be obtained without purification. For preparative purposes involving chromatographic purification higher boiling components are also accessible.[11]

This cleavage – cross-coupling reaction is in all cases salt-free, that is the exposed resin **2** functions as a "scavenger-resin" for the trifluoroacetic acid. The filtered, slightly yellowish resin is, after washing, active for coupling steps with diazonium salts and can therefore be recycled.

In conclusion, this salt-free cleavage – cross-coupling strategy allows the clean synthesis of a series of (cyclo)alkenyl-, alkynyl-, (cyclo)alkyl-, and aryl-substituted (hetero)arene derivatives and is especially suitable for automated synthesis. This building system comprising virtually any aminoarene or nitroarene after their reduction as well as alkenes or alkynes allows synthesis of highly lipophilic molecules and tolerates most functional groups.[4, 12, 13] Multicomponent Heck reactions (domino Heck Diels – Alder reaction, Heck – Stille reaction etc.)[14] should be possible in this context and might lead to a higher diversification.

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## An Oxidation-Labile Traceless Linker for Solid-Phase Synthesis**

Frank Stieber, Uwe Grether, and Herbert Waldmann*

The combinatorial synthesis of small-molecule libraries on polymeric supports is a powerful method for the discovery and development of new molecules with a predetermined profile of properties.[1] Vital to all solid-phase methodologies is the design and utilization of suitable anchor groups (linkers) that allow facile attachment, functionalization, and release of the molecules of interest. Typically, linkage to the polymeric support is achieved through functionality already present in the target molecule. However, after cleavage from the support

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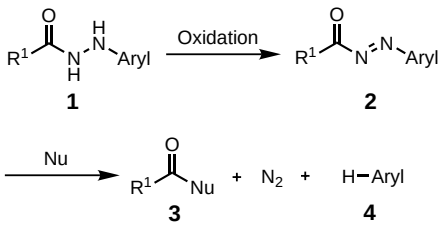
at the end of a synthetic sequence this functional group may have a negative effect on the biological or chemical activity of the target compounds. A highly desirable alternative linker would be capable of releasing a product while forming a C–H bond in place of the resin attachment, thus leaving behind no trace of a solid-phase synthesis. Such widely applicable "traceless" linkers introduced so far[2, 3] include aryl silanes,[2a–f] alkyl sulfides and sulfones,[2g] alkyl selenides,[2h,i] and aryl triazenes.[2j]

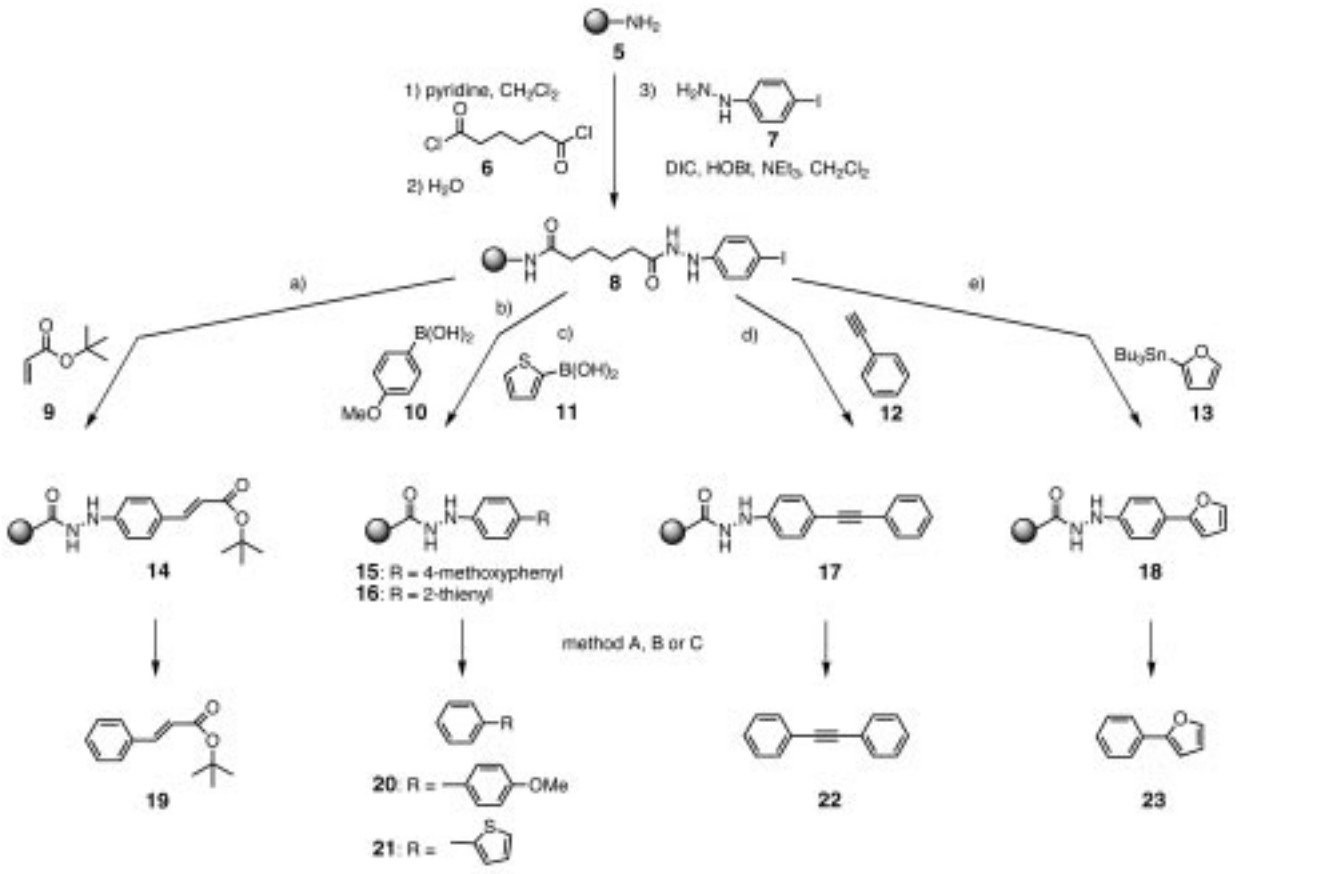
We now report the use of aryl hydrazides as traceless linkers that can be cleaved under mild oxidative conditions to afford aromatic alkenes, alkynes, and biaryl derivatives.

Oxidative cleavage of aryl hydrazides **1** to carboxylic acid derivatives **3**, nitrogen, and arenes **4** via a transient acyl diazene **2** has been applied in peptide chemistry both in solution[4] and on the solid support[5] to obtain peptide carboxylic acids, amides, and esters (Scheme 1, $R^1$ = peptide, Aryl = phenyl or phenyl linked to a polymeric support). Alternatively, this transformation clearly offers the opportunity to cleave aryl compounds from polymeric supports leaving only an Aryl–H bond behind (Scheme 1, $R^1$ = polymeric support, Aryl = substituted aromatic compound).

In order to investigate if hydrazides may be employed as efficient traceless linkers, three commercially and widely used amino-functionalized polymeric supports **5** (polystyrene-$NH_2$ [Fluka], TentaGel-$NH_2$ [Rapp Polymere], ArgoPore-$NH_2$ [Argonaut Technologies]) were acylated with adipic acid dichloride (**6**) to yield the corresponding carboxyfunctionalized resins after hydrolysis.[6] These supports were then condensed with 4-iodophenylhydrazine (**7**) to give polymer-bound phenylhydrazides **8** (Scheme 2). The immobilized aryl iodides of type **8** served as starting materials for different $Pd^0$-catalyzed coupling reactions. They were subjected to a Heck reaction with *tert*-butyl acrylate (**9**),[7] Suzuki reactions with 4-methoxyphenylboronic acid (**10**)[8a] and 2-thienylboronic acid (**11**),[8b] a Sonogashira coupling with phenylacetylene (**12**),[7] and a Stille reaction[9] with 2-furanyl-tri-*n*-butylstannane (**13**; Scheme 2). In order to release the products of the coupling reactions from the solid supports, the polymer-bound hydrazides were oxidized with $Cu(OAc)_2$ in methanol in the




Scheme 1. Oxidative cleavage of hydrazides.




Scheme 2. $Pd^0$-catalyzed C–C coupling reactions employing polymer-bound 4-iodoarylhydrazides **8** and traceless oxidative cleavage of the coupling products from the solid supports. For yields see Table 1. a) 6 equiv of **9**, 3 equiv NaOAc, 1 equiv $Bu_4NBr$, 0.2 equiv $Pd(OAc)_2$, dimethylacetamide, 100 °C, 24 h; b) 10 equiv of **10**, 2 equiv $K_3PO_4$, 0.02 equiv $[Pd(PPh_3)_4]$, dimethylformamide/water (6/1), 80 °C, 24 h; c) 5 equiv of **11**, 2 equiv $K_2CO_3$, 0.1 equiv $[Pd_2(dba)_3]$, dimethylformamide, 90 °C, 24 h; d) 6 equiv of **12**, 0.2 equiv CuI, 0.1 equiv $[Pd(PPh_3)_2Cl_2]$, dioxane/triethylamine (2/1), room temperature, 24 h; e) 5 equiv of **13**, 0.4 equiv $AsPh_3$, 0.1 equiv $[Pd_2(dba)_3]$ dioxane, 60 °C, 24 h. dba = *trans,trans*-dibenylideneacetone, DIC = diisopropylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole.

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presence of pyridine (method A),[5b, 10] with $Cu(OAc)_2$ in *n*-propylamine (method B),[5b, 10] or by treatment with *N*-bromosuccinimide in dichloromethane in the presence of pyridine followed by addition of methanol (method C).[4] In the course of these reactions, the hydrazides are converted into the analogous acyl diazenes (see **2**, Scheme 1), which are subsequently attacked by the nucleophile either present in the reaction mixture (i.e. methanol or *n*-propylamine, method A or B) or added after the oxidation step (i.e. methanol, method C). This attack results in the formation of a polymer-bound ester or amide, $N_2$, and the release of the desired coupling products **19**–**23** into solution. Representative results for this three-step sequence are given in Table 1. Cinnamic acid ester **19**, biaryl compounds **20**, **21**, and **23**, and diphenylacetylene **22** were isolated in high overall yields ranging from 50 to 96% over three steps.

Table 1. Representative results of the three-step reaction sequence on the solid support consisting of hydrazide formation, $Pd^0$-catalyzed coupling reaction and oxidative cleavage of the hydrazide linker (method A, B, or C).

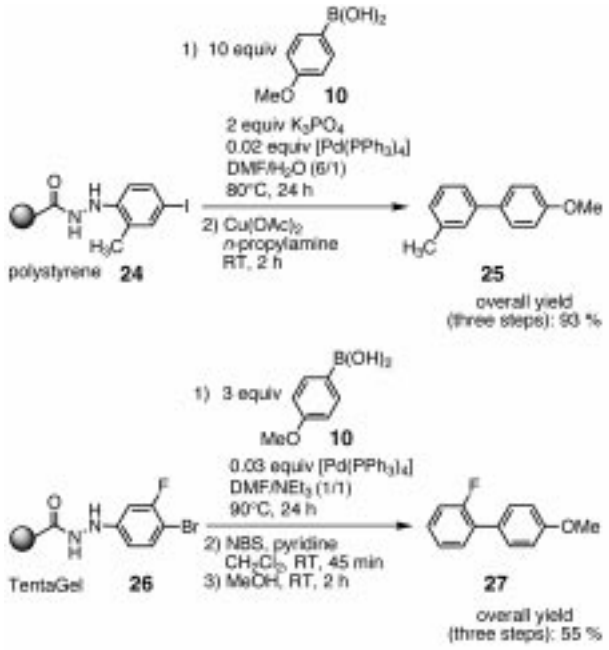
| No. | Compound | Polymeric support | Method[a] | Yield [%][b] (3 steps) |
|---|---|---|---|---|
| 1 | **19** | TentaGel | C | 83 |
| 2 | **19** | polystyrene | A | 85 |
| 3 | **19** | ArgoPore | A | 96 |
| 4 | **19** | ArgoPore | B | 89 |
| 5 | **20** | TentaGel | A | 86 |
| 6 | **20** | TentaGel | B | 93 |
| 7 | **20** | TentaGel | C | 74 |
| 8 | **20** | polystyrene | B | 67 |
| 9 | **20** | ArgoPore | C | 60 |
| 10 | **21** | polystyrene | A | 77 |
| 11 | **22** | TentaGel | B | 50 |
| 12 | **22** | polystyrene | A | 93 |
| 13 | **22** | polystyrene | B | 92 |
| 14 | **22** | ArgoPore | B | 86 |
| 15 | **22** | polystyrene | C | 64 |
| 14 | **23** | TentaGel | B | 90 |
| 15 | **23** | polystyrene | B | 79 |
| 16 | **23** | ArgoPore | A | 50 |
| 17 | **23** | ArgoPore | B | 80 |

[a] Method A: $Cu(OAc)_2$ (0.5 equiv), methanol, pyridine (10 equiv, room temperature, 2 h; method B: $Cu(OAc)_2$, (0.5 equiv) *n*-propylamine, room temperature, 2 h; method C: NBS (2 equiv), pyridine (2 equiv), $CH_2Cl_2$, room temperature, 45 min; after filtration addition of methanol. [b] Determined for the unpurified products. All products were >90% pure (HPLC, GC-MS, NMR).

Product isolation was very simple and convenient. When methods A or B were used, the solutions obtained after cleavage of the traceless linker were evaporated to dryness, the residue was taken up in a mixture of diethyl ether and 1N HCl, and after separation of the layers the organic solvent was evaporated. In all cases the remaining products were >90% pure as determined by HPLC, GC-MS, and NMR spectroscopy. The application of method C was particularly attractive and highly practical. The oxidation was performed without addition of any nucleophile.[11] Thus, the intermediate acyl diazene remained polymer-bound and all reagents and by-products were removed by simple washing of the resin. Subsequently, product release was initiated by addition of methanol, thereby rendering further extractive workup unnecessary. The coupling products were obtained in >90% purity by simple evaporation of the solvent.

The conditions for the oxidative cleavage of the hydrazide linker were very mild. If method A or B was used neither the double bond in **19** nor the triple bond in **22** was attacked. Notably, also the oxidation-labile furan in **23** and the thiophene incorporated into **21** were not harmed at all during the oxidative cleavage of the hydrazide linker. If method C was employed, acrylic acid derivative **19**, the biaryl **20**, and diphenylacetylene **22** were also easily obtained. In the latter case under these conditions, side reactions were observed and the product purity was diminished.[12] However, the desired alkyne was still formed in a 64% yield. Furthermore, the results given in Table 1 demonstrate that the hydrazide linker was effective with all three polymeric supports investigated.

In order to extend the scope of the linker methodology, we prepared polymeric hydrazides **24** and **26** as described above[13] (Scheme 3) and subjected them to Suzuki coupling with phenylboronic acid **10**.[8a, 2f] After cleavage of the traceless linker biphenyl derivatives **25** and **27** were obtained in overall yields of 93 and 55%, respectively, over the three-step sequence.




Scheme 3. $Pd^0$-catalyzed C–C coupling reactions employing polymer-bound 4-iodoarylhydrazide **24** and 4-bromoarylhydrazide **26** and traceless oxidative cleavage of the coupling products from the solid supports.

These results demonstrate that the method developed by us should be readily amenable to the construction of libraries of biphenyl compounds. Biphenyls are found in various pharmacologically active compounds such as in vitronectin receptor antagonists,[14] angiotensin receptor antagonists,[15] inhibitors of transthyretin-mediated amyloid fibril formation,[16] and novel antibacterial agents.[17] In addition, the biphenyl unit has been proposed as a general scaffold for the combinatorial generation of new drug candidates.[18]

In order to prove the viability of our approach, biphenyl derivative **32** was synthesized by employing the traceless hydrazide linker. Compound **32** is a representative member of a recently discovered new class of antibiotics active against

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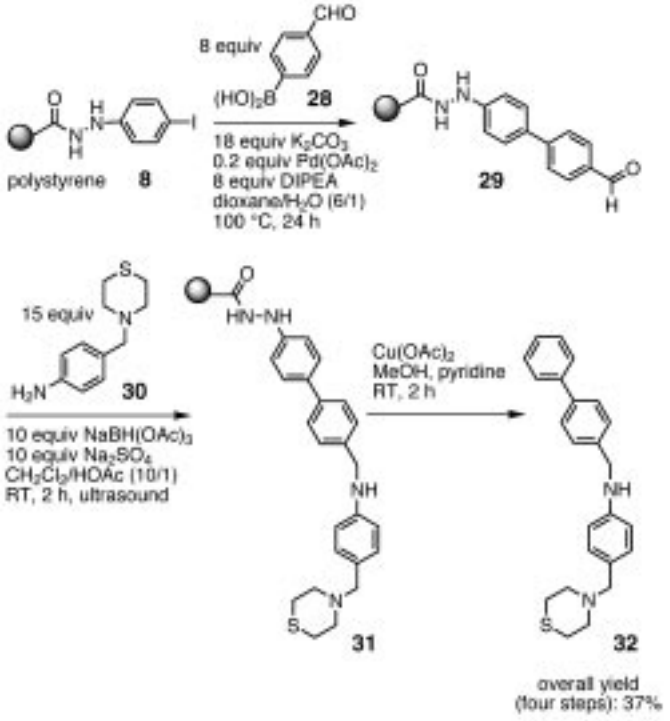
*Mycobacterium tuberculosis* (that is the germ that causes tuberculosis) and against atypical mycobacteria.[17] Antibiotic **32** was built up by coupling polymer-bound 4-iodophenylhydrazide (**8**) with 4-formyl phenylboronic acid (**28**)[9] (Scheme 4). The resulting biphenyl aldehyde **29** was then




Scheme 4. Solid-phase synthesis of antibiotic **32** employing the traceless hydrazide linker. DIPEA = diisopropylethylamine.

subjected to reductive amination[19] with thiomorpholine derivative **30** to yield polymer-bound secondary amine **31**. Finally, the traceless hydrazide linker was cleaved oxidatively under the conditions described above. The desired biphenyl antibiotic **32** was obtained in an overall yield of 37 %. Notably, the thioether present in **32** was stable under the conditions required for the cleavage of the linker group. The desired antibiotic **32** was obtained after simple extraction with aqueous $NaHCO_3$ (2 %) and subsequent evaporation of the organic solvent in > 95 % purity.

In conclusion, we have developed a new traceless linker technology for solid-phase chemistry. It is compatible with a number of reactions widely used in combinatorial synthesis (Heck, Suzuki, Sonogashira, and Stille coupling, reductive amination). The linker is cleaved under very mild oxidative conditions with double and triple bonds, furans, thiophenes, sulfides, and amines remaining unattached. Together with the experience gained in the use of hydrazides in peptide chemistry[4, 5] (i.e. hydrazides are stable to acids and bases) our findings suggest that the traceless phenylhydrazide linker should be applicable in solid-phase and combinatorial chemistry in general.

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[10] To guarantee rapid oxidation 0.5 equivalents of $Cu^{II}$ salt were employed; $Cu^{I}$ is reoxidized to $Cu^{II}$ by $O_2$. The coupling products of the Pd-catalyzed reactions remained bound to the solid support. This indicates that $Pd^{II}$ does not oxidize the hydrazides to the acyl diazenes.

[11] In the oxidation bromide ions are formed. The finding that the acyl diazenes remain polymer-bound shows that the nucleophilicity of $Br^-$ is not sufficient to cleave the oxidized linker.

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[12] The corresponding vinyl bromide resulting from hydrobromination of the triple bond was isolated as a side product.
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## Design of New Mesogenic Block Molecules: Formation of Columnar Mesophases by Calamitic Bolaamphiphiles with Lateral Lipophilic Substituents**

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The investigation of the driving forces of molecular self-organization is a present topic of chemical research. During the last decades the formation of supramolecular structures based on the microphase separation of incompatible subunits which are covalently linked within macromolecules (block copolymers) has been studied intensively.[1] Such segregation effects are not limited to polymers, but also play an important role in biological systems as well as in the self-organization of low molecular weight materials, especially for the formation of positionally ordered (smectic, columnar, and cubic) liquid crystalline phases.[2] Here, the ordered assemblies often result from the combined action of rigidity and microsegregation. In most cases these two driving forces act in the same direction, enhancing each other. If, however, microsegregation and rigidity compete with each other, novel low molecular weight block molecules should result which could be able to form new supramolecular structures.

Recently we reported on the liquid crystalline compound **1**, which can be regarded as a block molecule containing three incompatible portions: a rigid, rodlike terphenyl unit; two flexible, lipophilic chains; and a lateral hydrophilic group (Figure 1).[3] The large lateral substituent disturbs the parallel

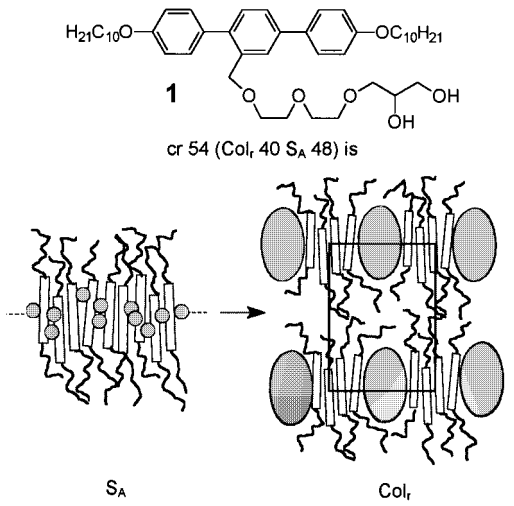


Figure 1. Structure of compound **1** and models of its organization in the mesophases (abbreviations: cr = crystalline phase, $S_A$ = smectic A phase, $Col_r$ = rectangular columnar phase, is = isotropic liquid).

alignment of the rigid cores, and in this way makes the formation of smectic layer structures difficult. However, it did not completely suppress the formation of mesophases, but gave rise to a rectangular columnar mesophase ($Col_r$). The formation of this columnar phase was explained by the microsegregation of the lateral polar chains from the rigid terphenyl cores into cylindrical domains with a locally enhanced concentration of the flexible and polar polyether chains. This leads to a fragmentation of the smectic layer structure into ribbonlike segments, which organize into the rectangular two-dimensional lattice of the columnar mesophase.[3]

In an attempt to generalize the conclusions made for the self-organization of **1**, we have now synthesized the novel low molecular weight triblock molecules **3** – **6**. The topology of the incompatible moieties is the reverse of that in **1** (Table 1).[4] Whereas in **1** the lipophilic chains are grafted in terminal positions and the hydrophilic group is attached in a lateral

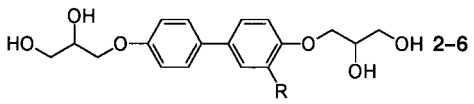


Table 1. Transition temperatures for **2** – **6**, as determined by polarized light microscopy.[a]

| Compd | R | $T$ [°C] |
|---|---|---|
| **2** | H | cr 245 $S_A$ 294 is[7c] |
| **3** | $CH_3$ | cr 104 $S_A$ 231 is |
| **4** | $n$-$C_3H_7$ | cr ?[b] $S_A$ 149 is |
| **5** | $n$-$C_9H_{19}$ | cr 67 Col 98 is |
| **6** | $n$-$C_{11}H_{23}$ | cr 84 $Col_r$ 116 is |

[a] Abbreviations are explained in the legend to Figure 1. [b] No crystalline phase has been obtained yet.

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