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Controlling Pd-catalyzed *N*-arylation and Dimroth rearrangement in the synthesis of *N*,1-diaryl-1*H*-tetrazol-5-amines

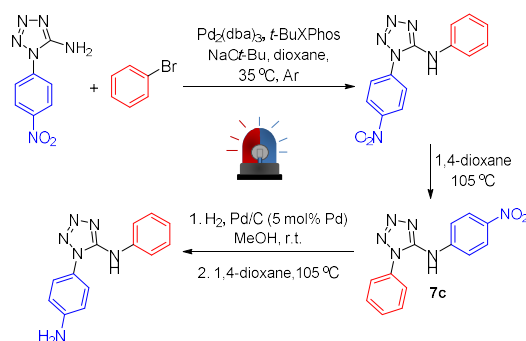
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ABSTRACT:

The Pd-catalyzed *N*-arylation method for the synthesis of eighteen *N*,1-diaryl-1*H*-tetrazol-5-amine derivatives is reported. By running the reactions at 35 °C, compounds were isolated as single isomers since the undesired Dimroth rearrangement was completely suppressed. Furthermore, the Dimroth rearrangement of *N*,1-diaryl-1*H*-tetrazol-5-amines was rationalized by conducting comprehensive experiments and NMR analysis as well as DFT calculations of thermodynamic stability of the compounds. It was established that the Dimroth rearrangement is thermodynamically controlled and the equilibrium of the reaction is determined by the stability of the corresponding isomers. The mechanism was investigated by additional DFT calculations and the opening of the tetrazole ring was shown to be the rate-determining step. By maneuvering Pd-catalyzed *N*-arylation and the subsequent Dimroth rearrangement two more *N*,1-diaryl-1*H*-tetrazol-5-amine derivatives were acquired, that otherwise cannot be synthesized by employing the C–N cross-coupling reaction.

Keywords: aminotetrazoles, Dimroth rearrangement, DFT, C–N cross-coupling, arylation

INTRODUCTION

The tetrazole scaffold is a well-known motif in bioactive compounds. This heterocyclic moiety can be found in FDA approved drugs, such as Losartan, an angiotensin II receptor blocker used to treat high blood pressure,¹ or Cefonicid, an antibiotic active against Gram-negative rods.² As its derivative, the 1*H*-tetrazol-5-amine scaffold is an important pharmacophore in drug discovery and development. Recently, 1-aryl-5-arylamino-1*H*-tetrazoles have been shown to possess antitubercular potential (compound **1**, Figure 1),³ while other 1-aryl-5-alkylamino derivatives are proven to be active against Gram-positive and Gram-negative strains (compound **2**, Figure 1).⁴ There have also been reports on antiallergic⁵ and antidiabetic⁶ activity of aminotetrazoles. Applications outside medicinal chemistry include protection against steel corrosion (compound **4**, Figure 1),⁷ as well as uses in coordination chemistry as ligands⁸ and in synthetic chemistry as reactive intermediates.⁹ Additionally, Krishnan et al. demonstrated the utility of aminotetrazole-functionalized nanoparticle composites for the removal of dyes and detection of heavy metal ions.¹⁰

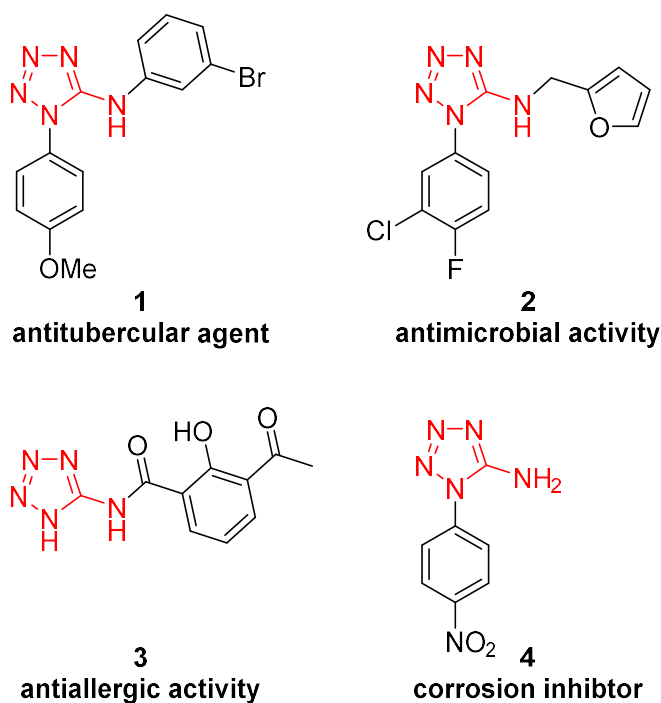


Figure 1. Selected molecules containing an aminotetrazole moiety

The most common approach for the synthesis of the *N*,1-diaryl-1*H*-tetrazol-5-amines is based on the formation of the tetrazole ring from *N*-substituted acyclic precursors,¹¹ however, this methodology usually provides the mixture of isomeric compounds.^{9b,11d} Having in mind the importance of this class

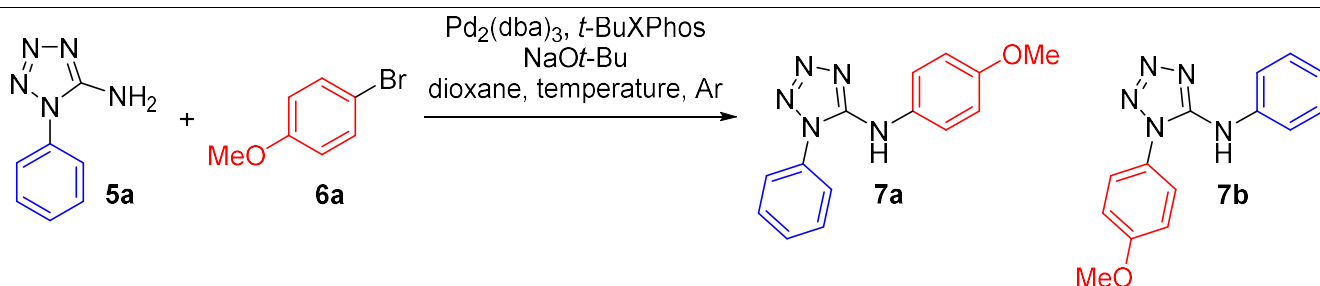
of heterocycles, and the aforementioned difficulties, the development of highly selective synthetic method presents a challenge.

RESULTS AND DISCUSSION

The palladium-catalyzed formation of the C–N bond between aryl-halides and amines is one of the most important reactions in modern organic chemistry and drug development process^{12,13} and under classical Buchwald-Hartwig reaction conditions, the reaction mixture is heated between 80 and 120 degrees Celsius.^{14,15} As a continuation of our previous research in the chemistry of tetrazoles, we sought to synthesize new 1-aryl-*N*-aryl-1*H*-tetrazol-5-amines. Applying previously used reaction conditions¹⁶ on **5a** and **6a** yielded a mixture of two regioisomeric compounds **7a** and **7b** (Table 1, entry 4). It is worth mentioning that compounds **7a** and **7b** could not be separated by standard chromatographic techniques. In-depth analysis showed that the mixture of compounds is a result of *N*-arylation followed by the Dimroth rearrangement. Therefore, our next step was to optimize the reaction conditions to suppress the rearrangement reaction. By lowering the reaction temperature to 80 °C the yield dropped and the rearrangement product **7b** was still the dominant one (Table 1, entry 3). Running the reaction at room temperature yielded solely the desired product **7a** albeit in low yield, while starting compound **5a** was recovered (Table 1, entry 1). Raising the temperature to 35 °C resulted in the formation of the desired product **7a**, which was obtained in high yield, whilst the rearrangement product **7b** was not detected (Table 1, entry 2). Additionally, we wanted to examine whether raising the reaction temperature to 130 °C would impact the ratio of the products and yield only one product (Table 1, entry 5). We concluded that the higher temperatures do not play a significant role in the product distribution of the Dimroth rearrangement and that, perhaps, structural parameters govern the outcome of the reaction.

Table 1. Temperature controlled outcome of Pd-catalyzed *N*-arylation

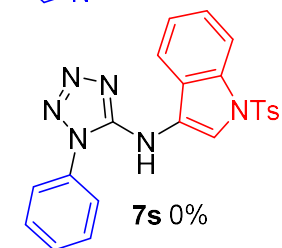
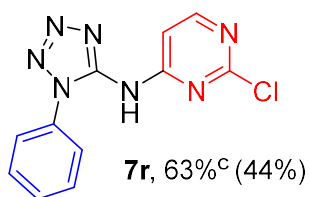
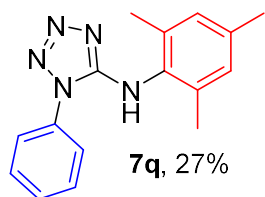
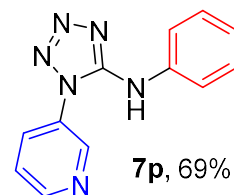
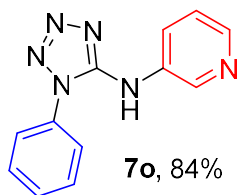
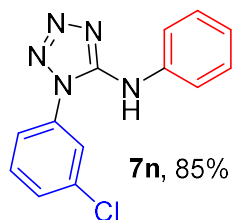
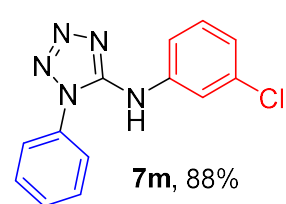
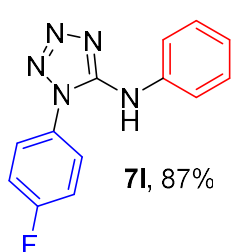
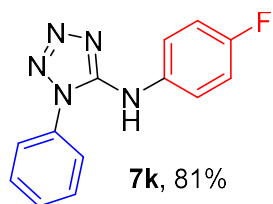
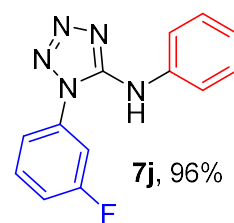
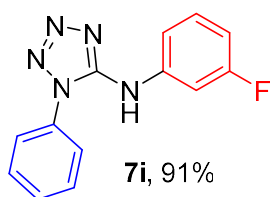
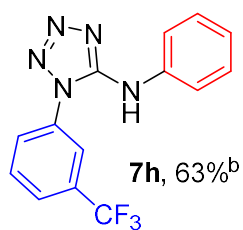
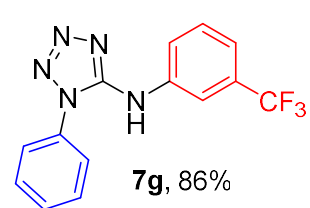
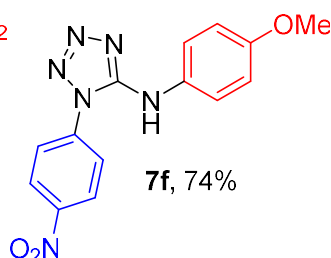
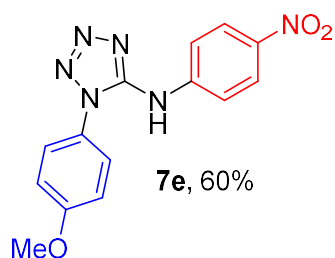
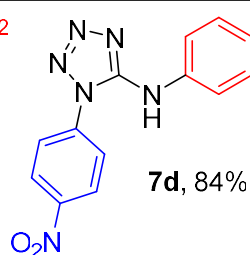
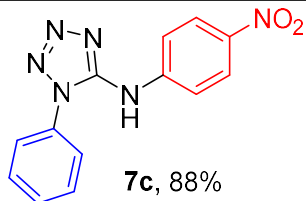
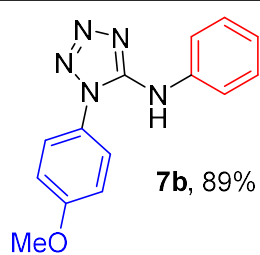
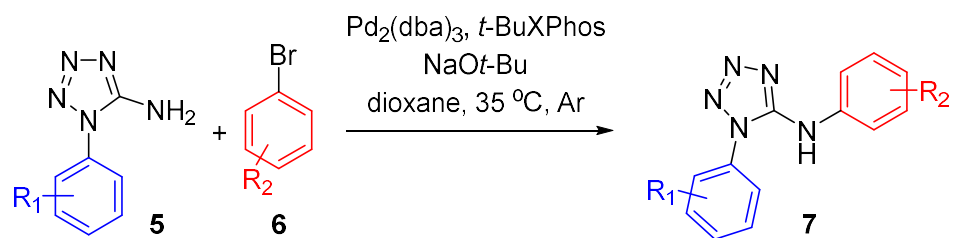
entry	temperature (°C)	yield (%)	isomer ratio ^b
1	r.t.	33%	1 : 0
2	35	98%	1 : 0
3	80	86% ^d	1 : 3.5



4	105	95% ^d	1 : 3.5
5	130	88% ^c	1 : 3.0

^aReactions conditions: **5a** (1.05 equiv), **6a** (1.0 equiv), Pd₂(dba)₃ (10 mol % Pd), *t*-BuXPhos (20 mol %), NaO*t*-Bu (1.05 equiv), 1,4-dioxane, 24 h, Ar. ^bIsomer ratio by ¹H NMR spectroscopy. ^cYield of a mixture of isomers.

In order to investigate the scope of the palladium catalyzed *N*-arylation reaction at 35 °C, we synthesized a series of 17 additional derivatives **7b-7r** (Table 2). These compounds would later be used as substrates for the rearrangement reaction and the detailed analysis of the relationship between the structural parameters and the isomer distribution. A series of aryl bromides and 1-aryl-1*H*-tetrazol-5-amines, including those with an electron-donating group (-OMe) and with electron-withdrawing groups (-NO₂, -CF₃) were transformed into the desired products in good to excellent yields (Table 2, **7b-7h**). Reactions of halogen substituted compounds **5** and **6** also gave the corresponding products **7i-7n** in high yields, showing excellent selectivity towards bromine atom. When sterically demanding 2-bromo-1,3,5-trimethylbenzene **6i** was reacted with **5a**, the desired product **7q** was obtained in 27% yield. The scope of this method was further expanded by utilizing heteroaryl bromides or 1-heteroaryl-1*H*-tetrazol-5-amines. The desired pyridine substituted tetrazoles **7o** and **7p** were obtained in 84% and 69% yield, respectively. By reacting 2,4-dichloropyrimidine **6j** with 1-phenyl-1*H*-tetrazol-5-amine **5a** in the presence of Pd₂(dba)₃, *t*-BuXPhos as a ligand and K₂CO₃ as a base in 1,4-dioxane, product **7r** was obtained in 44% yield. However, by changing the ligand to XantPhos, the yield of the desired product **7r** was raised to 63%. Unfortunately, there was no reaction when 3-bromo-1-tosyl-1*H*-indole **6k** was employed as a substrate (Table 2, **7s**). This indole derivative has been shown in literature to be problematic in this type of reactions. Notably, the reaction scale could be increased to 1 mmol, shown on the example of the compound **7h**. It is worth mentioning that all the products were isolated as single isomers, with no detection of side-products, showcasing the selectivity of this method and the hindering of the subsequent rearrangement reaction. This method allows for the synthesis of any isomer as a single compound as illustrated for **7b** (Table 1 and Table 2). As most of the desired compounds were synthesized in good to excellent yields, with broad substrate scope, this method could be utilized for further functionalization and the synthesis of more complex compounds.

Table 2. Substrate scope for palladium catalyzed *N*-arylation^a

^aReactions conditions: **5** (1.05 equiv), **6** (1.0 equiv), Pd₂(dba)₃ (10 mol % Pd), *t*-BuXPhos (20 mol %), NaOt-Bu (1.05 equiv), 1,4-dioxane, 35 °C, 24 h, Ar. ^bReaction performed on 1.1 mmol scale. ^cK₂CO₃ (1.05 eq) used as a base and XantPhos (20 mol%) used as a ligand.

Since Dimroth rearrangement is successfully employed as a method of attaining various heterocyclic structures, applied to industrial processes and even observed in biological systems, as a continuation of this research, we wanted to further study the said transformation on this heterocyclic system.¹⁷ Dimroth rearrangement of 1*H*-tetrazole-5-amine derivatives was first observed in 1953,^{18,19} during heating of various monosubstituted 5-aminotetrazoles and some 5-alkyl-1-aryl-1*H*-tetrazole-5-amines. A similar transformation was noticed by Dimroth in 1*H*-1,2,3-triazole-5-amine derivatives,²⁰ and later recognized as a valuable method for acquiring some previously unavailable aminotetrazoles.²¹ The occurrence of Dimroth rearrangement of tetrazoles still seems to be somewhat neglected in modern organic synthesis, appearing more often as an unexpected²² or unwanted²³ side reaction than as the desired transformation.²⁴

With a set of *N*,1-diaryl-1*H*-tetrazol-5-amines shown in Table 2, we sought to explore the outcome of Dimroth rearrangement. Firstly, the reaction conditions were studied. When compound **7a** was heated in 1,4-dioxane (105 °C, 24 h) without a palladium source and a ligand either in the presence of NaOt-Bu (1.05 equiv) or in the absence of the base, the isomer ratio remained the same, meaning that neither the base nor palladium play a role in the rearrangement. Changing the solvent to CD₃OD, CDCl₃, C₆D₆ and DMSO-*d*₆ and heating **7a** in the corresponding solvent at 105 °C for 24 h did not alter the ratio of the isomers, always giving **7a** : **7b** = 1 : 3.5 ratio. This strongly suggested that the solvent does not play an important role in the outcome of the reaction. Next, in order to investigate the influence of structural characteristics on the ratio of the isomers, we subjected all compounds to Dimroth rearrangement, by heating them at 105 °C for 24h in either 1,4-dioxane or DMSO-*d*₆ (Table 3). Based on the acquired results, several conclusions could be made. Primarily, the electronic effects of substituents play an important role. Compounds containing a phenyl core with electron-donating groups on the endocyclic nitrogen of the tetrazole ring will always be in excess after the reaction. This means that electron-withdrawing substituents show a preference for the exocyclic position. An additive effect could also be observed, when comparing entry 1 and entry 6 as well as entry 15 and entry 18 (Table 3). Additionally, the position of the substituent (*m*-F vs *p*-F) also impacts the outcome of the reaction (entries 10 and 12) - the difference in the isomer ratio of this pair of compounds can be attributed to the stronger influence of the inductive effect. Three methyl groups (entry 17) greatly affect the rearrangement with almost a complete conversion of one isomer to another. It is important to outline that the isomer ratio in the Dimroth reaction remained the same, regardless of which single

isomer was used as a starting compound. This suggests that the ratio was dictated by the stability of the compounds, implying a thermodynamic control of the reaction. We next sought to determine the temperature at which the reaction initiates. To achieve this, we chose a pair of substrates **7m** and **7n** and we recorded the ¹H NMR spectra while the sample was gradually heated (~1 °C/min) inside the NMR spectrometer (see the Supporting Information, Tables S1 and S2). We observed that **7n** begins to transform into **7m** at 80 °C, while for the corresponding **7m** we detected the formation of **7n** only at 99 °C. From the experimental data, we concluded that the transformation of different starting isomers proceeds at different rates at the same temperature presumably due to the difference in the activation energies. The two isomers exist in equilibrium and the stability of the compounds determines the position of the equilibrium between the two regioisomers. This hypothesis was further investigated and reinforced by *in silico* methods (Table 3, Table S3).

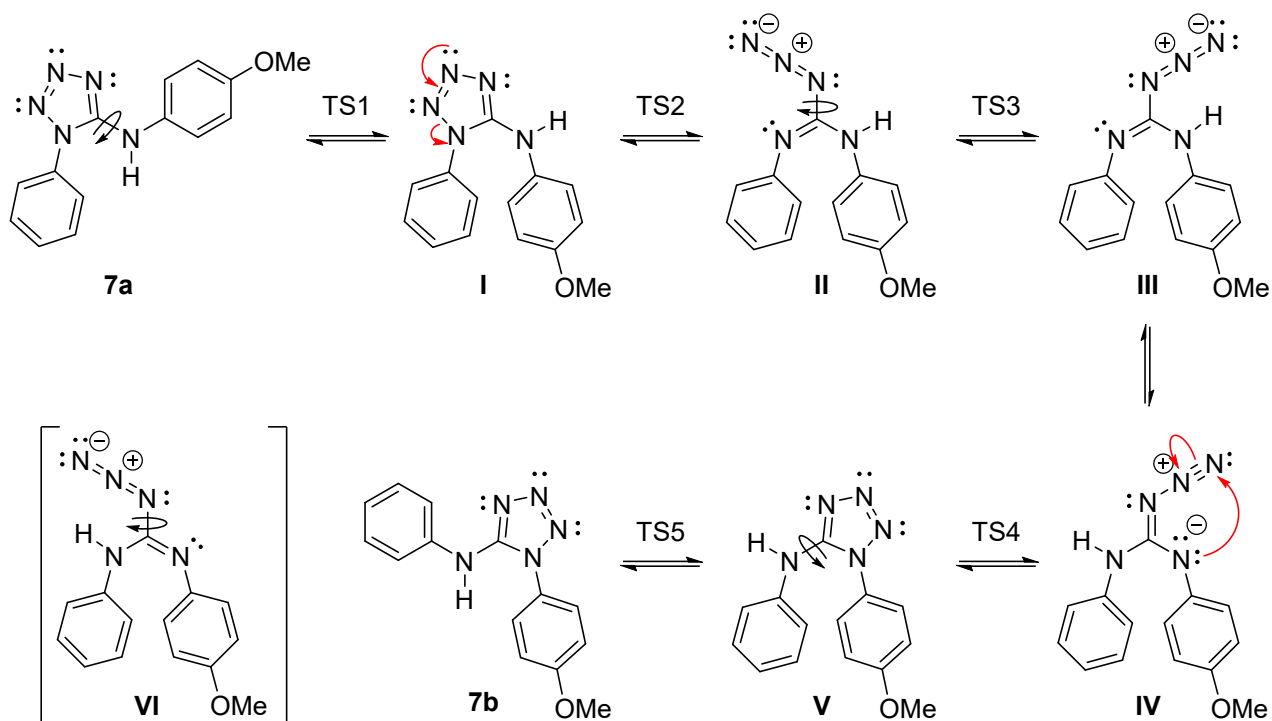
Table 3. Substrate scope for Dimroth rearrangement^a

entry	R ₁	R ₂	Ratio ^b of A : B	Ratio of isomers (based on Δ _r G) ^c
1	H	4-OMe	22:78	7a : 7b =13:87
2	4-OMe	H	78:22	
3	H	4-NO ₂	100:0	7c : 7d =99:1
4	4-NO ₂	H	0:100	
5	4-OMe	4-NO ₂	100:0	7e : 7f =100:0
6	4-NO ₂	4-OMe	0:100	
7	H	3-CF ₃	89:11	7g : 7h =88:12
8	3-CF ₃	H	12:88	
9	H	3-F	79:21	7i : 7j =80:20
10	3-F	H	25:75	
11	H	4-F	50:50	7k : 7l =51:49
12	4-F	H	50:50	
13	H	3-Cl	81:19	7m : 7n =85:15
14	3-Cl	H	19:81	
15	H	3-pyr	78:22	7o : 7p =90:10

16	3-pyr	H	22:78	
17	H	Mes	4:96	A:B =<1:>99
18	H	4-2-Cl-pyrimidine	100:0	A:B =76:24

^aReaction conditions: **7** (10 mg), 1,4-dioxane or DMSO-*d*₆ (0.5 mL), 105 °C, 24 h. ^bIsomer ratio by ¹H NMR spectroscopy (see the Supporting Information). ^cBased on the difference in Gibbs free energies of isomers (T=378.15 K) calculated at BLYP-D4/def2-TZVP(-f)-SMD (dioxane) level of theory.

Based on all the acquired data – experimental results, DFT calculations and NMR experiments, we propose the mechanism of Dimroth rearrangement (Scheme 1, Figure 2, Figure S1). The transformation proceeds through a thermally induced ring opening-ring closing process. The conformational changes arising from the rotation of the C5–N bond were chosen, for the sake of clarity, to represent the first and the last step, although they can occur at any stage of the reaction pathway. Temperature-induced opening of the tetrazole ring leads to a substituted guanylazide **II**, which can transform further to **IV** via bond rotation-proton transfer (via intermediate **III**) or proton transfer (intermediate **VI**) followed by bond rotation. The cyclization of guanylazide **II** and **IV** to **I** and **V**, respectively, are thermodynamically favorable. Notably, compound with an electron-rich aromatic ring in N1 position **7b** is more stable than the other isomer **7a** (Figure 2). It is also worth mentioning that the relative energies of **II** and **IV** are different and that the less stable **IV** has lower activation energy for cyclization to **7b**. This is in agreement with the fact that the electron-donating methoxy group destabilizes **IV**. Overall, it can be concluded that the reaction is thermodynamically controlled and that ring-opening is the rate-determining step. To the best of our knowledge, this is the first time that the mechanism has been studied on *N*,1-diaryl-1*H*-tetrazol-5-amines.



Scheme 1. Proposed mechanism for Dimroth rearrangement.

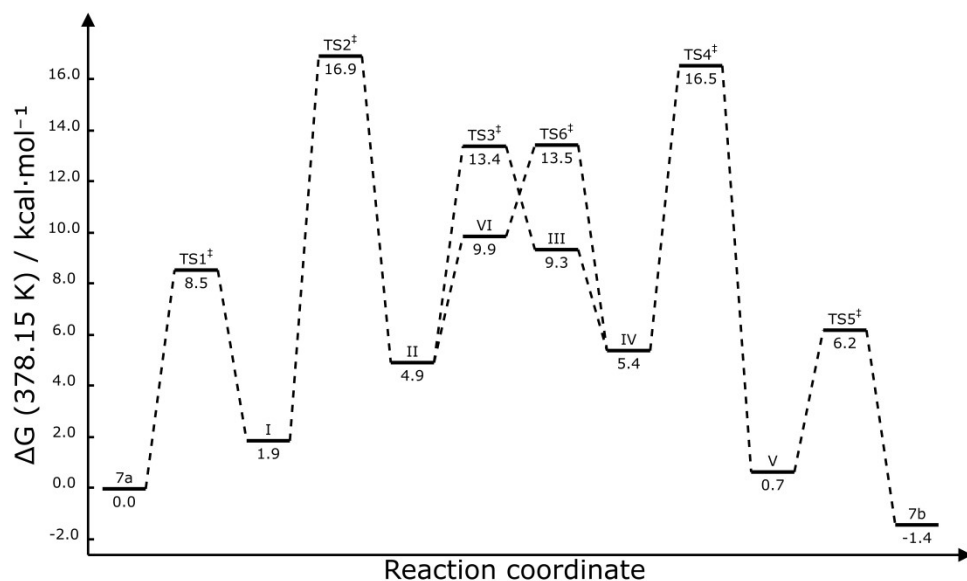
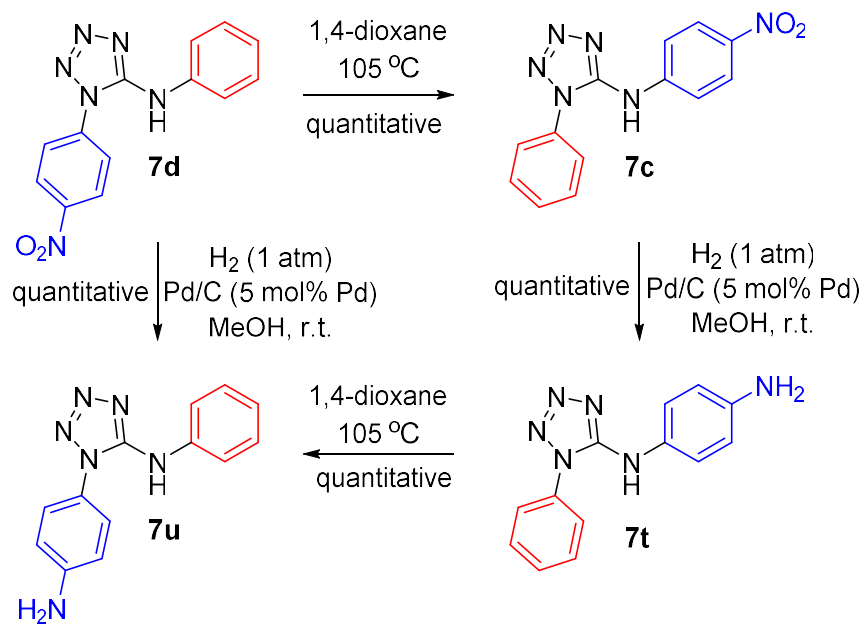


Figure 2. Calculated reaction profile for the Dimroth rearrangement of **7a** and **7b**. Gibbs free energies (in kcal/mol relative to **7a**) at 378.15 K, obtained using the BLYP-D4/def2-TRVP(-f)-SMD(dioxane) level of theory.

In order to further demonstrate the control of the Dimroth rearrangement and the applicability of the synthesized *N*,1-diaryl-1*H*-tetrazol-5-amines, compounds **7t** and **7u** were synthesized (Scheme 2). Compound **7d** was converted into **7c** using the conditions for Dimroth rearrangement (Table 3).

Compound **7t** was obtained in quantitative yield by reducing the nitro group of **7c**, under hydrogen atmosphere (1 atm) using Pd/C (5 mol % Pd) as a catalyst. By exploiting the selectivity of Dimroth rearrangement, compound **7t** was quantitatively converted into the compound **7u** when it was heated in 1,4-dioxane at 105 °C for 24h (Scheme 2). This result is in a good agreement with the results obtained by DFT calculations, where the ratio of isomers for **7t**:**7u** from Gibbs free energies is 4:96 (calculated at BLYP-D4/def2-TZVP(-f)-SMD(dioxane) level of theory at T=378.15 K). To further confirm the structure of **7u**, compound **7d** was reacted with hydrogen in the presence of Pd/C (5 mol % Pd) and **7u** was obtained in quantitative yield. It is important to outline that compounds **7t** and **7u** cannot be efficiently synthesized through Pd-catalyzed *N*-arylation of 1-phenyl-1*H*-tetrazol-5-amine **5a** or 1-(4-aminophenyl)-1*H*-tetrazol-5-amine, respectively, as there is a competing effect between the aminotetrazole and aniline moiety. Additionally, amino group represents another possible point for further derivatization of *N*,1-diaryl-1*H*-tetrazol-5-amines.



Scheme 2. Synthesis of **7t** and **7u**

CONCLUSIONS

In conclusion, we used Pd-catalysed *N*-arylation to synthesize a set of *N*,1-diaryl-1*H*-tetrazol-5-amines. By controlling the reaction temperature, unwanted Dimroth rearrangement was prevented and the desired compounds were isolated as single isomers. Better insight into the Dimroth rearrangement was gained by further studying the isomer distribution at elevated temperatures. The equilibrium was found to be a function of the thermodynamic stability of the products. The thermodynamic control of the reaction, as well as the distribution of isomers in the Dimroth rearrangement, was confirmed by *in*

silico methods. Additionally, DFT calculations were used to propose a reaction mechanism, elucidating the ring-opening as the rate-limiting step. Finally, with the newly gained understanding of the structural parameters that determine the rearrangement outcome, we applied a sequence of reactions to synthesize compounds that cannot otherwise be selectively obtained through Pd-catalyzed reactions.

EXPERIMENTAL SECTION

General Information.

Unless stated otherwise, all solvents and reagents were obtained from commercial sources and used without further purification. Dry-flash chromatography was performed on SiO₂ (0.018–0.032 mm). Melting points were determined on a Boetius PMHK apparatus and are not corrected. IR spectra were recorded on a Thermo-Scientific Nicolet 6700 FT-IR Diamond Crystal instrument. ¹H and ¹³C NMR spectra were recorded on a Bruker Ultrashield Avance III spectrometer (at 500 and 125 MHz, respectively) and Varian spectrometer (at 400 and 100 MHz, respectively). Chemical shifts are expressed in parts per million (ppm) on the (δ) scale. Chemical shifts were calibrated relative to those of the solvent. All new compounds were analyzed by high resolution tandem mass spectrometry using LTQ Orbitrap XL (Thermo Fisher Scientific Inc., USA) mass spectrometer. The sample was dissolved in MeCN and it was injected directly. Ionization was done in positive mode on heated electrospray ionization (HESI) probe. HESI parameters were: spray voltage 4.7 kV, vaporizer temperature 60 °C, sheath and auxiliary gas flow 24 and 10 (arbitrary units), respectively, capillary voltage 49 V, capillary temperature 275 °C, tube lens voltage 80 V, resolution (at m/z 400): 30000.

Synthesis.

Compounds 1-phenyl-1*H*-tetrazol-5-amine (**5a**),^{25a} 1-(4-methoxyphenyl)-1*H*-tetrazol-5-amine (**5b**),^{25b} 1-(4-nitrophenyl)-1*H*-tetrazol-5-amine (**5c**),^{25a} 1-(3-chlorophenyl)-1*H*-tetrazol-5-amine (**5g**),^{25c} 3-bromo-1-tosyl-1*H*-indole (**6k**)^{25d} were synthesized according to the previously reported procedures. Compounds 1-bromo-4-methoxybenzene (**6a**), bromobenzene (**6b**), 1-bromo-4-nitrobenzene (**6c**), 1-bromo-3-(trifluoromethyl)benzene (**6d**), 1-bromo-3-fluorobenzene (**6e**), 1-bromo-4-fluorobenzene (**6f**), 1-bromo-3-chlorobenzene (**6g**), 3-bromopyridine (**6h**), 2-bromo-1,3,5-trimethylbenzene (**6i**), 2,4-dichloropyrimidine (**6j**) are commercially available.

1-(3-(Trifluoromethyl)phenyl)-1*H*-tetrazol-5-amine (5d). A round-bottom reaction flask equipped with reflux condenser was charged with 3-(trifluoromethyl)aniline (772 μL, 6.20 mmol, 1.0 equiv),

NaN₃ (444 mg, 6.83 mmol, 1.1 equiv), triethyl orthoformate (3.1 mL, 19 mmol, 3 equiv) and glacial AcOH (28.4 mL, 49.6 mmol, 8 equiv). The mixture was stirred and heated at 80 °C in an oil bath for 4 h after which it was cooled to room temperature and diluted with brine (125 mL). Solid Na₂CO₃ was added to the stirring solution until the gas evolution ceased. The formed precipitate was separated by filtration, washed with H₂O and dried. The product, 1-(3-(trifluoromethyl)phenyl)-1*H*-tetrazole, was used in the next step without any additional purification.

A round-bottom reaction flask was charged with 1-(3-(trifluoromethyl)phenyl)-1*H*-tetrazole (1.000 g, 4.670 mmol, 1.0 equiv), NaN₃ (455 mg, 7.00 mmol, 1.5 equiv), NaOH (280 mg, 7.00 mmol, 1.5 equiv), Et₃N (1.3 mL, 9.3 mmol, 2 equiv) and *i*-PrOH (1.57 mL, 18.7 mmol, 4 equiv) after which DMSO (3.3 mL, 46.7 mmol, 10 equiv) was added dropwise. The reaction mixture was stirred at room temperature until the gas evolution ceased (2 h) and then it was treated with glacial AcOH (800 μL, 14.0 mmol, 3 equiv). The resulting solution was stirred and heated at 80 °C in an oil bath for 2 h, cooled to room temperature and diluted with brine (60 mL). The formed precipitate was separated by filtration, washed with H₂O and dried. Compound **5d** was obtained as a pale yellow powder (865 mg, 81%); m.p. 129 – 130 °C. IR (ATR) = 3317, 3142, 1658, 1582, 1505, 1477, 1347, 1322, 1308, 1277, 164, 1144, 1086, 1056, 903, 806, 702 cm⁻¹. ¹H NMR (400 Hz, DMSO-*d*₆): δ 7.97 – 7.81 (m, 4H), 7.05 (s, 2H) ppm. ¹³C{¹H} NMR (100 Hz, DMSO-*d*₆): δ 155.1, 134.1, 131.2, 130.5 (q, *J* = 33 Hz), 128.4, 126.1 (q, *J* = 4 Hz), 123.6 (q, *J* = 272 Hz), 121.2 (q, *J* = 4 Hz) ppm. HRMS (HESI/Orbitrap) *m/z*: [M + H]⁺ Calcd. for C₈H₇F₃N₅⁺ 230.0648; Found 230.0654.

1-(3-Fluorophenyl)-1*H*-tetrazol-5-amine (5e). Following the procedure described for the **5d**, compound **5e** was obtained as a pale yellow solid (369 mg, 46%) starting from 3-fluoroaniline (498 mg, 4.48 mmol); m.p. 146 – 147 °C. IR (ATR) = 3313, 3125, 1660, 1607, 1577, 1502, 1471, 1312, 1200, 1140, 1093, 875, 792, 677 cm⁻¹. ¹H NMR (400 Hz, CD₃OD): δ 7.69 – 7.59 (m, 1H), 7.48 – 7.37 (m, 2H), 7.36 – 7.28 (m, 1H) ppm. ¹³C{¹H} NMR (100 Hz, CD₃OD): δ 164.4 (d, *J* = 247 Hz), 156.4, 136.2 (d, *J* = 10 Hz), 132.8 (d, *J* = 9 Hz), 121.0 (d, *J* = 4 Hz), 117.6 (d, *J* = 22 Hz), 112.7 (d, *J* = 25 Hz) ppm. HRMS (HESI/Orbitrap) *m/z*: [M + H]⁺ Calcd. for C₇H₇FN₅⁺ 180.0680; Found 180.0687.

1-(4-fluorophenyl)-1*H*-tetrazol-5-amine (5f). Following the procedure described for the **5d**, compound **5f** was obtained as a pale yellow solid (328 mg, 45%) starting from 4-fluoroaniline (448 mg, 4.03 mmol); m.p. 160 – 162 °C. IR (ATR) = 3303, 3133, 2989, 1662, 1579, 1516, 1321, 1220, 1143, 1092, 843, 621 cm⁻¹. ¹H NMR (400 Hz, CD₃OD): δ 7.65 – 7.55 (m, 2H), 7.39 – 7.31 (m, 2H) ppm. ¹³C{¹H} NMR (100 Hz, CD₃OD): δ 164.4 (d, *J* = 248 Hz), 156.6, 131.0 (d, *J* = 3 Hz), 128.0 (d, *J* = 9

Hz), 117.9 (d, $J = 24$ Hz) ppm. HRMS (HESI/Orbitrap) m/z : $[M + H]^+$ Calcd. for $C_7H_7FN_5^+$ 180.0680; Found 180.0687.

1-(pyridin-3-yl)-1H-tetrazol-5-amine (5h). Following the procedure described for the **5d**, compound **5h** was obtained as a pale pink solid (230 mg, 27%) starting from 3-aminopyridine (500 mg, 5.31 mmol); m.p. 145 – 146 °C. IR (ATR) = 3108, 1672, 1584, 1491, 14, 1435, 1124, 1079, 806, 720 cm^{-1} . 1H NMR (400 Hz, DMSO- d_6): δ 8.85 – 8.77 (m, 1H), 8.77 – 8.71 (m, 1H), 8.08 – 8.02 (m, 1H), 7.69 – 7.62 (m, 1H), 7.05 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 Hz, DMSO- d_6): δ 155.3, 150.3, 145.2, 132.4, 130.4, 124.6 ppm. HRMS (HESI/Orbitrap) m/z : $[M + H]^+$ Calcd. for $C_6H_7N_6^+$ 163.0727; Found 163.0728.

General procedure for the palladium catalyzed *N*-arylation reacton. General procedure **A**.

***N*-(4-methoxyphenyl)-1-phenyl-1H-tetrazol-5-amine (7a).**^{9b} The previously reported procedure¹⁶ was modified in a way that the reaction mixture was heated at 35 °C in an oil bath for 24 h. Compounds 1-phenyl-1H-tetrazol-5-amine **5a** (41 mg, 0.25 mmol, 1.05 equiv) and 1-bromo-4-methoxybenzene **6a** (30 μ L, 0.24 mmol, 1.0 equiv) were coupled in the presence of $Pd_2(dba)_3$ (11 mg, 0.012 mmol, 10 mol % Pd), *t*-BuXPhos (20 mg, 0.048 mmol, 20 mol %) NaO*t*-Bu (24 mg, 0.25 mmol, 1.05 equiv) and 1,4-dioxane (1 mL). Compound **7a** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 7/3) as a pale yellow powder (63 mg, 98%); m.p. 132 – 133 °C. IR (ATR) = 3239, 3197, 3004, 1609, 1572, 1508, 1491, 1456, 1268, 1233, 1177, 1030, 811, 771 cm^{-1} . 1H NMR (400 Hz, CDCl₃): δ 7.65 – 7.56 (m, 3H), 7.54 – 7.49 (m, 2H), 7.42 (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.9$ Hz, 2H), 6.40 (s, 1H), 3.79 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 Hz, CDCl₃): δ 156.3, 152.3, 133.0, 131.3, 130.6, 130.5, 124.8, 120.7, 114.6, 55.7 ppm.

1-(4-Methoxyphenyl)-*N*-phenyl-1H-tetrazol-5-amine (7b).^{9b} Following the general procedure **A**, compound **7b** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 7/3) as a pale yellow powder (57 mg, 89%) from **5b** (48 mg, 0.25 mmol) and **6b** (25 μ L, 0.24 mmol); m.p. 166 – 169 °C. IR (ATR) = 1612, 1574, 1497, 1250, 1104, 838, 747 cm^{-1} . 1H NMR (400 MHz, CDCl₃): δ 7.50 – 7.45 (m, 2H), 7.41 – 7.37 (m, 2H), 7.32 – 7.26 (m, 2H), 7.07 – 7.00 (m, 3H), 3.85 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, CDCl₃ + CD₃OD): δ 161.1, 152.2, 138.3, 129.3, 126.9, 125.2, 123.3, 118.2, 115.5, 55.8 ppm.

***N*-(4-nitrophenyl)-1-phenyl-1H-tetrazol-5-amine (7c).** Following the general procedure **A**, compound **7c** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 8/2) as a

yellow powder (94 mg, 88%) from **5a** (64 mg, 0.40 mmol) and **6c** (77 mg, 0.38 mmol); m.p. 185 – 186 °C. IR (ATR) = 3266, 3098, 1623, 1582, 1534, 1493, 1333, 1255, 1109, 851 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.18 (s, 1H), 8.25 (d, *J* = 9.1 Hz, 2H), 7.86 (d, *J* = 9.1 Hz, 2H), 7.74 – 7.64 (m, 5H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 151.5, 146.3, 141.1, 132.8, 130.4, 130.0, 125.8, 125.2, 117.5 ppm. HRMS (HESI/Orbitrap) *m/z*: [M + H]⁺ Calcd. for C₁₃H₁₁N₆O₂⁺ 283.0938; Found 283.0943.

1-(4-Nitrophenyl)-*N*-phenyl-1*H*-tetrazol-5-amine (7d). Following the general procedure **A**, compound **7d** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 8/2) as a red powder (113 mg, 84%) from **5c** (103 mg, 0.500 mmol) and **6b** (50 μL mg, 0.48 mmol); m.p. 177 – 178 °C. IR (ATR) = 3233, 3192, 3115, 1599, 1588, 1521, 1497, 1455, 1340, 1313, 1241, 1104, 855, 752 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.54 (s, 1H), 8.49 (d, *J* = 9.0 Hz, 2H), 8.02 (d, *J* = 9.0 Hz, 2H), 7.63 – 7.58 (m, 2H), 7.37 – 7.32 (m, 2H), 7.06 – 7.01 (m, 1H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 152.4, 147.8, 139.6, 138.2, 128.9, 126.6, 125.2, 122.4, 118.4 ppm. HRMS (HESI/Orbitrap) *m/z*: [M + H]⁺ Calcd. for C₁₃H₁₁N₆O₂⁺ 283.0938; Found 283.0945.

1-(4-Methoxyphenyl)-*N*-(4-nitrophenyl)-1*H*-tetrazol-5-amine (7e). Following the general procedure **A**, compound **7e** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 7/3) as a yellow powder (47 mg, 60%) from **5b** (50 mg, 0.26 mmol) and **6c** (50 mg, 0.25 mmol); m.p. 237 °C. IR (ATR) = 3071, 3935, 1620, 1584, 1535, 1512, 1334, 1258, 1108, 749 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.06 (s, 1H), 8.24 (d, *J* = 9.2 Hz, 2H), 7.86 (d, *J* = 9.2 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 160.6, 151.8, 146.4, 141.0, 127.7, 125.3, 125.2, 117.4, 115.0, 55.7 ppm. HRMS (HESI/Orbitrap) *m/z*: [M + H]⁺ Calcd. for C₁₄H₁₃N₆O₃⁺ 313.1044; Found 313.1051.

***N*-(4-methoxyphenyl)-1-(4-nitrophenyl)-1*H*-tetrazol-5-amine (7f)**. Following the general procedure **A**, compound **7f** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 7/3) as an orange powder (58 mg, 74%) from **5c** (54 mg, 0.26 mmol) and **6a** (31 μL, 0.25 mmol); m.p. 98 – 99 °C. IR (ATR) = 3278, 3086, 2959, 2927, 2856, 1727, 1616, 1577, 1511, 1463, 1340, 1295, 1257, 1113, 1077, 1032, 854, 746 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.34 (s, 1H), 8.48 (d, *J* = 9.0 Hz, 2H), 8.01 (d, *J* = 9.0 Hz, 2H), 7.50 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 3.73 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 155.0, 152.8, 147.6, 138.3, 132.6, 126.5, 125.2, 120.6, 114.1, 55.2 ppm. HRMS (HESI/Orbitrap) *m/z*: [M + H]⁺ Calcd. for C₁₄H₁₃N₆O₃⁺ 313.1044; Found 313.1057.

***N*-phenyl-1-(3-(trifluoromethyl)phenyl)-1*H*-tetrazol-5-amine (7g)**. Following the general procedure **A**, compound **7g** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 9/1) as a pale yellow powder (155 mg, 86%) from **5a** (100 mg, 0.620 mmol) and **6d** (82 μL, 0.59 mmol); m.p. 103 – 106 °C. IR (ATR) = 3254, 3101, 3058, 1620, 1591, 1533, 486, 1463, 1339, 1320, 1292, 1150, 1112, 1094, 1068, 805, 766, 697 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.68 (s, 1H), 8.05 (s, 1H), 7.96 – 7.92 (m, 1H), 7.73 – 7.61 (m, 5H), 7.59 – 7.54 (m, 1H), 7.36 – 7.32 (m, 1H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 152.0, 140.7, 132.9, 130.3, 130.1, 130.0, 129.6 (q, *J* = 31 Hz), 125.8, 124.2 (q, *J* = 270 Hz), 121.8 (q, *J* = 1 Hz), 118.3 (q, *J* = 4 Hz), 114.4 (q, *J* = 4 Hz) ppm. HRMS (HESI/Orbitrap) *m/z*: [M + H]⁺ Calcd. for C₁₄H₁₁F₃N₅⁺ 306.0961; Found 306.0976.

***N*-phenyl-1-(3-(trifluoromethyl)phenyl)-1*H*-tetrazol-5-amine (7h)**. Following the general procedure **A**, compound **7h** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 9/1) as an orange powder (211 mg, 63%) from **5d** (250 mg, 1.17 mmol) and **6b** (115 μL, 1.10 mmol); m.p. 79 – 81 °C. IR (ATR) = 3192, 3081, 3038, 2997, 1613, 1572, 1532, 1495, 1470, 1451, 1334, 1313, 1250, 1161, 1135, 1098, 1073, 85, 749, 699 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.45 (s, 1H), 8.13 (s, 1H), 8.04 – 7.98 (m, 2H), 7.92 – 7.87 (m, 1H), 7.63 – 7.58 (m, 2H), 7.36 – 7.30 (m, 2H), 7.04 – 6.99 (m, 1H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 152.5, 139.7, 133.8, 131.3, 130.5 (q, *J* = 32 Hz), 130.1, 128.9, 126.9 (q, *J* = 4 Hz), 123.6 (q, *J* = 217 Hz), 123.1 (q, *J* = 4 Hz), 122.3, 118.4 ppm. HRMS (HESI/Orbitrap) *m/z*: [M + H]⁺ Calcd. for C₁₄H₁₁F₃N₅⁺ 306.0961; Found 306.0974.

***N*-(3-fluorophenyl)-1-phenyl-1*H*-tetrazol-5-amine (7i)**. Following the general procedure **A**, compound **7i** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 8/2) as an off-white powder (121 mg, 91%) from **5a** (90 mg, 0.56 mmol) and **6e** (58 μL, 0.52 mmol); m.p. 152 – 154 °C. IR (ATR): 3169, 3075, 2999, 2922, 1610, 1573, 1530, 1492, 1453, 1402, 1326, 1269, 1248, 1171, 1148, 1121, 1092, 1073, 1046, 1021, 992, 963, 924, 864, 824, 768, 727, 686, 631, 535 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.59 (s, 1H), 7.76 – 7.61 (m, 5H), 7.61 – 7.52 (m, 1H), 7.48 – 7.40 (m, 1H), 7.39 – 7.30 (m, 1H), 6.89 – 6.77 (m, 1H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 162.4 (d, *J* = 240 Hz), 152.0, 141.7 (d, *J* = 11 Hz), 132.9, 130.4 (d, *J* = 10 Hz), 130.2, 130.0, 125.7, 114.1 (d, *J* = 2 Hz), 108.4 (d, *J* = 21 Hz), 105.0 (d, *J* = 27 Hz) ppm. HRMS (HESI/Orbitrap) *m/z*: [M+H]⁺ Calcd. for C₁₃H₁₁FN₅⁺ 256.0993; Found 256.0993.

1-(3-Fluorophenyl)-*N*-phenyl-1*H*-tetrazol-5-amine (7j). Following the general procedure **A**, compound **7j** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 8/2) as an off-white powder (130 mg, 96%) from **5e** (100 mg, 0.560 mmol) and **6b** (55 μL, 0.53 mmol); m.p. 109 –

110 °C. IR (ATR) 3429, 3201, 3085, 3044, 2993, 2925, 1604, 1571, 1534, 1494, 1466, 1451, 1401, 1321, 1268, 1243, 1198, 1153, 1084, 1034, 1006, 984, 890, 865, 795, 747, 688, 523 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.38 (s, 1H), 7.74 – 7.60 (m, 4H), 7.57 – 7.47 (m, 2H), 7.37 – 7.29 (m, 2H), 7.05 – 6.99 (m, 1H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 162.2 (d, *J* = 244 Hz), 152.4, 139.7, 134.2 (d, *J* = 11 Hz), 131.7 (d, *J* = 9 Hz), 128.8, 122.2, 122.1 (d, *J* = 4 Hz), 118.4, 117.1 (d, *J* = 21 Hz), 113.5 (d, *J* = 25 Hz) ppm. HRMS (HESI/Orbitrap) *m/z*: [M + H]⁺ Calcd. for C₁₃H₁₁FN₅⁺ 256.0993; Found 256.0996.

***N*-(4-fluorophenyl)-1-phenyl-1*H*-tetrazol-5-amine (7k)**. Following the general procedure **A**, compound **7k** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 8/2) as an off-white powder (110 mg, 81%) from **5a** (100 mg, 0.559 mmol) and **6f** (55 μL, 0.53 mmol); m.p. 165 – 167 °C. IR (ATR): 3244, 3213, 3178, 3126, 3069, 3038, 3001, 2961, 2912, 2826, 2773, 1620, 1575, 1502, 1456, 1439, 1393, 1325, 1211, 1158, 1125, 1094, 1070, 1045, 1019, 992, 847, 814, 790, 770, 729, 692, 643, 621, 585, 506 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.35 (s, 1H), 7.84 – 7.44 (m, 7H), 7.24 – 7.10 (m, 2H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 157.5 (d, *J* = 237 Hz), 152.4, 136.2 (d, *J* = 2 Hz), 133.0, 130.1, 129.9, 125.6, 120.2 (d, *J* = 8 Hz), 115.3 (d, *J* = 23 Hz) ppm. HRMS (HESI/Orbitrap) *m/z*: [M+H]⁺ Calcd. for C₁₃H₁₁FN₅⁺ 256.0993; Found 256.0993.

1-(4-Fluorophenyl)-*N*-phenyl-1*H*-tetrazol-5-amine (7l). Following the general procedure **A**, compound **7l** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 8/2) as an off-white powder (118 mg, 87%) from **5f** (100 mg, 0.559 mmol) and **6b** (55 μL, 0.53 mmol); m.p. 145 – 147 °C. IR (ATR): 3260, 3207, 3125, 3095, 3060, 3010, 2940, 2866, 1620, 1575, 1539, 1508, 1462, 1422, 1322, 1228, 1184, 1157, 1127, 1094, 1039, 1014, 994, 889, 841, 807, 751, 693, 632, 597, 536, 501 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.29 (s, 1H), 7.80 – 7.70 (m, 2H), 7.66 – 7.58 (m, 2H), 7.55 – 7.47 (m, 2H), 7.36 – 7.28 (m, 2H), 7.03 – 6.97 (m, 1H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 162.7 (d, *J* = 246 Hz), 152.5, 139.8, 129.4 (d, *J* = 3 Hz), 128.8, 128.6 (d, *J* = 9 Hz), 122.1, 118.2, 116.9 (d, *J* = 23 Hz) ppm. HRMS (HESI/Orbitrap) *m/z*: [M+H]⁺ Calcd. for C₁₃H₁₁FN₅⁺ 256.0993; Found 256.0994.

***N*-(3-chlorophenyl)-1-phenyl-1*H*-tetrazol-5-amine (7m)**. Following the general procedure **A**, compound **7m** was obtained after dry-flash column chromatography (SiO₂: Hex/EtOAc = 8/2) as an off-yellow powder (60 mg, 88%) from **5a** (42 mg, 0.26 mmol) and **6g** (29 μL, 0.25 mmol); m.p. 114 – 117 °C. IR (ATR): 3233, 3160, 3072, 3033, 2974, 1612, 1595, 1566, 1527, 1496, 1479, 1455, 1091, 1072, 1020, 909, 872, 772, 766, 687 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.56 (s, 1H), 7.83 – 7.78

(m, 1H), 7.71 – 7.61 (m, 5H), 7.60 – 7.55 (m, 1H), 7.38 – 7.32 (m, 1H), 7.08 – 7.03 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 151.9, 141.4, 133.2, 132.9, 130.5, 130.2, 130.0, 125.7, 121.6, 117.6, 116.6 ppm. HRMS (HESI/Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd. for $\text{C}_{13}\text{H}_{11}\text{ClN}_5^+$ 272.0698; Found 272.0706.

1-(3-Chlorophenyl)-*N*-phenyl-1*H*-tetrazol-5-amine (7n). Following the general procedure **A**, compound **7n** was obtained after dry-flash column chromatography (SiO_2 : Hex/EtOAc = 8/2) as an off-yellow powder (58 mg, 85%) from **5g** (51 mg, 0.26 mmol) and **6b** (26 μL , 0.25 mmol); m.p. 96 – 98 $^\circ\text{C}$. IR (ATR): 3192, 3114, 3078, 3035, 2992, 2919, 1615, 1572, 1531, 1499, 1482, 1436, 1253, 1100, 1086, 787, 768, 749, 693 cm^{-1} . ^1H NMR (400 MHz, DMSO- d_6): δ 9.39 (s, 1H), 7.86 (s, 1H), 7.75 – 7.65 (m, 3H), 7.65 – 7.59 (m, 2H), 7.37 – 7.29 (m, 2H), 7.05 – 6.99 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 152.4, 139.7, 134.2, 134.0, 131.5, 130.2, 128.8, 126.0, 124.8, 122.2, 118.4 ppm. HRMS (HESI/Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd. for $\text{C}_{13}\text{H}_{11}\text{ClN}_5^+$ 272.0698; Found 272.0709.

***N*-(1-phenyl-1*H*-tetrazol-5-yl)pyridin-3-amine (7o).** Following the general procedure **A**, compound **7o** was obtained after dry-flash column chromatography (SiO_2 : Hex/EtOAc = 6/4) as a pale yellow powder (50 mg, 84%) from **5a** (42 mg, 0.26 mmol) and **6h** (24 μL , 0.25 mmol); m.p. 125 – 126 $^\circ\text{C}$. IR (ATR): 3258, 3051, 2962, 1611, 1570, 1532, 1499, 1486 cm^{-1} . ^1H NMR (400 MHz, DMSO- d_6): δ 9.58 (s, 1H), 8.82 – 8.78 (m, 1H), 8.25 – 8.20 (m, 1H), 8.13 – 8.08 (m, 1H), 7.73 – 7.63 (m, 5H), 7.40 – 7.35 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 152.1, 143.1, 140.4, 136.7, 132.9, 130.2, 130.0, 125.6, 125.1, 123.5 ppm. HRMS (HESI/Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_6^+$ 239.1040; Found 239.1044.

***N*-phenyl-1-(pyridin-3-yl)-1*H*-tetrazol-5-amine (7p).** Following the general procedure **A**, compound **7p** was obtained after dry-flash column chromatography (SiO_2 : Hex/EtOAc = 6/4) as a pale yellow powder (41 mg, 69%) from **5h** (43 mg, 0.26 mmol) and **6b** (26 μL , 0.25 mmol); m.p. 115 – 117 $^\circ\text{C}$. IR (ATR): 3263, 3205, 3121, 3090, 3044, 2924, 2853, 1611, 1571, 1533, 1501, 1434, 756, 696 cm^{-1} . ^1H NMR (400 MHz, DMSO- d_6): δ 9.48 (s, 1H), 8.94 – 8.88 (m, 1H), 8.86 – 8.79 (m, 1H), 8.20 – 8.14 (m, 1H), 7.74 – 7.69 (m, 1H), 7.66 – 7.59 (m, 2H), 7.37 – 7.30 (m, 2H), 7.05 – 6.99 (m, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 152.7, 151.0, 146.7, 139.6, 134.0, 130.2, 128.8, 124.7, 122.2, 118.3 ppm. HRMS (HESI/Orbitrap) m/z : $[\text{M}+\text{H}]^+$ Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_6^+$ 239.1040; Found 239.1050.

***N*-mesityl-1-phenyl-1*H*-tetrazol-5-amine (7q).** Following the general procedure **A**, compound **7q** was obtained after dry-flash column chromatography (SiO_2 : Hex/EtOAc = 8/2) as a pale yellow powder (18

mg, 27%) from **5a** (41 mg, 0.25 mmol) and **6i** (37 μ L, 0.24 mmol); m.p. 90 – 97 °C. IR (ATR): 3172, 3059, 2961, 2918, 2858, 1599, 1564, 1506, 1458, 1125, 1065, 760, 694 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.62 – 7.49 (m, 5H), 6.88 (s, 2H), 5.86 (s, 1H), 2.25 (s, 3H), 2.17 (s, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 153.7, 137.6, 135.2, 133.3, 131.9, 130.4, 130.2, 129.5, 124.4, 21.0, 18.4 ppm. HRMS (HESI/Orbitrap) m/z: $[\text{M}+\text{H}]^+$ Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_5^+$ 280.1557; Found 280.1567.

2-Chloro-N-(1-phenyl-1H-tetrazol-5-yl)pyrimidin-4-amine (7r). Following the general procedure **A**, compound **7r** was obtained after dry-flash column chromatography (SiO_2 : Hex/EtOAc = 8/2) colorless powder (30 mg, 44%) from **5a** (42 mg, 0.26 mmol) and **6j** (37 mg, 0.25 mmol).

Compounds 1-phenyl-1H-tetrazol-5-amine **5a** (42 mg, 0.26 mmol, 1.05 equiv) and 2,4-dichloropyrimidine **6j** (37 mg, 0.25 mmol, 1.0 equiv) were coupled in the presence of $\text{Pd}_2(\text{dba})_3$ (11 mg, 0.012 mmol, 10 mol % Pd), XantPhos (29 mg, 0.050 mmol, 20 mol %), K_2CO_3 (36 mg, 0.26 mmol, 1.05 equiv) and 1,4-dioxane (3.2 mL) at 35 °C in an oil bath for 24 h. Compound **7r** was obtained after dry-flash column chromatography (SiO_2 : Hex/EtOAc = 8/2) as a colorless powder (43 mg, 63%); m.p. 140 – 141 °C. IR (ATR): 3228, 3134, 3045, 2980, 2917, 1613, 1589, 1523, 1506, 1486, 1456, 1413, 1356, 1333, 1212, 988, 830, 769, 699, 682, 546 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 8.56 (d, $J = 4$ Hz), 8.31 (d, $J = 4$ Hz), 7.71 – 7.64 (m, 3H), 7.56 – 7.49 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 161.0, 158.8, 149.6, 149.6, 131.8, 131.6, 131.0, 125.3, 106.8 ppm. HRMS (HESI/Orbitrap) m/z: $[\text{M}+\text{H}]^+$ Calcd. for $\text{C}_{11}\text{H}_9\text{ClN}_7^+$ 274.0602; Found 274.0616.

General procedure for Dimroth-like rearrangement. General procedure B.

A flame-dried reaction tube charged with compound **7** (10 mg) and 1,4-dioxane (0.5 mL) was sealed and the mixture was heated at 105 °C in an oil bath for 24 h. The reaction mixture was cooled to room temperature and the solvent was removed under the reduced pressure. Isomer ratio was determined by NMR spectroscopy (Table 3).

NMR spectroscopic analysis in DMSO- d_6 :

A flame-dried reaction tube charged with compound **7** (10 mg) and $\text{DMSO-}d_6$ (0.5 mL) was sealed and the mixture was heated at 105 °C in an oil bath for 24 h. The reaction mixture was cooled to room temperature. Isomer ratio was determined by NMR spectroscopy (Table 3).

N¹-(1-phenyl-1H-tetrazol-5-yl)benzene-1,4-diamine (7t). A flame-dried round-bottom reaction flask was charged with compound **7c** (15 mg, 0.053 mmol, 1 equiv) and deoxygenated methanol (1 mL) after which Pd/C (3 mg, 0.003 mmol, 5 mol % Pd) was added. The flask was closed with a rubber septum and the reaction mixture, connected to a balloon of hydrogen, was stirred at room temperature for 2 h.

The reaction mixture was filtered and the solvent was removed under the reduced pressure to afford the pure **7t** as an orange powder (13 mg, quant.); m.p. 93 – 94 °C. IR (ATR) = 3344, 1609, 1575, 1517, 1497, 1458, 763 cm⁻¹. ¹H NMR (500 MHz, CD₃OD): δ 7.65 – 7.58 (m, 5H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H) ppm. ¹³C{¹H} NMR (125 MHz, CD₃OD): δ 155.1, 145.4, 134.7, 131.4, 131.2, 131.1, 126.3, 123.5, 117.0 ppm. HRMS (HESI/Orbitrap) m/z: [M + H]⁺ Calcd. for C₁₃H₁₃N₆⁺ 253.1196; Found 253.1208.

1-(4-Aminophenyl)-*N*-phenyl-1*H*-tetrazol-5-amine (7u). Following the procedure described for the **7t**, compound **7u** was obtained as a yellow solid (10 mg, quant) starting from **7d** (12 mg, 0.041 mmol, 1 equiv); m.p. 138 – 140 °C. IR (ATR) = 3640, 3476, 3063, 3254, 3236, 1610, 1576, 1528, 1501, 1319, 836 cm⁻¹. ¹H NMR (500 MHz, CD₃OD): δ 7.54 – 7.50 (m, 2H), 7.32 – 7.27 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.05 – 7.00 (m, 1H), 6.84 (d, *J* = 8.7 Hz, 2H) ppm. ¹³C{¹H} NMR (125 MHz, CD₃OD): δ 154.4, 151.8, 140.9, 130.0, 127.9, 123.9, 123.0, 120.0, 116.1 ppm. HRMS (HESI/Orbitrap) m/z: [M + H]⁺ Calcd. for C₁₃H₁₃N₆⁺ 253.1196; Found 253.1206.

Dimroth-like rearrangement of 7t to 7u.

A flame-dried reaction tube charged with compound **7t** (13 mg, 0.053 mmol) and 1,4-dioxane (0.5 mL) was sealed and the mixture was heated at 105 °C in an oil bath for 24 h. The reaction mixture was cooled to room temperature and the solvent was removed under the reduced pressure. NMR spectroscopy analysis showed a complete conversion of **7t** to **7u**.

COMPUTATIONAL METHODS

All DFT calculations were done with the Orca program package (version 4.1.2).²⁶ The def2-TZVP(-f) basis set was used for all atoms. The SMD solvation model (with dioxane as solvent)²⁷ was used in all calculations. Geometry optimizations were performed using general gradient functional consisting of Becke's exchange²⁸ and LYP correlation,²⁹ with Grimme's fourth-generation dispersion energy corrections,³⁰ i.e., BLYP-D4 functional. The resolution-of-the-identity approximation in the Split-RI-J variant and def2/J auxiliary basis sets was used. Numerical harmonic frequencies were calculated at the same level of theory to ascertain the nature of stationary points (minima or transition states). Vibrational analysis in quasi-harmonic approximation as proposed by Truhlar,³¹ with frequency cutoff 100 cm⁻¹, has been used to evaluate zero-point effects, entropic and thermal corrections to the Gibbs free energy. To assess the impact of the hybrid functional, single-point energies were computed with B3LYP-D4,³² with the chain-of-spheres approximation to the exact exchange, on the optimized BLYP-D4/def2-TZVP(-f) geometries (see the Supporting Information, Table S3).

ASSOCIATED CONTENT

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

Copies of ^1H and ^{13}C NMR spectra for the synthesized compounds (PDF)

Extended computational results, total electronic energies, number of imaginary frequencies and Cartesian coordinates of all structures.

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Notes

The authors declare no competing financial interest.

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