TECHNISCHE UNIVERSITÄT WIEN

DIPLOMARBEIT

Suzuki Cross Coupling of 4-Bromobenzyl-(*1H*)-tetrazole for a Rational Ligand Design in Series of Fe(II) Spin-Crossover Complexes

ausgeführt am

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Zusammenfassung

Seit 1982 Haasnoot *et al.* N-substituierte Tetrazole als Liganden für Spinübergangsverbindungen einführte, sind diese neben weiteren gängigen Ligandensystemen in Verwendung. Im Gegensatz zu anderen Systemen ist die Herstellung von komplizierteren Tetrazolen durch niedrigere Ausbeuten und schwierige synthethische Wege meist beschränkt.

Im Zuge dieser Arbeit wird eine neue Herangehensweise zur Herstellung von Tetrazolen untersucht, bei der das N-substituierte Tetrazol durch palladiumkatalysierte Kreuzkupplung mit dem Zielmolekül verbunden wird. Dadurch ergibt sich zusätzlich zu den bereits bestehenden Methoden ein weiterer Weg zur Darstellung verschieden funktionalisierter Tetrazole, was eine systematische Untersuchung des Spin-Übergang-Phänomens der damit komplexierten Eisen(II)-Salze weiter erleichtert und teilweise überhaupt erst ermöglicht.

Als Modellsystem wurde eine der bekanntesten und best untersuchten Kreuzkupplungen, die Suzuki-Miyaura Reaktion, untersucht. Als Testsubstrat wurde 4-Brombenzyl-*1H*-tetrazol gewählt. Durch sukzessive Optimierung der Parameter wurden Bedingungen gefunden, bei denen das Produkt in sehr zufriedenstellenden Ausbeuten erhalten wurde. Die Methode wurde auf unterschiedliche Moleküle angewandt, die Produkte wurden eingehend charakterisiert und auf ihre Anwendbarkeit hinsichtlich der Komplexierung mit Eisen(II) untersucht.

Anschließend wurden zwei weitere Kreuzkupplungsreaktionen, die Heck- und die Sonogashirakupplung, mit geeigneten Substraten untersucht. Dabei konnten ebenfalls Bedingungen gefunden werden, bei denen das Tetrazol mit dem Substrat eine Bindung eingeht, allerdings in weitaus niedrigeren Ausbeuten als bei der Suzuki-Reaktion.

Somit liefert diese Arbeit eine erste Einführung in Kreuzkupplungsreaktionen von N-substituierten Tetrazolen, wodurch sich neue Synthesepfade von ansonsten schwierig zugänglichen Tetrazolen ergeben.

Abstract

In 1982 Haasnoot *et al.* introduced N-substituted tetrazoles as ligands for spin-crossover compounds. Since then they have been used amongst other systems as spin-crossover ligands. In contrast to other systems the synthesis of complicated tetrazoles encounters difficulties due to low yields or difficult synthetic pathways.

Herein a new pathway for the synthesis of N-substituted tetrazoles via palladium-catalyzed cross coupling reactions is investigated. This establishes an additional method for the synthesis of formerly difficult accessible functionalized tetrazoles. Therefore, a systematic study of the SCO phenomenon using those compounds is drastically simplified.

As a model system one of the most famous and best studied cross coupling reactions was chosen, the Suzuki-Miyaura reaction. The reaction was investigated with 4-bromobenzyl-*1H*-tetrazole as test substrate. Optimization of the reaction parameters gave conditions under which satisfying yields were achieved. The scope of this reaction was studied and the products were characterized and tested for their potential use as SCO-ligands in iron(II) compounds.

Two further coupling reactions were investigated regarding their applicability for the introduction of the tetrazole moiety, the Heck and the Sonogashira reaction. For both reactions conditions were found with the tetrazole reacting with the substrate, although in far lower yields than in the Suzuki coupling.

Therefore, this work introduces palladium-catalyzed cross coupling reactions as an alternative pathway for the synthesis of otherwise inaccessible N1-substituted tetrazoles.

Contents

List of Abbreviations

AcOH	Acetic acid
ATR	Attenuated total reflection
B3LYP	Becke, 3-parameter, Lee-Yang-Parr
CD_2Cl_2	Dideuteromethylenechloride
$CDCl_3$	Deuterochloroform
COSY	Correlated nuclear magnetic resonance spectroscopy
Cs_2CO_3	Caesium carbonate
CuI	Copper(I) iodide
dec	Decomposition
DFT	Density functional theory
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
ESI-TOF	Electronspray ionization - time-of-flight mass spectrometry
Et_3N	Triethylamine
EtOH	Ethanol
$Fe(BF_4)_2$	Iron(II) tetrafluoroborate
FIR	Far-infrared
HCl	Hydrochloric acid
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HPLC	High performance liquid chromatography
HR-MS	High resolution mass spectrometry
HS	High spin
HSQC	Heteronuclear single quantum correlation spectroscopy
Hy	Heteroaryl

K_2CO_3	Potassium carbonate
KH_2PO_4	Monopotassium phosphate
LS	Low spin
MeOD	Tetradeuteromethanol
MIR	Mid-infrared
Na_2CO_3	Sodium carbonate
NaCl	Sodium chloride
$NaHCO_3$	Sodium bicarbonate
NaN_3	Sodium azide
NaOH	Sodium hydroxide
NH_3	Ammonia
$Ni(dppp)Cl_2$	[1,3-Bis(diphenylphosphino)propane]dichloronickel(II)
Ni(OAc)	Nickel(II) acetate
NIR	Near-infrared
NMR	Nuclear magnetic resonance spectroscopy
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Pd/C	Palladium on activated charcoal
$PdCl_2$	Palladium(II) chloride
PhMe	Toluene
SCO	Spin crossover
SiO_2	Silicon dioxide
THF	Tetrahydrofuran
Tz	Tetrazole
VSC-3	Vienna scientific cluster 3
VSM	Vibrating sample magnetometer

Chapter 1

Introduction

1.1 Spin-Crossover Phenomenon

Spin-Crossover (SCO) describes a phenomenon occuring in some first row transition metal compounds with electron configurations between d^4-d^7. First described in 1931 by Cambi and Szegö[1,2] and falsely attributed to different magnetic isomers it was later discovered to be an effect of the provided ligand field to induce a metastabile state, where either the high spin or the low spin state is favoured depending on different external factors like temperature, pressure or even the exposure to light of different wavelengths.[3–8]

In the first decades after its discovery spin-crossover was limited to iron(III) compounds. After some investigations of different donor sets and better understanding of the underlying chemistry, spin-crossover compounds were discovered for different metal centers with configurations between d^4 and d^7, such as iron(II),[4] cobalt(II),[9,10] cobalt(III)[11] or manganese(III).[12] The SCO behaviour is influenced by different factors. The most important is obviously the appropiate donor strength of the ligand but also factors like the nature of the counter anion or structurally incorporated solvent play a big role. Only if all these factors play together a spin-crossover compound is obtained.

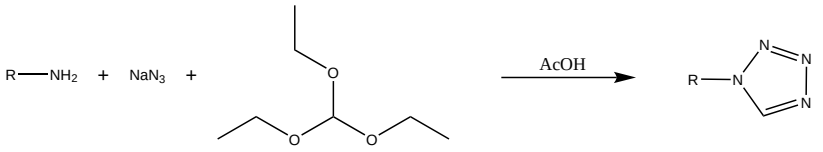
Although many efforts were taken to understand the phenomenon of SCO and to describe the factors governing the magnetic behavior precisely, the occurence of SCO still lacks predictability. Prior to synthesis it can not be said for sure if a compound would show spin crossover behaviour and in which temperature range it will occure. Therefore, there is no clear rule for the design of the ligand, although some systems proved to be suitable with a high degree of probability to feature SCO behavior. Nevertheless, the research in the field of spin-transition compounds is still restricted to a mainly trial-and-error approach.

To gain better insight into the mechanistics of the structure-property relationship of SCO compounds an easy modification of the ligand system is of utmost importance and allows for a systematic study of homologous series of ligands. One possible candidate for rather easy modification setting up building blocks for Fe(II) SCO compounds are N1-functionalized tetrazoles.

1.2 State of the Art: Syntheses of Tetrazoles

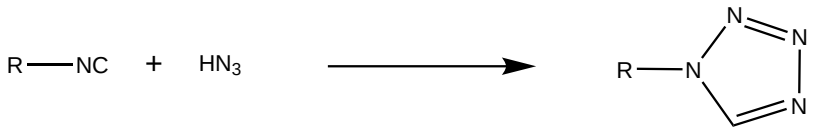
In 1982 Haasnoot *et al.* introduced N1-substituted tetrazoles as ligands for Fe-SCO compounds.[13] The detailed study of the propyl-*1H*-tetrazole[6,14] lead to further systematic investigations of homologous series based on N1-substituted tetrazoles.[15] The substitution on the N1-nitrogen restricts the metal coordination to the N4-nitrogen and therefore simplifies the study due to the absence of coordinational isomers.

For systematic studies a simple modification of the ligand system is of utmost importance. N1-substituted tetrazoles are mostly obtained via a ring-formation reaction starting from the corresponding primary amine.[13,16] This approach is most suitable for simple amines, but the yields on more sophisticated substituted amines proved to be rather unsatisfying.



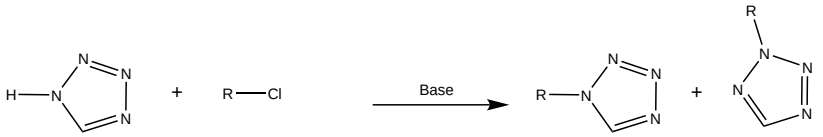
Scheme 1.1: Outline of the synthesis of N1-substituted tetrazoles as published by Franke.[13]

A well known synthetic protocol leading to 5-substituted tetrazoles uses the corresponding nitriles and sodium azide.[17,18] A similar approach leading to the 1-substituted analogue would proceed via the corresponding isonitrile (scheme 1.2) as reported by Smith and Kalenda.[19] As isonitriles are known to be very odorant and usually are prepared via a primary amine this route is rather unfavourable anyway.



Scheme 1.2: Synthetic pathway leading to N1-substituted tetrazoles via isonitriles.[19]

Additionally, a third pathway uses simple alkylation of the *1H*-tetrazole (scheme 1.3).[20,21] Due to the mutual isomerization of unsubstituted *1H*-tetrazole and *2H*-tetrazole this approach is essentially limited to yield a mixture of N1- and N2-substituted tetrazoles.



Scheme 1.3: Alkylation of *1H*-tetrazole leading to a mixture of N1 and N2-substituted tetrazoles.[20,21]

1.3 Aim of the Work

The previous section outlined the commonly used pathways for the synthesis of N1-substituted tetrazoles and their disadvantages. An additional route leading to N1-substituted tetrazoles, overcoming those restrictions, would greatly benefit the comparative investigations of the respective SCO behavior with tetrazoles as ligands in iron(II) compounds. In this thesis the introduction of the tetrazole moiety to the target molecule via palladium-catalyzed cross-coupling reactions is investigated. These reactions became popular over the course of the last decades as the conditions are often mild and the carbon-carbon bond formation is otherwise rather difficult to achieve. As the tetrazole can not usually withstand harsh reaction conditions, it was investigated, if conditions can be found, wherein the tetrazole moiety can be coupled onto target molecules, allowing for an easy to achieve library synthesis of similar substituted molecules.

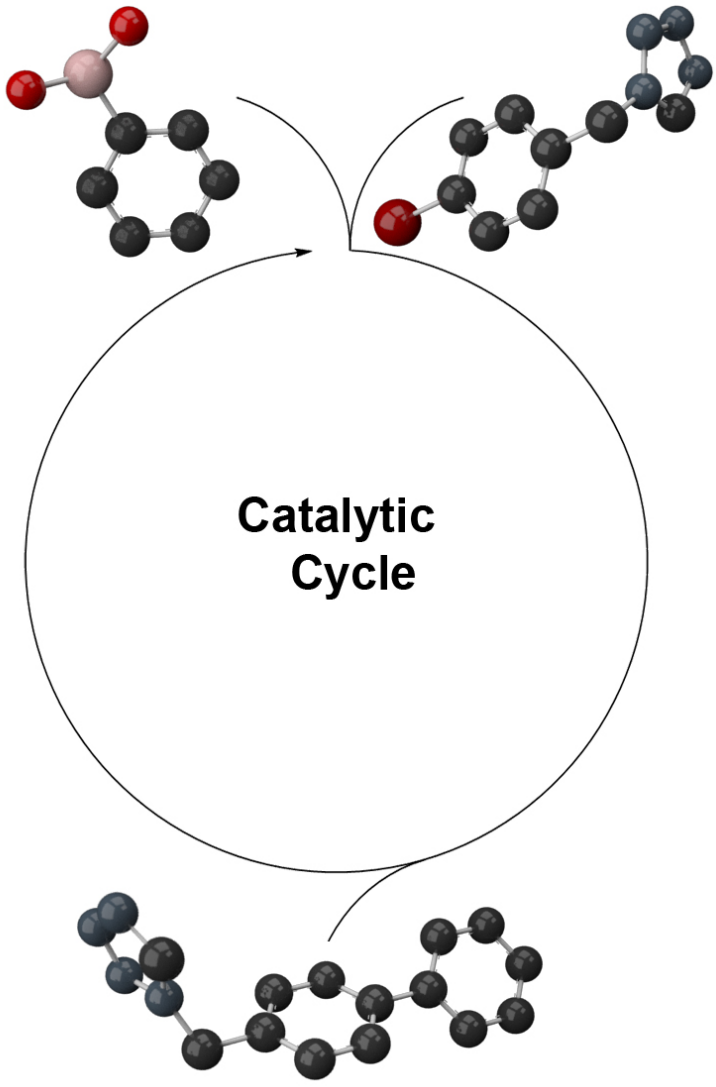
The first and main part of this work (chapter 2) investigates the Suzuki cross-coupling reaction with 4-bromobenzyl-*1H*-tetrazole and consists of the development of an optimized protocol, the synthesis of different molecules under these conditions and their application as ligands for iron(II) SCO compounds.

Then a short digression into the quantumchemical simulation of NMR-spectra tries to answer some questions that arose from the coupling products in the previous chapter.

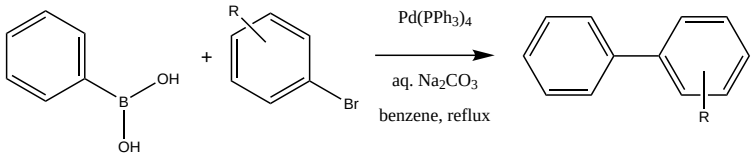
In chapter 4 further two well-known coupling reactions are investigated with N1-substituted tetrazoles as substrate: the Heck- and Sonogashira-type reactions. For the first time a successful coupling of alkenyl and alkynyl groups very close to the tetrazole moiety is reported which allows for the synthesis of compounds otherwise complicated to achieve.

Chapter 2

Suzuki Cross Coupling of Tetrazoles

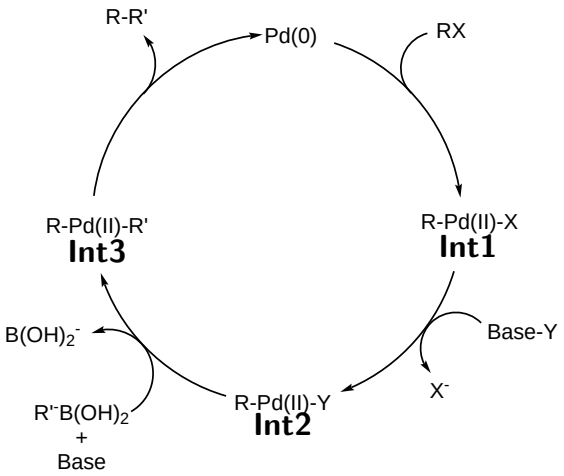


2.1 Introduction



Scheme 2.1: The first published method to prepare biaryls via a coupling reaction.[22]

In 1979 Akira Suzuki and Norio Miyaura published their palladium catalyzed reaction of alkenylboranes with aryl halides.[23] Two years later, in 1981, the scope of this reaction was expanded to the reaction of phenylboronic acid with aryl halides to yield unsymmetrical biaryls (see scheme 2.1).[22] The palladium catalyzed reaction of a boron species with a halide became subsequently known as Suzuki coupling or Suzuki-Miyaura reaction. The nowadays most accepted reaction mechanism is shown in scheme 2.2: A palladium(0) species, which can be generated in situ by variable methods, adds in an oxidative addition to the halide. This organopalladium species, in which the palladium has the oxidation state +2, reacts with a base to form the intermediate **Int2**. This intermediate reacts via transmetallation with the boron species to the organopalladium species **Int3** that yields the product via reductive elimination under regeneration of the catalytically active palladium(0) species. The intermediates **Int1** and **Int3** have been characterized by isolation or spectroscopic analysis[24] and the mechanism of the oxidative addition and reductive elimination are already reasonably well understood and are expected to be nearly the same in all cross coupling reactions. Regarding the transmetallation step the mechanism seems to dependent on the metallic species and used conditions.[25–29]



Scheme 2.2: General Catalytic Cycle for the Suzuki Cross Coupling Reaction.

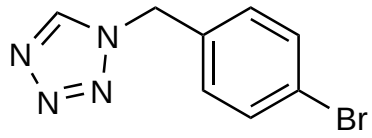
Advantages of the Suzuki Cross Coupling Reaction

The Suzuki coupling has many advantages, which make this reaction a very powerful tool for any synthetic or industrial work. The reactants are readily available, either commercially or via simple synthetic reactions,[30,31] and are generally thermally stable and inert to water and oxygen. Although most published couplings are performed in organic solvents, some report successful syntheses under aqueous[32,33] or heterogenous[33–35] conditions. Its high stereo- and regioselectivity and its high tolerance of a broad range of functional groups make the Suzuki reaction feasible where others would fail. All these reasons make it understandable why the Suzuki reaction is one of the most used and best studied cross coupling reactions today.

2.1.1 Known Couplings of Tetrazoles

One big advantage of the Suzuki coupling is its high tolerance for many different functional groups, which would usually interfere in traditional non-catalyzed reactions. In 1995 Sung-eun Yoo and Kyu Yang Yi published a study of coupling reactions with 5-Bromotetrazoles, with isolated yields of up to 96 %.[36] The reactivity of C5-substituted tetrazoles is known to be very different compared to the N1-substitution pattern. Therefore, the studies made by Yoo and Yi are not easily transferred to N1-substituted tetrazoles. Generally, the literature known references for tetrazoles in coupling reactions are very scarce[36–43] and usually concentrate on the C5-substituted kind as they posses a higher interest in the pharmaceutical field. A comprehensive systematic study of the coupling behaviour of N1-substituted tetrazoles would be very helpful to fill the gap of scientific work of tetrazoles in cross coupling reactions.

2.1.2 Study of the Coupling Reaction of 4-Bromobenzyl-*1H*-Tetrazole



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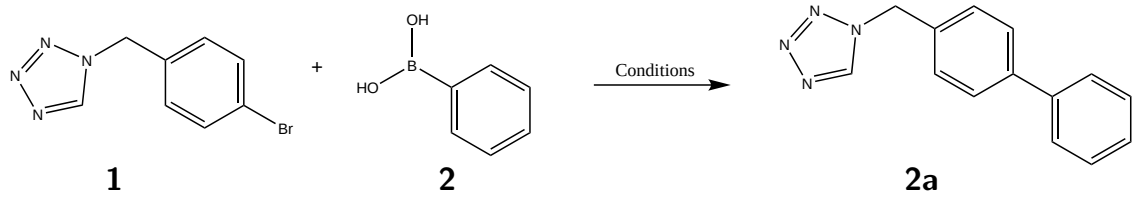
The reaction of 4-Bromobenzyl-*1H*-tetrazole **1** with a variety of different boronic acids was chosen as a model to investigate the coupling behaviour of N1-substituted tetrazoles in a systematic way. This reaction aligns with the early work published by Suzuki and Miyaura,[22] where an arylic halide reacts with aryl boronic acids to give unsymmetric biaryls. The tetrazole substrate was easily obtained from the corresponding amine in high yield. This corroborates the decision on 4-Bromobenzyl-*1H*-tetrazole as a reliable substrate.

2.2 Optimization of the Model Reaction

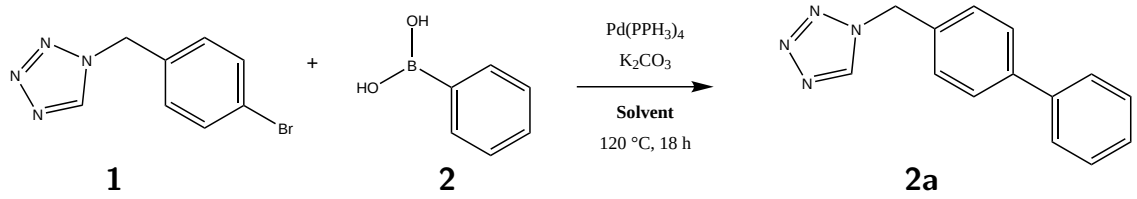


Scheme 2.3: Model Reaction.

Due to the availability at low cost phenyl boronic acid **2** was chosen as a test substrate in the optimization of coupling conditions in the Suzuki cross coupling reaction with 4-Bromobenzyl-*1H*-tetrazole **1**. In three subsequent steps the solvent, catalyst and base were optimized to give a robust coupling protocol.

The reaction parameters were altered towards a cheaper and environmentally benign protocol (aqueous solvent system).[32,44] In the second part the scope of the reaction conditions was determined via the coupling of 4-Bromobenzyl-*1H*-tetrazole **1** with a wide range of different aromatic and heteroaromatic boronic acids.

2.2.1 Influence of the Solvent



Scheme 2.4: Reaction conditions screening the influence of different solvents.

The influence of different solvents on the reaction of phenyl boronic acid and 4-Bromobenzyl-*1H*-tetrazole with tetrakis(triphenylphosphine)palladium(0) and potassium carbonate was investigated (scheme 2.4). As figure 2.1 shows, the best organic solvent under these conditions is toluene, with isolated yields of 97 %. A rather interesting observation was that a higher concentration of water content usually led to higher yields. This is best observed in the reaction with THF; the yield rises from 88 % in pure THF to 96 % in an 1:1 mixture of THF and water. This led to the conclusion that water might benefit the reaction. Therefore, pure water was chosen as one of the possible solvents for further screening. Additionally toluene as the best organic solvent was also chosen for further investigations. THF was excluded as a possible solvent, because the obtained crude product had more side-products and was colored in comparison to the other reaction solvents, although it is one of the most common solvents for the Suzuki reaction.

	Solvent	Yield (%)
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	Dioxane	95
7	PhMe	97
8	EtOH	62
9	EtOH:H_2O (3:1)	66
10	H_2O	80

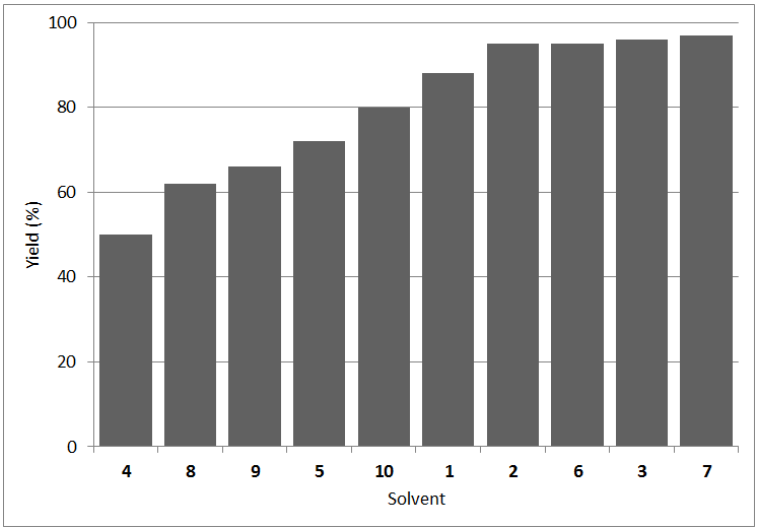
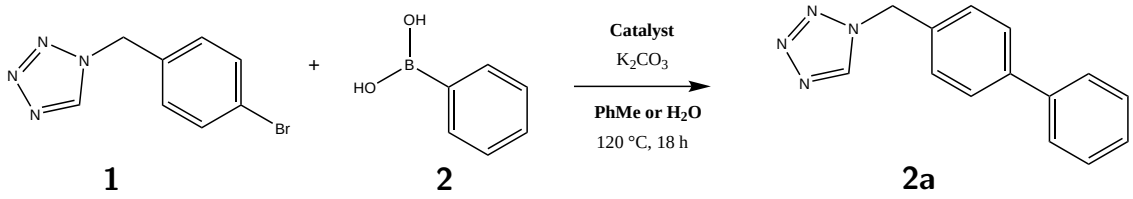


Figure 2.1: Influence of the solvent on the reaction shown in scheme 2.4

2.2.2 Influence of the Catalyst



Scheme 2.5: Reaction conditions for screening of the influence of different catalysts.

Tetrakis(triphenylphosphine)palladium(0) is one of the most common catalyst systems for Suzuki cross couplings. Without the necessity to generate the palladium(0) species in situ the reaction rate is usually higher compared to some other palladium(II) pre-catalytic systems. With toluene and water as the two solvents determined in the previous step, the reaction was performed with some common palladium catalysts and two nickel catalysts. As figure 2.2 shows, the reaction in toluene with tetrakis(triphenylphosphine)palladium(0) already investigated in step one leads to excellent yields of 96 %. Even more interesting is the fact that the same yield was obtained with palladium on activated charcoil, thus providing a cheap palladium source without the need of any ligands. Therefore, the reaction in toluene with Pd/C and potassium carbonate provides already attractive conditions with excellent yields if the use of an organic solvent is of no concern. As a possible environmentally benign alternative the influence of catalysts in aqueous solvent systems was investigated. As shown in figure 2.2, $PdCl_2$ proved to be the best catalyst in water with a yield of 83 %. The reaction of $PdCl_2$ in water was chosen for further investigations, although lower yield than Pd/C in toluene were obtained. This choice was made in favor of a possibly more environmentally

benign and attractive protocol.

Solvent	Catalyst	Yield (%)
PhMe		
	Pd/C	97
	$PdCl_2$	56
	$Pd(PPh_3)_2Cl_2$	none
	$Ni(dppp)Cl_2$	5
	Ni(OAc)	none
	$Pd(PPh_3)_4$	97
H_2O		
	Pd/C	27
	$PdCl_2$	83
	$Pd(PPh_3)_2Cl_2$	40
	$Ni(dppp)Cl_2$	none
	Ni(OAc)	none
	$Pd(PPh_3)_4$	80

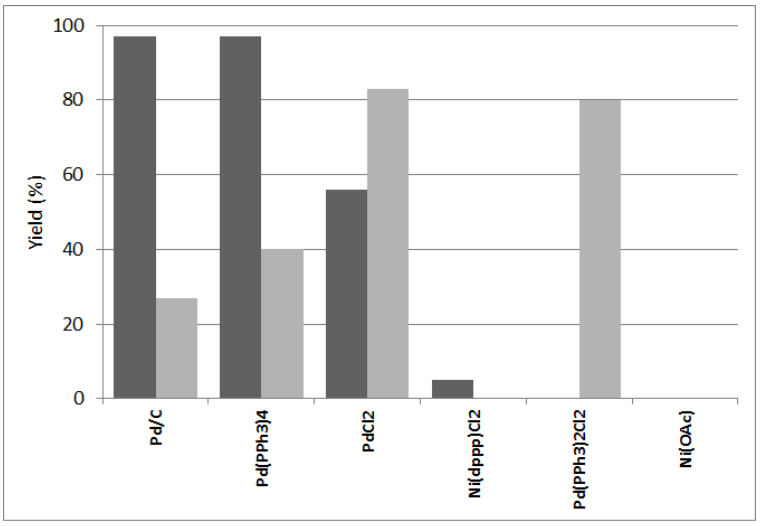


Figure 2.2: Influence of the catalysts on the reaction shown in scheme 2.5. Dark Grey = PhMe, Light Grey = H_2O

2.2.3 Influence of the Base

The influence of different bases on the aqueous conditions determined in the previous step was investigated (see figure 2.4). Triethylamine was found to give better yields than potassium carbonate. More noteworthy is the fact that the workup was drastically improved by the use of triethylamine, as far less side-products were formed and all unwanted reaction products stayed in the aqueous layer upon extraction with an organic solvent. This is depicted in the comparison between the crude product NMRs obtained from using potassium carbonate or triethylamine as base (see figure 2.3). These points led to the conclusion, that although potassium carbonate provides a cheap and less toxic base, triethylamine was used for all further reactions. If the toxicity of triethylamine should be of concern, which could be the case especially in larger scale applications, the coupling scope was also investigated with aqueous ammonia as base, as the industrial and larger scale application of ammonia in reactions is alreay well known and manageable.

2.2.4 Influence of the Atmosphere

During the optimization the question arose if an inert atmosphere is required or not. A set of reactions using either pure THF or THF/H_2O as solvent system an $PdCl_2$ as catalyst with Et_3N as base was performed under three different atmospheres: Argon, air and oxygen. Figure 2.5 compares the conversion of starting material as determined by NMR measurement.

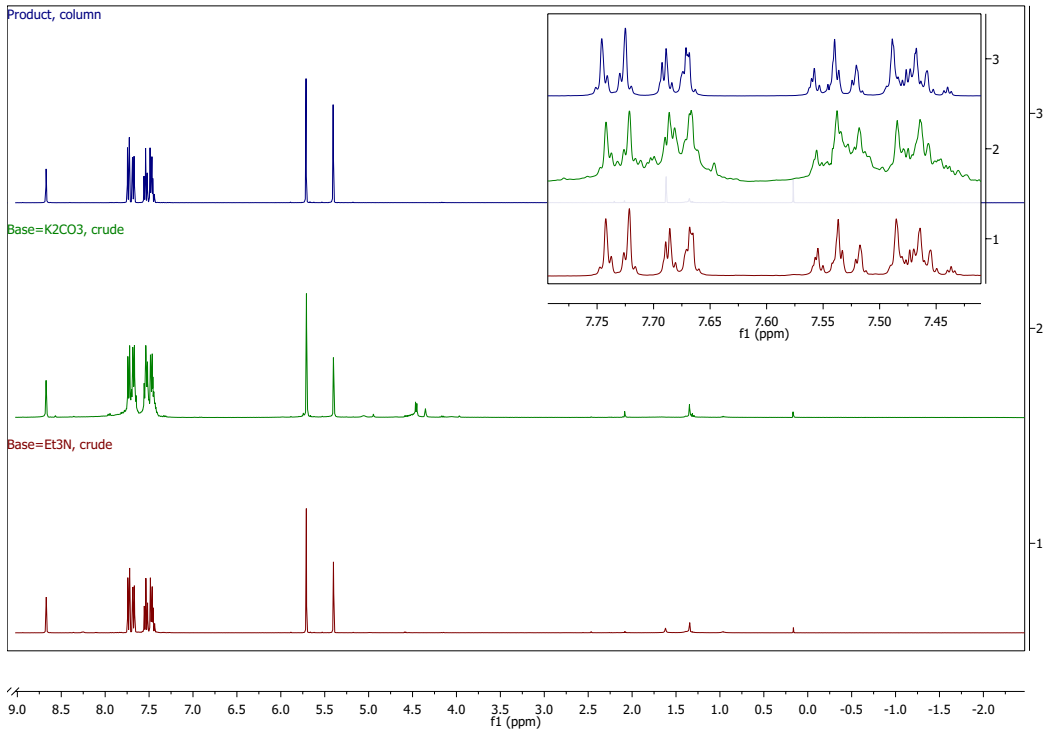


Figure 2.3: Pure compound **2a** (top) compared to the crude products obtained using K_2CO_3 (middle) or Et_3N (bottom) as base.

Base	Yield (%)
Et_3N	87
NH_3	85
K_2CO_3	83
Na_2CO_3	66
Cs_2CO_3	52
KH_2PO_4	35
NaOH	none

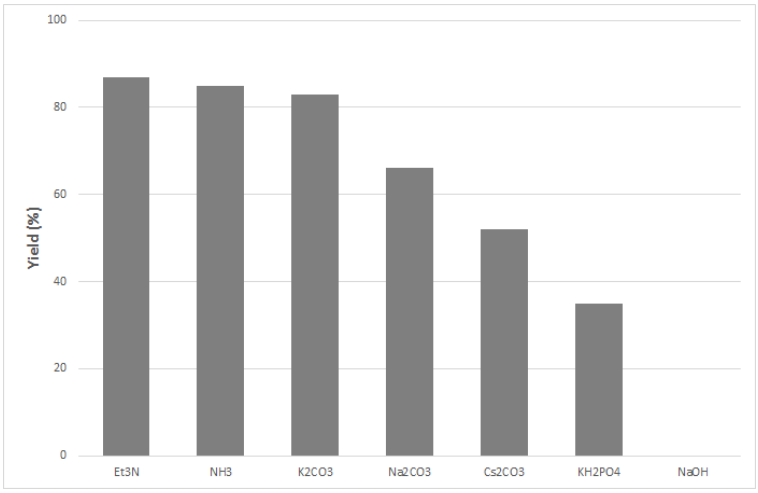


Figure 2.4: Influence of the base on the reaction shown in scheme 2.5 with $PdCl_2$ as catalyst and water as solvent.

Solvent	Atmosphere	Conversion (%)
THF		
	Argon	42
	Oxygen	35
	Air	35

Solvent	Atmosphere	Conversion (%)
THF/H_2O		
	Argon	100
	Oxygen	100
	Air	100

Figure 2.5: Influence of the atmosphere on the reaction shown in scheme 2.5.

This points out two important things for this coupling with $PdCl_2$: First, water is necessary for a reasonable conversion rate, and second, the atmosphere seems to have no notable influence on the conversion, as the reaction even works with an atmosphere of pure oxygen. Although a reaction in pure water might be very desirable, it only gives moderate yields, probably due to solability issues. Therefore, different aqueous solvent systems were tried and a 1:1 mixture of water and ethanol was found to give an excellent isolated yield of 97 % reaching a comparable yield as the reaction in toluene (see section 2.2.2).

2.2.5 Optimized Parameters

Based on the different screening steps, the optimized parameters are:

4-Bromobenzyl-*1H*-tetrazole **1** (1 eq.), phenylboronic acid (1.15 eq.), triethylamine (2 eq.) and $PdCl_2$ (3 mol %) in a 1:1 mixture of H_2O and ethanol at 120 °C for 18 h under an atmosphere of air.

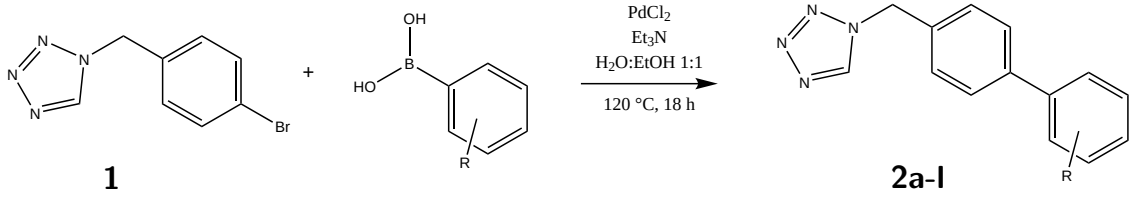
Additionally, the same conditions can be used with an aqueous solution of ammonia as base instead of triethylamine. The best conditions using a pure organic solvent were:

4-Bromobenzyl-*1H*-tetrazole **1** (1 eq.), phenylboronic acid (1.15 eq.), potassium carbonate (2 eq.) and Pd/C (3 mol %) in toluene at 120 °C for 18 h under an atmosphere of argon.

2.3 Screening of Boronic Acids

The scope of the conditions found in the previous section was determined by the coupling reaction of 4-Bromobenzyl-*1H*-tetrazole **1** with a wide range of aromatic and heretoaromatic boronic acids with different substitution patterns and functional groups. All boronic acids were bought from commercial sources and used without any further purification.

2.3.1 Screening of Aromatic Boronic Acids



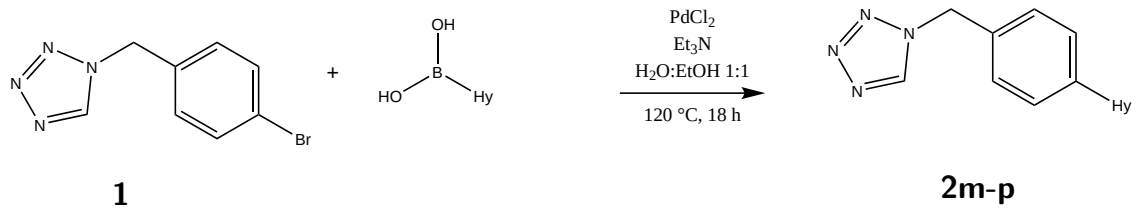
Scheme 2.6: Screening of aromatic boronic acids.

12 different aromatic boronic acids were reacted according to scheme 2.6. Table 2.1 shows the isolated yields of all performed reactions. All products were obtained in good to excellent yields in a range from 79–97 %. Most of them were isolated in high purity without challenging workup. Only two products (**2b** and **2h**) had to be purified via column chromatography to give the desired purity. This proves the liability of the discovered coupling protocol and its broad scope. The 3-nitro compound **2h** gave the lowest yield. This was to be expected as electron withdrawing substituents usually lower the yield of the Suzuki coupling. With an isolated yield of 79 % after column chromatography this was still a more than acceptable result. The best yields gave the unsubstitued compound **2a** and the 3-methyl substitued compound **2c**. The reaction with the chlorophenylboronic acids gave no isolated product with reaction temperatures of 120 °C, but it was found that the reaction at room temperature gave the desired product in good yields. Although, a reaction at room temperature would be very desirable, all other boronic acids were found to show only minor conversion at room temperature.

Table 2.1: Screening of Aromatic Boronic Acids.

Product	R	Yield (%)
2a	H	97
2b	2-methyl	91
2c	3-methyl	97
2d	4-methyl	86
2e	2-acetyl	87
2f	4-acetyl	87
2g	4-carboxyl	93
2h	3-nitro	79
2i	3-chloro	92
2j	4-chloro	90
2k	4-fluoro	89
2l	4-formyl	90

2.3.2 Screening of Heteroarylic Boronic Acids



1 **2m-p**

Scheme 2.7: Screening of heteroarylic boronic acids.

Additionally to the already extensive screening of aromatic boronic acids, the coupling reaction was performed with four different heteroarylic boronic acids as shown in table 2.2. Four products were obtained in good yields ranging from 81–91 %. Whereas the two pyridyl compounds **2m** and **2n** had to be purified via column chromatography, the two five-membered heteroaromates were obtained in satisfying purity after recrystallization from ethyl acetate.

Table 2.2: Screening of heteroarylic boronic acids.

Product	R	Yield(%)
2m	3-pyridyl	82
2n	4-pyridyl	81
2o	3-thienyl	91
2p	3-furyl	88

2.3.3 Comparison of Triethylamine with Aqueous Ammonia

Aqueous ammonia could prove as a viable alternative to triethylamine due to its easy handling and work-up. For large scale applications the handling of ammonia would be benefitial, even a gaseous application of ammonia to the reaction is also imaginable and would greatly increase the ease of the performed reaction on large scale. To determine the scope and its feasibility the same reaction conditions were applied, only with the change of base to a 30–33 % solution of ammonia in water.

The results are summarized in table 2.3.They show a very big dependency on the substrate. While some reactions even work better than with triethylamine, some do not work at all where triethylamine gave good yields previously. Therefore, ammonia could be benefitial in some specific reactions but overall triethylamine proves to be a more versatile base yielding good results with a wider scope of substrates.

Table 2.3: Comparison of the influence of aqueous ammonia versus triethyl amine as base.

Product		Et_3N Yield (%)	NH_3 Yield (%)
2a	H	97	95
2b	2-methyl	91	90
2c	3-methyl	97	99
2d	4-methyl	86	91
2e	2-acetyl	87	none
2f	4-acetyl	87	96
2g	4-carboxyl	93	40
2h	3-nitro	79	none
2i	3-chloro	92	98
2j	4-chloro	90	80
2k	4-fluoro	89	98
2l	4-formyl	90	
2m	3-pyridyl	82	none
2n	4-pyridyl	81	81
2o	3-thienyl	91	92
2p	3-furyl	88	none

2.3.4 Identification of Products

The structure of all obtained products was elucidated with 1D- and 2D-NMR experiments as well as infra-red spectroscopy. All products, except the 4-formyl substituted compound **2l**, were further identified by high resolution mass spectroscopy. The molecular structure of compound **2c** was confirmed via single-crystal x-ray diffraction shown in figure 2.6.

$Z = 4$	$P2_1/n$
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	wR2 6.06

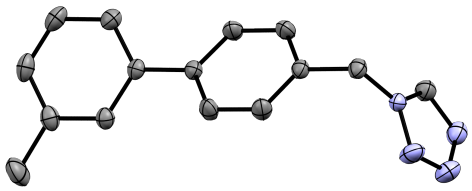


Figure 2.6: Molecular structure of **2c**. Hydrogen atoms were omitted for clarity.

2.4 Application

The obtained coupling products were investigated towards their use as ligands for iron(II) coordination compounds to obtain spin switchable compounds.

2.4.1 Coordination with Iron(II)

The coordination of the obtained coupling products with iron(II) tetrafluoroborate was performed in acetonitrile at 50 °C. After evaporation of the solvent the coordination compounds were obtained as white to off-white solids. The typical color change of iron(II) spin-crossover compounds to magenta was observed upon cooling with liquid nitrogen. The successful coordination could also be seen in the infrared band of the tetrazolic C-H vibration. The corrseponding typical shift to higher wavenumbers in comparison to the free ligand was observed on all coordination compounds.[45] The following table 2.4 shows a selection of coordination compounds and their respective shift of the tetrazolic vibration upon coordination to $Fe(BF_4)_2$. It also lists if a color change was observed upon cooling to liquid nitrogen temperature (SCO).

Table 2.4: Comparison of coordination with the methylated ligands

Ligand	ν_{free} (cm^{-1})	ν_{coord} (cm^{-1})	Δ(cm^{-1})	SCO
2b	3130	3149	19	yes
2c	3125	3146	21	yes
2d	3099	3143	44	yes

2.4.2 Spin Crossover Behavior

For some selected compounds their spin crossover behavior was investigated in detail via temperature dependent measurements of their magnetic susceptibility. This gives information about the completeness and abruptness of the spin transition and as well as the spin transition temperature $T_{1/2}$ (i.e. the temperature with a molar ration of $HS : LS = 1 : 1$).

Coordination of 2a

Investigation of the spin crossover behavior of the coordination compound of the unsubstituted coupling product **2a** shows a rather gradual incomplete transition seen in figure 2.7.

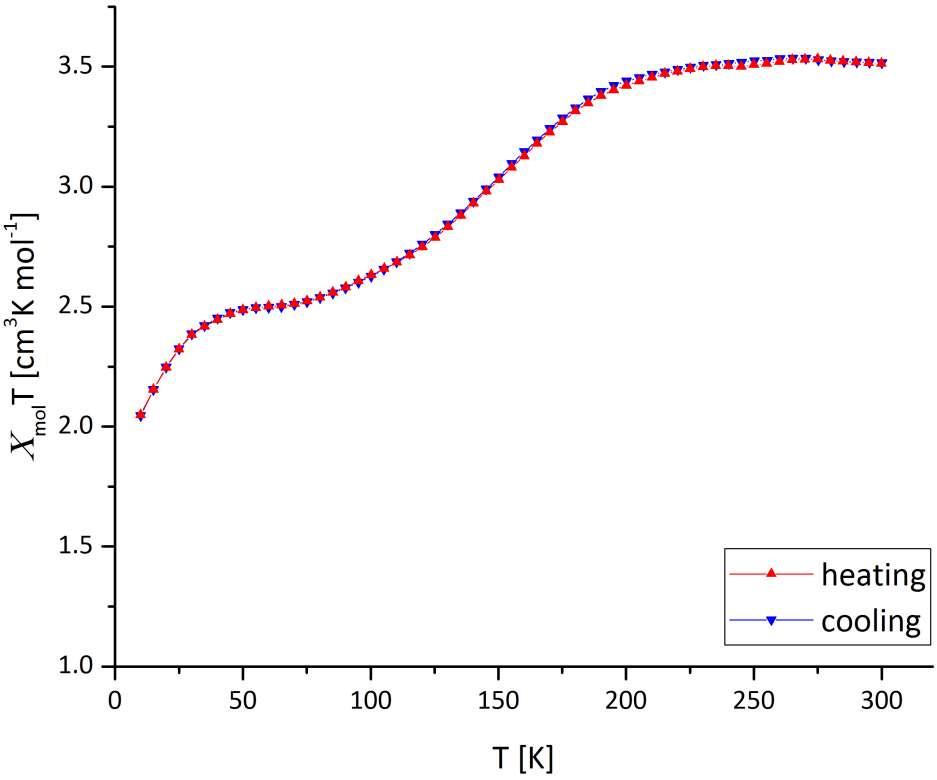


Figure 2.7: Temperature dependent magnetic moment of **3**.

The impact of substitution

To investigate the influence of the substitution pattern on the transition behavior, three methyl substituted compounds **2b**, **2c**, **2d** were measured. As the methyl group is rather far away from the coordinating site, little to no influence was expected. Figure 2.8 shows that this is not the case and the difference in transition behavior is rather pronounced. The para (**4**) and ortho (**5**) complexes show a more complete and abrupt transition at higher temperatures in comparison to the meta Fe-complex (**6**). The same influence was observed in the 4-chloro (**7**) and the 3-chloro (**8**) Fe-complexes (fig. 2.9). The ortho substituted compound shows a very gradual incomplete transition whereas the para substitution features a very abrupt and rather complete transition.

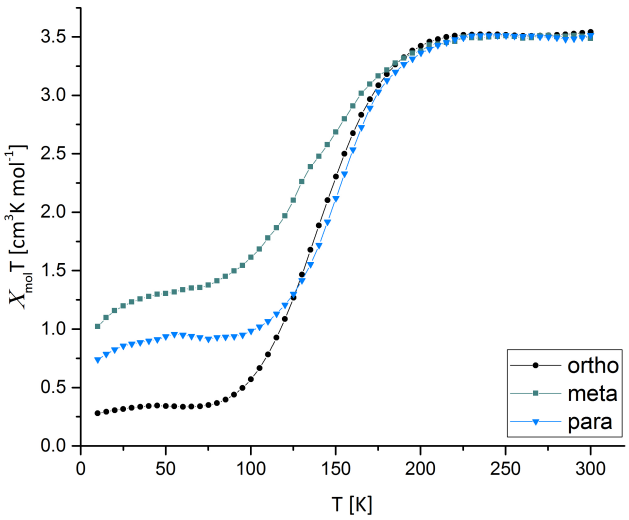


Figure 2.8: Temperature dependent magnetic moment of **4**, **5**, **6**.

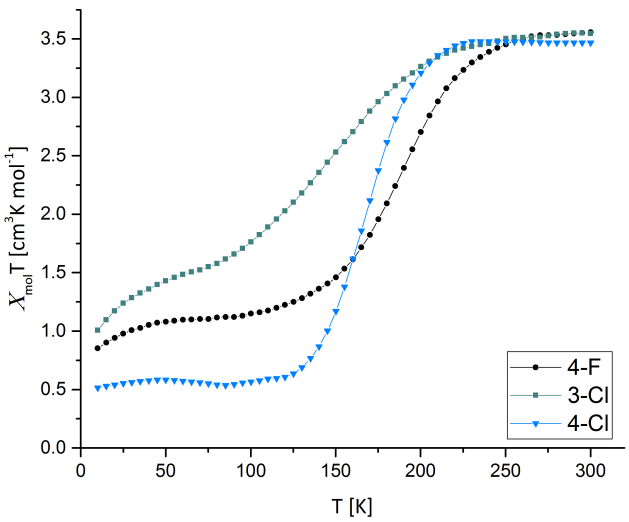


Figure 2.9: Temperature dependent magnecic moment of **7**, **8**.

The impact of electronic effects

In figure 2.10 the transition behavior between the 4-methyl (**4**), 4-chloro (**7**) and the 4-fluoro (**9**) complexes is compared and shows the impact of different functional groups with different electronic effects (fig. 2.10). A higher electronegativity seems to shift the spin-transition to higher temperatures, though with a loss of completeness.

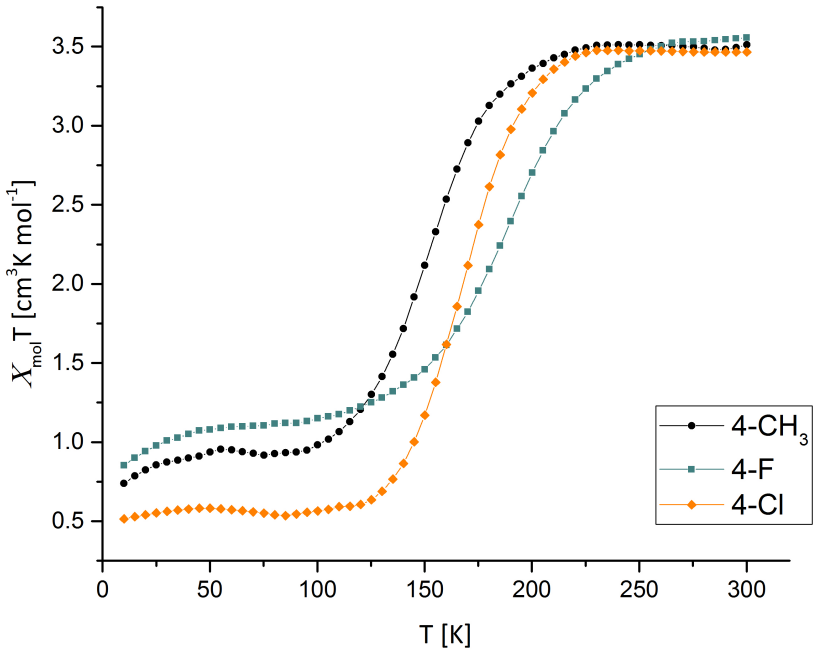


Figure 2.10: The influence of different substituents in para position.

Proof of concept

The obtained data proves the concept that a robust coupling protocol of tetrazoles could be used to obtain a wide range of ligands with systematic changes in substitution pattern or with different functional groups and to study the impact of those changes upon the spin transition behavior. The obtained magnetic data shows the trend such changes impose on the spin-transition behavior. The reason for the observed behavior might be found in the different crystal packing and structural alignment of the obtained compounds. Unfortunately, in the course of this work it was not possible to obtain any single crystals of the iron(II) complexes. The elucidation of the reason for the different behavior of those compounds is ,therefore, not part of this work. This task belongs to the future researchers on this topic.

2.5 Conclusion

For the Suzuki cross coupling reaction of 4-Bromobenzyl-*1H*-tetrazole with phenylboronic acid a very robust protocol was found, employing palladium chloride as a cheap catalytic source and a mixture of water and ethanol as a green and cheap solvent system. Additionally, conditions with toluene as pure organic solvent and palladium on activated charcoil as a cheap ligand-free catalyst were identified.

The scope of these conditions was investigated in reactions with a wide variety of different aromatic and heteroaromatic boronic acids, with good to excellent yields in a range of 79–96 %. All obtained compounds were thoroughly characterized by NMR and IR-spectroscopy and high resolution mass spectrometry. The molecular structure of one compound, **2c**, was elucidated by single-crystal X-ray diffraction measurements.

As a proof of concept all obtained compounds were used to synthesize the respective iron(II) spin-crossover compounds and the effect of substitutional pattern and functional group on the spin-transition behavior was investigated. All obtained coordination complexes showed spin-transition behavior. First results on the effect of substitution pattern were obtained via temperature dependent measurements of the magnetic susceptibility. Para- and ortho-substituted compounds showed a more abrupt spin transition at higher temperatures compared to the meta compound. Additionally, a dependency on electronic effects was found showing a shift of the transition to higher temperatures at higher electronegativity although with a loss of completeness.

2.6 Experimental

2.6.1 General Experimental Methods

All organic solvents were dried and degassed prior to use using standard methods.[46] Water was degassed for all aqueous reactions under inert atmosphere. This was done by sonication

of the solvent under constant argon flow for 15. All boronic acids were used as supplied by commercial sources.

^{1}H, ^{19}F and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker 400 spectrometer with broad-band probe head. All NMR chemical shifts are reported in ppm; ^{1}H and ^{13}C shifts are established on the basis of the residual solvent resonance. Detailed peak assignments were based on 2D NMR experiments (COSY, HSQC and HMBC).

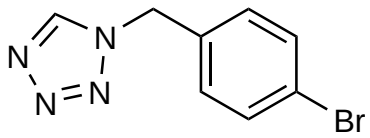
Mid-range IR spectra were recorded in attenuated total reflection (ATR) technique within the range of 4000–450 cm^{-1} using a Perkin-Elmer Spectrum Two Fourier-transform infrared spectrometer. The melting points were determined via a thermogravimetric analysis performed on a Netzsch TG 209-C in an Al crucible with a heating rate of 10 K min^{-1} in nitrogen atmosphere.

HR-MS analysis was carried out from methanol solutions (concentration: 10 µM) by using 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 Agilent 6230 AJS ESI-TOF mass spectrometer (Agilent Technologies, Palo Alto, United States).

The magnetic suscebtibility was measured using a Physical Property Measurement System (PPMS®) by Quantum Design. The experimental setup consisted of a vibrating sample magnetometer attachment (VSM), bearing a brass-sample holder with a quartz glas powder container. The moment was determined in an external field of 1 T in the range of 10–300 K. A final diamagnetic correction was applied.

2.6.2 Optimization

1 4-Bromobenzyl-*1H*-tetrazole



1

The synthesis of 4-Bromobenzyl-*1H*-tetrazole was performed according to the established Franke protocol.[13,16] 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 volatile compounds 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. (white solid, 11.2 g, 87 %)

Mp: 113.8–114.3 °C.

IR (cm^{-1}): 3114 (ν_{CHTz}).

^{1}H NMR (400 MHz, CD_2Cl_2, δ): 8.65 (s, 1H, Tz-CH), 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]+ Calcd for $C_8H_7BrN_4Na$ 260.9752, Found 260.9754.

General procedure for the optimization of parameters for the Suzuki Cross Coupling of 4-Bromobenzyl-*1H*-tetrazole 1 and phenylboronic acid 2

A sealable vial equipped with a stirring bar was charged with 4-Bromobenzyl-*1H*-tetrazole **1** (100 mg, 418 µmol), phenylboronic acid **2** (59 mg, 481 µmol), catalyst (3 mol %) and base (2 eq.),if solid, and put under argon atmosphere. After addition of 6 mL solvent and base, if liquid, the reaction was heated to 120 °C. After 18 h the reaction was allowed to cool to room temperature and poured onto 20 mL water. If the reaction was performed in a solvent not miscible with water it was used for the extraction, otherwise ethyl acetate was used. Upon short filtration over SiO_2 and evaporation of all volatile compounds under reduced pressure the crude product was obtained as white to yellow solid. Upon first examination of the crude yield and purity via NMR spectroscopy, pure product was obtained after recrystallization with dichloromethane / petroleum ether.

2.6.3 Screening

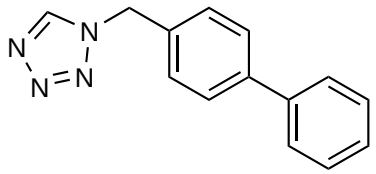
All reactions were perfomed in sealed vials closed under ambient conditions and an atmosphere of air.

General procedure for Suzuki Cross Coupling using 4-Bromobenzyl-*1H*-tetrazole and boronic acids

To a stirred mixture of 4-Bromobenzyl-*1H*-tetrazole **1** (1 eq.) and boronic acid (1.1 eq.) in H_2O:EtOH (1:1), triethyl amine (2 eq.) and 0.03 eq. of an 0.01 M aqueous solution of $PdCl_2$ were added rapidly. The dispersion was sealed, heated, if not stated otherwise, to 120 °C

and kept at this temperature for 18 h. The reaction mixture was allowed to cool to room temperature and was extracted with H_2O:ethyl acetate. After filtration of the organic phase over SiO_2 the solvent was removed under reduced pressure to yield the crude product.

2a ((4-biphenylyl)methyl)-*1H*-tetrazole



2a

Phenylboronic acid **2** (56.1 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was recrystallized with dichloromethane / petroleum ether to afford **2a** (white solid, 95.9 mg, 97.2 % yield).

Mp: 178.9–179.6 °C.

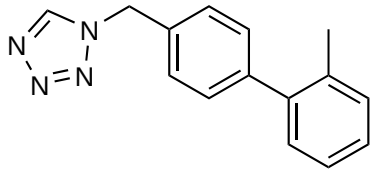
IR (cm^{-1}): 3113 (ν_{CHTz}).

^{1}H 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{^{1}H} 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 + H]+ Calcd for $C_{14}H_{13}N_4$ 259.0960; Found 259.0953.

2b ((2'-methyl-4-biphenylyl)methyl)-*1H*-tetrazole



2b

2-Methylphenylboronic acid (62.6 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. 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).

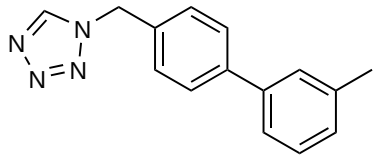
IR (cm^{-1}): 3130 (ν_{CHTz}).

^{1}H 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{^{1}H} NMR (101 MHz, CD_2Cl_2, 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]+ Calcd for $C_{15}H_{15}N_4$ 251.1297; Found 251.1299.

2c ((3'-methyl-4-biphenylyl)methyl)-*1H*-tetrazole



2c

3-Methylphenylboronic acid (62.6 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was recrystallized with dichloromethane / petroleum ether to afford **2c** (white solid, 101.6 mg, 97.1 % yield).

Mp: 122.2–123.6 °C.

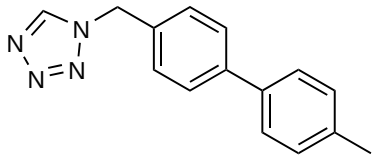
IR (cm^{-1}): 3126 (ν_{CHTz}).

^{1}H 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{^{1}H} 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]+ Calcd for $C_{15}H_{15}N_4$ 251.1297; Found 251.1297.

2d ((4'-methyl-4-biphenylyl)methyl)-*1H*-tetrazole



2d

4-Methylphenylboronic acid (62.6 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was recrystallized with dichloromethane / petroleum ether to afford **2d** (white solid, 90 mg, 86.1 % yield).

Mp: 167.0–168.3 °C.

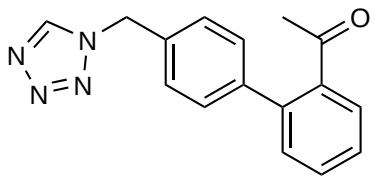
IR (cm^{-1}): 3099 (ν_{CHTz}).

^{1}H 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{^{1}H} NMR (101 MHz, CD_2Cl_2, 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]+ Calcd for $C_{15}H_{15}N_4$ 251.1297; Found 251.1295.

2e (4'-((*1H*-tetrazolyl)methyl)-2-biphenylyl)ethan-1-one



2e

(2-Acetylphenyl)boronic acid (75.44 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was recrystallized with dichloromethane

/ petroleum ether to afford **2e** (white solid, 101.3 mg, 87.0 % yield).

Mp: 122.7–123.4 °C.

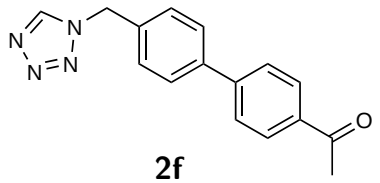
IR (cm^{-1}): 3136 (ν_{CHTz}), 1685 (C=O).

^{1}H 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{^{1}H} 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]+ Calcd for $C_{15}H_{15}N_4Na$ 301.1065; Found 301.1067.

2f (4'-((*1H*-tetrazolyl)methyl)-4-biphenylyl)ethan-1-one



2f

(4-Acetylphenyl)boronic acid (75.44 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was recrystallized with dichloromethane / petroleum ether to afford **2f** (white solid, 101.4 mg, 87.1 % yield).

Mp: 134.7–136.2 °C.

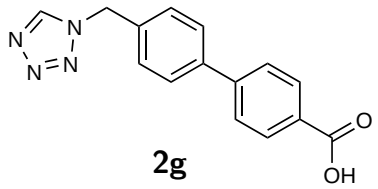
IR (cm^{-1}): 3106 (ν_{CHTz}), 1680 ($\nu_{C=O}$).

^{1}H 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{^{1}H} NMR (101 MHz, CD_2Cl_2, 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]+ Calcd for $C_{16}H_{15}N_4O$ 279.1246; Found 279.1247.

2g (4'-((*1H*-tetrazolyl)methyl)-4-biphenylyl)carboxylic acid



2g

4-boronobenzoic acid (76.35 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was recrystallized with ethyl acetate to afford **2g** (white solid, 109.0 mg, 93.8 % yield).

Mp: 267 °C (dec).

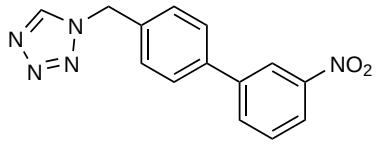
IR (cm^{-1}): 3118 (ν_{CHTz}), 1674 ($\nu_{C=O}$).

^{1}H 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{^{1}H} 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]+ Calcd for $C_{15}H_{15}N_4$ 281.1039; Found 281.1037.

2h ((3'-nitro-4-biphenylyl)methyl)-*1H*-tetrazole



2h

3-Nitrophenylboronic acid (76.80 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (2:1) to afford **2h** (slightly yellow solid, 97.9 mg, 79.7 % yield).

Mp: 146.4–147.5 °C.

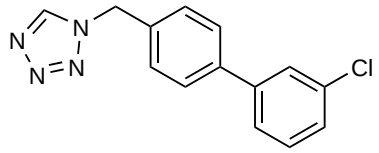
IR (cm^{-1}): 3125 (ν_{CHTz}).

^{1}H 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{^{1}H} 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]+ Calcd for $C_{14}H_{12}N_5O_2$ 282.0991; Found 282.0980.

2i ((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 dichloromethane / petroleum ether to afford **2i** (off-white solid, 104.2 mg, 92.8 % yield).

Mp: 137.0–138.2 °C.

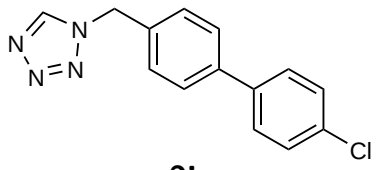
IR (cm^{-1}): 3122 (ν_{CHTz}).

^{1}H 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{^{1}H} 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 (2 ArCH), 128.46 (2 ArCH), 128.29 (ArCH), 127.68 (ArCH), 125.91 (ArCH), 52.28 (CH_2);

HRMS (ESI-TOF) m/z: [M + H]+ Calcd for $C_{14}H_{12}ClN_4$ 271.0751; Found 271.0748.

2j ((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 dichloromethane / petroleum ether to afford **2j** (white solid, 101.9 mg, 90.1 % yield).

Mp: 103.7–104.9 °C.

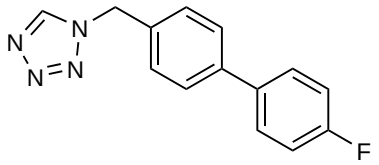
IR (cm^{-1}): 3113 (ν_{CHTz}).

^{1}H 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).

$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2, 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]+ Calcd for $C_{14}H_{12}ClN_4$ 271.0751; Found 271.0749.

2k ((4'-fluoro-4-biphenylyl)methyl)-*1H*-tetrazole



2k

4-Fluorophenylboronic acid (64.4 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was recrystallized with dichloromethane / petroleum ether to afford **2k** (white solid, 94.7 mg, 89.4 % yield).

Mp: 118.5–120.4 °C.

IR (cm^{-1}): 3105 (ν_{CHTz}).

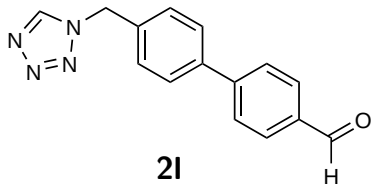
^{1}H NMR (400 MHz, CD_2Cl_2, δ): 8.59 (s, 1H, TzCH), 7.63–7.59 (m, 2H, ArH), 7.59–7.55 (m, 2H, ArH), 7.41–7.37 (m, 2H, ArH), 7.20–7.11 (m, 2H, ArH), 5.62 (s, 2H, CH_2).

^{13}C{^{1}H} 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_2Cl_2, δ): −115.66.

HRMS (ESI-TOF) m/z: [M + Na]+ Calcd for $C_{14}H_{11}FN_4Na$ 277.0865; Found 277.0871.

2l (4'-((*1H*-tetrazolyl)methyl)-4-biphenylyl)4-carbaldehyde



2l

4-formylphenylboronic acid (69.0 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was recrystallized with dichloromethane / petroleum ether to afford **2l** (white solid, 99.5 mg, 90.1 % yield).

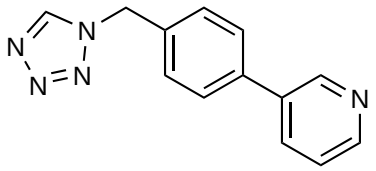
Mp: 117.5–118.4 °C.

IR (cm^{-1}): 3123 (ν_{CHTz}), 1678 ($\nu_{C=O}$)

^{1}H NMR (400 MHz, CD_2Cl_2, δ): 10.05 (s, 1H, CHO), 8.62 (s, 1H, TzCH), 8.00–7.92 (m, 2H, ArH), 7.77 (d, J = 8.4 Hz, 2H, ArH), 7.73–7.68 (m, 2H, ArH), 7.43 (d, J = 8.3 Hz, 2H, ArH), 5.65 (s, 2H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2, δ): 192.20 (C=O), 146.33 (ArC), 143.13 (TzCH), 141.23 (ArC), 136.28 (ArC), 133.92 (ArC), 130.72 (2ArCH), 129.51 (2ArCH), 128.77 (2ArCH), 128.25 (2ArCH), 52.28 (CH_2).

2m 3-(4-((*1H*-tetrazol-1-yl)methyl)phenyl)pyridine



2m

Pyridin-3-ylboronic acid (56.6 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was purified by column chromatography on silica gel with ethyl acetate/methanol (10:1) to afford **2m** (white solid, 81.6 mg, 82.2 % yield).

Mp: 96.5–98.7 °C.

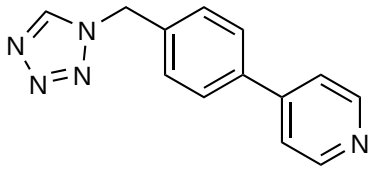
IR (cm^{-1}): 3111 (ν_{CHTz}).

^{1}H 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).

$13^{C}\{^{1}_{1}H\}$ 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]+ Calcd for $C_{13}H_{12}N_5$ 238.1093; Found 238.1085.

2n 4-(4-((*1H*-tetrazol-1-yl)methyl)phenyl)pyridine



2n

Pyridin-4-ylboronic acid (56.6 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was purified by column chromatography

on silica gel with ethyl acetate/methanol (10:1) to afford **2n** (white solid, 81.3 mg, 81.9 % yield).

Mp: 134.7–135.6 °C.

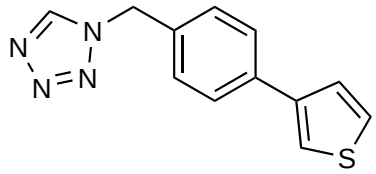
IR (cm^{-1}): 3111 (ν_{CHTz}).

^{1}H 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{^{1}H} 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]+ Calcd for $C_{13}H_{12}N_5$ 238.1093; Found 238.1089.

2o 1-(4-(thiophen-3-yl)benzyl)-*1H*-tetrazole



2o

Thiophen-3-ylboronic acid (58.9 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was recrystallized with ethyl acetate to afford **2o** (off-white solid, 93 mg, 91.8 % yield).

Mp: 184.8–185.9 °C.

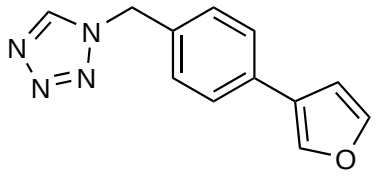
IR (cm^{-1}): 3110 (ν_{CHTz})

^{1}H 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{^{1}H} 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]+ Calcd for $C_{12}H_{11}N_4S$ 243.0704; Found 243.0699.

2p 1-(4-(furan-3-yl)benzyl)-*1H*-tetrazole



2p

Furan-3-ylboronic acid (51.5 mg, 460.1 µmol) and **1** (100 mg, 418.3 µmol) were reacted according to the general procedure. The crude product was recrystallized with ethyl acetate to afford **2p** (off-white solid, 83.9 mg, 88.7 % yield).

Mp: 141.1–142.1 °C.

IR (cm^{-1}): 3149 (ν_{CHTz})

^{1}H 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{^{1}H} 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]+ Calcd for $C_{12}H_{11}N_4O$ 227.0933; Found 227.0926.

2.6.4 Coordination Compounds

General procedure for the coordination of ligands with iron(II) tetrafluoroborate

A schlenk flask was equipped with a stirring bar and charged with ligand (6 eq.) and $Fe(BF_4)_2 \cdot 6\,H_2O$ (1 eq.) and set under an atmosphere of argon. Upon addition of dry acetonitrile all compounds dissolved and the reaction was warmed to 50 °C for 18 h. The solvent was evaporated to yield the product as white to off-white solid. The compound could be washed with dry n-Hexane for further purification. This was only done for colored products.

5 [Fe(((2'-methyl-4-biphenylyl)methyl)-*1H*-tetrazole)$_6$](BF$_4$)$_2$

((2'-methyl-4-biphenylyl)methyl)-*1H*-tetrazole **2b** (100 mg, 400 µmol) were reacted according to general procedure to yield the title compound **5** as off-white solid (quant. yield).

IR (cm^{-1}): 3149 (ν_{CHTz})

$T_{1/2}$: 140 K

6 [Fe(((3'-methyl-4-biphenylyl)methyl)-*1H*-tetrazole)$_6$](BF$_4$)$_2$

((3'-methyl-4-biphenylyl)methyl)-*1H*-tetrazole **2c** (100 mg, 400 µmol) were reacted according to general procedure to yield the title compound **6** as off-white solid (quant. yield).

IR (cm^{-1}): 3146 (ν_{CHTz})

$T_{1/2}$: 130 K

4 [Fe(((4'-methyl-4-biphenylyl)methyl)-*1H*-tetrazole)$_6$](BF$_4$)$_2$

((4'-methyl-4-biphenylyl)methyl)-*1H*-tetrazole **2d** (100 mg, 400 µmol) were reacted according to general procedure to yield the title compound **4** as white solid (quant. yield).

IR (cm^{-1}): 3143 (ν_{CHTz})

$T_{1/2}$: 167 K

10 [Fe(((4'-chloro-4-biphenylyl)methyl)-*1H*-tetrazole)$_6$](BF$_4$)$_2$

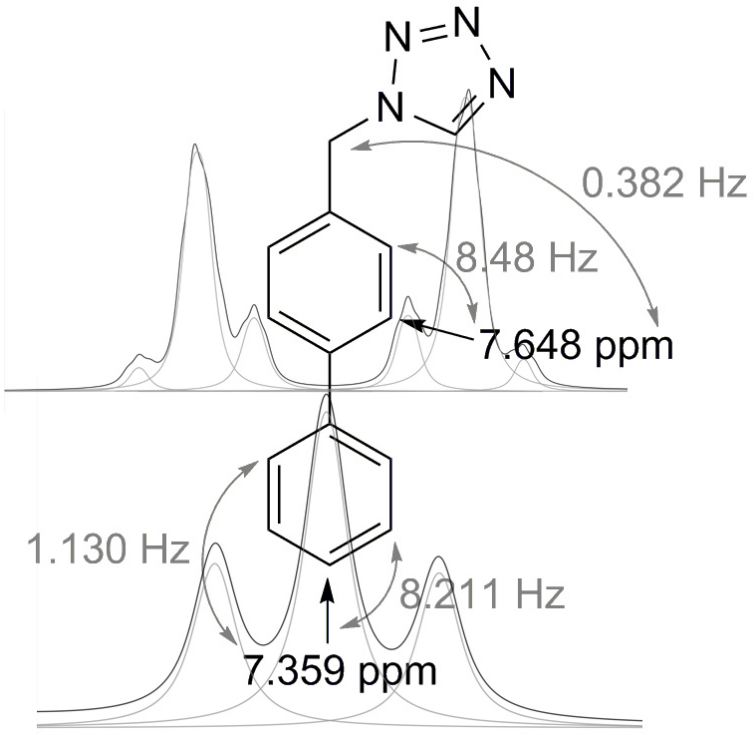
((4'-chloro-4-biphenylyl)methyl)-*1H*-tetrazole **2j** (100 mg, 369 µmol) were reacted according to general procedure to yield the title compound **7** as off-white solid (quant. yield).

IR (cm^{-1}): 3145 (ν_{CHTz})

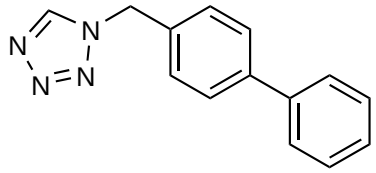
$T_{1/2}$: 170 K

Digression 3

On the Quantumchemical Simulation of NMR



3.1 Introduction - Aim



2a

During the course of the synthesis and characterization of the biaryl coupling products obtained in chapter 2 the question arose whether the fine spin-spin coupling constants and, therefore, the NMR spectra could be simulated via DFT calculations. Although standard DFT methods usually calculate static states and nuclear magnetic resonance at room temperature is obtained from molecules in rapid motion, methods were developed to bypass this limitation and simulate coupling constants with satisfying precision.[47–52] The following work, although independent, is closely based on the work already performed by Paul Rablen and coworkers.[50]

In the same approach as the experimental part, the calculations were optimized on the unsubstituted biaryl compound **2a**. As proof of concept, the optimized methods were applied on another substituted compound. The considerations leading to a reasonable fast and precise simulation are outlined in the following sections.

3.2 Calculation

All calculations were performed using Gaussian 09 Rev. D01[53] implemented on the Vienna Scientific Cluster 3 (VSC-3).

3.2.1 Optimization of the Starting Geometry

As a first step a simple geometry optimization of the given structure was performed. In principle, the accuracy of the used basis set has little influence, as the outcome is reoptimized in further steps, but an already good optimized structure drastically decreases the optimization time needed later on. Therefore, the optimization was performed using the B3LYP/6-31G(D) functional, but as for all geometry optimizations, this should be modified depending on the exact needs for each structure. For the biarylic systems investigated herein this was found to be a good compromise between accuracy and computing time.

Code Snippet 3.1: Geometry Optimization

```
# opt b3lyp/6-31g(d)
```

3.2.2 Rotamers

In standard NMR experiments in solution and at temperatures near room temperature most molecules have enough kinetic energy to overcome the energy barrier needed for the interconversion between different rotameric forms. During the measurement the molecule can interconvert freely and the obtained spin-spin couplings are a mixture of all rotamers present during the experiment. In principle even the most unfavoured rotamers contribute, although to a very small degree, to the final outcome, but for a theoretical modelling the calculation of every possible rotamer is nearly impossible. Hence the simplification was made to only consider the rotamers with the highest contribution. The influence of each rotamer can be calculated by the Maxwell-Boltzmann distribution (eq 3.1). Given the available kinetic energy, assuming a temperature of T=298.16 K, and the energy of the rotamer one can easily calculate its population in the Maxwell distribution. With the populations at hand one can easily ignore low contributing rotamers and concentrate on the few rotamers with the highest population and possessing the highest impact on the coupling constants. Obviously, this approach results in inaccuracies due to the omitted rotamers.

$$f(E) = e^{-\Delta E/kT} \tag{3.1}$$

For molecules with more than one rotatable bond the determination of all rotamers and the calculation of their energy gets exponentially time consuming, as every rotation around one bond needs to consider all other rotations around different single bonds as well. Therefore, another simplification step was made: Each rotatable bond was modelled with the angles of the other bonds fixed (snippet 3.2). With this approach the influence of each rotation on the energy of the molecule can be observed. These calculations can be performed in far less time than two- or even three-dimensional scans around multiple rotatable bonds.

Code Snippet 3.2: Potential Energy Surface Scan

```
# opt=modredundant b3lyp/6-31g(d)
...
D 2 1 20 22 S 10 36.0
D 5 4 11 14 F
D 4 11 14 16 F
```

Essentially, rotation with a stepsize of 36° is enough to obtain the well-known free-energy diagrams known for rotamers. Figure 3.1 shows the obtained diagrams for the unsubstituted biaryl with three rotatable bonds. With these diagrams at hand it is easy to determine the position of the angles with the lowest energy. For more complex molecules a step size of fewer degrees might be needed and should be adapted depending on the specific molecule.

Taking the above mentioned into consideration, the energy of every possible combination of the low-energy angles for each rotatable bond was determined. For the unsubstitued biaryl with three different rotatable bonds and 4, 3 and 2 minimal-energy angles, respectively, a sum of 24 different conformers was obtained. These conformers are most probably the highest populated and contribute the most to the overall coupling constants. Together with the $3 \cdot 10$ conformers determined during the scan around the rotatable bonds in 36° steps the energy of

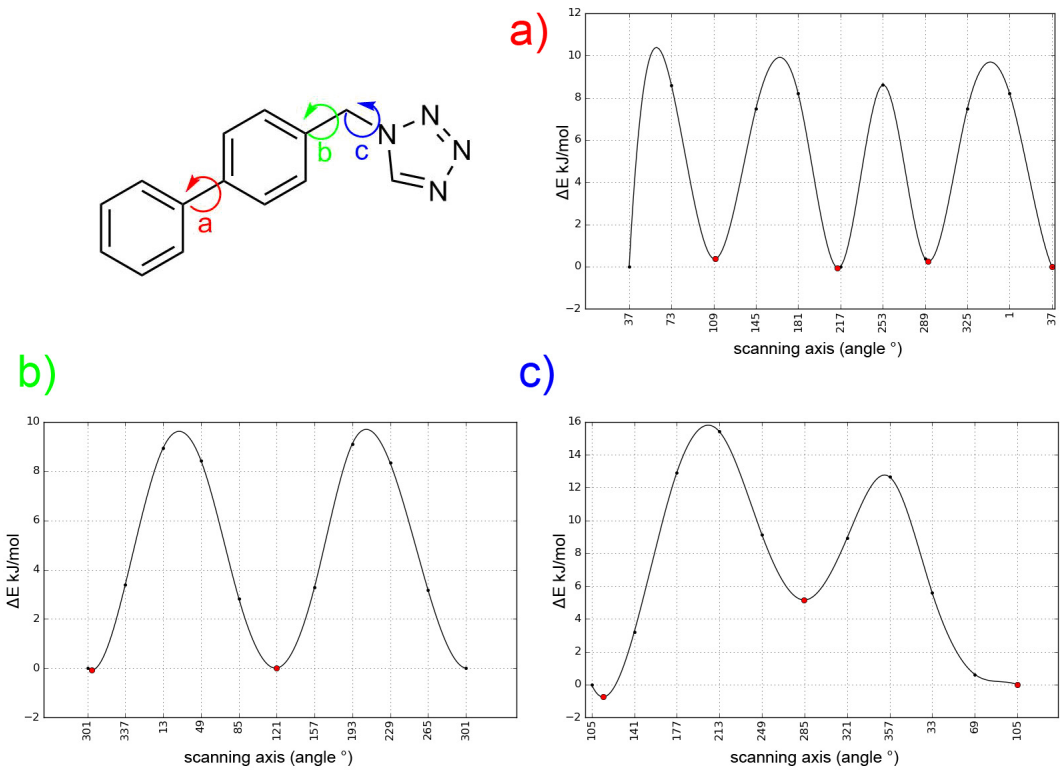


Figure 3.1: Potential Energy Surface Scan for each Rotatable Bond

54 molecules had to be calculated. This is substantially lower than for a more-dimensional scan, which would result in calculation of far more than 1000 molecules.

With the energy at hand it was easy to determine the population of each conformer according to Boltzmann-Maxwell (eq. 3.1). If the contribution of a conformer was below a threshold of 0.1 % it was discarded.

3.2.3 Calculation of Magnetic Properties

With a special emphasis on ^{1}H spin-spin couplings all subsequent optimizations were determined with respect to their applicability for the simulation of ^{1}H-NMR spectra.

Determination of the Functional and Basis Set

A variety of different functionals was investigated. The influence of the functional choosen has understandably a very high impact on the resulting coupling constants and chemical shifts. Dissapointingly, there is no universal method for the modelling of NMR data available, each functional has its strengths and weaknesses. And a method working for one molecule might result in less accurate data for another.

For the tetrazolic biaryls investigated herein, Rablens approach was found to give reasonable good results.[50] Therefore, the calculations were done as suggested and were split in two parts: first (1) the isotropic shielding constants were computed and in a second step (2) the spin-spin coupling constants were determined, considering only the fermi contact spin-spin terms.

Code Snippet 3.3: Calculation of NMR properties

```
(1) #n BLYP/cc-pVDZ nmr=GIAO SCRF(solvent=chloroform) iop(3/76=1000001189,
    3/77=0961409999,3/78=0000109999)
(2) #n B3LYP/gen nmr=(FCOnly,ReadAtoms) int=nobasistransform geom=check
```

Determination of Scaling Factors

In a standard NMR experiment the chemical shift is calculated using a reference substance using equation 3.2. Thus, the obtained resonance frequency of the sample is put in correlation with the frequency of the reference, which has a chemical shift of 0 by definition.

$$\delta = \frac{\nu_{sample} - \nu_{ref}}{\nu_{ref}} \tag{3.2}$$

This approach can also be applied on the simulated data, therefore, the resonance frequencies of a reference substance would be needed and then the relative shift of the molecule would be calculated like in equation 3.2. Since the molecule simulated herein is already measured and identified by real experiments, a linear correction approach was considered as appropriate. The calculated shielding constants were correlated with experimental data and a linear fitting was computed. A linear model over the whole range of calculated atoms gave a good fit with a coefficient of determination of $R2 = 0.991$. The shielding constants in the aromatic part of the molecule was found to be slightly off and since most of the atoms in the biarylic system are aromatic an additional correction for the shielding constants in a range of 24–25 Hz was determined.

Determination of the Chemical Shifts and Coupling Constants

In the last step all data obtained from all of the conformers had to be averaged according to their population in the Maxwell-Boltzmann distribution. And, finally, the relative shift was calculated according to the scaling factors determined previously. Usually averaging over the sum of all conformers helps to identify identical protons, as for example the aromatic protons in 2 and 6 position should be the same due to the fast rotation of two phenyl rings, because they would usually be averaged to have the same chemical shift. Interestingly, for the benzylic CH_2 this was not the case, but experimental data showed them to be identical, therefore, those two hydrogens had to be averaged manually, as it would have been the case for any terminal methyl group. The thereby obtained data was displayed using MestreNova 9.0 under assumption of a spectrometer frequency of 400 MHz and was compared to the experimental data in the following section.

General
^{1}H $slope = -1.0078$
$intercept = 32.1287$

Aromatic
^{1}H $slope = -2.5753$
$intercept = 70.4214$

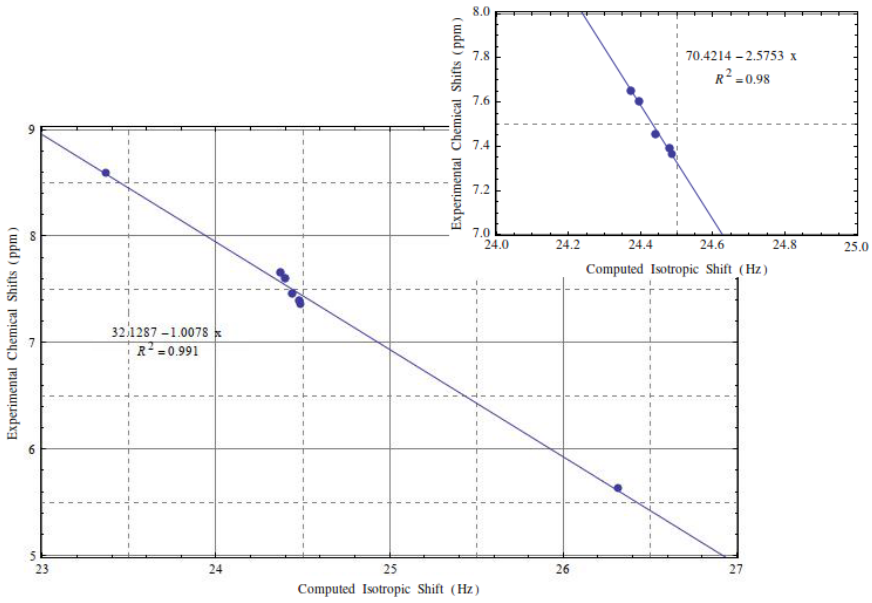


Figure 3.2: Scaling factors found based on a linear fit model with experimental data.

3.3 Results

3.3.1 2a ((4-biphenylyl)methyl)-*1H*-tetrazole

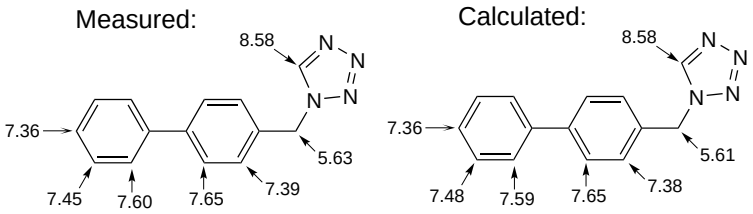


Figure 3.3: Comparison of chemical shifts.

Calculations on ((4-biphenylyl)methyl-*1H*-tetrazole **2a** according to the procedure outlined in section 3.2 led to the following results:

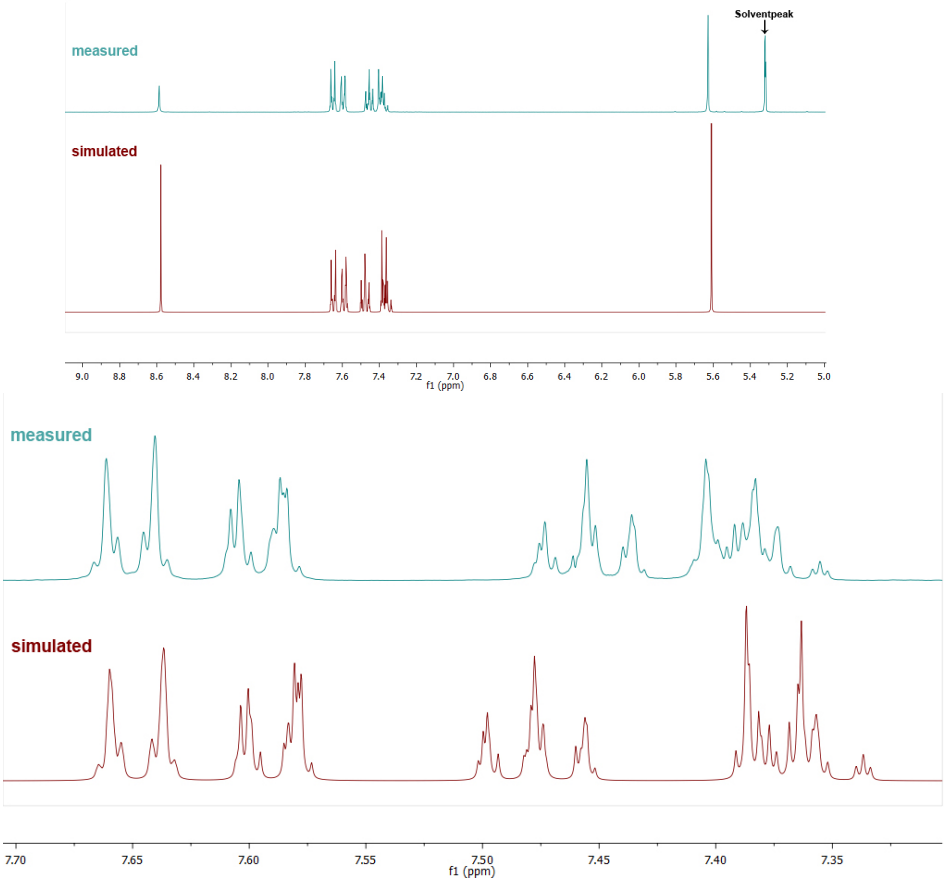


Figure 3.4: Comparison between the measured NMR-spectra (turquoise) and simulated NMR-spectra (red) **2a** with a close up of the aromatic area (bottom).

3.3.2 2m 3-(4-((*1H*-tetrazol-1-yl)methyl)phenyl)pyridine

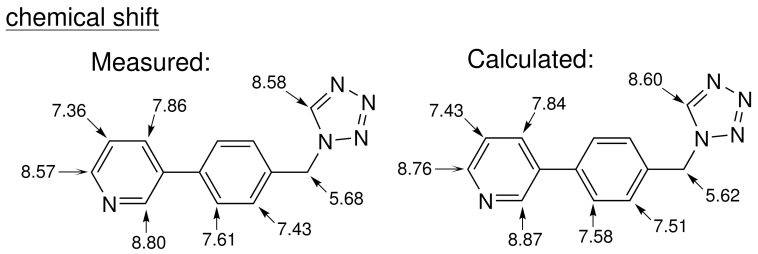


Figure 3.5: Comparison of chemical shifts.

Calculations on 3-(4-((*1H*-tetrazol-1-yl)methyl)phenyl)pyridine **2m** gave satisfying results without the need to correct the aromatic range separately.

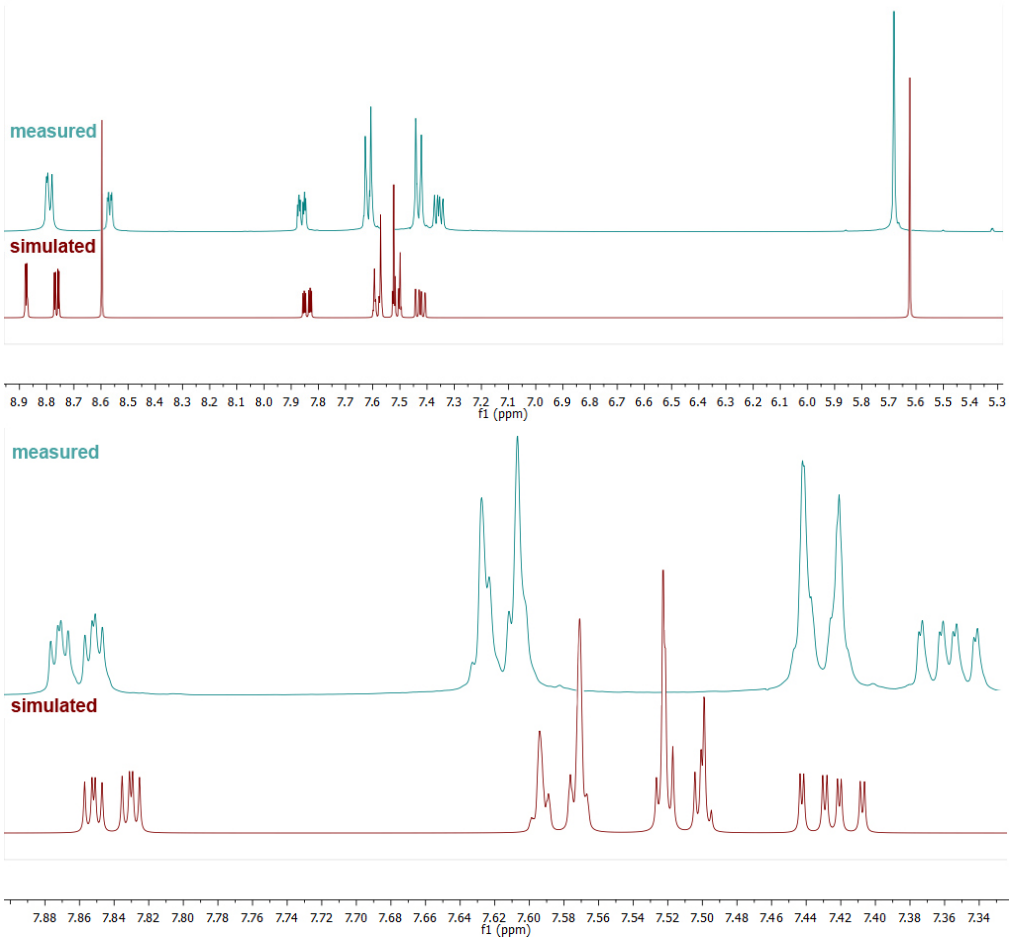


Figure 3.6: Comparison between the measured NMR-spectra (turquoise) and simulated NMR-spectra (red) of **2m** with a close up of the aromatic area (bottom).

Chapter 4

Further Coupling Reactions

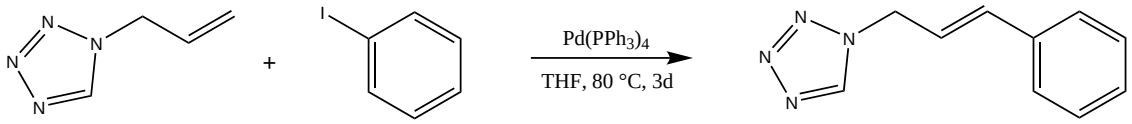
4.1 Heck Coupling of Allyl-*1H*-tetrazole

4.1.1 Introduction

In 1972 and 1973 Heck[54] and Mizoroki[55] respectively published their work on the palladium catalyzed coupling of iodobenzene with styrene to give stilbene. Reactions of this type became known as Heck reaction or Mizoroki-Heck reaction. Nowadays, Heck type reactions have been developed to react with many different aryl or vinyl halides and many different activated alkenes to give in almost all cases the *trans* product.[56–59] This already shows one of the biggest advantages of the Heck coupling reaction: Its outstanding trans stereoselectivity makes it a very useful reaction in many syntheses.

As the required conditions for the Heck coupling reaction are the same as for the Suzuki coupling reaction, namely a base and a palladium catalyst, the optimized conditions found in chapter 2 were tried on a suitable tetrazole substrate. The reaction of allyl-*1H*-tetrazole **11** with iodobenzene **12** to give cinnamyl-*1H*-tetrazole **13** was identified as an interesting show case to prove the concept of Heck type couplings with *1H*-tetrazoles (scheme 4.1).

4.1.2 Coupling Reactions



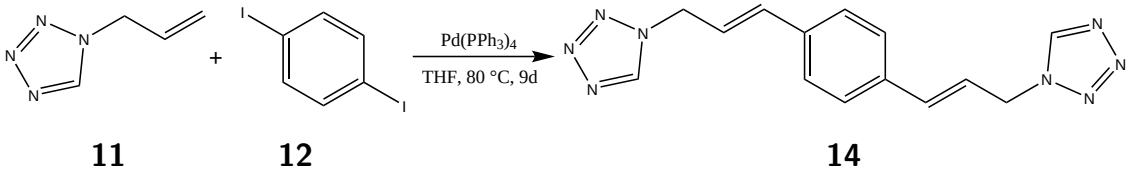
11 **12** **13**

Scheme 4.1: Preparation of Cinnamyl-*1H*-tetrazole.

In a first attempt the identical conditions found for the Suzuki reaction in chapter 2 were used. The allyl-*1H*-tetrazole **11** did not tolerate the high reaction temperatures of 120 °C and

decomposed. With a lower reaction temperature of 80 °C product was obtained, although in low yields and the reaction rates were very slow. Higher catalyst loadings and longer reaction times resulted in higher conversion but even after 4 days a conversion of only 57 % was observed. Although this proved that it was possible to perform a coupling reaction with the allylic tetrazole the results were not satisfying. As a possible reason the aqueous conditions were identified and since the $PdCl_2$ showed to be most effective in an aqueous solvent, both solvent and catalyst were abandoned and standard conditions were tried. The reaction in THF with the tetrakis(triphenylphosphine)palladium(0) catalyst showed full conversion after 3 days and the product could be isolated in 53 % yield.

Although these results are not even close to the reaction rates and yields for the Suzuki reactions reported in chapter 2, these results are very promising. For the first time an allylic group very close to an N1-substituted tetrazole is shown to work in a cross coupling reaction. The yield and reaction time could certainly be optimized as it was done for the coupling of 4-Bromobenzyl-*1H*-tetrazole, but due to the limited timeframe of this work further optimization steps were not performed.



11 **12** **14**

Scheme 4.2: Preparation of 1,4-bis(**11**)benzene

In another attempt to prove a possible coupling of allyl-*1H*-tetrazole in Heck reactions a doublefold coupling reaction with 1,4-diiodobenzene was investigated (scheme 4.2). The introduction of two tetrazole functionalities at once via a coupling reaction would be a novelty and would be certainly of interest for a further application in the synthesis of spin-crossover compounds. As it was the case for the synthesis of cinnamyl-*1H*-tetrazole **13** the reaction rate was very slow, even after 3 d only limited conversion to the bis-coupled product **14** was observed. Finally after 9 d nearly full conversion of starting material was observed, but the product could be isolated in only 22 % yield. Certainly a optimization of the mono coupling reaction to cinnamyl-*1H*-tetrazole would also improve the yield of the bis-coupled product. But since the traditional synthesis of bistetrazoles via diamines usually also gives poor yields a coupling protocol to bistetrazols would be a feasible alternative.

4.1.3 Application for Spin-Crossover Compounds

Since the two tetrazole compounds were synthesized for the first time, their applicability for spin-crossover compounds was tested. Therefore, a coordination of allyl-*1H*-tetrazole **11** and cinnamyl-*1H*-tetrazole **13** with iron(II) tetrafluoroborate was tested.

Coordination of Allyl-*1H*-tetrazole 11

A successful coordination compound was obtained using standard procedure with $Fe^{II}(BF_4)_2 \cdot 6\,H_2O$ in acetonitrile. The white solid showed a color change to magenta upon cooling to liquid nitrogen temperature. The spin-crossover behavior was studied in detail by measurement of the temperature dependent magnetic susceptibility (figure 4.1). The spin-transition is complete with a $T_{1/2}$ of 163 K.

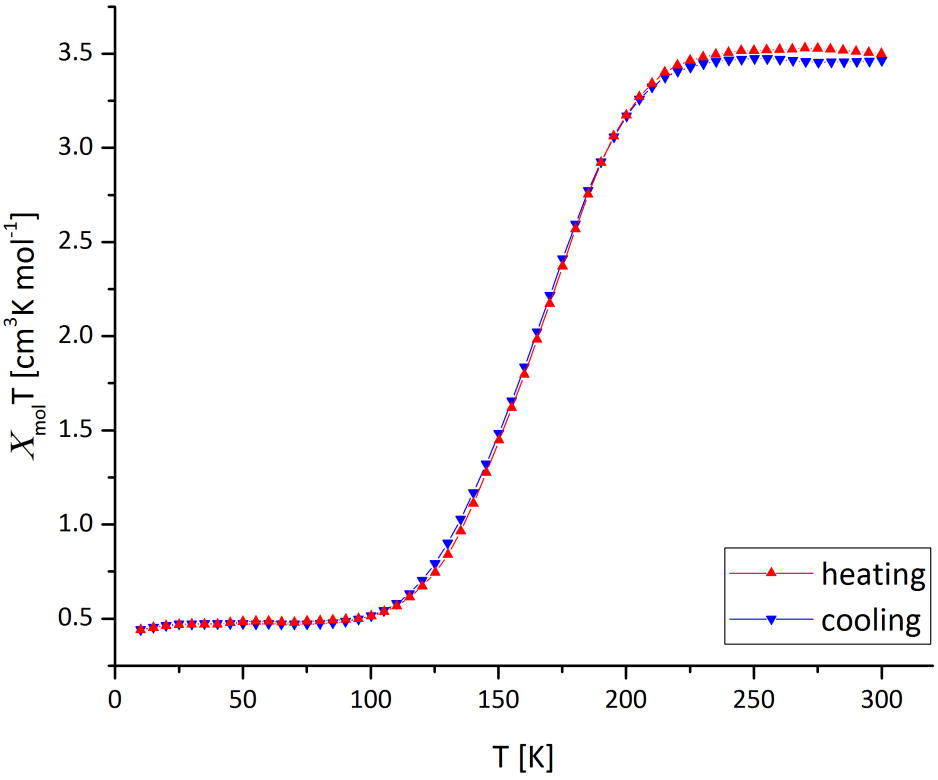


Figure 4.1: Temperature dependent magnetic moment of Fe(**11**)$_6$(BF$_4$)$_2$.

Coordination of Cinnamyl-*1H*-tetrazole 13

A successful coordination of cinnamyl-*1H*-tetrazole to iron(II) tetrafluoroborate was obtained using standard procedure in acetonitrile. The compound shows a color change upon cooling to liquid nitrogen temperature.

4.1.4 Conclusion

The range of possible coupling reactions to introduce tetrazole functionalities was expanded to Heck reactions. Preliminary tests proved to give the coupling product in an all-trans fashion with mediocre yields with a doubtless potential for optimization.

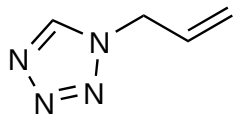
For the first time two N1-tetrazole functionalities were introduced via a coupling reaction at once.

The synthesized compounds were investigated for their applicability as ligands for spin-crossover compounds. All obtained compounds showed a spin-transition and the magnetic behavior of the coordination compound of allyl-*1H*-tetrazole was investigated in detail.

4.1.5 Experimental

The general methodology for the measurement of NMR and Mid-range IR spectra is the same as in section 2.6.1

11 Allyl-*1H*-tetrazole



11

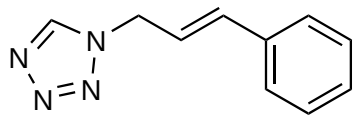
Synthesis of Allyl-*1H*-tetrazole **11** was performed according to the established Franke protocol.[13,16] Allyl amine (10 g, 175 mmol), sodium azide (17.1 g, 263 mmol) and triethyl orthoformate (40.2 mL, 271.5 mmol) were added sequentially to a 0 °C cooled solution of 50 mL glacial acetic acid. The solution turned orange-red immediately and was heated slowly to 95 °C. After refluxing the reaction for 18 h it was allowed to cool to room temperature and poured onto 200 mL ethyl acetate. The organic phase was extracted twice with 200 mL water and all volatile components were evaporated at reduced pressure. The resulting precipitate was stirred for 30 min in 200 mL isopropanol and the solids were filtered off and the filtrate was treated with activated charcoil. After filtration over celite, all volatile components were evaporated at reduced pressure to obtain the title compound as pale yellow liquid (10.4 g, 53.9 % yield).

IR (cm^{-1}): 3133 (ν_{CHTz}).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.74 (s, 1H, CHTz), 5.77 (ddt, J = 17.3, 10.3, 6.1 Hz, 1H, $-CH=$), 5.07 (dd, J = 10.3, 1.0 Hz, 1H, $=CH_2$), 5.02 (dd, J = 17.0, 0.9 Hz, 1H, $=CH_2$), 4.87 (dt, J = 6.1, 1.4 Hz, 2H, $-CH_2-$).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ): 142.64 (CHTz), 129.64 ($-CH=$), 120.34 ($=CH_2$), 49.95 ($-CH_2-$).

13 Cinnamyl-*1H*-tetrazole



13

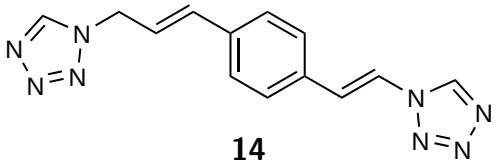
A microwave vial was charged with 131.2 mg tetrakis(triphenylphosphine)palladium(0) (5 mol %, 114 µmol), sealed and set under an atmosphere of argon. 12 mL of dry degassed THF were added and the solution stirred until all solids dissolved. To this solution were added in quick succession: triethylamine (0.63 mL, 4.5 mmol), allyl-*1H*-tetrazole **11** (250 mg, 2.27 mmol) and iodobenzene (486 mg, 2.38 mmol). The reaction was stirred at 80 °C. ^{1}H-NMR control gave full conversion of starting material after 72 h. The solution was poured onto 20 mL ethyl acetate and 20 mL water. The organic phase was washed twice with water and filtrated over a small amount of SiO_2 and eluated thoroughly with ethyl acetate. After evaporation of all volatile components at reduced pressure the crude product was obtained as a brownish oil. The crude product was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (1:1) to afford the title compound as off-white crystalline plates (226 mg, 53.5 % yield).

IR (cm^{-1}): 3118 (ν_{CHTz}).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.67 (s, 1H, CHTz), 7.41–7.29 (m, 5H, ArCH), 6.73 (d, J = 15.8 Hz, 1H, Ar−CH=), 6.33 (dt, J = 15.8, 6.8 Hz, 1H, =CH^-), 5.21 (dd, J = 6.8, 1.4 Hz, 2H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ): 142.37 (CHTz), 136.98 (Ar−CH=), 135.02 (ArC), 129.09 (ArCH), 128.95 (2ArCH), 126.92 (2ArCH), 119.90 (=CH^-), 50.52 (CH_2).

14 1,4−Bis((E)-(*1H*-tetrazolyl)propenyl)benzene



14

A microwave vial was charged with 105 mg tetrakis(triphenylphosphine)palladium(0) (10 mol %, 91 µmol) and 1,4-diiodobenzene (300 mg, 908 µmol) and put under an atmosphere of argon.

16 mL of dry, degassed THF were added and the solution stirred until all solids dissolved. To this solution were added in quick succession: triethylamine (0.5 mL, 3.6 mmol) and allyl-*1H*-tetrazole **11** (250 mg, 2.3 mmol). The dark red solution was heated to 80 °C and kept at this temperature for 9 d.

Precipitation from n-Hexane gave the title compound as beige to yellow solid (60 mg, 22.5 % yield).

IR (cm^{-1}): 3109 (ν_{CHTz}).

^{1}H NMR (400 MHz, DMSO−d_6, δ): 9.47 (s, 2H, CHTz), 7.46 (s, 4H, ArCH), 6.68 (d, J = 15.9 Hz, 2H, Ar−CH=), 6.53 (dt, J = 15.9, 6.5 Hz, 2H, =CH$^-$), 5.29 (dd, J = 6.5, 1.3 Hz, 4H, CH_2).

^{13}C{^{1}H} (101 MHz, DMSO−d_6, δ): 143.92 (CHTz), 135.49 (ArC), 133.80 (=CH$^-$), 127.04 (ArCH), 122.85 (Ar−CH=), 49.45 (CH_2), 39.52.

15 [Fe(Allyl-*1H*-tetrazole)$_6$](BF$_4$)$_2$

A schlenk flask was charged with allyl-*1H*-tetrazole **11** (100 mg, 908 µmol) and $Fe(BF_4)_2 \cdot 6\,H_2O$ (51 mg, 151 µmol) and put under an atmosphere of argon. Upon addition of dry acetonitrile all compounds dissolved and the solution was warmed to 50 °C for 18 h. The solvent was evaporated to yield the product as off-white solid in quantitative yield.

$T_{1/2} = 163\,°C$

16 [Fe(Cinnamyl-*1H*-tetrazole)$_6$](BF$_4$)$_2$

A schlenk flask was charged with cinnamyl-*1H*-tetrazole **13** (100 mg, 537 µmol) and $Fe(BF_4)_2 \cdot 6\,H_2O$ (30.2 mg, 89 µmol) and put under an atmosphere of argon. Upon addition of dry acetonitrile all compounds dissolved and the solution was warmed to 50 °C for 18 h. The solvent was evaporated to yield the product as white solid in quantitative yield.

IR (cm^{-1}): 3145 (ν_{CHTz})

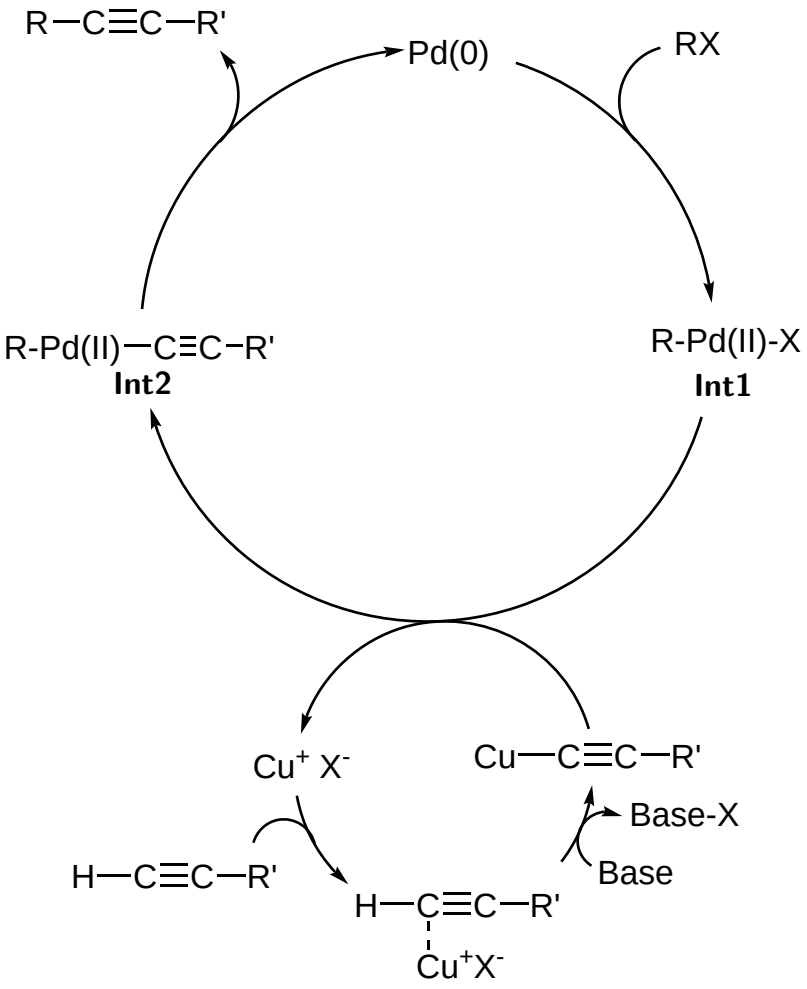
4.2 Sonogashira Coupling of Propargyl-1H-tetrazole

4.2.1 Introduction

The Sonogashira reaction introduced by Kenkichi Sonogashira and Coworkers in 1975 allows the C-C bond formation between an terminal alkyne and an aryl or alkenyl halide.[60] In comparison to other palladium-catalyzed cross coupling reactions the Sonogashira reaction makes use of another co-catalytic copper-cycle to activate the alkynylic species (see scheme 4.3).

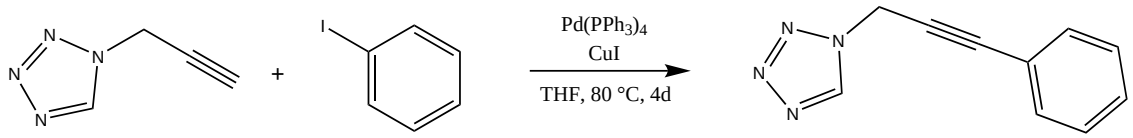
The coupling reaction with tetrazoles under Sonogashira conditions proved to be rather difficult as tetrazoles are known to coordinate copper, which would render the catalytic copper-cycle inactive. Recently, copper-free conditions were reported,[61–64] this would overcome the difficulties encountered. Unfortunately, most conditions investigated, with copper and copper-free conditions as well, failed to give satisfying conversions and pure product was never obtained.

Confident with the results obtained during the Heck reactions reported in section 4.1 another attempt was made with the conditions used for the successfull Heck coupling with a small amount of copper(I) iodide added in high dilution. Surprisingly these conditions gave full conversion of starting material after 4 d and finally product was isolated in 31 % yield.



Scheme 4.3: General Catalytic Cycle for the Sonogashira Cross Coupling Reaction.

4.2.2 Coupling Reactions



17 **12** **18**

Scheme 4.4: Preparation of 1-(3-phenylprop-2-yn-1-yl)-*1H*-tetrazole **18**.

As model reaction to prove the concept of a successful Sonogashira reaction with tetrazoles, the reaction of propargyl-*1H*-tetrazole[65] with iodobenzene was chosen. Propargyl-*1H*-tetrazole is a known SCO-ligand and possibly the smallest N1-substituted tetrazole with a terminal alkyne obtainable, as the molecule without the methyl group between the tetrazole and the alkyne is very likely too unstable for any type of reactions. Even the propargyl-*1H*-tetrazole does not tolerate harsh reaction conditions and decomposes at higher temperatures. Fortunately, Sonogashira reactions are known to run typically under mild conditions at room temperature, one of the reasons is the activation of the substrate as copper-acetylide, which is more prone to undergo transmetallation. Unfortunately, the coordination of the tetrazolic N4 onto copper is probably a competitive reaction, and reactions with typical concentrations of copper species at room temperatures gave only very poor results. A copper-free approach was taken, as this would be the best solution to overcome the competitive coordination reaction, but no conversion was observed at all. Finally, good conversions were achieved using low concentrations of copper in an very diluted system with prolonged reaction times with temperatures of 80 °C. Full conversion of starting material was observed after 4 d using a 13 mM concentration of copper(I) iodide. The pure product was obtained in 31 % yield after purification steps. Although this yield is moderately low, it proves that the so far very difficult Sonogashira coupling of tetrazoles is possible and further optimization steps of the reaction conditions and more importantly the purification steps might very likely lead to good yields with acceptable reaction rates.

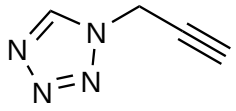
4.2.3 Conclusion

A N1-substituted tetrazole was found to undergo a Sonogashira-type coupling reaction. Very dilute systems with low copper-loadings lead to full conversion of starting material after several days. Although very low isolated yields were obtained this proves the possibility of Sonogashira couplings with tetrazoles. Further optimization steps regarding the catalytic system with respect to conversion rate need to be done, but these preliminary results are promising enough to continue this direction.

4.2.4 Experimental

The general methodology for the measurements of NMR and Mid-range IR spectra is the same as in section 2.6.1

17 Propargyl-1H-tetrazole



17

Propargyl-1H-tetrazole was synthesized according to the procedure already reported.[66] Propargylamine (21.6 g, 392 mmol), sodium azide (38.2 g, 588 mmol) and triethylorthoformate (90 g, 608 mmol) were dissolved in 100 mL glacial acetic acid and the solution was stirred at 90 °C for 21 h. The solvent was evaporated under reduced pressure and the residue was dissolved in 300 mL 2 M HCl and extracted with ethyl acetate. The organic phase was washed with sat. $NaHCO_3$ and sat. NaCl. The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to yield the crude product as yellow oil. The crude product was purified via bulb-to-bulb distillation (0.0025 mbar, 130–150 °C) to afford the title compound as slightly yellow oil (19 g, 45 % yield).

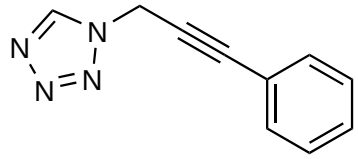
IR (cm^{-1}): 3280 ($\nu_{HC=C}$), 3138 (ν_{CHTz}), 2980 (ν_{CH2}), 2134 ($\nu_{C=C}$), 1481 (ν_{CNTz}), 1100 (ν_{Tz}).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.95 (s, 1H, CHTz), 5.21 (d, J = 2.8 Hz, 2H, $-CH_2-$), 2.64 (t, J = 2.7 Hz, 1H, −CH).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 142.74 (CHTz), 76.51 (C≡C), 73.77 (C≡C), 37.85 (CH_2).

Caution: Although no risks in handling the reported compound was encountered, proper and careful treatment is highly recommended!

18 Phenylpropargyl-*1H*-tetrazole



18

A microwave vial was charged with 127 mg Tetrakis(triphenylphosphine)palladium(0), 110 µmol and 42 mg copper(I) iodide (220 µmol), sealed and set under an atmosphere of argon. 16 mL of dry, degassed THF were added and the solution stirred at room temperature until all solids dissolved. To this solution were added in quick succession: triethylamine (0.6 mL, 4.4 mmol), propargyl-*1H*-tetrazole **17** (250 mg, 2.3 mmol) and iodobenzene (450 mg, 2.2 mmol). The reaction was stirred at 80 °C. 1 H-NMR control gave full conversion of starting material after 96 h. The solution was poured onto a mixture of 20 mL H_2O and 40 mL ethyl acetate and stirred for 30 min. The organic phase was washed twice with H_2O, once with a sat. solution of NaCl, filtrated over a small amount of SiO_2 and eluated thoroughly with ethyl acetate. After evaporation of all volatile components at reduced pressure the crude product was obtained as orange-red oil. The crude product was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (1:1) to afford the title compound **18** as slightly green oil (127 mg, 31.3 % yield).

IR (cm^{-1}): 3135 (ν_{CHTz}).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.86 (s, 1H, CHTz), 7.36 (dd, J = 8.1, 1.7 Hz, 2H, ArCH), 7.32–7.19 (m, 3H, ArCH), 5.39 (s, 2H, CH_2).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ): 142.53 (CHTz), 131.87 (2ArCH), 129.53 (ArCH), 128.50 (2ArCH), 120.82 (ArC), 88.01 (CH≡CH), 78.60 (CH≡CH), 39.05 (CH_2).

Conclusion

For the Suzuki cross coupling reaction of 4-Bromobenzyl-*1H*-tetrazole with phenylboronic acid very robust conditions were found, employing palladium chloride as a cheap catalytic source and a mixture of water and ethanol as environmentally benign and cheap solvent system. During the investigation it was found that the atmosphere had no influence on the yield. Therefore, this reaction was performed under an atmosphere of air. Furthermore, aqueous ammonia was identified as possible replacement for triethylamine, giving in most cases the same results as the organic base. Aside from those conditions, a system in toluene with palladium on activated charcoil and potassium carbonate was found to give excellent results.

The scope of the aqueous $PdCl_2$-system was investigated in reactions with a wide variety of different aromatic and heteroaromatic boronic acids, with good to excellent yields in a range of 79–96 %. Altogether 16 coupling products were synthesized and thoroughly characterized by means of NMR, IR and HR-MS measurements.

Some obtained compounds were used in iron(II) spin-crossover compounds. The effect of substitutional pattern and functional group on the spin-transition behavior was investigated by VSM measurements. Para- and ortho-substituted compounds were found to give a more abrupt spin transition with a $T_{1/2}$ shifted to higher temperatures compared to the meta compound. Additionally, different electronic effects of the functional group showed a shift of the transition with more electronegative substituents shifting to higher temperatures although with a loss of completeness.

These results show the viability of a simple coupling-protocol to achieve a library synthesis of similar substituted molecules to gain a better understanding of the trends of the spin-crossover behavior withing homologous series of compounds.

To gain a better understanding of the exact appearance of the NMR spectra of the compounds obtained, a DFT method was developed to precisely calculate the fine spin-spin coupling of those biarylic systems. With the help of Gaussian computational software all low-energy rotamers were generated and their spin-spin coupling constants and fermi spin-spin terms were calculated. The ^{1}H-NMR spectra generated by the obtained data was in excellent agreement with the experimental spectra.

In further experimental work the Heck reaction of allyl-*1H*-tetrazole with iodobenzene was investigated. After some optimization the product could be obtained in all-trans fashion with mediocre yield and a doubtless potential for optimization. This shows that the scope of possible coupling reaction is not limited to the Suzuki-Miyaura type. A second doublefold

reaction of allyl-1H-tetrazol with 1,4-diiodobenzen was investigated as well and was found to give full conversion but only low isolated yields.

The synthesized compounds were investigated for their applicability as ligands for spin-crossover compounds. All obtained compounds showed a spin-transition and the magnetic behavior of the coordination compound of allyl-*1H*-tetrazole was investigated in detail.

Propargyl-*1H*-tetrazole was found to undergo a Sonogashira-type coupling reaction with iodobenzene. Very dilute systems with low copper-loadings lead to full conversion of starting material after several days. Although low isolated yields were obtained this proves the possibility of Sonogashira couplings with tetrazoles.

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