Green Chemistry

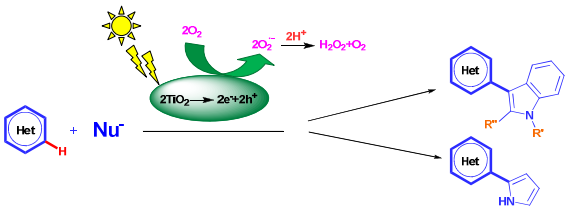
Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/greenchem

Table of contents

The pyrrolyl and indolyl derivatives of azaaromatics have been prepared by method of aerobic photo-induced oxidative C–H/C–H coupling in the presence of nanosized TiO_2.



Green Chemistry

PAPER

Aerobic oxidative C–H/C–H coupling of azaaromatics with indoles and pyrroles in the presence of TiO_2 as a photocatalyst

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

I. A. Utepova,[a,b] M. A. Trestsova,[a] O. N. Chupakhin,[a,b]* V. N. Charushin[a,b] and A. A. Rempel[a,c]

In this paper we wish to report a highly selective and benign method for the double C–H/C–H coupling of azaaromatics with indoles or pyrrole in the presence of air oxygen/TiO_2, as an effective photocatalytic oxidative system. It has been shown that this versatile approach can be applied for direct C-H functionalisation of a variety of azaaromatic systems, such as mono-, di,- and triazines, substituted and unsubstituted azines and their benzo-annelated analogues.

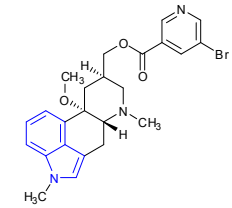
Introduction

Organic compounds, bearing pyrrole or indole moieties in their structures, appear to be very attractive for biological screening, since the data of biological tests indicate that derivatives of this family quite often become lead molecules.[1] Also azinyl fragments are dominating in the structures of biologically active compounds.[2] This is also true for pyrrolyl and indolyl substituted azaaromatic compounds bearing the C-C bond, linking two aromatic fragments; these structures are well presented in both natural and pharmaceutical products.[3]

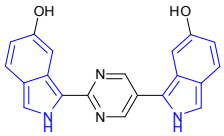
Several examples are given in Figure 1. Indeed, *Nicergoline*[4] acts as α-adrenoceptor blocking agent; it also possesses a pronounced spasmolytic activity in relation to cerebral vascular and peripheral vessels. *Hyrtinadine* A is an alkaloid, having 2,5-*bis*(indolyl) substituted pyrimidine structure,[5] which exhibits cytotoxic activity *in vitro* against murine leukemia L1210 cells and human epidermoid carcinoma KB cells. Another *bis*-indolyl alkaloid *Dragmacidin* E is a potent inhibitor of serine-threonine protein phosphatases (PP).[6] *Variolin* B has been shown to exhibit cytotoxic activity against a variety of human cancer cell lines.[7]

A great deal of efforts are currently undertaken in order to develop novel and advanced synthetic approaches for preparation of indolyl and pyrrolyl substituted azaaromatics, by using both metal-catalysed cross-coupling reactions and metal free C-H functionalisations, as well as multi-component reactions and other synthetic methodologies.

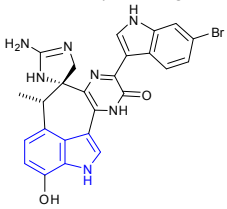
Classical palladium-catalysed cross-coupling reactions of halogenated heteroaromatics with organometallic derivatives[8] proved to be a well known and widely used synthetic methodology, enabling to obtain the above mentioned heterocyclic ensembles, bearing bi(hetero)aryl moieties.



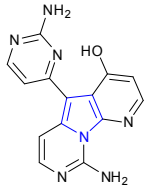
Nicergoline [ref. 4]
α_1-adrenoceptor antagonist



Hyrtinadine A [ref. 5]
cytotoxic activity



Dragmacidin E [ref. 6]
serine-threonine (PP) inhibitor



Variolin B [ref. 7]
antitumor activity

Fig. 1 Natural compounds bearing indole and azine moieties.

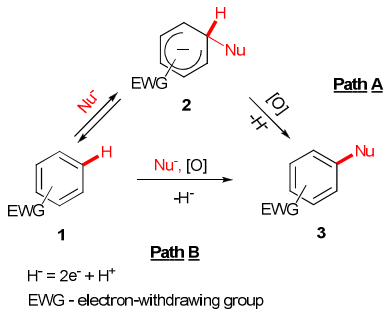
During the last decade a new synthetic methodology for the direct metal-catalysed functionalisation of the C(sp^2)-H bond in (hetero)aromatics, including the formation of new C-X (X= C, N, O, P, S) chemical bonds, has been advanced.[9] This C-H functionalisation methodology provides a better correspondence to the atom economy principle,[10] and it is certainly a more attractive from the ecological point of view, than other synthetic procedures, exploiting displacement of halogen atoms.

Cross-coupling reactions of π-deficient (hetero)aromatic compounds with nucleophilic heteroarenes, such as indoles or pyrroles, which are non-catalysed by transition metals, have received much less attention. At the same time, a remarkable progress in studying of these reactions, classified as

[a] Ural Federal University, 19 Mira Street, 620002 Ekaterinburg Russia
[b] Institute of Organic Synthesis of the Russian Academy of Sciences, 22 S. Kovalevskoy Street, 620219 Ekaterinburg, Russia
[c] Institute of Solid State Chemistry of the Russian Academy of Sciences, 91 Pervomaiskaya Street, 620990 Ekaterinburg, Russia, E-mail: rempel@ihim.uran.ru
* E-mail: chupakhin@ios.uran.ru; Fax: (+7343) 3693058; Tel: (+7343) 3741189
Electronic Supplementary Information (ESI) available: details of any supplementary information available should be included here. See DOI: 10.1039/x0xx00000x

nucleophilic aromatic substitution of hydrogen[11] S_N^HAr (briefly S_N^H), has been achieved during the last decade due to their practical advantages.[11,12] In these S_N^H reactions the formation of new bonds C(sp^2)-X (X= C, Hal, N, O, P, S, Si) requires neither a preliminary functionalisation of the parent (hetero)aromatic compounds, nor use of transition metals (usually Pd), as catalysts. The latter is very important for the synthesis of drugs and/or organic dyes for solar cells, in which even traces of transition metals are not permitted. This is why the direct metal-free C-H functionalisation of aromatics is considered to be so aspirational approach for both academic and industrial chemists, thus enabling them to avoid impurities of metals in the target products.

As far as the S_N^H reactions are concerned, these usually proceed according to the "Addition-Elimination" sequence of steps with the formal departure of the hydride ion H^- (Scheme 1). The first step involves a reversible addition of nucleophile to electron-deficient arene **1** to give the so-called σ^H-adduct **2**. Since spontaneous elimination of H^- from the intermediate σ^H-adduct **2** is unlikely, an oxidising agent is needed for rearomatisation of **2**, in order to take away a couple of electrons, while hydrogen is departed as proton H^+ (Scheme 1, Path A).[11,13] In a vast majority of cases, the S_N^H reactions proceed under rather mild conditions, and can be realised as one-pot procedure (Path B), without isolation of the intermediate σ^H-adducts **2**, and this synthetic procedure appears to be a convenient one for oxidative metal free cross-couplings.

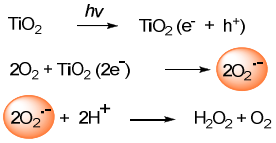


Scheme 1 The C-H functionalisation through nucleophilic substitution of hydrogen proceeding according the two-step "Addition-Oxidation" mechanism.

The oxidation step is a less studied one. Since not only intermediates **2**, but also nucleophilic species are vulnerable to oxidative processes, the right choice of an appropriate oxidant is of crucial value for C-H functionalisation reactions.[11e,12b,14] A variety of one- and two-electron oxidants, of both organic origin and inorganic nature,[11-13] have been used as aromatisation agents. For instance, Hartwig and co-workers have recently exploited AgF_2,[14d,15] which proved to be a very efficient oxidising agent for the S_N^H fluorination of azines. Besides transition metals,[16] hypervalent iodine compounds have been used in the oxidative C-H/C-H coupling reactions of (hetero)arenes.[16f, 17]

The data concerning use of heterogeneous catalysts are scarcely available in the literature.[18] Air oxygen is of special value as oxidant, since it affords water, as by-product, thus providing an opportunity to develop environmentally friendly processes.

In the course of our studies on using various oxidants and improvement of methods for the oxidative version of the S_N^H reactions we have paid our attention that, when irradiated with UV light, the system O_2/TiO_2 produces an electron/hole pair (e^-/h^+), and oxygen dissolved in a solution can be scavenged with the exited electrons, thus affording the superoxide radicals $O_2^{\bullet-}$ (Scheme 2),[19] as very active oxidative species.



Scheme 2 Formation superoxide radicals $O_2^{\bullet-}$.

It is worth mentioning that materials on the basis of TiO_2 and its doped forms have found quite wide application in organic synthesis.[20] A number of examples concerning use of TiO_2 for oxidation of alcohols,[21] transformation of amines into imines,[21] oxidative cyclisation of diamino compounds,[23] oxidation of tetrahydropyrimidin-2-ones,[24] and also to initiate the addition of alkynes to aldehydes,[25] have recently been described.

As far as application of TiO_2 in photo-induced oxidative S_N^H reactions is concerned, no data on this subject have so far been reported in the literature. In this paper we wish to describe the first examples of using the system air oxygen/TiO_2 for the S_N^H reactions of azaaromatic compounds with aromatic nucleophiles, as illustrated by the synthesis of indolyl-azinyl and pyrrolyl-azinyl heterocyclic ensembles.

Results and discussion

As mentioned above, the S_N^H reactions can be carried out as two-steps processes with isolation of the intermediates **2** (Scheme 1, Path A). On the other hand, taking into account that adducts **2** are able to undergo dissociation into starting materials, a more economical one-pot "through-out" three-component process, involving starting reagents and oxidant, appears to be a more attractive procedure (Scheme 1, Path B).[11,13] The target products of these one-pot S_N^H reactions are usually stable compounds, bearing two aromatic fragments, linked to each other due to C-H functionalisation of two C-H bonds of different nature.

We have established that azaaromatic compounds and their activated forms (*N*-H and *N*-alkyl quaternary salts, as well as azinones) are able to undergo the double C-H/C-H coupling reaction with indoles (**5a-d**) and pyrrole (**5e**) under aerobic conditions in the presence of nanosized particles of TiO_2 (commercial accessible, Hombifine N, 100% anatase). All reactions have been carried out in a quartz flask under irradiation with a Xe lamp (5000 K, 35 W). It has previously been shown that the catalysts Degussa P-25 and rutile TiO_2 exhibit a remarkably lower activity in oxidative reactions

relative to anatase TiO_2.[21b,24] In order to enhance the activity of TiO_2 and to avoid the coagulation of nano-sized particles, a mixture of starting materials has been previously treated in ultrasonic bath for 5 minutes. The catalyst used can be separated easily by filtration or centrifugation, washed and used repeatedly. It has been shown that it does not loose its catalytic activity for at least 5 catalytic cycles.

The S_N^H reactions of azaaromatics considered above are of general character, and can be applied to a variety of mono-, di- and triazines, including their benzo analogues and substituted derivatives. The data obtained and references to the previously described compounds are summarised in Tables 1-3. It is worth noting that interaction of azaaromatics with C-nucleophiles of aromatic nature, such as indoles and pyrroles (**5**), takes place regioselectively; no by-products due to self-coupling of starting materials, or other substitution reactions have been observed. Although some compounds have previously been described, we have suggested an environmentally benign approach, which takes place without oxidant (halogenes, hypohalides, permanganate, sulphur, chloranil, DDQ, *N*-bromosuccinimide, etc.) or additional reagents (acetyl or benzoyl chloride).[11e,13]

A number of experiments have been performed for optimisation of the reaction conditions: varying ratio of reagents and catalyst, reaction time, solvent and temperature. Acridine having the only electrophilic C-9 center, has been chosen as the model azine substrate (Table 1).

Table 1 Optimisation of the C–H/C–H coupling of acridine (**4a**) with indole (**5a**)[a]

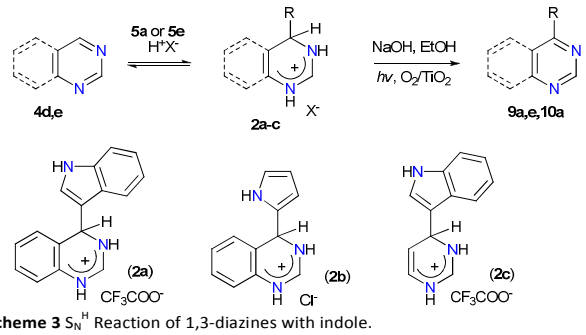
Entry	TiO_2, (mass.%)	Solvent	Temp., [°C]	Time, [h]	Yield, (%)
1	10	*n*-BuOH	120	5	-
2	10	CH_3CN	90	5	-
3	10	DMFA	160	5	10
4	**10**	**CH_3COOH**	**25**	**5**	**60**
5[b]	-	CH_3COOH	25	5	16
7	5	CH_3COOH	25	5	53
6	15	CH_3COOH	25	5	60
7	10	CH_3COOH	120	5	60
8	10	CH_3COOH	25	4	47
9	10	CH_3COOH	25	3	34
10	10	CF_3COOH	25	5	41
11	10 (rutile)	CH_3COOH	25	5	26
12	10 (Degussa P25)	CH_3COOH	25	5	32

[a] Reaction conditions: acridine **4a**, indole **5a**, TiO_2 catalysts, an appropriate solvent were irradiated with Xe lamp (5000 K, 35 W) under air oxygen, bubbling through the reaction mixture. [b] The reaction was carried out without irradiation.

It has been established that the best yield (60%) of the S_N^H product derived from the reaction of acridine (**4a**) with indole (**5a**) is reached under the following conditions: acetic acid as solvent, ambient temperature, and irradiation in the presence of anatase TiO_2 on bubbling air for 5 hours (Table 1, entry 4). Without irradiation the reaction of acridine (**4a**) with indole (**5a**) affords the target S_N^H product in only 16% yield. Also acidic catalysis is of great importance. Indeed, without an acid this S_N^H reaction does not occur, even on reflux in *n*-butanol or acetonitrile.

The optimal conditions, found for the reaction of acridine with indole, have been applied for the C-C coupling of other azines with indoles and pyrrole. Highly electrophilic azines, such as acridine (**4a**) (Table 2, entry 1), and 5-phenyl-1,2,5-oxadiazolo[3,4-*b*]pyrazine (**4c**) (Table 2, entry 3), have been found to react smoothly with indoles (**5a-c**) and pyrrole (**5e**) in acetic acid at room temperature to give compounds **6a-c,e** and **8a-c,e** in yields ranged from 49% to 99%. In case of 3,6-diphenyl-1,2,4-triazine (Table 2, entry 2) the reactions of **4b** with indoles (**5a-c**) and pyrrole (**5e**) have been carried out under acidic conditions at 120 °C to afford derivatives **7a-c,e** in 56-92% yields. Also less electrophilic pyridine, quinoline and isoquinoline do not undergo these double C-H/C-H coupling reactions of aromatics.

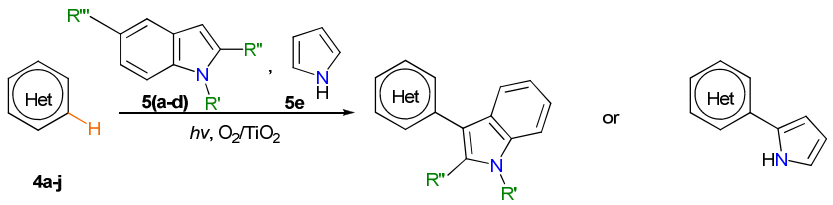
In the series of C-H/C-H transformations of azaaromatics by action of indoles, there are some features for the S_N^H reactions in the series of 1,3-diazines, such as pyrimidine (**4e**) or quinazoline (**4d**), which can be realised either through a step-wise mechanism with isolation of the intermediates **2** (Scheme 1, path A), or directly (Scheme 1, path B). It is known that diazines, being protonated in acidic media,[29] are capable of reacting with nucleophilic reagents to give fairly stable adducts **2a-c** (Scheme 3). Oxidation of the latter is usually carried out with $K_3Fe(CN)_6$ in aqueous solution of KOH.[29a,30] We have succeeded to isolate compounds **2a-c**, and have shown that the oxidative system O_2/TiO_2 can be used successfully for their aromatisation according to Scheme 2. It is worth mentioning that oxidation of **2a-c** takes place smoothly and quantitatively in aqueous alcohol in the presence of equivalent amounts of NaOH.



Scheme 3 S_N^H Reaction of 1,3-diazines with indole.

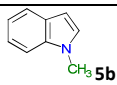
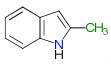
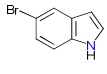
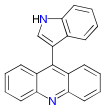
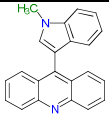
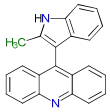
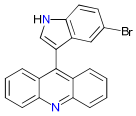
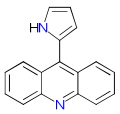
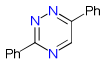
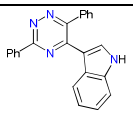
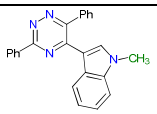
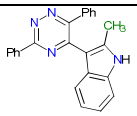
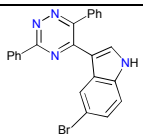
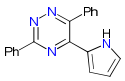
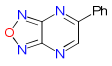
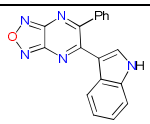
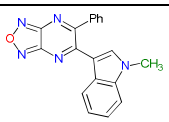
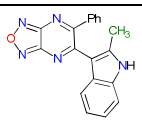
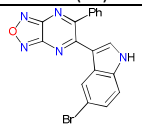
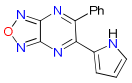
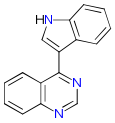
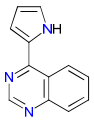
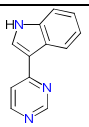
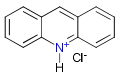
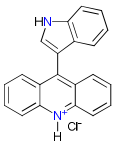
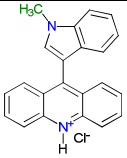
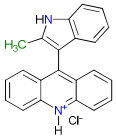
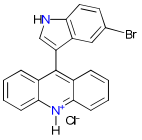
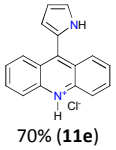
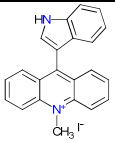
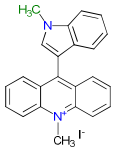
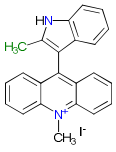
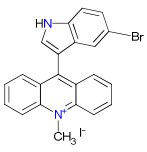
The S_N^H reactions of quinazoline (**4d**) and pyrimidine (**4e**) with indole (**5a**) or pyrrole (**5e**) have also been performed without isolation of intermediates **2** (Scheme 3). In this case the reactions have been carried out in a mixture of trifluoroacetic acid and benzene (1:2) for 5 hours (for **9a**, **10a**) or in a mixture of HCl and methanol (1:2) for 5 hours (for **9e**). After evaporation of acid and treatment with aqueous NaOH (2 equiv.) and catalytic amounts of TiO_2, an air flow was bubbled through the reaction mixture on irradiation to give compounds **9a,e**, 10a in 68-70% yields (Table 2, entries 4, 5).

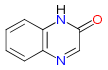
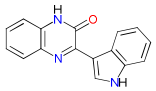
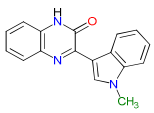
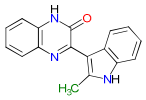
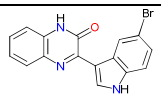
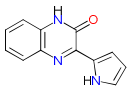
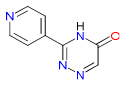
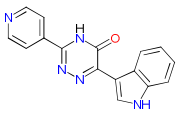
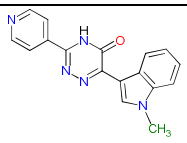
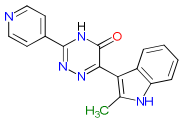
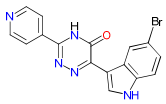
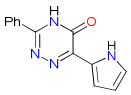
Table 2 The C–H/C–H coupling of azaaromatics with indoles and pyrrole[a]



4a-j 6-15(a-d) 6-15e

5: R', R'', R''' = H (**a**); R' = CH_3, R'', R''' = H (**b**); R' = R''' = H, R'' = CH_3 (**c**); R', R'' = H; R''' = Br (**d**)

Entry	Het–H	Solvent, temperature	 **5a**	 **5b**	 **5c**	 **5d**	 **5e**
1	 (**4a**)[b]	AcOH, RT (for **6a-c,e**) AcOH, 120 °C (for **6d**)	 60% (**6a**) 48%[26]	 80% (**6b**) 68%[26]	 85% (**6c**) 64%[26]	 38% (**6d**)	 49% (**6e**)
2	 (**4b**)	AcOH, 120 °C	 92% (**7a**) 43%[27]	 70% (**7b**) 80%[27]	 75% (**7c**) 33%[27]	 35% (**7d**)	 56% (**7e**) 73%[27]
3	 (**4c**)	AcOH, RT	 >99% (**8a**)	 >99% (**8b**)	 >99% (**8c**)	 89% (**8d**)	 98% (**8e**)
4	 (**4d**)	1) CF_3COOH - C_6H_6 (1:2) (for **9a**) or HCl - MeOH (1:2) (for **9e**) 2) NaOH (2 equiv.), RT	 70% (**9a**)				 68% (**9e**)
5	 (**4e**)	CF_3COOH - C_6H_6 (1:2), NaOH (2 equiv.), RT	 70% (**10a**)				
6	 (**4f**)	*n*-BuOH, RT	 70% (**11a**)	 55% (**11b**)	 63% (**11c**)	 46% (**11d**)	 70% (**11e**)
7	 (**4g**)	*n*-BuOH, RT	 >99% (**12a**) 38%[13]	 85% (**12b**)	 90% (**12c**)	 73% (**12d**)	86% (**12e**) 50%[13]
8	(**4h**)	*n*-BuOH, RT	75% (**13a**) 60%[13]	78% (**13b**)	74% (**13c**)	52% (**13d**)	46% (**13e**)

9	 (**4i**)	AcOH, 120 °C	 >99% (**14a**) 85%[28b]	 >99% (**14b**)	 92% (**14c**) 86%[28b]	 87% (**14d**) 86%[28b]	 99% (**14e**)
10	 (**4j**)	AcOH, 120 °C	 62% (**15a**)	 60% (**15b**)	 62% (**15c**)	 48% (**15d**)	 65% (**15e**)

[a] Reaction conditions: azaaromatics **4a-j**, indoles **5a-c** (or pyrrole **5d**), TiO_2 (10 mass.%, anatase), an appropriate solvent were irradiated with Xe lamp (5000 K, 35 W) under air oxygen, bubbling through the reaction mixture for 5 h. Yields of isolated, analytically pure products.

The C-C coupling of activated *N*-alkyl quaternary and *N*-H protonated salts of azaaromatics **4f-h** (Table 2) with indoles (**5a-d**) and pyrrole (**5e**) have been found to proceed smoothly even at room temperature under neutral conditions. In order to find optimal conditions the reaction of 10-methylacridinium iodide (**4g**) with indole has been carried out in two-phase systems (Table 3), however yields proved to be rather poor (below 5%).

Table 3 Optimisation of the C–H/C–H coupling of 10-methylacridinium iodide (**4g**) with indole (**5a**)[a]

Entry	TiO_2, (mass.%)	Solvent	Temp., [°C]	Time, [h]	Yields, (%)
1	10	Benzene/Water	60	5	5
2	10	DMFA/Water	60	5	Trace
3	10	CH_3CN	RT	5	71
4[b]	**10**	***n*-BuOH**	**RT**	**5**	**>99**
5	-	*n*-BuOH	RT	5	33
6	5	*n*-BuOH	RT	5	80
7	15	*n*-BuOH	RT	5	99
8	10	*n*-BuOH	RT	3	74

[a] Reaction conditions: 10-methylacridinium iodide (**4g**), indole (**5a**), anatase TiO_2, an appropriate solvent were irradiated with Xe lamp (5000 K, 35W) air oxygen, bubbling through the reaction mixture. [b] The reaction was carried out without irradiation.

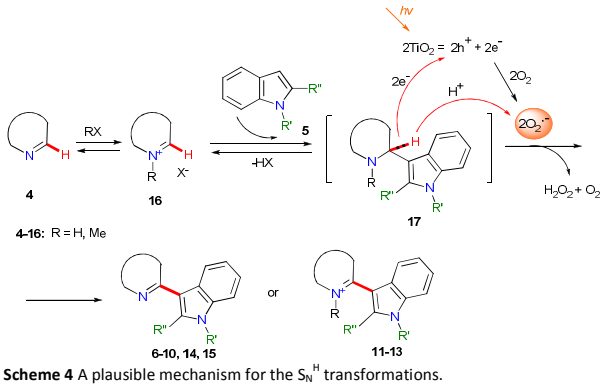
The activation of azaaromatics by means of their transformations into quaternary or *NH*-protonated salts **4f-h** (Table 2, entries 6-8) makes it possible to carry out their reactions with indoles (**5a-c**) and pyrrole (**5e**) under rather mild conditions, namely in *n*-butanol at room temperature. Yields of compounds **11a-c,e**, derived from acridinium hydrochloride (**4f**) proved to be in the range 55-70%. It can likely be explained by deprotonation of *NH*-azinium salts into nonactivated azines. Indeed, higher yields (85-99%) can be achieved by reacting of *N*-methylacridinium iodide (**4g**) with nucleophilic agents **5** (Table 2, entry 7). *N*-Alkylazinium salts are more stable, and have no tendency to loose their *N*-alkyl substituents in the reactions with nucleophilic reagents.[13] *N*-Methylquinoxalinium iodide (**4h**) proved to be less active toward nucleophiles **5** relative to the acridinium ion (**4g**), thus giving compounds **13a-c,e** in 74-78% yields (Table 2, entry 8), while quaternary salts of unsubstituted pyridine, quinoline and isoquinoline are unreactive under these conditions.

Azinones are rarely used as electrophilic agents in the S_N^H reactions.[28] We were able to show that quinoxalin-2-one (**4i**) (Table 2, entry 9) and 3-(pyridine-2-yl)-1,2,4-triazin-5(2*H*)-one (**4j**) (Table 2, entry 10) exhibit a high reactivity toward indoles (**5a-c**) and pyrrole (**5e**) in refluxing acetic acid, thus giving the S_N^H products **14a-c,e** and **15a-c,e** in yields of 92-99% and 60-62%, respectively.

As can be expected, electron-withdrawing substituents (Ac, CF_3) in the pyrrole ring have a negative effect on nucleophilic properties of pyrroles and indoles. Indeed, all attempts to carry out the C-H/C-H couplings of azaheterocycles with 2-acetyl- and 2-(trifluoromethyl) substituted pyrroles, as well as with 3-acetyl and 2-(trifluoromethyl) substituted indoles have failed. Positive results have been obtained only in the case of using 5-bromoindole (**5d**) as a nucleophilic reagent. The yields of compounds **6d-8d** and **11d-15d** are 35-89%. Also, it is worth noting that a more drastic reaction conditions (reflux in acetic acid) were needed to obtain compound **6d** (Table 2).

A plausible mechanism for participation of the oxidative system $h\nu/O_2/TiO_2$ in the S_N^H reactions of azaaromatics **4** is given in Scheme 4.

At the first step a reversible addition of nucleophilic reagents **5a-e** at a carbon atom of heteroarenes takes place. The second step involves elimination of hydrogen from the C-H bond of the intermediate σ^H-adducts **17**, as two electrons and H^+. The considered oxidative system (Schemes 2, 4) facilitates aromatization of dihydroazines **17** into S_N^H products **6-10**, **14**, **15** in case of neutral azines or **11-13** for cationic quaternary salts.

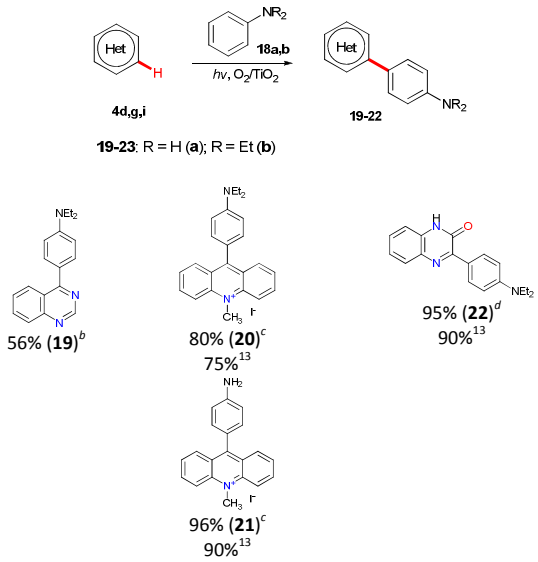


Scheme 4 A plausible mechanism for the S_N^H transformations.

Although the paper is dedicated to the synthesis of indoles and pyrroles derivatives, which are supposed to be interesting for medicinal chemistry, we have done a number of experiments, thus demonstrating that other aromatic C-nucleophiles, such as anilines and phenols, can be involved in

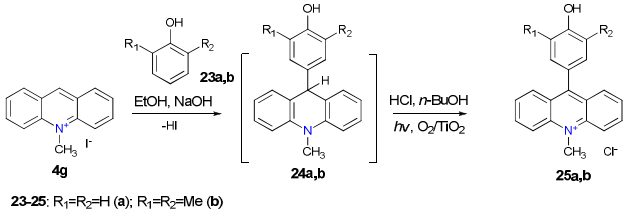
the conversions described above. Indeed, quinazoline easily adds diethylaniline at room temperature in a mixture trifluoroacetic acid-benzene (1:2) to give the corresponding σ^H-adduct (Table 2, entry 4) which is oxidised into 4-(4'-*N*,*N*-diethylaminophenyl)-quinazoline (**19**) in 56% yield. Heating of quinoxalin-2-one (**4i**) with *N*,*N*-diethylaniline in acetic acid affords compound **22** in 95% yield. 9-(4'-Diethylaminophenyl)-10-methylacridinium iodide (**20**) and 9-(4'-aminophenyl)-10-methylacridinium iodide (**21**) have been obtained at room temperature in *n*-BuOH in 75% and 96% yields, correspondingly (Table 4).

Table 4 C–H/C–H coupling of azaaromatics with anilines[a]



[a] Reaction conditions: azaaromatics **4**, anilines **18a,b**, TiO_2 (10 mass.%, anatase) were irradiated with Xe lamp (5000 K, 35 W) under air oxygen, bubbling through the reaction mixture for 5 h. Appropriate solvents and temperature: [b] CF_3COOH - C_6H_6 (1:2), NaOH (2 equiv.), RT; [c] *n*-BuOH, RT; [d] AcOH, 120 °C.

Phenol and 2,6-dimethylphenol (in their anionic forms) enter the reaction with *N*-methylacridinium iodide (**4g**) to give the dihydroacridines **24a**,**b**, which can be oxidised with O_2/TiO_2 system on irradiation in *n*-BuOH into biaryl derivatives **25a**,**b** in overall yields 80% and 90%, correspondingly.



Scheme 5 C–H/C–H coupling of **4g** with phenols **23a**,**b**.

A common feature of the studied reactions is that yields of vast majority of products derived from the C-H/C-H coupling of azaaromatics with indoles and pyrrole by using the aerobic oxidative procedure in the presence of TiO_2 and irradiation proved to be higher (from 5 to 50%), than those reported earlier in the literature[13,26-28] (Tables 2, 4). Use of the O_2/TiO_2 system for the synthesis of indolyl substituted acridines **6a-c** enables the temperature of the process to be decreased from 70 °C (for **6a-c**)[26] and 130 °C (for **21**)[13] to room temperature, while the reaction time for obtaining **12a** proved to be considerably reduced from 3 days[13] to 5 hours. Also the TiO_2-catalysed aerobic oxidative reactions of 3,6-diphenyl-1,2,4-triazine afford the S_N^H products **7a-c,e**, unlike the literature data,[27] without additional activation by benzoyl or acetyl chlorides.

Experimental

All reagents were purchased by Sigma Aldrich and used without any further purification. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were measured on a Bruker-400 AVANCE II spectrometer and recorded in ppm relative to an internal tetramethylsilane standard using DMSO-d_6 as the solvent. The mass spectra were measured on Bruker Daltonics micrOTOF-Q II mass spectrometer equipped with an orthogonal electrospray ionization (ESI) source, a six-port divert valve and syringe pump kd Scientific with flow rate 180 µl/hour. The elemental analysis was carried out on an automated Perkin Elmer PE 2400 series II CHNS/O analyzer. The course of the reactions was monitored by TCL on 0.25 mm silica gel plates (Merck 60F 254). The ultrasonic treatment was carried out on the digital ultrasonic cleaner Bandelin DT 31H (100 W, 35 kHz).

Synthesis of pyrrolyl and indolyl derivatives of acridine (6a-c,e) and 6-phenyl-[1,2,5]oxadiazolo[3,4-b]pyrazine (8a-e). A quartz tube containing a solution of acridine **4a** (1 mmol) or 6-phenyl-1,2,5-oxadiazolo[3,4-*b*]pyrazine **4c** (1 mmol), nucleophile (**5a-e**) (1 mmol) and TiO_2 (10 mass.%, anatase) in acetic acid (10 mL) was treated in ultrasonic bath for 5 min to obtain a suspension. The resulting mixture was exposed to Xe lamp (5000 K, 35 W) under air oxygen, bubbling through the reaction mixture at room temperature for 5 h. The reaction mixture was concentrated under a reduce pressure. The residue was purified by column chromatography on silica gel eluting with mixture hexane/ethyl acetate (8/2).

Synthesis of 9-(5-bromo-1*H*-indol-3-yl)acridine (6d) and pyrrolyl, indolyl derivatives of 3,6-diphenyl-1,2,4-triazine (7a-e). A quartz tube containing a solution of acridine **4a** or 3,6-diphenyl-1,2,4-triazine **4b** (1 mmol), nucleophile (**5a-e**) (2 mmol) and TiO_2 (10 mass.%, anatase) in acetic acid (10 mL) was treated in ultrasonic bath for 5 min to obtain a suspension. The resulting mixture was exposed to Xe lamp (5000 K, 35 W) under air oxygen, bubbling through the reaction mixture and was held at boiling for 5 h. The reaction mixture was concentrated under a reduce pressure. The residue was purified by column chromatography on silica gel eluting with mixture hexane/ethyl acetate (8/2).

Synthesis of 4-(1*H*-indol-3-yl)quinazoline (9a), 4-(1*H*-indol-3-yl)pyrimidine (10a) and 4-(4'-*N*,*N*-diethylaminophenyl)-quinazoline (19). To a round bottom flask were added a solution of quinazoline **4d** (1 mmol) or pyrimidine **4e** (1 mmol), indole **5a** (1 mmol) or *N*,*N*-diethylaniline **18b** (1,5 mmol) in

mixture trifluoroacetic acid/benzene 1/2 (10 mL). The reaction mixture was stirred at room temperature for 5 h. The solvent was further removed under vacuum. A quartz tube containing a solution of residue in ethanol, aqueous NaOH (2 equiv.) and TiO_2 (10 mass.%, anatase) was treated in ultrasonic bath for 5 min to obtain a suspension. The resulting mixture was exposed to Xe lamp (5000 K, 35 W) under air oxygen, bubbling through the reaction mixture at room temperature for 5 h. The reaction mixture was then transferred to separatory funnel. The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The organic extracts were combined and dried over Na_2SO_4, filtered and concentrated under a reduce pressure. The residue was purified by column chromatography on silica gel eluting with a mixture ethyl acetate/methanol (10/1).

Synthesis of 4-(1*H*-pyrrol-3-yl)quinazoline (9e). To a round bottom flask were added a solution of quinazoline **4d** (1 mmol), pyrrole **5e** (1 mmol) in mixture HCl/MeOH 1/2 (2 mL). The reaction mixture was stirred at room temperature for 10 h. The solvent was further removed under vacuum. A quartz tube containing a solution of residue in ethanol, aqueous NaOH (2 equiv.) and TiO_2 (10 mass.%, anatase) was treated in ultrasonic bath for 5 min to obtain a suspension. The resulting mixture was exposed to Xe lamp (5000 K, 35 W) under air oxygen, bubbling through the reaction mixture at room temperature for 5 h. The reaction mixture was then transferred to separatory funnel. The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The organic extracts were combined and dried over Na_2SO_4, filtered and concentrated under a reduce pressure. The residue was purified by column chromatography on silica gel eluting with a mixture ethyl acetate/methanol (10/1).

Synthesis of derivatives of acridinium chloride (11a-e), 10-methylacridinium iodide (12a-e, 20, 21) and 1-methylquinoxalin-1-ium iodide (13a-e). A quartz tube containing a solution of 10-hydroacridinium chloride **4f,** 10-methylacridinium iodide **4g** or 1-methylquinoxalinum iodide **4h** (1 mmol), nucleophile **5a-e** (2 mmol) or **18a,b** (2 mmol) in *n*-BuOH (10 mL) and TiO_2 (10 mass.%, anatase) was treated in ultrasonic bath for 5 min to obtain a suspension. The resulting mixture was exposed to Xe lamp (5000 K, 35 W) under air oxygen, bubbling through the reaction mixture at room temperature for 5 h. The reaction mixture was concentrated under a reduce pressure. Then dry diethyl ether was added to a solution and the form suspension was filtered. The residue was recrystallized from benzene or acetonitrile.

Synthesis of derivatives of quinoxalin-2(1*H*)-one (14a-e, 22), 3-(pyridin-4-yl)-1,2,4-triazin-5(4*H*)-one (15a-e). A quartz tube containing a solution of quinoxalin-2-one **4i** (1 mmol) or 3-(pyridine-2-yl)-1,2,4-triazin-5(2*H*)-one **4j** (1 mmol), nucleophile **5a-e** (1 mmol) or **18b** (2 mmol) and TiO_2 (10 mass.%, anatase) in acetic acid (10 mL) was treated in ultrasonic bath for 5 min to obtain a suspension. The resulting mixture was exposed to Xe lamp (5000 K, 35 W) under air oxygen, bubbling through the reaction mixture and was held at boiling for 5 h. The reaction mixture was concentrated under a reduce pressure. The residue was purified by column chromatography on silica gel eluting with mixture hexane/ethyl acetate (8/2) (for **14a-e, 22**) or mixture ethyl acetate/methanol (10/1) (for **15a-e**).

Synthesis of 9-(4'-hydroxyphenyl)-10-methylacridinium chloride (25a) and 9-(4'-hydroxy-3',5'-dimethylphenyl)-10-methylacridinium chloride (25b). To a round bottom flask were added a solution of phenol **23a** (1 mmol) or 2,6-dimethylphenol **23b** (1 mmol) in dry ethanol and NaOH. The reaction mixture was refluxed for 2 h. The hot solution of *N*-methylacridinium iodide **4g** was added in solution of phenol and refluxing was continued for 4 h. The reaction mixture was further concentrated under a reduce pressure. A quartz tube containing solution of residue and TiO_2 (10 mass.%, anatase) in *n*-BuOH and HCl (2 equiv.) was treated in ultrasonic bath for 5 min to obtain a suspension. The resulting mixture was exposed to Xe lamp (5000 K, 35 W) under air oxygen, bubbling through the reaction mixture at room temperature for 4 h. The reaction mixture was filtered. The solvent from filtrate was removed under vacuum. Then dry diethyl ether was added to resulting mixture and the form suspension was filtered. The residue was recrystallized from mixture ethyl acetate/methanol (1/1).

Conclusions

In conclusion, the aerobic photo-induced reactions of azines with indoles or pyrrole, proceeding in the presence of nanosized TiO_2, proved to be an easy, atom-economical, highly selective and environmentally benign method for the oxidative C-H/C-H coupling of two aromatic fragments. These S_N^H reactions have been shown to occur under ambient conditions, thus providing a convenient way to produce a variety of heterocyclic compounds of high value to pharmaceutical chemistry.

Acknowledgements

The research was financially supported by the Russian Science Foundation (Project No. 14-13-01177).

Notes and references

1 (a) M. Giampieri, A. Balbia, M. Mazzeia, P. La Collab, C. Ibbab, R. Loddo, *Antiviral Res.,* 2009, **83**, 179; (b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.,* 2010, **110***,* 4489; (c) M. A. A. Radwan, E. A. Ragab, N. M. Sabry, S. M. El-Shenawy, *Bioorg. Med. Chem.,* 2007, **15**, 3832; (d) Z. Jin, *Nat. Prod. Rep.,* 2009, **26**, 382; (e) I. S. Young, P. D. Thompson, A. Thompson, *Nat. Prod. Rep*., 2010, **27**, 1801; (f) J. Y. Choi, C. M. Calvet, D. F. Vieira, S. S. Gunatilleke, M. D. Cameron, J. H. McKerrow, L. M. Podust, W. R. Roush, *ACS Med. Chem. Lett*., 2014, **5**, 434; (g) M. E. McDonnell, H. Bian, J. Wrobel, G. R. Smith, S. Liang, H. Mab, A. B. Reitz, *Bioorg. Med. Chem. Lett*., 2014, **24**, 1116; (h) T. Ganesh, J. Jiang, R Dingledine, *Eur. J. Med. Chem.,* 2014, **82**, 521; (i) J. A. Sindac, S. J. Barraza, C. J. Dobry, J. Xiang, P. K. Blakely, D. N. Irani, R. F. Keep, D. J. Miller, S. D. Larsen, *J. Med. Chem*., 2013, **56**, 9222.

2 (a) I. M. Kompis, K. Islam, R. L. Then, *Chem. Rev.*, 2005, **105**, 593; (b) S. R. Walker, E. J. Carter, B. C. Huff, J. C. Morris,

Chem. Rev., 2009, **109**, 3080; (c) C. M. Marson, *Chem. Rev.* 2011, **111**, 7121; (d) H. Hussain, A. Al-Harrasi, A. Al-Rawahi, I. R. Green, S. Gibbons, *Chem. Rev*., 2014, **114**, 10369; (e) L. M. Blair, J. Sperry, *J. Nat. Prod.*, 2013, **76**, 794.

3 (a) M. Somei, F. Yamada, *Nat. Prod. Rep*., 2004, **21**, 278; (b) G. C. Muscia, S. Hautmann, G. Y. Buldain, S. E. Asis, M. Gutschow, *Bioorg. Med. Chem. Lett*., 2014, **24**, 1545; (c) G. Jie, A. Bao-Ling, A. V. Terry Jr., *Bioorg. Med. Chem. Lett*., 2014, **24**, 1472.

4 B. Winblad, M. Fioravanti, T. Dolezal, I. Logina, I. Gospodinov Milanov, D. C. Popescu, A. Solomon, *Clin. Drug Invest*., 2008, **28**, 533.

5 A. Mosquera, R. Riveiros, J. P. Sestelo, L. A. Sarandeses, *Org. Lett*., 2008, **10**, 3745.

6 (a) K. S. Feldman, P. Ngernmeesri, *Org. Lett*., 2011, **13**, 5704; (b) B. Wang, H. Qin, F. Zhang, Y. Jia, *Tetrahedron Lett.,* 2014, **55**, 1561.

7 M. Simone, E. Erba, G. Damia, F. Vikhanskaya, A. M. Di Francesco, R. Riccardi, Ch. Bailly, C. Cuevas, J. M. F. Sousa-Faro, M. D Incalci, *Eur. J. Cancer,* 2005, **41**, 2366.

8 (a) *Metal-Catalysed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2nd edn,. 2004, 938 p.; (b) *Palladium in Heterocyclic Chemistry*, ed. J. J. Li, G. W. Gribble, Pergamon Press, Oxford, 2000, 612 p., (c) L. Anastasia, E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, Wiley, New York, 2002, vol. 1 and 2, 3427 p.

9 (a) A. Armstrong, J. C. Collins, *Angew. Chem. Int. Ed*., 2010, **49**, 2282; (b) A. D. Yamaguchi, D. Mandal, Y. Yamaguchi, K. Itami, *Chem. Lett.,* 2011, **40**, 555; (c) R. Rossi, F. Bellina, M. Lessi, Ch. Manzinia, *Adv. Synth. Catal.,* 2014, **356**, 17; (d) F. Jafarpour, M. B. A. Olia, H. Hazratia, *Adv. Synth. Catal.,* 2013, **355**, 3407; (e) X. Liu, D. Wang, Y. Chen, D. Tang, B. Chena, *Adv. Synth. Catal.,* 2013, **355**, 2798; (f) Sh. Peng, L. Wang, J. Huang, Sh. Sun, H. Guo, J. Wang, *Adv. Synth. Catal.,* 2013, **355**, 2550; (g) W. Zhou, P. Li, Y. Zhang, L. Wang, *Adv. Synth. Catal.,* 2013, **355**, 2343; (h) M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.,* 2012, **51**, 6993; (i) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.*, 2012, **51**, 8960; (j) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* 2013, **52**, 11726; (k) L. Ackermann, *Chem. Rev.* 2011, **111**, 1315; (l) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740.

10 (a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.,* 2007, **9**, 411; (b) R. A. Sheldon, I. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, 2007, 448 p; (c) M. J. Mulvihill, E. S. Beach, J. B. Zimmerman, P. T. Anastas, *Annu. Rev. Environ. Resour.,* 2011, **36**, 271; (d) P. Anastas, N. Eghbali, *Chem. Soc. Rev.,* 2010, **39**, 301; (e) M. Lancaster, *Green Chemistry. An Introductory Text*, The Royal Society of Chemistry, Chembrige, 2nd edn, 2010, 328 p.; (f) J. Wencel-Delord, F. Glorius, *Nature Chem.,* 2013, **5**, 369.

11 (a) V. N. Charushin, O. N. Chupakhin, *Pure Appl. Chem.,* 2004, **76**, 1621; (b) M. Mąkosza, *Chem. Soc. Rev.,* 2010, **39**, 2855; c) M. Mąkosza, *Synthesis,* 2011, **15**, 2341; (d) M. Mąkosza, K. Wojciechowski, *Heterocycles,* 2014, **88**, 75; (e) *Metal Free C-H Functionalisation of Aromatics. Nucleophilic Displacement of Hydrogen*, ed. V. N. Charushin, O. N. Chupakhin, *in Topics in Heterocyclic Chemistry*, vol. 37, ed. B .U. W. Maes, J. Cossy, S. Poland, Springer, 2014, 283 p.; (f) F. Terrier, *Modern Nucleophilic Aromatic Substitution*, Wiley-VCH, Weinheim, 2013, 488 p.

12 (a) E. J. Corey, Y. Tian, *Org. Lett.,* 2005, **7**, 5535; (b) Q. Chen, T. León, P. Knochel, *Angew. Chem. Int. Ed.,* 2014, **53**, 8746; (c) I. A. Utepova, O. N. Chupakhin, P. O. Serebrennikova, A. A. Musikhina, V. N. Charushin, *J. Org. Chem*., 2014, **79**, 8659.

13 O. N. Chupakhin, V. N. Charushin, H. C. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, New York, San Diego, 1994, 367 p.

14 (a) O. N. Chupakhin, I. A.Utepova, I. S. Kovalev, V. L. Rusinov, Z. A. Starikova, *Eur. J. Org. Chem.,* 2007, **5**, 857; (b) I. A. Utepova, A. A. Musikhina, O. N. Chupakhin, P. A. Slepukhin, *Organometallics,* 2011, **30**, 3047; (c) M. V. Varaksin, I. A. Utepova, O. N. Chupakhin, V. N. Charushin, *J. Org. Chem.,* 2012, **77**, 9087; (d) P. S. Fier, J. F. Hartwig, *Science,* 2013, **342**, 956.

15 P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.,* 2014, **136**, 10139.

16 (a) R. E. Beveridge, B. A. Arndtsen, *Synthesis*, 2010, **6**, 1000; (b) O.-I. Patriciu, C. Pillard, A.-L. Fînaru, I Săndulescu, G. Guillaumet, *Synthesis,* 2007, **24**, 3868; (c) N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh, M. Miura, *Org. Lett.,* 2010, **12**, 2358; (d) H. Bonin, M. Sauthier, F.-X. Felpin, *Adv. Synth. Catal.*, 2014, **356**, 645; (e) M. Brasse, J. A. Ellman, R. G. Bergman, *Chem. Commun*., 2011, **47**, 5019; (f) J. A. Ashenhurst, *Chem. Soc. Rev.*, 2010, **39**, 540.

17 (a) L. Fra, A. Millán, J. A. Souto, K. Muñiz, *Angew. Chem. Int. Ed.*, 2014, **53**, 7349; (b) Y. Li, D. Zhang-Negrerie, Y. Du, K. Zhao, *Tetrahedron* 2015, **71**, 2927; (c) R. Samanta, K. Matcha, A. P. Antonchick, *Eur. J. Org. Chem*., 2013, 5769; (d) K. Moriyama, K. Ishida, H. Togo, *Chem. Commun.*, 2015, **51**, 2273; (e) R. Narayan, S. Manna, A. P. Antonchick, *Synlett*, 2015, **26**, doi: 10.1055/s-0034-1379912.

18 F. Saikh, R. De, S. Ghosh, *Tetrahedron Lett.,* 2014, **55**, 6171.

19 H. Kisch, *Angew. Chem. Int. Ed*., 2013, **52**, 812.

20 (a) H. Zhang, G. Chen, D. W. Bahnemann, *J. Mater. Chem.,* 2009, **19**, 5089; (b) G. Liu, L. Wang; H. G. Yang, H.-M. Cheng, G. Q. Lu, *J. Mater. Chem.,* 2010, **20**, 831; (c) H. Kominami, S. Iwasaki, T. Maeda, K. Imamura, K. Hashimoto, Y. Kera, B. Ohtani, *Chem. Lett.,* 2009, **38**, 410; (d) E. Vasilikogiannaki, Ch. Gryparis, V. Kotzabasaki, *Adv. Synth. Catal.,* 2013, **355**, 907.

21 (a) Q. Wang, M. Zhang, C. Chen, W. Ma, J. Zhao, *Angew. Chem. Int. Ed.,* 2010, **49**, 7976; (b) E. A. Kozlova, N. S. Kozhevnikova, S. V. Cherepanova, T. P. Lyubina, E. Yu. Gerasimov, V. V. Kaichev, A. V. Vorontsov, S. V. Tsybulya, A. A. Rempel, V. N. Parmon, *J. Photochem. Photobiol. A,* 2012, **250**, 103; (c) V. Augugliaro, T. Caronna, V. Loddo, G. Marcì, G. Palmisano, L. Palmisano, S. Yurdakal, *Chem. Eur. J.,* 2008, **14**, 4640; (d) S. Yurdakal, G. Palmisano, V. Loddo, O. Alagöz, V. Augugliaro, L. Palmisano, *Green Chem.,* 2009, **11**, 510; (e) C. Caro, K. Thirunavukkarasu, M. Anilkumar, N. R. Shiju, G. Rothenberg, *Adv. Synth. Catal*., 2012, **354**, 1327.

22 X. Lang, H. Ji, C. Chen, W. Ma, J. Zhao, *Angew. Chem. Int. Ed.,* 2011, **50**, 3934.

23 K. Selvam, M. Annadhasan, R. Velmurugan, M. Swaminathan, *Bull. Chem. Soc. Jpn*., 2010, **83**, 831.

24 H. R. Memarain, M. Ranjbar, *J. Mol. Catal. A - Chem.,* 2012, **356**, 46.

25 M. Yu, Y. Wang, W. Sun, X. Yao, *Adv. Synth. Catal.,* 2012, **354**, 71.

26 A. K. Sheinkman, A. N. Kost, S. G. Potashnikova, A. O. Ginzburg, S. N. Baranov, *Chem. Heterocycl. Compd*., 1971, **7**, 607.

27 V. L. Rusinov, D. N. Kozhevnikov, I. S. Kovalev, O. N. Chupakhin, G. G. Aleksandrov, *Russ. J. Organ. Chem*., 2000, **36**, 1050.

28 (a) I. Ya. Postovskii, O. N. Chupakhin, T.L. Pilicheva, Yu. Yu. Popelis, *Dokl. Akad. Nauk SSSR, ser. khim.* 1973, **212**, 1125 [*CA* 1974, **80**, 27193]; (b) Y.-Y. Han, Z.-J. Wub, X.-M. Zhang, W.-C. Yuan, *Tetrahedron Lett.,* 2010, **51**, 2023.

29 (a) W. P. K. Girke, *Chem. Ber*., 1979, **112**, 1348; (b) D. G. Beresnev, N. A. Itsikson, O. N. Chupakhin, V. N. Charushin, M. I. Kodess, A. I. Butakov, G. L. Rusinov, Yu. Yu. Morzherin, A. I. Konovalov, I. S. Antipin, *J. Org. Chem.*, 2006, **71**, 8272; (c) N.

A. Itsikson, D. G. Beresnev, G. L. Rusinov, O. N. Chupakhin, *Arkivoc*, 2004, **xii**, 6.

30 E. V. Verbitskiy, E. M. Cheprakova, E. F. Zhilina, M. I. Kodess, M. A. Ezhikova, M. G. Pervova, P. A. Slepukhin, J. O. Subbotina, A. V. Schepochkin, G. L. Rusinov, O. N. Chupakhin, V. N. Charushin, *Tetrahedron,* 2013, **69**, 5164.