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Aryl and heteroaryl N1- tetrazoles via ligand-free Suzuki-reaction under aerobic, aqueous conditions

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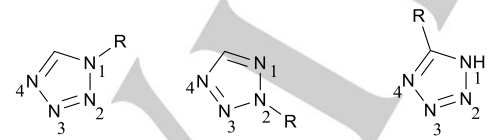
Abstract: Substituted 1-biaryl-*1H*-tetrazoles are classically obtained from the corresponding 1-aminobiaryls, limiting the selection of substrates. The development and substrate scope of a green, ligand-free Suzuki protocol in aqueous media under ambient atmosphere, leading to 1 biaryl- and heteroaryl- substituted 1H-tetrazoles in very good to excellent yields is presented. The combination of $PdCl_2$ / $N(Et)_3$ / H_2O-EtOH was found to combine high yields and high purity for all substrates investigated. Comparative experiments investigating the reaction rate showed, that the tetrazole does not act as a ligand for the palladium catalyst.

Introduction

Substituted tetrazoles are known mainly for their applicability as carboxylic acid bioisosteres in drug design[1] and as ligands for spin crossover complexes.[2] A substitution pattern is commonly introduced by using an appropriately substituted precursor for the ring formation, rather than by a functionalization after tetrazole synthesis. Whereas the N1 and N2-substituted derivatives are commonly used for coordination chemistry (scheme 1), the C5 substitution pattern displays a similar pK_a to the corresponding carboxylic acid and is metabolized as non-electrophilic glucuronide.[1b, 3]

Scheme 1. Substitution patterns of tetrazole rings



N1-substituted tetrazoles offer distinct advantages when used as ligands for Fe(II) spin crossover materials.[2d, 4] They feature a strict monodentate coordination via the *exo* located N4,[2b, 5] whereas their C5-substituted equivalents prefer in most cases a bridging coordination between metal-ions.[6] Nearly all synthetic approaches to substituted tetrazoles include a [2+3] cyclo-addition of an azide-source and primary amines and isonitriles -yielding N1-isomers- or nitriles, leading to the C5-isomers.[7] Commonly, N2-isomers are obtained after alkylation of *1H*-tetrazole and subsequent chromatographic separation.[8]

In this context, a major obstacle regarding a simple variation of substitution patterns or more sophisticated target structures is the limited availability or often tedious synthetic preparation of the necessary primary amines or isonitriles.

Therefore, we focused on possible post-functionalization procedures based on coupling protocols. Especially for libraries of substituted aryltetrazoles, suitable for the systematic investigations of substitution effects on the spin crossover behaviour of the respective iron(II) spin crossover compounds, a versatile coupling protocol would significantly reduce the required synthetic effort. Based on the concept of divergent synthesis and considering that tetrazole-synthesis is often hampered by low yields, an additional positive aspect of a tetrazole-compatible coupling protocol would be its introduction in the first step. According to the general aim for sustainable chemistry, special emphasize was the establishment of an environmentally benign coupling protocol.

Suzuki-Miyaura coupling was originally reported as the palladium catalyzed reaction of alkenylboranes with aryl halides.[9] The reaction has since expanded in scope to the current protocol coupling aryl boronic acids and aryl halides[10] and offers a versatile method accessing asymmetric biaryl motifs in a single synthetic step. With 4-bromobenzyl-*1H*-tetrazole in hand, an investigation of its performance in a Suzuki protocol would allow for easy access to libraries of substituted biaryl-tetrazoles without the necessity of the corresponding amine-precursor.

References to C–C coupling protocols using tetrazoles are very scarce. All examples of tetrazoles in coupling protocols reported thus far describe substitution at the C5 position directly, or remotely on an aryl group attached at the tetrazole C5-position.[11] It is well known, that C5-bisubsituted tetrazoles [12] differ notably not only in their coordination behavior,[5-6] but also in their C5 or N1 reactivity, from exclusively N1-substituted tetrazoles and are thus not directly chemically comparable. To the best of our knowledge, we report the first coupling-protocol with N1-substituted tetrazoles.

Results and Discussion

The reaction of 4-bromobenzyl-*1H*-tetrazole with phenylboronic acid (1.1 equivalents; scheme 2) was chosen as model system for development and optimization of a Suzuki protocol for the formation of N1-substituted tetrazoles.

Initially, the influence of reaction solvent was investigated. In THF using $Pd(PPh_3)_4$ and potassium carbonate led to **2a** in an isolated yield of 88 %. Variation of the solvents increased the yield to 97 %. A complete overview of the screening of various solvents is given in table 1.

Scheme 2. Model reaction for protocol development

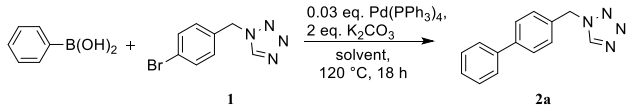


Table 1. Suzuki reaction of 4-Bromobenzyl-*1H*-tetrazole and $PhB(OH)_2$ in various solvents (1.1 eq. $PhB(OH)_2$, 0.03 eq. $Pd(PPh_3)_4$, 2 eq. K_2CO_3, 120 °C, 18 h)

entry	solvent[a]	yield [%][b]
1	THF	88
2	THF:H_2O (5:1)	95*
3	THF:H_2O (1:1)	96*
4	DMF	50*, **
5	DMF:H_2O (5:1)	72**
6	1,4-dioxane	95
7	EtOH	62*
8	EtOH:H_2O (3:1)	66
9	EtOH:H_2O (1:1)	96
10	H_2O	80
11	PhMe	97

* Impurities ** Product contaminated with starting material.

[a] 5 ml of solvent used. [b] Isolated yields.

The highest isolated yields of **2a** (97 %) were achieved with toluene as solvent. To deduce whether the coupling was sensitive to moisture, aqueous solvent mixtures were used. Comparing the results for dry THF, EtOH and DMF with the yields obtained for their aqueous mixtures it became apparent, that high water contents improved the reaction significantly: a 50 % water THF mixture yielded 96 % of **2a.** Increasing the water concentration up to 100 % water resulted in 80 % isolated yield. The beneficial effect of water may be attributed to the better solubility of polar reactants.[13] Although the isolated yield from aqueous THF mixtures seemed promising, a coloured and contaminated product was isolated. This was not the case for toluene. To develop an aqueous and therefore environmentally benign protocol for the further optimization steps toluene and water as solvents were selected.

The combination of $Pd(PPh_3)_4$ and toluene has already shown excellent performance for this reaction, but nevertheless further catalysts, including Ni-species, were compared regarding their performance (table 2). A special emphasis was put on the identification of reaction conditions for a ligand-free catalyst in water or at least aqueous media.

Table 2. Suzuki reaction of 4-Bromobenzyl-*1H*-tetrazole and $PhB(OH)_2$ with different catalysts (1.1 eq. $PhB(OH)_2$, 0.03 eq. catalyst, 2 eq. K_2CO_3, 120 °C, 18 h)

entry	catalyst	Solvent[a]	yield [%][b]	conversion [%][c]
1	$Pd(PPh_3)_4$	PhMe	97	100
2	$Pd(PPh_3)_4$	H_2O	80	100
3	$Pd(PPh_3)_2Cl_2$	PhMe	0	0
4	$Pd(PPh_3)_2Cl_2$	H_2O	40	45
5	Pd/C	PhMe	97*	100
6	Pd/C	H_2O	27*	30
7	$PdCl_2$	PhMe	56	60
8	$PdCl_2$	H_2O	74	81
9	$Ni(dppp)Cl_2$	PhMe	5	14
10	$Ni(dppp)Cl_2$	H_2O	0	0
11	Ni(OAc)	PhMe	0	0
12	Ni(OAc)	H_2O	0	0

* Impurities

[a] 5 ml of solvent used. [b] Isolated yields. [c] Determined by ^{1}H-NMR, refers to unreacted starting material.

The data in table 2 show that the presence of water affects the activity and thus choice of the catalyst. The activity of Pd(0) species is promoted by non-aqueous conditions, whereas Pd(II)-catalysts achieve higher yields in an aqueous solution.

The only one heterogeneous system investigated, Pd on charcoal, featured high yields (97 % in PhMe), but resulted in substantial by-product formation. The use of H_2O as solvent dramatically decreases the activity of the heterogeneous catalyst. In summary: toluene as organic solvent with $Pd(PPh_3)_4$, and water with $PdCl_2$ were identified as the most promising catalyst candidates. Although, Pd/C would offer the advantage of simple catalyst-separation,[14] the formation of by-products diminishes this advantage. For five comparable experiments using the conditions of the catalyst-screening, the catalyst loading was decreased to 0.05 mol% while maintaining temperature and reaction time. This resulted in a decreased conversion, whereas for a control experiment without any added palladium catalyst no product formation could be observed. Higher catalyst loadings than 5 mol% did not lead to significantly shorten

reaction times. Therefore, a loading of 3 mol% proved as the optimum concentration.

Among the Ni catalysts investigated, only with Ni(dppp)Cl_2 in PhMe could traces of **2a** be identified.

The catalyst screening resulted in two candidates of choice: Firstly, for a protocol using an organic solvent, the combination of toluene and $Pd(PPh_3)_4$ allowed for quantitative conversion and high isolated yields. Second, with the aim of a ligand-free coupling protocol under aqueous conditions, $PdCl_2$ in H_2O (74 % yield) was the catalyst of choice for further investigations.

To further optimize the environmental efficiency of the aqueous protocol, a selection of inorganic and organic bases was compared to the K_2CO_3, aiming for improved yields. In table 3 an overview of the performance of different bases, using water as solvent is given.

Table 3. Suzuki reaction of 4-Bromobenzyl-*1H*-tetrazole and $PhB(OH)_2$ with different bases (1.1 eq. $PhB(OH)_2$, 0.03 eq. $PdCl_2$, 2 eq. base, 120 °C, 18 h)

entry	base	yield [%][b]	conversion [%][b]
1	K_2CO_3	74	100
2	Na_2CO_3	66	84
3	Cs_2CO_3	52	100
4	KH_2PO_4	35	38
5	NaOH	0**	0
6	NH_4OH	82	100
7	DBU	0**	0
8	DIPEA	78	79
9	Et_3N	87	100

* Impurities ** Decomposition of **1**.

[a] Isolated yields. [b] Determined by ^{1}H-NMR, refers to unreacted starting material.

For K_2CO_3, Cs_2CO_3 NH_4OH and $N(Et)_3$ full conversion of the starting material was observed. DBU was completely inactive. NaOH led to decomposition of the 4-bromobenzyl-*1H*-tetrazole under formation of N-(4-bromobenzyl)cyanamide.[7a]

Several attempts varying the amount of the base showed, that two equivalents gave optimal results. To establish, whether the presence of a base was necessary due to the inherent basicity of the tetrazole conjugated base, a control experiment without additional base was performed. Absence of an auxiliary base led to complete recovery of the unreacted starting materials. Comparing $N(Et)_3$ and K_2CO_3, apart from higher yields with $N(Et)_3$ the workup was also simplified since fewer side-products were formed and upon extraction with an organic solvent these impurities remain in the aqueous layer. This is demonstrated in the direct comparison of the NMR-spectra of the crude product, obtained using potassium carbonate or triethylamine as base (see figure 1).

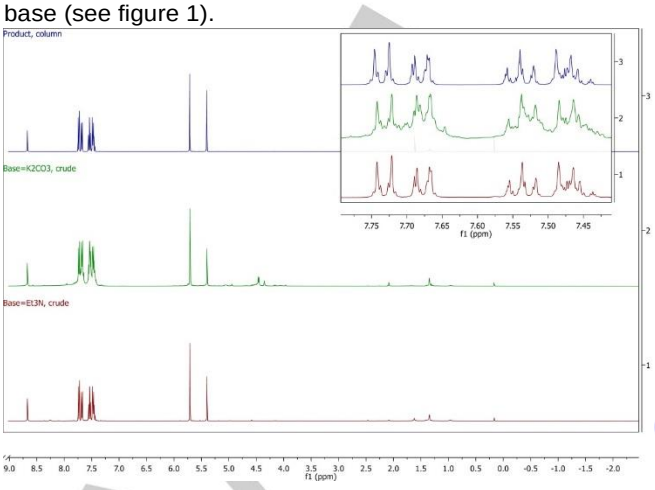


Figure 1. Pure compound 2a (top) compared to the crude products obtained using K_2CO_3 (middle) or Et_3N (bottom) as base.

According to this observation for all subsequent experiments $N(Et)_3$ was used. In case the toxicity of triethylamine is of concern, the coupling scope was also investigated with aqueous ammonia as base, leading to comparable yields.

Variation of the solvent, base and catalyst led to the conclusion, that although a ligand-free Suzuki coupling for **1** would be possible in pure water, a mixture of an organic solvent with water would possibly lead to higher yields. This was confirmed by using a 1:1 mixture of water and ethanol, resulting in excellent yields up to 97 % (see table 1).

All reactions described thus far were performed under argon atmosphere. Initial experiments using aqueous solvent mixtures and aerobic conditions led to yields and purities comparable to the earlier achieved ones, the influence of the oxygen concentration on the reaction was investigated. A set of reactions using either pure THF or THF/H_2O as solvent system and $PdCl_2$ as catalyst with Et_3N as base was performed comparing three different atmospheres: Argon, air and oxygen.

Table 4. Conversion of starting material determined by ^{1}H-NMR (1.1 eq. $PhB(OH)_2$, 0.03 eq. $PdCl_2$, 2 eq.$N(Et)_3$, 120 °C, 18 h)

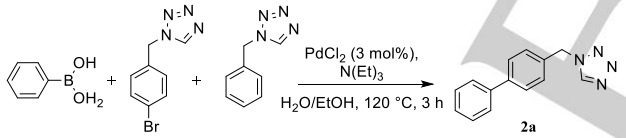
Solvent	Atmosphere	Conversion [%]
THF	Argon	42
	Air	35
	Oxygen	35
THF / H_2O (1:1)	Argon	100
	Air	100
	Oxygen	100

From table 4 two relevant things on the coupling-reaction can be deduced: First, water is absolutely necessary for optimal conversion when using a Pd(II)-catalyst and second, the atmosphere has no significant impact on the conversion, as the reaction works under an atmosphere of pure oxygen. All further studies were performed in sealed vessels under ambient atmosphere.

In summary, optimum-conditions for this Suzuki-coupling of N1-substituted tetrazoles were identified as a combination of 3 mol% $PdCl_2$ as catalyst with 2 eq. $N(Et)_3$ as base in a 1:1 mixture of aqueous ethanol at 120 °C. Following the reaction of **1** by ^{1}H-NMR showed full conversion after a reaction time of 3 h.

To shed light on a possible coordination of the tetrazole through its nitrogen-atoms and thus acting as ligand during the coupling reaction, competitive experiments with benzyl tetrazole and 4-bromobenzyl tetrazole were performed. In case the tetrazole would coordinate the palladium during the reaction, a change in the reaction rate would be expectable, when a 10-fold excess of benzyl tetrazole, not participating in the coupling and only coordinating to the palladium, was added. Using the conditions described in scheme 3, the reaction rates for one experiment without benzyl tetrazole and one with a 10-fold molar excess (based on the 4-bromobenzyl tetrazole) were compared.

Scheme 3. Competitive reaction with 4-bromobenzyl tetrazole and benzyl tetrazole

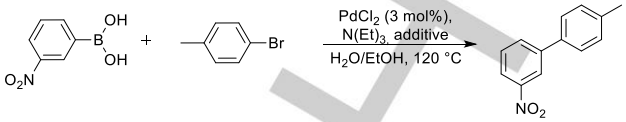


1, 1 eq. **BnTz**, 10 eq.

For both reactions a highly comparative conversion was derived from the NMR-results. To further support the hypothesis of the non-coordinative behaviour of the tetrazole towards the palladium during the reaction another reaction without a substituted tetrazole as reagent was investigated.

Using the same conditions as for all the tetrazole-containing coupling reactions, 3-nitrophenylboronic acid and 4-bromotoluene were coupled to 4'-methyl-3-nitro-1,1'-biphenyl (scheme 4). In five series, each repeated four times, the reaction was investigated without any additive, with 0.1 and 1.0 eq of benzyl tetrazole (BnTz), and 0.1 and 1.0 eq of triphenylphosphine (PPh_3) as additives. PPh_3 was chosen as additive which is known to act as ligand for Pd in Suzuki-reactions.

Scheme 4. Reaction of 3 nitrophenylboronic acid and 4-bromotoluene in the presence of different amounts of additive



In figure 2 the conversion versus time is plotted for all five series between 15 and 120 seconds.

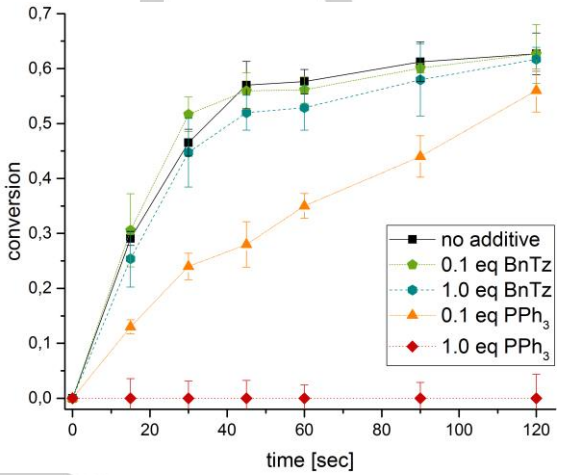
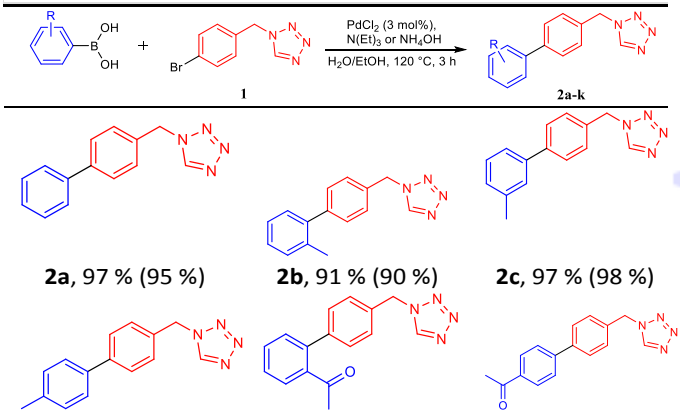


Figure 2. Conversion of 3 nitrophenylboronic acid and 4-bromotoluene with different amounts of additive

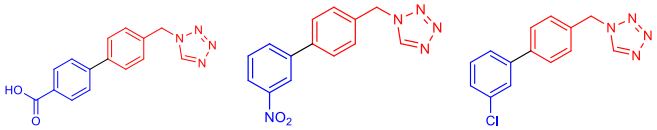
Comparing the reaction rate for the reaction without additive and with 0.1 eq. or 1.0 eq. of added benzyl tetrazole it becomes apparent, that there is no significant deviation in the reaction rate. In contrast, once although a stoichiometric amount (referring to the amount of Pd-catalyst) of PPh_3 is present in the reaction, the conversion is notably decelerated. In the case of a large excess as present in the series with 1.0 eq. of PPh_3 any product formation is completely suppressed.

Table 5. Scope of aryl-coupling protocol

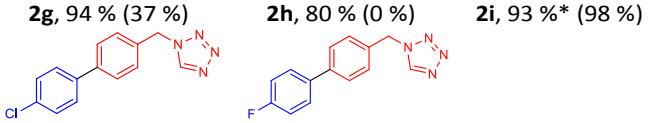


2a, 97 % (95 %) **2b**, 91 % (90 %) **2c**, 97 % (98 %)

2d, 86 % (91 %) **2e**, 87 % (0 %) **2f**, 87 % (96 %)



2g, 94 % (37 %) **2h**, 80 % (0 %) **2i**, 93 %* (98 %)



2j, 90 %* (80 %) **2k**, 89 % (98 %)

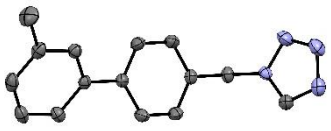
All these results confirm the hypothesis, that the tetrazole does not coordinate towards the palladium during the reaction and so the term ligand-free is appropriate for the herein presented coupling protocol.

Encouraged by the results achieved with phenylboronic acid, scope and substrate tolerance of this protocol were investigated using different phenylboronic acids (table 5). Considering potential costs and technical relevance, all experiments were performed in duplicate; once with $N(Et)_3$ and once with NH_4OH. The yields with NH_4OH as a base are shown in parenthesis in table 5.

All products could be obtained in good to excellent yields, ranging from 79-97 %, most of them in spectroscopic purity without further purification (see experimental). This clearly demonstrates the viability of the coupling protocol and its broad scope.

Aqueous ammonia could prove a practical alternative to triethylamine due to its easy handling and work-up. For larger scale application the handling of ammonia would be attractive and enhance the ease of the protocol. As can be seen from table 5, with NH_4OH as base a strong substrate-dependency is observed. Whereas some examples work slightly better, for **2e** and **2h** no product could be isolated. Therefore, from an overall perspective, $N(Et)_3$ is still the base of choice.

In many cases, directly after workup and recrystallization, the products were obtained in crystalline form, suitable for structural characterization. In figure 3 the molecular structure of **2c** is presented as an example.



Z=4		$P2_1/n$	
a [Å]	10.0896(5)	α [°]	90
b [Å]	10.1761(5)	β [°]	107.387(2)
c [Å]	13.1402(7)	γ [°]	90
V [Å^3]	1287.5	wR_2	6.06

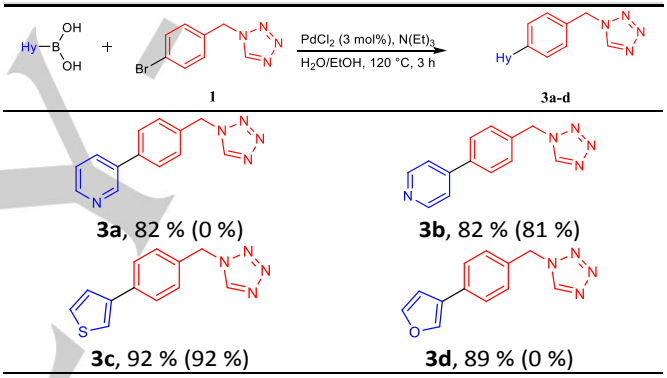
Figure 3. Molecular structure of **2c** (CCDC 1525257)

Only **2b** and **2h** required purification by flash-chromatography demonstrating the flexibility and substrate tolerance of the protocol. The comparably low yield for **2h** may be explained by the chromatographic work-up combined with the electron withdrawing substituent, known to reduce the performance of Suzuki reactions.

For chlorophenylboronic acids the reaction failed at 120 °C, yielding an inseparable mixture of decomposition products and product. Lowering the reaction temperature could circumvent the decomposition of the product, allowing for 93 % (**2i**) and 90 % (**2j**) yield at room-temperature. It should be mentioned, that after 18 h at room-temperature other boronic acid substrates yielded only traces of the desired product.

A further extension of the scope was possible using heteroarylboronic acids (table 6).

Table 6. Scope of heteroaryl (Hy)-coupling protocol



Compounds **3a-d** were obtained in very good yields after crystallization from ethyl acetate, whereas **3a** and **3b** required further chromatographic purification. In the case of heteroaryl-boronic acids substrate-dependent performance of NH_4OH is also found, since **3a** and **3d** did not react.

Conclusions

Suzuki coupling of N1-substituted tetrazoles yielding substituted tetrazolic biaryl-systems has been investigated and optimized protocols have been developed. These protocols expand upon the known procedures for C5- or C5 / N1-bisubstituted tetrazoles, resulting in novel N1-tetrazolic biaryl-systems with remarkably different reactivities. The use of $PdCl_2$ as ligand-free Pd-source in a 1:1 water-ethanol mixture led to excellent yields under mild and environmentally benign aerobic conditions. Optimal results were achieved using $N(Et)_3$ as base, since environmentally benign NH_4OH limits substrate scope, nevertheless NH_4OH offers an interesting alternative especially when considering technical scale syntheses and workup. In this case also the

use of gaseous NH_3 could be considered. Whereas an alternative protocol using $Pd(PPh_3)_4$ in toluene (featuring comparable yields) displays moisture- and oxygen sensitivity, the ligand-free protocol requires large water contents for complete conversion and high yields. In the latter case, the O_2-concentration had no effect on the reaction outcome.

Competitive experiments of 4-bromobenzyl tetrazole and benzyl tetrazole in the reaction leading to **1a** showed no significant deviation in the presence of an excess of benzyl tetrazole. Additionally, using benzyl tetrazole as an additive in the coupling reaction of 3-nitrophenylboronic acid with 4-bromotoluene did not affect the reaction rate. In contrast, even small amounts of PPh_3 notably decreased the conversion rate. Based on these results it could be confirmed, that the tetrazole is non-coordinative during the coupling reaction and therefore does not act as a ligand during the catalytic cycle.

The method developed is further characterized by broad substrate tolerance, including electron withdrawing groups and heterocycles. The protocol allows for easy synthesis of a library of tetrazoles with varying substitution patterns, which offers a valuable tool for the investigation of a substituent-effect driven structure-property relationships in iron(II) spin crossover materials. In addition, this work may act as stimulus for a further investigation of other coupling reactions for substituted tetrazoles, offering ready access to an even wider variety of tetrazole derivatives, many of which are currently accessible by multi-step reactions.

Experimental Section

Materials and methods

All organic solvents were dried and degassed in the ultrasonic bath prior to use according to standard methods.[15] Water was degassed prior to use. For all experiments under aerobic conditions solvents and reagents were used as supplied without further purification. All reagents and boronic acids were commercially obtained from Sigma Aldrich, TCI-Chemicals or Apollo Scientific and used as supplied. Unless otherwise stated, all reactions were performed in sealed vessels, closed under normal aerobic conditions.

^1H, ^{19}F and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker 400 spectrometer with broad-band probe head. All NMR chemical shifts are reported in ppm; ^1H and ^{13}C shifts are referenced to the residual solvent resonance. A detailed peak assignment was based on 2D NMR experiments (COSY, HSQC and HMBC) and is given in the supporting information.

Mid-range IR spectra were recorded in attenuated total reflection (ATR) technique within the range of 4000 – 450 cm^{-1} using a Perkin-Elmer Spectrum Two Fourier-transform infrared spectrometer.

The melting points were determined via thermogravimetric analysis performed on a Netzsch TG 209-C in a closed Al crucibles with a heating rate of 10 K min^{-1} under nitrogen atmosphere.

For high-resolution MS analysis methanolic solutions with a 10 µM sample concentration were used. The setup included an HTC PAL system autosampler (CTC Analytics AG, Zwingen, Switzerland), an Agilent 1100/1200 HPLC with binary pumps, degasser and column thermostat (Agilent Technologies, Waldbronn, Germany) and an Agilent 6230 AJS ESI-TOF mass spectrometer (Agilent Technologies, Palo Alto, United States).

Single crystals were attached to a glass fibre using perfluorinated oil and mounted on a Bruker KAPPA APEX II diffractometer equipped with a CCD detector. Data were collected at 200 K (Cryostream 800, Oxford Cryosystems) in a dry stream of nitrogen with Mo Kα radiation (Incoatec Microfocus Source IµS: 30 W, multilayer mirror, λ=0.71073 Å). Redundant data sets were collected.

Synthesis of the starting material

4-Bromobenzyl-1H-*tetrazole (1)* Synthesis of 4-Bromobenzyl-*1H*-tetrazole was performed according to the established Franke protocol[16]. A mixture of 4-Bromobenzylamine (10 g, 53.75 mmol), sodium azide (3.84 g, 59.12 mmol) and triethyl orthoformate (9.16 g, 61.81 mmol) in 200 ml acetic acid was heated to 95 °C for 18 h. After evaporation of all volatiles under reduced pressure, 200 ml of isopropyl alcohol were added and traces of remaining acetic acid were neutralized using sodium bicarbonate. The precipitate was filtered off and the residual solution was evaporated under reduced pressure. The crude product was obtained as off-white solid after recrystallization from MeOH. (11.2 g, 87 %)

Mp: 113.8-114.3 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3114; ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.65 (s, 1H, TzCH), 7.61 – 7.46 (m, 2H, ArH), 7.25 – 7.15 (m, 2H, ArH), 5.57 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2, δ): 143.14 (TzCH), 132.89 (2ArCH, ArC), 130.54 (2ArCH), 123.74 (ArC), 51.86 (CH_2); HRMS (ESI-TOF) m/z: [M + Na]+ Calc. for $C_8H_7BrN_4Na$ 260.9752, found 260.9754.

Coupling of arylboronic acids

General procedure To a stirred mixture of 4-Bromobenzyl-*1H*-tetrazole (1) (1 eq) and boronic acid (1.1 eq) in H_2O:EtOH (1:1), $N(Et)_3$ (2 eq) and 0.03 eq. of an 0.01 M aqueous solution of $PdCl_2$ were rapidly added. The dispersion was sealed, heated, if not stated otherwise, to 120 °C and kept at this temperature for 3 h. The reaction mixture was allowed to cool to room-temperature and extracted with EA. After filtration of the organic phase over

SiO_2 the solvent was removed under reduced pressure to yield the crude product.

((4-Biphenylyl)methyl)-1H-*tetrazole (2a)* The crude product was recrystallized from DCM:PE (1:1) to afford 2a (white solid, 95.9 mg, 97.2 % yield).

Mp: 178.9-179.6 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3113; ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.59 (s, 1H, Tz-CH), 7.65 (d, *J* = 8.6 Hz, 2H, ArH), 7.60 (dd, *J* = 8.4, 1.4 Hz, 2H, ArH), 7.50 – 7.43 (m, 2H, ArH), 7.42 – 7.36 (m, 3H, ArH), 5.63 (s, 2H CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2, δ): 143.07 (TzCH), 142.70 (ArC), 140.56 (ArC), 132.67 (ArC), 129.46 (ArC), 129.38 (2ArCH), 128.48 (2ArCH), 128.38 (ArCH), 127.61 (2ArCH), 52.42 (CH_2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calc. for $C_{14}H_{12}N_4Na$: 259.0960, found 259.0953.

((2'-Methyl-4-biphenylyl)methyl)-1H-*tetrazole (2b)* The crude product was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (1:1) to afford 2b (clear viscous liquid, 95.3 mg, 91.0 % yield).

$\nu_{CH(Tz)}$ cm^{-1}: 3130; ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.63 (s, 1H, TzCH), 7.37 (s, 4H, ArH), 7.31 – 7.14 (m, 4H, ArH), 5.64 (s, 2H, CH_2), 2.24 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl2, δ): 143.56, 143.13, 141.38, 135.85, 132.25, 130.95, 130.64, 130.12, 128.65, 128.17, 126.39, 52.45 (CH_2), 20.69 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{15}H_{15}N_4$: 251.1297, found 251.1299.

((3'-Methyl-4-biphenylyl)methyl)-1H-*tetrazole (2c)* The crude product was recrystallized with DCM:PE (1:1) to afford 2c (white solid, 101.6 mg, 97.1 % yield).

Mp: 122.2-123.6 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3126; ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.60 (s, 1H, TzCH), 7.64 (d, *J* = 8.3 Hz, 2H, ArH), 7.43 – 7.41 (m, 1H, ArH), 7.41 – 7.36 (m, 3H, ArH), 7.33 (t, *J* = 7.5 Hz, 1H, ArH), 7.20 (d, *J* = 1.0 Hz, 1H, ArH), 5.63 (s, 2H, CH_2), 2.41 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2, δ): 143.09 (TzCH), 142.80 (ArC), 140.45 (ArC), 139.23 (ArC), 132.56 (ArC), 129.32 (3ArCH), 129.09 (ArCH), 128.43 (2ArCH), 128.33 (ArCH), 124.66 (ArCH), 52.40 (CH_2), 21.77 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{15}H_{15}N_4$: 251.1297, found 251.1297.

((4'-Methyl-4-biphenylyl)methyl)-1H-*tetrazole (2d)* The crude product was recrystallized with DCM:PE (1:1) to afford 2d (white solid, 90 mg, 86.1 % yield).

Mp: 167.0-168.3 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3099; ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.59 (s, 1H, TzCH), 7.63 (d, *J* = 8.3 Hz, 2H, ArH), 7.49 (d, *J* = 8.3 Hz, 2H, ArH), 7.37 (d, *J* = 8.4 Hz, 2H, ArH), 7.27 (d, *J* = 7.9 Hz, 2H, ArH), 5.62 (s, 2H, CH_2), 2.39 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl2, δ): 143.07 (TzCH), 142.59 (ArC), 138.42 (ArC), 137.56 (ArC), 132.32 (ArC), 130.15 (2ArCH), 129.35 (2ArCH), 128.20 (2ArCH), 127.38 (2ArCH), 52.42 (CH_2), 21.37 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{15}H_{15}N_4$: 251.1297, found 251.1295.

*(4'-((*1H-*Tetrazol-1-yl)methyl)-2-biphenylyl)ethan-1-one (2e)* The crude product was recrystallized with DCM:PE (1:1) to afford 2e (white solid, 101.3 mg, 87.0 % yield).

Mp: 122.7-123.4 °C; $\nu_{CH(Tz)}cm^{-1}$: 3136, $\nu_{C=O}$ cm^{-1}: 1685; ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.68 (s, 1H, TzCH), 7.58 (ddd, *J* = 7.6, 1.5, 0.6 Hz, 1H, ArH), 7.53 (td, *J* = 7.5, 1.5 Hz, 1H, ArH), 7.44 (td, *J* = 7.5, 1.3 Hz, 1H, ArH), 7.39 – 7.33 (m, 5H, ArH), 5.66 (s, 2H, CH_2), 2.13 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2, δ): 203.82 (AcC), 143.22 (TzCH, 142.50 (ArC), 140.94 (ArC), 140.10 (ArC), 133.25 (ArC), 131.37 (ArCH), 131.02 (ArCH), 130.19 (2ArCH), 128.95 (2ArCH), 128.55 (ArCH), 128.29 (ArCH), 52.23 (CH_2), 30.66 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calc. for $C_{16}H_{14}N_4NaO$: 301.1065, found 301.1067.

*(4'-((*1H-*Tetrazolyl)methyl)-4-biphenylyl)ethan-1-one (2f)* The crude product was recrystallized with DCM:PE (1:1) to afford 2f (white solid, 101.4 mg, 87.1 % yield).

Mp: 134.7-136.2 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3106 (ν_{Tz}), $\nu_{C=O}$: 1680 (C=O); ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.61 (s, 1H, TzCH), 8.08 – 8.00 (m, 2H, ArH), 7.70 (dd, *J* = 8.6, 2.0 Hz, 4H, ArH), 7.45 – 7.39 (m, 2H, ArH), 5.65 (s, 2H, CH_2), 2.61 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl2, δ): 197.85 (C=O), 144.89 (ArC), 143.11 (TzCH), 141.40 (ArC), 136.98 (ArC), 133.67 (ArC), 129.48 (2ArCH), 129.44 (2ArCH), 128.67 (2ArCH), 127.75 (2ArCH), 52.32 (CH_2), 27.08 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{16}H_{15}N_4O$: 279.1246, found 279.1247.

*(4'-((*1H-*Tetrazolyl)methyl)-4-biphenylyl)carboxylic acid (2g)* The crude product was recrystallized with EA to afford 2g (white solid, 109,0 mg, 93.8 % yield).

Mp: 267 °C (decomp.); $\nu_{CH(Tz)}$ cm^{-1}: 3118, $\nu_{C=O}$: 1674; ^1H NMR (400 MHz, DMSO-d_6, δ): 13.00 (s, 1H, COOH), 9.57 (s, 1H, TzCH), 8.01 (d, *J* = 8.6 Hz, 2H, ArCH), 7.78 (dd, *J* = 11.2, 8.5 Hz, 4H, ArCH), 7.47 (d, *J* = 8.4 Hz, 2H, ArCH), 5.78 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6, δ): 167.05 (C=O), 144.09 (TzCH), 143.52 (ArC), 139.12 (ArC), 134.81 (ArC), 129.94 (2ArCH), 129.86 (ArC), 128.88 (2ArCH), 127.45 (2ArCH), 126.83 (2ArCH), 50.41 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{15}H_{13}N_4O_2$: 281.1039, found 281.1037.

((3'-Nitro-4-biphenylyl)methyl)-1H-*tetrazole (2h)* The crude product was purified by column chromatography on silica gel with EA:PE (2:1) to afford 2h (slightly yellow solid, 97.9 mg, 79.7 % yield).

Mp: 146.4-147.5 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3125; ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.63 (s, 1H), 8.44 (t, *J* = 2.0 Hz, 1H, TzCH), 8.21 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H, ArH), 7.93 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H, ArH), 7.73 – 7.68 (m, 2H, ArH), 7.65 (t, *J* = 8.0 Hz, 1H, ArH), 7.49 – 7.41 (m, 2H), 5.66 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2, δ): 149.39 (ArC), 143.13 (TzCH), 142.26 (ArC), 140.23 (ArC), 134.07 (ArC), 133.65 (ArCH), 130.54 (ArCH), 129.64 (2ArCH), 128.65 (2ArCH), 123.04 (ArCH), 122.44 (ArCH), 52.24 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{14}H_{12}N_5O_2$: 282.0991, Found 282.0980.

((3'-Chloro-4-biphenylyl)methyl)-1H-*tetrazole (2i)* 3-Chlorophenylboronic acid (72.0 mg, 460.1 µmol) and 1 (100

mg, 418.3 µmol) were reacted according to the general procedure at room temperature. The crude product was recrystallized with DCM:PE (1:1) to afford 2i (off-white solid, 104.2 mg, 92.8 % yield).

Mp: 137.0-138.2 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3122; ^1H NMR (400 MHz, CD_2Cl_2, δ) : 8.62 (s, 1H), 7.66 – 7.60 (m, 2H, ArH), 7.58 (t, *J* = 1.9 Hz, 1H, ArH), 7.49 (dt, *J* = 7.5, 1.6 Hz, 1H, ArH), 7.43 – 7.38 (m, 3H, ArH), 7.36 (dt, *J* = 7.9, 1.7 Hz, 1H, ArH), 5.64 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2, δ): 143.12 (TzCH), 142.45 (ArC), 141.17 (ArC), 135.21 (ArC), 133.39 (ArC), 130.78 (ArCH), 129.45 (2ArCH), 128.46 (2ArCH), 128.29 (ArCH), 127.68 (ArCH), 125.91 (ArCH), 52.28 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{14}H_{12}ClN_4$: 271.0751, found 271.0748.

((4'-Chloro-4-biphenylyl)methyl)-1H-*tetrazole (2j)* 4-Chlorophenylboronic acid (72.0 mg, 460.1 µmol) and 1 (100 mg, 418.3 µmol) were reacted according to the general procedure at room temperature. The crude product was recrystallized with DCM:PE (1:1) to afford 2j (white solid, 101.9 mg, 90.1 % yield).

Mp: 103.7-104.9 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3113; ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.60 (s, 1H, TzCH), 7.64 – 7.60 (m, 2H, ArH), 7.56 – 7.52 (m, 2H, ArH), 7.47 – 7.42 (m, 2H, ArH), 7.41 – 7.37 (m, 2H, ArH), 5.63 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl2, δ): 143.08 (TzCH), 141.41 (ArC), 139.10 (ArC), 134.39 (ArC), 133.05 (ArC), 129.57 (2ArCH), 129.46 (2ArCH), 128.96 (2ArCH), 128.34 (2ArCH), 52.34 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{14}H_{12}ClN_4$: 271.0751, found 271.0749.

((4'-Fluoro-4-biphenylyl)methyl)-1H-*tetrazole (2k)* The crude product was recrystallized with DCM:PE (1:1) to afford 2k (white solid, 94.7 mg, 89.4 % yield).

Mp: 118.5-120.4 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3105, (ν_{C-F}) cm^{-1}: 1252; ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.59 (s, 1H, TzCH), 7.63 – 7.59 (m, 2H, ArH), 7.59 – 7.55 (m, 2H, ArH), 7.41 – 7.37 (m, 2H, ArH), 7.20 – 7.11 (m, 2H, ArH), 5.62 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2, δ): 163.32 (d, *J* = 246.2 Hz, ArC), 143.07 (TzCH) , 141.69 (ArC) , 136.80 (d, *J* = 3.2 Hz, ArC), 132.71 (ArC) , 129.42 (2ArCH) , 129.33 (d, *J* = 8.1 Hz, 2ArCH)), 128.37 (2ArCH) , 116.28 (d, *J* = 21.6 Hz, 2ArCH)), 52.37 (CH_2); ^{19}F NMR (376 MHz, CD_2Cl2) δ -115.66; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calc. for $C_{14}H_{11}FN_4Na$: 277.0865, found 277.0871.

Coupling of heteroarylboronic acids

*3-(4-((*1H-*Tetrazol-1-yl)methyl)phenyl)pyridine (3a)* The crude product was purified by column chromatography on silica gel with EA:MeOH (10:1) to afford 3a (white solid, 81.6 mg, 82.2 % yield).

Mp: 96.5-98.7 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3111; ^1H NMR (400 MHz, CD_2Cl_2, δ): 8.81 – 8.79 (m, 1H, pyrH), 8.78 (s, 1H, TzCH), 8.57 (dd, *J* = 4.8, 1.7 Hz, 1H, pyrH), 7.86 (ddd, *J* = 7.9, 2.5, 1.5 Hz, 1H, pyrH), 7.61 (dd, *J* = 8.4, 2.1 Hz, 2H, ArH), 7.46 – 7.41 (m, 2H, ArH), 7.36 (ddd, *J* = 7.9, 4.8, 1.0 Hz, 1H, pyrH), 5.68 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2, δ): 149.39 (PyrCH), 148.62 (PyrCH), 143.30 (TzCH), 139.20 (PyrC), 135.88 (ArC), 134.64 (PyrCH), 133.67 (ArC), 129.50 (2ArCH), 128.34 (2ArCH), 124.06 (PyrCH), 52.12 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{13}H_{12}N_5$: 238.1093, found 238.1085.

*4-(4-((*1H-*Tetrazol-1-yl)methyl)phenyl)pyridine (3b)* The crude product was purified by column chromatography on silica gel with EA:MeOH (10:1) to afford 3b (white solid, 81.3 mg, 81.9 % yield).

Mp: 134.7-135.6 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3111; ^1H NMR (400 MHz, MeOD, δ): 9.29 (s, 1H, TzCH), 8.59 – 8.55 (m, 2H, PyrH), 7.78 (d, *J* = 8.6 Hz, 2H, ArH), 7.71 – 7.67 (m, 2H, PyrH), 7.51 (d, *J* = 8.7 Hz, 2H, ArH), 5.78 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, MeOD, δ): 150.64 (2PyrCH), 149.73 (PyrC), 144.82 (TzCH), 139.36 (ArC), 136.91 (ArC), 130.24 (2ArCH), 128.83 (2PyrCH), 123.12 (2ArCH), 52.28 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{13}H_{12}N_5$: 238.1093, found 238.1089.

1-(4-(Thiophen-3-yl)benzyl)-1H-*tetrazole (3c)* The crude product was recrystallized with EA to afford 3c (off-white solid, 93mg, 91.8 % yield).

Mp: 184.8-185.9 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3110; ^1H NMR (400 MHz, DMSO-d_6 , δ): 9.54 (s, 1H, TzCH), 7.92 – 7.87 (m, 1H), 7.78 – 7.71 (m, 2H), 7.64 (dd, *J* = 5.1, 2.8 Hz, 1H), 7.57 – 7.54 (m, 1H), 7.43 – 7.33 (m, 2H), 5.73 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6, δ): 143.98 (TzCH), 140.69, 135.25, 133.44, 128.76, 127.18, 126.48, 126.11, 121.44, 50.48 (CH_2); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{12}H_{11}N_4S$: 243.0704, found 243.0699.

1-(4-(Furan-3-yl)benzyl)-1H-*tetrazole (3d)* The crude product was recrystallized with EA to afford 3d (off-white solid, 83.9mg, 88.7 % yield).

Mp: 141.1-142.1 °C; $\nu_{CH(Tz)}$ cm^{-1}: 3149; ^1H NMR (400 MHz, DMSO-d_6, δ): 9.52 (s, 1H), 8.19 (t, *J* = 1.2 Hz, 1H), 7.74 (t, *J* = 1.7 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.34 (m, 2H), 6.96 (dd, *J* = 1.9, 0.9 Hz, 1H), 5.71 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6, δ): 144.35, 143.95, 139.63, 133.22, 132.17, 128.74, 125.92, 108.62, 50.52, 39.52; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calc. for $C_{12}H_{11}N_4O$: 227.0933, found 227.0926.

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Keywords: cross coupling • C-C coupling • ligand-free Suzuki reaction • N1-substituted tetrazoles • spin crossover

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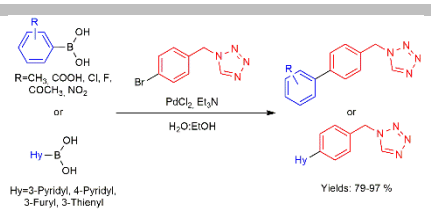
Entry for the Table of Contents

FULL PAPER

Development and substrate scope of a green, ligand-free Suzuki protocol in aqueous media under ambient atmosphere, leading to 1- biaryl- and heteroaryl- substituted *1H*-tetrazoles in very good to excellent yields is presented.



Cross-coupling*

Marco Seifried, Christian Knoll, Gerald Giester, Jan M. Welch, Danny Müller* and Peter Weinberger

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Aryl and heteroaryl N1- tetrazoles via ligand-free Suzuki-reaction under aerobic, aqueous conditions