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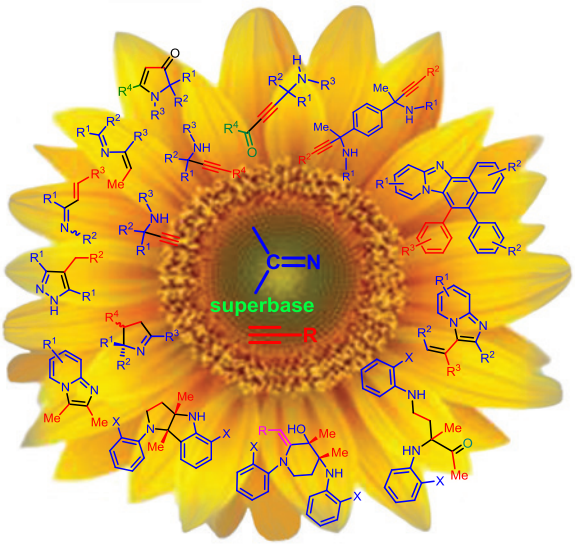
Reaction of acetylenic carbanions with C=N bond: dynamics of development, synthetic divergence, environmental safety

Elena Yu. Schmidt, Boris A. Trofimov*

A.E.Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 664033 Irkutsk, Russia

This review highlights the dynamics of the development and synthetic application of the recently discovered reaction of acetylenic carbanions, generated in superbase media, with the C=N bond of different classes of substrates. A fundamental feature of this reaction is its synthetic divergence, *i.e.* its ability to proceed in different directions, which manifests itself in novel transformations to selectively deliver structurally different synthetically important products (depending on the structure of the acetylenes and substrates with C=N bond). The review also discusses cascade processes, in which the key intermediates containing the C=N bond add acetylenes thereby participating in the self-organization of diverse and potentially useful compounds. The competitive advantage of the reaction and its daughter branches is environmental safety (neutrality), based on the fundamental chemical nature of these reactions as addition processes that occur without the release of by-products.
The bibliography includes 133 references.
Keywords: acetylenes; imines; amines, propargylamines, superbases.



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1. Introduction

Nowadays, the application of acetylene, its substituted analogues and functional derivatives as building blocks for the design of complex molecular architectures is one of the focal points of organic, medicinal chemistry and materials science, as evidenced by the ever-growing number of original research papers and reviews.[1–13] Such situation is predetermined by the industrial availability of acetylene,[14,15] its prospects to be renewable raw material (production from charcoal and lignocelluloses),[16–18] as well as high and multifaceted reactivity of the triple bond. The competitive advantage of acetylenes as an efficient and environmentally benign source of basic organic chemicals is that their reactions are mainly the addition processes, which exclude the release of any hazardous by-products, *i.e.*, such reactions are safe (neutral) for nature and humans. In addition, most reactions involving acetylenes are exothermic, *i.e.*, energy-saving. Another unique feature of acetylenes is the dichotomy of their chemical properties: they can react simultaneously (or sequentially) as nucleophiles and electrophiles that enables the self-organization of several acetylene molecules into complex ordered structures incorporating other small molecules.

The role of acetylenes in the organic synthesis is difficult to overestimate. The addition of acetylenic carbanions to the C=O bond alone, which usually occurs in the presence of bases (Favorsky reaction),[19,20] is a special direction in industrial and fine organic synthesis. A breakthrough in the development of this reaction occurred, when superbase media began to be systematically used to promote it.[21–23] In the presence of superbases, aldehydes and ketones add acetylene much more actively than under traditional conditions: various acetylenic

E.Yu.Schmidt. Doctor of Chemical Sciences, Chief Researcher at the A.E.Favorsky Irkutsk Institute of Chemistry.
E-mail: LSCHMIDT@irioch.irk.ru
Current research interests: nucleophilic reactions of acetylenes involving superbases as reactants and catalysts, heterocyclic chemistry.
B.A.Trofimov. Full Member of the Russian Academy of Sciences, Professor and Head of Research at the A.E.Favorsky Irkutsk Institute of Chemistry.
E-mail: boris_trofimov@irioch.irk.ru
Current research interests: organic synthesis based on acetylene and its derivatives, the chemistry of heterocyclic compounds, superbasic catalysis.

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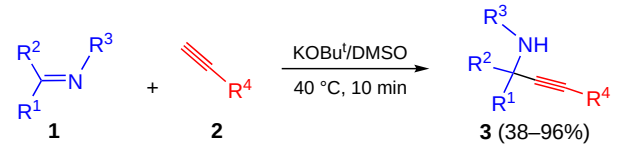
alcohols can be synthesized in high yields without pressure, cooling and large amounts of solvents (mandatory conditions of the classical ethynylation).

At the same time, despite the known examples of acetylene addition to imines promoted by salts and complexes of transition metals,[24–26] the addition of acetylenic carbanions, generated from terminal acetylenes in strongly base media (superbase media), to the C=N bond remained for a long time a *Terra incognita* of organic chemistry. At the first glance, a hurdle is that the attack of the weakly electrophilic C=N bond by the acetylenic carbanion is kinetically unfavorable. It has since been shown that this hurdle can be overcome by carrying out the reaction in superbase media, of which the simple, cheap and easy to use are systems such as KOBu^t/DMSO ($pK_a \sim 30–35$).[27,28] Indeed, in such a medium, the addition of acetylenes to the C=N bond is not only possible, but easily realizable.

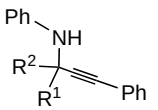
2. Reaction of acetylenic carbanions with *N*-arylimines

It was found that aryl- and hetarylacetylenes react with *N*-aryl(hetaryl)ketimines in the presence of the KOBu^t/DMSO system (40 °C, 10 min), providing a one-pot synthesis of propargylamines (Scheme 1).[29] The reaction involves the addition of acetylenic carbanions to the C=N bond. This is a first example of the nitrogen analog of the Favorsky reaction.

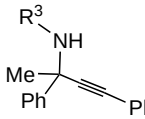
Scheme 1



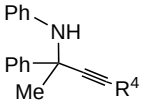
Selected examples



3a: $R^1 = R^2$ = Me (96%);
3b: $R^1–R^2 = (CH_2)_4$ (80%);
3c: $R^1 = R^2$ = Ph (76%);
3d: R^1 = 4-PhC_6H_4, R^2 = Me (78%);
3e: R^1 = 4-FC_6H_4, R^2 = Me (77%)



3f: R^3 = Ph (70%);
3g: R^3 = 2-MeC_6H_4 (66%);
3h: R^3 = 4-BrC_6H_4 (53%)
3i: R^3 = 3-Py (64%)



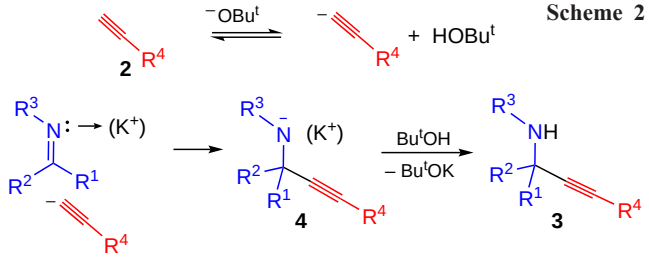
3j: R^4 = 4-MeC_6H_4 (79%);
3k: R^4 = 4-FC_6H_4 (83%);
3l: R^4 = 3-FC_6H_4 (62%)
3m: R^4 = 3-Th (84%);
3n: R^4 = 3-Py (76%)

Py is pyridyl, Th is thienyl

The reaction is efficient for *N*-aryl(hetaryl) ketimines **1** and a large series of aryl- and hetarylacetylenes **2** giving 38–96% yields of internal propargylamines. Evidently, this reaction is made possible, because in the superbase media, the concentration of acetylenic carbanions is increased with simultaneous enhancment of their nucleophilicity (due to desolvation). Also, electrophilicity of the C=N bond is strengthened due to the coordination of the potassium cation with the electron lone pair of the nitrogen atom (electrophilic assistance). Acetylene is also activated by coordination with the potassium cation (Tedeschi complexes)[30] and by complexation with dimethylsulfoxide (crystalline complexes of acetylene with DMSO are known).[31]

Generally, for the whole reaction, the integral substituent effect is consistent with the mechanism of the process, which

Scheme 2



represents a nucleophilic addition to the polarized C=N bond (Scheme 2).

Indeed, the formation of the tetrasubstituted carbon center (intermediate **4**), resulting from the initial nucleophilic attack of the acetylenic carbanion at C(sp^2) atom, should be sterically hindered, while the acceptor substituents, both in ketimine and acetylene, should facilitate the process, in particular by increasing the concentration of the acetylide anions and by distributing the negative charge appearing on the nitrogen atom in intermediate **4** over the adjacent aromatic (heteroaromatic) system (*aza*-analogue of benzyl anions).

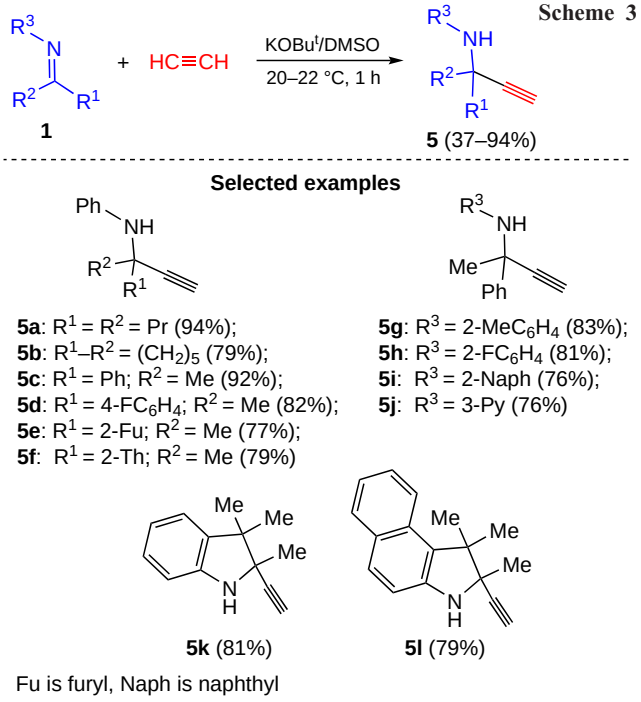
The reaction is thus general for various acetylenes and ketimines and opens a straightforward access to a large number of propargylamines, which find application as privileged molecules[32–35] due to their synthetic[36,37] and pharmaceutical[38–42] importance. The first syntheses of these compounds by catalyst-free (K.Mannich)[43] or copper-catalyzed (W.Reppe)[44,45] aminoalkylation of acetylenes were complemented in 2001 by the iridium-catalyzed three-component reaction between primary amines, aldehydes and acetylenes.[46,47] This approach (A^3 coupling) is currently being implemented in the presence of various transition metal catalysts.[48–52] The key step of A^3 coupling is shown[29,53,54] to be the nucleophilic substitution of the hydroxyl group in intermediate α-hydroxyalkyl amines by π/σ-metal acetylene complexes. At the same time, the similar reactions with ketones (especially with aromatic ketones), amines and acetylenes (KA^2 coupling) and thus the synthesis of the corresponding propargylamines with a quaternary carbon atom, remain undeveloped due to the lower reactivity of ketones in this process.[48,53,55–59] The above reaction between C=N bond and acetylenic carbanions now fills this gap.

The parent and most fundamental member of acetylenes, unsubstituted acetylene, has been out of the reaction scope for some time. Meanwhile acetylene now occupies a specific place among alkynes due to its double C–H acidic functionalities, higher and multifaceted reactivity, and much grater availability (industrial production). In this respect, the superbase-promoted reaction of acetylene gas with C=N bond to give terminal propargylamines is of paramount importance, particularly, because the latter are much more reactive[60–63] compared to their internal congeners.

It turns out that ethynyde-anions, generated from acetylene gas, add to the C=N bond of ketimines even more easily than acetylenic carbanions generated from aromatic and heteroaromatic alkynes: the reaction proceeds in the KOBu^t/DMSO system at room temperature under slightly excess acetylene pressure (~2 atm), providing terminal propargylamines **5** in up to 94% yield (Scheme 3).[64]

The synthesis covers various ketimines having aromatic and heteroaromatic substituents both in ketone and amine counterparts. Under atmospheric pressure, the ethynylation of ketimines with acetylene gas proceeds with almost the same efficiency. A facile ethynylation of indoles **1k**,**l** shows that the

Scheme 3



Fu is furyl, Naph is naphthyl

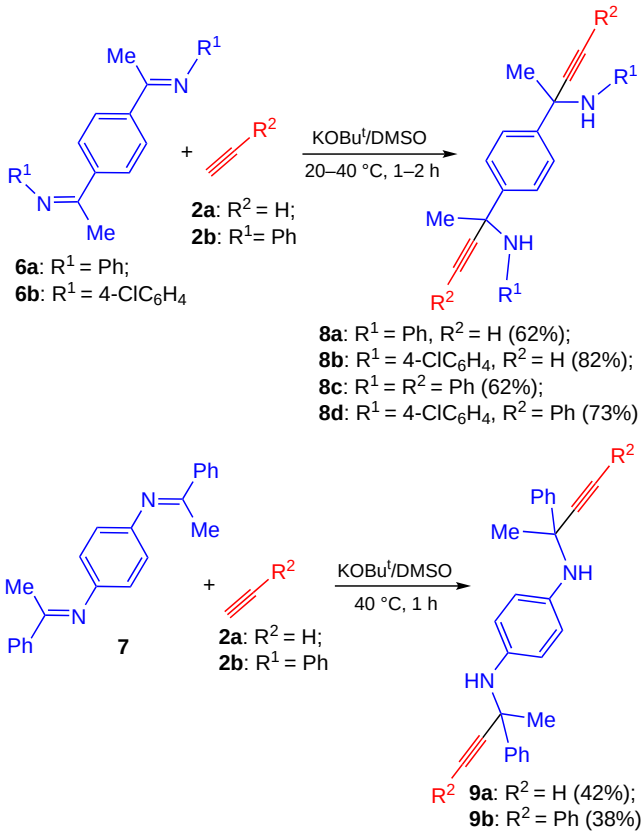
terminal acetylenic substituent can be directly introduced into nitrogen heterocycles.

The reaction is remarkably chemoselective: the expected products of the double ethynylation, 1,4-diaminobutynes, are not observed. This is due to a lower CH acidity and steric screening of the acetylene substituent at the quaternary carbon atom. It is noteworthy that the oxygen analogue of this synthesis (Favorsky reaction)[19] is commonly accompanied by the formation of acetylenic diols along with major products (acetylenic alcohols).

As a further development of the ethynylation of C=N bond-containing compounds, the KOBu^t/DMSO-promoted addition of acetylenes to structurally analogous C- and N-linked 1,4-bis(imino)benzenes **6**, **7** was studied.[65] The reaction proceeded under mild conditions (room temperature or slight heating) to produce double ethynylation products **8**, **9** (Scheme 4), attractive precursors for the preparation of novel functional materials.[66,67]

The above new families of propargylamines, particularly those with terminal acetylenic moiety, are now becoming rewarding objects for organic synthesis. So, Pd/Cu-catalyzed cross-coupling of propargylamines **5** with aromatic acyl chlorides providing α-(het)arylaminoacetylenic ketones **10**

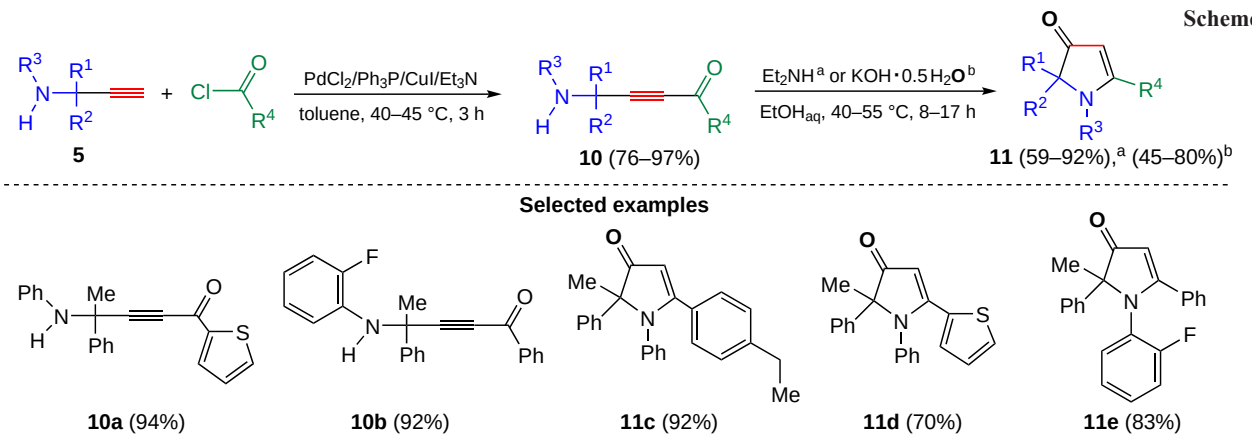
Scheme 4



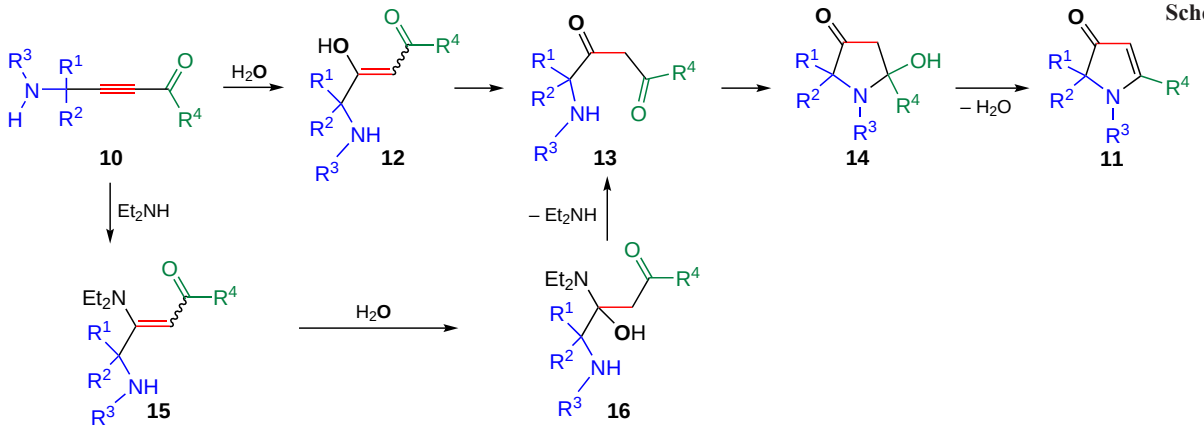
was realized.[68] After the treatment with bases (KOH or Et_2NH), these ketones undergo intramolecular cyclization to pharmaceutically promising[69–72] 1,2,5-tri(het)aryl-1,2-dihydro-3*H*-pyrrol-3-ones **11** (Scheme 5).[68] The substrate scope of this atom-economy approach allowed the simultaneous introduction of various aromatic, condensed aromatic and heteroaromatic substituents in 1, 2 and 5 positions of the pyrrolone scaffold.

The key step of the cyclization (Scheme 6) is the addition of a water molecule (in case of KOH · 0.5 H_2O catalysis) giving enols **12**, which rearrange to 1,3-diketones **13**. The latter undergo the ring closure by the attack of NH moiety at the carbonyl group to afford intermediates **14**, which, after elimination of a water molecule, produce pyrrolones **11**. In the case of Et_2NH catalysis, the first step of the cyclization is the addition of Et_2NH to the triple bond to form intermediate enamines **15**, which add a water molecule giving hemiaminals **16**. The latter, after release

Scheme 5



Scheme 6

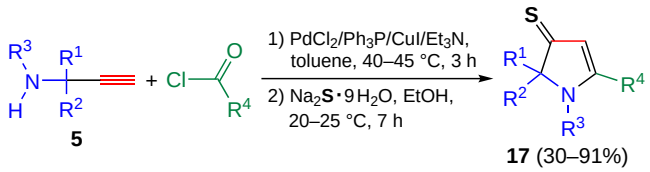


of Et_2NH, lead to the same 1,3-diketones **13**, which are transformed to pyrrolones **11**.

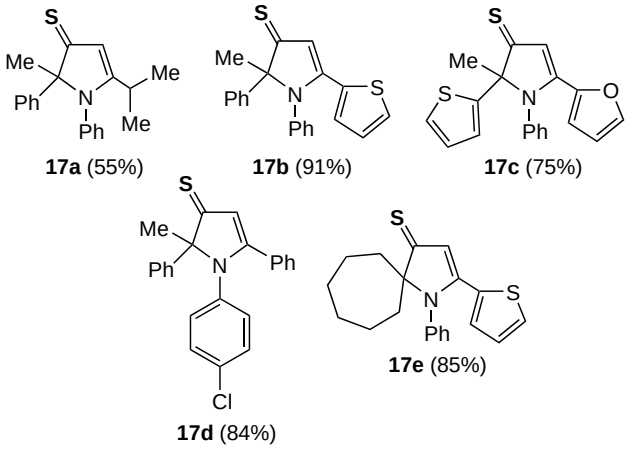
The synthesis of 3*H*-pyrrolones **11** can be implemented in a one-pot version by consecutive treatment of propargylamines **5** with acyl chlorides and bases.[68]

The efficient one-pot synthesis of 1,2,5-trisubstituted-1,2-dihydro-3*H*-pyrrole-3-thiones **17**, essentially new heterocyclic systems, by the successive treatment of propargylamines **5** with acyl chlorides and sodium sulfide has been developed (Scheme 7).[73] The synthesis comprises the addition of hydrosulfide-anions to the aminoacetylenic ketones **10** formed, followed by dehydrative cyclization of the prototropically rearranged adducts.[73]

Scheme 7

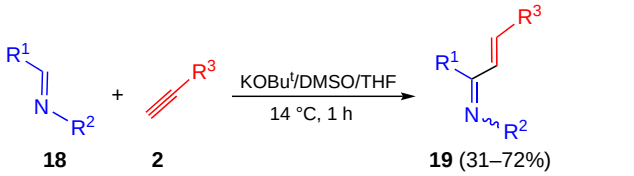


Selected examples



A fundamental feature of the reaction of acetylenic carbanions with the C=N bond is its substrate-driven divergence: each new class of the starting C=N bond-containing compounds gives structurally different products. For example, aldimines **18** react with acetylenes **2** in the superbase triad KOBu^t/DMSO/THF under mild conditions (14 °C) to afford 1-azadienes **19** of the *E* configuration relative to the C=C bond (Scheme 8).[74] The reaction has been successfully extended to aryl(hetaryl)-acetylenes and aldimines derived from aryl(hetaryl)substituted aldehydes and aryl(hetaryl)amines, providing a straightforward

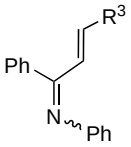
Scheme 8



Selected examples

19a: R^1 = Ph (72%);
19b: R^1 = 4-$MeOC_6H_4$ (70%);
19c: R^1 = 4-FC_6H_4 (61%);
19d: R^1 = 2-Fu (56%);
19e: R^1 = 2-Th (58%)

19f: R^2 = 2-MeC_6H_4 (59%);
19g: R^2 = 3-$MeOC_6H_4$ (58%);
19h: R^2 = 2-FC_6H_4 (64%);
19i: R^2 = 2-BrC_6H_4 (33%);
19j: R^2 = 2-Naph (43%)



19k: R^3 = 3-MeC_6H_4 (64%);
19l: R^3 = 4-PhC_6H_4 (43%);
19m: R^3 = 4-$MeOC_6H_4$ (63%);
19n: R^3 = 3-FC_6H_4 (60%);
19o: R^3 = 3-Th (52%)

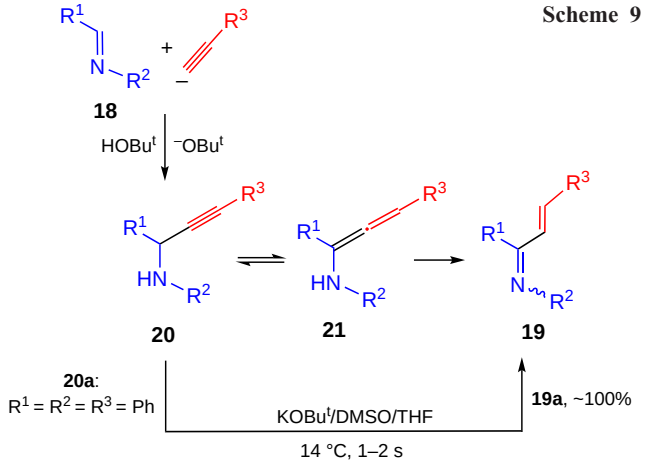
atom- and energy-economic access to 1-azadienes, versatile building blocks in organic chemistry[75–77] and privileged intermediates in the total syntheses of natural molecules.[78–81]

Apparently, the reaction starts with the addition of acetylenic carbanions to the C=N bond of aldimines **18** (Scheme 9). The propargylamines **20** thus formed undergo further prototropic isomerization to 1-azadienes **19** *via* allenic intermediates **21**. The fast double prototropic isomerization at low temperature (14 °C) has been proven experimentally: the specially synthesized intermediate propargylamine **20a**[82] is immediately and quantitatively transformed to 1-azadiene **19a** under the reaction conditions (see Scheme 9).

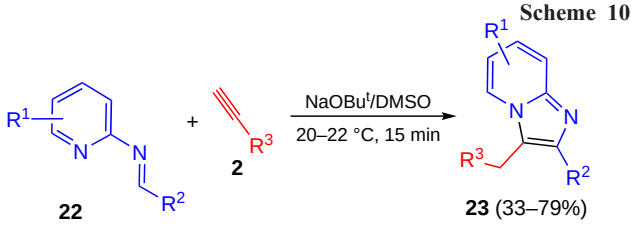
The result of the reaction of 2-iminopyridines **22** (another group of C=N bond-containing substrates) with aryl(hetaryl)-acetylenes **2** turned out to be unexpected: in the NaOBu^t/DMSO system at room temperature, the formation of benzyl imidazo[1,2-*a*]pyridines **23** was observed (Scheme 10).[83]

Even more unexpected was the result of the interaction of acetylenes **2** with a 2-fold excess of 2-iminopyridines **22**: under similar conditions, stilbene imidazo[1,2-*a*]pyridines **24** were stereoselectively assembled from two molecules of 2-iminopyridine **22** and one molecule of acetylene **2** (Scheme 11).[83]

Scheme 9



Scheme 10



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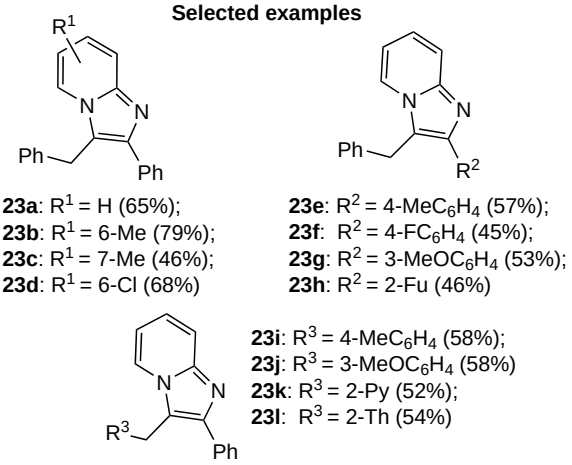


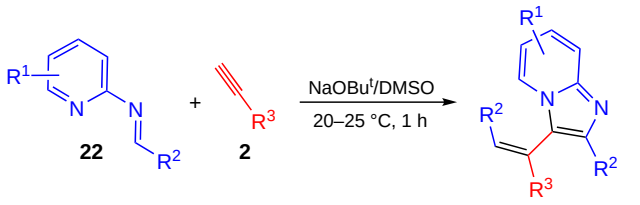
23a: R^1 = H (65%);
23b: R^1 = 6-Me (79%);
23c: R^1 = 7-Me (46%);
23d: R^1 = 6-Cl (68%)

23e: R^2 = 4-MeC$_6$H$_4$ (57%);
23f: R^2 = 4-FC$_6$H$_4$ (45%);
23g: R^2 = 3-MeOC$_6$H$_4$ (53%);
23h: R^2 = 2-Fu (46%)

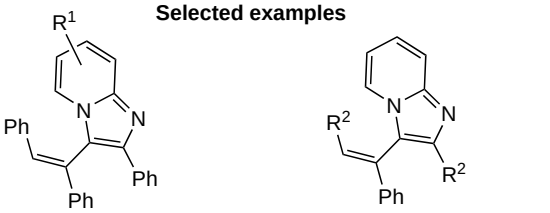
23i: R^3 = 4-MeC$_6$H$_4$ (58%);
23j: R^3 = 3-MeOC$_6$H$_4$ (58%)
23k: R^3 = 2-Py (52%);
23l: R^3 = 2-Th (54%)

These results can be understood as the addition of acetylenic carbanions to the C=N bond of imines **22** and further evolution of the intermediate propargyl-1,3-diaza-1,3,5-trienyl anions **25** involving their intramolecular cyclization to anions **26**, which are intercepted by a proton of the medium to give benzyl

Scheme 11

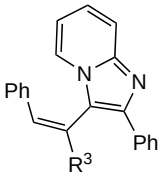


Selected examples



24a: R^1 = H (61%);
24b: R^1 = 6-Me (50%);
24c: R^1 = 7-Me (58%);
24d: R^1 = 6-Cl (71%)

24e: R^2 = 4-FC$_6$H$_4$ (76%);
24f: R^2 = 3-MeOC$_6$H$_4$ (51%);
24g: R^2 = 2-Fu (70%);

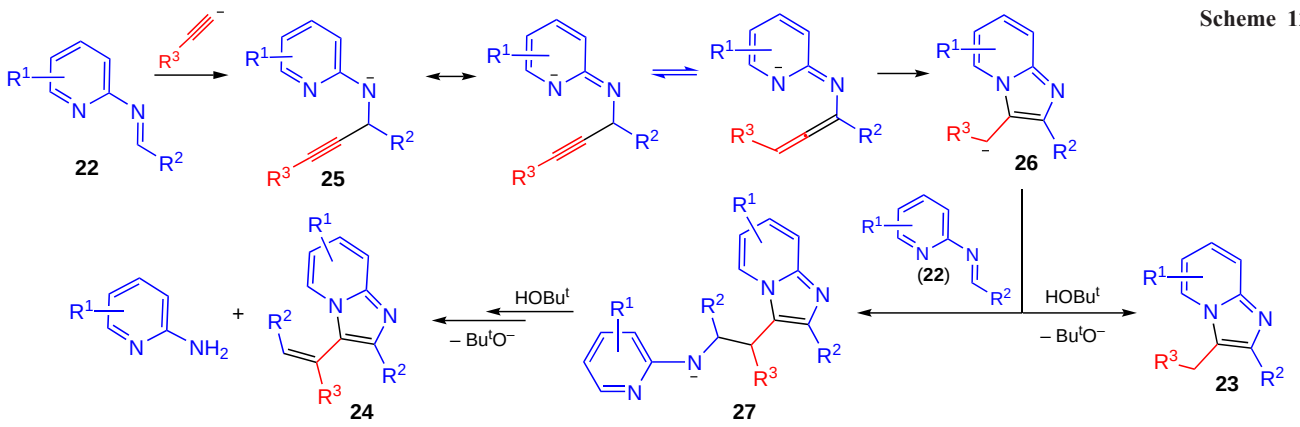


24h: R^3 = 4-PhC$_6$H$_4$ (89%);
24i: R^3 = 3-MeOC$_6$H$_4$ (64%);
24j: R^3 = 3-FC$_6$H$_4$ (80%);
24k: R^3 = 3-Py (71%)

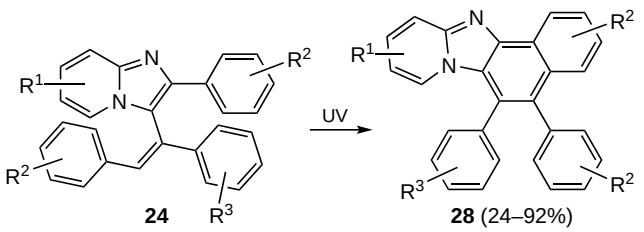
imidazopyridines **23** or by a second molecule of imine **22** followed by elimination of 2-aminopyridine from adducts **27** to give stilbene imidazopyridines **24** (Scheme 12).[83]

This cascade process (see Scheme 12) is characterized by the following features: 1) addition of acetylenic carbanions to the C=N bond with the long-range distribution of the negative charge appearing at the imine nitrogen atom over the whole pyridine ring of anionic intermediates **25**; 2) easy (room temperature) and fast (15 min) intramolecular nucleophilic addition of the pyridine nitrogen atom to the propargyl (allenyl)moiety of anions **25**; 3) extremely facile addition of benzylic carbanions **26** to the C=N bond of imines **22** followed by stereoselective elimination of the 2-aminopyridine molecule. Generally, this reaction provides a simple route to products incorporating the stilbene,[84–86] pyridine,[87–89] and imidazole[90–92] structural units, which are the focus of current medicinal research and materials science. Indeed, these compounds became the objects of photochemical researches. It was found that stilbene imidazo[1,2-*a*]pyridines **24** undergo selective oxidative cyclization upon UV irradiation (λ = 365 nm) to

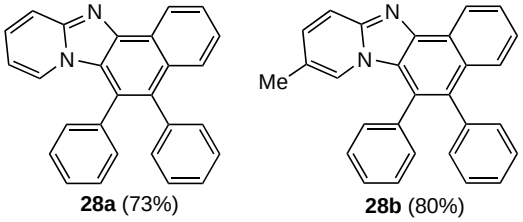
Scheme 12

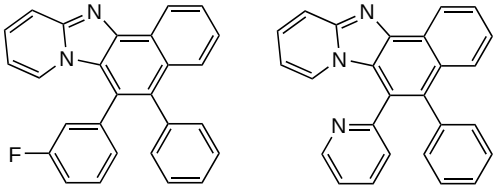


Scheme 13



Selected examples



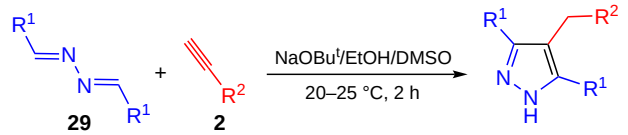


5,6-diarylnaphtho[1′,2′:4,5]imidazo[1,2-*a*]pyridines **28**, which fluoresce intensely in the blue region (λ_{em} = 417–441 nm) with quantum yields of 0.20–0.60 (Scheme 13).[93]

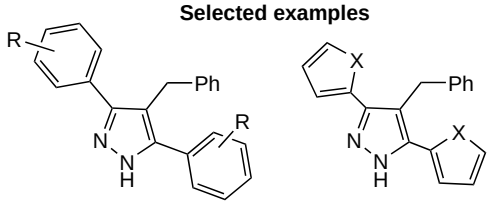
As a logical development of the acetylenic carbanion/C=N bond interaction, it was shown that aromatic aldazines **29**, the substrates containing two conjugated C=N bonds (2,3-diaza-1,3-dienes), readily react with arylacetylenes **2** in the NaOBu^t/EtOH/DMSO superbase triad at room temperature to give 4-arylmethyl-3,5-diaryl-1*H*-pyrazoles **30** (Scheme 14).[94]

The reaction was rationalized[94] as proceeding via the diazaallyl anions **31**, the adducts of acetylenic carbanions to the

Scheme 14

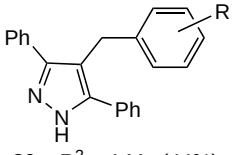


Selected examples

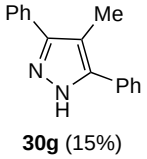


30a: R = H (47%);
30b: R = 4-Me (43%)

30c: X = O (34%);
30d: X =S (15%)

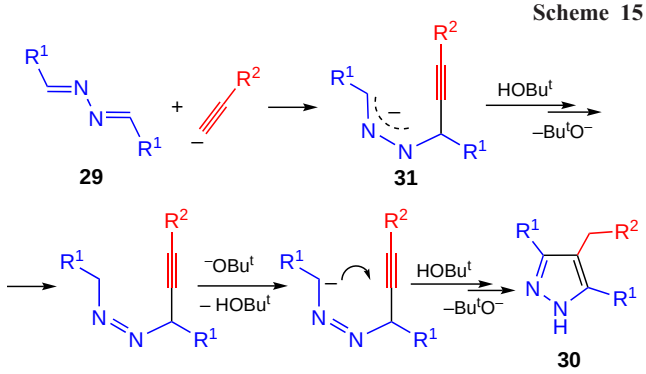


30e: R^2 = 4-Me (44%);
30f: R^2 = 3-F (38%)



30g (15%)

Scheme 15

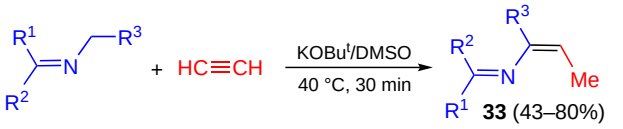


C=N bond, which further undergo the proton transfer processes and intramolecular cyclization to pyrazoles **30** (Scheme 15).

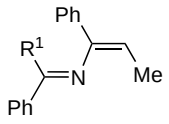
3. Reaction of acetylenic carbanions with *N*-benzylimines

The reaction of *N*-benzylketimines **32** with acetylene gas in the KOBu^t/DMSO system proceeded in a quite unexpected direction (another appearance of the synthetic divergence): instead of the formation of the corresponding propargylamines, the stereoselective assembly of 2-azadienes **33** was observed (Scheme 16).[95]

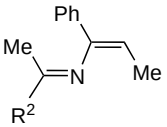
Scheme 16



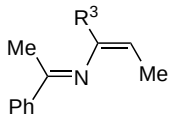
Selected examples



33a: R^1 = Me (71%);
33b: R^1 = Et (62%);
33c: R^1 = Pr^n (79%);
33d: R^1 = Ph (67%)



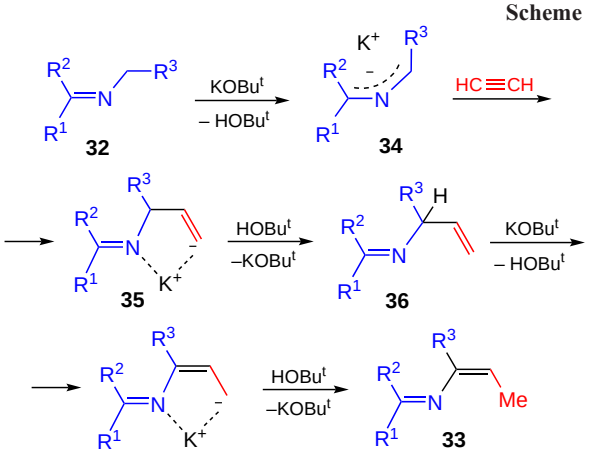
33e: R^2 = 4-MeC$_6$H$_4$ (65%);
33f: R^2 = 4-FC$_6$H$_4$ (80%);
33g: R^2 = 2-Naph (69%);
33h: R^2 = 2-Fu (67%)



33i: R^3 = 4-MeOC$_6$H$_4$ (48%);
33j: R^3 = 4-FC$_6$H$_4$ (51%);
33k: R^3 = 2-Fu (61%);
33l: R^3 = 3-Py (53%)

This is due to the higher acidity of the *N*-benzylketimines (pK_a ~ 24)[96,97] compared to acetylene (pK_a 29.7).[98] Consequently, the key step of this reaction is the addition of the deprotonated *N*-benzylketimines (azaallyl anions **34**) to acetylenic triple bond (Scheme 17). The electron density delocalization in anions **34** is extended over the adjacent aromatic (heteroaromatic) substituent that additionally stabilizes these anionic species and increases their concentration in the reaction mixture. The stereoselectivity of the reaction is likely originated from the chelation of the potassium cation with both sites of the azaallyl anions **34**. After the insertion of the acetylene molecule between the carbanionic center and the potassium cation and neutralization of the vinyl carbanions **35**, the intermediate nonconjugated azadienes **36** are formed. The latter are prototropically isomerized, still being retained in the coordination sphere of the potassium cation that ensures the *Z*

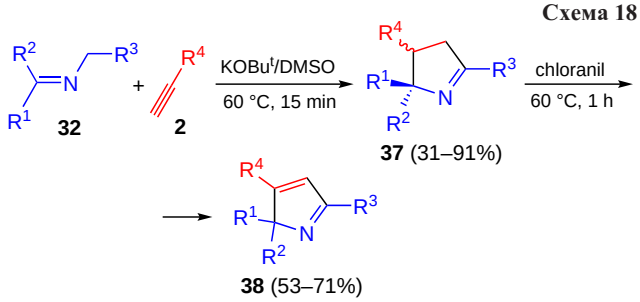
Scheme 17



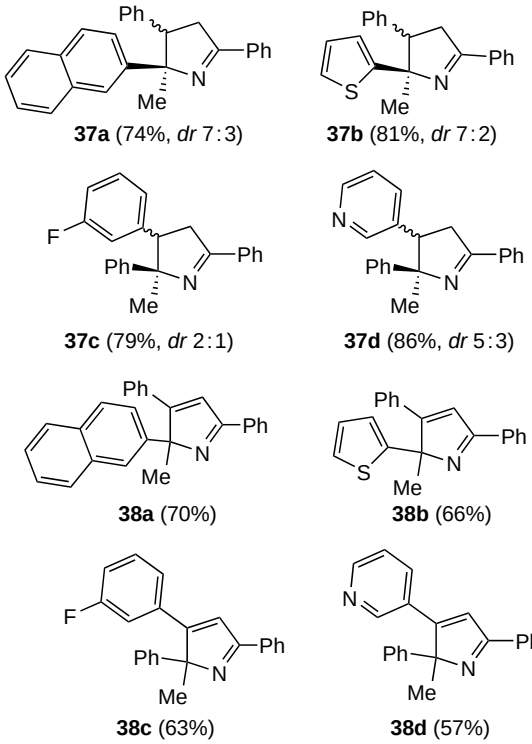
orientation of the forming Me group to give conjugated 2-aza-1,3-dienes **33**.

Another direction of the acetylene/C=N bond interaction in strongly base media is the formal [3+2] cycloaddition of *N*-benzylketimines **32** to aryl(hetaryl)acetylenes **2** to afford polyarylated 1-pyrrolines **37**, which are *in situ* oxidized to 2,3,5-tri(het)aryl-2*H*-pyrroles **38** (Scheme 18),[99] promising objects for applications in heterocyclic synthesis.[100,101] The

Схема 18



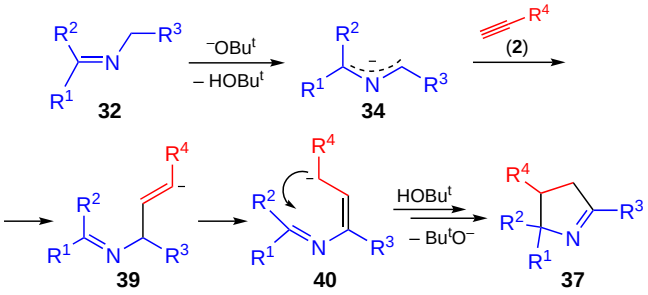
Selected examples



intermediate 1-pyrrolines **37**, valuable templates for new drugs[102] and their precursors,[103–105] can be isolated separately in up to 91% yield.

The assembly of pyrrolines **37** includes the addition of deprotonated *N*-benzylketimines (azaallyl anions **34**) to the triple bond of acetylenes **2** followed by the prototropic isomerization of carbanions **39** to the conjugated intermediates **40**. The latter attack the C=N bond to close the pyrroline ring (Scheme 19).

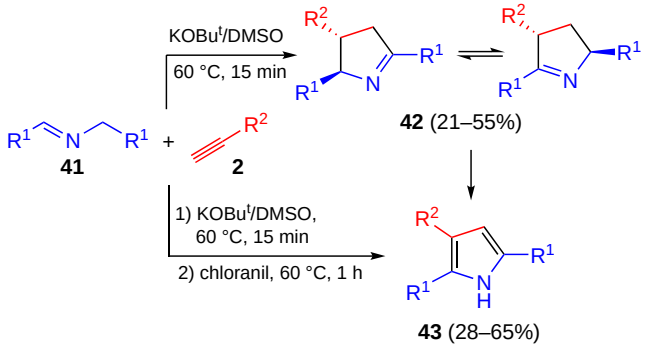
Scheme 19



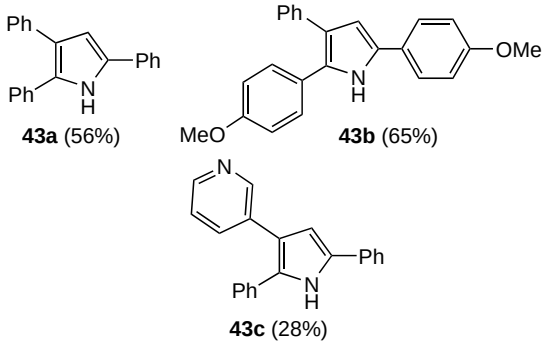
When *N*-benzylaldimines **41** were used instead of the *N*-benzylketimines **32** for the reaction with acetylenes **2**, the process proceeded again differently, giving 2,3,5-triaryl-1-pyrrolines **42** as two tautomers with 1,2- and 1,5-location of the double bond in a ratio of ~4:1 (Scheme 20).[106] A distinctive feature of this further branch of the acetylene/C=N bond interaction is its diastereoselectivity: both pyrroline tautomers are formed as *trans*-diastereomer. The oxidation of the tautomeric pyrrolines **42** (without their isolation from the reaction mixture) gave inaccessible[107–109] polyarylated 1*H*-pyrroles **43** (see Scheme 20).

The reaction was assumed[106] to involve the addition of azaallyl anions **44** to the acetylenic triple bond (Scheme 21). Emerging carbanions **45** attack the C=N bond closing the

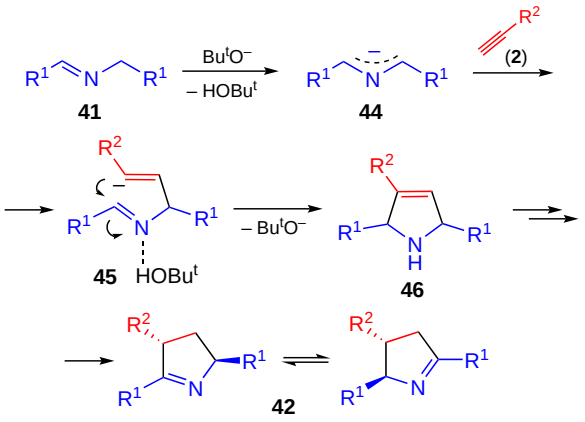
Scheme 20



Selected examples



Scheme 21



pyrroline cycle, probably with the electrophilic assistance of a proton from the medium. Intermediate pyrrolines **46** are rearranged by a series of proton transfers to give the final tautomeric pyrrolines **42**. The concerted nature of the cyclization stage has been supported by quantum-chemical calculations (B2PLYPD2/6-311+G**//B3LYP/6-31+G*).[110]

4. Addition of acetylenic carbanions to the C=N bond as a key stage in the self-organizations of complex molecules

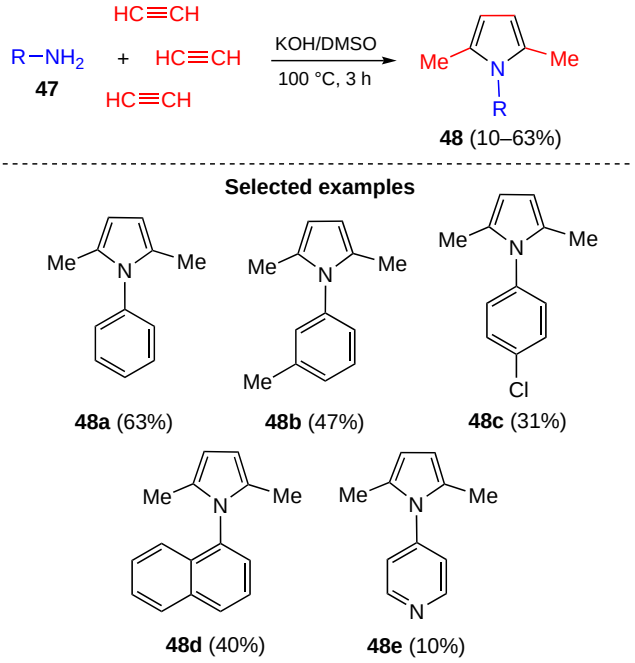
In the context of the acetylene/C=N bond interaction in superbase media, a phenomenon of self-organization of complex molecular structures from several molecules of acetylene and amines has been observed. These processes are initiated and controlled by the dichotomy of acetylene reactivity, *i.e.* its ability to act alternatively both as an electrophile and a nucleophile.[111] The key intermediates of this reaction cascade contain the C=N bond, which adds acetylenic carbanions thereby triggering the self-organization. Typical examples of the above self-assemblies are analyzed below.

Arylamines **47** react with excess acetylene gas in the KOH/DMSO system to form 1-aryl-2,5-dimethylpyrroles **48**, which are built up from three molecules of acetylene and one molecule of amine **47** (Scheme 22).[112] Various substituted anilines, condensed aromatic and heteroaromatic amines tolerate the reaction.

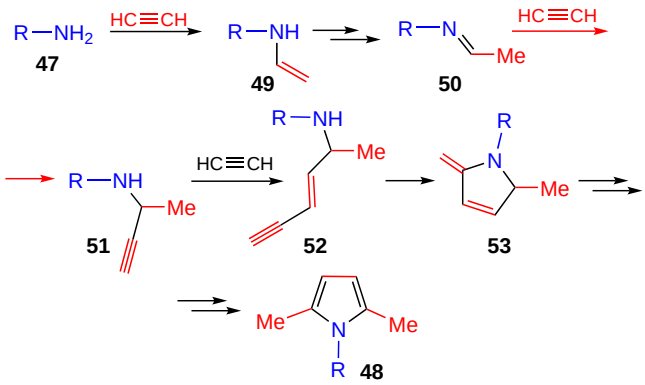
The reaction is initiated by the nucleophilic attack of arylamines **47** at the acetylenic triple bond to give *N*-vinylamines **49**, which, after the prototropic isomerization, are transformed to imines **50** (Scheme 23). The latter accept the second acetylene molecule (in carbanionic form) to generate intermediate propargyl amines **51**. The third acetylene molecule (in carbanionic form) is then inserted into the triple bond of propargyl amines **51**, and the intramolecular cyclization of intermediates **52**, after aromatization of dihydropyrroles **53**, gives the final pyrroles **48**. This mechanism has been supported by DFT calculations (B2PLYP(D3)/6-311+G**//B3LYP/6-31+G*) of activation barriers and thermodynamics of all steps.[113]

An even more sophisticated reaction cascade led to the self-organization of 1-aryl-3-ethyl-4-vinylpyrroles **54** from arylamines **47** and four molecules of acetylene, when the KOH/DMSO system was replaced by a more basic KOBu^t/DMSO system (Scheme 24).[114]

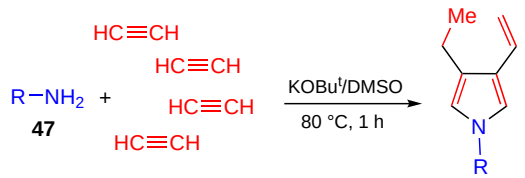
Scheme 22



Scheme 23



Scheme 24

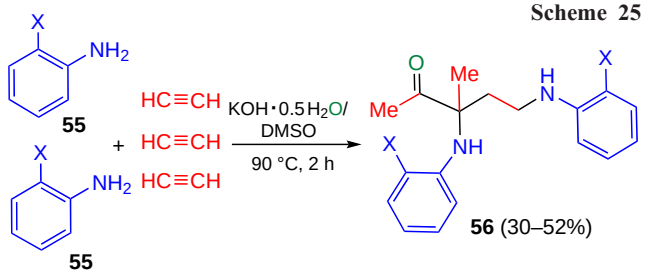


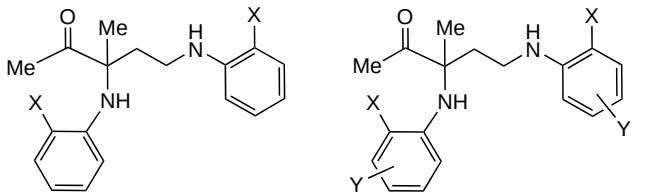
54a: R = Ph (20%);
54b: R = 3-FC$_6$H$_4$ (17%);
54c: R = 4-ClC$_6$H$_4$ (14%);
54d: R = 4-BrC$_6$H$_4$ (16%)

The few known syntheses of 3,4-disubstituted pyrroles are either multistep,[115,116] provide poor yields and restricted coverage,[117] or require costly chemicals[118] and catalysts.[119–121] Meanwhile, 3,4-disubstituted pyrroles with both α-positions unsubstituted are important in the synthesis of porphyrins[122] and other bioactive compounds.[115,116]

Interesting example of the self-organization phenomenon is the assembly of 1-acetyl-1,3-bis(haloarylamines) **56** from two molecules of *o*-halo arylamines **55**, three molecules of acetylene gas, and one molecule of water (Scheme 25).[123] Notably,

Scheme 25





56a: X = F (42%);
56b: X = Cl (47%);
56c: X = Br (52%);
56d: X = I (33%)

56e: X = Cl, Y = 5-Cl (40%);
56f: X = I, Y = 4-Me (31%);
56g: X = I, Y = 5-F (50%);
56h: X = Cl, Y = 5-CN (none)

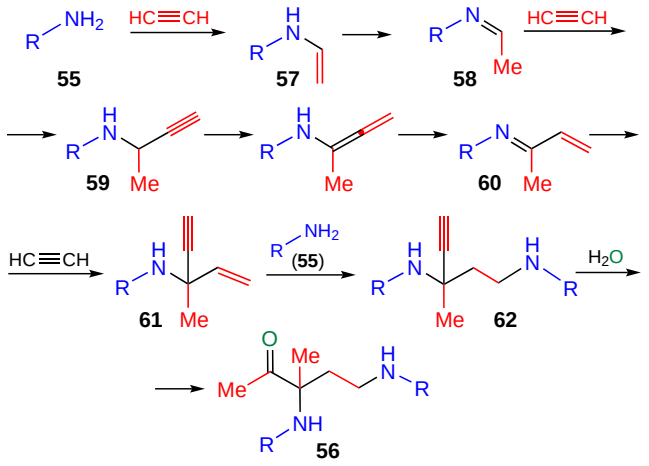
1,3-bisamines are important intermediates for the synthesis of natural alkaloid *manzacidin A*,[124,125] and HIV-1 protease inhibitors A-74704.[126,127]

The construction of 1-acetyl-1,3-bis(haloarylamines) **56** (Scheme 26) starts from the nucleophilic addition of amines **55** to the first molecule of acetylene to give *N*-vinyl amines **57**, which are prototropically isomerized to imines **58**. The latter add the second acetylene molecule (in carbanionic form) to the C=N bond, forming propargylamines **59**, which are transformed to azadienes **60**. The acetylene carbanion generated from the third acetylene molecule adds to the C=N bond of these intermediates to produce acetylenic amines **61**, which are attacked by the second molecule of amine **55**, and adducts **62** undergo hydration across the triple bond.

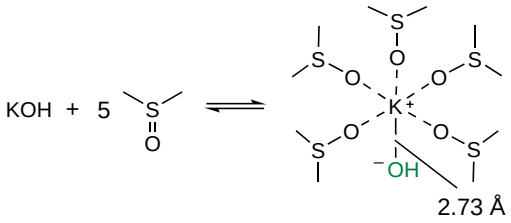
Quantum-chemical analysis (B2PLYP(D3)/6-311+G**//B3LYP/6-31+G*+PCM (B3LYP/6-31+G*))[128] does confirm that bisamines **56** are assembled via the sequential alternating addition of amine anions to acetylene and acetylenic carbanions to the C=N bond of the resulting intermediates. The driving force of this cascade process is that each subsequent stage proceeds with better thermodynamics (lower energy) than the previous one. According to the quantum-chemical calculations,[128] the reaction is catalyzed by a solvate complex of potassium hydroxide with five molecules of dimethylsulfoxide (KOH · 5 DMSO, Scheme 27), in which the hydroxide ion is significantly separated from the potassium cation (by ~0.5 Å *vs* the normal K–OH bond length) that imparts it superbasicity.[129,130]

According to the DFT analysis,[128] the mechanistic feature of the assembly of 1-acetyl-1,3-bis(haloarylamines) **56** is the shuttle-like proton transfers from neutral molecules (to transform

Scheme 26



Scheme 27

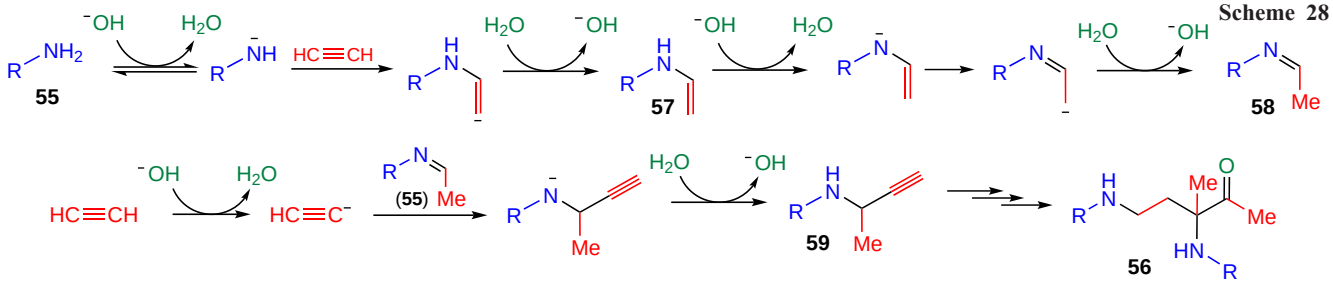


them to anions) to hydroxide ion and back from the water molecule thus formed to new anionic intermediates produced by accepting acetylene or arylamine molecules (Scheme 28). The hydroxide ion in the complex KOH · 5 DMSO plays the role of a 'hydrogen hub-dispatcher' ensuring proton migration ($H^+ + HO^- \rightarrow H_2O$) throughout the cascade process.

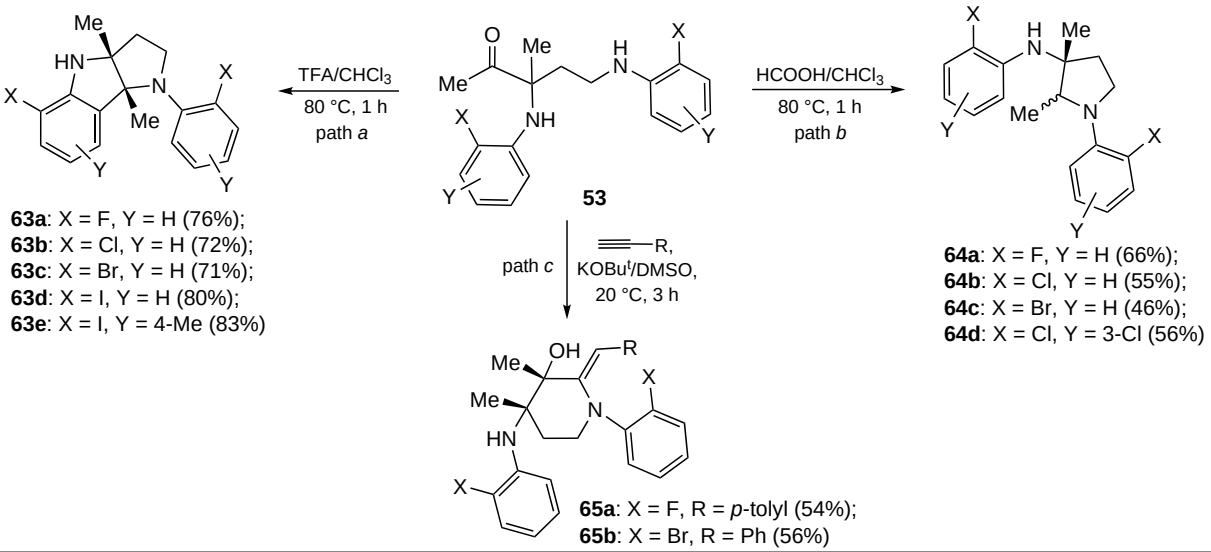
Apart from its obvious theoretical interest (see Scheme 25), this reaction is of a considerable synthetic value since it opens up simple routes to molecular complexity and diversity.[123] In particular, bisamines **56**, upon treatment with trifluoroacetic acid, undergo double intramolecular cyclization to diastereomerically pure hexahydropyrrolo[3,2-*b*]indoles **63** (Scheme 29, path *a*). In the presence of formic acid, bisamines **56** have been subjected to reductive cyclization to 3-amino-pyrrolidines **64** (Scheme 29, path *b*). Bisamines **56** also react readily with arylacetylenes **2** under the action of superbase KOBu^t/DMSO at room temperature to give benzylidene piperidinols **65** stereoselectively (Scheme 29, path *c*).

Another case of multi-molecular self-organization phenomenon, in which the addition of acetylenic carbanions to the C=N bond plays a leading role, is the reaction of substituted 2-aminopyridines **66** with acetylene gas. In the KOBu^t/DMSO system upon heating (80 °C) for a short time (5 min), the above reactants afforded imidazo[1,2-*a*]pyridines **67** (Scheme 30).[131] The structure of these products indicates that they are assembled

Scheme 28



Scheme 29



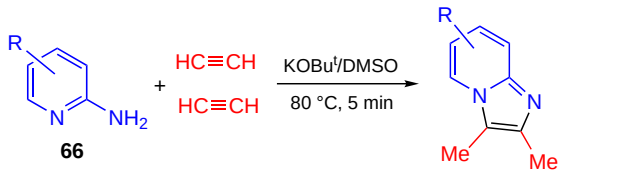
63a: X = F, Y = H (76%);
63b: X = Cl, Y = H (72%);
63c: X = Br, Y = H (71%);
63d: X = I, Y = H (80%);
63e: X = I, Y = 4-Me (83%)

53

64a: X = F, Y = H (66%);
64b: X = Cl, Y = H (55%);
64c: X = Br, Y = H (46%);
64d: X = Cl, Y = 3-Cl (56%)

65a: X = F, R = *p*-tolyl (54%);
65b: X = Br, R = Ph (56%)

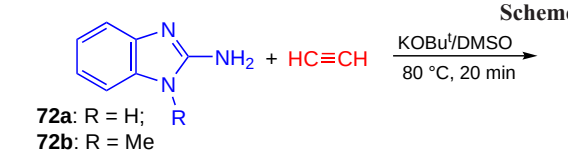
Scheme 30



66

67a: R = H (60%);
67b: R = 6-Me (53%);
67c: R = 7-Me (48%);
67d: R = 8-Me (50%)

Scheme 32



72a: R = H;
72b: R = Me

73a: R = CH=CH$_2$ (12%);
73b: R = Me (40%)

74a: R = CH=CH$_2$ (10%);
74b: R = Me (17%)

from one molecule of 2-aminopyridine **66** and two molecules of acetylene.

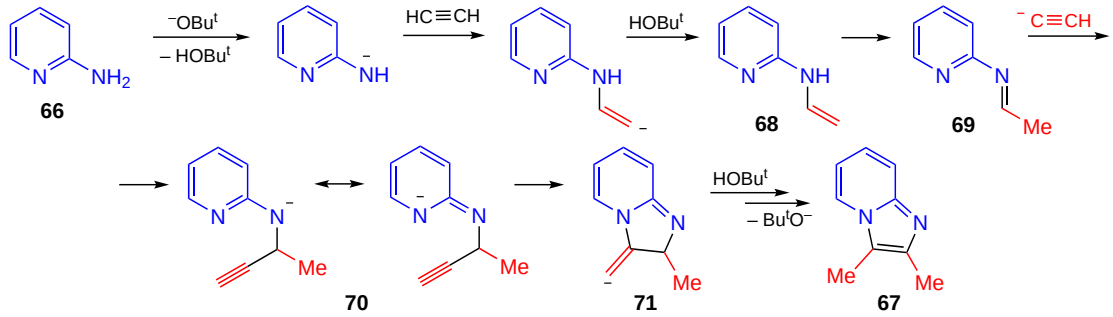
The assembly of imidazo[1,2-*a*]pyridines **67** includes the addition of deprotonated 2-aminopyridines **66** to acetylene (Scheme 31). The intermediate *N*-vinyl aminopyridines **68** isomerize to imines **69**, which add acetylenic carbanions across the C=N bond to form the nitrogen-centered anions **70**, the negative charge of which is transferred to the pyridine ring. The pyridine nitrogen atom closes the imidazole cycle by the addition to the triple bond and gives imidazopyridines **67** after protonation of anionic adducts **71** and prototropic rearrangement. Thus, in this cascade reaction, the addition of acetylenic carbanions to the C=N bond formed *in situ* is a driver of this assembly.

It was found that 2-aminobenzo[*d*]imidazole **72a** reacted with acetylene gas under similar conditions (KOBu^t/DMSO, 80 °C, 20 min) to give benzo[*d*]imidazo[1,2-*a*]imidazole **73a** and benzo[4,5]imidazo[1,2-*a*]pyrimidine **74a** formed *via* the self-organization of one molecule of 2-aminobenzo[*d*]imidazole **72a** with two or three molecules of acetylene (Scheme 32).[132]

This result suggests that the process involves all three nitrogen atoms of the starting 2-aminobenzo[*d*]imidazole **72a**. Similar products were obtained by the reaction of *N*-methyl-2-aminobenzo[*d*]imidazole **72b** with acetylene under the same conditions (see Scheme 32).

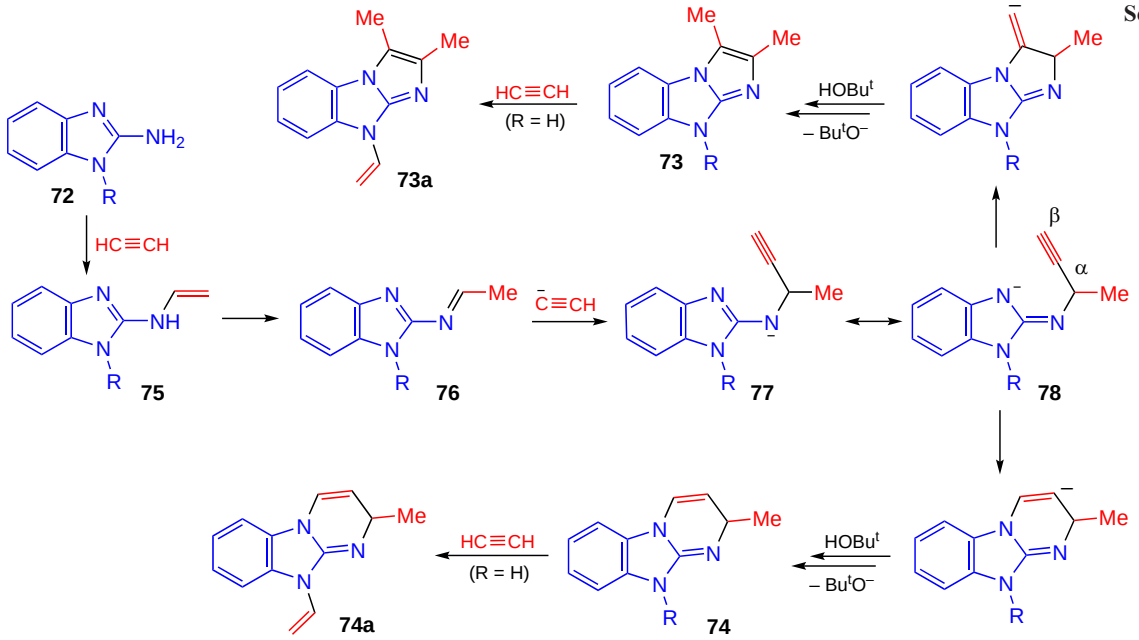
The self-assembly of heterocycles **73** and **74** (scheme 33) probably begins with the nucleophilic addition of 2-aminobenzo[*d*]imidazoles **72** to acetylene. The resulting *N*-vinyl adducts **75** isomerize into imines **76**, which are attacked by the second acetylene molecule (in carbanionic form) to generate nitrogen-centered anions **77**, in which the negative charge can be transferred to the imidazole ring. The intramolecular addition of anions **78** to the α- or β-carbon atom of the triple bond results (after protonation) in the formation of imidazo[1,2-*a*]imidazoles **73** or imidazo[1,2-*a*]pyrimidines **74**, respectively. In the case of 2-aminobenzo[*d*]imidazole **72a**, the

Scheme 31



66 **68** **69** **70** **71** **67**

Scheme 33



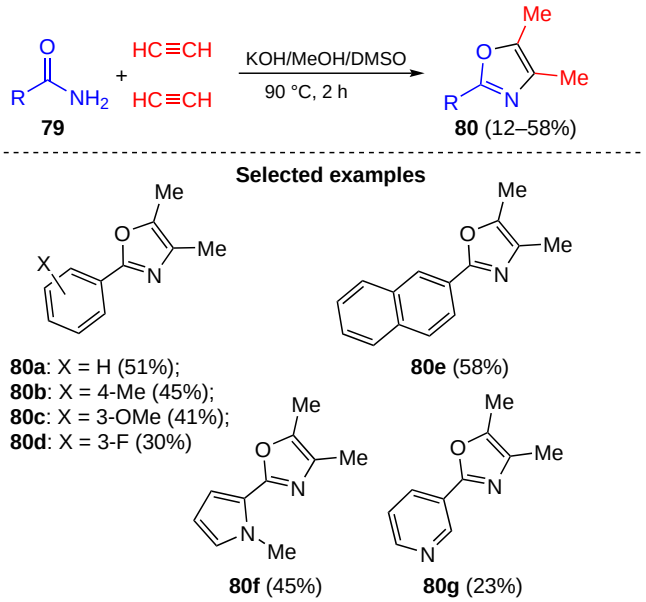
resulting products are further vinylated at the NH group by the third acetylene molecule.

As can be seen from Scheme 33, the process also involves the sequential addition of nitrogen-centered anions to the triple bond of acetylene and the addition of acetylenic carbanions to the C=N bond formed *in situ*.

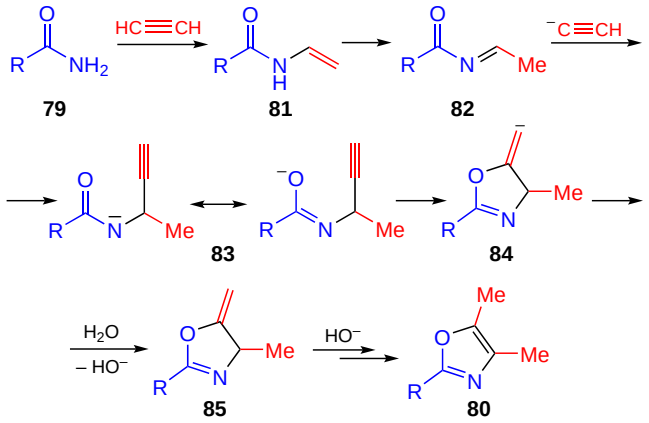
It was found that a molecule of primary amides **79** and two molecules of acetylene gas in the KOH/MeOH/DMSO superbase triad underwent a complex cascade transformations to give 2-substituted 3,4-dimethyloxazoles **80** (Scheme34).[133]

Apparently, the cascade sequence of oxazoles **80** assembly is triggered by the vinylation of amides **79** with acetylene (Scheme 35) followed by prototropic isomerization of vinyl amides **81** to imines **82**, which are attacked by acetylenic carbanions at the C=N bond to form propargyl amide anions **83**. These anionic intermediates in their oxygen-centered form are cyclized *via* the intramolecular vinylation involving the triple bond. Protonation of anionic adducts **84** and prototropic

Scheme 34



Scheme 35



rearrangement of methylene-dihydrooxazoles **85** provides oxazoles **80**.

5. Conclusions

As can be seen from the above, the reaction of acetylenic carbanions, generated in superbase media, with C=N bond, has now received a rapid development due to its obvious synthetic advantages such as mild conditions, simplest starting reagents (acetylenes, imines, amines), one-pot implementation, energy-saving, and environmental safety. In addition, the reaction occurs in the presence of only biogenic ions (K^+, Na^+, HO^-, H^+) in a non-toxic, easily recoverable solvent (dimethylsulfoxide), which allows large-scale syntheses to be implemented in a closed cycle. The characteristic feature of the reaction is its synthetic divergence, which is expressed in its metamorphosis into essentially new processes by changing the structure of the starting C=N bond containing compounds. Within a short period of time (6 years), this new fundamental reaction became the generator of a number of earlier unknown daughter reactions with high synthetic potential. The diversity of transformations of acetylenic carbanions with the C=N bond opens a straightforward access to novel groups of terminal and internal propargylamines, bis(propargyl)benzenes, 1-azadienes,

substituted pyrazoles, benzyl- and styryl imidazo[1,2-*a*]-pyridines. Unexpected reactions of acetylenes with *N*-benzylimines in superbase media have provided one-pot selective syntheses of 2-azadienes, 1-pyrrolines, 1*H*- and 2*H*-pyrroles. No less importantly, the addition of acetylenic carbanions to the C=N bond appeared to be the key step of the self-organization of complex molecules involving acetylene and amines, another vast unexplored area of organic synthesis.

Further development of the reaction of acetylene carbanions with the C=N bond offers exciting possibilities for targeted structural diversification of synthesized products with a view to application in other segments of organic synthesis, including carbon dioxide fixation (assembly of methyleneoxazolidinones from propargylamines and CO_2), reactions with carbonyl compounds (synthesis of methyleneoxazolidines), isothiocyanates (formation of thiazole derivatives), and other electrophiles for the preparation of new functional heterocyclic systems, potential drugs and their precursors, as well as starting compounds for the assembly of complex molecular architectures.

6. List of abbreviations

dr — diastereomeric ratio,
Fu — furyl,
Naph — naphthyl,
Py — pyridyl,
Th — thienyl.

7. References

1. K.S.Rodygin, G.Werner, F.A.Kucherov, V.P.Ananikov. *Chem. – Asian J*., **11**, 965 (2016); https://doi.org/10.1002/asia.201501323
2. V.V.Voronin, M.S.Ledovskaya, A.S.Bogachenkov, K.S.Rodygin, V.P.Ananikov. *Molecules*, **23**, 2442 (2018); https://doi.org/10.3390/molecules23102442
3. I.V.Alabugin, E.Gonzalez-Rodriguez. *Acc. Chem. Res*., **51**, 1206 (2018); https://doi.org/10.1021/acs.accounts.8b00026
4. S.B.Alyabyev, I.P.Beletskaya. *Russ. Chem. Rev*., **87**, 984 (2018); https://doi.org/10.1070/RCR4815
5. B.A.Trofimov, E.Yu. Schmidt. *Acc. Chem. Res*., **51**, 1117 (2018); https://doi.org/10.1021/acs.accounts.7b00618
6. I.V.Alabugin, E.Gonzalez-Rodriguez, R.K.Kawade, A.A.Stepanov, S.F.Vasilevsky. *Molecules*, **24**, 1036 (2019); https://doi.org/10.3390/molecules24061036
7. M.M.Heravi, M.Dehghani, V.Zadsirjan, M.Ghanbarian. *Curr. Org. Synth*., **16**, 205 (2019); https://doi.org/10.2174/1570179416666190126100744
8. N.A.Danilkina, A.V.Vasil'eva, I.A.Balova. *Russ. Chem. Rev*., **89**, 125 (2020); https://doi.org/10.1070/RCR4902
9. M.S.Ledovskaya, V.V.Voronin, K.S.Rodygin, V.P.Ananikov. *Synthesis*, **54**, 999 (2022); https://doi.org/10.1055/a-1654-2318
10. A.Ramani, B.Desai, M.Patel, T.Naveen. *Asian J. Org. Chem*., **11**, e202200047 (2022); https://doi.org/10.1002/ajoc.202200047
11. Å.M.Sørskår, H.Ø.K.Stenstrøm, Y.Stenstrøm, S.G.Antonsen. *Reactions*, **4**, 26 (2023); https://doi.org/10.3390/reactions4010002
12. E.O.Pentsak, M.S.Murga, V.P.Ananikov. *ACS Earth Space Chem.*, **8**, 798 (2024); https://doi.org/10.1021/acsearthspacechem.3c00223
13. S.Hosseininezhad, A.Ramazani. *RSC Adv*., **14**, 278 (2024); https://doi.org/10.1039/D3RA07670A
14. H.Schobert. *Chem. Rev*., **114**, 1743 (2014); https://doi.org/10.1021/cr400276u
15. I.-T.Trotuş, T.Zimmermann. F.Schüth. *Chem. Rev*., **114**, 1761 (2014); https://doi.org/10.1021/cr400357r
16. J.A.Lehmann. *Nature*, **447**, 143 (2007); https://doi.org/10.1038/447143a
17. G.Li, Q.Liu, Z.Liu, Z.C.Zhang, C.Li, W.Wu. *Angew. Chem., Int. Ed*., **49**, 8480 (2010); https://doi.org/10.1002/anie.201004169
18. J.Zhang, Z.Wang, S.Bennaceur, X.Jin. *Angew. Chem., Int. Ed*., **62**, e202301479 (2023); https://doi.org/10.1002/anie.202301479
19. A.E.Favorskii. *Zh. Ross. Fiziko-khim. O-va*, **37**, 643 (1905)
20. M.Smith, J.March. *March's Advanced Organic Chemistry.* (6th Edn). (New York: Wiley, 2007). P. 1360
21. B.A.Trofimov. *Curr. Org. Chem*., **6**, 1121 (2002); https://doi.org/10.2174/1385272023373581
22. B.A.Trofimov, N.K.Gusarova, *Russ. Chem. Rev*., **76**, 507 (2007); https://doi.org/10.1070/RC2007v076n06ABEH003712
23. B.A.Trofimov, E.Yu. Schmidt. *Russ. Chem. Rev*., **83**, 600 (2014); https://doi.org/ 10.1070/RC2014v083n07ABEH004425
24. L.Zani, C.Bolm. *Chem. Commun*., 4263 (2006); https://doi.org/10.1039/b607986p
25. K.Yamada, K.Tomioka. *Chem. Rev*., **108**, 2874 (2008); https://doi.org/10.1021/cr078370u
26. B.M.Trost, A.H.Weiss. *Adv. Synth. Catal*., **351**, 963 (2009); https://doi.org/10.1002/adsc.200800776
27. W.N.Olmstead, Z.Margolin, F.G.Bordwell. *J. Org. Chem*., **45**, 3295 (1980); https://doi.org/10.1021/jo01304a032
28. Y.Yuan, I.Thomé, S.H.Kim, D.Chen, A.Beyer, J.Bonnamour, E.Zuidema, S.Chang, C.Bolm. *Adv. Synth. Catal*., **352**, 2892 (2010); https://doi.org/10.1002/adsc.201000575
29. I.A.Bidusenko, E.Yu.Schmidt, I.A.Ushakov, B.A.Trofimov. *Eur. J. Org. Chem*., **2018**, 4845 (2018); https://doi.org/10.1002/ejoc.201800850
30. R.J.Tedeschi. *J. Org. Chem*., **30**, 3045 (1965); https://doi.org/10.1021/jo01020a037
31. R.Boese, M.T.Kirchner, W.E.Billups, L.R.Norman. *Angew. Chem., Int. Ed*., **42**, 1961 (2003); https://doi.org/10.1002/anie.200250634
32. T.K.Saha, R.Das. *ChemistrySelect*, **3**, 147 (2018); https://doi.org/10.1002/slct.201702454
33. K.Lauder, A.Toscani, N.Scalacci, D.Castagnolo. *Chem. Rev.*, **117**, 14091 (2017); https://doi.org/10.1021/acs.chemrev.7b00343
34. S.Arshadi, E.Vessally, M.Sobati, A.Hosseinian, A.Bekhradnia. *J. CO_2 Util.*, **19**, 120 (2017); https://doi.org/10.1016/j.jcou.2017.03.009
35. E.Vessally, M.Babazadeh, A.Hosseinian, L.Edjlali, L.Sreerama. *Curr. Org. Chem.*, **22**, 199 (2018); https://doi.org/10.2174/1385272821666170519113904
36. *Acetylene Chemistry. Chemistry, Biology and Material Science* (Eds F.Diederich, P.J.Stang, R.R.Tykwinski). (Weinheim: Wiley-VCH, 2005). P. 125
37. *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations.* (Eds C.-J.Li, B.M.Trost). (Weinheim: Wiley-VCH, 2015). P. 239
38. M.B.H.Youdim, J.J.Buccafusco. *J. Neural Transm*., **112**, 519 (2005); https://doi.org/10.1007/s00702-004-0214-z
39. I.Bolea, A.Gella, M.Unzeta. *J. Neural Transm*., **120**, 893 (2013); https://doi.org/10.1007/s00702-012-0948-y
40. F.T.Zindo, J.Joubert, S.F.Malan. *Future Med. Chem*., **7**, 609 (2015); https://doi.org/10.4155/fmc.15.12
41. O.Bar-Am, T.Amit, M.B.Youdim, O.Weinreb. *J. Neural Transm*., **123**, 125 (2016); https://doi.org/10.1007/s00702-015-1395-3
42. E.Szokő, T.Tabi, P.Riederer, L.Vecsei, K.Magyar. *J. Neural Transm*., **125**, 1735 (2018); https://doi.org/10.1007/s00702-018-1853-9
43. C.Mannich, F.T.Chang. *Ber. Dtsch. Chem. Ges.*, **66**, 418 (1933); https://doi.org/10.1002/cber.19330660323
44. W.Reppe, O.Hecht. US2273141A (1942)
45. W.Reppe. *Neue Entwicklungen auf dem Gebiete der Chemie des Acetylens und Kohlenoxyds*. (Berlin, Gottingen, Heidelberg: Springer, 1949). P. 23

46. S.Sakaguchi, T.Kubo, Y.Ishii. *Angew. Chem., Int. Ed*., **40**, 2534 (2001); https://doi.org/10.1002/1521-3773(20010702)40:13%3C2534::AID-ANIE2534%3E3.0.CO;2-2
47. C.Fischer, E.M.Carreira. *Org. Lett*., **3**, 4319 (2001); https://doi.org/10.1021/ol017022q
48. V.A.Peshkov, O.P.Pereshivko, E.V.Van der Eycken. *Chem. Soc. Rev*., **41**, 3790 (2012); https://doi.org/10.1039/C2CS15356D
49. A.Ramazani, H.Ahankar, Z.T.Nafeh, S.W.Joo. *Curr. Org. Chem*., **23**, 2783 (2019); https://doi.org/10.2174/1385272823666191113160643
50. J.Farhi, I.N.Lykakis, G.E.Kostakis. *Catalysts*, **12**, 660 (2022); https://doi.org/10.3390/catal12060660
51. M.Abedi, M.Hosseini, A.Arabmarkadeh, M.Kazemi. *Synth. Commun*., 51, 835 (2021); https://doi.org/10.1080/00397911.2020.1858320
52. A.Berrichi, R.Bachir, S.Bedrane. *Curr. Org. Chem*., **27**, 621 (2023); https://doi.org/10.2174/1385272827666230614151935
53. C.E.Meyet, C.J.Pierce, C.H.Larsen. *Org. Lett.*, **14**, 964 (2012); https://doi.org/10.1021/ol2029492
54. S.A.Shehzadi, A.Saeed, F.Lemiere, B.U.W.Maes, K.A.Tehrani. *Eur. J. Org. Chem.*, **2018**, 78 (2018); https://doi.org/10.1002/ejoc.201701567
55. C.J.Pierce, M.Nguyen, C.H.Larsen. *Angew. Chem., Int. Ed.*, **51**, 12289 (2012); https://doi.org/10.1002/anie.201206674
56. M.J.Albaladejo, F.Alonso, Y.Moglie, M.Yus. *Eur. J. Org. Chem.*, **2012**, 3093 (2012); 10.1002/ejoc.201200090
57. Y.Cai, X.Tang, S.Ma, *Chem. – Eur. J.*, **22**, 2266 (2016); https://doi.org/10.1002/chem.201504823
58. G.Bosica, R.Abdilla. *J. Mol. Catal. A*, **426**, 542 (2017); https://doi.org/10.1016/j.molcata.2016.09.028
59. A.Elhampour, F.Nemati, M.M.Heravi. *Monatsh. Chem.*, **148**, 1793 (2017); https://doi.org/10.1007/s00706-017-1948-2
60. L.Ye, W.He, L.Zhang. *Angew. Chem., Int. Ed*., **50**, 3236 (2011); https://doi.org/10.1002/anie.201007624
61. M.Crucianelli, F.De Angelis, F.Lazzaro, L.Malpezzi, A.Volonterio, M.Zanda. *J. Fluorine Chem*., **125**, 573 (2004); https://doi.org/10.1016/j.jfluchem.2003.11.034
62. T.Ullrich, P.Sulek, D.Binder, M.Pyerin. *Tetrahedron*, **56**, 3697 (2000); https://doi.org/10.1016/S0040-4020(00)00306-9
63. M.Bonanni, M.Marradi, S.Cicchi, C.Faggi, A.Goti. *Org. Lett*., **7**, 319 (2005); https://doi.org/10.1021/ol047691e
64. E.Yu. Schmidt, I.A.Bidusenko, N.I.Protsuk, Y.V.Demyanov, I.A.Ushakov, B.A.Trofimov. *Eur. J. Org. Chem*., **2019**, 5875 (2019); https://doi.org/10.1002/ejoc.201900932
65. E.Yu. Schmidt, N.V.Semenova, I.A.Bidusenko, N.I.Protsuk, I.A.Ushakov, B.A.Trofimov. *Mendeleev Commun*., **33**, 642 (2023); https://doi.org/10.1016/j.mencom.2023.09.017
66. M.Costa, G.P.Chiusoli, M.Rizzardi. *Chem. Commun*., 1699 (1996); https://doi.org/10.1039/CC9960001699
67. J.Fang, K.Tanaka, H.Kita, K.Okamoto. *Polymer*, **40**, 3051 (1999); https://doi.org/10.1016/S0032-3861(98)00523-0
68. P.A.Volkov, K.O.Khrapova, A.A.Telezhkin, I.A.Bidusenko, E.Yu. Schmidt, A.I.Albanov, B.A.Trofimov. *Adv. Synth. Catal*., **365**, 53 (2023); https://doi.org/10.1002/adsc.202201179
69. J.Bariwal, L.G.Voskressensky, E.V.van der Eycken. *Chem. Soc. Rev*., **47**, 3831 (2018); https://doi.org/10.1039/C7CS00508C
70. M.Jiang, S.Chen, J.Li, L.Liu. *Mar. Drugs*, **18**, 114 (2020); https://doi.org/10.3390/md18020114
71. P.Sharma, R.Kumar, G.Bhargava. *J. Heterocycl. Chem*., **57**, 4115 (2020); https://doi.org/10.1002/jhet.4143
72. A.Wati, M.Santoso, Z.Moussa, S.Fatmawati, A.Fadlan, Z.M.A.Judeh. *RSC Adv*., **11**, 25381 (2021); https://doi.org/10.1039/D1RA03091D
73. P.A.Volkov, K.O.Khrapova, E.M.Vyi, A.A.Telezhkin, I.A.Bidusenko, A.I.Albanov, E.Yu. Schmidt, B.A.Trofimov. *Org. Biomol. Chem*., **21**, 6903 (2023); https://doi.org/10.1039/D3OB01061A
74. E.Yu. Schmidt, I.A.Bidusenko, N.I.Protsuk, Y.V.Demyanov, I.A.Ushakov, A.V.Vashchenko, B.A.Trofimov. *J. Org. Chem*., **85**, 3417 (2020); https://doi.org/10.1021/acs.joc.9b03192
75. B.Groenendaal, E.Ruijter, R.V.Orru. *Chem. Commun*., 5474 (2008); https://doi.org/10.1039/B809206K
76. J.-C.M.Monbaliu, K.G.R.Masschelein, C.V.Stevens. *Chem. Soc. Rev*., **40**, 4708 (2011); 10.1039/C1CS15070G
77. S.Jayakumar, M.P.S.Ishar, M.P.Mahajan. *Tetrahedron*, **58**, 379 (2002); https://doi.org/10.1016/S0040-4020(01)01050-X
78. A.D.J.Calow, E.Fernández, A.Whiting. *Org. Biomol. Chem*., **12**, 6121 (2014); https://doi.org/10.1039/C4OB01142B
79. M.J.Schnermann, D.L.Boger. *J. Am. Chem. Soc*., **127**, 15704 (2005); 10.1021/ja055041f
80. J.Franzén, A.Fisher. *Angew. Chem., Int. Ed*., **48**, 787 (2009); https://doi.org/10.1002/anie.200805130
81. P.Yao, Z.Xu, S.Yu, Q.Wu, D.Zhu. *Adv. Synth. Catal*., **361**, 556 (2019); https://doi.org/10.1002/adsc.201801326
82. A.Sharifi, M.Mirzaei, M.R.Naimi-Jamal. *J. Chem. Res*., 2007, 129 (2007); https://doi.org/10.3184/030823407X191994
83. I.A.Bidusenko, E.Yu.Schmidt, I.A.Ushakov, A.V.Vashchenko, N.I.Protsuk, V.B.Orel, N.M.Vitkovskaya, B.A.Trofimov. *J. Org. Chem*., **87**, 12225 (2022); https://doi.org/10.1021/acs.joc.2c01372
84. M.Kluska, J.Jabłońska, W.Prukała. *Molecules*, **28**, 4482 (2023); https://doi.org/10.3390/molecules28114482
85. Doraghi, F.Yousefnejad, S.Farzipour, S.P.Aledavoud, B.Larijanid, M.Mahdavi. *Org. Biomol. Chem*., **21**, 1846 (2023); https://doi.org/10.1039/D2OB01982E
86. D.Villarón, S.J.Wezenberg. *Angew. Chem., Int. Ed*., **59**, 13192 (2020); https://doi.org/10.1002/anie.202001031
87. S.De, S.K.A.Kumar, S.K.Shah, S.Kazi, N.Sarkar, S.Banerjee, S.Dey. *RSC Adv*., **12**, 15385 (2022); https://doi.org/10.1039/D2RA01571D
88. E.Khan. *ChemistrySelect*, **6**, 3041 (2021); https://doi.org/10.1002/slct.202100332
89. S.R.Alizadeh, M.A.Ebrahimzadeh. *Mini-Rev. Med. Chem*., **21**, 2584 (2021); https://doi.org/10.2174/1389557521666210126143558
90. N.Rani, R.Singh, P.Kumar. *Curr. Org. Synth*., **20**, 630 (2023); https://doi.org/10.2174/1570179420666221118100525
91. H.V.Tolomeu, C.A.M.Fraga. *Molecules*, **28**, 838 (2023); https://doi.org/10.3390/molecules28020838
92. Y.-D.Lin, W.-W.Tsai, C.-W.Lu. *Chem. – Eur. J*., **29**, e202382361 (2023); https://doi.org/10.1002/chem.202382361
93. A.O.Ustyuzhanin, I.A.Bidusenko, E.K.Kouame, I.A.Ushakov, A.O.Gudovannyy, K.A.Lyssenko, E.Yu. Schmidt, A.G.Lvov. *Eur. J. Org. Chem*., **2022**, e202200921 (2022); https://doi.org/10.1002/ejoc.202200921
94. I.A.Bidusenko, E.Yu. Schmidt, N.I.Protsuk, I.A.Ushakov, B.A.Trofimov. *Mendeleev Commun*., **34**, 110 (2024); https://doi.org/10.1016/j.mencom.2024.01.033
95. I.A.Bidusenko, E.Yu. Schmidt, N.I.Protsuk, I.A.Ushakov, A.V.Vashchenko, A.V.Afonin, B.A.Trofimov. *Org. Lett*., **22**, 2611 (2020); https://doi.org/10.1021/acs.orglett.0c00564
96. S.Tang, X.Zhang, J.Sun, D.Niu, J.Chruma. *Chem. Rev*., **118**, 10393 (2018); https://doi.org/10.1021/acs.chemrev.8b00349
97. S.J.Malcolmson, K.Li, X.Shao. *Synlett*, **30**, 1253 (2019); https://doi.org/10.1055/s-0037-1611770
98. V.B.Kobychev, V.B.Orel, N.M.Vitkovskaya, B.A.Trofimov. *Dokl. Chem*., **457**, 126 (2014); https://doi.org/10.1134/S0012500814070040
99. I.A.Bidusenko, E.Yu. Schmidt, I.A.Ushakov, A.V.Vashchenko, B.A.Trofimov. *Org. Lett*., **23**, 4121 (2021); https://doi.org/10.1021/acs.orglett.1c01009
100. C.-X.Zhuo, Q.Cheng, W.-B.Liu, Q.Zhao, S.-L.You. *Angew. Chem., Int. Ed*., **54**, 8475 (2015); https://doi.org/10.1002/anie.201502259
101. D.Li, L.Wang, Y.Yang, M.Zhang, T.Peng, D.Yang, R.Wang. *Adv. Synth. Catal*., **361**, 3744 (2019); https://doi.org/10.1002/adsc.201900481

102. G.Dannhardt, W.Kiefer. *Arch. Pharm*., **334**, 183 (2001); https://doi.org/10.1002/1521-4184(200106)334:6<183::AID-ARDP183>3.0.CO;2-U
103. B.B.Snider, B.J.Neubert. *Org. Lett*., **7**, 2715 (2005); https://doi.org/10.1021/ol0509311
104. B.Lygo, E.H.M.Kirton, C.Lumley. *Org. Biomol. Chem*., **6**, 3085 (2008); https://doi.org/10.1039/B805951A
105. F.A.Davis, N.Theddu, R.Edupuganti. *Org. Lett*., **12**, 4118 (2010); https://doi.org/10.1021/ol1017118
106. I.A.Bidusenko, E.Yu. Schmidt, N.I.Protsuk, I.A.Ushakov, B.A.Trofimov. *Mendeleev Commun*., **33**, 24 (2023); https://doi.org/10.1016/j.mencom.2023.01.007
107. F.Bellina, R.Rossi. *Tetrahedron*, **62**, 7213 (2006); https://doi.org/10.1016/j.tet.2006.05.024
108. P.Polák, T.Tobrman. *Org. Lett*., **19**, 4608 (2017); https://doi.org/10.1021/acs.orglett.7b02219
109. M.Yamaguchi, S.Fujiwara, R.Manabe. *Org. Lett*., **21**, 6972 (2019); https://doi.org/10.1021/acs.orglett.9b02559
110. V.B.Orel, A.A.Zubarev, I.A.Bidusenko, I.A.Ushakov, N.M.Vitkovskaya. *J. Org. Chem*., **88**, 7058 (2023); https://doi.org/10.1021/acs.joc.3c00333
111. E.Yu. Schmidt, B.A.Trofimov. *Dokl. Chem*., **505**, 127 (2022); https://doi.org/10.1134/S0012500822700069
112. E.Yu. Schmidt, N.V.Semenova, E.V.Ivanova, I.A.Bidusenko, B.A.Trofimov. *Mendeleev Commun*., **30**, 109 (2020); https://doi.org/10.1016/j.mencom.2020.01.036
113. N.M.Vitkovskaya, V.B.Orel, D.Z.Absalyamov, B.A.Trofimov. *J. Org. Chem*., **85**, 10617 (2020); https://doi.org/10.1021/acs.joc.0c01185
114. E.Yu. Schmidt, N.V.Semenova, E.V.Ivanova, I.A.Ushakov, B.A.Trofimov. *Mendeleev Commun*., **30**, 315 (2020); https://doi.org/10.1016/j.mencom.2020.05.018
115. U.Robben, I.Lindner, W.Gärtner. *J. Am. Chem. Soc*., **130**, 11303 (2008); https://doi.org/10.1021/ja076728y
116. R.Di Santo, A.Tafi, R.Costi, M.Botta, M.Artico, F.Corelli, M.Forte, F.Caporuscio, L.Angiolella, A.T.Palamara. *J. Med. Chem*., **48**, 5140 (2005); https://doi.org/10.1021/jm048997u
117. E.J.Roskamp, P.S.Dragovich, J.B.Hartung, S.F.Pedersen. *J. Org. Chem*., **54**, 4736 (1989); https://doi.org/0.1021/jo00281a006
118. C.Martín-Santos, C.Jarava-Barrera, A.Parra, F.Esteban, C.Navarro-Ranninger, J.Alemán. *ChemCatChem,* **4**, 976 (2012); https://doi.org/10.1002/cctc.201200104
119. H.Shiraishi, T.Nishitani, T.Nishihara, S.Sakaguchi, Y.Ishii. *Tetrahedron*, **55**, 13957 (1999); https://doi.org/10.1016/S0040-4020(99)00855-8
120. M.Yasuda, J.Morimoto, I.Shibata, A.Baba. *Tetrahedron Lett*., **38**, 3265 (1997); https://doi.org/10.1016/S0040-4039(97)00598-4
121. F.Ragaini, S.Cenini, E.Borsani, M.Dompé, E.Gallo, M.Moret. *Organometallics*, **20**, 3390 (2001); https://doi.org/10.1021/om010076j
122. A.R.Battersby, C.J.R.Fookes, G.W.J.Matcham, E.McDonald. *Nature*, 285, 17 (1980); https://doi.org/10.1038/285017a0
123. E.Yu. Schmidt, N.V.Semenova, I.A.Ushakov, A.V.Vashchenko, B.A.Trofimov. *Org. Lett*., **23**, 4743 (2021); https://doi.org/10.1021/acs.orglett.1c01460
124. T.Hashimoto, K.Maruoka. *Org. Biomol. Chem*., **6**, 829 (2008); https://doi.org/10.1039/B716062C
125. Y.Ohfune, K.Oe, K.Namba, T.Shinada. *Heterocycles*, **85**, 2617 (2012); https://doi.org/10.3987/REV-12-746
126. S.S.Abdel-Meguid, B.Zhao, K.H.M.Murthy, E.Winborne, J.K.Choi, R.L.DesJarlais, M.D.Minnich, J.S.Culp, C.Debouck. *Biochemistry*, **32**, 7972 (1993); https://doi.org/10.1021/bi00082a019
127. D.Enders, U.Jegelka, B.Dücker. *Angew. Chem., Int. Ed*., **32**, 423 (1993); https://doi.org/10.1002/anie.199304231
128. D.Z.Absalyamov, N.M.Vitkovskaya, V.B.Orel, E.Yu.Schmidt, B.A.Trofimov. *Asian J. Org. Chem*., **12**, e202300042 (2023); https://doi.org/10.1002/ajoc.202300042
129. N.M.Vitkovskaya, E.Yu.Larionova, V.B.Kobychev, N.V.Kaempf, B.A.Trofimov. *Int. J. Quantum Chem*., **111**, 2519 (2011); https://doi.org/10.1002/qua.22643
130. N.M.Vitkovskaya, V.B.Orel, V.B.Kobychev, A.S.Bobkov, D.Z.Absalyamov, B.A.Trofimov. *Int. J. Quantum Chem*., **120**, e26158 (2020); https://doi.org/10.1002/qua.26158
131. N.V.Semenova, E.Yu.Schmidt, I.A.Ushakov, B.A.Trofimov. *Mendeleev Commun*., **33**, 164 (2023); https://doi.org/10.1016/j.mencom.2023.02.005
132. N.V.Semenova, I.A.Ushakov, E.Yu.Schmidt, B.A.Trofimov. *Russ. J. Org. Chem*., **60**, 353 (2024); https://doi.org/10.1134/S1070428024020192
133. E.Yu. Schmidt, N.V.Semenova, E.E.Ivanova, I.A.Ushakov, I.A.Bidusenko, A.S.Bobkov, N.M.Vitkovskaya, B.A.Trofimov. *Adv. Synth. Catal*., in the press (2024); https://doi.org/10.1002/adsc.202400953