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METALATION AND FUNCTIONALIZATION OF 5-MEMBERED HETEROCYCLES AND THE TROPOLONE SCAFFOLD USING TMP-BASES - AND - COBALT-CATALYZED NEGISHI CROSS-COUPLING REACTIONS OF (HETERO)ARYLZINC REAGENTS

von

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_____
(Diana Haas)

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Parts of this PhD Thesis have been published:

1) Diana Haas, Marc Mosrin, Paul Knochel, "Regioselective Functionalization of the Oxazole Scaffold Using TMP-Bases of Mg and Zn", *Org. Lett.* **2013**, *15*, 6162–6165.

2) Diana Haas, Tomke Bresser, Maximilian S. Hofmayer, Paul Knochel, „Zincation of 4,4-dimethyloxazoline using TMPZnCl·LiCl. A new preparation of 2-aryloxazolines", *Chem. Commun.* **2015**, 51, 6415–6417.

3) Jeffrey M. Hammann, Diana Haas, Paul Knochel, "Cobalt-Catalyzed Negishi Cross-Coupling Reactions of (Hetero)Arylzinc Reagents with Primary and Secondary Alkyl Bromides and Iodides", *Angew. Chem. Int. Ed.* **2015**, *54*, 4478–4481; *Angew. Chem.* **2015**, *127*, 4560–4563.

4) Diana Haas, Jeffrey M. Hammann, Ferdinand H. Lutter, Paul Knochel, "Mild Cobalt-Catalyzed Negishi Cross-Couplings of (Hetero)arylzinc Reagents with (Hetero)aryl Halides", *Angew. Chem. Int. Ed.* **2016**, *55*, 3809–3812; *Angew. Chem.* **2016**, *128*, 3873–3877.

5) Diana Haas, Jeffrey M. Hammann, Robert Greiner, Paul Knochel "Recent Developments in Negishi Cross-Coupling Reactions", *ACS Catal.* **2016**, *6*, 1540–1552.

All my life through, the new sights of nature made me rejoice like a child.

Marie Curie

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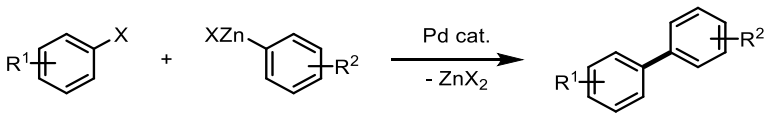
A INTRODUCTION

A INTRODUCTION

In 2010, Richard Heck, Ei-ichi Negishi, and Akira Suzuki joined the prestigious circle of Nobel laureates for their roles in discovering and developing highly practical methodologies for C-C bond forming reactions.[1] From their contributions the landscape of methods for organic synthesis irreversibly changed for chemists, both in academia and in industry. Until today, the transition metal-catalyzed transformations continue to find great attention from the chemical community. As Negishi picted out in his Nobel lecture, the goal of organic chemists in the 21st century is the synthesis of every imaginable compound to seek for new structures that could possibly solve mankind's problems in the near or far future.[2]

1 Overview

Pd-catalyzed cross-coupling reactions between unsaturated halides and organometallics have found broad applications. Cross-coupling reactions using boronic acids or esters, known as Suzuki cross-coupling reactions,[3] have been extensively used due to the broad availability and relative air- and moisture-stability of unsaturated boronic acid derivatives.[4] Nevertheless, the fast transmetalation of organozinc reagents to palladium compared to boronic acids often allows the achievement Negishi cross-couplings[2] between a broad range of unsaturated halides and zinc organometallics under very mild conditions (Scheme 1).



Scheme 1. General scheme of the Negishi cross-coupling reaction.

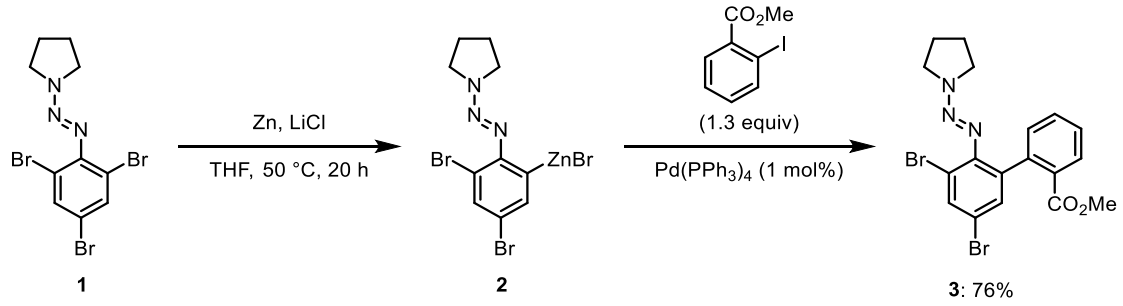
The low toxicity of zinc salts, as well as the growing number of commercially available zinc reagents has increased their employment in cross-coupling reactions. Furthermore, it has been shown in several cases that expensive Pd-based catalytic systems can be replaced by other transition metals, such as Ni, Fe, Co or Cu, providing alternative pathways for successful cross-coupling reactions of various organic (pseudo)halides with all kinds of organometallic compounds.

[1] "The Nobel Prize in Chemistry 2010". http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/; retrieved Feb 15 2016.
[2] E. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738.
[3] A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722.
[4] *Boronic Acids. Preparation and Applications in Organic Synthesis and Medicine*, 2nd ed., (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**, pp. 1-122.

2 Preparation of Zinc Organometallics

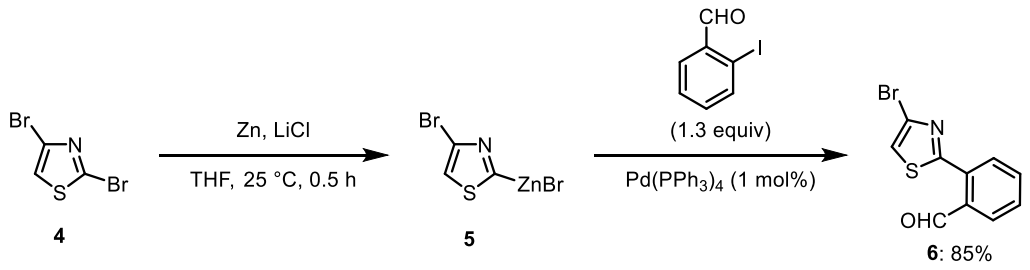
2.1 Oxidative Addition of Zinc Powder to Organic Halides

Organozinc reagents can be prepared directly by the insertion of zinc powder to various aromatic and heterocyclic iodides or bromides.[5] Thus, reduction of zinc chloride in THF using lithium naphthalenide provides highly activated zinc (Rieke-zinc).[6] Alternatively the insertion of commercial zinc powder in the presence of lithium chloride proceeds readily with aryl iodides, as well as activated aryl or heteroaryl bromides.[7] Hence, the bromo-triazene **1** inserts zinc in the presence of LiCl providing the zinc reagent **2** that leads to biphenyl **3** in 76% yield after Negishi cross-coupling with methyl 2-iodobenzoate (Scheme 2).[8]



Scheme 2. Regioselective insertion of zinc in the presence of LiCl.

Also, 2,4-dibromothiazole (**4**) regioselectively inserts zinc dust in the presence of LiCl to afford the zincated thiazole **5**, which undergoes a cross-coupling with 2-iodobenzaldehyde furnishing the 2-arylated thiazole **6** in 85% yield (Scheme 3).



Scheme 3. Regioselective insertion of zinc into 2,4-dibromothiazole

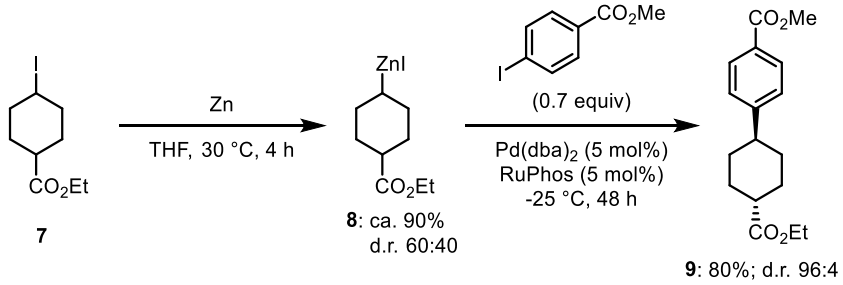
[5] G. Dagousset, C. Francois, T. Léon, R. Blanc, E. Sansiaume-Dagousset, P. Knochel, *Synthesis* **2014**, *46*, 3133.

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

[7] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

[8] N. Boudet, S. Sase, P. Sinha, C. Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358.

Addition of LiCl is not required, although it accelerates such Csp^3-halide insertions as it plays a multiple role: it removes the oxide impurities on the surface of zinc and solubilizes the newly formed zinc reagent (RZnX) at the active site of the zinc surface by forming complexes of the type RZnX·LiCl. The metal activation effect of LiCl is quite general and other metallic powders such as Mg,[9] In,[10] Mn[11] and Al[12] are also efficiently activated by LiCl. It should be mentioned that the presence of additional Lewis acids, such as $B(OR)_3$[13] or electron-transfer acceptors[14] further accelerates the metal insertion. The intermediate radicals resulting from the zinc insertion do not allow a stereoselective formation of secondary alkylzinc reagents, such as in the case of the substituted cyclohexylzinc **8**. However, the Negishi cross-coupling with methyl 4-iodobenzoate is stereoconvergent and produces the *trans*-cyclohexane derivative **9** in 80% yield in the presence of RuPhos (2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl)[15] (d.r. 96:4; Scheme 4).[16]



Scheme 4. Stereoconvergent cross-coupling of a secondary alkylzink reagent.

In the case of (*Z*)-alkenyl bromide **10**, the zinc insertion appears to be stereoselective as a result of the chelate-stabilization as shown in intermediate **11**. Subsequent Negishi cross-coupling affords (*Z*)-cinnamyl aldehyde **12** in 92% yield (*Z*:*E* > 99:1; Scheme 5).[17]

[9] a) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. – Eur. J.* **2009**, *15*, 7192. b) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.

[10] a) Y. H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648. b) Y. H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236. c) V. Papoian, T. Minehan, *J. Org. Chem.* **2008**, *73*, 7376.

[11] Z. Peng, P. Knochel, *Org. Lett.* **2011**, *13*, 3198.

[12] a) T. Bluemke, Y. H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313. b) K. Groll, T. D. Bluemke, A. Unsinn, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 11157.

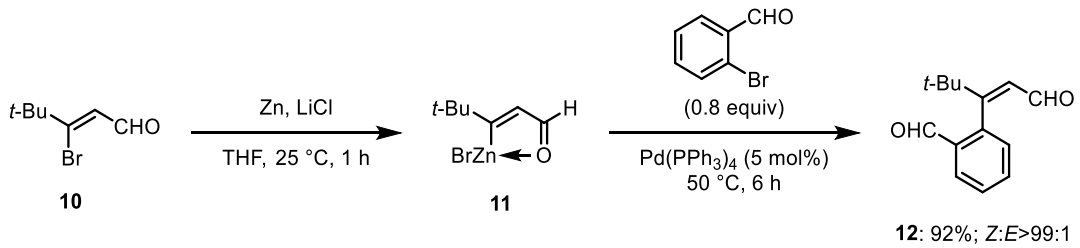
[13] B. A. Haag, C. Saemann, A. Jana, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 7290.

[14] Z. L. Shen, P. Knochel, *ACS Catal.* **2015**, *5*, 2324.

[15] a) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028. b) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.

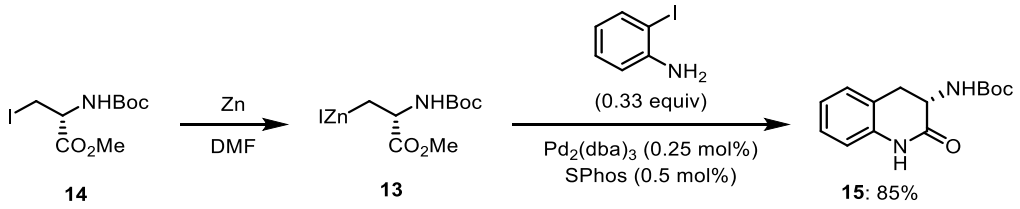
[16] K. Moriya, P. Knochel, *Org. Lett.* **2014**, *16*, 924.

[17] C. Saemann, M. A. Schade, S. Yamada, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 9495.



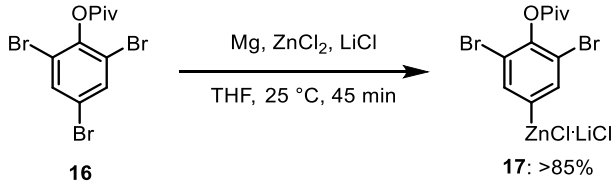
Scheme 5. Stereoselective Negishi cross-coupling using an alkenylzinc reagent.

Jackson[18] showed that this method allows the preparation of chiral amino-acid derived zinc reagents, such as **13**, starting from the readily available iodide **14**. Negishi cross-coupling with 2-iodoaniline[19] provides the chiral lactam **15** in 85% yield (Scheme 6).



Scheme 6. Preparation of Jackson's zinc reagent in DMF.

The reaction scope of such oxidative insertions was increased by replacing Zn with the bimetallic reagent couples Mg, $ZnCl_2$[20] or Mg, $Zn(OPiv)_2$.[21] Under these conditions, the insertion is fast and highly regioselective. Thus, the tribromoarene **16** reacts solely in *para*-position with the metallic-cocktail Mg, $ZnCl_2$, LiCl leading to zinc reagent **17** in high yield (**Scheme 7**).[9]

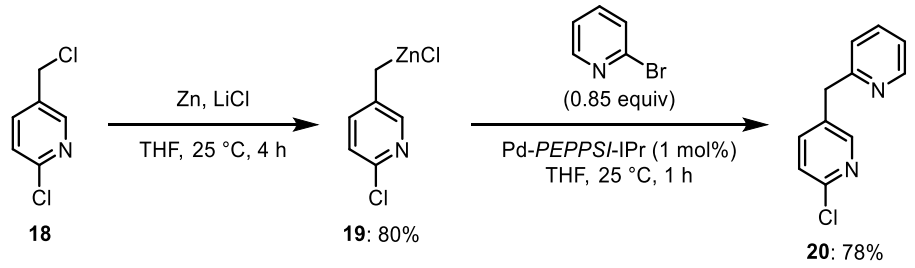


Scheme 7. Preparation of a zinc organometallic using Mg, $ZnCl_2$, LiCl.

Benzylic zinc reagents are readily prepared by Zn, LiCl insertion[20] and the method has been extended to a wide range of heterocyclic systems.[22] The chloromethyl-pyridine **18** is converted to zinc reagent

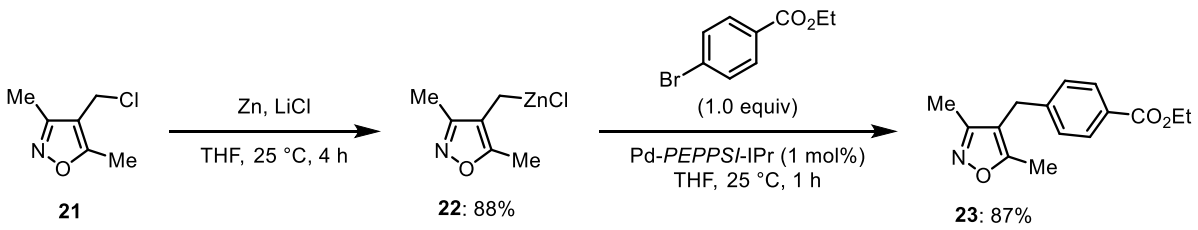
[18] A. J. Ross, H. L. Lang, R. F. W. Jackson, *J. Org. Chem.* **2010**, *75*, 245.
[19] G. Manolikakes, C. Muñoz Hernandez, M. A. Schade, A. Metzger, P. Knochel, *J. Org. Chem.* **2008**, *73*, 8422.
[20] a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824. b) C. Saemann, V. Dhayalan, P. R. Schreiner, P. Knochel, *Org. Lett.* **2014**, *16*, 2418.
[21] S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205.
[22] N. M. Barl, E. Sansiaume-Dagousset, G. Monzon, A. J. Wagner, P. Knochel, *Org. Lett.* **2014**, *16*, 2422.

19, followed by Pd-*PEPPSI*-IPr-catalyzed[23] cross-coupling with 2-bromopyridine providing the bis-pyridine **20** in 78% yield (Scheme 8).



Scheme 8. Preparation and cross-coupling of heterocyclic benzylic zinc reagents.

Similarly, the chloromethyl isoxazole derivative **21** leads to zinc reagent **22** and Negishi cross-coupling using Pd-*PEPPSI*-IPr furnishes the desired product **23** in 87% yield (Scheme 9).[24]



Scheme 9. Benzylic insertion into an isoxazole derivative.

2.2 Metal-Catalyzed Preparation of Organozinc Reagents

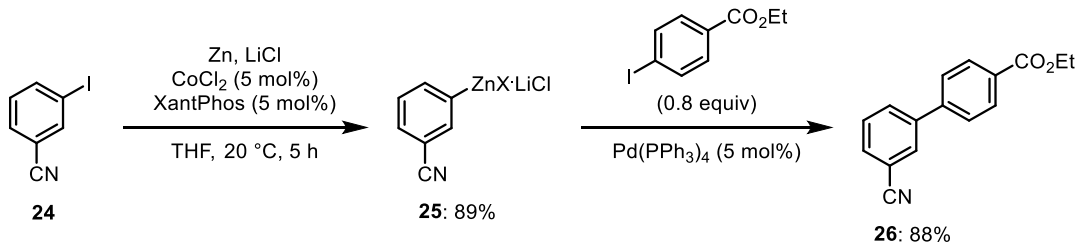
Gosmini[25] further showed that the preparation of various polyfunctional arylzinc reagents is efficiently possible under Co-catalysis using cobalt halides. Also, Yoshikai has reported that $CoCl_2$ catalyzes the zinc insertion into various aryl halides and that Pd-catalyzed cross-couplings can be subsequently achieved with these zinc reagents. Thus, 3-iodobenzonitrile (**24**) is converted to the corresponding zinc reagent **25** in 89% yield and subsequent Negishi cross-coupling provides the expected biphenyl **26** in high yield (Scheme 10).[26]

[23] a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. – Eur. J.* **2006**, *12*, 4743. b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. – Eur. J.* **2006**, *12*, 4749.

[24] L. Klier, C. Diène, M. Schickinger, A. Metzger, A. J. Wagner, K. Karaghiosoff, I. Marek, P. Knochel, *Chem. – Eur. J.* **2014**, *20*, 14096.

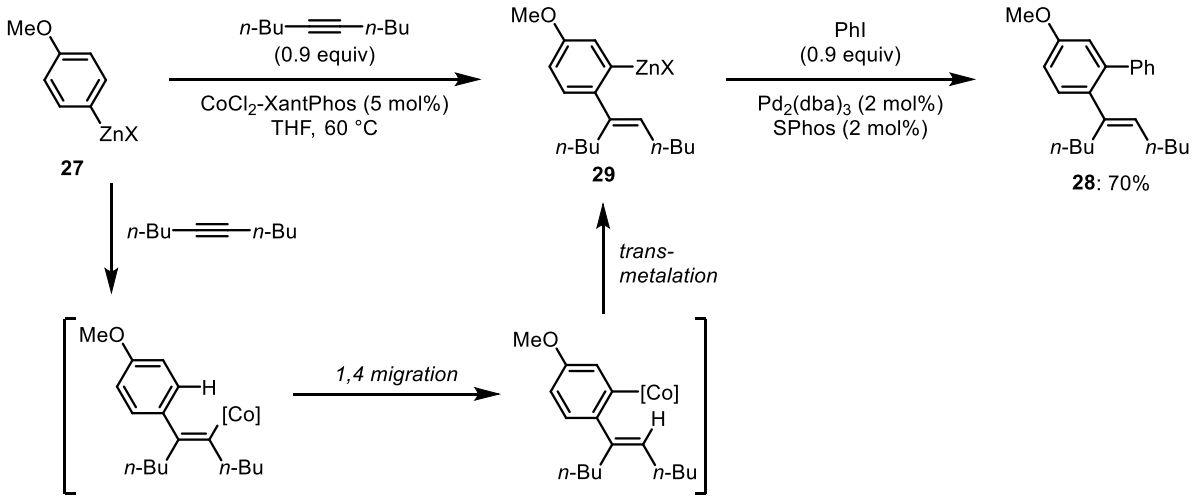
[25] a) I. Kazmierski, C. Gosmini, J. M. Paris, J. Périchon, *Tetrahedron Lett.* **2003**, *44*, 6417. b) C. Gosmini, M. Amatore, S. Claudel, J. Périchon, *Synlett* **2005**, 2171. c) H. Fillon, C. Gosmini, J. Périchon, *J. Am. Chem. Soc.* **2003**, *125*, 3867.

[26] M. Y. Jin, N. Yoshikai, *J. Org. Chem.* **2011**, *76*, 1972.



Scheme 10. Cobalt-catalyzed zinc insertion to an aryl iodide.

Yoshikai has also achieved impressive cascade reactions involving a 1,4-cobalt migration and subsequent palladium-catalyzed Negishi cross-couplings upon addition to an alkyne. This procedure allows the conversion of *p*-anisylzinc derivative **27** into the styrene derivative **28** *via* zinc intermediate **29** in 70% overall yield (Scheme 11).[27]

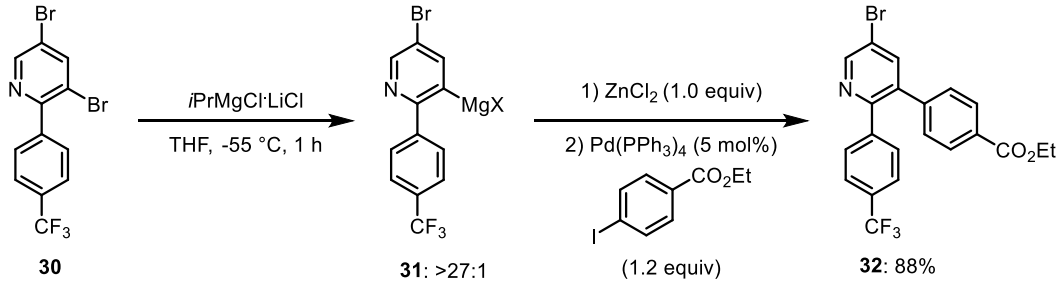


Scheme 11. 1,4-Cobalt migration and subsequent Negishi cross-coupling.

2.3 Transmetalation of Magnesium, Aluminum or Lithium Organometallics

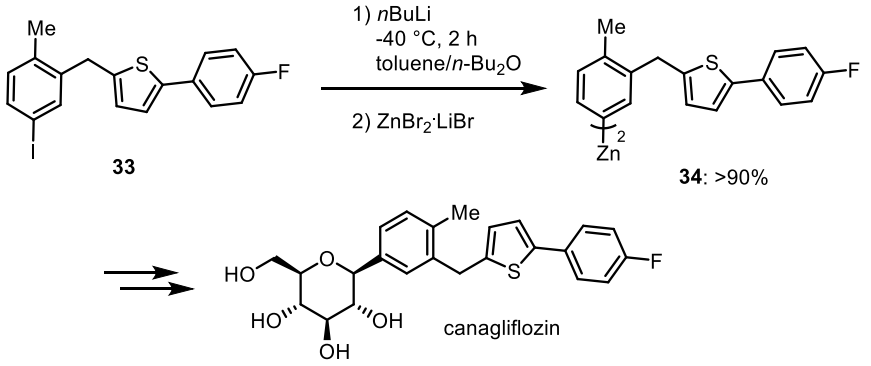
The transmetalation of lithium, magnesium or aluminum[12b] organometallics is a well-established method for preparing various organozinc reagents. A site-selective Br/Mg-exchange[28] of the 3,5-dibromopyridine **30** using *i*-PrMgCl·LiCl leads to the corresponding Grignard reagent **31**. Transmetalation with $ZnCl_2$, followed by Negishi cross-coupling gives the bis-arylated pyridine **32** in 88% yield (Scheme 12).[29]

[27] B. H. Tan, J. Dong, N. Yoshikai, *Angew. Chem. Int. Ed.* **2012**, *51*, 9610.
[28] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[29] C. Saemann, B. Haag, P. Knochel, *Chem. – Eur. J.* **2012**, *18*, 16145.



Scheme 12. Regioselective Br/Mg-exchange on a 3,5-dibromopyridine.

A low-temperature I/Li-exchange of the aryl iodide **33** with *n*-BuLi provides, after transmetalation with the THF soluble salt $ZnBr_2$·LiBr, bis-zinc reagent **34** that is employed in a diastereoselective Negishi cross-coupling for the preparation of canagliflozin (Scheme 13).[30]



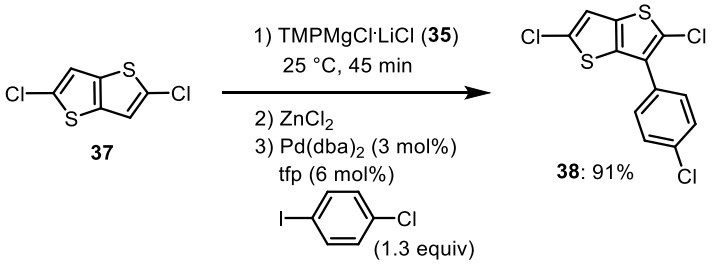
Scheme 13. Preparation of a bis-zinc reagent for the synthesis of canagliflozin.

2.4 Preparation of Zinc Reagents by Directed Metalation

The directed metalation[31] of unsaturated, aromatic and heterocyclic molecules using various TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl) of magnesium or zinc provides for the general preparation of the corresponding organometallic reagents.[32] The use of TMPMgCl·LiCl (**35**)[33] and the related zinc base TMPZnCl·LiCl (**36**)[34] proved to be the most useful. Thus, 2,5-dichlorothieno[3,2-*b*]thiophene (**37**) is readily magnesiated by the addition of TMPMgCl·LiCl (**35**). Transmetalation with $ZnCl_2$, followed by a Negishi cross-coupling reaction with 1-chloro-4-iodobenzene using $Pd(dba)_2$ (dba = dibenzylidene-

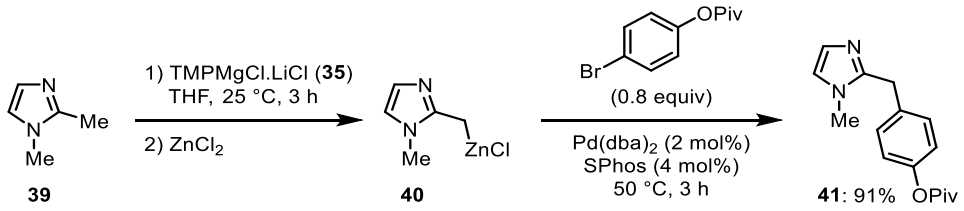
[30] S. Lemaire, I. N. Houpis, T. Xiao, J. Li, E. Digard, C. Gozlan, R. Liu, A. Gavryushin, C. Diene, Y. Wang, V. Farina, P. Knochel, *Org. Lett.* **2012**, *14*, 1480.
[31] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879. b) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802. c) D. Tilly, F. Chevallier, F. Mongin, P. C. Gros, *Chem. Rev.* **2014**, *114*, 1207.
[32] B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[33] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[34] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837.

acetone) and (*o*-furyl)$_3$P (tfp)[35] as a catalytic system leads to the mono-arylated thienothiophene **38** in 91% yield (Scheme 14).[36]



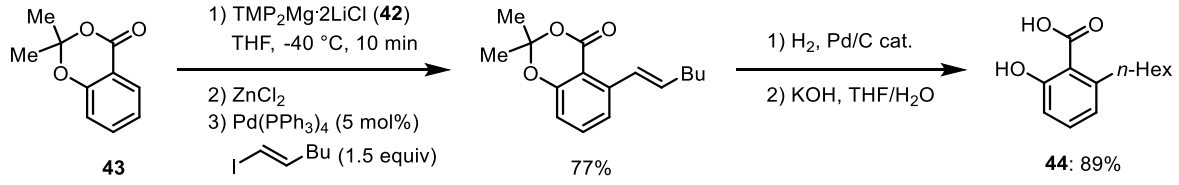
Scheme 14. Directed magnesiation of heterocyclic scaffolds with TMPMgCl·LiCl (35).

Interestingly, 1,2-dimethylimidazole (**39**) is selectively magnesiated at the lateral methyl group furnishing zinc reagent **40** after transmetalation with $ZnCl_2$, which then undergoes a smooth cross-coupling with an aryl bromide affording the benzylated imidazole **41** in 91% yield (Scheme 15).[37]



Scheme 15. Lateral metalation of 1,2-dimethylimidazole.

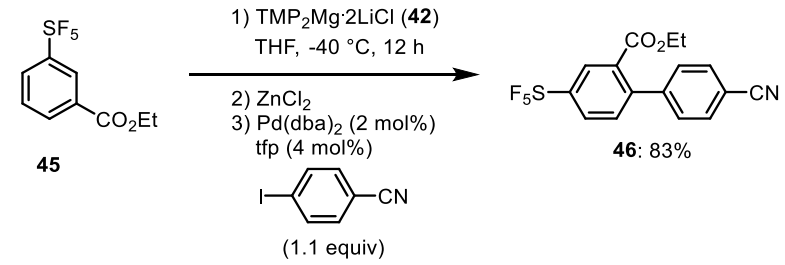
In the case of aromatic substrates bearing C-H bonds of moderate acidity or sensitive functional groups, the use of $TMP_2Mg{\cdot}2LiCl$ (**42**) can be advantageous. Thus, the magnesiation of the salicylic derivative (**43**) proceeds with $TMP_2Mg{\cdot}2LiCl$ (**42**) and after transmetalation with $ZnCl_2$ and Negishi cross-coupling with (*E*)-1-iodocyclohexene, the natural product **44** present in the essential oil of *Pelargonium sidoides DC* is obtained after hydrogenation and deprotection (Scheme 16).[38]



Scheme 16. Magnesiation of a sensitive substrate with $TMP_2Mg{\cdot}2LiCl$ (42).

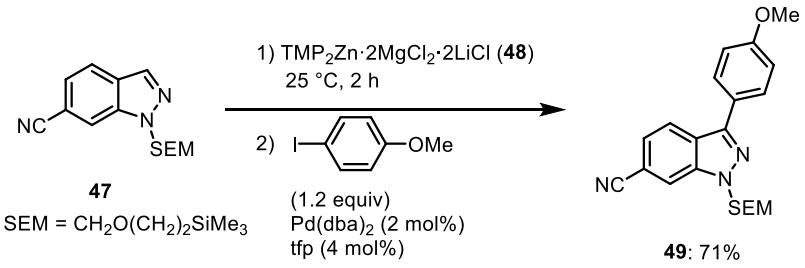
[35] a) V. Farina, S. R. Baker, D. Benigni, C. Sapino, Jr., *Tetrahedron Lett.* **1988**, *29*, 5739. b) V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585.
[36] T. Kunz, P. Knochel, *Chem. – Eur. J.* **2011**, *17*, 866.
[37] S. Duez, A. K. Steib, P. Knochel, *Org. Lett.* **2012**, *14*, 1951.
[38] G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681.

Furthermore, the presence of a SF_5-substituent decreases the metalation rate of ethyl benzoate **45** and the use of $TMP_2Mg{\cdot}2LiCl$ (**42**) is required to achieve a smooth magnesiation. After transmetalation with $ZnCl_2$ and Negishi cross-coupling, the desired product **46** is obtained in 83% yield (Scheme 17).[39]



Scheme 17. Magnesiation of a SF_5-substituted substrate.

The more covalent Zn-N bond in TMPZnCl·LiCl (**36**)[34] combined with the high thermal stability of the resulting zinc reagents at up to 120 °C without noticeable decomposition allowed the performance of directed zincations under a wide range of conditions.[40] Thus, indazoles, such as **47**, which are prone to undergo ring fragmentation after lithiation or magnesiation, are efficiently zincated at the C-3 position using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**).[41] After Negishi cross-coupling with an aryl iodide, the desired 3-arylated indazole **49** is obtained in 71% yield (Scheme 18).[42]

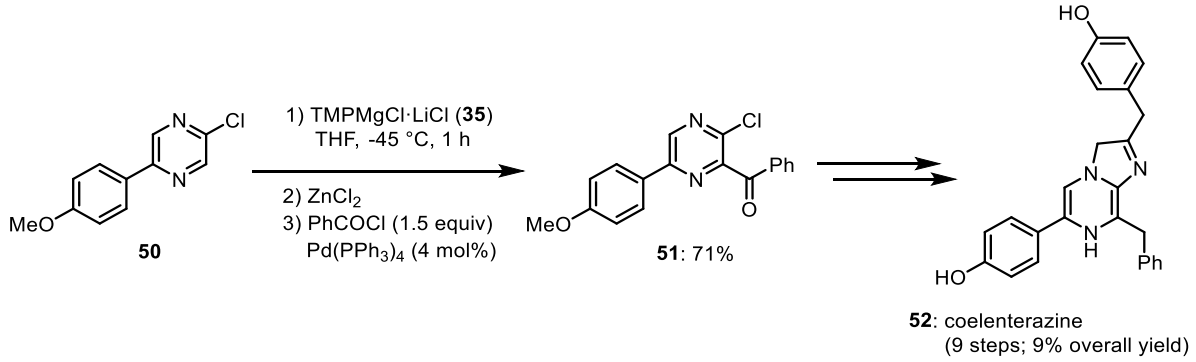


Scheme 18. Zincation of sensitive heterocycles using a TMP-zinc base.

The zincation of various chlorinated or brominated pyrazines is readily realized using TMPZnCl·LiCl (**36**).[43] However, the arylated pyrazine **50** is metalated best using TMPMgCl·LiCl (**35**) and after transmetalation with $ZnCl_2$ and Pd-catalyzed Negishi acylation,[44] the regioselectively substituted

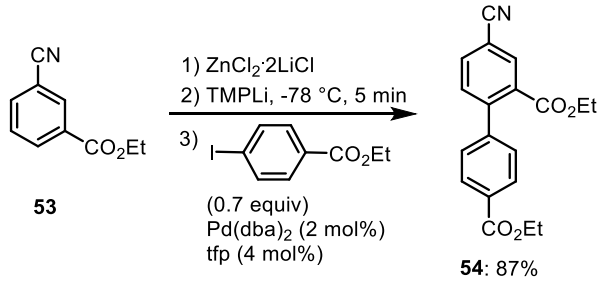
[39] A. Frischmuth, A. Unsinn, K. Groll, H. Stadtmueller, P. Knochel, *Chem. – Eur. J.* **2012**, *18*, 10234.
[40] M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615.
[41] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. b) Z. Dong, G. C. Clososki, S. H. Wunderlich, A. Unsinn, J. Li, P. Knochel, *Chem. – Eur. J.* **2009**, *15*, 457.
[42] A. Unsinn, P. Knochel, *Chem. Commun.* **2012**, *48*, 2680.
[43] A. Unsinn, M. J. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128.
[44] E. Negishi, V. Bagheri, S. Chatterjee, F. T. Luo, J. A. Miller, A. T. Stoll, *Tetrahedron Lett.* **1983**, *24*, 5181.

pyrazine **51** is obtained in 71% yield. In a few steps it is converted into coelenterazine (**52**), a bioluminescent natural product found in the jellyfish *Aequorea victoria* (Scheme 19).[45]



Scheme 19. Total synthesis of coelenterazine using a Negishi acylation.

A regioselective arylation can be achieved combining the use of bases **35** or **36** with (or without) $BF_3{\cdot}OEt_2$.[46] Extension of this regioselectivity switch can be extended to other Lewis acids, such as $MgCl_2$, as this Lewis acid allows a regioselective metalation of the chromone scaffold.[47] The compatibility of a strong Lewis acid with magnesium amides is reminiscent of the concept of frustrated Lewis pairs (FLP).[48] This methodology can be extended to lithium amides and it was recently found that TMPLi does not instantaneously react with $ZnCl_2$ or $MgCl_2$ allowing *in situ* trapping metalations followed by Negishi cross-couplings.[49] Thus, mixing the ethyl 3-cyanobenzoate (**53**) with $ZnCl_2{\cdot}2LiCl$, cooling the mixture to -78 °C and adding TMPLi allows the regioselective lithiation at position 6 and the lithium intermediate is immediately transmetalated with $ZnCl_2$. After a Negishi cross-coupling, the corresponding arylated product **54** is obtained in 87% yield (Scheme 20).



Scheme 20. *In situ* trapping metalation and Negishi cross-coupling.

[45] M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406.

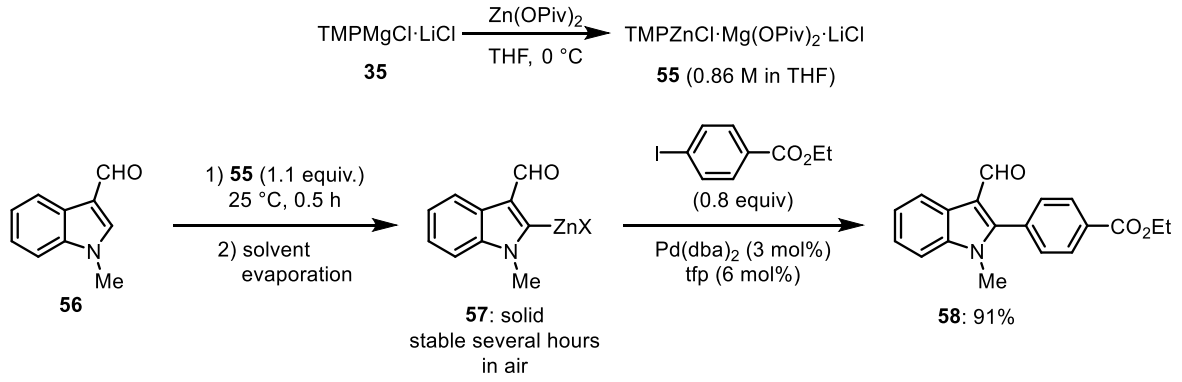
[46] a) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451. b) M. Jaric, B. A. Haag, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2011**, *13*, 2306. c) K. Groll, S. M. Manolikakes, X. M. du Jourdin, M. Jaric, A. Bredihhin, K. Karaghiosoff, T. Carell, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 6776.

[47] L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584.

[48] D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46.

[49] A. Frischmuth, M. Fernandez, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928.

However, performing these reactions not in batch, but in flow allows running these *in situ* trapping reactions at 0 °C.[50] Most organozinc halides are sensitive to water and to moisture, however, tuning of the reaction conditions for preparing unsaturated zinc reagents by the addition of either magnesium salts, such as magnesium pivalate,[51] or ligands, such as dioxane[52] or bis-pyridine, this moisture stability can be considerably attenuated.[53] Thus, the treatment of various aromatic or heterocyclic derivatives with TMPZnCl·Mg(OPiv)$_2$·LiCl (**55**), obtained by mixing TMPMgCl·LiCl (**35**) with Zn(OPiv)$_2$, readily provides solid zinc reagents that display considerable stability towards air and moisture after removal of all solvents.[54]



Scheme 21. Preparation and Negishi cross-coupling of solid air-stable zinc reagents.

In addition to their improved stability, these solid organozincs react very well in Negishi cross-couplings. The reaction of 3-formyl-indole **56** with the base **55** furnishes the solid zinc reagent **57** and after Pd-catalyzed cross-coupling the polyfunctional 2-arylated indole **58** is obtained in 91% yield (Scheme 21).[55] These zinc reagents were also proven to undergo copper-catalyzed acylation reactions and can be prepared from a broad range of polyfunctionalized substrates bearing groups, such as nitro, carboxy, cyano or formyl. Also, it should be mentioned that transition-metal free cross-couplings can be realized with various organozinc reagents especially with reactive benzylic zinc organometallics.[56]

[50] a) T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933. b) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501. c) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649.

[51] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205. b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9428. c) M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10662.

[52] J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754.

[53] A. B. Charette, J. F. Marcoux, C. Molinaro, A. Beauchemin, C. Brochu, É. Isabel, *J. Am. Chem. Soc.* **2000**, *122*, 4508.

[54] C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302.

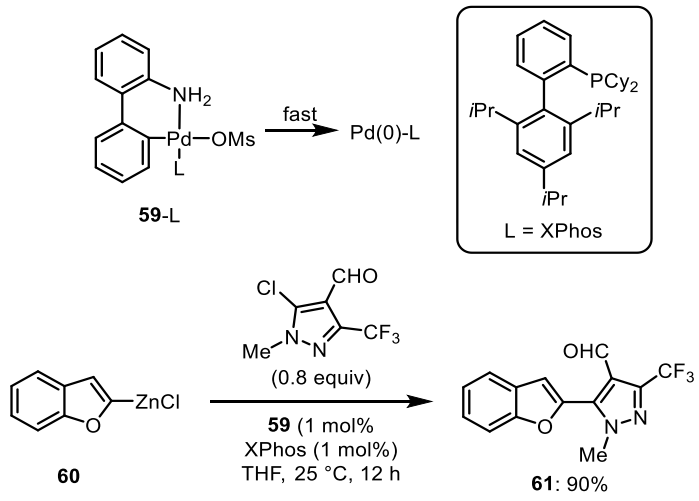
[55] a) A. Hernan-Gomez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, *53*, 2706. b) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. – Eur. J.* **2014**, *20*, 12289.

[56] a) Q. Chen, X. Mollat du Jourdin, P. Knochel, *J. Am. Chem. Soc.* **2013**, *135*, 4958. b) Q. Chen, T. Léon, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 8746. c) P. Quinio, D. S. Roman, T. Léon, S. William, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2015**, *17*, 4396.

3 Negishi Cross-Coupling Reactions

3.1 Palladium-Catalyzed Negishi Cross-Coupling Reactions

Negishi cross-couplings involve the use of organozinc reagents, an organic electrophile and a transition-metal catalyst. In recent years the variation of this transition-metal catalyst allowed to further broaden the synthetic scope of this important coupling procedure. The use of palladacycle precatalysts enables the performance of Negishi cross-couplings with a variety of substrates. Buchwald developed a new class of easily prepared, air- and moisture-stable aminobiphenyl-based palladacycle precatalysts capable of rapidly generating the catalytically active Pd(0)-L species under basic conditions, allowing Negishi cross-couplings to proceed at ambient temperature with low catalyst loading. Thus, the precatalyst palladacycle **59**-L (L = XPhos) considerably facilitates the formation of the highly active palladium-species LPd(0) leading to fast Negishi cross-couplings at room temperature. The 2-zincated benzofuryl derived reagent **60** reacts with a chloropyrazole providing the complex polyfunctional heterocyclic compound **61** in 90% yield (Scheme 22).[57]

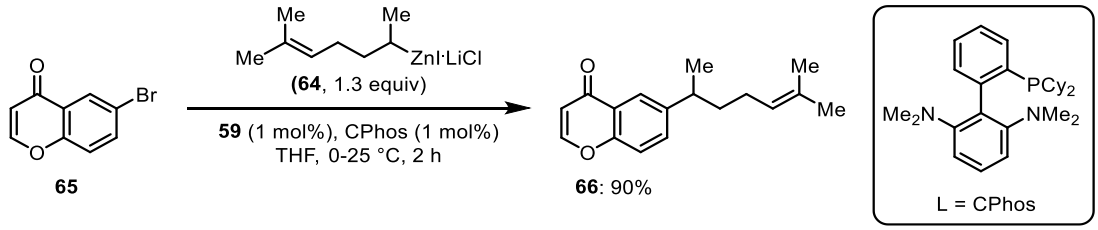


Scheme 22. Pd-precatalyst facilitated Negishi cross-coupling.

This strategy has been successfully applied to the performance of highly selective Negishi cross-couplings of secondary alkylzinc species. A major difficulty of this transformation is undesired β-hydride elimination/migratory insertion that compete with the desired reductive elimination leading to isomerized side products. In order to suppress this isomerization, the rate of reductive elimination relative to β-hydride elimination must be enhanced. Several research groups have addressed this issue by employing catalysts containing sterically-hindered phosphine ligands. A range of secondary alkylzinc

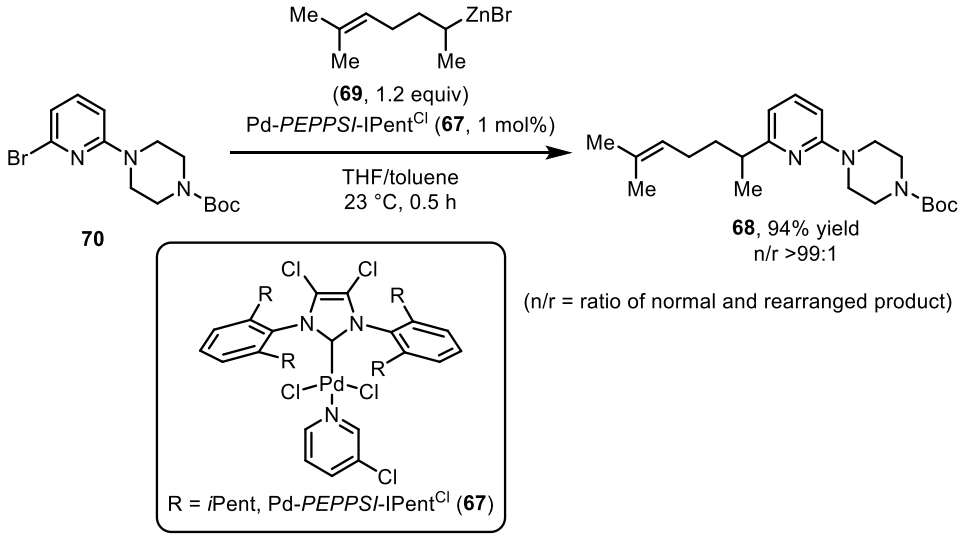
[57] Y. Yang, N. J. Oldenhuis, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 615.

reagents like **64** can be used with excellent results for the coupling of bromochromane **65** leading to the alkylated product **66** in 90% yield using the precatalyst **59**-L (L = CPhos; **Scheme 23**).[58]



Scheme 23. Pd-precatalyst for the cross-coupling of *sec*-alkylzinc reagents.

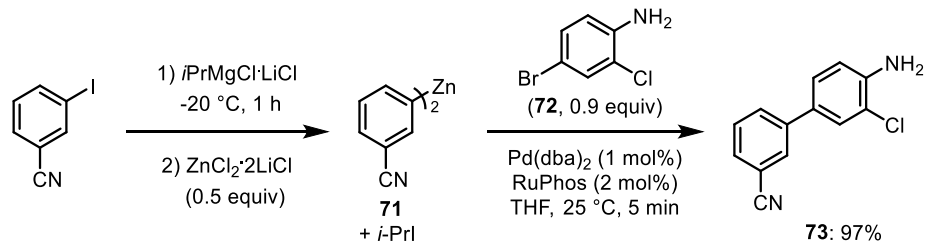
Additionally, Organ[59] and co-workers developed a series of new *N*-heterocyclic carbene-based Pd-complexes, which were used for the Negishi cross-coupling of aryl and heteroaryl halides with a variety of secondary alkylzinc reagents. It was shown that Pd-*PEPPSI*-IPent^{Cl} (**67**) had unprecedented selectivity, leading only to the single isomer **68** for reactions of a variety of alkylzincs, such as **69**, with highly functionalized (hetero)aromatic halides like **70** (Scheme 24).[60]



Scheme 24. Negishi cross-coupling of secondary alkylzincs using Pd-*PEPPSI*-IPent^{Cl}.

Interestingly, alkyl iodides such as *i*-PrI were found to accelerate Negishi cross-couplings.[61] The reaction of diarylzinc reagent **71**, prepared by a Br/Mg exchange, with aniline derivative **72** bearing a free NH_2-group leading to the biphenyl **73** in 97% yield. In absence of *i*-PrI, a conversion of only 37% was observed (Scheme 25).

[58] Y. Yang, K. Niedermann, C. Han, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 4638.
[59] S. Çalimsiz, M. G. Organ, *Chem. Commun.* **2011**, *47*, 5181.
[60] M. Pompeo, R. D. J. Froese, N. Hadei, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 11354.
[61] a) M. Kienle, P. Knochel, *Org. Lett.* **2010**, *12*, 2702. b) G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 205.



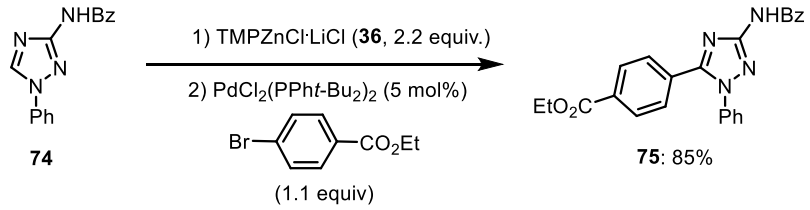
Scheme 25. *i*-PrI-accelerated Negishi cross-coupling.

The mechanism of the Negishi cross-coupling has been carefully studied by Espinet[62] and Koszinowski[63] using a combination of kinetic measurements, mass-spectrometry and NMR-methods. A structure-reactivity relationship in Negishi cross-coupling reactions by Mayr[64] showed that this reaction is accelerated by the presence of electron-acceptor substituted aryl bromides. On the other hand, the presence of an electron-acceptor substituent on the arylzinc halide diminishes the reaction rates. Additionally, Organ and co-workers[65] investigated the role of halide salt additives in the Negishi reaction involving arylzinc reagents. It was shown that diarylzincs easily transmetallate to palladium in THF with no salt present, leading to the corresponding coupling products. In contrast, arylzinc halides fail to couple in THF without additional salt. However, unlike alkylzincs that form higher-order zincates[66] in order to facilitate transmetallation, all that is needed for arylzincs is an increase in the solvent dielectric constant, which completely hempers the alkylzinc cross-coupling.

The original reaction scope has been considerably extended, as the excellent functional group tolerance of zinc reagents allows the Negishi cross-coupling of various bromo-substituted alkoxycarbene complexes of chromium, molybdenum or tungsten complexes as shown by Dvorak.[67] Also, Dughera reported Negishi cross-couplings with arenediazonium *o*-benzenedisulfonimides.[68] The combination of a Zr-catalyzed asymmetric carboalumination of alkenes (ZACA-reaction) with the Negishi cross-coupling allowed Negishi to prepare various chiral 1-alkanol derivatives in high enatiomeric purity.[69] Remarkable cross-couplings between heterocyclic moieties could be achieved with the Negishi cross-coupling. Thus, Zhang showed that 3-amino-1*H*-1,2,4-triazoles, such as **74**, were readily zincated with TMPZnCl·LiCl (**36**) and underwent a smooth Negishi cross-coupling with various

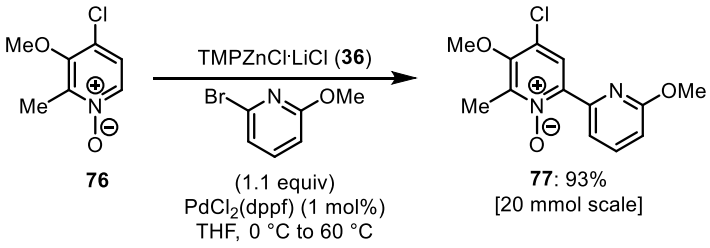
[62] E. Gioria, J. M. Martinez-Ilarduya, P. Espinet, *Organometallics* **2014**, *33*, 4394.
[63] K. Boeck, J. E. Feil, K. Karaghiosoff, K. Koszinowski, *Chem. – Eur. J.* **2015**, *21*, 5548.
[64] Z. B. Dong, G. Manolikakes, L. Shi, P. Knochel, H. Mayr, *Chem. – Eur. J.* **2010**, *16*, 248.
[65] L. C. McCann, M. G. Organ, *Angew. Chem. Int. Ed.* **2014**, *53*, 4386.
[66] a) L. C. McCann, H. N. Hunter, J. A. C. Clyburne, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 7024. b) H. N. Hunter, N. Hadei, V. Blagojevic, P. Patschinski, G. T. Achonduh, S. Avola, D. K. Bohme, M. G. Organ, *Chem. – Eur. J.* **2011**, *17*, 7845.
[67] T. Tobrman, I. Jurásková, D. Dvořák, *Organometallics* **2014**, *33*, 6593.
[68] M. Barbero, S. Cadamuro, S. Dughera, *Tetrahedron* **2014**, *70*, 8010.
[69] a) S. Xu, A. Oda, H. Kamada, E. Negishi, *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 8368. b) S. Xu, C. T. Lee, H. Rao, E. Negishi, *Adv. Synth. Catal.* **2011**, *353*, 2981.

aryl or alkenyl bromides enabling a smooth conversion into the arylated derivative **75** in 85% yield (Scheme 26).[70]



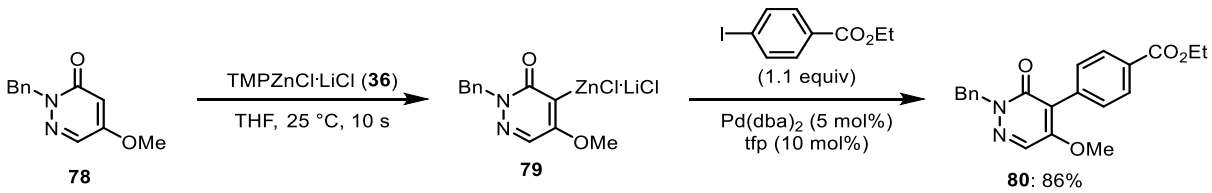
Scheme 26. Negishi cross-couplings of aminotriazole 74.

Gosselin showed that TMPZnCl·LiCl (**36**) can also be employed for the zincation of pyridine oxides, such as **76**. After a cross-coupling with a bromopyridine the desired bis-pyridine **77** was obtained in high yield (Scheme 27).[71]



Scheme 27. Cross-Coupling of pyridinyl oxide 76.

The zincation of pyridazine-3(2*H*)-ones, such as **78**, with TMPZnCl·LiCl (**36**) allows for the preparation of functionalized heterocycles that are of high interest as pesticides (Scheme 28).[72]

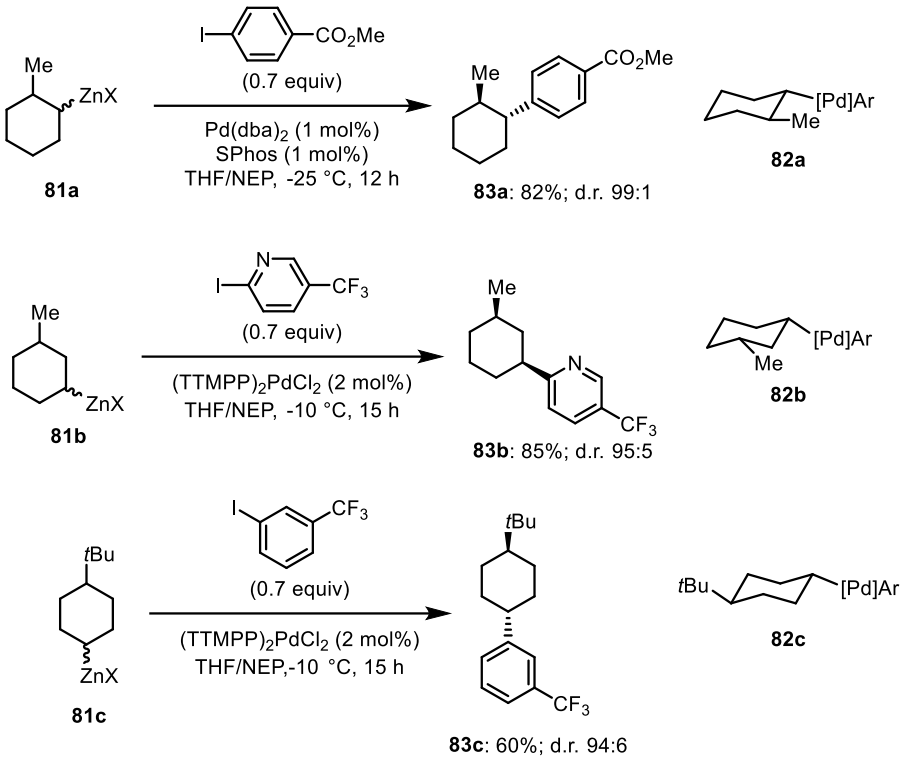


Scheme 28. Zincation and Negishi cross-coupling of pyridazinones.

Highly diastereoselective Negishi cross-couplings have been achieved by the treatment of various cyclic organozinc reagents, such as **81a**-**c**, with a range of aryl iodides in the presence of a palladium catalyst. The new carbon-carbon bond is formed preferentially *via* an intermediate having the C-Pd bond in an equatorial position, as shown in the intermediate structures **82a**-**c**, leading in the case of

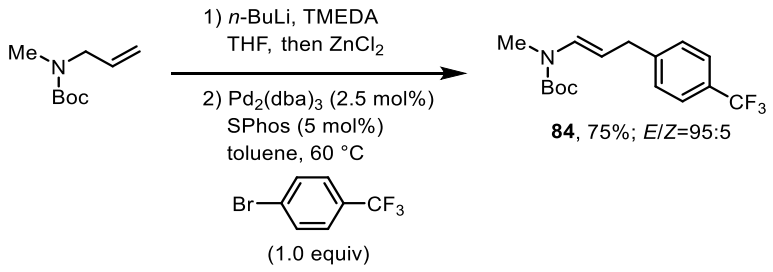
[70] J. Shen, B. Wong, C. Gu, H. Zhang, *Org. Lett.* **2015**, *17*, 4678.
[71] F. Gosselin, S. J. Savage, N. Blaquiere, S. T. Staben, *Org. Lett.* **2012**, *14*, 862.
[72] T. Verhelst, Z. Liu, J. Maes, B. U. W. Maes, *J. Org. Chem.* **2011**, *76*, 9648.

1,2- and 1,4-disubstituted zinc reagents to the *trans*-disubstituted products **83a** and **83c** and in the case of 1,3-disubstituted zinc reagents to the *cis*-1,3-disubstituted product **83b** (Scheme 29).[73]



Scheme 29. Diastereoselective arylation of cyclohexane derivatives.

This method can be extended to the stereoselective preparation of several types of piperidines,[74] such as **84**, and to the regioselective arylation of allylic amines as shown by Baudoin (Scheme 30).[75]



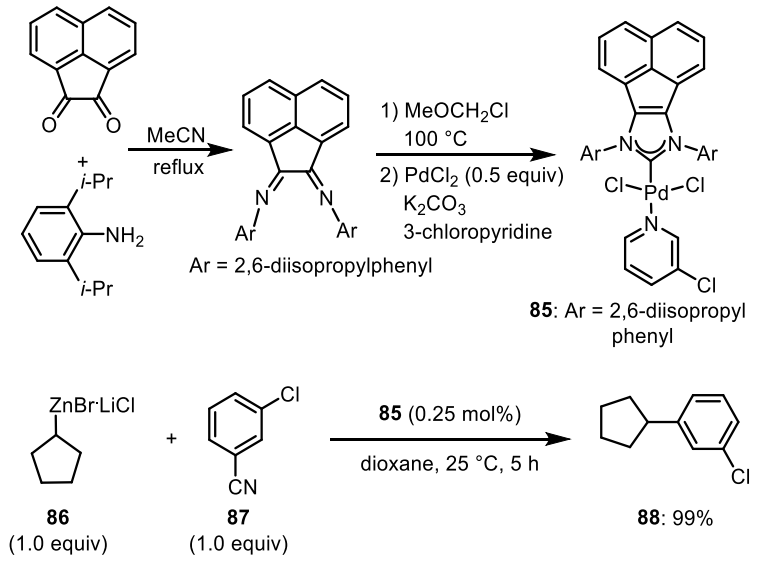
Scheme 30. Regioselective arylation of allylamines.

[73] T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer, P. Knochel, *Nature Chem.* **2010**, *2*, 125.

[74] a) T. K. Beng, R. E. Gawley, *Org. Lett.* **2011**, *13*, 394. b) S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2011**, *133*, 4774.

[75] A. Millet, O. Baudoin, *Org. Lett.* **2014**, *16*, 3998.

A broad range of catalytic systems are available and new catalysts and ligands are constantly reported. Thus, the *N*-heterocyclic precatalyst **85** proves to be especially efficient as it allows for Negishi cross-coupling reactions of alkylzinc reagents, such as **86**, or (hetero)arylzinc reagents with various (hetero)aryl halides like **87** under mild reaction conditions with low catalyst loading (Scheme 31).[76]



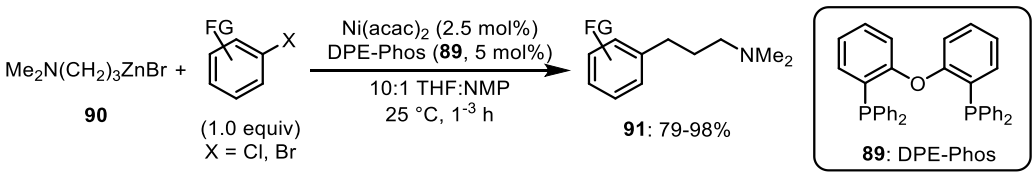
Scheme 31. *N*-heterocyclic carbenes for Negishi cross-couplings.

A range of important findings and mechanistic studies with practical applications have been reported and the difference observed in the role of salts in Negishi cross-couplings of arylzincs compared to alkylzincs has been studied in depth by Organ.[65]

3.2 Negishi Cross-Coupling Reactions Using Nickel-Catalysts

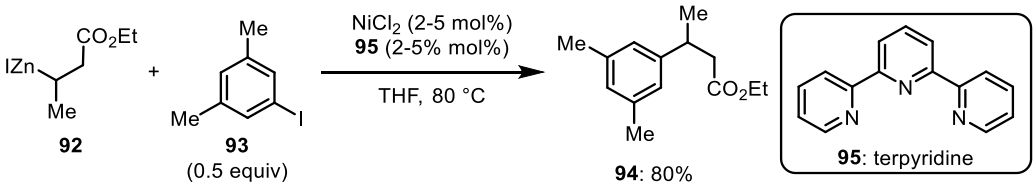
Although the use of palladium-catalysts ensures a broad applicability of the Negishi cross-coupling, environmental sustainability and cost concerns have led to the examination of other transition metal catalysts for these cross-couplings and the use of nickel has led to the most impressive developments. Standard nickel complexes, such as $Ni(acac)_2$ in combination with DPE-Phos (**89**),[77] were found to catalyze cross-couplings under milder conditions and a range of amino-substituted zinc reagents, such as **90**, afforded polyfunctional amines of type **91** (Scheme 32).[78]

[76] Z. Liu, N. Dong, M. Xu, Z. Sun, T. Tu, *J. Org. Chem.* **2013**, *78*, 7436.
[77] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, *14*, 3081.
[78] L. Melzig, T. Dennenwaldt, A. Gavryushin, P. Knochel, *J. Org. Chem.* **2011**, *76*, 8891.



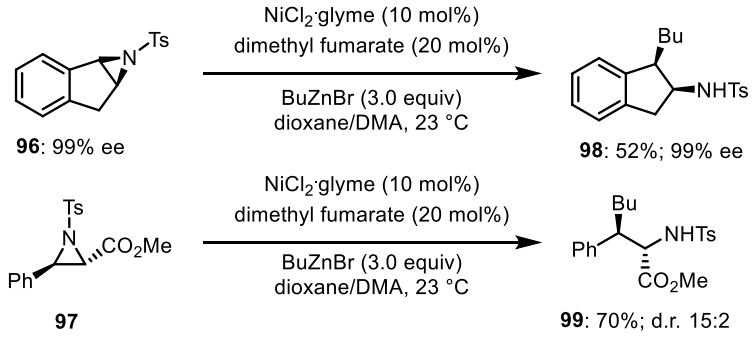
Scheme 32. Nickel-catalyzed Negishi cross-couplings.

Other ligands besides phosphines also show high efficiency especially for the cross-coupling of secondary alkylzinc reagents as shown by Biscoe.[79] Thus, the cross-coupling of functionalized zinc reagent **92** with 1-iodo-3,5-dimethylbenzene (**93**) provides the cross-coupling product **94** in 80% yield using terpyridine (**95**) as a ligand (Scheme 33).



Scheme 33. Nickel-catalyzed Negishi cross-coupling using secondary alkylzinc reagents.

Low-valent nickel readily inserts into the C-N bond of aziridines and they undergo smooth arylation with organozinc halides. This method can be applied to chiral aziridines, such as **96**, or disubstituted aziridines like **97** providing stereoselectively polyfunctional amines, such as **98** and **99**, in satisfactory yields and stereoselectivity (Scheme 34).[80]

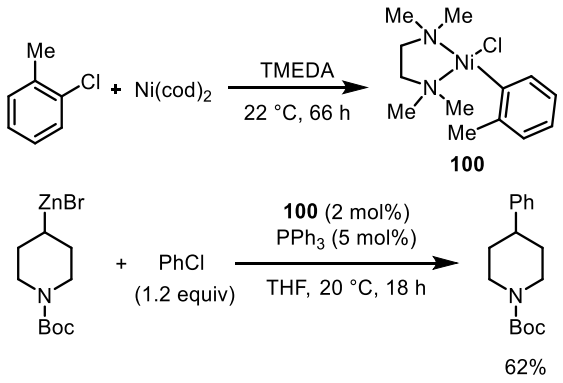


Scheme 34. Stereoselective Negishi cross-couplings with aziridines.

Furthermore, the above method allows for the generation of molecules with quaternary centers.[81] A remarkably simple and practical catalyst has been developed by Monfette[82] simply by treating $Ni(cod)_2$

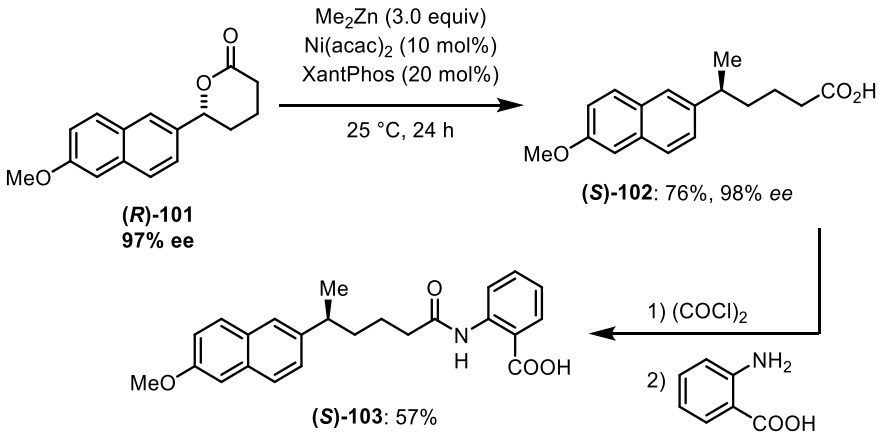
[79] A. Joshi-Pangu, M. Ganesh, M. R. Biscoe, *Org. Lett.* **2011**, *13*, 1218.
[80] C. Y. Huang, A. G. Doyle, *J. Am. Chem. Soc.* **2012**, *134*, 9541.
[81] C. Y. Huang, A. G. Doyle, *J. Am. Chem. Soc.* **2015**, *137*, 5638.
[82] J. Magano, S. Monfette, *ACS Catal.* **2015**, *5*, 3120.

and TMEDA with 2-chlorotoluene (**100**). This catalyst undergoes smooth Negishi cross-coupling reactions (Scheme 35).[83]



Scheme 35. Convenient nickel catalyst for Negishi cross-couplings.

Pincer-ligands are also popular ligands in the synthesis of Ni-complexes with good activity in Negishi cross-couplings even with unusual electrophiles, such as aryltrimethylammonium iodide.[84] Remarkable cross-couplings of aryl-substituted tetrahydrofurans, tetrahydropyrans, as well as lactones have been reported by Jarvo.[85] Thus, the ring opening of **(*R*)-101** in the presence of Me_2Zn provides **(*S*)-102** in 98% ee, which can be converted in two subsequent steps to the antidyslipidemia agent **(*S*)-103** (**Scheme 36**).

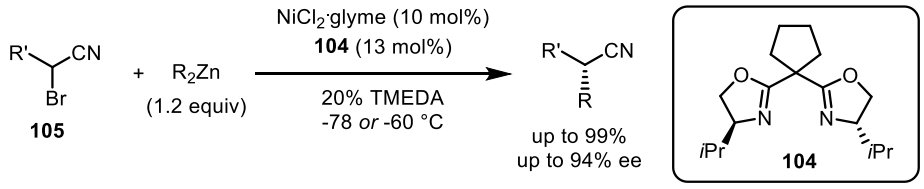


Scheme 36. Nickel-catalyzed Negishi cross-coupling.

Jarvo has also shown that these Ni-catalyzed cross-couplings of benzylic ethers and esters are general and are part of the modern tool-box for Negishi or Kumada cross-couplings. A range of catalytic asymmetric syntheses using Pfaltz's chiral bis(oxazoline)-type ligand[86] **104** are known and allow for

[83] X. Q. Zhang, Z. X. Wang, *J. Org. Chem.* **2012**, *77*, 3658.
[84] E. J. Tollefson, D. D. Dawson, C. A. Osborne, E. R. Jarvo, *J. Am. Chem. Soc.* **2014**, *136*, 14951.
[85] E. J. Tollefson, L. E. Hanna, E. R. Jarvo, *Acc. Chem. Res.* **2015**, *48*, 2344.
[86] C. C. Bausch, A. Pfaltz, in *Privileged Chiral Ligands and Catalysts* (Ed.: Q. L. Zhou), Wiley-VCH, Weinheim, **2011**, p. 221.

stereoconvergent Negishi arylations and alkenylations of racemic α-bromonitriles[87] of type **105** and other carbonyl derivatives,[88] as well as benzylic alcohols[89] or propargylic bromides (Scheme 37).[90]



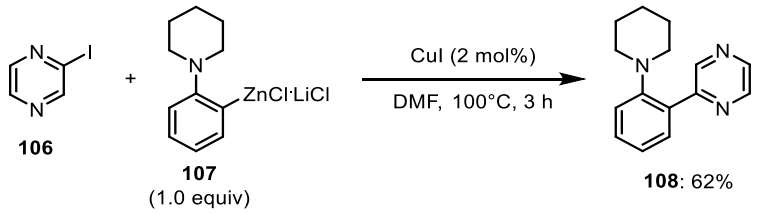
Scheme 37. Enantioselective Negishi cross-coupling reactions.

Remarkably, Fu also reported an enantioselective cyclization/Negishi cross-coupling reaction with alkyl electrophiles.[91] The use of strongly donating bis-dialkylphosphine nickel moieties efficiently promotes the Negishi cross-coupling reactions under practical and mild conditions as demonstrated by Gosmini and Mézailles.[92] Interestingly, it has been shown that Ni(II)-complexes that are relevant to Negishi cross-coupling reactions can be characterized both, structurally and spectroscopically.[93]

3.3 Negishi Cross-Coupling Reactions Using other Transition-Metal Catalysts

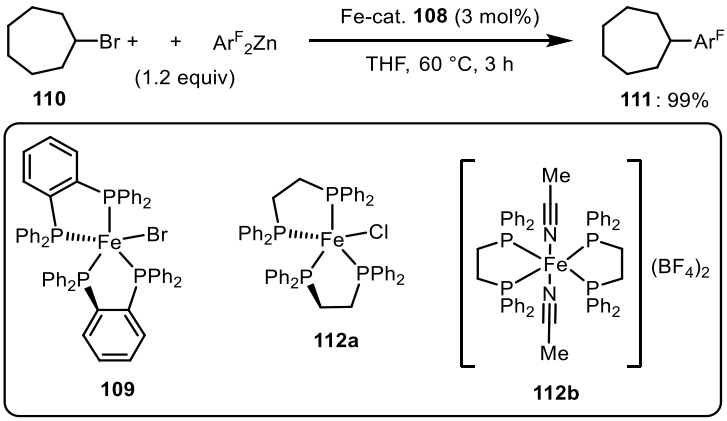
Although palladium and nickel are by far the most used metal catalysts for Negishi cross-couplings, a few other metallic salts, such as Cu, Fe and Co derivatives have been reported to promote efficiently Negishi cross-couplings. A quite general Negishi cross-coupling procedure involving the copper-catalyzed coupling between alkyl-, aryl- and alkynyl-zinc reagents with a range of heteroaryl iodides has been reported by Giri.[94] Thus, reaction of iodopyridazine (**106**) with the amino-substituted zinc compound **107** provides the desired coupling product **108** in 62% yield (Scheme 38).

[87] a) J. T. Binder, C. J. Cordier, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 17003. b) J. Choi, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 9102.
[88] Y. Liang, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 5520.
[89] H. Q. Do, E. R. R. Chandrashekar, G. C. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 16288.
[90] N. D. Schley, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 16588.
[91] H. Cong, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 3788.
[92] E. Nicolas, A. Ohleier, F. D'Accriscio, A. F. Pecharman, M. Demange, P. Ribagnac, J. Ballester, C. Gosmini, N. Mezailles, *Chem. – Eur. J.* **2015**, *21*, 7690.
[93] a) B. Zheng, F. Tang, J. Luo, J. W. Schultz, N. P. Rath, L. M. Mirica, *J. Am. Chem. Soc.* **2014**, *136*, 6499. b) L. Jin, J. Xin, Z. Huang, J. He, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 9607. c) J. Xin, G. Zhang, Y. Deng, H. Zhang, A. Lei, *Dalton Trans.* **2015**, *44*, 19777.
[94] S. Thapa, A. Kafle, S. K. Gurung, A. Montoya, P. Riedel, R. Giri, *Angew. Chem. Int. Ed.* **2015**, *54*, 8236.



Scheme 38. Ligand-free copper-catalyzed Negishi cross-coupling.

Also, iron-catalyzed cross-couplings have been reported using organozinc reagents, showing that monophosphines are excellent ligands for coupling alkyl bromides with diphenylzinc derivatives.[95] Of special interest is the Fe(I)-catalyzed cross-coupling procedure described by Bedford.[96] The readily available catalyst **109** allows a smooth cross-coupling between cycloheptyl bromide (**110**) and fluoroarylzinc reagents (Ar^F) providing the coupled product **111** in quantitative yield (Scheme 39).

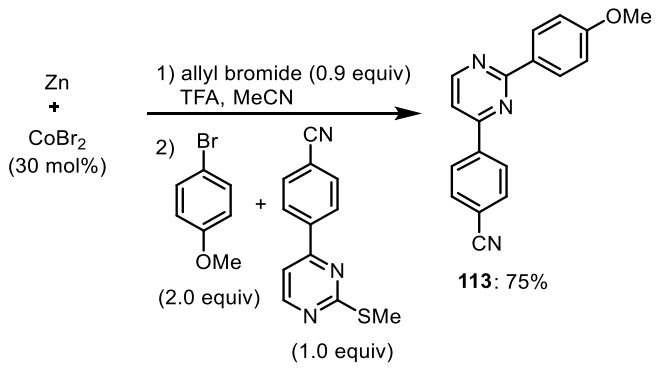


Scheme 39. Negishi cross-coupling reactions catalyzed by iron.

More convenient catalysts, such as **112a**-**b**, have been used especially for the cross-coupling of benzylic halides and cycloalkyl bromides with arylzinc derivatives with great success.[97]

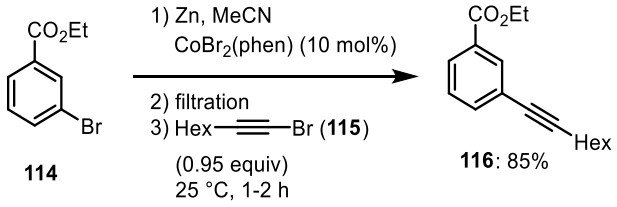
Cobalt salts have been used in Negishi cross-couplings as well and Gosmini has shown that the treatment of $CoBr_2$ with zinc and allyl bromide in MeCN and TFA, followed by the addition of the coupling partners, provides the cross-coupling products, such as **113**, in good yields (Scheme 40).[98]

[95] C. A. Brown, T. A. Nile, M. F. Mahon, R. L. Webster, *Dalton Trans.* **2015**, *44*, 12189.
[96] C. J. Adams, R. B. Bedford, E. Carter, N. J. Gower, M. F. Haddow, J. N. Harvey, M. Huwe, M. A. Cartes, S. M. Mansell, C. Mendoza, D. M. Murphy, E. C. Neeve, J. Nunn, *J. Am. Chem. Soc.* **2012**, *134*, 10333.
[97] R. B. Bedford, E. Carter, P. M. Cogswell, N. J. Gower, M. F. Haddow, J. N. Harvey, D. M. Murphy, E. C. Neeve, J. Nunn, *Angew. Chem. Int. Ed.* **2013**, *52*, 1285.
[98] a) J. M. Begouin, M. Rivard, C. Gosmini, *Chem. Commun.* **2010**, *46*, 5972. b) J. M. Begouin, C. Gosmini, *J. Org. Chem.* **2009**, *74*, 3221.



Scheme 40. Negshi cross-coupling reactions catalyzed by cobalt(II) bromide.

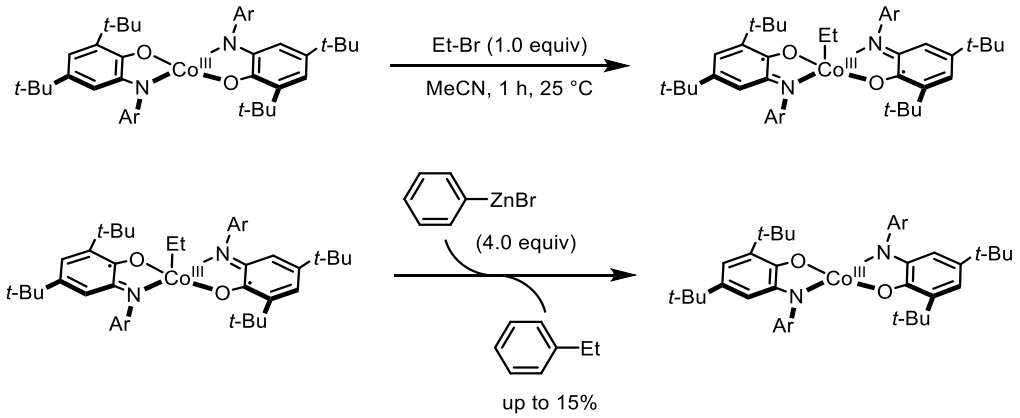
The methodology developed by Gosmini can be efficiently used to couple various organozinc halides with bromoalkynes.[99] Thus, the treatment of functionalized aryl bromides, such as **114**, with $CoBr_2$(phen) and zinc dust produces a zinc reagent that smoothly reacts with various bromoalkynes, such as **115**, to afford the desired cross-coupling product **116** in 85% yield (Scheme 41).



Scheme 41. Cobalt-catalyzed formation of zinc organometallics and Negishi cross-coupling.

Recently, it was shown by Soper *et al.* that a cobalt(III) complex bearing redox-active amidophenolate ligands is a possible catalyst for a Negishi-type cross-coupling of various alkyl halides, such as Et-Br with PhZnBr (Scheme 42).[100]

[99] M. Corpet, X.-Z. Bai, C. Gosmini, *Adv. Synth. Catal.* **2014**, *356*, 2937.
[100] A. L. Smith, K. I. Hardcastle, J. D. Soper, *J. Am. Chem. Soc.* **2010**, *132*, 14358.

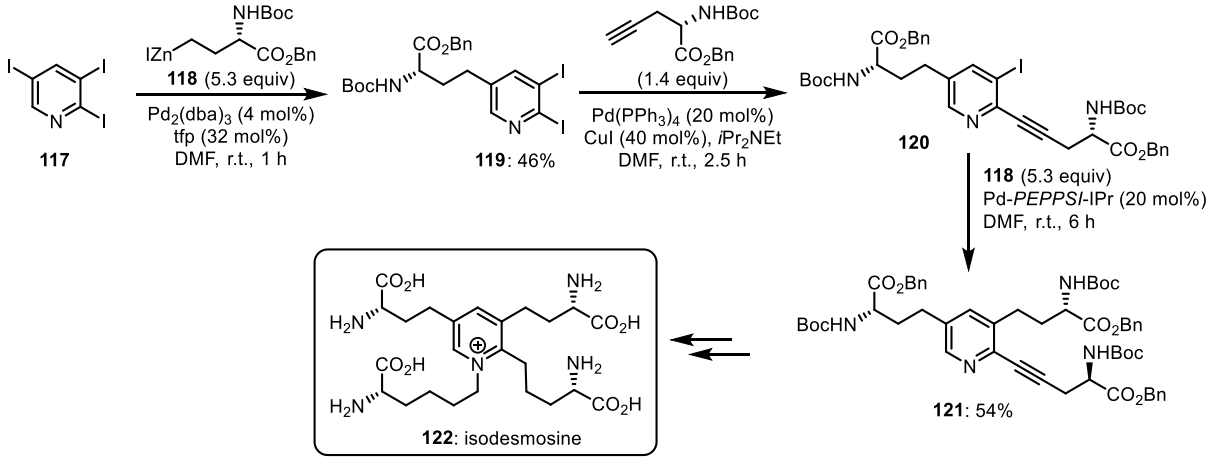


Scheme 42. Attempts towards a redox-active and ligand-mediated cobalt-catalyzed Negishi cross-coupling.

Though only 15% yield of the desired coupling product was afforded, it was shown that cobalt possesses interesting reactivities and is indeed a possible replacement of other transition metals privileged for this reaction.

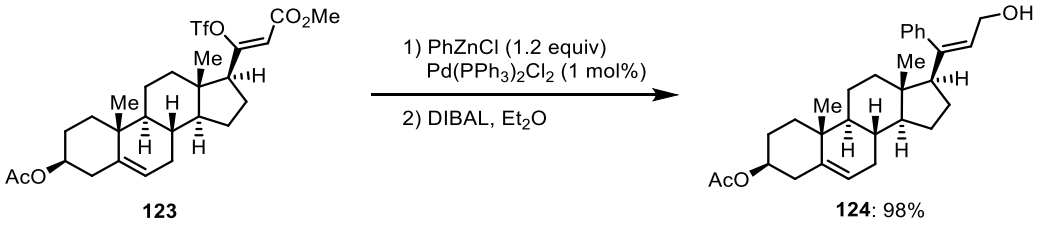
4 Applications of Negishi Cross-Couplings in Natural Product Synthesis

In the total synthesis of isodesmosine (**122**) the employment of a regioselective Negishi cross-coupling reaction proved to be critical.[101] The readily prepared tri-iodopyridine **117** undergoes a selective Negishi cross-coupling with Jackson's zinc reagent **118**[18] leading to the desired product **119** in 46% yield. A Sonogashira cross-coupling converts **119** into monoiodide **120** and a subsequent Negishi cross-coupling with **118** provides the tris-alkylated product **121** that was further converted to isodesmosine (**122**) in a few steps (Scheme 43).



Scheme 43. Preparation of isodesmosine *via* Negishi cross-coupling reactions.

Mazet used Negishi cross-couplings in an impressive way for the preparation of complex steroid derivatives.[102] The alkenyl triflate **123** was phenylated using PhZnCl to provide the corresponding alcohol **124** in 98% yield after DIBAL-reduction (Scheme 44).

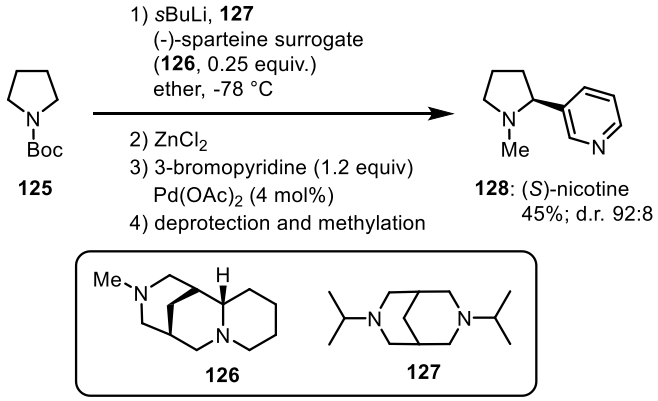


Scheme 44. Negishi cross-coupling reaction for the synthesis of complex steroid derivatives.

The enantioselective construction of pyrrolidines is important due to the range of highly pharmaceutically active molecules bearing such a ring system. O'Brien and Campos have developed a general methodology for the preparation of various chiral pyrrolidines using *s*-BuLi/(-)-sparteine or its

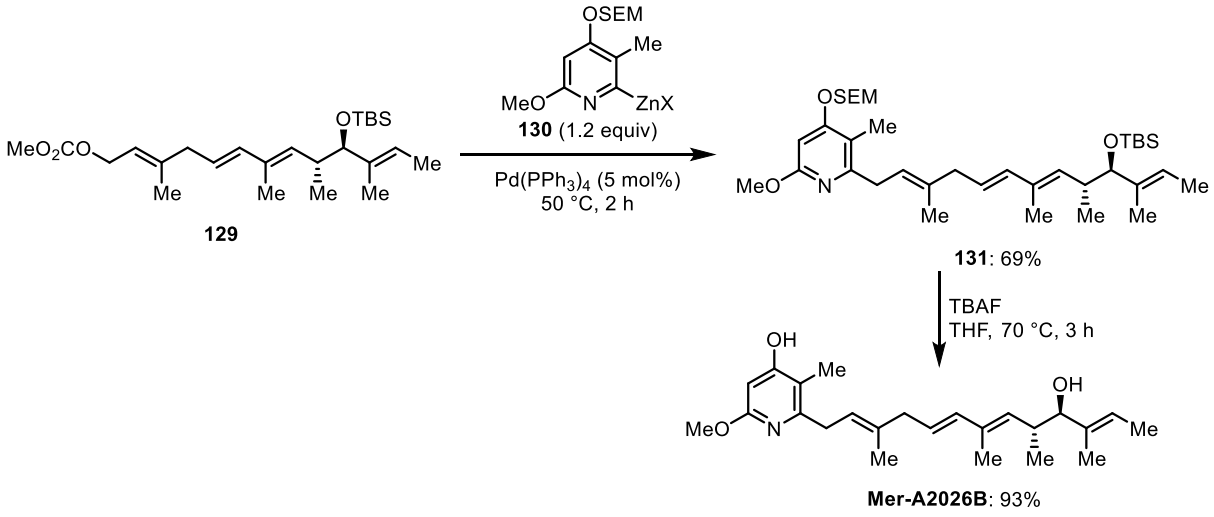
[101] Y. Koseki, T. Sugimura, K. Ogawa, R. Suzuki, H. Yamada, N. Suzuki, Y. Masuyama, Y. Y. Lin, T. Usuki, *Eur. J. Org. Chem.* **2015**, *2015*, 4024.
[102] H. Li, C. Mazet, *J. Am. Chem. Soc.* **2015**, *137*, 10720.

surrogate to obtain a chiral pyrrolidylzinc reagent, which is readily employed in a Negishi cross-coupling with retention of configuration. This general method is illustrated in a synthesis of (*S*)-nicotine. The metalation of pyrrolidine **125** with *s*-BuLi in the presence of the chiral sparteine-surrogate **126** and the diamine **17**, followed by transmetalation to zinc and cross-coupling with 3-bromopyridine provides (*S*)-nicotine (**128**) after deprotection and methylation (Scheme 45).[103]



Scheme 45. Synthesis of (*S*)-nicotine *via* Negishi cross-coupling.

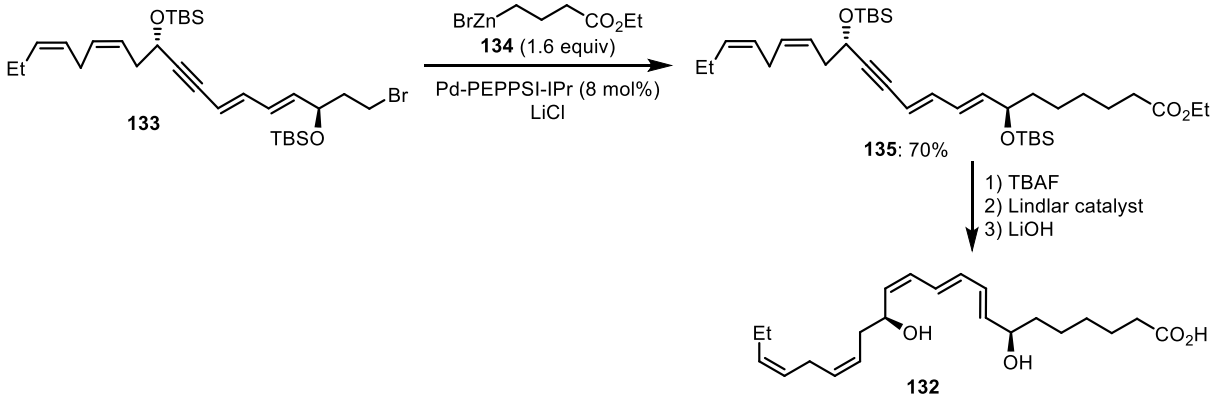
Gademann used a Negishi cross-coupling with success to perform the first total synthesis of the piericidin related natural products Mer-A2026B and JBIR-02.[104] Thus, the reaction of the complex carbonate **129** with the pyridylzinc reagent **130** leads to the desired Negishi cross-coupling product **131** in 69% yield and Mer-A2026B is afforded after deprotection (Scheme 46).



Scheme 46. Synthesis of Mer-A2026B *via* Negishi cross-coupling.

[103] G. Barker, J. L. McGrath, A. Klapars, D. Stead, G. Zhou, K. R. Campos, P. O'Brien, *J. Org. Chem.* **2011**, *76*, 5936.
[104] J. Hoecker, K. Gademann, *Org. Lett.* **2013**, *15*, 670.

Finally, the synthesis of the anti-inflammatory pro-resolving lipid **132** has been achieved using a Negishi cross-coupling between two C(sp^3)-bonds. Thus, the cross-coupling between the unsaturated bromide **133** and zinc reagent **134** provides the desired cross-coupling product **135** in 70% yield affording the drug **132** after a few steps (Scheme 47).[105]



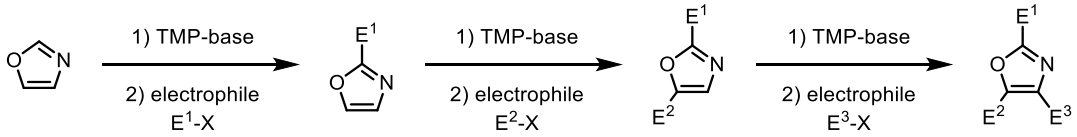
Scheme 47. Complex Negishi cross-coupling for the synthesis of an anti-inflammatory pro-resolving lipid.

Due to the mild conditions required to form new carbon-carbon bonds, the Negishi cross-coupling has found an increased number of synthetic applications. Although palladium is still the most commonly used metal catalyst for these cross-couplings, alternative metals, such as nickel, cobalt and iron may be useful complement methodologies in the future regarding toxicity, as well as ecological and price aspects. The broad and constantly increasing availability of zinc organometallics should further expand the use of the Negishi cross-coupling in organic synthesis.

[105] J. E. Tungen, M. Aursnes, J. Dalli, H. Arnardottir, C. N. Serhan, T. V. Hansen, *Chem. – Eur. J.* **2014**, *20*, 14575.

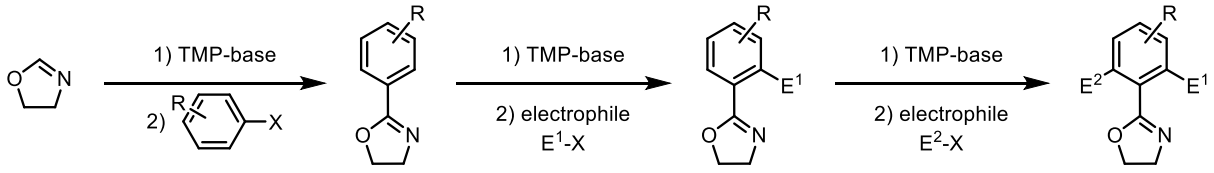
5 Objectives

The aim of the first part of this thesis was the development of a convenient method for the metalation and functionalization of sensitive 5-membered N,O-heterocycles. These scaffolds are of great interest due to their biological activities and the appearance of this moiety in several pharmaceutical agents. However, these heterocycles are sensitive scaffolds as they are prone to undergo ring fragmentation under lithiation conditions. Therefore, the deprotonation using zinc amide bases is an important method for the functionalization of these sensitive heterocycles as a variety of functional groups can be tolerated. First a general method for the regiocontrolled introduction of all substitutents should be investigated to achieve a complete functionalization of the oxazole scaffold (Scheme 48).



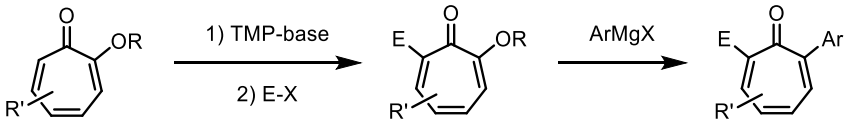
Scheme 48. General pathway for the complete functionalization of oxazole.

Also, oxazolines represent an important class of 5-membered heterocycles. Especially, 2-aryloxazolines exhibit a range of interesting biological activities. By now, the synthesis of functionalized 2-arylated oxazolines involves highly prefunctionalized starting materials or expensive reagents, respectively. Therefore, a procedure for a convenient preparation of 2-arylated oxazolines should be developed. Zincation of oxazoline using metal amide bases and reaction with electrophiles should provide the desired 2-substituted compounds. Additionally, 2-aryloxazolines should be further functionalized *via* directed metalation with amide bases using the oxazoline moiety as a directing group (Scheme 49).



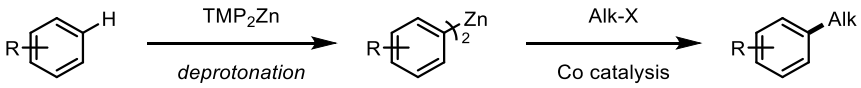
Scheme 49. Desired arylation of oxazoline and its use as a directing group for further functionalizations.

Additionally, due to its 7-membered ring scaffold the tropolone ring shows a range of interesting activitities, such as antioxidant properties. Up to date, the synthesis of functionalized tropolones is limited due to the harsh reaction conditions of current methods. Hence, a method for the smooth functionalization of the tropolone scaffold would be desirable. Metalation using metal amide bases and reaction of the generated organometallic species with various electrophiles should provide functionalized tropolones (Scheme 50).



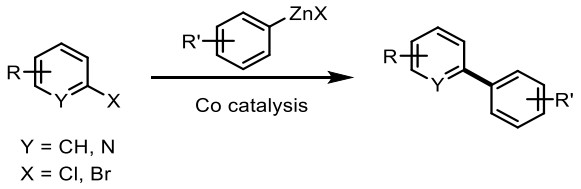
Scheme 50. Intended metalation and functionalization of tropolone derivatives.

The second part of the thesis deals with the replacement of expensive and/or toxic Pd and Ni catalysts by environmentally more benign metals, such as cobalt. A general method for the cobalt-catalyzed cross-coupling of organozinc reagents prepared *via* directed metalation with primary and secondary alkyl halides should be investigated. Special attention should be drawn to the coupling of secondary alkyl halides without rearrangement from branched to unbranched (Scheme 51). [106]



Scheme 51. Cobalt-catalyzed cross-coupling of organometallic reagents prepared *via* direct metalation with alkyl halides.

Furthermore, a Negishi cross-coupling reaction of (hetero)aryl halides with arylzinc reagents under cobalt catalysis should be investigated. [107] The Negishi cross-coupling represents an indispensable tool for organic chemistry due to the unique reactivity and the high functional group tolerance of organiczinc reagents. The replacement of Pd- and Ni-catalysts employed in this reaction by environmentally benign metals, such as cobalt, is therefore highly appreciated (Scheme 52).



Scheme 52. Intended cobalt-catalyzed cross-coupling of (hetero)aryl halides and arylzinc reagents.

[106] This project was developed in cooperation with Jeffrey M. Hammann, see: J. M. Hammann, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 4478–4481 and Jeffrey M. Hammann, Dissertation, LMU Munich.

[107] This project was developed in cooperation with Jeffrey M. Hammann, see: D. Haas, J. M. Hammann, F. H. Lutter, P. Knochel, *Angew. Chem. Int. Ed.* **2016**, *55*, 3809–3812 and Jeffrey M. Hammann, Dissertation, LMU Munich.

B RESULTS AND DISCUSSION

B RESULTS AND DISCUSSION

1 Regioselective Functionalization of the Oxazole Scaffold Using TMP-Bases of Mg and Zn

1.1 Introduction

The synthesis of oxazoles is an important task in organic chemistry as this structural motif can be found in many biologically active compounds such as analgesic, antibiotic, and anticancer agents.[108] In Ageroplas®, an antithrombotic agent developed by Merck KGAa, the oxazole derivative acts as a platelet aggregation inhibitor.[109] Pfizer's Darglitazone also includes this key structural unit in its peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, which exhibits insulin-sensitizing effects, by showing an improved glycemic and lipidemic control. As a further application, Darglitazone is a possible active substance for the treatment of metabolic disorders, such as type 2 diabetes mellitus.[110] In addition, GlaxoSmithKline investigated the activity of Retosiban, which also bears an oxazole moiety, as an oxytocin receptor antagonist and is currently being developed for the treatment of preterm labour (Figure 1).[111]

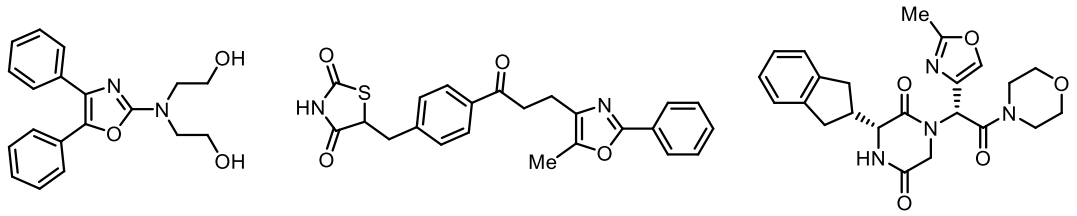


Figure 1. Pharmaceuticals containing an oxazole core.

To date, the preparation of highly functionalized oxazoles involves condensation reactions such as the Fischer[112] or the Robinson-Gabriel synthesis.[113] However, these methods have some limitations, such as poor regioselectivity in the ring construction, multistep syntheses of the starting materials, and

[108] a) P. Wipf, *Chem. Rev.* **1995**, *95*, 2115. b) M. Lautens, A. Roy, *Org. Lett.* **2000**, *2*, 555. c) P.-Y.Coqueron, C. Didier, M. A. Ciufolini, *Angew. Chem. Int. Ed.* **2003**, *42*, 1411. d) B. S. Lucas, V. Gopalsamuthiram, S. D. Burke, *Angew. Chem. Int. Ed.* **2007**, *46*, 769. e) E. Merkul, T. J. J. Müller, *Chem. Commun.* **2006**, 4817. f) D. Davyt, G. Serra, *Mar. Drugs* **2010**, *8*, 2755. g) H. D. Silva, W. P. Henry, C. U. Pitman, Jr., *Synthesis* **2012**, *44*, 3337.

[109] The Merck Index, 12th Edition, p. 3432.

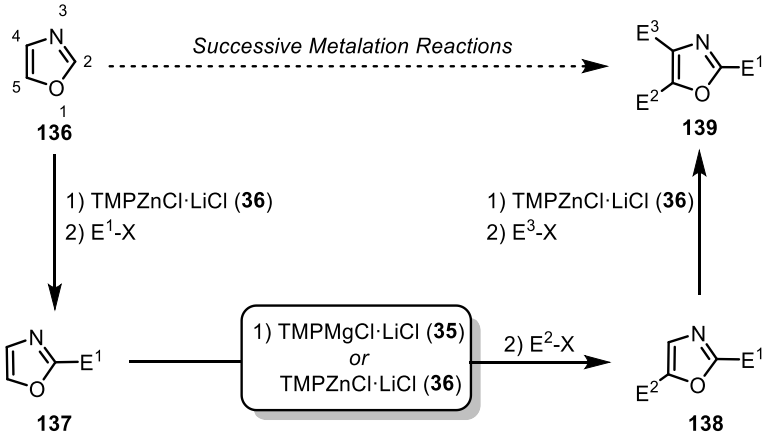
[110] B. Hulin, D. A. Clark, S. W. Goldstein, R. E. McDermott, P. J. Dambek, W. H. Kappeler, C. H. Lamphere, D. M. Lewis, J. P. Rizzi, *J. Med. Chem.* **1992**, *35*, 1853.

[111] J. Liddle, M. J. Allen, A. D. Borthwick, D. P. Brooks, D. E. Davies, R. M. Edwards, A. M. Exall, C. Hamlett, W. R. Irving, A. M. Mason, G. P. McCafferty, F. Nerozzi, S. Peace, J. Philp, D. Pollard, M. A. Pullen, S. S. Shabbir, S. L. Sollis, T. D. Westfall, P. M. Woollard, C. Wu, D. M. B. Hickey, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 90.

[112] a) E. Fischer, *Ber.* **1896**, *29*, 205. b) J. W. Cornforth, R. H. Cornforth, *J. Am. Chem. Soc.* **1949**, 1028.

[113] a) R. Robinson, *J. Chem. Soc.* **1909**, *95*, 2167. b) S. Gabriel, *Ber.* **1910**, *43*, 1283. c) I. J. Turchi, M. J. S. Dewar, *Chem. Rev.* **1975**, *75*, 389.

harsh reaction conditions. Additionally, C-H arylation is another approach for the functionalization of oxazoles. The method shows great potential and its scope is constantly increasing.[114] The difficulties of selective functionalization have been addressed by the development of alternative methods, in particular metalations of the oxazole scaffold. Indeed, there are many reports of successful lithiations of oxazoles at the C-2 position.[115] However, the direct functionalization of these heterocycles by lithiation is difficult due to side reactions such as ring opening to the corresponding isonitrile.[116] Although a few lithiation reactions at positions C-5 or C-4 have been reported,[117] these metalations require very low reaction temperatures, as well as prefunctionalized starting materials and do not tolerate the reaction of oxazole derivatives containing sensitive functional groups. *Knochel* and co-workers have shown that TMPZnCl·LiCl (**36**)[34] and TMPMgCl·LiCl (**35**)[33] are exceptionally active and chemoselective metal amide bases, allowing in particular for the metalation of sensitive heterocycles.



Scheme 53. Successive metalations of oxazole (136) in position 2, 5, or 4 using TMP-bases of Mg and Zn.

[114] a) C. Verrier, P. Lassalas, L. Théveau, G. Quéguiner, F. Trécourt, F. Marsais, C. Hoarau, *Beilstein J. Org. Chem.* **2011**, *7*, 1584. b) N. A. Strotman, H. R. Chobanian, Y. Guo, J. He, J. E. Wilson, *Org. Lett.* **2010**, *12*, 3578. c) L. Théveau, C. Verrier, P. Lassalas, T. Martin, G. Dupas, O. Querolle, L. Van Hijfte, F. Marsais, C. Hoarau, *Chem. – Eur. J.* **2011**, *17*, 14450. d) L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem. Int. Ed.* **2009**, *48*, 201.

[115] a) J. C. Hodges, W. C. Patt, C. J. Connolly, *J. Org. Chem.* **1991**, *56*, 449. b) N. K. Harn, C. J. Gramer, B. A. Anderson, *Tetrahedron Lett.* **1995**, *36*, 9453. c) E. Vedejs, S. D. Monahan, *J. Org. Chem.* **1996**, *61*, 5192. d) B. A. Anderson, N. K. Harn, *Synthesis* **1996**, 583. e) B. A. Anderson, L. M. Becke, R. N. Booher, M. E. Flaugh, N. K. Harn, T. J. Kress, D. L. Varie, J. P. Wepsiec, *J. Org. Chem.* **1997**, *62*, 8634. f) A. B. Smith, III, K. P. Minibiole, S. Freeze, , *Synlett* **2001**, 1739. g) M. R. Reeder, H. E. Gleaves, S. A. Hoover, R. J. Imbordino, J. Pangborn, *Org. Process Res. Dev.* **2003**, *7*, 696. h) D. R. Williams, L. Fu, *Org. Lett.* **2010**, *12*, 808.

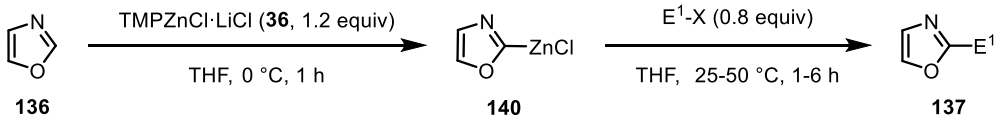
[116] a) A. I. Meyers, E. W. Collington, *J. Am. Chem. Soc.* **1970**, *92*, 6676. b) A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini, *Synthesis* **1987**, *1987*, 693. c) T. L. Gilchrist, *Adv. Heterocycl. Chem.* **1987**, *41*, 4. d) B. Iddon, *Heterocycles* **1994**, *37*, 1321. e) E. Crowe, F. Hossner, M. J. Hughes, *Tetrahedron Lett.* **1995**, *51*, 8889. f) E. Vedejs, L. M. Luchetta, *J. Org. Chem.* **1999**, *64*, 1011. g) O. Bayh, H. Awad, F. Mongin, C. Hoarau, L. Bischoff, F. Trécourt, G. Quéguiner, F. Marsais, F. Blanco, B. Abarca, R. Ballesteros, *J. Org. Chem.* **2005**, *70*, 5190. h) R. A. Miller, R. M. Smith, B. Marcune, *J. Org. Chem.* **2005**, *70*, 9074. i) M. C. Pirrung, S. Ghorai, *J. Am. Chem. Soc.* **2006**, *128*, 11772.

[117] a) A. I. Meyers, J. P. Lawson, *Tetrahedron Lett.* **1981**, *22*, 3163. b) D. R. Williams, D. A. Brooks, K. G. Meyer, M. Pagel, *Tetradedron Lett.* **1998**, *39*, 8023. c) B. Li, R. A. Buzon, Z. Zhang, *Org. Process Res. Dev.* **2007**, *11*, 951. d) K. Lee, C. M. Counceller, J. P. Stambuli, *Org. Lett.* **2009**, *11*, 1457.

Thus, successive zincations and/or magnesiations in positions 2, 5 or 4 of oxazole (**136**) and reaction with various electrophiles lead *via* 2-substituted (**137**) and 2,5-disubstituted oxazoles (**138**) to completely functionalized 2,4,5-trisubstituted oxazole derivatives of type **139** (Scheme 53).

1.2 Zincation of Oxazole in Position C-2

Thus, treatment of oxazole (**136**) with TMPZnCl·LiCl (**36**; 1.2 equiv) leads within 1 h at 0 °C to the quantitative formation of the corresponding 2-oxazolylzinc reagent (**140**), which is perfectly stable at 25 °C. The zincated species reacts smoothly with a variety of electrophiles (E^1-X) under mild reaction conditions affording 2-functionalized oxazoles of type **137** (Scheme 54).

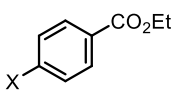
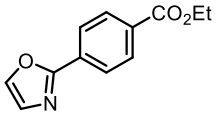
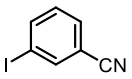
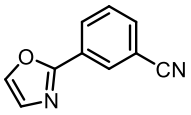
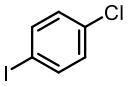
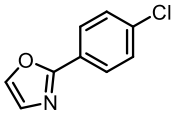
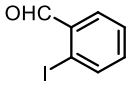
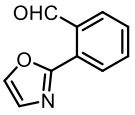
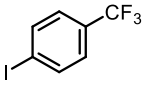
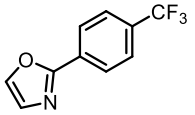
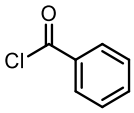
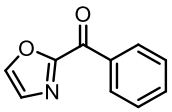
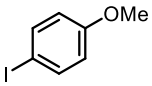
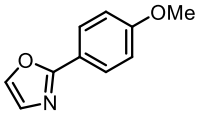
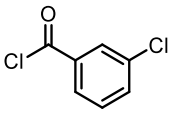
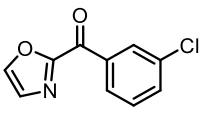
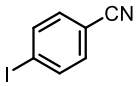
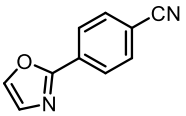
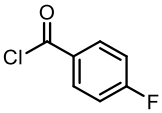
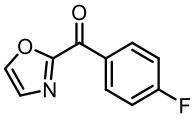
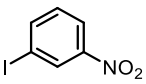
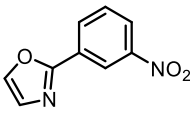
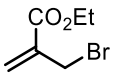
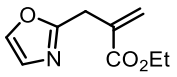


Scheme 54. Metalation of oxazole (136) using TMPZnCl·LiCl (36).

The prepared 2-oxazolylzinc reagent (**140**) successfully undergoes Negishi cross-coupling reactions[118] using $Pd(dba)_2$ and Farina's ligand ($(o\text{-furyl})_3P$)[35] with ethyl 4-iodobenzoate or ethyl 4-bromobenzoate to afford the corresponding cross-coupling product **137a** in 92% or 89% yield, respectively (Table 1, entry 1). Other *para*-substituted aryl iodides, such as 1-chloro-4-iodobenzene, 4-iodobenzotrifluoride, 4-iodoanisole or 4-iodobenzontrile also react in the cross-coupling reaction providing the products **137b**-**e** in 74-90% yield (entries 2-5). The cross-coupling also works well when using aryl iodides substituted with electron-withdrawing groups, such as 1-iodo-3-nitro-benzene, or other *meta*-substituted electrophiles, such as 3-iodobenzonitrile affording the expected products in 82-94% yield (entries 6 and 7). Remarkably, also the *ortho*-substituted 2-iodobenzaldehyde reacts in this cross-coupling furnishing the desired cross-coupling product **137h** in 79% yield (entry 8). The 2-oxazolylzinc reagent (**140**) is successfully employed in Pd-catalyzed Negishi acylation reactions[44] with benzoyl chloride, 3-chlorobenzoyl chloride and 4-fluorobenzoyl chloride providing the ketones **137i**-**k** in 61-86% yield (entries 9-11). The 2-zincated oxazole also reacts after transmetalation with $CuCN{\cdot}2LiCl$[119] in a copper(I)-mediated allylation reaction with ethyl 2-(bromomethyl)acrylate[120] to furnish the allylated oxazole **137l** in 78% yield (entry 12).

[118] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298. b) E. Negishi, M. J. Kobayashi, *J. Org. Chem.* **1980**, *45*, 5223. c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[119] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[120] J. Villieras, M. Rambaud, *Synthesis* **1982**, 924.

Table 1. Regioselective metalation of oxazole (136) using TMPZnCl·LiCl (36) and quenching with electrophiles.

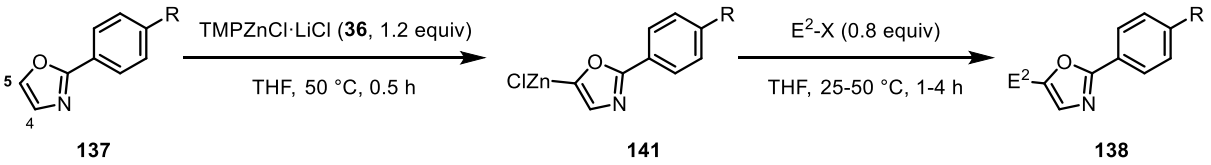
Entry	Electrophile E^1-X	Product / Yield[a]	Entry	Electrophile E^1-X	Product / Yield[a]
1			7		
	X = I, 50 °C, 4 h	**137a**, 92%[b]		50 °C, 4 h	**137g**, 82%[b]
	X = Br, 50 °C, 6 h	80%[c]			
2			8		
	50 °C, 2 h	**137b**, 83%[b]		50 °C, 2 h	**137h**, 79%[b]
3			9		
	25 °C, 4 h	**137c**, 74%[b]		25 °C, 3 h	**137i**, 73%[d]
4			10		
	25 °C, 6 h	**137d**, 90%[b]		25 °C, 4 h	**137j**, 86%[d]
5			11		
	25 °C, 4 h	**137e**, 87%[b]		25 °C, 4 h	**137k**, 61%[d]
6			12		
	50 °C, 1 h	**137f**, 94%[b]		25 °C, 1 h	**137l**, 78%[e]

[a]Isolated yield of analytically pure product. [b]Pd-catalyzed cross-coupling using 3 mol% $Pd(dba)_2$ and 6 mol% P(*o*-furyl)$_3$. [c]Pd-catalyzed cross-coupling using 4 mol% $Pd(PPh_3)_4$. [d]Pd-catalyzed acylation reaction using 4 mol% $Pd(PPh_3)_4$. [e]The zinc reagent was transmetalated using CuCN·2LiCl.

Sensitive functionalities, such as an ester (entries 1, 12), a nitrile (entries 5, 7) or an aldehyde (entry 8) are well tolerated during this cross-coupling procedure and the 2-functionalized oxazoles are afforded in high yields.

1.3 Zincation or Magnesiation of 2-Arylated Oxazole Derivatives

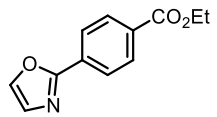
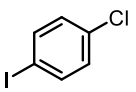
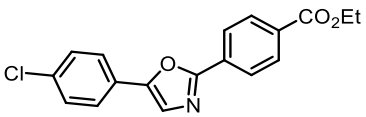
A second metalation of the 2-substituted oxazoles of type **137** occurs at the C-5 position and is readily achieved by adding either TMPMgCl·LiCl (**35**) or TMPZnCl·LiCl (**36**). The 5-zincated species is produced within 2 h at 50 °C by the reaction of 2-substituted oxazoles of type **137** with TMPZnCl·LiCl (**36**, 1.2 equiv). The corresponding zinc reagent (**141**) reacts with a variety of electrophiles (E^2-X) to yield highly functionalized 2,5-disubstituted oxazole derivatives of type **138** (Scheme 55).



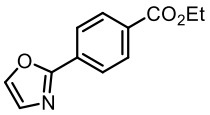
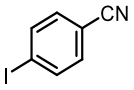
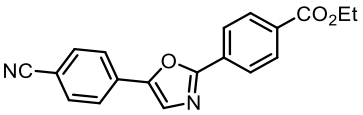
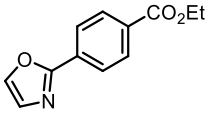
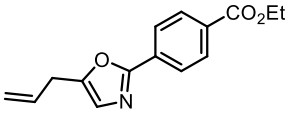
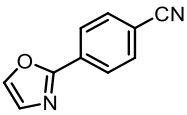
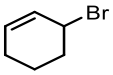
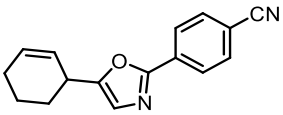
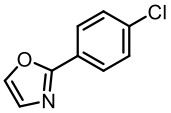
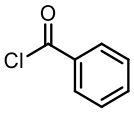
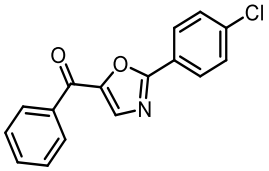
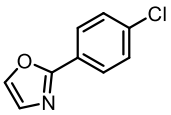
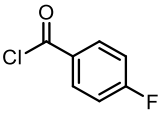
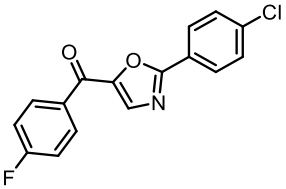
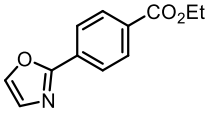
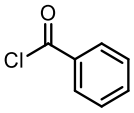
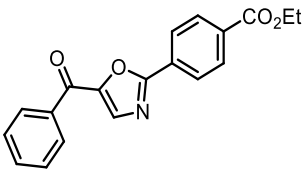
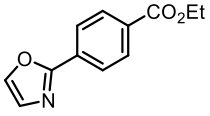
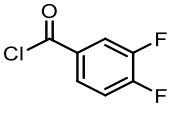
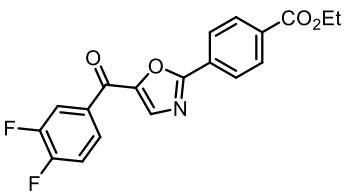
Scheme 55. Metalation of 2-aryloxazoles (137) using TMPZnCl·LiCl (36).

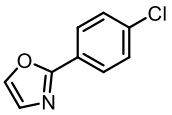
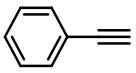
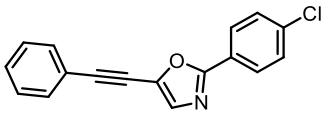
The zinc derivative of **137a** is subjected to Negishi cross-couplings with 1-chloro-4-iodobenzene or 4-iodobenzonitrile to provide the bisarylated oxazoles **138a** and **138b** in 83-92% yield (Table 2, entries 1, 2). After zincation of **137a** and **137e** and transmetalation with CuCN·2LiCl, a copper(I)-mediated allylation with allyl bromide or 3-bromocyclohexene leads to the desired oxazoles **138c** and **138d** in 76-79% yield (entries 3, 4). Pd-catalyzed acylation of **137a** or **137b** with benzoyl chloride, 4-fluorobenzoyl chloride, or 3,4-difluorobenzoyl chloride provides the corresponding oxazolyl ketones **138e**-**h** in 76-98% yield (entries 5-8). Furthermore, after zincation and reaction with iodine, the 2-substituted oxazole **137b** undergoes a regioselective Sonogashira reaction[121] *in situ* with phenylacetylene in the presence of 3 mol% $Pd(dba)_2$, 6 mol% P(*o*-furyl)$_3$, 4 mol% CuI, and TEA as solvent to afford the 2,5-disubstituted oxazole **138i** in 80% yield (entry 9).

Table 2. Regioselective zincation of 2-aryloxazoles of type 137 using TMPZnCl·LiCl (36).

Entry	Substrate	Electrophile E^2-X	Product / Yield[a]
1			
	137a	50 °C, 2 h	**138a**, 92%[b]

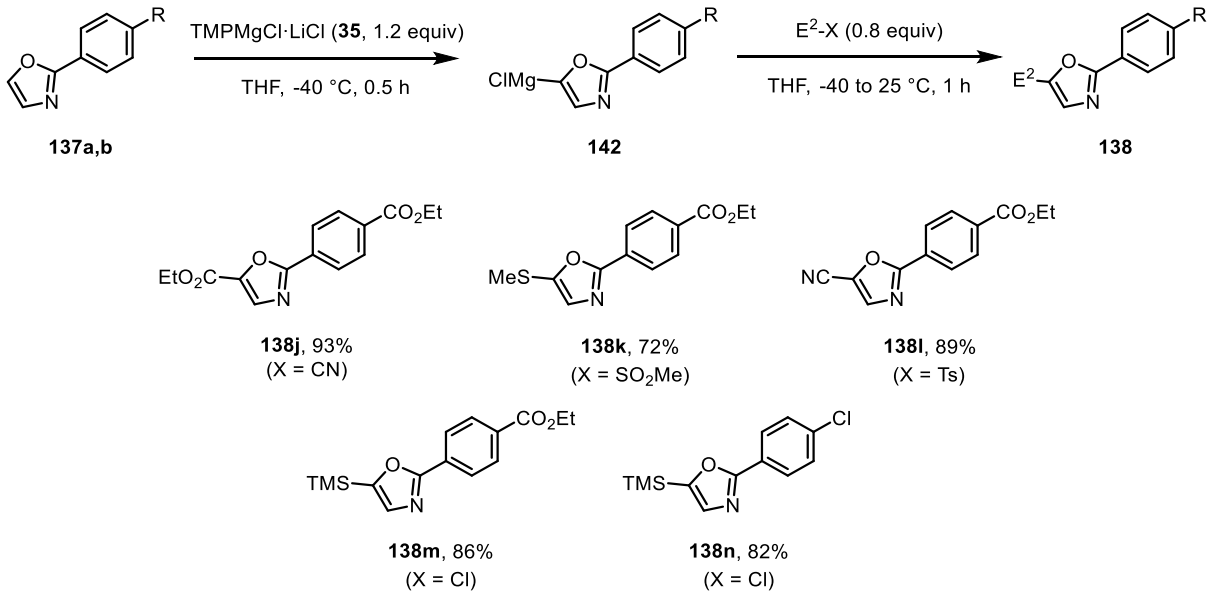
[121] a) K. Sonogashira, Y. M. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467. b) R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874. c) H. Doucet, J.-C. Hierso, *Angew. Chem. Int. Ed.* **2007**, *46*, 834. d) R. Chinchilla, C. Najera, *Chem. Soc. Rev.* **2011**, *40*, 5084. e) K. Sonogashira, in *Metal-catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**.

Entry	Substrate	Electrophile E^2-X	Product / Yield[a]
2			
	137a	50 °C, 6 h	**138b**, 83%[b]
3			
	137a	25 °C, 1 h	**138c**, 79%[c]
4			
	137e	25 °C, 1 h	**138d**, 76%[c]
5			
	137b	25 °C, 2 h	**138e**, 76%[d]
6			
	137b	25 °C, 4 h	**138f**, 86%[d]
7			
	137a	25 °C, 4	**138g**, 98%[d]
8			

Entry	Substrate	Electrophile E^2-X	Product / Yield[a]
	137a	25 °C, 1 h	**138h**, 87%[d]
9		I_2 *then* 	
	137b	25 °C, 1 h	**138i**, 80%[e]

[a]Isolated yield of analytically pure product. [b]Pd-catalyzed cross-coupling using 3 mol% $Pd(dba)_2$ and 6 mol% P(*o*-furyl)$_3$. [c]The zinc reagent was transmetalated using CuCN·2LiCl. [d]Pd-catalyzed cross-coupling using 4 mol% $Pd(PPh_3)_4$. [e]Pd-catalyzed crosscoupling using 3 mol% $Pd(dba)_2$ and 6 mol% P(*o*-furyl)$_3$, 4 mol%.

Alternatively, the 5-magnesiated species can be prepared by reaction with TMPMgCl·LiCl (**35**). Thus, treatment of the 2-arylated oxazoles **137a** and **137b** with TMPMgCl·LiCl (**35**, 1.2 equiv) leads to the quantitative formation of the 5-magnesiated oxazole of type **142** within 0.5 h at -40 °C. The oxazolylmagnesium reagents of type **142** readily react with various electrophiles, such as NC-CO_2Et, $MeSO_2SMe$,[122] TsCN, or TMSCl to provide the 2,5-disubstituted oxazoles **138j**-**n** in 72-93% yield (Scheme 56).



Scheme 56. Metalation of 2-aryloxazoles (137) using TMPMgCl·LiCl (35) and subsequent reaction with electrophiles.

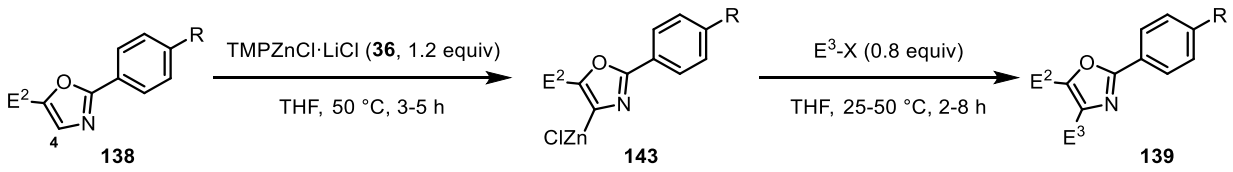
Remarkably, the metalation of 2-substituted oxazole derivatives with the mild amide-base TMPZnCl·LiCl (**36**) can be performed at 50 °C, whereas the use of TMPMgCl·LiCl (**35**) requires more accurate temperature control as the reaction temperature should be -40 °C. Moreover, the

[122] The thiomethylgroup can be subjected to cross-coupling reactions, see: L. S. Liebeskind, J. Srogl, *Org. Lett.* **2002**, *4*, 979.

regioselectivity of the second metalation and functionalization of 2-substituted oxazoles is supported by X-Ray data of compounds **138j** and **138l** showing exclusive formation of the 2,5-disubstituted derivatives.[123] Exceptionally, no regioisomers are detected during the reaction showing the advantage of the currend methodology over known procedures that deal with the problem of regioselectivity.

1.4 Zincation of 2,5-Disubstituted Oxazole Derivatives

The prepared 2,5-disubstituted oxazoles of type **138** can be further metalated at the C-4 position using TMPZnCl·LiCl (**36**, 1.2 equiv) to afford the expected 4-zincated species of type **143** within 3-5 h at 50 °C. These zincated polyfunctional oxazoles react with various electrophiles (E^3-X) and undergo Negishi cross-couplings, Pd-catalyzed acylation reactions, or copper(I)-mediated allylations (Scheme 57).

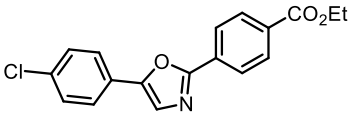
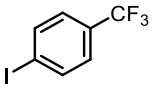
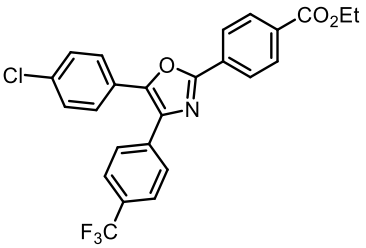
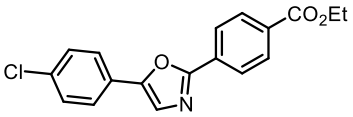
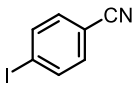
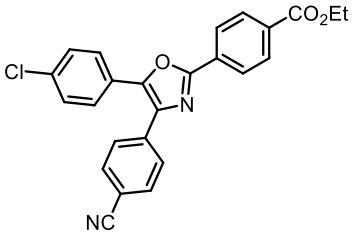
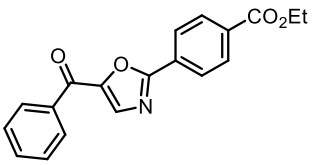
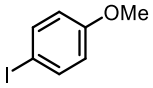
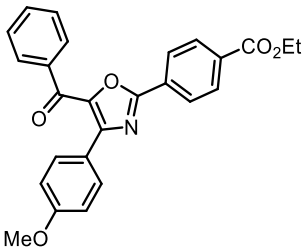
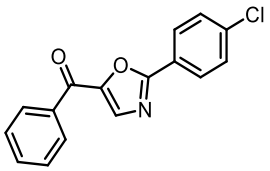
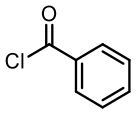
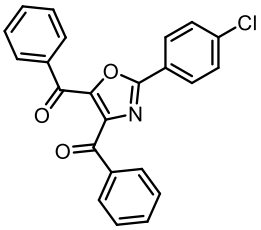


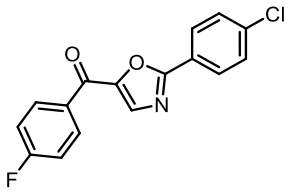
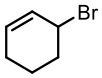
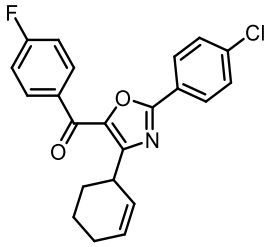
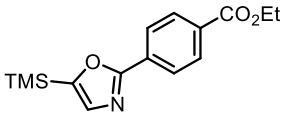
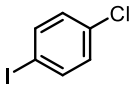
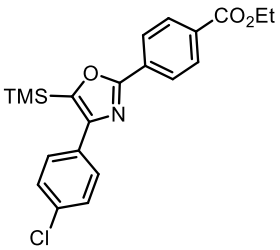
Scheme 57. Metalation of oxazole derivatives of type 138 in position 4 using TMPZnCl·LiCl (36) and subsequent reaction with electrophiles.

Thus, after the zincation of the 2,5-substituted oxazole **138a**, Negishi cross-couplings were performed with various aryl iodides, such as 1-iodo-4-(trifluoromethyl)benzene and 4-iodobenzonitrile, furnishing the desired 2,4,5-arylated oxazoles **139a** and **b** in 73-82% yield (Table 3, entries 1, 2). Similarly, the keto-substituted oxazole **138g** is an excellent substrate for a Negishi cross-coupling reaction with 4-iodoanisole and provides the desired trisubstituted oxazole **139c** in 76% yield. Furthermore, the 5-acylated oxazole **138e** undergoes a Pd-catalyzed Negishi acylation with benzoyl chloride, affording the trisubstituted oxazole **139d** in 78% yield (entry 4). Also, the allylation of the zincated oxazole derived from **138f** with 3-bromocyclohexene in the presence of CuCN·2LiCl leads to the expected trisubstituted oxazole **139e** in 74% (entry 5). Finally, the oxazole **138m** is arylated by our standard procedure with 1-chloro-4-iodobenzene, furnishing the 5-silyloxazole **139f** in 84% yield.[124]

[123] See Appendix for x-ray structures of compounds **138j** and **138l**.
[124] For removal of the TMS-group on heterocycles, see: C. Dunst, P. Knochel, *J. Org. Chem.* **2011**, *76*, 6972.

Table 3. Zincation of oxazole derivatives of type 138 at the C-4 position using TMPZnCl·LiCl (36) and subsequent reaction with electrophiles.

Entry	Substrate / Metalation conditions	Electrophile E^2-X	Product / Yield[a]
1			
	138a, 50 °C, 6 h	50 °C, 8 h	**139a**, 82%[b]
2			
	138a	50 °C, 6 h	**139b**, 73%[b]
3			
	138g, 50 °C, 3 h	50 °C, 6 h	**139c**, 76%[b]
4			
	138e, 50 °C, 3 h	25 °C, 3 h	**139d**, 78%[c]

Entry	Substrate / Metalation conditions	Electrophile E^2-X	Product / Yield[a]
5			
	138f, 50 °C, 3 h	25 °C, 2 h	**139e**, 74%[d]
6			
	138m, 50 °C, 5 h	50 °C, 6 h	**139f**, 84%[b]

[a]Isolated yield of analytically pure product. [b]Pd-catalyzed cross-coupling using 3 mol% $Pd(dba)_2$ and 6 mol% P(*o*-furyl)$_3$. [c]Pd-catalyzed acylation reaction using 4 mol% $Pd(PPh_3)_4$. [d]The zinc reagent was transmetalated using CuCN·2LiCl.

This new general method for performing multiple regioselective metalations of oxazole (**136**) *via* successive reactions using either TMPMgCl·LiCl (**35**) or TMPZnCl·LiCl (**36**) leads to a variety of oxazole derivatives. Regiocontrolled introduction of all substituents allows for the preparation of highly functionalized oxazoles.

2 Zincation of 4,4-Dimethyloxazoline Using TMPZnCl·LiCl. A New Preparation of 2-Aryloxazolines

2.1 Introduction

Oxazolines are an important class of heterocycles found in pharmaceuticals that display cytotoxic, antitumor, neuroprotective, antibiotic, or antifungal activities.[125] Servier developed the prescription drug Rilmenidine (Albarel®), used for the treatment of hypertension, containing a 2-aminooxazoline moiety.[126] RO-5166017 is another example with an oxazoline motif; it is an agonist for the trace amine-associated receptor 1 (TAAR), which is currently being investigated by Hoffmann-La Roche for prevention of stress-induced hyperthermia.[127] Additionally, Sanofi-Aventis marketed the oxazoline-containing glucocorticoid Deflazacort (Calcort®), which is prescribed as an anti-inflammatory and immunosuppressant. It is also effective for a potential treatment of Duchenne muscular dystrophy (Figure 2).[128]

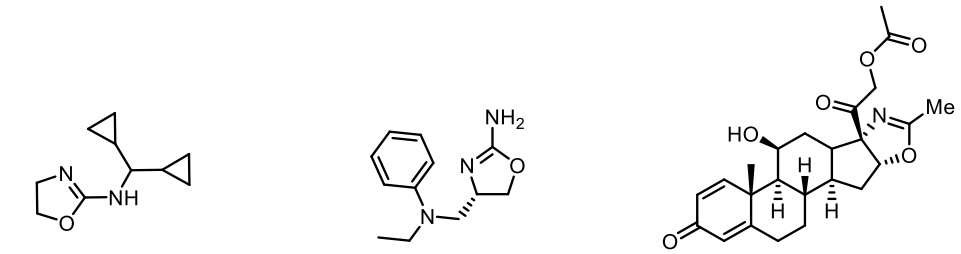


Figure 2: Pharmaceuticals containing an oxazoline moiety

The oxazoline scaffold also possesses great utility in organic synthesis[129] since this moiety is present in several ligands for asymmetric catalysis[130] and was also found to be an excellent *ortho*-directing

[125] a) S. Yamamoto, N. Okujo, Y. Fujita, M. Saito, T. Yoshida, S. Shinoda, *J. Biochem.* **1993**, *113*, 538. b) H. Shitakawa, S. Nakajima, M. Hirayama, H. Kondo, K. Kojiri, *Chem. Abstr.* **2000**, *132*, 150670. c) M. R. Prinsep, R. E. Moore, I. A. Levine, G. M. L. Patterson, *J. Nat. Prod.* **1992**, *55*, 140.

[126] a) P. Bousquet, J. Feldman, *Drugs* **1999**, *58*, 799. b) A. Remková, H. Kratochvíl'ová, *J. Hum. Hypertens.* **2002**, *16*, 549.

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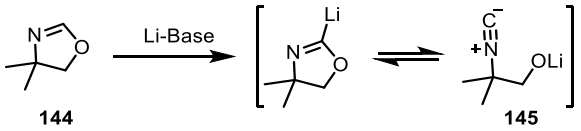
[129] a) M. Reuman, A. I. Meyers, *Tetrahedron* **1985**, *41*, 837. b) A. I. Meyers, E. D. Mihelich, *Angew. Chem. Int. Ed.* **1976**, *15*, 270. c) J. A. Frump, *Chem. Rev.* **1971**, *71*, 483.

[130] H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151.

group.[131,32] However, the direct lithiation of oxazolines at the C-2 position[132] is difficult due to a facile fragmentation of these sensitive heterocycles leading to isonitriles of type **145** (Scheme 58).[133,116a]



Scheme 58. Ring opening of 4,4-dimethyloxazoline (144) upon lithiation.

2-Aryloxazolines can be prepared using several methods, such as condensations[134] or similar multi-component reactions,[135] as well as C–H activations using diverse transition-metal catalysts.[136] However, to date the direct zincation and transition-metal catalyzed cross-coupling of the oxazoline scaffold for the synthesis of 2-substituted oxazolines has not yet been reported. This reaction is especially interesting, as particularly 2-aryloxazolines often exhibit potential biological activity.[137]

2.2 Metalation of 4,4-Dimethyloxazoline

The highly active sterically hindered zinc base TMPZnCl·LiCl (**36**)[34] has proven to be especially efficient for the metalation of sensitive heterocycles, such as oxazole, and moreover displays an excellent functional group tolerance. Thus, treatment of 4,4-dimethyloxazoline (**144**) with TMPZnCl·LiCl (**36**, 1.1 equiv) leads smoothly to the formation of the corresponding 4,4-dimethyloxazolinylzinc species (**146**) within 1 h at 0 °C in 94% yield as determined by GC-analysis after allylation.[138] In contrast to the corresponding lithium derivative (Scheme 58), this zinc reagent is perfectly stable at 25 °C and shows no tendency to undergo a ring fragmentation. Thus, the zinc reagent (**146**) undergoes smooth carbon–carbon bond formation with various electrophiles leading to 2-substituted oxazolines of type **147** in 64-92% yield (Scheme 59).

---

[131] For examples, see: a) S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* **2005**, *70*, 3113. b) P. Beak, A. Tse, J. Hawkins, C. W. Chen, S. Mills, *Tetrahedron* **1983**, *39*, 1983.

[132] L. Degennaro, V. Capriati, C. Carlucci, S. Florio, R. Luisi, I. Nuzzo, C. Cuocci, *Tetrahedron* **2009**, *65*, 8745.

[133] a) F. Gerhart, U. Schöllkopf, *Tetrahedron Lett.* **1968**, *9*, 6231. b) S. R. Neal, A. Ellern, A. D. Sadow, *J. Organomet. Chem.* **2010**, *696*, 228.

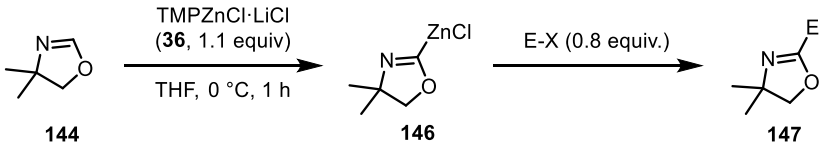
[134] a) G. A. Molander, W. Febo-Ayala, L. Jean-Gerard, *Org. Lett.* **2009**, *11*, 3830. b) P. Garg, S. Chaudhary, M. D. Milton, *J. Org. Chem.* **2014**, *79*, 8668. c) I. Mohammadpoor-Baltork, A. R. Khosropour, S. F. Hojati, *Synlett* **2005**, 2747. d) M. Brandstätter, F. Roth, N. W. Luedtke, *J. Org. Chem.* **2015**, *80*, 40.

[135] a) X.-F. Wu, H. Neumann, S. Neumann, M. Beller, *Chem. – Eur. J.* **2012**, *18*, 13619. b) L. Fan, E. Lobkovsky, B. Ganem, *Org. Lett.* **2007**, *9*, 2015.

[136] a) S. H. Kim, S. Chang, *Org. Lett.* **2010**, *12*, 1868. b) L. Ackermann, S. Barfuesser, C. Kornhaass, A. R. Kapdi, *Org. Lett.* **2011**, *13*, 3082. c) S. H. Wiedemann, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2004**, *6*, 1685.

[137] For examples, see: a) V. Padmavathi, K. Mahesh, G. D. Reddy, A. Padmaja, *Eur. J. Med. Chem.* **2010**, *45*, 3178. b) M. Tsuda, M. Yamakawa, S. Oka, Y. Tanaka, Y. Hoshino, Y. Mikami, A. Sato, H. Fujiwara, Y. Ohizumi, J. i. Kobayashi, *J. Nat. Prod.* **2005**, *68*, 462. c) Q. Li, K. W. Woods, A. Claiborne, S. L. Gwaltney, II, K. J. Barr, G. Liu, L. Gehrke, R. B. Credo, Y. H. Hui, J. Lee, R. B. Warner, P. Kovar, M. A. Nukkala, N. A. Zielinski, S. K. Tahir, M. Fitzgerald, K. H. Kim, K. Marsh, D. Frost, S.-C. Ng, S. Rosenberg, H. L. Sham, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 465.

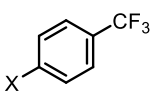
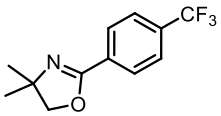
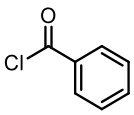
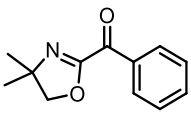
[138] Compare Table 4, entry 13; $C_{14}H_{30}$ was used as an internal standard.



Scheme 59. Metalation of 4,4-dimethyloxazoline (144) using TMPZnCl·LiCl (36) *via* zinc intermediate 146 and reaction with electrophiles (E-X).

Negishi cross-coupling reactions[118] of the oxazolinylzinc reagent (**146**) with electron-rich and -poor *para*-functionalized aryl bromides and iodides (FG = CF_3, CO_2Et, CN, OMe, Cl) using $Pd(dba)_2$ (3 mol%) or $Pd(OAc)_2$ (3 mol%) and SPhos (6 mol%)[139] furnished the corresponding 2-aryloxazolines **147a**-**e** in 71-92% yield (Table 4, entries 1–5). The oxazolinylzinc species (**146**) also reacts with the disubstituted diethyl 5-bromoisophthalate to provide the desired product (**147f**) in 68% yield (entry 6). Additionally, a cross-coupling reaction with 3-iodocyclohexenone affords the oxazoline (**147g**) in 68% yield (entry 7). Moreover, after transmetalation with CuCN·2LiCl,[119] acylation reactions employing various acid chlorides afford 2-acyl-2-oxazolines.[140] Thus, the reaction with benzoyl chloride leads to the acylated oxazoline (**147h**) in 69% yield (entry 8). The 4,4-dimethyloxazolinylzinc reagent (**146**) also reacts well in Negishi acylation reactions[44] with various electron-poor benzoyl chlorides bearing halogen-substituents, such as F, Br, and I, as well as 2-thiophenecarbonyl chloride to provide the ketones (**147i**-**l**) in 64-76% yield (entries 9-12). In addition, after transmetalation with CuCN·2LiCl, the zincated species undergoes a Cu-mediated allylation reaction with 3-bromocyclohexene affording the allylated product (**147m**) in 79% yield (entry 13). Finally, an *in situ* performed Sonogashira reaction[121] with phenylacetylene in the presence of $Pd(dba)_2$ (3 mol%), Farina's ligand[35] (P(*o*-furyl)$_3$, 6 mol%), CuI (4 mol%) and TEA (1.2 equiv) afforded the 2-substituted oxazoline (**147n**) in 79% yield (entry 14).

Table 4. 2-Substituted 4,4-dimethyloxazolines of type 147 obtained by zincation using TMPZnCl·LiCl (36) and reaction with electrophiles.

Entry	Electrophile E^1-X	Product / Yield[a]	Entry	Electrophile E^1-X	Product / Yield[a]
1			8		
	X = I, 50 °C, 4 h	**147a**, 79%[b]		-40 to 25 °C, 2 h	**147h**, 69%[d]
	X = Br, 50 °C, 3 h	77%[c]			

[139] a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685. b) K. L. Billingsley, K. W. Anderson, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 3484.

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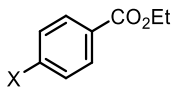
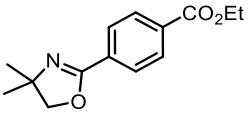
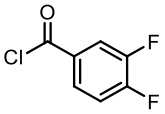
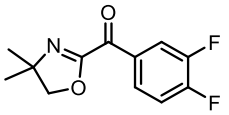
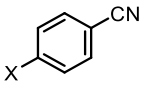
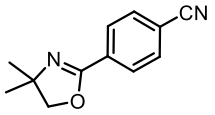
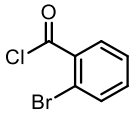
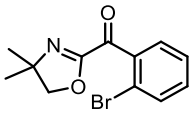
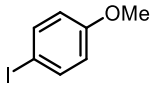
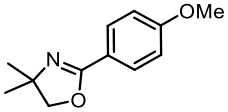
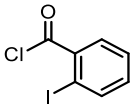
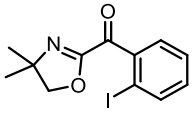
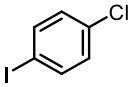
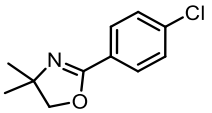
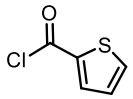
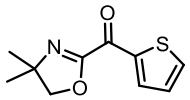
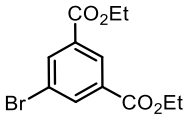
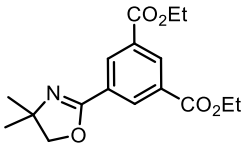
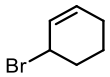
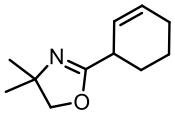
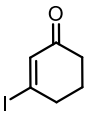
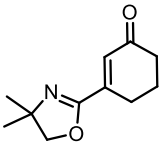
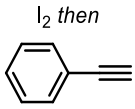
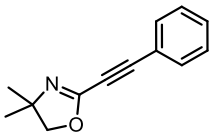
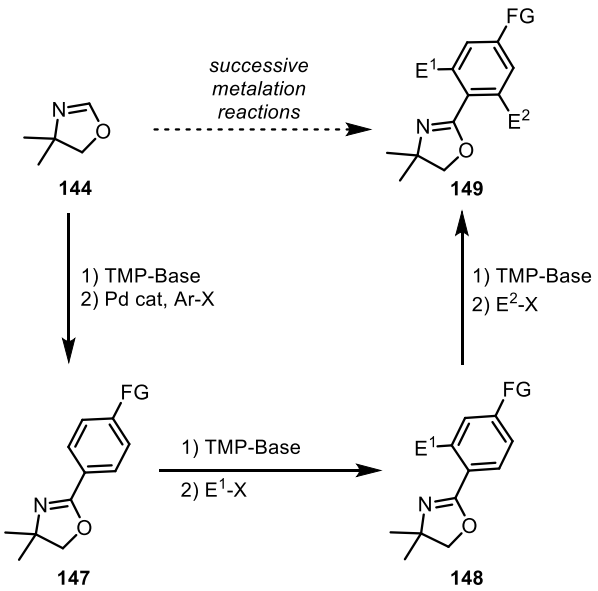
Entry	Electrophile E^1-X	Product / Yield[a]	Entry	Electrophile E^1-X	Product / Yield[a]
2			9		
	X = I, 50 °C, 4 h	**147b**, 78%[b]		-40 to 25 °C, 2 h	**147i**, 76%[d]
	X = Br, 50 °C, 3 h	92%[c]			
3			10		
	X = I, 50 °C, 4 h	**147c**, 80%[b]		-40 to 25 °C, 4 h	**147j**, 71%[d]
	X = Br, 50 °C, 2 h	87%[c]			
4			11		
	50 °C, 4 h	**147d**, 82%[c]		-40 to 25 °C, 4 h	**147k**, 65%[d]
5			12		
	50 °C, 2 h	**147e**, 71%[c]		-40 to 25 °C, 2 h	**147l**, 64%[d]
6			13		
	50 °C, 8 h	**147f**, 68%[c]		-40 to 25 °C, 6 h	**147m**, 79%[d]
7			14		
	25 °C, 1 h	**147g**, 68%[b]		25 °C, 4 h	**147n**, 71%[e]

[a]Isolated yield of analytically pure product. [b]Pd-catalyzed cross-coupling using 3 mol% $Pd(OAc)_2$ and 6 mol% SPhos. [c]Pd-catalyzed cross-coupling using 3 mol% $Pd(dba)_2$ and 6 mol% SPhos. [d]A Transmetalation with CuCN·2LiCl was performed. [e]Pd-catalyzed cross-coupling using 3 mol% $Pd(dba)_2$, 6 mol% P(*o*-furyl)$_3$, 4 mol% CuI and NEt_3 (1.2 equiv).

The simple, mild and efficient procedure for the zincation of 4,4-dimethyloxazoline (**144**) in the C-2 position using TMPZnCl·LiCl (**36**) affords a stable oxazolinylzinc reagent (**146**). Subsequent Negishi cross-couplings with various aryl iodides and bromides and Cu-mediated acylation and allylation reactions provide a variety of 2-functionalized 4,4-dimethyloxazolines of type **147**.

2.3 Oxazoline as a Directing Group for Further Functionalizations

Oxazolines serve as a useful activating and directing group in directed metalations,[141] thus facilitating *ortho*-metalation. The imino-functionality of the oxazoline moiety directs by coordination to the organometallic reagent and also stabilizes the resulting metal species by cyclic coordination.[142] Although, *Meyers*[143] and *Gschwend*[144] extensively examined the *ortho*-lithiation of 2-arylated oxazolines, we anticipated that the use of TMP-bases, such as TMPMgCl·LiCl (**35**) or $TMP_2Mg·2LiCl$ (**42**), will be advantageous for the synthesis of highly functionalized arenes of type **149** (Scheme 60).



Scheme 60. Functionalization of 4,4-dimethyloxazoline (144) and its use as a directing group for further functionalizations using TMP-bases.

Magnesiation of the 2-arylated oxazolines, such as **147b** or **147c**, is possible within 1.5 h at 0 °C using TMPMgCl·LiCl (**35**)[145] and the corresponding magnesium reagents reacted with a variety of electrophiles (E^1-X) affording *ortho*-functionalized aryloxazolines of type **148** (Scheme **61**).

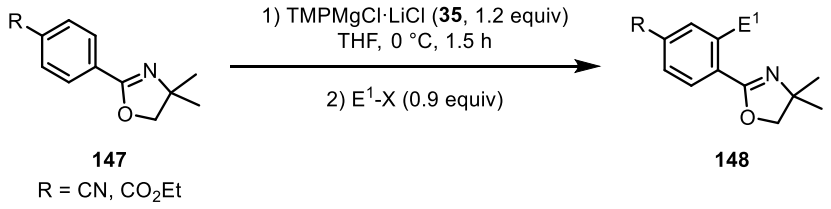
[141] a) A. I. Meyers, E. D. Mihelich, *J. Org. Chem.* **1975**, *40*, 3158. b) H. A. Chiong, Q.-N. Pham, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879. c) X. Chen, J.-J. Li, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78. d) S. T. Chadwick, A. Ramirez, L. Gupta, D. B. Collum, *J. Am. Chem. Soc.* **2007**, *129*, 2259.

[142] *The Chemistry of Heterocycles* (Ed.: I. J. Turchi), John Wiley & Sons Inc, Hoboken, NJ, **1986**, p. 971.

[143] T. G. Gant, A. I. Meyers, *Tetrahedron* **1994**, *50*, 2297.

[144] H. W. Gschwend, A. Hamdan, *J. Org. Chem.* **1975**, *40*, 2008.

[145] a) J. H. C. Batista, F. M. dos Santos, L. A. Bozzini, R. Vessecchi, A. R. M. Oliveira, G. C. Clososki, *Eur. J. Org. Chem.* **2015**, *2015*, 967. b) E. Bellamy, O. Bayh, C. Hoarau, F. Trécourt, G. Quéguiner, F. Marsais, *Chem. Commun.* **2010**, *46*, 7043.



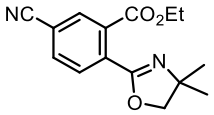
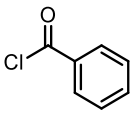
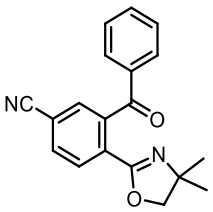
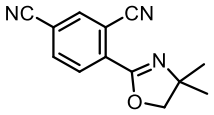
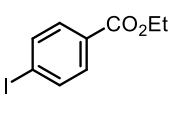
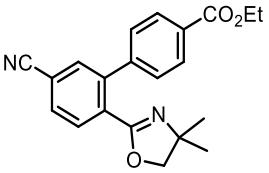
147
R = CN, CO_2Et

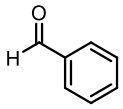
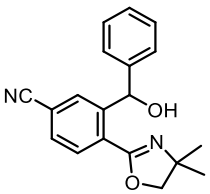
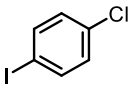
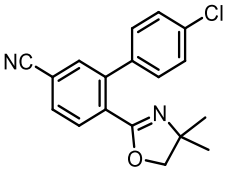
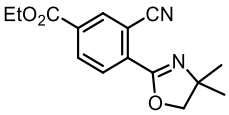
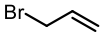
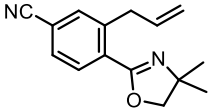
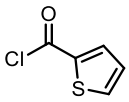
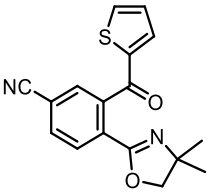
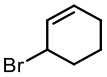
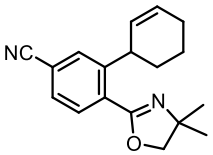
148

Scheme 61. *ortho*-Metalation of 2-aryloxazolines of type xx using TMPMgCl·LiCl (35).

The generated oxazolinylmagnesium reagents of **147b** and **147c** were reacted with Cl-CO_2Et, Tos-CN, or benzaldehyde to afford the desired *ortho*-functionalized aryloxazolines **148a**-**d** in 62-91% yield (Table 5, entries 1-4). Moreover, a Cu-mediated acylation could be performed by addition of CuCN·2LiCl and reaction with 2-thiophenecarbonyl chloride or benzoyl chloride to yield the corresponding ketones **148e**-**f** in 83% and 91% yield, respectively (entries 5 and 6). After transmetalation with $ZnCl_2$ and Pd-catalyzed cross-coupling with ethyl 4-iodobenzoate or 1-chloro-4-iodobenzene, the biaryls **148g**-**h** were afforded in 90-93% yield (entries 7 and 8). Likewise, after transmetalation with CuCN·2LiCl an allylation reaction with allyl bromide or 3-bromocyclohexene was performed and the products **148i**-**j** were isolated in 87-98% yield (entries 9 and 10).

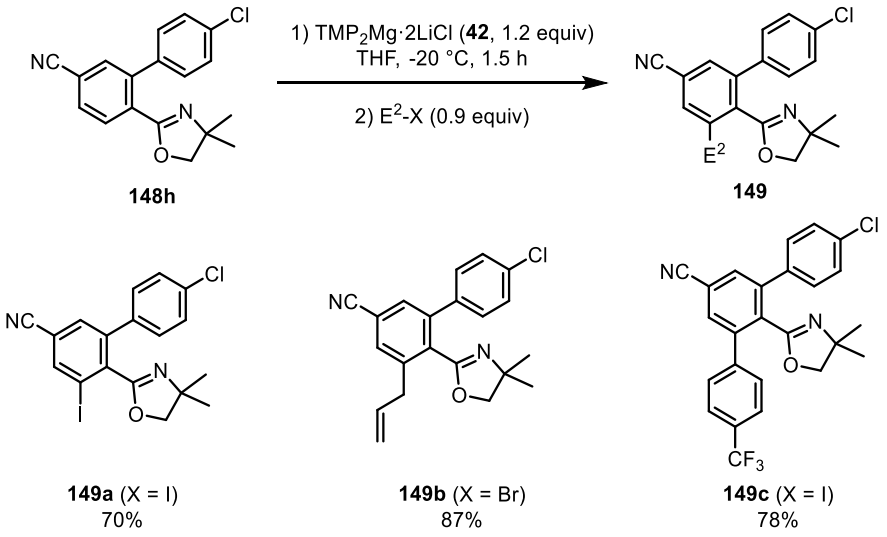
Table 5. *ortho*-Magnesiation of 2-arylated oxazolines (147) using TMPMgCl·LiCl (35).

Entry	Electrophile E^1-X	Product / Yield[a]	Entry	Electrophile E^1-X	Product / Yield[a]
1	Cl-CO_2Et		6		
	0 to 25 °C, 2 h	**148a**, 91%		-25 to 25 °C, 3 h	**148f**, 91%[b]
2	TosCN		7		
	0 to 25 °C, 2 h	**148b**, 83%		25 °C, 4 h	**148g**, 90%[c]

Entry	Electrophile E^1-X	Product / Yield[a]	Entry	Electrophile E^1-X	Product / Yield[a]
3			8		
	0 to 25 °C, 2 h	**148c**, 92%		0 to 25 °C, 2 h	**148h**, 93%[c]
4	TosCN		9		
	0 to 25 °C, 2 h	**148d**, 62%		0 to 25 °C, 2 h	**148i**, 87%[b]
5			10		
	-25 to 25 °C, 3 h	**148e**, 83%[b]		0 to 25 °C, 2 h	**148j**, 98%[b]

[a]Isolated yield of analytically pure product. [b]A transmetalation with CuCN·2LiCl was performed. [c]After transmetalation with $ZnCl_2$, a Pd-catalyzed cross-coupling using 3 mol% $Pd(dba)_2$ and 6 mol% P(*o*-furyl)$_3$ was performed.

Additionally, *ortho*-functionalized 2-aryloxazolines of type **148** reacted in a second metalation step using TMP_2Mg·2LiCl (**42**) within 1.5 h at -20 °C. The newly generated magnesium reagent reacted with I_2 to afford the iodinated compound **149a** in 70% yield. Transmetalation of the magnesium species using CuCN·2LiCl, followed by addition of allyl bromide furnished the desired oxazoline **149b** in 87% yield. Moreover, the *ortho*-functionalized oxazoline **148h** reacted in a Negishi cross-coupling reaction with 4-iodobenzotrifluoride yielding the bisarylated substrate **149c** in 78% yield (Scheme 62).



Scheme 62. Second *ortho*-metalation of 2-aryloxazolines.

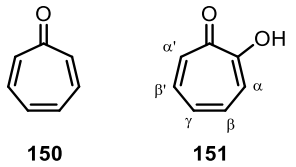
As shown by *Weinreb et al.*, oxazolines can be converted to carboxylic acids and new *ortho*,*ortho'*-disubstituted benzoic acids can be obtained after deprotection using standard methods.[146]

[146] a) P. Kocienski, *Protecting Groups*, 3rd ed., Georg Thieme Verlag, Stuttgart, **2005**. b) K. J. Edgar, C. K. Bradsher, *J. Org. Chem.* **1982**, *47*, 1585. c) J. I. Levin, S. M. Weinreb, *Tetrahedron Lett.* **1982**, *23*, 2347.

3 Metalation and Functionalization of the Tropolone Scaffold Using TMPZnCl·LiCl

3.1 Introduction

Tropone (**150**, 2,4,6-cycloheptatrien-1-one) and its derivative tropolone (**151**, 2-hydroxy-2,4,6-cycloheptatrien-1-one)[147] are 7-membered rings representing non-benzenoid aromatics with a six π-electron system (Scheme 63).[148] These scaffolds are of great importance not only because of their peculiar aromatic properties. Also, the tropolone moiety is known to strongly chelate metal ions which is key for the high biological activity, thus these scaffolds are found in many natural products exhibiting interesting properties.[149]



Scheme 63. Tropone (150) and tropolone (151)

Purpurogallin, a tropolone derivative with a [7]annulene structure, was found to act as an inhibitor of the TLR1/TLR2 pathway,[150] which is important for the regulation of innate immunity and a target for the treatment of immune disorders. Hinokitiol, also called β-Thujaplicin, is another natural product containing this moiety and is used as an antibacterial as it displays inhibitory effects on *Chlamydia trachomatis*.[151] The probably most well-known example containing a tropolone moiety is colchicine, which is extracted from *Colchicum autumnale* (meadow saffron). It can be used in low dose[152] for the treatment of gout, as well as e.g. pericarditis and atrial fibrillation (Figure 3).[153]

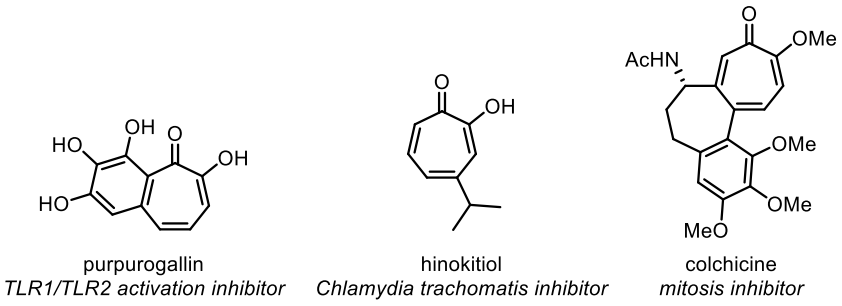
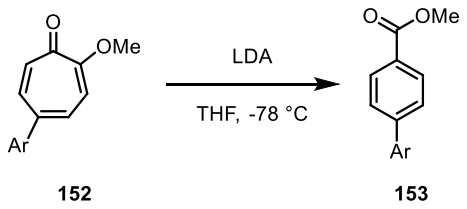


Figure 3. Natural tropolone analogues.

147 P. L. Pauson, *Chem. Rev.* **1955**, *55*, 9.
148 M. J. S. Dewar, *Nature* **1945**, *150*, 50.
149 S. N. Ononye, M. D. VanHeyst, E. Z. Oblak, W. Zhou, M. Ammar, A. C. Anderson, D. L. Wright, *ACS Med. Chem. Lett.* **2013**, *4*, 757.
150 K. Cheng, X. Wang, S. Zhang, H. Yin, *Angew. Chem. Int. Ed.* **2012**, *51*, 12246.
151 H. Yamano, T. Yamazaki, K. Sato, S. Shiga, T. Hagiwara, K. Ouchi, T. Kishimoto, *Antimicrob. Agents Chemother.* **2005**, 2519.
152 LD_{50}(oral) = 6 mg/kg (mouse); colchicine; MSDS No. AC227120000; Thermo Fisher Scientific: Waltham, USA, Sep 3, 2014.
153 P. M. Dewick, *Medicinal Natural Products. A Biosynthetic Approach*, 3rd ed., John Wiley & Sons Ltd., West Sussex, **2009**.

The synthesis of tropolones usually starts from cycloheptanone deriatives or relies on the ring enlargement of various benzene derivatives. However, to date the direct functionalization of the tropolone moiety using organometallic reagents has not been reported yet. Berg and Bladh have shown that treatment of 2-methoxy-5-aryltropone (**152**) with LDA at -78 °C induces ring contraction to yield the corresponding *p*-methoxycarbonylphenyl derivative (**153**) (Scheme 64).[154]

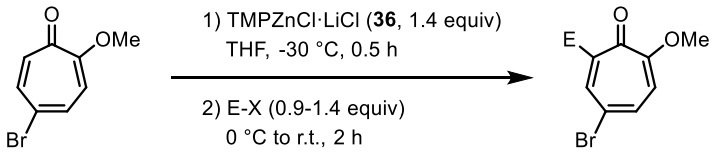


152 **153**

Scheme 64. Ring contraction of 2-methoxy-5-aryltropone (152) upon addition of LDA.

3.2 Metalation and Functionalization of 5-Bromo-2-methoxytropone Using TMPZnCl·LiCl

The mild and sterically hindered zinc base TMPZnCl·LiCl (**36**)[34] has proven to be especially efficient for the metalation of sensitive compounds and displays an excellent functional group tolerance. Particularly, the sensitive keto group should remain unaffected by using a zinc derivative of the TMP-bases as reactions with various organometallic reagents could favor a 1,2-addition to the ketone or result in decomposition. Treatment of 5-bromo-2-methoxytropone (**154**, 5-bromo-2-methoxycyclohepta-2,4,6-trien-1-one) with TMPZnCl·LiCl (**36**) at -30 °C leads within 0.5 h to the corresponding zinc reagent which reacts with a range of electrophiles to afford the desired α'-functionalized tropolone derivatives of type **155** (Scheme 65).



154 **155**

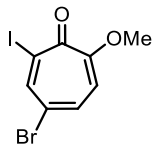
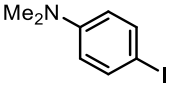
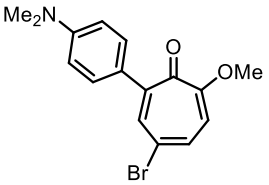
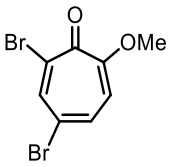
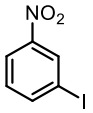
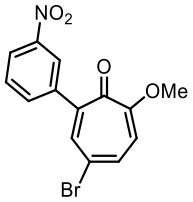
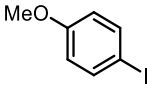
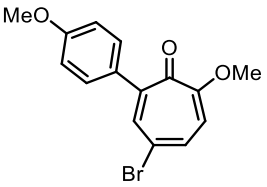
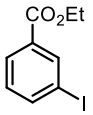
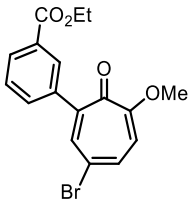
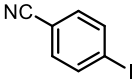
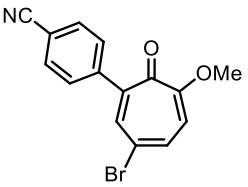
Scheme 65. Metalation of 5-bromo-2-methoxytropone (154) using TMPZnCl·LiCl (36) and reaction with electrophiles.

The newly generated zinc reagent reacted with I_2 or Br_2 to afford the halogenated compounds **155a,b** in 98% and 74% yield, respectively. Negishi cross-coupling reactions[118] of the organozinc reagent with electron-rich and -poor aryl iodides (FG = OMe, CN, NMe_2, NO_2, CO_2Et) using $Pd(dba)_2$ (3 mol%) and

[154] U. Berg, H. Bladh, *Acta Chem. Scand.* **1998**, *52*, 1380.

P(*o*-furyl)$_3$ (6 mol%) furnished the corresponding arylated 5-bromo-2-methoxytropones **155d**-**g** in 67-89% yield (Table 6, entries 3-7).

Table 6. Metalation of 5-bromo-2-methoxytropone (154) and reaction with various electrophiles.

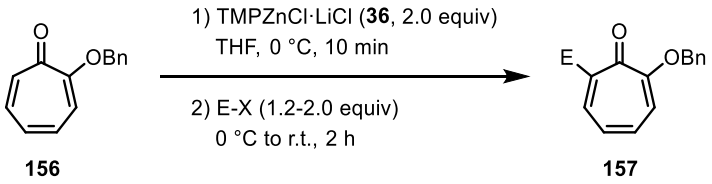
Entry	Electrophile E-X	Product / Yield[a]	Entry	Electrophile E-X	Product / Yield[a]
1	I_2	 **155a**, 98%	5		 **155e**, 67%[b]
2	Br_2	 **155b**, 74%	6		 **155f**, 89%[b]
3		 **155c**, 70%[b]	7		 **155g**, 73%[b]
4		 **155d**, 81%[b]			

[a]Isolated yield of analytically pure product. [b]A Pd-catalyzed cross-coupling using 3 mol% Pd(dba)$_2$ and 6 mol% P(*o*-furyl)$_3$ was performed.

3.3 Metalation and Functionalization of 2-Benzyloxytropone using TMPZnCl·LiCl

Similarly to the brominated 2-methoxytropone (**154**), the metalation of 2-benzyloxytropone (**156**, 2-(benzyloxy)cyclohepta-2,4,6-trien-1-one) is also possible within 10 min using TMPZnCl·LiCl (**36**) at 0 °C.

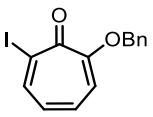
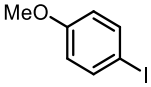
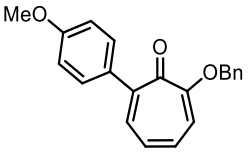
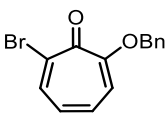
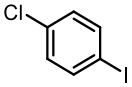
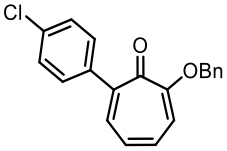
The resulting zinc reagent reacts with a variety of electrophiles producing functionalized tropolones of type **157**.

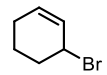
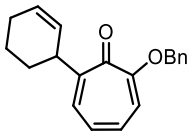
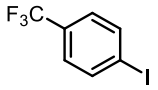
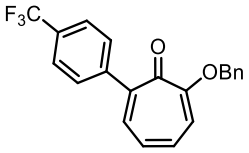
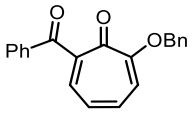
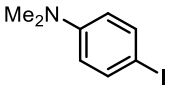
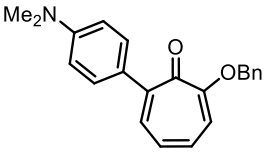
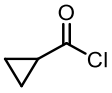
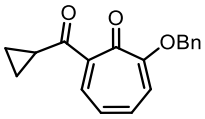
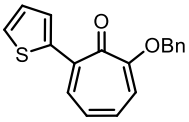
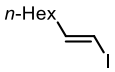
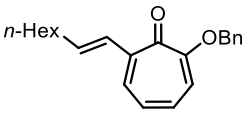


Scheme 66. Metalation of 2-benzyloxytropone (156) using TMPZnCl·LiCl (36) and subsequent reaction with electrophiles E-X.

Reactions of the newly generated zinc reagent with electrophiles, such as I_2 or 1,2-dibromotetrachloroethane, afforded the halogenated compounds **157a**,**b** in 83-89% yield (Table 7, entries 1, 2). Moreover, the zinc reagent reacted in a Cu-mediated allylation reaction with 3-bromocyclohexene using CuCN·2LiCl to obtain the allylated tropolone derivative **157c** in 94% yield (entry 3). Additionally, Cu-mediated acylation reactions with benzoyl chloride or cyclopropane-carbonyl chloride produced the ketones **157d**,**e** in 76% and 68% yield, respectively (entries 4, 5). The zinc reagent of **156** also reacted in various Negishi cross-coupling reactions with (*E*)-1-iodooct-1-ene, various *para*-functionalized aryliodides and 2-iodothiophene using $Pd(dba)_3$ (3 mol%) and P(*o*-furyl)$_3$ (6 mol%) as a catalytic system affording the corresponding coupling products in 75-91% yield (entry 6-11).

Table 7. Metalation of 2-benzyloxytropone (156) and quenching with electrophiles.

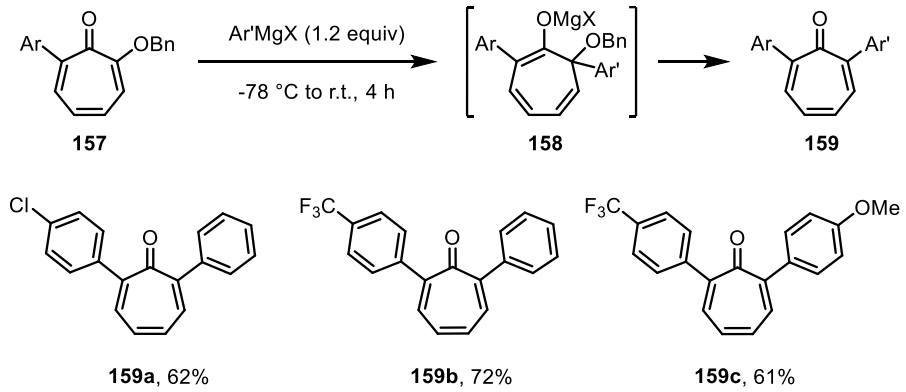
Entry	Electrophile E-X	Product / Yield[a]	Entry	Electrophile E-X	Product / Yield[a]
1	I_2	 **157a**, 89%	7		 **157g**, 77%[c]
2	$(CCl_2Br)_2$	 **157b**, 83%	8		 **157h**, 83%[c]

Entry	Electrophile E-X	Product / Yield[a]	Entry	Electrophile E-X	Product / Yield[a]
3		 **157c**, 94%[b]	9		 **157i**, 91%[c]
4		 **157d**, 76%[b]	10		 **157j**, 77%[c]
5		 **157e**, 68%[b]	11		 **157k**, 80%[c]
6		 **157f**, 75%[c]			

[a]Isolated yield of analytically pure product. [b]A transmetalation with CuCN·2LiCl was performed. [c]A Pd-catalyzed cross-coupling using 3 mol% $Pd(dba)_2$ and 6 mol% P(*o*-furyl)$_3$ was performed.

The reaction of few tropolone derivatives with several lithium and Grignard reagents is known.[155] In a similar fashion, treatment of 2-benzyloxy-7-aryl-tropone of type **157** with a Grignard reagent leads *via* **158** to the 2,7-diarylated tropone derivatives of type **159** in good yield (Scheme 67).

[155] a) T. Nozoe, T. Mukai, J. Minegishi, *Proc. Jpn. Acad.* **1951**, *27*, 419. b) T. Mukai, *Bull. Chem. Soc. Jpn.* **1958**, *31*, 852.



Scheme 67. Grignard Addition to 7-arylated 2-benzyloxytropones of type 157.

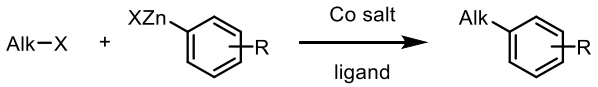
Reaction of the tropolones **157h** or **157i** with phenylmagnesium chloride (1.2 equiv) results in substitution of the benzyloxygroup affording the 2,7-diarylated tropones **159a** and **159b** in 62% and 72% yield,[156] respectively. Reaction of tropolone derivative **157i** with *p*-anisylmagnesium bromide (1.2 equiv) selectively produces the 2,7-diarylated compound **159c** in 61% yield (Scheme 67).

[156] X-ray analysis of compound **159c** did show exclusive formation of the α,α'-arylated tropone derivative.

4 Cobalt-Catalyzed Negishi Cross-Coupling Reactions of (Hetero)Aryl-zinc Reagents with Primary and Secondary Alkyl Bromides and Iodides

4.1 Introduction

Transition metal-catalyzed cross-coupling reactions are valuable tools for C-C bond-forming reactions and have found many applications for the syntheses of biologically active molecules.[157] As already previously mentioned, Pd- or Ni-catalyzed cross-coupling reactions dominate this field, but have several drawbacks, for example the toxicity[158] and high price of the metal,[159] as well as the requirement of sophisticated ligands to achieve a broad reaction scope. Recently, cross-coupling reactions with cobalt catalysts were found to be a valuable alternative.[160] However, despite the spectacular advances of Co-catalyzed coupling reactions between C(sp^2) and C(sp^3) centers by using magnesium reagents,[161] no Co-catalyzed Negishi-type[98,99] coupling reactions using arylzinc reagents have been described (Scheme 68).



Scheme 68. Co-catalyzed cross-coupling of arylzinc reagents and alkyl halides

Knochel and co-workers have reported a range of synthetic methods for the preparation of polyfunctional unsaturated zinc reagents.[162,32] In particular, the directed metalation[163,31a] of polyfunctional heterocycles and aromatic substrates has a broad reaction scope, and sterically hindered bases,[164,31b] such as $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**),[41] have given a straight forward entry to a range

[157] a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**. b) *Organotransition Metal Chemistry* (Ed.: J. F. Hartwig), University Science Books, Sausalito, CA, **2010**.

[158] a) *Handbook on the Toxicology of Metals* (Eds.: L. Friberg, G. F. Nordberg, V. B. Vouk), Elsevier, Amsterdam, **1986**. b) M. N. Hughes, in *Comprehensive Coordination Chemistry* (Eds.: G. Wilkinson, R. D. Gillard, J. A. McCleverty), Pergamon Press, Oxford, **1987**, pp. 643-648.

[159] world markt prices: Pd 8000 $/lb, Co 10 $/lb; http://www.infomine.com/; retrieved 11th April 2016.

[160] a) H. Shinokubo, K. Oshima, *Eur. J. Org. Chem.* **2004**, 2081. b) H. Yorimitsu, K. Oshima, *Pure Appl. Chem.* **2006**, *78*, 441. c) C. Gosmini, J.-M. Begouin, A. Moncomble, *Chem. Commun.* **2008**, 3221. d) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435. e) J. Yang, N. Yoshikai, *J. Am. Chem. Soc.* **2014**, *136*, 16748.

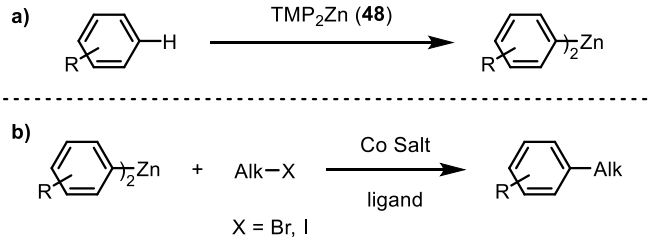
[161] For selected cobalt-catalyzed cross-coupling reactions using organomagnesium reagents, see: a) G. Cahiez, H. Avedissian, *Tetrahedron Lett.* **1998**, *39*, 6159. b) K. Wakabayashi, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 5374. c) H. Ohmiya, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 3093. d) G. Cahiez, C. Chaboche, C. Duplais, A. Moyeux, *Org. Lett.* **2009**, *11*, 277. e) L. Nicolas, P. Angibaud, I. Stansfield, P. Bonnet, L. Meerpoel, S. Reymond, J. Cossy, *Angew. Chem. Int. Ed.* **2012**, *51*, 11101. f) J. Zeng, K. M. Liu, X. F. Duan, *Org. Lett.* **2013**, *15*, 5342. g) C. F. Despiau, A. P. Dominey, D. C. Harrowven, B. Linclau, *Eur. J. Org. Chem.* **2014**, *2014*, 4335.

[162] a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302. b) T. Klatt, J. T. Markiewicz, C. Saemann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253.

[163] a) P. Beak, R. A. Brown, *J. Org. Chem.* **1982**, *47*, 34. b) P. Beak, A. Tse, J. Hawkins, C. W. Chen, S. Mills, *Tetrahedron* **1983**, *39*, 1983. c) Y. Zhao, V. Snieckus, *J. Am. Chem. Soc.* **2014**, *136*, 11224. d) K. Groom, S. M. S. Hussain, J. Morin, C. Nilewski, T. Rantanen, V. Snieckus, *Org. Lett.* **2014**, *16*, 2378.

[164] a) D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2006**, *45*, 3775. b) A. J. Martinez-Martinez, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, *Science* **2014**, *346*, 834.

of unsaturated and highly reactive diorganozinc compounds. In order to establish a cobalt-catalyzed Negishi cross-coupling it has been envisioned that diarylzinc reagents prepared by a directed C-H zincation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**) can be employed in a cross-coupling reaction with various primary and secondary alkyl halides (Scheme 69).

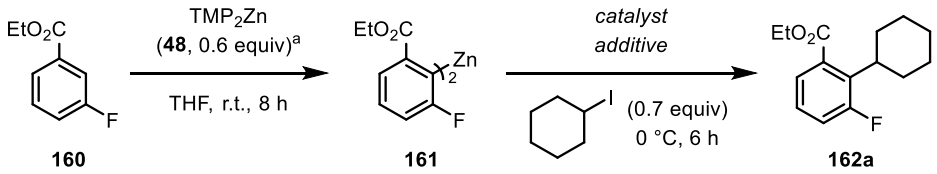


Scheme 69. Metalation reaction using TMP_2Zn (48) and cobalt-catalyzed cross-coupling of the diarylzinc species.
($MgCl_2$ and LiCl are omitted for the sake of clarity)

4.2 Design of the Coupling Procedure

In preliminary experiments, we have examined the cross-coupling of the diarylzinc reagent (**161**, which was generated by a directed metalation of ethyl 3-fluorobenzoate (**160**)[165] using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.6 equiv), with *c*-Hex-I in the presence of various metal catalysts (Table 8).

Table 8. Optimization of the reaction conditions for the Co-catalyzed cross-coupling.



Entry	Catalyst (mol%)	Additive (mol%)	Yield of **162a**[b]
1	$FeCl_2$ (20)	4-fluorostyrene (50)	0
2	$FeCl_2$ (20)	TMEDA (30)	13
3	$Co(acac)_2$ (20)	4-fluorostyrene (50)	0
4	$Co(acac)_2$ (20)	TMEDA (30)	18
5	$CoCl_2$ (20)	4-fluorostyrene (50)	42
6	$CoCl_2$ (20)	TMEDA (30)	84

[165] As a consequence of its electron-acceptor properties, the fluoro-substituent facilitates the zincation, as well as the cobalt-catalyzed cross-coupling reaction and therefore ethyl 3-fluorobenzoate was chosen as the model substrate.

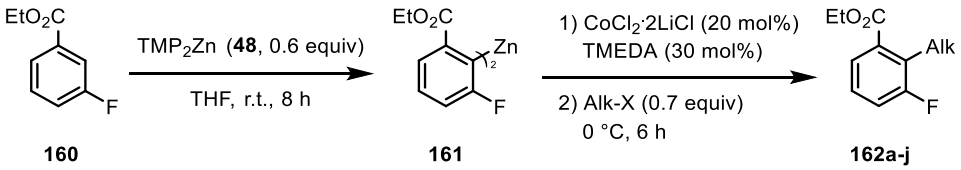
7	**$CoCl_2$·2LiCl (20)**	**TMEDA (30)**	**94 (87)[c]**
8	$CoCl_2$·2LiCl (20)	4-fluorostyrene (50)	38
9	$CoCl_2$·2LiCl (20)	Ligand **L1**[d]	40
10	$CoCl_2$·2LiCl (10)	TMEDA (30)	33

[a]$MgCl_2$ and LiCl are omitted for the sake of clarity. [b]Determined by GC using undecane ($C_{11}H_{24}$) as an internal standard. [c]Yield of isolated product. [d]**L1** = *trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine.

The addition of the zinc species to *c*-Hex-I in the presence of $Co(acac)_2$ or $FeCl_2$[166] resulted in the exclusive formation of the protonated zinc species (**160**) when using 4-fluorostyrene (50 mol%) as an additive (Table 8, entries 1 and 3).[167] Moderate yields of **162a** (13-18%) were obtained using *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA, 30 mol%) as a ligand (entries 2 and 4). Switching to $CoCl_2$ (20 mol%) and 4-fluorostyrene (50 mol%) or TMEDA (30 mol%) in THF at 0 °C furnished the desired cross-coupling product **162a** in 42% and 84% yield, respectively (entries 5 and 6). Significant improvements were achieved by using the THF-soluble $CoCl_2$·2LiCl (20 mol%)[168] and TMEDA (30 mol%), which afforded the desired coupling product **162a** in 87% isolated yield (entry 7). Further variation of the ligand[169] or lowering the amount of the catalyst loading from 20 mol% to 10 mol% led only to a decrease in the yield (entries 7-10).

4.3 Cobalt-Catalyzed Cross-Coupling of Zincated Ethyl 3-fluorobenzoate with Various Alkyl Halides

With these optimized reaction conditions in hand, we have performed a range of alkylations using various primary and secondary alkyl halides to afford alkylated benzoates of type **162** (Scheme 70).



160 **161** **162a-j**

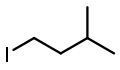
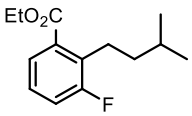
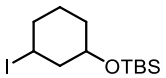
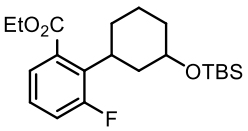
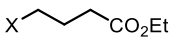
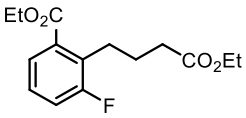
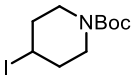
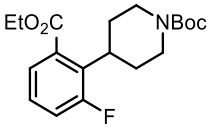
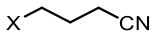
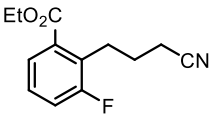
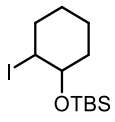
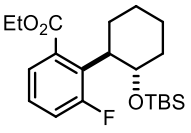
Scheme 70. Zincation of ethyl 3-fluorobenzoate (160) and cobalt-catalyzed cross-coupling with alkyl halides.

The reaction of the zincated species **161** with primary alkyl iodides led to the polyfunctional alkylated benzoates (**162a**-**c**) in 58-77% yield (Table 1, entries 1–3). Remarkably, the *ortho*,*ortho'* substituents present in the diarylzinc species (**161**) did not disturb the cross-coupling and most of the reactions

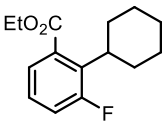
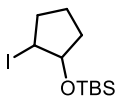
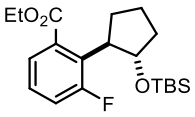
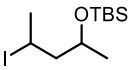
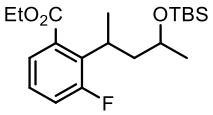
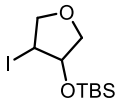
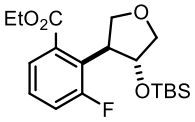
[166] B. Barré, L. Gonnard, R. Campagne, S. Reymond, J. Marin, P. Ciapetti, M. Brellier, A. Guerinot, J. Cossy, *Org. Lett.* **2014**, *16*, 6160.
[167] A. K. Steib, T. Thaler, K. Komeyama, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 3303.
[168] a) J. M. Hammann, A. K. Steib, P. Knochel, *Org. Lett.* **2014**, *16*, 6500. b) G. Cahiez, C. Chaboche, C. Duplais, A. Giulliani, A. Moyeux, *Adv. Synth. Catal.* **2008**, *350*, 1484.
[169] H. Ohmiya, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 1886.

were complete within 6 h at 0 °C. Primary alkyl bromides have also been successfully coupled, but with somewhat lower yields (entries 2-4), whereas cyclohexyl chloride only gave trace amounts of the desired product (compare entry 4). Functional groups, such as an ester or a nitrile, are well-tolerated in these cross-coupling reactions and products such as **162c-d** were isolated. Interestingly, also secondary alkyl iodides reacted smoothly to provide the alkylation products **162a**,**e**-**j** in 55-79% yield (entries 4-10). In no case did we observe rearrangement products (branched to unbranched; see entry 5 and Table 10).[170,80,88] When an oxygen substituent was present in α-position of the carbon-iodine bond, excellent diastereoselectivities were observed (up to d.r. 99:1, see entries 8-10) and the products **162h**-**j** were isolated in 55-69% yield. Additionally, this cross-coupling can also be performed with heterocyclic alkyl iodides, thereby leading to the expected products **162g** and **162j** in 79% and 55% yield, respectively (see entries 7 and 10).

Table 9. Scope of various primary and secondary alkyl iodides or bromides.

Entry	Alk-X	Product / Yield[a]	Entry	Alk-X	Product / Yield[a]
1		 **162b**, 63%	6		 **162f**, 79%, d.r. 50:50[d]
2		 **162c**, 58% (X = I) 38% (X = Br)	7		 **162g**, 79%
3		 **162d**, 71% (X = I) 51% (X = Br)	8		 **162h**, 68%, d.r. 99:1[d]

[170] a) K. Tamao, Y. Kiso, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 9268. b) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* **1984**, *106*, 158.

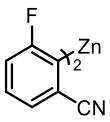
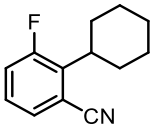
Entry	Alk-X	Product / Yield[a]	Entry	Alk-X	Product / Yield[a]
4		 **162a**, 61% (X = Br) 2% (X = Cl)[b]	9		 **162i**, 69%, d.r. 99:1[e]
5		 **162e**, 70%, d.r. 50:50[c]	10		 **162j**, 55%, d.r. 99:1[e]

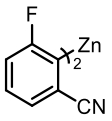
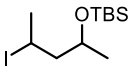
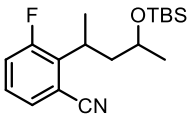
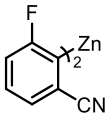
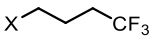
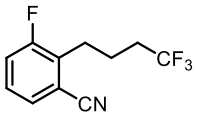
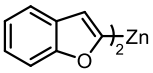
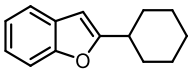
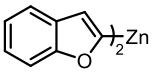
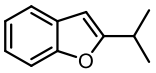
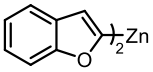
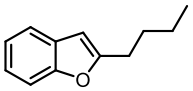
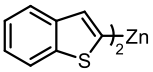
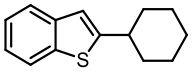
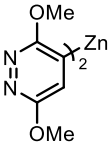
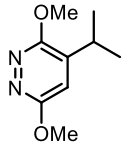
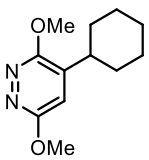
[a]Isolated yield of analytically pure product. [b]The yield was determined by GC using $C_{11}H_{24}$ as an internal standard. [c]The starting material was 99:1 *syn*/*anti*. [d]The starting material was 75:25 *cis*/*trans*. [e]The starting material was 99:1 *trans*/*cis*.

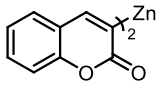
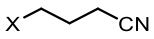
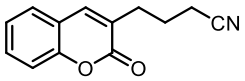
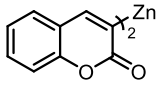
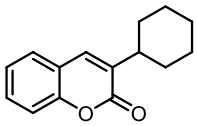
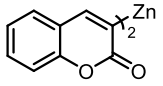
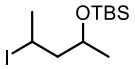
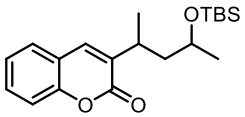
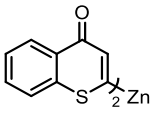
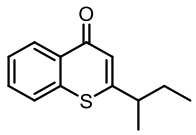
4.4 Cobalt-Catalyzed Cross-Coupling of Di(hetero)arylzinc Reagents with Alkyl Iodides

The reaction scope of this Co-catalyzed alkylation is quite broad and a range of diarylzinc reagents prepared by a directed deprotonation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.6 equiv) provided the isolated alkylated products **163a**-**m** in 51–88% yield (Table 10). Thus, this sequential one-pot metalation/cross-coupling procedure could be extended to other 1,3-disubstituted aromatic compounds: the zincation of 3-fluorobenzonitrile using **48** (0.6 equiv) proceeds within 12 h at 25 °C, and the subsequent coupling reactions with secondary alkyl iodides provide the desired products **163a**-**c** in 52-84% yield (entries 1-3). Remarkably, diheteroarylzinc reagents generated by directed zincation using **48** also undergo the alkylation reactions in good yields to afford the expected products **163d**-**m** (51-88% yield, entries 4-13). Thus, zincated benzofurans or benzothiophenes reacted with secondary alkyl iodides such as *c*-Hex-I, *i*-Pr-I, or *n*-Bu-I to furnish the corresponding cross-coupling products **163d**-**g** in 61-72% yield (entries 4-7).

Table 10. Cobalt-catayzed cross-coupling of various diaryl- and diheteroarylzinc reagents with alkyl iodides.

Entry	Zinc species	Alk-X	Product / Yield[a]
1			 **163a**, 84%

Entry	Zinc species	Alk-X	Product / Yield[a]
2			 **163b**, 63%[b]
3			 **163c**, 52%
4			 **163d**, 71%
5			 **163e**, 61%
6			 **163f**, 63%
7			 **163g**, 72%
8			 **163h**, 69%
9			 **163i**, 61%

Entry	Zinc species	Alk-X	Product / Yield[a]
10			 **163j**, 76%
11			 **163k**, 66%
12			 **163l**, 88%
13			 **163m**, 51%

[a]Isolated yield of analytically pure product. [b]The starting material was 99:1 *syn*/*anti*, the product was 50:50 *syn*/*anti*.

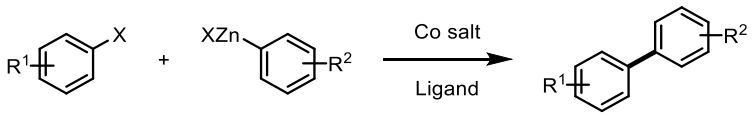
The metalation of benzofuran with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.6 equiv) was complete within in 12 h at 25 °C, thereby providing the corresponding zinc reagent. This species undergoes the Co-catalyzed cross-coupling with *n*-Bu-I to afford the substituted benzofuran **163f** in 63% yield (entry 6). This alkylated benzofuran (**163f**) is a key intermediate for the synthesis of amiodarone, an active antiarrhythmic agent.[171] Similarly, 3,6-dimethoxypyridazine was zincated using **48** (0.6 equiv, 4 h, 25 °C), and the cross-coupling with 2-iodopropane or *c*-Hex-I afforded the desired polyfunctional hetereocycles **163h**,**i** in 69% and 61% yield, respectively (entries 8 and 9). Coumarin is also an excellent substrate and its zincation is complete within 1 h at 25 °C. After alkylation with various primary and secondary alkyl iodides, the substituted coumarins **163j**-**l** were obtained in up to 88% yield (entries 10-12). Similarly, the regioselective zincation of thiochromone (-40 °C, 1 h)[47] at the α-position to sulfur followed by a Co-catalyzed alkylation with 2-iodobutane led to the desired product **163m** in 51% yield (entry 13).

[171] a) K. M. Zareba, *Drugs Today* **2006**, *42*, 75. b) H. R. Ha, B. Stieger, G. Grassi, H. R. Altorfer, F. Follath, *Eur. J. Clin. Pharmacol.* **2000**, *55*, 807. c) M. Witczak, H. Kwiecien, *Synth. Commun.* **2005**, *35*, 2223.

5 Mild Cobalt-Catalyzed Negishi Cross-Couplings of (Hetero)arylzinc Reagents with (Hetero)aryl Halides

5.1 Introduction

The formation of C(sp^2)-C(sp^2) bonds is of great interest for the synthesis of biologically active molecules and particularly the Negishi cross-coupling has attracted a lot of attention as a wide range of polyfunctional zinc reagents are available.[172] As already mentioned above, price and toxicity issues of transition metals, such as Ni and Pd, have encouraged the search for alternative metal sources, such as cobalt[160,173] and iron.[174] Bedford and co-workers demonstrated that the use of iron(I) complexes in Negishi cross-couplings leads to great efficiency.[96,97] Gosmini and Begouin showed that organozinc reagents can be generated *in situ* and cross-coupled with heteroaryl halides in a one-pot procedure.[98] Yoshikai and co-workers reported impressive organometallic cascade reactions, where arylzinc reagents were generated by Co-catalysis and then underwent cross-coupling with aryl iodides in the presence of a Pd catalyst.[27] Furthermore, Hayashi and co-workers reported cobalt-catalyzed asymmetric C(sp^2)-C(sp) couplings.[175]



Scheme 71. Cobalt-catalyzed cross-coupling of aryl halides with arylzinc reagents.

We have shown that arylzinc reagents that are prepared by directed metalation undergo smooth C(sp^2)-C(sp^3) cross-couplings with primary and secondary alkyl halides. Whereas this reaction proceeds under mild conditions, it suffers from a limited scope with respect to the arylzinc reagent, and the extension of this approach to C(sp^2)-C(sp^2) couplings under the reported reaction conditions was difficult.

[172] *Handbook of Functionalized Organometallics: Applications in Synthesis* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2004**.

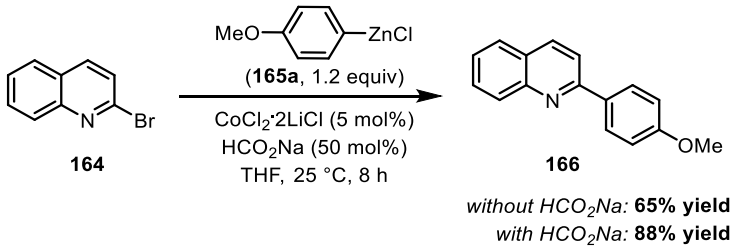
[173] For representative examples, see: a) T. J. Korn, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 2947. b) T. Hatakeyama, S. Hashimoto, K. Ishizuka, M. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 11949. c) M. Moselage, N. Sauermann, S. C. Richter, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 6352. d) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 8551. e) J. Wu, N. Yoshikai, *Angew. Chem. Int. Ed.* **2016**, *55*, 336.

[174] For selected reviews on iron-catalysis, see: a) C. Bolm, *Nat Chem* **2009**, *1*, 420. b) A. Fürstner, *Angew. Chem. Int. Ed.* **2009**, *48*, 1364. c) W. M. Czaplik, M. Mayer, J. Cvengroš, A. J. von Wangelin, *ChemSusChem* **2009**, *2*, 396. d) E. Nakamura, N. Yoshikai, *J. Org. Chem.* **2010**, *75*, 6061.

[175] a) T. Sawano, K. Ou, T. Nishimura, T. Hayashi, *Chem. Commun.* **2012**, *48*, 6106. b) T. Sawano, K. Ou, T. Nishimura, T. Hayashi, *J. Org. Chem.* **2013**, *78*, 8986.

5.2 Design of the Procedure

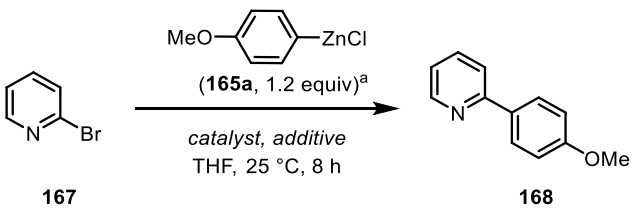
A new set of reaction conditions that enables smooth cross-couplings of various arylzinc reagents with (hetero)aryl chlorides or bromides within a few hours at room temperature was pursued. In a preliminary experiment, we treated 2-bromoquinoline (**164**) with *para*-anisylzinc chloride (**165a**, 1.2 equiv) in the presence of $CoCl_2$·2LiCl (5 mol%) and observed the formation of the desired cross-coupling product (**166**) in 65% yield. However, aside from the desired cross-coupling we observed extensive side reactions, including homocoupling. To improve the reaction outcome, we were inspired by the recent work of *Miller* and co-workers, who showed that the addition of potassium formate plays an important role in Suzuki reactions.[176] We anticipated that this salt could generate a more selective cobalt species with equal or superior catalytic activity. To our delight, the addition of HCO_2Na (50 mol%) led to an improved yield of 88% of the isolated product **166** (Scheme 72).



Scheme 72. Cobalt-catalyzed cross-coupling of 2-bromoquinoline (164) and *p*-$MeOC_6H_4ZnCl$ (165a) with and without sodium formate.

Preliminary kinetic studies showed that the main effect of HCO_2Na is to considerably reduce the occurrence of side reactions, thus, as anticipated, leading to more selective cross-couplings and higher reaction yields.[177] This effect proved to be general, and a broader screen of reaction conditions using 2-bromopyridine (**167**) showed that cobalt halides, such as $CoCl_2$ or $CoBr_2$, as well as $Co(acac)_2$, and $Co(acac)_3$ gave good results (Table 11, entries 1-5). In particular, $CoCl_2$·2LiCl,[168] which is conveniently soluble in THF, afforded product **168** in excellent yield in the presence of HCO_2Na (entry 7).

Table 11. Optimization of the reaction conditions for the Co-catalyzed cross-coupling



[176] W. D. Miller, A. H. Fray, J. T. Quatroche, C. D. Sturgill, *Org. Proc. Res. Dev.* **2007**, *11*, 359.

[177] Premixing of $CoCl_2$·2LiCl and HCO_2Na in THF using the same stoichiometry as in the standard reaction led to the same reaction outcome than the one-pot procedure (also, compare table 9, entry 7). For preliminary kinetic studies, see the experimental part for details.

Entry	Catalyst	Additive	Homocoupling [%]	Yield of **168**[b]
1	$CoCl_2$	-	14	82
2	$CoCl_2$[c]	-	18	76
3	$CoBr_2$	-	14	78
4	$Co(acac)_2$	-	10	72
5	$Co(acac)_3$	-	14	80
6	$CoCl_2$·2LiCl	-	13	83 (79)[d]
7	**$CoCl_2$·2LiCl**	**HCO_2Na**	**12**	**94 (87)[d]**
8	$CoCl_2$·2LiCl	PivONa	14	96
9	$CoCl_2$·2LiCl	DMPU	12	84
10	$CoCl_2$·2LiCl	TMEDA	7	51
11	$CoCl_2$·2LiCl	DMBA[e]	5	16
12	$Co(acac)_3$	HCO_2Na	16	89
13	-	HCO_2Na	-	-
14	$CrCl_2$	-	traces	traces
15	$FeCl_2$	-	traces	17

[a]$MgCl_2$ and LiCl are omitted for the sake of clarity. 5 mol% of the indicated catalyst and 50 mol% of the indicated additive were used. [b]Determined by GC using undecane ($C_{11}H_{24}$) as an internal standard. [c]99.99% purity. [d]Yield of isolated product. [e]2,6-Dimethylbenzoic acid.

Interestingly, when sodium pivalate (*t*-$BuCO_2Na$ = PivONa) was used as an additive, the reaction was equally efficient, showing that HCO_2Na does not act as a reducing agent, but rather as a ligand.[178] Control experiments using ultrapure $CoCl_2$ (99.99%) confirmed that the Co salts are the active catalysts and that metal impurities do not play a role (compare with entry 2). Polar solvents, such as *N*,*N*'-dimethylpropylene urea (DMPU), or the use of a typical additive, such as *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) or 2,5-dimethylbenzoic acid, did not improve the reaction outcome (entries 9-11). The use of $Co(acac)_3$ instead of $CoCl_2$·2LiCl was not advantageous (entry 12). Furthermore, we confirmed that HCO_2Na alone did not catalyze this coupling by additional metal impurities (entry 13). Additional control experiments indicated that Cr[179] and Fe[180] salts are not good catalysts for this reaction (entries 14 and 15).

[178] We propose that the halide ligands in $CoCl_2$·2LiCl are replaced by carboxylate ligands (HCO_2^-), which provides a more selective cobalt catalyst. In fact, halide ligands mostly lead to tetrahedral coordination (see, for example: N. S. Gill, F. B. Taylor, *Inorg. Synth.* **1967**, *9*,136), whereas carboxylate ligands lead to an octahedral coordination (see, for example: a) A. Kaufmann, C. Afshar, M. Rossi, D. E. Zacharias, J. P. Glusker, *Struct. Chem.* **1993**, *4*, 191; b) G. Aromí, A. S. Batsanov, P. Christian, M. Helliwell, A. Parkin, S. Parsons, A. A. Smith, G. A. Timco, R. E. P. Winpenny, *Chem. Eur. J.* **2003**, *9*, 5142). Furthermore, whereas $CoCl_2$·2LiCl in THF is a blue solution, the addition of HCO_2Na leads to a pink solution, which is typical for a coordination change.

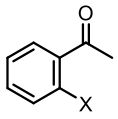
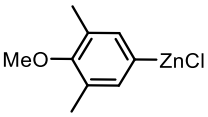
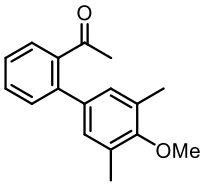
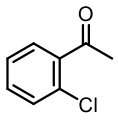
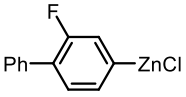
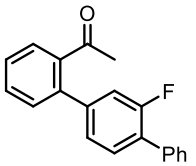
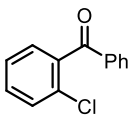
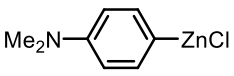
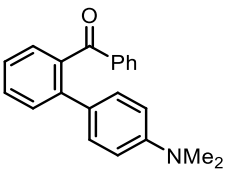
[179] A. K. Steib, O. M. Kuzmina, S. Fernandez, D. Flubacher, P. Knochel, *J. Am. Chem. Soc.* **2013**, *135*, 15346.

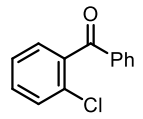
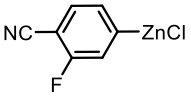
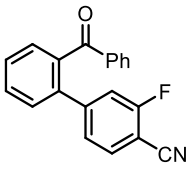
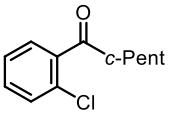
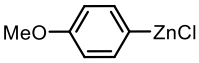
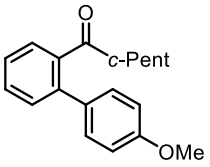
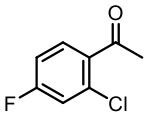
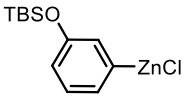
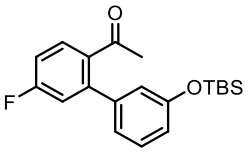
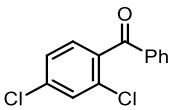
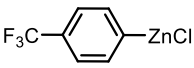
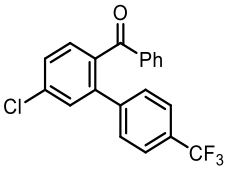
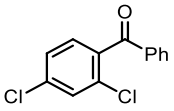
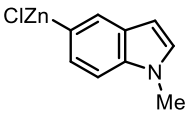
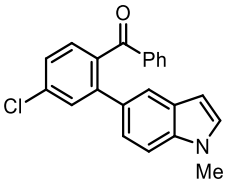
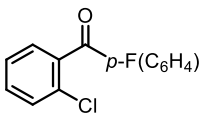
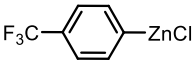
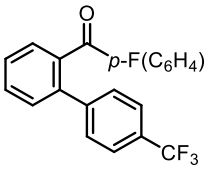
[180] O. M. Kuzmina, A. K. Steib, D. Flubacher, P. Knochel, *Org. Lett.* **2012**, *14*, 4818.

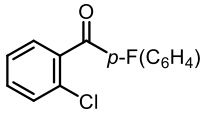
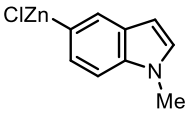
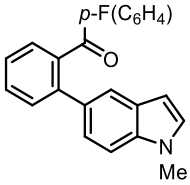
5.3 Cobalt-Catalyzed Cross-Coupling of 2-Halogenated Aromatic Ketones

The reaction scope of this cross-coupling proved to be quite broad. Thus, 2-halogenated, functionalized aceto- and benzophenones (**169a**-**g**) underwent the cobalt-catalyzed cross-coupling with a range of aryl- and heteroarylzinc reagents (**165a**-**h**), yielding the corresponding ketones (**170a**-**j**) in 61-98% yield (Table 12). 2-Chloro- and 2-bromoacetophenone (**169a**-**b**) reacted with zinc reagents bearing various functional groups, providing the expected products **170a-b** in 65-74% yield (entries 1 and 2). Interestingly, zinc reagents with a dimethylamino substituent or a cyano group (**165d**-**e**) were well tolerated as they reacted with 2-chlorobenzophenone (**169c**) to give **170c** and **170d** in 73% and 98% yield, respectively (entries 3 and 4). Remarkably, various other 2-chlorinated aromatic ketones (**169d**-**g**) underwent the cross-coupling with both electron-rich and -poor arylzinc reagents, yielding the desired products in 61-89% yield (entries 5-10). Heterocyclic zinc reagents, such as **165h**, provided the new ketones **170h** and **170j** in 61% and 62% yield, respectively (entries 8 and 10).

Table 12. Cobalt-catalyzed cross-coupling reactions between 2-chlorinated aromatic ketones and arylzinc reagents.

Entry	Electrophile	Zinc reagent	Product / Yield[a]
1			
	169a (X = Cl) **169b** (X = Br)	**165b**	**170a**, 65% (X = Cl) 74% (X = Br)
2			
	169a	**165c**	**170b**, 67%
3			
	169c	**165d**	**170c**, 73%

Entry	Electrophile	Zinc reagent	Product / Yield[a]
4			
	169c	**165e**	**170d**, 98%
5			
	169d	**165a**	**170e**, 76%
6			
	169e	**165f**	**170f**, 68%
7			
	169f	**165g**	**170g**, 89%
8			
	169f	**165h**	**170h**, 61%
9			
	169g	**165g**	**170i**, 73%

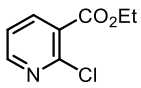
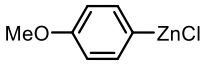
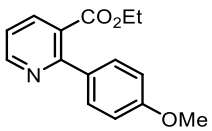
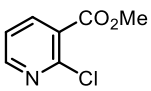
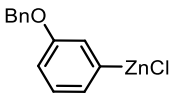
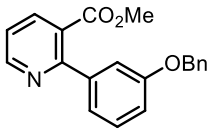
Entry	Electrophile	Zinc reagent	Product / Yield[a]
10			
	169g	**165h**	**170j**, 62%

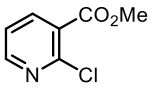
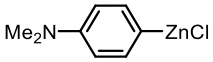
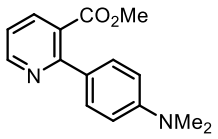
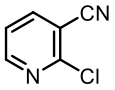
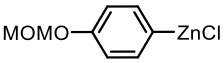
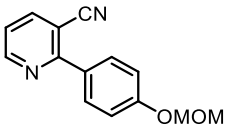
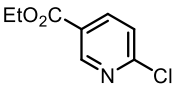
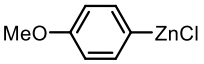
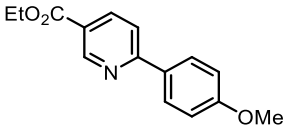
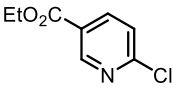
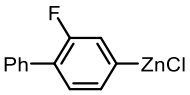
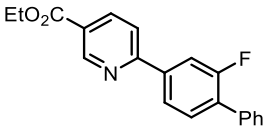
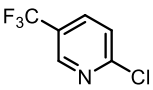
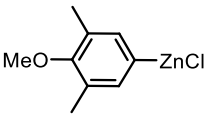
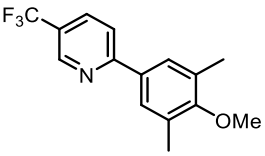
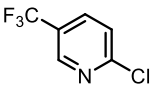
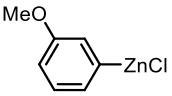
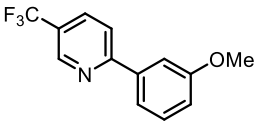
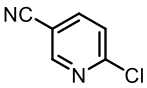
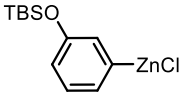
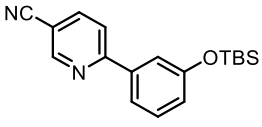
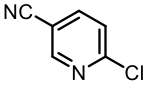
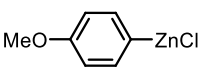
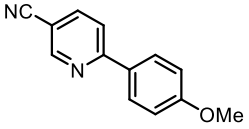
[a]Yield of isolated product. TBS = *tert*-butyldimethylsilyl

5.4 Cobalt-Catalyzed Cross-Coupling of 2-Chloropyridines

Furthermore, a range of 2,3-disubstituted *N*-heterocyclic chlorides can also be readily employed in this reaction (Table 13, entries 1-4). *p*-$MeOC_6H_4ZnCl$ (**165a**) reacted smoothly with ethyl 2-chloronicotinate (**171a**), leading to the 2,3-disubstituted pyridine **172a** in 70% yield (entry 1). The coupling of the electron-rich arylzinc reagents **165i** and **165d** with methyl 2-chloronicotinate (**171b**) afforded pyridines **172b** and **172c** in 71% and 91% yield, respectively (entries 2 and 3). Similarly, the cross-coupling of 2-chloronicotinonitrile (**161c**) and an organozinc reagent bearing a OMOM group (**165j**; MOM = methoxymethyl) led to the desired pyridine **172d** in 60% yield (entry 4). Furthermore, 2,5-disubstituted *N*-heterocyclic chlorides were also good substrates: the ester-substituted pyridine **171d** reacted smoothly with the arylzinc reagents **165a** and **165c** to yield the desired compounds **172e**,**f** in 89% and 88% yield, respectively (entries 5 and 6). Moreover, the 2,5-disubstituted pyridines **171e**,**f** were coupled with various arylzinc reagents delivering the arylated pyridines **172g**-**j** in 73-86% yield (entries 7-10).

Table 13. Cobalt-catalyzed cross-coupling reactions between 2-chloropyridines and arylzinc reagents.

Entry	Electrophile	Zinc reagent	Product / Yield[a]
1			
	171a	**165a**	**172a**, 70%
2			
	171b	**165i**	**172b**, 71%

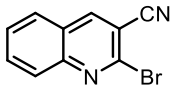
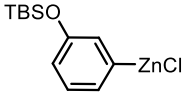
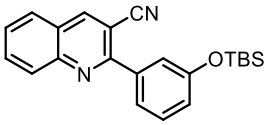
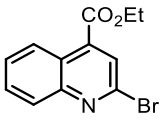
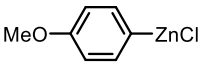
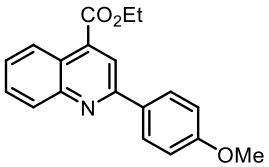
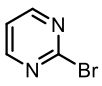
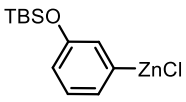
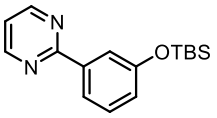
Entry	Electrophile	Zinc reagent	Product / Yield[a]
3			
	171b	**165d**	**172c**, 91%
4			
	171c	**165j**	**172d**, 60%
5			
	171d	**165a**	**172e**, 89%
6			
	171d	**165c**	**172f**, 88%
7			
	171e	**165b**	**172g**, 86%
8			
	171e	**165k**	**172h**, 73%
9			
	171f	**165f**	**172i**, 84%
10			
	171f	**165a**	**172j**, 84%

[a]Yield of isolated product.

5.5 Cobalt-Catalyzed Cross-Coupling of Various *N*-Heterocycles

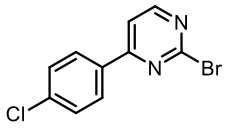
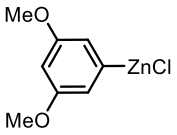
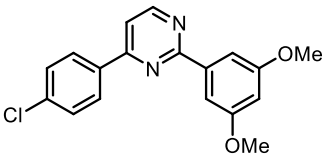
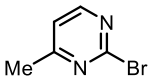
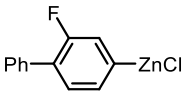
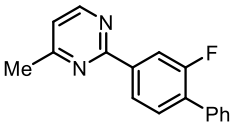
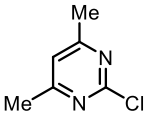
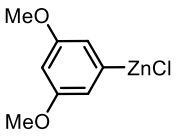
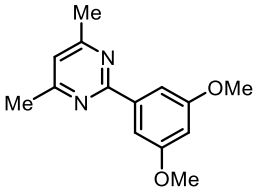
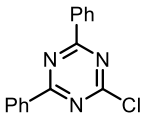
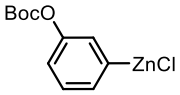
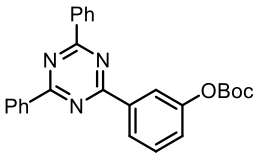
Moreover, halogenated quinolines, pyrimidines, and triazines also proved to be good substrates for this cross-coupling (Table 14). Substituted quinolines, such as 2-bromoquinoline-3-carbonitrile (**173a**) and ethyl 2-bromoquinoline-4-carboxylate (**173b**), can be rapidly coupled with the organozinc reagents **165f** and **165a** to provide the corresponding arylated quinolines **174a** and **174b** in 92% and 65% yield, respectively (entries 1 and 2). Pyrimidines, which are common scaffolds of pharmaceuticals,[181] were readily obtained by the coupling of 2-chloro- or 2-bromopyrimidine (**173c**-**f**) in 65-92% yield (entries 3-6). Triazines are also of great importance as building blocks for materials and agrochemicals.[182] The cross-coupling of 2-chloro-4,6-diphenyl-1,3,5-triazine (**173g**) with the arylzinc reagent **165m** led to the desired product **174g** in 61% yield (entry 7).

Table 14. Cobal-catalyzed cross-coupling between halogenated *N*-heterocycles and various arylzinc reagents.

Entry	Electrophile	Zinc reagent	Product / Yield[a]
1			
	173a	**165f**	**174a**, 92%
2			
	173b	**165a**	**174b**, 65%
3			
	173c	**165f**	**174c**, 92%

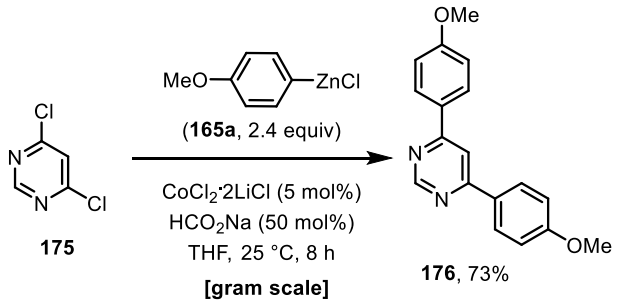
[181] M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Bio.* **2010**, *14*, 347.

[182] a) H. Zhong, H. Lai, Q. Fang, *J. Phys. Chem. C* **2011**, *115*, 2423. b) R. V. Patel, Y.-S. Keum, S. W. Park, *Mini-Rev. Med. Chem.* **2014**, *14*, 768.

Entry	Electrophile	Zinc reagent	Product / Yield[a]
4			
	173d	**165l**	**174d**, 86%
5			
	173e	**165c**	**174e**, 76%
6			
	173f	**165l**	**174f**, 65%
7			
	173g	**165m**	**174g**, 61%

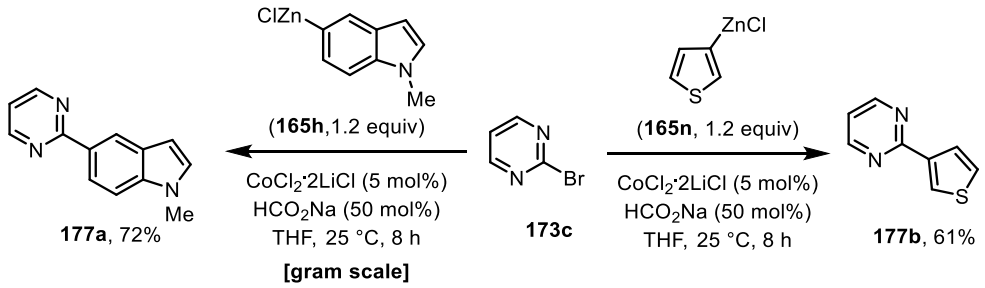
[a]Yield of isolated product.

The cross-coupling of 4,6-dichloropyrimidine (**175**) with *p*-$MeOC_6H_4ZnCl$ (**165a**; 2.4 equiv) afforded the bisarylated compound **176** in 73% yield on gram scale (Scheme 73).



Scheme 73. Cobalt-catalyzed cross-coupling reaction between 4,6-dichloropyrimidine (175) and *p*-$MeOC_6H_4ZnCl$ (165a).

The synthesis of heteroaryl–heteroaryl cross-coupling products is a challenge. When Pd or Ni catalysts are used, catalyst deactivation is often observed owing to chelation of the reagents with the catalyst.[183] However, in the presence of THF-soluble $CoCl_2 \cdot 2LiCl$ (5 mol%) and sodium formate (50 mol%), the cross-coupling of 2-bromopyrimidine (**173c**) with (1-methyl-1*H*-indol-5-yl)zinc chloride (**165h**) or thiophen-3-ylzinc chloride (**165n**) proceeded smoothly to afford the heteroaryl compounds **177a** and **177b** in 72 and 61% yield, respectively (Scheme 74).

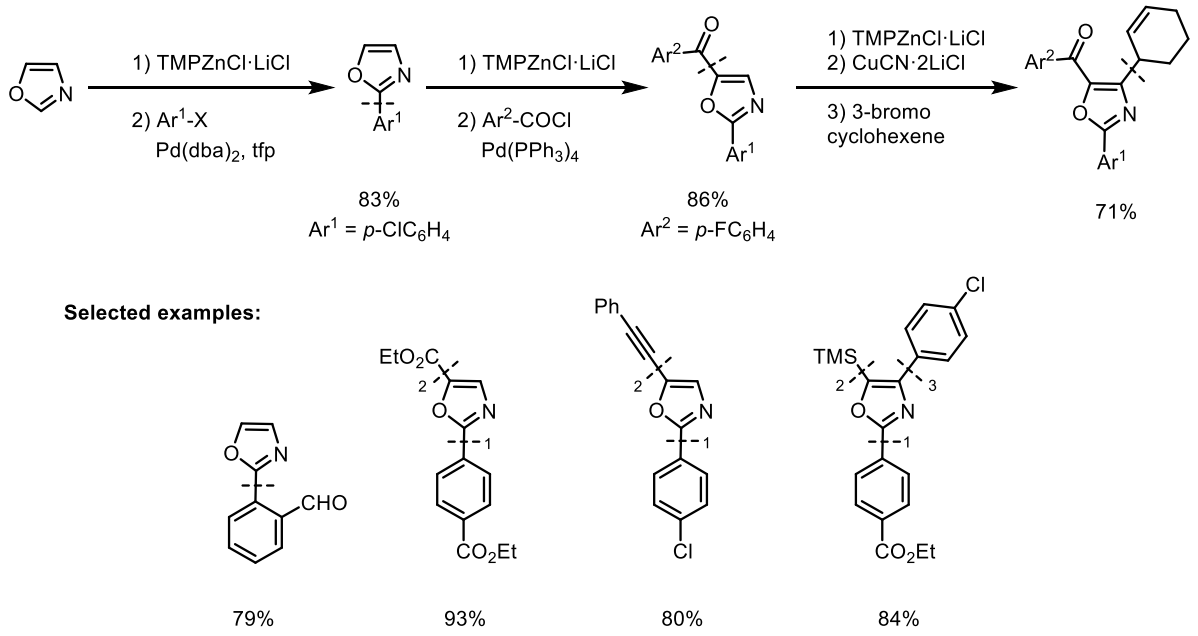


Scheme 74. Cobalt-catalyzed heteroaryl-heteroaryl cross-coupling of 2-bromopyrimidine (173c) and heteroarylzinc reagents.

[183] a) C. Kaes, A. Katz, M. W. Hosseini, *Chem. Rev.* **2000**, *100*, 3553. b) *Comprehensive Coordination Chemistry II, Vol. 1* (Eds.: J. A. McCleverty, T. J. Meyer), Elsevier, Oxford, **2004**.

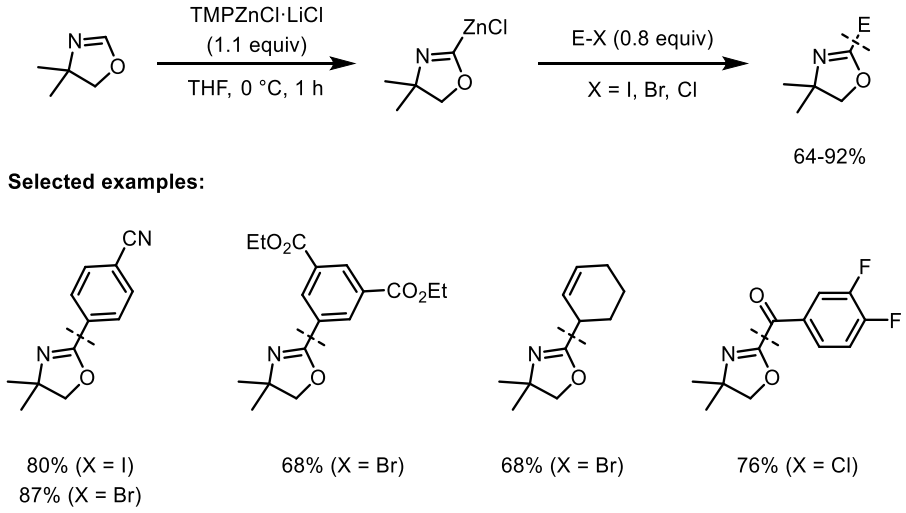
6 Summary

This work was focused on the chemo- and regioselective functionalization of sensitive heterocycles, such as oxazole and oxazolines *via* direct metalation. We have developed a new general method for performing multiple regioselective metalations of oxazole scaffold *via* successive reactions using TMPMgCl·LiCl (**35**) or TMPZnCl·LiCl (**36**) leading to a variety of new highly functionalized oxazole derivatives with the regiocontrolled introduction of all substituents (Scheme 75).



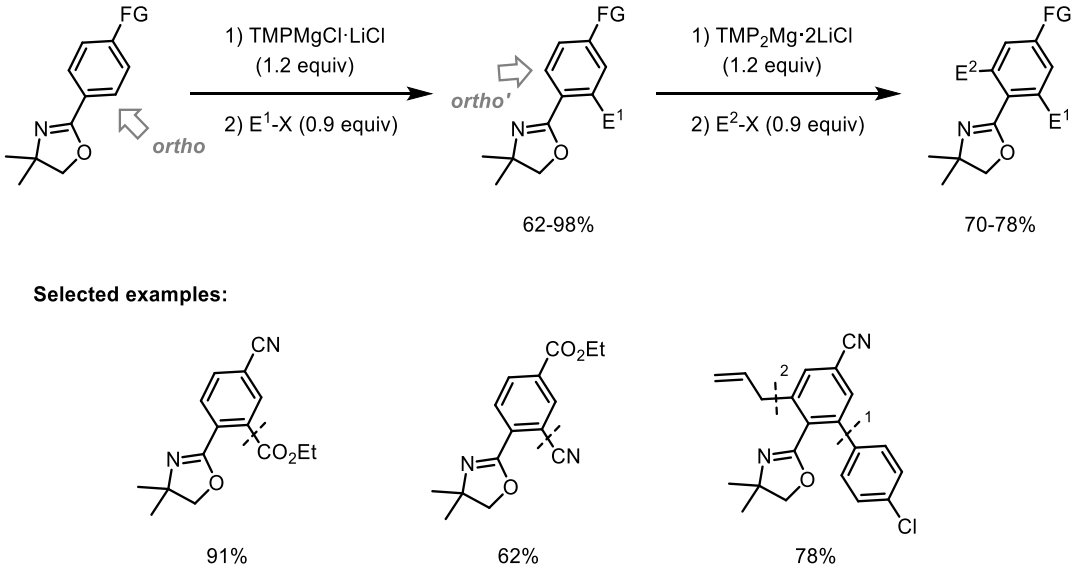
Scheme 75. Multiple regioselective metalations of oxazole using TMPZnCl·LiCl and reaction with electrophiles.

Moreover, we have reported a simple and efficient method for the zincation of 4,4-dimethyl-oxazoline in position 2 using TMPZnCl·LiCl (**36**). The resulting oxazolinylzinc reagents were arylated *via* Negishi cross-couplings with various aryl iodides and bromides under mild conditions. Additionally, Cu-mediated acylation and allylation reactions proceeded readily to yield 2-substituted 4,4-dimethyloxazolines in up to 92% yield (Scheme 76).



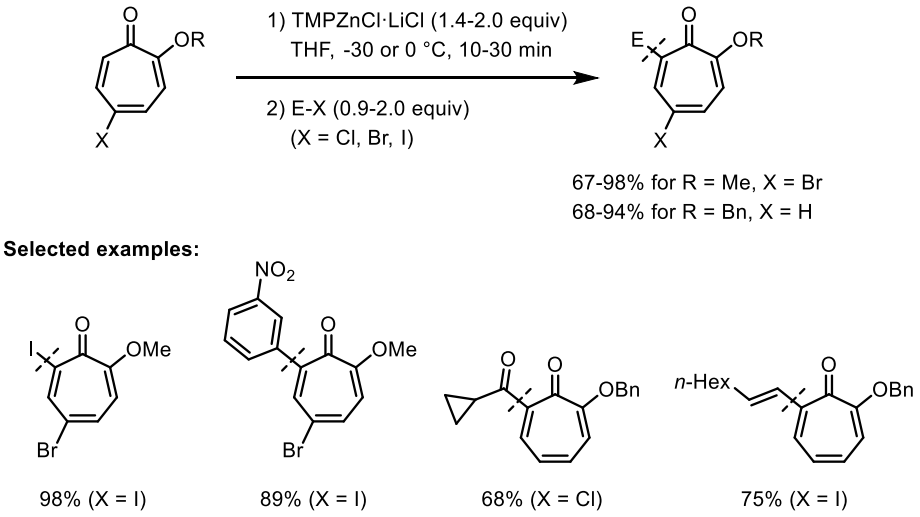
Scheme 76. Preparation of 2-substituted 4,4-dimethyloxazolines *via* directed metalation and reaction with electrophiles.

Since oxazolines serve as a useful directing group in metalation reactions, further functionalization using TMPMgCl·LiCl (**35**) or $TMP_2Mg·2LiCl$ (**42**) and reaction with various electrophiles led to a variety of *ortho*,*ortho'*-disubstituted 2-aryloxazolines in good yields (Scheme 77).



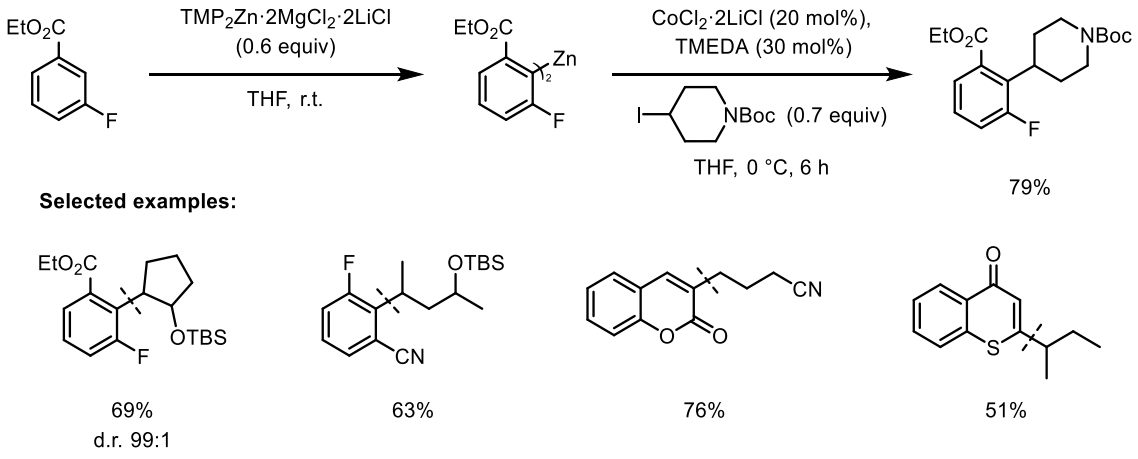
Scheme 77. *ortho*-Metalation of 2-aryloxazolines using TMP-bases of magnesium.

Additionally, we have reported a simple and fast method for the zincation of 2-methoxy- and 2-benzyloxytropones using TMPZnCl·LiCl (**36**). The generated organozinc reagents reacted with a variety of electrophiles in Cu-mediated allylation and acylation reactions, as well as in Pd-catalyzed Negishi cross-coupling reactions providing the α'-functionalized tropolones in very good yields (Scheme 78).



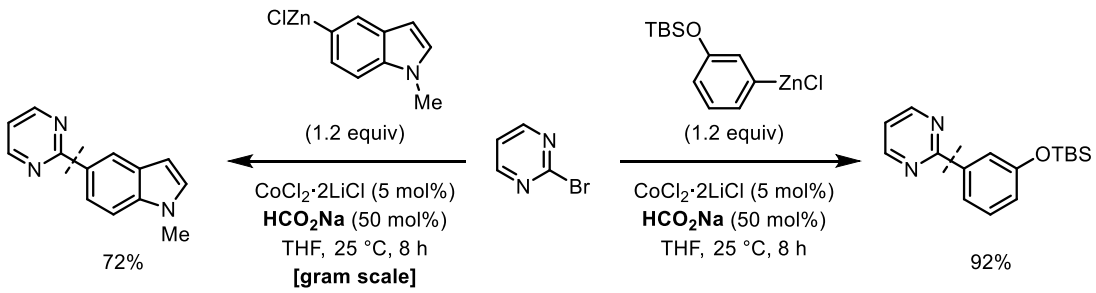
Scheme 78. Zincation and functionalization of tropolone derivatives.

Furthermore, cross-coupling reactions of arylzinc reagents with aryl and alkyl halides under cobalt-catalysis have been investigated. We have developed a new cobalt-catalyzed cross-coupling of polyfunctional diaryl- and diheteroarylzinc reagents prepared *via* directed metalation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**) with primary and secondary alkyl iodides or bromides using the highly soluble cobalt salt $CoCl_2{\cdot}2LiCl$. Remarkably, no rearrangement of the secondary alkyl group could be observed for the alkyl halides employed in this procedure. This cross-coupling proceeds under mild conditions and is compatible with various functional groups and hetereocyclic scaffolds (Scheme 79).

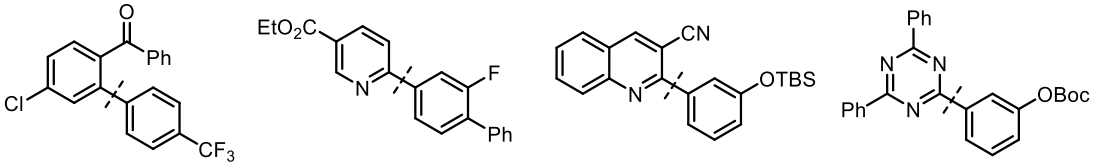


Scheme 79. Cobalt-catalyzed cross-coupling of zincated (hetero)arenes with primary and secondary alkyl halides.

Also, we have developed a new, practical, cobalt-catalyzed, sodium formate promoted $C(sp^2)$-$C(sp^2)$ cross-coupling reaction between *N*-heterocyclic chlorides or bromides and halogenated aromatic ketones with various (hetero)arylzinc reagents. The use of sodium formate was the key to the success of these cobalt-catalyzed cross-couplings (Scheme 80).



Selected examples:



Scheme 80. Cobalt-catalyzed cross-coupling of (hetero)aryl halides with (hetero)arylzinc reagents.

C EXPERIMENTAL PART

C EXPERIMENTAL PART

1 General Considerations

All reactions were carried out with magnetic stirring and in flame-dried glassware under argon atmosphere using *Schlenk* technique. Syringes used to transfer reagents and solvents were purged with argon prior to use.

1.1 Solvents

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2.

DME was predried over $CaCl_2$ and distilled from sodium benzophenone ketyl under argon atmosphere.

DMF was refluxed over CaH_2 (14 h), distilled from CaH_2 and stored over 4 Å MS under argon atmosphere.

DMPU was predried over CaH_2 (4 h) and distilled.

TEA was dried over KOH and distilled.

THF was continuously refluxed and distilled from sodium benzophenone ketyl under nitrogen and stored over 4 Å MS under argon atmosphere.

TMEDA was predried over CaH_2 (12 h) and distilled from sodium benzophenone ketyl under argon atmosphere.

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

1.2 Reagents

Commercially available starting materials were used without further purification.

TMPH was distilled from CaH_2 under argon prior to use.

***i*-PrMgCl·LiCl** was purchased as a solution in THF from Rockwood Lithium GmbH as a 14% solution in THF and was titrated with I_2 prior to use.

***n*-BuLi** was purchased as a solution in hexane from Rockwood Lithium GmbH.

$ZnCl_2$ solution in THF (1.0 M) was prepared by drying $ZnCl_2$ (40.9 g, 300 mmol) in a *Schlenk*-flask under high vacuum at 150 °C for 4 h. After cooling to 25 °C, anhydrous THF was added until a total volume of

300 mL was reached. The suspension was left stirring overnight at 25 °C and after 12 h the salts had completely dissolved. The stirring was stopped and the solution was left for some hours to become completely clear. The solution was stored over 4 Å MS under argon upon use.

CuCN·2LiCl solution in THF (1.0 M) was prepared by drying LiCl (17.0 g, 400 mmol) and CuCN (17.9 g, 200 mmol) in a *Schlenk*-flask under high vacuum at 150 °C for 4 h. After cooling to 25 °C, anhydrous THF was added until a total volume of 200 mL was reached. The suspension was left stirring overnight at 25 °C and after 12 h the salts had completely dissolved. The stirring was stopped and the solution was left for some more time to become completely clear. The solution was stored under argon upon use.

$CoCl_2$·2LiCl solution in THF (1.0 M) was prepared by drying LiCl (8.5 g, 200 mmol) in a *Schlenk*-flask under high vacuum at 130 °C for 3 h. After cooling to 25 °C, anhydrous $CoCl_2$ (13.0 g, 100 mmol) was added and the salts were further heated to 130 °C for 5 h under high vacuum. After cooling to 25 °C anhydrous THF (100 mL) was added. The mixture was vigorously stirred until all solids were dissolved and the reagent was obtained as a dark blue solution.

Preparation of TMPMgCl·LiCl (35)[33]

A 250 mL *Schlenk*-flask was charged with *i*-PrMgCl·LiCl (120 mmol, 100 mL, 1.2 M in THF). Freshly distilled 2,2,6,6-tetramethylpiperidine (TMPH; 126 mmol, 23.9 mL) was added dropwise at 25 °C and the mixture was stirred for 48 h.

Preparation of TMPZnCl·LiCl (36)[34]

A 250 mL *Schlenk*-flask was charged with freshly distilled TMPH (60 mmol, 10 mL) dissolved in THF (60 mL). The solution was cooled to -40 °C and *n*-BuLi (60 mmol, 25 mL, 2.4 m in hexane) was added dropwise. The reaction was allowed to warm slowly to -10 °C within 1 h. $ZnCl_2$ (66 mmol, 66 mL, 1 m in THF) was added dropwise and the resulting solution was stirred for 0.5 h at -10 °C and then 0.5 h at 25 °C. The solvents were removed *in vacuo* to afford a light yellow solid and freshly distilled THF was added under vigorous stirring until the salts were completely dissolved.

Preparation of TMP_2Mg·2LiCl (42)[38]

A 500 mL *Schlenk*-flask was charged with TMPH (7.1 g, 50 mmol) dissolved in THF (50 mL). The solution was cooled to -40 °C and *n*-BuLi (2.4 M in *n*-hexane, 50 mmol) was added at once. The resulting mixture was stirred for 15 min at -40 °C and at 0 °C for further 0.5 h. TMPMgCl·LiCl (**35**, 43.5 mL, 1.15 M in THF, 50 mmol) is added and the mixture is stirred at 0 °C for 0.5 h and then at 25 °C for 1 h. The solvents

are removed *in vacuo* and the resulting pale-brown solid is dissolved in dry THF and stirred for 10 min at 25 °C.

Preparation of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (48)[41]

A 500 mL *Schlenk*-flask was charged with TMPMgCl·LiCl (**35**, 348 mL, 400 mmol) and cooled to 0 °C. A solution of $ZnCl_2$ (1.0 M in THF, 200 mL, 200 mmol) was added over a period of 15 min. The mixture was stirred for 2 h at 0 °C and was then concentrated *in vacuo*.

The content of organometallic reagent was determined either by the method of *Paquette*[184] using *i*-PrOH and 1,10-phen as indicator (organolithium reagents) or the method of *Knochel*[185] using I_2 in THF (organomagnesium and -zinc reagents).

TMP-Bases were titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

1.3 Chromatography

Flash column chromatography was performed using silica gel 60 (40 – 63 µm 230-400 mesh ASTM) from Merck.

Thin layer chromatography (TLC) was performed using aluminum plates covered with SiO_2 (Merck 60, F-254) and visualized either by UV detection or by staining with $KMnO_4$ solution (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH solution in 200 mL H_2O).

1.4 Analytical Data

NMR spectra were recorded on Varian VXR 400S, Bruker Avance III HD 400 MHz and Bruker AMX 600 instruments. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak of $CHCl_3$ (δ_H = 7.26, δ_C = 77.0). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet), br (broad).

Mass spectra and **high resolution mass spectra (HRMS)** were recorded on a Finnigan MAT 95Q (EI) or a Thermo Finnigan LTQ FT instrument (ESI). Electron impact ionization (EI) was conducted with an electron energy of 70 eV. Electrospray ionization (ESI) was conducted with an IonMax ion-source equipped with an ESI head. It was performed with a voltage of 4 kV at the spray capillary tube, a heating filament temperature of 250 °C and a nitrogen flow of 25 units.

[184] H. S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[185] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.

Gas Chromatography (GC) was performed withmachines of the types Hewlett-Packard 6890 or 5890 Series II (Hewlett Packard, 5% phenylmethylpolysiloxane; column length: 15 m, diameter: 0.25 mm; film thickness: 0.25 μm). For the combination of gas chromatography with mass spectroscopic detection, a GC-MS from Hewlett Packard of type 6890/MSD 5973 was used.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a Perkin Elmer Spectrum BX-59343 instrument. For detection a Smiths Detection Dura Sampl*IR* II Diamond ATR sensor was used. The absorption bands ($\tilde{\nu}$) are reported in wave numbers (cm^{-1}).

Melting points (m.p.) were measured using a Büchi B-540 apparatus and are uncorrected.

Single Crystal X-Ray Diffraction Studies were performed with the CrysAlis CCD software and CrysAlis RED software was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan methodc) was applied. The structures were solved with SHELXS-97, refined with SHELXL-97 and finally checked using PLATON. Details for data collection and structure refinement are summarized in the appendix section. Single crystals of the corresponding compounds, suitable for X-ray diffraction, were obtained by slow evaporation of a hexane/CH_2Cl_2 solution. 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-Kα radiation (λ = 0.71071 Å̊).

2 Regioselective Functionalization of the Oxazole Scaffold Using TMP-Bases of Mg and Zn

2.1 Typical Procedures

Typical procedure for the metalation of oxazole derivatives using TMPZnCl·LiCl (36) (TP-1):

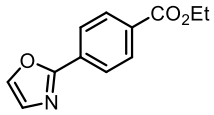
A dry and argon-flushed *Schlenk*-tube was charged with a solution of the oxazole derivative (1.0 equiv.) in dry THF (1.0 M solution). TMPZnCl·LiCl (**36**, 1.2 equiv.) was added dropwise at the given temperature and the reaction mixture was stirred for the indicated time. The completion of metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Typical procedure for the metalation of oxazole derivatives using TMPMgCl·LiCl (35) (TP-2):

A dry and argon-flushed *Schlenk*-tube was charged with a solution of the oxazole derivative (1.0 equiv.) in dry THF (1.0 M solution). TMPMgCl·LiCl (**35**, 1.2 equiv.) was added dropwise at -40 °C and the reaction mixture was stirred for 0.5 h. The completion of metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

2.2 Metalation of Oxazole and Oxazole Derivatives and Subsequent Reaction with Electrophiles

Ethyl 4-(oxazol-2-yl)benzoate (137a)



Preparation from ethyl 4-iodobenzoate:

Ethyl 4-(oxazol-2-yl)benzoate (**137a**) was prepared according to **TP-1** from oxazole (**136**, 663 mg, 9.6 mmol) and TMPZnCl·LiCl (**36**, 14.0 mL, 11.2 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture was stirred for 1 h, then $Pd(dba)_2$ (138 mg, 0.24 mmol), P(*o*-furyl)$_3$ (111 mg, 0.48 mmol) and ethyl 4-iodobenzoate (2.21 g, 8.0 mmol) were added. The reaction mixture was stirred at 50 °C for 4 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/diethyl ether 20:1) yielding **137a** (1.59 g, 92%) as colorless crystals.

Preparation from ethyl 4-bromobenzoate:

$Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and ethyl 4-bromobenzoate (229 mg, 1.0 mmol) were added to the freshly prepared zinc reagent (1.2 mmol). The reaction mixture was heated to 50 °C for 6 h and is then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/diethyl ether 20:1) yielding **137a** (174 mg, 80%) as colorless crystals.

m.p.: 69 – 72 °C

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.17 - 8.07 (m, 4 H), 7.75 (d, *J* = 0.8 Hz, 1 H), 7.28 (d, *J* = 0.8 Hz, 1 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

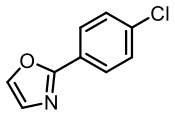
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 165.9, 161.1, 139.2, 131.9, 131.1, 130.0, 128.9, 126.2, 61.2, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3127, 2979, 1708, 1556, 1412, 1362, 1277, 1261, 1178, 1141, 1126, 1106, 1095, 1077, 1056, 1021, 1013, 920, 913, 875, 871, 859, 853, 844, 833, 776, 756, 716, 688, 666, 658, 654.

MS (EI, 70 eV): *m/z* (%) = 217 (21), 189 (10), 173 (6), 172 (51), 144 (11), 89 (7), 70 (8), 61 (12), 45 (11), 43 (100).

HR-MS (EI, 70 eV): [$C_{12}H_{11}NO_3$], calcd.: 217.0739; found: 217.0732.

2-(4-Chlorophenyl)oxazole (137b)



2-(4-Chlorophenyl)oxazole (**137b**) was prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture was stirred for 1 h, then $Pd(dba)_2$ (17 mg, 0.03 mmol), P(*o*-furyl)$_3$ (14 mg, 0.06 mmol) and 1-chloro-4-iodobenzene (238 mg, 1.0 mmol) were added. The reaction mixture was stirred at 50 °C for 2 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*-hexane:CH_2Cl_2 2:1) yielding **137b** (180 mg, 83%) as colorless solid.

m.p.: 81 – 83 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.01 – 7.96 (m, 2 H), 7.71 (d, *J* = 0.8 Hz, 1 H), 7.47 - 7.41 (m, 2 H), 7.24 (d, *J* = 0.8 Hz, 1 H).

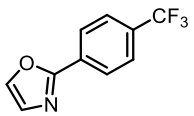
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 126.0, 127.6, 128.6, 129.1, 136.4, 138.8, 161.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3154, 3129, 1915, 1605, 1515, 1479, 1450, 1406, 1261, 1136, 1105, 1088, 1068, 1055, 1009, 918, 912, 833, 768, 749, 730, 694, 678, 663, 659.

MS (EI, 70 eV): *m/z* (%) = 181 (29), 180 (14), 179 (100), 153 (27), 151 (66), 150 (14), 126 (12), 124 (51), 123 (17), 97 (10), 89 (55), 83 (13), 73 (11), 71 (18), 69 (14), 57 (20), 55 (25), 50 (10), 44 (82), 43 (20), 42 (16), 41 (15).

HR-MS (EI, 70 eV): [C_9H_6ClNO], calcd.: 179.0138; found: 179.0131.

2-(4-(Trifluoromethyl)phenyl)oxazole (137c)



2-(4-(trifluoromethyl)phenyl)oxazole (**137c**) was prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture was stirred for 1 h, then $Pd(dba)_2$ (17 mg, 0.03 mmol), P(*o*-furyl)$_3$ (14 mg, 0.06 mmol) and 1-iodo-4-(trifluoromethyl)benzene (272 mg, 1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 4 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*-hexane:CH_2Cl_2 2:1) yielding **137c** (158 mg, 74%) as a light yellow solid.

m.p.: 59 – 61 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.16 (d, *J* = 8.3 Hz, 2 H), 7.76 (s, 1 H), 7.72 (d, *J* = 8.3 Hz, 2 H), 7.28 (s, 1 H).

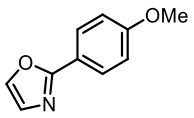
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 160.6, 139.3, 131.9 (q, *J* = 33 Hz), 130.6, 128.8, 126.6, 125.8 (q, *J* = 3.9 Hz) 123.8 (q, *J* = 272 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3176, 3144, 3058, 2638, 2102, 1941, 1711, 1620, 1588, 1561, 1523, 1504, 1495, 1416, 1322, 1298, 1266, 1241, 1188, 1160, 1127, 1100, 1070, 1051, 1012, 921, 914, 895, 884, 846, 774, 758, 747, 710, 697.

MS (EI, 70 eV): *m/z* (%) = 213 (100), 185 (78), 184 (24), 171 (17), 158 (92), 157 (11), 145 (16), 137 (21), 101 (25), 99 (12), 89 (27), 75 (94), 73 (21), 59 (22), 55 (13), 50 (9), 44 (15), 43 (16), 41 (23).

HR-MS (EI, 70 eV): [$C_{10}H_6F_3NO$], calcd.: 213.0401; found: 213.0388.

2-(4-Methoxyphenyl)oxazole (137d)



2-(4-Methoxyphenyl)oxazole (**137d**) was prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture was stirred for 1 h, then $Pd(dba)_2$ (17 mg, 0.03 mmol), P(*o*-furyl)$_3$ (14 mg, 0.06 mmol) and 1-iodo-4-methoxybenzene (234 mg, 1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 6 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/diethyl ether 20:1) yielding **137d** (158 mg, 90%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.01 – 7.95 (m, 2 H), 7.65 (d, *J* = 0.8 Hz, 1 H), 7.19 (d, *J* = 0.8 Hz, 1 H), 7.00 – 6.94 (m, 2 H), 3.85 (s, 3 H).

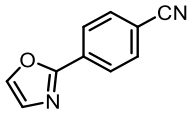
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 162.0, 161.3, 137.97, 128.2, 128.0, 120.4, 114.2, 55.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2940, 2837, 1721, 1663, 1609, 1586, 1561, 1523, 1493, 1463, 1441, 1423, 1365, 1303, 1248, 1172, 1139, 1101, 1073, 1059, 1024, 952, 918, 835, 797, 766, 735, 705, 662.

MS (EI, 70 eV): *m/z* (%) = 176 (12), 175 (100), 132 (45), 120 (48), 119 (24), 105 (10), 104 (19), 91 (49), 90 (19), 89 (15), 77 (61), 76 (28), 75 (12), 65 (12), 64 (15), 63 (29), 62 (14), 50 (50).

HR-MS (EI, 70 eV): [$C_{10}H_9NO_2$], calcd.: 175.0633; found: 175.0618.

4-(Oxazol-2-yl)benzonitrile (137e)



4-(Oxazol-2-yl)benzonitrile (**137e**) was prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture was stirred for 1 h, then $Pd(dba)_2$ (17 mg, 0.03 mmol), P(*o*-furyl)$_3$ (14 mg, 0.06 mmol) and 4-iodobenzenonitrile (229 mg, 1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 4 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/*i*-hexane 5:1) yielding **137e** (148 mg, 87%) as a colorless solid.

m.p.: 82 – 84 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.18 - 8.12 (m, 2 H), 7.78 (d, *J* = 0.8 Hz, 1 H), 7.77 - 7.73 (m, 2 H), 7.31 (d, *J* = 0.8 Hz, 1 H).

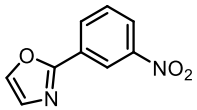
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 160.1, 139.7, 132.6, 131.2, 129.1, 126.8, 118.3, 113.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3159, 3126, 2924, 2854, 2229, 1946, 1717, 1658, 1578, 1512, 1489, 1480, 1409, 1315, 1263, 1182, 1144, 1110, 1102, 1080, 1070, 1057, 1026, 1018, 1003, 976, 921, 913, 898, 877, 866, 860, 846, 772, 758, 741, 704.

MS (EI, 70 eV): *m/z* (%) = 171 (9), 170 (100), 143 (5), 142 (54), 141 (7), 116 (4), 115 (44), 114 (14), 102 (4), 88 (5), 75 (3).

HR-MS (EI, 70 eV): [$C_{10}H_6O_1N_2$], calcd.: 170.0480; found: 170.0463.

2-(3-Nitrophenyl)oxazole (137f)



2-(3-Nitrophenyl)oxazole (**137f**) was prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture is stirred for 1 h, then $Pd(dba)_2$ (17 mg, 0.03 mmol), P(*o*-furyl)$_3$ (14 mg, 0.06 mmol) and 1-iodo-3-nitrobenzene (249 mg, 1.0 mmol) were added. The reaction mixture was stirred at 50 °C for 1 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2:*i*-hexane 20:1) yielding **137f** (179 mg, 94%) as a light yellow solid.

m.p.: 95 – 97 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.90 – 8.87 (m, 1 H), 8.38 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1 H), 8.30 (ddd, *J* = 8.3, 2.3, 1.1 Hz, 1 H), 7.79 (d, *J* = 0.8 Hz, 1 H), 7.70 – 7.62 (m, 1 H), 7.31 (d, *J* = 0.8 Hz, 1 H).

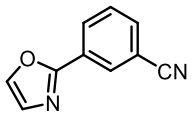
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 159.7, 148.6, 139.6, 131.9, 130.0, 129.0, 129.0, 124.7, 121.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3159, 3137, 3088, 2868, 1745, 1595, 1525, 1479, 1446, 1347, 1286, 1266, 1256, 1166, 1138, 1117, 1103, 1082, 1065, 1052, 998, 932, 913, 904, 882, 868, 814, 767, 760, 739, 710, 671, 657.

MS (EI, 70 eV): *m/z* (%) = 190 (64), 144(25), 116 (29), 115 (14), 102 (12), 90 (13), 89 (100), 88 (15), 87 (11), 86 (10), 77 (10), 76 (14), 75 (10), 63 (34), 62 (17), 50 (10).

HR-MS (EI, 70 eV): [$C_9H_6N_2O_3$], calcd.: 190.0378; found: 190.0370.

3-(Oxazol-2-yl)benzonitrile (137g)



3-(Oxazol-2-yl)benzonitrile (**137g**) was prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture was stirred for 1 h, then $Pd(dba)_2$ (17 mg, 0.03 mmol), P(*o*-furyl)$_3$ (14 mg, 0.06 mmol) and 3-iodobenzonitrile (229 mg, 1.0 mmol) were added. The reaction mixture was stirred at 50 °C for 4 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2:*i*-hexane 5:1) yielding **137g** (139 mg, 82%) as a colorless solid.

m.p.: 87 – 89 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.33 - 8.31 (m, 1 H), 8.26 (dq, *J* = 7.9, 0.9 Hz, 1 H), 7.76 (d, *J* = 0.9 Hz, 1 H), 7.71 (ddd, *J* = 7.8, 2.0, 0.8 Hz, 1 H), 7.61 - 7.55 (m, 1 H), 7.27 ppm (d, *J* = 0.9 Hz, 1 H).

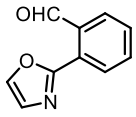
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.7, 139.5, 133.4, 130.2, 129.8, 129.7, 128.9, 128.7, 118.0, 113.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3159, 3132, 2230, 1553, 1512, 1476, 1463, 1458, 1438, 1406, 1369, 1356, 1279, 1267, 1183, 1175, 1169, 1147, 1117, 1091, 1078, 1072, 1062, 1053, 998, 928, 913, 906, 863, 825, 807, 785, 761, 724, 678.

MS (EI, 70 eV): *m/z* (%) = 170 (100), 143 (9), 142 (77), 141 (10), 114 (14), 97 (10), 83 (11), 71 (12), 57 (30), 55 (21), 44 (67), 43 (15), 41 (22).

HR-MS (EI, 70 eV): [$C_{10}H_6N_2O$], calcd.: 170.0480; found: 170.0482.

2-(Oxazol-2-yl)benzaldehyde (137h)



2-(Oxazol-2-yl)benzaldehyde (**137h**) was prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture was stirred for 1 h, then $Pd(dba)_2$ (17 mg, 0.03 mmol), P(*o*-furyl)$_3$ (14 mg, 0.06 mmol) and 2-iodobenzaldehyde (232 mg, 1.0 mmol) were added. The reaction mixture was stirred at 50 °C for 2 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The

combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2) yielding **137h** (137 mg, 79%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 10.88 (d, *J* = 0.83 Hz, 1 H), 8.03 (ddd, *J* = 7.53, 3.52, 1.38 Hz, 2 H), 7.82 (d, *J* = 0.83 Hz, 1 H), 7.73 - 7.63 (m, 1 H), 7.62 - 7.52 (m, 1 H), 7.33 (d, *J* = 0.83 Hz, 1 H).

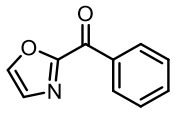
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 192.6, 159.7, 139.6, 134.7, 133.4, 130.4, 129.0, 128.9, 128.7, 128.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3179, 3062, 2914, 1687, 1653, 1597, 1556, 1512, 1480, 1439, 1398, 1352, 1273, 1250, 1190, 1130, 1114, 1096, 1077, 1051, 1034, 1005, 996, 919, 888, 850, 822, 773, 757, 733, 707.

MS (EI, 70 eV): *m/z* (%) = 173 (1), 146 (6), 145 (63), 117 (25), 116 (7), 90 (34), 89 (21), 88 (5), 73 (6), 70 (11), 63 (7), 61 (16), 45 (15), 43 (100), 42 (5).

HR-MS (EI, 70 eV): [$C_{10}H_7O_2N_1$], calcd.: 173.0477; found: 173.0462.

Oxazol-2-yl(phenyl)methanone (137i)



Oxazol-2-yl(phenyl)methanone (**137i**) was prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture was stirred for 1 h, then $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and benzoyl chloride (141 mg, 1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 3 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2:*i*-hexane 10:1) yielding **137i** (126 mg, 73%) as a colorless solid.

m.p.: 54 – 56 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.53 – 8.43 (m, 2 H), 7.92 (d, *J* = 0.7 Hz, 1 H), 7.71 – 7.59 (m, 1 H), 7.60 – 7.47 (m, 2 H), 7.43 (d, *J* = 0.7 Hz, 1 H).

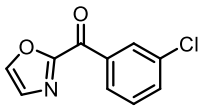
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 178.9, 157.8, 141.5, 135.0, 134.0, 130.8, 129.1, 128.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3147, 3128, 3057, 2922, 2850, 1791, 1698, 1661, 1628, 1597, 1579, 1574, 1538, 1476, 1445, 1373, 1341, 1313, 1293, 1287, 1274, 1225, 1187, 1177, 1138, 1120, 1089, 1079, 1070, 1035, 1025, 999, 972, 958, 940, 931, 915, 900, 869, 841, 811, 796, 737, 714, 690, 681.

MS (EI, 70 eV): *m/z* (%) = 173 (5), 146 (4), 145 (30), 117 (3), 106 (9), 105 (100), 89 (2), 78 (4), 75 (3), 74 (4), 62 (2), 58 (1), 52 (2), 50 (10).

HR-MS (EI, 70 eV): [$C_{10}H_7NO_2$], calcd.: 173.0477; found: 173.0474.

(3-Chlorophenyl)(oxazol-2-yl)methanone (137j)



(3-Chlorophenyl)(oxazol-2-yl)methanone (**137j**) wa prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture was stirred for 1 h, then $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 3-chlorobenzoyl chloride (175 mg, 1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 4 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2:*i*-hexane 1:1) yielding **137j** (179 mg, 86%) as a colorless solid.

m.p.: 121 – 123 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.53 – 8.50 (m, 1 H), 8.44 – 8.39 (m, 1 H), 7.93 (s, 1 H), 7.63 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1 H), 7.50 (t, *J* = 7.9 Hz, 1 H), 7.46 (s, 1 H).

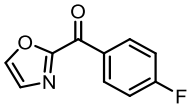
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 177.3, 157.4, 141.8, 136.4, 134.8, 133.9, 130.8, 129.8, 129.2, 129.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3153, 3134, 3094, 3069, 1651, 1590, 1565, 1541, 1480, 1474, 1417, 1374, 1299, 1289, 1274, 1261, 1176, 1162, 1147, 1124, 1095, 1085, 964, 922, 906, 886, 803, 767, 758, 674, 659.

MS (EI, 70 eV): *m/z* (%) = 208 (10), 179 (9), 139 (100), 127 (16), 111 (48), 109 (10), 97 (17), 96 (10), 85 (12), 83 (16), 81 (19), 77 (11), 75 (24), 71 (15), 70 (10), 69 (29), 67 (11), 57 (41), 56 (14), 55 (27), 43 (27), 41 (25).

HR-MS (EI, 70 eV): [$C_{10}H_6ClNO_2$], calcd.: 208.0160; found: 208.0156 $[M+H]^+$.

(4-Fluorophenyl)(oxazol-2-yl)methanone (137k)



(4-Fluorophenyl)(oxazol-2-yl)methanone (**137k**) was prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture is stirred for 1 h, then $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 4-fluorobenzoyl chloride (191 mg, 1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 2 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2) yielding **137k** (179 mg, 86%) as a colorless solid.

m.p.: 118 – 121 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.63 – 8.55 (m, 2 H), 7.92 (d, *J* = 0.7 Hz, 1 H), 7.43 (d, *J* = 0.6 Hz, 1 H), 7.25 – 7.15 (m, 2 H).

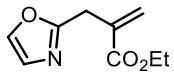
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 177.1, 166.4 (d, *J* = 256.9 Hz), 157.9, 141.6, 133.8 (d, *J* = 9.5 Hz), 131.3 (d, *J* = 3.0 Hz), 129.0, 115.7 (d, *J* = 21.9 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3149, 3123, 3091, 3065, 1651, 1590, 1565, 1541, 1480, 1474, 1417, 1374, 1299, 1289, 1274, 1261, 1176, 1162, 1147, 1124, 1095, 1085, 964, 922, 906, 886, 803, 767, 758, 674, 659.

MS (EI, 70 eV): *m/z* (%) = 191 (3), 183 (4), 163 (12), 140 (8), 123 (100), 95 (34), 83 (7), 7 (12), 74 (8), 71 (7), 69 (8), 59 (9), 57 (12), 55 (8), 45 (7), 44 (15), 43 (9), 41 (9).

HR-MS (EI, 70 eV): [$C_{10}H_6FNO_2$], calcd.: 191.0383; found: 191.0382.

Ethyl 2-(oxazol-2-ylmethyl)acrylate (137l)



Ethyl 2-(oxazol-2-ylmethyl)acrylate (**137l**) was prepared according to **TP-1** from oxazole (**136**, 83 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 0 °C. The reaction mixture was stirred for 1 h and was submitted to an allylation reaction by adding CuCN·2LiCl (1.4 mmol, 1.4 mL, 1 M solution in THF). The reaction mixture was stirred for 20 min and then ethyl 2-(bromomethyl)acrylate (193 mg, 1.0 mmol) was added. The reaction was allowed to warm to 25 °C, stirred for 1 h and was then quenched with aq. NH_4Cl/NH_3 (10:1) solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/diethyl ether 10:1) yielding **137l** (141 mg, 78%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.57 (d, *J* = 0.8 Hz, 1 H), 7.03 (d, *J* = 0.8 Hz, 1 H), 6.36 (dd, *J* = 1.6, 0.8 Hz, 1 H), 5.67 (dt, *J* = 1.4, 0.9 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 3.81 (dd, *J* = 1.3, 0.8 Hz, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

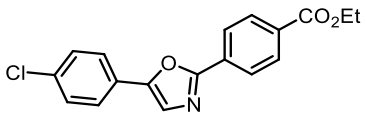
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 165.9, 161.9, 138.6, 135.1, 127.7, 127.2, 61.0, 31.0, 14.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981, 2938, 1711, 1635, 1611, 1573, 1526, 1476, 1465, 1445, 1422, 1400, 1391, 1368, 1330, 1299, 1247, 1190, 1142, 1113, 1097, 1071, 1023, 952, 913, 902, 859, 818, 753, 723, 705, 687, 680, 660, 656.

MS (EI, 70 eV): *m/z* (%) = 181 (23), 136 (49), 135 (67), 109 (22), 108 (41), 107 (100), 80 (10), 74 (37), 59 (38), 53 (21), 45 (32), 43 (20), 41 (14).

HR-MS (EI, 70 eV): [$C_9H_{11}NO_3$], calcd.: 181.0739; found: 181.0736.

Ethyl 4-(5-(4-chlorophenyl)oxazol-2-yl)benzoate (138a)



Ethyl 4-(5-(4-chlorophenyl)oxazol-2-yl)benzoate (**138a**) was prepared according to **TP-1** from ethyl 4-(oxazol-2-yl)benzoate (**137a**, 261 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 0.5 h, then $Pd(dba)_2$ (17 mg, 0.03 mmol), P(*o*-furyl)$_3$ (14 mg, 0.06 mmol) and 1-chloro-4-iodobenzene (238 mg, 1.0 mmol) were added and the reaction mixture was stirred at 50 °C for 2 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2) yielding **138a** (302 mg, 92%) as a colorless solid.

m.p.: 110 – 114 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.16 (s, 4 H), 7.70 – 7.65 (m, 2 H), 7.48 (s, 1 H), 7.47 – 7.40 (m, 2 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H).

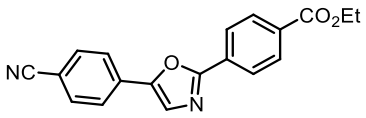
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 165.9, 160.4, 151.0, 134.6, 131.9, 130.9, 130.1, 129.3, 126.2, 126.1, 125.6, 124.2, 61.3, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3106, 2979, 1707, 1680, 1478, 1413, 1404, 1367, 1305, 1296, 1273, 1244, 1185, 1170, 1166, 1139, 1127, 1104, 1091, 1055, 1024, 1015, 952, 938, 879, 866, 853, 841, 823, 777, 760, 716, 692, 682, 675.

MS (EI, 70 eV): *m/z* (%) = 330 (6), 329 (33), 328 (16), 327 (100), 301 (6), 299 (17), 284 (13), 283 (7), 282 (35), 254 (7), 219 (6), 209 (5), 199 (8), 191 (8), 111 (6), 89 (8).

HR-MS (EI, 70 eV): [$C_{18}H_{14}ClNO_3$], calcd.: 327.0662; found: 327.0660.

Ethyl 4-(5-(4-cyanophenyl)oxazol-2-yl)benzoate (138b)



Ethyl 4-(5-(4-cyanophenyl)oxazol-2-yl)benzoate (**138b**) was prepared according to **TP-1** from ethyl 4-(oxazol-2-yl)benzoate (**137a**, 261 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 0.5 h, then $Pd(dba)_2$ (17 mg, 0.03 mmol), P(*o*-furyl)$_3$ (14 mg, 0.06 mmol) and 4-iodobenzonitrile (229 mg, 1.0 mmol) were added. The reaction mixture was stirred at 50 °C for 3 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2) yielding **138b** (264 mg, 83%) as a colorless solid.

m.p.: 178 – 181 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.17 (s, 4 H), 7.86 – 7.80 (m, 2 H), 7.78 – 7.71 (m, 2 H), 7.63 (s, 1 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H).

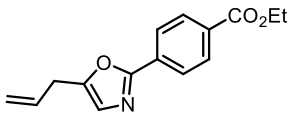
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 165.8, 161.4, 150.0, 132.9, 132.4, 131.6, 130.4, 130.1, 126.5, 126.3, 124.5, 118.4, 111.9, 61.4, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3110, 2971, 2905, 2227, 1711, 1642, 1610, 1408, 1358, 1307, 1291, 1266, 1248, 1182, 1174, 1166, 1102, 1090, 1072, 1056, 1013, 954, 937, 924, 872, 865, 844, 833, 776, 741, 715, 675.

MS (EI, 70 eV): *m/z* (%) = 319 (24), 318 (100), 290 (31), 274 (20), 273 (73), 245 (10), 190 (26), 102 (12), 57 (11), 55 (10).

HR-MS (EI, 70 eV): [$C_{19}H_{14}N_2O_3$], calcd.: 318.1004; found: 318.1001.

Ethyl 4-(5-allyloxazol-2-yl)benzoate (138c)



Ethyl 4-(5-allyloxazol-2-yl)benzoate (**138c**) was prepared according to **TP-1** from ethyl 4-(oxazol-2-yl)benzoate (**137a**, 261 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 0.5 h and the freshly prepared zinc reagent was then submitted to an allylation reaction by adding CuCN·2LiCl (1.4 mmol, 1.4 mL, 1 M solution in THF). The reaction mixture was stirred for 20 min and then allyl bromide (121 mg, 1.0 mmol) was added. The reaction mixture was allowed to warm to 25 °C, stirred for 1 h and was then quenched with aq. NH_4Cl/NH_3

(10:1) solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/diethyl ether 20:1) yielding **138c** (203 mg, 79%) as a colorless solid.

m.p.: 145 – 147 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.16 – 8.00 (m, 4 H), 6.93 (t, *J* = 1.1 Hz, 1 H), 5.96 (m, 1 H), 5.34 – 5.17 (m, 2 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 3.51 (ddd, *J* = 6.5, 2.7, 1.4 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

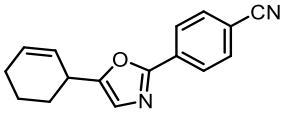
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 166.0, 160.1, 151.5, 132.2, 131.5, 131.3, 130.0, 125.8, 124.8, 118.1, 61.2, 30.2, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3118, 3079, 2979, 1941, 1714, 1643, 1614, 1592, 1462, 1435, 1409, 1367, 1306, 1268, 1243, 1173, 1166, 1121, 1101, 1091, 1063, 1015, 1000, 988, 953, 933, 921, 916, 908, 859, 823, 786, 776, 760, 752, 738, 715, 689.

MS (EI, 70 eV): *m/z* (%) = 258 (18), 257 (100), 216 (23), 215 (10), 212 (33), 188 (47), 177 (21), 160 (21), 82 (11), 54 (17).

HR-MS (EI, 70 eV): [$C_{15}H_{15}NO_3$], calcd.: 257.1052; found: 257.1041.

4-(5-(Cyclohex-2-en-1-yl)oxazol-2-yl)benzonitrile (138d)



4-(5-(Cyclohex-2-en-1-yl)oxazol-2-yl)benzonitrile (**138d**) was prepared according to **TP-1** from 4-(oxazol-2-yl)benzonitrile (**137e**, 1.2 mmol, 204 mg) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 0.5 h, and the freshly prepared zinc reagent was then submitted to an allylation reaction by adding CuCN·2LiCl (1.4 mmol, 1.4 mL, 1 M solution in THF). The reaction mixture was stirred for 20 min and then 3-bromocyclohexene (161 mg, 1.0 mmol) was added. The reaction mixture was allowed to warm to 25 °C, stirred for 1 h and was then quenched with aq. NH_4Cl/NH_3 (10:1) solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*-hexane:diethyl ether 2:1) yielding **138d** (190 mg, 76%) as a colorless solid.

m.p.: 132 – 134 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.13 - 8.07 (m, 2 H), 7.75 - 7.69 (m, 2 H), 6.91 (d, *J* = 1.1 Hz, 1 H), 6.06 - 5.87 (m, 1 H), 5.83 - 5.67 (m, 1 H), 3.64 - 3.55 (m, 1 H), 2.17 - 1.98 (m, 3 H), 1.90 - 1.57 (m, 3 H).

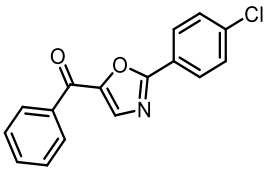
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 158.9, 157.1, 132.5, 131.5, 130.3, 126.4, 125.0, 124.4, 118.4, 113.1, 33.1, 27.7, 24.8, 20.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2945, 2926, 2864, 2225, 1729, 1688, 1612, 1586, 1567, 1543, 1490, 1446, 1410, 1361, 1351, 1292, 1282, 1251, 1244, 1202, 1183, 1146, 1120, 1109, 1098, 1083, 1064, 1043, 1018, 1004, 979, 884, 877, 847, 834, 826, 780, 770, 740, 727, 701, 674, 656.

MS (EI, 70 eV): *m/z* (%) = 251 (14), 250 (100), 249 (6), 222 (19), 169 (15), 142 (10), 141 (52), 130 (70), 120 (23), 114 (28), 104 (11), 102 (18), 94 (23), 80 (12), 79 (16), 77 (10), 66 (24), 53 (13), 43 (17).

HR-MS (EI, 70 eV): [$C_{16}H_{14}O_1N_2$], calcd.: 250.1106; found: 250.1104.

(2-(4-Chlorophenyl)oxazol-5-yl)(phenyl)methanone (138e)



(2-(4-Chlorophenyl)oxazol-5-yl)(phenyl)methanone (**138e**) was prepared according to **TP-1** from 2-(4-chlorophenyl)oxazole (**137b**, 216 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 50 °C. The reaction is stirred for 0.5 h, then $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and benzoyl chloride (141 mg, 1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 2 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*-hexane:diethyl ether 3:1) yielding **138e** (216 mg, 76%) as a colorless solid.

m.p.: 121 – 123 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.17 - 8.11 (m, 2 H), 8.02 - 7.96 (m, 2 H), 7.86 (s, 1 H), 7.70 - 7.62 (m, 1 H), 7.60 - 7.54 (m, 2 H), 7.54 - 7.48 (m, 2 H).

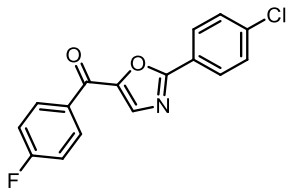
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 181.4, 163.8, 149.1, 138.3, 137.6, 136.8, 133.3, 129.4, 129.0, 128.8, 128.8, 124.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3072, 3055, 2925, 1911, 1636, 1597, 1578, 1550, 1523, 1472, 1459, 1446, 1406, 1350, 1315, 1306, 1291, 1278, 1260, 1242, 1172, 1153, 1134, 1114, 1090, 1075, 1012, 996, 976, 957, 946, 936, 895, 868, 850, 830, 808, 792, 742, 720, 694, 676.

MS (EI, 70 eV): *m/z* (%) = 285 (20), 284 (10), 283 (56), 219 (6), 178 (100), 150 (46), 123 (15), 105 (7), 88 (4), 77 (19), 69 (8), 57 (3), 55 (3), 45 (4), 44 (19), 43 (39), 42 (2), 41 (3).

HR-MS (EI, 70 eV): [$C_{16}H_{10}O_2N_1Cl_1$], calcd.: 283.0400; found: 283.0397.

(2-(4-Chlorophenyl)oxazol-5-yl)(4-fluorophenyl)methanone (138f)



(2-(4-Chlorophenyl)oxazol-5-yl)(4-fluorophenyl)methanone (**138f**) was prepared according to **TP-1** from 2-(4-chlorophenyl)oxazole (**137b**, 216 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 0.5 h, then $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 4-fluorobenzoyl chloride (159 mg, 1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 4 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2:*i*-hexane 3:1) yielding **138f** (259 mg, 86%) as a colorless solid.

m.p.: 152 – 154 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.18 – 8.09 (m, 2 H), 8.09 – 7.99 (m, 2H), 7.87 (s, 1H), 7.57 – 7.42 (m, 2 H), 7.30 – 7.18 (m, 2 H).

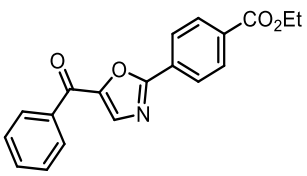
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 179.7, 165.9 (d, *J* = 255.7 Hz), 163.8, 149.0, 138.4, 137.4, 133.0 (d, *J* = 2.9 Hz), 131.6 (d, *J* = 9.4 Hz), 129.4, 128.7, 124.6, 116.1 (d, *J* = 22.0 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3118, 2167, 1908, 1638, 1598, 1583, 1522, 1506, 1470, 1406, 1356, 1344, 1309, 1296, 1235, 1177, 1164, 1156, 1095, 1012, 996, 945, 900, 842, 829, 812, 761, 738, 702, 694.

MS (EI, 70 eV): *m/z* (%) = 303 (25), 302 (14), 301 (64), 181 (36), 180 (11), 178 (100), 152 (28), 150 (76), 123 (30), 43 (12).

HR-MS (EI, 70 eV): [$C_{16}H_9ClFNO_2$], calcd.: 301.0306; found: 301.0300.

Ethyl 4-(5-benzoyloxazol-2-yl)benzoate (138g)



Ethyl 4-(5-benzoyloxazol-2-yl)benzoate (**138g**) was prepared according to **TP-1** from ethyl 4-(oxazol-2-yl)benzoate (**137a**, 261 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF)

at 50 °C. The reaction was stirred for 0.5 h, then $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and benzoyl chloride (141 mg, 1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 4 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*-hexane:diethyl ether 3:2) yielding **138g** (315 mg, 98%) as a colorless solid.

m.p.: 118 – 120 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.30 - 8.23 (m, 2 H), 8.23 - 8.15 (m, 2 H), 8.05 - 7.97 (m, 2 H), 7.90 (s, 1 H), 7.71 - 7.63 (m, 1 H), 7.62 - 7.52 (m, 2 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H).

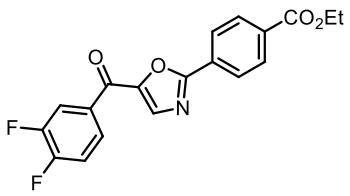
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 181.4, 165.7, 163.7, 149.4, 137.5, 136.7, 133.4, 133.3, 130.1, 129.8, 129.0, 128.8, 127.4, 61.4, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3131, 3066, 2980, 1708, 1643, 1598, 1577, 1526, 1480, 1448, 1413, 1356, 1303, 1269, 1248, 1224, 1179, 1174, 1160, 1104, 1075, 1016, 996, 972, 956, 947, 886, 861, 794, 781, 734, 718, 694, 678.

MS (EI, 70 eV): *m/z* (%) = 322 (9), 321 (50), 276 (9). 217 (11), 216 (100), 189 (7), 188 (61), 161 (3), 160 (29), 143 (10), 133 (10), 115 (17), 105 (15), 88 (8), 77 (27).

HR-MS (EI, 70 eV): [$C_{19}H_{15}O_4N_1$], calcd.: 321.1001; found: 321.1003.

Ethyl 4-(5-(3,4-difluorobenzoyl)oxazol-2-yl)benzoate (138h)



Ethyl 4-(5-(3,4-difluorobenzoyl)oxazol-2-yl)benzoate (**138h**) was prepared according to **TP-1** from ethyl 4-(oxazol-2-yl)benzoate (**137a**, 261 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 0.5 h, then $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and 3,4-difluorobenzoyl chloride (177 mg, 1.0 mmol) were added. The reaction mixture was stirred at 25 °C for 1 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2:*i*-hexane 5:1) yielding **138h** (311 mg, 87%) as a light yellow solid.

m.p.: 145 – 148 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.30 – 8.16 (m, 4 H), 7.95 (s, 1 H), 7.94 – 7.83 (m, 2 H), 7.43 – 7.31 (m, 1 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 1.43 (q, *J* = 7.2 Hz, 3 H).

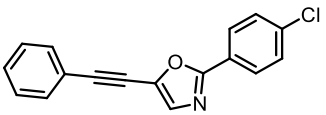
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 178.5, 165.6, 163.9, 155.6 (d, *J* = 12.8 Hz), 152.2 (dd, *J* = 12.9, 2.6 Hz), 148.8 (d, *J* = 12.5 Hz), 137.7, 133.5, 133.4 (d, *J* = 4.9 Hz), 130.2, 129.6, 127.4, 126.1 (dd, *J* = 7.5, 3.7 Hz), 118.6 (dd, *J* = 18.6, 1.8 Hz), 117.9 (d, *J* = 18.0 Hz), 61.5, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3123, 2986, 1719, 1704, 1652, 1646, 1530, 1514, 1481, 1415, 1314, 1285, 1277, 1240, 1164, 1128, 1112, 1106, 1017, 957, 859, 841, 825, 779, 753, 724.

MS (EI, 70 eV): *m/z* (%) = 359 (2), 358 (12), 357 (58), 312 (14), 216 (100), 189 (8), 188 (63), 160 (23), 133 (10),, 115 (12).

HR-MS (EI, 70 eV): [$C_{19}H_{13}F_2NO_4$], calcd.: 357.0813; found: 357.0806.

2-(4-Chlorophenyl)-5-(phenylethynyl)oxazole (138i)



2-(4-chlorophenyl)-5-(phenylethynyl)oxazole (**138i**) was prepared according to **TP-1** from 2-(4-chlorophenyl)oxazole (**137b**, 216 mg, 1.2 mmol) and TMPZnCl·LiCl (**36**, 1.75 mL, 1.4 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 0.5 h, then iodine (355 mg, 1.4 mmol) dissolved in dry THF (1 mL) was added dropwise at 0 °C and the resulting mixture was stirred for 1 h at 25 °C. To the solution of *in situ* generated 2-(4-chlorophenyl)-5-iodooxazole, CuI (8 mg, 0.04 mmol), $Pd(dba)_2$ (17 mg, 0.03 mmol), P(*o*-furyl) (14 mg, 0.06 mmol), TEA (2 mL) and phenylacetylene (103 mg, 1.0 mmol) were successively added. The reaction mixture was stirred at 25 °C for 1 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*-hexane:diethyl ether 10:1) yielding **138i** (224 mg, 80%) as a colorless solid.

m.p.: 103 – 105 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.05 – 7.99 (m, 2 H), 7.59 – 7.53 (m, 2 H), 7.48 – 7.43 (m, 2 H), 7.41 (s, 1 H), 7.41 – 7.38 (m, 3 H).

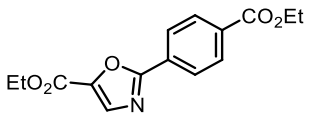
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 160.9, 137.0, 135.0, 132.6, 131.5, 129.3, 129.2, 128.5, 127.9, 125.4, 121.5, 98.0, 75.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920, 2213, 1692, 1678, 1603, 1596, 1582, 1564, 1534, 1486, 1475, 1451, 1444, 1403, 1380, 1306, 1280, 1246, 1179, 1162, 1136, 1111, 1092, 1070, 1026, 1012, 998, 977, 916, 886, 850, 836, 815, 812, 755, 734, 687.

MS (EI, 70 eV): *m/z* (%) = 282 (6), 281 (30), 280 (17), 279 (99), 226 (5), 225 (29) , 224 (15), 223 (100), 222 (6), 190 (7), 189 (46), 140 (6), 139 (5), 129 (5), 126 (6), 114 (7), 113 (7), 111 (8), 88 (9).

HR-MS (EI, 70 eV): [$C_{17}H_{10}O_1N_1Cl_1$], calcd.: 279.0451; found: 279.0445.

Ethyl 2-(4-(ethoxycarbonyl)phenyl)oxazole-5-carboxylate (138j)



Ethyl 2-(4-(ethoxycarbonyl)phenyl)oxazole-5-carboxylate (**138j**) was prepared according to **TP-2** from ethyl 4-(oxazol-2-yl)benzoate (**137a**, 261 mg, 1.2 mmol) and TMPMgCl·LiCl (**35**, 1.26 mL, 1.4 mmol, 1.11 M solution in THF). Ethyl cyanoformate (99 mg, 1.0 mmol) was added at -40 °C to the freshly prepared magnesium reagent. The reaction mixture was allowed to warm to 25 °C, stirred for 1 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/diethyl ether 90:1) to yield **138j** (269 mg, 93%) as colorless crystals.

m.p.: 85 – 87 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.25 – 8.13 (m, 4 H), 7.87 (s, 1 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H), 1.42 (t, *J* = 7.1 Hz, 3 H).

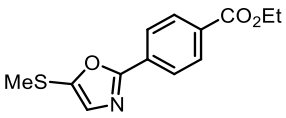
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 165.7, 163.1, 157.7, 142.9, 135.4, 133.0, 130.1, 130.0, 127.1, 61.6, 61.4, 14.3, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3130, 2978, 2921, 2167, 1725, 1703, 1535, 1414, 1369, 1301, 1293, 1270, 1254, 1184, 1155, 1147, 1109, 1097, 1072, 1026, 1017, 981, 941, 897, 872, 863, 851, 826, 808, 781, 765, 721, 692, 681, 672, 666.

MS (EI, 70 eV): *m/z* (%) = 290 (18), 289 (100), 261 (18), 244 (52), 233 (14), 217 (19), 216 (92), 189 (13), 188 (87), 160 (29), 133 (13), 115 (14), 88 (9).

HR-MS (EI, 70 eV): [$C_{15}H_{15}NO_5$], calcd.: 289.0950; found: 289.0944.

Ethyl 4-(5-(methylthio)oxazol-2-yl)benzoate (138k)



Ethyl 4-(5-(methylthio)oxazol-2-yl)benzoate (**138k**) was prepared according to **TP-2** from ethyl 4-(oxazol-2-yl)benzoate (**137a**, 261 mg, 1.2 mmol) and TMPMgCl·LiCl (**35**, 1.26 mL, 1.4 mmol, 1.11 M solution in THF). Then S-methyl methanethiolsulfonate (126 mg, 1.0 mmol) was added at -40 °C to the freshly prepared magnesium reagent. The reaction mixture was allowed to warm to 25 °C, stirred for 1 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*-hexane:ethyl acetate 3:2) to yield **138k** (190 mg, 72%) as a light yellow solid.

m.p.: 69 – 71 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.23 – 7.87 (m, 4 H), 7.22 (s, 1 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 2.50 (s, 3 H), 1.42 (t, *J* = 7.1 Hz, 3 H).

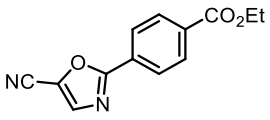
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 165.9, 162.8, 146.9, 132.0, 131.8, 130.8, 130.0, 126.1, 61.3, 18.8, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2993, 2976, 2928, 1710, 1680, 1612, 1581, 1547, 1455, 1409, 1367, 1306, 1291, 1269, 1247, 1241, 1174, 1167, 1138, 1103, 1092, 1063, 1013, 1004, 978, 962, 933, 870, 861, 841, 789, 777, 721, 691.

MS (EI, 70 eV): *m/z* (%) = 264 (9), 263 (52), 218 (18), 216 (23), 194 (12), 193 (100), 189 (9), 188 (59), 165 (8), 163 (8), 160 (26), 152 (11), 133 (10), 115 (13), 88 (8).

HR-MS (EI, 70 eV): [$C_{13}H_{13}NO_3S$], calcd.: 263.0616; found: 263.0613.

Ethyl 4-(5-cyanooxazol-2-yl)benzoate (138l)



Ethyl 4-(5-cyanooxazol-2-yl)benzoate (**138l**) was prepared according to **TP-2** from ethyl 4-(oxazol-2-yl)benzoate (**137a**, 261 mg, 1.2 mmol) and TMPMgCl·LiCl (**35**, 1.26 mL, 1.4 mmol, 1.11 M solution in THF). Then *p*-toluenesulfonyl cyanide (181 mg, 1.0 mmol) was added at -40 °C to the freshly prepared magnesium reagent. The reaction mixture was allowed to warm to 25 °C, stirred for 1 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic

phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*-hexane:diethyl ether 5:1) to yield **138l** (216 mg, 89%) as colorless crystals.

m.p.: 94 – 96 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): 8.25 – 8.12 (m, 4 H), 7.85 (s, 1 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H).

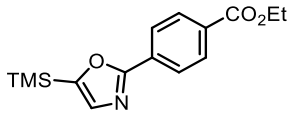
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 165.5, 163.8, 139.1, 133.7, 130.2, 129.0, 127.3, 124.8, 109.2, 61.5, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3135, 2987, 2940, 2234, 1720, 1711, 1585, 1488, 1409, 1293, 1274, 1247, 1173, 1135, 1126, 1106, 1088, 1017, 984, 969, 894, 864, 856, 778, 721, 688.

MS (EI, 70 eV): *m/z* (%) = 243 (4), 242 (32), 215 (6), 214 (43), 198 (17), 197 (100), 170 (7), 169 (21), 149 (13), 141 (11), 114 (16), 71 (14), 69 (11), 57 (23), 55 (11), 45 (11), 43 (16).

HR-MS (EI, 70 eV): [$C_{13}H_{10}N_2O_3$], calcd.: 242.0691; found: 242.0680.

Ethyl 4-(5-(trimethylsilyl)oxazol-2-yl)benzoate (138m)



Ethyl 4-(5-(trimethylsilyl)oxazol-2-yl)benzoate (**138m**) is prepared according to **TP-2** from ethyl 4-(oxazol-2-yl)benzoate (**137a**, 261 mg, 1.2 mmol) and TMPMgCl·LiCl (**35**, 1.26 mL, 1.4 mmol, 1.11 M solution in THF). Then chlorotrimethylsilane (109 mg, 1.0 mmol) is added at -40 °C to the freshly prepared magnesium reagent. The reaction mixture is allowed to warm to 25 °C, stirred for 1 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product is purified by flash column chromatography on silica gel (CH_2Cl_2/diethyl ether 99:1) to yield **138m** (249 mg, 86%) as a colorless solid.

m.p.: 69 – 71 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.14 (s, 4 H), 7.36 (s, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 0.36 (s, 9 H).

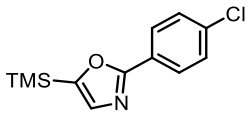
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 166.0, 164.4, 156.4, 137.5, 131.7, 131.4, 130.0, 126.4, 61.2, 14.3, -1.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 2902, 1706, 1668, 1612, 1581, 1550, 1475, 1411, 1365, 1307, 1290, 1271, 1247, 1229, 1175, 1137, 1121, 1105, 1090, 1062, 1016, 959, 937, 867, 837, 777, 763, 756, 721, 690, 662.

MS (EI, 70 eV): *m/z* (%) = 290 (17), 289 (90), 275 (7), 274 (39), 248 (28), 244 (14), 177 (9), 130 (13), 100 (8), 99 (100), 73 (68), 45 (8), 43 (7).

HR-MS (EI, 70 eV): [$C_{15}H_{19}NO_3Si$], calcd.: 289.1134; found: 289.1130.

2-(4-Chlorophenyl)-5-(trimethylsilyl)oxazole (138n)



2-(4-Chlorophenyl)-5-(trimethylsilyl)oxazole (**138n**) was prepared according to **TP-2** from 2-(4-chlorophenyl)oxazole (**137b**, 216 mg, 1.2 mmol) and TMPMgCl·LiCl (**35**, 1.26 mL, 1.4 mmol, 1.11 M solution in THF). Then chlorotrimethylsilane (109 mg, 1.0 mmol) was added at -40 °C to the freshly prepared magnesium reagent. The reaction mixture was allowed to warm to 25 °C, stirred for 1 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2) to yield **138n** (206 mg, 82%) as a colorless solid.

m.p.: 47 – 49 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.00 – 7.96 (m, 2 H), 7.45 – 7.38 (m, 2 H), 7.28 (s, 1 H), 0.32 (s, 9 H).

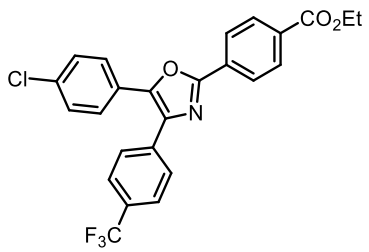
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 164.4, 155.7, 137.3, 136.2, 129.0, 127.8, 126.3, -1.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3124, 3069, 2953, 2881, 1915, 1658, 1604, 1595, 1582, 1552, 1471, 1453, 1404, 1314, 1272, 1250, 1226, 1135, 1109, 1090, 1063, 1012, 960, 951, 939, 832, 756, 736, 696, 667, 662, 656.

MS (EI, 70 eV): *m/z* (%) = 253 (20), 251 (68), 238 (15), 236 (42), 210 (21), 149 (19), 139 (12), 99 (100), 97 (13), 83 (14), 81 (12), 73 (80), 71 (17), 70 (10), 69 (18), 67 (10), 59 (10), 57 (29), 55 (25), 45 (11), 44 (46), 43 (22), 41 (28).

HR-MS (EI, 70 eV): [$C_{12}H_{14}ClNOSi$], calcd.: 251.0533; found: 251.0530.

Ethyl 4-(5-(4-chlorophenyl)-4-(4-(trifluoromethyl)phenyl)oxazol-2-yl)benzoate (139a)



Ethyl 4-(5-(4-chlorophenyl)-4-(4-(trifluoromethyl)phenyl)oxazol-2-yl)benzoate (**139a**) was prepared according to **TP-1** from ethyl 4-(5-(4-chlorophenyl)oxazol-2-yl)benzoate (**138a**, 197 mg, 0.6 mmol) and TMPZnCl·LiCl (**36**, 0.88 mL, 0.7 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 5 h, then $Pd(dba)_2$ (9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7 mg, 0.03 mmol) and 1-iodo-4-(trifluoromethyl)-benzene (136 mg, 0.5 mmol) were added. The reaction mixture was stirred at 50 °C for 8 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2:*i*-hexane 1:2) yielding **139a** (193 mg, 82%) as a colorless solid.

m.p.: 129 – 132 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.27 – 8.10 (m, 4 H), 7.91 – 7.75 (m, 2 H), 7.72 – 7.52 (m, 4 H), 7.47 – 7.35 (m, 2 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 1.43 (t, *J* = 7.1 Hz, 3 H).

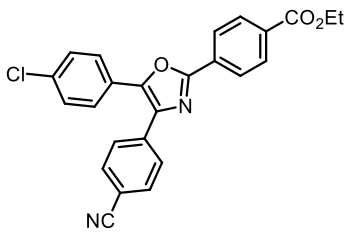
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 165.9, 159.7, 146.2, 136.1, 135.6, 135.4, 131.4 (d, *J* = 126.6 Hz), 130.4 (d, *J* = 32.6 Hz), 130.1, 129.3, 128.2 (d, *J* = 4.3 Hz), 126.6, 126.3, 125.7 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 286.1 Hz), 122.2, 118.6, 61.3, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2983, 2919, 2851, 1704, 1614, 1590, 1484, 1408, 1369, 1323, 1309, 1276, 1241, 1169, 1115, 1104, 1093, 1066, 1016, 1011, 966, 882, 863, 852, 842, 832, 787, 776, 765, 746, 735, 725, 715, 699, 693, 677, 667, 662.

MS (EI, 70 eV): *m/z* (%) = 474 (11), 473 (38), 472 (34), 471 (100), 443 (5), 426 (10), 370 (9), 272 (7), 233 (26), 232 (5), 201 (7), 209 (7), 199 (18), 165 (6), 164 (5), 163 (5), 138 (5).

HR-MS (EI, 70 eV): [$C_{25}H_{17}ClF_3NO_3$], calcd.: 471.0849; found: 471.0844.

Ethyl 4-(5-(4-chlorophenyl)-4-(4-cyanophenyl)oxazol-2-yl)benzoate (139b)



Ethyl 4-(5-(4-chlorophenyl)-4-(4-cyanophenyl)oxazol-2-yl)benzoate (**139b**) was prepared according to **TP-1** from ethyl 4-(5-(4-chlorophenyl)oxazol-2-yl)benzoate (**138a**, 197 mg, 0.6 mmol) and TMPZnCl·LiCl (**36**, 0.88 mL, 0.7 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 5 h, then$Pd(dba)_2$ (9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7 mg, 0.03 mmol) and 4-iodobenzonitrile (115 mg, 0.5 mmol) were added. The reaction mixture was stirred at 50 °C for 6 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2:*i*-hexane 2:1) yielding **139b** (157 mg, 73%) as a colorless solid.

m.p.: 132 – 134 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.22 – 8.15 (m, 4 H), 7.88 – 7.82 (m, 2 H), 7.73 – 7.67 (m, 2 H), 7.63 – 7.56 (m, 2 H), 7.47 – 7.41 (m, 2 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 1.44 (t, *J* = 7.1 Hz, 3 H).

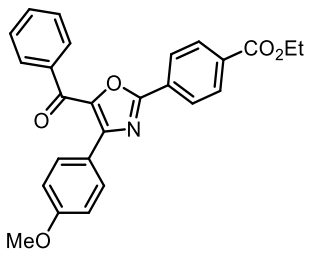
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 165.8, 159.9, 146.7, 136.5, 135.7, 135.6, 132.5, 132.3, 130.4, 130.1, 129.4, 128.4, 128.3, 126.5, 126.3, 118.6, 112.0, 61.4, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3101, 2961, 2913, 2215, 1707, 1637, 1601, 1396, 1299, 1259, 1237, 1162, 1124, 1133, 1091, 1071, 1045, 1007, 957, 933, 918, 881, 843, 832, 767, 714, 673.

MS (EI, 70 eV): *m/z* (%) = 431 (11), 430 (38), 429 (30), 428 (100), 383 (11), 327 (12), 272 (9), 209 (8), 199 (16), 191 (7), 190 (41), 111 (6).

HR-MS (EI, 70 eV): [$C_{25}H_{17}ClN_2O_3$], calcd.: 428.0928; found: 428.0913.

Ethyl 4-(5-benzoyl-4-(4-methoxyphenyl)oxazol-2-yl)benzoate (139c)



Ethyl 4-(5-benzoyl-4-(4-methoxyphenyl)oxazol-2-yl)benzoate (**139c**) was prepared according to **TP-1** from ethyl 4-(5-benzoyloxazol-2-yl)benzoate (**138g**, 193 mg, 0.6 mmol) and TMPZnCl·LiCl (**36**, 0.88 mL, 0.7 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 3 h, then $Pd(dba)_2$ (9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7 mg, 0.03 mmol) and 4-iodoanisole (117 mg, 0.5 mmol) were added. The reaction mixture was stirred at 50 °C for 6 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*-hexane:diethyl ether 4:1) yielding **139c** (162 mg, 76%) as a colorless solid.

m.p.: 135 – 137 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.25 - 8.20 (m, 2 H), 8.19 - 8.13 (m, 4 H), 8.01 - 7.92 (m, 2 H), 7.64 - 7.56 (m, 1 H), 7.49 (t, *J* = 7.60 Hz, 2 H), 7.00 - 6.92 (m, 2 H), 4.42 (q, *J* = 7.19 Hz, 2 H) 3.86 (s, 3 H) 1.42 (t, *J* = 7.19 Hz, 3 H).

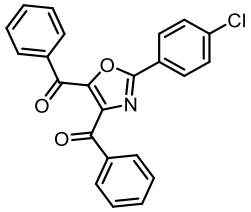
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 183.1, 165.7, 161.1, 160.6, 148.9, 143.2, 137.7, 133.0, 132.8, 131.0, 130.1, 130.0, 129.5, 128.4, 127.2, 122.8, 113.7, 61.4, 55.3, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052, 3006, 2969, 2927, 2842, 1713, 1643, 1581, 1535, 1501, 1487, 1467, 1444, 1412, 1363, 1317, 1303, 1289, 1266, 1255, 1231, 1182, 1174, 1160, 1114, 1102, 1027, 1015, 1003, 958, 895, 858, 835, 809, 798, 794, 780, 749, 725, 717, 700, 692, 682, 666.

MS (EI, 70 eV): *m/z* (%) = 429 (6), 428 (22), 427 (100), 426 (7), 382 (4), 148 (6), 147 (58), 119 (28), 105 (15), 77 (10).

HR-MS (EI, 70 eV): [$C_{26}H_{21}O_5N_1$], calcd.: 427.1420; found: 427.1415.

(2-(4-Chlorophenyl)oxazole-4,5-diyl)bis(phenylmethanone) (139d)



(2-(4-Chlorophenyl)oxazole-4,5-diyl)bis(phenylmethanone) (**139d**) was prepared according to **TP-1** from (2-(4-chlorophenyl)oxazol-5-yl)(phenyl)methanone (**138e**, 170 mg, 0.6 mmol) and TMPZnCl·LiCl (**36**, 0.88 mL, 0.7 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 3 h and was then allowed to cool to 25 °C. $Pd(PPh_3)_4$ (28 mg, 0.02 mmol) and benzoyl chloride (141 mg, 0.5 mmol) were added, the reaction mixture was stirred at 25 °C for 3 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column

chromatography on silica gel (*i*-hexane:diethyl ether 4:1) yielding **139d** (151 mg, 78%) as a colorless solid.

m.p.: 137 – 139 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.17 - 8.12 (m, 2 H), 7.98 - 7.93 (m, 2 H), 7.91 - 7.87 (m, 2 H), 7.61 - 7.54 (m, 2 H), 7.54 - 7.48 (m, 2 H), 7.46 - 7.40 (m, 4 H).

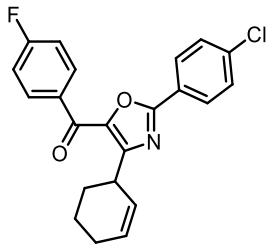
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 187.9, 182.0, 161.7, 148.0, 144.6, 138.6, 136.2, 136.1, 133.9, 133.8, 129.9, 129.5, 129.3, 128.8, 128.7, 128.6, 124.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3088, 3063, 2958, 1912, 1719, 1681, 1668, 1633, 1595, 1579, 1548, 1536, 1474, 1448, 1405, 1355, 1303, 1279, 1267, 1243, 1216, 1187, 1172, 1154, 1111, 1088, 1071, 1028, 1010, 1000, 954, 944, 894, 882, 849, 828, 797, 751, 742, 734, 709, 694, 684, 675, 664.

MS (EI, 70 eV): *m/z* (%) = 387 (5), 285 (2), 284 (12), 283 (5), 282 (40), 178 (6), 106 (6), 105 (100), 78 (5), 77 (46), 51 (6), 45 (3), 44 (7).

HR-MS (EI, 70 eV): [$C_{23}H_{14}O_3N_1Cl_1$], calcd.: 387.0662; found: 387.0659.

(2-(4-Chlorophenyl)-4-(cyclohex-2-en-1-yl)oxazol-5-yl)(4-fluorophenyl)methanone (139e)



(2-(4-Chlorophenyl)-4-(cyclohex-2-en-1-yl)oxazol-5-yl)(4-fluorophenyl)methanone (**139e**) was prepared according to **TP-1** from (2-(4-chlorophenyl)oxazol-5-yl)(4-fluorophenyl)methanone (**138f**, 0.6 mmol, 181 mg) and TMPZnCl·LiCl (**36**, 0.88 mL, 0.7 mmol, 0.8 M solution in THF) at 50 °C. The reaction was stirred for 3 h and was then allowed to cool to 25 °C. The freshly prepared zinc reagent was submitted to an allylation reaction by adding CuCN·2LiCl (0.7 mmol, 0.7 mL, 1 M solution in THF). The reaction mixture was stirred for 20 min at 25 °C and then 3-bromocyclohexene (81 mg, 0.5 mmol) was added. The reaction mixture was stirred for 2 h and was then quenched with aq. NH_4Cl/NH_3 (10:1) solution and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*-hexane:diethyl ether 10:1) yielding **139e** (141 mg, 74%) as a colorless solid.

m.p.: 128 – 130 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.17 - 8.07 (m, 2 H), 8.07 - 8.01 (m, 2 H), 7.50 - 7.42 (m, 2 H), 7.28 - 7.17 (m, 2 H), 6.00 - 5.86 (m, 1 H), 5.80 - 5.59 (m, 1 H), 4.36 - 4.07 (m, 1 H) 2.36 - 1.62 (m, 6 H).

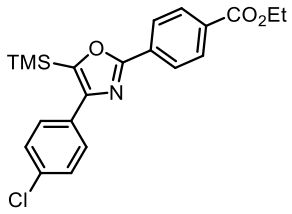
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 181.0, 165.6 (d, *J* = 255.0 Hz), 161.0, 156.7, 144.0, 137.9, 133.7 (d, *J* = 2.9 Hz), 132.0 (d, *J* = 9.3 Hz), 129.3, 128.9, 128.7, 127.3, 125.0, 115.7 (d, *J* = 22.0 Hz), 34.3, 28.2, 24.7, 21.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3075, 3025, 2927, 2836, 1638, 1597, 1578, 1552, 1534, 1504, 1475, 1409, 1362, 1312, 1296, 1286, 1250, 1233, 1178, 1173, 1158, 1140, 1118, 1106, 1092, 1013, 986, 917, 900, 876, 849, 834, 810, 792, 786, 762, 744, 736, 725, 708, 662, 652.

MS (EI, 70 eV): *m/z* (%) = 384 (8), 383 (33), 382 (24), 381 (100), 380 (9), 353 (9), 352 (10), 258 (7), 244 (7), 242 (12), 230 (7), 216 (7), 215 (7), 188 (6), 140 (6), 139 (19), 123 (62), 121 (20), 95 (23), 91 (11), 77 (15).

HR-MS (EI, 70 eV): [$C_{22}H_{17}O_2N_2Cl_1F_1$], calcd.: 381.0932; found: 381.0929.

Ethyl 4-(4-(4-chlorophenyl)-5-(trimethylsilyl)oxazol-2-yl)benzoate (139f)



Ethyl 4-(4-(4-chlorophenyl)-5-(trimethylsilyl)oxazol-2-yl)benzoate (**139f**) was prepared according to **TP-1** from ethyl 4-(5-(trimethylsilyl)oxazol-2-yl)benzoate (**138m**, 174 mg, 0.6 mmol) and TMPZnCl·LiCl (**36**, 0.88 mL, 0.7 mmol, 0.8 m solution in THF) at 50 °C. The reaction was stirred for 5 h, then $Pd(dba)_2$ (9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7 mg, 0.03 mmol) and 1-chloro-4-iodobenzene (238 mg, 0.5 mmol) were added. The reaction mixture was stirred at 50 °C for 6 h and was then quenched with sat. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2) yielding **139f** (168 mg, 84%) as a colorless solid.

m.p.: 114 – 116 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.21 - 8.12 (m, 4 H), 7.64 - 7.58 (m, 2 H), 7.45 - 7.38 (m, 2 H), 4.42 (q, *J* = 7.0 Hz, 2 H), 1.23 - 1.63 (t, *J* = 7.0 Hz, 3 H), 0.37 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 166.0, 163.4, 151.2, 150.5, 134.2, 131.8, 131.4, 131.2, 130.0, 129.4, 128.6, 126.4, 61.2, 14.3, -1.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3114, 2948, 2896, 1907, 1680, 1594, 1571, 1553, 1436, 1459, 1403, 1316, 1286, 1263, 1212, 1155, 1117, 1090, 1058, 1010, 958, 942, 938, 831, 776, 752, 736, 694, 683, 660, 652.

MS (EI, 70 eV): *m/z* (%) = 402 (10), 401 (42), 400 (28), 399 (100), 386 (23), 385 (14), 384 (55), 224 (11), 211 (17), 209 (47), 177 (12), 149 (11), 73 (42).

HR-MS (EI, 70 eV): [$C_{21}H_{22}O_3N_1Cl_1Si_1$], calcd.: 399.1057; found: 399.1056.

3 Zincation of 4,4-Dimethyloxazoline Using TMPZnCl·LiCl. A New Preparation of 2-Aryloxazolines

3.1 Typical Procedures

Typical procedure for the zincation of 4,4-dimethyloxazoline (144) using TMPZnCl·LiCl (36) (TP-3):

A dry and argon-flushed *Schlenk* flask was charged with a solution of 4,4-dimethyloxazoline (**144**, 1.0 equiv) in dry THF (1.0 M solution). The solution was cooled to 0 °C and TMPZnCl·LiCl (**36**, 1.2 equiv) was added dropwise. The reaction was stirred for 1 h at 0 °C to yield the corresponding 4,4-dimethyloxazolinylzinc reagent (**146**). The completion of metalation was checked by GC analysis of reaction aliquots quenched with a solution of 3-bromoyclohexene and CuCN·2LiCl in dry THF.

Typical procedure for the *ortho*-metalation of 2-aryloxazolines using TMPMgCl·LiCl (35) (TP-4):

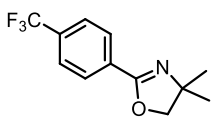
A dry and argon-flushed *Schlenk* flask was charged with a solution of the oxazoline derivative of type **147** (1.0 equiv) in dry THF (1.0 M solution). The solution was cooled to 0 °C and TMPMgCl·LiCl (**35**, 1.2 equiv) was added dropwise. The reaction was stirred for 1 h at 0 °C to yield the corresponding magnesium reagent. The completion of metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Typical procedure for the *ortho'*-metalation of functionalized 2-aryloxazolines using TMP_2Mg·2LiCl (42) (TP-5):

A dry and argon-flushed *Schlenk*-flask was charged with a solution of the oxazoline derivative of type **148** (1.0 equiv) in dry THF (1.0 M solution). The solution was cooled to -20 °C and TMP_2Mg·2LiCl (**42**, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 1.5 h at -20 °C to afford the corresponding magnesium reagent. The completion of metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

3.2 Zincation of 4,4-Dimethyloxazoline and Subsequent Reaction with Electrophiles

4,4-Dimethyl-2-(4-(trifluoromethyl)phenyl)oxazoline (147a)



Preparation from 1-iodo-4-(trifluoromethyl)benzene:

4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3** and was then subjected to a Pd-catalyzed cross-coupling reaction by addition of 1-iodo-4-(trifluoromethyl)benzene (272 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 3 mol%) and SPhos (25 mg, 6 mol%). The reaction was stirred for 4 h at 50 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 5:1) to afford **147a** (192 mg, 0.79 mmol, 79%) as colorless crystals.

Preparation from 1-bromo-4-(trifluoromethyl)benzene:

4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3** and is then subjected to a Pd-catalyzed cross-coupling reaction by addition of 1-bromo-4-(trifluoromethyl)benzene (225 mg, 1.0 mmol), $Pd(dba)_2$ (17 mg, 3 mol%) and SPhos (25 mg, 6 mol%). The reaction was stirred for 3 h at 50 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 5:1) to afford **147a** (187 mg, 0.77 mmol, 77%) as colorless crystals.

m.p.: 34 – 36 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.97 - 8.16 (d, *J* = 8.2 Hz, 2 H), 7.58 - 7.74 (d, *J* = 8.2 Hz, 2 H), 4.16 (s, 2 H), 1.41 (s, 6 H).

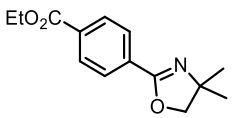
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.9, 132.8 (q, *J* = 33.0 Hz), 131.4, 128.6, 125.2 (q, *J* = 4.2 Hz), 123.8 (q, *J* = 272.1 Hz), 79.3, 67.9, 28.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2970, 2930, 1651, 1620, 1581, 1521, 1463, 1412, 1386, 1367, 1355, 1323, 1298, 1249, 1216, 1166, 1128, 1107, 1069, 1016, 989, 963, 921, 870, 852, 818, 774, 754, 687, 664.

MS (EI, 70 eV): *m/z* (%) = 243 (3), 242 (2), 230 (4), 229 (12), 228 (100), 224 (6), 214 (3), 200 (22), 173 (19), 172 (62), 171 (4), 121 (3), 95 (3), 57 (3), 57 (7), 42 (5). 41 (6).

HR-MS (EI, 70 eV): [$C_{12}H_{12}F_3NO$], calc.: 243.0871; found: 243.0868.

Ethyl 4-(4,4-dimethyloxazolinyl)benzoate (147b)



Preparation from ethyl 4-iodobenzoate:

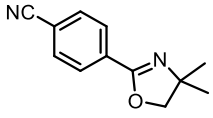
4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3** and was then subjected to a Pd-catalyzed cross-coupling reaction by addition of ethyl 4-iodobenzoate (276 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 3 mol%) and SPhos (25 mg, 6 mol%). The reaction was stirred for 3 h at 50 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:diethyl ether 2:1) to afford **147b** (193 mg, 0.78 mmol, 79%) as a yellow oil.

Preparation from ethyl 4-bromobenzoate:

4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3** and was then subjected to a Pd-catalyzed cross-coupling reaction by addition of ethyl 4-bromobenzoate (229 mg, 1.0 mmol), $Pd(dba)_2$ (17 mg, 3 mol%) and SPhos (25 mg, 6 mol%). The reaction was stirred for 5 h at 50 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:diethyl ether 2:1) to afford **147b** (228 mg, 0.92 mmol, 77%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.04 - 8.13 (m, 2 H), 7.97 - 8.04 (m, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 4.14 (s, 2 H), 1.32 - 1.50 (m, 9 H).
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 166.0, 161.4, 132.7, 131.9, 129.4, 128.2, 79.3, 67.8, 61.2, 28.3, 14.3.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2970, 2930, 2361, 2340, 1716, 1648, 1613, 1463, 1409, 1365, 1354, 1310, 1299, 1269, 1215, 1190, 1173, 1102, 1064, 1018, 990, 965, 922, 867, 849, 780, 710, 678.
MS (EI, 70 eV): *m/z* (%) = 247 (3), 246 (1), 233 (14), 232 (100), 217 (13), 204 (11), 202 (9), 176 (21), 159 (4), 148 (14), 130 (5), 103 (5), 102 (4), 76 (4).
HR-MS (EI, 70 eV): [$C_{14}H_{17}NO_3$], calc.: 247.1208; found: 247.1203

4-(4,4-Dimethyloxazolinyl)benzonitrile (147c)



Preparation from 4-iodobenzonitrile:

4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3** and was then subjected to a Pd-catalyzed cross-coupling reaction by addition of 4-iodobenzonitrile (229 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 3 mol%) and SPhos (25 mg, 6 mol%). The reaction was stirred for 5 h at 50 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:diethyl ether 5:1) to afford **147c** (160 mg, 0.80 mmol, 80%) as a white solid.

Preparation from 4-bromobenzonitrile:

4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3** and was then subjected to a Pd-catalyzed cross-coupling reaction by addition of 4-bromobenzonitrile (182 mg, 1.0 mmol), $Pd(dba)_2$ (17 mg, 3 mol%) and SPhos (25 mg, 6 mol%). The reaction was stirred for 2 h at 50 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:diethyl ether 5:1) to afford **147c** (174 mg, 0.87 mmol, 87%) as a white solid.

m.p.: 107 – 108 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.96 - 8.14 (d, *J* = 8.3 Hz, 2 H), 7.60 - 7.81 (d, *J* = 8.3 Hz, 2 H), 4.15 (s, 2 H), 1.39 (s, 6 H).

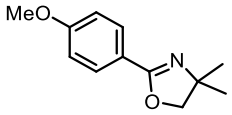
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 160.5, 132.2, 132.0, 128.8, 118.2, 114.6, 79.5, 68.0, 28.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2972, 2906, 2229, 1930, 1641, 1610, 1564, 1502, 1462, 1408, 1383, 1357, 1320, 1310, 1292, 1250, 1218, 1186, 1111, 1071, 1017, 952, 924, 872, 845, 831, 820, 741, 676.

MS (EI, 70 eV): *m/z* (%) = 204 (3), 200 (3), 199 (2), 186 (14), 185 (100), 170 (28), 157 (21), 130 (7), 129 (59), 128 (5), 102 (21), 75 (6), 74 (9), 59 (13), 57 (9), 45 (9), 44 (14), 43 (5), 42 (11), 41 (15).

HR-MS (EI, 70 eV): [$C_{12}H_{12}N_2O$], calc.: 200.0950; found: 200.0942.

2-(4-Methoxyphenyl)-4,4-dimethyloxazoline (147d)



4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3** and was then subjected to a Pd-catalyzed cross-coupling

reaction by addition of 4-bromoanisole (187 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 3 mol%) and SPhos (25 mg, 6 mol%). The reaction was stirred for 3 h at 50 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:diethyl ether 4:1) to afford **147d** (168 mg, 0.82 mmol, 82%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.84 - 7.91 (m, 2 H), 6.86 - 6.94 (m, 2 H), 4.08 (s, 2 H), 3.84 (s, 3 H), 1.37 (s, 6 H).

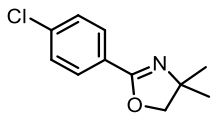
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 161.9, 161.8, 129.8, 120.5, 113.5, 79.0, 67.4, 55.3, 28.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2975, 1733, 1701, 1684, 1602, 1575, 1468, 1458, 1447, 1402, 1380, 1366, 1307, 1296, 1276, 1256, 1216, 1189, 1154, 1059, 1034, 1029, 992, 968, 927, 914, 901, 806, 794, 778, 742, 715, 691, 662.

MS (EI, 70 eV): *m/z* (%) = 205 (13), 191 (13), 190 (100), 175 (11), 162 (29), 135 (9), 134 (36), 133 (13), 119 (5), 103 (6), 97 (6), 92 (6), 91 (8), 90 (7), 77 (5), 69 (5), 57 (5), 40 (5).

HR-MS (EI, 70 eV): [$C_{12}H_{15}NO_2$], calc.: 205.1103; found: 205.1102.

Synthesis of 2-(4-chlorophenyl)-4,4-dimethyloxazoline (147e)



4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3** and was then subjected to a Pd-catalyzed cross-coupling reaction by addition of 4-bromo-1-chlorobenzene (191 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 3 mol%) and SPhos (25 mg, 6 mol%). The reaction was stirred for 2 h at 50 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:diethyl ether 9:1) to afford **147e** (149 mg, 0.71 mmol, 71%) as a white solid.

m.p.: 79 – 81 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.83 - 7.97 (m, 2 H), 7.31 - 7.53 (m, 2 H), 4.11 (s, 2 H), 1.38 (s, 6 H).

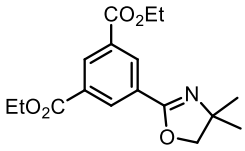
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.2, 137.3, 129.5, 128.5, 126.5, 79.2, 67.7, 28.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2968, 2929, 1650, 1599, 1492, 1463, 1404, 1352, 1312, 1297, 1246, 1214, 1186, 1173, 1090, 1062, 1015, 989, 963, 920, 870, 839, 820, 731, 678.

MS (EI, 70 eV): *m/z* (%) = 211 (2), 209 (7), 196 (30), 195 (10), 194 (100), 181 (5), 179 (16), 168 (6), 166 (18), 142 (14), 140 (15), 139 (11), 138 (50), 111 (12), 102 (9), 75 (12), 71 (9), 57 (5), 50 (5), 42 (6), 41 (12).

HR-MS (EI, 70 eV): [$C_{11}H_{12}ClNO$], calc.: 209.0607; found: 209.0596.

Diethyl 5-(4,4-dimethyloxazolinyl)isophthalate (147f)



4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3** and was then subjected to a Pd-catalyzed cross-coupling reaction by addition of diethyl 5-bromoisophthalate (301 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 3 mol%) and SPhos (25 mg, 6 mol%). The reaction was stirred for 8 h at 50 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:diethyl ether 2:1) to afford **147f** (217 mg, 0.68 mmol, 68%) as a yellowish solid.

m.p.: 83 – 85 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.69 - 8.85 (m, 3 H), 4.43 (q, *J* = 7.0 Hz, 4 H), 4.18 (s, 2 H), 1.30 - 1.50 (m, 12 H).

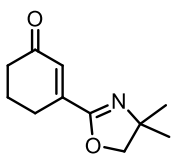
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 165.1, 133.1, 131.4, 79.5, 67.9, 61.5, 28.3, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2969, 2932, 1716, 1674, 1651, 1598, 1468, 1440, 1397, 1374, 1365, 1354, 1331, 1267, 1231, 1207, 1137, 1104, 1086, 1027, 999, 978, 939, 923, 901, 864, 817, 782, 764, 732, 721, 710, 663.

MS (EI, 70 eV): m/z (%) = 319 (2), 318 (3), 306 (3), 305 (19), 304 (100), 289 (17), 276 (13), 274 (15), 249 (4), 248 (17),246 (4), 220 (7), 202 (6), 192 (9), 174 (4), 43 (4), 41 (4).

HR-MS (EI, 70 eV): [$C_{17}H_{20}NO$], calc.: 318.1341; found: 318.1330 [M-H$^+$].

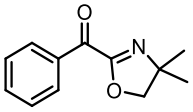
3-(4,4-Dimethyloxazolinyl)cyclohex-2-en-1-one (147g)



4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3** and was then subjected to a Pd-catalyzed cross-coupling reaction by addition of 3-iodocyclohex-2-en-1-one (222 mg, 1.0 mmol), $Pd(OAc)_2$ (7 mg, 3 mol%) and SPhos (25 mg, 6 mol%). The reaction was stirred for 1 h 25 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:diethyl ether 2:1) to afford **147g** (131 mg, 0.68 mmol, 68%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.56 (t, *J* = 1.7 Hz, 1 H), 4.03 (s, 2 H), 2.68 (td, *J* = 6.0, 1.7 Hz, 2 H), 2.36 - 2.54 (m, 2 H), 1.97 - 2.14 (m, 2 H), 1.34 (s, 6 H).
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 199.9, 161.8, 146.7, 130.5, 79.0, 68.1, 37.7, 28.2, 25.6, 22.3.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 2928, 1668, 1644, 1598, 1537, 1463, 1455, 1432, 1418, 1364, 1346, 1326, 1317, 1275, 1252, 1237, 1203, 1187, 1135, 1063, 1020, 953, 904, 890, 702.
MS (EI, 70 eV): *m/z* (%) = 195 (1), 194 (3), 193 (21), 178 (100), 165 (4), 164 (8), 163 (30), 150 (18), 134 (7), 123 (3), 122 (22), 108 (3), 107 (4), 93 (5), 67 (4), 66 (3), 65 (3), 41 (4).
HR-MS (EI, 70 eV): [$C_{11}H_{15}NO_2$], calc.: 193.1103; found: 193.1133.

(4,4-Dimethyloxazolinyl)(phenyl)methanone (147h)



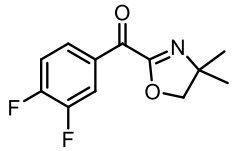
4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3**. The reaction mixture was cooled to -40 °C, CuCN·2LiCl (1.4 mL, 1.4 mmol, 1 M solution in THF) was added and the reaction was stirred for 15 min at this temperature. Then, benzoyl chloride (141 mg, 1.0 mmol) was added, the reaction is allowed to warm to 25 °C over 2 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:*i*-hexane 8:1) to afford **147h** (130 mg, 0.64 mmol, 64%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.23 - 8.31 (m, 2 H), 7.59 - 7.67 (m, 1 H), 7.46 - 7.53 (m, 2 H), 4.16 (s, 2 H), 1.45 (s, 6 H).
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 184.0, 157.6, 134.8, 134.2, 130.6, 128.5, 78.9, 69.2, 28.2.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2975, 1733, 1701, 1684, 1602, 1575, 1468, 1458, 1447, 1402, 1380, 1366, 1307, 1296, 1276, 1256, 1216, 1189, 1154, 1059, 1034, 1029, 992, 968, 927, 914, 901, 806, 794, 778, 742, 715, 691, 662.

MS (EI, 70 eV): *m/z* (%) = 205 (10), 204 (33), 203 (5), 189 (6), 188 (4), 175 (10), 160 (8), 119 (9), 106 (9), 105 (100), 77 (36), 73 (11), 57 (5), 51 (8), 45 (8).

HR-MS (EI, 70 eV): [$C_{12}H_{14}NO_2$], calc.: 204.1019; found: 204.1018 [M+H$^+$].

(3,4-Difluorophenyl)(4,4-dimethyloxazolinyl)methanone (147i)



4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3**. The reaction mixture was cooled to -40 °C, CuCN·2LiCl (1.4 mL, 1.4 mmol, 1 M solution in THF) was added and the reaction was stirred for 15 min at this temperature. Then, 3,4-difluorobenzoyl chloride (177 mg, 1.0 mmol) was added, the reaction was allowed to warm to 25 °C over 2 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:*i*-hexane 8:1) to afford **147i** (182 mg, 0.76 mmol, 76%) as a white solid.

m.p.: 55 – 56 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.23 - 8.33 (m, 1 H), 8.20 (ddd, *J* = 8.6, 4.2, 1.7 Hz, 1 H), 7.19 - 7.33 (m, 1 H), 4.15 (s, 2 H), 1.45 (s, 6 H).

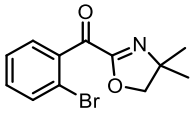
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 180.9, 157.2, 155.8, 155.6, 153.2, 153.1, 151.3, 151.2, 148.8, 148.7, 131.7, 131.7, 131.7, 128.2, 128.2, 128.1, 128.1, 120.3, 120.1, 117.5, 117.4, 78.8, 69.4, 28.1, 24.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2971, 2361, 1721, 1689, 1679, 1617, 1602, 1515, 1469, 1432, 1420, 1399, 1382, 1366, 1330, 1283, 1272, 1257, 1242, 1216, 1198, 1146, 1119, 1056, 1035, 998, 979, 958, 947, 932, 920, 889, 871, 864, 828, 798, 787, 774, 758, 704, 668, 656.

MS (EI, 70 eV): m/z (%) = 240 (5), 239 (10), 225 (4), 211 (4), 196 (4), 190 (4), 158 (4), 142 (8), 141 (100), 140 (4), 113 (28), 109 (4), 97 (6), 95 (4), 91 (4), 83 (5), 81 (4), 73 (9), 69 (7), 63 (5), 57 (7), 56 (4), 55 (6), 42 (5), 40 (4).

HR-MS (EI, 70 eV): [$C_{12}H_{11}F_2NO_2$], calc.: 239.0758; found: 239.0744.

(2-Bromophenyl)(4,4-dimethyloxazolinyl)methanone (147j)



4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3**. The reaction mixture was cooled to -40 °C, CuCN·2LiCl (1.4 mL, 1.4 mmol, 1 M solution in THF) was added and the reaction was stirred for 15 min at this temperature. Then, 2-bromobenzoyl chloride (219 mg, 1.0 mmol) was added, the reaction was allowed to warm to 25 °C over 4 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:*i*-hexane 8:1) to afford **147j** (200 mg, 0.71 mmol, 71%) as a yellowish solid.

m.p.: 57 – 59 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.63 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.58 - 7.61 (m, 1 H), 7.35 - 7.45 (m, 2 H), 4.19 (s, 2 H), 1.40 (s, 6 H).

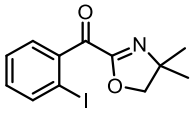
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 186.4, 157.9, 138.0, 133.5, 132.9, 130.7, 127.3, 120.7, 79.9, 69.0, 27.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2973, 1740, 1691, 1636, 1586, 1461, 1435, 1386, 1364, 1324, 1284, 1262, 1227, 1186, 1165, 1064, 1048, 1023, 981, 970, 955, 934, 905, 873, 860, 819, 782, 754, 724, 688.

MS (ESI, 70 eV): *m/z* (%) = 285 (11), 284 (88), 283 (12), 282 (86), 185 (100), 183 (82), 170 (5).

HR-MS (ESI, 70 eV): [$C_{12}H_{12}BrNO_2$], calc.: 282.0130; found: 282.0125 [M+H$^+$].

(2-Iodophenyl)(4,4-dimethyloxazolinyl)methanone (147k)



4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3**. The reaction mixture was cooled to -40 °C, CuCN·2LiCl (1.4 mL, 1.4 mmol, 1 M solution in THF) was added and the reaction was stirred for 15 min at this temperature. Then, 2-iodobenzoyl chloride (266 mg, 1.0 mmol) was added, the reaction was allowed to warm to 25 °C over 6 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:*i*-hexane 8:2) to afford **147k** (241 mg, 0.65 mmol, 65%) as a yellowish solid.

m.p.: 69 – 72 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.89 - 7.95 (m, 1 H), 7.58 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.46 (td, *J* = 7.6, 1.0 Hz, 1 H), 7.20 (td, *J* =7.7, 1.7 Hz, 1 H), 4.19 (s, 2 H), 1.41 (s, 6 H).

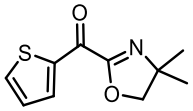
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 187.3, 157.4, 141.2, 140.2, 132.8, 130.5, 127.9, 92.8, 79.8, 69.1, 27.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2971, 1737, 1693, 1625, 1581, 1462, 1431, 1386, 1380, 1366, 1324, 1301, 1283, 1259, 1227, 1216, 1187, 1166, 1118, 1062, 1046, 1017, 986, 968, 949, 939, 903, 860, 816, 793, 781, 748, 723, 680.

MS (EI, 70 eV): *m/z* (%) = 330 (1), 315 (1), 314 (1), 286 (1), 271 (1), 260 (1), 257 (1), 247 (1), 245 (1), 232 (7), 231 (100), 203 (10), 202 (67). 174 (27), 1448 (28), 76 (32), 55 (10), 50 (10).

HR-MS (EI, 70 eV): [$C_{12}H_{12}INO_2$], calc.: 329.9985; found: 329.9984 [M+H$^+$].

(4,4-Dimethyloxazolinyl)(thiophen-2-yl)methanone (147l)



4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) is metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3**. The reaction mixture was cooled to -40 °C, CuCN·2LiCl (1.4 mL, 1.4 mmol, 1 M solution in THF) was added and the reaction was stirred for 15 min at this temperature. Then, thiophene-2-carbonyl chloride (147 mg, 1.0 mmol) was added, the reaction was allowed to warm to 25 °C over 2 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2 100%) to afford **147l** (134 mg, 0.64 mmol, 64%) as a yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.38 (dd, *J* = 3.9, 1.2 Hz, 1 H), 7.77 (dd, *J* = 4.9, 1.0 Hz, 1 H), 7.18 (td, *J* = 4.9, 3.9 Hz, 1 H), 4.16 (s, 2 H), 1.44 (s, 6 H).

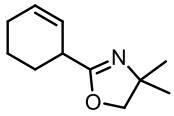
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 175.3, 157.6, 140.7, 137.3, 136.8, 128.5, 79.2, 69.1, 28.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974, 2931, 1736, 1689, 1681, 1649, 1614, 1582, 1548, 1525, 1513, 1501, 1467, 1440, 1430, 1407, 1380, 1360, 1344, 1301, 1277, 1257, 1233, 1220, 1187, 1153, 1079, 1049, 990, 972, 944, 915, 879, 846, 833, 794, 782, 714, 664.

MS (EI, 70 eV): *m/z* (%) = 209 (9), 112 (6), 111 (100), 83 (5), 83 (10), 71 (5), 70 (19), 69 (7), 57 (12), 56 (8), 55 (11), 43 (9), 43 (5), 41 (14).

HR-MS (EI, 70 eV): [$C_{10}H_{11}NO_2S$], calc.: 209.0510; found: 209.0505.

2-(Cyclohex-2-en-1-yl)-4,4-dimethyloxazoline (147m)



4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3**. The reaction mixture was cooled to -40 °C, CuCN·2LiCl (1.4 mL, 1.4 mmol, 1 M solution in THF) was added and the reaction was stirred for 15 min at this temperature. Then, 3-bromocyclohex-1-ene (161 mg, 1.0 mmol) was added, the reaction was allowed to warm to 25 °C over 4 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 6:1) to afford **147m** (142 mg, 0.79 mmol, 79%) as colorless crystals.

m.p.: 40 – 42 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.93 – 5.81 (m, 1H), 5.74 (d, *J* = 10.3 Hz, 1H), 3.92 (s, 2H), 3.17 – 2.98 (m, 1H), 2.13 – 1.46 (m, 6H), 1.28 (s, 6H).

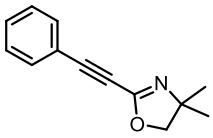
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.9, 129.4, 125.2, 79.0, 66.8, 35.2, 28.4, 28.3, 26.4, 24.7, 20.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3110, 2964, 2944, 2926, 2909, 2866, 2834, 1659, 1611, 1477, 1463, 1450, 1437, 1428, 1399, 1367, 1351, 1315, 1301, 1286, 1251, 1208, 1189, 1156, 1138, 1118, 1104, 1068, 1037, 996, 980, 958, 950, 915, 898, 878, 857, 843, 832, 823, 736, 702, 657.

MS (EI, 70 eV): *m/z* (%) = 180 (20), 179 (100), 178 (87), 165 (6), 164 (66), 152 (5), 151 (8), 150 (57), 148 (8), 138 (5), 134 (5), 124 (6), 113 (8), 108 (6), 95 (5), 81 (13)79 (6).

HR-MS (EI, 70 eV): [$C_{11}H_{17}NO$], calc.: 179.1310; found: 179.1294.

4,4-Dimethyl-2-(phenylethynyl)oxazoline (147n)



4,4-Dimethyloxazoline (**144**, 119 mg, 1.2 mmol) was metalated with TMPZnCl·LiCl (**36**, 1.21 mL, 1.4 mmol, 1.16 M solution) according to **TP-3**. Iodine (355 mg, 1.4 mmol) dissolved in dry THF (1 mL) was then added dropwise at 0 °C and the resulting mixture was stirred for 1 h at 0 °C. To the solution of the *in situ* prepared 2-iodo-4,4-dimethyloxazoline, CuI (8 mg, 0.04 mmol), $Pd(dba)_2$ (17 mg, 0.03 mmol), P(o-furyl) (14 mg, 0.06 mmol), TEA (2 mL) and phenylacetylene (206 mg, 2.0 mmol) were successively added. The reaction mixture was stirred at 25 °C for 1 h and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:diethyl ether 6:1) to afford **147n** (141 mg, 0.85 mmol, 71%) as yellowish liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.53 - 7.58 (m, 2 H), 7.33 - 7.44 (m, 3 H), 4.04 (s, 2 H), 1.35 (s, 6 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 148.2, 132.4, 130.0, 128.4, 120.4, 89.2, 78.9, 77.7, 67.9, 28.1.

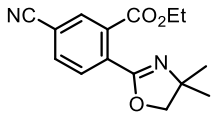
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2969, 2929, 2896, 2231, 1627, 1597, 1574, 1491, 1474, 1460, 1444, 1385, 1364, 1352, 1312, 1248, 1230, 1187, 1143, 1097, 1070, 999, 974, 928, 896, 820, 786, 755, 688.

MS (EI, 70 eV): *m/z* (%) = 200 (3), 199 (16), 185 (13), 184 (100), 170 (6), 169 (41), 157 (4), 156 (32), 129 (14), 128 (81), 127 (38), 115 (5), 101 (8), 100 (7), 84 (16), 77 (15), 75 (11), 74 (6), 63 (5), 57 (6), 54 (9), 51 (12), 50 (5), 42 (9).

HR-MS (EI, 70 eV): [$C_{13}H_{13}NO$], calc.: 199.0997; found: 199.0990.

3.3 Magnesiation of Aryloxazolines and Reaction with Electrophiles

Ethyl 5-cyano-2-(4,4-dimethyloxazolinyl)benzoate (148a)



4-(4,4-Dimethyloxazolinyl)benzonitrile (**147c**, 200 mg, 1.0 mmol) was metalated with TMPMgCl·LiCl (**35**, 1.08 mL, 1.2 mmol, 1.11 M solution in THF) according to **TP-4**. Ethyl chloroformate (98 mg, 0.9 mmol) was added and the reaction mixture was allowed to warm to 25 °C over 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 2:1) to afford **148a** (223 mg, 0.82 mmol, 91%) as a white solid.

m.p.: 111 – 112 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.99 (d, *J* = 1.7 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 4.14 (s, 2 H), 1.40 (s, 6 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

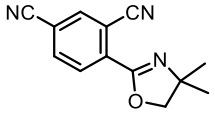
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 165.6, 160.9, 134.0, 133.7, 132.5, 132.1, 130.7, 117.2, 114.5, 80.9, 68.3, 62.2, 28.0, 14.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981, 2970, 2234, 1731, 1649, 1475, 1470, 1462, 1404, 1388, 1363, 1354, 1314, 1297, 1258, 1187, 1139, 1121, 1104, 1049, 1020, 985, 962, 930, 860, 842, 818, 788, 768, 749, 682, 673.

MS (EI, 70 eV): *m/z* (%) = 272 (4), 258 (10), 257 (70), 227 (11), 214 (11), 213 (87), 212 (14), 211 (100), 185 (8), 173 (30), 156 (6), 129 (8), 128 (7), 127 (13), 101 (9), 97 (6), 83 (6), 71 (6), 69 (8), 57 (8), 55 (9), 44 (6), 41 (8).

HR-MS (EI, 70 eV): [$C_{15}H_{16}N_2O_3$], calc.: 272.1161; found: 272.1147.

4-(4,4-Dimethyloxazolinyl)isophthalonitrile (148b)



4-(4,4-Dimethyloxazolinyl)benzonitrile (**147c**, 200 mg, 1.0 mmol) was metalated with TMPMgCl·LiCl (**35**, 1.08 mL, 1.2 mmol, 1.11 M solution in THF) according to **TP-4**. *p*-Toluenesulfonyl cyanide (163 mg, 0.9 mmol) was added and the reaction mixture was allowed to warm to 25 °C over 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 2:1) to afford **148b** (169 mg, 0.75 mmol, 83%) as a white solid.

m.p.: 123 – 125 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.21 (d, *J* = 8.2 Hz, 1 H), 8.03 – 8.01 (m, 1 H), 7.89 (ddd, *J* = 8.2, 1.7 Hz, 1 H), 4.23 (s, 2 H), 1.42 (s, 6 H).

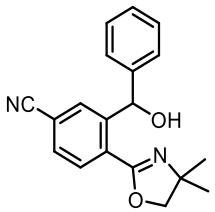
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 158.3, 137.6, 135.3, 134.1, 131.1, 116.1, 115.6, 115.4, 113.2, 80.9, 68.8, 28.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3073, 3051, 2974, 2362, 2237, 1651, 1501, 1464, 1365, 1353, 1311, 1292, 1273, 1217, 1182, 1139, 1049, 986, 965, 930, 924, 912, 856, 818, 758, 684, 675.

MS (EI, 70 eV): *m/z* (%) = 225 (11), 211 (15), 210 (90), 195 (40), 155 (12), 154 (70), 149 (31), 127 (12), 123 (15), 113 (18), 112 (16), 111 (27), 109 (17), 99 (13), 97 (38), 95 (24), 85 (29), 84 (11), 83 (39), 82 (14), 81 (38), 79 (12), 71 (58), 70 (26), 69 (90), 67 (21), 59 (12), 57 (100), 56 (26), 55 (58), 45 (15), 44 (87), 43 (58), 43 (43), 42 (37), 41 (65).

HR-MS (EI, 70 eV): [$C_{13}H_{11}N_3O$], calc.: 225.0902; found: 225.0900.

4-(4,4-Dimethyloxazolinyl)-3-(hydroxy(phenyl)methyl)benzonitrile (148c)



4-(4,4-Dimethyloxazolinyl)benzonitrile (**147c**, 200 mg, 1.0 mmol) was metalated with TMPMgCl·LiCl (**35**, 1.08 mL, 1.2 mmol, 1.11 M solution in THF) according to **TP-4**. Benzaldehyde (95 mg, 0.9 mmol) was added and the reaction mixture was allowed to warm to 25 °C over 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product

was purified by column chromatography on silica (*i*-hexane:ethyl acetate 2:1) to afford **148c** (254 mg, 0.83 mmol, 92%) as a white solid.

m.p.: 103 – 105 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.90 (d, *J* = 8.1 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.39 (br, 1 H), 7.32 (s, 1 H), 7.30 – 7.19 (m, 5 H), 5.93 (s, 1 H), 4.04 (d, *J* = 8.2 Hz, 1 H), 3.95 (d, *J* = 8.2 Hz, 1 H), 1.31 (s, 3 H), 1.05 (s, 3 H).

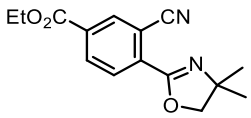
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 161.0, 146.2, 141.5, 133.4, 131.1, 131.1, 131.0, 128.2, 127.4, 126.6, 118.0, 114.8, 79.1, 73.6, 68.5, 28.4, 27.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3184, 2966, 2230, 1644, 1454, 1404, 1359, 1314, 1283, 1206, 1187, 1077, 1065, 1040, 1024, 963, 947, 938, 920, 846, 826, 785, 756, 746, 740, 700, 662.

MS (EI, 70 eV): *m/z* (%) = 307 (11), 306 (46), 275 (18), 235 (20), 234 (100), 233 (20), 229 (17), 219 (10), 200 (11), 190 (18), 185 (12), 158 (11), 155 (11), 130 (11), 105 (13), 77 (12).

HR-MS (EI, 70 eV): [$C_{19}H_{18}N_2O_2$], calc.: 306.1368; found: 306.1375.

Ethyl 3-cyano-4-(4,4-dimethyloxazolinyl)benzoate (148d)



Ethyl 4-(4,4-dimethyloxazolinyl)benzoate (**147b**, 247 mg, 1.0 mmol) was metalated with TMPMgCl·LiCl (**35**, 1.08 mL, 1.2 mmol, 1.11 M solution in THF) according to **TP-4**. *p*-Toluenesulfonyl cyanide (163 mg, 0.9 mmol) was added and the reaction mixture was allowed to warm to 25 °C over 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 1:1) to afford **148d** (152 mg, 0.56 mmol, 62%) as colorless crystals.

m.p.: 56 – 58 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.37 (d, *J* = 1.7 Hz, 1 H), 8.21 (dd, *J* = 8.2, 1.7 Hz, 1 H), 8.08 (d, *J* = 8.2 Hz, 1 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 4.18 (s, 2 H), 1.39 (s, 6 H), 1.39 (t, *J* = 7.2 Hz, 3 H).

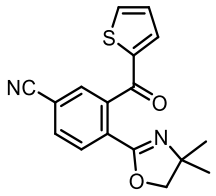
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 164.1, 159.0, 135.4, 134.0, 133.0, 133.0, 130.4, 116.9, 112.1, 79.9, 68.6, 62.0, 28.2, 14.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2970, 2228, 1715, 1633, 1462, 1403, 1368, 1356, 1312, 1286, 1253, 1248, 1216, 1181, 1122, 1108, 1058, 1020, 985, 955, 932, 920, 910, 875, 821, 792, 772, 744, 714, 676.

MS (EI, 70 eV): *m/z* (%) = 273 (5), 272 (25), 271 (11), 258 (25), 257 (100), 243 (13), 242 (57), 229 (22), 227 (23), 202 (11), 207 (71), 174 (10), 173 (45), 128 (15).

HR-MS (EI, 70 eV): [$C_{15}H_{16}N_2O_3$], calc.: 272.1161; found: 272.1153.

4-(4,4-Dimethyloxazolinyl)-3-(thiophene-2-carbonyl)benzonitrile (148e)



4-(4,4-Dimethyloxazolinyl)benzonitrile (**147c**, 200 mg, 1.0 mmol) was metalated with TMPMgCl·LiCl (**35**, 1.08 mL, 1.2 mmol, 1.11 M solution in THF) according to **TP-4**. The reaction mixture was cooled to -25 °C and CuCN·2LiCl (1.2 mL, 1.2 mmol, 1 M solution) was added and stirring was continued for 0.5 h. Then 2-thiophenecarbonyl chloride (132 mg, 0.9 mmol) was added and the reaction was allowed to warm to 25 °C over 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 1:1) to afford **148e** (233 mg, 0.75 mmol, 83%) as colorless crystals.

m.p.: 143 – 145 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.04 (d, *J* = 8.0 Hz, 1 H), 7.82 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.79 (d, *J* = 1.6 Hz, 1 H), 7.72 (dd, *J* = 4.9, 1.2 Hz, 1 H), 7.21 (dd, *J* = 3.9, 1.2 Hz, 1 H), 7.07 (dd, *J* = 4.9, 3.8 Hz, 1 H), 3.80 (s, 2 H), 1.12 (s, 6 H).

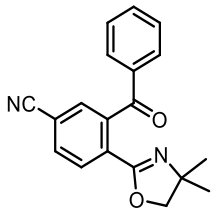
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 186.5, 159.7, 144.0, 140.5, 134.9, 134.3, 133.4, 131.6, 130.9, 130.1, 128.1, 117.4, 114.9, 79.9, 68.4, 27.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 2926, 2232, 1649, 1418, 1409, 1353, 1299, 1265, 1254, 1188, 1052, 1045, 953, 932, 912, 857, 803, 759, 736, 728, 679, 658.

MS (EI, 70 eV): *m/z* (%) = 311 (4), 310 (20), 282 (18), 281 (100), 266 (10), 265 (55), 237 (13), 227 (13), 211 (32), 196 (24), 155 (28), 127 (18), 111 (25), 55 (31), 41 (16).

HR-MS (EI, 70 eV): [$C_{17}H_{14}N_2O_2S$], calc.: 310.0776; found: 310.0774.

3-Benzoyl-4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzonitrile (148f)



4-(4,4-Dimethyloxazolinyl)benzonitrile (**147c**, 200 mg, 1.0 mmol) was metalated with TMPMgCl·LiCl (**35**, 1.08 mL, 1.2 mmol, 1.11 M solution in THF) according to **TP-4**. The reaction mixture was cooled to -25 °C and CuCN·2LiCl (1.2 mL, 1.2 mmol, 1 M solution) was added and stirring was continued for 0.5 h. Then benzoyl chloride (127 mg, 0.9 mmol) was added and the reaction was allowed to warm to 25 °C over 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 3:2) to afford **148f** (250 mg, 0.82 mmol, 91%) as white solid.

m.p.: 115 – 117 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.04 (d, *J* = 8.0 Hz, 1 H), 7.83 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.77 (d, *J* = 1.6 Hz, 1 H), 7.70 – 7.65 (m, 2 H), 7.59 – 7.52 (m, 1 H), 7.48 – 7.39 (m, 2 H), 3.67 (s, 2 H), 1.03 (s, 6 H).

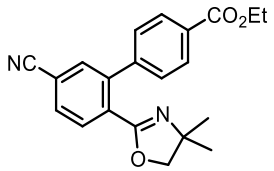
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 194.3, 159.8, 140.8, 136.8, 133.3, 133.3, 132.0, 130.8, 130.0, 129.1, 128.6, 117.4, 115.1, 79.7, 68.3, 27.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 2899, 2235, 1670, 1652, 1598, 1451, 1358, 1316, 1296, 1282, 1257, 1196, 1177, 1129, 1053, 980, 971, 957, 928, 875, 858, 828, 768, 709, 699, 686, 652.

MS (EI, 70 eV): *m/z* (%) = 304 (1), 289 (10), 276 (25), 275 (100), 245 (6), 221 (7), 218 (5), 211 (5), 190 (13), 155 (12), 127 (6), 105 (5), 77 (7).

HR-MS (EI, 70 eV): [$C_{19}H_{16}N_2O_2$], calc.: 304.1212; found: 304.1214.

Ethyl 5'-cyano-2'-(4,4-dimethyloxazolinyl)-[1,1'-biphenyl]-4-carboxylate (148g)



4-(4,4-Dimethyloxazolinyl)benzonitrile (**147c**, 200 mg, 1.0 mmol) was metalated with TMPMgCl·LiCl (**35**, 1.08 mL, 1.2 mmol, 1.11 M solution in THF) according to **TP-4**. Then, ethyl 4-iodobenzoate (248 mg, 0.9 mmol), $Pd(dba)_2$ (17 mg, 0.03 mmol) and P(*o*-furyl)$_3$ (14 mg, 0.06 mmol) were added. The reaction mixture was stirred for 4 h at 25 °C and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:diethyl ether 1:1) to afford **148g** (282 mg, 0.81 mmol, 90%) as a yellowish solid.

m.p.: 92 – 94 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.14 – 8.06 (m, 2 H), 7.93 (d, *J* = 7.9 Hz, 1 H), 7.71 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.68 – 7.66 (m, 1 H), 7.46 – 7.39 (m, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 3.84 (s, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H), 1.30 (s, 6 H).

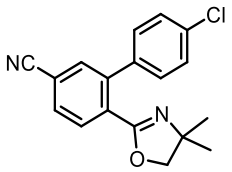
^{13}C-NMR (750 MHz, $CDCl_3$, ppm): δ = 166.2, 162.1, 143.3, 142.0, 133.6, 131.8, 131.2, 131.0, 130.3, 129.5, 128.3, 117.8, 114.6, 80.0, 67.9, 61.2, 27.9, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2967, 2361, 2340, 1718, 1706, 1648, 1606, 1292, 1273, 1178, 1103, 1074, 1039, 1019, 959, 864, 776, 760, 713, 700, 668.

MS (EI, 70 eV): *m/z* (%) = 349 (4), 348 (22), 347 (100), 333 (3), 319 (3), 305 (3), 303 (7), 293 (3), 245 (5), 231 (8), 203 (5), 176 (5).

HR-MS (EI, 70 eV): [$C_{21}H_{20}N_2O_3$], calc.: 348.1474; found: 348.1423.

4'-Chloro-6-(4,4-dimethyloxazolinyl)-[1,1'-biphenyl]-3-carbonitrile (148h)



4-(4,4-Dimethyloxazolinyl)benzonitrile (**147c**, 200 mg, 1.0 mmol) was metalated with TMPMgCl·LiCl (**35**, 1.08 mL, 1.2 mmol, 1.11 M solution in THF) according to **TP-4**. Then, 1-chloro-4-iodobenzene (215 mg, 0.9 mmol), $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were added. The reaction mixture was stirred for 4 h at r.t. and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:diethyl ether 1:1) to afford **148h** (260 mg, 0.84 mmol, 93%) as a yellowish solid.

m.p.: 96 – 97 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.87 (d, *J* = 8.1 Hz, 1 H), 7.68 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.64 (s, 1 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 3.86 (s, 2 H), 1.30 (s, 6 H).

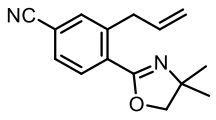
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.7, 141.6, 137.3, 134.4, 133.5, 132.2, 131.1, 130.7, 129.5, 128.5, 117.9, 114.3, 79.7, 68.0, 27.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2967, 2928, 2231, 1653, 1484, 1462, 1410, 1392, 1365, 1350, 1308, 1213, 1179, 1091, 1065, 1034, 1013, 986, 959, 920, 901, 828, 814, 763, 734, 724, 698, 668.

MS (EI, 70 eV): *m/z* (%) = 312 (6), 311 (38), 310 (23), 309 (100), 295 (6), 255 (8), 245 (12), 240 (6), 239 (11), 238 (9), 226 (8), 226 (8), 224 (23), 203 (13), 202 (8), 177 (11), 176 (12).

HR-MS (EI, 70 eV): [$C_{18}H_{15}ClN_2O$], calc.: 309.0795; found: 309.0797 [M-H$^+$].

3-Allyl-4-(4,4-dimethyloxazolinyl)benzonitrile (148i)



4-(4,4-Dimethyloxazolinyl)benzonitrile (**148i**, 200 mg, 1.0 mmol) was metalated with TMPMgCl·LiCl (**35**, 1.08 mL, 1.2 mmol, 1.11 M solution in THF) according to **TP-4**. CuCN·2LiCl (1.2 mL, 1.2 mmol, 1 M solution) was added and the reaction mixture was stirred for 0.5 h. Then allyl bromide (109 mg, 0.9 mmol) was added and the reaction was allowed to warm to 25 °C over 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 1:1) to afford **148i** (187 mg, 0.78 mmol, 87%) as a yellowish solid.

m.p.: 46 – 48 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.87 (d, *J* = 8.0 Hz, 1 H), 7.60 – 7.48 (m, 2 H), 6.01 – 5.84 (m, 1 H), 5.19 – 4.97 (m, 2 H), 4.10 (d, *J* = 1.2 Hz, 2 H), 3.80 (d, *J* = 6.5 Hz, 2 H), 1.39 (s, 6 H).

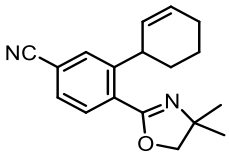
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 161.1, 141.8, 135.8, 133.8, 131.6, 130.8, 129.5, 118.3, 117.0, 114.3, 79.1, 68.2, 37.9, 28.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2971, 2927, 2889, 2230, 1643, 1497, 1460, 1366, 1352, 1311, 1284, 1250, 1207, 1193, 1175, 1084, 1042, 988, 964, 948, 921, 892, 848, 818, 730, 692.

MS (EI, 70 eV): *m/z* (%) = 246 (17), 241 (10), 240 (60), 239 (84), 226 (17), 225 (100), 213 (13), 209 (10), 195 (17), 185 (40), 171 (10), 169 (17), 168 (29), 167 (12), 156 (16), 155 (12), 154 (16), 153 (14), 142 (26), 141 (48), 140 (40), 115 (18), 114 (17), 57 (12), 56 (14), 55 (22), 41 (15).

HR-MS (EI, 70 eV): [$C_{15}H_{16}N_2O$], calc.: 240.1263; found: 240.1262.

6-(4,4-Dimethyloxazolinyl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carbonitrile (148j)



4-(4,4-Dimethyloxazolinyl)benzonitrile (**147c**, 200 mg, 1.0 mmol) was metalated with TMPMgCl·LiCl (**35**, 1.08 mL, 1.2 mmol, 1.11 M solution in THF) according to **TP-4**. CuCN·2LiCl (1.2 mL, 1.2 mmol, 1 M solution) was added and the reaction mixture was stirred for 0.5 h. Then, 3-bromocyclohexene (145 mg, 0.9 mmol) was added and the reaction was allowed to warm to 25 °C over 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4.

The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 2:1) to afford **148j** (247 mg, 0.88 mmol, 98%) as a yellowish solid.

m.p.: 76 – 78 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.73 (d, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 1.7 Hz, 1 H), 7.45 (dd, *J* = 8.1, 1.7 Hz, 1 H), 5.94 (ddd, *J* = 10.0, 5.0, 2.4 Hz, 1 H), 5.58 (dd, *J* = 10.3, 2.5 Hz, 1 H), 4.34 (ddt, *J* = 8.2, 5.6, 2.8 Hz, 1 H), 4.06 (s, 2 H), 2.05 (tdd, *J* = 12.8, 6.4, 3.3 Hz, 3 H), 1.65 – 1.52 (m, 2 H), 1.40 (ddd, *J* = 9.1, 7.6, 4.0 Hz, 1 H), 1.35 (s, 6H).

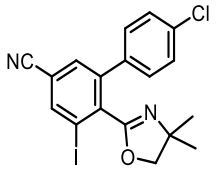
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.0, 147.9, 132.4, 130.5, 129.8, 129.1, 128.8, 118.6, 113.8, 78.9, 68.4, 37.5, 31.7, 28.3, 28.2, 24.9, 20.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2968, 2948, 2931, 2913, 2858, 2230, 1639, 1488, 1480, 1462, 1445, 1398, 1364, 1352, 1305, 1292, 1276, 1266, 1246, 1210, 1188, 1164, 1121, 1056, 1043, 961, 938, 922, 912, 873, 846, 838, 820, 770, 752, 721, 686.

MS (EI, 70 eV): *m/z* (%) = 281 (20), 280 (100), 279 (22), 265 (13), 251 (22), 225 (37), 223 (11), 209 (27), 208 (74), 207 (45), 206 (16), 193 (15), 192 (21), 191 (22), 190 (34), 180 (16), 168 (10), 166 (13), 153 (16), 152 (16), 140 (16), 74 (21), 59 (21), 55 (12), 44 (15).

HR-MS (EI, 70 eV): [$C_{18}H_{20}N_2O$], calc.: 280.1576; found: 280.1570.

4'-Chloro-6-(4,4-dimethyloxazolinyl)-5-iodo-[1,1'-biphenyl]-3-carbonitrile (149a)



4'-Chloro-6-(4,4-dimethyloxazolinyl)-[1,1'-biphenyl]-3-carbonitrile (**148h**, 131 mg, 0.5 mmol) was metalated with $TMP_2Mg{\cdot}2LiCl$ (**42**, 1.11 mL, 0.6 mmol, 0.54 M) according to **TP-5**. I_2 (253 mg, 1.0 mmol) was added dropwise as a 0.5 M solution THF and the reaction mixture was allowed to warm to 25 °C over 2 h. The reaction was quenched with sat. $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2 100%) to afford **149a** (153 mg, 0.35 mmol, 70%) as a yellowish solid.

m.p.: 133 – 135 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.12 (d, *J* = 1.5 Hz, 1 H), 7.60 (d, *J* = 1.5 Hz, 1 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 3.96 (s, 2 H), 1.20 (s, 6 H).

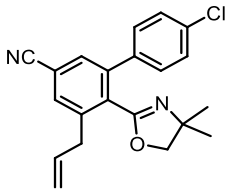
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.8, 143.1, 140.9, 138.8, 136.2, 135.0, 132.5, 130.0, 128.5, 116.3, 115.0, 97.2, 79.7, 68.6, 27.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2948, 2922, 2858, 1639, 1488, 1480, 1462, 1445, 1398, 1364, 1352, 1305, 1292, 1276, 1266, 1246, 1210, 1185, 1043, 961, 938, 922, 912, 873, 838, 820, 773.

MS (EI, 70 eV): *m/z* (%) = 438 (8), 437 (47), 436 (40), 435 (100), 421 (6), 380 (5), 370 (19), 351 (7), 349 (21), 238 (7), 211 (5), 203 (7), 202 (17), 188 (7), 176 (9), 175 (8), 55 (9).

HR-MS (EI, 70 eV): [$C_{18}H_{14}ClIN_2O$], calc.: 434.9761; found: 434.9753 [M-H$^+$].

5-Allyl-4'-chloro-6-(4,4-dimethyloxazolinyl)-[1,1'-biphenyl]-3-carbonitrile (149b)



4'-Chloro-6-(4,4-dimethyloxazolinyl)-[1,1'-biphenyl]-3-carbonitrile (**148h**, 131 mg, 0.5 mmol) was metalated with $TMP_2Mg{\cdot}2LiCl$ (**42**, 1.11 mL, 0.6 mmol, 0.54 M) according to **TP-5**. CuCN·2LiCl (0.6 mL, 0.6 mmol) was added at -20 °C and the reaction was stirred for 0.5 h. Allyl bromide (49 mg, 0.45 mmol) was added, the reaction was allowed to warm to 25 °C over 4 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2) to afford **149b** (137 mg, 0.39 mmol, 87%) as a white solid.

m.p.: 170 – 173 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56 (d, *J* = 1.5 Hz, 1 H), 7.49 (d, *J* = 1.7 Hz, 1 H), 7.40 - 7.45 (m, 2 H), 7.35 - 7.40 (m, 2 H), 6.00 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1 H), 5.18 - 5.23 (m, 1 H), 5.11 - 5.18 (m, 1 H), 3.68 (s, 2 H), 3.57 (d, *J* = 6.6 Hz, 2 H), 1.19 (s, 6 H).

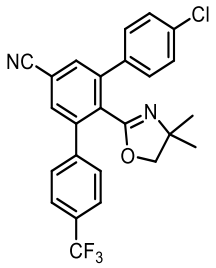
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.9, 140.3, 139.5, 139.4, 136.6, 135.6, 134.8, 132.2, 131.0, 130.1, 128.8, 118.0, 117.7, 113.1, 54.9, 51.1, 36.9, 24.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3264, 2924, 2237, 1630, 1603, 1555, 1494, 1470, 1455, 1445, 1432, 1416, 1387, 1364, 1327, 1300, 1262, 1238, 1092, 1016, 994, 927, 913, 891, 872, 844, 837, 831, 801, 758, 733, 714, 700, 677.

MS (EI, 70 eV): *m/z* (%) = 352 (20), 351 (42), 350 (53), 349 (100), 346 (39), 337 (21), 335 (62), 278 (20), 220 (32), 219 (77), 216 (20), 214 (22), 191 (48), 190 (59), 105 (20), 85 (19), 77 (79), 71 (23), 69 (22), 57 (40), 55 (50), 51 (26), 43 (27), 43 (20), 41 (37).

HR-MS (EI, 70 eV): [$C_{21}H_{18}ClN_2O$], calc.: 349.1108; found: 349.1098 [M-H$^+$].

4-Chloro-2'-(4,4-dimethyloxazolinyl)-4''-(trifluoromethyl)-[1,1':3',1''-terphenyl]-5'-carbonitrile (149c)



4'-Chloro-6-(4,4-dimethyloxazolinyl)-[1,1'-biphenyl]-3-carbonitrile (**148h**, 131 mg, 0.5 mmol) was metalated with $TMP_2Mg{\cdot}2LiCl$ (**42**, 1.11 mL, 0.6 mmol, 0.54 M) according to **TP-5**, then 4-iodobenzotrifluoride (122 mg, 0.45 mmol), $Pd(dba)_2$ (9 mg, 0.02 mmol) and P(*o*-furyl)$_3$ (7 mg, 0.03 mmol) were added. The reaction was allowed to warm to 25 °C over 3 h and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2/diethyl ether 10:1) to afford **149c** (178 mg, 0.39 mmol, 87%) as a yellowish solid.

m.p.: 181 – 183 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.67 (m, 4 H), 7.55 (d, *J* = 7.9 Hz, 2 H), 7.43 – 7.33 (m, 4 H), 3.62 (s, 2 H), 0.91 (s, 6 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 159.1, 142.7, 142.4, 141.9 (d, *J* = 1.7 Hz), 136.5, 134.8, 132.5, 132.4, 131.8, 130.6 (q, *J* = 32.7 Hz), 130.0, 129.2, 128.6, 125.3 (q, *J* = 272.3 Hz), 125.2 (q, *J* = 3.7 Hz), 122.6, 119.9, 117.6, 113.9, 79.4, 68.2, 27.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2971, 2930, 2242, 1662, 1492, 1324, 1299, 1294, 1284, 1176, 1160, 1129, 1111, 1093, 1072, 1061, 1039, 1017, 959, 924, 904, 893, 846, 828, 820, 766, 708, 663.

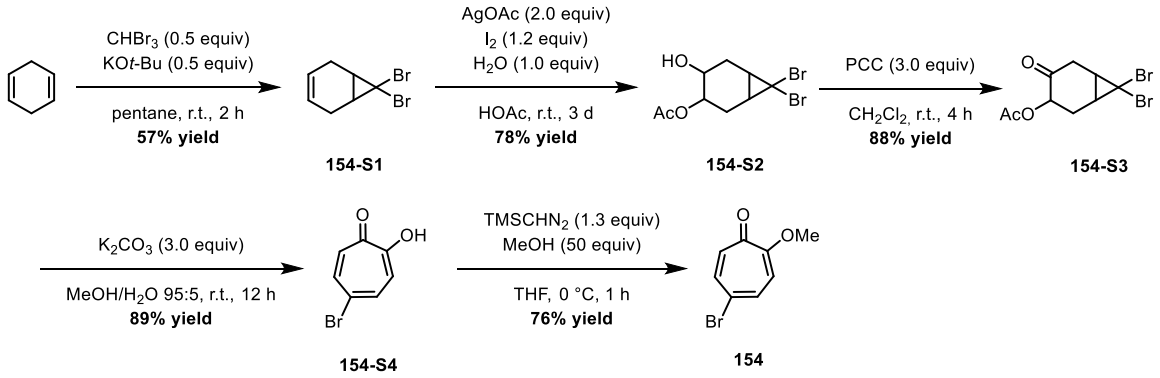
MS (EI, 70 eV): *m/z* (%) = 456 (10), 455 (34), 454 (32), 453 (100), 399 (8), 397 (5), 389 (5), 381 (5), 368 (13), 363 (13), 347 (5), 332 (6), 364 (6), 55 (16).

HR-MS (EI, 70 eV): [$C_{25}H_{18}ClF_3N_2O$], calc.: 453.0982; found: 453.0972 [M-H$^+$].

4 Metalation and Functionalization of the Tropolone Scaffold

4.1 Preparation of Starting Materials

5-Bromo-2-methoxytropone (154) was synthesized in 5 steps from 1,4-cyclohexadiene using modified literature procedures:



7,7-Dibromo-bicyclo[4.1.0]hept-3-ene (154-S1)

The title compound was synthesized from 1,4-cyclohexadiene using a modified procedure by Hofmann *et al.*[186] Potassium *tert*-butoxide (11.2 g, 100 mmol) was dried *in vacuo* for 6 h and was then suspended in *n*-pentane (200 mL). The suspension was cooled to 0 °C and 1,4-cyclohexadiene (16.0 g, 200 mmol) was added, followed by the addition of bromoform (8.75 mL, 25.3 g, 100 mmol) over 15 min. The reaction was stirred at r.t. for 2 h and was then quenched by the addition of water (200 mL). The organic layer was separated and the aqueous phase was extracted with *n*-pentane (3 x 150 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the crude product by column chromatography using *n*-pentane as an eluent afforded the title compound as colorless crystals (14.4 g, 57 mmol, 57%).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.51 (s, 2 H), 2.53 – 2.38 (m, 2 H), 2.17 – 2.03 (m, 2 H), 1.92 (dd, *J* = 5.4, 2.4 Hz, 2 H).

(1*α*,3β,4β,6α)-4-Acetoxy-7,7-dibromobicyclo[4.1.0]heptan-3-ol (154-S2)

The title compound was synthesized using a modified procedure by Banwell *et al.*[187] **154-S1** (14.0 g, 57 mmol) and silver acetate (19.0 g, 114 mmol) were dissolved in acetic acid (280 mL) and iodine (17.3 g, 68 mmol) was added over 15 min. Upon complete addition, water (1.0 mL, 57 mmol) was

[186] K. Hofmann, S. F. Orochena, S. M. Sax, G. A. Jeffrey, *J. Am. Chem. Soc.* **1959**, *81*, 992.
[187] M. G. Banwell, J. N. Lambert, M. E. Reum, R. Onrust, *Org. Prep. Proced. Int.* **1988**, *20*, 393.

added and the reaction was stirred for 48 h in the dark. Water and solid Na_2CO_3 were added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were washed successively with sat. aq. $NaHCO_3$ solution, 20% aq. $NaHSO_3$ solution, water and sat. aq. NaCl-solution, then dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using *i*-hexane:ethyl acetate 3:2 as an eluent affording **154-S2** as a white solid (14.4 g, 44 mmol, 78%)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.76 (td, *J* = 6.1, 3.3 Hz, 1 H), 3.79 – 3.68 (m, 1 H), 2.45 – 2.29 (m, 2 H), 2.21 – 2.08 (m, 1 H), 2.02 (s, 3 H), 1.94 – 1.75 (m, 3 H), 1.68 (ddd, *J* = 15.2, 7.7, 4.1 Hz, 1 H).

(1α,4β,6α)-4-Acetoxy-7,7-dibromobicyclo[4.1.0]heptan-3-one (154-S3)

The title compound was prepared using a modified procedure by Banwell.[187] **154-S2** (13.1 g, 40 mmol) was dissolved in CH_2Cl_2 (400 mL) and PCC (25.9 g, 120 mmol) was added at room temperature. The reaction mixture was stirred for 4 h at r.t. and was then filtered through a pad of celite using CH_2Cl_2 as an eluent. The solvents were removed *in vacuo* and the residue was purified by column chromatography using CH_2Cl_2:ethyl acetate 2:1 as an eluent to provide **154-S3** as a white solid (11.4 g, 35 mmol, 88%)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.12 (dd, *J* = 13.0, 7.5 Hz, 1 H), 2.90 – 2.62 (m, 3 H), 2.28 (ddd, *J* = 10.3, 8.3, 1.8 Hz, 1 H), 2.18 (dd, *J* = 10.1, 4.5 Hz, 1 H), 2.12 (s, 3 H), 2.01 (ddd, *J* = 14.2, 13.1, 4.5 Hz, 1 H).

5-Bromo-2-hydroxycyclohepta-2,4,6-triene-1-one (154-S4)

The title compound was prepared by dissolving **154-S3** (5.0 g, 16 mmol) in methanol/H_2O (600 mL, 95:5 mixture) and addition of K_2CO_3 (6.6 g, 48 mmol). The reaction was stirred for 16 h and was then diluted with 2 M HCl (400 mL). The mixture was extracted with CH_2Cl_2 (3 x 200 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated. Recrystallisation from $CHCl_3$ and hexane provided **154-S4** as yellow crystals (2.9 g, 14 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.04 (s, 1 H), 7.66 (d, *J* = 12.2 Hz, 2 H), 7.10 (d, *J* = 12.2 Hz, 2 H).

5-Bromo-2-methoxy-cyclohepta-2,4,6-triene-1-one (154)

Alcohol **154-S4** (2.5 g, 12.4 mmol) was dissolved in THF (100 mL) and the solution was cooled to 0 °C. (Trimethylsilyl)diazomethane (8.05 mL, 16.1 mmol, 2 M solution in hexane) and MeOH (25 mL) were added successively and the reaction was stirred for 1 h at 0 °C. The reaction mixture was treated with sat. aq. NH_4Cl and H_2O, the phases were separated and the aquoues phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica using CH_2Cl_2:diethyl ether 1:1 as an eluent to yield **154** as a brown solid (2.20 g, 9.4 mmol, 76%)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.47 – 7.36 (m, 2 H), 7.00 (d, *J* = 12.2 Hz, 1 H), 6.48 (d, *J* = 12.1 Hz, 1 H), 3.92 (s, 3 H).

2-Benzyloxytropone (156)[188]

Tropolone (**151**, 1.22 g, 10.0 mmol) and Bu_4NOH (40% in H_2O, 6.3 mL, 10.0 mmol) were stirred under at r.t. for 1 h. A solution of benzyl chloride (1.27 g, 10.0 mmol) in CH_2Cl_2 (25 mL) was added slowly at room temperature. The reaction was heated to reflux for 8 h and was then diluted with H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the crude product by chromatography on silica gel (CH_2Cl_2:ethyl acetate 2:1) obtained the title compound as a brown solid (1.29 g, 6.1 mmol, 61%).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.43 – 7.14 (m, 7 H), 7.02 – 6.74 (m, 3 H), 5.23 (s, 2H).

4.2 Typical Procedures

Typical procedure for the zincation of 5-bromo-2-methoxytropone (154) using TMPZnCl·LiCl (36) (TP-6):

A dry and argon-flushed *Schlenk* flask was charged with a solution of 5-bromo-2-methoxytropone (**154**, 1.0 equiv) in dry THF (0.5 M solution). The solution was cooled to -30 °C and TMPZnCl·LiCl (**36**, 1.4 equiv) was added dropwise. The reaction was stirred for 0.5 h at -30 °C to yield the corresponding zinc reagent. The completion of metalation was checked by TLC of reaction aliquots quenched with iodine in THF.

[188] I. Tamburlin-Thumin, M. P. Crozet, J.-C. Barrière, *Synthesis* **1999**, *7*, 1149.

Typical procedure for the zincation of 2-benzyloxytropone (156) using TMPZnCl·LiCl (36) (TP-7):

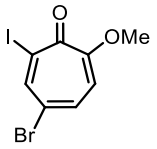
A dry and argon-flushed *Schlenk* flask was charged with a solution of 2-benzyloxytropone (**156**, 1.0 equiv) in dry THF (0.5 M solution). The solution was cooled to 0 °C and TMPZnCl·LiCl (**36**, 2.0 equiv) was added dropwise. The reaction was stirred for 10 min at 0 °C to yield the corresponding zinc reagent. The completion of metalation was checked by TLC of reaction aliquots quenched with iodine in THF.

Typical procedure for the addition of Grignard reagents to arylated 2-benzyloxytropones (157) (TP-8):

The arylated 2-benzyloxytropone of type **157** (1.0 equiv) was dissolved in THF (0.5 M solution), the mixture was cooled to -78 °C and the Grignard reagent (1.2 equiv) was added dropwise. The reaction was allowed to warm to room temperature over 4 h, followed by the addition of sat. aq. NH_4Cl. The mixture was extracted with ethyl acetate and the combined organic extracts were dried over Na_2SO_4.

4.3 Metalation and Functionalization of 5-Bromo-2-methoxytropone

4-Bromo-2-iodo-7-methoxycyclohepta-2,4,6-trien-1-one (155a)



5-Bromo-2-methoxytropone (**154**, 108 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.6 mL, 0.7 mmol, 1.16 M solution) according to **TP-6**. The reaction mixture was then cooled to -78 °C and I_2 (152 mg, 0.6 mmol) dissolved in THF (2.0 mL) was added. The reaction was allowed to warm to room temperature over 4 h and was then quenchend with sat. aq. $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:diethyl ether 4:1) to afford **155a** (167 mg, 0.49 mmol, 98%) as a yellow solid.

m.p.: 195 – 196 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.76 (d, *J* = 2.0 Hz, 1 H), 7.44 (dd, *J* = 10.7, 2.0 Hz, 1 H), 6.53 (d, *J* = 10.6 Hz, 1 H), 3.92 (s, 3 H).

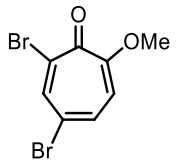
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 175.2, 159.1, 149.4, 134.8, 120.3, 120.2, 111.4, 57.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3086, 3049, 1584, 1558, 1541, 1451, 1347, 1260, 1249, 1234, 1172, 1118, 1024, 957, 903, 889, 848, 771, 741, 727, 714.

MS (EI, 70 eV): *m/z* (%) = 342 (57), 340 (58), 312 (13), 311 (15), 299 (22), 297 (22), 260 (17), 213 (32), 212 (31), 197 (15), 185 (66), 183 (65), 172 (45), 170 (46), 157 (15), 133 (28), 75 (29), 74 (20), 63 (100).

HR-MS (EI, 70 eV): [$C_8H_6BrIO_2$], calc.: 339.8596; found: 339.8585.

2,4-Dibromo-7-methoxycyclohepta-2,4,6-trien-1-one (155b)



5-Bromo-2-methoxytropone (**154**, 108 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.6 mL, 0.7 mmol, 1.16 M solution) according to **TP-6**. The reaction mixture was then cooled to -78 °C and Br_2 (0.03 mL, 96 mg, 0.6 mmol) was added. The reaction was allowed to warm to room temperature over 4 h and was then quenchend with sat. aq. $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:diethyl ether 4:1) to afford **155b** (109 mg, 0.37 mmol, 74%) as a yellow solid.

m.p.: 175 – 176 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.44 (d, *J* = 2.0 Hz, 1 H), 7.47 (dd, *J* = 10.7, 2.0 Hz, 1 H), 6.61 – 6.38 (m, 1 H), 3.94 (s, 3 H).

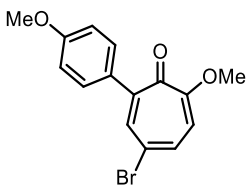
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 173.3, 161.9, 142.8, 137.0, 134.6, 119.5, 111.6, 56.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3094, 3054, 1600, 1583, 1576, 1569, 1564, 1559, 1545, 1540, 1533, 1368, 1340, 1264, 1254, 1238, 1173, 1123, 1028, 967, 901, 895, 846, 752, 737.

MS (EI, 70 eV): *m/z* (%) = 297 (4), 296 (24), 294 (48), 292 (26), 265 (26), 264 (21), 251 (25), 223 (32), 18 (69), 183 (62), 170 (21), 63 (100).

HR-MS (EI, 70 eV): [$C_8H_6Br_2O_2$], calc.: 291.8735; found: 291.8746.

4-Bromo-7-methoxy-2-(4-methoxyphenyl)cyclohepta-2,4,6-trien-1-one (155c)



5-Bromo-2-methoxytropone (**154**, 108 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.6 mL, 0.7 mmol, 1.16 M solution) according to **TP-6**. Then, 4-iodoanisole (105 mg, 0.45 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) were added. The reaction mixture was allowed to warm to r.t. over 4 h and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried

over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:ethyl acetate 9:1) to afford **155c** (103 mg, 0.32 mmol, 70%) as a yellowish solid.

m.p.: 133 – 134 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.69 (d, *J* = 2.1 Hz, 1 H), 7.47 – 7.40 (m, 2 H), 7.34 (dd, *J* = 10.4, 2.1 Hz, 1 H), 6.97 – 6.89 (m, 2 H), 6.47 (d, *J* = 10.4 Hz, 1 H), 3.92 (s, 3 H), 3.84 (s, 3 H).

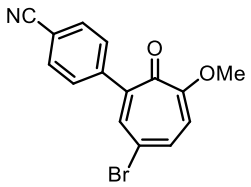
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 179.0, 164.7, 159.9, 146.2, 140.1, 132.5, 132.2, 130.8, 121.5, 113.6, 110.8, 56.6, 55.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3075, 2918, 2829, 1595, 1579, 1565, 1507, 1350, 1250, 1240, 1218, 1183, 1175, 1170, 1117, 1109, 1032, 976, 825, 812, 805.

MS (EI, 70 eV): *m/z* (%) = 323 (11), 322 (87), 321 (62), 320 (92), 319 (51), 291 (20), 241 (20), 198 (100), 183 (45), 155 (25), 127 (34).

HR-MS (EI, 70 eV): [$C_{15}H_{13}BrO_3$], calc.: 320.0048; found: 320.0040.

4-(3-Bromo-6-methoxy-7-oxocyclohepta-1,3,5-trien-1-yl)benzonitrile (155d)



5-Bromo-2-methoxytropone (**154**, 108 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.6 mL, 0.7 mmol, 1.16 M solution) according to **TP-6**. Then, 4-iodobenzonitrile (103 mg, 0.45 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) were added. The reaction mixture was allowed to warm to r.t. over 4 h and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:ethyl acetate 2:1) to afford **155d** (114 mg, 0.36 mmol, 81%) as a yellowish solid.

m.p.: 141 – 142 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.74 – 7.66 (m, 2 H), 7.65 (d, *J* = 2.1 Hz, 1 H), 7.59 – 7.51 (m, 2 H), 7.46 (dd, *J* = 10.5, 2.0 Hz, 1 H), 6.54 (d, *J* = 10.8 Hz, 1 H), 3.95 (s, 3 H).

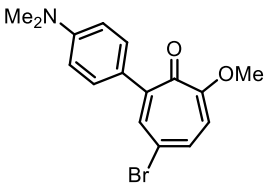
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 178.0, 165.5, 144.8, 144.5, 141.2, 134.5, 131.9, 130.2, 121.2, 118.7, 112.1, 111.1, 56.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3088, 2978, 1712, 1570, 1363, 1296, 1255, 1245, 1217, 1174, 1130, 1112, 1087, 992, 925, 845, 753, 697, 685.

MS (EI, 70 eV): *m/z* (%) = 316 (11), 317 (61), 316 (37), 315 (62), 314 (26), 286 (18), 236 (18), 206 (40), 194 (17), 193 (100), 190 (20), 165 (23), 164 (51), 87 (19).

HR-MS (EI, 70 eV): [$C_{15}H_{10}BrNO_2$], calc.: 314.9895; found: 314.9880.

4-Bromo-2-(4-(dimethylamino)phenyl)-7-methoxycyclohepta-2,4,6-trien-1-one (155e)



5-Bromo-2-methoxytropone (**154**, 108 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.6 mL, 0.7 mmol, 1.16 M solution) according to **TP-6**. Then, 4-iodo-*N*,*N*-dimethylaniline (111 mg, 0.45 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) were added. The reaction mixture was allowed to warm to r.t. over 4 h and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:ethyl acetate 2:1) to afford **155e** (101 mg, 0.30 mmol, 67%) as a yellowish solid.

m.p.: 195 – 196 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.70 (d, *J* = 2.0 Hz, 1 H), 7.49 – 7.40 (m, 2 H), 7.27 (dd, *J* = 10.4, 2.1 Hz, 1 H), 6.77 – 6.66 (m, 2 H), 6.44 (dd, *J* = 10.4, 0.8 Hz, 1 H), 3.91 (s, 3 H), 3.00 (s, 6 H).

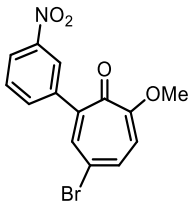
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 179.4, 164.2, 150.7, 146.5, 139.0, 131.4, 130.6, 127.4, 121.7, 111.7, 110.7, 56.6, 40.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925, 2840, 1593, 1587, 1567, 1516, 1356, 1253, 1242, 1228, 1167, 1111, 946, 898, 850, 818.

MS (EI, 70 eV): *m/z* (%) = 336 (5), 335 (19), 334 (5), 333 (21), 332 (3), 211 (17), 70 (12), 61 (17), 45 (16), 43 (100).

HR-MS (EI, 70 eV): [$C_{16}H_{16}BrNO_2$], calc.: 333.0364; found: 333.0359.

4-Bromo-7-methoxy-2-(3-nitrophenyl)cyclohepta-2,4,6-trien-1-one (155f)



5-Bromo-2-methoxytropone (**154**, 108 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.6 mL, 0.7 mmol, 1.16 M solution) according to **TP-6**. Then, 1-iodo-3-nitrobenzene (112 mg, 0.45 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) were added. The reaction mixture was allowed

to warm to r.t. over 4 h and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:ethyl acetate 2:1) to afford **155f** (134 mg, 0.40 mmol, 89%) as a light yellow solid.

m.p.: 177 – 178 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.29 (t, *J* = 2.0 Hz, 1 H), 8.23 (ddd, *J* = 8.3, 2.3, 1.1 Hz, 1 H), 7.78 (dt, *J* = 7.8, 1.3 Hz, 1 H), 7.70 (d, *J* = 2.0 Hz, 1 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.47 (dd, *J* = 10.5, 2.1 Hz, 1 H), 6.55 (d, *J* = 10.5 Hz, 1 H), 3.95 (s, 3 H).

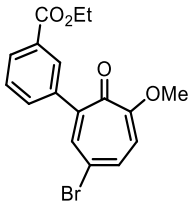
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 178.0, 165.6, 148.1, 144.2, 141.3, 141.3, 135.7, 134.6, 129.0, 124.5, 123.3, 121.2, 111.2, 56.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3063, 1604, 1590, 1572, 1527, 1347, 1266, 1249, 1218, 1118, 1098, 1084, 994, 894, 879, 837, 806, 729, 695, 687, 653.

MS (EI, 70 eV): *m/z* (%) = 337 (32), 336 (19), 335 (38), 334 (12), 320 (99), 318 (98), 290 (40), 288 (34), 260 (31), 148 (49), 246 (45), 139 (100).

HR-MS (EI, 70 eV): [$C_{14}H_{10}BrNO_4$], calc.: 334.9793; found: 334.9774.

Ethyl 3-(3-bromo-6-methoxy-7-oxocyclohepta-1,3,5-trien-1-yl)benzoate (155g)



5-Bromo-2-methoxytropone (**154**, 108 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.6 mL, 0.7 mmol, 1.16 M solution) according to **TP-6**. Then, ethyl 3-iodobenzoate (124 mg, 0.45 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) were added. The reaction mixture was allowed to warm to r.t. over 4 h and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:ethyl acetate 3:1) to afford **155g** (120 mg, 0.33 mmol, 73%) as a light yellow solid.

m.p.: 219 – 220 °C (decomp.).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.08 (t, *J* = 1.7 Hz, 1 H), 8.06 (dt, *J* = 7.7, 1.5 Hz, 1 H), 7.69 (d, *J* = 2.1 Hz, 1 H), 7.65 (dt, *J* = 7.8, 1.4 Hz, 1 H), 7.48 (td, *J* = 7.7, 0.6 Hz, 1 H), 7.42 (dd, *J* = 10.5, 2.1 Hz, 1 H), 6.51 (dd, *J* = 10.6, 0.7 Hz, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 3.94 (s, 3 H), 1.39 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 178.4, 166.3, 165.2, 145.8, 140.9, 140.1, 133.9, 133.7, 130.6, 130.3, 129.6, 128.1, 121.4, 110.9, 61.1, 56.7, 14.4.

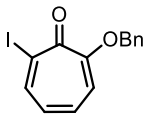
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925, 2852, 1779, 1720, 1609, 1578, 1312, 1252, 1166, 1113, 1058, 1034, 978, 911, 766, 671.

MS (EI, 70 eV): *m/z* (%) = 334 (1), 317 (87), 316 (44), 315 (81), 314 (33), 286 (21), 206 (59), 194 (23), 190 (29), 164 (100), 139 (21).

HR-MS (EI, 70 eV): [$C_{15}H_{11}BrO_4$], calc.: 333.9841; found: 333.9838 [M-Et]$^+$.

4.4 Metalation of 2-Benzyloxytropone

2-(Benzyloxy)-7-iodocyclohepta-2,4,6-trien-1-one (157a)



2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**. The reaction mixture was then cooled to -78 °C and I_2 (253 mg, 1.0 mmol) dissolved in THF (2.0 mL) was added. The reaction was allowed to warm to room temperature over 4 h and was then quenchend with sat. aq. $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:diethyl ether 5:1) to afford **157a** (152 mg, 0.45 mmol, 89%) as a brown solid.

m.p.: 101 – 103 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.52 (dd, *J* = 9.4, 1.0 Hz, 1 H), 7.47 – 7.41 (m, 2 H), 7.40 – 7.29 (m, 3 H), 7.09 – 6.99 (m, 1 H), 6.84 (d, *J* = 9.9 Hz, 1 H), 6.57 – 6.42 (m, 1 H), 5.23 (s, 2 H).

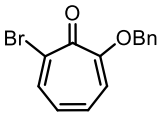
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 175.9, 159.0, 146.8, 135.2, 133.2, 128.7, 128.3, 127.2, 126.7, 122.1, 114.8, 71.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3028, 1580, 1572, 1458, 1451, 1274, 1232, 1194, 1179, 1098, 983, 881, 775, 743, 735, 694.

MS (EI, 70 eV): *m/z* (%) = 339 (1), 338 (3), 232 (19), 211 (9), 105 (9), 91 (100), 65 (9).

HR-MS (EI, 70 eV): [$C_{14}H_{11}IO_2$], calc.: 337.9804; found: 337.9798.

2-(Benzyloxy)-7-bromocyclohepta-2,4,6-trien-1-one (157b)



2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**. The reaction mixture was then cooled to -78 °C and 1,2-dibromotetrachloroethane (325 mg, 1.0 mmol) dissolved in THF (2.0 mL) was added. The reaction was allowed to warm to room temperature over 4 h and was then quenchend with sat. aq. $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:diethyl ether 4:1) to afford **157b** (122 mg, 0.42 mmol, 83%) as an off-white solid.

m.p.: 98 – 100 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.42 (d, *J* = 2.0 Hz, 1 H), 7.43 – 7.36 (m, 6 H), 7.36 – 7.30 (m, 1 H), 6.61 (d, *J* = 10.7 Hz, 1 H), 5.23 (s, 2 H).

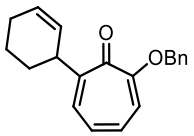
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 173.5, 160.8, 142.6, 137.5, 134.7, 134.4, 128.8, 128.5, 127.2, 120.0, 114.3, 71.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3065, 1583, 1460, 1449, 1279, 1236, 1198, 1100, 981, 977, 887, 776, 767, 754, 727, 693.

MS (EI, 70 eV): *m/z* (%) = 289 (2), 186 (8), 92 (8), 91 (100), 59 (25), 45 (29), 43 (70).

HR-MS (EI, 70 eV): [$C_{14}H_{11}BrO_2$], calc.: 289.9942; found: 289.9934.

2-(Benzyloxy)-7-(cyclohex-2-en-1-yl)cyclohepta-2,4,6-trien-1-one (157c)



2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**. CuCN·2LiCl (0.6 mL, 0.6 mmol, 1 M solution) was added at 0 °C and the reaction mixture was stirred for 0.5 h. Then 3-bromocyclohexene (97 mg, 0.6 mmol) was added and the reaction was allowed to warm to 25 °C over 2 h. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 2:1) to afford **157c** (137 mg, 0.47 mmol, 94%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.49 – 7.43 (m, 2 H), 7.41 – 7.27 (m, 4 H), 6.95 – 6.74 (m, 3 H), 5.97 (dtd, *J* = 9.9, 3.7, 2.2 Hz, 1 H), 5.55 (dq, *J* = 10.1, 2.4 Hz, 1 H), 5.19 (s, 2 H), 4.19 (tp, *J* = 5.6, 2.7 Hz, 1 H), 2.19 – 2.10 (m, 1 H), 2.07 (tq, *J* = 5.9, 2.6 Hz, 2 H), 1.73 – 1.53 (m, 2 H), 1.40 (dddd, *J* = 12.6, 8.8, 6.8, 3.4 Hz, 1 H).

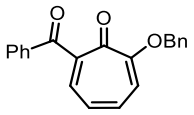
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 179.5, 163.1, 153.7, 135.9, 135.3, 130.6, 130.0, 129.6, 128.6, 128.0, 127.6, 127.1, 114.7, 70.9, 38.3, 29.9, 25.2, 20.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3016, 2923, 2857, 1591, 1572, 1495, 1461, 1453, 1371, 1268, 1244, 1222, 1184, 1175, 1146, 1128, 1080, 1059, 1027, 1002, 976, 910, 889, 872, 848, 803, 733, 694.

MS (EI, 70 eV): *m/z* (%) = 292 (5), 203 (14), 202 (89), 187 (5), 135 (8), 115 (6), 92 (9), 91 (100).

HR-MS (EI, 70 eV): [$C_{20}H_{20}O_2$], calc.: 292.1463; found: 292.1456.

2-Benzoyl-7-(benzyloxy)cyclohepta-2,4,6-trien-1-one (157d)



2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**. CuCN·2LiCl (0.6 mL, 0.6 mmol, 1 M solution) was added at 0 °C and the reaction mixture was stirred for 0.5 h. Then benzoyl chloride (141 mg, 1.0 mmol) and the reaction was allowed to warm to 25 °C over 2 h. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 4:1) to afford **157d** (120 mg, 0.38 mmol, 76%) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.91 – 7.77 (m, 2 H), 7.56 – 7.50 (m, 1 H), 7.46 – 7.28 (m, 8 H), 7.14 (ddd, *J* = 10.9, 9.8, 1.2 Hz, 1 H), 6.96 – 6.88 (m, 2 H), 5.24 (s, 2 H).

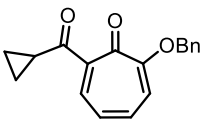
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.9, 178.7, 165.5, 146.7, 136.2, 135.5, 135.1, 134.5, 133.3, 129.3, 128.8, 128.6, 128.3, 127.4, 127.2, 115.0, 71.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2972, 2860, 1673, 1593, 1581, 1497, 1277, 1232, 1198, 1178, 1064, 1030, 944, 906, 753, 733, 696, 676, 662.

MS (EI, 70 eV): *m/z* (%) = 317 (6), 316 (24), 181 (7), 105 (30), 91 (100), 77 (24), 65 (6).

HR-MS (EI, 70 eV): [$C_{21}H_{16}O_3$], calc.: 316.1099; found: 316.1096.

2-(Benzyloxy)-7-(cyclopropanecarbonyl)cyclohepta-2,4,6-trien-1-one (157e)

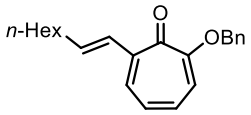


2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**. CuCN·2LiCl (0.6 mL, 0.6 mmol, 1 M solution) was added

at 0 °C and the reaction mixture was stirred for 0.5 h. Then cyclopropanecarbonyl chloride (104 mg, 1.0 mmol) and the reaction was allowed to warm to 25 °C over 2 h. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl/NH_3 solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 2:1) to afford **157e** (95 mg, 0.34 mmol, 68%) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.53 (dd, *J* = 8.8, 1.1 Hz, 1 H), 7.47 – 7.43 (m, 2 H), 7.42 – 7.30 (m, 3 H), 7.10 (ddd, *J* = 10.9, 9.8, 1.2 Hz, 1 H), 6.89 (ddd, *J* = 10.7, 8.7, 0.7 Hz, 1 H), 6.83 (d, *J* = 9.8 Hz, 1 H), 5.25 (s, 2 H), 2.41 (tt, *J* = 7.8, 4.6 Hz, 1 H), 1.27 – 1.18 (m, 2 H), 1.00 (dq, *J* = 7.4, 3.6 Hz, 2 H).
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 205.6, 179.1, 166.1, 146.2, 136.3, 135.1, 135.0, 128.8, 128.4, 127.3, 127.0, 114.0, 71.2, 21.2, 12.8.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3007, 1673, 1614, 1592, 1572, 1490, 1453, 1376, 1274, 1248, 1191, 1155, 1058, 1025, 969, 956, 921, 907, 862, 734, 695.
MS (EI, 70 eV): *m/z* (%) = 280 (3), 174 (8), 92 (7), 91 (100), 65 (7).
HR-MS (EI, 70 eV): [$C_{18}H_{16}O_3$], calc.: 280.1099; found: 280.1092.

(*E*)-2-(Benzyloxy)-7-(3-oxooct-1-en-1-yl)cyclohepta-2,4,6-trien-1-one (157f)



2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**, followed by addition of (*E*)-1-iodooct-1-ene (143 mg, 0.6 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) at 0 °C. The reaction mixture was allowed to warm to r.t. over 4 h and was then quenched by the addition of sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:ethyl acetate 6:1) to afford **157f** (90 mg, 0.38 mmol, 75%) as a yellow oil.

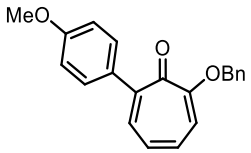
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56 (dd, *J* = 8.9, 1.3 Hz, 1 H), 7.49 – 7.44 (m, 2 H), 7.41 – 7.34 (m, 2 H), 7.34 – 7.27 (m, 1 H), 7.01 (dt, *J* = 15.8, 1.6 Hz, 1 H), 6.94 – 6.75 (m, 3 H), 6.39 (dt, *J* = 15.6, 7.0 Hz, 1 H), 5.22 (s, 2 H), 2.28 (qd, *J* = 7.1, 1.5 Hz, 2 H), 1.49 (ddd, *J* = 12.2, 8.2, 6.5 Hz, 2 H), 1.41 – 1.23 (m, 6 H), 0.96 – 0.79 (m, 3 H).
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 179.1, 163.2, 144.4, 136.3, 135.8, 132.4, 130.7, 129.1, 128.7, 128.1, 127.5, 127.1, 115.1, 70.9, 33.6, 31.8, 29.2, 29.0, 22.6, 14.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 2924, 2855, 1721, 1698, 1590, 1572, 1557, 1496, 1453, 1377, 1365, 1270, 1193, 1177, 1079, 1027, 1002, 968, 907, 849, 801, 734, 695, 652.

MS (EI, 70 eV): *m/z* (%) = 322 (5), 237 (18), 231 (25), 147 (15), 91 (100), 59 (13).

HR-MS (EI, 70 eV): [$C_{22}H_{26}O_2$], calc.: 322.1933; found: 322.1963.

2-(Benzyloxy)-7-(4-methoxyphenyl)cyclohepta-2,4,6-trien-1-one (157g)



2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**, followed by addition of 4-iodoanisole (140 mg, 0.6 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) at 0 °C. The reaction mixture was allowed to warm to r.t. over 4 h and was then quenched by the addition of sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (CH_2Cl_2:ethyl acetate 4:1) to afford **157g** (124 mg, 0.39 mmol, 77%) as a yellow solid.

m.p.: 105 – 106 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.51 – 7.41 (m, 5 H), 7.40 – 7.28 (m, 3 H), 6.96 – 6.90 (m, 3 H), 6.90 – 6.79 (m, 2 H), 5.21 (s, 2 H), 3.83 (s, 3 H).

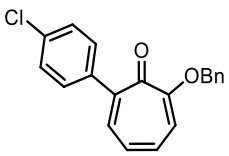
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 179.5, 164.7, 159.5, 147.3, 136.8, 135.8, 133.5, 131.0, 130.9, 128.7, 128.1, 127.5, 127.2, 114.8, 113.4, 71.0, 55.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3003, 2905, 1597, 1592, 1583, 1575, 1508, 1270, 1241, 1219, 1199, 1189, 1178, 1094, 1073, 1030, 992, 834, 823, 811, 767, 758, 739, 695

MS (EI, 70 eV): *m/z* (%) = 318 (10), 212 (12), 199 (32), 171 (12), 128 (10), 91 (40), 59 (22), 43 (100).

HR-MS (EI, 70 eV): [$C_{21}H_{18}O_3$], calc.: 318.1256; found: 318.1251.

2-(Benzyloxy)-7-(4-chlorophenyl)cyclohepta-2,4,6-trien-1-one (157h)



2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**, followed by addition of 1-chloro-4-iodobenzene

(143 mg, 0.6 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) at 0 °C. The reaction mixture was allowed to warm to r.t. over 4 h and was then quenched by the addition of sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 2:1) to afford **157h** (136 mg, 0.42 mmol, 83%) as a yellow solid.

m.p.: 98 – 100 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.48 – 7.28 (m, 10 H), 7.00 (ddd, *J* = 10.7, 9.5, 1.2 Hz, 1 H), 6.95 – 6.80 (m, 2 H), 5.24 (s, 2 H).

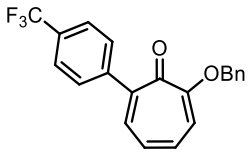
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 179.1, 165.0, 146.5, 139.5, 137.3, 135.5, 133.9, 131.9, 130.9, 128.7, 128.2, 128.1, 127.3, 127.2, 114.7, 71.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1583, 1555, 1493, 1454, 1271, 1219, 1210, 1181, 1155, 1092, 1073, 1013, 955, 917, 896, 846, 824, 799, 793, 751, 723, 705, 695, 665, 656.

MS (EI, 70 eV): *m/z* (%) = 324 (1), 322 (4), 216 (12), 181 (6), 92 (6), 91 (100), 43 (28).

HR-MS (EI, 70 eV): [$C_{20}H_{15}ClO_2$], calc.: 322.0761; found: 322.0754.

2-(Benzyloxy)-7-(4-(trifluoromethyl)phenyl)cyclohepta-2,4,6-trien-1-one (157i)



2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**, followed by addition of 4-iodobenzotrifluoride (163 mg, 0.6 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) at 0 °C. The reaction mixture was allowed to warm to r.t. over 4 h and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 2:1) to afford **157i** (164 mg, 0.46 mmol, 91%) as a yellow solid.

m.p.: 123 – 124 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.65 (d, *J* = 8.2 Hz, 2 H), 7.58 (d, *J* = 8.1 Hz, 2 H), 7.50 – 7.39 (m, 3 H), 7.40 – 7.35 (m, 2 H), 7.35 – 7.29 (m, 1 H), 7.04 (ddd, *J* = 10.7, 9.6, 1.1 Hz, 1 H), 6.95 – 6.84 (m, 2 H), 5.25 (s, 2 H).

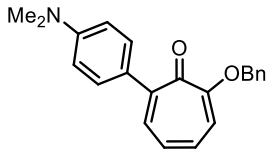
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 178.9, 165.3, 146.4, 144.7 (d, *J* = 1.7 Hz), 137.6, 135.4, 132.4, 129.8 (q, *J* = 32.4 Hz), 129.8, 128.7, 128.2, 127.2, 127.1, 124.9 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.0 Hz), 114.7, 71.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1597, 1582, 1497, 1325, 1275, 1222, 1155, 1102, 1096, 1063, 1011, 993, 853, 839, 761, 752, 733, 693, 685.

MS (EI, 70 eV): *m/z* (%) = 356 (4), 265 (7), 250 (16), 181 (6), 92 (9), 91 (100), 65 (8).

HR-MS (EI, 70 eV): [$C_{21}H_{15}F_3O_2$], calc.: 356.1024; found: 356.1037.

2-(Benzyloxy)-7-(4-(dimethylamino)phenyl)cyclohepta-2,4,6-trien-1-one (157j)



2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**, followed by addition of 4-iodo-*N*,*N*-dimethylaniline (148 mg, 0.6 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) at 0 °C. The reaction mixture was allowed to warm to r.t. over 4 h and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 2:1) to afford **157j** (128 mg, 0.39 mmol, 77%) as a yellow solid.

m.p.: 119 – 120 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.51 – 7.43 (m, 5 H), 7.40 – 7.33 (m, 2 H), 7.33 – 7.27 (m, 1 H), 6.90 – 6.84 (m, 2 H), 6.84 – 6.80 (m, 1 H), 6.78 – 6.70 (m, 2 H), 5.22 (s, 2 H), 2.99 (s, 6 H).

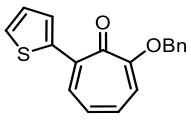
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 179.8, 164.3, 150.4, 147.7, 136.0, 135.9, 130.6, 130.0, 128.8, 128.6, 128.0, 127.6, 127.2, 115.1, 111.8, 71.0, 40.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925, 2811, 1595, 1587, 1571, 1522, 1444, 1360, 1264, 1222, 1214, 1199, 1180, 1173, 1153, 1079, 1067, 967, 945, 894, 819, 802, 795, 766, 755, 733, 697.

MS (EI, 70 eV): *m/z* (%) = 332 (7), 331 (33), 241 (15), 213 (19), 221 (100), 197 (14), 184 (50), 168 (13), 91 (21).

HR-MS (EI, 70 eV): [$C_{22}H_{21}NO_2$], calc.: 331.1572; found: 331.1569.

2-(Benzyloxy)-7-(thiophen-2-yl)cyclohepta-2,4,6-trien-1-one (157k)



2-Benzyloxytropone (**156**, 106 mg, 0.5 mmol) was metalated with TMPZnCl·LiCl (**36**, 0.86 mL, 1.0 mmol, 1.16 M solution) according to **TP-7**, followed by addition of 2-iodothiophene (126 mg, 0.6 mmol), $Pd(dba)_2$ (9 mg, 3 mol%) and P(*o*-furyl)$_3$ (7 mg, 6 mol%) at 0 °C. The reaction mixture was allowed to warm to r.t. over 4 h and was then quenched with sat. aq. NH_4Cl solution, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 9:1) to afford **157k** (118 mg, 0.40 mmol, 80%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.01 (dd, *J* = 9.0, 1.3 Hz, 1 H), 7.64 (dd, *J* = 3.9, 1.2 Hz, 1 H), 7.52 (dd, *J* = 5.2, 1.1 Hz, 1 H), 7.48 – 7.43 (m, 2 H), 7.40 – 7.28 (m, 3 H), 7.12 (dd, *J* = 5.1, 3.9 Hz, 1 H), 7.05 – 6.86 (m, 3 H), 5.24 (s, 2 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 177.2, 163.8, 140.4, 138.9, 135.6, 133.7, 131.3, 130.6, 128.7, 128.2, 127.3, 127.2, 127.1, 126.1, 115.3, 71.2.

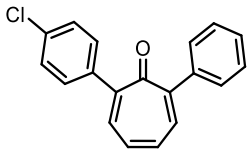
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3063, 2865, 1583, 1561, 1452, 1413, 1368, 1267, 1233, 1188, 1176, 1086, 1050, 1028, 1015, 954, 888, 851, 741, 693, 661.

MS (EI, 70 eV): *m/z* (%) = 295 (3), 294 (16), 267 (6), 262 (5), 188 (6), 175 (14), 147 (16), 115 (6), 91 (100), 65 (8).

HR-MS (EI, 70 eV): [$C_{18}H_{14}O_2S$], calc.: 294.0715; found: 294.0710.

4.5 Addition of Grignard Reagents to 7-Aryl-2-benzyloxytropones

2-(4-Chlorophenyl)-7-phenylcyclohepta-2,4,6-trien-1-one (159a)



Compound **159a** was prepared from 2-(benzyloxy)-7-(4-chlorophenyl)cyclohepta-2,4,6-trien-1-one (**157h**, 65 mg, 0.2 mmol) and phenylmagnesium chloride (0.15 mL, 0.24 mmol, 1.64 M solution in THF) according to **TP-8**. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 6:1) to afford **159a** as a yellow solid (36 mg, 0.12 mmol, 62%).

m.p.: 114 – 115 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.57 – 7.46 (m, 4H), 7.43 – 7.29 (m, 7H), 7.10 – 6.96 (m, 2H).

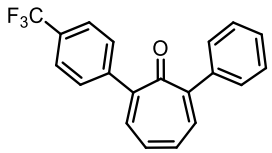
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 186.6, 151.0, 149.5, 140.1, 138.5, 134.5, 134.4, 134.3, 132.3, 131.8, 130.7, 129.2, 128.3, 128.3, 128.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923, 1573, 1489, 1347, 1091, 932, 824, 799, 778, 769, 746, 729, 695, 674, 665.

MS (EI, 70 eV): *m/z* (%) = 294 (24), 293 (34), 292 (62), 291 (70), 264 (28), 229 (68), 228 (26), 113 (22), 43 (100).

HR-MS (EI, 70 eV): [$C_{19}H_{12}ClO$], calc.: 291.0577; found: 291.0573 [M-H^+].

2-Phenyl-7-(4-(trifluoromethyl)phenyl)cyclohepta-2,4,6-trien-1-one (159b)



Compound **159b** was prepared from 2-(benzyloxy)-7-(4-(trifluoromethyl)phenyl)cyclohepta-2,4,6-trien-1-one (**157i**, 71 mg, 0.2 mmol) and phenylmagnesium chloride (0.15 mL, 0.24 mmol, 1.64 M solution in THF) according to **TP-8**. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 6:1) to afford **159b** as a yellow solid (47 mg, 0.14 mmol, 72%).

m.p.: 148 – 149 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.64 (s, 4 H), 7.56 – 7.51 (m, 2 H), 7.44 – 7.33 (m, 5 H), 7.13 – 6.98 (m, 2 H).

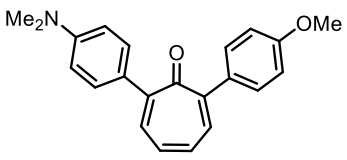
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 186.3, 151.6, 149.7, 143.9, 139.9, 135.1, 134.8, 132.9, 131.8, 130.1 (q, *J* = 32.6 Hz), 129.6, 129.2, 128.4, 128.2, 125.0 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.1 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922, 1617, 1574, 1324, 1316, 1292, 1272, 1192, 1184, 1168, 1154, 1129, 1105, 1070, 1060, 1018, 1004, 932, 836, 798, 780, 754, 738, 715, 693, 672.

MS (EI, 70 eV): *m/z* (%) = 327 (19), 326 (88), 325 (100), 298 (41), 283 (20), 257 (15), 229 (47), 228 (40), 226 (15).

HR-MS (EI, 70 eV): [$C_{20}H_{13}F_3O$], calc.: 326.0918; found: 326.0897.

2-(4-Methoxyphenyl)-7-(4-(trifluoromethyl)phenyl)cyclohepta-2,4,6-trien-1-one (159c)



Compound **159c** was prepared from 2-(benzyloxy)-7-(4-(dimethylamino)phenyl)cyclohepta-2,4,6-trien-1-one (**157j**, 66 mg, 0.2 mmol) and *p*-anisylmagnesium chloride (0.26 mL, 0.24 mmol, 0.94 M solution in THF) according to **TP-8**. The crude product was purified by column chromatography on silica (*i*-hexane:ethyl acetate 3:1) to afford **159c** as a yellow solid (40 mg, 0.12 mmol, 61%).

m.p.: 94 – 96 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.60 – 7.53 (m, 3 H), 7.27 (ddd, *J* = 14.4, 8.1, 1.4 Hz, 3 H), 6.98 – 6.83 (m, 4 H), 6.74 – 6.68 (m, 2 H), 3.82 (s, 3 H), 2.98 (s, 6 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 188.4, 159.5, 150.5, 148.7, 147.6, 132.6, 132.1, 131.0, 131.0, 130.4, 130.2, 129.9, 127.2, 113.6, 111.8, 55.3, 40.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922, 1600, 1570, 1505, 1438, 1352, 1288, 1244, 1225, 1202, 1176, 1163, 1030, 835, 824, 802, 794, 761.

MS (EI, 70 eV): *m/z* (%) = 332 (1), 221 (5), 330 (1), 303 (7), 73 (6), 70 (12), 61 (17), 45 (15), 43 (100).

HR-MS (EI, 70 eV): [$C_{22}H_{21}NO_2$], calc.: 331.1572; found: 331.1565.

5 Cobalt-Catalyzed Negishi Cross-Coupling of (Hetero)Arylzinc Reagents with Primary and Secondary Alkyl Bromides and Iodides

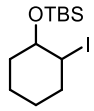
5.1 Preparation of Starting Materials

The following starting materials were prepared by standard procedures:

Protection of the alcohol: The respective diol (1.0 equiv) was dissolved in DMF (0.5 M solution), then imidazole (1.2 equiv) and TBSCl (1.2 equiv) were added portionwise. The reaction mixture was stirred for 12 h, then sat. aq. NH_4Cl solution was added and the phases were separated. The aqueous phase mixture was extracted with diethyl ether and the combined organic layers were dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography on silica to afford the TBS-protected alcohol.

Iodination: A suspension of I_2 (1.2 equiv) in CH_2Cl_2 (0.5 M solution) was cooled to 0 °C and PPh_3 was added portionwise. The reaction mixture was stirred for 1 h, then NMI (1.2 equiv) was added, followed by the addition of the TBS-protected cycloalcohol (1.0 equiv). The reaction mixture was stirred for 2 h and allowed to warm to 25 °C. Sat. aq. NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography on silica (*i*-hexane) to yield the TBS-protected alkyl iodide.

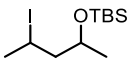
***tert*-Butyl((2-iodocyclohexyl)oxy)dimethylsilane[189]**



d.r.: 25:75 (*trans*/*cis*).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 4.53 - 4.39 (m, 1 H), 3.36 (s br, 1 H), 2.32 - 2.20 (m, 1 H), 1.96 - 1.84 (m, 1 H), 1.79 - 1.60 (m, 3 H), 1.57 - 1.30 (m, 3 H), 0.95 (s, 9 H), 0.14 (s, 3 H), 0.08 (s, 3 H).

***tert*-butyl((4-iodopentan-2-yl)oxy)dimethylsilane[190]**

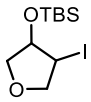


[189] M. R. Detty, M, D. Seidler, *J. Org. Chem.* **1981**, *46*, 1283.
[190] K. Moriya, D. Didier, M. Simon, J. M. Hammann, G. Berionni, K. Karaghiosoff, H. Zipse, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 2754.

d.r.: 50:50 (*syn*/*anti*)

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 4.17 (ddq, *J* = 7.9, 6.85, 6.84 Hz, 1 H), 3.92 (qt, *J* = 6.11, 6.10 Hz, 1 H), 2.19 (ddd, *J* = 14.4, 8.0. 6.6 Hz, 1 H), 1.93 (d, *J* = 6.8 Hz, 3 H), 1.70 (dt, *J* = 14.1, 6.5 Hz, 1 H), 1.12 (d, *J* = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.074 (s, 3 H), 0.068 (s, 3 H).

***tert*-Butyl((4-iodotetrahydrofuran-3-yl)oxy)dimethylsilane[168a]**



2,5-Dihydrofuran (10.0 mmol) was dissolved in DME (70 mL) and H_2O (25 mL) and the mixture was cooled to -20 °C. NIS (15 mmol) was added portionwise and the reaction was stirred for 5 h. Sat. aq. NaCl solution was added, the phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated. The residue was dissolved in DMF and imidazole (16 mmmol) and TBSCl (12 mmol) were added portionwise. The reaction was stirred for 12 h at 25 °C and then NH_4Cl was added. The phases were separated and the aqueous phase was extracted with diethy ether. The combined organic layers were dried over Na_2SO_4, the solvent was evaporated and the residue was subjected to column chromatography on silica (pentane/diethyl ether) yielding the title compound (2.4 g, 73% yield) as colorless oil.

d.r.: 99:1 (*trans*/*cis*).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 4.58 (dt, *J* = 4.4, 2.2 Hz, 1 H), 4.36 - 4.17 (m, 2 H), 4.10 - 3.97 (m, 2 H), 3.66 (dd, *J* = 9.3, 2.1 Hz, 1 H), 0.87 (s, 9 H), 0.14 - 0.01 (m, 6 H).

***tert*-Butyl((2-iodocyclopentyl)oxy)dimethylsilane[189]**

Cyclopentene (10.0 mmol) was dissolved in DME (70 mL) and H_2O (25 mL) and the mixture was cooled to -20 °C. NIS (15 mmol) was added portionwise and the reaction was stirred for 5 h. Sat. aq. NaCl solution was added, the phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated. The residue was dissolved in DMF and imidazole (16 mmmol) and TBSCl (12 mmol) were added

portionwise. The reaction was stirred for 12 h at 25 °C and then NH_4Cl was added. The phases were separated and the aqueous phase was extracted with diethy ether. The combined organic layers were dried over Na_2SO_4, the solvent was evaporated and the residue was subjected to column chromatography on silica (pentane/diethyl ether) yielding the title compound (2.5 g, 76% yield) as colorless oil.

d.r.: 99:1 (*trans*/*cis*).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 4.43 (ddd, *J* = 6.3, 3.6, 3.3 Hz, 1 H), 4.06 - 3.98 (m, 1 H), 2.41 - 2.28 (m, 1 H), 2.16 - 1.97 (m, 2 H), 1.80 (quin, *J* = 7.4 Hz, 2 H), 1.60 - 1.49 (m, 1 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H).

5.2 Typical Procedures

Typical procedure for the metalation of (hetero)arenes using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (48) (TP-9):

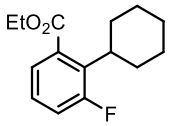
A dry and argon-flushed 10 mL *Schlenk*-tube was charged with a solution of the corresponding (hetero)arene (1.4 mmol, 1.0 equiv) in dry THF (1 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL, 0.6 equiv) was added dropwise at the given temperature and the reaction mixture was stirred at this temperature. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Typical procedure for the cobalt-catalyzed cross-coupling of (hetero)arylzinc reagents with alkyl halides (TP-10):

A dry and argon-flushed 10 mL *Schlenk*-tube was charged with a solution of $CoCl_2{\cdot}2LiCl$ (1 M in THF) (0.2 mmol, 0.2 mL, 20 mol%) and dry THF (1.0 mL). The respective alkyl iodide or bromide (1.0 mmol, 1.0 equiv) and TMEDA (0.3 mmol, 45 mg, 30 mol%) were added *via* syringe. The reaction mixture was cooled to 0 °C and a solution of the freshly prepared zinc reagent (1.4 mmol, 1.4 equiv) was added dropwise over 5 min. The reaction was allowed to warm to 25 °C and was monitored by GC-analysis (undecane $C_{11}H_{24}$ was used as an internal standard). Upon consumption of the starting material, saturated aqueous NH_4Cl solution (5 mL) and ethyl acetate (5 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

5.3 Cobalt-Catalyzed Negishi Cross-Coupling Reactions of (Hetero)Arylzinc Reagents with Alkyl Halides

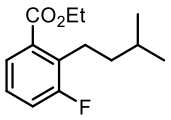
Ethyl 2-cyclohexyl-3-fluorobenzoate (162a)[191]



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (**160**, 235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to 25 °C, stirred for 8 h and was then added dropwise according to **TP-10** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (99:1) as an eluent to afford **162a** as a colorless oil (87%, 218 mg, 0.87 mmol).

^{1}H-NMR 300 MHz, $CDCl_3$, ppm): δ = 7.35 (ddd, *J* = 7.6, 1.5, 0.4 Hz, 1 H), 7.04-7.20 (m, 2 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 3.01-3.13 (m, 1 H), 1.68-1.93 (m, 7 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.26-1.37 (m, 3 H).

Ethyl 3-fluoro-2-isopentylbenzoate (162b)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (**160**, 235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP-10** to 1-iodo-3-methylbutane (198 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **162b** as a colorless oil (63%, 150 mg, 0.63 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.62 – 7.58 (m, 1 H), 7.23 – 7.11 (m, 2 H), 4.36 (q, *J* = 7.1 Hz, 0.4, 2 H), 3.03 – 2.89 (m, 2 H), 1.71 – 1.59 (m, 1 H), 1.51 – 1.43 (m, 2 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.08 – 0.88 (d, J = 6.4 Hz, 6 H).

[191] S. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.

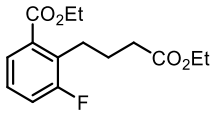
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 167.0, 161.2 (d, *J* = 246.1 Hz), 132.3 (d, *J* = 4.6 Hz), 131.8 (d, *J* = 17.3 Hz), 126.5 (d, *J* = 9.3 Hz), 125.9 (d, *J* = 3.5 Hz), 118.4 (d, *J* = 23.9 Hz), 61.1, 39.7, 28.5, 24.1, 22.4, 14.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2871, 1456, 1366, 1257, 1172, 1257, 1099, 1025, 907, 755.

MS (EI, 70 eV): *m/z* (%) = 238 (20), 195 (20), 193 (18), 183 (10), 182 (86), 167 (52), 163 (17), 154 (20), 153 (41), 149 (59), 08 (12).

HR-MS (EI, 70 eV): [$C_{14}H_{19}FO_2$], calcd.: 238.1369; found: 238.1356.

Ethyl 2-(4-ethoxy-4-oxobutyl)-3-fluorobenzoate (162c)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (**160**, 235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP-10** to either ethyl 4-iodobutanoate (X = I, 242 mg, 1.0 mmol) or 4-ethyl bromobutanoate (X = Br, 195 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (92:8) as an eluent to afford **162c** as a colorless oil (X = I: 58%, 164 mg, 0.58 mmol; X = Br: 38%, 107 mg, 0.38 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.67 – 7.60 (m, 1H), 7.25 – 7.11 (m, 2H), 4.34 (q, *J* = 7.1 Hz, 0.4, 2H), 4.17 – 4.04 (m, 2H), 3.00 (q, *J* = 7.3 Hz, 2H), 2.35 (t, *J* = 7.7 Hz, 2H), 1.99 – 1.86 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

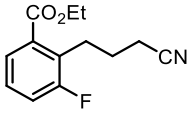
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 173.3, 166.6 (d, *J* = 3.5 Hz), 161.3 (d, *J* = 244.6 Hz), 132.2 (d, *J* = 4.2 Hz), 130.4 (d, *J* = 17.6 Hz), 127.0 (d, *J* = 9.0 Hz), 126.2 (d, *J* = 3.4 Hz), 118.6 (d, *J* = 24.0 Hz), 61.1, 60.2, 34.1, 25.6, 25.1, 14.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981, 1720, 1456, 1367, 1258, 1174, 1129, 1059, 1024, 934, 757, 732.

MS (EI, 70 eV): *m/z* (%) = 237 (45), 236 (55), 208 (15), 194 (21), 191 (15), 190 (18), 163 (31), 162 (12), 153 (16), 149 (32), 135 (16), 133 (11).

HR-MS (EI, 70 eV): [$C_{15}H_{19}FO_4$], calcd.: 282.1267; found: 282.1271.

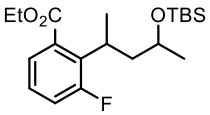
Ethyl 2-(3-cyanopropyl)-3-fluorobenzoate (162d)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (**160**, 235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP-10** to either 4-iodobutanenitrile (X = I, 195 mg, 1.0 mmol) or 4-bromobutanenitrile (X = Br, 148 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (97:3) as an eluent to afford **162d** as a colorless oil (X = I: 71%, 167 mg, 0.71 mmol; X = Br: 51%, 120 mg, 0.51 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.04 - 7.96 (m, 1 H), 7.05 – 6.90 (m, 2 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 3.18 – 3.03 (m, 2 H), 2.41 (t, *J* = 7.2 Hz, 2 H), 2.06 – 1.88 (m, 2 H), 1.40 (t, *J* = 7.2 Hz, 3 H).
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 166.1, 165.2 (d, *J* = 254.1 Hz), 154.5 (d, *J* = 8.4 Hz), 133.8 (d, *J* = 9.3 Hz), 125.6 (d, *J* = 2.8 Hz), 119.4, 117.8 (d, *J* = 21.6 Hz), 113.7 (d, *J* = 21.0 Hz), 61.1, 33.5, 26.7, 16.9, 14.3.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2254, 1715, 1458, 1261, 1139, 1056, 1020, 905, 760, 725.
MS (EI, 70 eV): *m/z* (%) = 235 (2), 217 (4), 190 (16), 189 (25), 188 (5), 167 (45), 109 (5).
HR-MS (EI, 70 eV): [$C_{13}H_{14}FNO_2$], calcd.: 235.1009; found: 235.1006.

Ethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)-3-fluorobenzoate (162e)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (**160**, 235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP-10** to *tert*-butyl((4-iodopentan-2-yl)oxy)dimethylsilane (328 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (95:5) as an eluent to afford **162e** as a colorless oil (70%, 258 mg, 0.70 mmol, d.r. 52:48).

Signals of both diastereomers are given:

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.38 (dddd, *J* = 13.3, 7.6, 1.5, 0.6 Hz, 2H), 7.25 – 7.02 (m, 4H), 4.34 (qdd, *J* = 7.1, 4.1, 2.1 Hz, 4H), 3.85 – 3.64 (m, 2H), 3.56 – 3.43 (m, 2H), 2.07 – 1.70 (m, 5H), 1.47 – 1.30 (m, 13H), 1.10 (dd, *J* = 6.1, 1.7 Hz, 6H), 0.92 – 0.81 (m, 18H), 0.04 – -0.07 (m, 12H).

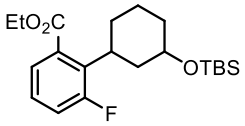
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 167.9 (d, *J* = 3.8 Hz), 167.9 (d, *J* = 3.9 Hz), 162.4 (d, *J* = 248.3 Hz), 162.1 (d, *J* = 247.1 Hz), 134.5 (d, *J* = 14.9 Hz), 134.0 (d, *J* = 6.5 Hz), 133.8 (d, *J* = 14.8 Hz), 133.5 (d, *J* = 6.6 Hz), 127.0 (d, *J* = 9.4 Hz), 126.8 (d, *J* = 9.4 Hz), 125.1 (d, *J* = 3.5 Hz), 124.8 (d, *J* = 3.5 Hz), 118.9 (d, *J* = 24.0 Hz), 118.6 (d, *J* = 23.8 Hz), 67.9, 66.7, 61.3 45.5, 45.1, 31.0, 30.5, 25.9, 25.8, 23.8, 23.7, 20.3, 19.4, 18.0, 18.0, 14.2, -4.4, -4.5, -4.8, -4.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 2930, 2857, 1723, 1451, 1367, 1278, 1255, 1178, 1142, 1037, 909, 834, 808, 773, 733.

MS (EI, 70 eV): *m/z* (%) = 311 (73), 265 (27), 223 (19), 163 (24), 159 (6), 149 (19), 121 (4), 103 (10), 75 (24), 73 (16).

HR-MS (EI, 70 eV): [$C_{16}H_{24}FO_3Si$], calcd.: 311.1479; found: 311.1488.

Ethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-3-fluorobenzoate (162f)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (**160**, 235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP-10** to *tert*-butyl((3-iodocyclohexyl)oxy)dimethylsilane (340 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (98:2) as an eluent to afford **162f** as a colorless oil (79%, 301 mg, 0.79 mmol, d.r. 51:49).

Signals of both diastereomers are given:

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.41 (d, *J* = 7.3 Hz, 1 H), 7.32 (d, *J* = 7.6 Hz, 1 H), 7.16 - 7.25 (m, 2 H), 7.05 - 7.15 (m, 2 H), 4.24 - 4.48 (m, 4 H), 4.15 (br, 1 H), 3.54 - 3.68 (m, 2 H), 3.13 - 3.24 (m, 1 H), 2.05 - 2.16 (m, 1 H), 1.64 - 2.01 (m, 12 H), 1.44 - 1.61 (m, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.33 - 1.37 (m, 1 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 168.5 (d, *J* = 3.7 Hz), 168.2 (d, *J* = 3.7 Hz), 162.6 (d, *J* = 248.0 Hz), 162.3 (d, *J* = 248.0 Hz), 134.8 (d, *J* = 6.6 Hz), 133.6 (d, *J* = 6.6 Hz), 132.9 (d, *J* = 14.7 Hz), 132.4 (d, *J* = 14.7

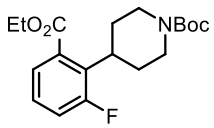
Hz), 127.2 (d, *J* = 8.8 Hz), 127.0 (d, *J* = 9.5 Hz), 125.1 (d, *J* = 3.7 Hz), 124.5 (d, *J* = 3.70 Hz), 119.1 (d, *J* = 24.2 Hz), 118.6 (d, *J* = 24.2 Hz), 71.7, 67.0, 61.4, 40.1 (d, *J* = 4.4 Hz), 37.8 (d, *J* = 1.5 Hz), 37.7, 37.6, 35.7, 33.1 (d, *J* = 1.5 Hz), 32.9, 30.7 (d, *J* = 2.9 Hz), 29.8 (d, *J* = 4.4 Hz), 25.9, 25.8, 24.8, 20.4, 18.2, 18.1, 14.3, 14.3, -4.6, -4.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 2857, 1724, 1453, 1367, 1280, 1269, 1251, 1230, 1174, 1140, 1120, 1091, 1057, 1038, 1026, 981, 856, 834, 805, 773, 758.

MS (EI, 70 eV): m/z (%) = 365 (2), 335 (8), 325 (7), 324 (24), 323 (100), 305 (5), 278 (9), 277 (43), 260 (5), 259 (25), 249 (19), 235 (9), 227 (10), 221 (10), 203 (19)m 202 (8), 185 (29), 183 (22), 175 (12), 165 (15), 147 (19), 133 (13).

HR-MS (EI, 70 eV): [$C_{21}H_{33}FO_3{}^{28}Si$], calc.: 365.1948; found: 365.1939 [M^+-CH_3].

***tert*-Butyl 4-(2-(ethoxycarbonyl)-6-fluorophenyl)piperidine-1-carboxylate (162g)**



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (**160**, 235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP-10** to *tert*-butyl 4-iodopiperidine-1-carboxylate (311 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **162g** as a colorless oil (79%, 277 mg, 0.79 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.41 (d, *J* = 1.4 Hz, 1 H), 7.27 – 7.06 (m, 2 H), 4.36 (q, *J* = 7.1, 2 H), 4.21 (d, *J* = 13.2 Hz, 2 H), 3.40 – 3.25 (m, 1 H), 2.82 – 2.65 (m, 2 H), 2.17 – 1.95 (m, 2 H), 1.72 (d, *J* = 1.7 Hz, 2 H), 1.47 (s, 9 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

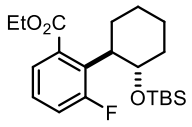
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 167.8, 162.1 (d, *J* = 249.1 Hz), 154.9, 133.6 (d, *J* = 6.9 Hz), 131.9 (d, *J* = 14.3 Hz), 127.5 (d, *J* = 8.9 Hz), 125.3 (d, *J* = 3.8 Hz), 119.2 (d, *J* = 23.9 Hz), 79.3, 61.4, 44.7, 37.9, 29.9, 28.5, 14.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2978, 2863, 1719, 1684, 1450, 1424, 1366, 1275, 1244, 1165, 1118, 1018, 905, 758, 728.

MS (EI, 70 eV): *m/z* (%) = 292 (3), 278 (5), 252 (6), 251 (26), 250 (6), 222 (31), 203 (5), 132 (3), 57 (11).

HR-MS (EI, 70 eV): [$C_{19}H_{26}FNO_4$], calcd.: 351.1846; found: 351.1831.

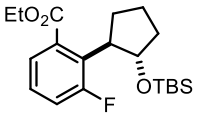
Ethyl 2-((1*R*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-3-fluorobenzoate (162h)[192]



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (**160**, 235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP-10** to *tert*-butyl((2-iodocyclohexyl)-oxy)dimethylsilane (340 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (99:1) as an eluent to afford **162h** as a colorless oil (68%, 259 mg, 0.68 mmol, d.r. 99:1 (*trans*:*cis*)).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.39 (d, *J* = 7.7 Hz, 1 H), 7.22 – 7.05 (m, 2 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 4.03 – 4.12 (m, 1 H), 3.21 – 3.31 (m, 1 H), 1.86 – 2.01 (m, 3 H), 1.70 – 1.82 (m, 2 H), 1.27 – 1.42 (m, 6 H), 0.61 (s, 9 H), -0.10 (s, 3 H), -0.42 (s, 3 H).

Ethyl 2-((1*R*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)-3-fluorobenzoate (162i)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (**160**, 235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP-10** to *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (326 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (98:2) as an eluent to afford **162i** as a colorless oil (69%, 253 mg, 0.69 mmol, d.r. 99:1 (*trans*:*cis*)).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.43 (d, *J* = 7.6 Hz, 1 H), 7.21 (td, *J* = 7.9, 5.3 Hz, 1 H), 7.09 - 7.17 (m, 1 H), 4.42 - 4.50 (q, *J* = 7.3 Hz, 1 H), 4.34 (m, 2 H), 3.51 - 3.66 (m, 2 H), 2.10 - 2.21 (m, 1 H), 2.07 - 2.01 (m, 1 H), 1.75 - 1.96 (m, 3 H), 1.58 - 1.70 (m, 1 H), 1.38 (t, *J* = 7.1 Hz, 3 H), 0.74 (s, 9 H) -0.20 (s, 3 H), -0.31 (s, 3 H).

[192] A. K. Steib, T. Thaler, K. Komeyama, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 3303.

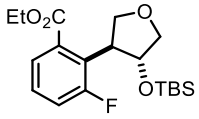
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.9 (d, *J* = 4.4 Hz), 161.9 (d, *J* = 246.5 Hz), 135.1 (d, *J* = 6.6 Hz), 131.58 (d, *J* = 13.2 Hz), 127.0 (d, *J* = 9.5 Hz), 124.9 (d, *J* = 2.9 Hz), 118.5 (d, *J* = 23.5 Hz), 79.0 (d, *J* = 5.1 Hz), 61.3, 48.4 (d, *J* = 2.2 Hz), 36.0, 30.3 (d, *J* = 3.7 Hz), 25.7, 22.9, 17.9, 14.2, -5.25, -5.34.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2930, 2857, 1724, 1472, 1454, 1283, 1250, 1181, 1128, 1112, 1084, 1061, 1025, 1007, 937, 892, 866, 835, 813, 774, 758, 668.

MS (EI, 70 eV): m/z (%) = 351 (1), 321 (6), 311 (5), 310 (17), 309 (71), 265 (7), 264 (23), 263 (100), 245 (9), 235 (15), 221 (10), 189 (28), 171 (27), 75 (26), 73 (23).

HR-MS (EI, 70 eV): [$C_{20}H_{31}FO_3{}^{28}Si$], calc.: 351.1792; found: 351.1785 [M^+-CH_3].

Ethyl 2-((3*S*,4*R*)-4-((tert-butyldimethylsilyl)oxy)tetrahydrofuran-3-yl)-3-fluorobenzoate (162j)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 m, 1.91 mL) was added to ethyl 3-fluorobenzoate (**160**, 235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP-10** to *tert*-butyl((4-iodotetrahydrofuran-3-yl)oxy)dimethylsilane (328 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (95:5) as an eluent to afford **162j** as a colorless oil (55%, 202 mg, 0.55 mmol, d.r. 99:1 (*trans*:*cis*)).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.84 (dd, *J* = 8.7, 6.1 Hz, 1 H), 7.08 (dd, *J* = 10.5, 2.6 Hz, 1 H), 6.95 (dd, *J* = 8.7, 7.7 Hz, 1 H), 4.40 – 4.28 (m, 4 H), 4.23 – 4.19 (m, 1 H), 4.12 – 4.01 (m, 1 H), 3.86 (dd, *J* = 8.7, 3.9 Hz, 1 H), 3.75 – 3.65 (m, 1 H), 1.44 – 1.33 (m, 3 H), 0.84 (d, *J* = 0.6 Hz, 9 H), -0.01 – -0.08 (m, 6 H).

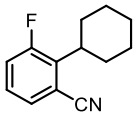
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 166.7, 165.1 (d, *J* = 252.4 Hz), 146.1 (d, *J* = 8.1 Hz), 132.6 (d, *J* = 9.3 Hz), 126.8 (d, *J*=3.3 Hz), 114.5 (d, *J*=23.1 Hz), 113.4 (d, *J*=21.6 Hz), 79.8, 75.1, 73.6, 61.1, 50.7, 25.7, 17.9, 14.2, -4.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 2857, 1719, 1608, 1585, 1472, 1272, 1248, 1112, 1084, 1009, 906, 835, 777, 729.0

MS (EI, 70 eV): *m/z* (%) = 311 (64), 237 (8), 235 (7), 191 (18), 163 (18), 149 (7), 117 (8), 75 (12).

HR-MS (EI, 70 eV): [$C_{15}H_{20}FO_4Si$], calcd.: 311.1115; found: 311.1088 [M^+-*t*-Bu].

2-Cyclohexyl-3-fluorobenzonitrile (163a)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 3-fluorobenzonitrile (170 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was stirred at r.t. for 12 h and was then added dropwise according to **TP-10** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (20:1) as an eluent to afford **163a** as a white solid (84%, 171 mg, 0.84 mmol).

m.p.: 73-74 °C

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.40 - 7.47 (m, 1 H), 7.21 - 7.31 (m, 2 H), 3.02 - 3.17 (m, 1 H), 1.84 - 2.04 (m, 4 H), 1.80 (m, 3 H), 1.23 - 1.54 (m, 3 H).

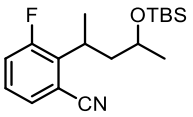
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 161.3 (d, *J* = 248.7 Hz), 137.8 (d, *J* = 16.9 Hz), 129.4 (d, *J* = 3.7 Hz), 128.0 (d, *J* = 9.5 Hz), 121.0 (d, *J* = 24.2 Hz), 117.7 (d, *J* = 3.7 Hz), 113.5 (d, *J* = 8.8 Hz), 30.8, 30.7, 26.7, 25.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2935, 2854, 2232, 1572, 1462, 1449, 1248, 1240, 1223, 1193, 1160, 1135, 1002, 948, 890, 860, 795, 733.

MS (EI, 70 eV): m/z (%) = 204 (5), 203 (33), 202 (19), 188 (12), 186 (7), 175 (17), 174 (31), 162 (34), 161 (21), 160 (14), 149 (22), 148 (43), 147 (100), 146 (10), 135 (17), 134 (38), 133 (13), 120 (10), 107 (9).

HR-MS (EI, 70 eV): [$C_{13}H_{14}FN$], calc.: 203.1110; found: 203.1107.

2-(4-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)-3-fluorobenzonitrile (163b)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 3-fluorobenzonitrile (170 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was stirred at r.t. for 12 h and was then added dropwise according to **TP-10** to *tert*-butyl((4-iodopentan-2-yl)oxy)dimethylsilane (328 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The

crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **163b** as a colorless oil (63%, 202 mg, 0.63 mmol, d.r. 52:48).

Signals of both diastereomers are given:

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.43 – 7.19 (m, 6 H), 3.86 – 3.58 (m, 3 H), 3.53 – 3.21 (m, 3 H), 2.13 – 1.57 (m, 6 H), 1.41 – 1.32 (m, 3 H), 1.23 (dd, *J* = 7.0, 2.7 Hz, 3 H), 1.19 – 1.09 (m, 8 H), 0.90 – 0.79 (m, 18 H), 0.07 – -0.12 (m, 12 H).

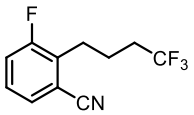
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 162.8, 161.9, 161.6, 159.5, 158.6, 158.3, 141.0, 140.8, 140.5, 140.3, 138.3, 138.1, 137.8, 129.4, 129.3, 129.3, 129.2, 129.2, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 121.0, 120.6, 119.3, 119.3, 119.0, 118.9, 117.8, 117.8, 117.5, 117.5, 117.4, 117.3, 113.7, 113.6, 110.9, 110.9, 110.8, 110.7, 68.1, 67.9, 67.4, 66.6, 66.4, 66.1, 65.3, 47.8, 46.5, 46.0, 45.0, 44.9, 30.0, 29.3, 25.9, 25.8, 25.8, 24.1, 24.0, 23.7, 21.9, 20.6, 20.2, 19.2, 18.0, 18.0, -4.1, -4.2, -4.3, -4.4, -4.8, -4.8, -4.9, -5.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2857, 1462, 1362, 1252, 1091, 1050, 1038, 906, 834, 774, 797, 730.

MS (EI, 70 eV): *m/z* (%) = 264 (17), 222 (26), 208 (12), 130 (13), 77 (6), 75 (22), 73 (8), 57 (5), 43 (6).

HR-MS (EI, 70 eV): [$C_{14}H_{19}FNOSi$], calcd.: 264.1220; found: 264.1259.

3-Fluoro-2-(4,4,4-trifluorobutyl)benzonitrile (163c)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 3-fluorobenzonitrile (170 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was stirred at r.t. for 12 h and was then added dropwise according to **TP-10** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (20:1) as an eluent to afford **163c** as a yellow oil (52%, 120 mg, 0.52 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.44 - 7.51 (m, 1 H), 7.28 - 7.40 (m, 2 H), 2.97 (t, *J* = 7.70 Hz, 2 H), 2.09 - 2.29 (m, 2 H), 1.85 - 2.02 (m, 2 H).

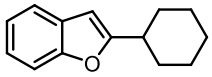
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 160.8 (d, *J* = 248.7 Hz), 132.0 (d, *J* = 19.1 Hz), 129.0 (d, *J* = 5.1 Hz), 128.9, 126.8 (q, *J* = 276.1 Hz), 120.5 (d, *J* = 22.7 Hz), 116.7 (d, *J* = 4.40 Hz), 114.5 (d, *J* = 5.9 Hz) 33.3 (q, *J* = 29.1 Hz), 26.9 (d, *J* = 2.2 Hz), 22.3 - 22.2 (m).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2950, 2232, 1578, 1465, 1441, 1392, 1339, 1316, 1279, 1251, 1208, 1131, 1112, 1021, 970, 936, 793, 733, 681, 658.

MS (EI, 70 eV): m/z (%) = 231 (13), 148 (3), 147 (3), 135 (8), 134 (100), 107 (11), 97 (5), 83 (6), 71 (6), 69 (13), 57 (11), 55 (7), 44 (34), 43 (12).

HR-MS (EI, 70 eV): [$C_{11}H_9F_4N$], calc.: 231.0671; found: 231.0665.

2-Cyclohexylbenzofuran (163d)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to benzofuran (165 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 12 h and was then added dropwise according to **TP-10** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane as an eluent to afford **163d** as a colorless oil (71%, 142 mg, 0.70 mmol).

m.p.: 35 – 37 °C.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.47 - 7.56 (m, 1 H), 7.43 (d, J = 7.3 Hz, 1 H), 7.13 - 7.25 (m, 2 H), 6.36 (s, 1 H), 2.78 (tt, J = 11.1, 3.4 Hz, 1 H), 2.07 - 2.23 (m, 2 H), 1.86 (ddd, J = 12.5, 3.1, 2.9 Hz, 2 H), 1.71 - 1.81 (m, 1 H), 1.22 - 1.59 (m, 5 H).

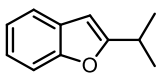
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 164.1, 154.3, 128.9, 123.0, 122.3, 120.2, 110.7, 99.7, 37.6, 31.3, 26.1, 25.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3048, 2932, 2925, 2854, 2847, 1599, 1592, 1584, 1471, 1453, 1421, 1299, 1256, 1248, 1220, 1183, 1162, 1149, 1124, 1104, 1007, 946, 922, 890, 883, 856, 830, 797, 786, 749, 736, 728, 690, 685.

MS (EI, 70 eV): m/z (%) = 201 (10), 200 (72), 199 (3), 171 (10), 158 (14), 157 (100), 145 (10), 144 (41), 132 (13), 131 (31), 128 (11), 115 (20).

HR-MS (EI, 70 eV): [$C_{14}H_{16}O$], calc.: 200.1201; found: 200.1191.

2-*i*-Propylbenzofuran (163e)

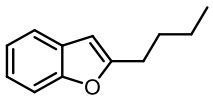


$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to benzofuran (165 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for

12 h and was then added dropwise according to **TP-10** to 2-iodopropane (170 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane as an eluent to afford **163e** as colorless oil (61%, 98 mg, 0.61 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.47 - 7.53 (m, 1 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 7.13 - 7.26 (m, 2 H), 6.38 (s, 1 H), 3.09 (spt, *J* = 6.9 Hz, 1 H), 1.36 (d, *J* = 6.9 Hz, 6 H).
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 164.9, 154.5, 128.8, 123.0, 122.3, 120.3, 110.7, 99.7, 28.2, 20.9.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2967, 2929, 2874, 1586, 1467, 1454, 1385, 1301, 1253, 1236, 1182, 1167, 1127, 1105, 1067, 1045, 1009, 942, 926, 884, 795, 750, 738, 684.
MS (EI, 70 eV): m/z (%) = 160 (15), 146 (11), 145 (74), 125 (16), 115 (21), 113 (17), 111 (18), 97 (30), 95 (12), 85 (28), 57 (100), 83 (22), 82 (11), 81 (25), 71 (53), 70 (22), 69 (41), 67 (17), 56 (28), 55 (40), 43 (86), 43 (17), 41 (58).
HR-MS (EI, 70 eV): [$C_{11}H_{12}O$], calc.: 160.0888; found: 160.0887.

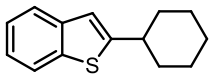
2-*n*-Butylbenzofuran (163f)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to benzofuran (165 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 12 h and was then added dropwise according to **TP-10** to 1-iodobutane (184 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (95:5) as an eluent to afford **163f** as a colorless oil (63%, 110 mg, 0.63 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56 – 7.41 (m, 2 H), 7.28 – 7.14 (m, 2 H), 6.40 (s 1 H), 2.85 – 2.72 (t, *J* = 7.4 Hz, 2 H), 1.85 – 1.67 (m, 2 H), 1.55 – 1.35 (m, 2 H), 0.99 (t, *J* = 7.3 Hz, 3 H).
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 159.7, 154.6, 129.0, 123.0, 122.3, 120.1, 110.6, 101.7, 29.8, 28.1, 22.3, 13.8.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2930, 1601, 1587, 1454, 1252, 1168, 945, 905, 795, 749, 738.
MS (EI, 70 eV): m/z (%) = 174 (12), 133 (1), 132 (13), 131 (54), 115 (21), 103 (16), 77 (31).
HR-MS (EI, 70 eV): [$C_{12}H_{14}O$], calc.: 174.1045; found: 174.1054.

2-Cyclohexylbenzothiophene (163g)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to thiobenzofuran (188 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t., stirred for 12 h and was then added dropwise according to **TP-10** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane as an eluent to afford **163g** as a white solid (72%, 156 mg, 0.72 mmol).

m.p.: 60 – 62 °C.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.78 (d, *J* = 8.1 Hz, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 7.21 - 7.28 (m, 1 H), 7.02 (s, 1 H), 2.89 (tt, *J* = 11.3, 3.4 Hz, 1 H), 2.04 - 2.19 (m, 2 H), 1.87 (dt, *J* = 12.7, 3.1 Hz, 2 H), 1.71 - 1.81 (m, 1 H), 1.37 - 1.60 (m, 4 H), 1.20 - 1.36 (m, 1 H).

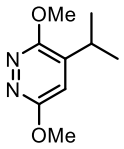
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 153.0, 140.0, 138.6, 123.9, 123.3, 122.7, 122.2, 118.1, 40.0, 35.0, 26.4, 26.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056, 2938, 2922, 2853, 2844, 1534, 1456, 1446, 1436, 1295, 1264, 1234, 1194, 1172, 1128, 1067, 1016, 987, 930, 892, 861, 846, 819, 798, 736, 725, 706, 658.

MS (EI, 70 eV): m/z (%) = 217 (12), 216 (67), 187 (7), 175 (6), 174 (17), 173 (100), 171 (5), 161 (19), 160 (27), 148 (21), 147 (36), 134 (22), 129 (10), 128 (9), 115 (17), 45 (10).

HR-MS (EI, 70 eV): [$C_{14}H_{16}S$], calc.: 216.0973; found: 216.0966.

4-*iso*-Propyl-3,6-dimethoxypyridazine (163h)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 3,6-dimethoxypyridazine (196 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t. for 4 h and was added dropwise according to **TP-10** to 2-iodopropane (170 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **163h** as a colorless oil (69%, 126 mg, 0.69 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 6.75 (s, 1 H), 4.06 (s, 3 H), 4.02 (s, 3 H), 3.07 (spt, *J* = 6.9 Hz, 1 H), 1.20 (d, *J* = 6.9 Hz, 6 H).

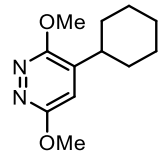
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 162.6, 160.5, 142.0, 116.2, 54.5, 54.3, 27.0, 21.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951, 2875, 1617, 1462, 1390, 1381, 1367, 1330, 1231, 1202, 1183, 1139, 1122, 1094, 1081, 1054, 1026, 1012, 927, 892, 771, 724, 666.

MS (EI, 70 eV): m/z (%) = 182 (100), 181 (87), 167 (91), 154 (23), 153 (16), 151 (14), 137 (21), 96 (12), 86 (12), 84 (19), 83 (15), 74 (12), 71 (13), 69 (34), 67 (25), 59 (19), 57 (23), 56 (14), 55 (24), 53 (27), 45 (90), 45 (17), 44 (33).

HR-MS (EI, 70 eV): [$C_9H_{14}N_2O_2$], calc.: 182.1055; found: 182.1052.

4-Cyclohexyl-3,6-dimethoxypyridazine (163i)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 3,6-dimethoxypyridazine (196 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was allowed to warm to r.t. for 4 h and was added dropwise according to **TP-10** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (8:2) as an eluent to afford **163i** as a colorless oil (61%, 135 mg, 0.61 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 6.64 (d, *J* = 0.9 Hz, 1 H), 3.98 (s, 3 H), 3.95 (s, 3 H), 2.73 – 2.48 (m, 1 H), 1.86 – 1.64 (m, 5 H), 1.45 – 1.06 (m, 5 H).

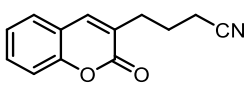
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 162.5, 160.4, 140.9, 116.5, 54.4, 54.2, 36.6, 31.6, 26.3, 25.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929, 2854, 1617, 1465, 1389, 1370, 1247, 1227, 1150, 1038, 1013, 1006, 906, 879, 750, 726.

MS (EI, 70 eV): *m/z* (%) = 222 (64), 221 (62), 193 (26), 191 (38), 167 (15), 163 (13), 154 (10), 40 (14).

HR-MS (EI, 70 eV): [$C_{12}H_{18}N_2O_2$], calcd.: 222.1368; found: 222.1366.

4-(2-Oxo-2H-chromen-3-yl)butanenitrile (163j)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to coumarin (204 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was stirred for 1 h at r.t. and was then added dropwise according to **TP-10** to 4-iodobutanenitril (195 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **163j** as a yellowish solid (76%, 162 mg, 0.76 mmol).

m.p.: 102 – 104 °C.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.61 (s, 1 H) 7.44 - 7.55 (m, 2 H) 7.25 - 7.36 (m, 2 H) 2.76 (t, *J* = 7.5 Hz, 2 H) 2.44 (t, *J* = 7.0 Hz, 2 H) 2.06 (qd, *J* = 7.3, 7.1 Hz, 2 H).

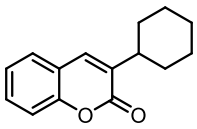
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 161.4, 153.3, 140.2, 131.2, 127.4, 127.2, 124.5, 119.2, 119.1, 116.5, 30.2, 23.6, 16.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923, 2360, 2244, 1716, 1634, 1620, 1605, 1455, 1421, 1284, 1175, 1069, 1016, 922, 772, 763, 742, 712.

MS (EI, 70 eV): m/z (%) = 234 (5), 214 (13), 213 (56), 212 (7), 174 (12), 173 (100), 172 (8), 161 (11), 160 (92), 259 (61), 144 (10), 132 (15), 131 (42), 128 (7), 126 (8), 115 (42), 102 (8), 77 (17), 63 (7).

HR-MS (EI, 70 eV): [$C_{13}H_{11}NO_2$], calc.: 213.0790; found: 213.0790.

3-Cyclohexyl-2H-chromen-2-one (163k):



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to coumarin (204 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was stirred for 1 h at r.t. and was then added dropwise according to **TP-10** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (95:5) as an eluent to afford **163k** as a white solid (66%, 151 mg, 0.66 mmol).

m.p.: 93 – 95 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.47 – 7.36 (m, 3 H), 7.29 – 7.17 (m, 2 H), 2.82 – 2.68 (m, 1 H), 2.00 – 1.66 (m, 5 H), 1.50 – 1.15 (m, 5 H).

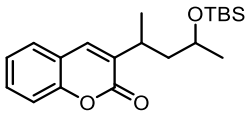
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.5, 152.7, 136.3, 134.8, 130.4, 127.3, 124.10, 119.6, 116.2, 38.2, 32.1, 26.5, 26.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1706, 1609, 1456, 988, 904, 755, 726.

MS (EI, 70 eV): *m/z* (%) = 228 (46), 227 (9), 171 (34), 146 (13), 128 (9), 115 (24), 43 (19).

HR-MS (EI, 70 eV): [$C_{15}H_{16}O_2$], calcd.: 228.1150; found: 228.1145.

3-(4-((*tert*-Butyldimethylsilyl)oxy)pentan-2-yl)-2H-chromen-2-one (163l)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to coumarin (204 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP-9**. The reaction mixture was stirred for 1 h at r.t. and was then added dropwise according to **TP-10** to *tert*-butyl((4-iodopentan-2-yl)oxy)dimethylsilane (328 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **163l** as a colorless oil (88%, 305 mg, 0.88 mmol, d.r. 62:38).

Signals of both diastereomers are given:

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.42 - 7.51 (m, 6 H), 7.32 (d, *J* = 8.3 Hz, 2 H), 7.23 - 7.29 (m, 2 H), 3.76 - 3.95 (m, 2 H), 3.02 - 3.18 (m, 2 H), 1.83 - 1.95 (m, 2 H), 1.59 - 1.71 (m, 2 H), 1.26 (m, 6 H), 1.19 (d, *J* = 6.1 Hz, 6 H), 0.89 (d, *J* = 2.5 Hz, 9 H), -0.08 - 0.12 (m, 12 H).

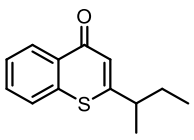
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 161.1 (2 C), 152.9, 137.1, 136.9, 134.9, 1345, 130.5 (2 C), 127.2 (2 C), 124.2 (2 C), 119.5 (2 C), 116.3, 67.0, 66.4, 45.2, 45.0, 31.8, 31.2, 25.9 (2 C), 24.1, 23.9, 20.4, 19.8, 18.1, -4.2 (2 C), -4.7 (2 C).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2928, 2856, 1722, 1610, 1456, 1373, 1254, 1177, 1142, 1132, 1121, 1094, 1051, 1030, 1006, 989, 972, 922, 834, 807, 773, 753, 735, 721.

MS (EI, 70 eV): m/z (%) = 331 (2), 291 (7), 290 (23), 289 (100), 216 (7), 215 (35), 179 (20), 173 (8), 157 (5), 115 (12), 75 (27), 73 (15), 57 (5), 41 (9).

HR-MS (EI, 70 eV): [$C_{20}H_{30}O_3{}^{28}Si$], calc.: 331.1729; found: 331.1720 [M^+-CH_3].

2-(*sec*-Butyl)-4H-thiochromen-4-one (163m)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**48**, 0.84 mmol, 0.44 M, 1.91 mL) was added to thiochromone (227 mg, 1.4 mmol) in THF (1.0 mL) at -40 °C according to **TP-9**. The reaction mixture was stirred for 1 h and was then added dropwise according to **TP-10** to 2-iodobutane (184 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (8:2) as an eluent to afford **163m** as a colorless oil (51%, 111 mg, 0.51 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.46 (d, *J* = 7.8 Hz, 1 H), 7.58 – 7.50 (m, 2 H), 7.45 – 7.42 (m, 1 H), 6.86 (s, 1 H), 2.76 – 2.43 (m, 1 H), 1.79 – 1.56 (m, 2 H), 1.31 (d, *J* = 6.9 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H).
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 180.7, 161.9, 137.6, 131.2, 128.4, 127.4, 126.4, 122.7, 44.1, 30.0, 21.0, 11.9.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1617, 1591, 1439, 1326, 1100, 904, 778, 723, 689, 668.
MS (EI, 70 eV): *m/z* (%) = 218 (77), 190 (92), 176 (62), 161 (51), 136 (41), 128 (19), 69 (7).
HR-MS (EI, 70 eV): [$C_{13}H_{14}OS$], calc.: 218.0767**;** found: 218.0765.

6 Cobalt-Catalyzed Negishi Cross-Couplings of (Hetero)Arylzinc Reagents with (Hetero)Aryl Halides

6.1 Preparation of Organometallic Reagents

Preparation of zinc reagents (165a-d, f, h-n)

LiCl (1.1 equiv) was dried under high vacuum and allowed to cool to room temperature, then Mg turnings (1.2 equiv), $ZnCl_2$ solution (1 M in THF, 1.1 equiv) and THF (1 M solution relating to the aryl bromide) were added. The reaction mixture was cooled to 0 °C and the corresponding aryl bromide (1.0 equiv) was added dropwise. The reaction was stirred until iodolysis of a reaction aliquot indicated full consumption of the starting material.

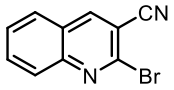
Preparation of zinc reagents (165e, g)

The corresponding aryl bromide (1.0 equiv) was dissolved in THF (1 M solution relating to the aryl bromide) and the reaction mixture was cooled to -30 °C. Then *i*-PrMgCl·LiCl was added dropwise and the reaction was stirred at this temperature until reaction aliquots quenched with iodine showed full consumption of the starting material. Transmetalation with $ZnCl_2$ solution (1 M in THF, 1.1 equiv) at 0 °C (1 h) provided the corresponding zinc reagent.

6.2 Preparation of Starting Materials

The following starting materials were prepared according to literature procedures. The spectral data of known compounds are in full agreement with the cited literature.

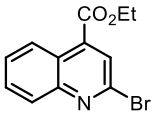
2-Bromoquinoline-3-carbonitrile (173a)[193]



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.51 (s, 1 H), 8.12 – 8.09 (m, 1 H), 7.95 – 7.87 (m, 2 H), 7.72 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1 H).

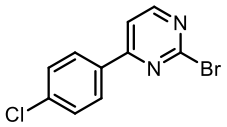
[193] N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525-5528.

Ethyl 2-bromoquinoline-4-carboxylate (173b)[194]



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 (s, 1 H), 8.25 (d, *J* = 8.5 Hz, 1 H), 7.93 (d, *J* = 8.1 Hz, 1 H), 7.88 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1 H), 7.68 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1 H), 4.49 (q, *J* = 7.2 Hz, 2 H), 1.47 (t, *J* = 7.1 Hz, 3 H).

2-Bromo-4-(4-chlorophenyl)pyrimidine (173d)[194]



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.58 (d, *J* = 5.2 Hz, 1 H), 8.04 (m, 2 H), 7.65 (d, *J* = 5.2 Hz, 1 H), 7.52 – 7.43 (m, 2 H).

6.3 Typical Procedure

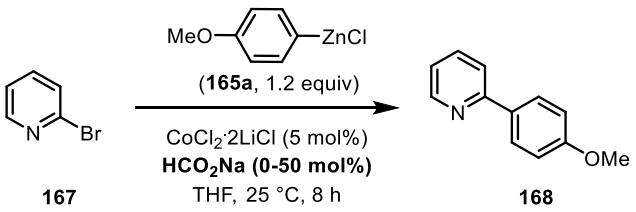
Typical procedure for the cobalt-catalyzed cross-coupling of organozinc reagents (TP-11):

A dry and argon-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with a solution of $CoCl_2 \cdot 2LiCl$ (1 M in THF) (0.05 mmol, 50 µL, 5 mol%) and dry THF (1.0 mL). The respective aryl halide (1.0 mmol, 1.0 equiv) and HCO_2Na (0.5 mmol, 34 mg, 50 mol%) were added at room temperature. Then, a solution of the appropriate zinc reagent (1.2 mmol, 1.2 equiv) was added dropwise over 15 min *via* syringe. The reaction was stirred and monitored by GC-analysis ($C_{11}H_{24}$ was used as an internal standard). Upon consumption of the starting material, saturated aqueous NH_4Cl solution (5 mL) and ethyl acetate (5 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography on silica yielding the respective title compound.

[194] M. Mosrin, M. Petrera, P. Knochel, *Synthesis* **2008**, 22, 3697-3702.

6.4 Kinetic Investigation of the Cross-Coupling Reaction

For observation of the effect of sodium formate, the course of the cross-coupling reaction with and without sodium formate was investigated over several hours by GC. For this experiment, the reaction of 2-bromopyridine (**167**) and *p*-anisylzinc chloride (**166a**) was performed as described above (**TP-11**) using 50 mol% HCO_2Na or no additive on a 1 mmol scale and the average GC-yields of three runs were used using undecane ($C_{11}H_{24}$) as an internal standard (Scheme 81).



Scheme 81: Cobalt-catalyzed cross-coupling of 2-bromopyridine (167) and *p*-$MeOC_6H_4ZnCl$ (168).

Table 15. Yield of the reaction with and without HCO_2Na over the time course of 11 h.

time [h]	yield of 168 without HCO_2Na [%]	yield of 168 with HCO_2Na [%]
1	8	10
1,5	16	18
2	26	28
3	35	39
4	47	52
5	58	66
6	68	85
8	**74**	**92**
9	79	94
10	80	95
11	80	95

The chart of both reactions shows that the rate of the cross-coupling reaction stays equal, but the addition of HCO_2Na causes a higher reaction yield (92% vs. 74% after 8 h at r.t.) due to suppression of undesired side reactions (Figure 4).

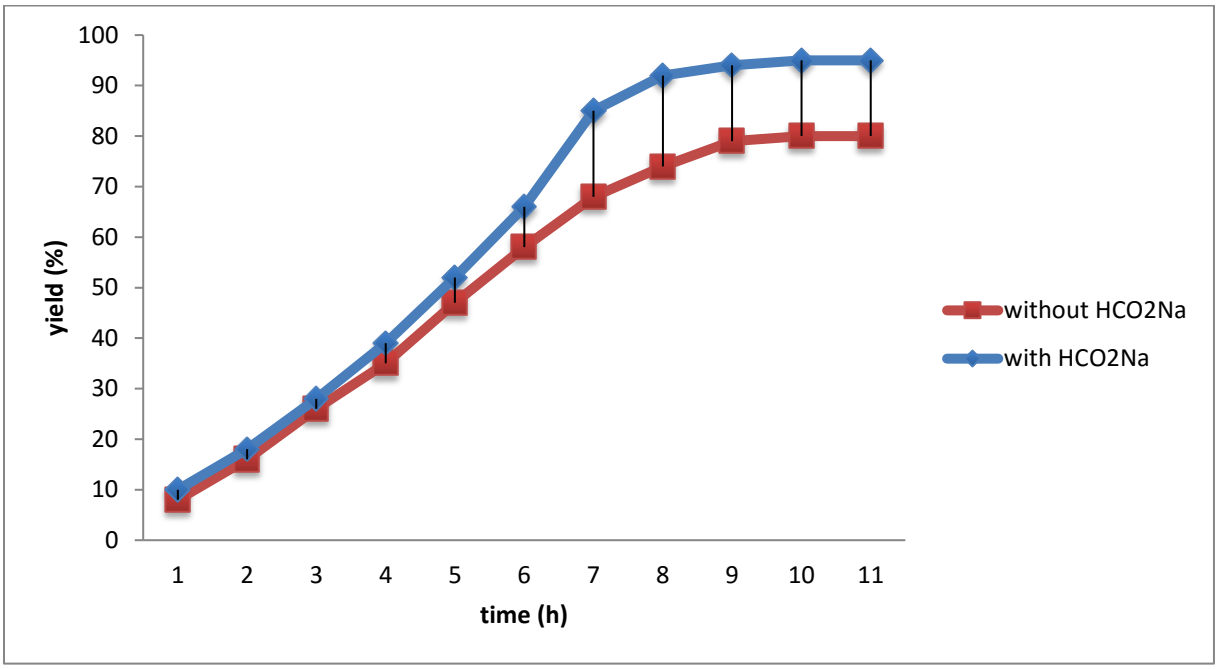
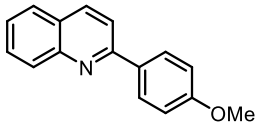


Figure 4. Depiction of the time course of the cobalt-catalyzed cross-coupling reaction of 2-bromopyridine (167) and *p*-anisylzinc chloride (165a) with (blue) or without HCO_2Na (red) over time.

6.5 Cobalt-Catalyzed Cross-Coupling of (Hetero)Arylzinc Reagents with (Hetero)Aryl Halides

2-(4-Methoxyphenyl)quinoline (166):



Isolated yield: 207 mg, 0.88 mmol, 88% yield; colorless crystals

Purification: *i*-hexane:ethyl acetate 7:3

m.p.: 124 – 125 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.20 – 8.09 (m, 4 H), 7.84 – 7.76 (m, 2 H), 7.71 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 7.49 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1 H), 7.08 – 6.99 (m, 2 H), 3.87 (s, 3 H).

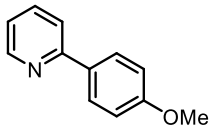
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 160.8, 156.9, 148.3, 136.6, 132.3, 129.6, 129.5, 128.9, 127.5, 126.9, 125.91, 118.5, 114.2, 55.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960, 2920, 1594, 1495, 1467, 1430, 1289, 1247, 1174, 1156, 1028, 975, 948, 811, 789, 748, 726.

MS (EI, 70 eV): *m/z* (%) = 237 (2), 236 (16), 235 (100), 234 (3), 220 (21), 192 (23), 191 (24), 190 (6).

HR-MS (EI, 70 eV): [$C_{16}H_{13}ON$], calcd.: 235.0997; found: 235.0998.

2-(4-Methoxyphenyl)pyridine (168)



Isolated yield: 161 mg, 0.87 mmol, 87% yield; white solid

Purification: *i*-hexane:ethyl acetate 4:1

m.p.: 53 – 54 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.65 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1 H), 7.99 – 7.91 (m, 2 H), 7.75 – 7.62 (m, 2 H), 7.17 (ddd, *J* = 7.1, 4.8, 1.5 Hz, 1 H), 7.05 – 6.94 (m, 2 H), 3.86 (s, 3 H).

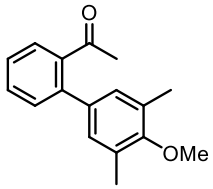
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.5, 157.1, 149.5, 136.7, 132.0, 128.2, 121.4, 119.8, 114.1, 55.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2997, 2836, 1603, 1586, 1512, 1460, 1432, 1272, 1243, 1175, 1151, 1112, 1036, 1021, 1005, 838, 776, 736, 717.

MS (EI, 70 eV): *m/z* (%) = 186 (12), 185 (100), 170 (22), 142 (29), 141 (15), 61 (9).

HR-MS (EI, 70 eV): [$C_{12}H_{11}NO$], calcd.: 185.0841; found: 185.0836.

1-(4'-Methoxy-3',5'-dimethyl-[1,1'-biphenyl]-2-yl)ethan-1-one (170a)



Isolated yield: 165 mg, 0.65 mmol, 65% yield for X = Cl; colorless oil

188 mg, 0.74 mmol, 74% yield for X = Br

Purification: *i*-hexane:ethyl acetate 9:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.51 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.40 – 7.33 (m, 2 H), 6.98 (s, 2 H), 3.76 (s, 3 H), 2.32 (s, 6 H), 2.02 (s, 3 H).

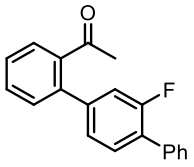
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 205.2, 156.9, 140.8, 140.3, 136.1, 131.2, 130.6, 130.1, 129.3, 127.7, 127.1, 59.8, 30.4, 16.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932, 1684, 1471, 1443, 1419, 1353, 1276, 1235, 1194, 1165, 1116, 1088, 1007, 966, 889, 871, 761, 741, 700.

MS (EI, 70 eV): *m/z* (%) = 255 (12), 254 (67), 253 (10), 240 (12), 239 (73), 224 (14), 196 (10), 165 (10), 70 (12), 61 (17), 45 (15), 43 (100).

HR-MS (EI, 70 eV): [$C_{17}H_{18}O_2$], calcd.: 254.1307; found: 254.1301.

1-(3'-Fluoro-[1,1':4',1''-terphenyl]-2-yl)ethan-1-one (170b)



Isolated yield: 194 mg, 0.67 mmol, 67% yield; white solid

Purification: *i*-hexane:ethyl acetate c 98:2 to 90:10

m.p.: 85 – 87 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.65 – 7.56 (m, 3 H), 7.59 – 7.50 (m, 1 H), 7.53 – 7.35 (m, 6 H), 7.22 – 7.16 (m, 1 H), 7.17 (s, 1 H), 2.19 (s, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 204.1, 159.6 (d, *J* = 249.5 Hz), 141.8 (d, *J* = 8.1 Hz), 140.6, 138.9 (d, *J* = 1.8 Hz), 135.2 (d, *J* = 1.4 Hz), 130.9, 130.8 , 130.3, 129.0 (d, *J* = 3.0 Hz), 128.5, 128.49, 128.3, 128.1, 127.9 (d, *J* = 6.4 Hz), 125.0 (d, *J* = 3.4 Hz), 116.4 (d, *J* = 23.7 Hz), 30.5.

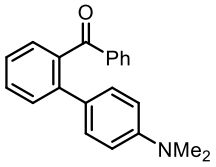
^{19}F-NMR (376 MHz, $CDCl_3$, ppm): δ = -117.39.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060, 1686, 1474, 1404, 1354, 1274, 1235, 1183, 893, 834, 759, 746, 722, 696, 682.

MS (EI, 70 eV): *m/z* (%) = 292 (6), 291 (33), 290 (73), 289 (16), 276 (23), 275 (100), 273 (10), 255 (13), 246 (22), 225 (22), 141 (14), 139 (49), 111 (15).

HR-MS (EI, 70 eV): [$C_{20}H_{15}FO$], calcd.: 290.1107; found: 290.1103.

(4'-(Dimethylamino)-[1,1'-biphenyl]-2-yl)(phenyl)methanone (170c)



Isolated yield: 219 mg, 0.73 mmol, 73% yield; yellowish crystals

Purification: *i*-hexane:ethyl acetate 9:1

m.p.: 114 – 116 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.67 – 7.61 (m, 2 H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.45 – 7.40 (m, 2 H), 7.40 – 7.31 (m, 2 H), 7.25 – 7.21 (m, 2 H), 7.13 – 7.07 (m, 2 H), 6.56 – 6.48 (m, 2 H), 2.83 (s, 6 H).

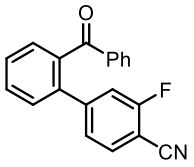
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 199.3, 149.7, 141.2, 138.6, 137.5, 132.7, 130.2, 130.0, 129.8, 129.7, 128.7, 128.1, 128.1, 126.0, 112.2, 40.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1664, 1613, 1594, 1526, 1479, 1448, 1350, 1315, 1281, 1247, 1222, 1204, 1169, 1161, 1149, 932, 922, 824, 776, 766, 720, 704, 690, 676.

MS (EI, 70 eV): *m/z* (%) = 303 (3), 302 (25), 301 (100), 300 (38), 224 (9), 180 (5), 152 (7), 105 (7).

HR-MS (EI, 70 eV): [$C_{21}H_{19}NO$], calcd.: 301.1467; found: 301.1462.

2'-Benzoyl-3-fluoro-[1,1'-biphenyl]-4-carbonitrile (170d)



Isolated yield: 295 mg, 0.98 mmol, 98% yield; colorless oil

Purification: *i*-hexane:ethyl acetate 8:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.70 – 7.64 (m, 2 H), 7.65 – 7.60 (m, 1 H), 7.58 – 7.41 (m, 5 H), 7.39 – 7.32 (m, 2 H), 7.18 – 7.10 (m, 2 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 197.5, 162.7 (d, *J* = 259.7 Hz), 147.9 (d, *J* = 8.2 Hz), 138.8, 138.4 (d, *J* = 1.9 Hz), 137.0, 133.5, 133.2, 130.9, 129.9, 129.9, 129.4, 128.6, 128.5, 125.5 (d, *J* = 3.4 Hz), 116.9 (d, *J* = 20.2 Hz), 113.8, 100.1 (d, *J* = 15.5 Hz).

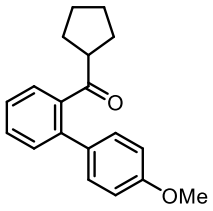
^{19}F-NMR (376 MHz, $CDCl_3$, ppm): δ = -106.19 – -106.31 (m).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061, 1660, 1619, 1448, 1412, 1279, 1260, 928, 902, 832, 762, 737, 724, 703, 689, 680.

MS (EI, 70 eV): *m/z* (%) = 302 (19), 301 (88), 300 (19), 273 (8), 272 (16), 225 (11), 224 (77), 196 (19), 195 (21), 105 (100), 76 (43).

HR-MS (EI, 70 eV): [$C_{20}H_{12}FNO$], calcd.: 301.0903; found: 301.0897.

Cyclopentyl(4'-methoxy-[1,1'-biphenyl]-2-yl)methanone (170e)



Isolated yield: 213 mg, 0.76 mmol, 76% yield; white solid

Purification: *i*-hexane:ethyl acetate 95:5

m.p.: 99 – 101 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.51 – 7.42 (m, 1 H), 7.44 – 7.33 (m, 3 H), 7.30 – 7.22 (m, 2 H), 6.98 – 6.91 (m, 2 H), 3.85 (s, 3 H), 2.79 – 2.65 (m, 1 H), 1.74 – 1.53 (m, 4 H), 1.51 – 1.29 (m, 4 H).

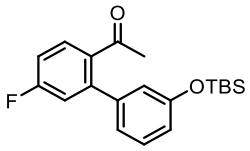
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 212.2, 159.3, 141.4, 139.3, 132.9, 130.0, 130.0, 129.9, 127.7, 126.9, 114.1, 55.3, 51.1, 30.3, 26.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2941, 1673, 1609, 1518, 1463, 1439, 1307, 1256, 1211, 1186, 1180, 1039, 998, 834, 822, 781, 766, 727.

MS (EI, 70 eV): *m/z* (%) = 281 (4), 280 (21), 212 (19), 211 (100), 168 (14), 139 (9), 61 (9), 43 (53).

HR-MS (EI, 70 eV): [$C_{19}H_{20}O_2$], calcd.: 280.1463; found: 280.1458.

1-(3'-((*tert*-Butyldimethylsilyl)oxy)-5-fluoro-[1,1'-biphenyl]-2-yl)ethan-1-one (170f)



Isolated yield: 224 mg, 0.68 mmol, 68% yield; colorless oil

Purification: *i*-hexane:ethyl acetate 95:5

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.57 (dd, *J* = 8.5, 5.8 Hz, 1 H), 7.29 (t, *J* = 7.9 Hz, 1 H), 7.13 – 7.03 (m, 2 H), 6.92 – 6.86 (m, 2 H), 6.81 (t, *J* = 2.0 Hz, 1 H), 1.99 (s, 3 H), 0.99 (s, 9 H), 0.21 (s, 6 H).

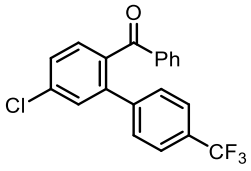
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 203.3, 163.6 (d, *J* = 252.0 Hz), 156.0, 143.1 (d, *J* = 8.5 Hz), 141.1 (d, *J* = 1.7 Hz), 137.0 (d, *J* = 3.1 Hz), 130.5 (d, *J* = 9.2 Hz), 129.9, 121.9, 120.4, 120.3, 116.9 (d, *J* = 22.0 Hz), 114.5 (d, *J* = 21.5 Hz), 30.4, 25.7, 18.2, -4.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 2859, 1688, 1600, 1572, 1473, 1307, 1279, 1260, 1241, 1216, 1174, 968, 872, 838, 823, 810, 780, 706, 694.

MS (EI, 70 eV): *m/z* (%) = 344 (15), 288 (18), 287 (73), 272 (26), 271 (54), 269 (32), 253 (28), 213 (24), 75 (15), 70 (11), 61 (15), 45 (12), 43 (100).

HR-MS (EI, 70 eV): [$C_{20}H_{25}FO_2Si$], calcd.: 344.1608; found: 344.1603.

(5-Chloro-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)(phenyl)methanone (170g)



Isolated yield: 321 mg, 0.89 mmol, 89% yield; white solid

Purification: *i*-hexane:ethyl acetate 9:1

m.p.: 80 – 81 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.68 – 7.61 (m, 2 H), 7.52 – 7.45 (m, 6 H), 7.39 – 7.29 (m, 4 H).

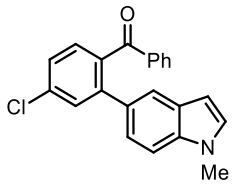
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 197.0, 142.5, 141.7, 137.2, 137.0, 136.6, 133.4, 130.5, 130.1, 129.8, 129.9 (q, *J* = 32.4 Hz), 129.2, 128.4, 127.9, 125.4 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.1 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1666, 1591, 1581, 1321, 1278, 1247, 1166, 1152, 1109, 1096, 1066, 1031, 1014, 928, 896, 844, 828, 815, 800, 767, 704, 686, 675.

MS (EI, 70 eV): *m/z* (%) = 362 (13), 361 (16), 360 (42), 359 (23), 325 (20), 284 (18), 282 (53), 220 (24), 105 (47), 77 (20), 70 (14), 61 (18), 45 (14), 43 (100).

HR-MS (EI, 70 eV): [$C_{20}H_{12}ClF_3O$], calcd.: 360.0529; found: 360.0522.

(4-Chloro-2-(1-methyl-1H-indol-6-yl)phenyl)(phenyl)methanone (170h)



Isolated yield: 210 mg, 0.61 mmol, 61% yield; yellow oil

Purification: *i*-hexane:ethyl acetate 8:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.61 – 7.55 (m, 2 H), 7.52 – 7.47 (m, 2 H), 7.43 (tdd, *J* = 4.4, 1.4, 0.7 Hz, 2 H), 7.36 (ddd, *J* = 7.6, 6.2, 2.2 Hz, 1 H), 7.07 – 7.04 (m, 2 H), 6.92 (d, *J* = 3.1 Hz, 1 H), 6.81 – 6.75 (m, 2 H), 6.32 (dd, *J* = 3.1, 0.7 Hz, 1 H), 3.65 (s, 3 H).

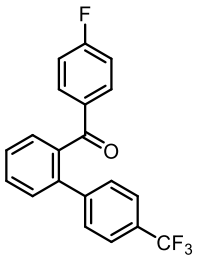
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 197.9, 166.5, 163.9, 142.1, 138.9, 136.0, 132.4, 132.3, 131.4, 130.5, 130.3, 128.5, 126.4, 122.9, 121.5, 115.1, 114.9, 109.0, 101.2, 32.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2943, 2252, 1662, 1586, 1470, 1448, 1280, 1245, 1091, 905, 727.

MS (EI, 70 eV): *m/z* (%) = 347 (11), 346 (10), 345 (28), 344 (15), 267 (6), 104 (4), 76 (40< 58 (4), 42 (11).

HR-MS (EI, 70 eV): [$C_{22}H_{16}ClNO$], calcd.: 345.0920; found: 345.0919.

(4-Fluorophenyl)(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)methanone (170i)



Isolated yield: 251 mg, 0.73 mmol, 73% yield; white solid

Purification: *i*-hexane:ethyl acetate 95:5

m.p.: 98 – 99 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.65 – 7.58 (m, 2 H), 7.55 (ddd, *J* = 7.6, 5.4, 3.5 Hz, 1 H), 7.48 – 7.38 (m, 5 H), 7.33 – 7.27 (m, 2 H), 6.96 – 6.88 (m, 2 H).

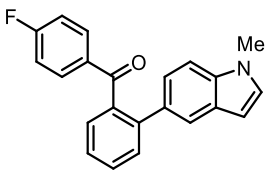
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.6, 166.9, 164.4, 143.7, 139.7, 138.7, 133.7, 132.6 (d, *J* = 9.4 Hz), 130.2, 129.7, 129.4 (q, *J* = 283 Hz), 129.2, 128.8, 125.3 (q, *J* = 4.3 Hz), 122.3, 115.6 (d, *J* = 24.1 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061, 1660, 1617, 1596, 1504, 1407, 1325, 1304, 1259, 1225, 1160, 1113, 1104, 1067, 926, 843, 838, 765, 745, 733, 673.

MS (EI, 70 eV): *m/z* (%) = 345 (12), 344 (53), 343 (23), 275 (15), 249 (38), 201 (15), 152 (10), 123 (54), 95 (20), 85 (10), 83 (16).

HR-MS (EI, 70 eV): [$C_{20}H_{12}F_4O$], calcd.: 344.0824; found: 344.0818.

(4-Fluorophenyl)(2-(1-methyl-1H-indol-6-yl)phenyl)methanone (170j)



Isolated yield: 204 mg, 0.62 mmol, 62% yield; orange oil

Purification: *i*-hexane:ethyl acetate 8:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.59 – 7.54 (m, 2 H), 7.48 (dd, *J* = 2.0, 0.5 Hz, 1 H), 7.44 (dd, *J* = 1.7, 0.8 Hz, 1 H), 7.38 – 7.25 (m, 3 H), 7.17 – 7.12 (m, 2 H), 7.08 – 7.00 (m, 2 H), 6.92 (d, *J* = 3.1 Hz, 1 H), 6.32 (dd, *J* = 3.2, 0.8 Hz, 1 H), 3.64 (s, 3 H).

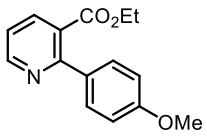
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 198.2, 144.2, 137.5, 137.2, 136.2, 135.9, 132.8, 130.4, 130.2, 130.0, 129.8, 129.5, 128.5, 128.0, 126.3, 122.7, 121.5, 109.1, 101.4, 32.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2943, 2250, 1661, 1597, 1503, 1473, 1303, 1284, 1240 , 1148, 931, 907, 756, 729.

MS (EI, 70 eV): *m/z* (%) = 330 (20), 329 (87), 328 (43), 300 (17), 234 (16), 165 (10), 164 (11), 95 (7), 58 (7), 42 (17).

HR-MS (EI, 70 eV): [$C_{22}H_{16}FNO$], calcd.: 329.1216; found: 329.1214.

Ethyl 2-(4-methoxyphenyl)nicotinate (172a)



Isolated yield: 180 mg, 0.70 mmol, 70% yield; colorless oil

Purification: *i*-hexane:ethyl acetate 95:5

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.64 (dd, *J* = 4.8, 1.8 Hz, 1 H), 7.96 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.47 – 7.36 (m, 2 H), 7.18 (dd, *J* = 7.8, 4.8 Hz, 1 H), 6.95 – 6.78 (m, 2 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.75 (s, 3 H), 1.04 (t, *J* = 7.1 Hz, 3 H).

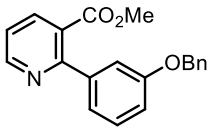
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 168.4, 160.2, 158.2, 151.0, 137.7, 132.5, 130.0, 127.1, 121.0, 113.6, 61.5, 55.2, 13.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 1714, 1608, 1582, 1515, 1428, 1298, 1280, 1250, 1175, 1130,1095, 1054, 1024, 838, 780.

MS (EI, 70 eV): *m/z* (%) = 257 (13), 229 (13), 228 (100), 212 (11), 185 (18), 169 (12), 142 (13), 141 (19), 114 (14).

HR-MS (EI, 70 eV): [$C_{15}H_{15}NO_3$], calcd.: 257.1052; found: 257.1053.

Methyl 2-(3-(benzyloxy)phenyl)nicotinate (172b)



Isolated yield: 226 mg, 0.71 mmol, 71% yield; yellow oil

Purification: *i*-hexane: ethyl acetate 7:3

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.71 (dd, *J* = 4.8, 1.8 Hz, 1 H), 8.01 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.40 – 7.25 (m, 7 H), 7.18 – 7.17 (m, 1 H), 7.04 – 6.96 (m, 2 H), 5.05 (s, 2 H), 3.62 (s, 3 H).

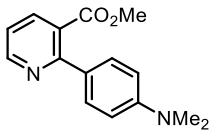
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 168.5, 158.8, 158.5, 151.2, , 141.4, 137.8, 136.9, 129.2, 128.6, 127.9, 127.6, 127.2, 121.6, 121.3, 115.7, 114.6, 70.0, 52.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960, 2254, 1635, 1587, 1560, 1483, 1403, 1313, 1190, 1078, 968, 952, 902, 722.

MS (EI, 70 eV): *m/z* (%) = 319 (28), 161 (8), 91 (8), 90 (103), 83 (5), 58 (6), 43 (11).

HR-MS (EI, 70 eV): [$C_{20}H_{17}NO_3$], calcd.: 319.1208; found: 319.1203.

Methyl 2-(4-(dimethylamino)phenyl)nicotinate (172c)



Isolated yield: 232 mg, 0.91 mmol, 91% yield; yellow oil

Purification: *i*-hexane:ethyl acetate 9:1 to 2:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.71 (dd, *J* = 4.8, 1.8 Hz, 1 H), 7.98 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.54 – 7.45 (m, 2 H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1 H), 6.81 – 6.70 (m, 2 H), 3.76 (s, 3 H), 3.01 (s, 6 H).

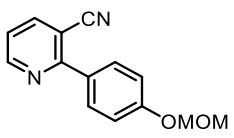
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 169.7, 158.4, 151.1, 150.9, 137.7, 129.7, 127.4, 126.1, 120.1, 111.8, 52.4, 40.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1717, 1607, 1579, 1565, 1525, 1422, 1356, 1313, 1282, 1216, 1193, 1169, 1122, 1094, 1053, 945, 824, 777, 751.

MS (EI, 70 eV): *m/z* (%) = 257 (17), 256 (100), 255 (53), 241 (43), 225 (14), 98 (12), 44 (15).

HR-MS (EI, 70 eV): [$C_{15}H_{16}N_2O_2$], calcd.: 256.1212; found: 256.1208.

2-(4-(Methoxymethoxy)phenyl)nicotinonitrile (172d)



Isolated yield: 145 mg, 0.60 mmol, 60% yield; white solid

Purification: *i*-hexane:ethyl acetate 2:1

m.p.: 84 – 85 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.84 (dd, *J* = 4.8, 1.8 Hz, 1 H), 8.04 (dd, *J* = 7.9, 1.8 Hz, 1 H), 7.95 – 7.87 (m, 2 H), 7.32 (dd, *J* = 7.9, 4.8 Hz, 1 H), 7.20 – 7.12 (m, 2 H), 5.25 (s, 2 H), 3.50 (s, 3 H).

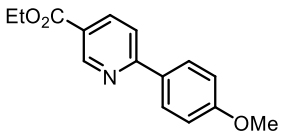
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.5, 159.0, 152.6, 141.9, 130.7, 130.4, 121.1, 118.0, 116.3, 106.8, 94.2, 56.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2225, 1607, 1581, 1574, 1552, 1517, 1432, 1410, 1306, 1256, 1248, 1209, 1178, 1155, 1108, 1038, 982, 948, 934, 851, 828, 812, 803, 771, 719.

MS (EI, 70 eV): *m/z* (%) = 241 (4), 240 (27), 210 (24), 179 (5), 167 (5), 45 (100), 43 (23).

HR-MS (EI, 70 eV): [$C_{14}H_{12}N_2O_2$], calcd.: 240.0899; found: 240.08942.

Ethyl 6-(4-methoxyphenyl)nicotinate (172e)



Isolated yield: 230 mg, 0.89 mmol, 89% yield; white solid

Purification: *i*-hexane:ethyl acetate 4:1

m.p.: 81 – 82 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.24 (dd, *J* = 2.2, 0.8 Hz, 1 H), 8.30 (dd, *J* = 8.3, 2.2 Hz, 1 H), 8.08 – 7.99 (m, 2 H), 7.74 (dd, *J* = 8.4, 0.9 Hz, 1 H), 7.06 – 6.96 (m, 2 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 3.88 (s, 3 H), 1.42 (t, *J* = 7.1 Hz, 3 H).

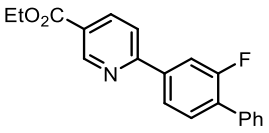
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 165.5, 161.2, 160.4, 150.9, 137.7, 130.9, 128.8, 123.7, 118.9, 114.3, 61.3, 55.4, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2839, 1706, 1592, 1583, 1561, 1475, 1461, 1379, 1366, 1285, 1247, 1182, 1144, 1131, 1112, 1033.

MS (EI, 70 eV): *m/z* (%) = 259 (17), 257 (100), 256 (3), 231 (30), 215 (9), 214 (10), 213 (51), 186 (10), 184 (9), 157 (15).

HR-MS (EI, 70 eV): [$C_{15}H_{15}NO_3$], calcd.: 257.1052; found: 257.1048.

Ethyl 6-(2-fluoro-[1,1'-biphenyl]-4-yl)nicotinate (172f)



Isolated yield: 283 mg, 0.88 mmol, 88% yield; white solid

Purification: *i*-hexane:ethyl acetate 9:1

m.p.: 111 – 112 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.30 (dd, *J* = 2.2, 0.9 Hz, 1 H), 8.37 (dd, *J* = 8.3, 2.2 Hz, 1 H), 7.97 – 7.90 (m, 1 H), 7.91 (t, *J* = 0.9 Hz, 1 H), 7.83 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.65 – 7.54 (m, 3 H), 7.52 – 7.44 (m, 2 H), 7.44 – 7.37 (m, 1 H), 4.45 (q, *J* = 7.1 Hz, 2 H), 1.44 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 165.2, 161.4, 159.0 (d, *J* = 2.5 Hz), 158.9, 151.1, 139.3 (d, *J* = 7.9 Hz), 138.0, 135.2 (d, *J* = 1.4 Hz), 131.1 (d, *J* = 3.8 Hz), 130.5 (d, *J* = 13.7 Hz), 129.0 (d, *J* = 3.1 Hz), 128.6, 128.1, 127.9, 125.0, 123.0 (d, *J* = 3.3 Hz), 119.7, 115.0 (d, *J* = 24.9 Hz).

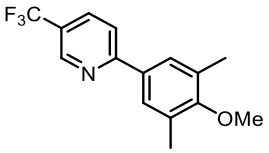
^{19}F-NMR (375 MHz, CDCl, ppm): δ = -117.20.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1712, 1593, 1470, 1417, 1380, 1287, 1274, 1261, 1155, 1124, 1024, 1011, 897, 851, 829, 780, 761, 740, 728, 718, 694.

MS (EI, 70 eV): *m/z* (%) = 322 (19), 321 (100), 293 (35), 277 (11), 276 (57), 248 (14), 221 (21), 220 (18), 170 (13), 44 (10), 43 (24).

HR-MS (EI, 70 eV): [$C_{20}H_{16}FNO_2$], calcd.: 321.1165; found: 321.1158.

2-(4-Methoxy-3,5-dimethylphenyl)-5-(trifluoromethyl)pyridine (172g)



Isolated yield: 242 mg, 0.86 mmol, 86% yield; colorless oil

Purification: *i*-hexane:ethyl acetate 4:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.90 (dt, *J* = 2.5, 0.9 Hz, 1 H), 7.93 (ddd, *J* = 8.3, 2.4, 0.7 Hz, 1 H), 7.82 – 7.75 (m, 1 H), 7.69 (2 H), 3.77 (s, 3 H), 2.37 (s, 6 H).

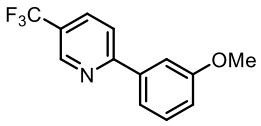
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.5 (d, *J* = 1.5 Hz), 158.9, 146.4 (q, *J* = 4.1 Hz), 133.8 (q, *J* = 3.5 Hz), 133.4, 131.5, 127.9, 124.3 (q, *J* = 33.0 Hz), 123.9 (q, *J* = 272.8 Hz), 119.6, 59.7, 16.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929, 1606, 1567, 1476, 1326, 1199, 1164, 1125, 1075, 1012, 839, 718.

MS (EI, 70 eV): *m/z* (%) = 282 (16), 281 (100), 280 (3), 267 (16), 266 (79), 238 (34), 222 (15), 61 (12).

HR-MS (EI, 70 eV): [$C_{15}H_{14}ClF_3NO$], calcd.: 281.1027; found: 281.1020.

2-(3-Methoxyphenyl)-5-(trifluoromethyl)pyridine (172h)



Isolated yield: 185 mg, 0.73 mmol, 73% yield; colorless crystals

Purification: *i*-hexane:diethyl ether 10:1

m.p.: 53 – 55 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.95 – 8.93 (m, 1 H), 7.98 (ddd, *J* = 8.3, 2.4, 0.8 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 7.63 (dd, *J* = 2.6, 1.6 Hz, 1 H), 7.58 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 7.03 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1 H), 3.91 (s, 3 H).

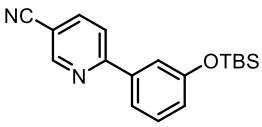
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.4 (d, *J* = 1.4 Hz), 160.2, 146.5 (q, *J* = 4.1 Hz), 139.4, 133.9 (q, *J* = 3.5 Hz), 130.0, 124.9 (td, *J* = 31.4 Hz), 123.8 (q, *J* = 273.9 Hz), 120.1, 119.6, 116.1, 112.4, 55.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2838, 1608, 1589, 1566, 1476, 1328, 1304, 1296, 1242, 1220, 1180, 1166, 1124, 1082, 1052, 1033, 1014, 945, 881, 853, 843, 793, 782, 764, 717, 691.

MS (EI, 70 eV): *m/z* (%) = 254 (12), 253 (100), 252 (95), 224 (51), 223 (54), 222 (54), 154 (20), 141 (21), 44 (23), 43 (64).

HR-MS (EI, 70 eV): [$C_{13}H_{10}F_3NO$], calcd.: 253.0714; found: 253.0716.

6-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)nicotinonitrile (172i)



Isolated yield: 261 mg, 0.84 mmol, 84% yield; white solid

Purification: *i*-hexane:ethyl acetate 95:5

m.p.: 69 – 70 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.93 (dd, *J* = 2.2, 0.9 Hz, 1 H), 7.99 (dd, *J* = 8.3, 2.2 Hz, 1 H), 7.81 (dd, *J* = 8.4, 0.9 Hz, 1 H), 7.61 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1 H), 7.54 (t, *J* = 2.1 Hz, 1 H), 7.37 (t, *J* = 7.9 Hz, 1 H), 6.97 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 1 H), 1.01 (s, 9 H), 0.24 (s, 6 H).

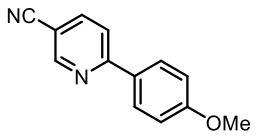
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.3, 156.4, 152.4, 139.8, 138.8, 130.1, 122.3, 120.3, 120.1, 119.1, 117.1, 107.9, 25.7, 18.2, -4.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 2857, 2229, 1594, 1582, 1553, 1464, 1432, 1373, 1310, 1288, 1259, 1252, 1236, 1217, 1206, 936, 892, 830, 799, 779, 760, 739, 690, 681, 662.

MS (EI, 70 eV): *m/z* (%) = 311 (2), 310 (6), 295 (2), 254 (19), 253 (100), 43 (11).

HR-MS (EI, 70 eV): [$C_{18}H_{22}N_2OSi$], calcd.: 310.1501; found: 310.1499.

6-(4-Methoxyphenyl)nicotinonitrile (172j)



Isolated yield: 176 mg, 0.84 mmol, 84% yield; white solid

Purification: *i*-hexane:ethyl acetate 9:1

m.p.: 104 – 106 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.88 (dd, *J* = 2.2, 0.9 Hz, 1 H), 8.03 – 7.99 (m, 2 H), 7.96 – 7.90 (m, 1 H), 7.78 – 7.73 (m, 1 H), 7.03 – 6.99 (m, 2 H), 3.87 (s, 3 H).

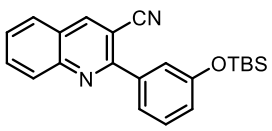
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.8, 160.0, 152.4, 139.6, 129.8, 128.86, 118.9, 117.2, 114.4, 106.8, 55.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3053, 2841, 2220, 1607, 1587, 1515, 1474, 1442, 1378, 1303, 1245, 1169, 1113, 1042, 1017, 817, 757.

MS (EI, 70 eV): *m/z* (%) = 210 (22), 196 (1), 195 (5), 179 (1), 168 (1), 167 (9), 166 (4), 141 (1), 140 (2), 86 (3), 84 (5)

HR-MS (EI, 70 eV): [$C_{13}H_{10}N_2O$], calcd.: 210.0793 found: 210.0788.

2-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)quinoline-3-carbonitrile (174a)



Isolated yield: 328 mg, 0.92 mmol, 92% yield; yellow oil

Purification: *i*-hexane:ethyl acetate 8:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.59 (d, *J* = 0.8 Hz, 1 H), 8.14 (dq, *J* = 8.2, 1.0 Hz, 1 H), 7.86 - 7.80 (m, 2 H), 7.60 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1 H), 7.52 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1 H), 7.42 - 7.32 (m, 2 H), 6.95 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 1 H), 0.95 (s, 9 H), 0.20 (s, 6 H).

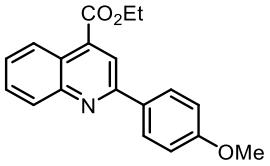
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 157.7, 155.9, 148.6, 144.2, 139.0, 132.9, 130.0, 129.8, 128.0, 127.7, 125.1, 122.1, 121.9, 120.8, 117.9, 105.6, 25.7, 18.2, -4.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3064, 2856, 2225, 1715, 1619, 1582, 1557, 1460, 1440, 1287, 1250, 1220, 944, 900, 831, 774, 730.

MS (EI, 70 eV): *m/z* (%) = 305 (17), 304 (71), 303 (237), 287 (23), 274 (14), 273 (35), 144 (14).

HR-MS (EI, 70 eV): [$C_{22}H_{24}N_2OSi$], calcd.: 360.1658; found: 360.1657.

Ethyl 2-(4-methoxyphenyl)quinoline-4-carboxylate (174b)



Isolated yield: 199 mg, 0.65 mmol, 65% yield; white solid

Purification: *i*-hexane:ethyl acetate 9:1

m.p.: 80 – 82 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 (dd, *J* = 8.6, 0.7 Hz, 1 H), 8.30 (s, 1 H), 8.17 – 8.08 (m, 3 H), 7.70 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1 H), 7.54 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1 H), 7.04 – 6.94 (m, 2 H), 4.50 (q, *J* = 7.1 Hz, 2 H), 3.85 (s, 3 H), 1.46 (t, *J* = 7.1 Hz, 3 H).

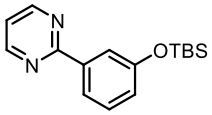
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.6, 161.1, 156.3, 149.2, 136.0, 131.4, 130.1, 129.8, 128.9, 127.3, 125.4, 123.7, 119.8, 114.3, 61.9, 55.4, 14.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981, 1714, 1504, 1271, 1244, 1232, 1194, 1178, 1151, 1136, 1113, 1023, 835, 797, 780, 736, 678.

MS (EI, 70 eV): *m/z* (%) = 309 (2), 308 (24), 307 (100), 236 (12), 235 (57), 234 (12), 191 (23), 190 (10).

HR-MS (EI, 70 eV): [$C_{19}H_{17}NO_3$], calcd.: 307.1208; found: 307.1203.

2-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)pyrimidine (174c)



Isolated yield: 264 mg, 0.92 mmol, 92% yield; colorless oil

Purification: *i*-hexane:ethyl acetate 9:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.80 (d, *J* = 4.8 Hz, 2 H), 8.04 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1 H), 7.94 (dd, *J* = 2.5, 1.6 Hz, 1 H), 7.35 (t, *J* = 7.9 Hz, 1 H), 7.18 (t, *J* = 4.8 Hz, 1 H), 6.97 (ddd, *J* = 8.1, 2.6, 1.0 Hz, 1 H), 1.01 (s, 9 H), 0.24 (s, 6 H).

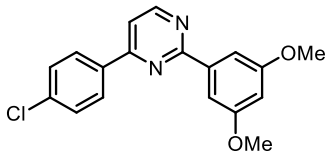
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 164.6, 157.2, 156.1, 139.1, 129.5, 122.6, 121.2, 119.8, 119.1, 25.7, 18.2, -4.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931, 2858, 1713, 1553, 1450, 1422, 1409, 1281, 1250, 1225, 1177, 1150, 939, 834, 816, 796, 779, 690.

MS (EI, 70 eV): *m/z* (%) = 287 (3), 286 (12), 230 (6), 229 (20), 288 (100), 213 (5), 167 (5).

HR-MS (EI, 70 eV): [$C_{16}H_{22}N_2OSi$], calcd.: 286.1501; found: 286.1496.

4-(4-Chlorophenyl)-2-(3,5-dimethoxyphenyl)pyrimidine (174d)



Isolated yield: 281 mg, 0.89 mmol, 86% yield; white solid

Purification: *i*-hexane:ethyl acetate 4:1

m.p.: 113 – 114 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.84 (dd, *J* = 5.3, 0.9 Hz, 1 H), 8.21 – 8.11 (m, 2 H), 7.76 (d, *J* = 2.4 Hz, 2 H), 7.57 (dd, *J* = 5.3, 1.1 Hz, 1 H), 7.55 – 7.46 (m, 2 H), 6.63 (t, *J* = 2.4 Hz, 1 H), 3.92 (s, 6 H).

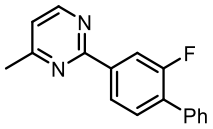
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 164.3, 162.6, 161.0, 157.9, 139.8, 137.3, 135.3, 129.2, 128.5, 114.5, 106.1, 103.5, 55.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3019, 2840, 1604, 1595, 1568, 1543, 1493, 1471, 1435, 1421, 1405, 1380, 1291, 1208, 1158, 1088, 1068, 1045, 1011, 930, 869, 828, 810, 791, 774, 702, 689, 663.

MS (EI, 70 eV): *m/z* (%) = 329 (7), 328 (36), 327 (38), 326 (100), 325 (64), 298 (8), 297 (19), 296 (17), 295 (10), 163 (11).

HR-MS (EI, 70 eV): [$C_{18}H_{15}ClN_2O_2$], calcd.: 326.0822; found: 326.0814.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-4-methylpyrimidine (174e)



Isolated yield: 200 mg, 0.76 mmol, 76% yield; white solid

Purification: *i*-hexane:ethyl acetate 9:1

m.p.: 94 – 95 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 (d, *J* = 5.1 Hz, 1 H), 8.34 – 8.23 (m, 2 H), 7.67 – 7.60 (m, 2 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.51 – 7.44 (m, 2 H), 7.43 – 7.36 (m, 1 H), 7.08 (d, *J* = 5.0 Hz, 1 H), 2.61 (s, 3 H).

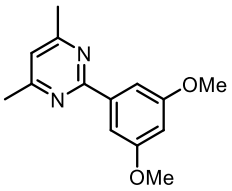
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.4, 163.0 (d, *J* = 2.9 Hz), 160.0 (d, *J* = 247.2 Hz), 156.9, 139.1 (d, *J* = 8.1 Hz), 135.5 (d, *J* = 1.5 Hz), 131.0 (d, *J* = 13.7 Hz), 130.8 (d, *J* = 3.7 Hz), 129.0 (d, *J* = 3.1 Hz), 128.5, 128.0, 124.0 (d, *J* = 3.3 Hz), 119.0, 115.8 (d, *J* = 25.1 Hz), 24.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2252, 1578, 1557, 1436, 1416, 1390, 904, 832, 828, 797, 768, 723, 697.

MS (EI, 70 eV): *m/z* (%) = 266 (1), 265 (20), 264 (100), 263 (4), 249 (11), 198 (6), 197 (27), 196 (6), 170 (6).

HR-MS (EI, 70 eV): [$C_{17}H_{13}FN_2$], calcd.: 264.1063; found: 264.1056.

2-(3,5-Dimethoxyphenyl)-4,6-dimethylpyrimidine (174f)



Isolated yield: 158 mg, 0.65 mmol, 65% yield; white solid

Purification: *i*-hexane:ethyl acetate 4:1

m.p.: 127 – 128 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.63 (d, *J* = 2.4 Hz, 2 H), 6.93 (s, 1 H), 6.58 (t, *J* = 2.4 Hz, 1 H), 3.89 (s, 6 H), 2.53 (s, 6 H).

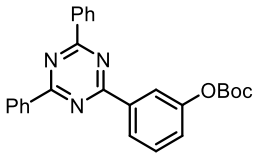
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.7, 163.8, 160.9, 140.3, 118.2, 105.9, 103.3, 55.5, 24.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926, 2834, 1610, 1584, 1540, 1465, 1450, 1440, 1427, 1384, 1360, 1318, 1284, 1240, 1203, 1170, 1154, 1096, 1057, 1002, 985, 941, 926, 877, 867, 835, 812, 794, 754, 690.

MS (EI, 70 eV): *m/z* (%) = 245 (4), 244 (25), 243 (23), 215 (6), 214 (7), 191 (8), 88 (5), 70 (10).

HR-MS (EI, 70 eV): [$C_{14}H_{16}N_2O_2$], calcd.: 244.1212; found: 244.1204.

***tert*-Butyl (3-(4,6-diphenyl-1,3,5-triazin-2-yl)phenyl) carbonate (174g)**



Isolated yield: 260 mg, 0.61 mmol, 61% yield; white solid

Purification: *i*-hexane:ethyl acetate 4:1

m.p.: 182 – 183 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.81 – 8.73 (m, 4 H), 8.67 (dt, *J* = 7.8, 1.3 Hz, 1 H), 8.56 (dd, *J* = 2.5, 1.6 Hz, 1 H), 7.67 – 7.54 (m, 7 H), 7.46 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 1 H), 1.62 (s, 9 H).

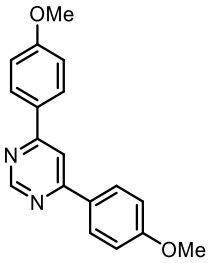
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 171.7, 170.8, 151.8, 151.5, 138.0, 136.1, 132.6, 129.6, 129.0, 128.7, 126.3, 125.5, 121.7, 83.9, 27.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 1757, 1519, 1447, 1363, 1253, 1218, 1147, 909, 770, 732, 689.

MS (EI, 70 eV): *m/z* (%) = 426 (1), 326 (21), 325 (100), 104 (18), 103 (21), 57 (33).

HR-MS (EI, 70 eV): [$C_{26}H_{23}N_3O_3$+H^+], calcd.: 426.1812; found: 426.1811.

4,6-Bis(4-methoxyphenyl)pyrimidine (176)



The title compound was prepared from 4,6-dichloropyrimidine (**175**) according to **TP-11** using 2.4 equiv of the appropriate zinc species (**165a**).

Isolated yield: 225 mg, 0.77 mmol, 77% yield (1 mmol scale)

2.13 g, 7.29 mmol, 73% yield (10 mmol scale); white solid

Purification: *i*-hexane:ethyl acetate 7:1

m.p.: 147 – 148 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.14 (d, *J* = 1.3 Hz, 1 H), 8.09 – 8.01 (m, 4 H), 7.91 (d, *J* = 1.3 Hz, 1 H), 7.03 – 6.93 (m, 4 H), 3.83 (s, 6 H).

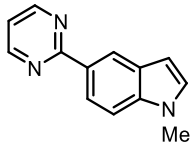
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.9, 161.9, 159.0, 129.6, 128.7, 114.4, 111.0, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3009, 1602, 1583, 1506, 1457, 1443, 1379, 1298, 1255, 1231, 1170, 1112, 1021, 825, 804, 780.

MS (EI, 70 eV): *m/z* (%) = 293 (20), 292 (100), 277 (19), 41 (9), 249 (6), 234 (5), 146 (8).

HR-MS (EI, 70 eV): [$C_{18}H_{16}N_2O_2$], calcd.: 292.1212; found: : 292.1205.

1-Methyl-6-(pyrimidin-2-yl)-1*H*-indole (177a)



Isolated yield: 144 mg, 0.69 mmol, 69% yield (1 mmol scale); white solid

1.51 g, 7.22 mmol, 72% yield (10 mmol scale)

Purification: *i*-hexane:ethyl acetate 7:3

m.p.: 123 – 124 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.75 – 8.67 (m, 3 H), 8.29 (dd, *J* = 8.7, 1.7 Hz, 1 H), 7.34 (dt, *J* = 8.8, 0.8 Hz, 1 H), 7.09 – 6.99 (m, 2 H), 6.53 (dd, *J* = 3.1, 0.9 Hz, 1 H), 3.77 (s, 3 H).

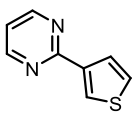
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.0, 157.1, 138.4, 129.7, 129.1, 128.7, 121.9, 121.8, 118.1, 109.2, 102.5, 33.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3098, 1612, 1563, 1552, 1433, 1404, 1339, 1277, 1240, 1148, 919, 790, 769, 728, 698.

MS (EI, 70 eV): *m/z* (%) = 209 (100), 208 (24), 156 (24), 155 (12), 104 (10), 85 (20), 83 (30).

HR-MS (EI, 70 eV): [$C_{13}H_{11}N_3$], calcd.: 209.0953; found: 209.0950.

2-(Thiophen-3-yl)pyrimidine (177b)



Isolated yield: 99 mg, 0.61 mmol, 61% yield; white solid

Purification: *i*-hexane:ethyl acetate 8:2

m.p.: 97 – 99 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.67 (d, *J* = 4.9 Hz, 2 H), 8.23 (dd, *J* = 3.1, 1.2 Hz, 1 H), 7.83 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.32 (dd, *J* = 5.1, 3.1 Hz, 1 H), 7.06 (t, *J* = 4.9 Hz, 1 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.9, 157.2, 141.5, 127.9, 127.3, 126.1, 118.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3117, 2925, 2360, 1566, 1557, 1530, 1435, 1376, 866, 804, 773, 698.

MS (EI, 70 eV): *m/z* (%) = 244 (11), 163 (15), 162 (19), 161 (42), 135 (12), 110 (12), 109 (78), 58 (41), 57 (12), 49 (11), 42 (9).

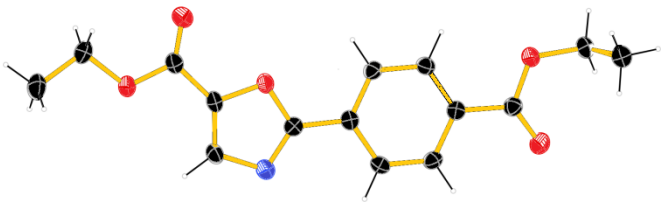
HR-MS (EI, 70 eV): [$C_8H_6N_2S$], calcd.: 162.0252; found: 162.0243.

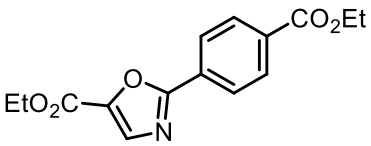
D APPENDIX

D APPENDIX

1 X-Ray Structures

Ethyl 2-(4-(ethoxycarbonyl)phenyl)oxazole-5-carboxylate (**138j**)

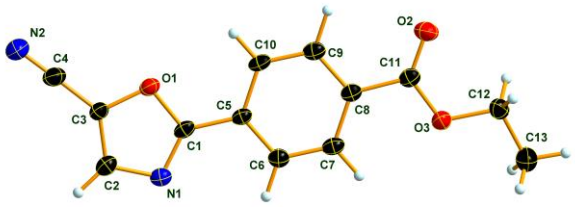


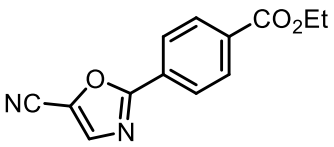


Crystal Data

Empirical formula	$C_{15}H_{15}N_1O_5$
Formula weight	289.28
Crystal size [mm]	0.04 x 0.06 x 0.12
T [K]	173
Radiation	MoKα
Diffractometer	XCalibur
Crystal system	monoclinic
Space group	*P*21/c
a [Å]	6.0862 (4)
b [Å]	33.4685 (19)
c [Å]	6.8474 (4)
α [°]	90
β [°]	93.235 (2)
γ [°]	90
V [Å^3]	1392.57 (15)
Z	4
ρ_{calcd} [g cm^{-3}]	1.380
μ [mm^{-1}]	0.105
F(000)	608
θ range [°]	3.0 – 25.4
Index ranges	$-7 \le h \le 7$
	$-40 \le k \le 40$
	$-8 \le l \le 8$
Reflns. collected	24185
Reflns. observed	2067
Reflns. unique	2562
	(R_{int} = 0.036)
R_1 (F_{obs})	0.0356
Rω (F_2)	0.0987
S	1.03
Peak/hole [e Å^3]	0.24/-0.17

Ethyl 4-(5-cyanooxazol-2-yl)benzoate (**138l**)

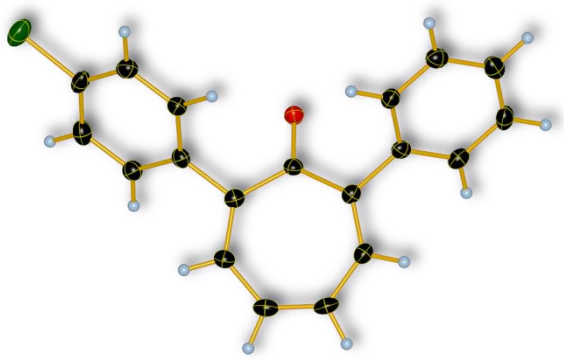


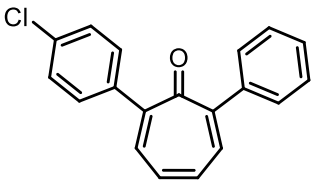


Crystal Data

Empirical formula	$C_{13}H_{10}N_2O_3$
Formula weight	242.23
Crystal size [mm]	0.17 x 0.20 x 0.39
T [K]	100
Radiation	MoKα
Diffractometer	XCalibur
Crystal system	monoclinic
Space group	*P*21/n
a [Å]	4.5247 (2)
b [Å]	28.9366 (17)
c [Å]	9.1022 (6)
α [°]	90
β [°]	99.297 (6)
γ [°]	90
V [Å^3]	1176.09 (12)
Z	4
ρ_{calcd} [g cm^{-3}]	1.368
μ [mm^{-1}]	0.099
F(000)	171
θ range [°]	4.2 – 26.4
Index ranges	-5 ≤ *h* ≤ 5
	-36 ≤ *k* ≤ 26
	-11 ≤ *l* ≤ 11
Reflns. collected	7943
Reflns. observed	1765
Reflns. unique	2387
	(R_{int} = 0.043)
R_1 (F_{obs})	0.0739
$R\omega$ (F_2)	0.1380
S	1.13
Peak/hole [e Å^3]	0.27/-0.25

2-(4-Chlorophenyl)-7-phenylcyclohepta-2,4,6-trien-1-one (**159a**)





Crystal Data

Empirical formula	$C_{19}H_{13}ClO$
Formula weight	292.74
Crystal size [mm]	0.17 x 0.20 x 0.39
T [K]	123
Radiation	MoKα
Diffractometer	Xcalibur
Crystal system	triclinical
Space group	P1
a [Å]	3.899 (2)
b [Å]	7.3033 (5)
c [Å]	12.6436 (7)
α [°]	98.100 (5)
β [°]	95.517 (5)
γ [°]	101.420 (5)
V [Å^3]	346.53 (4)
Z	1
ρ_{calcd} [g cm^{-3}]	1.403
μ [mm^{-1}]	0.270
F(000)	152
θ range [°]	4.7 – 31.7
Index ranges	$-5 \le h \le 5$
	$-9 \le k \le 9$
	$-16 \le l \le 16$
Reflns. collected	5815
Reflns. observed	3412
Reflns. unique	3070
	(R_{int} = 0.0269)
R_1 (F_{obs})	0.0456
$R\omega$ (F_2)	0.0799
S	1.026
Peak/hole [e Å^3]	0.29/-0.17

2 List of Abbreviations

Ac	acetyl
acac	acetylacetonate
Alk	alkyl
aq	aqueous
Ar	Aryl
ATR	attenuated total reflection (IR)
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
calc.	calculated
conc.	concentrated
CPhos	2-dicyclohexylphosphino-2',6'-bis(*N*,*N*-dimethylamino)biphenyl
Cy	cyclohexyl
δ	chemical shifts in ppm (parts per million)
dba	*trans*,*trans*-dibenzylidenacetone
DMBA	2,5-dimethylbenzoic acid
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethylpropyleneurea
E	electrophile
EI	electron impact ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FG	functional group
FLP	frustrated Lewis pairs
GC	gas chromatography
HRMS	high resolution mass spectrometry
IPent	1,3-bis(diisopentylphenyl)-imidazol-2-ylidene
IPr	1,3-bis(diisopropylphenyl)-imidazol-2-ylidene
i-Pr	*iso*-propyl
IR	infrared
J	coupling constant (NMR)
M	molarity
m	meta
m.p.	melting point
Me	methyl
MOM	methoxymethyl
MS	mass spectrometry
NEP	*N*-ethyl-2-pyrrolidone
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho

p	para
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
Ph	phenyl
phen	phenanthroline
Piv	pivaloyl
PPAR	peroxisome proliferator-activated receptor
R	organic substituent
r.t.	room temperature
RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
sat.	saturated
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TAAR	trace amine-associated receptor
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-Butyl
TEA	triethylamine
tfp	tris(*o*-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
TTMPP	tris(2,4,6-trimethoxyphenyl)phosphine
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
ZACA	Zr-catalyzed asymmetric carboalumination

3 Curriculum Vitae

Diana Haas

Date of birth: 03.04.1988 in Traunstein, Germany
Nationality: German

WORK EXPERIENCE

07/2013 – 06/2016	**LMU Munich, Germany** Faculty of Chemistry and Pharmacy **PhD Thesis in the research group of Prof. Dr. Paul Knochel** (organic synthesis, organometallic chemistry, homogeneous catalysis)
12/2013 – present	**Georg Thieme Verlag** Contributor of the *Synfacts* magazine (monthly appearing chemistry journal)

EDUCATION

10/2012 – 05/2013	**LMU Munich, Germany** **Master of Science M. Sc.**; with distinction Main subjects: organic chemistry, inorganic chemistry, patent law Master's thesis under the guidance of Prof. Dr. Paul Knochel: "Functionalization of Oxazoles and Oxazolines via directed metalation using 2,2,6,6-Tetramethylpiperidyl Bases".
09/2011 – 02/2012	**Università degli Studi di Padova, Padou, Italy** Student exchange in the course of the European Erasmus exchange programme
05/2011 – 08/2011	**University of Illinois at Urbana-Champaign, USA** Research stay in the group of Prof. Dr. Scott Denmark working in the field of asymmetric phase-transfer catalysis.
08/2007 – 09/2010	**LMU Munich, Germany** **Bachelor of Science, B.Sc.** Main subjects: chemistry, biochemistry Bachelor's thesis under the guidance of Prof. Dr. Heinz Langhals: "Rubicen-Derivatives as Optical Components in Functional Materials".

SCHOOL

06/2007	**Annette-Kolb-Gymnasium, Traunstein** Allgemeine Hochschulreife (university entry qualification) Major courses: English, biology

PARTICIPATION IN CONFERENCES AND SEMINARS

05/2016	EUCHEM Conference on Stereochemistry (Bürgenstock), Brunnen, Schweiz • Posterpräsentation: "Ligand-Promoted Co-Catalyzed Cross-Coupling of (Hetero)Arylzinc Reagents and (Hetero)Aryl Halides".
07/2015	18th IUPAC Symposium on Organometallic Chemistry (OMCOS 18), Sitges/Barcelona, Spain

- Poster presentation: Co-Catalyzed Negishi Cross-Coupling Reactions of Arylzinc Reagents with Primary and Secondary Alkyl Halides".

02/2014 CarLa Winter School 2014 (Catalysis Research Laboratory of the University of Heidelberg und BASF SE), Ludwigshafen, Germany
- Oral presentation and poster presentation: „Selective Metalation and Functionalization of Oxazoles and Oxazolines Using 2,2,6,6-Tetramethylpiperidyl Bases".

07/2013 17th IUPAC Symposium on Organometallic Chemistry (OMCOS 17), Fort Collins, Colorado, USA
- Poster presentation: "Chemo- and Regioselective Functionalization of the Oxazole Scaffold Using TMPZnCl·LiCl and TMPMgCl·LiCl".

FELLOWSHIPS AND AWARDS

07/2015 **German Chemical Society (GdCh)**
Travel fellowship for the participation at the IUPAC Symposium (OMCOS 18)

12/2013 **Römer prize of the LMU Munich, Germany**
Faculty award for outstanding achievements during the Master's course

09/2012 – 03/2013 **Fellowship of the Stiftung Dombrowski, Siegsdorf, Germany**
Fellowship for the support of regional talents in south-eastern Bavaria, Germany

09/2011 – 02/2012 **Erasmus-Sokratis-Fellowship**
Fellowship for a student exchange at the University of Padou, Italy

06/2011 **Oskar-Karl-Forster Fellowship of the LMU Munich, Germany**

04/2010 – 09/2010 **Fellowship of the John Loesch Foundation, Germany**

PUBLICATIONS

1. Diana Haas, Jeffrey M. Hammann, Ferdinand H. Lutter, Paul Knochel, "Mild Cobalt-Catalyzed Negishi Cross-Couplings of (Hetero)Arylzinc Reagents with (Hetero)Aryl Halides", *Angew. Chem. Int. Ed.* **2016**, *55*, 3809–3812.

2. Diana Haas, Jeffrey M. Hammann, Robert Greiner, Paul Knochel, "Recent Developments in Negishi Cross-Coupling Reactions", *ACS Catal.* **2016**, *6*, 1540–1552.

3. Diana Haas, Jeffrey M. Hammann, Alban Moyeux, Gérard Cahiez, Paul Knochel, "Oxidative Homocoupling of Diheteroaryl- or Diarylmanganese Reagents Generated via Directed Manganation Using TMP_2Mn", *Synlett* **2015**, *26*, 1515–1519.

4. Jeffrey M. Hammann, Diana Haas, Paul Knochel, "Highly Diastereoselective Cobalt-Mediated $C(sp^3)$-$C(sp^2)$ Cross-Coupling Reactions of Cyclic Halohydrins with (Hetero)Aryl Grignard Reagents", *Synthesis* **2015**, *47*, 1461–1468.

5. Diana Haas, Maximilian S. Hofmayer, Tomke Bresser, Paul Knochel, "Zincation of 4,4-dimethyloxazoline using TMPZnCl·LiCl. A new preparation of 2-aryloxazolines", *Chem. Commun.* **2015**, *51*, 6415–6417.

6. Jeffrey M. Hammann, Diana Haas, Paul Knochel, "Cobalt-Catalyzed Negishi Cross-Coupling Reactions of (Hetero)Arylzinc reagents with Primary and Secondary Alkyl Bromides and Iodides", *Angew. Chem. Int. Ed.* **2015**, *54*, 4478–4481.

7. Diana Haas, Marc Mosrin, Paul Knochel, “Chemo- and Regioselective Functionalization of the Oxazole Scaffold Using TMPZnCl·LiCl and TMPMgCl·LiCl”, *Org. Lett*. **2013**, *15*, 6162–6165.

8. Klaus Groll, Tobias D. Blümke, Andreas Unsinn, Diana Haas, Paul Knochel, “Direct Pd-Catalyzed Cross-Coupling of Functionalized Organoaluminum Reagents“, *Angew. Chem. Int. Ed.* **2012**, *51*, 11157–11161.