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A Concise Synthesis of Photoactivatable 4-Aroyl-L-phenylalanines

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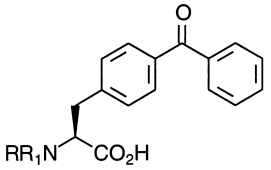
Abstract—An efficient preparation of the title compounds from 4-iodo-L-phenylalanines using a carbonylative Stille cross-coupling reaction as the key-step is described.

The use of benzophenone (BP) photophores in biochemistry has increased considerably during the past 10 years, owing to their advantages over previously employed diazoester, azide, and diazirine probes.[1] In particular, the development of 4-benzoyl-L-phenylalanine (BPA, **1a**),[2] a BP-containing amino acid, brought a significant advance in the application of photoaffinity labeling to the study of peptide–protein interactions.

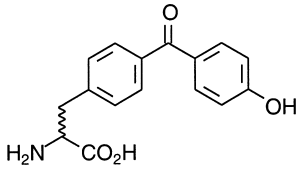
The original report on BPA has involved a non-selective preparation of the DL-form followed by an enzymatic resolution.[2] A similar strategy has been adopted also in the preparation of tritiated BPAs.[3] More recently, the synthesis and the use of (*RS*)-4-(4-hydroxybenzoyl)phenylalanine (*rac*-HBPA, **2**), a photoreactive amino acid also amenable to radioiodination, have been described.[4] Eventually, enantioselective syntheses of *S*- and *R*-enantiomers of HBPA (**2a**,**b**) and of (*S*)-Boc-*N*-methyl-4-benzoylphenylalanine (**1b**) have been accomplished using Schöllkopf and Oppolzer chiral auxiliary reagents, respectively.[5,6]

In recent years, a wide variety of structurally modified phenylalanine derivatives have been synthesized in enantiopure forms exploiting transition metal-catalyzed reactions.[7] The introduction of an aroyl moiety in a phenylalanine derivative by a palladium-catalyzed reaction would provide a conceptually simple and straightforward approach to 4-aroylphenylalanines. We now report on such a conversion which is based on a carbonylative Stille reaction[8] as well on the availability of 4-iodo-L-phenylalanine derivatives such as **3a**.[7y]

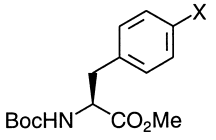
Aryl iodides can be carbonylatively coupled with organostannanes to afford ketones, but the number of examples in the literature is limited, due to the versatility of aryl triflates in this strategy.[8] Our attempt at coupling the tyrosine triflate derivative **3b**[7a,b] with $C_6H_5SnBu_3$[9] under conditions developed by Stille (CO, $PdCl_2$/dppf, LiCl, DMF)[10] has proven, however, to be surprisingly unsuccessful and **3b** was recovered practically unchanged after 24 h at 90 °C. In contrast, the reaction of iodide **3a** with tributylphenyltin under atmospheric CO



1 a: R = H; R_1 = H
1 b : R = Me; R_1 = Boc
1 c: R = H; R_1 = Boc



2 a: (*S*)-isomer
2 b: (*R*)-isomer



3 a: X = I
3 b: X = OTf
3 c: X = COC_6H_5
3 d: X = COC_6H_4-4-OCO_2-*t*-Bu

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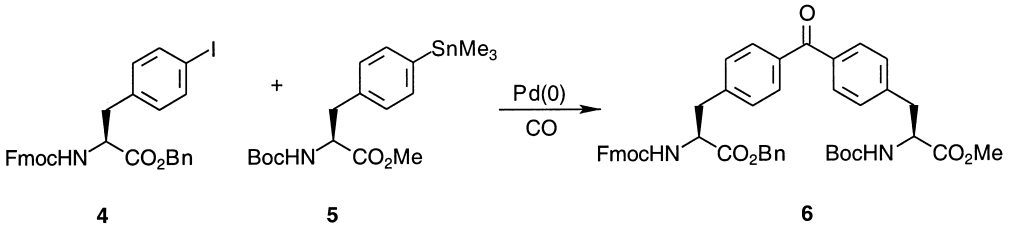
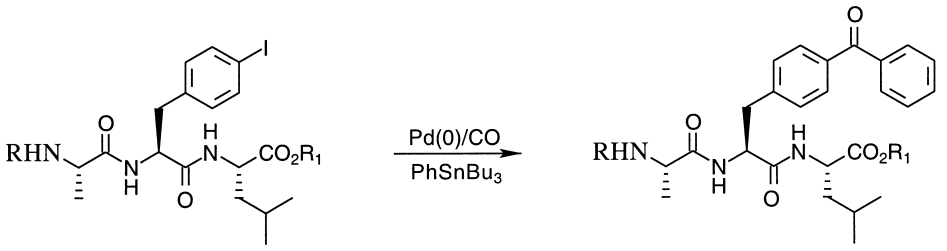


Scheme 1.



Scheme 2.

pressure in the presence of $PdCl_2/2PPh_3$ proceeded smoothly to give the 4-benzoyl derivative **3c** in 88% yield.[11] Repetition of the procedure with 4-*t*-BuOCO $OC_6H_4SnBu_3$[12] afforded **3d** in 87% yield.[13] Removal of the ester group of **3c** with NaOH/MeOH/H_2O at room temperature and complete deprotection of **3d** (NaOH/MeOH/H_2O, rt, then TFA/CH_2Cl_2, rt) afforded almost quantitatively **1c** and **2a**, respectively, whose physical data, in particular optical rotations, were in good agreement with the values reported in literature.[14] The carbonylative coupling of **3a** with phenylboronic acid $C_6H_5B(OH)_2$ according to Suzuki (CO, $PdCl_2/2PPh_3$, K_2CO_3, dioxane, 80 °C)[15] was also explored but resulted in a lower yield of **3c** (64%) and a longer reaction time (18 h).

A number of interesting reports have already appeared in the literature on synthetic work concerning covalent linkages between aromatic side chains of two amino-acids with the aim at investigating conformationally restricted analogues of bioactive peptides.[7y,16] On this basis, a 4,4′-bis(alanyl)benzophenone, which could act as a photoactivatable bis(phenylalanine) analogue, has been synthesized in the differentially protected form **6**[17] in 80% yield by carbonylative coupling between *N*-Fmoc-4-iodo-L-phenylalanine benzyl ester (**4**)[18] and *N*-Boc-4-trimethylstannyl-L-phenylalanine methyl ester (**5**)[7o] (Scheme 1).

The presence of the BPA moiety in a peptide renders it light-sensitive. Special precautions are therefore to be taken during synthesis of BPA-containing probes and dithioketal formation for temporary protection followed by regeneration with $Hg(OCOCF_3)_2$ or $AgNO_3$ has been suggested.[19] In this view, it would be advantageous to introduce the benzoyl moiety at a late stage, i.e., into the fully coupled peptide. To demonstrate the feasibility of this approach, we have extended our methodology to the model peptide Ala-4-I-Phe-Leu. The tripeptide was prepared in two differently protected forms (**7a**,**b**) through standard solution phase techniques[20] and subjected to carbonylative cross-coupling reaction with $C_6H_5SnBu_3$. Smooth conversions to the BPA-containing peptides **8a**,**b**[21] were accomplished in 96 and 88% isolated yields, respectively (Scheme 2).

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11. A mixture of **3a** (405 mg, 1 mmol), $C_6H_5SnBu_3$ (404 mg, 1.1 mmol), $PdCl_2$ (9 mg, 0.05 mmol), and PPh_3 (26 mg, 0.10 mmol) in dry DMF (4 mL) was purged with carbon monoxide for 5 min and then stirred under a CO balloon at 90 °C for 5 h. The reaction mixture was then diluted with AcOEt (100 mL) and stirred at room temperature with a saturated aqueous KF solution (1 mL) for 30 min. The precipitate was removed by filtration and the organic phase was washed three times with water, dried (Na_2SO_4), and evaporated. The residue (548 mg) was chromatographed on silica gel (17 g) using hexane:AcOEt = 8:2 as eluent to give 336 mg (88%) of **3c**: oil; $[\alpha]_D^{20}+51°$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3435, 1741, 1710, 1656, 1499, 1367, 1279, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H, s, *t*-Bu), 3.12 (1H, dd, *J* = 13.8, 6.6 Hz, CHH), 3.24 (1H, dd, *J* = 13.8, 5.4 Hz, CHH), 3.73 (3H, s, CO_2Me), 4.65 (1H, m, α-CH), 5.15 (1H, d, *J* = 7.8 Hz, NH), 7.25–7.79 (9H, m, ArH); ^{13}C NMR δ 28.24, 38.33, 52.29, 54.20, 79.95, 128.15, 129.18, 129.82, 130.21, 132.24, 136.15, 137.49, 141.08, 154.89, 171.85, 196.08.

12. Obtained in 74% overall yield from 4-iodophenol by sequential *O*-derivatization ($(Boc)_2O$/pyridine/THF, rt) and stannylation according to Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49.

13. **3d**: oil; $[\alpha]_D^{20}+36°$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3438, 1754, 1710, 1657, 1601, 1501, 1370, 1274, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H, s, BocNH), 1.58 (9H, s, BocO), 3.12 (1H, dd, *J* = 13.5, 6.1 Hz, CHH), 3.23 (1H, dd, *J* = 13.5, 5.7 Hz, CHH), 3.74 (3H, s, CO_2Me), 4.64 (1H, m, α-CH), 5.07 (1H, d, *J* = 8.1 Hz, NH), 7.24–7.84 (8H, m, ArH); ^{13}C NMR δ 27.65, 28.25, 38.36, 52.32, 54.18, 80.03, 84.10, 121.01, 129.24, 130.14, 131.42, 134.83, 136.08, 141.11, 151.06, 154.04, 154.87, 171.81, 194.90.

14. **1c**: mp 85–88 °C; $[\alpha]_D^{20}+18.5°$ (*c* 2.0, EtOH) [lit.[2] mp 91–92 °C; $[\alpha]_D^{20}+18.5°$ (*c* 1.03, EtOH)]; IR ($CHCl_3$) 3435, 3281, 1703, 1657, 1607, 1497, 1367, 1279, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (9H, s, *t*-Bu), 3.07 (1H, m, CHH), 3.25 (1H, m, CHH), 4.54 (1H, m, α-CH), 5.35 (1H, m, NH), 7.29–7.75 (9H, m, ArH), 8.05 (1H, br s, CO_2H); ^{13}C NMR δ 28.25, 37.97, 54.85, 80.19, 128.16, 129.29, 129.88, 130.23, 132.31, 136.01, 137.42, 141.62, 155.56, 175.89, 196.40. **2a** (TFA salt): wax; $[\alpha]_D^{20}-5°$ (*c* 0.2, MeOH:H_2O = 3:1 by volume) [lit.[5] $[\alpha]_D^{20}-5.5°$ (*c* 0.2, MeOH:H_2O = 3:1 by volume)]; IR (KBr) 3171, 1640, 1606, 1586, 1524, 1380, 1315, 1282, 1256, 1174 cm^{-1}; ^1H NMR (300 MHz, disodium salt, D_2O) δ 2.92 (1H, dd, *J* = 13.9, 7.5 Hz, CHH), 3.08 (1H, dd, *J* = 13.9, 5.2 Hz, CHH), 3.56 (1H, m, α-CH), 6.62, 7.70 (4H, ABq, *J* = 8.8 Hz, ArH), 7.38, 7.60 (4H, ABq, *J* = 8.2 Hz, ArH); ^{13}C NMR δ 43.54, 60.07, 121.75, 124.66, 131.86, 132.34, 137.46, 139.60, 145.29, 177.87, 184.86, 201.39.

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17. **6**: mp 159–161 °C; $[\alpha]_D^{20}+27°$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3431, 1738, 1711, 1650, 1608, 1500, 1279, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H, s, *t*-Bu), 3.20 (4H, m, ββ′-CH_2), 3.74 (3H, s, CO_2Me), 4.20 (1H, t, *J* = 6.8 Hz, FmocCH), 4.41 (1H, dd, *J* = 10.5, 6.8 Hz, FmocCHH), 4.48 (1H, dd, *J* = 10.5, 6.8 Hz, FmocCHH), 4.65 (1H, m, α-CH), 4.76 (1H, m, α′-CH), 5.05 (1H, d, *J* = 8.4 Hz, NH), 5.13, 5.21 (2H, ABq, *J* = 11.9 Hz, CH_2Ph), 5.34 (1H, d, *J* = 8.1 Hz, N′H) 7.06–7.77 (21H, m, ArH); ^{13}C NMR δ 28.29, 38.21, 38.44, 47.21, 52.38, 54.26, 54.62, 66.96, 67.52, 80.19, 120.04, 124.99, 127.10, 127.78, 128.71, 128.75, 129.32, 130.29, 134.87, 136.35, 140.59, 141.12, 141.37, 143.68, 143.78, 155.03, 155.51, 171.02, 172.01, 195.75.

18. Obtained in 78% overall yield from 4-iodo-L-phenylalanine by *N*-protection with Fmoc-ONSu/Na_2CO_3/DMF–H_2O, rt followed by esterification with BnBr/$NaHCO_3$/Bu_4NCl/CH_2Cl_2/H_2O, rt. **4**: mp 157–160 °C; $[\alpha]_D^{20}-4°$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3428, 1719, 1509, 1342, 1183 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.03 (2H, m, β-CH_2), 4.19 (1H, t, *J* = 6.9 Hz, FmocCH), 4.33–4.49 (2H, m, FmocCH_2), 4.67 (1H, m, α-CH), 5.08, 5.18 (2H, ABq, *J* = 12.0 Hz, CH_2Ph), 5.28 (1H, m, NH), 6.68, 7.76 (4H, ABq, *J* = 7.3 Hz, 4-I-ArH), 7.24–7.56 (13H, m, ArH); ^{13}C NMR δ 37.72, 47.17, 54.53, 66.92, 67.44, 92.63, 120.03, 124.99, 127.09, 127.76, 128.71, 128.74, 131.34, 134.84, 135.18, 137.59, 141.35, 143.65, 143.81, 155.48, 171.01.

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20. **7a:** (a) *N*-Boc-4-I-Phe-OH, H-Leu-OMe·HCl, *i*-BuOCOCl, NMM, CH_2Cl_2, rt; (b) $SOCl_2$, MeOH, 45 °C; (c) Ac-Ala-OH, TEA, HOBt, EDC, DMF, rt, 78% overall yield; mp 248–250 °C; $[\alpha]_D^{20}-52°$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3425, 1740, 1659, 1504, 1371, 1277 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$:CD_3OD = 3:1 by volume) δ 0.92 (6H, t, *J* = 6.8 Hz, $CH(CH_3)_2$), 1.26 (3H, d, *J* = 7.2 Hz, $CHCH_3$), 1.60 (3H, m, $CH_2CH(CH_3)_2$), 1.95 (3H, s, CH_3CONH), 2.91 (1H, dd, *J* = 13.8, 7.9 Hz, CHHAr), 3.10 (1H, dd, *J* = 13.8, 6.0 Hz, CHHAr), 3.71 (3H, s, CO_2Me), 4.31 (1H, m, α-CH Ala), 4.48 (1H, m, α-CH Leu), 4.59 (1H, m, α-CH 4-I-Phe), 6.98, 7.59 (4H, ABq, *J* = 8.2 Hz, ArH); ^{13}C NMR δ 17.57, 21.66, 22.49, 22.86, 24.95, 37.30, 40.80, 51.11, 52.43, 54.08, 92.20, 131.61, 136.47, 137.54, 164.42, 171.16, 171.55, 173.30. **7b**: (a) *N*-Fmoc-4-I-Phe-OH, H-Leu-O*t*Bu·HCl, *i*-BuOCOCl, NMM, CH_2Cl_2, rt; (b) piperidine, DMF, rt; (c) *N*-Fmoc-Ala-OH, *i*-BuOCOCl, NMM, CH_2Cl_2, rt, 75% overall yield; mp 170–172 °C; $[\alpha]_D^{20}-22°$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3421, 1722, 1666, 1520, 1501, 1369, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (6H, br s, $CH(CH_3)_2$), 1.32 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.44 (9H, s, *t*-Bu), 1.52 (3H, m, $CH_2CH(CH_3)_2$), 2.97 (1H, dd, *J* = 13.8, 6.3 Hz, CHHAr), 3.05 (1H, dd, *J* = 13.8, 6.5 Hz, CHHAr), 4.22 (2H, m, α-CH Ala and FmocCH), 4.40 (3H, m, α-CH Leu and FmocCH_2), 4.68 (1H, m, α-CH 4-I-Phe), 5.42 (1H, d, *J* = 5.7 Hz, FmocNH),

6.47 and 6.72 (2H, m, amidic NHs), 6.92, 7.76 (4H, ABq, $J = 8.0$ Hz, 4-I-ArH), 7.26–7.60 (8H, m, FmocArH); ^{13}C NMR δ 18.45, 22.11, 22.68, 24.85, 28.00, 37.58, 41.65, 47.13, 50.64, 51.57, 53.95, 67.21, 82.07, 92.51, 120.04, 125.07, 127.12, 127.78, 131.44, 135.88, 137.59, 141.35, 143.75, 156.01, 169.72, 171.54, 172.15.

21. **8a**: mp 232–235 °C; $[\alpha]_D^{20} -54°$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3421, 1738, 1658, 1607, 1513, 1279 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$:CD_3OD = 10:1 by volume) δ 0.91 (6H, s, $CH(C\underline{H}_3)_2$), 1.27 (3H, d, $J = 6.9$ Hz, $CHC\underline{H}_3$), 1.60 (3H, m, $C\underline{H}_2C\underline{H}(C\underline{H}_3)_2$), 1.94 (3H, s, $C\underline{H}_3CONH$), 3.06 (1H, dd, $J = 13.8$, 8.4 Hz, $C\underline{H}HAr$), 3.28 (1H, dd, $J = 13.9$, 5.8 Hz, $CH\underline{H}Ar$), 3.70 (3H, s, $C\underline{O}_2Me$), 4.39 (1H, m, α-CH Ala), 4.52 (1H, m, α-CH Leu), 4.70 (1H, m, α-CH Bpa), 7.32–7.79 (9H, m, ArH); ^{13}C NMR δ 17.85, 21.70, 22.69, 22.76, 24.82, 37.66, 40.90, 50.92, 52.31, 53.96, 54.04, 128.31, 129.36, 129.98, 130.21, 132.56, 135.99, 137.46, 141.91, 170.71, 170.98, 172.91, 173.10, 196.97. **8b**: mp 174–175 °C; $[\alpha]_D^{20} -25°$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3417, 1722, 1659, 1607, 1498, 1278, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (6H, br s, $CH(C\underline{H}_3)_2$), 1.34 (3H, d, $J = 6.3$ Hz, $CHC\underline{H}_3$), 1.43 (9H, s, *t*-Bu), 1.55 (3H, m, $C\underline{H}_2C\underline{H}(CH_3)_2$), 3.12 (1H, dd, $J = 13.2$, 6.0 Hz, $C\underline{H}HAr$), 3.23 (1H, dd, $J = 13.2$, 6.6 Hz, $CH\underline{H}Ar$), 4.18 (2H, m, α-CH Ala and FmocCH), 4.38 (3H, m, α-CH Leu and $FmocCH_2$), 4.76 (1H, m, α-CH Bpa), 5.42 (1H, br s, FmocNH), 6.46 and 6.80 (2H, m, amidic NHs), 7.26–7.76 (17H, m, ArH); ^{13}C NMR δ 18.46, 22.10, 22.64, 24.85, 27.94, 38.02, 41.65, 47.09, 50.68, 51.57, 54.02, 67.16, 82.04, 119.99, 125.01, 127.08, 127.74, 128.23, 129.34, 129.94, 130.41, 132.31, 136.28, 137.60, 141.29, 143.73, 156.01, 169.66, 171.52, 172.18, 196.21.