The Elusive 1,4-Diazabutatrienes: Lurking in the Shadows

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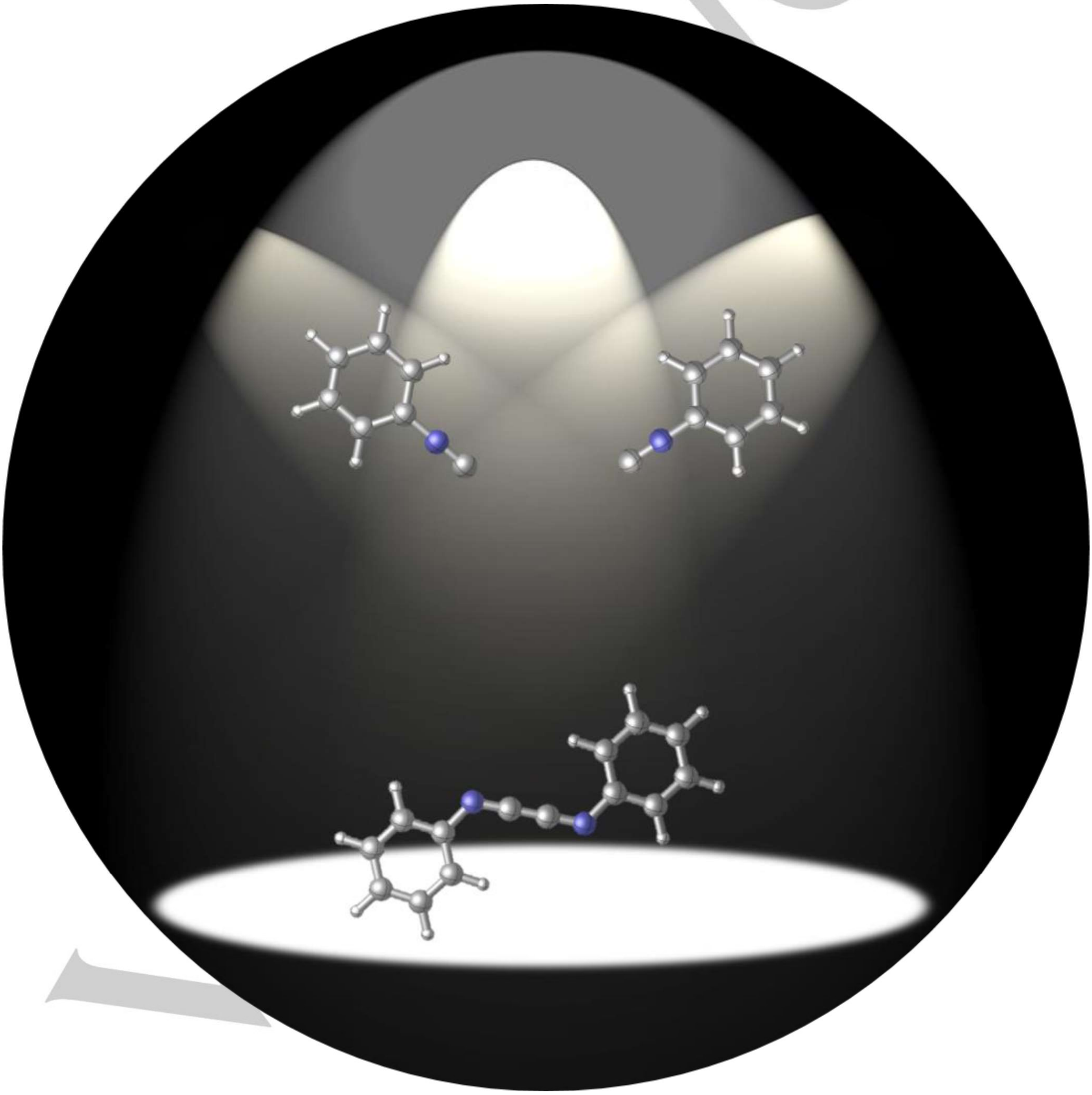
Dedicated to the memory of Professor Angel Vidal



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Abstract: Isocyanides are isomers of cyanides in which its terminal carbon atom can exist in a divalent state. Their ambivalent electronic nature as nucleophile or electrophile and wide reactivity turn the isocyanide scaffold in a valuable synthon for the synthesis of structurally complex molecules, in particular azacycles. Although they are known to polymerize easily, the dimerization of isocyanides affording head-to-head dimers, namely 1,4-diazabutatrienes R^1-N=C=C=N-R^1, has been scarcely explored. Nowadays the experimental isolation of this kind of heterocumulenes is still a challenge. In this minireview, covering a period of sixty years, we highlight the role of 1,4-diazabutatienes as putative reaction intermediates in the homo- and heterodimerization of different types of isocyanides. Added to this, we revise a set of reported reactions in which the formation of a transient 1,4-diazabutatriene intermediate has not been proposed but could be considered as a plausible alternative.

1. Introduction

Carbon monoxide CO and isocyanides R^1-NC (isonitriles) are formally divalent species widely used in coordination and organometallic chemistry and two well-known valuable classes of C1 synthons for the building of a wide range of molecular architectures. Thus, CO is a key cornerstone in important industrial processes for the synthesis of fine chemicals[1,2] whereas isocyanides, as its azo-equivalents with a variable group R^1, play versatile roles in diverse synthetic strategies.[3–5]

For decades the dimerization of carbon monoxide to ethylenedione has been a controversial theme of research and the O=C=C=O putative dimer strongly pursued as a synthetic target. Curiously, for a long time this deceptively simple molecule was misconceived as a “miracle drug” to fight a huge number of health affections. Only recently, ethylenedione could be successfully observed and studied as a short-lived species by photoelectron spectroscopy.[6]

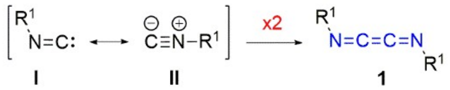
Whereas isocyanides are known to polymerize by the action of organometallic catalysts,[7] its dimerization in a head-to-head manner to structural analogous of ethylenedione, namely the 1,4-diazabutatrienes R^1-N=C=C=N-R^1, has been rarely studied and, to the best of our knowledge, these putative heterocumulenes have been never isolated or unequivocally characterized, although were once postulated as ligands at the coordination sphere of a molybdenum atom.[8]

Isocyanides react through its terminal C atom with nucleophiles, electrophiles and radicals under different reaction conditions affording imine derivatives.[9,10] The rich reactivity of isocyanides is ruled by their particular electronic nature represented by their two resonant forms **I** and **II** (Scheme 1).[11,12] The structure **II** would give a major contribution, as revealed by the characteristic infrared band absorption at ~2000-2100 cm^{-1} due to the N≡C triple bond.[13] Therefore, the dimerization of isocyanides towards 1,4-diazabutatrienes **1** might be formally described as the reaction of two isocyanide molecules having both a double reactive role, as electrophile and nucleophile simultaneously (Scheme 1).

Marta Marin-Luna graduated in Chemistry at the University of Murcia, where she also received her PhD under the supervision of Profs. M. Alajarin and A. Vidal (2014). After a short postdoctoral stay with Profs. I. Alkorta and J. Elguero at the Institute of Medical Chemistry (Madrid) she joined to the group of Profs. C. Silva and O. N. Faza at the University of Vigo. In 2016, she moved to the group of Prof. H. Zipse at the Ludwig-Maximilians-Universität of Munich. In 2019, she returned to the University of Murcia as Assistant Professor at its Organic Chemistry Department.

Mateo Alajarin completed his Ph. D. in 1980 with Prof. P. Molina at the Universidad de Murcia, Spain. After postdoctoral research (1980-1981) with Prof. Alan R. Katritzky at the University of Florida (USA) he returned to the Universidad de Murcia where he is currently Full Professor at its Department of Organic Chemistry. His research interest focuses on the chemistry of heterocumulenes, organophosphorus and supramolecular chemistry as well as on mechanically interlocked molecules.

Likewise, the formation of **1** could be envisaged as the coupling of two carbene-like carbon atoms.



Scheme 1. General reaction for the formation of 1,4-diazabutatrienes **1**

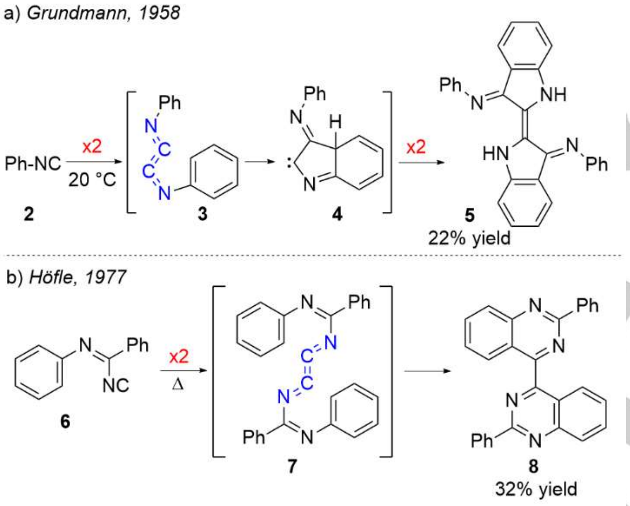
Whereas the formation of the parent 1,4-diazabutatriene, ethenediimine (**1**, R^1 = H) resulting from the dimerization of hydrogen (iso)cyanide, has been widely studied by theoretical methods,[14–19] we have not found works in which *N*-substituted 1,4-diazabutatrienes were thoroughly analyzed. Curiously, in the last decade two publications disclosed the design and study by computational methods of *N,N'*-diaryl-1,4-diazabutatrienes as potentially useful molecular wires.[20,21]

Nevertheless, the 1,4-diazabutatrienes have been also the target of some unsuccesfull synthetic efforts[22] as well cited as elusive intermediates in some processes. As such they show a speculative but rich reactivity, in some way resembling that of ketenimines and allenes which have been both the object of our previous research interest.[23–25] Nevertheless it is worth noting that the literature on 1,4-diazabutatrienes is surprisingly scarce. In this minireview we first present a chronologically ordered summary of the works in which the 1,4-diazabutatriene structure was either pursued or at least considered as a reactive intermediate. Following this we deal with a few other reactions in which these heterocumulenes could be, in our view, reasonably considered as putative intermediates although they were not explicitly proposed as such.

2. 1,4-Diazabutatrienes

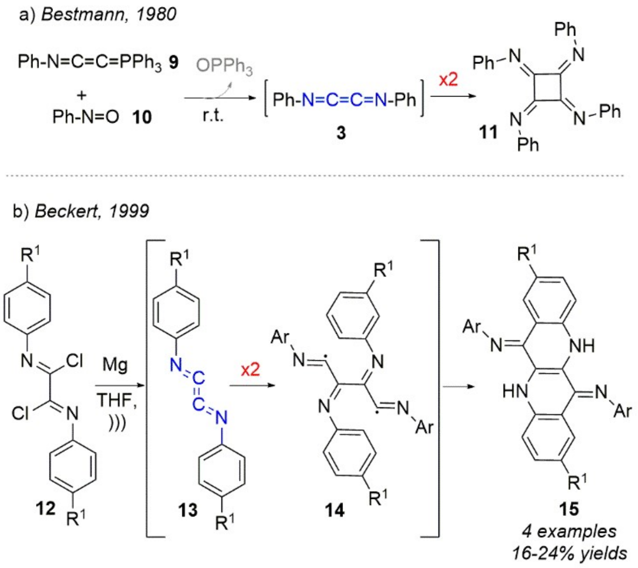
2.1. Second-half of the 20th century

Whereas the chemistry of the isocyanides started in 1859[26] it was one century later when Grundmann, who was most probably the pioneer in this area, proposed for the first time a 1,4-diazabutatriene structure **3** as an intermediate, followed by the formation of the NHC species **4**, to explain the formation of indigo dianil **5** by tetramerization of phenylisocyanide **2** under mild reaction conditions (Scheme 2a).[27]
Later on, in 1977 Höfle and Lange postulated a similar dimer (**7**) of an imidoyl isocyanide **6** for reasoning the obtention of a 4,4'-bisquinazoline **8** (32% yield) as a side-product in the thermal isomerization of the isocyanide to its cyanide partner (Scheme 2b).[28] The isocyanide-cyanide isomerization is a well-known process that usually proceeds at temperatures higher than 200 ºC.[9]



Scheme 2. Proposals of the 1,4-diazabutatrienes **3** and **7** as reaction intermediates (1958-1977)

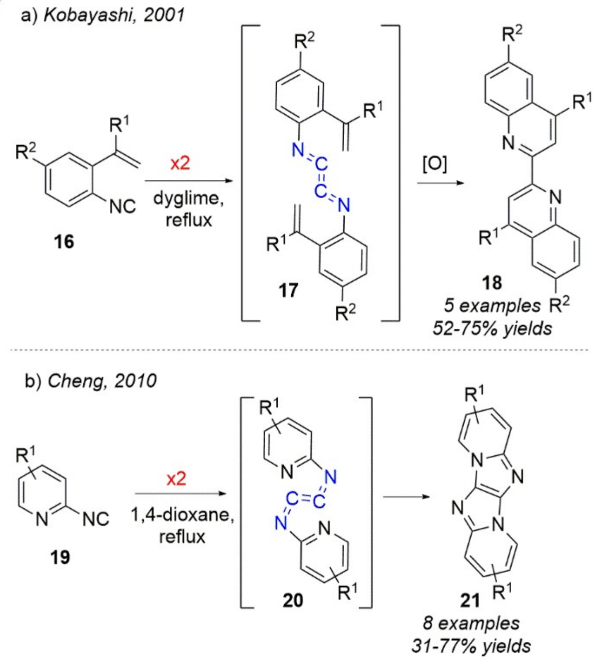
Bestmann in 1980 also considered the phenylisocyanide dimer 1,4-diphenyl-1,4-diazabutatriene **3** as the potential precursor of tetrakis(phenylimino)cyclobutane **11** (Scheme 3a), a tetramer of phenylisocyanide obtained as red-violet crystals in 53% yield by the Wittig-like reaction of (phenyliminovinylidene) triphenylphosphorane **9** with nitrosobenzene **10** at room temperature.[29] The structure of the cyclobutane tetraimine **11** was elucidated by ^{13}C NMR, EI mass and IR spectroscopy and confirmed by X-Ray diffraction.
After almost two decades of absence the 1,4-diazabutatrienes reappeared in the scientific literature in 1999 when Beckert et al. attempted the systematic preparation of several of 1,4-diaryl-1,4-diazabutatrienes **13** by reduction of a range of bisimidoyl chlorides **12** derived from oxalic acid with magnesium under sonication.[30] However, these processes led, presumably by means of the biradical intermediates **14**, to dimeric species as indigo dianils and dibenzo[*b,g*][1,5]naphthyridine-6,12-diimines **15** in low yields (Scheme 3b).



Scheme 3. Proposals of the 1,4-diazabutatrienes **3** and **13** as reaction intermediates (1980-1999)

2.2. First decade of the 21st century

Two reports were published in the first decade of the current century dealing with 1,4-diazabutatrienes. Kobayashi et al. reported in 2001 the conversion of *o*-isocyanostyrenes **16** into its dimeric structures 2,2´-biquinolines **18**, a result interpreted as occurring through the intermediacy of the elusive 1,4-diazabutatrienes **17** and a further oxidative double cyclization (Scheme 4a).[31]



Scheme 4. Proposals of the 1,4-diazabutatrienes **17** and **20** as reaction intermediates (2001-2010)

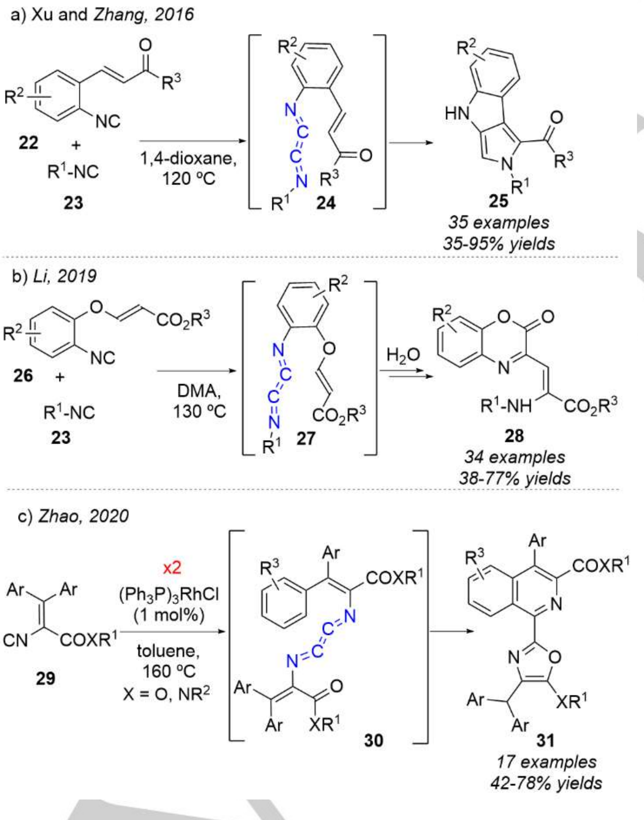
In 2010 Cheng and coworkers found that the heating of 2-pyridylisocyanides **19** in dioxane solution led to the strongly fluorescent, π-extended fused heteroarenes pyrido[2”,1”:2’,3’]imidazo[4’,5’:4,5]imidazo[1,2-*a*]pyridines **21** presumably via the dimeric 1,4-diazabutatrienes **20** (Scheme 4b).[32]

2.3. Latest five years

In the last five years a few more research groups disclosed articles dealing with head-to-head R^1-NC dimers. Thus, Xu and Zhang [33] reported what probably is the first instance of a possible isocyanide heterodimerization between 2-isocyanochalcones **22** and several aryl isocyanides **23** to give an intermediate 1,4-diazabutatriene **24** then experiencing an intramolecular [3+2] cross-cycloaddition leading to the final pyrrolo[3,4-*b*]indoles **25** in good yields (Scheme 5a).

In a related strategy, Li et al. heterodimerized 2-isocyanophenoxy acrylates **26** with alkyl or aryl isocyanides **23** to give the putative nonsymmetric 1,4-diazabutatrienes **27** which further react with water in the reaction medium to give benzoxazinone derivatives **28** (Scheme 5b).[34] This protocol was effective for the synthesis of 34 examples in moderate yields.

Finally, this year Zhao et al. reported[35] what they interpreted as the Rh-catalyzed homodimerization of some vinylisocyanates **29** and further heterocyclization of the postulated heterocumulenic key intermediates **30** to yield 2-(1-isoquinolyl)oxazoles **31** (Scheme 5c).

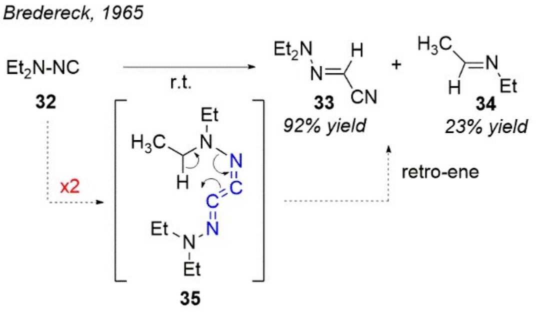


Scheme 5. Proposals of the 1,4-diazabutatrienes **24, 27** and **30** as reaction intermediates (2016-2020)

2.4. Alternative mechanisms involving 1,4-diazabutatrienes

The brief summary of articles where a speculative 1,4-diazabutatriene structure has been depicted as reaction intermediate ends here. However, by a cautious browsing of the old and new chemical literature dealing with isocyanides, we have found a few more reports that, although not mechanistically interpreted as occurring through this type of elusive intermediates, could, in our opinion, at least rise the suspect of involving R^1-N=C=C=N-R^1 species at some stage of its reaction stages. A key structural hint for detecting such reports is obviously the substructural fragments -N-C-C-N- in the reaction products as far as resulting from connecting two isocyanide units, equals or not, by its terminal carbon atoms.

In 1965 Brederek et al.[36] disclosed the conversion at room temperature of *N*-isocyanodiethylamine **32** into the *N,N*-diethylhydrazone **33** of the nitrile derived from glyoxylic acid and the *N*-ethylimine of acetaldehyde **34** in lower yield, a process that could be interpreted as resulting from a fragmentation of the isocyanide dimer **35** by a peculiar type of retro-ene reaction as indicated in the Scheme 6. Originally, the authors proposed that the decomposition of the *N*-isocyanide amine would proceed via a synchronous fragmentation involving two separated isocyanide molecules.

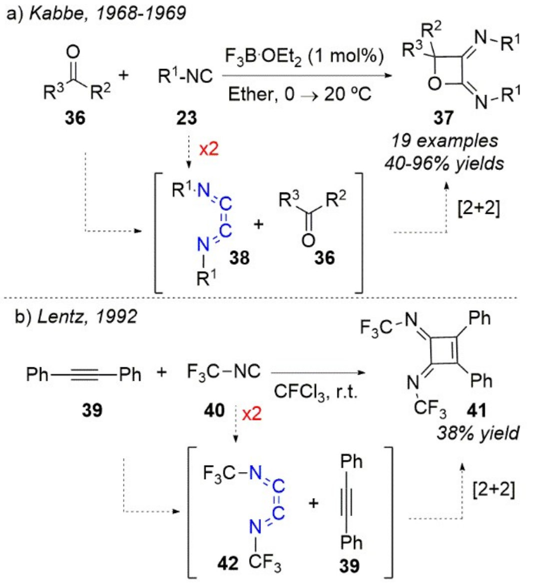


Scheme 6. Alternative mechanistic proposal involving the 1,4-diazabutatriene **35**

As structurally related heterocumulenes,[37–39] the 1,4-diazabutatrienes might participate in cycloaddition reactions as 2π-component. Thus, the second example of such reports is the old reaction[40,41] of isocyanides **23** with aldehydes or ketones **36** yielding, under boron trifluoride catalysis, the corresponding 2,3-bis(alkylamino)oxetanes **33** (Scheme 7a). These reaction products could well be the result of a [2+2] cycloaddition between the C=O bond of the carbonyl counterpart **37** and the central C=C bond of an eventual homodimeric 1,4-diazabutatriene **38**.

In close similarity, the reported reaction[42] of tolane **39** with trifluoromethylisocyanide **40** yielding 1,2-diphenyl-3,4-bis(trifluoromethylimino)cyclobutene **41** (38% yield), which was fully characterized by X-Ray diffraction, could be also interpreted as the result of a [2+2] cycloaddition between the acetylenic triple bond and the C=C bond of a transient isocyanide dimer **42** (Scheme 7b). A precise mechanistic proposal is absent in that report.

Recently, palladium(II) complexes were reported as effective catalysts in the polymerization of isocyanides.[43] Therefore it looks probable this metal could mediate the formation of



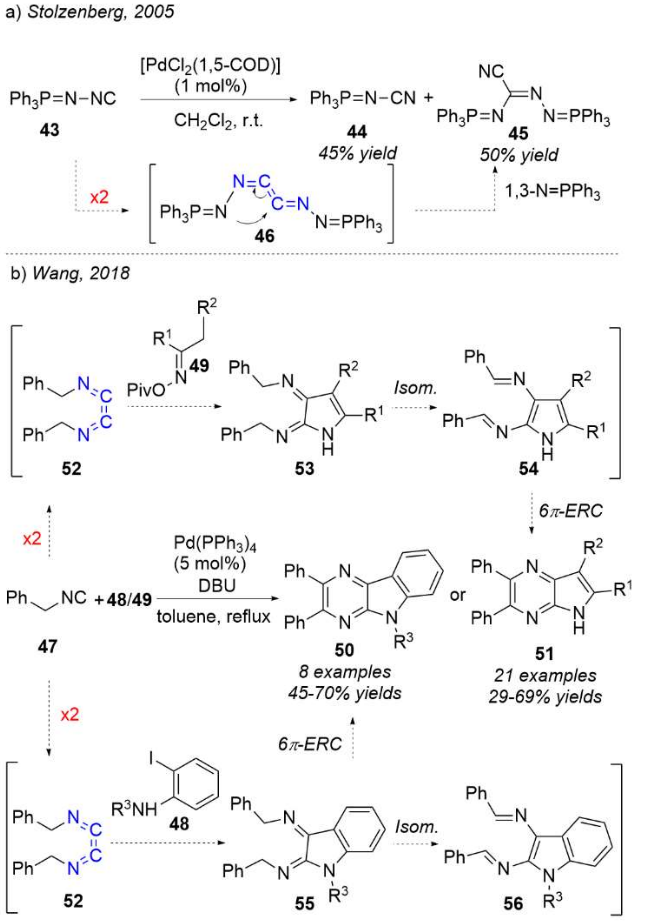
Scheme 7. Alternative mechanistic proposals involving the 1,4-diazabutatrienes **38** and **42**

1,4-diazabutatrienes and this seems to be the case. Thus, in the Pd(II)-catalyzed conversion of $Ph_3P=N-NC$ **43** into its isomeric nitrile **44**[44] a secondary product was identified as the dimeric bisphosphazene **45** that could result from the initial formation of the homodimeric 1,4-diazabutatriene **46** and further N to C migration of a $Ph_3P=N$ group (Scheme 8a). The reported BF_3-catalyzed dimerization of *tert*-butylisocyanide to the *tert*-butylimine of pivaloyl cyanide could be interpreted in a similar way.[45]

Finally, in the synthesis of fused 5,6-diphenylpyrazines **50** and **51** by Pd(0)-mediated reaction of benzylisocyanides **47** with either 2-iodoanilines **48** or *O*-protected oximes **49** in basic medium recently reported by Wang et al. (Scheme 8b), [46] the reaction products show a N-C-C-N substructural fragment. This moiety could potentially result of the transient formation of an isocyanide homodimer **52**, probably catalyzed by palladium. This interpretation would be an alternative to the original, and of course also reasonable, proposal of two successive isonitrile insertions occurring in the coordination sphere of the metal.[47] Further isomerization between intermediates **53/54** and **55/56** and a final 6π-electrocyclic ring closure with a subsequent oxidation step would thus afford the pyrazine derivatives **50** and **51**.

3. Conclusions and Outlook

In this minireview, we have revised the role of 1,4-diazabutatrienes, resulting from the homo- and heterodimerization of isocyanides, as transient reaction intermediates. As shown, putative 1,4-diazabutatrienes have been proposed as taking part in dimerizations, [2 + 2] and [3 + 2] cycloadditions, and electrocyclization processes. A few mechanisms involving plausible 1,4-diazabutatrienes are here proposed as an alternative way to explain the formation of some species containing N-C-C-N fragments in their structures and coming from the coupling of two isocyanide molecules. We humbly believe that 1,4-diazabutatrienes, although poorly regarded during a long time perhaps due to its challenging preparation and isolation, are a type of species that all researchers involved in isocyanide chemistry should bear in mind. This is probably of some relevance in the present times in which the investigations on isocyanide chemistry are experiencing an apparent renaissance. We hope this report could also encourage the chemical community to turn the view towards these peculiar, elusive and not sufficiently understood heterocumulenes.



Scheme 8. Alternative mechanistic proposals involving the 1,4-diazabutatriene **46** and *N,N'*-dibenzyl-1,4-diazabutatriene **52**

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Keywords: 1,4-diazabutatriene • dimerization • isocyanides • reaction mechanism

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