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Multipin solid-phase synthesis of biaryls via Suzuki cross coupling reaction of aryltriflates

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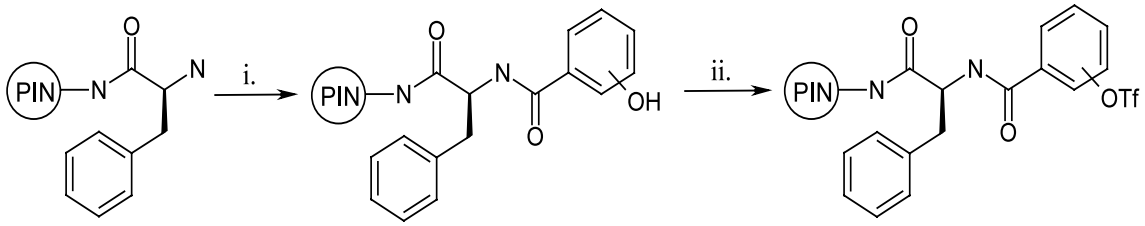
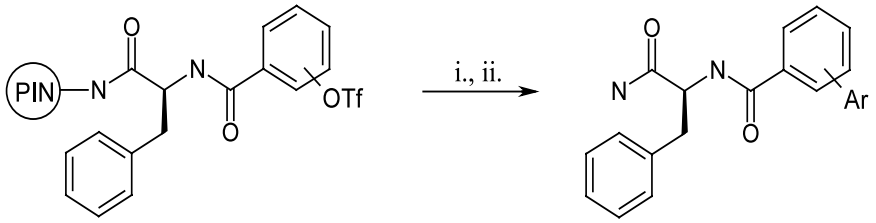
Abstract—We have developed a general method for the triflation of phenols on Multipin solid supports followed by Suzuki cross coupling reaction with aryl boronic acids. This methodology was extended to the arylation of thyrosine containing peptides.

Solid-phase synthesis is increasingly employed as a useful method for the generation of diverse compound libraries within the hit and lead generation process.[1] In recent publications an increasing number of solution-phase methodologies were transferred successfully to the solid phase.[2] Most polymers used for solid-phase synthesis are based on cross-linked polystyrene beads originating from peptide and oligonucleotide chemistry.[3] An alternative approach to the bead-based polymer supports is the Multipin technology. Here, fixed polymer crowns are used in a 96-well plate format for the synthesis of single compound collections. Although the Multipin technology is well established in peptide synthesis[4] only a few articles relate to the synthesis of small molecule libraries.[5] Herein we report a general procedure for the triflation of phenols (Scheme 1) and subsequent Suzuki cross coupling reaction[6] (Scheme 2) on Multipin crowns.



1 **3a, b** **5a, b**

Scheme 1. *Reagents*: (i) 3-, 4-Hydroxybenzoic acid (**2**), TBTU, NMM, DMF; (ii) $PhNTf_2$ (**4**), DIPEA, DCM.



5a, b **8a-m**

Scheme 2. *Reagents*: (i) $ArB(OH)_2$ (**6**), K_3PO_4, KBr, $Pd(PPh_3)_4$ (**7**), dioxane/H_2O (1:1); (ii) TFA.

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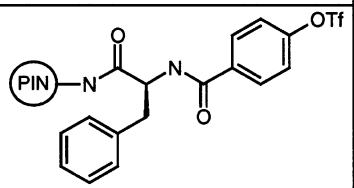
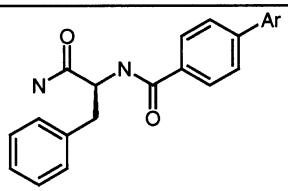
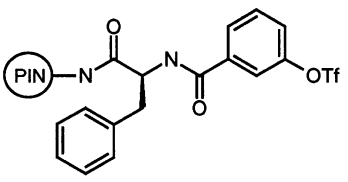
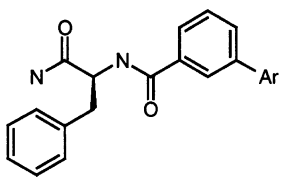
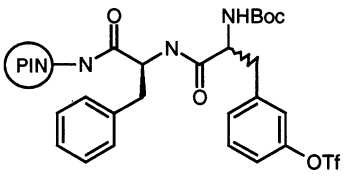
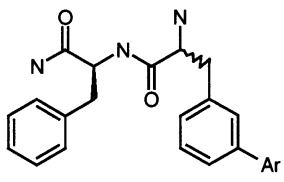
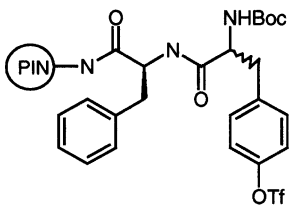
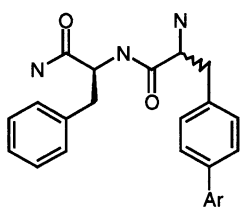
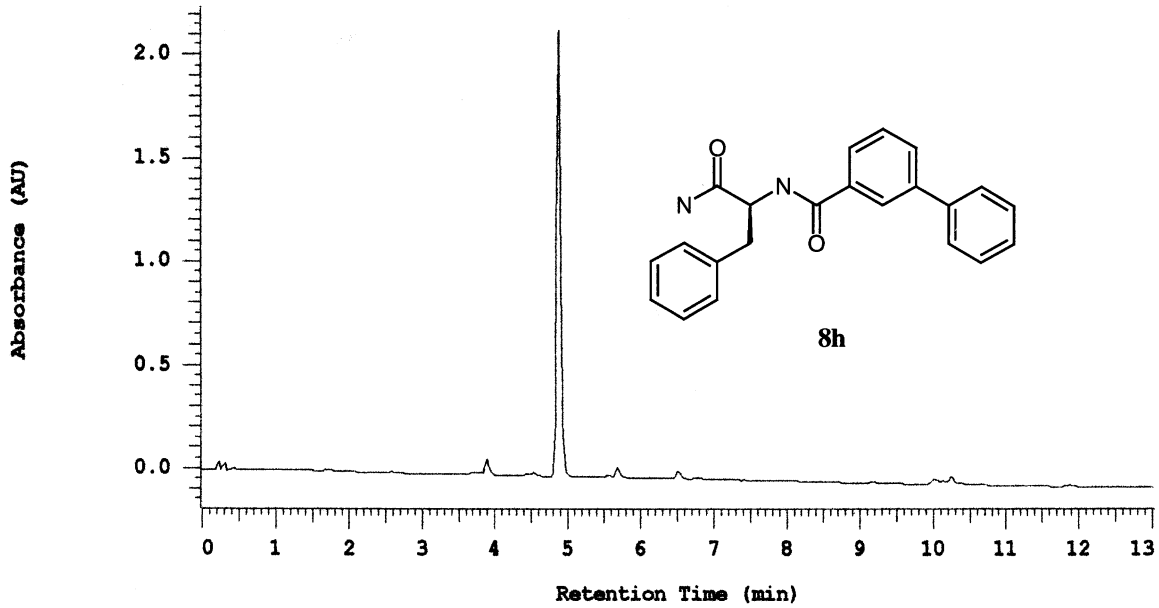
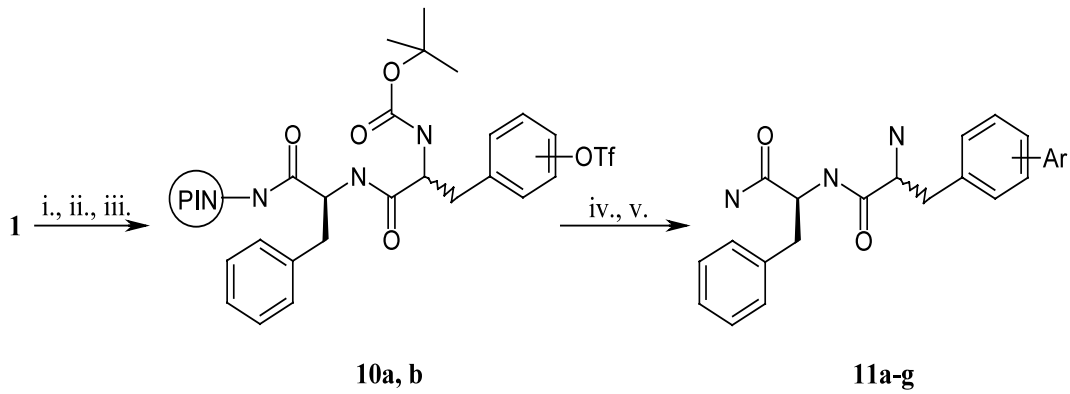
Starting from Rink-MA/DMA polyethylene grafted crowns,[7,8] FmocPheOH was immobilized under standard conditions.[4] Fmoc-deprotection gave resin **1** (20% piperidine/DMF; 30 min). The coupling of **1** with either 3- or 4-hydroxybenzoic acid was performed using TBTU[4] as the activating agent. Completion of the reaction was monitored by the Ninhydrin test. The coupling of 2-hydroxybenzoic acid using different coupling reagents such as TBTU, PyBOP, HATU and DIC[9] resulted in incomplete conversion and low

Table 1. Purity determined by HPLC analysis (RP-18), CH_3CN/H_2O, 0.1% TFA, UV-det. at 220 nm[a]

Entry	Triflate	$ArB(OH)_2$ (6)	Product	Purity (%)[a]	ESMS $[M+1]^+$ found
					
1	5a	Ph	Ph **8a**	87	345.2
2	5a	4-Me-Ph	4-Me-Ph **8b**	89	359.4
3	5a	3-MeO-Ph	3-MeO-Ph **8c**	94	375.4
4	5a	4-F-Ph	4-F-Ph **8d**	88	363.2
5	5a	3-F_3C-Ph	3-F_3C-Ph **8e**	90	413.2
6	5a	2-Napht.	2-Napht. **8f**	81	395.2
7	5a	3-NO_2-Ph	3-NO_2-Ph **8g**	79	390.1
					
8	5b	Ph	Ph **8h**	89	345.2
9	5b	4-Me-Ph	4-Me-Ph **8i**	76	359.3
10	5b	3-MeO-Ph	3-MeO-Ph **8j**	89	375.3
11	5b	4-Cl-Ph	4-Cl-Ph **8k**	69	379.1
12	5b	4-F-Ph	4-F-Ph **8l**	85	363.2
13	5b	3-NO_2-Ph	3-NO_2-Ph **8m**	84	390.1
					
14	10a	Ph	Ph **11a**	78	388.3
15	10a	3-MeO-Ph	3-MeO-Ph **11b**	89	418.2
16	10a	4-F-Ph	4-F-Ph **11c**	88	406.2
17	10a	3-F_3C-Ph	3-F_3C-Ph **11d**	90	406.3
					
18	10b	Ph	Ph **11e**	77	388.3
19	10b	3-MeO-Ph	3-MeO-Ph **11f**	80	418.2
20	10b	4-F-Ph	4-F-Ph **11g**	83	406.3



Scheme 3. HPLC chromatogram of crude product **8h** (89%).



Scheme 4. *Reagents and conditions*: (i) **9a** or **9b**, TBTU, NMM, DMF; (ii) $Pd(PPh_3)_4$, morpholine, DCM; (iii) $PhNTf_2$, DIPEA, DCM; (iv) $ArB(OH)_2$, $Pd(PPh_3)_4$, KBr, K_3PO_4, dioxane/H_2O, 90°C; (v) 20% TFA, DCM/MeOH (9:1).

product purity (40–60% by RP-HPLC). Final triflation of *meta*- and *para*-hydroxybenzamide **3a**,**b** with a 2 M solution of $PhNTf_2$ **4** and DIPEA in DCM for 16 h yielded triflates **5a** and **b** in high purity (91 and 92%) as determined by HPLC after cleavage.[10] Unsatisfactory results were observed for lower concentrations (0.1–1.0 M solution) even after 2 days.

Preliminary results for the Suzuki cross coupling reaction on Multipin crowns using $Pd(PPh_3)_4$ **7** and K_3PO_4 as a base, indicated that the presence of KBr is essential to suppress triflate reduction by stabilizing the cationic (σ-aryl)-palladium transition state.[11] Omitting KBr from the reaction, triflate decomposition becomes predominant. Besides the desired product, reduction and deprotection of the triflate is observed (up to 60%). With optimized reaction conditions in hand further examples were examined (Table 1, entries 1–13).[13] The crude products **8a**–**8m** were obtained in reasonable to high purity (69–94%, Table 1, Scheme 3). Compound characterization was carried out using mass spectrometry.

Finally, the reaction protocol was further applied to the derivatization of Tyr-containing peptides. Therefore racemic *m*- or *p*-BocNTyr(Allyl)OH **9a**,**b** was coupled under standard conditions to **1**.[4] Allylether cleavage[12] and subsequent triflation of the liberated phenol led to compounds **10a**,**b**. Additional Pd(0)-catalyzed Suzuki cross coupling gave the corresponding products **11a**–**g** (see Table 1, entries 14–20, Scheme 4). In conclusion, a general procedure for allylether cleavage, triflation of phenols and subsequent Suzuki cross coupling of the intermediates on Multipin solid supports is shown. The addition of KBr and a large excess of aryl boronic acids turned out to be essential for complete conversion of the triflated intermediate. The final crude products were obtained in high purity after multi step reactions.

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10. *General procedure for phenol triflation*: The pre-loaded Multipin crowns were placed in a 50 mL flask and a 2 M solution of $PhNTf_2$ **4** and 2 M DIPEA in DCM were added. After 16 h the crowns were washed† with DMF, MeOH, THF, DCM (3×each) and dried under vacuum for 4 h. After TFA cleavage the products **5a**, **5b** were obtained in high purity (91 and 92% HPLC: 220 nm, MS: calcd: 416.4; found: MH^+ 417.2 (**6a**) and MH^+ 417.3 (**6b**)).
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12. *General procedure for allyl-deprotection of phenols*: A solution of 0.02 M $Pd(PPh_3)_4$ **7** (2 mL) and 0.2 M morpholine in DCM was added to the Multipin crowns for 2 h. He crowns were washed with dioxane, DMF, sodium diethyldithio-carbamate/DIPEA (1:1) in DMF (0.2 M), DMF, MeOH, THF, DCM (3×each) and the product cleaved with 20% TFA in DCM/MeOH (9:1) for 1 h.
13. *General procedure for Suzuki cross coupling of aryl triflates*: In a reaction tube with septum was placed a single Multipin crown (1.5 μmol) and the aryl boronic acid (150 μmol). After purging with argon 500 μl of a 2 μM $Pd(PPh_3)_4$ solution in dioxane, 125 μL of an aqueous 2 M K_3PO_4 solution, and 125 μL of an aqueous 2 M KBr solution were added. All solvents were degassed prior to use. The reaction was performed at 90°C for 16 h. After washing with dioxane, DMF, sodium diethyldithio-carbamate/DIPEA (1:1) in DMF (0.2 M), DMF, MeOH, THF, DCM (3×each), the crowns were dried under vacuum for 6 h. After cleavage (20% TFA in DCM/MeOH (9:1) for 1 h) and evaporation of the solvent the crude product was analyzed by HPLC and ES/MS (see Table 1).

† All washing steps were performed under sonication.