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Focus Article, *Mendeleev Commun.*, 2015, **25**, 399–409
Mendeleev Communications

Novel approaches to pharmacology-oriented and energy rich organic nitrogen–oxygen systems

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DOI: 10.1016/j.mencom.2015.11.001

Organic compounds bearing semi-polar nitrogen–oxygen bonds are considered as perspective platform for designing socially important medications and high energy materials. Herein, recently developed original syntheses of monocyclic and fused 1,2,3,4-tetrazine 1,3-dioxides, various (methylene)bis(1-oxy-1-triazene 2-oxide) derivatives, furoxan-containing polyheterocyclic scaffolds and diastereo- or enantiomerically enriched functionalized aliphatic nitro compounds are summarized. Prospects for their practical applications are outlined.

Introduction

Organic compounds incorporating semi-polar nitrogen–oxygen bonds possess versatile and useful properties. For decades, nitro compounds are used as energetic materials for industrial and military applications.[1] On the other hand, some of them along with a number of other types of organic *N*-oxides exhibit useful biological activities associated with their capability of releasing nitric oxide (NO) under physiological conditions. A classic example of this duality of properties is nitroglycerin – a well-known compound, which is extensively used as a key component of high energy compositions (in particular, powders) and simultaneously serves as efficient and expeditious medication for alleviation of acute angina attack. In the late 1990's the Nobel Prize winners Furchgott, Ignarro and Murad discovered that nitric oxide is a ubiquitous and crucial regulator for cellular metabolism, affecting various physiological and pathophysiological processes in mammalians.[2] Compounds that combine a NO release benefit (NO-donors) with maintaining the activity of the native drug has proved to be useful for treating cardiovascular, inflammatory, bacterial, fungal, viral, parasitic, ocular diseases and cancer. A design of novel properly composed NO-donor hybrid drugs capable of releasing this vitally important regulator in the body, either enzymatically, or independently of NO synthases, is an important focus in modern medicinal

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chemistry. Furthermore, functionalized nitro alkanes are precursors to derivatives of another important neuromediator – γ-aminobutyric acid (GABA).[4] They are also used for the synthesis of natural enzyme (phosphodiasterase-IV, neuraminidase, cyclin-dependent kinase IV, p53/MDM2, *etc.*) inhibitors which have already found clinical applications or advanced to clinical trials as remedies for efficient treatment of socially important acute and chronic diseases.[5]

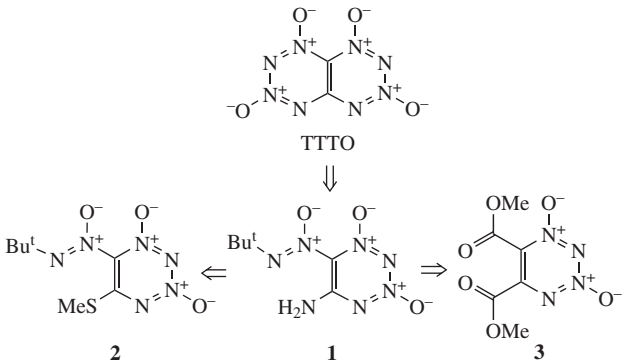
This article covers recently developed by the authors and other research teams prospective syntheses of specific types of organic *N*-oxides (1,2,3,4-tetrazine 1,3-dioxides, 1-alkoxytriazene 2-oxides and 1,2,5-oxadiazole 2-oxides) that possess useful to pharmacology NO-donor ability and, simultaneously, can be potentially used as 'explosophores' in many energetic materials. Modern approaches to stereo- and enantioselective synthesis of aliphatic nitro compounds and their synthetically useful derivatives (nitronates) as versatile precursors to most active enantiomers of important medications are considered.

Design and preparation of 1,2,3,4-tetrazine 1,3-dioxides

Unsaturated cyclic compounds with alternated nitrogen atoms and *N*-oxide fragments are currently considered as perspective high energy density materials. Unique polynitrogen heterocycles, 1,2,3,4-tetrazine 1,3-dioxides (TDOs), developed by A. M. Churakov, S. L. Ioffe and V. A. Tartakovsky pertain to such systems.[6]

A number of theoretical studies were performed over the past decade to cover both non-annulated[7] and annulated TDOs,[8] with tetrazino-tetrazine 1,3,6,8-tetraoxide (TTTO) being the most energetically reach compound[9] (Scheme 1). According to calculated data, TTTO should have heat of formation about 206 kcal mol^{-1}, density 1.98 g cm^{-3}, estimated detonation velocity 9.71 km s^{-1} and detonation pressure 432 kbar, which ranks it together with the most powerful known explosives.[9(c)]

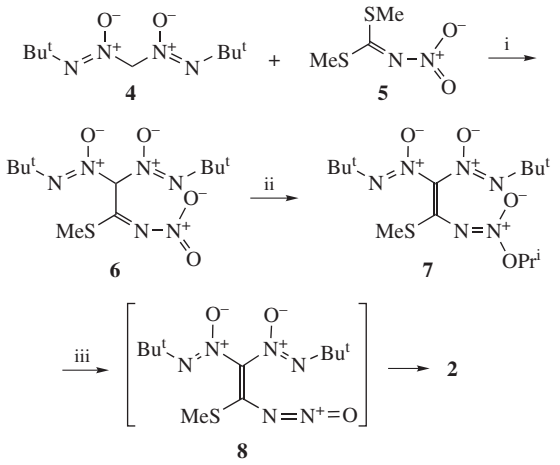
However, a synthesis of this interesting compound has not been reported so far. According to retro-synthetic analysis (see Scheme 1), the TTTO could be obtained from TDO **1**, which in turn could be derived from TDOs **2** or **3**. Though, the synthesis of TDOs **2** and **3** is a chemical challenge itself.[10]



Scheme 1

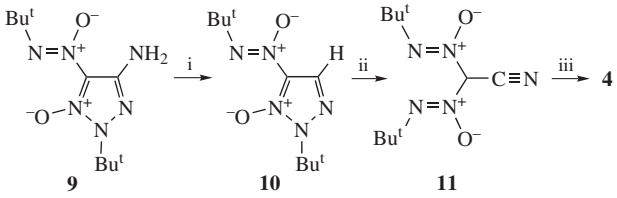
Recently, a novel strategy for the synthesis of TDO **2**, which employed bisazoxymethane **4** as a key starting material, has been developed.[10(a)] The synthetic scheme included coupling of **4** with nitroimidodithiocarbonate **5** followed by a reaction of the Ag salt of nitroimine **6** with 2-bromopropane and cyclization of O-alkylated product **7** to TDO **2** under the action of $BF_3{\cdot}Et_2O$ (Scheme 2). Presumably, this cyclization proceeds *via* the formation of intermediate oxodiazonium ion **8** and this is the first reported intramolecular reaction of aliphatic oxodiazonium ion.

Implementation of this scheme was complicated by the absence of a convenient synthetic route to aliphatic compounds with two



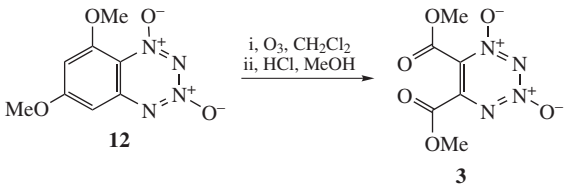
Scheme 2 *Reagents*: i, NaH, MeCN; ii, Bu^{t}OK, then $AgNO_3$, then Pr^{i}Br; iii, $BF_3{\cdot}Et_2O$.

geminal Alk-NNO-azoxy groups. Therefore, the authors had to develop an original approach to the synthesis of starting bisazoxymethane **4**, which included deamination of aminotriazole **9**, ring opening of triazole **10** and hydrolysis of the cyano group in compound **11** (Scheme 3).



Scheme 3 *Reagents*: i, $NaNO_2$, AcOH; ii, LDA, THF; iii, KOH, H_2O.

The proposed synthesis of compound **3**, which is another key precursor to TTTO **1**, was based on a scission of the benzene ring in benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs). It may be achieved by a thermolysis of (polyazido)benzotetrazine-1,3-dioxides.[10(b)] However, very recently, the same research group suggested an alternative procedure, which includes ozonolysis of BTDO bearing electron-donating groups, *e.g.*, 6,8-dimethoxy-BTDO **12**.[10(c)] Unexpectedly, the reaction of compound **12** with ozone in CH_2Cl_2 proceeded selectively and afforded oxidation product (most likely, corresponding trioxolane) bearing tetrazine 1,3-dioxide cycle. Acidic treatment of the latter resulted in TDO **3** (Scheme 4). This compound is rather stable (decomposition point, ~190 °C) and can be used as a precursor to a number of new non-annulated and annulated TDOs.

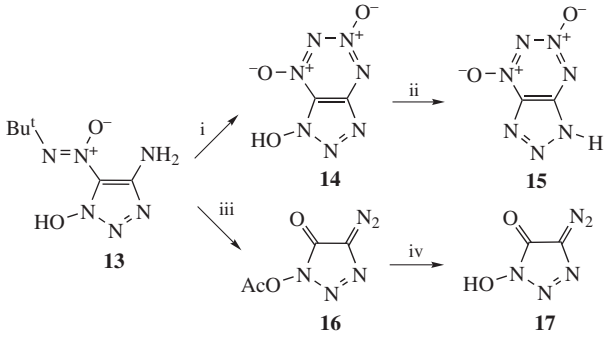


Scheme 4

Being perspective high energy compounds, TDOs are interesting as a new class of NO donors.[11] BTDO 5- and 7-nitro derivatives are effective thiol-dependent activators of soluble guanylate cyclase.[12] They also show the hypotensive activity and reduce the activity of caspase-3. The parent BDTO and its 6-, 7-bromo and 6,7-dibromo derivatives were identified as inhibitors of ADP-induced aggregation of human platelets and exhibited antimetastatic properties.[13] Furthermore, the 6- and 7-bromo-BTDOs

irreversibly and selectively inhibit activity of H,K-adenosine triphosphatase in microsomal fraction of stomach mucosa.[14]

Recently a synthesis of TDO **14**, which is the first TDO annulated with 1-hydroxy-1,2,3-triazole ring, has been developed[15] (Scheme 5). The procedure is based on oxidative cyclization of aminotriazole **13** with a mixture of HNO_3 and H_2SO_4. The reaction course depended on the acid ratio. The desired TDO **14** was attained at HNO_3/H_2SO_4 molar ratio 1:2. However, when HNO_3/H_2SO_4 molar ratio was changed to 2:1, the reaction afforded O-acetylated diazo compound **16**, which could be hydrolyzed to diazo compound **17**.† Selective reduction of TDO **14** with PCl_3 resulted in TDO **15** – a perspective platform for designing a series of derivatives for biological testing.[16]



Scheme 5 *Reagents*: i, Ac_2O, HNO_3/H_2SO_4 (1:2); ii, PCl_3; iii, Ac_2O, HNO_3/H_2SO_4 (2:1); iv, H_2O.

Synthesis of (methylene)bis(1-oxy-1-triazene 2-oxides) and their analogues

(Methylene)bis(1-oxy-1-triazene 2-oxides) and their isomers represent a specific group of 1-hydroxy-1-triazene 2-oxide derivatives. The latter are considered as promising nitric oxide donors within living organisms and have been extensively studied over the last decades with the aim of synthesizing medications for the treatment of cardiovascular and renal diseases, cancer, lung insufficiency or diabetes.[17] Furthermore, due to relatively high enthalpies of formation and the presence of so-called 'active oxygen', 1-hydroxy-1-triazene 2-oxide derivatives may be of practical interest as components of energetic blends.

Over 400 papers and patents on the synthesis and bioactivity of 1-hydroxy-1-triazene 2-oxide derivatives,[18] including 3-substituted functional derivatives,[19] have been published, some of them quite recently.

(Methylene)bis(1-oxy-1-triazene 2-oxides) **A** and isomeric analogues **B**–**D** bearing two linked by a methylene group and arranged in various combinations 1-oxy-1-triazene 2-oxide structural fragments are of particular interest as they are potentially capable of releasing larger amount of nitric oxide per molecule than corresponding compounds containing just one 1-hydroxy-1-triazene 2-oxide group (Figure 1).

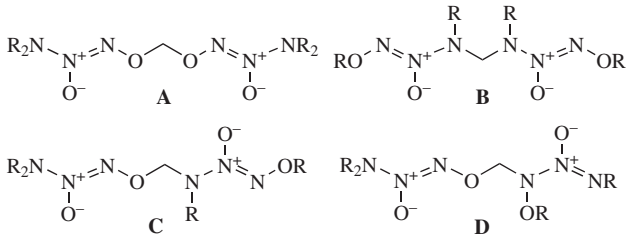
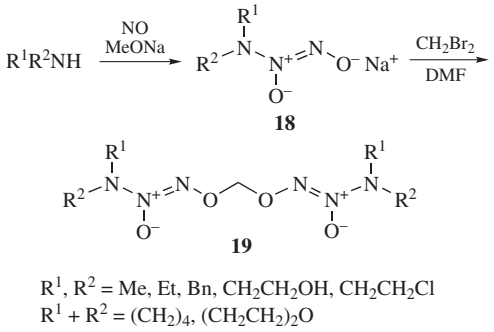


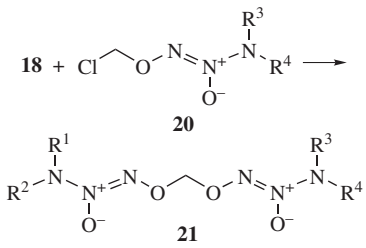
Figure 1

The first representatives of (methylene)bis(1-oxy-1-triazene 2-oxides) **19** (compounds of type **A**) have been recently synthesized in moderate yields (up to 30%) by a reaction of 1-hydroxy-3,3-disubstituted-1-triazene 2-oxide sodium salts **18** with dibromomethane in DMF (Scheme 6).[20,‡] Starting salts **18** were readily obtained by treatment of corresponding secondary amines with NO under basic conditions.



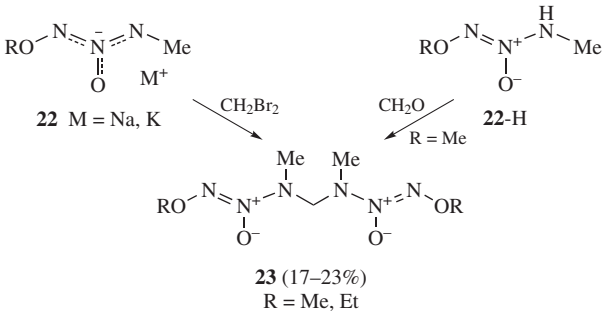
Scheme 6

Non-symmetric compounds **21** were prepared in two steps through the intermediate 1-chloromethoxy-1-triazene 2-oxides **20** followed by their reaction with salts **18** (Scheme 7).[20] This scheme is also suitable for the synthesis of symmetric compounds **21** ($R^1 = R^3$, $R^2 = R^4$). Moreover, the yields of synthesized products were usually 1.5–2 times higher than the yields of similar compounds **19** prepared from **18** and dibromomethane.



Scheme 7

Interestingly, alkali metal salts of 1-alkoxy-3-methyl-1-triazene 2-oxide **22** reacted with dibromomethane in DMF affording N-alkylation products **23**, which have not been reported so far (Scheme 8).‡ Compound **23** (R = Me) also formed in the reaction of 1-methoxy-3-methyl-1-triazene 2-oxide **22**-H with paraformaldehyde in the presence of catalytic amounts of weak bases, such as potassium carbonate.

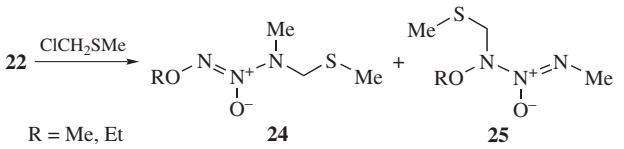


Scheme 8

† A. A. Voronin, A. M. Churakov, I. V. Fedyanin, V. P. Zelenov and V. A. Tartakovsky, *Russ. Chem. Bull., Int. Ed.*, 2015, in press.

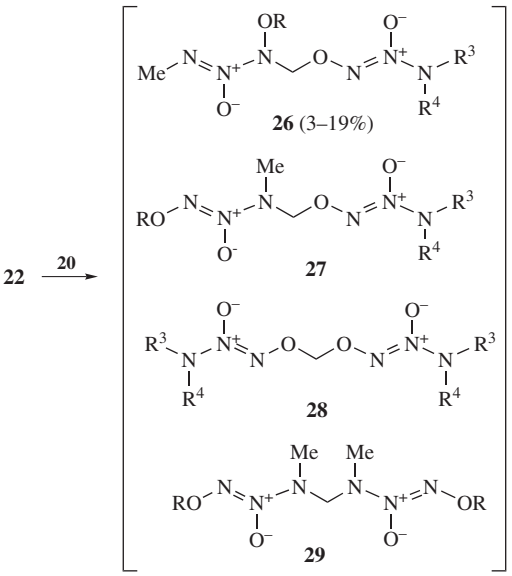
‡ G. A. Smirnov, P. B. Gordeev, S. V. Nikitin, T. V. Ternikova, G. V. Pokhvisneva and O. A. Luk'yanov, *Russ. Chem. Bull., Int. Ed.*, 2015, in press.

Unexpectedly, similar reactions of ambident 1-alkoxy-3-methyl-1-triazene 2-oxide salts **22** with chloromethyl sulfide proceeded in a less selective manner affording a mixture of regioisomeric N-alkylation products **24** and **25** in the 2:1 molar ratio[§] (Scheme 9). The exact chemical structure was unambiguously assigned to isomers **24** and **25** based on the 2D NOESY NMR.



Scheme 9

Reactions of **22** with 1-chloromethoxy-1-triazene 2-oxides **20** furnished even more complex mixtures of products. Along with anticipated intermolecular N-alkylation products **26** and **27** which formed in modest yields, symmetric compounds **28** and **29** were also generated in this case (Scheme 10). Obviously, further optimization of reaction conditions is required to improve product yields and selectivity of the reaction.



Scheme 10

Novel approaches to 1,2,5-oxadiazole 2-oxides (furoxans)

An important class of cyclic polynitrogen compounds bearing *N*-oxide moiety and capable of releasing NO is 1,2,5-oxadiazole 2-oxides (furoxans)[21] and benzofuroxans.[22] A significant impact on the furoxan chemistry was made by Khmel'nitskii with co-authors.[23] Over the past decade, the design of bioactive furoxans has been focused on the development of hybrid molecules[24] which combine several pharmacophoric structural fragments.[25] This research strategy was pioneered by Gasco and has recently resulted in preparation of several promising compounds (Figure 2).[26]

At the same time, furoxan derivatives attract considerable attention as high energy compounds due to a positive enthalpy of formation and the presence of active oxygen atoms in the furoxan ring (Figure 3).[27]

Over the past decade, Makhova with co-authors significantly contributed to modern chemistry of both energetic (amino-, nitro-, azo-, azoxy-substituted)[28] and NO-donor furoxan derivatives.[29] A series of novel hybrid structures, containing pharmacophoric

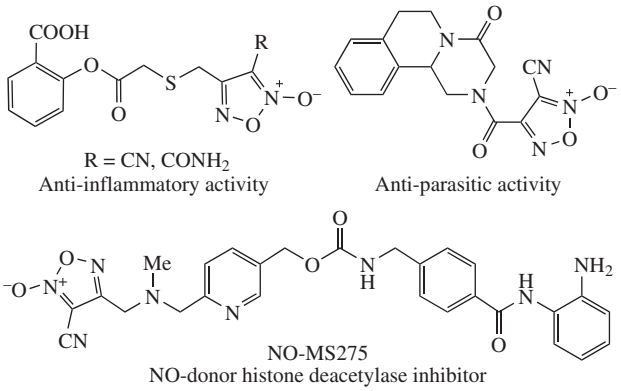


Figure 2

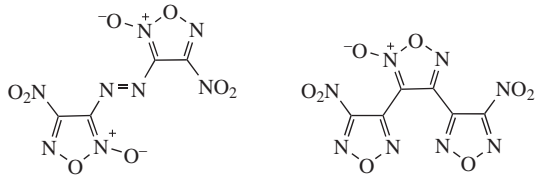
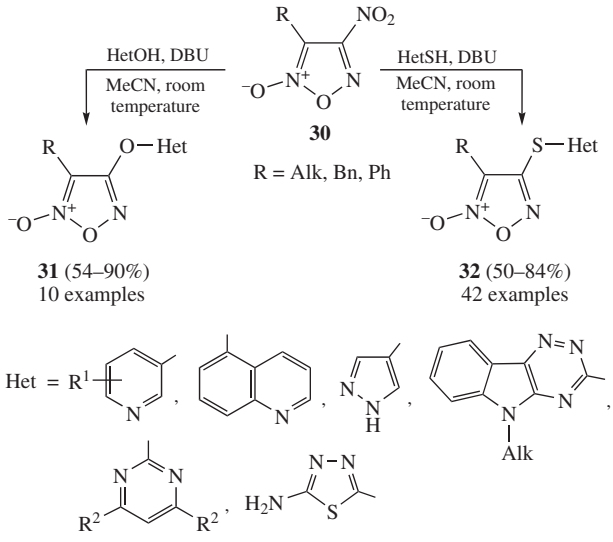


Figure 3

and/or energy rich polynitrogen heterocycles (1,2,3- and 1,2,4-triazoles, 1,2,4-oxadiazoles, tetrazole, *etc*.) attached to furoxan ring either directly or by means of a heteroatom (S or O) have been recently synthesized. The research strategy was based on two complementary synthetic approaches. The first approach included nucleophilic substitution of the nitro group in nitrofuroxans **30** to prepare mercapto, oxyazole or azido derivatives. The second one was based on versatile transformations of the cyano group in cyanofuroxans to afford various polyheterocyclic compounds.

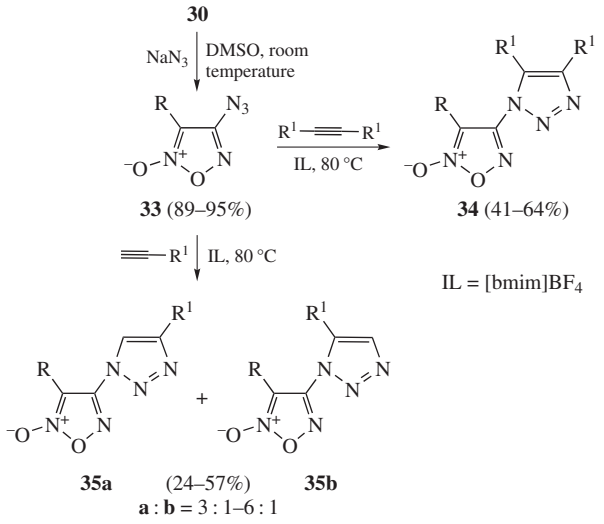
Successful realization of the first approach made it possible to efficiently synthesize so far unknown heterocyclic systems **31** and **32** containing a 3-substituted furoxan ring linked to pharmacophoric heterocyclic fragment *via* the oxygen or sulfur atoms (Scheme 11).[30]



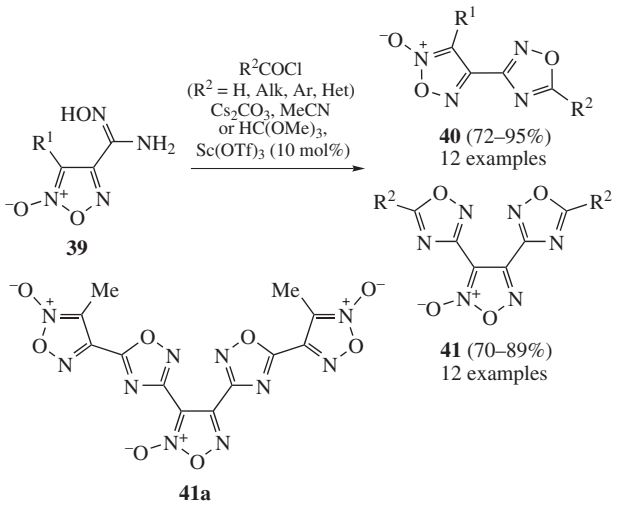
Scheme 11

Furthermore, 4-nitrofuroxans **30** readily reacted with sodium azide to afford 4-azidofuroxans **33**. The latter underwent [3+2]-cycloaddition to internal or terminal acetylenes in ionic liquid

[§] G. A. Smirnov, P. B. Gordeev, S. V. Nikitin, Yu. A. Strelenko, T. V. Ternikova, G. V. Pokhvisneva and O. A. Luk'yanov, *Russ. Chem. Bull., Int. Ed*., 2015, in press.



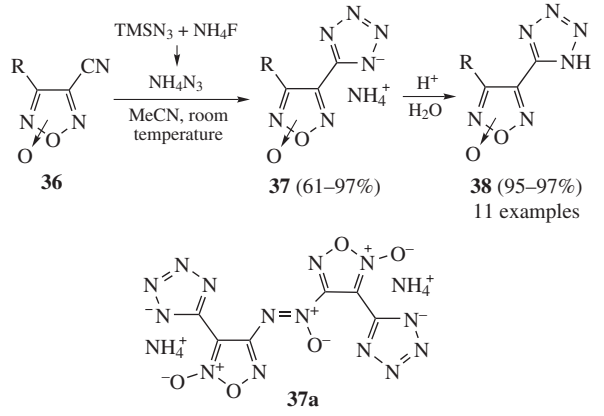
Scheme 12



Scheme 14

media producing corresponding (1*H*-1,2,3-triazol-1-yl)furoxans **34** and **35a**,**b** in moderate yields but with relatively high regioselectivity (in case of terminal acetylenes) (Scheme 12).[31]

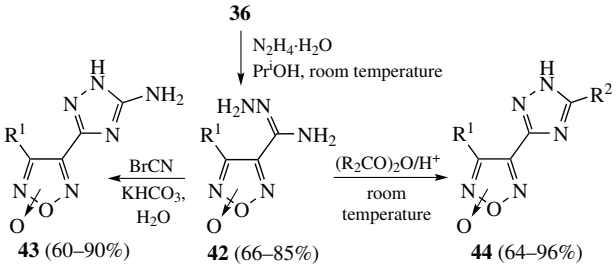
Cyanofuroxans **36** and their derivatives (amidoximes, amidrazones) appeared even more versatile synthetic building blocks. [3+2]-Cycloaddition of **36** to ammonium azide, generated *in situ* from $TMSN_3$ and NH_4F, is a general, facile and effective straightforward synthesis of (1*H*-tetrazol-5-yl)furoxan ammonium salts **37** (Scheme 13).[32] The method is also suitable for the preparation of the corresponding NH-acids **38** by acidification of **37** in aqueous medium. Thus obtained (1*H*-tetrazol-5-yl)furoxan ammonium salts, in particular compound **37a**, possess a high enthalpy of formation and promising density and may be useful as perspective components of energetic formulations.



Scheme 13

The cyanofuroxan-derived furoxanylamidoximes **39** proved to be suitable starting compounds for the synthesis of novel heterocyclic systems incorporated mono- and bis(1,2,4-oxadiazol-3-yl)furoxan cores.[33] Compounds **39** react with aliphatic, aromatic or heterocyclic carboxylic acid chlorides under the mild conditions (Cs_2CO_3, MeCN, 20 °C) to afford prolonged ensembles **40** or **41** containing up to five linked heterocycles in one molecule (see, for example, compound **41a**) (Scheme 14). Furthermore, a solvent-free approach to (1,2,4-oxadiazol-3-yl)furoxans **40** or **41** (R^2 = H) has been developed, which is based on the $Sc(OTf)_3$-catalysed reaction of **39** with the trimethyl orthoformate. The advantages of step economy and wide scope make these reactions a powerful tool for assembling heterocyclic scaffolds for high energy chemistry and biomedical applications.

Furthermore, cyanofuroxans **36** can be readily transformed to synthetically useful amidrazones **42**. The latter react with BrCN or acetic (trifluoroacetic) anhydrides under mild conditions leading to scarcely known (1*H*-1,2,4-triazol-3-yl)furoxans **43** and **44** in high yields and with remarkable selectivity (Scheme 15).[34]

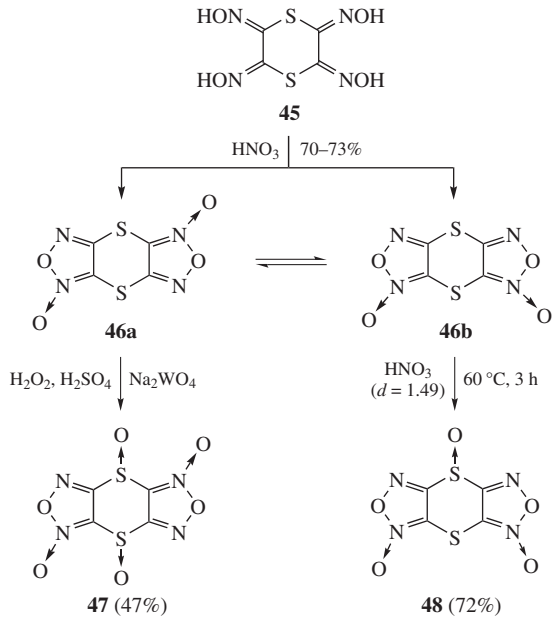


R^1 = 3-Me, 4-Ph, 3-CN, 4-NH_2, 4-AcNH
R^2 = Me, CF_3

Scheme 15

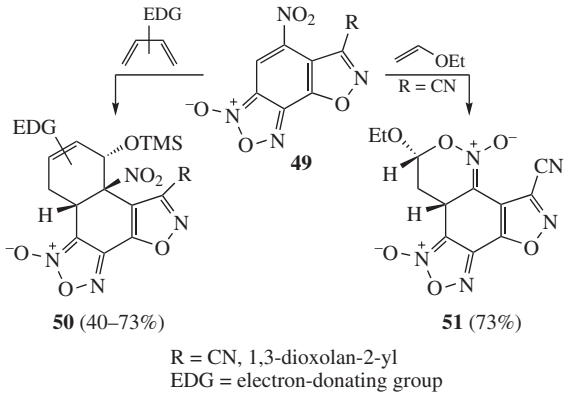
Fused furoxan derivatives, which incorporate several furoxan fragments, are attractive as potential NO-donors for pharmacological applications. Recently, Rakitin with co-authors succeeded in synthesizing novel furoxan-containing N-O-S hybrid systems from 1,4-dithiane-2,3,5,6-tetraone tetraoxime **45**.[35] A treatment of compound **45** with nitric acid afforded [1,4]dithiino[2,3-*c*:5,6-c′]-bis[1,2,5]oxadiazole di-*N*-oxide as an equilibrium mixture of isomers **46a** and **46b**. Surprizingly, these isomers exhibited quite different reactivity in S-oxidation reactions. Compound **46a** produced *S*,*S*-dioxide **47** under the action of persulfonic acid, whereas in the reaction of isomer **46b** with concentrated nitric acid *S*-oxide **48** was regioselectively generated under drastic conditions (Scheme 16).

Another prospective approach to pharmacologically relevant polycyclic furoxan derivatives has been recently suggested by Shevelev and Dalinger with co-workers utilizing nitrofuroxanobenzo[*d*]isoxazoles **49**.[36] Heterocycles **49**, which incorporate electron-deficient nitrovinyl group, appeared capable of acting as dienophiles or heterodienes (Scheme 17). Excellent opportunities of the first reaction mode was elegantly demonstrated by the Diels–Alder reactions of **49** with electron-rich dienes to afford cycloadducts **50** in moderate to high yields. The alternative pathway was accomplished in the reaction of **49** with ethyl vinyl ether, where densely functionalized compound **51** bearing two *N*-oxide fragments was generated as the major product. The obtained compounds, which combine in one molecule several useful pharmaco-



Scheme 16

phore fragments (NO-donor furoxan ring and substituted isoxazole unit), may be considered as promising platforms for the design of compounds with dual biological activity.



Scheme 17

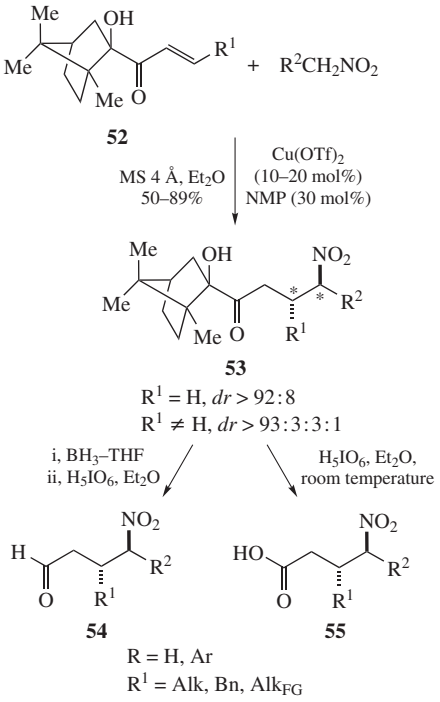
In vitro biological testing of hetarylfuroxans considered above showed that some of them exhibit a pronounced cytotoxic activity. Studies aimed at the synthesis of new furoxan-derived pharmacologically-oriented heterocyclic scaffolds and prospective energy rich compounds for energetic formulations are currently underway in aforementioned research groups.

Stereo- and enantioselective synthesis and transformations of nitro compounds

Nitro compounds represent a very important class of organic compounds which are extensively applied as key components of explosives, propellants and powders.[1] Furthermore, a number of *O*- and *N*-nitro compounds exhibit useful biological activities as NO-donors[3(*b*),17(*a*),37] that persistently inspires researchers to develop novel methods of their preparation.[38] Corresponding researches in the area of high energy *C*-nitro compounds, in particular, aliphatic nitro compounds, have also been carried out for decades.[39] However, unique potential of functionalized nitroalkanes for medicinal chemistry had not been clearly recognized for a long time and has become a subject of growing interest just over the past decade.[40] Their availability along with versatile reactivity make them valuable intermediates in stereoselective synthesis of nitrogen-containing pharmacologically relevant substances.[41] In this section recent advances in stereo- and enantioselective synthesis and pharmacology-oriented transformations of nitroalkanes and their derivatives are outlined.

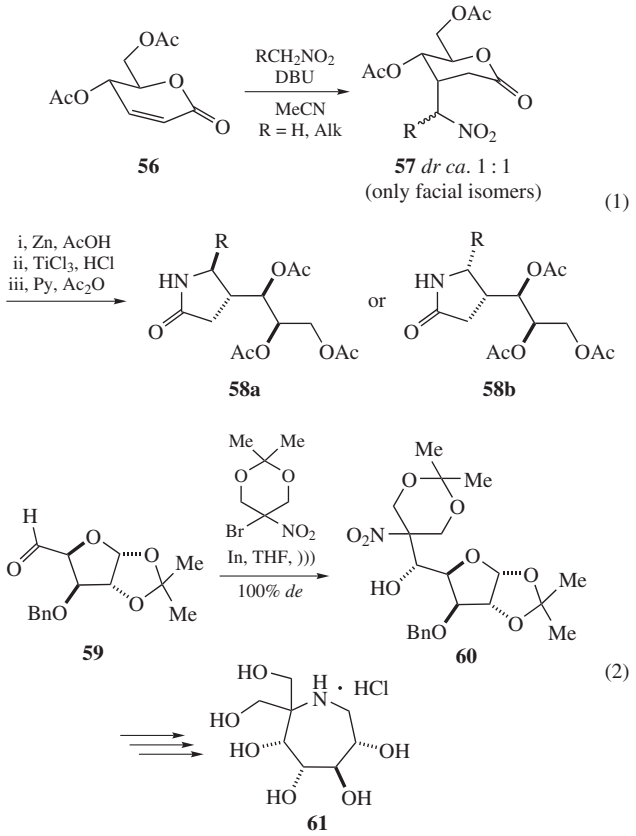
The nitroalkanes are commonly considered as α-C-nucleophilic synthons due to their significant C–H acidity and facile generation of nitronate-anions by deprotonation. In the presence of organic (amines) or inorganic bases nitroalkanes readily react with various electrophiles such as aldehydes, Schiff bases and Michael acceptors. In case of prochiral nitroalkanes and electrophiles at least one new stereogenic center is formed as a result of Ad_N addition leading to mixtures of stereoisomeric products. By employing electrophiles bearing chiral auxiliary groups or performing the reactions in the presence of chiral organocatalysts enantiomerically and diastereomerically pure adducts can be accessed.

An indicative example of the chiral auxiliary approach is $Cu(OTf)_2$-catalysed addition of nitroalkanes $R^1CH_2NO_2$ to camphor-derived α,β-unsaturated ketones **52** (Scheme 18).[42] This transformation leads to the corresponding γ-nitro ketones **53** with a high degree of stereoinduction in the formation of stereo center bearing the nitro group. β-Substituted α,β-unsaturated ketones **52** ($R^1 \neq H$) stereoselectively produce *anti*-isomers of nitroadducts **53** in good yields. Subsequent oxidative cleavage of camphor auxiliary group with H_5IO_6 affords enantiopure γ-nitro aldehydes **54** or γ-nitro acids **55**, which are important building blocks in the synthesis of various bioactive molecules.



Scheme 18

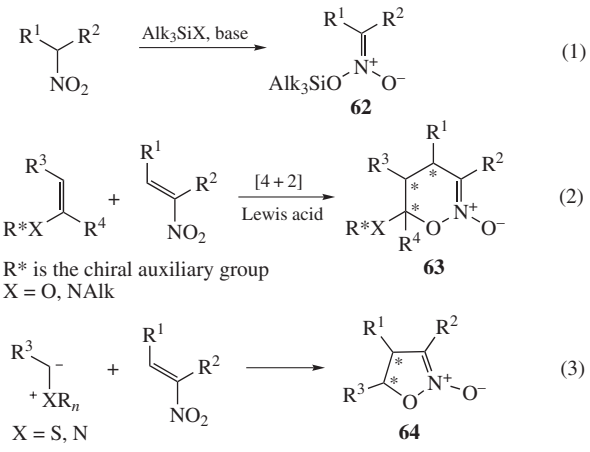
Sugar-derived electrophiles are also convenient substrates for stereoselective synthesis of enantiopure nitro compounds.[43] In particular, an elegant synthesis of isomeric enantiomerically pure polyhydroxylated pyrrolidones **58a** and **58b** from α,β-unsaturated δ-lactone **56** (derived from 3,4,6-tri-*O*-acetyl-D-glucal) was developed by Li and Meng [Scheme 19, equation (1)].[43(*a*)] In this process, δ-lactone **56** reacted with simple nitroalkanes in the presence of DBU to produce a separable mixture of diastereomeric nitro sugars **57** (facial isomers) differing in the configuration of carbon atom bounded with the nitro group. Reduction of these products with zinc followed by treatment of the resulting hydroxamic acids with $TiCl_3$ and acetylation of the remaining OH group provided enantiomerically pure lactams **58a** and **58b**.



Scheme 19

Similarly, condensation of sugar-derived aldehydes of type **59** with α-bromonitroalkanes in the presence of indium [Scheme 19, equation (2)] affords the corresponding nitro alcohols **60** with high *anti*-selectivity.[43(b)] Compound **60** is a key precursor to branched polyhydroxylated azepam **61**, which is a glycosidase inhibitor.

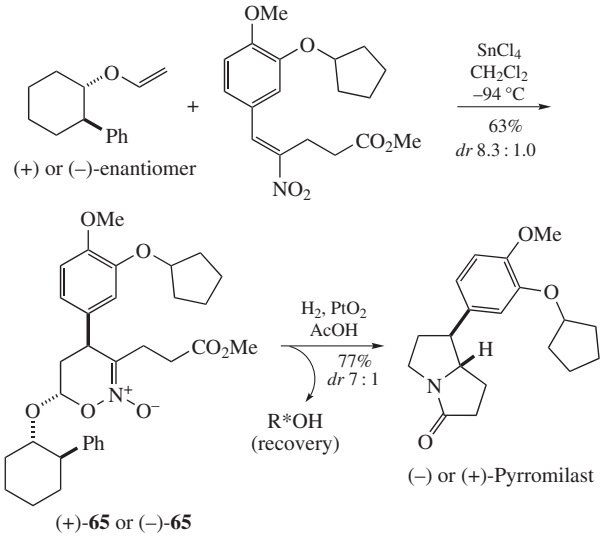
The synthetic potential of nitroalkane-derived nitronates has been a matter of considerable interest in the recent years.[44] Acyclic silyl nitronates **62** are readily available by silylation of the corresponding nitroalkanes [Scheme 20, equation (1)]. Cyclic nitronates are usually synthesized from nitroolefins by [4+2]-cycloaddition to electron-rich alkenes [six-membered nitronates **63**, Scheme 20, equation (2)][45] and by [4+1]-cycloaddition with ylides or their equivalents[46] [five-membered nitronates **64**, Scheme 20, equation (3)]. High stereocontrol in the [4+2]-cycloadditions is achieved by employing alkenes with chiral auxiliary groups (*e.g.*, chiral enamines or vinyl ethers),[45(a),(b)] while asymmetric [4+1]-cycloadditions require the use of either chiral ylides[46(a)] or chiral organocatalysts.[46(b)]



Scheme 20

Nitronates exhibit diverse reactivity. In some transformations they serve as α-C-nucleophiles thus behaving as synthetic equivalents of corresponding nitroalkanes. In particular, asymmetric Henry-type[47] and Michael reactions[48] of silyl nitronates **62** are useful tools for the preparation of optically pure functionalized aliphatic nitro compounds.

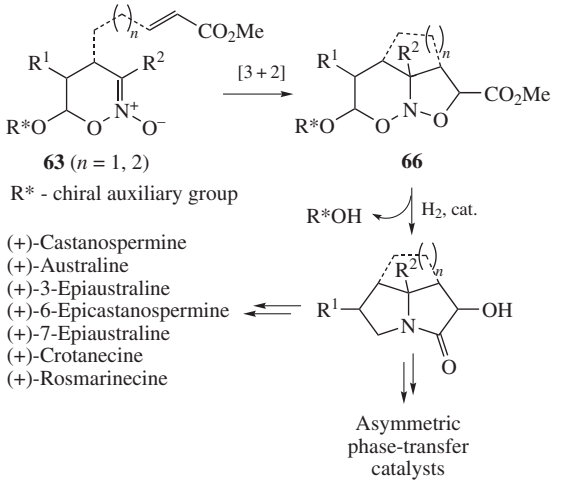
Similar to nitroalkanes, reduction of nitronates can be considered as a route to amines. In this context, cyclic nitronates offer additional opportunities for the ring-formation reactions. Thus, reduction of six-membered cyclic nitronates bearing a chiral alkoxy group in the position C-6 (*e.g.*, **65**, Scheme 21) leads to pyrrolidines *via* a multi-step domino process. Recently, this approach was used by Sukhorukov and Ioffe with co-authors in an elegant stereoselective asymmetric synthesis of highly potent type IV phosphodiesterase inhibitor Pyrromilast.[49]



Scheme 21

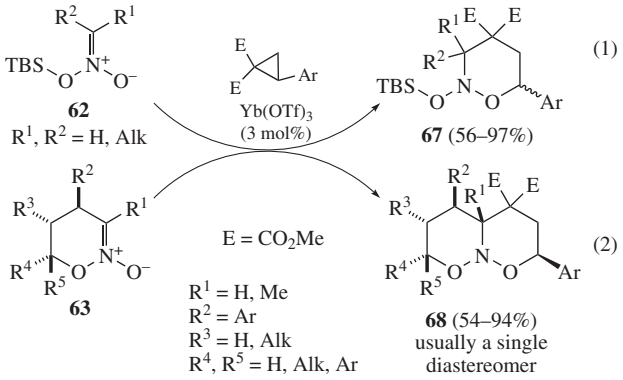
In spite of obvious similarity, some aspects of nitronates reactivity, in particular their ability to participate in cycloaddition reactions, differ them from nitroalkanes. Stereoselective [3+2]-cycloaddition of nitronates **63** to olefins followed by reduction of the resulting five-membered cyclic nitroso acetals **66** developed by Denmark have proven to be an efficient strategy for the synthesis of various alkaloids and polycyclic amine-derived asymmetric phase-transfer catalysts (Scheme 22).[45(a),(b)]

An extension of this strategy is the recently developed [3+3]-cycloaddition of nitronates **62** and **63** to donor–acceptor cyclo-



Scheme 22

propanes to afford six-membered cyclic nitroso acetals **67** and **68**, which may be considered as intermediates in the synthesis of bioactive functionalized amines bearing several contiguous stereogenic centers (Scheme 23).[50]

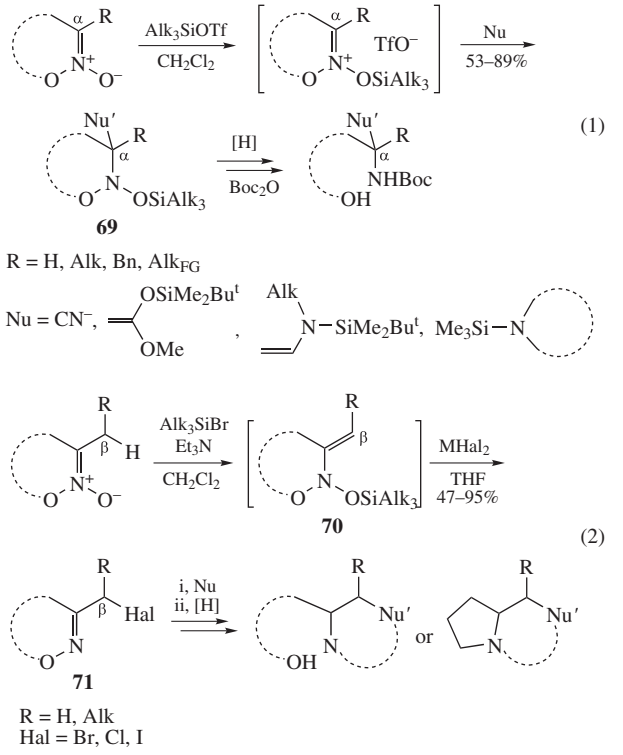


Scheme 23

Since nitronate group is isoelectronic to carbonyl one, some aspects of nitronate chemistry mimic the reactivity of carbonyl compounds.[51] Thus, nitronates easily react with σ- and π-nucleophiles in the presence of silyl Lewis acids thus behaving as α-C-electrophiles [Scheme 24, equation (1)].[51(c),(d)] The resulting nitroso acetals **69** are formed with high stereoselectivity. Reduction of the latter opens access to functionalized amines with a quaternary stereogenic center.

Furthermore, C–H functionalization of β-carbon atom in nitronates can be achieved by their silylation to bis(oxy)enamines **70** followed by treatment with metal halides to access cyclic or acyclic halo-oxime ethers **71** [Scheme 24, equation (2)].[52] Replacement of halide with nucleophile and subsequent stereoselective reduction of the oxime group provide a route towards bioactive amino acids, amino alcohols, pyrrolidines, γ-pyrrolidones, *etc*.[53]

A remarkable level of enantiocontrol has been recently delivered to asymmetric synthesis, in particular, to the synthesis of aliphatic

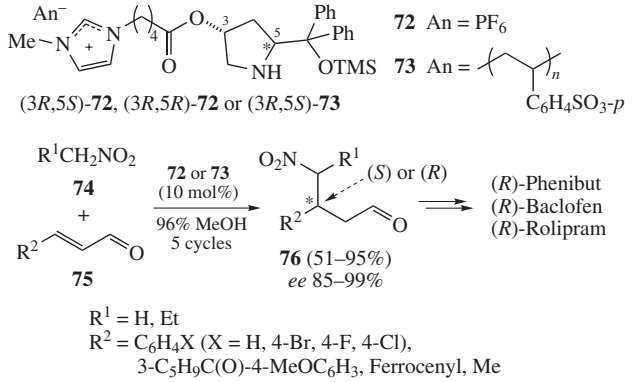


Scheme 24

nitro compounds,[40(a),54] by extensive application of novel catalytic methodologies. They are based on the use of small metal-free chiral organocatalysts (mainly, amines or their derivatives), which act as both activators and stereoinductors in the catalytic processes.[55] In the presence of these catalysts, asymmetric reactions of nitro alkanes with electrophiles or α-nitro olefins with nucleophiles commonly proceed under simple experimental conditions with very high diastereo- and enantioselectivity affording biologically useful functionalized nitro compounds. In particular, valuable analogues of important natural neurotransmitter γ-aminobutyric acid (GABA), that are used in clinics as antidepressants and anticonvulsant drugs (*e.g.*, phenibut,[56] baclofen,[57] pregabaline,[58] *etc*.) were synthesized in highly enantioselective manner. Moreover, organocatalysts allow one to perform facile synthesis of functionalized nitro compounds, which are precursors to important enzyme inhibitors – perspective drugs or drug candidates for treatment of serious diseases. Among enantioselectively prepared in this way bioactive molecules are: a type IV phosphodiesterase inhibitor rolipram (for curing chronic obstructive lung decease),[59] neuraminidase inhibitor oseltamivir (for treatment of type A and type B human influenza),[60] dipeptidyl peptidase IV inhibitor (a drug candidate for treatment of type 2 diabetes mellitus),[61] p53/MDM2 inhibitor nutlin-362 (anticancer remedy)[62] and CYP51 inhibitor VNI63 (efficient against acute Chagas infection).[63] Furthermore, a number of other bioactive compounds of natural or synthetic origin, in particular, various alkaloid derivatives,[64] cardiovascular remedy trandolapril,[65] anti-HIV drug DPC 083,[66] antifungal drug sulconazole,[67] antidepressant venlafaxine,[68] and some others useful molecules,[69] can be selectively prepared *via* the substituted nitro compounds.

Unlike organometal catalysts, organocatalysts do not contaminate products with toxic heavy metals and that is important in terms of medicinal chemistry.[5(a),(b),70] However, in some cases, they can bring about hardly separable and potentially dangerous organic impurities. To facilitate product purification and recovery of precious chiral catalysts, immobilized forms of organocatalysts tagged to polymers[71] or ionic groups[72] have been designed. These groups significantly reduce solubility of a catalyst in organic and/or aqueous phases and facilitate its recovery. Furthermore, in some cases a supporting group allows for tuning catalytic performance of the hybrid catalyst to attain maximal catalytic efficiency.

A perspective class of supported organocatalysts is represented by compounds **72** and **73** bearing O-silylated α,α-diphenyl (*S*)- or (*R*)-prolinol units tagged to the imidazolium cation accompanied by the PF_6[73] or a sulfated polystyrene anion,[74] respectively. Chiral amines **72** and **73** effectively catalyse asymmetric Michael additions of nitroalkanes **74** to α,β-enals **75**, which proceed *via* an iminium ion formation step, to afford (*S*) or (*R*)-enantiomers of γ-nitroaldehydes **76** in high yields (up to 95%) and with up to



Scheme 25

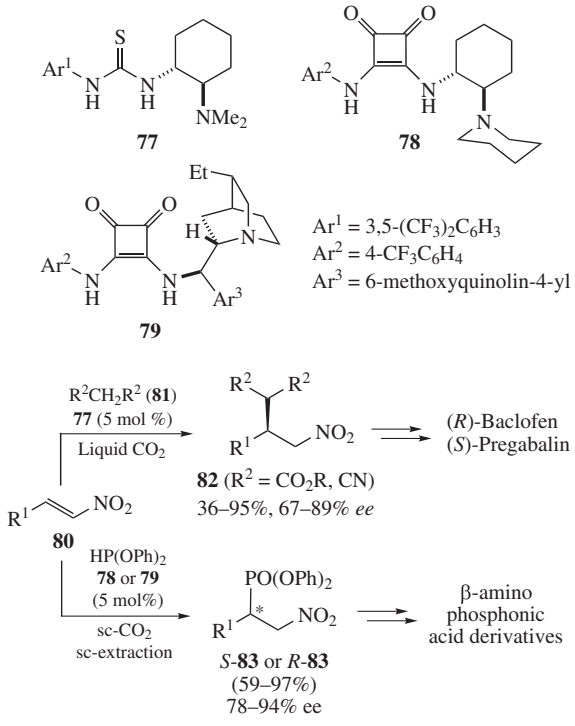
99% *ee*. Compounds (*R*)-**76** can be readily converted to most active antipodes of phenibut, baclofen, and rolipram (Scheme 25).

However, in the presence of atmospheric oxygen, active lifetime of both catalysts in catalytic reactions was limited by five reaction/regeneration cycles. A careful study of deactivation pathways of catalyst (3*R*,5*S*)-**72** by the electrospray ionization mass spectrometry (ESI-MS) made it possible to reveal undesirable oxidative side-reactions that destroyed the catalyst and propose an efficient approach (argon atmosphere) to extend its operation period.[75]

Very recently, a series of novel efficient and sustainable chiral diamine-derived organocatalysts of asymmetric aldol, Michael and Mannich-type reactions have been synthesized by Zlotin with co-workers.[76] It is hoped that some of these catalysts would be useful for enantioselective syntheses of pharmacologically valuable nitro compounds.

Another perspective approach to enantioselective synthesis of functionalized nitro compounds is based on performing catalytic reactions in liquid or supercritical (sc) carbon dioxide. This abundant and non-toxic 'green' solvent is produced from renewable natural (plants) and industrial (burning of fuels) sources, and, providing facile removal and recycling, is likely to be a prospective medium for future chemical processes.[77] In the presence of bifunctional tertiary amine-thiourea catalyst **77** (5 mol%) nitro olefins **80** enantioselectively reacted with CH acids **81** (dialkyl malonates, malononitrile or anthranone) in liquid CO_2 to afford corresponding enantioenriched Michael adducts **82**.[78] As a rule, yields and *ee* values of adducts **82** in the CO_2 medium were comparable with those in organic solvents (toluene) or even higher. Some of the prepared compounds are precursors to chiral medications baclofen and pregabalin (Scheme 26). The method is scalable and environment friendly: after the decompression, the products and the catalyst can be routinely isolated from the residue and volatile carbon dioxide can be, if necessary, recycled.

The CO_2 medium appeared useful in asymmetric catalytic additions of P-nucleophiles to nitro olefins **80**. The best results were attained in the supercritical state in the presence of tertiary amines **78** or **79** bearing an H-bonding squaramide unit.[79] Both enantiomers of β-nitrophosphonates **83**, which are precursors to bioactive β-aminophosphonic acid antipodes, were stereodivergently prepared in high yields and with promising enantioselectivity using catalysts **78** or **79** (see Scheme 26). Importantly, sc-CO_2 may serve not only as a prospective medium for the studied reaction, but also as a substitute for organic solvents during the work-up. Nitro compounds **83** were isolated by the fractional extraction with sc-CO_2 from the reaction mixture and remaining catalyst **78** was recycled. The obtained results contribute to green chemistry as they eliminate toxic organic solvents originated from exhausting hydrocarbon resources and facilitate separation and purification steps that usually have the highest environmental impact in chemical processes.



Scheme 26

Conclusions

Organic nitrogen–oxygen systems create a perspective and versatile platform for designing new pharmaceutical ingredients and high energy materials. Among useful compounds of this type, 1,2,3,4-tetrazine 1,3-dioxides, 1,2,5-oxadiazole 2-oxides (furoxans), 1-hydroxy-1-triazene 2-oxides and nitro compounds are capable of releasing nitric oxide (a crucial regulator for cellular metabolism) under physiological conditions, which makes them promising drug candidates for treating cardiovascular, inflammatory, bacterial, viral, and some other deceases. Furthermore, functionally substituted nitro alkanes are key precursors to valuable derivatives of GABA (an important neuromediator) and natural enzyme inhibitors, which are used as remedies for efficient treatment of socially important acute and chronic diseases. On the other hand, many representatives of nitrogen–oxygen systems possess a high enthalpy of formation and unique values of detonation velocity and pressure, which ranks them together with the most powerful components of energetic blends.

It is expected that further pharmacology-oriented investigations of these interesting versatile compounds will be aimed at the development of carefully designed pro-drug molecules capable of releasing a precisely controllable amount of nitric oxide as both deficit or excess of the latter might result in the evolution of serious pathologies. Highly efficient and applicable to pharmacology stereo- and enantioselective syntheses of functionalized nitro compounds and their derivatives (precursors to demanding drugs) still remains a challenge.

Prospective directions of high energy-oriented studies on organic nitrogen–oxygen systems include elaboration of efficient synthetic approaches to tetrazino-tetrazine 1,3,6,8-tetraoxide and prolonged heterocyclic scaffolds containing furoxan units. Most likely, novel explosion-safe and environment friendly technologies for industrial production of energy rich nitro compounds will be developed in the near future.

This work was supported by the Russian Science Foundation (grant no. 14-50-00126).

References

1 J. P. Agrawal and R. D. Hodgson, *Organic Chemistry of Explosives*, Wiley, Chichester, 2007.

2 (*a*) F. Furchgott, *Angew. Chem. Int. Ed.*, 1999, **38**, 1870; (*b*) F. Murad, *Angew. Chem. Int. Ed.*, 1999, **38**, 1856; (*c*) L. J. Ignarro, *Angew. Chem. Int. Ed.*, 1999, **38**, 1882.

3 (*a*) M. Willmot, L. Gray, C. Gibson, S. Murphy and P. M. Bath, *Nitric Oxide*, 2005, **12**, 141; (*b*) *Nitric Oxide Donors: For Pharmaceutical and Biological Applications*, eds. P. G. Wang, T. B. Cai and N. Taniguchi, Wiley-VCH, Weinheim, 2005; (*c*) R. Scatena, P. Bottoni, A. Pontoglio and B. Giardina, *Curr. Med. Chem.*, 2010, **17**, 61; (*d*) P. Krause, E. Waetzig, H. Acil, S. Koenig, K. Unthan-Fechner, D. Tsikas and I. Probst, *Nitric Oxide*, 2010, **23**, 220; (*e*) R. A. M. Serafim, M. C. Primi, G. H. G. Trossini and E. I. Ferreira, *Curr. Med. Chem.*, 2012, **19**, 386.

4 (*a*) *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, eds. J. G. Hardman, L. E. Limbird and A. G. Gilman, McGraw-Hill, New York, 2001; (*b*) *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*, eds. G. J. Siegel, R. W. Albers, S. Brady and D. Price, Academic Press, Elsevier, Boston, 2006.

5 (*a*) E. Marqués-López, R. P. Herrera and M. Christmann, *Nat. Prod. Rep*., 2010, **27**, 1138; (*b*) O. V. Maltsev, I. P. Beletskaya and S. G. Zlotin. *Russ. Chem. Rev*., 2011, **80**, 1067 (*Usp. Khim.*, 2011, **80**, 1119).

6 A. M. Churakov and V. A. Tartakovsky, *Chem. Rev.*, 2004, **104**, 2601.

7 (*a*) Q. Wu, Y. Pan, X. Xia, Y. Shao, W. Zhu and H. Xiao, *Struct. Chem.*, 2013, **24**, 1579; (*b*) F. Xiang, Q. Wu, W. Zhu and H. Xiao, *Can. J. Chem*., 2013, **91**, 1233; (*c*) Q. Wu, W. Zhu and H. Xiao, *J. Chem. Eng. Data*, 2013, **58**, 2748.

8 (*a*) B. Tan, M. Huang, H. Huang, X. Long, J. Li, F. Nie and J. Huang, *Propellants Explos. Pyrotech*., 2013, **38**, 372; (*b*) T. Wang, C. Zheng, J. Yang, X. Zhang, X. Gong and M. Xia, *J. Mol. Model*., 2014, **20**, 2261; (*c*) W.-P. Lai, P. Lian, Y.-Z. Liu, T. Yu, Z.-X. Ge and J. Lv, *J. Mol. Model*., 2014, **20**, 2479; (*d*) T. Wang, T. Zhang, L. Xu, X. Wu, X. Gong and M. Xia, *J. Mol. Model*., 2014, **20**, 2516.

9 (*a*) K. O. Christe, D. A. Dixon, M. Vasiliu, R. I. Wagner, R. Haiges, J. A. Boatz and H. L. Ammon, *Propellants Explos. Pyrotech*., 2015, **40**, 463; (*b*) K. R. Jorgensen, G. A. Oyedepo and A. K. Wilson, *J. Hazard. Mater*., 2011, **186**, 583; (*c*) P. Politzer, P. Lane and J. S. Murray, *Cent. Eur. J. Energ. Mater*., 2013, **10**, 37; (*d*) J. L. Mendoza-Cortes, Q. An, W. A. Goddard III, C. Ye and S. Zybin, *J. Comput. Chem*., 2015, **3**, DOI: 10.1002/jcc.23893.

10 (*a*) M. S. Klenov, O. V. Anikin, A. M. Churakov, Yu. A. Strelenko, I. V. Fedyanin, I. V. Ananyev and V. A. Tartakovsky, *Eur. J. Org. Chem.*, 2015, 6170; (*b*) A. Yu. Tyurin, A. M. Churakov, Yu. A. Strelenko, M. O. Ratnikov and V. A. Tartakovsky, *Russ. Chem. Bull., Int. Ed*., 2006, **55**, 1648 (*Izv. Akad. Nauk, Ser. Khim.*, 2006, 1589); (*c*) M. S. Klenov, A. M. Churakov, Yu. A. Strelenko, I. V. Ananyev, K. A. Lyssenko and V. A. Tartakovsky, *Tetrahedron Lett*., 2015, **56**, 5437.

11 (*a*) N. V. Pyatakova, Yu. V. Khropov, A. M. Churakov, N. I. Tarasova, V. A. Serezhenkov, A. F. Vanin, V. A. Tartakovsky and I. S. Severina, *Biochemistry (Moscow)*, 2002, **67**, 329 (*Biokhimiya*, 2002, **67**, 396); (*b*) A. E. Frumkin, A. M. Churakov, Yu. A. Strelenko, V. V. Kachala and V. A. Tartakovsky, *Org. Lett*., 1999, **1**, 721.

12 A. M. Churakov, S. L. Ioffe, V. A. Tartakovskii, O. G. Busygina, Yu. V. Khropov and I. S. Severina, *RF Patent 2123526*, 1998 (*Chem. Abstr.*, 2000, **133**, 55324).

13 N. V. Pyatakova, A. M. Kozlov, A. M. Churakov, O. Yu. Smirnov, Yu. V. Khropov, N. S. Saprykina, N. G. Bogdanova, S. L. Ioffe, I. S. Severina and V. A. Tartakovsky, *RF Patent 2192857*, 2002 (*Chem. Abstr*., 2003, **138**, 314555).

14 N. V. Dolgova, A. M. Churakov, O. Yu. Smirnov, Yu. V. Khropov, N. G. Bogdanova, N. V. Mast, S. L. Ioffe, O. D. Lopina and V. A. Tartakovsky, *RF Patent 2186108*, 2002 (*Chem. Abstr*., 2003, **138**, 133153).

15 A. A. Voronin, V. P. Zelenov, A. M. Churakov, Y. A. Strelenko, I. V. Fedyanin and V. A. Tartakovsky, *Tetrahedron*, 2014, **70**, 3018.

16 A. A. Voronin, V. P. Zelenov, A. M. Churakov, Y. A. Strelenko and V. A. Tartakovsky, *Russ. Chem. Bull., Int. Ed*., 2015, **64**, 699 (*Izv. Akad. Nauk, Ser. Khim*., 2015, 699).

17 (*a*) V. G. Granik and N. B. Grigoriev, *Oksid azota (NO). Novyi put' k poisku lekarstv (Nitric oxide (NO). New Route to Drug Design)*, Vuzovskaya Kniga, Moscow, 2004 (in Russian); (*b*) J. A. Hrabie and L. K. Keefer, *Chem. Rev*., 2002, **102**, 1135.

18 (*a*) D. Biswas, R. J. Holland, J. R. Deschamps, Z. Cao, L. K. Keefer and J. E. Saavedra, *J. Org. Chem.*, 2012, **77**, 10804; (*b*) R. S. Drago and B. R. Karstetter, *J. Am. Chem. Soc*., 1961, **83**, 1819; (*c*) D. Biswas, J. A. Hrabie, J. E. Saavedra, Z. Cao, L. K. Keeffer, J. Jvanic and R. J. Holland, *J. Org. Chem.*, 2014, **79**, 4612.

19 (*a*) R. J. Holland, J. R. Klose, J. R. Deschampe, Z. Cao, L. K. Keefer and J. E. Saavedra, *J. Org. Chem*., 2014, **79**, 9389; (*b*) R. S. Nandurdikar, A. E. Maciag, Z. Cao, L. K. Keefer and J. E. Saavedra, *Bioorg. Med. Chem.*, 2012, **20**, 2026.

20 G. A. Smirnov, P. B. Gordeev, S. V. Nikitin, T. V. Ternikova, G. V. Pokhvisneva and O. A. Luk'yanov, *Russ. Chem. Bull., Int. Ed*., 2015, **64**, 1057 (*Izv. Akad. Nauk, Ser. Khim*., 2015, 1057).

21 C. Jovene, E. A. Chugunova and R. Goumont, *Mini-Rev. Med. Chem*., 2013, **13**, 1089.

22 S. P. Korolev, O. V. Kondrashina, D. S. Druzhilovsky, A. M. Starosotnikov, M. D. Dutov, M. A. Bastrakov, I. L. Dalinger, D. A. Filimonov, S. A. Shevelev, V. V. Poroikov, Y. Y. Agapkina and M. B. Gottikh, *Acta Naturale*, 2013, **5**, 65.

23 (*a*) L. I. Khmel'nitskii, S. S. Novikov and T. I. Godovikova, *Khimiya furoksanov. Stroenie i sintez (Chemistry of Furoxans. Structure and Synthesis)*, 2nd edn., Nauka, Moscow, 1996 (in Russian); (*b*) L. I. Khmel'nitskii, S. S. Novikov and T. I. Godovikova, *Khimiya furoksanov. Reaktsii i primenenie (Chemistry of Furoxans. Reactions and Application)*, 2nd edn., Nauka, Moscow, 1996 (in Russian).

24 V. P. Ananikov, E. A. Khokhlova, M. P. Egorov, A. M. Sakharov, S. G. Zlotin, A. V. Kucherov, L. M. Kustov, M. L. Gening and N. E. Nifantiev, *Mendeleev Commun*., 2015, **25**, 75.

25 (*a*) C. Cena, M. Bertinaria, D. Boschi, M. Giorgis and A. Gasco, *ARKIVOC*, 2006, **7**, 301; (*b*) G. N. Nikonov and S. Bobrov, in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Amsterdam, 2008, vol. 5, pp. 316–393.

26 (*a*) L. Lazzarato, C. Cena, B. Rolando, E. Marini, M. L. Lolli, S. Guglielmo, E. Guaita, G. Morini, G. Coruzzi, R. Fruttero and A. Gasco, *Bioorg. Med. Chem*., 2011, **19**, 5852; (*b*) E. Borretto, L. Lazzarato, F. Spallotta, C. Cencioni, Yu. D'Alessandra, C. Gaetano, R. Fruttero and A. Gasco, *ACS Med. Chem. Lett*., 2013, **4**, 994; (*c*) S. Guglielmo, D. Cortese, F. Vottero, B. Rolando, V. P. Kommer, D. L. Williams, R. Fruttero and A. Gasco, *Eur. J. Med. Chem*., 2014, **84**, 135.

27 (*a*) A. I. Stepanov, D. V. Dashko and A. A. Astrat'ev, *Central Eur. J. Energ. Mater*., 2012, **9**, 329; (*b*) V. I. Pepekin, B. L. Korsunskii and Yu. N. Matyushin, *Comb. Expl. Shock Waves*, 2008, **44**, 110 (*Fiz. Goreniya Vzryva*, 2008, **44**, 123); (*c*) A. O. Chizhov, N. N. Makhova, I. V. Kuchurov, A. B. Sheremetev and S. G. Zlotin, *Mendeleev Commun*., 2014, **24**, 165; (*d*) D. Fischer, T. M. Klapötke and J. Stierstorfer, *Eur. J. Inorg. Chem*., 2014, 5808.

28 (*a*) N. N. Makhova, A. S. Kulikov, S. I. Molotov and E. L. Baryshnikova, *Pure Appl. Chem*., 2004, **76**, 1691; (*b*) I. V. Ovchinnikov, A. O. Finogenov, M. A. Epishina, A. S. Kulikov, Yu. A. Strelenko and N. N. Makhova, *Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 2137 (*Izv. Akad. Nauk, Ser. Khim*., 2009, 2072); (*c*) N. N. Makhova and A. C. Kulikov, *Russ. Chem. Rev.*, 2013, **82**, 1007; (*d*) L. L. Fershtat, I. V. Ovchinnikov and N. N. Makhova, *Tetrahedron Lett*., 2014, **55**, 2398; (*e*) L. L. Fershtat, M. I. Struchkova, A. S. Goloveshkin, I. S. Bushmarinov and N. N. Makhova, *Heteroat. Chem.*, 2014, **25**, 226.

29 A. Ya. Kots, M. A. Grafov, Yu. V. Khropov, V. L. Betin, N. N. Belushkina, O. G. Busyrgina, M. Yu. Yazykova, I. V. Ovchinnikov, A. S. Kulikov, N. N. Makhova, N. A. Medvedeva, T. V. Bulargina and I. S. Severina, *Brit. J. Pharm*., 2000, **129**, 1163.

30 (*a*) L. L. Fershtat, M. A. Epishina, A. S. Kulikov, M. I. Struchkova and N. N. Makhova, *Chem. Heterocycl. Compd*., 2015, **51**, 176 (*Khim. Geterotsikl. Soedin*., 2015, **51**, 176); (*b*) L. L. Fershtat, M. A. Epishina, A. S. Kulikov and N. N. Makhova, *Mendeleev Commun.*, 2015, **25**, 36.

31 L. L. Fershtat, S. S. Ashirbaev, A. S. Kulikov, V. V. Kachala and N. N. Makhova, *Mendeleev Commun*., 2015, **25**, 257.

32 L. L. Fershtat, M. A. Epishina, A. S. Kulikov, I. V. Ovchinnikov, I. V. Ananyev and N. N. Makhova, *Tetrahedron*, 2015, **71**, 6764.

33 L. L. Fershtat, I. V. Ananyev and N. N. Makhova, *RSC Adv.*, 2015, **5**, 47248.

34 L. L. Fershtat, M. A. Epishina, I. V. Ovchinnikov and N. N. Makhova, *Chem. Heterocycl. Compd.*, 2015, **51**, 754 (*Khim. Geterotsikl. Soedin*., 2015, **51**, 754).

35 L. S. Konstantinova, S. A. Amelichev, S. G. Zlotin, M. I. Struchkova, T. I. Godovikova, L. I. Khmel'nitskii and O. A. Rakitin, *Mendeleev Commun*., 2015, **25**, 339.

36 M. A. Bastrakov, A. M. Starosotnikov, V. V. Kachala, I. L. Dalinger and S. A. Shevelev, *Chem. Heterocycl. Compd*., 2015, **51**, 496 (*Khim. Geterotsikl. Soedin*., 2015, **51**, 496).

37 B. Xuan, T. Wang, G. C. Y. Chiou, I. L. Dalinger, T. K. Shkineva and S. A. Shevelev, *J. Ocular Pharmacol. Ther*., 2001, **17**, 505.

38 (*a*) I. V. Kuchurov, I. V. Fomenkov, S. G. Zlotin and V. A. Tartakovsky, *Mendeleev Commun*., 2012, **22**, 67; (*b*) M. N. Zharkov, I. V. Kuchurov, I. V. Fomenkov, S. G. Zlotin and V. A. Tartakovsky, *Mendeleev Commun*., 2015, **25**, 15; (*c*) I. A. Vatsadze, O. V. Serushkina, M. D. Dutov, T. K. Shkineva, K. Yu. Suponitsky, B. I. Ugrak and I. L. Dalinger, *Chem. Heterocycl. Compd*., 2015, **51**, 695 (*Khim. Geterotsikl. Soedin*., 2015, **51**, 695).

39 (*a*) S. S. Novikov, G. A. Shvekhgeimer, V. V. Sevostyanova and V. A. Shlyapochnikov, *Khimiya alifaticheskikh i tsikloalifaticheskikh nitrosoedinenii (Chemistry of Aliphatic and Cycloaliphatic Nitro Compounds)*, Khimiya, Moscow, 1974 (in Russian); (*b*) E. E. Gilbert and G. P. Sollott, *J. Org. Chem.*, 1980, **45**, 5405; (*c*) T. G. Archibald, K. Baum, M. C. Cohen and L. C. Garver, *J. Org. Chem*., 1989, **54**, 2869; (*d*) R. P. Kashyap, A. P. Marchand, R. Sharma, W. H. Watson and U. R. Zope, *J. Org. Chem.*, 1993, **58**, 759; (*e*) P. E. Eaton, R. Gilardi, J. Hain, N. Kanomata, J. Li, K. A. Lukin and E. Punzalan, *J. Am. Chem. Soc*., 1997, **119**, 9591.

40 (*a*) L. S. Aitken, N. R. Arezki, A. Dell'Isola and A. J. A. Cobb, *Synthesis*, 2013, **45**, 2627; (*b*) S. Z. Zard, *Helv. Chim. Acta*, 2012, **95**, 1730;

(*c*) R. Ballini and M. Petrini, *ARKIVOC*, 2009, **9**, 195; (*d*) R. Ballini and M. Petrini, *Tetrahedron*, 2004, **60**, 1017.
41 N. Ono, *The Nitro Group in Organic Chemistry*, Wiley-VCH, Weinheim, 2001.
42 J. M. Garcıa, M. A. Maestro, M. Oiarbide, J. M. Odriozola, J. Razkin and C. Palomo, *Org. Lett.*, 2009, **11**, 3826.
43 (*a*) Y.-P. Li, Z.-J. Li and X.-B. Meng, *Carbohydr. Res*., 2011, **346**, 1801; (*b*) R. G. Soengas and A. M. Estévez, *Eur. J. Org. Chem*., 2010, 5190; (*c*) L. Kh. Faizullina, M. G. Safarov, L. V. Spirikhin, V. S. Kolosnitsyn, Yu. A. Kondrova and F. A. Valeev, *Russ. J. Org. Chem*., 2011, **47**, 914 (*Zh. Org. Khim.*, 2011, **47**, 897).
44 S. L. Ioffe, in *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis. Novel Strategies in Synthesis*, 2nd edn., ed. H. Feuer, Wiley, Hoboken, 2008.
45 (*a*) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137; (*b*) S. E. Denmark, N. D. Gould and L. M. Wolf, *J. Org. Chem.*, 2011, **76**, 4260; (*c*) D. Seebach, X. Sun, M.-O. Ebert, W. B. Schweizer, N. Purkayastha, A. K. Beck, J. Duschmal, H. Wennemers, T. Mukaiyama, M. Benohoud, Y. Hayashi and M. Reiher, *Helv. Chim. Acta*, 2013, **96**, 799; (*d*) G. Sahoo, H. Rahaman, Á. Madarász, I. Papai, M. Melarto, A. Valkonen and P. M. Pihko, *Angew. Chem. Int. Ed.*, 2012, **51**, 13144; (*e*) V. Yu. Korotaev, A. Yu. Barkov, P. A. Slepukhin, M. I. Kodess and V. Y. Sosnovskikh, *Tetrahedron Lett*., 2011, **52**, 5764; (*f*) A. A. Mikhaylov, P. A. Zhmurov, A. S. Naumova, Yu. A. Khoroshutina, A. Yu. Sukhorukov and S. L. Ioffe, *Mendeleev Commun.*, 2015, **25**, 449.
46 (*a*) C.-Y. Zhu, X.-M. Deng, X.-L. Sun, J.-C. Zhenga and Y. Tang, *Chem. Commun*., 2008, 738; (*b*) T. Kano, A. Yamamoto, S. Song and K. Maruoka, *Chem. Commun.*, 2011, 4358; (*c*) C. D. Schmidt, J. Kaschel, T. F. Schneider, D. Kratzert, D. Stalke and D. B. Werz, *Org. Lett*., 2013, **15**, 6098.
47 T. Risgaard, K. V. Gothelf and K. A. Jørgensen, *Org. Biomol. Chem*., 2003, **1**, 153.
48 T. Ooi, K. Doda and K. Maruoka, *J. Am. Chem. Soc*., 2003, **125**, 9022.
49 A. Yu. Sukhorukov, Y. D. Boyko, Yu. V. Nelyubina, S. Gerard, S. L. Ioffe and V. A. Tartakovsky, *J. Org. Chem*., 2012, **77**, 5465.
50 (*a*) A. A. Mikhaylov, R. A. Novikov, Yu. A. Khomutova, D. E. Arkhipov, A. A. Korlyukov, A. A. Tabolin, Yu. V. Tomilov and S. L. Ioffe, *Synlett*, 2014, **25**, 2275; (*b*) A. A. Tabolin, R. A. Novikov, Y. A. Khomutova, A. A. Zharov, G. A. Stashina, Y. V. Nelyubina, Y. V. Tomilov and S. L. Ioffe, *Tetrahedron Lett.*, 2015, **56**, 2102.
51 (*a*) J. E. Wilson, A. D. Casarez and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 11332; (*b*) N. A. Aksenov, O. N. Nadein and I. V. Aksenova, *Synlett*, 2010, 2628; (*c*) V. O. Smirnov, Y. A. Khomutova, V. A. Tartakovsky and S. L. Ioffe, *Eur. J. Org. Chem*., 2012, 3377; (*d*) A. A. Mikhaylov, A. D. Dilman, Y. A. Khomutova, D. E. Arkhipov, A. A. Korlyukov and S. L. Ioffe, *Eur. J. Org. Chem*., 2013, 5670.
52 A. Yu. Sukhorukov, M. A. Kapatsyna, T. L. T. Yi, H. R. Park, Y. A. Naumovich, P. A. Zhmurov, Y. A. Khomutova, S. L. Ioffe and V. A. Tartakovsky, *Eur. J. Org. Chem.*, 2014, **36**, 8148.
53 (*a*) A. Yu. Sukhorukov and S. L. Ioffe, *Chem. Rev.*, 2011, **111**, 5004; (*b*) P. A. Zhmurov, A. Yu. Sukhorukov, V. I. Chupakhin, Yu. A. Khomutova, S. L. Ioffe and V. A. Tartakovsky, *Org. Biomol. Chem.*, 2013, **11**, 8082; (*c*) A. N. Semakin, D. P. Agababyan, S. Kim, S. Lee, A. Yu. Sukhorukov, K. G. Fedina, J. Oh and S. L. Ioffe, *Tetrahedron Lett.*, 2015, **56**, 6335.
54 (*a*) A. Z. Halimehjani, I. N. N. Namboothiri and S. E. Hooshmand, *RSC Adv.*, 2014, **4**, 31261; (*b*) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero and P. Merino, *Tetrahedron: Asymmetry*, 2010, **21**, 2561.
55 (*a*) *Science of Synthesis: Asymmetric Organocatalysis*, eds. B. List and K. Maruoka, Thieme, Stuttgart, 2012, vols. 1, 2; (*b*) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, ed. P. I. Dalco, Wiley-VCH, Weinheim, 2013, vols. 1–3.
56 (*a*) M. Dambrova, L. Zvejniece, E. Liepinsh, H. Cirule, O. Zharkova, G. Veinberg and I. Kalvinsh, *Eur. J. Pharmacol*., 2008, **583**, 128; (*b*) M. Tsakos, C. G. Kokotos and G. Kokotos, *Adv. Synth. Catal*., 2012, **354**, 740.
57 (*a*) D. F. Smith, *J. Neural Transm*., 1984, **60**, 63; (*b*) Y. Hayashi, T. Itoh and H. Ishikawa, *Angew. Chem. Int. Ed*., 2011, **50**, 3920; (*c*) K. L. Jensen, P. H. Poulsen, B. S. Donslund, F. Morana and K. A. Jørgensen, *Org. Lett*., 2012, **14**, 1516.
58 (*a*) H. Gotoh, H. Ishikawa and Y. Hayashi, *Org. Lett*., 2007, **9**, 5307; (*b*) J.-m. Liu, X. Wang, Z.-m. Ge, Q. Sun, T.-m. Cheng and R.-t. Li, *Tetrahedron*, 2011, **67**, 636; (*c*) K. L. Kimmel, J. D. Weaver and J. A. Ellman, *Chem. Sci*., 2012, **3**, 121.
59 (*a*) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, Á. Puente and S. Vera, *Angew. Chem. Int. Ed*., 2007, **46**, 8431; (*b*) P. García-García, A. Ladépêche, R. Halder and B. List, *Angew. Chem. Int. Ed*., 2008, **47**, 4719.
60 (*a*) H. Ishikawa, T. Suzuki and Y. Hayashi, *Angew. Chem. Int. Ed.*, 2009, **48**, 1304; (*b*) S. Zhu, S. Yu, Y. Wang and D. Ma, *Angew. Chem. Int. Ed.*, 2010, **49**, 4656; (*c*) T. Mukaiyama, H. Ishikawa, H. Koshino and Y. Hayashi, *Chem. Eur. J*., 2013, **19**, 17789.
61 L. Huo, A. Ma, Y. Zhang and D. Ma, *Adv. Synth. Catal.*, 2012, **354**, 991.
62 T. A. Davis, A. E. Vilgelm, A. Richmond and J. N. Johnston, *J. Org. Chem.*, 2013, **78**, 10605.
63 M. C. Dobish, F. Villalta, M. R. Waterman, G. I. Lepesheva and J. N. Johnston, *Org. Lett*., 2012, **14**, 6322.
64 (*a*) N. K. Rana, H. Huang and J. C.-G. Zhao, *Angew. Chem. Int. Ed.*, 2014, **53**, 7619; (*b*) X.-L. Meng, T. Liu, Z.-W. Sun, J.-C. Wang, F.-Z. Peng and Z.-H. Shao, *Org. Lett.*, 2014, **16**, 3044; (*c*) B.-C. Hong, W.-K. Liao, N. S. Dange and J.-H. Liao, *Org. Lett*., 2013, **15**, 468.
65 E. Rodrigo, J. L. G. Ruano and M. B. Cid, *J. Org. Chem*., 2013, **78**, 10737.
66 H. Xie, Y. Zhang, S. Zhang, X. Chen and W. Wang, *Angew. Chem. Int. Ed.*, 2011, **50**, 11773.
67 R. Kowalczyk, A. E. Nowak and J. Skarzewski, *Tetrahedron: Asymmetry*, 2013, **24**, 505.
68 S. P. Chavan, S. Garai and K. P. Pawar, *Tetrahedron Lett*., 2013, **54**, 2137.
69 (*a*) L. Liu, S. Zhang, F. Xue, G. Lou, H. Zhang, S. Ma, W. Duan and W. Wang, *Chem. Eur. J*., 2011, **17**, 7791; (*b*) Y. Zhang, Z. J. Li, H. S. Xu, Y. Zhang and W. Wang, *RSC Adv.*, 2011, **1**, 389.
70 J. Alemán and S. Cabrera, *Chem. Soc. Rev*., 2013, **42**, 774.
71 T. E. Kristensen and T. Hansen, in *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions and Applications*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2013, vol. II, pp. 651–672.
72 (*a*) D. E. Siyutkin, A. S. Kucherenko and S. G. Zlotin, in *Comprehensive Enantioselective Organocatalysis: Catalysis, Reactions and Applications*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2013, vol. II, pp. 617–650; (*b*) H. L. Brozinski, J. P. Delaney and L. C. Henderson, *Aust. J. Chem.*, 2013, **66**, 844; (*c*) A. S. Kucherenko, D. E. Siyutkin, O. V. Maltsev, S. V. Kochetkov and S. G. Zlotin, *Russ. Chem. Bull., Int. Ed*., 2012, **61**, 1313 (*Izv. Akad. Nauk, Ser. Khim*., 2012, 1299).
73 O. V. Maltsev, A. S. Kucherenko, I. P. Beletskaya, V. A. Tartakovsky and S. G. Zlotin, *Eur. J. Org. Chem.*, 2010, 2927.
74 O. V. Maltsev, A. S. Kucherenko and S. G. Zlotin, *Mendeleev Commun*., 2011, **21**, 146.
75 (*a*) O. V. Maltsev, A. O. Chizhov and S. G. Zlotin, *Chem. Eur. J*., 2011, **17**, 6109; (*b*) S. G. Zlotin, A. S. Kuherenko, O. V. Maltsev and A. O. Chizhov, *Top. Catal.*, 2013, **56**, 923.
76 (*a*) A. S. Kucherenko, V. G. Lisnyak, A. O. Chizhov and S. G. Zlotin, *Eur. J. Org. Chem.*, 2014, 3808; (*b*) A. S. Kucherenko, V. V. Gerasimchuk, V. G. Lisnyak, Y. V. Nelyubina and S. G. Zlotin, *Eur. J. Org. Chem*., 2015, 5649; (*c*) S. V. Kochetkov, A. S. Kucherenko and S. G. Zlotin, *Mendeleev Commun.*, 2015, **25**, 168; (*d*) S. G. Zlotin and S. V. Kochetkov, *Russ. Chem. Rev*., 2015, **84**, 1077; (*e*) V. G. Lisnyak, A. S. Kucherenko, E. F. Valeev and S. G. Zlotin, *J. Org. Chem*., 2015, **80**, 9570.
77 (*a*) R. Noyori, *Chem. Commun*., 2005, 1807; (*b*) *Handbook of Green Chemistry: Supercritical Solvents*, eds. W. Leitner and P. G. Jessop, Wiley-VCH, Weinheim, 2010, vol. 4, p. 1412.
78 A. G. Nigmatov, I. V. Kuchurov, D. E. Siyutkin and S. G. Zlotin, *Tetrahedron Lett*., 2012, **53**, 3502.
79 I. V. Kuchurov, A. G. Nigmatov, E. V. Kryuchkova, A. A. Kostenko, A. S. Kucherenko and S. G. Zlotin, *Green Chem.*, 2014, **16**, 1521.

Received: 16th September 2015; Com. 15/4734