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Synthesis of non-proteinogenic phenylalanine analogues by Suzuki cross-coupling of a serine-derived alkyl boronic acid

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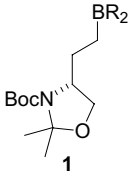
Abstract—Protected serine-derived boronic acids have been prepared as β-anionic alanine equivalents, and undergo efficient Suzuki cross-coupling with a variety of aryl halides to give, after elaboration, non-proteinogenic phenylalanine analogues.

The synthesis of enantiopure non-proteinogenic α-amino acids is of great importance due to their roles as pharmaceuticals, chiral ligands and building blocks in natural product synthesis. Among recent developments in the preparation of such compounds[1] has been the modification of readily available derivatives of proteinogenic α-amino acids.[2–7] In particular, anionic equivalents of alanine have been exploited by Jackson and co-workers,[6] whose zinc-alanine species can be transmetallated and coupled with electrophiles.



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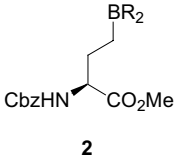

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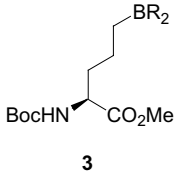

3

BR_2 = 9-BBN

Organoboron reagents, particularly boronic acids, are rapidly increasing in popularity as the nucleophilic components in palladium-catalysed cross-coupling reactions due to their stability, ready preparation and lack of toxicity.[8] Traditionally, in contrast to aryl- and alkenylboron species, alkyl reagents were not considered suitable for cross-coupling reactions due to their low nucleophilicity, leading to a lack of reactivity, and their propensity to undergo β-hydride elimination after transmetallation. A judicious choice of catalyst and conditions can, however, overcome these problems.[9–12] For instance, we have previously utilised the homoalanine and bishomoalanine boranes **1**, **2** and **3**, prepared by hydroboration of the corresponding alkenes, in Suzuki cross-couplings to access a variety of non-proteinogenic amino acids.[3] We also attempted to hydroborate dehydroamino acid derivatives to obtain alaninyl-organoborane reagents, but without success.[13]

We were therefore pleased to find, during the course of our recent work in this area,[7] that the organolithium reagents **5** (Scheme 1), prepared from L-serine via chlorides **4**, could be quenched with triisopropylborate and the intermediate boronic esters hydrolysed to afford the boronic acids **6**.

The purpose of the present work was to determine whether the alkyl boronic acids **6** would be amenable to the Suzuki cross-coupling reaction and, in the first instance, whether phenylalanine analogues could be

Keywords: Amino acid; Suzuki; Cross-coupling; Boronic acid.
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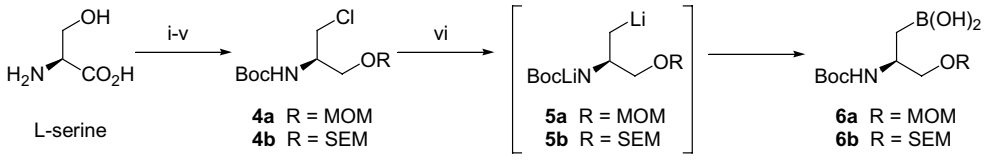
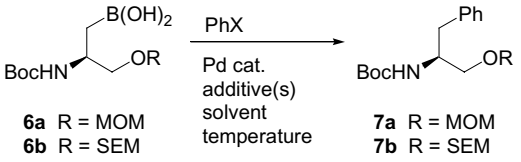


Scheme 1. Reagents and conditions:[7] (i) CH_3COCl, MeOH, 0–65 °C; (ii) $(Boc)_2O$, NEt_3, THF, 0–20 °C (74% over two steps); (iii) C_2Cl_6, PPh_3, CH_2Cl_2; (iv) $LiBH_4$, EtOH, THF, 0–20 °C (69% over two steps); (v) MOMCl or SEMCl, $N(i\text{-}Pr)_2Et$, CH_2Cl_2, 0–20 °C (78% of **4a**; 83% of **4b**); (vi) *n*-BuLi, THF, −78 °C then lithium naphthalenide then $B(Oi\text{-}Pr)_3$ then 0.5 M HCl (80% of **6a**; 77% of **6b**). MOM = methoxymethyl; SEM = 2-(trimethylsilyl)ethoxymethyl.

Table 1. Optimisation of the Suzuki cross-coupling reaction of alkylboronic acids **6a** and **6b** with halobenzenes[a]



Entry	R	Catalyst (mol%)	Solvent	Temperature (°C)	PhX (equiv)	Additive(s) (equiv)	Time	Yield[b] (%)
i	MOM	$PdCl_2(dppf)$ (9)	THF/H_2O (10:1)	70	PhBr (2.0)	K_2CO_3 (3)	16 h	54
ii	MOM	$PdCl_2(dppf)$ (9)	THF/H_2O (10:1)	70	PhBr (2.2)	K_2CO_3 (3)	3 d	79
iii	MOM	$PdCl_2(dppf)$ (9)	THF/H_2O (10:1)	70	PhBr (1.2)	K_2CO_3 (3)	3 d	54
iv	MOM	$PdCl_2(dppf)$ (3×4)	THF/H_2O (10:1)	70	PhBr (1.2)	K_2CO_3 (3)	5 d	63
v	MOM	$PdCl_2(dppf)$ (9)	THF/H_2O (10:1)	70	PhBr (2.2)	Tl_2CO_3 (2.6)	23 h	71
vi	MOM	$Pd(PPh_3)_4$ (11)	Dioxane	100	PhBr (2.1)	K_2CO_3 (3)	20 h	47
vii	MOM	$Pd_2(dba)_3$, dppf (10)	Dioxane	75	PhBr (2.2)	Cs_2CO_3	2.5 d	17
viii	MOM	$Pd(PPh_3)_2(succ)Br$ (9)	THF/H_2O (10:1)	70	PhBr (1.7)	K_2CO_3 (3)	2 d	41
ix	MOM	$Pd(OAc)_2$, PCy_3 (10)	Dioxane	100	PhBr (1.1)	KO*t*-Bu (3)	3 d	0
x	MOM	$Pd(OAc)_2$, $P(t\text{-}Bu)_2Me$ (5)	Dioxane	25	PhBr (1.0)	KO*t*-Bu (3)	24 h	0
xi	SEM	$PdCl_2(dppf)$ (9)	THF/H_2O (10:1)	70	PhBr (1.8)	K_2CO_3 (3)	3 d	78
xii	SEM	$PdCl_2(dppf)$ (10)	THF	80 (sealed tube)	PhBr (1.9)	K_2CO_3 (3), Ag_2O (2.5)	15 h	59
xiii	SEM	$PdCl_2(dppf)$ (9)	THF	70	PhBr (2.0)	K_2CO_3 (3), Ag_2O (2.5)	21 h	72
xiv	SEM	$PdCl_2(dppf)$ (9)	THF	70	PhI (2.1)	K_2CO_3 (3), Ag_2O (2.5)	21 h	73
xv	SEM	$PdCl_2(dppf)$ (9)	THF	70	PhCl (2.2)	K_2CO_3 (3), Ag_2O (2.5)	21 h	0
xvi	SEM	$PdCl_2(dppf)$ (9)	THF	70	PhOTf (2.2)	K_2CO_3 (3), Ag_2O (2.5)	21 h	0[c]

[a] All reactions performed on ca. 0.11–0.23 mmol scale at ca. 0.1 mol L^{-1} concentration.
[b] Yields are based on boronic acids **6a** or **6b**.
[c] Addition of LiI (2.2 equiv) gave no improvement.

synthesised in this way. To this end, the MOM-protected compound **6a** was treated with bromobenzene using a variety of catalysts and conditions as shown in Table 1. Thus, the conditions reported by Molander and Yun,[11] involving palladium(II) dichloro-1,1′-bis(diphenylphosphino)ferrocene [$PdCl_2(dppf)$] as catalyst in THF/H_2O at reflux gave 54% of the protected phenylalaninol **7a**[†] after 16 h (entry i). By increasing the

[†] All new compounds were fully characterised spectroscopically and by HRMS.

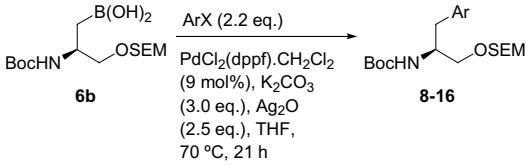
reaction time, we were able to improve the yield to 79% after 3 days (entry ii). Reduction in the amount of added electrophile was detrimental to the yield (entry iii). Adding the catalyst in batches did not rectify this problem, 63% yield being obtained when 12 mol% was added in three batches over 2 days followed by refluxing the reaction for a further 3 days (entry iv). In an effort to increase the rate of transmetallation, usually considered to be the rate-limiting step,[14] thallium carbonate[15] was substituted for potassium carbonate. This did provide 71% yield after only 1 day (entry v), but the high toxicity of this reagent encouraged us to investigate alternative means for activation. A number of other catalyst systems were tested[16] (entries vi–x) but none gave satisfactory results. Of particular note, the electron-rich phosphine ligands PCy_3 and $P(t\text{-}Bu)_2Me$[12] (entries ix and x) did not allow formation of any product. A control reaction in the absence of bromobenzene confirmed that the substrate boronic acid **6a** degraded under these conditions.

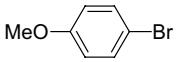
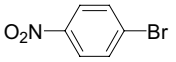
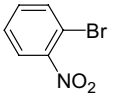
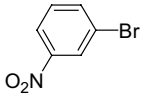
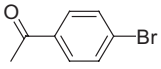
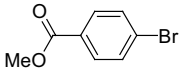
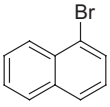
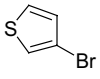
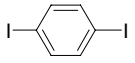
We also explored the use of the SEM-protected compound **6b** as our concurrent work[7] showed that more flexibility was available in its deprotection than in that of the MOM group. Thus, reaction of **6b** with bromobenzene under the best prior conditions gave 78% of the SEM-protected phenylalaninol **7b** after 3 days (entry xi). Activation of alkyl boronic acid couplings with silver(I) oxide has been pioneered by Falck and co-workers[10] and Mu and Gibbs.[17] Following the conditions optimised by Falck and co-workers,[10] we obtained a 59% yield of product **7b** after 15 h at 80 °C in a sealed tube (entry xii). Simply performing the reaction at reflux under atmospheric pressure for 21 h increased the yield to 72% (entry xiii). As expected, iodobenzene also provided good results (73%, entry xiv), whereas chlorobenzene did not react at all (entry xv). Surprisingly, our efforts to perform the reaction with phenyl trifluoromethylsulfonate (PhOTf) were not successful (entry xvi), despite such conditions being used previously with triflates.[10]

The results obtained from bromo- and iodobenzene were encouraging,[18] and so these conditions were applied to a range of electrophiles using boronic acid **6b** (Table 2). We were pleased to observe that the electron-rich *p*-bromoanisole gave a respectable yield of product **8** (entry i), as did the electron-deficient system *p*-bromonitrobenzene (entry ii), affording coupled **9**. It was established that 1,2- and 1,3-substitution patterns were tolerated by using *o*- and *m*-bromonitrobenzenes (providing **10** and **11**) (entries iii and iv). These results were particularly encouraging in light of the poorer yields with *ortho*-substituted electrophiles obtained by Jackson et al. in their related methodology.[6a,c] Furthermore, the steric hindrance at the reacting alanine centre of boronic acid **6b** is indicated by its slower reaction when compared to the substrates of Falck and co-workers[10] and Molander and Yun,[11] and so the good yield obtained in the *ortho* case is especially gratifying. The presence of carbonyl functionalities in the electrophile was tolerated as indicated by use of 4-bromoacetophenone (entry v) and methyl 4-bromobenzoate (entry vi). Reaction of 1-bromonaphthalene with the boronic acid **6b** under the standard conditions also proceeded smoothly and efficiently to provide product **14** (entry vii).

Unfortunately, these conditions did not provide satisfactory results when heterocyclic electrophiles were

Table 2. Suzuki cross-coupling of alkyl boronic acid **6b** with aromatic halides[a]



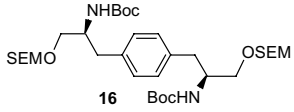
Entry	Ar–X	Yield[b] (%)	Product
i		65	**8**
ii		65	**9**
iii		70	**10**
iv		67	**11**
v		58	**12**
vi		52	**13**
vii		73	**14**
viii		19 (27[c])	**15**
ix		35	**16**[d]

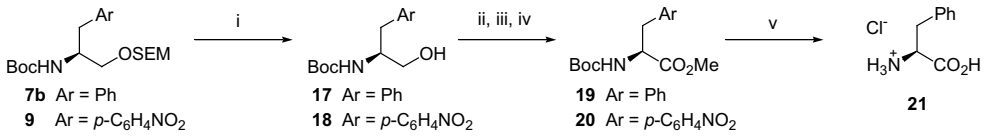
[a] All reactions performed on 0.10–0.13 mmol scale at ca. 0.1 mol L^{-1} concentration.

[b] Yields are based on boronic acid **6b**.

[c] Reagents and conditions: 3.2 M aqueous NaOH (3.0 equiv), $Pd(PPh_3)_4$ (6 mol%), 1,4-dioxane, 100 °C, 2 days.

[d] 0.5 equiv of dihalide used; doubly coupled product **16** formed:





Scheme 2. Reagents and conditions: (i) CH_3COCl, MeOH then $(Boc)_2O$, NEt_3, THF (72% of **17**, 86% of **18**); (ii) Dess–Martin periodinane, CH_2Cl_2; (iii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; (iv) Me_3SiCHN_2, PhMe, MeOH (three steps: 75% of **19**, 51% of **20**); (v) 6 M aqueous HCl, anisole (quantitative).

used. Thus, 3-bromofuran, 3-bromopyridine, 2-bromopyridine-*N*-oxide and ethyl 2-chlorooxazole-4-carboxylate provided none of the expected products. 3-Bromothiophene gave the coupled product **15** in only 19% yield (entry viii) and prolonged reaction times did not significantly improve the results. Reversion to the non-silver promoted reaction conditions of Molander and Yun[11] was not beneficial either. Occasionally, the use of a stronger base has allowed successful Suzuki cross-coupling of heterocycles,[19] but here only a marginal improvement was observed with aqueous sodium hydroxide.

A doubly coupled product, **16**, could be isolated in a modest 35% yield by reacting the boronic acid **6b** with 0.5 equiv of 1,4-diiodobenzene (entry ix). Such aryl-scaffolded systems are potentially useful as synthetic building blocks[20] and as peptidomimetics, particularly as analogues of cysteines.[21]

The bromobenzene and *p*-bromonitrobenzene systems were demonstrated to be amenable to a modest scale-up (ca. 0.46 mmol), giving a reasonable 63% yield of **7b** and a better 71% yield of **9**, respectively. No problems are foreseen in further scale-ups.

Compounds **7b** and **9** were SEM-deprotected to afford alcohols **17** and **18** (Scheme 2) in 72% and 86% yields, respectively. A two-step oxidation to the carboxylic acids and immediate methyl ester formation[7] provided the known protected amino acids **19** and **20** in 75% and 51%, respectively, over three steps. The optical rotations of these esters matched their literature values,[22] thus indicating that the stereochemical integrity at the α-position has been maintained throughout the chemical transformations from L-serine. Global deprotection of compound **19** afforded L-phenylalanine hydrochloride (**21**) in good yield, thus demonstrating that the amino acids are accessible from the Suzuki products. The optical rotation of this final product matched the literature value {$[\alpha]_D^{23}$ −8.1 (*c* 0.91, H_2O); [lit.[23] $[\alpha]_D^{23}$ −8.2 (*c* 1, H_2O)]} and other data were in accordance with the structure. It is expected that conversion of the other SEM-protected coupling products **8** and **10**–**16** to the respective amino acids will proceed equally efficiently.

In conclusion, the syntheses of several phenylalanine analogues have been achieved through Suzuki cross-coupling of the alkyl boronic acid **6b** with a variety of aryl halides. This procedure complements our earlier reports[3] dealing with the preparation of higher homologues of these compounds from boranes prepared by alkene hydroboration. We have also demonstrated the utility of the Falck and co-workers[10] methodology on complex structures with a variety of functionalities. Current work is focusing on the extension of this Suzuki methodology to the synthesis of unsaturated α-amino acid derivatives.

Representative procedure

The boronic acid **6b** (41 mg, 0.12 mmol), K_2CO_3 (49 mg, 0.35 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.6 mg, 0.011 mmol) and Ag_2O (68 mg, 0.29 mmol) were placed under Ar. Tetrahydrofuran (1.0 mL) and 4-bromoanisole (30 μL, 0.24 mmol) were added and the resulting mixture was refluxed for 21 h. The reaction mixture was filtered through a 0.5 cm pad of Celite™ and eluted with diethyl ether (40 mL). The filtrate was concentrated to afford a yellow oil. Subjection of this material to flash chromatography [1:3 diethyl ether/petroleum ether (40–60 °C)] and concentration of the appropriate fractions (R_f 0.18) provided *tert*-butyl 2-(4-methoxyphenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethylcarbamate **8** as a pale yellow oil (31 mg, 65%). $[\alpha]_D^{20}$ −13.1 (*c* 0.93, $CHCl_3$). Found (CI^+): 412.2520. $C_{21}H_{38}NO_5Si$ requires (MH^+): 412.2519 (0.1 ppm error). ν_{max}/cm^{-1} (thin film) 3359, 2953, 1714, 1613, 1513, 1248, 1173. ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* 8.2 Hz, 2H), 6.82 (d, *J* 8.2 Hz, 2H), 4.92 (broad d, *J* 8.0 Hz, 1H), 4.68 (m, 2H), 3.89 (broad m, 1H), 3.78 (s, 3H), 3.63 (m, 2H), 3.46 (m, 2H), 2.86 (dd, *J* 13.1, 4.9 Hz, 1H), 2.75 (dd, *J* 13.1, 8.2 Hz, 1H), 1.42 (s, 9H), 0.95 (m, 2H), 0.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) 158.3 (C), 155.5 (C), 130.5 (CH), 130.3 (C), 114.0 (CH), 95.4 (CH_2), 79.3 (C), 68.6 (CH_2), 65.5 (CH_2), 55.4 (CH_3), 51.9 (CH), 37.1 (CH_2), 28.5 (CH_3), 18.2 (CH_2), −1.3 (CH_3).

Acknowledgements

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