Dissertation zur Erlangung des Doktorgrades

der Fakultät für Chemie und Pharmazie

der Ludwig-Maximilians-Universität München

Highly Regioselective Addition of Organozinc Reagents to [1.1.1]Propellane

- and -

Selective Metalation of Nitrogen Containing Heterocycles Using 2,2,6,6-Tetramethylpiperidyl Bases

von

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aus Innichen, Italien

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Erklärung

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Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

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Parts of this Ph.D. thesis have been published:

1. Kuno Schwärzer, Hendrik Zipse, Konstantin Karaghiosoff and Paul Knochel, “Highly Regioselective Addition of Allylic Zinc Halides and Various Zinc Enolates to [1.1.1]Propellane”, *Angew. Chem. Int. Ed.* **2020**, *59*, 20235-20241; *Angew. Chem.* **2020**, *132*, 20412-20418.

2. Kuno Schwärzer, Carl Phillip Tüllmann, Simon Graßl, Bartosz Górski, Cara E. Brocklehurst and Paul Knochel, “Functionalization of 1,3,4-Oxadiazoles and 1,2,4-Triazoles via Selective Zincation or Magnesiation using 2,2,6,6-Tetramethyl-piperidyl Bases”, *Org. Lett.* **2020**, *22*, 1899-1902.

“We are going to die, and that makes us the lucky ones. Most people are never going to die because they are never going to be born. The potential people who could have been here in my place but who will in fact never see the light of day outnumber the sand grains of Arabia. Certainly those unborn ghosts include greater poets than Keats, scientists greater than Newton. We know this because the set of possible people allowed by our DNA so massively exceeds the set of actual people. In the teeth of these stupefying odds it is you and I, in our ordinariness, that are here. We privileged few, who won the lottery of birth against all odds, how dare we whine at our inevitable return to that prior state from which the vast majority have never stirred?”

Richard Dawkins

MEINEN ELTERN

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List of abbreviations

°C	degree *Celsius*
Å	Ångström
aq.	aqueous
Ar	aryl
atm	standard atmosphere
ATR	attenuated total reflection
B3LYP	Becke, 3-parameter, Lee-Yang-Parr
BCP	bicyclopentane
Bn	benzyl
BOVB	breathing-orbital valence bond
Bu	butyl
Bz	benzoyl
cod	1,5-cyclooctadiene
conc.	concentrated
COSY	correlation spectroscopy
δ	chemical shift in ppm downfield relative to a standard
d	doublet
DBE	di-*n*butyl ether
DFT	density-functional theory
DMF	*N*,*N'*-dimethylformamide
DMSO	dimethyl sulfoxide
DOSY	diffusion-ordered NMR spectroscopy
dppf	1,1'-bis(diphenylphosphino)ferrocene
EI	electron ionization

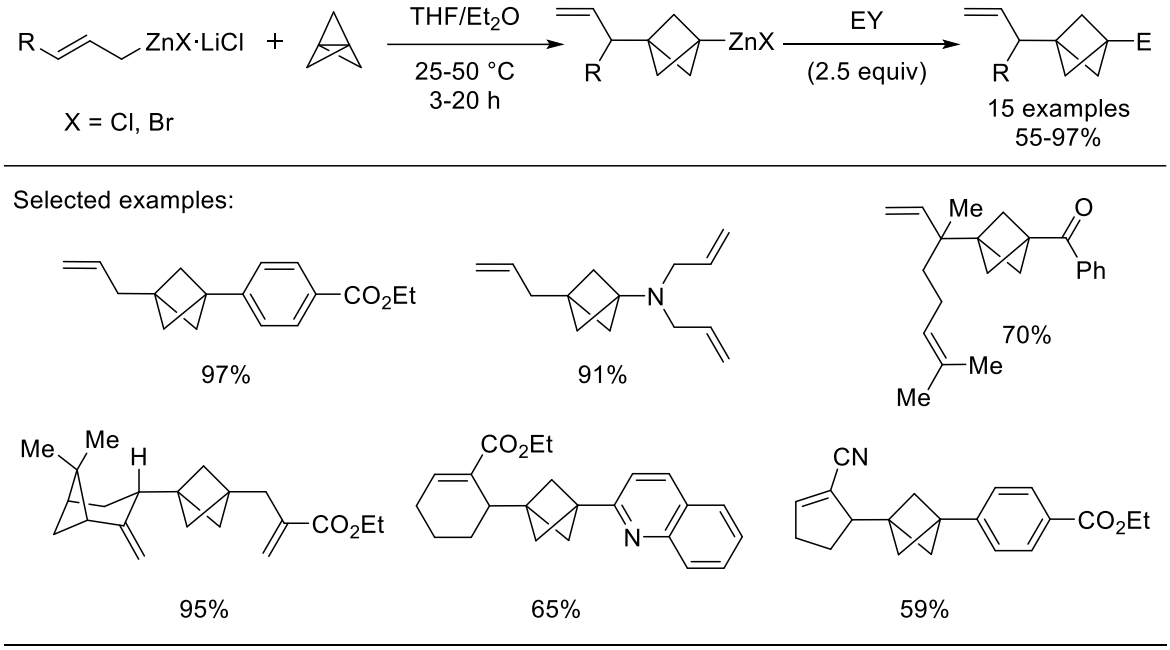
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
et. al.	and others
FDA	food and drug administration
g	gram
GC	gas chromatography
h	hour(s)
HetAr	heteroaryl
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
i-	*iso-*
IR	infrared spectroscopy
J	coupling constant (NMR)
LDA	lithium diisopropyl amide
m	multiplet
M	molar
Me	methyl
mg	milligram
min	minute(s)
mL	millilitre

mmol	millimole
mp	melting point
MS	mass spectrometry
NBO	natural bond orbital
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NPA	natural population analysis
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
Ph	phenyl
pin	pinacolato
ppm	parts per million
Pr	propyl
q	quartet
R	organic substituent
RE_{cs}	charge-shift resonance energy
s	singlet
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SMD	solvation model based on density
SVP	split valence polarization
t	triplet, time
T	temperature
TES	triethylsilyl
THF	tetrahydrofuran

TMB	2,2,3,3-tetramethylbutane
TMP	2,2,6,6-tetramethylpiperidyl
TLC	thin-layer chromatography
TP	typical procedure
TZVPP	valence triple-zeta with two sets of polarization functions
UV	ultraviolet
VB	valence bond
WBI	*Wiberg* bond index

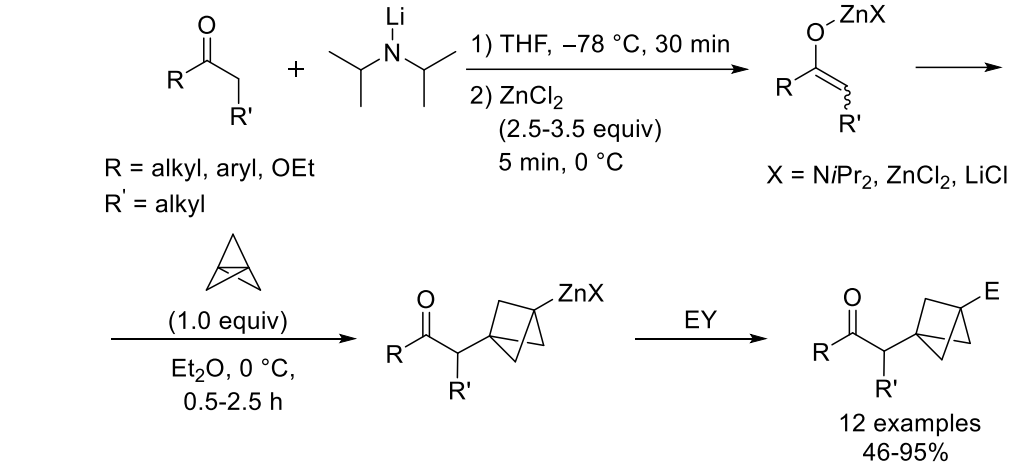
Abstract

For the first part of this thesis the addition of various organozinc reagents to [1.1.1]propellane was investigated. This was first achieved using allylic organozinc halides (Scheme A). The additions proceeded with an extraordinarily high stereoselectivity, as only the products resulting from an allylic rearrangement were observed. The resulting zincated BCPs were successfully trapped using *Negishi*-type cross-couplings, thiolations, cobalt-catalyzed electrophilic aminations, as well as copper-mediated allylations and acylations. The protocol showed a good tolerance of functional groups, such as esters and nitriles, due to the relatively low reactivity of the organozinc halides.

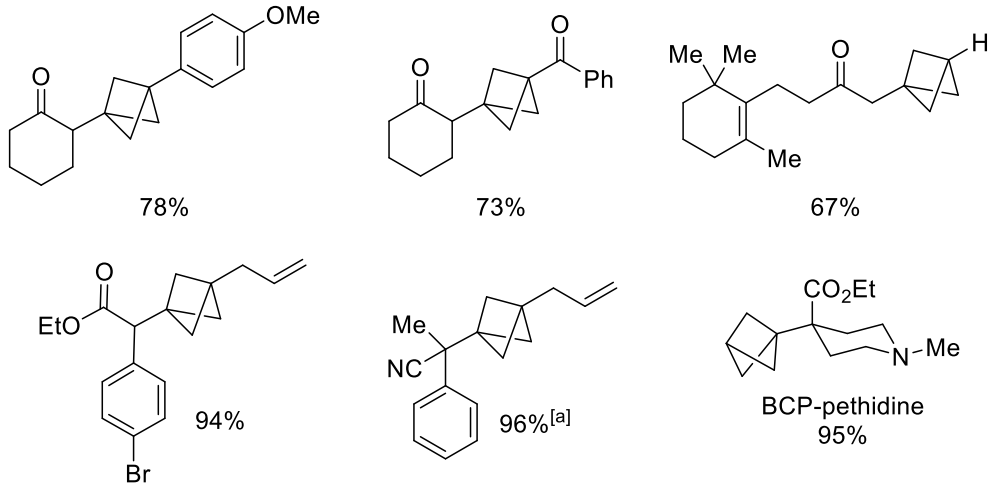


Scheme A. Summary of the addition of allylic organozinc halides to [1.1.1]propellane.

The methodology was extended to various zinc enolates, prepared from ketones, esters and nitriles through the deprotonation with LDA, followed by a transmetalation with $ZnCl_2$ (Scheme B). Once again the resulting zincated BCPs were submitted to different electrophilic trapping reactions, such as protonations, copper-catalyzed allylations, palladium-catalyzed *Negishi*-type cross-couplings, acylations and cyanations. The protocol was also used to synthesize a BCP-bioisoster of the synthetic opioid pethidine.



Selected examples:

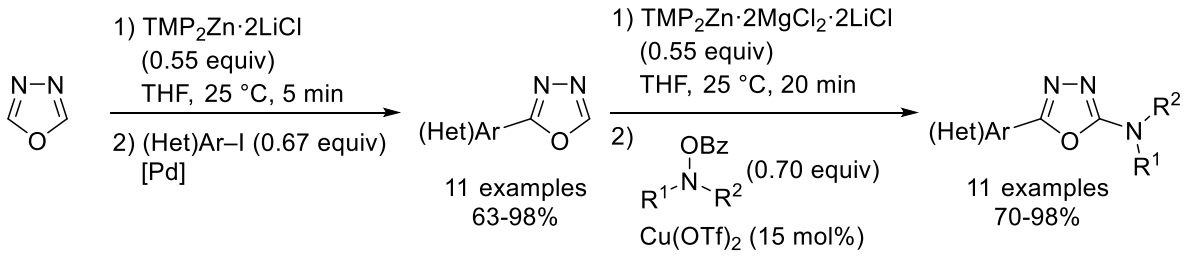


[a] Using a nitrile instead of a carbonyl compound.

Scheme B. Summary of the addition of zinc enolates to [1.1.1]propellane.

The high regioselectivity of the reaction was rationalized using DFT calculations, which showed that the allylic rearrangement proceeds via a cyclic transition state involving ZnBr2, LiCl, the allylic zinc halide and [1.1.1]propellane.

The topic of the second part of this thesis was the metalation of various nitrogen containing heterocycles using TMP bases. This was first achieved in the case of 1,3,4-oxadiazole using the base $TMP_2Zn{\cdot}2LiCl$ (Scheme C). The resulting zincated 1,3,4-oxadiazole was reacted in a series of *Negishi*-type cross-couplings with electron-deficient, electron-rich and heterocyclic iodides. The mono substituted 1,3,4-oxadiazoles were then metalated a second time using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, followed by a series of copper-catalyzed electrophilic aminations using hydroxylamino benzoates.



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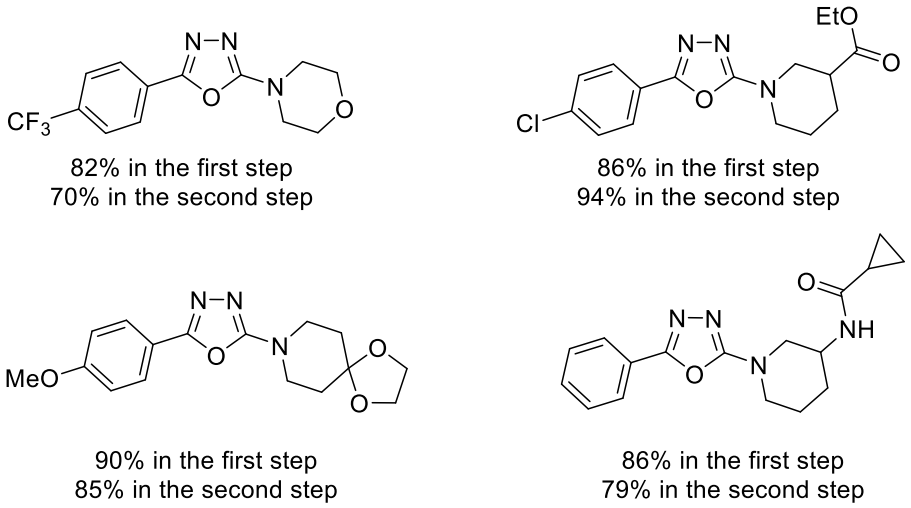
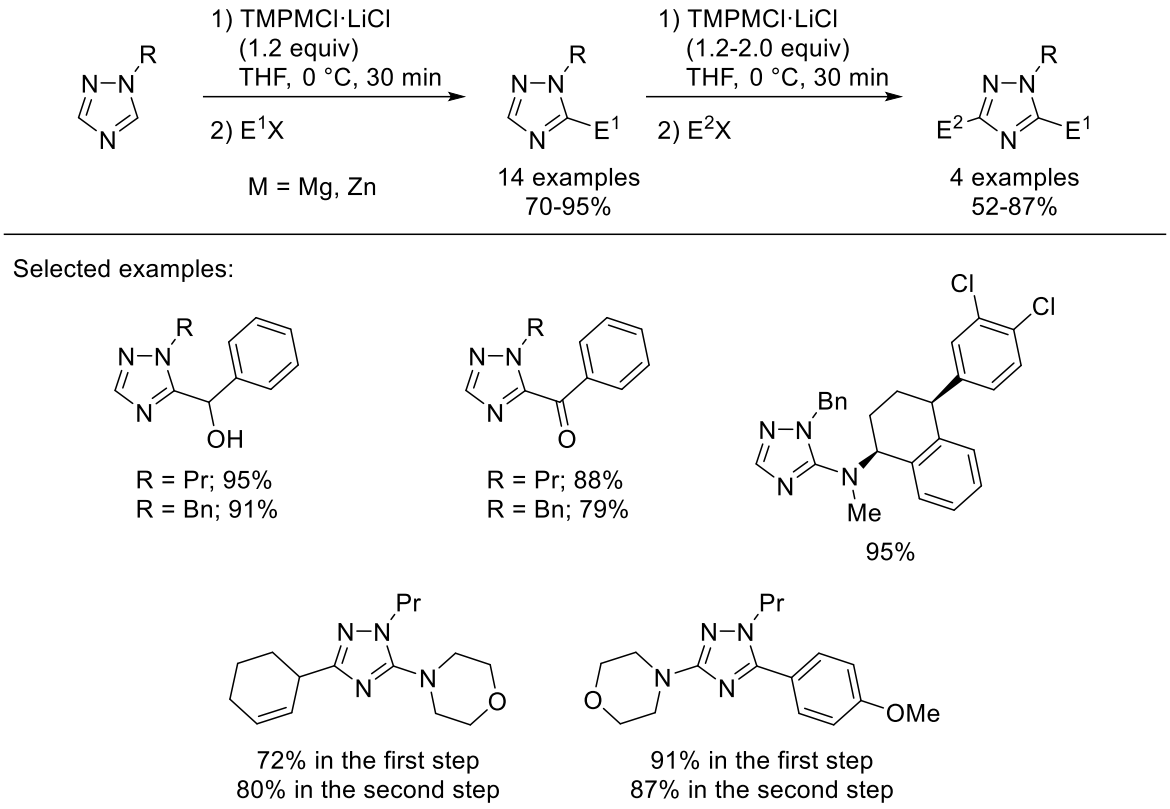


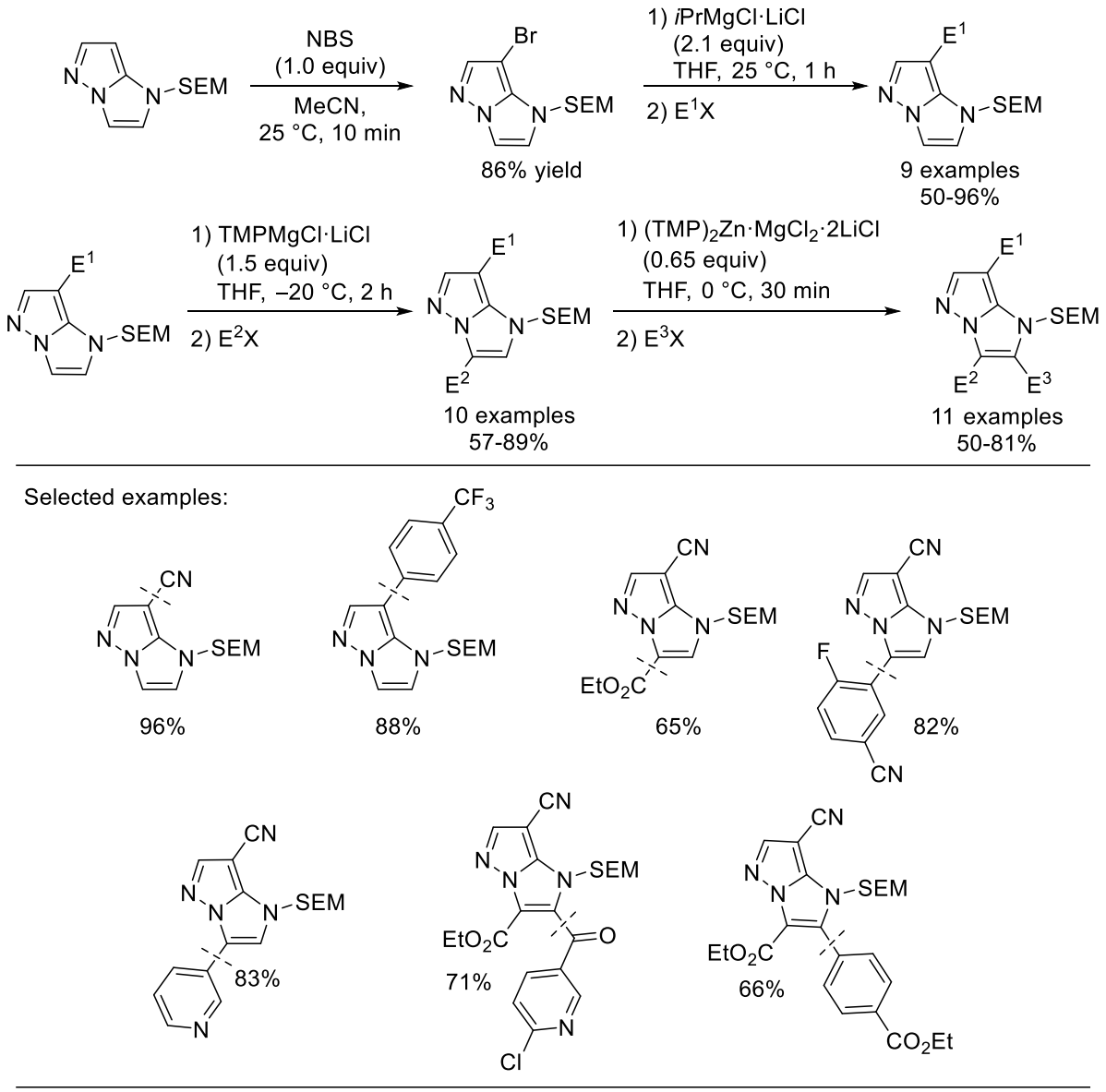
Scheme C. Summary of the functionalization of 1,3,4-oxadiazole.

N-propyl and *N*-benzyl 1,2,4-triazole were investigated as a second heterocyclic system (Scheme D). In this case the first metalation was achieved using TMPMgCl·LiCl or TMPZnCl·LiCl. The metalated 1,2,4-triazoles were subsequently submitted to a variety of electrophilic trapping reactions, including copper-catalyzed allylations and acylations, as well as *Negishi*-type cross-couplings and copper-catalyzed electrophilic aminations. A second metalation was performed on two different substrates using the same TMP bases.



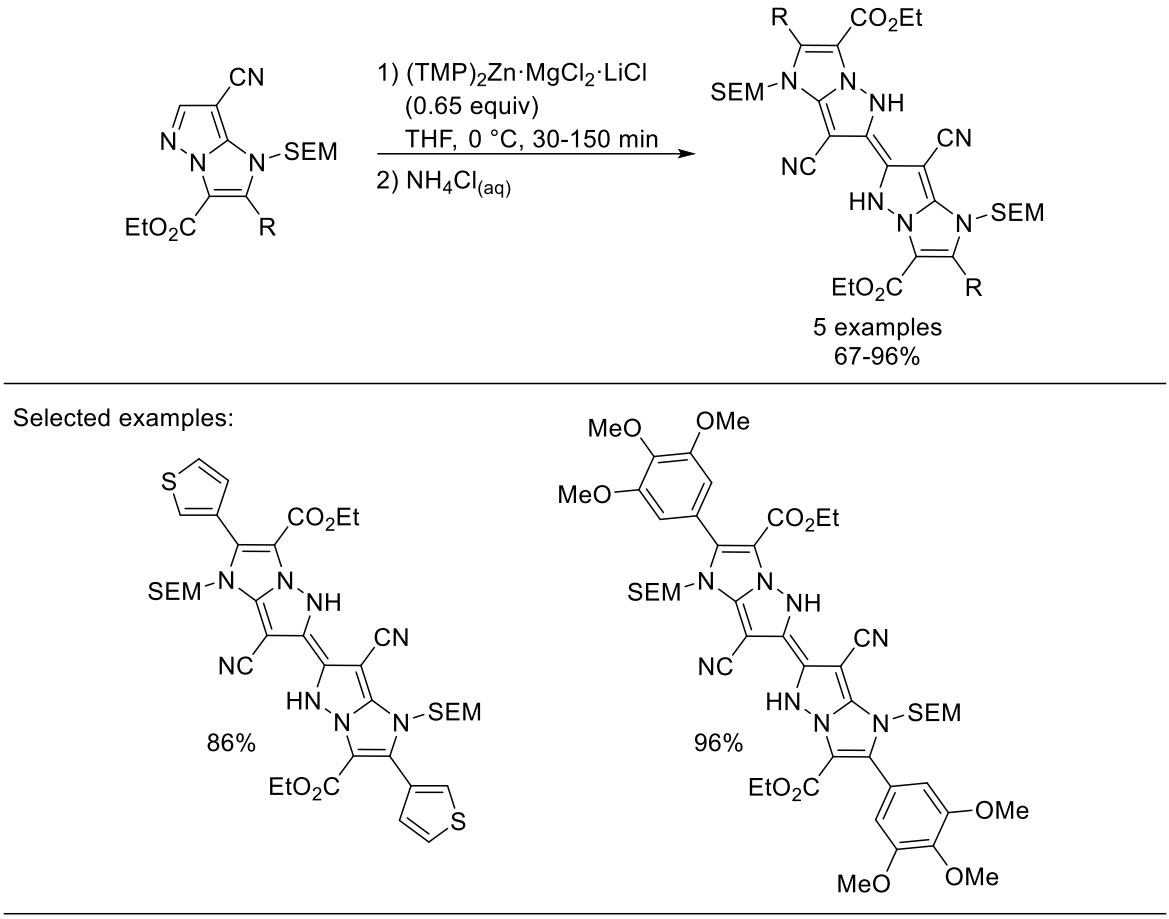
Scheme D. Summary of the functionalization of 1,2,4-triazoles.

Finally, the functionalization of 1*H*-imidazo[1,2-*b*]pyrazole was explored (Scheme E). The free NH-group of the heterocycle was protected with a SEM-group. The first functionalization was achieved via a selective bromination in the 7-position using NBS, followed by a bromine-magnesium exchange and different electrophilic trapping reactions. A second selective metalation in the 3-position was performed using TMPMgCl·LiCl. The metalated intermediates could once again be reacted with a variety of electrophiles. The third metalation with $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ went selectively in the 2-position and allowed the synthesis of a multitude of acylation and cross-coupling products.



Scheme E. Summary of the functionalization of 1*H*-imidazo[1,2-*b*]pyrazole.

The treatment of 2,3,7-trifunctionalized 1*H*-imidazo[1,2-*b*]pyrazoles with $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ let to the formation of a series of novel 1*H*,1'*H*,5*H*,5'*H*-6,6'-biimidazo-[1,2-*b*]pyrazolylidenes, which exhibited fluorescence in solution under UV-light (Scheme F).



Scheme F. Summary of the synthesis of novel 1*H*,1'*H*,5*H*,5'*H*-6,6'-biimidazo[1,2-*b*]-pyrazolylidenes.

Part I: Highly Regioselective Addition of Organozinc Reagents to [1.1.1]Propellane

1 Introduction

1.1 Properties of [1.1.1]Propellane

The term propellane was first introduced in 1966 by *Ginsburg et. al.* to describe tricyclic hydrocarbons, which share a common carbon-carbon single bond.[1] The established shortened nomenclature defines them as [*k*.*l*.*m*]propellanes, where *k*, *l* and *m* indicate the size of the three bridges ($k \geq l \geq m$). Based on the size of the rings forming the propellane the hybridization of the bridgehead carbons changes significantly, thus influencing the reactivity of the central bond. Propellanes with large rings ($k + l + m > 8$) usually behave similar to common hydrocarbons, while small-ring propellanes ($k + l + m \leq 8$) exhibit a unique reactivity that is typically attributed to their highly strained nature.[2] This unique reactivity is especially prevalent in the smallest member of the propellane family, [1.1.1]propellane and will be discussed in the following sections.

1.1.1 Synthesis of [1.1.1]Propellane

[1.1.1]Propellane was first synthesized by *Wiberg et. al.* in 1982 through the reaction of 1,3-dibromobicyclo[1.1.1]pentane with butyllithium.[3] Subsequently, *Szeimies et. al.* developped a more convenient way to access [1.1.1]propellane,[4] which is still being used to this day with only minor modifications. For this synthesis 3-chloro-2-(chloromethyl)prop-1-ene is first converted to 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane via a cyclopropanation with dibromocarbene. Then two subsequent bromine-lithium exchanges with methyllithium lead to two intramolecular ring closures and thus form [1.1.1]propellane (Scheme 1).[5] The tricyclic compound is surprisingly stable even at room temperature and can be stored in ethereal solution below 0 °C for months without significant amounts of decomposition or polymerization.[6]

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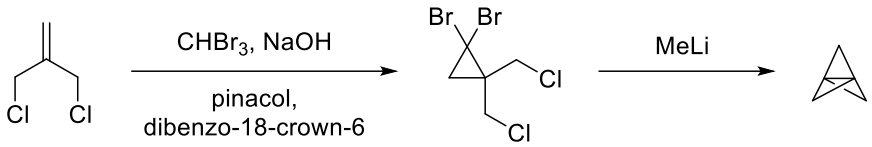
[1] J. Altman, E. Babad, J. Itzchaki, D. Ginsburg, *Tetrahedron* **1966**, *Suppl. 8*, 279-304.
[2] A.-D. Schlüter, H. Bothe, J.-M. Gosau, *Makromol. Chem.* **1991**, *192*, 2497-2519.
[3] K. B. Wiberg, F. H. Walker, *J. Am. Chem. Soc.* **1982**, *104*, 5239-5240.
[4] a) K. Semmler, G. Szeimies, J. Belzner, *J. Am. Chem. Soc.* **1985**, *107*, 6410-6411; b) J. Belzner, U. Bunz, K. Semmler, G. Szeimies, K. Opitz, A.-D. Schlüter, *Chem. Ber.* **1989**, *122*, 397-398.
[5] K. R. Mondanaro, W. P. Daily, *Org. Synth.* **1998**, *75*, 98-101.
[6] K. B. Wiberg, S. T. Waddell, *J. Am. Chem. Soc.* **1990**, *112*, 2194-2216.

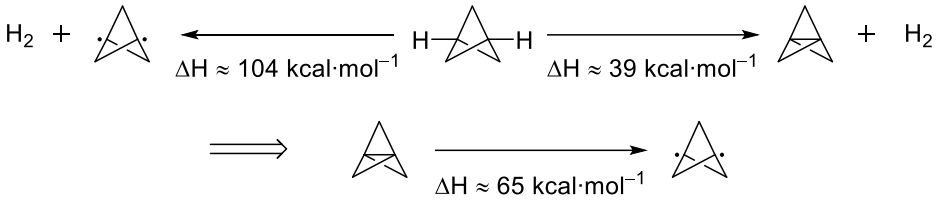


Scheme 1. Synthesis of [1.1.1]propellane according to *Szeimies*.[4,5]

1.1.2 Nature of the Central Carbon-Carbon Bond

A consequence of the bonding situation in [1.1.1]propellane is that the bridgehead carbons deviate strongly from the tetrahedral coordination typically found in sp^3-hybridized systems, as the central bond is inverted. The exact nature of this central bond has been extensively studied and debated over the years.

On one hand there is evidence pointing at a strong bonding interaction between the bridgehead carbons: From the enthalpy change during the conversion of bicyclo[1.1.1]pentane into [1.1.1]propellane plus two hydrogen atoms *Wiberg et. al.* calculated the strength of the central bond to be between approximately 65 kcal·mol^{-1} by assuming a C-H bond dissociation energy of 104 kcal·mol^{-1} (Scheme 2).[3] In addition, a diradical triplet state of [1.1.1]propellane was calculated to lie 79 kcal·mol^{-1} higher than the singlet state.[7] The exceptionally short distance between the bridgehead carbons of only 1.6 Å, as determined by low-temperature X-ray diffraction[8] and gas-phase electron diffraction[9] also hints at a strong bonding interaction alongside the central bond.



Scheme 2. Calculation of the strength of the central bond in [1.1.1]propellane as performed by *Wiberg*.[3]

On the other hand some observations seem to contradict the existence of the central bond: It was discovered that the electron density at the bond critical point of the bridge bond is

[7] a) J. E. Jackson, L. C. Allen, *J. Am. Chem. Soc.* **1984**, *106*, 591-599; b) D. Feller, E. R. Davidson, *J. Am. Chem. Soc.* **1987**, *109*, 4133-4139.
[8] P. Seiler, *Helv. Chim. Acta* **1990**, *73*, 1574-1585.
[9] L. Hedberg, K. Hedberg, *J. Am. Chem. Soc.* **1985**, *107*, 7257-7260.

depleted, as indicated by a positive Laplacian $\nabla^2\rho(r)$ of the electron density $\rho(r)$.[10] The Laplacian is the sum of all unmixed partial derivatives in the *Cartesian* coordinates x_i and thus corresponds to the trace of the *Hessian* matrix (equation 1):

$$\nabla^2 = \sum_{i=1}^{n} \frac{\partial^2}{\partial x_i^2} \tag{1}$$

The bond critical point refers to a maximum, minimum or saddle point of the charge density along the binding path between two atoms.[11] A positive Laplacian of the electron density at the bond critical point is typically associated with ionic bonds. As the central bond is formed between two identical atoms with identical electronegativity one would however expect it to be of covalent nature.[12] In addition, [1.1.1]propellane also displays a negative total overlap population, which according to *Mulliken* points at an anti-bonding interaction.[13] Molecular orbital calculations resulted in a closed-shell singlet state with the HOMO being a bonding molecular orbital connecting the bridgehead atoms, and the LUMO being its anti-bonding counterpart.[14] However, the HOMO has an overall destabilizing character, as evidenced by the fact that it gets stabilized when the central bond is stretched.[7a,14] In addition, the removal of electron density from the HOMO, either through ionization to the radical cation or through halogen bonding, results in a shortening of the bridge bond.[7b,15]

1.1.3 The Central Bond in [1.1.1]Propellane as a Charge-Shift Bond

A possible explanation for the seemingly contradicting properties of the central bond in [1.1.1]propellane was proposed by *Shaik et. al.* who classified it as a "charge-shift bond":[16] In modern valence bond (VB) theory the VB wave function Ψ(VB) of a bond A-X is seen as a combination of a covalent form Φ_{cov} (A·-·X), which is stabilized via spin pairing, and two ionic forms $\Phi_{ion}(A^+X^-)$ and $\Phi'_{ion}(A^-X^+)$, which are stabilized via electrostatic interactions (equation 2):

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[10] M. Messerschmidt, S. Scheins, L. Grubert, M. Plätzel, G. Szeimies, C. Paulmann, P. Luger, *Angew. Chem. Int. Ed.* **2005**, *44*, 3925-3928.
[11] K. B. Wiberg, R. F. W. Bader, C. D. H. Lau, *J. Am. Chem. Soc.* **1987**, *109*, 985-1001.
[12] Y. Yang, *J. Phys. Chem. A* **2012**, *116*, 10150-10159.
[13] M. D. Newton, J. M. Schulman, *J. Am. Chem. Soc.* **1972**, *94*, 773-778.
[14] W. D. Stohrer, R. Hoffmann, *J. Am. Chem. Soc.* **1972**, *94*, 779-786.
[15] a) E. Honegger, H. Huber, E. Heilbronner, W. P. Dailey, K. B. Wiberg, *J. Am. Chem. Soc.* **1985**, *107*, 7172-7174; b) J. Joy, E. Akhil, E. D. Jemmis, *Phys. Chem. Chem. Phys.* **2018**, *20*, 25792-25798.
[16] a) S. Shaik, D. Danovich, B. Silvi, D. L. Lauvergnat, P. C. Hiberty, *Chem. Eur. J.* **2005**, *11*, 6358-6371; b) S. Shaik, D. Danovich, W. Wu, P. C. Hiberty, *Nat. Chem.* **2009**, *1*, 443-449.

$$\Psi(VB) = c_1\Phi_{cov} + c_2\Phi_{ion} + c_3\Phi'_{ion} \quad (2)$$

In conventional covalent or ionic bonds only one of these three terms constitutes the majority of the bonding energy. Even in polar-covalent bonds the bonding energy is typically mostly attributed to Φ_{cov} with one of the ionic terms being of secondary importance. However, in some cases, for example in the F_2 and HF molecules, this simplified description is not able to correctly describe the bonding situation, as there is a significant amount of covalent-ionic mixing. This mixing leads to a resonance energy stabilization, the "charge-shift resonance energy" (RE_{cs}), which is defined as the energy difference between the ground state and the major VB structure (either covalent or ionic). Bonds in which the RE_{cs} contributes to more than 50% of the overall bonding energy are considered charge-shift bonds.[16] *Shaik et. al.* calculated Φ_{cov} to be the predominant component of the central bond in [1.1.1]propellane with a weight of 62%. The two ionic components each have a weight of 19%. However, the calculated energy of the covalent VB structure of [1.1.1]propellane at the experimentally determined bridgehead bond length of 1.6 Å was +11 kcal·mol^{-1}, while the ground state lies at −61 kcal·mol^{-1}. Thus, the bridgehead bond in [1.1.1]propellane exhibits an exceptionally large RE_{cs} of 72 kcal·mol^{-1} and can be classified as a charge-shift bond. In addition, the covalent VB structure was found to be repulsive with its energy decreasing when the bridgehead bond is stretched from 1.6 to 1.8 Å. Only when accounting for RE_{cs} the calculated ground state correctly predicts the energetic minimum at the equilibrium distance of 1.6 Å (Figure 1). Such a discrepancy between the covalent dissociation curve and the ground state dissociation curve is also typical for charge-shift bonds.[17]

[17] W. Wu, J. Gu, J. Song, S. Shaik, P. C. Hiberty, *Angew. Chem. Int. Ed.* **2009**, *48*, 1407-1410.

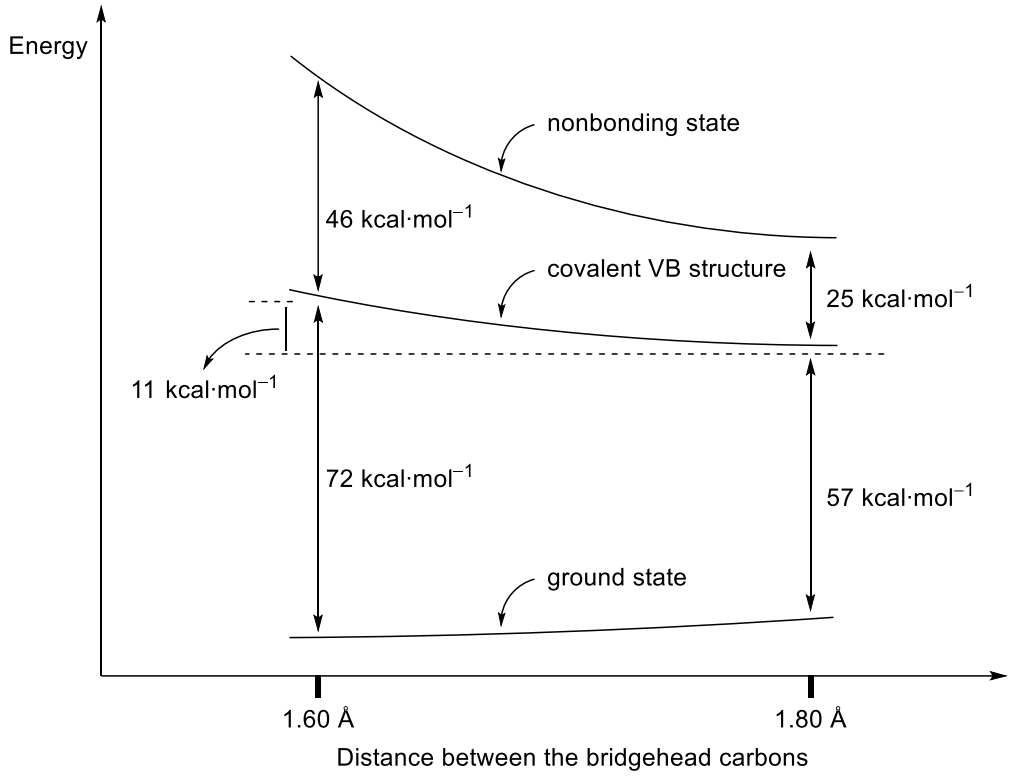


Figure 1. Dissociation curves for the ground state, covalent VB structure and the nonbonding state of [1.1.1]propellane as calculated by *Shaik* at the BOVB level.[17]

1.2 From [1.1.1]Propellane to Bicyclo[1.1.1]pentanes

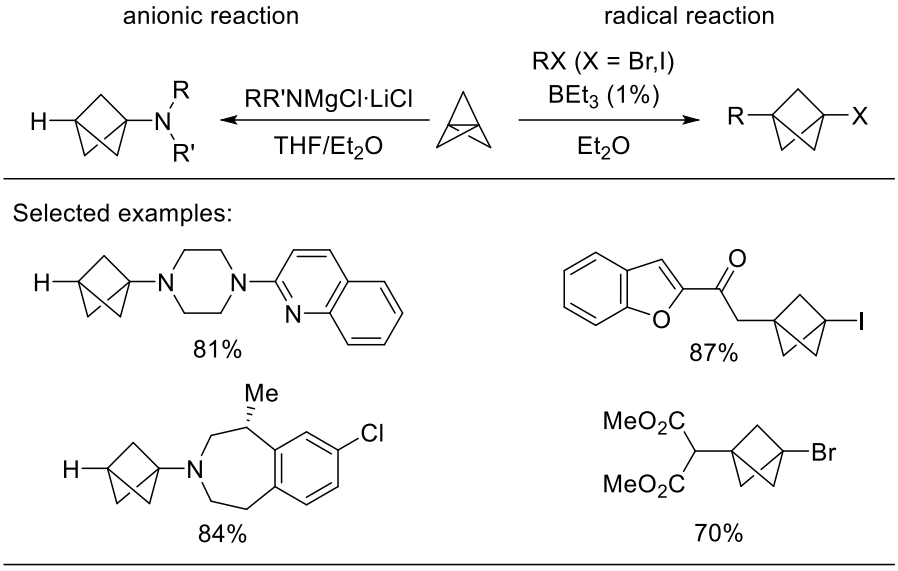
A consequence of the unique bonding situation in [1.1.1]propellane is its "omniphilic" reactivity towards cations, anions as well as radicals.[18] While the reactions with cationic reagents typically result in a mostly unselective cage fragmentation,[19] the reactions with anions[20] and radicals[21] result in the formation of bicyclo[1.1.1]pentanes (BCPs). This includes

[18] A. J. Sterling, A. B. Dürr, R. C. Smith, E. A. Anderson, F. Duarte, *Chem. Sci.* **2020**, *11*, 4895-4903.

[19] a) K. B. Wiberg, W. P. Dailey, F. H. Walker, S. T. Waddell, L. S. Crocker, M. D. Newton, *J. Am. Chem. Soc.* **1985**, *107*, 7247-7257; b) D. Lasányi, G. L. Tolnai, *Org. Lett.* **2019**, *21*, 10057-10062; c) S. Yu, A. Noble, R. B. Bedford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2019**, *141*, 20325-20334.

[20] a) R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, *351*, 241-246; b) J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 3209-3226; c) J. M. E. Hughes, D. A. Scarlata, A. C.-Y. Chen, J. D. Burch, J. L. Gleason, *Org. Lett.* **2019**, *21*, 6800-6804; for the addition of organometallics see section 1.3.

the anionic strain-release aminations by *Baran*[20a,b] and *Gleason*,[20c] as well as the triethylborane catalyzed radical additions by *Anderson*[21e] (Scheme 3).



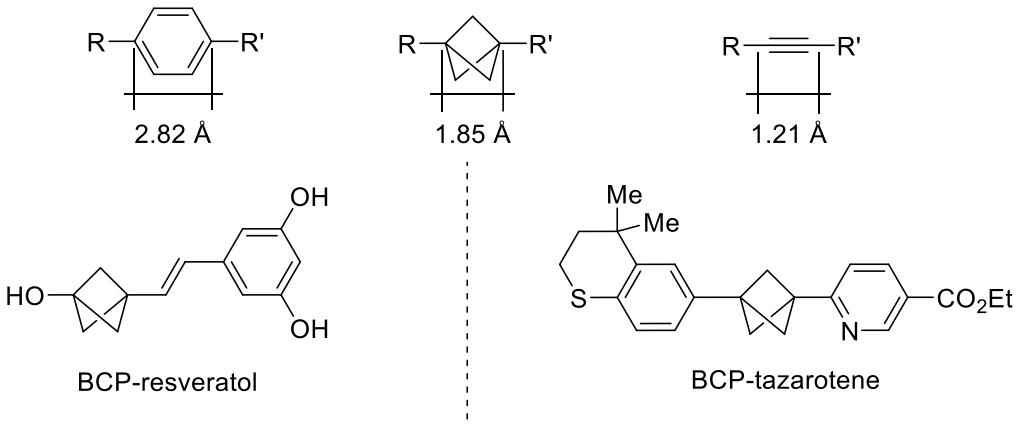
Scheme 3. Strain-release amination[20b] and triethylboran catalyzed radical addition to [1.1.1]propellane.[21e]

The bicyclo[1.1.1]pentane moiety has sparked a lot of interest in recent years as a bioisoster in pharmaceutical compounds. As the dihedral angle between the two substituents in a BCP derivative is 180° they have been explored as bioisosteres for both *para*-phenyl[22] as well as

[21] a) K. B. Wiberg, S. T. Waddell, K. Laidig, *Tetrahedron Lett.* **1986**, *27*, 1553-1556; b) K. B. Wiberg, S. T. Waddell, *J. Am. Chem. Soc.* **1990**, *112*, 2194-2216; c) J. Kanazawa, K. Maeda, M. Uchiyama, *J. Am. Chem. Soc.* **2017**, *139*, 17791-17794; d) R. M. Bär, S. Kirschner, M. Nieger, S. Bräse, *Chem. Eur. J.* **2018**, *24*, 1373-1382; e) D. F. J. Caputo, C. Arroniz, A. B. Dürr, J. J. Mousseau, A. F. Stepan, S. J. Mansfield, E. A. Anderson, *Chem. Sci.* **2018**, *9*, 5295-5300; f) M. L. J. Wong, J. J. Mousseau, S. J. Mansfield, E. A. Anderson, *Org. Lett.* **2019**, *21*, 2408-2411; g) J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte, E. A. Anderson, *ACS Catal.* **2019**, *9*, 9568-9574; h) S. K. Rout, G. Marghem, J. Lan, T. Leyssens, O. Riant, *Chem Commun.* **2019**, *55*, 14976-14979; i) J. Nugent, B. R. Shire, D. F. J. Caputo, H. D. Pickford, F. Nightingale, I. T. T. Houlsby, J. J. Mousseau, E. A. Anderson, *Angew. Chem. Int. Ed.* **2020**, *59*, 11866-11870; j) J. H. Kim, A. Ruffoni, Y. S. S. Al-Faiyz, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2020**, *59*, 8225-8231.

[22] a) A. F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O'Sullivan, K. J. DiRico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddel, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchinson, A. J. Hallgreen, C. E. Oborski, A. E. Robshaw, B. Sneed, C. J. O'Donnell, *J. Med. Chem.* **2012**, *55*, 3414-3424; b) Y. P. Auberson, C. Brocklehurst, M. Furegati, T. C. Fessard, G. Koch, A. Decker, L. La Vecchia, E. Briard, *ChemMedChem* **2017**, *12*, 590-598; c) Y. L. Goh, Y. T. Cui, V. Pendharkar, V. A. Adsool, *ACS Med. Chem. Lett.* **2017**, *8*, 516-520.

alkyne[23] moieties (Scheme 4), for example in resveratol (*para*-phenyl)[22c] or tazarotene (alkyne).[23] When substituting the *para*-phenyl unit with a bicyclo[1.1.1]pentane a significant improvement of some physicochemical properties over multiple different examples was observed. This included a decrease in undesired nonspecific binding (NSB) as well as an increased water solubility.[22b] In addition, BCPs have been used as potential bioisosteres for terminal *tert*-butyl groups,[24] as well as rigid-linear linkers in rods, liquid crystals, molecular rotors and polymers.[25]



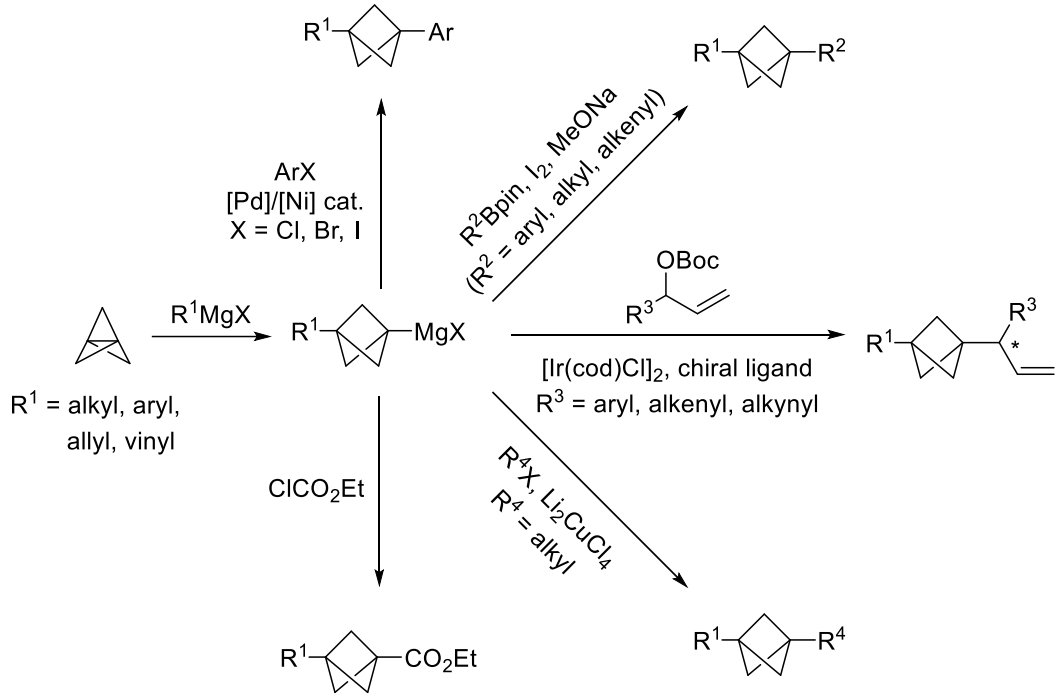
Scheme 4. Bicyclo[1.1.1]pentanes as bioisosteres of *para*-phenyl[22c] and alkyne[23] moieties.

1.3 Addition of Organometallic Compounds to [1.1.1]Propellane

The first successful addition of organometallic reagents to [1.1.1]propellane was described in 1998 by *S. Guffler* in his Ph.D. thesis under the guidance of *G. Szeimies*.[26] His work included the addition of several aryl and alky *Grignard* reagents to [1.1.1]propellane, a reactivity that was further developed by *de Meijere*,[27] *Knochel*,[23] *Aggarwal*[28] and *Cossy*.[29] The main

[23] I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12774-12777.
[24] a) M. R. Barbachyn, D. K. Hutchinson, D. S. Toops, R. J. Reid, G. E. Zurenko, B. H. Yagi, R. D. Schaadt, J. W. Allison, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 671-676; b) M. V. Westphal, B. T. Wolfstädter, J.-M. Plancher, J. Gatfield, E. M. Carreira, *ChemMedChem* **2015**, *10*, 461-469.
[25] a) A. M. Dilmaç, E. Spuling, A. de Meijere, S. Bräse, *Angew. Chem. Int. Ed.* **2017**, *56*, 5684-5718; b) G. M. Locke, S. S. R. Bernhard, M. O. Senge, *Chem. Eur. J.* **2019**, *25*, 4590-4647.
[26] S. Guffler, Wege zu 1,3-disubstituierten Bicyclo[1.1.1]pentanen: synthetische und mechanistische Aspekte, Ph.D. thesis, Humboldt-Universität Berlin, **1998**.
[27] M. Messner, S. I. Kozhushkov, A. de Meijere, *Eur. J. Org. Chem.* **2000**, 1137-1155.
[28] a) S. Yu, C. Jing, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2020**, *59*, 3917-3921; b) S. Yu, C. Jing, A. Noble, V. K. Aggarwal, *Org. Lett.* **2020**, *22*, 5650-5655.

advantage of this methodology is the formation of BCP-*Grignards*, which can be further functionalized to access a multitude of different BCP derivatives. The range of reported follow-up reactions includes nickel- and palladium-catalyzed cross couplings,[23,27] three-component couplings with organoboronic esters,[28a] iridium-catalyzed asymmetric allylic substitutions,[28b] copper-catalyzed alkylations,[29] and the reaction with ethyl chloroformate[23] (Scheme 5).

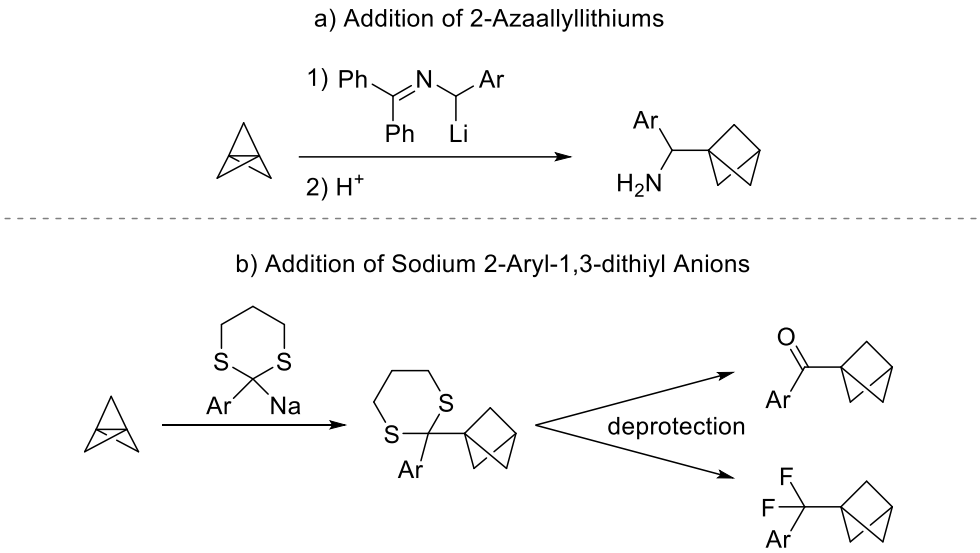


Scheme 5. Addition of *Grignard* reagents to [1.1.1]propellane followed by different functionalizations.[23,26-29]

In addition, some reactions of [1.1.1]propellane with organo-alkali reagents have been reported: *Aggarwal et. al.* achieved a successful addition of secondary and tertiary alkyllithium reagents, whereas primary alkyllithiums were unreactive at −78 °C and let to polymerization at elevated temperatures.[28a] *Walsh et. al.* developed a synthetic route towards BCP benzylamines by adding 2-azaallyllithiums to [1.1.1]propellane, followed by an acidic work-up (Scheme 6a).[30] The same group also reported the addition of sodium 2-aryl-1,3-

[29] C. Andersen, V. Ferey, M. Daumas, P. Bernardelli, A. Guérinot, J. Cossy, *Org. Lett.* **2020**, *22*, 6021-6025.
[30] R. A. Shelp, P. J. Walsh, *Angew. Chem. Int. Ed.* **2018**, *57*, 15857-15861.

dithiyl anions, leading to BCP dithianes, which could easily be transformed into either BCP ketones or *gem*-difluoro BCPs[31] (Scheme 6b).



Scheme 6. Addition of 2-azaallyllithiums[30] and sodium 2-aryl-1,3-dithiyl anions[31] to [1.1.1]propellane.

1.4 Organozinc Reagents

Organozinc reagents were among the first synthesized organometallic reagents, with *E*. *Frankland* reporting the formation of ethyl zinc iodide and diethylzinc starting from ethyl iodide and granulated zinc in 1849.[32]

Due to the significantly higher electronegativity of zinc (1.65 calculated according to the *Pauling* scale) compared to lithium (0.98) or magnesium (1.31),[33] the carbon-metal bond in organozinc reagents is less polarized, which results in a lower reactivity (Figure 2). This leads to an increased functional group tolerance, allowing for clean reactions in the presence of moieties that would be attacked by organomagnesium or organolithium reagents, such as

[31] N. Trongsiriwat, Y. Pu, Y. Nieves-Quinones, R. A. Shelp, M. C. Kozlowski, P. J. Walsh, *Angew. Chem. Int. Ed.* **2019**, *58*, 13416-13420.
[32] E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171-213.
[33] a) L. Pauling, *J. Am. Chem. Soc.* **1932**, *54*, 3570-3582; b) A. L. Allred, *J. Inorg. Nucl. Chem.* **1961**, *17*, 215-221.

carbonyl compounds or nitriles.[34] This functional group tolerance is even observed in the case of allylic organozinc reagents, which are significantly more reactive than alkylic, aromatic or even benzylic organozinc reagents, due to the higher ionic character of the allylic carbon-zinc bond.[35]

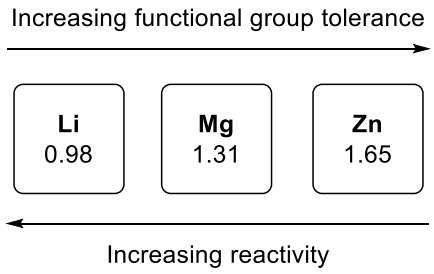


Figure 2. Comparison of the electronegativities of lithium, magnesium and zinc according to *Pauling*.[33]

There are three main ways to synthesize organozinc reagents.[36] The most common strategy is the oxidative insertion of elemental zinc into organic halides.[37] These reactions are especially successful if activated zinc is utilized, which can be generated through the reduction of zinc chloride with lithium naphthalenide (*Rieke*-zinc).[38] Another way to improve

[34] a) R. Dieter, *Tetrahedron* **1999**, *55*, 4177-4236; b) T. Harada in *The Chemistry of Organozinc Compounds* (Ed.: I. M. Zvi Rappoport), John Wiley & Sons, Ltd, Chichester, UK, **2007**, pp. 685-711; c) P. Knochel, H. Leuser, L.-Z. Cong, S. Perrone, F. F. Kneisel in *Handbook of Functionalized Organometallics* (Ed. P. Knochel), John Wiley & Sons, Ltd, New York, United States, **2008**, pp. 251-346.

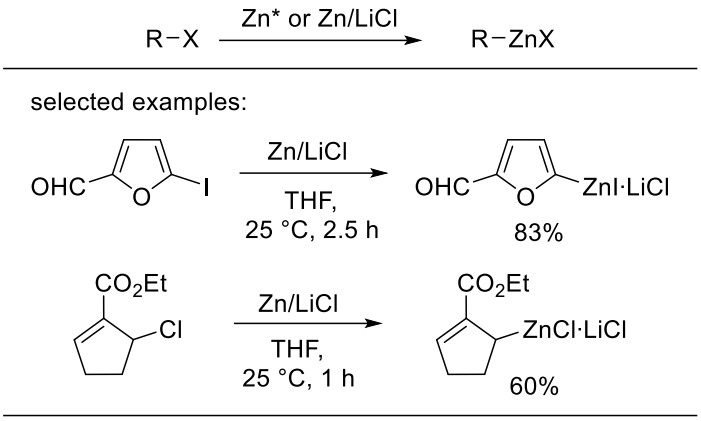
[35] a) G. Courtois, A. Al-Arnaout, L. Miginiac, *Tetrahedron Lett.* **1985**, *26*, 1027-1030; b) P. Knochel, R. Singer, *Chem. Rev.* **1993**, *93*, 2117-2188; c) M. Nakamura, A. Hirai, M. Sogi, E. Nakamura, *J. Am. Chem. Soc.* **1998**, *120*, 5846-5847; d) I. Marek, G. Sklute, *Chem. Commun.* **2007**, 1683-1691; e) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376-5377; f) M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10662-10665; g) Y. Dembélé, C. Belaud, P. Hitchcock, J. Villiéras, *Tetrahedron Asymmetry* **1992**, *3*, 351-354; h) V. Nyzam, C. Belaud, F. Zammattio, J. Villiéras, *Tetrahedron Asymmetry* **1996**, *7*, 1835-1843; i) C. Sämann, P. Knochel, *Synthesis* **2013**, *45*, 1870-1876.

[36] D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540-1552.

[37] G. Dagousset, C. Francois, T. Leon, R. Blanc, E. Sansiaume-Dagousset, P. Knochel, *Synthesis* **2014**, *46*, 3133-3171.

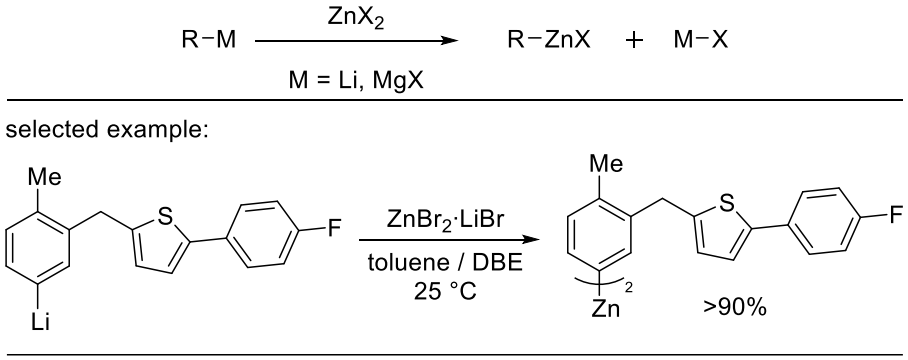
[38] a) R. D. Rieke, R. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323-4324; b) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445-1453; c) R. D. Rieke, M. V. Hanson, J. D. Brown, Q. J. Niu, *J. Org. Chem.* **1996**, *61*, 2726-2730; d) R. D. Rieke, *Science* **1989**, *246*, 1260-1264.

the insertion of elemental zinc into organic halides is the addition of lithium chloride to the reaction mixture (Scheme 7).[39]



Scheme 7. Synthesis of organozinc reagents via oxidative insertion.[39]

A further well-established way towards organozinc reagents is the transmetalation of lithium or magnesium organometallics with different zinc^{II} salts. This reactivity stems from the higher electronegativity of zinc compared to the other metals. Thus, the resulting organozinc reagent and the formed metal salt are thermodynamically more stable than the starting materials (Scheme 8).[40]

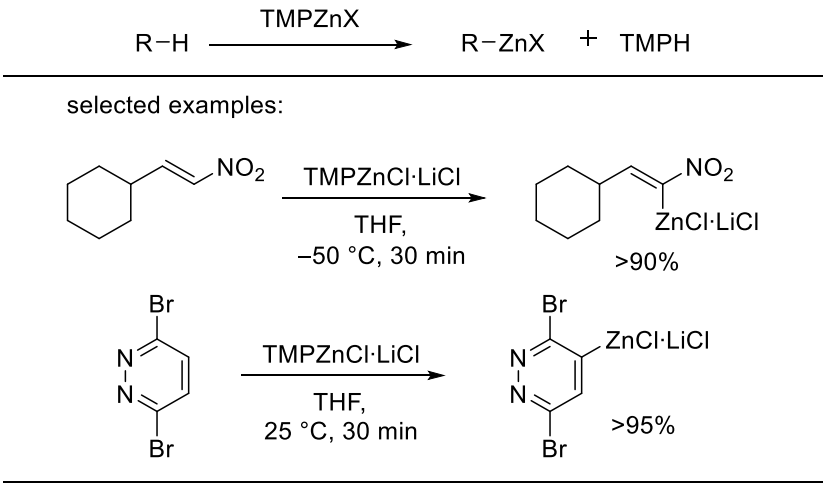


Scheme 8. Synthesis of organozinc reagents via transmetalation.[40]

[39] a) A. Krasovskiy, V. Malakov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040-6044; b) N. Boudet, S. Sae, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358-12359.

[40] a) R. F. W. Jackson in *Organozinc Reagents – A Practical Approach* (Eds.: P. Knochel, P. Jones), Oxford University Press, Oxford, UK, **1999**, pp. 37-56; b) S. Lemaire, I. N. Houpis, T. Xiao, J. Li, E. Digard, C. Gozlan, R. Liu, A. Gavryushin, C. Diène, Y. Wang, V. Farina, P. Knochel, *Org. Lett.* **2012**, *14*, 1480-1483.

Finally, the directed metalation of unsaturated, aromatic and heterocyclic molecules using various zinc TMP bases (TMP = 2,2,6,6-tetramethylpiperidyl) gives access to the corresponding zinc reagents (Scheme 9).[41]

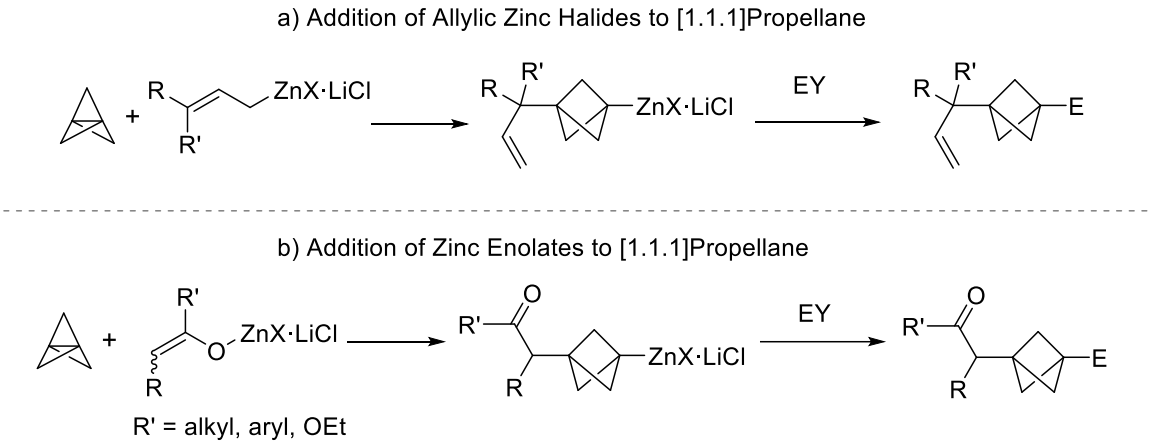


Scheme 9. Synthesis of organozinc reagent via directed metalation.[41]

[41] a) T. Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914-1917; b) A. Unsinn, M. J. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128-1131; the different TMP bases are discussed in greater detail the introduction of Part II of this thesis.

2 Objective

Unlike organomagnesium or organolithium reagents, an addition of organozinc halides to [1.1.1]propellane has not yet been reported. Indeed, preliminary experiments showed that alkyl-, aryl- and benzylzinc halides were not able to react with [1.1.1]propellane even under harsh conditions (100 °C, up to 60 h). Since allylic zinc halides display an enhanced reactivity due to a more polar carbon-zinc bond,[35] it was envisioned that they could add to [1.1.1]propellane, allowing the formation of zincated BCPs (Scheme 10a). Subsequent trapping with various electrophiles (EY) would then provide double functionalized BCPs. A similar reactivity would be expected for zinc enolates generated from ketones and esters,[42] leading to a different class of zincated BCPs, which could also be trapped with various electrophiles (Scheme 10b). The objective was to optimize conditions for these additions. Another goal was to utilize this new protocol to synthesize a BCP-bioisostere of the synthetic opioid pethidine, which could then be compared to the original drug. Finally, this unprecedented reactivity should be rationalized via density-functional theory calculations.



Scheme 10. Addition of allylic zinc halides and ketone and ester zinc enolates to [1.1.1]propellane, followed by trapping with electrophiles (EY).

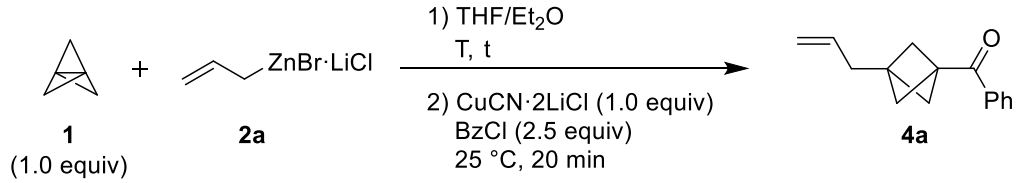
[42] a) J. Dekker, A. Schouten, P. H. M. Budzelaar, J. Boersma, G. J. M. van der Kerk, *J. Organomet. Chem.* **1987**, *320*, 1-12; b) G. K. Jarugumilli, C. Zhu, S. P. Cook, *Eur. J. Org. Chem.* **2012**, 1712-1715; c) A. Baba, M. Yasuda, Y. Nishimoto in *Comprehensive Organic Synthesis II*, Vol. 2 (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, pp. 523-542.

3 Results and Discussion

3.1 Optimization of Reaction Conditions

Reaction conditions for the addition to [1.1.1]propellane (**1**) were optimized using allylzinc bromide complexed with lithium chloride (**2a**). Under the conditions, that had been optimized for the addition of arylmagnesium halides to [1.1.1]propellane[23] (**1**, 2.0 equiv of organometallic species, 50 °C, 65 h or 100 °C, 3 h, Table 1, entries 1 and 2), the desired functionalized BCP **4a** was obtained in 95-96% yield after a copper mediated acylation with benzoyl chloride. This indicates that the intermediary zincated BCP of type **3** is very stable even at high temperatures. Further reaction temperature variation showed that the addition was completed after only 2 hours at 25 °C (entries 3 and 4). In comparison, the reaction of alkyl- and arylmagnesium halides with [1.1.1]propellane (**1**) requires 3-7 days at 25 °C, resulting in moderate yields.[26-29] A reduction of the amount of zinc reagent to 1.5 equivalents lowered the yield to 71% (entry 5).

Table 1. Screening of reaction conditions for the addition of allyl zinc bromide complexed with lithium chloride (**2a**) to [1.1.1]propellane (**1**) followed by copper-catalyzed acylation.



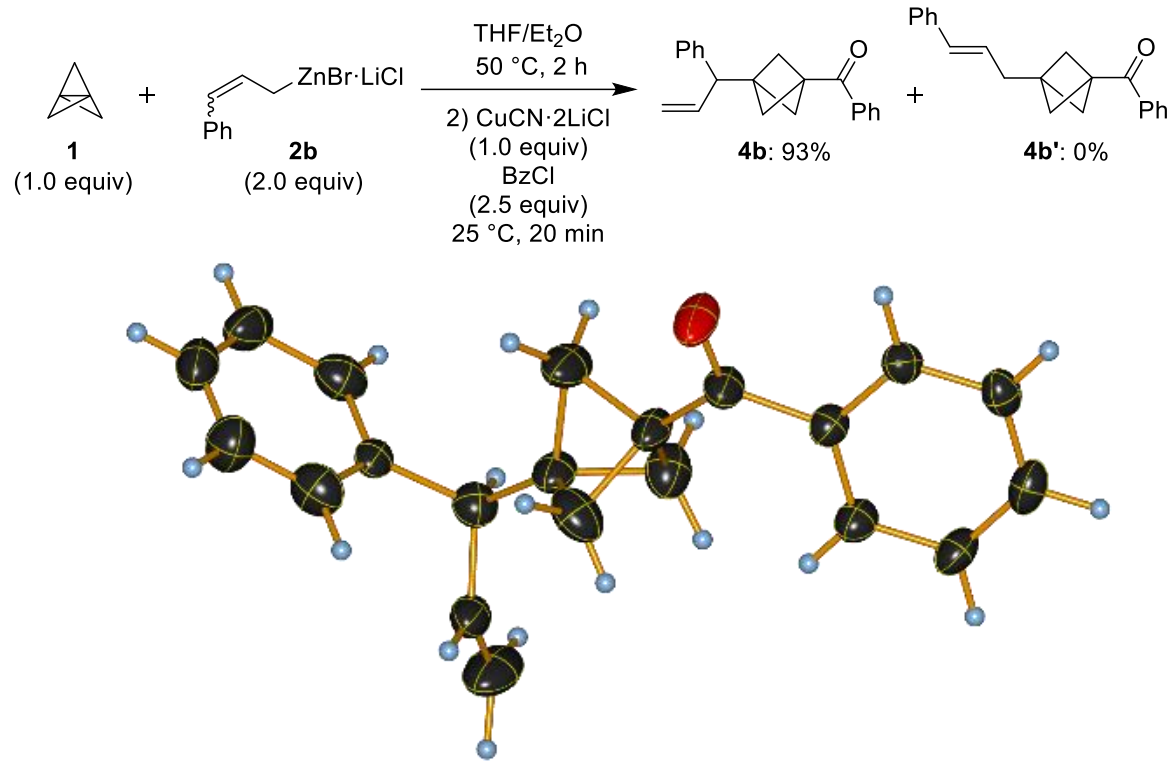
1 (1.0 equiv) **2a** **4a**

entry	equivalents of **2a**	reaction conditions	yield [%][a]
1	2.0	50 °C, 65 h	96[b]
2	2.0	100 °C, 3 h	95
3	2.0	25 °C, 1 h	88
4	2.0	25 °C, 2 h	96[b]
5	1.5	25 °C, 2 h	71[c]

[a] GC-yields using undecane as an internal standard. [b] Isolated yield of analytically pure product. [c] No yield improvement was observed after an additional hour of reaction time.

Interestingly, when switching to cinnamylzinc bromide complexed with lithium chloride (**2b**), only the regioisomer **4b** was obtained in 93% yield (Scheme 11). The structure of this product was confirmed via X-ray analysis and indicates an allylic rearrangement of the

organozinc species **2b** during the reaction. The other regioisomer **4b'** with the phenyl group attached to the terminal position of the allylic system was not observed.[43]



Scheme 11. Addition of cinnamyl zinc bromide complexed with lithium chloride (**2b**) to [1.1.1]propellane (**1**) and X-ray structure of the resulting product **4b**.

3.2 Addition of Allylic Organozinc Halides to [1.1.1]Propellane

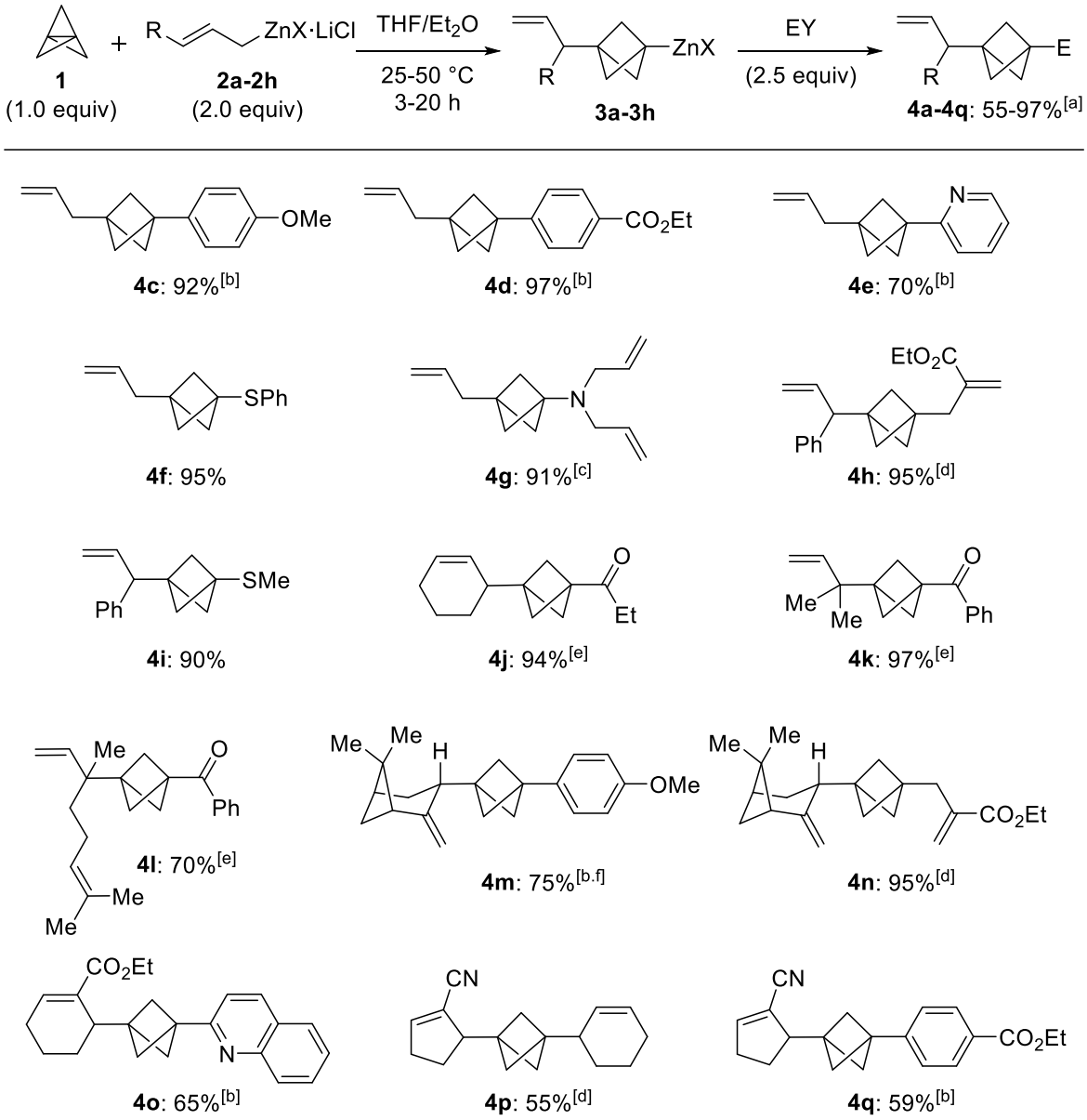
With the optimized procedure in hand, a variety of BCP-derivatives were prepared using allylzinc bromide (**4a**, **4c-4g**, Scheme 12), cinnamylzinc bromide (**4b**, **4h**, **4i**) and cyclohex-2-en-1-ylzinc bromide (**4j**), as well as allylic zinc reagents derived from terpenoids,[35f,44] such as prenol (**4k**), geraniol (**4l**) and (–)-myrtenol (**4m**, **4n**), in 70-97% yield. In addition, allylic zinc

[43] A test reaction with prenylmagnesium chloride showed that the reaction of allylic magnesium halides with [1.1.1]propellane (**1**) is also much quicker than the reaction of alkyl or aryl magnesium halides and was completed within 2 h at room temperature. The exclusive formation of the regioisomer that results from an allylic rearrangement was observed. This suggests that the reactions of allylic zinc and magnesium reagents with [1.1.1]propellane proceed via the same mechanism.

[44] a) G. Courtois, A. Al-Arnaout, L. Miginiac, *Tetrahedron Lett.* **1985**, *26*, 1027-1030; b) P. Knochel, R. Singer, *Chem. Rev.* **1993**, *93*, 2117-2188; c) M. Nakamura, A. Hirai, M. Sogi, E. Nakamura, *J. Am. Chem. Soc.* **1998**, *120*, 5846-5847; d) I. Marek, G. Sklute, *Chem. Commun.* **2007**, 1683-1691; e) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376-5377.

reagents bearing functional groups such as an ester or a nitrile[35] reacted smoothly, leading to the corresponding functionalized BCPs **4o**-**4q** in 55-65% yield. In all cases, only a single regioisomer of the product was observed. The intermediate zincated BCPs of type **3** were successfully trapped using *Negishi*-type cross-couplings[45] with electron-rich (**4c**, **4m**), electron-deficient (**4d**, **4q**) and heterocyclic (**4e**, **4o**) halides in 59-97% yield,[46] as well as thiolations with *S*-aryl (**4f**) and *S*-alkyl sulfonothioates (**4i**)[47] in 90-95% yield. A cobalt-catalyzed electrophilic amination with *N*,*N*-diallyl-*O*-benzoylhydroxylamine[48] provided the aminated BCP **4g** in 91% yield. Finally, the zincated BCPs of type **3** underwent copper-mediated allylations and acylations using various allylic halides and acid chlorides,[49] leading to the functionalized BCPs **4a**, **4b**, **4h**, **4j**, **4k**, **4l**, **4n** and **4p** in 55-97% yield.

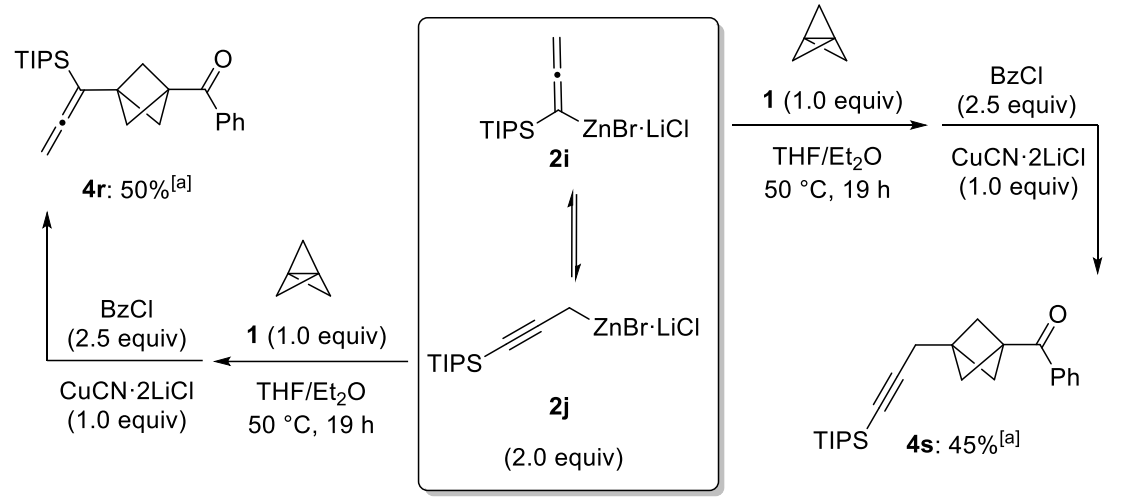
[45] A. O. King, N. Okukado, E.-I. Negishi, *J. Chem. Soc. Chem. Commun.* **1977**, *19*, 683-684.
[46] Without CuCN·2LiCl as a cocatalyst the yields of the cross-coupling were approximately 50% lower. CuI was a significantly less effective cocatalyst than CuCN·2LiCl.
[47] K. Fujiki, N. Tanifuji, Y. Sasaki, T. Yokoyama, *Synthesis* **2002**, *3*, 343-348.
[48] a) Y.-H. Chen, S. Graßl, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 1108-1111; b) S. Graßl, Y.-H. Chen, C. Hamze, C. P. Tüllmann, P. Knochel, *Org. Lett.* **2019**, *212*, 494-497.
[49] M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1988**, *29*, 2395-2396.



[a] Isolated yields of analytically pure product. [b] Catalyzed by $PdCl_2(dppf)\cdot CH_2Cl_2$ (5%) and CuCN·2LiCl (10%). [c] Catalyzed by $CoCl_2$ (3%). [d] Catalyzed by CuCN·2LiCl (20%). [e] Mediated by CuCN·2LiCl (1.0 equiv). [f] Structure confirmed via X-ray analysis.

Scheme 12. Addition of allylic zinc halides of type **2** to [1.1.1]propellane (**1**) yielding the functionalized BCPs **4a-4q**.

When employing the allenic zinc reagent **2i**, which is in equilibrium with the propargylic zinc reagent **2j**,[50] a separable mixture of the allenic product **4r** (50% yield) and the propargylic product **4s** (45% yield) was obtained after a copper-mediated acylation with benzoyl chloride (2.5 equiv, Scheme 13). This leads to the assumption, that both of the isomeric zinc reagents **2i** and **2j** react with [1.1.1]propellane (**1**) with similar reaction rates.



[a] Isolated yields of analytically pure product.

Scheme 13. Addition of an equilibrium mixture of the allenic zinc reagent **2i** and the propargylic zinc reagent **2j** to [1.1.1]propellane (**1**) yielding the functionalized BCPs **4r** and **4s**.

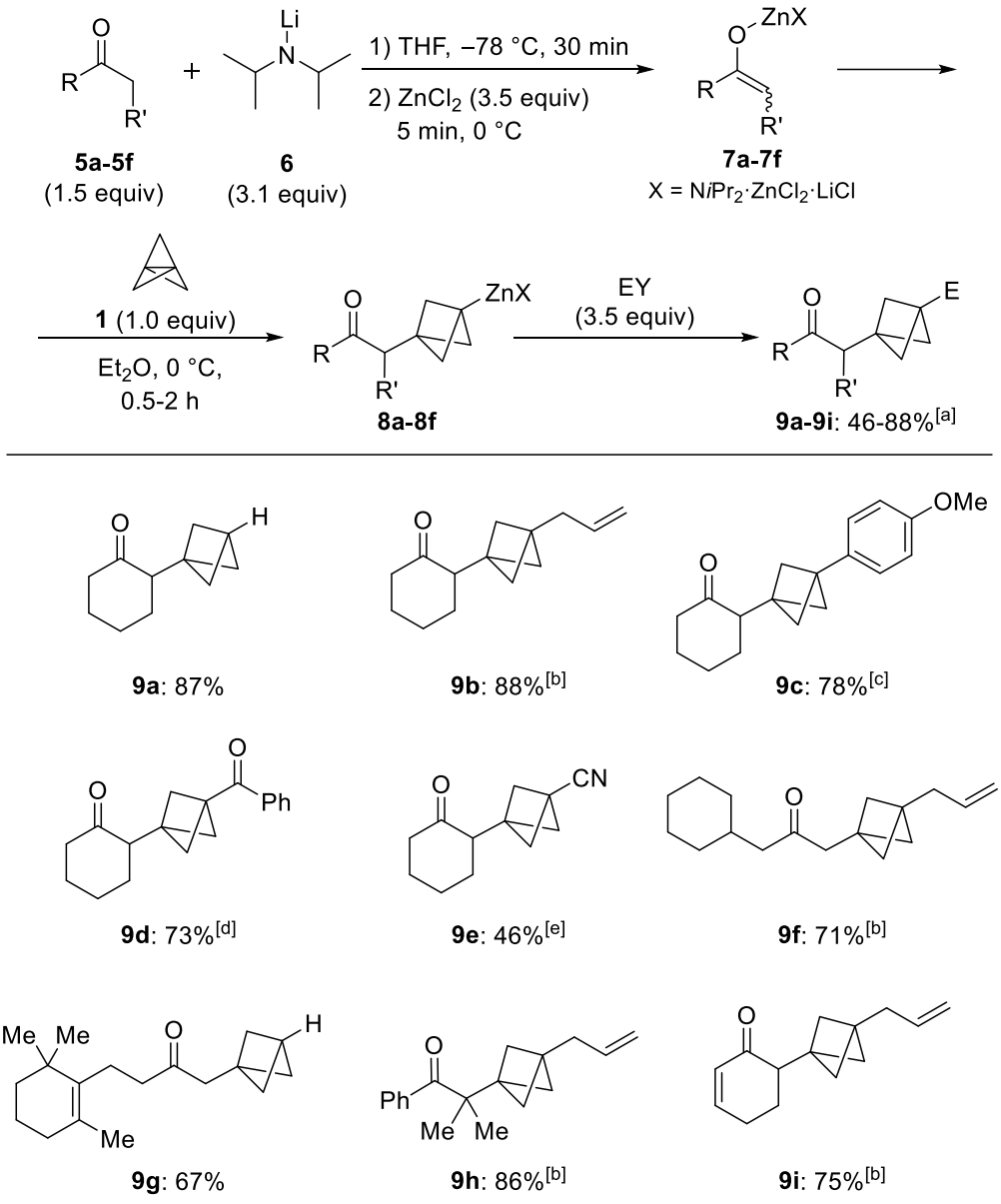
3.3 Addition of Zinc Enolates to [1.1.1]Propellane

In order to generate zinc enolates ketones of type **5** were treated with an equimolar amount of LDA (**6**) at −78 °C, followed by the same amount of $ZnCl_2$. The resulting zinc enolates added smoothly to [1.1.1]propellane (1, 0.5-2 h, 0 °C, Scheme 14). However, the newly generated zincated BCPs were mostly protonated before they could be trapped with electrophiles, probably due to the competitive deprotonation of the acidic protons in α-position to the carbonyl group. This problem was solved by using 2 equivalents of LDA for 1 equivalent of the ketone, followed by transmetalation with $ZnCl_2$ (2.3 equiv), presumably

[50] a) J. A. Marshall, B. W. Gung, M. L. Grachan in *Modern Allene Chemistry*, Vol. 1 (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**, pp. 493-592; b) J. A. Marshall in *The Chemistry of Organozinc Compounds* Vol. 1 (Eds.: Z. Rappoprt, I. Marek), John Wiley & Sons, Inc., Hoboken, **2006**, pp.:421-455; c) D. R. Fandrick, J. Saha, K. R. Fandrick, S. Sanyal, J. Ogikubo, H. Lee, F. Roschangar, J. J. Song, C. H. Senanayake, *Org. Lett.* **2011**, *13*, 5616-5619.

leading to mixed zinc enolates coordinated with N*i*Pr$_2$ (**7**). The zincated BCPs of type **8** that resulted from the addition of these amidozinc enolates to [1.1.1]-propellane (**1**, 0.5-2 h, 0 °C, Scheme 14) were apparently much less prone to protonation compared to the standard zincated BCPs.[51] Alternatively, the additional amide might also deprotonate the ketone products, thus removing the acidic protons. Possible trapping reactions included protonation (**9a**, **9g**), copper-catalyzed allylations (**9b**, **9f**, **9h**, **9i**), a palladium-catalyzed *Negishi*-type cross-coupling (**9c**),[45] an acylation (**9d**) and a cyanation performed with tosyl cyanide (**9e**). The overall yield of the sequence including enolate addition and electrophilic trapping was 46-88%. In the case of cyclohexyl acetone and dihydro-β-ionone a regioselective enolate formation was achieved and only the products **9f** and **9g**, in which the BCP unit is attached to the terminal methyl groups, were obtained in 67-71% yield. Moreover, the sterically hindered isobutyrophenone was added to **1**, leading to the BCP-derivative **9h** in 86% yield. The reaction with cyclohex-2-en-1-one led to the formation of the expected cyclohexenone derivative **9i** in 75% yield.

[51] The enhanced stability of the zincated BCPs towards protonation in the presence of additional amide is reminiscent to the effect observed for organozinc pivalates. For reference see: a) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9428-9432; b) 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*, 2706-2710; c) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289-12297; d) Y.-H. Chen, M. Ellwart, V. Malakhov, P. Knochel, *Synthesis* **2017**, *49*, 3215-3223.

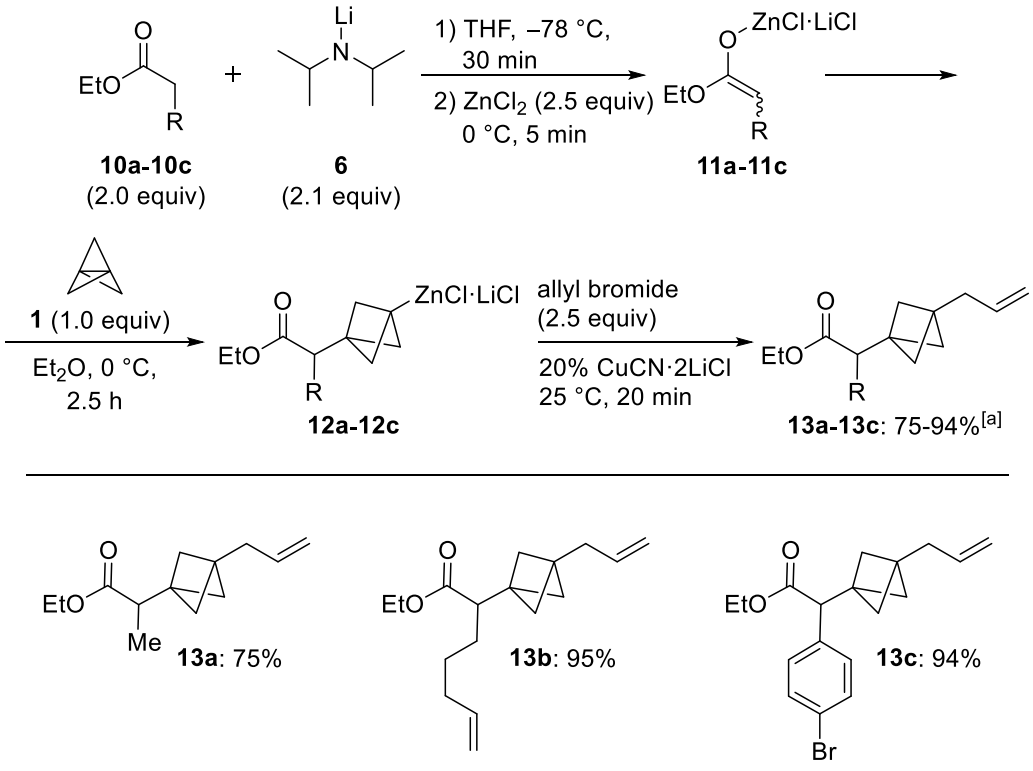


[a] Isolated yields of analytically pure product. [b] Catalyzed by CuCN·2LiCl (20%). [c] Catalyzed by $PdCl_2(dppf)\cdot CH_2Cl_2$ (5%) and CuCN·2LiCl (10%); structure confirmed by X-ray analysis. [d] Mediated by CuCN·2LiCl (1.0 equiv). [e] Mediated by CuCN·2LiCl (3.5 equiv).

Scheme 14. Addition of zinc enolates of type **7** to [1.1.1]propellane (**1**) yielding the functionalized BCPs **9a-9i** after electrophile trapping.

When using esters (**10a**-**10c**, 2.0 equiv) as starting materials, only a slight excess of LDA (**6**, 2.1 equiv) was necessary to achieve good overall yields (Scheme 15). The zinc enolates of type **11**, obtained after transmetalation with $ZnCl_2$ (2.5 equiv), added to [1.1.1]propellane (**1**, 1.0 equiv) within 2.5 h at 25 °C. The resulting zincated BCPs of type **12** were subsequently submitted to a copper-catalyzed allylation with allyl bromide (2.5 equiv). Thus, ethyl propionate was converted to the BCP **13a** in 75% yield. When using ethyl hept-6-enoate as a

starting material, the expected BCP **13b** was isolated in 95% yield without any traces of radical ring-closure side-products. The reaction was also compatible with the benzylic ester ethyl 2-(4-bromophenyl)acetate, leading to the BCP **13c** in 94% yield.



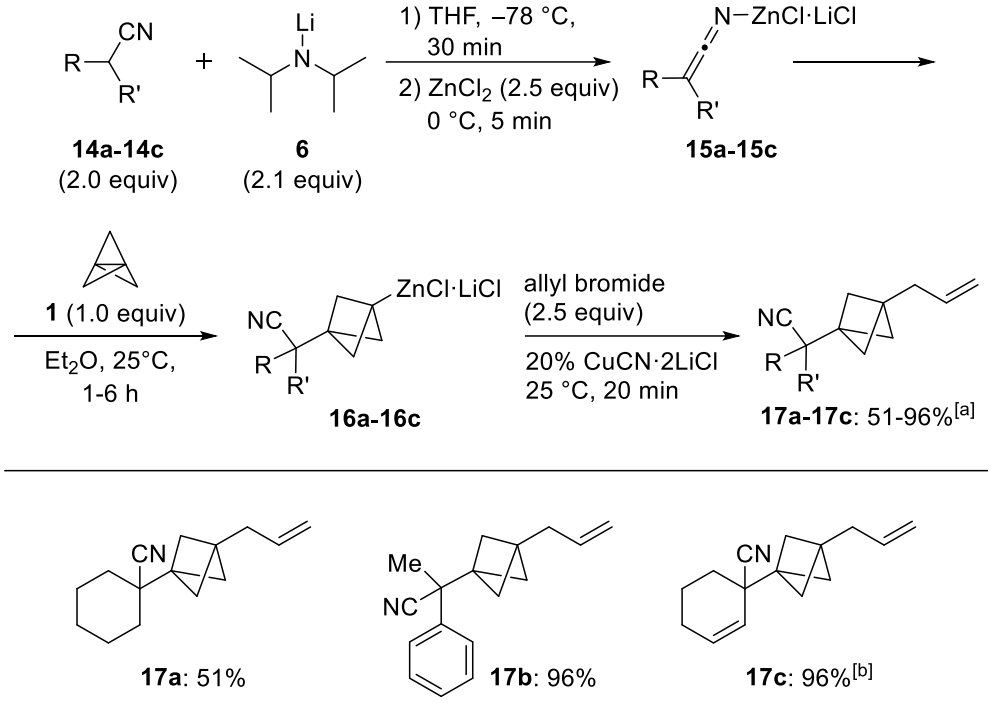
[a] Overall yields of isolated analytically pure products.

Scheme 15. Addition of zinc enolates of type **11** to [1.1.1]propellane (**1**) yielding the functionalized BCPs **13a-13c**.

Finally, the α-deprotonation of nitriles (**14a**-**14c**, 2.0 equiv) with LDA (**6**, 2.1 equiv) followed by a transmetalation with $ZnCl_2$ (2.5 equiv) led to the formation of nitrile-stabilized carbanions of type **15**,[52] which added to [1.1.1]propellane (**1**) within 1-6 h at 25 °C. The resulting zincated BCPs of type **16** were then submitted to a copper-catalyzed allylation with allyl bromide (2.5 equiv, Scheme 16). This protocol was used to prepare BCP-derivatives of cyclohexanecarbonitrile (**17a**) and 2-phenylpropanenitrile (**17b**) in 51-96% yield. When using 1-cyanocyclohexene as a starting material, the BCP **17c** was isolated in 96% yield. This can

[52] a) S. Arseniyadis, K. S. Kyler, D. S. Watt in *Organic Reactions*, Vol. 31, (Eds.: W. G. Dauben), John Wiley & Sons, Inc., Hoboken, **1984**, pp.: 1-344; b) X. Yang, F. F. Fleming, *Acc. Chem. Res.* **2017**, *50*, 2556-2568.

be explained due to a rearrangement after the initial deprotonation in the allylic position, resulting in the formation of the most stabilized anion.[53]



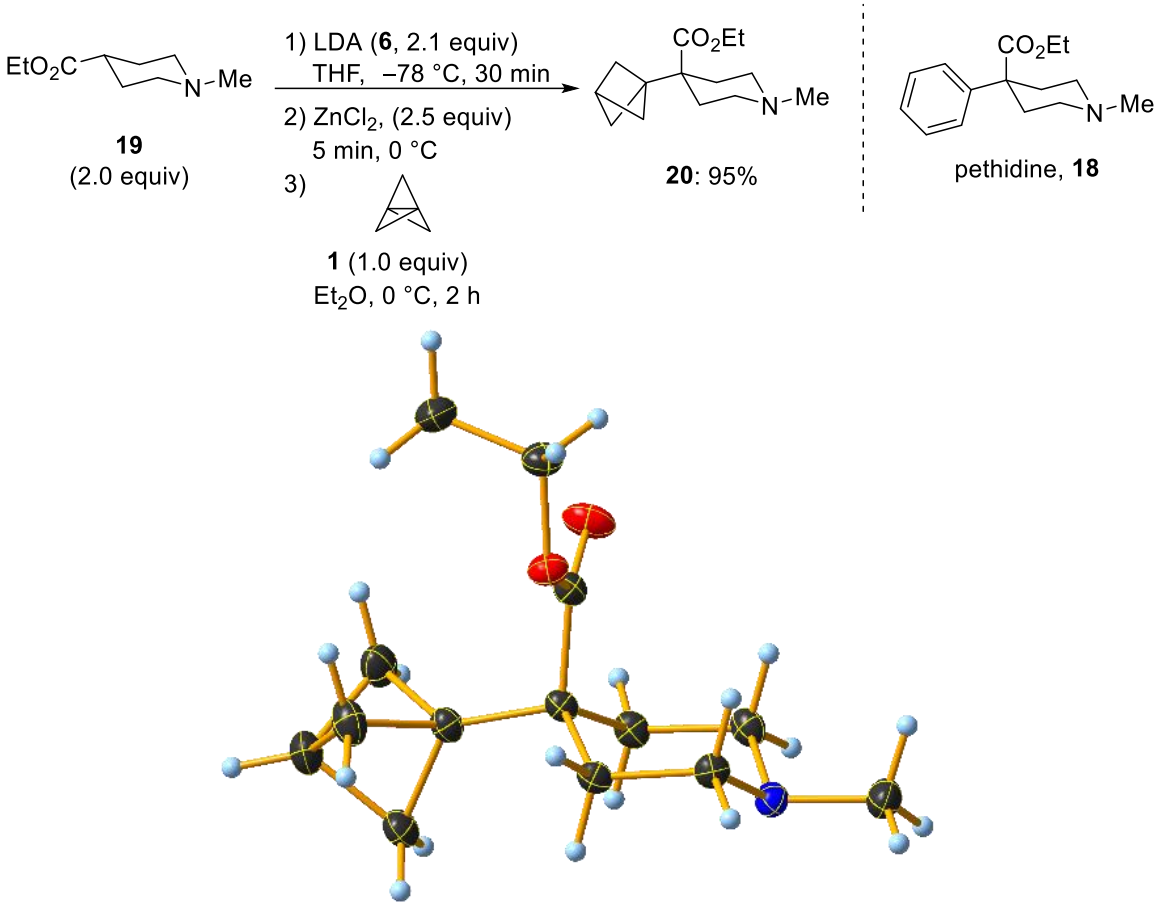
[a] Isolated yields of analytically pure product. [b] Starting from 1-cyanocyclohexene.

Scheme 16. Addition of zincated nitriles of type **15** and their addition to [1.1.1]propellane (**1**) yielding the functionalized BCPs **17a-17c**.

3.4 Synthesis of BCP-Pethidine

With the optimized procedure the synthesis of the BCP-analogue of the synthetic opioid pethidine[54] was carried out (**18**, Scheme 17). The deprotonation of commercially available ethyl 1-methylpiperidine-4-carboxylate (**19**, 2.0 equiv) with LDA (**6**, 2.1 equiv) proceeded smoothly within 30 min at −78 °C in THF. After the addition of $ZnCl_2$ (2.5 equiv) the resulting zinc enolate was reacted with [1.1.1]propellane (**1**, 1.0 equiv) at 0 °C for 2 h. The generated zincated BCP was trapped through the addition of a saturated aqueous solution of NH_4Cl. The crude mixture was purified using column chromatography, affording the pethidine analogue **20** in 95% yield on a 1.5 mmol scale in a single step. The structure of the isolated product was confirmed by X-ray analysis.

[53] X. Yang, D. Nath, J. Morse, C- Ogle, E. Yurtoglu, R. Altundas, F. Fleming, *J. Org. Chem.* **2016**, *81*, 4098-4102.
[54] L. E. Mather, P. J. Meffin, *Clin. Pharmacokinet.* **1978**, *3*, 352-368.



Scheme 17. Synthesis and X-ray structure of BCP-pethidine **20**.

The impact of the substitution of the terminal phenyl group with a BCP unit was evaluated by measuring some physicochemical properties of the BCP-pethidine **20**. The bioisoster was slightly more basic than the original drug **18**, with the pK_a of the conjugated acid increasing from 8.8 to 9.0. The lipophilicity was estimated by measuring the 1-octanol/water partition coefficient (logP) and the distribution coefficient at pH 7.4 (log$D_{7.4}$) and comparing them to the literature values of pethidine (**18**).[55] The measured logP (2.9) and log$D_{7.4}$ (1.3) were very close to the reported values for pethidine (respectively 2.7 and 1.4). This indicates that the lipophilicity of the bioisoster **20** is similar to that of pethidine. Contrastingly, the substitution of an internal *para*-phenyl group with a BCP unit resulted in a significant decrease of the lipophilicity for a number of different drug candidates.[22b] Overall, in this case the substitution of the terminal phenyl group seems to have a relatively small impact on the physicochemical properties of the compound.

[55] a) L. Z. Benet, F. Broccatelli, T. I. Oprea, *AAPS J.* **2011**, *13*, 519-547; b) L. Xu, L. Li, J. Huang, S. Yu, J. Wang, N. Li, *J. Pharm. Biomed. Anal.* **2015**, *102*, 409-416.

3.5 NMR Studies

To study the influence of lithium and zinc salts on [1.1.1]propellane (**a**) a series of ^{13}C-NMR-spectra was measured (Figure 3). All of the NMR samples were prepared in a mixture of THF and Et_2O (1:1) with a sealed capillary tube filled with deuterated benzene (**d**) as NMR-standard for shimming. All samples contained traces of bromobenzene (**c**) and dibutyl ether (**b**), which result from the preparation and distillation of the [1.1.1]propellane.[56]

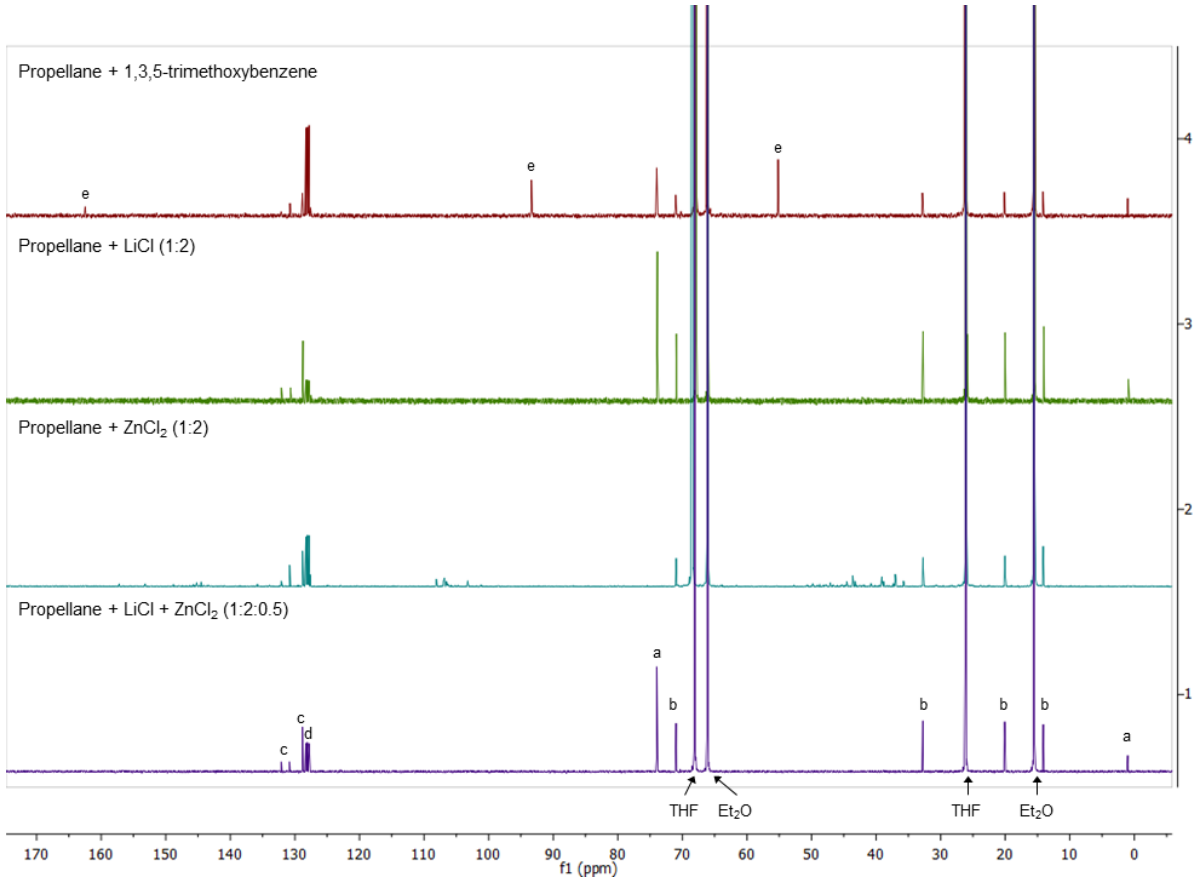


Figure 3. ^{13}C-NMR spectra of [1.1.1]propellane solutions containing lithium and zinc salts (**a** = [1.1.1]propellane, **b** = Bu_2O, **c** = PhBr, **d** = C_6D_6, **e** = 1,3,5-trimethoxybenzene).

As a reference a sample of [1.1.1]propellane with the NMR-standard 1,3,5-trimethoxy-benzene (**e**) was measured, showing the two expected signals of [1.1.1]propellane (**a**) at 1.0 and 74.0 ppm. The addition of 2 equivalents of LiCl had no effect on the [1.1.1]propellane. However, the addition of 2 equivalents of $ZnCl_2$ let to a complete decomposition of the

[56] See the experimental part of this thesis for a detailed procedure.

[1.1.1]propellane within 1 minute at room temperature as evidenced by the disappearance of the initial signals. A multitude of new signals between 35-55 ppm, 100-110 ppm and 130-160 ppm hints at the formation of a complex mixture of different products. A decomposition of [1.1.1]propellane in the presence of *Lewis* acidic transition-metal ions has been reported by *Wiberg* in the case of $AgBF_4$ and $[Rh(CO)_2Cl]_2$, leading to mixtures of different oligomers.[6] Interestingly, no decomposition was observed when the $ZnCl_2$ was premixed with 4 equivalents of LiCl in THF. This observation can be explained by assuming the formation of a zincate ($Li^+ZnCl_3^-$), which significantly reduces the *Lewis* acidity of the zinc. In addition, this leads to the conclusion that the complexes present in the solutions of allylic zinc halides (with or without complexated LiCl) are not *Lewis* acidic enough to cause the decomposition of [1.1.1]propellane, thus allowing the formation of the respective ring-opening products in high yields.

3.6 DOSY Spectroscopy

In order to explore the aggregation state of the allylic zinc reagents a DOSY (Diffusion-Ordered NMR Spectroscopy) experiment was performed (Figure 4).[57] Therefore, a solution of allylzinc bromide coordinated with lithium chloride in THF was prepared according to the procedure detailed in the experimental part of this thesis. The solvent was removed under high vacuum using a cooling trap and a small amount of the resulting solid was transferred to an NMR-tube under argon. In addition, 2,2,3,3,-tetramethylbutane (TMB), anthracene and tetrakis(trimethylsilyl)silane (0.06 mmol each) were added as internal standards. The solids were dissolved in 0.5 mL of THF-d_8 and the sample was submitted to the DOSY-experiment (measured on a *Bruker* AV400TR with a 5 mm PABBO BB/19F-1H/19F/D Z-GRD Z863001/0025 probe at 400.13 MHz using TopSpin by *Bruker Biospin*, Karlsruhe; pulse sequence: ledbpgp2s, 32 scans; transformation was performed in *MestreNova* 12.0 using Peak Heights Fit).

[57] D. Li, I. Keresztes, R. Hopson, P. G. Williard, *Acc. Chem. Res.* **2009**, *42*, 270-280.

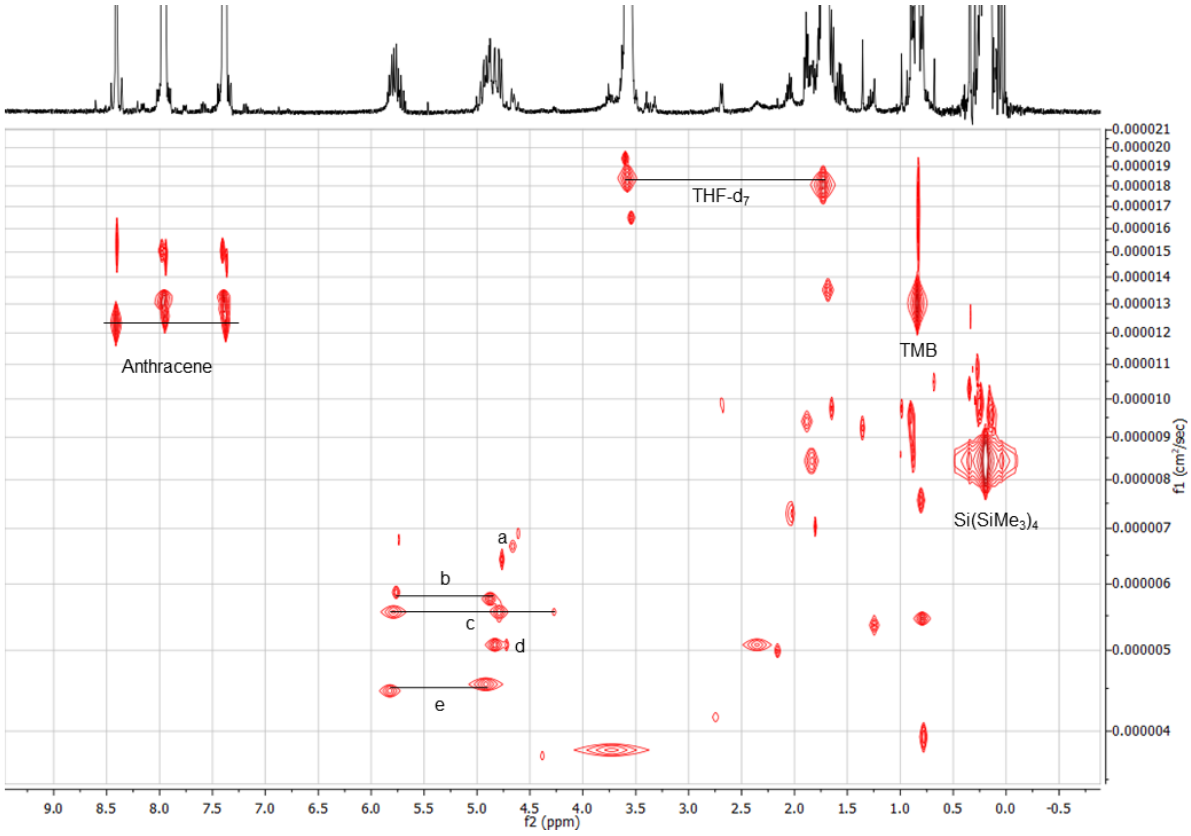


Figure 4. DOSY-NMR of allylzinc bromide coordinated with lithium chloride in THF-d_8.

The DOSY-spectrum showed a multitude of different signals (**a**-**e**) corresponding to the allylic protons between 4.5 and 6.0 ppm. The diffusion coefficients D of these signals ranged from $6.43*10^{-6}$ to $4.51*10^{-6}$ cm^2/s. The signals of the internal standards were used to determine a calibration curve (Figure 5).

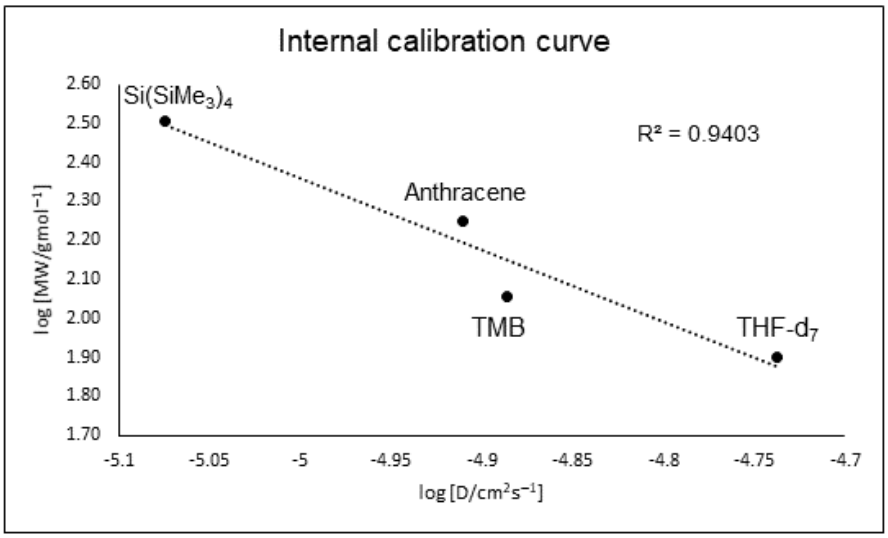


Figure 5. Internal calibration curve of the DOSY-spectrum of allylzinc bromide coordinated with lithium chloride.

The multitude of allylic signals leads to the conclusion, that the solution contains various clusters of allylzinc bromide in different aggregation states. The molecular weights of these clusters were estimated with the help of the internal calibration curve (Table 2).

Table 2. Diffusion parameters and calculated molecular weights for the different clusters present in allylzinc bromide coordinated with lithium chloride.

Compound	D [cm^2/s]	log [D/cm^2s^{-1}]	MW [g/mol]	log [$MW_{calc}/gmol^{-1}$]	MW_{calc} [g/mol]
THF-d7	1,83E−05	−4,737549	79,1	1,88	75
TMB	1,30E−05	−4,886056	114,2	2,15	141
Anthracene	1,23E−05	−4,9100949	178,2	2,19	156
$Si(SiMe_3)_4$	8,43E−06	−5,0741724	320,8	2,50	313
a	6,43E−06	−5,1917890	-	2,71	516±124
b	5,82E−06	−5,2350770	-	2,79	620±149
c	5,60E−06	−5,2518120	-	2,82	665±160
d	5,08E−06	−5,2941363	-	2,90	796±191
e	4,51E−06	−5,3458235	-	3,00	992±238

When applying the internal calibration to the diffusion parameters of the standards, the calculated molecular weights deviate from the actual values by 3% ($Si(SiMe_3)_4$) to 24% (TMB). By assuming similar margins of error for the allylic organozinc clusters, the molecular

weights of the clusters **a**-**e** were estimated to range from 392 to 1230 g/mol. These molecular weights are significantly higher than the molecular weight of a monomer of allylzinc bromide coordinated by one equivalent of LiCl and THF-d_8 (309 g/mol). Therefore, the DOSY experiments confirm the existence of oligomeric aggregates. A dimeric cluster of the formula $(allylZnBr)_2{\cdot}(LiCl)_2{\cdot}(THF\text{-}d_8)_2$ possesses a molecular weight of 618 g/mol, which is in good accordance with the value obtained for the signal **b** (620±149 g/mol). When substituting one of the allylzinc bromides by $ZnBr_2$, the resulting cluster $(allylZnBr){\cdot}(ZnBr_2){\cdot}(LiCl)_2{\cdot}(THF\text{-}d_8)_2$ weights 657 g/mol, which is close to the molecular weight determined for the signal **c** (665±160 g/mol). The signals **d** and **e** most likely correspond to more highly aggregated clusters.

3.7 Density Functional Theory Calculations

In order to rationalize the exquisite regioselectivity observed in transformations with unsymmetrically substituted allylic zinc species, theoretical calculations have been performed for the reaction of propellane (**1**) with prenylzinc bromide complexed with lithium chloride (**2d**), whose sole reaction product is the BCP **4k** (Scheme 12). Following effectively the same protocol used in earlier studies of organozinc reagents,[58] free energies in THF solution have been calculated at the SMD(THF)/B2PLYP/def2-TZVPP level of theory. Calculations start from the cubic cluster **21** assembled from 2 equivalents of LiCl, $ZnBr_2$,[59] and prenylzinc bromide (**2d**). Complexation of propellane to one of the zinc centres in **21** displaces one of the cluster bromide atoms and generates the adduct **22** in a mildly exergonic first step. Formation of the adduct **22** is accompanied by a minor degree of charge transfer from the propellane unit to the cluster **21** by 0.11 e, but leads to practically no change of the propellane structure itself.[60] Backside attack of the prenyl side chain at the bound propellane unit through the transition state **23** then carries the system over to the product side, whose ultimate end point is the cubic cluster **24** located –42.7 kJ mol^{-1} lower than the separate reactants. That the barrier for this reaction amounts to only 52 kJ mol^{-1} demonstrates the intrinsic flexibility of the salt cluster that thus acts as a template for the reacting organozinc/propellane units. As can readily be seen from the 3D presentation of the transition state **23** in Figure 6, formation of the C-Zn bond is almost complete at

[58] M. Ellwart, I. S. Makarov, F. Achrainer, H. Zipse, P. Knochel, *Angew. Chem. Int. Ed.* **2016**, *44*, 10502-10506.
[59] Small amounts of $ZnBr_2$ are present in the allylic zinc reagents as a result of partial homocoupling during the zinc insertion.
[60] An extensive discussion of the bonding situation and charge distribution in selected intermediates can be found in the appendix of this thesis.

r(C-Zn) = 205 pm, while formation of the C-C bond between the propellane and prenyl units is still underway with r(C-C) = 203 pm. From the almost perfect alignment of both reacting bonds along the propellane axis it is also apparent, that the cluster template exerts practically no external strain onto the reacting fragments. The overall reaction cycle is completed by salt metathesis of the product cluster **24** with one equivalent of the prenylzinc reagent **2d**, yielding the starting cluster **21** and the product organozinc species **3d** (Scheme 18). This reaction is almost thermoneutral at ΔG_{298} = –2.5 kJ mol^{-1}.

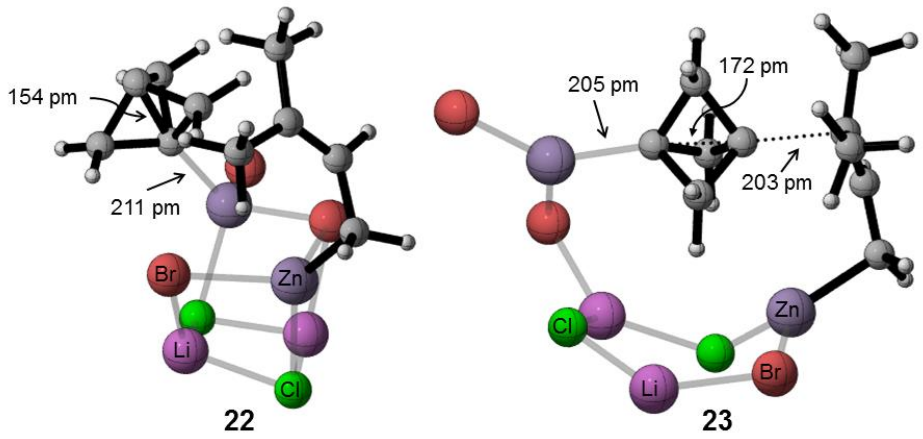
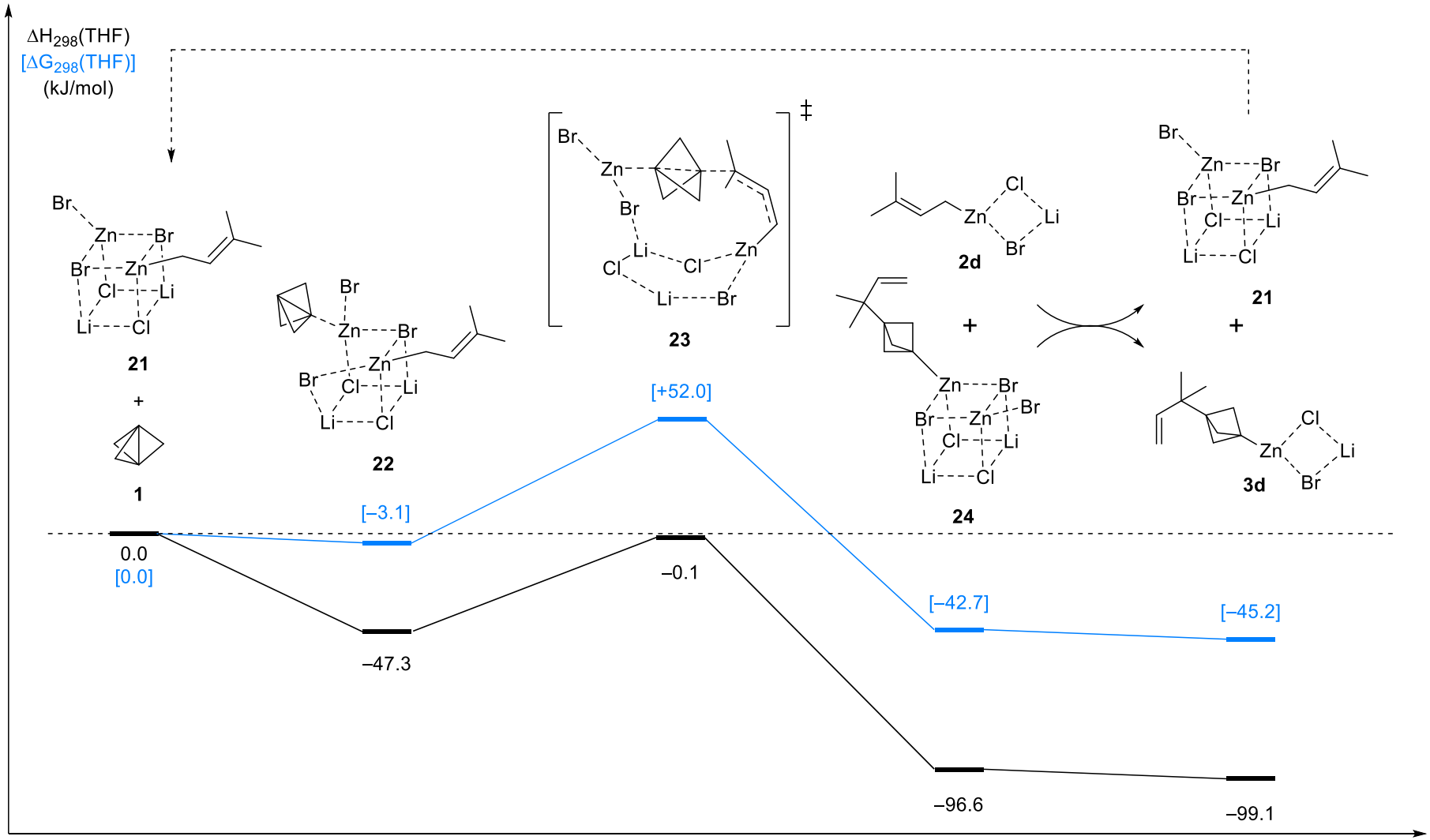


Figure 6. Calculated geometries of [1.1.1]propellane coordinated to a cubic cluster containing prenylzinc bromide (**22**) and the transition state **23**.

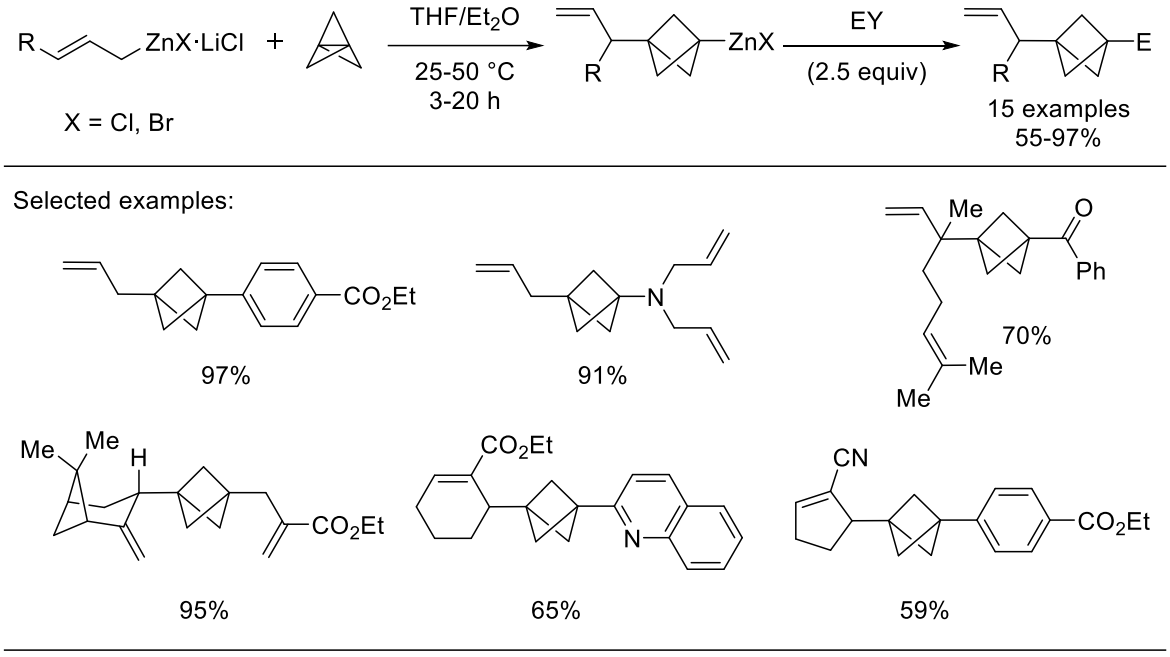


Scheme 18. Calculated mechanism for the reaction of a cubic cluster containing prenylzinc bromide (**21**) with [1.1.1]propellane (**1**) (SMD(THF)/B2PLYP-D3/def2TZVPP//B3LYP-D3/def2SVP).

The activation of propellane (**1**) by other cluster designs or through other activation modes has also been studied, but all of these variations are energetically less favourable than the reaction pathway shown in Scheme 18. This includes the reaction with a cluster containing the regioisomeric form of prenylzinc bromide, in which the zinc is located at the tertiary carbon atom. For this cluster the calculated reaction barrier was 43.6 kJ mol^{-1} higher than the one detailed in Scheme 18. Therefore, the high regioselectivity can be attributed to a kinetic selectivity. A reaction pathway starting with the coordination of [1.1.1]propellane to lithium instead of zinc resulted in a reaction barrier that was 82.5 kJ mol^{-1} higher than the one detailed in Scheme 18.

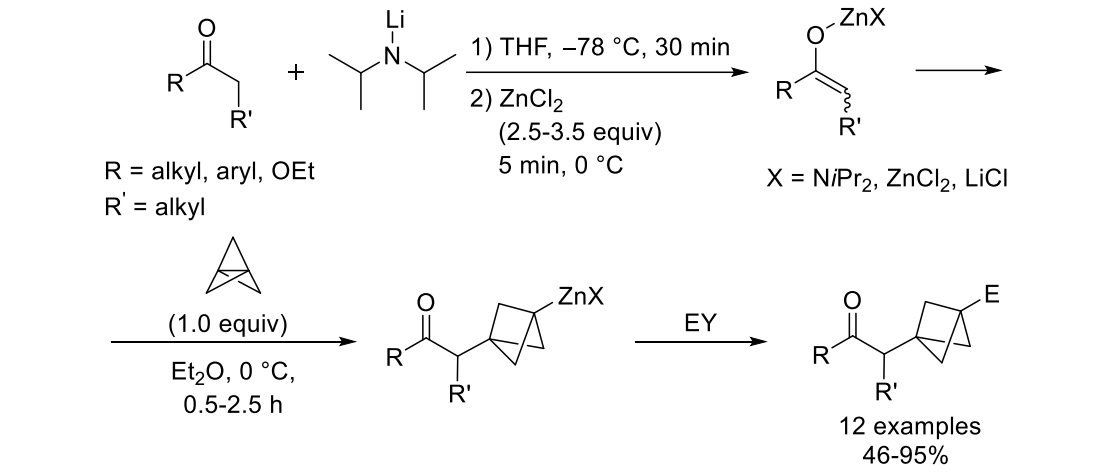
4 Summary

For the first part of this thesis the addition of various organozinc reagents to [1.1.1]propellane was investigated. This was first achieved using allylic organozinc halides (Scheme 19). The additions proceeded with an extraordinarily high stereoselectivity, as only the products resulting from an allylic rearrangement were observed. The resulting zincated BCPs were successfully trapped using *Negishi*-type cross-couplings, thiolations, cobalt-catalyzed electrophilic aminations, as well as copper-mediated allylations and acylations. The protocol showed a good tolerance of functional groups, such as esters and nitriles, due to the relatively low reactivity of the organozinc halides.

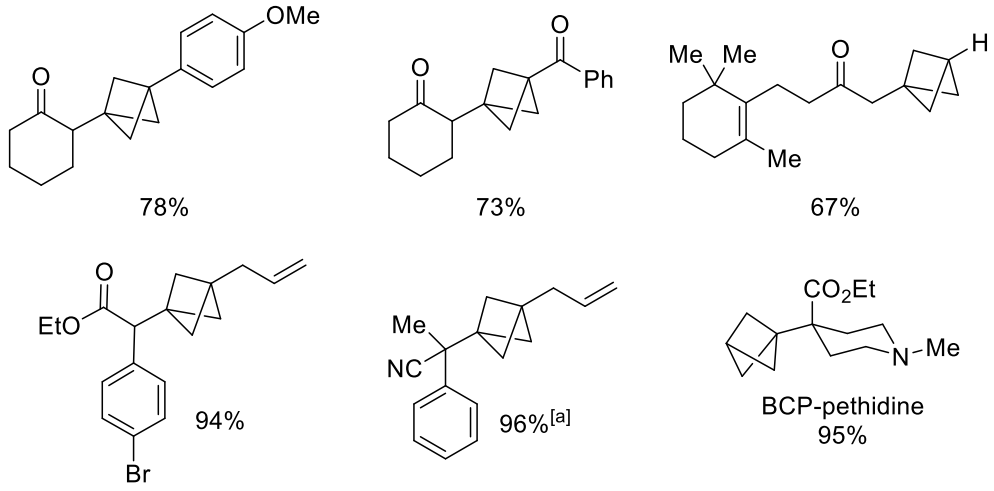


Scheme 19. Summary of the addition of allylic organozinc halides to [1.1.1]propellane.

The methodology was extended to various zinc enolates, prepared from ketones, esters and nitriles through the deprotonation with LDA, followed by a transmetalation with $ZnCl_2$ (Scheme 20). Once again the resulting zincated BCPs were submitted to different electrophilic trapping reactions, such as protonations, copper-catalyzed allylations, palladium-catalyzed *Negishi*-type cross-couplings, acylations and cyanations. The protocol was also used to synthesize a BCP-bioisoster of the synthetic opioid pethidine.



Selected examples:



[a] Using a nitrile instead of a carbonyl compound.

Scheme 20. Summary of the addition of zinc enolates to [1.1.1]propellane.

The high regioselectivity of the reaction was rationalized using DFT calculations, which showed that the allylic rearrangement proceeds via a cyclic transition state involving $ZnBr_2$, LiCl, the allylic zinc halide and [1.1.1]propellane.

Part II: Selective Metalation of Nitrogen Containing Heterocycles Using 2,2,6,6-Tetramethylpiperidyl Bases

1 Introduction

1.1 Nitrogen Containing Heterocycles

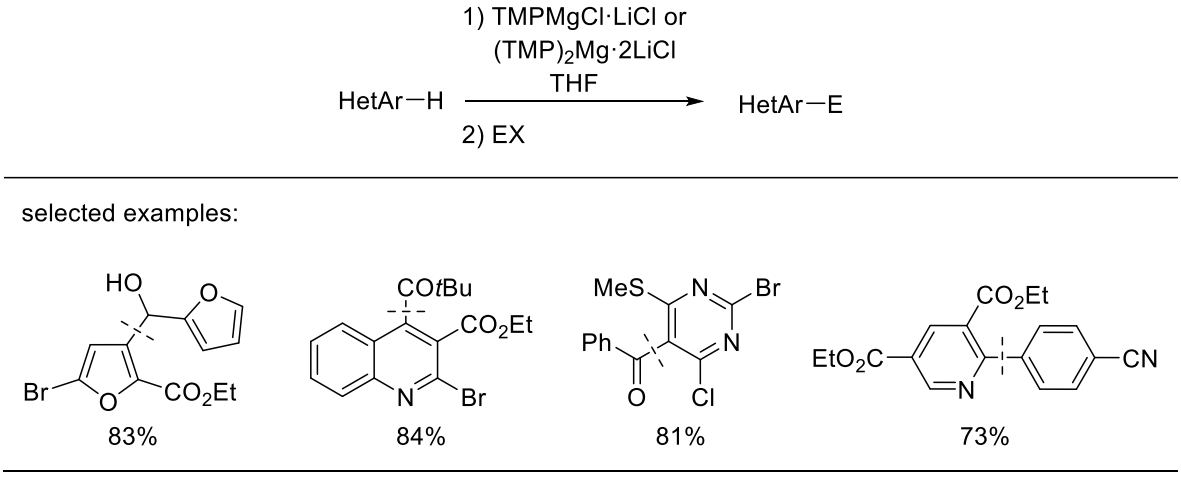
Nitrogen containing heterocycles are extremely common in both medicinal as well as agricultural chemistry with 59% of all unique small-molecule drugs that were approved by the U.S. FDA (Food and Drug Administration) in 2014 containing at least one nitrogen heterocycle. Among them five- and six-membered rings are by far the most prevalent, with 39% and 59% respectively.[61] The abundance of nitrogen heterocycles in pharmaceutical compounds results from their often favourable influence on molecular properties such as lipophilicity, polarity, metabolic stability and toxicity.[62] Thus, the development of new methodologies to access large libraries of substituted nitrogen containing heterocycles for pharmaceutical trials is of great interest. In this work the main focus was placed on the aromatic five-membered 1,3,4-oxadiazole and 1,2,4-triazole as well as on the fused heterocycle 1*H*-imidazo[1,2-*b*]pyrazole.

1.2 Selective Metalation of Heterocycles using 2,2,6,6-Tetramethylpiperidyl (TMP) Bases

Selective metalations are an attractive way to generate a large variety of functionalized heterocycles, as the resulting metalated heterocycles can be reacted with many different electrophiles. This methodology takes advantage of the generally low pk_a-values of protons in aromatic heterocycles (typically between 38 and 24).[63] Historically, metalations were mostly conducted using strong lithium-reagents like *n*BuLi.[64] However, their high nucleophilicity can lead to undesired side-reactions and thus significantly reduces the scope of possible substrates. A solution to this problem was achieved with the introduction of the less nucleophilic sterically hindered lithium amide bases like LDA and TMPLi.[65] Due to their high reactivity the resulting lithiated heterocycles are usually only stable at low temperatures and tend to react with many important functional groups such as esters and nitriles even under mild conditions. Therefore, a variety of different magnesium and zinc TMP bases have

[61] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274.
[62] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845-5859.
[63] M. Balkenhohl, H. Jangra, I. S. Makarov, S.-M. Yang, H. Zipse, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 14992-14999.
[64] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109-112.
[65] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879-933; b) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376-393.

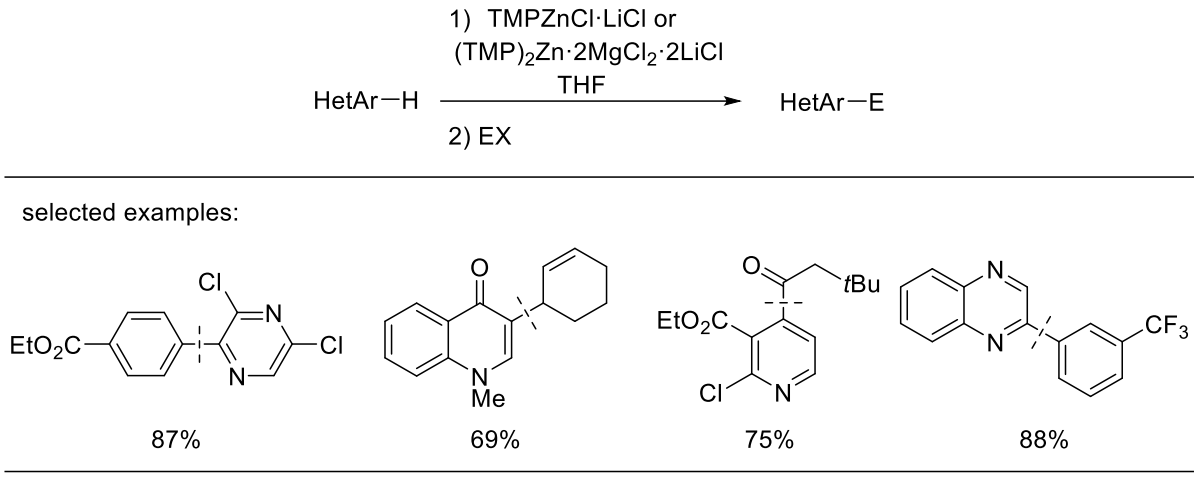
been developed by *Knochel et. al.* over the last years.[66-69] These bases can be used at significantly higher temperature compared to the lithium amide bases, while tolerating many functional groups. In order to avoid the aggregation of the TMP bases, which leads to poor solubility and a low protophilicity, most of them contain a stoichiometric amount of LiCl. The most prominent example is TMPMgCl·LiCl, which was prepared by reacting TMPH with *i*PrMgCl·LiCl and can be stored at room temperature under inert gas for multiple months without a significant drop in reactivity.[66] For less activated substrates the *bis*-base $(TMP)_2Mg·2LiCl$ has been developed.[67] Both bases enable magnesiations of various heterocycles with excellent regio- and chemoselectivity at convenient temperatures (Scheme 21).[66-69]



Scheme 21. Regio- and chemoselective functionalizations of heterocycles using TMPMgCl·LiCl or $(TMP)_2Mg·2LiCl$.

The use of milder zinc bases, such as TMPZnCl·LiCl[68] or $(TMP)_2Zn·2MgCl_2·2LiCl$,[69] allows the functionalization of even more sensitive substrates and tolerates even aldehydes or nitro groups (Scheme 22).

[66] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958-2961; b) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525-5528; c) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497-2500.
[67] G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681-7684.
[68] a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837-1840; b) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584-13587.
[69] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685-7688; b) Z. Dong, G. C. Clososki, S. H. Wunderlich, A. Unsinn, J. Li, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 457-468.



Scheme 22. Regio- and chemoselective functionalizations of heterocycles using TMPZnCl·LiCl or $(TMP)_2Zn·2MgCl_2·2LiCl$.

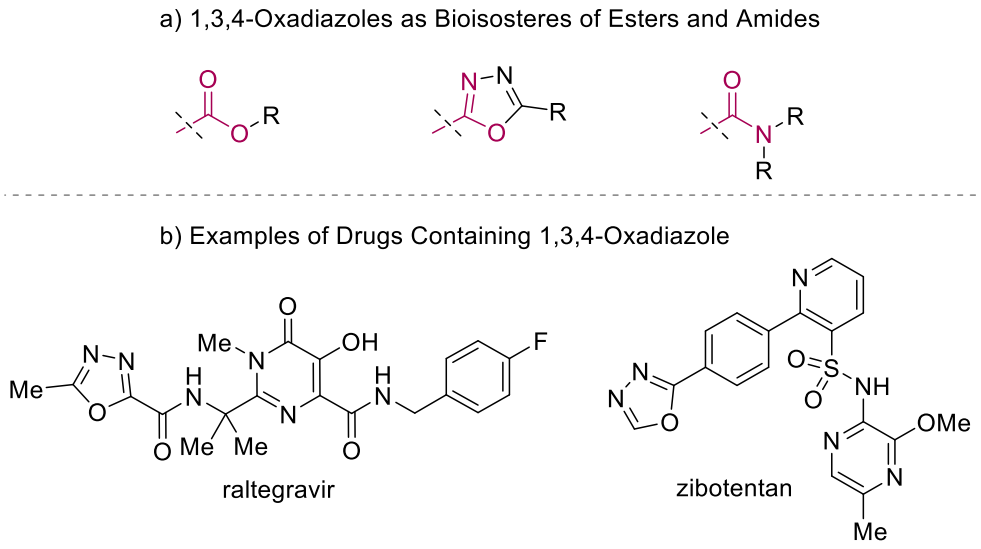
1.3 1,3,4-Oxadiazole

Over the last decades the 1,3,4-oxadiazole scaffold gained a lot of attention in pharmaceutical research, as it was found to improve the physicochemical and pharmacokinetic properties of drugs. This includes an improved metabolic stability and water solubility. In addition, it is a good acceptor for hydrogen bonding and thus able to efficiently interact with many different receptors.[70] Of particular interest is the application of 1,3,4-oxadiazoles as bioisosteres of amides and esters: The heterocyclic core maintains the receptor binding profile of the carbonyl derivatives, while offering a higher lipophilicity, which helps in transmembrane diffusion (Scheme 23a). The spectrum of biological activities exhibited by 1,3,4-oxadiazole derivatives is very diverse and includes antibacterial, antimalarial, anti-inflammatory, antidepressive, anticancer, antiviral, antifungal and analgesic effects.[70] Among them are raltegravir, which is used in the treatment of HIV,[71] and the experimental anticancer drug zibotentan (Scheme 23b).[72]

[70] a) H. Khalilullah, M. J. Ahsan, M. Hedaitullah, S. Kahn, B. Ahmed, *Mini-Rev. Med. Chem.* **2012**, *12*, 789-801; b) S. Bajaj, V. Asati, J. Singh, P. P. Roy, *Eur. J. Med. Chem.* **2015**, *97*, 124-141; c) A. Hoshi, T. Sakamoto, J. Takayama, M. Xuan, M. Okazaki, T. L. Hartman, R. W. Buckheit Jr., C. Pannecouque, M. Cushman, *Bioorg. Med. Chem.* **2016**, *24*, 3006-3022; d) T. Glomb, K. Szymankiewicz, P. Świątek; *Molecules* **2018**, *26*, 3361-3376.

[71] V. Summa, A. Petrocchi, F. Bonelli, B. Crescenzi, M. Donghi, M. Ferrara, F. Fiore, C. Gardelli, O. G. Paz, D. J. Hazuda, P. Jones, O. Kinzel, R. Laufer, E. Monteagudo, E. Muraglia, E. Nizi, F. Orvieto, P. Pace, G. Pescatore, R. Scarpelli, K. Stillmock, M. V. Witmer, M. V.; M. Rowley, *J. Med. Chem.* **2008**, *51*, 5843-5855.

[72] C. D. Morris, A. Rose, J. Curwen, A. M. Hughes, D. J. Wilson, D. J. Webb, *Br. J. Cancer* **2005**, *92*, 2148-2152.

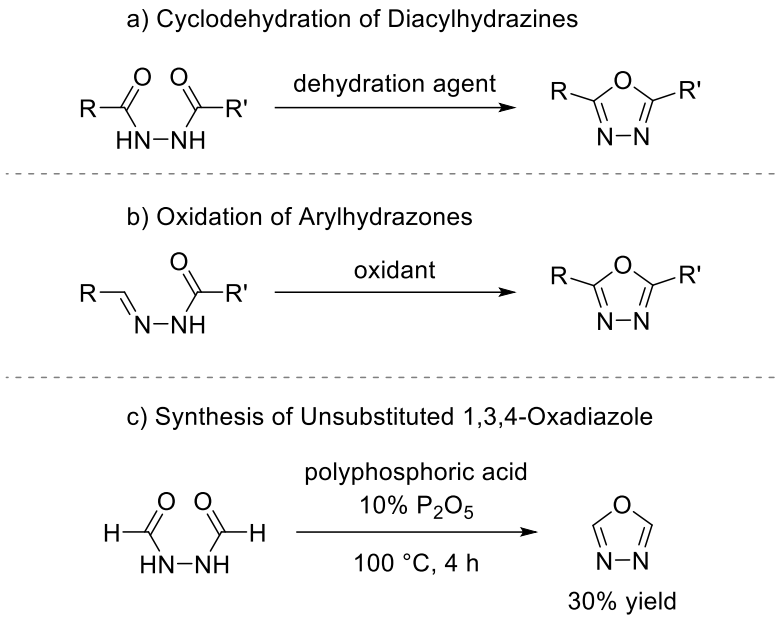


Scheme 23. 1,3,4-Oxadiazoles as bioisosteres of esters and amides and their application in drugs.

In addition, aromatic substituted 1,3,4-oxadiazoles have been widely used as electron-transporting/hole-blocking materials or emitting layers in electroluminescent diodes and non-linear optic materials as they provide high photoluminescence quantum yields and excellent thermal and chemical stabilities.[73]

1,3,4-Oxadiazoles are mainly synthesized via two different pathways: the cyclodehydration of diacylhydrazines (Scheme 24a) and the oxidation of arylhydrazones (Scheme 24b).[74] The synthesis of unsubstituted 1,3,4-oxadiazole is challenging and only in 2012 *Aitken* was able to develop a reliable method to access the parent heterocycle in acceptable yield via the cyclodehydration of *N,N'*-diformylhydrazine (Scheme 24c).[75]

[73] a) G. Hughes, M. R. Bryce, *J. Mater. Chem.* **2005**, *15*, 94-107; b) J. Han, *J. Mater. Chem. C* **2013**, *1*, 7779-7797.
[74] Ž. Jakopin, M. Sollner Dolenc, *Curr. Org. Chem.* **2008**, *15*, 850-898.
[75] K. M. Aitken, R. A. Aitken, *Arkivoc* **2012**, *5*, 75-79.



Scheme 24. Synthesis of 1,3,4-oxadiazoles.

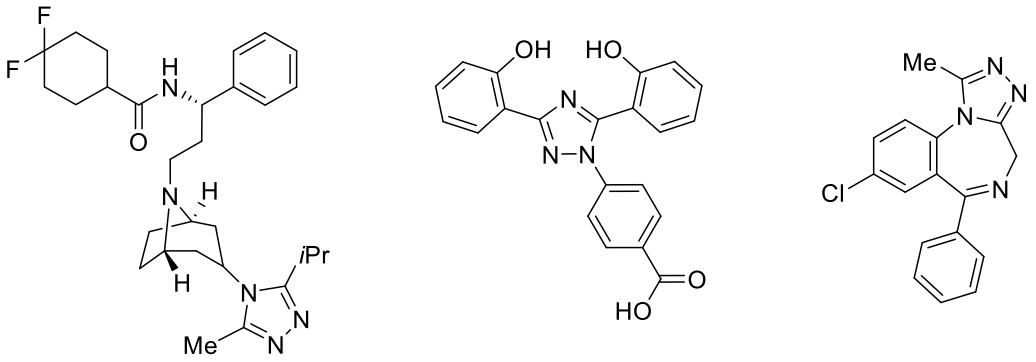
1.4 1,2,4-Triazole

1,2,4-Triazoles have been known for a long time, with the first reports dating back to the late 19th century.[76] The unsubstituted parent heterocycle exists in two tautomeric forms, with the hydrogen connected to the nitrogen in the 1- and 4-position respectively. Microwave, NMR and ab initio quantum mechanics studies showed that the 1*H* tautomer is significantly more stable and therefore predominates in both the gas phase as well as in solution.[77]

The 1,2,4-triazole core exhibits some interesting properties for pharmaceutical and agricultural applications. It can act as both a hydrogen bond acceptor and donor and thus can significantly increase the solubility of compounds in polar solvents.[78] Other favourable properties include a moderate dipole character and good stability towards chemical and metabolic degradation.[79] 1,2,4-Triazole derivatives have been used as linkers and bioisosteres of amides, esters, carboxylic acids and olefinic double bonds. Their activities include antimicrobial, anti-inflammatory, antitubercular, antianxiety, anticancer and antiviral

[76] a) J. A. Bladin, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 1544-1551; b) J. A. Bladin, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2598-2604.
[77] a) K. T. Potts, *Chem. Rev.* **1961**, *61*, 87-127; b) J. R. Cox, S. Woodcock, I. H. Hillier, M. A. Vincent, *J. Phys. Chem.* **1990**, *94*, 5499-5501.
[78] R. Kaur, A. R. Dwivedi, B. Kumar, V. Kumar, *Anticancer Agents Med. Chem.* **2016**, *16*, 465-489.
[79] S. Zhang, Z. Xu, C. Gao, Q.-C. Ren, L. Chang, Z.-S. Lv, L.-S. Feng, *Eur. J. Med. Chem.* **2017**, *138*, 501-513.

effects.[80] Examples include maraviroc, which is used in the treatment of HIV,[81] the iron chelator deferasirox[82] and alprazolam, which is used in the medication of anxiety disorders[83] (Figure 7).



maraviroc deferasirox alprazolam

Figure 7. Commercial drugs containing a 1,2,4-triazole core.

1.5 1*H*-Imidazo[1,2-*b*]pyrazole

The synthesis of a 1*H*-imidazo[1,2-*b*]pyrazole derivative was first reported in 1973 by *Elguero et. al.*.[84] Since then 1*H*-imidazo[1,2-*b*]pyrazoles have attracted the attention of medicinal chemist due to their antimicrobial,[85] anti-inflammatory[86] and anticancer activities[87] (Figure 8).

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[80] a) R. Kharb, P. C. Sharma, M. S. Yar, *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 1-21; b) M. S. Malik, S. A. Ahmed, I. I. Althagafi, M. A. Ansari, A. Kamal, *RSC Med. Chem.* **2020**, *11*, 327-348.

[81] P. Dorr, M. Westby, S. Dobbs, P. Griffin, B. Irvine, M. Macartney, J. Mori, G. Rickett, C. Smith-Burchnell, C. Napier, R. Webster, D. Armour, D. Price, B. Stammen, A. Wood, M. Perros, *Antimicrob. Agents Chemother.* **2005**, *49*, 4721-4732.

[82] U. Heinz, K. Hegetschweiler, P. Acklin, B. Faller, R. Lattmann, H. P. Schnebli, *Angew. Chem. Int. Ed.* **1999**, *38*, 2568-2570.

[83] J. B. Hester Jr., A. D. Rudzik, B. V. Kamdar, *J. Med. Chem.* **1971**, *14*, 1078-1081.

[84] J. Elguero, R. Jacquier, S. Mignonac-Mondon, *J. Heterocycl. Chem.* **1973**, *10*, 411-412.

[85] a) A. O. Abdelhamid, E. K. A. Abdelall, Y. H. Zaki, *J. Heterocycl. Chem.* **2010**, *47*, 477-482; b) M. V. Murlykina, M. N. Kornet, S. M. Desenko, S. V. Shishkina, O. V. Shishkin, A. A. Brazhko, V. I. Musatov, E. V. Van der Eycken, V. A. Chebanov, *Beilstein J. Org. Chem.* **2017**, *13*, 1050-1063.

[86] A. H. Shridhar, G. Banuprakash, J. H. Hoskeri, Y. T. Vijaykumar, *Int. Res. J. Pharm.* **2017**, *8*, 25-33.

[87] a) A. T. Baviskar, C. Madaan, R. Preet, P. Mohapatra, V. Jain, A. Agarwal, S. K. Guchhait, C. N. Kundu, U. C. Banerjee, P. V. Bharatam, *J. Med. Chem.* **2011**, *54*, 5013-5030; b) S. Grosse, V. Mathieu, C. Pillard, S. Massip, M. Marchivie, C. Jarry, P. Bernard, R. Kiss, G. Guillaumet, *Eur. J. Med. Chem.* **2014**, *84*, 718-730; c) A. Demjén, R. Alföldi, A. Angyal, M. Gyuris, L. Hackler Jr., G. J. Szebeni, J. Wölfling, L. G. Puskás, I. Kanizsai, *Arch. Pharm. Chem. Life Sci.* **2018**, *351*, 1-21.

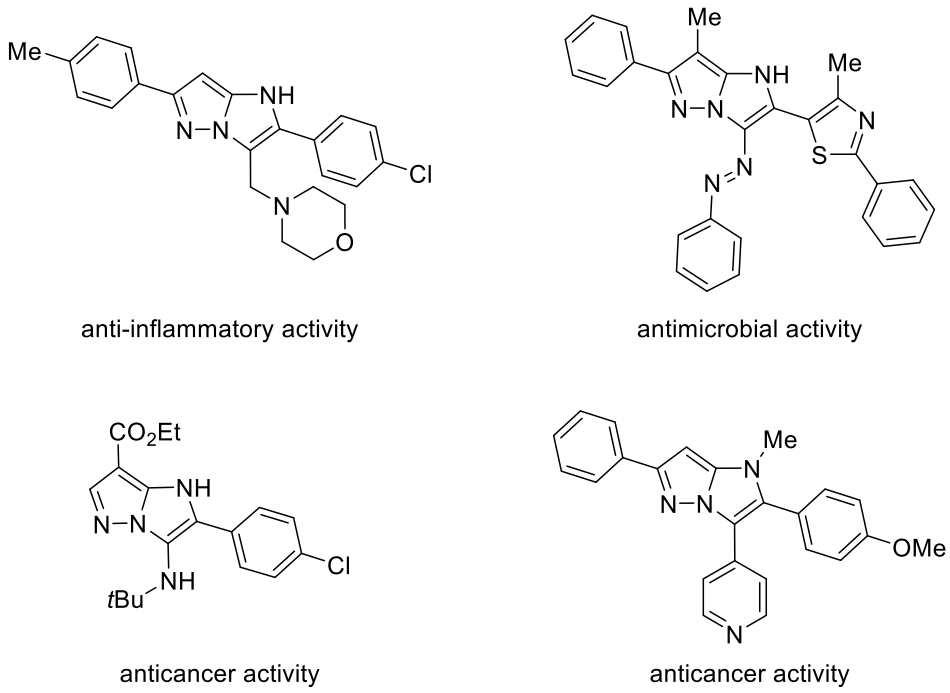
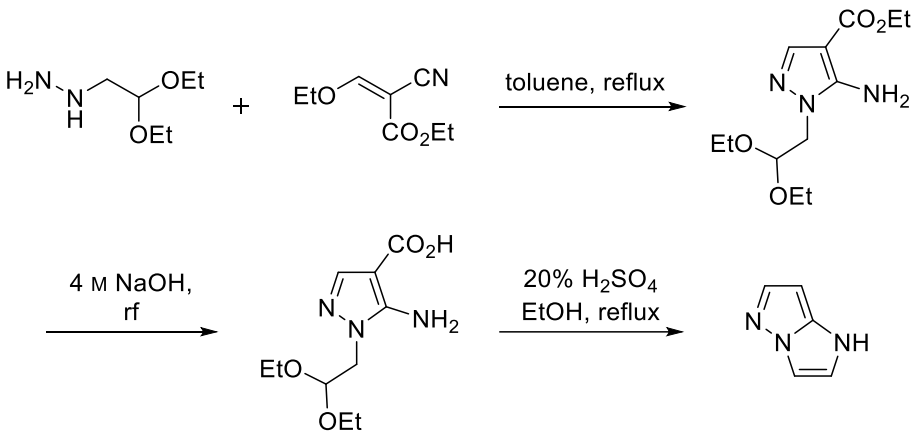


Figure 8. Examples of 1*H*-imidazo[1,2-*b*]pyrazoles with biological activities.

In 1994 *Vanotti et. al.* reported a convenient synthesis of 1*H*-imidazo[1,2-*b*]pyrazole.[88] In a later publication, they improved their strategy to allow the synthesis of up to 70 g of the heterocycle in a single batch. The first step of this route is the formation of ethyl 5-amino-1-(2,2-diethoxyethyl)-1*H*-pyrazole-4-carboxylate through the reaction between (2,2-diethoxyethyl)hydrazine and ethyl 2-cyano-3-ethoxyacrylate. This is followed by a saponification with sodium hydroxide. The resulting 5-amino-1-(2,2-diethoxyethyl)-1*H*-pyrazole-4-carboxylic acid is refluxed with 20% H_2SO_4 in ethanol, leading to the deprotection of the aldehyde, which then cyclizes onto the amine. The acidic reaction conditions also lead to a complete decarboxylation to generate the parent heterocycle (Scheme 25).[89] The general strategy of forming 1*H*-imidazo[1,2-*b*]pyrazoles by annulating the imidazole ring onto a preformed pyrazole scaffold is also used in the vast majority of all reported syntheses of substituted variations of this heterocycle.[90]

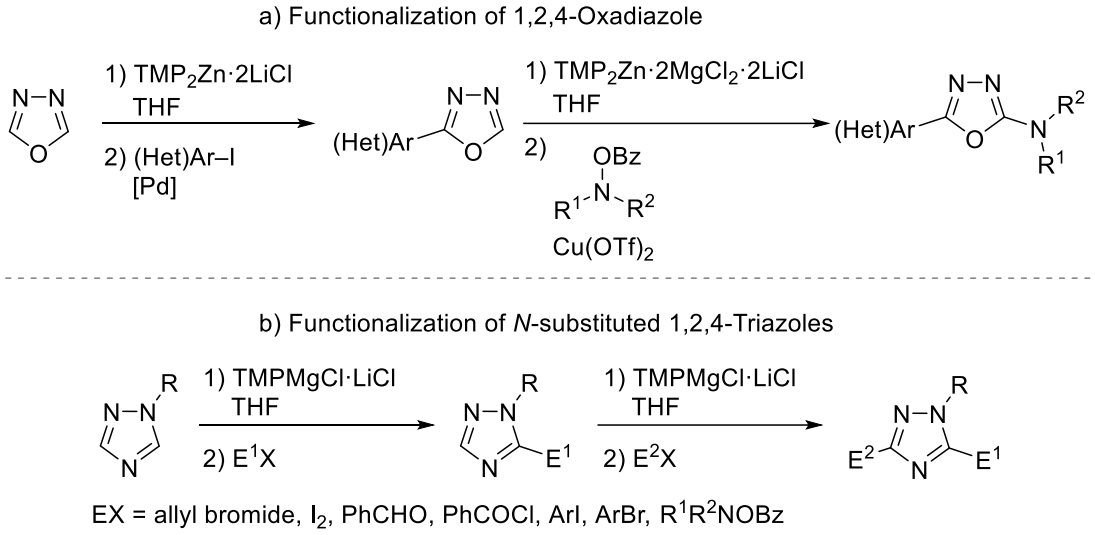
[88] E. Vanotti, F. Fiorentini, M. Villa, *J. Heterocycl. Chem.* **1994**, *31*, 737-743.
[89] P. Seneci, M. Nicola, M. Inglesi, E. Vanotti, G. Resnati, *Synth. Commun.* **1999**, *29*, 311-341.
[90] a) R. E. Khidre, B. F. Abdel-Wahab, O. Y. Alothman, *J. Chem.* **2014**, 1-15; b) J. Khalafy, A. P. Marjani, F. Salami, *Tetrahedron Lett.* **2014**, *55*, 6671-6674; c) N. N. Kolos, B. V. Kibkalo, L. L. Zamigaylo, I. V. Omel'chenko, O. V. Shishkin, *Russ. Chem. Bull. Int. Ed.* **2015**, *64*, 864-871.



Scheme 25. Synthesis of 1*H*-imidazo[1,2-*b*]pyrazole according to *Vanotti*.[89]

2 Objective

Due to its highly sensitive nature no metalations of unsubstituted 1,3,4-oxadiazole have been reported previous to this work. In the case of *N*-substituted 1,2,4-triazoles only the metalation with the very reactive and unselective base BuLi was known from literature.[91] As the sterically hindered TMP bases have been successfully employed in the selective functionalization of a range of different heterocyclic substrates, they might also be able to achieve a full functionalization of the 1,3,4-oxadiazole (Scheme 26a) and 1,2,4-triazole scaffolds (Scheme 26b). The goal of this work was to find suitable conditions for the selective metalations of the different heterocycles, followed by reactions with various electrophiles with special emphasis on palladium-catalyzed *Negishi*-type cross-coupling reactions[45] and copper-catalyzed electrophilic aminations using hydroxylamino benzoates.[48]

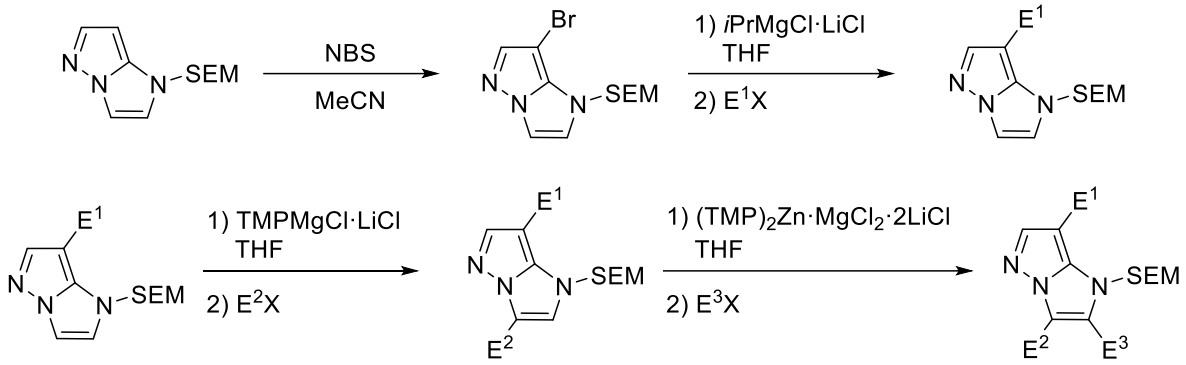


Scheme 26. Stepwise functionalization of 1,3,4-oxadiazole and *N*-substituted 1,2,4-triazoles using TMP bases.

As the 1*H*-imidazo[1,2-*b*]pyrazole scaffold is not as easily accessible as other heterocycles its functionalization has not yet been explored thoroughly. All of the reported syntheses of functionalized 1*H*-imidazo[1,2-*b*]pyrazoles install the substituents in a precursor of the heterocycle before the final cyclization.[90] Therefore, it is very expensive and time consuming to synthesize a large library of these compounds. A selective bromination, followed by a bromine-magnesium exchange and a series of selective metalations using TMP bases might

[91] a) R. G. Micetich, P. Spevak, T. W. Hall, B. K. Bains, *Heterocycles* **1985**, *23*, 1645-1649; b) S. Ohta, I. Kawasaki, A. Fukuno, M. Yamashita, T. Tada, T. Kawabata, *Chem. Pharma. Bull.* **1993**, *41*, 1226-1231.

however give access to a large variety of different substitution patterns starting from the *N*-SEM-protected heterocycle without the need to synthesize multiple different precursors (Scheme 27).



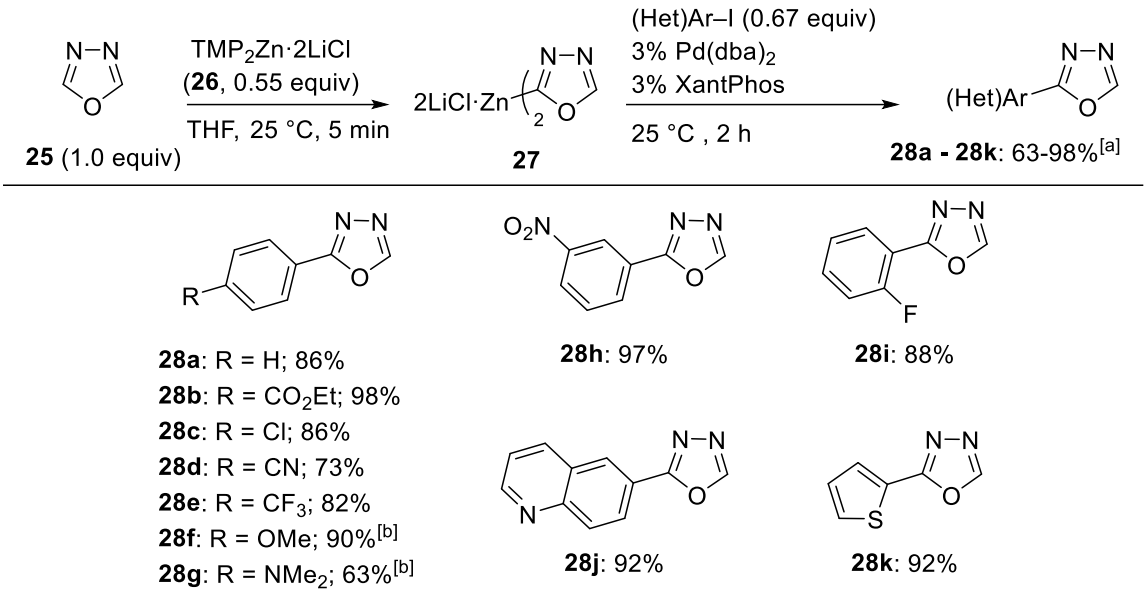
Scheme 27. Stepwise functionalization of *N*-SEM-protected 1*H*-imidazo[1,2-*b*]pyrazole.

3 Results and Discussion

3.1 Selective Functionalization of 1,3,4-Oxadiazole

Preliminary studies have shown that in the case of 1,3,4-oxadiazole (**25**), the freshly prepared base $TMP_2Zn{\cdot}2LiCl$ (**26**)[92] provided the best results, leading to a complete conversion after 5 min at 25 °C.[93] The resulting zincated 1,3,4-oxadiazole **27** was subsequently submitted to *Negishi*-type cross-coupling (Scheme 28).[45] A mixture of $Pd(dba)_2$ (3%) and XantPhos[94] (3%) provided excellent results with a variety of electron-deficient aryl iodides at 25 °C, producing the desired cross-coupling products **28a-28e**, **28h** and **28i** in 73-98% yield. When employing electron-rich aryl iodides, $Pd(PPh_3)_4$ (7.5%) was the best catalyst and afforded the heterocycles **28f** and **28g** in 63-90% yield (50 °C, 2 h). Due to the relatively low reactivity of the intermediate organozinc species **27** various functional groups were tolerated, including an ester (**28b**), a chloride (**28c**), a nitrile (**28d**), an amine (**28g**) and a nitro group (**28h**). In addition, heterocyclic iodides, such as 6-iodoquinoline and 2-iodothiophene, have been successfully coupled, providing the heterocycles **28j** and **28k** in 92% yield.

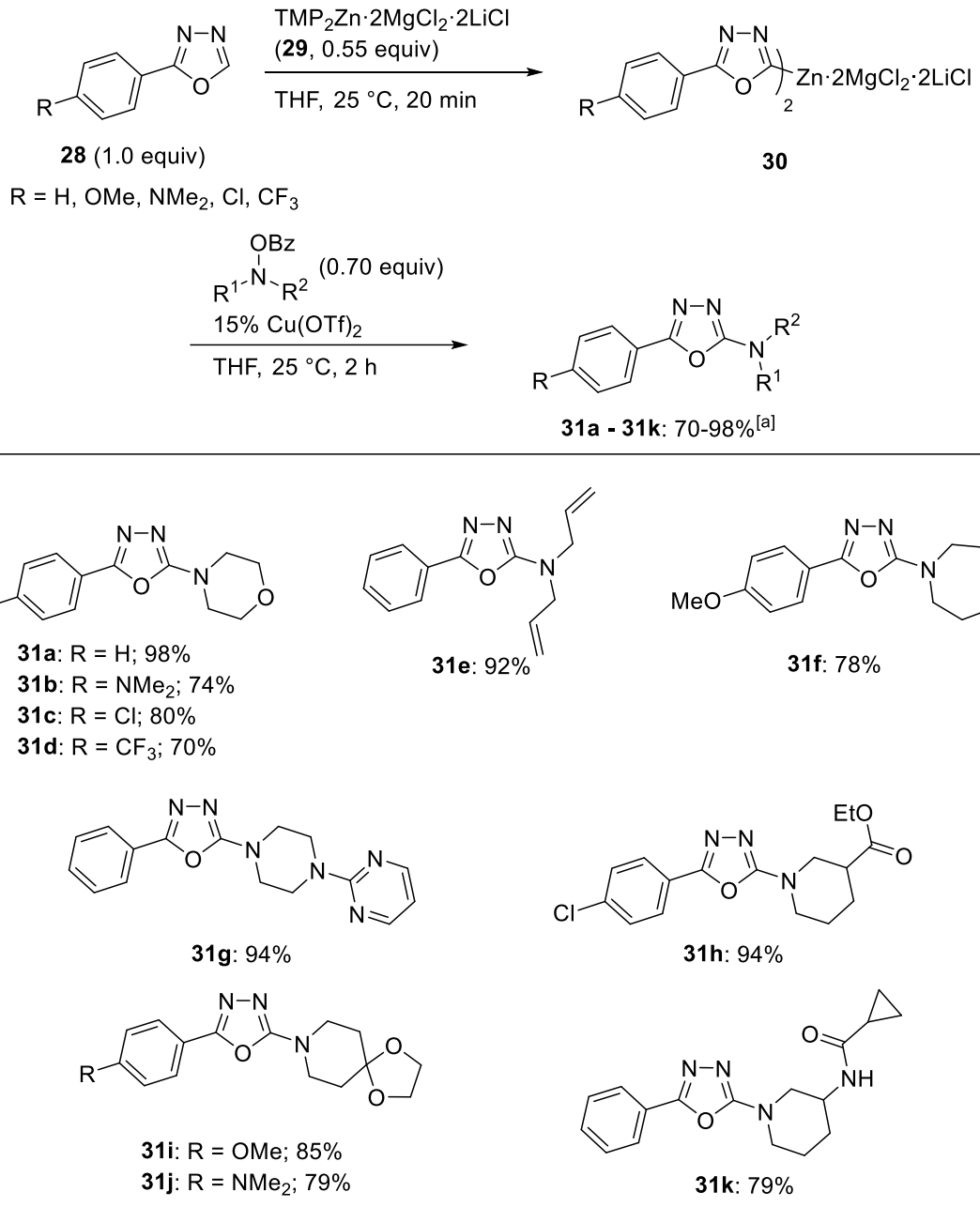
[92] The base was prepared according to the procedure detailed in the experimental part of this thesis and used within 3 hours. A longer storage of the base reduced the yields significantly.
[93] For a detailed summary of the optimization see the experimental part of this thesis.
[94] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 3081-3089.



[a] Isolated yields of analytically pure product. [b] Using 7.5% $Pd(PPh_3)_4$ at 50 °C.

Scheme 28. Zincation of 1,3,4-oxadiazole (**25**) using $TMP_2Zn·2LiCl$ (**26**) followed by *Negishi* coupling leading to mono-substituted 1,3,4-oxadiazoles of type **28**.

With the mono-substituted 1,3,4-oxadiazoles of type **28** in hand, a second metalation using the freshly prepared base $TMP_2Zn·2MgCl_2·2LiCl$ (**29**) was performed, resulting in a complete zincation within 20 min at 25 °C (Scheme 29). The zincated heterocycles **30** were then aminated at 25 °C using hydroxylamino benzoates[48] in the presence of 15% $Cu(OTf)_2$, providing a variety of aminated 1,3,4-oxadiazoles of type **31** in 54-98% yield. This sequence proceeded well with both electron-rich (**31b**, **31f**, **31i**, **31j**) as well as electron-deficient (**31c**, **31d**, **31h**) 1,3,4-oxadiazoles. The scope of hydroxylamino benzoates was also explored, including reagents derived from morpholine, diallyl amine, azepane and piperazine, leading to the products **31a-31g** in 70-98% yield. In addition, a variety of amines bearing functional groups such as an ester (**31h**), a protected ketone (**31i-31j**) or an amide (**31k**) could be prepared in 79-94% yield.



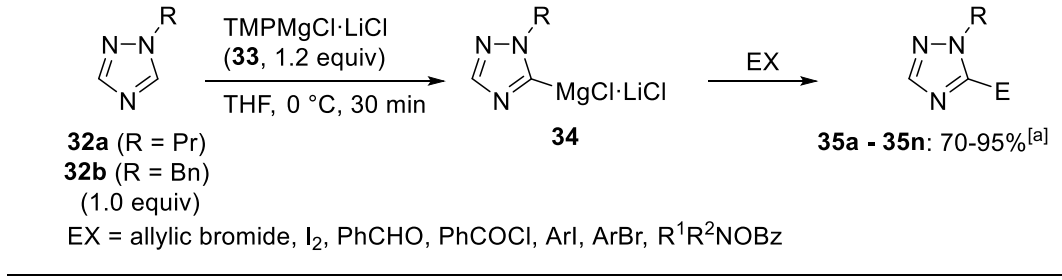
[a] Isolated yields of analytically pure product.

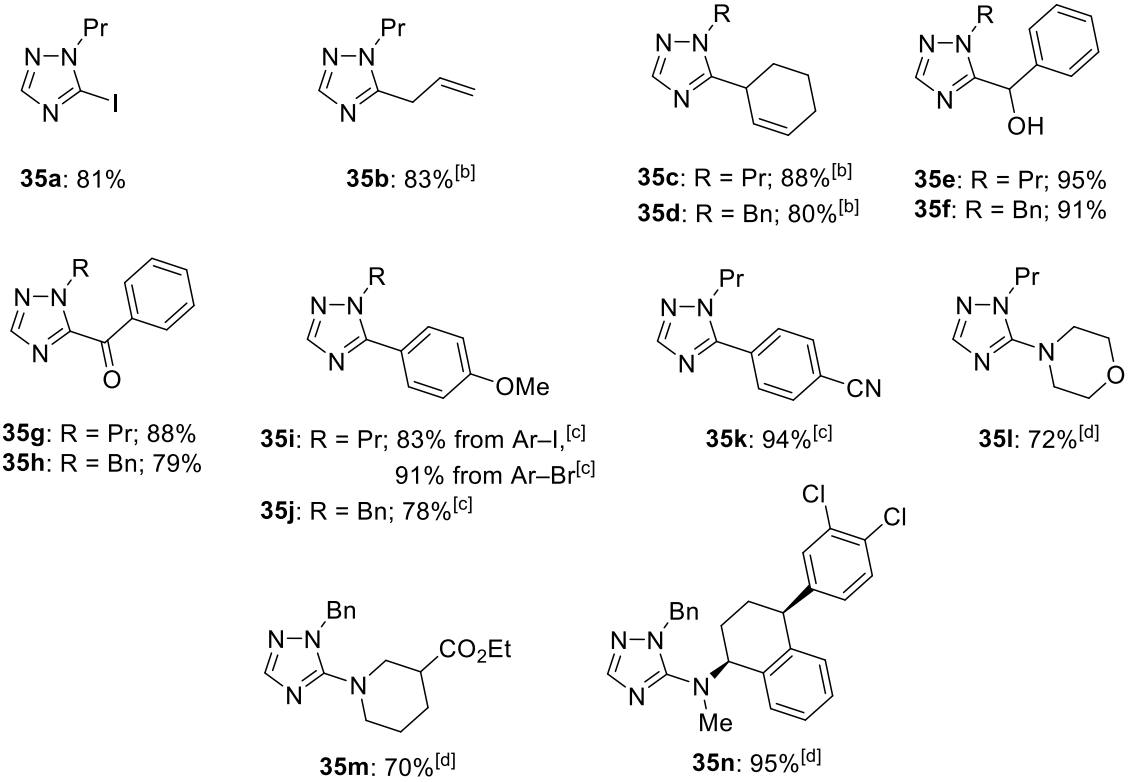
Scheme 29. Zincation of mono-substituted 1,3,4-oxadiazoles of type **28** using $TMP_2Zn·2MgCl_2·2LiCl$ (**29**) followed by electrophilic amination leading to aminated 1,3,4-oxadiazoles of type **31**.

3.2 Selective Functionalization of 1,2,4-Triazoles

In the case of *N*-propyl and *N*-benzyl 1,2,4-triazoles (**32a, 32b**) a complete magnesiation was achieved within 30 min at 0 °C using TMPMgCl·LiCl (**33**) (Scheme 30). The resulting magnesiated triazoles of type **34** were trapped with a variety of electrophiles such as iodine,

allylic bromides, benzaldehyde and benzoyl chloride, providing the 5-substituted-1,2,4-triazoles **35a-35h** in 79-95% yield. In addition, a metalation with TMPZnCl·LiCl (**36**) under the same conditions enabled Pd-catalyzed *Negishi*-type cross-couplings with both electron-rich (**35i-35j**) as well as electron-deficient aryl halides (**35k**) in 78-94% yield. Finally, zincation followed by copper-catalyzed electrophilic amination with hydroxylamino benzoates derived from morpholine, nipecotic acid and sertraline[95] led to the 5-aminated-1,2,4-triazoles **35l**, **35m** and **35n** in 70-95% yield.



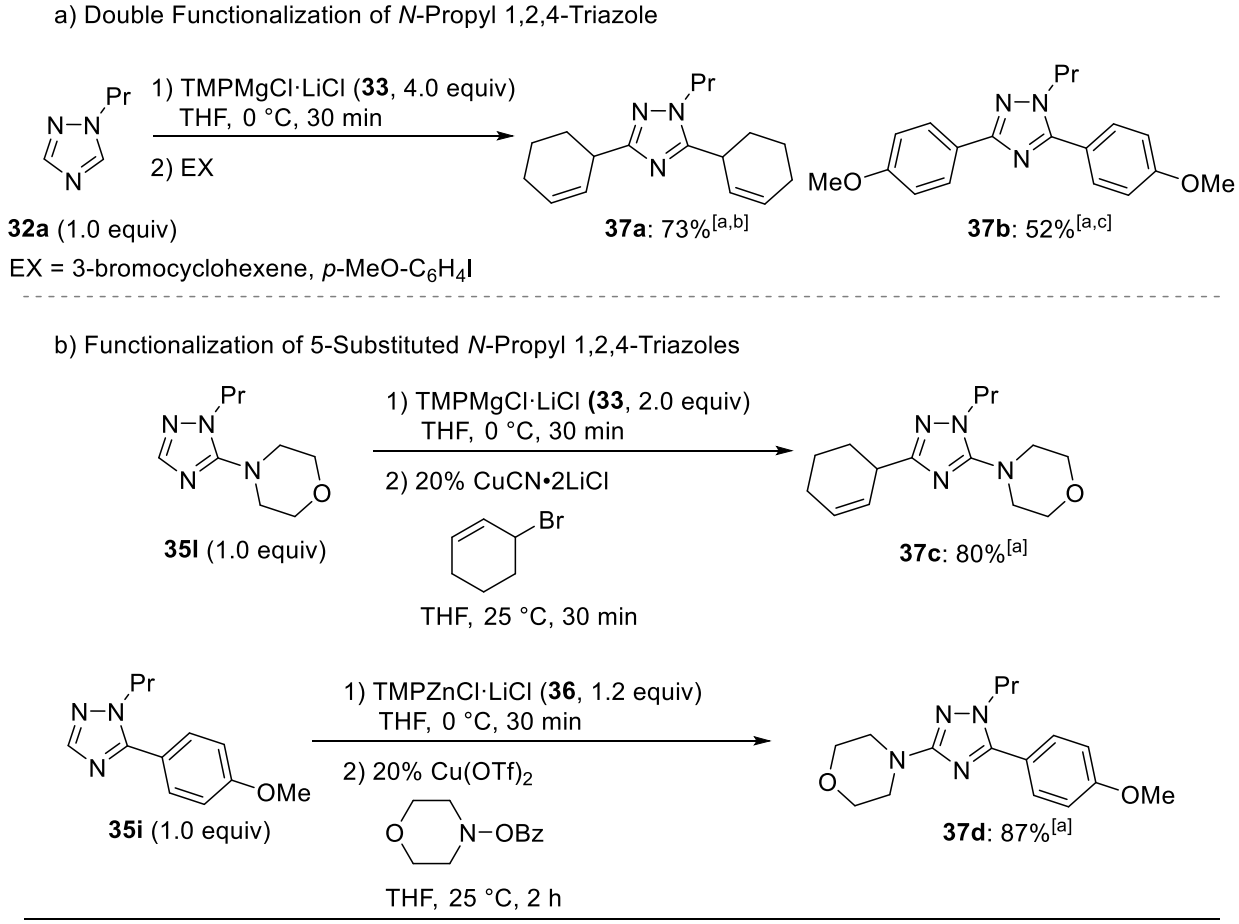


[a] Isolated yields of analytically pure product. [b] Catalyzed by CuCN·2LiCl (20%). [c] Zincation using TMPZnCl·LiCl (**36**) and subsequent cross-coupling catalyzed with 5% $Pd(OAc)_2$ and 10% SPhos. [d] Zincation using TMPZnCl·LiCl (**36**) and subsequent amination catalyzed with 15% $Cu(OTf)_2$.

Scheme 30. Metalation of *N*-substituted 1,2,4-triazoles of type **32** using $TMPMgCl_2$·LiCl (**33**) followed by electrophile trapping leading to functionalized 1,2,4-triazoles of type **35**.

[95] B. K. Koe, A. Weissmann, W. M. Welch, R. G. Browne, *Psychopharmacol. Bull.* **1983**, *19*, 687-691.

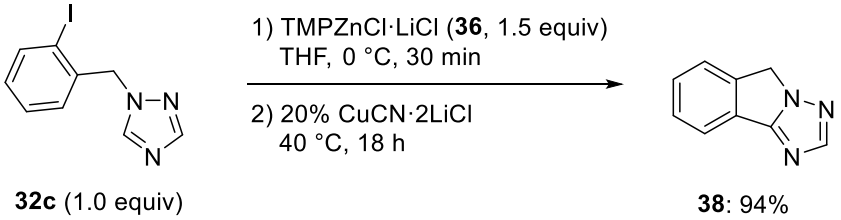
Two approaches have been developed to prepare fully functionalized 1,2,4-triazoles of type **37**: On one hand a double magnesiation of *N*-propyl 1,2,4-triazole (**32a**) was achieved by using an excess of TMPMgCl·LiCl (**7**, 4.0 equiv, 0 °C, 30 min). Subsequent trapping with cyclohexyl bromide provided the double allylated triazole **37a** in 73% yield. In addition, transmetalation to zinc followed by a *Negishi*-type cross-coupling with 4-iodoanisole led to the formation of the double arylated triazole **37b** in 52% yield (Scheme 31a). On the other hand, a second metalation of 5-substituted 1,2,4-triazoles of type **35** could be achieved using TMPMgCl·LiCl (**33**, 2.0 equiv, 0 °C, 30 min) or TMPZnCl·LiCl (**36**, 1.2 equiv, 0 °C, 30 min). This procedure was used to allylate the 3-amino triazole **35l** as well as to aminate the 3-anisyl triazole **35i**, giving access to the fully functionalized triazoles **37c** and **37d** in 80% and 87% yield (Scheme 31b).



[a] Isolated yields of analytically pure product. [b] Catalyzed by CuCN·2LiCl (20%). [c] Catalyzed by $Pd(OAc)_2$ (5%) and SPhos (10%).

Scheme 31. Double functionalization of *N*-propyl 1,2,4-triazole (**32a**) leading to fully functionalized 1,2,4-triazoles of type **37**.

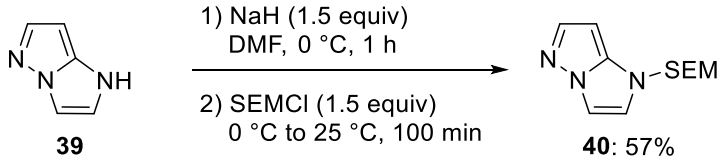
Using the *N*-2-iodobenzyl protected 1,2,4-triazole **32c** a copper catalyzed cyclization was performed after a zincation with TMPZnCl·LiCl (**36**, 1.5 equiv, 0 °C, 30 min, Scheme 32). The cyclization was completed after 18 h at 40 °C and afforded 5*H*-[1,2,4]triazole[5,1-*a*]-isoindole[96] (**38**) in 94% yield.



Scheme 32. Copper-catalyzed cyclization of a zincated 1,2,4-triazole.

3.3 Functionalization of 1*H*-Imidazo[1,2-*b*]pyrazole

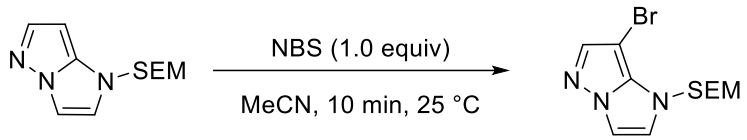
As the NH-proton represents the most acidic position in 1*H*-imidazo[1,2-*b*]pyrazole (**39**), it was necessary to install a protection group on the nitrogen before attempting any metalations. The SEM group has previously used to protect imidazoles, pyrazoles and 1,2,4-triazoles during a series of metalations as it is generally easy to introduce, stable to a wide variety of conditions and can be removed using conditions that tolerate other functional groups.[97] The protection was achieved by first deprotonating 1*H*-imidazo[1,2-*b*]pyrazole (**39**) with 1.5 equivalents of sodium hydride in DMF, followed by the addition of 1.5 equivalents of SEMCl at 0 °C. After 100 minutes the reaction was worked up and purified via column chromatography to yield the SEM-protected 1*H*-imidazo[1,2-*b*]pyrazole **40** in 57% yield (Scheme 33).



Scheme 33. SEM-protection of 1*H*-imidazo[1,2-*b*]pyrazole (**39**).

[96] N. Barbero, R. SanMartin, E. Domínguez, *Org. Biomol. Chem.* **2010**, *8*, 841-645.
[97] a) J. P. Whitten, D. P. Matthews, J. R. McCarthy, *J. Org. Chem.* **1986**, *51*, 1891-1894; b) N. Fugina, W. Holzer, M. Wasicky, *Heterocycles* **1992**, *34*, 303-314; c) C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326-3329.

The first functionalization of the SEM-protected 1*H*-imidazo[1,2-*b*]pyrazole **40** was achieved via a bromination with *N*-bromosuccinimide in acetonitrile (Scheme 34). The reaction was extremely quick, with full conversion after only 10 minutes in acetonitrile. This can be attributed to the highly electron-rich nature of the system. It was also important to use exactly 1.0 equivalents of *N*-bromosuccinimide, as even a slight excess led to the formation of a double brominated side-product. The reaction was also highly regioselective and only a single product (**41**), with the bromine in the 7-position, was isolated. This selectivity is in accordance with the behaviour of pyrazoles, where electrophilic aromatic halogenations favour the 4-position.[98] The product had to be protected from light and heat during the work-up and purification to avoid decomposition. It could however be stored at −30 °C for a month without any signs of decomposition.



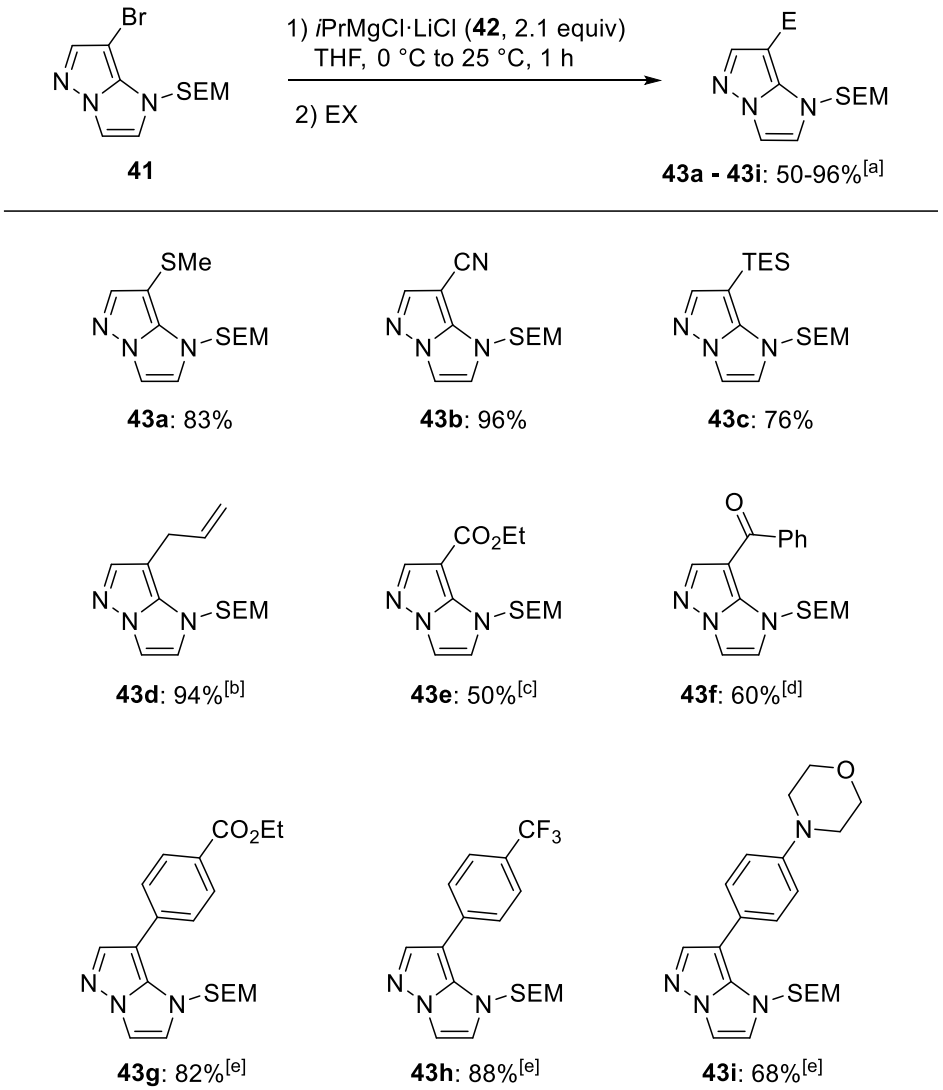
40 **41**: 86%

Scheme 34. Selective bromination of the SEM-protected 1*H*-imidazo[1,2-*b*]pyrazole **40** in the 7-position.

In order to access a wide range of different functionalizations in the 7-position, the brominated 1*H*-imidazo[1,2-*b*]pyrazole **41** was treated with *i*PrMgCl·LiCl (**42**, 2.1 equiv, 0 °C to 25 °C, 1 h) in THF. The resulting magnesiated 1*H*-imidazo[1,2-*b*]pyrazole was successfully reacted with a variety of electrophiles (Scheme 35), including *S*-methyl sulfonothioate (**43a**),[47] tosyl cyanide (**43b**) and TESCl (**43c**) in 76-96% yield. The addition of CuCN·2LiCl allowed an allylation (**43d**) in 94% yield and the formation of the ethyl ester **43e** with ethyl cyanoformate in 50% yield. Additional reactions included an acylation catalyzed by $Pd(PPh_3)_4$ (**43f**) in 60% yield and a range of *Kumada*-type cross-couplings with electron-deficient (**43g**, **43h**) and electron-rich (**43i**) iodides catalyzed by PEPPSI-*i*Pr[99] in 68-88% yield.

[98] a) M. McLaughlin, K. Marcantonio, C.-Y. Chen, I. W. Davies, *J. Org. Chem.* **2008**, *73*, 4309-4312; b) R. Goikhman, T. L. Jacques, D. Sames, *J. Am. Chem. Soc.* **2009**, *131*, 3042-3048.

[99] M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O`Brien, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150-157.

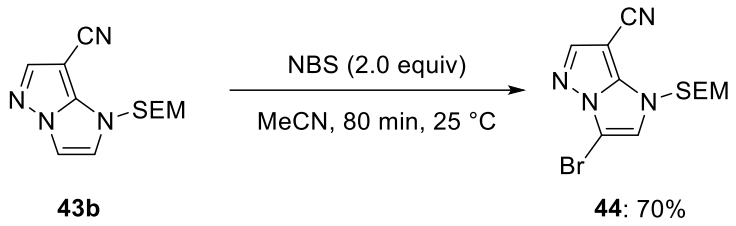


[a] Isolated yields of analytically pure product. [b] Catalyzed by CuCN·2LiCl (20%). [c] Mediated by CuCN·2LiCl (1.0 equiv). [d] Catalyzed by $Pd(PPh_3)_4$ (5%). [e] Catalyzed by PEPPSI-*i*Pr (2%).

Scheme 35. Selective functionalization of the 1*H*-imidazo[1,2-*b*]pyrazole **41** via bromine-magnesium exchange leading to 7-functionalized 1*H*-imidazo[1,2-*b*]pyrazoles of type **43**.

In order to explore the further functionalization of the 1*H*-imidazo[1,2-*b*]pyrazole scaffold the substrate **43b** with a nitrile in the 7-position was chosen as a starting material, as it could be synthesized in excellent yields even at a scale of more than 1 gram. Initially, conditions for a second bromination using *N*-bromosuccinimide in acetonitrile were explored (Scheme 36). This time the bromination was significantly slower and 2.0 equivalents of NBS were necessary to achieve a full conversion after 80 minutes at 25 °C. The bromination was highly selective, as only a single product **44** was isolated in 70% yield. The structure of **44** was

explored via 2D-NMR spectroscopy, which showed that the bromine was introduced in the 3-position.

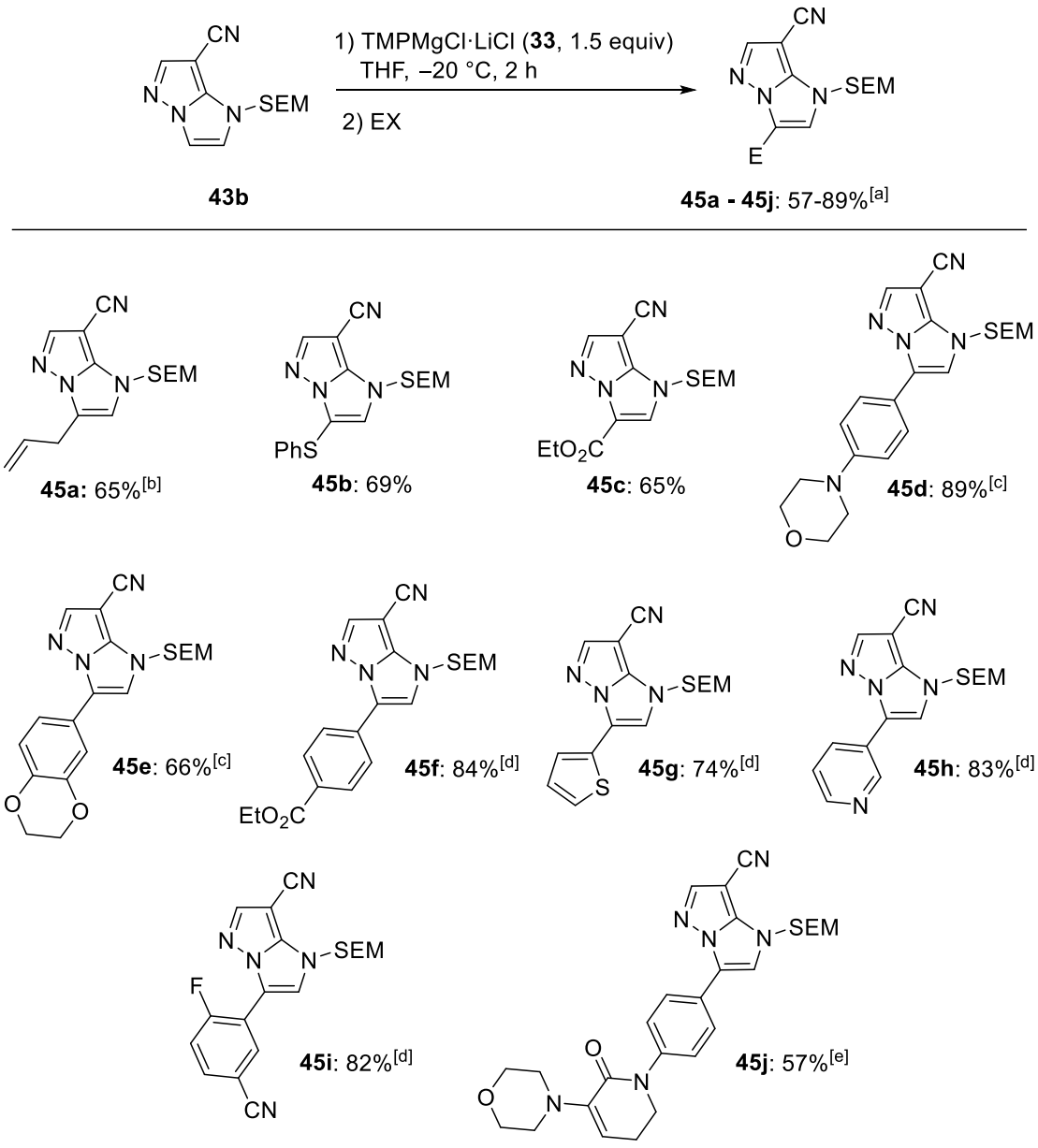


43b **44**: 70%

Scheme 36. Selective bromination of the 1*H*-imidazo[1,2-*b*]pyrazole **43b** using NBS.

As the second bromination was significantly slower than the first one and required a large excess of NBS, the use of TMPMgCl·LiCl (**33**, 1.5 equiv, −20 °C, 2 h) to achieve the second functionalization without needing to handle a sensitive bromide was explored instead (Scheme 37). The TMP base resulted in a selective magnesiation in the 3-position. The metalated 1*H*-imidazo[1,2-*b*] pyrazole was successfully reacted with a variety of electrophiles in 57-89% yield (**45a-45j**). This included a copper-catalyzed allylation (**45a**) in 65% yield, a thiolation with *S*-phenyl sulfonothioate (**45b**)[47] in 69% yield and the reaction with ethyl cyanoformate (**45c**) in 65% yield. A transmetalation with $ZnCl_2$ allowed a series of Negishi-type cross-couplings[45] in 57-89% yield (**45d-45j**). When electron-rich iodides where employed (**45d**, **45e**), a mixture of $Pd(OAc)_2$ (5%) and SPhos[100] (10%) yielded the best results. For electron-deficient halides (**45f-45i**) the NHC catalyst PEPPSI-*i*Pr (2%) performed significantly better. By increasing the reaction temperature from 40 °C to 60 °C, it was even possible to conduct the cross-coupling with a less reactive bromide instead of an iodide (**45i**). The use of the more active catalyst PEPPSI-*i*Pent[101] (3%) at 60 °C allowed the reaction with a highly functionalized iodide containing an α,β-unsaturated amide and an amine in 57% yield (**45j**).

[100] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696.
[101] M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi, A. L. Lough, *Angew. Cmem. Int. Ed.* **2009**, *48*, 2383-2387.

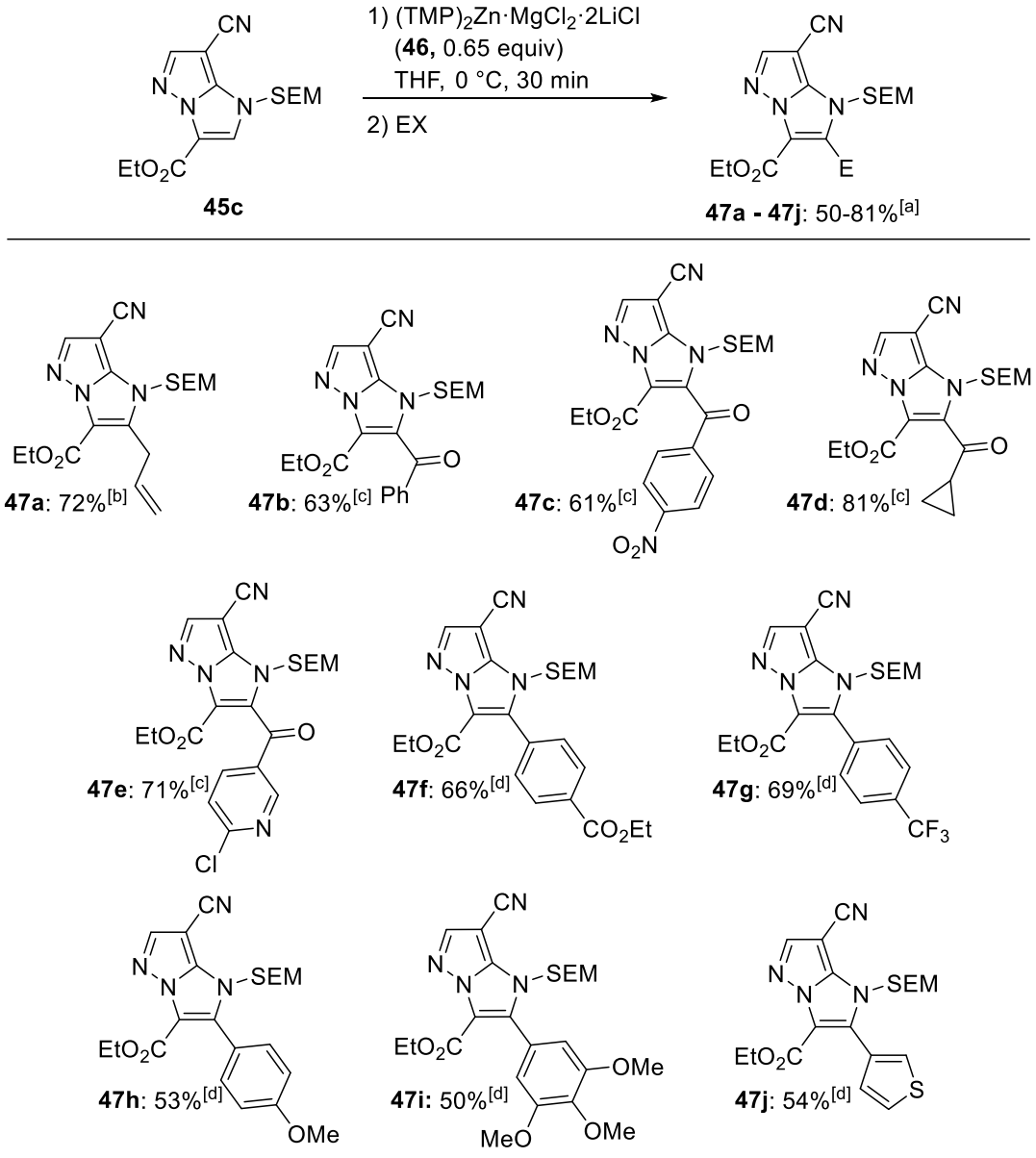


[a] Isolated yields of analytically pure product. [b] Catalyzed by CuCN·2LiCl (20%). [c] Transmetalated using $ZnCl_2$ (1.5 equiv) and catalyzed by $Pd(OAc)_2$ (5%) and SPhos (10%). [d] Transmetalated using $ZnCl_2$ (1.5 equiv) and catalyzed by PEPPSI-*i*Pr (2%). [e] Transmetalated using $ZnCl_2$ (1.5 equiv) and catalyzed by PEPPSI-*i*Pent (3%).

Scheme 37. Selective metalation of the 1*H*-imidazo[1,2-*b*]pyrazoles **43b** using TMPMgCl·LiCl (**33**) followed by electrophile trapping leading to 3-substituted 1*H*-imidazo-[1,2-*b*]pyrazoles of type **45**.

The third functionalization was optimized using ethyl 7-cyano-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate (**45c**) as a substrate (Scheme 38). An initial screening showed, that the *bis*-base $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ (**46**, 0.65 equiv), prepared from TMPLi through the addition of half an equivalent each of a freshly prepared $MgCl_2$ and $ZnCl_2$

solution in THF, yielded the best results. The metalation targeted selectively the 2-position and was completed after 30 minutes at 0 °C. The zincated 1*H*-imidazo[1,2-*b*]pyrazole was reacted in a copper-catalyzed allylation, yielding 72% of the corresponding product **47a**. In addition, a series of copper-catalyzed acylations with aromatic (**47b**, **47c**), aliphatic (**47d**) and heteroaromatic (**47e**) acyl chlorides was conducted in 61-81% yield. Finally, a range of *Negishi*-type cross-couplings catalyzed by $Pd(PPh_3)_4$ (5%) gave access to the products **47f-47j** in 50-69% yield. The scope of possible substrates included electron-deficient (**47f**, **47g**), electron-rich (**47h**, **47i**) and heterocyclic (**47j**) iodides. The low reactivity of the intermediate zinc species allowed the use of electrophiles containing sensitive functional groups, such as an ester (**47f**) or a nitro group (**47c**), without significant amounts of undesired side-products.

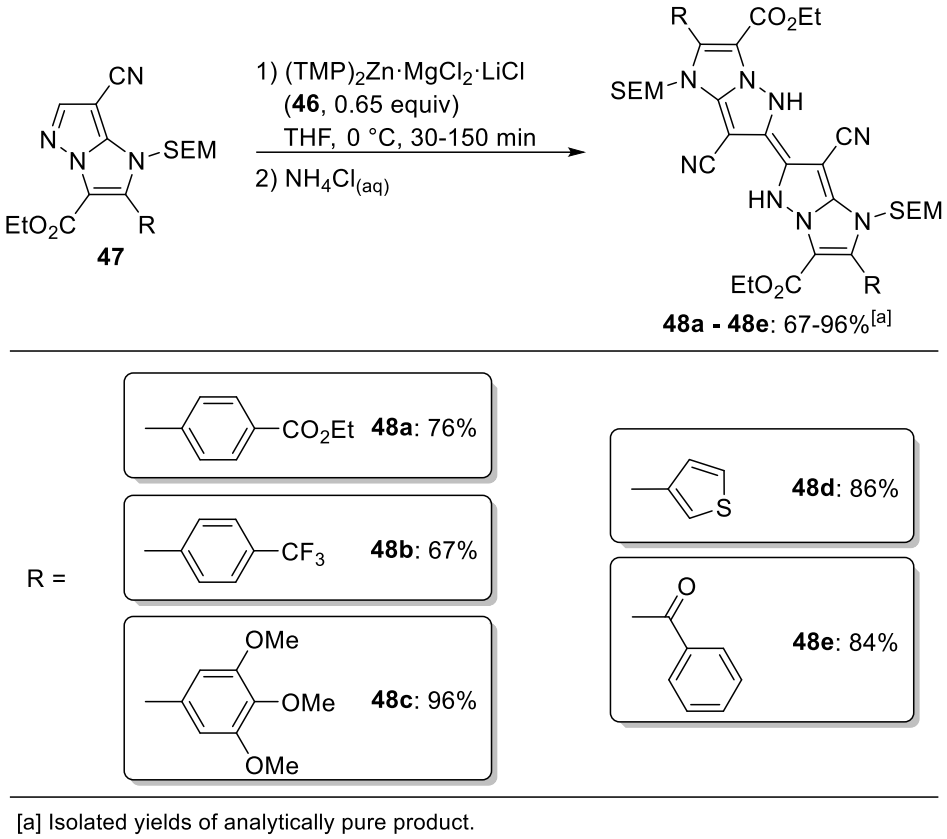


[a] Isolated yields of analytically pure product. [b] Catalyzed by CuCN·2LiCl (20%).
[c] Catalyzed by CuCN·2LiCl (50%). [d] Catalyzed by $Pd(PPh_3)_4$ (5%).

Scheme 38. Selective metalation of the 1*H*-imidazo[1,2-*b*]pyrazoles **45c** using $(TMP)_2Zn·MgCl_2·2LiCl$ (**46**) followed by electrophile trapping leading to 2-substituted 1*H*-imidazo[1,2-*b*]pyrazoles of type **47**.

When attempting the final functionalization of a series of 2,3,7-trifunctionalized 1*H*-imidazo-[1,2-*b*]pyrazoles of type **47** using $(TMP)_2Zn·MgCl_2·2LiCl$ (**46**, 0.65 equiv), the starting materials were fully consumed within 30-150 minutes at 0 °C, without the addition of any electrophile (Scheme 39). TLC analysis of hydrolysed aliquots showed the formation of a single highly polar new spot in all cases. The new products of type **48** were purified via column chromatography on Florisil® and analysed via ESI mass spectrometry and NMR

spectroscopy. The data hinted at the presence of a previously unknown 1*H*,1'*H*,5*H*,5'*H*-6,6'-biimidazo[1,2-*b*]pyrazolylidene core. The formation of this unusual new class of products can be explained through the attack of a zincated 1*H*-imidazo[1,2-*b*]pyrazole molecule on the 6-position of a second 1*H*-imidazo[1,2-*b*]pyrazole unit. A second deprotonation then leads to the formation of the central double bond.[102] A final aqueous work-up leads to the formation of the products **48a-48e** in 67-96% yield. The reaction was successfully performed with 1*H*-imidazo[1,2-*b*]pyrazoles containing aryl substituents with electron withdrawing (**48a**, **48b**) and electron donating (**48c**) groups in the 2-position. Other substituents included a 3-thienyl (**48d**) and a benzoyl group (**48e**).



Scheme 39. Treatment of 2,3,7-trifunctionalized 1*H*-imidazo [1,2-*b*]pyrazoles of type **47** with $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ (**46**) leading to 1*H*,1'*H*,5*H*,5'*H*-6,6'-biimidazo[1,2-*b*]pyrazolylidenes of type **48**.

Most of these novel 1*H*,1'*H*,5*H*,5'*H*-6,6'-biimidazo[1,2-*b*]pyrazolylidenes of type **48** exhibited fluorescence in solution when irradiated by UV-light (366 nm, Figure 9). The colour of the emitted light correlated with the structure of the substituents in the 2-positions: The electron

[102] The exact configuration of the central double bond remains to be determined. NMR-spectroscopy confirms the presence of only a single conformer.

donating substituents in **48c** and **48d** led to the emission of blue light. The inductively electron withdrawing CF_3-groups in **48b** resulted in a green light, while the inductive and mesomeric electron withdrawal of the esters in **48a** led to the emission of orange light. A solution of the compound **48e** with benzoyl substituents in the 2-positions did not exhibit any fluorescence under the 366 nm UV-lamp. However, it showed a very intense yellow colour, hinting at a strong absorption in the blue range of visible light.

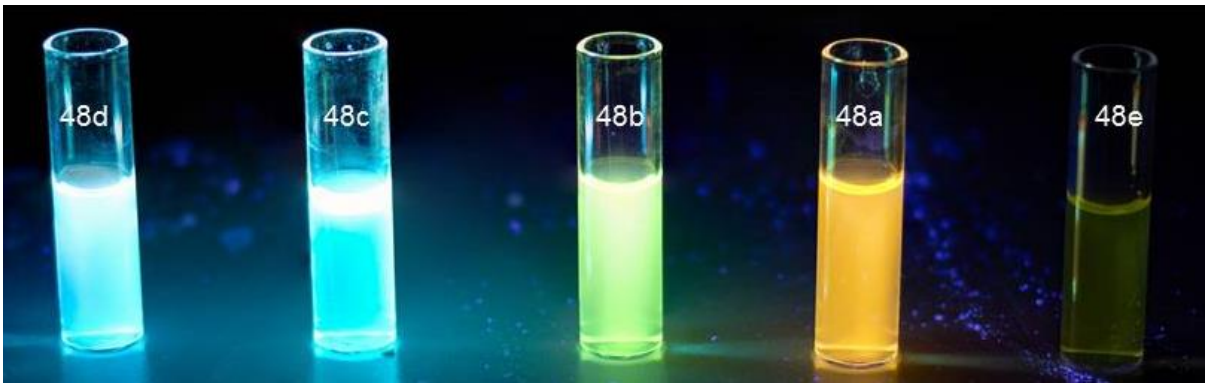
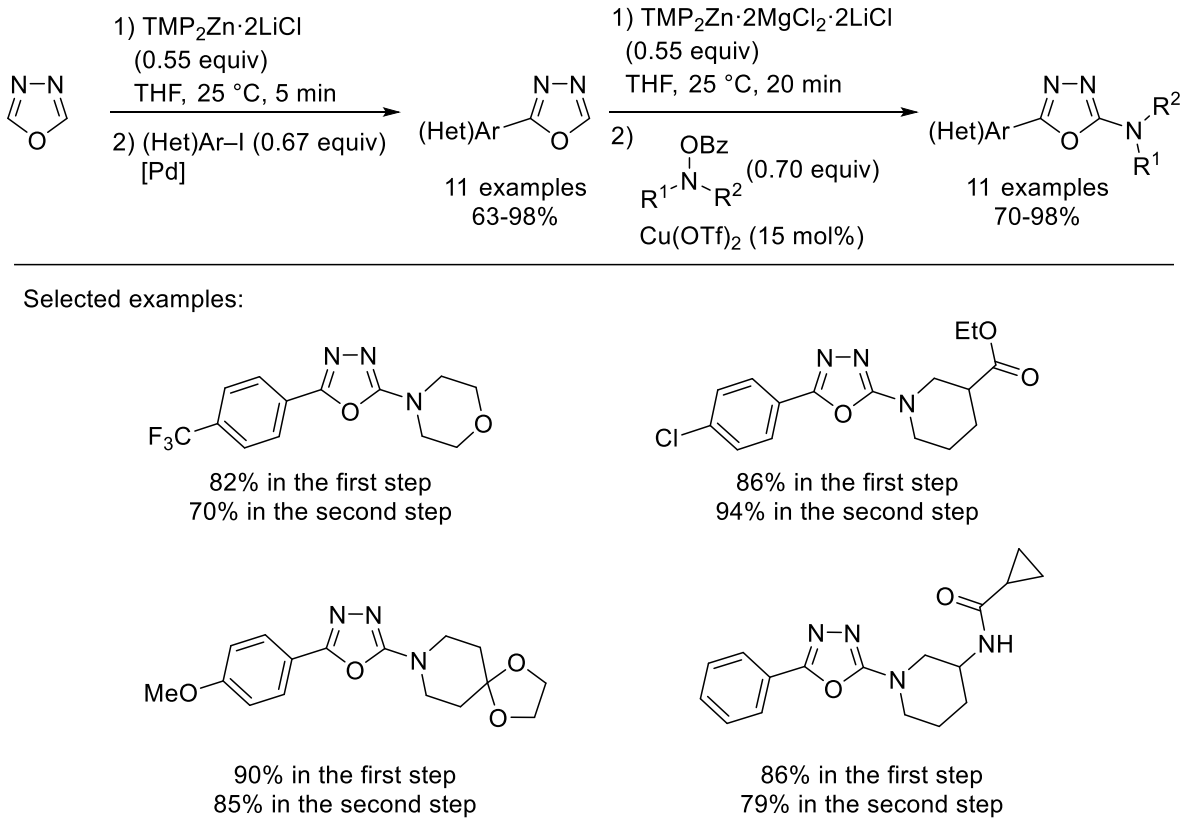


Figure 9. Fluorescence of 1*H*,1'*H*,5*H*,5'*H*-6,6'-biimidazo[1,2-*b*]pyrazolylidenes of type **48** in acetone under UV-light (366 nm).

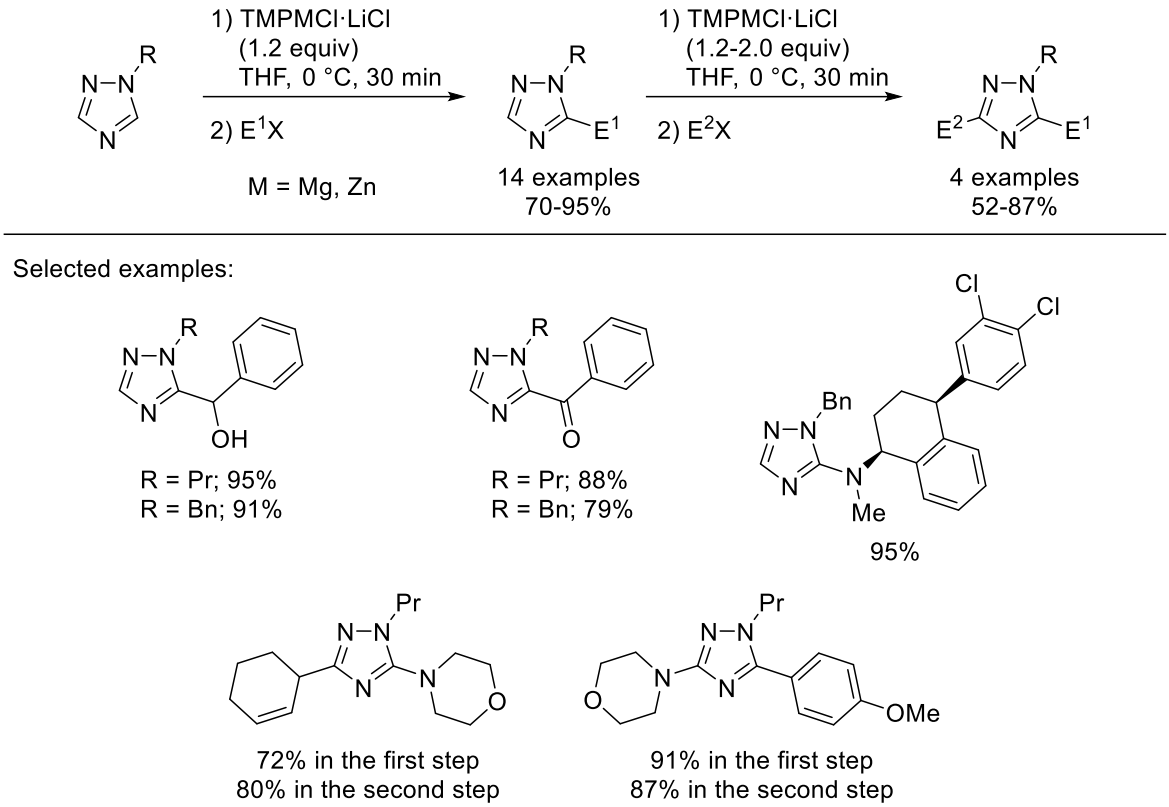
4 Summary

The topic of the second part of this thesis was the metalation of various nitrogen containing heterocycles using TMP bases. This was first achieved in the case of 1,3,4-oxadiazole using the base $TMP_2Zn{\cdot}2LiCl$ (Scheme 40). The resulting zincated 1,3,4-oxadiazole was reacted in a series of *Negishi*-type cross-couplings with electron-deficient, electron-rich and heterocyclic iodides. The mono substituted 1,3,4-oxadiazoles were then metalated a second time using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, followed by a series of copper-catalyzed electrophilic aminations using hydroxylamino benzoates.



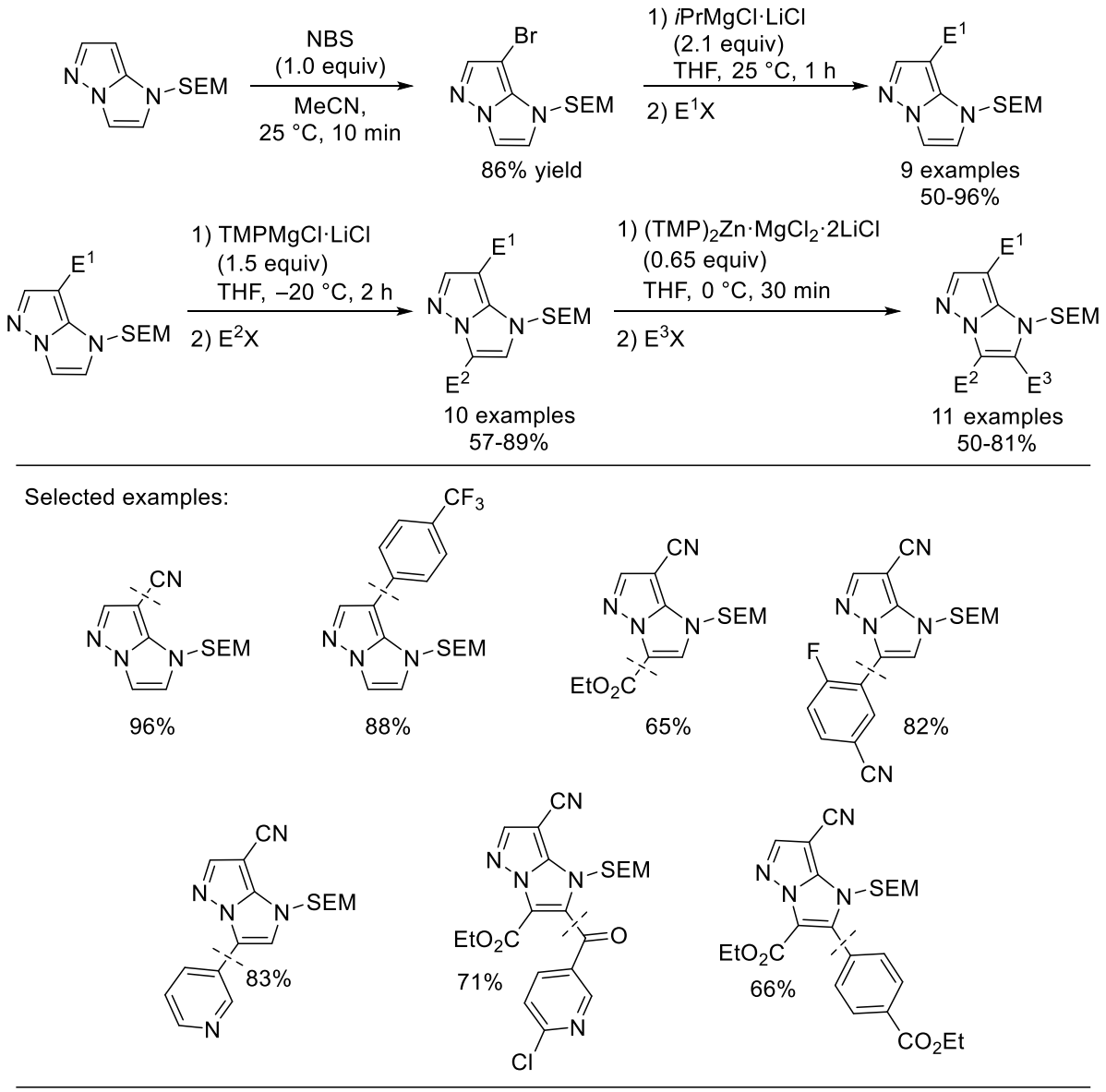
Scheme 40. Summary of the functionalization of 1,3,4-oxadiazole.

N-propyl and *N*-benzyl 1,2,4-triazole were investigated as a second heterocyclic system (Scheme 41). In this case the first metalation was achieved using TMPMgCl·LiCl or TMPZnCl·LiCl. The metalated 1,2,4-triazoles were subsequently submitted to a variety of electrophilic trapping reactions, including copper-catalyzed allylations and acylations, as well as *Negishi*-type cross-couplings and copper-catalyzed electrophilic aminations. A second metalation was performed on two different substrates using the same TMP bases.



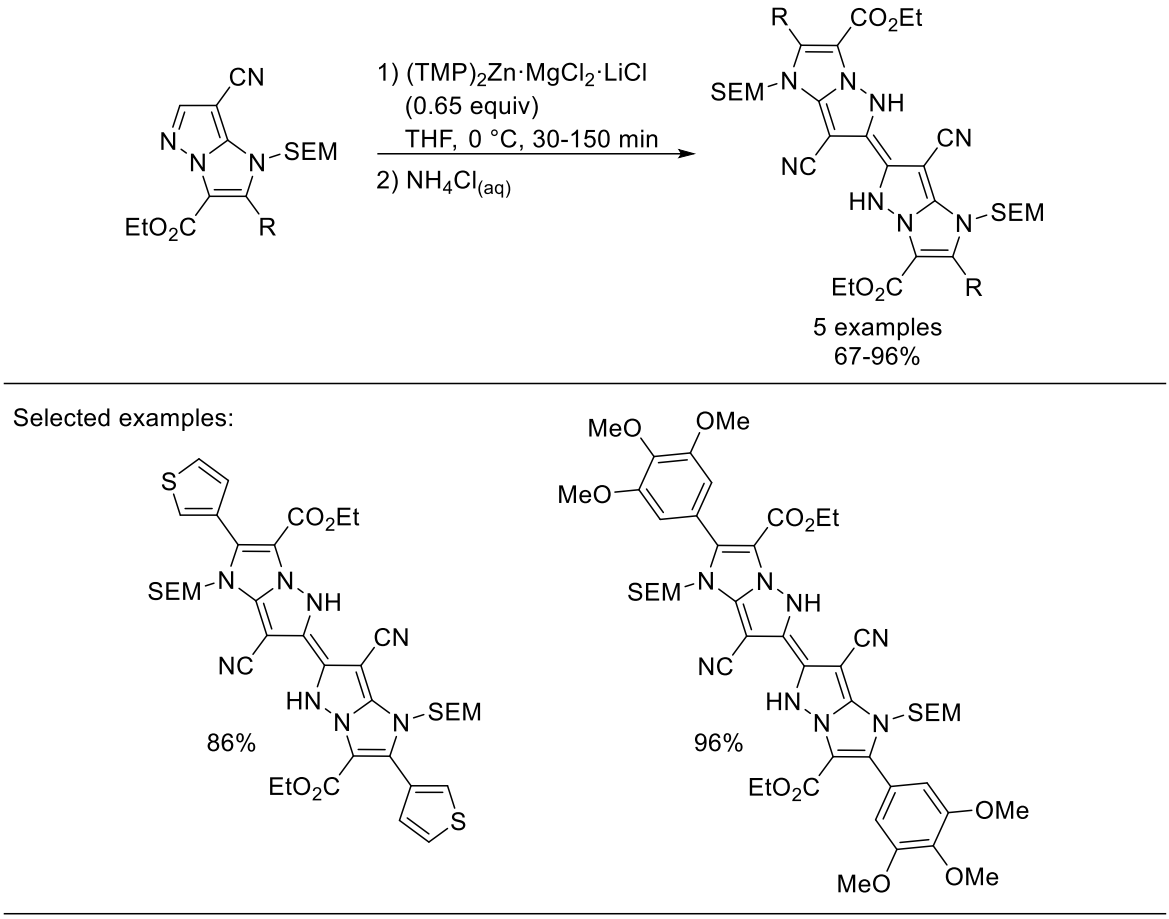
Scheme 41. Summary of the functionalization of 1,2,4-triazoles.

Finally, the functionalization of 1*H*-imidazo[1,2-*b*]pyrazole was explored (Scheme 42). The free NH-group of the heterocycle was protected with a SEM-group. The first functionalization was achieved via a selective bromination in the 7-position using NBS, followed by a bromine-magnesium exchange and different electrophilic trapping reactions. A second selective metalation in the 3-position was performed using TMPMgCl·LiCl. The metalated intermediates could once again be reacted with a variety of electrophiles. The third metalation with $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ went selectively in the 2-position and allowed the synthesis of a multitude of acylation and cross-coupling products.



Scheme 42. Summary of the functionalization of 1*H*-imidazo[1,2-*b*]pyrazole.

The treatment of 2,3,7-trifunctionalized 1*H*-imidazo[1,2-*b*]pyrazoles with $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ let to the formation of a series of novel 1*H*,1'*H*,5*H*,5'*H*-6,6'-biimidazo-[1,2-*b*]pyrazolylidenes, which exhibited fluorescence in solution under UV-light (Scheme 43).



Scheme 43. Summary of the synthesis of novel 1*H*,1'*H*,5*H*,5'*H*-6,6'-biimidazo[1,2-*b*]-pyrazolylidenes.

Part III: Experimental Section

1 General Considerations

Unless otherwise stated all reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. Reactions at high temperatures containing volatile compounds were conducted in BIOTAGE microwave vials sealed with the appropriate caps (up to 3 mL total volume) or Ace pressure vials. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Reaction mixtures were cooled using an acetone / dry ice bath and heated using an oil bath on a magnetic stirrer. The suspension formed during the work-up of reactions containing CuCN·2LiCl was dissolved by adding appropriate amounts of concentrated aqueous ammonia solution.

1.1 Solvents

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2 under nitrogen atmosphere.

Et_2O was predried over $CaCl_2$ and passed through activated aluminium oxide (solvent purification system *SPS-400-2* from *Innovative Technologies Inc.*)

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves.

All other solvents were purchased from chemical suppliers (*Merck*, *Acros Organics*) and used without further purification.

Solvents for reaction workups and column chromatography were distilled prior to use.

1.2 Reagents

***n*BuLi** and **PhLi** solutions in hexane or dibutyl ether were purchased from *Albemarle* or *Merck* and the concentration was determined by titration against *N*-benzylbenzamide in THF at −40 °C or 0 °C respectively.[103]

[103] A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281-283.

TMPH was purchased from *Albemarle* (Frankfurt, Germany), freshly distilled over CaH_2 and stored under argon.

Diisopropylamine was purchased from *Acros Organics*, freshly distilled over CaH_2 and stored under argon.

CuCN·2LiCl solution (1.00 M in THF) was prepared by drying CuCN (8.96 g, 100 mmol, 1.00 equiv) and LiCl (8.48 g, 200 mmol, 2.00 equiv) in a *Schlenk*-flask under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (100 mL) was added and the resulting mixture was stirred until the salts were dissolved.

$ZnCl_2$ solution (1.00 M in THF) was prepared by drying $ZnCl_2$ (27.3 g, 200 mmol) in a *Schlenk*-flask under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (200 mL) was added and the resulting mixture was stirred until the salts were dissolved.

***i*PrMgCl·LiCl** in THF was prepared by flame drying magnesium turnings (24 g, 1.0 mol, 2.0 equiv) and anhydrous LiCl (25 g, 0.60 mol, 1.2 equiv) in a *Schlenk*-flask under vacuum at 450 °C. After the addition of anhydrous THF (500 mL), *i*PrCl (39 g, 0.50 mol, 1.0 equiv) was added dropwise at 25 °C using a dropping funnel until the reaction started. Then the reaction mixture was cooled to 0 °C and the addition was continued overnight while allowing the flask to warm up to 25 °C. The remaining solids were filtered off and the *i*PrMgCl·LiCl solution was titrated against iodine.

TMPH was purchased from *Albemarle* (Frankfurt, Germany), freshly distilled over CaH_2 and stored under argon.

1.3 Chromatography

Flash column chromatography was performed using silica gel 60 (40-63 µm, 230-400 mesh ASTM), alumina 90 active acidic (63-200 µm, 70-230 mesh ASTM), or Florisil® PR grade (149-250 µm, 60-100 mesh) from *Merck.* The activity of the alumina was set to grade III by adding 4.5% distilled water and stirring at 40 °C for 2 h.

Thin layer chromatography (TLC) was performed using aluminium 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 reagents below, followed by heating with a heat gun if necessary.

- $KMnO_4$ (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 conc. H_2SO_4 (50 mL) in water (450 mL).
- Neat iodine absorbed on silica gel (no heating required).
- Vanillin (15 g) and conc. H_2SO_4 (2.5 mL) in EtOH (250 mL).
- *p*-Anisaldehyde (3.7 mL), conc. H_2SO_4 (5 mL) and acetic acid (1.5 mL) in EtOH (135 mL).

Preparative HPLC purification was performed on an *Agilent Technologies* 1260 Infinity HPLC-System, consisting of two prep-pumps (acetonitrile/water, no additives), a MWD-detector (210 nm wavelength, 40 nm bandwidth, ref-wavelength 400 nm, ref-bandwidth 100 nm) and a fraction collector. Three different columns were used: 1) *Kinetix* EVO C18 5 µm column (length: 150 mm, diameter: 10 mm), 2) *Kinetix* EVO C18 5 µm column (length: 150 mm, diameter: 21.2 mm) and 3) *Waters* XBridge Prep C8 5 µm column (length: 150 mm, diameter: 30 mm).

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 ppm relative to the deuterated solvent peak: $CDCl_3$ (δ_H: 7.26; δ_C: 77.16), DMSO-d_6 (δ_H: 2.50; δ_C: 39.52), C_6D_6 (δ_H: 7.16; δ_C: 128.06) Acetone-d_6 (δ_H: 2.05; δ_C: 206.26 / 29.84). For the observation of the observed signal multiplicities, the following abbreviations and combinations thereof were used: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). 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. In the cases where a steric centre is located next to a bicyclopentane core, the protons of the methylene groups in the BCP unit are diastereotopic and show the splitting pattern expected for the resulting $[AB]_3$-system.

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

Infrared spectra were recorded from 4000-400 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 chromatographical analysis (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).

Single crystals of compounds suitable for **X-ray diffraction** were obtained by slow evaporation of either EtOAc or $CDCl_3$ solutions. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection was performed with the CrysAlis CCD software;[104] CrysAlis RED software[105] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[106] was applied. The structures were solved with SHELXS-97,[107] refined with SHELXL-97[108] and finally checked using PLATON.[109] Details for data collection and structure refinement are summarized in the tables at the end of this document.

The **1-octanol/water partitioning coefficient (logP)** was determined using a miniaturized Shake-Flask equilibrium method. Prior to start the experiment the two phases were pre-saturated, so “water-saturated 1-octanol” and “1-octanol-saturated water” were used. The samples were initially dissolved in DMSO as a 10 mM stock concentration. The samples and an internal standard were dispensed in a 1ml deepwell plate and DMSO is evaporated prior to be dissolved in 1-octanol at a target concentration of 150 µM by shaking at 1000 rpm for 8 hours. The pH 7.4 buffer was added with a phase ratio K of 1 (where $K = V_{water}/V_{octanol}$) and then the samples were shaken 4 hours on a shaker at 1000 rpm. The deepwell plate was centrifuged at 3000rpm prior to phase separation. A x10 dilution for the aqueous phase and a

[104] CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).
[105] CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).
[106] SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C), Oxford Diffraction, Ltd., 2005.
[107] G. M. Sheldrick (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[108] G. M. Sheldrick (1997) SHELXS-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[109] A. L. Spek (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, the Netherlands.

x1000 dilution for the octanol phase are prepared and quantified by LC-HRMS against an internal standard (Dexamethasone) with a known logD = 1.9 with the following equation 3:[110]

$$logD = \log\left(\frac{Analyte\ peak\ area\ in\ octanol * 1000 \Big/ IS\ peak\ area\ in\ octanol \Big/ 0.794}{Analyte\ peak\ area\ in\ aqueous * 10 \Big/ IS\ peak\ area\ in\ aqueous}\right) \quad (3)$$

Column used: Zorbax_SB_AQ 50 x 2.1 mm 1.8 µm – Column oven temperature = 50 °C

Mobile phase: A= 100% water UHPLC grade + 0.08% formic acid. B = 100% ACN + 0.08% Formic acid. Flow rate = 0.5 ml/min. Gradient mode: starting at 95% A up to 95% B in 0.5 min and kept constant during 1min before to restore initial conditions within 0.1 min. Vinj = 5 µl. Full MS acquisition mode – Full scan 130 to 1800 m/z and resolution = 35'000. $[M+H]^+$ ion chromatogram was extracted for each compounds.

Potentiometric ionization constants were determined on the commercial SiriusT3 instruments (Pion-inc.com) as described by *Takács-Novák et. al.* 1997. Briefly, 0.3 to 1 mM of test solutions were titrated from pH 2 to 12 for bases or 12 to 2 for acids. Titrations were conducted at 25 °C and in 0.15 M ionic strength. Aqueous titrations were performed in triplicate in 0.15 M KCl, while sparingly soluble test compounds were titrated in 10-60 %wt methanol, 1,4-dioxane, or dimethyl sulfoxide co-solvent. A minimum of three titrations in varying amounts of cosolvent were performed for extrapolation to the aqueous pK_a. For each titration, initial estimates of pK_a values were obtained from Bjerrum difference plots (number of bound protons versus pH) and then were refined by a weighted non-linear least-squares procedure (Avdeef 1992, 1993) available in the instrument software. Experimental variability was determined from 389 duplicate measurements from different days and experimentalists, with a standard deviation of 0.28.

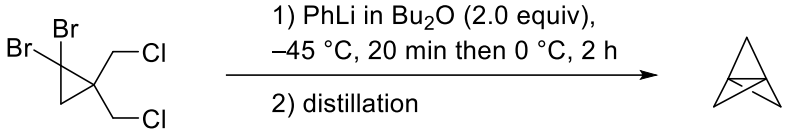
[110] Y. W. Low, F. Blasco, P. Vachaspati, *Eur. J. Pharm. Sci.* **2016**, *92*, 110-116.

2 Experimental Section Part I: Highly Regio-selective Addition of Organozinc Reagents to [1.1.1]Propellane

2.1 Preparation of Starting Materials

The following reagents were prepared according to literature procedures: 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane,[111] *N,N*-diallyl-*O*-benzoylhydroxylamine,[48] *S*-phenyl benzenesulfonothioate *,* *S*-methyl benzenesulfonothioate,[112] ethyl 2-(bromomethyl)acrylate,[113] ethyl 6-chlorocyclohex-1-ene-1-carboxylate[114], (1*R*)-myrtenyl bromide[115] and 5-bromocyclopent-1-enecarbonitrile.[116]

Preparation of the solution of [1.1.1]propellane (1) in diethyl ether



In a dry *Schlenk*-flask 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (5.9 g, 20 mmol, 1.0 equiv) was dissolved in Et_2O (20 mL) and cooled to −45 °C. Phenyllithium (1.8 M in dibutyl ether, 22 mL, 40 mmol, 2.0 equiv) was added dropwise over 15 min using a syringe pump. The resulting mixture was stirred for 5 min at −45 °C and 2 h at 0 °C. Then an argon flushed distillation head connected to a collector *Schlenk*-tube immersed into an acetone/ dry ice bath (T = −78 °C) was attached and the distillation was started at 200 mbar. The reaction flask was removed from the ice bath and the pressure was gradually lowered to 45 mbar. After approximately 30 min the distillation was stopped and the system was filled with argon. An aliquot (0.1 mL) of the solution was analysed by NMR spectroscopy with 1,3,5-trimethoxybenzene (16.8 mg, 0.10 mmol) as a standard to determine the concentration.

[111] K. R. Mondanaro, W. P. Dailey, *Org. Synth.* **1998**, *75*, 98-101.
[112] K. Fujiki, N. Tanufuji, Y. Sasaki, T. Yokoyama, *Synthesis* **2002**, *3*, 343-348.
[113] J. Caillé, M. Pantin, F. Boeda, M. S. M. Pearson-Long, P. Bertus, *Synthesis* **2019**, *51*, 1329-1341.
[114] Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8516-8519.
[115] R. K. de Richter, M. Bonato, M. Follet, J.-M. Kamenka, *J. Org. Chem.* **1990**, *55*, 2855-2860
[116] G. L. Lackner, K. W. Quasdorf, G. Pratsch, L. E. Overman, *J. Org. Chem.* **2015**, *80*, 6012-6024.

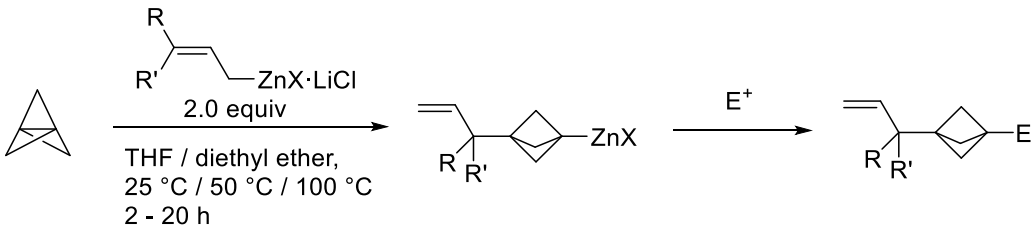
The average concentration of the [1.1.1]propellane solution was 0.5-0.7 M. The solution was stored at −25 °C under argon.

General procedure for the preparation of allylic organozinc reagents of type 2 in THF

A *Schlenk*-flask was loaded with zinc dust (2.0 equiv) and lithium chloride (1.2 equiv) and flame dried with a heat gun under vacuum at 450 °C. Once the flask was cooled down it was filled with argon and THF (1 mL/mmol halide). The zinc was activated by adding a drop of 1,2-dibromoethane and heating until a slight gas evolution started. Then the reaction mixture was cooled to 0 °C and the respective organohalide (1.0 equiv) was added dropwise. The reaction mixture was stirred over night while slowly warming up to room temperature. The remaining zinc dust was removed using a syringe filter and the concentration was determined via titration against iodine.[117]

2.2 Typical Procedures

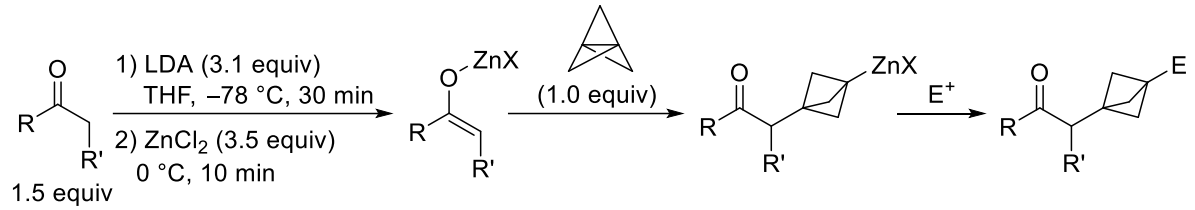
TP1: Typical procedure for the reaction of allylic organozinc reagents of type 2 with [1.1.1]propellane (1) followed by electrophile addition



A BIOTAGE Microwave vial under argon was loaded with the allylic organozinc reagent in THF (0.40 mmol, 2.0 equiv), followed by [1.1.1]propellane in diethyl ether (0.20 mmol, 1.0 equiv). The vial was sealed and stirred at the respective temperature (25 °C / 50 °C / 100 °C) for the indicated amount of time. Then the reaction mixture was cooled down to room temperature and the electrophile was added. The reaction was stirred until GCMS analysis showed full conversion. Afterwards a saturated aqueous solution of NH_4Cl (1 mL) was added and the reaction mixture was extracted with EtOAc (3 times), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via silica gel column chromatography using an appropriate mixture of *i*-hexane and EtOAc as eluent.

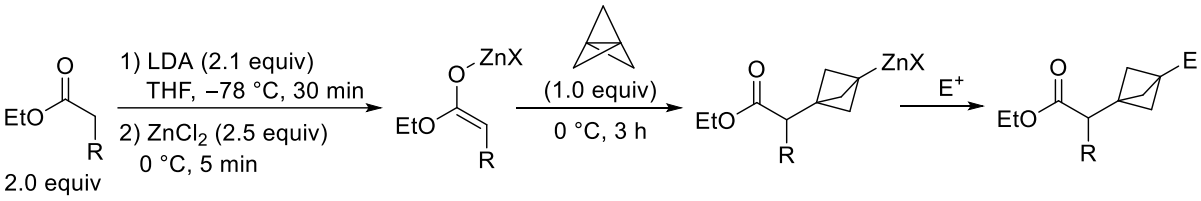
[117] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890-891.

TP2: Typical procedure for the reaction of zinc enolates of type 7 with [1.1.1]propellane (1) followed by electrophile addition



Diisopropylamine (63 mg, 0.62 mmol, 3.1 equiv) was dissolved in THF (0.6 mL) and BuLi (2.55 M in hexane, 0.24 mL, 0.62 mmol, 3.1 equiv) was added dropwise at 0 °C. The mixture was stirred for 5 min and cooled to −78 °C. Then the ketone (0.30 mmol, 1.5 equiv) was added. After 30 min a solution of $ZnCl_2$ in THF (1.0 M, 0.70 mL, 0.70 mmol, 3.5 equiv) was added and the mixture was stirred at 0 °C for 5 min before adding [1.1.1]propellane in diethyl ether (0.20 mmol, 1.0 equiv). After stirring at 0 °C or 25 °C for the indicated time the electrophile was added and the mixture was stirred until GCMS analysis showed full conversion. Then a saturated aqueous solution of NH_4Cl (1 mL) was added and the reaction mixture was extracted with EtOAc (3 times), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via silica gel column chromatography using an appropriate mixture of *i*-hexane and EtOAc as eluent.

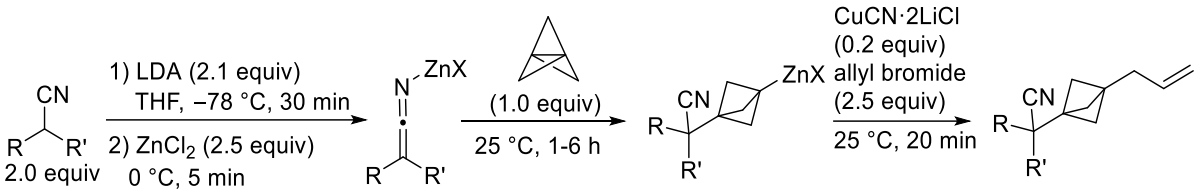
TP3: Typical procedure for the reaction of zinc ester enolates of type 11 with [1.1.1]propellane (1) followed by electrophile addition



Diisopropylamine (43 mg, 0.42 mmol, 2.1 equiv) was dissolved in THF (0.5 mL) and BuLi (2.55 M in hexane, 0.16 mL, 0.42 mmol, 2.1 equiv) was added dropwise at 0 °C. The mixture was stirred for 5 min and cooled to −78 °C. Then the ester (0.40 mmol, 2.0 equiv) was added. After 30 min a solution of $ZnCl_2$ in THF (1.0 M, 0.50 mL, 0.50 mmol, 2.5 equiv) was added and the mixture was stirred at 0 °C for 5 min before adding [1.1.1]propellane in diethyl ether (0.20 mmol, 1.0 equiv). After stirring at 0 °C for 3 h the electrophile was added and the mixture was stirred until GCMS analysis showed full conversion. Then a saturated aqueous solution of NH_4Cl (1 mL) was added and the reaction mixture was extracted with EtOAc (3 times), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude

product was purified via silica gel column chromatography using an appropriate mixture of *i*-hexane and EtOAc as eluent.

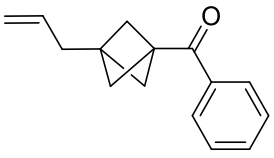
TP4: Typical procedure for the reaction of nitrile-stabilized zinc enolates of type 15 with [1.1.1]propellane (1) followed by copper-catalyzed allylation



Diisopropylamine (43 mg, 0.42 mmol, 2.1 equiv) was dissolved in THF (0.5 mL) and BuLi (2.55 M in hexane, 0.16 mL, 0.42 mmol, 2.1 equiv) was added dropwise at 0 °C. The mixture was stirred for 5 min and cooled to −78 °C. Then the nitrile (0.40 mmol, 2.0 equiv) was added. After 30 min a solution of $ZnCl_2$ in THF (1.0 M, 0.50 mL, 0.50 mmol, 2.5 equiv) was added and the mixture was stirred at 0 °C for 5 min before adding [1.1.1]propellane in diethyl ether (0.20 mmol, 1.0 equiv). After stirring at 25 °C for the indicated time CuCN·2LiCl in THF (1.0 M, 0.04 mL, 0.04 mmol, 20%) and allyl bromide (61 mg, 0.50 mmol, 2.5 equiv) were added and the mixture was stirred for 20 min at 25 °C. Then a saturated aqueous solution of NH_4Cl (1 mL) was added and the reaction mixture was extracted with EtOAc (3 times), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified via silica gel column chromatography using an appropriate mixture of *i*-hexane and EtOAc as eluent.

2.3 Products

(3-Allylbicyclo[1.1.1]pentan-1-yl)(phenyl)methanone (4a)



(3-Allylbicyclo[1.1.1]pentan-1-yl)(phenyl)methanone was prepared according to **TP1** using allylzinc bromide coordinated with lithium chloride (0.90 M, 0.44 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 25 °C for 2 h before adding CuCN·2LiCl in THF (1.0 M, 0.20 mL, 0.20 mmol, 1.0 equiv) and benzoyl chloride (70 mg, 0.50 mmol, 2.5 equiv). The resulting

mixture was stirred at 25 °C for 4 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) afforded the desired compound **4a** (41 mg, 0.19 mmol, 96%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.5, 1.2 Hz, 2 H), 7.53 (tt, *J* = 7.5, 1.2 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 2 H), 5.82 – 5.68 (m, 1 H), 5.10 – 5.00 (m, 2 H), 2.30 (dt, *J* = 7.2, 1.2 Hz, 2 H), 2.15 (s, 6 H).

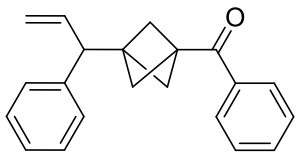
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 197.9, 136.8, 134.7, 132.9, 129.0, 128.5, 116.7, 53.4, 45.0, 39.8, 36.5.

MS (70 eV, EI) *m/z* (%): 212 (1) $[M]^{\cdot+}$, 197 (11), 171 (23), 153 (11), 143 (10), 141 (11), 128 (19), 105 (100), 91 (20), 79 (13), 77 (43).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3074, 2974, 2910, 2874, 1719, 1662, 1641, 1598, 1579, 1510, 1447, 1340, 1302, 1289, 1267, 1204, 1176, 1086, 1070, 1025, 992, 912, 867, 759, 712, 692, 675.

HRMS (EI) calculated for $C_{15}H_{15}O^{\cdot+}$: 211.1117, found 212.1118 $[M–H]^{\cdot+}$.

Phenyl(3-(1-phenylallyl)bicyclo[1.1.1]pentan-1-yl)methanone (4b)



Phenyl(3-(1-phenylallyl)bicyclo[1.1.1]pentan-1-yl)methanone was prepared according to **TP1** using cinnamylzinc bromide coordinated with lithium chloride (0.53 M, 0.75 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 7 h before adding CuCN·2LiCl in THF (1.0 M, 0.20 mL, 0.20 mmol, 1.0 equiv) and benzoyl chloride (70 mg, 0.50 mmol, 2.5 equiv). The resulting mixture was stirred at 25 °C for 3 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) afforded the desired compound **4b** (54 mg, 0.19 mmol, 93%) as colorless crystals. The structure was confirmed via single crystal X-ray diffraction studies.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.96 (d, *J* = 7.1 Hz, 2 H), 7.53 (tt, *J* = 7.5, 2.0 Hz, 1 H), 7.42 (t, *J* = 7.7 Hz, 2 H), 7.34 (t, *J* = 7.4 Hz, 2 H), 7.28 – 7.22 (m, 1 H), 7.18 (d, *J* = 6.8 Hz, 2 H), 6.12 (ddd, *J* = 17.0, 10.3, 8.4 Hz, 1 H), 5.21 – 5.07 (m, 2 H), 3.50 (d, *J* = 8.4 Hz, 1 H), 2.15 (A part of an $[AB]_3$-system, 3 H), 2.09 (B part of an $[AB]_3$-system, 3 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 197.9, 141.3, 137.6, 136.7, 132.9, 129.0, 128.6, 128.5, 128.0, 126.6, 116.6, 52.3, 51.7, 45.0, 43.5.

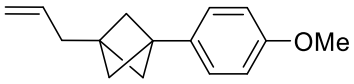
MS (70 eV, EI) *m/z* (%): 287 (3) $[M–H]^{\cdot+}$, 183 (14), 171 (20), 168 (17), 167 (23), 165 (12), 155 (20), 153 (30), 152 (12), 143 (15), 141 (38), 129 (14), 128 (55), 117 (33), 115 (61), 105 (100), 91 (22), 77 (38).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 1661, 1636, 1595, 1577, 1488, 1447, 1331, 1277, 1203, 1175, 1069, 1022, 998, 931, 877, 839, 784, 759, 730, 699, 676.

HRMS (EI) calculated for $C_{21}H_{19}O^{\cdot+}$: 287.1430, found 287.1432 $[M–H]^{\cdot+}$.

mp: 86.8 – 88.4 °C.

1-Allyl-3-(4-methoxyphenyl)bicyclo[1.1.1]pentane (4c)



1-Allyl-3-(4-methoxyphenyl)bicyclo[1.1.1]pentane was prepared according to **TP1** using allylzinc bromide coordinated with lithium chloride (0.90 M, 0.44 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 3 h before adding 4-iodoanisole (117 mg, 0.50 mmol, 2.5 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.2 mg, 0.010 mmol, 5%) and CuCN·2LiCl in THF (1.0 M, 0.020 mL, 0.020 mmol, 10%). The resulting mixture was stirred at 45 °C for 3 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) and HPLC afforded the desired compound **4c** (39 mg, 0.18 mmol, 92%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.14 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 5.79 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1 H), 5.09 – 4.97 (m, 2 H), 3.79 (s, 3 H), 2.30 (dt, *J* = 7.3, 1.2 Hz, 2 H), 1.88 (s, 6 H).

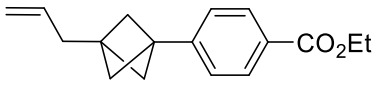
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 158.3, 135.8, 134.0, 127.2, 115.9, 113.6, 55.4, 52.2, 41.9, 37.8, 36.9.

MS (70 eV, EI) *m/z* (%): 214 (18) $[M]^{\cdot+}$, 199 (42), 186 (97), 185 (34), 184 (33), 173 (43), 171 (66), 159 (20), 158 (99), 155 (29), 148 (64), 145 (18), 144 (17), 141 (30), 133 (100), 129 (21), 128 (37), 121 (55), 118 (22), 115 (42), 105 (15), 103 (21), 91 (30), 89 (16), 79 (17), 77 (18).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2956, 2903, 2865, 2834, 1641, 1610, 1578, 1519, 1503, 1463, 1441, 1413, 1353, 1294, 1263, 1243, 1172, 1132, 1098, 1037, 991, 908, 832, 801, 791, 666.

HRMS (EI) calculated for $C_{15}H_{18}O^{\cdot+}$: 214.1352, found 214.1350 $[M]^{\cdot+}$.

Ethyl 4-(3-allylbicyclo[1.1.1]pentan-1-yl)benzoate (4d)



Ethyl 4-(3-allylbicyclo[1.1.1]pentan-1-yl)benzoate was prepared according to **TP1** using allylzinc bromide coordinated with lithium chloride (0.90 M, 0.44 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 3 h before adding 4-iodobenzoate (138 mg, 0.50 mmol, 2.5 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.2 mg, 0.010 mmol, 5%) and CuCN·2LiCl in THF (1.0 M, 0.020 mL, 0.020 mmol, 10%). The resulting mixture was stirred at 45 °C for 19 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) and HPLC afforded the desired compound **4d** (50 mg, 0.19 mmol, 97%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.96 (d, *J* = 8.3 Hz, 2 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 5.77 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1 H), 5.12 – 4.96 (m, 2 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 2.31 (dt, *J* = 7.2, 1.2 Hz, 2 H), 1.93 (s, 6 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

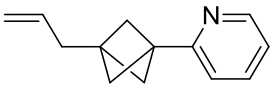
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 166.8, 146.6, 135.4, 129.6, 128.5, 126.2, 116.2, 60.9, 52.2, 42.3, 38.2, 36.7, 14.5.

MS (70 eV, EI) *m/z* (%): 256 (1) $[M]^{\cdot+}$, 228 (20), 211 (11), 200 (13), 183 (16), 169 (10), 168 (15), 167 (16), 165 (10), 156 (12), 155 (100), 154 (15), 153 (31), 152 (11), 145 (23), 143 (30), 142 (20), 141 (94), 129 (27), 128 (60), 117 (11), 115 (52), 91 (24), 77 (11).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2964, 2906, 2868, 1713, 1641, 1610, 1445, 1407, 1367, 1307, 1266, 1174, 1156, 1104, 1093, 1020, 991, 907, 857, 780, 755, 700.

HRMS (EI) calculated for $C_{17}H_{20}O_2^{\cdot+}$: 256.1458, found 256.1457 $[M]^{\cdot+}$.

2-(3-Allylbicyclo[1.1.1]pentan-1-yl)pyridine (4e)



2-(3-Allylbicyclo[1.1.1]pentan-1-yl)pyridine was prepared according to **TP1** using allylzinc bromide coordinated with lithium chloride (0.90 M, 0.44 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 25 °C for 2 h before adding 2-bromopyridine (79 mg, 0.50 mmol, 2.5 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.2 mg, 0.010 mmol, 5%) and CuCN·2LiCl in THF (1.0 M, 0.020 mL, 0.020 mmol, 10%). The resulting mixture was stirred at 45 °C for 19 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 19 / 1) and HPLC afforded the desired compound **4e** (26 mg, 0.14 mmol, 70%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.54 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H), 7.60 (td, *J* = 7.7, 1.8 Hz, 1 H), 7.17 (dt, *J* = 7.8, 1.1 Hz, 1 H), 7.11 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1 H), 5.78 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 1 H), 5.10 – 4.98 (m, 2 H), 2.32 (dt, *J* = 7.2, 1.3 Hz, 2 H), 2.00 (s, 7 H).

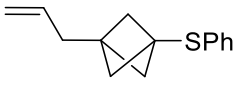
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 160.1, 149.3, 136.4, 135.4, 121.5, 120.8, 116.2, 51.9, 43.1, 38.3, 36.7.

MS (70 eV, EI) *m/z* (%): 184 (22) $[M-H]^{+}$, 170 (16), 168 (15), 158 (10), 156 (15), 154 (10), 145 (10), 144 (100), 143 (32), 142 (15), 130 (13), 117 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 2967, 2907, 2869, 1641, 1589, 1567, 1514, 1474, 1432, 1362, 1289, 1265, 1169, 1050, 992, 912, 788, 753, 698.

HRMS (EI) calculated for $C_{13}H_{14}N^{+}$: 184.1121, found 184.1119 $[M-H]^{+}$.

(3-Allylbicyclo[1.1.1]pentan-1-yl)(phenyl)sulfane (4f)



(3-Allylbicyclo[1.1.1]pentan-1-yl)(phenyl)sulfane was prepared according to **TP1** using allylzinc bromide coordinated with lithium chloride (0.90 M, 0.44 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 3 h before adding *S*-phenyl benzenesulfonothioate (125 mg, 0.50 mmol, 2.5 equiv). The resulting mixture was stirred at 25 °C for 4 h. Workup according to **TP1** and purification via column chromatography (*i*Hex) afforded the desired compound **4f** (41 mg, 0.19 mmol, 95%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.39 – 7.32 (m, 2 H), 7.25 – 7.16 (m, 3 H), 5.65 – 5.49 (m, 1 H), 4.96 – 4.78 (m, 2 H), 2.15 (d, *J* = 7.2 Hz, 2 H), 1.71 (s, 6 H).

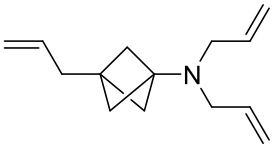
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 135.0, 134.3, 133.6, 128.8, 127.5, 116.4, 54.1, 42.4, 40.3, 36.5.

MS (70 eV, EI) *m/z* (%): 216 (10) $[M]^{\cdot+}$, 188 (22), 173 (22), 147 (16), 142 (11), 141 (11), 135 (31), 134 (14), 123 (11), 111 (10), 110 (21), 109 (16), 107 (35), 105 (27), 91 (100), 79 (87), 77 (16), 10 (65).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3075, 2975, 2907, 2870, 1640, 1583, 1473, 1438, 1272, 1188, 1131, 1091, 1066, 1024, 1011, 991, 912, 891, 741, 690.

HRMS (EI) calculated for $C_{14}H_{16}S^{\cdot+}$: 216.0967, found 216.0966 $[M]^{\cdot+}$.

***N*,*N*,*3*-Triallylbicyclo[1.1.1]pentan-1-amine (4g)**



N,*N*,*3*-Triallylbicyclo[1.1.1]pentan-1-amine was prepared according to **TP1** using allylzinc bromide coordinated with lithium chloride (0.90 M, 0.44 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 3 h before adding $CoCl_2$ (0.78 mg, 0.0060 mmol, 3%.) and *N,N*-diallyl-*O*-benzoylhydroxylamine (109 mg, 0.50 mmol, 2.5 equiv). The resulting mixture was stirred at 45 °C for 17 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 9 / 1) afforded the desired compound **4g** (37 mg, 0.18 mmol, 91%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.85 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 2 H), 5.70 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1 H), 5.18 – 5.04 (m, 4 H), 5.04 – 4.92 (m, 2 H), 3.15 (dt, *J* = 6.5, 1.4 Hz, 4 H), 2.26 (dt, *J* = 7.1, 1.3 Hz, 2 H), 1.65 (s, 6 H).

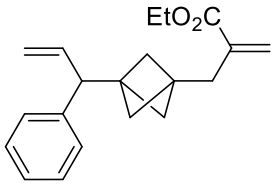
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 136.5, 135.9, 117.0, 115.8, 57.8, 53.0, 50.1, 35.6, 34.9.

MS (70 eV, EI) *m/z* (%): 202 (46) $[M–H]^{\cdot+}$, 188 (43), 174 (57), 172 (10), 163 (11), 162 (93), 160 (62), 157 (10), 148 (23), 147 (16), 146 (53), 136 (22), 134 (55), 132 (54), 122 (36), 121 (21), 120 (100), 118 (31), 106 (31), 105 (25), 94 (32), 93 (26), 91 (75), 81 (21), 80 (28), 79 (84), 77 (42), 67 (21), 41 (71).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3075, 2961, 2923, 2867, 1858, 1783, 1722, 1641, 1446, 1418, 1379, 1277, 1237, 1113, 1047, 993, 913, 807, 712.

HRMS (EI) calculated for $C_{14}H_{20}N^{\cdot+}$: 202.1590, found 202.1590 $[M–H]^{\cdot+}$.

Ethyl 2-((3-(1-phenylallyl)bicyclo[1.1.1]pentan-1-yl)methyl)acrylate (4h)



Ethyl 2-((3-(1-phenylallyl)bicyclo[1.1.1]pentan-1-yl)methyl)acrylate was prepared according to **TP1** using cinnamylzinc bromide coordinated with lithium chloride (0.53 M, 0.75 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 7 h before adding CuCN·2LiCl in THF (1.0 M, 0.040 mL, 0.040 mmol, 20%) and ethyl 2-(bromomethyl)acrylate (97 mg, 0.50 mmol, 2.5 equiv). The resulting mixture was stirred at 25 °C for 16 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) and HPLC afforded the desired compound **4h** (54 mg, 0.19 mmol, 93%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.28 (t, *J* = 7.3 Hz, 2 H), 7.19 (tt, *J* = 7.3, 2.1 Hz, 1 H), 7.12 (d, *J* = 6.7 Hz, 2 H), 6.12 (d, *J* = 1.7 Hz, 1 H), 6.05 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1 H), 5.42 (dt, *J* = 1.8, 1.0 Hz, 1 H), 5.11 – 4.97 (m, 2 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.38 (d, *J* = 8.3 Hz, 1 H), 2.48 (d, *J* = 0.9 Hz, 2 H), 1.46 (A part of an $[AB]_3$-system, 3 H), 1.41 (B part of an $[AB]_3$-system, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

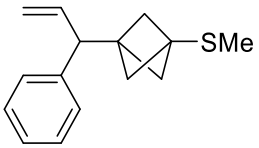
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 167.3, 142.2, 138.6, 138.5, 128.3, 128.0, 126.1, 125.8, 115.6, 60.7, 52.0, 49.2, 42.5, 39.5, 34.9, 14.3.

MS (70 eV, EI) ***m/z*** **(%):** 223 (5) $[M–CO_2Et]^{\cdot+}$, 207 (19), 193 (14), 192 (11), 184 (11), 183 (79), 181 (25), 179 (22), 178 (16), 168 (38), 167 (40), 166 (15), 165 (33), 155 (56), 154 (10), 153 (26), 142 (19), 141 (86), 133 (35), 131 (23), 129 (42), 128 (59), 117 (65), 116 (10), 115 (100), 107 (11), 105 (97), 103 (13), 91 (83), 79 (30), 77 (15).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2964, 2905, 2867, 1715, 1631, 1601, 1493, 1445, 1368, 1308, 1251, 1234, 1155, 111, 1094, 1027, 943, 914, 859, 821, 755, 699.

HRMS (EI) calculated for $C_{19}H_{21}O_2^{\cdot+}$: 281.1536, found 281.1533 $[M–CH_3]^{\cdot+}$.

Methyl(3-(1-phenylallyl)bicyclo[1.1.1]pentan-1-yl)sulfane (4i)



Methyl(3-(1-phenylallyl)bicyclo[1.1.1]pentan-1-yl)sulfane was prepared according to **TP1** using cinnamylzinc bromide coordinated with lithium chloride (0.53 M, 0.75 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 7 h before adding *S*-methyl benzenesulfonothioate (94 mg, 0.50 mmol, 2.5 equiv). The resulting mixture was stirred at 25 °C for 16 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) afforded the desired compound **4i** (41 mg, 0.18 mmol, 90%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.31 (t, *J* = 7.3 Hz, 2 H), 7.22 (tt, *J* = 7.3, 2.1 Hz, 1 H), 7.14 (d, *J* = 6.8 Hz, 2 H), 6.06 (ddd, *J* = 17.0, 10.2, 8.3 Hz, 1 H), 5.17 – 5.02 (m, 2 H), 3.47 (d, *J* = 8.4 Hz, 1 H), 2.03 (s, 3 H), 1.77 (A part of an $[AB]_3$-system, 3 H), 1.72 (B part of an $[AB]_3$-system, 3 H).

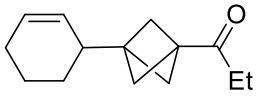
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 141.6, 137.9, 128.4, 127.9, 126.4, 116.3, 51.8, 51.6, 43.6, 41.8, 13.7.

MS (70 eV, EI) *m/z* (%): 215 (17), 202 (30), 187 (12), 183 (21), 181 (24), 168 (18), 167 (89), 166 (17), 165 (28), 156 (12), 155 (100), 154 819), 153 (33), 152 (19), 142 (11), 141 (95), 129 (15), 128 (30), 117 (12), 115 (59), 91 (37).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3027, 2975, 2906, 2870, 1637, 1601, 1492, 1451, 1317, 1259, 1195, 1131, 1070, 1030, 990, 960, 915, 895, 840, 754, 715, 698, 660.

HRMS (EI) calculated for $C_{15}H_{17}S^{+}$: 229.1045, found 229.1043 $[M–H]^{+}$.

1-(3-(Cyclohex-2-en-1-yl)bicyclo[1.1.1]pentan-1-yl)propan-1-one (4j)



1-(3-(Cyclohex-2-en-1-yl)bicyclo[1.1.1]pentan-1-yl)propan-1-one was prepared according to **TP1** using cyclohex-2-en-1-ylzinc bromide coordinated with lithium chloride (0.34 M, 1.18 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 6 h before adding CuCN·2LiCl in THF (1.0 M, 0.20 mL, 0.20 mmol, 1.0 equiv) and propionyl chloride (46 mg, 0.50 mmol, 2.5 equiv). The resulting mixture was stirred at 25 °C for 1 h. Workup according to **TP1** and

purification via column chromatography (*i*Hex / EtOAc = 49 / 1) and HPLC afforded the desired compound **4j** (38 mg, 0.19 mmol, 94%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.73 (dtd, *J* = 10.0, 3.7, 2.6 Hz, 1 H), 5.54 – 5.46 (m, 1 H), 2.46 (q, *J* = 7.3 Hz, 2 H), 2.22 – 2.13 (m, 1 H), 1.98 – 1.91 (m, 2 H), 1.89 – 1.80 (($[AB]_3$-system, 6 H), 1.71 – 1.64 (m, 2 H), 1.55 – 1.44 (m, 1 H), 1.31 – 1.20 (m, 1 H), 1.02 (t, *J* = 7.3 Hz, 3 H).

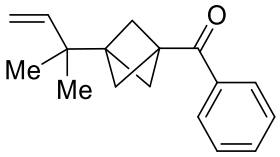
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 209.7, 128.4, 127.5, 49.6, 43.9, 42.4, 36.1, 32.0, 25.5, 25.1, 21.3, 7.5.

MS (70 eV, EI) *m/z* (%): 203 (2) $[M–H]^{\cdot+}$, 189 (12), 176 (41), 175 (45), 161 (65), 143 (33), 133 (18), 117 (51), 105 (76), 91 (100), 77 (94).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3349, 2977, 2913, 2876, 1694, 1653, 1509, 1449, 1408, 1361, 1268, 1170, 1020, 957, 890, 823, 733, 702.

HRMS (EI) calculated for $C_{14}H_{19}O^{\cdot+}$: 203.1430, found 203.1431 $[M–H]^{\cdot+}$.

(3-(2-Methylbut-3-en-2-yl)bicyclo[1.1.1]pentan-1-yl)(phenyl)methanone (4k)



(3-(2-Methylbut-3-en-2-yl)bicyclo[1.1.1]pentan-1-yl)(phenyl)methanone was prepared according to **TP1** using prenylzinc bromide coordinated with lithium chloride (0.61 M, 0.66 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 17 h before adding CuCN·2LiCl in THF (1.0 M, 0.20 mL, 0.20 mmol, 1.0 equiv) and benzoyl chloride (70 mg, 0.50 mmol, 2.5 equiv). The resulting mixture was stirred at 25 °C for 1 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) and HPLC afforded the desired compound **4k** (47 mg, 0.19 mmol, 97%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.02 – 7.94 (m, 2 H), 7.54 (tt, *J* = 7.4, 1.3 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 5.81 (dd, *J* = 17.3, 10.9 Hz, 1 H), 5.03 – 4.93 (m, 2 H), 2.07 (s, 6 H), 1.00 (s, 6 H).

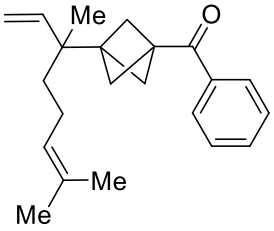
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 198.5, 144.6, 136.8, 132.9, 129.0, 128.5, 111.8, 50.2, 47.3, 42.7, 36.0, 22.9.

MS (70 eV, EI) *m/z* (%): 225 (14) $[M-CH_3]^{+}$, 171 (41), 153 (12), 143 (15), 128 (22), 105 (100), 93 (10), 91 (18), 77 (41).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2965, 2910, 2874, 1663, 1638, 1598, 1579, 1509, 1461, 1448, 1414, 1377, 1360, 1331, 1280, 1205, 1177, 1134, 1055, 1025, 1001, 913, 872, 820, 765, 694, 676.

HRMS (EI) calculated for $C_{17}H_{19}O^{+}$: 239.1430, found 239.1428 $[M-H]^{+}$.

(3-(3,7-Dimethylocta-1,6-dien-3-yl)bicyclo[1.1.1]pentan-1-yl)(phenyl)methanone (4l)



(3-(3,7-Dimethylocta-1,6-dien-3-yl)bicyclo[1.1.1]pentan-1-yl)(phenyl)methanone was prepared according to **TP1** using geranylzinc bromide coordinated with lithium chloride (0.40 M, 5.0 mL, 2.0 mmol, 2.0 equiv) and [1.1.1]propellane dissolved in diethyl ether (0.43 M, 2.3 mL, 1.0 mmol, 1.0 equiv). The reaction was stirred at 50 °C for 6 h before adding CuCN·2LiCl in THF (1.0 M, 1.0 mL, 1.0 mmol, 1.0 equiv) and benzoyl chloride (353 mg, 2.5 mmol, 2.5 equiv). The resulting mixture was stirred at 25 °C for 17 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) and HPLC afforded the desired compound **4l** (216 mg, 0.70 mmol, 70%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.99 (d, *J* = 7.0 Hz, 2 H), 7.54 (tt, *J* = 7.5, 2.0 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 5.67 (dd, *J* = 17.5, 10.8 Hz, 1 H), 5.16 – 5.04 (m, 2 H), 4.96 (dd, *J* = 17.5, 1.4 Hz, 1 H), 2.08 ($[AB]_3$-system, 6 H), 1.94 – 1.78 (m, 2 H), 1.69 (d, *J* = 1.5 Hz, 3 H), 1.59 (d, *J* = 1.4 Hz, 3 H), 1.41 – 1.24 (m, 2 H), 0.98 (s, 3 H).

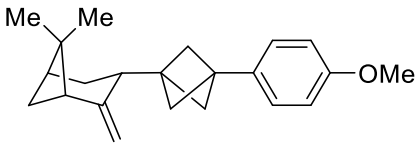
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 198.5, 142.9, 136.8, 132.9, 131.5, 129.0, 128.5, 124.9, 113.5, 50.3, 47.5, 43.0, 39.2, 36.9, 25.9, 23.1, 17.8, 17.7.

MS (70 eV, EI) *m/z* (%): 211 (7), 171 (10), 128 (10), 119 (12), 105 (100), 93 (9), 91 (19), 77 (30).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2913, 2874, 1664, 1598, 1579, 1508, 1448, 1412, 1373, 1205, 1176, 1143, 1025, 1001, 912, 873, 843, 765, 694, 676.

HRMS (EI) calculated for $C_{22}H_{27}O^{+}$: 307.2056, found 307.2054 $[M-H]^{+}$.

(1*R*,3*R*,5*R*)-3-(3-(4-Methoxyphenyl)bicyclo[1.1.1]pentan-1-yl)-6,6-dimethyl-2-methylene-bicyclo[3.1.1]heptane (4m)



(1*R*,3*R*,5*R*)-3-(3-(4-Methoxyphenyl)bicyclo[1.1.1]pentan-1-yl)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptane was prepared according to **TP1** using myrtenylzinc bromide coordinated with lithium chloride (0.43 M, 0.93 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 8 h before adding 4-iodoanisole (117 mg, 0.50 mmol, 2.5 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.2 mg, 0.010 mmol, 5%) and CuCN·2LiCl in THF (1.0 M, 0.020 mL, 0.020 mmol, 10%). The resulting mixture was stirred at 45 °C for 15 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) and HPLC afforded the desired compound **4m** (46 mg, 0.15 mmol, 75%) as colorless crystals. The structure was confirmed via single crystal X-ray diffraction studies.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.17 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 4.71 (dt, *J* = 22.0, 1.9 Hz, 2 H), 3.80 (s, 3 H), 2.72 – 2.66 (m, 1 H), 2.42 (t, *J* = 5.4 Hz, 1 H), 2.33 – 2.24 (m, 1 H), 2.05 – 1.95 (m, 2 H), 1.90 (s, 6 H), 1.78 (dt, *J* = 14.2, 3.5 Hz, 1 H), 1.26 (s, 3 H), 1.19 (d, *J* = 9.9 Hz, 1 H), 0.77 (s, 3 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 158.2, 152.1, 134.1, 127.2, 113.6, 109.0, 55.4, 52.1, 51.1, 43.5, 41.7, 40.5, 40.4, 36.2, 27.6, 27.4, 26.0, 21.7.

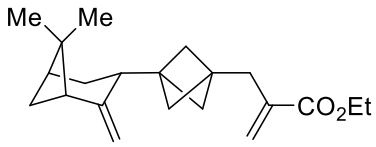
MS (70 eV, EI) *m/z* (%): 308 (2) $[M]^{\cdot+}$, 265 (12), 237 (18), 223 (13), 211 (11), 209 (12), 197 (11), 185 (12), 173 (26), 171 (12), 165 (12), 159 (11), 158 (24), 157 (71), 148 (15), 147 (13), 145 (13), 143 (20), 142 (36), 141 (13), 135 (54), 134 (10), 133 (40), 131 (41), 130 (10), 129 (100), 128 (18), 121 (86), 117 (20), 115 (32), 105 (19), 91 (33), 79 (11), 77 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2948, 1918, 2865, 1636, 1608, 1578, 1519, 1501, 1455, 1380, 1366, 1345, 1293, 1259, 1244, 1175, 1159, 1132, 1098, 1034, 934, 878, 857, 835, 822, 791, 697.

HRMS (EI) calculated for $C_{22}H_{28}O^{\cdot+}$: 308.2135, found 308.2136 $[M-H]^{\cdot+}$.

mp: 99.7 – 100.9 °C.

Ethyl 2-((3-((1*R*,3*R*,5*R*)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl)bicyclo-[1.1.1]pentan-1-yl)methyl)acrylate (4n)



Ethyl 2-((3-((1*R*,3*R*,5*R*)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl)bicyclo[1.1.1]pentan-1-yl)methyl)acrylate was prepared according to **TP1** using myrtenylzinc bromide coordinated with lithium chloride (0.43 M, 0.93 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 8 h before adding CuCN·2LiCl in THF (1.0 M, 0.040 mL, 0.040 mmol, 20%) and ethyl 2-(bromomethyl)acrylate (97 mg, 0.50 mmol, 2.5 equiv). The resulting mixture was stirred at 25 °C for 2 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) and HPLC afforded the desired compound **4n** (60 mg, 0.19 mmol, 95%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 6.13 (d, *J* = 1.7 Hz, 1 H), 5.47 – 5.44 (m, 1 H), 4.65 (t, *J* = 1.9 Hz, 1 H), 4.57 (t, *J* = 1.9 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 2.58 – 2.52 (m, 1 H), 2.51 (d, *J* = 0.9 Hz, 2 H), 2.33 (t, *J* = 5.4 Hz, 1 H), 2.20 (dtd, *J* = 9.9, 5.9, 2.1 Hz, 1 H), 1.94 – 1.85 (m, 2 H), 1.65 (ddd, *J* = 14.1, 4.0, 2.8 Hz, 1 H), 1.47 (s, 6 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.21 (s, 3 H), 1.09 (d, *J* = 9.8 Hz, 1 H), 0.70 (s, 3 H).

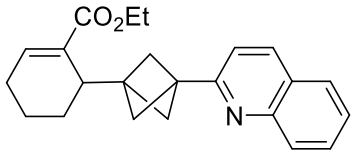
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 167.5, 152.2, 138.8, 125.7, 108.8, 60.7, 52.9, 52.1, 49.3, 44.5, 40.4, 39.1, 36.3, 35.0, 27.5, 27.3, 26.0, 21.7, 14.4.

MS (70 eV, EI) *m/z* (%): 225 (13), 207 (32), 197 (62), 185 (12), 183 (19), 182 (11), 181 (14), 171 (32), 169 (54), 167 (13), 161 (20), 159 (59), 157 (72), 156 (24), 155 (79), 145 (71), 143 (71), 142 (27), 141 (57), 133 (27), 131 (77), 130 (11), 129 (86), 128 (42), 119 (50), 117 (100), 115 (38), 107 (15), 105 (85), 93 (25), 91 (84), 79 (30), 77 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2959, 2906, 2865, 1717, 1663, 1534, 1455, 1383, 1367, 1300, 1255, 1236, 1174, 1154, 1097, 1027, 940, 881, 856, 820, 729, 696.

HRMS (EI) calculated for $C_{21}H_{30}O_2^{\cdot+}$: 299.2006, found 299.2004 $[M–CH_3]^{+}$.

Ethyl 6-(3-(quinolin-2-yl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carboxylate (4o)



Ethyl 6-(3-(quinolin-2-yl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carboxylate was prepared according to **TP1** using (2-(ethoxycarbonyl)cyclohex-2-en-1-yl)zinc chloride coordinated with lithium chloride (0.74 M, 0.54 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 15 h before adding 2-bromoquinoline (104 mg, 0.50 mmol, 2.5 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.2 mg, 0.010 mmol, 5%) and CuCN·2LiCl in THF (1.0 M, 0.020 mL, 0.020 mmol, 10%). The resulting mixture was stirred at 45 °C for 7 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 9 / 1) and HPLC afforded the desired compound **4o** (45 mg, 0.13 mmol, 65%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.07 (t, *J* = 8.8 Hz, 2 H), 7.75 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.66 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 7.47 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1 H), 7.32 (d, *J* = 8.4 Hz, 1 H), 7.01 (t, *J* = 3.9 Hz, 1 H), 4.28 – 4.12 (m, 2 H), 2.99 – 2.88 (m, 1 H), 2.30 – 2.03 (m, 8 H), 1.95 – 1.86 (m, 1 H), 1.74 – 1.53 (m, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H).

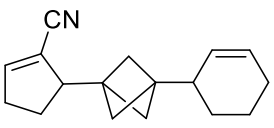
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 168.3, 160.4, 147.9, 140.1, 136.3, 131.7, 129.5, 129.2, 127.6, 127.0, 126.0, 119.2, 60.4, 52.2, 42.4, 42.2, 33.2, 25.7, 25.1, 18.0, 14.4.

MS (70 eV, EI) *m/z* (%): 347 (1) $[M]^{\cdot+}$, 274 (5), 195 (14), 194 (100), 193 (8), 192 (8), 180 (8), 167 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2967, 2905, 2868, 1707, 1643, 1618, 1599, 1559, 1514, 1501, 1446, 1425, 1373, 1345, 1328, 1296, 1253, 1235, 1181, 1139, 1114, 1091, 1061, 1049, 1017, 941, 929, 913, 875, 837, 802, 786, 749, 735, 702, 675.

HRMS (EI) calculated for $C_{23}H_{25}NO_2^{\cdot+}$: 347.1880, found 347.1879 $[M]^{\cdot+}$.

5-(3-(Cyclohex-2-en-1-yl)bicyclo[1.1.1]pentan-1-yl)cyclopent-1-ene-1-carbonitrile (4p)



5-(3-(Cyclohex-2-en-1-yl)bicyclo[1.1.1]pentan-1-yl)cyclopent-1-ene-1-carbonitrile was prepared according to **TP1** using (2-cyanocyclopent-2-en-1-yl)zinc bromide coordinated with

lithium chloride (0.54 M, 0.74 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 25 °C for 17 h before adding CuCN·2LiCl in THF (1.0 M, 0.040 mL, 0.040 mmol, 20%) and 3-bromocyclohex-1-ene (81 mg, 0.50 mmol, 2.5 equiv). The resulting mixture was stirred at 25 °C for 1 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) and HPLC afforded the desired compound **4p** (26 mg, 0.11 mmol, 55%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 6.65 (td, *J* = 2.7, 1.7 Hz, 1 H), 5.75 – 5.67 (m, 1 H), 5.52 (dq, *J* = 10.1, 2.3 Hz, 1 H), 3.02 – 2.94 (m, 1 H), 2.49 – 2.41 (m, 2 H), 2.20 – 2.12 (m, 1 H), 2.06 – 1.98 (m, 1 H), 1.97 – 1.91 (m, 2 H), 1.81 – 1.74 (m, 1 H), 1.61 – 1.49 (m, 8 H), 1.31 – 1.20 (m, 2 H).

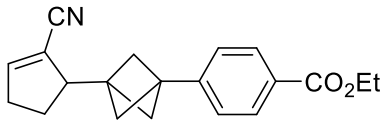
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 149.6, 128.3, 127.9, 117.5, 117.0, 48.3, 47.1, 42.9, 40.8, 36.4, 32.9, 26.7, 25.7, 25.2, 21.4.

MS (70 eV, EI) *m/z* (%): 238 (19) $[M-H]^{+}$, 224 (10), 210 (11), 196 (16), 182 (16), 170 (10), 168 (12), 156 (15), 147 (21), 131 (11), 130 (16), 129 13), 119 (29), 117 (16), 116 (13), 115 (16), 107 (32), 105 (86), 93 (18), 92 (15), 91 (100), 81 (12), 79 (99), 78 (11), 77 (22), 65 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3425, 2957, 2924, 2865, 2216, 1727, 1653, 1612, 1446, 1433, 1409, 1304, 1257, 1227, 1171, 1142, 1020, 950, 895, 869, 822, 740, 721, 668.

HRMS (EI) calculated for $C_{17}H_{20}N^{+}$: 238.1590, found 238.1590 $[M-H]^{+}$.

5-(3-(4-Methoxyphenyl)bicyclo[1.1.1]pentan-1-yl)cyclopent-1-ene-1-carbonitrile (4q)



5-(3-(4-Methoxyphenyl)bicyclo[1.1.1]pentan-1-yl)cyclopent-1-ene-1-carbonitrile was prepared according to **TP1** using (2-cyanocyclopent-2-en-1-yl)zinc bromide coordinated with lithium chloride (0.54 M, 0.74 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 25 °C for 17 h before adding 4-iodobenzoate (138 mg, 0.50 mmol, 2.5 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.2 mg, 0.010 mmol, 5%) and CuCN·2LiCl in THF (1.0 M, 0.020 mL, 0.020 mmol, 10%). The resulting mixture was stirred at 45 °C for 5 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 19 / 1) afforded the desired compound **4q** (36 mg, 0.12 mmol, 59%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.97 (d, *J* = 8.3 Hz, 2 H), 7.26 (d, *J* = 8.3 Hz, 2 H), 6.71 (q, *J* = 2.6 Hz, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 3.13 – 3.05 (m, 1 H), 2.56 – 2.47 (m, 2 H), 2.15 – 1.97 (m, 7 H), 1.89 – 1.79 (m, 1 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 166.7, 150.0, 145.8, 129.6, 128.7, 126.2, 117.3, 116.5, 61.0, 51.0, 47.9, 42.1, 40.5, 32.9, 26.6, 14.5.

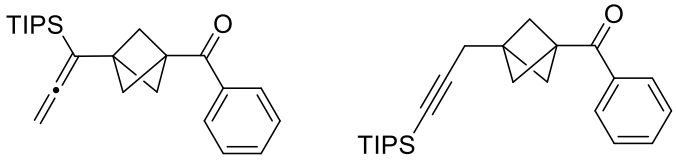
MS (70 eV, EI) *m/z* (%): 307 (1) $[M]^{\cdot+}$, 281 (27), 262 (17), 261 (36), 253 (13), 246 (18), 234 (47), 233 (19), 232 (10), 225 (16), 219 (11), 218 (15), 215 (23), 208 (13), 207 (100), 206 (13), 191 (18), 177 (32), 169 (17), 162 (34), 145 (55), 143 (55), 142 (19), 141 (36), 131 (10), 129 (18), 128 (47), 117 (11), 115 (40), 91 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2968, 2945, 2906, 2868, 2214, 1714, 1608, 1467, 1451, 1428, 1407, 1367, 1307, 1294, 1268, 1212, 1176, 1146, 1130, 1104, 1092, 1045, 1017, 978, 944, 923, 904, 875, 860, 850, 815, 800, 761, 719, 700.

HRMS (EI) calculated for $C_{20}H_{21}NO_2^{\cdot+}$: 307.1567, found 307.1568 $[M]^{\cdot+}$.

mp: 84.1 – 85.9 °C.

Phenyl(3-(1-(triisopropylsilyl)propa-1,2-dien-1-yl)bicyclo[1.1.1]pentan-1-yl)methanone (4r) and Phenyl(3-(3-(triisopropylsilyl)prop-2-yn-1-yl)bicyclo[1.1.1]pentan-1-yl)methanone (4s)



Phenyl(3-(1-(triisopropylsilyl)propa-1,2-dien-1-yl)bicyclo[1.1.1]pentan-1-yl)methanone and phenyl(3-(3-(triisopropylsilyl)prop-2-yn-1-yl)bicyclo[1.1.1]pentan-1-yl)methanone were prepared according to **TP1** using (3-(triisopropylsilyl)prop-2-yn-1-yl)zinc bromide coordinated with lithium chloride (0.24 M, 1.67 mL, 0.40 mmol, 2.0 equiv). The reaction was stirred at 50 °C for 19 h before adding CuCN·2LiCl in THF (1.0 M, 0.20 mL, 0.20 mmol, 1.0 equiv) and benzoyl chloride (70 mg, 0.50 mmol, 2.5 equiv). The resulting mixture was stirred at 25 °C for 1 h. Workup according to **TP1** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) and HPLC afforded phenyl(3-(1-(triisopropylsilyl)propa-1,2-dien-1-yl)bicyclo-[1.1.1]pentan-1-yl)methanone **4r** (37 mg, 0.10 mmol, 50%) as a colorless solid and phenyl(3-(3-(triisopropylsilyl)-prop-2-yn-1-yl)bicyclo[1.1.1]pentan-1-yl)methanone **4s** (33 mg, 0.09 mmol, 45%) as a colorless liquid.

Phenyl(3-(1-(triisopropylsilyl)propa-1,2-dien-1-yl)bicyclo[1.1.1]pentan-1-yl)methanone (4r):

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.02 – 7.95 (m, 2 H), 7.54 (tt, *J* = 7.3, 1.3 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 4.44 (s, 2 H), 2.35 (s, 6 H), 1.28 – 1.15 (m, 3 H), 1.13 – 1.04 (m, 18 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 212.7, 198.1, 136.8, 133.0, 129.0, 128.6, 91.1, 69.5, 56.3, 44.6, 39.8, 18.8, 12.0.

MS (70 eV, EI) *m/z* (%): 324 (17), 323 (82) $[M–C_3H_7]^{\cdot+}$, 281 (16), 253 (12), 225 (21), 209 (11), 208 (10), 207 (70), 193 (31), 191 (15), 179 (15), 178 (100), 165 (21), 152 (14), 131 (19), 115 (11), 105 (11), 103 (55), 77 (12), 75 (87), 73 (16), 61 (14), 59 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2940, 2863, 2176, 1922, 1665, 1598, 1578, 1505, 1460, 1446, 1381, 1364, 1332, 1312, 1268, 1209, 1176, 1070, 1018, 990, 941, 920, 882, 839, 822, 805, 766, 699, 674.

HRMS (EI) calculated for $C_{24}H_{33}OSi^{\cdot+}$: 365.2295, found 365.2298 $[M–H]^{\cdot+}$.

mp: 77.7 – 79.2 °C.

Phenyl(3-(3-(triisopropylsilyl)prop-2-yn-1-yl)bicyclo[1.1.1]pentan-1-yl)methanone (4s):

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.02 – 7.95 (m, 2 H), 7.55 (tt, *J* = 7.4, 1.2 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 2.54 (s, 2 H), 2.24 (s, 6 H), 1.11 – 1.02 (m, 21 H).

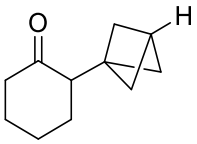
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 197.7, 136.7, 133.0, 129.0, 128.6, 104.8, 82.1, 53.5, 44.3, 38.4, 23.7, 18.8, 11.4.

MS (70 eV, EI) *m/z* (%): 324 (23), 323 (100) $[M–C_3H_7]^{\cdot+}$, 295 (29), 281 (11), 233 (12), 207 (20), 193 (44), 191 (17), 179 (16), 178 (79), 165 (24), 153 (10), 152 (11), 145 (10), 129 (13), 128 (13), 115 (17), 105 (30), 91 (13), 77 (17), 75 (36), 61 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2941, 2864, 2172, 1728, 1666, 1598, 1580, 1511, 1462, 1448, 1419, 1382, 1338, 1297, 1266, 1205, 1176, 1086, 1070, 1027, 1011, 994, 926, 881, 760, 694, 675, 659.

HRMS (EI) calculated for $C_{24}H_{34}OSi^{\cdot+}$: 366.2373, found 366.2380 $[M]^{\cdot+}$.

2-(Bicyclo[1.1.1]pentan-1-yl)cyclohexan-1-one (9a)



2-(Bicyclo[1.1.1]pentan-1-yl)cyclohexan-1-one was prepared according to **TP2** using cyclopentanone (29 mg, 0.30 mmol, 1.5 equiv). The reaction was stirred at 0 °C for 30 min before adding a saturated aqueous solution of NH_4Cl (1 mL). The resulting mixture was stirred at 25 °C for 10 min. Workup according to **TP2** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) afforded the desired compound **9a** (29 mg, 0.17 mmol, 87%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 2.48 (s, 1 H), 2.36 (dd, *J* = 8.4, 5.8 Hz, 1 H), 2.27 (dd, *J* = 7.3, 5.8 Hz, 2 H), 1.97 – 1.72 (m, 10 H), 1.66 – 1.56 (m, 2 H).

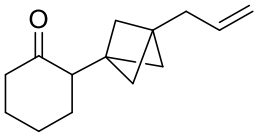
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 212.3, 51.6, 50.2, 45.0, 42.2, 30.3, 28.0, 27.3, 23.6.

MS (70 eV, EI) *m/z* (%): 163 (3) $[M–H]^+$, 149 (42), 135 (43), 131 (13), 121 (11), 117 (10), 107 (15), 105 (54), 95 (17), 93 (89), 92 (22), 91 (80), 81 (12), 79 (100), 77 (42), 67 (32).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958, 2939, 2865, 2175, 2006, 1921, 1708, 1665, 1598, 1578, 1447, 1365, 1333, 1265, 1196, 1125, 1070, 1018, 990, 941, 883, 837, 805, 766, 699, 674.

HRMS (EI) calculated for $C_{11}H_{15}O^+$: 163.1117, found 163.1116 $[M–H]^+$.

2-(3-Allylbicyclo[1.1.1]pentan-1-yl)cyclohexan-1-one (9b)



2-(3-Allylbicyclo[1.1.1]pentan-1-yl)cyclohexan-1-one was prepared according to **TP2** using cyclopentanone (29 mg, 0.30 mmol, 1.5 equiv). The reaction was stirred at 0 °C for 30 min before adding CuCN·2LiCl in THF (1.0 M, 0.040 mL, 0.040 mmol, 20%) and allyl bromide (85 mg, 0.70 mmol, 3.5 equiv). The resulting mixture was stirred at 25 °C for 2 h. Workup according to **TP2** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) afforded the desired compound **9b** (36 mg, 0.18 mmol, 88%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.70 (ddt, *J* = 16.7, 10.4, 7.2 Hz, 1 H), 5.01 – 4.93 (m, 2 H), 2.38 (dd, *J* = 8.7, 5.8 Hz, 1 H), 2.27 (dd, *J* = 7.1, 6.0 Hz, 2 H), 2.20 (dt, *J* = 7.1, 1.3 Hz, 2 H), 1.97 – 1.70 (m, 4 H), 1.64 – 1.53 (m, 8 H).

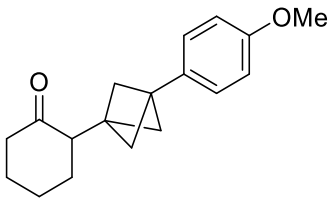
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 212.3, 135.8, 115.8, 51.0, 50.0, 42.2, 40.0, 39.1, 36.9, 30.5, 27.4, 23.7.

MS (70 eV, EI) *m/z* (%): 189 (11) $[M-CH_3]^{+}$, 164 (12), 163 (100), 145 (13), 143 (13), 135 (13), 133 (10), 129 (12), 119 (21), 117 (18), 107 (24), 106 (11), 105 (52), 93 (20), 91 (86), 79 (44), 77 (21), 67 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2937, 2866, 1705, 1640, 1447, 1425, 1370, 1316, 1255, 1218, 1146, 1124, 1066, 991, 946, 910, 652.

HRMS (EI) calculated for $C_{14}H_{19}O^{+}$: 203.1430, found 203.1429 $[M-H]^{+}$.

2-(3-(4-Methoxyphenyl)bicyclo[1.1.1]pentan-1-yl)cyclohexan-1-one (9c)



2-(3-(4-Methoxyphenyl)bicyclo[1.1.1]pentan-1-yl)cyclohexan-1-one was prepared according to **TP2** using cyclopentanone (29 mg, 0.30 mmol, 1.5 equiv). The reaction was stirred at 0 °C for 30 min before adding 4-iodoanisole (164 mg, 0.70 mmol, 3.5 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.2 mg, 0.010 mmol, 5%) and CuCN·2LiCl in THF (1.0 M, 0.020 mL, 0.020 mmol, 10%). The resulting mixture was stirred at 40 °C for 3 h. Workup according to **TP2** and purification via column chromatography (*i*Hex / EtOAc = 19 / 1) afforded the desired compound **9c** (42 mg, 0.16 mmol, 78%) as a colorless solid. The structure was confirmed via single crystal X-ray diffraction studies.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.14 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 3.78 (s, 3 H), 2.49 (dd, *J* = 9.2, 5.6 Hz, 1 H), 2.32 (dd, *J* = 7.4, 5.7 Hz, 2 H), 2.06 – 1.58 (m, 12 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 212.2, 158.3, 133.6, 127.2, 113.6, 55.4, 51.9, 50.7, 42.4, 41.8, 38.5, 30.6, 27.4, 24.0.

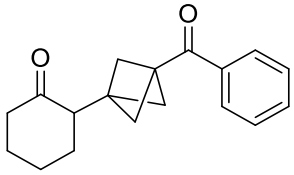
MS (70 eV, EI) *m/z* (%): 270 (1) $[M]^{\cdot+}$, 256 (19), 255 (100), 199 (8), 173 (51), 172 (18), 171 (10), 163 (8), 158 (39), 141 (7), 133 (9), 128 (7), 115 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2934, 2867, 1704, 1608, 1576, 1518, 1503, 1460, 1442, 1373, 1343, 1315, 1292, 1266, 1243, 1211, 1185, 1172, 1163, 1148, 1133, 1123, 1067, 1034, 953, 923, 905, 889, 862, 846, 829, 791, 783, 720, 702, 659.

HRMS (EI) calculated for $C_{18}H_{22}O_2^{\cdot+}$: 270.1614, found 270.1617 $[M]^{\cdot+}$.

mp: 120.0 – 121.8 °C.

2-(3-Benzoylbicyclo[1.1.1]pentan-1-yl)cyclohexan-1-one (9d)



2-(3-Benzoylbicyclo[1.1.1]pentan-1-yl)cyclohexan-1-one was prepared according to **TP2** using cyclopentanone (29 mg, 0.30 mmol, 1.5 equiv). The reaction was stirred at 0 °C for 30 min before adding CuCN·2LiCl in THF (1.0 M, 0.020 mL, 0.020 mmol, 10%) and benzoyl chloride (141 mg, 1.0 mmol, 5.0 equiv). The resulting mixture was stirred at 25 °C for 1 h. Workup according to **TP2** and purification via column chromatography (*i*Hex / EtOAc = 9 / 1) and HPLC afforded the desired compound **9d** (30 mg, 0.15 mmol, 73%) as a colorless solid.

^{1}H-NMR (CDCl$_3$, 400 MHz, ppm): δ = 8.04 – 7.98 (m, 2 H), 7.54 (tt, *J* = 7.3, 1.2 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 2.46 (dd, *J* = 10.9, 5.6 Hz, 1 H), 2.36 – 2.25 (m, 8 H), 2.11 – 1.96 (m, 2 H), 1.91 – 1.83 (m, 1 H), 1.78 – 1.62 (m, 2 H), 1.59 – 1.47 (m, 1 H).

^{13}C-NMR (CDCl$_3$, 101 MHz, ppm): δ = 211.7, 197.7, 136.6, 133.0, 129.1, 128.5, 53.0, 50.3, 45.0, 42.5, 40.2, 30.6, 27.5, 24.4.

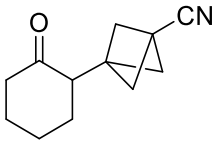
MS (70 eV, EI) *m/z* (%): 198 (19) $[M–C_4H_6O]^{\cdot+}$, 179 (12), 171 (17), 163 (15), 123 (47), 105 (100), 91 (19), 77 (37).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2928, 2875, 1706, 1659, 1595, 1578, 1509, 1446, 1374, 1333, 1313, 1284, 1203, 1171, 1123, 1106, 1071, 1041, 1018, 967, 931, 875, 848, 815, 766, 712, 699, 679.

HRMS (EI) calculated for $C_{18}H_{20}O_2^{\cdot+}$: 268.1458, found 268.1460 $[M]^{\cdot+}$.

mp: 82.2 – 83.9 °C.

3-(2-Oxocyclohexyl)bicyclo[1.1.1]pentane-1-carbonitrile (9e)



3-(2-Oxocyclohexyl)bicyclo[1.1.1]pentane-1-carbonitrile was prepared according to **TP2** using cyclopentanone (29 mg, 0.30 mmol, 1.5 equiv). The reaction was stirred at 0 °C for 30 min before adding CuCN·2LiCl in THF (1.0 M, 070 mL, 0.70 mmol, 3.5 equiv) and tosyl cyanide (145 mg, 0.80 mmol, 4.0 equiv). The resulting mixture was stirred at 25 °C for 18 h. Workup according to **TP2** and purification via column chromatography (*i*Hex / EtOAc = 85 / 15) afforded the desired compound **9e** (17 mg, 0.09 mmol, 46%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 2.37 (dd, *J* = 11.9, 5.5 Hz, 1 H), 2.23 (s, 8 H), 2.07 – 1.93 (m, 2 H), 1.91 – 1.78 (m, 1 H), 1.68 – 1.54 (m, 2 H), 1.44 – 1.31 (m, 1 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 210.7, 117.9, 53.6, 49.6, 43.9, 42.4, 30.6, 27.4, 24.5, 24.4.

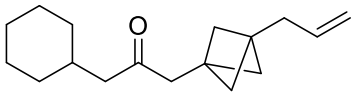
MS (70 eV, EI) *m/z* (%): 174 (10) $[M–CH_3]^{+}$, 161 (10), 160 (100), 146 (21), 145 (11), 144 (100), 133 (13), 132 (24), 130 (69), 118 (31), 117 (36), 116 (20), 115 (10), 105 (15), 104 (40), 93 (13), 91 (46), 79 (38), 78 (11), 77 (27), 67 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2936, 2861, 2228, 1706, 1446, 1430, 1377, 1338, 1303, 1272, 1256, 1225, 1211, 1145, 1124, 1105, 1081, 1068, 1041, 1009, 963, 931, 914, 892, 847, 793, 771, 705, 660.

HRMS (EI) calculated for $C_{12}H_{14}NO^{+}$: 188.1070, found 188.1069 $[M–H]^{+}$.

mp: 45.8 – 47.6 °C.

1-(3-Allylbicyclo[1.1.1]pentan-1-yl)-3-cyclohexylpropan-2-one (9f)



1-(3-Allylbicyclo[1.1.1]pentan-1-yl)-3-cyclohexylpropan-2-one was prepared according to **TP2** using cyclohexyl acetone (42 mg, 0.30 mmol, 1.5 equiv). The reaction was stirred at 0 °C for 2 h before adding CuCN·2LiCl in THF (1.0 M, 0.040 mL, 0.040 mmol, 20%) and allyl bromide (85 mg, 0.70 mmol, 3.5 equiv). The resulting mixture was stirred at 25 °C for 2 h. Workup according to **TP2** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) afforded the desired compound **9f** (35 mg, 0.14 mmol, 71%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.76 – 5.62 (m, 1 H), 5.02 – 4.93 (m, 2 H), 2.53 (s, 2 H), 2.24 (d, *J* = 6.8 Hz, 2 H), 2.19 (d, *J* = 7.2 Hz, 2 H), 1.86 – 1.75 (m, 1 H), 1.71 – 1.61 (m, 5 H), 1.59 (s, 6 H), 1.29 – 1.21 (m, 2 H), 1.18 – 1.09 (m, 1 H), 0.96 – 0.83 (m, 2 H).

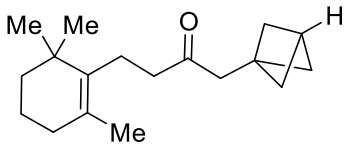
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 209.5, 135.6, 115.9, 51.4, 51.4, 46.3, 39.7, 36.8, 36.5, 33.7, 33.4, 26.4, 26.3.

MS (70 eV, EI) *m/z* (%): 205 (0.5) $[M–C_3H_5]^{+}$, 125 (20), 98 (7), 97 (100), 91 (7), 79 (7), 69 (12), 55 (29).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 2921, 2852, 1711, 1640, 1611, 1447, 1404, 1354, 1293, 1255, 1206, 1148, 1047, 991, 965, 909, 803, 708.

HRMS (EI) calculated for $C_{16}H_{23}O^{+}$: 231.1743, found 231.1740 $[M–CH_3]^{+}$.

1-(Bicyclo[1.1.1]pentan-1-yl)-4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-one (9g)



1-(Bicyclo[1.1.1]pentan-1-yl)-4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-one was prepared according to **TP2** using dihydro-β-ionone (58 mg, 0.30 mmol, 1.5 equiv). The reaction was stirred at 0 °C for 2 h before adding a saturated aqueous solution of NH_4Cl (1 mL). The resulting mixture was stirred at 25 °C for 10 min. Workup according to **TP2** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) afforded the desired compound **9g** (35 mg, 0.14 mmol, 67%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 2.54 (s, 2 H), 2.50 – 2.41 (m, 3 H), 2.27 – 2.19 (m, 2 H), 1.89 (t, *J* = 6.2 Hz, 2 H), 1.78 (s, 6 H), 1.60 – 1.51 (m, 5 H), 1.44 – 1.36 (m, 2 H), 0.97 (s, 6 H).

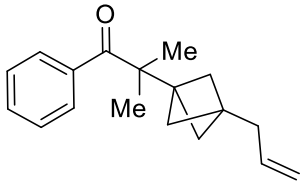
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 209.5, 136.1, 127.8, 51.6, 46.5, 44.4, 41.4, 39.8, 35.2, 32.9, 28.6, 28.5, 22.1, 19.9, 19.6.

MS (70 eV, EI) *m/z* (%): 260 (8) $[M]^{\cdot+}$, 245 (12), 242 (18), 227 (11), 179 (13), 163 (15), 161 (35), 145 (12), 137 (29), 136 (52), 135 (16), 123 (38), 122 (14), 121 (100), 109 (14), 104 (10), 95 (25), 67 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2962, 2926, 2906, 2868, 1711, 1472, 1457, 1407, 1360, 1279, 1256, 1195, 1147, 1116, 1083, 1066, 1041, 1020, 970, 953, 873.

HRMS (EI) calculated for $C_{18}H_{28}O^{\cdot+}$: 260.2135, found 260.2131 $[M]^{\cdot+}$.

2-(3-Allylbicyclo[1.1.1]pentan-1-yl)-2-methyl-1-phenylpropan-1-one (9h)



2-(3-Allylbicyclo[1.1.1]pentan-1-yl)-2-methyl-1-phenylpropan-1-one was prepared according to **TP2** using isobutyrophenone (44 mg, 0.30 mmol, 1.5 equiv). The reaction was stirred at 0 °C for 2 h before adding CuCN·2LiCl in THF (1.0 M, 0.040 mL, 0.040 mmol, 20%) and allyl bromide (85 mg, 0.70 mmol, 3.5 equiv). The resulting mixture was stirred at 25 °C for 2 h. Workup according to **TP2** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) afforded the desired compound **9h** (44 mg, 0.17 mmol, 86%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.62 – 7.56 (m, 2 H), 7.45 – 7.41 (m, 1 H), 7.40 – 7.34 (m, 2 H), 5.68 (ddt, *J* = 16.4, 10.9, 7.2 Hz, 1 H), 5.02 – 4.92 (m, 2 H), 2.19 (dt, *J* = 7.3, 1.3 Hz, 2 H), 1.53 (s, 6 H), 1.27 (s, 6 H).

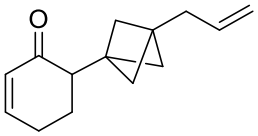
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 208.1, 140.3, 135.5, 130.7, 127.9, 127.7, 115.8, 48.2, 47.8, 45.6, 37.1, 36.6, 23.4.

MS (70 eV, EI) *m/z* (%): 253 (1) $[M–H]^{\cdot+}$, 239 (3), 148 (3), 147 (4), 119 (6), 107 (5), 106 (8), 105 (100), 93 (5), 91 (12), 79 (5), 77 (28).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3075, 2963, 2906, 1921, 1668, 1641, 1597, 1578, 1467, 1445, 1385, 1362, 1331, 1258, 1209, 1168, 1126, 1077, 1018, 991, 967, 909, 883, 806, 795, 767, 739, 698, 676.

HRMS (EI) calculated for $C_{18}H_{21}O^{+}$: 253.1587, found 253.1590 $[M-H]^{+}$.

6-(3-Allylbicyclo[1.1.1]pentan-1-yl)cyclohex-2-en-1-one (9i)



6-(3-Allylbicyclo[1.1.1]pentan-1-yl)cyclohex-2-en-1-one was prepared according to **TP2** using cyclohex-2-en-1-one (29 mg, 0.30 mmol, 1.5 equiv). The reaction was stirred at 0 °C for 30 min before adding CuCN·2LiCl in THF (1.0 M, 0.040 mL, 0.040 mmol, 20%) and allyl bromide (85 mg, 0.70 mmol, 3.5 equiv). The resulting mixture was stirred at 0 °C for 30 min. Workup according to **TP2** and purification via column chromatography (*i*Hex / EtOAc = 19 / 1) afforded the desired compound **9i** (30 mg, 0.15 mmol, 75%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 6.89 (dt, *J* = 10.1, 4.0 Hz, 1 H), 5.93 (dt, *J* = 10.1, 2.1 Hz, 1 H), 5.69 (ddt, *J* = 16.5, 10.5, 7.2 Hz, 1 H), 5.01 – 4.91 (m, 2 H), 2.48 – 2.35 (m, 2 H), 2.32 – 2.22 (m, 1 H), 2.19 (d, *J* = 7.2 Hz, 2 H), 2.05 (ddt, *J* = 13.0, 7.6, 5.3 Hz, 1 H), 1.87 (td, *J* = 13.3, 5.9 Hz, 1 H), 1.65 – 1.55 ($[AB]_3$-system, 6 H).

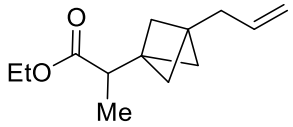
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 200.0, 149.6, 135.7, 130.0, 115.8, 50.3, 47.2, 40.3, 38.8, 36.8, 25.7, 24.3.

MS (70 eV, EI) *m/z* (%): 187 (8) $[M-CH_3]^{+}$, 161 (57), 159 (16), 143 (15), 131 (14), 128 (15), 119 (37), 117 (25), 115 (13), 105 (33), 96 (13), 95 (17), 93 (24), 91 (100), 79 (22), 77 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3075, 2961, 2904, 1673, 1640, 1620, 1448, 1428, 1411, 1386, 1352, 1307, 1286, 1252, 1170, 1118, 1019, 991, 946, 909, 835, 763, 713, 686.

HRMS (EI) calculated for $C_{14}H_{17}O^{+}$: 201.1274, found 201.1272 $[M-H]^{+}$.

Ethyl 2-(3-allylbicyclo[1.1.1]pentan-1-yl)propanoate (11a)



Ethyl 2-(3-allylbicyclo[1.1.1]pentan-1-yl)propanoate was prepared according to **TP3** using ethyl propionate (41 mg, 0.40 mmol, 2.0 equiv). After stirring at 0 °C for 3 h, CuCN·2LiCl in THF (1.0 M, 0.040 mL, 0.040 mmol, 20%) and allyl bromide (61 mg, 0.50 mmol, 2.5 equiv) were added. Workup according to **TP3** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) afforded the desired compound **11a** (31 mg, 0.15 mmol, 75%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.77 – 5.62 (m, 1 H), 5.02 – 4.93 (m, 2 H), 4.19 – 4.03 (m, 2 H), 2.54 (q, *J* = 7.0 Hz, 1 H), 2.20 (dt, *J* = 7.2, 1.3 Hz, 2 H), 1.51 (s, 6 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.05 (d, *J* = 7.0 Hz, 3 H).

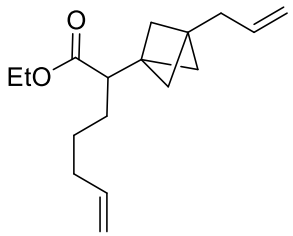
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 174.6, 135.7, 115.9, 60.2, 49.1, 41.15, 41.1, 37.9, 36.8, 14.6, 13.5.

MS (70 eV, EI) *m/z* (%): 167 (8) $[M–C_3H_5]^{+}$, 139 (73), 135 (17), 133 (11), 119 (50), 107 (77), 106 (10), 105 (53), 93 (52), 91 (100), 79 (60), 77 (26), 44 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2962, 2907, 2869, 1733, 1641, 1456, 1409, 1374, 1336,1289, 1255, 1227, 1183, 1148, 1096, 1053, 1019, 1009, 911, 859, 822, 791, 708, 668.

HRMS (EI) calculated for $C_{10}H_{15}O_2^{+}$: 167.1067, found 167.1066 $[M–C_3H_5]^{+}$.

Ethyl 2-(3-allylbicyclo[1.1.1]pentan-1-yl)hept-6-enoate (11b)



Ethyl 2-(3-allylbicyclo[1.1.1]pentan-1-yl)hept-6-enoate was prepared according to **TP3** using ethyl hept-6-enoate (156 mg, 1.0 mmol, 2.0 equiv) and [1.1.1]propellane in diethyl ether (0.50 mmol, 1.0 equiv). After stirring at 0 °C for 3 h, CuCN·2LiCl in THF (1.0 M, 0.10 mL, 0.10 mmol, 20%) and allyl bromide (151 mg, 1.3 mmol, 2.5 equiv) were added. Workup

according to **TP3** and purification via column chromatography (*i*Hex / EtOAc = 99 / 1) and HPLC afforded the desired compound **11b** (125 mg, 0.48 mmol, 95%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.85 – 5.62 (m, 2 H), 5.03 – 4.90 (m, 4 H), 4.12 (qd, *J* = 7.1, 3.8 Hz, 2 H), 2.47 – 2.39 (m, 1 H), 2.20 (dt, *J* = 7.2, 1.3 Hz, 2 H), 2.08 – 1.99 (m, 2 H), 1.63 – 1.58 (m, 1 H), 1.53 (A part of an $[AB]_3$-system, 3 H), 1.49 (B part of an $[AB]_3$-system, 3 H), 1.42 – 1.29 (m, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

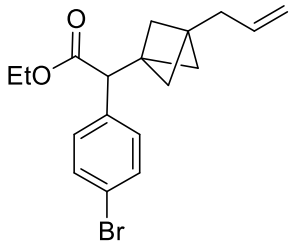
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 174.0, 138.7, 135.7, 115.9, 114.7, 60.1, 49.5, 47.4, 40.6, 38.1, 36.8, 33.8, 28.5, 27.2, 14.6.

MS (70 eV, EI) *m/z* (%): 221 (2) $[M–C_3H_5]^{+}$, 193 (10), 165 (10), 147 (57), 145 (18), 137 (61), 133 (24), 131 (32), 125 (16), 121 (10), 119 (61), 117 (23), 107 (61), 93 (34), 91 (100), 81 (15), 79 (67), 77 (23), 67 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3077, 2963, 2905, 2868, 1732, 1641, 1444, 1370, 1344, 1254, 1174, 1124, 1027, 991, 909, 805.

HRMS (EI) calculated for $C_{14}H_{21}O_2^{+}$: 221.1536, found 221.1535 $[M–C_3H_5]^{+}$.

Ethyl 2-(3-allylbicyclo[1.1.1]pentan-1-yl)-2-(4-bromophenyl)acetate (11c)



Ethyl 2-(3-allylbicyclo[1.1.1]pentan-1-yl)-2-(4-bromophenyl)acetate was prepared according to **TP3** using ethyl 2-(4-bromophenyl)acetate (97 mg, 1.0 mmol, 2.0 equiv). After stirring at 0 °C for 3 h, CuCN·2LiCl in THF (1.0 M, 0.10 mL, 0.10 mmol, 20%) and allyl bromide (151 mg, 1.3 mmol, 2.5 equiv) were added. Workup according to **TP3** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) afforded the desired compound **11c** (66 mg, 0.19 mmol, 94%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.42 (d, *J* = 8.4 Hz, 2 H), 7.17 (d, *J* = 8.5 Hz, 2 H), 5.73 – 5.57 (m, 1 H), 5.00 – 4.90 (m, 2 H), 4.22 – 4.05 (m, 2 H), 3.68 (s, 1 H), 2.18 (dt, *J* = 7.2, 1.3 Hz, 2 H), 1.52 (s, 6 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

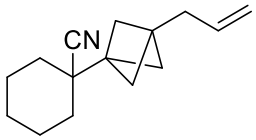
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 171.7, 136.0, 135.4, 131.4, 130.4, 121.2, 116.0, 60.8, 53.0, 49.7, 41.0, 39.3, 36.7, 14.4.

MS (70 eV, EI) *m/z* (%): 307 (6) $[M–C_3H_5]^{+}$, 281 (41), 279 (41), 215 (13), 214 (13), 196 (58), 195 (20), 182 (14), 181 (100), 180 (19), 179 (27), 172 (13), 171 (43), 169 (43), 168 (25), 167 (47), 166 (32), 165 (45), 155 (32), 154 (63), 153 (72), 152 (28), 151 (78), 141 (25), 135 (15), 134 (16), 129 (21), 128 (47), 116 (16), 115 (50), 107 (29), 105 (22), 91 (34), 89 (20), 79 (33), 77 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3075, 2965, 2905, 2868, 1732, 1640, 1488, 1464, 1445, 1408, 1367, 1336, 1302, 1248, 1197, 1156, 1121, 1073, 1011, 991, 911, 880, 835, 757, 737, 712, 683.

HRMS (EI) calculated for $C_{18}H_{21}BrO_2^{+}$: 348.0719, found 348.0700 $[M]^{+}$.

1-(3-Allylbicyclo[1.1.1]pentan-1-yl)cyclohexane-1-carbonitrile (17a)



1-(3-Allylbicyclo[1.1.1]pentan-1-yl)cyclohexane-1-carbonitrile was prepared according **TP4** using cyclohexanecarbonitrile (44 mg, 0.40 mmol, 2.0 equiv). The reaction mixture was stirred 6 h at 25 °C. Trapping and workup according to **TP4** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) afforded the desired compound **17a** (22 mg, 0.10 mmol, 51%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.70 (ddt, *J* = 16.4, 11.0, 7.2 Hz, 1 H), 5.05 – 4.93 (m, 2 H), 2.25 (dt, *J* = 7.2, 1.3 Hz, 2 H), 1.87 – 1.69 (m, 5 H), 1.56 (s, 8 H), 1.21 – 1.06 (m, 3 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 135.2, 122.4, 116.3, 47.1, 43.8, 39.7, 37.3, 36.5, 32.0, 25.3, 23.1.

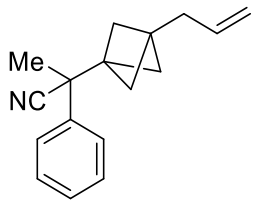
MS (70 eV, EI) *m/z* (%): 214 (6) $[M–H]^{+}$, 186 (13), 172 (18), 160 (19), 158 (13), 146 (29), 144 (21), 132 (14), 131 (11), 130 (11), 118 (11), 117 (13), 107 (40), 105 (33), 93 (12), 92 (14), 91 (67), 81 (14), 79 (100), 77 (16), 67 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 2963, 2933, 2907, 2861, 2227, 1641, 1447, 1286, 1265, 1249, 1213, 1179, 1136, 991, 937, 910, 870, 811, 713.

HRMS (EI) calculated for $C_{15}H_{20}N^{+}$: 214.1590, found 214.1588 $[M–H]^{+}$.

mp: 33.5 – 35.3 °C.

2-(3-Allylbicyclo[1.1.1]pentan-1-yl)-2-phenylpropanenitrile (17b)



2-(3-Allylbicyclo[1.1.1]pentan-1-yl)-2-phenylpropanenitrile was prepared according **TP4** using α-methylbenzyl cyanide (52 mg, 0.40 mmol, 2.0 equiv). The reaction mixture was stirred 3 h at 25 °C. Trapping and workup according to **TP4** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) afforded the desired compound **17b** (46 mg, 0.19 mmol, 96%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.39 – 7.27 (m, 5 H), 5.72 – 5.58 (m, 1 H), 5.02 – 4.92 (m, 2 H), 2.21 (dt, *J* = 7.2, 1.3 Hz, 2 H), 1.70 (s, 3 H), 1.51 (s, 6 H).

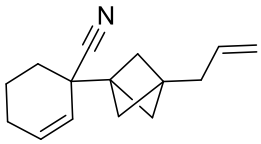
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 137.7, 134.9, 128.6, 127.8, 126.0, 122.3, 116.4, 47.6, 45.1, 43.3, 37.7, 36.4, 21.9.

MS (70 eV, EI) *m/z* (%): 236 (5) $[M–H]^{+}$, 222 (6), 194 (6), 181 (10), 180 (11), 167 (9), 154 (12), 153 (10), 141 (12), 131 (51), 130 (34), 129 (22), 128 (21), 127 (11), 116 (14), 115 (21), 107 (51), 105 (26), 104 (16), 103 (53), 102 (10), 92 (11), 91 (79), 79 (100), 78 (18), 77 (63), 67 (15), 65 (22), 53 (14), 51 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2909, 2872, 2235, 1641, 1601, 1493, 1446, 1378, 1325, 1247, 1174, 1134, 1076, 1026, 992, 913, 801, 744, 697, 657.

HRMS (EI) calculated for $C_{17}H_{18}N^{+}$: 236.1434, found 236.1433 $[M–H]^{+}$.

1-(3-Allylbicyclo[1.1.1]pentan-1-yl)cyclohex-2-ene-1-carbonitrile (17c)



1-(3-Allylbicyclo[1.1.1]pentan-1-yl)cyclohex-2-ene-1-carbonitrile was prepared according **TP4** using 1-cyanocyclohexene (43 mg, 0.40 mmol, 2.0 equiv). The reaction mixture was stirred 2 h at 25 °C. Trapping and workup according to **TP4** and purification via column chromatography (*i*Hex / EtOAc = 49 / 1) afforded the desired compound **17c** (41 mg, 0.19 mmol, 96%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.92 (ddd, *J* = 9.9, 4.6, 2.9 Hz, 1 H), 5.76 – 5.63 (m, 1 H), 5.52 – 5.46 (m, 1 H), 5.04 – 4.96 (m, 2 H), 2.25 (dt, *J* = 7.2, 1.3 Hz, 2 H), 2.13 – 2.03 (m, 1 H), 2.02 – 1.91 (m, 2 H), 1.82 – 1.73 (m, 2 H), 1.64 – 1.55 ($[AB]_3$-system, 6 H), 1.55 – 1.48 (m, 1 H).

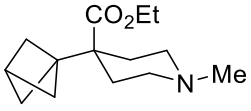
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 134.9, 131.8, 123.4, 121.8, 116.3, 47.3, 42.9, 38.1, 38.0, 36.4, 29.7, 24.4, 19.2.

MS (70 eV, EI) *m/z* (%): 212 (4) $[M-H]^{\cdot+}$, 184 (9), 170 (16), 156 (23), 145 (16), 144 (15), 143 (15), 142 (11), 131 (12), 130 (30), 129 (29), 128 (16), 117 (24), 116 (15), 115 (22), 107 (21), 105 (32), 103 (12), 92 (10), 91 (81), 80 (10), 79 (100), 77 (36), 65 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3028, 2966, 2908, 2870, 2230, 1641, 1446, 1432, 1257, 1230, 1194, 1144, 1019, 992, 912, 884, 845, 730, 695, 668.

HRMS (EI) calculated for $C_{15}H_{18}N^{\cdot+}$: 212.1434, found 212.1433 $[M-H]^{\cdot+}$.

Ethyl 4-(bicyclo[1.1.1]pentan-1-yl)-1-methylpiperidine-4-carboxylate (20)



Diisopropylamine (320 mg, 3.2 mmol, 2.1 equiv) was dissolved in THF (3.5 mL) and BuLi (2.3 M in hexane, 1.4 mL, 3.2 mmol, 2.1 equiv) was added dropwise at 0 °C. The mixture was stirred for 5 min and cooled to −78 °C. Then ethyl 1-methylpiperidine-4-carboxylate (510 mg, 3.0 mmol, 2.0 equiv) was added dropwise. After 30 min a solution of $ZnCl_2$ in THF (1.0 M, 3.8 mL, 3.8 mmol, 2.5 equiv) was added and the mixture was stirred at 0 °C for 5 min before

adding the [1.1.1]propellane in diethyl ether (0.53 M, 2.8 mL, 1.5 mmol, 1.0 equiv). After stirring at 0 °C for 2 h a saturated aqueous solution of NH_4Cl (5 mL) was added. The reaction mixture was stirred for another 10 min at 25 °C, extracted with EtOAc (3 times), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification via column chromatography (alumina, grade III, *i*Hex / NEt_3 = 19 / 1) afforded the desired compound **20** (340 mg, 1.4 mmol, 95%) as colorless crystals. The structure was confirmed via single crystal X-ray diffraction studies.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 4.16 (q, *J* = 7.1 Hz, 2 H), 2.75 (d, *J* = 11.8 Hz, 2 H), 2.44 (s, 1 H), 2.22 (s, 3 H), 2.06 (d, *J* = 13.5 Hz, 2 H), 1.84 (t, *J* = 12.2 Hz, 2 H), 1.62 (s, 6 H), 1.45 (td, *J* = 13.2, 3.8 Hz, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 173.8, 60.3, 53.6, 49.3, 47.9, 46.4, 46.1, 30.1, 25.3, 14.7.

MS (70 eV, EI) *m/z* (%): 237 (28) $[M]^{\cdot+}$, 236 (21), 222 (11), 208 (42), 192 (19), 168 (26), 165 (12), 164 (100), 162 (42), 148 (13), 140 (20), 136 (24), 122 (14), 120 (11), 105 (10), 96 (22), 94 (27), 91 (19), 79 (13), 71 (14), 70 (35), 42 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2964, 2935, 2908, 2872, 2840, 2739, 1723, 1467, 1441, 1427, 1378, 1365, 1315, 1290, 1229, 1208, 1199, 1183, 1155, 1142, 1094, 1058, 1024, 1004, 966, 949, 891, 863, 852, 789, 762, 701.

HRMS (EI) calculated for $C_{14}H_{23}NO_2^{\cdot+}$: 237.1723, found 237.1725 $[M]^{\cdot+}$.

mp: 27.4 – 29.5 °C.

3 Experimental Section Part II: Selective Metalation of Nitrogen Containing Heterocycles Using 2,2,6,6-Tetramethylpiperidyl Bases

3.1 Preparation of Starting Materials

1,3,4-Oxadiazole (25)

1,3,4-Oxadiazole was prepared according to a literature procedure.[75] Polyphosphoric acid (108 g) was heated to 100 °C before adding P_2O_5 (12 g, 42 mmol, 0.31 equiv). After stirring for 15 min *N,N'*-diformylhydrazine (12 g, 136 mmol, 1.0 equiv) was added, the resulting mixture was stirred at 100 °C for 4 h and then poured on ice (100 g). Neutralization with solid $NaHCO_3$, extraction with DCM, drying over $MgSO_4$ and evaporation of the solvents *in vacuo* yielded 1,3,4-oxadiazole **25** (2.5 g, 36 mmol, 26%) as a colorless liquid. The product was protected from light and stored at 5 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.51 (s, 2 H).

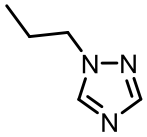
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 152.9.

N-Substituted 1*H*-1,2,4-triazoles (32)

N-Substituted 1*H*-1,2,3-triazoles were prepared according to a literature procedure.[118] A dry and argon-flushed 250mL round-bottom flask equipped with a magnetic stirrer and a septum was charged with 1*H*-1,2,4-triazole (6.91 g, 100 mmol), the respective bromide (105 mmol) and THF (100 mL). After cooling to 4 °C 1,8-diazabicyclo(5.4.0)undec-7-ene (17.9 ml, 18.3 g, 120 mmol) was added to the solution. The mixture was stirred for 18 h at room temperature, quenched with water (100 mL) and extracted with DCM (3 × 80 mL). The combined organic phases were washed with brine (80 mL) and dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification via column chromatography on silica gel or vacuum distillation afforded the desired *N*-substituted 1*H*-1,2,3-triazole **32**.

[118] A. R. Katritzky, W. Kuzmierkiewiecz, J. V. Greenhill, *Rec. Trav. Chim. Pays Bas* **1991,** 110, 369-373.

1-Propyl-1H-1,2,4-triazole (32a)

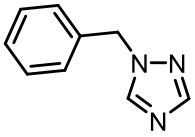


1-Propyl-1H-1,2,4-triazole was prepared using 1-bromopropane (9.6 ml, 13 g, 110 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 1:1) yielded the title compound **32a** (6.8 g, 61 mmol, 56%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.01 (s, 1 H), 7.88 (s, 1 H), 4.12 – 4.03 (m, 2 H), 1.93 – 1.79 (m, 2 H), 0.92 – 0.82 (m, 3 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 151.8, 142.9, 51.5, 23.3, 11.1.

1-Benzyl-1*H*-1,2,4-triazole (32b)

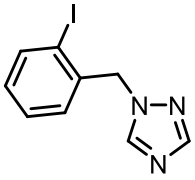


1-Benzyl-1*H*-1,2,4-triazole was prepared using benzyl bromide (18.0 g, 105 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 1:1) yielded the title compound **32b** (7.98 g, 50.1 mmol, 48%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.06 (s, 1 H), 7.98 (s, 1 H), 7.46 – 7.30 (m, 3 H), 7.30 – 7.23 (m, 2 H), 5.35 (s, 2 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 152.3, 143.2, 134.6, 129.1, 128.7, 128.1, 53.6.

1-(2-Iodobenzyl)-1*H*-1,2,4-triazole (32c)

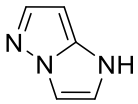


1-(2-Iodobenzyl)-1*H*-1,2,4-triazole was prepared using 2-iodobenzyl bromide (9.57 mL, 12.9 g, 105 mmol). Purification via vacuum distillation (2 mbar, 111-114 °C) yielded the title compound **32c** (5.98 g, 53.8 mmol, 54%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.18 (s, 1 H), 8.01 (s, 1 H), 7.90 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.13 (dd, *J* = 7.7, 1.7 Hz, 1 H), 7.07 (td, *J* = 7.7, 1.6 Hz, 1 H), 5.43 (s, 2 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 152.33, 143.76, 139.91, 137.10, 130.40, 129.80, 129.00, 98.74, 57.96.

***1H*-Imidazo[1,2-*b*]pyrazole (39)**



1H-Imidazo[1,2-*b*]pyrazole was synthesized using a slightly modified literature procedure[89]: A solution of $N_2H_4 \cdot H_2O$ (77 mL, 500 mmol) in absolute ethanol (250 mL) was heated to reflux before adding bromoacetaldehyde diethyl acetal (121 mL, 2.5 mol) dropwise over 45 min. The resulting solution was refluxed for an additional 3 h and the solvents were removed *in vacuo*. The residue was taken up in aqueous NaOH (35%, 60 mL) and a saturated aqueous solution of NaCl (50 mL) and the mixture was extracted with toluene (2x250 mL).

The resulting solution of (2,2-diethoxyethyl)hydrazine in toluene was treated with ethyl 2-cyano-3-ethoxyacrylate (85 g, 500 mmol) under argon atmosphere and stirred at 25 °C over night. Then the reaction mixture was heated for 3.5 h while distilling of an azeotrope of toluene, ethanol and water at around 73 °C. The remaining toluene was removed *in vacuo* and the residue containing ethyl 5-amino-1-(2,2-diethoxyethyl)-1*H*-pyrazole-4-carboxylate was treated with NaOH (4 M, 1 L) and heated to 110 °C for 2 h. The mixture was cooled down, extracted with DCM (2x200mL) and the organic phase was washed with brine (50 mL). The combined aqueous phases were cooled to 0 °C and treated with HCl (6 M) until pH 4.5. The resulting solid was filtered off, washed with cold water and dried to obtain pure 5-amino-1-(2,2-diethoxyethyl)-1*H*-pyrazole-4-carboxylic acid (97 g, 400 mmol, 80% over 3 steps) as a colorless solid.

The 5-amino-1-(2,2-diethoxyethyl)-1*H*-pyrazole-4-carboxylic acid was dissolved in absolute ethanol (100 mL) and H_2SO_4 (20%, 700 mL) and heated to 75 °C for 75 min. After cooling to 25 °C the mixture was poured on crushed ice (1 L) and slowly treated with solid $NaHCO_3$ until pH 9. The formed solid was filtered off and washed with cold water. The aqueous phase was extracted with EtOAc (3x500 mL), the combined organic phase was dried over $MgSO_4$ and evaporated. The resulting solid was combined with the solid from the filtration and

purified via flash column chromatography (silica gel, EtOAc/MeOH = 49:1) to yield *1H*-imidazo[1,2-*b*]pyrazole (**39**, 25 g, 240 mmol, 60%) as a slightly yellow solid.

^{1}H-NMR (DMSO-*d*$_6$, 400 MHz, ppm): δ = δ 10.96 (brs, 1 H), 7.48 (dd, *J* = 2.1, 0.7 Hz, 1 H), 7.44 (dd, *J* = 2.1, 1.3 Hz, 1 H), 7.13 (dd, *J* = 2.1, 1.3 Hz, 1 H), 5.61 (dd, *J* = 2.2, 0.7 Hz, 1 H).

^{13}C-NMR (DMSO-*d*$_6$, 101 MHz, ppm): δ = 141.9, 141.0, 117.9, 107.3, 78.3.

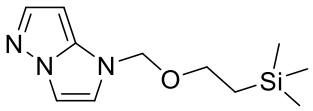
MS (70 eV, EI) *m/z* (%): 107 (100) $[M]^{+}$, 106 (17), 80 (27), 79 (15), 44 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3157, 3132, 3051, 3005, 2741, 2691, 1594, 1463, 1441, 1393, 1348, 1282, 1171, 1097, 1074, 1045, 957, 914, 867, 831, 789, 763, 697, 677.

HRMS (EI) calculated for $C_5H_5N_3^{\cdot+}$: 107.0478, found 107.0478 $[M]^{\cdot+}$.

mp: 149.5 – 151.2 °C.

1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole (40)



To a solution of *1H*-imidazo[1,2-*b*]pyrazole (2.1 g, 20 mmol, 1.0 equiv) in DMF (40 mL) was slowly added sodium hydride (0.71 g, 30 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h before adding SEMCl (5.3 mL, 30 mmol, 1.5 equiv). The reaction was warmed to 25 °C and stirred for 2 h before slowly adding a concentrated aqueous solution of NH_4Cl (20 mL). The reaction mixture was extracted with EtOAc (3x30 mL), washed with brine (3x30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification via column chromatography (silica gel, *i*Hex/EtOAc = 2:1 to pure EtOAc) yielded 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole (**40**, 2.7 g, 11 mmol, 57%) as a slightly yellow liquid alongside unreacted *1H*-imidazo[1,2-*b*]pyrazole (**39**, 0.47 g, 4.4 mmol, 22%).

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.65 – 7.60 (m, 1 H), 7.33 (d, *J* = 1.9 Hz, 1 H), 6.83 – 6.80 (m, 1 H), 5.75 (d, *J* = 1.8 Hz, 1 H), 5.22 (s, 2 H), 3.52 (t, *J* = 8.2 Hz, 2 H), 0.90 (t, *J* = 8.2 Hz, 2 H), –0.04 (s, 9 H).

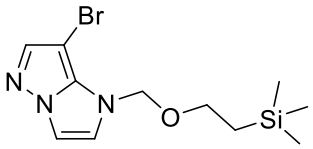
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 144.5, 143.7, 120.6, 110.4, 80.6, 78.3, 68.1, 19.1, 0.0.

MS (70 eV, EI) *m/z* (%): 237 (16) $[M]^{+}$, 179 (70), 151 (10), 121 (33), 120 (56), 103 (11), 93 (16), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3131, 2952, 2892, 1589, 1547, 1463, 1412, 1379, 1315, 1282, 1247, 1229, 1210, 1193, 1178, 1070, 1032, 973, 936, 917, 856, 831, 758, 690.

HRMS (EI) calculated for $C_{11}H_{19}N_3OSi^{+}$: 237.1292, found 237.1291 $[M]^{+}$.

7-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole (41)



To a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole (1.7 g, 5.0 mmol, 1.0 equiv) in MeCN (20 mL) was added *N*-bromosuccinimide (1.3 g, 5.0 mmol, 1.0 equiv) and the resulting mixture was stirred at 25 °C for 10 min. The solvent was removed *in vacuo* at 30 °C and the crude product was directly purified via column chromatography (silica gel, *i*Hex/EtOAc = 4:1) to yield 7-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole (**41**, 1.9 g, 6.0 mmol, 86%) as a colorless liquid. The compound was stored in the dark as a solid at −30 °C to prevent decomposition.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.55 (s, 1 H), 7.34 – 7.31 (m, 1 H), 6.86 (s, 1 H), 5.41 (s, 2 H), 3.60 (t, *J* = 8.2 Hz, 2 H), 0.91 (t, *J* = 8.2 Hz, 2 H), −0.03 (s, 9 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 143.2, 138.3, 120.1, 109.7, 75.5, 66.7, 64.8, 17.9, −1.3.

MS (70 eV, EI) *m/z* (%): 317 (13), 315 (13) $[M]^{+}$, 259 (53), 257 (53), 200 (31), 198 (33), 178 (25), 151 (13), 119 (33), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3133, 2952, 2895, 1736, 1606, 1551, 1463, 1412, 1378, 1324, 1294, 1276, 1247, 1210, 1194, 1177, 1153, 1081, 1069, 1027, 1003, 972, 916, 857, 833, 758, 689.

HRMS (EI) calculated for $C_{11}H_{18}BrN_3OSi^{+}$: 315.0397, found 315.0397 $[M]^{+}$.

$(TMP)_2Zn{\cdot}2LiCl$ (26)

TMPH (1.7 mL, 10 mmol, 1.0 equiv) was dissolved in THF (10 mL) and cooled to −40 °C before adding a solution of BuLi in hexanes (2.3 M, 4.4 mL, 10 mL, 1.0 equiv). The resulting mixture was stirred at 0 °C for 30 min, a solution of $ZnCl_2$ in THF (1.0 M, 5.0 mL, 5.0 mmol,

0.50 equiv) was added, the reaction was protected from light using aluminium foil and stirred at 25 °C for 1-2 h. The formed solids were removed using a syringe filter and the base was titrated against benzoic acid using 4-(phenylazo)-diphenylamine as an indicator.

$(TMP)_2Zn·2MgCl_2·2LiCl$ (29)

Freshly titrated TMPMgCl·LiCl (10 mmol, 1.0 equiv) was added dropwise to a solution of $ZnCl_2$ in THF (1.0 M, 5.3 mL, 5.3 mmol, 0.53 equiv). The resulting mixture was protected from light using aluminium foil and stirred at 25 °C for 2 h before titrating the base against benzoic acid using 4-(phenylazo)-diphenylamine as an indicator.

TMPMgCl·LiCl (33)

TMPH (14.8 g, 105 mmol, 1.05 equiv) was slowly added to a solution of *i*PrMgCl·LiCl in dry THF (1.05 M, 95 mL, 1.0 equiv). The resulting mixture was stirred under argon at 25 °C for 3 days before titrating the base against benzoic acid using 4-(phenylazo)-diphenylamine as an indicator.

TMPZnCl·LiCl (36)

TMPH (1.7 mL, 10 mmol, 1.0 equiv) was dissolved in THF (10 mL) and cooled to −40 °C before adding a solution of BuLi in hexanes (2.3 M, 4.4 mL, 10 mL, 1.0 equiv). The resulting mixture was stirred at 0 °C for 30 min, a solution of $ZnCl_2$ in THF (1.0 M, 10 mL, 10 mmol, 1.0 equiv) was added, the reaction was stirred at 25 °C for 1-2 h before titrating the base against benzoic acid using 4-(phenylazo)-diphenylamine as an indicator.

$(TMP)_2Zn·MgCl_2·2LiCl$ (46)

Magnesium shavings (182 mg, 7.5 mmol) were placed in a *Schlenk*-flask under vacuum and dried with a heat gun at 650 °C for 5 min. After the flask was cooled down it was filled with argon and THF (15 mL). 1,2-Dichloroethane (0.59 mL, 7.5 mmol) was added dropwise over 20 min, leading to gas evolution. The reaction was stirred for at least 1 h, leading to the formation of a 0.50 M solution of $MgCl_2$ in THF. In a second *Schlenk*-flask TMPH (1.9 mL, 11 mmol, 1.0 equiv) was dissolved in THF (11 mL) and cooled to −40 °C. Then freshly titrated BuLi (1.40 M in hexane, 7.86 mL, 11 mmol, 1.0 equiv) was added and the resulting

solution was stirred for 30 min. Then the freshly prepared $MgCl_2$ solution (0.50 M in THF, 11 mL, 5.5 mmol, 0.50 equiv) and $ZnCl_2$ solution (1.0 M in THF, 5.5 mL, 5.5 mmol, 0.50 equiv) were added. The resulting mixture was brought to room temperature, protected from light with aluminium foil and stirred for at least 1 h before titration against benzoic acid using 4-(phenylazo)-diphenylamine as an indicator. The base was stored in a closed *Schlenk*-flask covered with aluminium foil at room temperature for up to one week without a significant change in reactivity.

3.2 Typical Procedures

TP5: Metalation of 1,3,4-oxadiazole (25) with $(TMP)_2Zn{\cdot}2LiCl$ (26) followed by cross-coupling

1,3,4-Oxadiazole (**25**, 137 mg, 0.30 mmol, 1.0 equiv) was dissolved in THF (0.90 mL) and freshly prepared $(TMP)_2Zn{\cdot}2LiCl$ (**26**, 0.24 M, 0.68 mL, 0.17 mmol, 0.55 equiv) was added dropwise. The resulting suspension was stirred at 25 °C for 5 min before adding $Pd(dba)_2$ (14 mg, 0.0060 mmol, 3%), XantPhos (3.5 mg, 0.0060 mmol, 3%) and the respective aryl iodide (0.20 mmol, 0.67 equiv). After stirring for 2 h a saturated aqueous solution of NH_4Cl (1 mL) was added. Extraction with EtOAc, drying over $MgSO_4$, evaporation of the solvents *in vacuo* and purification via silica gel column chromatography yielded the desired mono-substituted 1,3,4-oxadiazole **28**.

TP6: Metalation of mono-substituted 1,3,4-oxadiazoles of type 28 with $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ (29) followed by copper catalysed electrophilic amination

Mono-substituted 1,3,4-oxadiazole of type (**28**, 0.50 mmol, 1.0 equiv) was dissolved in THF (1.0 mL) and freshly prepared $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ (**29**, 0.34 M, 0.81 mL, 0.28 mmol, 0.55 equiv) was added dropwise. After stirring at 25 °C for 20 min the mixture was added to a solution of the respective hydroxyamino benzoate (0.35 mmol, 0.70 equiv) and copper(II) triflate (27 mg, 0.075 mmol, 15%) in THF (1 mL) and stirred for additional 2 h at 25 °C. Then a saturated aqueous solution of NH_4Cl (1 mL) was added,. Extraction with EtOAc, drying over $MgSO_4$, evaporation of the solvents *in vacuo* and purification via silica gel column chromatography yielded the desired functionalized 1,3,4-oxadiazole **31**.

TP7: Metalation of *N*-substituted 1*H*-1,2,4-triazoles (32) with TMPMgCl·LiCl (33) followed by electrophilic trapping

N-Substituted 1H-1,2,4-triazole (**32**, 0.50 mmol, 1.0 equiv) was dissolved in THF (1.5 mL) and cooled to 0 °C. TMPMgCl·LiCl solution (**33**, 0.60 mmol, 1.2 equiv) was slowly added to the vigorously stirred solution. After 30 min the respective electrophile (0.60 mmol, 1.2 equiv) was added and the ice bath was removed. After stirring for 30 min 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 **35** was purified by flash column chromatography.

TP8: Metalation of *N*-substituted 1*H*-1,2,4-triazoles (32) with TMPZnCl·LiCl (36) followed by cross-coupling

N-Substituted 1*H*-1,2,4-triazole (**32**, 0.50 mmol, 1.0 equiv) was dissolved in THF (1.5 mL) and cooled to 0 °C. TMPZnCl·LiCl solution (**36**, 0.65 mmol, 1.3 equiv) was slowly added to the stirred solution. A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with the respective aromatic bromide or iodide (0.6 mmol, 1.2 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5%), SPhos (20.5 mg, 0.050 mmol, 10%) and THF (1.0 mL). After 30 min the metalated species was slowly added to the vigorously stirred solution. The reaction mixture was stirred at 40 °C for 18 h, quenched with sat. aq. NH_4Cl solution (15 mL), extracted with DCM (3×15 mL) and dried over anhydrous $MgSO_4$. The crude product **35** was purified by flash column chromatography.

TP9: Metalation of *N*-substituted 1*H*-1,2,4-triazoles (32) with TMPZnCl·LiCl (36) followed by copper-catalyzed electrophilic amination

N-Substituted 1*H*-1,2,4-triazole (**32**, 0.50 mmol, 1.0 equiv) was dissolved in THF (1.5 mL) and cooled to 0 °C. TMPZnCl·LiCl solution (**36**, 1 mmol, 2.0 equiv) was slowly added to the stirred solution. A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with amine benzoate (0.6 mmol, 1.2 equiv), copper (II) triflate (36 mg, 0.1 mmol, 20%) and THF (2.0 mL). After 30 min the metalated species was slowly added to the 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 **35** was purified by flash column chromatography.

TP10: Double functionalization of *N*-substituted 1*H*-1,2,4-triazoles (32) with TMPMgCl·LiCl (33)

N-Substituted 1*H*-1,2,4-triazole (**32**, 0.50 mmol, 1.0 equiv) was dissolved in THF (1.5 mL) and cooled down to 0 °C. TMPMgCl·LiCl solution (**33**, 2.0 mmol, 4.0 equiv) was slowly added to the vigorously stirred solution. After 30 min the respective electrophile (2.2 mmol, 4.1 equiv) was added and the ice bath was removed. After 30 min 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 **37** was purified by flash column chromatography.

TP11: Bromine-magnesium exchange of 7-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole (41) followed by electrophile trapping

To a solution of 7-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole (**41**, 1.0 equiv) in THF (0.5 M) was added *i*PrMgCl·LiCl (**42**, 2.1 equiv) dropwise at 0 °C. The reaction mixture was warmed up to 25 °C and stirred for 1 h before adding the respective electrophile. After stirring for the indicated time a saturated aqueous solution of NH_4Cl was added. The reaction was extracted with EtOAc (3x), washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified via silica gel column chromatography to yield the desired 7-substituted 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole of type **43**.

TP12: Metalation of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (43b) with TMPMgCl·LiCl (33) followed by electrophile trapping

To a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (**43b**, 1.0 equiv) in THF (0.5 M) was added a solution of TMPMgCl·LiCl (**33**, typically 0.95-1.05 M in THF, 1.5 equiv) dropwise at −20 °C. The mixture was stirred at −20 °C for 2 h before adding the respective electrophile. After stirring for the indicated time a saturated aqueous solution of NH_4Cl was added. The reaction was extracted with EtOAc (3x), washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified via silica gel column chromatography to yield the desired 3-substituted 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile of type **43**.

TP13: Metalation of ethyl 7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo-[1,2-*b*]pyrazole-3-carboxylate (45c) with $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ (46) followed by electrophile trapping

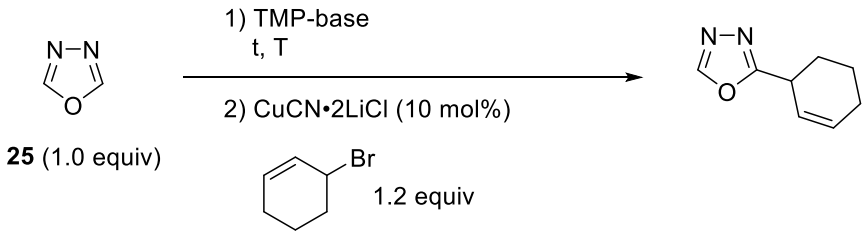
To a solution of 7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate (**45c**, 1.0 equiv) in THF (0.20 mL) was added a solution of $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ (**46**, typically 0.14-0.16 M in THF, 0.65 equiv for allylations and acylations, 0.55 equiv for cross-couplings) dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min before adding the respective electrophile. After stirring for the indicated time a saturated aqueous solution of NH_4Cl was added. The reaction was extracted with EtOAc (3x), washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified via silica gel column chromatography to yield the desired 2-substituted ethyl 7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate of type **47**.

TP14: Dimerization of 2-functionalized ethyl 7-cyano-1-((2-(trimethylsilyl)-ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylates of type 47 with $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ (46)

To a solution of the respective 7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]-pyrazole-3-carboxylate of type **47** (1.0 equiv) in THF (0.5 M) was added a solution of $(TMP)_2Zn{\cdot}MgCl_2{\cdot}LiCl$ (**46**, typically 0.14-0.16 M in THF, 0.65 equiv) dropwise at 0 °C. The mixture was stirred at 0 °C for the indicated time before adding a saturated aqueous solution of NH_4Cl. The reaction was extracted with EtOAc (3x), washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified via column chromatography on Florisil® (*i*Hex/EtOAc = 4:1, then *i*Hex/ EtOAc = 1:1, then EtOAc, then EtOAc/MeOH = 10:1) to yield the desired 1*H*,1'*H*,5*H*,5'*H*-6,6'-biimidazo[1,2-*b*]pyrazolylidene of type **48**.

3.3 Optimization of the Conditions for the Metalation of 1,3,4-Oxadiazole

The conditions for the metalation of 1,3,4-oxadiazole were screened via GC chromatography after a copper-catalyzed allylation with 3-bromocyclohexene (Scheme 44). Magnesium bases yielded only traces of the desired product. A significant improvement was achieved by switching to zinc bases, with the bis-base $(TMP)_2Zn{\cdot}2LiCl$ giving the best results. The yields were significantly higher if the solid formed during the preparation of the base was filtered off before the use. The optimal amount of base was determined to be 0.55 equivalents, which resulted in an isolated yield of the product of 63% after only 5 minutes of metalation time.

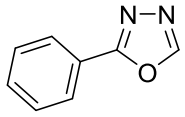


Base	conditions	GC yield
TMPMgCl•LiCl (1.1 equiv)	r.t., 30 min	<2%
$(TMP)_2MgCl•2LiCl$ (0.55 equiv)	r.t., 30 min	<3%
TMPZnCl•LiCl (1.1 equiv)	r.t., 30 min	20%
$(TMP)_2Zn•2MgCl_2•2LiCl$ (0.55 equiv)	r.t., 30 min	20%
$(TMP)_2Zn•2LiCl$ (suspension) (0.55 equiv)	r.t., 30 min	39%
$(TMP)_2Zn•2LiCl$ (filtered) (0.55 equiv)	r.t., 30 min	53%
$(TMP)_2Zn•2LiCl$ (filtered) (0.65 equiv)	r.t., 30 min	35%
$(TMP)_2Zn•2LiCl$ (filtered) (0.55 equiv)	r.t., 5 min	63% (isolated yield)
$(TMP)_2Zn•2LiCl$ (filtered) (0.50 equiv)	r.t., 5 min	52%

Scheme 44. Optimization of the conditions for the metalation of 1,3,4-oxadiazole.

3.4 Products

2-Phenyl-1,3,4-oxadiazole (28a)



2-Phenyl-1,3,4-oxadiazole was prepared according to **TP5** using phenyl iodide (41 mg, 0.20 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1) yielded the title compound **28a** (25 mg, 0.17 mmol, 86%) as colorless crystals.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.48 (s, 1 H), 8.12 – 8.02 (m, 2 H), 7.60 – 7.46 (m, 3 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 164.8, 152.7, 132.0, 129.1, 127.1, 123.5.

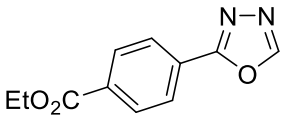
MS (70 eV, EI) *m/z* (%): 146 (100) $[M]^{+}$, 105 (42), 91 (11), 90 (32), 89 (19), 77 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3231, 3131, 1706, 1663, 1609, 1589, 1555, 1514, 1481, 1449, 1340, 1288, 1234, 1179, 1105, 1077, 1063, 1025, 1002, 955, 944, 927, 849, 777, 709, 687.

HRMS (EI) calculated for $C_8H_6N_2O^{\cdot+}$: 146.0475, found 146.0475 $[M]^{\cdot+}$.

mp: 33.8 – 35.1 °C.

Ethyl 4-(1,3,4-oxadiazol-2-yl)benzoate (28b)



Ethyl 4-(1,3,4-oxadiazol-2-yl)benzoate was prepared according to **TP5** using ethyl 4-iodobenzoate (55 mg, 0.20 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **28b** (43 mg, 0.197 mmol, 98%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.53 (s, 1 H), 8.21 – 8.13 (m, 4 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 165.6, 164.1, 153.0, 133.5, 130.3, 127.1, 127.0, 61.6, 14.3.

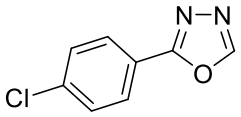
MS (70 eV, EI) *m/z* (%): 218 (7) $[M]^{\cdot+}$, 190 (64), 174 (10), 173 100), 149 (14), 145 (14), 118 (8), 90 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3124, 1701, 1553, 1477, 1414, 1370, 1310, 1277, 1178, 1131, 1105, 1069, 1013, 955, 874, 847, 779, 714.

HRMS (EI) calculated for $C_{11}H_{11}N_2O_3^{\cdot+}$: 218.0686, found 218.0688 $[M]^{\cdot+}$.

mp: 93.8 – 95.5 °C.

2-(4-Chlorophenyl)-1,3,4-oxadiazole (28c)



2-(4-Chlorophenyl)-1,3,4-oxadiazole was prepared according to **TP5** using 1-chloro-4-iodobenzene (48 mg, 0.20 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1) yielded the title compound **28c** (31 mg, 0.17 mmol, 86%) as a slightly brown solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.48 (s, 1 H), 8.02 (d, *J* = 8.6 Hz, 2 H), 7.50 (d, *J* = 8.6 Hz, 2 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 164.0, 152.7, 138.4, 129.6, 128.4, 121.9.

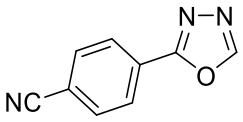
MS (70 eV, EI) *m/z* (%): 182 (35), 181 (13), 180 (100) $[M]^{\cdot+}$, 141 (24), 139 (95), 137 (20), 125 (17), 124 (20), 111 (22), 89 (29), 85 (14), 75 (21), 71 (19), 69 (10), 57 (21), 43 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3148, 2921, 1983, 1716, 1605, 1583, 1549, 1513, 1480, 1406, 1332, 1278, 1215, 1172, 1114, 1091, 1062, 1009, 971, 959, 951, 941, 859, 830, 741, 730, 693.

HRMS (EI) calculated for $C_8H_5ClN_2O^{\cdot+}$: 180.0085, found 180.0081 $[M]^{\cdot+}$.

mp: 132.7 – 134.6 °C.

4-(1,3,4-Oxadiazol-2-yl)benzonitrile (28d)



4-(1,3,4-Oxadiazol-2-yl)benzonitrile was prepared according to **TP5** using 4-iodobenzonitrile (46 mg, 0.20 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 6:4) yielded the title compound **28d** (25 mg, 0.15 mmol, 73%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.50 (s, 1 H), 8.15 (d, *J* = 8.7 Hz, 2 H), 7.77 (d, *J* = 8.7 Hz, 2 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 163.3, 153.3, 133.0, 127.6, 127.3, 117.8, 115.6.

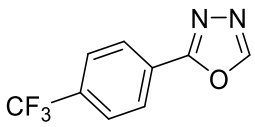
MS (70 eV, EI) *m/z* (%): 171 (69) $[M]^{\cdot+}$, 130 (57), 128 (16), 116 (37), 115 (100), 114 (36), 91 (11), 88 (13), 76 (17), 75 (20), 62 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3154, 2922, 2228, 1581, 1551, 1501, 1489, 1405, 1282, 1225, 1091, 1068, 1015, 956, 867, 839, 736, 698.

HRMS (EI) calculated for $C_9H_5N_3O^{\cdot+}$: 171.0427, found 171.0425 $[M]^{\cdot+}$.

mp: 145.6 – 147.7 °C.

2-(4-(Trifluoromethyl)phenyl)-1,3,4-oxadiazole (28e)



2-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole was prepared according to **TP5** using 1-iodo-4-(trifluoromethyl)benzene (55 mg, 0.20 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1) yielded the title compound **28e** (35 mg, 0.16 mmol, 82%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.54 (s, 1 H), 8.22 (d, *J* = 7.7 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 163.7, 153.1, 133.7 (q, *J* = 33.0 Hz), 127.5, 126.7, 126,2 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 273.1 Hz).

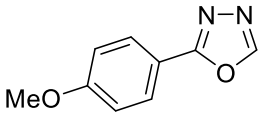
MS (70 eV, EI) *m/z* (%): 214 (100) $[M]^{\cdot+}$, 195 (13), 173 (69), 167 (10), 158 (71), 145 (38), 138 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3153, 2923, 1562, 1516, 1414, 1319, 1224, 1186, 1157, 1111, 1071, 1056, 1010, 947, 867, 847, 748, 705.

HRMS (EI) calculated for $C_9H_5F_3N_2O^{\cdot+}$: 214.0348, found 214.0348 $[M]^{\cdot+}$.

mp: 114.1 – 115.9 °C.

2-(4-Methoxyphenyl)-1,3,4-oxadiazole (28f)



2-(4-Methoxyphenyl)-1,3,4-oxadiazole was prepared according to **TP5** using 1-iodo-4-methoxybenzene (47 mg, 0.20 mmol). The cross-coupling was conducted at 50 °C using $Pd(PPh_3)_4$ (17 mg, 0.015 mmol, 7.5%) as a catalyst. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 6:4) yielded the title compound **14f** (32 mg, 0.18 mmol, 90%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.41 (s, 1 H), 8.01 (d, *J* = 8.9 Hz, 2 H), 7.01 (d, *J* = 8.9 Hz, 2 H), 3.88 (s, 3 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 164.7, 162.5, 152.2, 128.9, 116.0, 114.5, 55.5.

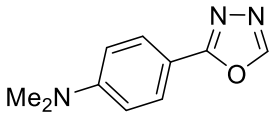
MS (70 eV, EI) *m/z* (%): 176 (100) $[M]^{\cdot+}$, 136 (8), 135 (95), 91 (6), 77 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3126, 2922, 2851, 1718, 1612, 1587, 1559, 1517, 1494, 1456, 1438, 1422, 1302, 1257, 1179, 1122, 1110, 1097, 1066, 1017, 973, 959, 939, 860, 832, 818, 797, 738, 702.

HRMS (EI) calculated for $C_9H_8N_2O_2^{\cdot+}$: 176.0580, found 176.0580 $[M]^{\cdot+}$.

mp: 64.6 – 66.2 °C.

_N,N_-Dimethyl-4-(1,3,4-oxadiazol-2-yl)aniline (28g)



_N,N_-Dimethyl-4-(1,3,4-oxadiazol-2-yl)aniline was prepared according to **TP5** using 4-iodo-_N,N_-dimethylaniline (49 mg, 0.20 mmol). The cross-coupling was conducted at 50 °C using $Pd(PPh_3)_4$ (17 mg, 0.015 mmol, 7.5%) as a catalyst. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 7:3) yielded the title compound **28g** (24 mg, 0.13 mmol, 63%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.35 (s, 1 H), 7.91 (d, *J* = 9.0 Hz, 2 H), 6.74 (d, *J* = 9.0 Hz, 2 H), 3.05 (s, 6 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 165.5, 152.5, 151.7, 128.6, 111.7, 110.6, 40.2.

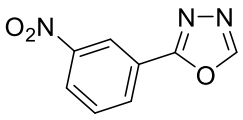
MS (70 eV, EI) *m/z* (%): 189 (100) $[M]^{\cdot+}$, 188 (60), 161 (7), 148 (30), 145 (13), 132 (13), 118 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}):

HRMS (EI) calculated for $C_{10}H_{11}N_3O^{\cdot+}$: 189.0897, found 189.0896 $[M]^{\cdot+}$.

mp: 134.2 – 136.1 °C.

2-(3-Nitrophenyl)-1,3,4-oxadiazole (28h)



2-(3-Nitrophenyl)-1,3,4-oxadiazole was prepared according to **TP5** using 1-iodo-3-nitrobenzene (50 mg, 0.20 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 6:4) yielded the title compound **28h** (37 mg, 0.19 mmol, 97%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.91 (t, *J* = 2.0 Hz, 1 H), 8.58 (s, 1 H), 8.45 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1 H), 8.42 (ddd, *J* = 8.3, 2.3, 1.1 Hz, 1 H), 7.76 (t, *J* = 8.0 Hz, 1 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 163.0, 153.3, 148.6, 132.7, 130.6, 126.5, 125.1, 122.1.

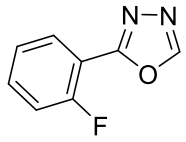
MS (70 eV, EI) *m/z* (%): 191 (86) $[M]^{\cdot+}$, 150 (49), 145 (15), 118 (21), 117 (14), 104 (13), 90 (77), 89 (100), 88 (14), 87 (18), 86 (16), 76 (42), 75 (39), 74 (26), 63 (47), 62 (19), 50 (12), 46 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3160, 3092, 2923, 2853, 1620, 1591, 1556, 1530, 1508, 1475, 1352, 1253, 1238, 1166, 1122, 1104, 1061, 1001, 976, 963, 953, 906, 883, 871, 856, 812, 753, 739, 711, 668.

HRMS (EI) calculated for $C_8H_5N_3O_3^{\cdot+}$: 191.0325, found 191.0324 $[M]^{\cdot+}$.

mp: 127.6 – 129.3 °C.

2-(2-Fluorophenyl)-1,3,4-oxadiazole (28i)



2-(2-Fluorophenyl)-1,3,4-oxadiazole was prepared according to **TP5** using 1-fluoro-2-iodobenzene (44 mg, 0.20 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1) yielded the title compound **28i** (29 mg, 0.18 mmol, 88%) as a slightly brown liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.54 (s, 1 H), 8.08 (ddd, *J* = 7.9, 7.1, 1.8 Hz, 1 H), 7.59 – 7.51 (m, 1 H), 7.31 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.26 (ddd, *J* = 10.5, 8.3, 1.1 Hz, 1 H).

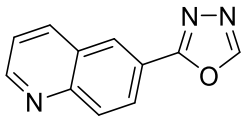
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 161.7 (d, *J* = 4.9 Hz), 160.1 (d, *J* = 258.6 Hz), 153.0 (d, *J* = 1.2 Hz), 133.9 (d, *J* = 8.5 Hz), 129.9, 124.8 (d, *J* = 3.8 Hz), 117.1 (d, *J* = 20.8 Hz), 112.0 (d, *J* = 11.7 Hz).

MS (70 eV, EI) *m/z* (%): 164 (100) $[M]^{\cdot+}$, 123 (36), 109 (20), 108 (57), 107 (24).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3117, 1621, 1591, 1550, 1515, 1492, 1472, 1442, 1405, 1346, 1272, 1262, 1223, 1159, 1102, 1069, 1053, 1027, 955, 856, 820, 765, 740, 700, 663.

HRMS (EI) calculated for $C_8H_5FN_2O^{\cdot+}$: 164.0380, found 164.0379 $[M]^{\cdot+}$.

2-(Quinolin-6-yl)-1,3,4-oxadiazole (28j)



2-(Quinolin-6-yl)-1,3,4-oxadiazole was prepared according to **TP5** using 6-iodoquinoline (51 mg, 0.20 mmol). Purification via column chromatography (silica gel, EtOAc) yielded the title compound **28j** (36 mg, 0.19 mmol, 92%) as a slightly yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 9.01 (dd, *J* = 4.3, 1.7 Hz, 1 H), 8.57 (d, *J* = 1.9 Hz, 1 H), 8.55 (s, 1 H), 8.37 (dd, *J* = 8.8, 1.9 Hz, 1 H), 8.28 (d, *J* = 8.4 Hz, 1 H), 8.23 (d, *J* = 8.9 Hz, 1 H), 7.50 (dd, *J* = 8.3, 4.2 Hz, 1 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 164.5, 153.1, 152.5, 149.4, 137.0, 130.9, 128.0, 127.7, 127.1, 122.4, 121.6.

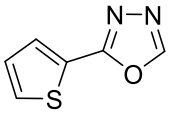
MS (70 eV, EI) *m/z* (%): 197 (98) $[M]^{\cdot+}$, 157 (10), 156 (100), 141 (10), 140 (12), 128 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3351, 3080, 2923, 2852, 1628, 1578, 1549, 1509, 1495, 1438, 1367, 1331, 1310, 1249, 1187, 1127, 1089, 1059, 1037, 977, 958, 939, 911, 889, 850, 834, 798, 768, 723.

HRMS (EI) calculated for $C_{11}H_7N_3O^{\cdot+}$: 197.0584, found 197.0582 $[M]^{\cdot+}$.

mp: 119.1 – 121.5 °C.

2-(Thiophen-2-yl)-1,3,4-oxadiazole (28k)



2-(Thiophen-2-yl)-1,3,4-oxadiazole was prepared according to **TP5** using 2-iodothiophene (42 mg, 0.20 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1) yielded the title compound **28k** (28 mg, 0.18 mmol, 92%) as a slightly brown liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.40 (s, 1 H), 7.79 (dd, *J* = 3.8, 1.2 Hz, 1 H), 7.57 (dd, *J* = 5.0, 1.2 Hz, 1 H), 7.18 (dd, *J* = 5.0, 3.7 Hz, 1 H).

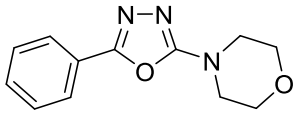
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 161.0, 152.0, 130.6, 130.3, 128.3, 124.7.

MS (70 eV, EI) *m/z* (%): 152 (100) $[M]^{\cdot+}$, 110 (49), 96 (22), 70 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3228, 3106, 3000, 1703, 1652, 1593, 1578, 1520, 1490, 1419, 1372, 1355, 1297, 1233, 1214, 1096, 1061, 1010, 953; 919, 851, 720.

HRMS (EI) calculated for $C_6H_4N_2OS^{\cdot+}$: 152.0039, found 152.0038 $[M]^{\cdot+}$.

4-(5-Phenyl-1,3,4-oxadiazol-2-yl)morpholine (31a)



4-(5-Phenyl-1,3,4-oxadiazol-2-yl)morpholine was prepared according to **TP6** using 2-phenyl-1,3,4-oxadiazole **28a** (73 mg, 0.50 mmol) and morpholino benzoate (73 mg, 0.35 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **31a** (79 mg, 0.34 mmol, 98%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.88 – 7.78 (m, 2 H), 7.38 (dq, *J* = 6.6, 2.8, 1.8 Hz, 3 H), 3.82 – 3.73 (m, 4 H), 3.53 (dd, *J* = 5.8, 3.9 Hz, 4 H).

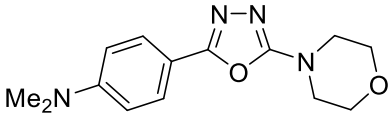
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 164.0, 159.6, 130.7, 128.9, 125.9, 124.4, 66.0, 46.2.

MS (70 eV, EI) *m/z* (%): 231 (80) $[M]^{\cdot+}$, 207 (25), 135 (100), 70 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2398, 2377, 1798, 1721, 1355, 1348, 1250, 688.

HRMS (EI) calculated for $C_{12}H_{13}N_3O_2^{\cdot+}$: 231.1008, found 231.1003 $[M]^{\cdot+}$.

***N*,*N*-Dimethyl-4-(5-morpholino-1,3,4-oxadiazol-2-yl)aniline (31b)**



N,*N*-Dimethyl-4-(5-morpholino-1,3,4-oxadiazol-2-yl)aniline was prepared according to **TP6** using *N*,*N*-dimethyl-4-(1,3,4-oxadiazol-2-yl)aniline **28g** (95 mg, 0.50 mmol) and morpholino benzoate (73 mg, 0.35 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **31b** (71 mg, 0.26 mmol, 74%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.83 – 7.63 (m, 2 H), 6.78 – 6.62 (m, 2 H), 3.88 – 3.72 (m, 4 H), 3.66 – 3.48 (m, 4 H), 3.01 (s, 6 H).

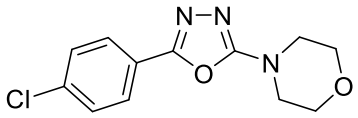
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 163.6, 160.5, 151.8, 127.3, 111.7, 66.1, 46.4, 40.2.

MS (70 eV, EI) *m/z* (%): 274 (86) $[M]^{\cdot+}$, 207 (35), 135 (100), 120 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972, 2917, 2893, 2857, 1605, 1572, 1510, 1452, 1445, 1432, 1364, 1272, 1258, 1228, 1192, 1170, 1117, 1071, 1062, 951, 945, 909, 820, 761, 725, 704.

HRMS (EI) calculated for $C_{14}H_{18}N_4O_2^{\cdot+}$: 274.1430, found 274.1438 $[M]^{\cdot+}$.

4-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)morpholine (31c)



4-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)morpholine was prepared according to **TP6** using 2-(4-chlorophenyl)-1,3,4-oxadiazole **28c** (90 mg, 0.50 mmol) and morpholino benzoate (73 mg, 0.35 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **31c** (74 mg, 0.28 mmol, 80%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.86 – 7.71 (m, 2 H), 7.45 – 7.31 (m, 2 H), 3.84 – 3.70 (m, 4 H), 3.65 – 3.48 (m, 4 H).

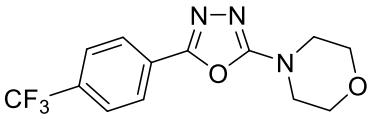
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 164.2, 158.9, 136.8, 129.4, 127.2, 123.0, 66.1, 46.3.

MS (70 eV, EI) *m/z* (%): 265 (78) $[M]^{\cdot+}$, 207 (29), 135 (100), 70 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 1706, 1637, 1618, 1614, 1603, 1577, 1485, 1440, 1434, 1421, 1396, 1390, 1359, 1273, 1258, 1221, 1120, 1114, 1092, 1060, 1012, 912, 837, 732.

HRMS (EI) calculated for $C_{12}H_{12}ClN_3O_2^{\cdot+}$: 265.0618, found 265.0615 $[M]^{\cdot+}$.

4-(5-(4-(Trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)morpholine (31d)



4-(5-(4-(Trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)morpholine was prepared according to **TP6** using 2-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole **28e** (107 mg, 0.50 mmol) and morpholino benzoate (73 mg, 0.35 mmol). Purification via column chromatography (silica gel,

*i*hexane / EtOAc = 3:1) yielded the title compound **31d** (73 mg, 0.25 mmol, 70%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.01 (d, *J* = 8.1 Hz, 2 H), 7.70 (d, *J* = 8.3 Hz, 2 H), 3.84 (dd, *J* = 6.0, 3.8 Hz, 4 H), 3.61 (dd, *J* = 5.8, 3.9 Hz, 4 H).

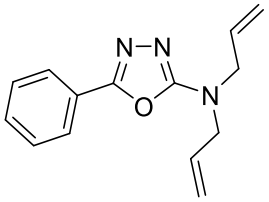
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 164.3, 158.4, 132.2 (d, *J* = 32.8 Hz), 127.6, 126.0, 126.0 (d, *J* = 3.9 Hz, 2C), 123.7 (d, *J* = 272.4 Hz), 65.9, 46.2.

MS (70 eV, EI) *m/z* (%): 299 (43) $[M]^{+}$, 242 (65), 173 (100), 145 (79), 114 (45).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2921, 2860, 1711, 1693, 1613, 1584, 1563, 1452, 1425, 1323, 1274, 1258, 1167, 1113, 1070, 1025, 1016, 913, 847, 730, 714, 685.

HRMS (EI) calculated for $C_{13}H_{12}F_3N_3O_2^{\cdot+}$: 299.0882, found 299.0874 $[M]^{\cdot+}$.

***N*,*N*-Diallyl-5-phenyl-1,3,4-oxadiazol-2-amine (31e)**



N,*N*-Diallyl-5-phenyl-1,3,4-oxadiazol-2-amine was prepared according to **TP6** using 2-phenyl-1,3,4-oxadiazole **28a** (73 mg, 0.50 mmol) and *N*,*N*-diallyl-O-benzoylhydroxylamine (76 mg, 0.35 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **31e** (78 mg, 0.32 mmol, 92%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.89 (dt, *J* = 5.9, 3.6 Hz, 2 H), 7.48 – 7.38 (m, 3 H), 5.87 (ddt, *J* = 17.2, 10.1, 6.0 Hz, 2 H), 5.33 – 5.20 (m, 4 H), 4.09 (dt, *J* = 6.0, 1.5 Hz, 4 H).

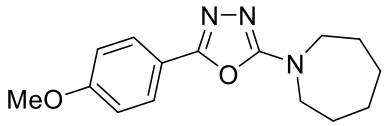
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 164.0, 159.1, 132.2, 130.4, 128.8, 125.7, 124.7, 118.5, 50.6.

MS (70 eV, EI) *m/z* (%): 241 (6) $[M]^{\cdot+}$, 200 (16), 174 (29), 105 (82), 77 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2920, 2359, 1712, 1643, 1613, 1604, 1583, 1556, 1491, 1449, 1418, 1355, 1281, 1255, 1221, 1179, 1113, 1057, 1024, 1004, 991, 964, 925, 888, 769, 728, 689, 683, 668.

HRMS (EI) calculated for $C_{14}H_{15}N_3O^{\cdot+}$: 241.1215, found 241.1213 $[M]^{\cdot+}$.

2-(Azepan-1-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (31f)



2-(Azepan-1-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole was prepared according to **TP6** using 2-(4-methoxyphenyl)-1,3,4-oxadiazole **28f** (88 mg, 0.50 mmol) and azepan-1-yl benzoate (77 mg, 0.35 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **31f** (75 mg, 0.27 mmol, 78%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.84 (d, *J* = 8.3 Hz, 2 H), 6.95 (d, *J* = 8.2 Hz, 2 H), 3.85 (s, 3 H), 3.74 – 3.55 (m, 3 H), 1.80 (d, *J* = 25.9 Hz, 5 H), 1.62 (p, *J* = 2.6 Hz, 4 H).

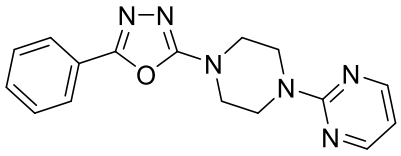
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 161.1, 127.3, 117.6, 114.2, 55.4, 48.4, 28.2, 27.6.

MS (70 eV, EI) *m/z* (%): 273 (20) $[M]^{\cdot+}$, 175 (100), 133 (19), 98 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2856, 1710, 1624, 1607, 1583, 1562, 1502, 1463, 1443, 1425, 1378, 1360, 1301, 1280, 1252, 1219, 1172, 1113, 1103, 1059, 1025, 996, 884, 836, 812, 798, 735, 721, 683.

HRMS (EI) calculated for $C_{15}H_{19}N_3O_2^{\cdot+}$: 273.1477, found 273.1480 $[M]^{\cdot+}$.

2-Phenyl-5-(4-(pyrimidin-2-yl)piperazin-1-yl)-1,3,4-oxadiazole (31g)



2-Phenyl-5-(4-(pyrimidin-2-yl)piperazin-1-yl)-1,3,4-oxadiazole was prepared according to **TP6** using 2-phenyl-1,3,4-oxadiazole **28a** (73 mg, 0.50 mmol) and 4-(pyrimidin-2-yl)piperazin-1-yl benzoate (100 mg, 0.35 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **31g** (101 mg, 0.33 mmol, 94%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.30 (d, *J* = 4.7 Hz, 2 H), 7.94 – 7.85 (m, 2 H), 7.46 – 7.36 (m, 3 H), 6.52 (t, *J* = 4.7 Hz, 1 H), 4.02 – 3.89 (m, 4 H), 3.67 – 3.55 (m, 4 H).

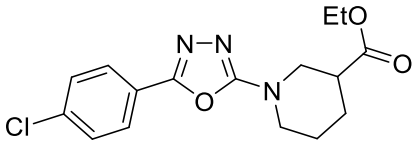
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 164.1, 161.5, 159.5, 157.8, 130.6, 128.9, 125.8, 124.4, 110.6, 46.0, 42.8.

MS (70 eV, EI) *m/z* (%): 308 (21) $[M]^{\cdot+}$, 146 (39), 134 (100), 122 (75).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2359, 2342, 2338, 1738, 1733, 1708, 1605, 1580, 1552, 1464, 1456, 1446, 1436, 1419, 1354, 1247, 1219, 949, 725, 694, 684, 668.

HRMS (EI) calculated for $C_{16}H_{16}N_6O^{\cdot+}$: 308.1386, found 308.1379 $[M]^{\cdot+}$.

Ethyl 1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)piperidine-3-carboxylate (31h)



Ethyl 1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)piperidine-3-carboxylate was prepared according to **TP6** using 2-(4-chlorophenyl)-1,3,4-oxadiazole **28c** (90 mg, 0.50 mmol) and ethyl 1-(benzoyloxy)-piperidine-3-carboxylate (97 mg, 0.35 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **31h** (110 mg, 0.33 mmol, 94%) as a colorless oil.

^{1}H-NMR (CDCl$_3$, 400 MHz, ppm): δ = 7.83 (d, *J* = 8.6 Hz, 2 H), 7.45 – 7.36 (m, 2 H), 4.20 – 4.08 (m, 3 H), 3.91 (dt, *J* = 12.8, 4.0 Hz, 1 H), 3.36 (dd, *J* = 13.1, 10.0 Hz, 1 H), 3.18 (ddd, *J* = 13.5, 10.5, 3.3 Hz, 1 H), 2.64 (ddd, *J* = 10.1, 6.1, 4.0 Hz, 1 H), 2.18 – 2.07 (m, 1 H), 1.90 – 1.78 (m, 1 H), 1.78 – 1.59 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

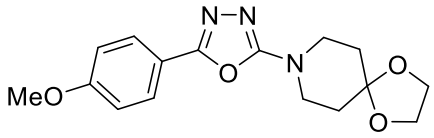
^{13}C-NMR (CDCl$_3$, 101 MHz, ppm): δ = 172.8, 164.1, 158.5, 136.6, 129.3, 127.1, 123.1, 61.0, 48.0, 46.6, 40.7, 26.8, 23.6, 14.3.

MS (70 eV, EI) *m/z* (%): 335 (9) $[M]^{\cdot+}$, 262 (100), 137 (22).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2937, 2359, 2334, 1726, 1615, 1600, 1576, 1552, 1485, 1465, 1450, 1396, 1382, 1301, 1265, 1183, 1135, 1092, 1058, 1028, 1013, 928, 908, 857, 833, 727, 681, 668.

HRMS (EI) calculated for $C_{16}H_{18}ClN_3O_3^{\cdot+}$: 335.1037, found 335.1032 $[M]^{\cdot+}$.

8-(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (31i)



8-(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane was prepared according to **TP6** using 2-(4-methoxyphenyl)-1,3,4-oxadiazole **28f** (88 mg, 0.50 mmol) and 1,4-dioxa-8-azaspiro[4.5]decan-8-yl benzoate (92 mg, 0.35 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **31i** (94 mg, 0.30 mmol, 85%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.83 (s, 2 H), 7.00 – 6.82 (m, 2 H), 3.96 (s, 4 H), 3.80 (s, 3 H), 3.72 (s, 4 H), 1.80 (s, 4 H).

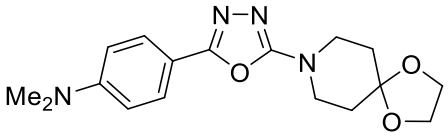
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 161.4, 127.5, 114.3, 106.3, 64.5, 55.4, 44.6, 34.1.

MS (70 eV, EI) *m/z* (%): 317 (100) $[M]^{+}$, 203 (15), 135 (66), 57 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2963, 2877, 1708, 1625, 1621, 1608, 1582, 1562, 1503, 1464, 1443, 1425, 1403, 1365, 1306, 1256, 1174, 1148, 1114, 1080, 1025, 945, 925, 837, 719.

HRMS (EI) calculated for $C_{16}H_{19}N_3O_4^{\cdot+}$: 317.1376, found 317.1371 $[M]^{\cdot+}$.

4-(5-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)-1,3,4-oxadiazol-2-yl)-*N*,*N*-dimethylaniline (31j)



4-(5-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)-1,3,4-oxadiazol-2-yl)-*N*,*N*-dimethylaniline was prepared according to **TP6** using *N*,*N*-dimethyl-4-(1,3,4-oxadiazol-2-yl)aniline **28g** (95 mg, 0.50 mmol) and 1,4-dioxa-8-azaspiro[4.5]decan-8-yl benzoate (92 mg, 0.35 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **31j** (91 mg, 0.28 mmol, 79%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.80 – 7.62 (m, 2 H), 6.73 – 6.58 (m, 2 H), 3.96 (s, 4 H), 3.73 – 3.57 (m, 4 H), 2.98 (s, 6 H), 1.93 – 1.72 (m, 4 H).

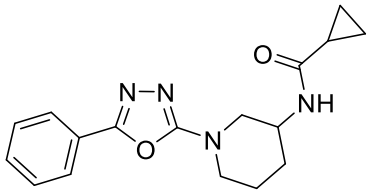
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 163.4, 160.1, 151.6, 127.1, 111.9, 111.6, 106.5, 64.5, 44.8, 40.1, 34.1.

MS (70 eV, EI) *m/z* (%): 330 (100) $[M]^{+}$, 216 (11), 96 (22), 57 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958, 2929, 2884, 1603, 1571, 1555, 1509, 1466, 1445, 1432, 1363, 1282, 1262, 1230, 1191, 1170, 1147, 1111, 1079, 1034, 1022, 944, 924, 886, 820, 737.

HRMS (EI) calculated for $C_{17}H_{22}N_4O_3^{\cdot+}$: 330.1692, found 330.1695 $[M]^{\cdot+}$.

***N*-(1-(5-Phenyl-1,3,4-oxadiazol-2-yl)piperidin-3-yl)cyclopropanecarboxamide (31k)**



N-(1-(5-Phenyl-1,3,4-oxadiazol-2-yl)piperidin-3-yl)cyclopropanecarboxamide was prepared according to **TP6** using 2-phenyl-1,3,4-oxadiazole **28a** (73 mg, 0.50 mmol) and 3-(cyclopropanecarboxamido)piperidin-1-yl benzoate (101 mg, 0.35 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 3:1) yielded the title compound **31k** (86 mg, 0.28 mmol, 79%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.94 – 7.80 (m, 2 H), 7.42 (d, *J* = 6.5 Hz, 3 H), 6.52 (d, *J* = 7.4 Hz, 1 H), 4.19 – 4.08 (m, 1 H), 3.86 – 3.73 (m, 1 H), 3.62 – 3.43 (m, 3 H), 1.96 – 1.81 (m, 2 H), 1.73 (dd, *J* = 10.6, 6.7 Hz, 2 H), 1.41 (tt, *J* = 8.1, 4.5 Hz, 1 H), 0.98 – 0.59 (m, 4 H).

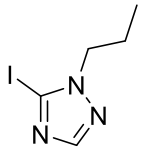
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 173.5, 171.3, 130.9, 129.0, 126.0, 124.2, 50.9, 46.7, 44.8, 29.1, 21.8, 14.7, 7.4, 7.4.

MS (70 eV, EI) *m/z* (%): 312 (1) $[M]^{+}$, 227 (100), 145 (45), 77 (43).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929, 2856, 2356, 2334, 1642, 1626, 1585, 1557, 1450, 1270, 1247, 1031, 930, 772, 729, 690.

HRMS (EI) calculated for $C_{17}H_{20}N_4O_2^{\cdot+}$: 312.1586, found 312.1583 $[M]^{+}$.

5-Iodo-1-propyl-1*H*-1,2,4-triazole (35a)



5-Iodo-1-propyl-1*H*-1,2,4-triazole was prepared according to **TP7** using iodine (152 mg, 0.60 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) yielded the title compound **35a** (96 mg, 0.41 mmol, 81%) as an orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.94 (s, 1 H), 4.19 – 4.11 (m, 5 H), 1.90 (h, *J* = 7.4 Hz, 2 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

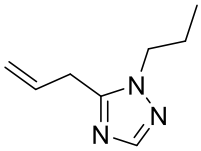
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 154.5, 99.7, 52.5, 23.3, 11.1.

MS (70 eV, EI) *m/z* (%): $[M]^{\cdot+}$ 237 (1) $[M]^{\cdot+}$, 209 (25), 208 (12), 196 (27), 195 (100), 168 (16), 110 (68), 55 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3448, 3114, 2966, 2935, 2877, 2626, 2362, 1740, 1636, 1470, 1416, 1385, 1346, 1315, 1266, 1206, 1168, 1116, 1088, 1022, 966, 899, 875, 801, 747, 683.

HRMS (EI) calculated for $C_5H_8IN_3^{\cdot+}$: 236.9757, found 236.9758 $[M]^{\cdot+}$.

5-Allyl-1-propyl-1*H*-1,2,4-triazole (35b)



5-Allyl-1-propyl-1*H*-1,2,4-triazole was prepared according to **TP7**. After the metalation a solution of CuCN·2LiCl (0.04 mL, 0.04 mmol, 20%, 1.0 M in THF) and allyl bromide (0.07 mL, 0.60 mmol) were added. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) yielded the title compound **35b** (63 mg, 0.42 mmol, 83%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.83 (s, 1 H), 5.96 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1 H), 5.23 – 5.10 (m, 2 H), 4.05 – 3.98 (m, 2 H), 3.56 (d, *J* = 6.3 Hz, 2 H), 1.87 (h, *J* = 7.4 Hz, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

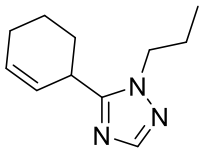
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 153.0, 150.4, 131.9, 118.3, 50.0, 30.6, 23.3, 11.2.

MS (70 eV, EI) *m/z* (%): 151 (17) $[M]^{\cdot+}$, 150 (100), 136 (14), 123 (40), 122 (79), 110 (34), 108 (80), 84 (26), 83 (16), 81 (11), 68 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3426, 3084, 2968, 2936, 2878, 2361, 1740, 1642, 1511, 1483, 1427, 1401, 1348, 1275, 1185, 1152, 1090, 1047, 994, 920, 877, 811, 748, 688, 678.

HRMS (EI) calculated for $C_8H_{13}N_3^{\cdot+}$: 151.1104, found 151.1101 $[M]^{\cdot+}$.

5-(Cyclohex-2-en-1-yl)-1-propyl-1*H*-1,2,4-triazole (35c)



5-(Cyclohex-2-en-1-yl)-1-propyl-1*H*-1,2,4-triazole was prepared according to **TP7**. After the metalation a solution of CuCN·2LiCl (0.04 mL, 0.04 mmol, 20%, 1.0 M in THF) and 3-bromocyclohexene (0.05 mL, 0.60 mmol) were added. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) yielded the title compound **35c** (84 mg, 0.44 mmol, 88%) as a pale yellow solid.

^{1}H-NMR (CDCl$_3$, 400 MHz, ppm): δ = 7.81 (s, 1 H), 6.01 – 5.91 (m, 1 H), 5.64 (dd, *J* = 10.0, 2.2 Hz, 1 H), 4.12 – 3.99 (m, 2 H), 3.70 – 3.62 (m, 1 H), 2.25 – 1.97 (m, 3 H), 1.96 – 1.76 (m, 4 H), 1.72 – 1.59 (m, 1 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

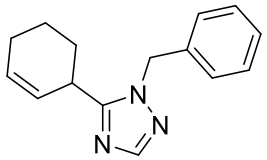
^{13}C-NMR (CDCl$_3$, 101 MHz, ppm): δ = 158.0, 150.3, 130.2, 125.4, 49.9, 33.3, 28.5, 24.6, 23.6, 21.1, 11.3.

MS (70 eV, EI) *m/z* (%): 192 (4) $[M]^{\cdot+}$, 191 (7), 190 (17), 176 (32), 163 (25), 162 (100), 150 (15), 148 (41), 134 (28), 120 (61), 108 (13), 96 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3433, 3027, 2935, 2877, 2361, 1653, 1506, 1470, 1398, 1348, 1273, 1217, 1188, 1133, 1052, 1040, 992, 932, 898, 882, 842, 807, 772, 744, 720, 671.

HRMS (EI) calculated for $C_{11}H_{17}N_3^{\cdot+}$: 191.1417, found 191.1415 $[M]^{\cdot+}$.

5-(Cyclohex-2-en-1-yl)-1-benzyl-1*H*-1,2,4-triazole (35d)



5-(Cyclohex-2-en-1-yl)-1-benzyl-1*H*-1,2,4-triazole was prepared according to **TP7**. After the metalation a solution of CuCN·2LiCl (0.04 mL, 0.04 mmol, 20%, 1.0 M in THF) and 3-bromocyclohexene (0.05 mL, 0.60 mmol) were added. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) yielded the title compound **35d** (96 mg, 0.40 mmol, 80%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.88 (s, 1 H), 7.43 – 7.29 (m, 3 H), 7.20 – 7.15 (m, 2 H), 5.95 (ddt, *J* = 10.0, 4.2, 2.8 Hz, 1 H), 5.61 – 5.55 (m, 1 H), 5.37 (s, 2 H), 3.67 (ddp, *J* = 8.5, 5.7, 2.8 Hz, 1 H), 2.22 – 2.00 (m, 2 H), 1.95 – 1.80 (m, 2 H), 1.80 – 1.70 (m, 1 H), 1.67 – 1.54 (m, 1 H).

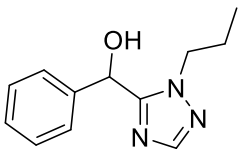
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 158.5, 150.7, 135.7, 130.0, 128.9, 128.2, 127.1, 125.2, 52.0, 33.4, 28.2, 24.5, 20.9.

MS (70 eV, EI) *m/z* (%): 239 (19) $[M]^{\cdot+}$, 238 (43), 210 (58), 207 (38), 172 (10), 148 (25), 133 (13), 120 (25), 106 (18), 91 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3031, 2937, 1710, 1676, 1497, 1455, 1397, 1360, 1274, 1222, 1188, 1136, 1089, 1030, 991, 884, 803, 770, 719, 694, 670.

HRMS (EI) calculated for $C_{15}H_{17}N_3^{\cdot}$: 239.1422, found 239.1421 $[M]^{\cdot}$.

Phenyl(1-propyl-1*H*-1,2,4-triazol-5-yl)methanol (35e)



Phenyl(1-propyl-1*H*-1,2,4-triazol-5-yl)methanol was prepared according to **TP7** using benzaldehyde (0.06 mL, 0.60 mmol) as electrophile. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 1:1 + 5% triethylamine) yielded the title compound **35e** (103 mg, 0.48 mmol, 95%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.82 (s, 1 H), 7.40 – 7.28 (m, 5 H), 6.02 (s, 1 H), 3.94 – 3.88 (m, 2 H), 1.62 (h, *J* = 7.4 Hz, 2 H), 0.78 – 0.71 (m, 3 H).

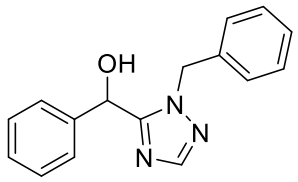
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 156.1, 149.5, 139.5, 129.0, 128.7, 126.6, 68.6, 50.6, 22.8, 11.0.

MS (70 eV, EI) *m/z* (%): 217 (60) $[M]^{\cdot+}$, 216 (12), 184 (13), 175 (17), 174 (40), 170 (100), 158 (41), 143 (48), 140 (18), 118 (26), 116 (14), 110 (20), 105 (28), 98 (26), 77 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3202, 2967, 2936, 2877, 1652, 1603, 1492, 1451, 1385, 1321, 1281, 1228, 1184, 1155, 1086, 1058, 1027, 984, 900, 877, 849, 800, 749, 718, 697, 674.

HRMS (EI) calculated for $C_{12}H_{15}N_3O^{\cdot+}$: 217.1210, found 217.1208 $[M]^{\cdot+}$.

Phenyl(1-benzyl-1*H*-1,2,4-triazol-5-yl)methanol (35f)



Phenyl(1-benzyl-1H-1,2,4-triazol-5-yl)methanol was prepared according to **TP7** using benzaldehyde (0.06 mL, 0.60 mmol) as electrophile. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 2:1 + 5% triethylamine) yielded the title compound **35f** (121 mg, 0.46 mmol, 91%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = δ 7.88 (s, 1 H), 7.37 – 7.28 (m, 5 H), 7.29 – 7.23 (m, 2 H), 7.05 – 6.98 (m, 2 H), 6.00 (s, 2 H), 5.27 (d, *J* = 15.2 Hz, 1 H), 5.10 (d, *J* = 15.2 Hz, 1 H), 2.89 (br. s, 1 H).

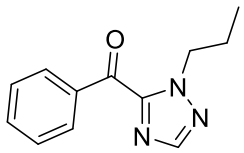
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 156.2, 149.4, 139.0, 134.6, 129.1, 128.9, 128.8, 128.5, 127.8, 126.8, 68.7, 52.9.

MS (70 eV, EI) *m/z* (%): 265 (6) $[M]^{\cdot+}$, 247 (37), 246 (16), 186 (19), 174 (100), 170 (15), 167 (13), 158 (28), 131 (14), 117 (17), 105 (36), 104 (27), 96 (13), 91 (67), 77 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3064, 2862, 2361, 1602, 1494, 1453, 1436, 1399, 1358, 1334, 1303, 1280, 1264, 1178, 1099,1071, 1052, 1028, 989, 954, 899, 853, 779, 735, 714, 699, 690.

HRMS (EI) calculated for $C_{16}H_{15}N_3O^{\cdot+}$: 265.1210, found 265.1212 $[M]^{\cdot+}$.

Phenyl(1-propyl-1*H*-1,2,4-triazol-5-yl)methanone (35g)



Phenyl(1-propyl-1*H*-1,2,4-triazol-5-yl)methanone was prepared according to **TP7** using benzoyl chloride (0.07 mg, 0.60 mmol) as electrophile. Purification via column chromatography (silica gel, *i*hexane + 5% triethylamine) yielded the title compound **35g** (95 mg, 0.44 mmol, 88%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.33 – 8.27 (m, 2 H), 8.03 (s, 1 H), 7.69 – 7.61 (m, 1 H), 7.57 – 7.48 (m, 2 H), 4.59 – 4.53 (m, 2 H), 1.96 (h, *J* = 7.4 Hz, 2 H), 0.97 (t, *J* = 7.4 Hz, 3 H).

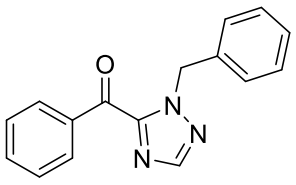
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 183.7, 150.1, 149.1, 136.1, 134.2, 131.0, 128.7, 52.9, 23.8, 11.1.

MS (70 eV, EI) *m/z* (%): 215 (16) $[M]^{+}$, 214 (57), 187 (11), 186 (100), 108 (15), 105 (35), 77 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2968, 2878, 1659, 1598, 1579, 1495, 1449, 1431, 1375, 1266, 1212, 1178, 1144, 1063, 1002, 977, 912, 807, 737, 680.

HRMS (EI) calculated for $C_{12}H_{13}N_3O^{+}$: 215.1053, found 215.1051 $[M]^{+}$.

(1-Benzyl-1*H*-1,2,4-triazol-5-yl)(phenyl)methanone (35h)



(1-Benzyl-1*H*-1,2,4-triazol-5-yl)(phenyl)methanone was prepared according to **TP7** using benzaldehyde (0.06 mL, 0.60 mmol) as electrophile. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 2:1 + 5% triethylamine) yielded the title compound **35h** (104 mg, 0.40 mmol, 79%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.26 – 8.20 (m, 2 H), 7.99 (s, 1 H), 7.60 – 7.53 (m, 1 H), 7.47 – 7.41 (m, 2 H), 7.34 – 7.20 (m, 5 H), 5.74 (s, 2 H).

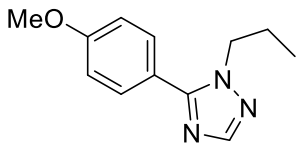
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 183.4, 150.4, 148.9, 135.8, 135.5, 134.1, 131.0, 128.8, 128.5, 128.3, 128.2, 54.5.

MS (70 eV, EI) *m/z* (%): 264 (13), 263 (79) $[M]^{\cdot+}$, 262 (29), 236 (15), 235 (36), 186 (10), 160 (12), 158 (52), 157 (37), 133 (18), 131 (100), 116 (13), 105 (75), 104 (66), 91 (23), 77 (44).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3064, 1659, 1597, 1578, 1495, 1484, 1448, 1426, 1372, 1319, 1266, 1175, 1098, 1072, 1029, 1002, 976, 911, 807, 785, 717, 681.

HRMS (EI) calculated for $C_{16}H_{13}N_3O^{\cdot+}$: 263.1053, found 263.1055 $[M]^{\cdot+}$.

5-(4-Methoxyphenyl)-1-propyl-1*H*-1,2,4-triazole (35i)



5-(4-Methoxyphenyl)-1-propyl-1H-1,2,4-triazole was prepared according to **TP8** using 4-bromoanisole (112 mg, 0.6 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) yielded the title compound **35i** (99 mg, 0.46 mmol, 91%) as an orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.95 (s, 1 H), 7.59 – 7.54 (m, 2 H), 7.05 – 7.00 (m, 2 H), 4.20 – 4.13 (m, 2 H), 3.87 (s, 3 H), 1.92 (h, *J* = 7.4 Hz, 2 H), 0.90 (t, J = 7.4 Hz, 3 H).

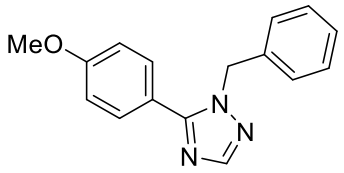
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 161.1, 154.5, 150.5, 130.4, 120.3, 114.5, 55.6, 50.9, 23.5, 11.2.

MS (70 eV, EI) *m/z* (%): 217 (32) $[M]^{\cdot+}$, 188 (63), 175 (100), 160 (25), 134 (90), 133 (13), 132 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3426, 2965, 2936, 2877, 2839, 2361, 2049, 1740, 1613, 1579, 1541, 1486, 1461, 1440, 1384, 1297, 1277, 1250, 1177, 1163, 1111, 1085, 1031, 1017, 1003, 973, 900, 880, 836, 798, 748, 713, 669.

HRMS (EI) calculated for $C_{12}H_{15}N_3O^{\cdot+}$: 217.1210, found 217.1209 $[M]^{\cdot+}$.

5-(4-Methoxyphenyl)-1-benzyl-1*H*-1,2,4-triazole (35j)



5-(4-Methoxyphenyl)-1-benzyl-1*H*-1,2,4-triazole was prepared according to **TP8** using 4-iodoanisole (140 mg, 0.6 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) yielded the title compound **35j** (103 mg, 0.39 mmol, 78%) as an colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.00 (s, 1 H), 7.52 (d, *J* = 8.8 Hz, 2 H), 7.41 – 7.28 (m, 3 H), 7.16 (d, *J* = 6.6 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 5.42 (s, 2 H), 3.85 (s, 3 H).

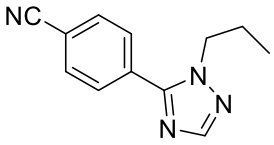
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 161.2, 155.3, 151.3, 136.1, 130.3, 129.1, 128.2, 127.0, 120.3, 114.4, 55.5, 52.8.

MS (70 eV, EI) *m/z* (%): 265 (100) $[M]^{\cdot+}$, 264 (26), 132 (15), 131 (12), 119 (11), 91 (55).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3032, 2938, 2837, 1612, 1578, 1541, 1486, 1462, 1439, 1381, 1298, 1276, 1252, 1176, 1124, 1112, 1077, 1037, 1020, 1005, 973, 883, 836, 779, 748, 726, 694, 668.

HRMS (EI) calculated for $C_{16}H_{15}N_3O^{\cdot+}$: 265.1210, found 265.1210 $[M]^{\cdot+}$.

4-(1-Benzyl-1*H*-1,2,4-triazol-5-yl)benzonitrile (35k)



4-(1-Benzyl-1*H*-1,2,4-triazol-5-yl)benzonitrile was prepared according to **TP8** using 4-iodobenzonitrile (137 mg, 0.6 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) yielded the title compound **35k** (100 mg, 0.47 mmol, 94%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.00 (s, 1 H), 7.84 – 7.80 (m, 2 H), 7.79 – 7.75 (m, 2 H), 4.23 – 4.15 (m, 2 H), 1.94 (h, *J* = 7.4 Hz, 2 H), 0.90 (t, *J* = 7.4 Hz, 3 H).

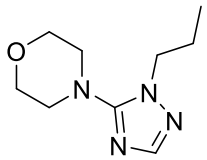
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 152.9, 151.2, 132.8, 132.5, 129.6, 118.1, 114.1, 51.3, 23.5, 11.1.

MS (70 eV, EI) *m/z* (%): 212 (11) $[M]^{\cdot+}$, 211 (26), 184 (17), 183 (70), 170 (100), 143 (34), 129 (40).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2968, 2879, 2231, 1614, 1485, 1462, 1406, 1385, 1283, 1283, 1241, 1197, 1182, 1164, 1111, 1010, 974, 901, 845, 804, 782, 747, 713, 700.

HRMS (EI) calculated for $C_{12}H_{12}N_4^{\cdot+}$: 212.1056, found 212.1055 $[M]^{\cdot+}$.

4-(1-Propyl-1*H*-1,2,4-triazol-5-yl)morpholine (35l)



4-(1-Propyl-1*H*-1,2,4-triazol-5-yl)morpholine was prepared according to **TP9** using morpholino benzoate (124 mg, 0.6 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 2:1 + 5% triethylamine) yielded the title compound **35l** (71 mg, 0.36 mmol, 72%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.67 (s, 1 H), 3.94 – 3.89 (m, 2 H), 3.86 – 3.82 (m, 4 H), 3.17 – 3.12 (m, 4 H), 1.90 (h, *J* = 7.4 Hz, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H).

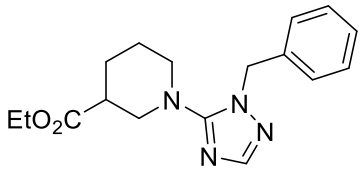
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 158.4, 149.2, 66.6, 51.0, 49.4, 22.6, 11.3.

MS (70 eV, EI) *m/z* (%): 196 (6) $[M]^{\cdot+}$, 167 (28), 139 (100), 123 (19), 97 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3434, 2966, 2855, 2362, 1636, 1523, 1492, 1451, 1412, 1371, 1331, 1304, 1272, 1262, 1200, 1175, 1146, 1115, 1072, 1036, 975, 947, 928, 876, 846, 805, 752, 661.

HRMS (EI) calculated for $C_9H_{16}N_4O^{\cdot+}$: 196.1319, found 196.1316 $[M]^{\cdot+}$.

Ethyl 1-(1-benzyl-1*H*-1,2,4-triazol-5-yl)piperidine-3-carboxylate (35m)



Ethyl 1-(1-benzyl-1*H*-1,2,4-triazol-5-yl)piperidine-3-carboxylate was prepared according to **TP9** using ethyl 1-(benzoyloxy)piperidine-3-carboxylate (166 mg, 0.6 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 2:1 + 5% triethylamine) yielded the title compound **35m** (94 mg, 0.35 mmol, 70%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.63 (s, 1 H), 7.30 – 7.21 (m, 3 H), 7.19 – 7.14 (m, 2 H), 5.15 (d, *J* = 2.3 Hz, 2 H), 4.14 – 3.90 (m, 2 H), 3.30 (ddt, *J* = 12.2, 3.8, 1.3 Hz, 1 H), 3.15 – 3.03 (m, 2 H), 2.87 (ddd, *J* = 12.2, 9.4, 3.0 Hz, 1 H), 2.66 – 2.53 (m, 1 H), 1.97 – 1.75 (m, 1 H), 1.76 – 1.67 (m, 2 H), 1.15 (t, *J* = 7.1 Hz, 4 H).

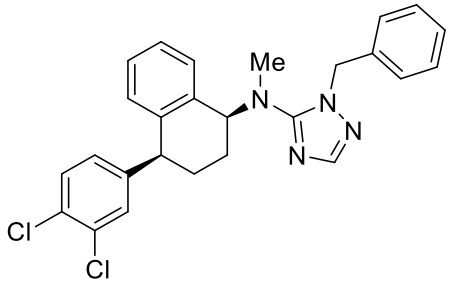
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 173.1, 159.1, 149.6, 135.8, 128.8, 127.9, 127.3, 60.7, 52.7, 51.3, 51.1, 41.0, 26.2, 23.9, 14.2.

MS (70 eV, EI) *m/z* (%): 314 (11) $[M]^{+}$, 313 (55), 269 (15), 241 (86), 237 (26), 207 (29), 177 (19), 156 (16), 149 (17), 91 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2940, 2855, 1985, 1726, 1636, 1526, 1488, 1454, 1381, 1309, 1273, 1181, 1128, 1096, 1030, 963, 939, 859, 727, 696, 658.

HRMS (EI) calculated for $C_{17}H_{22}N_4O_2^{\cdot}$: 314.1743, found 314.1746 $[M]^{\cdot}$.

1-Benzyl-*N*-((1*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methyl-1*H*-1,2,4-triazol-5-amine (35n)



1-Benzyl-*N*-((1*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methyl-1*H*-1,2,4-triazol-5-amine was prepared according to **TP9** using *O*-benzoyl-*N*-((1*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methylhydroxylamine (256 mg,

0.6 mmol). Purification via column chromatography (silica gel, *i*hexane / EtOAc = 2:1 + 5% triethylamine) yielded the title compound **35n** (220 mg, 0.48 mmol, 95%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.63 (s, 1 H), 7.35 – 7.15 (m, 5 H), 7.15 – 7.04 (m, 4 H), 6.99 (d, J = 2.1 Hz, 1 H), 6.84 (dd, *J* = 7.0, 2.0 Hz, 1 H), 6.71 (dd, *J* = 8.3, 2.1 Hz, 1 H), 5.33 – 5.15 (m, 2 H), 4.72 (dd, *J* = 10.4, 5.8 Hz, 1 H), 4.03 (dd, *J* = 5.8, 3.1 Hz, 1 H), 2.64 (s, 3 H), 2.08 – 1.53 (m, 4 H).

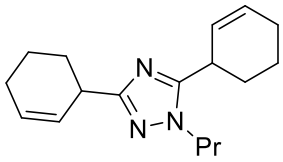
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 159.3, 149.3, 147.1, 138.3, 136.3, 132.3, 130.8, 130.7, 130.1, 130.1, 128.9, 128.0, 128.0, 127.6, 127.5, 127.4, 126.6, 60.5, 52.2, 43.1, 33.6, 29.9, 20.4.

MS (70 eV, EI) *m/z* (%): 464 (27) $[M]^{+}$, 462 (42), 447 (22), 277 (36), 275 (58), 188 (56), 187 (33), 160 (61), 158 (100), 129 (60), 91 (94).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2938, 1540, 1488, 1466, 1453, 1417, 1395, 1356, 1317, 1279, 1204, 1131, 1080, 1029, 986, 964, 920, 878, 849, 817, 791, 768, 727, 704, 694, 678, 665.

HRMS (EI) calculated for $C_{26}H_{24}Cl_2N_4^{\cdot+}$: 462.1373, found 462.1372 $[M]^{\cdot+}$.

3,5-Di(cyclohex-2-en-1-yl)-1-propyl-1*H*-1,2,4-triazole (37a)



3,5-Di(cyclohex-2-en-1-yl)-1-propyl-1H-1,2,4-triazole was prepared according to **TP10**. After the metalation a solution of CuCN·2LiCl (0.04 mL, 0.04 mmol, 20%, 1.0 M in THF) and 3-bromocyclohexene (0.25 mL, 2.2 mmol)) were added. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 9:1 + 5% triethylamine) yielded the title compound **37a** (99 mg, 0.37 mmol, 73%) as an orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.96 – 5.80 (m, 3 H), 5.67 – 5.60 (m, 1 H), 4.05 – 3.89 (m, 2 H), 3.69 – 3.49 (m, 2 H), 2.22 – 1.95 (m, 6 H), 1.93 – 1.71 (m, 6 H), 1.68 – 1.56 (m, 2 H), 0.91 (t, *J* = 7.4 Hz, 3 H).

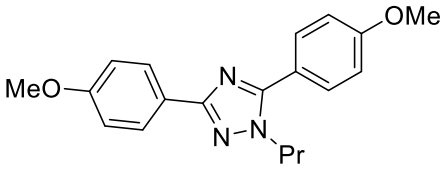
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 165.9, 157.9, 129.7, 128.4, 127.8, 125.8, 49.6, 35.7, 33.8, 29.0, 28.6, 24.9, 24.5, 23.7, 21.5, 21.2, 11.1.

MS (70 eV, EI) *m/z* (%): 271 (100) $[M]^{\cdot+}$, 270 (78), 256 (45), 242 (66), 230 (11), 228 (53), 216 (12), 214 (36), 205 (29), 200 (42), 190 (12), 188 (17), 176 (14), 163 (16), 148 (11), 81 (13), 79 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3026, 2933, 2875, 2836, 2362, 1652, 1497, 1447, 1435, 1361, 1326, 1297, 1258, 1239, 1218, 1190, 1155, 1134, 1063, 1044, 991, 932, 893, 850, 809, 722, 679.

HRMS (EI) calculated for $C_{17}H_{25}N_3^{\cdot}$: 271.2048, found 271.2047 $[M]^{\cdot}$.

3,5-Bis(4-methoxyphenyl)-1-propyl-1*H*-1,2,4-triazole (37b)



3,5-Bis(4-methoxyphenyl)-1-propyl-1*H*-1,2,4-triazole was prepared according to **TP10**. After the metalation a solution of $ZnCl_2$ (2.0 mL, 2.0 mmol, 1.0 M in THF), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5%), SPhos (20.5 mg, 0.05 mmol, 10%) and 4-iodoanisole (515 mg, 2.2 mmol) were added. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) yielded the title compound **37b** (84 mg, 0.26 mmol, 52%) as an orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.12 – 8.04 (m, 2 H), 7.63 – 7.56 (m, 2 H), 7.06 – 6.99 (m, 2 H), 6.98 – 6.93 (m, 2 H), 4.19 – 4.11 (m, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 1.95 (h, *J* = 7.4 Hz, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

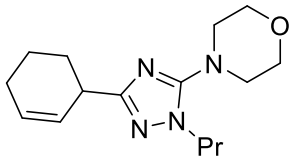
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 161.1, 161.0, 160.5, 155.5, 130.4, 127.9, 124.2, 121.0, 114.4, 114.0, 55.6, 55.4, 50.9, 23.7, 11.2.

MS (70 eV, EI) *m/z* (%): 323 (100) $[M]^{\cdot+}$, 295 (11), 294 (67), 282 (13), 281 (77), 267 (11), 207 (16), 161 (21), 134 (45), 133 (76).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2963, 2936, 2837, 2361, 1739, 1612, 1532, 1465, 1441, 1349, 1294, 1245, 1169, 1134, 1107, 1029, 981, 902, 836, 797, 764, 736, 692.

HRMS (EI) calculated for $C_{19}H_{21}N_3O^{\cdot+}$: 323.1628, found 323.1627 $[M]^{\cdot+}$.

4-(3-(Cyclohex-2-en-1-yl)-1-propyl-1*H*-1,2,4-triazol-5-yl)morpholine (37c)



4-(1-Propyl-1*H*-1,2,4-triazol-5-yl)morpholino (**35l**, 86 mg, 0.44 mmol, 1.0 equiv) was dissolved in THF (1.5 mL) and cooled to 0 °C. TMPMgCl·LiCl solution (**33**, 0.88 mmol, 2.0 equiv) was slowly added to the vigorously stirred solution. After 30 min a solution of CuCN·2LiCl (0.04 mL, 0.04 mmol, 20%, 1.0 M in THF) and 3-bromocyclohexene (0.05 mL, 0.60 mmol) were added. After stirring for 30 min the mixture was quenched with sat. aq. NH_4Cl solution (15 mL), extracted with DCM (3×15 mL) and dried over anhydrous $MgSO_4$. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) yielded the title compound **37c** (97 mg, 0.35 mmol, 80%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 5.86 – 5.75 (m, 2 H), 3.85 – 3.79 (m, 2 H), 3.79 – 3.73 (m, 4 H), 3.42 (ddd, *J* = 8.7, 5.7, 3.0 Hz, 1 H), 3.10 – 3.03 (m, 4 H), 2.11 – 1.94 (m, 3 H), 1.87 – 1.66 (m, 4 H), 1.62 – 1.50 (m, 1 H), 0.86 (t, *J* = 7.4 Hz, 3 H).

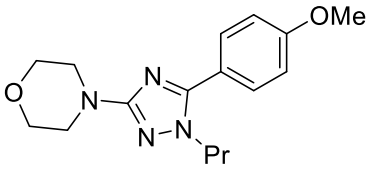
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 164.5, 158.5, 128.4, 127.6, 66.6, 50.9, 49.0, 36.0, 28.7, 24.9, 22.7, 21.2, 11.1.

MS (70 eV, EI) *m/z* (%): 276 (60) $[M]^{+}$, 275 (19), 247 (37), 233 (20), 220 (13), 219 (100), 210 (19), 205 (14), 203 (11), 189 (10), 177 (31), 167 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2935, 2858, 1713, 1530, 1497, 1453, 1372, 1261, 1219, 1117, 1072, 1029, 984, 964, 945, 921, 881, 849, 792, 727, 678.

HRMS (EI) calculated for $C_{15}H_{24}N_4O^{+}$: 276.1945, found 276.1946 $[M]^{+}$.

4-(5-(4-methoxyphenyl)-1-propyl-1H-1,2,4-triazol-3-yl)morpholine (37d)



5-(4-Methoxyphenyl)-1-propyl-1H-1,2,4-triazole (**35i**, 95 mg, 0.44 mmol, 1.0 equiv) was dissolved in THF (1.5 mL) and cooled to 0 °C. TMPZnCl·LiCl solution (**36**, 0.53 mmol, 1.2 equiv) was slowly added to the vigorously stirred solution. A dry, argon flushed *Schlenk*-

flask equipped with a magnetic stirring bar and a septum was charged with morpholino benzoate (109 mg, 0.53 mmol, 1.2 equiv), copper (II) triflate (36 mg, 0.1 mmol, 20%) and THF (2.0 mL). After 30 min the metalated species was slowly added to the 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 $MgSO_4$. Purification via column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) yielded the title compound **37d** (115 mg, 0.38 mmol, 87%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.54 – 7.47 (m, 2 H), 7.02 – 6.95 (m, 2 H), 4.01 – 3.92 (m, 2 H), 3.85 (s, 3 H), 3.84 – 3.79 (m, 4 H), 3.48 – 3.41 (m, 4 H), 1.86 (h, *J* = 7.4 Hz, 2 H), 0.87 (t, *J* = 7.4 Hz, 3 H).

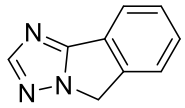
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 161.0, 153.8, 142.3, 138.1, 130.4, 114.4, 66.7, 55.5, 50.5, 47.2, 23.4, 11.2.

MS (70 eV, EI) *m/z* (%): 303 (14) $[M]^{\cdot+}$, 302 (93), 287 (24), 271 (26), 271 (17), 246 (11), 245 (100), 244 (29), 243 (16), 229 (10), 215 (32), 203 (31), 202 (27), 188 (12), 134 (36).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3442, 2964, 2838, 2361, 1614, 1579, 1547, 1527, 1482, 1452, 1411, 1379, 1357, 1331, 1304, 1273, 1250, 1174, 1115, 1073, 1032, 1002, 926, 902, 835, 797, 765, 733, 661.

HRMS (EI) calculated for $C_{16}H_{22}N_4O_2^{+}$: 302.1737, found 302.1736 $[M]^{\cdot+}$.

5*H*-[1,2,4]Triazolo[5,1-*a*]isoindole (38)



A dry, argon flushed *Schlenk*-flask equipped with a magnetic stirring bar and a septum was charged with 1-(2-Iodobenzyl)-1*H*-1,2,4-triazole (**32c**, 143 mg, 0.5 mmol, 1.0 equiv) and THF (1.5 mL). The mixture was cooled down to 0 °C and a solution of TMPZnCl·LiCl (**36**, 0.75 mmol, 1.5 equiv) was slowly added. After 30 min a solution of CuCN·2LiCl (0.10 mL, 0.10 mmol, 20%, 1.0 M in THF) was added. The mixture was heated to 40 °C for 18 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (15 mL), extracted with DCM (3×15 mL) and dried over anhydrous $MgSO_4$. After filtration and evaporation, the crude product was purified by flash column chromatography (silica gel, *i*hexane / EtOAc = 4:1 + 5% triethylamine) to obtain 5*H*-[1,2,4]triazolo[5,1-*a*]isoindole **38** (0.147g, 0.47 mmol, 94%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.11 (s, 1 H), 7.98 – 7.91 (m, 1 H), 7.59 – 7.46 (m, 3 H), 5.10 (s, 2 H).

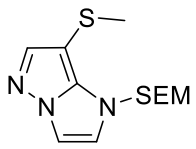
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 160.2, 155.8, 142.2, 129.7, 129.1, 127.1, 124.1, 121.9, 50.4.

MS (70 eV, EI) *m/z* (%): 157 (100) $[M]^{+}$, 130 (16), 129 (14), 103 (25), 102 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3088, 2954, 1722, 1539, 1506, 1447, 1403, 1317, 1274, 1248, 1215, 1191, 1175, 1136, 1101, 1011, 969, 941, 918, 895, 883, 816, 769, 730, 699, 689, 679, 655.

HRMS (EI) calculated for $C_9H_7N_3^{\cdot+}$: 157.0634, found 157.0632 $[M]^{+}$.

7-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole (43a)



7-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole was synthesized according to **TP11** on a 0.88 mmol scale using *S*-methyl benzenesulfonothioate (412 mg, 2.2 mmol, 2.5 equiv) as electrophile (30 min, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 2:1) yielded the title compound **43a** (206 mg, 0.73 mmol, 83%) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.60 (d, *J* = 1.1 Hz, 1 H), 7.27 (d, *J* = 2.3 Hz, 1 H), 6.83 (t, *J* = 2.3, 1.1 Hz, 1 H), 5.50 (s, 2 H), 3.57 (t, *J* = 8.1 Hz, 2 H), 2.23 (s, 2 H), 0.89 (t, *J* = 8.3 Hz, 2 H), –0.06 (s, 9 H).

^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 148.7, 141.3, 119.6, 109.5, 84.9, 75.4, 66.5, 22.7, 17.9, –1.4.

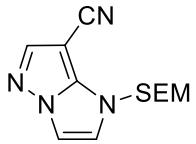
MS (70 eV, EI) *m/z* (%): 283 (27) $[M]^{+}$, 225 (14), 210 (19), 166 (21), 111 (9), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3156, 3111, 3055, 2951, 2917, 1588, 1539, 1466, 1442, 1416, 1317, 1288, 1273, 1248, 1218, 1172, 1151, 1096, 1069, 1009, 971, 930, 857, 834, 766, 728, 718, 706, 683.

HRMS (EI) calculated for $C_{12}H_{21}N_3OSSi^{\cdot+}$: 283.1169, found 283.1164 $[M]^{+}$.

mp: 63.6 – 65.0 °C.

1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (43b)



1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile was synthesized according to **TP11** on a 5.0 mmol scale using tosyl cyanide (2.2 g, 11 mmol, 2.2 equiv) as electrophile (1 h, 25 °C). The white solid that was formed during the reaction was filtered off through a pad of Celite before the work-up. Purification via column chromatography (silica gel, *i*Hex/EtOAc = 2:1 + 5% Net_3) yielded the title compound **43b** (1.31 g, 4.79 mmol, 96%) as a slightly yellow solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.56 (d, *J* = 1.1 Hz, 1 H), 6.62 (d, *J* = 2.3 Hz, 1 H), 5.86 (dd, *J* = 2.2, 1.2 Hz, 1 H), 4.62 (s, 2 H), 3.42 (t, *J* = 8.1 Hz, 2 H), 0.79 (t, *J* = 8.1 Hz, 2 H), −0.08 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 146.3, 141.7, 120.0, 114.3, 109.9, 76.1, 67.7, 67.3, 17.7, −1.4.

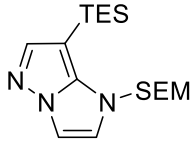
MS (70 eV, EI) *m/z* (%): 262 (24) $[M]^{\cdot+}$, 219 (14), 204 (100), 189 (30), 145 (14), 73 (65).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3150, 3102, 3055, 2953, 2920, 2896, 2869, 2216, 1611, 1543, 1491, 1478, 1454, 1399, 1381, 1335, 1309, 1289, 1260, 1245, 1225, 1196, 1179, 1123, 1085, 1068, 1035, 1018, 972, 916, 875, 843, 832, 779, 742, 721, 709, 690, 663.

HRMS (EI) calculated for $C_{12}H_{18}N_4OSi^{\cdot+}$: 262.1244, found 262.1245 $[M]^{\cdot+}$.

mp: 79.0 – 79.6 °C.

7-(Triethylsilyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole (43c)



7-(Triethylsilyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole was synthesized according to **TP11** on a 0.20 mmol scale using TESCl (75 mg, 0.50 mmol, 2.5 equiv) as electrophile (2 h, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:1) yielded the title compound **43c** (53 mg, 0.15 mmol, 76%) as a colorless liquid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.92 (s, 1 H), 6.99 (d, *J* = 2.3 Hz, 1 H), 6.03 – 6.01 (m, 1 H), 4.74 (s, 2 H), 3.23 (t, *J* = 8.0 Hz, 2 H), 1.04 (t, *J* = 7.8 Hz, 9 H), 0.87 (q, *J* = 7.7 Hz, 6 H), 0.79 (t, *J* = 8.1 Hz, 2 H), –0.09 (s, 9 H).

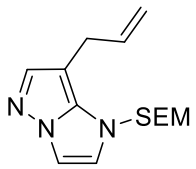
^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 150.4, 145.8, 119.6, 108.4, 82.4, 77.0, 65.9, 17.7, 7.9, 5.1, –1.4.

MS (70 eV, EI) *m/z* (%): 351 (16) $[M]^{+}$, 292 (14), 264 (52), 250 (14), 236 (12), 234 (38), 220 (24), 208 (28), 192 (16), 178 (14), 165 (21), 164 (11), 150 (20), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3132, 2952, 2874, 1565, 1543, 1458, 1413, 1376, 1321, 1248, 1158, 1075, 1041, 1003, 971, 916, 833, 691.

HRMS (EI) calculated for $C_{17}H_{33}N_3OSi_2^{+}$: 351.2157, found 351.2156 $[M]^{+}$.

7-Allyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole (43d)



7-Allyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole was synthesized according to **TP11** on a 1.69 mmol scale using allyl bromide (0.37 mL, 4.23 mmol, 2.5 equiv) and CuCN·2LiCl (1.0 M in THF, 0.34 mL, 0.34 mmol, 0.20 equiv) as electrophile (30 min, 25 °C.). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 3:7) yielded the title compound **43d** (438 mg, 1.58 mmol, 94%) as a colorless liquid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.67 (s, 1 H), 6.93 (d, *J* = 2.3 Hz, 1 H), 6.03 – 5.93 (m, 2 H), 5.09 – 4.95 (m, 2 H), 4.65 (s, 2 H), 3.37 – 3.31 (m, 2 H), 3.23 (t, *J* = 7.8 Hz, 2 H), 0.74 (t, *J* = 7.8 Hz, 2 H), –0.11 (s, 9 H).

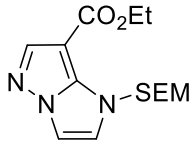
^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 143.8, 139.9, 139.4, 119.4, 114.6, 108.5, 92.6, 76.4, 65.8, 28.4, 17.7, –1.4.

MS (70 eV, EI) *m/z* (%): 277 (38) $[M]^{+}$, 219 (27), 218 (36), 204 (21), 192 (34), 191 (14), 160 (42), 133 (22), 119 (14), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3130, 2952, 2894, 1638, 1609, 1544, 1490, 1413, 1379, 1322, 1247, 1216, 1169, 1074, 994, 914, 832, 758, 688.

HRMS (EI) calculated for $C_{14}H_{23}N_3OSi^{\cdot+}$: 277.1605, found 277.1603 $[M]^{\cdot+}$.

Ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carboxylate (43e)



Ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carboxylate was synthesized according to **TP11** on a 0.20 mmol scale using ethyl cyanoformate (0.05 mL, 0.5 mmol, 2.5 equiv) and CuCN·2LiCl (1.0 M in THF, 0.20 mL, 0.20 mmol, 1.0 equiv) as electrophile (2 h, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:1) yielded the title compound **43e** (31 mg, 0.10 mmol, 50%) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.02 (d, *J* = 1.1 Hz, 1 H), 7.37 (d, *J* = 2.2 Hz, 1 H), 6.95 (t, *J* = 2.2, 1.1 Hz, 1 H), 5.82 (s, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 3.56 (t, *J* = 8.2 Hz, 2 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 0.88 (t, *J* = 8.2 Hz, 2 H), –0.07 (s, 9 H).

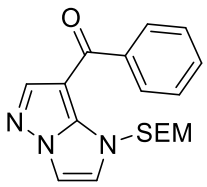
^{13}C-NMR ($CDCl_3$, 101 MHz, ppm): δ = 163.2, 146.2, 140.8, 120.2, 110.1, 91.9, 76.8, 66.4, 59.9, 17.9, 14.7, –1.4.

MS (70 eV, EI) *m/z* (%): 309 (9) $[M]^{\cdot+}$, 279 (10), 251 (37), 250 (42), 238 (11), 236 (34), 223 (13), 208 (49), 206 (14), 192 (25), 182 (13), 164 (35), 148 (29), 134 (18), 133 (100), 73 (49).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3132, 2953, 2898, 1687, 1597, 1548, 1488, 1394, 1375, 1344, 1292, 1269, 1248, 1204, 1194, 1174, 1085, 1056, 971, 916, 856, 833, 768, 731, 691.

HRMS (EI) calculated for $C_{14}H_{23}N_3O_3Si^{\cdot+}$: 309.1503, found 309.1502 $[M]^{\cdot+}$.

Phenyl(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)methanone (43f)



Phenyl(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)methanone was synthesized according to **TP11** on a 0.2 mmol scale using benzoyl chloride (0.035 mL, 0.50 mmol, 2.5 equiv) as electrophile and $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol, 5%) as catalyst (2 h, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 7:3) yielded the title compound **43f** (41 mg, 0.12 mmol, 60%) as a colorless liquid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 8.04 – 8.00 (m, 1 H), 7.94 (dd, *J* = 7.9, 1.6 Hz, 2 H), 7.21 – 7.10 (m, 3 H), 6.85 (d, *J* = 2.0 Hz, 1 H), 6.24 (dd, *J* = 2.1, 1.2 Hz, 1 H), 5.83 (s, 2 H), 3.65 (t, *J* = 8.0 Hz, 2 H), 0.89 (t, *J* = 8.0 Hz, 2 H), −0.09 (s, 9 H).

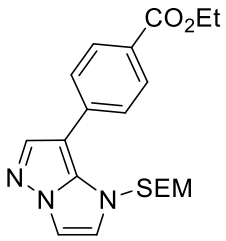
^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 186.6, 148.0, 142.0, 140.8, 131.2, 129.1, 128.5, 120.6, 109.8, 102.6, 77.3, 66.2, 17.9, −1.4.

MS (70 eV, EI) *m/z* (%): 341 (12) $[M]^{\cdot+}$, 298 (13), 283 (10), 282 (100), 269 (10), 268 (83), 255 (25), 241 (11), 240 (54), 224 (11), 206 (14), 73 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3128, 3066, 2952, 2892, 1614, 1599, 1568, 1481, 1418, 1365, 1324, 1293, 1269, 1248, 1217, 1195, 1176, 1124, 1068, 1028, 1013, 982, 936, 916, 899, 857, 831, 795, 760, 736, 694, 663.

HRMS (EI) calculated for $C_{18}H_{23}N_3O_2Si^{\cdot+}$: 341.1554, found 341.1549 $[M]^{\cdot+}$.

Ethyl 4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)benzoate (43g)



Ethyl 4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)benzoate was synthesized according to **TP11** on a 0.2 mmol scale using ethyl 4-iodobenzoate (166 mg, 0.60 mmol, 3.0 equiv) as electrophile and PEPPSI-*i*Pr (2.7 mg, 0.004 mmol, 2%) as catalyst (4 h, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 2:1) yielded the title compound **43g** (63 mg, 0.16 mmol, 82%) as a slightly yellow oil.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 8.27 (d, *J* = 8.4 Hz, 2 H), 7.89 (d, *J* = 1.1 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 6.91 (d, *J* = 2.3 Hz, 1 H), 6.00 (dd, *J* = 2.1, 1.1 Hz, 1 H), 4.65 (s, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.14 (t, *J* = 7.9 Hz, 2 H), 1.07 (t, *J* = 7.1 Hz, 3 H), 0.65 (t, *J* = 7.9 Hz, 2 H), –0.16 (s, 9 H).

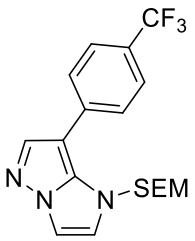
^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 166.3, 143.2, 138.7, 138.4, 130.7, 127.7, 127.0, 120.8, 108.7, 99.1, 76.1, 66.2, 60.7, 17.7, 14.4, –1.5.

MS (70 eV, EI) *m/z* (%): 385 (13) $[M]^{\cdot+}$, 327 (43), 268 (12), 210 (12), 209 (100), 195 (13), 194 (17), 181 (42), 154 (13), 73 (53).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3134, 2981, 2951, 2915, 1699, 1608, 1563, 1548, 1520, 1474, 1414, 1368, 1347, 1309, 1270, 1249, 1220, 1181, 1149, 1121, 1099, 1066, 1042, 1024, 1013, 993, 983, 935, 834, 772, 743, 715, 695.

HRMS (EI) calculated for $C_{20}H_{28}N_3O_3Si^{\cdot+}$: 385.1816, found 385.1815 $[M]^{\cdot+}$.

7-(4-(Trifluoromethyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]-pyrazole (43h)



7-(4-(Trifluoromethyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole was synthesized according to **TP11** on a 0.2 mmol scale using 1-iodo-4-(trifluoromethyl)-benzene (163 mg, 0.60 mmol, 3.0 equiv) as electrophile and PEPPSI-*i*Pr (2.7 mg, 0.004 mmol, 2%) as catalyst (2 h, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 1:1) yielded the title compound **43h** (67 mg, 0.18 mmol, 88%) as a slightly yellow solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.85 (s, 1 H), 7.51 – 7.39 (m, 4 H), 6.89 (d, *J* = 2.3 Hz, 1 H), 5.95 (s, 1 H), 4.58 (s, 2 H), 3.10 (t, *J* = 7.9 Hz, 2 H), 0.64 (t, *J* = 7.9 Hz, 2 H), −0.16 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 143.1, 138.3, 137.8, 127.4, 127.2 (q, *J* = 32.4 Hz), 126.0 (q, *J* = 3.9 Hz), 125.6 (q, *J* = 271.9 Hz) 120.7, 108.7, 98.4, 76.0, 66.2, 17.6, −1.5.

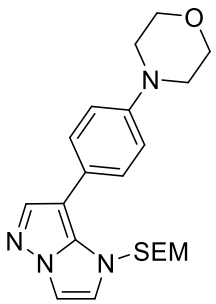
MS (70 eV, EI) *m/z* (%): 381 (20) $[M]^{+}$, 323 (56), 264 (47), 231 (36), 230 (38), 204 (12), 196 (11), 195 (15), 194 (22), 181 (17), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3178, 3114, 3069, 2952, 2892, 1614, 1592, 1553, 1523, 1481, 1464, 1416, 1367, 1325, 1298, 1260, 1249, 1223, 1193, 1174, 1162, 1150, 1105, 1061, 1031, 1012, 982, 937, 897, 859, 850, 831, 760, 745, 736, 671, 694, 686, 671, 666.

HRMS (EI) calculated for $C_{18}H_{22}F_3N_3OSi^{+}$: 381.1479, found 381.1477 $[M]^{+}$.

mp: 65.5 – 66.4 °C.

4-(4-(1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)phenyl)-morpholine (43i)



4-(4-(1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazol-7-yl)phenyl)morpholino was synthesized according to **TP11** on a 0.2 mmol scale using 4-(4-iodophenyl)morpholine (174 mg, 0.60 mmol, 3.0 equiv) as electrophile and PEPPSI-*i*Pr (2.7 mg, 0.004 mmol, 2%) as catalyst (2 h, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 1:1) yielded the title compound **43i** (54 mg, 0.14 mmol, 68%) as a slightly yellow solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 8.02 (d, *J* = 1.0 Hz, 1 H), 7.53 (d, *J* = 8.7 Hz, 2 H), 6.97 (d, *J* = 2.3 Hz, 1 H), 6.78 (d, *J* = 8.7 Hz, 2 H), 6.04 – 5.99 (m, 1 H), 4.78 (s, 2 H), 3.59 (t, *J* = 4.8 Hz, 4 H), 3.19 (t, *J* = 7.9 Hz, 2 H), 2.80 (t, *J* = 4.7 Hz, 4 H), 0.70 (t, *J* = 7.9 Hz, 2 H), –0.14 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 149.9, 142.9, 138.5, 129.0, 125.5, 120.2, 116.5, 108.8, 99.1, 75.8, 67.0, 66.1, 49.7, 17.8, –1.4.

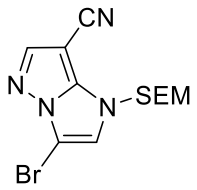
MS (70 eV, EI) *m/z* (%): 398 (17) $[M]^{\cdot+}$, 340 (11), 299 (12), 281 (36), 267 (19), 265 (12), 240 (13), 225 (60), 209 (31), 208 (14), 207 (100), 194 (15), 191 (23), 181 (15), 155 (14), 75 (28), 73 (46), 44 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3105, 2813, 1653, 1591, 1558, 1521, 1506, 1484, 1447, 1376, 1363, 1340, 1312, 1259, 1250, 1242, 1232, 1220, 1183, 1118, 1069, 1048, 991, 927, 853, 844, 828, 763, 739, 722, 702, 655.

HRMS (EI) calculated for $C_{21}H_{30}N_4O_2Si^{\cdot+}$: 398.2133, found 398.2134 $[M]^{\cdot+}$.

mp: 149.7 – 150.9 °C.

3-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (44)



1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (135 mg, 0.50 mmol, 1.0 equiv) was dissolved in MeCN (3.5 mL) and treated with N-bromosuccinimide (178 mg, 1.0 mmol, 2.0 equiv). After stirring for 80 min at 25 °C the solvent was removed *in vacuo* and the residue was directly purified via column chromatography (silica gel, *i*Hex/EtOAc = 4:1 + 5% Net_3) to yield the title compound **44** (79 mg, 0.35 mmol, 70%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.46 (d, *J* = 1.2 Hz, 1 H), 5.74 (d, *J* = 1.2 Hz, 1 H), 4.52 (s, 2 H), 3.38 (t, *J* = 8.0 Hz, 2 H), 0.79 (t, *J* = 8.0 Hz, 2 H), –0.07 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 146.4, 141.4, 119.6, 113.8, 94.7, 76.3, 69.2, 67.5, 17.7, –1.4.

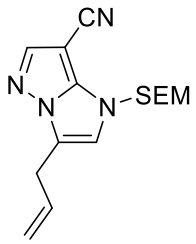
MS (70 eV, EI) *m/z* (%): 340 (0.2) $[M]^{\cdot+}$, 284 (72), 282 (71), 225 (10), 223 (10), 218 (32), 176 (35), 144 (13), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3132, 2952, 2922, 2897, 2211, 1607, 1544, 1485, 1456, 1418, 1380, 1362, 1336, 1304, 1288, 1251, 1190, 1172, 1124, 1104, 1089, 1058, 1036, 1026, 979, 938, 916, 903, 874, 856, 833, 789, 752, 733, 722, 697, 664.

HRMS (EI) calculated for $C_{12}H_{17}BrN_4OSi^{\cdot+}$: 340.0350, found 340.0349 $[M]^{\cdot+}$.

mp: 117.5 – 118.9 °C.

3-Allyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (45a)



3-Allyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile was synthesized according to **TP12** on a 0.2 mmol scale using allyl bromide (0.04 mL, 0.44 mmol, 2.2 equiv) and CuCN·2LiCl (1.0 M in THF, 0.04 mL, 0.04 mmol, 0.20 equiv) as electrophile (5 min, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:1 + 5% NEt_3) yielded the title compound **45a** (39 mg, 0.13 mmol, 65%) as a colorless liquid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.55 (d, *J* = 1.1 Hz, 1 H), 5.77 (d, *J* = 1.1 Hz, 1 H), 5.71 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1 H), 5.02 – 4.93 (m, 2 H), 4.69 (s, 2 H), 3.50 (t, *J* = 8.0 Hz, 2 H), 3.19 – 3.13 (m, 2 H), 0.83 (t, *J* = 8.1 Hz, 2 H), –0.06 (s, 9 H).

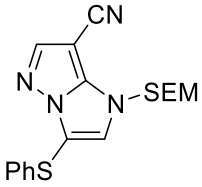
^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 146.0, 141.6, 132.2, 122.4, 118.0, 116.4, 114.5, 76.0, 67.9, 67.3, 27.7, 17.8, –1.4.

MS (70 eV, EI) *m/z* (%): 302 (2) $[M]^{\cdot+}$, 259 (13), 245 (11), 244 (100), 243 (95), 229 (11), 217 (12), 185 (25), 73 (66).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3121, 2952, 2894, 2215, 1613, 1600, 1488, 1457, 1419, 1379, 1335, 1302, 1248, 1221, 1183, 1104, 1080, 1031, 992, 970, 916, 856, 833, 748, 693, 667.

HRMS (EI) calculated for $C_{15}H_{22}N_4OSi^{\cdot+}$: 302.1557, found 302.1558 $[M]^{\cdot+}$.

3-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (45b)



3-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile was synthesized according to **TP12** on a 0.2 mmol scale using *S*-methyl

benzenesulfonothioate (75 mg, 0.30 mmol, 1.5 equiv) as electrophile (2 h, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:1 + 5% NEt_3) and HPLC yielded the title compound **45b** (51 mg, 0.14 mmol, 69%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.46 (d, *J* = 1.0 Hz, 1 H), 7.37 – 7.31 (m, 2 H), 6.96 – 6.89 (m, 2 H), 6.88 – 6.82 (m, 1 H), 6.24 (d, *J* = 1.1 Hz, 1 H), 4.59 (s, 2 H), 3.41 (t, *J* = 8.0 Hz, 2 H), 0.79 (t, *J* = 8.1 Hz, 2 H), –0.09 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 146.2, 142.0, 134.3, 129.7, 129.5, 127.8, 127.7, 126.0, 113.8, 76.4, 69.4, 67.5, 17.8, –1.4.

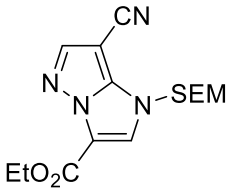
MS (70 eV, EI) *m/z* (%): 370 (8) $[M]^{+}$, 313 (19), 312 (86), 285 (13), 253 (15), 121 (11), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3128, 3058, 2949, 2893, 2862, 2221, 1603, 1583, 1538, 1474, 1454, 1440, 1398, 1377, 1334, 1296, 1281, 1242, 1196, 1180, 1169, 1136, 1085, 1022, 997, 977, 922, 909, 857, 835, 781, 755, 735, 715, 695, 686, 670.

HRMS (EI) calculated for $C_{18}H_{22}N_4OSSi^{+}$: 370.1278, found 370 1276 $[M]^{+}$.

mp: 74.0 – 75.5 °C.

Ethyl 7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate (45c)



Ethyl 7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate was synthesized according to **TP12** on a 0.2 mmol scale using ethyl cyanoformate (30 mg, 0.30 mmol, 1.5 equiv) as electrophile (2 h, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 2:1 + 5% NEt_3) yielded the title compound **45c** (35 mg, 0.11 mmol, 53%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.56 (d, *J* = 1.3 Hz, 1 H), 6.89 (d, *J* = 1.2 Hz, 1 H), 4.60 (s, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.39 (t, *J* = 8.0 Hz, 2 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 0.80 (t, *J* = 8.0 Hz, 2 H), –0.07 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 158.0, 146.6, 142.1, 126.9, 116.6, 113.6, 76.7, 69.0, 67.7, 61.3, 17.8, 14.3, −1.4.

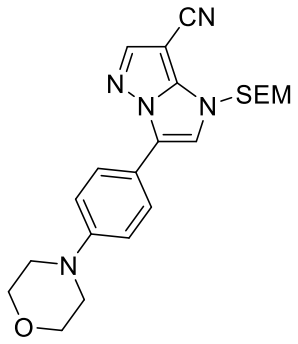
MS (70 eV, EI) *m/z* (%): 334 (4) $[M]^{\cdot+}$, 291 (11), 277 (12), 276 (57), 204 (10), 158 (7), 74 (8), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3158, 3112, 2953, 2895, 2219, 1704, 1603, 1581, 1471, 1451, 1398, 1370, 1249, 1318, 1258, 1249, 1192, 1094, 1036, 948, 933, 918, 856, 833, 768, 749, 710, 684.

HRMS (EI) calculated for $C_{15}H_{22}N_4O_3SSi^{\cdot+}$: 334.1456, found 334.1456 $[M]^{\cdot+}$.

mp: 105.2 – 107.7 °C.

3-(4-Morpholinophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (45d)



3-(4-Morpholinophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile was synthesized according to **TP12** on a 0.2 mmol scale. After the metalation a $ZnCl_2$ solution (1.0 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) was added before adding 4-(4-iodophenyl)morpholine (46 mg, 0.16 mmol, 0.8 equiv) as electrophile and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5%) in combination with SPhos (8.2 mg, 0.02 mmol, 10%) as catalyst (2 h, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 2:1 + 5% NEt_3) and HPLC yielded the title compound **45d** (67 mg, 0.14 mmol, 89%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 8.02 (d, *J* = 8.8 Hz, 2 H), 7.72 – 7.58 (m, 1 H), 6.71 (d, *J* = 8.8 Hz, 2 H), 6.44 – 6.37 (m, 1 H), 4.82 (s, 2 H), 3.61 – 3.42 (m, 6 H), 2.79 – 2.66 (m, 4 H), 0.87 (t, *J* = 8.0 Hz, 2 H), −0.05 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 151.5, 146.1, 142.1, 126.5, 124.6, 118.5, 115.4, 114.5, 114.3, 76.2, 67.8, 67.4, 66.7, 48.6, 17.8, −1.4.

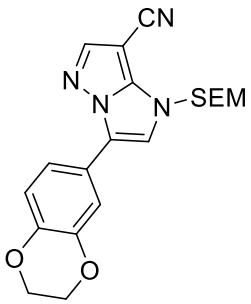
MS (70 eV, EI) *m/z* (%): 423 (19) $[M]^{+}$, 366 (23), 365 (100), 311 (6), 307 (7), 306 (14), 234 (5), 73 (33).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3118, 2951, 2922, 2895, 2857, 2210, 1606, 1557, 1512, 1485, 1458, 1449, 1428, 1379, 1336, 1316, 1306, 1263, 1248, 1229, 1221, 1192, 1120, 1099, 1072, 1055, 1029, 1003, 975, 933, 921, 902, 858, 826, 815, 770, 753, 743, 712, 682, 665.

HRMS (EI) calculated for $C_{22}H_{29}N_5O_2Si$:423.2091, found 423.2090 [M].

mp: 118.9 – 120.1 °C.

3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo-[1,2-*b*]pyrazole-7-carbonitrile (45e)



3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]-pyrazole-7-carbonitrile was synthesized according to **TP12** on a 0.2 mmol scale. After the metalation a $ZnCl_2$ solution (1.0 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) was added before adding 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine (42 mg, 0.16 mmol, 0.8 equiv) as electrophile and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5%) in combination with SPhos (8.2 mg, 0.02 mmol, 10%) as catalyst (2 h, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 2:1 + 5% NEt_3) yielded the title compound **45e** (42 mg, 0.11 mmol, 66%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.91 (d, *J* = 2.1 Hz, 1 H), 7.57 (d, *J* = 1.2 Hz, 1 H), 7.53 (dd, *J* = 8.5, 2.2 Hz, 1 H), 6.99 (d, *J* = 8.5 Hz, 1 H), 6.22 (d, *J* = 1.3 Hz, 1 H), 4.73 (s, 2 H), 3.55 – 3.47 (m, 6 H), 0.86 (t, *J* = 8.0 Hz, 2 H), −0.06 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 146.0, 144.4, 142.0, 124.0, 121.1, 119.0, 118.1, 115.0, 114.8, 114.4, 76.1, 67.8, 67.3, 64.3, 64.2, 17.8, −1.4.

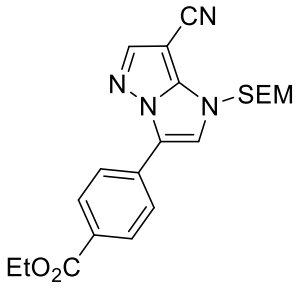
MS (70 eV, EI) *m/z* (%): 396 (10) $[M]^{+}$, 340 (5), 339 (20), 338 (100), 284 (14), 279 (15), 265 (5), 73 (56).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 2358, 2340, 2217, 1613, 1593, 1579, 1558, 1539, 1506, 1490, 1468, 1456, 1436, 1424, 1395, 1381, 1333, 1324, 1287, 1262, 1248, 1241, 1223, 1191, 1179, 1134, 1109, 1081, 1068, 1054, 1044, 1032, 945, 923, 890, 879, 866, 831, 772, 762, 750, 726, 701, 676, 668, 660.

HRMS (EI) calculated for $C_{20}H_{24}N_4O_3Si^{\cdot+}$: 396.1612, found 396.1608 $[M]^{\cdot+}$.

mp: 147.2 – 148.5 °C.

Ethyl 4-(7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazol-3-yl)-benzoate (45f)



Ethyl 4-(7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazol-3-yl)benzoate was synthesized according to **TP12** on a 0.2 mmol scale. After the metalation a $ZnCl_2$ solution (1.0 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) was added before adding ethyl 4-iodo benzoate (44 mg, 0.16 mmol, 0.8 equiv) as electrophile and PEPPSI-*i*Pr (2.7 mg, 0.004 mmol, 2%) as catalyst (2 h, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:1 + 5% NEt_3) yielded the title compound **45f** (55 mg, 0.13 mmol, 84%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 8.23 (d, *J* = 8.6 Hz, 2 H), 7.97 (d, *J* = 8.6 Hz, 2 H), 7.54 (d, *J* = 1.1 Hz, 1 H), 6.25 (d, *J* = 1.1 Hz, 1 H), 4.73 (s, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.54 (t, *J* = 8.1 Hz, 2 H), 1.04 (t, *J* = 7.1 Hz, 3 H), 0.89 (t, *J* = 8.1 Hz, 2 H), –0.04 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 165.8, 146.2, 142.2, 131.5, 130.43, 130.39, 124.9, 123.2, 117.3, 114.1, 76.3, 68.2, 67.6, 61.1, 17.9, 14.3, –1.4.

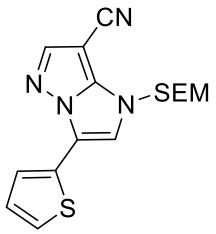
MS (70 eV, EI) *m/z* (%): 367 (8) $[M–C_3H_8]^{\cdot+}$, 353 (20), 352 (100), 298 (13), 293 (12), 281 (11), 234 (20), 225 (14), 207 (29), 75 (11), 73 (63).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3124, 2958, 2219, 1700, 1606, 1590, 1558, 1488, 1456, 1368, 1338, 1326, 1289, 1275, 1248, 1195, 1177, 1109, 1089, 1066, 1049, 1035, 1019, 941, 919, 862, 837, 790, 768, 741, 725, 707, 697, 660.

HRMS (EI) calculated for $C_{18}H_{19}N_4O_3Si^{+}$: 367.1221, found 367.1221 $[M-C_3H_8]^{+}$.

mp: 136.0 – 137.6 °C.

3-(Thiophen-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (45g)



3-(Thiophen-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile was synthesized according to **TP12** on a 0.2 mmol scale. After the metalation a $ZnCl_2$ solution (1.0 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) was added before adding 2-iodotiophene (34 mg, 0.16 mmol, 0.8 equiv) as electrophile and PEPPSI-*i*Pr (2.7 mg, 0.004 mmol, 2%) as catalyst (2 h, 60 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:1 + 5% NEt_3) yielded the title compound **45g** (41 mg, 0.12 mmol, 74%) as a colorless oil.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.93 (dd, *J* = 3.5, 1.3 Hz, 1 H), 7.56 (d, *J* = 1.3 Hz, 1 H), 6.77 – 6.70 (m, 2 H), 6.21 (d, *J* = 1.2 Hz, 1 H), 4.63 (s, 2 H), 3.47 (t, *J* = 8.0 Hz, 2 H), 0.84 (t, *J* = 8.0 Hz, 2 H), –0.06 (s, 9 H).

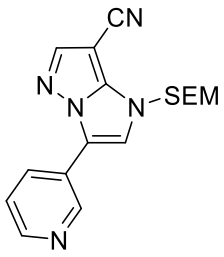
^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 146.3, 141.5, 126.2, 124.8, 119.8, 115.0, 114.1, 76.1, 68.3, 67.4, 17.8, –1.4.

MS (70 eV, EI) *m/z* (%): 344 (1) $[M]^{+}$, 287 (12), 286 (100), 259 (12), 232 (28), 227 (22), 213 (10), 207 (24), 159 (11), 73 (29).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3107, 2951, 2897, 2215, 1605, 1510, 1484, 1418, 1379, 1335, 1307, 1247, 1220, 1185, 1081, 1046, 1014, 939, 915, 856, 833, 738, 722, 692, 661.

HRMS (EI) calculated for $C_{16}H_{20}N_4OSSi^{+}$: 344.1122, found 344.1121 $[M]^{+}$.

3-(Pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (45h)



3-(Pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile was synthesized according to **TP12** on a 0.2 mmol scale. After the metalation a $ZnCl_2$ solution (1.0 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) was added before adding 3-iodopyridine (33 mg, 0.16 mmol, 0.8 equiv) as electrophile and PEPPSI-*i*Pr (2.7 mg, 0.004 mmol, 2%) as catalyst (2 h, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 1:1 + 5% NEt_3) yielded the title compound **45h** (45 mg, 0.13 mmol, 83%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 9.03 (d, *J* = 1.8 Hz, 1 H), 8.41 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.35 (dt, *J* = 8.0, 1.9 Hz, 1 H), 7.55 (d, *J* = 1.0 Hz, 1 H), 6.78 (dd, *J* = 7.8, 5.0 Hz, 1 H), 6.27 (d, *J* = 1.0 Hz, 1 H), 4.74 (s, 2 H), 3.53 (t, *J* = 8.1 Hz, 2 H), 0.88 (t, *J* = 8.1 Hz, 2 H), –0.04 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 149.3, 146.5, 146.3, 142.0, 131.9, 123.8, 123.5, 121.1, 116.5, 114.1, 76.3, 68.3, 67.6, 17.9, –1.4.

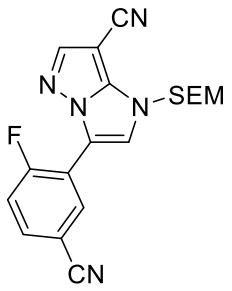
MS (70 eV, EI) *m/z* (%): 339 (0.3) $[M]^{\cdot+}$, 296 (9), 282 (14), 281 (100), 254 (10), 227 (10), 222 (15), 208 (9), 73 (46).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3048, 2951, 2925, 1619, 1568, 1558, 1490, 1456, 1413, 1394, 1380, 1340, 1262, 1249, 1210, 1178, 1130, 1108, 1088, 1072, 1025, 938, 928, 905, 862, 832, 810, 768, 759, 748, 719, 708, 687.

HRMS (EI) calculated for $C_{17}H_{21}N_5OSi^{\cdot+}$: 339.1510, found 339.1511 $[M]^{\cdot+}$.

mp: 92.5 – 93.9 °C.

3-(5-Cyano-2-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (45i)



3-(5-Cyano-2-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile was synthesized according to **TP12** on a 0.2 mmol scale. After the metalation a $ZnCl_2$ solution (1.0 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) was added before adding 3-bromo-4-fluorobenzonitrile (32 mg, 0.16 mmol, 0.8 equiv) as electrophile and PEPPSI-*i*Pr (2.7 mg, 0.004 mmol, 2%) as catalyst (17 h, 60 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:1 + 5% NEt_3) yielded the title compound **45i** (50 mg, 0.13 mmol, 82%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 9.15 (dd, *J* = 7.1, 2.1 Hz, 1 H), 7.53 (d, *J* = 1.3 Hz, 1 H), 6.89 (dd, *J* = 3.2, 1.3 Hz, 1 H), 6.71 (ddd, *J* = 8.6, 4.8, 2.1 Hz, 1 H), 6.38 (dd, *J* = 11.2, 8.6 Hz, 1 H), 4.72 (s, 2 H), 3.52 (t, *J* = 8.1 Hz, 2 H), 0.88 (t, *J* = 8.1 Hz, 2 H), –0.04 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 160.1 (d, *J* = 258.1 Hz), 146.1, 141.4, 132.7, 131.3, 121.2 (d, *J* = 17.3 Hz), 117.9, 117.6 (d, *J* = 13.2 Hz), 116.5 (d, *J* = 23.3 Hz), 116.0 (d, *J* = 2.9 Hz), 113.7, 109.8 (d, *J* = 3.5 Hz), 76.5, 68.6, 67.7, 17.9, –1.4.

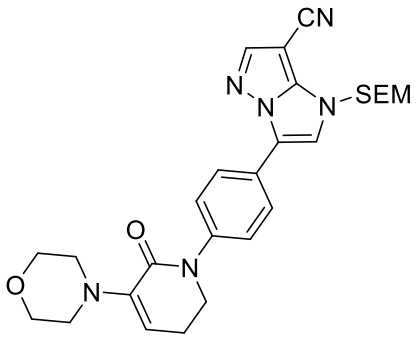
MS (70 eV, EI) *m/z* (%): 381 (3) $[M]^{\cdot+}$, 338 (10), 325 (5), 324 (17), 323 (86), 264 (9), 250 (5), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3132, 3067, 2952, 2228, 2215, 1604, 1576, 1505, 1489, 1456, 1394, 1340, 1323, 1297, 1245, 1229, 1187, 1167, 1124, 1109, 1080, 1052, 1038, 1027, 935, 911, 894, 861, 824, 754, 728, 714, 697, 669.

HRMS (EI) calculated for $C_{19}H_{20}FN_5OSi$: 381.1421, found 381.13422 [M].

mp: 144.0 – 144.0 °C.

3-(4-(5-Morpholino-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)phenyl)-1-((2-(trimethylsilyl)-ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (45j)



3-(4-(5-Morpholino-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile was synthesized according to **TP12** on a 0.2 mmol scale. After the metalation a $ZnCl_2$ solution (1.0 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) was added before adding 1-(4-iodophenyl)-3-morpholino-5,6-dihydropyridin-2(1*H*)-one (62 mg, 0.16 mmol, 0.8 equiv) as electrophile and PEPPSI-*i*Pent (4.8 mg, 0.006 mmol, 3%) as catalyst (2 h, 60 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:6 + 5% NEt_3) yielded the title compound **45j** (47 mg, 0.09 mmol, 57%) as a colorless solid.

^{1}H-NMR (CD_2Cl_2, 400 MHz, ppm): δ = 8.06 (d, *J* = 8.6 Hz, 2 H), 7.98 (s, 1 H), 7.44 (d, *J* = 8.6 Hz, 2 H), 7.29 (s, 1 H), 5.68 (t, *J* = 4.7 Hz, 1 H), 5.48 (s, 2 H), 3.83 – 3.73 (m, 6 H), 3.68 (t, *J* = 8.3 Hz, 2 H), 2.87 (t, *J* = 4.4 Hz, 4 H), 2.50 (q, *J* = 6.5 Hz, 2 H), 0.98 (t, *J* = 8.3 Hz, 2 H), −0.01 (s, 9 H).

^{13}C-NMR (CD_2Cl_2, 101 MHz, ppm): δ = 161.8, 146.7, 144.2, 143.6, 142.3, 126.0, 125.8, 124.9, 124.2, 116.6, 115.3, 114.6, 77.3, 67.9, 67.2, 51.0, 49.2, 23.9, 18.2, 1.3, −1.3.

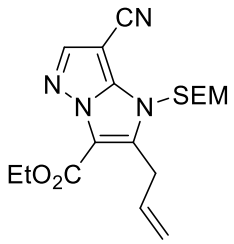
MS (70 eV, EI) *m/z* (%): 518 (15) $[M]^{+}$, 461 (25), 460 (81), 443 (16), 442 (41), 402 (10), 401 (25), 73 (100), 44 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3117, 2952, 2928, 2846, 2823, 2208, 1652, 1605, 1512, 1486, 1472, 1452, 1418, 1378, 1349, 1338, 1327, 1310, 1261, 1250, 1217, 1208, 1192, 1111, 1048, 1025, 975, 948, 930, 921, 902, 857, 831, 795, 780, 750, 712, 682.

HRMS (EI) calculated for $C_{27}H_{34}N_6O_3Si^{+}$: 518.2456, found 518.2457 $[M]^{+}$.

mp: 232.7 – 234.4 °C.

Ethyl 2-allyl-7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate (47a)



Ethyl 2-allyl-7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate was synthesized according to **TP13** on a 0.2 mmol scale using allyl bromide (0.03 mL, 0.33 mmol, 1.7 equiv) and CuCN·2LiCl (1 M in THF, 0.04 mL, 0.04 mmol, 0.20 equiv) as electrophile (20 min, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 9:1 + 5% NEt_3) yielded the title compound **47a** (54 mg, 0.14 mmol, 72%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.56 (s, 1 H), 4.95 – 4.88 (m, 2 H), 4.84 (s, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.63 (d, *J* = 6.2 Hz, 2 H), 3.55 (t, *J* = 8.2 Hz, 2 H), 1.07 (t, *J* = 7.1 Hz, 3 H), 0.86 (t, *J* = 8.2 Hz, 2 H), −0.05 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 159.1, 145.7, 141.5, 139.7, 132.8, 117.7, 114.0, 113.5, 73.8, 68.5, 67.7, 61.2, 28.3, 17.9, 14.3, −1.4.

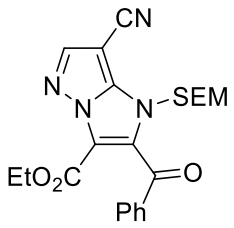
MS (70 eV, EI) *m/z* (%): 374 (1) $[M]^{+}$, 317 (11), 316 (70), 281 (21), 270 (37), 254 (11), 253 (10), 243 (10), 209 (14), 208 (13), 207 (100), 198 (21), 197 (15), 191 (18), 170 (20), 169 (11), 143 (22), 75 (14), 73 (70), 44 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2924, 2218, 1716, 1642, 1601, 1565, 1479, 1467, 1446, 1407, 1375, 1351, 1317, 1275, 1265, 1248, 1183, 1139, 1108, 1088, 1066, 1046, 1019, 991, 940, 922, 883, 859, 835, 807, 769, 701, 672.

HRMS (EI) calculated for $C_{18}H_{26}N_4O_3Si^{+}$: 374.1769, found 374.1769 $[M]^{\cdot+}$.

mp: 51.5 – 53.7 °C.

Ethyl 2-benzoyl-7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate (47b)



Ethyl 2-benzoyl-7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate was synthesized according to **TP13** on a 0.2 mmol scale using benzoyl chloride (42 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl (1 M in THF, 0.10 mL, 0.10 mmol, 0.50 equiv) as electrophile (1 h, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 9:1 + 5% NEt_3) yielded the title compound **47b** (55 mg, 0.13 mmol, 63%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.64 (d, *J* = 7.2 Hz, 2 H), 7.60 (s, 1 H), 7.05 (t, *J* = 7.4 Hz, 1 H), 6.95 (t, *J* = 7.6 Hz, 2 H), 5.06 (s, 2 H), 3.74 (q, *J* = 7.1 Hz, 2 H), 3.34 (t, *J* = 8.2 Hz, 2 H), 0.59 (dt, *J* = 11.5, 7.7 Hz, 5 H), –0.18 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 185.4, 157.1, 147.6, 142.2, 137.3, 134.3, 133.7, 129.7, 128.9, 115.9, 113.3, 74.8, 69.3, 67.6, 61.5, 17.6, 13.5, –1.5.

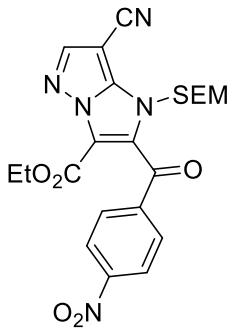
MS (70 eV, EI) *m/z* (%): 438 (2) $[M]^{\cdot+}$, 395 (11), 381 (18), 380 (65), 366 (21), 365 (75), 293 (14), 262 (23), 105 (22), 91 (15), 77 (13), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2945, 2220, 1731, 1666, 1614, 1597, 1562, 1556, 1482, 1461, 1448, 1375, 1349, 1320, 1278, 1242, 1234, 1191, 1174, 1146, 1113, 1094, 1024, 962, 941, 920, 861, 838, 760, 709, 688, 676.

HRMS (EI) calculated for $C_{22}H_{26}N_4O_4Si^{\cdot+}$: 438.1718, found 438.1718 $[M]^{\cdot+}$.

mp: 127.6 – 128.5 °C.

Ethyl 7-cyano-2-(4-nitrobenzoyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]-pyrazole-3-carboxylate (47c)



Ethyl 7-cyano-2-(4-nitrobenzoyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate was synthesized according to **TP13** on a 0.2 mmol scale using 4-nitrobenzoyl chloride (56 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl (1 M in THF, 0.10 mL, 0.10 mmol, 0.50 equiv) as electrophile (2 h, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:1 + 5% NEt_3) yielded the title compound **47c** (59 mg, 0.12 mmol, 61%) as a yellow solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.71 (d, *J* = 8.8 Hz, 2 H), 7.55 (s, 1 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 5.05 (s, 2 H), 3.77 (q, *J* = 7.1 Hz, 2 H), 3.36 (t, *J* = 8.2 Hz, 2 H), 0.75 – 0.57 (m, 5 H), –0.17 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 184.3, 157.2, 150.9, 147.9, 142.4, 141.0, 132.6, 130.2, 123.9, 116.6, 113.0, 74.6, 69.3, 67.8, 62.0, 17.6, 13.7, –1.6.

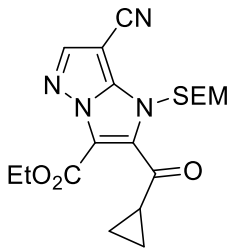
MS (70 eV, EI) *m/z* (%): 483 (0.3) $[M]^{\cdot+}$, 426 (12), 425 (43), 410 (20), 307 (8), 103 (7), 74 (7), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3108, 2951, 2226, 1727, 1690, 1664, 1605, 1562, 1551, 1524, 1475, 1409, 1369, 1344, 1312, 1276, 1245, 1231, 1179, 1137, 1110, 1020, 967, 942, 911, 853, 835, 803, 789, 760, 753, 735, 702, 665.

HRMS (EI) calculated for $C_{22}H_{25}N_5O_6Si^{\cdot+}$: 483.1569, found 483.1561 $[M]^{\cdot+}$.

mp: 164.9 – 166.3 °C.

Ethyl 7-cyano-2-(cyclopropanecarbonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate (47d)



Ethyl 7-cyano-2-(cyclopropanecarbonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo-[1,2-*b*]pyrazole-3-carboxylate was synthesized according to **TP13** on a 0.2 mmol scale using cyclopropanecarbonyl chloride (31 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl (1 M in THF, 0.10 mL, 0.10 mmol, 0.50 equiv) as electrophile (1 h, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:1 + 5% NEt_3) yielded the title compound **47d** (65 mg, 0.16 mmol, 81%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.55 (s, 1 H), 5.13 (s, 2 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 3.49 (t, *J* = 8.1 Hz, 2 H), 2.20 (tt, *J* = 7.9, 4.5 Hz, 1 H), 1.33 – 1.26 (m, 2 H), 1.02 (t, *J* = 7.1 Hz, 3 H), 0.83 (t, *J* = 8.1 Hz, 2 H), 0.72 (dd, *J* = 7.6, 3.6 Hz, 2 H), −0.08 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 194.4, 158.0, 147.7, 142.0, 135.4, 116.2, 113.3, 74.8, 69.1, 67.7, 62.0, 24.1, 17.9, 14.4, 14.1, −1.4.

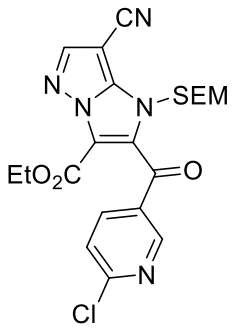
MS (70 eV, EI) *m/z* (%): 402 (1) [M], 345 (10), 344 (35), 330 (11), 329 (45), 283 (18), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 2226, 1724, 1686, 1674, 1612, 1556, 1481, 1441, 1405, 1377, 1359, 1346, 1315, 1305, 1276, 1263, 1247, 1196, 1184, 1166, 1111, 1086, 1057, 1039, 1017, 1002, 945, 921, 897, 860, 834, 792, 772, 759, 723, 697, 682, 666.

HRMS (EI) calculated for $C_{19}H_{26}N_4O_4Si$: 402.1723, found 402.1724 [M].

mp: 85.2 – 86.4 °C.

Ethyl 2-(6-chloronicotinoyl)-7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo-[1,2-*b*]pyrazole-3-carboxylate (47e)



Ethyl 2-(6-chloronicotinoyl)-7-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate was synthesized according to **TP13** on a 0.2 mmol scale using 6-chloronicotinoyl chloride (53 mg, 0.30 mmol, 1.5 equiv) and CuCN·2LiCl (1 M in THF, 0.10 mL, 0.10 mmol, 0.50 equiv) as electrophile (2 h, 25 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 9:1 + 5% NEt_3) yielded the title compound **47e** (67 mg, 0.14 mmol, 71%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.59 (s, 1 H), 7.55 (dd, *J* = 3.0, 1.2 Hz, 2 H), 7.21 (dd, *J* = 5.0, 1.2 Hz, 1 H), 6.83 (dd, *J* = 5.0, 3.0 Hz, 1 H), 4.68 (s, 2 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 3.68 – 3.60 (m, 2 H), 0.98 (t, *J* = 7.1 Hz, 3 H), 0.88 – 0.82 (m, 2 H), –0.03 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 158.3, 146.1, 141.7, 135.5, 130.2, 130.1, 125.9, 125.4, 114.0, 113.4, 74.2, 68.8, 68.1, 61.1, 18.2, 14.2, –1.4.

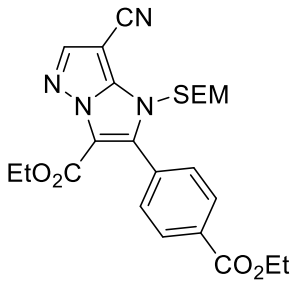
MS (70 eV, EI) *m/z* (%): 473 (2) $[M]^{\cdot+}$, 417 (18), 416 (12), 415 (45), 400 (22), 297 (10), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 2220, 1731, 1676, 1607, 1583, 1563, 1478, 1412, 1363, 1311, 1291, 1275, 1245, 1186, 1134, 1093, 1068, 1021, 980, 963, 935, 923, 860, 836, 820, 783, 765, 741, 707, 692.

HRMS (EI) calculated for $C_{21}H_{24}ClN_5O_4Si^{\cdot+}$: 473.1281, found 473.1281 $[M]^{\cdot+}$.

mp: 137.5 – 139.2 °C.

Ethyl 7-cyano-2-(4-(ethoxycarbonyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate (47f)



Ethyl 7-cyano-2-(4-(ethoxycarbonyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo-[1,2-*b*]pyrazole-3-carboxylate was synthesized according to **TP13** on a 0.2 mmol scale using ethyl 4-iodo benzoate (44 mg, 0.16 mmol, 0.8 equiv) as electrophile and $Pd(PPh_3)_4$ (6.9 mg, 0.006 mmol, 3%) as catalyst (90 min, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 7:1 + 5% NEt_3) yielded the title compound **47f** (51 mg, 0.11 mmol, 66%) as a slightly yellow solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 8.17 (d, *J* = 8.5 Hz, 2 H), 7.64 (s, 1 H), 7.37 (d, *J* = 8.5 Hz, 2 H), 4.66 (s, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.01 (q, *J* = 7.1 Hz, 2 H), 3.63 – 3.49 (m, 3 H), 1.03 (t, *J* = 7.1 Hz, 3 H), 0.91 (t, *J* = 7.1 Hz, 3 H), 0.88 – 0.80 (m, 2 H), –0.05 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 165.5, 158.0, 146.3, 141.9, 139.2, 132.7, 131.7, 130.6, 129.5, 113.9, 113.7, 74.2, 69.0, 68.0, 61.3, 61.2, 18.2, 14.2, 14.1, –1.4.

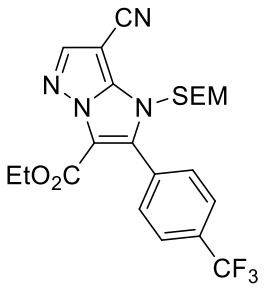
MS (70 eV, EI) *m/z* (%): 424 (3) $[M–C_4H_{10}]^{+}$, 281 (22), 225 (60), 209 (30), 208 (13), 207 (100), 191 (25), 73 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3097, 2952, 2223, 1709, 1602, 1574, 1503, 1479, 1443, 1392, 1376, 1314, 1274, 1250, 1195, 1171, 1088, 1019, 938, 914, 883, 857, 835, 763, 743, 717, 695, 666.

HRMS (EI) calculated for $C_{24}H_{30}N_4O_5Si^{+}$: 482.1980, found 482.1975 $[M]^{+}$.

mp: 110.4 – 111.5 °C.

Ethyl 7-cyano-2-(4-(trifluoromethyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate (47g)



Ethyl 7-cyano-2-(4-(trifluoromethyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo-[1,2-*b*]pyrazole-3-carboxylate was synthesized according to **TP13** on a 0.2 mmol scale using 1-iodo-4-(trifluoromethyl)benzene (44 mg, 0.16 mmol, 0.8 equiv) as electrophile and $Pd(PPh_3)_4$ (6.9 mg, 0.006 mmol, 3%) as catalyst (90 min, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 7:1 + 5% NEt_3) yielded the title compound **47g** (53 mg, 0.11 mmol, 69%) as a slightly yellow solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.61 (s, 1 H), 7.37 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 4.58 (s, 2 H), 4.00 (q, *J* = 7.1 Hz, 2 H), 3.62 – 3.54 (m, 2 H), 0.91 (t, *J* = 7.1 Hz, 3 H), 0.88 – 0.82 (m, 2 H), −0.04 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 158.0, 146.4, 141.9, 138.5, 132.2 (q, *J* = 32.7 Hz), 132.2, 130.0, 125.8 (q, *J* = 272.7 Hz), 125.2 (q, *J* = 3.6 Hz), 113.8, 113.8, 74.2, 69.0, 68.2, 61.3, 18.2, 14.0, −1.5.

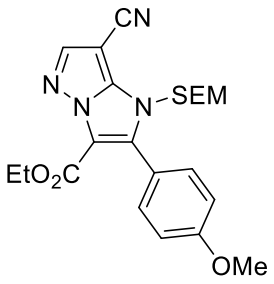
MS (70 eV, EI) *m/z* (%): 478 (0.2) $[M]^{+}$, 435 (21), 421 (22), 420 (96), 349 (12), 348 (72), 328 (18), 320 (12), 315 (14), 302 (26), 287 (12), 275 811), 256 (33), 172 (10), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 2221, 1720, 1606, 1572, 1513, 1478, 1443, 1409, 1378, 1354, 1321, 1274, 1249, 1167, 1127, 1101, 1068, 1018, 942, 915, 834, 765, 722, 692, 671.

HRMS (EI) calculated for $C_{22}H_{25}F_3N_4O_3Si^{+}$: 478.1643, found 478.1643 $[M]^{+}$.

mp: 96.8 – 98.5 °C.

Ethyl 7-cyano-2-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo-[1,2-*b*]pyrazole-3-carboxylate (47h)



Ethyl 7-cyano-2-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]-pyrazole-3-carboxylate was synthesized according to **TP13** on a 0.2 mmol scale using 1-iodo-4-methoxybenzene (37 mg, 0.16 mmol, 0.8 equiv) as electrophile and $Pd(PPh_3)_4$ (6.9 mg, 0.006 mmol, 3%) as catalyst (80 min, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 4:1 + 5% NEt_3) and HPLC yielded the title compound **47h** (37 mg, 0.08 mmol, 53%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.65 (s, 1 H), 7.37 (d, *J* = 8.8 Hz, 2 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 4.73 (s, 2 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 3.63 (t, *J* = 8.3 Hz, 2 H), 3.25 (s, 3 H), 0.98 (t, *J* = 7.1 Hz, 3 H), 0.87 (t, *J* = 8.3 Hz, 2 H), –0.03 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 161.6, 158.4, 146.0, 141.7, 140.7, 133.2, 118.3, 114.1, 113.9, 113.2, 74.1, 69.0, 67.9, 61.0, 54.9, 18.2, 14.2, –1.4.

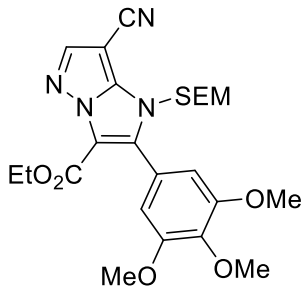
MS (70 eV, EI) *m/z* (%): 440 (2) $[M]^{\cdot+}$, 397 (15), 383 (22), 382 (100), 311 (10), 310 (60), 282 (31), 277 (11), 264 (31), 256 (13), 236 (11), 209 (10), 183 (20), 73 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2930, 2220, 1720, 1604, 1582, 1568, 1510, 1477, 1462, 1438, 1412, 1376, 1344, 1314, 1296, 1265, 1256, 1248, 1180, 1171, 1119, 1088, 1056, 1036, 1024, 1014, 1008, 944, 933, 916, 874, 858, 838, 790, 768, 758, 728, 701, 686, 676.

HRMS (EI) calculated for $C_{22}H_{28}N_4O_4Si^{\cdot+}$: 440.1874, found 440.1876 $[M]^{\cdot+}$.

mp: 100.7 – 101.8 °C.

Ethyl 7-cyano-2-(3,4,5-trimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate (47i)



Ethyl 7-cyano-2-(3,4,5-trimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo-[1,2-*b*]pyrazole-3-carboxylate was synthesized according to **TP13** on a 0.3 mmol scale using 5-iodo-1,2,3-trimethoxybenzene (71 mg, 0.24 mmol, 0.8 equiv) as electrophile and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol, 5%) as catalyst (4 h, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 6:1 + 5% NEt_3) yielded the title compound **47i** (60 mg, 0.12 mmol, 50%) as a slightly yellow solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.68 (s, 1 H), 6.74 (s, 2 H), 4.82 (s, 2 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 3.83 (s, 3 H), 3.65 (t, *J* = 8.4 Hz, 2 H), 3.54 (s, 6 H), 0.98 (t, *J* = 7.1 Hz, 3 H), 0.88 (t, *J* = 8.4 Hz, 2 H), −0.03 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 158.4, 153.7, 146.2, 141.6, 141.1, 140.7, 121.0, 114.1, 113.2, 109.6, 74.4, 69.0, 68.0, 61.0, 60.6, 56.1, 18.4, 14.2, −1.4.

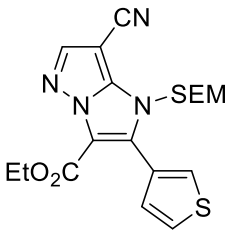
MS (70 eV, EI) *m/z* (%): 500 (5) $[M]^{\cdot+}$, 443 (27), 442 (100), 418 (10), 427 (42), 381 (10), 370 (20), 355 (13), 342 (13), 324 (15), 243 (10), 73 (32).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3094, 2946, 2836, 2214, 1719, 1612, 1591, 1560, 1509, 1493, 1467, 1456, 1421, 1395, 1382, 1366, 1358, 1353, 1317, 1281, 1249, 1228, 1181, 1165, 1128, 1098, 1067, 1033, 990, 945, 931, 859, 834, 791, 772, 758, 748, 724, 711, 691.

HRMS (EI) calculated for $C_{24}H_{32}N_4O_6Si^{\cdot+}$: 500.2086, found 500.2087 $[M]^{\cdot+}$.

mp: 153.8 – 155.3 °C.

Ethyl 7-cyano-2-(thiophen-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]-pyrazole-3-carboxylate (47j)



Ethyl 7-cyano-2-(thiophen-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[1,2-*b*]pyrazole-3-carboxylate was synthesized according to **TP13** on a 0.30 mmol scale using 3-iodothiophene (34 mg, 0.16 mmol, 0.8 equiv) as electrophile and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol, 5%) as catalyst (4 h, 40 °C). Purification via column chromatography (silica gel, *i*Hex/EtOAc = 7:1 + 5% NEt_3) yielded the title compound **47j** (54 mg, 0.13 mmol, 54%) as a colorless solid.

^{1}H-NMR (C_6D_6, 400 MHz, ppm): δ = 7.59 (s, 1 H), 7.55 (dd, *J* = 3.0, 1.2 Hz, 1 H), 7.21 (dd, *J* = 5.0, 1.2 Hz, 1 H), 6.83 (dd, *J* = 5.0, 3.0 Hz, 1 H), 4.68 (s, 2 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 3.67 – 3.61 (m, 2 H), 0.98 (t, *J* = 7.1 Hz, 3 H), 0.88 – 0.82 (m, 2 H), –0.03 (s, 9 H).

^{13}C-NMR (C_6D_6, 101 MHz, ppm): δ = 158.3, 146.1, 141.7, 135.5, 130.2, 130.1, 125.9, 125.4, 114.0, 113.4, 74.2, 68.8, 68.1, 61.1, 18.2, 14.2, –1.4.

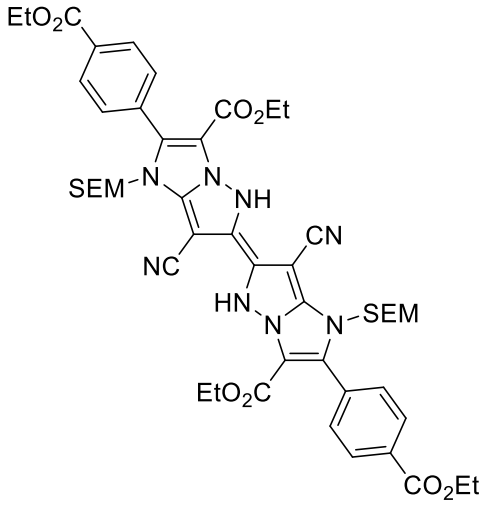
MS (70 eV, EI) *m/z* (%): 416 (1) $[M]^{+}$, 373 (12), 359 (19), 358 (100), 286 (68), 258 (38), 253 (17), 240 (43), 232 (13), 225 (10), 212 (12), 207 (10), 159 (16), 73 (74).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3097, 2945, 2218, 1713, 1606, 1582, 1519, 1501, 1476, 1443, 1416, 1373, 1337, 1310, 1267, 1243, 1220, 1189, 1166, 1088, 1060, 1018, 942, 912, 837, 810, 764, 721, 711, 689, 660.

HRMS (EI) calculated for $C_{19}H_{24}N_4O_3SSi^{+}$: 416.1333, found 416.1334 $[M]^{+}$.

mp: 100.1 – 102.8 °C.

Diethyl (*E*)-7,7'-dicyano-2,2'-bis(4-(ethoxycarbonyl)phenyl)-1,1'-bis((2-(trimethylsilyl)-ethoxy)methyl)-1*H*,1'*H*,5*H*,5'*H*-[6,6'-biimidazo[1,2-*b*]pyrazolylidene]-3,3'-dicarboxylate (48a)



Diethyl (*E*)-7,7'-dicyano-2,2'-bis(4-(ethoxycarbonyl)phenyl)-1,1'-bis((2-(trimethylsilyl)ethoxy)-methyl)-1*H*,1'*H*,5*H*,5'*H*-[6,6'-biimidazo[1,2-*b*]pyrazolylidene]-3,3'-dicarboxylate was synthesized according to **TP14** on a 0.087 mmol scale. The reaction was completed within 40 min and yielded the title compound **48a** (32 mg, 0.033 mmol, 76%) as a yellow solid.

^{1}H-NMR (acetone-d$_6$, 400 MHz, ppm): δ = 8.08 (d, *J* = 8.4 Hz, 4 H), 7.64 (d, *J* = 8.4 Hz, 4 H), 5.19 (s, 4 H), 4.38 (q, *J* = 7.1 Hz, 4 H), 4.11 (q, *J* = 7.1 Hz, 4 H), 3.49 (t, *J* = 8.2 Hz, 4 H), 1.39 (t, *J* = 7.1 Hz, 6 H), 1.05 (t, *J* = 7.1 Hz, 6 H), 0.85 (t, *J* = 8.2 Hz, 4 H), –0.03 (s, 18 H).

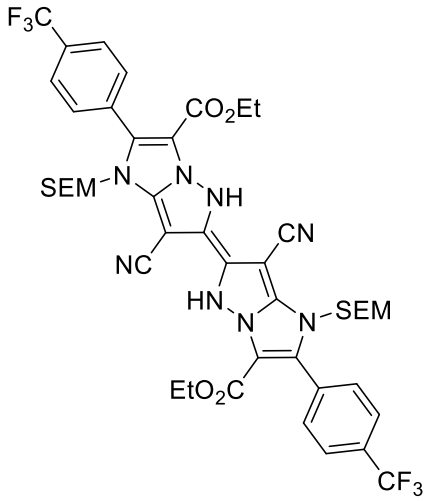
^{13}C-NMR (acetone-d$_6$, 101 MHz, ppm): δ = 166.4, 165.0, 153.1, 136.2, 135.1, 132.1, 131.2, 129.4, 128.2, 125.2, 73.0, 65.7, 61.6, 61.0, 24.6, 18.4, 14.6, 14.2, –1.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 2186, 2143, 1714, 1694, 1612, 1575, 1519, 1466, 1403, 1378, 1366, 1270, 1248, 1180, 1101, 1079, 1025, 963, 939, 916, 859, 834, 774, 759, 724, 706, 667.

HRMS (ESI) calculated for $C_{48}H_{59}N_8O_{10}Si_2^-$: 963.3898, found 963.38977 $[M-H]^-$.

mp: 84.0 – 93.0 °C.

Diethyl (*E*)-7,7'-dicyano-2,2'-bis(4-(trifluoromethyl)phenyl)-1,1'-bis((2-(trimethylsilyl)-ethoxy)methyl)-1*H*,1'*H*,5*H*,5'*H*-[6,6'-biimidazo[1,2-*b*]pyrazolylidene]-3,3'-dicarboxylate (48b)



Diethyl (*E*)-7,7'-dicyano-2,2'-bis(4-(trifluoromethyl)phenyl)-1,1'-bis((2-(trimethylsilyl)ethoxy)-methyl)-1*H*,1'*H*,5*H*,5'*H*-[6,6'-biimidazo[1,2-*b*]pyrazolylidene]-3,3'-dicarboxylate was synthesized according to **TP14** on a 0.096 mmol scale. The reaction was completed within 30 min and yielded the title compound **48b** (30 mg, 0.032 mmol, 67%) as a slightly orange solid.

^{1}H-NMR (acetone-d$_6$, 400 MHz, ppm): δ = 7.89 (q, *J* = 8.4 Hz, 8 H), 5.30 (s, 4 H), 4.14 (q, *J* = 7.1 Hz, 4 H), 3.57 – 3.44 (m, 4 H), 1.07 (t, *J* = 7.1 Hz, 6 H), 0.93 – 0.80 (m, 4 H), −0.03 (s, 18 H).

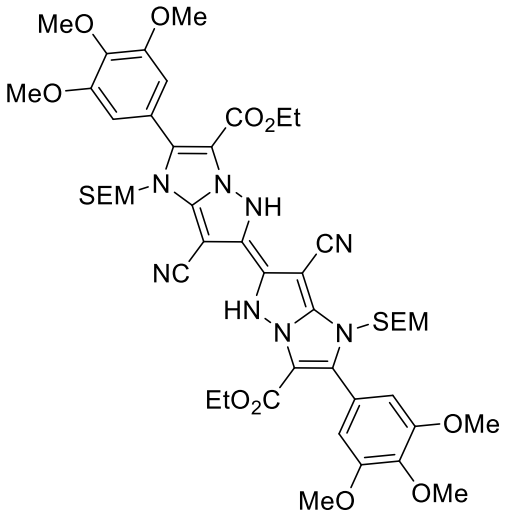
^{13}C-NMR (acetone-d$_6$, 101 MHz, ppm): δ = 159.7, 152.0, 136.5, 133.0, 132.0 (q, *J* = 32.4 Hz) 131.7, 126.0 (q, *J* = 3.8 Hz), 125.1 (q, *J* = 271.7 Hz), 120.6, 119.7, 73.6, 66.5, 61.9, 28.2, 18.3, 14.1, –1.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3050, 2954, 2897, 2746, 2213, 2171, 2149, 1725, 1614, 1599, 1518, 1465, 1431, 1408, 1371, 1323, 1298, 1262, 1250, 1228, 1214, 1203, 1184, 1163, 1126, 1108, 1082, 1067, 1026, 1013, 947, 924, 854, 835, 774, 758, 743, 711, 697, 674.

HRMS (ESI) calculated for $C_{44}H_{49}F_6N_8O_6Si_2^-$: 955.3223, found 955.3220 $[M–H]^-$.

mp: 134.1 – 135.4 °C.

Diethyl (*E*)-7,7'-dicyano-2,2'-bis(3,4,5-trimethoxyphenyl)-1,1'-bis((2-(trimethylsilyl)-ethoxy)methyl)-1*H*,1'*H*,5*H*,5'*H*-[6,6'-biimidazo[1,2-*b*]pyrazolylidene]-3,3'-dicarboxylate (48c)



Diethyl (*E*)-7,7'-dicyano-2,2'-bis(3,4,5-trimethoxyphenyl)-1,1'-bis((2-(trimethylsilyl)ethoxy)-methyl)-1*H*,1'*H*,5*H*,5'*H*-[6,6'-biimidazo[1,2-*b*]pyrazolylidene]-3,3'-dicarboxylate was synthesized according to **TP14** on a 0.148 mmol scale. The reaction was completed within 40 min and yielded the title compound **48c** (71 mg, 0.071 mmol, 96%) as a slightly yellow solid.

^{1}H-NMR (acetone-d$_6$, 400 MHz, ppm): δ = 6.80 (s, 4 H), 5.20 (s, 4 H), 4.13 (q, *J* = 7.1 Hz, 4 H), 3.85 (s, 12 H), 3.78 (s, 6 H), 3.59 – 3.47 (m, 4 H), 1.09 (t, *J* = 7.1 Hz, 6 H), 0.92 – 0.84 (m, 4 H), –0.02 (s, 18 H).

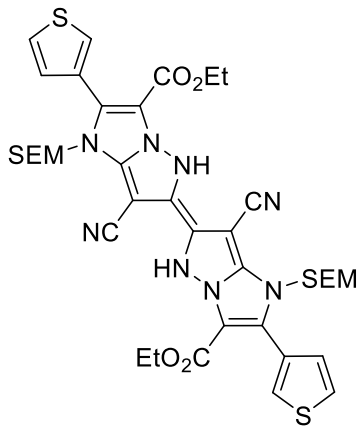
^{13}C-NMR (acetone-d$_6$, 101 MHz, ppm): δ = 165.4, 153.7, 152.2, 139.5, 137.7, 127.3, 125.4, 125.3, 109.5, 72.9, 65.6, 60.8, 60.6, 56.5, 24.4, 18.6, 14.3, –1.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2951, 2184, 2140, 1687, 1605, 1584, 1520, 1500, 1464, 1411, 1379, 1364, 1341, 1319, 1245, 1189, 1124, 1077, 1028, 1003, 938, 834, 788, 769, 726, 693.

HRMS (ESI) calculated for $C_{48}H_{63}N_8O_{12}Si_2^-$: 999.4109, found 999.41095 $[M–H]^-$.

mp: 68.5 – 70.0 °C.

Diethyl (*E*)-7,7'-dicyano-2,2'-di(thiophen-3-yl)-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1*H*,1'*H*,5*H*,5'*H*-[6,6'-biimidazo[1,2-*b*]pyrazolylidene]-3,3'-dicarboxylate (48d)



Diethyl (*E*)-7,7'-dicyano-2,2'-di(thiophen-3-yl)-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1*H*,1'*H*,5*H*,5'*H*-[6,6'-biimidazo[1,2-*b*]pyrazolylidene]-3,3'-dicarboxylate was synthesized according to **TP14** on a 0.115 mmol scale. The reaction was completed within 150 min at 25 °C and yielded the title compound **48d** (41 mg, 0.049 mmol, 86%) as a yellow solid.

^{1}H-NMR (acetone-d$_6$, 400 MHz, ppm): δ = 7.67 (dd, *J* = 3.0, 1.1 Hz, 2 H), 7.54 (dd, *J* = 5.0, 3.0 Hz, 2 H), 7.28 (dd, *J* = 5.0, 1.1 Hz, 2 H), 5.21 (s, 4 H), 4.14 (q, *J* = 7.1 Hz, 4 H), 3.54 (t, *J* = 8.1 Hz, 4 H), 1.12 (t, *J* = 7.1 Hz, 6 H), 0.89 (t, *J* = 8.1 Hz, 4 H), –0.01 (s, 18 H).

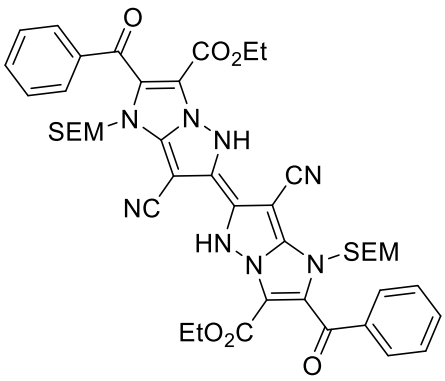
^{13}C-NMR (acetone-d$_6$, 101 MHz, ppm): δ = 165.3, 152.4, 132.6, 132.6, 131.1, 129.9, 127.9, 127.7, 125.4, 72.8, 65.7, 60.9, 24.5, 18.4, 14.2, –1.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 2184, 2142, 1683, 1629, 1521, 1396, 1377, 1341, 1262, 1248, 1189, 1077, 1027, 964, 939, 916, 857, 833, 809, 785, 756, 722, 692, 668.

HRMS (ESI) calculated for $C_{38}H_{48}N_8NaO_6S_2Si_2^+$: 855.2569, found 855.25681 $[M+Na]^+$.

mp: 95.5 – 98.2 °C.

Diethyl (*E*)-2,2'-dibenzoyl-7,7'-dicyano-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1*H*,1'*H*,5*H*,5'*H*-[6,6'-biimidazo[1,2-*b*]pyrazolylidene]-3,3'-dicarboxylate (48e)



Diethyl (*E*)-2,2'-dibenzoyl-7,7'-dicyano-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1*H*,1'*H*,5*H*,5'*H*-[6,6'-biimidazo[1,2-*b*]pyrazolylidene]-3,3'-dicarboxylate was synthesized according to **TP14** on a 0.185 mmol scale. The reaction was completed within 40 min and yielded the title compound **48e** (68 mg, 0.078 mmol, 84%) as a yellow solid.

^{1}H-NMR (acetone-d$_6$, 400 MHz, ppm): δ = 7.80 (d, *J* = 7.0 Hz, 4 H), 7.62 (t, *J* = 7.4 Hz, 2 H), 7.50 (t, *J* = 7.6 Hz, 4 H), 5.64 (s, 4 H), 3.75 (q, *J* = 7.1 Hz, 4 H), 3.54 – 3.43 (m, 4 H), 0.77 – 0.67 (m, 10 H), –0.10 (s, 18 H).

^{13}C-NMR (acetone-d$_6$, 101 MHz, ppm): δ = 186.1, 163.4, 154.7, 139.8, 135.6, 132.6, 129.8, 129.0, 128.3, 123.6, 72.5, 65.2, 60.3, 25.0, 17.4, 12.7, –2.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 2359, 2194, 2150, 1703, 1638, 1599, 1581, 1543, 1518, 1494, 1473, 1449, 1423, 1402, 1363, 1354, 1340, 1307, 1277, 1262, 1249, 1218, 1205, 1179, 1143, 1082, 1063, 1033, 998, 956, 936, 919, 861, 848, 835, 812, 790, 761, 733, 724, 695, 683.

HRMS (ESI) calculated for $C_{44}H_{51}N_8O_8Si_2^-$: 875.3374, found 875.33763 $[M–H]^-$.

mp: 249.8 – 250.9 °C.

Appendix

1 Single Crystal X-Ray Diffraction Studies

Phenyl(3-(1-phenylallyl)bicyclo[1.1.1]pentan-1-yl)methanone (4b)

Table 3. Details for X-ray data collection and structure refinement for compound **4b**.

	4b
Empirical formula	$C_{21}H_{20}O$
Formula mass	288.37
T[K]	143(2)
Crystal size [mm]	0.40 × 0.10 × 0.10
Crystal description	colorless rod
Crystal system	monoclinic
Space group	*P*21/*n*
a [Å]	10.7427(6)
b [Å]	10.4700(4)
c [Å]	14.4147(7)
α [°]	90.0
β [°]	93.099(5)
γ [°]	90.0
V [Å^3]	1618.94(14)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.183
μ [mm^{-1}]	0.071
F(000)	616
Θ range [°]	4.27 – 25.24
Index ranges	-13 ≤ *h* ≤ 12
	-12 ≤ *k* ≤ 10
	-16 ≤ *l* ≤ 17
Reflns. collected	11265
Reflns. obsd.	2144
Reflns. unique	3050 (R_{int} = 0.0438)
R_1, wR_2 (2σ data)	0.0725, 0.1831
R_1, wR_2 (all data)	0.1006, 0.2079
GOOF on F^2	1.030
Peak/hole [e Å^{-3}]	0.776 / -0.251

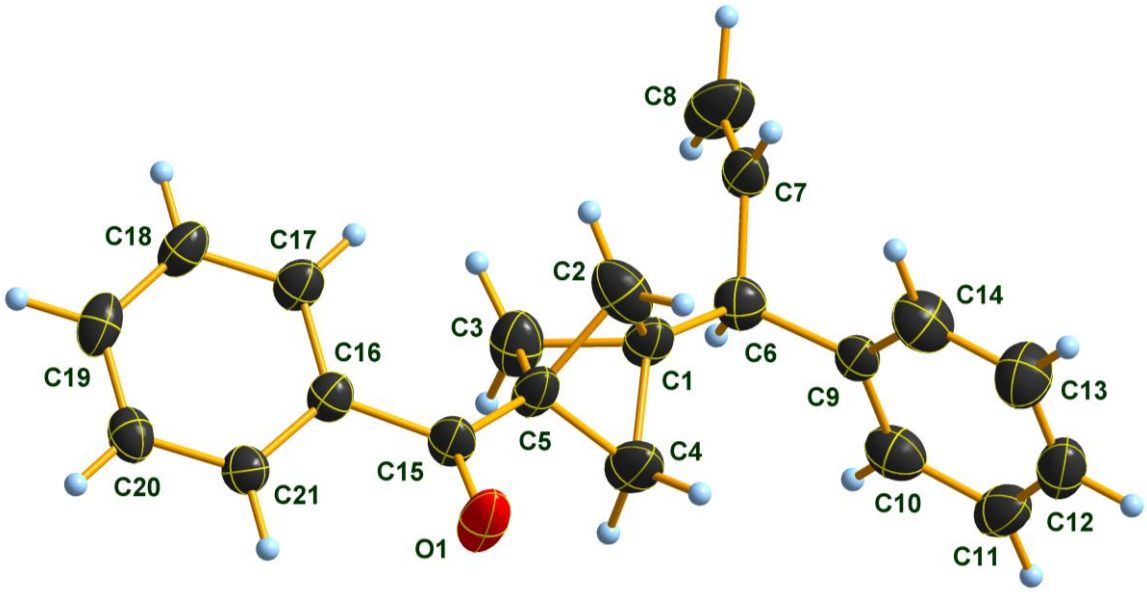


Figure 10. Molecular structure of compound **4b** in the crystal. DIAMOND[119] representation; thermal ellipsoids are drawn at 50 % probability level.

(1*R*,3*R*,5*R*)-3-(3-(4-Methoxyphenyl)bicyclo[1.1.1]pentan-1-yl)-6,6-dimethyl-2-methylene-bicyclo[3.1.1]heptane (4m)

Table 4. Details for X-ray data collection and structure refinement for compound **4m**.

	4m
Empirical formula	$C_{22}H_{28}O$
Formula mass	308.44
T[K]	143(2)
Crystal size [mm]	0.40 × 0.15 × 0.02
Crystal description	colorless platelet
Crystal system	monoclinic
Space group	*P*21
a [Å]	8.0515(6)
b [Å]	6.4231(5)
c [Å]	17.0787(16)
α [°]	90.0
β [°]	92.434(8)
γ [°]	90.0

[119] DIAMOND, Crystal Impact GbR, Version 3.2i.

V [Å^3]	882.44(13)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.161
μ [mm^{-1}]	0.069
F(000)	336
Θ range [°]	4.20 – 25.24
Index ranges	-8 ≤ *h* ≤ 10
	-7 ≤ *k* ≤ 8
	-21 ≤ *l* ≤ 21
Reflns. collected	5879
Reflns. obsd.	2613
Reflns. unique	3357 (R_{int} = 0.0380)
R_1, wR_2 (2σ data)	0.0530, 0.0876
R_1, wR_2 (all data)	0.0788, 0.0995
GOOF on F^2	1.054
Peak/hole [e Å^{-3}]	0.215 / -0.178

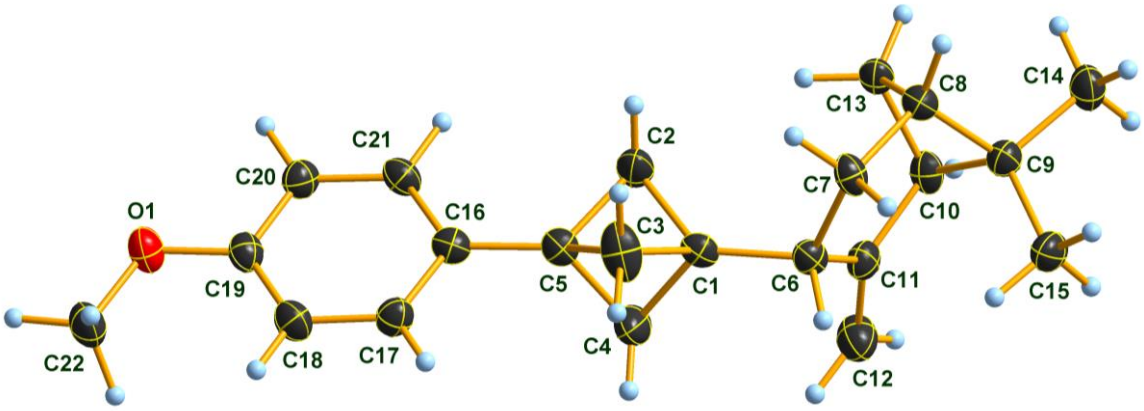


Figure 11. Molecular structure of compound **4m** in the crystal. DIAMOND[119] representation; thermal ellipsoids are drawn at 50 % probability level.

2-(3-(4-Methoxyphenyl)bicyclo[1.1.1]pentan-1-yl)cyclohexan-1-one (9c)

Table 5. Details for X-ray data collection and structure refinement for compound **9c**.

	9c
Empirical formula	$C_{18}H_{22}O_2$
Formula mass	270.35
T[K]	143(2)
Crystal size [mm]	0.40 × 0.35 × 0.25
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	12.8464(4)
b [Å]	7.7678(3)
c [Å]	15.0626(4)
α [°]	90.0
β [°]	99.686(3)
γ [°]	90.0
V [Å^3]	1481.64(8)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.212
μ [mm^{-1}]	0.077
F(000)	584
Θ range [°]	3.41 – 25.24
Index ranges	-16 ≤ *h* ≤ 16
	-9 ≤ *k* ≤ 9
	-18 ≤ *l* ≤ 18
Reflns. collected	20402
Reflns. obsd.	2429
Reflns. unique	2863 (R_{int} = 0.0292)
R_1, wR_2 (2σ data)	0.0767, 0.2031
R_1, wR_2 (all data)	0.0863, 0.2142
GOOF on F^2	1.027
Peak/hole [e Å^{-3}]	0.733 / -0.280

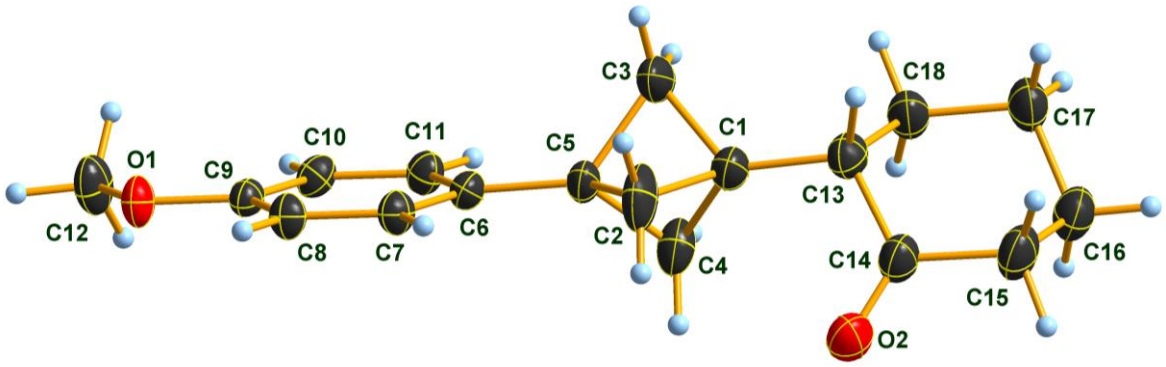


Figure 12. Molecular structure of compound **9c** in the crystal. DIAMOND[119] representation; thermal ellipsoids are drawn at 50 % probability level.

Ethyl 4-(bicyclo[1.1.1]pentan-1-yl)-1-methylpiperidine-4-carboxylate (20)

Table 6. Details for X-ray data collection and structure refinement for compound **20**.

	20
Empirical formula	$C_{14}H_{23}NO_2$
Formula mass	237.33
T[K]	123(2)
Crystal size [mm]	0.40 × 0.40 × 0.35
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	15.4834(7)
b [Å]	5.9795(3)
c [Å]	14.7917(7)
α [°]	90.0
β [°]	97.994(4)
γ [°]	90.0
V [Å^3]	1356.15(11)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.162
μ [mm^{-1}]	0.077
F(000)	520
Θ range [°]	2.66 – 25.24
Index ranges	-22 ≤ *h* ≤ 22

	-8 ≤ *k* ≤ 8
	-21 ≤ *l* ≤ 21
Reflns. collected	26420
Reflns. obsd.	3121
Reflns. unique	4124 (R_{int} = 0.0472)
R_1, wR_2 (2σ data)	0.0452, 0.1104
R_1, wR_2 (all data)	0.0658, 0.1242
GOOF on F^2	1.026
Peak/hole [e Å^{-3}]	0.377 / -0.198

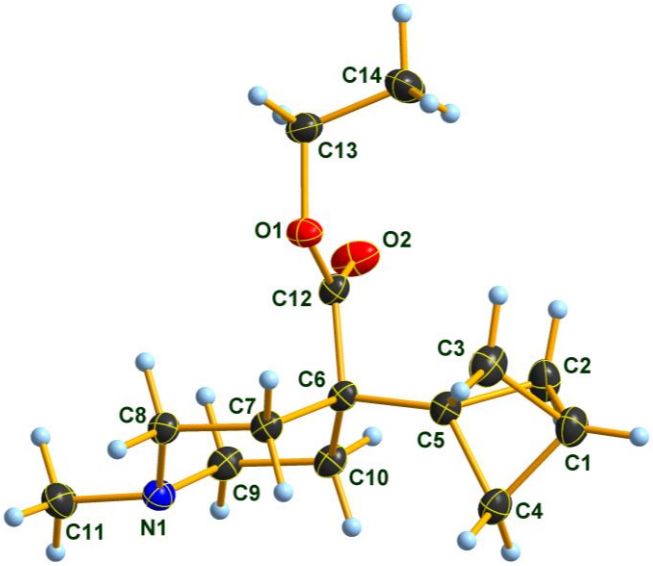


Figure 13. Molecular structure of compound **20** in the crystal. DIAMOND[119] representation; thermal ellipsoids are drawn at 50 % probability level.

2 Details of the Computational Calculations

Geometry optimizations have been performed using the B3LYP hybrid functional[120] complemented by the D3 dispersion correction.[121] The def2SVP all electron basis set[122] has been used for all elements. Thermal corrections to enthalpies at 298.15 K have been calculated at the same level using the rigid rotor/harmonic oscillator model. The abbreviation "qh" has been added where entropies and free energies at 298.15 K (S_{298} and G_{298}) have been calculated using the quasi-harmonic approximation with a cutoff value of 100 cm^{-1}. Single point energies have subsequently been calculated with the double-hybrid B2PLYP-D3 functional[121,123] in combination with the def2-TZVPP basis set,[122] and combined with thermal corrections obtained at B3LYP-D3/def2SVP level in order to calculate enthalpies at 298.15 K. Solvent effects in tetrahydrofuran (THF) have been evaluated through single point calculations with the SMD continuum solvation model[124] at the B3LYP-D3/def2SVP level using gas phase geometries. Free energies in solution have been corrected to a reference state of 1 mol/l at 298.15 K through addition of RTln(24.46) = +7.925 kJ/mol (= 0.0030185 Hartree) to the gas phase (1 atm) free energies. All calculations have been performed with *Gaussian 09*.[125] The value for R = 8.31451 J K^{-1} mol^{-1}. Natural Bond Orbital (NBO) analysis was performed using NBO 6.0.[126]

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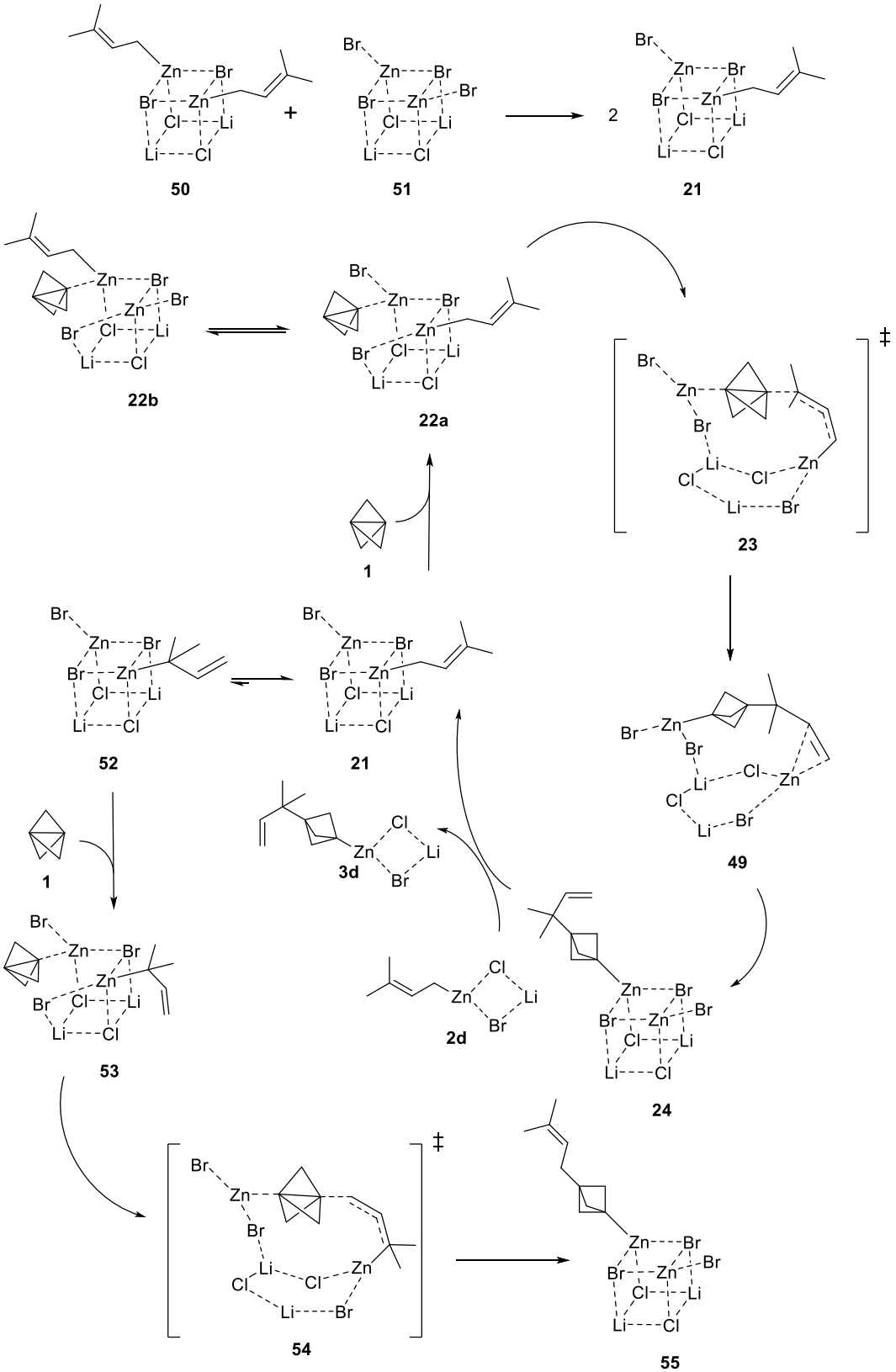


Scheme 45. Reaction mechanism for the addition of propellane (**1**) to the prenylzinc reagent **2d** via the cubic cluster **21**.

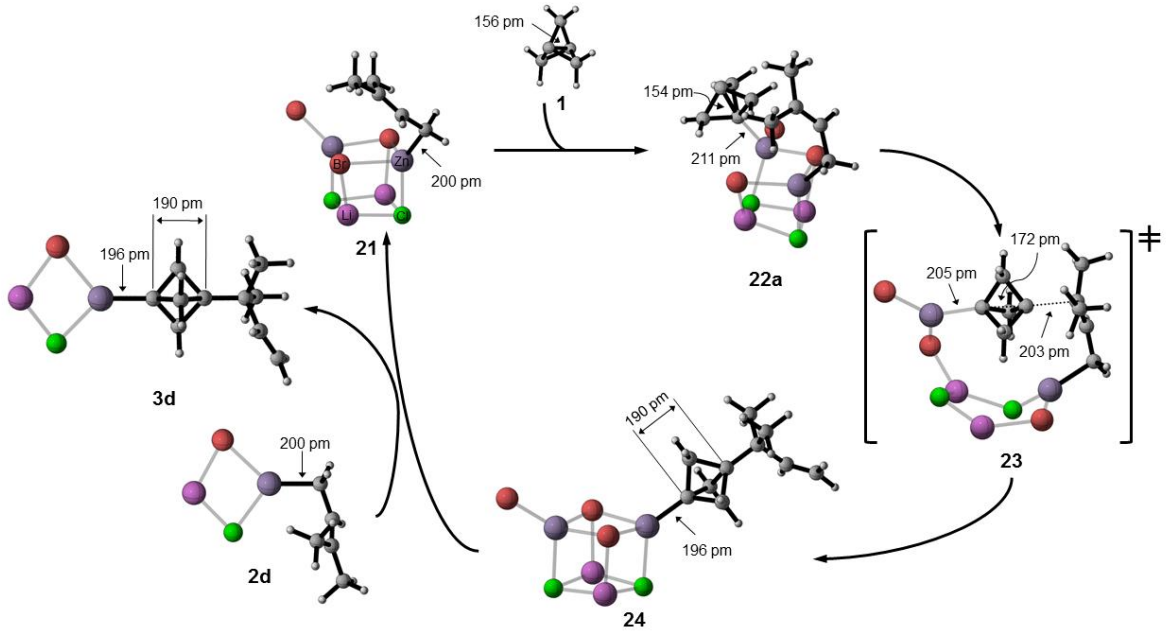


Figure 14. Calculated geometries of selected intermediates shown in Figure 12 (B3LYP-D3/def2SVP).

Table 7. Total energies and enthalpies for the systems shown in Scheme 45 (in kJ/mol).

system	ΔH_{298} SMD(THF)/ B2PLYP-D3/ def2TZVPP// [kJ/mol]	ΔG_{298}(qh,1M) SMD(THF)/ B2PLYP-D3/ def2TZVPP// [kJ/mol]
1+21	0.0	0.0
1+52	+27.9	+28.4
22a	-47.3	-3.1
22b	-68.8	-25.5
23	-0.1	+52.0
49	-35.0	+19.6
24	-96.6	-42.7
53	-20.9	+25.1
54	+44.6	+95.6
55	-107.6	-56.5

Table 8. Total energies and enthalpies for the systems shown in Scheme 45 (in kJ/mol).

system	ΔH_{298} SMD(THF)/ B2PLYP-D3/ def2TZVPP// [kJ/mol]	ΔG_{298}(qh,1M) SMD(THF)/ B2PLYP-D3/ def2TZVPP// [kJ/mol]
Eq. 52 > 21	-27.9	-28.4
50 + 51 > 2 x 21	-6.9	-4.4
Step 1: 1 + 21 > 22a	-47.3	-3.1
Step 2: 22a > 23	+47.2	+55.1
Step 3: 23 > 49	-34.9	-32.4
Step 4: 49 > 24	-61.6	-62.3
Step 5: 24 + 2d > 21 + 3d	-2.5	-2.5
sum of steps (1 + 2d > 3d)	-99.1	-45.2
Step 1': 1 + 52 > 53	-48.8	-3.3
Step 2': 53 > 54	+65.5	+70.5
Step 3' + 4': 54 > 55	-152.1	-152.1

Table 9. Total energies and enthalpies for the systems shown in Scheme 45 (in Hartree).

system	E_{tot} B3LYP-D3/ def2SVP	H_{298} B3LYP-D3/ def2SVP	G_{298} B3LYP-D3/ def2SVP	$<S^2>$ B3LYP-D3/ def2SVP	G_{298}(qh) B3LYP-D3/ def2SVP	E_{tot} B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP	$<S^2>$ B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP
1							
kn13_005	**-193.87237324**	-193.774506	-193.803999	0.00	-193.803999	-193.9042284	0.00
kn13_002	-193.87235922	-193.774498	-193.805682	0.00	-193.805682	-193.9042207	0.00
21							
ks01_085	**−12411.5110482**	−12411.352496	−12411.432143	0.00	−12411.427599	−12411.0653400	0.00
ks01_084	−12411.5104746	−12411.351721	−12411.431056	0.00	−12411.426373	−12411.0641721	0.00
ks01_086	−12411.5094574	−12411.351089	−12411.432633	0.00	−12411.426892	−12411.0649448	0.00
ks01_006	−12411.5090628	−12411.350600	−12411.432506	0.00	−12411.426177	−12411.0654693	0.00
ks01_002	−12411.5089516	−12411.350515	−12411.432601	0.00	−12411.426285	−12411.0649217	0.00
ks01_005	−12411.5086638	−12411.350324	−12411.431980	0.00	−12411.426091		0.00
22a							
ks01_024 (from ks01_023)	**−12605.4152459**	−12605.156649	−12605.251456	0.00	−12605.243086	−12604.998245	0.00
ks01_023	−12605.4151470	−12605.156301	−12605.249776	0.00	−12605.242495	−12604.9975198	0.00
ks01_090	−12605.4148468	−12605.156225	−12605.249669	0.00	−12605.242501		0.00
ks01_034 (from ks01_021)	−12605.4140028	−12605.155483	−12605.249663	0.00	−12605.242096	−12604.996697	0.00
ks01_021	−12605.4137674	−12605.155215	−12605.248320	0.00	−12605.241204	−12604.9959609	0.00
ks01_036 (from ks01_013)	−12605.4137559	−12605.155175	−12605.249919	0.00	−12605.241970		0.00
ks01_091	−12605.4135722	−12605.154924	−12605.250584	0.00			0.00
ks01_037 (from ks01_020)	−12605.4135522	−12605.154932	−12605.251021	0.00	−12605.242016		0.00
ks01_035 (from ks01_019)	−12605.4133826	−12605.154734	−12605.249638	0.00	−12605.241274		0.00
ks01_019	−12605.4132439	−12605.154567	−12605.248122	0.00	−12605.240648		0.00
ks01_013	−12605.4131086	−12605.154491	−12605.248727	0.00	−12605.240952		0.00
ks01_020	−12605.4130679	−12605.154399	−12605.249756	0.00	−12605.241095		0.00
ks01_027 (from ks01_022)	−12605.4126888	−12605.154128	−12605.249455	0.00	−12605.240981		0.00
ks01_022	−12605.4119964	−12605.153462	−12605.248601	0.00	−12605.240038		0.00
22b							
ks01_026	**−12605.4188114**	−12605.160220	−12605.253088	0.00	−12605.246978	−12605.0022938	0.00
ks01_040	−12605.4186432	−12605.160117	−12605.253158	0.00	−12605.246883	−12605.0025190	0.00
ks01_042	−12605.4098360	−12605.151405	−12605.245772	0.00	−12605.238174		0.00
ks01_041	−12605.4098354	−12605.151404	−12605.245781	0.00	−12605.238174		0.00

23							
ks01_050	−12605.3825283	−12605.124945	−12605.216249	0.00	−12605.208368	−12604.9667026	0.00
49							
ks01_051	−12605.4032362	−12605.142944	−12605.231908	0.00	−12605.225409	−12604.9869363	0.00
24							
ks01_014	**−12605.4371295**	−12605.177082	−12605.268961	0.00	−12605.259814	−12605.0211343	0.00
ks01_011	−12605.4371134	−12605.177034	−12605.268950	0.00	−12605.259735	−12605.0211232	0.00
ks01_012	−12605.4370486	−12605.177082	−12605.269143	0.00	−12605.259890		0.00
ks01_010	−12605.4370146	−12605.176998	−12605.268294	0.00	−12605.259761		0.00
ks01_038 (from ks01_010)	−12605.4367909	−12605.176699	−12605.267519	0.00	−12605.259407		0.00
ks01_015	−12605.4336522	−12605.173626	−12605.265466	0.00	−12605.256550		0.00
2d							
kn13_009	-5016.6575135	-5016.514420	-5016.572439	0.00	-5016.569117	-5016.4976610	0.00
kn13_008	-5016.6573729	-5016.514302	-5016.572214	0.00	-5016.569054	-5016.4980160	0.00
kn13_004	-5016.6573728	-5016.514302	-5016.572214	-	-	-	-
kn13_001	-5016.6567449	-5016.513644	-5016.572378	0.00	-5016.568774	-5016.4975508	0.00
3d							
kn13_013	-5210.5856109	-5210.340783	-5210.408077	0.00	-5210.403184	-5210.4549339	0.00
kn13_011	-5210.5855788	-5210.341796	-5210.406118	0.00	-5210.402634	-5210.4549318	0.00
50							
ks02_042	**-10033.3929298**	-10033.104189	-10033.194703	0.00	-10033.189135	-10033.0573258	0.00
ks02_038	-10033.3927713	-10033.104375	-10033.196645	0.00	-10033.190157	-10033.0571647	0.00
ks02_039	-10033.3922736	-10033.103966	-10033.196127	0.00			0.00
ks02_003	-10033.3921815	-10033.103941	-10033.198071	0.00	-10033.189771	-10033.0560727	0.00
ks02_037	-10033.3908662	-10033.102662	-10033.195757	0.00	-10033.188428		0.00
ks02_040	-10033.3906193	-10033.102392	-10033.196595	0.00			0.00
ks02_041	-10033.3894988	-10033.101210	-10033.195488	0.00			0.00
51							
ks01_108	-14789.6266544	-14789.598119	-14789.666955	0.00	-14789.663493	-14789.0735976	0.00
52							
ks01_083	**-12411.5003651**	-12411.341884	-12411.424430	0.00	-12411.416821	-12411.5285638	0.00
ks01_097	-12411.5002209	-12411.341705	-12411.423409	0.00	-12411.416611	-12411.5283789	0.00

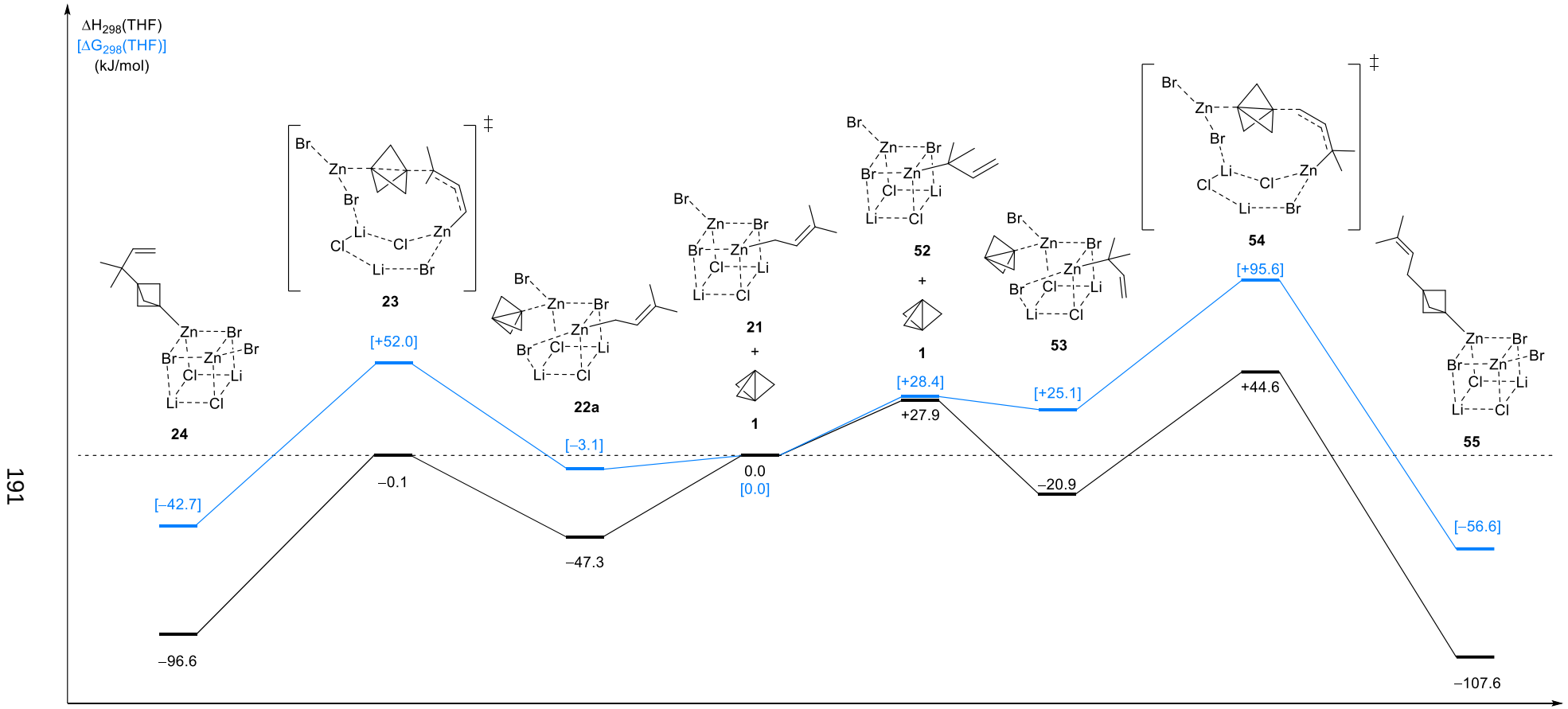
53							
ks01_110 (from ks01_024)	−12605.4058751	−12605.147206	−12605.240677	0.00	−12605.232991	−12604.988232	0.00
54							
ks01_111 (from ks01_050)	−12605.3733249	−12605.115643	−12605.208393	0.00	−12605.199519	−12604.95576	0.00
55							
ks01_112	-12605.4421728	-12605.182058	-12605.275534	0.00	-12605.265748	-12605.023727	0.00
ks01_113	-12605.4422142	-12605.182165	-12605.276281	0.00	-12605.266013	-12605.023752	0.00
ks01_114	-12605.4421319	-12605.182082	-12605.275692	0.00			0.00

Table 10. Total energies and enthalpies for the systems shown in Scheme 45 (in Hartree).

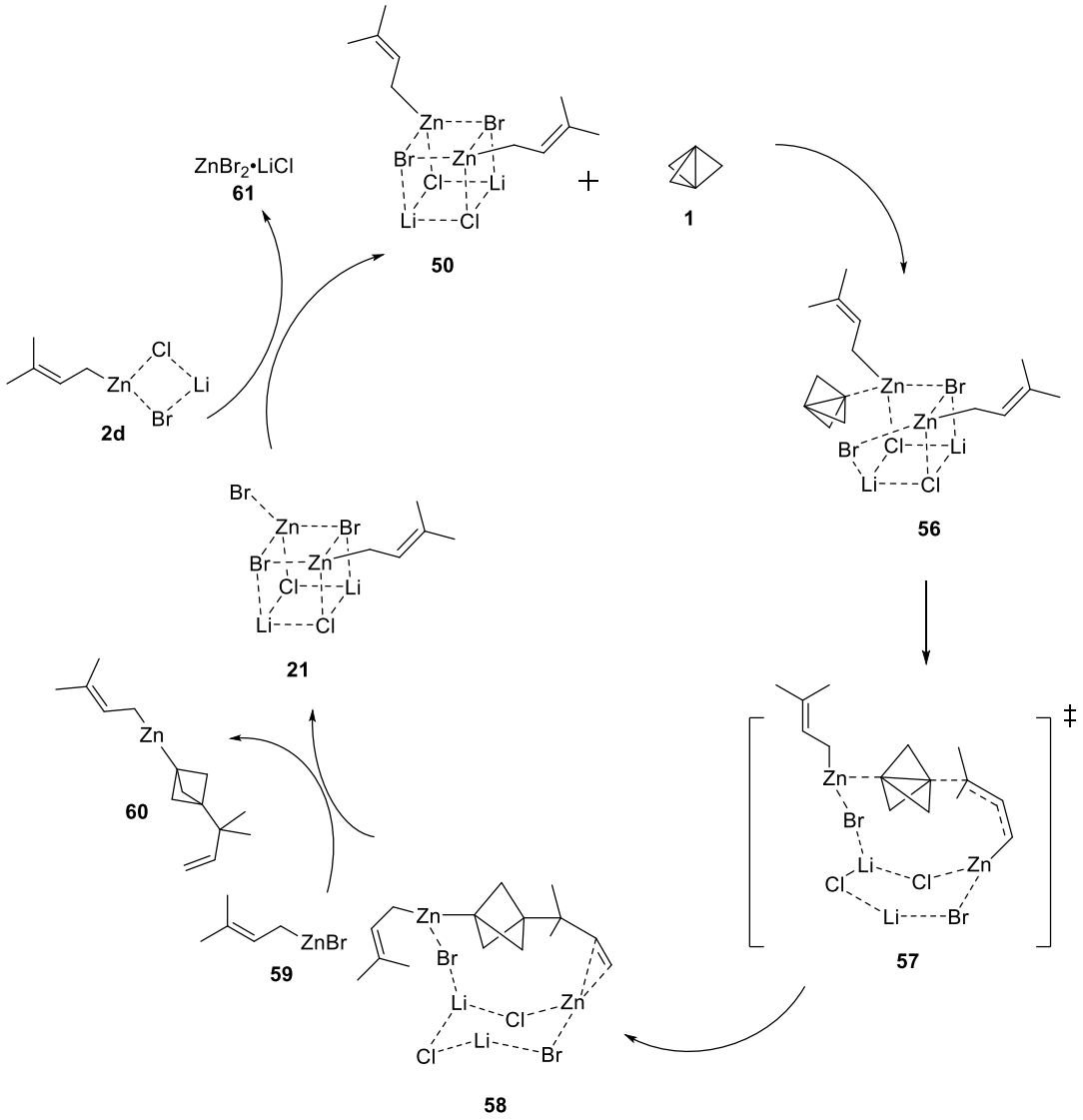
system	E_{tot} B3LYP-D3/ def2SVP	H_{298} B3LYP-D3/ def2SVP	G_{298}(qh) B3LYP-D3/ def2SVP (qh)	E_{tot} B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP	E_{tot} SMD(THF)/ B3LYP-D3/ def2SVP	G_{298}(qh,1M) SMD(THF)/ B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP
1						
kn13_005	**-193.87237324**	-193.774506	-193.803999	-193.9042284	-193.88523394	-193.8456964
kn13_002	-193.87235922	-193.774498	-193.805682	-193.9042207	-193.88523469	**-193.8474005**
21						
ks01_085	**−12411.5110482**	−12411.352496	−12411.427599	−12411.0653400	−12411.5408086	**-12411.0086327**
ks01_084	−12411.5104746	−12411.351721	−12411.426373	−12411.0641721	−12411.5412006	-12411.0077780
ks01_086	−12411.5094574	−12411.351089	−12411.426892	−12411.0649448	−12411.5373398	-12411.0072433
ks01_006	−12411.5090628	−12411.350600	−12411.426177	−12411.0654693	−12411.5368335	-12411.0073357
ks01_002	−12411.5089516	−12411.350515	−12411.426285	−12411.0649217	−12411.5367619	-12411.0070469
ks01_005	−12411.5086638	−12411.350324	−12411.426091		−12411.5363737	
22a						
ks01_024 (from ks01_023)	**−12605.4152459**	−12605.156649	−12605.243086	−12604.998245	−12605.4493860	**-12604.8572067**
ks01_023	−12605.4151470	−12605.156301	−12605.242495	−12604.9975198	−12605.4480332	-12604.8547355
ks01_090	−12605.4148468	−12605.156225	−12605.242501	−12604.9980338	−12605.4492291	-12604.8570518
ks01_034 (from ks01_021)	−12605.4140028	−12605.155483	−12605.242096	−12604.996697	−12605.4483264	-12604.8560953
ks01_021	−12605.4137674	−12605.155215	−12605.241204	−12604.9959609	−12605.4473458	-12604.8539574
ks01_036 (from ks01_013)	−12605.4137559	−12605.155175	−12605.241970		−12605.4476853	
ks01_037 (from ks01_020)	−12605.4135522	−12605.154932	−12605.242016		−12605.4473518	

ks01_035 (from ks01_019)	−12605.4133826	−12605.154734	−12605.241274		−12605.4483837	
ks01_019	−12605.4132439	−12605.154567	−12605.240648		−12605.4475184	
ks01_013	−12605.4131086	−12605.154491	−12605.240952		−12605.4465225	
ks01_020	−12605.4130679	−12605.154399	−12605.241095		−12605.4465365	
ks01_027 (from ks01_022)	−12605.4126888	−12605.154128	−12605.240981		−12605.4470863	
ks01_022	−12605.4119964	−12605.153462	−12605.240038		−12605.4459708	
22b						
ks01_026	−12605.4188114	−12605.160220	−12605.246978	−12605.0022938	−12605.4571148	**-12604.8657453**
ks01_040	−12605.4186432	−12605.160117	−12605.246883	−12605.002519	−12605.4565069	-12604.8656040
ks01_042	−12605.4098360	−12605.151405	−12605.238174		−12605.4472447	
ks01_041	−12605.4098354	−12605.151404	−12605.238174		−12605.4472396	
23						
ks01_050	−12605.3825283	−12605.124945	−12605.208368	−12604.9667026	−12605.429241	**-12604.8362365**
49						
ks01_051	−12605.4032362	−12605.142944	−12605.225409	−12604.9869363	−12605.4457196	**-12604.8485740**
24						
ks01_014	**−12605.4371295**	−12605.177082	−12605.259814	−12605.0211343	−12605.4686426	**-12604.8723134**
ks01_011	−12605.4371134	−12605.177034	−12605.259735	−12605.0211232	−12605.4685560	-12604.8721689
ks01_012	−12605.4370486	−12605.177082	−12605.259890		−12605.4680948	
ks01_010	−12605.4370146	−12605.176998	−12605.259761		−12605.4681572	
ks01_038 (from ks01_010)	−12605.4367909	−12605.176699	−12605.259407		−12605.4682164	
ks01_015	−12605.4336522	−12605.173626	−12605.256550		−12605.4646365	
2d						
kn13_009	-5016.6575135	-5016.514420	-5016.569117	-5016.4976610	-5016.6817050	-5016.4304375
kn13_008	-5016.6573729	-5016.514302	-5016.569054	-5016.4980160	-5016.6821803	**-5016.4314860**
kn13_001	-5016.6567449	-5016.513644	-5016.568774	-5016.4975508	-5016.6810878	-5016.4309043
3d						
kn13_013	-5210.5856109	-5210.340783	-5210.403184	-5210.4549339	-5210.6122602	**-5210.2961378**
kn13_011	-5210.5855788	-5210.341796	-5210.402634	-5210.4549318	-5210.6121604	-5210.2955501
50						
ks02_042	-10033.3929298	-10033.104189	-10033.189135	-10033.0571647	-10033.4190869	-10032.8765085
ks02_038	-10033.3927713	-10033.104375	-10033.190157	-10033.0571647	-10033.4186489	**-10032.8774095**
ks02_039	-10033.3922736	-10033.103966				
ks02_003	-10033.3921815	-10033.103941	-10033.189771	-10033.0560727	-10033.4172632	-10032.8757254

ks02_037	-10033.3908662	-10033.102662	-10033.188428			
ks02_040	-10033.3906193	-10033.102392				
ks02_041	-10033.3894988	-10033.101210				
51						
ks01_108	-14789.6266544	-14789.598119	-14789.663493	-14789.0735976	-14789.6574140	-14789.1381773
52						
ks01_083	-12411.5003651	-12411.341884	-12411.416821	-12411.0561902	-12411.5285638	**-12410.9978263**
ks01_097	-12411.5002209	-12411.341705	-12411.416611	-12411.0559051	-12411.5283789	-12410.9974347
53						
ks01_110 (from ks01_024)	−12605.4058751	−12605.147206	−12605.232991	−12604.988232	−12605.4400322	-12604.8464865
54						
ks01_111 (from ks01_050)	−12605.3733249	−12605.115643	−12605.199519	−12604.95576	−12605.4140140	-12604.8196247
55						
ks01_113	-12605.4422142	-12605.182165	-12605.266013	-12605.023752	-12605.4752537	**-12604.7967423**
ks01_112	-12605.4421728	-12605.182058	-12605.265748	-12605.023727	-12605.4751313	-12604.7965707
ks01_114	-12605.4421319	-12605.182082				



Scheme 46. Comparison of the Enthalpies and Free Energies of the reactions of the two regioisomeric clusters **21** and **52** (SMD(THF)/B2PLYP-D3/def2TZVPP//B3LYP-D3/def2SVP).



Scheme 47. Reaction mechanism for the addition of propellane (**1**) to the prenylzinc reagent **2d** via the cubic cluster **50**.

Table 11. Total energies and enthalpies for the systems shown in Scheme 47 (in kJ/mol).

system	ΔH_{298} SMD(THF)/ B2PLYP-D3/ def2TZVPP// [kJ/mol]	ΔG_{298}(qh,1M) SMD(THF)/ B2PLYP-D3/ def2TZVPP// [kJ/mol]
1+50	0.0	0.0
56	-58.4	-11.3
57	+16.0	+71.6
58	-14.9	+44.1

Table 12. Total energies and enthalpies for the systems shown in Scheme 47 (in kJ/mol).

system	ΔH_{298} SMD(THF)/ B2PLYP-D3/ def2TZVPP// [kJ/mol]	ΔG_{298}(qh,1M) SMD(THF)/ B2PLYP-D3/ def2TZVPP// [kJ/mol]
Step 1: 1 + 50 > 56	-58.4	-11.3
Step 2: 56 > 57	+74.4	+82.9
Step 3: 57 > 58	-30.9	-27.5
58 + 59 > 21 + 60	-103.5	-107.7
21 + 2d > 61 + 50	+11.4	+10.5
sum of steps (1 + 59 + 2d > 60 + 61)	-106.9	-53.1

Table 13. Total energies and enthalpies for the systems shown in Scheme 47 (in Hartree).

system	E_{tot} B3LYP-D3/ def2SVP	H_{298} B3LYP-D3/ def2SVP	G_{298} B3LYP-D3/ def2SVP	$<S^2>$ B3LYP-D3/ def2SVP	G_{298}(qh) B3LYP-D3/ def2SVP	E_{tot} B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP	$<S^2>$ B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP
1							
kn13_005	**-193.87237324**	-193.774506	-193.803999	0.00	-193.803999	-193.9042284	0.00
kn13_002	-193.87235922	-193.774498	-193.805682	0.00	-193.805682	-193.9042207	0.00
50							
ks02_042	**-10033.3929298**	-10033.104189	-10033.194703	0.00	-10033.189135	-10033.0573258	0.00
ks02_038	-10033.3927713	-10033.104375	-10033.196645	0.00	-10033.190157	-10033.0571647	0.00
ks02_039	-10033.3922736	-10033.103966	-10033.196127	0.00			0.00
ks02_003	-10033.3921815	-10033.103941	-10033.198071	0.00	-10033.189771	-10033.0560727	0.00
ks02_037	-10033.3908662	-10033.102662	-10033.195757	0.00	-10033.188428		0.00
ks02_040	-10033.3906193	-10033.102392	-10033.196595	0.00			0.00
ks02_041	-10033.3894988	-10033.101210	-10033.195488	0.00			0.00
56							
ks02_012	**-10227.3052237**	-10226.916679	-10227.021301	0.00	-10227.012715	-10226.9960038	0.00
ks02_010	-10227.2984725	-10226.910081	-10227.014552	0.00	-10227.006872	-10226.9905268	0.00
ks02_001	-10227.2978486	-10226.909531	-10227.013319	0.00	-10227.005947	-10226.9896733	0.00
ks02_009	-10227.2975953	-10226.909347	-10227.013587	0.00			0.00
ks02_014	-10227.2975313	-10226.909173	-10227.012846	0.00			0.00
ks02_013	-10227.2968184	-10226.908633	-10227.013779	0.00			0.00

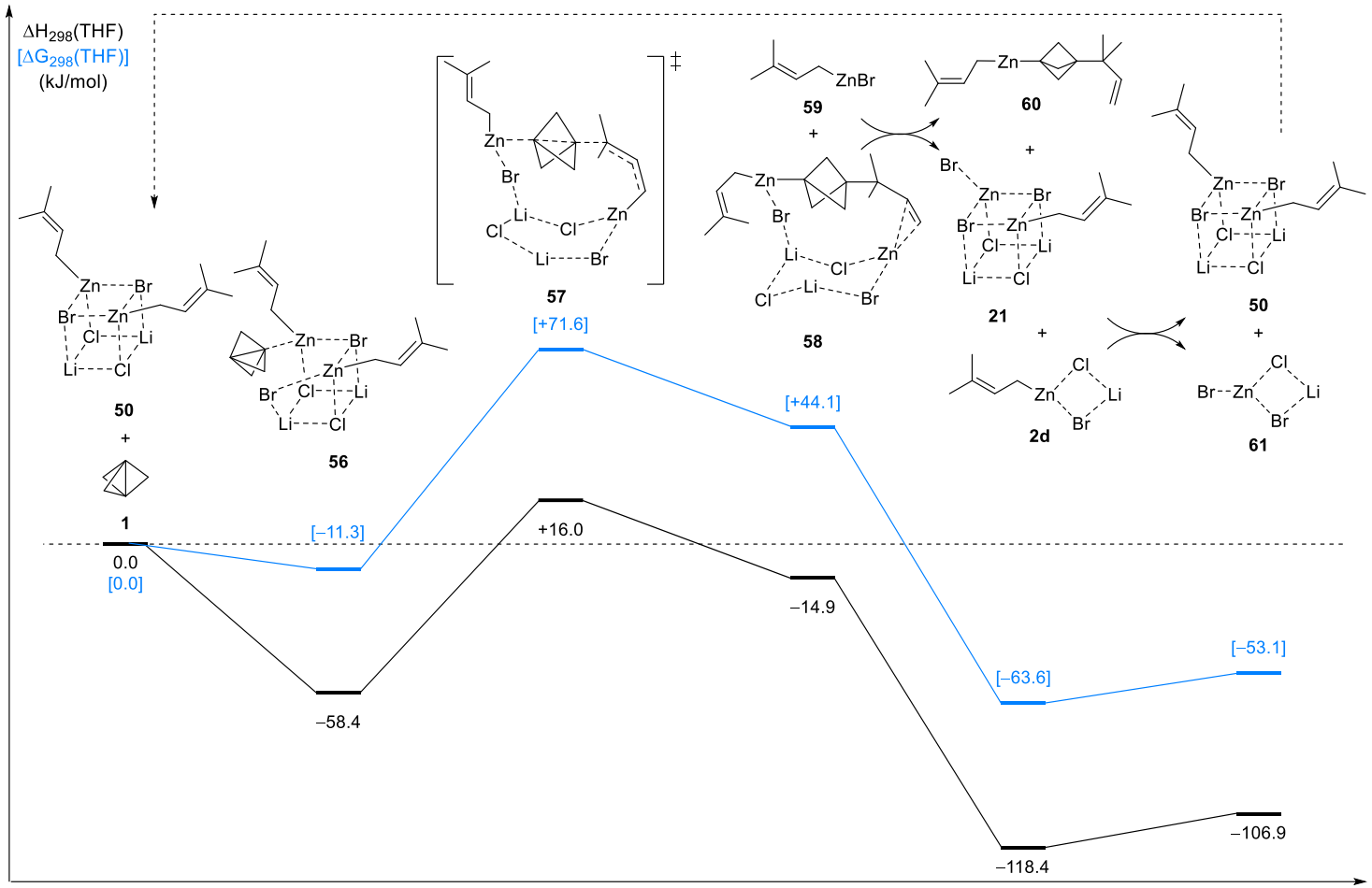
ks02_011	-10227.2956843	-10226.907444	-10227.014436	0.00			0.00
ks02_015	-10227.2917191	-10226.903294	-10227.008026	0.00			0.00
ks02_016	-10227.2902996	-10226.901975	-10227.008498	0.00			0.00
57							
ks02_018	-10227.2626470	-10227.875338	-10227.975248	0.00	-10226.967933	-10226.9542079	0.00
ks02_008	-10227.2612208	-10226.873876	-10226.974168	0.00	-10226.966646	-10226.9529420	0.00
58							
ks02_033	-10227.2808404	-10226.891156	-10226.989474	0.00	-10226.982642	-10226.9713185	0.00
59							
ks02_044	-4548.92915993	-4548.792373	-4548.841518	0.00	-4548.839792	-4548.7779531	0.00
60							
ks02_035	-2364.73274204	-2364.364799	-2364.436727	0.00	-2364.430222	-2364.7183248	0.00
21							
ks01_085	**−12411.5110482**	−12411.352496	−12411.432143	0.00	−12411.427599	−12411.0653400	0.00
ks01_084	−12411.5104746	−12411.351721	−12411.431056	0.00	−12411.426373	−12411.0641721	0.00
ks01_086	−12411.5094574	−12411.351089	−12411.432633	0.00	−12411.426892	−12411.0649448	0.00
ks01_006	−12411.5090628	−12411.350600	−12411.432506	0.00	−12411.426177	−12411.0654693	0.00
ks01_002	−12411.5089516	−12411.350515	−12411.432601	0.00	−12411.426285	−12411.0649217	0.00
ks01_005	−12411.5086638	−12411.350324	−12411.431980	0.00	−12411.426091		0.00
2d							
kn13_009	-5016.6575135	-5016.514420	-5016.572439	0.00	-5016.569117	-5016.4976610	0.00
kn13_008	-5016.6573729	-5016.514302	-5016.572214	0.00	-5016.569054	-5016.4980160	0.00
kn13_004	-5016.6573728	-5016.514302	-5016.572214	-	-	-	-
kn13_001	-5016.6567449	-5016.513644	-5016.572378	0.00	-5016.568774	-5016.4975508	0.00
61							
ks02_030	-7394.77658141	-7394.763260	-7394.808503	0.00	-7394.807686	-7394.5089863	0.00

Table 14. Total energies and enthalpies for the systems shown in Scheme 47 (in Hartree).

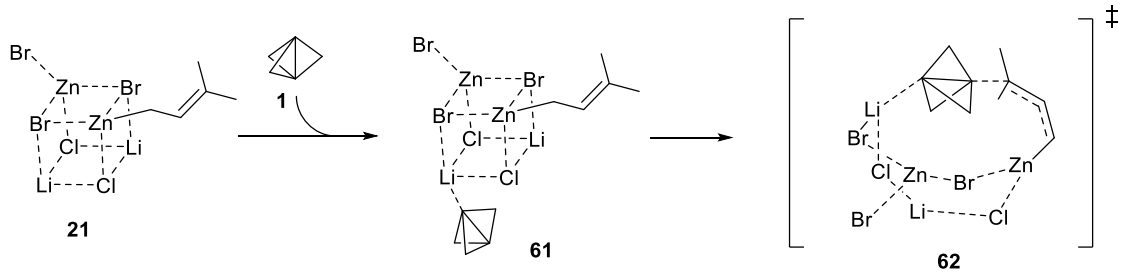
system	E_{tot} B3LYP-D3/ def2SVP	H_{298} B3LYP-D3/ def2SVP	G_{298}(qh) B3LYP-D3/ def2SVP (qh)	E_{tot} B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP	E_{tot} SMD(THF)/ B3LYP-D3/ def2SVP	G_{298}(qh,1M) SMD(THF)/ B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP
1						
kn13_005	**-193.87237324**	-193.774506	-193.803999	-193.9042284	-193.88523394	-193.8456964
kn13_002	-193.87235922	-193.774498	-193.805682	-193.9042207	-193.88523469	**-193.8474005**

50						
ks02_042	-10033.3929298	-10033.104189	-10033.189135	-10033.0571647	-10033.4190869	-10032.8765085
ks02_038	-10033.3927713	-10033.104375	-10033.190157	-10033.0571647	-10033.4186489	**-10032.8774095**
ks02_039	-10033.3922736	-10033.103966				
ks02_003	-10033.3921815	-10033.103941	-10033.189771	-10033.0560727	-10033.4172632	-10032.8757254
ks02_037	-10033.3908662	-10033.102662	-10033.188428			
ks02_040	-10033.3906193	-10033.102392				
ks02_041	-10033.3894988	-10033.101210				
56						
ks02_012	-10227.3052237	-10226.916679	-10227.012715	-10226.9960038	-10227.3338794	**-10226.7291323**
ks02_010	-10227.2984725	-10226.910081	-10227.006872	-10226.9905268	-10227.3305239	-10226.7279592
ks02_001	-10227.2978486	-10226.909531	-10227.005947	-10226.9896733	-10227.3311231	-10226.7280277
ks02_009	-10227.2975953	-10226.909347				
ks02_014	-10227.2975313	-10226.909173				
ks02_013	-10227.2968184	-10226.908633				
ks02_011	-10227.2956843	-10226.907444				
ks02_015	-10227.2917191	-10226.903294				
ks02_016	-10227.2902996	-10226.901975				
57						
ks02_008	-10227.2612208	-10226.873876	-10226.966646	-10226.9529420	-10227.3034165	**-10226.6975444**
ks02_018	-10227.2626470	-10227.875338	-10226.967933	-10226.9542079	-10227.3024963	-10226.6963247
58						
ks02_033	-10227.2808404	-10226.891156	-10226.982642	-10226.9713185	-10227.3187442	-10226.7080054
59						
ks02_044	-4548.92915993	-4548.792373	-4548.839792	-4548.7779531	-4548.94937872	-4548.7057855
60						
ks02_035	-2364.73274204	-2364.364799	-2364.430222	-2364.7183248	-2364.76613737	-2364.4461816
21						
ks01_085	**−12411.5110482**	−12411.352496	−12411.427599	−12411.0653400	−12411.5408086	**-12411.0086327**
ks01_084	−12411.5104746	−12411.351721	−12411.426373	−12411.0641721	−12411.5412006	-12411.0077780
ks01_086	−12411.5094574	−12411.351089	−12411.426892	−12411.0649448	−12411.5373398	-12411.0072433
ks01_006	−12411.5090628	−12411.350600	−12411.426177	−12411.0654693	−12411.5368335	-12411.0073357
ks01_002	−12411.5089516	−12411.350515	−12411.426285	−12411.0649217	−12411.5367619	-12411.0070469
ks01_005	−12411.5086638	−12411.350324	−12411.426091		−12411.5363737	
2d						
kn13_009	-5016.6575135	-5016.514420	-5016.569117	-5016.4976610	-5016.6817050	-5016.4304375
kn13_008	-5016.6573729	-5016.514302	-5016.569054	-5016.4980160	-5016.6821803	**-5016.4314860**
kn13_001	-5016.6567449	-5016.513644	-5016.568774	-5016.4975508	-5016.6810878	-5016.4309043

61						
ks02_030	-7394.77658141	-7394.763260	-7394.807686	-7394.5089863	-7394.79822615	-7394.5587171



Scheme 48. Enthalpies and Free Energies for the reaction with the symmetric cluster **50** (SMD(THF)/B2PLYP-D3/def2TZVPP//B3LYP-D3/def2SVP).



Scheme 49. Coordination of [1.1.1]propellane on a lithium atom in cluster **21**, leading towards the transition state **62**.

Table 15. Reaction energies for the systems shown in Scheme 49 (in Hartree) and comparison to the system shown in Scheme 49.

system	ΔH_{298} SMD(THF)/ B2PLYP-D3/ def2TZVPP// [kJ/mol]	ΔG_{298}(qh,1M) SMD(THF)/ B2PLYP-D3/ def2TZVPP// [kJ/mol]
Step 1: 1 + 21 > 61	-44.8	-2.0
Step 2: 61 > 62	+81.8	+137.6
Scheme 45:		
Step 1: 1 + 21 > 22a	-47.3	-3.1
Step 2: 22a > 23	+47.2	+55.1

Table 16. Total energies and enthalpies for the systems shown in Scheme 49 (in Hartree).

system	E_{tot} B3LYP-D3/ def2SVP	H_{298} B3LYP-D3/ def2SVP	G_{298} B3LYP-D3/ def2SVP	$<S^2>$ B3LYP-D3/ def2SVP	G_{298}(qh) B3LYP-D3/ def2SVP	E_{tot} B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP	$<S^2>$ B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP
1							
kn13_005	**-193.87237324**	-193.774506	-193.803999	0.00	-193.803999	-193.9042284	0.00
kn13_002	-193.87235922	-193.774498	-193.805682	0.00	-193.805682	-193.9042207	0.00
21							
ks01_085	**−12411.5110482**	−12411.352496	−12411.432143	0.00	−12411.427599	−12411.0653400	0.00
ks01_084	−12411.5104746	−12411.351721	−12411.431056	0.00	−12411.426373	−12411.0641721	0.00
ks01_086	−12411.5094574	−12411.351089	−12411.432633	0.00	−12411.426892	−12411.0649448	0.00
ks01_006	−12411.5090628	−12411.350600	−12411.432506	0.00	−12411.426177	−12411.0654693	0.00

ks01_002	−12411.5089516	−12411.350515	−12411.432601	0.00	−12411.426285	−12411.0649217	0.00
ks01_005	−12411.5086638	−12411.350324	−12411.431980	0.00	−12411.426091		0.00
61							
ks03_002	-12605.4166014	-12605.157925	-12605.252647	0.00	-12605.244888	-12605.4474671	0.00
62							
ks03_011	-12605.3709199	-12605.114046	-12605.201209	0.00	-12605.196046	-12604.9528455	0.00

Table 17. Total energies and enthalpies for the systems shown in Scheme 49 (in Hartree).

system	E_{tot} B3LYP-D3/ def2SVP	H_{298} B3LYP-D3/ def2SVP	G_{298}(qh) B3LYP-D3/ def2SVP (qh)	E_{tot} B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP	E_{tot} SMD(THF)/ B3LYP-D3/ def2SVP	G_{298}(qh,1M) SMD(THF)/ B2PLYP-D3/ def2TZVPP// B3LYP-D3/ def2SVP
1						
kn13_005	**-193.87237324**	-193.774506	-193.803999	-193.9042284	-193.88523394	-193.8456964
kn13_002	-193.87235922	-193.774498	-193.805682	-193.9042207	-193.88523469	**-193.8474005**
21						
ks01_085	**−12411.5110482**	−12411.352496	−12411.427599	−12411.0653400	−12411.5408086	**-12411.0086327**
ks01_084	−12411.5104746	−12411.351721	−12411.426373	−12411.0641721	−12411.5412006	-12411.0077780
ks01_086	−12411.5094574	−12411.351089	−12411.426892	−12411.0649448	−12411.5373398	-12411.0072433
ks01_006	−12411.5090628	−12411.350600	−12411.426177	−12411.0654693	−12411.5368335	-12411.0073357
ks01_002	−12411.5089516	−12411.350515	−12411.426285	−12411.0649217	−12411.5367619	-12411.0070469
ks01_005	−12411.5086638	−12411.350324	−12411.426091		−12411.5363737	
61						
ks03_002	-12605.4166014	-12605.157925	-12605.244888	-12605.0006701	-12605.4474671	-12604,8568039
62						
ks03_011	-12605.3709199	-12605.114046	-12605.196046	-12604.9528455	-12605.3995730	-12604,8036062

Table 18. *Wiberg* Bond Index (WBI) and distances for reaction centers.

Structure	WBI of central C-C bond (B3LYP-D3/def2-SVP)	WBI of central C-C bond (B3LYP-D3/def2-TZVP)	WBI of C-M-bond (B3LYP-D3/def2-SVP)	WBI of C-M-bond (B3LYP-D3/def2-TZVP)	distance between bridgehead carbons (B3LYP-D3/def2-SVP) [pm]
1	0.7691	0.7906	-	-	156.3
22a	0.6557	0.6638	0.1291	0.1489	154.2
23	0.3393	0.3216	0.2194	0.2452	171.9
24	0.0579	0.0509	0.4775	0.5092	189.7
61	0.7260	0.7395	0.0374	0.0639	154.8

The coordination of [1.1.1]propellane (**1**) to zinc (**22a**) results in a reduction of the bonding order of the central bond indicated by a decrease of the *Wiberg* Bond Index (WBI). However, at the same time the length of the bond decreases by 2 pm. This is in accordance with the results of Jemmis,[15b] who observed similar results when investigating complexes of [1.1.1]propellane with electron-accepting halogen-bond donors. Overall, the removal of electron density from the mostly non-bonding HOMO seems to increase the strength of the central bond.

As expected, the WBI of the central bond decreases significantly when moving to the transition state **23**. In the product cluster **24** there is almost no bonding interaction between the bridgehead carbons. The WBI of the carbon-zinc bond in the intermediate **22a** is approximately 4 times smaller than the one of the carbon-zinc bond in the product cluster **24**. Similar trends were observed for the coordination of [1.1.1]propellane to lithium (**61**), albeit on a significantly smaller scale.

The NBO presentation of the central bond in [1.1.1]propellane includes two partially occupied lone pairs at the bridgehead carbon atoms. A strong donor-acceptor interaction between the lone pair of one of the bridgehead carbons and a vacant orbital of the neighbouring zinc in intermediate **22a** was confirmed by the NBO analysis:

113. (1.60735) LP (1) C 25 s(53.79%)p 0.86(46.12%)d 0.00(0.08%)f 0.00(0.01%)

141. (0.50812) LV (1)Zn 7 s(99.67%)p 0.00(0.17%)d 0.00(0.16%)f 0.00(0.00%)

144. (0.74142) LV (1) C 26 s(9.16%)p 9.87(90.35%)d 0.05(0.47%)f 0.00(0.02%)

SECOND ORDER PERTURBATION THEORY ANALYSIS OF FOCK MATRIX IN NBO BASIS

Threshold for printing: 0.50 kcal/mol

Donor (L) NBO	Acceptor (NL) NBO	E(2) kcal/mol	E(NL)-E(L) a.u.	F(L,NL) a.u.
113. LP (1) C 25	141. LV (1)Zn 7	68.37	0.30	0.129

Table 19. Calculated length of the central bond in [1.1.1]propellane using different basis sets.

method	B3LYP-D3/def2-SVP	B3LYP-D3/def2-TZVPP	B3LYP-D3/def2-QZVPP	experimental value[9]
length of the central C-C bond in **1** [pm]	156.3	156.7	156.6	159.4

The Natural Population Analysis (NPA) was employed to examine the charge distribution in selected intermediates (Table 20).

Table 20. Charges of fragments in [1.1.1]propellane in selected intermediates as determined by Natural Population Analysis.

Intermediate	charge of the bridgehead carbon next to zinc [a.u.]	charge of the bridgehead carbon opposite to zinc [a.u.]	charge of the bridge CH_2-groups (hydrogens summed into carbons) [a.u.]	total charge of the cage [a.u.]
1	−0.023	−0.023	+0.015	0
22a	−0.322	+0.086	+0.120/+0.119/+0.105	+0.108
23	−0.390	+0.019	+0.054/+0.067/+0.015	−0.233

The coordination of [1.1.1]propellane to the metal cluster in intermediate **22a** results in a localization of electron density at the bridgehead carbon adjacent to the zinc. This is compensated by a slight positive charge on the opposite bridgehead carbon and all of the CH_2-units, resulting in a total charge for the propellane unit of +0.108 e. In the transition state **23** the negative charge on the bridgehead carbon next to zinc is even larger. The remaining cage still holds a positive charge. This is in contrast to previously reported reactions of anions with [1.1.1]propellane, where the delocalization of additional electron density onto the bridge carbons and the resulting electronic repulsion was found to be responsible for the relatively high activation barriers.[18]

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