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[16] Modeling was performed by using a Macromodel v5.5, Amber* forcefield. Pore blocking was necessary to define a cavity. This involved replacing the equatorial hydrogen atoms on each module's six-membered ring with a cyclopropyl group. Volumes are based upon a static structure and calculated as described in reference [15].

[17] The twelve phenyl groups of the glycolurils present their edges to the cavity which accounts for the downfield shifts of guests' signals from their "free" positions.

[18] Ferrocene derivatives were modeled by using MacSpartan Plus and their volumes were calculated by using MacroModel.

[19] Dimer **12**·**12** displayed poor solubility and dimer **11**·**11** was only moderately soluble in [D$_{12}$]mesitylene. This probably results from the poor shape complementarity of two encapsulated mesitylenes (PCs = 0.57 and 0.51, respectively) with the cavities.

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A Surprising Solid-Phase Effect: Development of a Recyclable "Traceless" Linker System for Reactions on Solid Support**

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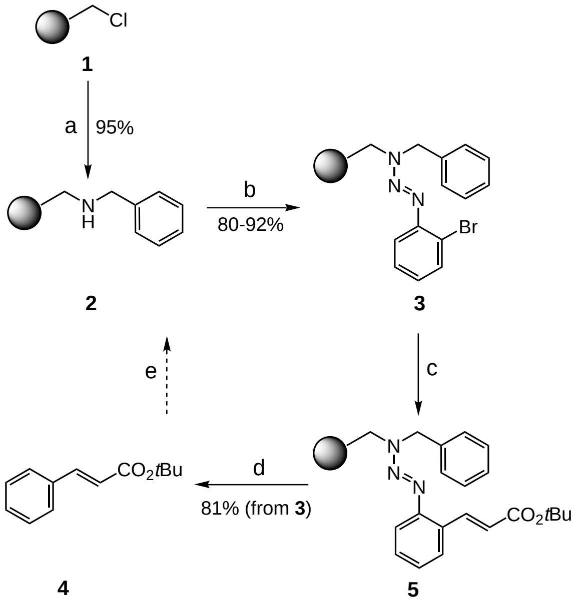
The development of high-throughput screening (HTS) processes and the associated demand for large substance libraries has recently led to an expansion of new synthetic strategies, often described as "combinatorial chemistry".[1] In connection with these developments was a renaissance in solid-phase synthesis. While mixtures of substances were synthesized initially, more recently parallel solid-phase synthesis of single compounds has been given a great deal of attention, because of the advantages of its ease of automation and unambiguous test results in HTS. The associated strategies for the construction of organic molecules and their functionalization are often limited by the nature of the linker.[2] Since most linkers are derived from protecting groups linked to the solid support the seceding molecules generated upon cleavage always contain a functional group that has to be present at the beginning of the synthesis and on which transformations cannot be carried out. To overcome this disadvantage the attached synthetic building block has to be connected to the resin in such a manner that only a C–H bond remains on the target molecule after cleavage ("traceless" cleavage). Only a few solutions exist for this particular problem, none of which are general.[3–5] During our work towards the synthesis of functionalized arenes by organometallic methods we were challenged by the problem of attachment and traceless removal of functionalized arenes. The published strategies of Ellman et al., Veber et al. and others.[3] that use the recently commercialized "silyl linker" suffer from the length of the synthesis and the sensitivity. Herein we report a new "traceless linker" system without these disadvantages, which in contrast, possesses the advantage that the resin can be regenerated.

One possible method by which functionalized arenes can be converted into the corresponding hydrocarbons is the reduction of diazonium compounds. Since they react with amines to yield triazenes,[6] which can be transformed under mildly acidic conditions back to diazonium compounds, the use of triazenes as "linkers" seemed to be very promising. The attachment of triazenes to a solid support is an immobilization method that is rarely used.[7]

Commercially available Merrifield resin (**1**; 1% divinylbenzene, 200–400 mesh, 0.72 mmol g^{-1} Cl) could be treated with benzylamine to yield **2** (Scheme 1) or with piperazine to give the corresponding resin (90–97%).[8] Coupling was



Scheme 1. Synthesis of **3** and Heck reaction. a) BnNH$_2$, DMF, 48 h, 60 °C; b) ArN$_2^+$, THF, 0→25 °C; c) H$_2$C=CHCO$_2t$Bu, Pd(OAc)$_2$, PPh$_3$, NEt$_3$, DMF, 24 h, 80 °C, ultrasound; d) HCl/THF or H$_3$PO$_2$/Cl$_2$HCCO$_2$H; e) regeneration.

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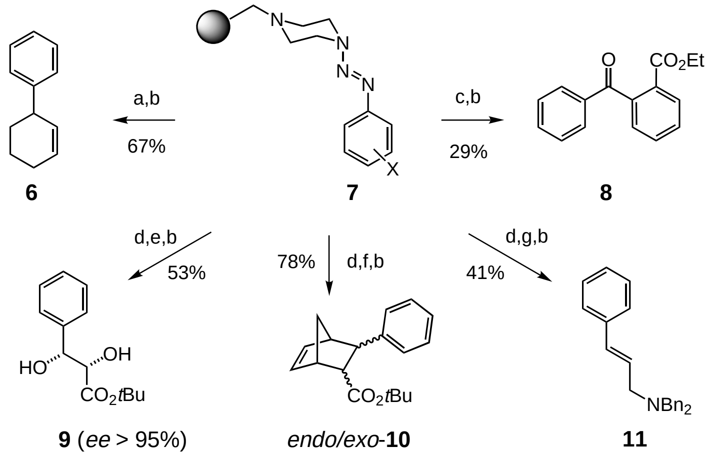
subsequently conducted with various diazonium salts. These salts were prepared from primary aromatic amines under nonaqueous conditions ($BF_3 \cdot OEt_2$, *t*BuONO). A multiple repetition (three times) of the coupling step was necessary to achieve good yields (> 80% loading). Therefore, the resins **2** and the analogous piperazine resin were respectively swollen in THF, treated at room temperature with 1.0–1.5 equivalents of the diazonium salts, and agitated for 15 min. After washing the resin twice with THF/Et_3N (2/1) the coupling step was repeated. The resins **3** and **7** are air and water stable [9] and can be stored for long periods without loss of activity.

The halogenated resins **3** and **7** were used in Heck reactions[10] (12–24 h) with a variety of olefins (styrene, acrylate, dihydrofuran, cyclohexene). The expected products **4** (Scheme 1) and **6** (Scheme 2) were obtained after cleavage (see below) from the modified resins (such as **5**) in modest to good yields (42–81%) and excellent purities (> 90%, NMR). The solid-bound triazenes are thermally stable. A thermal Diels–Alder reaction of the polymer-bound cinnamic ester proceeded cleanly at 100 °C within 24 h[11] and yielded the expected mixture of *exo* and *endo* cycloadducts **10** after cleavage (Scheme 2). Remarkable is the fact that because of the ease of removal of the diene the reaction can be carried out in pure cyclopentadiene. Asymmetric functionalization of the polymer-bound cinnamic ester proceeded cleanly by dihydroxylation[12] and afforded the dihydroxy ester **9** (53%, *ee* 95%). A sequence that started from a Heck reaction of **7** (X = *p*-I) with *tert*-butyl acrylate, DIBAL-H reduction, esterification of the cinnamyl alcohol with acetic anhydride and subsequent palladium-catalyzed allylic substitution[13] with dibenzyl amine furnished the allyl amine **11** in satisfactory yields (41%) after cleavage. Metal–halogen exchange (*n*BuLi, −78 °C) on resin **7** (X = *p*-I) yielded, after reaction with diethyl phthalate and cleavage, the benzophenone derivative **8** in a nonoptimized yield of 29%.



Scheme 2. Reactions on the triazene resin **7** (X = *p*-I). a) Cyclohexene, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 24 h, 80 °C, ultrasound; b) THF/conc. HCl (10/1), 5 min, 50 °C, ultrasound; c) *n*BuLi (3 equiv), −78 °C, 30 min, then diethyl phthalate, 25 °C; d) $H_2C{=}CHCO_2tBu$, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 24 h, 80 °C, ultrasound; e) AD-mix*β*, acetone/H_2O (10/1), methanesulfonamide, 72 h; f) cyclopentadiene, 100 °C, 24 h; g) 1. DIBAL-H, CH_2Cl_2, −78 °C, 1 h; 2. Ac_2O, NEt_3, CH_2Cl_2; 3. $[Pd(dba)_2]$, PPh_3, Bn_2NH, THF, 24 h. DIBAL-H = diisobutylaluminum hydride, dba = dibenzylideneacetone.

A variety of conditions could be used to achieve the cleavage of the functionalized arenes from the resins. The resins underwent reductive deamination with H_3PO_2[14] in dichloroacetic acid after 8 h to give the products in satisfactory total yields. In the search for a more efficient cleavage method investigations in the liquid phase were conducted on the corresponding triazenes parallel to experiments on the solid phase. Here, a surprising solid-phase effect was observed. While in the liquid phase triazenes were transformed cleanly with hydrogen halides into the corresponding halides, in the solid phase the triazenes react with HCl to give solely the hydrocarbons.[15] The use of HCl in THF furnished the desired products with high purity after five minutes of ultrasound, with side products being undetected or formed in only trace amounts (< 5%).[16] Yields of between 29 and 81%[17] were obtained from the triazene resins **3** or **7**. Acid-sensitive groups such as *tert*-butyl ester, secondary hydroxyl groups, or alkenes were found to be stable under these conditions. The resins could be reused directly for another diazotation with only a slight loss in activity (< 10%). In addition, the intermediately regenerated diazonium salts (after cleavage with HBF_4 or TFA at 0 °C) can also be converted into a variety of functionalized arenes[18] (aryl halides,[7, 19] phenols,[6b] cross-coupling products).[10] These new cleavage products could potentially be used for further chemistry.

In conclusion, the triazene system presents a linker system that can be cleaved by "traceless" methods or by introduction of new functionalities. It is distinct from the existing alternatives by its accessibility, robustness, and ability to regenerate the resin. The reactions conducted at the resin can only be seen as examples. The broadness of applications in a number of organic reactions can be anticipated.

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[15] This kind of effect in which solid-phase chemistry is different to the corresponding reactions in the liquid phase is known.[1] Therefore, observations in either system are not always transferable. In this case a Meerwein reduction of the regenerated diazonium salt seems to be favored on the solid phase since the resin might enhance a radical mechanism relative to an ionic pathway.

[16] After longer reaction times (>10 min) or higher reaction temperatures (>50 °C) polymers of the solvent could be detected, which were removed by solid-phase extraction. Literature known compounds are identified by their spectroscopic data and by comparison with authentic samples. All new compounds gave correct spectroscopic data (IR, MS, NMR).

[17] The purity of the products are reproducibly excellent. In the case of lower yields, repetitive cleavage results in more material.

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Quantitative Monitoring of Solid-Phase Synthesis Using Gated Decoupling ^{13}C NMR Spectroscopy with a ^{13}C-Enriched Protecting Group and an Internal Standard in the Synthesis of Sialyl Lewis^{X} Tetrasaccharide**

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Polymer-supported organic synthesis is gaining increasing attention in connection to combinatorial chemistry. Despite the recent success of polymer-supported oligosaccharide synthesis, methods for the the qualitative and quantitative nondestructive monitoring of the reaction have not yet been developed. Among such monitoring approaches, those based on NMR spectroscopy[1] are perhaps the most useful. We are particularly interested in using ^{13}C NMR spectroscopy in this context since it can be performed with conventional high-field NMR spectrometers.[2] The ordinary method is, however, not realistic due to the low signal intensities and the lack of quantitative information, especially when small amounts of compounds are being synthesized for screening purposes. To overcome this problem, Look et al. reported the use of ^{13}C-enriched synthetic blocks in polymer-supported organic synthesis as a potential application to combinatorial chemistry.[2d] This method is indeed important; however, the incorporation of ^{13}C nuclei into a synthon will determine the practicality of the approach. The nuclear Overhauser effect (NOE) from directly attached proton(s) may also affect the integration. To demonstrate a successful application of the method to oligosaccharide synthesis, we have used a ^{13}C-enriched protecting group for the glycosylation reagents together with a ^{13}C-enriched internal standard. Also, the gated decoupling ^{13}C NMR spectroscopy[3] is performed in the presence of a relaxation agent to avoid complications arising from NOEs in the quantitative monitoring of the reaction. Hence the reaction progress can be monitored by integration of the ^{13}C NMR signal of the protecting group and comparing with that of the internal integral standard. Using this strategy, we report herein the first chemical solid-phase synthesis of sialyl Lewis^{X} tetrasaccharide (sLe^{x}), which is a ligand of selectins involved in inflammatory reactions.[4, 5]

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