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Use of the SPhos Ligand to Suppress Racemization in Arylpinacolboronate Ester Suzuki Couplings Involving α-Amino Acids. Synthesis of Biaryl Derivatives of 4-Hydroxyphenylglycine, Tyrosine, and Tryptophan

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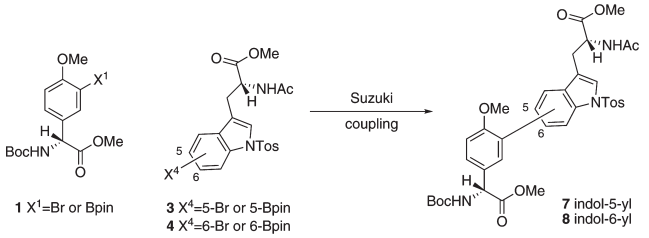
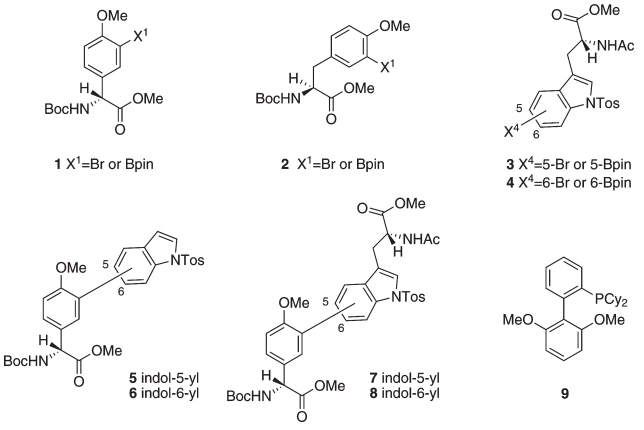


α-Amino acid derivatives, particularly those of phenylglycine, can suffer significant racemization in Suzuki couplings. When arylpinacolboronate esters are used as coupling partners this unwanted side reaction can be suppressed by the use of $Pd(OAc)_2$ as Pd(0) source, in the presence of Buchwald's SPhos ligand. The syntheses of biaryl amino acids of tyrosine, phenylglycine, and tryptophan, including Phg-Trp units similar to those found in the chloropeptin family of natural products, are reported.

The Suzuki coupling[1−3] is currently one of the most effective procedures for the formation of carbon−carbon bonds. Among its most important advantages is a tolerance for a wide variety of functional groups in the coupling partners and the relatively nontoxic byproduct it generates. Although the mechanism by which it proceeds[4] is known to be complex in its details,[5,6] there is broad consensus on the main stages of the catalytic cycle. As a consequence of the intensive study of this reaction over the last couple of decades, increasingly complex coupling partners can now be exploited, including those incorporating multiple functional groups and stereogenic elements.[1] The use of such delicate substrates, however, does bring with it the risk that their more sensitive stereogenic centers may racemize.[7]

This issue has been addressed by several groups[8−13] and more systematic investigations have been carried out by both Hocek[14] and ourselves.[15] Hocek studied the Suzuki couplings of a phenylalaninylboronic acid with halopurine derivatives and circumvented racemization by switching from the Suzuki to a copper-mediated Stille coupling.[14] In our own study we showed that racemization in Suzuki couplings of brominated hydroxyphenylglycine and tyrosine derivatives with different arylboronic acids could be avoided by judicious modification of the conditions of the coupling reaction itself, allowing enantiomerically pure products to be obtained.[15]



Here we disclose new results that extend and complement our previous report. The widely used arylpinacolboronate esters were chosen as coupling partners rather than arylboronic acids because they do not require strong bases for their formation from aryl halides and are more amenable to chromatography on silica gel. We performed Suzuki couplings involving derivatives of 4-hydroxyphenylglycine **1**,

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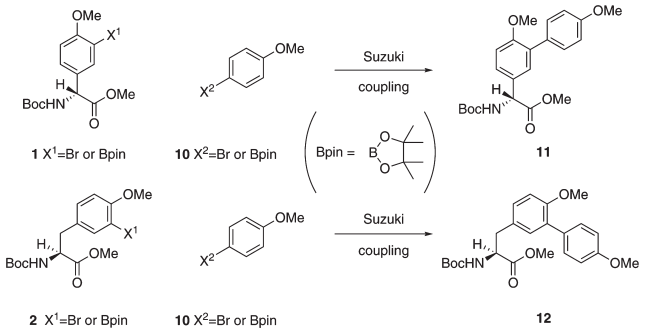
TABLE 1. Racemization in Suzuki Couplings Involving Phg, Tyr, and Trp

coupling partners	biaryl	conditions[a]	yield (%)	racemization	
1 (X^1 = Br) + **10** (X^2 = Bpin)	**11**	std	68	48[b]	26[d]
1 (X^1 = Br) + **10** (X^2 = Bpin)	**11**	rsp	84	100[b]	0[d]
2 (X^1 = Br) + **10** (X^2 = Bpin)	**12**	std	87	100[b]	0[d]
1 (X^1 = Bpin) + **10** (X^2 = Br)	**11**	std	50	36[b]	32[d]
2 (X^1 = Bpin) + **10** (X^2 = Br)	**12**	std	63	60[b]	20[d]
1 (X^1 = Br) + **13** (X^3 = Bpin)	**5**	rsp	98	96[b]	2[d]
1 (X^1 = Br) + **14** (X^3 = Bpin)	**6**	rsp	94	92[b]	4[d]
1 (X^1 = Bpin) + **3** (X^4 = Br)	**7**	std	52	44[c]	28.0[e]
1 (X^1 = Bpin) + **4** (X^3 = Br)	**8**	std	55	36[c]	32.0[e]
1 (X^1 = Br) + **3** (X^4 = Bpin)	**7**	rsp	75	90[c]	0.5[e]
1 (X^1 = Br) + **4** (X^4 = Bpin)	**8**	rsp	85	72[c]	5.9[e]

[a]std = "standard", rsp = "racemization-suppressing". [b]ee (%). [c]de (%). [d]% unwanted enantiomer. [e]% racemization at Phg and at Trp.

SCHEME 1. Model Reactions



tyrosine **2**, and tryptophans **3** and **4** under reaction conditions that are generally considered to be typical [$PdCl_2$(dppf) as catalyst and K_3PO_4 as base in 1,4-dioxane, (hereafter referred to as "standard conditions", see Table 1)]. We then measured the amount of unwanted enantiomer in the biaryl products[15,16] and found that significant racemization could occur. As no improvement was discernible on changing to $Pd(Ph_3P)_4$ as Pd(0) source, nor to Na_2CO_3 or sodium succinate as base, we were gratified to discover that racemization could be suppressed using conditions described by Buchwald[17−19] [$Pd(OAc)_2$ as Pd(0) source, SPhos ligand **9**, and K_3PO_4 as base, in a mixture of toluene−water (9:1) (hereafter referred to as "racemization-suppressing conditions", see Table 1)]. We also report on the synthesis of indolylphenylglycines **5** and **6** and of Phg-Trp biaryl bisamino acids **7** and **8** that are similar to those present in the chloropeptins.[20,21]

We focused initially on the model reactions shown in Scheme 1. Suzuki couplings between (*R*)-phenylglycine **1** (X^1 = Br) and 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **10** (X^2 = Bpin) under "standard conditions" gave biaryl amino acid **11** in yields up to 68%, after 20 h at reflux. HPLC analysis of this compound on a chiral stationary phase showed that up to 26% of the (*S*) enantiomer was present. Similar couplings of tyrosine **2** (X^1 = Br) with **10** (X^2 = Bpin) gave the biaryl product **12** in yields of up to 87%. HPLC analysis showed that this product was enantiomerically pure.

Nevertheless, racemization in the coupling of **1** (X^1 = Br) with **10** (X^2 = Bpin) could be completely avoided by using "racemization suppressing conditions". After 6 h of reaction time, enantiomerically pure **11** was obtained in a yield of 84%.

When the coupling partner roles were swapped,[22] racemization became a more challenging problem since amino acids **1** and **2** must themselves first be converted into arylpinacolboronate esters before being submitted to Suzuki reaction. The experimental conditions required to effect this conversion typically involve treating **1** (X^1 = Br) and **2** (X^1 = Br) with bis(pinacolato)diboron in the presence of a Pd(0) source and a weak base such as KOAc. Nevertheless, even this base can present a risk to the chiral integrity of sensitive molecules especially since reaction times of several hours may be required in order to achieve acceptable yields. Once formed, the arylpinacolboronate derivative must then be subjected to Suzuki coupling with the concomitant exposure to a second, stronger base such as K_3PO_4 that this entails. These two separate contacts with basic conditions make racemization correspondingly more likely.

The arylpinacolboronate esters **1** (X^1 = Bpin) and **2** (X^1 = Bpin) were prepared with use of conditions similar to those described for the synthesis of **10** (X^2 = Bpin) (see the Supporting Information) in yields of 28% and 33%, respectively, after chromatography. We believe that these rather low yields are due to partial decomposition of the products during workup and purification on silica gel. HPLC analysis revealed the presence of the unwanted enantiomer in both cases. In **1** (X^1 = Bpin) up to 22% of the (*S*)-enantiomer was detected and, somewhat more surprisingly, in **2** (X^1 = Bpin) up to 10% of the (*R*)-enantiomer was found. Hocek has reported on a similar result with phenylalanine derivatives.[14]

Attempts to prepare enantiomerically pure samples of these arylpinacolboronate esters from **1** (X^1 = Br) or **2** (X^1 = Br), using $Pd(OAc)_2$, ligand **9**, and KOAc or K_3PO_4 as base, in toluene−water (9:1) or 1,4-dioxane were unsuccessful. Only poor yields of **1** (X^1 = Bpin) and **2** (X^1 = Bpin) were obtained together with large amounts of dehalogenated side products [**1** (X^1 = H) and **2** (X^1 = H)]. Stadlweiser[23] has reported similar observations. We did not, however,

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attempt their preparation from the corresponding aryl iodides or chlorides.

When **1** (X^1 = Bpin) and **2** (X^1 = Bpin) were submitted to Suzuki coupling with **10** (X^2 = Br) under standard conditions biaryl amino acids **11** and **12** were obtained in yields of 50% and 63%, respectively. HPLC analysis of the purified products revealed that the percentages of unwanted enantiomer were up to 10% greater than those initially observed in the amino acid arylpinacolboronate ester precursors.

Although this additional racemization, engendered in the Suzuki couplings themselves, could be suppressed by using Buchwald's conditions, the amount produced initially in the formation of the arylpinacolboronate esters could not, as has been seen above. Consequently, when the amino acid was made to act as the arylpinacolboronate partner in our model Suzuki couplings we were unable to obtain enantiomerically pure biaryls.

In the case of the sensitive phenylglycine **1** (X^1 = Bpin), the significant racemization observed may not have been unexpected. Nevertheless, the level of unwanted enantiomer detected in the case of the relatively robust chiral substrate tyrosine **2** (X^1 = Bpin) was more noteworthy. As seen above, **2** (X^1 = Br) suffered no racemization when acting as the aryl halide component in couplings with arylpinacolboronate ester **10** (X^1 = Bpin) even under standard conditions. In view of this we suggest that α-amino acid derivatives should, wherever possible, be made to act as the aryl halide components in Suzuki couplings.

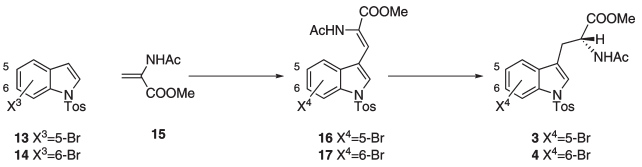
As a first stage in the synthesis of Phg-Trp bis-amino acid derivatives, phenylglycine **1** (X^1 = Br) was coupled under racemization-suppressing conditions with *N*-tosylindole derivatives[22] **13** (X^3 = 5-Bpin) and **14** (X^3 = 6-Bpin). After chromatography this furnished the *N*-tosylindolylphenylglycines **5** and **6** in yields of 98% and 94%, respectively. HPLC analysis of these compounds indicated the presence of only 2% of the (*S*) enantiomer in **5** (96% ee) and 4% of the (*S*) enantiomer in **6** (92% ee) (see Table 1).

Synthesis of the desired Phg-Trp biaryl bis-amino acids themselves required the preparation of tryptophan derivatives **3** and **4** as shown in Scheme 2.

Heck reaction between *N*-tosylindoles **13** (X^3 = Br) and **14** (X^3 = Br) and methyl 2-acetamidoacrylate **15** furnished the dehydrotryptophans **16** (X^4 = Br) and **17** (X^4 = Br), in yields of 41% and 38%, respectively. NMR studies established that in both cases the *Z* isomers were produced, as previously reported by Yokoyama.[24] Asymmetric catalytic hydrogenation with [(COD)Rh(*R*,*R*)-Et-DuPHOS]$^+$ TfO$^-$ as catalyst[25,26] then furnished enantiomerically pure (*R*)-5- and 6-bromotryptophans **3** (X^4 = 5-Br) and **4** (X^4 = 6-Br) in yields of 84% and 89%, respectively.

Suzuki coupling of these bromotryptophans with protected phenylglycine **1** (X^1 = Bpin), under standard conditions, gave protected biaryl bis-amino acids **7** (indol-5-yl) and **8** (indol-6-yl), in yields of 52% and 55%, respectively. However, as expected, severe racemization was observed in the phenylglycine moiety as evidenced by HPLC analysis of the products. Up to 28% of the diastereomer resulting from phenylglycine racemization was detected in the case of **7** and up to 32% in the case of **8** (see Table 1). As discussed above, the major portion (≈22%) occurred in the formation of the arylpinacolboronate ester **1** (X^1 = Bpin), while the remainder occurred in the Suzuki coupling itself. In contrast, no racemization was detected in the tryptophan moiety.

SCHEME 2[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$, (1.5 equiv), AcOH, 130 °C, 24 h; (b) H_2, [(COD)Rh(*R*,*R*)-Et-DuPHOS]$^+$ TfO$^-$, MeOH−CH_2Cl_2, rt, 24 h.

On the other hand, the racemization suppressing effect of the SPhos ligand **9** was clearly illustrated in Suzuki couplings in which the coupling partner roles were reversed, i.e. in which the phenylglycine derivative was the aryl bromide. Such couplings first required the conversion of bromotryptophans **3** (X^4 = 5-Br) and **4** (X^4 = 6-Br) into their corresponding arylpinacolboronate esters **3** (X^4 = 5-Bpin) and **4** (X^4 = 6-Bpin) and were achieved in yields of 69% and 83%, respectively, after chromatographic purification. HPLC analysis revealed the presence of up to 5% of the unwanted (*S*) enantiomer in **3** (X^4 = 5-Bpin) and up to 9% in **4** (X^4 = 6-Bpin). These levels of racemization are similar to that suffered by tyrosine **2** (X^2 = Br) on conversion to its arylpinacolboronate ester **2** (X^2 = Bpin).

Suzuki coupling of arylpinacolboronate esters **3** (X^4 = 5-Bpin) and **4** (X^4 = 6-Bpin) with protected phenylglycine **1** (X^1 = Br) under racemization-suppressing conditions then furnished the biaryl bis-amino acids **7** (indol-5-yl) and **8** (indol-6-yl) in yields of 85% and 75%, respectively. HPLC analysis of these biaryls revealed that no racemization of the phenylglycine moiety had occurred during Suzuki coupling in the case of **7** and less than 5% was detected in the case of **8**. Moreover, no further racemization had occurred in the tryptophan moiety in either **7** or **8** (see Table 1).

In summary, this work shows that α-amino acid derivatives can suffer significant degradation of their chiral integrity when they are submitted to Suzuki coupling under reaction conditions that are considered to be typical. To avoid this, careful assignment of the coupling partner roles is important (where possible the α-amino acid should be the aryl halide component), as is judicious choice of reaction conditions—Buchwald's racemization-suppressing S-Phos ligand **9** gives excellent results.

Phenylglycine derivative **1** is a useful probe molecule for assaying the reaction conditions of Suzuki couplings for possible racemization in the coupling partners. Such is the sensitivity of **1** that most other chiral substrates would be expected to be less vulnerable to this unwanted side reaction.

Experimental Section

Methyl (*R*)-*N*-(*tert*-Butoxycarbonyl)-3-(4-methoxyphenyl)-4-methoxyphenylglycinate (11). Arylpinacolboronate ester (**10**,

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X^2 = Bpin) (0.066 g, 0.28 mmol), methyl (*R*)-*N*-(*tert*-butoxycarbonyl)-3-bromo-4-methoxyphenylglycinate (**1**, X^1 = Br) (0.070 g, 0.19 mmol), K_3PO_4 (0.079 g, 0.37 mmol), $Pd(OAc)_2$ (0.5 mg, 0.002 mmol), and ligand **9** (1.6 mg, 0.004 mmol) were suspended in toluene (0.3 mL) and H_2O (0.03 mL) under Ar in a Schlenk tube. The resulting mixture was stirred at 100 °C for 6 h. The solvents were evaporated and the resulting crude was purified by column chromatography [silica gel, AcOEt in hexanes (0−12%)] furnishing the product as a white semisolid (0.063 g, 84%). Mp 129−132 °C (lit.[15] mp 129−132 °C); IR (film NaCl) 3377, 2956, 2933, 2838, 1746, 1715, 1519, 1495, 1248, 1167, 1049, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 3.72 (3H, s), 3.80 (3H, s), 3.84 (3H, s), 5.29 (1H, d, J = 7.2 Hz), 5.51 (1H, d, J = 6.0 Hz), 6.92−6.96 (3H, m), 7.27−7.29 (2H, m), 7.42−7.46 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (CH_3), 52.6 (CH_3), 55.3 (CH_3), 55.6 (CH_3), 57.0 (CH), 80.1 (C), 111.4 (CH), 113.5 (CH), 127.0 (CH), 129.1 (C), 129.3 (CH), 130.2 (C), 130.6 (CH), 130.8 (C), 154.8 (C), 156.5 (C), 158.8 (C), 171.9 (C); MS m/z 440 [$(M + K)^+$, 97%] 424 [$(M + Na)^+$, 100%]; HRMS calcd for $C_{22}H_{27}NO_6$ $(M)^{\bullet+}$ 401.1838, found 401.1856; $[\alpha]_D$ −95.9 ($CHCl_3$, *c* 1.30).

Methyl (*R*)-*N*-(*tert*-Butoxycarbonyl)-3-(1-tosylindol-5-yl)-4-methoxyphenylglycinate (5). As for **11**, from indolylpinacolboronate ester (**13**, X^3 = Bpin) (0.050 g, 0.13 mmol), methyl (*R*)-*N*-(*tert*-butoxycarbonyl)-3-bromo-4-methoxyphenylglycinate (**1**, X^1 = Br) (0.031 g, 0.084 mmol), K_3PO_4 (0.036 g, 0.17 mmol), $Pd(OAc)_2$ (0.2 mg, 0.001 mmol), and ligand **9** (0.7 mg, 0.002 mmol) in toluene (0.2 mL) and H_2O (0.02 mL), stirring for 8 h. Chromatography [silica gel, AcOEt in hexanes (0−20%)] furnished the product as a colorless oil (0.046 g, 98%). IR (film NaCl) 3402, 2979, 1744, 1713, 1499, 1370, 1250, 1169, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (9H, s), 2.35 (3H, s), 3.72 (3H, s), 3.79 (3H, s), 5.29 (1H, d, J = 7.2 Hz), 5.53 (1H, d, J = 6.8 Hz), 6.67 (1H, d, J = 3.6 Hz), 6.95 (1H, d, J = 8.4 Hz), 7.23−7.32 (4H, m), 7.44 (1H, dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz), 7.56 (1H, d, J = 3.6 Hz), 7.64 (1H, d, J = 1.2 Hz), 7.80 (2H, d, J = 8.4 Hz), 7.99 (1H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3), 28.3 (CH_3), 52.7 (CH_3), 55.7 (CH_3), 57.0 (CH), 80.1 (C), 109.1 (CH), 111.4 (CH), 113.0 (CH), 122.2 (CH), 126.3 (CH), 126.6 (CH), 126.9 (CH), 127.3 (CH), 129.1 (C), 129.8 (CH), 129.9 (CH), 130.7 (C), 131.1 (C), 133.1 (C), 134.0 (C), 135.3 (C), 144.9 (C), 154.8 (C), 156.5 (C), 171.8 (C); MS m/z 603 [$(M + K)^+$, 100%], 587 [$(M + Na)^+$, 29%]; HRMS calcd for $C_{30}H_{32}N_2O_7S$ $(M)^{\bullet+}$ 564.1930, found 564.1950; $[\alpha]_D$ −59.3 (CH_2Cl_2, *c* 0.14).

Methyl (*R*)-*N*-(*tert*-butoxycarbonyl)-3-(1-tosylindol-6-yl)-4-methoxyphenylglycinate (6). As for **5**, from indolylpinacolboronate ester (**14**, X^3 = Bpin) (0.050 g, 0.13 mmol) and methyl (*R*)-*N*-(*tert*-Butoxycarbonyl)-3-bromo-4-methoxyphenylglycinate (**1**, X^1 = Br) (0.031 g, 0.084 mmol), furnishing the product as a colorless oil (0.044 g, 94%). IR (film NaCl) 3400, 2977, 1746, 1713, 1499, 1370, 1250, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s), 2.35 (3H, s), 3.75 (3H, s), 3.82 (3H, s), 5.34 (1H, d, J = 6.8 Hz), 5.57 (1H, d, J = 6.8 Hz), 6.65 (1H, d, J = 3.2 Hz), 6.98 (1H, d, J = 8.4 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.31−7.37 (3H, m), 7.53 (1H, d, J = 8.4 Hz), 7.58 (1H, d, J = 4.0 Hz), 7.81 (2H, d, J = 8.4 Hz), 8.15 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3), 28.3 (CH_3), 52.7 (CH_3), 55.7 (CH_3), 57.0 (CH), 80.2 (C), 108.8 (CH), 111.5 (CH), 114.6 (CH), 120.7 (CH), 125.0 (CH), 126.7 (CH), 126.9 (CH), 127.4 (CH), 129.2 (C), 129.8 (C), 129.9 (CH), 130.0 (CH), 131.2 (C), 134.4 (C), 134.7 (C), 135.3 (C), 144.9 (C), 154.8 (C), 156.5 (C), 171.8 (C); MS m/z 603 [$(M + K)^+$, 100%] 587 [$(M + Na)^+$, 62%]; HRMS calcd for $C_{30}H_{32}N_2O_7S$ $(M)^{\bullet+}$ 564.1930, found 564.1916; $[\alpha]_D$ −66.1 (CH_2Cl_2, *c* 0.44).

Methyl (*R*)-*N*-(*tert*-Butoxycarbonyl)-3-[(*R*)-methoxy-*N*-acetyl-1-tosyltryptophan-5-yl]-4-methoxyphenylglycinate (7). As for **5**, from tryptophanylpinacolboronate ester (**3**, X^4 = Bpin) (0.11 g, 0.20 mmol), methyl (*R*)-*N*-(*tert*-butoxycarbonyl)-3-bromo-4-methoxyphenylglycinate (**1**, X^1 = Br) (0.046 g, 0.13 mmol), K_3PO_4 (0.052 g, 0.25 mmol), $Pd(OAc)_2$ (0.3 mg, 0.001 mmol), and ligand **9** (1.0 mg, 0.002 mmol) in toluene (0.3 mL) and H_2O (0.03 mL). Chromatography [silica gel, AcOEt in hexanes (25−65%)] furnished the product as a colorless oil (0.074 g, 85%). IR (film NaCl) 3377, 2956, 1744, 1713, 1503, 1465, 1439, 1370, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.93 (3H, s), 2.36 (3H, s), 3.19 (1H, dd, J_1 = 14.8 Hz, J_2 = 5.6 Hz), 3.26 (1H, dd, J_1 = 14.8 Hz, J_2 = 5.6 Hz), 3.65 (3H, s), 3.72 (3H, s), 3.79 (3H, s), 4.92 (1H, dt, J_1 = 7.4 Hz, J_2 = 5.6 Hz), 5.28 (1H, d, J = 7.2 Hz), 5.57−5.62 (1H, m), 6.08 (1H, d, J = 7.2 Hz), 6.95 (1H, d, J = 8.4 Hz), 7.26 (3H, m), 7.31 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 7.36 (1H, s), 7.44 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 7.55 (1H, dd, J_1 = 5.6 Hz, J_2 = 0.8 Hz), 7.77 (2H, d, J = 8.4 Hz), 7.97 (1H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3), 23.1 (CH_3), 27.5 (CH_2), 28.3 (CH_3), 52.3 (CH_3), 52.4 (CH), 52.7 (CH_3), 55.7 (CH_3), 80.1 (C), 111.4 (CH), 113.2 (CH), 117.2 (C), 120.1 (CH), 124.5 (CH), 126.8 (CH), 127.5 (CH), 129.1 (C), 129.8 (C), 129.9 (CH), 130.6 (C), 130.9 (C), 133.3 (C), 134.1 (C), 135.2 (C), 145.0 (C), 156.5 (C), 169.7 (C), 171.1 (C), 171.9 (C); MS m/z 746 [$(M + K)^+$, 21%] 730 [$(M + Na)^+$, 100%]; HRMS calcd for $C_{36}H_{41}N_3NaO_{10}S$ $(M + Na)^+$ 730.2410, found 730.2404; $[\alpha]_D$ −68.33 (CH_2Cl_2, *c* 0.60).

Methyl (*R*)-*N*-(*tert*-Butoxycarbonyl)-3-[(*R*)-methoxy-*N*-acetyl-1-tosyltryptophan-6-yl]-4-methoxyphenylglycinate (8). As for **7**, from tryptophanylpinacolboronate ester (**4**, X^4 = Bpin) (0.18 g, 0.35 mmol), methyl (*R*)-*N*-(*tert*-butoxycarbonyl)-3-bromo-4-methoxyphenylglycinate (**1**, X^1 = Br) (0.087 g, 0.14 mmol), K_3PO_4 (0.099 g, 0.46 mmol), $Pd(OAc)_2$ (0.6 mg, 0.002 mmol), and ligand **9** (2.0 mg, 0.005 mmol), furnishing the product as a colorless oil (0.12 g, 85%). IR (film NaCl) 3318, 2954, 1754, 1713, 1666, 1503, 1368, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.99 (3H, s), 2.36 (3H, s), 3.21 (1H, dd, J_1 = 14.8 Hz, J_2 = 5.2 Hz), 3.29 (1H, dd, J_1 = 14.8 Hz, J_2 = 5.6 Hz), 3.71 (3H, s), 3.76 (3H, s), 3.83 (3H, s), 4.95 (1H, dt, J_1 = 7.6 Hz, J_2 = 5.2 Hz), 5.34 (1H, d, J = 6.8 Hz), 5.57 (1H, d, J = 6.8 Hz), 6.06 (1H, d, J = 7.2 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.26 (2H, m), 7.30 (1H, d, J = 2.0 Hz), 7.33−7.39 (3H, m), 7.46 (1H, d, J = 8.0 Hz), 7.77 (2H, d, J_1 = 8.4 Hz), 8.13 (1H, d, J = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3), 23.2 (CH_3), 27.5 (CH_2), 28.3 (CH_3), 52.5 (CH_3), 52.7 (CH), 55.7 (CH_3), 57.0 (CH_3), 80.2 (C), 111.6 (CH), 114.8 (CH), 116.9 (C), 118.7 (CH), 124.7 (CH), 125.0 (CH), 126.9 (CH), 127.5 (CH), 129.3 (C), 129.9 (C), 131.0 (CH), 134.8 (C), 134.9 (C), 135.2 (C), 145.0 (C), 154.8 (C), 156.5 (C), 169.7 (C), 171.1 (C), 171.8 (C); MS m/z 746 [$(M + K)^+$, 100%] 730 [$(M + Na)^+$, 88%]; HRMS calcd for $C_{36}H_{41}N_3NaO_{10}S$ $(M + Na)^+$ 730.2410, found 730.2394; $[\alpha]_D$ −85.1 (CH_2Cl_2, *c* 0.58).

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Supporting Information Available: Comprehensive experimental procedures for the synthesis of compounds **1**−**8**, **10**−**14**, **16**, and **17** together with their characterization data, copies of the ^1H and ^{13}C NMR spectra for these compounds, and HPLC traces for the ee determinations for compounds **1**−**8**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.