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In Situ trapping of Boc-2-pyrrolidinylmethylzinc Iodide with Aryl Iodides: Direct Synthesis of 2-Benzylpyrrolidines

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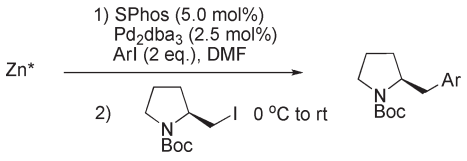
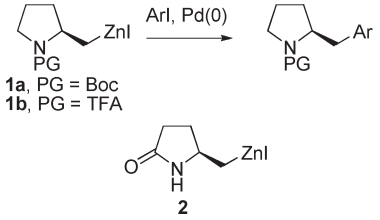


Addition of (*S*)-(+)-*tert*-butyl 2-(iodomethyl)pyrrolidine-1-carboxylate to activated zinc, aryl halides, and a catalyst derived from $Pd_2(dba)_3$ (2.5 mol %) and SPhos (5 mol %) in DMF allows trapping of the corresponding organozinc reagent, with formation of Boc-protected 2-benzylpyrrolidines (20−72%).

2-Benzylpyrrolidines feature as structural components of a number of natural products, including the tylophora alkaloids which contain a phenanthroindolizidine skeleton.[1] Simple 2-benzylpyrrolidines have been shown to be key components of orally active dopamine analogues[2] and of a series of calcium-sensing receptor antagonists.[3] They have also been used as precursors to chiral acyclic diaminocarbene ligands for use in the Suzuki reaction.[4]

Various routes to enantiomerically pure 2-benzylpyrrolidines have been developed, with the simplest involving addition of Grignard reagents to proline derivatives, followed by reduction of the aryl ketone.[2,3] Asymmetric syntheses of 2-benzylpyrrolidines include addition of the Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxane to *N*-*tert*-butanesulfinyl aldimines, followed by cyclization;[5] stereoselective hydrogenation of *N*-acylhydrazonium salts incorporating Enders' SAMP hydrazone as auxiliary, followed by lactam reduction;[6] and both copper-catalyzed[7,8] and palladium-catalyzed[9] intramolecular asymmetric carboamination of alkenes. 2-Arylpyrrolidines have been made via asymmetric deprotonation of Boc-pyrrolidine, transmetalation with $ZnCl_2$, and subsequent Negishi cross-coupling with aryl bromides,[10,11] although this approach has not yet been extended to 2-benzylpyrrolidines.

In an extension of our general approach to amino acid[12,13] and amine synthesis,[14,15] it appeared reasonable to consider the possibility that 2-benzylpyrrolidines could be prepared using protected 2-pyrrolidinylmethylzinc iodides **1**. Negishi cross-coupling of **1** with a variety of aryl halides should give protected 2-benzylpyrrolidines in a single step (eq 1), offering a flexible route to these targets.



(1)

While the pyroglutamic acid derived zinc reagent **2** is stable enough to undergo copper-catalyzed reaction with propargylic halides,[16] bromoallenes, and iodoalkynes,[17] two groups[1,18] have independently reported that attempts to prepare the corresponding Boc-protected proline-derived zinc reagent **1a** were unsuccessful, with the presumed reagent undergoing rapid elimination to give the corresponding alkene. We tried to prepare zinc reagent **1a** and also observed only the product of elimination, in complete agreement with the previous reports.[1,18] We now report a practical method to carry out Negishi cross-couplings with this previously elusive reagent.

Recent work has shown that replacement of the Boc group with the trifluoroacetyl group results in stabilization of protected β-aminoalkylzinc iodides toward elimination.[19] We have therefore investigated the preparation of the

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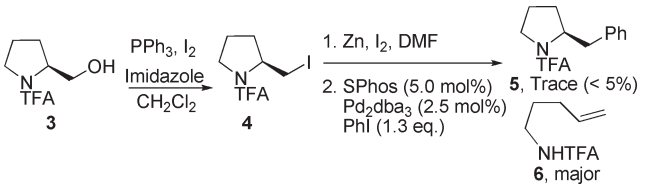
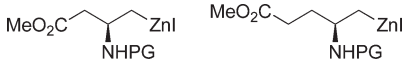
SCHEME 1. Attempted Trapping of TFA-Protected Zinc Reagent 1b



TFA-protected proline-derived zinc reagent **1b** and subsequent Negishi coupling with aryl iodides using catalysts incorporating SPhos as ligand.[20−22] Such catalysts are highly effective in Negishi cross-coupling reactions.[13,20,23] The necessary precursor **4** was prepared from TFA-protected prolinol **3**.[24] Attempted formation of the organozinc reagent **1b** by treatment of iodide **4** with activated zinc in DMF at room temperature, followed by addition of iodobenzene, $Pd_2(dba)_3$ (2.5 mol %), and SPhos (5 mol %), gave only trace amounts of the desired cross-coupled product **5**, in addition to the alkene elimination product **6** (Scheme 1). A reaction at lower temperature (0−4 °C) showed no improvement.

The nitrogen protecting group of β-aminoalkylzinc iodides influences not only the stability of the reagents but also their reactivity in Negishi cross-coupling reactions.[19] For example, the TFA-protected aspartic acid derived reagent **7b** was more stable, but less reactive, than the corresponding Boc-protected reagent **7a**, with the result that yields in Negishi cross-coupling reactions were essentially the same. However, the TFA-protected glutamic acid-derived reagent **8b** was both more stable, and more reactive, than the corresponding Boc-protected reagent **8a** in Negishi cross-coupling reactions, giving significantly higher yields.[19] These observations demonstrate that apparently small changes in structure can have a significant influence on the outcome of preparative reactions.



7a, PG = Boc
7b, PG = TFA
8a, PG = Boc
8b, PG = TFA

It was clear that neither of the proline-derived reagents **1a** and **1b** was sufficiently stable to be prepared in a conventional manner. We therefore attempted to generate the organozinc reagents **1a** and **1b** in the same pot as the catalyst and iodobenzene, so that it could be trapped as soon as it was formed. One potential advantage of this method is that there will be an excess of Pd(SPhos)PhI (the likely intermediate)[21,25] relative to the zinc reagent, so the residence time of the zinc reagent in the reaction mixture is minimized. Some precedent for this approach can be found in recent reports on

SCHEME 2. In Situ Trapping of TFA-Protected Zinc Reagent 1b

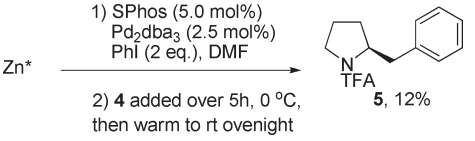
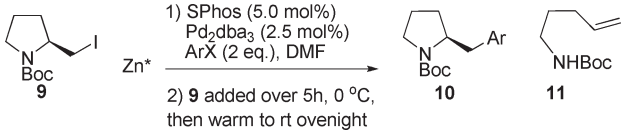


TABLE 1. Synthesis of 2-Benzylpyrrolidine Derivatives 10a−n

entry	ArX	product	Ar	yield (%)
1	C_6H_5I	**10a**	C_6H_5	43
2	2-$MeOC_6H_4I$	**10b**	2-$MeOC_6H_4$	38
3	2-HOC_6H_4I	**10c**	2-HOC_6H_4	40
4	3-$MeOC_6H_4I$	**10d**	3-$MeOC_6H_4$	44
5	3-ClC_6H_4I	**10e**	3-ClC_6H_4	39
6	3-$F_3CC_6H_4I$	**10f**	3-$F_3CC_6H_4$	62
7	4-$MeOC_6H_4I$	**10g**	4-$MeOC_6H_4$	57
8	4-$MeOC_6H_4Br$	**10g**	4-$MeOC_6H_4$	37
9	4-HOC_6H_4I	**10h**	4-HOC_6H_4	51
10	4-$H_2NC_6H_4I$	**10i**	4-$H_2NC_6H_4$	41
11	4-$MeO_2CC_6H_4I$	**10j**	4-$MeO_2CC_6H_4$	30
12	4-MeC_6H_4I	**10k**	4-MeC_6H_4	38
13	3,4-$(MeO)_2C_6H_3I$	**10l**	3,4-$(MeO)_2C_6H_3$	72
14	2-bromopyridine	**10m**	2-pyridyl	32
15	3-bromothiophene	**10n**	3-thienyl	20

SCHEME 3. In Situ Preparation of 2-Benzylpyrrolidines 10



the in situ preparation of simple alkylzinc halides in,[26] and on,[27] water and elsewhere.[28] After extensive optimization, we established that slow addition of the iodide **4** to activated zinc and iodobenzene in DMF at 0 °C, in the presence of the catalyst derived from $Pd_2(dba)_3$ (2.5 mol %) and SPhos (5 mol %), gave the desired product **5** (Scheme 2). This demonstrated that reagent **1b** can be trapped, albeit in poor yield.

Application of the same conditions to the iodide **9**[30] now allowed the target Boc-2-benzylpyrrolidine **10a** to be obtained in a substantially better yield (43%), together with the alkene **11**, arising from competitive decomposition of the zinc reagent. This result shows that the Boc-protected reagent **1a** can be trapped more efficiently than the TFA-protected reagent **1b**. The results obtained from in situ trapping of reagent **1a** using a variety of aryl halides are shown in Table 1 and Scheme 3. While aryl bromides appear to be less suitable substrates (cf. entries 7 and 8), an electron-poor (entry 14) and an electron-rich heterocycle (entry 15) can be used. Free phenols are tolerated (entries 3 and 9).[29] In all cases, varying amounts of the alkene **11** were formed, highlighting the intrinsic instability of reagent **1a**. The yields of the 2-benzylpyrrolidines **10** obtained therefore reflect the relative rates of productive Negishi cross-coupling and unproductive elimination.

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In conclusion, although the zinc reagent **1a** is evidently too unstable to be prepared in a conventional manner, it is sufficiently reactive that it can be trapped with varying levels of efficiency in situ. This general approach may be applicable to other unstable organozinc reagents.

Experimental Section

All NMR spectra were recorded in DMSO-d_6 at 80 °C.

Negishi Cross-Coupling Using Iodide 9. Zinc dust (190 mg, 3 mmol) was added to a flame-dried, nitrogen-purged, round-bottom flask. Dry DMF (0.7 mL) was added via syringe, followed by iodine (40 mg, 0.15 mmol); the yellow color rapidly faded. Pd_2dba_3 (22 mg, 0.025 mmol), SPhos (21 mg, 0.05 mmol), and aryl halide (2.0 mmol) were added to the flask, and the reaction mixture was cooled in an ice bath. The iodide **9** (311 mg, 1 mmol) in DMF (0.8 mL) was added in 10 portions, via syringe, over 5 h. The reaction mixture was allowed to warm to room temperature overnight. The crude reaction mixture was applied directly to a silica gel column to give the product **10**. In some cases, the product coeluted with alkene **11**, which could be removed by Kugelrohr distillation (90 °C, 0.3 mmHg).

(*S*)-(+)-*tert*-Butyl 2-Benzylpyrrolidine-1-carboxylate, 10a. The general cross-coupling method using iodobenzene (224 μL, 2.0 mmol) gave, after chromatographic purification (10% EtOAc in petroleum ether) and removal of **11** by Kugelrohr distillation, **10a** (112 mg, 43%) as a colorless oil: R_f 0.5 (20% EtOAc in petroleum ether); IR ν_{max} (film)/cm^{-1} 2974, 2927, 2862, 1692, 1454, 1392; NMR δ_H (500 MHz) 1.43 (9H, s), 1.55−1.82 (4H, m), 2.60 (1H, dd, J = 13.0, 8.9 Hz), 2.97 (2H, dd, J = 13.1, 3.6 Hz), 3.23−3.30 (1H, m), 3.14−3.20 (2H, m), 3.88−3.94 (1H, m), 7.15−7.22 (3H, m), 7.28 (2H, t, J = 7.6 Hz); NMR δ_C (500 MHz) 22.1, 28.7, 27.7, 27.9, 45.7, 57.8, 77.8, 125.6, 127.8, 128.8, 138.6, 153.1, one peak obscured; $[\alpha]^{22}_D$ +9.8 (*c* 1.02, $CHCl_3$); MS *m*/*z* (ES) found MH^+ 262.1815, $C_{16}H_{24}NO_2$ requires MH^+ 262.1807.

(*S*)-(+)-*tert*-Butyl 2-(2-Methoxybenzyl)pyrrolidine-1-carboxylate, 10b. The general cross-coupling method using 2-iodoanisole (260 μL, 2.0 mmol) gave, after chromatographic purification (5% EtOAc in petroleum ether), **10b** (113 mg, 38%) as a colorless oil: R_f 0.42 (20% EtOAc in petroleum ether); IR ν_{max} (film)/cm^{-1} 2968, 1687, 1493, 1390, 1364, 1242, 1169, 1107; NMR δ_H (500 MHz) 1.40 (9H, s), 1.55−1.63 (1H, m), 1.64−1.80 (3H, m), 2.61 (1H, dd, J = 12.8 and 8.9 Hz), 2.94 (1H, dd, J 13.0, 4.7 Hz), 3.17−3.31 (2H, m), 3.78 (3H, s), 3.96−4.04 (1H, m), 6.86 (1H, dt, J = 7.3 and 0.9 Hz), 6.94 (1H, d, J = 8.2 Hz), 7.08 (1H, dd, J = 7.3 and 1.4 Hz), 7.18 (1H, dt, J = 7.9 and 1.7 Hz); NMR δ_C (126 MHz) 27.8, 45.5, 55.0, 56.7, 77.6, 110.7, 119.9, 127.0, 130.3, quaternary carbons are not observed; $[\alpha]^{22}_D$ +30.7 (*c* 1.14, $CHCl_3$); MS *m*/*z* (ES) found MH^+ 292.1907, $C_{17}H_{25}NO_3$ requires MH^+ 292.1913.

(*S*)-(+)-*tert*-Butyl 2-(2-Hydroxybenzyl)pyrrolidine-1-carboxylate, 10c. The general cross-coupling method using iodobenzene (226 μL, 2.0 mmol) gave, after chromatographic purification (10−15% EtOAc in petroleum ether) and removal of **11** by Kugelrohr distillation, **10c** (112 mg, 40%) as an orange oil: R_f 0.39 (20% EtOAc in petroleum ether); IR ν_{max}(film)/cm^{-1} 3274, 2975, 2926, 2871, 1655, 1595, 1487, 1456, 1417; NMR δ_H (500 MHz) 1.40 (9H, s), 1.62−1.83 (4H, m), 2.59 (1H, dd, J = 13.0 and 9.0 Hz), 2.89 (1H, dd, J = 13.2 and 3.9 Hz), 3.16−3.31 (2H, m), 3.93−4.02 (1H, m), 6.69 (1H, dt, J 7.5 and 1.2), 6.77 (1H, d, J 8.2), 6.98 (2H, t, J 7.5), 8.90 (1H, s); δ_C (126 MHz) 22.2, 27.9, 28.7, 33.0, 45.5, 57.1, 77.7, 114.8, 118.5, 125.0, 126.6, 130.3, 153.2, 155.1; $[\alpha]_D^{22}$ +40.0 (c 1.0, $CHCl_3$); MS *m*/*z* (ES) Found MH^+ 278.1762. $C_{16}H_{24}NO_3$ requires MH^+ 278.1756.

(*S*)-(+)-tert-Butyl 2-(3-methoxybenzyl)pyrrolidine-1-carboxylate, 10d. The general cross-coupling method using 3-iodoanisole (238 μL, 2.0 mmol) gave, after chromatographic purification (5% EtOAc in petroleum ether), **10d** (127 mg, 44%) as a colorless oil: R_f 0.44 (20% EtOAc in petroleum ether); IR ν_{max}(film)/cm^{-1} 2969, 1689, 1563, 1493, 1393, 1243, 1161, 1109; NMR δ_H (500 MHz) 1.40 (9H, s), 1.55−1.64 (1H, m), 1.63−1.79 (3H, m), 2.61 (1H, dd, J = 13.0 and 8.8 Hz), 2.94 (1H, dd, J = 13.0, 4.7 Hz), 3.05 (3H, s), 3.17−3.31 (1H, m), 3.97−4.04 (1H, m), 6.86 (1H, dt, J = 7.4 and 0.8 Hz), 6.94 (1H, d, J 8.2 Hz), 7.08 (1H, dd, J = 7.4 and 1.4 Hz), 7.18 (1H, dt, J = 7.8 and 1.7 Hz); NMR δ_C (126 MHz) 22.1, 27.8, 28.7, 45.5, 55.0, 56.7, 77.6, 110.7, 119.9, 126.8, 127.0, 130.3, one quaternary carbon not observed and one peak obscured; $[\alpha]^{22}_D$ +23.5 (*c* 1.02, $CHCl_3$); MS *m*/*z* (ES) found MH^+ 292.1902, $C_{17}H_{25}NO_3$ requires MH^+ 292.1913.

(*S*)-(+)-*tert*-Butyl 2-(3-Chlorobenzyl)pyrrolidine-1-carboxylate, 10e. The general cross-coupling method using 3-chloroiodobenzene (247 μL, 2.0 mmol) gave, after chromatographic purification (5−10% EtOAc in petrol), **10e** (115 mg, 39%) as a colorless oil: R_f 0.42 (20% EtOAc in petroleum ether); IR ν_{max} (film)/cm^{-1} 2971, 1686, 1389, 1364, 1167; NMR δ_H (500 MHz) 1.41 (9H, s), 1.58−1.66 (1H, m), 1.68−1.75 (2H, m), 1.76−1.85 (1H, m), 2.65 (1H, dd, J = 13.0 and 8.6 Hz), 2.93 (1H, dd, J = 13.0 and 3.7 Hz), 3.13−3.20 (1H, m), 3.28 (1H, td, J = 10.2 and 7.7 Hz), 3.87−3.95 (1H, m), 7.13 (1H, d, J = 7.5 Hz), 7.21 (1H, s), 7.24 (1H, d, J = 8.2 Hz), 7.30 (1H, t, J = 7.7 Hz); NMR δ_C (126 MHz) 22.1, 27.8, 28.9, 45.7, 57.6, 77.9, 125.6, 127.4, 128.6, 129.5, 132.6, 141.2, 153.1, one peak obscured; $[\alpha]^{22}_D$ +6.0 (*c* 1.0, $CHCl_3$); MS *m*/*z* (ES) found MH^+ 296.1431, $C_{16}H_{22}NO_2Cl$ requires MH^+ 296.1417.

(*S*)-(−)-*tert*-Butyl 2-(3-(Trifluoromethyl)benzyl)pyrrolidine-1-carboxylate, 10f. The general cross-coupling method using 3-iodobenzotrifluoride (288 μL, 2.0 mmol) gave, after chromatographic purification (7% EtOAc in petrol), **10f** (204 mg, 62%) as an orange oil: R_f 0.47 (20% EtOAc in petroleum ether); IR ν_{max} (film)/cm^{-1} 2973, 2928, 2862, 1812, 1769, 1756, 1693, 1456, 1395; NMR δ_H (500 MHz) 1.41 (9H, s), 1.57−1.75 (4H, m), 1.76−1.88 (1H, m), 2.78 (1H, dd, J = 13.0 and 8.4 Hz), 3.00 (1H, dd, J = 13.2 and 4.1 Hz), 3.22−3.35 (1H, m), 3.91−4.00 (1H, m), 7.46−7.57 (4H, m); NMR δ_C (126 MHz) 22.1, 28.9, 77.9, 110.2, 140.1, 153.1, 27.7, 30.9, 45.7, 57.6, 122.4, 125.2, 128.8, 132.9, one peak obscured; $[\alpha]^{22}_D$ −18.5 (*c* 1.08, $CHCl_3$); MS *m*/*z* (ES) found MNa^+ 352.1507, $C_{17}H_{22}NO_2F_3Na$ requires MNa^+ 352.1500.

(*S*)-(+)-*tert*-Butyl 2-(4-Methoxybenzyl)pyrrolidine-1-carboxylate, 10g. The general cross-coupling method using 4-iodoanisole (468 mg, 2.0 mmol) gave, after chromatographic purification (7% EtOAc in petroleum ether), **10g** (165 mg, 57%) as a colorless oil: R_f 0.5 (20% EtOAc in petroleum ether); IR ν_{max} (film)/cm^{-1} 2967, 1688, 1297, 1363, 1252, 1165, 1112; NMR δ_H (500 MHz) 1.43 (9H, s), 1.55−1.81 (4H, m), 2.54 (1H, dd, J = 13.0 and 9.0 Hz), 2.88 (1H, dd, J = 13.2 and 3.4 Hz), 3.11−3.19 (1H, m), 3.21−3.31 (1H, m), 3.73 (3H, s), 3.81−3.90 (1H, m), 6.85 (2H, d, J = 8.6 Hz), 7.07 (2H, d, J = 8.6 Hz); NMR δ_C (126 MHz) 22.1, 28.6, 27.9, 45.8, 54.7, 57.9, 77.8, 113.5, 129.7, 130.5, 153.1, 157.5, one peak obscured; $[\alpha]^{22}_D$ +2.4 (*c* 1.04, $CHCl_3$); MS *m*/*z* (ES) found MH^+ 292.1920, $C_{17}H_{25}NO_3$ requires MH^+ 292.1913.

Using 4-bromoanisole (250 μL, 2.0 mmol) under the same conditions gave **10g** (108 mg, 37%).

(*S*)-(−)-*tert*-Butyl 2-(4-Hydroxybenzyl)pyrrolidine-1-carboxylate, 10h. The general cross-coupling method using 4-iodophenol (440 mg, 2.0 mmol) gave, after chromatographic purification (10−15% EtOAc in petroleum ether), **10h** (140 mg, 51%) as a colorless oil: R_f 0.17 (20% EtOAc in petroleum ether); IR ν_{max}(film)/cm^{-1} 3264, 2970, 1655, 1514, 1410, 1365, 1232, 1164, 1154, 1105; NMR δ_H (500 MHz) 1.43 (9H, s), 1.56−1.80 (5H, m), 2.84 (1H, dd, J = 13.2 and 3.5 Hz), 3.11−3.19 (1H, m), 3.21−3.30 (1H, m), 3.79−3.88 (1H, m), 6.68 (2H, d, J = 8.4 Hz), 6.95 (2H, d, J = 8.4 Hz), 8.87 (1H, s), one peak obscured; NMR δ_C (126 MHz) 22.1, 27.9, 28.6, 45.8, 58.0, 114.8, 128.7, 129.5, 155.3, two quaternary carbons are not observed and one peak is obscured; $[\alpha]^{22}_D$ −13 (*c* 1.0, $CHCl_3$);

MS m/z (ES) found MH^+ 278.1755, $C_{16}H_{23}NO_3$ requires MH^+ 278.1756.

(*S*)-(−)-*tert*-Butyl 2-(4-Aminobenzyl)pyrrolidine-1-carboxylate, 10i. The general cross-coupling method using 4-iodoaniline (438 mg, 2.0 mmol) gave, after chromatographic purification (10−15% EtOAc in petroleum ether), **10i** (112 mg, 41%) as a yellow oil: R_f 0.40 (40% EtOAc in petroleum ether); IR ν_{max}(film)/cm^{-1} 3391, 3293, 2970, 1655, 1514, 1410, 1365, 1232, 1164, 1154, 1105; NMR δ_H (500 MHz) 1.44 (9H, s), 1.58−1.77 (4H, m), 2.41 (1H, dd, J = 13.1 and 9.1 Hz), 2.78 (1H, dd, J = 13.2 and 3.5 Hz), 3.11−3.18 (1H, m), 6.02−6.61 (2H, m), 3.20−3.27 (1H, m), 3.76−3.83 (1H, m), 4.62 (2H, s), 6.51 (2H, d, J = 8.4 Hz), 6.82 (2H, d, J = 8.3 Hz); NMR δ_C (126 MHz) 22.0, 27.9, 28.5, 45.8, 58.1, 77.7, 113.8, 125.7, 129.1, 146.2, 153.1, one peak obscured; $[\alpha]^{22}_D$ −2.0 (c 1.0, $CHCl_3$); MS m/z (ES) found MH^+ 277.1905, $C_{16}H_{25}N_2O_2$ requires MH^+ 277.1916.

(*S*)-(+)-*tert*-Butyl 2-(4-(Methoxycarbonyl)benzyl)pyrrolidine-1-carboxylate, 10j. The general cross-coupling method using methyl 4-iodobenzoate (524 mg, 2.0 mmol) and iodide **9** (311 mg, 1 mmol) gave, after chromatographic purification (5−10% EtOAc in petroleum ether), **10j** (96 mg, 30%) as a colorless oil: R_f 0.32 (20% EtOAc in petroleum ether); IR ν_{max}(film)/cm^{-1} 2930, 1721, 1689, 1610, 1391, 1275, 1103; NMR δ_H (500 MHz) 1.42 (9H, s), 1.56−1.66 (1H, m), 1.66−1.73 (2H, m), 1.74−1.84 (1H, m), 2.71 (1H, dd, J = 13.0 and 8.6 Hz), 3.14−3.20 (1H, m), 3.23−3.32 (1H, m), 3.84 (3H, s), 3.91−3.98 (1H, m), 7.32 (2H, d, J = 8.1 Hz), 7.88 (2H, d, J = 8.1 Hz); $[\alpha]^{22}_D$ +30.0 (c 1.0, $CHCl_3$); MS m/z (ES) found MH^+ 320.1876, $C_{18}H_{25}NO_4$ requires MH^+ 320.1862.

(*S*)-(+)-*tert*-Butyl 2-(4-Methylbenzyl)pyrrolidine-1-carboxylate, 10k. The general cross-coupling method using 4-iodotoluene (436 mg, 2.0 mmol) gave, after chromatographic purification (10% EtOAc in petroleum ether) and removal of **11** by Kugelrohr distillation, **10k** (104 mg, 38%) as a colorless oil: R_f 0.49 (20% EtOAc in petroleum ether); IR ν_{max}(film)/cm^{-1} 2964, 2922, 2854, 1695, 1516, 1454, 1392; NMR δ_H (500 MHz) 1.43 (9H, s), 1.56−1.80 (4H, m), 2.26 (3H, s), 2.54 (1H, dd, J = 13.1 and 9.0 Hz), 2.92 (1H, dd, J = 13.1 and 3.4 Hz), 3.13−3.20 (1H, m), 3.21−3.30 (1H, m), 3.83−3.90 (1H, m), 7.06 (4H, dd, J = 18.8 and 8.0 Hz); NMR δ_C (126 MHz) 20.1, 22.1, 27.9, 28.7, 45.8, 57.9, 77.8, 128.4, 128.6, 134.6, 135.5, 153.1, one peak obscured; $[\alpha]^{22}_D$ +10.2 (c 0.98, $CHCl_3$); m/z (ES) found MNa^+ 298.1781, $C_{17}H_{25}NO_2Na$ requires MNa^+ 298.1783.

(*S*)-(+)-*tert*-Butyl 2-(3,4-Dimethoxybenzyl)pyrrolidine-1-carboxylate, 10l. The general cross-coupling method using 3,4-dimethoxyiodobenzene (528 mg, 2.0 mmol) and iodide **9** (311 mg, 1 mmol) gave, after chromatographic purification (10−15% EtOAc in petroleum ether), **10l** (230 mg, 72%) as a yellow oil: R_f 0.19 (20% EtOAc in petroleum ether); IR ν_{max}(film)/cm^{-1} 2968, 1686, 1510, 1390, 1364, 1259, 1236, 1154, 1112, 1028; NMR δ_H (500 MHz) 1.44 (9H, s), 1.61−1.72 (3H, m), 1.72−1.80 (1H, m), 2.54 (1H, dd, J = 13.1 and 8.8 Hz), 2.87 (1H, dd, J = 13.1 and 3.5 Hz), 3.01−3.07 (1H, m), 3.11−3.21 (1H, m), 3.21−3.32 (1H, m), 3.73 (3H, s), 3.74 (3H, s), 3.85−3.91 (1H, m), 6.69 (1H, dd, J = 8.1 and 1.9 Hz), 6.74 (1H, d, J = 1.9 Hz), 6.84−6.88 (1H, m); NMR δ_C (126 MHz) 22.1, 27.9, 28.7, 45.8, 55.4, 55.6, 57.9, 77.8, 112.5, 113.6, 121.0, 131.4, 147.4, 148.7, 153.1, one peak obscured; $[\alpha]^{22}_D$ +4.0 (c 1.0, $CHCl_3$); MS m/z (ES) found MH^+ 322.2029, $C_{18}H_{27}NO_4$ requires MH^+ 322.2018.

(*S*)-(+)-*tert*-Butyl 2-(Pyridin-2-ylmethyl)pyrrolidine-1-carboxylate, 10m. The general cross-coupling method using 2-bromopyridine (191 μL, 2.0 mmol) gave, after chromatographic purification (40% EtOAc in petroleum ether), **10m** (85 mg, 32%) as a pale yellow oil: R_f 0.21 (50% EtOAc in petroleum ether); IR ν_{max}(film)/cm^{-1} 2972, 2925, 2862, 1690, 1590, 1563, 1475, 1434, 1394; NMR δ_H (500 MHz) 1.40 (9H, s), 1.64−1.83 (4H, m), 2.73 (1H, dd, J = 13.0 and 9.0 Hz), 3.12 (2H, dd, J = 13.0 and 3.7 Hz), 3.14−3.22 (1H, m), 3.22−3.31 (1H, m), 4.04−4.12 (1H, m), 7.12−7.20 (2H, m), 7.66 (1H, dt, J = 7.7 and 1.7 Hz), 8.46 (1H, d, J = 4.1 Hz); NMR δ_C (126 MHz) 22.1, 27.8, 28.9, 45.7, 56.7, 77.8, 120.8, 123.0, 135.7, 148.5, 153.1, 158.6, one peak obscured; $[\alpha]^{22}_D$ +10.0 (c 1.0, $CHCl_3$); MS m/z (ES) found MH^+ 263.1765, $C_{15}H_{23}N_2O_2$ requires MH^+ 263.1760.

(*S*)-(−)-*tert*-Butyl 2-(Thiophene-3-ylmethyl)pyrrolidine-1-carboxylate, 10n. The general cross-coupling method using 3-bromothiophene (187 μL, 2.0 mmol) gave, after chromatographic purification (7% EtOAc in petroleum ether) and removal of **11** by Kugelrohr distillation, **10n** (53 mg, 20%) as a colorless oil: R_f 0.6 (20% EtOAc in petroleum ether); IR ν_{max}(film)/cm^{-1} 2973, 2924, 1691, 1454, 1393; NMR δ_H (500 MHz) 1.42 (9H, s), 1.57−1.70 (3H, m), 1.75−1.85 (1H, m), 2.69 (1H, dd, J = 13.6 and 8.8 Hz), 2.92 (1H, dd, J = 13.6 and 3.3 Hz), 3.11−3.18 (1H, m), 3.21−3.29 (1H, m), 3.86−3.93 (1H, m), 6.92 (1H, d, J = 4.9 Hz), 7.09−7.13 (1H, m), 7.40 (1H, dd, J = 4.7 and 2.9 Hz); NMR δ_C (126 MHz) 22.1, 29.0, 27.9, 45.8, 57.1, 77.8, 121.3, 125.2, 128.3, 138.7, 153.1, one peak obscured; $[\alpha]^{22}_D$ −9.3 (c 1.07, $CHCl_3$); MS m/z (ES) found MH^+ 268.1378, $C_{14}H_{22}NO_2S$ requires MH^+ 268.1371.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all compounds and experimental procedures for the preparation of starting materials and compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.