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Synthesis of novel cyclic α-amino acid derivatives via a one-pot sequential Petasis reaction/palladium catalysed process

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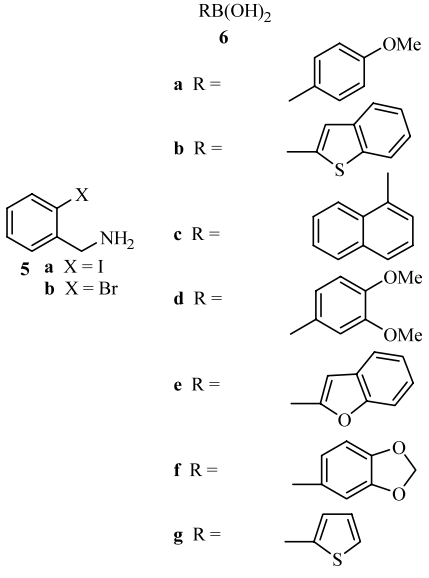
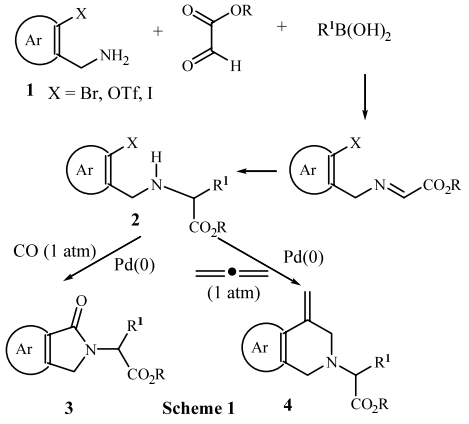
Abstract—A novel one pot Petasis reaction/palladium catalysed process is described involving 2-iodo/bromo benzylamine, ethyl glyoxalate and aryl/heteroaryl boronic acids. The in situ generated carbinolamine/imine undergoes the Petasis reaction to afford **2** which reacts with carbon monoxide or allene (1 atm) in the presence of Pd(0) to generate acyl palladium or π-allyl palladium species which are intercepted intramolecularly by the proximal secondary amine to afford isoindolone/4-methylene-3,4-dihydroisoquinoline α-amino acid derivatives in good yield.

In recent years there has been an increasing interest in new methods that access novel non-proteinogenic α-amino acid derivatives. The latter are attractive building blocks in combinatorial chemistry and drug discovery.[1] Although many routes to amino acids have been developed, the Petasis reaction provides a concise and convergent approach that allows structure variability and facile incorporation of functional groups.[2,3]



Recently, allenes have become a useful building block in palladium catalysed processes.[4] We have demonstrated that carbon monoxide and allene are powerful relay switches in our palladium catalysed cyclisation/anion capture cascades.[5] As part of our ongoing interest in interfacing the latter processes, in a tactical combination with core reactions we have devised two sequential one-pot processes that furnish novel non-proteinogenic α-amino acid derivatives (Scheme 1). Compounds of type **1** react with glyoxalate esters and aryl/heteroaryl boronic acids to give secondary α-amino acid derivatives **2**. The level of molecular complexity inherent in **2** can be considerably increased by two Pd catalysed cascade processes (Scheme 1). In the first of these **2** undergoes a palladium catalysed carbonylation



Scheme 1.

Keywords: Petasis; palladium.

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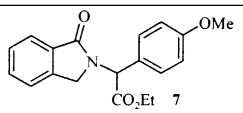
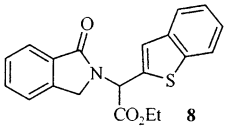
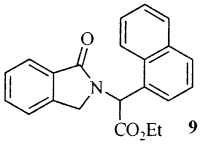
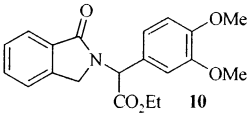
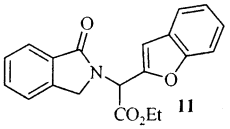
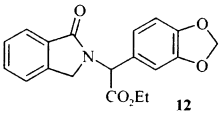
Table 1. Sequential Petasis reaction/palladium catalysed carbonylation/amination process[a]

Entry	Aryl iodide	Boronic Acid	Product	Yield (%)[b]
1	**5a**	**6a**	 **7**	60
2	**5a**	**6b**	 **8**	54
3	**5a**	**6c**	 **9**	56
4	**5a**	**6d**	 **10**	62
5	**5a**	**6e**	 **11**	59
6	**5a**	**6f**	 **12**	58

[a]All reactions were carried out in toluene, initially at 45–50°C for 24 h employing aryl iodide (1 mmol), ethyl glyoxalate (1 mmol) and boronic acid (1 mmol), followed by addition of carbon monoxide (1 atm), 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Cs_2CO_3 (2 mol eq) and heated at 90–100°C for 19–24 h.
[b]Isolated yields

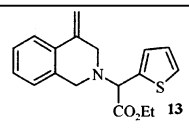
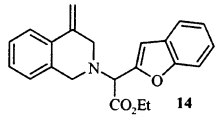
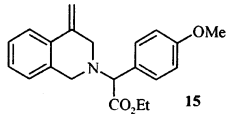
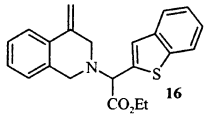
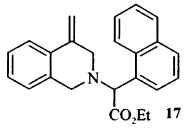
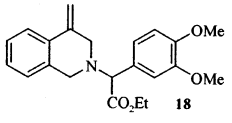
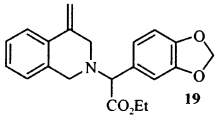
followed by intramolecular nucleophilic attack on the corresponding acyl palladium species to afford novel isoindolone α-amino acid derivatives **3** (Scheme 1).

We selected **5a**,**b** as the prototypical dual aryl halides/nucleophiles to evaluate this novel four component process. Thus **5a** (1 mmol), ethyl glyoxalate (1 mmol) and aryl/heteroaryl boronic acids **6a**–**f** (1 mmol) were reacted in toluene at 45–50°C for 24 h, followed by the addition of 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Cs_2CO_3 (2 mol equiv.) and carbon monoxide (1 atm). The mixture was stirred and heated at 90–100°C for 19–24 h to afford the isoindolone α-amino acid derivatives **7**–**12** in good yields (Table 1). Overall this sequential one-pot process combines four components in four steps and results in the formation of four new bonds, one ring and one stereocentre. The yields per bond formed are 86–89%.

Previously we have reported a one pot procedure for the synthesis of isoindolone α-amino acid derivatives using *o*-phthalaldehyde and natural α-amino acid esters,[6] and more recently described two catalytic processes for accessing simple[7] and complex isoindolones.[8]

Next we studied combination of the Petasis reaction with palladium catalysed reactions with allenes (Scheme 1). In this case **2** undergoes a palladium catalysed allenylation, followed by intramolecular nucleophilic attack on the corresponding π-allyl palladium species to afford novel 4-methylene-3,4-dihydroisoquinoline α-amino acid derivatives **4** (Scheme 1). Thus **5a**–**b** (1 mmol) reacted with ethyl glyoxalate (1 mmol) and aryl/heteroaryl boronic acids **6a**–**g** (1 mmol) in toluene at 45–50°C for 24 h followed by addition of allene (1 atm), 10 mol% $Pd(OAc)_2$, 20 mol% TFP, Et_4NCl

Table 2. Sequential Petasis reaction/palladium catalysed allenylation/amination process[a,b]

Entry	Aryl iodide	Boronic Acid	Product	Yield (%)[c]
1	**5b**	**6g**	 **13**	50[b]
2	**5b**	**6e**	 **14**	50[b]
3	**5a** **5b**	**6a**	 **15**	50[a] 61[b]
4	**5a** **5b**	**6b**	 **16**	53[a] 50[b]
5	**5a** **5b**	**6c**	 **17**	65[a] 72[b]
6	**5a** **5b**	**6d**	 **18**	49[a] 53[b]
7	**5a** **5b**	**6f**	 **19**	55[a] 46[b]

[a] All reactions were carried out in toluene, initially at 45–50°C for 24 h employing aryl iodide (1 mmol), ethyl glyoxalate (1 mmol) and boronic acid (1 mmol), followed by addition of allene (1 atm), 10 mol% $Pd(OAc)_2$, 20 mol% TFP, Et_4NCl (1 mol eq), Cs_2CO_3 (2 mol eq) heated at 90–100°C for 19 h.
[b]Catalyst system consisted of 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-Tol)$_3$, K_2CO_3 (1.5 mol eq) in toluene at 130°C for 24 h.
[c]Isolated yields

(1 mol equiv.) and Cs_2CO_3 (2 mol equiv.). The resulting mixture was heated at 90–100°C for 19 h affording 4-methylene-3,4-dihydroisoquinoline α-amino acid derivatives **13**–**19** in yields which equate to 83–92% per bond formed (Table 2). When **5b** was employed as an aryl iodide, a modified catalyst system consisting of 10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-Tol)$_3$ and K_2CO_3 (1.5 mol equiv.) in toluene at 135°C was used (Table 2). This sequential one-pot process combines four components in four steps and results in the formation of four new bonds, one ring and one stereocentre. Recently we have reported related palladium catalysed cascade processes which afford 4-methylene-3,4-dihydroisoquinoline derivatives in good yields.[9,10]

In conclusion we have demonstrated two novel four component processes which combine the Petasis reaction with palladium catalysed processes forming four new bonds (83–92% per new bond), one ring and one stereocentre in good yields. These processes result in a considerable increase in molecular complexity.

Acknowledgements

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