Pd- Mediated C-C Bond Formation with Olefins and Acetylenes on Solid Support: A Scope and Limitations Study

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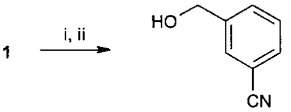
Abstract. In this paper we report the scope and limitations of Pd(0)-mediated coupling reactions between aromatic iodides linked to a polystyrene resin and terminal acetylenes and olefins (*Heck* reactions). Optimized reaction conditions were evaluated with a number of different reagents. The optimized reaction conditions were frequently found to be superior to those previously reported in the literature and resulted in excellent yields of the products upon cleavage from the solid phase.

In the preceding paper we reported the Pd(0)-mediated coupling reactions between aromatic halides linked to a polystyrene resin and boronic acid derivatives (*Suzuki* coupling), aromatic and vinylic tin compounds (*Stille* coupling), as well as thiols.[1] Here we disclose further efforts in optimizing Pd-mediated coupling reactions between resin bound aromatic iodides and terminal acetylenes and olefins. The structures of the polymer linked substrates were identical to those reported previously and are recalled in Figure 1.[1] All reactions reported here were performed on a scale (typically 150-200 mg beads; 0.7 mmol/g) allowing the isolation of at least 20 mg crude product. Yields, therefore, refer to the weight of the crude products corrected by the purity evaluated by ^{1}H NMR (400 MHz). In some cases, weight of products purified by flash chromatography are reported in parentheses. Analysis of the crude products was performed by ^{1}H NMR and mass spectroscopy, as previously described.

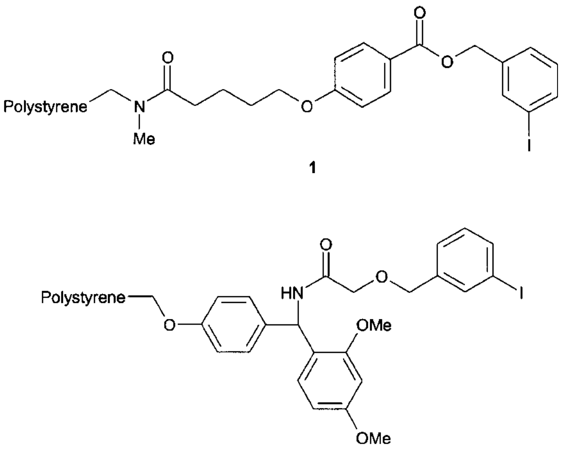
Coupling with terminal acetylenes. A powerful reaction for combinatorial chemistry is the coupling of aromatic iodides with terminal acetylenes.[2] Surprisingly, only limited examples on solid phase have been so far reported in the literature.[3] We found reaction conditions involving the use of $PdCl_2(Ph_3P)_2$ as a catalyst most favorable (Table 1 and 2). Under those reaction conditions, products were formed in good to excellent yields. In some examples, the use of double amount of reagents (entries 2, 4, Table 2) or double couplings (entries 6, 8, 12, 14, table 2) was required to push the reactions towards completion.[4] Noteworthy are the mild reaction conditions, requiring only temperatures of 25→50°C. Many functional groups are compatible with these reaction conditions and do not need to be protected. Nevertheless, we found the coupling involving propargyl amine ineffective, while the corresponding BOC protected substrate (entry 7, Table 1) gave excellent results.[5]

Coupling with cyanide. We have also demonstrated that KCN can be used efficiently in Pd-mediated couplings on solid support. The nitrile **3** (scheme 1) was obtained in 86% yield upon base mediated cleavage from the solid phase.[6]



3

Scheme 1. i: 6eq. KCN, 0.2eq. Pd_2dba_3, 0.8eq. dppf, N-methylpyrrolidone, 60°C, 24h; ii. 6eq. NaOMe, MeOH:dioxane (1:4), RT, 24h, 86% (no iodide detected)

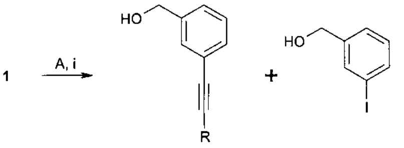


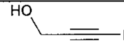
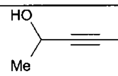
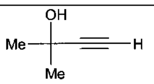
1

2

Figure 1. Polymer bound aromatic iodides

Table 1. Couplings with terminal acetylenes and base labile linker



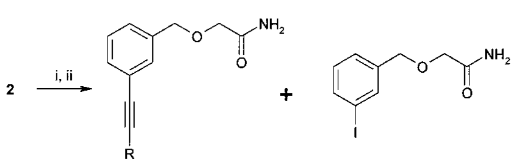
Entry	R—≡—H	Yields (%)[a)]	Recovered Ar-I (%)
1	^{t}Bu—≡—H	95 (77)	0
2		93	0
3		95	0
4	nC_4H_9—≡—H	95	0
5	Ph—≡—H	95	0
6		95	0
7		96	0

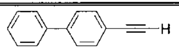
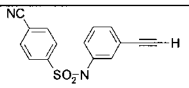
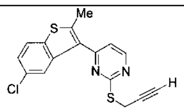
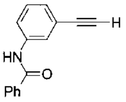
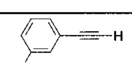
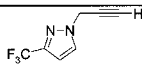
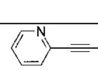
a) yields in parentheses are yields of isolated product after purification.

Reaction conditions: A: 4eq. R-≡-H, 0.1eq. $PdCl_2(Ph_3P)_2$, 0.2eq. CuI, Et_3N : dioxane (1:2), RT, 24h.
i: 6eq. NaOMe, MeOH : dioxane (1:4), RT, 24h

Heck reactions. Conditions had to be carefully optimized in order to achieve complete conversions in the *Heck* reaction on solid phase.[7,8] $Pd(OAc)_2$ was by far the best catalyst for this reaction and $n$$Bu_4NCl$ as additive was essential. As much as 2 eq. of $n$$Bu_4NCl$ were required to achieve complete conversion of the starting material. Although the use of organic bases (such as $i$$Pr_2NEt$) gave good results in control experiments performed in solution, incomplete conversion was obtained when these reaction conditions were applied to the solid phase (entries 1, 2, Table 3). The use of the inorganic base NaOAc gave much superior

Table 2. Couplings with terminal acetylenes and *Rink* linker

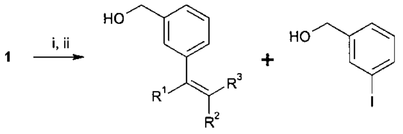


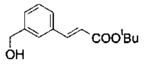
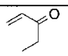
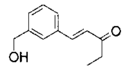
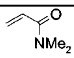
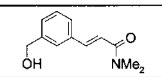
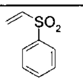
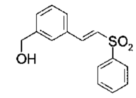
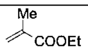
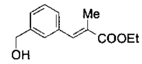
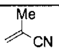
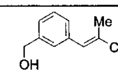
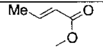
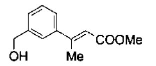
Entry	R—≡—H	Reaction Conditions i	Yields (%)[a)]	Recovered Ar-I (%)
1		A	52	38
2		B	79	11
3		A	36	49
4		B	91	5
5		C	71	11
6		D	91 (43)	5
7		C	67	20
8		D	95 (69)	0
9		C	84	6
10		D	83 (91)	2
11		C	76	16
12		D	80	38
13		C	81	14
14		D	95 (98)	0

a) yields in parentheses are yields of isolated product after purification.

Reaction conditions: i: A: 4eq. R-≡-H, 0.1eq. $PdCl_2(Ph_3P)_2$, 0.2eq. CuI, Et_3N : dioxane (1:2), RT, 24h. B: 8eq. R-≡-H, 0.2eq. $PdCl_2(Ph_3P)_2$, 0.4eq. CuI, Et_3N : dioxane (1:2), RT, 24h. C: 4eq. R-≡-H, 0.1eq. $PdCl_2(Ph_3P)_2$, 0.2eq. CuI, iPr_2EtN : dioxane (1:2), 50°C, 24h. D: 4eq. R-≡-H, 0.1eq. $PdCl_2(Ph_3P)_2$, 0.2eq. CuI, iPr_2EtN : dioxane (1:2), 50°C, 24h, double coupling.
ii: $CF_3COOH:CH_2Cl_2$ (1:4), RT, 5 min

Table 3. Couplings with olefins and base labile linker



Entry	Olefin	Reaction Conditions i	Product	Yields (%)[a),b)]	Recovered Ar-I (%)
1		A		54 (82) (E:Z=93:7)	46
2		B		95 (90)	5
3		C		77 (69)	23
4		D		94 (87)	6
5		E		96 (90) (E only)	0
6		F		90 (E only)	0
7		F		92 (E only)	0
8		F		96 (E only)	0
9		F		88 (68) (Z(E):E(Z)= 1:7)	0
10		F		50 (Z:E=1:1)	0
11		F		48 (E(Z) only)	0

a) yields in parentheses are yields of isolated product after purification.
b) only minor amounts (<10%) of MeONa/MeOH addition products on the C=C double bond were observed in a few cases after cleavage from the resin.

Reaction conditions: i: A: 6eq. olefin, 3eq. $iProp_2NEt$, 1eq. Bu_4NCl, 0.2eq. $Pd(OAc)_2$, dioxane, 0.05M, 100°C, 24h. B: 6eq. olefin, 3eq. $iProp_2NEt$, 1eq. Bu_4NCl, 0.2eq. $Pd(OAc)_2$, DMA, 0.05M, 100°C, 24h. C: 6eq. olefin, 3eq.K_2CO_3, 1eq. Bu_4NCl, 0.2eq. $Pd(OAc)_2$, DMA:H_2O (3:1), 0.05M, 100°C, 24h. D: 6eq. olefin, 3eq. Na_2CO_3, 1eq. Bu_4NCl, 0.2eq. $Pd(OAc)_2$, DMA, 0.05M, 100°C, 24h. E: 6eq. olefin, 3eq. NaOAc, 1eq. Bu_4NCl, 0.2eq. $Pd(OAc)_2$, DMA, 0.05M, 100°C, 24h. F: 8eq. olefin, 3eq. NaOAc, 2eq. Bu_4NCl, 0.25eq. $Pd(OAc)_2$, DMA, 0.025M, 100°C, 24h.
ii: 6eq. NaOMe, MeOH : dioxane (1:4), RT, 24h.

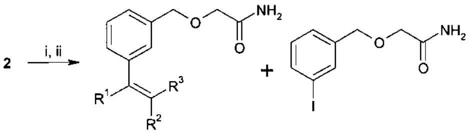
results (entry 5, Table 3). Other inorganic bases (K_2CO_3, Na_2CO_3) also resulted in incomplete conversion under otherwise comparable reaction conditions (entries 3, 4, Table 3). The use of dimethylacetamide as solvent had a beneficial effect compared to the use of dioxane (compare entries 1 and 2, Table 3). Terminal olefins bearing electron withdrawing substituents gave products in high yield, (entries 1-9, Table 4) except in the case of the dimethyl vinylphosphonate (entry 2, Table 4). Additional substituents on the olefin α or β to the electron withdrawing group are well tolerated in this process (entries 4,6,8-12, 15, Table 4). Only methyl crotonate and methacrylonitrile gave somewhat disappointing results (entries 10,11, Table 3; entries 1,5, Table 4). Acylated α,β-unsaturated amino acid could be also coupled efficiently as demonstrated in one example (entries 13-15, Table 4). However the use of a larger excess of reagent and double coupling was required for complete conversion.[9]

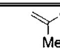
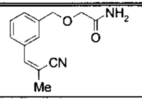
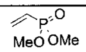
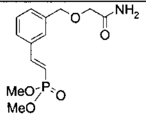
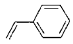
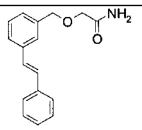
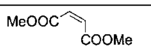
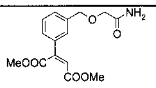
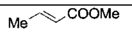
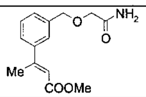
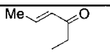
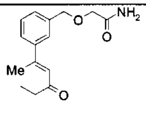
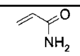
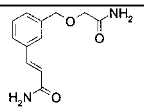
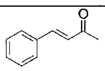
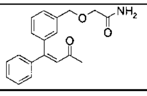
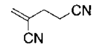
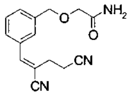
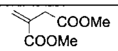
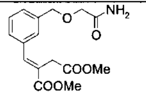
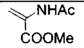
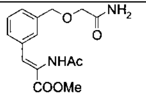
Among the Pd-mediated reactions that we investigated on the solid phase, the coupling of the aryl iodides with acetylenes seems to be extremely efficient under very mild conditions (RT). Due to the very large number of functionalized terminal acetylenes commercially available and due to the ease of transformation of C≡C triple bonds, this process is suitable for the elaboration of combinatorial libraries of compounds. The addition of aryl iodides to olefins (*Heck* reaction) is also very useful on solid phase, although the reaction conditions are more substrate dependent.

References and Notes

1. Wendeborn, S.; Berteina, S.; Brill, W. K.-D; De Mesmaeker, A. *Synlett* **1998**, 671.
2. a) de Meijere, A; Meyer, F.E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379. b) Heck, R.F. *Palladium Reagents in Organic Synthesis*; Academic Press, 1985. c) Dieck, H.A.; Heck, F.R. *J. Organometallic Chem.* **1975**, *93*, 259.
3. a) Yu, K.-L.; Deshpande, M.S.; Dolatrai, M.V. *Tetrahedron Lett.* **1994**, *35*, 8919. b) Young, K.-Y.; Nelson, J.C.; Moore, J.S. *J. Am. Chem. Soc.* **1994**, *116*, 10841. c) Fagnola, M.C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307. d) Fancelli, D.; Fagnola, M.C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311.
4. Double couplings imply complete removal of all reagents and side products through washing of the resin before submitting it under

Table 4. Couplings with olefins and *Rink* linker



Entry	Olefin	Reaction Conditions i	Product	Yields (%)[a)]	Recovered Ar-I (%)
1		F		40 (*E*(*Z*):*Z*(*E*) =2:3)	0
2		F		40	0
3		F		96 (*E* only)	0
4		F		96 (*E*(*Z*):*Z*(*E*) =97:3)	0
5		F		76 (*E*(*Z*) only)	0
6		F		90 (*E*(*Z*) only) (84)	6
7		F		88 (65) (*E* only)	7
8		F		90 (71) (*E*(*Z*):*Z*(*E*) =75:25)	0
9		F		84	12
10		G		80 (57)	0
11		F		85	11
12		G		90 (67)	0
13		F		47	48
14		G		59	37
15		H		95	0

a) yields in parentheses are yields of isolated product after purification.

Reaction conditions i: see Table 3 for condition F. G: 8 eq. olefin, 3 eq. NaOAc, 2 eq. Bu_4NCl, 0.25 eq. $Pd(OAc)_2$, DMA, 0.025M, 100°C, 24h, double coupling. H: 15 eq. olefin, 5 eq. NaOAc, 4 eq. Bu_4NCl, 0.5 eq. $Pd(OAc)_2$, DMA, 0.025M, 100°C, double coupling
ii: $CF_3COOH:CH_2Cl_2$ (1:4), RT, 5 min.

identical coupling conditions for a second time. If the washing step is avoided, no significantly increased yields were observed, presumably due to accumulation of catalyst poisoning side products.

5. Representative protocol for the coupling with terminal acetylenes on the solid phase: To resin **1** (0.5 g, 0.256 mmol) was added dioxane (6.8 ml), Et_3N (3.4 ml), CuI (9.8 mg, 0.051 mmol) and 3,3-dimethyl-1-butyne and the resulting suspension was degassed for 20 min. Bis(triphenylphosphine)palladium(II) chloride (18 mg, 0.026 mmol) was added and the reaction mixture was shaken at 25°C for 24h. The solid phase was filtered and washed with 5 ml each of dioxane (6 x), H_2O (6 x), H_2O:EtOH (1:1, 3 x), EtOH (3 x) and Et_2O (3 x). The resin was dried under vacuum and suspended in dioxane (8.3 ml). Sodium (35 mg, 1.54 mmol) was dissolved in MeOH (2.1 ml) and the resulting solution of NaOMe was added. The reaction mixture was shaken for 24h at RT. The resin was filtered off and further extracted with 5 ml each of dioxane (4 x), H_2O (6 x), phosphate buffer, pH=7 (3 x), dioxane (3 x), EtOH:H_2O (1:1, 3 x), EtOH (3 x), ether (3 x). The combined liquid phases were concentrated and the resulting solid was extracted with CH_2Cl_2. After filtration through celite and concentration 46 mg (95%) of crude product (entry 1, Table 1) was obtained which was shown to be pure by ^{1}H-NMR (400 MHz).
6. Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1118.
7. a) Heck, R.F. *Org. React.* **1982**, *27*, 345. b) Heck, R.F. *Comprehensive Organic Synthesis*, Trost, B.M. and Fleming, I.; Eds; Pergamon Press: New York, 1991, Vol. 4. pp 833.
8. For previous *Heck* reactions on solid phase see: reference 3a) and a) Hiroshige, M.; Hauske, J.R.; Zhou, P. *Tetrahedron Lett.* **1995**, *36*, 4567. For intramolecular *Heck* reactions on the solid phase see: b) Goff, D.A.; Zuckermann, R.N. *J. Org. Chem.* **1995**, *60*, 5748. c) Yun W.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 7189.
9. Representative protocol for the *Heck* reaction on solid phase: To resin **2** (0.2 g, 0.094 mmol) was added *N,N*-dimethylacetamide (4.7 ml), CH_3COONa (23.1 mg, 0.282 mmol), Bu_4NCl (55.6 mg, 0.188 mmol) and dimethylitaconate and the resulting suspension was degassed for 20 min. $Pd(OAc)_2$ (5.3 mg, 0.024 mmol) was added and the reaction mixture was shaken at 100°C for 24h. The solid phase was filtered and washed with 5 ml each of dioxane (6 x), H_2O (6 x), H_2O:EtOH (1:1, 3 x), EtOH (3 x), dioxane (6 x), CH_2Cl_2 (6 x) and Et_2O (3 x). This coupling and washing process was then repeated for a second time, after which the resin was dried under vacuum and treated 4 x with $CF_3COOH:CH_2Cl_2$ (2:8, 5 ml) for 1 min each time. The combined organic layers were concentrated and the resulting residue was coevaporated with toluene (4x) and dried under vacuum to give 33 mg (90%) of crude product (entry 12, Table 4) which was shown to be contaminated only with traces of Bu_4N^+-salts by ^{1}H-NMR (400 MHz).