate:hexanes, UV) = 0.39. **Exact mass** calculated for $[C_{20}H_{23}NO_3S\ Na]^+$ requires *m/z* 380.1291 Found 380.1291 (ESI+).



Boc-11

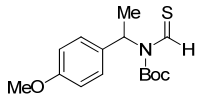
***N*-Boc-thioformamide Boc-11.** Following Typical Procedure C, **Boc-11** was isolated from the kinetic resolution reaction as a yellow oil (22.7 mg, 0.066 mmol, 49%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.40 – 7.39 (m, 2H), 7.23 – 7.14 (m, 2H), 6.76 (q, *J* = 6.9, 1H), 1.70 (d, *J* = 7.0, 3H), 1.29 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.20, 150.60, 142.79, 130.10, 129.85, 129.21, 124.78, 122.40, 85.48, 51.50, 27.59, 15.71. **IR** (film, cm^{-1}) 2979, 2936, 1735, 1596, 1569, 1477, 1403, 1369, 1327, 1241, 1080, 1016, 844, 771, 699, 682. **R_f** (1:9 ethyl acetate:hexanes, UV) = 0.42. **Exact mass** calculated for $[C_{14}H_{18}BrNO_2S\ Na]^+$ requires *m/z* 368.0114 Found 368.0112 (ESI+).



Boc-12

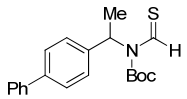
***N*-Boc-thioformamide Boc-12.** Following Typical Procedure C, **Boc-12** was isolated from the kinetic resolution reaction as a yellow oil (20.9 mg, 0.064 mmol, 48%). **^{1}H**

NMR (500 MHz, $CDCl_3$) δ 10.51 (s, 1H), 6.68 (q, *J* = 6.9, 1H), 6.40 – 6.37 (m, 2H), 6.36 – 6.35 (m, 1H), 3.76 (s, 6H), 1.68 (d, *J* = 7.0, 3H), 1.29 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.17, 160.78, 150.91, 142.89, 104.27, 98.54, 85.12, 55.34, 52.19, 27.59, 15.87. **IR** (film, cm^{-1}) 2978, 2939, 2835, 1736, 1602, 1585, 1491, 1406, 1370, 1325, 1241, 1151, 1132, 1039, 1017, 846, 783, 772, 696. **R_f** (1:9 ethyl acetate:hexanes, UV) = 0.28. **Exact mass** calculated for $[C_{16}H_{23}NO_4S\ H]^+$ requires *m/z* 326.1421 Found 326.1423 (ESI+).



Boc-13

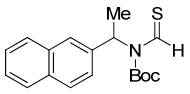
***N*-Boc-thioformamide Boc-13.** Following Typical Procedure C, **Boc-13** was isolated from the kinetic resolution reaction as a yellow oil (19.5 mg, 0.066 mmol, 49%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.50 (s, 1H), 7.18 (d, *J* = 8.2, 2H), 6.85 (d, *J* = 8.8, 2H), 6.73 (q, *J* = 7.0, 1H), 3.80 (s, 3H), 1.71 (d, *J* = 7.0, 3H), 1.29 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.27, 158.58, 150.92, 132.35, 127.36, 113.48, 84.99, 55.28, 51.80, 27.59, 15.93. **IR** (film, cm^{-1}) 2978, 2936, 2836, 1732, 1612, 1513, 1407, 1370, 1298, 1243, 1149, 1080, 1014, 837, 772, 633. **R_f** (1:9 ethyl acetate:hexanes, UV) = 0.36. **Exact mass** calculated for $[C_{15}H_{21}NO_3S\ Na]^+$ requires *m/z* 318.1134 Found 318.1143 (ESI+).



Boc-14

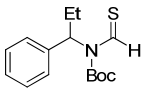
***N*-Boc-thioformamide Boc-14.** Following Typical Procedure C, **Boc-14** was isolated from the kinetic resolution reaction as a yellow solid (22.3 mg, 0.065 mmol, 49%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.64 – 7.54 (m, 4H), 7.45 (dd, *J* = 7.6, 7.6, 2H), 7.36 – 7.33 (m, 3H), 6.84 (q, *J* = 6.9, 1H), 1.78 (d, *J* = 7.0, 3H), 1.28 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.27, 150.86, 140.57, 139.85, 139.44, 128.79, 127.33, 126.96, 126.87, 126.43, 85.20, 51.98, 27.56, 15.83. **IR** (film, cm^{-1}) 3029, 2979, 2936, 1734, 1487, 1405, 1370, 1242, 1150, 1134, 1082, 1014, 846, 763, 697. **R_f** (1:9 ethyl

acetate:hexanes, UV) = 0.42. **Exact mass** calculated for $[C_{20}H_{23}NO_2S\ H]^+$ requires *m/z* 342.1522 Found 342.1519 (ESI+).



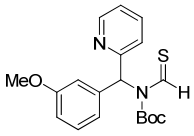
Boc-15

***N*-Boc-thioformamide Boc-15.** Following Typical Procedure C, **Boc-15** was isolated from the kinetic resolution reaction as a yellow solid (21.8 mg, 0.069 mmol, 52%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.60 (s, 1H), 7.84 – 7.80 (m, 2H), 7.79 (d, *J* = 8.6, 1H), 7.73 (s, 1H), 7.52 – 7.45 (m, 2H), 7.31 (d, *J* = 8.5, 1H), 6.94 (q, *J* = 6.9, 1H), 1.85 (d, *J* = 6.9, 3H), 1.18 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.37, 150.88, 137.78, 133.07, 132.36, 127.98, 127.78, 127.56, 126.22, 125.82, 124.68, 124.32, 85.10, 52.33, 27.49, 15.82. **IR** (film, cm^{-1}) 3055, 2978, 2936, 1732, 1404, 1369, 1310, 1239, 1148, 1083, 1015, 845, 774, 749. **R_f** (1:9 ethyl acetate:hexanes, UV) = 0.42. **Exact mass** calculated for $[C_{18}H_{21}NO_2S\ H]^+$ requires *m/z* 316.1366 Found 316.1381 (ESI+).



Boc-16

***N*-Boc-thioformamide Boc-16.** Following Typical Procedure C, **Boc-16** was isolated from the kinetic resolution reaction as a yellow oil (17.3 mg, 0.062 mmol, 46%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.64 (s, 1H), 7.34 – 7.22 (m, 5H), 6.69 (dd, *J* = 9.2, 6.5, 1H), 2.39 – 2.23 (m, 2H), 1.30 (s, 9H), 1.01 (t, *J* = 7.4, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.63, 150.95, 139.56, 128.16, 127.14, 126.74, 85.08, 57.55, 27.59, 23.86, 10.88. **IR** (film, cm^{-1}) 2975, 2935, 2879, 1735, 1407, 1370, 1310, 1239, 1149, 1120, 1072, 1036, 1009, 848, 773, 743, 698. **R_f** (1:9 ethyl acetate:hexanes, UV) = 0.42. **Exact mass** calculated for $[C_{15}H_{21}NO_2S\ Na]^+$ requires *m/z* 302.1185 Found 302.1187 (ESI+).



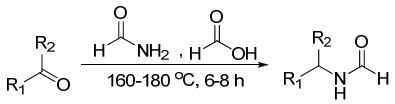
Boc-17

***N*-Boc-thioformamide Boc-17.** Following Typical Procedure C, **Boc-17** was isolated from the kinetic resolution reaction as a yellow oil (19.7 mg, 0.055 mmol, 41%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.59 (d, *J* = 4.8, 1H), 7.87 (s, 1H), 7.62 (dd, *J* = 7.8, 7.8, 1H), 7.29 (dd, *J* = 7.9, 7.9, 1H), 7.19 (dd, *J* = 7.4, 4.9, 1H), 7.10 (d, *J* = 8.0, 1H), 7.04 (d, *J* = 7.7, 1H), 7.02 (s, 1H), 6.88 (d, *J* = 8.2, 1H), 3.79 (s, 3H), 1.29 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.46, 159.58, 157.66, 150.92, 149.02, 138.61, 136.16, 129.34, 122.20, 121.94, 121.90, 115.44, 113.23, 85.21, 62.34, 55.23, 27.57. **IR** (film, cm^{-1}) 2980, 2835, 1738, 1601, 1588, 1491, 1463, 1406, 1369, 1310, 1242, 1147, 1049, 1012, 850, 778, 750, 696. **R_f** (1:4 ethyl acetate:hexanes, UV) = 0.26. **Exact mass** calculated for $[C_{19}H_{22}N_2O_3S\ H]^+$ requires *m/z* 359.1424 Found 359.1414 (ESI+).

XI. Preparation of Formamides from Ketones and Thioformamides

As an exception, formamide **2** was synthesized from readily available α-methylbenzylamine and ethyl formate in quantitative yield as described on page S-25 and in section **VII**. Generally, formamides may also be synthesized directly from the corresponding amines in high yields by using formic-acetic anhydride.[5]

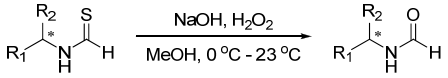
Typical Procedure G: Formamides from Ketones. The following describes the typical procedure for the Leukart-Wallach reaction to convert unsymmetrical ketones directly to chiral formamides.[6]



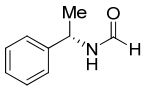
To a flask equipped with a magnetic stir bar and reflux condenser were added the ketone (2–30 mmol), formamide (12 equiv), and formic acid (12 equiv). The reaction mixture was heated under nitrogen in a sand bath at 180 °C for 6–8 h. The reaction was allowed to cool to room temperature, diluted with water (10–150 mL; saturated aqueous sodium bicarbonate was used for the precursor to substrate **17**), and extracted with dichloromethane (3 × 10–150 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated to yield the crude formamide, which was purified by flash column chromatography (50–100% ethyl acetate/hexanes). Racemic

formamide precursors to the thioformamide substrates **9–17** were synthesized by this method.

Typical Procedure H: Formamides from Thioformamides. Following the kinetic resolution reactions, recovered thioformamide substrates were converted to the corresponding formamides for determination of enantiomeric ratio and optical rotation.[7]



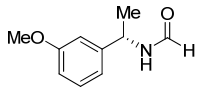
The thioformamide recovered from the kinetic resolution was dissolved in methanol (6.3 mL/mmol of thioformamide) in a vial with a stir bar and cooled to 0 °C. An aqueous solution of NaOH (2 M, 3.1 mL/mmol of thioformamide) was added by micropipette, which was quickly followed by the addition of 30% hydrogen peroxide (2.5 mL/mmol of thioformamide). The solution flashed yellow and then became cloudy white. The reaction was stirred vigorously at 0 °C for 5 min and then removed from the ice bath. Another aliquot of hydrogen peroxide (2.5 mL/mmol of thioformamide) was added and the reaction was allowed to stir at ambient temperature for 20 min, during which time the solution became homogeneous. The reaction was diluted with 1 mL of water, cooled to 0 °C, and neutralized with 1M HCl (except in the case of thioformamide **17**). Excess peroxide was carefully quenched with 350 μL of saturated aqueous sodium thiosulfate. The reaction mixture was transferred to a separatory funnel, diluted again with 2 mL water, and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried with sodium sulfate and concentrated. The resulting formamide was passed through a short silica plug (50% to 75% ethyl acetate/hexanes) to provide the analytical sample. The stereochemistry shown in the formamides below is an extension of the absolute stereochemistry of **(*S*)-2**, which was determined experimentally as described in section **VII**.



(*S*)-2, 7-F

Formamide (*S*)-2 or 7-F. Racemic **2** was synthesized from α-methylbenzylamine (3.0 g, 25 mmol) by refluxing in ethyl formate (80 mL) for 8 hr. The reaction mixture was

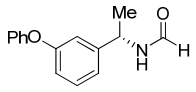
concentrate under vacuum to yield quantitative clean product (3.7 g, 25 mmol). Following Typical Procedure H, resolved thioformamide **7** (8.1 mg, 0.049 mmol) yielded enantioenriched **7-F** as a colorless solid (7.1 mg, 0.048 mmol, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$) Major Rotamer (5.8:1 major:minor): δ 8.00 (s, 1H), 7.34 – 7.18 (m, 5H), 6.78 (br s, 1H), 5.10 (dq, *J* = 7.1, 7.1, 1H), 1.42 (d, *J* = 7.0, 3H). Distinguishable Peaks for Minor Rotamer: δ 8.03 (d, *J* = 12.1, 1H), 4.59 (dq, *J* = 7.1, 7.1, 1H), 1.48 (d, *J* = 6.9, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.20, 160.42, 142.76, 142.62, 128.69, 128.46, 127.50, 127.19, 125.91, 125.60, 51.63, 47.37, 23.34, 21.69. **IR** (film, cm^{-1}) 3235, 3054, 2988, 2966, 2927, 2880, 1649, 1547, 1492, 1448, 1380, 1372, 1250, 1118, 1006, 760, 698. **R_f** (1:1 ethyl acetate:hexanes, CAM) = 0.19. **$[\alpha]_D^{20}$** = –99.2 (*c* 0.5, $CHCl_3$, 91:9 e.r.). **Exact mass** calculated for $[C_9H_{11}NO\ H]^+$ requires *m/z* 150.0913 Found 150.0912 (ESI+). **HPLC** Chiralcel OD; 3.0% 2-propanol/hexanes; flow rate = 0.75 mL/min; t_r = 56.6 min. (minor enantiomer), t_r = 76.7 min. (major enantiomer).



9-F

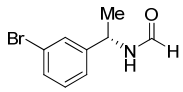
Formamide 9-F. Following Typical Procedure G, 3'-methoxyphenyl methyl ketone (5.0 g, 33 mmol) provided racemic **9-F** (3.1 g, 17 mmol, 52%). Following Typical Procedure H, resolved thioformamide **9** (9.7 mg, 0.050 mmol) yielded enantioenriched **9-F** as a colorless solid (7.0 mg, 0.039 mmol, 79%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (4.6:1 major:minor): δ 8.20 (s, 1H), 7.30 (dd, *J* = 7.9, 7.9, 1H), 6.95 (d, *J* = 7.6, 1H), 6.89 (s, 1H), 6.87 – 6.83 (m, 1H), 5.89 (br s, 1H), 5.22 (dq, *J* = 7.1, 7.1, 1H), 3.84 (s, 3H), 1.55 (d, *J* = 6.9, 3H). Distinguishable Peaks for Minor Rotamer: δ 8.19 (d, *J* = 12.3, 1H), 6.02 (br s, 1H), 4.70 (dq, *J* = 7.1, 7.1, 1H), 3.85 (s, 3H), 1.59 (d, *J* = 6.9, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.95, 160.13, 160.01, 159.88, 144.43, 144.18, 130.01, 129.80, 118.31, 117.97, 112.81, 112.67, 112.20, 111.79, 55.26, 55.22, 51.52, 47.56, 23.55, 21.69. **IR** (film, cm^{-1}) 3341, 3064, 3010, 2976, 2938, 2872, 2839, 1651, 1594, 1510, 1485, 1467, 1433, 1384, 1346, 1324, 1254, 1224, 1172, 1160, 1042, 1026, 868, 790, 701, 676. **R_f** (3:1 ethyl acetate:hexanes, CAM) = 0.23. **$[\alpha]_D^{20}$** = –142.2 (*c* 0.5, $CHCl_3$, 98.5:1.5 e.r.). **Exact mass** calculated for $[C_{10}H_{13}NO_2\ H]^+$ requires *m/z* 180.1019 Found 180.1017 (ESI+). **HPLC** Chiralcel OD; 5.0% to 8.0% 2-propanol/hexanes (0 – 30 min.), 8.0% 2-

propanol/hexanes (30 – 75 min.); flow rate = 0.75 mL/min; t_r = 37.6 min. (minor enantiomer), t_r = 55.1 min. (major enantiomer).



10-F

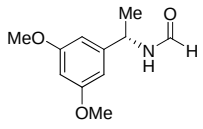
Formamide 10-F. Following Typical Procedure G, 3'-phenoxyphenyl methyl ketone (512 mg, 2.42 mmol) provided racemic **10-F** (448 mg, 2.02 mmol, 84%). Following Typical Procedure H, resolved thioformamide **10** (11.3 mg, 0.044 mmol) yielded enantioenriched **10-F** as a colorless oil (9.1 mg, 0.038 mmol, 86%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (4.7:1 major:minor): δ 8.16 (s, 1H), 7.39 – 7.27 (m, 3H), 7.16 – 7.09 (m, 1H), 7.06 (d, *J* = 7.7, 1H), 7.03 – 6.96 (m, 3H), 6.96 – 6.86 (m, 1H), 5.80 (br s, 1H), 5.19 (dq, *J* = 7.1, 7.1, 1H), 1.50 (d, *J* = 6.9, 3H). Distinguishable Peaks for Minor Rotamer: δ 8.15 (d, *J* = 12.4, 1H), 5.88 (br s, 1H), 4.66 (dq, *J* = 7.1, 7.1, 1H), 1.55 (d, *J* = 6.9, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.89, 160.16, 157.85, 157.60, 156.84, 156.66, 144.87, 144.67, 130.27, 130.03, 129.85, 129.79, 123.62, 123.43, 120.92, 120.32, 119.06, 118.95, 117.73, 117.57, 116.38, 116.12, 51.34, 47.37, 23.50, 21.83. **IR** (film, cm^{-1}) 3269, 3039, 2975, 2930, 2867, 1655, 1582, 1530, 1483, 1442, 1377, 1235, 1210, 1162, 1071, 1022, 936, 888, 754, 690. **R_f** (1:1 ethyl acetate:hexanes, CAM) = 0.25. **$[\alpha]_D^{20}$** = –117.8 (*c* 0.5, $CHCl_3$, 99.7:0.3 e.r.). **Exact mass** calculated for $[C_{15}H_{15}NO_2\ H]^+$ requires *m/z* 242.1176 Found 242.1174 (ESI+). **HPLC** Chiralcel OJ-H; 1.0% to 5.0% 2-propanol/hexanes (0 – 60 min.), 5.0% 2-propanol/hexanes (60 – 85 min.); flow rate = 0.75 mL/min; t_r = 66.4 min. (minor enantiomer), t_r = 72.6 min. (major enantiomer).



11-F

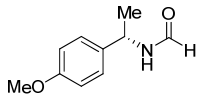
Formamide 11-F. Following Typical Procedure G, 3'-bromophenyl methyl ketone (448 mg, 2.25 mmol) provided racemic **11-F** (251 mg, 1.10 mmol, 49%). Following Typical Procedure H, resolved thioformamide **11** (11.3 mg, 0.046 mmol) yielded enantioenriched **11-F** as a colorless oil (7.9 mg, 0.035 mmol, 75%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (4.6:1 major:minor): δ 8.18 (s, 1H), 7.46 (s, 1H), , 7.40 (d, *J* = 7.7, 1H), 7.24 –

7.20 (m, 2H), 5.79 (br s, 1H), 5.18 (dq, *J* = 7.1, 7.1, 1H), 1.50 (d, *J* = 7.0, 3H). Distinguishable Peaks for Minor Rotamer: δ 8.16 (d, *J* = 12.0, 1H), 7.43 (m, 1H), 5.87 (br s, 1H), 4.68 (dq, *J* = 7.6, 7.6, 1H), 1.56 (d, *J* = 6.9, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.78, 160.13, 145.11, 144.93, 130.94, 130.64, 130.54, 130.32, 129.15, 129.02, 124.92, 124.40, 123.04, 122.82, 51.03, 47.14, 23.44, 21.71. **IR** (film, cm^{-1}) 3268, 3044, 2976, 2869, 1658, 1530, 1477, 1379, 1239, 785, 695. **R_f** (1:1 ethyl acetate:hexanes, CAM) = 0.20. **$[\alpha]_D^{20}$** = –121.8 (*c* 0.5, $CHCl_3$, 94.5:5.5 e.r.). **Exact mass** calculated for $[C_9H_{10}BrNO\ H]^+$ requires *m/z* 228.0019 Found 228.0018 (ESI+). **HPLC** Chiralcel OD; 1.0% to 13.0% 2-propanol/hexanes (0 – 60 min.); flow rate = 0.75 mL/min; t_r = 39.1 min. (minor enantiomer), t_r = 45.5 min. (major enantiomer).



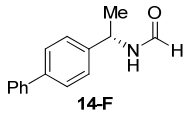
12-F

Formamide 12-F. Following Typical Procedure G, 3',5'-dimethoxyphenyl methyl ketone (1.5 g, 8.3 mmol) provided racemic **12-F** (670 mg, 3.2 mmol, 38%). Following Typical Procedure H, resolved thioformamide **12** (9.6 mg, 0.043 mmol) yielded enantioenriched **12-F** as a faintly brown solid (6.7 mg, 0.032 mmol, 75%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (4.4:1 major:minor): δ 8.18 (s, 1H), 6.46 (s, 2H), 6.37 (s, 1H), 5.72 (br s, 1H), 5.15 (dq, *J* = 7.1, 7.1, 1H), 3.79 (s, 6H), 1.50 (d, *J* = 6.9, 3H). Distinguishable Peaks for Minor Rotamer: δ 8.14 (s, 1H), 6.41 (s, 2H), 5.76 (br s, 1H), 4.62 (dq, *J* = 7.1, 7.1, 1H), 1.54 (d, *J* = 6.9, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.91, 161.22, 161.07, 160.13, 145.22, 144.94, 104.31, 103.93, 99.19, 99.12, 55.38, 55.35, 51.59, 47.71, 23.54, 21.67. **IR** (film, cm^{-1}) 3270, 2972, 2839, 1658, 1597, 1530, 1461, 1380, 1347, 1293, 1204, 1154, 1055, 837, 697, 585. **R_f** (3:1 ethyl acetate:hexanes, CAM) = 0.22. **$[\alpha]_D^{20}$** = –135.0 (*c* 0.5, $CHCl_3$, 99:1 e.r.). **Exact mass** calculated for $[C_{11}H_{15}NO_3\ H]^+$ requires *m/z* 210.1125 Found 210.1122 (ESI+). **HPLC** Chiralcel OJ-H; 3.0% to 4.0% 2-propanol/hexanes (0 – 30 min.), 4.0% 2-propanol/hexanes (30 – 60 min.), 4.0% to 6.0% 2-propanol/hexanes (60 – 90 min.); flow rate = 0.60 mL/min; t_r = 69.5 min. (minor enantiomer), t_r = 75.4 min. (major enantiomer).



13-F

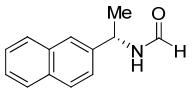
Formamide 13-F. Following Typical Procedure G, 4'-methoxyphenyl methyl ketone (2.5 g, 17 mmol) provided racemic **13-F** (930 mg, 5.2 mmol, 31%). Following Typical Procedure H, resolved thioformamide **13** (9.2 mg, 0.047 mmol) yielded enantioenriched **13-F** as a colorless solid (6.6 mg, 0.037 mmol, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) Major Rotamer (5.2:1 major:minor): δ 8.09 (s, 1H), 7.24 (d, *J* = 8.8, 2H), 6.86 (d, *J* = 8.8, 2H), 6.56 (br s, 1H), 5.13 (dq, *J* = 7.1, 7.1, 1H), 3.78 (s, 3H), 1.48 (d, *J* = 6.9, 3H). Distinguishable Peaks for Minor Rotamer: δ 8.10 (d, *J* = 9.9, 1H), 7.20 (d, *J* = 8.8, 2H), 4.62 (dq, *J* = 7.0, 7.0, 1H), 3.79 (s, 3H), 1.53 (d, *J* = 6.9, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.12, 160.29, 158.83, 158.64, 134.78, 134.71, 127.18, 126.84, 114.01, 113.81, 55.14, 55.11, 51.04, 46.79, 23.38, 21.55. **IR** (film, cm^{-1}) 3267, 3026, 2969, 2902, 2873, 2842, 1677, 1648, 1526, 1509, 1468, 1446, 1374, 1350, 1294, 1243, 1176, 1121, 1102, 1034, 998, 840, 821, 723, 710. **R_f** (3:1 ethyl acetate:hexanes, CAM) = 0.29. **$[\alpha]_D^{20}$** = –150.8 (*c* 0.5, $CHCl_3$, 94:6 e.r.). **Exact mass** calculated for $[C_{10}H_{13}NO_2\ Na]^+$ requires *m/z* 202.0838 Found 202.0836 (ESI+). **HPLC** Chiralcel OD; 1.8% 2-propanol/hexanes (0 – 15 min.), 1.8% to 9.0% 2-propanol/hexanes (15 – 17 min.), 9.0% 2-propanol/hexanes (17 – 60 min.); flow rate = 0.70 mL/min (0 – 15 min.), 0.70 mL/min to 1.30 mL/min (15 – 17 min.), 1.30 mL/min (17 – 60 min.); t_r = 32.2 min. (minor enantiomer), t_r = 34.7 min. (major enantiomer).



14-F

Formamide 14-F. Following Typical Procedure G, 4'-biphenyl methyl ketone (441 mg, 2.25 mmol) provided racemic **14-F** (296 mg, 1.31 mmol, 58%). Following Typical Procedure H, resolved thioformamide **14** (12.5 mg, 0.052 mmol) yielded enantioenriched **14-F** as a colorless solid (7.8 mg, 0.035 mmol, 67%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (3.8:1 major:minor): δ 8.21 (s, 1H), 7.60 – 7.57 (m, 4H), 7.48 – 7.32 (m, 5H), 5.82 (br s, 1H), 5.28 (dq, *J* = 7.1, 7.1, 1H), 1.57 (d, *J* = 6.9, 3H). Distinguishable

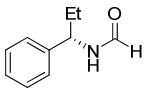
Peaks for Minor Rotamer: δ 8.21 (d, *J* = 11.9, 1H), 5.93 (br s, 1H), 4.76 (dq, *J* = 7.1, 7.1, 1H), 1.61 (d, *J* = 6.9, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.96, 160.19, 141.66, 141.48, 140.78, 140.59, 140.55, 140.37, 128.82, 128.78, 127.63, 127.48, 127.36, 127.06, 126.57, 126.21, 51.26, 47.32, 23.57, 21.67. **IR** (film, cm^{-1}) 3305, 3034, 2981, 2870, 1644, 1530, 1486, 1391, 1232, 838, 764, 727, 693. **R_f** (1:1 ethyl acetate:hexanes, CAM) = 0.18. **$[\alpha]_D^{20}$** = –149.8 (*c* 0.5, $CHCl_3$, 89:11 e.r.). **Exact mass** calculated for $[C_{15}H_{15}NO\ H]^+$ requires *m/z* 226.1226 Found 226.1225 (ESI+). **HPLC** Chiralcel OD; 4.0% 2-propanol/hexanes (0 – 15 min.), 4.0% to 6.0% 2-propanol/hexanes (15 – 20 min.), 6.0% 2-propanol/hexanes (20 – 35 min.), 6.0% to 8.0% 2-propanol/hexanes (35 – 37.5 min.), 8.0% 2-propanol/hexanes (37.5 – 80 min.); flow rate = 0.75 mL/min (0 – 15 min.), 0.75 mL/min to 0.50 mL/min (15 – 20 min.), 0.50 mL/min (20 – 80 min.); t_r = 59.4 min. (major enantiomer), t_r = 69.9 min. (minor enantiomer).



15-F

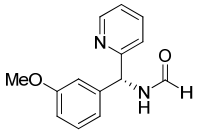
Formamide 15-F. Following Typical Procedure G, 2'-naphthyl methyl ketone (383 mg, 2.25 mmol) provided racemic **15-F** (267 mg, 1.34 mmol, 60%). Following Typical Procedure H, resolved thioformamide **15** (10.5 mg, 0.049 mmol) yielded enantioenriched **15-F** as a colorless solid (8.0 mg, 0.040 mmol, 83%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (4.9:1 major:minor): δ 8.16 (s, 1H), 7.84 – 7.80 (m, 3H), 7.74 (s, 1H), 7.53 – 7.44 (m, 2H), 7.41 (d, *J* = 8.5, 1H), 6.22 (br s, 1H), 5.35 (dq, *J* = 7.1, 7.1, 1H), 1.57 (d, *J* = 6.9, 3H). Distinguishable Peaks for Minor Rotamer: δ 8.16 (d, *J* = 11.2, 1H), 7.69 (s, 1H), 7.35 (d, *J* = 8.5, 1H), 6.37 (br s, 1H), 4.78 (dq, *J* = 7.2, 7.2, 1H), 1.59 (d, *J* = 7.0, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.15, 160.29, 140.09, 139.87, 133.21, 133.17, 132.67, 132.66, 128.79, 128.49, 127.81, 127.61, 127.55, 126.48, 126.24, 126.17, 125.93, 124.50, 124.49, 124.27, 123.85, 51.66, 47.53, 23.33, 21.57. **IR** (film, cm^{-1}) 3287, 3050, 2979, 2933, 2873, 1650, 1529, 1442, 1383, 1234, 1113, 1080, 995, 861, 829, 742, 706, 660. **R_f** (1:1 ethyl acetate:hexanes, CAM) = 0.17. **$[\alpha]_D^{20}$** = –179.4 (*c* 0.5, $CHCl_3$, 95.5:4.5 e.r.). **Exact mass** calculated for $[C_{13}H_{13}NO\ H]^+$ requires *m/z* 200.1070 Found 200.1069 (ESI+). **HPLC** Chiralcel OD; 1.0% to 4.0% 2-propanol/hexanes (0 – 30 min.), 4.0% 2-propanol/hexanes (30 – 60 min.), 4.0% to 10.0% 2-propanol/hexanes (60 –

90 min.); flow rate = 0.75 mL/min to 0.60 mL/min (0 – 30 min.), 0.60 mL/min (30 – 60 min.), 0.60 mL/min to 0.75 mL/min (60 – 90 min.); t_r = 43.6 min. (minor enantiomer), t_r = 52.2 min. (major enantiomer).



16-F

Formamide 16-F. Following Typical Procedure G, phenyl ethyl ketone (3.0 g, 22 mmol) provided racemic **16-F** (750 mg, 4.6 mmol, 21%). Following Typical Procedure H, resolved thioformamide **16** (8.3 mg, 0.046 mmol) yielded enantioenriched **16-F** as a colorless oil (6.9 mg, 0.042 mmol, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) Major Rotamer (4.6:1 major:minor): δ 8.12 (s, 1H), 7.40 – 7.22 (m, 5H), 6.86 (br d, *J* = 6.9, 1H), 4.94 (dt, *J* = 7.6, 7.6, 1H), 1.82 (dq, *J* = 7.4, 7.4, 2H), 0.91 (t, *J* = 7.4, 3H). Distinguishable Peaks for Minor Rotamer: δ 8.10 (d, *J* = 9.9, 1H), 7.00 (br m, 1H), 4.35 (dt, *J* = 6.5, 8.3, 1H), 0.95 (t, *J* = 7.5, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.64, 160.68, 141.78, 141.64, 128.66, 128.42, 127.48, 127.17, 126.40, 126.02, 58.16, 53.56, 30.09, 29.00, 10.57. **IR** (film, cm^{-1}) 3238, 3048, 2985, 2966, 2939, 2872, 2755, 1659, 1546, 1490, 1452, 1382, 1258, 1231, 1129, 1104, 1073, 965, 751, 699, 634. **R_f** (1:1 ethyl acetate:hexanes, CAM) = 0.19. **$[\alpha]_D^{20}$** = –111.6 (*c* 0.5, $CHCl_3$, 90.5:9.5 e.r.). **Exact mass** calculated for $[C_{10}H_{13}NO\ H]^+$ requires *m/z* 164.1070 Found 164.1068 (ESI+). **HPLC** Chiralcel OD; 1.0% to 10.0% 2-propanol/hexanes (0 – 60 min.); flow rate = 0.75 mL/min; t_r = 38.5 min. (minor enantiomer), t_r = 48.9 min. (major enantiomer).



17-F

Formamide 17-F. Following Typical Procedure G, 2'-pyridyl 3'-methoxyphenyl ketone (1.0 mg, 4.7 mmol) provided racemic **17-F** (374 mg, 1.54 mmol, 33%). Following Typical Procedure H, resolved thioformamide **17** (13.9 mg, 0.054 mmol) yielded enantioenriched **17-F** as a faintly yellow solid (9.1 mg, 0.038 mmol, 71%). **^{1}H NMR** (500 MHz, $CDCl_3$) Major Rotamer (11.8:1 major:minor): δ 8.57 (d, *J* = 4.7, 1H), 8.34 (s,

1H), 7.73 (br s, 1H), 7.64 (dd, *J* = 7.7, 7.7, 1H), 7.28 – 7.17 (m, 3H), 6.93 (d, *J* = 7.7, 1H), 6.88 (s, 1H), 6.77 (d, *J* = 8.3, 1H), 6.19 (d, *J* = 7.2, 1H), 3.76 (s, 3H). Distinguishable Peaks for Minor Rotamer: δ 8.28 (d, *J* = 12.2, 1H), 5.73 (d, *J* = 7.2, 1H), 3.77 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.00, 160.24, 159.76, 158.02, 149.28, 148.83, 142.95, 142.92, 137.04, 137.01, 130.09, 129.73, 122.81, 122.72, 122.64, 122.02, 119.61, 119.24, 113.29, 113.10, 112.90, 112.80, 59.98, 55.92, 55.25, 55.18. **IR** (film, cm^{-1}) 3270, 3010, 2837, 1666, 1589, 1489, 1434, 1382, 1257, 1149, 1038, 777, 751, 699. **R_f** (3:1 ethyl acetate:hexanes, CAM) = 0.21. **$[\alpha]_D^{20}$** = –100.4 (*c* 0.5, $CHCl_3$, 79.5:20.5 e.r.). **Exact mass** calculated for $[C_{14}H_{14}N_2O_2\ H]^+$ requires *m/z* 243.1128 Found 243.1124 (ESI+). **HPLC** Chiralcel OD; 1.0% to 5.0% 2-propanol/hexanes (0 – 30 min.), 5.0% 2-propanol/hexanes (30 – 60 min.), 5.0% to 15.0% 2-propanol/hexanes (60 – 120 min.); flow rate = 0.750 mL/min; t_r = 89.1 min. (minor enantiomer), t_r = 95.7 min. (major enantiomer).

XII. References

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