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Olena Kuleshova, Olga Khilya, Yulian Volovenko, Sonia Mallet-Ladeira, Viktoriya Dyakonenko, et al.. Expedited route to fully substituted amino-pyrazole building blocks and their further transformations. ACS Omega, 2017, 2 (12), pp.8911-8927. 10.1021/acsomega.7b01419 . hal-01939736

**HAL Id: hal-01939736**

**<https://hal.science/hal-01939736>**

Submitted on 27 Jan 2024

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# Expedited Route to Fully Substituted Amino-Pyrazole Building Blocks and Their Further Transformations

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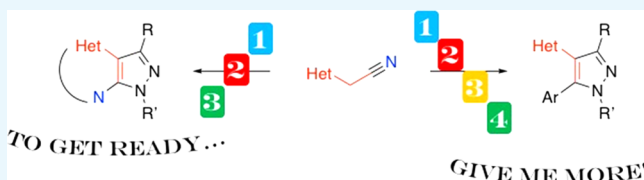
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## S Supporting Information

**ABSTRACT:** We report here an efficient and easily reproducible two-step approach to heterocycle-substituted amino-pyrazoles from heterocyclic acetonitriles and their unprecedented subsequent transformations to fully substituted pyrazoles. Such transformations include regioselective derivatization from polyamino derivatives, formation of tetracyclic compounds in up to 45% overall yield, and deaminative transformations through diazotization, followed by arylation through Suzuki–Miyaura cross-coupling and C–H activation, providing arylated pyrazoles in up to 71% yield over four steps. This strategy allows the swift introduction of significant molecular complexity to a range of scaffolds.



## 1. INTRODUCTION

Heterocyclic chemistry has been a field of continuous research for more than a century, and it remains an active domain of research because heterocyclic compounds have shown potential in numerous applications and various fields such as medicinal chemistry,<sup>1,2</sup> photophysics,<sup>3–5</sup> and material sciences.<sup>6</sup> This continuous activity is driven by the requirement of particular functionalization that can require awkward synthetic processes. It is therefore still important to develop approaches that achieve direct access to unprecedented substitution patterns on heterocyclic compounds. This is especially true for 5-amino-pyrazole, which is a scaffold commonly found as a synthetic intermediate en route to numerous biologically active compounds such as pyrazolopyrimidine.<sup>7–12</sup>

There are only a few strategies used to access the pyrazole scaffold.<sup>13</sup> A first one is the formal intramolecular hydroamination of an alkyne with a tethered hydrazine derivative (Scheme 1, path a).<sup>14–25</sup> Another strategy, recently reported, is based on copper catalyzed N–N bond formation of the pyrazole (Scheme 1, path b).<sup>25</sup> A third approach relies on the cycloaddition of a range of 1,3-dipoles with an alkyne or alkene. Among the dipoles involved, diazo compounds have found numerous applications, as have nitrilimines (generated in situ from halogenated hydrazoyles) and sydnone after CO<sub>2</sub> extrusion (Scheme 1, path c).<sup>26–28</sup> Such an approach has also recently found a formal intramolecular extension under Pd catalysis.<sup>29</sup> Finally, the fourth and most documented one is the condensation of 1,3-dielectrophilic synthons with hydrazine or its substituted forms (Scheme 1, path d).<sup>13,30</sup> This approach encompasses not only these 1,3-dicarbonyl precursors but has

also been exemplified by multicomponent versions generating the 1,3-dicarbonyl precursors or their equivalent in situ.

Yet, such 1,3-dicarbonyl precursors, especially those featuring aromatic heterocycles on position 2, require multiple step syntheses of a precursor. Moreover, the involvement of substituted hydrazines can introduce potential losses of regioselectivity that hamper the overall efficiency of the synthetic process.

As this has very recently been illustrated,<sup>31</sup> targeting densely functionalized pyrazoles still represents a challenge that is currently attracting significant research efforts. Therefore, providing a short, efficient, and selective route to 5-amino-pyrazoles and their further deaminative transformations presents an exciting innovation toward the generation of diversely functionalized pyrazole derivatives. We report here the simple generation of heterocyclic-substituted 1,3-dicarbonyl-compound equivalents and their facile transformation into densely substituted 5-aminopyrazoles (and isoxazoles). Further transformation of the 5-amino group for generation of fused polyheterocycles and the creation of C–C bonds have been achieved by different palladium-catalyzed approaches, as illustrated in Scheme 2.

## 2. RESULTS AND DISCUSSION

As stated above, the first issue related to the Knorr pyrazole synthesis is the generation of the 1,3-dielectrophile featuring

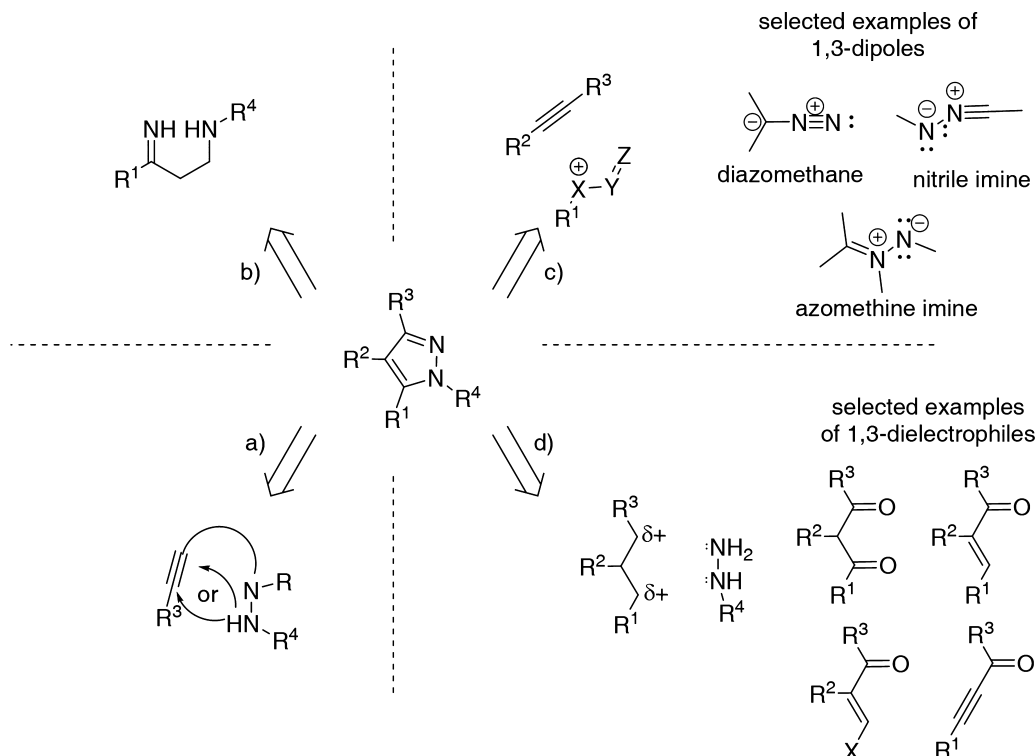
**Received:** September 24, 2017

**Accepted:** November 23, 2017

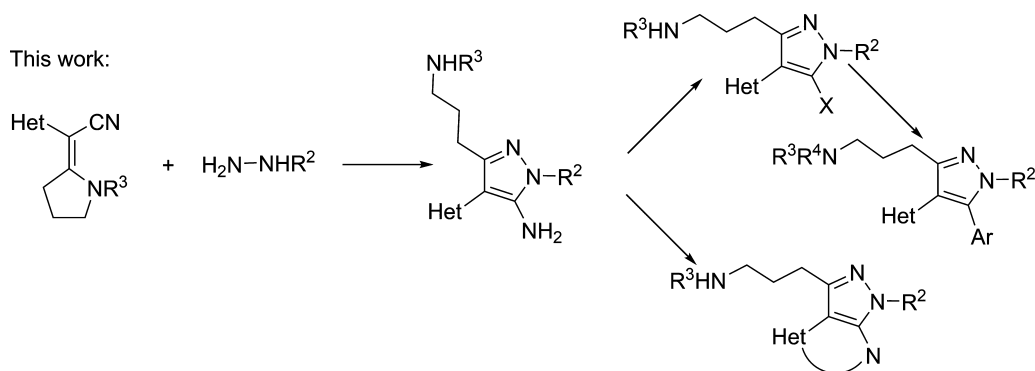
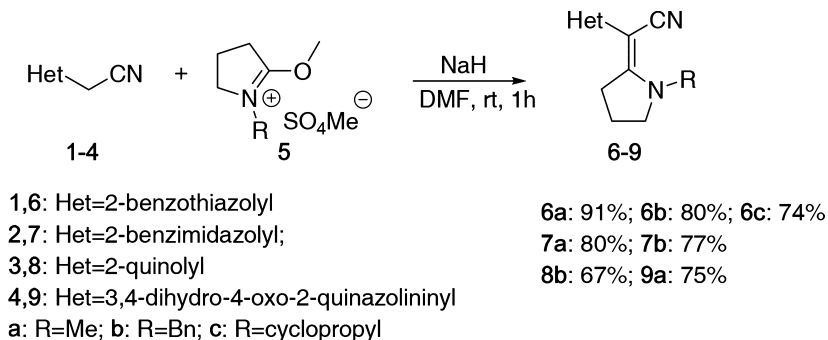
**Published:** December 13, 2017



Scheme 1. General Routes to Pyrazoles



Scheme 2. Straightforward and Selective Access to Densely Functionalized Pyrazoles

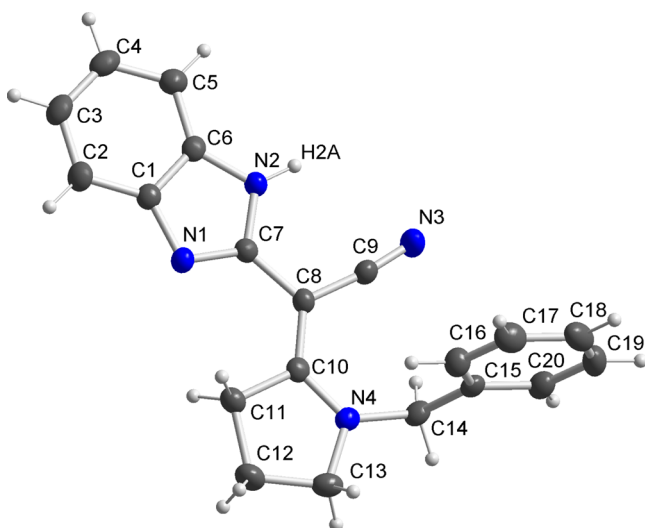
Scheme 3. Synthesis of 2-Hetaryl-2-(1-*R*-pyrrolidin-2-ylidene)acetonitriles 6–9

the desired substituents. We identified compounds 6–9 as readily accessible 1,3-dielectrophile equivalents that could allow a highly selective generation of pyrazoles from substituted hydrazines in an overall atom- and step-economical fashion. Such derivatives can be accessed through the condensation of

the anion of 2-azahetarylacetonitriles 1–4 (obtained via deprotonation by NaH) and 5-methoxy-1-*R*-3,4-dihydro-2*H*-pyrrol-1-ium salt 5 in dimethylformamide (DMF) (Scheme 3).<sup>a</sup>

The reaction proceeded immediately at room temperature (rt) leading to the desired 2-hetaryl-2-(1-*R*-pyrrolidin-2-ylidene)-acetonitriles **6–9** in good yields (67–91%) after precipitation from water and further filtration.

Single crystals suitable for X-ray diffraction (XRD) study were obtained by solvent diffusion. The structures in the solid state revealed, as illustrated in Figure 1 for **7b**, that the diastereoisomer featuring lower steric strain (N-alkyl and CN in the *cis* position) is preferentially formed, as expected.



**Figure 1.** Crystal structure **7b** obtained by X-ray diffraction with the atom numbering used in the crystallographic analysis. Thermal ellipsoids are drawn at 50% probability level.

For all structures, the pyrrolidine rings are almost planar (deviation from plane below 0.16 Å) and are coplanar with the heterocyclic substituent (dihedral angle under 9°), which is indicative of the delocalization of the enamine moiety both toward the nitrile and heterocycle. This promotes a general trend toward N4–C10 bond shortening and C10–C8 bond elongation (as compared to standard bond length values<sup>32</sup>). A clear correlation between the C8–C9–N3 angle values and the electron-withdrawing abilities of the heterocyclic substituent is observed, which implies that both the nitrile and the heterocycle are involved in electron delocalization (Table 1).

Interestingly, such delocalization promotes a shift in the enamine–iminium equilibrium, enhancing the electrophilicity of the C10 center and simultaneously lowering that of the nitrile group. The deshielding of C10 corroborates this trend as its chemical shift is found within the 164.3–170.2 ppm range. Moreover, a partial isomerization around the double bond can be observed in solution NMR.

These combined findings suggested that these 1,3-dielectrophilic compounds can be expected to react with hydrazine derivatives in a very regioselective fashion.<sup>33–38</sup>

We therefore engaged these compounds toward the synthesis of 3-(*ω*-aminoalkyl)-4-hetaryl-5-aminopyrazole (or isoxazole) **10–16** by addition of hydrazine (and its derivatives) or hydroxylamine (Scheme 4). The reaction proceeded smoothly in refluxing dioxane with 10–20 equiv excess of the binucleophile reagent and provided the pyrazoles and isoxazoles in moderate to good yields (Scheme 4). The use of unsymmetrical methylhydrazine provided the methylpyrazole with complete regioselectivity. The nature of the alkyl substituent on the pyrrolidine nitrogen was shown to only moderately affect the efficiency of the reaction (**10a–c**). Moving from methylhydrazine to hydrazine hydrate was found to promote a decrease in reaction yields (**10c** vs **11c**), whereas no discernable effect was observed upon switching from methylhydrazine to hydroxylamine (**13b** vs **14b**). Finally, variations in the nature of the heterocyclic moiety did not significantly affect the overall efficiency, although benzothiazole substitution systematically provided better efficiencies, all things being otherwise equivalent.

3-(*ω*-Aminoalkyl)-4-hetaryl-5-aminopyrazole (isoxazole) **10–16** were isolated with satisfactory analytical quality after solvent evaporation and purification by trituration in acetone or acetonitrile, or by column chromatography.

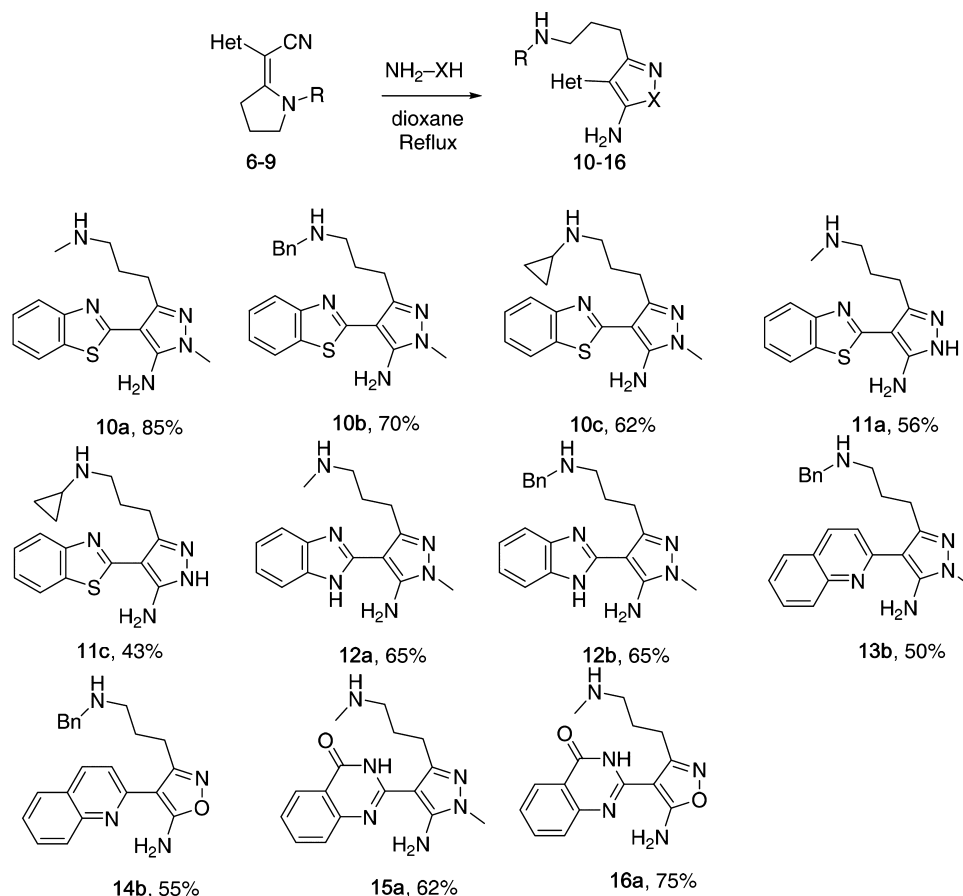
The involvement of the nitrile group, initially present in **6–9**, in the reaction is highlighted by the disappearance of its characteristic stretching vibration absorptions in the 2198–2178 cm<sup>−1</sup> range of the IR spectra.

Thorough structural analysis of the compounds was carried out using <sup>1</sup>H NMR, <sup>13</sup>C MNR, two-dimensional (2D) NMR techniques (correlation spectroscopy (COSY), heteronuclear multiple-bond correlation (HMBC), heteronuclear multiple-quantum correlation (HMQC)), and IR. Particularly, in DMSO-*d*<sub>6</sub>, a characteristic singlet of NH<sub>2</sub> in the <sup>1</sup>H NMR spectrum is observed at 6.25–6.94 ppm. Interestingly, this signal is shifted up-field for isoxazoles, probably as a consequence of oxygen electronegativity (**16a**, 8.04 ppm; **14b**, 8.20 ppm). In both cases, addition of D<sub>2</sub>O promotes the disappearance of these singlets, evidencing the exchangeable nature of the corresponding protons. The <sup>13</sup>C NMR spectra of **10–16** show three signals corresponding to the carbons of the pyrazoles (isoxazoles). The first one, found at a chemical shift in the 147.1–149.0 ppm range, was assigned to the C5 atom of the pyrazole ring, and again, this signal was shifted up-field for isoxazoles (at around 169.2–170.5 ppm). The signals within the range 90.3–100.8 and 148.6–161.3 ppm correspond to C4 connected with a heterocyclic substituent and to C3 bonded with the *ω*-aminoalkyl chain, respectively.

Pleasingly, 4-hetarylaminopyrazoles **10a**, **10c**, and **15a** formed crystals suitable for XRD study, allowing careful

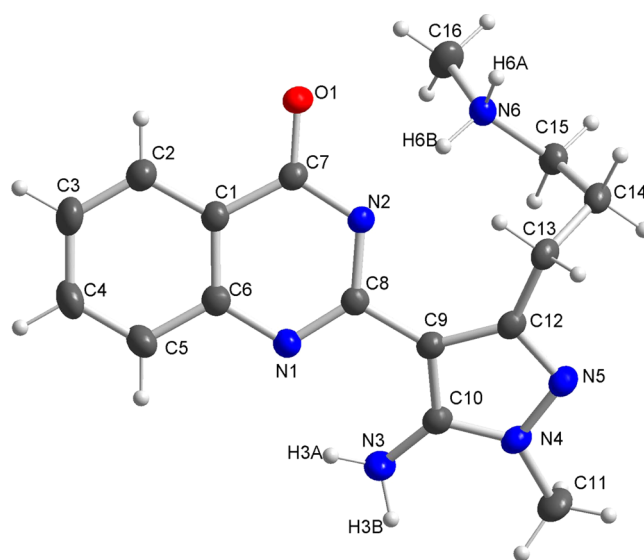
**Table 1.** Lengths of Bonds and C8–C9–N3 Angles of Selected Compounds

entry	compd no.	length of pyrrolidine C–N bond (Å)	length of enamine C=C bond (Å)	C8–C9–N3 angle (deg)	dihedral angle between heterocycle and pyrrolidine ring planes (deg)	deviation of pyrrolidine ring from plane (Å)
1	<b>6b</b>	1.334	1.403	176.1	5.3	0.027
2	<b>6c</b>	1.353	1.373	174.6	4.3	0.051
3	<b>7a</b>	1.328	1.382	173.7	8.8	0.161
4	<b>7b</b>	1.337	1.389	173.4	2.4	0.068
5	<b>8b</b>	1.348	1.395	175.5	5.9	0.026
6	<b>9a</b>	1.339	1.401	177.5	1.9	0.019

Scheme 4. Synthesis of 3-( $\omega$ -Aminoalkyl)-4-hetaryl-5-aminopyrazole (Isoxazole) 10–16

analysis of their structure. The benzothiazolyl substituent is almost coplanar with the pyrazole ring, with a dihedral angle of 6.48 and 1.16° for **10a** and **10c**, respectively. The flattened orientation of the planar fragments is stabilized by an intramolecular hydrogen bond between one of the protons of the amino group and the nitrogen of the benzothiazole. For **15a** (Figure 2) featuring a quinazolinonyl substituent, distinct changes in conformation were observed. Unexpectedly, the hydrogen located, initially, at N2 in **9a** was found to be covalently bound with the secondary amino group in the aliphatic chain of **15a** (N6–H6B 0.93 Å). The lone pair on N2 exhibits stronger conjugation with its adjacent carbonyl group, as shown by the shortened N2–C7 (1.340 Å) and elongated C7–O1 (1.273 Å) bond lengths, when compared to that of **9a** (N2–C7, 1.378 Å; C7–O1, 1.230 Å). N2 forms an intramolecular hydrogen bond with H6B (N2···H6B, 1.89 Å; N6–H6B···N2, 175.49°), whereas O1 forms an intermolecular hydrogen bond with H6A (O1···H6A, 1.78 Å; N6–H6A···O1 170.96°) of an adjacent molecule. The positioning of the pyrazole and quinazolinone planes (dihedral angle of 19.65°) in **15a** allows the molecule to adopt an energetically favored conformation, placing both N2–H6B and N1–H3A in close proximity (H3A···N1, 2.24 Å; N3–H3A···N1, 127.29°).

Considering the analytical and structural data obtained for the pyrrolidine precursors, as well as precedents from the literature,<sup>33,34,36</sup> a ring conversion from pyrrolidine to pyrazole (or isoxazole) is expected to proceed via nucleophilic attack of the unsaturated carbon of the pyrrolidine yielding **B**; spiro intermediates **C** would then form upon attack of the second atom of the binucleophile on the nitrile group in a favored 5-

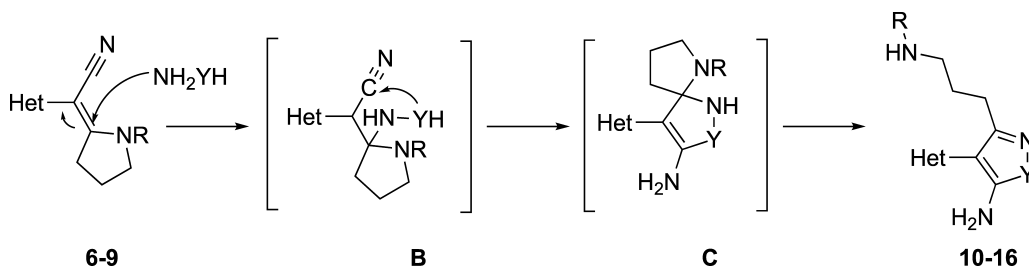


**Figure 2.** Molecular structure of compound **15a** according to X-ray diffraction with the atom numbering used in the crystallographic analysis. Thermal ellipsoids are drawn at 50% probability level.

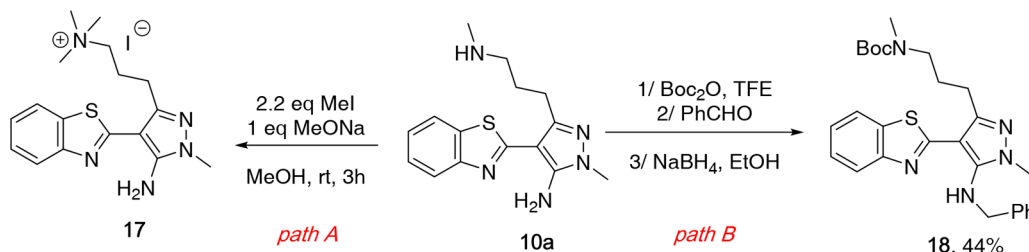
exo-dig fashion. Finally, ring opening of the pyrrolidine ring promotes the aromatization of the azole ring and provides the nitrogen-substituted aliphatic chain. Such an addition of nucleophile-spiro annulation-ring opening (ANSARO) mechanism is thought to be operative in this transformation.



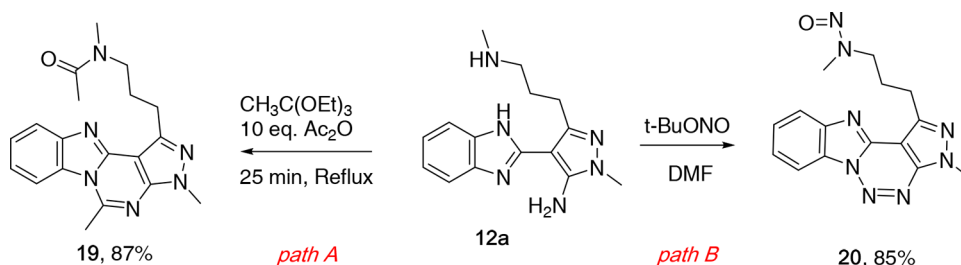
Scheme 5. Proposed Mechanism for the Ring Conversion



Scheme 6. Regioselective Alkylation of Amino Groups from 10a



Scheme 7. Straightforward Access to Fused Tetracyclic Structures



Having this straightforward access to densely functionalized pyrazoles in hand, we further explored their synthetic potential by assessing the ability to selectively introduce structural variations on their reactive centers, namely, the amino groups.

The first approach was to illustrate the possibility of selectively functionalizing the amino groups substituting the pyrazole core. For that purpose, we confirmed that the secondary alkylamine is significantly more nucleophilic than the primary aromatic one. Indeed, alkylation of the secondary amino group could be achieved simply by stirring **10a** with 1 equiv of the base and 2.2 equiv of alkylating reagent at room temperature, leaving the primary amino group unaffected (Schemes 5 and 6, path A). The reaction produced a white precipitate, which structure was confirmed to be **17** by analysis of the filtrated solid by  $^1\text{H}$ ,  $^{13}\text{C}$ , and 2D NMR as well as high-resolution mass spectrometry (HRMS). Expectedly, the symmetry achieved through formation of the ammonium salt significantly lowers the quadrupolar coupling constant of nitrogen, allowing observation in the  $^{13}\text{C}$  NMR spectrum of the  $^{14}\text{N}$ – $^{13}\text{C}$  coupling for the methyl and the methylene carbons of the ammonium. Extensive attempts to perform Hofmann elimination from **17** failed to provide the corresponding alkene, leading to ammonium recovery or degradation when reaction conditions were forced.

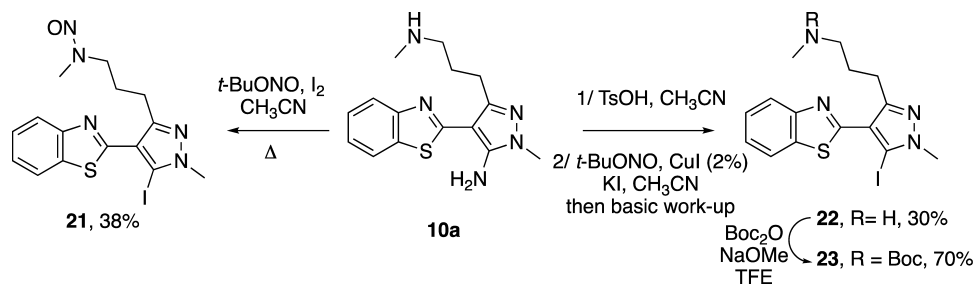
Consequently, the substitution of the primary aromatic amino group was found to require the protection of the secondary amine (Scheme 6, path B). This could be achieved in 93% yield by simple treatment of **10a** with a slight excess of  $\text{Boc}_2\text{O}$  in trifluoroethanol for 10 min at room temperature

followed by column chromatography. With this protection in place, we could perform a reductive amination of the primary amino group to access **18**, which was isolated after column chromatography in 47% yield (44% over three steps from **10a**) in a stepwise fashion (quantitative yield based on recovered starting material for the reductive amination).

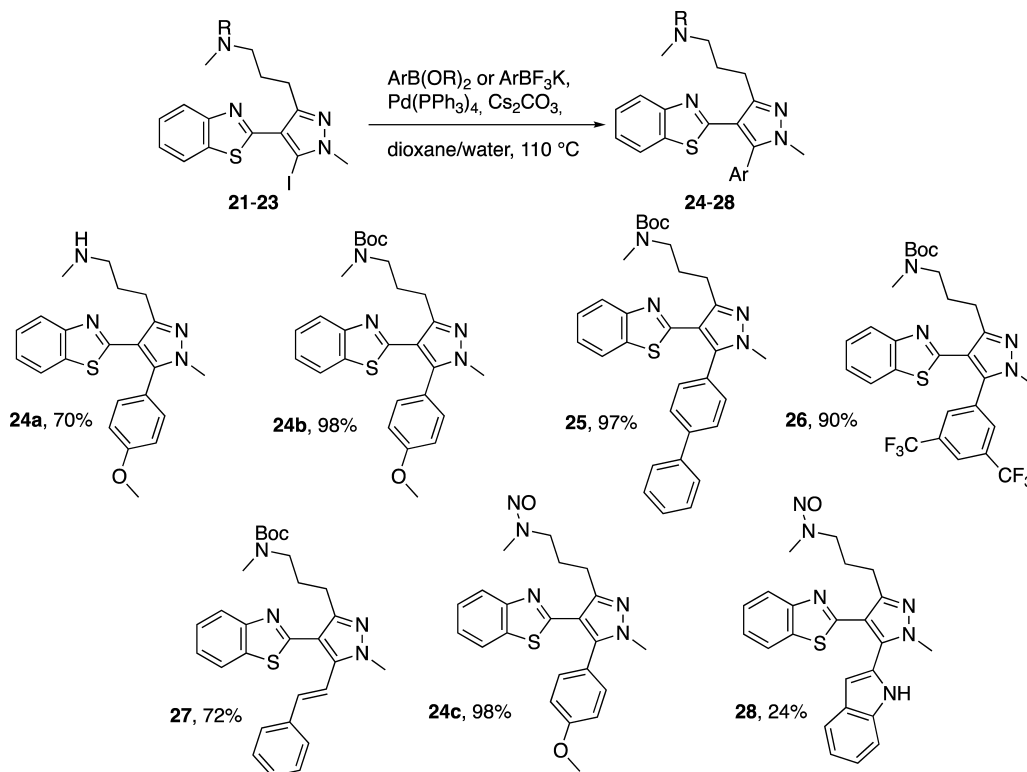
To further highlight the usefulness of heterocycle introduction on the pyrazole core, we then turned our attention to the formation of fused tetracyclic compounds (Scheme 7). For that purpose, we focused on the benzimidazole-substituted pyrazole **12a**. Indeed, in this specific case, having the pendant amino group on the pyrazole and proximate NH of the benzimidazole allows condensation with electrophiles such as orthoesters. This approach could deliver pyrazolopyrimidine scaffolds of interest for medicinal chemistry purposes, as has been exemplified in the development of inhibitors of glycogen synthase kinase 3, an enzyme involved in numerous diseases such as type II diabetes, Alzheimer's disease, cancer, bipolar disorder, and inflammation.<sup>39</sup>

Upon boiling a mixture of **12a** and 1,1,1-triethoxyethane in the presence of acetic anhydride, we could achieve the synthesis of 3H-benzo[4,5]imidazo[1,2-c]pyrazolo[4,3-e]pyrimidine **19** (Scheme 7, path A); it is important to note that a dehydrating agent is required to bring the reaction to completion. This illustrates the previously unreported, weak stability of the formed pyrimidine ring that only tends to hydrolyze back to the acylated starting material both under strongly acidic and basic conditions.<sup>40</sup> Yet, under neutral conditions, **19** could be isolated and thoroughly characterized. The  $^1\text{H}$  NMR spectrum

Scheme 8. Sandmeyer Iodination of the aminopyrazole Core



Scheme 9. Suzuki–Miyaura Cross Coupling of Iodinated Pyrazoles



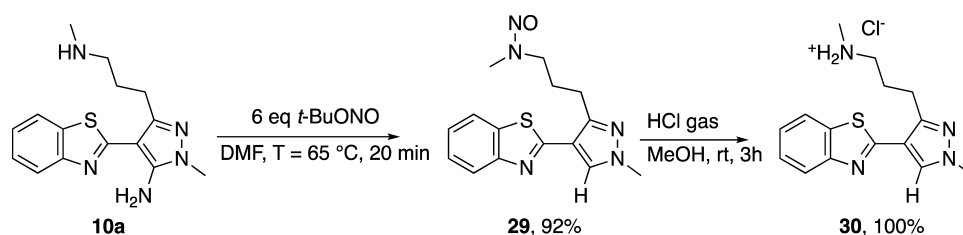
of **19** in CDCl<sub>3</sub> shows two sets of peaks corresponding to two unequally populated rotamers. Moreover, the symmetry of the benzimidazole moiety initially found in **12a** is disrupted through this transformation, promoting the split of the two aromatic signals of **12a** into four signals for **19**, namely, two doublets at 7.94 and 8.04 ppm and two doublets of doublets at 7.41 and 7.53 ppm.

A similar tetracyclic aromatic compound was also accessed by simple treatment of **12a** with an excess of *tert*-butyl nitrite in DMF (Scheme 7, path B). Under these conditions, the diazonium intermediate could indeed be trapped by the imidazole nitrogen to generate the corresponding triazene **20**, with concomitant protection of the secondary amine as a nitrosoamine. **20** was isolated in 85% yield after column chromatography and fully characterized. It exhibits a unique tetracyclic structure that has never been previously described, and as such, expands the chemical space of heterocyclic chemistry.

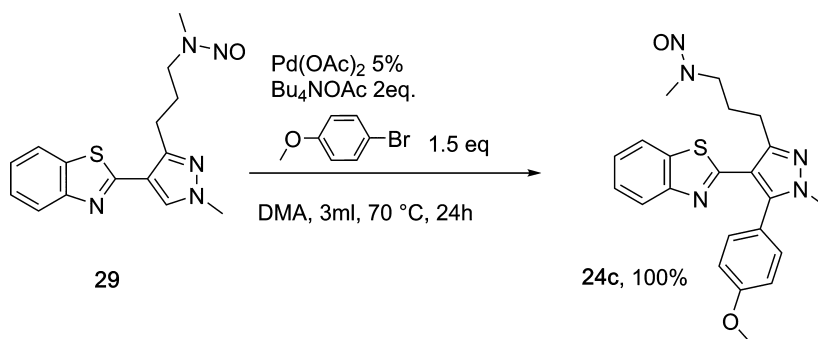
Finally, following this diazotization strategy, we investigated the lability of the 5-amino group. At first, we explored the ability of these heterocyclic-substituted aminopyrazoles to undergo Sandmeyer-type reactions. After extensive investiga-

tion, we found that to avoid the formation of numerous byproducts, the reaction had to be carried out at 65 °C with excess *tert*-butyl nitrite (5 equiv) and I<sub>2</sub> (4.3 equiv) in acetonitrile,<sup>41</sup> furnishing iodopyrazole **21** in 38% yield (Scheme 8). As stated above for the formation of **20**, the secondary amine was converted to its nitrosoamine derivative. We found that this could be avoided by first adding TsOH to the reaction mixture; under these acidic conditions, the secondary amine is protected as a weakly acidic ammonium salt avoiding nitrosation. Thus, only the primary aromatic ammonium formed under these conditions appears acidic enough to undergo nitrosation and water elimination to form the transient diazonium salt, which finally generates the iodopyrazole **22** in 30% yield. Interestingly, under these acidic conditions, the reaction proceeds with the formation of the reductive deamination byproduct (C–H bond formation). The introduction of iodine is easily monitored by the <sup>13</sup>C NMR spectrum of **22** characterized by considerable shielding of C5 by the adjacent I atom (**10a**, 147.1 ppm; **22**, 86.5 ppm). Further, Boc protection of the secondary amine could be achieved in trifluoroethanol yielding **23** in 70% yield. This two-step iodination–protection proved only moderately efficient,

**Scheme 10. Two-Step Approach to 3-(4-(Benzo[*d*]thiazol-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-*N*-methylpropan-1-aminium Chloride **30** Synthesis**



**Scheme 11. Functionalization of Pyrazole through C–H Activation**



highlighting the nitrosamine as a potentially useful alternate protecting group.

With these iodinated pyrazoles in hand, we explored potential C–C bond formation by way of Suzuki–Miyaura cross-coupling with a range of boronic acids (Scheme 9). A first attempt using **22** and 4-methoxyboronic acid under conventional conditions (5% Pd(PPh<sub>3</sub>)<sub>4</sub>, dioxane–H<sub>2</sub>O, Cs<sub>2</sub>CO<sub>3</sub>) provided the desired cross-coupling compound **24a** in 71% yield. Yet the presence of the secondary amine made chromatographic analysis and purification tedious. We therefore turned to **23** as the starting pyrazole and were pleased to achieve the cross-coupling to **24b** isolated in quantitative yield. We could further exemplify this reactivity by isolating **25** and **26** quantitatively, and **27** in 72% yield. Yet, moving to ortho-substituted 2-nitrophenylboronic acid and 2,6-bis-(trifluoromethyl)phenylboronic acid fully inhibited the coupling reactivity due to the steric bulk around the reactive site of the iodopyrazole derivative. We could also access the tris-heterocyclic compound **28** using *N*-Boc-indole 2-trifluoroborate, albeit with a moderate yield and under harsher conditions (140 °C) that promoted the thermolysis of the Boc group.

Considering the more efficient access to **21** (ca. 40% vs ca. 20% for **23**), we envisaged the unprecedented use of nitrosamine as a protecting group during the Suzuki–Miyaura cross-coupling. This was found to be a successful approach because the cross-coupling leading to **24c** occurred in quantitative fashion.

Finally, considering the observation of reduced product (~1:1 relative to iodinated product) during the Sandmeyer reaction, we investigated the possibility of performing such a reduction more efficiently. On the basis of former reports, we could achieve radical deamination of benzothiazole substituted pyrazole **10a** to **29** with *tert*-butyl nitrite in dimethylformamide (Scheme 10).<sup>42</sup> Indeed, opposite to the reaction with benzimidazole **12a**, no intramolecular trapping to the triazene can be achieved from **10a**. Therefore, the classical homolytic decomposition during diazotization allowed hydrogen abstrac-

tion from the solvent by the pyrazolyl radical to afford the desired reduced compound **29**, which was isolated and fully characterized. Similarly to the transformations described above, the reaction proceeds with concomitant nitrosation of the secondary amine. The <sup>1</sup>H NMR spectrum of **29** shows two sets of peaks corresponding to two unequally populated rotamers, and the characteristic singlet of the newly introduced proton arises at 7.88 ppm. Deprotection of the nitrosamine to the corresponding ammonium salt could be easily achieved by bubbling HCl gas in a methanol solution of **29**.<sup>43</sup> This two-step procedure gave 3-(4-(benzo[*d*]thiazol-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-*N*-methylpropan-1-aminium chloride **30** in 89% overall yield. The <sup>1</sup>H NMR spectrum of **30** recorded in DMSO-*d*<sub>6</sub> features a broad singlet for the two protons of the ammonium at 8.94 ppm that disappeared upon D<sub>2</sub>O addition. Although nitrosamines are considered as having limited value as protective groups (mainly as they are considered carcinogenic),<sup>44</sup> we believe, through all our observations, that in this specific case, their facile generation and deprotection make them an attractive option, provided cautious experimental procedures are followed. Moreover, nitrosamines are also known to promote the umpolung reaction of secondary amines through deprotonation, and as such, they represent an interesting functionalization.<sup>45</sup>

Having this reduced adduct in hand, we explored the possibility of further functionalization through the C–H activation reaction, as previously reported on pyrazoles.<sup>46,47</sup> We found that heating **29** at 70 °C in the presence of Pd(OAc)<sub>2</sub>, 4-bromoanisole, and tetrabutylammonium acetate in dimethylacetamide (DMA) for 24 h provided straightforward access to **30c** in quantitative yield (Scheme 11).

Once again, this illustrates the excellent compatibility of nitrosamine protection with palladium-catalyzed cross-coupling reactions. Moreover, this reaction path provides a highly efficient approach to densely substituted pyrazoles featuring both aryl and hetaryl substituents at the 4 and 5 positions, as



24c is isolated in 71% overall yield from benzothiazolylacetonitrile.

### 3. CONCLUSIONS

In summary, we have described a two-step procedure for the synthesis of fully substituted 4-hetaryl-5-aminoazoles from readily available starting materials in a modified Knorr-type reaction. The reaction was found to be fully selective thanks to an evidenced marked difference between the two centers of the 1,3-dielectrophile. These highly functionalized azoles have been shown to represent entries to various polyheterocyclic compounds, providing a straightforward route to a wide chemical space. Indeed, further reactivity of the 4-hetaryl-5-aminopyrazoles obtained was investigated, providing highly regioselective transformations and giving access to both known and unknown derivatives with high nitrogen contents. Moreover, transformation of the 5-amino substituent allowed the straightforward introduction of aryl and hetaryl moieties at this position providing a four-step route to densely functionalized pyrazoles. This also illustrates the efficient nitrogen protection as a nitrosamine during the Pd-catalyzed cross-coupling reaction. We consider that this approach opens new routes to enlarge the chemical space of pyrazole-containing pharmacophores as it introduces chemical complexity in an unprecedented swift fashion from simple starting materials.

### 4. EXPERIMENTAL SECTION

**4.1. Instrumentation.** For monitoring reaction progress, analytical thin layer chromatography (TLC) was performed using pre-coated Merck glass backed silica gel plates (Silica gel 60 F254). Visualization was achieved using ultraviolet light (254 nm). An elution system was set for an  $R_f$  of the product to be not more than 0.5.

Preparative chromatography was performed either manually with silica gel (63–200  $\mu\text{m}$ ) or with an automated flash chromatography Interchim Puriflash medium-pressure liquid chromatography system using Interchim high-purity grade silica gel (30 or 50  $\mu\text{m}$ ) prepacked columns.

$^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer, or on a Bruker Avance III 400 (400 MHz) spectrometer. Two-dimensional (2D) (COSY, HMQC, HMBC) spectra were recorded on a Bruker Avance III 400 (400 MHz) spectrometer. All spectra were recorded at ambient temperature (298 K) unless otherwise stated. Chemical shifts ( $\delta$ ) are reported in ppm relative to the peak of the deuterated solvent ( $\text{CDCl}_3$ : 7.28 for  $^1\text{H}$  and 77.0 for  $^{13}\text{C}$ ;  $\text{DMSO}-d_6$ : 2.50 for  $^1\text{H}$  and 40.0 for  $^{13}\text{C}$ ;  $\text{MeOD}$ : 3.31 ppm for  $^1\text{H}$  and 47.6 for  $^{13}\text{C}$ ), and coupling constants are reported in Hz. The multiplicity of signals is indicated using the following abbreviations: s = singlet, bs = broad singlet, d = doublet, t = triplet, quint = quintet, dd = doublet of doublets, ddd = doublet of doublets of doublets, and m = multiplet.

Infrared (IR) spectra were recorded on a PerkinElmer Spectrum One Fourier transform infrared (FT-IR) spectrometer of thin films deposited in  $\text{CH}_3\text{CN}$ ,  $\text{CHCl}_3$ , or  $\text{CH}_3\text{OH}$  (attenuated total reflection measurement) and on a PerkinElmer BX II FT-IR spectrometer with KBr pellets. Vibration frequencies are expressed in  $\text{cm}^{-1}$ ; only characteristic bands are given.

High-resolution mass spectrometry (HRMS) was run at the Mass Spectrometry Service at the University Paul Sabatier.

Melting points were assigned using a Kofler-type hot stage microscope (Boetius VEB Analytik) and on the Stuart melting point apparatus SMP10.

X-ray crystallography was performed on single crystal diffractometers: Agilent Gemini, Bruker Nonius, Bruker Kappa Apex II, and Xcalibur 3. All crystals were grown by the gas diffusion method.

**4.2. Materials.**  $N,N$ -Dimethylformamide (DMF) and 1,4-dioxane (ACS reagents) were purchased from Sigma-Aldrich and used without further purification. Toluene, tetrahydrofuran (THF),  $\text{Et}_2\text{O}$ , and  $\text{CH}_2\text{Cl}_2$  were dried using standard methods.<sup>48,49</sup>

Sodium hydride (NaH, 60%, dispersion in paraffin liquid), hydroxylamine ( $\text{NH}_2\text{OH}$ , 50% solution in water), hydrazine hydrate ( $\text{NH}_2\text{NH}_2$ , 50–60% reagent grade), methylhydrazine ( $\text{MeNHNH}_2$ ), *tert*-butyl nitrite (90%), and other chemicals were purchased at the highest commercial quality and used without further purification unless noted otherwise.

2-(Quinolin-2-yl)acetonitrile **3** was purchased from Enamine Ltd. 2-(4-Oxo-3,4-dihydroquinazolin-2-yl)acetonitrile **4** was synthesized according to known procedures.<sup>50</sup>

1-*R*-Pyrrolidin-2-ones were synthesized according to a known procedure.<sup>51</sup>

**4.3. General Consideration.** Reactions were performed in oven-dried, round-bottom flasks equipped with a reflux condenser and protected from humidity by a  $\text{CaCl}_2$  tube unless otherwise noted.

The ratio between compounds in a reaction mixture and the ratio between *Z* and *E* stereoisomers were found by comparing the integration sum under the peaks in the  $^1\text{H}$  NMR spectrum of the reaction mixture.

**4.3.1. 2-(Benzo[d]thiazol-2-yl)acetonitrile (1).** 2-Amino-benzenethiol (125 g, 107 mL, 1 mol) was added to a strongly stirred solution of malononitrile (66 g, 1 mol) and glacial acetic acid (60 g, 1 mol) in ethanol (300 mL). The reaction mixture was stirred at 15–17  $^\circ\text{C}$  over a 10–30 min period until sudden heating-up and formation of precipitate occurred. At this point, the stirring ceased and the reaction mixture was heated to reflux over a 5 min period, cooled down, and the formed precipitate was filtered off, washed with cold ethanol, and recrystallized from ethanol to give 148 g of the product (0.85 mol, 85%) as a yellowish solid.  $^1\text{H}$  NMR (400 MHz, chloroform- $d$ )  $\delta$  4.26 (s, 2H), 7.47 (ddd,  $J$  = 8.1, 7.4, 1.2 Hz, 1H), 7.55 (ddd,  $J$  = 8.2, 7.3, 1.3 Hz, 1H), 7.92 (d,  $J$  = 8.1 Hz, 1H), 8.06 (d,  $J$  = 8.1 Hz, 1H).

**4.3.2. 2-(1*H*-Benzo[d]imidazol-2-yl)acetonitrile (2).** A mixture of *o*-phenylenediamine (32.4 g, 0.3 mol) and ethylcyanoacetate (50 mL, 0.47 mol) was heated at 180  $^\circ\text{C}$  for 4.5 h. The formed solid was cooled down to rt and triturated with 1,4-dioxane (60 mL). The resulting precipitate was filtered off, washed with cold dioxane then ethanol, and recrystallized from an ethanol/water mixture to give 31.2 g (0.2 mol, 66%) of beige solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  4.26 (s, 2H), 7.51 (bs, 2H), 7.02–7.32 (m, 2H), 12.48 (s, 1H).

**4.4. General Procedure for 5-Methoxy-1-*R*,3,4-dihydro-2*H*-pyrrol-1-ium Methylsulfate Salt Synthesis (5).** 1-Alkyl-pyrrolidin-2-one (50 mmol) and dimethyl sulfate (4.74 mL, 55 mmol) were stirred for 2 h at 80  $^\circ\text{C}$  to give the desired pyrrolium salt as a viscous oil, which was used directly in the next step without further purification. Reaction progress was controlled by  $^1\text{H}$  NMR spectroscopy through the disappearance of 1-*R*-pyrrolidin-2-one in the crude reaction mixture.

**4.4.1. 1-Methylpyrrolidin-2-one.**  $^1\text{H}$  NMR (300 MHz, chloroform- $d$ )  $\delta$  1.93–2.05 (m, 2H), 2.33 (t,  $J$  = 8.2 Hz, 2H), 2.80 (t,  $J$  = 0.7 Hz, 3H), 3.28–3.40 (m, 2H).

**4.4.2. 1-Benzylpyrrolidin-2-one.**  $^1\text{H}$  NMR (300 MHz, chloroform- $d$ )  $\delta$  1.93–2.10 (m, 2H), 2.44 (t,  $J$  = 8.1 Hz, 2H), 3.26 (t,  $J$  = 7.1 Hz, 2H), 4.45 (s, 2H), 7.21–7.38 (m, 5H).

**4.4.3. 1-Cyclopropylpyrrolidin-2-one.**  $^1\text{H}$  NMR (300 MHz, chloroform- $d$ )  $\delta$  0.61–0.69 (m, 2H), 0.69–0.78 (m, 2H), 1.88–2.00 (m, 2H), 2.35 (t,  $J$  = 8.1 Hz, 2H), 2.56–2.70 (m, 1H), 3.28 (t,  $J$  = 7.0 Hz, 2H).

Alternatively, such pyrrolium salts could be obtained as solids upon treatment with  $\text{KPF}_6$  in water.

**4.4.4. 5-Methoxy-1-methyl-3,4-dihydro-2H-pyrrol-1-ium Hexafluorophosphate Salt.** **5a** (1g, 4.4 mmol) was added dropwise to a strongly stirred solution of  $\text{KPF}_6$  (1.47 g, 8 mmol) in water (25 mL) at rt. The suspension was allowed to stir for 30 min. The white precipitate was filtrated off to yield 0.65 g of the title compound (2.5 mmol, 56%) as a white solid.

$^1\text{H}$  NMR (300 MHz, acetone- $d_6$ )  $\delta$  2.33–2.55 (m, 2H), 3.24 (s, 3H), 3.35–3.44 (m, 2H), 4.02–4.10 (m, 2H), 4.43 (s, 3H).  $^{31}\text{P}$  NMR (121 MHz, acetone- $d_6$ )  $\delta$  -144.37 (hept,  $J$  = 707.5 Hz).

**4.5. General Procedure for 2-Hetaryl-*N*-R-pyrrolidin-2-ylideneacetonitrile Synthesis (6–9).** A solution of hetarylacetonitrile (4 mmol) in DMF (10 mL) was added dropwise to a strongly stirred suspension of NaH (107 mg, 4 mmol) in DMF (5 mL), and the reaction mixture was stirred for 10 min until complete evolution of gas had occurred. A solution of 5-methoxy-1-*R*-3,4-dihydro-2H-pyrrol-1-ium salt (6 mmol) in DMF (3 mL) was subsequently added to the reaction mixture, and stirring was pursued until complete conversion of the starting material had occurred (TLC control). Water was then added to the mixture, promoting precipitation. The suspension was additionally stirred for 30 min, and the precipitate was then filtered and washed with cyclohexane. Further precipitation was achieved by concentration of the initial mother liquid (water, DMF) and trituration of the residues at 0 °C with water, filtration, and subsequent washing with cyclohexane. Purification was carried out by column chromatography or recrystallization from the appropriate solvent. The products are obtained as a mixture of *Z* and *E* stereoisomers.

Note: the aliquot for TLC was taken from the crude reaction mixture followed by addition of water and extraction with EtOAc.

**4.5.1. 2-(Benzo[d]thiazol-2-yl)-2-(1-methylpyrrolidin-2-ylidene)acetonitrile (6a).** The product (900 mg, 3.52 mmol, 88% yield) was obtained as a white solid (mp 186 °C) after filtration over charcoal in hot ethanol. TLC elution system:  $\text{CHCl}_3$ – $\text{CH}_3\text{OH}$  (95:5). The reaction was directly scaled up to 10.45 g of starting material affording 13.94 g (91% yield) of the desired product.

IR (KBr): 2178 (CN), 1573 (C=N, C=C).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.99 (quint,  $J$  = 7.5 Hz, 2H), 3.38 (s, 3H), 3.43 (t,  $J$  = 7.5 Hz, 2H), 3.68 (t,  $J$  = 7.3 Hz, 2H), 7.25 (t,  $J$  = 7.7 Hz, 1H), 7.39 (t,  $J$  = 7.7 Hz, 1H), 7.72 (d,  $J$  = 7.7 Hz, 1H), 7.93 (d,  $J$  = 7.7 Hz, 1H) ppm;  $^{13}\text{C}$  NMR (75 MHz, DMSO)  $\delta$  20.0 ( $\text{CH}_2$ ), 36.2 ( $\text{CH}_3$ ), 37.2 ( $\text{CH}_2$ ), 58.1 ( $\text{CH}_2$ ), 68.4 ( $\text{C}_q$ ), 120.9 (CH), 121.4 ( $\text{C}_q$ ), 121.7 (CH), 123.6 (CH), 126.4 (CH) 133.1 ( $\text{C}_q$ ), 154.6 ( $\text{C}_q$ ), 167.3 ( $\text{C}_q$ ), 167.6 ( $\text{C}_q$ ) ppm; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_3\text{S}$  ( $\text{M} + \text{H}^+$ ): 256.0908, found: 256.0909.

**4.5.2. 2-(Benzo[d]thiazol-2-yl)-2-(1-benzylpyrrolidin-2-ylidene)acetonitrile (6b).** The product (1.06 g, 3.6 mmol, 80% yield) was obtained as a white solid (mp 134–135 °C)

after manual column chromatography. Elution system:  $\text{CH}_2\text{Cl}_2$ –EtOAc (7:3).

IR (neat film): 2183 (CN), 1588, 1559 (C=N, C=C). DMSO- $d_6$  *E* isomer, *Z* isomer traces.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.02 (quint,  $J$  = 7.4 Hz, 2H), 3.56 (t,  $J$  = 7.6 Hz, 2H), 3.63 (t,  $J$  = 7.2 Hz, 2H), 5.13 (s, 2H), 7.26 (t,  $J$  = 7.6 Hz, 1H), 7.36–7.49 (m, 6H), 7.74 (d,  $J$  = 8.1 Hz, 1H), 7.93 (d,  $J$  = 7.8 Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  20.1 ( $\text{CH}_2$ ), 37.6 ( $\text{CH}_2$ ), 51.0 ( $\text{CH}_2$ ), 56.2 ( $\text{CH}_2$ ), 68.6 ( $\text{C}_q$ ), 120.9 ( $\text{C}_q$ ), 121.2 (CH), 121.8 (CH), 123.9 (CH), 126.5 (CH), 127.5 (2CH), 128.0 (CH), 129.3 (2CH), 133.2 ( $\text{C}_q$ ), 136.2 ( $\text{C}_q$ ), 154.5 ( $\text{C}_q$ ), 167.2 ( $\text{C}_q$ ), 167.4 ( $\text{C}_q$ ). HRMS (ESI) calcd for  $\text{C}_{20}\text{H}_{18}\text{N}_3\text{S}$  ( $\text{M} + \text{H}^+$ ): 332.1221, found: 332.1212.

**4.5.3. 2-(Benzo[d]thiazol-2-yl)-2-(1-cyclopropylpyrrolidin-2-ylidene)acetonitrile (6c).** The product (832 mg, 2.96 mmol, 74% yield) was obtained as a whitish solid (mp 144 °C).

IR (neat film): 2182 (CN), 1548 (C=N, C=C).  $\text{CDCl}_3$  ratio *E*:*Z* = 9:1. *E* isomer:  $^1\text{H}$  NMR (300 MHz, chloroform- $d$ )  $\delta$  0.95–1.03 (m, 2H), 1.08–1.18 (m, 2H), 2.04 (quint,  $J$  = 7.6 Hz, 2H), 3.08–3.21 (m, 1H), 3.51 (t,  $J$  = 7.8 Hz, 2H), 3.60 (t,  $J$  = 7.3 Hz, 2H), 7.26 (ddd,  $J$  = 8.3, 7.4, 1.3 Hz, 1H), 7.39 (ddd,  $J$  = 8.5, 7.7, 1.3 Hz, 1H), 7.79 (dd,  $J$  = 5.6, 0.8 Hz, 1H), 7.82 (dd,  $J$  = 5.6, 0.9 Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz, chloroform- $d$ )  $\delta$  10.6 ( $\text{CH}_2$ ), 20.6 ( $\text{CH}_2$ ), 30.1 (CH), 36.4 ( $\text{CH}_2$ ), 54.3 ( $\text{CH}_2$ ), 71.8 ( $\text{C}_q$ ), 120.9 ( $\text{C}_q$ ), 121.0 (CH), 121.2 (CH), 123.4 (CH), 125.7 (CH), 134.0 ( $\text{C}_q$ ), 154.4 ( $\text{C}_q$ ), 167.1 ( $\text{C}_q$ ), 167.5 ( $\text{C}_q$ ). HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_3\text{S}$  ( $\text{M} + \text{H}^+$ ): 282.1065, found: 282.1071.

**4.5.4. 2-(1H-Benzo[d]imidazol-2-yl)-2-(1-methylpyrrolidin-2-ylidene)acetonitrile (7a).** NaH (2.1 equiv, 0.336 g, 8.4 mmol) were used to deprotonate the methylene group in the presence of the benzimidazole moiety. The product (760 mg, 3.2 mmol, 80% yield) was obtained as a white solid (mp 262 °C) after trituration with boiling 2-propanol. TLC elution system:  $\text{CHCl}_3$ – $\text{CH}_3\text{OH}$  (95:5).

IR (KBr): 3297 (NH), 2184 (CN), 1575, 1528 (C=N, C=C). DMSO- $d_6$  ratio *E*:*Z* = 5:1. *E* isomer:  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  1.93 (quint, 7.6 Hz, 2H), 3.33 (t,  $J$  = 7.6 Hz, 2H), 3.37 (s, 3H), 3.62 (t,  $J$  = 7.2 Hz, 2H), 7.32–7.46 (m, 2H), 7.00–7.08 (m, 2H), 11.75 (s, 1H) ppm;  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  20.3 ( $\text{CH}_2$ ), 36.0 ( $\text{CH}_3$ ), 36.3 ( $\text{CH}_2$ ), 57.8 ( $\text{CH}_2$ ), 62.3 ( $\text{C}_q$ ), 111.0 (CH), 117.5 (CH), 121.1 (CH), 121.2 (CH), 122.7 ( $\text{C}_q$ ), 134.7 ( $\text{C}_q$ ), 144.5 ( $\text{C}_q$ ), 151.6 ( $\text{C}_q$ ), 167.0 ( $\text{C}_q$ ). *Z* isomer:  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.01 (quint, 7.6 Hz, 2H), 2.78 (s, 3H), 3.00 (t,  $J$  = 7.8 Hz, 2H), 3.65 (t,  $J$  = 7.2 Hz, 2H), 7.08–7.16 (m, 2H), 7.32–7.46 (m, 1H), 7.51 (d,  $J$  = 8.4 Hz, 1H), 12.25 (s, 1H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  20.5 ( $\text{CH}_2$ ), 36.3 ( $\text{CH}_3$ ), 37.3 ( $\text{CH}_2$ ), 59.0 ( $\text{CH}_2$ ), 62.3 ( $\text{C}_q$ ), 111.2 (CH), 118.3 (CH), 121.2 ( $\text{C}_q$ ), 121.5 (CH), 122.0 (CH), 134.6 ( $\text{C}_q$ ), 144.0 ( $\text{C}_q$ ), 147.8 ( $\text{C}_q$ ), 164.9 ( $\text{C}_q$ ). HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_4$  ( $\text{M} + \text{H}^+$ ): 239.1297, found: 239.1299.

**4.5.5. 2-(1H-Benzo[d]imidazol-2-yl)-2-(1-benzylpyrrolidin-2-ylidene)acetonitrile (7b).** The product (970 mg, 3.08 mmol, 77% yield) was obtained as a white solid (mp 264–265 °C) after trituration with boiling 2-propanol. TLC elution system:  $\text{CHCl}_3$ – $\text{CH}_3\text{OH}$  (95:5).

IR (KBr): 3289 (NH), 2188 (CN), 1588, 1576, 1524 (C=N, C=C). DMSO- $d_6$  ratio *E*:*Z* = 5:1. *E* isomer:  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  1.97 (quint,  $J$  = 7.4 Hz, 2H), 3.43 (t,  $J$  = 7.7 Hz, 2H), 3.58 (t,  $J$  = 7.2 Hz, 2H), 5.11 (s, 2H), 7.00–7.55 (m, 9H), 11.83 (s, 1H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  20.4 ( $\text{CH}_2$ ), 36.6 ( $\text{CH}_2$ ), 50.7 ( $\text{CH}_2$ ), 55.8 ( $\text{CH}_2$ ), 62.8 ( $\text{C}_q$ ), 111.1

(CH), 117.6 (CH), 120.5 (C<sub>q</sub>), 121.3 (CH), 121.4 (CH), 127.5 (CH), 127.9 (CH), 129.2 (CH), 134.7 (C<sub>q</sub>), 136.7 (C<sub>q</sub>), 144.4 (C<sub>q</sub>), 151.2 (C<sub>q</sub>), 166.5 (C<sub>q</sub>). Z isomer: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 2.03 (quint, *J* = 7.4 Hz, 2H), 3.09 (t, *J* = 7.7 Hz, 2H), 3.65 (t, *J* = 7.1 Hz, 2H), 4.92 (s, 2H), 6.87–6.93 (m, 2H), 7.02–7.52 (m, 7H), 12.14 (s, 1H); <sup>13</sup>C NMR (101 MHz, DMSO) δ 20.7 (CH<sub>2</sub>), 37.4 (CH<sub>2</sub>), 51.8 (CH<sub>2</sub>), 57.6 (CH<sub>2</sub>), 63.8 (C<sub>q</sub>), 111.3 (CH), 118.2 (CH), 121.5 (CH), 122.2 (CH), 122.6 (C<sub>q</sub>), 127.55 (2CH), 127.63 (CH), 128.8 (2CH), 134.6 (C<sub>q</sub>), 136.6 (C<sub>q</sub>), 143.8 (C<sub>q</sub>), 147.5 (C<sub>q</sub>), 163.6 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>20</sub>H<sub>19</sub>N<sub>4</sub> (M + H<sup>+</sup>): 315.1610, found: 315.1608.

**4.5.6. 2-(1-Benzylpyrrolidin-2-ylidene)-2-(quinolin-2-yl)-acetonitrile (8b).** The product (872 mg, 2.68 mmol, 67% yield) was obtained as a white solid (mp 141 °C) after manual column chromatography and further recrystallization from 2-propanol. First column: CH<sub>2</sub>Cl<sub>2</sub> (100%); second column: CHA–EtOAc (5:1).

IR (neat film): 2179 (CN), 1561, 1533, 1498 (C=N, C=C). DMSO-*d*<sub>6</sub> ratio E:Z = 1:3.3. Z isomer: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.96 (quint, *J* = 7.5 Hz, 2H), 3.47 (t, *J* = 7.7 Hz, 2H), 3.56 (t, *J* = 7.1 Hz, 2H), 5.15 (s, 2H), 7.29–7.47 (m, 5H), 7.46 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.68 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1H), 7.83 (d, *J* = 6.7 Hz, 1H), 7.86 (d, *J* = 6.8 Hz, 1H), 8.21 (d, *J* = 8.7 Hz, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 20.85 (CH<sub>2</sub>), 36.5 (CH<sub>2</sub>), 51.2 (CH<sub>2</sub>), 55.2 (CH<sub>2</sub>), 72.5 (C<sub>q</sub>), 120.0 (CH), 122.1 (C<sub>q</sub>), 125.3 (C<sub>q</sub>), 125.4 (CH), 127.6 (2CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 129.2 (2CH), 130.0 (CH), 136.5 (CH), 136.9 (C<sub>q</sub>), 147.5 (C<sub>q</sub>), 156.7 (C<sub>q</sub>), 167.4 (C<sub>q</sub>). E isomer: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 2.08 (quint, *J* = 7.5 Hz, 2H), 3.15 (t, *J* = 7.8 Hz, 2H), 3.70 (t, *J* = 7.1 Hz, 2H), 4.78 (s, 2H), 6.79–6.93 (m, 2H), 7.11–7.24 (m, 3H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.29–7.47 (m, 1H), 7.60–7.64 (m, 2H), 7.80–7.88 (m, 1H), 8.10 (d, *J* = 8.6 Hz, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 20.81 (CH<sub>2</sub>), 37.9 (CH<sub>2</sub>), 53.2 (CH<sub>2</sub>), 57.9 (CH<sub>2</sub>), 74.6 (C<sub>q</sub>), 121.4 (CH), 122.1 (C<sub>q</sub>), 124.2 (C<sub>q</sub>), 125.9 (CH), 127.2 (2CH), 127.5 (CH), 128.0 (CH), 128.1 (CH), 128.7 (2CH), 130.1 (CH), 136.4 (CH), 136.6 (C<sub>q</sub>), 147.1 (C<sub>q</sub>), 154.5 (C<sub>q</sub>), 163.9 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>22</sub>H<sub>20</sub>N<sub>3</sub> (M + H<sup>+</sup>): 326.1657, found: 326.1663.

**4.5.7. 2-(1-Methylpyrrolidin-2-ylidene)-2-(4-oxo-3,4-dihydroquinazolin-2-yl)acetonitrile (9a).** NaH (2.1 equiv, 0.336 g, 8.4 mmol) was used to deprotonate the methylene group in the presence of the quinazolinone moiety. The product (800 mg, 3.2 mmol, 75% yield) was obtained as a brownish solid (mp 203–204 °C) after filtration over charcoal in boiling ethanol. TLC elution system: EtOAc–CHA (1:1).

IR (neat film): 3200, 3143 (NH<sub>ν</sub>), 2187 (CN), 1661 (C=O), 1561 (C=N, C=C). CDCl<sub>3</sub> E isomer 100%, Z isomer traces: <sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 2.10 (quint, *J* = 7.4 Hz, 2H), 3.48 (s, 3H), 3.58 (t, *J* = 7.9 Hz, 2H), 3.69 (t, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.67 (t, *J* = 7.3 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 9.10 (s, 1H); <sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 20.3 (CH<sub>2</sub>), 36.7 (CH<sub>3</sub>), 36.9 (CH<sub>2</sub>), 57.9 (CH<sub>2</sub>), 66.6 (C<sub>q</sub>), 119.4 (C<sub>q</sub>), 119.8 (C<sub>q</sub>), 125.0 (CH), 126.4 (CH), 126.5 (CH), 134.5 (CH), 149.4 (C<sub>q</sub>), 150.4 (C<sub>q</sub>), 161.9 (C<sub>q</sub>), 170.2 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>15</sub>H<sub>15</sub>N<sub>4</sub>O (M + H<sup>+</sup>): 267.1246, found: 267.1252.

**4.6. General Procedure for the Synthesis of 3-(ω-Aminoalkyl)-4-hetaryl-5-aminopyrazole (or Isoxazole) (10–16).** Ten equivalents of binucleophile (NH<sub>2</sub>NH<sub>2</sub>/NH<sub>2</sub>OH/NH<sub>2</sub>NH<sub>2</sub>Me) were added to a strongly stirred

solution of 2-hetaryl-*N*-*R*-pyrrolidin-2-ylideneacetonitrile (1 mmol) in dioxane (0.1 M). The reaction mixture was then heated to reflux for 3–8 h, cooled down, and concentrated under reduced pressure. Purification by column chromatography or by trituration with a minimal quantity of acetone/acetonitrile yielded the desired product.

**4.6.1. 4-(Benzo[d]thiazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine (10a).** The product (187 mg, 0.62 mmol, 62% yield) was obtained as a whitish solid (mp 158–159 °C) after trituration with a minimal quantity of acetone. TLC elution system: CHCl<sub>3</sub>–CH<sub>3</sub>OH (20:1). The reaction was directly scaled up to 12.61 g of starting material affording 10.3 g (85% yield) of the desired product.

IR (neat film): 3376, 3292 (NH<sub>ν</sub>, NH<sub>2</sub>ν), 1623 (NH<sub>2</sub>δ), 1564, 1536 (C=C, C=N). <sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 1.98 (quint, *J* = 7.4 Hz, 2H), 2.48 (s, 3H), 2.76 (t, *J* = 7.1 Hz, 2H), 2.85–2.97 (m, 2H), 3.66 (s, 3H), 5.77 (s, 2H), 7.28 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.43 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H); <sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 26.2 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 33.8 (CH<sub>3</sub>), 36.5 (CH<sub>3</sub>), 51.9 (CH<sub>2</sub>), 97.9 (C<sub>q</sub>), 121.08 (CH), 121.09 (CH), 123.5 (CH), 125.9 (CH), 132.4 (C<sub>q</sub>), 147.1 (C<sub>q</sub>), 149.5 (C<sub>q</sub>), 152.7 (C<sub>q</sub>), 162.2 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>15</sub>H<sub>20</sub>N<sub>5</sub>S (M + H<sup>+</sup>): 302.1451, found: 302.1446.

**4.6.2. 4-(Benzo[d]thiazol-2-yl)-3-(3-(benzylamino)propyl)-1-methyl-1H-pyrazol-5-amine (10b).** The product (264 mg, 0.70 mmol, 70% yield) was obtained as a whitish solid (mp 192–193 °C) after trituration of the residues with acetone. TLC elution system: CHCl<sub>3</sub>–CH<sub>3</sub>OH (20:1).

IR (neat film) 3391, 3298 (NH<sub>ν</sub>, NH<sub>2</sub>ν), 1622 (NH<sub>2</sub>δ), 1539 (C=C, C=N, NH δ). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 2.05 (quint, 7.4 Hz, 2H), 2.82 (t, *J* = 7.4 Hz, 2H), 2.95 (t, 7.8 Hz, 2H), 3.58 (s, 3H), 4.04 (s, 2H), 6.86 (s, 2H), 7.31 (ddd, 8.4 Hz, 7.5 Hz, 0.9 Hz, 1H), 7.52–7.35 (m, 6H), 7.89 (d, *J* = 7.9 Hz, 1H), 8.00 (d, *J* = 7.5 Hz, 1H); <sup>13</sup>C NMR (75 MHz, methanol-*d*<sub>4</sub>) δ 25.4 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>), 33.9 (CH<sub>3</sub>), 47.9 (CH<sub>2</sub>), 52.1 (CH<sub>2</sub>), 97.8 (C<sub>q</sub>), 121.9 (2CH), 124.6 (CH), 127.0 (CH), 130.0 (2CH), 130.3 (CH), 130.6 (2CH), 132.7 (C<sub>q</sub>), 133.2 (C<sub>q</sub>), 148.7 (C<sub>q</sub>), 149.6 (C<sub>q</sub>), 153.8 (C<sub>q</sub>), 162.6 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>21</sub>H<sub>24</sub>N<sub>5</sub>S (M + H<sup>+</sup>): 378.1752, found: 378.1747.

**4.6.3. 4-(Benzo[d]thiazol-2-yl)-3-(3-(cyclopropylamino)propyl)-1-methyl-1H-pyrazol-5-amine (10c).** The product (203 mg, 0.62 mmol, 62% yield) was obtained as a whitish solid (mp 171 °C) after trituration of the residues with acetonitrile. TLC elution system: CHCl<sub>3</sub>–CH<sub>3</sub>OH (20:1).

IR (neat film): 3396, 3376, 3292 (NH<sub>ν</sub>, NH<sub>2</sub>ν), 1623 (NH<sub>2</sub>δ), 1563, 1540 (C=C, C=N). <sup>1</sup>H NMR (300 MHz, chloroform-*d*) δ 0.33–0.41 (m, 2H), 0.41–0.48 (m, 2H), 1.99 (quint, *J* = 7.6 Hz, 2H), 2.13–2.23 (m, 1H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.91 (t, *J* = 7.7 Hz, 2H), 3.68 (s, 3H), 5.76 (s, 2H), 7.29 (ddd, *J* = 8.2, 7.6, 1.2 Hz, 1H), 7.44 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.3, 1H), 7.89 (dd, *J* = 8.2, 1.2, 1H); <sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 6.3 (2CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 30.2 (CH<sub>3</sub>), 33.8 (CH), 49.3 (CH<sub>2</sub>), 97.9 (C<sub>q</sub>), 121.07 (CH), 121.10 (CH), 123.5 (CH), 125.9 (CH), 132.4 (C<sub>q</sub>), 147.1 (C<sub>q</sub>), 149.5 (C<sub>q</sub>), 152.7 (C<sub>q</sub>), 162.2 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>17</sub>H<sub>22</sub>N<sub>5</sub>S (M + H<sup>+</sup>): 328.1596, found: 328.1592.

**4.6.4. 4-(Benzo[d]thiazol-2-yl)-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine (11a).** The product (161 mg, 0.56 mmol, 56% yield) was obtained as a light orange solid (mp 121–123



°C) after trituration of the residues with acetone. TLC elution system: CHCl<sub>3</sub>–CH<sub>3</sub>OH (20:1).

IR (neat film): 3311 (NH, NH<sub>2</sub>ν), 1624 (NH<sub>2</sub>δ), 1580, 1543 (C=C, C=N, NH δ), 1455 (C–Hδ). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.74–1.91 (m, 2H), 2.29 (s, 3H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.76–2.91 (m, 2H), 6.23 (s, 2H), 7.30 (ddd, *J* = 7.6, 7.3, 1.1 Hz, 1H), 7.44 (ddd, *J* = 8.0, 7.7, 1.3 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 25.2 (CH<sub>2</sub>), 28.5 (CH<sub>2</sub>), 36.6 (CH<sub>3</sub>), 51.7 (CH<sub>2</sub>), 97.4 (C<sub>q</sub>), 121.3 (CH), 122.0 (CH), 124.0 (CH), 126.6 (CH), 132.4 (C<sub>q</sub>), 146.4 (C<sub>q</sub>), 153.0 (2C<sub>q</sub>), 162.6 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>14</sub>H<sub>18</sub>N<sub>5</sub>S (M + H<sup>+</sup>): 288.1283, found: 288.1281.

**4.6.5. 4-(Benzo[d]thiazol-2-yl)-3-(3-(cyclopropylamino)propyl)-1H-pyrazol-5-amine (11c).** The product (134 mg, 0.43 mmol, 43% yield) was obtained as a whitish solid (mp 121–123 °C) after trituration of the residues with acetonitrile. TLC elution system: CHCl<sub>3</sub>–CH<sub>3</sub>OH (20:1).

IR (neat film): 3411, 3291, 3197 (NHν, NH<sub>2</sub>ν), 1602 (NH<sub>2</sub>δ), 1539, 1540, 1496 (C=C, C=N, NH δ). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 0.20–0.32 (m, 2H), 0.34–0.47 (m, 2H), 1.85 (quint, *J* = 7.3 Hz, 2H), 2.08–2.18 (m, 1H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.83 (t, *J* = 7.4 Hz, 2H), 6.25 (s, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 6.1 (2CH<sub>2</sub>), 25.2 (CH<sub>2</sub>), 28.2 (CH), 30.5 (CH<sub>2</sub>), 49.0 (CH<sub>2</sub>), 97.8 (C<sub>q</sub>), 121.2 (CH), 122.0 (CH), 124.0 (CH), 126.6 (CH), 132.3 (C<sub>q</sub>), 146.9 (C<sub>q</sub>), 152.9 (2C<sub>q</sub>), 162.3 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>16</sub>H<sub>20</sub>N<sub>5</sub>S (M + H<sup>+</sup>): 314.1439, found: 314.1438.

**4.6.6. 4-(1H-Benzo[d]imidazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine (12a).** The product (186 mg, 0.65 mmol, 65% yield) was obtained as a whitish solid (mp 181–183 °C) after manual column chromatography (elution system: CHCl<sub>3</sub>–CH<sub>3</sub>OH 10:3) and further trituration of the obtained yellowish oil with acetone for its consolidation.

IR (neat film): 3300 (NH, NHν, NH<sub>2</sub>ν), 1623 (NH<sub>2</sub>δ), 1579 (NHδ, C=C, C=N). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.95 (quint, *J* = 6.9 Hz, 1H), 2.45 (s, 3H), 2.79 (t, *J* = 6.7 Hz, 2H), 2.92 (t, *J* = 7.2 Hz, 2H), 3.58 (s, 3H), 6.54 (s, 2H), 7.04–7.16 (m, 2H), 7.46–7.57 (m, 2H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 25.0 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 33.8 (CH<sub>3</sub>), 34.5 (CH<sub>3</sub>), 48.7 (CH<sub>2</sub>), 92.4 (C<sub>q</sub>), 114.5 (2CH), 121.3 (2CH), 146.5 (2C<sub>q</sub>), 148.6 (2C<sub>q</sub>), 149.3 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>15</sub>H<sub>21</sub>N<sub>6</sub> (M + H<sup>+</sup>): 285.1828, found: 285.1825.

**4.6.7. 4-(1H-Benzo[d]imidazol-2-yl)-3-(3-(benzylamino)propyl)-1-methyl-1H-pyrazol-5-amine (12b).** The product (186 mg, 0.65 mmol, 65% yield) was obtained as a whitish solid (mp 181–183 °C) after manual column chromatography (elution system: CHCl<sub>3</sub>–CH<sub>3</sub>OH 10:3) and further trituration of the obtained yellowish oil with a minimal quantity of acetone for its consolidation.

IR (neat film): 3300 (NHν, NH<sub>2</sub>ν), 1623 (NH<sub>2</sub>δ), 1579 (NHδ, C=C, C=N). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.84 (quint, *J* = 6.7 Hz, 2H), 2.55 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 7.0 Hz, 2H), 3.56 (s, 3H), 3.74 (s, 2H), 6.49 (s, 2H), 7.01–7.08 (m, 2H), 7.22–7.29 (m, 1H), 7.29–7.40 (m, 6H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 24.8 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 34.4 (CH<sub>3</sub>), 46.8 (CH<sub>2</sub>), 52.7 (CH<sub>2</sub>), 92.6 (C<sub>q</sub>), 121.2 (2CH), 127.2 (CH), 128.7 (6 CH), 140.3 (3C<sub>q</sub>), 147.2 (C<sub>q</sub>), 148.6 (C<sub>q</sub>), 149.7 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>21</sub>H<sub>25</sub>N<sub>6</sub> (M + H<sup>+</sup>): 361.2141, found: 361.2140.

**4.6.8. 3-(3-(Benzylamino)propyl)-1-methyl-4-(quinolin-2-yl)-1H-pyrazol-5-amine (13b).** The product (204 mg, 0.55 mmol, 55% yield) was obtained as a yellow solid (mp 170–171 °C) after manual column chromatography (elution system: CHCl<sub>3</sub>–CH<sub>3</sub>OH (20:1)) and further trituration of the obtained yellowish oil with acetone for its consolidation.

IR (neat film): 3261 (NHν, NH<sub>2</sub>ν), 1619 (NH<sub>2</sub>δ), 1599, 1547, 1518 (C=C, C=N). <sup>1</sup>H NMR (300 MHz, chloroform-*d*) δ 2.01 (quint, *J* = 7.0 Hz, 2H), 2.82 (t, *J* = 6.8 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H), 3.57 (s, 3H), 3.84 (s, 2H), 6.04 (s, 2H), 7.23–7.38 (m, 5H), 7.41 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.64 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.71 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H). <sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 27.5 (CH<sub>2</sub>), 28.1 (CH<sub>2</sub>), 33.6 (CH<sub>3</sub>), 48.8 (CH<sub>2</sub>), 53.4 (CH<sub>2</sub>), 100.8 (C<sub>q</sub>), 118.9 (CH), 124.8 (CH), 125.3 (C<sub>q</sub>), 127.2 (CH), 127.4 (CH), 127.8 (CH), 128.3 (CH), 128.4 (CH), 129.5 (CH), 136.1 (CH), 139.2 (C<sub>q</sub>), 147.4 (C<sub>q</sub>), 147.8 (C<sub>q</sub>), 148.9 (C<sub>q</sub>), 154.8 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>23</sub>H<sub>26</sub>N<sub>5</sub> (M + H<sup>+</sup>): 372.2188, found: 372.2181.

**4.6.9. 3-(3-(Benzylamino)propyl)-4-(quinolin-2-yl)isoxazol-5-amine (14b).** The product (204 mg, 0.50 mmol, 50% yield) was obtained as a light orange solid (mp 125–126 °C) after manual column chromatography (elution system: CHCl<sub>3</sub>–CH<sub>3</sub>OH (20:1)).

IR (neat film): 3327 (NHν, NH<sub>2</sub>ν), 1631 (NH<sub>2</sub>δ), 1598, 1541 (NHδ, C=C, C=N), 1294 (C–O). <sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 2.06 (quint, *J* = 7.0 Hz, 2H), 2.85 (t, *J* = 6.9 Hz, 2H), 3.06 (t, *J* = 7.5 Hz, 2H), 3.86 (s, 2H), 7.03 (s, 2H), 7.24–7.31 (m, 1H), 7.32–7.42 (m, 4H), 7.46 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.68 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.75 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 1H); <sup>13</sup>C NMR (75 MHz, chloroform-*d*) δ 25.4 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 48.4 (CH<sub>2</sub>), 53.6 (CH<sub>2</sub>), 91.7 (C<sub>q</sub>), 117.9 (CH), 125.2 (CH), 125.5 (C<sub>q</sub>), 127.2 (CH), 127.5 (CH), 127.8 (CH), 128.3 (2CH), 128.5 (2CH), 129.8 (CH), 136.5 (CH), 139.4 (C<sub>q</sub>), 147.3 (C<sub>q</sub>), 152.5 (C<sub>q</sub>), 161.3 (C<sub>q</sub>), 169.2 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>22</sub>H<sub>23</sub>N<sub>4</sub>O (M + H<sup>+</sup>): 359.1872, found: 359.1862.

**4.6.10. 2-(5-Amino-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-4-yl)quinazolin-4(3H)-one (15a).** The product (194 mg, 0.62 mmol, 62% yield) was obtained as a whitish solid (mp 173 °C) after trituration of the residues with water and subsequently boiling acetone. The suspension was allowed to cool down, and the precipitate was filtered off. TLC elution system: CHCl<sub>3</sub>–CH<sub>3</sub>OH (20:1).

IR (neat film): 3358, 3284 (NHν, NH<sub>2</sub>ν), 1668 (C=O), 1575, 1557, (NH<sub>2</sub>δ, C=C, C=N). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.93 (quint, *J* = 6.8 Hz, 2H), 2.38 (s, 3H), 2.55 (t, *J* = 5.7 Hz, 2H), 2.83 (t, *J* = 6.3 Hz, 2H), 3.55 (s, 3H), 6.65 (s, 2H), 7.22 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.59 (ddd, 8.4, 7.6, 1.4 Hz, 1H), 7.99 (dd, 1.2 Hz, 1H), 9.53 (s, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 23.4 (CH<sub>2</sub>), 27.6 (CH<sub>2</sub>), 33.4 (CH<sub>3</sub>), 34.4 (CH<sub>3</sub>), 46.9 (CH<sub>2</sub>), 98.5 (C<sub>q</sub>), 120.5 (C<sub>q</sub>), 123.5 (CH), 125.8 (CH), 126.0 (CH), 133.1 (CH), 146.9 (C<sub>q</sub>), 149.0 (C<sub>q</sub>), 150.7 (C<sub>q</sub>), 156.2 (C<sub>q</sub>), 167.2 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>15</sub>H<sub>21</sub>N<sub>6</sub> (M + H<sup>+</sup>): 313.1777, found: 313.1772.

**4.6.11. 2-(5-Amino-3-(3-(methylamino)propyl)isoxazol-4-yl)quinazolin-4(3H)-one (16a).** The product (224 mg, 0.75 mmol, 75% yield) was obtained as a light orange powder (mp 171–172 °C) after trituration of the residues with boiling acetone. The suspension was allowed to cool down, and the

precipitate was filtered off. TLC elution system:  $\text{CHCl}_3$ – $\text{CH}_3\text{OH}$  (20:1).

IR (neat film): 3347, 3284 ( $\text{NH}_\nu$ ,  $\text{NH}_2\nu$ ), 1633 ( $\text{C}=\text{O}$ ), 1607, 1571 ( $\text{NH}_2\delta$ ,  $\text{C}=\text{C}$ ,  $\text{C}=\text{N}$ ), 1243 ( $\text{C}-\text{O}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.92–2.07 (m, 2H), 2.51 (s, 3H), 2.75–2.83 (m, 2H), 2.92–3.03 (m, 2H), 7.18 (t,  $J = 7.2$  Hz, 1H), 7.50 (d,  $J = 7.6$  Hz, 1H), 7.55 (t,  $J = 7.2$  Hz, 1H), 7.96 (d,  $J = 7.0$  Hz, 1H), 8.04 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  21.7 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 33.0 ( $\text{CH}_3$ ), 47.0 ( $\text{CH}_2$ ), 90.3 ( $\text{C}_q$ ), 120.8 ( $\text{C}_q$ ), 123.2 ( $\text{CH}$ ), 125.7 ( $\text{CH}$ ), 126.0 ( $\text{CH}$ ), 132.4 ( $\text{CH}$ ), 151.1 ( $\text{C}_q$ ), 157.0 ( $\text{C}_q$ ), 160.8 ( $\text{C}_q$ ), 169.5 ( $\text{C}_q$ ), 170.5 ( $\text{C}_q$ ). HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{18}\text{N}_5\text{O}_2$  ( $\text{M} + \text{H}^+$ ): 300.1460, found: 300.1462.

**4.6.12. 3-(5-Amino-4-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)-N,N,N-trimethylpropan-1-aminium iodide (17).** MeI (0.137 mL,  $d = 2.28$  g/mL, 2.2 mmol) was added dropwise to a stirred solution of 4-(benzo[d]thiazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine **10a** (301 mg, 1 mmol) and MeONa (54 mg, 1 mmol) in MeOH (6 mL). Stirring was pursued for 3 h. The resulting white precipitate (mp 249–250 °C) was filtered off and analyzed without additional purification steps. We observed complete conversion of the starting material to the desired product but we suspected the presence of NaI.

IR (neat film): 3393 ( $\text{NH}_2\nu$ ), 1614 ( $\text{NH}_2\delta$ ), 1563, 1535 ( $\text{C}=\text{C}$ ,  $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR (300 MHz, methanol- $d_4$ )  $\delta$  2.21–2.36 (m, 2H), 2.96 (t,  $J = 7.3$  Hz, 2H), 3.17 (s, 9H), 3.48–3.59 (m, 2H), 3.65 (s, 3H), 7.30 (ddd,  $J = 8.2$ , 7.6, 1.2 Hz, 1H), 7.45 (ddd,  $J = 8.2$ , 7.3, 1.3 Hz, 1H), 7.86–7.93 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, methanol- $d_4$ )  $\delta$  21.3 ( $\text{CH}_2$ ), 24.3 ( $\text{CH}_2$ ), 32.8 ( $\text{CH}_3$ ), 52.2 (t,  $J = 4.0$  Hz, 3 $\text{CH}_3$ ), 65.9 (t,  $J = 3.0$  Hz, 2- $\text{CH}_2$ ), 96.7 ( $\text{C}_q$ ), 120.79 ( $\text{CH}$ ), 120.84 ( $\text{CH}$ ), 123.5 ( $\text{CH}$ ), 125.9 ( $\text{CH}$ ), 132.0 ( $\text{C}_q$ ), 147.0 ( $\text{C}_q$ ), 148.5 ( $\text{C}_q$ ), 152.8 ( $\text{C}_q$ ), 161.4 ( $\text{C}_q$ ). HRMS (ESI) calcd for  $\text{C}_{17}\text{H}_{24}\text{N}_5\text{S}$  ( $\text{M} + \text{H}^+$ ): 330.1752, found: 330.1758.

**4.6.13. 4-(Benzo[d]thiazol-2-yl)-N-benzyl-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine (18).** Di-*tert*-butyl dicarbonate (120 mg, 0.55 mmol) was added to a stirred solution of 4-(benzo[d]thiazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine **10a** (151 mg, 0.5 mmol) in trifluoroethanol (TFE) (3 mL) at rt. The reaction was completed in 10 min. After evaporation of volatiles under reduced pressure, the crude product was purified by automated flash chromatography (elution system: gradient of  $\text{CH}_2\text{Cl}_2$ –acetone, 9:1 to  $\text{CH}_2\text{Cl}_2$ –acetone, 2:3) to yield 187 mg (0.47 mmol, 93% yield) of white solid (mp 129–130 °C).

IR (neat film): 3384, 3300 ( $\text{NH}_2\nu$ ), 1673 ( $\text{C}=\text{O}$ ), 1619 ( $\text{NH}_2\delta$ ), 1562, 1532 ( $\text{C}=\text{C}$ ,  $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR (400 MHz, chloroform- $d$ )  $\delta$  1.46 (s, 9H), 1.92–2.05 (m, 2H), 2.81–2.87 (m, 2H), 2.90 (br s, 3H), 3.37–3.44 (m, 2H), 3.63 (s, 3H), 5.86 (s, 2H), 7.26 (t,  $J = 7.4$  Hz, 1H), 7.41 (t,  $J = 7.6$  Hz, 1H), 7.80 (d,  $J = 7.8$  Hz, 1H), 7.86 (d,  $J = 8.1$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, chloroform- $d$ )  $\delta$  25.8 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 28.5 ( $\text{CH}_3$ ), 33.8 ( $\text{CH}_3$ ), 34.3 ( $\text{CH}_3$ ), 48.9 ( $\text{CH}_2$ ), 79.3 ( $\text{C}_q$ ), 97.7 ( $\text{C}_q$ ), 121.0 ( $\text{CH}$ ), 121.1 ( $\text{CH}$ ), 123.5 ( $\text{CH}$ ), 125.9 ( $\text{CH}$ ), 132.3 ( $\text{C}_q$ ), 147.2 ( $\text{C}_q$ ), 149.1 ( $\text{C}_q$ ), 152.7 ( $\text{C}_q$ ), 155.9 ( $\text{C}_q$ ), 162.0 ( $\text{C}_q$ ). HRMS (ESI) calcd for  $\text{C}_{20}\text{H}_{28}\text{N}_5\text{O}_2\text{S}$  ( $\text{M} + \text{H}^+$ ): 402.1964, found: 402.1963.

A suspension of *tert*-butyl 3-(5-amino-4-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl(methyl)carbamate (187 mg, 0.47 mmol), AcOH (0.05 mL, 0.94 mmol), benzaldehyde (0.06 mL, 0.56 mmol), and activated molecular sieves in toluene (5 mL) was stirred in a sealed vessel overnight at 120

°C. At this point, two spots were detected by TLC ( $\text{CH}_2\text{Cl}_2$ –acetone, 9:1) corresponding to the reactant ( $R_f = 0.27$ ) and the desired imine ( $R_f = 0.67$  (bright yellow spot)). The reaction was broken off at that point, filtrated through a plug of celite, and the liquid was concentrated under reduced pressure. The obtained solid was redissolved in dry ethanol (5 mL) and 3 equiv of  $\text{NaBH}_4$  (53 mg, 1.4 mmol) was subsequently added. The reaction was stirred for 30 min at rt (during this time, the color of the reaction mixture changed from yellow to white due to reduction of the imine to amine) under Ar. Dilution of the reaction mixture with ethanol, filtration through a plug of Celite, and concentration under reduced pressure gave a mixture of **10a** and **18** at 100% yield. After compound separation by automated flash chromatography (elution system: gradient of  $\text{CH}_2\text{Cl}_2$ –acetone, 19:1 to  $\text{CH}_2\text{Cl}_2$ –acetone, 9:1), secondary amine **18** was obtained as a colorless oil (108 mg, 0.22 mmol, 47%).

IR (neat film): 3271 ( $\text{NH}$ ), 1690 ( $\text{C}=\text{O}$ ), 1560 ( $\text{C}=\text{C}$ ,  $\text{C}=\text{N}$ ), 1249 ( $\text{C}-\text{O}$ ), 1164 ( $\text{C}-\text{N}$ ).  $^1\text{H}$  NMR (400 MHz, chloroform- $d$ )  $\delta$  1.47 (s, 9H), 1.95–2.07 (m, 2H), 2.82–2.94 (m, 5H), 3.28–3.50 (m, 2H), 3.81 (s, 3H), 4.55 (s, 2H), 7.28–7.38 (m, 4H), 7.39–7.47 (m, 3H), 7.80–7.88 (m, 2H), 7.79 (bs, NH).  $^{13}\text{C}$  NMR (101 MHz, chloroform- $d$ )  $\delta$  25.8 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 28.5 (3 $\text{CH}_3$ ), 34.3 ( $\text{CH}_3$ ), 36.8 ( $\text{CH}_3$ ), 48.9 ( $\text{CH}_2$ ), 50.3 ( $\text{CH}_2$ ), 79.2 ( $\text{C}_q$ ), 100.6 ( $\text{C}_q$ ), 121.0 ( $\text{CH}$ ), 121.2 ( $\text{CH}$ ), 123.7 ( $\text{CH}$ ), 126.0 ( $\text{CH}$ ), 127.1 (2 $\text{CH}$ ), 127.5 ( $\text{CH}$ ), 128.7 (2 $\text{CH}$ ), 132.5 ( $\text{C}_q$ ), 138.9 ( $\text{C}_q$ ), 149.3 ( $\text{C}_q$ ), 149.5 ( $\text{C}_q$ ), 152.5 ( $\text{C}_q$ ), 155.8 ( $\text{C}_q$ ), 162.0 ( $\text{C}_q$ ). HRMS (ESI) calcd for  $\text{C}_{27}\text{H}_{34}\text{N}_5\text{O}_2\text{S}$  ( $\text{M} + \text{H}^+$ ): 492.2433, found: 492.2433.

**4.6.14. N-(3-(3,5-Dimethyl-3H-benzo[4,5]imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidin-1-yl)propyl)-N-methylacetamide (19).** A solution of 4-(1H-benzo[d]imidazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine **12a** (142 mg, 0.5 mmol) in 1,1,1-triethoxyethane (10 mL) was refluxed for 20 min, and  $\text{Ac}_2\text{O}$  (0.47 mL,  $d = 1.087$  g/mL, 5 mmol) was added to the reaction mixture at this point. After another 5 min of stirring, the reaction ceased (TLC elution system:  $\text{CHCl}_3$ –acetone, 2:1) and the mixture was concentrated under reduced pressure. The crude product was purified by automated flash chromatography (elution system: gradient of  $\text{CHCl}_3$ –acetone, 2:1) to yield 152 mg (0.43 mmol, 87% yield) of white solid (mp 97–98 °C).

IR (neat film): 1656 ( $\text{C}=\text{O}$ ), 1623, 1601, 1544, 1525 ( $\text{C}=\text{C}$ ,  $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR (300 MHz, chloroform- $d$ ) (mixture of rotamers)  $\delta$  2.09 (s, 1.2H), 2.14 (s, 1.8H), 2.22–2.39 (m, 2H), 2.98 (s, 1.8H), 3.07 (s, 1.2H), 3.18–3.29 (m, 5H), 3.45–3.53 (m, 1.2H), 3.55–3.63 (m, 0.8H), 4.10 (s, 1.2H), 4.11 (s, 1.8H), 7.37–7.47 (m, 1H), 7.51–7.60 (m, 1H), 7.92–8.00 (m, 1H), 8.00–8.08 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, chloroform- $d$ ) (mixture of rotamers)  $\delta$  21.2 ( $\text{CH}_3$ ), 22.0 ( $\text{CH}_3$ ), 24.4 ( $\text{CH}_3$ ), 24.5 ( $\text{CH}_3$ ), 25.7 ( $\text{CH}_2$ ), 25.9 ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 26.9 ( $\text{CH}_2$ ), 33.3 ( $\text{CH}_3$ ), 34.1 ( $\text{CH}_3$ ), 34.2 ( $\text{CH}_3$ ), 36.2 ( $\text{CH}_3$ ), 47.1 ( $\text{CH}_2$ ), 50.5 ( $\text{CH}_2$ ), 99.3 ( $\text{C}_q$ ), 113.9 ( $\text{CH}$ ), 114.0 ( $\text{CH}$ ), 119.8 ( $\text{CH}$ ), 122.1 ( $\text{CH}$ ), 122.2 ( $\text{CH}$ ), 125.5 ( $\text{CH}$ ), 125.7 ( $\text{CH}$ ), 128.8 ( $\text{C}_q$ ), 145.2 ( $\text{C}_q$ ), 145.2 ( $\text{C}_q$ ), 145.7 ( $\text{C}_q$ ), 145.8 ( $\text{C}_q$ ), 146.5 ( $\text{C}_q$ ), 146.9 ( $\text{C}_q$ ), 147.0 ( $\text{C}_q$ ), 149.8 ( $\text{C}_q$ ), 150.0 ( $\text{C}_q$ ), 170.5, 170.6 ( $\text{C}_q$ ). HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_6\text{O}$  ( $\text{M} + \text{H}^+$ ): 351.1929, found: 351.1928.

**4.6.15. N-Methyl-N-(3-(3-methyl-3H-benzo[4,5]imidazo[1,2-*c*]pyrazolo[4,3-*e*][1,2,3]triazin-1-yl)propyl)nitrous Amide (20).** *t*-BuONO (0.12 mL,  $d = 0.867$  g/mL, 1 mmol) was added dropwise to a strongly stirred solution of 4-(1H-benzo[d]imidazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyra-



zol-5-amine **12a** (142 mg, 0.5 mmol) in DMF (5 mL, 65 °C), and the gas evolution was observed by bubble counter. After 10 min of stirring, TLC control (CH<sub>2</sub>Cl<sub>2</sub>–acetone, 9:1) indicated the presence of two spots corresponding to the starting material and new product. The pH of the reaction mixture was slightly basic. Another portion of *t*-BuONO (0.24 mL, 2 mmol) was added dropwise, and the pH of the reaction mixture turned to acidic (pH ~ 3). After 10 min of stirring, another TLC control was made to ensure the conversion of starting material and formation of one main product. The reaction mixture was allowed to cool to rt, and pH was brought to neutral–slightly basic by addition of saturated aq. NaHCO<sub>3</sub>. This aqueous phase was extracted with EtOAc (three times), and collected organic extracts were washed with brine and dried over MgSO<sub>4</sub>. The solution was concentrated under reduced pressure and the residue was purified by automated flash chromatography (elution system: CH<sub>2</sub>Cl<sub>2</sub>–acetone, 19:1) to yield 137 mg (0.42 mmol, 85% yield) of **20** as a bright yellow solid (mp 163–164 °C).

Note: (1) the aliquot for TLC was taken from the reaction mixture followed by addition of saturated aq. NaHCO<sub>3</sub> to make pH neutral–slightly basic and extraction with EtOAc. (2) The solution of *t*-BuONO is acidic when purchased from commercial sources. Its acidity is enough to generate the nitrosonium ion and bring the reaction to completion.

IR (neat film): 1652, 1527, 1447 (C=N, C=C, N=O), 1280 (N=O), 1333 (N=O), 1038 (N–N), 1129 (C–N). <sup>1</sup>H NMR (300 MHz, chloroform-*d*) (mixture of rotamers) δ 2.22–2.35 (m, 0.4H), 2.45–2.63 (m, 1.6H), 3.14 (s, 2.4H), 3.20–3.26 (m, 0.4H), 3.28–3.38 (m, 1.6H), 3.75–3.83 (m, 0.4H), 3.85 (s, 0.6H), 4.32–4.41 (m, 1.6H), 4.38 (s, 3H), 7.52–7.60 (m, 1H), 7.60–7.69 (m, 1H), 7.94–8.00 (m, 1H), 8.33–8.40 (m, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (mixture of rotamers) δ 24.2 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 31.4 (CH<sub>3</sub>), 35.5 (CH<sub>3</sub>), 38.9 (CH<sub>3</sub>), 44.0 (CH<sub>2</sub>), 53.1 (CH<sub>2</sub>), 101.2 (C<sub>q</sub>), 111.9 (CH), 120.0 (CH), 123.7 (CH), 127.2 (CH), 128.8 (C<sub>q</sub>), 136.7 (C<sub>q</sub>), 142.6 (C<sub>q</sub>), 144.2 (C<sub>q</sub>), 145.1 (C<sub>q</sub>), 145.3 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>15</sub>H<sub>17</sub>N<sub>8</sub>O (M + H<sup>+</sup>): 325.1525, found: 325.1529.

**4.6.16. N-(3-(4-(Benzo[d]thiazol-2-yl)-5-iodo-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous Amide (21).** *t*-BuONO (0.6 mL, *d* = 0.876 g/mL, 5 mmol) was added dropwise to a stirring suspension of **10a** (301 mg, 1 mmol) and I<sub>2</sub> (1.1 g, 4.3 mmol) in acetonitrile (10 mL) at 65 °C. After stirring for 20 min, the mixture was cooled to room temperature, and saturated aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added. The mixture was extracted three times with ethyl acetate, and the combined organic extracts were washed with saturated aq. NaCl and dried over MgSO<sub>4</sub>. Evaporation of volatiles under reduced pressure and further purification by automated flash chromatography (elution system: CH<sub>2</sub>Cl<sub>2</sub>–acetone, 19:1) yielded 168 mg of **21** (0.38 mmol, 38%) as a light orange solid (mp 104–105 °C).

The reaction was directly scaled up to 1.8 g (6 mmol) of starting material, affording 0.83 g (32% yield) of the desired product.

IR (neat film): 1538 (C=N, C=C), 1450, 1435 (N=O), 1332 (N=O), 1040 (N–N), 1144 (C–N). <sup>1</sup>H NMR (400 MHz, chloroform-*d*) (mixture of rotamers) δ 1.93–2.04 (m, 0.4H), 2.15–2.28 (m, 1.6H), 3.01–3.06 (m, 0.4), 3.08 (s, 2.4H), 3.11–3.17 (m, 1.6H), 3.70–3.76 (m, 0.4H), 3.78 (s, 0.6H), 4.00 (s, 0.6H), 4.01 (s, 2.4H), 4.25–4.31 (m, 1.6H), 7.41 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 7.51 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.93 (ddd, *J* = 7.9, 1.1, 0.6 Hz, 1H), 8.04 (ddd, *J* = 8.2,

1.1, 0.6 Hz, 0.8H), 8.08 (ddd, *J* = 8.2, 1.1, 0.6 Hz, 0.2H). <sup>13</sup>C NMR (101 MHz, chloroform-*d*) (mixture of rotamers) δ 24.8 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 27.2 (CH<sub>2</sub>), 31.4 (CH<sub>3</sub>), 39.1 (CH<sub>3</sub>), 40.51 (CH<sub>3</sub>), 40.53 (CH<sub>3</sub>), 44.5 (CH<sub>2</sub>), 53.5 (CH<sub>2</sub>), 86.7 (C<sub>q</sub>), 120.2 (C<sub>q</sub>), 121.3 (CH), 122.8 (CH), 125.0 (CH), 126.2 (CH), 134.3 (C<sub>q</sub>), 152.3 (C<sub>q</sub>), 153.0 (C<sub>q</sub>), 159.0 (C<sub>q</sub>). MS (ESI) *m/z*: [M + H]<sup>+</sup> found for C<sub>15</sub>H<sub>17</sub>IN<sub>5</sub>OS: 442.55; *m/z*: [M + Na]<sup>+</sup> found for C<sub>15</sub>H<sub>16</sub>IN<sub>5</sub>OSNa: 564.60. Elemental anal. calcd for C<sub>15</sub>H<sub>16</sub>IN<sub>5</sub>OS: C, 40.83; H, 3.65; N, 15.87. Found: C, 40.95; H, 3.29; N, 15.67.

**4.6.17. 3-(4-(Benzo[d]thiazol-2-yl)-5-iodo-1-methyl-1H-pyrazol-3-yl)-N-methylpropan-1-amine (22).** *p*-TsOH monohydrate (1.52 g, 8 mmol) was added portionwise to a strongly stirred solution of 4-(benzo[d]thiazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine **10a** (0.602 g, 2 mmol) in MeCN (10 mL), and the reaction mixture was stirred over a 5 min period. The flask was then cooled to 0 °C in an ice-water bath and KI (0.83 g, 5 mmol), CuI (1 mg, 0.005 mmol), and *t*-BuONO (0.302 mL, *d* = 1.368 g/mL, 4 mmol) were added subsequently to the reaction mixture. The solution was stirred at 0 °C for 20 min then allowed to warm to rt, and stirring was continued for a further 2 h. Then, the reaction mixture was quenched with water (30 mL), 5% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (30 mL), and saturated aq. NaHCO<sub>3</sub> solution to reach pH 8–9. This mixture was transferred to a separatory funnel, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous MgSO<sub>4</sub>, filtered, and then concentrated under reduced pressure. The crude mixture was purified by automated flash chromatography (elution system: gradient of CHCl<sub>3</sub>–Et<sub>3</sub>N, 10:1 to CHCl<sub>3</sub>–Et<sub>3</sub>N–CH<sub>3</sub>OH, 10:1:0.2) to give 0.247 g (0.6 mmol, 30% yield) of **22** as a white solid (mp 189 °C) after trituration of the residues with MeCN.

The reaction was directly scaled up to 1.8 g (6 mmol) of starting material, affording 0.74 g (30% yield) of the desired product.

IR (neat film): 3394 (NH<sub>ν</sub>), 1537 (C=C, C=N). <sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 1.95 (quint, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 2.69 (t, *J* = 6.9 Hz, 2H), 3.11 (t, *J* = 7.5 Hz, 2H), 4.01 (s, 3H), 7.35–7.46 (m, 1H), 7.48–7.55 (m, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H); <sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 25.4 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 36.1 (CH<sub>3</sub>), 40.5 (CH<sub>3</sub>), 51.2 (CH<sub>2</sub>), 86.5 (C<sub>q</sub>, C-I), 120.1 (C<sub>q</sub>), 121.3 (CH), 122.8 (CH), 124.9 (CH), 126.1 (CH), 134.5 (C<sub>q</sub>), 153.0 (C<sub>q</sub>), 153.3 (C<sub>q</sub>), 159.5 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>15</sub>H<sub>18</sub>N<sub>4</sub>SI (M + H<sup>+</sup>): 413.0297, found: 413.0297.

**4.6.18. tert-Butyl (3-(4-(Benzo[d]thiazol-2-yl)-5-iodo-1-methyl-1H-pyrazol-3-yl)propyl)(methyl)carbamate (23).** Di-*tert*-butyl dicarbonate (120 mg, 0.55 mmol) was added to a stirred solution of **22** (206 mg, 0.5 mmol) in TFE (3 mL) at rt followed by the addition of NaOMe (30 mg, 0.55 mmol). The reaction was completed in 30 min. After evaporation of volatiles under reduced pressure, the crude product was purified by automated flash chromatography (elution system: gradient of CH<sub>2</sub>Cl<sub>2</sub>–acetone, 19:1 to CH<sub>2</sub>Cl<sub>2</sub>–acetone, 9:1) to yield 179 mg (0.35 mmol, 70% yield) of **23** as a white solid (mp 122 °C).

IR (neat film): 1690 (C=O), 1519 (C=C, C=N), 1030, 1250 (C–O). <sup>1</sup>H NMR (300 MHz, chloroform-*d*) δ 1.42 (s, 9H), 1.86–2.04 (m, 2H), 2.86 (s, 3H), 2.98–3.11 (m, 2H), 3.23–3.41 (m, 2H), 4.01 (s, 3H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H). <sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 25.5 (CH<sub>2</sub>), 27.2 (CH<sub>2</sub>), 28.4 (3CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 40.4 (CH<sub>3</sub>), 48.7 (CH<sub>2</sub>),

79.1 (C<sub>q</sub>), 86.6 (C<sub>q</sub>), 120.0 (C<sub>q</sub>), 121.2 (CH), 122.9 (CH), 124.9 (CH), 126.1 (CH), 134.5 (C<sub>q</sub>), 153.0 (C<sub>q</sub>), 153.4 (C<sub>q</sub>), 155.8 (C<sub>q</sub>), 159.3 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>20</sub>H<sub>26</sub>IN<sub>4</sub>O<sub>2</sub>S (M + H<sup>+</sup>): 513.0821, found: 513.0817.

**4.7. General Procedure for the Synthesis of *R*-(3-(4-(Benzo[d]thiazol-2-yl)-5-aryl/hetaryl/styryl-1-methyl-1H-pyrazol-3-yl)propyl-1-amine (24–28).** *N*-(3-(4-(Benzo[d]thiazol-2-yl)-5-iodo-1-methyl-1H-pyrazol-3-yl)propyl)-*N*-methylpropan-1-amine **22**/*N*-methylnitrous amide **21**/*tert*-butyl-(methyl)carbamate **23** (0.15 mmol), boronic acid (**24a–c**, **25**)/its diethanolamine ester (**26**, **27**)/trifluoroborate salt (**28**) (0.17 mmol), Cs<sub>2</sub>CO<sub>3</sub> (64 mg, 0.18 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (9 mg, 0.0075 mmol) were placed in a two-necked flask fitted with a water condenser and rubber septum. The system was evacuated and back-filled with argon. This sequence was repeated three times. Dioxane–H<sub>2</sub>O, 5:1 mixture (8 mL) was degassed beforehand by the Freeze–Pump–Thaw method and transferred to the reaction vessel under a positive pressure of argon. The resulting mixture was stirred under argon at 110 °C overnight. After cooling to room temperature, the reaction mixture was diluted with H<sub>2</sub>O, transferred to the separatory funnel, and extracted three times with EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by automated flash chromatography.

**4.7.1. 3-(4-(Benzo[d]thiazol-2-yl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-3-yl)-*N*-methylpropan-1-amine (24a).** The product (41 mg, 0.11 mmol, 70% yield) was obtained as a yellowish solid (mp 96–97 °C) after automated flash chromatography (elution system: CH<sub>2</sub>Cl<sub>2</sub>–CH<sub>3</sub>OH–Et<sub>3</sub>N, 8:1:1).

IR (neat film): 3303 (NH<sub>ν</sub>), 1519 (C=C, C=N), 1249 (C–O). <sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 1.81 (s, 1H), 2.01 (quint, *J* = 7.0 Hz, 2H), 2.44 (s, 3H), 2.73 (t, *J* = 6.9 Hz, 2H), 3.11–3.26 (m, 2H), 3.69 (s, 3H), 3.90 (s, 3H), 7.01–7.08 (m, 2H), 7.24 (ddd, *J* = 8.3, 7.3, 1.1 Hz, 1H), 7.29–7.35 (m, 2H), 7.39 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.66 (ddd, *J* = 7.9, 1.1, 0.6 Hz, 1H), 7.92–7.98 (m, 1H, ddd, *J* = 8.0, 1.1, 0.6 Hz, 1H). <sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 25.5 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 36.3 (CH<sub>3</sub>), 36.8 (CH<sub>3</sub>), 51.6 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 113.7 (C<sub>q</sub>), 114.6 (CH), 121.0 (CH), 121.1 (C<sub>q</sub>), 122.3 (CH), 124.2 (CH), 125.7 (CH), 131.9 (2CH), 134.4 (C<sub>q</sub>), 143.8 (C<sub>q</sub>), 151.4 (C<sub>q</sub>), 153.2 (C<sub>q</sub>), 160.9 (C<sub>q</sub>), 161.1 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>22</sub>H<sub>25</sub>N<sub>4</sub>O<sub>2</sub>S (M + H<sup>+</sup>): 393.1749, found: 393.1743.

**4.7.2. *tert*-Butyl 3-(4-(Benzo[d]thiazol-2-yl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-3-yl)propyl(methyl)-carbamate (24b).** The product (72 mg, 0.15 mmol, 98% yield) was obtained as a yellowish solid (mp 116 °C) after automated flash chromatography (elution system: CHA–EtOAc, 6:4).

IR (neat film): 1691 (C=O), 1519 (C=C, C=N), 1251 (C–O). <sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 1.45 (s, 9H), 1.95–2.13 (m, 2H), 2.92 (s, 3H), 3.09–3.21 (m, 2H), 3.34–3.47 (m, 2H), 3.70 (s, 3H), 3.93 (s, 3H), 7.04–7.10 (m, 2H), 7.27 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.31–7.36 (m, 2H), 7.41 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.69 (ddd, *J* = 8.0, 1.2, 0.6 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H). <sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 25.5 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 28.5 (3CH<sub>3</sub>), 34.0 (CH<sub>3</sub>), 36.8 (CH<sub>3</sub>), 48.9 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 79.0 (C<sub>q</sub>), 113.5 (C<sub>q</sub>), 114.6 (2CH), 120.96 (CH), 121.04 (C<sub>q</sub>), 122.5 (CH), 124.3 (CH), 125.7 (CH), 131.9 (2CH), 134.4 (C<sub>q</sub>), 143.9 (C<sub>q</sub>), 151.3 (C<sub>q</sub>), 153.2 (C<sub>q</sub>), 155.9 (C<sub>q</sub>), 160.9 (C<sub>q</sub>), 161.0 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>27</sub>H<sub>33</sub>N<sub>4</sub>O<sub>3</sub>S (M + H<sup>+</sup>): 493.2273, found: 493.2273.

**4.7.3. *N*-(3-(4-(Benzo[d]thiazol-2-yl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-3-yl)propyl)-*N*-methylnitrous Amide (24c).** The product (62 mg, 0.15 mmol, 98% yield) was obtained as a light orange solid (mp 140 °C) after automated flash chromatography (system: gradient of CH<sub>2</sub>Cl<sub>2</sub>–acetone, 19:1 to CH<sub>2</sub>Cl<sub>2</sub>–acetone, 9:1).

IR (neat film): 1519 (C=N, C=C), 1451 (N=O), 1333 (N=O), 1029, 1249 (C–O), 1175 (C–N). <sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 2.03–2.13 (m, 0.4H), 2.24–2.35 (m, 1.6H), 3.09–3.17 (m, 0.4H), 3.13 (s, 2.4H), 3.19–3.30 (m, 1.6H), 3.69 (s, 0.6H), 3.70 (s, 1.4H), 3.78–3.86 (m, 0.4H), 3.83 (s, 0.6H), 3.93 (s, 0.6H), 3.94 (s, 2.4H), 4.36 (t, *J* = 7.2 Hz, 1.6H), 7.06–7.11 (m, 2H), 7.27 (ddd, *J* = 8.0, 7.6, 1.1 Hz, 1H), 7.31–7.37 (m, 2H), 7.42 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 3H), 7.68 (ddd, *J* = 8.0, 1.4, 0.6 Hz, 1H), 7.95 (ddd, *J* = 8.2, 1.3, 0.6 Hz, 0.8H), 7.98 (ddd, *J* = 8.2, 1.3, 0.6 Hz, 0.2H). <sup>13</sup>C NMR (101 MHz, chloroform-*d*) (only the shifts corresponding to the main rotamer are mentioned) δ 25.3 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 31.4 (CH<sub>3</sub>), 36.8 (CH<sub>3</sub>), 53.8 (CH<sub>3</sub>), 55.4 (CH<sub>2</sub>), 113.7 (C<sub>q</sub>), 114.7 (2CH), 120.8 (C<sub>q</sub>), 121.0 (CH), 122.4 (CH), 124.4 (CH), 125.8 (CH), 131.9 (2CH), 134.3 (C<sub>q</sub>), 144.1 (C<sub>q</sub>), 150.2 (C<sub>q</sub>), 153.1 (C<sub>q</sub>), 160.9 (C<sub>q</sub>), 161.0 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>22</sub>H<sub>24</sub>N<sub>5</sub>O<sub>2</sub>S (M + H<sup>+</sup>): 422.1651, found: 422.1652.

**4.7.4. *tert*-Butyl 3-(5-([1,1'-Biphenyl]-4-yl)-4-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl(methyl)-carbamate (25).** The product (78 mg, 0.15 mmol, 97% yield) was obtained as a yellowish solid (mp 124–125 °C) after automated flash chromatography (system: gradient of CH<sub>2</sub>Cl<sub>2</sub>–acetone, 19:1 to CH<sub>2</sub>Cl<sub>2</sub>–acetone, 23:2).

IR (neat film): 1688 (C=O), 1522 (C=C, C=N), 1245 (C–O). <sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 1.46 (s, 9H), 2.00–2.12 (m, 2H), 2.93 (s, 3H), 3.07–3.23 (m, 2H), 3.34–3.50 (m, 2H), 3.77 (s, 3H), 7.27 (ddd, *J* = 8.0, 7.6, 1.1 Hz, 1H), 7.39–7.47 (m, 1H), 7.42 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.47–7.55 (m, 4H), 7.69 (ddd, *J* = 8.0, 1.3, 0.6 Hz, 1H), 7.68–7.76 (m, 2H), 7.75–7.82 (m, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H). <sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 25.4 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 28.5 (3CH<sub>3</sub>), 34.0 (CH<sub>3</sub>), 37.0 (CH<sub>3</sub>), 48.9 (CH<sub>2</sub>), 79.0 (C<sub>q</sub>), 113.6 (C<sub>q</sub>), 121.0 (CH), 122.6 (CH), 124.4 (CH), 125.8 (CH), 127.1 (2CH), 127.7 (2CH), 127.9 (C<sub>q</sub>), 128.0 (CH), 129.0 (2CH), 130.9 (2CH), 134.5 (C<sub>q</sub>), 140.0 (C<sub>q</sub>), 142.7 (C<sub>q</sub>), 143.7 (C<sub>q</sub>), 151.4 (C<sub>q</sub>), 153.2 (C<sub>q</sub>), 155.9 (C<sub>q</sub>), 160.7 (C<sub>q</sub>). HRMS (ESI) calcd for C<sub>32</sub>H<sub>35</sub>N<sub>4</sub>O<sub>2</sub>S (M + H<sup>+</sup>): 539.2481, found: 539.2485.

**4.7.5. *tert*-Butyl 3-(4-(Benzo[d]thiazol-2-yl)-5-(3,5-bis(trifluoromethyl)phenyl)-1-methyl-1H-pyrazol-3-yl)propyl(methyl)carbamate (26).** The product (81 mg, 0.14 mmol, 90% yield) was obtained as a white solid (mp 126 °C) after automated flash chromatography (system: gradient of CH<sub>2</sub>Cl<sub>2</sub>–acetone, 19:1 to CH<sub>2</sub>Cl<sub>2</sub>–acetone, 23:2).

IR (neat film): 1689 (C=O), 1522 (C=C, C=N), 1248 (C–O). <sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 1.46 (s, 9H), 1.97–2.12 (m, 2H), 2.91 (s, 3H), 3.01–3.16 (m, 2H), 3.34–3.49 (m, 2H), 3.78 (s, 3H), 7.33 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 7.45 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 7.77 (ddd, *J* = 8.1, 1.2, 0.6 Hz, 1H), 7.93 (ddd, *J* = 8.2, 1.3, 0.5 Hz, 1H), 8.01 (s, 2H), 8.06 (s, 1H). <sup>19</sup>F NMR (376 MHz, chloroform-*d*) δ –62.88. <sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 25.3 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 28.5 (3CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 37.3 (CH<sub>3</sub>), 48.8 (CH<sub>2</sub>), 79.1 (C<sub>q</sub>), 114.3 (C<sub>q</sub>), 122.9 (q, *J* = 272.8 Hz, 2CF<sub>3</sub>), 121.1 (CH), 122.8 (CH), 123.5 (CH), 124.9 (CH), 126.2 (CH), 127.0 (C<sub>q</sub>), 131.1 (2CH), 131.5 (C<sub>q</sub>), 132.2 (q, *J* = 33.7 Hz, 2C<sub>q</sub>CF<sub>3</sub>), 134.3 (C<sub>q</sub>), 140.3 (C<sub>q</sub>), 151.5 (C<sub>q</sub>), 153.0 (C<sub>q</sub>), 155.8 (C<sub>q</sub>),

159.0 ( $C_q$ ). MS (ESI)  $m/z$ :  $[M + H]^+$  found for  $C_{28}H_{29}F_6N_4O_2S$ : 599.13;  $m/z$ :  $[M + Na]^+$  found for  $C_{28}H_{28}F_6N_4O_2S$  Na: 621.75. Elemental anal. calcd for  $C_{28}H_{28}F_6N_4O_2S$ : C, 56.18; H, 4.71; N, 9.36. Found: C, 56.12; H, 4.35; N, 9.19.

**4.7.6. (E)-tert-Butyl (3-(4-(Benzo[d]thiazol-2-yl)-1-methyl-5-styryl-1H-pyrazol-3-yl)propyl)(methyl)carbamate (27).** The product (53 mg, 0.11 mmol, 72% yield) was obtained as a light orange solid (mp 105–106 °C) after automated flash chromatography (system: gradient of  $CH_2Cl_2$ –acetone, 19:1 to  $CH_2Cl_2$ –acetone, 23:2).

IR (neat film): 1684 (C=O), 1542 (C=C, C=N), 1244 (C–O).  $^1H$  NMR (400 MHz, chloroform- $d$ )  $\delta$  1.44 (s, 9H), 1.88–2.07 (m, 2H), 2.88 (s, 3H), 2.97–3.13 (m, 2H), 3.30–3.44 (m, 2H), 4.01 (s, 3H), 7.04 (d,  $J$  = 16.7 Hz, 1H), 7.34 (d,  $J$  = 16.6 Hz, 1H), 7.33–7.40 (m, 2H), 7.40–7.46 (m, 2H), 7.49 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 7.53–7.57 (m, 2H), 7.87 (ddd,  $J$  = 7.9, 1.3, 0.7 Hz, 1H), 7.98–8.11 (m, 1H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  25.1 ( $CH_2$ ), 27.0 ( $CH_2$ ), 28.5 (3 $CH_3$ ), 34.1 ( $CH_3$ ), 37.9 ( $CH_3$ ), 48.8 ( $CH_2$ ), 79.1 ( $C_q$ ), 113.2 ( $C_q$ ), 115.2 (CH), 121.2 (CH), 122.8 (CH), 124.6 (CH), 126.0 (CH), 126.9 (2CH), 128.9 (2CH), 134.7 ( $C_q$ ), 136.2 ( $C_q$ ), 137.0 (CH), 140.5 ( $C_q$ ), 150.9 ( $C_q$ ), 153.4 ( $C_q$ ), 155.8 ( $C_q$ ), 160.5 ( $C_q$ ). HRMS (ESI) calcd for  $C_{28}H_{33}N_4O_2S$  ( $M + H^+$ ): 489.2324, found: 489.2322.

**4.7.7. N-(3-(4-(Benzo[d]thiazol-2-yl)-5-(1H-indol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous Amide (28).** Reaction conditions: Teflon reactor, 140 °C, 24 h. Note: indole was implemented into the reaction in the form of trifluoroborate salt with nitrogen protected with *tert*-butyl carbamate.

The product (15 mg, 0.4 mmol, 24% yield) was obtained as a light yellow solid (mp 178 °C) after automated flash chromatography (system: gradient of  $CH_2Cl_2$ , 100% to  $CH_2Cl_2$ –acetone, 93:7).

IR (neat film): 3185 ( $NH\nu$ ), 1532 (C=N, C=C), 1454, 1427 (N=O, C–H), 1333 (N=O).  $^1H$  NMR (400 MHz, chloroform- $d$ ) (mixture of rotamers)  $\delta$  2.05 (quint,  $J$  = 7.6 Hz, 0.4H), 2.28 (quint,  $J$  = 7.3 Hz, 1.6H), 2.99–3.05 (m, 0.4H), 3.09 (s, 2.2H), 3.10–3.15 (m, 1.6H), 3.74–3.79 (m, 0.4H), 3.80 (s, 0.6H), 4.10 (s, 2.4H), 4.11 (s, 0.6H), 4.32 (t,  $J$  = 7.1 Hz, 1.6H), 6.81–6.86 (m, 1H), 7.19 (ddd,  $J$  = 7.8, 7.5, 0.9 Hz, 1H), 7.30 (ddd,  $J$  = 8.1, 7.6, 1.0 Hz, 1H), 7.40 (ddd,  $J$  = 8.2, 7.6, 1.0 Hz, 1H), 7.53 (ddd,  $J$  = 8.2, 7.6, 1.1 Hz, 1H), 7.55 (d, 8.3 Hz, 1H), 7.72 (d,  $J$  = 7.8 Hz, 1H), 7.85 (d,  $J$  = 7.8 Hz, 1H), 8.10 (d,  $J$  = 8.0 Hz, 1H), 11.67 (s, 0.8H), 11.84 (s, 0.2H).  $^{13}C$  NMR (101 MHz, chloroform- $d$ ) (mixture of rotamers, only the major rotamer is described hereafter)  $\delta$  25.0 ( $CH_2$ ), 27.2 ( $CH_2$ ), 31.5 ( $CH_3$ ), 39.0 ( $CH_3$ ), 53.5 ( $CH_2$ ), 104.9 (CH), 111.7 (CH), 113.0 ( $C_q$ ), 120.4 (CH), 120.9 (CH), 121.4 (CH), 122.2 (CH), 123.3 (CH), 125.2 (CH), 125.6 ( $C_q$ ), 126.5 (CH), 128.0 ( $C_q$ ), 134.6 ( $C_q$ ), 136.2 ( $C_q$ ), 136.3 ( $C_q$ ), 149.6 ( $C_q$ ), 152.2 ( $C_q$ ), 161.0 ( $C_q$ ). HRMS (ESI) calcd for  $C_{23}H_{23}N_6OS$  ( $M + H^+$ ): 431.1648, found: 431.1650.

**4.7.8. N-(3-(4-(Benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous Amide (29).** *t*-BuONO (0.24 mL,  $d$  = 0.867 g/mL, 2 mmol) was added dropwise to a strongly stirred solution of 4-(benzo[d]thiazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine **10a** (0.301 g, 1 mmol) in DMF (5 mL, 65 °C), and the gas evolution was observed by bubble counter. After 10 min of stirring, the TLC control ( $CH_2Cl_2$ –acetone, 9:1) indicated the presence of two spots corresponding to the starting material and new product.

The pH of the reaction mixture was slightly basic. Another portion of *t*-BuONO (0.48 mL, 4 mmol) was added dropwise, and the pH of the reaction mixture turned to acidic (pH  $\sim$  3). After 10 min of stirring, another TLC control was made to ensure the conversion of starting material and formation of one main product. The reaction mixture was allowed to cool to rt, and pH was brought to neutral–slightly basic by addition of saturated aq.  $NaHCO_3$ . This aqueous phase was extracted with EtOAc (three times), and collected organic extracts were washed with brine and dried over  $MgSO_4$ . The solution was concentrated under reduced pressure, and the residue was purified by automated flash chromatography (system: gradient of EtOAc–CHA, 7:3 to EtOAc, 100%) to yield 290 mg (0.92 mmol, 92% yield) of white solid (mp 72–73 °C).

Note: (1) the aliquot for TLC was taken from the reaction mixture followed by addition of saturated aq.  $NaHCO_3$  to bring pH to neutral–slightly basic and extraction with EtOAc. (2) The solution of *t*-BuONO is acidic when purchased from commercial sources. Its acidity is enough to generate the nitrosonium ion and bring the reaction to completion.

IR (neat film): 1566, 1556 (O=N, C=C, C=N), 1425 (N=O), 1331 (N=O), 1038 (N–N), 1140 (C–N).  $^1H$  NMR (400 MHz, chloroform- $d$ ) (mixture of rotamers)  $\delta$  2.03 (quint,  $J$  = 7.6 Hz, 0.4H), 2.25 (quint,  $J$  = 7.5 Hz, 1.6 H), 3.03 (t,  $J$  = 7.5 Hz, 0.4 H), 3.11 (s, 2.4 H), 3.13 (t,  $J$  = 7.5 Hz, 1.6 H), 3.76 (t,  $J$  = 7.4 Hz, 0.4 H), 3.79 (s, 0.6 H), 3.90 (s, 0.6 H), 3.91 (s, 2.4 H), 4.31 (t,  $J$  = 7.2 Hz, 1.6 H), 7.31–7.37 (m, 1H), 7.43–7.50 (m, 1H), 7.84 (d,  $J$  = 8.0 Hz, 1H), 7.88 (s, 1H), 7.93–8.00 (m, 1H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ) (mixture of rotamers)  $\delta$  24.88 ( $CH_2$ ), 24.92 ( $CH_2$ ), 25.4 ( $CH_2$ ), 27.3 ( $CH_2$ ), 30.3 ( $CH_3$ ), 31.5 ( $CH_3$ ), 39.1 ( $CH_3$ ), 44.5 ( $CH_2$ ), 53.6 ( $CH_2$ ), 115.1 ( $C_q$ ), 121.3 (CH), 121.48 (CH), 121.5 (CH), 124.64 (CH), 124.67 (CH), 126.2 (CH), 131.64 (CH), 131.71 (CH), 134.01 ( $C_q$ ), 134.06 ( $C_q$ ), 150.25 ( $C_q$ ), 150.32 ( $C_q$ ), 153.79 ( $C_q$ ), 153.82 ( $C_q$ ), 160.04 ( $C_q$ ), 160.08 ( $C_q$ ). HRMS (ESI) calcd for  $C_{15}H_{18}N_5OS$  ( $M + H^+$ ): 316.1232, found: 316.1231.

**4.7.9. 3-(4-(Benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)-N-methylpropan-1-aminium Chloride (30).** HCl gas (generated by dropwise addition of  $H_2SO_4$  on solid NaCl) was bubbled vigorously through an ice-cold solution of N-(3-(4-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous amide **29** (158 mg, 0.5 mmol) in dry methanol (8 mL) for 20 min. The resultant precipitate was filtered off and washed with ether to yield 157 mg (0.485 mmol, 97% yield) of white solid (mp 152–153 °C).

IR (neat film): 3431 ( $NH_2\nu$ ), 1603, 1559, 1529 (C=C, C=N,  $NH_2\delta$ ).  $^1H$  NMR (400 MHz, methanol- $d_4$ )  $\delta$  2.23 (quint,  $J$  = 7.3 Hz, 2H), 2.73 (s, 3H), 3.10–3.21 (m, 4H), 3.98 (s, 3H), 7.52 (t,  $J$  = 7.7 Hz, 1H), 7.62 (t,  $J$  = 7.7 Hz, 1H), 8.00 (d,  $J$  = 8.2 Hz, 1H), 8.07 (d,  $J$  = 8.1 Hz, 1H), 8.44 (s, 1H);  $^{13}C$  NMR (101 MHz, methanol- $d_4$ )  $\delta$  24.0 ( $CH_2$ ), 24.4 ( $CH_2$ ), 32.2 ( $CH_3$ ), 38.1 ( $CH_3$ ), 48.4 ( $CH_2$ ), 112.3 ( $C_q$ ), 119.8 (CH), 122.1 (CH), 125.8 (CH), 127.4 (CH), 132.0 ( $C_q$ ), 133.5 (CH), 148.5 ( $C_q$ ), 150.1 ( $C_q$ ), 162.8 ( $C_q$ ). HRMS (ESI) calcd for  $C_{15}H_{19}N_4S$  ( $M + H^+$ ): 287.1330, found: 287.1337.

**4.7.10. N-(3-(4-(Benzo[d]thiazol-2-yl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous Amide (24c).** N-(3-(4-(Benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous amide **29** (95 mg, 0.3 mmol),  $Pd(OAc)_2$  (3.4 mg, 0.015 mmol), and  $Bu_4NOAc$  (181 mg, 0.6 mmol) were placed in a flame-dried two-necked flask fitted with a water condenser and rubber septum. The system was



evacuated and back-filled with argon. This sequence was repeated three times. DMA (3 mL) and 4-bromoanisole (0.06 mL,  $d = 1.494$  g/mL, 0.45 mmol) were sequentially added under a stream of argon at room temperature. The resulting mixture was stirred at 70 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, filtered through a plug of Celite, and eluted with additional EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified using automated flash chromatography (system: gradient of  $\text{CH}_2\text{Cl}_2$ –acetone, 19:1 to  $\text{CH}_2\text{Cl}_2$ –acetone, 9:1) to yield 126 mg (0.3 mmol, 100%) of **24c** as a light orange solid (mp 140 °C).

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b01419.

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all compounds, COSY, HMQC, and HMBC when required as well as X-ray structures of **6b**, **6c**, **7a**, **7b**, **8b**, **9a**, **10a**, **10c**, **11a**, and **15a** (PDF)

Crystallographic data (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The authors acknowledge the generous support from the French Embassy in Kiev, Ukraine, and Campus France for mobility allowance of O.K., the GDRI “Groupement Franco-Ukrainien en Chimie Moléculaire” for supporting such international collaboration, ANR for funding, and the CNRS, the Université de Toulouse, and the Taras Shevchenko National University of Kyiv for hosting our research.

## ■ ADDITIONAL NOTE

<sup>a</sup>To obtain pyrrol-1-ium salts **5**, 1-*R*-pyrrolidin-2-ones were treated with dimethyl sulfate at 80 °C for 2 h as described in the experimental section. Oils obtained were used without any additional treatment. Alternatively, such pyrrolinium salts could be obtained as solids upon treatment with a saturated solution of  $\text{KPF}_6$  in water.

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