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The Virtue of the Multifunctional Triazene Linkers in the Efficient Solid-Phase Synthesis of Heterocycle Libraries

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ABSTRACT

With the implementation of combinatorial chemistry into the modern drug discovery process, the approach to novel diverse heterocycle libraries is an indispensable requirement. Triazenes, which are concealed diazonium salts, can be used to link functionalized arenes and amines to generate various heterocyclic structures, namely, benzoannelated nitrogen heterocycles, upon cleavage from the resin. Since triazene anchors are stable toward various reagents and perform well under a range of reaction conditions, these multifunctional linkers are well suited for automated solid-phase syntheses and the syntheses of complex organic molecules, such as natural products, on solid supports.

1. Introduction

One of the main objectives of organic and medicinal chemistry is the design and small-scale synthesis of drug leads and large-scale production of molecules valuable as human therapeutic agents. Over the past decade, the drug discovery paradigm has undergone extraordinary changes. With the rapid exploration of potential drug candidates via high-throughput screening, the current challenge is the ever-increasing demand for novel low molecular weight compounds to satisfy and sustain such screening efforts. As a result, innovative combinatorial approaches[1] toward novel druglike compounds have become key tools for successful drug discovery programs.

Advances in solid-phase organic synthesis (SPOS) are vital for the success of combinatorial chemistry in drug discovery. This method offers the opportunity to synthesize molecules via innovative routes, which may be difficult, if not impossible, to achieve using traditional solution-phase methods. It also offers the possibility of rapidly synthesizing druglike molecules without the tedious and time-consuming purifications that are typically associated with solution-phase chemistry.

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The generation of libraries creating molecular diversity for drug discovery was originally focused on the syntheses of peptide and nucleotide libraries. However, the limitation of such libraries is associated with the pharmacokinetic properties of large polymeric and often hydrophilic structures, which in turn make these molecules less suitable as leads in drug discovery.[2] The rapid generation of nonpolymeric small molecule libraries with sufficient diversity can be effectively executed by employing combinatorial or simultaneous parallel syntheses on solid supports.[3,4]

Heterocycles such as indoles,[5] tetrahydroquinolines, and dihydrobenzofurans play a pivotal role in the drug discovery process.[6] Substituted heterocyclic compounds generally offer a high degree of structural diversity and have had a substantial impact when used as therapeutic agents. Therefore, the cost-effective creation of new and versatile heterocyclic core structures and the approach to them are vital for many innovative drug discovery programs. The roots of validated syntheses of heterocycles on solid supports can be traced back to the early 1970s when Camps et al.[7] demonstrated the synthesis of benzodiazepines on solid supports. These heterocyclic structures are a particularly interesting class of compounds with far-reaching biological activities and favorable pharmacokinetic properties.[8]

The initial spark in the interest for small-molecule libraries emerged from seminal discoveries in the early 1990s. With the announcement of a benzodiazepine library by the Ellman group in 1992,[9] the development of strategies for the generation of heterocyclic libraries on solid supports became a great point of interest in combinatorial chemistry.[10] At that time, innovative carbon−carbon bond forming reactions and the manipulation of oxidation states, necessary for the synthesis of diverse small molecule libraries, were rarely used in solid-phase synthesis. Within the past decade, an exponential increase of new methods for solid-phase chemistry has emerged.

2. Multifunctional Linkers

Although transformations of chemical functionalities and assemblies of building blocks on solid supports are similar to those in conventional solution-phase chemistry, linkers and their associated strategies play a pivotal role in the successful implementation of solid-phase organic chemistry and its application to combinatorial chemistry.[11,12] The bond between a linker and an immobilized compound is sensitive to certain reaction conditions leading to bond cleavage and the release of the final compound from the immobilized linker. Traditionally, linkers were designed to release one particular functional group, acting more or less like bulky protecting groups. These types of linkers could be defined as monofunctional linkers. While the release of carboxylic acids and amines, which are essential for peptide synthesis, has been extensively studied, the synthesis of low molecular weight compound

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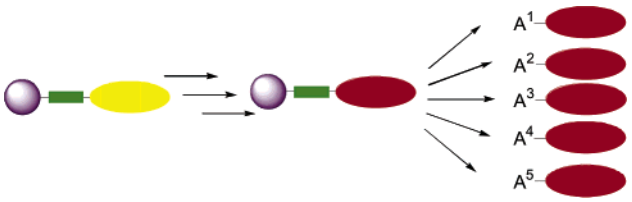


FIGURE 1. Diversity through Multifunctional Cleavage.

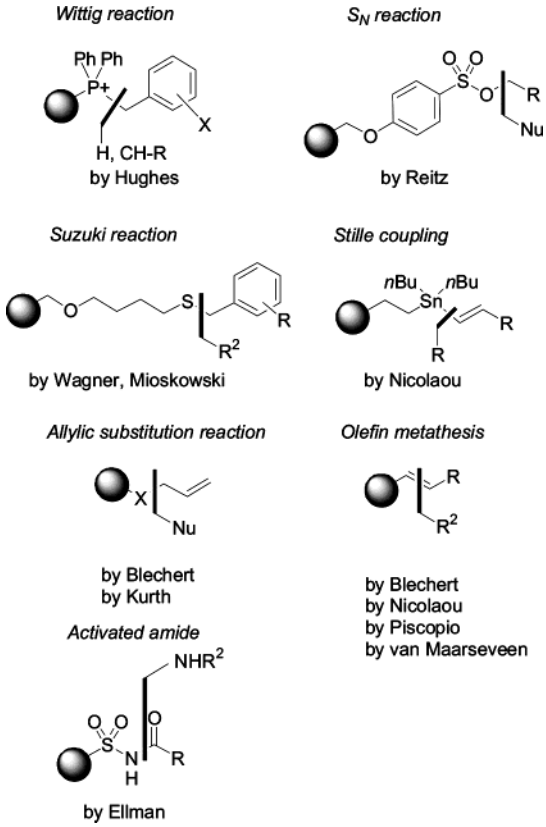


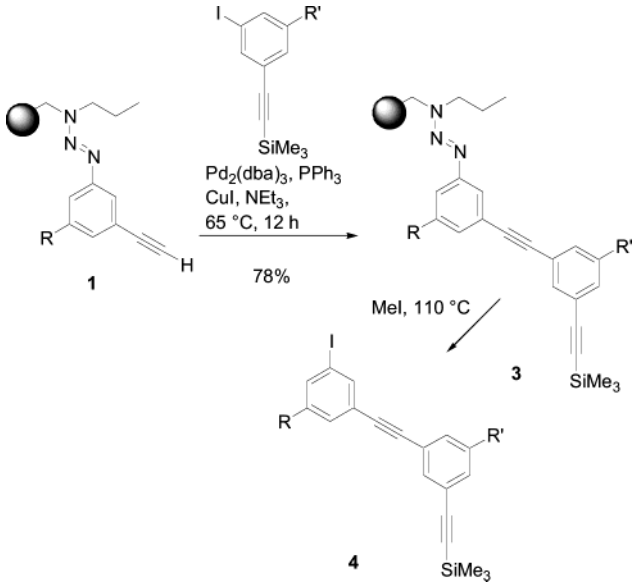
FIGURE 2. Examples for Multifunctional Linkers.[12]

libraries requires more versatile linkers and cleavage strategies.[13]

One advantage that so-called multifunctional linkers have over their monofunctional counterparts is that they offer the opportunity to incorporate additional diversities upon cleavage.[14] Monofunctional linkers on the other hand are limited to the synthesis of only one type of compound in a library. Therefore, the number of new functionalities can multiply the number of compounds produced. This approach is particular attractive if the solid-phase synthesis has been performed in a linear sequence rather than a combinatorial mode. This is especially interesting in the syntheses of complex molecules, such as natural products, on solid supports.

If the linker is susceptible to cleavage upon treatment with different building blocks, then a substantial library of novel molecules could be prepared from one linked compound (Figure 1). Literature examples for multifunctional linkers can be found for various types of anchoring groups (Figure 2).[12] Notable examples are the metal-catalyzed cleaving reactions that offer the possibility of generating diversity upon cleavage from solid supports. At this point, it should be taken into account that heavy

Scheme 1. Early Use of Triazenes as Linkers in the Synthesis of Iodinated Arenes by Moore et al.[15]



metals may interfere with the biological testing of liberated compounds. Therefore, sequestering techniques, such as scavenger resins, are indispensable.

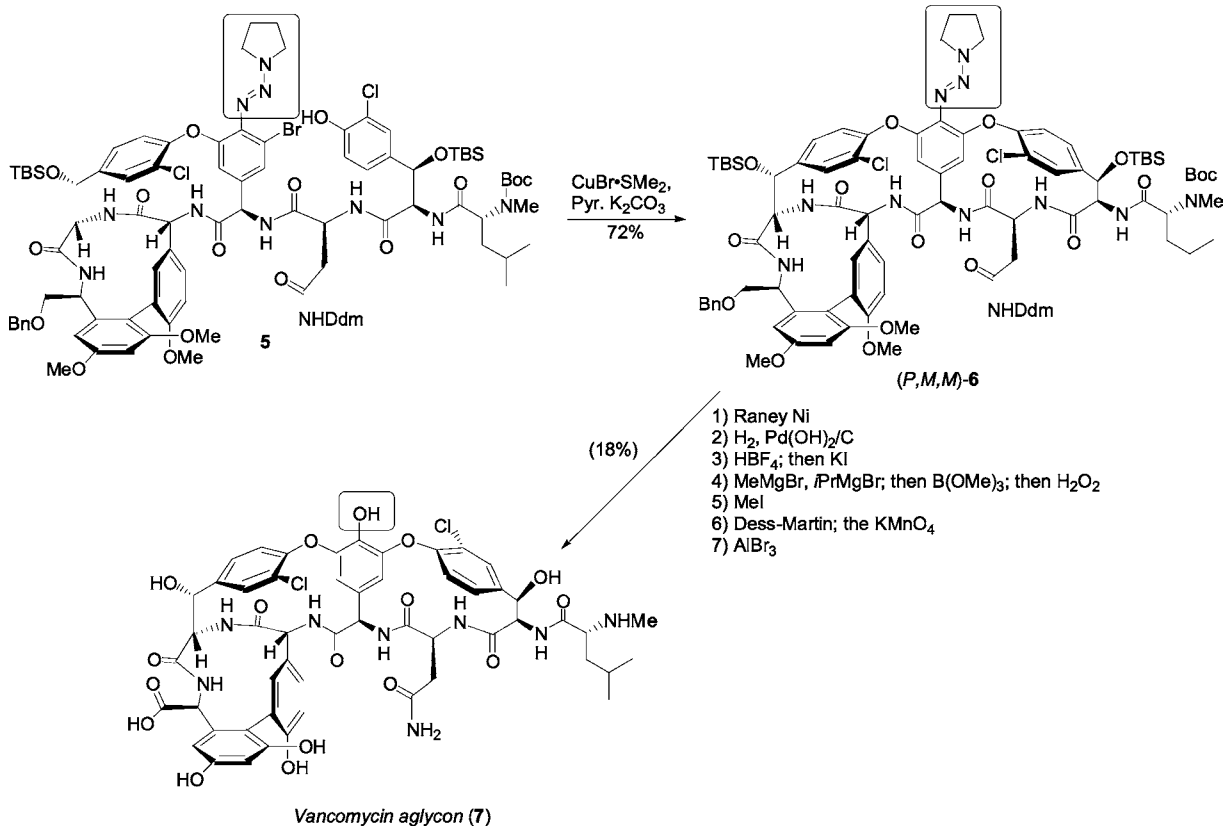
When thinking about using a multifunctional linker, one must first consider the nature of the cleavage reagent and the cleaving step. For example, cleavage of an immobilized compound anchored via an ester linkage with excess of a Grignard reagent will require an aqueous workup. In addition to the development of tedious workup and product-isolation procedures, during the workup itself, it is likely that valuable material will be lost. Thus, supplementary building blocks need to possess the ability to easily be removed (i.e., must be volatile, soluble in certain solvents, able to react with scavenger resins, etc.) and should not interfere with the characteristics of the whole library, such as their biological properties.

3. Triazenes as Linkers

The chemistry of diazonium salts provides tremendous opportunities for the construction of various compounds with particular emphasis on heterocyclic structures. Triazenes, which are protected diazonium ions, have much to offer. They allow for interesting new possibilities for activation of the ortho position of arenes by coordination of metal ions, by lowering the electron density of the arene ring, or both and are also quite robust, making them ideal precursors for diazonium salts. Inspired by the pioneering work of Moore et al.[15] and Tour et al.[16] in the synthesis of triazenes on solid supports to produce iodoarenes (Scheme 1; resin **8**, Figure 3) and the flexible use of triazenes in the total synthesis of the complex glycopeptide natural product vancomycin by the Nicolaou group[17] (Scheme 2), we developed two sets of linker systems based on the triazene chemistry (Figure 3).[18]

The T1 linker system consists of 3,3-dialkyl-1-aryl triazenes bound to the support via the alkyl chain (Figure 3) either with a dibenzyl-type (resin **9**) or a piperazinyl-

Scheme 2. Key Step Using Triazenes in the Total Synthesis of the Vancomycin Aglycon by Nicolaou et al.[17]



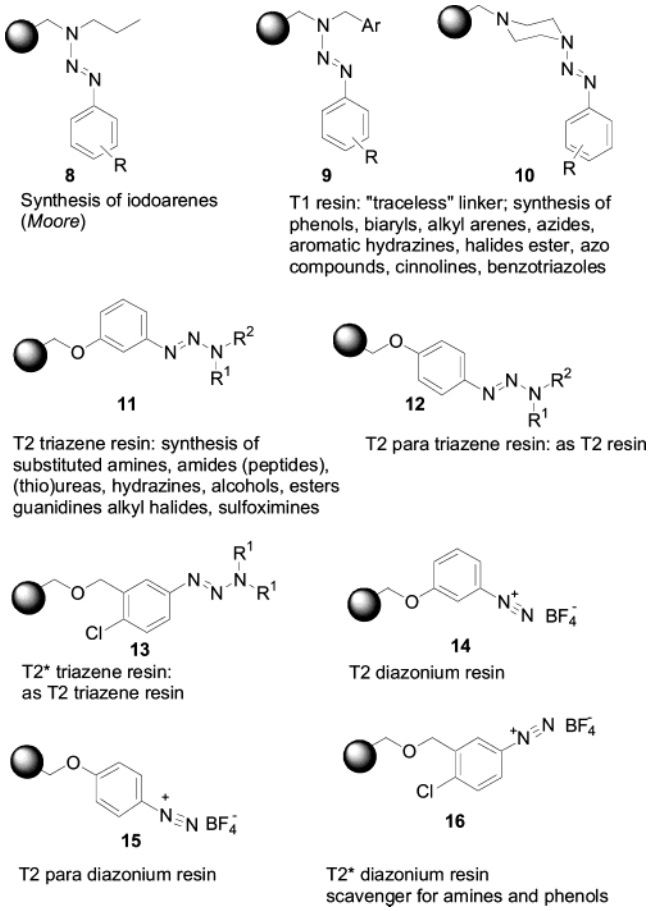
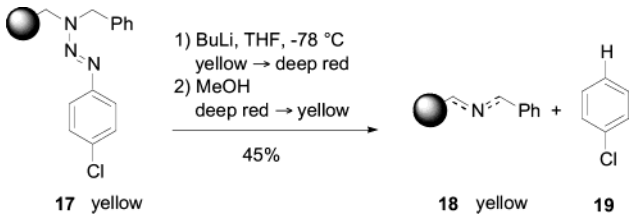


FIGURE 3. The Triazene Linkers.

Scheme 3. Metalation and Fragmentation of Triazene T1 Resin 17



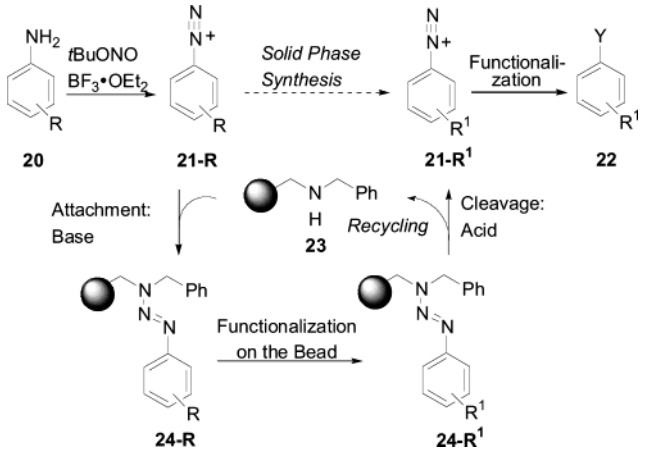
type (resin **10**) anchoring. This enables the synthesis of functionalized arenes, including so-called traceless cleavage[18] (see below). The T2 linker family is based on immobilized aryl diazonium salts (compounds **14**,[19] **15**,[20] and **16**[21]) and aryl triazenes **11**−**13**.

Triazenes generally are stable toward daylight (for a laser-assisted photo cleavage of the T2 system at 355 nm[22]), oxygen (air), moisture, reducing agents, oxidizing agents, and transition metal complexes. Alkyllithium reagents can be used for the metalation of simple alkyl-substituted triazenes such as the piperazinyl-type T1 linker.[18] Benzylic-substituted triazenes on the other hand undergo a metalation/fragmentation reaction due to their enhanced acidity (Scheme 3).[23,24] However, triazenes are generally labile toward Brønsted acids and certain Lewis acids, producing diazonium salts and amines.

4. The Triazene T1 Linker

The triazene T1 linker has successfully been used as a linker for arenes. Up to now, approximately 100 different anilines **20** have been immobilized by our group (Scheme

Scheme 4. Concept of the T1 Linker[27]



4).[25] The synthesis usually starts with the diazotation of an aniline in an organic solvent using alkyl nitrite reagents. The immobilization on solid support has been successfully carried out using benzylaminopolystyrene or piperazinylmethylpolystyrene resins, each one accessible from the Merrifield resin in only one step with loadings at about 1 mmol/g (1−2% cross-linked with divinylbenzene). Although both linkers are equally suitable, they both have slight drawbacks. The benzylamino resin is more sensitive toward strong bases (i.e., BuLi),[18,24] while the piperazine resin is not available with a high loading capacity due to possible cross-linking during its preparation from the Merrifield resin.

Functionalization on the polymer bead has been demonstrated extensively. Acidic cleavage of the triazene resin yields the recyclable amine resin **23** and the modified aryl diazonium salts **21-R^1**, which can be further transformed directly during the cleavage step in high yields (>90%) and purities (>90−95%) (Scheme 5).

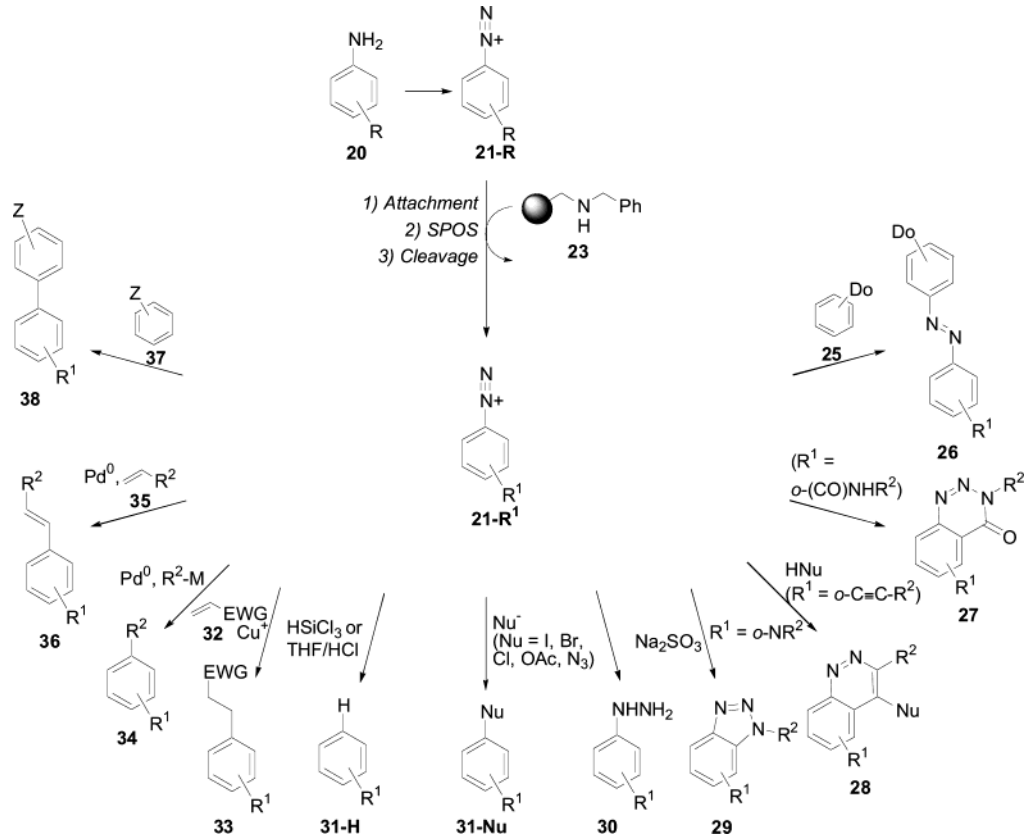
5. Concepts for Heterocycle Synthesis

We therefore anticipated using the triazene T1 linker for the synthesis of diverse heterocycle libraries. In concept I, the heterocyclic core is generated on the bead using (classical) ring-formation reactions followed by a subsequent multifunctional cleavage (Scheme 6). This leads to the library members. In concept II (Scheme 6), however, the diazonium ion was incorporated directly into the heterocycle core to add two extra nitrogen atoms. The flexibility of the azide functionality[26] has been advantageously used in concept III (Scheme 6) to yield heterocycles with an odd number of nitrogen atoms.

6. Traceless Linkers Are Useful for the Synthesis of Unbiased Compound Libraries

One prominent class of monofunctional anchors that provide access to molecules having "no attachment memory" for solid-phase synthesis are called traceless or "clean break" linkers.[13,27−30] Although this definition could be used for the classification of linkers, one would advantageously define a traceless linker as being able to

Scheme 5. Possibilities of the T1 Triazene Linker



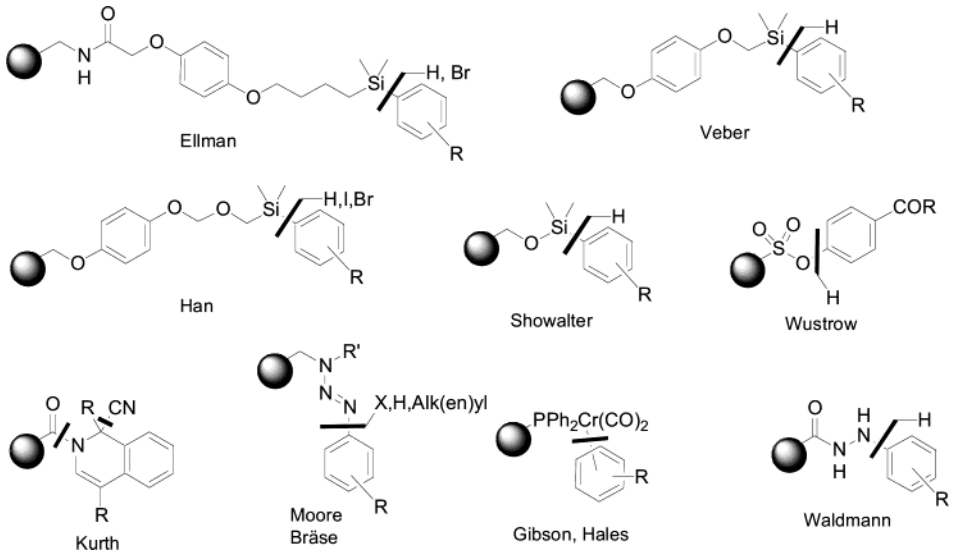
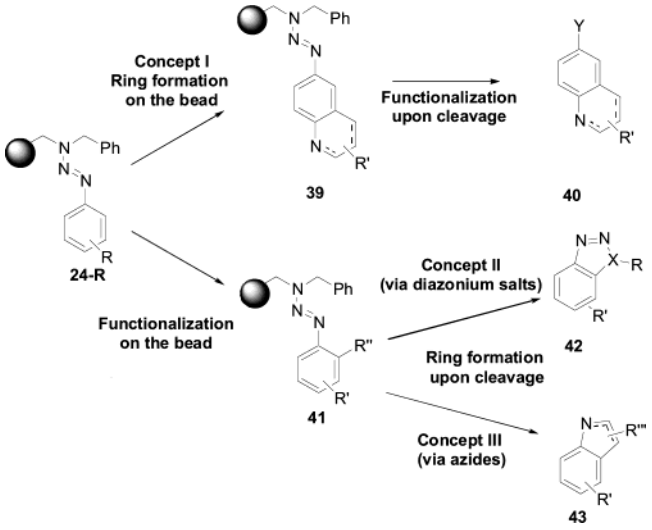
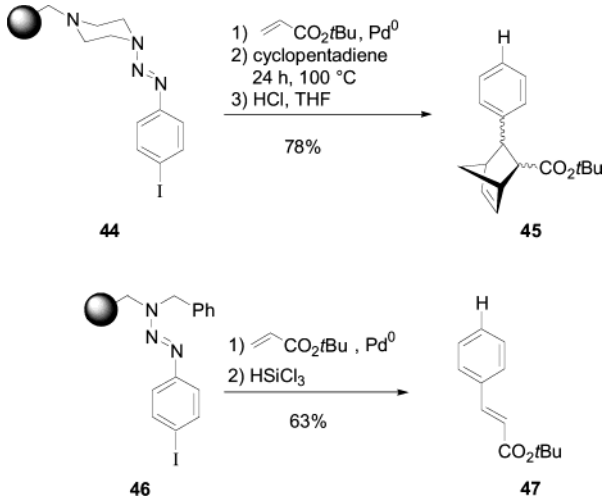


FIGURE 4. Some Linkers for Traceless Cleavage.

Scheme 6. Concept for Cleavage/Heterocyclization with the T1 System



Scheme 7. The T1 Linker for Traceless Cleavage

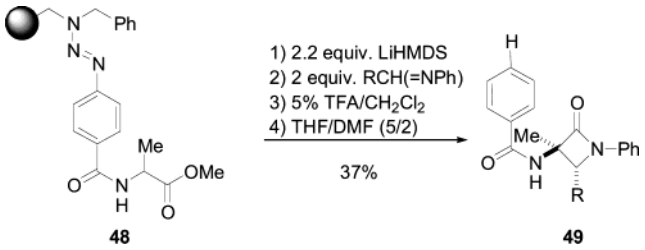


generate new C−H bonds or to keep all functionalities unchanged upon cleavage. Thus, this type of linker allows for the formation of arenes, alkanes, alkenes, and alkynes while bearing no chemical evidence of attachment to a support. For that reason, this anchoring mode potentially has no undesirable constraints on the structure of the products. Traceless linkers have been developed based on silyl linkers,[31] acylhydrazines,[32] dialkyl sulfones,[33] olefin metathesis cleavage (RCM),[12] arylsulfonates,[34] phosphonium salts,[35] phosphine−chromium complexes,[36] and α-aryloxy ketones (Figure 4).[37] At the beginning of our studies at the end of 1997, the silicon-derived linkers were essentially the only option available for the traceless detachment of arenes. Therefore, the triazene linkers were anticipated as traceless linkers at the start point of our studies.

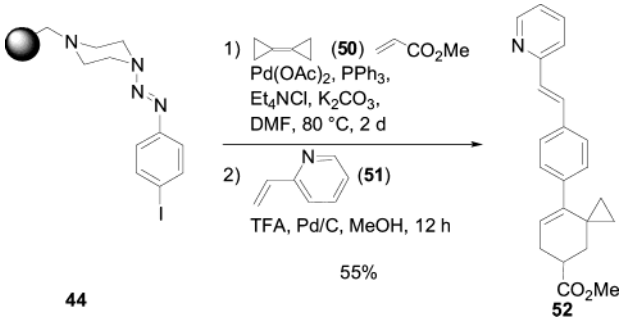
As pointed out above, acidic media cleave the triazenes to yield the diazonium salts. The diazonium salts can be further functionalized, as demonstrated in the case of the reduction to the hydrocarbon **31-Nu** (Nu = H) in THF with the aid of ultrasound[18] via a radical pathway. A newly found reagent for this reduction is trichlorosilane.[23] This volatile, inexpensive reagent not only serves as a source of trace-quantity hydrochloric acid to cleave the triazene moiety but also serves as a hydride donor, cleanly reducing the diazonium ions (Scheme 7). The synthetic benefit of the T1 linker has been demonstrated in various short reaction sequences. For example, cinnamic esters were synthesized in a sequence starting from the iodoarene resins **44** and **46**. A Heck coupling[38] with acrylates using palladium catalysis yields immobilized cinnamates. After further transformations such as a Diels−Alder reaction, they could have been cleaved with a HCl/THF mixture and could generate high yields of ester **45** without the need of further purification or workup procedures (Scheme 7). Alternately, these could have been detached directly with trichlorosilane to give rise to cinnamate derivative **47**.

An application of the T1 linker toward the synthesis of heterocycle libraries was demonstrated by Enders et al.[39] They used the traceless cleavage mode of the triazene T1

Scheme 8. Synthesis of β-Lactams by Enders et al. Using the T1 Linker



Scheme 9. Three-Component Heck–Diels–Alder Regime and Subsequent Cleavage by Heck Reaction



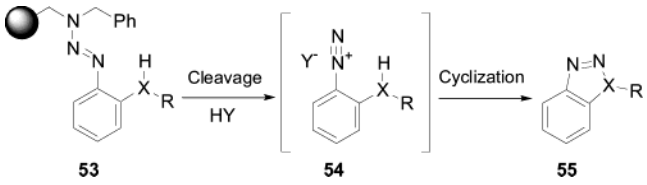
linker to generate β-lactams **49** via the imine-ester enolate condensation route (Scheme 8).

7. Multifunctional Cleavage

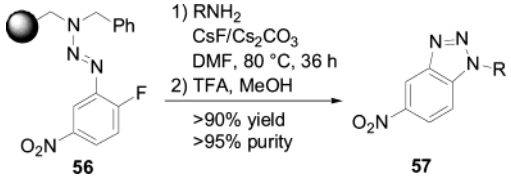
Functionalization during the cleavage process is still an attractive strategy to research for the generation of diverse compound libraries. Triazene linkers are ideal for this purpose.

As already shown by Moore et al. and Tour et al., the addition of methyl iodide to a triazene resin at elevated temperatures (110 °C) gives rise to aryl iodides **31-Nu** (Nu = I) in excellent yields.[15,16] While the range of electrophiles that could have been employed was quite broad, the most versatile benefit was the development of a cleavage cross-coupling strategy.[40] Starting from modified triazene resins, a one-pot cleavage cross-coupling reaction was conducted with 2 equiv of trifluoroacetic acid in MeOH at 0 °C to yield a diazonium intermediate **21-R¹**. In situ coupling with either electron-deficient or electron-rich alkenes **35** in the presence of catalytic amounts (5 mol %) of palladium(II) acetate provided the corresponding products **36** in excellent yields and purities (Scheme 5). This one-pot cleavage cross-coupling reaction affords salt-free products, since the present resin **23** also participates as a "scavenger resin", trapping the excess trifluoroacetic acid. In addition, using palladium on charcoal as the catalyst in the cross-coupling reaction has the advantage of decreasing palladium contamination as well as providing the conditions for a subsequent hydrogenation reaction. Multicomponent Heck reactions such as the domino Heck–Diels–Alder reaction in Scheme 9 are possible in this context leading to further diversification.[41]

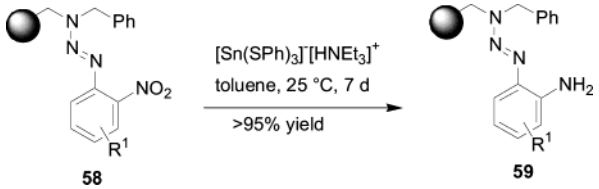
Scheme 10. Concept II for Cleavage/Heterocyclization Using the Diazonium Functionality



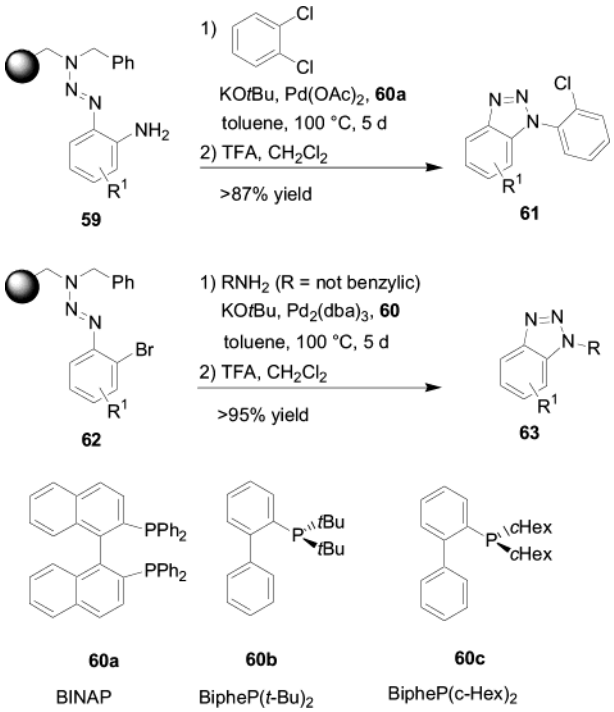
Scheme 11. Synthesis of 5-Nitrobenzotriazoles 57 Using Fluoronitro Resin 56



Scheme 12. Reduction of *o*-Nitro-Substituted Resins



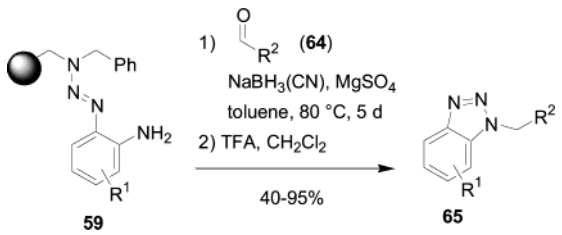
Scheme 13. Hartwig–Buchwald Reactions on Immobilized Anilines or Aryl Halides



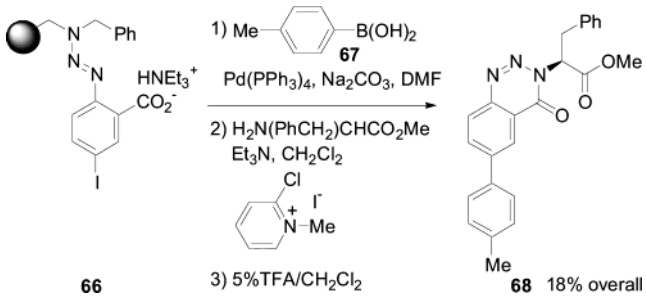
8. Concept II: Cleavage Directly Crafts the Heterocycle

Concept II in Scheme 6 represents a straightforward synthesis of benzoannelated heterocycles (i.e., cinnolines, benzotriazoles, etc.) via a diazonium intermediate and a nucleophilic ortho substituent. While the diazonium group can be lost as nitrogen gas upon cleavage from the resin as shown in the previous examples, a suitable nucleophilic

Scheme 14. Synthesis of Benzotriazoles 65 Using the Reductive Amination Regime



Scheme 15. Synthesis of 6-Aryl-3*H*-benzo[*a*][1,2,3]triazinones 68 Using a Three-Step Sequence



ortho substituent favors cyclization to give heterocyclic structures (Scheme 10). With this approach, various heterocyclic structures are possible.

Benzotriazoles are produced directly through cleavage of *o*-aminoaryl-substituted triazenes instantly followed by a heterocyclization. The latter are accessible, for example, through a nucleophilic displacement[42] from *o*-haloaryl-substituted triazenes.[43] Benzotriazoles are valuable tools for the synthesis of various functional groups, though only benzotriazoles with a simple substitution pattern are used for this purpose.[44] Various 1-alkyl benzotriazoles are biologically active and show nanomolar binding affinities to various proteins despite the fact that this structural unit is not found in nature. However, the antiemetic and neuroleptic compound alizapride (Vergentan) is a 1-unsubstituted 1*H*-benzotriazole used for the treatment of side effects in chemotherapy when cisplatin (Platinol) is used as an antitumor agent.

Thus, it was appealing to combine a S_NAr reaction with the flexibility of the diazonium chemistry. In this case, an immobilized fluoronitrophenyl triazene would have been the equivalent to the Sanger reagent.[42,43]

Starting from commercially available 2-fluoro-5-nitroaniline, this aniline was diazotized and coupled to benzylaminomethylpolystyrene to give the immobilized triazene **56**. After nucleophilic displacement with primary amines to furnish an aniline resin, the cleavage with trifluoroacetic acid in dichloromethane proceeded smoothly at room temperature within minutes, resulting in the desired 1-alkyl-5-nitro-1*H*-benzotriazoles **57** in excellent yield and purities (Scheme 11). This route was successfully adopted for the synthesis of a 200-member library by means of automated synthesis.[43]

Because this strategy is limited to the generation of 5-nitro-substituted benzotriazoles, we sought a different pathway to access the *o*-amino-substituted triazenes. Starting from the *o*-nitro triazenes **58**, reduction under modified Bartra-conditions[45,46] suitable for acid sensitive linkers gave access to the *o*-amino-substituted resins **59** (Scheme 12). The resulting *o*-amino resins **59**, as well as *o*-halo resins **62**, can be used for the preparation of 1-alkyl- and 1-aryl-substituted 1*H*-benzotriazoles under Hartwig–Buchwald conditions.[47] This palladium-catalyzed carbon–nitrogen coupling reaction is well suited for both immobilized anilines and aryl halides, respectively, thus making it particularly attractive (Scheme 13). A drawback is that the absence of moisture and oxygen is crucial for its success. The ligands **60b** and **60c**, however, provide more robust catalyst systems.[47a]

Complementary 1-benzyl- and 1-alkyl-substituted benzotriazoles **65** can be prepared from *o*-amino resins **59** and carbaldehydes **64** via reductive amination (Scheme 14). Aromatic carbaldehydes provide the best results.[46]

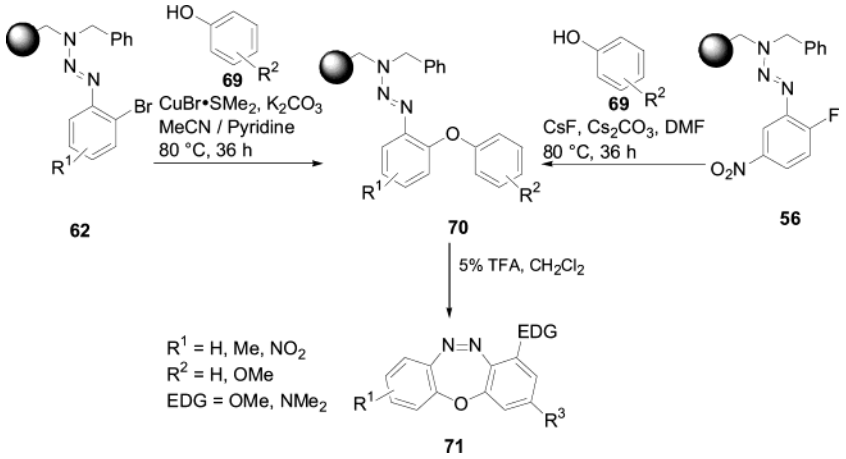
Because the attack of a neighboring nucleophile to the diazonium moiety proceeds in an intramolecular coupling step and the compounds produced are largely less sensitive to acid than dialkyl-substituted triazenes, even the weak nucleophilicity of secondary amides can be used for the generation of heterocycles. Benzo[*a*][1,2,3]triazinones **68** can therefore be formed upon cyclization of suitable substituted benzamides. The latter are accessible from carboxylate resins **66** and amines by peptide coupling methods (Scheme 15). A second point of diversity was established in this case via a Suzuki-type reaction with arylboronic acids **67** to yield a library of 6-aryl-3*H*-benzo-[*a*][1,2,3]triazinones **68** after cleavage.[48]

The Nicolaou variant[49] of the Ullmann diaryl ether synthesis, which takes advantage of the metal-complexing properties of triazenes, was performed for the first time on solid supports with the triazene T1 linker. Immobilized aryl bromides **62** were treated with different phenols **69** in the presence of copper salts furnishing polymer-bound diaryl ethers **70** (Scheme 16). Alternatively, the diaryl ether moiety was formed by nucleophilic substitution reactions with the fluoro nitro resin **56**.[43] Cleavage–intramolecular azo coupling reactions of electron-rich diaryl ethers **70** furnished dibenzoxadiazepines **71** in good yields.[50]

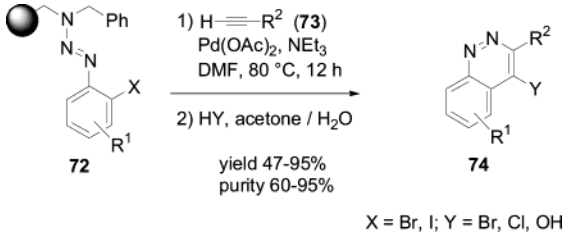
Other heterocyclic systems that can be prepared include cinnolines **74**, which are synthesized from *o*-alkenylaryl or *o*-alkynylaryl triazenes via a cleavage–cyclization strategy. Cyclizations of diazonium salts having an ortho positioned electron-rich double or triple bond have been known for over a century from the von Richter (*ortho*-alkynyl),[51] Widman–Stoermer (*ortho*-alkenyl),[52,53] or Borsche–Koelsch (*ortho*-acetyl)[54,55] reactions; they all yield cinnoline derivatives, an interesting set of building blocks for biologically active compounds. The first solid-phase von Richter[56] reactions were reported with the triazene T1 linker.

Starting with the immobilization of diverse *ortho*-haloaryl diazonium compounds, the palladium-catalyzed cross-coupling reactions[38] were performed under standard conditions [$Pd(OAc)_2$, NEt_3, DMF, 105 °C] with different alkynes affording *ortho*-alkynylarene resins. The von Richter cleavage reactions were conducted with aqueous

Scheme 16. Synthesis of Dibenzoxadiazepines 71



Scheme 17. Synthesis of Cinnolines by the von Richter Reaction[56]



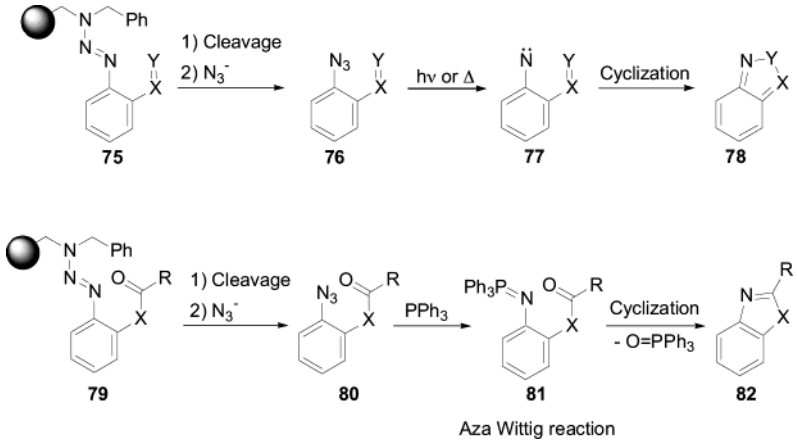
hydrogen chloride or hydrogen bromide to generate the expected cinnoline library format (146 member) in a 47−95% yield range as determined by weight and with a 60−95% purity according to HPLC analysis without any further purifications (Scheme 17).

9. Aryl Azides: Synthesis of Versatile Intermediates for Heterocycle Libraries by a Postcleavage Modification Route of Concept III

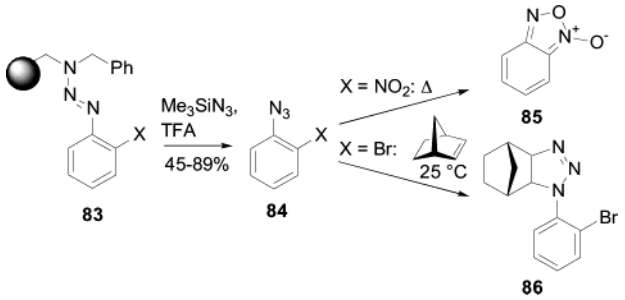
Concept III is based on the flexibility of the azide functionality (Scheme 18). Upon thermolysis or photolysis, appropriately substituted aryl azides lose nitrogen gas to give intermediate nitrenes. These, in turn, cyclize with suitable ortho substituents to give benzoannelated heterocycles. An unsaturated ortho substituent consisting of double bonds incorporating carbon, oxygen, or nitrogen atoms then gives indoles/carbazoles (starting from C═C), indazoles (C═N), benzoisozazoles (C═O), benzooxadiazoles (benzofurazanes) (N═O),[57] benzimidazoles (N═C), or benzotriazoles (N═N) (see also Scheme 11). Alternatively, the intra- or intermolecular *aza*-Wittig reaction[26,58] might also be envisaged and in which case larger ring sizes (six- and seven-membered rings) are also achievable.

As a result, a direct access to aryl azides was conceived. Aryl diazonium salts and azide transfer reagents react directly without the need of a catalyst to generate aryl azides. In contrast to the general Sandmeyer reaction, this reaction does not proceed through the cleavage of the carbon−heteroatom bond. In this particular case, an open-chain pentazene or a cyclic pentazole is formed; this, in turn, loses nitrogen to give the desired aryl azide.[59] With this information at hand, a solid-phase synthetic protocol was developed for the syntheses of aryl azides.[43,57] This synthesis was achieved via cleavage of the triazene resin with 10% TFA in dichloromethane at room temperature in the presence of trimethylsilyl azide, a commercially available, less volatile, and safer azide derivative.[60] The aryl azides **31-Nu** (Nu = N_3) were isolated in good yields (mostly >90%) and high purities (>95%) without further purifications (Schemes 5 and 19).[43,57] The required mild cleavage conditions allow the synthesis of various func-

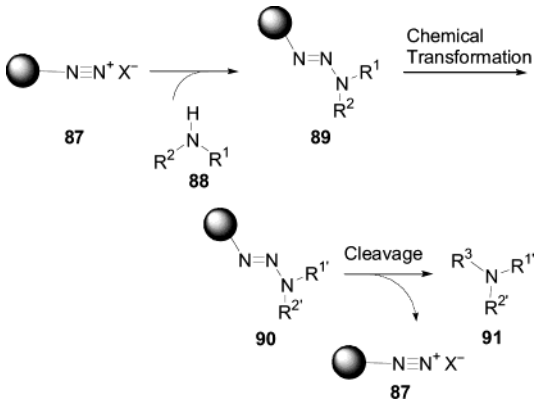
Scheme 18. Concept III for Cleavage/Heterocyclization Using Azide Functionality



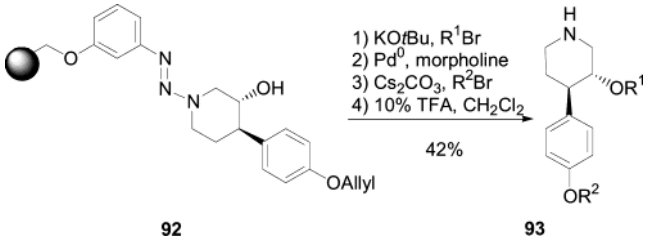
Scheme 19. Synthesis and Postcleavage Modification of Aryl Azides



Scheme 20. The Concept of the Diazonium Anchor T2



Scheme 21. Synthesis of Aspartic Peptidase Inhibitors by Rich et al.[62]



tionalized arenes. This was demonstrated in the preparation of 4-azido-2-nitrophenyl-substituted amines,[43] 2-aryloxyaryl azides,[50] and benzofurazones **85** (Scheme 19).[57] Furthermore, aryl azides prepared by this route were used for postcleavage cycloaddition reaction with alkenes to yield triazoles (Scheme 19).[57] In conclusion, the T1 displays a unique linker with various possibilities to generate heterocycles and other aromatic compound libraries.

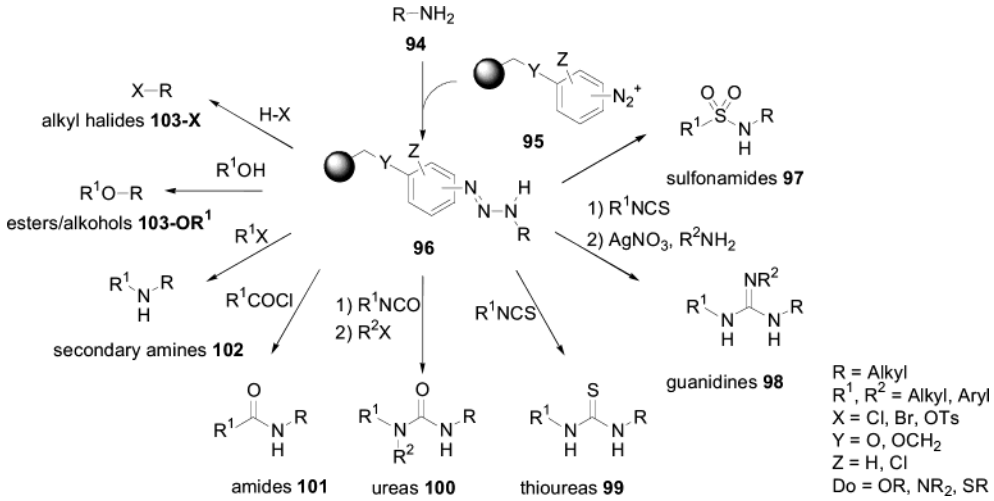
10. The Triazene T2 Linker

Whereas the T1 linker involves an immobilization of a diazonium salt on an amine resin, the T2 linker represents the reversal of this concept (Scheme 20). The T2 linker is largely being used for the attachment and detachment of sensitive systems containing heterocyclic[19] and amidic[61] structures. Coupling of the diazonium resins such as the T2 or T2* diazonium resin **14**[19] and **16**, respectively, with various primary or secondary amines proceeds smoothly to the formation of a series of new triazene resins **11**[19] and **13**,[21] respectively (Figure 3).

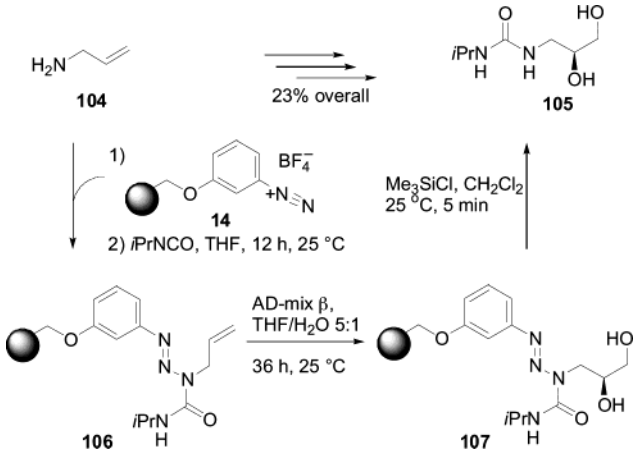
An excellent application of the T2 linker was demonstrated by Rich et al. in their synthesis of 3-alkoxy-4-aryl piperidines **93** as aspartic peptidase inhibitors (Scheme 21).[62] In addition to secondary amines, attachment of primary amines (Scheme 22), hydroxylamine, hydrazines, sulfoximines, or phenols proceed equally well. Secondary amines can be cleaved directly from the resins, while primary amines lead to a different reaction pathway (Scheme 22). Primary amines can be derivatized on the free N−H functionality and therefore be modified to an array of products. Thus, ureas **100** (Scheme 23),[61] thioureas **99**,[63] guanidines **98**,[63] and carboxamides **101**[61] were prepared in excellent yields (Scheme 22).

The triazene T2 linker[19] and the improved T2*[21] offer a unique approach to the formation of guanidines in which all three substituents could be varied to a wide extent. Starting from disubstituted triazene on the T2* linker, deprotonation using NaH/DMF and subsequent acylation by the addition of isothiocyanates yielded a library of resin-bound thioureas. For the reaction of the thioureas with amines, the use of mercury(II) oxide proved to be the superior reagent of those that were examined. Traces of the formed insoluble black mercury(II) sulfide were efficiently removed by simple filtration of the cleavage

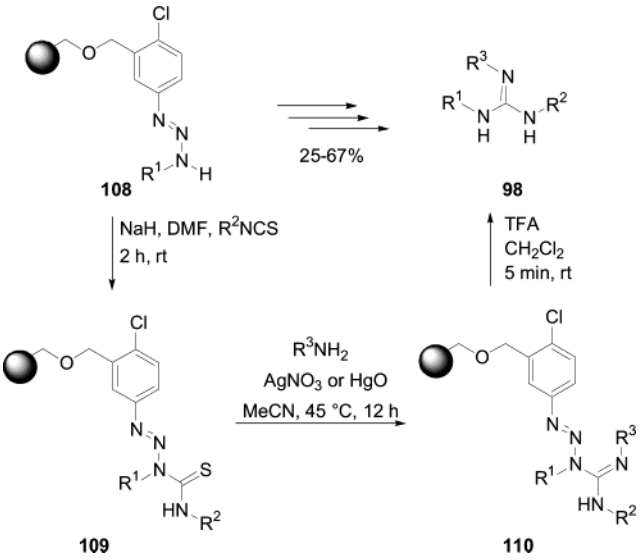
Scheme 22. Possibilities with the T2/T2* Linker



Scheme 23. Synthesis of Ureas Using the T2 Linker



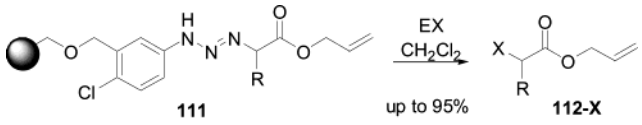
Scheme 24. Synthesis of Guanidine Libraries



solution over a short pad of silica gel. In the final diversification step before cleavage, the reaction of the thiourea resins **109** with ammonia and primary and secondary amines was conducted under the optimized reaction conditions. Cleavage of polymer-supported guanidines with 10% TFA yielded guanidines **98** as their trifluoroacetate salts with high purities (>90%) and high yields (Scheme 24).

While the cleavage of trisubstituted triazenes could give rise to the formation of secondary amines in excellent yields, the cleavage of disubstituted triazene **111** leads to aliphatic diazonium salts. The newly formed diazonium ion undergoes substitution with the nucleophile present in the reaction mixture. Therefore, alkyl halides **103-X**,[64] alcohols **103-OH**, and ethers **103-OR^1**, as well as alkyl carboxylic esters **103-OCOR**, sulfonic esters **103-OSO$_2$R**,[65] phosphoric esters **103-OPO(OR)$_2$**,[66] and phosphinic esters **103-OPO(H)(OR)**,[66] could be formed by cleavage with trimethylsilyl halides (X = I, Br, Cl), aqueous trifluoroacetic acid,[64] carboxylic acids, sulfonic acids, phosphoric acids, and phosphinic acids, respectively. The regioselectivity of the cleavage can be explained by the presence of one tautomer of the triazene in which the hydrogen atom is

Scheme 25. The Multifunctional Cleavage of the T2* Linker



E***X*** = TMS***Cl***, TMS***Br***, TMS***I***, H***OAc***, H***OTfa***

on the triazene nitrogen, which is linked to the arene ring. Overall, this reaction sequence provides the possibility for substituting an amino group for an oxygen or a halogen (Cl, Br, I) atom (Scheme 25).

In summary, the triazene T2 linker system displays an original anchoring group with ample possibilities for variations (Scheme 22). In addition, it serves as an anchor for modular ligand systems suitable for the synthesis of transition metal complex libraries.[67]

11. Summary, Conclusion, and Future Perspectives

Triazenes can be used beneficially to link functionalized arenes and amines to generate various heterocyclic structures, particularly benzoannelated nitrogen heterocycles imbedding classical and unusual yet useful nitrogen rings upon cleavage from the resin. They therefore offer flexibility in the synthesis of diverse heterocycle libraries needed for a successful drug discovery program. Since triazene anchors are stable toward various reagents and perform well under a range of reaction conditions, these multifunctional linkers will certainly be used for the synthesis of complex organic molecules, such as natural products, on solid supports in the future.

My greatest appreciation goes to an exceptionally motivated group of co-workers, who are individually identified in the references and have participated in our solid-phase adventure. The work presented here has been financially supported by the Deutsche Forschungsgemeinschaft (Grant BR 1730), the "Fonds der Chemischen Industrie" (Liebig fellowship to S.B.), and the European Community, as well as Bayer, BASF, Grünenthal, Merck KGaA, and Lundbeck. I would particularly like to acknowledge the fruitful collaborations with R. Lazny and J. Köbberling in the early stages of this project and the continuous support and encouragement by Professor Dieter Enders in particular.

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