CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Benzazetidines and Related Compounds: Synthesis and Potential

Authors: Riccardo Salvio, Placidi Simone, and Marco Bella

To be cited as: *Chem. Eur. J.* 10.1002/chem.201905668

Link to VoR: http://dx.doi.org/10.1002/chem.201905668

Supported by
ACES

WILEY-VCH

10.1002/chem.201905668

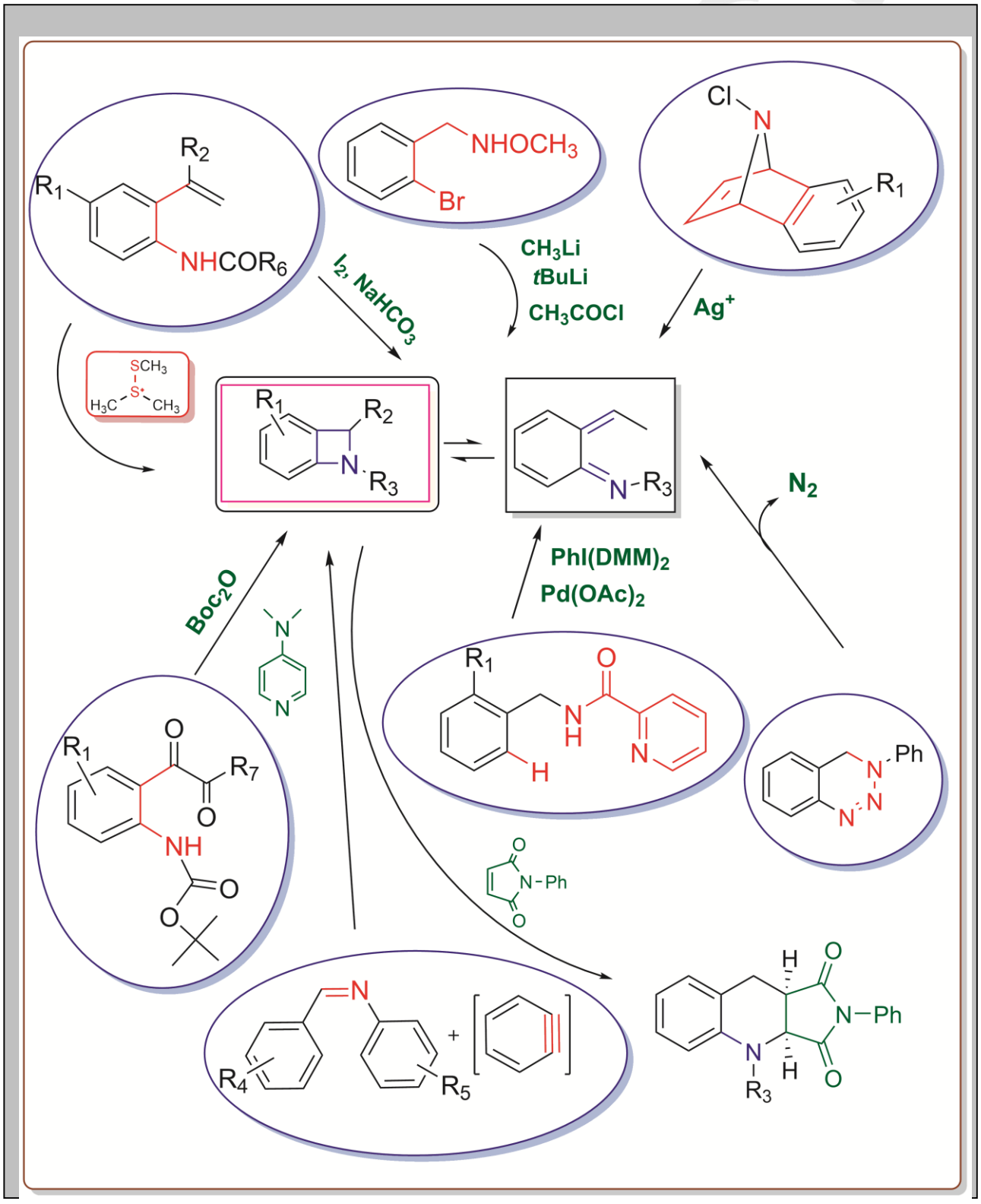
WILEY-VCH

MINIREVIEW

Benzazetidines and Related Compounds: Synthesis and Potential

Riccardo Salvio*[a][b], Simone Placidi,[c] and Marco Bella[c]

Dedication ((optional))



10.1002/chem.201905668

WILEY-VCH

MINIREVIEW

[a] Riccardo Salvio, P*h*D - **Corresponding Author**
Dipartimento di Scienze e Tecnologie Chimiche, Università "Tor Vergata"
Via della Ricerca Scientifica, 1, I-00133 Roma, Italy.
E-mail: riccardo.salvio@uniroma2.it

[b] ISB - CNR Sezione Meccanismi di Reazione, Università La Sapienza, 00185 Roma.

[c] Dipartimento di Chimica, Sapienza Università di Roma,
P.le Aldo Moro 5, 00185 Roma, Italy

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Abstract: Benzazetidines are a class of *N*-heterocycles potentially very interesting for a variety of purposes, including biological applications and drug design. In the past, their high ring strain has hampered the development of trustable, general and efficient synthetic methodologies for their preparation. In this review article we aim to disclose all the literature contributions about the synthesis of these compounds and the study of their reactivity, from the early examples to the most recent synthetic approaches. Recently, we noted a growth of interest for this heterocycle pushed by the publication of novel synthetic methodologies based on palladium catalyzed intramolecular C-H amination and organocatalyzed ring closure of 2-(*N*-Boc-anilino)-*α*-ketoesters/amides.

1. Introduction

Benzazetidines are organic compounds that feature a benzo-fused four-membered azetidine motif.[1-4] Nitrogen heterocycles are the most significant components of pharmaceuticals since about 60% of the drugs approved by USA FDA contain at least a nitrogen heterocycle.[5] For this reason benzazetidines, as *N*-heterocycles, are potentially interesting for applications in biomedical research and drug design. In this field, among the four-membered *N*-heterocycles, azetidones play a central role as they are part of *β*-lactam antibiotics. Despite this, several research groups have designed and created analogues that maintain the overall shape of classical cephalosporin but lack the electrophilic *β*-lactam ring and therefore they are devoid of the acylating potential toward the serine residues of the target proteins.[6-9] In a recent contribution, the authors have reported the design, the synthesis and the study of the biological activity as antibacterials of various compounds, from indoles, indolines and acyl amides to highly strained benzazetidines.[10] In this regard, the development of new synthetic approaches for the preparation of this class of heterocycles may open new paths to pharmaceutically active antibacterial agents acting as bioisosteres[11] of *β*-lactams. Benzazetidines are also promising as building blocks and precursor of key reactive intermediate in organic synthesis, [2,12,13] such as ortho-quinone methide imines,[14-16] for instance.

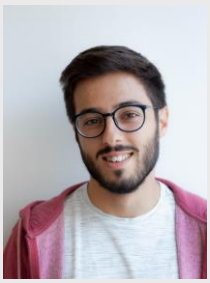
Despite their significance, the synthetic approaches for the preparation of these compounds and the study of their reactivity are largely unexplored. Indeed, at least till a few years ago, there was a paucity of synthetic methodologies for the preparation of this class of compounds which comes from their high ring strain and, consequently, from their pronounced instability in a number of cases and under certain conditions. In addition to that, as remarked above, in the category of four-membered *N*-heterocycles, the fused *β*-lactams, i.e. benzazetidones and similar systems, account for the largest share of research efforts, because of their well-known potential antibiotic properties.[17,18]

Azetidines, the analogous unfused heterocycles, are accessible via a variety of synthetic procedures, e.g. intramolecular nucleophilic substitution of halogenated precursors or intramolecular Michael addition.[19] However the synthetic procedures to prepare azetidines are generally not applicable for the preparation of the analogous benzo-fused derivatives. As a result of that, in the scientific literature, there is a lack of diversity among this family of compounds.

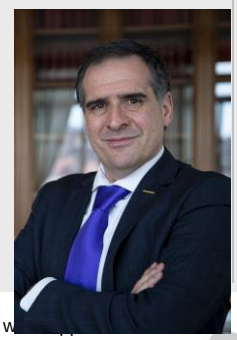
Recently, a few groups reported novel preparation pathways for the synthesis of benzazetidines promoted by palladium-based catalysts and by an organocatalytic approach, as thoroughly discussed later on in this review article. This evidence is indicating an upcoming growth of interest for this molecular scaffold. For this reason, and also considering that, as the best of our knowledge, no previous review article was specifically dedicated to benzazetidines, we believe appropriate to report and discuss in a critical manner all the synthetic methodologies and the reactivity issues reported in the literature so far about this class of compounds, from the early examples to the most recent literature reports. A well-ordered systematic review may have the utility to disclose the state-of-the-art of this research topic and push scientists to develop new methodologies for the preparation of these heterocyclic compounds.

Riccardo Salvio was born in Rome, Italy. He received his P*h*D in 2005 from University of Rome La Sapienza in the group of Prof. Luigi Mandolini. He spent the years 2005–2007 at The Scripps Research Institute, La Jolla, USA, as a Research Associate under the supervision of Prof. Julius Rebek. After this experience he moved to The Netherlands and joined the group of Prof. David Reinhoudt as a Postdoc. In 2009, he moved back to Italy with a fellowship "Rientro dei Cervelli" and worked in La Sapienza as independent researcher till 2019, when he moved, as a research staff member, to University of Rome Tor Vergata. His research interests include homogeneous catalysis, supramolecular chemistry, as well as organocatalysis and organic synthesis.

10.1002/chem.201905668



Simone Placidi achieved his master degree in Organic Chemistry in 2017 at University of Rome La Sapienza. In the same year he started his P*h*D program in the School of Chemical Science 'Vito Volterra' at La Sapienza University under the supervision of Riccardo Salvio. Currently he is a visiting P*h*D student in the group of Professor Nuno Maulide at University of Vienna. His research is focused on the development of new enantioselective synthetic strategies for the preparation of bioactive molecules.

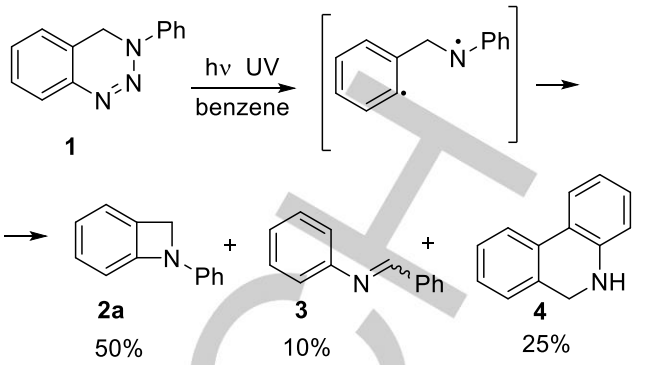


Marco Bella obtained his P*h*D from La Sapienza University in 2000. Then he joined as a Postdoc the group of K. C. Nicolaou at The Scripps Research Institute (2000–2003, La Jolla, CA) and after that he moved to Aarhus University to work in the group of K. A. Jørgensen (2003–2005, Aarhus, Denmark). He moved back to his hometown as "Ricercatore" in 2005, in La Sapienza University, where he started his independent research career in the field of organic synthesis and organocatalysis. In 2015 he w[illegible] professor. In 2018 he has been elected in the National Parliament. Currently he is a member of "Camera dei Deputati" and plays an active role in the decisions about research and university policy.

2. Synthetic Approaches for the Synthesis of Benzazetidines

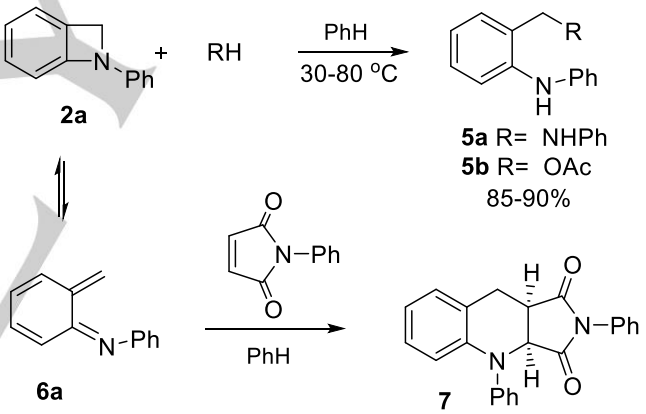
2.1. Early examples of the preparation of benzazetidines: syntheses based on elimination reactions by pyrolysis, FVP and photoirradiation.

Since the early 1960s the interest in the construction of benzo-fused four-membered heterocycles has grown for several reasons such as the possibility of benzenoid bond fixation resulting from the small ring fusion,[20] the study of valence isomerism and the possibility to obtain anions, isoelectronic with naphthalene, with potential aromatic properties. The first reported example for the synthesis of the benzazetidine structure was accomplished starting from 3-phenyl-4*H*-benzo-1,2,3-triazine (**1**), derived from *N*-(*o*-aminobenzyl)aniline, described in Scheme 1.[21] The *N*-phenylbenzazetidine **2a** was obtained with a 50% yield, in mixture with benzalaniline **3** (10%) and 9,10*H*-phenanthridine **4** (25%) as side products. This evidence points to the formation of a 1,4-diradical intermediate which undergoes either a coupling reaction affording the product, or alternatively, a hydrogen migration leading to sideproducts **3** and **4**.



Scheme 1. Photostimulated preparation of *N*-phenylbenzazetidine from 3-phenyl-4H-benzo-1,2,3-triazine and formation of side products.

Compounds **2** turn out to be much more nucleophilic compared to the analogous azetidines,[2,19,21] probably because of their ring strain. Indeed, they easily reacts both as neutral compounds and as the corresponding conjugated acids. **2a** reacts with aniline quite rapidly in benzene, at temperatures higher than 30 °C, leading to the relief of the strain energy through the ring opening (Scheme 2).[21] Likewise, in the presence of sodium acetate or acetate buffer, **2a** undergoes the analogous ring opening reaction affording compound **5b**.[21]

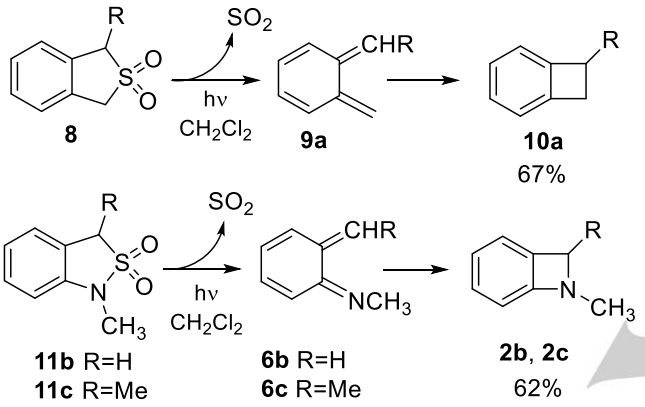


Scheme 2. Isomerization equilibrium of *N*-phenylbenzazetidine **2a** and its reactivity towards nucleophiles and dienophiles.

Another indication of the high reactivity of the *N*-phenylbenzazetidine **2a**, and other benzazetidines in general, is the tendency to isomerize, upon thermal or photochemical excitation to its valence isomer **6a** according to the equilibrium depicted in Scheme 2, formally classified as a 4π electrocyclic reaction. An indirect evidence of this equilibrium is the reaction of **6a** with *N*-phenylmaleimide to yield the 1:1 adduct **7**, obtained through the [4+2] cycloaddition reaction illustrated in Scheme 2.[21]

With a contrariwise pathway, the preparation of *N*-alkylbenzazetidine was reported starting from sultams **11**.[22] This compounds are converted into the *o*-quinonemethide imine intermediates **6b** and **6c** by photolytic extrusion of sulfur dioxide (300 nm, CH_2Cl_2). Compound **2b** is obtained as white crystalline material by recrystallization of the reaction crude with ethanol (62% yield, Scheme 3).[22] This approach was inspired by the similar behavior of benzocyclobutenes, that have been

extensively used in the synthesis of natural products. One of the most convenient method to prepare benzocyclobutenes is the thermal elimination of sulfur dioxide from sulfones **8**. They easily form *o*-quinodimethide intermediates **9a** which partially isomerizes to benzocyclobutene **10a** (Scheme 3), or alternatively can be trapped by 4+2 cycloaddition with several dienophiles[1]. Intermediates **9**, and related compounds, can also be obtained by flash vacuum pyrolysis (FVP)[23-25] from a wide number of different precursor leading to cyclobutarenes. The reaction products obtained by FVP are mainly collected by matrix isolation techniques,[26] with different yields, depending on the experimental conditions.[27-30] Since with the matrix isolation methodology a limited amount of product and reagents are trapped, for many procedures a trustable and reproducible value of reaction yields can not be given.

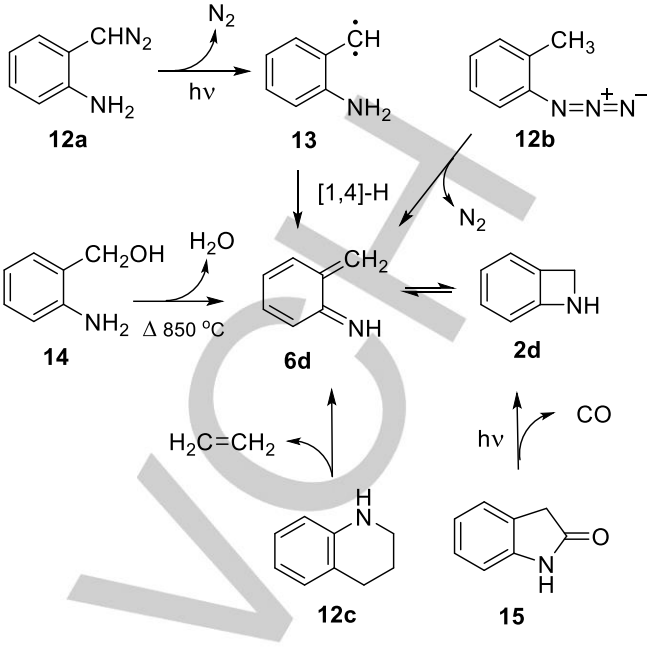


Scheme 3 Elimination of sulfur dioxide from sulfones and sultams affording benzocyclobutenes and benzazetidines respectively.

Alternative methods for the preparation of benzazetidines through the formation of *o*-quinonemethide imine intermediates, can be accomplished with different starting materials. Elimination of nitrogen from (*o*-aminophenyl)diazomethane **12a** is accomplished by photolysis (λ=544 nm) in argon at 10 K.[31,32] Most likely, the formation of quinonemethide imine intermediate **6d** is accomplished with a [1,4] hydrogen shift in *o*-aminophenylcarbene **13**.[31]

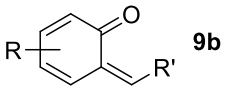
The intermediate **6d**, and therefore also the benzazetidine **2d**, can be prepared also by dehydration of aminoalcohol **14** at high temperature and by photolysis of 2-indolidone **15** which slowly affords a mixture of **2d** and **6d** although in low yields.[31] Azide **12b** and tetrahydroquinoline **12c** also afford a mixture of **6d** and **2d** via elimination of nitrogen and ethylene respectively.[32-34] Unfortunately this mixture is prone to oligomerize and polymerize. It is also sensitive to the presence of any nucleophile that can result in a ring opening reaction.[33]

The valence isomerization between **2d** and **6d** was investigated both experimentally and by theoretical calculations.[32,34,35] These studies have come to the conclusion that this equilibrium is strongly affected by the temperature and can be shifted to one of the two directions upon a change of the experimental conditions.[35]



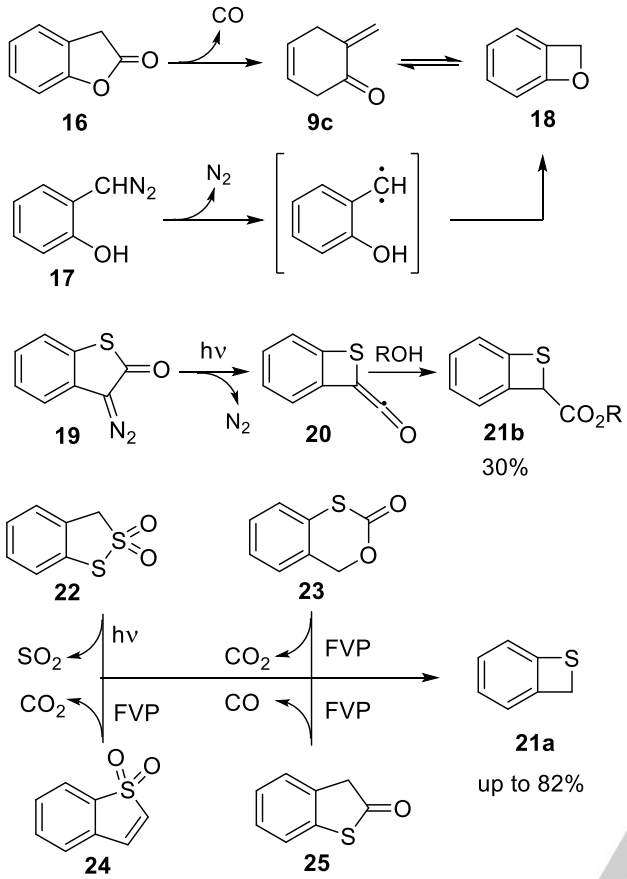
Scheme 4 Synthetic pathways for the preparation of an equilibrium mixture of quinonemethide imine and benzazetidine **2d** by FVP.

The equilibrium between *o*-quinonemethide imine and the corresponding benzazetidine is conceptually and structurally correlated to *ortho*-quinone methides (**9b**). These compounds were observed for the first time by Chapman and McIntosh using IR spectroscopy at low temperature,[36] as they are also very labile and reactive. However, despite their transiency, they are often used by nature for a variety of biological purposes,[37] by researchers in natural product synthesis[38] and for other synthetic purposes. Their primary reaction modes include nucleophilic additions and electrocyclizations. As there is an abundancy of recent research papers about this compounds and their discussion is beyond the purpose of this article, we refer to recent reviews about this topic.[37-41]



9b

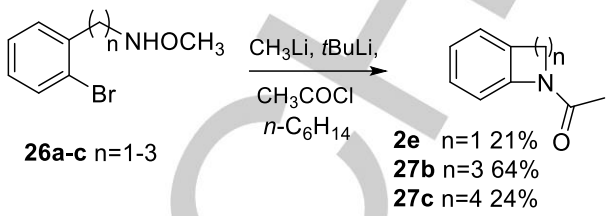
The preparation of the analogous benzo-fused heterocycles with oxygen and sulfur can be achieved with similar strategies, as illustrated in Scheme 5. Benzofuranone **16** and the *o*-hydroxyphenyldiazomethane **17** can be converted, through liberation of carbon monoxide and nitrogen respectively, to benzoxete **18** either by irradiation[42] and by flash vacuum pyrolysis.[43] The first successful synthesis of a benzothiete was accomplished by Wolff rearrangement of 3-diazobenzo[*b*]thiophen-2(3*H*)-one (**19**) that under irradiation generates ketene **20**.[44,45] This intermediate can be easily trapped with alcohols leading to esters **21b**. Alternative syntheses of the benzothiete scaffold consist in cycloelimination reactions of compounds **22**-**25** that liberate small gas-phase molecules such as sulphur dioxide,[46] carbonic anhydride[47-50] or carbon monoxide[51,52] (Scheme 5).



Scheme 5 Examples of synthetic procedure for the preparation of analogous four membered benzo-fused sulfur and oxygen heterocycles.

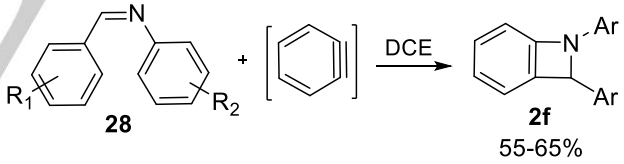
2.2 Syntheses based on organometallic intermediates, cycloaddition reactions, and rearrangements of bicyclic compounds

The syntheses described so far, in a relevant number of cases, are defective because of limited scope, low yields, formation of side-products and the use of expensive and uncommon equipment, i.e. Flash Vacuum Pyrolysis apparatus.[24,25] A radically different approach for the preparation of benzazetidines and other nitrogen-containing bicyclic system was presented by Beak and Selling.[53] This amination strategy can be used to form benzazetidines and other benzo-fused *N*-heterocycles. This approach extends the already reported amination method based on displacement of an alkoxy group from an alkoxylamine by an organolithium reagent.[54] The strategy consists in the preparation of the appropriate (*o*-bromophenyl)alkanylmethoxylamine (**26a**-**c**) from the corresponding formyl or bromomethyl derivatives. The crucial step is the double lithiation of the arylbromide affording (*o*-lithiophenyl)alkylithiomethoxylamide. This highly reactive intermediate, prepared from **26a**, undergoes a ring closure affording the *N*-acetylbenzazetidine **2e,** (Scheme 6, 21% yield), whose structure was assigned by standard methods, including *X*-Ray diffractometry.[53] Unfortunately, the procedure employs *t*BuLi and consequently is not compatible with several functional groups. The synthetic method, whenever the appropriate precursor is employed, can be used to synthesize also the *N*-acetyltetrahydroquinoline **27b** and the *N*-acetylbenzazapine **27c**, whereas the preparation of the higher homologous benzazocine ring could not be achieved this way. This evidence is probably ascribable to the slower cyclization rate of the ring closure of an eight-membered ring which is overcome by the decomposition rate of the lithioalkoxyamide.[53]



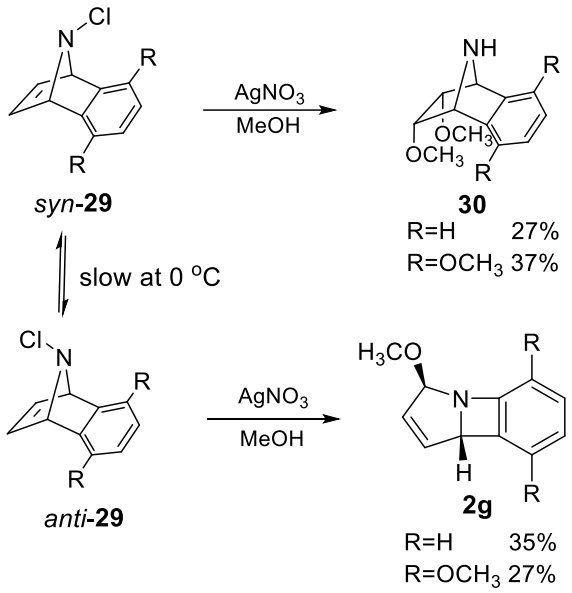
Scheme 6 Preparation of benzo-fused *N*-heterocycles based on intramolecular displacement of lithioalkoxyamides by arylorganometallic moiety.

Another possibility to afford the benzazetidine structure consists in the trapping of benzyne, generated *in situ* by aprotic diazotization of anthranilic acid in 1,2-dichoroethane (DCE).[55] Benzyne promptly reacts with the active carbon-nitrogen double bond with various substituted azomethines (**28**) to give the corresponding [2+2] cycloadducts **2f** (see Scheme 7).[56] Since the azomethines can be easily synthesized by condensation reactions of various derivatives of benzaldehyde and aromatic amines, this method was applied for the preparation of a large series of compounds with reaction yield range of 55-65%.
Interestingly, the cycloaddition of azomethines with benzyne was also investigated by other two groups in independent studies.[57-58] Their attempts to obtain the desired product were fruitless, however they found convincing evidences for the formation of benzazetidine **2f** and its participation in further reactions.[57,58,16]



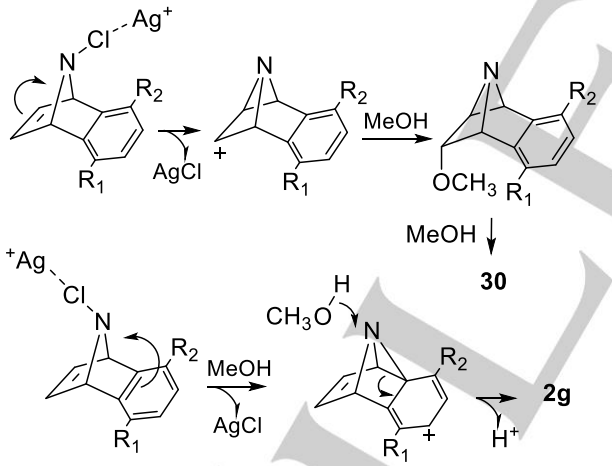
Scheme 7 Preparation of 1,2-diarylbenzazetidenes via [2+2] cycloaddition reaction of azomethines with benzyne.

Malpass and his coworkers noted an unexpected result in the course of an investigation about the solvolysis of *N*-chloro derivatives of 1,4-dihydro-1,4-iminonaphtalene (7-azabenzonorbornadiene) in methanol.[59] These halogenated derivatives are configurationally stable at the nitrogen center at temperature lower than 0 °C. They show, in this regard, a behavior similar to that of aziridines,[60] due to their ring strain.
The 7-azabenzonorbornadienes can be chlorinated in aprotic solvents with *N*-chlorosuccinimide (NCS) affording a mixture of *syn* an *anti* isomers of **29** either under kinetic and thermodynamic control.[61,62] The two invertomers (Scheme 8) can be separated exploiting their different solubility in fluorinated solvents.[59] Surprisingly *syn*-**29** and *anti*-**29** show a dramatically different reactivity in solvolytic conditions in the presence of $AgNO_3$. The *anti*-**29** leads to compound **2g** as major product (35% yield), whereas the *syn* invertomer affords the solvolysis product **30**.



Scheme 8 Reactivity of the *N*-chloro-7-azabenzonorbornadiene invertomers in the presence of Ag^+, under solvolytic conditions. The *anti*-**29**, unlike the *syn* isomer, affords compound **2g** containing the benzazetidine scaffold.

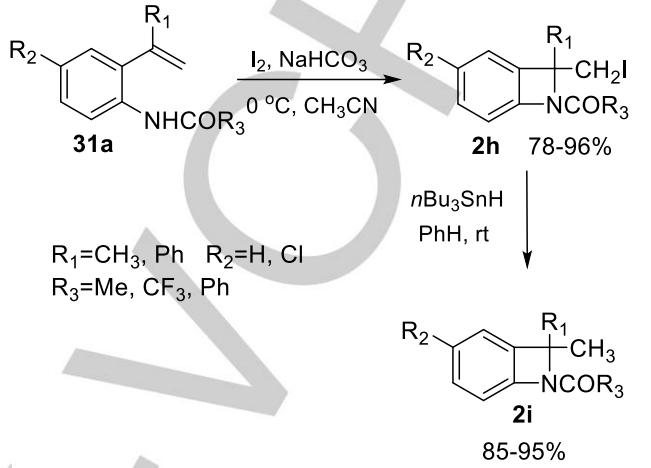
This dissimilarity in the reactivity can be explained with the participation of etheno-π-electrons in the loss of the chloride ion from *syn*-**29** and the participation of the benzo-π-electrons in the loss of chloride from *anti*-**29**, as illustrated in Scheme 9.



Scheme 9 Postulated mechanisms for the reactivity of the *syn* and *anti* invertomers of *N*-chloro-7-azabenzonorbornadiene in methanol.

2.3. Syntheses of benzazetidines from *o*-aminostyrene derivatives

A significant step further in the synthesis of benzazetidine has been presented 2005.[63] The authors developed a method based on an intramolecular haloamination reaction, previously employed for the preparation of other nitrogen heterocycles,[64,65] which offers a simple access to the construction of benzazetidine derivatives. The intramolecular iodoamination of the *o*-(acylamino)styrene derivatives can be easily accomplished in acetonitrile in presence of iodine and sodium bicarbonate according to Scheme 10 (78-96% yields). The ready availability of the starting materials and the ease of the procedure make the present method a valid alternative for the synthesis of this scaffold.



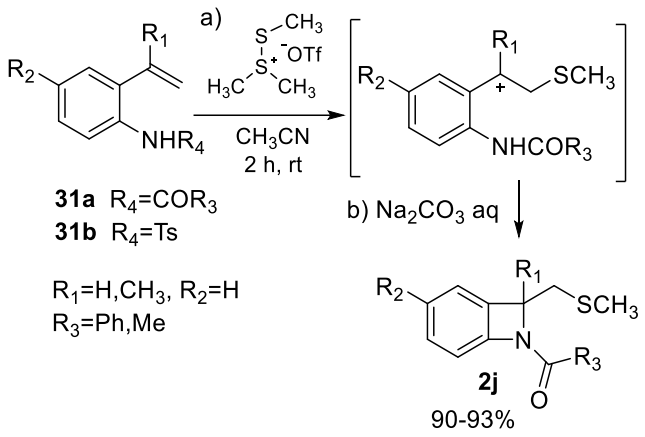
Scheme 10 Intramolecular iodoamination of *o*-(acylamino)styrene derivatives reported by Kobayashi and coworkers.[63]

Benzazetidines **2h** can be reduced to the corresponding dehalogenated compound **2i** by treatment with tributyltin hydride in benzene (Scheme 10). This reaction is also useful to confirm the (iodomethyl)benzazetidine structure of **2h**, and exclude the formation of the five-membered dihydroindole structure, by comparison with other data reported in the literature.[63] Furthermore, the mass analysis rules out the formation of the symmetrical dimer of **2h**.[63]

The same iodoamination reaction leading to benzazetidines can be performed with *N*-iodosuccinimide in CH_2Cl_2,[66] although the authors of a previous research report claim that the major product, in very similar reaction conditions, is the 3-iodomethyl-*N*-acetylindoline.[67] The nucleophilic substitution of the iodine of **2h** can be accomplished with a number of nucleophiles, e.g. sodium benzenethiolate to give a 2-(phenylthiomethyl)benzazetidine in satisfactory yields (55-66%).[63]

A variation of this synthetic approach was accomplished by Okuma *et al.*[66] They reported a synthetic procedure using the same starting material as the synthesis in Scheme 10, i.e. *o*-vinylbenzanilide **31a**. The treatment of this compound with dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST), followed by the addition of aqueous sodium carbonate, leads to the benzazetidine **2j** in high yields (90-93%, Scheme 11) and short reaction times, i.e. 2-3 h. The sulfur-sulfur bond in DMTST, and in other alkylated disulfides is reactive toward nucleophiles and has been widely applied to the synthesis of glycosides.[68-71] This reagent is a alkenylsulfenylating agent, or potential source of alkenylsulfenyl ions (RS^+).[72] Most likely the reaction proceeds through the intermediate represented in Scheme 11, which undergoes intramolecular attack by the nitrogen atom. Chemical shifts of the ^{13}C signals, by comparison with other compounds previously reported,[73,74] allowed to confirm the structure and rule out the formation of the five-membered ring.

10.1002/chem.201905668

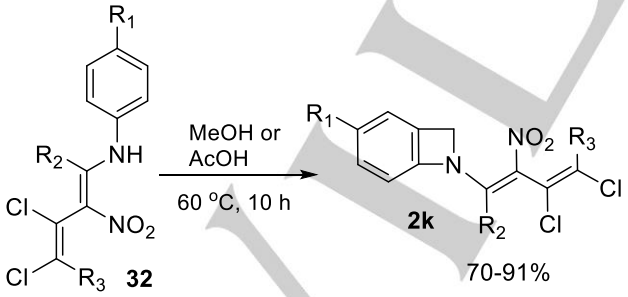


Scheme 11 Synthesis of the benzazetidine scaffold by treatment of *o*-(acylamino)styrenes with dimethyl(methylthio)sulfonium trifluoromethanesulfonate and aqueous basic hydrolysis.

When the *o*-vinyl-*N*-*p*-tosylanilide **31b** is used as starting material the corresponding five-membered ring is obtained, i.e. 3-methylthio-*N*-tosylindoline (77% yield). Since the reactivity is essentially the same in the case of the *o*-isopropenyl-*N*-methanesulfonylanilide, the authors infer that the bulkiness of the group do not play a crucial role in the transformation and attribute the reactive behavior to higher acidity of sulfonamides (p*K*a=6-10)[75-76] compared to that of acetamides and benzamides (p*K*a=17).[76]
Okuma and his group reinvestigated this reaction and one year later in a literature research paper they revised the product to be a benzoxazine instead of previously reported benzazetidine.[77]

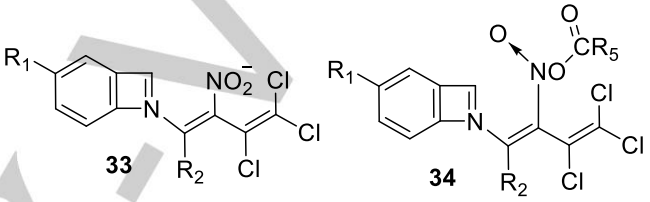
2.4 Other synthetic approaches to the preparation of activated benzazetidine.

In 2001 an alternative synthesis for this class of compounds from phenylaminobutadienes was reported. Heating the halonitrodienes **32** in methanol or acetic acid leads to the formation 2-(1-nitro-trihalo-2-propenylidene)benzazetidines **2k** in good yields (Scheme 12).[78]

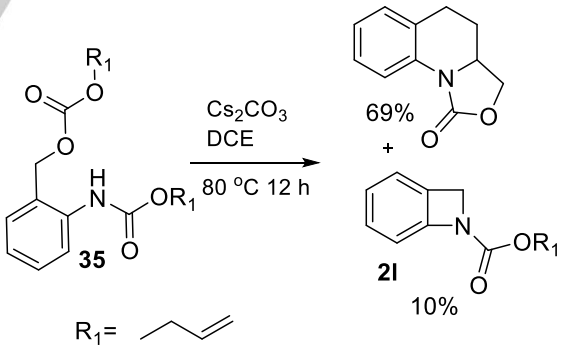


Scheme 12 Synthesis of the benzazetidine from phenylaminobutadienes derivatives.

In this reaction the nature of the azolyl fragment has no appreciable impact on the performance of the process, whereas the nature and the position of the substituent in the 1-arylamino fragment has a dramatic impact on it. This procedure was not effective with aniline, *m*-toluidine, *p*-aminobenzoic acid, *p*- and *m*-bromoaniline and 2,4-diamino-toluene. The identity of the structure was confirmed by NMR, mass analysis, IR and elemental analysis. In the reaction a single stereoisomer is formed. Taking into consideration the possibility of the formation of a six-membered ring involving the amino and the nitro groups, the authors hypothesize the formation of the *Z* isomers.[78]
In presence of bases such as alkoxides or amines the benzazetidines **2k** with R_3=Cl is transformed into benzazete, and the nitro group is turned into *aci*-nitro with the formation of the corresponding salts **33** (70-80% yield). These salts are soluble in water, alcohols and acetone and turned out to be stable in those media. The treatment of these compounds with hydrochloric acids quantitatively returns the initial benzazetidine structure. In addition, the treatment with benzoyl and chloroacetyl chlorides in pyridine of benzoazetidines **2k** (R_3=Cl) leads to the formation of anhydrates **34**.

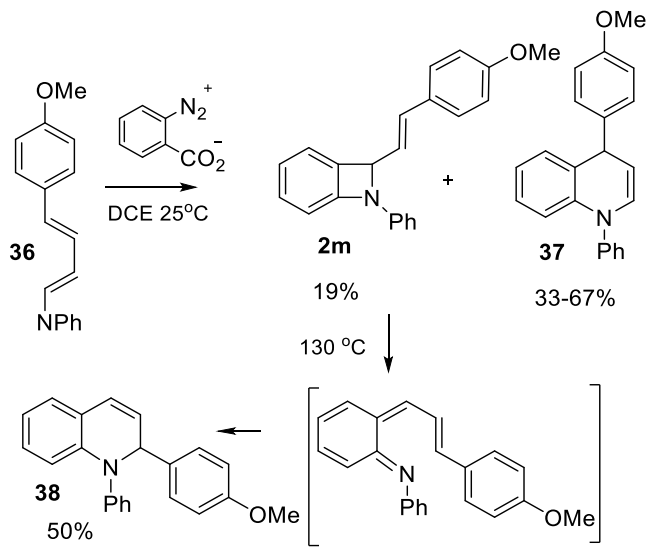


The same group reported also a procedure consisting in a further functionalization of product **2k** with the addition of methyl or phenyl lithium. This process affords the replacement of one or two chlorine atoms in the structure. [79]
In is noteworthy to mention that the formation of the benzazetidine structure was observed as byproduct (10% yield) in the preparation of tetrahydroquinolines from carbonate **35** (Scheme 13).[80]

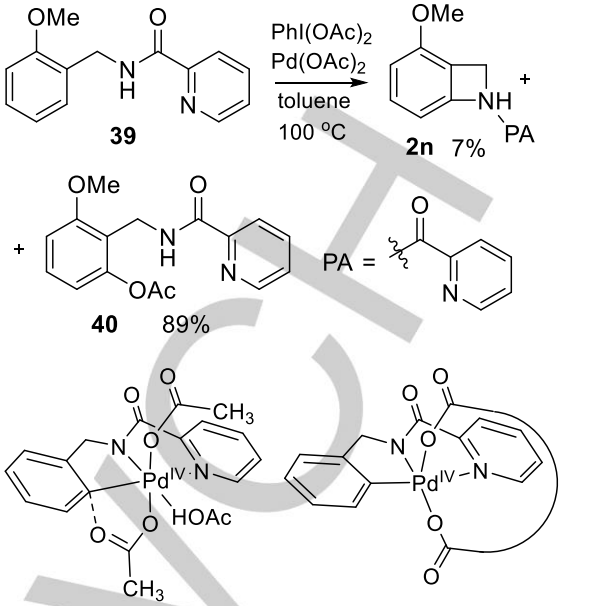


Scheme 13 Synthesis of tetrahydroquinolines from carbonates **35** affording a benzazetidine as byproduct.

Similarly, another group noted the formation of benzazetidine **2m** during the procedure for the preparation of dihydroquinolines using a [4+2] addition between benzyne and various aryl substituted 1-azadienes (Scheme 14).[81]
In an attempt to understand the absence of benzazetidine **2m** at high temperature, this compound was isolated was heated in chlorobenzene. The procedure leads to dihydroquinolines **38** instead of its isomer **37**. This is presumably formed by electrocyclic ring opening of **2m** followed by intramolecular [4+2] cycloaddition of the azaxylylene intermediate represented in Scheme 14.



Scheme 14 Preparation of dihydroquinolines through addition between benzyne and phenylazadienes and reaction path of isolated benzazetidine **2m** affording the dihydroquinolines isomer **38** through an azaxylylene intermediate.

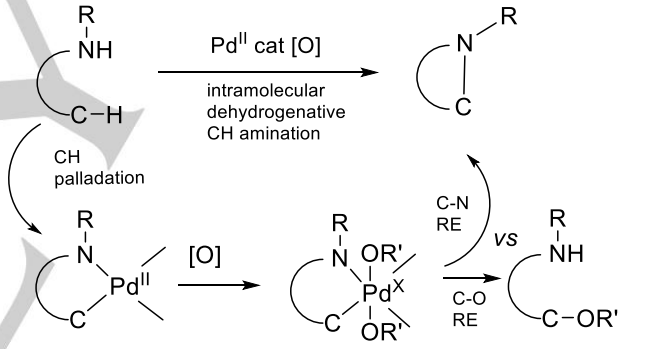


Scheme 15 Pd-catalyzed *ortho* C-H functionalization of *N*-benzyl picolinamide **39** using $Ph(OAc)_2$ as oxidant (top). Mechanistic model which compares the transition states for C-H acetoxylation in the presence of acetate or dicarboxylic acid. The ring strain in the transition state with dicarboxylic acids justifies the suppressed C-O reductive elimination (bottom).

2.4. Recent examples of benzazetidine preparation based on Pd and organocatalysts

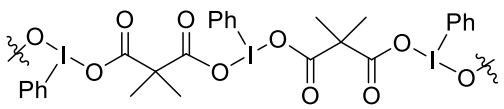
In 2016 He, Liu and Chen[82] reported the preparation of a series of benzazetidines through a novel approach consisting in an intramolecular palladium-catalyzed C-H amination. This approach represents a practical and high-yielding synthetic method for the preparation of a wide range of benzazetidine from easily accessible starting materials. The authors were inspired by a palladium catalyzed intramolecular dehydrogenative C-H amination (IDCA) of picolinamide (PA) *N*-protected benzylamines **39**.[83] These compounds undergo C-H acetoxylation in the presence of $Pd(OAc)_2$ as catalyst affording compound **40** (Scheme 15). They have noted, after careful examination of the reaction mixture, that a small amount (7%) of the benzazetidine product **2n** is formed along with the C-H acetoxylated product **40**.[82] An investigation about the reaction oxidants revealed that phenyliodonium carboxylate reagents are the only effective for this C-N cyclization. In the present case there are two competitive reaction pathway of the putative picolinamide-chelated Pd^{IV} intermediate (see Scheme 15) and each of them can give rise to the corresponding product.[84] The two competitive reaction pathways are illustrated in Scheme 16.

The C-N reductive elimination is unfavorable because is affected by a high ring strain. There are evidences in the literature suggesting that the C-OAc reductive elimination from Pd proceeds through a five-membered transition state in which the new C-O bond is formed with the carbonyl oxygen.[85,86] In an attempt to suppress the C-O reaction, the authors tested a number of tethered carboxylate ligands as additives under the $PhI(OAc)_2$-oxidized conditions, in order to constrain the conformation of the high-valent Pd intermediate.[82] No positive results were obtained in these conditions as compound **40** was still the major reaction product. Most likely the reason was the interference of the acetate introduced with $PhI(OAc)_2$.

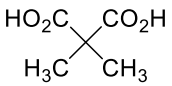


Scheme 16 Reaction sequence of IDCA catalyzed by Pd in oxidative conditions. N-directed C-H palladation, oxidation of the intermediate and competition between the C-N and C-O reductive elimination. OR'=oxygen ligand.

To overcome this inconvenience the authors tested a pre-made phenyliodonium oxidants that carried various dicarboxylate ligands.[82] These reagents were obtained by mixing the diacid with $PhI(OAc)_2$ in chloroform at 45 °C and then removing the acetic acid under reduced pressure. Among these reagents the phenyliodonium dimethylmalonate, PhI(DMM) **41**, derived from the dimethylmalonic acid **42**, significantly improved the yield of the intramolecular dehydrogenative C−H amination. **41** exists as mixture of oligomers because of the peculiar T-shaped structure of phenyliodine (III) compounds.[87]

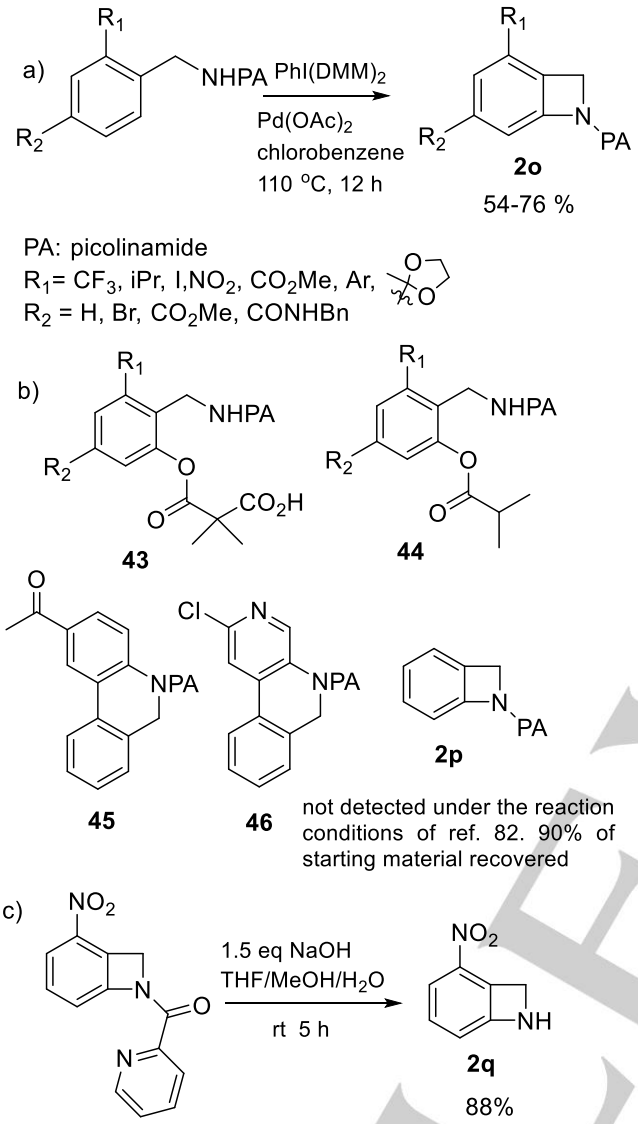


41



42

Under the optimized PhI(DMM)-mediated Pd-catalyzed conditions, benzazetidines were obtained in a significantly improved yield, along with the C-H acyloxylation/decarboxylation side products **43** and **44**.



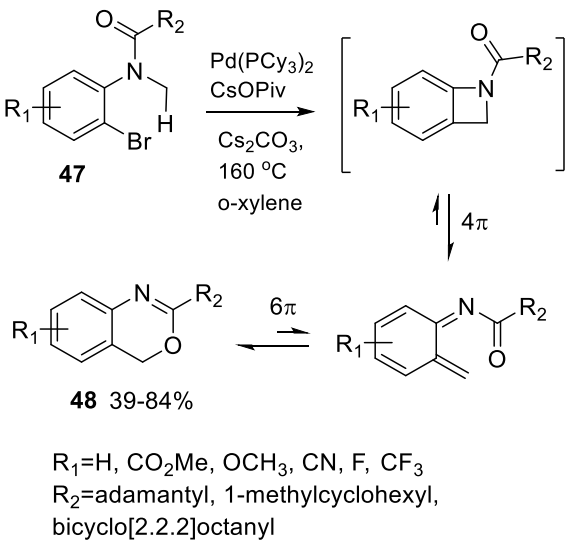
Scheme 17 a) Reaction conditions and scope for the synthesis of benzazetidine using palladium catalyst and phenyliodonium dimethylmalonate reported in ref. 82; b) reaction products detected in the reaction mixture; c) removal of the tertiary amide-linked picolinamide group under mild conditions and at room temperature to give the *N*-unsubstituted benzazetidine in good yield.

The key of the efficiency of this reaction, besides the use of **41**, is the presence of picolinamide directing group, initially introduced by Daugulis et al.[88] The reaction scope was evaluated under the conditions indicated in Scheme 17. The yield and selectivity of the cyclization of these substrates are substantially improved by the use of **41**. A wide range of functional groups including ketone, ester, amide, iodo and cyclic ketal was tolerated. *ortho*-Arylbenzylamine substrates, easily prepared through the PA-directed Pd-catalyzed ortho C-H arylation of unsubstituted benzylamine with aryl iodide, also worked very well in the intramolecular dehydrogenative C−H amination leading to the corresponding benzazetidines (**2o** with R_1=Ar). In the reaction mixture of these biaryls substrates acyloxylated side products are detected in a very little amount and the formation of the highly strained benzazetidine structure was favored over that of the six-membered C-N cyclization products, e.g. compounds **45** and **46**. The ^{1}H and ^{13}C NMR signals confirm the identity of the compounds together with a X-ray crystal structure (*vide infra*). The signals of the methylene unit bound to the nitrogen have a chemical shift around 5-5.5 ppm (^{1}H) and between 55-65 ppm (^{13}C). These values are slightly downfield shifted compared to signals of analogous compounds in the same chemical environment. This effect is ascribable to the ring strain of the benzo-fused four membered ring.

Mechanistic investigations and DFT calculations point to the existence of Pd^{III}/Pd^{III} dimer in the transition state of the reaction.[82] Surprisingly, unsubstituted benzylamine was almost unreactive in the same conditions affording no detectable amount of **2p** and only trace amounts of the C-H acyloxylated side products. The authors do not provide an explanation of this experimental evidence. It is possible to hypothesize that the steric hindrance in position 3 and the electron withdrawing capacity of the substituents play a crucial role in the transformation.

The picolinamide group of benzazetidines **2o** can be promptly removed with 1.5 equiv. of NaOH in MeOH/THF/H_2O at room temperature affording the nitro derivative of the free NH benzazetidine (**2q**, Scheme 17c). The structure of the *N*-unsubstituted 2-nitrobenzazetidine was confirmed by X-ray analysis. This is the first synthesis, to the best of our knowledge, of *N*-unsubstituted benzazetidine.[82]

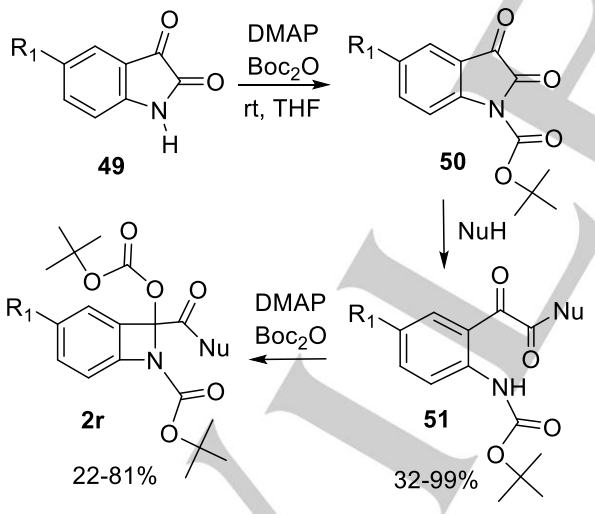
Recently, Baudoin and coworkers considered an alternative synthesis of benzazetidine through a Pd^0-catalyzed intramolecular C-(sp^3)-H arylation from easily accessible 2-bromo-*N*-methylanilides (Scheme 18).[89] This approach was initially reported by Ohno *et al.* for the preparation of indolines[90] and afterwards the scope was significantly expanded by other research groups.[91-93] In addition, it is noteworthy to underline that this approach was employed for the synthesis of other strained four-membered rings such as *β*-lactams[94] and benzocyclobutenes.[95]



Scheme 18 Palladium catalyzed reaction of 2-bromo-*N*-methylanilides affording 4*H*-3,1-benzoxazine through non isolated benzazetidine via a domino sequence of C(sp^3)-H arylation/electrocyclic reaction.

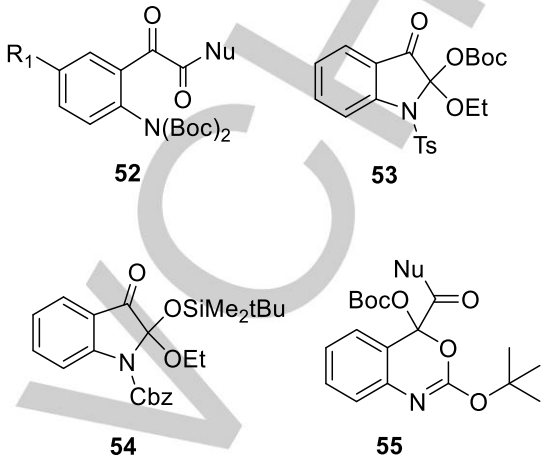
Initially they studied the influence of the nitrogen substituent (R_2 in Scheme 18) which turned out to be crucial. Indeed, the compound with the adamantylamide, and those provided with very bulky non-activatable groups, furnished the benzoxazine as the main product. The presence of these groups disfavors undesired reaction pathways. Benzazetidine ring was never observed, even at short reaction times.[89] Performing the reaction at lower temperatures only resulted in incomplete conversion. Until now, they were unable to extend the benzocyclobutenes synthesis to benzazetidine. The failure can be ascribed, besides to the intrinsic ring strain of benzazetidines, to a difficult C-H activation step, unlike benzocyclobutenes that benefit from the Thorpe-Ingold effect for the presence of a quaternary benzylic carbon.[95] Furthermore this method suffers from the instability of benzazetidines under the high temperatures typically required in such reactions.

In 2019 Bella, Salvio and their coworkers, in the course of their studies about enantioselective organocatalysis, [96-98] reported an organocatalytic synthesis of benzazetidines[99] starting from inexpensive materials that does not require any additive based on transition metals, unlike the procedure recently reported and illustrated above.[82] The starting materials of this preparation are isatin and its derivatives. These compounds can be promptly turned in their corresponding *N*-protected derivatives with Boc_2O.[99,100] The protection induces a higher reactivity in the carbonyl in position 2, at variance with unprotected isatins **49**. For this reason, compounds **50** undergoes the attack of nitrogen or oxygen nucleophiles (NuH). The last step of the preparation consists in an intramolecular attack of the nitrogen atom of **51** onto the carbonyl group affording the di-Boc-protected benzazetidines **2r** in satisfactory to good yields (Scheme 19). Only in a few cases lower yields were observed.



Scheme 19. Synthetic pathway for the organocatalyzed synthesis of benzazetidines starting from isatin derivatives **49**.

Interestingly, compounds **2r** contain a diprotected hemiaminal fragment. This functionality, intermediate in the formation of imines, is usually highly unstable, and rarely directly observed.[101-103] The cyclization reaction that affords **2r** is favored over the competitive formation of the *N*-diprotected side-product **52** isolated from most of the crude reaction mixtures.



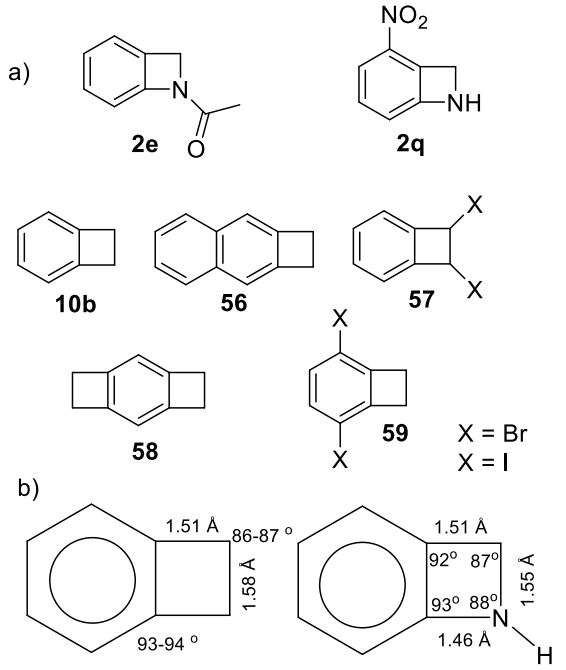
Benzazetidines synthesized with this procedure are stable both as oil and in solution. The different reactivity of a carbonate from a carbamate can be exploited to selectively remove the two Boc protecting groups. Small amount of perchloric acid rapidly cleave the carbonate converting the hemiaminal **2r** into the corresponding acyclic precursor **51**. The other protecting unit can be removed with TFA to afford the starting material **49**. The authors also explored the possibility to obtain benzazetidines with different protecting groups instead of Boc. No detectable amount of benzazetidine was observed in any of these attempts. On the other hand, in two cases, quantities of five-membered cyclic products **53** and **54** were isolated from the reaction mixture.

Benzazetidines **2r** are obtained as oils or amorphous solids. On account of that, no X-ray experiments could be carried out to confirm their structure. However, on the basis of mono- and bidimentional NMR spectra, together with IR experiments, the structure **2r** can be assigned to all the synthesized compounds, as consisting of the four-membered benzo-fused system.[82] Furthermore, on the basis of ^{15}N NMR, UV-Vis spectra and GIAO DFT calculations of ^{13}C chemical shifts, the formation of the alternative 6-membered cyclic acetal structure **55** could be ruled out.[99]

2.5. Crystal Structures from X-ray Investigations

X-Ray crystal structure of two benzazetidines are reported in the literature, i.e. for compounds **2e**[53] and **2q**.[82] The crystal structures of benzocyclobutenes **10b**,[104,105] **56**,[106] **57**, [107,108] **58**,[104] and **59**[109] are also available (Scheme 20a). The comparison between the geometry of the two benzo-fused compounds are summarized in Scheme 20b that shows the averages and intervals for the bond angles and the bond lengths. The values are quite similar for the two classes except for a slightly smaller N-Ar distance in benzazetidines whenever compared with the C-Ar distance in benzocyclobutenes. As an additional information we note that in compound **2e** the geometry

of the acetyl group is not significantly affected by the presence of the *N*-heterocycle: the bond lengths of 1.35 Á between the carbonyl carbon and the nitrogen and of 1.23 Á for the carbonyl double bond are consistent with a common amide functional group.

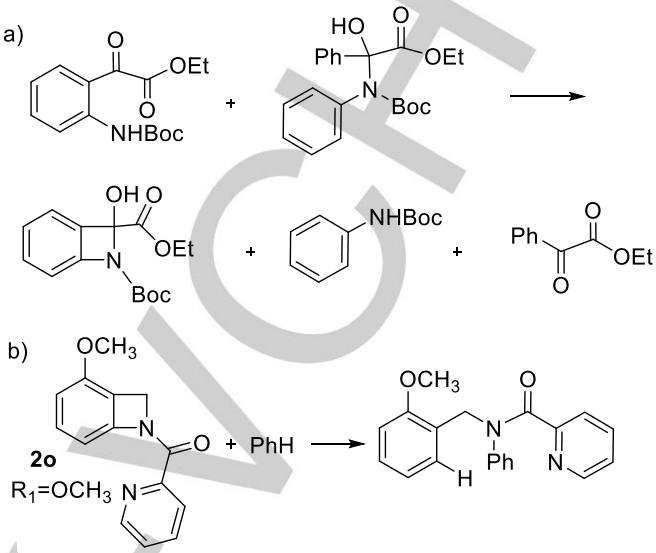


Scheme 20. a) Benzazetidines and benzocyclobutenes whose structures have been determined by X-ray crystallography; b) comparison of average and interval of bond lengths and bond angles in benzazetidines and benzocyclobutenes.

2.6. Evaluation of the ring strain in benzazetidines

As remarked above, the ring strain of benzazetidines strongly affects its geometry and reactivity. A possible method to quantitatively evaluate this quantity is the strain energy.[110] Although the rigorous definition of the strain energy is applicable only to cycloalkanes, its evaluation can be done using an homodesmotic reaction.[111] This is a real or hypothetical chemical reaction in which the type of chemical bonds broken in the reactant are the same as the type of bonds formed in the reaction product. In homodesmotic, at variance with the isodesmic reactions, also the states of hybridization of the atoms are taken in consideration. This expedient is often used in computational thermochemistry to increase the accuracy of the calculations.[111] Bella and Salvio calculated the value of the strain energy of compounds **2r**. The DFT calculation consists in the determination of energy differences, corrected for the zero-point vibrational energy, of the homodesmotic reaction in Scheme 21a. This reaction can be considered the intermolecular counterpart of the intramolecular one occurring in the cyclization.

The calculations afforded a strain energy for the four membered ring of **2r** of 32.7 kcal mol^{-1}. A similar value has been calculated for the strain energy of compounds **2o** through isodesmic reaction in Scheme 21b, i.e. 31.0 kcal mol^{-1}. These values are higher than those of other analogous strained cycles such as cyclobutane (26.5 kcal mol^{-1}) and azetidine (23−27 kcal mol^{-1}).[112] This data overcomes even the value of strain energy of cyclopropane (27.5 kcal mol^{-1}),[111] probably because of the presence of two sp^2 carbon atoms in the aromatic ring far away from their ideal geometry of 120°.



Scheme 21. a) Reactions with the proper model compounds used to determine the ring strain of compounds **2r** (a) and **2o** (b).

3. Conclusions

In this overview an exhaustive set of examples concerning the preparation of the benzazetidine scaffold were collected and critically discussed. A chronological sequence has been chosen to describe all the research paper starting from the first examples based on photostimulated or thermostimulated radical reactions, in a number of cases performed with a flash vacuum photolysis apparatus. More advanced synthetic approaches, based organolithium intermediates, cycloaddition reactions and rearrangements of bicyclic compounds were described.

In the last few years, with a growth of interest in the preparation of these *N*-heterocycles, other radically different synthetic approaches were presented. The use of transition metal as catalyst, i.e. palladium, was first introduced in an intramolecular C-H amination reaction. Several aspects make this synthesis attractive, including the rather wide scope, the use of a new oxidizer specifically designed to perform the reaction and the possibility to remove the protecting group. The deprotection of the picolinamide moiety results in the preparation of the *N*-unsubstituted benzazetidine, for the first time in the literature. Interestingly, an organocatalyzed trapping of hemiaminals in the benzazetidine scaffold, using isatin as starting material has been reported. This procedure features good yields, very mild reaction conditions, the employment of common and inexpensive reagents and the absence of any catalyst based on transition metals.

While a number of reviews have been dedicated the preparation method of several heterocycles, benzazetidine so far received relatively little attention, despite their significance and potentials. At the present time no enantioselective synthesis of benzazetidines has been reported in the literature. Therefore, this can be the next goal to be attained. It is expected that, with a

disclose of the state of the art of the preparation of this compounds, this review might serve as inspiration for developing novel transformations toward this class of *N*-heterocycles.

4 Acknowledgements

Authors wish to thank Università di Roma La Sapienza and Università di Roma Tor Vergata for financial support through "Progetti di Ateneo" 2016 (grant ID:RP116154C50627A3) and 2017 (grant ID: AR11715C824DA349) and 2019 (E84I19002340005). The authors are indebted to Prof. Luigi Mandolini for several useful discussions. Tea Majnoni D'Intignano, Claudia Metitieri and Monica Messina are acknowledged for playing an active role in the group, as master students, about the development of a chiral version of the benzazetidines synthesis illustrated in the present review. Dr Achille Antenucci is also acknowledged for the help and the willingness.

Keywords: *N*-heterocycles • azetidines • ring strain • cyclization reactions • organocatalysis

References

[1] A. K. Sadana, R. K. Saini, W. E. Billups, *Chem. Rev.* **2003**, *103*, 1539-1602.
[2] A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **2008**, *108*, 3988–4035.
[3] Katritzky, A. R.; Ramsden, C. A.; Joule, J. A.; Zhdankin, V. V. Ed.s *Handbook of Heterocyclic Chemistry*, 3rd ed., Elsevier 2010.
[4] Alvarez-Builla, J.; Vaquero, J. J; Barluenga, J. Ed.s *Modern Heterocyclic Chemistry*, 4 Volume Set, Wiley-VCH 2011.
[5] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274.
[6] M. I. Konaklieva, B. J. Plotkin, *Curr. Med. Chem. - Anti-Infect. Agents* **2003**, *2*, 287-302.
[7] P. Devi, P. J. Rutledge, *ChemBioChem* **2017**, *18*, 338-351.
[8] J. W. Johnson, M. Gretes, V. J. Goodfellow, L. Marrone, M. L. Heynen, N. C. J. Strynadka, G. I. Dmitrienko, *J. Am. Chem. Soc.* **2010**, *132*, 2558-2560.
[9] L. N. Jungheim, S. K. Sigmund, *J. Org. Chem.* **1987**, *52*, 4007-4013.
[10] D. J. Cesta, S. Somersan Karakaya, K. Saito, P. E. Javidnia, J. Roberts, Y. Ling, B. S. Gold, L. Lopez Quezada, D. Zhang, T. M. Abramyan, D. B. Kireev, J. Aubé, S. M. Scarry, *Asian J. Org. Chem.* **2019**, *8* 1053-1057.
[11] Nathan Brown Ed. *Bioisosteres in Medicinal Chemistry* Wiley-VCH Verlag GmbH & Co. KGaA, 2012
[12] D. Didier, A. N. Baumann, M. Eisold, *Tetrahedron Lett.* **2018**, *59*, 3975-3987.
[13] For exhaustive recent reports about the chemistry of heterocyclic compounds and their application see *Advances in Heterocyclic Chemistry,* Vol. 105-129. Elsevier, 2012-2019.
[14] A. S. Caillé, L. Trimble, C. Berthelette, C. K. Lau, *Synlett.* **1996**, 669-671.
[15] M. Kretzschmar, F. Hofmann, D. Moock, C. Schneider, *Angew. Chem. Int. Ed.* **2018**, *57*, 4774-4778.
[16] K. Wojciechowski, *Eur. J. Org. Chem.* **2001**, 3587-3605.
[17] Lee, J. J. Ed. *Heterocyclic Chemistry in Drug Discovery*; Wiley-VCH, 2013.
[18] Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, 2nd Edition Wiley-VCH 2011.
[19] F. Couty, G. Evano, *Synlett* **2009**, *19*, 3053-3064.
[20] M. P. Cava, B. Hwang, J. P. Van Meter, *J. Am. Chem. Soc.* **1963**, *85*, 4032-4033.
[21] E. M. Burgess, L. McCullagh, *J. Am. Chem. Soc.* **1966**, *88*, 1580–1581.
[22] M. Lancaster, D. J. H. Smith, *J. Chem. Soc. Chem. Commun.* **1980**, 471-472.
[23] T. Hudlicky, *ACS Omega* **2018**, *3*, 17326-17340.
[24] C. Wentrup, *Angew. Chem. Int. Ed.* **2017**, *56*, 14808-14835.
[25] C. Wentrup, *Aust. J. Chem.* **2014**, *67*, 1150.
[26] V. E. Bondybey, A. M. Smith, J. Agreiter, *Chem. Rev.* **1996**, *96*, 2113-2134.
[27] P. Schiess, M. Heitzmann, S. Rutschmann, R. Stähele, *Tetrahedron Lett.* **1978**, *46*, 4569-4572.
[28] P. Schiess, S. Rutschmann, V. V. Toan, *Tetrahedron Lett.* **1982**, *23*, 3669-3672.
[29] P. Schiess, *Thermochim. Acta* **1987**, *112*, 31-46.
[30] S. Sakai, *J. Phys. Chem.* **2000**, *104*, 11615-11621.
[31] W. Sander, J. Morawietz, *Tetrahedron Lett.* **1993**, *34*, 1913-1916.
[32] J. Morawietz, W. Sander, M. Traubel, *J. Org. Chem.* **1995**, *60*, 6368-6378.
[33] M. Letulle, P. Guenot, J.-L. Ripoll, *Tetrahedron Lett.* **1991**, *32*, 2013-2016
[34] G. Pfister-Guillouzo, F. Gracian, A. Senio, M. Letulle, J.-L. Ripoll, *Tetrahedron Lett.* **1992**, *33*, 5753-5756.
[35] A. Chrostowska, F. Gracian, J.-M. Sotiropoulos, G. Pfister-Guillouzo, K. Wojciechowski, *Eur. J. Org. Chem.* **2000**, 313-318.
[36] C. L. McIntosh, O. L. Chapman, *J. Chem. Soc. D* **1971**, 383 – 384.
[37] Quinone Methides (Ed.: S. E. Rokita), Wiley, New York, **2009**
[38] N. J. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160-9173.
[39] W. J. Bai, J. G. David, Z. G. Feng, M. G. Weaver, K. L. Wu, T. R. Pettus, *Acc. Chem. Res.* **2014**, *47*, 3655-3664.
[40] T. P. Pathak, M. S. Sigman, *J. Org. Chem.* **2011**, *76*, 9210-9215.
[41] R. W. Van De Water, T. R. R. Pettus, *Tetrahedron* **2002**, *58*, 5367-5405.
[42] H. Tmioka, T. Matsushita, *Chem. Lett.* **1997**, 399-400.
[43] G. G. Qiao, K. Lenghaus, D. H. Solomon, A. Reisinger, I. Bytheway, C. Wentrup, *J. Org. Chem.* **1998**, *63*, 9806-9811.
[44] E. Voigt, H. Meier, *Angew. Chem. Int. Ed.* **1976**, *15*, 117.
[35] H. Meier, *Molecules* **2012**, *17*, 1548-1570.
[46] A. G. Hortmann, A. J. Aron, A. K. Bhattacharya, *J. Org. Chem.* **1978**, *43*, 3374-3378.
[47] H. Meier, A. Mayer, *Synthesis* **1996**, *1996*, 327-329.
[48] K. A. Kolmakov, A. J. Kresge, *Can. J. Chem.* **2008**, *86*, 119-123.
[49] W. J. M. van Tilborg, R. Lomp, *J. Chem. Soc. Chem. Commun.* **1977**, 130-131.
[50] W. J. M. van Tilborg, R. Plomb, *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 282-286.
[51] K. Kanakarajan, H. Meier, *J. Org. Chem.* **1983**, *48*, 881-883.
[52] R. Schulz, A. Schweig, *Tetrahedron Lett.* **1980**, *21*, 343-346.
[53] P. Beak, G. W. Selling, *J. Org. Chem.* **1989**, *54*, 5574-5580.
[54] P. Beak, A. Basha, B. Kokko, *J. Am. Chem. Soc.* **1984**, *106*, 1511-1512.
[55] W.-G. Shou, Y.-Y. Yang, Y.-G. Wang, *J. Org. Chem.* **2006**, *71*, 9241-9243.
[56] K. K. Singal, J. Kaur, *Synthetic Commun.* **2001**, *31*, 2809-2815.
[57] J. Nakayama, H. Midorikawa, M. Yoshida, *Bull. Chem. Soc. Jpn.* **1975**, *488*, 1063-1064.
[58] C. W. G. Fishwick, R. C. Gupta, R. C. Storr, *J. Chem. Soc. Perkin Trans. I* **1984**, 2827-2829.
[59] M. L. Durrant, J. R. Malpass, *Tetrahedron* **1995**, *51*, 7063-7076.

[60] Eliel, E. L.; Wilen, S. H. Stereochemistry of Organic Compound, John Wiley & Sons Inc., 1994

[61] J. W. Davies, M. L. Durrant, M. P. Walker, D. Belkacemi, J. R. Malpass, *Tetrahedron* **1992**, *48*, 861-884.

[62] J. W. Davies, M. L. Durrant, M. P. Walker, J. R. Malpass, *Tetrahedron* **1992**, *48*, 4379-4398.

[63] K. Kobayashi, K. Miyamoto, O. Morikawa, H. Konishi, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 886-889.

[64] J. Barluenga, M. Trincado, E. Rubio, J. M. Gonzalez, *Angew. Chem. Int. Ed.* **2003**, *42*, 2406-2409.

[65] S. H. L. Verhelst, B. P. Martinez, M. S. M. Timmer, G. Lodder, G. A. v. d. Marel, H. S. Overkleeft, J. H. v. Boom, *J. Org. Chem.* **2003**, *68*, 9598-9603.

[66] K. Okuma, I. Takeshita, T. Yasuda, K. Shioji, *Chem. Lett.* **2006**, *35*, 1122-1123.

[67] M. Arisawa, Y. Ando, M. Yamanaka, M. Nakagawa, A. Nishida, *Synlett.* **2002**, 1514-1516. The authors of this paper state that the major product is the *N*-acetylindoline derivatives. However, another research group affirm they could get the benzazetidine moiety following the same conditions. See previous reference.

[68] *Electronic Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley-Interscience, 2002, DOI: 10.1002/047084289X.rd349

[69] J. Tatai, P. Fugedi, *Org. Lett.* **2007**, *9*, 4647-4650.

[70] S. Oscarson, F. W. Sehgelmeble, *J. Org. Chem.* **2002**, *67*, 8457-8462.

[71] S. S. Kulkarni, Y.-H. Liu, S.-C. Hung, *J. Org. Chem.* **2005**, *70*, 2808-2811.

[72] S. H. Smallcombe, M. C. Caserío, *J. Am. Chem. Soc.* **1971**, *93*, 5826-5833.

[73] M. Dias, M. Gibson, J. Grimshaw, I. Hill, J. Trocha-Grimshaw, O. Hammerich, *Acta Chem. Scand.* **1998**, *52*, 549-554.

[74] J. A. Murphy, F. Rasheed, S. Gastaldi, T. Ravishanker, N. Lewis, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1549-1558.

[75] *Dictionary of Organic Compounds 6th ed.* Cadogan, J. I. G.; Ley, S. V.; Pattenden, G.; Raphael, R. A.; Rees, C. W.1996, Chapman & Hall, London

[76] *Advanced Organic Chemistry* 6th ed., March, J.; Smith, M. B. – 2007, Wiley

[77] K. Okuma, T. Yasuda, K. Shioji, Y. Yokomori, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1824-1827.

[78] V. I. Potkin, V. A. Zapol'skii, V. A. Knizhnikov, R. V. Kaberdin, A. A. Yanuchok, S. K. Petkevich, *Russ. J. Org. Chem.* **2001**, *37*, 689-694.

[79] V. I. Potkin, V. A. Knizhnikov, A. A. Yanuchok, R. V. Kaberdin, *Russ. J. Org. Chem* **2001**, *37*, 640-643.

[80] F. Avemaria, S. Vanderheiden, S. Bräse, *Tetrahedron* **2003**, *59*, 6785-6796.

[81] K. Mead, S. Stokes, M. Bekkam, M. Rupp, *Synlett.* **2012**, *23*, 389-392.

[82] G. He, G. Lu, Z. Guo, P. Liu, G. Chen, *Nat. Chem.* **2016**, *8*, 1131 - 1136.

[83] F.-R. Gou, X.-C. Wang, P.-F. Huo, H.-P. Bi, Z.-H. Guan, Y.-M. Liang, *Org. Lett.* **2009**, *11*, 5726-5729.

[84] G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3-6.

[85] J. B. Gary, M. S. Sanford, *Organometallics* **2011**, *30*, 6143-6149.

[86] M. C. Nielsen, E. Lyngvi, F. Schoenebeck, *J. Am. Chem. Soc.* **2013**, *135*, 1978-1985.

[87] V. V. Zhdankin, *Chem. Rev.* **2008**, *108*, 5299–5358.

[88] V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154-13155.

[89] R. Rocaboy, D. Dailler, F. Zellweger, M. Neuburger, C. Salom, E. Clot, O. Baudoin, *Angew. Chem. Int. Ed.* **2018**, *57*, 12131 –12135.

[90] T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 1759-1762.

[91] S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou, O. Baudoin, *J. Am. Chem. Soc.* **2010**, *132*, 10706-10716.

[92] M. Nakanishi, D. Katayev, C. Besnard, E. P. Kundig, *Angew. Chem. Int. Ed.* **2011**, *50*, 7438-7441.

[93] T. Saget, S. J. Lemouzy, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 2238-2242.

[94] D. Dailler, R. Rocaboy, O. Baudoin, *Angew. Chem. Int. Ed.* **2017**, *56*, 7218-7222.

[95] M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J. L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc.* **2008**, *130*, 15157-15166.

[96] R. Salvio, M. Moliterno, D. Caramelli, L. Pisciottani, A. Antenucci, M. D'Amico, M. Bella, *Catal. Sci. Technol.* **2016**, *6*, 2280–2288.

[97] A. Puglisi, C. Giustini, A. Ricucci, E. Perotti, L. Massaro, D. Morra, F. Ciucci, A. Zucchet, A. Antenucci, M. Moliterno, S. Placidi, F. Sciubba, L. Galantini, R. Salvio, M. Bella, *Chem. Eur. J.* **2018**, *24*, 6941-6945.

[98] R. Salvio, L. Massaro, A. Puglisi, L. Angelini, A. Antenucci, S. Placidi, F. Sciubba, L. Galantini, M. Bella, *Org. Biomol. Chem.* **2018**, *16*, 7041-7049.

[99] R. Salvio, S. Placidi, A. Sinibaldi, A. Di Sabato, D. C. Buscemi, A. Rossi, A. Antenucci, A. Malkov, M. Bella, *J. Org. Chem.* **2019**, *84*, 7395-7404.

[100] A. Noole, N. S. Sucman, M. A. Kabeshov, T. Kanger, F. Z. Macaev, A. V. Malkov, *Chem. Eur. J.* **2012**, *18*, 14929-14933.

[101] T. Iwasawa, R. J. Hooley, J. Rebek, *Science* **2007**, *317*, 493-496.

[102] T. Kawamichi, T. Haneda, M. Kawano, M. Fujita, *Nature* **2009**, *461*, 633-635.

[103] Y. Zhou, Y. Yuan, L. You, E. V. Anslyn, *Chem. Eur. J.* **2015**, *21*, 8207-8213.

[104] R. Boese, D. Blaser, *Angew. Chem. Int. Ed.* **1988**, *27*, 304-305.

[105] J. L. Lawarence, S. G. G. McDonald *Acta Crystallogr*. **1969**, *B25*, 978.

[106] J. L. Crawford, R. E. Marsh, *Acta Crystallogr*. **1973**, *B29*, 1238.

[107] A. Stanger, N. Ashkenazi, A. Shachter, D. Bläser; P. Stellberg, R. Boese, *J. Org. Chem*. **1996**, *61*, 2549.

[108] G. L. Hardgrove, L. K. Templeton, D. H. Templeton *J. Phys. Chem*. **1968**, *72*, 668.

[109] G. A. Deeter, D. Venkatraman, J. W. Kampf, J. S. Moore *Macromolecules* **1994**, *27*, 2647

[110] E. V. Anslyn, D. A. Dougherty *Modern Physical Organic Chemistry*; University Science Books: Sausalito, California, 2006

[111] S. E. Wheeler, K. N. Houk, P. v. R. Schleyer, W. D. Allen, *J. Am. Chem. Soc.* **2009**, *131*, 2547–2560.

[112] S. A. Smith, K. E. Hand, M. L. Love, G. Hill, D. H. Magers, *J. Comput. Chem.* **2013**, *34*, 558-565.

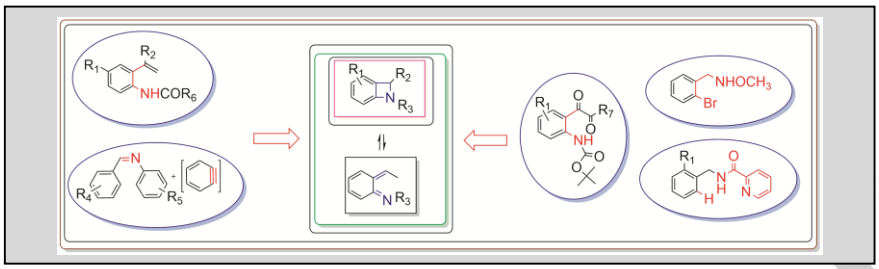
10.1002/chem.201905668

WILEY-VCH

MINIREVIEW

Entry for the Table of Contents

Insert graphic for Table of Contents here. ((Please ensure your graphic is in **one** of following formats))



Benzazetidines, compounds that feature a benzo-fused four-membered azetidine ring, are highly strained *N*-heterocycles. They are interesting for a variety of purposes, including applications in biomedical research, drug design and synthesis of reactive intermediates. In this paper all the synthetic approaches proposed for the synthesis of these compounds, from the early examples to the most recent syntheses, are reviewed and critically discussed.

Institute and/or researcher Twitter usernames: ((optional))