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Synthesis of 4-(Arylmethyl)proline Derivatives

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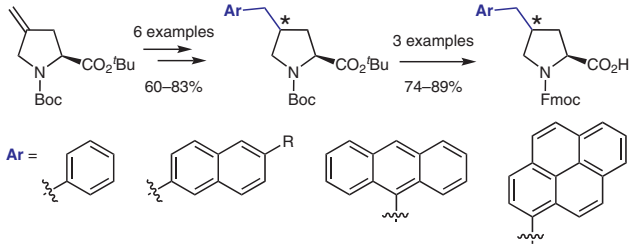

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Abstract A synthesis of 4-(arylmethyl)proline by using Suzuki cross-couplings was developed. The route permits access to a variety of 4-substituted proline derivatives bearing various aryl moieties that expand the toolbox of proline analogues for studies in chemistry and biology.

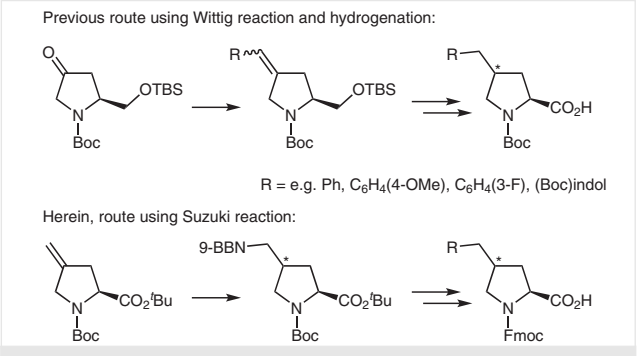
Key words arylmethylprolines, prolines, hydroboration, Suzuki cross-coupling

Proline is the only proteogenic amino acid with a cyclic backbone, which confers to this residue a uniquely restricted conformation. Nature and scientists have used proline and its derivatives to regulate numerous processes, ranging from ion-gating and the structural integrity of skin to asymmetric catalysis.[1–4] The development of proline analogues and their incorporation into peptides and other compounds is therefore of great interest. Proline derivatives with different substituents at Cγ are the most common, due to their natural occurrence and the ease of functionalization of (2*S*,4*R*)-4-hydroxyproline.[1,5] Examples include derivatives with heteroatoms at Cγ, e.g., F, Cl, N_3, NH_2, or alkyl groups, e.g., Me and ^{t}Bu.[1,6] In contrast, derivatives with arylmethyl substituents at Cγ are less commonly utilized, possibly due to a lack of a straightforward synthetic route.

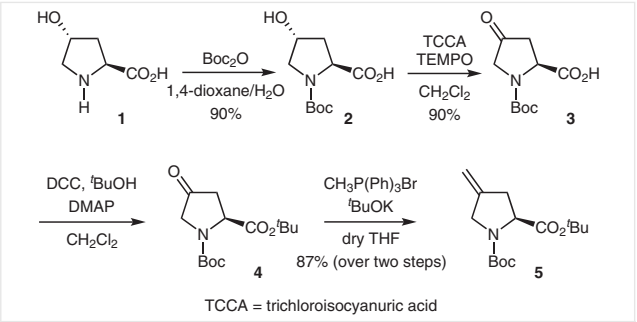
We became interested in proline derivatives bearing naphthyl moieties, for their value in the molecular recognition of RNA.[7] Synthetic routes have been reported for the functionalization of proline at Cγ with benzylic or indolylmethyl substituents.[6a,8,9] However, we had limited success in transferring these reaction conditions, which rely on Wittig reactions of 4-oxoproline followed by hydrogenation, to larger aryl moieties (Scheme 1, top).

We therefore sought an alternative route and we envisioned Suzuki reactions between an organoborane–proline derivative and aryl halides as a strategy that might provide access to proline derivatives with various aryl groups (Scheme 1, bottom). Here, we report a general synthetic route to arylmethyl proline derivatives that permits the introduction of a broad range of aryl moieties at Cγ.

Our synthetic route relies on the hydroboration of the Boc/^{t}Bu-protected 4-methyleneproline **5**, which was obtained from (2*S*,4*R*)-4-hydroxyproline (**1**) by slight modification of a previously published procedure (Scheme 2).[10] This four-step synthesis started with Boc-protection of **1**, followed by oxidation to ketone **3**, protection of the carboxylic acid as the ^{t}Bu ester in **4**, and introduction of an exocyclic methylene group by a Wittig reaction.[11]

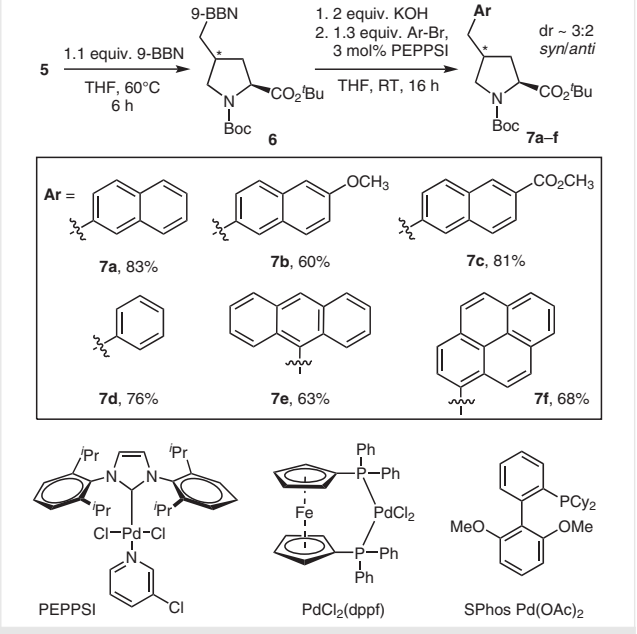


Scheme 1 Synthetic routes to 4-(arylmethyl)proline derivatives



Scheme 2 Synthesis of the common precursor *tert*-butyl *N*-(*tert*-butoxycarbonyl)-4-methyleneprolinate (**5**)

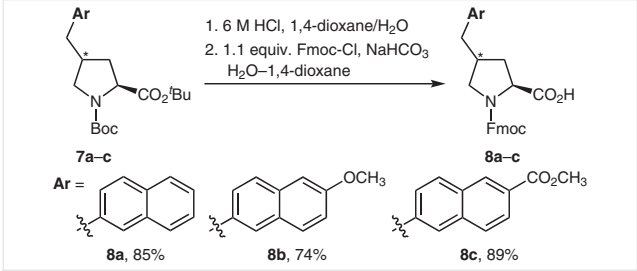
Hydroboration of the 4-methyleneproline **5** with 9-BBN provided the organoborane **6**, which was used for the Suzuki reaction without further purification (Scheme 3, top). For the Suzuki reaction, various catalysts and conditions were explored by using 2-bromonaphthalene as a model aryl bromide. We focused in particular on catalysts that had proven valuable for cross-couplings with other amino acid derivatives (Scheme 3, bottom).[12] Among the tested palladium-based catalysts, reactions with PEPPSI[13] showed the highest conversion of **5** and 2-bromonaphthalene into the Suzuki reaction product **7a**. Under optimized conditions [5 M aq KOH, ArBr (1.3 equiv), PEPPSI(3% mol)], the 4-(2-naphthylmethyl)proline derivative **7a** was obtained in a yield of 83%. Note that 3 mol% of PEPPSI was enough to obtain these results. Because PEPPSI is more air-stable than other palladium catalysts,[14] this catalyst was used for all further experiments.



Scheme 3 Top: Suzuki cross-coupling reaction to yield various 4-(arylmethyl)proline derivatives **7a–f**. Bottom: Catalysts tested in the Suzuki cross-coupling reaction.

Reassuringly, this route also permitted the synthesis of proline derivatives bearing substituted naphthyl moieties (**7b** and **7c**) as well as phenyl (**7d**), 9-anthryl (**7e**), or pyren-1-yl (**7f**) substituents in good overall yields (60–83%; Scheme 3).[15] All derivatives were obtained with a diastereoselectivity of ~3:2 in favor of the *syn*-product, as determined by analysis of ^{1}H NMR NOE spectroscopy.[11]

Because peptide syntheses typically require Fmoc-protected amino acids, we converted **7a–c** into the respective Fmoc-amino acids **8a–c**. Simultaneous removal of the ^{t}Bu protecting groups in 6 M HCl in 1,4-dioxane, and subsequent Fmoc-protection afforded **8a–c** in yields of 74–89% (Scheme 4). The diastereoisomers were separated by preparative reverse-phase HPLC to obtain enantiomerically pure amino acids at a scale of up to 2.5 g.[15,16]



Scheme 4 Synthesis of Fmoc-protected amino acids **8a–c**

In conclusion, we have introduced a synthetic route to access proline derivatives bearing a variety of arylmethyl substituents at the γ-position. The products were obtained in good yields for every tested aromatic moiety. The diastereoselectivity of the hydroboration step was modest, but the diastereoisomeric products could be separated on a gram scale. Installation of a Fmoc-protecting group was straightforward. Thus, the route provides access to proline derivatives with a variety of arylmethyl moieties at Cγ that are suitably protected for solid-phase peptide synthesis. We envision these derivatives as being valuable additions to the toolkit of proline analogues for applications in chemistry and chemical biology.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611672.

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(15) ***tert*-Butyl (4*S*/4*R*)-*N*-(*tert*-Butoxycarbonyl)-4-(2-naphthylmethyl)-L-prolinate (7a); Typical Procedure**

An oven-dried Schlenk flask was charged with methylene derivative **5** (4.0 g, 14.1 mmol, 1 equiv) under N_2. A 0.5 M soln of 9-BBN in THF (31.0 mL, 15.5 mmol, 1.1 equiv) was added in one portion, and the solution was stirred vigorously at 60 °C for 6 h. The mixture was then allowed to cool to r.t. and 5 M aq. KOH (5.6 mL, 5 M, 28.0 mmol, 2 equiv) was added. The mixture was stirred for 20 min, then 2-bromonaphthalene (**7a**; 3.8 g, 18.36 mmol, 1.3 equiv) was added together with PEPPSI (287.7 mg, 423 µmol, 0.03 equiv). The mixture was stirred for a further 16 h at r.t., then H_2O (120 mL) and EtOAc (120 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 120 mL), and the organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated. The resulting yellow–brown oil (9.9 g) was purified by column chromatography (silica gel, 0–25% EtOAc–hexane) to give a colorless oil; yield: 4.8 g (83%).

^{1}H NMR (500 MHz, $C_2Cl_4D_2$, 60 °C): δ = 7.82–7.71 (m, 3 H), 7.59–7.52 (m, 1 H), 7.48–7.37 (m, 2 H), 7.27 (dd, *J* = 8.4, 1.7 Hz, 1 H), 4.26–4.02 (m, 1 H), 3.75–3.55 (m, 1 H), 3.14 (dd, *J* = 10.6, 9.0 Hz, 1 H), 2.89–2.76 (m, 2 H), 2.72–2.44 (m, 1 H), 2.42–1.88 (m, 1 H), 1.63 (ddd, *J* = 12.8, 9.5, 7.9 Hz, 1 H), 1.51–1.33 (m, 18 H). ^{13}C NMR (126 MHz, $C_2Cl_4D_2$, 60 °C): δ = 172.2, 172.0, 153.6, 137.6, 137.4, 133.5, 133.5, 132.1, 128.1, 128.1, 127.6, 127.5, 127.4, 127.2, 127.1, 126.8, 126.8, 126.1, 125.4, 80.9, 80.8, 79.6, 79.5, 59.8, 59.7, 52.1, 51.6, 39.3, 39.2, 37.7, 36.7, 36.4, 28.4, 28.0, 28.0. HRMS (ESI+): *m/z* [M + H]$^+$ calcd $C_{25}H_{34}NO_4$: 412.2482; found: 412.2485.

(4*S*)- and (4*R*)-1-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-4-(2-naphthylmethyl)-L-proline (8a); Typical Procedure

Prolinate **7a** (4.8 g, 11.7 mmol, 1 equiv) was dissolved in a 6 M soln of HCl in 1,4-dioxane (110 mL), and the mixture was stirred for 3 h at r.t. The pH was adjusted to 8–9 with sat. aq $NaHCO_3$, then a soln of FmocCl (3.6 g, 14.0 mmol, 1.2 equiv) in 1,4-dioxane (50 mL) was added, and the mixture was stirred at r.t. for 2 h. Low-boiling volatiles were removed under reduced pressure, and EtOAc (50 mL) was added. The solution was acidified to pH 2–3 with 1 M HCl, and the organic phase was separated and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. All volatiles were removed under reduced pressure, and the product was purified by column chromatography (silica gel, 0–5% MeOH in CH_2Cl_2 with 0.1% HCO_2H) to give a white powder: yield: 4.7 g (84%). The diastereoisomers were subsequently separated by reverse-phase semipreparative HPLC [Reprosil-Gold 120 C18, 10 µm; 250 × 30 mm column, MeCN and H_2O–MeCN–TFA (100:1:0.1)].

(4*S*)-Diastereomer

$[\alpha]_D$ –40.7 ± 0.5 (*c* 0.2, MeOH). TLC (silica gel, 2% MeOH in CH_2Cl_2): R_f = 0.56. FTIR (neat): 3051, 2923, 1701, 1421, 1352, 1247, 1176, 1122, 1006, 972, 843, 739 cm^{-1}.

^{1}H NMR (500 MHz, $C_2Cl_4D_2$, 60 °C): δ = 7.92–7.79 (m, 3 H; Ar), 7.77–7.60 (m, 3 H; Ar), 7.59–7.44 (m, 4 H; Ar), 7.43–7.21 (m, 5 H; Ar), 4.55–4.41 (m, 2 H; CH_2–Fmoc), 4.41–4.28 (m, 1 H; Hα), 4.28–4.18 (m, 1 H; CH–Fmoc), 3.77–3.52 (m, 1 H; Hδ), 3.25–3.16 (m, 1 H; Hδ), 3.01–2.79 (m, 2 H; CH_2-Naph), 2.57 (hept, *J* = 7.7 Hz, 1 H; Hγ), 2.50–2.36 (m, 1 H; Hβ), 2.12–1.93 (m, 1 H; Hβ). ^{13}C NMR (500 MHz, $C_2Cl_4D_2$, 60 °C): δ = 173.2 (CO_2H), 156.4 ($C{=}O_{Fmoc}$), 143.5 (Ar), 141.1 (Ar), 137.0 (Ar), 133.4 (Ar), 132.1 (Ar), 128.2 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 127.0 (Ar), 126.9 (Ar), 126.7 (Ar), 126.1 (Ar), 125.5 (Ar), 124.8 (Ar), 119.8 (Ar), 67.9 (CH_2–Fmoc), 59.4 (Cα), 52.2 (Cδ), 47.1 (CH–Fmoc), 39.7 (Cγ), 38.8 (CH_2–Naph), 34.4 (Cβ). HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{31}H_{28}NO_4$: 478.2013; found: 478.2003.

(4*R*)-Diastereomer

$[\alpha]_D$ –10.8 ± 0.3 (*c* 0.2, MeOH). TLC (silica gel, 2% MeOH in CH_2Cl_2): R_f = 0.56. FTIR (neat): 3045, 2966, 1700, 1661, 1417, 1351, 1241, 1282, 1122, 1002, 947, 887, 737 cm^{-1}.

^{1}H NMR (500 MHz, $C_2Cl_4D_2$, 60 °C): δ = 7.91–7.80 (m, 3 H; Ar), 7.73 (dd, *J* = 7.6, 2.9 Hz, 2 H; Ar), 7.62 (s, 1 H; Ar), 7.59–7.48 (m, 4 H; Ar), 7.39 (tt, *J* = 7.6, 1.4 Hz, 2 H; Ar), 7.35–7.27 (m, 3 H; Ar), 4.56–4.36 (m, 3 H; Hα, CH_2–Fmoc), 4.32–4.19 (m, 1 H; CH–Fmoc), 3.74–3.49 (m, 1 H; Hδ), 3.31–3.10 (m, 1 H; Hδ), 2.97–2.80 (m, 2 H; CH_2–Naph), 2.80–2.65 (m, 1 H; Hγ), 2.47–1.88 (m, 2 H; Hβ). ^{13}C NMR (500 MHz, $C_2Cl_4D_2$, 60 °C): δ = 173.8 (CO_2H), 156.1 ($C{=}O_{Fmoc}$), 143.5 (Ar), 141.1 (Ar), 136.8 (Ar), 133.4 (Ar), 132.1 (Ar), 128.2 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 127.0 (Ar), 127.0 (Ar), 126.8 (Ar), 126.1 (Ar), 125.5 (Ar), 124.8 (Ar), 119.82 (Ar), 67.9 (CH_2–Fmoc), 59.2 (Cα), 51.7 (Cδ), 47.1 (CH–Fmoc), 38.9 (CH_2–Naph, Cγ), 34.3 (Cβ). HRMS (ESI+): *m/z* [M + H]$^+$ calcd $C_{31}H_{28}NO_4$: 478.2013; found: 478.2003.

(16) Note that the Suzuki reaction is not compatible with the use of Fmoc-protected amines. The stereochemistry at the stereogenic centers was retained during the synthesis.