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The scope and limitations of the Suzuki–Miyaura cross-coupling reactions of 6- and 8-substituted 1,2,3,4-tetrahydroisoquinoline-3-carboxylates

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Abstract—6- and 8-Aryl-1,2,3,4-tetrahydroisoqinoline-3-carboxylates have been prepared by Suzuki–Miyaura cross-coupling reactions of the triflates or corresponding boronate esters. We have shown for the first time that a one-pot arylation of a triflate via the boronate ester can be achieved using an aryl chloride.

During the course of a recent medicinal chemistry program we became interested in the synthesis of the tetrahydroisoquinoline derived analogues of *meta*-biphenylalanine (*m*-BiPhe), and further derivatives in which variations could be made in the remote (with respect to the parent α-amino acid) aromatic ring. The use of these constrained analogues of amino acids can lead to peptidomimetics of greater biological activity and also proteolytic stability.[1] The 1,2,3,4-tetrahydroisoqinoline-3-carboxylic acid (Tic) nucleus has been successfully used in ACE[2] and renin[3] inhibitors and bradykinin[4] and opioid[5] antagonists.

A Pictet–Spengler cyclization of *meta*-biphenylalanine to the corresponding 1,2,3,4-tetrahydroisoqinoline-3-carboxylic acid is plausible, though few examples of a Pictet–Spengler cyclization exist in which an unactivated aromatic ring has been successfully utilized to direct the tetrahydroisoquinoline ring formation.[6] Further complicating this approach would be the lack of ability to control the regioselectivity of cyclization (8- or 6-isomer; Fig. 1). Herein we report our efforts toward regioselective routes to these two isomers and the generality of our approach to constrained *meta*-biarylalanine analogues.

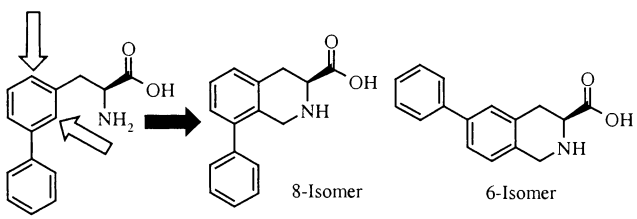

Figure 1.

We envisaged that the synthesis of these Tic analogues would be possible from a common intermediate, namely *meta*-tyrosine **1**. The inherent advantages within this strategy were the ease of incorporation of many functional groups into the isoquinoline nucleus via recent advances in palladium chemistry and the mild conditions for the ring formation due to the phenolic functionality (Scheme 1). Thus, treatment of **1** under Pictet–Spengler conditions yielded the expected 6-hydroxyl isomer in excellent yield.[7] Following esterification and *N*-protection the Tic analogue **4** was ready for introduction of the second aryl unit through a palladium mediated cross-coupling of its corresponding triflate. In order to derive the 8-isomer, we brominated *meta*-tyrosine,[8] thereby directing the subsequent Pictet–Spengler cyclization through the vacant *ortho* position.[9] Cyclization, esterification and *N*-protection were conducted under identical conditions as before yielding **8**, easily identified through analysis of its ^{1}H NMR spectrum, a pair of coupled doublets at δ 7.34 and 6.73 with $J=8.6$ Hz.

Hydrogenolytic removal of the bromine atom yielded the desired 8-hydroxy-tetrahydroisoquinoline in excellent yield. The triflates of both derivatives were easily prepared using trifluoromethanesulfonic anhydride in

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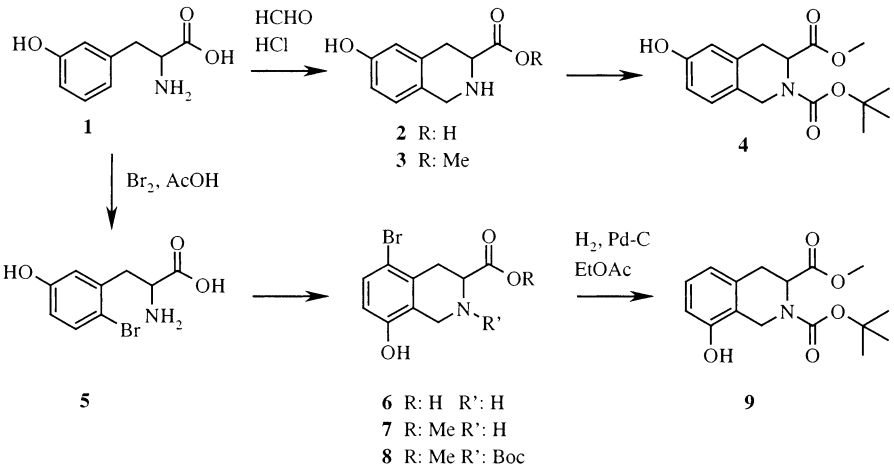


Scheme 1.

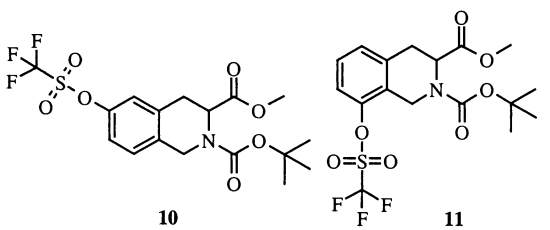
dichloromethane at 0°C. The utility of triflates is well recognized within the sphere of palladium chemistry, and their use in biaryl couplings with either boron (Suzuki–Miyaura) and tin (Stille) containing arenes has been extensively demonstrated.[10] We wished to exploit this knowledge in two ways: firstly, through the Suzuki reaction of the triflate and secondly to exploit the generality of the 'inverse' Suzuki coupling-strategy employing a variety of halides and the corresponding boronate esters.[11] This latter aspect was deemed advantageous since the accessibility to a wide variety of halides is far greater when compared with the corresponding boronic acids or esters. Furthermore, this approach allowed the possibility of realizing a *one-pot protocol* for this arylation via the boronate ester.

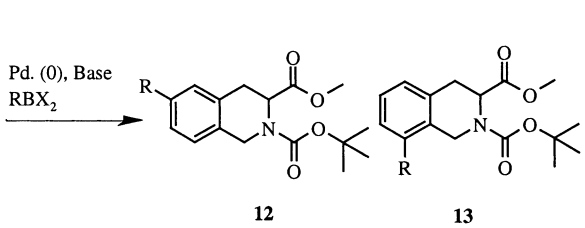
The Suzuki reactions[12] with a variety of boronic acids (Table 1) proceeded well for either the 6- or 8-regioisomeric triflates, yielding the desired biaryl derivatives.

We found that the two triflates were able to undergo the desired cross couplings within 4 h at 90°C. Through our investigations of the Suzuki–Miyaura reactions for these constrained amino acid aryl triflates we found that the boron cross-coupling component could be either a boronic acid or boronate ester, electron rich or electron deficient, heterocyclic or sterically demanding. In all cases the desired cross-coupled products were generated in good to excellent yields (Table 1: **12**/**13a**–**f**). Similarly, the palladium catalysed process for the preparation of the corresponding boronate esters, as reported by Miyaura,[13] proceeded well for both of the regioisomeric triflates (Table 2: **12**/**13g**). We found this to be especially true when additional dppf ligand was added to the reaction to stabilize the palladium catalyst, although the solvent of choice for the two substrates needed some optimization. (Table 2).[14–16] Interestingly the reactivities of the resulting boronate esters **12g** and **13g** were drastically different.

In examining the reactivity of the 6-isomer **12g** (Table 3) we found that the cross-coupling reaction with iodides, bromides and chlorides[17] yielded the desired biaryl in good yields through careful choice of the correct solvent and catalyst. The base had a dramatic effect on yield, with less dramatic effects seen varying either the catalyst or solvent, of which the catalyst

Table 1. Suzuki–Miyaura cross-coupling reactions of triflates **10** and **11**





a: phenyl
b: 4-chlorophenyl
c: 3-trifluoromethylphenyl
d: 2-methoxy
e: 2,4,6-trimethylphenyl
f: 3-thiophenyl
g: pinacolatoboryl
h: 3-carboxyethylphenyl
i: 3-trifluoromethylphenyl

Substrate	Product	Yield (%)	Aryl boronic acid	Substrate	Product	Yield (%)
10	**12a**	79	Phenyl	**11**	**13a**	80
10	**12b**	80	4-Chlorophenyl	**11**	**13b**	91
10	**12c**	76	3-Trifluoromethylphenyl	**11**	**13c**	88
10	**12d**	55	2-Methoxyphenyl	**11**	**13d**	53
10	**12e**	66	2,4,6-Trimethylphenyl[a]	**11**	**13e**	77
10	**12f**	83	3-Thiophene	**11**	**13f**	54

[a] Conducted using 2,2-dimethyltrimethylene cyclic boronate ester, 1.0 mmol substrate, $Pd(PPh_3)_4$ 5 mol%, K_3PO_4 (2.0 equiv.), DMF at 100°C.

Table 2. Preparation of boronate esters **12g** and **13g**

Substrate	Product	Yield (%)	Conditions[a]
10	**12g**	17	Dioxane
10	**12g**	50	DMSO
11	**13g**	68	Dioxane, dppf
11	**13g**	35	DMSO, dppf
10	**12g**	65	Dioxane, dppf
10	**12g**	77	DMSO, dppf
10	**12g**	69	DMF, dppf

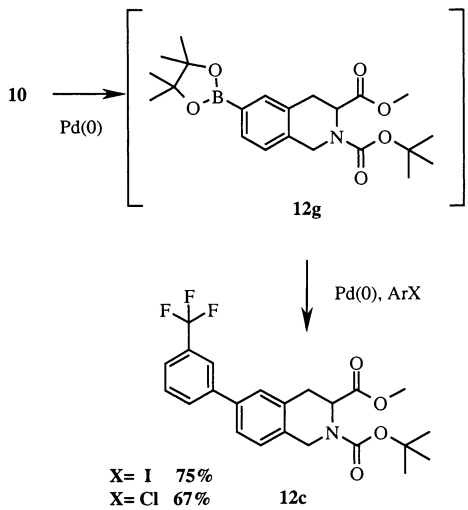
[a] All reactions were carried out using $Pd(dppf)Cl_2$ 5 mol%, KOAc (3.0 equiv.), bis(pinacolato)diboron (1.1 equiv.), in the presence or absence of additional dppf ligand (Pd:L 1:1) as indicated at 80°C.

choice seemed to be the more important. Thus, our best conditions for both rate and yield were the choices of DMF as solvent and $Pd(dppf)Cl_2$ as catalyst.

The 8-isomer **13g** failed to yield any cross-coupling products in DME or DMF under the previous conditions. Through our change of the triflate to boronate ester within the Tic substrate we speculate that we have directly impacted its role in the catalytic cycle.[11] Accordingly, for the Tic triflates, we believe a 14-electron PdL_2 species to have oxidatively inserted into the C–O bond of the triflate and thereafter transmetallation and reductive elimination proceeded to yield the desired cross-coupled biaryl. In the latter boronate ester case the Tic nucleus, in contrast, would now be incorporated during the transmetallation step of the catalytic cycle. We propose that the now coordinatively saturated 16-electron palladium species R-PdL_2-OR is unable to undergo transmetallation with this 8-boronate ester due to steric and not electronic limitations. We only recover from the reaction the homodimer of the initial halide. In attempts to drive this reaction we employed a strong base in a polar aprotic solvent and two variations of the counter-ion of the base. Increasing base strength within the Suzuki reaction is known to facilitate the reaction, particularly when the boronic acid or ester is sterically encumbered.[18] Alternatively, insoluble metal halide (Ag(I)X, or Tl(I)X herein) have also been indicated to aid the reactions by facilitating the transmetallation step.[19] In our hands, all of these reaction conditions failed to yield cross-coupling products of **13g**.

With this noted reactivity difference of the boronate esters in hand, we attempted the utilization of the 6-triflate in a *one-pot strategy* to yield the desired biaryl compounds.[15,20] Thus, **10** was treated in DMF under palladium catalysis with bis(pinacolato)diboron and dppf for 3 h to derive **12g** in situ and thereafter with 3-iodo-benzotrifluoride and potassium phosphate in an effort to prepare **12c** (Scheme 2). The reaction generated the desired biaryl **12c** in 75% yield and hence we attempted the identical protocol utilizing 3-*chloro*-benzotrifluoride. The reaction was carried out again in DMF but with dichlorobis(tricyclohexylphosphino)-palladium(II) as the catalyst and cesium fluoride as base for the latter coupling following the in situ preparation of the boronate ester. Pleasingly the reaction proceeded to generate **12c** in 67% yield.

Hence, as a consequence of the differing reactivity of the two boronate esters prepared, only for the 6-isomer **10** were we able to perform a one-pot transformation via the boronate. We were able to show that this one-pot protocol was possible both using an iodide and chloride under appropriate conditions. The one-pot protocol using the aryl chloride was successful and it appears that the one-pot protocol is superior to the sequential process. Thus, access to constrained biaryl-alanine α-amino acids[21] is possible through two Suzuki–



Scheme 2.

Table 3. Suzuki–Miyaura cross-coupling reactions of boronate esters **12g** and **13g**

Substrate	Product	Solvent	Catalyst	Halide	Base	Yield (%)
12g	**12h**	DME	$Pd(dppf)Cl_2$	3I-$PhCO_2Et$	K_3PO_4	55
12g	**12h**	DME	$Pd(dppf)Cl_2$	3I-$PhCO_2Et$	K_2CO_3	27
12g	**12h**	DMF	$Pd(dppf)Cl_2$	3I-$PhCO_2Et$	K_3PO_4	62
12g	**12h**	DMF	$Pd(PPh_3)_4$	3I-$PhCO_2Et$	K_3PO_4	45
12g	**12i**	DMF	$Pd(dppf)Cl_2$	3I-Benzotrifluoride	K_3PO_4	66
12g	**12i**	DMF	$Pd(dppf)Cl_2$	3Br-Benzotrifluoride	K_3PO_4	57
12g	**12i**	NMP	$Pd(PCy_3)_2Cl_2$	3Cl-Benzotrifluoride	CsF	69
13g	**13i**	DME	$Pd(dppf)Cl_2$	3I-Benzotrifluoride	K_3PO_4	No Reaction
13g	**13i**	DMF	$Pd(PPh_3)_4$	3I-Benzotrifluoride	K_3PO_4	No Reaction
13g	**13i**	Benzene	$Pd(PPh_3)_4$	3I-Benzotrifluoride	Ag_2CO_3	No Reaction
13g	**13i**	Benzene	$Pd(PPh_3)_4$	3I-Benzotrifluoride	Tl_2CO_3	No Reaction

Miyaura strategies. We will report our findings toward the realization of an enantioselective synthesis of these and similar derivatives in due course.

Acknowledgements

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12. **Representative example**: The triflate **10** (0.440 g, 1.00 mmol), 3-thiopheneboronic acid (0.150 g, 1.17 mmol), $Pd(PPh_3)_4$ (0.015 g, 5 mol%), 2N Na_2CO_3 (1.2 ml, 2.40 mmol), toluene:EtOH (4:1; 5 ml) were combined and purged, then heated at 90°C for 24 h. Following partitioning between water and EtOAc, washing and drying the crude product was subjected to SiO_2 eluting with EtOAc:hexane (1:5) to yield **12f** (0.310 g, 83%); mp 136–137°C; ^{1}H NMR (DMSO, 353 K) δ 7.77 (1H, dd, $J=2.8$, 1.2), 7.59 (1H, dd, $J=5.0$, 3.0), 7.54 (3H, m), 7.24 (1H, d, $J=8.2$), 4.87 (1H, br m), 4.63 (1H, d, $J=16.3$), 4.44 (1H, d, $J=16.3$), 3.59 (3H, s), 3.18 (2H, m), 1.46 (9H, s); ^{13}C NMR (DMSO, 353 K) δ 171.2, 153.5, 140.8, 133.5, 132.3, 126.4, 126.1, 125.7, 125.1, 124.0, 120.2, 79.4, 54.0, 51.4, 43.4, 30.4, 27.6; m/z 374; HRMS calcd for $C_{20}H_{24}NO_4S$: 374.1426. Found: 374.1428. Anal. calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.46; H, 6.19; N, 3.82%.
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