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aza-Wittig Reaction with Nitriles: How Carbonyl Function Switches from Reacting to Activating

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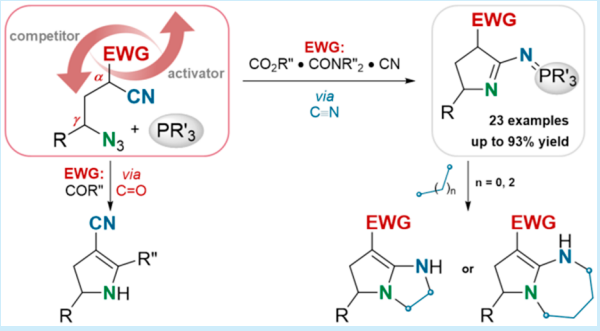
Supporting Information

ABSTRACT: Transformations of α-EWG-substituted (electron-withdrawing group, EWG) γ-azidobutyronitriles proceeding via unusual *aza*-Wittig reactions between the phosphazene and nitrile functions and affording pyrrole-derived iminophosphazenes were developed. α-EWGs were found to control chemoselectivity and, depending on their nature, act as CN group activators (e.g., ester, amide, or nitrile) or competitors (e.g., ketone) in *aza*-Wittig reactions. To demonstrate the synthetic utility of the obtained iminophosphazenes as *N,N*-binucleophiles, their transformations into pyrrole-fused systems, pyrrolo[1,2-*a*]imidazoles and pyrrolo-[1,2-*a*][1,3]diazepines, were carried out.



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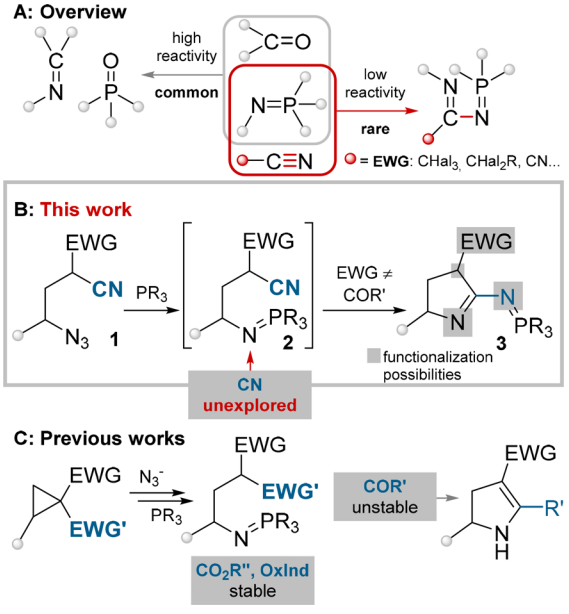
The *aza*-Wittig reaction, a well-known rapid access to C=N bond construction,[1] provides numerous opportunities for the synthesis of *N*-containing organic molecules. In this context, the use of the *aza*-Wittig reaction for the synthesis of *N*-heterocycles[2] is of primary concern, owing to a broad abundance of such structures in both natural and synthetic bioactive compounds. Moreover, among U.S. FDA-approved unique small-molecule pharmaceuticals, 59% of drugs contain an *N*-heterocycle.[3]

Among various types of *aza*-Wittig reactions, the interactions between *aza*-Wittig reagents, phosphazenes, and compounds containing polar double bonds (primarily in the carbonyl group) are the most explored. Oppositely, reactions involving the triple C≡X bonds of acetylenes or nitriles are described scarcely. This is apparently related to the lower reactivities of C≡X units toward phosphazenes, which is due to the insufficient electrophilicity of the carbon centers. In particular, the very few scattered examples of the *aza*-Wittig reaction with the C≡N bond are mostly limited to nitriles activated with strong electron-withdrawing groups (EWGs) ($CHal_3$, $CHal_2R$, CN) (Scheme 1A).[4] Two additional similar examples were reported to proceed in the Pt(II) coordination sphere.[5] The reactions between phosphazenes and nitriles are distinct in that new *aza*-Wittig reagents are formed in their process. Therefore, when the problem of low nitrile reactivity is solved, this challenging type of *aza*-Wittig reaction could allow for installing an additional nitrogen atom in the assembled molecules and, thus, synthesizing various heterocyclic systems with at least two nitrogen atoms. Meanwhile, there are no examples of *aza*-Wittig reactions wherein the

Scheme 1. Strategy of This Work



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usually low-reactive nitrile can compete with an unchallenged carbonyl group.

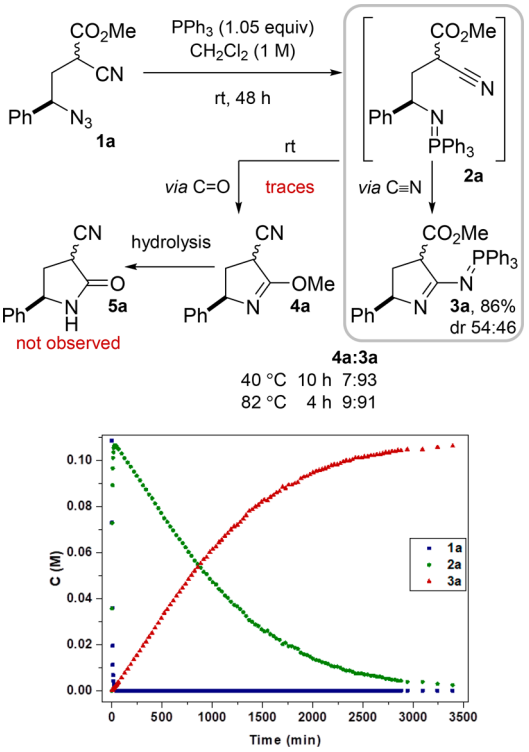
Here, we report an *aza*-Wittig reaction wherein the efficient control of the competition between the C≡N and C═O groups provides for chemoselective assembly of *N*-heterocycles. The strategy of our current work relies on new precursors of *aza*-Wittig reagents, azides **1** (Scheme 1B). Recently, we developed a convenient approach to similar azides via nucleophilic ring opening of donor−acceptor (DA) cyclopropanes[6] with the azide ion.[7] The strategic arrangement of the functionalities in the obtained azides allows for their successful transformations into *N*-heterocycles via various pathways which incorporate the *aza*-Wittig reaction. Moreover, in reactions with PPh_3, these azides with ester or oxindole groups as EWGs yield stable phosphazenes (Scheme 1C).[7,8] Particularly, ester derivatives do not undergo spontaneous 1,5-cyclization via intramolecular *aza*-Wittig reactions under ambient conditions, whereas an increase in temperature facilitates their cyclization into 2-alkoxypyrroline derivatives. When keto groups act as an EWG, an intramolecular reaction between the generated phosphazene and carbonyl units occurs spontaneously.[7] At the same time, the reactivity of similar CN-substituted phosphazenes remained unexplored.

In this work, the reactions of azides **1** with triaryl/trialkylphosphines were unexpectedly found to afford cyclic iminophosphazenes **3** through the spontaneous trapping of a phosphazene fragment in acyclic *aza*-Wittig intermediates **2** by the CN group (Scheme 1B). Apparently, the advantageous 1,3-relationship between the CN and N_3 groups in **1** as well as the presence of an α-activating EWG stimulate the nitrile unit to participate in subsequent *aza*-Wittig reactions. Meanwhile, the nature of the EWG was found to influence the reaction chemoselectivity which can be switched from the phosphazene attack on the nitrile moiety (EWG = ester, amide, or nitrile groups) toward a typical attack on the EWG (EWG = keto group).

Compounds **3** can be viewed as multifunctionalized aminopyrrole building blocks. As *N*,*N*-binucleophiles, compounds **3** provide ample opportunities for the construction of pyrrole-derived *N*,*N*-heterocyclic systems in which the number and the size of fused rings can be controlled by the nature of the bielectrophilic counterpart used. Herein, we transformed iminophosphazenes **3** into pyrrolo[1,2-*a*]imidazoles and pyrrolo[1,2-*a*][1,3]diazepines, employing oxalyl, succinyl, or *ortho*-phthaloyl chlorides as bielectrophiles.

Initially, we examined the reaction of azide **1a**, containing an ester group at the α-position, toward the CN fragment, with triphenylphosphine under ambient conditions, using CH_2Cl_2 as a solvent (Scheme 2). According to the results of ^{1}H NMR monitoring of this reaction mixture (25 °C, $CDCl_3$), the reaction was completed in 48 h after PPh_3 had been added. Surprisingly, cyclic iminophosphazene **3a** was the predominant product, apparently formed through the cyclization of intermediate phosphazene **2a** *via* the C≡N group. The competitive product of phosphazene interacting with the C═O group, **4a**, was formed in trace amounts under these conditions, whereas the formation of its hydrolyzed successor **5a** was not observed. However, increasing the reaction temperature to 40 °C while allowing the reaction to complete in 10 h facilitates a competitive process of **4a** formation *via* an *aza*-Wittig reaction with the ester group. When performed at 82 °C (CH_3CN under reflux) for 4 h, the reaction yielded a mixture of **3a** and **4a** in a 91:9 molar ratio, according to ^{1}H NMR data. The presence of an external electrophile (e.g., benzaldehyde) did not induce an intermolecular *aza*-Wittig reaction under these same conditions. The replacement of triphenylphosphine by the more active tributylphosphine led to the more labile iminophosphazene **3a′** which was isolated upon column chromatography on SiO_2 in a 21% yield only due to considerable degradation. Consequently, the application of the moderately active PPh_3 in CH_2Cl_2 at ambient temperature steers the reaction toward exclusive formation of iminophosphazene **3a**.

Scheme 2. Transformation of γ-Azidonitrile 1a into Iminophosphazene 3a: Accumulation and Consumption of Intermediate Phosphazene 2a



Using identical conditions, we then explored the scope of **1**-into-**3** transformation while varying the α-substituent R, located at the geminal position to the N_3 group in **1** (Scheme 3A). We found that this reaction was completely tolerant toward aryl substituents with both electron-donating and electron-withdrawing groups, as well as hetaryl and alkenyl substituents. In most of the studied cases, iminophosphazenes **3** were isolated in very good yields (up to 93%). Some decrease in the yield was only observed for phosphazene **3h** containing a bulky *ortho*-OMOM substituent in the aryl fragment. Although the reaction does not directly involve stereocenters at the C2 and C4 atoms of azides **1**, diastereomeric ratios (dr) of **3** can be regulated by the keto−enol equilibrium. Therefore, their values differ from the dr values for the initial azides **1**. Notably, in the cases of **3l** and **3o**, dr values rose slightly (*ca.* 2:1) in comparison with those for **1l,o** (*ca.* 1:1). The obtained diastereomers cannot be separated by the means of column chromatography apparently, owing to the same keto−enol equilibrium. However, we succeeded in growing crystals from the diastereomeric mixture for the individual *trans*-isomer of **3p**. Its structure was unambiguously proved by single crystal X-ray analysis.

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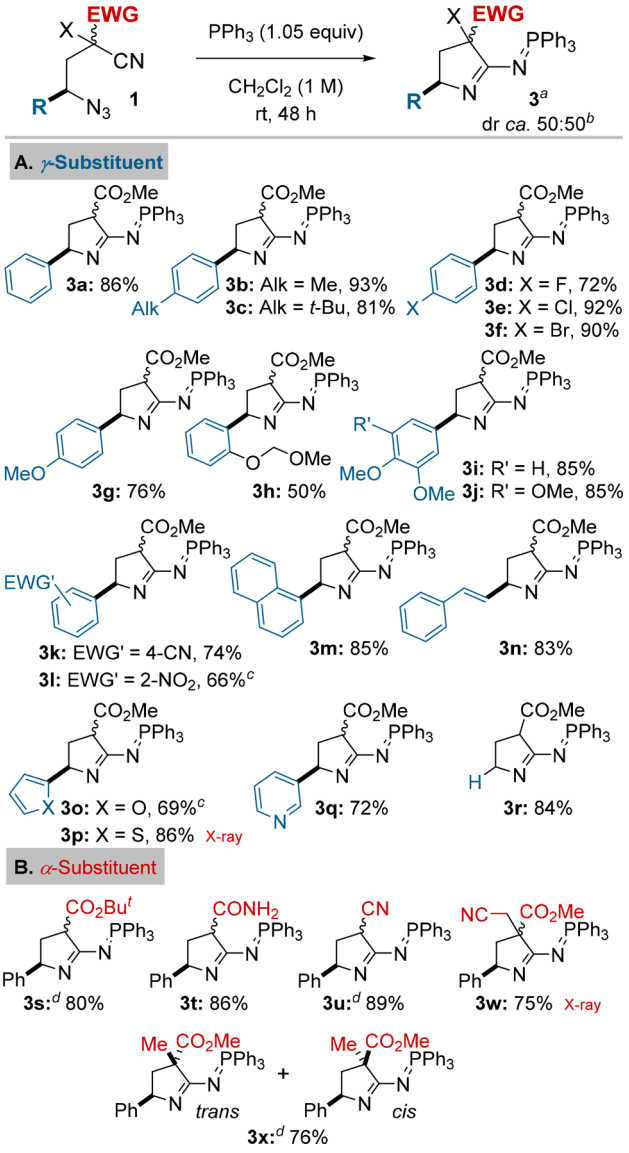
Scheme 3. Scope of 1-into-3 Transformation under Variation of γ- and α-Substituents

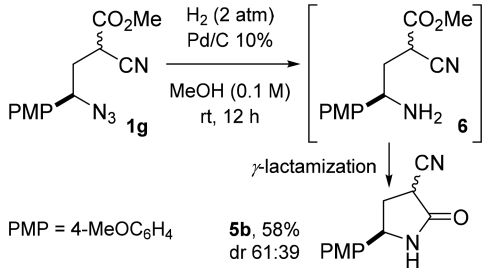


[a]Isolated yield. [b]Diastereomeric ratios (dr) were determined by the ^{1}H NMR analysis of crude products. [c]dr 63:37 [d]Reaction time was 90 h (**3s**), 4 h (**3u**), 8 h (*trans*-**3x**), and 35 h (*cis*-**3x**).

In all the cases, reactions of **1** with PPh_3 proceeded with exceptional chemoselectivity: only trace amounts of alkoxypyrrolines **4** or γ-lactams **5** can be detected. Meanwhile, the reduction of the N_3 group in γ-azidonitrile **1g** as a model substrate with the H_2−Pd/C reductive system led to the exclusive formation of γ-lactam **5b** via spontaneous 1,5-cyclization of intermediate γ-aminoester **6** under reaction conditions (Scheme 4). Therefore, 1,5-cyclizations of phosphazenes **2** and amines **6** can be considered complementary, allowing for chemoselectivity to switch between the attacks on the C≡N and the C=O groups and, thus, providing divergent approaches to iminophosphazenes **3** and γ-lactams **5**, respectively.

To define the scope of the CN group reactivity toward the phosphazene moiety as dependent on the geminal functional group, we examined the reactions of PPh_3 with γ-azidobutyronitriles **1s**−**x** containing EWGs other that the CO_2Me group.

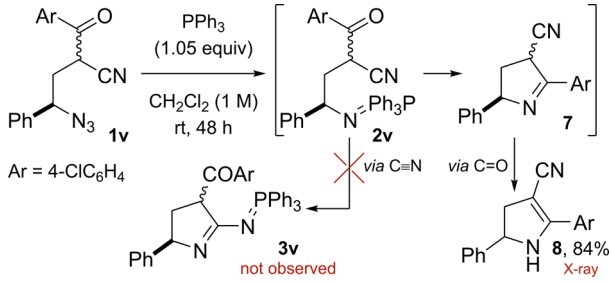
Scheme 4. Reductive 1,5-Cyclization of γ-Azidonitrile 1g into Lactam 5b



We found that its replacement with the bulkier CO_2Bu^t group (**1s**) as well as amide (**1t**) or nitrile (**1u**) groups did not influence the chemoselectivity of the reactions, affording the corresponding iminophosphazenes **3s**−**u** in high yields (Scheme 3B). On the other hand, the reaction time can be influenced. For **1s**-to-**3s** transformation, the reaction time was increased to 90 h, whereas **1u**-to-**3u** transformation was completed in 4 h. The reaction of **1w** which contains an additional CN group (X = CH_2CN) chemoselectively led to a similar five-membered iminophosphazene **3w** via interaction of the only α-EWG-activated CN substituent. Due to the presence of the third α-substituent that successfully blocked the interconversion of diastereomers, we succeeded in singling out individual reaction times for transformations of (2*RS*,4*SR*)-**1x** into *trans*-**3x** (8 h) and (2*RS*,4*RS*)-**1x** into *cis*-**3x** (35 h).

In the case of keto-derived γ-azidonitrile **1v**, the CN group was found to be noncompetitive in comparison with the more active CO group in intermediate **2v** (Scheme 5). As a result, the reaction yielded 2-pyrroline **8** (apparently, via intermediate 1-pyrroline **7**) rather than iminophosphazene **3v**.

Scheme 5. Transformation of Keto-Derived γ-Azidonitrile 1s into 2-Pyrroline 8



In order to determine the extent of the influence that the geminal EWG has on the CN reactivity, we carried out the reaction of PPh_3 with the EWG-free γ-azidonitrile **9a**, obtained from **1f** via Krapcho demethoxycarbonylation (Scheme 6). The reaction yielded stable phosphazene **10a** which did not undergo spontaneous *aza*-Wittig cyclization under the standard conditions. Additionally, the heating of **10a** in toluene under reflux also did not induce an intramolecular *aza*-Wittig reaction, with a slow degradation of **10a** into a complex mixture of unidentified products taking place in its stead. The more reactive PBu_3 also gave acyclic phosphazene **10b** which was not prone to *aza*-Wittig cyclization (despite its higher reactivity leading to considerable tarring and decrease in the yield). The introduction of an alkyl substituent (**9c**: R′ = Et) also did not facilitate an intramolecular *aza*-Wittig reaction.

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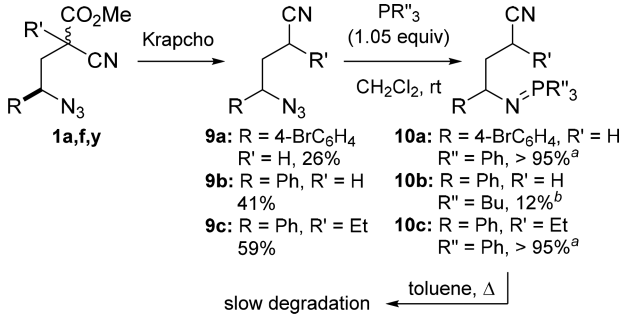
Scheme 6. Formation of Stable Phosphazenes 10 in Absence of α-Activating EWG



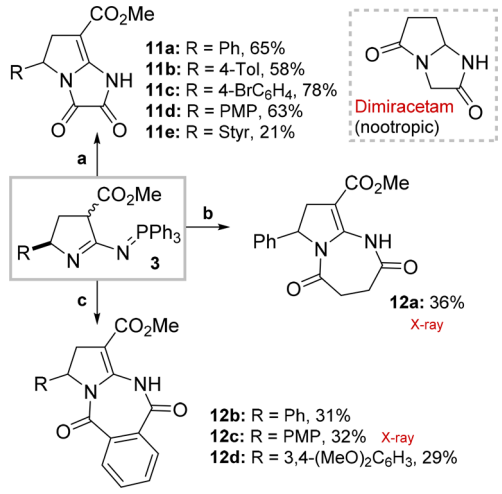
[a]Yield according to ^{1}H NMR. [b]Yield after column chromatography (SiO_2).

Therefore, the interaction between **9c** and PPh_3 afforded acyclic phosphazene **10c** as the final product.

Next we performed DFT calculations at the B3LYP[9]/def2-SVP[10]/RIJCOSX[11] level of theory using ORCA 3.0.[12] After optimizing geometries for various stereoisomers of **2a**, we identified reacting conformers for both CN- and CO-mode *aza*-Wittig reactions. Relying on the reported results of the DFT study for the reaction between aldehydes and phosphazenes,[13] we easily localized stationary points and then built analogous profiles for cyclization via CO in both diastereomers of cyanoester **2a**. The computation of cyclization via CN proved to be a less trivial task. We successfully optimized TS geometries for the [2 + 2]-cycloaddition step in each reacting conformer, but the calculated intermediates proved to be relatively unstable. Although the TS of the cycloreversion step could be localized, this is a virtually barrier-less process. The energy diagrams with the lowest TS energy for the rate-determining step (RDS) for both pathways are visualized using CYLview[14] in Figure 1. Since the entire reactions are irreversible, and the dr values for **2a**, **3a**, or **4a** are determined by the keto−enol equilibrium, the **3a**:**4a** ratio should correlate to the difference in the TS energies of the corresponding RDS. The difference, amounting to 3.2 kcal/mol, is roughly consistent with the experimental ratio: **3a**:**4a** > 95:5.

Compounds **3** are quite stable ylides, owing to conjugation of the phosphazene and imine fragments. This inhibits reactions of **3** with the most common carbonyl compounds such as benzaldehydes even at increased temperatures. At the same time, **3** react with the more reactive aliphatic aldehydes and acyl halides. However, in the case of acetic aldehyde or acetyl chloride, the reactions resulted in a complex mixture of products.[15] Accounting for the presence of two *N*-nucleophilic sites in the molecules of **3**, we studied their reactions with bielectrophilic reactants containing two halocarbonyl groups. To our delight, phosphazenes **3** readily reacted with oxalyl, succinyl, and *ortho*-phthaloyl chlorides, producing pyrrolo[1,2-*a*]imidazoles **11** and pyrrolo[1,2-*a*][1,3]diazepines **12**, respectively (Scheme 7). The structures of **12a,c** were supported by single crystal X-ray analysis.

Scheme 7. Transformation of Iminophosphazenes 3 into Pyrroloimidazoles 11 and Pyrrolodiazepines 12[a]



[a]Conditions: (a) oxalyl, (b) succinyl, (c) *ortho*-phthaloyl chlorides (1.1 equiv), CH_2Cl_2 (0.4 M), Δ, 30 min.

Pyrroloimidazoles **11** are structural analogues of dimiracetame and its derivatives which are nootropic agents of the racetam family. A preliminary MTT assay of compounds **11**

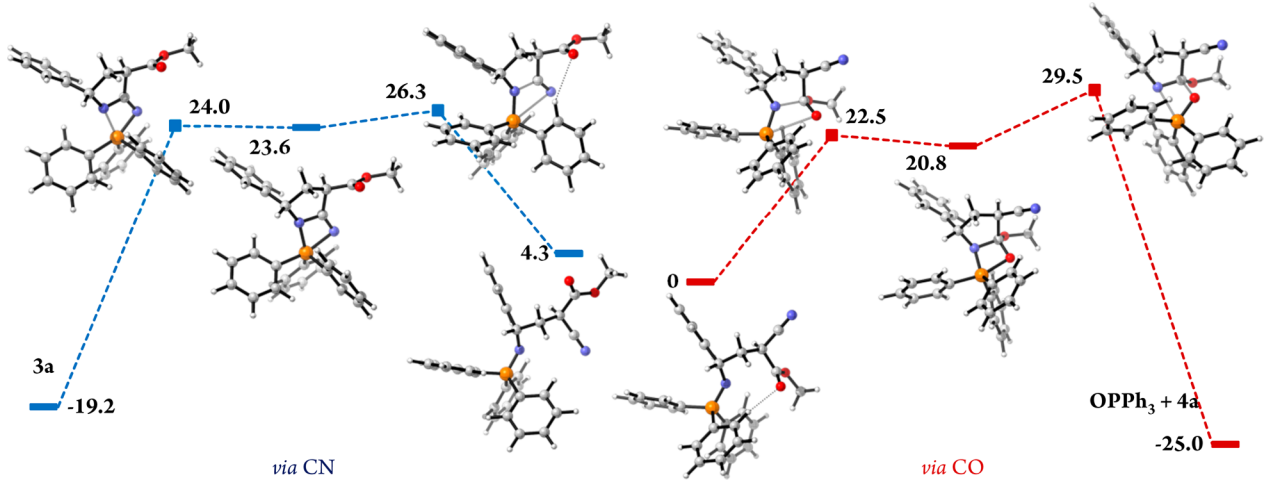


Figure 1. Energy diagrams for *aza*-Wittig reactions in isomers of **2a** with the lowest TS energies for RDS (ΔG_{298}, kcal/mol). Geometries of **3a** and **4a** correspond to the conformers with the lowest relative energy, not to the reacting conformers.

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toward four cell lines (HEK, Va13, MCF7, A549) did not reveal any noticeable cytotoxic effects. This allows for further assay of other biological properties of **11**, including their nootropic activity.

In conclusion, we have developed a new synthetic transformation of γ-azidobutyronitriles into pyrrole-derived iminophosphazenes proceeding via unusual *aza*-Wittig reactions between the phosphazene and α-EWG-activated nitrile units. The reactivity of this type was revealed for ester, amide, or nitrile groups as activating α-EWGs. Alternatively, for α-keto derivatives, the chemoselectivity was switched toward the common *aza*-Wittig reaction between the phosphazene and carbonyl groups. The obtained iminophosphazenes were found to exhibit properties of typical *N,N*-binucleophiles, readily reacting with such bielectrophiles as oxalyl, succinyl, or *ortho*-phthaloyl chlorides to afford pyrrolo[1,2-*a*]imidazole and pyrrolo[1,2-*a*][1,3]diazepine systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04135.

Experimental procedures, analytical data, details of DFT calculations, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1838688−1838689 (**12b** and *trans*-**3p**), 1852202 (**8**), 1852209 (**12a**), 1865323 (**S2c**), and 1873067 (*cis*-**3w**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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