The catalytic *ortho*-arylation of tyrosine†

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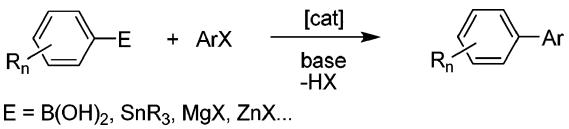
The rhodium-catalysed direct *ortho*-arylation of protected racemic 2-*tert*-butyl tyrosine has been developed. The subsequent removal of the *tert*-butyl group yields the 2-arylated tyrosine which can undergo further rhodium-based arylation at the 6-position. In one instance a product formed by further arylation of the diarylated species was isolated.

Introduction

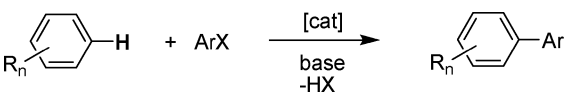
The biaryl subunit is an important structural motif found in many compounds including natural products, polymers, liquid crystals and ligands for homogeneous catalysis; cross-coupling reactions (Scheme 1), particularly the Suzuki reaction (E = $B(OH)_2$, $B(OR)_2$), are routinely employed in their syntheses.[1]



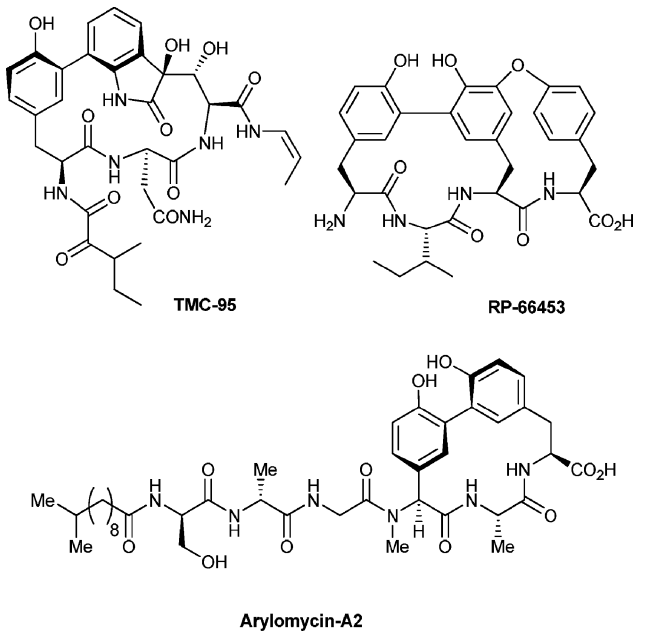
Scheme 1 Biaryl bond-formation by catalytic cross-coupling.

One such biaryl motif is the 2-arylated tyrosine moiety which is seen, for instance, in the proteasome inhibitor TMC-95,[2] the neurotensin antagonist RP-66453,[3] and the antibacterial arylomycin-A2, originally isolated from *Streptomyces* strain TU6075.[4] A recent synthesis of the latter compound by Roberts and co-workers exploited a Suzuki reaction for the formation of the biaryl unit.[5]

A more elegant approach to biaryl bond formation involves exploiting a catalytic aromatic C–H activation process to generate the nucleophilic coupling partner rather than relying on organometallic aromatic nucleophiles (Scheme 2). Such aromatic C–H activation processes are rapidly becoming powerful tools for the construction of biaryls,[6,7] not least because they circumvent many of the steps in cross-coupling chemistry giving shorter, cleaner syntheses with fewer purifications necessary.



Scheme 2 C–H activation to form biaryl compounds.



One class of biaryl bond formation that proceeds through aromatic C–H activation is the rhodium-catalysed *ortho*-selective arylation of phenols (Scheme 3).[8] Here the catalytic transformation is reliant on the formation of a rhodacyclic intermediate which is produced by orthometallation of a coordinated phosphinite or related ligand. The rhodacycle then oxidatively adds the aryl halide; subsequent reductive elimination leads to the *ortho*-arylated phenol which in turn is liberated by transesterification with the starting phenol.[9]

The direct arylation of 2-substituted phenols proceeds well using $[RhCl(PPh_3)_3]$ in the presence of a co-catalytic phosphinite ligand, $PR_2(OAr)$, the corresponding chlorophosphine, PR_2Cl or $P(NMe_2)_3$.[8] Electronically activated, non-activated and deactivated aryl bromides along with sterically challenging species are all well tolerated. We wished to extend our catalytic methodology to more challenging biologically and pharmaceutically relevant phenols and were interested to see whether the reaction could be adapted to the synthesis of mono- and diarylated tyrosine substrates.[10] This indeed proves to be the case and the results from this study are presented below.

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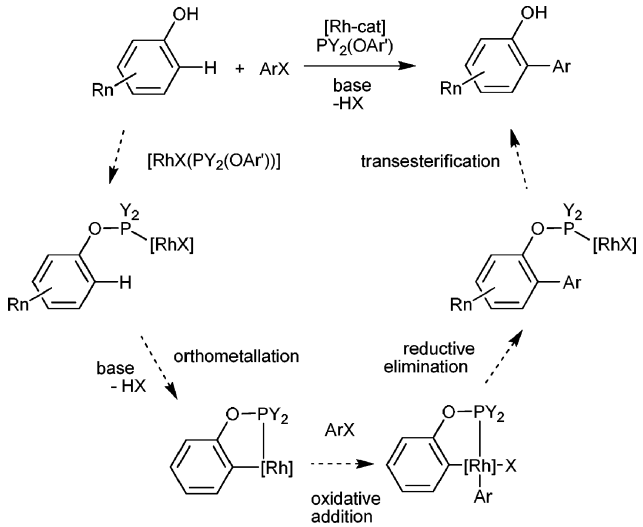
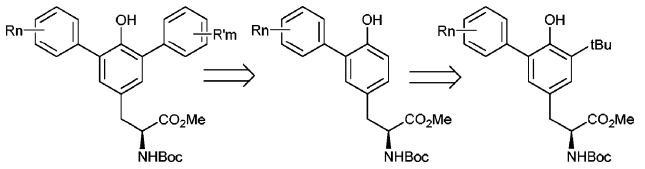
† Electronic supplementary information (ESI) available: General experimental details; spectroscopic data for all new compounds, determination of enantiopurity, X-ray structure data for **3a**. CCDC reference number 725600. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b906119c



Scheme 3 The rhodium-catalysed *ortho*-arylation of phenols.

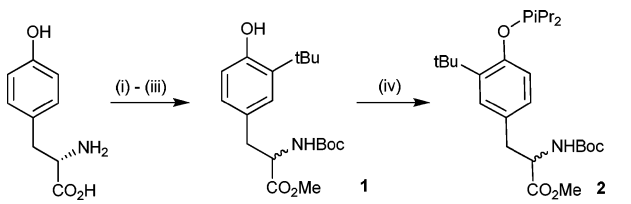


Scheme 4

Results and discussion

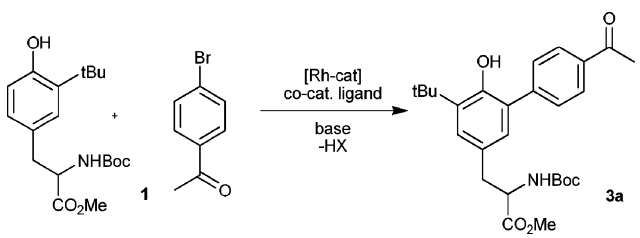
We envisaged that *ortho*-arylation of tyrosine could be exploited to generate both mono- and diarylated tyrosines according to the disconnection outlined in Scheme 4.

In the first instance it was necessary to produce a suitable tyrosine substrate. We have found that catalytic *ortho*-arylation is most effective when there is a bulky group at the 6-position of the phenol.[8a,c,d] The reactions of 2,6-unsubstituted phenols are substantially more challenging and lead exclusively to the 2,6-diarylated products (unless blocked by steric hindrance in the *meta* position). Since an *ortho*-*tert*-butyl group should be relatively easy to remove, it could in principle be exploited to speed up mono-arylation while preventing diarylation and then be removed to furnish the desired mono-arylated phenol which could, in turn, be further elaborated at the 6-position. A relatively facile route to the fully protected tyrosine substrate **1** was achieved on a multi-gram scale following the method outlined in Scheme 5, based on modified literature methods.[11–13] Unfortunately, both polarimetry and ^{1}H NMR analysis with a chiral shift reagent indicated that **1** was racemic.†



Scheme 5 Conditions: (i) H_3PO_4, ^{t}BuOH, 65 °C, 60 h; (ii) acetyl chloride, MeOH, reflux, 15 h; (iii) NEt_3, MeOH, 0 °C followed by Boc_2O, 0 °C to rt 18 h; (iv) P^iPr_2Cl, NEt_3, toluene, 110 °C, 18 h.

Table 1 Optimisation studies[a]



Entry	Rh source (mol% Rh)	Ligand (mol%)	Base	Temperature/°C	Time/h	Conversion (%)[b]
1	$[RhCl(PPh_3)_3]$ (5)	**2** (15)	Cs_2CO_3	110	18	41
2	***$[RhCl(PPh_3)_3]$ (7.5)***	***2* (22.5)**	***Cs_2CO_3***	***110***	***18***	***93.5***
3	$[RhCl(PPh_3)_3]$ (7.5)	**2** (15)	NaO^tBu	110	18	35.5
4	$[RhCl(PPh_3)_3]$ (7.5)	**2** (15)	K_3PO_4	110	18	40
5	$[RhCl(PPh_3)_3]$ (7.5)	**2** (15)	Cs_2CO_3	110	24	70
6	$[RhCl(PPh_3)_3]$ (7.5)	**2** (15)	Cs_2CO_3	120	18	67
7	$[RhCl(PPh_3)_3]$ (7.5)	**2** (15)	Cs_2CO_3	130	18	85
8	$[RhCl(PPh_3)_3]$ (5)	**2** (15)	Cs_2CO_3	130[c]	3	54
9	$[\{RhCl(PPh_3)_2\}_2]$ (5)	**2** (15)	Cs_2CO_3	130	3	80
10	$[\{RhCl(NBD)\}_2]$ (5), PPh_3 (4 equiv.)	**2** (10)	Cs_2CO_3	110	3	0
11	$[\{RhCl(dppe)\}_2]$ (5)	**2** (15)	Cs_2CO_3	120	3	16.5
12	$[\{RhCl(COD)\}_2]$ (5)	**2** (15)	Cs_2CO_3	120	3	21
13	$[\{RhCl(COD)\}_2]$ (5)	P^iPr_2Cl (15)	Cs_2CO_3	120	3	26
14	$[\{RhCl(NBD)\}_2]$ (5)	P^iPr_2Cl (15)	Cs_2CO_3	120	3	9
15	$[RhCl(COD)(P^iPr_2Cl)]$ (5)	—	Cs_2CO_3	120	3	17.5
16	$[RhCl(PPh_3)_3]$ (7.5)	P^iPr_2Cl (30)	Cs_2CO_3	120	3	17

[a] Conditions: **1** (0.178 mmol), 4-BrC_6H_4COMe (0.256 mmol), base (0.290 mmol), catalyst and co-ligands as per entry, toluene (5 mL). [b] Spectroscopic yield of **3a** determined by ^{1}H NMR spectroscopy, 1,3,5-$C_6H_3(OMe)_3$ internal standard, average of two runs. [c] Microwave heating.

Previous studies showed that the *ortho*-arylation of 2-substituted phenols, HOAr, is particularly effective when using the corresponding phosphinite ligands $P^iPr_2(OAr)$ as co-catalysts to direct the orthometallation.[8a,c,d] Therefore phosphinite **2** was synthesised by the reaction of **1** with chlorodiisopropylphosphine; the ^{31}P NMR spectrum of **2** shows a singlet at δ 138.5.

The specific reaction chosen for the catalyst optimisation studies is shown in Table 1. 4-Bromoacetophenone was chosen as coupling partner since it readily undergoes oxidative addition reactions.

As can be seen, the best results were obtained when Wilkinson's catalyst was employed at 7.5y% with 3 equivalents of $P^iPr_2(OAr)$ using caesium carbonate as the base (entry 2), although good conversions were seen at 5 mol% Rh loading, providing the temperature was increased to 130 °C (entry 7). Similarly, microwave heating could be used to good effect (compare entries 1 and 8). Under the higher temperature, conventional heating conditions, the preformed dimeric complex $[\{RhCl(PPh_3)_2\}_2]$ performed comparably to Wilkinson's catalyst (entry 9), however the *in situ* reaction of $[\{RhCl(NBD)\}_2]$ with triphenylphosphine did not yield an active catalyst (entry 10) and replacing the triphenylphosphine ligands with 1,2-bis(diphenylphosphino)ethane (dppe) proved deleterious (entry 11). Contrary to previous findings, the use of $[\{RhCl(COD)\}_2]$–phosphinite mixtures gave poor yields (entry 12).[8c] Similarly, contrary to findings in the *ortho*-arylation of simpler 2-*tert*-butylphenols,[8d] the formation of the phosphinite ligand *in situ* from either free or coordinated P^iPr_2Cl and a variety of rhodium sources gave poor results (entries 13–16). Taken together these data indicate that in many cases the amino acid functionality is probably retarding activity, presumably by competitive coordination.

Having established the best catalyst system and conditions we next applied these to a range of aryl bromide substrates and the results from this study are summarised in Table 2. In general electronically deactivated as well as activated substrates are well tolerated, as are sterically hindered aryl bromides. The isolated yields of the desired products ranged from acceptable through to excellent, although no clear electronic trends are immediately apparent. For instance, little variation in catalyst performance was seen with 4-bromoacetophenone, 4-bromotoluene, 4-bromoanisole and 4-bromo-*N*,*N*-dimethylaniline (entries 1, 5, 6 and 7) despite the considerable difference in the electronic properties of these substrates.[14] Conversely 4-bromobenzophenone, methyl 4-bromobenzoate and bromobenzene all showed unexpectedly low yields (entries 2–4). ^1H NMR analyses of crude product mixtures indicated that these reactions were genuinely low yielding and not that product was lost during work-up.

Interestingly, the introduction of steric hindrance in the 2-position of the aryl bromide gave diastereomeric products **3j** and **k** (entries 10 and 11) due to restricted rotation about the biaryl axis, at least on the NMR timescale at room temperature.

The single crystal X-ray structure of **3a**‡ was determined and the unit cell (space group $P\bar{1}$) contains both *S*- and *R*-enantiomers; the *S*-enantiomer is shown in Fig. 1.†‡ The packing in the solid state (see Fig. S2, ESI†) consists of ribbons of pairs of enantiomers held together by hydrogen bonds. The pairs of opposite enantiomers hydrogen bond between the NH and the CO of the Boc-protected amino residues while one pair of enantiomers joins to the next in the chain with pairs of hydrogen bonds between the phenolic OHs and the acetyl oxygens.

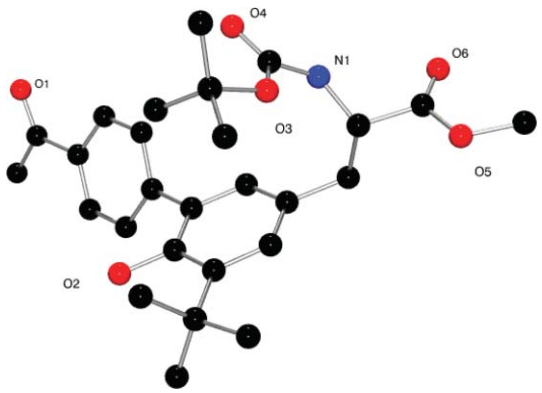
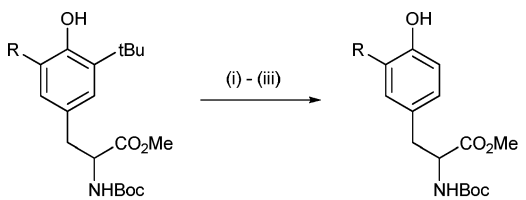


Fig. 1 X-Ray crystal structure of **3a** (*S*-enantiomer shown), hydrogen atoms removed for clarity.

Having established a convenient methodology for the *ortho*-arylation of the substrate **1**, we next attempted the removal of the 2-*tert*-butyl protecting group. Various methodologies based on reacting **1** with Lewis acids in the presence of carboxylic acids, such as zinc acetate–acetic acid,[15] proved ineffective. However, a test reaction based on **1** with $AlCl_3$–$MeNO_2$ in toluene,[16] followed by reprotection of the amino acid function of the crude, unisolated product, yielded the protected tyrosine **4a** in 78% overall yield after three steps (Scheme 6). Subjecting **3e** to the same methodology gave the desired 2-arylated tyrosine **4b** in 77% overall yield.

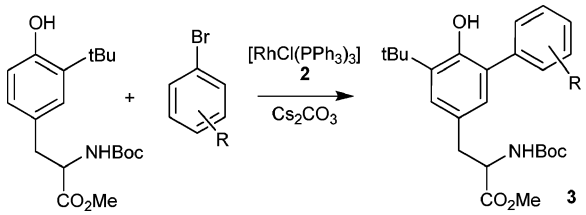


Scheme 6 Removal of the 2-*tert*-butyl group. Conditions: (i) $MeNO_2$, $AlCl_3$, toluene, –40 °C to rt, 18 h; (ii) acetyl chloride, MeOH, reflux, 15 h; (iii) NEt_3, MeOH, 0 °C followed by Boc_2O, 0 °C to rt, 18 h.

With the arylated tyrosine **4b** in hand, we next examined its application to the synthesis of *ortho*-diarylated tyrosines, **5** (Scheme 7) employing the methodology developed above. Reaction of **4b** with 4-bromoacetophenone yielded two arylated products: the desired species **5a** and the by-product **6a**, formed by a further arylation of **5a**, in a combined yield of 66%. Such secondary arylations have been seen previously in the rhodium-catalysed *ortho*-arylation of phenols.[8] It appears that there is essentially complete selectivity for the site of the secondary arylation with none occurring on the tolyl residue. The reactions of

‡ *Crystal data:* **3a**: $C_{27}H_{35}NO_6$, M = 469.56, triclinic, a = 9.9888(10), b = 10.6897(10), c = 13.5774(13) Å, α = 85.729(6), β = 68.552(5), γ = 71.738(5)°, V = 1280.1(2) Å^3, T = 100(2) K, space group $P\bar{1}$, Z = 2, μ = 0.085 mm^{-1}, R_{int} = 0.0373 (for 21665 measured reflections), R_1 = 0.0404 [for 4427 unique reflections with $>2\sigma(I)$], wR_2 = 0.1054 (for all 5869 unique reflections).

Table 2 *Ortho*-arylation of **1** with a range of aryl bromides[a]



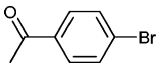
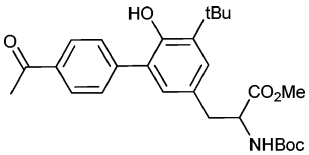
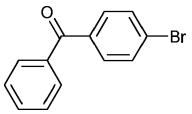
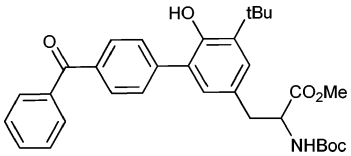
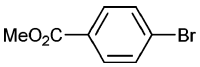
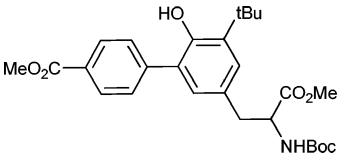
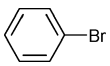
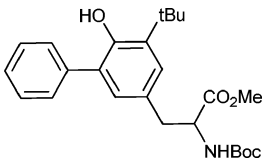
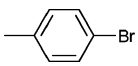
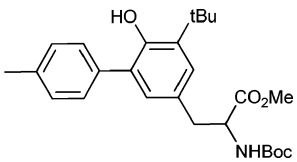
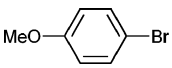
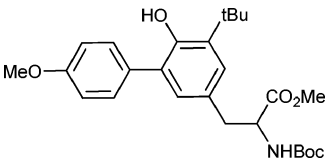
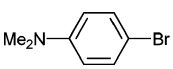
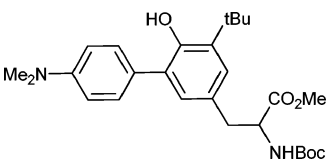
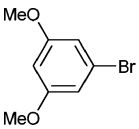
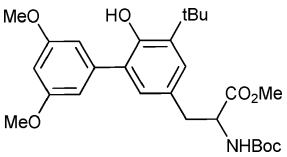
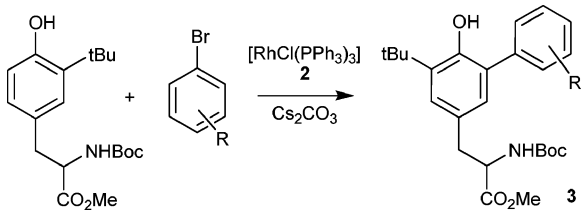
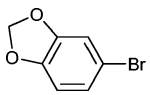
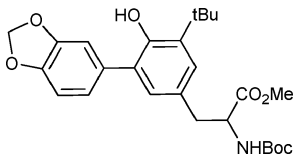
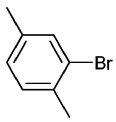
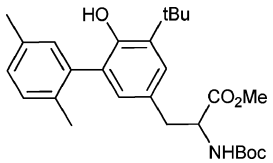
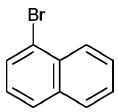
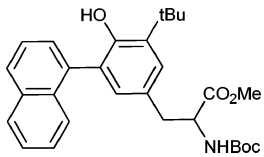
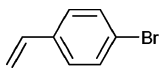
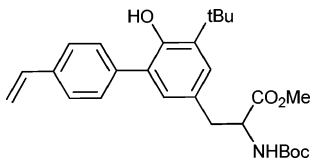
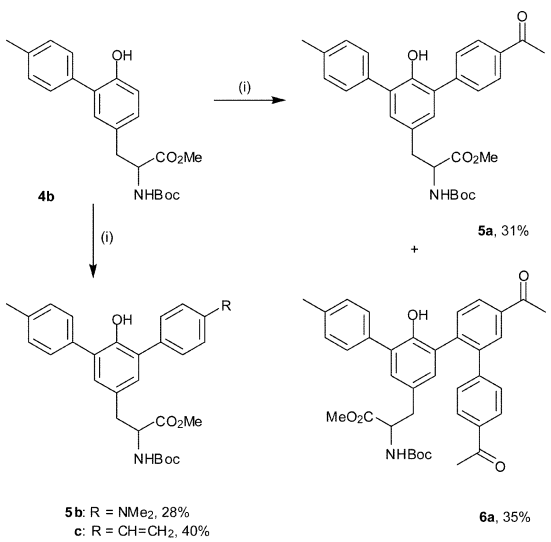
Entry	Aryl bromide	Product (yield, %)[b] [spec. yield][c]	
1			**3a** (89)
2			**3b** (24) [40]
3			**3c** (24) [30]
4			**3d** (41) [45]
5			**3e** (71)
6			**3f** (83)
7			**3g** (96)
8			**3h** (52)

Table 2 *(Contd.)*



Entry	Aryl bromide	Product (yield, %)[b] [spec. yield][c]	
9			**3i** (36)
10			**3j** (33)[d]
11			**3k** (61)[e]
12			**3l** (67)

[a] Conditions: **1** (0.854 mmol), aryl bromide (1.474 mmol), Cs_2CO_3 (1.670 mmol), [$RhCl(PPh_3)_3$] (0.049 mmol), **2** (0.128 mmol), toluene (8 mL), 110 °C, 18 h. [b] Isolated yield. [c] Spectroscopic yield determined by ^1H NMR spectroscopy, 1,3,5-$C_6H_3OMe_3$ internal standard. [d] Diastereomeric ratio: 1 : 1 (determined by ^1H NMR spectroscopy, $CDCl_3$, 25 °C). [e] Diastereomeric ratio: 0.9 : 1.1 (determined by ^1H NMR spectroscopy, $CDCl_3$, 25 °C).



Scheme 7 *Ortho*-arylation of **4b**. Conditions: (i) ArBr, [{RhCl(COD)}$_2$], $P(NMe_2)_3$, Cs_2CO_3, toluene, Δ, 18 h.

4b with 4-bromostyrene and 4-bromo-*N*,*N*-dimethyl aniline gave modest yields of the diarylated tyrosines.

Conclusions

In summary we have developed the rhodium catalysed direct *ortho*-arylation of 2-*tert*-butyl protected tyrosine using aryl bromide substrates. Subsequent removal of the *tert*-butyl group yields the 2-arylated tyrosine, this in turn allows the introduction of a second, different aryl group into the 6-position. Thus a small library of mono- and diarylated tyrosines has been produced, as has an example of a triarylated tyrosine. The protected tyrosine substrate **1** is racemic, with racemisation occurring prior to catalysis, thus we are at present unable to determine whether the *ortho*-arylation proceeds with retention of stereochemistry. We are currently exploring ways to either produce optically pure **1** or develop new C–H activation routes that do not require the introduction of a *tert*-butyl group, in order to develop arylation reactions with a focus on retention of chirality. These results will be published in due course.

Experimental section

3-*tert*-Butyltyrosine

L-Tyrosine (15.0 g, 82.8 mmol) was added to a solution of *tert*-butanol (17.5 mL, 183.0 mmol) in conc. H_3PO_4 (45 mL). The reaction mixture was stirred continuously at 65 °C for 60 h then allowed to cool to rt, and quenched by pouring into NaOH (aq.) (1 M, 500 mL). The resulting precipitate was collected by filtration, washed with H_2O followed by Et_2O and then dried under vacuum. The product was afforded as a white powder, 15.1 g (77%). R_f 0.3095 (MeOH–NH_3 (aq., 35%), 99 : 1); ^{1}H NMR (400 MHz, DMSO) δ 7.03 (d, J = 1.9 Hz, 1H), 6.88 (dd, J = 8.0, 1.9 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 3.30 (app. dd, J = 8.4, 4.3 Hz, 1H), 3.03 (dd, J = 12.0, 4.0 Hz, 1H), 2.72 (dd, J = 12.0, 8.0 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, DMSO) δ 170.6, 155.3, 135.3, 128.1, 127.3, 116.7, 56.5, 34.8, 30.9, 29.9; IR neat, ν (cm^{-1}) 1051 (m), 1153 (m), 1229 (m), 1255 (m), 1332 (s), 1367 (m), 1423 (s), 1510 (m), 1598 (s), 1614 (s), 2956 (w), 3254 (w), 33575 (w); mp 246.5–248.3 °C; HRMS (EI) (M + Na)$^+$ calcd for $C_{13}H_{19}NNaO_3$ 260.1257, found 260.1267; anal. calcd for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.1; N, 5.9%, found: C, 65.1; H, 8.2; N, 6.2%.

Methyl 3-*tert*-butyltyrosinate

Acetyl chloride (6.3 mL, 88.5 mmol) was added to MeOH (60 mL) at 0 °C; the solution was allowed to warm to rt then 3-*tert*-butyltyrosine (3.0 g, 12.6 mmol) was added. The solution was heated at reflux temperature for 15 h, cooled to room temperature, poured into saturated $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting off-white solid was sufficiently pure to use in the next step without further purification, 1.31 g (76%). R_f 0.058 (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 2.2 Hz, 1H), 6.87 (dd, J = 8.0, 2.2 Hz, 1H), 6.57 (d, J = 7.8 Hz, 1H), 3.75 (s, 1H), 3.74 (s, 3H), 3.03 (dd, J = 13.7, 5.2 Hz, 1H), 2.83 (dd, J = 13.7, 7.5 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 154.2, 136.6, 127.9, 127.7, 127.5, 116.7, 55.7, 52.2, 40.2, 34.4, 29.6; IR neat, ν (cm^{-1}) 1023 (m), 1089 (w), 1177 (s), 1199 (s), 1261 (m), 1509 (w), 1606 (w), 1733 (s), 2602 (w), 2952 (m), 3000 (w), 3135 (w), 3359 (w); mp 134.8–136.3 °C; HRMS (ESI) calcd for $C_{14}H_{21}NO_3Na$ (M + Na)$^+$ 274.1413, found 274.1421; anal. calcd for $C_{14}H_{21}NO_3$: C, 66.9; H, 8.4; N, 5.6%, found: C, 66.8; H, 8.8; N, 5.7%.

Methyl *N*-Boc-3-*tert*-butyltyrosinate, 1

NEt_3 (1.03 mL, 7.41 mmol) was added to a solution of methyl 3-*tert*-butyltyrosinate (1.24 g, 4.94 mmol) in dry methanol (30 mL) under N_2 and the mixture was cooled to 0 °C. Di-*tert*-butyl dicarbonate (1.19 g, 5.43 mmol) was added and the reaction stirred for 30 min, then allowed to warm to room temperature and stirred for a further 18 h. The solution was acidified to pH 1 with HCl (aq.) (10 mL, 2 M) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting off-white solid was purified by column chromatography (5% methanol in CH_2Cl_2) to afford **1** as a white powder, 1.31 g (76%). R_f 0.492 (MeOH–CH_2Cl_2, 1 : 19); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 2.2 Hz, 1H), 6.81 (dd, J = 8.1, 2.0 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 5.14 (s, 1H), 4.98 (d, J = 8.6 Hz, 1H), 4.56 (app. dd, J = 8.1, 5.8 Hz, 1H), 3.73 (s, 3H), 3.07-2.97 (m, 2H), 1.45 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 155.4, 153.9, 136.2, 128.1, 127.6, 127.0, 116.7, 80.3, 54.7, 52.4, 37.8, 34.6, 29.6, 28.4; IR neat, ν (cm^{-1}) 1013 (m), 1060 (s), 1213 (m), 1360 (s), 1423 (m), 1496 (m), 1610 (w), 1701 (s), 1704 (s), 2959 (w), 3009 (w), 3439 (w); mp 95.3–97.8 °C; HRMS (ESI) calcd for $C_{19}H_{29}NNaO_5$ (M + Na)$^+$ 374.1938, found 374.1950; anal. calcd for $C_{19}H_{29}NO_5$: C, 64.9; H, 8.3; N, 4.0%, found: C, 66.0; H, 8.2; N, 65.4%. Compound **1** was shown to be racemic by ^{1}H NMR experiments and polarimetry.†

Phosphinite ligand, 2

To **1** (0.58 g, 1.65 mmol), in a Schlenk tube under an atmosphere of nitrogen, was added anhydrous NEt_3 (0.26 mL, 1.85 mmol), chlorodiisopropylphosphine (0.26 mL, 1.62 mmol) and anhydrous toluene (10 mL). The mixture was then heated at reflux temperature for 18 h, allowed to cool to room temperature and then filtered through a pad of Celite® under nitrogen to remove the precipitated triethylamine hydrochloride. The solvent was removed *in vacuo* to yield **2** as a white opaque gum, 0.53 g (81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, J = 8.1, 6.7 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.85 (dd, J = 7.3, 2.0 Hz, 1H), 4.97 (d, J = 8.2 Hz, 1H), 4.55 (app. dd, J = 8.3, 5.7 Hz, 1H), 3.70 (s, 3H), 3.11–2.99 (m, 2H), 2.09–1.92 (m, 2H), 1.42 (s, 9H), 1.37 (s, 9H), 1.18–1.06 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 156.7, 155.2, 138.3, 128.1, 127.5, 116.6, 116.2, 79.8, 54.5, 52.2, 37.7, 34.8, 30.1, 28.1, 17.8, 17.6; ^{31}P NMR (122 MHz, d_8-toluene) δ 138.5 (s); HRMS (ESI) calcd for $C_{25}H_{42}NNaO_5P$ (M + Na)$^+$ 490.2693, found 490.2698; anal. calcd for $C_{25}H_{42}NO_5P$: C, 64.2; H, 9.05; N, 3.0%, found: C, 64.6; H, 8.9; N, 3.1%.

Optimisation of the rhodium catalysed *ortho*-arylation of 1 with 4-bromoacetophenone (Table 1)

To a Schlenk tube under N_2 was added the appropriate rhodium precursor, ligand(s), toluene (5 mL), 4-bromoacetophenone (0.051 g, 0.256 mmol), **1** (0.060 g, 0.178 mmol), and Cs_2CO_3 (0.095 g, 0.290 mmol). The mixture was stirred at reflux temperature for 18 h then allowed to cool to room temperature. HCl (aq.) (2 M, 5 mL) was added and the organic phase extracted into dichloromethane (3 × 10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. A standard solution of 1,3,5-trimethoxybenzene in $CDCl_3$ (1.00 M, 0.178 mL) and then $CDCl_3$ (~1 mL) were added and the spectroscopic yield was determined by ^{1}H NMR spectroscopy.

General methodology for the *ortho*-arylation of 1 using Wilkinson's catalyst and phosphinite 2 (Table 2)

[$RhCl(PPh_3)_3$] (0.045 g, 0.049 mmol) was added to a Schlenk tube under an atmosphere of N_2 along with toluene (8 mL), the appropriate aryl halide (1.5 eq., 1.474 mmol), **1** (0.300 g, 0.854 mmol), phosphinite **2** (0.060 g, 0.128 mmol), and Cs_2CO_3 (0.544 g, 1.670 mmol). The mixture was stirred at reflux temperature for 18 h then allowed to cool to room temperature. HCl (aq.) (2 M, 5 mL) was added and the organic phase extracted into dichloromethane (3 × 20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel to afford the product.

3a (Table 2, entry 1)

White solid, 0.357 g (89%); R_f 0.37 (Et_2O–pentane, 7 : 3); ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (app. dt, J = 8.6, 1.9 Hz, 2H), 7.56 (app. dt, J = 6.6, 1.8 Hz, 2H), 7.04 (d, J = 1.9 Hz, 1H), 6.83 (d, J = 1.8 Hz, 1H), 5.26 (s, 1H), 5.01 (d, J = 8.4 Hz, 1H), 4.59 (app. dd, J = 8.6, 6.0 Hz, 1H), 3.74 (s, 3H), 3.13–3.00 (m, 2H), 2.66 (s, 3H), 1.43 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 172.5, 155.1, 150.1, 142.4, 136.8, 136.5, 129.8, 129.4, 128.7, 128.5, 127.5, 80.0, 54.5, 52.3, 35.0, 29.7, 28.4, 26.8; IR neat, ν (cm^{-1}) 1027 (m), 1163 (s), 1277 (s), 1362 (s), 1432 (m), 1562 (m), 1604 (m), 1671 (s), 1701 (s), 1748 (s), 2951 (w), 3152 (w), 3258 (w), 3344 (w); mp 153.0–153.3 °C; HRMS (ESI) calcd for $C_{27}H_{35}NNaO_6$ $(M + Na)^+$ 492.2357, found 492.2365; anal. calcd for $C_{27}H_{35}NO_6$: C, 69.0; H, 7.5; N, 3.0%, found: C, 69.0; H, 7.7; N, 3.2%. Crystals suitable for X-ray analysis were grown by slow evaporation of a diethyl ether solution. See ESI for crystallographic data.†

3b (Table 2, entry 2)

White solid, 0.109 g (24%); R_f 0.67 (MeCN–CH_2Cl_2, 1 : 10); ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.9 Hz, 2H), 7.84 (dd, J = 8.2, 1.2 Hz, 2H), 7.62-7.46 (m, 5H), 7.04 (s, 1H), 6.86 (s, 1H), 5.32 (s, 1H), 5.00 (d, J = 8.2 Hz, 1H), 4.58 (app. dd, 8.4, 5.7 Hz, 1H), 3.73 (s, 3H), 3.13–2.99 (m, 2H), 1.42 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 172.4, 155.0, 150.0, 141.6, 137.4, 137.0, 136.7, 132.6, 131.1, 130.0, 129.4, 128.6, 128.4, 128.3, 127.4, 79.9, 54.4, 52.2, 37.6, 34.9, 29.7, 28.3; IR neat, ν (cm^{-1}) 1025 (m), 1063 (m), 1159 (s), 1222 (m), 1276 (m), 1360 (m), 1446 (m), 1601 (w), 1650 (s), 1681 (s), 1713 (s), 1753 (m), 2870 (w), 2957 (w), 3329 (w), 3557 (w); mp 99.5–101.0 °C; HRMS (ESI) calcd for $C_{32}H_{37}NNaO_6$ $(M + Na)^+$ 554.2513, found 554.2532; anal. calcd for $C_{32}H_{37}NO_6$: C, 72.3; H, 7.0; N, 2.6%, found: C, 72.75; H, 7.2; N, 3.05%.

3c (Table 2, entry 3)

White solid, 0.099 g (24%); R_f 0.47 (MeCN–CH_2Cl_2, 1 : 40); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (app. dt, J = 8.0, 2.0 Hz, 2H), 7.51 (app. dt, J = 8.5, 2.0 Hz, 2H), 7.02 (d, J = 2.5 Hz, 1H), 6.81 (d, J = 1.7 Hz, 1H), 5.29 (s, 1H), 5.00 (d, J = 8.3 Hz, 1H), 4.56 (app. dd, J = 8.4, 5.6 Hz, 1H), 3.94 (s, 3H), 3.71 (s, 3H), 3.10-2.98 (m, 2H), 1.41 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 166.8, 155.1, 150.0, 142.2, 136.8, 130.7, 129.7, 129.6, 128.7, 128.4, 127.9, 127.4, 116.5, 80.0, 54.5, 52.3, 37.7, 35.0, 29.7, 28.4; IR neat, ν (cm^{-1}) 1102 (m), 1115 (m), 1161 (s), 1280 (s), 1436 (m), 1505 (m), 1610 (m), 1703 (s), 1720 (s), 1734 (s), 2246 (w), 2957 (w), 2991 (w), 3419 (w), 3458 (w); mp 90.0–91.5 °C; HRMS (ESI) calcd for $C_{27}H_{35}NNaO_7$ $(M + Na)^+$ 508.2306, found 508.2314; anal. calcd for $C_{27}H_{35}NO_7$: C, 66.8; H, 7.3; N, 2.9%, found: C, 67.1; H, 6.8; N, 2.9%.

3d (Table 2, entry 4)

White solid, 0.150 g (41%); R_f 0.37 (Et_2O–pentane, 2 : 5); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–7.40 (m, 5H), 7.01 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 1.8 Hz, 1H), 5.41 (s, 1H), 5.01 (d, J = 8.3 Hz, 1H), 4.58 (app. dd, J = 8.4, 5.6 Hz, 1H), 3.72 (s, 3H), 3.11–2.99 (m, 2H), 1.42 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 155.0, 150.0, 137.1, 136.2, 129.5, 128.7, 128.0, 127.9, 127.6, 126.8, 79.8, 65.8, 52.2, 37.6, 34.9, 29.6, 28.3; IR neat, ν (cm^{-1}) 1016 (m), 1059 (m), 1155 (s), 1201 (m), 1364 (m), 1432 (m), 1497 (m), 1599 (w), 1710 (s), 1742 (s), 2162 (w), 2954 (w), 3407 (w), 3543 (w); mp 60.8–62.4 °C; HRMS (ESI) calcd for $C_{25}H_{33}NNaO_5$ $(M + Na)^+$ 450.2251, found 450.2265; anal. calcd for $C_{25}H_{33}NO_5$: C, 70.2; H, 7.8; N, 3.3%, found: C, 70.9; H, 7.4; N, 3.6%.

3e (Table 2, entry 5)

White solid, 0.249 g (71%); R_f 0.14 (Et_2O–pentane, 1 : 5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 4H), 7.00 (d, J = 1.8 Hz, 1H), 6.82 (d, J = 1.7 Hz, 1H), 5.44 (s, 1H), 5.00 (d, J = 8.5 Hz, 1H), 4.60 (app. dd, J = 8.3, 5.6 Hz, 1H), 3.75 (s, 3H), 3.11–3.02 (m, 2H), 2.44 (s, 3H), 1.44 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 155.0, 150.1, 137.8, 136.1, 134.0, 130.1, 129.3, 128.71, 128.67, 127.4, 126.7, 79.8, 54.5, 52.1, 37.6, 34.9, 29.6, 28.3, 21.2; IR neat, ν (cm^{-1}) 1015 (m), 1081 (m), 1154 (s), 1227 (s), 1286 (s), 1442 (m), 1502 (m), 1612 (w), 1712 (s), 1726 (s), 1918 (w), 2911 (w), 2953 (w), 2966 (w), 3426 (w), 3481 (w), 3674 (w); mp 141.5–142.2 °C; HRMS (ESI) calcd for $C_{26}H_{35}NNaO_5$ $(M + Na)^+$ 464.2407, found 464.2413; anal. calcd for $C_{26}H_{35}NO_5$: C, 70.7; H, 8.0; N, 3.2%, found: C, 70.5; H, 8.1; N, 3.6%.

3f (Table 2, entry 6)

White solid, 0.324 mg (83%); R_f 0.33 (Et_2O–pentane, 2 : 5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (app. dt, J = 8.8, 2.5 Hz, 2H), 7.01 (app. dt, J = 8.8, 2.5 Hz, 2H), 6.97 (d, J = 1.7 Hz, 1H), 6.79 (s, 1H), 5.38 (s, 1H), 5.00 (d, J = 8.3 Hz, 1H), 4.56 (app. dd, J = 8.1, 5.6 Hz, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.08–2.99 (m, 2H), 1.41 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 159.5, 155.2, 150.3, 136.2, 130.8, 128.9, 127.4, 126.8, 114.9, 113.6, 79.9, 55.5, 54.6, 52.3, 37.7, 35.0, 29.7, 28.4; IR neat, ν (cm^{-1}) 1023 (m), 1160 (s), 1246 (s), 1364 (m), 1432 (m), 1513 (m), 1609 (w), 1700 (s), 1741 (s), 2957 (w), 3362 (w), 3536 (w), 3675 (w); mp 62.9–64.9 °C; HRMS (ESI) calcd for $C_{26}H_{35}NNaO_6$ $(M + Na)^+$ 480.2357, found 480.2351; anal. calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.7; N, 3.1%, found: C, 68.20 H, 7.6; N, 3.5%.

3g (Table 2, entry 7)

White solid, 0.386 g (96%); R_f 0.30 (Et_2O–pentane, 2 : 5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (app. dt, J = 8.8, 2.5 Hz, 2H), 6.95 (d, J = 1.7 Hz, 1H), 6.83–6.80 (m, 3H), 5.53 (s, 1H), 5.01 (d, J = 9.0 Hz, 1H), 4.56 (app. dd, J = 8.8, 5.5 Hz, 1H), 3.72 (s, 3H), 3.03 (d, J = 5.2 Hz, 2H), 2.99 (s, 6H), 1.42 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 150.5, 150.3, 135.9, 130.3, 129.1, 128.9, 126.9, 126.6, 124.3, 113.2, 79.9, 54.6, 52.3, 40.6, 37.8, 35.0, 29.8, 28.5; IR neat, ν (cm^{-1}) 1018 (m), 1059 (w), 1161 (s), 1357 (s), 1433 (m), 1522 (s), 1611 (m), 1712 (s), 1743 (m), 2953 (w), 3442 (w), 3521 (w); mp 67.1–68.6 °C; HRMS (ESI) calcd for $C_{27}H_{38}N_2NaO_5$ $(M + Na)^+$ 493.2673, found 493.2672; anal. calcd for $C_{27}H_{38}N_2O_5$: C, 68.9; H, 8.1; N, 5.95%, found: C, 68.8; H, 8.0; N, 6.3%.

3h (Table 2, entry 8)

White solid, 0.216 g (52%); R_f 0.60 (MeCN–CH_2Cl_2, 1 : 10); ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 2.2 Hz, 1H), 6.85 (d, J = 1.5 Hz, 1H), 6.56 (d, J = 2.2 Hz, 2H), 6.51 (t, J = 2.2 Hz,

1H), 5.63 (s, 1H), 5.01 (d, $J = 9.2$ Hz, 1H), 4.59 (app. dd, $J = 9.2$, 5.9 Hz, 1H), 3.85 (s, 6H), 3.75 (s, 3H), 3.11–3.02 (m, 2H), 1.44 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 161.8, 155.2, 150.2, 139.2, 136.3, 128.7, 128.4, 127.8, 126.8, 107.3, 100.2, 79.9, 55.6, 54.6, 52.3, 37.7, 35.0, 29.7, 28.4; IR neat, ν (cm^{-1}) 1018 (m), 1062 (m), 1260 (s), 1204 (m), 1362 (m), 1417 (m), 1591 (m), 1712 (s), 1743 (m), 2015 (w), 2953 (w), 3387 (w), 3517 (w); mp 58.4–60.4 °C; HRMS (ESI) calcd for $C_{27}H_{37}NNaO_7$ $(M + Na)^+$ 510.2462, found 510.2468; anal. calcd for $C_{27}H_{37}NO_7$: C, 66.5; H, 7.65; N, 2.9%, found: C, 66.8; H, 7.75; N, 2.9%.

3i (Table 2, entry 9)

White solid, 0.145 g (36%); R_f 0.56 (MeCN–CH_2Cl_2, 1 : 20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.85–6.79 (m, 3H), 6.71 (s, 1H), 5.94 (s, 2H), 5.36 (s, 1H), 4.91 (d, $J = 7.6$ Hz, 1H), 4.49 (app. dd, $J = 7.3$, 5.4 Hz, 1H), 3.65 (s, 3H), 3.01–2.90 (m, 2H), 1.35 (s, 9H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 154.0, 149.1, 147.6, 146.5, 135.1, 129.6, 127.7, 127.3, 126.4, 125.7, 121.6, 109.0, 108.0, 100.3, 78.8, 53.4, 51.2, 36.6, 33.8, 28.6, 27.3; IR neat, ν (cm^{-1}) 1037 (m), 1161 (s), 1201 (m), 1228 (s), 1364 (m), 1437 (m), 1490 (m), 1503 (m), 1607 (w), 1710 (s), 1743 (s), 2187 (w), 2959 (w), 3405 (w), 3528 (w); mp 128.2–129.9 °C; HRMS (ESI) calcd for $C_{26}H_{33}NNaO_7$ $(M + Na)^+$ 494.2149, found 494.2153; anal. calcd for $C_{26}H_{33}NO_7$: C, 66.2; H, 7.05; N, 3.0%, found: C, 65.7; H, 6.9; N, 3.1%.

3j (Table 2, entry 10)

White gum, 0.128 g (33%), inseparable mixture of diastereomers (1 : 1); R_f 0.48 (MeCN–CH_2Cl_2, 1 : 30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.22 (s, 1H), 7.16 (d, $J = 1.7$ Hz, 1H), 7.14 (d, $J = 1.5$ Hz, 1H), 7.09 (d, $J = 1.2$ Hz, 1H), 7.06 (d, $J = 1.2$ Hz, 1H), 7.00 (d, $J = 2.1$ Hz, 2H), 6.73 (d, $J = 1.2$ Hz, 2H), 5.03 (d, $J = 8.3$ Hz, 1H), 4.98 (d, $J = 8.3$ Hz, 1H), 4.94 (s, 1H), 4.93 (s, 1H), 4.61–4.55 (m, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.10-3.01 (m, 4H), 2.37 (2 s, 6H), 2.11 (s, 3H), 2.09 (s, 3H), 1.44 (2 s, 18H), 1.43 (2 s, 18H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 172.5, 155.1, 150.1, 136.8, 136.5, 129.8, 129.4, 128.7, 128.5, 127.5, 80.0, 54.5, 52.3, 35.0, 29.7, 28.4; IR neat, ν (cm^{-1}) 1017 (m), 1060 (m), 1164 (s), 1230 (m), 1364 (m), 1436 (m), 1498 (m), 1612 (w), 1709 (s), 1743 (s), 2248 (w), 2872 (w), 2954 (w), 3442 (w), 3533 (w); HRMS (ESI) calcd for $C_{27}H_{37}NNaO_5$ $(M + Na)^+$ 478.2564, found 478.2571; anal. calcd for $C_{27}H_{37}NO_5$: C, 71.2; H, 8.2; N, 3.1%, found: C, 71.7; H, 7.6; N, 3.1%.

3k (Table 2, entry 11)

White solid, 0.249 g (61%); inseparable mixture of diastereomers (0.9 : 1.1); R_f 0.36 (Et_2O–pentane, 2 : 5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 2H), 7.91 (s, 2H), 7.60–7.48 (m, 10H), 7.09 (d, $J = 2.2$ Hz, 2H), 6.85 (s, 2H), 5.06 (d, $J = 8.4$ Hz, 1H), 5.02 (d, $J = 9.4$ Hz, 1H), 4.96 (s, 1H), 4.92 (s, 1H), 4.63–4.56 (m, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 3.13–3.00 (m, 4H), 1.43 (s, 18H), 1.42 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 155.1, 151.0, 136.3, 134.2, 132.3, 129.7, 129.0, 128.5, 128.0, 126.9, 126.5, 125.9, 125.8, 79.9, 54.7, 52.3, 37.9, 35.0, 29.7, 28.4; IR neat, ν (cm^{-1}) 1018 (m), 1058 (m), 1160 (s), 1259 (m), 1364 (m), 1434 (m), 1505 (m), 1591 (w), 1710 (s), 1742 (m), 2869 (w), 2963 (w), 3049 (w), 3442 (w), 3534 (w); mp 65.9–67.9 °C; HRMS (ESI) calcd for $C_{29}H_{35}NNaO_5$ $(M + Na)^+$ 500.2407, found 500.2412; anal. calcd for $C_{29}H_{35}NO_5$: C, 72.9; H, 7.4; N, 2.9%, found: C, 72.4; H, 7.4; N, 3.1%.

3l (Table 2, entry 12)

White solid, 0.259 g (67%); R_f 0.17 (Et_2O–pentane, 1 : 4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (app. dt, $J = 8.3$, 1.8 Hz, 2H), 7.39 (app. dt, $J = 8.3$, 1.9 Hz, 2H), 7.00 (d, $J = 1.8$ Hz, 1H), 6.81 (s, 1H), 6.77 (dd, $J = 17.5$, 10.9 Hz, 1H), 5.82 (dd, $J = 17.6$, 0.8 Hz, 1H), 5.37 (s, 1H), 5.32 (dd, $J = 10.8$, 0.7 Hz, 1H), 5.00 (d, $J = 8.3$ Hz, 1H), 4.57 (app. dd, $J = 8.3$, 6.0 Hz, 1H), 3.72 (s, 3H), 3.11–2.98 (m, 2H), 1.41 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 155.2, 150.2, 137.4, 136.6, 136.4, 136.2, 129.7, 128.7, 128.5, 127.8, 127.3, 127.0, 114.8, 79.9, 54.6, 52.3, 37.8, 35.0, 34.2, 29.7, 28.4, 22.5, 14.2; IR neat, ν (cm^{-1}) 1019 (m), 1065 (m), 1142 (s), 1193 (m), 1366 (m), 1434 (m), 1515 (m), 1594 (w), 1697 (s), 1738 (s), 2184 (w), 2929 (w), 2969 (w), 3368 (w); mp 112.1–113.4 °C; HRMS (ESI) calcd for $C_{27}H_{35}NNaO_5$ $(M + Na)^+$ 476.2407, found 476.2396; anal. calcd for $C_{27}H_{35}NO_5$: C, 71.5; H, 7.8; N, 3.1%, found: C, 71.8; H, 7.8; N, 3.2%.

Removal of *tert*-butyl groups of 1 and 3e

To a Schlenk tube under an atmosphere of N_2, **1** or **3e** was added (0.23 or 0.45 mmol respectively) in 15 mL toluene. The reaction vessel was cooled to –40 °C at which point $MeNO_2$ (33 equiv.) and $AlCl_3$ (7.75 equiv.) were added. The reaction was allowed to warm to rt over the course of 18 h. The reaction mixture was quenched with H_2O (~1 mL) and the solvent was removed *in vacuo*. The crude mixture was then subjected to esterification and Boc protection following earlier protocol to provide **4a** or **4b**.

4a

Isolated as a white solid 0.052 g (77%). Spectroscopically identical to the known compound.[12]

4b

White solid, 133 mg (78%); R_f 0.53 (MeOH–CH_2Cl_2, 1 : 20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, $J = 7.9$ Hz, 2H), 7.27 (d, $J = 7.5$ Hz, 2H), 7.00–6.93 (m, 2H), 6.87 (d, $J = 8.8$ Hz, 1H), 5.62 (br. s, 1H), 5.03 (d, $J = 6.1$ Hz, 1H), 4.56 (app. dd, $J = 7.8$, 5.8 Hz, 1H), 3.71 (s, 3H), 3.11–2.97 (m, 2H), 2.40 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 155.3, 151.9, 137.7, 134.2, 131.2, 129.9, 129.7, 129.0, 128.2, 128.0, 116.0, 80.1, 54.6, 52.3, 37.5, 28.4, 21.3; IR neat, ν (cm^{-1}) 1148 (m), 1163 (s), 1221 (s), 1363 (s), 1439 (m), 1505 (s), 1609 (w), 1692 (s), 1740 (s), 2924 (w), 3319 (w); mp 104.1–105.7 °C; HRMS (ESI) calcd for $C_{22}H_{27}NNaO_5$ $(M + Na)^+$ 408.1781, found 408.1786; anal. calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.1; N, 3.6%, found: C, 68.2; H, 7.2; N, 3.8%.

General method for the *ortho*-arylation of 4b

$[\{RhCl(COD)\}_2]$ (0.003 g, 0.011 mmol) was added to a Schlenk tube under an atmosphere of N_2 along with toluene (5 mL), the appropriate aryl halide (1.5 eq., 0.163 mmol), **4b** (0.042 g, 0.109 mmol), $P(NMe_2)_3$ (0.012 mL, 0.065 mmol), and Cs_2CO_3 (0.060 g, 0.185 mmol). The mixture was stirred at reflux temperature for 18 h then allowed to cool to room temperature. HCl

(aq.) (2 M, 5 mL) was added and the organic phase extracted into dichloromethane (3 × 10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel to afford the product.

5a

White solid, 17 mg (31%); R_f 0.31 (MeOH–CH_2Cl_2, 1 : 20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (app. dt, J = 8.5, 2.0 Hz, 2H), 7.69 (app. dt, J = 8.6, 2.0 Hz, 2H), 7.39 (app. dt, J = 6.1, 1.7 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.05 (s, 1H), 7.02 (s, 1H), 5.41 (s, 1H), 5.06 (d, J = 8.3 Hz, 1H), 4.62 (app. dd, J = 13.2, 5.6 Hz, 1H), 3.74 (s, 3H), 3.17 (dd, J = 13.8, 5.7 Hz, 1H), 3.06 (dd, J = 14.3, 5.7 Hz, 1H), 2.65 (s, 3H), 2.43 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 171.3, 154.0, 147.5, 141.9, 137.1, 134.8, 132.6, 130.2, 129.7, 129.0, 128.5, 128.0, 127.4, 127.2, 126.5, 79.0, 53.4, 51.3, 36.4, 27.3, 25.6, 20.2; IR neat, ν (cm^{-1})1015 (s), 1112 (m), 1163 (s), 1222 (s), 1267 (s), 1363 (m), 1462 (m), 1512 (m), 1604 (m), 1680 (m), 1710 (s), 1740 (s), 2974 (w), 3361 (w); mp 81.8–82.5 °C; HRMS (ESI) calcd for $C_{30}H_{33}NNaO_6$ $(M + Na)^+$ 526.2200, found 526.2202; anal. calcd for $C_{30}H_{33}NO_6$: C, 71.55; H, 6.6; N, 2.8%, found: C, 71.45; H, 6.9; N, 3.05%.

5b

White solid, 15 mg (28%); R_f 0.40 (MeOH–CH_2Cl_2, 1 : 20); ^{1}H NMR (500 MHz, CD_3CN) δ 7.45 (app. dt, J = 8.3, 1.8 Hz, 2H), 7.40 (app. dt, J = 8.9, 2.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.04 (s, 1H), 7.03 (s, 1H), 6.88 (app. dt, J = 8.8, 1.8 Hz, 1H), 5.97 (s, 1H), 5.56 (s, 1H), 4.62 (app. dd, J = 12.3, 5.8 Hz, 1H), 3.71 (s, 3H), 3.13 (dd, J = 14.1, 5.8 Hz, 1H), 3.00 (s, 6H), 2.99 (dd, J = 14.3, 5.5 Hz, 1H), 2.42 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, CD_3CN) δ 172.8, 149.0, 137.2, 135.6, 130.5, 130.2, 130.1, 129.6, 129.2, 112.9, 79.1, 55.1, 54.5, 51.2, 49.1, 40.0, 36.6, 27.7, 20.4; HRMS (ESI) calcd for $C_{30}H_{37}N_2O_5$ $(M + H)^+$ 505.2697, found 505.2721.

5c

White solid, 21 mg (40%); R_f 0.64 (MeOH–CH_2Cl_2, 1 : 20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 4H), 7.44 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.03 (s, 1H), 7.02 (s, 1H), 6.80 (dd, J = 17.5, 10.9 Hz, 1H), 5.84 (d, J = 17.5 Hz, 1H), 5.41 (s, 1H), 5.33 (dd, J = 10.8, 4.7 Hz, 1H), 5.08 (d, J = 8.3 Hz, 1H), 4.64 (app. dd, J = 7.9, 5.7 Hz, 1H), 3.76 (s, 3H), 3.19–3.06 (m, 2H), 2.44 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 155.2, 148.6, 137.8, 137.0, 136.5, 130.8, 130.7, 129.8, 129.6, 129.4, 129.2, 128.1, 126.7, 114.4, 80.1, 54.6, 52.4, 37.5, 28.4, 21.3; IR neat, ν (cm^{-1})1015 (s), 1162 (s), 1221 (m), 1248 (m), 1365 (m), 1457 (m), 1495 (m), 1607 (w), 1711 (s), 1742 (s), 2971 (w), 3421 (w); mp 81.8–82.5 °C; HRMS (ESI) calcd for $C_{30}H_{33}NNaO_5$ $(M + Na)^+$ 510.2251, found 510.2274; anal. calcd for $C_{30}H_{33}NO_5$: C, 73.9; H, 6.8; N, 2.9%, found: C, 74.3; H, 7.2; N, 3.1%.

6a

White solid, 19 mg (35%); R_f 0.22 (MeOH–CH_2Cl_2, 1 : 20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05–8.03 (m, 2H), 7.85 (dd, J = 8.5, 1.8 Hz, 2H), 7.56 (d, J = 8.5 Hz, 1H), 7.30 (app. dt, J = 8.4, 1.8 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 7.9 Hz, 2H), 6.89 (s, 1H), 6.87 (s, 1H), 4.94–4.89 (m, 2H), 4.52 (app. dd, J = 6.3 Hz, 1H), 3.68 (s, 3H), 3.07–2.95 (m, 2H), 2.68 (s, 3H), 2.59 (s, 3H), 2.36 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 197.5, 172.1, 154.9, 148.1, 145.7, 141.1, 138.0, 136.8, 135.5, 131.5, 131.1, 130.5, 130.0, 129.7, 129.3, 128.7, 128.0, 127.9, 80.0, 54.5, 52.2, 37.5, 28.3, 26.7, 21.2; IR neat, ν (cm^{-1}) 1015 (m), 1162 (s), 1231 (s), 1357 (m), 1459 (m), 1514 (m), 1605 (m), 1682 (s), 1712 (s), 1742 (s), 1750 (s), 2925 (w), 3350 (w); mp 87.0–88.3 °C; HRMS (ESI) calcd for $C_{38}H_{39}NNaO_7$ $(M + Na)^+$ 644.2619, found 644.2651; anal. calcd for $C_{38}H_{39}NO_7$: C, 73.4; H, 6.3; N, 2.25%, found: C, 73.1; H, 7.0; N, 2.6%.

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