exclusively of a *single*, delocalized, bishomoaromatic species in the gas phase, remain as yet an intriguing myth.

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Efficient Cleavage–Cross-Coupling Strategy for Solid-Phase Synthesis—A Modular Building System for Combinatorial Chemistry**

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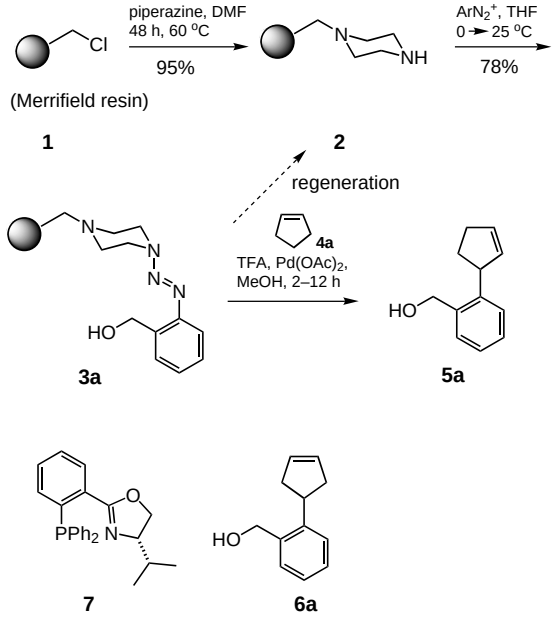
Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday

Solid-phase reactions play an important role in parallel synthesis and combinatorial chemistry, particularly in the area of medicinal chemistry, where its potential has emerged due to the possibility of automation.[1] Research has focused on the synthesis of small, nonpeptidic molecules, because they are applicable systemically and their properties can be modified so that they can cross the blood–brain barrier more easily.[2] Cross-coupling reactions serve as efficient methods for their synthesis because they proceed under mild conditions with the formation of C–C bonds.[3, 4] Recently, we have shown that triazenes are suitable for the linkage of anilines to solid supports and that they may be cleaved to form hydrocarbons.[4] An advantage of this linker type is its accessibility from a pool of aminoarenes. The cleavage of this traceless linker proceeds via arene diazonium ions. We report herein on the possibilities of a cleavage–cross-coupling strategy starting from these diazonium ions.

The Heck reaction[5] of arene diazonium salts bearing little or no functionalization or triazenes, cleaved by acids, with simple olefins proceeds in general under mild thermal conditions to give the expected products in moderate to good yields.[5, 6] Preliminary experiments with triazenes in methanol as the solvent showed that the reduction products are formed in various amounts together with aryl ether by-products through reaction with the solvent.

The reactions on solid supports were conducted with the known amine resin **2**[4] (Scheme 1). Benzyl alcohol **3** bound through the triazene system initially served as a test system. The one-pot cleavage–cross-coupling reaction was conducted with cyclopentene (**4a**), a moderately reactive alkene for the Heck reaction. The resin was cleaved with two equivalents of trifluoracetic acid (TFA) in MeOH at 0 °C to give the diazonium ion. In situ coupling with the alkene in the



Scheme 1. Synthesis and cleavage–cross-coupling reactions on the triazene resin **3a**.

presence of catalytic amounts (5 mol%) of palladium(II) acetate furnished 2-cyclopent-2-eneylbenzyl alcohol (**5a**) in over 92% purity (HPLC, GC, and NMR) and up to 95% yields after 12 h at 40 °C in MeOH, filtration to remove the resin, and removal of the solvent with a rotary evaporator. The regioisomeric, achiral cyclopentene derivative **6a** was isolated as a by-product in 5% yield. An examination of the use of various phosphane types as ligands gave the following result: addition of triphenylphosphane lowered the purity

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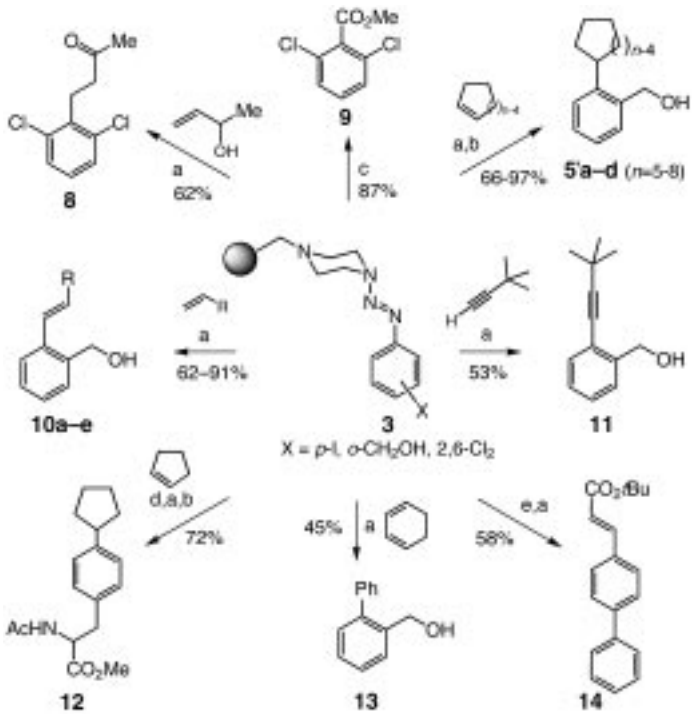
(80%, HPLC) and led to a change of the ratio of the isomers (**5a**:**6a** = 3:1). 2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphinyl)butane (DIOP) as ligand reversed this ratio and gave the cyclopentene derivative **6a** in 63% yield. The oxazoline **7**[5, 7] furnished the chiral product **5a**, but with low asymmetric induction (75% yield, < 10% *ee*). The HPLC analysis of the crude product showed the presence of the corresponding phosphane oxides: presumably under the reaction conditions the ligand is oxidized, for example through the diazonium salt, resulting in a partial dissociation that suggests that the ligand type is not suitable for asymmetric induction. By using palladium on charcoal, the coupling is achieved in lower purity (87%); however, the method is advantageous in regard to the ease of removal of the palladium catalyst, that is the filtrate is nearly colorless. A remarkable feature of this new concept is that a multiple phase change (solid – liquid – solid – liquid) is observed.[8]

Cleavage with functionalization from the resin has been used only seldomly,[9] since the coupling reagent or partner are in general difficult to separate; however, this is possible in the present case due to the volatility of the alkenes used. This case is the first example of a solid support linker being used to generate a reactive species for Heck reactions.

After these successful reactions a series of activated alkenes (styrene, *tert*-butyl acrylate, 2-vinylpyridine) were employed in coupling reactions and yielded the desired *trans*-configured products **10a – c** in excellent purities and yields (> 92% HPLC, GC) (Scheme 2). Even nonactivated alkenes such as 1-hexene or 1-octene were found to react smoothly at the terminal position. However, an unexpected mixture of double-bond regio- and diastereomeric products **10d, e** (1*E*:2*E*:2*Z* ≈ 50:45:5) were isolated. Cyclic alkenes (cyclopentene to cyclooctene, **4a – e**) also reacted smoothly (in general > 92% purity for **5a – d**). In addition, the palladium catalyst on charcoal was still active for hydrogenation reactions (1 bar H_2, 25 °C, 2 h) and allows the formal coupling of alkyl units in high yields and purities. Thus, the phenylalanine derivative **12** was furnished by Heck coupling of the resin **3** (X = *p*-I) with acetamido acrylate, cleavage Heck reaction with cyclopentene (**4a**), and subsequent hydrogenation of the double bond.



Scheme 2. Cleavage – cross-coupling reactions on the triazene resin **3**: a) **3**, alkene, alkyne, or diene, $Pd(OAc)_2$ or Pd/C, 2 equiv TFA, MeOH, 2 h, 40 °C; b) H_2 (1 bar), 2 h, 25 °C; c) **3** (X = 2,6-Cl_2), CO (1 bar), $Pd(OAc)_2$, 2 equiv TFA, MeOH, 2 h, 40 °C; d) (*p*-I), CH_2=C(NHAc)CO_2Me, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 24 h, 80 °C; e) (*p*-I), PhI, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 24 h, 80 °C; **10a**: R = Ph; **10b**: R = CO_2tBu; **10c**: R = 2-pyridyl; **10d**: R = butyl; **10e**: R = hexyl.

Allyl alcohols such as but-1-en-3-ol were found to react smoothly and gave the ketones **8**. Enol ethers were however not suitable for this reaction and yielded mixtures of products by acid hydrolysis.

The reaction with 1,3-cyclohexadiene gave neither the expected dienes nor the possible cyclization product;[5] only the corresponding phenyl derivative **13** was detected (45% yield, 92% purity). Seemingly, under the acidic conditions various oxidative insertion/reductive elimination processes or transfer hydrogenation can occur. These novel reaction sequences offer the possibility of a formal biaryl coupling and thus provide a potential alternative to Stille and Suzuki couplings.[3a] A comparable experiment with phenyl boronic acid for a Suzuki coupling yielded the expected product, however, separation of excess of the coupling component is more laborious.

The reaction under an atmosphere of carbon monoxide (1 bar) in the absence of an alkene furnished the corresponding benzoate **9** in 87% yield (92% purity). Basic amine functionalities such as pyridine derivatives did not interfere with the coupling procedure providing that the reaction was conducted with an appropriate excess of trifluoroacetic acid.

Alkynes may also be used as the coupling component: *tert*-butylacetylene furnished the expected product **11** in 85% purity. The alkyne di- and trimerized under the reaction conditions, thus, separation by chromatography or solid-phase extraction was required to ensure sufficient purity. Alkyne coupling reactions with diazonium salts have not been reported to date.

In this context, a novel unsymmetric biaryl synthesis on solid support has been developed. The observation that Heck reactions with unreactive alkenes led to dimerization of the halogen component has allowed the development of a synthesis of symmetrical biaryl units.[5, 10] The reaction of the polymer-bound iodoarene **3** (X = *p*-I) with iodobenzene in presence of a palladium catalyst under Heck conditions ($Pd(OAc)_2$, PPh_3, NEt_3, DMF, 24 h, 80 °C) furnished a biaryl resin **3** (X = *p*-Ph), which could be subsequently used in a second, cleavage – cross-coupling reaction with acrylate to give the functionalized arene **14** in good yield and purity.

The examples above have been chosen based on the boiling point of the alkene to be coupled in order to ensure the removal of the excess upon evaporation. With a boiling point lower than or in the range of dimethyl sulfoxide, one of the standard solvents for the high-throughput screening, coupling with components such as 1-decene or crotonic acid can be achieved. Up to this molecule size the cleavage products can

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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**

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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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