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PREPARATION AND APPLICATIONS OF NEW SOLID ORGANOZINC REAGENTS FOR THE FUNCTIONALIZATION OF AROMATICS, HETEROAROMATIC AND ALKYNYL COMPOUNDS

von

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ERKLÄRUNG

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……

(Carl Phillip Tüllmann)

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1) "*Preparation of Solid Organozinc Pivalates and Their Reaction in Pd-Catalyzed Cross-Couplings*"
M. Ellwart, Y.-H Chen, C. P. Tüllmann, V. Malakhov, P. Knochel *Org. Synth.* **2018**, *95*, 127

2) "*New Class of Solid Polyfunctional Alkynylzinc Pivalates with Enhanced Air and Moisture Stability for Organic Synthesis*"
Y.-H. Chen, C. P. Tüllmann, M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 9236.

3) "*Preparation and Reactions of Mono- and Bis-Pivaloyloxyzinc Acetylides*"
C. P. Tüllmann, Y.-H. Chen, R. J. Schuster, P. Knochel, *Org. Lett.* **2018**, *15*, 4601.

4) "*Preparation and Reactions of (1H-tetrazol-5-yl)zinc pivalates*"
C. P. Tüllmann, S. Steiner, P. Knochel, *Synthesis* **2020,** *52*, A–G.

“The saddest aspect of life right now is that science gathers knowledge faster than society gathers wisdom.”

Isaac Asimov (1902-1992)

Abbreviations

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
ATR	attenuated total reflection
Bu	butyl
Bn	benzyl
calc.	calculated
dba	*trans*,*trans*-dibenzylideneacetone
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
e.g.	*exempli gratia*, for example
EI	electron ionization (MS)
equiv	equivalent(s)
Et	ethyl
EX	electrophile
FG	functional group
GC	gas chromatography
Hal	halogen
Het	undefined heteroaryl substituent
HRMS	high resolution mass spectrometry
i	*iso*
i.e.	*id est*, that is
IR	infrared spectroscopy
J	coupling constant (NMR)
M	mol L^{-1}
Me	methyl
Met	metal
mol%	equiv.•10^{-2}
m.p.	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
PG	protecting group
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
Pr	propyl

R	undefined organic substituent
sat.	saturated
t	*tert*
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TP	typical procedure
vol	volume

Table of Contents

A. INTRODUCTION 1

1 Overview 2

2 Organozinc Compounds 4

2.1 Overview 4

2.2 Preparation of Organozinc Compounds 4

3 Solid Salt Stabilized Organozinc Reagents 9

3.1 Overview 9

3.2 Preparation of Organozinc Pivalates from (Hetero-)Aryl Halides 10

3.3 Preparation of Organozinc Pivalates by Metalation 12

3.4 Preparation of Organozinc Pivalates from Allyl Halides 14

3.5 Preparation and Application of Pivaloxy Zinc Amide Enolates 16

4 Objectives 18

B. RESULTS AND DISCUSSION 19

1 A New Class of Solid Polyfunctional Alkynylzinc Pivalates with Enhanced Air and Moisture Stability for Organic Synthesis 20

1.1 Introduction 20

1.2 Preparation of Polyfunctional Alkynyl Zinc Pivalates 21

1.3 Application of Solid Alkynyl Zinc Pivalates in Negishi Cross-Coupling Reactions 23

1.4 Acylation, Allylation and Aldehyde Addition of Solid Alkynyl Zinc Pivalates 24

1.5 Application of Solid Alkynylzinc Pivalates in Copper-catalazed regioselective Azide-alyne Cycloaddition 25

1.6 Synthesis of Carboxyamidotriazole using Alkynyl Zinc Pivalates 27

2 Preparation and Reactions of Mono- and Bis-Pivaloyloxyzinc Acetylides 28

2.1 Introduction 28

2.2 Preparation and Activity of Mono-pivaloyloxyzinc Acetylide (98) and Bis-pivaloyloxyzinc Acetylide (99) 28

2.3 Application of Solid Mono-pivaloyloxyzinc Acetylide (98) in Negishi Cross-Coupling Reactions 30

2.4 One-pot Synthesis of Non-symmetrical bis-arylated Acetylenes (102) using Mono-pivaloyloxyzinc Acetylide (98) 31

2.5 Synthesis of 1,5-disubstituted Triazoles 105 using Mono-pivaloyloxyzinc Acetylide (98) 32

2.6 Application of Solid Bis-pivaloyloxyzinc Acetylide (99) in Negishi Cross-Coupling Reactions 33

2.7 Synthesis of 1,2,5-Trisubstituted Triazole 108 followed by a Ring-closing Metathesis to generate the Benzotriazole Derivative 109 35

3 Preparation and Reactions of (1*H*-tetrazol-5-yl)zinc Pivalates 36

3.1 Introduction 36

3.2 Preparation and Activity of (1*H*-tetrazol-5-yl)zinc Pivalates of Type 111 37

3.3 Application of (1*H*-tetrazol-5-yl)zinc pivalate 111b in Negishi Cross-Coupling Reactions 38

3.4 Deprotection of arylated 1*H*-tetrazoles 112 39

3.5 Amination of (1*H*-tetrazol-5-yl)zinc Pivalate 111b 39

4 Summary 41

4.1 New Class of Solid Polyfunctional Alkynylzinc Pivalates with Enhanced Air and Moisture Stability for Organic Synthesis 41

4.2 Preparation and Reactions of Mono- and Bis-Pivaloyloxyzinc Acetylides 42

4.3 Preparation and reactions of (1*H*-tetrazol-5-yl)zinc pivalates 44

C. EXPERIMENTAL PART 46

1 General Considerations 47

1.1 Solvents 47

1.2 Reagents 47

1.3 Chromatography 49

1.4 Analytical data 49

2 New Class of Solid Polyfunctional Alkynylzinc Pivalates with Enhanced Air and Moisture Stability for Organic Synthesis. 50

2.1 Typical Procedures (TP) 50

2.2 Stability of Alkynylzinc reagents of Type 71 in Air 51

2.3 Catalysts screening for Negishi Cross-coupling 52

2.4 Preparation of the Solid Alkynylzinc Pivalates 52

2.5 Preparation of Negishi Cross-Coupling Products 55

2.6 Fukuyama coupling, allylation and aldehyde addition 60

2.7 Copper catalyzed 1,3-dipolar cycloaddition with solid alkynylzinc pivalates 62

2.8 Synthesis of Carboxyamidotriazole (96) 65

3 Preparation and Reactivity of Ethynylzinc Pivalate and Dipivaloyoxyzinc acetylene 69

3.1 Preparation of Zinc pivalates 69

3.2 Typical Procedures (TP) 69

3.3 Preparation of the aryl acetylenes (101) 71

3.4 Preparation of Asymmetrical Bis-arylated Alkynes (102) 74

3.5 Preparation of 1,5-disubstituted 1,2,3-triazoles (105) 77

3.6 Preparation of symmetrical bis-arylated alkynes 106) 79

4 Preparation and reactions of (1*H*-tetrazol-5-yl)zinc pivalates 85

4.1 Synthesis of protected 1*H*-tetrazoles of type 110 85

4.2 Synthesis of the (1*H*-tetrazol-5-yl)zinc pivalates of type 111 85

(1-Benzyl-1*H*-tetrazol-5-yl)zinc pivalate (111a) 85

4.3 Typical Procedures (TP) 86

4.4 Metalation of Tetrazoles using TMPZnOPiv and subsequent Negishi cross-coupling reactiongs with aryl halides 87

4.5 Preparation of unprotected aryl tetrazoles using ammonium formate and palladium on charcoal 92

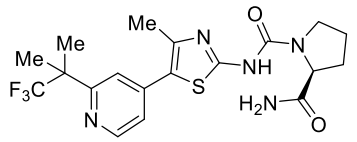
4.6 Amination of 1*H*-tetrazoles using TMPZnOPiv and amine benzoate 94

A. INTRODUCTION

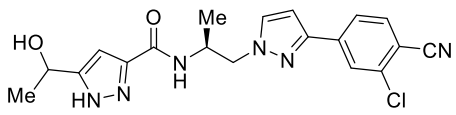
1 Overview

In 2018, according to the International Agency of Research on Cancer (IARC), an estimated 18.1 million new cases of cancer occurred worldwide causing 9.6 million deaths.[1] In the following 5 years there will be an estimated 43.8 million people diagnosed with this deadly disease. By 2030, the global burden is expected to rise up to 21.7 million new cancer cases simply due to the aging and increase of the world's population. This tremendous expansion of cancer accompanied by other epidemics or terminal illnesses require a constant development of new drugs that can fight against these diseases or at least relieve occurring pain in the most bearable way.

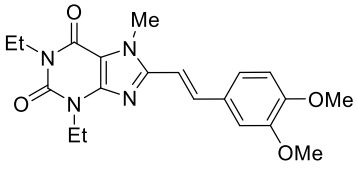
To tackle these challenges, the FDA's Center for Drug Evaluation and Research (CDER) approved 48 new drugs in 2019, which is the third highest approval number in history. In 2018 with 59 approvals, the development of new compounds reached its temporary high.[2] The majority of the new therapeutic drugs (35) are still categorized in the broad class of small organic molecules with a low molecular weight (< 900 g mol^{-1}). Alpelisib (Piqray®, Novartis, anti-breast cancer, **1**), Darolutamide (Nubeqa®, Roche, anti-prostate cancer, **2),** Istradefylline (Nourianz®, Kyowa Kirin, Parkinson, **3**) and Lumateperone (Caplyta®, intra-cellular-therapies, **4**) are four typical examples for such approved small molecule drugs. Nowadays, these agents are identified in high throughput screenings using large chemical libraries of synthetic small molecules or natural products. This process is known as classical pharmacology in which the tools and knowledge of a synthetic organic chemist are irreplaceable.[3]



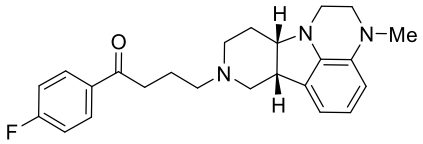
Alpelisib (**1**)



Darolutamide (**2**)



Istradefylline (**3**)



Lumateperone (**4**)

Figure 1: Selected small molecules approved as therapeutic drugs in the U.S. by the FDA in 2019.

1 International Agency for Research on Cancer (2018, September 12th): *Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018*; Retrieved from: https://www.iarc.fr/www.iarc.fr › wp-content › uploads › 2018/07 › pr223_E

2 A. Mullard (2020, January 8th): *2019 FDA drug approvals;* Retrieved from: doi: 10.1038/d41573-020-00001-7

3 J. A. Lee, M. T. Uhlik, C. M. Moxham, D. Tomandl, D. J. Sall, *J. Med. Chem.* **2012**, *55*, 4527.

In fact, the field of organometallics have turned out to be capable of developing such difficult scaffolds, where the conventional synthetic methods reached their limits.[4] Nobel Prize laureate E.-I. Negishi once said: "*Nowadays, it is not only unwise but rather difficult to accomplish an efficient and selective multiple synthesis without using organometallics.*"[5] Since 1760, when Louis-Claude Cadet de Gassicourt prepared the first organometallic species,[6] these compounds have shown a variable applicability in the formation of new carbon-carbon and carbon-heteroatom bonds and with that in hand, they provide access to complex molecules and many applications in total synthesis.[7]

However, the reactivity of organometallic reagents is determined by the polarity of the carbon-metal bond. Compounds with a high ionic character (Figure 2), such as organolithium, are highly reactive, but often require low temperatures reaction temperatures (below –78 °C)[8] and need to be stored in hydrocarbon solvents to avoid degradation by ethereal solvents.[9] Due to their high reactivity, functional group tolerance is comparatively low, which can lead to side reactions. Because of their less polarized metal-carbon bond, magnesium and aluminum organometallics are significantly less reactive with an improved tolerance of functional groups.

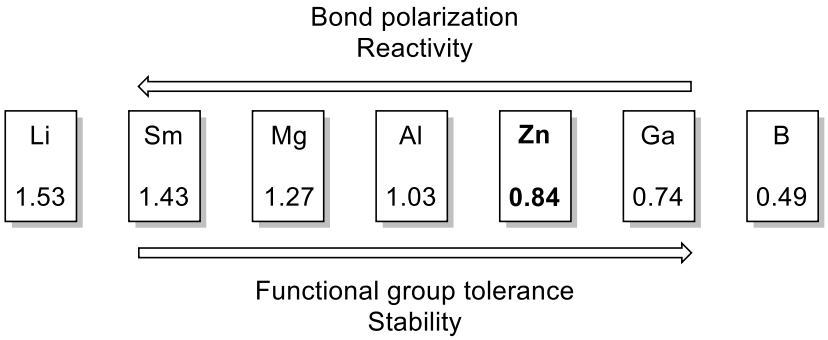


Figure 2: Electronegativity difference of selected metals relative to carbon (Pauling electronegativity scale).[10]

On the other end of the scale, there are elements like gallium and bor. Further, these elements are likely to tolerate a broad scope of reaction partners with a minor reactivity. Whereas, zinc organometallics show a perfect balance between reactivity and functional group tolerance and additionally being prone to be quite stable in solution.

4 R. H. Crabtree, *Organometallics* **2011**, *30*, 17.
5 E.-I. Negishi, *Organometallics in Organic Synthesis*, Wiley-VCH, Weinheim, **1980**.
6 D. Seyferth, *Organometallics* **2011**, *20*, 1488.
7 K. C. Nicolaou, J. S. Chen, in *Classics in Total Synthesis III*, Wiley-VCH Verlag GmbH, **2011**.
8 For a general review, see: a) P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. Kneisel in *Handbook of Functionalized Organometallics*, (Eds.: P. Knochel), Wiley-VCH, Weinheim **2005**; b) P. Knochel, P. Millot, A. L. Rodriguez, C. E. Tucker in *Organic reactions*, (Eds.: L. E. Overman), Wiley & Sons Inc., New York, **2001**, p. 1.
9 H. Gilman, B. J. Gaj, *J. Org. Chem.* **1957**, *22*, 1165.
10 A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *39*, 4414.

2 Organozinc Compounds

2.1 Overview

The research field of organozinc compounds can look back on a history, which last already for over 170 years. In 1849, Frankland and co-workers already discovered diethyl- and dimethyl zinc as the first organozinc compounds.[11] Since then, organozinc compounds played in important role in numerous applications in modern organic synthesis. The Simmons-Smith cyclopropanation[12] and the Reformatsky reaction[13] are two well-known examples. Furthermore, due to the presence of empty p-orbitals of appropriate energy, which facilitates 4-membered transition states leading to mixed zinc-copper species, organozinc compounds easily undergo transmetalation reactions with various copper salts. These zinc-copper reagents are more reactive due to the presence of nonbonding, nucleophilic d-electrons that interact in an oxidative process with the electrophile and mediate the formation of the new carbon-carbon bond, despite containing the thermodynamically more stable carbon-copper bond.[14] The ability to transmetalate to palladium in the Negishi cross-coupling reactions granted the organozinc compounds being a powerful and essential tool in organic synthesis. In 2010, Ei-ichi Negishi, Richard F. Heck and Akira Suzuki were rewarded with the Nobel Prize in Chemistry for their pre-eminent work in the field of carbon-carbon bond formation.[15] Organozinc compounds are one of the most versatile and advantageous reagents in cross-coupling chemistry. They have a high functional group tolerance and good reactivity without producing any toxic byproducts.[16] However, organozinc compounds show an instability when exposed to air, which can be related to hydrolysis by air.

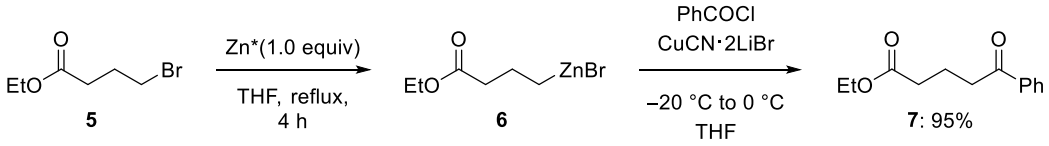
2.2 Preparation of Organozinc Compounds

2.2.1 Oxidative Insertion

Based on the preparation of organomagnesium compounds, the most common method for the direct preparation of organozinc reagents is the insertion into organic halides using zinc powder. To avoid the typical drawbacks of using expensive organic iodides and high reaction temperatures, Rieke et al. developed highly active zinc (Zn*), which is prepared by reduction of $ZnCl_2$ with lithium naphtatilde. These reagents allow the preparation of functionalized organozinc compounds from the less reactive

[11] E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*¸ 171.
[12] a) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323; b) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 5323; c) H. Lebel, J.-F. Marcoux, C. Molinaro., A. B. Charette, *Chem. Rev* **2003**, *203, 977.*
[13] a) S. Reformatsky, *Chem. Ber.* **1887**, *20*, 1210; **1895**, *28*, 2842; b) R. Ocampo, *Tetrahedron* **2004**, *60*, 9325.
[14] P. Knochel, H. Leuser, L.-Z. Cong, S. Perrone, F. F. Kneisel, in *Handbook of FunctionalIized Organometallics*, Wiley-VCH Verlag GmbH **2008**, pp.251.
[15] X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **1020**, *49*, 9047.
[16] a) P. Knochel, J. Almena, P. Jones, *Tetrahedron* **1998**, *54*, 8275; b) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; c) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417; d) A. Lemire, A. Côté, M. K. Janes, A. B. Charette, *Aldrichimica Acta* **2009**, *42*, 71.

alkyl bromides (Scheme 1).[17] Hence, starting from ethyl 4-bromobutyrate (**5**) the organozinc bromide (**6**) was formed using the Rieke zinc. In a subsequent addition to benzoyl chloride in the presence of CuCN·2LiBr the desired ethyl 5-oxo-5-phenylpentatnoeate (**7**) was formed in 95% yield over two steps (Scheme 1).[17b]



Scheme 1: Zinc insertion using Rieke zinc and subsequent acylation.[17b]

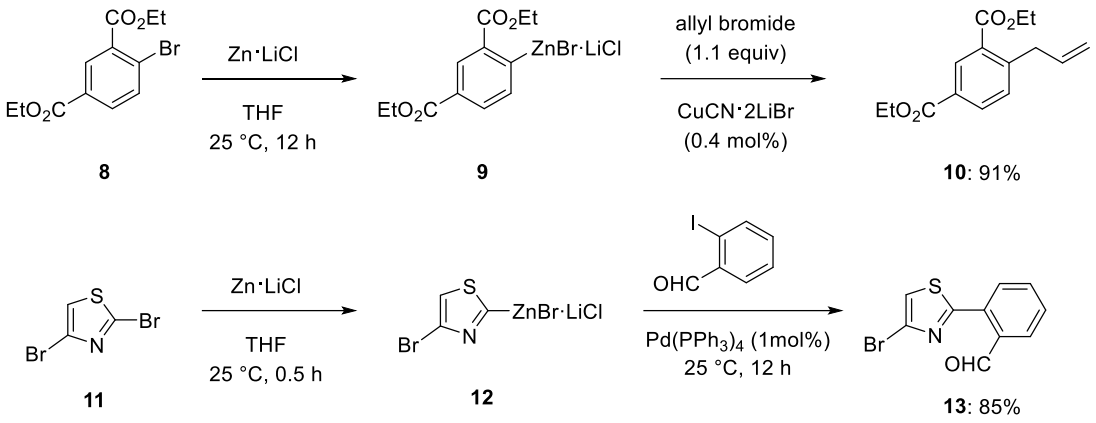
Since the Rieke reagent always has to be freshly prepared, Knochel and co-workers developed a procedure using commercially available zinc powder in the presence of LiCl for the insertion to highly functionalized halides under mild conditions (Scheme 2).[18] With this method in hand, the preparation of benzylic, aromatic and heteroaromatic zinc reagents has been developed, tolerating a variety of functional groups like nitriles, aldehydes and esters. The role of LiCl has been investigated by means of experimental, computational and analytical studies.[19] Furthermore, LiCl increases the solubility of the formed organozinc reagents in THF. Thus, in the insertion reaction a "clean" metal surface is regenerated, which allows a further reaction with the starting halide.[18a,20] Therefore, the aromatic bromide **8** was converted into the zinc species **9** at 25 °C and subsequently underwent a copper catalyzed allylation forming the allylated product **10** in 91% yield. Furthermore, the preparation and palladium-catalyzed cross-coupling of zinc reagent **12** led to the arylated heteroatomic compound **13** in 85% yield (Scheme 2).[18a.b]

[17] a) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4322; b) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.

[18] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem.* **2006**, *118*, 6186; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.

[19] a) C.-Y. Liu, X. Wang, T. Furuyama, S. Yasuike, A. Muranaka, K. Morokuma, M. Uchiyama, *Chem. Eur. J.* **2010**, *16*, 1780; b) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771; c) J. E. Fleckenstein, K. Koszinowski, *Organometallics* **2011**, *30*, 5018.

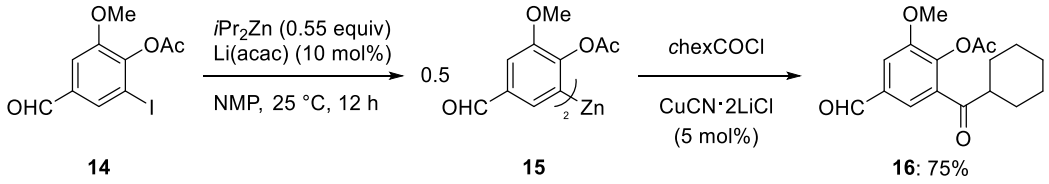
[20] a) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159; b) C. Feng, D. W. Cunningham, Q. T. Easter, S. A. Blum, *J. Am. Chem. Soc.* **2016**, *138*, 11156.



Scheme 2: Preparation of functionalized organozinc reagents using zinc dust in the presence of LiCl.[18a,b]

2.2.2 Iodine-Zinc Exchange

Alternatively, organozinc compounds can be formed from organic iodides. They are prepared through an exchange reaction using a more reactive organozinc reagent. The driving force in this reaction is the formation of the more stable organometallic reagent.[21] For instance, *i*Pr$_2$Zn in the presence of Li(acac) (acac = acetylacetonate) can perform iodine-zinc exchange on various iodinated aromatics and heteraromatics.[22] Using this method, the aryl iodide **14** could be transformed into the diorganozinc species **15** at room temperature and furnishes 2-(cyclohexanecarbonyl)-4-formyl-6-methoxyphenyl acetate (**16**) after a smooth acylation in 75% yield (Scheme 3).[22]



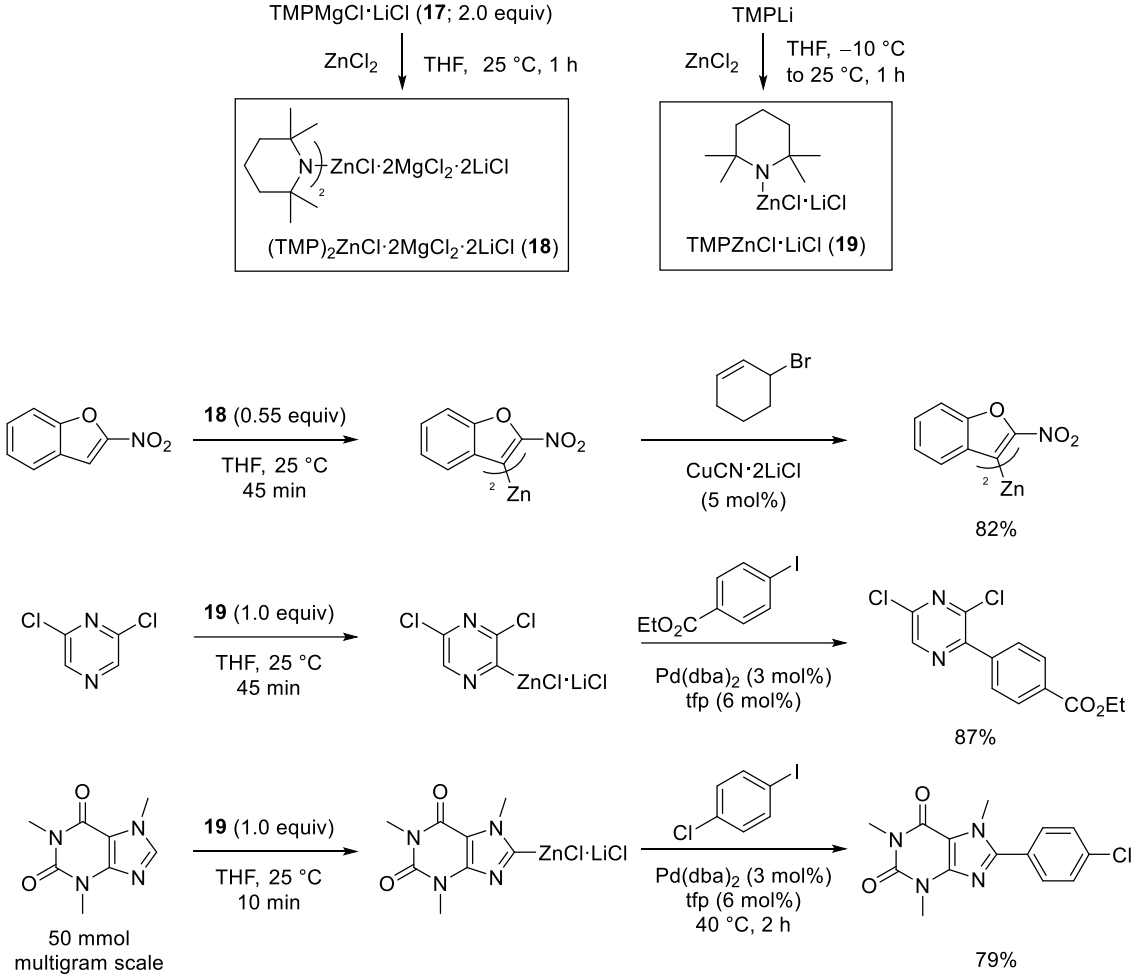
Scheme 3: Preparation of diorganozinc reagents through a Li(acac)-mediated iodide-zinc reaction.[22]

2.2.3 Metalation

The directed metalation using metal bases is another approach to obtain functionalized organometallics. Strong alkyllithium bases and lithium amides, such as *n*-BuLi or LDA, are extensively used for this matter. Due to their very high reactivity, undesired side reactions often occure. In addition, their strong nucleophilicity and low functional group tolerance have been a serious problem for the use of these bases. Another disadvantage of lithium bases is their low stability in THF at room temperature. Thus, reaction temperatures below –78 °C are necessary to perform these metalations. Knochel and co-workers solved this problem, by developing the highly active mixed Mg/Li-bases of type

[21] D. Hauk, S. Lang, A. Murso,*Org. Process Res. Dev.* **2006**, *10*, 733.
[22] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.

$R_2NMgCl{\cdot}LiCl$.[23] TMP (2,2,6,6-tetrametyhlpiperydin) has shown to be the best amine for this kind of metalations. Since then TMPMgCl·LiCl (**17**) has been used in a variety of metalations.[24] As, this base still has a limited functional group tolerance and high reactivity, Knochel and co-workers developed the high chemoselective TMP-zinc bases $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ (**18**) and TMPZnCl·LiCl (**19**). Both bases have the ability to metalate sensitive heterocycles and aromatics under mild conditions (Scheme 4).[25]



Scheme 4: TMP-bases **18** and **19** developed by Knochel and co-worker for the regioselective metalation and functionalization of aromatic and heteroaromatic scaffolds.[25a,c]

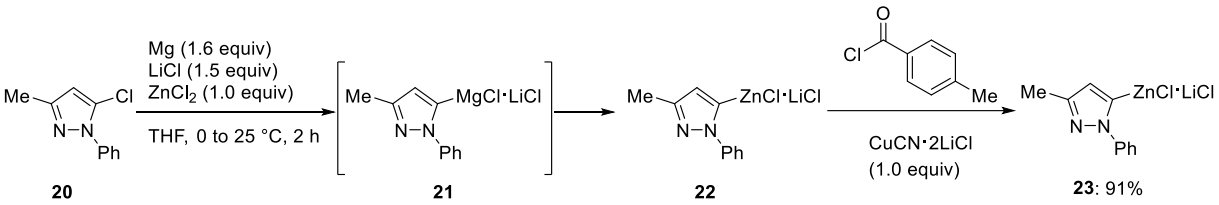
[23] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) T. Kunz, P. Knochel, *Angew. Chem.* **2012**, *124*, 1994; *Angew. Chem. Int. Ed.* **2012**, *51*, 1958.

[24] a) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794; b) S. M. Manolikakes, N. M. Barl, C. Sämann, P. Knochel, *Z. Naturforsch., B: Chem. Sci.* **2014**, *68*, 411.

[25] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; c) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; d) T. Bresser, G. Monzon, M. Mosrin, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 1299; e) S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel, *Org. Process Res. Dev.* **2010**, 14, 339.

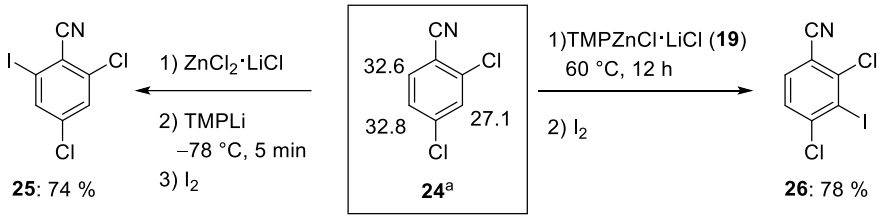
2.2.4 Transmetalation

A different approach towards functionalized organozinc reagents is the treatment of organomagnesium or organolithium compounds with a $ZnCl_2$ solution in THF leading to the transmetalation to the corresponding organozinc compounds. The driving force in this reaction is the more covalent and thereby more stable C–Zn bond. For example, the magnesium insertion into 5-chloro-3-methyl-1-phenyl-1H-pyrazole (**20**) in the presence of $ZnCl_2$ leads to the intermediate formation of the organomagnesium compound **22** (Scheme 5). Avoiding undesired side reactions the zinc salt traps this reagent and results in the stable zinc compound **22**. A subsequent acylation in the presence of CuCN·2LiCl provides the desired ketone **23** in 91% yield.[26]



Scheme 5: Transmetalation of organomagnesium compound of type **21** in the presence of $ZnCl_2$.[26]

An important tool for the functionalization of complex aromatic scaffolds is the lithiation of arenes and heteroarenes. This method has major drawbacks like an exceptionally high reactivity, instability at ambient temperature and limitations in terms of functional group tolerance. To solve this issue, Knochel and co-worker developed a procedure, which allows the use of TMPLi in the presence $ZnCl_2$, $MgCl_2$ or CuCN. For instance, the use of TMPZnCl·LiCl (**19**) in a reaction with 2,4-dichlorobenzonitrile leads to the metalation and subsequent trapping with I_2 of the most acidic 3-position providing the functionalized aromatic **25**, whereas the metalation with TMPLi in the presence of $ZnCl_2$·LiCl furnishes the kinetic iodinated product **26**. Furthermore, it was shown that the reaction of TMPLi with **24** is more than six times faster than the reaction of TMPLi with $ZnCl_2$·LiCl which leads to this high regioselectivity (Scheme 6).[27]



Scheme 6: Regioselectivity switch in the metalation of **24** using TMPLi in the presence of $ZnCl_2$·LiCl or TMPZnCl·LiCl (**19**). [a]Calculated pk_a for H3, H5 and H6.[27]

[26] F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.
[27] A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928.

3 Solid Salt Stabilized Organozinc Reagents

3.1 Overview

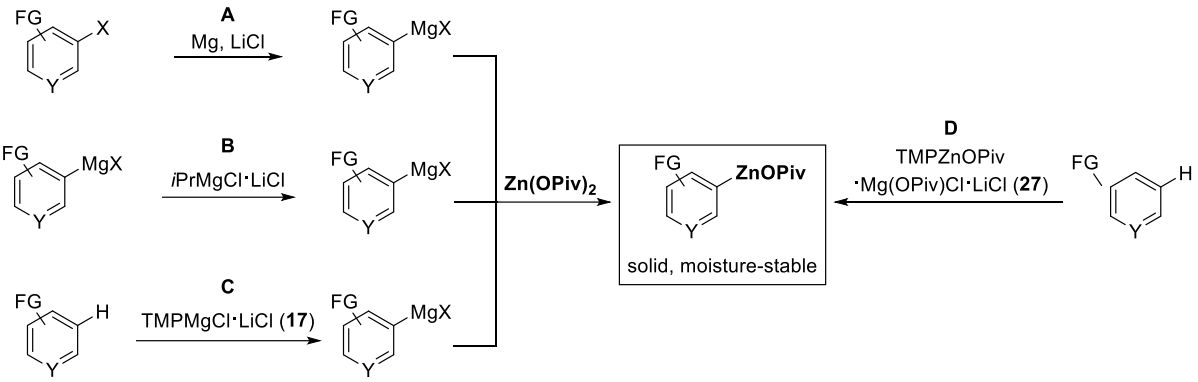
As mentioned in Chapter 2, organozinc compounds play an important role in organometallic chemistry. With their high compatibility with a broad variety of functional groups, they are valuable reagents for transition metal mediated C–C bond formations, namely allylations,[28] acylation[29] or the Negishi cross-coupling[30] reactions. To overcome the problem of instability towards air and moisture, Knochel and co-workers developed a new class of solid zinc organometallic compounds, which show enhanced air and moisture stability. After evaporation of the solvent, the obtained powders can readily be used on the benchtop and stored under argon for several weeks.[31] These so called zinc pivalates can be prepared by magnesium insertion or halogen–magnesium exchange followed by transmetalation with $Zn(OPiv)_2 \cdot 2LiCl$ (OPiv = pivalate) to give the corresponding aryl, heteroaryl, and benzylic zinc reagents described with the proposed formula $RZnOPiv \cdot Mg(OPiv)X \cdot 2LiCl$ (X = Cl, Br, I) (Scheme 7, A and B).[31a] A halogen–lithium exchange followed by transmetalation with $Zn(OPiv)_2$ proved to be a feasible way to prepare 2-pyridylzinc reagents.[27d] Another possible route is directed metalation using the sterically hindered base TMPMgCl·LiCl (**17**)[23,24] and subsequent addition of $Zn(OPiv)_2$, giving organozinc reagents described as $RZnOPiv \cdot Mg(OPiv)Cl \cdot LiCl$ (Scheme 7, C). The air-stability of such zinc organometallics was substantially superior to organozinc pivalates prepared by magnesium insertion or exchange.[31b] In the presence of sensitive functionalities such as an aldehyde or a nitro group, the milder zinc amide base TMPZnOPiv·Mg(OPiv)Cl·LiCl (**27**) [31c] may be used for highly selective metalation reactions to give the desired organozinc reagents, which undergoes a range of reactions with various electrophiles (Scheme 7, D).

[28] a) F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379; b) F. Dübner, P. Knochel, *Tetrahedron*, **2000**, *41*, 9233; c) H. Malda, A. W. van Zijl, L. A. Arnold, B. L. Feringa, *Org. Lett.* **2001**, *3*, 1169; d) C. A. Falciola, A. Alexakis, *Eur. J. Org. Chem.* **2008**, 3765; e) K. Geurts, S. P. Fletcher, A. W. van Zijl, A. J. Minnaard, B. L. Feringa, *Pure Appl. Chem.* **2008**, *5*, 1025; f) E. Erdik, M. Koçoğlu, *J. Organomet. Chem.* **2009**, *694*, 1890.

[29] a) E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1982**, *106*, 3368; b) P. Knochel, M. Yeh, S. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; c) P. Knochel, S. A. Rao, *J. Am. Chem. Soc.* **1990**, *112*, 6146.

[30] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) G. Wang, N. Yin, E. Negishi, *Chem. Eur. J.* **2011**, *17*, 4118; d) E. Negishi, X. Zeng, Z. Tan, M. Qian,Q. Hu, Z. Huang in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, A. de Meijere), 2nd ed., Wiley-VCH, Weinheim, **2004**; e) A. A. Zemtsov, N. S. Kondratyev, V. V. Levin, M. I. Struchkova, A D. Dilman *J. Org. Chem.* **2014**, *79*, 818.

[31] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205; b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed*. **2012**, *51*, 9428; c) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302; d) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754; e) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289. f) M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10662. g) T.J. Greshock, K. P. Moore, R. T. McClain, A. Bellomo, C. K. Chung, S. D. Dreher, P.S. Kutchikian, Z. Peng, I. W. Davies, P. Vachal, M. Ellwart, S. M. Manolikakes, P. Knochel, P. G. Natermet, *Angew. Chem. Int. Ed.* **2016**, *55*, 13714–13718 h) J. M. Hammann, F. H. Lutter, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 1082–1086. i) Y.-H. Chen, M. Ellwart, G. Toupalas, Y. Ebe, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 4612.



Scheme 7: Protocols for the preparation of (hetero-)aromatic organozinc pivalates developed by Knochel and co-workers.[31a-c,e]

Due to the presence of many different salts in these compounds, the resulting structure of these reagents is very complex. Mulvey and co-workers performed structural studies on the crystal as well as in solution. They came to the conclusion, that adding solid zinc pivalate to metalated species leads to a complete transmetalation to the corresponding organozinc halide and $Mg(OPiv)_2$. This salt then acts as an air and moisture scavenger and is likely to be responsible for the air and moisture stability of these reagents.[32]

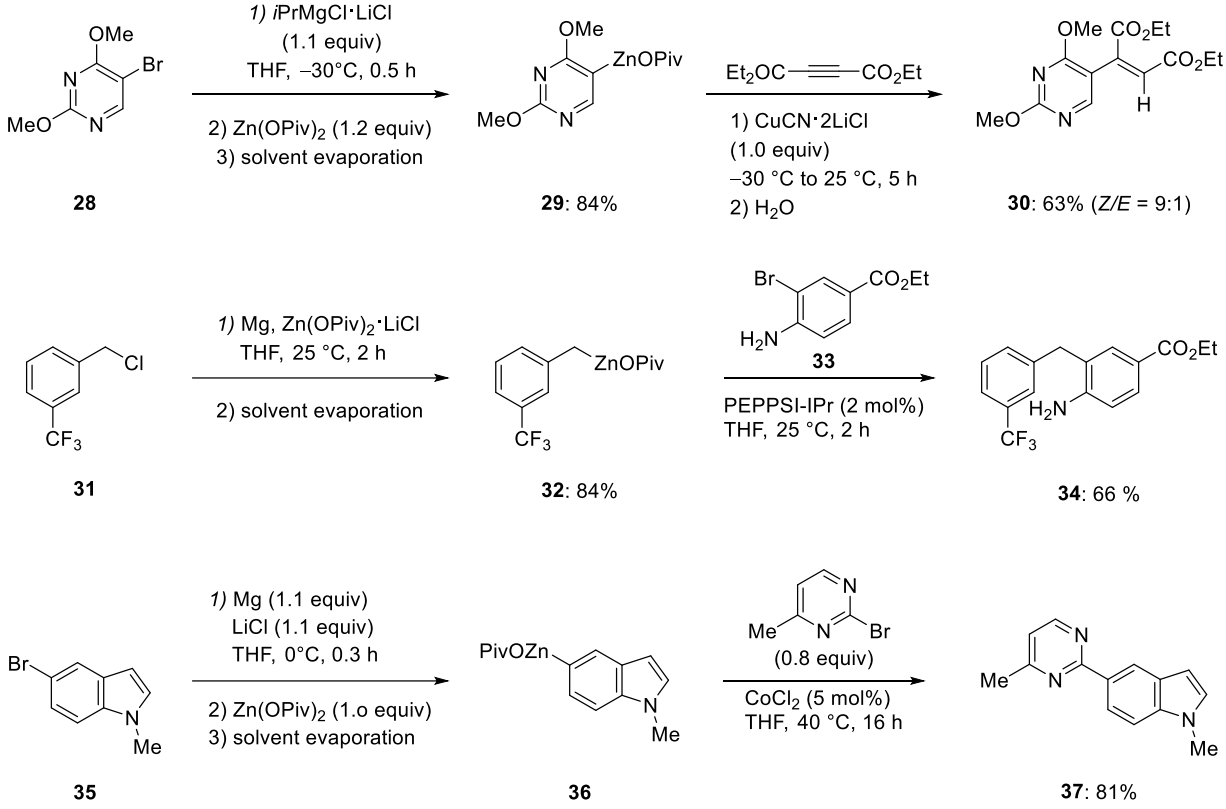
Therefore, a more accurate way to describe these trimetallic clusters would be the general formula: "$RZnX \cdot Mg(OPiv)_2 \cdot n$LiCl" (X = Br, I, Cl; n = 1–2). For the sake of clarity, the abbreviation RZnOPiv was used in this thesis.

3.2 Preparation of Organozinc Pivalates from (Hetero-)Aryl Halides

As mentioned in Chapter 3.1, starting from (hetero-)aromatic or benzylic halides the magnesium insertion reaction in the presence of LiCl at ambient temperature followed by addition of solid $Zn(OPiv)_2$ led to the corresponding organozinc pivalates. Exchange reactions were performed by using *i*PrMgCl·LiCl at low temperature and a subsequent transmetalation with $Zn(OPiv)_2$ gave the desired organozinc pivalates. In both cases, the solid organozinc pivalates were obtained after solvent evaporation in high vacuum (0.1 mbar, 3–6 h). Thus, the addition of *i*PrMgCl·LiCl to 5-bromo-2,4-dimethoxypyrimidine (**28**) and a subsequent transmetalation with solid $Zn(OPiv)_2$ led to the solid, air-stable zinc reagent **29**. This reagent underwent a carbocupration in the presence of CuCN·2LiCl with diethyl but-2-ynedioate (**30**), which was trapped with water furnishing the desired alkyne in 63% yield in which the Z-isomer was the major product (*Z*/*E* = 9:1).[31e] Starting from 1-(chloromethyl)-3-(trifluoromethyl)benzene (**31**) the insertion of magnesium in the presence of the THF-soluble salt $Zn(OPiv)_2 \cdot 2$LiCl led to the benzylic zinc reagent **32,** which after addition of 2 mol% PEPPSI-IPr and aryl bromide **33** produces the cross-coupling product **34** in 66% yield. Furthermore, Knochel and co-

[32] A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, *53*, 2706.

workers recently found out, that zinc pivalates also undergo cobalt-catalyzed cross-coupling reactions.[31g] Thus, the addition of $Zn(OPiv)_2$ to the freshly prepared Grignard reagent from the corresponding aryl bromide **35** lead to the solid zinc reagent **36** in quantitative yields. In a subsequent cobalt-catalyzed cross-coupling reaction the heteroaryl-heteroaryl compound **37** was obtained in 81 % yield (Scheme 8).

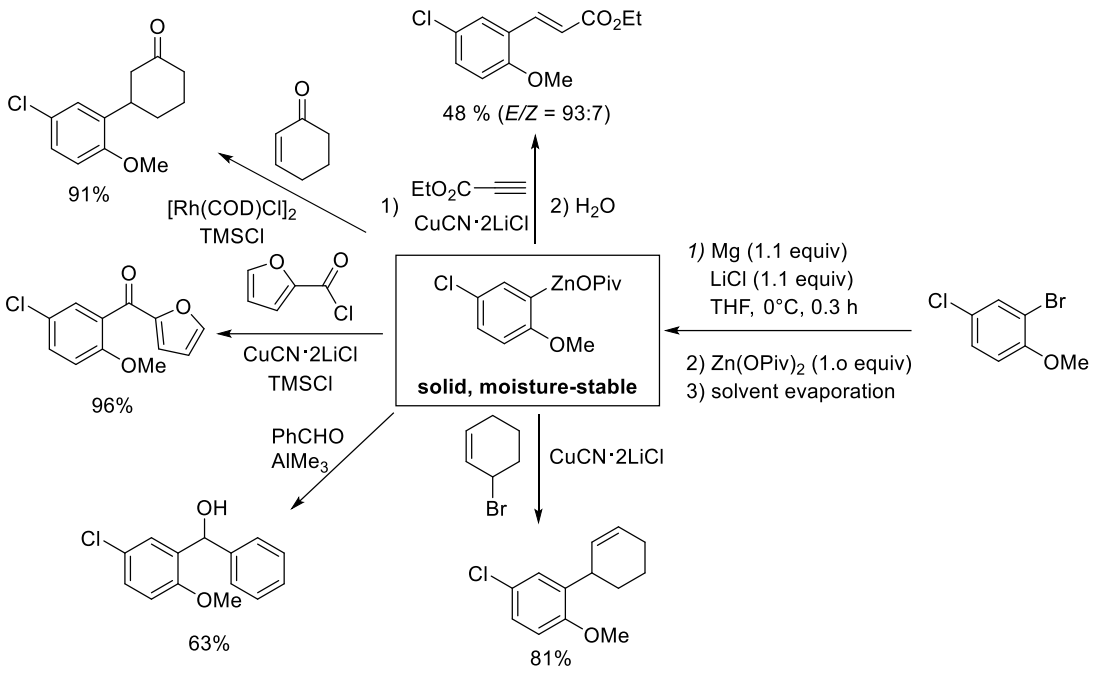


Scheme 8: Preparation of solid, salt stabilized organozinc reagents and their application in carbometalations, Negishi cross-coupling reactions and in cobalt-catalyzed heteroaryl-heteroaryl cross-coupling reactions.[31a,e,g]

After further investigation it was found, that zinc pivalates do not only show an excellent reactivity in Negishi cross-couplings. They also react in carbocuprations,[33] 1,4-additions[34] as well as acylation reactions, allylation and additions to aldehydes (Scheme **9**).[31e]

[33] a) A. Abramovitch, I. Marek, *Eur. J. Org. Chem.* **2008**, 4924; b) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128; c) B. Dutta, N. Gilboa, I. Marek, *J. Am. Chem. Soc.* **2010**, *132*, 5588; d) C. Dunst, A. Metzger, E. A. Zaburdaeva, P. Knochel, *Synthesis* **2011**, 3453; e) A. Frischmuth, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 10084; f) Y. Minko, M. Pasco, H. Chechik, I. Marek, *Beilstein J. Org. Chem.* **2013,** *9*, 526; g) W. Gati, F. Couty, T. Boubaker, M. M. Rammah, M. B. Rammah, G. Evano, *Org. Lett.* **2013**, *15*, 3122; For reviews on carbocupration reactions see also: h) J. F. Normant, A. Alexakis, *Synthesis* **1981**, 841; i) N. Krause in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**; j) N. Chinkov, D. Tene, I. Marek in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, A. de Meijere), 2nd ed. Wiley-VCH, Weinheim, **2004**.

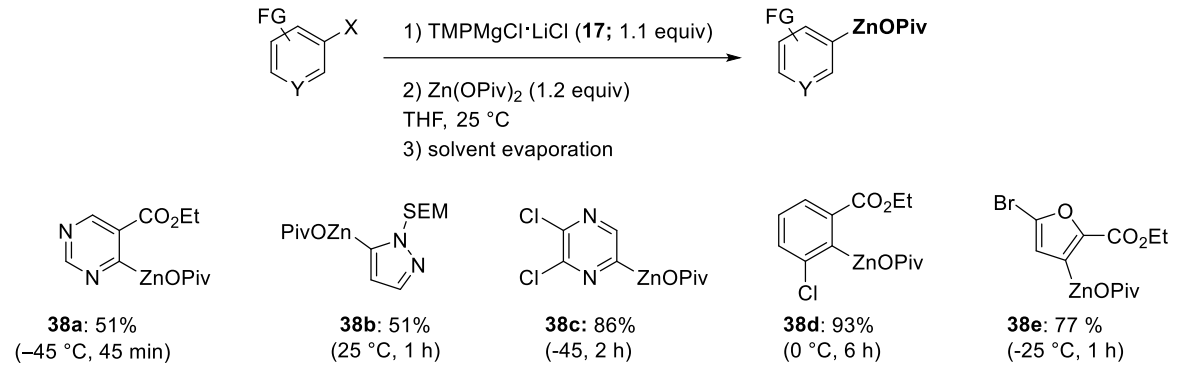
[34] Rh-catalysis: a) M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4229; b) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003,** *103*, 2829; c) T. Hayashi, *Russ. Chem. Bull. Int. Ed.* **2003**, *52*, 2595; d) J. Le Nôtre, D. van Mele, C. G. Frost, *Adv. Synth. Catal*. **2007**, *349*, 432; e) J. C. Allen, G. Kociok-Köhn, C. G. Frost, *Org. Biomol. Chem*. **2012**, *10*, 32; Cu-catalysis: f) E. Nakamura, S. Matsuzawa, Y. Horiguchi, I. Kuwajima,



Scheme 9: Selected examples for the extended applications of arylzinc pivalates.[31]

3.3 Preparation of Organozinc Pivalates by Metalation

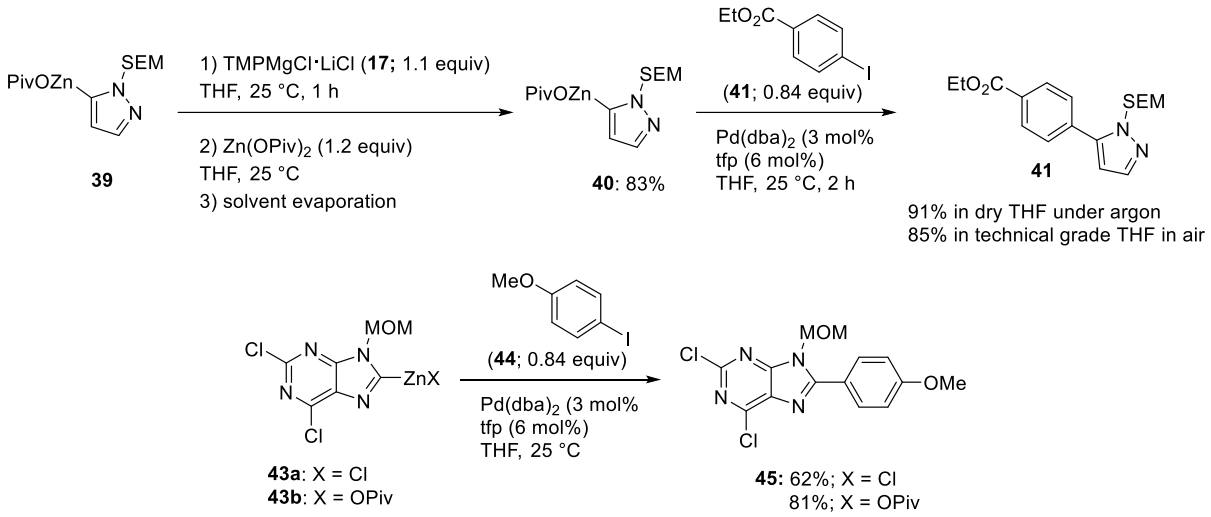
In addition, Knochel and co-workers developed a procedure for the direct metalation of aryl compounds using the sterically hindered base TMPMgCl·LiCl (**17**). The obtained magnesium compound was directly transmetalated with $Zn(OPiv)_2$ and after evaporation of the solvent the solid zinc pivalates of type **38** were obtained. This procedure opens the scope to various arenes and heteroarenes furnishing solid zinc reagents with a very high stability towards air and moisture. As a general trend, the activity of the new zinc compounds is higher than 94% after 2 h exposure and even after 4 h these reagents still show an activity greater than 85% (Scheme 10).[31b]



Scheme 10: Selected examples for the metalation of arenes and heterocycles using TMPMgCl·2LiCl (**17**) followed by addition of $Zn(OPiv)_2$ and evaporation of the solvent.

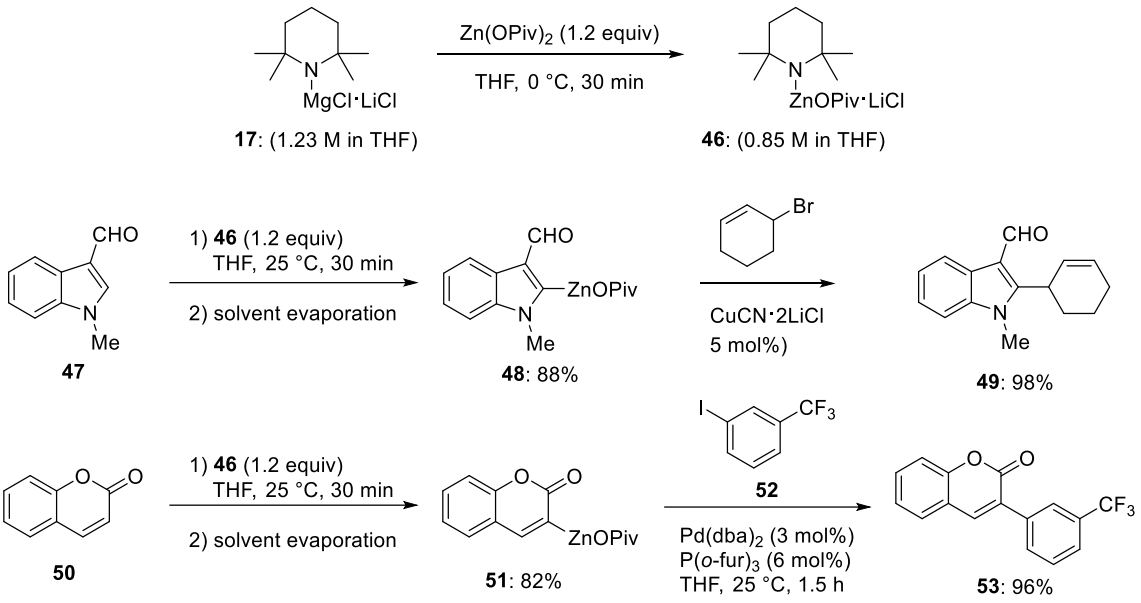
Tetrahedron Lett. **1986**, *34*, 4029; g) V. Wendisch, N. Sewald, *Tetrahedron Asymmetry*, **1997**, *8*, 1253; h) M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999; i) M. Tissot, A. Pérez Hernández, D. Müller, M. Mauduit, A. Alexakis, *Org. Lett.* **2011**, *13*, 1524.

Furthermore, these zinc pivalates can be stored over several months under nitrogen or argon in a sealed flask. They can always be redissolved in dry THF and undergo several reactions like acylations, allylations or cross-coupling reactions. Hence, the pyrazole derivative **39** was transformed into a zinc pivalate using the TMP-base **17** at –30 °C for 30 min followed by transmetalation with $Zn(OPiv)_2$. After titration with iodine an exact amount of this solid was dissolved in THF under argon and underwent a palladium-catalyzed Negishi cross-coupling reactions obtaining the desired heterocyclic compound **42** in 91% (Scheme 11). The same transformation was performed in technical grade THF and in air. Surprisingly, the yield only dropped by just 85%, which displays the moisture scavenger ability of the $Mg(OPiv)_2$. In addition, the performance of zinc pivalates compared to their corresponding zinc chlorides was investigated. The zinc chloride of 2,6-dichloro-9-(methoxymethyl)-9H-purine (**43a**) underwent a Negishi cross-coupling with 4-iodoanisol **(44**) furnishing the desired product **45** in 62% yield. The corresponding zinc pivalate **43b** lead to the same product with 81% over 12 h reaction time.



Scheme 11: Preparation of the zinc pivalate **40** and Negishi cross-coupling reaction in different qualities of THF and under argon or in air. Comparison of the reactivity of 2,6-dichloropurinylzinc pivalate **43b** and the corresponding zinc chloride **43a** in Negishi cross-coupling with 4-iodoanisole **44**.[31b]

However, the methods for the preparation of solid organozinc reagents described above are not applicable for sensitive functionalities such as aldehydes or related carbonyl groups. To overcome this limitation Knochel and co-workers envisioned the use of a milder zinc amide base namely, TMPZnOPiv·Mg(OPiv)Cl·2LiCl (**46**) which is synthesized by addition of $Zn(OPiv)_2$ to a solution of TMPMgCl·LiCl (**17**) in THF at 0 °C. A subsequent dilution with dry THF until a clear solution appeared led to a final concentration of 0.85–0.99 M. This amide base is compatible with functionalities like nitro groups, heteroaromatic rings or aldehydes (Scheme 12).[31c]



Scheme 12: Preparation and reactivity of TMPZnOPiv·Mg(OPiv)Cl·2LiCl (**46**) and selected examples for application and stability of the resulting organozinc pivalates.[31c]

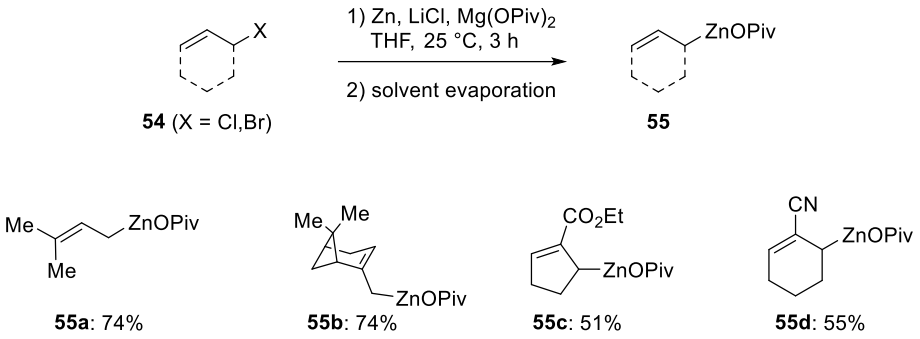
Thus, using TMPZnOPiv·Mg(OPiv)Cl·2LiCl (**46**; abbreviated as TMPZnOPiv) readily metalated 1-methyl-1H-indole-3-carbaldehyde (**47**) in 2-position. After evaporation of the solvent, the zinc pivalate **48** was obtained as a solid in 88%. After determination of the activity by titration with iodine, the solid was dissolved in THF and underwent a smooth copper-catalyzed allylation, furnishing the desired product **49** in 98% yield. In addition, the air and moisture stable cumarin zinc pivalate **51** underwent a palladium catalyzed Negishi cross-coupling, obtaining the desired product **53** in 96% yield.[31c]

3.4 Preparation of Organozinc Pivalates from Allyl Halides

Allylic zinc reagents are powerful and useful reagents in modern synthetic chemistry. They possess a high reactivity while having a tolerance to a broad scope of functional groups like esters and cyano functions.[35] In addition, these zinc compounds are easily synthesized through zinc insertion into the corresponding allyl halide of type **54**. Consequently, Knochel and co-workers developed a procedure to obtain solid allylic zinc reagents with an enhanced air and moisture stability.[31f] Using an insertion with Zn in the presence of LiCl and freshly prepared $Mg(OPiv)_2$ into several allylic halides of type **54** the corresponding zinc pivalates **55** were obtained in 51–91% yield. This reaction tolerates functional

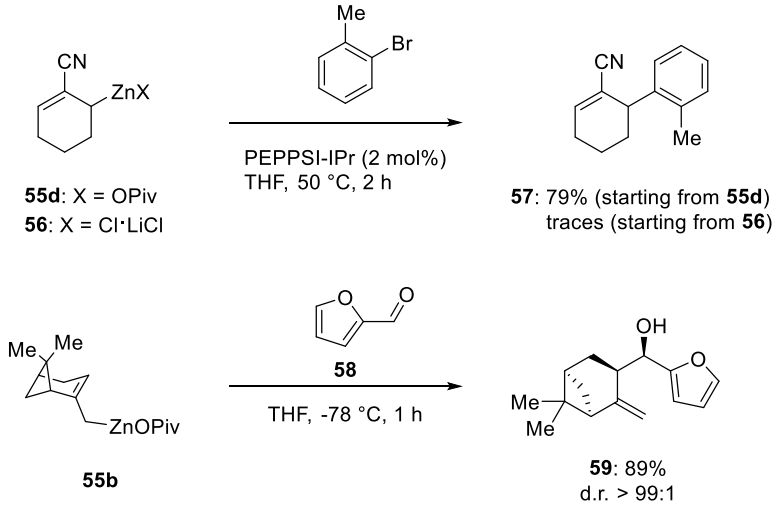
35 a) P. Knochel , R. Singer, *Chem. Rev.* **1993**, *93*, 2117; b) Y. Tamaru, A. Tanaka, K. Yasui, S. Goto, S. Tanaka, *Angew. Chem. Int. Ed.* **1995**, *34*, 787; c) M. Uchiyama, M. Koike, M. Kameda, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1996**, *118*, 8733; d) M. Nakamura, A. Hirai, M. Sogi, E. Nakamura, *J. Am. Chem. Soc.* **1998**, *120*, 5846; e) A. Côté, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 2771; f) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128; g) W. Shi , C. Liu, A. Lei, *Chem. Soc. Rev.* **2011**, *40*, 2761.

groups such as esters and nitriles. Even though these solids react easily with air and moisture, they can be stored under argon and –24 °C for several months with a half time up to two years (Scheme 13).



Scheme 13: Preparation of functionalized solid allylic zinc pivalates of type **55**.[31f]

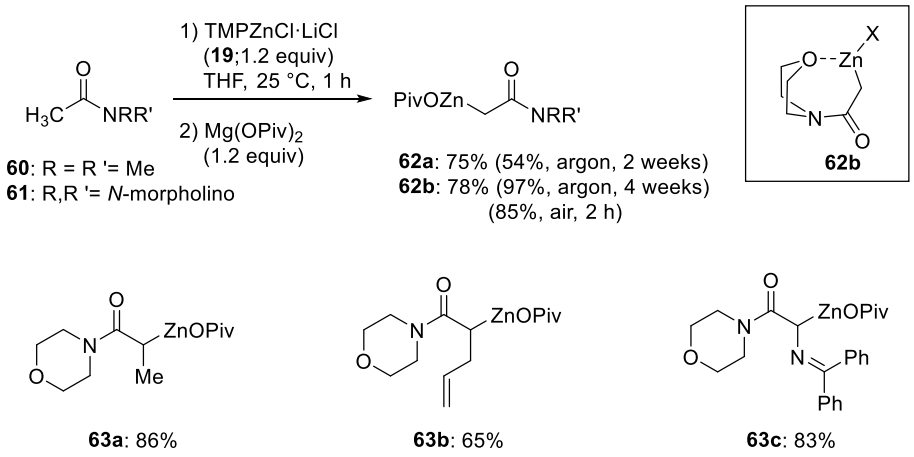
In addition, it was found that LiCl was able to activate the zinc powder, whereas the $Mg(OPiv)_2$ was found to be the key reagents for the long-term stability of the solid allylic reagents. As mentioned in chapter 3.3, zinc pivalates sometimes lead to higher yields than their corresponding zinc chlorides. Thus, Knochel and co-worker performed palladium catalyzed Negishi cross-coupling reactions with the cyclohex-1-ene-1-carbonitrile zinc reagents **55d** and **56**. This time, the zinc chloride **56** was not able to undergo any reaction (just traces were found), whereas the corresponding zinc pivalate **55a** leads to the desired allylated heterocycle **57** in 79% yield. Moreover, it was found that the allylic zinc reagents of type **55** undergo smooth reactions with electrophiles such as carbonyl derivatives or acid chlorides with very high regioselectivity (Scheme **14**).



Scheme 14: Selected applications of allylic zinc reagents of type **55.**

3.5 Preparation and Application of Pivaloxy Zinc Amide Enolates

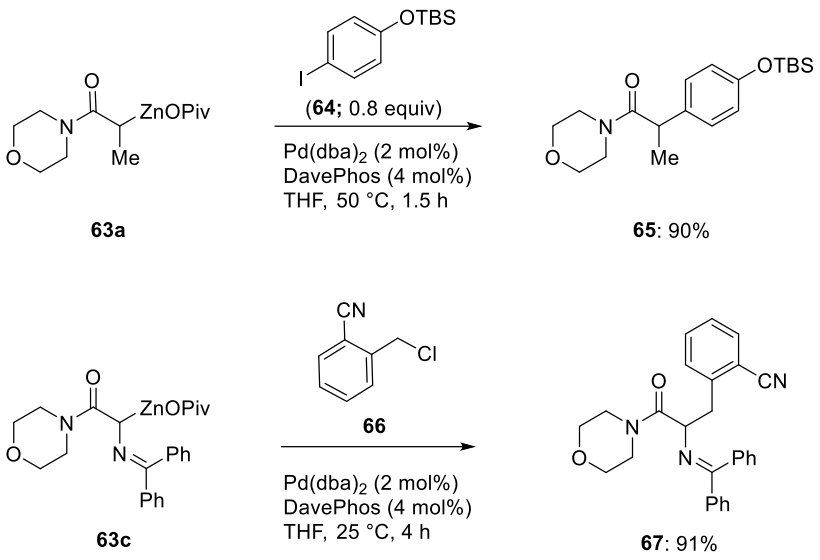
The arylation of enolates is an important transformation in organic chemistry. The so-called Reformatsky reagents are *in situ* generated ester zinc enolates.[36] They have proven their utility in organic synthesis including palladium-catalyzed arylations, even though their lack of air and moisture stability.[37] Like all other zinc pivalates, after evaporation of the solvent these compounds are obtained as powders with enhanced air and moisture stability. They are synthesized using the TMP-base **19** with a subsequent mixing with $Mg(OPiv)_2$.[31i] Amides proved to be the best precursor for such a solid Reformatsky reagent. The use of *N*-morpholino acetamide (**62b**) furnished a stable compound, which could be stored for 4 weeks without an significant loss of activity (Scheme **15**).



Scheme 15: Preparation of several solid pivaloxy zinc amide enolates of type **62**.[31i]

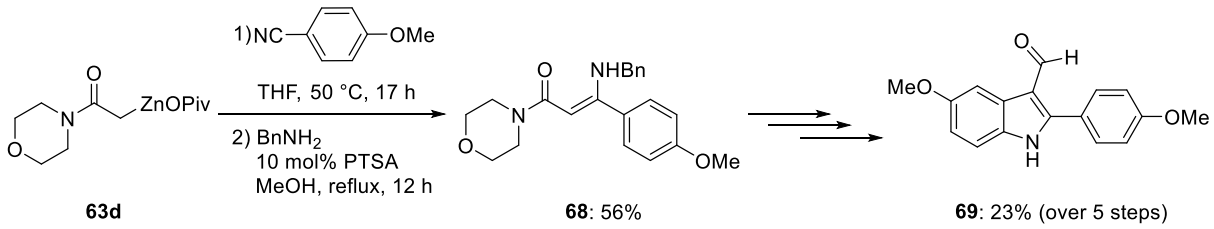
Thus, in the presence of $Pd(dba)_2$ (2 mol%) and DavePhos (4 mol%) the solid zinc reagent **63a** underwent a smooth Negishi cross-coupling reaction with the aryl iodide **64**, yielding the arylated enolate **65** in 90% yield. In addition, the zincated glycine derivate **63c** reacted in a palladium-catalyzed benzylation with the 2-(chloromethyl)benzonitrile (**66**) at 25 °C over 4 h, providing the desired benzylated amide **67** in 91% (Scheme 16).

[36] P. G. Cozzi, *Angew. Chem.* **2007**, *119*, 2620-2623; *Angew. Chem. Int. Ed.* **2007**, *46*, 2568.
[37] a) J. F. Fauvarque, A. Jutand, *J. Organomet. Chem.* **1977**, *132*, C17-C19; b) J. F. Fauvarque, A. Jutand, *J. Organomet. Chem.* **1979**, *177*, 273; c) F. Orsini, F. Pelizzoni, *Synth. Commun.* **1987**, *17*, 1389; d) F. Orsini, F. Pelizzoni, L. M. Vallarino, *J. Organomet. Chem.* **1989**, *367*, 375; e) M. L. Hlavinka, J. R. Hagadorn, *Tetrahedron Lett.* **2006**, *47*, 5049-5053; f) S. Duez, S. Bernhardt, J. Heppekausen, F. F. Fleming, P. Knochel, *Org. Lett.* **2011**, *13*, 1690.



Scheme 16: Arylation of solid zinc amide enolate **63a** with aryl iodide **64**. Palladium-catalyzed benzylation of the zincated glycine derivative **63cd**.[31i]

To demonstrate the applicability of the zinc reagents of type **63d**, a synthesis of the potent anti-breast-cancer agent (**69**) was performed. Starting from the readily metalated zinc reagent **63d,** the desired product was obtained over 5-steps, including a cross-coupling and a Nenitzescu reaction, in 23% overall yield (Scheme 17).



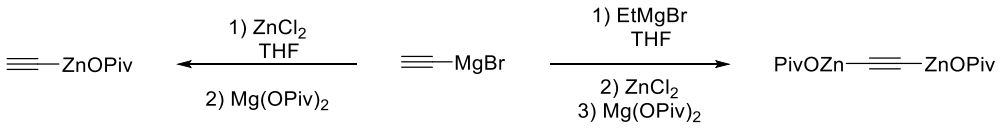
Scheme 17: Synthesis of the anti-breast-cancer drug candidate **69** starting from solid amide zinc enolate **63d**.[31i]

4 Objectives

Based on previous results regarding the allyl zinc pivalates we studied the preparation of the first solid alkynyl zinc compounds. Therefore, a novel protocol for the preparation of $Mg(OPiv)_2$ stabilized reagents from corresponding alkynes using TMPZnOPiv (TMP = 2,2,6,6-tetramethylpiperidyl) as base was investigated. To reduce the instability against air and moisture this base was prepared without the additional hydroscopic LiCl. Thus, it was envisioned that the lack of LiCl might lead to less sensitive alkynyl zinc pivalates (Scheme 18).

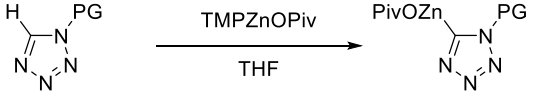
Scheme 18: Novel protocol for the preparation of alkynyl zinc pivalates.

Moreover, the development of unprotected mono-pivaloyloxyzinc acetylide might be a powerful extension to the scope of the zinc pivalates. Such air-stable reagents are highly desirable organometallic building blocks, since the corresponding lithium or halogenomagnesium acetylides, which are widely used reagents for ethynylation, are highly air and moisture sensitive. The use of these reagents in copper catalyzed [3+2]-cycloadditions under a high regioselectivity in 5-position was also of large interest. To the best of our knowledge, this regioselectivity in 5-position has not been observed in copper-catalyzed regioselective azide-alkyne cycloadditions (CuAAC) so far and has only been realized by Fokin using a ruthenium catalyst. Furthermore, the preparation and application of bis-pivaloyloxyzinc pivalate was investigated (Scheme 19).



Scheme 19: Preparation of solid mono- and bis-pivaloyloxyzinc acetylides using ethynyl magnesium bromide and $ZnCl_2$.

Another goal was, the preparation of solid (1*H*-tetrazol-5-yl)zinc pivalates. Thus, it was envisioned that the use of TMPZnOPiv might lead to the directed metalation in the 5-position of an *N*-protected 1*H*-tetrazole to obtain the desired pivalate (Scheme 20).



Scheme 20: Preparation of (1*H*-tetrazol-5-yl)zinc pivalates using TMPZnOPiv.

B. RESULTS AND DISCUSSION

1 A New Class of Solid Polyfunctional Alkynylzinc Pivalates with Enhanced Air and Moisture Stability for Organic Synthesis

1.1 Introduction

Polyfunctional alkynes are important target molecules in material and medicinal chemistry.[38] They are also key intermediates for the synthesis of other common functional groups such as *E*- and *Z*- alkenes.[39] Alkynyl organometallics are privileged reagents for the synthesis of various functionalized alkynes.[40] Recently, we have reported[41] a new class of zinc organometallics of the general formula RZnX·Mg(OPiv)$_2$·nLiCl (abbreviated as RZnOPiv).[32] The nature of R can be quite diverse: aryl[31a,b,h], heteroaryl,[31c,d] benzyl,[31g,42] alkynyl,[43] ethynyl,[44] allyl[31f] and C-enolates.[31i] Due to the presence of Mg(OPiv)$_2$ these new zinc reagents show an enhanced air and moisture stability.[32] These zinc organometallics were found to be valuable reagents for the performance of high-throughput screenings of biomolecules.[31gc] Related solid Reformatsky-enolates have been used for organic synthesis. Aryl- and heteroaryl-zinc pivalates proved to be unique bench-stable solid reagents for the performance of cobalt-catalyzed cross- couplings.[31hd]

[38] Recent reviews: a) B. M. Trost, C.-J. Li, in *Modern Alkyne Chemistry*, Wiley-VCH Weinheim, **2014**, 424 pp; b) A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 2794; c) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027.

[39] B. M. Trost, J. T. Masters, *Chem. Soc. Rev*. **2016**, *45*, 2212.

[40] a) S. M. Rummelt, G.-J. Cheng, P. Gupta, W. Thiel, A. Fürstner, *Angew. Chem. Int. Ed.* **2017**, *56*, 3599; b) B. M. Trost, J. T. Masters, F. L. Le Vaillant, J.-P. Lumb, *J. Org. Chem.* **2016**, *81*, 10023; c) S. Thapa, A. Kafle, S. K. Gurung, A. Montoya, P. Riedel, R. Giri, *Angew. Chem. Int. Ed.* **2015**, *54*, 8236; d) S. Tang, L. Zeng, Y. Liu, A. Lei, *Angew. Chem. Int. Ed.* **2015**, *54*, 15850; e) G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, *6667*, 8416; f) M. Sonoda, A. Inaba, K. Itahashi, Y. Tobe, *Org. Lett.* **2001**, *3*, 2419; g) T. Ooi, T. Miura, K. Takaya, H. Ichikawa, K. Maruoka, *Tetrahedron*, **2001**, *57*, 867; h) M. J. Dabdoub, V. B. Dabdoub, J. P. Marino, *Tetrahedron Lett.* **2000**, *41*, 437; i) D. Tzalis, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 1463; j) J. H. Babler, V. P. Liptak, N. Phan, *J. Org. Chem.* **1996**, *61*, 416.

[41] a) Y.-H. Chen, M. Ellwart, V. Malakhov, P. Knochel *Synthesis* **2017**, *49*, 3215; b) S. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel *Chem. Eur. J.* **2014**, *20*, 12289.

[42] Y.-H. Chen, S. Graßl, P. Knochel *Angew. Chem. Int. Ed.* **2018**, *57*, 1108.

[43] a) Y.-H. Chen, C. P. Tüllmann, M. Ellwart, P. Knochel *Angew. Chem. Int. Ed.* **2017**, *56*, 9236; b) J. M. Hammann, L. Thomas, Y.-H. Chen, D. Haas, P. Knochel *Org. Lett.* **2017**, *19*, 3847.

[44] C. P. Tüllmann, Y.-H. Chen, R.J. Schuster, P. Knochel *Org. Lett.* **2018**, *15*, 4601.

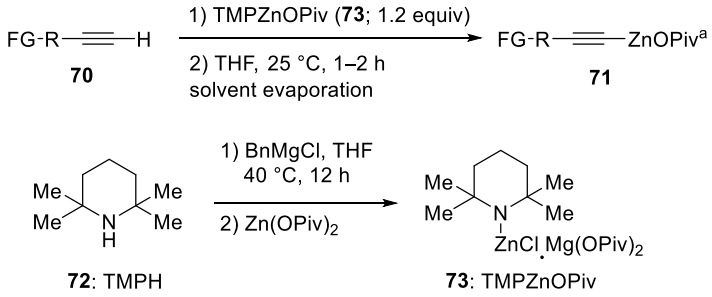
1.2 Preparation of Polyfunctional Alkynyl Zinc Pivalates

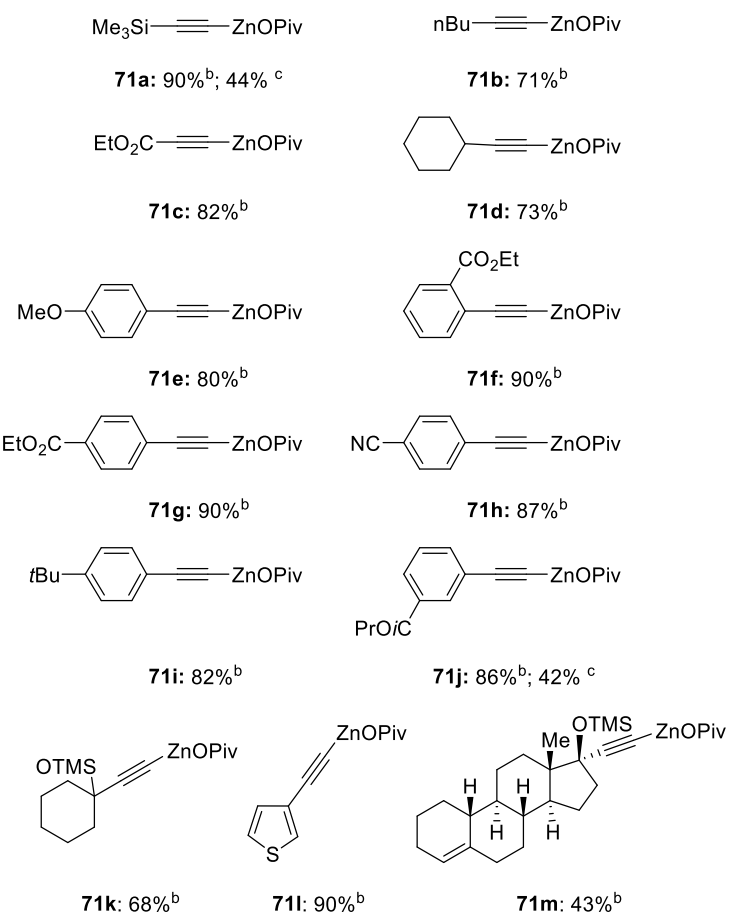
Thus, the preparation of a new class of alkynylzinc pivalates of type **71** bearing various functional groups and displaying an enhanced air and moisture stability was described. They are obtained in high yields from the corresponding alkynes of type **70** by deprotonation using the mixed zinc-magnesium base TMPZnCl·Mg(OPiv)2 (3; TMP = 2,2,6,6-tetramethylpiperidyl; abbreviated as TMPZnOPiv). Further, the utility of alkynylzinc reagents of type **71** for the formation of new carbon-carbon bonds including their participation in 1,3-dipolar-cycloadditions without the cleavage of the carbon-zinc bond was demonstrated. An application to the preparation of a carboxyamidotriazole with significant anti-cancer activity completed our study.

Preliminary studies have shown that the deprotonation of trimethylsilylacetylene (**70a**) with TMPZnOPiv·LiCl (**46**) proceeded smoothly but produced a solid alkynylzinc reagent (**71a**) with moderate air stability (44% activity after 4 h in air). We speculated that this problematic air and moisture sensitivity was due to the presence of LiCl and designed therefore a new synthesis of TMPZnOPiv (**73**) which did not contain LiCl.

Thus, the treatment of TMP-H (**72**) with benzylmagnesium chloride in THF[45] (40 °C, 12 h) followed by the addition of $Zn(OPiv)_2$ provided TMPZnOPiv (**73**) in quantitative yield. The deprotonation of **70a** with TMPZnOPiv (**73**, 1.2 equiv) afforded after solvent evaporation the corresponding alkynylzinc pivalate **71a** with highly improved air stability (90% yield, determined after 4 h exposure to air) as shown in Scheme 21. This behaviour proved to be general and a range of polyfunctional alkynylzinc pivalates **71a**–**m**) were obtained in 43-90% yield after 4 h of air exposure at 25 °C. Remarkably, a range of important functional groups such as a ketone, a nitrile or an ester are tolerated in the zinc reagents of type **71**.

[45] X. Zhang, T. J. Emge, K. C. Hultzsch, *Angew. Chem. Int. Ed.* **2012**, *51*, 394; *Angew. Chem.* **2012**, *124*, 406.



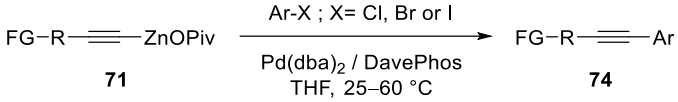


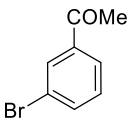
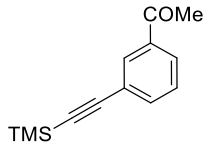
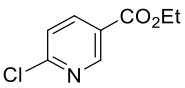
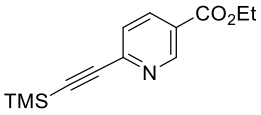
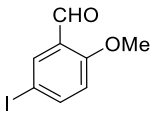
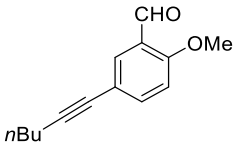
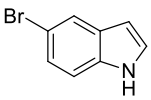
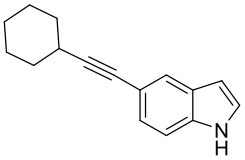
Scheme 21: Preparation of alkynylzinc pivalates of type **71** from the corresponding alkynes of type **70** using TMPZnCl·Mg(OPiv)2 (**73**; abbreviated as TMPZnOPiv). [a]Alkynylzinc chlorides and Mg(OPiv)2 complexes are abbreviated as alkynylzinc pivalates for clarity. [b]The indicated yields are obtained after 4 h of exposure to air. [c]Preparation with TMPZnOPiv in the presence of LiCl (1 equiv).

1.3 Application of Solid Alkynyl Zinc Pivalates in Negishi Cross-Coupling Reactions

Furthermore, we examined the reactivity of these new solid alkynylzinc pivalates of type **71** for the performance of Negishi cross-coupling reactions[46] with various aryl halides. The screening of several palladium catalytic systems showed that the Buchwald ligand, DavePhos[47], gave the best results in combination with $Pd(dba)_2$ (2 mol%; dba = dibenzylideneacetone). Under these conditions, a range of aryl or heteroaryl iodides, bromides or chlorides of type **75**–**77** underwent smooth Negishi cross-couplings producing arylated alkynes of type **74** (Table 1). Remarkably, a variety of sensitive functional groups were tolerated in these cross-couplings such as a ketone (entry 1), an aldehyde (entry 3), an unprotected indole (entry 4) or an amide (entry 7). The use of ethyl 6-chloronicotinate (**76**) provided alkyne **74b** in 74% yield (entry 2) which was a key intermediate for the synthesis of tazarotene.[48]

Table 1: Pd-catalyzed Negishi cross-coupling with solid alkynylzinc reagents of type **71** with various aryl halides leading to alkynes of type **74**.[a]

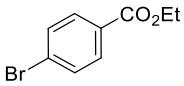
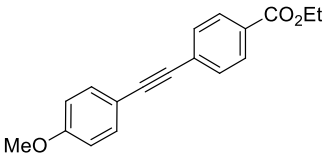
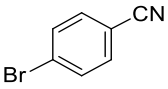
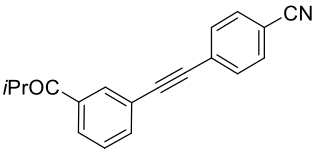
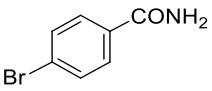
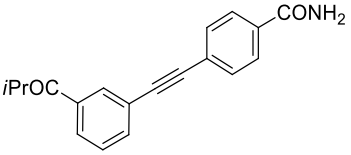
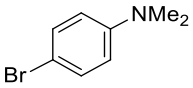
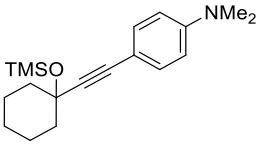
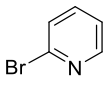
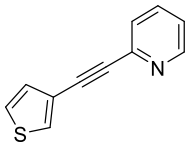


Entry	Alkynylzinc reagent	Electrophile	Product[a]
			
1	**71a**	**75a**	**74a**: 89% (25 °C, 6 h)
			
2	**71a**	**76**	**74b**: 74% (60 °C, 16 h)
			
3	**71b**	**77**	**74c**: 76% (40 °C, 12 h)
			
4	**71d**	**75b**	**74d**: 68% (50 °C, 2 d)

[46] a) E.-i. Negishi, G. Wang, H. Rao, Z. Xu, *J. Org. Chem.* **2010**, *75*, 3151; b) E.-i. Negishi, M. Qian, F. Zeng, L. Anastasia, D. Babinski, *Org. Lett.* **2003**, *5*, 1597; c) E.-i. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979; d) A. O. King, E.-i. Negishi, *J. Org. Chem.* **1978**, *43*, 358; e) A. O. King, N. O. Okukado, E.-i. Negishi, *J. Chem. Soc., Chem. Comm.* **1977**, 683-684.

[47] a) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27.

[48] S. Frigoli, C. Fuganti, L. Malpezzi, S. Serra, *Org. Process Res. Dev.* **2005**, *9*, 646.

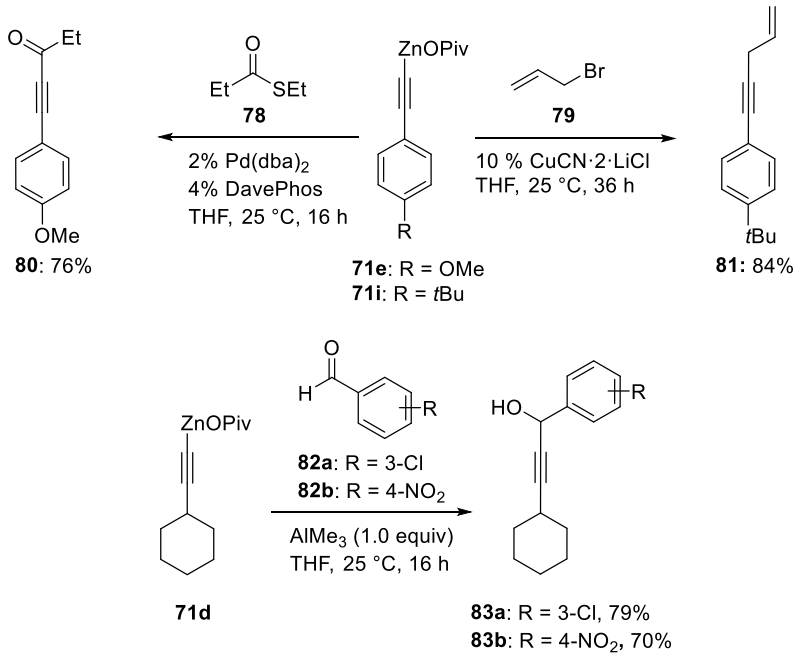
5	**71e**	 **75c**	 **74e**: 91% (40 °C, 14 h)
6	**71j**	 **75d**	 **74f**: 93% (40 °C, 16 h)
7	**71j**	 **75e**	 **74g:** 87% (50 °C, 2 d)
8	**71k**	 **75f**	 **74h**: 80% (40 °C, 12 h)
9	**71l**	 **75g**	 **74i**: 92% (40 °C, 12 h)

[a]Yield of analytically pure isolated product.

1.4 Acylation, Allylation and Aldehyde Addition of Solid Alkynyl Zinc Pivalates

We also found that the alkynylzinc pivalates **71** undergo a smooth Pd-catalyzed acylation using thioesters as acylation reagents, a reaction pioneered by Fukuyama.[49] The use of 4% DavePhos in combination with 2% $Pd(dba)_2$ proved to be an excellent catalytic system. Thus, the alkynylzinc pivalate **1e** reacted with the thioester **78** providing alkynyl ketone **80** in 76% yield (Scheme 22). Furthermore the alkynylzinc pivalate **71i** underwent a copper-catalyzed allylation with allyl bromide (**79**) using $CuCN{\cdot}2LiCl$[50] (10 mol%) as catalyst to afford the enyne **81** in 84% yield. Although such alkynylzinc reagents did not react readily with ketones, a smooth addition to aldehydes was promoted by $AlMe_3$ as reported by Woodward.[51] Thus, the alkynylzinc pivalate **71** added to benzaldehydes **82a–b** at 25 °C within 16 h leading to propargylic alcohols **83a-b** in 70-79% yield.

[49] H. Tokuyama, S. Yokoshima, T. Yamashita, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 3189.
[50] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[51] J. Shannon, D. Bernier, D. Rawson, S. Woodward, *Chem. Commun.* **2007**, 3945.



Scheme 22: Acylation, allylation and aldehyde addition using a solid alkynylzinc pivalates of type **71**.

1.5 Application of Solid Alkynylzinc Pivalates in Copper-catalyzed regioselective Azide-alkyne Cycloaddition

In 2002, Sharpless, Fokin and Meldal reported copper-catalyzed regioselective azide−alkyne cycloaddition (CuAAC) leading to 1,4-substituted triazoles.[52] This reaction is widely used in organic synthesis, drug discovery, biochemistry and polymer chemistry.[53]

Now, we have found that the robust zinc reagents of type **71** underwent copper-catalyzed 1,3-dipolar cycloadditions[54] with in situ generated benzyl azide **84** (from NaN_3 and benzyl bromide) or aryl azides **85a-b** with complete regioselectivity.[55] Smooth deuterolysis, allylation, amination[56] or arylation proved the integrity of the carbon-zinc bond in intermediate **8** and produced the valuable 1,2,3-triazoles **87a-d**

[52] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057.

[53] a) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905; b) S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J.* **2011**, *6*, 2696; c) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302; d) S. K. Mamidyala, M. G. Finn, *Chem. Soc. Rev.* **2010**, *39*, 1252; e) P. L. Golas, K. Matyjaszewski, *Chem. Soc. Rev.* **2010**, *39*, 1338; f) J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272; g) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952; h) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249.

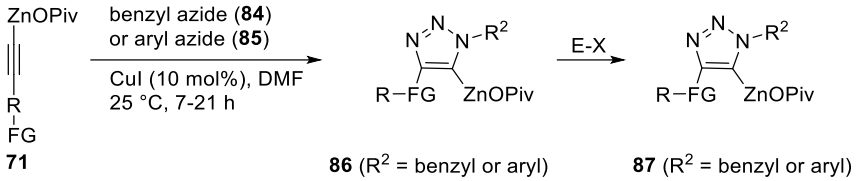
[54] R. Huisgen, Angew. *Chem. Int. Ed.* **1963**, *2*, 565.

[55] The regioselectivity was confirmed by ^{1}H-NMR, ^{13}C-NMR, NOESY, HSQC and HMBC.

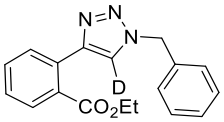
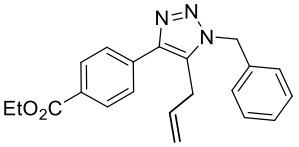
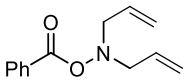
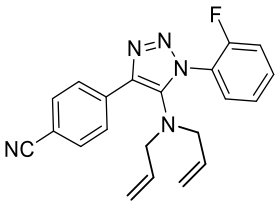
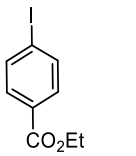
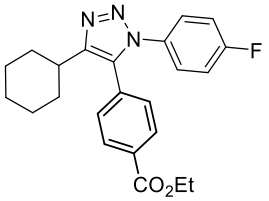
[56] a) A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680; b) A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2005**, *70*, 364; c) A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2006**, *71*, 219; d) M. Campbell, J. S. Johnson, *Org. Lett.* **2007**, *9*, 1521; e) S. L. McDonald, Q. Wang, *Chem. Commun.* **2014**, *50*, 2535.

in 69-91% yield (Table 2).[57] To the best of our knowledge, copper-catalyzed 1,3-dipolar cycloadditions with alkynylzinc derivatives have not been reported yet.[58]

Table 2: Copper-catalyzed dipolar cycloadditions with alkynylzinc pivalates of type **71** providing 1,2,3-triazoles of type **87** *via* zinc intermediates **86**.



86 (R^2 = benzyl or aryl) **87** (R^2 = benzyl or aryl)

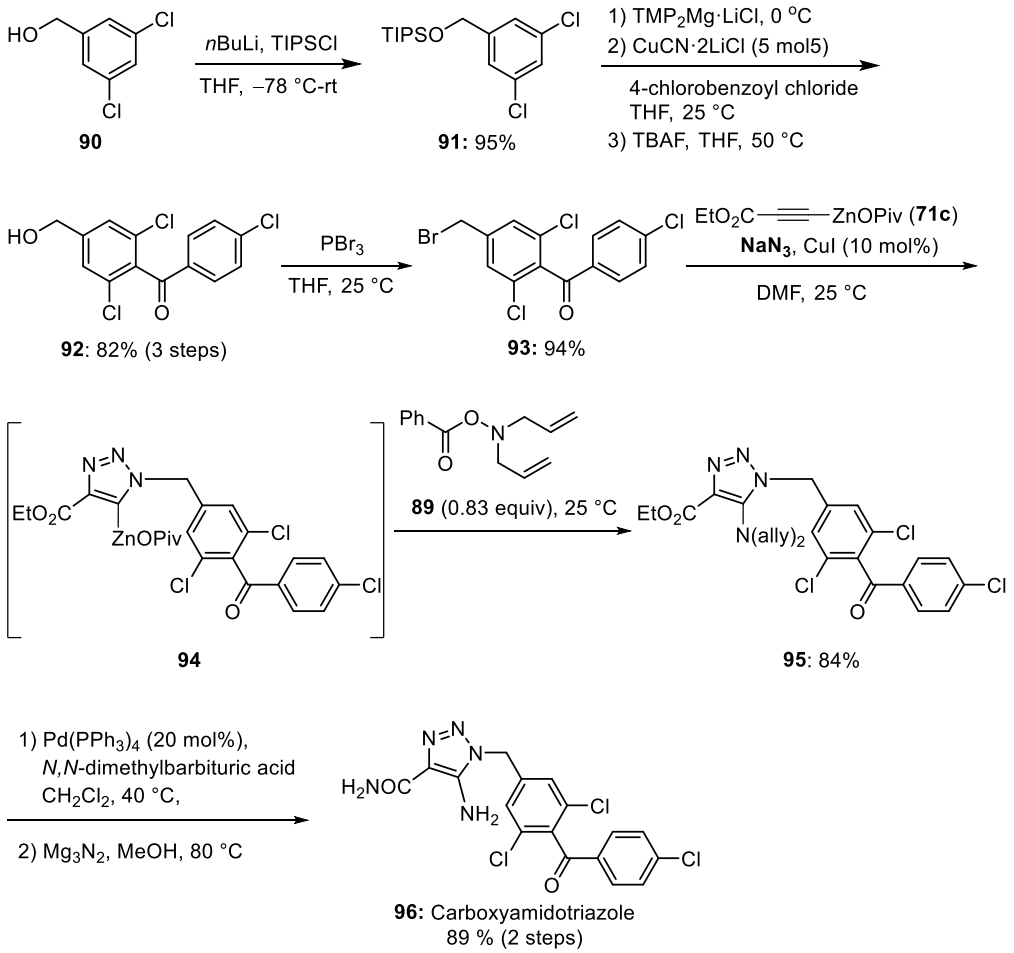
Entry	Alkynylzinc reagent	Electrophile	Product
		CH_3CO_2D	
1	**71f**	**88**	**87a**: 91%
			
2	**71g**	**79**	**87b**: 87%
			
3	**71h**	**89**	**87c**: 69%
			
4	**71d**	**41**	**87d**: 72%

[57] Copper-catalyzed synthesis of 5-metallotriazoles using metal acetylides [Sn, Cu, Bi, Al and Au]: a) F. Wei, T. Zhou, Y. Ma, C.-H. Tung, Z. Xu, *Org. Lett.* **2017**, *19*, 2098; b) W. Wang, X. Peng, F. Wei, C.-H. Tung, Z. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 649; c) W. Wang, F. Wei, Y. Ma, C.-H. Tung, Z. Xu, *Org. Lett.* **2016**, *18*, 4158; d) F. Wei, W. Wang, Y. Ma, C.-H. Tung, Z. Xu, *Chem. Commun.* **2016**, *52*, 14188; e) F. Wei, H. Li, C. Song, Y. Ma, L. Zhou, C.-H. Tung, Z. Xu, *Org. Lett.* **2015**, *17*, 2860; f) B. T. Worrell, S. P. Ellery, V. V. Fokin, *Angew. Chem. Int. Ed.* **2013**, *52*, 13037.

[58] Synthesis of 4-metallotriazole from metal acetylides (Mg, Zn) without copper catalyst: a) A. Krasiński, V. V. Fokin, K. B. Sharpless, *Org. Lett.* **2004**, *6*, 1237; b) A. Akao, T. Tsuritani, S. Kii, K. Sato, N. Nonoyama, T. Mase, N. Yasudab, *Synlett*, **2007**, 31; c) C. D. Smith, M. F. Greaney, *Org. Lett.* **2013**, *15*, 4826; d) Y. Li, X. Qi, Y. Lei, Y. Lan, *RSC Adv.* **2015**, *5*, 49802.

1.6 Synthesis of Carboxyamidotriazole using Alkynyl Zinc Pivalates

The synthetic utility of alkynylzinc pivalates is further demonstrated in the preparation of an orally-active agent carboxyamidotrazole (**96**) with potential antineoplastic activity (Scheme **23**).[59] Thus, the protection of commercially available benzylic alcohol **80** with TIPSCl produced the silyl ether **91** which was smoothly magnesiated at position 4 with $TMP_2Mg\cdot LiCl$[60] followed by copper-mediated acylation[50] with 4-chlorobenzoyl chloride. After desilylation using TBAF (tetra-*n*-butylammonium fluoride), the benzylic alcohol **92** was isolated in 82% yield. The resulting alcohol was brominated with PBr_3 at 25 °C affording benzylic bromide **93** in 94% yield.



Scheme 23: Synthesis of carboxyamidotriazole **96** using the alkynyl zinc pivalate **71c**.

This benzylic bromide **93** was treated with NaN_3 and the ester-substituted alkynylzinc pivalate **71c** in the presence of 10% CuI in DMF at 25 °C for 18 h affording the 1,2,3-triazolylzinc pivalate **94** which was directly aminated with benzoyloxy-diallylamine **89**[56] furnishing the trisubstituted 1,2,3-triazole **95**

[59] a) R. Ju, L. Guo, J. Li, L. Zhu, X. Yu, C. Chen, W. Chen, C. Ye, D. Zhang , *Cancer Lett.* **2016**, *370*, 232; b) M. J. Soltis, H. J. Yeh, K. A. Cole, N. Whittaker, R. P. Wersto, E. C. Kohn, *Drug Metab. Dispos.* **1996**, *24*, 799.
[60] A. Unsinn, C. J. Rohbogner, P. Knochel, *Adv. Synth. Cat.* **2013**, *355*, 1553.

in 84% yield via a 4-component one-pot synthesis.[61] After a Pd-catalyzed deallylation[62] and an amidation using Mg_3N_2 as reported by Ley,[28] the desired carboxyamidotriazole (**96**) was obtained in 89% yield (8 steps, 55% overall yield).

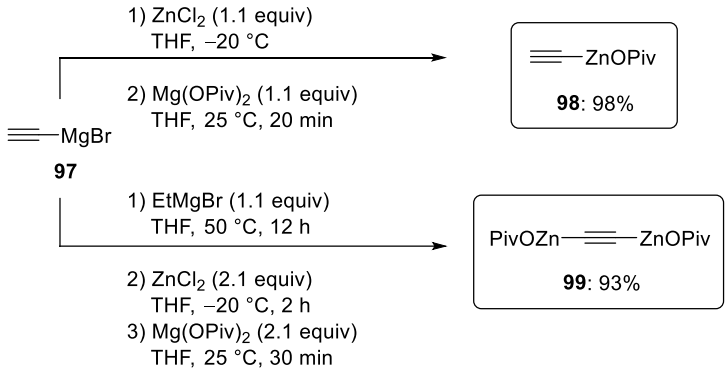
2 Preparation and Reactions of Mono- and Bis-Pivaloyloxyzinc Acetylides

2.1 Introduction

Organozinc reagents are important reagents in organic synthesis, since they tolerate a variety of functional groups and react with various electrophiles in the presence of an appropriate transition metal catalyst.[63] For instance, alkynylzinc pivalates[43a] tolerate a broad range of functionalities and represent a reactive class of versatile c_{sp}-centered nucleophiles that are stable for several hours when exposed to air.

2.2 Preparation and Activity of Mono-pivaloyloxyzinc Acetylide (98) and Bis-pivaloyloxyzinc Acetylide (99).

We reported the preparation and reactivity of two new alkynylzinc pivalates, namely mono-pivaloyloxyzinc acetylide (**98**) and bis-pivaloyloxyzinc acetylide (**99**) as storable solids with appreciable air and moisture stability (Scheme 24).[44]



Scheme 24: Preparation of mono-pivaloyloxyzinc acetylide (**98**) and bis-pivaloyloxyzinc acetylide (**99**).

[61] a) C. Zhou, J. Zhang, P. Liu, J. Xie, B. Dai, *RSC Adv.* **2015**, *5*, 6661; b) Y. Jiang, D. Kong, J. Zhao, W. Zhang, W. Xu, W. Li, G. Xu, *Tetrahedron Lett.* **2014**, *55*, 2410; c) T. Cook, J. A. Walker Jr, J. Mack, *Green. Chem.* **2013**, *15*, 617; d) S. Mohammeda, A. K. Padalaa, B. A. Darb, B. Singhb, B. Sreedharc, R. A. Vishwakarma, *Tetrahedron*, **2012**, *68*, 8156.

[62] F. Garro-Helion, A. Merzouk, F. Guibé, *J. Org. Chem.* **1993**, *58*, 6109.

[63] (a) Handbook of Functionalized Organometallics: Applications in Synthesis; P. Knochel 2nd Ed.; Wiley: Weinheim, 2005; (b) Organometallics in Synthesis: Third Manual; M. Schlosser, Ed.; Wiley: Weinheim, 2013.

Such air-stable reagents are highly desirable organometallic building blocks, since the corresponding lithium or halogenomagnesium acetylides, which are widely used reagents for ethynylation,[64] are highly air and moisture sensitive. Additionally, lithium acetylide is prone to undergo disproportionation to dilithium acetylide and acetylene in the absence of stabilizing agents above -25 °C.[65] The zinc reagents **98** and **99** were conveniently prepared in almost quantitative yields from commercially available ethynylmagnesium bromide (**97**; see Scheme 24). Thus, the treatment of a solution of **97** with $ZnCl_2$ in THF at -20 °C for 2 h, followed by the addition of a freshly prepared solution of $Mg(OPiv)_2$[32] at 25 °C for 20 min, produced after evaporation of the solvent, a white-yellowish powder of mono-pivaloyloxyzinc acetylide (**98**) in 98% yield. Notably, the direct addition of $Zn(OPiv)_2$ to **97** afforded a mixture of **98** and **99** in the ratio of 4:1. Bis-pivaloyloxyzinc acetylide (**99**) was prepared selectively by treating ethynylmagnesium bromide (**97**) with EtMgBr (1.1 equiv) at 50 °C for 12 h, followed by the addition of $ZnCl_2$ (2.1 equiv) at -20 °C for 2 h and $Mg(OPiv)_2$ (2.1 equiv) at 25 °C for 0.5 h. After solvent evaporation, **99** was obtained as a white powder in quantitative yield as indicated by a titration with iodine.[66] A scale-up to 50 mmol was readily performed with the same yield. The resulting powders can be handled for a short time on the benchtop and have a half-life time in air of about 5 h at 25 °C (Table 3).

Table 3: Activity of mono-pivaloyloxyzinc acetylide (**98**) and bis-pivaloyloxyzinc acetylide (**99**) after exposure to air at 25 °C.

Zinc species	0 h	1 h	2 h	4 h
≡—ZnOPiv **98**	100%[a]	88%[a]	75%[a]	65%[a]
PivOZn—≡—ZnOPiv **99**	100%[a]	85%[a]	73%[a]	65%[a]

[a]Activity determined by titration with iodine.[66]

[64] a) M. M. Midland, F. Gallou, F. 2006; *Lithium Acetylide*; e-EROS Encyclopedia of Reagents for Organic Synthesis; b) A. V. Rama Rao 2001; *Dilithium Acetylide*; e-EROS Encyclopedia of Reagents for Organic Synthesis; c) M. M. Midland 2001; *Ethynylmagnesium Bromide*; e-EROS Encyclopedia of Reagents for Organic Synthesis; d) R. Schmid, P. L. Huesmann, W. S. J. Johnson *J. Am. Chem. Soc.* **1980**, *102*, 5123; e) G. Stork, J. M. Stryker *Tetrahedron Lett.* **1983**, *24*, 4887; f) K. M. Brummond, M. M. Davis, C. Huang *J. Org. Chem.* **2009**, *74*, 8314; g) H. Zhou, Q. Zhou, Q. Zhou, L. Ni, Q. Chen *RSC Adv.* **2015**, *5*, 12161; h) L. C. Burrow, L. T. Jesikiewicz, G. Lu, S. J. Geib, P. Liu, K. M. Brummond *J. Am. Chem. Soc.* **2017**, *139*, 15022.

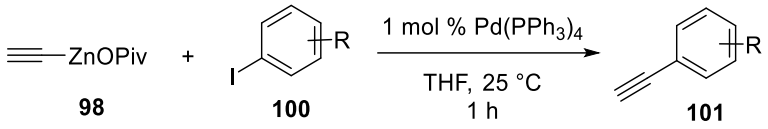
[65] a) O. F. Beumel, R. F. Harris, *J. Org. Chem.* **1963**, *28*, 2775; b) J. Mortier, M. Vaultier, F. Carreaux, J.-M. Douin *J. Org. Chem.* **1998**, *63*, 3515.

[66] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.

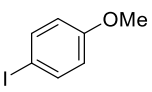
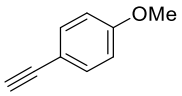
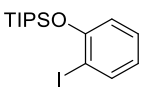
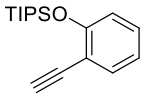
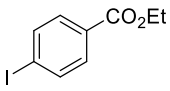
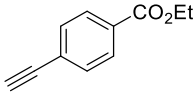
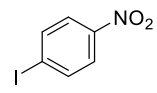
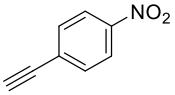
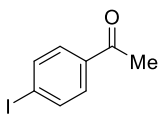
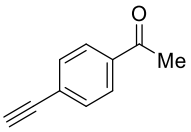
2.3 Application of Solid Mono-pivaloyloxyzinc Acetylide (98) in Negishi Cross-Coupling Reactions

Mono-pivaloyloxyzinc acetylide (**98**) underwent Negishi cross-couplings[46] with aryl iodides of type **100** leading to aryl- and heteroaryl-alkynes of type **101** (see Table 4). These reactions proceeded at 25 °C within 1 h in the presence of 1% $Pd(PPh_3)_4$ producing the desired ethynylated arenes. Electron-rich aryl iodides (entries 1 and 2), electron-poor aryl iodides (entries 3-5) as well as 3-iodothiophene (**100f**, entry 6) gave the desired cross-coupling products **101a-f** in 76-98% yields.[67] Thus, reagent **98** directly provided a range of terminal alkynes without the need of using a silyl protecting group as usually done to introduce an ethynyl moiety.[68]

Table 4: Negishi cross-coupling reactions between mono-pivaloyloxyzinc acetylide (**98**) and various aryl iodides of type **100**.

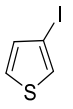
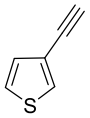


98 **100** **101**

Entry	Electrophile	Product
		
1	**100a**	**101a**: 98%
		
2	**100b**	**101b**: 86%
		
3	**100c**	**101c**: 81%
		
4	**100d**	**101d**: 76%
		
5	**100e**	**101e**: 95%

[67] Aryl chlorides were found unreactive; aryl bromides gave mixtures of aryl alkynes and bis-arylated alkynes under various conditions.

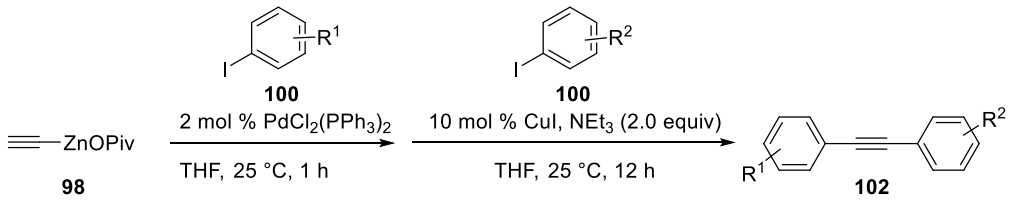
[68] a) R. Severin, J. Reimer, S. Doye *J. Org. Chem.* **2010**, *75*, 3518; b) T. Kim, K. H. Jeong, Y. Kim, T. Noh, J. Choi, J.; J. Ham *Eur. J. Org. Chem.* **2017**, 17, 2425; c) S. Qiu, C. Zhang, R. Qiu, G. Yin, J. Huang *Adv. Synth. Catal.* **2018**, *360*, 313.

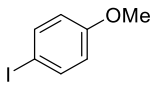
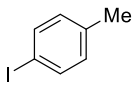
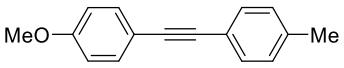
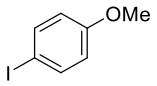
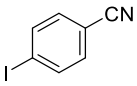
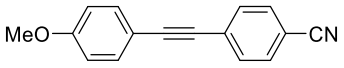
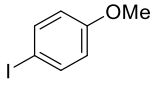
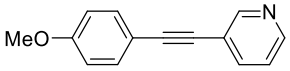
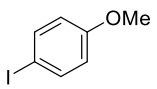
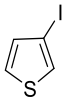
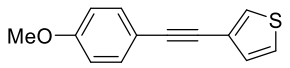
6			**101f**: 80%

2.4 One-pot Synthesis of Non-symmetrical bis-arylated Acetylenes (102) using Mono-pivaloyloxyzinc Acetylide (98)

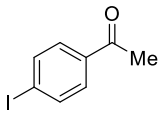
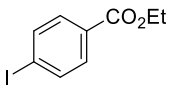
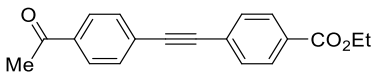
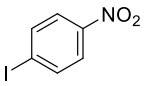
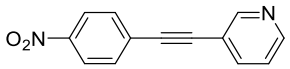
Furthermore, non-symmetrical bis-arylated alkynes of type **102** were prepared in a one-pot reaction using, at first, the previously developed Negishi cross-coupling performed in the presence of 2% $PdCl_2(PPh_3)_2$, followed by a Sonogashira cross-coupling[69] using 10 mol% CuI and Et_3N (2.0 equiv) at 25 °C for 12 h (see Table 5). The successive cross-coupling of **98** with **100**, followed by a Sonogashira coupling with the (hetero)aryl iodides **100c** and **100f–i** resulted in the corresponding non-symmetrical bis-arylated alkynes of type **102** in 74-90% yields (entries 1-4). Remarkably, this reaction tolerates sensitive functional groups such as ketones, esters and nitro-arenes (entries 5 and 6) resulting in the desired alkynes **100e–f** in 65–75% yields.

Table 5: One-pot synthesis of non-symmetrical bis-arylated acetylenes of type **102**.



Entry	(Hetero)aryliodides (**100**)		Product
			
1	**100a**	**100g**	**102a**: 88%
			
2	**100a**	**100h**	**102b**: 90%
			
3	**100a**	**100i**	**102c**: 81%
			

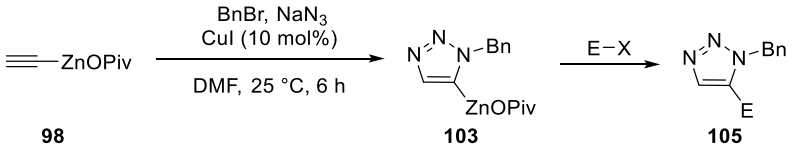
[69] a) K. Sonogashira, Y. Tohda, N. Hagihara *Tetrahedron Lett.* **1975**, *16*, 4467; b) R. Chinchilla, C. Nájera *Chem. Rev.* **2007**, *107*, 874–922; c) R. Chinchilla, C. Nájera *Chem. Rev.* **2011**, *40*, 5084.

4	**100a** 	**100f** 	**102d**: 74% 
5	**100e** 	**100c** 	**102e**: 65% 
6	**100d**	**100i**	**102f**: 75%

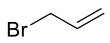
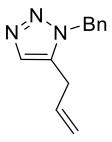
2.5 Synthesis of 1,5-disubstituted Triazoles 105 using Mono-pivaloyloxyzinc Acetylide (98)

As shown in chapter 2.4, we reported that alkynylzinc pivalates readily undergo 1,3-dipolar cycloadditions with retention of the carbon-zinc bond.[43a] Thus, we have performed copper-catalyzed regioselective azide-alkyne cycloadditions (CuAAC)[70] with mono-pivaloyloxyzinc acetylide (**98**) with in situ generated benzyl azides (Table 6). Only one regioisomeric cyclo-addition product **105** was formed under the usual copper-catalyzed conditions (10% CuI in DMF at 25 °C for 6 h).[71] To the best of our knowledge, this regioselectivity has not been observed in CuAACs so far and has only been realized by Fokin using a ruthenium catalyst.[72] The heterocyclic zinc pivalate **103** was trapped with several electrophiles. Thus, zinc reagent **103** underwent a smooth allylation when it was treated with allyl bromide (**79**) leading to the corresponding 1,5-disubstitued 1,2,3-triazole **105a** in 49% yield (entry 1). Furthermore, a subsequent Negishi cross-coupling was performed with 2 mol% $PdCl_2(PPh_3)_2$ at 50 °C for 12 h leading to the arylated triazole **105b** in 82% yield (entry 2).[43a] Notably, the addition of hydroxylamine benzoates **104** and **89** gave the aminated 1,2,3-triazoles **105c**–**d** in 51%-74% yields (entries 3–4).

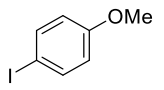
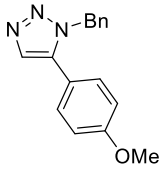
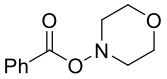
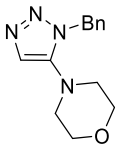
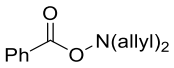
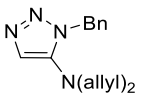
Table 6: Synthesis of 1,5-disubstituted triazoles (**105**).



98 **103** **105**

Entry	Electrophile	Product[a]
1	**79** 	**105a**: 49%[b] 

[70] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; b) C. W. Tornøe, C. Christensen, M. Meldal *J. Org. Chem*. **2002**, *67*, 3057.
[71] The regioselectivity was confirmed by ^{1}H-NMR, ^{13}C-NMR, NOESY, HSQC and HMBC.
[72] a) J.E. Hein, V. V. Fokin *Chem. Soc. Rev.* **2010**, *39*, 1302; b) Y. Li, X. Qi, Y. Lan *RSC Adv.* **2015**, *5*, 49802.

		
2	**100a**	**105b**: 82%[c]
		
3	**104**	**105c**: 74%[d]
		
4	**89**	**105d**: 51%[d]

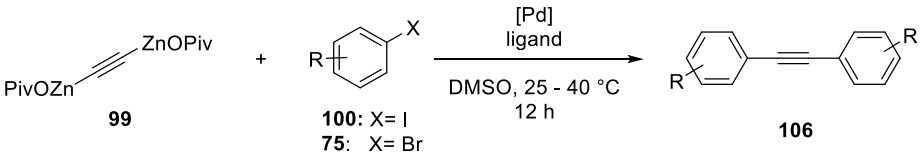
[a]Isolated yield, [b]Reaction was treated with allylbromide (**79**) (2.5 equiv), [c]Reaction was performed with 2 mol% of $PdCl_2(PPh_3)_2$ at 50 °C for 12 h, [d]Reaction was treated with hydroxylamines benzoates **104** and **89** (1.2 equiv).

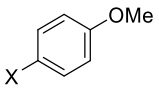
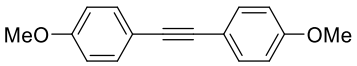
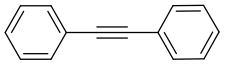
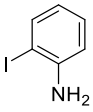
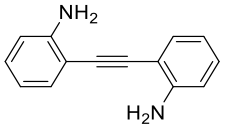
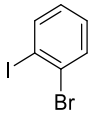
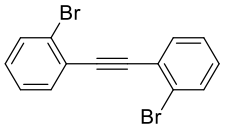
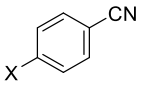
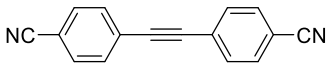
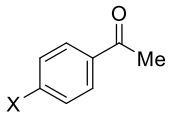
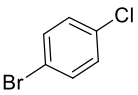
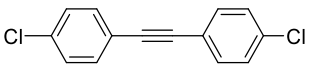
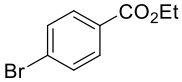
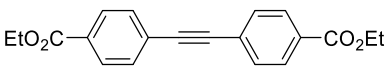
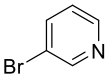
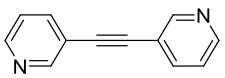
2.6 Application of Solid Bis-pivaloyloxyzinc Acetylide (99) in Negishi Cross-Coupling Reactions

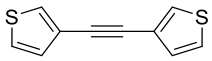
Next, we have examined the Negishi cross-coupling of bis-pivaloyloxyzinc acetylide (**99**) with aryl and heteroaryl iodides or bromides. Due to the low solubility of **99** in THF, DMSO was the preferred solvent for these reactions. All cross-coupling reactions were completed within 3 h at 25 °C using 3 mol% $Pd(dba)_2$ (dba = dibenzylideneacetone) and 6 mol% SPhos[73] providing the desired bis-arylated alkynes **106a-f** in 74-98% yields (Table 7). Both electron-rich aryl iodides (entries 1-3) and electron-poor aryl iodides (entries 4-6) smoothly underwent these cross-couplings. Encouraged by these results, we further tested the scope of this cross-coupling with various aryl bromides affording the desired bis-arylated products of type **106** in 75-94% yield (entries 1 and 5-10) using 5 mol% $Pd(dba)_2$ and 5 mol% XantPhos[74] as ligand at 40 °C.[75] Notably, the reaction was compatible with sensitive functional groups such as primary amines, nitriles, ketones and esters.

[73] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald *J. Am. Chem. Soc.* **2005**, *127*, 4685.
[74] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leuuwen, K. Goubitz, J. Fraanje O*rganometallics* **1995**, *14*, 3081.
[75] Aryl chlorides were found unreactive under various conditions.

Table 7: Negishi cross-couplings reactions between zinc pivalate **99** and various aryl halides.



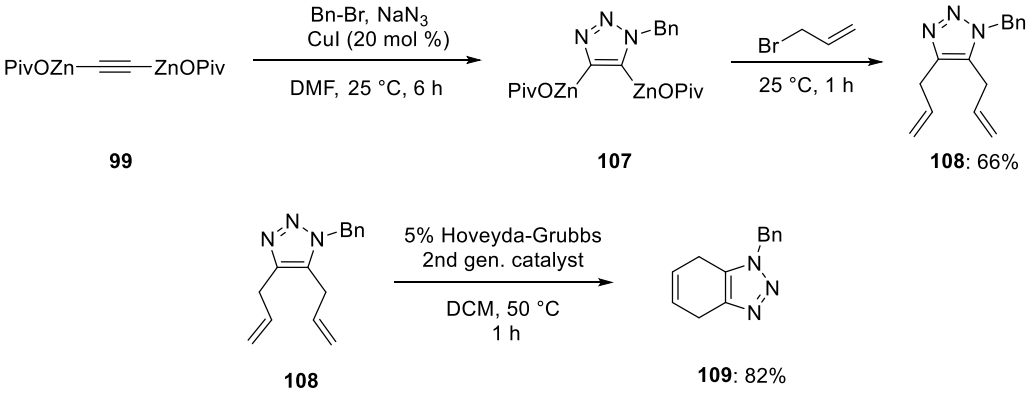
Entry	Electrophile	Product[b]
1	 **100a:** X=I **75h**: X=Br	 **106a:** X=I: 98%b X=Br: 82%c
2	 **100j**	 **106b**: 93%b
3	 **100k**	 **106c**: 93%b
4	 **100l**	 **106d**: 74%b
5	 **100h:** X=I **75d**: X=Br	 **106e:** X=I: 88%b X=Br: 84%c
6	 **100e:** X=I **75i**: X=Br	 **106f:** X=I: 95%b X=Br: 75%c
7	 **75j**	 **106g**: 88%c
8	 **75c**	 **106h**: 88%c
9	 **75k**	 **106i**: 82%c

10			**106j**: 94%c

*a*Isolated yield, *b*Performed with 3 mol% $Pd(dba)_2$ and 6 mol% SPhos, *c*Performed with 5 mol% $Pd(dba)_2$ and 5 mol% Xantphos.

2.7 Synthesis of 1,2,5-Trisubstituted Triazole 108 followed by a Ring-closing Metathesis to generate the Benzotriazole Derivative 109

The bis-pivaloyloxyzinc acetylide (**99**) also underwent a [3+2]-cycloaddition in the presence of 10 mol% CuI leading to the 1,2-bis-zincated triazole **107** with two reactive zinc functionalities (Scheme 25). After quenching with allyl bromide (3.0 equiv, 25 °C, 1 h), the triazole **108** was obtained in 66% yield.[76] This bis-allylated triazole **108** underwent a ring-closing metathesis[77] in the presence of 5 mol% Hoveyda-Grubbs catalyst (2nd generation)[78] in DCM at 50 °C leading to the 1,2,3-triazole **109** in 82% yield. To the best of our knowledge, compounds **108** and **109** were not previously synthesized and can be an interesting addition to the triazole-class.[79]



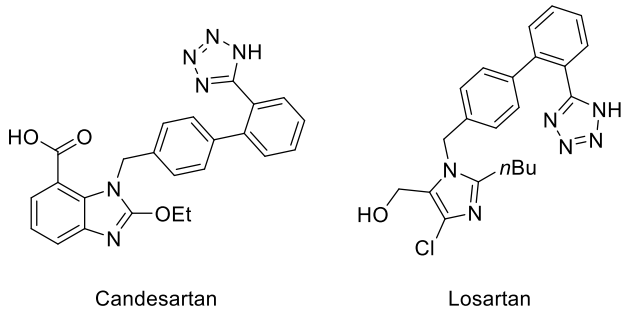
Scheme 25: Synthesis of 1,2,5-trisubstituted triazole **108** followed by a ring-closing metathesis to benzotriazole derivative **109**.

[76] A differentiation of the two nucleophilic positions of triazole **107** could not be achieved.
[77] Handbook of Metathesis, Volume 2: Applications in Organic Synthesis; R. H. Grubbs, D. J. O'Leary *2nd Ed.*; Wiley: Weinheim, 2015.
[78] a) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda *J. Am. Chem. Soc.* **2000**, *122*, 8168; b) S. Gessler, S. Randl, S. Blechert *Tetrahedron* **2000**, *41*, 9973.
[79] a) M. Wijtmann, C. de Graaf, G. de Kloe, E. P. Istyastono, J. Smit, H. Lim, R. Boonnak, S. Nijmeijer, R. A. Smits, A. Jongejan, O. Zuiderveld, I. J. P. de Esch, R. Leurs *J. Med. Chem.* **2011**, *54*, 1693; b) W. Yan, X. Ye, N. G. Akhmedov, J. L. Petersen, X. Shi *Org. Lett.* **2012**, *14*, 2358; c) H. Y. V. Ching, X. Wang, M. He, N. P. Holland, R. Guillot, C. Slim, S. Griveau, H. C. Bertrand, C. Policar, F. Bedioui, M. Fontecave *Inorg. Chem.* **2017**, *56*, 2966; d) M. R. Jones, E. Mathieu, C. Dyrager, S. Faissner, Z. Vaillancourt, K. J. Korshavn, M. H. Lim, A. Ramamoorthy, V. W. Yong, S. Tsutsui, P. K. Stys, T. Storr *Chem. Sci.* **2017**, *8*, 5636.

3 Preparation and Reactions of (1*H*-tetrazol-5-yl)zinc Pivalates

3.1 Introduction

The 1*H*-tetrazole scaffold is a popular building block in pharmaceutical chemistry and materials science.[80] It has been used for many different purposes, for example as ligands[81], explosives[82] or propellants.[83] 5-Substituted-1*H*-tetrazoles play also an important role in medicinal chemistry and biology. Based on steric and electrophilic considerations, they are considered as non-classical isosteres or bioisosteres of the carboxylic acid moiety. Interestingly, they possess very similar physicochemical and biological properties. Both are planar and acidic molecules with a related pKa value (around 4.2 to 4.9) and thus, both are ionized at a physiological pH value of 7.4.[84] Due to these useful pharmacological properties, 1*H*-tetrazoles have been incorporated in several target drug molecules including anticancer[85] or antiviral[86] medication, such as anti-HIV[87] and others. Candesartan is as a famous drug that is applied for the treatment of hypertension and heart failure. Losartan is mainly used to treat high blood pressure (Scheme 1).[88–89]



Scheme 26: Pharmaceuticals containing a 1*H*-tetrazole ring.

5-substituted-1*H*-tetrazoles can be synthesized in a number of ways. The most common way is via [3+2]-dipolar cycloadditions reaction between azides and nitriles. Other methods available include the

[80] V. A. Ostrovskii, G. I. Koldobskii, R. E. Trifonov, *Comprehensive Heterocyclic Chemistry III*, Vol.6, Elsevier, Oxford, UK, **2008**.
[81] S. Mukhopadhyay, J. Lasri, M. F. C. G. da Silva, M. A. J. Charmier, A. J. L. Pombeiro, *Polyhedron* **2008**, *27*, 2883.
[82] R. P. Singh, R. D. Verma, D. T. Meshri, J. M. Shreeve, *Angew. Chem. Int. Ed.* **2006**, *45*, 3584.
[83] K. Koguro, T. Oga, S. Mitsui, R. Orita, *Synthesis* **1998**, *6*, 910.
[84] B. C. Bookser, *Tetrahedron Lett.* **2000**, *41*, 2805.
[85] A. O. De Souza, M. T. Pedrosa, J. B. Alderete, A. F. Cruz, M. A. Prado, R. B. Alves, C. L. Silva, *Pharmazie* **2005**, *60*, 396.
[86] E. Vieira, J. Huwyler, S. Jolidon, F. Knoflach, V. Mutel, J. Wichmann, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4628.
[87] A. Gagnon, S. Landry, R. Coulombe, A. Jakalian, I. Guse, B. Thavonekham, P. R. Bonneau, C. Yoakim, B. Simoneau, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1199.
[88] V. Aureggi, G. Sedelmeier, *Angew. Chem. Int. Ed.* **2007**, *46*, 8440.
[89] A. Alonen, J. Jansson, S. Kallonen, A. Kiriazis, O. Aitio, M. Finel, R. Kostiainen, *Bioorg. Chem.* **2008**, *36*, 148.

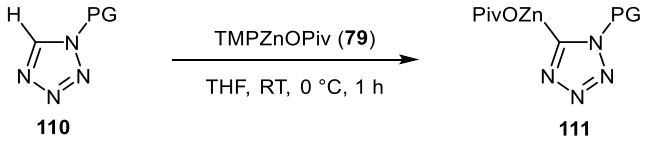
reaction of an amidrazone with sodium nitride in acetic acid or the synthesis based on the reaction of triethoxymethane with sodium azide and ammonium chloride.[90]

Until now, the usage of 1*H*-tetrazoles as nucleophilic reagents has been limited to lithium,[91] tin,[84] potassium and magnesium reagents.[92] Langille and co-workers have achieved a zinc insertion in the 5-position and have used the zincated tetrazole for a subsequent Negishi cross-coupling.[92]

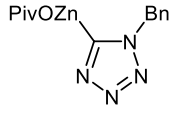
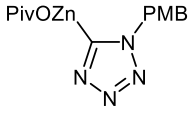
3.2 Preparation and Activity of (1*H*-tetrazol-5-yl)zinc Pivalates of Type 111

Consequently, we reported the preparation and reactivity of new organozinc pivalates, namely (1*H*-tetrazol-5-yl)zinc pivalates (**111a–b**) as storable solids with appreciably air and moisture stability (91–92% activity, determined after 4 h exposure to air; see Table 8). They are obtained in high yields from the *N*-protected 1*H*-tetrazoles of type **110** by deprotonation using the mixed zinc–magnesium base TMPZnCl·Mg(OPiv)$_2$ (**73**)[43] in THF at room temperature for 1 h. After solvent evaporation, **111a** and **111b** were obtained as white powders in quantitative yield as indicated by a titration with iodine.[66] The resulting powders can be handled for a short time on the benchtop and retain more than 91% activity after an air exposure of 4 h at 25 °C (Table 8)

Table 8: Activity of (1*H*-tetrazol-5-yl)zinc pivalates of type **111** after exposure to air at 25 °C.



110 **111**

Zinc species	0	1	2	4
 **111a**	100%[a]	96%[a]	93%[a]	91%[a]
 **111b**	100%[a]	97%[a]	95%[a]	92%[a]

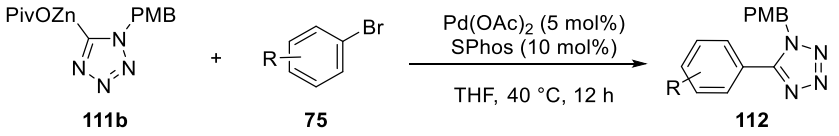
[a]Activity determined by titration with iodine.

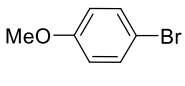
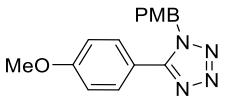
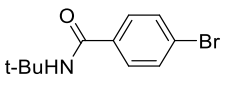
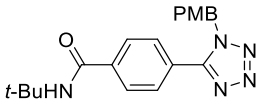
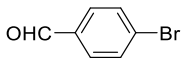
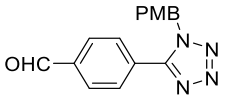
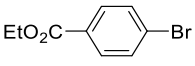
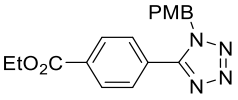
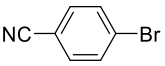
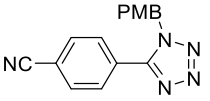
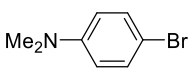
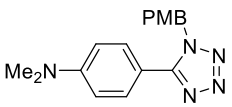
[90] J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 5th edition, Wiley-Blackwell, Oxford, UK, **2010**.
[91] Y. Satoh, J. Moliterni *Synlett* **1998**, *5*, 528.
[92] S. H. Wiedemann, M. M. Bio, L. M. Brown, K. B. Hansen, N. F. Langillle *Synlett* **2012**, *23*, 2231.

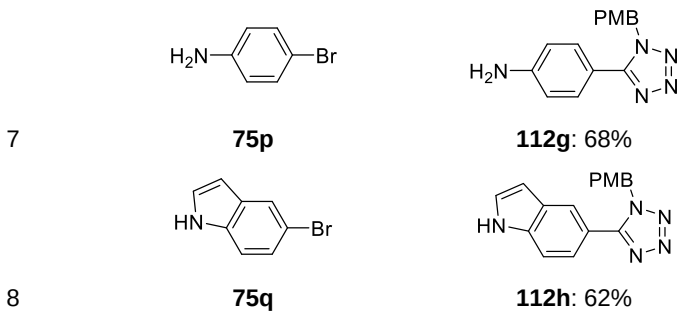
3.3 Application of (1*H*-tetrazol-5-yl)zinc pivalate 111b in Negishi Cross-Coupling Reactions

Furthermore, we examined the reactivity of these new solid (*1H*-tetrazol-5-yl)zinc pivalates (**111a–b**) in Negishi cross-coupling reactions[46] with various aryl halides using the more air stable tetrazole **111b**. The screening of several palladium catalysts showed that the Buchwald ligand, SPhos (10 mol%),[73] gave the best results in combination with $Pd(OAc)_2$ (5 mol%). Under these conditions, a range of (hetero)aryl bromides of type **75** underwent smooth Negishi cross-couplings producing arylated tetrazoles of type **112** in 58–90% yields (Table 9). Remarkably, a variety of sensitive functional groups were tolerated in these cross-couplings such as an amide (entry 2), an aldehyde (entry 3), an ester (entry 4), a nitrile (entry 5), either a protected or unprotected amine (entries 6 – 7) and an unprotected indole (entry 8) were tolerated in these cross-coupling reactions.

Table 9: Negishi cross-coupling of (1*H*-tetrazol-5-yl)zinc pivalate **111b** with Aryl Bromides (**75**)

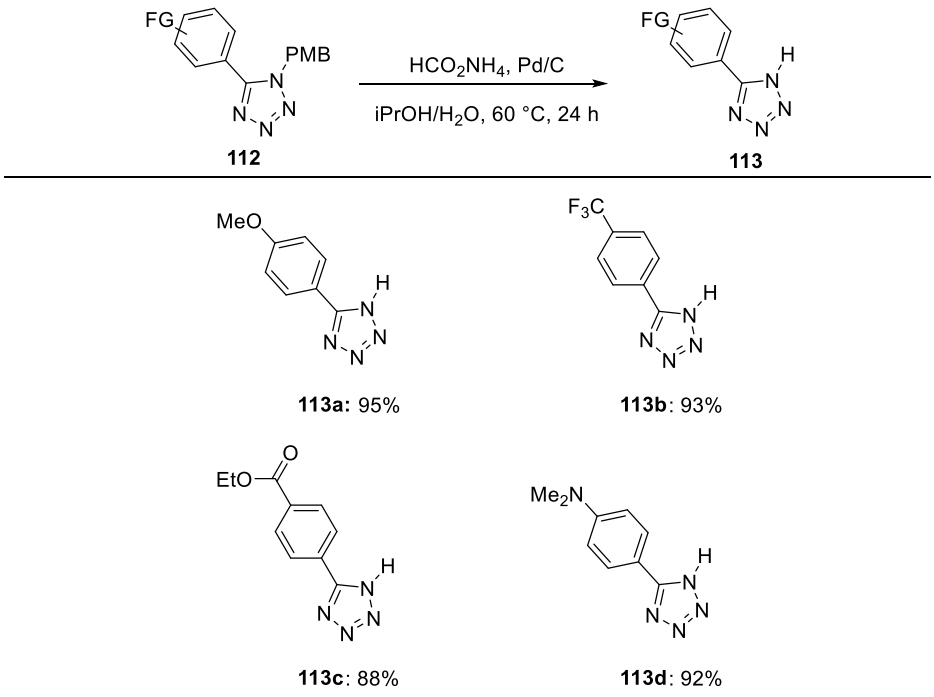


Entry	Electrophile	Product
		
1	**75h**	**112a**: 90%
		
2	**75m**	**112b**: 67%
		
3	**75n**	**112c**: 82%
		
4	**75c**	**112d**: 58%
		
5	**75d**	**112e**: 65%
		
6	**75o**	**112f:** 74%



3.4 Deprotection of arylated 1*H*-tetrazoles 112

Next, we have examined the debenzylation of several previously obtained arylated tetrazoles of type **112**. The use of ammonium formate with palladium on charcoal (5 mol%) in *i*PrOH/H_2O (1:1) at 60 °C for 24 h proved to be an excellent catalytic system[93] giving the desired unprotected 1*H*-tetrazoles **113** in 88–95% yield (Scheme 27).



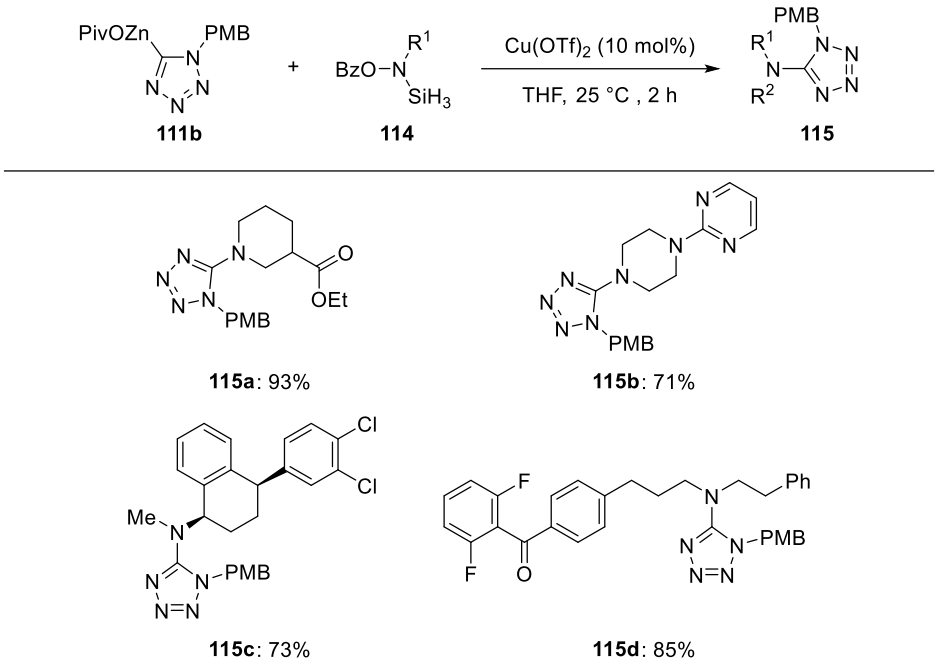
Scheme 27: Debenzylation of Arylated 1*H*-tetrazoles (**112**).

3.5 Amination of (1*H*-tetrazol-5-yl)zinc Pivalate 111b

In addition, the metalated tetrazole **111b** underwent a copper-catalyzed electrophilic amination using *N*-hydroxyl amine benzoates.[94] Thus, the zincated tetrazole **111b** was aminated with hydroxylamine benzoates of type **114** in the presents of copper(II)-triflate (10 mol%) in THF at 25 °C for 2 h leading

[93] M. Seki *Synthesis* **2014**, *46*, 3249.
[94] a) A. M. Berman, J. S. Johnson *J. Am. Chem. Soc.* **2004**, *126*, 5680; b) S. L. McDonald, C. E. Hendrick, Q. Wang *Angewandt. Chem. Int. Ed.* **2014**, *53*, 4667.

to different 5-amino-1*H*-tetrazoles of type **115** in 71–93% yield. Hydroxylamine benzoates derived from biological active molecules such as a nicotinic acid (**115a**) or sertraline (**115c**)[95] have been functionalized using this method (Scheme 28).



Scheme 28: Amination of (1*H*-tetrazol-5-yl)zinc pivalate **111b** using hydroxylamine benzoates of type (**114**) in the presence of catalytic amounts of $Cu(OTf)_2$.

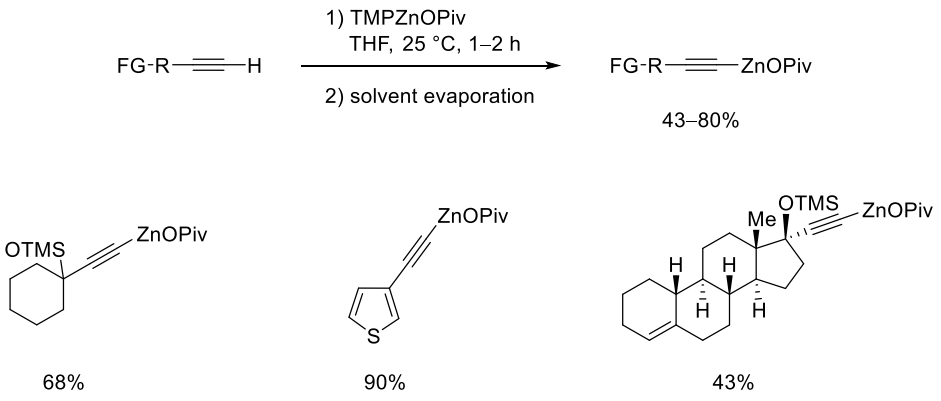
[95] R. S. Obach, L. M. Cox, L. M. Tremaine *Drug Metabolism and Disposition* **2006**, *33*, 262.

4 Summary

This work focused on the development of solid alkynylzinc reagents prepared from the corresponding alkynes through a deprotonation under mild conditions using TMPZnCl·Mg(OPiv)2 as base. After evaporation of the solvent, the resulting solid alkynyl zinc pivalates can be handled in air for several hours without significant decomposition. These zinc reagents show an excellent reactivity in various carbon-carbon bond forming reactions including 1,3-dipolar cycloadditions. Such an alkynylzinc pivalate has been used to prepare a carboxyamidotriazole with potential antineoplastic activity in eight steps in 55% overall yield. In addition, the preparation of mono- and bis-pivaloyloxyzinc acetylides, which display enhanced air and moisture stability was examined. Mono-zinc acetylide pivalate underwent Negishi cross-couplings to form (hetero)aryl alkynes. A subsequent Sonogashira cross-coupling led to the synthesis of asymmetric bis-arylated alkynes without employing silyl protection steps. Furthermore, this zinc reagent underwent a copper-catalyzed azide-alkyne cycloaddition (CuAAC), which selectively led to 1,5-disubstituted 1,2,3-triazoles. In addition, bis-pivaloyloxyzinc acetylide reacted in Negishi cross-couplings with aryl halides, yielding symmetrical bis-arylated alkynes. Finally, the preparation of (1*H*-tetrazol-5-yl)zinc pivalates as storable solids with appreciably high air and moisture stability was developed. They were obtained in high yields from protected 1*H*-tetrazoles by deprotonation using TMPZnCl·Mg(OPiv)2. Subsequent cross-couplings and copper-catalyzed aminations using hydroxylamino benzoates gave access to functionalized 1*H*-tetrazoles while tolerating many functional groups.

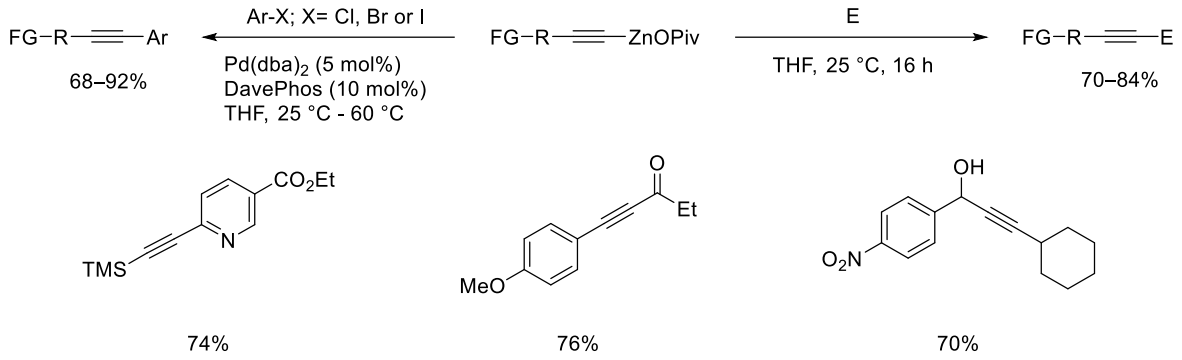
4.1 New Class of Solid Polyfunctional Alkynylzinc Pivalates with Enhanced Air and Moisture Stability for Organic Synthesis

The preparation of solid and air-stable polyfunctionalized alkynylzinc pivalates from the corresponding alkynes using TMPZnOPiv as base has been reported. These organozinc pivalates were obtained as powders under mild conditions in excellent yields and can be handled in air for several hours without significant decomposition (Scheme 29).



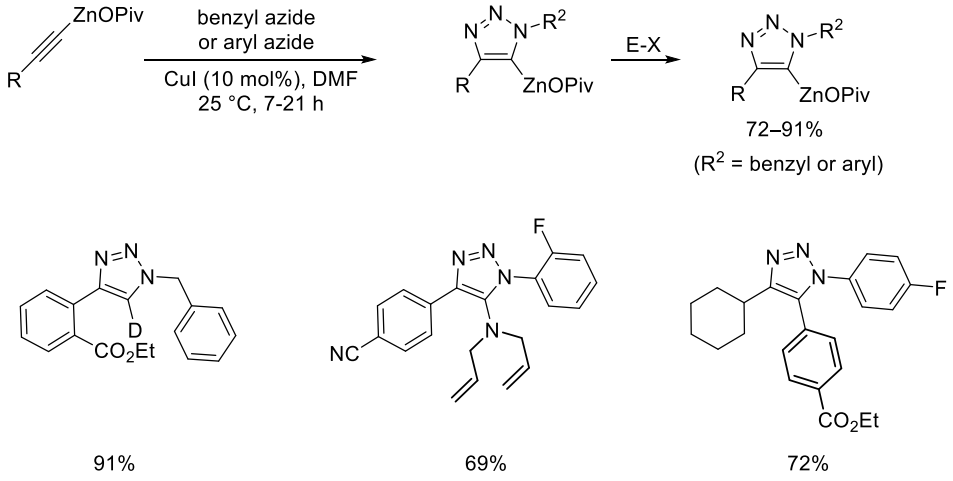
Scheme 29: Preparation of alkynylzinc pivalates from the corresponding alkynes using TMPZnCl·Mg(OPiv)2.

The reactivity of this novel alkynyl zinc pivalates in Pd-catalyzed Negishi cross-coupling reactions with various aryl halides in the presence of various Pd-catalysts was examined. In our hands DavePhos (10 mol%) gave the best results in combination with $Pd(dba)_2$ (5 mol%). In addition, the solid alkynyl zinc reagents reacted with other reactions such as acylation, allylation and aldehyde addition (Scheme 30).



Scheme 30: DavePhos/$Pd(dba)_2$-catalyzed Negishi cross-couplings and reaction with various electrophiles.

Furthermore it was found, that the robust zinc reagents underwent copper-catalyzed 1,3-dipolar cycloadditions with *in situ* generated benzyl or aryl azides with complete regioselectivity. Smooth allylation, amination or arylation proved the integrity of the carbon-zinc bond in the intermediate and produced valuable 1,2,3-triazoles of in 72–91% yields (Scheme 31).

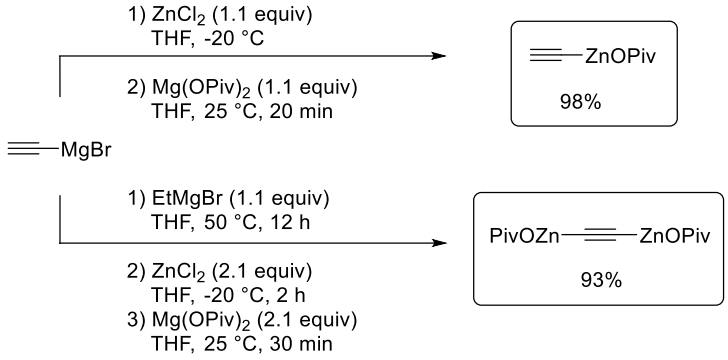


Scheme 31: Copper-catalyzed dipolar cycloadditions with alkynylzinc pivalates providing 1,2,3-triazoles *via* stable zinc intermediates.

4.2 Preparation and Reactions of Mono- and Bis-Pivaloyloxyzinc Acetylides

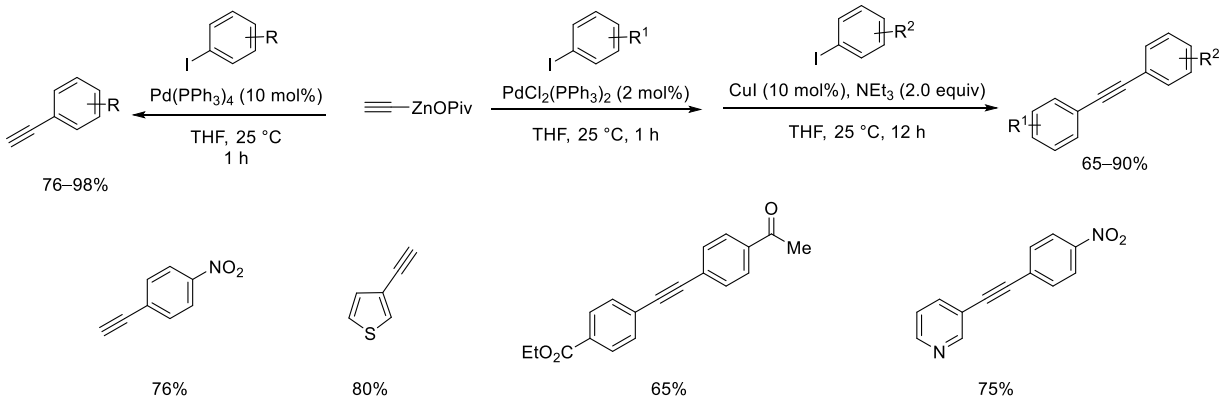
Mono-pivaloyloxyzinc acetylide and bis-pivaloyloxyzinc acetylide were selectively prepared from ethynylmagnesium bromide in quantitative yields. These zinc reagents were conveniently prepared in almost quantitative yields from commercially available ethynylmagnesium bromide (Scheme 32). The

resulting powders can be handled for a short time on the benchtop and have a half-life time in air of about 5 h at 25 °C.



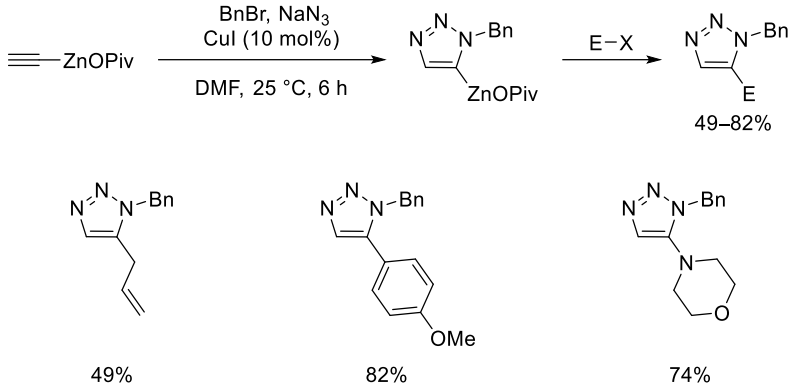
Scheme 32: Preparation of mono-pivaloyloxyzinc acetylide and bis-pivaloyloxyzinc acetylide.

Furthermore, mono-pivaloyloxyzinc acetylide underwent Negishi cross-couplings with aryl iodides to aryl- and heteroaryl-alkynes in 76–98% yields (Scheme 33). In addition, non-symmetrical bis-arylated alkynes were prepared in a one-pot reaction using, at first, the previously developed Negishi cross-coupling performed in the presence of $PdCl_2(PPh_3)_2$ (2 mol%), followed by a Sonogashira cross-coupling using CuI (10 mol%) and NEt_3 (2.0 equiv).



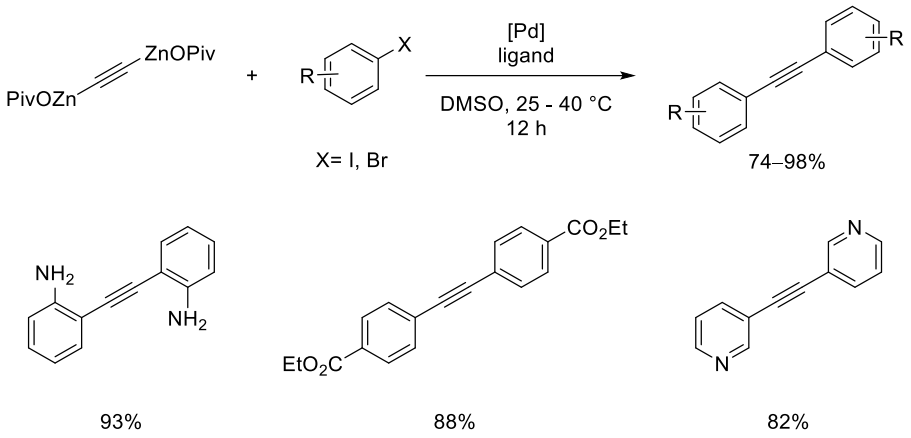
Scheme 33: Negishi cross-coupling reactions between mono-pivaloyloxyzinc acetylide and various aryl iodides and one-pot synthesis of non-symmetrical bis-arylated acetylenes.

Remarkably mono-pivaloyloxyzinc acetylide readily underwent 1,3-dipolar copper-catalyzed regioselective azide-alkyne cycloadditions with retention of the carbon-zinc bond (Scheme 34). Only one regioisomeric cyclo-addition product was formed under the usual copper-catalyzed conditions (10 mol% CuI in DMF at 25 °C for 6 h). Thus, mono-pivaloyloxyzinc acetylide underwent a subsequent allylation, cross-coupling and amination under retention of the position.



Scheme 34: Synthesis of 1,5-disubstituted triazoles.

Next, the Negishi cross-coupling reaction of bis-pivaloyloxyzinc acetylide with aryl and heteroaryl iodides or bromides was examined. Due to the low solubility of the organozinc reagent in THF, DMSO was the preferred solvent for these reactions. Notably, the reaction was compatible with sensitive functional groups such as primary amines, nitriles, ketones and esters.

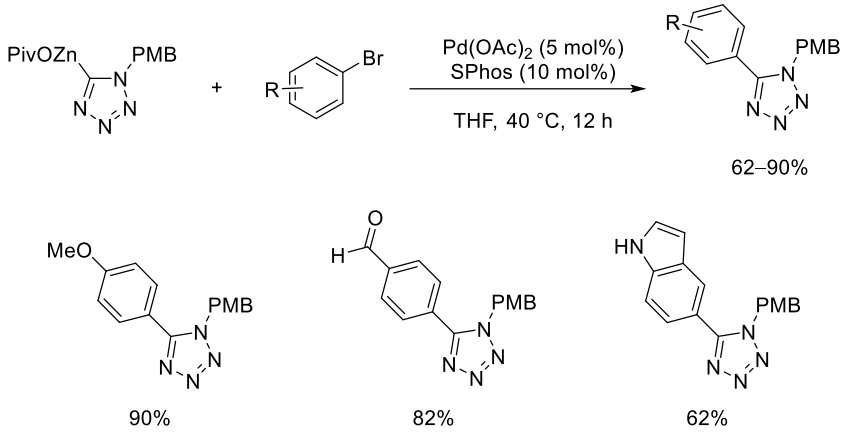


Scheme 35: Negishi cross-couplings reactions between bis-pivaloyloxyzinc acetylide and various aryl halides.

4.3 Preparation and reactions of (1*H*-tetrazol-5-yl)zinc pivalates

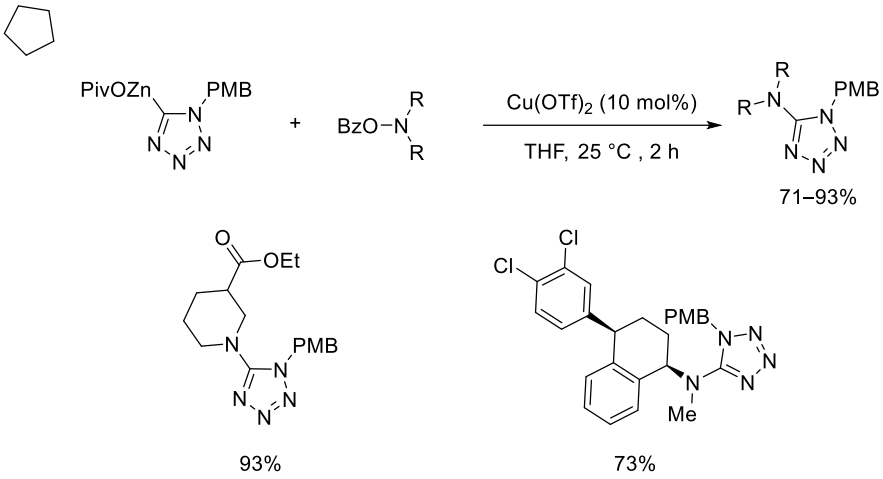
Finally, we reported the preparation and reactivity of new organozinc pivalates, namely (1*H*-tetrazol-5-yl)zinc pivalates as storable solids with appreciably air and moisture stability. They are obtained in high yields from the protected 1*H*-tetrazoles by deprotonation using TMPZnCl·Mg(OPiv)$_2$ in THF at 0 °C for 30 min. Furthermore, the reactivity of these new solid (1*H*-tetrazol-5-yl)zinc pivalates in Negishi cross-coupling reactions with various aryl halides was investigated using the more air stable (1-(4-methoxybenzyl)-1H-tetrazol-5-yl)zinc pivalate (Scheme 36). The screening of several palladium catalysts showed that the Buchwald ligand, SPhos (10 mol%), gave the best results in combination with

$Pd(OAc)_2$ (5 mol%). Under these conditions, a range of (hetero)aryl bromide underwent smooth Negishi cross-couplings producing arylated tetrazoles in 62–90% yields .



Scheme 36: Negishi Cross-coupling of (1-(4-methoxybenzyl)-1H-tetrazol-5-yl)zinc pivalate with aryl bromides .

In addition, the (1-(4-methoxybenzyl)-1H-tetrazol-5-yl)zinc underwent a copper-catalyzed electrophilic amination using *N*-hydroxylamine benzoates. Thus, zinc reagent was aminated with hydroxylamine benzoates in the presence of copper(II)-triflate (10 mol%) in THF. Hydroxylamine benzoates derived from biological active molecules such as a nicotinic acid or sertraline have been functionalized using this method (Scheme 37).



Scheme 37: Amination of (1-(4-methoxybenzyl)-1H-tetrazol-5-yl)zinc pivalate using hydroxylamine benzoates in the presence of catalytic amounts of $Cu(OTf)_2$.

C. EXPERIMENTAL PART

1 General Considerations

If not otherwise stated, all reactions have been carried out using standard Schlenk-techniques in flame-dried glassware under argon. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC.

1.1 Solvents

Solvents were dried according to standard methods by distillation from drying agents as stated below and were stored under argon. Otherwise they were obtained from commercial sources and used without further purification.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves.
Et$_2$O was freshly distilled from sodium benzophenone ketyl under argon and stored over molecular sieves.
***n*Hexane** was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves.
Dichloromethane was continuously refluxed and freshly distilled from CaH_2 under nitrogen.
Solvents for column chromatography were distilled prior to use.

1.2 Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated.
***i*PrMgCl•LiCl** was prepared by careful addition of *i*PrCl (78.54 g, 91.3 mL, 1.00 mol, 1.0 equiv.) to a suspension of Mg (26.74 g, 1.1 mol, 1.1 equiv.) and LiCl (46.63 g, 1.1 mol, 1.1 equiv.) in dry THF (900 mL). The reaction mixture was stirred for 12 h and afterwards the floating particles were allowed to settle. The solution was cannulated into a flame-dried and argon flushed Schlenk-flask and its concentration was determined by titration against I_2 in THF.[96]
***n*BuLi, *s*BuLi, *t*BuLi** solutions in hexane were purchased from Albemarle and their concentration was determined by titration against *N*-benzylbenzamide in THF at −20 °C.[97]
TMPH was purchased from Albemarle, freshly distilled from CaH_2 and stored over argon.
CuCN•2LiCl solution (1.00 M in THF) was prepared by drying CuCN (44.78 g, 500 mmol, 1.0 equiv.) and LiCl (42.39 g, 1.00 mol, 2.0 equiv.) in a Schlenk-flask under vacuum for 5 h at 150 °C. After

[96] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.
[97] A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281.

cooling to 25 °C, dry THF (480 mL) was added and the suspension was stirred until all salts were dissolved. Then dry THF was added until a previously set 500 mL mark was matched.

$MgCl_2$ solution (0.50 M in THF) was prepared by suspending Mg turnings (6.68 g, 275 mmol) in dry THF (500 mL) in a flame-dried and argon flushed Schlenk-flask. Then 1,2-dichloroethane (24.74 g, 19.70 mL, 250 mmol) was added carefully over 1 h (strong gas evolution), while the temperature was kept below 25 °C. The reaction mixture was stirred overnight at 25 °C until gas evolution was complete.

$ZnCl_2$ solution (1.00 M in THF) was prepared by drying $ZnCl_2$ (68.15 g, 500 mmol, 1.0 equiv.) in a Schlenk-flask under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (480 mL) was added and stirred until all salts were dissolved. Then, dry THF was added until a previously set 500 mL mark was matched.

TMPLi solution in THF was prepared by addition of *n*BuLi (38.2 mL, 2.62 M in hexane, 100 mmol, 1.00 equiv.) to a solution of TMPH (14.13 g, 16.87 mL, 100 mmol, 1.0 equiv.) in THF (100 mL) at −40 °C. The mixture was allowed to warm up to 0 °C and its concentration was determined by titration against *N*-benzylbenzamide in THF at –20 °C.

TMPMgCl•LiCl was prepared by addition of TMPH (14.83 g, 17.72 mL, 105 mmol, 1.05 equiv.) to *i*PrMgCl•LiCl (95.24 mL, 1.05 M, 100 mmol, 1.00 equiv.) at 25 °C. The mixture was stirred for 48 h until all gas evolution ceased. The concentration was determined by titration against benzoic acid in THF using 4-(phenylazo)diphenylamine as indicator.

TMPZnCl·Mg(OPiv)$_2$ was prepared by placing TMPH (5.94 g, 7.14 mL, 42 mmol) in a dry and argon-flushed 100 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, and dissolving in dry THF (20 mL). To that solution benzylmagnesium chloride was added (20 mL, 2.0 m in THF, 40 mmol) over a period of 5 min at room temperature. The resulting solution was continued to stir at 40 °C for 12 hours (a white precipitation was formed). The reaction mixture was cooled to room temperature followed by the addition of $Zn(OPiv)_2$ (10.70 g, 40.0 mmol) in one portion. Stirring was continued at room temperature for 1 h, during which time a clear orange solution was formed to afford the base solution (0.6-0.7 m determined by titration with benzoic acid).

Titration of Organozinc Reagents Using Iodine

Accurately weighted aliquots (350 mg) of the crude organozinc material were dissolved in dry THF, so that the total volume of the solution was 2 mL. To the resulting solution, a standard solution of iodine (1 M, in dry THF) was added until the complete appearance of the dark brown color of iodine. Thus, the concentration of the active species (in mmol/g) is determined and thereof the yield of the zinc reagent formation.

Stability Studies of Zinc Reagents in Air

To evaluate the stability of organozinc reagents in air, accurately weighed aliquots of the solid material were placed in opened Schlenk-flasks at 25 °C. After exposure to air for a given time, the flask was closed, evacuated, filled with argon and dissolved in THF. The resulting solution was titrated against

iodine, according to the procedure described above and the measured concentration was compared to the one before the exposure to air.

1.3 Chromatography

Flash column chromatography was performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck.

Thin layer chromatography (TLC) was performed using aluminum plates covered with SiO_2 (Merck 60, F–254). Spots were visualized by UV light irradiation and/or by staining of the TLC plate with one of the solutions below, followed by heating with a heat gun.

- $KMnO_4$ (0.3 g), K_2CO_3 (20 g) and KOH (0.3 g) in water (300 mL).
- $Ce(SO_4)_2$ (5.0 g), $(NH_4)_6Mo_7O_{24}•4H_2O$ (25 g) and concentrated H_2SO_4 (50 mL) in water (450 mL).
- Neat iodine absorbed on silica gel.

1.4 Analytical data

NMR spectra were recorded on *Bruker* ARX 200, AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in parts-per-million (ppm) relative to the residual solvent peak: $CDCl_3$ (δ_H: 7.26; δ_C: 77.16). For the observation of the observed signal multiplicities, the following abbreviations and combinations thereof were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), m (multiplet) and br (broad). If not otherwise noted, the coupling constants given are either H-H or H-F coupling constants for proton signals and C-F coupling constants for carbon signals.

Melting points are uncorrected and were measured on a *Büchi* B.540 apparatus.

Infrared spectra were recorded from 4000–650 cm^{-1} on a Perkin Elmer Spectrum BX-59343 instrument. For detection a Smiths Detection DuraSampl IR II Diamond ATR sensor was used. The main absorption peaks are reported in cm^{-1}.

Gas chromatography (GC) was performed with instruments of the type Hewlett-Packard 6890 or 5890 Series II, using a column of the type HP 5 (Hewlett-Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm, film thickness 0.25 μm). The detection was accomplished using a flame ionization detector.

Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a Finnigan MAT 95Q or Finnigan MAT 90 instrument for electron impact ionization (EI). For the combination of gas chromatography with mass spectroscopic detection, a GC–MS of the type Hewlett-Packard 6890/MSD 5793 networking was used (column: HP 5–MS, Hewlett–Packard; 5% phenylmethylpolysiloxane; length: 15 m, diameter: 0.25 mm, film thickness: 0.25 μm).

2 New Class of Solid Polyfunctional Alkynylzinc Pivalates with Enhanced Air and Moisture Stability for Organic Synthesis.

2.1 Typical Procedures (TP)

TP1: Typical Procedure for the Preparation of the Solid Alkynylzinc Pivalates

A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the corresponding alkynes of type **70** (10.0 mmol). TMPZnOPiv (**73**, 0.6 M in THF, 12.0 mmol) was added. After stirring the reaction mixture for 1-2 h at room temperature, the solvent was removed *in vacuo* (at least 6 h) and the dried solid alkynylzinc pivalate (**71**) (having the aspect of a fine powder) was titrated using iodine in order to determine the yield.

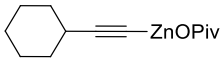
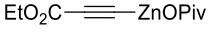
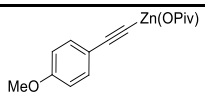
TP2: Typical Procedure for Negishi Couplings Using Alkynylzinc Pivalates

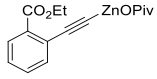
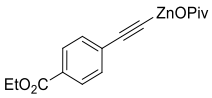
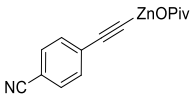
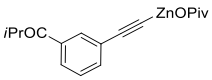
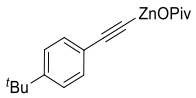
A dry and argon-flushed flask equipped with a magnetic stirring bar and a septum was charged with the solid alkynylzinc pivalate of type **71** (0.50 mmol), $Pd(dba)_2$ (2 mol%), DavePhos (4 mol%) and THF (1 mL) to give a 0.5 M solution to the respective zinc pivalate. The electrophile (0.42 mmol) was added and the resulting solution was stirred at the given temperature for the given time. The reaction mixture was quenched with sat. aq. NH_4Cl solution (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with sat. aq. NaCl solution (3 mL) and dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo*. Purification *via* flash column chromatography yielded the Negishi cross-coupling product.

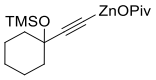
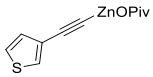
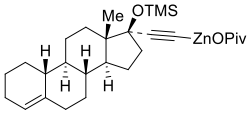
TP3: Typical Procedure for the Aldehyde Addition Using Alkynylzinc Pivalates

A dry and argon-flushed flask equipped with a magnetic stirring bar and a septum was charged with the solid alkynylzinc pivalate of type **71** (1.0 mmol) and diluted in THF (1 mL). To this solution was added a solution of $AlMe_3$ (0.8 M in toluene, 1.0 mmol) at the given temperature and was stirred for 10 min. A solution of the electrophile (0.25 M in toluene, 0.8 mmol) was added dropwise and the resulting solution was stirred at the given temperature for the given time. The reaction mixture was quenched with 10 % aq. potassium sodium tartrate tetrahydrate solution (5 mL) und stirred for 1 h. The mixture was extracted with EtOAc (3 x 2 ml) and the combined organic layers were dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo*. Purification *via* flash column chromatography yielded the desired product.

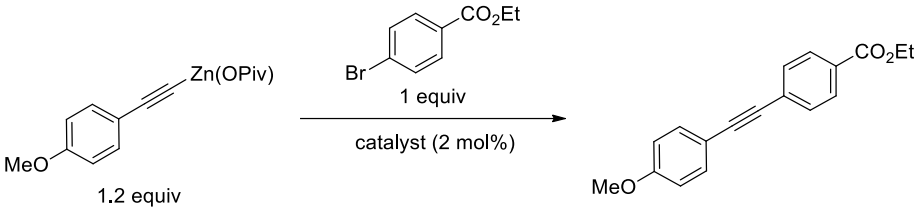
2.2 Stability of Alkynylzinc reagents of Type 71 in Air

	71a	**71b**	 **71c**	 **71d**	 **71e**
t[h] In air	Remaining active alkynylzinc species[a]				
1	98%	94%	93%	97%	98%
2	95%	88%	88%	92%	95%
4	**90%**	**71%**	**73%**	**82%**	**80%**

	 **71f**	 **71g**	 **71h**	 **71i**	 **71j**
t[h] In air	Remaining active alkynylzinc species[a]				
1	99%	98%	99%	97%	97%
2	95%	97%	97%	92%	92%
4	**90%**	**90%**	**87%**	**86%**	**82%**

	 **71k**	 **71l**	 **71m**
t[h] In air	Remaining active alkynylzinc species[a]		
1	85%	99%	84%
2	74%	97%	70%
4	**68%**	**90%**	**43%**

2.3 Catalysts screening for Negishi Cross-coupling

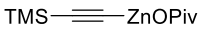


Entry	Catalyst	Conversion
1	$Pd[P(^tBu)_3]$	20%
2	PEPPSI	ND
3	$Pd(OAC)_2$/SPhos (1:1)	ND
4	$Pd(PPh_3)_4$	8%
5	$Pd(dba)_2$/DavePhos (1:2)	**91%**
6	$Pd(dba)_2$/^{t}BuDavePhos (1:2)	15%

Procedure: To a solution of solid zinc reagent in THF (0.5 M) was treated with ethyl 4-bromobenzoate (1 equiv) and catalyst (2 mol%). The resulting solution was stirred at 40 °C overnight. The conversion was identified via GC analysis.

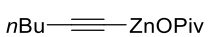
2.4 Preparation of the Solid Alkynylzinc Pivalates

((Trimethylsilyl)ethynyl)zinc pivalate (71a)



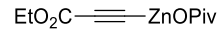
According to **TP1** TMPZnOPiv (12.0 mmol) was added to trimethylsilyl acetylene **70a** (983 mg, 10.0 mmol). The mixture was stirred for 2 h at room temperature followed by removal of the solvent to furnish the title compound as a white solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 1.10 mmol/g corresponding in 99% yield.

(Hex-1-yn-1-yl)zinc pivalate (71b)



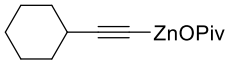
According to **TP1** TMPZnOPiv (12.0 mmol) was added to 1-hexyne **70b** (847 mg, 10.0 mmol). The mixture was stirred for 2 h at room temperature followed by removal of the solvent to furnish the title compound as a white solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 1.08 mmol/g corresponding in 98% yield.

(3-Ethoxy-3-oxoprop-1-yn-1-yl)zinc pivalate (71c)



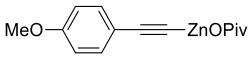
According to **TP1** TMPZnOPiv (7.2 mmol) was added to ethyl propiolate **70d** (590 mg, 6.0 mmol). The mixture was stirred for 1 h at room temperature followed by removal of the solvent to furnish the title compound as a yellowish solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 1.15 mmol/g corresponding in 99% yield.

(Cyclohexylethynyl)zinc pivalate (71d)



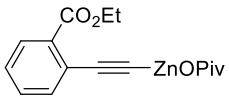
According to **TP1** TMPZnOPiv (12.0 mmol) was added to cyclohexylacetylene **70c** (1.1 g, 10.0 mmol). The mixture was stirred for 2 h at room temperature followed by removal of the solvent to furnish the title compound as a white solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 1.13 mmol/g corresponding in 98% yield.

((4-Methoxyphenyl)ethynyl)zinc pivalate (71e)



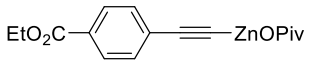
According to **TP1** TMPZnOPiv (12.0 mmol) was added to 4-ethynylanisole **70e** (1.33 g, 10.0 mmol). The mixture was stirred for 2 h at room temperature followed by removal of the solvent to furnish the title compound as a light yellowish solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 1.10 mmol/g corresponding in 99% yield.

((2-(Ethoxycarbonyl)phenyl)ethynyl)zinc pivalate (71f)



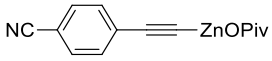
According to **TP1** TMPZnOPiv (6.1 mmol) was added to 2-ethynyl benzoic Acid ethylester **70f** (888 mg, 5.10 mmol). The mixture was stirred for 1 h at room temperature followed by removal of the solvent to furnish the title compound as a light yellowish solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 1.15 mmol/g corresponding in 97% yield.

((4-(Ethoxycarbonyl)phenyl)ethynyl)zinc pivalate (71g)



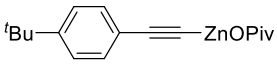
According to **TP1** TMPZnOPiv (6.43 mmol) was added to 4-ethynyl benzoic Acid ethylester **70g** (934 mg, 5.40 mmol). The mixture was stirred for 1 h at room temperature followed by removal of the solvent to furnish the title compound as a light yellowish solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 1.11 mmol/g corresponding in 97% yield.

((4-Cyanophenyl)ethynyl)zinc pivalate (71h)



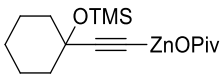
According to **TP1** TMPZnOPiv (7.2 mmol) was added to 4-ethynylbenzonitrile **70h** (788 mg, 6.0 mmol). The mixture was stirred for 1 h at room temperature followed by removal of the solvent to furnish the title compound as a light yellowish solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 1.05 mmol/g corresponding in 98% yield.

((4-(tert-Butyl)phenyl)ethynyl) zinc pivalate (71i)



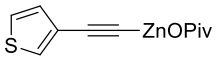
According to **TP1** TMPZnOPiv (12.0 mmol) was added to 4-*tert*-butylphenylacetylene **70i** (1.7 g, 10.0 mmol). The mixture was stirred for 2 h at room temperature followed by removal of the solvent to furnish the title compound as a white solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 1.11 mmol/g corresponding in 98% yield.

((1-((Trimethylsilyl)oxy)cyclohexyl)ethynyl)zinc pivalate (71k)



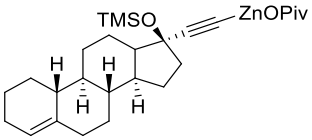
According to **TP1** TMPZnOPiv (6.0 mmol) was added to alkyne **70k** (982 mg, 5.0 mmol). The mixture was stirred for 2 h at room temperature followed by removal of the solvent to furnish the title compound as a white solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 0.88 mmol/g corresponding in 93% yield.

(Thiophen-3-ylethynyl)zinc pivalate (71l)



According to **TP1** TMPZnOPiv (6.0 mmol) was added to 3-ethynylthiophene **70l** (541 mg, 5.0 mmol). The mixture was stirred for 1.5 h at room temperature followed by removal of the solvent to furnish the title compound as a light yellowish solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 1.13 mmol/g corresponding in 98% yield.

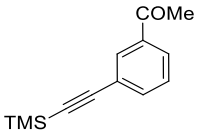
(((8*R*,9*S*,10*R*,14*S*,17*S*)-17-((trimethylsilyl)oxy)-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethynyl)zinc pivalate (71m)



According to **TP1** TMPZnOPiv (3.6 mmol) was added to alkyne **70m** (1.03 g, 3.00 mmol). The mixture was stirred for 2 h at room temperature followed by removal of the solvent to furnish the title compound as a light yellowish solid. Determination of the content of active zinc species by titration[96] with iodine indicated a concentration of 0.95 mmol/g corresponding in 94% yield.

2.5 Preparation of Negishi Cross-Coupling Products

1-(3-((Trimethylsilyl)ethynyl)phenyl)ethanone (**74a**)



According to **TP2** 3-bromoacetophenone **75a** (93 mg, 0.46 mmol) was added to a solution of ((trimethylsilyl)ethynyl)zinc pivalate **71a** (0.55 mmol), $Pd(dba)_2$ (5 mg, 2 mol%) and DavePhos (7 mg, 4 mol%) in THF (1 mL) at 25 °C. The resulting solution was stirred at 25 °C for 6 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 15:1) afforded the title compound as a yellowish oil (88 mg, 89% yield).

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 8.03 (t, *J* = 1.7 Hz, 1H), 7.90 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.64 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 2.60 (s, 3H), 0.26 (s, 9H).

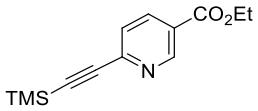
^{13}C-NMR (201 MHz, $CDCl_3$): δ / ppm = 197.5, 137.2, 136.3, 132.1, 128.7, 128.2, 123.9, 104.0, 95.7, 26.8, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2899, 2156, 1689, 1596, 1574, 1477, 1422, 1358, 1275, 1249.

MS (EI, 70 eV): *m/z* (%) = 216 (M+, 13), 202 (19), 201 (100), 73 (25), 43 (17).

HRMS (EI): *m/z* calc. for [$C_{13}H_{16}OSi$]: 216.0970; found: 216.0963 (M^+).

Ethyl 6-((trimethylsilyl)ethynyl)nicotinate (**74b**)



According to **TP2,** ethyl 6-chloropyridine-3-carboxylate **76** (154 mg, 0.83 mmol) was added to a solution of ((trimethylsilyl)ethynyl)zinc pivalate **71a** (1.00 mmol), $Pd(dba)_2$ (10 mg, 2 mol%) and DavePhos (13 mg, 4 mol%) in THF (2 mL) at 25 °C. The resulting solution was stirred at 60 °C for 16 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 5:1 to 3:1) afforded the title compound as a yellowish solid (152 mg, 74% yield).

M.p. (°C): 61.3–64.0.

$_1$H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.14 (dd, *J* = 2.1, 0.9 Hz, 1H), 8.23 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.51 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.27 (s, 9H).

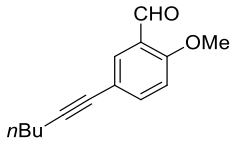
$_{13}$C-NMR (151 MHz, $CDCl_3$): δ / ppm = 164.9, 151.1, 146.6, 137.2, 126.8, 125.2, 103.2, 98.4, 61.7, 14.4, -0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962, 1721, 1590, 1468, 1368, 1286, 1251, 1223, 1111.

MS (EI, 70 eV): *m/z* (%) = 247 (M+, 9), 233 (11), 232 (100), 218 (19), 204 (65), 176 (12).

HRMS (EI): *m/z* calc. for [$C_{13}H_{17}NO_2Si$]: 247.1029; found: 247.1019 (M^+).

5-(Hex-1-yn-1-yl)-2-methoxybenzaldehyde (**74c**)



According to **TP2,** ethyl 5-iodo-2-methoxybenzaldehyde **77** (149 mg, 0.57 mmol) was added to a solution of hexynyl zinc pivalate **71b** (0.52 mmol), $Pd(dba)_2$ (7 mg, 2 mol%) and DavePhos (9 mg, 4 mol%) in THF (1 mL) at 25 °C. The resulting solution was stirred at ambient temperature for 16 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a colorless liquid (85 mg, 76% yield).

$_1$H-NMR (600 MHz, $CDCl_3$): δ / ppm = 10.41 (s, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.56 (dd, J = 8.6, 2.2 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 3.93 (s, 3H), 2.39 (t, J = 7.0 Hz, 2H), 1.64 – 1.37 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H).

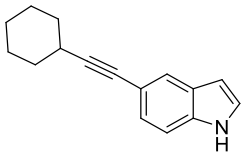
$_{13}$C-NMR (151 MHz, $CDCl_3$): δ / ppm = 189.3, 161.0, 138.8, 132.0, 124.8, 117.0, 111.8, 90.2, 79.2, 56.0, 30.9, 22.2, 19.2, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2862, 1687, 1605, 1496, 1264, 1166, 1027, 818.

MS (EI, 70 eV): *m/z* (%) = 216 (M+, 78), 201 (87), 173 (100), 158 (77), 115 (62)

HRMS (EI): *m/z* calc. for [$C_{14}H_{16}O_2$]: 216.1150; found: 216.1147 (M^+).

5-(Cyclohexylethynyl)-1H-indole (**74d**)



According to **TP2,** 5-bromoindole **75b** (90 mg, 0.46 mmol) was added to a solution of zinc pivalate **71d** (0.73 mmol), $Pd(dba)_2$ (6 mg, 2 mol%) and DavePhos (8 mg, 4 mol%) in THF (1.5 mL) at 25 °C. The resulting solution was stirred at 50 °C for 48 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 5:1 to 2:1) afforded the title compound as a brownish solid (70 mg, 68% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.17 (bs, 1H), 7.84 – 7.64 (m, 1H), 7.33 – 7.23 (m, 2H), 7.19 (dd, *J* = 3.2, 2.4 Hz, 1H), 6.51 (ddd, *J* = 3.1, 2.0, 0.9 Hz, 1H), 2.62 (tt, *J* = 9.2, 3.8 Hz, 1H), 2.02 – 1.84 (m, 2H), 1.79 (dtt, *J* = 8.6, 6.5, 2.7 Hz, 2H), 1.65 – 1.50 (m, 3H), 1.44 – 1.28 (m, 3H).

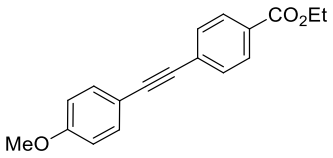
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 135.2, 127.9, 125.9, 124.9, 124.4, 115.4, 111.0, 102.8, 91.8, 81.8, 33.1, 29.9, 26.2, 25.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3413, 2925, 2851, 1616, 1574, 1467, 1414, 1308, 1235, 1090.

MS (EI, 70 eV): *m/z* (%) = 247 (M+, 9), 233 (11), 232 (100), 218 (19), 204 (65), 176 (12).

HRMS (EI): *m/z* calc. for [$C_{13}H_{17}NO_2Si$]: 247.1029; found: 247.1019 (M^+).

Ethyl 4-((4-methoxyphenyl)ethynyl)benzoate (**74e**)



According to **TP2,** ethyl 4-bromobenzoate **75c** (101 mg, 0.44 mmol) was added to a solution of zinc pivalate **71e** (0.53 mmol), $Pd(dba)_2$ (5 mg, 2 mol%) and DavePhos (7 mg, 4 mol%) in THF (1.0 mL) at 25 °C. The resulting solution was stirred at 40 °C for 14 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 15:1) afforded the title compound as a white solid (112 mg, 91% yield).

M.p. (°C): 90.1–92.4.

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 8.02 – 8.00 (m, 2H), 7.58 – 7.53 (m, 2H), 7.51 – 7.47 (m, 2H), 6.91 – 6.87 (m, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H).

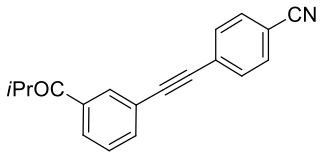
^{13}C-NMR (201 MHz, $CDCl_3$): δ / ppm = 166.3, 160.1, 133.4, 131.4, 129.6, 129.6, 128.4, 114.9, 114.2, 92.6, 87.7, 61.2, 55.5, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 2842, 2215, 1705, 1599, 1518, 1500.

MS (EI, 70 eV): *m/z* (%) = 280 (M+, 100), 252 (14), 235 (30), 164 (11), 163 (12).

HRMS (EI): *m/z* calc. for [$C_{18}H_{16}O_3$]: 280.1099; found: 280.1095 (M^+).

4-((3-Isobutyrylphenyl)ethynyl)benzonitrile (**74f**)



According to **TP2,** 4-bromobenzonitrile **75d** (184 mg, 1.0 mmol) was added to a solution of zinc pivalate **71j** (1.2 mmol), $Pd(dba)_2$ (12 mg, 2 mol%) and DavePhos (16 mg, 4 mol%) in THF (2.0 mL) at 25 °C. The resulting solution was stirred at 40 °C for 16 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 10:1) afforded the title compound as a yellowish solid (253 mg, 93% yield).

M.p. (°C): 99.9–101.5.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.11 (td, *J* = 1.8, 0.7 Hz, 1H), 7.95 (ddd, *J* = 7.9, 1.8, 1.1 Hz, 1H), 7.71 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.67 – 7.58 (m, 4H), 7.49 (td, *J* = 7.8, 0.6 Hz, 1H), 3.55 (p, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H).

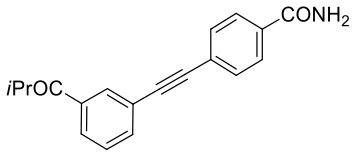
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 203.7, 136.7, 135.7, 132.3, 132.2, 131.8, 129.1, 128.9, 127.9, 123.0, 118.6, 112.0, 92.8, 88.6, 35.7, 19.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2933, 2873, 2227, 1685, 1604, 1217.

MS (EI, 70 eV): *m/z* (%) = 273 (M+, 16), 230 (17), 229 (100), 201 (19), 200 (15).

HRMS (EI): *m/z* calc. for [$C_{19}H_{15}NO$]: 273.1154; found: 273.1148 (M^+).

4-((3-Isobutyrylphenyl)ethynyl)benzamide (**74g**)



According to **TP2,** 4-bromobenzonitrile **75e** (184 mg, 1.0 mmol) was added to a solution of zinc pivalate **71j** (1.2 mmol), $Pd(dba)_2$ (12 mg, 2 mol%) and DavePhos (16 mg, 4 mol%) in THF (2.0 mL) at 25 °C. The resulting solution was stirred at 40 °C for 16 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 10:1) afforded the title compound as a yellowish solid (253 mg, 93% yield).

M.p. (°C): 183.8–187.5.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.11 (t, *J* = 1.7 Hz, 1H), 7.94 (ddd, *J* = 7.9, 1.8, 1.1 Hz, 1H), 7.85–7.78 (m, 2H), 7.7 –7.69 (m, 1H), 7.66–7.60 (m, 2H), 7.50–7.46 (m, 1H), 6.08 (bs, 1H), 5.68 (bs, 1H), 3.56 (p, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.9, 6H).

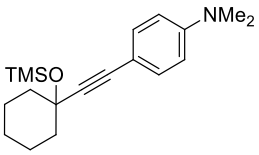
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 203.8, 168.5, 136.6, 135.7, 133.0, 132.0, 131.7, 129.0, 128.5, 127.6, 126.9, 123.5, 91.1, 89.4, 35.7, 19.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3371, 3180, 2971, 2934, 1682, 1644, 1618, 1415.

MS (EI, 70 eV): *m/z* (%) = 291 (M+, 23), 249 (15), 248 (100), 220 (10), 176 (15).

HRMS (EI): *m/z* calc. for [$C_{19}H_{17}NO_2$]: 291.1259; found: 291.1252 (M^+).

***N,N*-Dimethyl-4-((1-((trimethylsilyl)oxy)cyclohexyl)ethynyl)aniline** (**74h**)



According to **TP2**, 4-bromo-N,N-dimethylaniline **75f** (128 mg, 0.64mmol) was added to a solution of zinc pivalate **71k** (0.77 mmol), $Pd(dba)_2$ (7.4 mg, 2 mol%) and DavePhos (10 mg, 4 mol%) in THF (2.0 mL) at 25 °C. The resulting solution was stirred at 40 °C for 16 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 50:1) afforded the title compound as a colorless liquid (156 mg, 78% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.31 (d, *J* = 9.0 Hz, 2H), 6.64 (d, *J* = 9.0 Hz, 2H), 2.97 (s, 6H), 1.94–1.92 (m, 2H), 1.74 1.42 (m, 8H), 0.22 (s, 9H).

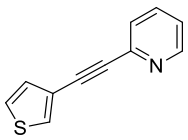
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 150.1, 132.6, 112.0, 110.6, 91.1, 86.4, 70.6, 41.7, 40.4, 25.6, 23.5, 2.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932, 2856, 2215, 1608, 1519, 1355, 1246, 1084, 837.

MS (EI, 70 eV): *m/z* (%) = 315 (M+, 89), 286 (20), 271 (100),

HRMS (EI): *m/z* calc. for [$C_{19}H_{29}ONSi$]: 315.2018; found: 215.2015 (M^+).

2-(Thiophen-3-ylethynyl)pyridine (**74i**)



According to TP2, 2-bromopyridine **75g** (52 mg, 0.3 mmol) was added to a solution of zinc pivalate **71l** (0.4mmol), $Pd(dba)_2$ (4 mg, 2 mol%) and DavePhos (5 mg, 4 mol%) in THF (2.0 mL) at 25 °C. The resulting solution was stirred at 40 °C for 16 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 8:2) afforded the title compound as a yellowish liquid (56 mg, 92% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.63–8.59 (m, 1H), 7.70–7.60 (m, 2H), 7.51(dt, *J* = 7.9, 1.1 Hz, 1H), 7.31 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.28–7.17 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 150.0, 143.4, 136.2, 130.2, 130.0, 127.0, 125.5, 122.7, 121.4, 88.2, 84.6.

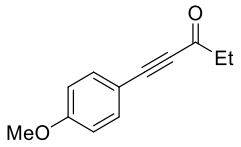
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3106, 2926, 2212, 1581, 1461, 1276, 989, 871, 776.

MS (EI, 70 eV): *m/z* (%) = 185 (M+, 100) 159 (18), 141 (14), 128 (5).

HRMS (EI): *m/z* calc. for [$C_{11}H_7NS$]: 185.0299; found: 185.0292 (M^+).

2.6 Fukuyama coupling, allylation and aldehyde addition

1-(4-Methoxyphenyl)pent-1-yn-3-one (**80**)



According to **TP2,** *S*-ethyl thiopropionate **78** (95 mg, 0.1 mL, 0.8 mmol) was added to a solution of zinc pivalate **(71e**; 0.95 mmol), $Pd(dba)_2$ (10 mg, 2 mol%) and DavePhos (13 mg, 4 mol%) in THF (2.0 mL) at 25 °C. The resulting solution was stirred at 25 °C for 16 h. Diethyl ether (5 mL) was added and the suspension was passed through a pad of celite. The filtrate was washed with 1N HC1, sat. $NaHCO_3$, brine and dried over Na_2SO_4. Filtration and concentration on rotary evaporator afforded a crude product. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 10:1 to 5:1) afforded the title compound (114 mg, 76% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.55 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 2.70 (q, *J* = 7.4 Hz, 2H), 1.24 (t, *J* = 7.4 Hz, 3H).

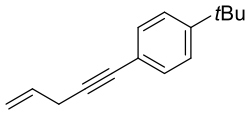
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 188.8, 161.7, 135.2, 114.5, 112.0, 91.9, 87.7, 55.6, 38.8, 8.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2975, 2938, 2190, 1665, 1603, 1509, 1253, 1112, 1045.

MS (EI, 70 eV): *m/z* (%) = 188 (M+, 8), 160 (11), 159 (100), 144 (11).

HRMS (EI): *m/z* calc. for [$C_{12}H_{12}O_2$]: 188.0837; found: 188.0831 (M^+).

1-(tert-Butyl)-4-(pent-4-en-1-yn-1-yl)benzene (**81**)



To a solution of alkynylzinc reagent **71i** (0.50 mmol) in THF (1.0 mL) was added CuCN·2LiCl (10 mol%) and allylbromide (**79**; 41 mg, 0.33 mmol) at 25 °C. The solution was stirred for 36 h at 25 °C before quenched with sat. aq. NH_4Cl solution. The extractions were performed with EtOAc (3 × 1 mL). The combined organic layers were washed with sat. aq. NaCl solution (2 mL) and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. Purification *via* flash column chromatography (pure isohexane) furnished the title compound (54 mg, 82% yield).

^{1}H-NMR (400 MHz, CDCl3): δ / ppm = 7.36 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.90 (ddt, *J* = 17.1, 10.2, 5.2 Hz, 1H), 5.46–5.35 (m, 1H), 5.16 (dd, *J* = 10.0, 1.8 Hz, 1H), 3.19 (dd, *J* = 5.0, 2.3 Hz, 2H), 1.30 (s, 9H).

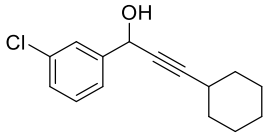
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.1, 132.7, 131.4, 125.3, 120.8, 116.3, 85.9, 83.1, 34.8, 31.3, 23.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 2963, 2361, 1642, 1503, 1268, 1109, 915, 834.

MS (EI, 70 eV): *m/z* (%) = 198 (M+, 41), 184 (16), 183 (100), 1128 (9).

HRMS (EI): *m/z* calc. for [$C_{15}H_{18}$]: 198.1409; found: 198.1402 (M^+).

1-(3-Chlorophenyl)-3-cyclohexylprop-2-yn-1-ol (**83a**)



According to **TP3,** to the solution of zinc pivalate **71d** (1.0 mmol) was added a solution of $AlMe_3$ (0.8 M in toluene, 1.0 mmol) at the ambient temperature and was stirred for 10 min. A solution of 3-chlorobenzaldehyde **82g** (0.25 M in toluene, 0.8 mmol) was added dropwise and the resulting solution was stirred at ambient temperature for 16 h. The reaction mixture was quenched with 10 % aq. potassium sodium tartrate tetrahydrate solution (5 mL) und stirred for 1 h. The mixture was extracted with EtOAc (3 x 2 ml) and the combined organic layer were dried over $MgSO_4$. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a colourless liquid (196 mg, 79% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.56 (d, *J* = 2.1 Hz, 1H), 7.4 –7.39 (m, 1H), 7.33–7.27 (m, 2H), 5.44 (d, *J* = 1.8 Hz, 1H), 2.51–2.39 (m, 1H), 1.83 (dq, *J* = 12.7, 3.5 Hz, 2H), 1.71 (tdd, *J* = 12.4, 6.5, 3.7 Hz, 2H), 1.49 (dtd, *J* = 22.6, 9.4, 7.6, 4.5 Hz, 3H), 1.32 (qd, *J* = 10.4, 5.2 Hz, 3H).

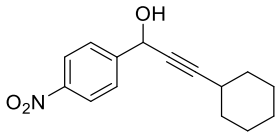
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 143.3, 134.5, 129.9, 128.4, 127.0, 124.9, 92.4, 79.4, 64.3, 32.6, 29.2, 25.9, 25.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3323, 2928, 2853, 2228, 1597, 1448, 1190, 986, 786, 717.

MS (EI, 70 eV): *m/z* (%) = 248 (M+, 15), 213 (100), 157 (13), 138 (33), 128 (18), 115 (15).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}O$]: 248.0968; found: 248.0964 (M^+).

3-Cyclohexyl-1-(4-nitrophenyl)prop-2-yn-1-ol (**83b**)



According to **TP3,** to the solution of zinc pivalate **71d** (1.0 mmol) was added a solution of $AlMe_3$ (0.8 M in toluene, 1.0 mmol) at the ambient temperature and was stirred for 10 min. A solution of 4-nitrobenzaldehyde **82b** (0.25 M in toluene, 0.8 mmol) was added dropwise and the resulting solution was stirred at ambient temperature for 16 h. The reaction mixture was quenched with 10 % aq. potassium sodium tartrate tetrhydrate solution (5 mL) und stirred for 1 h. The mixture was extracted

with EtOAc (3 x 2 ml) and the combined organic layer were dried over $MgSO_4$. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 8:2) afforded the title compound as a colorless liquid (81 mg, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = δ 8.23 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 5.56 (d, *J* = 1.8 Hz, 1H), 2.52–2.37 (m, 1H), 1.82 (dq, *J* = 12.4, 3.5 Hz, 2H), 1.70 (h, *J* = 5.4 Hz, 2H), 1.49 (dqd, *J* = 25.8, 9.5, 3.2 Hz, 3H), 1.30 (ddd, *J* = 21.1, 11.8, 6.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 148.3, 147.8, 127.5, 123.9, 93.1, 79.0, 63.9, 32.6, 29.2, 25.9, 25.0.

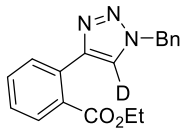
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3382, 2929, 2854, 2226, 1606, 1520, 1346, 986, 853.

MS (EI, 70 eV): *m/z* (%) = 258 (M+, 1), 212 (24), 160 (75), 135 (100), 107 (85), 79 (92).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}NO_3$]: 259.1208; found: 258.1130 (M^+).

2.7 Copper catalyzed 1,3-dipolar cycloaddition with solid alkynylzinc pivalates

Ethyl 2-(1-benzyl-5D-1,2,3-triazol-4-yl)benzoate (87a)



To a solution of alkynylzinc reagent **71f** (0.75 mmol) in DMF (1.5 mL) was added sodium azide (45 mg, 0.68 mmol), benzyl bromide (117 mg, 0.68 mmol) and copper iodide (13 mg, 10 mol%) under argon at 25 °C. The resulting solution was stirred at 25 °C for 7 h followed by the addition of CH_3COOD/D_2O (0.5 mL/0.5 mL) and stirring was continued for 30 min before quenched with saturated NH_4Cl. The extractions were performed with ethyl acetate and organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography (silica gel, isohexane/EtOAc = 2:1) to yield the title compound (190 mg, 91% yield) including *9% ethyl 2-(1-benzyl-5H-1,2,3-triazol-4-yl)benzoate*.

M.p. (°C): 44.3–45.9.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.82–7.78 (m, 1H), 7.78–7.75 (m, 1H), 7.52 (td, *J* = 7.6, 1.4 Hz, 1H), 7.42–7.34 (m, 4H), 7.33–7.30 (m, 2H), 5.57 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H).

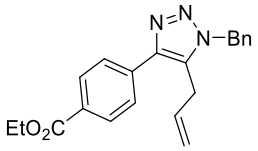
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.5, 146.2, 134.9, 131.4, 130.8, 130.3, 130.2, 129.7, 129.2, 128.9, 128.2, 128.1, 122.7, 61.4, 54.3, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1720, 1290, 1067, 764.

MS (EI, 70 eV): *m/z* (%) = 308 (M^+, 3), 279 (10), 251 (17), 91 (100).

HRMS (EI): *m/z* calc. for [$C_{18}H_{16}DN_3O_2$]: 308.1384; found: 308.1382 (M^+).

Ethyl 4-(5-allyl-1-benzyl-1H-1,2,3-triazol-4-yl)benzoate (87b)



To a solution of alkynylzinc reagent **71g** (0.50 M in DMF, 0.9 mL, 0.45 mmol), sodium azide (27 mg, 0.41 mmol), benzyl bromide (70 mg, 0.41 mmol) and copper iodide (8 mg, 0.04 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 7 h before the addition of allyl bromide (**79**; 54 mg, 0.45 mmol). The resulting solution was stirred for 1 h before quenched with sat. aq. NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with sat. aq. NaCl solution and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 2:1 to 1:1) afforded the title compound (125 mg, 87% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.10 (d, *J* = 8.1 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.39–7.29 (m, 3H), 7.22–7.18 (m, 2H), 5.82 (ddt, *J* = 16.3, 10.4, 5.2 Hz, 1H), 5.55 (d, *J* = 1.1 Hz, 2H), 5.17 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.91 (dd, *J* = 17.2, 1.9, Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.48 (d, *J* = 5.0 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

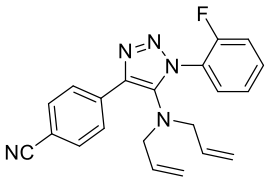
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 166.5, 145.0, 135.7, 134.8, 131.9, 131.3, 130.1, 129.8, 129.2, 128.6, 127.4, 126.9, 118.2, 61.2, 52.3, 27.2, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 1710, 1614, 1366, 1272, 1101.

MS (EI, 70 eV): *m/z* (%) = 347 (M+, 12), 299 (12), 298 (100), 91 (21).

HRMS (EI): *m/z* calc. for [$C_{21}H_{21}N_3O_2$]: 347.1634; found: 347.1628 (M^+).

4-(5-(Diallylamino)-1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl)benzonitrile (87c)



To a solution of alkynylzinc reagent **71h** (0.76 mmol) in DMF (1.5 mL) was added 1-azido-2-fluorobenzene (0.5 M in *t*butyl methyl ether, 1.38 mL, 0.69 mmol) and copper iodide (13 mg, 10 mol%) under argon at 25 °C. The resulting solution was stirred at 25 °C for 21 h followed by the addition of electrophile **89** (166 mg, 0.76 mmol) and continued strring for 1.5 h before quenched with saturated NH_4Cl. The extractions were performed with ethyl acetate and the combined organic layers were dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography (silica gel, isohexane/EtOAc = 2:1 to 1:1) to yield the title compound (170 mg, 69% yield).

M.p. (°C): 96.2–100.7.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.98–7.93 (m, 2H), 7.77–7.71 (m, 2H), 7.60–7.56 (m, 1H), 7.52–7.46 (m, 1H), 7.40–7.29 (m, 2H), 5.58 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 2H), 5.14–4.85 (m, 4H), 3.48 (dt, *J* = 6.5, 1.3 Hz, 4H).

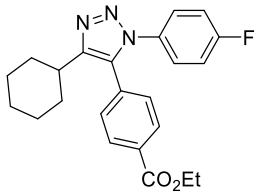
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 157.2 (d, *J* = 254.3 Hz), 143.3, 136.4, 135.8, 133.2, 132.2, 129.2, 127.6, 124.8, 124.6 (d, *J* = 12.6 Hz, 4H), 119.1 (d, *J* = 29.7 Hz), 119.0, 117.1 (d, *J* = 19.3 Hz), 111.2, 54.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3079, 2847, 2226, 1610, 1577, 1506, 1417, 1382, 1269, 1234, 1109, 981.

MS (EI, 70 eV): *m/z* (%) = 359 (M^+, 6.7), 331 (27), 330 (24), 316 (30), 290 (20), 236(11), 223 (100).

HRMS (EI): *m/z* calc. for [$C_{21}H_{18}FN_5$]: 359.1546; found: 359.1535 (M^+).

Ethyl 4-(4-cyclohexyl-1-(4-fluorophenyl)-1H-1,2,3-triazol-5-yl)benzoate (87d)



To a solution of alkynylzinc reagent **71d** (0.5 mmol) in DMF (1.0 mL) was added 1-azido-4-fluorobenzene (0.5 M in *t*butyl methyl ether, 0.91 mL, 0.46 mmol) and copper iodide (9 mg, 10 mol%) under argon at 25 °C. The resulting solution was stirred at 25 °C for 21 h followed by the addition of ethyl 4-iodobenzoate **41** (100 mg, 0.36 mmol), $Pd(dba)_2$ (6 mg, 2 mol%) and DavePhos (8 mg, 4 mol%). The reaction continued strring for 18 h at 50 °C before quenched with aq. sat. NH_4Cl solution. The extractions were performed with ethyl acetate and the combined organic layers were dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography (silica gel, isohexane/EtOAc = 5:1 to 1:1) to yield the title compound (101 mg, 72% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.08–8.02 (m, 2H), 7.26–7.23 (m, 2H), 7.23–7.20 (m, 2H), 7.07–7.02 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.65 (tt, *J* = 11.6, 3.5 Hz, 1H), 1.93–1.60 (m, 7H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.32–1.21 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.8, 162.4 (d, *J* = 250.0 Hz), 151.1, 132.7, 132.1 (d, *J* = 7.0 Hz), 131.0, 130.0, 129.7, 126.9 (d, *J* = 8.8 Hz), 116.4 (d, *J* = 23.0 Hz), 61.3, 34.9, 33.0, 26.5, 25.8, 14.3.

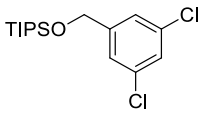
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2854, 1714, 1512, 1272, 1225, 1105.

MS (EI, 70 eV): *m/z* (%) = 365 (39), 336 (44), 322 (100), 294 (76), 292 (26), 249 (72), 248 (64), 202 (63), 135 (59).

HRMS (EI): *m/z* calc. for [$C_{23}H_{24}FN_3O_2$]: 393.1853; found: 392.1766 (M^+-H).

2.8 Synthesis of Carboxyamidotriazole (96)

((3,5-Dichlorobenzyl)oxy)triisopropylsilane (91)



In a 50 mL round-bottom flask with 3,5-dichlorobenzylalcohol **90** (1.06 g, 6 mmol) was dissolved in anhydrous THF (12 mL) followed the addition of *n*BuLi (2.55 M solution in hexane, 2.47 mL, 6.3 mmol) dropwise at -50 °C. The resulting solution was stirred at -50 °C for 10 min followed by the addition of DMAP (5 mol%) and TIPSCl (1.41 mL, 6.6 mmol). The reaction was stirred at 25 °C for 3 h before quenched quenched with aq. sat. NH_4Cl solution. The extractions were performed with ethyl acetate and the combined organic layers were dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography (silica gel, isohexane/EtOAc = 1:0 to 15:1) to yield the title compound (1.90 g, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.23 (s, 3H), 4.78 (s, 2H), 1.26–1.12 (m, 3H), 1.09 (s, 18H).

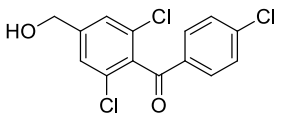
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 145.3, 134.9, 127.0, 124.2, 64.0, 18.1, 12.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944, 2866, 1593, 1572, 1462, 1430, 1122.

MS (EI, 70 eV): *m/z* (%) = 291 (40), 289 (58), 263 (24), 261 (37), 235 (22), 233 (35), 219 (30), 161 (62), 159 (100), 125 (37).

HRMS (EI): *m/z* calc. for [$C_{16}H_{26}Cl_2OSi$]: 332.1130; found: 332.0577 (M^+-*i*Pr).

(4-Chlorophenyl)(2,6-dichloro-4-(hydroxymethyl)phenyl)methanone (92)



In a 20 mL round-bottom flask with compound **91** (667 mg, 2 mmol) was dissolved in anhydrous THF (3.0 mL) followed the addition of $TMP_2Mg{\cdot}LiCl$ (2.2 mmol) at 0 °C dropwise. The resulting solution was stirred at 0 °C for 1.5 h then cooled down to -20 °C before the addition of $CuCN{\cdot}2LiCl$ (2.2 mmol) and 4-chlorobenzoyl chloride (0.22 mL, 1.66 mmol). The reaction mixture was warmed up slowly and stirred at 25 °C over night before quenched with aq. sat. NH_4Cl solution. The extractions were performed with ethyl acetate and the combined organic layers were dried over Na_2SO_4 followed by concentration to afford crude mixture which was run through a short plug of silica and used for next steps without further purification. The residue in THF (2 mL) was added TBAF (1.0 M solution in THF, 2.2 mL, 2.2 mmol) at 25 °C and stirred at 50 °C for 1.5 h and quenched with aq. sat. NH_4Cl solution. The extractions were performed with ethyl acetate and the combined organic layers were dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash

chromatography (silica gel, isohexane/EtOAc = 5:1 to 2:1) to yield the title compound (430 mg, 82% yield).

M.p. (°C): 142.5–144.5.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.75 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.39 (s, 2H), 4.75 (d, *J* = 5.5 Hz, 2H), 2.08 (t, *J* = 5.8 Hz, 1H).

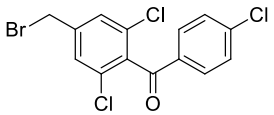
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.7, 145.0, 141.1, 136.1, 134.0, 132.1, 131.1, 129.5, 126.2, 63.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3413, 2927, 2866, 1671, 1586, 11550, 1399, 1270, 1091.

MS (EI, 70 eV): *m/z* (%) = 316 (21), 314 (M^+, 22), 205 (31), 203 (49), 141 (33), 139 (100).

HRMS (EI): *m/z* calc. for [$C_{14}H_9Cl_3O_2$]: 313.9668; found: 313.9662 (M^+).

(4-(Bromomethyl)-2,6-dichlorophenyl)(4-chlorophenyl)methanone (93)



To a solution of benzyl alcohol **92** (316 mg, 1.0 mmol) in THF (2.0 mL) was added phosphorus tribromide (0.1 mL, 1 mmol) under argon at 25 °C. The resulting solution was stirred at 25 °C for 18 h before quenched with aq. sat. $NaHCO_3$ solution. The extractions were performed with ethyl acetate and the combined organic layers were dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography (silica gel, isohexane/EtOAc = 20:1 to 15:1) to yield the title compound (354 mg, 94% yield).

M.p. (°C): 83.7–84.7.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.78–7.74 (m, 2H), 7.49–7.44 (m, 2H), 7.42 (s, 2H), 4.43 (s, 2H).

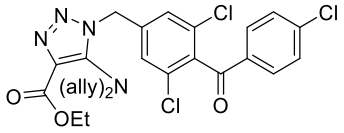
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 191.1, 141.4, 141.2, 137.1, 133.8, 132.3, 131.1, 129.6, 128.8, 30.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1676, 1588, 1548, 1398, 1268, 1235, 1160, 1093.

MS (EI, 70 eV): *m/z* (%) = 380 (24), 378 (38), 375 (M^+, 19), 301 (31), 299 (98), 297 (100), 271 (40), 139 (37).

HRMS (EI): *m/z* calc. for [$C_{14}H_8BrCl_3O$]: 375.8824; found: 375.8821 (M^+).

Ethyl 5-(diallylamino)-1-(3,5-dichloro-4-(4-chlorobenzoyl)benzyl)-1H-1,2,3-triazole-4-carboxylate (95)



To a solution of alkynylzinc reagent **71l** (0.74 mmol) in DMF (1.5 mL) was added benzyl bromide **93** (267 mg, 0.70 mmol), sodium azide (48 mg, 0.74 mmol) and copper iodide (16 mg, 10 mol%) successively under argon at 25 °C. The resulting solution was stirred at 25 °C for 18 h followed by the addition of electrophile **89** (127 mg, 0.58 mmol) and continued stirring for 2 h before quenched with aq. sat. NH_4Cl solution. The extractions were performed with ethyl acetate and the combined organic layers were dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography (silica gel, isohexane/EtOAc = 3:1 to 2:1) to yield the title compound (261 mg, 84% yield).

M.p. (°C): 125.8–127.2.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.70 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.26 (s, 2H), 5.60 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 2H), 5.45 (s, 2H), 5.20–5.01 (m, 4H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.69 (dd, *J* = 6.7, 1.2 Hz, 4H), 1.45 (t, *J* = 7.1 Hz, 3H).

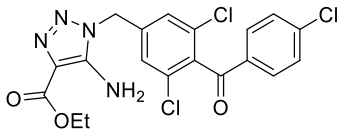
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.9, 161.1, 148.4, 141.3, 138.7, 137.2, 133.7, 133.5, 133.5, 132.6, 131.0, 129.6, 127.5, 119.7, 61.5, 56.4, 49.0, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3079, 2981, 1713, 1679, 1587, 1552, 1454, 1400, 1270, 1160.

MS (EI, 70 eV): *m/z* (%) = 532 (M^+, 0.28), 492 (16), 301 (16), 299 (51), 297 (50), 271 (39), 199 (28), 139 (46), 111 (23), 96 (38), 41 (100).

HRMS (EI): *m/z* calc. for [$C_{25}H_{23}Cl_3N_4O_3$]: 532.0836; found: 532.0836 (M^+).

Ethyl 5-amino-1-(3,5-dichloro-4-(4-chlorobenzoyl)benzyl)-1H-1,2,3-triazole-4-carboxylate



In a 10 mL round-bottom flask with triazole **95** (55 mg, 0.1 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) followed the addition of *N*,*N*-dimethylbarbituric acid (94 mg, 0.6 mmol) and tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.01 mmol). The resulting solution was stirred at 40 °C for 24 h and another batch of catalyst (12 mg, 0.01 mmol) was added. The reaction mixture was stirred 24 h at 40 °C before quenching with saturated NH_4Cl. The extractions were performed with ethyl acetate and organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography (silica gel, isohexane/EtOAc = 3:1 to 1:1) to yield title compound (41 mg, 91% yield).

M.p. (°C): 223.9-231.6

$_{1}$H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.72 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.21 (s, 2H), 5.42 (s, 2H), 5.16 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

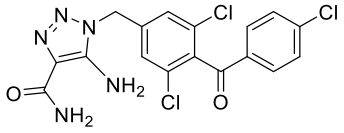
$_{13}$C-NMR (101 MHz, CDCl$_3$): δ / ppm = 191.0, 162.7, 145.8, 141.5, 137.6, 137.6, 133.6, 133.1, 131.1, 129.7, 126.9, 122.0, 61.1, 48.8, 14.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3452, 3324, 2982, 1681, 1632, 1588, 1514, 1401, 1272, 1093.

MS (EI, 70 eV): *m/z* (%) = 454 (20), 452 (M^+, 26), 382 (31), 381 (22), 380 (35), 379 (46), 377 (41), 353 (67), 352 (28), 351 (71), 277 (50), 262 (42), 207 (26), 199 (51), 139 (100).

HRMS (EI): *m/z* calc. for [$C_{19}H_{15}Cl_3N_4O_3$]: 452.0210; found: 452.0202 (M^+).

5-Amino-1-(3,5-dichloro-4-(4-chlorobenzoyl)benzyl)-1H-1,2,3-triazole-4-carboxamide (96)



To a stirred solution of ethyl ester triazole (30 mg, 0.07 mmol) in methanol (1.0 mL) at 0 °C in a microwave vial was added magnesium nitride (34 mg, 0.34 mmol) in a single portion. The vial was sealed immediately and allowed to warm to room temperature. After 1 hour the reaction was heated at 80 °C for 24 h. The reaction was allowed to cool to room temperature and diluted with chloroform (5 mL) and water (5 mL). The aqueous layer was neutralised with 2N HCl and the organic layer separated. The aqueous layer was further extracted with chloroform (2 x 5 mL) and the organic layers combined, dried with Na_2SO_4 and concentrated *in vacuo* to afford the title compound (29 mg, 98% yield).

$_{1}$H-NMR (400 MHz, DMSO-*d*$_6$): δ / ppm = 7.80–7.72 (m, 2H), 7.70–7.60 (m, 2H), 7.46 (s, 2H), 6.51 (s, 2H), 5.52 (s, 2H).

$_{13}$C-NMR (101 MHz DMSO-*d*$_6$): δ / ppm = 190.7, 164.1, 144.9, 140.6, 140.1, 135.7, 133.2, 131.0, 130.7, 129.8, 127.5, 121.8, 47.0.

MS (EI, 70 eV): *m/z* (%) = 427 (27), 426 (14), 425 (66), 423 (M^+, 61), 379 (60), 377 (52), 271 (31), 199 (44), 141 (36), 139 (100).

HRMS (EI): *m/z* calc. for [$C_{17}H_{12}Cl_3N_5O_2$]: 423.0057; found: 423.0042 (M^+).

3 Preparation and Reactivity of Ethynylzinc Pivalate and Dipivaloyoxyzinc acetylene

3.1 Preparation of Zinc pivalates

Preparation of mono-pivaloyloxyzinc acetylide (98)

A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with a solution of ethnynyl magnesium bromide in THF (30 mL, 0.5 M, 15 mmol) and cooled to -20 °C. A solution of $ZnCl_2$ in THF (16.5 mL, 1 M, 16.5 mmol) was added dropwise at -20 °C and the reaction was stirred for 2 h at room temperature. To that reaction mixture was added a freshly prepared solution of $Mg(OPiv)_2$[232] in THF (30 mL, 0.5 M, 15 mmol) at room temperature and stirred for another 30 min. The solvent was removed *in vacuo* for at least 6 h and the dried solid ethynylzinc pivalate (**1**) was obtained as a white-yellowish powder in 98% yield.[98]

Preparation of bis-pivaloyloxyzinc acetylide (99)

A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with a solution of ethyl magnesium bromide in THF (16.5 mL, 1 M, 16.5 mmol) and heated to 40 °C. A solution of ethnynyl magnesium bromide in THF (30 mL, 0.5 M, 15 mmol) was added and the reaction was stirred for 12 h. The reaction mixture was cooled to -20 °C and a solution of $ZnCl_2$ in THF (16.5 mL, 1 M, 16.5 mmol) was added dropwise at that temperature. After stirring the reaction mixture for 2 h at room temperature a freshly prepared solution of $Mg(OPiv)$**Error! Bookmark not defined.** in THF (30 mL, 0 .5 M, 15 mmol) was added dropwise at room temperature and the reaction was stirred for another 30 min. The solvent was removed *in vacuo* for at least 6 h and the dried solid dipivaloyoxyzinc acetylene (**2)** was obtained as a white powder in 93% yield.[98]

3.2 Typical Procedures (TP)

TP4: Typical procedure for the preparation of arylacetylenes using mono-pivaloyloxyzinc acetylide (98)

A dry and argon-flushed flask equipped with a magnetic stirring bar and a septum was charged with the ethynylzinc pivalate (0.75 mmol), $Pd(PPh_3)_4$ (1 mol%) and THF (2 mL). The electrophile (0.5 mmol) was added and the resulting solution was stirred at 25 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers

[98] Determined by titration with iodine.[66]

were washed with sat. aq. NaCl solution (3 mL) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. Purification via flash column chromatography yielded the desired product.

TP5: Typical procedure for a one-pot synthesis of non-symmetrical bis-arylated acetylenes

A dry and argon-flushed flask equipped with a magnetic stirring bar and a septum was charged with the ethynylzinc pivalate (0.375 mmol), $Pd(PPh_3)_2Cl_2$ (2 mol%) and THF (3 mL). The first electrophile of type **100** (0.25 mmol) was added and the resulting solution was stirred at 25 °C for 1 h. To that reaction mixture the second electrophileof type **100** (0.3 mmol), CuI (10 mol%) and NEt_3 (0.5 mmol) were added at 25 °C and stirred for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with sat. aq. NaCl solution (3 mL) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. Purification via flash column chromatography yielded the desired product.

TP6: Typical procedure for the preparation of symmetrical bis-arylated acetylenes using bis-pivaloyloxyzinc acetylide (99) and aryl iodides

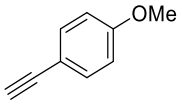
A dry and argon-flushed flask equipped with a magnetic stirring bar and a septum was charged with the bis-zinc acetylide pivalate (0.25 mmol), $Pd(dba)_2$ (7 mg, 0.0125 mmol), SPhos (10 mg, 0.025 mmol) and DMSO (2 mL). The aryl iodide (0.55 mmol) was added and the resulting solution was stirred at 25 °C for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with sat. aq. NaCl solution (3 mL), water (2x 10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo*. Purification *via* flash column chromatography yielded the desired product.

TP7: Typical procedure for the preparation of symmetrical bis-arylated acetylenes using bis-pivaloyloxyzinc acetylide (99) and aryl bromides

A dry and argon-flushed flask equipped with a magnetic stirring bar and a septum was charged with the bis-pivaloyloxyzinc acetylide (0.25 mmol), $Pd(dba)_2$ (5 mol%), Xantphos[74] (5%) and DMSO (2 mL). The aryl bromide (0.55 mmol) was added and the resulting solution was stirred at 25 °C for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with sat. aq. NaCl solution (3 mL), water (2x 10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. Purification via flash column chromatography yielded the desired product.

3.3 Preparation of the aryl acetylenes (101)

1-Ethynyl-4-methoxybenzene (101a)



According to **TP4** 1-iodo-4-methoxybenzene (**100a**; 117 mg, 0.5 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.75 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 0.05 mmol) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 19:1) afforded the title compound as a yellowish oil (65 mg, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.46 (d, *J* = 8.8, 2H), 6.86 (s, 1H), 3.84 (s, 3H), 3.02 (s, 1H).

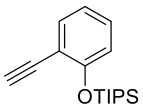
^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 159.9, 133.5, 113.9, 83.6, 75.7, 55.2.

MS (EI, 70 eV): *m/z* (%) 132 (100), 117 (31), 89 (60), 63 (10).

HRMS (EI): *m/z* calc. for [C_9H_8O]: 132.0575; found: 132.0567 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[99]

(2-Ethynylphenoxy)triisopropylsilane (101b)



According to **TP4** (2-iodophenoxy)triisopropylsilane (**100b**; 188 mg, 0.5 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.75 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 0.05 mmol) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, 100% isohexane) afforded the title compound as a red oil (118 mg, 86% yield).

1H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.44 (dd, *J* = 7.6, 1.7, 1H), 7.22 (td, *J* = 7.8, 1.7, 1H), 6.95–6.81 (m, 2H), 3.21 (s, 1H), 1.41–1.25 (m, 3H), 1.15 (d, *J* = 7.4, 19H).

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 157.6, 134.0, 129.9, 120.7, 119.1, 114.3, 81.1, 80.8, 18.0, 13.0.

MS (EI, 70 eV): *m/z* (%) = 231 (M+, 32), 189 (35), 179 (34), 161 (100), 115 (40), 91 (18).

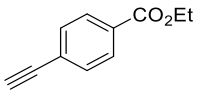
HRMS (EI): *m/z* calc. for [$C_{17}H_{26}OSi$]: 274.1753; found: 272.1590 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[100]

[99] A. Rosiak, W. Frey, J. Christoffers, *Eur. J. Org.Chem.* **2006**, *17*, 4044.

[100] M. D. Morin; Y. Wang, B. T. Jones, L. Su, M. M. R. P. Surakattula, M. Berger, H. Huang, E. K. Beutler, H. Zhang, B. Beutler, D. L. Boger, *J. Med. Chem.* **2016**, *59*, 4812.

Ethyl 4-ethynylbenzoate (101c)



According to **TP4** ethyl 4-iodobenzoate (**100c**; 138 mg, 0.5 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.75 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 0.05 mmol) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 19:1) afforded the title compound as a yellowish oil (82 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 8.02 (d, *J* = 8.2, 2H), 7.57 (d, *J* = 8.1, 2H), 4.40 (q, *J* = 7.1, 2H), 3.25 (s, 1H), 1.42 (t, *J* = 7.1, 3H).

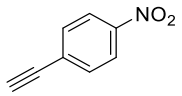
^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 165.9, 132.0, 130.4, 129.4, 126.6, 82.8, 79.9, 61.2, 14.3.

MS (EI, 70 eV): *m/z* (%) = 174 (5), 146 (51), 129 (100), 101 (19), 75 (11)

HRMS (EI): *m/z* calc. for [$C_{11}H_{10}O_2$]: 174.0681; found: 174.0669 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[101]

1-Ethynyl-4-nitrobenzene (101d)



According to **TP4** iodo-4-nitrobenzene (**100d**, 125 mg, 0.5 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.75 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 1 mol%) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 100:1) afforded the title compound as a yellowish oil (59 mg, 80% yield).

^{1}H NMR (400 MHz $CDCl_3$) δ / ppm = 8.20 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 3.36 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm: 132.9, 128.8, 123.5, 82.0, 81.5.

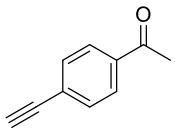
MS (EI, 70 eV): *m/z* (%) = 147 (100), 129 (28), 117 (76), 101 (21), 89 (65), 75 (51), 74 (17).

HRMS (EI): *m/z* calc. for [$C_8H_5O_2N$]: 147.0320; found: 147.0314 (M^+).

The ^{1}H and ^{13}C NMR data are in accordance with those reported in the literature.[102]

[101] Y. Tang, K. Ogawa, G. P. Lopez, K. S. Schanze, D. G. Whitten, *Langmuir* **2009**, *25*, 21.
[102] Y. Wang, B. Huang, S. Sheng, M. Cai, *J. Chem. Res.* **2007**, *12*, 728.

1-(4-Ethynylphenyl) ethan-1-one (101e)



According to **TP4** (4-iodophenyl)ethan-1-one (**100e**; 123 mg, 0.5 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.75 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 0.05 mmol) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 50:1) afforded the title compound as a yellowish oil (68 mg, 95% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ / ppm = 7.91 (d, *J* = 7.8, 2H), 7.57 (d, *J* = 7.8, 2H), 7.26 (s, 1H), 3.25 (d, *J* = 0.8, 1H), 2.61 (s, 3H).

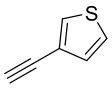
^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm: 197.2, 136.4, 132.2, 128.7, 126.8, 82.7, 80.3, 26.6.

MS (70 eV, EI) m/z (%): 144 (12), 130 (10), 129.04 (18), 129.03 (100), 101 (11), 75 (9),

HRMS (EI): *m/z* calc. for [$C_{10}H_8O$]: 144.0575; found: 144.0568 (M^+).

The ^{1}H and ^{13}C NMR data are in accordance with those reported in the literature.[102]

3-Ethynylthiophene (101f)



According to **TP4** 3-iodo-thiophene (**100f**; 105 mg, 0.5 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.75 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 0.05 mmol) in THF (2 mL) at 25 °C The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, 100% isohexane) afforded the title compound as a yellowish oil (43 mg, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.50 (dd, *J* = 3.0, 1.2, 1H), 7.27–7.23 (m, 1H), 7.13 (dd, *J* = 5.1, 1.2, 1H), 3.02 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 130.0, 130.0, 125.3, 121.2, 78.8, 76.9.

MS (70 eV, EI) m/z (%): 108 (100), 81 (13), 68 (5).

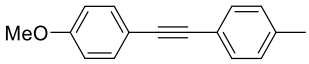
HRMS (EI): *m/z* calc. for [$C_{10}H_8O$]: 108.0034; found: 108.0027 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[103]

[103] M. Beshai, B. Dhudshia, R. Mills, A. N. Thadani, *Tetrahedron Lett.* **2008**, *49*, 6794.

3.4 Preparation of Asymmetrical Bis-arylated Alkynes (102)

1-Methoxy-4-(p-tolylethynyl)benzene (102a)



According to **TP5** 1-iodo-4-methoxybenzene (**100a**; 59 mg, 0.25 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.375 mmol) and $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. To that reaction mixture 4-iodo-toluene (**100g**; 65 mg, 0.3 mmol), CuI (4.8 mg, 0.025 mmol) and NEt_3 (70 µl, 0.5 mmol) were added at 25 °C and stirred for 12 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 19:1) afforded the title compound as a yellowish oil (48 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.48–7.41 (m, 2H), 7.39 (d, *J* = 8.1, 2H), 7.16–7.07 (m, 2H), 6.91–6.76 (m, 2H), 3.81 (s, 3H), 2.35 (s, 3H).

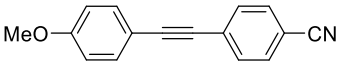
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 159.5, 138.0, 132.9, 131.3, 129.0, 120.5, 115.6, 113.9, 88.6, 88.2, 55.3, 21.4.

MS (70 eV, EI) m/z (%): 222 (100), 207 (65), 179, (42), 178 (66), 152 (36), 43 (29).

HRMS (EI): *m/z* calc. for [$C_{16}H_{14}O$]: 222.1045; found: 222.1039 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[104]

4-((4-Methoxyphenyl)ethynyl)benzonitrile (102b)



According to **TP5** 1-iodo-4-methoxybenzene (**100a**; 59 mg, 0.25 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.375 mmol) and $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. To that reaction mixture 4-iodo-benzonitrile (**100h**) (69 mg, 0.3 mmol), CuI (4.8 mg, 0.025 mmol) and NEt_3 (70 µl, 0.5 mmol) were added at 25 °C and stirred for 12 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 10:1) afforded the title compound as a yellowish oil (52 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.67–7.57 (m, 4H), 7.54–7.49 (m, 2H), 6.96–6.89 (m, 2H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 160.3, 134.1, 133.4, 132.0, 131.9, 128.7, 118.7, 114.2, 111.1, 94.1, 86.7, 55.4.

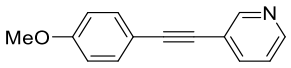
MS (70 eV, EI) m/z (%): 233 (100), 218 (59), 207 (18), 190 (73), 163 (20), 128 (11).

HRMS (EI): *m/z* calc. for [$C_{16}H_{11}ON$]: 233.0841; found: 233.0836 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[105]

[104] K. G. Thakur, G. Sekar, *Synthesis* **2009**, *16*, 2785.
[105] M. L. N. Rao, D. N. Jadhav, Dasgupta, P.; *Org. Lett.* **2010**, *9*, 2048.

3-((4-Methoxyphenyl)ethynyl)pyridine (102c)



According to **TP5** 1-iodo-4-methoxybenzene (**100a**; 59 mg, 0.25 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.375 mmol) and $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. To that reaction mixture 3-iodo-pyridine (**100i;** 62 mg, 0.3 mmol), CuI (4.8 mg, 0.0025 mmol) and NEt_3 (70 µl, 0.5 mmol) were added at 25 °C and stirred for 12 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 2:1) afforded the title compound as a yellowish oil (42 mg, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 8.73 (s, 1H), 8.51 (d, *J* = 4.9, 1H), 7.76 (dt, *J* = 7.9, 2.0, 1H), 7.51–7.43 (m, 2H), 7.26 (dd, *J* = 5.0, 0.9, 1H), 6.88 (d, *J* = 8.9, 2H), 3.82 (s, 3H).

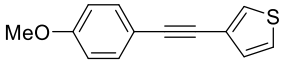
^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 160.0, 152.1, 148.2, 138.2, 133.2, 122.9, 114.6, 114.1, 92.7, 84.7, 77.3, 77.2, 77.0, 76.7, 55.3.

MS (70 eV, EI) m/z (%): 209 (100), 194 (60), 166 (35), 149 (40), 113 (8).

HRMS (EI): *m/z* calc. for [$C_{14}H_{11}ON$]: 209.0841; found: 209.0836 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature[104]

3-((4-Methoxyphenyl)ethynyl)thiophene (102d)



According to **TP5** 1-iodo-4-methoxybenzene (**100a**; 59 mg, 0.25 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.375 mmol) and $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. To that reaction mixture 3-iodo-thiophene (**100f**; 63 mg, 0.3 mmol), CuI (4.8 mg, 0.0025 mmol) and NEt_3 (70 µl, 0.5 mmol) were added at 25 °C and stirred for 12 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 19:1) afforded the title compound as a white solid (40 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.46 (dd, *J* = 3.0, 1.2, 1H), 7.45–7.40 (m, 2H), 7.27 (dd, *J* = 5.0, 3.0, 1H), 7.16 (dd, *J* = 5.0, 1.2, 1H), 6.90–6.81 (m, 2H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 159.6, 132.9, 129.8, 128.0, 125.2, 122.6, 115.3, 114.0, 88.7, 83.1, 55.3.

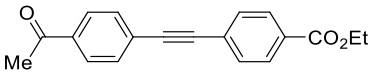
MS (70 eV, EI) m/z (%): 214 (100), 199 (85), 171 (50), 155 (12), 127 (9).

HRMS (EI): *m/z* calc. for [$C_{13}H_{10}OS$]: 214.0452; found: 214.0448 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[106]

[106] B. G. Van den Hoven, H. J. Alper, *Org. Chem.* **1999**, *64*, 9640.

Ethyl 4-((4-acetylphenyl)ethynyl)benzoate (102e)



According to **TP5** 1-(4-iodophenyl)ethan-1-one (**100e**; 59 mg, 0.25 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.375 mmol) and $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. To that reaction mixture ethyl 4-iodobenzoate (**100c**) (83 mg, 0.3 mmol), CuI (4.8 mg, 0.025 mmol) and NEt_3 (70 µl, 0.5 mmol) were added at 25 °C and stirred for 12 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1 to 3:1) afforded the title compound as a yellowish solid (47 mg, 64% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ / ppm = 8.07 – 8.03 (m, 2H), 7.97 – 7.94 (m, 2H), 7.65 – 7.59 (m, 4H), 4.39 (q, *J* = 7.1, 2H), 2.62 (s, 3H), 1.41 (t, *J* = 7.2, 3H).

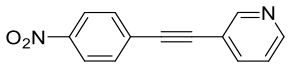
^{13}C NMR (150 MHz, $CDCl_3$) δ / ppm = 197.3, 166.0, 136.6, 131.8, 131.6, 130.3, 129.5, 128.3, 127.6, 127.2, 91.8, 91.2, 61.2, 26.7, 14.3.

MS (70 eV, EI) m/z (%): 292 (30), 249 (43), 247 (26), 204 (18), 176 (100), 165 (17), 150 (32), 116 (18), 88 (20).

HRMS (EI): *m/z* calc. for [$C_{19}H_{16}O_3$]: 292.1099; found: 292.1090 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[107]

3-((4-Nitrophenyl)ethynyl)pyridine (102f)



According to **TP5** 1-iodo-4-nitrobenzene (**100d**; 62 mg, 0.25 mmol) was added to a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.375 mmol) and $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol) in THF (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. To that reaction mixture 3-iodopyridine (**100i**) (62 mg, 0.3 mmol), CuI (4.8 mg, 0.025 mmol) and NEt_3 (70 µl, 0.5 mmol) were added at 25 °C and stirred for 12 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 3:1) afforded the title compound as a yellowish solid (42 mg, 75% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ / ppm = 8.81 (s, 1H), 8.62 (s, 1H), 8.28–8.22 (m, 2H), 7.85 (dt, *J* = 7.9, 1.9, 1H), 7.74–7.66 (m, 2H), 7.34 (dd, *J* = 7.9, 4.8, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ / ppm = 152.4, 149.5, 147.4, 138.7, 132.6, 132.4, 129.4, 123.8, 123.7, 90.9, 90.5, 77.2, 77.0, 76.8.

MS (70 eV, EI) m/z (%): 224 (100), 194 (41), 177 (32), 166 (32), 151 (32), 150 (39), 139 (25).

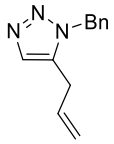
HRMS (EI): *m/z* calc. for [$C_{13}H_8O_2N_2$]: 224.0586; found: 224.0579 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[108]

[107] C. He, J. Ke, H. Xu, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 1527.
[108] G. Chelucci, F. Capitta, S. Baldino, *Tetrahedron* **2008**, *64*, 10250.

3.5 Preparation of 1,5-disubstituted 1,2,3-triazoles (105)

5-Allyl-1-benzyl-1H-1,2,3-triazole (105a)



To a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.325 mmol) in DMF (1.5 mL) was added sodium azide (16 mg, 0.25 mmol), benzyl bromide (**83**; mg, 0.25 mmol) and copper iodide (48 mg, 0.25 mmol) under argon at 25 °C. The reaction mixture was stirred at 25 °C for 12 h before the addition of allyl bromide (63 mg, 0.625 mmol). The resulting solution was stirred for 1 h before quenched with sat. aq. NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with sat. aq. NaCl solution, water (2x 10 mL) and dried over Mg_2SO_4. After filtration, the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 7:3) afforded the title compound as a yellowish liquid (25 mg, 49% yield).

$_1$H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.51 (s, 1H), 7.40–7.29 (m, 3H), 7.17–7.10 (m, 2H), 5.79 (ddt, *J* = 16.5, 10.1, 6.3, 1H), 5.52 (s, 2H), 5.16 (dq, *J* = 10.1, 1.4, 1H), 5.05 (dq, *J* = 17.0, 1.6, 1H), 3.27 (dq, *J* = 6.3, 1.4, 2H).

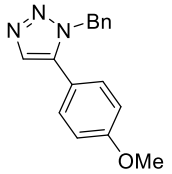
$_{13}$C NMR (100 MHz, $CDCl_3$) δ / ppm = 134.9, 134.8, 133.4, 132.1, 129.0, 128.3, 127.1, 118.2, 77.4, 77.1, 76.7, 51.7, 27.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 1641, 1548, 1455, 1359, 1236, 1095, 985, 921, 826, 714, 694.

MS (EI, 70 eV): *m/z* (%) = 170 (53), 117 (14), 91 (100), 65 (11).

HRMS (EI): *m/z* calc. for [$C_{12}H_{13}N_3$]: 199.1109 found: 199.1100 (M^+).

1-Benzyl-5-(4-methoxyphenyl)-1H-1,2,3-triazole (105b)



To a solution of mono-pivaloyloxyzinc acetylide (**99**; 0.325 mmol) in DMF (1.5 mL) was added sodium azide (16 mg, 0.25 mmol), benzyl bromide (43 mg, 0.25 mmol) and copper iodide (48 mg, 0.25 mmol) under argon at 25 °C. The reaction mixture was stirred at 25 °C for 12 h followed by the addition of ethyl 4-iodoanisole (**100a**; 70 mg, 0.30 mmol), $Pd(Cl_2(PPh_3)_2$ (9 mg, 0.005 mmol). The reaction continued stirring for 12 h at 50 °C before quenched with aq. sat. NH_4Cl solution. The extractions were performed with ethyl acetate (2 x 3 mL), washed with water (2 x 10 mL) the combined organic layers were dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified

by flash chromatography (silica gel, isohexane/EtOAc = 2:1) to yield the title compound as colorless oil (54 mg, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.72 (s, 1H), 7.36 – 7.29 (m, 3H), 7.23 – 7.15 (m, 2H), 7.14 – 7.08 (m, 2H), 6.98 – 6.91 (m, 2H), 5.55 (s, 2H), 3.86 (s, 3H).

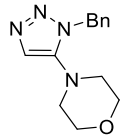
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 160.5, 138.0, 135.7, 133.1, 130.3, 128.8, 128.1, 127.1, 119.0, 114.4, 77.3, 77.0, 76.7, 55.4, 51.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936, 2836, 1613, 1495, 1454, 1249, 1177, 1020, 828, 717.

MS (EI, 70 eV): *m/z* (%) = 265 (15), 236 (25), 207 (65), 146 (81), 119 (19), 104 (31), 91 (100), 65 (15).

HRMS (EI): *m/z* calc. for [$C_{16}H_{15}N_3O$]: 265.1215; found: 265.1208 (M^+-H).

4-(1-Benzyl-1H-1,2,3-triazol-5-yl)morpholine (105c)



To a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.325 mmol) in DMF (1.5 mL) was added sodium azide (16 mg, 0.25 mmol), benzyl bromide (43 mg, 0.25 mmol) and copper iodide (48 mg, 0.25 mmol) under argon at 25 °C. The reaction mixture was stirred at 25 °C for 12 h before the addition of morpholino benzoate[42] (**104a**; 62 mg, 0.3 mmol). The resulting solution was stirred for 1 h before quenched with sat. aq. NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with sat. aq. NaCl solution, water (2x 10 mL) and dried over Mg_2SO_4. After filtration, the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 1:4) afforded the title compound as white solid (45 mg, 74% yield).

M.p. (°C): 80.3 – 82.1.

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.41 (s, 1H), 7.40–7.30 (m, 3H), 7.28–7.24 (m, 2H), 5.46 (s, 2H), 3.81–3.71 (m, 4H), 2.88–2.75 (m, 4H).

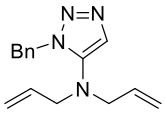
^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 147.0, 135.4, 128.9, 128.2, 127.4, 123.7, 66.6, 52.7, 50.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2852, 1555, 1452, 1261, 1237, 1114, 981, 913, 730, 695.

MS (EI, 70 eV): *m/z* (%) = 244 (43), 185 (11), 157 (25), 130 (10), 91 (100).

HRMS (EI): *m/z* calc. for [$C_{13}H_{16}ON_4$]: 244.1324 found: 244.1320 (M^+).

N,N-diallyl-1-benzyl-1H-1,2,3-triazol-5-amine (105d)



To a solution of mono-pivaloyloxyzinc acetylide (**98**; 0.325 mmol) in DMF (1.5 mL) was added sodium azide (16 mg, 0.25 mmol), benzyl bromide (43 mg, 0.25 mmol) and copper iodide (48 mg, 0.25 mmol) under argon at 25 °C. The reaction mixture was stirred at 25 °C for 12 h before the addition of N,N-diallyl-O-benzoylhydroxylamine[42] (**89b**; 54 mg, 0.3 mmol). The resulting solution was stirred for 1 h before quenched with sat. aq. NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with sat. aq. NaCl solution, water (2x 10 mL) and dried over Mg_2SO_4. After filtration, the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 2:1) afforded the title compound as a white solid (32 mg, 51% yield).

M.p. (°C): 84.2 – 86.3

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.36 (s, 1H), 7.38–7.30 (m, 2H), 7.30–7.23 (m, 3H), 5.68 (ddt, *J* = 16.7, 10.3, 6.2, 2H), 5.44 (s, 2H), 5.19–5.08 (m, 4H), 3.45 (dt, *J* = 6.3, 1.4, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 145.8, 135.5, 133.0, 128.7, 128.1, 127.4, 125.6, 118.9, 77.3, 77.0, 76.7, 56.3, 50.2.

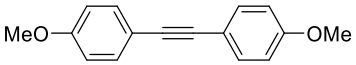
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2925, 2848, 1552, 1455, 1232, 991, 923, 726.

MS (EI, 70 eV): *m/z* (%) = 225 (22), 211 (10), 183 (11), 135 (25), 91 (100).

HRMS (EI): *m/z* calc. for [$C_{13}H_{16}ON_4$]: 254.1531 found: 254.1527 (M^+).

3.6 Preparation of symmetrical bis-arylated alkynes 106)

1,2-Bis(4-methoxyphenyl)ethyne (106a)



According to **TP6**, 1-iodo-4-methoxybenzene (**100**; 128 mg, 0.55 mmol) was added to a solution of bis-pivaloyloxyzinc acetylide (**99**; 0.25 mmol) and $Pd(dba)_2$ (7 mg, 0.0125 mmol), SPhos (10 mg, 0.025 mmol) in DMSO (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 50:1) afforded the title compound as a white solid (58 mg, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.47 (d, *J* = 8.8, 1H), 6.89 (d, *J* = 8.8, 1H), 3.85 (s, 2H).

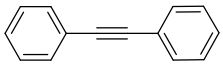
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 159.4, 132.9, 115.7, 114.0, 87.9, 55.3.

MS (EI, 70 eV): *m/z* (%) = 238 (100), 223 (89), 195 (28), 152 (24).

HRMS (EI): *m/z* calc. for [$C_{16}H_{14}O_2$]: 238.0994; found: 238.0986 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[105]

1,2-Diphenylethyne (106b)



According to **TP6**, iodotoluene (**100j;** (111 mg, 0.55 mmol) was added to a solution of bis-pivaloyloxyzinc acetylide (**99**; 0.25 mmol) and $Pd(dba)_2$ (7 mg, 0.0125 mmol), SPhos (10 mg, 0.025 mmol) in DMSO (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, 100% isohexane) afforded the title compound as a white solid (41 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.61–7.51 (m, 2H), 7.43–7.30 (m, 8H).

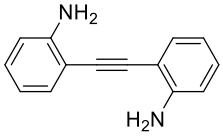
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 131.6, 128.4, 123.3, 89.4.

MS (70 eV, EI) m/z (%): 179 (15), 178 (100), 177 (7), 176 (24), 152 (12), 151 (5), 150 (6).

HRMS (EI): *m/z* calc. for [$C_{14}H_{10}$]: 178.0783; found: 178.0776 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[109]

2,2'-(Ethyne-1,2-diyl)dianiline (106c)



According to **TP6**, 2-iodoaniline (**100k**; 113 mg, 0.55 mmol) was added to a solution of bis-pivaloyloxyzinc acetylide (**99**; 0.25 mmol) and $Pd(dba)_2$ (7 mg, 0.0125 mmol), SPhos (10 mg, 0.025 mmol) in DMSO (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 2:1) afforded the title compound as a white solid (48 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.42–7.34 (m, 2H), 7.17 (m, *J* = 8.2, 7.3, 1.6, 2H), 6.80–6.69 (m, 4H), 4.29 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 147.6, 132.0, 129.7, 118.0, 114.4, 108.1, 91.1.

MS (70 eV, EI) m/z (%): 208 (100), 207 (47), 180 (12), 104 (7), 90 (5).

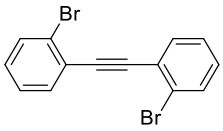
HRMS (EI): *m/z* calc. for [$C_{14}H_{12}N_2$]: 208.1000; found: 208.0997 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[110]

[109] Y. Yoshida, K. Nogi, H. Yorimitsu, *Synlett* **2017**, *28*, 2561.

[110] A. Andranova, F. Szydlo, F. Teply, M. Tobrmanova, A. Volot, I. G. Stara, I. Stary, I. Rulisek, D. Saman, J. Cvacka, P. Fiedler, P. Voitsek; *Collect. Czech. Chem. Commun* **2009**, *74*, 189.

1,2-Bis(2-bromophenyl)ethyne (106d)



According to **TP6**, 1-bromo-2-iodobenzene (**100l**; 155 mg, 0.55 mmol) was added to a bis-pivaloyloxyzinc acetylide (**99**; 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.0125 mmol) and SPhos (10 mg, 0.025 mmol) in DMSO (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 100:1) afforded the title compound as a white solid (62 mg, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.65 (ddd, *J* = 7.6, 3.9, 1.5, 4H), 7.34 (td, *J* = 7.6, 1.2, 2H), 7.26–7.20 (m, 2H).

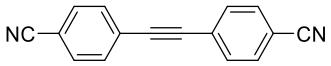
^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 133.7, 132.6, 129.8, 127.1, 125.6, 125.2, 92.3.

MS (70 eV, EI) m/z (%): 335 (22), 176 (100), 174 (13) 150 (20) 88 (19).

HRMS (EI): *m/z* calc. for [$C_{14}H_8Br_2$]: 333.8993; found: 333.8995 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[111]

4,4'-(ethyne-1,2-diyl)dibenzonitrile (106e)



According to **TP3**, 4-iodobenzonitrile (**100h**; 99 mg, 0.55 mmol) was added to a solution bis-pivaloyloxyzinc acetylide (**99**; 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.0125 mmol) and SPhos (10 mg, 0.025 mmol) in DMSO (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 100:1) afforded the title compound as a white solid (50 mg, 84% yield).

^{1}H NMR (400 MHz, CDCl) δ / ppm = 7.69–7.57 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 132.2, 132.2, 127.0, 118.2, 112.4, 91.5.

MS (70 eV, EI) m/z (%): 228 (100), 201 (12), 151 (8), 98 (7), 74 (8).

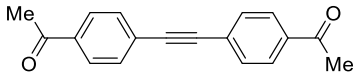
HRMS (EI): *m/z* calc. for [$C_{16}H_8N_2$]: 228.0687; found: 228.0681 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[112]

[111] I. V. Alabugin,; K. Gilmore, S. Patil, M. Manoharan, S. V. Kovalenko, R. J. Clark, I. Ghiviriga, *J. Am. Chem. Soc.* **2008**, *130*, 11535.

[112] L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948.

1,1'-(Ethyne-1,2-diylbis(4,1-phenylene))bis(ethan-1-one) (106f)



According to **TP6**, 1-(4-iodophenyl)ethan-1-one (**100e**; 135 mg, 0.55 mmol) was added to a solution of bis-pivaloyloxyzinc acetylide (**99**; 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.025 mmol) and SPhos (10 mg, 0.025 mmol) in DMSO (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a white solid (62 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 8.02–7.93 (m, 4H), 7.71–7.61 (m, 4H), 2.65 (s, 6H).

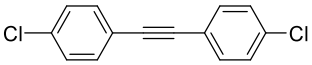
^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 197.3, 136.6, 131.9, 128.3, 127.5, 91.7, 26.7.

MS (70 eV, EI) m/z (%): 263 (9), 262 (46), 248 (19), 247 (100), 219 (10), 204 (13), 176 (24), 150 (8).

HRMS (EI): *m/z* calc. for [$C_{18}H_{14}O_2$]: 262.0994; found: 262.0987 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[113]

1,2-Bis(4-chlorophenyl)ethyne (106g)



According to **TP7**, 1-bromo-4-chlorobenzene (**75d**; 135 mg, 0.55 mmol) was added to a solution of bis-pivaloyloxyzinc acetylide (**2**; 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.025 mmol) and Xantphos (7 mg, 0.0125 mmol) in DMSO (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, 100% isohexane) afforded the title compound as a white solid (62 mg, 95% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ / ppm = 7.52–7.44 (m, 4H), 7.39–7.32 (m, 4H).

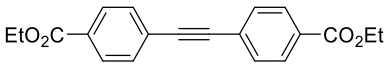
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 134.5, 132.8, 128.8, 121.4, 89.2.

MS (70 eV, EI) m/z (%): 247 (63), 245 (100), 176 (59) 150 (11), 98 (3).

HRMS (EI): *m/z* calc. for [$C_{14}H_8Cl_2$]: 246.0003; found: 245.9996 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[112]

Diethyl 4,4'-(ethyne-1,2-diyl)dibenzoate (106h)



According to **TP7**, ethyl 4-bromobenzoate (**75c**;135 mg, 0.55 mmol) was added to a solution of bis-pivaloyloxyzinc acetylide (**99**; 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.025 mmol) and Xantphos (7 mg, 0.0125 mmol) in DMSO (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a white solid (72 mg, 88% yield).

[113] J. Heppekausen, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2010,** *132,* 11053**.**

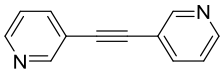
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 8.07–7.93 (m, 2H), 7.66–7.53 (m, 2H), 4.38 (q, *J* = 7.1, 2H), 1.39 (t, *J* = 7.1, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 165.9, 131.5, 130.3, 129.5, 127.2, 91.3, 61.2, 14.3.

MS (70 eV, EI) m/z (%): (%): 323 (22), 322 (100), 294 (25), 278 (19), 277 (99), 266 (21), 249 (57), 176 (51).**HRMS (EI):** *m/z* calc. for [$C_{20}H_{18}O_4$]: 322.1005; found: 322.1198 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[112]

1,2-Di(pyridin-3-yl)ethyne (106i)



According to **TP7**, 3-bromopyridine (**75k**; 87 mg, 0.55 mmol) was added to a solution of bis-pivaloyloxyzinc acetylide (**299**; 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.025 mmol) and Xantphos (7 mg, 0.0125 mmol) in DMSO (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 2:1) afforded the title compound as a white solid (37 mg, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 8.77 (dd, *J* = 2.2, 0.9, 2H), 8.57 (dd, *J* = 4.9, 1.6, 2H), 7.85 – 7.78 (m, 2H), 7.29 (ddd, *J* = 7.9, 4.9, 0.9, 2H).

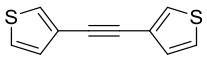
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 152.3, 149.1, 138.5, 123.1, 119.7, 89.1.

MS (70 eV, EI) m/z (%): (%): 180 (100), 179 (33), 152 (11), 127 (8), 74 (4).

HRMS (EI): *m/z* calc. for [$C_{12}H_8N_2$]: 180.0687; found: 180.0679 (M^+).

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[114]

1,2-Di(thiophen-3-yl)ethyne (106j)



According to **TP7** 3-bromothiophene (**75l;** 180 mg, 1.1 mmol) was added to a solution of bis-pivaloyloxyzinc acetylide (**99**; 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.025 mmol) and Xantphos (7 mg, 0.0125 mmol) in DMSO (2 mL) at 25 °C. The resulting solution was stirred at 25 °C for 1 h. Purification of the crude product by flash chromatography (silica gel, 100% isohexane) afforded the title compound as a white solid (89mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.53 (dd, *J* = 3.0, 1.2, 2H), 7.32 (dd, *J* = 5.0, 3.0, 2H), 7.21 (dd, *J* = 5.0, 1.2, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 129.8, 128.5, 125.4, 122.2, 84.0.

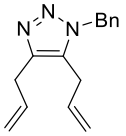
MS (70 eV, EI) m/z (%): (%): 190 (12), 189 (100), 145 (13), 114 (6), 94 (6), 44 (10).

HRMS (EI): *m/z* calc. for [$C_{10}H_6S_2$]: 189.9911; found: 189.9898 (M^+).

[114] M. Bindl, R. Stade, E. K. Heilmann, A. Picot, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2009**, *131*, 9468,

The ^{1}H and ^{13}C-NMR data are in accordance with those reported in the literature.[115]

Preparation of 4,5-diallyl-1-benzyl-1*H*-1,2,3-triazole (108)



To a solution of bis-pivaloyloxyzinc acetylide (**99**; 7.5 mmol) in DMF (15 mL) was added sodium azide (325 mg, 5 mmol), benzyl bromide (855 mg, 5 mmol) and copper iodide (1.9 g, 10 mmol) under argon at 25 °C. The reaction mixture was stirred at 25 °C for 12 h before the addition of allyl bromide (3.6 g, 30 mmol). The resulting solution was stirred for 1 h before quenched with sat. aq. NH_4Cl solution (20 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl solution, water (2x 100 mL) and dried over Mg_2SO_4. After filtration, the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 2:1) afforded the title compound as a dark yellow liquid (792 mg, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.41–7.30 (m, 3H), 7.19–7.11 (m, 2H), 5.98 (ddt, *J* = 17.4, 9.7, 6.4, 1H), 5.65 (ddt, *J* = 17.1, 10.1, 5.9, 1H), 5.50 (s, 2H), 5.13–5.03 (m, 3H), 4.92 (dq, *J* = 17.2, 1.7, 1H), 3.46 (dt, *J* = 6.4, 1.6, 2H), 3.25 (dt, *J* = 5.9, 1.7, 2H).

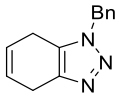
^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 143.7, 135.2, 135.2, 132.2, 130.9, 128.9, 128.2, 127.1, 117.4, 116.1, 77.3, 77.0, 76.7, 52.0, 29.9, 26.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 2925, 1639, 1455, 1248, 992, 913, 725, 694.

MS (EI, 70 eV): *m/z* (%) = 239 (18), 238 (19), 210 (9),120, (15), 91 (100), 65 (10).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}N_4$]: 239.1422 found: 239,1417 (M^+).

Preparation of 1-benzyl-4,7-dihydro-1H-benzo[d][1,2,3]triazole (109)



To a solution of 4, 5-diallyl-1-benzyl-1H-1,2,3-triazole (**108;** 280 mg, 1.17 mmol) in DCM (10 mL) was added Hoveyda-Grubbs Catalyst™ 2nd generation (35 mg, 0.06 mmol) and stirred for 12 h at 45 °C. The resulting solution was stirred for 1 h before quenched with sat. aq. NH_4Cl solution (20 mL). The mixture was extracted with EtOAc (3 × 20 mL). After filtration, the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 3:1) afforded the title compound as a colourless solid (202 mg, 66% yield).

M.p. (°C): 106.2 – 110.5.

[115] W. Zhand, H. Wu, Z. Liu, P. Zhong, L. Zhang, X. Huang, J. Cheng, *Chem. Commun.* **2006**, *46*, 4826.

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.41–7.30 (m, 3H), 7.25–7.19 (m, 2H), 6.03–5.83 (m, 1H), 5.75 (dtt, *J* = 10.1, 3.3, 2.2, 1H), 3.56–3.37 (m, 2H), 3.21–3.02 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 141.2, 134.8, 129.5, 129.0, 128.4, 127.5, 125.2, 121.1, 52.2, 24.1, 22.2.

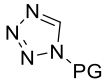
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3036, 2888, 2837, 1590, 1456, 1431, 1193, 1096, 950, 732, 714, 672.

MS (EI, 70 eV): *m/z* (%) = 211 (1), 182 (21), 180 (29), 91 (100), 65 (8).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}N_4$]: 211.1109 found: 211,1102 (M^+).

4 Preparation and reactions of (1*H*-tetrazol-5-yl)zinc pivalates

4.1 Synthesis of protected 1*H*-tetrazoles of type 110

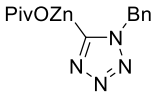


1H-tetrazoles (**110a–b**) were synthesized according to the literature.[92]

The respective benzylamine (100 mmol, 1.0 equiv), triethyl orthoformate (23.68 g, 160 mmol, 1.6 equiv) and sodium azide (9.75 g, 150 mmol, 1.5 equiv) were suspended in acetic acid (100 mL) and stirred at 85 °C for 12 h. The mixture was cooled to room temperature and the solvents were evaporated in vacuo. The residue was diluted with water and extracted twice with ethyl acetate. The combined organic layers were washed with hydrochloric acid (1 M), water, a saturated $NaHCO_3$ solution and brine. Subsequently, they were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (silica gel, isohexane/EtOAc = 1:1).

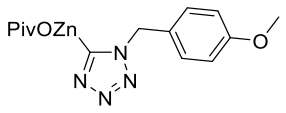
4.2 Synthesis of the (1*H*-tetrazol-5-yl)zinc pivalates of type 111

(1-Benzyl-1*H*-tetrazol-5-yl)zinc pivalate (111a)



A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the 1-benzyl-1H-tetrazole (**110b**) (5.0 mmol). TMPZnOPiv (0.6 M in THF, 6.0 mmol) was added. After stirring the reaction mixture for 1-2 h at room temperature at 0 °C, the solvent was removed *in vacuo* (at least 6 h) and the dried solid (1-benzyl-1*H*-tetrazol-5-yl)zinc pivalate (**111a**) was obtained as a fine powder in quantitative yield.

(1-Benzyl-1*H*-tetrazol-5-yl)zinc pivalate (111b)



A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the 1-(4-methoxybenzyl)-1*H*-tetrazole (**110b**) (5.0 mmol). TMPZnOPiv (0.6 M in THF, 6.0 mmol) was added. After stirring the reaction mixture for 1-2 h at room temperature at 0 °C, the solvent was removed *in vacuo* (at least 6 h) and the dried solid (1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)zinc pivalate (**111b**) was obtained as a fine powder in quantitative yield.

4.3 Typical Procedures (TP)

TP8: Typical procedure for the metalation of tetrazoles using TMPZnOPiv and subsequent Negishi cross coupling with aryl halides

A dry and argon-flushed flask equipped with a magnetic stirrer and a septum was charged with THF. Subsequently, 1-(4-methoxybenzyl)-1*H*-tetrazole (**110b**; 0.6 mmol, 95 mg, 1.2 equiv) was dissolved and TMPZnOPiv (1.25 mmol, 2.5 equiv) was added dropwise while cooling with an ice bath. The solution was stirred for 1 h and was allowed to warm to room temperature. Then, the electrophile (0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.025 mmol, 4 mg, 5 mol%) and SPhos (0.05 mmol, 20 mg,10 mol%) were added and the mixture was stirred overnight at 45 °C. The suspension was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified twice via column chromatography und yielded the desired product.

TP9: Typical procedure for the deprotection of aryl tetrazoles using ammonium formate

A pressure resistant flask equipped with a cover and a magnetic stirrer was charged with water and isopropyl alcohol in equal ratio. Subsequently, the protected aryl tetrazole of type **112** (0.2 mmol, 1.0 equiv) was suspended and palladium on charcoal (50 mg, 0.05 mmol, 5 mol%) and ammonium formate (198 mg, 3.15 mmol, 15 equiv) were added. The reaction mixture was stirred overnight at 65 °C. The suspension was filtered through celite and washed with isopropyl alcohol. The filtrate was extracted with DCM three times and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated *in vacuo*. The residue was purified *via* column chromatography and yielded the desired product.

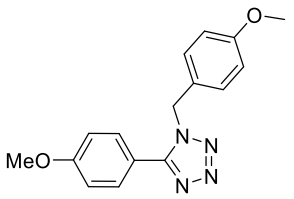
TP10: Typical procedure for the amination of tetrazoles using TMPZnOPiv and amine benzoate

1-(4-Methoxybenzyl)-1*H*-tetrazole (**110b**; 0.5 mmol, 95 mg) was dissolved in THF (1.5 mL) and cooled down to 0 °C. TMPZnOPiv solution (1 mmol, 2.0 equiv) was slowly added to the stirred solution. A dry, argon flushed Schlenk-flask equipped with magnetic stirring bar and septum was

charged with amine benzoate (0.5 mmol), copper (II) triflate (36 mg, 0.1 mmol, 20% mol) and THF (2.0 mL). The metalated species was slowly added to vigorously stirred solution. After 2 h the mixture was quenched with sat. aq. NH_4Cl solution (15 mL), extracted with DCM (3×15 mL) and dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography.

4.4 Metalation of Tetrazoles using TMPZnOPiv and subsequent Negishi cross-coupling reactiongs with aryl halides

1-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-1*H*-tetrazole (112a)



1-(4-Methoxybenzyl)-5-(4-methoxyphenyl)-1*H*-tetrazole (**112a**) was prepared according to **TP8** 4-iodo-anisol (**75h**; 93.5 mg, 0.5 mmol) as electrophile. The product was purified by flash column chromatography (isohexane : EtOAc 9:1 + 5% triethylamine) to obtain the desired product (0.133 g, 0.45 mmol, 90%) as an white solid.

M.p. (°C): 120–122.

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.50–7.44 (m, 2H), 7.07–6.99 (m, 2H), 6.98–6.89 (m, 2H), 6.83–6.75 (m, 2H), 5.47 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ / ppm = 161.9, 154.6, 134.1, 130.4, 129.2, 129.0, 128.7, 127.9, 127.4, 127.1, 115.7, 114.7, 55.5, 51.3, 27.1, 26.7.

IR (Diamond-ATR, neat): 3072, 0 29647, 2929, 2842, 1601, 1519, 1475, 1465, 1449, 1294, 1246, 1163 cm^{-1}.

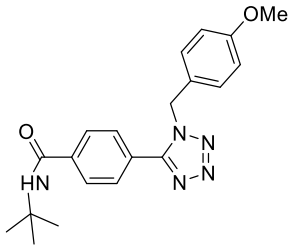
MS (EI, 70 eV): *m/z* (%) 296 (4), 121 (100), 97 (12), 85 (13), 71 (17), 57 (24), 43 (21).

HRMS (EI): *m/z* calc. for [$C_{16}H_{16}N_4O_2$]: 296.1273; found: 296.1268 (M^+).

The ^{1}H data are in accordance with those reported in the literature.[116]

[116] L. E. Kaim, L. Grimaud, P. Patil, *Org. Lett* **2011**, *13*, 1261.

_N_-(tert-butyl)-4-(1-(4-methoxybenzyl)-1_H_-tetrazol-5-yl)benzamide (112b)



_N_-(tert-butyl)-4-(1-(4-methoxybenzyl)-1_H_-tetrazol-5-yl)benzamide (**112b**) was prepared according to **TP8** using 4-bromo-_N_-(_tert_-butyl) benzamide (**75m**; 128 mg, 0.500 mmol, 1.0 equiv) as electrophile. The product was purified by flash column chromatography (isohexane : EtOAc 2:1 + 5% triethylamine) to obtain the desired product (0.122 g, 0.335 mmol, 67%) as an white solid.

M.p. (°C): 120–125.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, _J_ = 8.4 Hz, 2H), 7.57 (d, _J_ = 8.4 Hz, 2H), 7.04 (d, _J_ = 8.7 Hz, 2H), 6.81 (d, _J_ = 8.7 Hz, 2H), 6.27 (s, 1H), 5.50 (s, 2H), 3.74 (s, 3H), 1.45 (s, 9H).

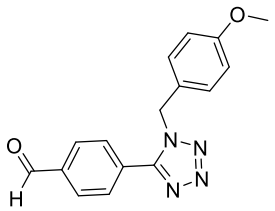
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 160.1, 153.9, 138.6, 129.2, 128.9, 127.7, 126.4, 125.7, 114.7, 55.5, 52.2, 51.3, 28.9.

IR (Diamond-ATR, neat): 3418 (w), 2965 (m), 2932 (m), 2864 (w), 2361 (w), 1590 (s), 1478 (vs), 1460 (s), 1420 (s), 1278 (s), 1023 (s), 720 (s).

MS (EI, 70 eV): _m/z_ (%) 365 (16), 293 (10), 122 (7), 121 (100).

HRMS (EI): _m/z_ calc. for [$C_{20}H_{23}N_5O_2$]: 365.1852; found: 365.1846.

4-(1-(4-Methoxybenzyl)-1_H_-tetrazol-5-yl)benzaldehyde (112c)



4-(1-(4-Methoxybenzyl)-1_H_-tetrazol-5-yl)benzaldehyde (**112c**) was prepared according to **TP8** using 4-bromobenzaldehyde (**75n**; 93 mg, 0.5 mmol. 1.0 eq) as electrophile. The product was purified by flash column chromatography (isohexane : EtOAc 2:1 + 5% triethylamine) to obtain the desired product (0.120 g, 0.41 mmol, 82%) as an white oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.06–7.84 (m, 2H), 7.84–7.60 (m, 2H), 7.06–6.95 (m, 2H), 6.89–6.68 (m, 2H), 5.52 (s, 2H), 3.73 (s, 3H).

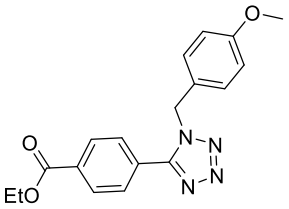
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 159.9, 153.8, 133.0, 130.2, 127.9, 125.5, 114.6, 61.6, 55.3, 51.3, 14.3.

IR (Diamond-ATR, neat): 2961 (w), 2922 (w), 2838 (w), 1714 (m), 1700 (m), 1610 (m), 1513 (s), 1459 (m), 1451 (m), 1294 (m), 1253 (vs), 1246 (s), 1208 (s), 1178 (s), 1115 (m), 1028 (s), 742 (s), 687 (s).

MS (70 eV, EI) m/z (%): 294 (5), 238 (14), 207 (3), 122 (9), 121 (110), 91 (6), 77 (5).

HRMS (EI): m/z calc. for [$C_{16}H_{14}N_4O_2$]: 294.1117; found: 294.1111 (M^+).

Ethyl 4-(1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)benzoate (112d)



Ethyl 4-(1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)benzoate (**112d**) was prepared according to **TP8** using ethyl 4-bromobenzoate (**75c**; 106 mg, 0.5 mmol. 1.0 eq) as electrophile. The product was purified by flash column chromatography (isohexane : EtOAc 2:1 + 5% triethylamine) to obtain the desired product (0.098 g, 0.29 mmol, 58%) as an white solid.

M.p. (°C): 110–114.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.12 (m, 2H), 7.72 – 7.63 (m, 2H), 7.13 – 7.05 (m, 2H), 6.89 – 6.81 (m, 2H), 5.57 (s, 2H), 4.43 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H).

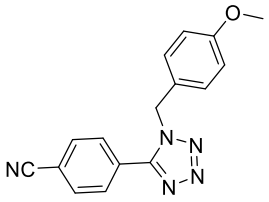
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 160.0, 153.8, 133.0, 130.2, 128.8, 127.9, 125.5, 114.6, 61.6, 55.4, 51.3, 14.3.

IR (Diamond-ATR, neat): 3087 (w), 2954 (w), 2928 (w), 1538 (m), 1481 (s), 1446 (m), 1247 (m), 1137 (m), 769 (m), 730 (vs), 699 (m), 690 (m), 679 (m), 655 (s).

MS (70 eV, EI) m/z (%): 338 (13), 277 (72), 183 (17), 121 (100), 91 (44), 71 (39), 57 (52).

HRMS (EI): m/z calc. for [$C_{18}H_{18}N_4O_3$]: 338.1373; found: 338.1367 (M^+).

5-(4-Isocyanophenyl)-1-(4-methoxybenzyl)-1*H*-tetrazole (112e)



5-(4-Isocyanophenyl)-1-(4-methoxybenzyl)-1*H*-tetrazole (**112e**) was prepared according to **TP8** using 4-bromobenzonitrile (**75d**; 92 mg, 0.5 mmol, 1.0 equiv) as electrophile. The product was purified by flash column chromatography (isohexane : EtOAc 2:1 + 5% triethylamine) to obtain the desired product (0.93 g, 0.32 mmol, 64%) as an white solid.

M.p. (°C): 106–108.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.70–7.60 (m, 2H), 7.04–6.96 (m, 2H), 6.82 – 6.78 (m, 2H), 5.51 (s, 3H), 3.73 (s, 3H).

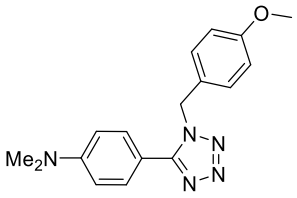
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 153.0, 132.8, 129.6, 128.6, 128.3, 125.2, 117.5, 115.2, 114.7, 55.3, 51.4.

IR (Diamond-ATR, neat): 2934 (w), 2845 (w), 2214 (w), 1611 (s), 1586 (m), 1512 (vs), 1250 (vs), 1178 (s), 1106 (s), 1031 (s), 848 (s), 771 (s), 679 (m), 655 (s).

MS (70 eV, EI) m/z (%): 291 (6), 235 (10), 121 (100), 78 (14), 77 (13), 71 (11), 57 (19), 55 (11), 43 (16).

HRMS (EI): *m/z* calc. for [$C_{16}H_{13}N_5O$]: 291.1120; found: 291.1136.

4-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)-N,N-dimethylaniline (112f)



4-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)-*N*,*N*-dimethylaniline (**112f**) was prepared according to **TP8** using 4-bromo-*N*,*N*-dimethylaniline (**75o**;100 mg, 0.5 mmol, 1.0 equiv)as electrophile. The product was purified by flash column chromatography (isohexane : EtOAc 2:1 + 5% triethylamine) to obtain the desired product (0.114 g, 0.37 mmol, 74%) as an white solid.

M.p. (°C): 120–122.

$_1$H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.51 (d, *J* = 9.0 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 5.55 (s, 2H), 3.79 (s, 3H), 3.04 (s, 6H).

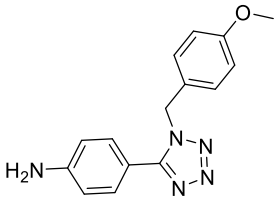
$_{13}$C NMR (100 MHz, $CDCl_3$) δ / ppm = 159.7, 154.9, 152.0, 129.9, 128.6, 126.5, 114.5, 111.8, 110.1, 55.4, 50.8, 40.1.

IR (Diamond-ATR, neat): 2938 (w), 2839 (w), 2231 (w), 2220 (vw), 1612 (m), 1514 (vs), 1469 (m), 1454 (m), 1251 (vs), 1178 (s), 1052 (w), 847 (m), 1028 (s), 840 (s), 833 (s), 821 (s), 776 (vs), 742 (s), 687 (s).

MS (EI, 70 eV): *m/z* (%) 309 (20), 281 (10), 253 (17), 252 (16), 145 (12), 132 (25), 121 (100), 78 (14), 77 (13).

HRMS (EI): *m/z* calc. for [$C_{17}H_{19}N_5O$]: 309.3730; found: 309.1579.

4-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)aniline (112g)



4-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)aniline (**112g**) was prepared according to **TP8** using 4-bromoaniline (**75p**; 86 mg, 0.50 mmol, 1.0 equiv) as electrophile. The product was purified by flash

column chromatography (isohexane : EtOAc 1:2 + 5% triethylamine) to obtain the desired product (95 mg, 0.34 mmol, 68 %) as an white solid.

M.p. (°C): 118–120.

$_1$H NMR (400 MHz, $CDCl_3$) δ / ppm 7.40 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 5.52 (s, 2H), 4.06 (s, 2H), 3.78 (s, 3H).

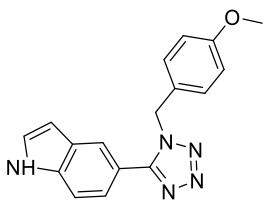
$_{13}$C NMR (101 MHz, $CDCl_3$) δ / ppm 159.8, 154.8, 149.4, 130.3, 128.8, 126.3, 115.0, 114.9, 112.8, 55.5, 50.9.

IR (Diamond-ATR, neat): 2924 (m), 2867 (w), 2853 (w), 1612 (vs), 1514 (s), 1492 (s), 1252 (m), 1234 (w), 821 (m), 847 (m), 776 (vs), 742 (s), 687 (s).

MS (EI, 70 eV): *m/z* (%) 281 (8), 225 (9), 210 (18), 122 (11), 121 (100), 78 (16), 77 (19).

HRMS (EI): *m/z* calc. for [$C_{15}H_{15}N_5O$]: 281.1277; found: 281.1268.

5-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)-1*H*-indole (112h)



5-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)-1*H*-indole (**112h**) was prepared according to **TP8** using 5-bromo-1*H*-indole (**75q**; 98 mg, 0.5 mmol, 1.0 equiv) as electrophile. The product was purified by flash column chromatography (isohexane : EtOAc 1:2 + 5% triethylamine) to obtain the desired product (94 mg, 0.32 mmol, 62 %) as an white solid.

M.p. (°C): 115–118.

$_1$H NMR (400 MHz, $CDCl_3$) δ / ppm 9.36 (s, 1H), 7.86–7.84 (m, 1H), 7.51–7.47 (m, 1H), 7.36 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.33–7.30 (m, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.60–6.55 (m, 1H), 5.56 (s, 2H), 3.77 (s, 3H).

$_{13}$C NMR (101 MHz, $CDCl_3$) δ / ppm 159.7, 156.0, 137.2, 129.0, 128.0, 126.4, 126.3, 122.2, 122.0, 114.5, 114.4, 112.2, 103.1, 55.3, 50.9.

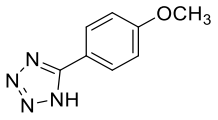
IR (Diamond-ATR, neat): 2925 (m), 2853 (m), 1613 (m), 1515 (vs), 1458 (s), 1252 (vs), 1178 (m), 1076 (w), 1007 (w), 821 (m), 770 (m), 847 (m), 679 (m), 655 (s).

MS (EI, 70 eV): *m/z* (%) 305 (18), 249 (8), 234 (7), 122 (8), 121 (100), 78 (6), 77 (7).

HRMS (EI): *m/z* calc. for [$C_{17}H_{15}N_5O$]: 305.1277; found: 305.1268.

4.5 Preparation of unprotected aryl tetrazoles using ammonium formate and palladium on charcoal

5-(4-Methoxyphenyl)-1*H*-tetrazole (113a)



According to **TP9** 1-(4-methoxybenzyl)-5-(4-methoxyphenyl)-1*H*-tetrazole (**112a**; 75 mg, 0.25 mmol, 1.0 equiv) was suspended in water (2 mL) and isopropyl alcohol (2 mL). Subsequently, palladium on carbon (53 mg, 0.50 mmol, 5%) and ammonium formate (209 mg, 3.75 mmol, 15 equiv) were added and the mixture was stirred overnight at 65 °C. The crude product was purified twice by column chromatography (silica gel, DCM/MeOH = 4:1). Compound (**113a**; 41 mg, 0.24 mmol, 95%) was obtained as colorless solid.

M.p. (°C): 218–220.

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm 7.98 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 6.37 (s, 1H), 3.81 (s, 3H).

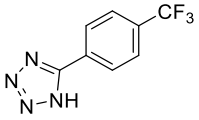
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm 161.0, 155.6, 128.4, 117.6, 114.7, 55.4.

IR (Diamond-ATR, neat): 2842 (w), 1611 (s), 1499 (s), 1259 (s), 1164 (m), 1026 (m), 1020 (s), 832 (vs), 750 (vs), 821 (m), 770 (m), 847 (m), 679 (m), 655 (s)

MS (EI, 70 eV): *m/z* (%) 176 (20), 148 (33), 134 (16), 133 (100), 105 (19), 103 (17), 90 (21), 57 (13), 44 (79), 43 (48).

HRMS (EI): *m/z* calc. for [$C_8H_8N_4O$]: 176.0698; found: 176.0687.

5-(4-(Trifluoromethyl)phenyl)-1*H*-tetrazole (113b)



According to **TP9** 1-(4-methoxybenzyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-tetrazole (**112i**; 64 mg, 0.21 mmol, 1.0 equiv) was suspended in water (2 mL) and isopropyl alcohol (2 mL). Subsequently, palladium on carbon (50 mg, 0.05 mmol, 5%) and ammonium formate (198 mg, 3.15 mmol, 15 equiv) were added and the mixture was stirred overnight at 65 °C. The crude product was purified twice by column chromatography (silica gel, DCM/MeOH = 10:1). Compound (**113b**; 42mg, 0.19 mmol, 93%) was obtained as colorless solid.

M.p. (°C): 202–205.

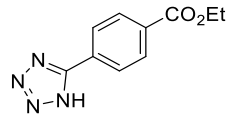
^{1}H NMR (400 MHz, DMSO-d_6) δ / ppm 8.18 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H).

^{13}C NMR (101 MHz DMSO-d_6) δ / ppm 136.1, 128.1, 127.7, 126.7, 126.3, 125.88 (q, *J* = 3.9 Hz).

IR (Diamond-ATR, neat): 2927 (w), 1455 (s), 1323 (vs), 1167 (s), 1123 (s), 1067 (vs), 1013 (s), 986 (w), 849 (s), 729 (s), 847 (m), 679 (m), 655 (s).

MS (EI, 70 eV): *m/z* (%) 214 (11), 186 (82), 171 (100), 152 (38), 121 (51), 102 (13), 50 (10).
HRMS (EI): *m/z* calc. for [$C_8H_5F_3N_4$]: 214.0466; found: 214.0443.

Ethyl 4-(1*H*-tetrazol-5-yl)benzoate (113c)



According to **TP9** ethyl 4-(1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)benzoate (**112c**; 114 mg, 0.33 mmol, 1.0 equiv) was suspended in water (2 mL) and isopropyl alcohol (2 mL). Subsequently, palladium on carbon (16 mg, 0.26 mmol, 5%) and ammonium formate (316 mg, 1.04 mmol, 15 equiv) were added and the mixture was stirred overnight at 65 °C. The crude product was purified twice by column chromatography (silica gel, DCM/MeOH = 10:1). Compound (**113c**) (64mg, 0.294 mmol, 88%) was obtained as colorless solid.

M.p. (°C): 220–224.

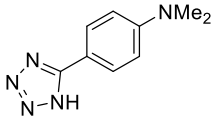
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ / ppm 8.18–8.03 (m, 2H), 8.03–7.84 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz DMSO-*d*$_6$) δ / ppm 165.7, 130.4, 127.3, 61.4, 55.4, 45.8, 14.6, 8.9.

IR (Diamond-ATR, neat): 2968 (m), 2936 (m), 2361 (vw), 1660 (w), 1502 (m), 1401 (s), 1275 (s), 994 (s), 729 (s), 847 (m), 679 (m), 655 (s), 1115 (m), 1028 (s), 840 (s), 833 (s), 821 (s), 776 (vs), 742 (s).

MS (EI, 70 eV): *m/z* (%) 218 (64), 202 (100), 175 (44), 147 (54), 129 (18), 102 (19), 87 (11).
HRMS (EI): *m/z* calc. for [$C_{10}H_{10}N_4O_2$]: 218.0804; found: 218.1051.

***N*,*N*-dimethyl-4-(1H-tetrazol-5-yl)aniline (113d)**



According to **TP9** 4-(1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)-*N*,*N*-dimethylaniline (**112f**; 103 mg, 0.330 mmol, 1.0 equiv) was suspended in water (2 mL) and isopropyl alcohol (2 mL). Subsequently, palladium on carbon (70 mg, 0.66 mmol, 5%) and ammonium formate (340 mg, 5.00 mmol, 15 equiv) were added and the mixture was stirred overnight at 65 °C. The crude product was purified twice by column chromatography (silica gel, DCM/MeOH = 10:1). Compound (**113d**; 57 mg, 0.31 mmol, 92%) was obtained as colorless solid.

M.p. (°C): 218–220.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ / ppm 7.85 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 3.00 (s, 6H).

^{13}C NMR (101 MHz DMSO-*d*$_6$) δ / ppm 155.4, 152.4, 128.6, 128.4, 112.4, 110.8.

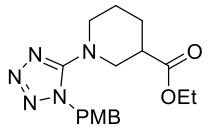
MS (EI, 70 eV): *m/z* (%) 189 (66), 161 (65), 160 (100), 147 (11), 146 (40), 145 (50), 132 (11), 118 (12), 80 (10).

IR (Diamond-ATR, neat): 2926 (w), 2853 (w), 2531 (w), 2133 (w), 1658 (w), 1505 (m), 1407 (m), 1206 (m), 944 (m), 749 (s), 729 (s), 847 (m), 679 (m), 655 (s).

HRMS (EI): *m/z* calc. for [$C_9H_{11}N_5$]: 189.1014; found: 189.1011.

4.6 Amination of 1*H*-tetrazoles using TMPZnOPiv and amine benzoate

Ethyl 1-(1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)piperidine-3-carboxylate (115d)



Ethyl 1-(1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)piperidine-3-carboxylate (**155d**) was prepared according to **TP10** using 1-(benzoyloxy)piperidine-3-carboxylate (**114a**; 138 mg, 0.5 mmol) as electrophile. The desired product (163 mg, 0.475 mmol, 95 %) was obtained *via* column chromatography (silica gel, isohexane/ethylacetate 1:1) as a colourless solid.

M.p. (°C): 172–175.

$_1$H NMR (400 MHz, DMSO-*d*$_6$) δ / ppm 7.18–7.08 (m, 2H), 6.94–6.80 (m, 2H), 5.41 (s, 2H), 4.10–3.92 (m, 2H), 3.70 (s, 3H), 3.44 (dd, *J* = 12.6, 3.8 Hz, 1H), 3.29 (s, 1H), 3.17 (dd, *J* = 12.6, 8.6 Hz, 1H), 3.01 (ddd, *J* = 12.5, 9.3, 3.2 Hz, 1H), 2.61 (dq, *J* = 8.5, 4.2 Hz, 1H), 1.88–1.77 (m, 1H), 1.72–1.57 (m, 2H), 1.51 (qt, *J* = 9.7, 5.1 Hz, 1H), 1.11 (t, *J* = 7.1 Hz, 3H).

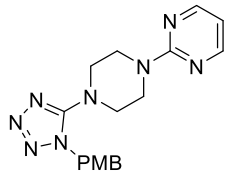
$_{13}$C NMR (101 MHz DMSO-*d*$_6$) δ / ppm 172.9, 159.5, 158.7, 130.3, 129.2, 127.0, 114.6, 60.6, 55.6, 51.5, 50.1, 49.8, 26.1, 23.4, 14.4.

IR (Diamond-ATR, neat): 2250 (vw), 2116 (vw), 1977 (vw), 1944 (vw), 1725 (vw), 1663 (vw), 1515 (vw), 1252 (vw), 1109 (vw), 887 (vw), 821 (m), 797 (vw), 758 (m).

MS (EI, 70 eV): *m/z* (%) 345(1), 317 (11), 156 (14), 122 (10), 121 (100), 92, (2),78 (4), 76 (4).

HRMS (EI): m/z calc. for [$C_{17}H_{23}N_5O_3$]: 345.1801; found: 345.1803.

2-(4-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)piperazin-1-yl)pyrimidine (115b)



2-(4-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)piperazin-1-yl)pyrimidine (**114b**) was prepared according to **TP10** using 4-(pyrimidin-2-yl)piperazin-1-yl benzoate (142 mg, 0.5 mmol, 1.0 eq) as electrophile. The desired product (115 mg, 0.34 mmol, 68 %) was obtained *via* column chromatography (silica gel, isohexane/ethylacetate 2:1) as a colourless solid.

M.p. (°C): 175–177.

$_1$H NMR (400 MHz, DMSO-*d*$_6$) δ / ppm 8.35 (d, *J* = 4.7 Hz, 2H), 7.27–7.13 (m, 2H), 6.98–6.78 (m, 2H), 6.63 (t, *J* = 4.7 Hz, 1H), 5.47 (s, 2H), 3.88–3.74 (m, 4H), 3.70 (s, 3H), 3.38–3.21 (m, 4H).

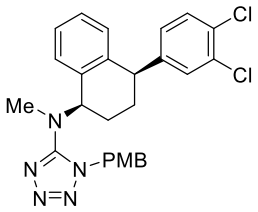
$_{13}$C NMR (101 MHz DMSO-*d*$_6$) δ / ppm 161.5, 159.5, 158.5, 158.4, 129.5, 126.9, 114.7, 111.0, 55.6, 50.1, 49.3, 43.1.

IR (Diamond-ATR, neat): 2868 (w), 2167 (w), 1586 (s), 1539 (s), 1484 (s), 1421 (m), 1315 (w), 1250 (vs), 1176 (s), 1022 (s), 957 (s), 816 (vs), 762 (m), 756 (m).

MS (EI, 70 eV): *m/z* (%) 352 (13), 148 (11), 136 (10), 134 (39), 122 (26), 121 (100), 80 (25), 77 (12), 44 (28).

HRMS (EI): *m/z* calc. for [$C_{17}H_{20}N_8O$]: 352.1760; found: 352.1755.

***N*-((1*R*,4*R*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-methoxybenzyl)-N-methyl-1*H*-tetrazol-5-amine (115c)**



N-((1*R*,4*R*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-methoxybenzyl)-N-methyl-1*H*-tetrazol-5-amine (**115c**) was prepared according to **TP10** using *O*-benzoyl-*N*-((1*R*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methylhydroxylamine (**114c**; 213 mg, 0.5 mmol)) as electrophile. The desired product (180 mg, 0.365 mmol, 73 %) was obtained *via* column chromatography (silica gel, isohexane/ethylacetate 1:1) as a colourless solid.

M.p. (°C): 155–160.

$_1$H NMR (400 MHz, DMSO-*d*$_6$) δ / ppm 7.34 (d, J = 8.2 Hz, 1H), 7.23–7.14 (m, 2H), 7.13–7.07 (m, 2H), 7.07–6.99 (m, 2H), 6.96 (dd, J = 7.0, 2.1 Hz, 1H), 6.94–6.88 (m, 2H), 6.81 (dd, J = 8.3, 2.1 Hz,

1H), 5.62 (d, J = 16.1 Hz, 1H), 5.38 (d, J = 16.1 Hz, 1H), 5.05 (dd, J = 9.9, 6.7 Hz, 1H), 4.15 (dd, J = 5.8, 2.8 Hz,1H), 3.84 (s, 3H), 2.78 (s, 3H), 2.18–2.03 (m, 1H), 2.02–1.89 (m, 1H), 1.86–1.69 (m, 2H).

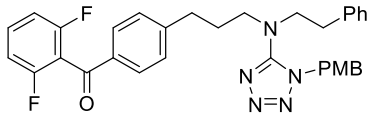
^{13}C NMR (101 MHz DMSO-*d*$_6$) δ / ppm 159.8, 158.8, 146.8, 138.3, 135.4, 132.3, 130.9, 130.6, 130.1, 128.1, 128.0, 127.8, 127.5, 127.3, 126.4, 114.6, 60.4, 60.2, 55.4, 50.8, 42.9, 33.1, 29.8, 27.0, 23.8.

IR (Diamond-ATR, neat): 2938 (w), 1584 (m), 1572 (m), 1514 (s), 1466 (m), 1249 (s), 1178 (m), 1055 (s), 1027 (vs), 1006 (s), 820 (s), 791 (m), 766 (m), 746 (m), 738 (s), 679 (m).

MS (EI, 70 eV): *m/z* (%) 493 (4), 273 (8), 271 (12), 201 (12), 159 (20), 129 (13), 121 (100), 43 (10).

HRMS (EI): *m/z* calc. for [$C_{26}H_{25}Cl_2N_5O$]: 493.1436; found: 493.1431.

(2,6-Difluorophenyl)(4-(3-((1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)(phenethyl)amino)propyl)-phenyl)methanone (115d)



(2,6-Difluorophenyl)(4-(3-((1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)(phenethyl)amino)propyl)-phenyl)methanone (**115d**) was prepared according to **TP10** using (4-(3-((benzoyloxy)(phenethyl)amino)propyl)phenyl)(2,6-difluorophenyl)methanone (**114d**; 250 mg, 0.5 mmol) as electrophile. The desired product (240 mg, 0.425 mmol, 85 %) was obtained *via* column chromatography (silica gel, isohexane/ethylacetate 1:1) as a colourless solid.

M.p. (°C): 184–185.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ / ppm 7.85–7.74 (m, 2H), 7.48 (tt, *J* = 8.5, 6.3 Hz, 1H), 7.28–7.19 (m, 3H), 7.19–7.13 (m, 2H), 7.09–6.98 (m, 4H), 7.00–6.91 (m, 2H), 6.88–6.81 (m, 2H), 5.17 (s, 2H), 3.77 (s, 3H), 3.50–3.36 (m, 2H), 3.31–3.20 (m, 2H), 2.73 (dd, *J* = 8.5, 6.5 Hz, 2H), 2.50 (t, *J* = 7.7 Hz, 2H), 1.90–1.71 (m, 2H).

^{13}C NMR (101 MHz DMSO-*d*$_6$) δ / ppm 188.4, 161.0, 161.0, 159.7, 158.5, 158.5, 157.6, 148.3, 138.2, 135.0, 132.0, 131.9, 131.8, 130.0, 128.7, 128.7, 128.6, 128.2, 126.6, 125.9, 114.4, 112.1, 112.0, 111.9, 111.8, 111.8, 55.3, 53.6, 51.4, 50.0, 33.8, 32.9, 28.5.

IR (Diamond-ATR, neat): 938 (w), 2919 (w), 2168 (w), 1672 (s), 1623 (s), 1514 (s), 1501 (w), 1464 (vs), 1279 (s), 1252 (s), 1006 (s), 931 (s), 792 (s).

MS (EI, 70 eV): *m/z* (%) 567 (2), 476 (17), 313 (5), 232 (26), 141 (17), 122 (10), 121 (100), 105 (10).

HRMS (EI): *m/z* calc. for [$C_{33}H_{31}F_2N_5O_2$]: 567.2446; found: 567.2468.