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HECK REACTIONS IN SOLID PHASE SYNTHESIS

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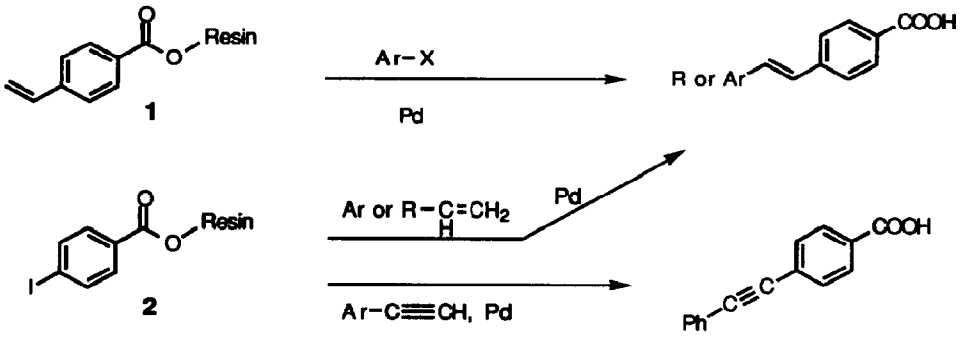
Abstract: Heck reactions of polymer bound aryl iodide (1) or styrene (2) with olefins or aryl halides generally gave good yields of products of high purity. The methodology developed can be applied as a convenient procedure for generating 1,2-disubstituted olefins in combinatorial chemical libraries.

Screening of natural products and compound databases is one of the major strategies for identifying leads against novel biological targets.[1] A new paradigm in drug discovery in the form of combinatorial organic synthesis is now evolving, which presents the synthetic chemist an opportunity for creating large and structurally diverse databases.[2] Combinatorial chemistry techniques combined with sophisticated automation and high throughput screening have the potential to significantly accelerate the process of drug discovery. Initial work in combinatorial chemistry was limited to the preparation of libraries of peptides, oligonucleotides and other biopolymers which have disadvantages of *in vivo* instability and/or poor bioavailability. Recently, this technology has been extended to combine solid phase synthesis and general organic reactions to prepare chemical libraries of diverse functionalities beyond traditional biopolymers. This new approach can not only generate chemical libraries for random screening, but also enables the medicinal chemist to design series of structurally related compounds for structure-activity relationship (SAR) studies.[3] For solid phase chemistry to be useful in generating non-oligomeric diversity, the repertoire of reactions that can be reliably carried out on solid support has to be increased. Herein we report our investigation of Heck reactions in solid phase synthesis.

The Heck reaction[4] is a very useful process for preparing disubstituted olefins which commonly exist in organic compounds. The reaction involves palladium catalyzed carbon-carbon bond formation between an aryl halide and a vinyl functionality. The Heck reaction is generally very mild, and does not require strict anhydrous or inert atmosphere conditions which makes it easily amenable to automation. Intrigued by the potential use of Heck reaction in combinatorial chemistry, we have investigated the Heck reaction on solid support.

4-Vinylbenzoic acid or 4-iodobenzoic acid were attached to commercially available Wang resin[5] using dicyclohexylcarbodiimide and 4-N,N-dimethylaminopyridine (DMAP) in DMF at

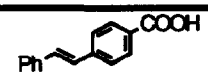
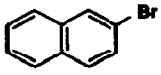
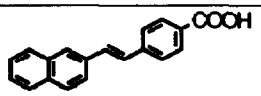
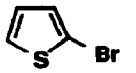
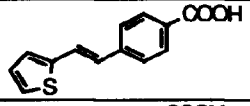
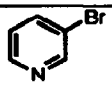
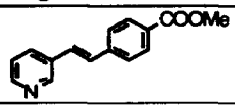
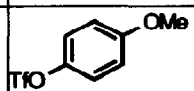
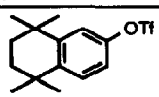
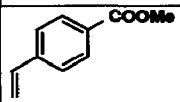
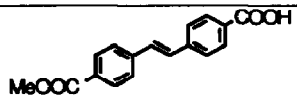
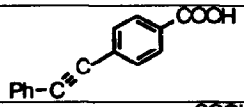
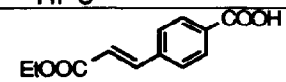
60°C. Reactions were performed by reacting resins 1 or 2 with aryl halides/triflates or olefins/phenylacetylene, respectively, under the conditions described in the table. The resulting mixture was filtered, and the resins were thoroughly washed with ethanol and methylene chloride to remove impurities. The resins were dried in vacuum, and then treated with 90% trifluoroacetic acid in methylene chloride (room temparature, 1 h). The mixture was filtered, and the resins were thoroughly washed with ethanol and methylene chloride. The filtrate was evaporated, and the residue was dried under vacuum, analyzed by NMR spectroscopy.



Couplings between aromatic iodides and olefins proceeded smoothly in presence of $Pd(OAc)_2$ (entries 1, and 7-9). However, under similar conditions, 4-vinylbenzoic acid was recovered unreacted and required the presence of P(2-Tol)3 as a ligand to effect coupling with aromatic bromides (entries 2-4). These results are consistent with the reactivity differences observed for homogeneous couplings of aromatic iodides and bromides with olefins.[4a] The observation that reactions between polymer bound aromatic halides and olefins (entries 7-9) gave comparable results to reactions between polymer bound olefins and aromatic halides (entries 1-4) demonstrates the versatility of solid phase Heck reactions. No reaction occurred for triflates (entries 5 and 6) in the presence of $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, or $Pd_2(dba)_3$-P(2-Tol)3 due to the low reactivity of the olefin towards the triflates.[6] Reaction of 2 and highly activated ethyl propionate (entry 10) gave a mixture of polymerized products. It is noteworthy that attempts to release the resin-bound products by transesterification with $MeOH/Et_3N$[7] were unsuccessful.

In summary, we have demonstrated that solid phase Heck reactions between aryl iodides and olefins provide products in satisfactory yields and purity. The results from this study suggest that Heck reaction may be applied as a convenient procedure for vinylation or acetylenylation of aryl/vinyl halides in generating combinatorial chemical libraries.

TABLE.

Entry	X-resin	Reactant	Reaction Conditions[a]	Product	Yield[b]
1	1	Ph-I	A		81%
2	1		A B		NR 64%
3	1		B		76%
4	1		A B		NR 87%[c]
5	1		A B	--	NR NR
6	1		A B	--	NR NR
7	2		A		90%
8	2	Ph-C≡CH	B		90%
9	2		A		91%
10	2	HC≡C-COOEt	A B	--	*d*

a. Conditions: resin **1** or **2** (200 mg), the reactant (100 mg), Et_3N (50 μL) in 3 mL of DMF. A: $Pd(OAc)_2$ (20 mg), n-Bu_4NCl (20 mg), 80-90 °C, 16 h; B: $Pd_2(dba)_3$ (30 mg), $P(2\text{-Tol})_3$ (20 mg), 100 °C, 20 h.

b. The product was identified by ^1H NMR and mass spectroscopy. The purity is greater than 90% as measured by ^1H-NMR / HPLC. The yield of the reaction was based on the recovery of 4-vinylbenzoic acid and 4-iodo benzoic acid after treatment of 200 mg of **1** and **2**, respectively, with 90% TFA/CH_2Cl_2. NR = no reaction.

c. Product was treated with HCl/MeOH and purified by chromatography to provide the methyl ester.

d. A mixture of products was obtained.

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References:

1. Drug Discovery & Development. M. Williams and J. B. Malick, Ed. Humana Press, New Jersey, 1987.

2. a) Alper, J. *Science*, **1994**, *264*, 1399. b) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fordor, S. P. A. and Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1232. c) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fordor, S. P. A. and Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1386. d) Pavia, M. R.; Sawyer, T. K. and Moos, W. H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 387.

3. a) Deshpande, M.S. *Tetrahedron Lett.* **1994**, 35, 5613. b) Chen, C.; Ahberg Randall, L. A.; Miller, R. B.; Jones, A. D. and Kurth, M. J. *J. Am. Chem. Soc.* **1994**,*116*, 2661. c) Bunin, B. A. and Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997. d) Dewitt, S.; Kiely, J.; Stankovich, M.; Schroeder, D.; Cody, D.; Pavia, M. *Proc. Natl. Acad. Sci. USA*, **1993**, *90*, 6909.

4. a) Heck, R. F. *Org. React.* **1982**, *27*, 345. b) Heck, R. F. in Comprehensive Organic Synthesis, Trost, B. M. and Fleming, I. Ed. Pergamon Press, New York, 1991, Vol. 4, pp 833.

5. Wang, S. *J. Am. Chem. Soc.*. **1973**, *95*, 1328.

6. Scott, W. J.; Pena, M. R.; Sward, K.; Stoessel, S. J. and Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302.

7. Lyle, T.; Brady, S.; Ciccarone, T.; Colton, C.; Paleveda, W.; Veber, D. and Nutt, R. *J. Org. Chem.* **1987**, *52*, 3752.

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