Pd-Mediated C-C and C-S Bond Formation on Solid Support: A Scope and Limitations Study

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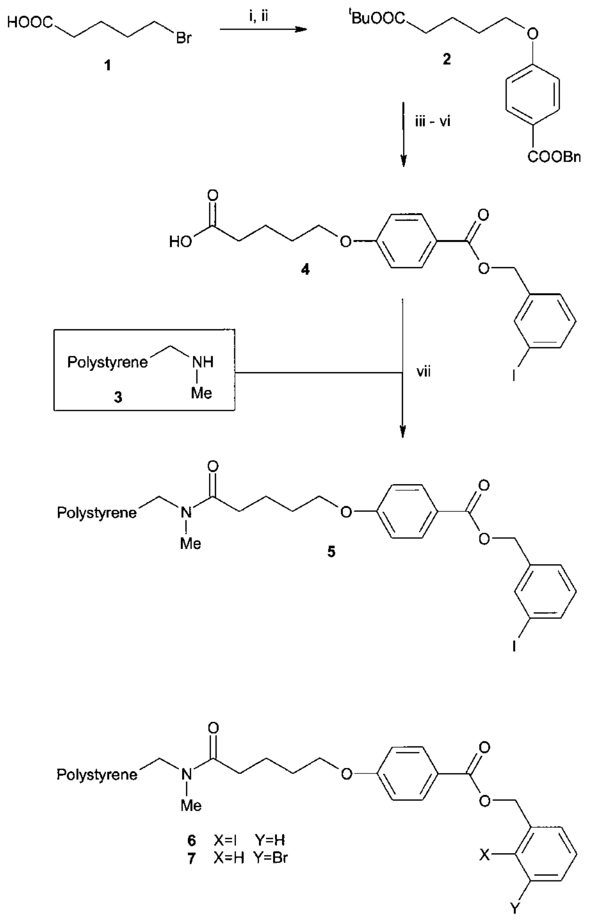
Abstract. The scope and limitations of Pd(0)-mediated coupling reactions between aromatic halides linked to a polystyrene resin and boronic acid derivatives (*Suzuki* coupling), aromatic and vinylic tin compounds (*Stille* coupling), as well as thiols are reported. For all reactions, conditions were optimized and evaluated with various reagents. In many cases, upon cleavage from the solid support, products were obtained in excellent yields. In most cases, the optimized reaction conditions are superior to those previously reported in the literature.

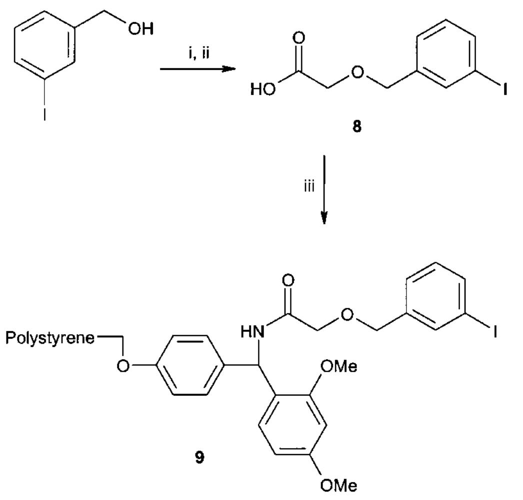
The emergence of combinatorial chemistry stimulated intensive efforts in the application of reactions broadly used in solution to the solid phase synthesis.[1] Among the versatile reactions already investigated on solid support, the Pd-mediated C-C bond formation received much attention due to its enormous potential for the derivatization of functionalized structures.[2] A major feature of the Pd-catalyzed coupling reactions between aromatic (or vinylic) iodides and various nucleophilic reagents is their compatibility with most functional groups, which, consequently, do not require to be protected. Although several recent reports encouraged the use of Pd-mediated C-C bond-forming reactions on solid support, generally applicable procedures leading to single products of defined structures in high purity and high overall yield were not yet available.[3] We describe here improved procedures resulting from our scope and limitation studies which allow, in many cases, high conversion of the starting material into the desired products. The improved procedures described here were identified using polystyrene bound aryl iodides. Later on, these procedures were successfully translated with only marginal changes to various highly functionalized core structures.[4]

For the work described, we used three linkers for the connection of aromatic iodides to polystyrene.[5] Aromatic aryl halides attached through a base labile linker were readily obtained as outlined in Scheme 1. The *p*-alkoxybenzoate esters **5**, **6** and **7** were resistant to basic conditions required for the *Suzuki* coupling, but were found to be sufficiently labile for transesterification with NaOMe at RT, allowing efficient recovery of reaction products from the solid phase. The acid labile *Rink* linker **9** was also used in this study (Scheme 2).[6] In many instances, we observed that products obtained from the base labile linker **5** had higher purity compared with those obtained from the *Rink*-resin **9**. It must be stressed, that 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. The structure of all compounds were established by ^{1}H-NMR and mass spectroscopy. The use of HPLC for yield- and purity determination was avoided, thus allowing a fair comparison of results obtained by traditional solution chemistry and solid phase chemistry.



Scheme 1. i: isobutene, H_2SO_4 cat, CH_2Cl_2, RT, 48h, 96%; ii: 1eq. HO-Ph-COOBn, 1eq. NaI, 1.1eq. NaH, DMF, 60°C, 24h, 93%; iii: H_2 (1atm), Pd-C (5%), THF, RT, 12h, 88%; iv: 1.1eq. $Me_2C{=}C(NMe_2)Cl$, CH_2Cl_2, RT, 3h; v: 1eq. m-I-Ph-CH_2OH, 10eq. pyridine, 0.2eq. DMAP, 1.5eq. Et_3N, CH_2Cl_2, RT, 16h, 88%; vi: CF_3COOH : CH_2Cl_2 (1:3), RT, 20h, 96%; vii: 4eq. **4**, 4.4eq. Et_3N, 4.4eq. O-(1H-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, 2eq. N-hydroxybenzotriazole, dioxane, RT, 5h; **3** , 10eq. Et_3N, 1eq. DMAP, dioxane, 24h; Ac_2O : pyridine (3:1), 10eq. Et_3N, 1eq. DMAP, RT, 24h

***Suzuki* couplings**.[7] Table 1 summarizes the results obtained using 21 boronic acid derivatives in the Pd-mediated couplings with **5** and **7** under various reaction conditions. Entries 1 and 2 compare the coupling efficiency of an aryl bromide *vs.* an aryl iodide under our standard reaction conditions (B). These results suggest that aryl bromides (not activated by electron withdrawing substituents) are much less suitable for solid phase *Suzuki* coupling reactions. Whereas the use of both catalysts, $Pd(Ph_3P)_4$ and $Pd(OAc)_2$ results in complete consumption of starting material, the reaction under 'ligand free' conditions is much cleaner based on ^{1}H-NMR of the crude product (entries 3 and 4).[8] Conditions recently recommended in the literature for solution phase chemistry (entries 9, 10) gave unsatisfactory results, even at 140°C.[9] Entries 5-8 elude to the time required for the reaction to reach completion: the starting material is not completely consumed if reaction times are less than 12h. This is in contrast to rather short reaction times in control experiments performed in solution, where completion was reached in less than 1h under similar conditions. Therefore, reactions were run for 24h to assure complete conversion. In most cases, these reaction conditions gave satisfactory to excellent results, with a few exceptions (entries 13, 15, 32). In case of the aldehyde containing boronic acid (entry 15) we were uncertain whether the coupling- or the



Scheme 2. i: 1.2eq. NaH, THF, 1.2eq. $BrCH_2COOtBu$, RT, 24h, 54%; ii: $CF_3COOH:CH_2Cl_2$ (1:3), RT, 24h, 98%; iii: 4.4eq. **8**, 4.4eq. O-(1H-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, 2eq. N-hydroxy benzotriazole, dioxane, RT, 4h; Rink-amine, 10eq. Et_3N, 1eq. DMAP, dioxane, 48h

cleavage reactions were responsible for the reduced yields. Additional experiments (Table 3) revealed, that coupling yields with 4-formylphenylboronic acid are low irrespective of the reaction and cleavage conditions used. In some cases, reactions did not reach completion (for example entries 23 - 28): doubling the amount of all reagents lead to increased yields and crude product quality (B→C). However, yields were even higher when double couplings were performed (B→D).[10] Noteworthy is the distinct difference in reactivity between the 2-thiopheneboronic acid and the 3-thiopheneboronic acid (entries 23 - 28). Both substrates gave incomplete conversion under the standard conditions B. However, the 3-thiopheneboronic acid required more stringent reaction conditions than the 2-thiopheneboronic acid (entries 25 and 28). The 4-hydroxymethylphenylboronic acid (entry 29) gave poor results, presumably due to low solubility of the reagent under the reaction conditions, even though this substrate gave excellent results in control experiments in solution. *Ortho* electron withdrawing substituents on the phenylboronic acids disfavor the coupling, presumably due to a combination of steric hindrance and increased rate of base catalyzed deboronation (entries 16 - 19).[11b] Incomplete conversion is observed even when larger excess of reagent (conditions C) or double coupling (conditions D) are employed. The cyclic boronate ester (entry 20) can be used efficiently in the Pd-mediated coupling reaction under nonaqueous reaction conditions, where deboronation does not take place.[11] This modification is also useful when non aqueous reaction conditions are required for other reasons. In contrast to the electron withdrawing *ortho* substituents, electron releasing *ortho* substituents on the boronic acid gave satisfactory results, even though conditions C or D are required to reach complete reactions. Alkyl-9BBN derivatives can be coupled efficiently to aryl halides (entry 40).[12]

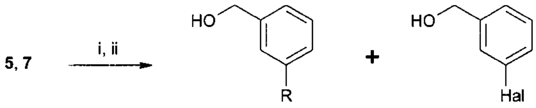
Coupling with the corresponding 2-iodobenzylalcohols **6** proceeded also well, as shown in Table 2 (compare entry 2, Table 2 with entry 22, Table 1).

In order to determine whether low coupling yields with 4-formylphenylboronic acid were due to the strongly basic coupling and/or cleavage conditions (entry 15, Table 1), we performed the coupling with an aryl iodide bound to the solid support by the acid labile *Rink* linker (**9**, Table 3). Even under less basic reaction conditions (entries 1-5, Table 3) substituting K_2CO_3 by KF, and acidic cleavage conditions, the yields of the desired product remained low and large amounts of unreacted aryl iodide were recovered.[13] The use of methoxy ethanol instead of the dioxane-H_2O mixture disfavors the coupling reaction (compare entry 30, Table 1 with entry 6 Table 3).[14]

***Stille* couplings.**[15,16] Upon screening several reaction conditions, two protocols were found to work best for *Stille* coupling on solid phase (Table 4). The procedure involving $Pd_2(dba)_3$ and triphenyl arsine gave superior results in most cases.[16a] Electron poor aryl tin reagents gave less satisfactory results (entry 3). It is worthwhile pointing out, that coupling results with electron rich aryltin derivatives (entries 8, 9, Table 4) were much inferior to the results obtained with the corresponding boronic acids (entry 33, Table 1).[17] The *Stille* coupling reactions were also performed on aryl iodides bound to the *Rink* resin with comparable results (data not shown).[18]

Coupling with terminal thiols. The coupling of thiols with aromatic halides has received relatively little attention.[19] We decided to investigate this reaction for the elaboration of combinatorial libraries, realizing the large number of commercially available thiols and the rich chemistry of sulfur containing compounds. Table 5 summarizes our results. All thiols coupled in excellent yields under optimized reaction

Table 1. *Suzuki* couplings with base labile linker



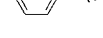
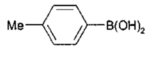
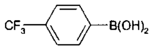
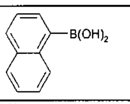
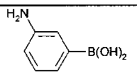
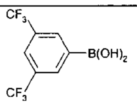
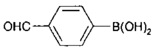
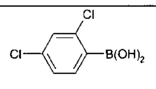
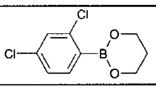
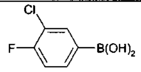
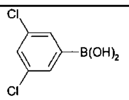
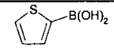
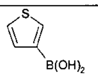
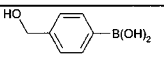
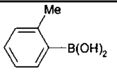
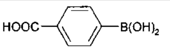
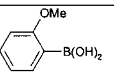
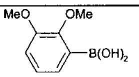
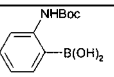
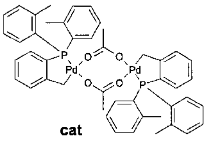
Entry	Hal	R-BX$_2$	Reaction Conditions i	Yields (%)[a)]	Recovered Ar-Hal (%)
1	Br		B	58 (37)	30
2	I		B	95 (85)	0
3	I		A	84	0
4	I		B (6h)	95 (86)	0
5	I		B	96 (91)	0
6	I		B (4h)	89 (91)	11
7	I		B (6h)	95 (91)	3
8	I		B (12h)	95	0
9	I		G	16	79
10	I		H	37 (29)	58
11	I		B	90	0
12	I		B	76	0
13	I		B	51 (22)	40
14	I		B	89	0
15	I		B	56 (41)	0
16	I		B	69	31
17	I		C	80	20
18	I		D	83 (60)	17

Table 1. (continued)

Entry	Hal	R-BX$_2$	Reaction Conditions i	Yields (%)[a)]	Recovered Ar-Hal (%)
19	I		E	86 (53)	14
20	I		F	96 (71)	0
21	I		B	97 (88)	3
22	I		B	97 (86)	3
23	I		B	66	30
24	I		C	86 (62)	9
25	I		D	97 (91)	0
26	I		B	79	16
27	I		D	91	4
28	I		E	96	0
29	I		B	70 36	20
30	I		B	91	5
31	I		C	96	0
32	I		C	0	100 (92)
33	I		B	89	7
34	I		B	79	17
35	I		C	91	0
36	I		D	96	0
37	I		B	89	7
38	I		C	91	2
39	I		D	93	0
40	I	n-C_6H_{13}-9BBN	I	90	0

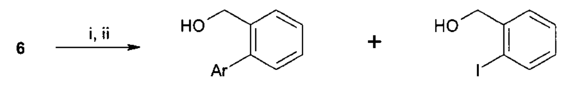
a) yields in parentheses are yields of isolated product after purification.

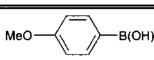
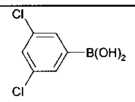
Reaction conditions i: A: 4eq. Ar-$B(OH)_2$, 9eq. K_2CO_3, 0.1eq. $Pd(Ph_3P)_4$, dioxane : H_2O, (6:1), 0.05M, 100°C, 24h. B: 4eq. Ar-$B(OH)_2$, 9eq. K_2CO_3, 0.1eq. $Pd(OAc)_2$, dioxane : H_2O, (6:1), 0.05M, 100°C, 24h. C: 8eq. Ar-$B(OH)_2$, 18eq. K_2CO_3, 0.2eq. $Pd(OAc)_2$, dioxane : H_2O, (6:1), 0.05M, 100°C, 24h. D: 4eq. Ar-$B(OH)_2$, 9eq. K_2CO_3, 0.1eq. $Pd(OAc)_2$, dioxane : H_2O, (6:1), 0.05M, 100°C, 24h; double coupling. E: 8eq. Ar-$B(OH)_2$, 18eq. K_2CO_3, 0.2eq. $Pd(OAc)_2$, dioxane : H_2O, (6:1), 0.05M, 100°C, 24h; double coupling. F: 8eq. Ar-$B(O(CH_2)_3O)$, 18eq. K_3PO_4, 0.2eq. $Pd(OAc)_2$, dioxane, 0.025M, 100°C, 24h. G: 6eq. Ar-$B(OH)_2$, 13eq. K_3PO_4, 0.2 eq. **cat**, xylene, 0.025M, 120°C, 24h. H: 6eq. Ar-$B(OH)_2$, 13eq. K_3PO_4, 0.2 eq. **cat**, xylene, 0.025M, 140°C, 24h. I: 3eq. 9-BBN-R, 6eq. K_3PO_4, 0.2 eq. $PdCl_2(MeCN)_2$, 0.2eq. dppf, dioxane : DMF (1:6), 50°C, 30h.
ii: 6eq. NaOMe, MeOH : dioxane (1:4), RT, 24h.



cat

Table 2. *Suzuki* couplings in *ortho* position with base labile linker

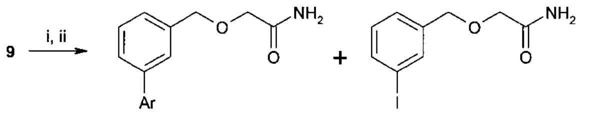


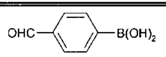
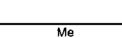
Entry	Ar-$B(OH)_2$	Reaction Conditions i	Yields (%)[a)]	Recovered Ar-I (%)
1		B	97 95	0
2		B	92 (83)	8
3		C	97 (86)	0

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

Reaction conditions see Table 1

Table 3. *Suzuki* couplings with *Rink* linker



Entry	Ar-$B(OH)_2$	Reaction Conditions i	Yields (%)[a)]	Recovered Ar-I (%)
1		C	71	24
2		E	89 (82)	5
3		I	43	52
4		J	68	27
5		K	77 (60)	18
6		L	40	45

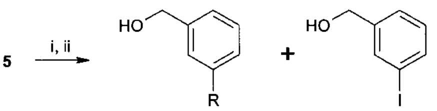
a) yields in parentheses are yields of isolated product after purification.

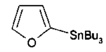
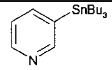
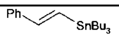
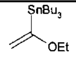
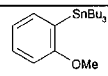
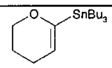
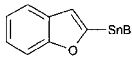
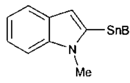
Reaction conditions i: C,E: see Table 1. I: 4eq. Ar-$B(OH)_2$, 9eq. KF, 0.1eq. $Pd(OAc)_2$, dioxane : H_2O, (6:1), 0.05M, 100°C, 24h. J: 8eq. Ar-$B(OH)_2$, 18eq. KF, 0.2eq. $Pd(OAc)_2$, dioxane : H_2O, (6:1), 0.05M, 100°C, 24h. K: 8eq. Ar-$B(OH)_2$, 18eq. KF, 0.2eq. $Pd(OAc)_2$, dioxane : H_2O, (6:1), 0.05M, 100°C, 24h; double coupling. L: 4eq. Ar-$B(OH)_2$, 9eq. K_2CO_3, 0.1eq. $Pd(OAc)_2$, $MeOCH_2CH_2OH$, 0.05M, 100°C, 24h.
ii: 20% CF_3COOH, CH_2Cl_2, RT, 5 min

conditions. Only one example (entries 2, 3) required the use of double amount of reagents in order to achieve complete conversion. For a successful reaction, it was important to premix all reagents at 60°C, prior to adding the thiol. Otherwise, reactions did not reach completion, presumably due to unproductive binding of the thiol to the catalyst.[20]

Although Pd-mediated reactions on solid support of aryl iodides with tin, boronic acid and thiol derivatives furnished generally the desired products in high yield and purity, it is necessary to use a large excess of reagents, substantial amounts of "catalyst", and long reaction times at elevated temperature. In several cases, even under optimized conditions, unsatisfactory results were obtained.

Table 4. *Stille* couplings with base labile linker

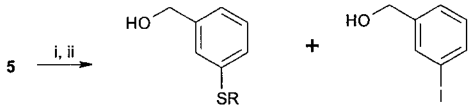


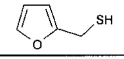
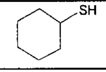
Entry	R-$SnBu_3$	Reaction Conditions i	Yields (%)[a)]	Recovered Ar-I (%)
1		A	96 (82)	0
2		B	96 (90)	0
3		A	65 (46)	0
4		B	90 (49)	
5	 (E:Z=95:5)	B	90 (49)	0
6		A	70	0
7		B	80	0
8		A	20 (16)	0
9		B	-	30
10		A	60	0
11		B	80	
12		A	76	0
13		B	96	0
		A	80	0
14		B	95	0

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

Reaction conditions i: A: 3eq. R-$SnBu_3$, 0.1eq. $Pd(Ph_3P)_4$, dioxane, 0.05M, 100°C, 24h.
B: 3eq. R-$SnBu_3$, 0.1eq. $Pd_2(dba)_3$, 0.4eq. $AsPh_3$, dioxane, 0.05M, 50°C, 24h.
ii: 6eq. NaOMe, MeOH : dioxane (1:4), RT, 24h

Table 5. Couplings between thiols and resin bound aromatic iodides



Entry	R-SH	Reaction Conditions i	Yields (%)	Recovered Ar-I (%)
1	$Ph(CH_2)_3SH$	A	96	0
2	$PhCH_2SH$	A	51	45
3		B	96	0
4	$Me(CH_2)_7SH$	A	96	0
5		A	95	0
6		A	95	0
7	$MeC(O)NH(CH_2)_2SH$	A	93	0

Reaction conditions i: A: 4eq. RSH, 0.2eq. Pd_2dba_3, 0.8eq. dppf, 8eq. $iProp_2NEt$, DMA, 0.02M, 60°C, 24h. B: 8eq. RSH, 0.4eq. Pd_2dba_3, 1.6 eq. dppf, 16eq. iPr_2NEt, DMA, 0.02M, 60°C, 24h.
ii: 6eq. NaOMe, MeOH : dioxane (1:4), RT, 24h

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3. In most examples (reference 2) much more reactive electron poor aromatic halides are used in the Pd-coupling reactions.
4. Manuscripts in preparation.
5. Polystyrene beads, cross-linked with 1% divinyl benzene were used for all experiments; functionalization was approximately 0.7 mmol/g.
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10. Double couplings imply complete removal of all reagents and side products through washing of the resin before submitting it under 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.
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14. Representative protocol for the *Suzuki*-coupling on the solid phase: To resin **5** (0.4 g, 0.205 mmol) were added freshly distilled dioxane (3.5 ml,), *p*-trifluoromethylbenzene boronic acid (156 mg, 0.820 mmol) and K_2CO_3 (138 mg, 1.85 mmol) dissolved in H_2O (0.56 ml) and the resulting suspension was degassed with argon for 20 min. $Pd(OAc)_2$ (5 mg, 0.02 mmol) was added at once and the reaction 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), EtOH:H_2O (1:1, 3 x), EtOH (3 x) and Et_2O (3 x). The resin was dried under high vacuum and suspended in dioxane (6.6 ml). Sodium (28 mg, 1.23 mmol) was dissolved in MeOH (1.6 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 46.7 mg (90.3%) of crude product (entry 11, Table 1) was obtained which was shown to be pure by ^{1}H-NMR (400 MHz).

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18. Representative protocol for the *Stille*-coupling on the solid phase: To resin **5** (0.5 g, 0.256 mmol) were added freshly distilled dioxane (5.1 ml), 2-(tributylstannyl)furan (297 mg, 0.769 mmol) and Ph_3As (32 mg, 0.103 mmol) and the resulting suspension was degassed with argon for 20 min. $Pd_2(dba)_3$ (23.5 mg, 0.026 mmol) was added at once and the reaction was shaken at 50°C for 24h. The solid phase was filtered and washed with 5 ml each of dioxane (6 x), CH_2Cl_2 (6 x), MeOH (3 x), dioxane (3 x) and Et_2O (3 x). The resin was dried under vacuum and suspended in dioxane (8.3 ml). Sodium (35 mg, 1.53 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 43.8 mg (98%) of crude product (entry 2, Table 4) was obtained which was shown to be 98% pure by ^{1}H-NMR (400 MHz).

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20. Representative protocol for the coupling with terminal thiols on the solid phase: To resin **5** (0.3 g, 0.154 mmol) was added DMA (6.1 ml), 1,1’-bis(diphenylphosphino)ferrocene (68.1 mg, 0.123 mmol), tris(dibenzylideneacetone)dipalladium(0) (28.2 mg, 0.031 mmol) and Et_2N^iPr (158 mg, 1.23 mmol) and the resulting suspension was degassed for 20 min. 3-Phenylpropyl mercaptan (93 mg, 0.614 mmol) was added and the reaction mixture was shaken at 60°C for 24h. The solid phase was filtered and washed with 5 ml each of dioxane (6 x), CH_2Cl_2 (6 x), MeOH (3 x), dioxane (3 x) and Et_2O (3 x). The resin was dried under vacuum and suspended in dioxane (4.9 ml). Sodium (21 mg, 0.922 mmol) was dissolved in MeOH (1.2 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 38 mg (96%) of crude product (entry 1, Table 5) was obtained which was shown to be pure by ^{1}H-NMR (400 MHz).