

Review

New Trends in Diaziridine Formation and Transformation (a Review)

Zetryana Puteri Tachrim ^{1,2,*}, Lei Wang ^{1,3}, Yuta Murai ^{1,4} and Makoto Hashimoto ^{1,*}

¹ Division of Applied Bioscience, Graduate School of Agriculture, Hokkaido University, Kita 9, Nishi 9, Kita-ku, Sapporo 060-8589, Japan; leiwang@dlut.edu.cn (L.W.); ymurai@sci.hokudai.ac.jp (Y.M.)

² Research Center for Chemistry, Indonesian Institute of Sciences, Kawasan Puspiptek, Serpong, South Tangerang 15314, Banten, Indonesia

³ State Key Laboratory of Fine Chemicals, Department of Pharmacy, School of Chemical Engineering, Dalian University of Technology, Dalian 116024, China

⁴ Frontier Research Center for Post-Genome Science and Technology, Faculty of Advanced Life Science, Hokkaido University, Kita 21, Nishi 11, Kita-ku, Sapporo 001-0021, Japan

* Correspondence: zetr001@lipi.go.id (Z.P.T.); hashimoto@abs.agr.hokudai.ac.jp (M.H.); Tel./Fax: +81-11-706-3849 (M.H.)

Abstract: This review focuses on diaziridine, a high strained three-membered heterocycle with two nitrogen atoms that plays an important role as one of the most important precursors of diazirine photoaffinity probes, as well as their formation and transformation. Recent research trends can be grouped into three categories, based on whether they have examined non-substituted, *N*-monosubstituted, or *N,N*-disubstituted diaziridines. The discussion expands on the conventional methods for recent applications, the current spread of studies, and the unconventional synthesis approaches arising over the last decade of publications.

Keywords: diaziridines; substituted diaziridines; diazirines; formation; synthesis; transformation; reactivity



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1. Introduction

An important intermediate and precursor in organic chemistry, diaziridine [1] is a highly strained three-membered heterocycle with two nitrogen atoms [2]. The other excellent properties of diaziridine include a weak N–N bond, low toxicity, hydrazine amination duality [3], and neurotropic activity [4]. Diaziridines, independently discovered by three research groups (Schmitz's, Paulsen's, and Abendroth and Henrich's research groups) between 1958 and 1959, progressively achieved popularity in the field of chemistry over the two decades following these first publications [5]. Non-substituted diaziridine (diaziridine without any substituent on the nitrogen atom, **1**) was developed as a reagent for a variety of oxidative transformations [6] and employed in the synthesis of carbene-mediated photoaffinity-labeled photophores of 3*H*-diazirines [7–10]. The trend of using diaziridine **1** as a precursor for the diazirine photoaffinity probe has been progressively updated until the present day, and a series of reviews have discussed it since the 2010s [7,11–15]. Although the chemistry of *N*-monosubstituted diaziridine **2** has not been studied as extensively as that of non-substituted diaziridine **1**, there are examples documenting its application as an *N*-transfer reagent with α,β -unsaturated amides to form stereopure aziridines [16]. As for *N,N*-disubstituted diaziridine **3**, these valuable heterocycles have also been used as a versatile reagent via selective C–N or N–N cleavage in organic synthesis, particularly their bicyclic analogues of 1,5-diazabicyclo[3.1.0]hexanes, which possess a strained *cis-N,N*-disubstituted diaziridine fragment for 1,3-dipolar cycloaddition [17]. The advancements in substituted diaziridine with respect to its nitrogen atom(s) synthesis and applications have been summarized in several reviews [3–5,18–20]. On the basis of these excellent reviews, only a few studies have been fully dedicated to investigating the potential properties diaziridine with respect to its monocyclic synthetic methods [20] or its reactivity

towards electrophilic reagents [5]. Here in this review, the scope is limited to the current formation and transformation of diaziridines. Then, the trends in these areas are simplified into three categories—non-, *N*-mono-, and *N,N*-disubstituted diaziridines (Figure 1)—in which the discussion describes recent conventional uses, the current field of studies, and unconventional approaches that have emerged over the last decade of publications.

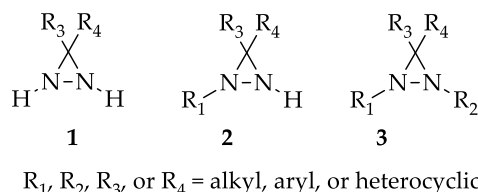


Figure 1. Structure of non-substituted diaziridine (1), *N*-monosubstituted diaziridine (2), *N,N*-disubstituted diaziridine (3).

2. The Chemistry of Diaziridines

Three key approaches are known for the construction of monocyclic diaziridines **4**, and these were summarized by Makhova et al. in their previous 2008 review of diaziridine (Figure 2) [20]. First, the reaction of primary aliphatic amines or ammonia **5** with the condensation products of carbonyl compounds **6** and aminating reagents. Second, the reaction of imines **7** (the condensation product of carbonyl compounds and primary aliphatic amines) is conducted with aminating reagent **8**. Last, a three-component condensation reaction involving the carbonyl compound **9**, primary aliphatic amines or ammonia **10**, and aminating reagents (hydroxylamine-*O*-sulfonic acid (HOSA) or halo(alkyl)amine, **11**). In addition, in their summary, Meijler et al. [7] emphasized that diaziridine synthesis as a precursor of 3-aryl-3-trifluoromethyl-3*H*-diazirine can start from the preparation of corresponding α, α, α -trifluoroacetophenone via oximation and tosylation (or mesylation)—the condensation products of carbonyl compounds **6**—followed by the treatment of ammonia. In consequence, these known approaches can be described as the “conventional” synthesis methods that have generally been used for the synthesis of diaziridine up until the most recent past. The reactivity of diaziridine was then pursued in order to broaden the advanced applications of these three-membered heterocycles, with reactions that can take place with or without any ring cleavage [1], or the transformation of its unprotected form into respective diazirines through oxidation. Diaziridine transformation induced by electrophilic reagents started being studied in the early 1950s and these reactions are primarily associated with the steric strain of the diaziridine ring and the presence of its two nitrogen atoms [5].

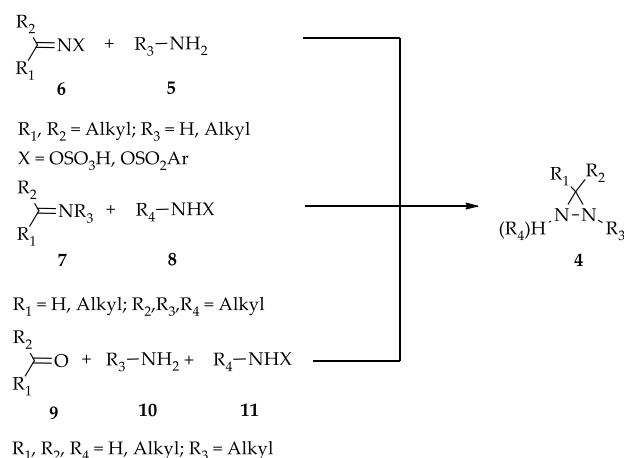


Figure 2. General construction of monocyclic diaziridines.

The rapid improvement in the quality of analysis instrumentation for experimental structure identification and detailed stereocenter has led to the intensive study of the detailed structure determination of diaziridine. Experimental data regarding the structures of diaziridines are important for achieving deeper insight into the previously elucidated features of the diaziridine ring structure, in particular, for the comparison of its corresponding N-N or C-N bond length [21]. Recently, experimental data were obtained for the structural determination of *N,N*-disubstituted diaziridine [22] and its trisubstituted form, which possesses an additional alkyl group at position 3 [23,24], bis-diaziridine [25], and bicyclic diaziridine [26] derivatives by the method of gas electron diffraction. Most diaziridine derivatives are liquids; thus, the recent experimental determination of its structures on the basis of X-ray diffraction studies [21,27] has only been performed in a few cases. Investigation of conformational and configurational changes in order to understand the effect of the interconversion barrier on the steric hindrance of the diaziridine substituent has also been conducted using dynamic gas chromatography [28–30]. The identification of equilibrium (molecular) structures using joint analysis of gas phase electron diffraction, quantum chemistry, and spectroscopic data [25,26] is becoming a trend and has made diaziridine stereochemical study more visible. Table 1 summarizes the details of recent experimental structure identification studies of several diaziridine derivatives.

Table 1. Recent experimental structure identification studies of diaziridine derivatives.

No.	Analysis *					Possible Conformations/Configurations
	GED	XRD	DGC	QC	S	
1	[22]	-	[28–30]	[22]	[28–30]	<p>R_1 or R_2 = Me, Et, Pr, Prⁱ, <i>t</i>-But, $n = 1, 2, 3$</p>
2	[23]	-	-	[23]	[23]	<p><i>trans</i> <i>cis-I</i> <i>cis-II</i></p>
3	[24]	-	-	[24]	[24]	<p><i>gauche (trans)</i> <i>anti (trans)</i> <i>anti (cis-I)</i> <i>anti (cis-II)</i></p>
4	[25]	[27]	[27]	[25]	[25,27]	<p>$S_N S_N - R_N R_N$ $S_N S_N - S_N S_N$ $R_N R_N - R_N R_N$</p>
5	[26]	-	-	[26]	[26]	<p><i>boat</i> <i>chair</i> <i>half-chair</i> <i>twist</i></p>

* GED (gas electron diffraction), XRD (X-ray diffraction), DGC (dynamic gas chromatography), QC (quantum calculation), S (spectroscopy data).

Since the strained ring compound exhibits high detonation performance when releasing a large amount of strain energy during ring opening, diaziridine properties were taken into consideration in this study. The design and theoretical investigation of a series of trinitromethane derivatives of diaziridines as candidates for high-energy-density materials were conducted [31]. A computational study of several properties of diaziridines was performed by using Density Functional Theory—B3LYP functional and the aug-cc-pVDZ basis set with the Gaussian 09 program. The formation heat, energetic properties, stability, impact sensitivity, and the calculation of vibrational frequency were studied, and it was found that the trinitromethane substituent was beneficial for enhancing the detonation properties. Among the diaziridines tested, **12** (Figure 3A) and 1-(trinitromethyl)diaziridine (**13**, Figure 3B) were confirmed to possess good potential as a high-density materials, possessing good detonation performance and higher stability.

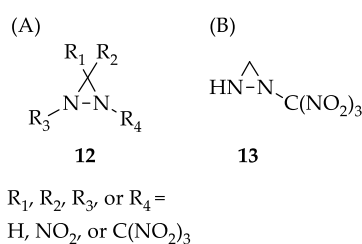


Figure 3. Structure of trinitromethane derivatives of diaziridine **12** (A) and 1-(trinitromethyl)diaziridine **13** (B).

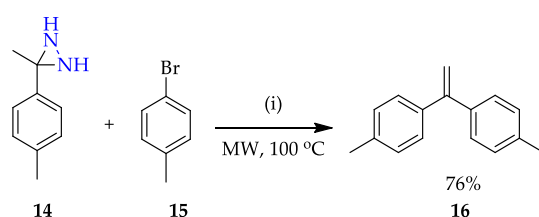
3. Diaziridine Formation and Transformation

3.1. Non-Substituted Diaziridines

3.1.1. Conventional Method for Recent Uses

The concept of using the conventional method for the advanced synthesis and application of diaziridines that are non-substituted at their *N*-terminal started with the use of a programmable batch of synthesis robots to design and develop a diazirine-based photoreactive compound [32]. This recent study mimicked the manual organic synthesis workflow by first synthesizing the 3*H*-diazirine-based crosslinker that mediates the formation of diaziridine from ketone. The automatization was constructed through the addition of methanol-NH₃ and NH₂OSO₃H to the ketone, filtration and evaporation of the resulting diaziridine, all followed by the formation of 3*H*-diazirine by an I₂-Et₂O system at low temperature, ready for the next reaction process. The feasibility of the robotic synthesis workflow is possibly due to the convenient formation of diaziridine as an intermediate for the synthesis of diazirine, which can be formed using commercial starting materials and universal reagents. Therefore, the recent automatization of the conventional method for synthesis of 3*H*-diazirine broadens the potential of the formation of diaziridine as an intermediate for advanced uses.

The reactivity of non-substituted diaziridines towards oxidants for the feasible synthesis of 3*H*-diazirines expands its applicability as an important intermediate. In a study exploring the process of Pd(0)-catalyzed cross-coupling of diazirines with aryl halides assisted by microwave irradiation [33], 3-methyl-3-(*p*-tolyl)diaziridine **14** was employed for the Pd(0)-catalyzed cross-coupling with 4-bromotoluene **15**—resulting in the product 4,4'-(ethene-1,1-diyl)bis(methylbenzene) **16**—under oxidative conditions following the addition of Ag₂O as an oxidant (Scheme 1). The Pd(0)-catalyzed cross-coupling is the first example of a transition-metal-catalyzed reaction of diazirines supported by combination with the conventional oxidation of diaziridine, and significantly expands the chemistry of three-membered heterocycles.



Scheme 1. Oxidative Pd(0)-catalyzed cross-coupling of 3-methyl-3-(*p*-tolyl)diaziridine with aryl halides. Reagents: (i) Pd₂(dba)₃, Xphos (2-dicyclo-hexylphosphino-2',4',6'-triisopropylbiphenyl), Et₃N, Ag₂O, DCE.

In continuation of the oxidation of diaziridine followed by oxidation into diazirine, it is possible to construct the ¹⁵N—¹⁵N moiety when synthesizing the three-membered heterocycle diazirine (Figure 4). The conventional transformation of ketone **17** into diaziridine **18** can result in the formation of ¹⁵N₂-diaziridine **19** molecular tags—hyperpolarized heteronuclei—contained in the diazirine moiety, supporting its potential as a molecular tag for NMR and MRI [34,35]. The readily oxidized ¹⁵N₂-diaziridine **18** was possible to synthesize using ¹⁵NH₃ and ¹⁵N-labeled hydroxylamine *O*-sulfonic acid (¹⁵NH₂OSO₃H), whereby the common I₂-Et₃N system was used for the formation of the final ¹⁵N₂-diazirine product. Although the overall yield achieved for the synthesized ¹⁵N₂-diazirine molecular tag was less than 50%, this is sufficient for further modification and analysis. Therefore, the development of subsequent utilizations of this isotope-labeled compound is to be expected.

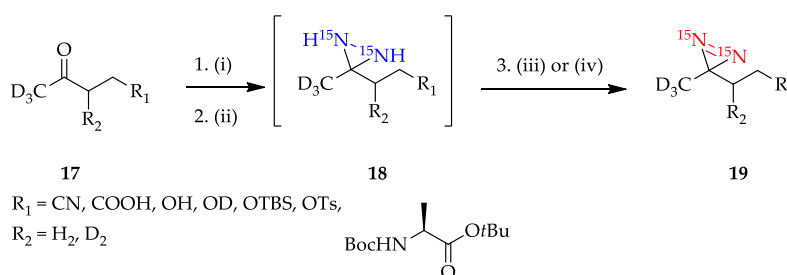


Figure 4. N₂-diazirine molecular tags synthesis via ¹⁵N₂-diaziridine oxidation by conventional system. Reagents: (i) ¹⁵NH₃ (ii) ¹⁵NH₂OSO₃H; (iii) I₂, Et₃N; (iv) I₂ then TsCl.

The synthesis of spirocyclic 3*H*-diazirine-containing building blocks has been discussed in the literature to a lesser extent [36]; however, it can potentially be employed to probe underexplored parts of proteome with libraries derived from structurally similar scaffolds of the parent's analogues [13,14,37]. Currently, spirocyclic 3*H*-diazirines can be found in steroid [38–40], proline [41,42], the simplified structure of chamuvarinin [43] analogues, and 1,5-disubstituted tetrazoles containing 3*H*-diazirine [44]. In a process with fewer steps, the crude diaziridine formed using the conventional method can be used directly for the synthesis of functionalized spirocyclic 3*H*-diazirine without using the chromatographic technique [36]. The transformation of the five- to seven-membered heterocycle or bicycle ketone **20** (Figure 5A) into diazirine **21** via NH₃ and NH₂OSO₃H can be used for the formation of diaziridine **22**, when subjected to an I₂-Et₃N system after filtration and concentration. Despite the use of the conventional NH₂OSO₃H as a reagent for the formation of diaziridine as an intermediate, four-membered heterocyclic 3*H*-diazirine **23** can be achieved by the sequential formation of oxime **24** from ketone **25** and *O*-sulfonylation for the formation of diaziridine **26**, followed by oxidation into diazirine **23** (Figure 5B). This method is commonly used for the synthesis of 3-phenyl-3-(trifluoromethyl)-3*H*-diazirine (TPD) instead of spirocyclic (aliphatic skeleton) 3*H*-diazirine. Both conventional methods can be used to achieve scales of up to 50 g when synthesizing functionalized spirocyclic 3*H*-diazirine mediated by diaziridine formation. By using this one-pot approach, two types of spirocyclic compounds (compound **47g–h**, Table 2, Entries 7–8) can also be successfully synthesized, and will be discussed in next section.

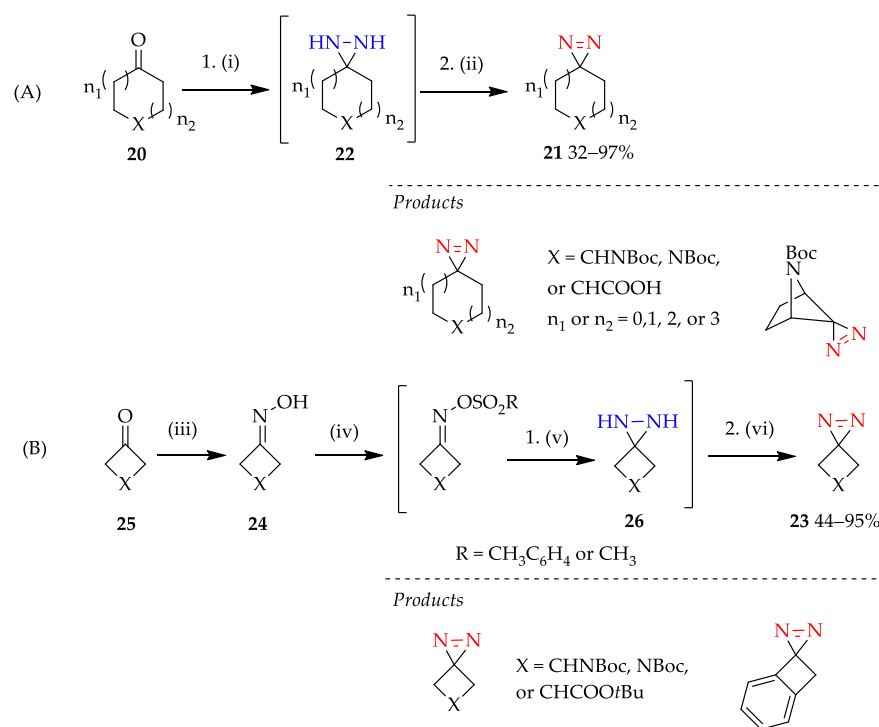
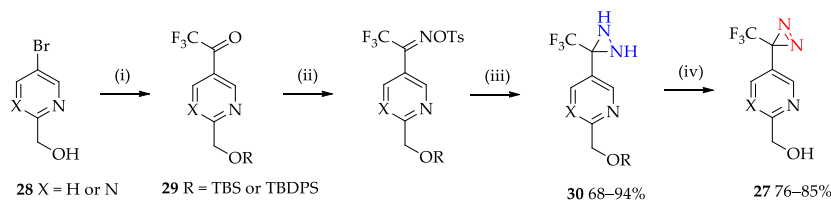


Figure 5. Diaziridine-mediated functionalized spirocyclic 3*H*-diazirine synthesis. (A) Five- to seven-membered heterocycle or bicycle ketone **20** as starting material. (B) Four-membered heterocycle ketone **25** as starting material. Reagents: (i) NH₃-MeOH then NH₂OSO₃H, (ii) I₂-Et₃N, (iii) NH₂OH·HCl and MeOH, (iv) Mesyl chloride or tosyl chloride and Et₃N, (v) NH₃, (vi) I₂ and NaHCO₃.

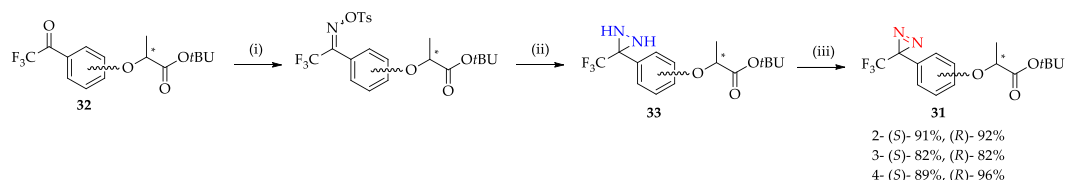
An ambient light stable-favored photoaffinity labeling probe comprising 3-pyridyl- and 3-pyrimidyl-substituted 3-trifluoromethyl-diazirines **27** [45] was synthesized from alcohols **28**, which directly transformed into an important scaffold representative, ketone **29** (Scheme 2). The replacement of the phenyl group with an electron-withdrawing pyridine or pyrimidine ring indicates that there were no obstacles during the sequential process of oxime formation and *O*-sulfonylation for diaziridine **30** formation. The conventional methods offered by the study showed that the 3-pyridyl- and 3-pyrimidyl-substituted 3-trifluoromethyl-diaziridines were stable and could be readily oxidized into diazirine **27** with Ag₂O-ether system.



Scheme 2. Syntheses of 3-pyridyl- and 3-pyrimidyl-substituted 3-trifluoromethyl-3*H*-diazirines **27**. Conditions: (i) 1. TBS-Cl or TBDPS-Cl, imidazole, DCM, RT, 16 h, 2. *n*-BuLi, ether, 3. methyltrifluoroacetate, ether, 4 h; (ii) 1. NH₂OH·HCl, AcONa, ethanol, reflux, 16 h, 2. pyridine, DMAP, Ts₂O, DCM, 0 °C to RT or DIEA, DMAP, TsCl, DCM, −50 °C to 0 °C; (iii) liquid NH₃, ether, 16 h; (iv) 1. Ag₂O, ether, 2–16 h, 2. TBAF, THF, RT, 2 h.

The novel asymmetric synthesis of trifluoromethyldiazirine-based lactisole derivatives **31** occurs as a result of the preparation of trifluoroacetyl modified on the aromatic ring of lactisole, which then introduces the diazirinyl three-membered ring on the trifluoroacetyl group [46]. However, to synthesize the starting material, advanced methods are required; since the 2-, 3-, and 4-trifluoroacetyl lactisole derivatives **32** (Scheme 3) need to consider

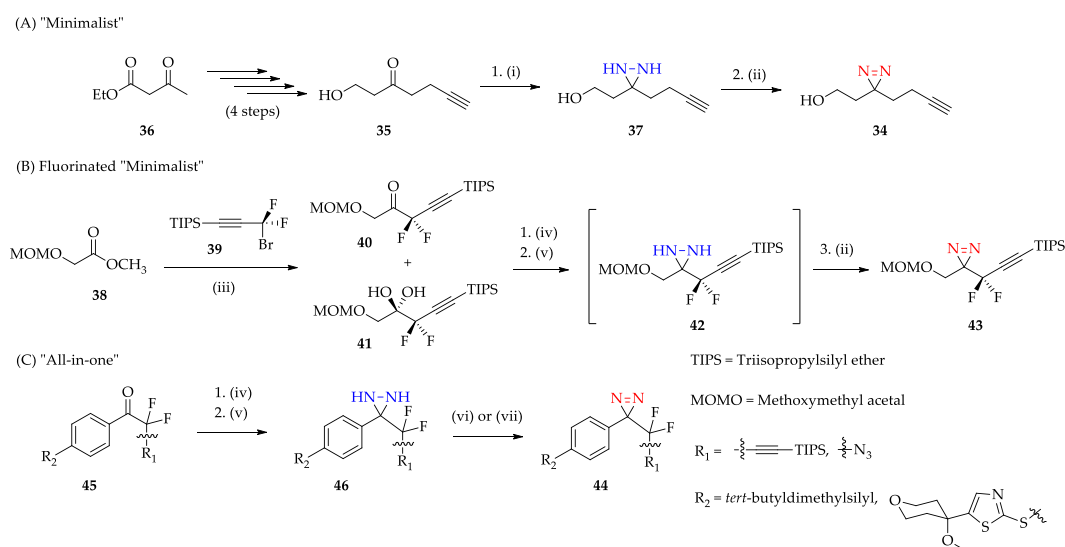
the optical retention of the protected lactate counterpart, the conventional diazirine **31** construction via diaziridine **33** formation can be easily conducted, starting with oximation with hydroxylamine hydrochloride, tosylation for the hydroxyl group of oxime, diaziridine formation with liquid ammonia, and a final step of oxidation with activated MnO_2 to obtain diazirine. The chiral center configuration was checked for every step, and asymmetric 2-, 3-, and 4- trifluoromethyl diazirine-based lactisole **31** were able to be synthesized with fine yields.



Scheme 3. Synthesis of 2-, 3- and 4-trifluoromethyl diazirinyl lactisole derivatives **31**. Conditions: (i) $\text{NH}_2\text{OH}\cdot\text{HCl}$, pyridine, EtOH, 60°C , 12 h then tosyl chloride, DMAP, CH_2Cl_2 , rt, 45 min; (ii) NH_3 (l), Et_2O , rt, 12 h; (iii) MnO_2 , CH_2Cl_2 , rt, 2 h.

3.1.2. Diaziridine as an Intermediate for “Minimalist” into “All-in-One” 3H-Diazirine

The term “minimalist” aliphatic diazirine-based probe for photoaffinity labeling was popularized by Yao’s group in 2013 [47], and while it was describes as “minimalist” diazirine linkers in a recent review [48]. The first generation [47] of so-called “minimalist” diazirine-based linkers was able to minimize the interference towards target binding and was built upon an alkyl diazirine and a terminal alkyne connected by short aliphatic chains [47,49,50]. These “minimalist” linkers **34** were made possible by synthesized representative aliphatic ketone containing alkyne **35**, which had previously been transformed from ethyl acetoacetate **36** as the starting material (Scheme 4A). The minimum length was limited to 2 carbons on both sides of the diazirine moiety in the linker in order to enable the linker to possess different functional groups and to prevent any side reaction during the requisite $\text{NH}_3/\text{NH}_2\text{SO}_3\text{H}$ step in diaziridine **37** formation. Subsequently, the first-generation “minimalist” diazirine linker’s **34** alkyne terminal was changed into cyclopropenes, which are similar in size, by rhodium-catalyzed reaction of α -diazo esters with alkynes, which have since been claimed to be the second generation of minimalist linkers [51,52].

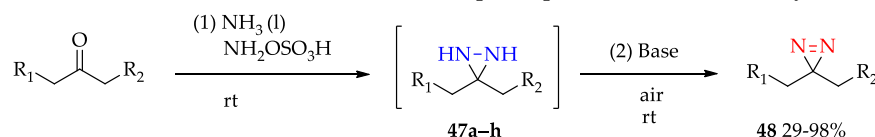


Scheme 4. Diaziridine as intermediate for (A) “minimalist” **34**; (B) fluorinated “minimalist” **43**; (C) “all-in-one” **44** 3H-diazirine. Reagents: (i) $\text{NH}_3\text{-NH}_2\text{SO}_3\text{H}$, (ii) $\text{I}_2\text{-Et}_3\text{N}$ or $\text{I}_2\text{-Et}_3\text{N}$ and MeOH, (iii) $n\text{-BuLi}$, THF-ether (2:1), (iv) NH_2OH , HCl, pyridine or ethanol, (v) tosyl chloride, pyridine or CH_2Cl_2 or DMAP, then NH_3 , Et_2O or CH_2Cl_2 , (vi) $\text{Ag}_2\text{O-Et}_2\text{O}$, (vii) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , then Et_3N .

The strategy for the adjustment of fluorine into the “minimalist” aliphatic diazirine linker can be initiated by the reaction of ester **38** and monobromodifluoroalkyne **39** in order to form an equimolar mixture of difluoroketone **40** along with in situ formation of its hydrate **41**, depending on the electrophilicity of the difluoroketone (Scheme 4B). This 1:1 mixture is then treated with hydroxylamine, followed by tosyl chloride in pyridine and ammonia in sequence [53], thus forming difluorodiaziridine **42** as an intermediate prior to oxidation with the I₂-Et₃N system, which results in 3*H*-diazirine **43**. From this approaches, the trend of “minimalist” diazirine-based compounds has shifted towards: (1) the synthesis of aliphatic 3*H*-diaziridine via activation of tosyl oxime formation, in contrast to the conventional methods; and (2) addition of difluoro moiety into the “minimalist” diazirine-based compounds as an approach to mimicking the superior stability and selectivity [54] of 3-phenyl-3-(trifluoromethyl)-3*H*-diazirine (TPD).

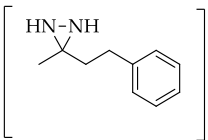
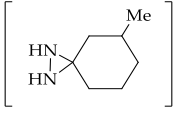
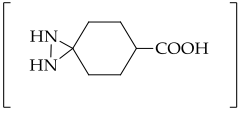
The compact, “all-in-one” structure of the diaziridine-mediated radioisotope-free photoaffinity labeling probe can be categorized as a “minimalist” aliphatic 3*H*-diazirine that includes the aromatics, as well as the addition of the fluorine moiety. The parts of the “all-in-one” photoaffinity labeling probe comprise a diazirine as a photo-crosslinker (a carbene-generating group), a fluorinated carbon at the aliphatic 3*H*-diazirine side chain of the aromatics for mimicking TPD, and an alkyne [55] or azide [56] as a tag for the attachment of a detectable group via bioorthogonal click chemistry. “All-in-one” 3*H*-diazirine **44** containing both alkyne and azide are constructed from representative ketone **45** containing aromatics, fluorine moiety, and alkyne or azide terminal in advance, before transformation into the diaziridine **46** intermediate via tosyl oxime formation. The Swern oxidation—dimethylsulfoxide and oxalyl chloride followed by the addition of triethylamine—can be used for the oxidation of the diaziridine **46** intermediate instead of Ag₂O-Et₂O, resulting in the “all-in-one” 3*H*-diazirine **44** (Scheme 4C).

Table 2. Diaziridine in-situ formation in one-pot aliphatic 3*H*-diazirine **48** syntheses.



Entries	Possible Diaziridine Formation (In-Situ)	Base (equiv.)	Reference
1	 47a	<i>t</i> BuOK (2.3 equiv.) KOH (2.3 equiv.)	[57] [58]
2	 47b	<i>t</i> BuOK (2.3 equiv.) KOH (2.3 equiv.)	[57] [58]
3	 47c <i>n</i> = 1,2,3	<i>t</i> BuOK (3.3 equiv.) KOH (3.3 equiv.)	[57] [58]
4	 47d	<i>t</i> BuOK (4.3 equiv.) KOH (4.3 equiv.)	[57] [58]
5	 47e	KOH (2.3 equiv.)	[58]

Table 2. Cont.

Entries	Possible Diaziridine Formation (In-Situ)	Base (equiv.)	Reference
6	 47f	<i>t</i> BuOK (2.3 equiv.)	[57]
		KOH (2.3 equiv.)	[58]
7	 47g	<i>t</i> BuOK (2.3 equiv.)	[57]
		KOH (2.3 equiv.)	[58]
8	 47h	<i>t</i> BuOK (3.3 equiv.)	[57]
		KOH (3.3 equiv.)	[58]

3.1.3. In Situ Formation of Diaziridines in One-Pot Synthesis of 3*H*-Diazirine

The dehydrogenation of the NH–NH bond in aliphatic diaziridine is a crucial transformation for generating the N=N double bond that acts as the main skeleton of aliphatic 3*H*-diazirine [57]. In the conventional method, different oxidants, including silver oxide or iodine in the presence of triethylamine, are introduced in order to transform diaziridines into 3*H*-diazirine following the removal of the ammonia [14,58–60]. Diaziridines are basic and form salts, and in several cases, the pure form of diaziridines can be difficult to isolate [59]. During the synthesis of 3*H*-diazirine as a photoaffinity labeled-based photophore, 3*H*-diazirine can be readily used for the further post-functional synthesis of the corresponding probe [8], and “bypassing” the prior synthesis steps of 3*H*-diazirine is the ideal way to run. Thus, the strategy for the current development of 3*H*-diazirine synthesis is the in situ formation of diaziridine, and approaches for one-pot synthesis of 3*H*-diazirine take advantage of this more comprehensive method.

Aliphatic diaziridine is generally synthesized from ketone treated with liquid ammonia to form the imine, followed by reaction with hydroxylamine-*O*-sulfonic acid (HOSA, NH₂OSO₃H), enabling intramolecular cyclization to the diaziridine. The addition of a base to the synthesis process of conventional aliphatic diaziridine from aliphatic ketone can provide the direct dehydrogenation of the in situ formed diaziridine into 3*H*-diazirine. The alternative method for dehydrogenation of hydroazobenzene, combining the least expensive bulk chemicals of liquid NH₃ as a solvent and the readily available *t*BuOK system as a base, could be applied for the dehydrogenation of diaziridine [57]. Following this improvement, the use of base that can be easily handled and stored, as well as being highly available, such as KOH could enable gram-scale production [58]. Table 2 (Entries 1–8) shows the representative in situ formation of diaziridine **47a–h** for the synthesis of 3*H*-diazirine **48**. Kinetic study of the KOH-mediated direct transformations of diaziridine **47f** into 3*H*-diazirine **48** (Table 2, Entry 6) based on ¹H-NMR analysis indicated that diaziridine possessed appropriate reactivity for ready transformation into 3*H*-diazirine [58]. When adding HOSA to liquid ammonia in ketone at room temperature for 12 h, the corresponding diaziridine **47f** (Table 2, Entry 6) was detected, as well as a trace amount of its 3*H*-diazirine form. Upon further treatment with KOH for 2 h, the 3*H*-diazirine was dramatically improved, indicating that diaziridine, as a precursor, can be converted directly, with the detection of no other by-products.

A carbene precursor, 3-phenyl-3-(trifluoromethyl)-3*H*-diazirine (TPD) derivatives are known for their ability to not promote cell death in the generation of active species in in vitro photoaffinity experiments [8]. Unlike the conventional synthesis of 3*H*-diazirine

from diaziridine as an intermediate, the multistep reaction of TPD derivatives is performed from a phenyl trifluoromethyl ketone, which is transformed into the active species tosyl oxime, which is treated with an ammonia-Et₂O solution at $-78\text{ }^{\circ}\text{C}$, then brought to room temperature to allow the formation of diaziridine, which is oxidized with the I₂-Et₃N system as a final step to result in TPD [7,14,54]. Since the treatment of TPD after oxidation is time-consuming and yield-diminishing, the inevitable isolation of diaziridines can be skipped by using an alternative one-pot synthesis starting from tosyl oxime [61].

The treatment of tosyl oxime **49** with conventional reagents, depending on the temperature and the reaction time, can result in the formation of diaziridine **50** and/or its direct transformation into 3*H*-diazirine **51** [61]. The proposed mechanism for the transformation of tosyl oxime into diaziridine in past decades described the formation of the intermediate *gem*-diamine [62] following attack by NH₃, and by removing the tosyl group and the proton, diaziridine is formed [61]. The current developments suggest that the necessity of using liquid ammonia for the generation of NH₂[−] species can elongate the deprotonation of diaziridine to form diazirine. The self-ionization of liquid NH₃ into NH₂[−] species seems crucial for this reaction, as demonstrated by the search for additives to increase this species, which has determined in studies that LiNH₂ is superior to the inhibitor of NH₄Cl (Figure 6). It should be noted that diaziridine formation is crucial, and the aim to achieve diaziridine isolation by removing the ammonia from the reaction, in terms of the conventional method, overlooks the important involvement of ammonia in the transformation of diaziridine **50** into 3*H*-diazirine **51** using tosyl oxime **49** as the starting material.

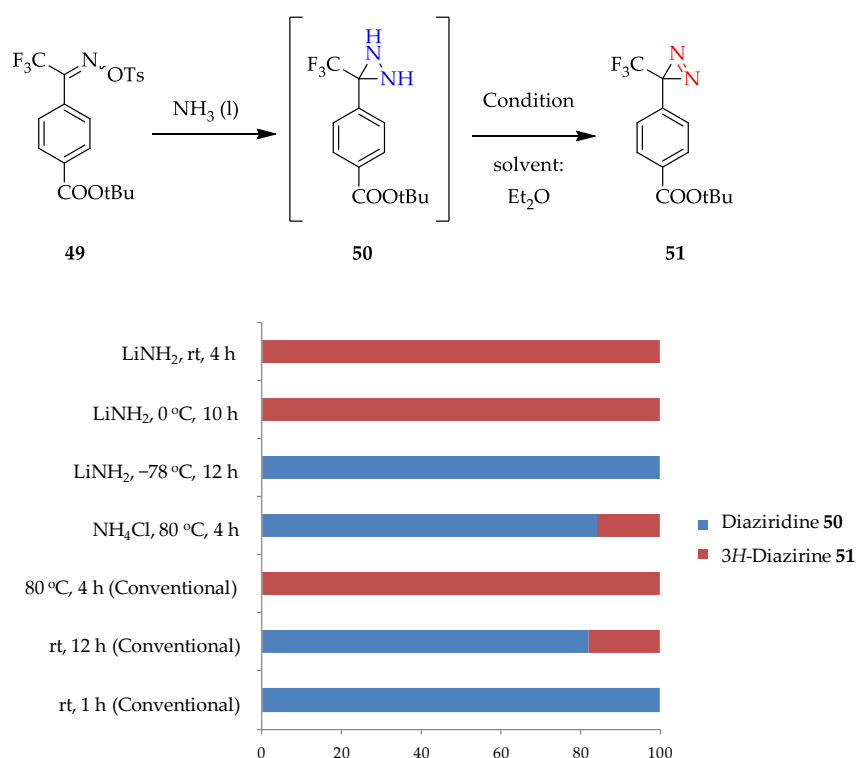


Figure 6. Diaziridine **50** formation in one-pot approaches for synthesis of 3-phenyl-3-(trifluoromethyl)-3*H*-diazirine (**51**, TPD) from tosyl oxime **49**.

In order to broaden the applications of diaziridine-intermediated **52**, and the one-pot synthesis TPD **54** from tosyl oxime **53**, there are several viable substituents in the aromatic moiety of the starting material. Optically pure (trifluoromethyl)diazirinyphenylalanine ((Tmd)Phe) has been used as important building block in synthesis involving tosyl oxime as a precursor following the one-pot reaction method [61]. Method A prolongs the optical retention of (Tmd)Phe **55** and **56**, while the addition of LiNH₂ in Method B results in the racemization of the product **55**. (Tmd)Phe **57**, deuterated at the aromatic moiety,

was synthesized via Method A, and its optical activity was retarded. Furthermore, the synthesis of 3-nitro **58** or 3-aminol **59** and 3-/4-methyl TPD **60–61** for the construction of phenylthiourea derivatives [63] and saccharin derivatives [64], respectively, using a one-pot (method A or B) system resulted in an almost quantitative yield compared with the conventional stepwise Method C (Figure 7).

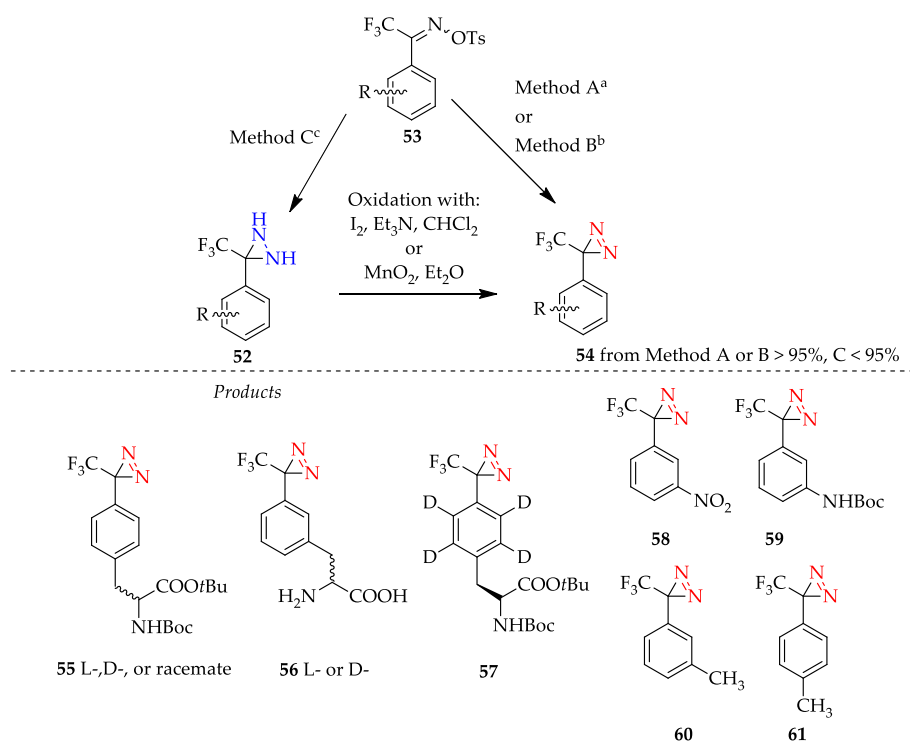


Figure 7. Comparison of conventional methods and the one-pot system for the synthesis of 3-phenyl-3-(trifluoromethyl)-3H-diazirine **54** (TPD) from tosyl oxime **53**. ^a Method A: NH_3 (l), 80°C . ^b Method B: NH_3 (l), LiNH_2 , rt. ^c Method C: NH_3 , Et_2O , rt (Conventional).

3.1.4. Improved Method for the Synthesis of 3-[3-(Trifluoromethyl)-3H-diazirin-3-yl]aniline Derivatives

The needs of the aniline skeleton as a precursor for the multistep synthesis of the 3-phenyl-3-(trifluoromethyl)-3H-diazirine-based photoaffinity labeling probe faces an obstacle with respect to obtaining high overall yields. Studies describing the synthesis methods employed in previous decades [65–68] provide limited experimental details or analytical data; thus, it has become necessary to improve on these methods. In a brief (Figure 8), recent study has successfully synthesized 3-[3-(trifluoromethyl)-3H-diazirin-3-yl]aniline **62** with excellent yield through the reduction of nitrobenzene derivatives following the formation of 3H-diazirine **63a–b** [63] or the protection of the amino group from undergoing 3H-diazirine formation, followed by its deprotection, resulting in **63c–e** [63,69]. This new improvement showed that it is preferable to protect the amino group at the 3-position with —Boc (**63c**), enabling convenient acidic deprotection after 3H-diazirine formation [63,69]. Meanwhile, the amino group at the 4-position can be subjected to two types of protecting group (—Boc **63d** or —phthalimide **63e**), and in the case of —phthalimide group (**63e**), this protecting group can be directly oxidized in conjunction with the diaziridine **64** moiety by $\text{MnO}_2\text{-CH}_2\text{Cl}_2$ into a final product of 3-[3-(trifluoromethyl)-3H-diazirin-3-yl]aniline derivative **62** [63].

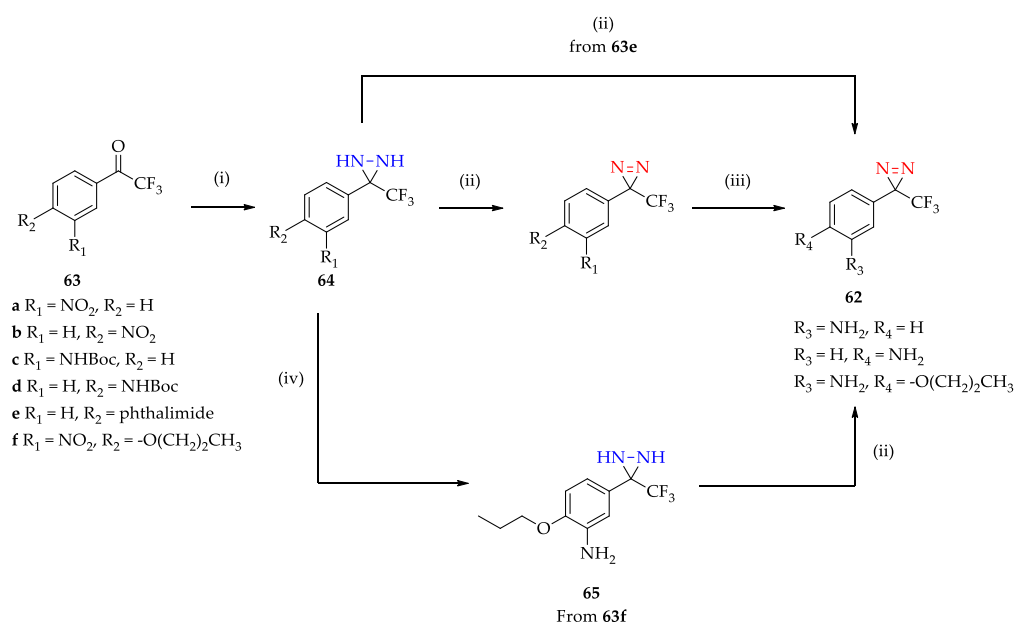


Figure 8. Improved method of NH₂-substituted 3-phenyl-3-(trifluoromethyl)-3*H*-diazirine **62**. Reagents: (i) 1. NH₂OH-HCl, pyridine or EtOH; 2. TsCl, Et₃N, acetone or DMAP; 3. NH₃, Et₂O or CH₂Cl₂, (ii) MnO₂, CH₂Cl₂ or Et₂O, or with I₂-Et₃N, MeOH, (iii) TFA, CH₂Cl₂, or Fe, EtOH, HCl, or NaSH, EtOH, or HCl, dioxane, or PPh₃, THF-H₂O, (iv) Na₂S₂O₄/THF, EtOH, H₂O.

A few studies have performed the final step of forming the 3-[3-(trifluoromethyl)-3*H*-diazirin-3-yl] aniline derivatives from nitrobenzene derivatives through the reduction of the nitro moiety in sodium dithionite [68,70]. During the synthesis of photoreactive 2-propoxyaniline derivatives as artificial sweeteners [71], the reduction by sodium dithionite after 3*H*-diazirine formation did not take place, and the diazirinyl moiety was unable to tolerate this condition, causing decomposition to occur. A possible route for this was diaziridine **65** formation following reduction with sodium dithionite (Figure 8). A moderate yield was obtained without breaking the diaziridinyl moiety, and validated the essential aspects of diaziridine formation, enabling a better understanding of the improved method for NH₂-substituted 3-phenyl-3-(trifluoromethyl)-3*H*-diazirine **62**.

3.1.5. Expansion of Fluorous 3*H*-Diaziridine as a Basis for 3*H*-Diazirine Application

A new fluorous 3*H*-diazirine-based photoaffinity labeling probe taking advantage of fluorous chromatography and fluorous solid phase extraction was developed. These techniques aim to retard fluorinated compounds on fluorinated silica gel, while all other organic material is washed off the column with the appropriate organic mobile phase. A new fluorous 3*H*-diaziridine-based photoaffinity labeling probe, with a longer perfluoroalkyl residue substituted for the trifluoromethyl group in the non-radioactive photoaffinity labeling probe, can be synthesized starting from the transformation of perfluoroalkylated ketone **66** (perfluorobutyl and perfluorooctyl (Figure 9A) [72]) into diaziridine **67** through the conventional approach of oxime formation, tosylation, and treatment with liquid ammonia. The temporary silylation of the diaziridine moiety of compound **68** was performed by means of trimethylsilyl triflate, bromide–lithium exchange, and carboxylation with carbon dioxide for the conversion of benzoic acid. The final product was observed after the oxidation of diaziridine **68** into diazirine **69** with I₂-Et₃N. Prior to the study reporting the perfluoroalkylated 3*H*-diaziridine-based photoaffinity labeling probe, the perfluoropropyl and perfluorohexyl [73] residues had also been studied using the conventional approach, starting from the modification of perfluoroalkylated ketone **70** to result in diaziridine **71**, which can readily be oxidized to 3*H*-diazirine **72** (Figure 9B).

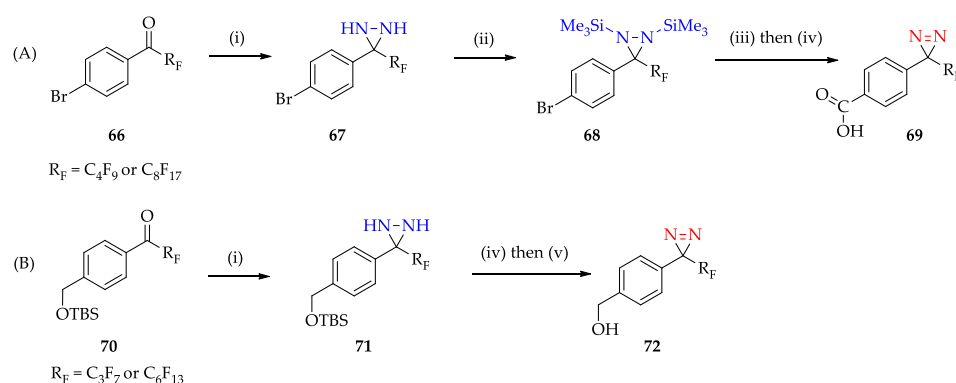


Figure 9. Perfluoroalkylated aryldiazirine synthesis: (A) perfluorobutyl and perfluorooctyl residue **69**. (B) perfluoropropyl and perfluorohexyl residue **72**. Conditions: (i) 1. $\text{NH}_2\text{OH}\cdot\text{HCl}$, pyridine, EtOH, 60°C or 85°C , 2. *p*-TsCl, DMAP, Et_3N , CH_2Cl_2 , 0°C to r.t., 3. $\text{NH}_3(\text{l})$, CH_2Cl_2 or EtOH, -78°C to r.t., 16 h; (ii) Me_3SiOTf , Et_3N , CH_2Cl_2 , -78°C to r.t.; (iii) 1. *n*BuLi, THF, 2. CO_2 , -78°C to r.t., 3. H_2O , (iv) I_2 , Et_3N , MeOH, r.t., (v) TBAF, THF, rt, 1 h.

Diazirine-based crosslinkers (synthesized from the counterpart diaziridine) have been explored due to their ability to act as carbene-generating reagents. Since the 3-trifluoromethyl *3H*-diazirine can be photoreactivated with light at 350 nm to generate carbene, this photophore is categorized as a high reactive species, and is able to rapidly form crosslinks to biomolecules with short photoirradiation times [8]. This universal crosslinker for aliphatic polymers, the simple bis-diazirine reagent, contains the known compound 1,3-bis(3-(trifluoromethyl)-*3H*-diazirin-3-yl)benzene or its pyridyl analog **73**, which is volatile, and is prone to explosion (Figure 10A) [74]. Thus, the bis-diazirine crosslinker was improved by the addition of an electron-deficient linker at the *para* position of diazirine compound **74** [74], which can be handled under ambient conditions, preventing any self-reaction due to the absence of any aliphatic C-H bonds (Figure 10B). The so-called second-generation bis-diazirine **75** is an elongated perfluoroalkylated chain inspired by the first-generation bis-diazirine **74** [75]. The highly fluorinated bis-diazirines designed in the study can be developed into a flexible covalent adhesive (Figure 10C). The simple 1st-generation and 2nd-generation bis-diazirines are highly useful as crosslinkers for a broad range of feasible synthesis applications starting from representative ketone **76–78** into diaziridine **79–81**, which can be directly oxidized by the I_2 – Et_3N system.

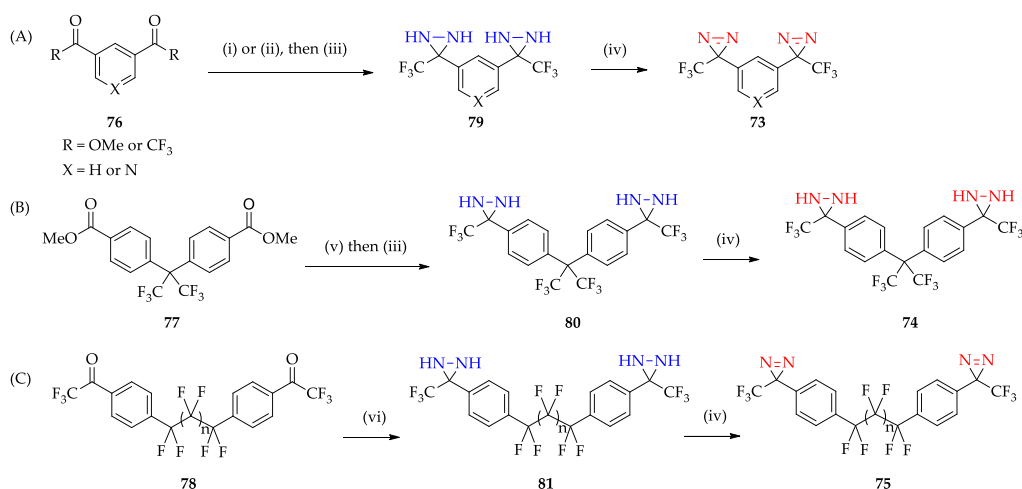


Figure 10. Fluorous *3H*-diazirine-based crosslinker: (A) Simple bis-diazirine **73**, (B) 1st generation bis-diazirine **74**, (C) 2nd-generation bis-diazirine **75**. Conditions: (i) 1. $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, reflux, 2 h, 2. $\text{NaOH}(\text{aq})$, reflux, 2 h, (ii) 1. TMSCF_3 , TBAF, DCM, 2. $\text{NH}_2\text{OH}\cdot\text{HCl}$, NaOH , EtOH/ H_2O , reflux, 2 h, (iii) TsCl , NET_3 , DMAP, DCM, 0°C , then $\text{NH}_3(\text{l})$, DCM, -78°C to r.t., (iv) I_2 , NET_3 , DCM, 0°C , (v) 1. TMSCF_3 , TBAF, THF, -10°C to r.t. 2. $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, reflux, 2 h, (vi) 1. $\text{NH}_2\text{OH}\cdot\text{HCl}$, 2. *p*-TsCl, NET_3 , 3. $\text{NH}_3(\text{l})$, -78°C to r.t.

3.1.6. Unconventional Non-Substituted Diaziridine Synthesis Approaches

Recently, there have been two methods that have taken advantage of the conventional concept and turned it into brand new approaches to developing diaziridine synthesis. The first is the use of resin-bound sulfonyl oximes for the synthesis of 3-trifluoromethyl-3-phenyldiaziridine [76]. A commercially available polystyrene-sulfonyl chloride **82**, used as an equivalent to replace the common reagents mesyl or tosyl chloride, was previously reacted with oxime **83** to provide the desired solid-supported sulfonyl oxime. The conventional-like active species sulfonyl oxime **84–86** were then transformed by ammonia/dioxane solution to obtain a set of substituted diaziridines **87**. The presence of the trifluoromethyl group has a role in the cleavage of the immobilized sulfonyl oxime precursors from their solid supports, therefore allowing good results for diaziridine **87** formation. The compatibility of the immobilization and cleavage protocols in this method was tested with several aromatic building blocks and alkyne groups (Figure 11). An optical retention study of the optical active-aromatic substituents or building blocks remains to be performed for this method in the future.

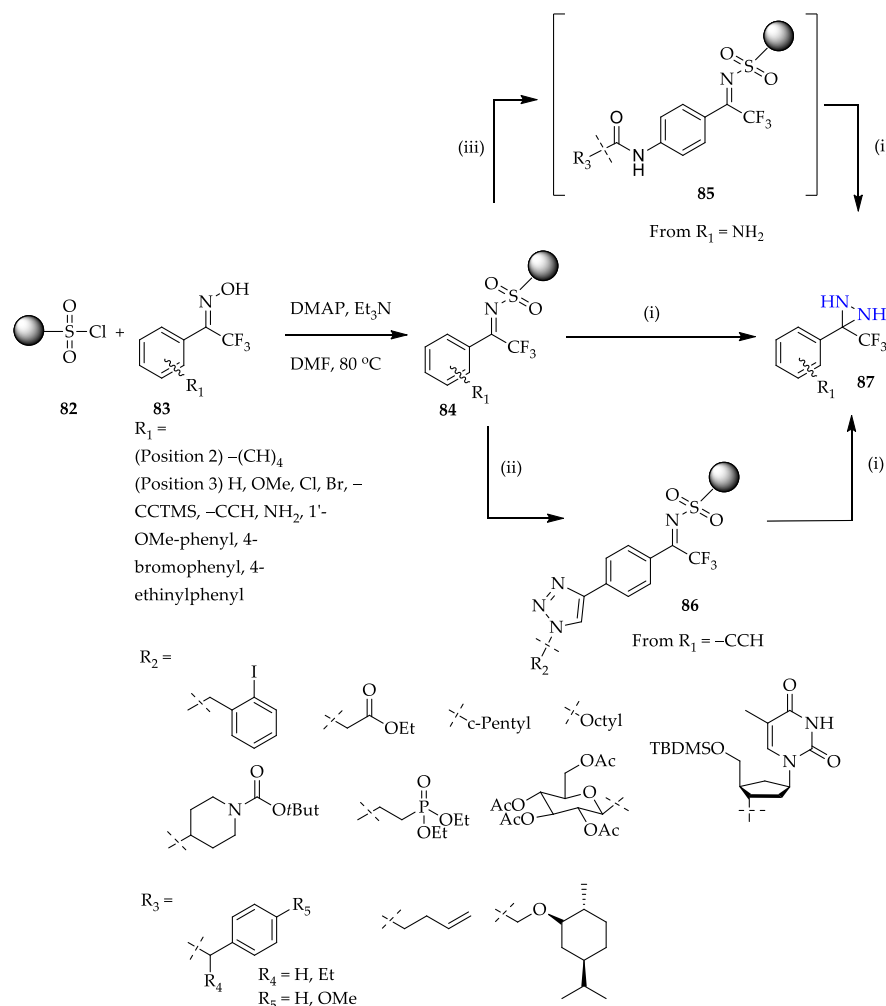


Figure 11. Synthesis of diaziridines **87** via unconventional resin-bound sulfonyl oxime **82** reagent. Reagents: (i) NH_3 -dioxane; (ii) $\text{R}_2\text{-N}_3$, CuI, DIPEA, DMF, H_2O ; (iii) $\text{R}_3\text{-COCl}$, Et_3N or $\text{R}_3\text{-CO}_2\text{H}$, DIC, HOBT.

The second unconventional method is the ammonia-free synthesis of 3-trifluoromethyl-3-phenyldiaziridine **88** [77]. The study started with the preparation of trifluoromethyl phenyl imines **89** using lithium bis(trimethylsilyl)amide [78] into trifluoromethyl phenyl ketone **90**, resulting in *N*-TMS-ketimine **91** (Figure 12). The solvolysis of this *N*-TMS-ketimine

with methanol provides the representative imine for direct diaziridine formation. Since the use of the conventional reagent HOSA, which acts as the *O*-sulfonyl hydroxylamine source, did not yield the desired diaziridine product due to the reduced nucleophilicity of the amine function of the formed zwitterions, this study therefore then reacted *p*-toluenesulfonyl hydroxylamine with trifluoromethyl phenyl imines **89** as an advanced ammonia-free methodology for the synthesis of diaziridine **88** (Figure 12). The ammonia-free synthesis was carried out in significantly fewer reaction steps and with less purification of the intermediate compared to the multiple overnight steps of the conventional method. Various 3-trifluoromethyl-3-phenyldiaziridine derivatives can be explored for further study based on ammonia-free methods, despite the difficulty of synthesizing the imine intermediate. In addition, both of the unconventional methods described here successfully oxidized the resulting 3-trifluoromethyl-3-phenyldiaziridine into representative diazirine using the common oxidation reagents MnO_2 [76] or Ag_2O [77].

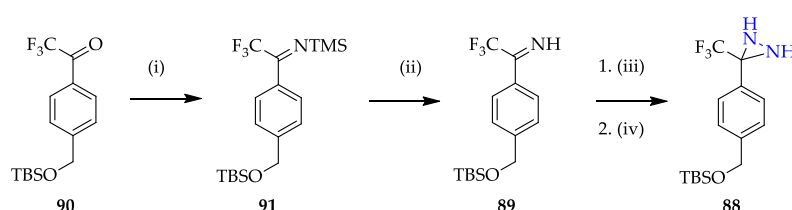


Figure 12. Synthesis of diaziridine **91** via unconventional reagents in an ammonia-free method. Reagents: (i) $\text{LiN}(\text{TMS})_2$ in THF, toluene; (ii) methanol; (iii) *p*-toluenesulfonyl hydroxylamine in THF; (iv) piperidine.

3.2. *N*-Monosubstituted Diaziridines

3.2.1. Conventional Method for Recent Uses

In general, conventional methods for the synthesis of diaziridines with HOSA have been performed in various solvents, such as water [79], methanol [80], or pure liquid ammonia [81]. When conventional methods were used for the reaction of cyclooctanone **92**, benzylamine **93**, and HOSA, the corresponding bicyclic diaziridine, 1,2 diazasp[2,7]decane **94** (Figure 13), was produced with quite a low yield (~20%) [81]. In order to achieve a better understanding of this, the solvent dependency of the *N*-monosubstituted diaziridine **94** yield was studied by means of GC-MS [82]. The highest yield of the product *N*-monosubstituted diaziridine **94** (~42%) corresponded to the use of an apolar aprotic solvent, such as cyclohexane or toluene.

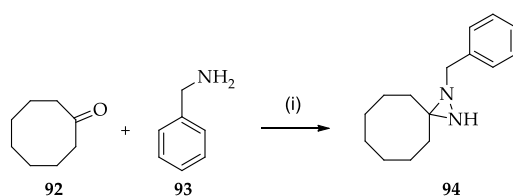
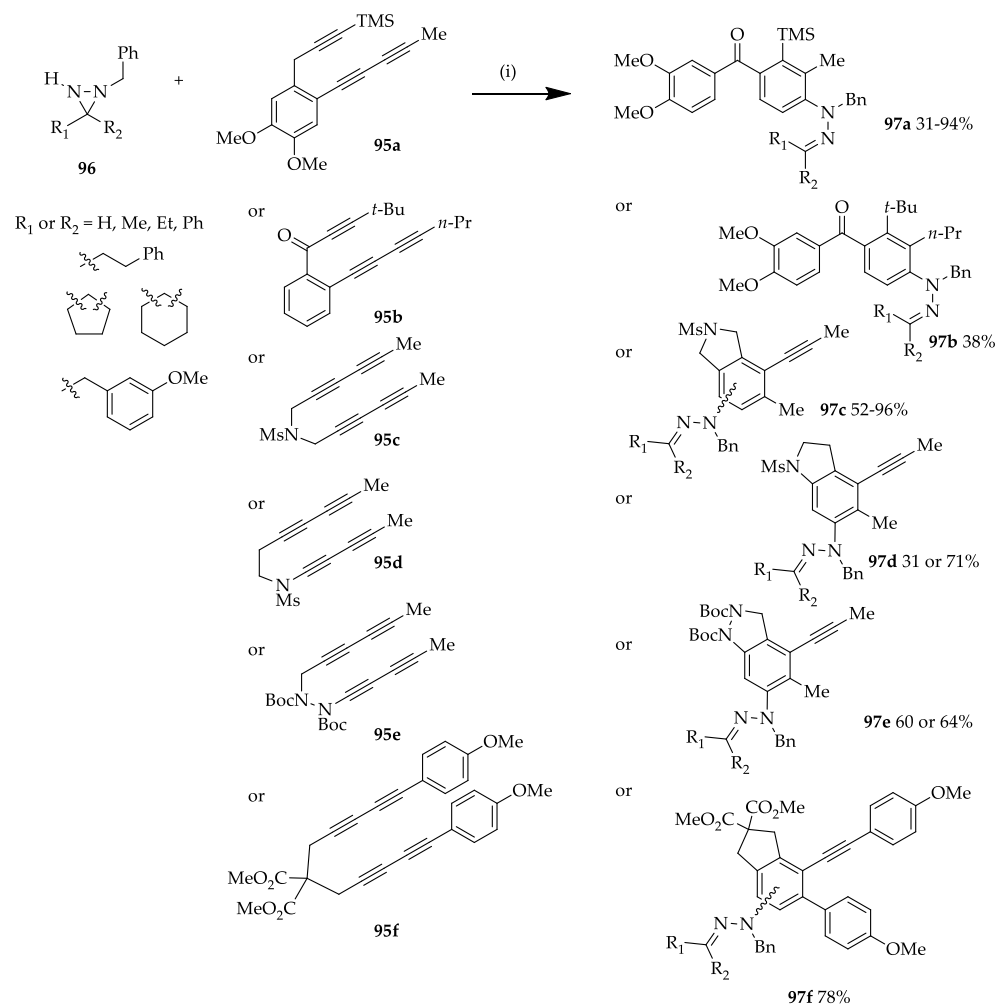


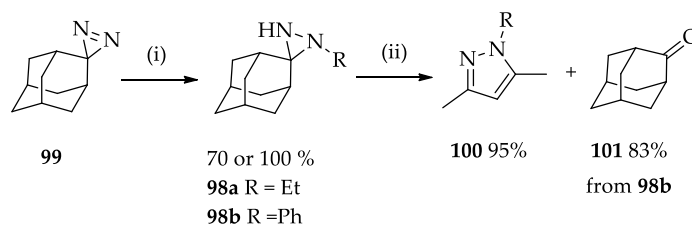
Figure 13. Solvent dependency of *N*-monosubstituted diaziridine **94**. Conditions: (i) HOSA, rt, 3 h, solvent (pentane, hexane, dichloromethane, cyclohexane, toluene, acetonitrile, diethyl ether, tetrahydrofuran, methyl *tert*-butyl ether, ethyl acetate, methanol, ethanol, isopropyl alcohol, 1-butanol, 1,4-butanediol).

The reactions of nucleophilic diaziridines with electrophilic alkynes were established decades ago [83], and by means of the ^{15}N -labeling experiment, it was shown that the mechanism of the reaction could be assumed to involve the initial addition of an alkylated nitrogen atom (*N*-monosubstituted diaziridine counterpart) to provide an intermediate that could subsequently undergo ring-opening and proton transfer, resulting in the adduct product [84]. The trapping reaction resulted in thermally generated benzyne species **95a–f** with heteroatom-rich diaziridine **96** leading to *N*-arylated hydrazones **97a–f** in a single step, while these could be converted into fused-ring indole derivatives **97c–e** in some

cases (Scheme 5). The conventional method for the synthesis of diaziridines has been used in recent years to form *N*-ethyl diaziridine **98a** in quantitative yield from the reaction of 2-adamantane-2,3-[3H]-diazirine **99** with alkyl Grignard reagents (Scheme 6). Despite this success, the use of aryl Grignard reagents did not lead to *N*-phenyl diaziridine, and the expected diaziridine **98b** was obtained only upon the addition of phenyl lithium. The direct reaction with acetylacetone was then conducted from the pure resulting *N*-phenyl diaziridine **98b**, allowing pyrazole **100** and adamantanone **101** to be obtained with excellent yields (Scheme 6) [85].



Scheme 5. The reactions of diaziridines **96** with benzynes **95a–f** to produce *N*-arylhydrazones **97**.



Scheme 6. Diaziridine **98a–b** synthesis from Grignard reaction of diazirine **99** and its reaction, resulting in pyrazole **100** and adamantanone **101**. Condition: (i) EtMgBr or PhLi, Et₂O, 0 °C or –78 °C, 2 h; (ii) acetylacetone, *p*-TsOH, EtOH, 80 °C, 24 h.

3.2.2. Base Addition for Enhancement of *N*-Monosubstituted Diaziridine Formation

It is known that the formation of monocyclic diaziridine the three-component condensation of carbonyl compounds, primary aliphatic amines, and HOSA in protic medium is

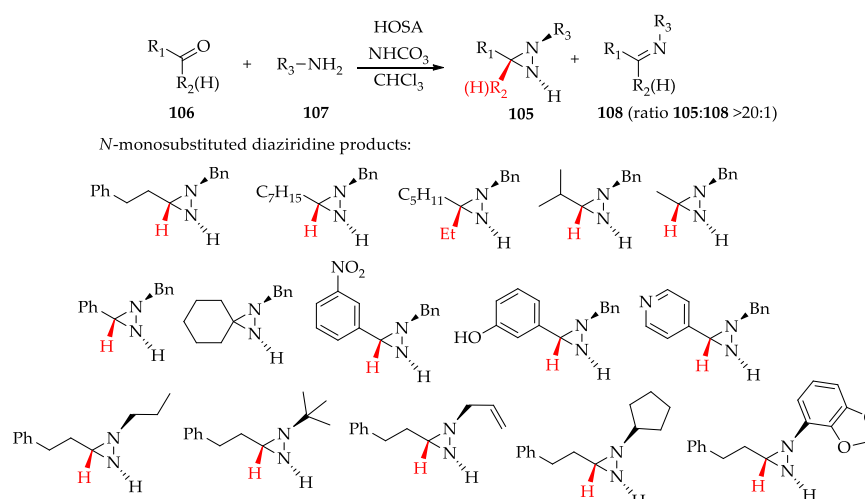


Figure 14. *N*-monosubstituted diaziridines **105** synthesis from simple aldehydes or ketones **106** with amines **107**.

3.2.3. Unconventional *N*-Monosubstituted Diaziridine Synthesis Approach

When an excess of the mixture of CS_2 and KOH was added to hydrazide **109** spirit boiling solution, the hydrogen sulphide evolved in the reaction. As a result of the elimination of hydrogen sulphide, three-membered diaziridine **110** was formed, along with another product, 1,3,4-thiadiazolidine [2]. Although the amounts of CS_2 and KOH were varied, the same substances were formed, with the amount of CS_2 affecting only the yield of the final product. The maximum reaction yield was observed when hydrazide, CS_2 , and KOH were taken in a molar ratio of 1:1.7:2.0, indicating that diaziridine **110** had been formed, while for thiadiazolidine cycle formation, an excess CS_2 of more than double is required. At first, it is possible to form potassium salt, which is then converted into diaziridine derivative under the action of hydrochloric acid. Using this unconventional method, compound **110** can be either thion or thiol tautomeric (Figure 15A). Using the described method, the 1-(4-methoxy-6-methyl-pyrimidin-2-yl)-diaziridine-3-thion **111** can also be established from hydrazide **112** (Figure 15B). As for the influence of the carbonyl group on the reaction, similar interactions were carried out using 4,6-bis-dimethylamino- [1,3,5]triazine-2-carboxylic acid hydrazide **113** (Figure 15C) and 3,4-dimethyl-2-thioxo-2,3-dihydro-thiazole-5-carboxylic acid hydrazide **114** (Figure 15D). The *N*-monosubstituted diaziridine of (4,6-bis-dimethylamino-[1,3,5]triazine-2-yl)-(3-thioxo-diaziridin-1-yl)-methanone **115** and (3,4-dimethyl-2-thioxo-2,3-dihydro-thiazole-5-yl)-(3-thioxo-diaziridin-1-yl)-methanone **116** can be obtained (Figure 15C,D).

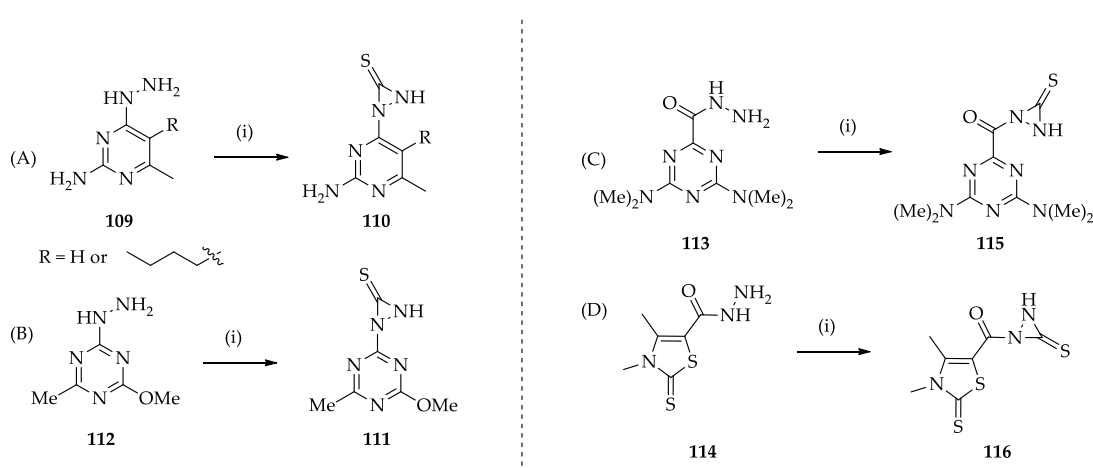


Figure 15. Synthesis of *N*-monosubstituted diaziridines **110**, **111**, **115**, and **116** via the unconventional method by elaborating hydrazine, CS_2 , and KOH . (A) pyrimidine, (B) 1,3,5-triazine, (C) carbonylated 1,3,5-triazine and (D) carbonylated thiazole-2(3*H*)-thione. Reagents: (i) CS_2 , KOH , ethanol.

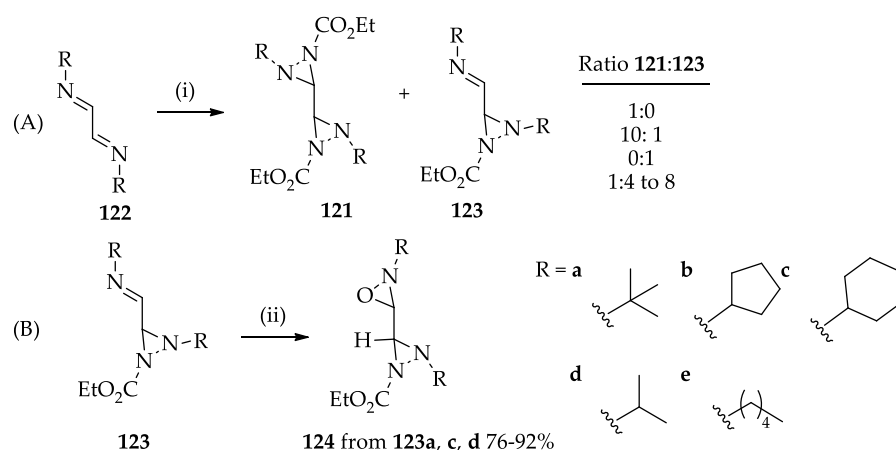
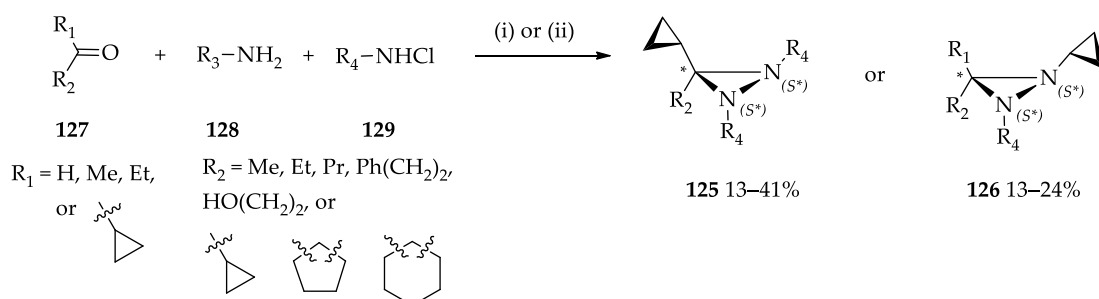
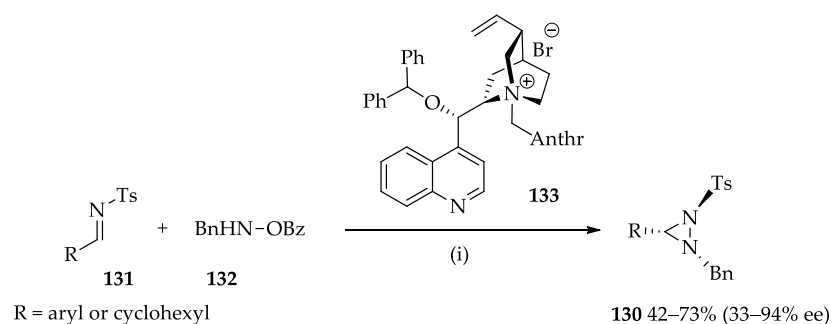


Figure 16. Synthesis of monodiaziridine **123** and bidiaziridine **121** from α -diimines **122** (A) and further substitution for **123** (B). Conditions: (i) $\text{NsONHCO}_2\text{Et}$, $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$, CaO , rt; (ii) *m*-CPBA, CH_2Cl_2 , 0°C .

In line with the synthesis of the hybrid compound, a diastereoselective method for the synthesis of diaziridines with *N*- and/or *C*-cyclopropyl substituents (**125** and/or **126**) was developed [90] using the conventional methods. A one-pot, three-component condensation of cyclopropyl-containing carbonyl compounds **127**, primary aliphatic amines, including cyclopropylamine **128**, and *N*-chloroalkylamines **129** was conducted in the organic solvents. This typical reaction was carried out under mild conditions and in the presence of bases (Scheme 9), resulting in the predominance of diaziridine product **125** and/or **126**, with the major diastereomer being the racemic mixture of two meso-forms, and the racemic mixtures of two enantiomers for the minor diastereomer. The use of K_2CO_3 as a base, and an aprotic solvent (CHCl_3) obtained from equimolar amounts of aldehyde, cyclopropylamine, and pre-synthesized *N*-chloroalkylamines can provide access to compounds with cyclopropyl substituents on the nitrogen atom of the diaziridine ring. As for the enantio- and diastereoselective synthesis of diaziridines **130** via aziridination of *N*-tosyl aldimines **131** while applying modified hydroxylamine **132** under asymmetric phase-transfer catalysis **133**, it was recognized that K_2CO_3 was too weak to mediate this reaction [91]. Thus, K_2PO_4 was then utilized, and the reaction rate was significantly enhanced, and gave diaziridine with similar selectivity. By taking advantage of a phase-transfer catalyzed nitrogen insertion into the π -system of *N*-tosyl aldimines **131** and the use of *N*-transfer agent of *N*-benzyl-*O*-benzoyl hydroxylamine **133**, the afforded *N*-tosyl-*N'*-benzyl-diaziridines **130** can be synthesized as a single diastereomer in up to high yields with high to excellent enantioselectivity (up to 96% ee, Scheme 10).



Scheme 9. Synthesis of diaziridines with *N*- and/or *C*-cyclopropyl substituents **125** and/or **126**. Conditions: (i) excess of the corresponding amine, MeOH , $0\text{--}5^\circ\text{C}$; (ii) $\text{K}_2\text{CO}_3/\text{CHCl}_3$, $\sim 20^\circ\text{C}$.



Scheme 10. Catalytic enantio- and diastereoselective synthesis of *N,N*-disubstituted diaziridines **130**. Conditions: (i) K_3PO_4 , Toluene, -12°C , 72 h.

3.3.2. The Green Transformation of 6-Aryl-1,5-diazabicyclo[3.1.0]hexanes

Green chemistry is leading the development of ionic liquids as alternative solvents that possess useful physicochemical properties, such as non-inflammability, low vapor pressure, and ease of regeneration. These trends have led to the transformation of *N,N*-disubstituted diaziridines under ionic liquid solvent-based reaction. The 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **134** can be thermally (by refluxing in toluene or xylene) or catalytically (by the addition of 20 mol % Lewis acid ($\text{BF}_3 \cdot \text{Et}_2\text{O}$)) transformed into active species of azomethine imines **135** (Figure 17). In [92,93], mild conditions were represented by the use of ionic liquid medium, and it was found that the reaction could be managed by ionic liquid, rather than the organic solvent, of MeCN [94]. In some case, heating was required (40°C or 50°C) to initiate the reaction with olefins **136**, which resulted in the [3 + 2] cycloaddition products of 1,5-diazabicyclo[3.3.0]octane derivatives **137**. High diastereoselectivity can be achieved through the [3 + 2] cycloaddition of azomethine imines derived from 6-aryl-1,5-diazabicyclo[3.1.0]hexanes to acrylonitrile and 4-nitrophenyl vinyl sulfone in ionic liquid of [emim][OTf] [93]. The transformation of diaziridine **134** into active species of azomethine imines **135** showed different reactivity when reacted with arylidenemalononitrile **138** (Figure 17). The presence of an electron-withdrawing NO_2 substituent in the aromatic ring of arylidenemalononitrile, as the starting material, resulted in pyrazoline **139**, and the isolation of arylidenemalononitriles containing aromatic fragments of the starting bicyclic diaziridines **140** was also achieved [95]. The annulations of azomethine imines **135**, derived from the representative diaziridine **134** with 1*H*-indole-2,3-diones **141**, can occur on the basis of the reaction between azomethine imines and carbonyl compounds. There are two types of product introduced in the ionic liquid of [bmim][BF₄] systems: pyrazolines **142**, which are proposed to be proceed by the induction of a formal 1,4-H shift in azomethine imine; and pyrazoles **143** (Figure 17), which are most likely to emerge as a result of the oxidation of pyrazolines by air oxygen [96]. Moreover, the reaction between 6-aryl-1,5-diazabicyclo[3.1.0]hexanes and 1,3-diarylpropanones was also conducted under microwave irradiation (110°C), which is compliant with the principles of green chemistry in organic synthesis [97]. The [3 + 2] cycloaddition products of perhydropyrazolopyrazoles were formed in fine yields as single diastereomers.

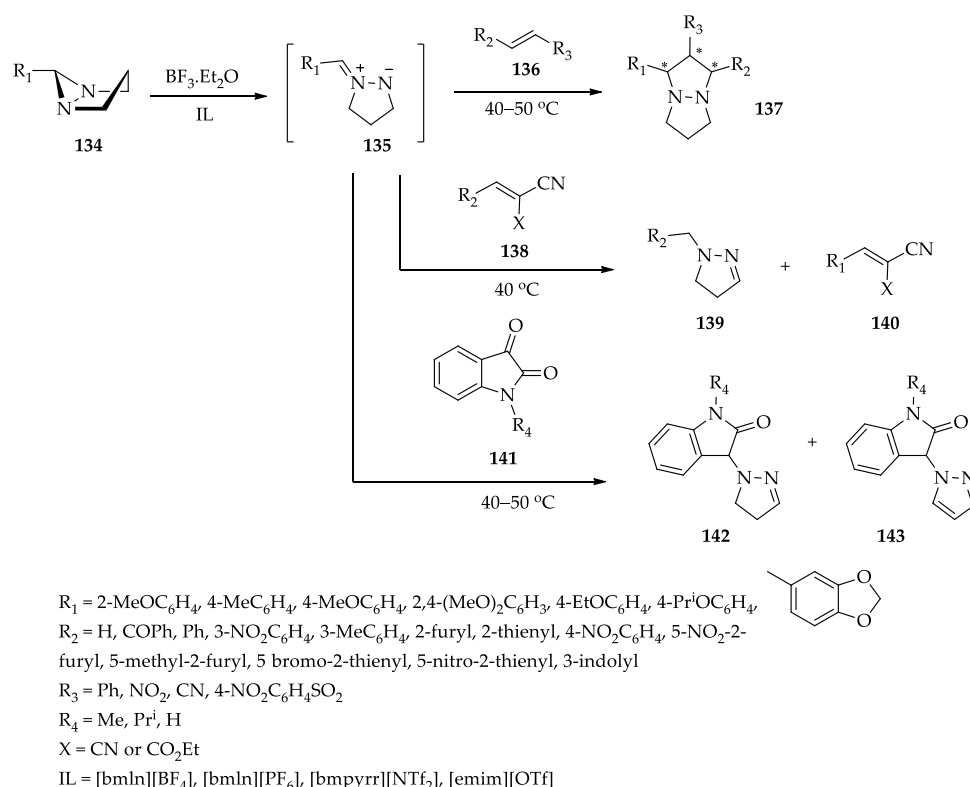


Figure 17. Reaction of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **134** upon reaction with olefins **136**, arylidenemalononitrile **138**, and 1*H*-indole-2,3-diones **141** in ionic liquids.

3.3.3. Metal Catalysis of Diaziridines Ring Opening

A single reagent that is able to catalyze multiple mechanistically distinct processes in a chemical reaction is known as an auto-tandem catalyst [98], and the transition metal used for this process is gold(I). The ring opening of diaziridines [99] is initiated by the synthesis of *N*-monosubstituted diaziridine by the conventional method of reacting ketone **144**, benzyl, and the aminating reagent $\text{NH}_2\text{OSO}_3\text{H}$. A minimal modification at the free *N*-terminal of diaziridine resulted in 1-benzyl-1,2-diazaspiro[2.5]octane **145**, which was then used as the starting material for an auto-tandem catalysis reaction mediated by gold(I). The model reaction was conducted by reacting diaziridine **145** with phenylacetylene **146**, and it was found that the product 3-pyrazoline **147** was preferentially obtained using $\text{Ph}_3\text{AuNTf}_2$ as the catalyst, rather than other catalysts. The alkyne insertion product **146** was possibly an intermediate in the process, since it can be directly transformed into the product 3-pyrazoline **147** by the use of $\text{Ph}_3\text{AuNTf}_2$. Taken together, gold(I) as an auto-tandem catalyst is capable of being used to pursue the typical subsequent ring opening of diaziridine **145** and the cyclization of **148** (Figure 18).

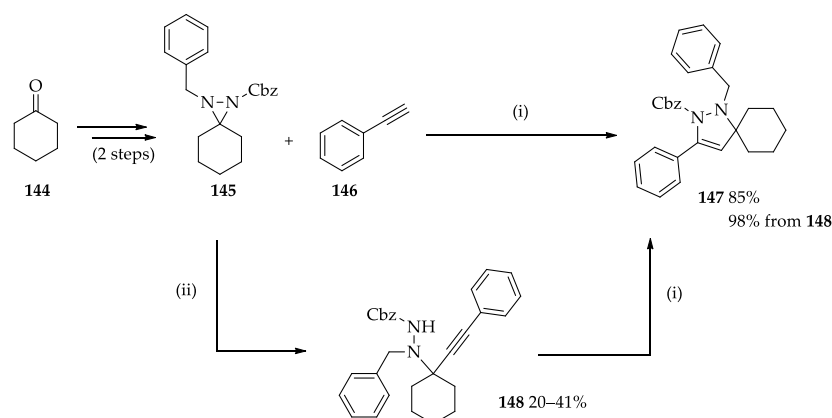
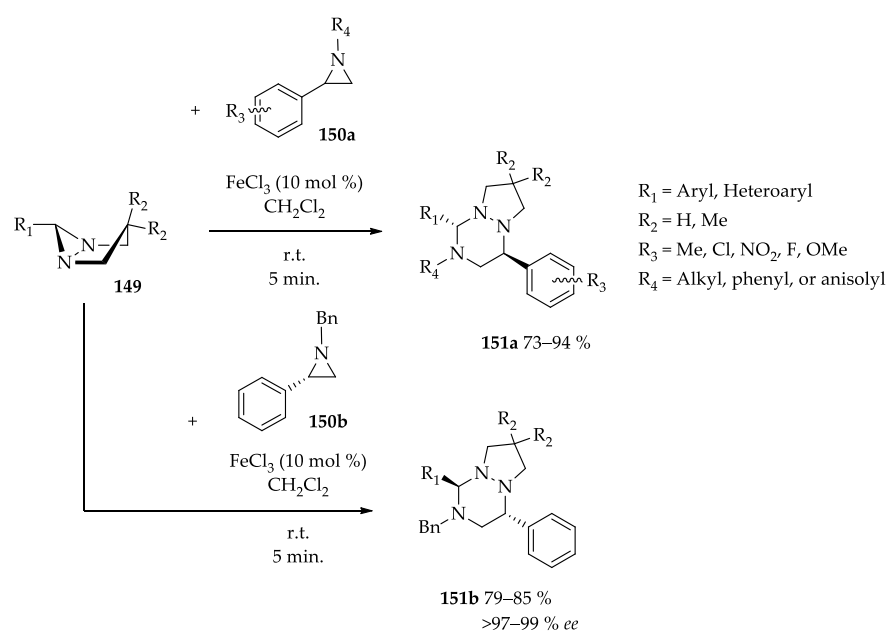


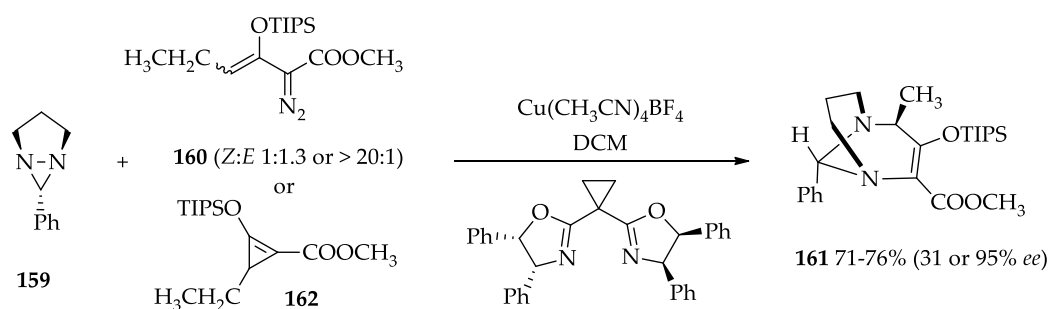
Figure 18. Metal-catalyzed formation of 3-pyrazolines **147** through cycloaddition of diaziridine **145** to alkynes **146**. Conditions: (i) 10 mol % $\text{Ph}_3\text{AuNTf}_2$, toluene, rt or 70 °C, 12 h or 18 h; (ii) 10 mol % AgOTf or AuCl_3 or $\text{Zn}(\text{OTf})_2$ or $\text{Cu}(\text{OTf})_2$, toluene, 70 °C, 18 h; Cbz = carbamate group.

The [3+3]-annulation of bicyclic diaziridines **149** with *N*-substituted aziridines **150a,b** in iron salt can be processed into [1,2,4]-triazines **151a,b** as a single diastereoisomer by using FeCl_3 (Scheme 11). The chelation of aziridines with FeCl_3 can lead to stereospecific ring opening using azomethine imine intermediate derived from diaziridine and the diastereoselectivity potentially obtained by the steric factors during the approaches of aziridine with the azomethine imine. Diaziridine **149** was tested using optically active aziridine **150b**, demonstrating the stereoselectivity of this typical iron-catalyzed reaction [100]. The one-pot reaction of bicyclic diaziridines **152** and (2-bromo-2-nitrovinyl)arenes **153** resulting in bicyclic cationic **154** (2,3-dihydro-1H-pyrazolo[1,2-*a*]pyrazol-4-ium as cation and $[\text{Ce}^{3+}(\text{NO}_3)_6]^{3-}$ as anion) can only be conducted under the action of ceric ammonium nitrate (CAN) and MeCN (Figure 19). CAN as the catalyst can trigger in situ diaziridine ring opening of bicyclic diaziridines or metathesis of azomethine imine, the occurrence of [3+2] cycloaddition of (2-bromo-2-nitrovinyl)arenes, followed by the aromatization of the formed pyrazolidine ring [101]. This metal catalysis of diaziridine ring opening approaches (Scheme 11 and Figure 19) provides the advantage of simplicity, and is a powerful tool for the synthesis of hydrazine bicyclic compounds.



Scheme 11. Iron-catalyzed cycloaddition of diaziridines **149** with aziridines **150**.

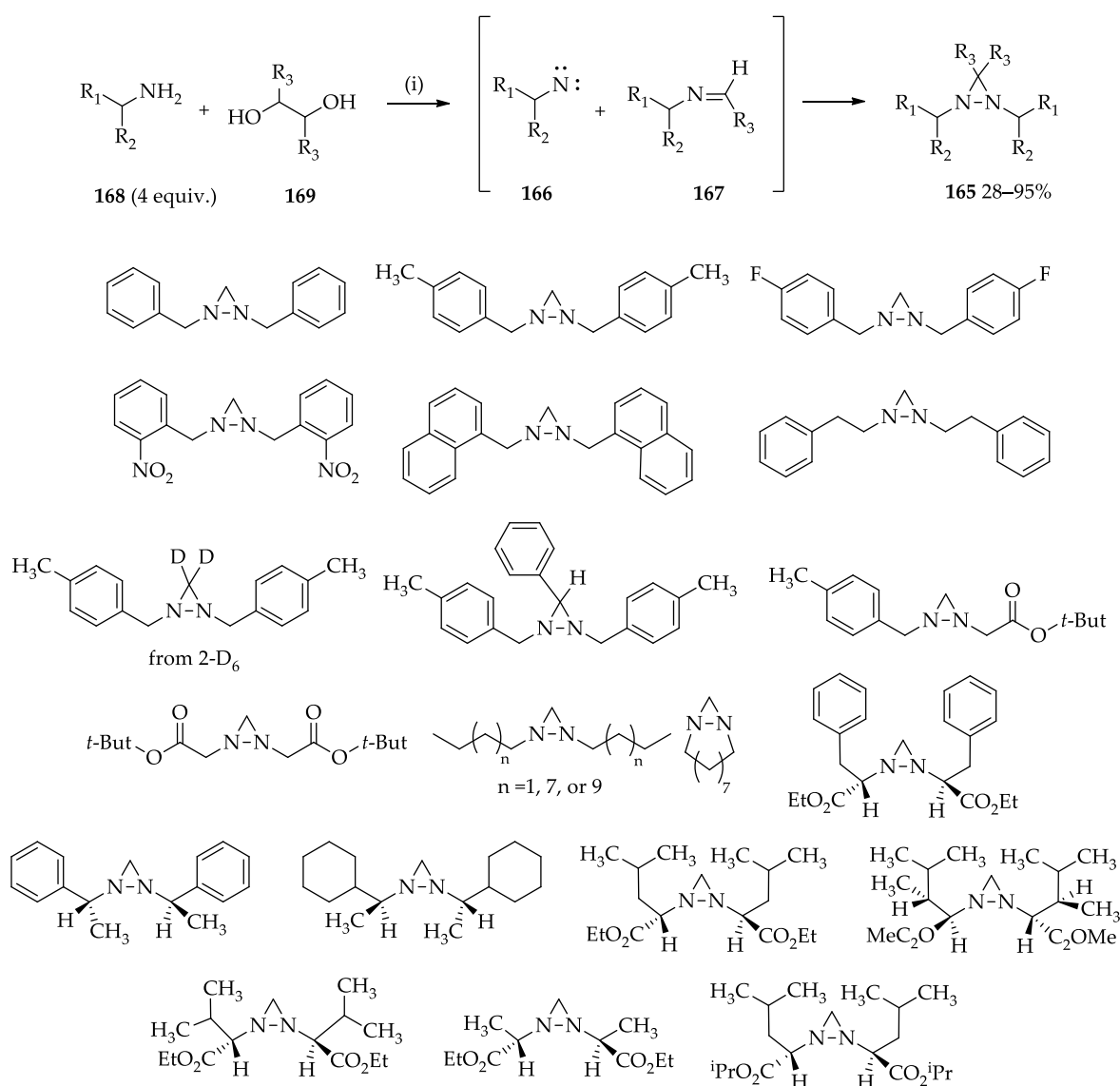
Since diaziridine is a strained ring system that can undergo N–N bond cleavage, the ring opening of bicyclic diaziridine **159** was continued for its reaction with enoldiazoacetates **160**, which resulted in the cycloadduct **161** (Scheme 12). The metallo-enolcarbenes was initially generated to undergo the novel [3 + 2]-cycloaddition. The asymmetric synthesis process is able to produce the cycloaddition product **161** with 31% ee or 95% ee, depending on the isomeric mixture of the starting material. The metallo-carbene source of donor–acceptor cyclopropene **162** is also able to form the cycloaddition product **161** in 95% ee (Scheme 12), suggesting that the initially generated cycloaddition of metallo-enolcarbenes is possible at a faster rate than the formation of the corresponding donor–acceptor cyclopropene **162** [104].



Scheme 12. The [3 + 2]-cycloaddition of diaziridine **159** with enoldiazoacetate **160** or cyclopropene **162**.

3.3.5. Unconventional *N,N*-Disubstituted Diaziridine Synthesis Approach

An unconventional nonmetallic and photocatalytic approach to *N,N*-disubstituted diaziridine synthesis was developed [105], excluding hydroxylamine-*O*-sulfonic acid [20] and ethyl nosyloxycarbamate [18] for the mediation of condensations of carbonyl compounds, amines, or ammonia. A blue LED, an organic photocatalyst (rose Bengal **163**), and a Lewis acid such as the oxidant $\text{PhI}(\text{OAc})_2$ **164** were used to generate functionalized diaziridines with excellent reaction rates and yields that also showed high stereoselectivities for the synthesis of diaziridines **165** with chiral substituents. The reaction proceeded through the in situ formation of nitrene **166** and an imine **167** intermediate, whereby their formation involved the light-activated Rose Bengal in order to convert related species from the combination of $\text{PhI}(\text{OAc})_2$ **164**, amine **168**, with 1,2-diol **169** or the simultaneous combination of $\text{PhI}(\text{OAc})_2$ directly with amine. The typical *N,N*-disubstituted diaziridine **165** synthesized using this novel and extraordinary method is summarized in Scheme 13.



Scheme 13. The unconventional *N,N*-disubstituted diaziridine synthesis. Conditions: (i) Rose Bengal (**163**, 1 mol %), blue LED, $\text{PhI}(\text{OAc})_2$ (**164**, 4 equiv.), CH_2Cl_2 , rt, 20–40 min.

4. Conclusions

The non-, *N*-mono-, and *N,N*-disubstituted diaziridines are attractive skeletons as building blocks in the synthesis of important intermediates and precursors with excellent stereochemical properties. The trend of diaziridine formation is still following the conventional concept, wherein valuable synthesized diaziridine derivatives are added together with various substituents. More unconventional approaches are limited to the period of the last decade, and further studies aiming to extend these unconventional methods remain to be performed. The study of diaziridine transformation in the field of organic and pharmaceutical chemistry—especially to become a precursor in diazirine-based photoaffinity labeling probes for drug design—as well as its stereochemistry, offer great opportunities for further exploration.

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