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Stereospecific Stille Cross-Couplings Using $Mn(II)Cl_2$

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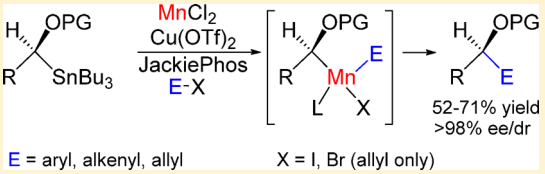
Supporting Information

ABSTRACT: Cross-coupling reactions are a staple in organic synthesis, especially for C−C bond formation with sp- and sp^2-carbon electrophiles. In recent years, the range of accessible C−C bonds has been extended to stereogenic centers which expedites access to greater molecular complexity. However, these reactions predominantly depend upon late transition metal (LTM) catalysts whose cost, toxicity, and/or environmental impact have come under increasing scrutiny and governmental regulation. Here, we report $Mn(II)Cl_2$ complexes alone, or with assistance from copper, catalyze the stereospecific cross-coupling of α-alkoxyalkylstannanes with organic electrophiles with complete retention of configuration.



INTRODUCTION

Late transition metal (LTM)-catalyzed cross-couplings are well established and popular synthetic procedures, especially for additions to sp- and sp^2-carbon electrophiles.[1,2] Continuous refinement of these processes has significantly improved reaction conditions and expanded the range of accessible C−C bonds. Couplings to stereogenic centers, in particular, have attracted wide attention for their ability to increase molecular complexity[3−12] and drug-like functionality.[13] Nevertheless, limitations still persist for many cross-coupling reactions,[14] e.g., (i) sensitivity to oxygen and water, (ii) dimerization and/or decomposition of reactive electrophiles,[15−18] (iii) rearrangements,[19−21] and (iv) β-elimination.[19−21] In addition, the cost, toxicity, and/or environmental impact of many of the LTM catalysts have come under increasing scrutiny and governmental regulation.[22] These restrictions as well as our long-standing interest[19−21] in Stille cross-couplings at α-functionalized carbons prompted us to evaluate manganese because it is among the most abundant and economic of all transition metals, just behind iron and titanium, and comparatively nontoxic.[23,24]

RESULTS AND DISCUSSION

The use of Mn(II) salts in C−C bond formation dates back to 1976,[25−27] but it was 1997 before it was applied to Stille cross-couplings.[28,29] Adducts were obtained in generally good yields at 100 °C in DMF or NMP, although the organostannane must be added slowly to minimize dimerization. Homocoupling of organostannanes,[30] also at 100 °C in DMF or NMP, using $MnBr_2$ and iodine has been reported. Conspicuously absent are practical Mn(II)-catalyzed cross-couplings at stereogenic centers. Hence, the cross-coupling of protected α-alkoxy(tri-*n*-butyl)stannanes[31,32] with organic electrophiles was selected as a readily available model system to probe the stereospecificity of Mn(II)-mediated C−C bond formation at an sp^3-center.[33] Preliminary optimization studies demonstrated that $MnCl_2$ outperformed other common manganese salts as well as salen-type complexes. Acceptable yields, however, required PyBOX ligands. Among typical solvents, the combination of toluene/EtOAc (4:1) afforded the best yields. CH_2Cl_2, THF, DMF, NMP, and EtOH gave low or no cross-coupled adduct. Stoichiometric amounts of NaCl also proved helpful, although more than 3 equiv did not improve the yields. Other chloride salts gave poor results. The inclusion of TEMPO (1.2 equiv) had only a minor impact, suggesting that the reaction does not involve a radical intermediate.

The scope of the $MnCl_2$/(*S*)-$BnCH_2$PyBOX catalytic system for C−C bond formation was established using **1**[19] and a panel of representative electrophiles (Figure 1, panel A). Aryl iodides bearing either electron-withdrawing (**2a−h**) or electron-rich substituents (**2i,j**) were suitable coupling partners for stannane **1**, although the reactions were slow even at temperatures up to 82 °C. In sharp contrast to the extensive or complete Newman−Kwart rearrangement of the thiocarbamate that accompanied copper(I)−thiophene-2-carboxylate (CuTC)-mediated cross-couplings,[19,21] we observed no rearrangement using $MnCl_2$/(*S*)-$BnCH_2$PyBOX with any of the examples in Figure 1. Repetition of the CuTc reactions as previously described but in the presence of (*S*)-$BnCH_2$PyBOX did not prevent the Newman−Kwart rearrangement.

Aryl bromides were generally unreactive, although cinnamyl bromide led to homoallylic alcohol **2k** in good yield. Heterocyclic iodides, which often decompose, protodehalogenate, or dimerize during LTM-mediated cross-couplings,[17] were well behaved with $MnCl_2$ (**2l−p**). Most notably, bond formation between (*S*)-**1**[31] and a variety of electrophiles proceeded with >98% retention of configuration (Figure 1, panel B, (*R*)-**2q−t**).[33] This suggested that manganese was participating in the type of oxidative addition−reductive elimination process normally associated with LTMs.[34,35] The presence of an adjacent asymmetric center as in acetonide **3**

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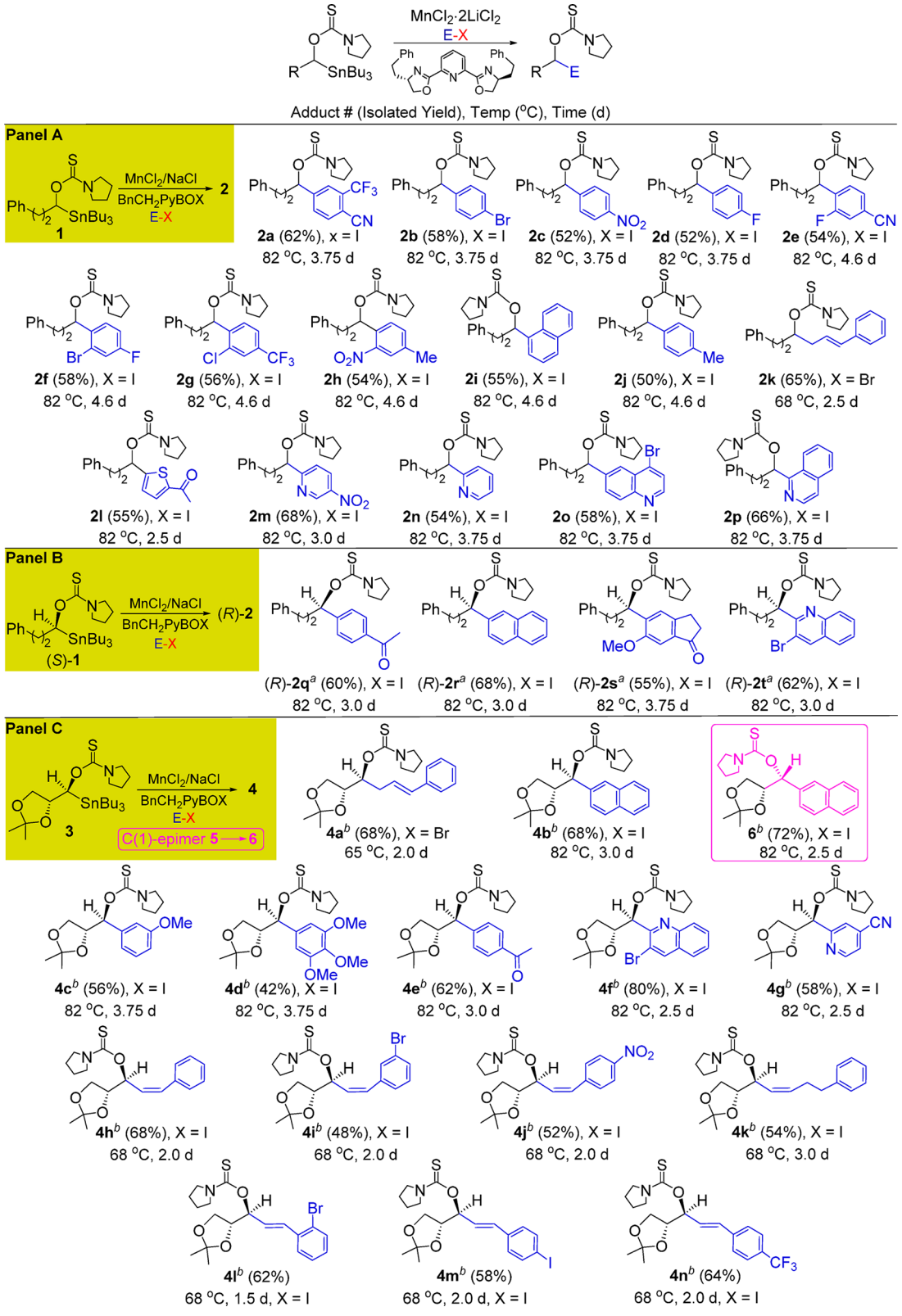

Figure 1. Cross-coupling of α-alkoxy(tri-*n*-butyl)stannanes with organic electrophiles using $MnCl_2$. Reaction conditions: E-X (1.2 equiv), $MnCl_2$ and (*S*,*S*)-$BnCH_2$PyBOX (0.5 equiv), NaCl (3 equiv) at 0.5 M in $PhCH_3$/EtOAc (4:1), except **2k** that used $PhCH_3/CH_2Cl_2$ (1:1). [a]>98% ee by chiral phase HPLC. [b]>98% de by ^{1}H NMR.

and its C(1)-epimer **5** (Figure 1, panel C) did not affect the stereofidelity of the cross-coupling and in some instances actually improved yields, e.g., rising to 80% for **4f** (cf., **2t**). Cross-coupled adducts were obtained from allylic, aryl, heteroaryl, and olefinic electrophiles containing such common functionality as nitro, cyano, acetyl, methoxy, trifluoromethyl, bromide, and iodide (Figure 1, panel C, **4a**–**g**, **6**). The stereochemistry of olefinic partners was also preserved, i.e., *Z*-

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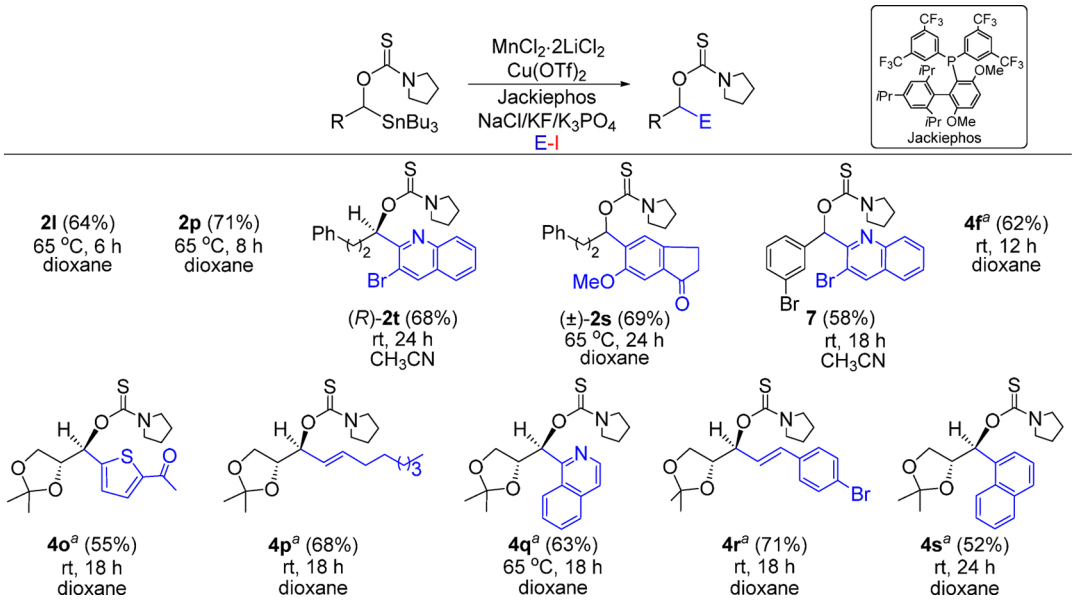

Figure 2. Stereospecific Mn(II)/Cu(II)-cocatalyzed cross-couplings with electrophiles. Reaction conditions: E-I (1.2 equiv), $MnCl_2{\cdot}2LiCl_2$ and Jackiephos (0.25 equiv), $Cu(OTf)_2$ (0.2 equiv), NaCl and KF (3 equiv), K_3PO_4 (2 equiv), Ar atmosphere. [a]>98% dr by $^1H/^{13}C$ NMR.

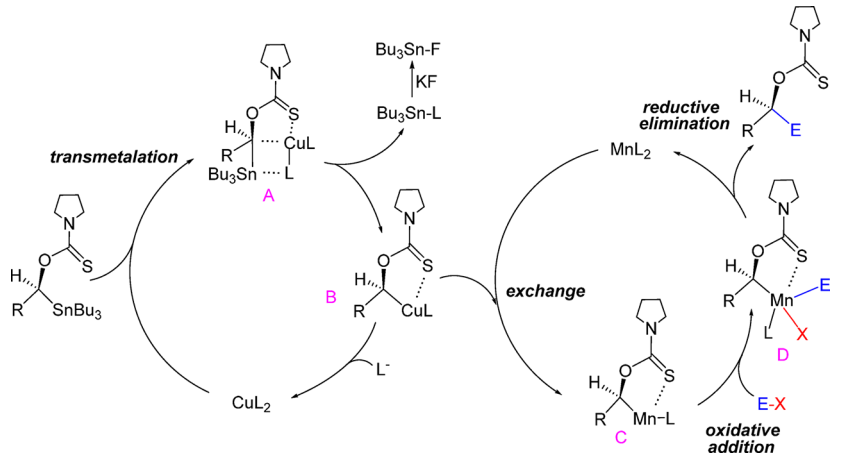

Figure 3. Proposed mechanism for Mn/Cu-cocatalyzed cross-coupling.

and *E*-olefinic iodides gave rise to *Z*- (**4h–k**) and *E*-adducts (**4l–n**), respectively. Comparable couplings of **1** and **3** with the same iodo electrophiles mediated by any of more than four dozen LTM catalysts (Supporting Information (SI): Table S4) and conditions commonly utilized in Stille reactions (SI: Table S5) led to complex product mixtures and little, if any, cross-coupled adducts.

Having established the heretofore unappreciated ability of $MnCl_2$ to catalyze the kind of stereospecific cross-couplings that typically rely upon LTMs, we turned our attention to the issue of synthetic practicality, i.e., the long reaction times and moderately high temperatures used for the examples in Figure 1, and conducted screening studies. Despite numerous reports of copper(I)[34,36]/palladium-cocatalyzed Stille couplings, the combination of copper(I) salts and $MnCl_2$ was disappointing. On the other hand, $Cu(OTf)_2/MnCl_2$, especially in the presence of the JackiePhos ligand,[37,38] proved superior to the original reaction conditions. While rare, the use of copper(II)/palladium for Stille couplings has been reported.[39] Also, K_3PO_4 helped suppress side reactions and thereby provided a cleaner product. It likely functions as a mild base to neutralize any adventitious acid. These new reaction conditions proved significantly faster (6–24 h) and milder because many cross-couplings now progressed at rt (Figure 2). The stereospecificity remained >98% for all applicable examples (i.e., **4f,o–s**) and no thiocarbamate Newman–Kwart rearrangement was observed.

A tentative mechanistic hypothesis for the Mn/Cu-cocatalyzed cross-couplings is shown in Figure 3. Specifically, the organostannane undergoes initial transmetalation with copper to generate intermediate **B** via cyclic transition state **A**. Exchange of the copper in B with Mn(II) gives rise to intermediate **C**. Subsequent oxidative addition with the electrophile leads to organomanganate **D** that undergoes reductive elimination to yield the final product. Consistent with the essential role of manganese in the cross-couplings, reaction of **3** or **3** plus 3-bromo-2-iodoquinoline with $Cu(OTf)_2$ (25 mol %) as described in Figure 1, but in the absence of $MnCl_2$, resulted in mainly the β-elimination product (*E*)-*O*-(3-hydroxyprop-1-en-1-yl)pyrrolidine-1-carbothioate.[19] This suggests that the exchange between **B** and **C** must be closely coupled to avoid β-elimination. Conversely, **3** was recovered mostly intact (85%) after stirring with $MnCl_2$ (100

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mol %) in dioxane for 24 h at rt with Jackiephos (25 mol %), NaCl (3 equiv), KF (3 equiv), and K_3PO_4 (2 equiv) but no copper salts; none of the β-elimination product was observed. Coupling of **3** with 3-bromo-2-iodoquinoline [dioxane Jackiephos (25 mol %), NaCl (3 equiv), KF (3 equiv), K_3PO_4 (2 equiv)] catalyzed by $MnCl_2$ (100 mol %) alone required 72 h at 82 °C to give **4f** (67%). This contrasts sharply with synergistic Mn(II)/Cu(II) cocatalysis that proceeds at rt in just 12 h to yield **4f** (62%) (Figure 2).[40]

Inclusion of KF, while not essential, did accelerate the reaction rate, presumably by forming an insoluble adduct with the tri-*n*-butylstannane byproduct, but might also involve exchange with the metal ligands as proposed for Pd-catalyzed cross-couplings.[41]

CONCLUSION

$MnCl_2$, or $MnCl_2$ assisted by $Cu(OTf)_2$, provides a viable alternative to LTM catalysts for the stereospecific cross-coupling of α-alkoxyalkylstannanes with highly reactive electrophiles that are prone to dimerization and/or decomposition under traditional conditions. While much additional work is needed to validate the mechanism of this new variant of the Stille reaction, these results provide some insights into the rich and complex chemistry lurking among the less well-studied transition metals.[42]

EXPERIMENTAL SECTION

General Procedures and Materials. Nuclear magnetic resonance spectra were recorded on a Bruker AV II 400 MHz spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 101 MHz) or a Varian 500 MHz spectrometer (^{1}H NMR at 500 MHz, ^{13}C NMR at 126 MHz). The ^{1}H NMR chemical shifts were measured relative to $CDCl_3$ (δ = 7.26 ppm) or CD_3OD (δ = 3.31 ppm) as internal reference, unless otherwise stated. The ^{13}C NMR chemical shifts were measured relative to $CDCl_3$ (δ = 77.00 ppm) or CD_3OD (δ = 49.00 ppm) as internal reference. ^{1}H NMR data are reported as chemical shift (ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, app q = apparent quartet, qn = quintet, app qn = apparent quintet, m = multiplet), and coupling constant (Hz). High resolution mass spectra (HRMS) were obtained from the Shimadzu Center for Advanced Analytical Chemistry, Univ. of Texas at Arlington, using a LCMS-8050 triple quadrupole liquid chromatograph mass spectrometer and at the Medical College of Wisconsin, Dept. of Pharmacology and Toxicology, using an Agilent 6460 triple quadrupole-LC mass spectrometer. Melting points were measured with a Stanford Research Systems OptiMelt and are uncorrected. Optical rotations were measured at room temperature on a Rudolph Research Analytical Autopol IV polarimeter. Analytical thin layer chromatography (TLC) used glass plates precoated with EMD Chemicals TLC silica gel 60 F_{254} (0.040–0.063 mm) with visualization by UV light and/or $KMnO_4$ or phosphomolybdic acid (PMA) solution followed by heating. Chromatographic purifications utilized preparative TLC or flash chromatography on prepacked, commercial SiO_2 columns on a CombiFlash Rf200 chromatograph (Teledyne Isco). Yields refer to isolated, purified material with spectral data consistent with assigned structures or, if known, concordant with literature values. All reactions were conducted under an argon atmosphere in oven-dried glassware with magnetic stirring, unless otherwise noted. Reaction solvents were dried immediately before use via passage through drying columns under positive nitrogen pressure. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise noted.

Standard Stille Cross-Couplings Using $MnCl_2$ (Figure 1). A Schlenk tube was charged with α-alkoxy-tri-*n*-butylstannane[19,31] (0.093 mmol), neutralized $MnCl_2$ (0.047 mmol, 50 mol %) (see preparation of neutralized $MnCl_2$ below), NaCl (0.27 mmol, 300 mol %), (*S*)-$BnCH_2$PYBOX (0.047 mmol, 50 mol %), and anhydrous toluene/EtOAc (3 mL, 4:1) and then degassed via four alternating high vacuum–argon cycles. The electrophile (0.11 mmol, 120 mol %) in anhydrous toluene (1 mL) was added via syringe. The reaction mixture was stirred at room temperature for 2 h, during which time the color changed from pale pink to yellow-brown, and was then heated at 68–82 °C as indicated for specific examples until TLC analysis showed that all the stannane was consumed (24–120 h). The resultant reddish-brown reaction mixture was cooled to rt, diluted with Et_2O (10 mL), and filtered through a small bed of neutral alumina. The filter bed was washed with fresh Et_2O (5 mL), and the combined filtrates were concentrated under reduced pressure. Purification of the residue via flash column chromatography gave the cross-coupled adducts in the indicated yields.

Preparation of neutralized $MnCl_2$: Manganese(II) chloride tetrahydrate (99.99% trace metals basis, Aldrich, CAS no. 13446-34-9) (1 g, 5.05 mmol) was stirred at rt with dry triethylamine (0.2 mL) in anhydrous toluene (5 mL). After 5 min, all volatiles were removed on a rotary evaporator, and the residue was further dried under high vacuum for 16 h. The neutralized $MnCl_2$ was used immediately for cross-couplings.

*O-(1-(4-Cyano-3-(trifluoromethyl)phenyl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2a**).* Stirring *O*-(3-phenyl-1-tri-*n*-butylstannyl)-propyl) pyrrolidine-1-carbothioate (**1**)[19] (50 mg, 0.093 mmol) and 4-iodo-2-(trifluoromethyl)benzonitrile (33 mg, 0.11 mmol) at 82 °C for 3.75 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2a** (24 mg, 62%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: $R_f \approx 0.4$ (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 1H), 7.69 (s, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.30–7.09 (m, 5H), 6.52 (dd, J = 8.4, 4.9 Hz, 1H), 3.69–3.65 (m, 2H), 3.55–3.52 (m, 2H), 2.71–2.68 (m, 2H), 2.34–2.31 (m, 1H), 2.15–2.14 (m, 1H), 2.00–1.89 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.5, 147.1, 140.4, 134.8, 133.2, 132.85, 130.4, 128.5, 128.25, 126.25, 124.75 (q, $J_{C,F}$ = 5.0 Hz), 120.9, 115.3, 109.1, 79.7, 52.3, 48.0, 38.1, 31.8, 25.65, 24.4. HRMS Calcd for $C_{22}H_{21}F_3N_2NaOS$ $[M + Na]^+$ 441.1219, found 441.1220.

*O-(1-(4-Bromophenyl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2b**).* Stirring **1** (50 mg, 0.093 mmol) and 1-bromo-4-iodobenzene (31 mg, 0.11 mmol) at 82 °C for 3.75 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2b** (21 mg, 58%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: $R_f \approx 0.5$ (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.41 (m, 2H), 7.31–7.09 (m, 7H), 6.42 (dd, J = 7.6, 5.7 Hz, 1H), 3.75–3.60 (m, 2H), 3.52–3.48 (m, 2H), 2.73–2.53 (m, 2H), 2.15–2.11 (m, 1H), 2.09–2.01 (m, 1H), 1.95–1.81 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.1, 141.2, 139.7, 131.55, 128.5, 128.4, 128.3, 125.9, 121.7, 80.7, 52.05, 47.8, 38.1, 31.7, 25.6, 24.5. HRMS Calcd for $C_{20}H_{22}BrNNaOS$ $[M + Na]^+$ 426.0498, found 426.0505.

*O-(1-(4-Nitrophenyl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2c**).* Stirring **1** (50 mg, 0.093 mmol) and 1-iodo-4-nitrobenzene (27 mg, 0.11 mmol) at 82 °C for 3.75 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2c** (17 mg, 52%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: $R_f \approx 0.5$ (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23–8.15 (m, 2H), 7.53–7.43 (m, 2H), 7.30–7.10 (m, 5H), 6.52 (dd, J = 8.0, 5.3 Hz, 1H), 3.70–3.65 (m, 2H), 3.58–3.53 (m, 2H), 2.69–2.66 (m, 2H), 2.35–2.33 (m, 1H), 2.19–2.16 (m, 1H), 1.99–1.84 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.8, 148.2, 140.8, 128.5, 128.25, 127.4, 126.1, 123.8, 80.1, 52.2, 47.9, 38.2, 31.7, 25.65, 24.5. HRMS Calcd for $C_{20}H_{22}N_2NaO_3S$ $[M + Na]^+$ 393.1249, found 393.1240.

*O-(1-(4-Fluorophenyl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2d**).* Stirring **1** (50 mg, 0.093 mmol) and 1-fluoro-4-iodobenzene (25 mg, 0.11 mmol) at 82 °C for 3.75 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2d** (16 mg, 52%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: $R_f \approx 0.5$ (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 2H),

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7.26−7.22 (m, 2H), 7.18−7.13 (m, 3H), 7.09−6.96 (m, 2H), 6.45 (dd, J = 7.8, 5.9 Hz, 1H), 3.76−3.60 (m, 2H), 3.52−3.48 (m, 2H), 2.67−2.58 (m, 2H), 2.35−2.31 (m, 1H), 2.20−2.05 (m, 1H), 1.97−1.81 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.2, 162.2 (d, $J_{C,F}$ = 246.1 Hz), 141.3, 136.4 (d, $J_{C,F}$ = 3.1 Hz), 128.5 (d, $J_{C,F}$ = 8.4 Hz), 128.3, 128.3, 125.9, 115.3 (d, $J_{C,F}$ = 21.5 Hz), 80.8, 52.0, 47.8, 38.3, 31.8, 25.6, 24.5. HRMS Calcd for $C_{20}H_{22}FNNaOS$ $[M + Na]^+$ 366.1298, found 366.1294.

*O-(1-(4-Cyano-2-fluorophenyl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2e**).* Stirring **1** (50 mg, 0.093 mmol) and 3-fluoro-4-iodobenzonitrile (27 mg, 0.11 mmol) at 82 °C for 4.6 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2e** (18 mg, 54%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: R_f ≈ 0.45 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.10 (m, 8H), 6.64 (dd, J = 8.2, 5.1 Hz, 1H), 3.75−3.45 (m, 4H), 2.71−2.65 (m, 2H), 2.34−2.29 (m, 1H), 2.21−2.19 (m, 1H), 2.04−1.82 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.6, 159.2 (d, $J_{C,F}$ = 246.1 Hz), 140.7, 134.4 (d, $J_{C,F}$ = 13.0 Hz), 129.1 (d, $J_{C,F}$ = 4.6 Hz), 128.4, 128.2, 126.1, 119.4 (d, $J_{C,F}$ = 25.3 Hz), 117.45 (d, $J_{C,F}$ = 2.3 Hz), 112.7 (d, $J_{C,F}$ = 10.0 Hz), 75.8, 52.2, 47.9, 36.95, 31.8, 25.65, 24.5. HRMS Calcd for $C_{21}H_{21}FN_2NaOS$ $[M + Na]^+$ 391.1251, found 391.1247.

*O-(1-(2-Bromo-4-fluorophenyl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2f**).* Stirring **1** (50 mg, 0.093 mmol) and 2-bromo-4-fluoro-1-iodobenzene (33 mg, 0.11 mmol) at 82 °C for 4.6 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2f** (22 mg, 58%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: R_f ≈ 0.4 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.23 (m, 4H), 7.20−7.18 (m, 3H), 7.04−7.02 (m, 1H), 6.68 (dd, J = 7.8, 4.9 Hz, 1H), 3.78−3.50 (m, 4H), 2.80−2.72 (m, 2H), 2.23−2.21 (m, 2H), 2.01−1.93 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.9, 161.5 (d, $J_{C,F}$ = 250.3 Hz), 141.3, 136.5 (d, $J_{C,F}$ = 3.8 Hz), 128.4, 128.35, 125.95, 122.1 (d, $J_{C,F}$ = 9.6 Hz), 120.1 (d, $J_{C,F}$ = 24.0 Hz), 114.8 (d, $J_{C,F}$ = 21.1 Hz), 80.2, 52.2, 47.9, 37.4, 32.0, 25.7, 24.5. HRMS Calcd for $C_{20}H_{21}BrFNNaOS$ $[M + Na]^+$ 444.0403, found 444.0391.

*O-(1-(2-Chloro-4-(trifluoromethyl)phenyl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2g**).* Stirring **1** (50 mg, 0.093 mmol) and 2-chloro-1-iodo-4-(trifluoromethyl)benzene (34 mg, 0.11 mmol) at 82 °C for 4.6 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2g** (22 mg, 56%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: R_f ≈ 0.4 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 2.4 Hz, 1H), 7.53−7.43 (m, 2H), 7.30−7.27 (m, 2H), 7.20−7.18 (m, 3H), 6.84 (dd, J = 8.1, 4.6 Hz, 1H), 3.73−3.70 (m, 2H), 3.60−3.50 (m, 2H), 2.82−2.71 (m, 2H), 2.29−2.11 (m, 2H), 2.03−1.85 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.8, 141.0, 140.1, 130.3, 128.4, 128.34, 128.29, 126.0, 125.35 (q, $J_{C,F}$ = 3.4 Hz), 124.2 (app q), 78.05, 52.3, 47.9, 37.0, 31.95, 25.7, 24.4. HRMS Calcd for $C_{21}H_{21}ClF_3NNaOS$ $[M + Na]^+$ 450.0877, found 450.0862.

*O-(1-(4-Methyl-2-nitrophenyl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2h**).* Stirring **1** (50 mg, 0.093 mmol) and 1-iodo-4-methyl-2-nitrobenzene (29 mg, 0.11 mmol) at 82 °C for 4.6 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2h** (19 mg, 54%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: R_f ≈ 0.45 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.42−7.34 (m, 2H), 7.28−7.23 (m, 2H), 7.21−7.16 (m, 3H), 6.82 (dd, J = 8.3, 4.4 Hz, 1H), 3.71−3.48 (m, 4H), 2.90−2.81 (m, 2H), 2.40 (s, 3H), 2.34−2.31 (m, 2H), 1.99−1.88 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0, 148.1, 141.4, 138.5, 134.55, 134.2, 128.35, 128.33, 127.5, 125.9, 124.7, 77.6, 52.1, 47.7, 38.2, 32.7, 25.7, 24.4, 20.8. HRMS Calcd for $C_{21}H_{24}N_2NaO_3S$ $[M + Na]^+$ 407.1400, found 407.1394.

*O-(1-(Naphthalen-1-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2i**).* Stirring **1** (50 mg, 0.093 mmol) and 1-iodonaphthalene (28 mg, 0.11 mmol) at 82 °C for 4.6 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2i** (19 mg, 55%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: R_f ≈ 0.55 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.60−7.44 (m, 4H), 7.36−7.23 (m, 3H), 7.20 (d, J = 7.3 Hz, 2H), 3.81−3.58 (m, 4H), 2.77−2.74 (m, 2H), 2.52−2.41 (m, 2H), 2.01−1.90 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.4, 141.5, 136.6, 133.9, 130.5, 128.9, 128.4, 128.35, 126.2, 125.9, 125.6, 125.3, 124.3, 123.6, 79.4, 52.1, 48.0, 38.0, 32.25, 25.7, 24.5. HRMS Calcd for $C_{24}H_{25}NNaOS$ $[M + Na]^+$ 398.1549, found 398.1550.

*O-(3-Phenyl-1-(p-tolyl)propyl) Pyrrolidine-1-carbothioate (**2j**).* Stirring **1** (50 mg, 0.093 mmol) and 1-iodo-4-methylbenzene (24 mg, 0.11 mmol) at 82 °C for 4.6 d following Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2j** (15 mg, 50%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: R_f ≈ 0.65 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.22 (m, 4H), 7.18−7.16 (m, 5H), 6.47 (t, J = 6.8 Hz, 1H), 3.77−3.62 (m, 2H), 3.54−3.52 (m, 2H), 2.70−2.61 (m, 2H), 2.43−2.32 (m, 4H), 2.19−2.17 (m, 1H), 2.02−1.84 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.3, 141.6, 137.6, 137.5, 129.1, 128.3, 126.8, 125.8, 81.5, 52.0, 47.8, 38.25, 31.9, 25.6, 24.5, 21.2. HRMS Calcd for $C_{21}H_{25}NNaOS$ $[M + Na]^+$ 362.1549, found 362.1541.

*(E)-O-(1,6-Diphenylhex-5-en-3-yl) Pyrrolidine-1-carbothioate (**2k**).* Stirring **1** (50 mg, 0.093 mmol) and (*E*)-cinnamyl bromide (22 mg, 0.11 mmol) at 68 °C for 2.5 d following the Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2k** (22 mg, 65%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. The spectral data of **2k** were concordant with literature values.[32]

*O-(1-(5-Acetylthiophen-2-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2l**).* Stirring **1** (50 mg, 0.093 mmol) and 1-(5-iodothiophen-2-yl)ethan-1-one (28 mg, 0.11 mmol) at 82 °C for 2.5 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2l** (19 mg, 55%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: R_f ≈ 0.35 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 3.9 Hz, 1H), 7.28−7.26 (m, 2H), 7.25−7.15 (m, 3H), 7.09 (d, J = 3.9 Hz, 1H), 6.80 (dd, J = 7.3, 5.9 Hz, 1H), 3.80−3.66 (m, 2H), 3.61−3.45 (m, 2H), 2.72−2.69 (m, 2H), 2.55 (s, 3H), 2.43−2.41 (m, 1H), 2.31−2.26 (m, 1H), 2.00−1.91 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.8, 183.5, 153.2, 143.6, 140.8, 132.4, 128.5, 128.35, 126.4, 126.1, 76.9, 52.25, 48.1, 38.4, 31.6, 26.6, 25.6, 24.5. HRMS Calcd for $C_{20}H_{23}NNaO_2S_2$ $[M + Na]^+$ 396.1062, found 396.1059.

*O-(1-(5-Nitropyridin-2-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2m**).* Stirring **1** (50 mg, 0.093 mmol) and 2-iodo-5-nitropyridine (28 mg, 0.11 mmol) at 82 °C for 3.0 d as described in the Standard Stille Cross-Coupling using $MnCl_2$ (vide supra) afforded **2m** (23 mg, 68%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: R_f ≈ 0.3 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (d, J = 2.5 Hz, 1H), 8.43 (dd, J = 8.6, 2.6 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.31−7.15 (m, 5H), 6.56 (dd, J = 7.5, 5.1 Hz, 1H), 3.78−3.64 (m, 3H), 3.62−3.47 (m, 1H), 2.77 (t, J = 7.8 Hz, 2H), 2.48−2.33 (m, 2H), 2.09−1.84 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.9, 166.5, 144.8, 143.05, 140.9, 131.5, 128.4, 128.35, 128.3, 126.1, 121.3, 81.1, 52.3, 48.1, 36.4, 31.8, 25.7, 24.5. HRMS Calcd for $C_{19}H_{21}N_3NaO_3S$ $[M + Na]^+$ 394.1196, found 394.1185.

*O-(3-Phenyl-1-(pyridin-2-yl)propyl) Pyrrolidine-1-carbothioate (**2n**).* Stirring **1** (50 mg, 0.093 mmol) and 2-iodopyridine (22 mg, 0.11 mmol) at 82 °C for 3.75 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2n** (16 mg, 54%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: R_f ≈ 0.25 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (dd, J = 4.9, 1.8, Hz, 1H), 7.67−7.66 (m, 1H), 7.35−7.33 (m, 1H), 7.27−7.25 (m, 2H), 7.23−7.13 (m, 4H), 6.55 (dd, J = 7.7, 5.2 Hz, 1H), 3.79−3.62 (m, 3H), 3.57−3.52 (m, 1H), 2.80−2.66 (m, 2H), 2.41−2.37 (m, 2H), 2.04−1.87 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.4, 159.6, 149.4, 141.6, 136.5, 128.4, 128.3, 125.8, 122.5, 121.5, 81.9, 52.2, 47.95, 36.7, 31.9, 25.7, 24.5. HRMS Calcd for $C_{19}H_{22}N_2NaOS$ $[M + Na]^+$ 349.1345, found 349.1339.

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*O-(1-(4-Bromoquinolin-6-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2o**).* Stirring **1** (50 mg, 0.093 mmol) and 4-bromo-6-iodoquinoline (37 mg, 0.11 mmol) at 82 °C for 3.75 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2o** (24 mg, 58%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: $R_f \approx 0.4$ (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 4.7 Hz, 1H), 8.20−8.04 (m, 2H), 7.80−7.65 (m, 2H), 7.30−7.12 (m, 5H), 6.71 (dd, J = 7.5, 5.6 Hz, 1H), 3.72−3.58 (m, 4H), 2.75−2.68 (m, 2H), 2.52−2.38 (m, 1H), 2.35−2.21 (m, 1H), 2.06−1.81 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.1, 149.8, 148.55, 141.1, 140.6, 134.2, 130.3, 129.0, 128.4, 128.3, 127.6, 126.0, 125.3, 124.6, 80.9, 52.1, 47.9, 38.25, 31.8, 25.7, 24.5. HRMS Calcd for $C_{23}H_{23}BrN_2NaOS$ $[M + Na]^+$ 477.0607, found 477.0605.

*O-(1-(Isoquinolin-1-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2p**).* Stirring **1** (50 mg, 0.093 mmol) and 1-iodoisoquinoline (28 mg, 0.11 mmol) at 82 °C for 3.75 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **2p** (23 mg, 66%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: $R_f \approx 0.4$ (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, J = 5.6 Hz, 1H), 8.35 (d, J = 8.5 Hz, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.72−7.64 (m, 1H), 7.64−7.57 (m, 2H), 7.33−7.15 (m, 6H), 3.72−3.66 (m, 4H), 2.86−2.83 (m, 1H), 2.80−2.71 (m, 1H), 2.61−2.52 (m, 1H), 2.49−2.43 (m, 1H), 2.03−1.83 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.5, 158.1, 141.9, 141.4, 136.5, 129.9, 128.4, 128.34, 128.30, 127.4, 127.3, 126.4, 125.85, 124.9, 120.7, 78.5, 52.1, 48.1, 36.2, 32.2, 25.6, 24.5. HRMS Calcd for $C_{23}H_{24}N_2NaOS$ $[M + Na]^+$ 399.1502, found 399.1500.

*(R)-O-(1-(4-Acetylphenyl)-3-phenylpropyl) Pyrrolidine-1-carbothioate [(R)-**2q**].* Stirring (*S*)-**1**[31] (50 mg, 0.093 mmol) and 1-(4-iodophenyl)ethan-1-one (27 mg, 0.11 mmol) at 82 °C for 3.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded (*R*)-**2q** (20 mg, 60%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: $R_f \approx 0.3$ (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99−7.91 (m, 2H), 7.48−7.40 (m, 2H), 7.33−7.24 (m, 2H), 7.24−7.14 (m, 3H), 6.53 (dd, J = 7.3, 5.4 Hz, 1H), 3.78−3.51 (m, 4H), 2.77−2.65 (m, 2H), 2.60 (s, 3H), 2.37−2.31 (m, 1H), 2.22−2.20 (m, 1H), 2.05−1.85 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7, 184.0, 146.1, 141.2, 136.5, 128.6, 128.43, 128.41, 128.3, 126.8, 126.0, 80.8, 52.1, 47.9, 38.2, 31.8, 26.7, 25.7, 24.5. HRMS Calcd for $C_{22}H_{25}NNaO_2S$ $[M + Na]^+$ 390.1498, found 390.1498. HPLC: 99.2% ee (see HPLC chromatogram in SI).

*(R)-O-(1-(Naphthalen-2-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate [(R)-**2r**].* Stirring (*S*)-**1** (50 mg, 0.093 mmol) and 2-iodonaphthalene (28 mg, 0.11 mmol) at 82 °C for 3.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded (*R*)-**2r** (23 mg, 68%] as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: $R_f \approx 0.3$ (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.80 (m, 4H), 7.56−7.44 (m, 3H), 7.32−7.23 (m, 2H), 7.22−7.15 (m, 3H), 6.69 (dd, J = 7.3, 6.0 Hz, 1H), 3.72−3.59 (m, 4H), 2.72−2.62 (m, 2H), 2.52−2.45 (m, 1H), 2.34−2.26 (m, 1H), 1.97−1.86 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.3, 141.5, 137.9, 133.15, 133.05, 128.35, 128.32, 128.1, 127.7, 126.14, 126.11, 126.0, 125.9, 124.5, 81.7, 52.05, 47.9, 38.2, 31.9, 25.6, 24.5. HRMS Calcd for $C_{24}H_{25}NNaOS$ $[M + Na]^+$ 398.1549, found 398.1556. HPLC: 97.6−98.9% ee (see HPLC chromatogram in SI).

*(R)-O-(1-(6-Methoxy-1-oxo-2,3-dihydro-1H-inden-5-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate [(R)-**2s**].* Stirring (*S*)-**1** (50 mg, 0.093 mmol) and 5-iodo-6-methoxy-2,3-dihydro-1*H*-inden-1-one (32 mg, 0.11 mmol) at 82 °C for 3.75 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded (*R*)-**2s** (20 mg, 55%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: $R_f \approx 0.3$ (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.08 (m, 7H), 6.78 (t, J = 5.9 Hz, 1H), 3.87 (s, 3H), 3.78−3.49 (m, 4H), 3.04 (app d, J = 6.6 Hz, 2H), 2.81−2.63 (m, 4H), 2.28−2.16 (m, 2H), 2.06−1.83 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 184.1, 156.0, 147.7, 141.6, 138.1, 137.1, 128.5, 128.3, 125.8, 123.8, 104.0, 77.1, 55.9, 52.1, 47.8, 36.8, 31.9, 25.7, 25.3, 24.5. HRMS Calcd for $C_{24}H_{27}NNaO_3S$ $[M + Na]^+$ 432.1604, found 432.1612. HPLC: 96.2% ee (see HPLC chromatogram in SI).

*(R)-O-(1-(3-Bromoquinolin-2-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate [(R)-**2t**].* Stirring (*S*)-**1** (50 mg, 0.093 mmol) and 3-bromo-2-iodoquinoline (37 mg, 0.11 mmol) at 82 °C for 3.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded (*R*)-**2t** (26 mg, 62%) as an oil following chromatographic purification of the crude product using 10% EtOAc/hexanes. TLC: $R_f \approx 0.35$ (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.67 (t, J = 8.0 Hz, 2H), 7.51 (d, J = 7.0 Hz, 1H), 7.32−7.11 (m, 5H), 6.82 (dd, J = 8.2, 4.7 Hz, 1H), 3.99−3.88 (m, 1H), 3.75−3.59 (m, 3H), 2.96−2.90 (m, 1H), 2.86−2.79 (m, 1H), 2.51−2.30 (m, 2H), 2.01−1.89 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.6, 157.0, 146.3, 141.45, 139.2, 129.6, 129.5, 128.45, 128.34, 128.31, 127.2, 126.5, 125.9, 116.8, 80.0, 52.1, 48.2, 35.4, 32.25, 25.7, 24.6. HRMS Calcd for $C_{23}H_{23}BrN_2NaOS$ $[M + Na]^+$ 477.0612, found 477.0608. HPLC: 96.4% ee (see HPLC chromatogram in SI).

*O-((S,E)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4-phenylbut-3-en-1-yl) Pyrrolidine-1-carbothioate (**4a**).* Stirring *O*-((*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(tri-*n*-butylstannyl)methyl) pyrrolidine-1-carbothioate (**3**)[31] (50 mg, 0.093 mmol) and (*E*)-(3-bromoprop-1-en-1-yl)benzene (22 mg, 0.11 mmol) at 82 °C for 3.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4a** (22 mg, 68%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: $R_f \approx 0.5$ (20% EtOAc/hexanes). Spectral data were concordant with literature values.[32] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.14 (m, 5H), 6.44 (d, J = 15.8 Hz, 1H), 6.20 (dt, J = 15.7, 7.2 Hz, 1H), 5.71 (q, J = 5.6 Hz, 1H), 4.33 (q, J = 6.0 Hz, 1H), 4.05 (dd, J = 8.4, 6.7 Hz, 1H), 3.92 (dd, J = 8.4, 6.0 Hz, 1H), 3.77−3.64 (m, 2H), 3.58−3.42 (m, 2H), 2.68−2.64 (m, 2H), 1.95−1.80 (m, 4H), 1.43 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.3, 137.3, 133.0, 128.5, 127.2, 126.1, 125.0, 109.6, 79.3, 76.7, 66.3, 52.1, 47.8, 34.3, 26.45, 25.55, 25.1, 24.4.

*O-((S)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(naphthalen-2-yl)-methyl) Pyrrolidine-1-carbothioate (**4b**).* Stirring **3** (50 mg, 0.093 mmol) and 2-iodonaphthalene (28 mg, 0.11 mmol) at 82 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 3.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4b** (23 mg, 68%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: $R_f \approx 0.5$ (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90−7.78 (m, 4H), 7.57−7.43 (m, 3H), 6.72 (d, J = 5.4 Hz, 1H), 4.62 (d, J = 5.9 Hz, 1H), 4.09 (app d, J = 6.3 Hz, 2H), 3.82−3.64 (m, 4H), 2.08−1.89 (m, 4H), 1.38 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.0, 134.7, 133.2, 133.1, 128.2, 128.1, 127.7, 126.9, 126.2, 126.16, 125.14, 110.0, 81.0, 78.0, 66.1, 52.3, 48.1, 26.5, 25.7, 25.25, 24.5. HRMS Calcd for $C_{21}H_{25}NNaO_3S$ $[M + Na]^+$ 394.1447, found 394.1447.

*O-((R)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(naphthalen-2-yl)-methyl) Pyrrolidine-1-carbothioate (**6**).* Stirring **5** (50 mg, 0.093 mmol) and 2-iodonaphthalene (28 mg, 0.11 mmol) at 82 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 2.5 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **6** (25 mg, 72%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: $R_f \approx 0.45$ (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89−7.79 (m, 4H), 7.57−7.44 (m, 3H), 6.68 (d, J = 6.3 Hz, 1H), 4.65 (d, J = 6.3 Hz, 1H), 3.89−3.76 (m, 3H), 3.75−3.62 (m, 3H), 2.09−1.83 (m, 4H), 1.50 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.2, 134.55, 133.3, 133.0, 128.3, 128.2, 127.7, 127.35, 126.3, 126.2, 125.2, 110.3, 81.8, 77.9, 65.9, 52.2, 48.1, 26.7, 25.7, 25.5, 24.5. HRMS Calcd for $C_{21}H_{25}NNaO_3S$ $[M + Na]^+$ 394.1447, found 394.1447.

*O-((S)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(3-methoxyphenyl)-methyl) Pyrrolidine-1-carbothioate (**4c**).* Stirring **3** (50 mg, 0.093 mmol) and 1-iodo-3-methoxybenzene (26 mg, 0.11 mmol) at 82 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 3.75 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4c** (18 mg, 56%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: $R_f \approx 0.4$ (20%

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EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.24 (m, 1H), 7.00−6.89 (m, 2H), 6.89−6.81 (m, 1H), 6.55 (d, J = 5.3 Hz, 1H), 4.54−4.44 (m, 1H), 4.03 (dd, J = 6.2, 1.2 Hz, 2H), 3.81 (s, 3H), 3.79−3.60 (m, 4H), 2.05−1.87 (m, 4H), 1.38 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0, 159.5, 138.8, 129.4, 119.6, 113.4, 113.1, 109.9, 80.5, 78.0, 65.8, 55.2, 52.2, 48.0, 26.4, 25.6, 25.2, 24.5. HRMS Calcd for $C_{18}H_{25}NNaO_4S$ $[M + Na]^+$ 374.1397, found 374.1390.

*O-((S)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(3,4,5-trimethoxyphenyl)methyl) Pyrrolidine-1-carbothioate (**4d**).* Stirring **3** (50 mg, 0.093 mmol) and 5-iodo-1,2,3-trimethoxybenzene (33 mg, 0.11 mmol) at 82 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 3.75 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4d** (16 mg, 42%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f ≈ 0.2 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (app s, 2H), 6.50 (d, J = 5.7 Hz, 1H), 4.49 (q, J = 6.0 Hz, 1H), 4.11−3.98 (m, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 3.75−3.71 (m, 3H), 3.64−3.54 (m, 1H), 2.07−1.87 (m, 4H), 1.40 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0, 153.1, 137.85, 132.6, 110.0, 104.7, 80.9, 77.9, 77.2, 66.1, 60.75, 56.1, 52.3, 48.0, 26.5, 25.65, 25.2, 24.5. HRMS Calcd for $C_{20}H_{29}NNaO_6S$ $[M + Na]^+$ 434.1608, found 434.1607.

*O-((S)-(4-Acetylphenyl)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-methyl) Pyrrolidine-1-carbothioate (**4e**).* Stirring **3** (50 mg, 0.093 mmol) and 1-(4-iodophenyl)ethan-1-one (27 mg, 0.11 mmol) at 82 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 3.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4e** (21 mg, 62%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f ≈ 0.35 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98−7.91 (m, 2H), 7.46 (dd, J = 8.1, 0.7 Hz, 2H), 6.51 (d, J = 5.9 Hz, 1H), 4.50−4.44 (m, 1H), 4.09−4.00 (m, 2H), 3.72−3.66 (m, 4H), 2.58 (s, 3H), 2.04−1.89 (m, 4H), 1.36 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 183.7, 178.9, 142.7, 136.75, 128.4, 127.7, 110.15, 80.45, 77.7, 66.2, 52.3, 48.1, 26.6, 26.4, 25.7, 25.1, 24.5. HRMS Calcd for $C_{19}H_{25}NNaO_4S$ $[M + Na]^+$ 386.1397, found 386.1402.

*O-((S)-(3-Bromoquinolin-2-yl)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl) Pyrrolidine-1-carbothioate (**4f**).* Stirring **3** (50 mg, 0.093 mmol) and 3-bromo-2-iodoquinoline (37 mg, 0.11 mmol) at 82 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 2.5 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4f** (33 mg, 80%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f ≈ 0.25 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.04−7.94 (m, 1H), 7.78−7.62 (m, 2H), 7.54−7.52 (m, 1H), 6.94 (d, J = 5.5 Hz, 1H), 4.71−4.70 (m, 1H), 4.46 (dd, J = 8.6, 5.4 Hz, 1H), 4.07 (dd, J = 8.6, 6.8 Hz, 1H), 3.93−3.91 (m, 1H), 3.76−3.53 (m, 3H), 2.08−1.92 (m, 4H), 1.53 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.9, 154.8, 146.4, 139.1, 129.6, 129.5, 128.6, 127.45, 126.6, 118.1, 109.8, 78.8, 76.7, 65.8, 52.15, 48.3, 26.35, 25.7, 25.05, 24.6. HRMS Calcd for $C_{20}H_{23}BrN_2NaO_3S$ $[M + Na]^+$ 473.0505, found 473.0513.

*O-((S)-(5-Cyanopyridin-2-yl)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-methyl) Pyrrolidine-1-carbothioate (**4g**).* Stirring **3** (50 mg, 0.093 mmol) and 6-iodonicotinonitrile (25 mg, 0.11 mmol) at 82 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 2.5 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4g** (19 mg, 58%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f ≈ 0.3 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (dd, J = 5.1, 0.9 Hz, 1H), 7.68−7.64 (m, 1H), 7.45 (dd, J = 5.0, 1.5 Hz, 1H), 6.55 (d, J = 5.0 Hz, 1H), 4.77−4.73 (m, 1H), 4.11 (dd, J = 6.2, 1.5 Hz, 2H), 3.74−3.68 (m, 4H), 2.08−1.92 (m, 4H), 1.33 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.55, 150.1, 127.1, 125.4, 124.2, 120.5, 110.0, 80.5, 78.7, 65.8, 52.5, 48.3, 26.3, 25.7, 25.0, 24.5. HRMS Calcd for $C_{17}H_{21}N_3NaO_3S$ $[M + Na]^+$ 370.1196, found 370.1186.

*O-((S,Z)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-phenylallyl) Pyrrolidine-1-carbothioate (**4h**).* Stirring **3** (50 mg, 0.093 mmol) and (*Z*)-(2-iodovinyl)benzene (25 mg, 0.11 mmol) at 68 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 2.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4h** (22 mg, 68%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f ≈ 0.45 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.40 (m, 2H), 7.37−7.29 (m, 2H), 7.26−7.24 (m, 1H), 6.70 (d, J = 11.7 Hz, 1H), 6.52 (ddd, J = 9.0, 4.3, 1.2 Hz, 1H), 5.64 (dd, J = 11.7, 9.0 Hz, 1H), 4.40−4.35 (m, 1H), 4.02 (dd, J = 8.4, 6.8 Hz, 1H), 3.82 (dd, J = 8.2, 6.2 Hz, 1H), 3.69−3.66 (m, 2H), 3.55−3.53 (m, 1H), 3.43−3.42 (m, 1H), 1.98−1.83 (m, 4H), 1.35 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.8, 136.2, 134.2, 128.7, 128.3, 127.5, 125.9, 109.7, 76.8, 76.4, 65.9, 52.1, 47.85, 26.0, 25.6, 25.0, 24.5. HRMS Calcd for $C_{19}H_{25}NNaO_3S$ $[M + Na]^+$ 370.1447, found 370.1448. HPLC: 96.8%ee (see HPLC chromatogram in SI).

*O-((S,Z)-3-(3-Bromophenyl)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl) Pyrrolidine-1-carbothioate (**4i**).* Stirring **3** (50 mg, 0.093 mmol) and (*Z*)-1-bromo-3-(2-iodovinyl)benzene (34 mg, 0.11 mmol) at 68 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 2.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4i** (19 mg, 48%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f ≈ 0.55 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.47−7.35 (m, 2H), 7.28−7.16 (m, 1H), 6.67 (d, J = 11.9 Hz, 1H), 6.41 (ddd, J = 9.0, 5.2, 1.2 Hz, 1H), 5.70 (dd, J = 11.9, 8.8 Hz, 1H), 4.37−4.35 (m, 1H), 4.06 (dd, J = 8.5, 6.8 Hz, 1H), 3.84 (dd, J = 8.5, 6.4 Hz, 1H), 3.77−3.65 (m, 2H), 3.54−3.51 (m, 1H), 3.44−3.41 (m, 1H), 2.04−1.84 (m, 4H), 1.39 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.6, 138.35, 132.8, 131.55, 130.4, 129.8, 127.5, 127.2, 122.3, 109.9, 76.7, 76.3, 66.2, 52.2, 47.9, 26.1, 25.6, 25.1, 24.5. HRMS Calcd for $C_{19}H_{24}BrNNaO_3S$ $[M + Na]^+$ 448.0552, found 448.0546.

*O-((S,Z)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(4-nitrophenyl)-allyl) Pyrrolidine-1-carbothioate (**4j**).* Stirring **3** (50 mg, 0.093 mmol) and (*Z*)-1-(2-iodovinyl)-4-nitrobenzene (30 mg, 0.11 mmol) at 68 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 2.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4j** (19 mg, 52%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f ≈ 0.3 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 11.9 Hz, 1H), 6.36 (dd, J = 9.2, 5.8 Hz, 1H), 5.81 (dd, J = 11.9, 9.2 Hz, 1H), 4.36−4.34 (m, 1H), 4.08 (dd, J = 8.5, 6.7 Hz, 1H), 3.85 (dd, J = 8.5, 6.1 Hz, 1H), 3.71−3.69 (m, 2H), 3.59−3.42 (m, 2H), 1.95−1.92 (m, 4H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.4, 168.2, 142.8, 132.1, 129.8, 129.5, 123.5, 110.0, 109.99, 76.6, 76.3, 66.3, 52.3, 47.9, 26.0, 25.6, 25.0, 24.45. HRMS Calcd for $C_{19}H_{24}N_2NaO_5S$ $[M + Na]^+$ 415.1298, found 415.1304.

*O-((S,Z)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-5-phenylpent-2-en-1-yl) Pyrrolidine-1-carbothioate (**4k**).* Stirring **3** (50 mg, 0.093 mmol) and (*Z*)-(4-iodobut-3-en-1-yl)benzene (29 mg, 0.11 mmol) at 68 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 3.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4k** (19 mg, 54%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f ≈ 0.65 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.15 (m, 5H), 6.28 (dd, J = 9.3, 4.7 Hz, 1H), 5.79−5.58 (m, 1H), 5.43−5.34 (m, 1H), 4.18−4.11 (m, 1H), 4.00 (dd, J = 8.3, 6.8 Hz, 1H), 3.81−3.70 (m, 3H), 3.62−3.47 (m, 2H), 2.81−2.79 (m, 1H), 2.75−2.64 (m, 2H), 2.60−2.47 (m, 1H), 1.95−1.92 (m, 4H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0, 141.5, 135.7, 128.6, 128.3, 125.8, 124.5, 109.6, 77.0, 76.0, 65.8, 52.1, 47.9, 35.5, 30.5, 26.3, 25.6, 25.1, 24.5. HRMS Calcd for $C_{21}H_{29}NNaO_3S$ $[M + Na]^+$ 398.1760, found 398.1761.

*O-((S,E)-3-(2-Bromophenyl)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl) Pyrrolidine-1-carbothioate (**4l**).* Stirring **3** (50 mg, 0.093 mmol) and (*E*)-1-bromo-2-(2-iodovinyl)benzene (29 mg, 0.11 mmol) at 68 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 1.5 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4l** (24 mg, 62%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f

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≈ 0.35 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.50 (m, 2H), 7.29−7.21 (m, 1H), 7.14−7.07 (m, 1H), 7.02 (d, J = 15.2 Hz, 1H), 6.30−6.21 (m, 2H), 4.49−4.43 (m, 1H), 4.13 (dd, J = 8.5, 6.8 Hz, 1H), 3.98 (dd, J = 8.5, 5.9 Hz, 1H), 3.78−3.67 (m, 4H), 2.04−1.93 (m, 4H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.6, 138.35, 132.8, 131.55, 130.4, 129.8, 127.5, 127.2, 122.3, 109.9, 76.7, 76.3, 66.2, 52.2, 47.9, 26.1, 25.6, 25.1, 24.5. HRMS Calcd for $C_{19}H_{24}BrNNaO_3S$ $[M + Na]^+$ 448.0552, found 448.0566.

*O-((S,E)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(4-iodophenyl)-allyl) Pyrrolidine-1-carbothioate (**4m**).* Stirring **3** (50 mg, 0.093 mmol) and (*E*)-1-iodo-4-(2-iodovinyl)benzene (40 mg, 0.11 mmol) at 68 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 2.0 d as described for Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4m** (25 mg, 58%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f ≈ 0.35 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.59 (m, 2H), 7.17−7.10 (m, 2H), 6.63 (d, J = 15.1 Hz, 1H), 6.30−6.19 (m, 2H), 4.44−4.41 (m, 1H), 4.11 (dd, J = 8.5, 6.8 Hz, 1H), 3.92 (dd, J = 8.6, 6.1 Hz, 1H), 3.77−3.74 (m, 2H), 3.71−3.55 (m, 2H), 2.04−1.90 (m, 4H), 1.43 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.7, 137.6, 135.7, 133.1, 131.8, 128.4, 124.7, 110.0, 79.8, 77.05, 66.1, 52.3, 48.0, 26.3, 25.6, 25.2, 24.5. HRMS Calcd for $C_{19}H_{24}INNaO_3S$ $[M + Na]^+$ 496.0414, found 496.0416.

*O-((S,E)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(4-(trifluoromethyl)phenyl)allyl)pyrrolidine-1-carbothioate (**4n**).* Stirring **3** (50 mg, 0.093 mmol) and (*E*)-1-(2-iodovinyl)-4-(trifluoromethyl)benzene (33 mg, 0.11 mmol) at 68 °C in anhydrous toluene/EtOAc (3 mL, 4:1) for 2.0 d as described in Standard Stille Cross-Coupling Using $MnCl_2$ (vide supra) afforded **4n** (24 mg, 64%) as an oil following chromatographic purification of the crude product using 20% EtOAc/hexanes. TLC: R_f ≈ 0.5 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 6.74 (d, J = 16.0 Hz, 1H), 6.36 (dd, J = 16.0, 6.5 Hz, 1H), 6.26 (ddd, J = 6.4, 4.8, 1.2 Hz, 1H), 4.48−4.40 (m, 1H), 4.13 (dd, J = 8.5, 6.8 Hz, 1H), 3.94 (dd, J = 8.6, 6.0 Hz, 1H), 3.77−3.74 (m, 2H), 3.67−3.62 (m, 2H), 2.05−1.91 (m, 4H), 1.44 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.9, 139.7, 132.6, 126.9, 126.8, 126.7, 125.5 (d, $J_{C,F}$ = 3.9 Hz), 110.1, 110.0, 79.65, 77.0, 66.1, 52.3, 48.0, 26.35, 25.6, 25.1, 24.5. HRMS Calcd for $C_{20}H_{24}F_3NNaO_3S$ $[M + Na]^+$ 438.1327, found 438.1312.

General Procedure for Manganese/Copper Stille Cross-Couplings (Figure 2). A mixture of $MnCl_2$·2LiCl (0.023 mmol, 25 mol %, 0.5 M solution in THF; Aldrich Chem. Co.), electrophile (0.11 mmol, 120 mol %), $Cu(OTf)_2$ (20 mol %), Jackiephos (0.023 mmol, 25 mol %), KF (0.27 mmol, 300 mol %), K_3PO_4 (0.18 mmol, 200 mol %), and NaCl (0.27 mmol, 300 mol %) in anhydrous dioxane (3 mL), unless otherwise stated, was degassed via four alternating high vacuum-argon cycles. After 1 h, the mixture developed a bright yellow coloration indicative of the Jackiephos complex with manganese and then a solution of α-alkoxy-tri-*n*-butylstannane (0.093 mmol) in anhydrous dioxane (1 mL) was added via syringe. The reaction mixture was stirred either at room temperature or heated at 68 °C as indicated until TLC analysis showed all stannane was consumed. The resultant maroon-colored reaction mixture was diluted with Et_2O (10 mL) and filtered through a small bed of neutral alumina, and the filter bed was washed with fresh Et_2O (5 mL). The combined filtrates were concentrated under reduced pressure, and the residue was purified via flash SiO_2 column chromatography to afford the cross-coupled adducts in the indicated yields.

*O-(1-(5-Acetylthiophen-2-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2l**).* Stirring **1** (50 mg, 0.093 mmol) and 1-(5-iodothiophen-2-yl)ethan-1-one (28 mg, 0.11 mmol) in dioxane (3 mL) at 65 °C for 6 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) afforded **2l** (22 mg, 64%) as an oil identical in all respects with an authentic sample following SiO_2 chromatographic purification using 10% EtOAc/hexanes. TLC: R_f ≈ 0.35 (10% EtOAc/hexanes).

*O-(1-(Isoquinolin-1-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate (**2p**).* Stirring **1** (50 mg, 0.093 mmol) and 1-iodoisoquinoline (28 mg, 0.11 mmol) at 65 °C for 8 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) and chromatographic purification of the crude product using 20% EtOAc/hexanes afforded **2p** (25 mg, 71%) as an oil whose physical and spectral properties matched an authentic sample. TLC: R_f ≈ 0.2 (10% EtOAc/hexanes).

*(R)-O-(1-(3-Bromoquinolin-2-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate [(R)-**2t**].* Stirring (*S*)-**1**[31] (50 mg, 0.093 mmol) and 3-bromo-2-iodoquinoline (37 mg, 0.11 mmol) at rt in anhydrous acetonitrile (3 mL) for 24 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) and chromatographic purification of the crude product using 20% EtOAc/hexanes afforded (*R*)-**2t** (28 mg, 68%) as an oil whose physical and spectral properties matched an authentic sample. TLC: R_f ≈ 0.35 (10% EtOAc/hexanes). HPLC: 98.0% ee (see HPLC chromatogram in SI).

*O-(1-(6-Methoxy-1-oxo-2,3-dihydro-1H-inden-5-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate [(±)-**2s**].* Stirring **1** (50 mg, 0.093 mmol) and 5-iodo-6-methoxy-2,3-dihydro-1*H*-inden-1-one (32 mg, 0.11 mmol) at 65 °C for 24 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) and chromatographic purification of the crude product using 20% EtOAc/hexanes afforded (±)-**2s** (26 mg, 69%) as an oil whose spectral and physical properties, except chirality, matched an authentic sample. TLC: R_f ≈ 0.3 (10% EtOAc/hexanes).

*O-((3-Bromophenyl)(3-bromoquinolin-2-yl)methyl) Pyrrolidine-1-carbothioate (**7**).* *n*-BuLi (1.6 M in hexanes, 4.72 mL, 7.56 mmol, 1.2 equiv) was added over 5 min to a stirring 0 °C solution of *N,N*-diisopropylamine (1.05 mL, 7.56 mmol, 1.2 equiv) in THF (15 mL). After 30 min, tri-*n*-butyltin hydride (1.85 mL, 2.0 g, 6.87 mmol, 1.1 equiv) was added dropwise over 10 min to the light yellow solution of LDA. Following an additional 30 min, the reaction mixture was cooled to −78 °C and a solution of 3-bromobenzaldehyde (1.1 g, 6.1 mmol, 1.00 equiv) in THF (2 mL) was slowly added. After 3 h, the reaction mixture was quenched with saturated aq NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The extracts and organic layer were combined and washed sequentially with aq 1 N HC1 (2 × 5 mL), H_2O (2 × 10 mL), and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude (3-bromophenyl)(tri-*n*-butylstannyl)methanol (1.1 g crude) as a yellowish oil. TLC: R_f ≈ 0.45 (20% EtOAc/hexanes). Without purification, the crude adduct was dissolved in CH_2C1_2 (15 mL) containing DMAP (10 mg) and thiocarbonyldiimidazole (0.45 g, 2.54 mmol, 1.1 equiv). After 2 h, the reaction mixture was filtered through a short bed of silica gel and the product was eluted with 30% EtOAc/hexane (100 mL) to give the labile *O*-((3-bromophenyl)(tri-*n*-butylstannyl)methyl) 1*H*-imidazole-1-carbothioate that was concentrated in vacuo and used immediately in the next reaction without further characterization.

The imidazole in the above thiocarbamate was exchanged by stirring the residue in a 2 M THF solution of pyrrolidine (4 mL) for 3 h.[43] The excess pyrrolidine was evaporated in vacuo, and the residue was flash chromatographed using 5−10% EtOAc/hexane to give *O*-((3-bromophenyl)(tri-*n*-butylstannyl)methyl) pyrrolidine-1-carbothioate (42% overall) as a light yellowish oil. TLC: R_f ≈ 0.75 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.14 (m, 3H), 6.67 (s, 1H), 3.79−3.66 (m, 4H), 2.07−1.97 (m, 4H), 1.44−1.37 (m, 6H), 1.29−1.23 (m, 6H), 0.95−0.85 (m, 15H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.9, 146.0, 130.0, 127.8, 126.4, 122.7, 122.0, 78.8, 52.2, 47.9, 28.91, 28.89, 27.4, 25.9, 24.6, 13.7, 10.6. HRMS Calcd for $C_{24}H_{40}NNaOSBrSn$ $[M + Na]^+$ 612.0920, found 612.0917.

Stirring the above *O*-((3-bromophenyl)(tri-*n*-butylstannyl)methyl) pyrrolidine-1-carbothioate (50 mg, 0.084 mmol) and 3-bromo-2-iodoquinoline (34 mg, 0.11 mmol) at rt in anhydrous acetonitrile (3 mL) for 18 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) and chromatographic purification of the crude product using 15% EtOAc/hexanes afforded **7** (25 mg, 58%) as an oil. TLC: R_f ≈ 0.3 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.92 (s, 1H), 7.81−7.71 (m, 3H), 7.61−7.54 (m, 2H), 7.46 (dd, J = 8.0, 2.0 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 4.19−4.06 (m, 1H), 3.79−3.69 (m, 3H), 2.08−2.03 (m, 2H), 2.00−1.94 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.0, 155.6, 146.4, 139.6, 139.5, 131.5, 129.9, 129.79, 129.77, 128.6, 127.6, 127.4,

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126.6, 122.4, 117.0, 80.1, 52.2, 48.55, 25.75, 24.7. HRMS Calcd for $C_{21}H_{19}Br_2N_2OS$ $[M + H]^+$ 504.9579, found 504.9580.

*O-((S)-(3-Bromoquinolin-2-yl)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl) Pyrrolidine-1-carbothioate (**4f**).* Stirring **3** (50 mg, 0.093 mmol) and 3-bromo-2-iodoquinoline (37 mg, 0.11 mmol) at rt in anhydrous dioxane (3 mL) for 12 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) and chromatographic purification of the crude product using 20% EtOAc/hexanes afforded **4f** (26 mg, 62%) as an oil whose physical and spectral properties matched an authentic sample. TLC: $R_f \approx 0.25$ (20% EtOAc/hexanes).

*O-((R)-(5-Acetylthiophen-2-yl)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl) Pyrrolidine-1-carbothioate (**4o**).* Stirring **3** (50 mg, 0.093 mmol) and 1-(5-iodothiophen-2-yl)ethan-1-one (28 mg, 0.11 mmol) at rt in anhydrous dioxane (3 mL) for 18 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) and chromatographic purification of the crude product using 20% EtOAc/hexanes afforded **4o** (19 mg, 55%) as an oil. TLC: $R_f \approx 0.25$ (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J = 3.8, 1.2 Hz, 1H), 7.17−7.14 (m, 1H), 6.81 (d, J = 6.0 Hz, 1H), 4.53−4.49 (m, 1H), 4.13 (ddd, J = 8.7, 6.6, 1.2 Hz, 1H), 4.03 (ddd, J = 8.7, 5.3, 1.2 Hz, 1H), 3.73−3.65 (m, 4H), 2.55 (s, 3H), 2.05−1.92 (m, 4H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 183.2, 149.2, 144.3, 132.2, 127.6, 110.4, 77.5, 76.9, 66.2, 52.45, 48.2, 29.7, 26.5, 25.6, 25.1, 24.5. HRMS Calcd for $C_{17}H_{24}NO_4S_2$ $[M + H]^+$ 370.1147, found 370.1151.

*O-((S,E)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)non-2-en-1-yl) Pyrrolidine-1-carbothioate (**4p**).* Stirring **3** (50 mg, 0.093 mmol) and (*E*)-1-iodooct-1-ene (26 mg, 0.11 mmol) at rt in anhydrous dioxane (3 mL) for 12 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) and chromatographic purification of the crude product using 20% EtOAc/hexanes afforded **4p** (22 mg, 68%) as an oil. TLC: $R_f \approx 0.25$ (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, CD_3CN) δ 6.07−6.00 (m, 1H), 5.89−5.78 (m, 1H), 5.56−5.47 (m, 1H), 4.35−4.27 (m, 1H), 4.05 (dd, J = 8.3, 6.7 Hz, 1H), 3.88 (dd, J = 8.3, 5.8 Hz, 1H), 3.72−3.53 (m, 4H), 2.15−2.06 (m, 2H), 2.03−1.91 (m, 4H), 1.48−1.27 (m, 15H), 0.93 (t, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.2, 136.8, 123.9, 109.7, 80.1, 77.2, 65.9, 52.1, 47.8, 32.4, 31.6, 28.8, 28.7, 26.3, 25.6, 25.2, 24.5, 22.6, 14.1. HRMS Calcd for $C_{19}H_{34}NO_3S$ $[M + H]^+$ 356.2259, found 356.2250.

*O-((S)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(isoquinolin-1-yl)-methyl) Pyrrolidine-1-carbothioate (**4q**).* Stirring **3** (50 mg, 0.093 mmol) and 1-iodoisoquinoline (28 mg, 0.11 mmol) at 65 °C in anhydrous dioxane (3 mL) for 18 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) and chromatographic purification of the crude product using 35% EtOAc/hexanes afforded **4q** (22 mg, 63%) as an oil. TLC: $R_f \approx 0.15$ (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (dd, J = 7.5, 1.9 Hz, 1H), 8.50 (d, J = 5.5 Hz, 1H), 7.83 (dd, J = 7.5, 1.9 Hz, 1H), 7.73−7.58 (m, 3H), 7.50 (d, J = 5.0 Hz, 1H), 4.87 (dt, J = 6.6, 5.2 Hz, 1H), 4.42 (dd, J = 8.7, 5.3 Hz, 1H), 4.24 (dd, J = 8.7, 6.8 Hz, 1H), 3.79−3.59 (m, 4H), 2.00−1.90 (m, 4H), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.5, 156.1, 141.7, 136.4, 130.1, 127.6, 127.3, 127.1, 125.7, 121.2, 109.3, 77.5, 77.3, 66.4, 52.3, 48.2, 26.3, 25.6, 24.7, 24.5. HRMS Calcd for $C_{20}H_{25}N_2O_3S$ $[M + H]^+$ 373.1580, found 373.1588.

*O-((S,E)-3-(4-Bromophenyl)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl) Pyrrolidine-1-carbothioate (**4r**).* Stirring **3** (50 mg, 0.093 mmol) and (*E*)-1-bromo-4-(2-iodovinyl)benzene (34 mg, 0.11 mmol) at rt in anhydrous dioxane (3 mL) for 18 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) and chromatographic purification of the crude product using 20% EtOAc/hexanes afforded **4r** (28 mg, 71%) as an oil. TLC: $R_f \approx 0.25$ (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 14.3 Hz, 1H), 6.29−6.14 (m, 2H), 4.40 (td, J = 6.3, 2.9 Hz, 1H), 4.10 (dd, J = 8.5, 6.8 Hz, 1H), 3.90 (dd, J = 8.4, 6.1 Hz, 1H), 3.78−3.52 (m, 4H), 1.99−1.90 (m, 4H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0, 135.2, 133.0, 131.6, 128.3, 128.2, 124.6, 121.8, 110.0, 79.8, 77.3, 66.1, 52.3, 48.0, 26.4, 25.6, 25.2, 24.5. HRMS Calcd for $C_{19}H_{24}BrNNaO_3S$ $[M + Na]^+$ 448.0552, found 448.0560.

*O-((S)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(naphthalen-1-yl)-methyl) Pyrrolidine-1-carbothioate (**4s**).* Stirring **3** (5:50 mg, 0.093 mmol) and 1-iodonaphthalene (28 mg, 0.11 mmol) at rt in anhydrous dioxane (3 mL) for 24 h as described in General Mn/Cu Stille Cross-Coupling Procedure (vide supra) and chromatographic purification of the crude product using 20% EtOAc/hexanes afforded **4s** (18 mg, 52%) as an oil. TLC: $R_f \approx 0.25$ (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.4 Hz, 1H), 7.89−7.76 (m, 2H), 7.63−7.39 (m, 5H), 4.71−4.61 (m, 1H), 4.16 (dd, J = 8.5, 5.7 Hz, 1H), 3.97−3.62 (m, 5H), 2.07−1.84 (m, 4H), 1.39 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.2, 133.7, 133.3, 130.7, 128.8, 128.79, 126.4, 125.8, 125.2, 124.4, 123.5, 109.9, 78.0, 77.7, 65.5, 52.3, 48.1, 26.4, 25.7, 25.05, 24.5. HRMS Calcd for $C_{21}H_{26}NO_3S$ $[M + H]^+$ 372.1633, found 372.1634.

(*S*)-Standard of 2r [*O*-(1-(naphthalen-2-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate]. $Ti(OiPr)_4$ (383.6 mg, 1.35 mmol) was added dropwise into a rt solution of (*S*)-BINOL (57.2 mg 0.2 mmol) in dry TBME (1 mL) under an argon atmosphere. In a separate round-bottom flask, phenethylmagnesium chloride (2.4 mL, 2.4 mmol, 1.0 mmol/mL in THF) was added over 5 min to a 0 °C solution of bis(2-dimethylaminoethyl)ether (384.6 mg, 2.4 mmol, 99%; BDAEE) in dry MTBE (2 mL) under an argon atmosphere. After stirring for 30 min, the $Ti(OiPr)_4$/(*S*)-BINOL mixture was introduced via cannula to the phenethylmagnesium/BDAEE mixture and then allowed to warm to rt. After 1 h, the yellow reaction mixture was recooled to 0 °C and a solution of 2-naphthaldehyde (0.156 mg, 1.0 mmol) in THF (2 mL) was added dropwise. After stirring at rt for 4 h, the reaction mixture was quenched with cold 5% aq HCl to pH 4 and extracted with ether (3 × 15 mL). The combined ethereal extracts were washed with brine (8 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash SiO_2 column chromatography using 15% EtOAc/hexane afforded (*S*)-1-(naphthalen-2-yl)-3-phenylpropan-1-ol[44] (207 mg, 79%). TLC: $R_f \approx 0.25$ (10% EtOAc/hexanes). The absolute configuration was assigned by analogy with literature precedent.[44] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96−7.87 (m, 4H), 7.62−7.51 (m, 3H), 7.40−7.26 (m, 5H), 4.87 (dd, J = 7.7, 5.6 Hz, 1H), 2.90−2.72 (m, 2H), 2.33−2.15 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0, 141.9, 133.4, 133.1, 128.6, 128.5, 128.46, 128.1, 127.8, 126.3, 126.0, 125.98, 124.8, 124.2, 74.0, 40.4, 32.2. The % ee was measured following the next step.

1,1′-Thiocarbonyldiimidazole (112 mg, 0.63 mmol) was added to a stirring solution of the above (*S*)-1-(naphthalen-2-yl)-3-phenylpropan-1-ol (150 mg, 0.57 mmol) in dry CH_2Cl_2 (5 mL) containing DMAP (7 mg, 0.057 mmol) under an argon atmosphere.[43] After 10 h, the reaction mixture was filtered through a small pad of silica gel and the filter cake was washed with EtOAc (5 mL). The combined filtrate was concentrated under reduced pressure, and the residue was dissolved in a 2 M THF solution of pyrrolidine (4 mL). After 2−4 h, all volatiles were removed in vacuo and the residue was chromatographed over SiO_2 using 10% EtOAc/hexane affording (*S*)-*O*-(1-(naphthalen-2-yl)-3-phenylpropyl) pyrrolidine-1-carbothioate [(*S*)-**2r**] (163 mg, 76%) as a sticky semisolid. TLC: $R_f \approx 0.35$ (10% EtOAc/hexanes). ^{1}H/^{13}C NMR data were in complete agreement with those of (*R*)-**2r** produced via Mn cross-coupling. HPLC: 82.7% ee (see HPLC chromatogram in SI). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93−7.89 (m, 4H), 7.66−7.48 (m, 3H), 7.45−7.20 (m, 5H), 6.77 (t, J = 6.7 Hz, 1H), 3.89−3.58 (m, 4H), 2.83−2.79 (m, 2H), 2.77−2.74 (m, 1H), 2.39−2.36 (m, 1H), 2.10−1.86 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.4, 141.6, 138.0, 133.2, 133.1, 128.44, 128.40, 128.2, 127.75, 126.23, 126.17, 126.1, 126.0, 124.6, 81.8, 52.1, 48.0, 38.3, 32.0, 25.7, 24.6. HRMS Calcd for $C_{24}H_{25}NNaOS$ $[M + Na]^+$ 398.1555, found 398.1549.

Standard of (±)-*O*-(1-(naphthalen-2-yl)-3-phenylpropyl) Pyrrolidine-1-carbothioate [(±)-2r]. Phenethylmagnesium chloride (2.4 mL, 2.4 mmol, 1.0 M in THF) added dropwise over 10 min to a stirring, 0 °C solution of 2-naphthaldehyde (0.156 mg, 1.0 mmol) in TBME/THF (8 mL, 1:1). After stirring for an additional 3 h at rt, the reaction mixture was quenched with cold aqueous 5% HCl to pH 4 and extracted with ether (3 × 15 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified via SiO_2 chromatography using 15% EtOAc/

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hexane to afford 1-(naphthalen-2-yl)-3-phenylpropan-1-ol (152 mg, 71%). TLC: $R_f \approx 0.25$ (10% EtOAc/hexanes). Spectral data were in complete agreement with literature values.[44]

1,1′-Thiocarbonyldiimidazole (112 mg, 0.63 mmol) was added to a stirring solution of 1-(naphthalen-2-yl)-3-phenylpropan-1-ol (150 mg, 0.57 mmol) in dry CH_2Cl_2 (5 mL) containing DMAP (7 mg, 0.057 mmol) under an argon atmosphere.[43] After 10 h, the reaction mixture was filtered through a small pad of silica gel and the filter cake was washed with EtOAc (5 mL). The combined filtrate was concentrated under reduced pressure, and the residue was dissolved in a 2 M THF solution of pyrrolidine (4 mL). After 4 h, all volatiles were removed in vacuo and the residue was chromatographed over SiO_2 using 10% EtOAc/hexane to give (±)-**2r** (163 mg, 76%) as a sticky semisolid. TLC: $R_f \approx 0.75$ (10% EtOAc/hexanes). Spectral data were in complete agreement with those of **2r**.

Standards of (*R*,*R*)- and (*R*,*S*)- of *O*-((2,2-Dimethyl-1,3-dioxolan-4-yl)(naphthalen-2-yl)methyl) Pyrrolidine-1-carbothioate (4b and 6). Following literature procedure,[45] magnesium turnings (0.96 g, 40 mmol, 2.0 equiv) were added to a two-neck round-bottom flask equipped with a stir bar and condenser. The reaction apparatus was flame-dried under vacuum and cooled under an argon atmosphere. Anhydrous THF (18 mL) was added to the reaction apparatus, followed by a single crystal of I_2 (ca. 2 mg), and then 2-bromonaphthlene (4.1 g, 20 mmol, 1.0 equiv) was added portionwise over 1 h. The reaction was stirred at ambient temperature for an additional 1 h. The Grignard concentration was assumed to be 0.49 M from the reported method.

The above 2-naphthylmagnesium bromide (3.5 mL of 0.49 M solution in THF, 1.73 mmol, 1.5 equiv) was added to a stirring solution of CuI (0.372 mg, 1.96 mmol, 1.7 equiv) in THF/Me_2S (5:1) at −78 °C under an argon atmosphere. After 20 min, a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde[31] (0.15 mg, 1.15 mmol, 1 equiv) in THF (2 mL) was added dropwise over 15 min and the reaction mixture was then allowed to gradually warm to rt over 2 h. The reaction mixture was quenched with saturated aq NH_4Cl (8 mL) and extracted with ether (3 × 15 mL). The combined ethereal extracts were washed with brine (8 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue via SiO_2 column chromatography using 30% EtOAc/hexane afforded (*R*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(naphthalen-2-yl)methanol (172 mg, 58%) whose stereochemistry was assigned by analogy with literature precedent.[46,47] TLC: $R_f \approx 0.35$ (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.81 (m, 4H), 7.51−7.45 (m, 3H), 4.72 (dd, J = 7.6, 2.8 Hz, 1H), 4.33 (dt, J = 7.6, 6.1 Hz, 1H), 3.82−3.75 (m, 2H), 2.86 (s, 1H, OH), 1.52 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1, 133.3, 133.2, 128.5, 128.0, 127.7, 126.3, 126.2, 126.18, 124.5, 110.2, 80.2, 76.1, 66.1, 27.0, 25.4. HRMS Calcd for $C_{16}H_{18}NaO_3$ [M + Na]$^+$ 281.1148, found 281.1143.

Following literature procedure,[43] 1,1′-thiocarbonyldiimidazole (112 mg, 0.63 mmol) was added to a stirring solution of the above (*R*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(naphthalen-2-yl)methanol (146 mg, 0.56 mmol) in dry CH_2Cl_2 (5 mL) containing DMAP (7 mg, 0.057 mmol) under an argon atmosphere. After 10 h, the reaction mixture was filtered through a small pad of SiO_2 and the filter cake was washed with EtOAc (5 mL). The combined filtrate was concentrated under reduced pressure, and the residue was dissolved in a solution of pyrrolidine (4 mL, 2 M THF). After 4 h, all volatiles were removed in vacuo and the residue was chromatographed over SiO_2 (20% EtOAc/hexane) to give *O*-((*R*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-(naphthalen-2-yl)methyl) pyrrolidine-1-carbothioate (**6**) (151 mg, 72%) as an oil whose spectral and physical characteristics were congruent with an authentic sample. TLC: $R_f \approx 0.45$ (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89−7.79 (m, 4H), 7.57−7.44 (m, 3H), 6.68 (dd, J = 6.5, 1.2 Hz, 1H), 4.67−4.63 (m, 1H), 3.89−3.79 (m, 3H), 3.74−3.65 (m, 3H), 2.09−1.83 (m, 4H), 1.50 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.3, 134.6, 133.3, 133.1, 128.3, 128.2, 127.7, 127.35, 126.3, 126.26, 125.3, 110.25, 81.8, 78.0, 65.9, 52.2, 48.1, 26.7, 25.7, 25.6, 24.5. HRMS Calcd for $C_{21}H_{25}NNaO_3S$ [M + Na]$^+$ 394.1447, found 394.1438.

The above 2-naphthylmagnesium bromide (7.1 mL of 0.49 M solution in THF, 3.46 mmol, 3.0 equiv) was added to a stirring, rt solution of $ZnCl_2$ (2.3 mL of 0.5 M solution in THF, 1.15 mmol, 1.0 equiv) under an argon atmosphere. After 30 min, the triorganozincate solution was cannulated slowly over 15 min into a −78 °C solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**6**) (0.15 mg, 1.15 mmol, 1 equiv) under an argon atmosphere. After 1 h, the reaction mixture was quenched with aq NH_4Cl (8 mL) and extracted with ether (3 × 15 mL). The combined ethereal extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by SiO_2 column chromatography using 30% EtOAc/hexane afforded (*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(naphthalen-2-yl)-methanol (107 mg, 36%). TLC: $R_f \approx 0.34$ (25% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95−7.79 (m, 4H), 7.62−7.44 (m, 3H), 5.09 (d, J = 4.4 Hz, 1H), 4.43 (td, J = 6.7, 4.4 Hz, 1H), 4.06 (dd, J = 8.4, 6.7 Hz, 1H), 3.82−3.75 (m, 1H), 2.74 (s, 1H, OH), 1.52 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.0, 133.3, 133.1, 128.3, 128.0, 127.7, 126.25, 126.0, 124.9, 123.9, 109.65, 79.3, 72.7, 64.5, 26.6, 25.2. HRMS Calcd for $C_{16}H_{18}NaO_3$ [M + Na]$^+$ 281.1148, found 281.1140.

Following literature procedure,[43] 1,1′-thiocarbonyldiimidazole (75 mg, 0.42 mmol) was added to a stirring solution of the above (*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(naphthalen-2-yl)methanol (100 mg, 0.38 mmol) in dry CH_2Cl_2 (5 mL) containing DMAP (5 mg, 0.038 mmol) under an argon atmosphere. After 10 h, the reaction mixture was filtered through a small pad of SiO_2 and the filter cake was washed with EtOAc (5 mL). The combined filtrate was concentrated under reduced pressure, and the residue was dissolved in a THF solution of pyrrolidine (4 mL, 2 M). After 4 h, all volatiles were removed in vacuo and the residue was chromatographed over SiO_2 using 20% EtOAc/hexane to yield *O*-((*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(naphthalen-2-yl)methyl) pyrrolidine-1-carbothioate (**4b**) (92 mg, 64%). TLC: $R_f \approx 0.5$ (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90−7.80 (m, 4H), 7.58−7.44 (m, 3H), 6.73 (d, J = 5.5 Hz, 1H), 4.62 (q, J = 6.1 Hz, 1H), 4.09 (d, J = 6.3 Hz, 2H), 3.84−3.63 (m, 4H), 2.07−1.85 (m, 4H), 1.39 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.0, 134.7, 133.2, 133.1, 128.2, 128.1, 127.7, 126.9, 126.2, 126.16, 125.1, 110.0, 81.0, 78.0, 66.1, 52.3, 48.1, 26.5, 25.7, 25.25, 24.5. HRMS Calcd for $C_{21}H_{25}NNaO_3S$ [M + Na]$^+$ 394.1447, found 394.1442.

(*Z*)-1-Bromo-3-(2-iodovinyl)benzene. Following literature procedure,[48] NaHMDS (1 mL of a 1 M solution in THF, 1.0 mmol, 1.2 equiv) was added slowly to a suspension of (iodomethyl)-triphenylphosphonium iodide (0.550 g, 1.0 mmol, 1.2 equiv) in THF (2.3 mL) and then cooled to −60 °C. HMPA (0.3 mL) was added, and the solution was cooled further to −78 °C. 3-Bromobenzaldehyde (0.16 mg, 0.8 mmol, 1 equiv) was added, and the mixture was stirred at −78 °C for 5 min and then allowed to warm to rt over 35 min. Et_2O (20 mL) was added, and the mixture was filtered over Celite and concentrated in vacuo. Purification of the residue by SiO_2 chromatography yielded (*Z*)-1-bromo-3-(2-iodovinyl)benzene as a pale yellow liquid (0.177 g, 68%). TLC: R_f = 0.72 (hexanes, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.62−7.56 (m, 1H), 7.51 (dd, J = 8.2, 1.6 Hz, 1H), 7.29 (td, J = 7.8, 1.6 Hz, 2H), 6.69 (dd, J = 8.7, 1.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 137.3, 131.3, 131.25, 129.8, 127.0, 122.3, 81.5. HRMS Calcd for C_8H_6BrI [M]$^+$ 307.8693, found 307.8698.

(*E*)-1-Iodo-4-(2-iodovinyl)benzene. Following literature procedure,[49] a solution of CH_2I_2 (644 μL, 8.0 mmol) in THF (1.9 mL) was added dropwise to a −78 °C solution of LiHMDS (8 mL of a 1 M solution in THF, 1.34 g, 8.0 mmol) in ether (8 mL) in a darkened room. After 20 min, a solution of 1-(bromomethyl)-4-iodobenzene (1.2 g, 4.0 mmol) in THF (3 mL) was added dropwise. The reaction mixture was allowed to slowly warm to rt. After 16 h, DBU (1.19 mL, 8.0 mmol) was added dropwise, stirred for 1 h, and then diluted with Et_2O (50 mL). The reaction mixture was filtered through a bed of Celite (approximately 3 cm) layered on top of a bed of SiO_2 (approximately 3 cm). The filtrate was concentrated under reduced pressure, and the residue was purified by SiO_2 chromatography using 100% hexane to give (*E*)-1-iodo-4-(2-iodovinyl)benzene (1.0 g, 69%,

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99:1 *E*/*Z*) as an oil. TLC: R_f = 0.74 (100% hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 15.0 Hz, 1H), 7.03 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 15.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 137.8, 137.1, 127.6, 93.9, 77.7. HRMS $C_8H_6I_2$ $[M]^+$ 355.8567, found 355.8559.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02780.

Exploratory/control experiments, scanned NMR spectra, and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vols. *1 and 2*.
(2) *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005; Vol. *2*.
(3) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587.
(4) Heravi, M. M.; Hashemi, E.; Azimian, F. *Tetrahedron* **2014**, *70*, 7.
(5) Wang, C.-Y.; Derosa, J.; Biscoe, M. R. *Chem. Sci.* **2015**, *6*, 5105.
(6) Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2013**, *69*, 5799.
(7) Cordovilla, C.; Bartolomé, C.; Martinez-Ilarduya, J. M.; Espinet, P. *ACS Catal.* **2015**, *5*, 3040.
(8) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666.
(9) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.
(10) Kagoshima, H.; Takahashi, N. *Tetrahedron Lett.* **2013**, *54*, 4558.
(11) Graña, P.; Paleo, M. R.; Sardina, F. J. *J. Am. Chem. Soc.* **2002**, *124*, 12511.
(12) Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491.
(13) Biajoli, A. F. P.; Schwalm, C. S.; Limberger, J.; Claudino, T. S.; Monteiro, A. L. *J. Braz. Chem. Soc.* **2014**, *25*, 2186.
(14) *Side Reactions in Organic Synthesis*; Dörwald, F. Z., Ed.; Wiley-VCH: Weinheim, 2005.
(15) Huang, W.; Jiao, G.; Liu, S.; Li, Q.; Shi, X.; Fu, N.; Wang, L.; Zhao, B.; Huang, W. *Chem. Commun.* **2015**, *51*, 15846.
(16) Stanetty, P.; Schnürch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2006**, *71*, 3754.
(17) Li, L.; Wang, C.-Y.; Huang, R.; Biscoe, M. R. *Nat. Chem.* **2013**, *5*, 607.
(18) Carsten, B.; He, F.; Son, H. J.; Xu, T.; Yu, L. *Chem. Rev.* **2011**, *111*, 1493.
(19) Falck, J. R.; Patel, P. K.; Bandyopadhyay, A. *J. Am. Chem. Soc.* **2007**, *129*, 790; Correction. *J. Am. Chem. Soc.* **2008**, *130*, 2372.
(20) Goli, M.; He, A.; Falck, J. R. *Org. Lett.* **2011**, *13*, 344.
(21) Li, H.; He, A.; Falck, J. R.; Liebeskind, L. S. *Org. Lett.* **2011**, *13*, 3682.
(22) Le Grognec, E.; Chrétien, J.-M.; Zammattio, F.; Quintard, J.-P. *Chem. Rev.* **2015**, *115*, 10207.
(23) Hasan, H. *Manganese*; Rosen Publishing Group: New York, 2008; p 31.
(24) Valyaev, D. A.; Lavigne, G.; Lugan, N. *Coord. Chem. Rev.* **2016**, *308*, 191.
(25) Cahiez, G.; Duplais, C.; Buendia, J. *Chem. Rev.* **2009**, *109*, 1434.
(26) Carney, J. R.; Dillon, B. R.; Thomas, S. P. *Eur. J. Org. Chem.* **2016**, *23*, 3912.
(27) *The Chemistry of Organomanganese Compounds*; Patai, S., Ed.; Wiley-VCH: Weinheim, 2011.
(28) Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* **1997**, *62*, 4208.
(29) Kang, S.-K.; Kim, W.-Y.; Lee, Y.-T.; Ahn, S.-K.; Kim, J.-C. *Tetrahedron Lett.* **1998**, *39*, 2131.
(30) Kang, S.-K.; Baik, T.-G.; Jiao, X. H.; Lee, Y. T. *Tetrahedron Lett.* **1999**, *40*, 2383.
(31) He, A.; Falck, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6586.
(32) Mohapatra, S.; Bandyopadhyay, A.; Barma, D. K.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4759.
(33) Hoffmann, R. W.; Hölzer, B. *J. Am. Chem. Soc.* **2002**, *124*, 4204.
(34) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.
(35) García-Melchor, M.; Braga, A. A. C.; Lledós, A.; Ujaque, G.; Maseras, F. *Acc. Chem. Res.* **2013**, *46*, 2626.
(36) Cu(I)/Pd: Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132.
(37) Cu(I)/Pd: Zhu, F.; Rourke, M. J.; Yang, T.; Rodriguez, J.; Walczak, M. A. *J. Am. Chem. Soc.* **2016**, *138*, 12049.
(38) Pd/PyBox: Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720.
(39) Cu(II)/Pd: Floeistrup, E.; Goede, P.; Stroemberg, R.; Malm, J. *Tetrahedron Lett.* **2011**, *52*, 209.
(40) Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, J. T. B. H.; Gossage, R. A.; Cahiez, G.; van Koten, G. *J. Organomet. Chem.* **1998**, *558*, 61.
(41) Grimaud, L.; Jutand, A. *Synthesis* **2017**, *49*, 1182.
(42) Layfield, R. A. *Chem. Soc. Rev.* **2008**, *37*, 1098.
(43) Barma, D. K.; Bandyopadhyay, A.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4755.
(44) Liu, Y.; Da, C.-S.; Yu, S.-L.; Yin, X.-G.; Wang, J.-R.; Fan, X.-Y.; Li, W.-P.; Wang, R. *J. Org. Chem.* **2010**, *75*, 6869.
(45) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083.
(46) Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, *22*, 1636.
(47) Jung, J. E.; Ho, H.; Kim, H.-D. *Tetrahedron Lett.* **2000**, *41*, 1793.
(48) Mousseau, J. J.; Bull, J. A.; Ladd, C. L.; Fortier, A.; Roman, D. S.; Charette, A. B. *J. Org. Chem.* **2011**, *76*, 8243.
(49) Bull, J. A.; Mousseau, J. J.; Charette, A. B. *Org. Lett.* **2008**, *10*, 5485.

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