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Racemization in Suzuki Couplings: A Quantitative Study Using 4-Hydroxyphenylglycine and Tyrosine Derivatives as Probe Molecules

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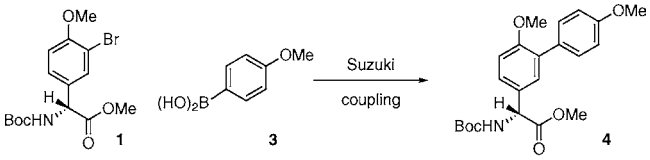

Base	Equivalents	Yield of **4**(%)	R/S (%)
Na_2CO_3	0.75	75	80:20
$NaHCO_3$	0.75	75	90:10
$(CH_2COONa)_2$	3.1	55	100:0
KOAc	3.1	54	100:0

Reaction conditions considered to be typical in Suzuki couplings can cause significant (up to 34% of the unwanted enantiomer) loss of optical purity in sensitive substrates such as hydroxyphenylglycine **1**. This may be remedied using sodium succinate instead of sodium carbonate as base, but chemical yields are somewhat lower. Optically pure biaryl amino acids related to those found in the chloropeptins and vancomycin were synthesized by Suzuki coupling of **1** with indolylboronic acids **6**−**8** and with cyclic boronic acid **9**.

The Suzuki coupling has established itself[1−3] as a powerful and versatile synthetic procedure for the formation of carbon−carbon bonds. Advances and improvements in the chemistry of the reaction have allowed increasingly complex coupling partners to be exploited, including those incorporating multiple functional groups and stereogenic elements.[1]

Since addition of base is normally necessary to ensure good yields in reasonable reaction times, there is a risk that the more sensitive stereogenic centers in a molecule will racemize.[4] To our knowledge, this issue has not been addressed in any published study to date. Here we disclose the results of a systematic investigation into the racemization produced in certain aryl−aryl Suzuki couplings.

Initially, we focused on the model reactions shown in Scheme 1, where the aryl halide coupling partner is a racemizeable probe molecule and its counterpart a simple arylboronic acid. Any racemization in the biaryl products should be quantifiable by HPLC analysis on a chiral stationary phase.[5]

We chose the brominated and protected derivatives of (*R*)-phenylglycine **1** and (*S*)-tyrosine **2** as probe molecules. While the former provided a sensitive test molecule on account of its susceptibility to base-induced racemization, we reasoned that it might also give rise to atypically high quantities of the enantiomeric Suzuki coupling product. We opted to use a tyrosine derivative as a second probe molecule in order to gauge more accurately what we felt would be more typical levels of substrate racemization.[6,7] We elected to use inexpensive and easily prepared arylbromides as substrates in all Suzuki couplings. Although they are somewhat less reactive than the more expensive aryl iodides,[8,9] they are considerably more reactive than the corresponding aryl chlorides.

We proposed attempting to suppress any racemization produced in these model couplings by judicious choice of inorganic base or other reaction parameters. We planned to continue our study by submitting the phenylglycine derivatives **1** to Suzuki couplings with more complex aryl partners in order to produce optically pure biaryl amino acids related to those found in certain natural products. In particular, we were interested in employing the indolylboronic acids[10,11] **6**−**8** and the cyclic boronic acid[12] derivative **9**. The indolyl amino acids **10**−**12** produced are models of the biaryl bisamino acids found in the chloropeptins.[13,14] The biaryl amino acid **16**, derived from Suzuki coupling product **13** by subsequent synthetic manipulations, is an analog of actinoidinic acid found in vancomycin.[15]

$Pd(Ph_3P)_4$ was used as catalyst, and all couplings were carried out in a mixture of toluene−MeOH−H_2O. The inorganic salts KOAc, $(CH_2COONa)_2$, $NaHCO_3$, Na_2CO_3, and K_3PO_4 were screened as bases (see below). Each series of couplings was carried out using similar stoichiometries, catalyst batches, solvent compositions, concentrations, reaction times, and temperatures. The conditions employed reflect typical current

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(1) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 4442−4489.
(2) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83−90.
(3) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145−157.
(4) Benoiton, N. L. *Int. J. Peptide Protein Res.* **1994**, *44*, 399−400.
(5) Steinauer, R.; Chen, F. M. F.; Benoiton, N. L. *J. Chromatogr.* **1985**, *325*, 111−126.
(6) Benoiton, N. L. *Chemistry of Peptide Synthesis*; CRC Press: Boca Raton, 2006.
(7) Lloyd-Williams, P.; Albericio, F.; Giralt, E. *Chemical Approaches to the Synthesis of Peptides and Proteins*; CRC Press: Boca Raton, 1997.
(8) Espuña, G.; Arsequell, G.; Valencia, G.; Barluenga, J.; Pérez, M.; González, J. M. *Chem. Commun.* **2000**, 1307−1308.
(9) Espuña, G.; Arsequell, G.; Valencia, G.; Barluenga, J.; Alvarez-Gutierrez, J. M.; Ballesteros, A.; Gonzalez, J. M. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 325−329.
(10) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106−5110.
(11) Prieto, M.; Zurita, E.; Rosa, E.; Muñoz, L.; Lloyd-Williams, P.; Giralt, E. *J. Org. Chem.* **2004**, *69*, 6812−6820.
(12) Brown, A. G.; Crimmin, M. J.; Edwards, P. D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 123−130.
(13) Deng, H. B.; Jung, J. K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032−9034.
(14) Shinohara, T.; Deng, H. B.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 7334−7336.
(15) Nicolaou, K. C.; Boddy, C. N. C. *J. Am. Chem. Soc.* **2002**, *124*, 10451−10455.

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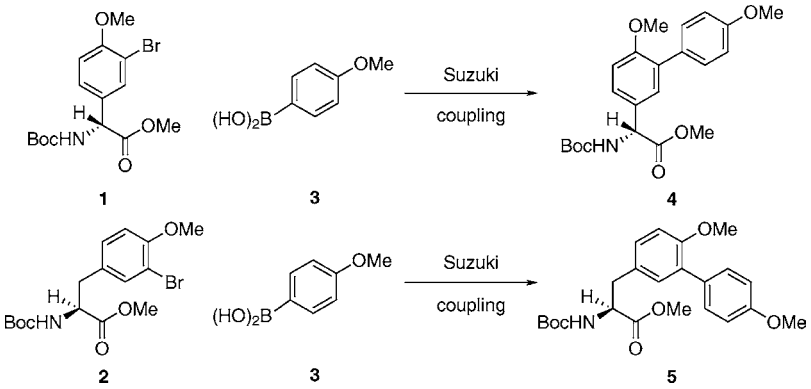
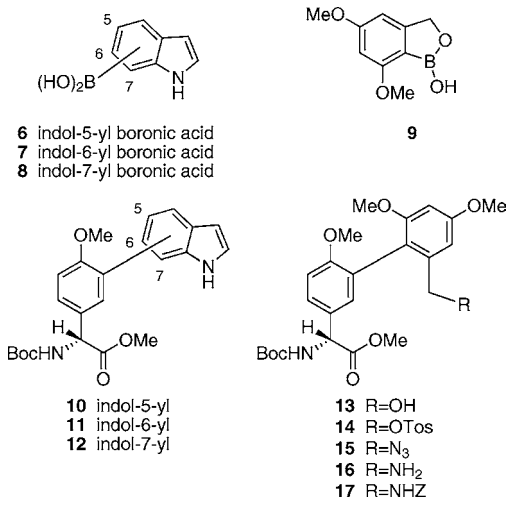
SCHEME 1. Model Reactions



practice for such couplings. Each reaction was performed at least twice and repeated as necessary to establish yield reproducibility. No attempt was made to maximize these yields since the primary objective of this investigation was to ascertain the effect of variation of inorganic base strength and stoichiometry on the degree of racemization engendered.



Optically pure probe molecules **1** and **2** were synthesized using standard chemistry. (See Supporting Information for reaction schemes and experimental data.) In preliminary experiments we noted that Suzuki couplings between **1** and 4-methoxyphenylboronic acid **3** gave biaryl **4** in yields and levels of optical purity that depended on the amount of Na_2CO_3 used. With 1.5 equiv of this base with respect to **1**, a yield of 57% of **4** was obtained. HPLC analysis of this product on a chiral stationary phase indicated 34% of the unwanted enantiomer. On reducing the amount of base to 0.75 equiv, yields of **4** rose to 75% and optical purity was also improved (20% of the undesired enantiomer). When the amount of base was lowered further to 0.25 equiv, yields of **4** were 55% with 13% of the unwanted enantiomer still being detected.

Similar Suzuki couplings involving **2**, on the other hand, gave moderate to good yields of optically pure biaryl **5**. Even when 3.1 equiv of Na_2CO_3 were used, no unwanted enantiomer was detected (see Table 1).

In attempting to suppress racemization in the Suzuki couplings between **1** and 4-methoxyphenylboronic acid **3**, we screened the inorganic bases, KOAc, $(CH_2COONa)_2$, and $NaHCO_3$, as alternatives to Na_2CO_3. The results of couplings

TABLE 1. Na_2CO_3 Stoichiometry vs Racemization in Suzuki Couplings between Probe Molecules 1 or 2 and Arylboronic Acid 3

probe	Na_2CO_3 (equiv)	yield	*R*/*S* (%)
1	1.50	57%	66:34
1	0.75	75%	80:20
1	0.25	55%	87:13
2	3.10	65%	100:0
2	1.50	61%	100:0
2	0.75	47%	100:0

TABLE 2. Base Type and Stoichiometry vs Racemization in Suzuki Couplings between Probe Molecule 1 and Arylboronic Acid 3

base	equiv	yield **4**	*R*/*S* (%)
Na_2CO_3 (pK_a 10.3)	1.50	57%	66:34
	0.75	75%	80:20
	0.25	55%	87:13
$NaHCO_3$ (pK_a 6.35)	1.50	70%	84:16
	0.75	75%	90:10
	0.50	52%	94:6
$(CH_2COONa)_2$ (pK_a 5.61)	3.1	55%	100:0
	2.1	52%	100:0
	1.5	44%	100:0
KOAc (pK_a 4.74)	3.1	54%	100:0
	2.1	40%	100:0
	1.5	36%	100:0

carried out with different quantities of these bases are summarized in Table 2.

Although $NaHCO_3$ is a weaker base than Na_2CO_3, it promoted similar yields of biaryl **4** in Suzuki couplings between **1** and **3**. However, the optical purity of the coupling product was significantly improved in comparison to that obtained using Na_2CO_3. We were unable to suppress racemization completely using these bases. On the other hand, use of either $(CH_2COONa)_2$ or KOAc, both of which are weaker than $NaHCO_3$, did allow optically pure biaryl **4** to be obtained, albeit at the cost of diminished chemical yields in comparison with Na_2CO_3 and $NaHCO_3$. Marginally better yields of optically pure biaryl **4** were obtained using $(CH_2COONa)_2$.

Having achieved the synthesis of the optically pure biaryls in our model Suzuki couplings, we proceeded to subject **1** to Suzuki coupling with indolylboronic acids **6**−**8** and cyclic boronic acid **9**. Yields and optical purities for these couplings, mediated by both sodium carbonate and sodium succinate, are listed in Table 3.

When 1.5 equiv of Na_2CO_3 was used as base in couplings between **1** and **6**−**8**, biaryls **10**−**12** were produced in yields of 85%, 68%, and 77%, respectively. HPLC analysis of biaryl **10**

TABLE 3. Comparison of Sodium Carbonate and Sodium Succinate in Suzuki Couplings between Probe Molecule 1 and Indolylboronic Acids 6−8 and Cyclic Boronic Acid 9

		yield (%)		*R*/*S* (%)	
$ArB(OH)_2$	biaryl	Na_2CO_3	$(CH_2COONa)_2$	Na_2CO_3	$(CH_2COONa)_2$
6	10	85	52	71:29	100:0
7	11	68	46	a	100:0
8	12	77	42	a	100:0
9	13	54	20	62:38	100:0

[a] Enantiomer ratios were not determined for these couplings

on a chiral stationary phase indicated that 29% of the enantiomer had been produced. When these same couplings were carried out using 2.1 equiv of $(CH_2COONa)_2$ as base, yields of **10**−**12** dropped to 52%, 46%, and 42%, respectively, but all three compounds were optically pure. Indolylphenylglycines **10**−**12** are related to the biaryl amino acids found in the chloropeptins.

The Suzuki coupling between probe molecule **1** and the cyclic boronic acid derivative **9** gave analogous results. When Na_2CO_3 was used as base biaryl **13** was formed in 54% yield. HPLC analysis on a chiral stationary phase indicated the presence of 38% of the epimer. Using 2.1 equiv of $(CH_2COONa)_2$ as base the coupling yield dropped to 20% but **13** was produced optically pure. This biaryl alcohol was transformed via tosylate **14**, azide **15**, and amine **16** into the protected amino derivative **17**, which may be considered to be a model of actinoidinic acid, a component of the vancomycin family of antibiotics. No racemization was observed in these subsequent synthetic operations.

This study shows that reaction conditions that are considered to be typical for Suzuki couplings can give rise to significant loss of optical purity with sensitive substrates such as **1**. This can be completely suppressed using sodium succinate as base, although yields are somewhat lower. The sensitivity of probe molecule **1** to racemization makes it an excellent test case for screening reaction conditions in Suzuki couplings of other racemization-sensitive substrates.

Experimental Section

Methyl (*R*)-*N*-Boc-3-(4′-methoxyphenyl)-4-methoxyphenylglycinate (4). Solutions of $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) in toluene (0.8 mL) and of 4-methoxyphenylboronic acid (32 mg, 0.21 mmol) in MeOH (0.35 mL) were added to a solution of sodium succinate (91 mg, 0.57 mmol) and methyl (*R*)-*N*-Boc-3-bromo-4-methoxyphenylglycinate (100 mg, 0.27 mmol) in toluene (0.8 mL) and H_2O (0.7 mL) under an argon atmosphere. The resulting mixture was stirred at 90 °C for 1 h. The additions of 4-methoxyphenylboronic acid (17 mg, 0.11 mmol) in MeOH (0.35 mL) and $Pd(PPh_3)_4$ (4 mg, 0.003 mmol) in toluene (0.4 mL) were repeated a further three times at 60 min intervals. The mixture was then stirred for a further 5 h. After cooling, the solvents were evaporated and the crude product was purified by column chromatography [silica gel, AcOEt in hexanes (0−13%)], furnishing **4** as a white semisolid (56 mg, 52%): 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), 5.51 (1H, d, *J* 6.0), 6.92−6.96 (3H, m), 7.27−7.39 (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), 129.0 (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*-Boc-3-(indol-5-yl)-4-methoxyphenylglycinate (10). KH (32 mg, 0.80 mmol) was suspended in anhydrous THF (0.2 mL) under an argon atmosphere at 0 °C. 5-Bromoindole (152 mg, 0.78 mmol) in anhydrous THF (1.3 mL) was added, and the mixture was stirred for 15 min. After cooling to −78 °C, a solution of ^{t}BuLi in pentane (1.53 mmol), previously cooled to −78 °C, was added dropwise. The mixture was brought to rt, stirred for 10 min, and re-cooled to −78 °C. $B(OMe)_3$ (0.18 mL, 1.53 mmol) was added, and stirring was continued for a further 3 h at rt. H_2O (5 mL) was added, and the mixture was extracted with AcOEt (2 × 10 mL). The aqueous phase was acidified to pH 1 with 10% HCl and re-extracted with AcOEt (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The solvents were evaporated, leaving the crude indolylboronic acid **6** as a pale brown oil.

Solutions of $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in toluene (0.5 mL) and of the crude indolylboronic acid **6** (2/5 of the product prepared above) in MeOH (0.4 mL) were added to a stirred solution of sodium succinate (65 mg, 0.4 mmol) and methyl (*R*)-*N*-Boc-3-bromo-4-methoxyphenylglycinate (72 mg, 0.19 mmol) in toluene (0.6 mL) and H_2O (0.4 mL) under an argon atmosphere. The mixture was brought to 90 °C and stirred for 60 min. The additions of indolylboronic acid **6** (1/5 of the crude prepared above) in MeOH (0.2 mL) and $Pd(PPh_3)_4$ (5 mg, 0.005 mmol) in toluene (0.3 mL) were repeated a further three times at 60 min intervals. The mixture was then stirred for a further 5 h. The solvents were evaporated, and the crude product was purified by column chromatography [silica gel, AcOEt in hexanes (0−15%)], giving the product as a yellow oil (41 mg, 52%): IR (film NaCl) 3405, 1701, 1607, 1499, 1368, 1250, 1163 cm^{-1}; ^1H NMR (200 MHz, d_6-acetone) δ 1.42 (9H, s), 3.68 (3H, s), 3.80 (3H, s), 5.29 (1H, d, *J* 8.0), 6.51 (1H, m), 6.75 (1H, d, *J* 6.8), 7.06 (1H, d, *J* 8.4), 7.28−7.47 (5H, m), 7.72 (1H, s), 10.27 (1H, s); ^{13}C NMR (50 MHz, d_6-acetone) δ 28.5 (CH_3), 52.5 (CH_3), 55.9 (CH_3), 58.3 (CH), 79.4 (C), 102.5 (CH), 111.3 (CH), 112.3 (CH), 121.9 (CH), 124.1 (CH), 125.7 (C), 125.8 (CH), 127.8 (CH), 128.8 (C), 129.8 (C), 130.0 (C), 130.8 (CH), 133.1 (C), 136.3 (C), 157.4 (C), 172.5 (C); MS *m*/*z* 449 [$(M + K)^+$, 68%], 433 [$(M + Na)^+$, 100%]; HRMS calcd for $C_{23}H_{26}N_2O_5$ ($M^{+\bullet}$), 410.1842: found, 410.1845; $[\alpha]_D$ −92.3 (CH_3Cl, *c* 1.1).

Methyl (*R*)-*N*-Boc-3-(2′,4′-dimethoxy-6′-hydroxymethylphenyl)-4-methoxyphenylglycinate (13). A solution of ^{n}BuLi in hexanes (4.2 mmol) was added to a stirred solution of 3,5-dimethoxy-2-bromobenzyl alcohol (494 mg, 20 mmol) in anhydrous THF (4 mL) under an argon atmosphere at −78 °C. The mixture was allowed to warm to rt over 15 min. After re-cooling to −78 °C, $B(OMe)_3$ (0.45 mL, 4.0 mmol) was added and the mixture was allowed to warm to rt and stirred for 2 h. H_2O (4 mL) was added, and the phases were separated. The aqueous phase was extracted with AcOEt (10 mL), acidified to pH 1 with 10% HCl, and re-extracted with AcOEt (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and solvent removal gave the crude boronic acid **9** as a pale yellow semisolid.

Solutions of $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) in toluene (1 mL) and of the crude arylboronic acid **9** (1/3 of the product prepared above) in MeOH (0.9 mL) were added to a stirred mixture of sodium succinate (254 mg, 1.57 mmol) and methyl (*R*)-*N*-Boc-3-bromo-4-methoxyphenylglycinate (184 mg, 0.5 mmol) in toluene (2 mL) and H_2O (1 mL) under an argon atmosphere. The mixture was heated to 90 °C and stirred for 4 h. The additions of arylboronic acid **9** (1/3 of the crude prepared above) in MeOH (0.8 mL) and $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) in toluene (1 mL) were repeated twice more at 4-h intervals. The mixture was then stirred for a further 16 h at 90 °C. The solvents were evaporated, and the crude product was purified by column chromatography [silica gel, AcOEt in hexanes (20−55%)], furnishing the product as a yellow oil (45 mg, 20%): IR (film NaCl) 3384, 2927, 2856, 1717, 1605, 1507, 1488, 1466, 1264, 1200, 1160, 1059, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (18H, s), 3.67 (3H, s), 3.68 (3H, s), 3.71

(3H, s), 3.72 (3H, s), 3.73 (6H, s), 3.86 (6H, s), 4.19−4.31 (4H, m), 5.27 (2H, d *J* 6.8), 5.50 (2H, sa), 6.49−6.50 (2H, m), 6.71 (1H, d, *J* 2.0), 6.72 (1H, d, *J* 2.0), 6.95 (1H, d, *J* 8.8), 6.96 (1H, d, *J* 8.4) 7.10 (1H, d, *J* 2.4), 7.13 (1H, d, *J* 1.6), 7.30−7.35 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (CH_3), 52.5 (CH_3), 55.3 (CH_3), 55.7 (CH_3), 55.8 (CH_3), 63.5 (CH_2), 80.0 (C), 98.3 (CH), 104.0 (CH), 111.4 (CH), 125.5 (C), 127.5 (CH), 128.7 (C), 131.2 (CH), 141.5 (C), 154.8 (C), 157.2 (C), 158.0 (C), 160.3 (C), 171.8 (C); MS *m*/*z* 500 [$(M + K)^+$, 38%], 484 [$(M + Na)^+$, 100%]; HRMS calcd for $C_{24}H_{31}NO_8$ ($M^{+\bullet}$), 461.2050: found: 461.2065; $[\alpha]_D$ −64.5 ($CHCl_3$, *c* 1.00).

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Supporting Information Available: Reaction schemes for the synthesis of probe molecules **1** and **2**; experimental procedures for the synthesis of compounds **1**, **2**, **5**, **11**, **12**, and **17**−**21** together with their characterization data; copies of the ^{1}H and ^{13}C NMR spectra for compounds **1**, **2**, **4**, **5**, **10**−**13**, **17**, and **18**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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