Reactivity of N-protected 5-(2-bromophenyl)tetrazoles in palladium-catalyzed direct arylation of heteroarenes or fluorobenzenes

Sabah Chikhi, Safia Djebbar, Jean-François Soulé, Henri Doucet

► To cite this version:

Sabah Chikhi, Safia Djebbar, Jean-François Soulé, Henri Doucet. Reactivity of N-protected 5-(2-bromophenyl)tetrazoles in palladium-catalyzed direct arylation of heteroarenes or fluorobenzenes. *Journal of Organometallic Chemistry*, 2017, 831, pp.55-63. 10.1016/j.jorganchem.2016.12.026 . hal-01475812

HAL Id: hal-01475812

<https://hal-univ-rennes1.archives-ouvertes.fr/hal-01475812>

Submitted on 11 Apr 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Reactivity of *N*-Protected 5-(2-Bromophenyl)tetrazoles in Palladium-Catalyzed Direct Arylation of Heteroarenes or Fluorobenzenes

Sabah Chikhi,^{a,b} Safia Djebbar,^b Jean-François Soulé,^{a*} Henri Doucet^{a*}.

^a UMR 6226 CNRS-Université de Rennes 1 "Organométalliques, Matériaux et Catalyse", Campus de Beaulieu, 35042 Rennes, France.

^b Laboratoire d'Hydrométallurgie et Chimie Inorganique Moléculaire, Faculté de Chimie U.S.T.H.B. Bab-Ezzouar, Alger, Algeria.

KEYWORDS. Palladium, Heterocycles, Aryl Bromides, Tetrazoles, Catalysis, C–H Activation.

ABSTRACT. A new route allowing the one-step synthesis of (2-heteroarylphenyl)tetrazole and fluorinated biphenyltetrazole derivatives is disclosed. By using 2 mol% of an air-stable diphosphine-palladium catalyst [PdCl(C₃H₅)(dppb)], potassium pivalate as base and dimethylacetamide as solvent, a wide range of heteroarenes (*e.g.*, thiazoles, (benzo)thiophenes, furans, pyrroles, and imidazo[1,2-*a*]pyridine) and polyfluorobenzenes was easily coupled with *N*-protected (2-bromophenyl)tetrazoles in high yields.

INTRODUCTION

Angiotensin II receptor blockers (ARBs) are an important class of medicinal drugs, which modulate the renin–angiotensin system, prescribed to regulate the high blood pressure, or used in case of diabetic nephropathy or against congestive heart failure. Nonpeptide ARBs based on a biphenyltetrazole motif, such as Losartan and Candesartan, have emerged as highly effective antihypertensives, which could be orally administered (Figure 1).^[1] Embusartan is an analogue containing a fluorinated biphenyl unit,^[2] and Zolarsartan contains an heteroaromatic ring (benzofuran) as spacer (Figure 1).^[3] Due to their wide use and relatively high cost, the discovery of new routes for the synthesis of ARBs represents a major socio-economic challenge for pharmaceutical companies and an important challenge for academic research groups.

Figure 1. Structure of Angiotensin II Receptor Blockers

One of the most widespread disconnections of the 5-biphenyl tetrazole motif involves the C–C bond between the two phenyls of the biphenyl unit. Therefore, palladium-catalyzed cross-coupling reactions using aryl halides in the presence of nucleophilic organometallic or main group element reagents, represent an appropriate approach for their preparation.^[4] In recent years, the transition metal-catalyzed direct arylation, *via* a C–H bond activation, has become one of the most sustainable methods for the C–C bond formation.^[5] Indeed, compared to other classical transition metal-catalyzed reactions such as Stille, Suzuki or Negishi couplings, they do not require the preliminary synthesis of organometallic derivatives, and only HX associated to a base is generated as by-product. In this line, Seki described an elegant approach for the synthesis of 5-biaryltetrazole derivatives involving ruthenium-catalyzed *ortho* C–H bond arylation of *N*-protected 5-phenyltetrazole in the presence of aryl bromides.^[6] The reaction proceeds in high yield using hydrated-RuCl₃ associated to PPh₃ as catalytic system in the presence of potassium carbonate as base in *N*-methylpyrrolidone. However, only 4-bromobenzyl acetate has been used as substrate leading to Valsartan in only a few steps. [RuCl₂(C₆H₆)]₂ was also found to be a very efficient catalyst for the C–H bond activation/arylation of *N*-protected 5-phenyltetrazoles and was applied to the synthesis of Losartan.^[7] Using the same strategy, but with [RuCl₂(*p*-cymene)]₂ as catalyst, Seki described the environmental-friendly total synthesis of Candesartan Cilxetil.^[8] In 2013, Akermann and co-workers demonstrated a significant rate-acceleration by using carboxylates as additives, in ruthenium(II)-catalyzed C–H bond arylation of 5-aryltetrazoles. They employed a very broad substrate scope including two heteroaryl bromides (2-bromothiophene and 3-bromopyridine).^[9] To our knowledge, the reverse C–H bond functionalization strategy, namely the use of 5-(2-bromophenyl)tetrazole derivatives and (hetero)arenes has not yet been described, although it could open a new route to the straightforward synthesis of novel (2-heteroarylphenyl)tetrazole and fluorinated biphenyltetrazole analogues. From this consideration, we decided to explore the reactivity of different *N*-protected 5-(2-bromophenyl)tetrazoles in the palladium-catalyzed direct arylation in the presence of a wide range of heteroarenes and fluorobenzenes.

RESULTS AND DISCUSSION

First, the reaction between 5-(2-bromophenyl)tetrazole and 2-ethyl-4-methylthiazole was attempted in the presence of 2 mol% of Pd(OAc)₂ or PdCl(C₃H₅)(dppb) as catalysts associated to 2 equivalents of potassium acetate (KOAc) in DMA. However, no formation of the desired coupling product was detected. We attributed this lack of reactivity to the free NH of the tetrazole moiety, which might poison the palladium catalyst by coordination. Therefore, we decided to protect the tetrazole using different protecting group. 5-(2-Bromophenyl)tetrazole was treated by 2 equivalents of sodium hydride in DMF, then benzyl

bromide, pivaloyl chloride, or methyl iodide were introduced to furnish the desired *N*-protected 5-(2-bromophenyl)tetrazoles **1a-1c** in good yields (Scheme 1).

Scheme 1. Protection of 5-(2-bromophenyl)tetrazole.

Having the *N*-protected 5-(2-bromophenyl)tetrazoles **1a-1c** in hand, we next evaluated their reactivities in Pd-catalyzed direct arylation with a set of (hetero)arenes. *N*-benzyl-5-(2-bromophenyl)tetrazole **1a** was firstly used as aryltetrazole source (Scheme 2). The arylation of 2-ethyl-4-methylthiazole occurred at C5 position in the presence of 2 mol% of PdCl(C₃H₅)(dppb) associated to 2 equivalents of PivOK in DMA to allow the synthesis of **2** in 75% yield. It is important to note that the use of KOAc as base or Pd(OAc)₂ as catalyst was less effective than the use of PivOK or of PdCl(C₃H₅)(dppb), as under these conditions, **2** was obtained in only 12% or 34% yields, respectively. Using 2 mol% PdCl(C₃H₅)(dppb), PivOK in DMA as reactions conditions, 2-isobutylthiazole was also arylated at C5 position to give the coupling product **3** in 79% yield. Then, we turned our attention to the formation of 5-(2-(thiophen-2-yl)phenyl)tetrazole, which is also an important motif, as some of these analogues display biological properties in regulation of blood pressure acting on the Angiotensin II receptors.^[10] 2-Methylthiophene, 2-acetyl-3-methylthiophene or benzothiophene were arylated at their C5 or C2 positions to allow the formation of phenyl(benzo)thiophene analogues **4-6** in 69-74% yields. Furans are also suitable coupling partners. For examples, 2-*n*-butylfuran and 2-butanoylfuran in the presence of *N*-benzyl-5-(2-bromophenyl)tetrazole **1a** were arylated at C5 position to deliver the 5-(2-(furan-2-yl)phenyl)tetrazole derivatives **7** and **8** in 82% and 88% yields, respectively. *N*-Methylpyrrole was also successfully coupled with **1a**, but 4 equivalents of this reactant were used to prevent the 2,5-diarylation of pyrrole, affording selectively the C2-arylated product **9** in an excellent yield. Imidazo[1,2-*a*]pyridine is a heterocycle present in many pharmaceutical products. *N*-Benzyl-5-(2-bromophenyl)tetrazole **1a** smoothly reacted with imidazo[1,2-*a*]pyridine to afford **10** in 98% yield. Polyfluorinated molecules are ubiquitous in medicinal chemistry, owing to fluorine atom properties (i.e., electronegativity, size, lipophilicity, and electrostatic interactions), which induce a dramatic change in the molecules behavior. However, the introduction of fluorine atoms at specific positions of a molecule remains challenging. Alternatively, the use of starting materials containing fluorine atoms in palladium-catalyzed C-H bond arylations offers straightforward routes to (poly)fluorinated molecules.^[11] We used similar reaction conditions to those we had previously described for the direct arylation of fluorobenzene derivatives.^[11b] Such conditions promoted the coupling of pentafluorobenzene with **1a** allowing the formation of **11** in 75% yield. The reaction was also performed with 3,5-difluorobenzonitrile, and the single regioisomer **12** was isolated in 67% yield. As expected, the arylation took place at the position flanked by the two fluorine atoms, which is known to be the most reactive site under concerted metalation-deprotonation mechanism.^[12] It is important to note that, after benzyl deprotection and nitrile reduction into an amino group, the derivative **12** could represent an intermediate for the preparation of fluorinated analogues of Losartan, Candesartan, or Embusartan (*c.f.*, Figure 1).

Scheme 2. Scope of (Hetero)Arenes in Pd-Catalyzed direct Arylation of **1a**. [a] $\text{Pd}(\text{OAc})_2$ (2 mol%) was used instead of $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$. [b] KOAc was used instead of PivOK. [c] 4 Equiv. of *N*-methylpyrrole were used.

Next, we investigated the reactivity of 5-(2-bromophenyl)-1-pivaloyltetrazole **1b** as aryl source in Pd-catalyzed direct arylation of a set of heteroarenes and polyfluorobenzenes (Scheme 3). In contrast to the benzyl protecting group that can be removed by Pd-catalyzed hydrogenolysis,^[13] pivaloyl protected tetrazoles can be deprotected under reductive conditions.^[14] In almost all cases, higher yields were obtained with the pivaloyl tetrazole **1b** than with **1a**, which bears a benzyl as protecting group. This higher reactivity might be explained by the electron withdrawing character of the pivaloyl group. Indeed, thiazole derivatives were easily coupled with **1b**, affording **13** and **14** in 88% and 91% yields, respectively. 2-Methylthiophene, 2-acetyl-4-methylthiophene and benzothiophene also displayed high reactivities, as the desired products **15-17** were isolated in very high yields. The *N*-protected 5-(2-(furan-2-yl)phenyl)tetrazoles **18** and **19** were obtained in 95% and 97% yields from 2-*n*-butylfuran and 2-butyrylfuran, respectively. Again, *N*-methylpyrrole was found to be a suitable coupling partner, albeit 4 equivalents were required to afford **20** in an excellent yield, without formation of the 2,5-diarylated pyrrole. Fluorinated biphenyls were also synthesized by this route. The C–H bond activation of 1,2,3,4-tetrafluorobenzene led to **21** in 67% yield.

Scheme 3. Scope of (hetero)arenes in Pd-catalyzed direct arylation of **1b**. [a] 4 Equiv. of *N*-methylpyrrole were used.

Fluorinated biphenyl **21** contains a reactive C–H bond in palladium catalysis (i.e., C–H bond flanked by two fluorine atoms). Hence, the direct arylation of this reactive C–H bond was attempted using 4-bromobenzonitrile. In the presence of the previous reaction conditions, namely 2 mol% PdCl(C₃H₅)(dppb) associated to 2 equivalents of PivOK in DMA, the triphenyl derivative **22** was obtained in 63% yield (Scheme 4). This compound could allow, after reduction of the nitrile group, the formation of analogues of Losartan, which contains a 1,2,3,4-tetrafluorophenyl unit as spacer.

Scheme 4. Direct Arylation of **21**.

N-Methyl tetrazoles are very important motifs, embedded in many compounds with wide range of applications in materials for energy,^[15] bioorganic chemistry,^[16] and pharmacology.^[17] Therefore, we decided to examine the reactivity of 5-(2-bromophenyl)-1-methyltetrazole **1c** as coupling partner in the presence of a set of heteroarenes and polyfluorobenzenes, for the efficient synthesis of *N*-methyl 5-((hetero)biphenyl-2-yl)-tetrazole derivatives (Scheme 5). Again, thiazoles were arylated at C5 position allowing the formation

of the 5-(2-(thiazol-5-yl)phenyl)tetrazole **23** and **24** in 89% and 93% yields. 2-*n*-Pentylthiophene also displayed a high reactivity in such couplings, as C5-arylated thiophene **25** was isolated in 81% yield. Furans such as 2-methylfuran and 1-(furan-2-yl)propan-2-one were smoothly arylated at the C5 position with **1c** to deliver the coupling products **26** and **27** in 90% and 86% yields, respectively. It is important to note that the acidic $\text{sp}^3\text{-C-H}$ bonds at *ortho* position of ketone function of 1-(furan-2-yl)propan-2-one was not reactive under these reaction conditions, as no other coupling product than **27** was detected in the crude mixture. Again the reaction between **1c** and 4 equivalents of *N*-methylpyrrole afforded C2-arylated pyrrole **28** in an excellent yield of 93%. Finally, the synthesis of 5-([biphenyl]-2-yl)-1-methyltetrazole was surveyed. From pentafluorobenzene, 1,2,3,4-tetrafluorobenzene and 3,5-difluorobenzonitrile, the desired fluorinated biphenyls **29-31** were obtained in 65-70% yields, through the activation of the C-H bond flanked by the two fluorine atoms.

Scheme 5. Scope of (hetero)arenes in Pd-catalyzed direct arylation of **1c**. [a] 4 Equiv. of *N*-methylpyrrole were used.

CONCLUSION

In summary, this study demonstrates that *N*-protected 5-(2-bromophenyl)tetrazoles can be efficiently coupled with a wide variety of heteroarenes (e.g., thiazoles, (benzo)thiophenes, furans, *N*-methylpyrrole, imidazo[1,2-*a*]pyridine) under $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$ -catalyzed C-H bond arylation procedure. This procedure which employs an air-stable catalyst and an inexpensive base is efficient, rapid and environmentally attractive. The major by-products are pivalic acid and potassium bromide, instead of the metallic salts produced with more classical cross-coupling reactions such as Suzuki, Stille or Negishi couplings. Moreover, the preparation of an organometallic reagent is not required, reducing the number of steps and therefore the amount of waste in the preparation of these molecules. This methodology is an efficient tool for the synthesis of phenyltetrazoles *ortho*-substituted by heteroarenes or the synthesis of fluorinated biphenyltetrazoles, and as all the products which have been synthesized by this procedure are new, it could attract interest of medicinal chemists.

EXPERIMENTAL SECTION

All reactions were carried out under argon atmosphere with standard Schlenk techniques. DMA (*N,N*-dimethylacetamide) (99%) was purchased from Acros. $[\text{Pd}(\text{C}_3\text{H}_5\text{Cl})_2]$ (56.5%) and dppb [1,4-bis(diphenylphosphino)butane] (98%) were purchased from Alfa Aesar. These compounds were not purified before use. ^1H NMR spectra were recorded on Bruker GPX (400 or 300 MHz) spectrometer. Chemical shifts (δ) were reported in parts per million relative to residual CDCl_3 (7.26 ppm (s) ppm for ^1H ; 77.0 ppm for ^{13}C), constants were reported in Hertz. ^1H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ^{13}C NMR spectra were recorded at 100 or 75 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

Preparation of the $\text{PdCl}(\text{dppb})(\text{C}_3\text{H}_5)$ catalyst:^[18] An oven-dried 40-mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[\text{Pd}(\text{C}_3\text{H}_5\text{Cl})_2]$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The yellow powder was used without purification. ^{31}P NMR (81 MHz, CDCl_3) δ (ppm) = 19.3 (s).

1-Benzyl-5-(2-bromophenyl)tetrazole (1a): To a stirred suspension of NaH (60% in oil, 0.80 g, 20 mmol) in DMF (20 mL) was added in small portions 5-(2-bromophenyl)tetrazole (2.25 g, 10 mmol) at 0 °C, and the mixture was stirred at RT for about 1 hour until NaH disappearance. To this sodio tetrazole mixture, benzyl bromide (2.05 g, 12 mmol) was added and the resulting mixture was stirred at RT for 12 h. Then, the reaction mixture was quenched with saturated NH_4Cl solution (25 mL), diluted with water (25 mL), and extracted with AcOEt (3 x 50 mL). The organic phase was washed with brine (50 mL), dried (Na_2SO_4) and filtered. After removal of all volatiles, the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 85:15) to afford **1a** (2.80 g, 89%) as a white solid (mp = 45-47 °C). ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.86 (dd, J = 1.8 and 8.0 Hz, 1H), 7.75 (dd, J = 1.2 and 8.0 Hz, 1H), 7.50 – 7.37 (m, 6H), 7.37 – 7.30 (m, 1H), 5.87 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 164.4, 134.1, 133.2, 131.7, 131.2, 129.0, 129.0, 128.6, 128.4, 127.4, 122.1, 56.9. Elemental analysis: calcd (%) for $\text{C}_{14}\text{H}_{11}\text{BrN}_4$ (315.17): C 53.35, H 3.52; found: C 53.45, H 3.21.

5-(2-Bromophenyl)-1-pivalyltetrazole (1b): To a stirred suspension of NaH (60% in oil, 0.80 g, 20 mmol) in DMF (20 mL) was added in small portions 5-(2-bromophenyl)tetrazole (2.25 g, 10 mmol) at 0 °C, and the mixture was stirred at RT for about 1 hour until NaH disappearance. To this sodio-tetrazole mixture, pivaloyl chloride (1.45 g, 12 mmol) was added and the resulting mixture was stirred at RT for 12 h. Then, the reaction mixture was quenched with saturated NH_4Cl solution (25 mL), diluted with water (25 mL), and extracted with AcOEt (3 x 50 mL). The organic phase was washed with brine (50 mL), dried (Na_2SO_4) and filtered. After removal of all volatiles, the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 85:15) to afford **1b** (2.41 g, 78%) as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.96 (dd, J = 1.8 and 7.7 Hz, 1H), 7.76 (dd, J = 1.3 and 8.0 Hz, 1H), 7.47 (dt, J = 1.3 and 7.5 Hz, 1H), 7.40 (dd, J = 1.8 and 7.9 Hz, 1H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 173.8, 163.6, 134.4, 132.3, 131.7, 127.5, 125.8, 121.6, 32.5, 28.2. Elemental analysis: calcd (%) for $\text{C}_{12}\text{H}_{13}\text{BrN}_4\text{O}$ (309.17): C 46.62, H 4.24; found: C 46.89, H 4.31.

5-(2-Bromophenyl)-1-methyltetrazole (1c): To a stirred suspension of NaH (60% in oil, 0.80 g, 20 mmol) in DMF (20 mL) was added in small portions 5-(2-bromophenyl)tetrazole

(2.25 g, 10 mmol) at 0 °C, and the mixture was stirred at RT for about 1 hour until NaH disappearance. To this sodio-tetrazole mixture, methyl iodide (1.70 g, 12 mmol) was added and the resulting mixture was stirred at RT for 12 h. Then, the reaction mixture was quenched with saturated NH₄Cl solution (25 mL), diluted with water (25 mL), and extracted with AcOEt (3 x 50 mL). The organic phase was washed with brine (50 mL), dried (Na₂SO₄) and filtered. After removal of all volatiles, the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 85:15) to afford **1c** (2.18 g, 91%) as a white solid (mp = 43-45 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.84 (dd, *J* = 1.8 and 7.7 Hz, 1H), 7.73 (dd, *J* = 1.3 and 8.0 Hz, 1H), 7.42 (dt, *J* = 1.3 and 7.6 Hz, 1H), 7.32 (dd, *J* = 1.8 and 7.6 Hz, 1H), 4.43 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 164.3, 134.1, 131.7, 131.2, 128.5, 127.5, 122.0, 39.7. Elemental analysis: calcd (%) for C₈H₇BrN₄ (239.08): C 40.19, H 2.95; found: C 40.28, H 3.06.

General Procedure. As a typical experiment, the reaction of the *N*-protected 5-(2-bromophenyl)tetrazole (0.5 mmol), (hetero)arene (0.75 mmol), and PivOK (140 mg, 1 mmol) at 150 °C over 16 h in 2 mL of DMA in the presence of PdCl(C₃H₅)(dppb) (6.1 mg, 0.01 mmol), under argon affords the coupling product after evaporation of the solvent and purification on silica gel.

5-(2-(1-Benzyltetrazol-5-yl)phenyl)-2-ethyl-4-methylthiazole (2): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and 2-ethyl-4-methylthiazole (95 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **2** (136 mg, 75%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.05 – 7.94 (m, 1H), 7.55 – 7.47 (m, 2H), 7.47 – 7.42 (m, 1H), 7.40 – 7.32 (m, 3H), 7.27 (dt, *J* = 2.4 and 6.8 Hz, 2H), 5.67 (s, 2H), 2.97 (q, *J* = 7.6 Hz, 2H), 1.95 (s, 3H), 1.36 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 170.7, 164.8, 148.4, 133.2, 132.4, 131.5, 130.0, 129.8, 128.9, 128.9, 128.7, 128.4, 128.3, 128.1, 56.7, 26.8, 15.2, 14.2. Elemental analysis: calcd (%) for C₂₀H₁₉N₅S (361.46): C 66.46, H 5.30; found: C 66.59, H 5.11.

5-(2-(1-Benzyltetrazol-5-yl)phenyl)-2-isobutylthiazole (3): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and 2-isobutylthiazole (106 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **3** (148 mg, 79%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.86 – 7.78 (m, 1H), 7.56 – 7.52 (m, 1H), 7.49 (td, *J* = 1.9 and 7.0 Hz, 2H), 7.46 (s, 1H), 7.39 – 7.30 (m, 5H), 5.72 (s, 2H), 2.79 (d, *J* = 7.2 Hz, 2H), 2.05 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 170.6, 164.8, 140.8, 135.6, 133.2, 131.4, 131.3, 130.7, 130.1, 129.0, 128.9, 128.5, 128.3, 127.1, 56.8, 42.3, 29.8, 22.3. Elemental analysis: calcd (%) for C₂₁H₂₁N₅S (375.49): C 67.17, H 5.64; found: C 67.31, H 5.56.

1-Benzyl-5-(2-(5-methylthiophen-2-yl)phenyl)tetrazole (4): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and 2-methylthiophene (74 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **4** (120 mg, 72%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.70 (d, *J* = 7.7 Hz, 1H), 7.57 (dd, *J* = 1.5 and 7.7 Hz, 1H), 7.50 (dt, *J* = 1.5 and 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.40 – 7.31 (m, 5H), 6.59 (d, *J* = 3.5 Hz, 1H), 6.55 (d, *J* = 3.5 Hz, 1H), 5.77 (s, 2H), 2.42 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 165.4, 140.4, 139.3, 135.1, 133.5, 130.8, 130.0, 128.9, 128.8, 128.8, 128.3, 127.5, 126.8, 126.5, 125.3, 56.7, 15.3. Elemental analysis: calcd (%) for C₁₉H₁₆N₄S (332.43): C 68.65, H 4.85; found: C 68.98, H 5.10.

1-(5-(2-(1-Benzyltetrazol-5-yl)phenyl)-4-methylthiophen-2-yl)ethan-1-one (5): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and 1-(4-methylthiophen-2-yl)ethan-1-one (105 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 60:40) to afford the desired compound **5** (139 mg, 74%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.08 – 8.01 (m, 1H), 7.60 – 7.49 (m, 2H), 7.46 – 7.40 (m, 1H), 7.37 – 7.33 (m, 3H), 7.32 (s, 1H), 7.27 – 7.21 (m, 2H), 5.66 (s, 2H), 2.52 (s, 3H), 1.71 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 190.6, 164.8, 145.5, 141.9, 136.4, 134.8, 133.3, 132.8, 132.0, 130.0, 130.0, 129.2, 129.0, 128.5, 127.8, 56.8, 26.8, 14.1. Elemental analysis: calcd (%) for C₂₁H₁₈N₄OS (374.46): C 67.36, H 4.85, found: C 67.49, H 5.19.

5-(2-(Benzo[b]thiophen-2-yl)phenyl)-1-benzyltetrazole (6): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and benzo[b]thiophene (101 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 80:20) to afford the desired compound **6** (127 mg, 69%) as a yellow solid (mp = 76–78 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.85 (dd, *J* = 1.2 and 7.1 Hz, 1H), 7.76 (ddd, *J* = 0.8, 1.8 and 7.0 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.60 – 7.47 (m, 2H), 7.42 – 7.31 (m, 2H), 7.30 – 7.23 (m, 1H), 7.20 – 7.15 (m, 4H), 7.08 (s, 1H), 5.68 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 165.0, 142.2, 140.5, 140.0, 134.7, 133.1, 131.4, 130.7, 130.1, 128.8, 128.7, 128.5, 128.2, 127.1, 124.2, 124.1, 123.7, 123.6, 122.1, 56.7. Elemental analysis: calcd (%) for C₂₂H₁₆N₄S (368.45): C 71.71, H 4.38, found: C 72.00, H 4.39.

1-Benzyl-5-(2-(5-butylfuran-2-yl)phenyl)tetrazole (7): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and 2-*n*-butylfuran (93 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 80:20) to afford the desired compound **7** (147 mg, 82%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.73 (dd, *J* = 1.3 and 7.9 Hz, 1H), 7.61 (dd, *J* = 1.4 and 7.7 Hz, 1H), 7.51 (dt, *J* = 1.4 and 7.7 Hz, 1H), 7.47 – 7.37 (m, 4H), 7.36 (dd, *J* = 1.3 and 7.6 Hz, 1H), 6.01 (d, *J* = 3.2 Hz, 1H), 5.90 (d, *J* = 3.2 Hz, 1H), 5.82 (s, 2H), 2.43 (t, *J* = 7.6 Hz, 2H), 1.55 – 1.40 (m, 2H), 1.39 – 1.21 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 165.8, 156.6, 150.2, 133.4, 131.3, 131.1, 130.1, 129.0, 128.9, 128.5, 127.7, 127.0, 124.4, 109.4, 106.5, 56.7, 30.0, 27.6, 22.2, 13.8. Elemental analysis: calcd (%) for C₂₂H₂₂N₄O (358.44): C 73.72, H 6.19, found: C 74.02, H 6.37.

1-(5-(2-(1-Benzyltetrazol-5-yl)phenyl)furan-2-yl)butan-1-one (8): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and 1-(furan-2-yl)butan-1-one (104 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **8** (164 mg, 88%) as a brown yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.86 – 7.70 (m, 2H), 7.58 (dt, *J* = 1.5 and 7.6 Hz, 1H), 7.52 (dt, *J* = 1.4 and 7.6 Hz, 1H), 7.42 – 7.35 (m, 5H), 7.09 (d, *J* = 3.6 Hz, 1H), 6.28 (d, *J* = 3.7 Hz, 1H), 5.78 (s, 2H), 2.50 (t, *J* = 7.3 Hz, 2H), 1.63 (sext., *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 189.5, 165.0, 155.6, 152.3, 133.1, 131.1, 130.3, 129.6, 129.2, 129.2, 129.1, 129.1, 128.5, 125.9, 117.8, 111.0, 56.9, 40.1, 17.6, 13.8. Elemental analysis: calcd (%) for C₂₂H₂₀N₄O₂ (372.42): C 70.95, H 5.41, found: C 71.28, H 5.17.

1-Benzyl-5-(2-(1-methylpyrrol-2-yl)phenyl)tetrazole (9): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and *N*-methylpyrrole (162 mg, 2 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **9** (145 mg, 92%) as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.12 – 7.97 (m, 1H), 7.58 – 7.45 (m, 3H), 7.42 – 7.36 (m, 3H), 7.36 – 7.28

(m, 2H), 6.60 – 6.50 (m, 1H), 6.22 – 6.13 (m, 1H), 6.04 (dd, J = 1.8 and 3.5 Hz, 1H), 5.69 (s, 2H), 3.06 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 165.3, 133.4, 132.9, 132.5, 132.5, 129.8, 129.6, 128.9, 128.8, 128.6, 128.2, 128.1, 122.1, 108.7, 107.4, 56.6, 33.9. Elemental analysis: calcd (%) for $\text{C}_{19}\text{H}_{17}\text{N}_5$ (315.37): C 72.36, H 5.43, found: C 72.36, H 5.22.

3-(2-(1-Benzyltetrazol-5-yl)phenyl)imidazo[1,2-*a*]pyridine (10): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and imidazo[1,2-*a*]pyridine (89 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 70:30) to afford the desired compound **10** (173 mg, 98%) as a yellow solid (mp = 170-172 °C). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.35 – 8.21 (m, 1H), 7.67 – 7.58 (m, 4H), 7.59 – 7.53 (m, 1H), 7.43 (d, J = 7.0 Hz, 1H), 7.35 – 7.23 (m, 3H), 7.07 (ddd, J = 1.3, 6.7 and 9.2 Hz, 1H), 7.05 – 6.98 (m, 2H), 6.45 (dd, J = 6.7 and 6.8 Hz, 1H), 5.42 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 164.2, 145.4, 132.9, 132.9, 132.7, 130.6, 130.0, 129.5, 128.9, 128.8, 128.4, 127.7, 127.7, 124.4, 123.9, 123.6, 117.7, 111.8, 56.6. Elemental analysis: calcd (%) for $\text{C}_{21}\text{H}_{16}\text{N}_6$ (352.39): C 71.58, H 4.58, found: C 71.69, H 4.37.

1-Benzyl-5-(2',3',4',5',6'-pentafluoro-[1,1'-biphenyl]-2-yl)tetrazole (11): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and pentafluorobenzene (126 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 70:30) to afford the desired compound **11** (151 mg, 75%) as a yellow solid (mp = 99-102 °C). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.29 (dd, J = 1.6 and 7.9 Hz, 1H), 7.64 (dt, J = 1.6, 7.6 Hz, 1H), 7.59 (dt, J = 1.6, 7.5 Hz, 1H), 7.47 – 7.34 (m, 4H), 7.28 – 7.21 (m, 2H), 5.67 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 164.2, 144.3 (dm, J = 253.1 Hz), 140.7 (dm, J = 253.1 Hz), 137.4 (dm, J = 253.1 Hz), 132.8, 131.8, 130.2, 130.0, 129.7, 129.1, 128.9, 128.4, 127.5, 125.1, 115.4 (t, J = 8.5 Hz), 56.8. Elemental analysis: calcd (%) for $\text{C}_{20}\text{H}_{11}\text{F}_5\text{N}_4$ (402.32): C 59.71, H 2.76, found: C 59.98, H 2.51.

2'-(1-Benzyltetrazol-5-yl)-2,6-difluoro-[1,1'-biphenyl]-4-carbonitrile (12): Following the general procedure using 1-benzyl-5-(2-bromophenyl)tetrazole **1a** (158 mg, 0.5 mmol) and 3,5-difluorobenzonitrile (104 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 80:20) to afford the desired compound **12** (125 mg, 67%) as a yellow solid (mp = 172-174 °C). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.29 (dd, J = 1.7 and 7.5 Hz, 1H), 7.70 – 7.53 (m, 2H), 7.47 – 7.33 (m, 4H), 7.26 – 7.15 (m, 2H), 7.08 – 6.96 (m, 2H), 5.63 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 164.4, 160.0, (dd, J = 7.7 and 252.4 Hz), 133.0, 131.4, 130.1, 129.9, 129.6, 129.2, 129.0, 128.4, 127.1, 126.2, 123.8 (t, J = 20.4 Hz), 116.8 (t, J = 3.5 Hz), 115.2 (d, J = 31.8 Hz), 112.6 (t, J = 12.8 Hz), 56.8. Elemental analysis: calcd (%) for $\text{C}_{21}\text{H}_{13}\text{F}_2\text{N}_5$ (373.36): C 67.56, H 3.51; found: C 67.63, H 3.19.

5-(2-(1-Pivalyltetrazol-5-yl)phenyl)-2-ethyl-4-methylthiazole (13): Following the general procedure using 5-(2-bromophenyl)-1-pivalyltetrazole **1b** (155 mg, 0.5 mmol) and 2-ethyl-4-methylthiazole (95 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 70:30) to afford the desired compound **13** (156 mg, 88%) as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.14 – 8.07 (m, 1H), 7.59 – 7.47 (m, 2H), 7.43 (dd, J = 2.0, 6.4 Hz, 1H), 2.98 (q, J = 7.6 Hz, 2H), 2.08 (s, 3H), 1.37 (t, J = 7.6 Hz, 3H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 173.5, 171.1, 164.4, 148.9, 132.5, 131.3, 131.0, 130.0, 128.9, 127.8, 125.1, 32.3, 27.9, 26.8, 15.1, 14.3. Elemental analysis: calcd (%) for $\text{C}_{18}\text{H}_{21}\text{N}_5\text{OS}$ (355.46): C 60.82, H 5.95; found: C 61.08, H 6.11.

5-(2-(1-Pivalyltetrazol-5-yl)phenyl)-2-isobutylthiazole (14): Following the general procedure using 5-(2-bromophenyl)-1-pivalyltetrazole **1b** (155 mg, 0.5 mmol) and 2-

isobutylthiazole (106 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **14** (168 mg, 91%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.98 (dd, *J* = 1.6 and 7.8 Hz, 1H), 7.61 – 7.49 (m, 3H), 7.47 (s, 1H), 2.86 (d, *J* = 7.2 Hz, 2H), 2.17 – 2.06 (m, 1H), 1.30 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 173.7, 171.0, 164.3, 140.7, 135.0, 131.7, 131.2, 131.1, 130.6, 128.8, 124.2, 42.4, 32.3, 29.7, 28.0, 22.3. Elemental analysis: calcd (%) for C₁₉H₂₃N₅OS (369.48): C 61.76, H 6.27; found: C 62.07, H 6.35.

5-(2-(5-Methylthiophen-2-yl)phenyl)-1-pivalyltetrazole (15): Following the general procedure using 5-(2-bromophenyl)-1-pivalyltetrazole **1b** (155 mg, 0.5 mmol) and 2-methylthiophene (74 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **15** (139 mg, 85%) as a yellow solid (mp = 88–90 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.92 – 7.86 (m, 1H), 7.57 – 7.50 (m, 2H), 7.44 (ddd, *J* = 3.8, 5.1 and 7.7 Hz, 1H), 7.01 – 6.24 (m, 2H), 2.47 (s, 3H), 1.29 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 173.6, 164.9, 140.8, 138.9, 135.0, 131.1, 131.0, 130.6, 127.9, 126.6, 125.4, 123.8, 32.2, 27.9, 15.2. Elemental analysis: calcd (%) for C₁₇H₁₈N₄OS (326.42): C 62.55, H 5.56; found: C 62.75, H 5.69.

1-(5-(2-(1-Pivalyltetrazol-5-yl)phenyl)-4-methylthiophen-2-yl)ethan-1-one (16): Following the general procedure using 5-(2-bromophenyl)-1-pivalyltetrazole **1b** (155 mg, 0.5 mmol) and 1-(4-methylthiophen-2-yl)ethan-1-one (105 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 60:40) to afford the desired compound **16** (153 mg, 83%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.17 – 8.11 (m, 1H), 7.64 – 7.54 (m, 2H), 7.49 (s, 1H), 7.47 – 7.40 (m, 1H), 2.54 (s, 3H), 1.92 (s, 3H), 1.24 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 190.2, 173.3, 164.0, 144.4, 142.3, 136.5, 134.2, 132.3, 131.8, 130.9, 129.7, 129.1, 124.4, 32.0, 27.6, 16.5, 13.7. Elemental analysis: calcd (%) for C₁₉H₂₀N₄O₂S (368.45): C 61.94, H 5.47; found: C 62.09, H 5.11.

5-(2-(Benzo[*b*]thiophen-2-yl)phenyl)-1-pivalyltetrazole (17): Following the general procedure using 5-(2-bromophenyl)-1-pivalyltetrazole **1b** (155 mg, 0.5 mmol) and benzo[*b*]thiophene (101 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 80:20) to afford the desired compound **17** (143 mg, 79%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.01 (dd, *J* = 1.6 and 7.6 Hz, 1H), 7.82 (dd, *J* = 2.0 and 7.5 Hz, 1H), 7.72 (dd, *J* = 2.0 and 7.8 Hz, 1H), 7.67 (dd, *J* = 1.5 and 7.7 Hz, 1H), 7.62 (dt, *J* = 1.6 and 7.5 Hz, 1H), 7.55 (dt, *J* = 1.5 and 7.5 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.10 (s, 1H), 1.10 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 173.7, 164.6, 141.5, 140.3, 139.9, 134.5, 131.3, 131.2, 130.6, 128.8, 124.5, 124.5, 124.3, 123.6, 123.5, 122.0, 32.2, 27.7. Elemental analysis: calcd (%) for C₂₀H₁₈N₄OS (362.45): C 66.28, H 5.01; found: C 66.49, H 5.34.

5-(2-(5-Butylfuran-2-yl)phenyl)-1-pivalyltetrazole (18): Following the general procedure using 5-(2-bromophenyl)-1-pivalyltetrazole **1b** (155 mg, 0.5 mmol) and 2-*n*-butylfuran (93 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 80:20) to afford the desired compound **18** (167 mg, 95%) as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.76 (dd, *J* = 0.9 and 8.0 Hz, 1H), 7.71 (dd, *J* = 1.1 and 7.7 Hz, 1H), 7.56 (dt, *J* = 1.4 and 7.7 Hz, 1H), 7.39 (dt, *J* = 1.3 and 7.6 Hz, 1H), 6.19 (d, *J* = 3.3 Hz, 1H), 6.02 (d, *J* = 3.3 Hz, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 1.66 – 1.53 (m, 2H), 1.40 (s, 9H), 1.40 – 1.31 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 173.5, 165.0, 157.2, 149.8, 131.3, 131.2, 131.1, 127.8, 127.3, 121.3, 109.5, 106.8, 32.4, 29.9, 28.2, 27.8, 22.3, 13.8. Elemental analysis: calcd (%) for C₂₀H₂₄N₄O₂ (352.43): C 68.16, H 6.86; found: C 68.24, H 6.54.

1-(5-(2-(1-Pivalyltetrazol-5-yl)phenyl)furan-2-yl)butan-1-one (19): Following the general procedure using 5-(2-bromophenyl)-1-pivalyltetrazole **1b** (155 mg, 0.5 mmol) and 1-(furan-2-yl)butan-1-one (104 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **19** (178 mg, 97%) as a pale green oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.93 (dd, *J* = 1.5 and 7.8 Hz, 1H), 7.79 (dd, *J* = 1.4 and 7.8 Hz, 1H), 7.65 (dt, *J* = 1.3 and 7.7 Hz, 1H), 7.57 (dt, *J* = 1.3 and 7.5 Hz, 1H), 7.22 (d, *J* = 3.6 Hz, 1H), 6.49 (d, *J* = 3.6 Hz, 1H), 2.70 (d, *J* = 7.4 Hz, 2H), 1.73 (sext., *J* = 7.4 Hz, 2H), 1.36 (s, 9H), 0.99 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 189.4, 173.7, 164.2, 155.1, 152.7, 142.1, 131.4, 131.0, 129.5, 129.4, 122.8, 117.9, 111.1, 40.3, 32.4, 28.1, 17.6, 13.8. Elemental analysis: calcd (%) for C₂₀H₂₂N₄O₃ (366.41): C 65.56, H 6.05, found: C 65.87, H 6.35.

5-(2-(1-Methylpyrrol-2-yl)phenyl)-1-pivalyltetrazole (20): Following the general procedure using 5-(2-bromophenyl)-1-pivalyltetrazole **1b** (155 mg, 0.5 mmol) and *N*-methylpyrrole (162 mg, 2 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **20** (148 mg, 96%) as a red solid (mp = 80-83 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.13 (dd, *J* = 1.7 and 7.3 Hz, 1H), 7.60 – 7.45 (m, 3H), 6.67 (dd, *J* = 1.8 and 2.7 Hz, 1H), 6.18 (dd, *J* = 2.7 and 3.6 Hz, 1H), 6.07 (dd, *J* = 1.8 and 3.6 Hz, 1H), 3.29 (s, 3H), 1.29 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 173.5, 164.9, 132.8, 132.5, 131.7, 130.9, 129.6, 128.3, 125.1, 122.4, 109.1, 107.9, 33.9, 32.3, 27.9. Elemental analysis: calcd (%) for C₁₇H₁₉N₅O (309.37): C 66.00, H 6.19, found: C 66.21, H 6.00.

1-Pivalyl-5-(2',3',5',6'-tetrafluoro-[1,1'-biphenyl]-2-yl)tetrazole (21): Following the general procedure using 5-(2-bromophenyl)-1-pivalyltetrazole **1b** (155 mg, 0.5 mmol) and 1,2,3,5-tetrafluorobenzene (113 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **21** (127 mg, 67%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.31 – 8.17 (m, 1H), 7.74 – 7.56 (m, 2H), 7.44 (dd, *J* = 3.1 and 6.0 Hz, 1H), 7.15 (tt, *J* = 7.3 and 9.5 Hz, 1H), 1.34 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 173.1, 163.5, 145.8 (dm, *J* = 250.1 Hz), 143.9 (dm, *J* = 250.1 Hz), 132.0, 131.3, 129.9, 129.4, 126.1, 124.2, 120.6 (d, *J* = 17.7 Hz), 105.6 (t, *J* = 22.5 Hz), 32.3, 27.9. Elemental analysis: calcd (%) for C₁₈H₁₄F₄N₄O (378.32): C 57.14, H 3.73, found: C 57.31, H 4.02.

2',3',5',6'-Tetrafluoro-2''-(1-pivaloyltetrazol-5-yl)-[1,1':4',1''-terphenyl]-4-carbonitrile (22): Following the general procedure using 4-bromobenzonitrile (100 mg, 0.55 mmol) and 1-pivalyl-5-(2',3',5',6'-tetrafluoro-[1,1'-biphenyl]-2-yl)tetrazole **21** (189 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 80:20) to afford the desired compound **22** (151 mg, 63%) as a yellow solid (mp = 207-209 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.31 – 8.17 (m, 1H), 7.88 – 7.78 (m, 2H), 7.75 – 7.64 (m, 4H), 7.50 (dd, *J* = 3.2 and 5.9 Hz, 1H), 1.40 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 173.1, 163.3, 144.5 (dm, *J* = 251.1 Hz), 143.6 (dm, *J* = 251.1 Hz), 132.4, 132.2, 132.0, 131.3, 131.0, 130.1, 129.3, 125.8, 124.1, 120.3 (t, *J* = 16.4 Hz), 118.4 (d, *J* = 15.0 Hz), 118.2, 113.1, 32.4, 28.0. Elemental analysis: calcd (%) for C₂₅H₁₇F₄N₅O (479.43): C 62.63, H 3.57; found: C 62.79, H 3.69.

2-Ethyl-4-methyl-5-(2-(1-methyltetrazol-5-yl)phenyl)thiazole (23): Following the general procedure using 5-(2-bromophenyl)-1-methyltetrazole **1c** (120 mg, 0.5 mmol) and 2-ethyl-4-methylthiazole (95 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **23** (127 mg, 89%) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.02 – 7.91 (m, 1H), 7.55 – 7.47 (m, 2H), 7.44 (dd, *J* = 3.5 and 5.8 Hz, 1H), 4.27 (s, 3H), 2.99 (q, *J* = 7.6 Hz, 2H), 2.02 (s, 3H), 1.38 (t,

$J = 7.6$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 170.9, 164.7, 148.4, 132.5, 131.5, 130.1, 129.8, 128.7, 128.4, 128.1, 39.4, 26.8, 15.3, 14.3. Elemental analysis: calcd (%) for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{S}$ (285.37): C 58.92, H 5.30; found: C 58.72, H 5.45.

2-Isobutyl-5-(2-(1-methyltetrazol-5-yl)phenyl)thiazole (24): Following the general procedure using 5-(2-bromophenyl)-1-methyltetrazole **1c** (120 mg, 0.5 mmol) and 2-isobutylthiazole (106 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 70:30) to afford the desired compound **24** (139 mg, 93%) as a pale yellow oil. ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.86 – 7.77 (m, 1H), 7.57 – 7.51 (m, 2H), 7.51 – 7.47 (m, 1H), 7.45 (s, 1H), 4.31 (s, 3H), 2.84 (d, $J = 7.2$ Hz, 2H), 2.09 (m, 1H), 1.00 (d, $J = 6.8$ Hz, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 170.7, 164.7, 140.8, 135.6, 131.5, 131.2, 130.7, 130.1, 128.6, 127.1, 42.3, 39.4, 29.8, 22.2. Elemental analysis: calcd (%) for $\text{C}_{15}\text{H}_{17}\text{N}_5\text{S}$ (299.39): C 60.18, H 5.72; found: C 60.11, H 5.49.

1-Methyl-5-(2-(5-pentylthiophen-2-yl)phenyl)tetrazole (25): Following the general procedure using 5-(2-bromophenyl)-1-methyltetrazole **1c** (120 mg, 0.5 mmol) and 2-*n*-pentylthiophene (116 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 70:30) to afford the desired compound **25** (127 mg, 81%) as a pale yellow oil. ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.68 (dd, $J = 1.6$ and 7.7 Hz, 1H), 7.59 (dd, $J = 1.5$ and 7.7 Hz, 1H), 7.51 (dt, $J = 1.6$ and 7.4 Hz, 1H), 7.42 (dt, $J = 1.5$ and 7.4 Hz, 1H), 6.69 (d, $J = 3.5$ Hz, 1H), 6.64 (d, $J = 3.5$ Hz, 1H), 4.35 (s, 3H), 2.83 – 2.70 (m, 2H), 1.76 – 1.58 (m, 2H), 1.44 – 1.30 (m, 4H), 0.92 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 165.3, 146.8, 139.0, 135.1, 130.9, 130.9, 130.0, 127.5, 126.6, 126.4, 124.1, 39.4, 31.3, 30.0, 22.4, 14.0. Elemental analysis: calcd (%) for $\text{C}_{17}\text{H}_{20}\text{N}_4\text{S}$ (312.43): C 65.35, H 6.45; found: C 65.49, H 6.72.

1-Methyl-5-(2-(5-methylfuran-2-yl)phenyl)tetrazole (26): Following the general procedure using 5-(2-bromophenyl)-1-methyltetrazole **1c** (120 mg, 0.5 mmol) and 2-methylfuran (62 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 70:30) to afford the desired compound **26** (108 mg, 90%) as a brown yellow oil. ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.75 (dd, $J = 1.2$ and 7.5 Hz, 1H), 7.62 (dd, $J = 1.5$ and 7.5 Hz, 1H), 7.53 (dt, $J = 1.5$ and 7.7 Hz, 1H), 7.38 (dt, $J = 1.2$ and 7.5 Hz, 1H), 6.07 (d, $J = 3.2$ Hz, 1H), 6.00 – 5.92 (m, 1H), 4.41 (s, 3H), 2.43 – 1.70 (m, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 165.6, 152.1, 150.4, 131.1, 131.1, 130.1, 127.8, 127.1, 124.3, 109.7, 107.5, 39.4, 13.6. Elemental analysis: calcd (%) for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}$ (240.26): C 64.99, H 5.03; found: C 65.18, H 5.39.

1-(5-(2-(1-Methyltetrazol-5-yl)phenyl)furan-2-yl)propan-2-one (27): Following the general procedure using 5-(2-bromophenyl)-1-methyltetrazole **1c** (120 mg, 0.5 mmol) and 1-(furan-2-yl)propan-2-one (93 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 70:30) to afford the desired compound **27** (121 mg, 86%) as a brown yellow oil. ^1H NMR (300 MHz, CDCl_3) δ (ppm) 7.76 – 7.64 (m, 2H), 7.54 (dt, $J = 1.5$ and 7.7 Hz, 1H), 7.43 (dt, $J = 1.4$ and 7.5 Hz, 1H), 6.30 (d, $J = 3.3$ Hz, 1H), 6.22 (d, $J = 3.3$ Hz, 1H), 4.42 (s, 3H), 3.61 (s, 2H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 203.8, 165.3, 152.3, 148.2, 131.1, 130.6, 130.1, 128.3, 127.8, 125.0, 110.1, 109.6, 43.3, 39.5, 29.2. Elemental analysis: calcd (%) for $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_2$ (282.30): C 63.82, H 5.00; found: C 64.08, H 4.97.

1-Methyl-5-(2-(1-methylpyrrol-2-yl)phenyl)tetrazole (28): Following the general procedure using 5-(2-bromophenyl)-1-methyltetrazole **1c** (120 mg, 0.5 mmol) and *N*-methylpyrrole (162 mg, 2 mmol), the residue was purified by flash chromatography on silica gel (pentane- Et_2O , 70:30) to afford the desired compound **28** (110 mg, 92%) as a yellow solid

(mp = 99-101 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.09 – 7.92 (m, 1H), 7.63 – 7.41 (m, 3H), 6.67 – 6.64 (m, 1H), 6.17 (dd, *J* = 2.7 and 3.5 Hz, 1H), 6.03 (dd, *J* = 1.8 and 3.5 Hz, 1H), 4.29 (s, 3H), 3.25 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 165.2, 132.9, 132.5, 129.8, 129.7, 128.2, 128.2, 122.0, 108.8, 107.4, 39.4, 34.2. Elemental analysis: calcd (%) for C₁₃H₁₃N₅ (239.28): C 65.25, H 5.48; found: C 65.34, H 5.79.

1-Methyl-5-(2',3',4',5',6'-pentafluoro-[1,1'-biphenyl]-2-yl)tetrazole (29): Following the general procedure using 5-(2-bromophenyl)-1-methyltetrazole **1c** (120 mg, 0.5 mmol) and pentafluorobenzene (126 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **29** (113 mg, 69%) as a yellow solid (mp = 72-74 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.35 – 8.21 (m, 1H), 7.71 – 7.54 (m, 2H), 7.41 (td, *J* = 1.9 and 7.2 Hz, 1H), 4.31 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 164.2, 144.4 (dm, *J* = 253.2 Hz), 140.9 (dm, *J* = 253.2 Hz), 137.6 (dm, *J* = 253.2 Hz), 132.0, 130.2, 130.0, 129.7, 127.4, 125.1, 115.4 (m), 39.5. Elemental analysis: calcd (%) for C₁₄H₇F₅N₄ (326.22): C 51.54, H 2.16; found: C 51.74, H 2.06.

1-Methyl-5-(2',3',5',6'-tetrafluoro-[1,1'-biphenyl]-2-yl)tetrazole (30): Following the general procedure using 5-(2-bromophenyl)-1-methyltetrazole **1c** (120 mg, 0.5 mmol) and 1,2,3,5-tetrafluorobenzene (113 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70:30) to afford the desired compound **30** (100 mg, 65%) as a yellow solid (mp = 178-181 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.26 (dd, *J* = 2.3 and 7.4 Hz, 1H), 7.68 – 7.57 (m, 2H), 7.44 (dd, *J* = 2.0 and 6.8 Hz, 1H), 7.11 (tt, *J* = 7.3 and 9.7 Hz, 1H), 4.29 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 164.3, 145.9 (dm, *J* = 248.4 Hz), 144.0 (dm, *J* = 248.4 Hz), 131.8, 130.1, 129.8, 129.7, 127.3, 121.2 (d, *J* = 22.7 Hz), 105.2 (t, *J* = 22.5 Hz), 39.4. Elemental analysis: calcd (%) for C₁₄H₈F₄N₄ (308.23): C 54.55, H 2.62, found: C 54.76, H 2.49.

2,6-Difluoro-2'-(1-methyltetrazol-5-yl)-[1,1'-biphenyl]-4-carbonitrile (31): Following the general procedure using 5-(2-bromophenyl)-1-methyltetrazole **1c** (120 mg, 0.5 mmol) and 3,5-difluorobenzonitrile (104 mg, 0.75 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 80:20) to afford the desired compound **31** (104 mg, 70%) as a yellow solid (mp = 205-208 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.33 – 8.21 (m, 1H), 7.70 – 7.56 (m, 2H), 7.48 – 7.37 (m, 1H), 7.31 – 7.21 (m, 2H), 4.27 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 164.3, 160.3 (dd, *J* = 8.7 and 251.2 Hz), 131.5, 130.1, 129.9, 129.6, 127.1, 126.1, 124.1 (t, *J* = 20.6 Hz), 116.8 (t, *J* = 3.6 Hz), 115.4 (d, *J* = 30.1 Hz), 112.9 (t, *J* = 11.9 Hz), 39.5. Elemental analysis: calcd (%) for C₁₅H₉F₂N₅ (297.26): C 60.61, H 3.05; found: C 60.46, H 3.08.

REFERENCES

- [1] a) D. J. Carini, J. V. Duncia, P. E. Aldrich, A. T. Chiu, A. L. Johnson, M. E. Pierce, W. A. Price, J. B. Santella, G. J. Wells, *J. Med. Chem.* **1991**, *34*, 2525-2547; b) K. Kubo, Y. Kohara, Y. Yoshimura, Y. Inada, Y. Shibouta, Y. Furukawa, T. Kato, K. Nishikawa, T. Naka, *J. Med. Chem.* **1993**, *36*, 2343-2349; c) C. A. Bernhart, P. M. Perreaut, B. P. Ferrari, Y. A. Muneaux, J. L. A. Assens, J. Clement, F. Haudricourt, C. F. Muneaux, J. E. Taillades, *J. Med. Chem.* **1993**, *36*, 3371-3380; d) R. R. Wexler, W. J. Greenlee, J. D. Irvin, M. R. Goldberg, K. Prendergast, R. D. Smith, P. B. M. W. M. Timmermans, *J. Med. Chem.* **1996**, *39*, 625-656.
- [2] L. Iouzalet, O. Stepien, P. Marche, *J. Pharmacol. Exp. Ther.* **1999**, *289*, 181-187.
- [3] A. Alonen, M. Finel, R. Kostianen, *Biochem. Pharmacol.* **2008**, *76*, 763-772.
- [4] a) R. D. Larsen, A. O. King, C. Y. Chen, E. G. Corley, B. S. Foster, F. E. Roberts, C. Yang, D. R. Lieberman, R. A. Reamer, D. M. Tschaen, T. R. Verhoeven, P. J. Reider, Y. S. Lo, L. T. Rossano, A. S. Brookes, D. Meloni, J. R. Moore, J. F. Arnett, *J. Org. Chem.* **1994**, *59*, 6391-6394; b) R. Rai, K. B. Aubrecht, D. B. Collum, *Tetrahedron Lett.* **1995**, *36*, 3111-3114; c) N. Cousaert, P. Toto, N. Willand, B. Deprez, *Tetrahedron Lett.* **2005**, *46*, 6529-6532; d) N. Cousaert, N. Willand, J.-C. Gesquiere, A.

- Tartar, B. Deprez, R. Deprez-Poulain, *Tetrahedron Lett.* **2008**, *49*, 2743-2747; e) U. Beutler, M. Boehm, P. C. Fuenfschilling, T. Heinz, J.-P. Mutz, U. Onken, M. Mueller, W. Zaug, *Org. Process Res. Dev.* **2007**, *11*, 892-898; f) S. K. N., S. B. Reddy, B. K. Sinha, K. Mukkanti, R. Dandala, *Org. Process Res. Dev.* **2009**, *13*, 1185-1189.
- [5] a) F. Bellina, S. Cauteruccio, R. Rossi, *Curr. Org. Chem.* **2008**, *12*, 774-790; b) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013-3039; c) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826; d) F. Bellina, R. Rossi, *Chem. Rev.* **2009**, *110*, 1082-1146; e) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269-10310; f) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115; g) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673-714; h) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147-1169; i) E. M. Beck, M. J. Gaunt, *Top. Curr. Chem.* **2010**, *292*, 85-121; j) T. Satoh, M. Miura, *Synthesis* **2010**, 3395-3409; k) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677-685; l) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068-5083; m) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236-10254; n) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588-5598; o) M. C. White, *Synlett* **2012**, *23*, 2746-2748; p) S. I. Kozhushkov, L. Ackermann, *Chem. Sci.* **2013**, *4*, 886-896; q) H. Liu, G. Laurenczy, N. Yan, P. J. Dyson, *Chem. Commun.* **2014**, *50*, 341-343; r) R. Rossi, F. Bellina, M. Lessi, C. Manzini, *Adv. Synth. Catal.* **2014**, *356*, 17-117; s) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li, W. Su, *Org. Chem. Front.* **2014**, *1*, 843-895; t) K. Yuan, J.-F. Soulé, H. Doucet, *ACS Catal.* **2015**, *5*, 978-991; u) M. R. Yadav, R. K. Rit, M. Shankar, A. K. Sahoo, *Asian J. Org. Chem.* **2015**, *4*, 846-864; v) C. B. Bheeter, L. Chen, J.-F. Soulé, H. Doucet, *Catal. Sci. Technol.* **2016**, *6*, 2005-2049.
- [6] M. Seki, *ACS Catal.* **2011**, *1*, 607-610.
- [7] M. Seki, M. Nagahama, *J. Org. Chem.* **2011**, *76*, 10198-10206.
- [8] M. Seki, *Synthesis* **2012**, *44*, 3231-3237.
- [9] E. Diers, N. Y. Phani Kumar, T. Mejuch, I. Marek, L. Ackermann, *Tetrahedron* **2013**, *69*, 4445-4453.
- [10] R. A. Rivero, N. J. Kevin, E. E. Allen, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1119-1124.
- [11] a) M. He, J.-F. Soulé, H. Doucet, *ChemCatChem* **2014**, *6*, 1824-1859; b) T. Yan, L. Zhao, M. He, J.-F. Soulé, C. Bruneau, H. Doucet, *Adv. Synth. Catal.* **2014**, *356*, 1586-1596; c) M. He, J.-F. Soulé, H. Doucet, *ChemCatChem* **2015**, *7*, 2130-2140.
- [12] M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754-8756.
- [13] M. Seki, *Synthesis* **2014**, *46*, 3249-3255.
- [14] C. Behloul, A. Chouti, D. Guijarro, C. Najera, M. Yus, *Synthesis* **2015**, *47*, 507-510.
- [15] R. P. Singh, R. D. Verma, D. T. Meshri, J. n. M. Shreeve, *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 3584-3601.
- [16] E. Vieira, J. Huwyler, S. Jolidon, F. Knoflach, V. Mutel, J. Wichmann, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4628-4631.
- [17] R. S. Upadhayaya, S. Jain, N. Sinha, N. Kishore, R. Chandra, S. K. Arora, *Eur. J. Med. Chem.* **2004**, *39*, 579-592.
- [18] T. Cantat, E. Génin, C. Giroud, G. Meyer, A. Jutand, *J. Organomet. Chem.* **2003**, *687*, 365-376.

Graphical Table of Contents**Reactivity of *N*-Protected 5-(2-Bromophenyl)tetrazoles in Palladium-Catalyzed Direct Arylation of Heteroarenes or Fluorobenzenes.***S. Chikhi, S. Djebbar, J.-F. Soulé, * H. Doucet*.*

N-protected 5-(2-bromophenyl)tetrazole derivatives have been used as aryl sources in C–H bond arylation of a wide range of heteroarenes and some polyfluorobenzenes, using an air-stable diphosphine palladium catalyst to afford (2-heteroarylphenyl)tetrazoles and fluorinated biphenyltetrazoles in high yields.

Highlights.

- *N*-protected 5-(2-bromophenyl)tetrazoles can be efficiently coupled heteroarenes
- The poisoning effect tetrazole was inhibited using *N*-alkyl or *N*-acyl substituents
- 30 novel (2-(hetero)arylphenyl)tetrazole derivatives were synthesized.