

Synthesis of 4-(Arylmethyl)proline Derivatives

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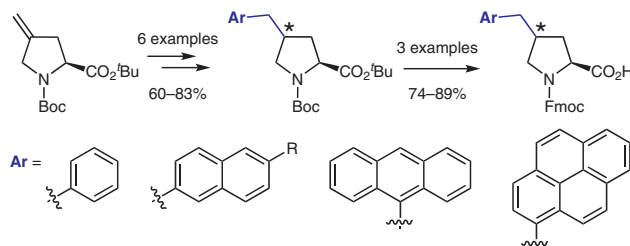
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Abstract A synthesis of 4-(arylmethyl)proline by using Suzuki cross-couplings was developed. The route permits access to a variety of 4-substituted proline derivatives bearing various aryl moieties that expand the toolbox of proline analogues for studies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

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

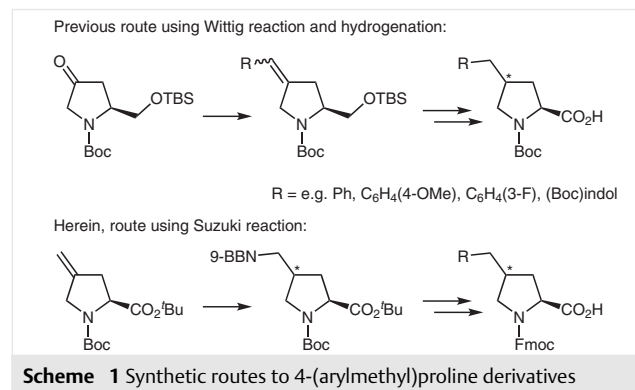
Proline is the only proteogenic amino acid with a cyclic backbone, which confers to this residue a uniquely restricted conformation. Nature and scientists have used proline and its derivatives to regulate numerous processes, ranging from ion-gating and the structural integrity of skin to asymmetric catalysis.^{1–4} The development of proline analogues and their incorporation into peptides and other compounds is therefore of great interest. Proline derivatives with different substituents at C γ 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 C γ , e.g., F, Cl, N₃, NH₂, or alkyl groups, e.g., Me and ^tBu.^{1,6} In contrast, derivatives with arylmethyl substituents at C γ are less commonly utilized, possibly due to a lack of a straightforward synthetic route.

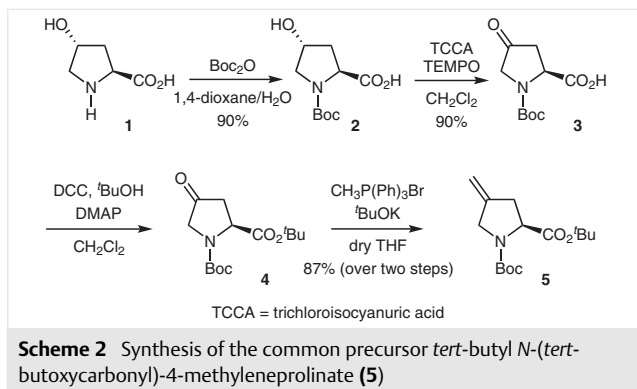
We became interested in proline derivatives bearing naphthyl moieties, for their value in the molecular recognition of RNA.⁷ Synthetic routes have been reported for the functionalization of proline at C γ with benzylic or indolylmethyl substituents.^{6a,8,9} However, we had limited success

in transferring these reaction conditions, which rely on Wittig reactions of 4-oxoproline followed by hydrogenation, to larger aryl moieties (Scheme 1, top).

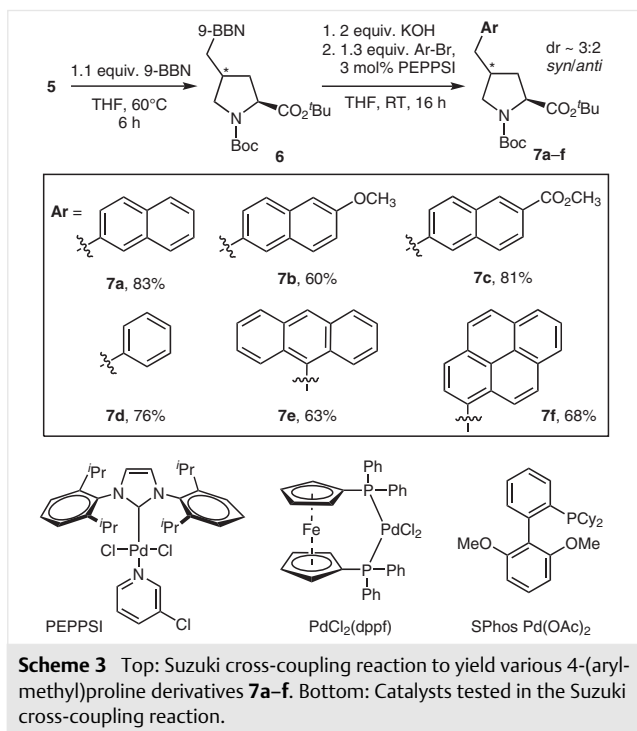
We therefore sought an alternative route and we envisioned Suzuki reactions between an organoborane–proline derivative and aryl halides as a strategy that might provide access to proline derivatives with various aryl groups (Scheme 1, bottom). Here, we report a general synthetic route to arylmethyl proline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

Our synthetic route relies on the hydroboration of the Boc/^tBu-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 ^tBu ester in **4**, and introduction of an exocyclic methylene group by a Wittig reaction.¹¹



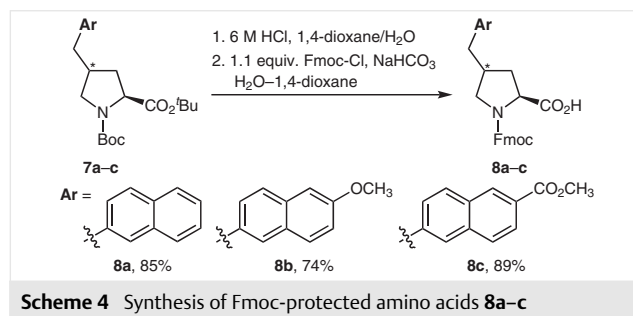


Hydroboration of the 4-methyleneproline **5** with 9-BBN provided the organoborane **6**, which was used for the Suzuki reaction without further purification (Scheme 3, top). For the Suzuki reaction, various catalysts and conditions were explored by using 2-bromonaphthalene as a model aryl bromide. We 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 PEPPSI¹³ 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.



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 ¹H 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}



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 γ 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 (4S/4R)-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 N₂. 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 H₂O (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 (MgSO₄), 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%).
¹H NMR (500 MHz, C₂Cl₄D₂, 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). ¹³C NMR (126 MHz, C₂Cl₄D₂, 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 C₂₅H₃₄NO₄: 412.2482; found: 412.2485.
- (4S)- and (4R)-1-[(9H-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 NaHCO₃, 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 (MgSO₄), and filtered. All volatiles were removed under reduced pressure, and the product was purified by column chromatography (silica gel, 0–5% MeOH in CH₂Cl₂ with 0.1% HCO₂H) to give a white powder; yield: 4.7 g (84%). The diastereoisomers were subsequently separated by reverse-phase semipreparative HPLC [Reposil-Gold 120 C18, 10 μm; 250 × 30 mm column, MeCN and H₂O–MeCN–TFA (100:1:0.1)].
- (4S)-Diastereomer**
[α]_D –40.7 ± 0.5 (c 0.2, MeOH). TLC (silica gel, 2% MeOH in CH₂Cl₂): R_f = 0.56. FTIR (neat): 3051, 2923, 1701, 1421, 1352, 1247, 1176, 1122, 1006, 972, 843, 739 cm⁻¹.
¹H NMR (500 MHz, C₂Cl₄D₂, 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; CH₂-Fmoc), 4.41–4.28 (m, 1 H; H_α), 4.28–4.18 (m, 1 H; CH-Fmoc), 3.77–3.52 (m, 1 H; H_δ), 3.25–3.16 (m, 1 H; H_δ), 3.01–2.79 (m, 2 H; CH₂-Naph), 2.57 (hept, J = 7.7 Hz, 1 H; H_γ), 2.50–2.36 (m, 1 H; H_β), 2.12–1.93 (m, 1 H; H_β). ¹³C NMR (500 MHz, C₂Cl₄D₂, 60 °C): δ = 173.2 (CO₂H), 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 (CH₂-Fmoc), 59.4 (C_α), 52.2 (C_δ), 47.1 (CH-Fmoc), 39.7 (C_γ), 38.8 (CH₂-Naph), 34.4 (C_β). HRMS (ESI+): m/z [M + H]⁺ calcd for C₃₁H₂₈NO₄: 478.2013; found: 478.2003.
- (4R)-Diastereomer**
[α]_D –10.8 ± 0.3 (c 0.2, MeOH). TLC (silica gel, 2% MeOH in CH₂Cl₂): R_f = 0.56. FTIR (neat): 3045, 2966, 1700, 1661, 1417, 1351, 1241, 1282, 1122, 1002, 947, 887, 737 cm⁻¹.
¹H NMR (500 MHz, C₂Cl₄D₂, 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; H_α, CH₂-Fmoc), 4.32–4.19 (m, 1 H; CH-Fmoc), 3.74–3.49 (m, 1 H; H_δ), 3.31–3.10 (m, 1 H; H_δ), 2.97–2.80 (m, 2 H; CH₂-Naph), 2.80–2.65 (m, 1 H; H_γ), 2.47–1.88 (m, 2 H; H_β). ¹³C NMR (500 MHz, C₂Cl₄D₂, 60 °C): δ = 173.8 (CO₂H), 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), 119.8 (Ar), 67.9 (CH₂-Fmoc), 59.2 (C_α), 51.7 (C_δ), 47.1 (CH-Fmoc), 38.9 (CH₂-Naph, C_γ), 34.3 (C_β). HRMS (ESI+): m/z [M + H]⁺ calcd C₃₁H₂₈NO₄: 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.