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# The strategy of combined application of nucleophilic aromatic substitution of hydrogen ($S_N^H$) and transition metal-catalyzed cross-coupling reactions

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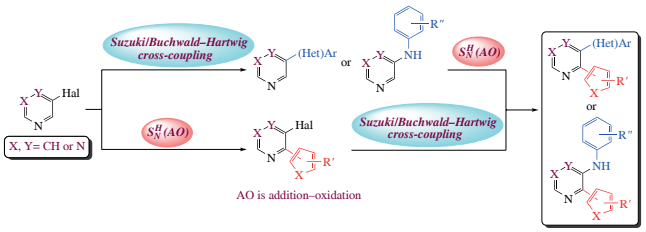
**Two powerful tools of organic synthesis, transition metal-catalyzed cross-coupling reactions and metal-free $S_N^H$ reactions leading to nucleophilic displacement of hydrogen of the C($sp^2$)–H bond, have been combined into one convenient synthetic strategy. This idea has made it possible to obtain a wide variety of substituted azine derivatives, including push–pull systems, new biologically active compounds, organic semiconductors and sensor materials.**




*Keywords*: C–H functionalization, $S_N^H$ reactions, Suzuki–Miyaura reaction, Buchwald–Hartwig reaction, Sonogashira reaction, Heck reaction, cross-coupling, pyrimidines, pyrazines, triazines, fused aza-aromatic compounds.

Transition metal-catalyzed cross-coupling reactions represent a group of related catalytic processes that provide the family of the universal and versatile methods for the formation of carbon–carbon or carbon–heteroatom bonds.[1–3] The process can be clearly illustrated by a straightforward reaction scheme which summarizes the combination of two molecular fragments derived from an organic reagent with a good leaving group ($Ar^1$–X) and an organometal/metaloid species ($Ar^2$–M) (Scheme 1). To combine the two organic molecules efficiently, an organometallic transformation has to take place, mediated by a transition metal complex serving as a catalyst. Since the groundbreaking studies performed by Heck, Negishi, and Suzuki, which were honored with the Nobel Prize in Chemistry in 2010,[4,5] palladium complexes have long been recognized as the most versatile and effective catalysts for cross-coupling processes.[6] The catalytic cycle is generally straightforward and can be outlined in three distinct steps (see Scheme 1). First, an organic halide undergoes an oxidative addition reaction with palladium(0), resulting in the formation of a palladium(II) complex. Next, a transmetalation occurs, producing another $Pd^{II}$ complex containing two moieties which are supposed to be coupled. Finally, reductive elimination takes place, leading to the formation of the coupling product with simultaneous regeneration of the active $Pd^0$ catalyst.

While cross-coupling reactions offer notable convenience for applications, they have also significant drawbacks. These include the reliance on expensive catalysts, particularly those based on palladium and other transition metals. Additionally, these reactions often require the use of ligands, typically toxic and often expensive phosphines. Furthermore, there is usually a need for the preliminary functionalization of (hetero)arenes with halogens, resulting in an inevitable dependence on the so-called chlorine-based technologies.

There are several approaches to overcome these shortcomings in organic synthesis procedures. (1) To decrease reliance on palladium catalysts, the effective application of 'homeopathic' palladium catalysis has been thoroughly investigated for a number of cross-coupling reactions. Pioneering studies performed by the groups of Beletskaya, Reetz, de Vries, and

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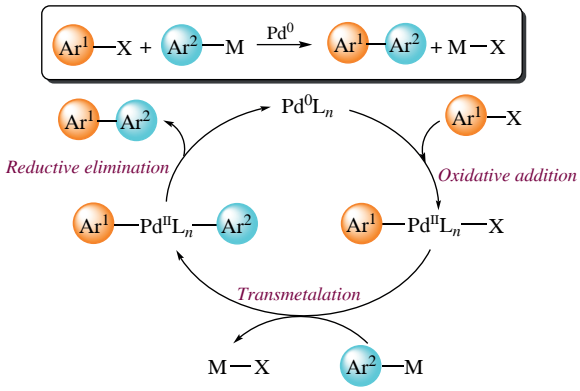



**Scheme 1** A general representation of Pd-catalyzed cross-coupling catalytic cycle.

Ananikov have demonstrated that palladium nanoparticles could effectively catalyze the various Heck and Suzuki–Miyaura reactions at the ppm concentration levels.[7–12] In addition, palladium-based catalysts can be replaced by equally effective catalysts based on nickel, iron, and other cheaper transition metals.[13–15] (2) Promising eco-friendly synthetic protocols for carrying out cross-coupling reactions without ligands have been developed.[16] (3) A considerable attention has been focused on the incorporation of direct, metal-free methods for nucleophilic C–H functionalization of (hetero)aromatics in both the theory and practice of organic synthesis.[17] These methods dramatically change traditional approaches to organic synthesis, regarding the C($sp^2$)–H bond as a functional group. This allows one to modify the molecules without the need in preliminary incorporation of good leaving groups. As a result, these methods provide a more efficient, low-stage, and low-waste pathways for molecule transformations, corresponding to the PASE (Pot-Atom-Step-Economic) principle.[18,19]

Direct C–H bond functionalization relies on two primary synthetic approaches: transition metal catalysis and metal-free reactions. Numerous articles and reviews published over the past decade have demonstrated that direct transition metal-catalyzed C–H (het)arylation reactions provided an effective and powerful tool for the regioselective synthesis of azaaromatic compounds.[20–25] However, considering priority of the environmentally benign processes, transition metal-free reactions are certainly more attractive procedures, and one of the most advanced in this series appears to be the reaction of nucleophilic aromatic substitution of hydrogen ($S_N^H$). The pioneer review by Profs. Oleg Chupakhin and Isaac Postovsky, published in the Russian Chemical Reviews in 1976, marked the beginning of the development of the $S_N^H$ methodology.[26]

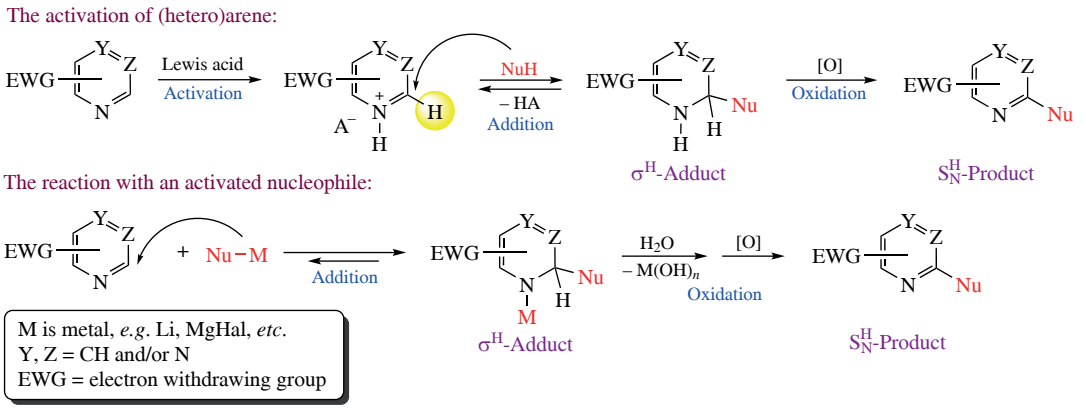
The currently accepted concepts involve two approaches for conducting $S_N^H$ reactions (Scheme 2).[27] The first approach is based on activation of the heterocyclic substrate through interaction with the Lewis acids, while the second one utilizes activated nucleophiles such as organolithium or organomagnesium derivatives. Generally, these reactions can be described as two-step processes. In the first step, nucleophilic species are reversibly added to the azaheterocyclic ring to form the corresponding $\sigma^H$-adducts. In the second step, the $\sigma^H$-adducts undergo aromatization, typically through oxidation. In some cases, atmospheric oxygen can act as an oxidant. This kind of process is considered as the 'addition–oxidation' mechanism $S_H^N$(AO). Another known mechanism, the 'addition–elimination' pathway $S_H^N$(AE), involves the removal of hydrogen from the $\sigma^H$-adducts, and it requires the presence of special auxiliary groups.

Several books and monograph chapters, and an extensive list of review articles have been published on this topic, featuring hundreds of references to the original research studies.[28–50] These works highlight the significant role of transition metal-free direct C–H functionalization as one of the key methodologies in modern organic synthesis.

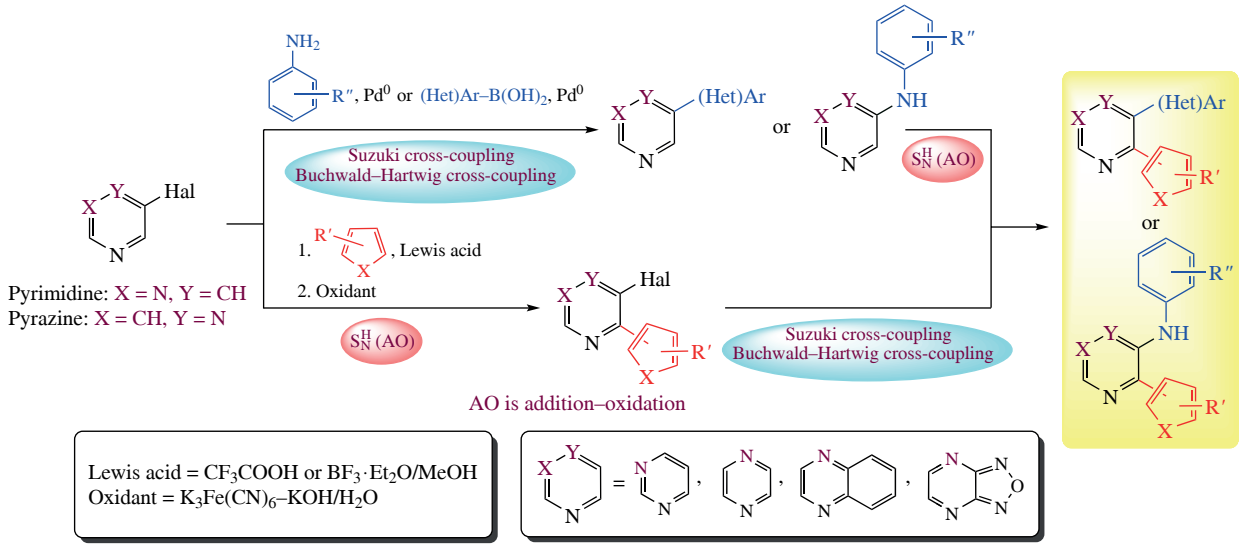
This review summarizes the cooperative use of the $S_N^H$ reactions alongside transition metal-catalyzed cross-couplings (Scheme 3).

Metal-free $S_N^H$ and metal-catalyzed cross-coupling reactions can be complementary to each other, as illustrated by transformations of the appropriate substrates such as 5-bromopyrimidine. Specifically, a palladium-catalyzed cross-coupling reaction can be employed to modify the less active $C^5$ position of the pyrimidine ring. In contrast, the $S_N^H$ methodology is effective for the nucleophilic C–H functionalization of a more reactive $C^4$ position. It is important to note that various combinations of these two types of C–C coupling reactions, such as addition–oxidation or addition–elimination, along with different sequences of steps, can be utilized to obtain a variety of 4,5-disubstituted pyrimidines (Schemes 4 and 5).[51–55]

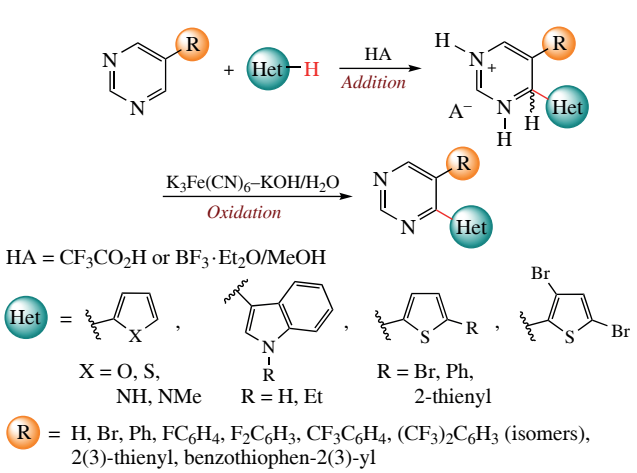
The use of 2-chloropyrimidine as the starting material, followed by the *ipso*-substitution of 2-positioned chlorine atom, enabled to perform the synthesis of 2,4,5-trisubstituted pyrimidines (Scheme 6).[56] It is important to note that the introduction of an electron-donative (thio)morpholino substituent (step i) decreases the electrophilicity of the pyrimidine ring. Under acid activation conditions, this led to the formation of the target products only in trace amounts (step iii). To address this, nucleophile activation was beneficial; indeed, thienyllithium proved to react with 5-bromo-substituted pyrimidine (step iv). Subsequent cross-coupling resulted in the target products with yields of up to 80%. In the series of mono-, di-, and trisubstituted pyrimidines obtained, the compounds exhibiting a significant anti-tuberculosis activity against *Mycobacterium tuberculosis* $H_{37}Rv$, as well as against multiple drug-resistant strains, were identified.[53–56]




**Scheme 2** A general representation of two versions for the $S_H^N$(AO) reactions.




**Scheme 3** Combination of the metal-free $S_N^H$ and metal-catalyzed cross-coupling reactions for 1,3-/1,4-diazine derivatives developed at the Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences.



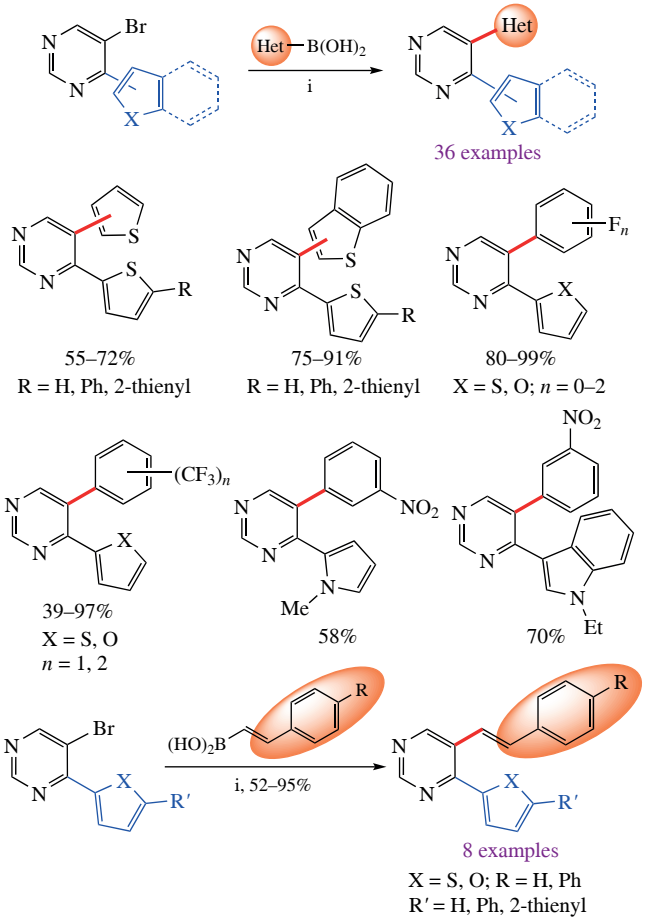

**Scheme 4** Synthesis of 4-(hetero)aryl- and 4,5-di(hetero)arylpyrimidines through the $S_N^H$ methodology.

The synthesis of *N*-aryl-4-(5-nitrofuran-2-yl)pyrimidin-5-amines was achieved through a series of reactions involving nucleophilic aromatic substitution of hydrogen with furan, followed by nitration and the Buchwald–Hartwig amination. The protocol was based on using available 5-bromopyrimidine as the starting material (Scheme 7).[57,58] Notably, all derivatives obtained proved to exhibit a broad spectrum of antibacterial activity.

Indolo[2,3-*b*]quinoxaline scaffold is a significant core of many pharmacologically active compounds exhibiting antiviral, antitumor, and antidiabetic activities.[59] The use of the Buchwald–Hartwig cross-coupling and the intramolecular $S_N^H$ reaction for some 2-(hetero)aryl-substituted quinoxalines allowed us to develop a new synthetic approach to indolo[2,3-*b*]quinoxaline derivatives and their heteroanalogues. These polycyclic compounds have shown to possess promising antitubercular and anticoagulant properties (Scheme 8).[60–62]

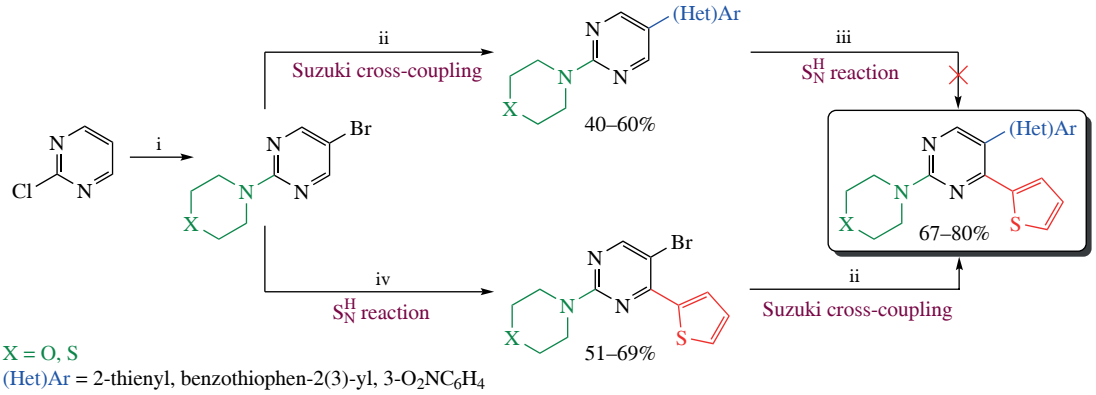
The strategy that combines nucleophilic aromatic substitution of hydrogen (the $S_N^H$ reactions) and transition metal-catalyzed cross-couplings does not only facilitate the creation of biologically active compounds, but also serves as an effective method to obtain a wide range of linear, V-shaped, and branched push–pull systems (Scheme 9).[63–72]

The push–pull compounds obtained were estimated as sensors for detecting model nitro-explosives in solutions and the vapor phase. It has been shown that the detection limits correlate with

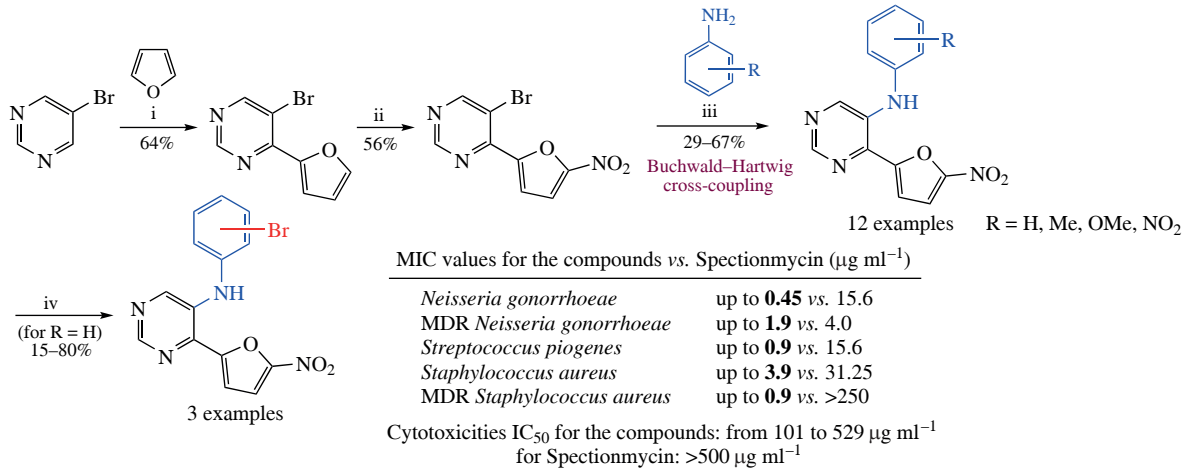



**Scheme 5** Synthesis of 4,5-di(hetero)arylpyrimidines through the Suzuki–Miyaura cross-coupling reactions. *Reagents and conditions*: i, $Pd(PPh_3)_4$, $K_2CO_3$, 1,4-dioxane, $H_2O$, MW, 165 °C, 20 min.

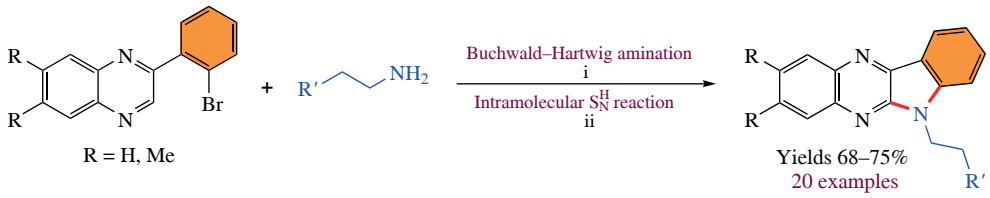
the structures of the push–pull systems. Generally, limits of detection (LODs) for linear or slightly sterically hindered V-shaped systems proved to have the lowest values (in other words, their sensitivities were at the highest level). In contrast, azolo annulation or introduction of additional substituents at the $C^5$ position of the pyrimidine ring resulted in a notable decrease in sensitivity (Figure 1). Additionally, these fluorophores have demonstrated high sensitivity and selectivity in relation to the vapors of nitroaromatic compounds (Figure 2).[73] The same push–pull compounds were exploited to develop an ultra-

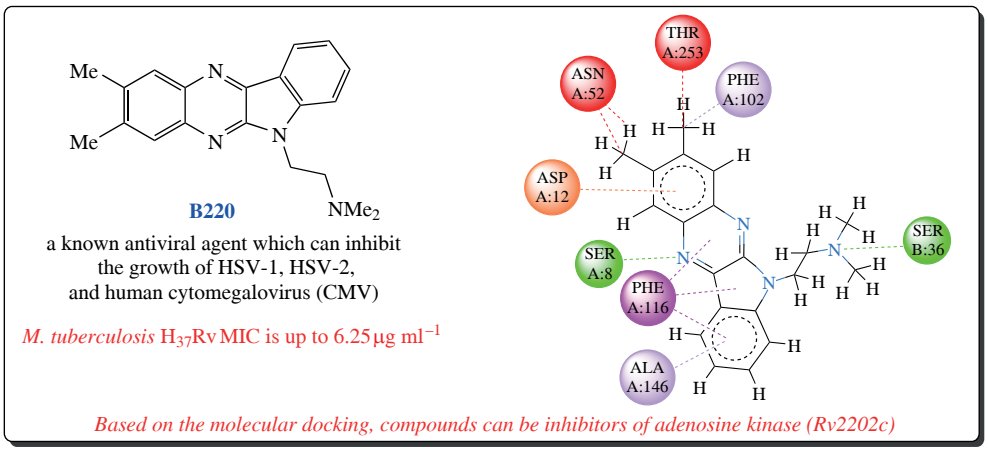



**Scheme 6** Synthesis of 4,5-di(het)aryl-2-(thio)morpholinopyrimidines from 2-chloropyrimidine. *Reagents and conditions*: i, (thio)morpholine, then $Br_2$; ii, (Het)ArB$(OH)_2$, $Pd(PPh_3)_4$, $K_2CO_3$, THF–$H_2O$, MW (155 °C), 20 min; iii, thiophene, $CF_3CO_2H$, then $K_3Fe(CN)_6$, KOH, $H_2O$; iv, 2-lithiothiophene, $Et_2O$, then $K_3Fe(CN)_6$, KOH, $H_2O$.




**Scheme 7** Synthesis of *N*-aryl-4-(5-nitrofuran-2-yl)pyrimidin-5-amines through combination of the $S_N^H$ and Buchwald–Hartwig amination reactions. *Reagents and conditions*: i, $CF_3CO_2H$, room temperature, 24 h, then $K_3Fe(CN)_6$, KOH, $H_2O$, room temperature, 24 h; ii, $HNO_3$, $H_2SO_4$, $CH_2Cl_2$, –10 °C; iii, $Pd(OAc)_2$, $K_3PO_4$, ligand, 1,4-dioxane, MW (150 °C), 10 min; iv, NBS (1–3 equiv.).

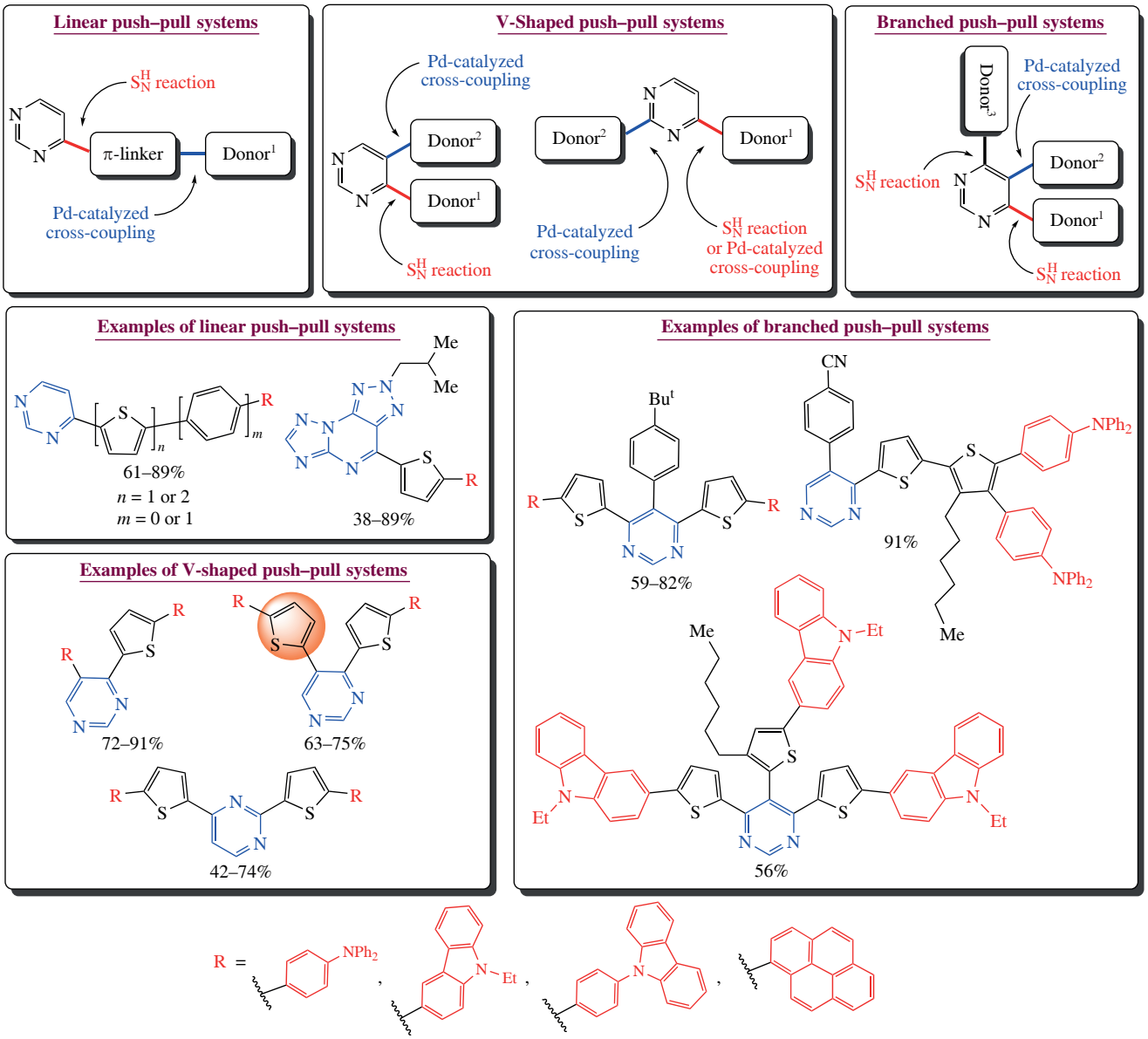



**Scheme 8** A new approach to biologically active indolo[2,3-*b*]quinoxaline derivatives and their heteroanalogues through the Buchwald–Hartwig cross-coupling and the $S_N^H$ reactions. *Reagents and conditions*: i, $Pd(OAc)_2$, phosphine ligand, base, solvent, MW, 15 min; ii, $O_2$ (air), acid, room temperature, 2 h.

sensitive electrochemical sensor measuring nitrobenzene in water and food products.[74]

Another promising application of aza-aromatic push–pull systems is their use as unconventional anchor groups in dye-sensitized solar cells, commonly known as the Graetzel cells.[75] In 2014, the development and properties of solar cell photosensitizers based on pyrimidine push–pull systems were reported for the first time, achieving an efficiency of 0.91%.[53,54]




**Scheme 9** Approaches to linear, V-shaped, and branched push–pull systems based on 1,3-diazines.

In 2020, theoretical studies suggested the potential for solar cells using these systems to reach efficiencies of 7–8%.[76] These calculations were confirmed experimentally in 2022, when appropriate dyes demonstrated the performance up to 6.37%.[77]

Photoactive V-shaped push–pull systems based on the 1,2,4-triazine core were obtained similarly using combinations of the $S_N^H$ and Suzuki cross-coupling reactions (Scheme 10).[78]

The use of two $S_N^H$ (nucleophilic aromatic substitution of hydrogen) and the Kumada cross-coupling reactions proved to

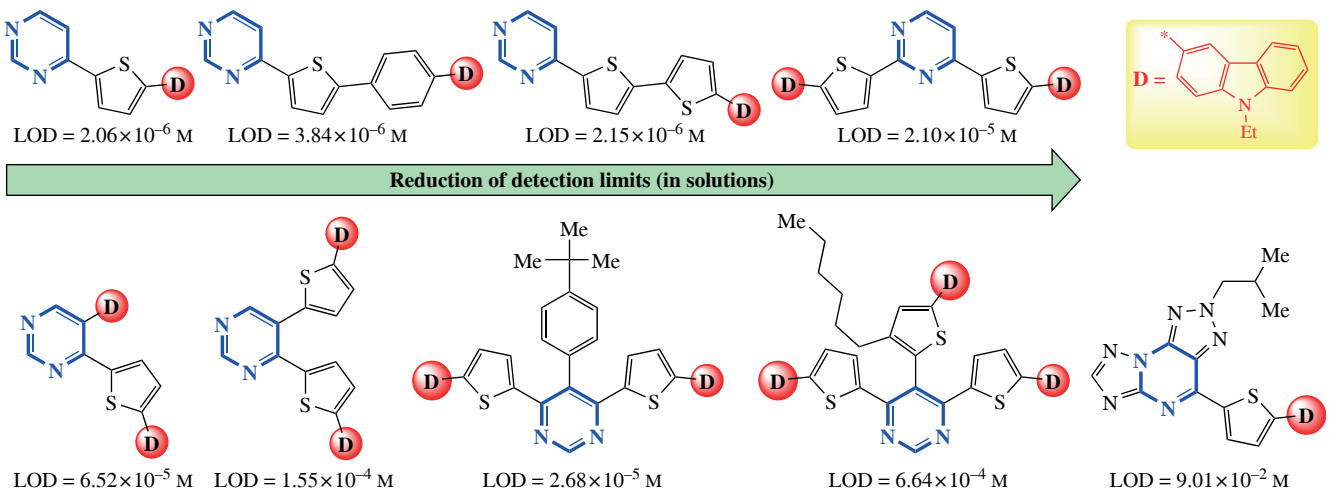
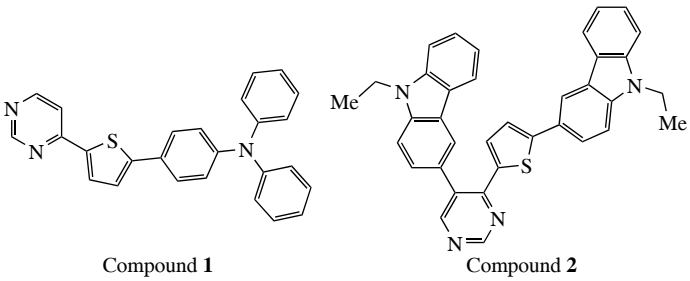
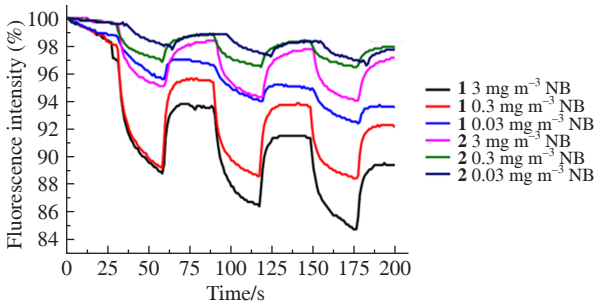



**Figure 1** Structural effects of pyrimidine-based push–pull systems on TNT detection limits.

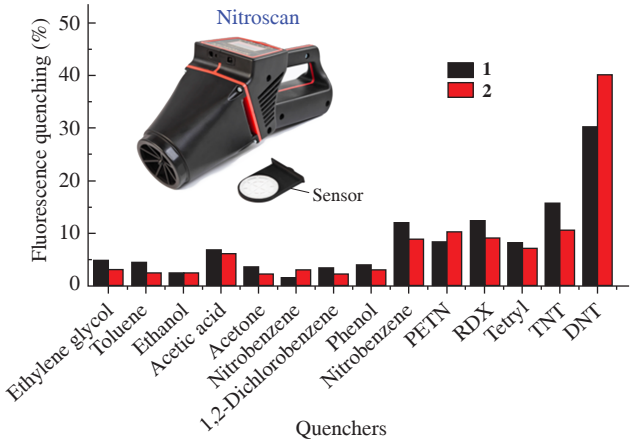



Compound **1** Compound **2**

Structures of fluorophores **1** and **2** with the best data for detection limits in acetonitrile solutions.

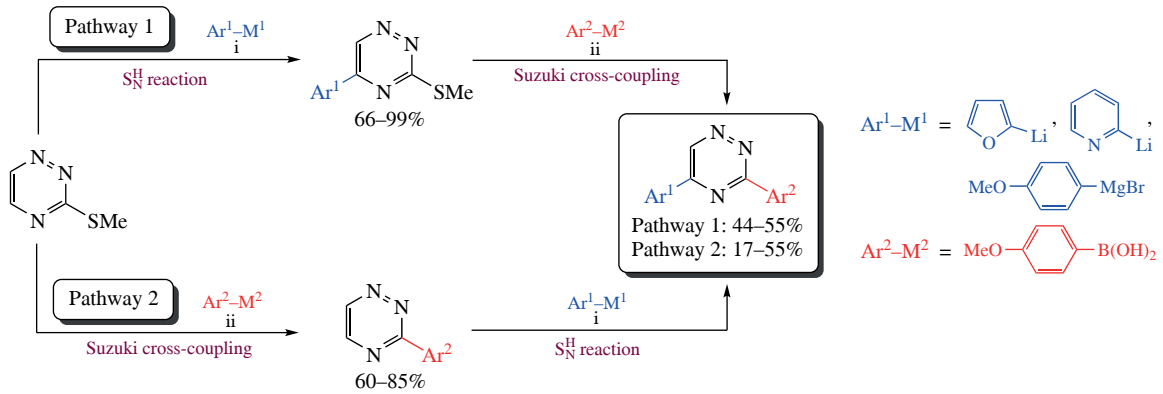



Fluorescent recovery cycles for the sensor on the basis of **1** and **2** in the device 'Nitroscan' with exposure to nitrobenzene (NB) vapor with various concentrations.

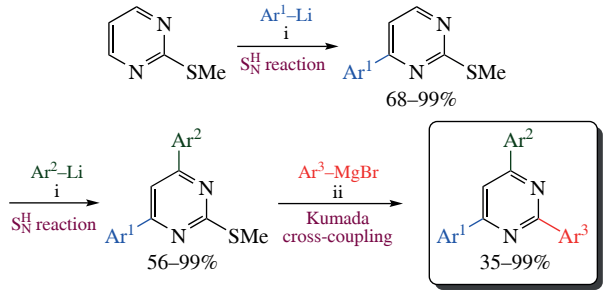



Sensor's **1** and **2** fluorescence quenching (%) in the first cycle towards various nitro-explosives and volatile interferents at room temperature.

**Figure 2** Sensitivity and selectivity of pyrimidine-based push–pull systems in relation to the vapors of nitroaromatic compounds.




**Scheme 10** Synthesis of V-shaped push–pull systems based on the 1,2,4-triazine core. *Reagents and conditions*: i, $Ar^1$–$M^1$, THF, then $NH_4Cl$, $H_2O$, DDQ; ii, $Ar^2$–$M^2$, $Pd(PPh_3)_4$, 2-$MeOC_6H_4C(O)OCu$, THF.



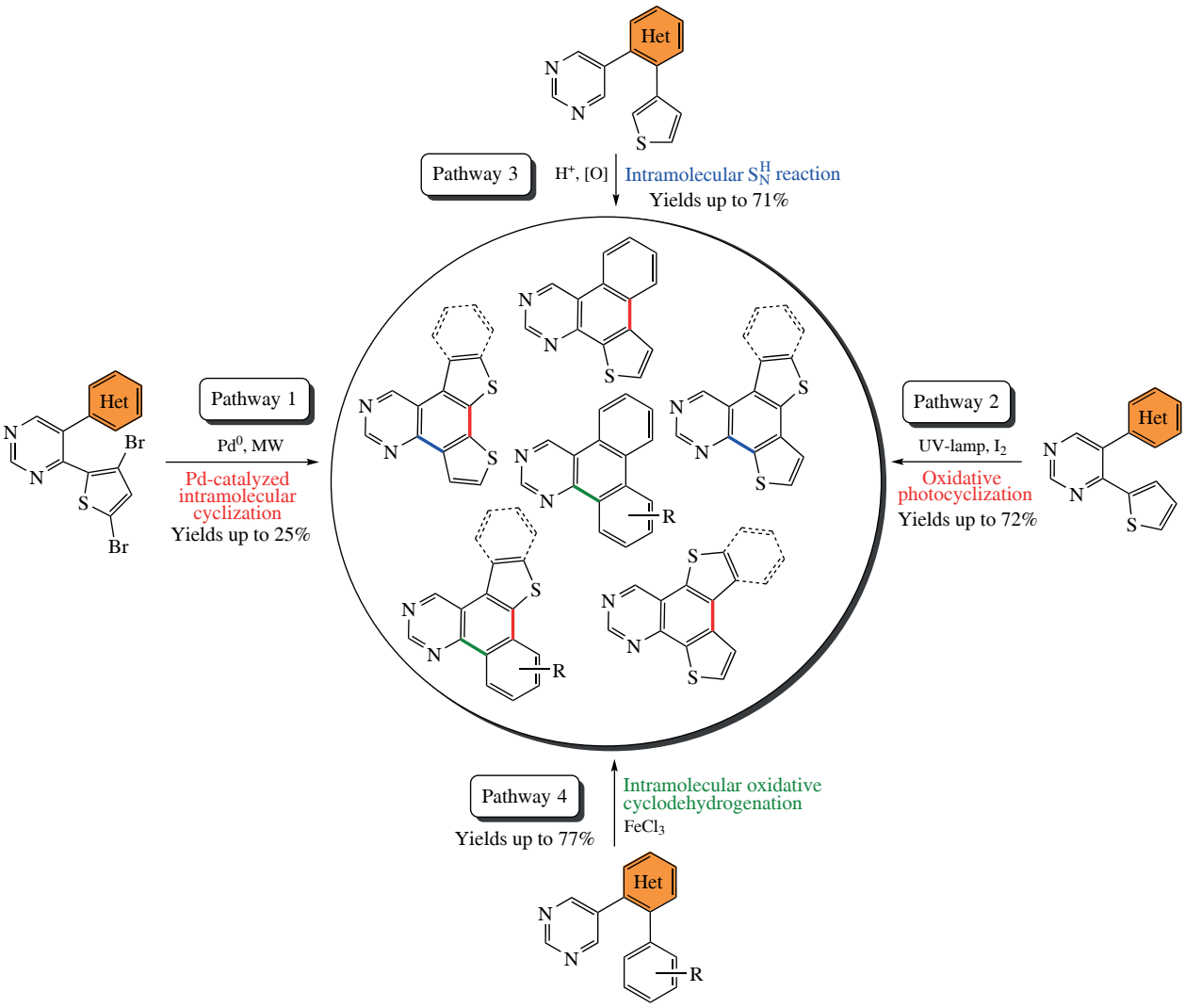

Ar¹, Ar², Ar³ = Ph, *o*/*m*/*p*-$MeOC_6H_4$, *p*-$BuC_6H_4$, *p*-$Me_2NC_6H_4$, *p*-$FC_6H_4$, *p*-$F_3CC_6H_4$, *p*-$PhC_6H_4$, 1-naphthyl, 2-naphthyl

**Scheme 11** Synthesis of star-shaped push–pull systems based on the pyrimidine core. *Reagents and conditions*: i, $Ar^1Li$ or $Ar^2Li$, THF, 0 °C, then AcOH, DDQ, room temperature; ii, $Ar^3MgBr$, $NiCl_2$(dppe), PhMe, 60 °C, 24 h.

be a convenient pathway to obtain pyrimidine-based star-shaped push–pull systems exhibiting interesting photophysical properties (Scheme 11).[79]

Furthermore, the synthetic strategy outlined can be regarded as a powerful tool for developing a diversity of both known and novel polycyclic systems based on azines, which are promising as organic semiconductor materials.[80] Since 2014, various synthetic methods have been advanced to obtain 1,3-diazatriphenylene derivatives and their heteroanalogues (Scheme 12). These methods include Pd-catalyzed intramolecular cyclizations (Pathway 1),[81] oxidative photocyclizations (Pathway 2),[82] and intramolecular $S_N^H$ reactions catalyzed by protic acids (Pathway 3),[83] as well as Lewis acids (Pathway 4).[84]

Research studies indicate a direct correlation between the types of charge carriers in organic thin-film transistors (OTFTs) and the experimentally estimated levels of frontier molecular orbitals.[85] These studies have demonstrated that materials with such electronic characteristics, as the lowest unoccupied molecular orbital (LUMO) level (below –3.15 eV) and the highest occupied molecular orbital (HOMO) level (above –5.60 eV), could exhibit semiconductor behavior for both *n*-type and *p*-type electrons. Therefore, 1,3-diazatriphenylene derivatives can be classified as ambipolar organic semiconductors (Figure 3).[84] Furthermore, these polycyclic compounds have been exploited to create sky-blue emitting thermally activated delayed fluorescence (TADF) layers in high-performance organic diodes.[86]




**Scheme 12** Various synthetic approaches to 1,3-diazatriphenylenes and heteroanalogues.

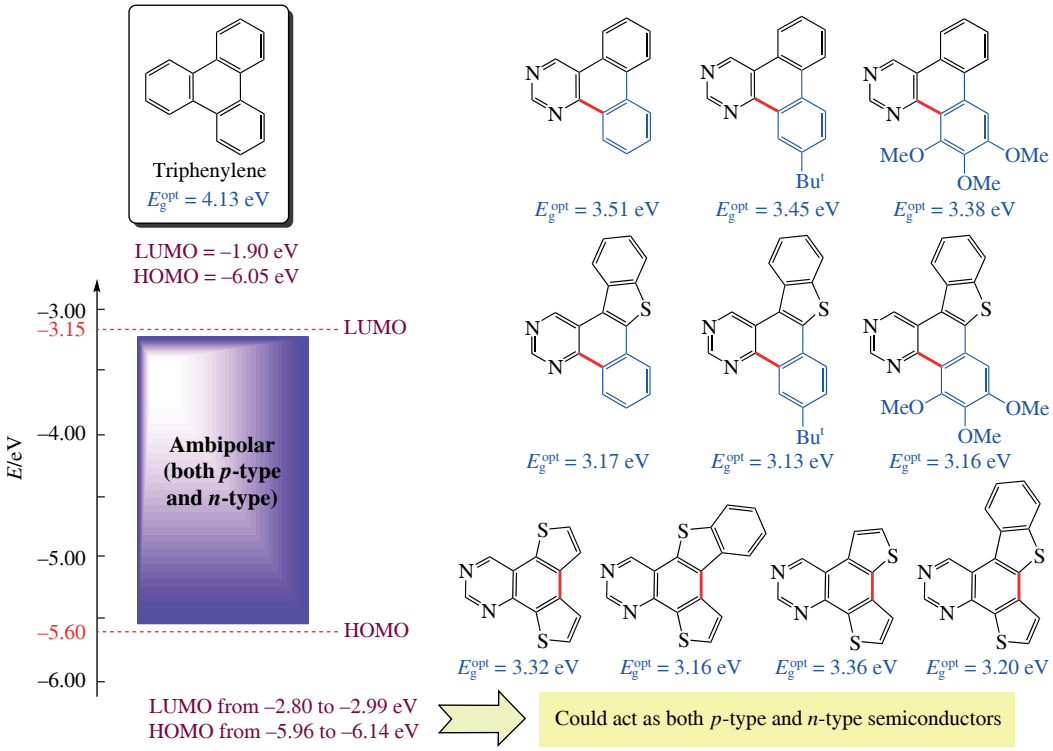
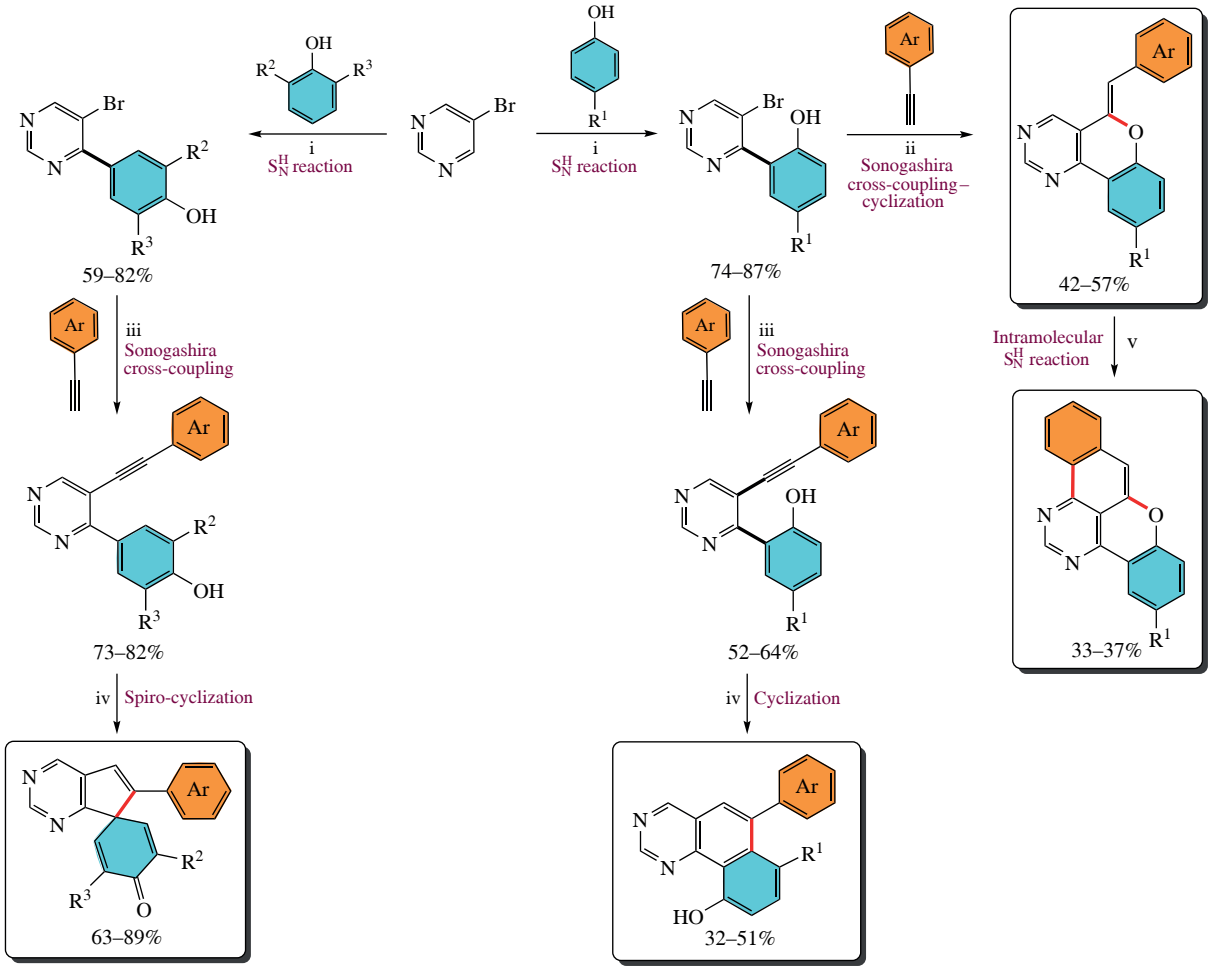



**Figure 3** Characteristics of the energy levels for 1,3-diazatriphenylene derivatives and their heteroanalogues.




**Scheme 13** Synthetic approach to various polycyclic systems through combinations of the $S_N^H$ and the Sonogashira cross-coupling reactions. *Reagents and conditions*: i, $MeSO_3H$, then $K_3Fe(CN)_6$, KOH, $H_2O$; ii, $PdCl_2(PPh_3)_2$, CuI, $PPh_3$, DIPEA, 150 °C, 25 min; iii, $PdCl_2(PPh_3)_2$, CuI, $PPh_3$, DIPEA, 60 °C, 180 min; iv, $MeSO_3H$; v, $O_2$ (air), TfOH.

Similar synthetic procedures proved to be appropriate for the construction of polycyclic π-conjugated systems from [1,2,5]-chalcogenadiazolo[3,4-*b*]pyrazines, which have exhibited properties of strictly *n*-type semiconductors and can find application in organic light-emitting diodes and perovskite solar cells.[87–90]

A combination of nucleophilic substitution of hydrogen at the $C^4$–H bond in 5-bromopyrimidine by action of phenols and the Sonogashira cross-coupling of the resulting 4-aryl-5-bromopyrimidines with arylacetylides afforded 4,5-di-substituted pyrimidines; treatment of the latter with acids caused their transformation into various polycyclic systems (Scheme 13).[91]

## Conclusions

In summary, we have demonstrated a wide range of opportunities through the combined application of nucleophilic aromatic substitution of hydrogen (the $S_N^H$ reactions) and transition metal-catalyzed cross-couplings. The following achievements have been reached using this strategy. (1) New synthetic methods leading to promising biologically active substances have been advanced; the compounds obtained proved to exhibit antiplatelet, antiviral, antibacterial, and anti-tuberculosis activities, including effectiveness against strains with multiple drug resistance. Furthermore, we have got the data on the development of compounds with antipsychotic[92] and neuroprotective[93,94] properties. Some of these derivatives have been recommended for further biological studies. (2) The first study has been carried out to obtain sensitizers for dye-sensitized solar cells (also known as the Graetzel cells) that exploit pyrimidine push–pull systems with unconventional anchor groups. (3) A new concept has been developed that employs azaheterocyclic push–pull systems as highly efficient multifunctional optical and electrochemical chemosensors for detecting nitroaromatic compounds in both solutions and the gas phase. This includes the use of original portable detectors for nitro explosives. A significant practical result of this strategy is the development of fluorescent sensors, as prototypes for commercial handheld sniffers, such as 'Nitroscan' and 'Zaslon-M'.† (4) Multipurpose methods have been developed for the preparation of a wide variety of both known and new polycyclic systems based on azines. These systems appear to be promising for creating organic semiconductor materials. We believe that this synthetic strategy will become widely adopted and will be extended not only to diazines and triazines, but also to pyridines and other electron-deficient (hetero)arenes. This expansion will facilitate the discovery of new biologically active compounds as well as materials for technological applications.

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