Traceless Linkers—Only Disappearing Links in Solid-Phase Organic Synthesis?

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Abstract: Traceless linkers, which enable the attachment of arenes and alkanes to a polymeric support, have received increased attention in recent years. These anchoring groups allow chemical transformations on the polymer-bound molecules, which can be cleaved from the resin leaving no residual functionality to bias the library. Various approaches based on different Group 14 to Group 16 heteroatoms have been developed in the past and used in new syntheses of diverse compound libraries.

Keywords: combinatorial chemistry · functionalized resins · solid-phase synthesis · traceless linker

Introduction

The development of high-throughput-screening processes (HTS) and the associated demand for diverse libraries of compounds has recently led to an expansion of new synthetic strategies, often described as "combinatorial chemistry".[1]

Solid-phase synthesis experienced a renaissance by virtue of its applicability to automation and efficient parallel synthesis. While initially mixtures of substances were synthesized (e.g., mix-and-split method), more recently the parallel or tagged split-pool synthesis of single compounds has been given a great deal of attention, owing to the advantages of its ease of automation and unambiguous test results in HTS.

Solid-phase strategies associated with the construction of organic molecules and their functionalization are often limited by the nature of the anchoring group or the linker.[2] Since most linkers are developed for the support of specific functional groups (e.g., alcohols, amines, etc.) and are derived from protecting groups attached to solid support, upon cleavage the seceding molecules always contain a functional group that has to be present at the beginning of the synthesis and on which transformations cannot be carried out.

If the synthetic aim was to create a library of compounds that do not have a suitable functional group for the immobilization on solid support, the attached building block has to be connected to the resin in such a manner, that after cleavage no memory of the immobilization (traceless cleavage) remains on the target.[2a] In theory "no memory" could be defined in such a way that the *detached* target molecule behaves as if it had no memory of the immobilization on the solid support, but appears as if it had been synthesized in solution by using the same reaction/reaction sequence. Thus no influence of the linkage upon reactivity and possible product structures should be apparent.

In our opinion, this definition of anchoring with "no memory" is not possible, because every attachment of alkanes uses at least one C–X bond of the molecule, which is no longer available for chemical transformations. The immobilization of arenes does not only block at least one C–X bond, but also influences the chemical properties of the attached molecule by mesomeric and inductive effects of the anchoring group. Even the attachment by π complexation, shown below, which does not block the connectivities of the arene, influences its reactivity strongly. The chemical possibilities are changed or even restricted in such a manner that this cannot be regarded as an immobilization with "no memory".

Considering "traceless linking" as "leaving no functionality", would mean for arenes and alkanes that only a C–H bond remained at the original position of attachment. The replacement of the linker group by functional groups or atoms other than hydrogen would result in a functionality. Thus, we would like to define a "traceless linker" as a linker, which upon cleavage leads to the formation of a C–H bond on the seceding molecule and which enables the preparation of pure hydrocarbons (*unsubstituted* alkanes, alkenes, alkynes, and arenes). A broadening of this definition to OH or NH groups is not useful, because otherwise every linker derived from polymeric protecting groups would have to be regarded as a traceless linker.

A linker *system* in addition provides the whole protocol for the attachment to and cleavage from the resin. The cleavage might be traceless or with functionalization of the linking site, whatever is desired (Scheme 1). In the latter case, which is also known as the multidirectional cleavage strategy,[3] the amount of library compounds is multiplied by the number of

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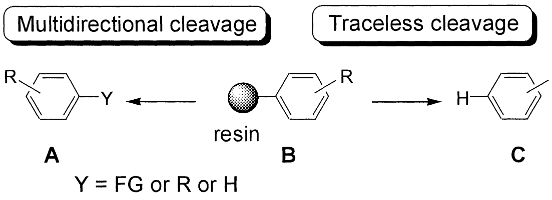
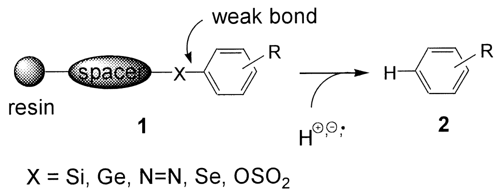


Scheme 1. Multidirectional cleavage and traceless cleavage.

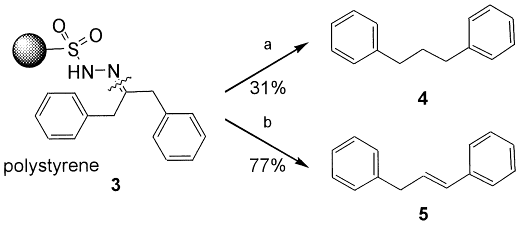
building blocks or functional groups that can be incorporated in the cleavage step. Hence, an anchoring group capable of functionalization *and* traceless linking is a versatile tool for enhancing diversity in a given system.

From the point of designing a traceless linker, one has to start from a heteroatom–carbon bond, which is labile towards protogenolytic, hydrogenolytic, or hydridolytic cleavage (Scheme 2). Since most heteroatom–carbon single bonds are less stable than a carbon–carbon bond [e.g., E (C–C) = 350–360 kJ mol^{-1}; E (C–N) = 305–314 kJ mol^{-1}; E (C–Si) = 310 kJ mol^{-1}; E (C–Sn) = 217 kJ mol^{-1}], traceless linkers can be synthesized based on nearly all heteroatoms. However, the enthalpies of C–X bonds are only relevant for homolytic bond scission. Many linkers are cleaved heterolytically, and the kinetic stability towards heterolytic bond cleavage is decisive in these cases.



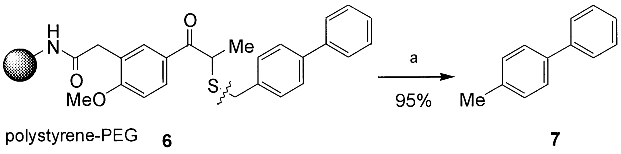
Scheme 2. Strategy for an arene traceless linker.

Nitrogen linker 1—the early hydrazone linker (Kamogawa): The first traceless linker was developed by Kamogawa and coworkers as early as 1983.[4] Starting from a polymer-bound sulfonylhydrazine, which is now commercially available,[5a] formation of a sulfonylhydrazone resin **3** was achieved by reaction with ketones or aldehydes. The cleavage step was conducted either by reduction with borohydride or alanate to yield the alkanes **4** or by treatment with base to give corresponding alkenes **5** (Bamford–Stevens reaction, Scheme 3). Although the term traceless was not used in this early protocol and the yields are not all in cases satisfactory, apparently because the resin type was not fully elaborated, this paper is clearly a pioneering work which has not very often been cited in solid-phase organic synthesis literature.



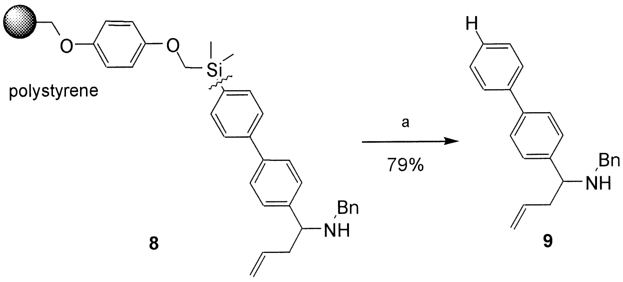
Scheme 3. The sulfonylhydrazone based traceless linker by Kamogawa: a) NaBH$_4$, THF, 8 h, reflux; b) NaOCH$_2$CH$_2$OH, HOCH$_2$CH$_2$OH, 2 h, reflux.

The early thioether linker (Sucholeiki): One of the first papers dealing with traceless linkers was published in 1994 by Sucholeiki[6] and describes the use of thioethers **6**, which are attached to the resin through an aromatic core that enhances the photolytic cleavage. Irradiation at 350 nm gives rise to the formation of the hydrocarbon **7** (Scheme 4). Although not fully explored and limited in the range of functionalized arenes (phenyl instead of biphenyl results in the formation of disulfides), this seminal paper opened a productive avenue to a new kind of linker.

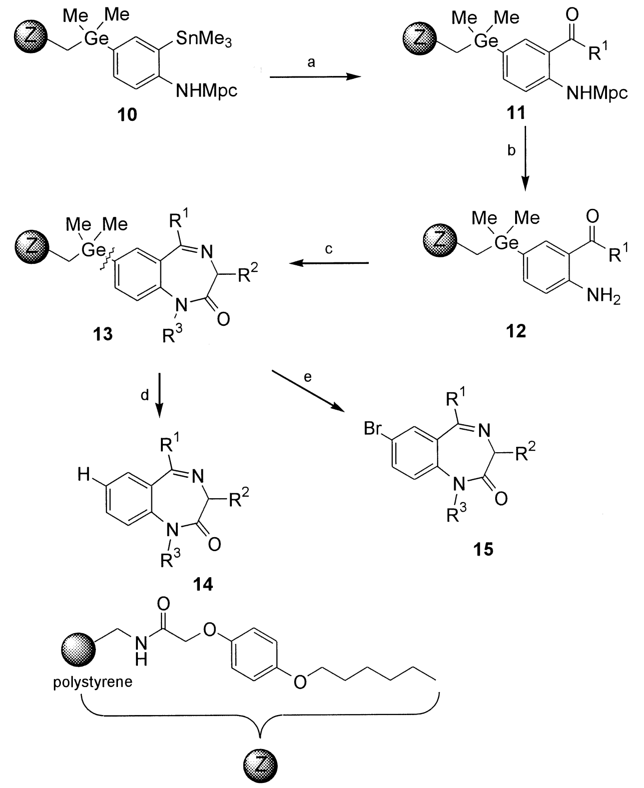


Scheme 4. The photo-cleavable thioether linker by Sucholeiki: a) *hν* (350 nm), MeCN.

Silicon (Ellman and Veber) and germanium (Ellman) linkers: The first traceless linkers for arenes were described independently by Ellman[7] et al. and Veber et al. in 1995.[8] Realizing, that at this time no silicon linker for arenes had been disclosed, these groups developed a system that allows the introduction of a proton on the binding site of the silicon moiety by *ipso* substitution on the arene (Scheme 5). This linker type was used in Ellman's synthesis of a benzodiazepine library, which is a milestone in the solid-phase synthesis of small organic molecules (Scheme 6). The synthesis of the silicon linker involves a lithium–halogen exchange and, after chlorosilane attachment, subsequent coupling with an aryl halide. As the silyl arene might be cleaved in the unwanted direction to give silylated arenes, further improvement led to the development of a germanium linker[9] **10**, which gives rise to the formation of pure material **14**. In addition, cleavage of these linkers can be accomplished by electrophiles other than protons to yield halogenated residues **15** (Scheme 6); hence, the linker is rendered into a multiple-cleavage linker system.[3] The range of electrophiles is limited so far, since only small, reactive electrophiles (e.g., iodine, bromine, and chlorine) react to give the desired products.



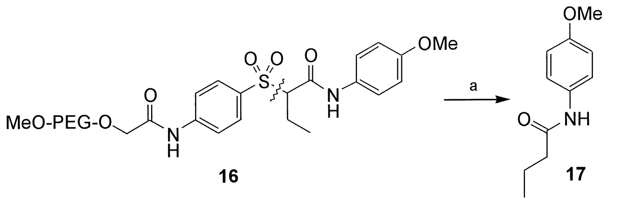
Scheme 5. The silicon traceless linker by Veber: a) TFA, 25 °C.



Scheme 6. Synthesis of a benzodiazepine library with the use of a germanium traceless linker by Ellman: a) R^1COCl, $[Pd_2(dba)_3]$, K_2CO_3, iPr$_2$EtN, THF; b) 2-Chlorobenzo[1,2,3]dioxaborole, iPr$_2$EtN, CH_2Cl_2; c) 1. $R^2CH(NHFmoc)COF$, 2. piperidine, 3. AcOH, 4. base, R^3X; d) TFA, 60 °C, 24 h; e) Br_2, CH_2Cl_2.

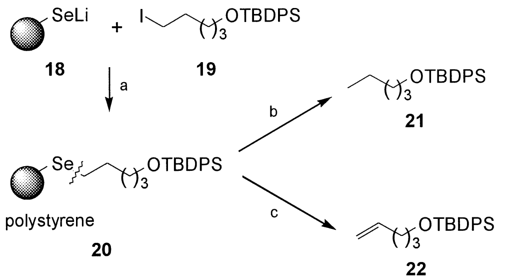
The silicon linker, which is now commercially available,[5b] has been improved by various other groups[10] and is also suitable as a traceless linker for allyl silanes to give alkenes.[11a]

Sulfone linker (Janda): Recently, Janda et al. reported the use of sulfones as suitable anchoring groups for alkanes in soluble polymer chemistry.[12] After oxidation of a sulfide to a sulfone **16**, treatment of these sulfones with sodium/mercury gives rise to the formation of the parent hydrocarbon **17** in high yields (Scheme 7). However, aqueous work-up is necessary to provide the pure products.



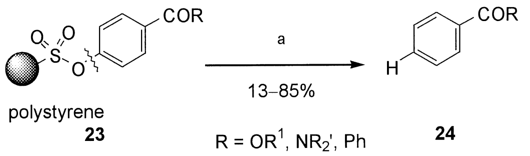
Scheme 7. The sulfone traceless linker for alkanes: a) 5% Na/Hg, Na_2HPO_4, MeOH, −40 °C→0 °C, 96%.

Selenium linker (Nicolaou, Ruhland): The selenium–carbon bond is prone, owing to its weakness, to undergo homolytic cleavage to give radicals. This fact was first recognized and used for solid-phase synthesis by Heitz et al. in 1976.[13a] Recently Nicolaou et al.[13b] and Ruhland et al.[13c] independently developed more efficient methods for the preparation of selenium-containing supports in their development of traceless linkers. Starting from polystyrene, various steps, including selenation with selenium powder or MeSeSeMe, give rise to the formation of selenium resins, which may be alkylated to give selenoethers **20**. The traceless cleavage yielding alkanes **21** can be conducted by reduction with tributyltinhydride, while the formation of alkenes **22** can be observed after mild oxidation (Scheme 8). This linker holds promise for wide applicability, since the starting materials (alkenes, alkyl halides) are widely available, although toxicity of reagents and starting materials have to be considered.



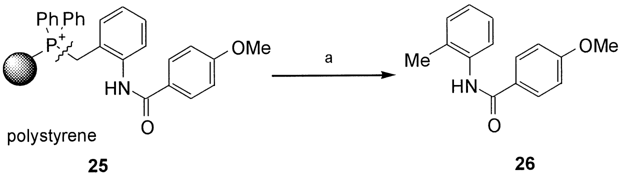
Scheme 8. The selenium traceless linker for alkanes and arenes: a) THF, 23 °C, 12 h; b) 2 equiv of Bu_3SnH, AIBN (0.5 mol%), PhMe, reflux, 6 h, 89% (2 steps); c) 1 equiv of H_2O_2 (30%), THF, 23 °C, 12 h, 78% (2 steps).

Oxygen linker (Wustrow): Electron-poor aryl sulfonates are suitable candidates for oxidative palladium insertion. Hence, immobilized phenol sulfonates **23** have been employed in a palladium-catalyzed reductive cleavage that uses formic acid to yield arenes **24** with overall traceless cleavage (Scheme 9).[14] It might be anticipated that this type of linker is also suitable for functionalization (see below).



Scheme 9. The sulfonate traceless linker for arenes: a) HCO_2H, Et_3N, $[Pd(OAc)_2]$, dppp, DMF, 140 °C; dppp = 1,3-bis(diphenylphosphino)propane.

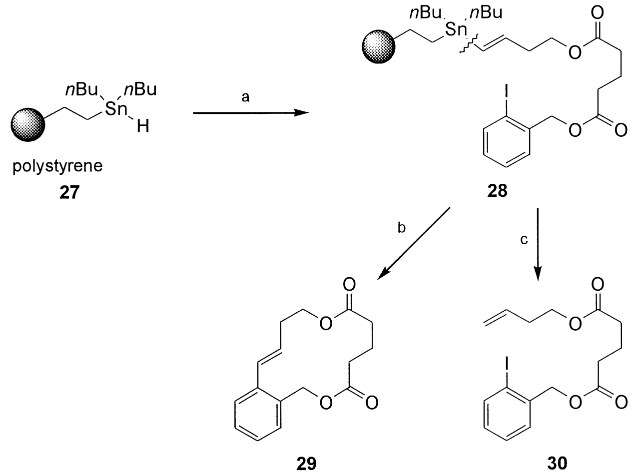
Phosphorous-based linker (Hughes): It is well known that the phosphorus–carbon bond in phosphonium salts is readily cleavable as demonstrated in their use as Wittig salts. However, this bond can also be cleaved by the aid of a base in absence of an aldehyde. Hence, the polymer-bound phosphonium salt **25** gives a direct access to methylarenes **26** (Scheme 10). An interesting feature of this linker is the fact



Scheme 10. The phosphorus traceless linker for methylarenes: a) NaOMe, MeOH, reflux.

that carbonyl compounds can be olefinated and this leads to a cleavage – olefination linker system.[15]

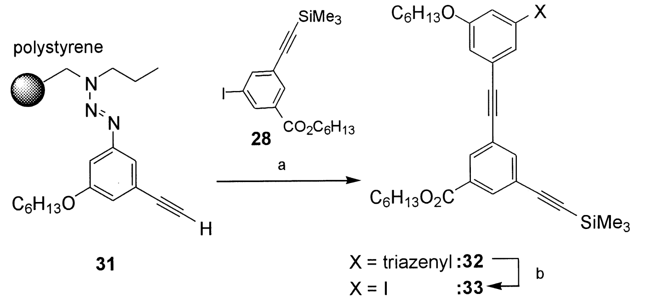
Tin-based linker (Nicolaou): Tin hydride reagents are versatile tools for the functionalization of alkenes and alkynes. Based on this concept, Nicolaou and co-workers developed a polymer-bound tin hydride **27**,[16] which reacts under hydrostannylation (or nucleophilic attack on the tin chloride with a vinyl lithium) with alkynes to give alkenylstannanes **28** (Scheme 11). The latter undergo, after further transformation, proteolytic traceless cleavage, to yield unsubstituted alkenes **30**. Moreover, the stannane can be employed as a starting material for an intramolecular Stille reaction to produce larger ring systems (e.g., compound **29**, Scheme 11).[16b]



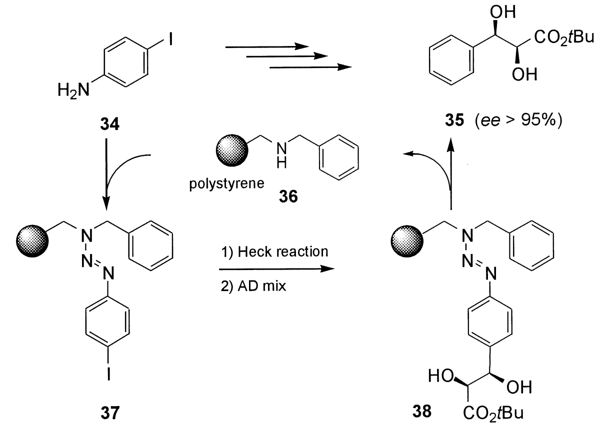
Scheme 11. The tin traceless linker for alkenes: a) 1. 3-butynol, AIBN, 110 °C; 2. glutar anhydride, DMAP; 3. DCC, DMAP, (2-iodophenyl)-methanol; b) $[Pd(PPh_3)_4]$, toluene, 100 °C, 51 %; c) H^+.

Decarboxylation: The decarboxylation of arenes[17] and alkanes[18] has been used to generate the parent hydrocarbons. Since the neighboring group effect is essential, limitation to special substrates is required.

Nitrogen linker 2—the triazene T1 linker (Moore, Tour, Bräse): One possible method for converting functionalized arenes into the corresponding hydrocarbons is the reduction of diazonium compounds. As these compounds react with amines to yield triazenes, which can be transformed back to diazonium compounds under mildly acidic conditions, the use of triazenes as linkers seemed to be a very promising strategy. Inspired by the use of triazenes in the total synthesis of vancomycin[19] and the pioneering work of Moore et al.[20] and Tour et al.[21] in the attachment of triazenes to a solid support and the final detachment to give iodoarenes **33** (Scheme 12), we were interested in developing a traceless-linker system based on triazenes.[22] Starting from a secondary amine resin **36**, and diazonium salts derived from readily available anilines **34**, the triazene system **37** was built up in a single step (Scheme 13). After chemical transformation, for example, the Heck reaction and asymmetric dihydroxylation (**37**→**38**), cleavage can be affected by treatment with acid in the presence of a reducing agent, such as THF, to give the product **35** in good yield (Scheme 13). It is distinct from the existing alternatives by its accessibility and robustness, as well as its ability to regenerate the resin. The broadness of applications in a number of organic reactions can be anticipated. The **T1** triazene linker system is now commercially available.[5b]

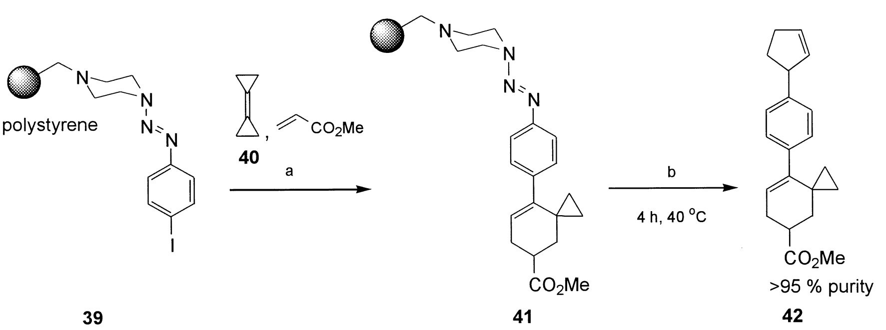


Scheme 12. The triazene linker for the synthesis of iodo arenes: a) $[Pd_2(dba)_3]$, CuI, PPh_3, Et_3N, 65 °C, 12 h; b) MeI, 110 °C.

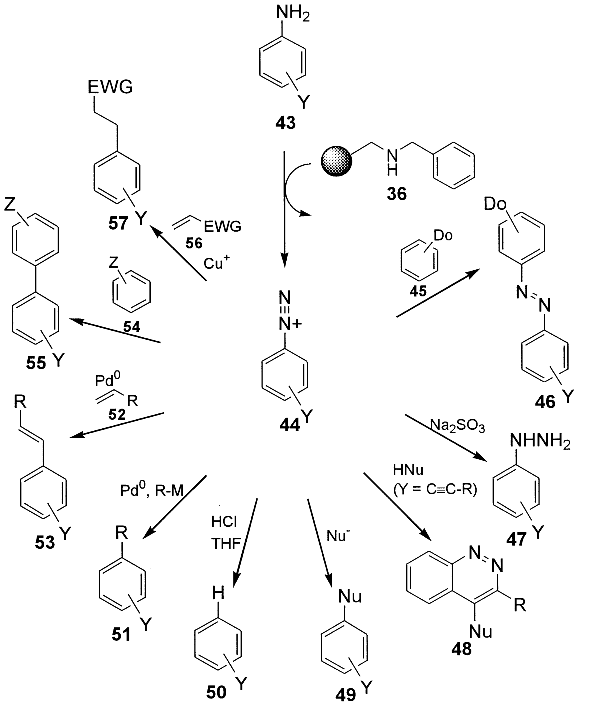


Scheme 13. The triazene C–H traceless linker (**T1**) for arenes.

Possibilities for T1—Heck cross-coupling and other multidirectional cleavage reactions: Besides the possibility of conducting traceless cleavage from solid support, a cleavage – cross-coupling can be achieved by using palladium catalysis.[23] Diazonium salts are known to undergo insertion of palladium, thus making them suitable substrates for a Heck reaction. Starting from the triazene resin **39**, an all-carbon three-component reaction with the strained bicyclopropylidene **40**[24a] gives rise to a spirooctene resin **41**. Liberation of the diazonium salt and subsequent coupling with various alkenes proceeded smoothly under mild thermal conditions (12 h at 40 °C in MeOH) to give the product **42** in high yield (Scheme 14).[23, 24b] The use of palladium on charcoal as catalyst allows couplings in lower purity (87 %), but is advantageous with regard to its ease of removal by filtration, that is, the filtrate is nearly colorless. The catalyst can be used for a subsequent hydrogenation reaction, thus allowing the formal coupling of alkyl groups. In addition, functionalization of triazene resins upon cleavage leads to the formation of aryl halides (**49**, Nu = halogen),[25b] phenols and aryl ethers (**49**, Nu = OH and OR),[25b] azo compounds **46**, biaryls **55** by a Gomberg – Bachmann reaction, Meerwein alkylation products **57**, or Richter products like cinnolines **48** (Scheme 15).[25a]



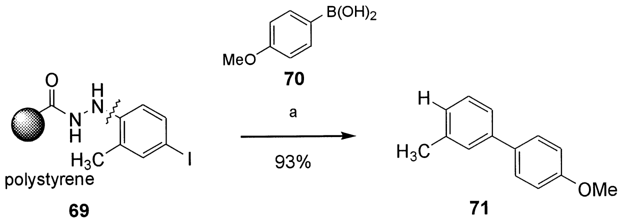
Scheme 14. The triazene linker for the Heck cross-coupling strategy: a) [Pd(OAc)$_2$], PPh$_3$, Et$_3$N, DMF, 24 h, 80 °C; b) cyclopentene, [Pd(OAc)$_2$], TFA, MeOH.



Scheme 15. Possibilities with the **T1** linker.

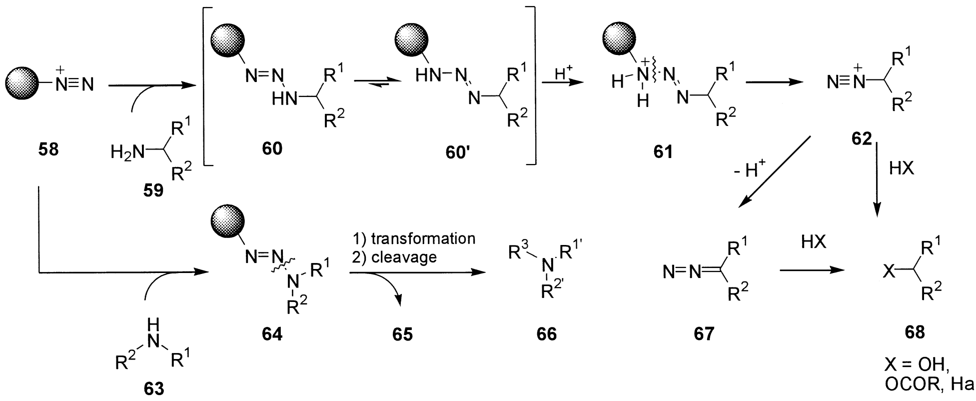
The T2 linker: A new linker strategy for the attachment of primary and secondary aliphatic amines was developed based on the established triazene concept. Starting from Merrifield resin, an immobilized diazonium salt **58** was prepared in two steps. Treatment with various primary (**59**) or secondary amines (**63**) gave the triazenes **60** and **64**, respectively, which in turn were cleaved off by treatment with mild acids (Scheme 16). The triazenes have been shown to be base stable and were used in various types of transformations. The overall process is high-yielding and efficient, and even sensitive amines, such as 4-piperidone, can successfully be attached to a solid support.[26] Moreover, disubstituted triazenes **60** undergo cleavage to yield aliphatic diazonium ions **62**, which in turn solvolyze in the presence of nucleophiles to give alkyl halides or esters **68**.[27]

Nitrogen linker 3—hydrazides (Waldmann): Acyl aryl diazenes are known to fragment upon treatment with nucleophiles, a strategy that has been used for a linker for carboxylic acid derivatives.[28a] Waldmann et al. recently developed a traceless linker for arenes based on this methodology.[28b] Starting from a hydrazide resin **69**, which is converted into an activated species by oxidation, detachment of the molecule is carried out by the addition of nucleophiles (Scheme 17). This safety-catch principle—the activated linker is generated prior to cleavage—shows promising stability in palladium-catalyzed reactions.



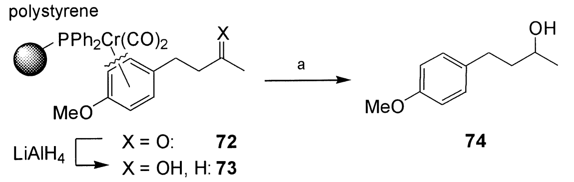
Scheme 17. The hydrazide linker for arenes: a) 1. 10 equiv **70**, 2 equiv K$_3$PO$_4$, 0.02 equiv [Pd(PPh$_3$)$_4$], DMF/H$_2$O (6/1), 80 °C, 24 h; 2. [Cu(OAc)$_2$], nPrNH$_2$, RT, 2 h.

π-Complexation strategy (Gibson and Hales): The presented examples of traceless linkers have one common feature: An unfunctionalized C–H bond is the result of the cleavage of a



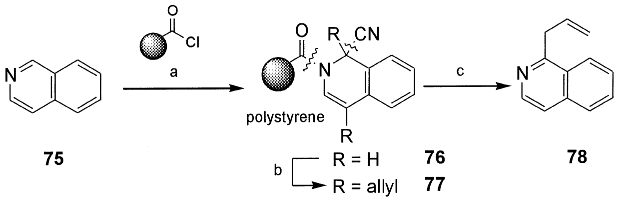
Scheme 16. The concept of a triazene linker for amines (**T2**).

carbon–heteroatom bond that makes a functionalization at this point of attachment impossible. Recently, Gibson, Hales, and Peplow demonstrated that arenes could be attached to a solid support through the use of chromium arene complexes **72** (Scheme 18).[29a] This method even allows, at least from a theoretical point of view, complete variation of the arene backbone; however, modification of the arene ring system might be limited to a certain extent. It has already been shown that various other metals or unsaturated molecules (e.g., alkynes with dicobalt fragments) can lead to interesting examples.[29d]



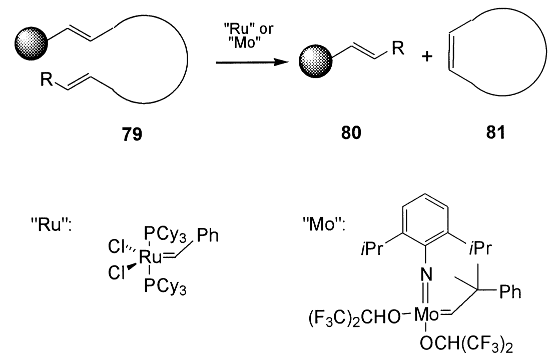
Scheme 18. The π-complexation strategy for arenes: a) pyridine, 2 h, reflux.

“Expanded valency”—the Reissert concept (Kurth): The only example so far for an attachment of heteroarenes by an addition/elimination strategy has been devised by Kurth et al.[30] While arenes are more or less resistant towards addition, heteroaromatic systems such as isoquinolines **75** are prone to the addition of nucleophiles. Subsequent addition of electrophiles furnishes the so-called Reissert compounds **76** (Scheme 19). These are stable compounds that, for example, can be alkylated. In case of solid-phase synthesis, the electrophile was chosen to be a polymer-based acid chloride. The detachment can be carried out by simple addition of hydroxide ions. This concept, although not traceless by the above definition, has the potential to be expanded to other (hetero)cyclic systems.



Scheme 19. Reissert complex strategy: a) TMSCN, CH_2Cl_2, 48 h; b) LDA, allylbromide; c) KOH, THF/H_2O.

Cleavage by metathesis (Maarseveen, Blechert, Nicolaou): Cleavage by metathesis was used by various groups to accomplish either detachment by cyclization (ring-closing metathesis, RCM),[31] intermolecular metathesis (cross metathesis)[32] or intramolecular metathesis (Scheme 20).[33] One advantage of cleavage by metathesis is the possibility to introduce fragments with additional functionalities. The successful examples include the total synthesis of epothilone by this cleavage strategy.[34]



Scheme 20. Cleavage by metathesis.

Conclusion

If we try to answer the question in the title “Traceless linkers—only disappearing links in solid-phase organic synthesis?” we have to say “Yes”. A traceless linker is cleaved leaving no functionalization at the original linking site and its purpose is to just *disappear*. For multidirectional-cleavage linker systems the answer is “No”. Linker systems allow the introduction of certain atoms or molecule fragments and will play an important role for the development of diverse organic substance libraries. It is important to point out that the final diversification is achieved in the cleavage step and not in an additional solution-phase reaction step after the cleavage. However, only few linkers systems that are applicable for a wider range of substrates have been developed so far. As these linker systems offer the widest possibilities for the final diversification of the synthesized library, they will experience increasing attention in the future.

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