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1,3-Dipolar Cycloadditions of Cyanoheteroarenes with non-stabilized Azomethine Ylides : C≡N *vs* Aromatic C=C Reactivity

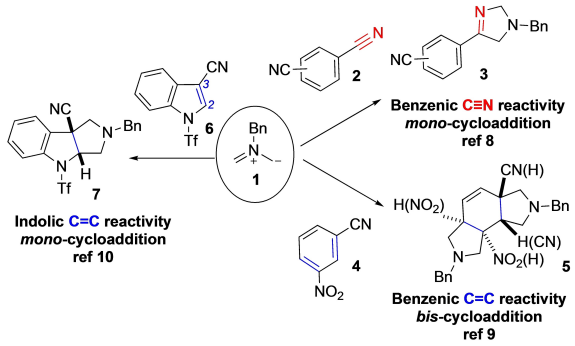
Batoul Rkein,[a] Maxime Manneveau,[a] Hélène Gérard,[b] Julien Legros,[a] and Isabelle Chataigner*[a, b]

Dedicated to Professor Cesare Gennari on the occasion of his 70th birthday

Indoles, benzofurans and benzothiophenes substituted by a cyano group at positions 2 or 3 are shown to behave differently toward azomethine ylide 1,3-dipole **1**, in (3+2) cycloadditions. While the C2=C3 aromatic double bond of 3-cyanoheteroarene reacts as dipolarophile to generate the corresponding dearomatized cycloadducts, the C≡N bond of 2-cyanobenzofuran reveals more reactive and imidazoline are obtained in this case. 2-Cyanoindole substituted by an electron-withdrawing triflyl group on the nitrogen atom allows the formation of the bis-cycloadduct where the C=C and C≡N moieties both reacted. The C≡N vs C=C reactivity is nicely supported by DFT computations.

Introduction

In 1963, Rolf Huisgen wrote in a review paper about the cycloaddition that bears his name: "*The 1,3-dipolar cycloaddition offers a remarkably wide range of utility in the synthesis of five-membered heterocycles*". It turned out to be wise in view of the widespread use of this reaction nowadays in organic synthesis.[1] Among the large variety of useful 1,3-dipoles developed over the years, non-stabilized azomethine ylides (AY) such as **1** (Scheme 1) are fairly popular and these nitrogen centered highly reactive dipoles have provided chemists with efficient ways of generating azacycles.[2] When reacted with a C=C dipolarophile, AY leads to the common pyrrolidinic motif, found in many compounds of interest, such as natural products or organocatalysts for instance. AY are electron-rich species, type I dipoles according to Sustmann classification,[3] reacting with different electron-poor dipolarophiles such as alkenic/alkynic Michael acceptors,[2] carbonyls, imines,[4] isocyanides[5] or nitriles[6] for instance. (3+2)-Cycloadditions involving dipole **1** and electron-poor aromatic dipolarophiles have mainly involved aldehydes and imines as C=O and C=N heterodipolarophiles.[7] Similarly, dicyanobenzenes **2** easily react with AY **1** in a (3+2) heterocycloaddition process, yielding the corresponding imidazolines **3** (Scheme 1).[8] In



Scheme 1. Reactivity of electron-poor cyano/nitrobenzenes and 3-cyanoindole toward non-stabilized AY **1**.

contrast, nitrobenzenes were shown to react as all carbon dipolarophiles, the cycloaddition involving the C=C(NO_2) double bond in this case.[9] Thanks to the presence of the more electron-withdrawing nitro group, the reaction between **1** and cyanonitrobenzene **4** also occurs on the aromatic C=C bond, leading to the dearomatized bis-pyrrolidinic adduct **5**, having incorporated two AY moieties.

When switching to less aromatic indolic heterocycles, the 3-formylindoles proved to react as heterodipolarophiles with **1**[9b] while 3-cyanoindoles **6** preferably react as carbon dipolarophiles, involving the C2=C3 double bond of the heterocycle (Scheme 1).[10] This dichotomic behavior led us to study on the compared reactivity of different cyanoheterocycles toward AY **1** according to their nature (indole, benzofuran, benzothiophene) and the position (C2 or C3) of the cyano group (Scheme 2). The highly reactive non-stabilized dipole **1** is generated *in situ* to immediately interact with the dipolarophile. Various methods for its generation have been reported.[7a,11] For practical reasons and in line with our previous studies, we have chosen the TFA catalyzed method starting from the commercially available *N*-

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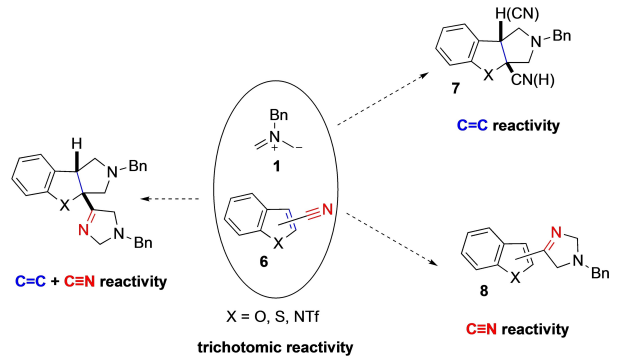
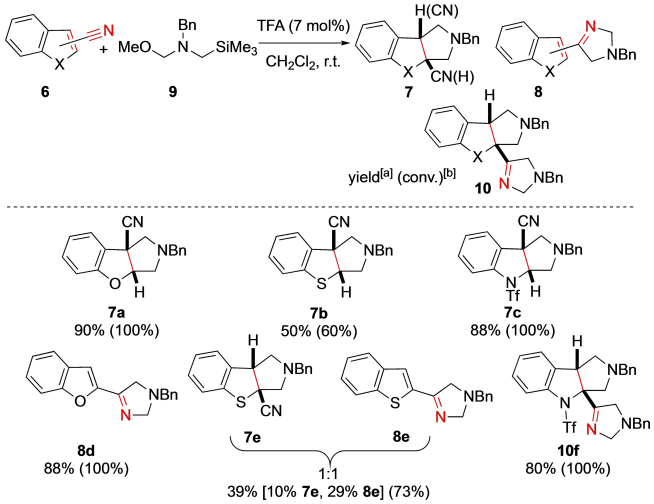


Scheme 2. This work.

(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine, since it does not require any heating of the reaction medium.

Results and Discussion

When reacted with an excess of *N*-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**9**), in dichloromethane and in the presence of 7 mol% TFA, as previously reported,[10] 3-cyanobenzofuran (**6a**) led to a complete conversion of the starting aromatic and the unique formation of the tetrahydrobenzofuropyrrole **7a**, resulting from a reaction on the C2=C3 aromatic double bond and isolated in a 90% yield (Scheme 3). The 3-cyanobenzothiophene (**6b**) proved less reactive toward the AY and led to a 60% conversion of the starting aromatic, after 16 hours. As for the benzofuran derivative, it reacted as a C=C dipolarophile and furnished **7b**, as the only cycloadduct, isolated in 50% yield. As previously described,[10] 3-cyano-*N*-trifluoromethylsulfonylindole (**6c**) also led to a reaction at C2=C3 and formation of the cyanoindoline **7c** in a good 88% yield.[12]

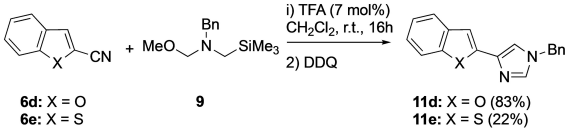


Scheme 3. Cycloaddition reaction between cyanoheteroarene **6** and hemiaminal ether **9** in acidic conditions. [a] Isolated yield. [b] Conversion of the arene.

We then moved to the heterocycles substituted at position 2. The cycloaddition involving 2-cyanobenzofuran **6d** led to full conversion of the starting heterocycle. In this case, only cycloadduct **8d**, resulting from a cycloaddition at the cyano group was observed. No competitive reaction on the aromatic core could be detected. Even if sensitive on silica, the imidazoline was isolated in 88% yield. 2-Cyanobenzothiophene (**6e**) reacted with **1**, furnishing this time a 1:1 mixture of cycloadduct **7e** and heterocycloadduct **8e**. The dipolarophilic reactivity of the C≡N and the C2=C3 bonds of 2-cyanobenzothiophene thus proves to be in the same range. 73% Conversion was observed with this substrate resulting in an overall yield of 39%. The discrepancy between conversion and isolated yields is due to the difficulty to separate the two cycloadducts (isolated in 10 and 29% yields, respectively) and the unreacted starting material on silica. In this series, 2-cyano-*N*-Tf-indole **6f** led to the full conversion of the starting material after 16 hours. In this case, the crude mixture displayed a single product, whose structure proved to be the corresponding dearomatized *bis*-cycloadduct **10f** isolated in 80% yield. In line with previous results in (4+2) processes,[13] the bis-cycloaddition occurs here most probably on the C=C aromatic double bond first, before the heterocycloaddition on the remaining C≡N moiety. Noteworthy no trace of bis-cycloadduct formation could be detected on the crude mixtures in the other cases, where a large excess of **9** was used. The difference observed with this indole partner **6f** can be attributed to the presence of an electron-withdrawing *N*Tf moiety α to the C≡N reacting group on the assumed cycloadduct **7f**, which activates the cyano toward the electron-rich AY used in excess.

The imidazolines **8d** and **8e** could be oxidized *in situ* into the corresponding rearomatized imidazoles **11d** and **11e** using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as oxidizing agent (Scheme 4). The benzofuran derivative **6d**, which leads to the sole formation of the intermediate heterocycloadduct **8d** furnished the imidazole in a good 83% yield, while the benzothiophene compound led to a much lower yield. Here again, this can be attributed to the mixture obtained before oxidation (containing cycloadducts **7e** and **8e** plus the remaining unreacted starting benzothiophene), generating an even more complex mixture difficult to separate after oxidation.

Experimentally, the nature of the heterocycle as well as the position of the cyano group lead to surprising discrepancies in chemoselectivity. While the aromatic C2=C3 bond of the 3-cyano compounds is the most reactive, the C≡N bond of 2-cyanobenzofuran is more reactive. We thus started a computational work in order to get some insight into the chemoselectivity of these cycloadditions. We investigated the



Scheme 4. Combined one-pot heterocycloaddition and oxidation

reaction with a model *N*-methylated AY **12** and cyanoheterocycles. Quantitative evaluation of the reaction and activation energies of both cycloaddition (**A**) and heterocycloaddition (**B**) pathways was undertaken by localization of the products and transition states (TSs) of the (3 + 2) cycloaddition on the C2=C3 double bond and on the cyano moiety (Scheme 5).

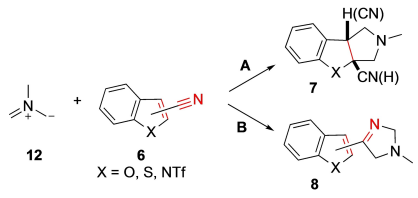
The two routes (**A**/**B**), combined with two possible approaches of the dipole (similar to *endo*/*exo* approaches) led us to consider four approaches in each case. Only the most favoured approaches are considered in the Table 1 below (for more details, see Supporting Information (SI)). The cycloadditions are highly exergonic in each case, the heterocycloadducts **8** being generally more stable than the dearomatized cycloadducts **7**, as a result of the conservation of the aromatic character of the bicyclic arene in former cases. This suggests a kinetically controlled transformation.

These cycloadditions appear to be concerted processes, characterized by early transition states. All attempts to localize zwitterionic intermediates remained unsuccessful. The cycloadditions (A-pathway, Scheme 5) prove asynchronous, with a difference between the two forming bonds of 0.4 to 0.7 Å, except in the case of **6d**, for which the forming bonds distances only differ by 0.1 Å. The heterocycloaddition processes (B-pathways) are less markedly asynchronous with a difference of around 0.4 Å in the forming bonds, with the shorter bond being the C–C bond in all cases. This higher synchronic character for the heterocycloaddition pathway is surprising in view of the different nature of the bonds created, as well as the greater length of the generated CC bond, compared to the CN, in the cycloadduct.

The most favoured transition states are the cycloaddition A-pathways, involving the C2=C3 double bond as dipolarophile, in most cases (Table 1, Figure 1). This preference for the A-pathway is important ($\geq$3.0 kcal.mol^{-1}) when the 3-cyanoheteroarenes (**6a–6c**) are considered (entries 1–3), in line with the exclusive formation of the dearomatized cycloadducts **7a–7c** observed experimentally with these arenes. Only 2-cyanobenzofuran **6d** leads to a smaller barrier for the heterocycloaddition B-pathway ($\Delta\Delta G^{\neq} = -2.5$ kcal.mol^{-1}), involving the C≡N bond as heterodipolarophile, also in line with experimental results (entry 4). The 2-cyanobenzothiophene case appears more mitigated ($\Delta\Delta G^{\neq} = 1.1$ kcal.mol^{-1}), leading to a slightly preferred A-pathway (entry 5). Experimentally, this arene leads to a 1 : 1 mixture of cycloadducts **7e** and **8e**. With the 2-cyanoindole derivative **6f**, the great preference for the A-pathway ($\Delta\Delta G^{\neq} = 5.1$ kcal.mol^{-1}) supports our hypothesis that the bis-cycloadduct **10f** is formed through a sequential cycloaddition/heterocycloaddition pathway.[15]

Analysis of the electron population on the optimized heteroarenes using NBO reveals that the charge at the carbon atom of the cyano group is in the 0.24–0.29 range for all compounds (Table 2). In contrast, the charge at the reacting C2/C3 position of the 3-cyano/2-cyano derivatives, respectively,[16] varies a lot, going from negative to positive charges (−0.37 to +0.22, Table 2). No clear link between the electronic charges of the arene and its reactivity can be drawn, meaning that these cycloadditions are not purely under charge control. They involve the HOMO orbital of the AY (-6.0 eV) and the LUMO of the heteroarene, whose energies are between 1.4 and 2.4 eV for all compounds. The 2-cyanoheteroarenes have slightly lower LUMO energies than their 3-cyano counterparts and the order of energies is *N*-Tf-indole < benzothiophene < benzofuran. This should lead, under orbital control, to an inverse order of reactivity which is not entirely in line with experimental results that reveal lower conversions in the case of benzothiophenes.

A distortion/interaction activation-strain (D/I AS) analysis was then performed.[17] $\Delta E_e^{\neq}$ was broken down into the distortion energy (ΔE_{dist}, Scheme 6 left) and the interaction energy (ΔE_{int}, Scheme 6 right). The ΔE_{dist} represents the energetic cost to deform the ground states of the reactants into their transition state geometries, while the ΔE_{int} is the energetic benefit resulting from stabilizing electronic interactions between fragments in the transition state.



Scheme 5. Different pathways examined by DFT computations at the SMD (CH_2Cl_2) - MN12SX/6-31 + G(d,p) level.[14]

Table 1. Cycloaddition involving cyanoheteroarenes **6** and N-methyl azomethine ylide **12**.

Entry	arene	$\Delta G^{\neq}$ (ΔG_r)[a] (A path) (kcal.mol^{-1})	$\Delta G^{\neq}$ (ΔG_r)[a] (B path) (kcal.mol^{-1})	$\Delta\Delta G^{\neq}$ ($\Delta\Delta G_r$)[b] (A/B paths) (kcal.mol-1)	Exp. CA[c]
1	**6a**	11.7 (−37.7)	14.7 (−37.7)	3.0 (0)	**7a**
2	**6b**	12.5 (−29.0)	16.2 (−36.3)	3.7 (−7.3)	**7b**
3	**6c**	10.0 (−33.0)	15.5 (−37.7)	5.4 (−4.7)	**7c**
4	**6d**	15.0 (−34.5)	12.5 (−41.4)	−2.5 (−6.9)	**8d**
5	**6e**	14.0 (−31.5)	15.1 (−37.7)	1.1 (−6.2)	**7e/8e**
6	**6f**	11.0 (−36.2)	16.1 (−36.6)	5.1 (−0.4)	**9f**

Table 2. NPA and LUMO energies of the heteroarenes.

Entry	arene	NPA Charge[a] at C(≡N)	NPA Charge[a] at C2/C3	Atom considered[b]	E_{LUMO}[c] (eV)
1	**6a**	+0.29	+0.22	C2	2.4
2	**6b**	+0.29	−0.37	C2	2.1
3	**6c**	+0.28	+0.06	C2	1.9
4	**6d**	+0.24	+0.24	C3	1.8
5	**6e**	+0.27	−0.19	C3	1.6
6	**6f**	+0.25	−0.19	C3	1.4

[a] Natural Population analysis calculated at the MN12SX/6-31 + G(d,p) level.
[b] The arene carbon atom considered is the one leading to the smallest forming bond with AY in the TS (path A) [c] LUMO energy in eV calculated at the HF/6-31G(d) level starting on the MN12SX optimized geometry.[12]

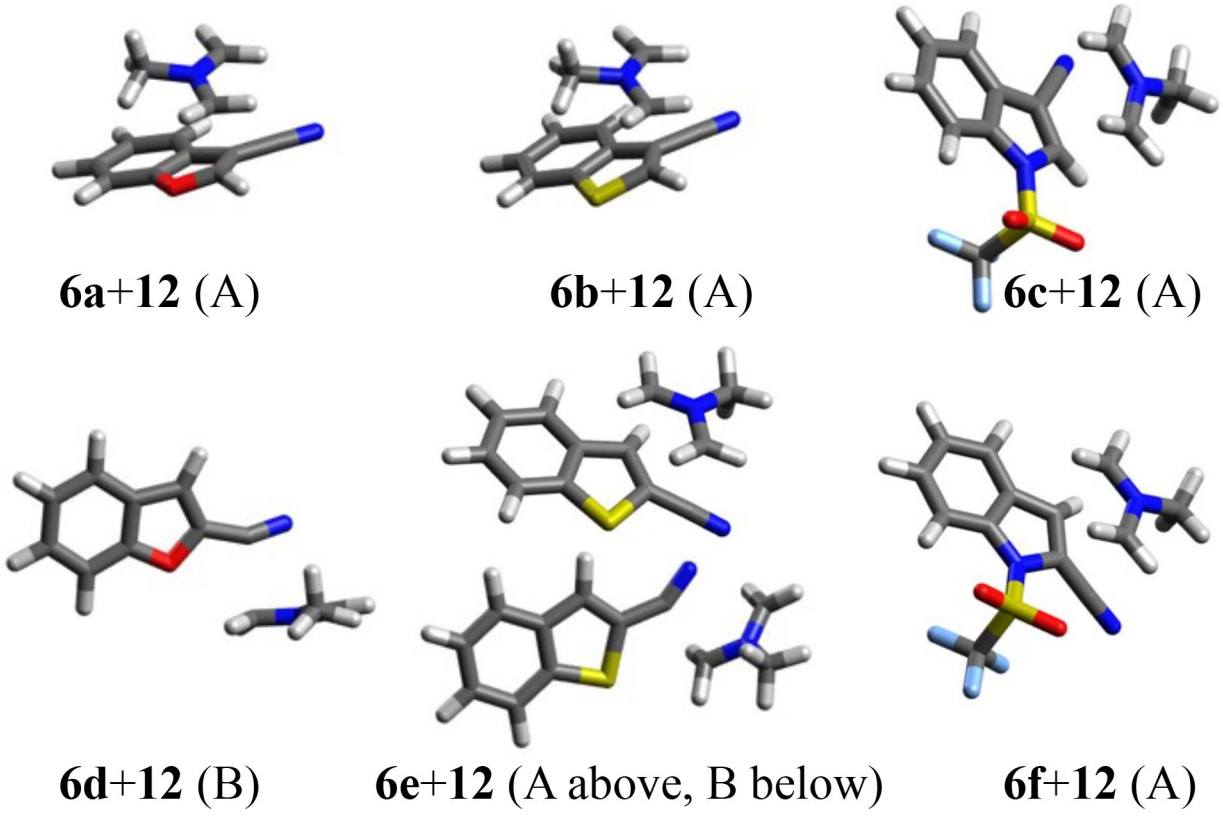
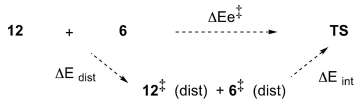


Figure 1. 3D representations of the most favoured transition states.



Scheme 6. D/I AS analysis scheme. **X** stands for optimized geometry of the molecule **X**, whereas X^{+} stands for the geometry of the fragment **X** in the TS.

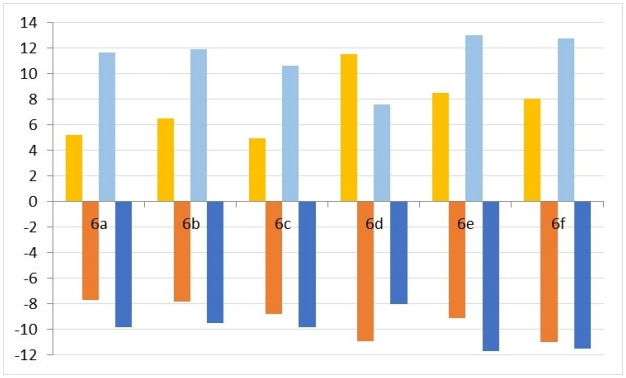


Figure 2. D/I AS analysis for the cycloaddition A-pathway (orange, left) and heterocycloaddition B-pathway (blue, right) : ΔE_{dis} global distortion (light colors, positive values) in kcal.mol^{-1}; ΔE_{int} interaction (dark colors, negative values), in kcal.mol^{-1}.

These two terms were computed for the 6 cyanoheteroarenes. Results are represented in Figure 2, for pathway A (in orange, left) and B (in blue, right). These data clearly show that, with the exception of **6d**, the distortion is about 4 kcal.mol^{-1} larger in the case of the heterocycloaddition pathway (light blue columns in Figure 2). This important distortion is associated to a larger interaction for pathway B, but by only about 2 kcal mol^{-1}, which is not sufficient to overcome the preference for path A. In the case of **6d**, the opposite behavior is observed. The distortion energy in the case of the heterocycloaddition B-pathway is much smaller compared to other heteroarenes whereas it is larger for pathway A. Here again, the largest distortion is associated to the most stabilizing interaction of the fragment, but the largest stabilization for pathway A is not sufficient to overcome the effect of the largest distortion as pathway B is preferred for **6d**.

Details of the computed values are given in Table 3. Closer examination of the distortion terms shows that, in general, the largest distorsions are obtained for the arene in the case of the heterocycloaddition pathway, a phenomenon most probably associated to the bending of the C≡N group in the TSs (Table 3, compare col. 3 and 4). The lowest distortion is observed in the case of 2-cyanobenzofuran (**6d**), which preferentially reacts on the cyano group. In line with this result, the C–C–N angle is slightly less bended in this peculiar TS (153°) compared to the other heteroarenes (146–150°).

The cost for pyramidalization of the aromatic carbon atoms along the A pathway is not as large as what could have been

Table 3. Distortion/interaction activation-strain Analysis.

Entry	6	ΔE_{dist} Arene[a]		ΔE_{dist} AY[a]		ΔE_{dist}[b]		ΔE_{int}[c]	
		A[d]	B[e]	A[d]	B[e]	A[d]	B[e]	A[d]	B[e]
1	6a	3.6	8.7	1.6	2.9	5.2	11.6	−7. 7	−9.8
2	6b	4.4	9.0	2.1	2.9	6.5	11.9	−7.8	−9.5
3	6c	3.2	8.1	1.7	2.5	4.9	10.6	−8.8	−9.8
4	*6d*	*6.5*	*6.0*	*5.0*	*1.6*	*11.5*	*7.6*	*−10.9*	*−8.0*
5	6e	5.3	9.9	3.2	3.1	8.5	13.0	−9.1	−11.7
6	6f	4.9	9.5	3.1	3.2	8.0	12.7	−11.0	−11.5

[a] distortion for the arene or AY component, ΔE_{dist} in kcal.mol^{-1}; [b] global distortion, ΔE_{dist} in kcal.mol^{-1}; [c] global interaction, ΔE_{int} in kcal.mol^{-1}; [d] for the cycloaddition A-pathway, involving the C2=C3 bond as dipolarophile: [e] for the heterocycloaddition B-pathway, involving the C≡N bond as heterodipolarophile.

expected and is lower with the 3-cyanoarenes (col. 2, entries 1–3) when compared to the 2-substituted compounds (entries 4–6). The biggest distortion is observed with **6 d** again, which remains a peculiar case in the series. This bigger distortion of **6 d** in the A-path is accompanied by a significant distortion of the AY **12**. In this case, the TS is not significantly later when compared to other cases (similar 2.4 Å length for the shorter bond forming in the TS) but appears to be more synchronous (2.5 Å for the longer bond forming to be compared to 2.7–3.0 Å with the other arenes), and this difference can explain the greater global distortion, which *in fine* leads to a less favourable path in this case.

Conclusion

Indoles, -benzofurans and -benzothiophenes substituted by a cyano group at positions 2 or 3 behave differently toward non-stabilized azomethine ylide 1,3-dipole **1**, in (3 + 2) cyclo-additions. While the C2=C3 aromatic double bond of the heteroarene substituted at position 3 reacts as a C2=C3 dipolarophile to generate the corresponding dearomatized indolines, the C≡N bond of 2-cyanobenzofuran reveals more reactive and imidazoline are obtained in this case. 2-Cyano-*N*-triflylindole leads to a *bis*-cycloaddition process. The adducts generated represent high-added value scaffolds and interesting motifs obtained in one step, from easily accessible starting materials. The dichotomic CC vs CN reactivity is nicely supported by DFT computations, which reveal that the greatest part of the energetical cost associated to these cycloadditions comes from the distortion of the heteroarene in the TSs.

Experimental Section

General information

Unless otherwise noted, all chemicals were used as received from commercial sources without further purification. Dichloromethane was dried over calcium hydride. Chromatographic purifications were performed on silica gel (mesh size 60–80 μm) using the procedure described by Still.[18] ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker DPX 300 spectrometer (Bruker, Wissembourg, France) equipped with a 5 mm BBFO probe including shielded z gradients. Chemical shifts are expressed in parts per million (ppm) using the residual solvent peak for calibration. Coupling constants (*J*) are expressed in Hz. The following abbreviations were used in the spectral description: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), br (broad signal), m (multiplet). Infrared spectra (IR) were obtained on Perkin-Elmer spectrum 100 FT-IR. Wavelength (ν) were reported in cm^{-1} and only the strongest or structurally most important peaks are listed. High-resolution mass spectrometry (HRMS) spectra were recorded either on a Thermo LTQ Orbitrap XL apparatus equipped with an ESI source or on a LCT Premier XE bench top orthogonal acceleration time-of-flight mass spectrometer (Waters Micromass) equipped with an ESI source. Melting points (mp) were measured with a Kofler apparatus from Wagner and Munz.

General procedure 1 for the (3 + 2) cycloaddition reaction between the cyanoheteroarenes 6 and hemiaminal 10

To a solution of hemiaminal ether 9 (4.5 mmol, 9.0 equiv) and the requisite cyano heterocycle derivative 6 (0.5 mmol, 1.0 equiv) in dry CH_2Cl_2 (0.25 M) at 0 °C, was added dropwise a solution of TFA in CH_2Cl_2 (0.36 mmol, 0.18 M). The mixture was allowed to warm to room temperature under an inert atmosphere over 16 hours. The mixture was then concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel to afford the desired product.

(3a*R,8b*R**)-2-Benzyl-1,2,3,3 a-tetrahydro-8b*H*-benzofuro[2,3-c]pyrrole-8 b-carbonitrile (7 a)**. The target compound was prepared according to the general procedure. The crude mixture was purified by flash chromatography on silica gel (toluene/AcOEt 9/1) followed by a second purification (DCM/MeOH 99/1) to afford the desired product as a white solid (125 mg, 90 % yield); mp 93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.26 (m, 3H), 7.26–7.23 (m, 2H), 7.21–7.14 (m, 2H), 6.97 (ddd ≈ td, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.83 (ddd ≈ dt, *J* = 8.1, 8.1, 0.8 Hz, 1H), 5.42 (dd, *J* = 5.1, 1.5 Hz, 1H), 3.65 (s, 2H), 3.25–3.15 (m, 2H), 2.96 (d, *J* = 9.5 Hz, 1H), 2.82–2.74 (m, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 160.4, 137.1, 130.7, 128.5 (2 C), 128.4 (2 C), 127.5, 125.3, 124.0, 121.7, 120.2, 110.0, 90.1, 60.9, 60.6, 58.1, 49.1. HRMS (TOF MS ES^{+}): m/z Calcd. for $C_{18}H_{17}N_2O$ $[M+H]^+$: 277.1341; Found: 277.1340. IR (neat) ν 2958, 2923, 2786, 2244, 1597, 1480, 1461, 1251, 866, 763, 747, 701, 462 cm^{-1}.

(3a*R,8b*R**)-2-benzyl-1,2,3,3 a-tetrahydro-8b*H*-benzo[4,5]thieno[2,3-*c*]pyrrole-8 b-carbonitrile (7 b)**. The target compound was prepared according to the general procedure. The

crude mixture was purified by flash chromatography on silica gel (toluene/cyclohexane 9/1) to afford the desired product as a colorless oil (73 mg, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.15 (m, 7H), 7.10–7.02 (m, 2H), 4.47 (dd, J = 7.0, 5.3 Hz, 1H), 3.64 (d, J = 13.2 Hz, 1H), 3.56 (d, J = 13.2 Hz, 1H), 3.37 (d, J = 9.4 Hz, 1H), 3.24 (dd, J = 9.9, 7.0 Hz, 1H), 2.88 (d, J = 9.4 Hz, 1H), 2.69 (dd, J = 9.9, 5.3 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 141.2, 137.4, 136.5, 130.0, 128.6 (4 C), 127.5, 125.5, 125.0, 122.2, 121.6, 65.7, 62.8, 58.3, 55.3, 54.2. HRMS (TOF MS ES$^+$): m/z Calcd. for $C_{18}H_{17}N_2S$ $[M+H]^+$: 293.1112; Found: 293.1108. IR (neat) ν 2237, 1728, 1444, 1129, 878, 728, 698, 439 cm^{-1}.

(3a*R,8b*S**)-2-Benzyl-4-((trifluoromethyl)sulfonyl)-2,3,3 a,4-tetrahydropyrrolo[3,4-*b*]indole-8 b(1*H*)-carbonitrile (7 c)**. The target compound was prepared according to the general procedure. The crude mixture was purified by flash chromatography on silica gel (Toluene 100%) to afford the desired product as colorless oil (179 mg, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J = 8.3 Hz, 1H), 7.45–7.35 (m, 2H), 7.34–7.23 (m, 4H), 7.19–7.11 (m, 2H), 5.15 (dd, J = 6.3, 2.7 Hz, 1H), 3.66 (d, J = 15.0 Hz, 1H), 3.61 (d, J = 15.0 Hz, 1H), 3.18–3.12 (m, 2H), 3.12–3.00 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 139.8, 136.6, 130.8, 129.2, 128.6 (2 C), 128.5 (2 C), 127.7, 127.7, 126.6, 124.7, 120.1 (q, J = 325 Hz), 119.1, 114.9, 71.4, 64.4, 57.7, 47.6. ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ −72.33. HRMS (TOF MS ES$^+$): m/z Calcd. for $C_{19}H_{17}N_3F_3O_2S$ $[M+H]^+$: 408.0994; Found: 408.0989. IR (neat) ν 1481, 1462, 1402, 1227, 1196, 1141, 1049, 750, 699, 602, 573 cm^{-1}.

4-(benzofuran-2-yl)-1-benzyl-2,5-dihydro-1*H*-imidazole (8 d). The target compound was prepared according to the general procedure. The crude mixture was purified by flash chromatography on silica gel (cyclohexane/EtOAc 7/3) to afford the desired product as a white solid (121 mg, 88% yield). mp 92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68-7.50 (m, 2H), 7.42–7.21 (m, 7H), 7.07 (s, 1H), 4.93 (t, J = 3.8 Hz, 2H), 3.95 (t, J = 3.8 Hz, 2H), 3.83 (s, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 161.7, 155.4, 149.3, 138.8, 128.5 (2 C), 128.4 (2 C), 127.5, 127.3, 126.6, 123.4, 122.1, 111.9, 109.9, 84.0, 60.1, 59.1. HRMS (TOF MS ES$^+$): m/z Calcd. for $C_{18}H_{17}N_2O$ $[M+H]^+$: 277.1341; Found: 277.1336. IR (neat) ν 1626, 1448, 1254, 1140, 881, 818, 700 cm^{-1}.

(3a*R,8b*R**)-2-benzyl-1,2,3,8 b-tetrahydro-3aH-benzo[4,5]thieno[2,3-c]pyrrole-3 a-carbonitrile (7 e) and 4-(benzo[b]thiophen-2-yl)-1-benzyl-2,5-dihydro-1H-imidazole (8 e)**. The target compounds were prepared according to the general procedure. The crude mixture, obtained as a 1:1 mixture of **7 e** and **8 e**, was purified by flash chromatography on silica gel (DCM 100% then cyclohexane/EtOAc 7/3) to afford **7 e** as a colorless oil (14 mg) and **8 e** as a white solid (43 mg, mp 109 °C) (overall 39% yield).

(3a*R,8b*R**)-2-benzyl-1,2,3,8 b-tetrahydro-3a*H*-benzo[4,5]thieno[2,3-*c*]pyrrole-3 a-carbonitrile (7 e)**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–6.84 (m, 9H), 4.48 (dd, J = 7.7, 5.5 Hz, 1H), 3.74 (d, J = 13.2 Hz, 1H), 3.66 (d, J = 13.2 Hz, 1H), 3.41 (d, J = 10.0 Hz, 1H), 3.35–3.26 (dd ≈ t, J = 9.1, 7.7 Hz, 1H), 3.04 (d, J = 10.0 Hz, 1H), 2.71 (dd, J = 9.1, 5.5 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.9, 138.6, 137.5, 129.0, 128.6 (2 C), 128.6 (2 C), 127.6, 125.7, 125.0, 121.7, 121.4, 67.2, 60.7, 60.3, 58.4, 51.4. HRMS (TOF MS ES$^+$): m/z Calcd. for $C_{18}H_{17}N_2S$ $[M+H]^+$: 293.1112; Found: 293.1104. IR (neat) ν 1586, 1468, 1444, 1128, 742, 698, 472 cm^{-1}.

4-(benzo[*b*]thiophen-2-yl)-1-benzyl-2,5-dihydro-1*H*-imidazole (8 e). 1H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 7.2 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.44–7.12 (m, 8H), 4.89 (t, J = 3.6 Hz, 2H), 4.01 (t, J = 3.6 Hz, 2H), 3.86 (s, 2H). 13 C{1H} NMR (75 MHz, CDCl3): δ 165.7, 141.1, 139.5, 139.0, 137.3, 128.7 (2 C), 128.6 (2 C), 127.5, 126.9, 126.4, 124.8, 124.7, 122.8, 83.9, 60.6, 59.4. HRMS (TOF MS ES+): m/z Calcd. for $C_{18}H_{17}N_2S$ $[M+H]^+$: 293.1112; Found: 293.1105. IR (neat) ν 1604, 1434, 1344, 1118, 834, 727, 585 cm^{-1}.

(3a*R,8b*R**)-2-benzyl-3 a-(1-benzyl-2,5-dihydro-1*H*-imidazol-4-yl)-4-(trifluoromethyl)sulfonyl)-1,2,3,3 a,4,8 b-hexahydropyrrolo[3,4-*b*]indole (10 f)**. The target compound was prepared according to the general procedure. The crude mixture was purified by flash chromatography on silica gel (cyclohexane/EtOAc 3/7) then by an Inverse Phase HPLC (water/ACN 90/10 to 0/100 over 45 min) to afford the desired product as a colorless oil (162 mg, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58–7.32 (m, 13H), 7.29–7.16 (m, 1H), 4.88–4.81 (m, 2H), 4.11–3.80 (m, 5H), 3.83–3.50 (m, 4H), 2.98–2.86 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.3, 140.6, 138.8, 137.9, 131.3, 128.8 (2 C), 128.8 (3 C), 128.6 (3 C), 127.4 (3 C), 125.1 (3 C), 119.9 (q, J = 325.7 Hz), 114.0, 83.6, 80.7, 61.7, 60.8, 59.9, 59.3, 59.0. ^{19}F {1H} NMR (282 MHz, $CDCl_3$): δ −74.42. HRMS (TOF MS ES+): m/z Calcd. for $C_{28}H_{28}N_4O_2F_3S$ $[M+H]^+$: 541.0994; Found: 541.1872. IR (neat) ν 1484, 1461, 1393, 1196, 1140, 908, 730, 601 cm^{-1}.

4-(benzofuran-2-yl)-1-benzyl-1*H*-imidazole (11 d). The target compound was prepared according to the general procedure after which DDQ (0.65 mmol, 1.3 equiv) was added portionwise. The mixture was stirred for 5 hours. The crude mixture was filtered over celite and then purified by flash chromatography on silica gel (cyclohexane/acetone 8/2) to afford the desired product as a white solid (114 mg, 83% yield). mp 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.47 (m, 2H), 7.49–7.43 (m, 1H), 7.40–7.12 (m, 9H), 5.06 (s, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 154.4, 152.0, 138.1, 135.6, 134.6, 129.2, 129.1 (2 C), 128.4, 127.4 (2 C), 123.7, 122.8, 120.8, 116.9, 110.8, 100.3, 51.0. HRMS (TOF MS ES$^+$): m/z Calcd. for $C_{18}H_{15}N_2O$ $[M+H]^+$: 275.1184; Found: 275.1176. IR (neat) ν 1667, 1446, 1258, 1154, 822, 722, 693 cm^{-1}.

4-(benzo[b]thiophen-2-yl)-1-benzyl-1*H*-imidazole (11 e). The target compound was prepared according to the general procedure after which DDQ (0.65 mmol, 1.3 equiv) was added portionwise. The reaction mixture was stirred for 5 hours. The crude mixture was then filtered over celite and purified by flash chromatography on silica gel (Cyclohexane/EtOAc 5/5) to afford the desired product as a white solid (32 mg, 22% yield). *mp* 129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 0.9 Hz, 1H), 7.50 (bs, 1H), 7.42–7.14 (m, 8H), 5.11 (s, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 140.7, 138.9, 138.0, 137.8, 137.7, 135.7, 129.2 (2 C), 128.6, 127.5 (2 C), 124.4, 123.9, 123.3, 122.3, 118.0, 115.9, 51.2. HRMS (TOF MS ES$^+$): m/z Calcd. for $C_{18}H_{15}N_2S$ $[M+H]^+$: 291.0956; Found: 291.0947. IR (neat) ν 1667, 1446, 1258, 1154, 822, 722, 693 cm^{-1}.

Supporting Information Summary

Supporting information contains associated experimental procedures, characterization and NMR spectra for all products.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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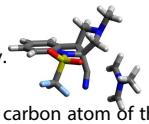
[15] It should also be noted that the transition state corresponding to the heterocycloaddition on the CN group leading to the bis-cycloadduct from the indoline cycloadduct could be localized with an activation barrier of 12.5 kcal.mol^{-} (See figure below). Notably, this barrier is in the same range as the one computed for the first cycloaddition on the C2=C3 bond and supports the formation of the bis-cycloadduct only. 
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