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The Stille Cross Coupling Reactions on Solid Support. Link to Solution Phase Directed *ortho* Metalation. An Ester Linker Approach to Styryl, Biaryl and Heterobiaryl Carboxylic Acids

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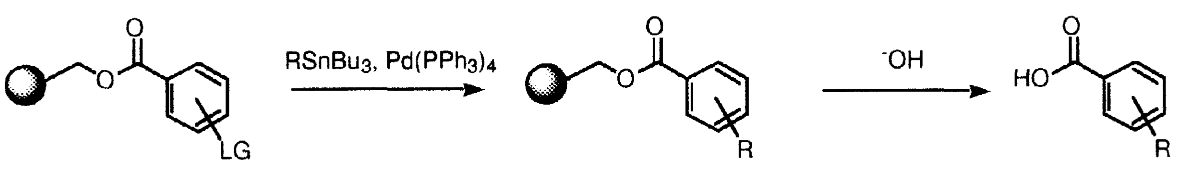
Abstract: The synthesis of the titled compounds by Stille cross coupling on Merrifield resin - linked halo benzoates with stannanes followed by LiOH hydrolysis is reported.

Combinatorial chemistry and high throughput screening constitute terms which have swiftly entered the vocabulary of chemists and have sparked a renaissance[1] in solid support-mediated synthetic method development. Although very much in its infancy, solid support (SS) synthesis is already making a powerful impact on the methodology and time-scale of all industrial drug discovery programs by allowing the rapid generation of large and diverse compound libraries. Considerable emphasis has been placed on the transition metal catalyzed cross coupling reaction, which is reflected in the intense activity to effect solution phase to SS translations.[2] Herein we report on an ester linker Stille cross coupling SS protocol for the generation of arrays of functionalized biaryl, heterobiaryl and styryl derivatives (**Scheme 1**) and, in the accompanying Letter,[5] on a parallel Suzuki-Miyaura cross coupling based on acetal linker technology. In comparison to previous results,[2] these methods offer additional synthetic advantage and diversity in the derived products by links to Directed *ortho*-[3] and remote metalation[4] (DoM and DreM) tactics.



Scheme 1

Commercial Merrifield resin (1% cross linked, 1 mequiv Cl/g) was esterified with various bromo and iodo benzoic acids according to previously optimized conditions (3 equiv Cs_2CO_3/0.5 equiv KI/1.5 equiv benzoic acid/DMF/80 °C/16 h).[2b] Ester cleavage for the determination of the benzoic acid loading according to the described method (NaOMe/MeOH/THF)[2b] proved to be temperamental giving methyl benzoates contaminated with varying amounts of the corresponding acids presumably formed by hydroxide hydrolysis due to the retention of water within the polymer structure. With the aim of providing a SS method which produces pure materials suitable for direct bioscreening regimens, other conditions were tested. After considerable experimentation, hydrolysis to the benzoic acids using LiOH/H_2O/MeOH/THF was found to give highest yields and reproducible reactions.[6]

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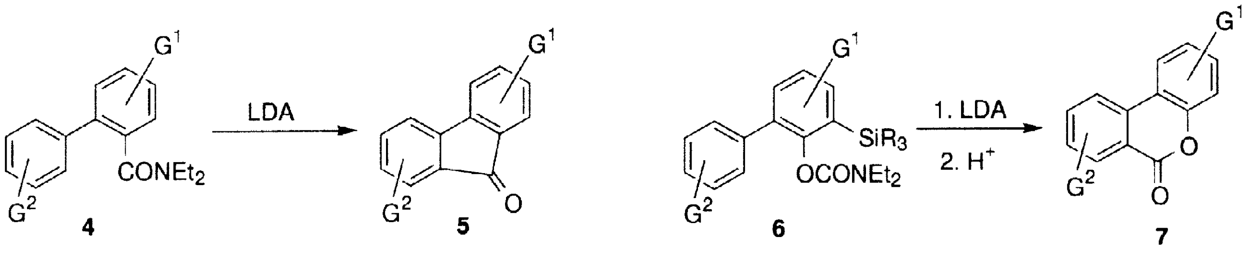
Stille cross coupling reactions of aryl and vinyl stannanes with a range of SS - attached halo benzoic acids **1** were carried out in DMF under argon using excess stannanes and $Pd(PPh_3)_4$ catalysis.[7] As gleaned from the **Table**, in the absence of steric influences, good yields and purities of biaryl, heterobiaryl and styryl carboxylic acids were obtained. In 2-substituted cases (entries 1 and 2), longer LiOH hydrolysis times were necessary to achieve good yields of the *ortho*-coupled derivatives, presumably owing to steric effects and/or to the alteration of the resin by *ortho*-substitution which obstructs penetration of hydroxide. In contrast to solution phase reactions, no general trends of ArI > ArBr higher yield and rate effects were observed. Heterocyclic bromides (entries 19-22) were loaded and cross coupled successfully although, in general, longer reaction times were required. A similar trend was observed with stannanes prepared *via* D*o*M[3] (entries 17 and 18) to give products in excellent purities. Attempts to cross couple SS-4-bromocinnamates under the standard conditions led to complex mixtures, which were deemed to be of little synthetic utility.

To improve the scope of the methodology, cross coupling reactions of SS-arylstannanes prepared from **1** (LG = I) by treatment with $((Bu_3)Sn-)_2$ under $Pd(PPh_3)_4$ catalysis[8] with iodobenzene and bromobenzene under $Pd(PPh_3)_4$ (10 mol %) catalysis was carried out. The results (35-74% purities of biaryl products) indicate that synthetic utility is compromised by inversion of the cross coupling partners although the comparison is inappropriate since two cross coupling reactions are involved in this sequence.

Aside from the well known lithiation-stannylation sequence to obtain the stannylated aryl and, especially, heteroaryl cross coupling partners (e.g. entries 7, 8), the methodology establishes a SS - Stille - D*o*M link (entries 17, 18). The derived products **4** and **6** are candidates for solution phase DreM reactions leading to fluorenones **5** and dibenzopyranones **7** respectively as already reported.[4]



Scheme 2

In conclusion, Stille cross coupling reactions on solid support using an ester linker have been achieved leading to biaryl, heterobiaryl, and styryl carboxylic acids in high yields and purities. Furthermore, connection of this process to D*o*M and DreM is indicated. The application of this methodology to diverse library synthesis may be anticipated.[9]

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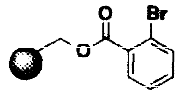
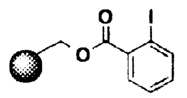
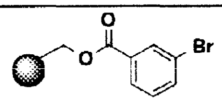
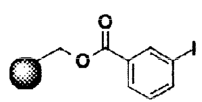
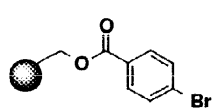
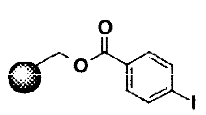
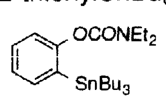
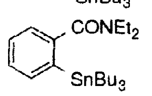
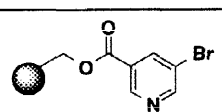
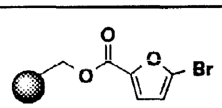
Table. Synthesis of Benzoic Acids **3** by Stille Solid Support Cross Coupling Reactions

Entries	Starting Polymer	X-Coupling Partner	Reaction time (h)[a] X-Coupling	Reaction time (h)[a] Cleavage	Reaction Composition (%)[b] Product 3	Reaction Composition (%)[b] SM	Yield (%)[c]
1		Ph-$SnBu_3$	24	42	94	4	>95
2		Ph-$SnBu_3$	24	42	90	7	88
3		$H_2C{=}CH$-$SnBu_3$	24	18	84[d]	11	71
4		Ph-$SnBu_3$	24	18	95	4	94
5		Ph-$SnBu_3$	24	18	96	0	91
6		$H_2C{=}CH$-$SnBu_3$	24	18	96	0	87
7		2-furyl$SnBu_3$	24	18	96	0	86
8		2-thienyl$SnBu_3$	24	18	98	0	89
9		Ph-$SnBu_3$	24	18	93[d]	0	93
10		$H_2C{=}CH$-$SnBu_3$	24	18	96	0	88
11		2-furyl$SnBu_3$	24	18	96	0	84
12		2-thienyl$SnBu_3$	24	18	98	0	91
13		Ph-$SnBu_3$	24	18	97	0	>95
14		$H_2C{=}CH$-$SnBu_3$	24	18	98	0	>95
15		2-furyl$SnBu_3$	24	18	86	0	80
16		2-thienyl$SnBu_3$	24	18	95	0	93
17			48	18	95	0	78
18			48	18	95	0	80
19		Ph-$SnBu_3$	48	18	96	1	-[f]
20		$H_2C{=}CH$-$SnBu_3$	48	18	48[d,e]	3	-[f]
21		Ph-$SnBu_3$	24	18	75[e]	2	-[f]
22		$H_2C{=}CH$-$SnBu_3$	48	18	68[d,e]	2	-[f]

[a] Optimized reaction time. [b] Reaction composition determined by HPLC and ^1H NMR. [c] Isolated yields after column chromatography. [d] $Pd_2(dba)_3$, $(2\text{-furyl})_3P$ used as catalyst. Yields were considerably lower when $Pd(PPh_3)_4$ was used. [e] Insignificant amounts (0-4%) of dehalo SM were obtained for all reactions with the exceptions of entries 20 (47%), 21 (15%) and 22 (11%). [f] Isolated yield not determined.

References and Footnotes

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6. The loadings of the halo-benzoic acids were approximatively 0.8 mequiv/g for each case.
7. *Typical Cross Coupling and Cleavage Procedure:* Resin **1** (0.15 g) was swollen in anhydrous DMF (5 mL) and the system was flushed with argon (30 min). $Pd(PPh_3)_4$ (0.05 equiv) was added and the reaction mixture was stirred (10 min). The stannane (3 equiv) was added and the mixture was stirred at 60 °C (24 h), cooled to rt, and treated with satd. NH_4Cl solution (5 mL) and stirred (10 min). The resin was removed by filtration (fritted glass funnel) and the filtrate was washed successively with DMF (5 mL), DMF:H_2O (1:1) (10 mL), 0.3 M HCl (10 mL), H_2O (15 mL), DMF (5 mL), EtOAc (10 mL), EtOAc:MeOH (1:1) (10 mL), MeOH (15 mL), and dried *in vacuo* (12 h). To cleave the product from the SS, the resin **3** was swollen in THF (2.5 mL) for 30 min, LiOH•H_2O (5 equiv) dissolved in MeOH:H_2O (2:1, 1.5 mL) was added, and the mixture was refluxed for 18 - 42 h. After cooling to rt, a solution of 1M HCl (3 mL) was added and the whole was stirred (10 min) and subjected to filtration (fritted glass funnel). The resin was successively washed with THF (30 mL), THF: 1M HCl (1:1, 30 mL), and Et_2O (30 mL) and the filtrate was repeatedly extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4) and evaporated to dryness to give the benzoic acid which was analyzed by HPLC and ^1H NMR. The extent of cleavage was established by monitoring the ester carbonyl absorption in the IR spectrum.
8. Sheppard, G.S.; Pireh, D.; Carrera, G.S.; Bures, M.G.; Heyman, R.H.; Steinman, D.; Davidsen, S.K.; Philips, J.G.; Guinn, D.E.; May, P.D.; Conway, R.G.; Rhein, D.A.; Calhoun, W.C.; Albert, D.H.; Magoc, T.J.; Carter, G.W.; Summers J.B. *J. Med. Chem* . **1994**, *37*, 2011.
9 All new compounds showed satisfactory spectroscopic (NMR, HRMS) and analytical data.