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# Formation of Carbon-Carbon Bond on Solid Support: Application of the Stille Reaction

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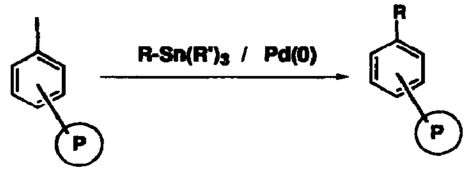
***Abstract :** Vinyl/Aryl stannanes couple smoothly with polymer bound aryl iodides . The cross-coupled products are obtained in excellent yield and purity after cleavage from the solid support.*

Generating molecular diversity (via combinatorial synthesis) for novel drug discovery is currently actively pursued in biotechnology and pharmaceutical industry.[1] Several methods have recently been developed for solid phase combinatorial synthesis of libraries of oligomers[2] as well as small organic molecules.[3] Screening of such libraries has produced compounds with high affinity towards a receptor or an enzyme of interest. However, it is only in areas of peptides and oligonucleotides that solid phase chemistry has been optimized. In our efforts to expand the scope of solid phase synthesis, well characterized homogeneous reactions were attempted on polymer-bound substrates. In this communication, application of the Stille reaction for efficient carbon-carbon bond formation on solid support is reported. Such a reaction has potential for generating non-oligomeric diversity, and is illustrated by coupling of polymer-bound aryl iodides with vinyl/aryl stannanes (equation 1)

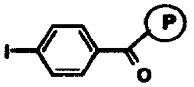
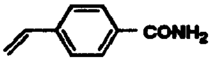
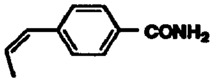
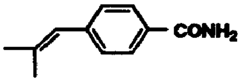
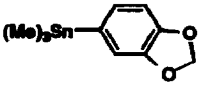
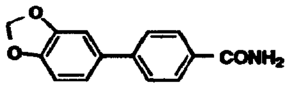
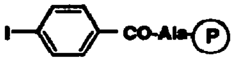
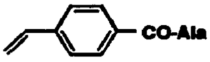
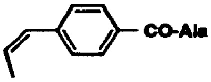


Eq. 1

Commercially available Fmoc-Rink amide resin[4] or Fmoc-Ala-Wang resin[5] was deprotected (20% piperidine/$CH_2Cl_2$) and coupled with 4-iodobenzoic acid (DCC/NMP; resin beads negative to Kaiser ninhydrin test). Polymer bound 4-iodobenzoic acid was subjected to Stille cross-coupling reactions using a variety of stannanes (Table). Typical protocol for the cross-coupling reaction is as follows: To a degassed suspension of polymer bound aryliodide in anhydrous NMP is added $Pd_2dba_3$ (5 mol%) and $AsPh_3$ (20 mol%). After 5 min the appropriate stannane is added and the reaction allowed to stand overnight at 45°. The reaction mixture is transferred to a fritted syringe and throughly washed with NMP; $CH_2Cl_2$; EtOH and $CH_2Cl_2$. The cross-coupled product is cleaved from the resin to yield the desired compounds in excellent yield and purity (Table). Under these conditions, difficult couplings with a hindered stannane (entry #3) and an aryl stannane (entry #5)[6] also proceed in good yield.

As seen from the table, formation of cross-coupled products in high yield indicates that oxidative addition of Pd(0) species to aryl iodide and subsequent transmetalation are efficient processes even in a heterogeneous reaction medium. Experiments to build a combinatorial library using above mentioned reaction, as well as generation of molecular diversity using variety of coupling partners (e.g. vinyl triflate and vinyl/aryl stannane) are in progress and will be reported in due course.

**Table. Coupling of polymer bound aryl iodide to vinyl/aryl stannanes**

| Entry | Aryl Iodide | Stannane | Product[c] | Yield[d] |
|---|---|---|---|---|
| 1.[a] |  |  |  | 89 |
| 2. | |  |  | 91 |
| 3. | |  |  | 85 |
| 4. | |  |  | 89 |
| 5. | |  |  | 90 |
| 6.[b] |  |  |  | 92 |
| 7. | |  |  | 88 |

a. Polymer = Rink amide resin; product cleaved from the resin with 5% TFA/$CH_2Cl_2$ b. Polymer = Wang resin; Ala = alanine; product cleaved from the resin with 90% TFA. c. All products gave satisfactory analytical data, and had purity >90% by HPLC. d. yields based on incorporation of 4-iodobenzoic acid on to the resin.

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