Dissertation zur Erlangung des Doktorgrades

der Fakultät für Chemie und Pharmazie

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Lewis-Acid Triggered Regioselective Metallation of Chromones, 4-Pyrones, Uracils, Uridines and Cytidines.

Isoxazole Embedded Allylic Zinc Reagent for the Diastereoselective Preparation of Highly Functionalized Aldol-Type Derivatives Bearing a Stereocontrolled Quaternary Center.

von

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aus

Herdecke

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Erklärung

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Eidesstattliche Versicherung

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Lydia M. Klier

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Publications

C. Despotopoulou, L. Klier, P. Knochel, "Total Functionalization of Pyrazole Derivatives by Selective Magnesiations." *Org. Lett.*, **2009**, *11*, 3326.

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L. Klier, C. R. Diène, M. Schikinger, A. Metzger, A. J. Wagner, K. Karaghiosoff, I. Marek, P. Knochel, "Isoxazole Embedded Allylic Zinc Reagent for the Diastereoselective Preparation of Highly Functionalized Aldol-Type Derivatives Bearing a Stereocontrolled Quaternary Center." *Chem. Eur. J.*, **2014**, *20*, 14096.

Contributions to Conferences

L. Klier, E. Aranzamendi, D. Ziegler and Paul Knochel "Lewis Acid-Triggered Selective Metalation of Uracils and Uridines"; OMCOS 17, July 2013, Fort Collins Colorado, USA.

List of Abbreviations

Ac	acetyl
AcOH	acetic acid
aq	aqueous
Ar	aryl
Bu	butyl
BuLi	butyl lithium
calc.	calculated
conc.	concentrated
dba	*trans*,*trans*-dibenzylideneacetone
dist.	distilled
DMAC	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMG	directed metalation group
DMSO	dimethyl sulfoxide
DoM	directed *ortho* metalation
δ	chemical shifts in ppm
E	electrophile
EDG	electron-donating group
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
GC	gas chromatography
h	hour
*i*hexane	*iso*-hexane
HSQC	heteronuclear single quantum coherence
HRMS	high resolution mass spectrometry
HMBC	heteronuclear multiple bond correlation
*i*Pr	*iso*propyl
IR	infra-red
J	coupling constant (NMR)
LA	Lewis acid
LDA	lithium di*iso*propylamide
M	molarity
m	*meta*
*m*CPBA	*m*-chloroperoxybenzoic acid
m.p.	melting point
Me	methyl
Met	metal
min	minute
mmol	millimole
MOM	methoxymethyl
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PEPPSI-*i*Pr	[1,3-bis(2,6-di(*iso*propyl)-phenyl)imidazol-2-ylidene] (3-chloropyridyl)-palladium(II) dichloride
Ph	phenyl
ppm	parts per million
R	organic substituent
sat.	saturated
S-Phos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
TMEDA	*N*,*N*,*N*′,*N*′-tramethylethylendiamin
tfp	tris-(2-furyl)phosphine
THF	tetrahydrofuran
TIPS	tri(*iso*propylsilyl)
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethyl-piperidyl
TMPH	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
X-Phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

1 Overview

Heterocyclic compounds are widely distributed in nature and are used in modern society as herbicides, pesticides, insecticides, dyes and copolymers.[1] They play a vital role in many biological processes,[2] there are vast numbers of pharmacologically active heterocyclic compounds, with many of them being used in clinical routine. In 2010, more than 80% of drugs sold in the United States of America contained a heterocyclic fragment.[3] Some of these heterocycles are natural products, however the large majority of pharmaceuticals is of synthetic origin. Scientists around the world have been attempting to design new drugs for treatment of malignant diseases like AIDS or cancer. For the development of new drugs it is essential to determine the biological active site of a molecule. In order to optimize the biological activity, it is often necessary to create libraries of differently functionalized and modified scaffolds.[4] For this purpose, scientists have developed a broad variety of synthetic strategies to prepare functionalized heterocycles. One method involves the construction of a heterocyclic core by cyclisation after functional groups have been installed.[1a] Alternatively, it is possible to functionalize an existing heterocycle by replacing different substituents in a successive order.[1a] This approach offers greater flexibility with respect to the choice of substituents and provides an easy access to various derivatives. It may include traditional aromatic substitution chemistry, directed metallation methods, halogen-metal exchanges, as well as cross-coupling reactions.

[1] (a) *Comprehensive Heterocyclic Chemistry III*, Vol. 1 (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K.Taylor), Elsevier, Oxford, United Kingdom, **2008**, p. xxii. (b) *Heterocycles in Live and Society* (Eds.: A. F. Pozharskii, A. T. Soldatenkov, A. R. Katrinzky), John Wiley & Sons, Chichester, United Kingdom, **2011**.
[2] *Medicinal Natural Products*, 3. Edition (Ed.: P. M. Dewick), John Wiley & Sons, United Kingdom, **2009**, p. 1.
[3] A. Gomtsyan, *Chem. Heterocycl. Compd.* **2012**, *48*, 7.
[4] N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529.

2 Organometallic Chemistry

2.1 Historical Background

Historically, the beginning of organometallic chemistry can be traced back to the research of the French chemist L. C. Cadet (1760), who prepared As_2Me_4 while working on the preparation of invisible ink.[5] Nearly 150 years later, Victor Grignard received the Nobel Prize for his pioneering work on organomagnesium reagents. Since then, organometallic chemistry has remained a constantly growing field and a powerful tool in both academia and industry.[6] The significance of organometallic reagents in catalysis and in general synthetic chemistry, is underlined by further Nobel Prizes awarded in these fields: 1963 to Ziegler and Natta, 1973 to Wilkinson and Fischer, 1989 to Brown and Wittig, 2001 to Knowles, Noyori and Sharpless, 2005 to Chauvin, Grubbs and Schrock, and 2010 to Heck, Negishi and Suzuki. A large number of organometallic reagents have been prepared and their chemical properties vary widely, but they can roughly be classified by the polarisation of the metal-carbon bond. In general, the reactivity of an organometallic species increases with the ionic character of its carbon metal-bond (Figure 1).[7]

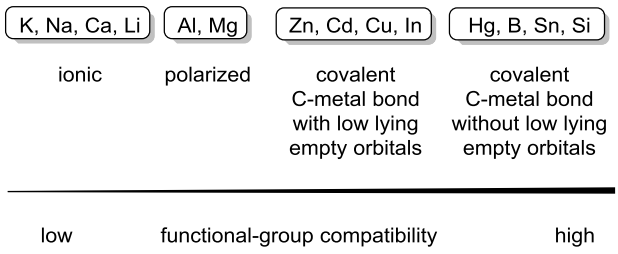


Figure 1: Functional group tolerance and polarity of organometallic reagents.[8]

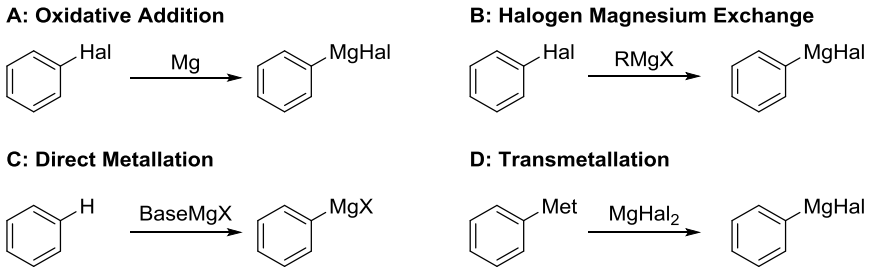
[5] D. Seyferth, *Organometallics* **2001**, *20*, 1488.
[6] (a) *Organomagnesium Compounds* (Eds.: Z. Rappoport, I. Marek), John Wiley & Sons, Chichester, United Kingdom, **2006**. (b) *Main Group Metals in Organic Synthesis* (Eds. H. Yamamoto, K. Oshima), VCH, Wiley, Weinheim, Germany, **2004**.
[7] (a) *Organometallics in Organic Synthesis* (Ed.: N. Negishi), VCH, Wiley, Weinheim, Germany, **1996**. (b), *Applications of Organometallic Compounds* (Ed.: I. Omae), VCH, Wiley, Chichester, United Kingdom, **1998**. (c) *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), VCH, Wiley, Weinheim, Germany **2005**. (d) *The Chemistry of Organometallic Compounds* (Eds.: E. G. Rochow, D. T. Hurd, R. N. Lewis), VCH, Wiley, New York, United States **1957**. (e) *Principle of Organometallic Chemistry* (Ed.: Powell), Chapman and Hall, London, United Kingdom, **1988**.
[8] B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.

Highly reactive organometallics derived from alkali metals such as organo lithium, sodium and potassium reagents, have a strongly ionic carbon-metal bond, which drastically lowers their functional group tolerance. Lithium compounds are the only of these polar organometallic reagents that display a broad field of application.[9] At the other end of the spectrum, covalent bonded organometallics like organoborons,[10] and organosilicons[11] provide a high functional group tolerance.

2.2 Organomagnesium Reagents

Although organomagnesium compounds were among the earliest reported organometallic compounds, their synthetic potential was recognized only at the beginning of the last century.[6] In 1900, Victor Grignard[12] introduced the first organomagnesium reagents; the importance of this work was underlined by the Nobel Prize awarded in 1912. The facile synthesis of the so-called Grignard reagents, their good stabilities and excellent reactivities towards a wide range of different electrophiles made them important nucleophiles in both chemical laboratories and in industrial processes.[13] The reactivity of the carbon-magnesium bond depends strongly on the reaction temperature. At temperatures above 25 °C, Grignard reagents react with most functional groups containing polar multiple bonds, strained rings, acidic protons, and highly polar single bonds.[14] The oxidative insertion of magnesium into alkyl or aryl halides is still the most straightforward method for the preparation of organomagnesium reagents (A, Scheme 1).[13c]

[9] (a) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev*. **2004**, *104,* 2667. (b) *The chemistry of organolithium compounds* (Eds.: Z. Rappoport, I. Marek), John Wiley & Sons, Chichester, United Kingdom, **2004**. (b) *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications* (Eds.: R. Luisi, V. Capriati), VCH, Wiley, Weinheim, Germany, **2014**.
[10] *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), VCH, Wiley, Weinheim, Germany **2005**, p. 45-103.
[11] *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), VCH, Wiley, Weinheim, Germany **2005**, p. 173-197.
[12] V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322.
[13] (a) *Grignard Reagents* (Ed.: H. G. Richey), VCH, Wiley, New York, **2000**. (b) *Handbook of Grignard-Reagents* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **2000**. (c) *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), VCH, Wiley, Weinheim, Germany, **2005**, p. 109-164.
[14] *Handbook of Grignard-Reagents* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**.



Scheme 1: Synthetic methods for the preparation of Grignard reagents.

According to standard protocols, the insertion reaction is highly exothermic and is normally performed under reflux conditions in Et_2O or THF,[15] precluding the presence of most functional groups. If, however, the oxidative addition reaction is conducted at low temperature, sensitive groups can be tolerated. This can be achieved by using activated magnesium (Rieke magnesium, Mg*)[16] or by the addition of LiCl.[17] The halogen-magnesium exchange is the method of choice for the preparation of Grignard reagents containing sensitive functionalities, since they can be performed at low temperatures assuring a higher functional group tolerance (B, Scheme 1).[18] The addition of LiCl enhances the exchange reaction and thus provides the possibility of using less reactive substrates like bromides in Br/Mg exchange.[19] A further prominent method to generate organometallic compounds is the direct metallation by deprotonation of organic molecules by organometallic bases (C, Scheme 1).[8,20] Magnesium reagents can also be prepared by transmetallation from a corresponding organoalkali metal reagent, by the addition of magnesium salts (D, Scheme 1).[21]

[15] *Organikum* (Ed.: H. G. O. Becher), VCH, Wiley, Weinheim, Germany, **2004**.
[16] (a) R. D. Rieke, *Science* **1989**, 246, 1260. (b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, 1925.
[17] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew.Chem. Int. Ed.* **2008**, *47*, 6802.
[18] For a review see: 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.
[19] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 3333.
[20] K. W. Henderson, W. J. Kerr, *Chem. Eur. J.* **2001**, *7*, 3430.
[21] Main Group Metals in Organic Synthesis (Eds.: H. Yamamoto, K. Oshima), VCH, Wiley, Weinheim Germany **2004**, p 55.

2.3 Organozinc Reagents

Organozinc compounds have been known since the pioneering work of Frankland on diethylzinc in 1849.[22] These carbon–metal bonds have a covalent character and a relatively low polarity, therefore they are unreactive towards a number of electrophiles. Historically, organozinc reagents have therefore been rarely used, in comparison to the more reactive magnesium reagents.[23] Their true potential as carbon nucleophiles in organic chemistry today lies in the combination of this functional group tolerance and the potential of transmetallation with transition metals, allowing the formation of reactive organometallic intermediates, which can perform reactions like cross-couplings efficiently.[24] The most common method to prepare organozinc reagents is the oxidative addition of zinc dust to functionalized organic halides (A, Scheme 2).[24b,25,] This allows the preparation of a broad range of organozinc reagents bearing various functionalities like esters, acetates, cyano groups, halides and ketones.[26,24c] The activation of the zinc dust is of great importance for a successful insertion, since the metallic zinc is covered by an oxide layer.[27] Treating zinc with 1,2-dibromoethane and Me_3SiCl removes this oxidation layer chemically,[28,27] and thus activates it. Furthermore, the use of Rieke-zinc (Zn*),[29] Li salts like LiCl[30] or polar co-solvents is known to accelerate the insertion reaction. Alternatively, organozinc reagents can also be prepared *via* halogen-zinc exchange using transition metal catalysed reaction with Et_2Zn (B, Scheme 2)[31] or by direct metallation (C, Scheme 2).[8] Furthermore transmetallation from more polar organometallic reagents is a method that is often performed to prepare organozinc reagents (D, Scheme 2).[32]

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[22] E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171.

[23] (a) S. Reformatsky, *Chem. Ber.* **1887**, *20*, 1210 (b) S. Reformatsky, *Chem. Ber.* **1895**, *28*, 2842 (c) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323. (d) H. E. Simmons, T. L. Cairns, A. Vladuchick, C. M. Hoiness, *Org. React.* **1972**, 20, 1. (e) J. Furukawa, N. Kawabat, J. Nishimma, *Tetrahedron Lett.* **1966**, *7*, 3353.

[24] (a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) E. Erdik, *Tetrahedron* **1992**, *48*, 9577. (c) P. Knochel, J. J. Almena-Perea, P. Jones, *Tetrahedron* **1998**, *54*, 8275. (d) *Organozinc Reagents. A Practical Approach* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**. (c) A. Sidduri, J. W. Tilley, N. Fotouhi, *Synthesis* **2014**, *46*, 430. (d) E. Erdik, *Tetrahedron* **1992**, *48*, 9577.

[25] *Chemistry of Organozinc Compounds* (Eds.: Z. Rappoport, I. Marek), John Wiley & Sons Ltd., Chichester, United Kingdome, **2006**.

[26] P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93* 2117.

[27] E. Erdik, *Tetrahedron* **1987**, 2203.

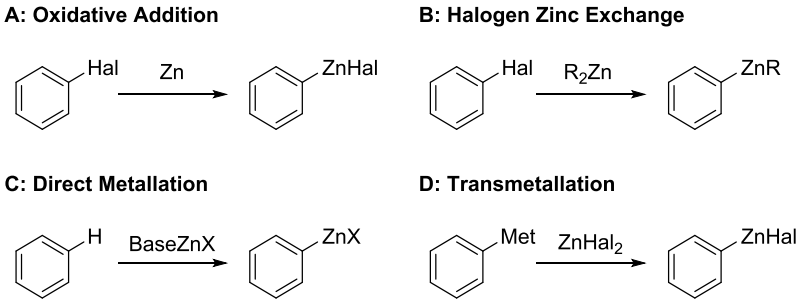
[28] (a) J. K. Gawronsky, *Tetrahedron Lett.* **1984**, 25, 2605. (b) G. Picotin, P. Miginiac, *Tetrahedron Lett.* **1987**, *28*, 4551. (c) P. Knochel, M. C. P. Yeh, S .C. Berkam, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

[29] R. D. Rieke, *Science* **1989**, *246*, 1260. (b) M. V. Hanson, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.

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

[31] (a) M. J. Rozema, A. R. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1957. (b) H. Stadtmüller, R. Lentz, W. Dörner, T. Stüdemann, C .E. Tucker, P. Knochel, *J. Am. Chem. Soc.* **1993**, *115*, 7027.

[32] *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), VCH, Wiley, Weinheim, Germany, **2005**, p. 261.



Scheme 2: Synthetic methods for the preparation of organozinc reagents.

2.4 Direct Metallation

Direct functionalization of unsaturated heterocycles can be performed by metallation, using a stoichiometric amount of a metal base followed by subsequent trapping with electrophiles. Since the pioneering work by Gilman,[33] Wittig,[34] and Snieckus,[35] directed *ortho*-metallation (DoM) has been widely used for the regioselective functionalization of aromatic and heteroaromatic systems. Substituents such as a carbamates, amides, methoxy, or cyano groups proved to ortho direct the metallation with strong lithium bases. Organolithium reagents, such as BuLi (butyl lithium), as well as lithium amides, such as LDA (lithium diisopropylamide) or LiTMP (lithium 2,2,6,6-tetramethylpiperidinyl) are among the most frequently used bases for direct lithiations.[8] The major drawback of organolithium reagents is their high reactivity towards functional groups, since aryl lithium compounds react with most functional groups at temperatures above –20 °C.[36] To overcome these limitations, the corresponding magnesium reagents which have a less polarized carbon–metal bond can be prepared. In 1947, Hauser and Walker reported magnesium amide bases of the general formula R_2NMgX and $(R_2N)_2Mg$, (Hauser bases).[37] The group of Eaton demonstrated the potential of Hauser bases for the directed ortho-magnesiation of aromatic compounds.[37c] Despite the use of several magnesium bases in organic synthesis,[38] their general use was limited due to their low solubility in common organic solvents providing a low kinetic basicity. These limitations were overcome in 2006, when Knochel and co-workers reported the first LiCl-solubilized TMP base TMPMgCl·LiCl (**1**).[39] Since then a number of these bases were prepared, the most important being lithium chloride solubilized magnesium and zinc bases [(TMPMgCl·LiCl (**1**),[39] TMP_2Mg·2LiCl (**2**),[40] TMPZnCl·LiCl (**3**),[41] and TMP_2Zn·2LiCl (**4**)[42]]. Due to an increased negative charge on nitrogen in TMP_2Mg·2LiCl (**2**) compared to TMPMgCl·LiCl (**1**),

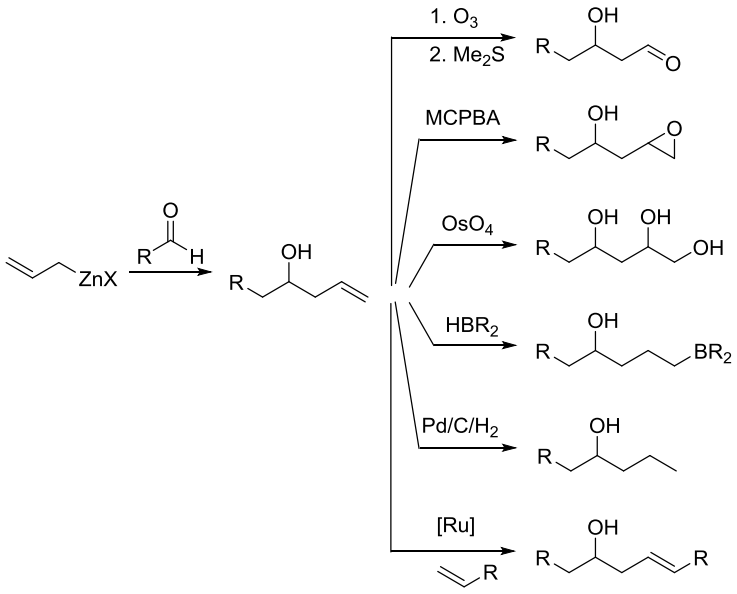
[33] H. Gilman,W. Langham, A. L. Jacoby, *J. Am. Chem. Soc*. **1939**, *61*, 106.
[34] G. Wittig, G. Fuhrmann, *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 1197.
[35](a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879, (b) T. K. Macklin, J. Panteleev, V. Snieckus, *Angew. Chem. Int. Ed.* **2008**, *47*, 2097.
[36] (a) P. Stanetty, M. D. Mihovilovic, *J. Org. Chem.* **1997**, *62*, 1514. (b) *Handbook of Functionalized Organometallics, Vol. 1* (Ed.: P. Knochel), Wiley-VCH, Weinheim, Germany **2005**, p. 7.
[37] (a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc*. **1947**, *69*, 295. (b) K. W. Henderson, W. J. Kerr, *Chem. Eur. J*. **2001**, *7*, 3430. (c) P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016. (d) P. E. Eaton, Y. Xiong, R. Gilardi, *J. Am. Chem. Soc.* **1993**, *115*, 10195. (e) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11370. (f) M. X. Zhang, P. E. Eaton, *Angew. Chem. Int. Ed.* **2002**, *41*, 2169. (g) P. E. Eaton, M. X. Zhang, N. Komiya, C. G. Yang, I. Steele, R. Gilardi, *Synlett.* **2003**, 1275.
[38] (a) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414. (b) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Liebigs Ann. Chem.* **1995**, 1441. (c) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Synthesis* **1995**, 1225.
[39] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[40] G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, 46, 7681.
[41] M. Mosrin, P. Knochel, *Org. Lett*. **2009**, *11*, 1837.
[42] S. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed*. **2007**, *46*, 7685.

$TMP_2Mg·2LiCl$ (**2**) displays a higher reactivity, allowing metallation of aromatic substrates bearing electron-donating or weakly electron-accepting substituents. Whereas the use of magnesium bases displays a high tolerance toward nitriles, esters, and aryl ketones, there are a number of important functional groups, such as nitro, aldehyde, methyl ketone, or electron-poor *N*-heterocycles, that are not compatible with their use. A higher functional group tolerance is achieved either by transmetallation of the corresponding magnesium reagent with $ZnCl_2$ or by using the milder base TMPZnCl·LiCl (**3**), since the formed carbon–zinc bonds have essentially covalent character. Zincation mediated by TMPZnCl·LiCl (**3**) is possible over a broad temperature range; even temperatures up to 100 °C are feasible. The base $TMP_2Zn·2MgCl_2·2LiCl$ (**4**) is more reactive than TMPZnCl·LiCl (**3**) due to the increased negative charge on the nitrogen, providing the possibility to zincate relatively unreactive, unsaturated substrates.

3 Allylic Organometallics

3.1 General Introduction

Allylic organometallics have been thoroughly described since the 1960s. In the beginning, scientists focused mainly on structural determinations[43] of allylmetals such as the stereochemistry of the double bond and the regioselectivity of reactions with electrophiles. Since the 1970s, the focus has shifted towards the controlling of the stereochemistry for the C-C bond formation. This was mainly triggered by the pioneering work of Gaudemar[44], Heathcock,[45] Hoffmann[46] and Yamamoto[47] who studied the stereocontrolled allylation of carbonyl derivatives. The reaction of allylic organometallic reagents with aldehydes[48] is synthetically analogous to the aldol addition of metal enolates, since the resulting homoallyl alcohol can be easily converted to the aldol product by ozonolysis (Scheme 3).[49] The double bond can participate in other synthetically useful transformations, like cycloadditions, dihydroxylation, hydro- or carbometallations, hydrogenation and olefin methathesis, making it a versatile tool in organic synthesis (Scheme 3).



Scheme 3: Synthetically useful transformations of homoallyl alcohols.

[43] (a) R. A. Benkeser, *Synthesis* **1971**, 347. (b) G. Courtois, L. Miginiac, *J. Organomet. Chem.* **1974**, 69, 1. (c) E. A. Hill, *J. Organomet. Chem.* **1975**, *91*, 123.
[44] (a) E. Favre, M. Gaudemar, *J. Organomet. Chem.* **1974**, 76, 297. (b) E. Favre, M. Gaudemar, *J. Organomet. Chem.* **1974**, *76*, 305. (c) E. Favre, M. Gaudemar, *J. Organomet. Chem.* **1975**, 92, 17.
[45] C. T. Buse, C. H. Heathcock, *Tetrahedron Lett.* **1978**, 1685.
[46] R. W. Hoffmann, H. J. Zeiss, *Angew. Chem. Int. Ed.* **1979**, *18*, 306.
[47] Y. Yamamoto, H. Yatagai, Y. Naruta, K. Maruyama, *J. Am. Chem. Soc.* **1980**, *102*, 7107.
[48] *Modern Carbonyl Chemistry* (Ed.: J. Otera), VCH, Wiley, Weinheim, Germany, **2000**.
[49] Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207.

3.2 Regioselectivity in Allylic Reactions

The regioselectivity of allylic organometallics depends on the organometallic compound, the nature of the electrophile, the steric hindrance in the vicinity of the site of the reaction, and the reaction conditions, like solvent and temperature.[50,51]

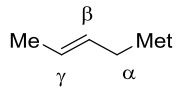


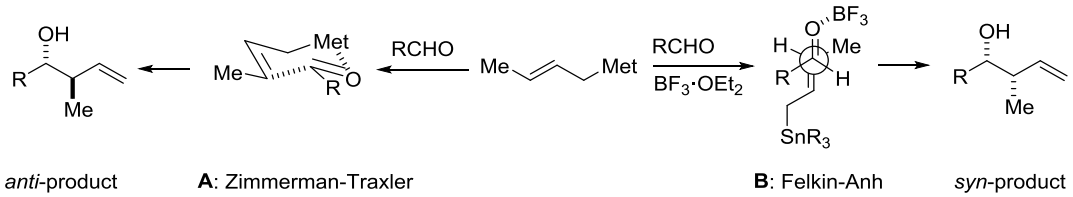
Figure 2: Allylic organometallic reagent.

While unsymmetrical allyl lithium reagents react with aldehydes nonselectively, with a slight preference for attack at the most substituted allyl terminus,[52] Grignard and zinc reagents generally react with aromatic and aliphatic aldehydes *via* an allylic rearrangement in the γ-position (Figure 2). However, despite the difficulty in obtaining an α-adduct from organozinc reagents, some examples of α-regioselective allylation of aldehydes and ketones have been reported.[53]

3.3 Diastereoselectivity in Allylic Rearrangements

Substituted allylic organometallics display a high level of diastereoselectivity, since they usually react at the γ-position through an ordered cyclic or acyclic transition state (Scheme 4).[54] The diastereoselectivity of the reaction of aldehydes with allylic organometallics can be rationalized by a six-membered Zimmerman-Traxler[55] like transition state of type A in which the metal center is coordinated by the oxygen (Scheme 4). The most favored transition state structure, with R in the pseudo-equatorial position, provides the relative stereochemistry in the product. Therefore, *E*-allylic organometallics provide selectively the *anti*-alcohol, while *Z*-allylic organometallics provide the *syn*-products.

[50] A. Yanagisawa, S. Habaue, H. Yamamoto, *J. Org. Chem.* **1989**, *54*, 5199.
[51] F. Barbot, P. Miginiac, *Tetrahedron Lett.* **1975**, 3829.
[52] T. Cohen, B. S. Guo, *Tetrahedron* **1986**, *42*, 2803.
[53] (a) B. S. Guo, W. Doubleday, T. Cohen, *J. Am. Chem. Soc.* **1987**, *109*, 4710. (b) A. Yanagisawa, S. Habaue, H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 8955. (c) A. Yanagisawa, S. Habaue, K. Yasue, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 6130. (d) R. E. Estevez, R. E., J. Justicia, B. Bazdi, N. Fuentes, M. Paradas, D. Choquesillo-Lazarte, J. M. Garcia-Ruiz, R. Robles, A, Gansauer, J. M. Cuerva, J. Oltra, *Chem. Eur. J.* **2009**, *15*, 2774. (e) L. M. Zhao, H. S. Jin, L. J. Wan, L. M. Zhang, *J. Org. Chem.* **2011**, *76*, 1831.
[54] M. Yus, J. C. González-Gómez F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774.
[55] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.***1957**, *79*, 1920.



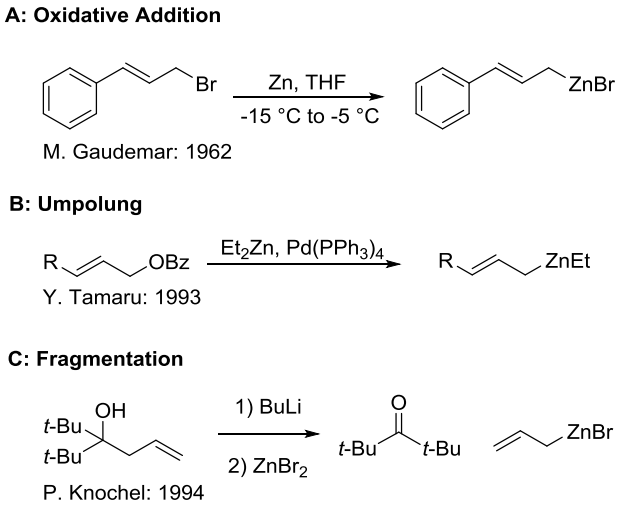
Scheme 4: Diastereoselectivity obtained for the cyclic or acyclic transition state.

However, the BF_3 mediated reaction of 2-butenylstannane with benzaldehyde exhibits an entirely different stereochemistry, where the *syn*-homoallyl alcohol is obtained from both *E*- and *Z*-allylic organometallic reagents.[49,56] Y. Yamamoto proposed that the coordination of the Lewis acid BF_3 to the oxygen prevents the coordination of the carbonyl to the metal atom.[56b] The reaction was proposed to proceed over an acyclic transition state B, providing the *syn*-homoallyl alcohol from both *E*- and *Z*-allylic organometallic reagents. Therefore, the Lewis acid serves both as a stereoshielding group, as well as an activator for the carbonyl group.

3.4 Preparation of Allylic Zinc Reagents

Allylic zinc reagents are especially versatile organometallic species since their behavior is more predictable than the behavior of the corresponding allylic magnesium or lithium reagents.[57] Several methods have been described for their preparation.[58,7c] In 1962, Gaudemar reported the preparation of allylic zinc reagents from allylhalides *via* zinc insertion reactions (A, Scheme 5).[59] Allylic zinc reagents can also be prepared from the corresponding allylic benzoates by an umpolung reaction (B, Scheme 5)[60] or by fragmentation of sterically hindered homoallylic alcohols (C, Scheme 5).[61]

[56] (a) Y. Yamamoto, Y. Yatagai, Naruta, K. Maruyama, *J. Am. Chem. Soc.* **1980**, *102*, 7107. (b) Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, K. Maruyama, *Tetrahedron* **1984**, 2239. (c) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763.
[57] (a) G. Courtois, L. Miginiac, *J. Organomet. Chem.* **1974**, *69*, 1. (b) Y. Yamamoto, *Acc. Chem. Rev.* **1987**, *20*, 243. (c) M. Schlosser, O. Despond, R. Lehmann, E. Moret, G. Rauchschwalbe, *Tetrahedron* **1993**, *49*, 10175.
[58] (a) *Organozinc Reagents, A Practical Application* (Ed.: Paul Knochel), Oxford University Press, Oxford United Kingdom, **1999**.
[59] M. Gaudemar, *Bull. Soc. Chim. Fr.* **1962**, 974.
[60] (a) Y. Masuyama, N. Kinugawa, N. Kurusu, *J. Org. Chem.* **1987**, *52*, 3702. (b) W. Qui, Z. J. Wang, *J. Chem. Soc. Chem. Commun.* **1989**, 356. (c) K. Yasui, Y. Goto, T. Yajima, Y. Taniseki, K. Fugami, A. Tanaka, Y. Tamaru, *Tetrahedron Lett.* **1993**, *34*, 7619. (d) Y. Tamaru, A. Tanaka, K. Yasui, S. Goto, S. Tanaka, *Angew. Chem. Int. Ed.* **1995**, *34*, 787. (e) J. A. Marshall, *Chem. Rev.* **2000**, *100*, 3163.
[61] (a) P. Jones, N. Millot, P. Knochel, *Chem. Commun.* **1994**, 2405. (b) P. Jones, P. Knochel, *Chem. Commun.* **1994**, 2407. (c) P. Jones, P. Knochel, *J. Org. Chem.* **1994**, *64*, 186.



Scheme 5: Synthetic methods for the preparation allylic zinc reagents.

4 Metallation of Chromone, 4-Pyrone, Uracil and Uridine

4.1 General Concept

Numerous important heterocycles contain a pyrone-like core structure having a carbonyl group in conjugation with a heteroatom X *via* a double bond (Figure 3).

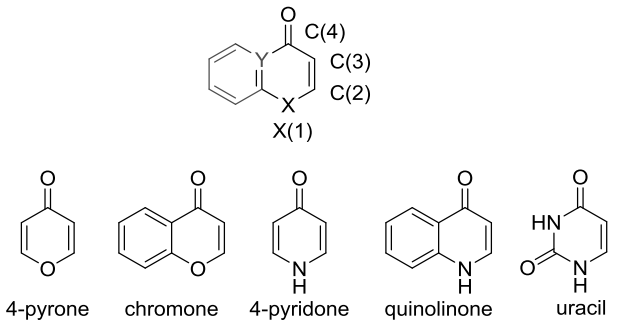
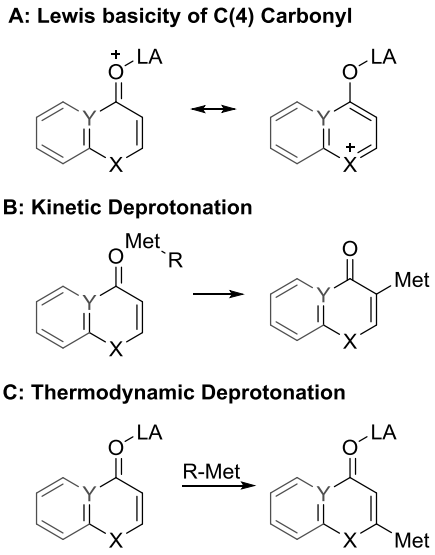


Figure 3: Naturally occurring heterocyclic scaffolds possessing this structural motive.

If the heteroatom X is more electronegative than the carbon (X = O, N), an electron withdrawal reduces the electronic density in C(2), resulting in an increased acidity of the proton in C(2) compared to C(3) (Figure 3). As a result of the conjugation of the heteroatom X to the carbonyl group, the carbonyl oxygen becomes more basic.[62] If more than one Lewis acid is present in a reaction, the strongest Lewis acid (LA) will coordinate to the carbonyl oxygen (A, Scheme 6). Since the metal center of an organometallic base (R-Met) can be considered as Lewis acidic, it was envisioned, that depending on the reaction conditions, the regioselectivity of the metallation could be directed. Coordination of the carbonyl group to the organometallic reagent will direct the metallation at C(3) *via* the DMG (directing metallation group) effect, providing the kinetic product (B, Scheme 6). However, if a stronger Lewis acid than the cation of the organometallic base is present, this Lewis acid will coordinate to the C(4) carbonyl, and the metallation will occur at C(2), providing the thermodynamic product (C, Scheme 6).

[62] "Chromone is a weak base (pK_a –2.00) which is protonated on the carbonyl oxygen to afford hydroxyl benzopyrylium salts." From: *Chromenes, Chromanones and Chromones* (Ed. G. P. Ellis), John Wiley & Sons, United Kingdom, **1977**, p. 561.
"4-Pyrone is a weak base, pKa –0.03 which is protonated on the carbonyl oxygen to afford often crystalline 4-hydroxypyrylium salts." From: *Heterocyclic Chemistry*, 4. Edition, (Eds.: J. A. Joule, K. Mills), Blackwell Publishing, Oxford, United Kingdome, **2000**, p.165.



Scheme 6: Concept for the metallation of chromone by kinetic or thermodynamic deprotonation.

4.2 Metallation of Chromone

4.2.1 General Introduction

The chromone scaffold (**5**, Figure 4) is the core structure of a major class of oxygen containing heterocycles that are abundant in nature.[63]

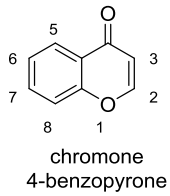


Figure 4: IUPAC numbering of Chromone (**5**).[64]

They are common secondary metabolites and accumulate in almost every part of the plant, from the roots to the flower petals. They make up flower pigments,[65] and flavones like quercetrin obtained from the inner bark of *Quercus velutina*, have been used as dyes, as they impart various shades of yellow to wool (Figure 5).[65] Considerable amounts of chromones are consumed daily since they are present in regularly consumed food, like vegetables, fruits,

[63] *Flavonoids: Chemistry, Biochemistry and Applications* (Eds.: O. M. Andersen, K. R. Markham), CRC Press, Boca Raton, United States, **2006**.
[64] *The Alkaloids*, Vol. 31 (Eds.: P. J. Houghton, A. Brossi), Academic Press, San Diego, USA, **1987**, p. 67.
[65] *Heterocyclic Chemistry*, 4. Edition, (Eds.: J. A. Joule, K. Mills), Blackwell Publishing, Oxford, United Kingdome, **2000**, p. 170.

olive oil, and in beverages like tea and wine.[66] Apart from their physiological role in plants, some derivatives have been reported to possess various biological properties such as anti-inflammatory, antiplatelet, anticancer, and antimicrobial activity.[67] For example, the isoflavone daidzein from *Trifolium*, has oestrogenic activity and affects the reproduction of grazing animals (Figure 5).[68]

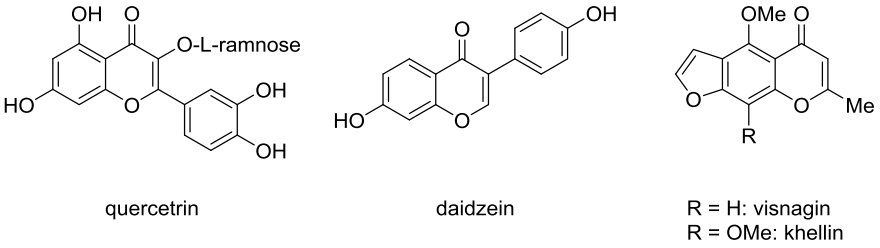


Figure 5: Examples of the naturally occurring chromones.

The role of plants and their extracts in various traditional medicines has spurred scientific interest in the isolation of the pharmaceutically active compounds.[69] Khellin and visnagin are found in the fruits of *Ammi visnaga*, and are the active principle of a plant drug that has been used in folk medicine in Egypt (Figure 5).[70] The chromone core structure is found in marketed drugs[71] like cromoglycate (Lomudal®),[70] diosmin (Daflon®), and Flavoxate® (Figure 6).[72] Owing to the interesting bioactivity, the chromone system has been thoroughly described in the literature.[73,67a]

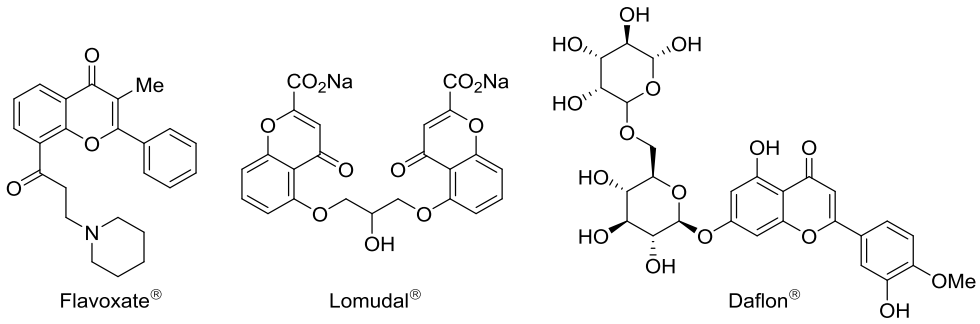
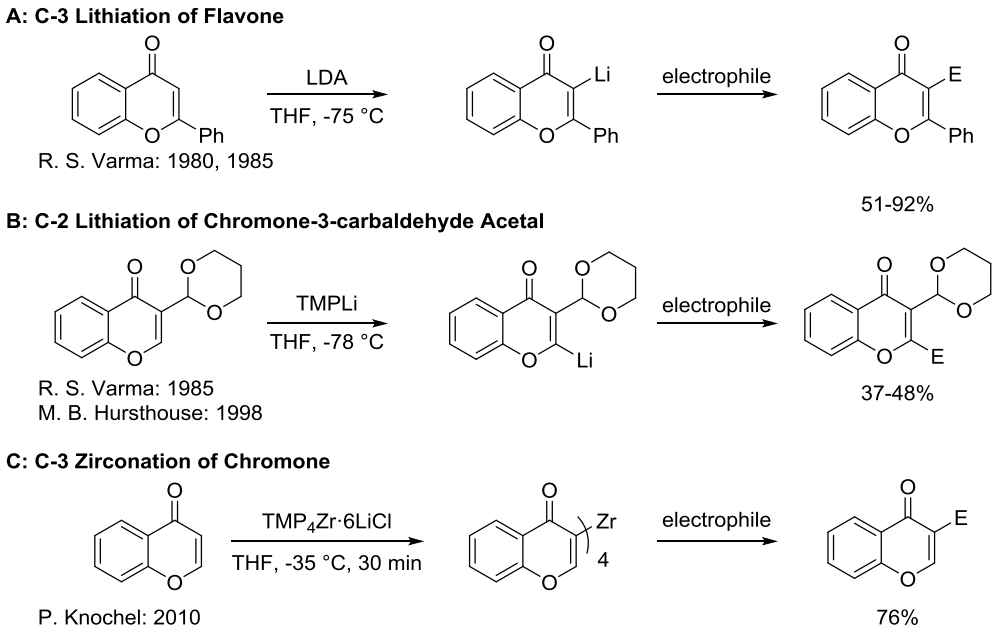


Figure 6: Examples of commercially available drugs containing a chromone scaffold.

[66] F. Chimenti, R. Fioravanti, A. Bolasco, P. Chimenti, D. Secci, F. Rossi, M. Yáñez, F. Orallo, F. Ortuso, S. Alcaro, R. Cirilli, R. Ferretti, M. L. Sanna, *Bioorg. Med. Chem.* **2010**, *18*, 1273.
[67] (a) A. Gaspar, M. J. Matos, J. Garrido, E. Uriarte, F. Borges, *Chem. Rev.* **2014**, *114*, 4960. (b) S. Khadem, R. J. Marles, *Molecules* **2012**, *17*, 191.
[68] (a) *Medicinal Natural Products*, 3. Edition, (Ed.: P. M. Dewick), John Wiley & Sons, United Kingdom, **2009**, p. 175. (b) K. R. Price, G. R. Fenwick, *Food Addit. Contam.* **1985**, *73*, 106. (c) D. A. Shutt, R. H. Weston, J. P. Hogan, *Aust. J. Agric. Res.* **1970**, *21*, 713.
[69] S. T. Saengchantara, T. W. Wallace, *Nat. Prod. Rep.* **1986**, 465.
[70] *Medicinal Natural Products* (Ed. P. M. Dewick), John Wiley & Sons, United Kingdom, **2009**, p. 112.
[71] R. S. Keri, S. Budagumpi, R. K. Pai, R. G. Balakrishna, *Eur. J. Med. Chem.* **2014**, *78*, 340.
[72] M. S. Butler, A. A. Robertson, M. A. Copper, *Nat. Prod. Rep.* **2014**, DOI: 10.1039/c4np00064.
[73] *Comprehensive Heterocyclic Chemistry III*, Vol. 7 (Eds: D. S. C Black, A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K.Taylor), Elsevier, Oxford, United Kingdom, **2008**, p. 337-418.

4.2.2 State of Research for the Metallation of Chromone

Generally, the total synthesis of simple chromones can be attained using starting materials that do not have a γ-pyran ring in their structure.[67a] Many of these synthetic approaches have been known for a considerable time and are still in use because of their efficiency and simplicity.[67a] However, there is a need to speed up the drug discovery process, for establishing structure-activity relationship studies in medicinal chemistry programs, and consequently a number of methods have been developed to functionalize the molecule after the chromone scaffold has been installed.[73]



Scheme 7: Literature reported metallation of chromone.

Relatively few examples are reported for the direct metallation of chromone (**5**). It has been determined that chromones in which the C(2) position is blocked provide the C(3) lithiated chromone when treated with LDA (A, Scheme 7).[74] Chromones that are unsubstituted at the C(2) are prone to Michael addition and concomitant ring opening. Consequently, lithiation of C(2) is difficult to achieve and requires assistance of a DMG in position C(3) to proceed adequately.[75,74a] The lithiation of chromone-3-carbaldehyde acetal at C-2 is reported in the literature (B, Scheme 7). However, for unsubstituted chromones, a selective metallation in

[74] (a) A. M. S. B. R. C. S. Costa, F. M. Dean, M. A. Jones, R. S. Varma, *J. Chem. Soc. Perkin Trans. I* **1985**, 799. (b) A. M. S. B. R. C. S. Costa, F. M. Dean, M. A. Jones, D. A. Smith, R. S. Varma, *J. Chem. Soc. Chem. Commun*. **1980**, 1224.
[75] G. E. Daia, C. D. Gabbutt, J. D. Hepworth, B. M. Heron, D. E. Hibbs, M. B. Hursthouse, *Tetrahedron Lett.* **1998**, *39*, 1215.

position C(2) or C(3) has not yet been achieved. The lithiation of unsubstituted chromone with TMP-Li or LDA produces a complex mixture of products.[74,75] Selective C(3) zirconation of chromone with $TMP_4Zr \cdot 6LiCl$ was recently achieved (C, Scheme 7).[76]

4.2.3 Metallation of Chromone: General Concept

The chromone system contains two directing groups,[35] the vinyl-etheral oxygen and the carbonyl oxygen, which are next to the protons in C(2) or C(3), respectively. Theoretical calculations[77,78] showed that the thermodynamically most acidic hydrogen of chromone (**5**) is attached to C(2) (Figure 7).

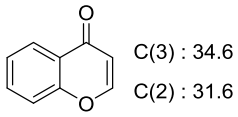
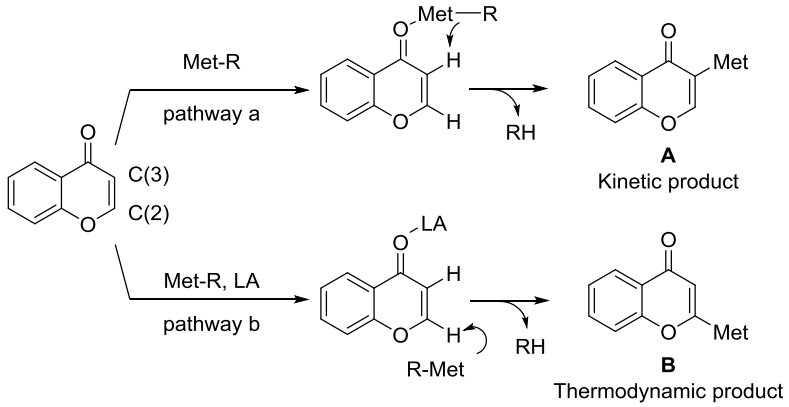


Figure 7: Calculated pK_a-values of chromone in DMSO.

The metallation of vinyl ethers usually occurs predominantly at the 2-position, as coordination with the oxygen atom increases the inductive effect and brings the base closer to the α-position.[79,74a] However, the carbonyl oxygen in chromone is highly negatively charged due to the pyrone system. [62] Therefore, the Lewis acid coordinates more effectively at the carbonyl oxygen than at the etheral oxygen. Coordination of the C(4) carbonyl to the metal base (R-Met) would lead to ortho metallation and the formation of the kinetic product A (pathway a, Scheme 8). In the presence of a stronger Lewis acid than the metallating base, complexation of the Lewis acid occurs at the carbonyl group and the thermodynamic C(2)-metallated heterocycle is obtained (pathway b, Scheme 8).

[76] M. Jeganmohan, P. Knochel, *Angew. Chem. Int. Ed*. **2010**, *49*, 8520.
[77] L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584.
[78] The theoretical calculations were performed by Dr. Tobias A. Nigst (Ludwig-Maximilians-Universtät München).
[79] (a) R. K. Boeckman, K. J. Bruza, *Tetrahedron Lett.* **1977**, 4187. (b) F. T. Oakes, J. F. Sebastian, *J. Org. Chem.* **1980**, *45*, 4959.

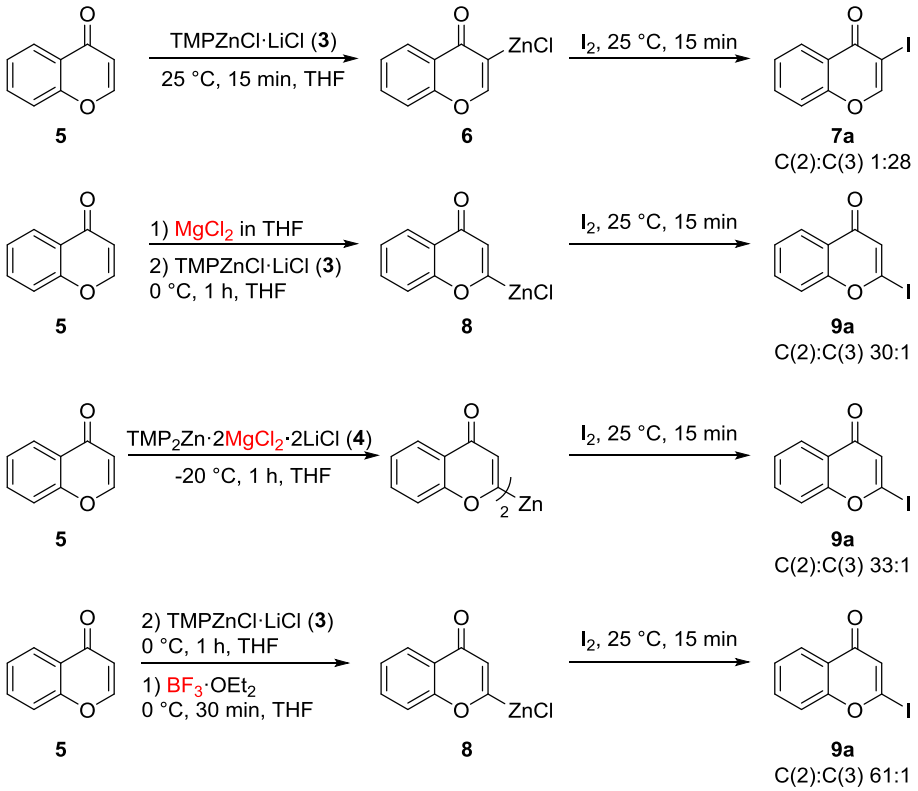


Scheme 8: Regioselective metallation of chromone in the kinetic and thermodynamic position.

4.2.3.1 Metallation Conditions and Optimisation of the Reaction[80]

In accordance with the proposed concept, treatment of chromone (**5**) with 1.2 equiv. of the amide base TMPZnCl·LiCl (**3**) at 25 °C in THF, provided the zincated chromone (**6**) in a regioselectivity of 1:28 C(2):C(3) as confirmed by GC analysis of reaction aliquots quenched with iodine (Scheme 9).[81] Full conversion was observed after 15 min. The regioselectivity of the metallation was determined by 2D-NMR analysis of both the zincated species (**6**) and isolated iodolysis product (**7a**). Furthermore, the influence of the presence of additional Lewis acids on the zincation was investigated (Scheme 9). Metallation of chromone with 1.2 equiv. TMPZnCl·LiCl (**3**) in the presence of 2 equiv. $MgCl_2$ proceeded best at 0 °C, providing full conversion to the zincated species **8** after 1 h in a regioselectivity of C(2):C(3) 30:1 (Scheme 9).[81] The reaction of chromone (**5**) with $TMP_2Zn·2MgCl_2·2LiCl$ (**4**) at –20 °C led to a regioselectivity of C(2):C(3) 33:1 (Scheme 9). The regioselectivity was assigned by 2D-NMR analysis of both, the zincated species (**8**) and isolated iodolysis product (**9a**). A similar regioselectivity reversal was achieved by addition of $BF_3·OEt_2$ as Lewis acid, at a reaction temperature of –20 °C which was required to avoid decomposition. An excess of TMPZnCl·LiCl (1.6 equiv.) was neccesery to achieve full conversion. Using these conditions, a selectivity of 61:1 C(2):C(3) was observed (Scheme 9).

[80] Lydia Klier, *Selective Functionalization of Chromone and Related Systems*, M. Sc. Thesis, Ludwig-Maximilians-Universität München, Germany, **2011**.
[81] The reaction was optimized on a 2 mmol scale.



Scheme 9: Regioselectivities obtained for the zincation of chromone (**5**) with TMPZnCl·LiCl (**3**) or $TMP_2Zn·2LiCl·2MgCl_2$ (**4**) at different reaction conditions, and subsequent reaction with iodine.

4.2.3.2 NMR Experiments to Determine the Metallated Species and Coordination Site of BF_3

To prove the regioselectivity of the reaction of chromone (**5**) with TMPZnCl·LiCl (**3**) in THF, the obtained zinc reagent was characterized by NMR-spectroscopy. The ^{1}H- and ^{13}C-NMR spectra indicate the presence of a temperature dependent *Schlenk*-equilibrium.[82] To obtain mainly one species, this equilibrium was shifted either by the addition of $ZnCl_2$ or by changing the solvent to dioxane. The obtained ^{1}H, ^{13}C, COSY, HSQC, and HSBC spectra confirmed the identity of C(3)-zincated chromone (**6**).[83] The C(2)-zincation for the reaction of chromone (**5**) with $TMP_2Zn·2MgCl_2·2LiCl$ (**4**) was confirmed by ^{1}H, ^{13}C, COSY, HSQC, and HSBC spectra.[83] In accordance with our concept, the coordination of the carbonyl group to

[82] (a) R. Abegg. *Ber*. **1905**, *26*, 4112. (b) W. Schlenk, W. Schlenk, *J. Chem. Ber.* **1929**, *62*, 920. (c) Organomagnesium Compounds, (Eds.: Z. Rappoport, I. Marek), John Wiley & Sons, Chichester, United Kingdom, **2006**, p. 107-109.
[83] For further details see experimental part 7.7.1.

the Lewis acid BF_3 could be confirmed by ^{13}C-NMR experiments, while a coordination of the etheral oxygen to BF_3 could not be measured.[83]

4.2.3.3 Scalable Preparation of Chromone Derivatives *via* Direct Metallation Using TMPZnCl·LiCl

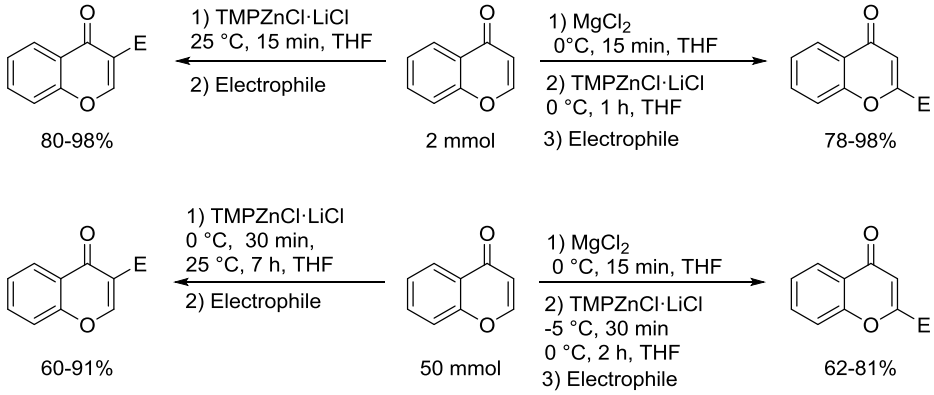
The metallation methodology described in 4.2.3.1. was further extended from a 2 mmol scale to a 50 mmol scale and the scope of the reaction was tested with various electrophiles. The regioselectivity and progress of the reactions were monitored by GC analysis of reaction aliquots quenched with iodine. Treatment of 2 mmol chromone (**5**) with TMPZnCl·LiCl (**3**, 1.2 equiv.) in THF at 25 °C for 15 minutes, resulted in a full conversion to produce the C(3)-zincated reagent (**6**). After iodolysis, 3-iodo-chromone (**7a**) was isolated in 80% yield (entry 1, Table 1). When the reaction was scaled up to 50 mmol, TMPZnCl·LiCl was added over 30 minutes at 0 °C. The lower reaction temperature and the slow addition rate were necessary to avoid a decrease in regioselectivity presumably caused by an increase of the reaction temperature. After the addition was completed, the reaction mixture was stirred at 25 °C for additional 7 h. Transmetallation of zincated chromone **6** with CuCN·2LiCl (1.2 equiv.)[84] and subsequent reaction with allyl bromide provided the chromone **7b** in 98% yield after 2 h (entry 2a, 2 mmol) or 91% after 12 h (entry 2b, 50 mmol), respectively. The reaction with 3,4-difluorobenzoyl chloride afforded the expected ketone **7c** in 82% (entry 3a, 2 mmol) or 60% yield (entry 3b, 50 mmol). Pd-catalyzed *Negishi* cross-coupling[24a,85] using 2% $Pd(PPh_3)_4$ with 4-bromobenzaldehyde led to the cross-coupling product **7d** 96% (entry 5a, 2 mmol) and 84% yield (entry 5b, 50 mmol), respectively.

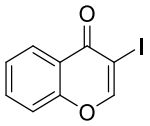
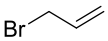
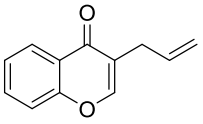
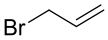
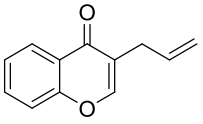
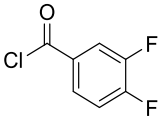
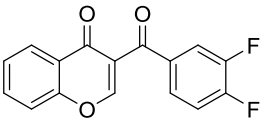
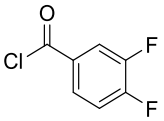
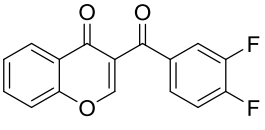
As described in 4.2.3.1, complexation of chromone **5** with 2 equiv. $MgCl_2$ at 0 °C for 15 minutes and subsequent addition of TMPZnCl·LiCl (**3**) provided the C(2) zincated chromone **8** after 1 h as shown by iodolysis product **9a** (entry 5a, Table 1). When the reaction was scaled up to 50 mmol, $MgCl_2$ was added to a solution of chromone in THF at 0 °C and stirred for further 30 minutes. It was observed, that the selectivity for C(2) metallation depends on both the reaction temperature and the amount of $MgCl_2$ in solution. A reaction temperature of –5 °C during the addition of TMPZnCl·LiCl (over 30 minutes) was necessary to avoid a reduced selectivity caused by higher reaction temperatures. Lower reaction temperatures than –5 °C caused the precipitation of $MgCl_2$, and therefore provided lower selectivities. After addition of TMPZnCl·LiCl, the reaction had to be stirred for further 2 h at

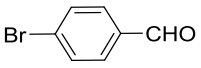
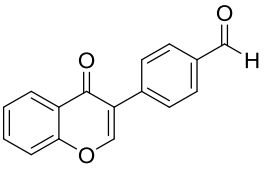
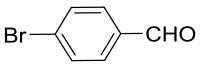
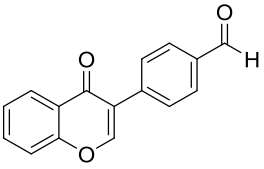
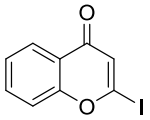
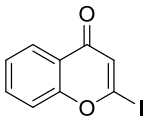
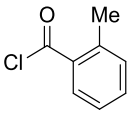
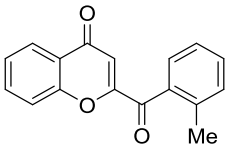
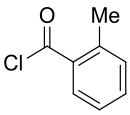
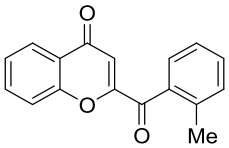
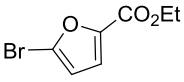
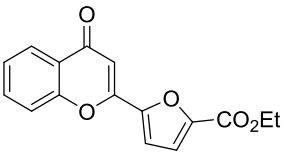
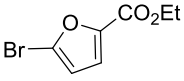
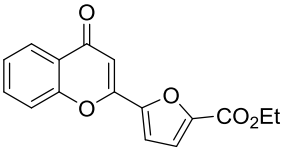
[84] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[85] (a) M. Kobayashi, E. Negishi, *J. Org. Chem.* **1980**, *45*, 5223. (b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.

0 °C to obtain full conversion. Iodolysis, copper-mediated acylation or Pd-catalyzed *Negishi* cross-coupling of the C(2) zincated chromone (**8**) furnished the expected C(2)-substituted chromones **9a-9c** in 62-81% yield (entries 5b, 6b, 7b, Table 1, 50 mmol). Generally, the reaction time increased when the reaction was scaled up from 2 mmol to 50 mmol. Even though full conversion was observed for both small and large scale reactions, a decrease in yields was observed when the reaction was scaled up.

Table1: Direct Metallation of Chromone at C(2) and C(3)



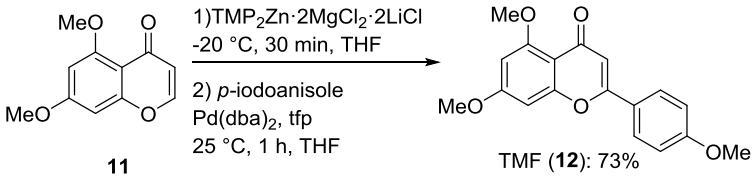
Entry	Scale (mmol)	Metallation Conditions	Electrophile (E)	Reaction conditions	Product	Yield (%)[a]
1	2	TMPZnCl·LiCl 25 °C, 30 min, THF	I_2	25 °C, 15 min	 **7a**	80
2a	2	TMPZnCl·LiCl 25 °C, 30 min, THF		25 °C, 2 h	 **7b**	98[b]
2b	50	TMPZnCl·LiCl 0 °C, 7 h, THF		25 °C, 12 h	 **7b**	91[b]
3a	2	TMPZnCl·LiCl 25 °C, 30 min, THF		–40 °C to 25 °C 12 h	 **7c**	82[b]
3b	50	TMPZnCl·LiCl 0 °C, 7 h, THF		–50 °C to 25 °C 12 h then 25 °C 36 h	 **7c**	60[b]

Entry	Scale (mmol)	Metallation Conditions	Electrophile (E)	Reaction conditions	Product	Yield (%)[a]
4a	2	TMPZnCl·LiCl 25 °C, 30 min, THF		25 °C, 12 h	 **7d**	96[c]
4b	50	TMPZnCl·LiCl 0 °C, 7 h, THF		25 °C, 18 h	 **7d**	84[c]
5a	2	$MgCl_2$, TMPZnCl·LiCl 0 °C, 1 h, THF	I_2	25 °C, 15 min	 **9a**	84
5b	50	$MgCl_2$, TMPZnCl·LiCl 0 °C, 2 h, THF	I_2	25 °C, 2 h	 **9a**	80
6a	2	$MgCl_2$, TMPZnCl·LiCl 0 °C, 1 h, THF		–40 °C to 0 °C 6 h	 **9b**	98[b]
6b	50	$MgCl_2$, TMPZnCl·LiCl 0 °C, 2 h, THF		–40 °C to –10 °C, 12 h	 **9b**	81[b]
7a	2	$MgCl_2$, TMPZnCl·LiCl 0 °C, 1 h, THF		25 °C, 2 h	 **9c**	78[c]
7b	50	$MgCl_2$, TMPZnCl·LiCl 0 °C, 2h, THF		25 °C, 24 h	 **9c**	62[c]

[a] Yield of isolated, analytically pure product. [b] Obtained after transmetallation with CuCN·2LiCl (1.2 equiv., –40 °C, 30 min). [c] Obtained by *Negishi* cross-coupling using 2% $Pd(PPh_3)_4$.

4.2.3.4 Application to the Total Synthesis of Naturally Occurring Chromones

As an application of this metallation methodology, some naturally occurring flavones and isoflavones were prepared, starting from the common precursor 5,7-dihydroxy chromone (**10**).[86] First, the methodology was applied on methyl protected chromone **11** in order to prepare 5,7,4'-trimethoxyflavone (**12**, TMF), a secondary metabolite isolated from the Thai medicinal plant *Kaempferia parviflora*.[87]

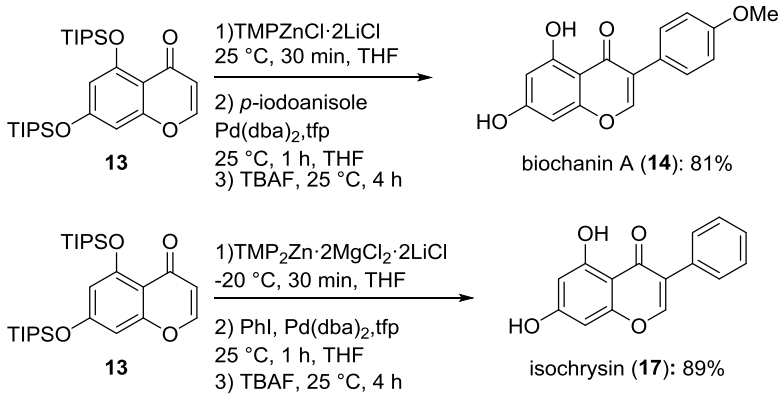


Scheme 10: Preparation of 5,7,4'-trimethoxyflavone (**12**).

Reaction of 5,7-dimethoxy chromone **11** with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**) in THF, and subsequent palladium catalyzed cross-coupling using 2% $Pd(dba)_2$ and 4% tfp[88] with *p*-iodoanisole provided the natural product TMF (**12**) in 73% yield (Scheme 10). Since methyl protecting groups generally require harsh conditions for deprotection,[89] TIPS-protected chromone **13** was used for the preparation of the isoflavone biochanin A (**14**), which is commonly found in soy beans or in red clover.[90] Metallation of **13** with TMPZnCl·LiCl (**3**) and subsequent reaction of the obtained C(3) zincated species **15** in a *Negishi* cross-coupling with *p*-iodoanisole, followed by deprotection, provided isoflavone **14** in a one-pot procedure in excellent yield (81%, Scheme 11). Further attempts were made to prepare the flavone chrysin (**16**) which is present in honey and propolis and in low concentrations in fruit and vegetables.[91] Unexpectedly, the metallation concept was not applicable for the C(2) metallation of TIPS protected chromone **13** using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**). When TIPS protected chromone **13** was treated with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**), and reacted with

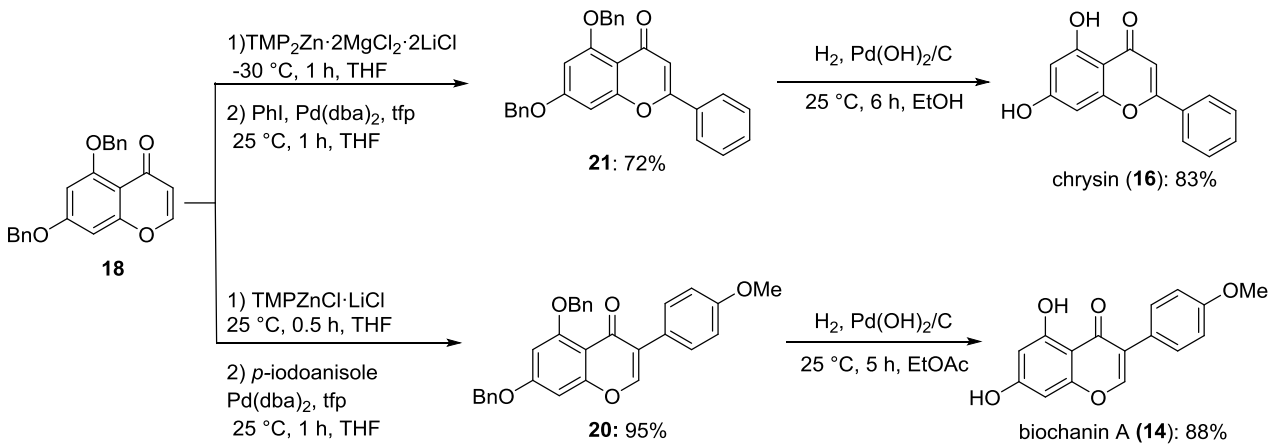
[86] T. Korenaga, K. Hayashi, Y. Akaki, R. Maenishi, T. Sakai, *Org. Lett.* **2011**, *13*, 2022.
[87] P. Sawasdee, C. Sabphon, D. Sitthiwongwanit, U. Kokpol, *Phytother. Res.* **2009**, *23*, 1792.
[88] dba = trans, trans-dibenzylideneacetone; tfp = tris-(2-furyl)phosphine; (a) V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585. (b) V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5905. (c) I. Klement, M. Rottländer, C. E. Tucker, T. N. Majid, P. Knochel, P. Venegas. G. Cahiez, *Tetrahedron* **1996**, *52*, 7201.
[89] *Greene's Protective Groups in Organic synthesis*, 4. Edition, (Eds.: P. G. M. Wuts, T. W. Greene), VCH, Wiley, New Jersey, United States, **2007**, p. 27.
[90] E. Walz, *Justus Liebig Ann.* **1931**, *489*, 118.
[91] I. C. Villar, M. Galisteo, R. Vera, F. O'Valleb, M. F. García-Saura, A. Zarzuelo, J. Duarte, *J. Vasc. Res.* **2004**, *41*, 509.

iodobenzene in a cross-coupling reaction, the C(3) functionalized isochrysin **17** was obtained instead of the C(2) functionalized chrysin **16** (Scheme 11).



Scheme 11: Preparation of the natural products biochanin A (**14**) and isochrysin (**16**).

Therefore, benzyl protected chromone **18** was employed. The protected flavone **21** was easily prepared, when **18** was treated with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**) and the obtained zinc species **22** reacted in a *Negishi* cross-coupling (2% $Pd(dba)_2$, 4% tfp) with PhI (Scheme 12). Deprotection of the flavone **21** with $H_2/Pd(OH)_2$ in EtOH proceeded smoothly within 6 h to provide full conversion and 83% yield of isolated product **16**. Metallation of **18** with TMPZnCl·LiCl (**3**) leads to the C(3)-zincated intermediate **19**, subsequent Pd-catalyzed cross-coupling (2% $Pd(dba)_2$, 4% tfp) with *p*-iodoanisole provided protected isoflavone **20** in 95% yield (Scheme 12). However, deprotection of **20** required milder reaction conditions since the reaction in EtOH was accompanied by ring opening. When the less polar solvent EtOAc was used, 90% conversion to the natural product **14** was monitored after 5 h by ^{1}H-NMR of crude product. After purification biochanin A (**14**) was obtained in 88% yield (Scheme 12).



Scheme 12: Preparation of biochanin A (**14**) and chrysin (**16**).

4.3 Metallation of 4-Pyrone

4*H*-Pyran-4-one (**23**), commonly known as 4-pyrone or γ-pyrone, is found as a core structure in many natural products[92] like maltol, a flavor enhancer, or allixin, a known antitumor promotor (Figure 8). Furthermore, γ-pyrone based heterocycles are known to possess a wide range of biological activity.[92b]

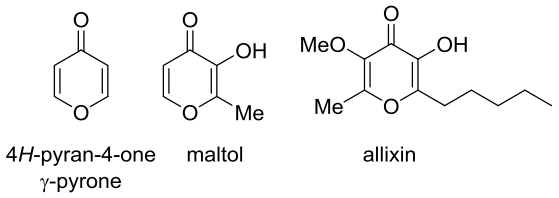
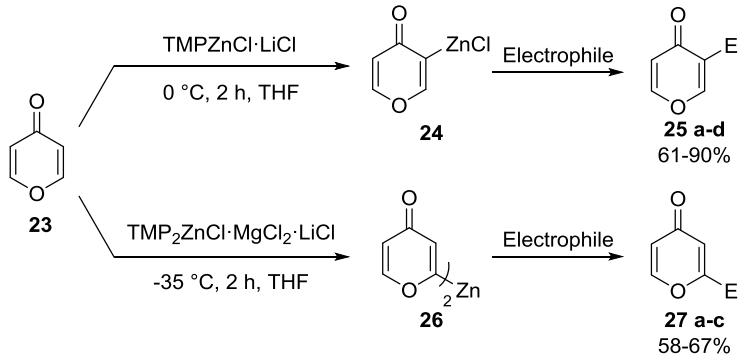


Figure 8: Pyrone core structure and selected natural products.

Due to its similar structure to chromone, the metallation approach is extended to γ-pyrone. The progress and the regioselectivity of the reaction was monitored by ^{1}H-NMR of the crude mixture of iodolysis product **25a** or **27a**.

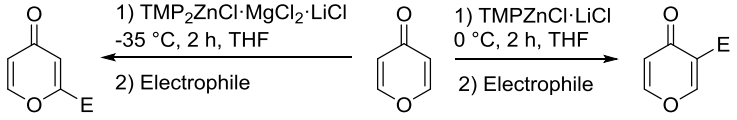


Scheme 13. Reactions and conditions for the preparation of C(5) and C(6) substituted pyrones **25** and **27**.

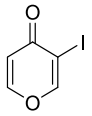
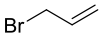
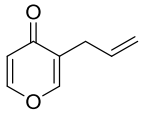
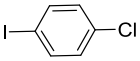
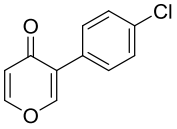
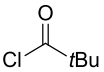
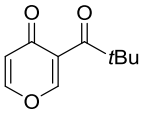
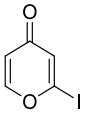
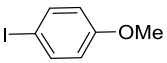
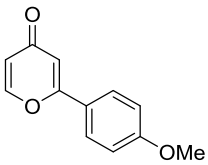
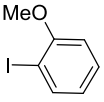
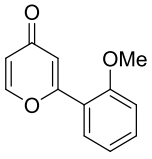
A selective zincation at C(3) was achieved, when pyrone (**23**) was treated with TMPZnCl·LiCl (**3**) at 0 °C in THF (Scheme 13). Thus, trapping of zincated pyrone **24** with representative electrophiles furnished the 3-substituted pyranones **25 a-d** in moderate to good yields (61-90%, entries 1-4, Table 2). Metallation of **23** with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**), provided the C(2)-metallated pyranone **26** as confirmed by iodolysis product **27a** (48%, entry 5).

[92] (a) *Science of Synthesis, Houben-Weyl, Volume14 : Pyranones and Pyrathiones* (Ed.: Y. Yammamoto), Gerog Thime Verlag, **2004**, p. 320. (b) W. Wink, H. Waldmann, M. Kaiser, *Bioorg. Med. Chem.* **2009**, *17*, 2301.

Table 2: Functionalizatuion of 4-pyranone **23** in C(2) and C(3)



27 **23** **25**

Entry	Metallation Condition	Electrophile (E)	Product	Yield (%)[a]
1	TMPZnCl·LiCl, 0 °C, 2 h, THF	I_2	 **25a**	80
2	TMPZnCl·LiCl, 0 °C, 2 h, THF		 **25b**	65[b]
3	TMPZnCl·LiCl, 0 °C, 2 h, THF		 **25c**	90[c]
4	TMPZnCl·LiCl, 0 °C, 2 h, THF		 **25d**	61[b]
5	$TMP_2Zn·2MgCl_2·2LiCl$, –35 °C, 2 h, THF	I_2	 **27a**	48
6	$TMP_2Zn·2MgCl_2·2LiCl$, –35 °C, 2 h, THF		 **27b**	56b[c]
7	$TMP_2Zn·2MgCl_2·2LiCl$, –35 °C, 2 h, THF		 **27c**	67c[c]

[a] Yield of isolated, analytically pure product.[b] Obtained after transmetallation with CuCN·2LiCl (1.2 equiv., –40 °C, 30 minutes); [c] 2% $Pd(dba)_2$, 4% tfp, ArI (1.2 equiv. 25 °C, 1 h).

The formation of a new carbon-carbon bond is readily performed by a *Negishi* cross-coupling of **26** with iodoanisole providing **27b** in 58% yield (Table 2, entry 6).[93] Furthermore the metallation procedure was applied to the preparation of the natural product 2-(2-methoxyphenyl)-4*H*-pyran-4-one (**27c**), isolated from Seagrass-derived fungus polyporales PSU-ES44, from *Thalassia hemprichii*.[94] Thus, Pd-catalyzed *Negishi* cross-coupling of the C(2)-zincated pyranon **26** with iodo-2-methoxybenzene provided the natural product **27c** in 67% yield (Table 2, entry 7).

[93] R. C. Barcelos, J. C. Pastre, V. Caixeta, D. B. Vendramini-Costa, J. E. de Carvalho, R. A. Pilli, *Bioorg. Med. Chem.* **2010**, *20*, 3635.
[94] (a) V. Rukachaisirikul, S. Kannai, S. Klaiklay, S. Phongpaichit, J.Sakayaroj, *Tetrahedron* 69, **2013**, 6981. (b) J. Toda, T. Saitoh, T. Oyama, Y. Horiguchi, T. Sano, *Heterocycles* **1996**, *43*, 2457.

4.4 Metallation of Uracil and Uridine

4.4.1 General Introduction

Figure 9 shows the structures of the pyrimidones uracil (**28**), thymine (**29**) and cytosine (**30**) and their nucleotides **31**-**33** that are found in the DNA and RNA.

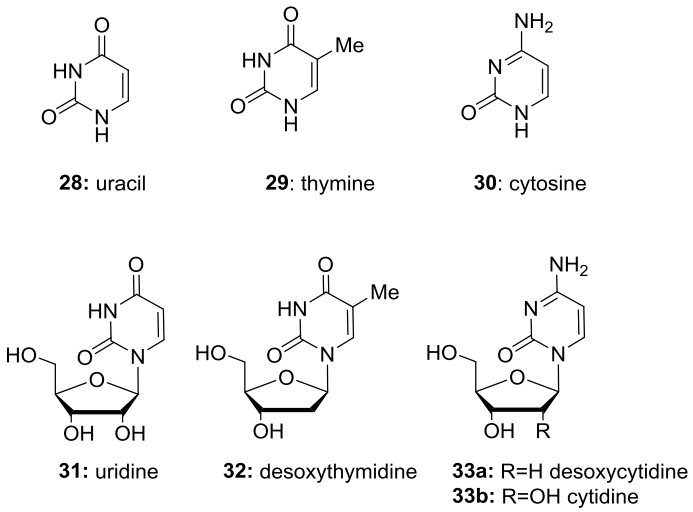


Figure 9: Pyrimidine nucleobases uracil, thymine, cytosine and their nucleosides uridine, desoxythymidine, desoxycytidine and cytidine.

Furthermore, the pyrimidine scaffold is present in numerous natural products.[95] Uracil is found in the non-proteogenic amino acid willardiine, isolated in 1959 from *Acacia willardiana* (Figure 10). The peptide penilumamide,[96] isolated from *Penecillum* in 2010 and the alkaloide rigidin A, isolated in 1990 from *Eudisromu cf. rigida*, contain an uracil skeleton (Figure 10).[97]

[95] I. M. Lagoja, *Chem. Biodiversity* **2005**, *2*, 1
[96] S. W. Meyer, T. F. Mordhorst, C. Lee, P. R. Jensen, W. Fenical, M. Köck, *Org. Biomol. Chem.* **2010**, *8*, 2158. M. Chen, C. L. Shao, X. M. Fu, C. J. Kong, Z. G. She, C. Y. Wang. *J. Nat. Prod.* **2014**, *77*, 1601.
[97] (a) J. Kobayashi, J. Cheng, Y. Kikuchi, M. Ishibashi, S. Yamamura, Y. Ohizumi, T. Ohtac, S. Nozoec *Tetrahedron Lett.* **1990**, *31*, 4617. (b) M. Tsuda, K. Nozawa, K. Shimbo, J. Kobayashi, *J. Nat. Prod.* **2003**, *66*, 292. (c) R. A. Davis, L. V. Christensen, A. D. Richardson, R. M. Da Rocha, C. M. Ireland, *Mar. Drugs* **2003**, *1*, 27.

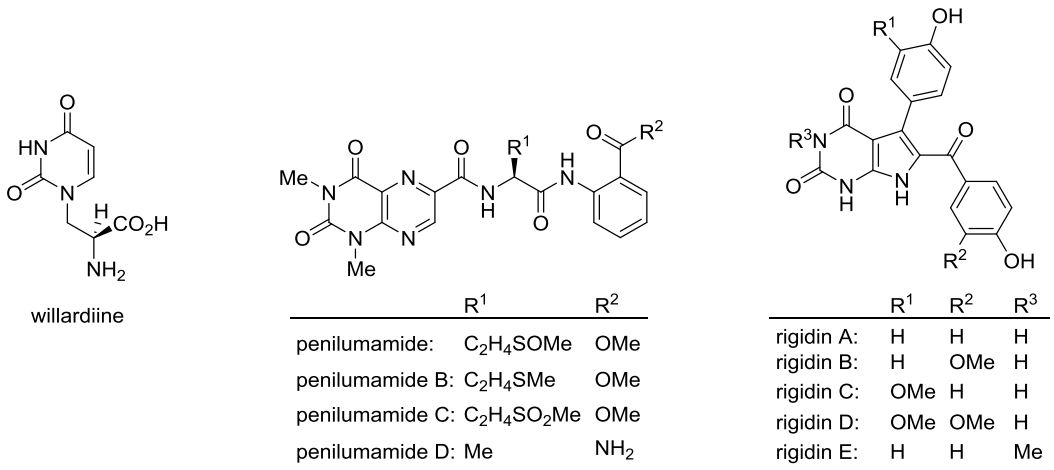


Figure 10: Examples for natural products containing an uracil core structure.

In addition to their biological significance, pyrimidine nucleobases and nucleosides display important pharmaceutical properties.[98] They are known to display antibiotic, antifungal, anticancer, and antiviral activity.[99]

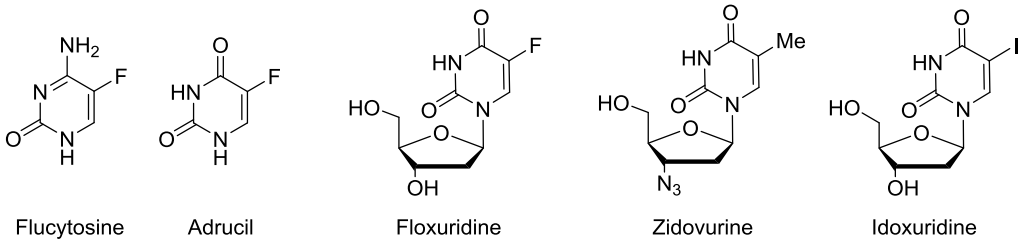


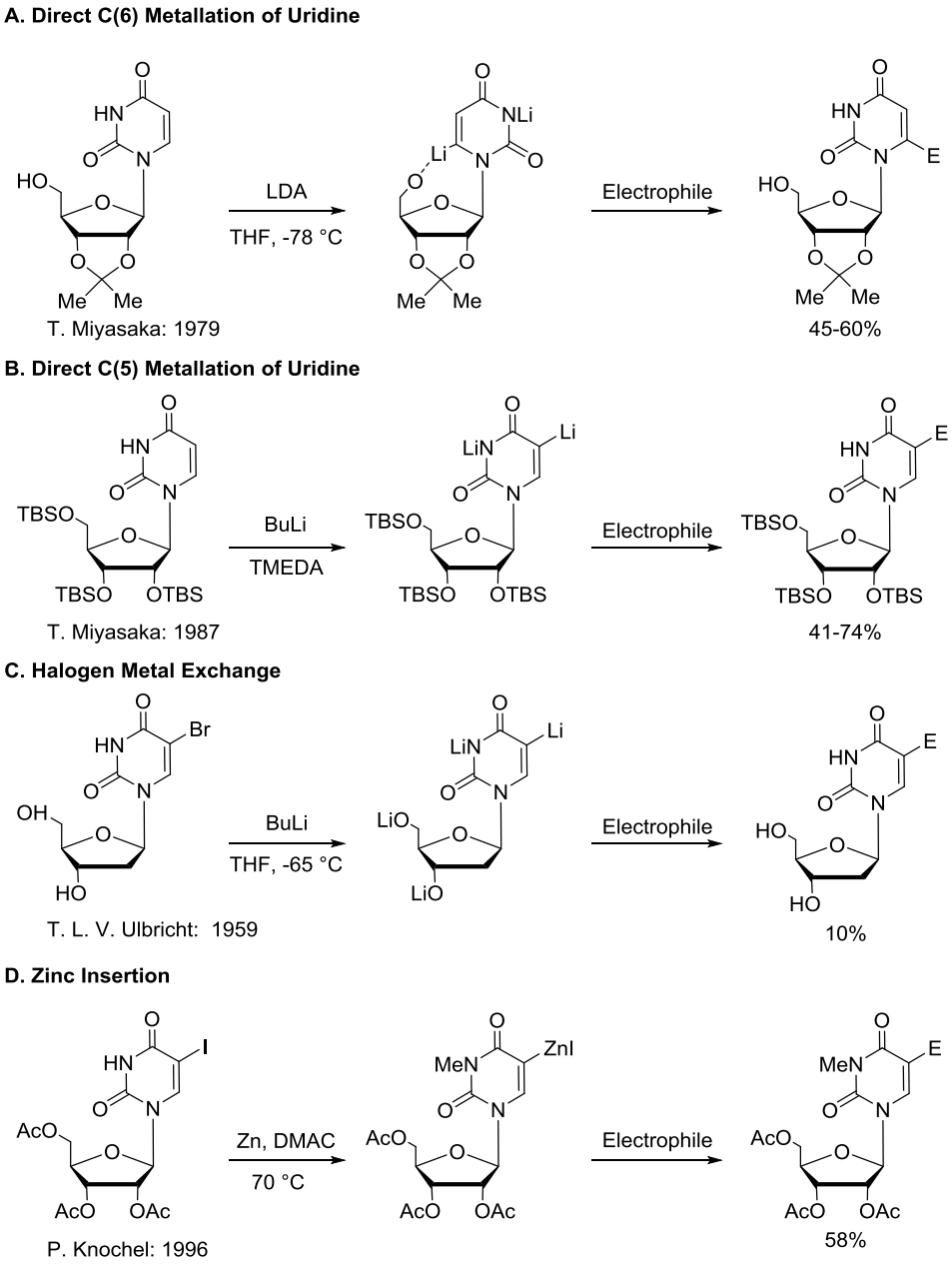
Figure 11: Examples for modified uracil and uridines, displaying biological activity.

For example, 5-fluorocytosine (Flucytosine) shows antimycotic activity, while 5-fluorouracil (Adrucil) and 5-fluorodesoxyuridine (Floxuridine) are clinically established anticancer drugs (Figure 11).[99] Many antiviral agents are based on modified nucleosides including both modifications at the sugar moiety or heterocyclic system. Zidovurine (Retrovit, AZT) for example is an anti-HIV protease inhibitor while Idoxuridine shows activity against hepatitis (Figure 11).[99]

[98] *Science of Synthesis, Houben-Weyl, Volume 6: Six-Membered Hetarenes with Two Identical Heteroatoms* (Ed. Y. Yammamoto), Gerog Thime Verlag, **2004**, p. 379
[99] *Heterocyclic Chemistry*, 5. Edition (Eds.: J. A. Joule, K. Mills), John Wiley & Sons, West Sussex, United Kingdom, **2010**, p. 661.

4.4.2 State of Research for the Metallation of Uracil and Uridine

Since the uracil scaffold **28** is such an important pharmacophor, the functionalization of this heterocyclic system is of special synthetic importance and has been studied thoroughly in the literature.[100]

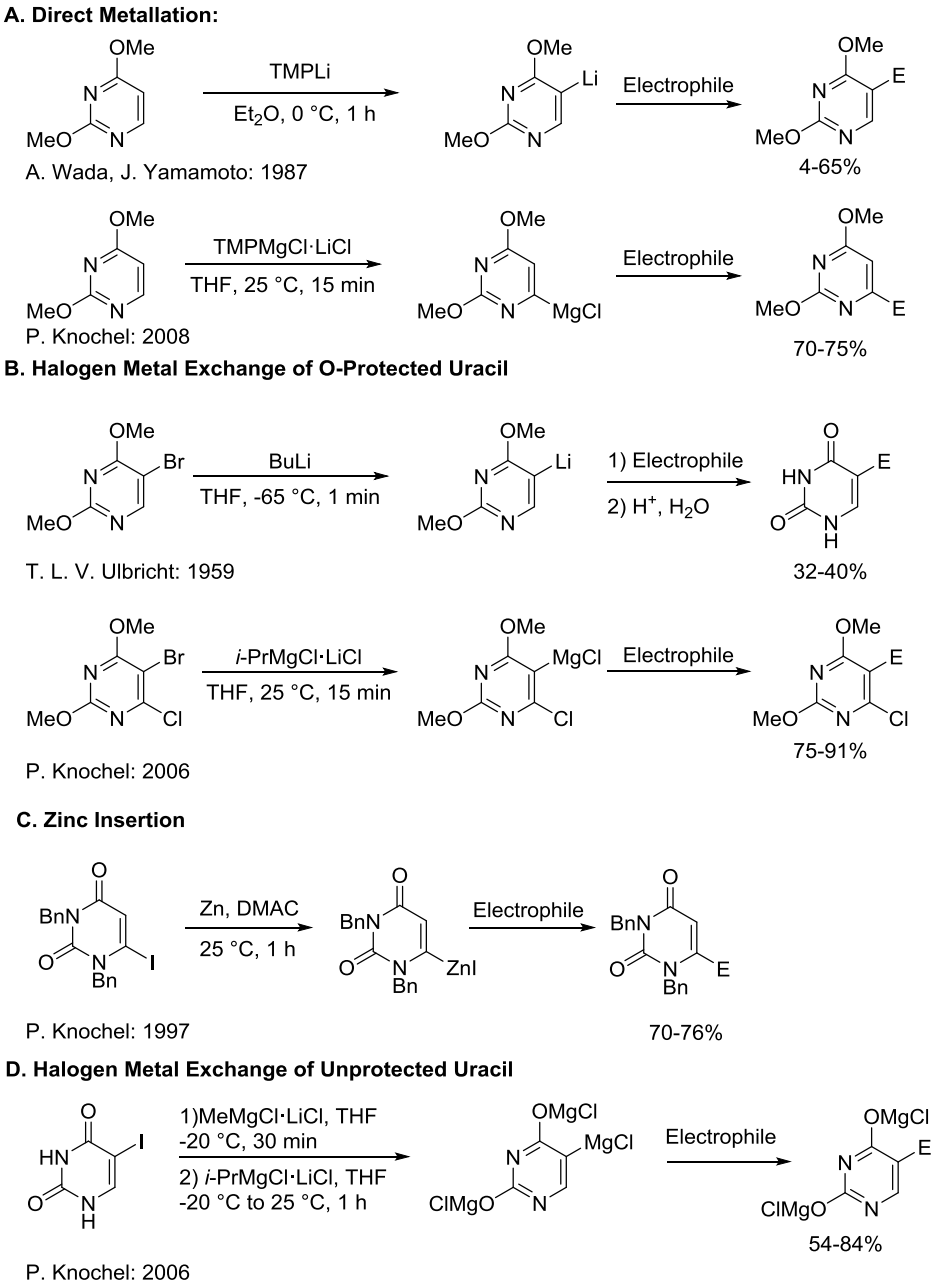


Scheme 14: Reported examples for the metallation of uridine.

[100] *Comprehensive Heterocyclic Chemistry III, Volume 8: Pyridazines and their Benzo Derivatives* (Eds.: R. K. Alan, A. R. Christopher, F. V. S. Eric, J. K. T. Richard), Elsevier, Oxford, **2008**, p. 1-253.

Metallation of uridine **31** has been reported to occur at the C(5) and C(6) positions (Scheme 14).[101,102,103] The direct lithiation of uridine at position C(6) (A, Scheme 14)[101a] was achieved either by equilibration conditions[102b] from thr C(5) lithiated uridine, or by taking advantage of the coordinating effect of hydroxyl- or methoxymethyl-groups at C'(5) of the sugar moiety to lithiumdiisopropylamid (LDA). Direct metallation of C(5) using *s*-BuLi and further functionalizations have also been achieved, when weakly chelating siloxy groups were used for C'(5) protecting (B, Scheme 14).[102a] The main limitation with the use of lithium reagents is their very high reactivity due to the ionic character of the C-Li bond. For this reason, the choice of potential electrophiles is strongly limited and the functionalized uracil derivatives were obtained in moderate yields. Furthermore, functionalization of protected uridine was achieved by halogen-metal exchange (C, Scheme 14)[103a] or zinc insertion (D, Scheme 14)[103b] and subsequent reaction with electrophile. The metallation of uracil **28** has been performed at C(5) and C(6), and generally requires the protection by *N*-alkylation or *O*-alkylation (Scheme 15). [104-107] Several *O*-protected pyrimidines have been metalated at C(5) and C(6) *via* direct metallation (A, Scheme 15)[104a,105] or halogen-metal exchange reaction (B, Scheme 15)[103a,104c] at low temperatures. Zincation of *N*-protected uracil derivatives was performed *via* oxidative insertion (C, Scheme 15).[106] Unprotected 5-ioduracil has also been metallated successfully *via* the formation of a trimagnesiated species (D, Scheme 15).[107]

[101] (a) H. Tanaka, I. Nasu, T. Miyasaka, *Tetrahedron Lett*. **1979**, *20*, 4755. (b) H. Tanaka, H. Hayakawa, T. Hiyasaka, *Tetrahedron* **1982**, *38*, 2635 (c) M. Shimizu, H. Tanaka, H. Hayakawa, T. Miyasaka, *Tetrahedron Lett*. **1990**, *31*, 1295.
[102] (a) H. Hayakawa, H. Tanaka, K. Obi, M. Itoh, T. Miyasaka. *Tetrahedron Lett.* **1987**, *28*, 87. (b) M. Shimizu, H. Tanaka, H. Hayakawa, T. Miyasaka, *Tetrahedron Lett.* **1990**, *31*, 1295.
[103] (a) T. L. V. Ulbricht, *Tetrahedron* **1959**, *6*, 225. (b) T. M. Stevenson, B. A. S. Prasad, J. R. Citineni, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 8375. (c) B. A. S. Prasad, T. M. Stevenson, J. R. Citineni, V. Nyzam, P. Knochel, *Tetrahedron* **1997**, *53*, 7237.
[104] (a) A. Wada, J. Yamamoto, S. Kanatomo, *Heterocycles* **1987**, *3*, 585 (b) A. Wada, J. Yamamoto, Y. Hamoaka, S. Ohki, S. Nagai, S. Kanamoto, *J. Heterocycl. Chem.* **1990**, *27*, 1831. (c) N. Boudet, P. Knochel, *Org. Lett.* **2006**, *8*, 3737. (d) For a review see: *Comprehensive Heterocyclic Chemistry III* (Eds.: R. K. Alan, A. R. Christopher, F. V. S. Eric, J. K. T. Richard), Elsevier, Oxford, **2008**, p. 151-161.
[105] M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237.
[106] A. S. B. Prasad, P. Knochel, *Tetrahedron Lett*. **1997**, *53*, 16711.
[107] F. Kopp, P. Knochel, *Org. Lett.* **2007**, *9*, 1639.



Schene 15: Reported examples for the metallation of uracil.

4.4.3 Chemoselective Metallation of Uracil and Uridine Derivatives

It was anticipated that the metallation procedure of chromone **5** could be extended to protected uridine **31**. Thus, the strongest Lewis acid will coordinate to the C(4) carbonyl, directing the metallation of uracils and uridines either to position C(5) or C(6) (Figure 12).

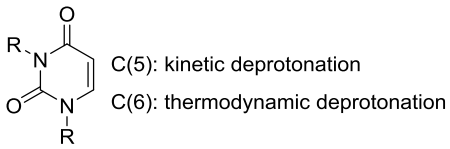
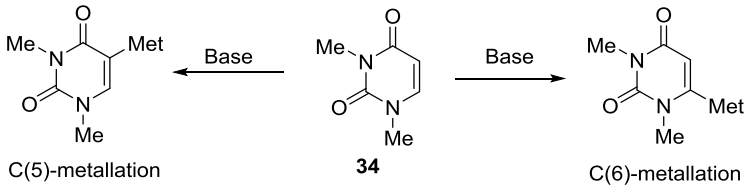


Figure 12: Regioselective metallation of uracil and uridine derivatives in position C(5) and C(6).

4.4.3.1 Optimization of the Reaction Conditions

First, the direct metallation with TMP-bases on the uracil core structure was studied. As model system, the metallation of methyl protected uracil **34** was examined, since this protecting group should not influence the reaction by coordinating or steric effects. To determine the optimum reaction conditions, the metallation of methyl protected uracil **34** was performed with different bases at varying temperatures in THF (Table 3). The progress of the reaction and the regioselectivity was checked by GC analysis of reaction aliquots quenched with iodine.

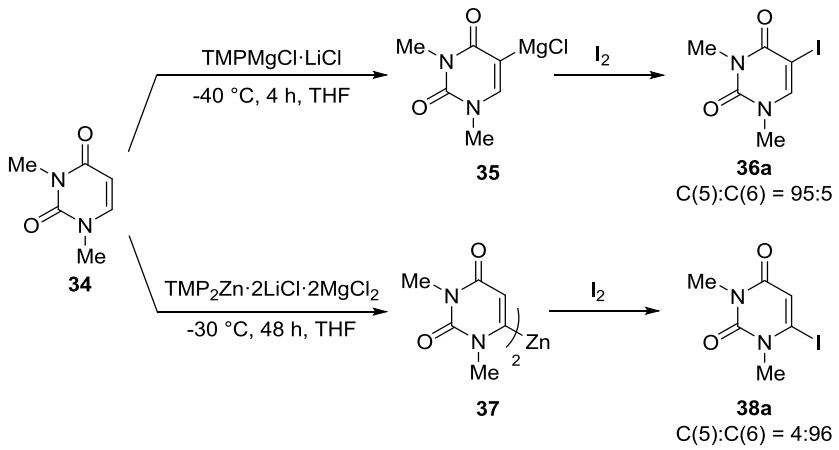
Table 3: Observed Selectivities for the Metallation of Uracil **34** in THF



entry	Base	Temperature	Reaction time	conversion	C(5):C(6)
1	TMPZnCl·LiCl	25 °C	30 min	100%	50:50
2	TMPZnCl·LiCl	–20 °C	21 h	62%	89:11
3	TMPZnCl·LiCl	–40 °C	21 h	24%	91:9
4	TMPMgCl·LiCl	–40 °C	4 h	100%	95:5
5	$TMP_2Zn·2MgCl_2·2LiCl$	–30 °C	48 h	100%	4:96

The reaction of **34** with TMPZnCl·LiCl (**3**) at 25 °C required 2 equiv. of the base to achieve full conversion, providing a 1:1 mixture of C(5) and C(6) metallated products (Table 3, entry 1). It was envisioned that lower reaction temperatures might favour the formation of the C(5) metallated product. When the reaction was performed at –20 °C, the regioselectivity improved

to 89:11, however the conversion decreased to 62%, even after 21 h reaction time (entry 2). Since the selectivity could only be improved at expense of the conversion (entry 3, Table 3), a stronger and better coordinating base was selected for metallation. Treating uracil **34** with 1.2 equiv. TMPMgCl·LiCl (**1**) at –40 °C provided full conversion after 4 h, yielding 95% of C(5) metalated derivative **35** (entry 4, Table 3). Our concept was further confirmed by the selective zincation at C(6) in the presence of the Lewis acid $MgCl_2$. Thus, the treatment of uracil with 0.5 equiv. $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**) at –30 °C in THF, yielded the C(6) metallated product quantitatively. The iodolysis product **38a** indicates a selectivity of 4:96 (entry 5).

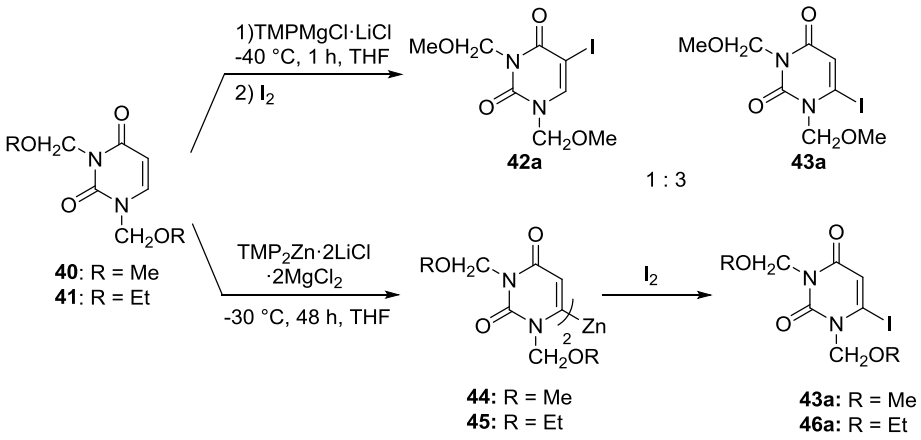


Scheme 16: Optimized reaction conditions for the metallation of methyl protected uracil.

Since the methyl protection group generally requires harsh deprotection conditions,[89] the metallation of benzyl protected uracil **39** was also investigated. The progress of the reaction and the regioselectivity was checked by GC analysis of reaction aliquots quenched with iodine. Reaction of uracil **39** with TMPMgCl·LiCl (**1**) at –40 °C provided C(5) metallation in a regioselective manner, however the conversions never exceeded 78%. To improve the conversion, the stronger base $TMP_2Mg{\cdot}2LiCl$ was used, however, even at –80 °C the reaction was accompanied by decomposition. When the benzyl protected uracil **39** was treated with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**) at –78 °C, a regioselectivity of 97:3 C(6):C(5) was observed and even reaction times up to 72 h did not improve the conversion beyond 58%. Since the protecting groups Me and Ph change the electronic properties of uracil marginally, it was assumed that the lower conversions are mainly caused by sterical effects.

Furthermore, the influence of a protection group with etheral oxygen was investigated on the regioselectivity. The metallation of methoxymethyl protected uracil (**40**) and ethoxymethyl

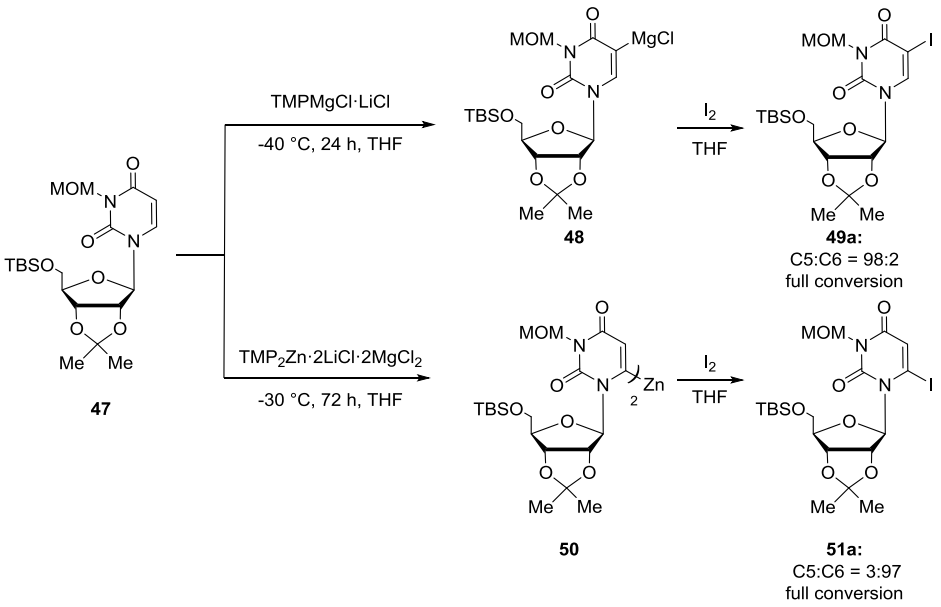
protected uracil (**41**) was examined (Scheme 17). Thus, treatment of **40** with TMPMgCl·LiCl (**1**) at –40 °C and subsequent iodolysis provided a 1:3 mixture of C(5) and C(6) iodinated product **42a**:**43a**, as observed by ^{1}H-NMR analysis of the crude product (Scheme 17). Providing regioselectively the C(5) metallated species by varying the reaction temperature and the base was not possible. This is rationalized by the competing coordination of the TMP bases **1** and **3** to both, the C(4) carbonyl and the ethereal oxygen of the protection group. When $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ (**4**) was used instead, deprotonation of **40** occurred only at the more acidic position C(6), providing the thermodynamic metallation product **44**, as confirmed by crude ^{1}H-NMR of the iodolysis product **43a** (Scheme 17). The same selectivities are observed for ethoxymethyl protected uracils **41**. Thus, treatment of **41** with TMPMgCl·LiCl (**1**) or TMPZnCl·LiCl (**2**) proceeded unselectively, while the reaction of $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ (**4**) provided the C(6) metallated product **45**, selectively as confirmed by ^{1}H NMR analysis of the iodolydis product **46a**.



Scheme 17: Reaction conditions for the metallation of methoxymethyl and methoxyethyl protected uracil.

This metallation procedure was finally extended to the nucleoside uridine **31**. Since it was observed that the ethereal oxygen of methoxyethyl protected uracil **41** influenced the regioselectivity of the metallation due to competing coordination, it was anticipated, that this competitive coordination could be reduced by steric shielding. A bulky TBS (TBS = tert-butyldimethylsilyl) protecting group was introduced at the C'(5)-hydroxy group, envisioning that the coordination of both C'(5)-oxygen and the ethereal oxygen would be less favoured. Metallation of **47** with TMPMgCl·LiCl yielded the C(5)-magnesiated intermediate **48** in a regio specific manner after 24 h, as confirmed by crude ^{1}H-NMR of the iodolysis crude product **49a** (Scheme 18). Metallation of **47** with $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ (**4**) provided the

C(6) zincated uridine **50** after 72 h (Scheme 18). The regioselectivity of the metallation product was confirmed by ^{1}H-NMR of the iodolysis crude product **51a.**

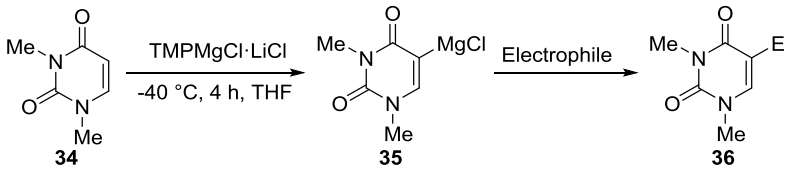


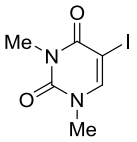
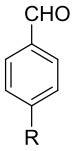
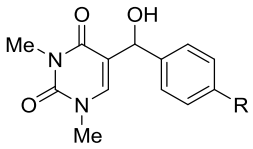
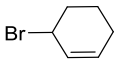
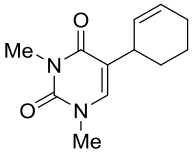
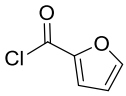
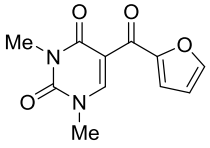
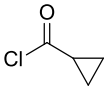
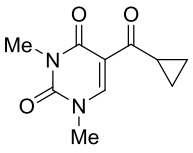
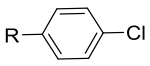
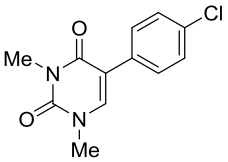
Scheme 18: Reaction conditions for the metallation of protected uridine **47**.

4.4.3.2 Functionalization of protected Uracil

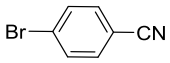
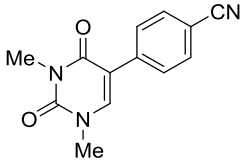
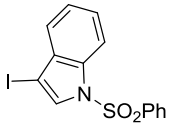
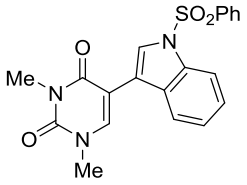
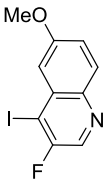
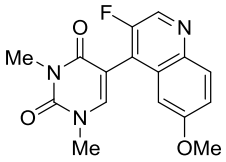
With the optimized metallation conditions in hand, the scope of the reaction with different electrophiles was tested. Thus, methyl protected uracil **34** reacted with TMPMgCl·LiCl (**1**), leading to a regiospecific metallation at C(5) (**35**), allowing the direct functionalization at C(5), providing products **36a-k** in moderate to good yields (Table 4). Reaction of **35** with aldehydes afforded the alcohols **36b**-**36d** in 48-74% yield (entries 2a-c). Transmetallation of **35** with CuCN·2LiCl and subsequent reaction with 3-bromocyclohexene provided the allylation product **36e** (56% yield, entry 3). Thus, acylation with furoyl chloride or cyclopropanecarbonyl chloride afforded the expected ketones **36f-g** in 66% and 71% yield, respectively (entries 4-5). Transmetallation of **35** with $ZnCl_2$ and subsequent Pd-catalyzed *Negishi* cross-couplings (2% $Pd(dba)_2$, 4 mol% P(2-furyl)$_3$ or 2% $Pd(OAc)_2$ 4 mol% X-Phos) with aromatic, heteroaromatic or alkenyl halides led to the cross-coupling products **36h-k** (47-78%, entries 6-9).

Table 4: Products Obtained by C(5) Magnesiation of Uracil (**34**) with TMPMgCl·LiCl (**1**) and Subsequent Reaction with Electrophiles.



Entry	Electrophile	Product	Yield[%][a]
1	I_2	 **36a**	72
			
2a	R = CN	**36b**	70[108]
2b	R = H	**36c**	74
2c	R = OMe	**36d**	48[108]
3		 **36e**	56[b]
4		 **36f**	66[b]
5		 **36g**	71[b]
			
6a	R = I	**36h**	78[c]
6b	R = Br	**36h**	47[c,108]

[108] The reaction was performed by Eider Aranzamendi (University of the Basque Country, Bilbao, Spain)

Entry	Electrophile	Product	Yield[%][a]
7		 **36i**	78[d,108]
8		 **36j**	73[c]
9		 **36k**	56[c]

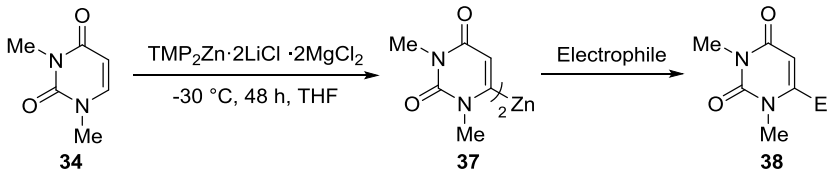
[a] Yield of isolated, analytically pure product. [b] Obtained after transmetallation with CuCN·2LiCl (1.2 equiv.). [c] Obtained after transmetallation with $ZnCl_2$ (1.2 equiv.) 2 mol% $Pd(dba)_2$ and 4 mol% P(2-furyl)$_3$ [d] Obtained after transmetallation with $ZnCl_2$ (1.2 equiv.), 2 mol% $Pd(OAc)_2$ and 4 mol% XPhos.

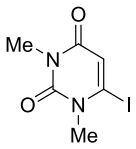
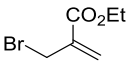
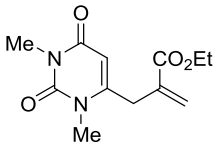
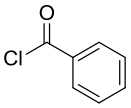
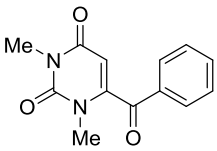
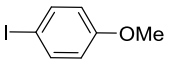
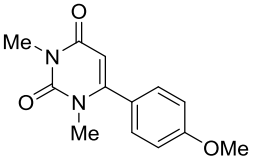
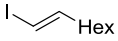
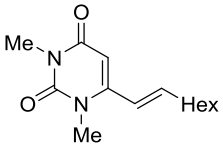
The reaction of methyl protected uracil **34** with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**) at –30 °C provided the bis-heterocyclic zinc reagent **37** allowing the direct functionalization at C(6) (Table 5). Iodolysis of the zinc reagent **37** provided 6-iodouracil (**38a**) in 81% yield (entry 1). Similarly, copper-mediated allylation with ethyl 2-(bromomethyl)acrylate[109] or acylation with benzoyl chloride afforded the C(6) functionalized uracil derivatives **38b** (69%, entry 2) and **38c** (84%, entry 3). Pd-catalyzed *Negishi* cross-coupling (2 mol% $Pd(dba)_2$ and 4 mol% P(2-furyl)$_3$) with *p*-iodoanisole or 1-iodooct-1-ene furnished the expected C(6)-substituted uracils **38d** (83%, entry 4) and **38e** (74%, entry 5).

Furthermore, we examined the scope of the reaction of C(6) metallated uracil derivatives **44** and **45** with representative electrophiles such as aryl iodides (Negishi cross-couplings) or allyl halides and acid chlorides (in the presence of CuCN·2LiCl) providing products **46a-d** (70 to 82% yield, Table 6, entries 2, 4-6) and **43a-c** (45 to 72% yield, Table 6, entries 1, 3, 7, 8).

[109] J. Villieras, M. Rambaud *Org. Synth*. **1988**, *66*, 220.

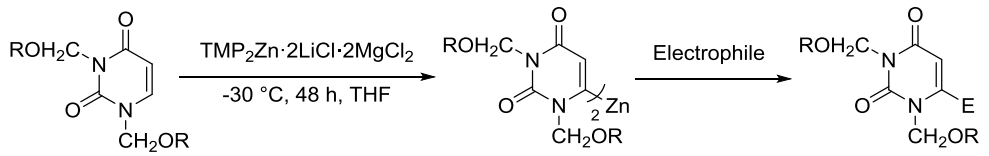
Table 5: Preparation of C(6) Substituted Uracils **38a-e** Using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (2) and Subsequent Reaction with Electrophiles.



Entry	Electrophile (E)	Product	Yield[%][a]
1	I_2	 **38a**	81
2		 **38b**	69[b]
3		 **38c**	84[b]
4		 **38d**	84[c]
5		 **38e**	74[c]

[a] Yield of isolated, analytically pure product. [b] Obtained after transmetallation with CuCN·2LiCl (1.2 equiv.). [c] Obtained after transmetallation with $ZnCl_2$ (1.2 equiv.), 2 mol% $Pd(dba)_2$ and 4 mol% P(2-furyl)$_3$.

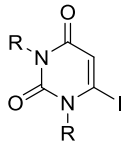
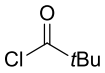
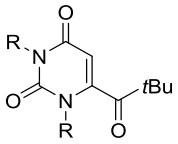
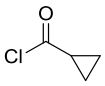
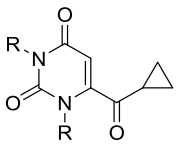
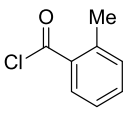
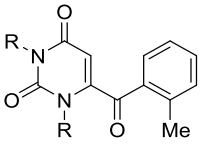
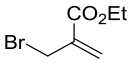
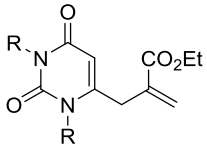
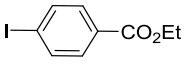
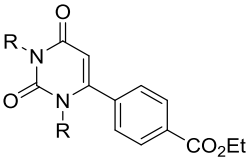
Table 6: Preparation of C(6) Substituted Uracils (**43a-d** and **46a-d)** Using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (2) and Subsequent Reaction with Electrophiles.



40 : R = Me
41 : R = Et

44 : R = Me
45 : R = Et

43 : R = Me
46 : R = Et

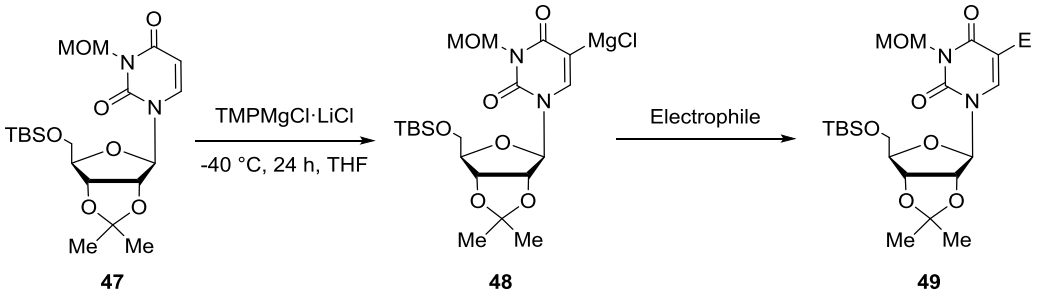
Entry	Substrate	Electrophile	Product	Yield[%][a]
				
1	**41**	I_2	**46a**: R = methoxyethyl	81
2	**40**	I_2	**43a**: R = methoxymethyl	70[108]
				
3	**41**		**46b**: R = methoxyethyl	82[b]
4	**40**		**43b:** R = methoxymethyl	68[b,108]
				
5	**40**		**43c:** R = methoxymethyl	45[b,108]
				
6	**40**		**43d:** R = methoxymethyl	72[b,108]
				
7	**41**		**46c**: R = methoxyethyl	67[b]
				
8	**41**		**46d**: R = methoxyethyl	81[c]

[a] Yield of isolated, analytically pure product. [b] Obtained after transmetallation with CuCN·2LiCl (1.2 equiv.). [c] Obtained after transmetallation with $ZnCl_2$ (1.2 equiv.), 2 mol% $Pd(dba)_2$ and 4 mol% P(2-furyl)$_3$.

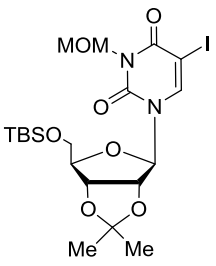
4.4.3.3 Functionalization of protected Uridines

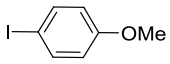
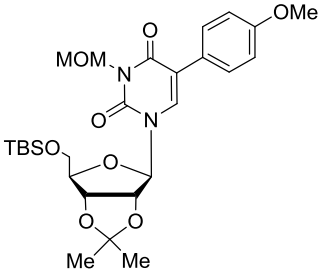
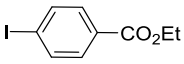
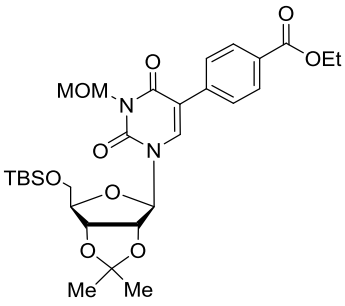
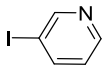
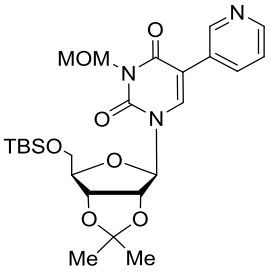
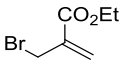
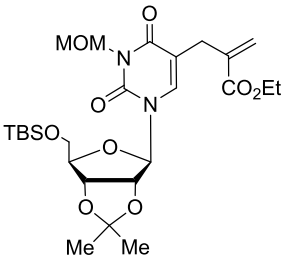
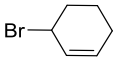
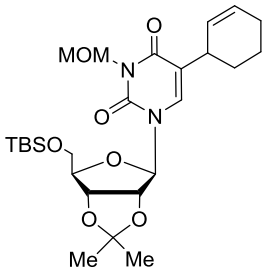
With the optimized metallation conditions in hand, a number of C(5) and C(6) functionalized uridines were prepared. Reaction of the C(5) magnesiated uridine **48** with appropriate electrophiles led to products **49a-f** (Table 7). Thus, after transmetallation of **48** to zinc, Pd-catalyzed *Negishi* cross-coupling (2 mol% $Pd(dba)_2$ and 4 mol% $P(2\text{-furyl})_3$) with *p*-iodoanisole, ethyl-*p*-iodobenzoate or *m*-iodopyridine provided the products **49b-d** (66-81%, entries 2-4). Similarly, copper-mediated allylation or alkylation with ethyl 2-(bromomethyl)acrylate, bromocyclohexene or methyliodide afforded the C(5) functionalized uridine derivatives **49e-g** in 31 to 86% yield (entries 5-7). The ketone **49h** was obtained in 71% yield when **48** reacted in a copper-catalyzed acylation reaction with cyclopropanecarbonyl chloride (entry 8). Aldehyde **49i** was obtained in 30% yield, when **48** reacted with morpholine-4-carbaldehyde (entry 10). Upon treatment of **48** with ethyl cyanoformate, the functionalized ester **49j** was formed in 44% yield (entry 11). Furthermore **48** reacted with various aldehydes to give the corresponding alcohols **49k-m** (30 to 47%, entries 12-14).

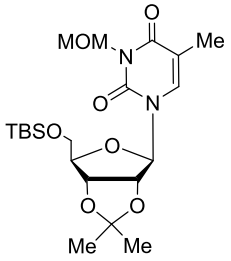
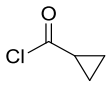
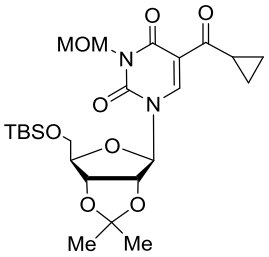
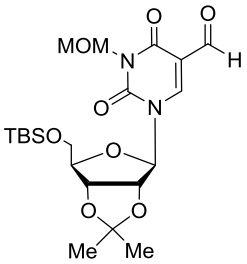
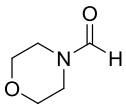
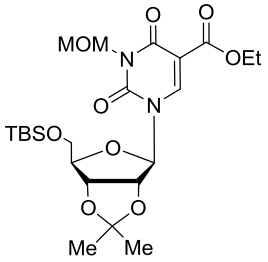
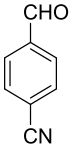
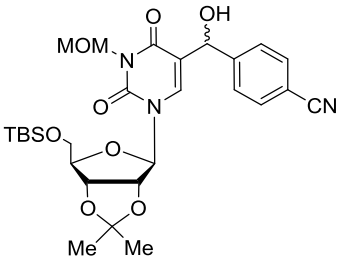
Table 7: Functionalization of Uridine **47** by C(5) Magnesiation Using with TMPMgCl·LiCl (**1**) and Subsequent Reaction with Electrophiles.

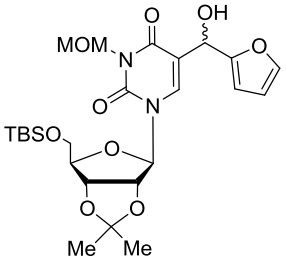
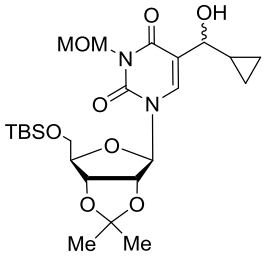


47 **48** **49**

Entry	Electrophile	Product	Yield[%][a]
1	I_2	 **49a**	70

Entry	Electrophile	Product	Yield[%][a]
2		 **49b**	81[c]
3		 **49c**	66[c]
4		 **49d**	73[c]
5		 **49e**	86[b]
6		 **49f**	60[b]

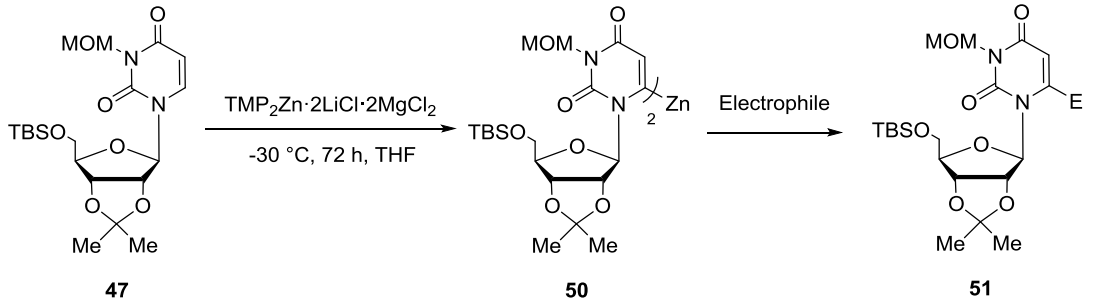
Entry	Electrophile	Product	Yield[%][a]
7	MeI	 **49g**	31[b]
8		 **49h**	71[b]
9	DMF	 **49i**	0
10		**49i**	32
11	$NCCO_2Et$	 **49j**	44
12		 **49k**	47

Entry	Electrophile	Product	Yield[%][a]
13		 **49l**	43
14		 **49m**	30

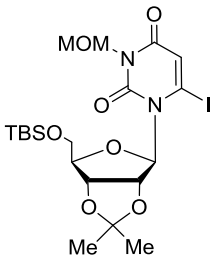
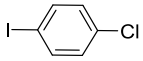
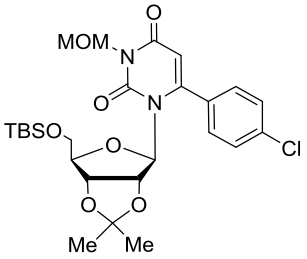
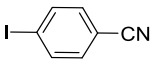
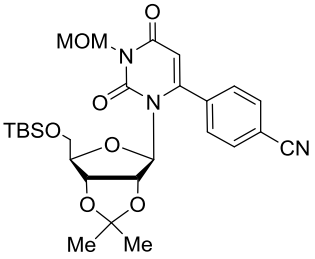
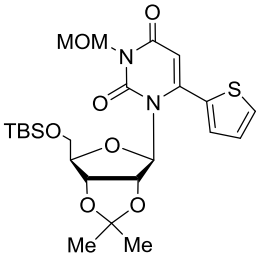
[a] Yield of isolated, analytically pure product. [b] Obtained after transmetallation with CuCN·2LiCl (1.2 equiv.). [c] Obtained after transmetallation with $ZnCl_2$ (1.2 equiv.), 2 mol% $Pd(dba)_2$ and 4 mol% P(2-furyl)$_3$.

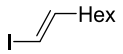
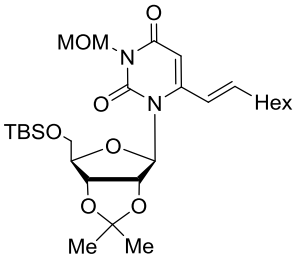
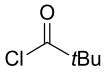
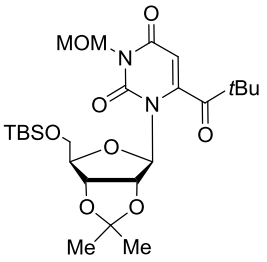
Reaction of protected uridine **47** with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**) provided zincation at C(6). The C(6)-zincated uridine **50** reacted in copper-mediated allylation, copper-mediated acylation and Pd-catalyzed cross-coupling reactions (2 mol% $Pd(dba)_2$ and 4 mol% P(2-furyl)$_3$) providing the products **51a-f** in 67 to 99% yield (Table 8, entries 1-6).

Table 8: Functionalization of Uridines at C(6)



47 **50** **51**

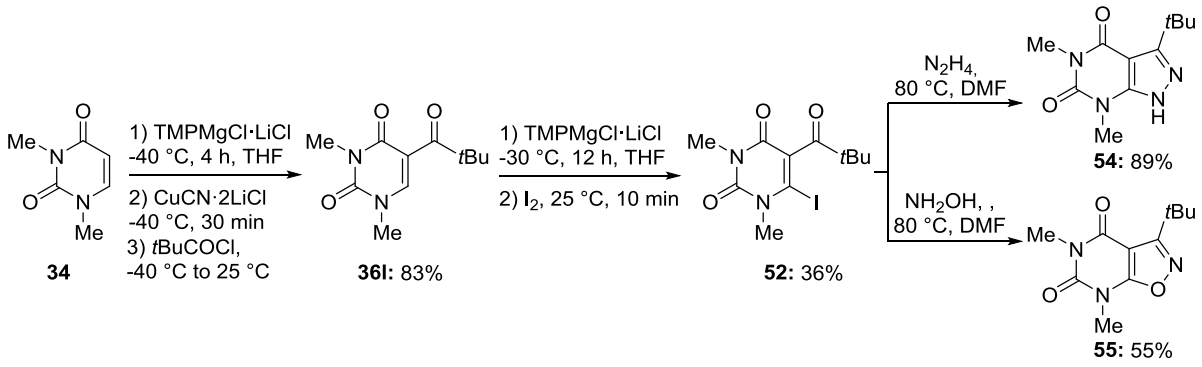
Entry	Electrophile (E)	Product	Yield[%][a]
1	I_2	 **51a**	95
2		 **51c**	84[c]
3		 **51c**	69[c]
4		 **51d**	97[c]

Entry	Electrophile (E)	Product	Yield[%][a]
5		 **51e**	67[c]
6		 **51f**	97[b]

[a] Yield of isolated, analytically pure product. [b] Obtained after transmetallation with CuCN·2LiCl (1.2 equiv.). [c] Obtained after transmetallation with $ZnCl_2$ (1.2 equiv.), 2 mol% $Pd(dba)_2$ and 4 mol% P(2-furyl)$_3$

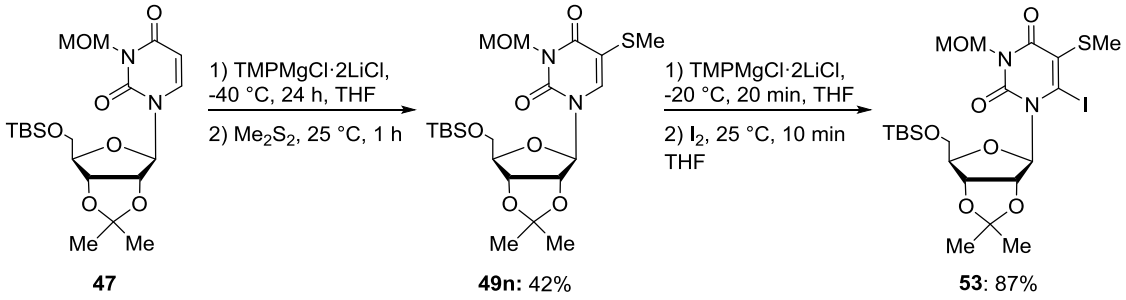
4.4.3.4 Preparation of 5,6-Disubstituted Uracil Derivatives

We further examined the effect of substituents at C(5) or C(6) on the direct metallation reaction. Metallation of alkyl or halogen substituted uracils (**36a**, **36e**, **36h-k**, **38a-b**, **38d-e**) using various TMP-bases and reaction temperatures gave limited results in terms of metallated species, as observed by TLC or ^{1}H-NMR of reaction aliquots quenched with iodine. However, it was observed that metallation was successful when the substituent at C(5) or C(6) induced a strong directing metallation effect. Thus, uracils and uridines containing thioethers and ketones could be metallated easily. 5,6-Disubstituted uracils **52** and **53** were obtained by two successive metallation-functionalization sequences (Scheme 19). In the first step, methyl protected uracil **34** reacted with TMPMgCl·LiCl (**1**, 4 h, –40 °C). Copper mediated acylation of C(5)-zincated uracil **35** provided the ketone **36l** in 83% yield (Scheme 19). A second metallation was performed with TMPMgCl·LiCl (**1**, 12 h at –30 °C) and subsequent iodolysis provided the 5,6-disubstituted uracil **52** in moderate yield (36%). Ring-closing reactions were easily performed when **52** was treated with hydrazine or hydroxylamine for 2 h at 80 °C in DMF, providing the pyrazole **54** and the isoxazole **55** in 55-89% yield (Scheme 19).



Scheme 19: Preparation of pyrazole and isoxazole derivatives **54** and **55**.

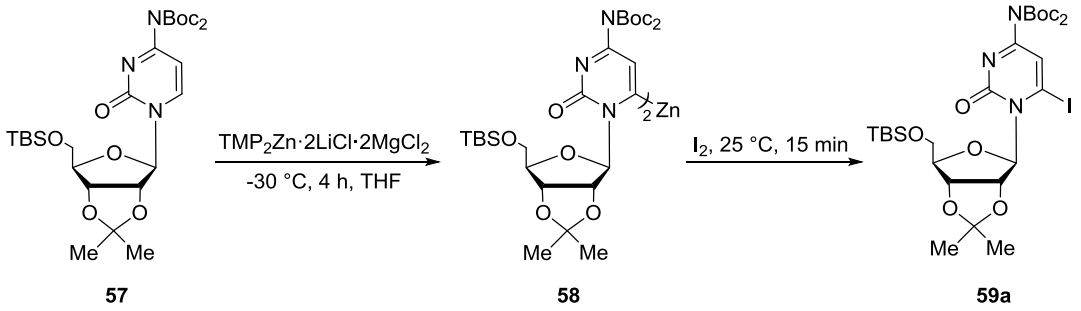
Furthermore, a bifunctionalized uridine was performed in the presence of a directing thioether group. Metallation of **47** with TMPMgCl·LiCl (–40 °C, 24 h), and subsequent reaction with dimethyldisulfane provided **49n** in 42% yield. When **49n** was treated with TMPMgCl·LiCl at –20 °C for 20 minutes in THF, and the obtained magnesium species **56** reacted with iodine, **53** was obtained in 87% yield (Scheme 20).



Scheme 20: Preparation of 5,6-difunctianalized uridine **53**.

4.5 Metallation of Cytidine

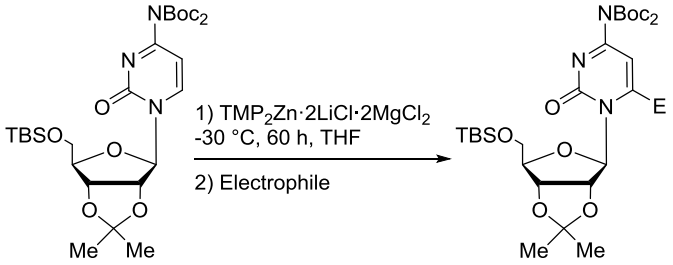
We further expanded our metallation procedure to the nucleobase cytidine (**33b**, Figure 9). Treatment of bis-Boc protected cytidine (**57**) with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**) at –30 °C in THF provided C(6)-zincated species **58** as single regioisomer, with a maximum conversion of 68% after 12 h, as confirmed by ^1H NMR of the iodolysis product **59a** (Scheme 21).



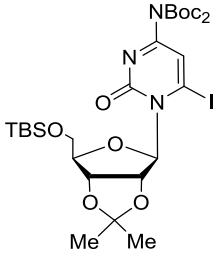
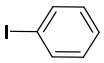
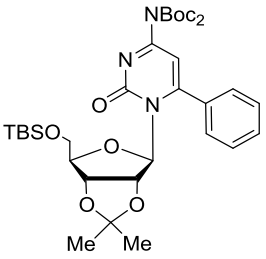
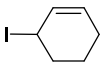
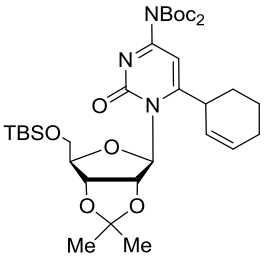
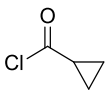
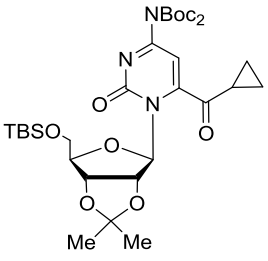
Scheme 21: Regioselective C(6) zincation of cytidine **57**.

When cytidine **57** was treated with TMPMgCl·LiCl (**1**) or TMPZnCl·LiCl (**3**) and subsequently reacted with iodine, the expected C(5)-iodinated product could not be isolated but only the C(6)-iodinated product. Thus, the introduction of the bulky Boc protecting group was assumed to block the metallation at C(5). The C(6)-zincated cytidine (**58**) reacted with representative electrophiles, providing products **59a-d** in moderate yields of 43-61% (Table 9, entries 1-4).

Table 9: Functionalization of Cytidine **59** in C(6)



57 **59**

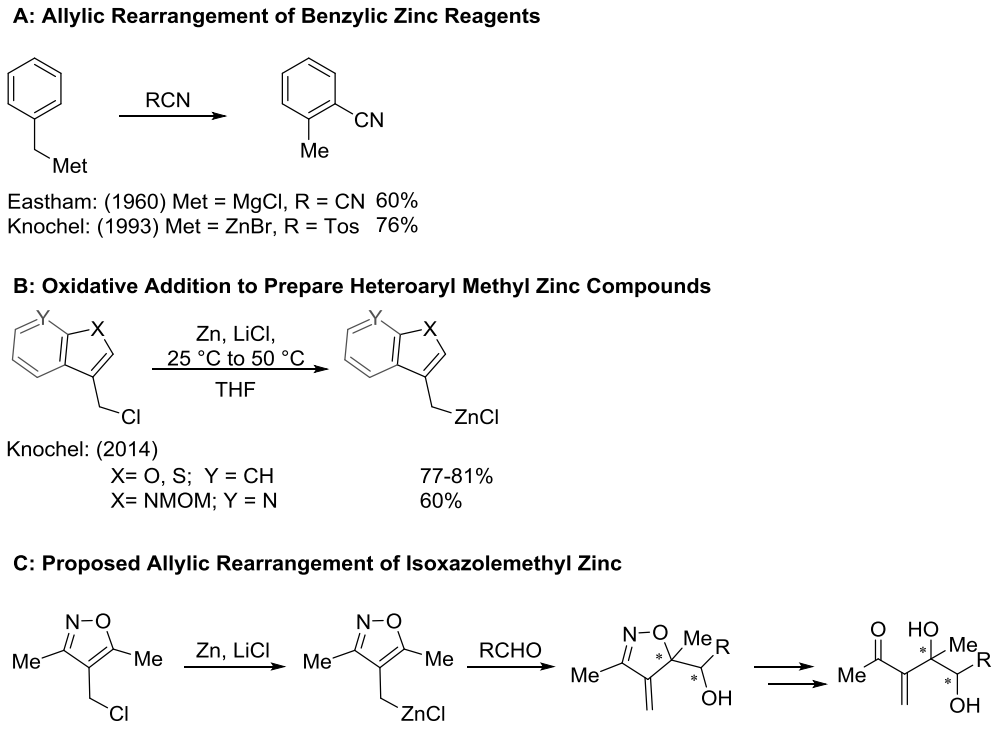
Entry	Electrophile	Product	Yield[%][a]
1	I_2	 **59a**	61
2		 **59b**	43[b]
3		 **59c**	52[c]
4		 **59d**	52[c]

[a] Yield of isolated, analytically pure product. [b] 2 mol% $Pd(dba)_2$ and 4 mol% $P(2\text{-furyl})_3$ [c] Obtained after transmetallation with CuCN·2LiCl (1.2 equiv).

5 Influence of Lewis Acids on the Regio- and Diastereoselectivity of the Reaction of Isoxazole Methylzinc Compounds with Aldehydes

5.1 Rearrangement Concept for Heteroaryl Methylzinc Reagents

The allylic reactivity of benzylic magnesium and zinc reagents has been reported in the literature (A, Scheme 22).[110] Since benzylic zinc reagents are easily prepared *via* oxidative addition in the presence of LiCl (B, Scheme 22),[111] it is envisioned that such an allylic rearrangement might be applicable to recently described heteroaryl methylzinc compounds (C, Scheme 22). Of special interest is the allylic addition of isoxazolemethyl zinc compounds to carbonyl derivatives. After ring opening, the obtained isoxazolines provide *β*-hydroxy carbonyls, which are interesting building blocks in natural product synthesis (C, Scheme 22).



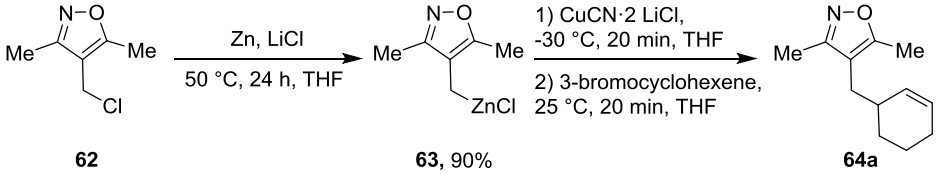
Scheme 22: Reported rearrangement of benzylic zinc reagents and proposed rearrangement concept.

[110] M. Tiffeneau, R. Delange, *Compt. rend.* **1903**, *137*, 573. (b) J. R. Johnson, *J. Am. Chem. Soc.* **1933**, *55*, 3029. (c) E. Sherman , E. D. Amstutz, *J. Am. Chem. Soc.* **1950**, *72*, 2195. (d) V. F. Raaen, F. Eastham, *J. Am. Chem. Soc.***1960**, *82*, 1349. (e) I. Klement, K. Lennick, C. E. Tucker, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 4623.

[111] For LiCl accelerated zinc insertin for the preparation of benzylic zinc reagents see (a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, *44*, 5824. (b) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107. For LiCl accelerated zinc insertin for the preparation of heteroaryl methylzinc compounds see: (c) N. M. Barl, E. Sansiaume-Dagousset, G. Monzón, A. J. Wagner, P. Knochel *Org. Lett.* **2014**, *16*, 2422.

5.2 Reaction Conditions and Optimisation

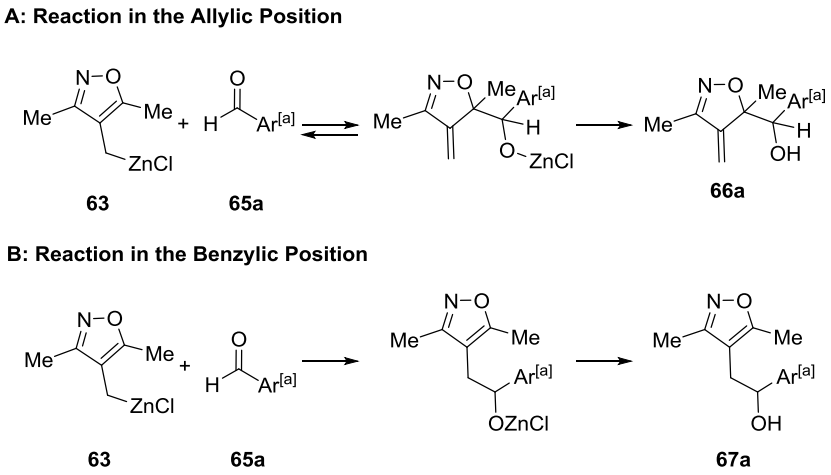
Thus, commercially available 4-(chloromethyl)-3,5-dimethylisoxazole (**62**) undergoes a zinc insertion using zinc powder (1.5 equiv.) in the presence of LiCl (1.5 equiv.) in THF,[30] providing the heterocyclic zinc reagent **63** within 24 h at 50 °C (Scheme 23).[112] Iodometric titration[113] of the reaction mixture indicated up to 90% conversion to the zinc reagent **63**. This heterocyclic zinc reagent reacts in the benzylic position in a copper catalyzed allylation reaction with 3-bromocyclohexene providing product **64a**.



Scheme 23: LiCl-mediated zinc insertion into 4-(chloromethyl)-3,5-dimethylisoxazole (**62**) leading to the heterocyclic zinc reagent **63** and its benzylic reaction.

Since benzylic zinc reagents are known to react with aldehydes without further activation,[111b] zinc reagent **63** was treated with 3,4-dichlorobenzaldehyde **65a** (Scheme 24). The reaction provided both the allylic addition product **66a** and the benzylic addition product **67a** in a ratio of 83:17 (Scheme 25). The zinc reagent reacted predominantly *via* an allylic rearrangement[114] (A, Scheme 24) providing the dearomatized exo-methylene product **66a** in 49% yield with a moderate diastereomeric ratio (dr) of 61:39 (Scheme 25). Longer reaction times led to lower diastereo selectivities, presumably due to a retro-allylation reaction (Scheme 24).[115] The relative stereochemistry of the major diastereoisomer **66a** was assigned by crystal structure analysis (Figure 13).

[112] This reaction was optimized by A. Metzger and A. Wagner (Ludwig-Maximilians-Universität München).
[113] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890.
[114] For papers on allylic rearrangements see (a) G. Courtois, L. Miginiac, *J. Organomet. Chem.* **1974**, *69*, 1. (b) Y. Yamamoto, W. Ito, *Tetrahedron* **1988**, *44*, 5415. (b) I. Klement, K. Lennick, C. E. Tucker, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 4623. (c) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376.
[115] For papers on the reversibility of allylation reactions see (a) P. Miginiac, C. Bouchoule, *Bull. Chim. Soc. Fr.* **1968**, 4675. (b) F. Barbot, P. Miginiac, *Tetrahedron Lett.* **1975**, 3829. (c) F. Barbot, P. Miginiac, *J. Organomet. Chem.* **1977**, *132*, 445. (d) A. Bocoum, D. Savoia, A. Umani-Ronchi, *J. Chem. Soc., Chem. Commun.* **1993**, 1542. (e) P. Jones, P. Knochel, *J. Org. Chem.* **1999**, *64*, 186.



Scheme 24: Reaction pathways of zinc reagent **63** with aldehyde **65a** leading to alcohols of type **66a** and **67a**, [a] For Ar see Figure 13.

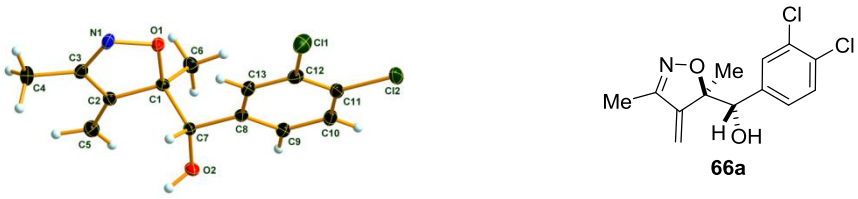
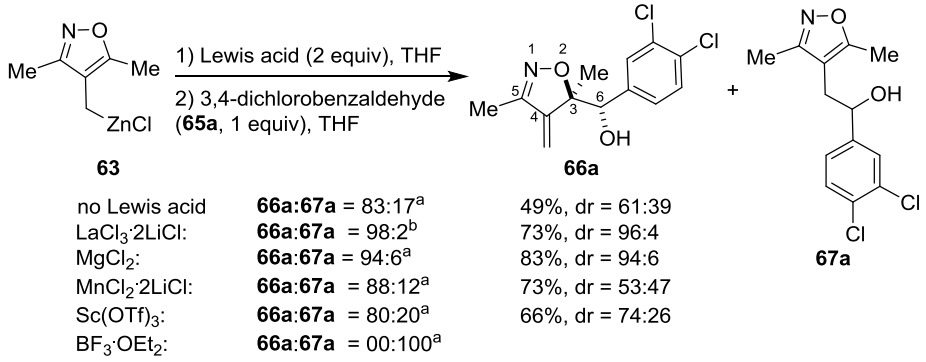


Figure 13: ORTEP view of the crystal structure of **66a**.

Since Lewis acids are known to activate aldehydes,[48,116] the influence of a range of Lewis acid promotors was examined (Scheme 25). This study showed that the addition of Lewis acids influences both regioselectivity and diastereoselectivity and therefore a change in the reaction mechanism is supposedly involved. The formation of the allylic addition product **66a** increased when $LaCl_3 \cdot 2LiCl$ and $MgCl_2$ were added (Scheme 25). The regioselectivity was marginally influenced upon the addition of $Sc(OTf)_3$ and $MnCl_2$. However, the benzylic addition product **67a** was the single regioisomer found when $BF_3 \cdot OEt_2$ was added to the reaction. These opposing selectivities were unexpected. However, similar selectivity changes are reported in the literature. [110b,117,118] In 1993, Knochel et. al. reported that when Cu(I) salts were added to benzylic zinc reagents and reacted with TosCN, a switch from the allylic to the benzylic position occurred.[110b] Furthermore, it is reported that the addition of copper or nickel

[116] (a) *Lewis-Acids in Organic Synthesis, Vol. 2*, (Ed.: H. Yamamoto), VCH, Wiley, Weinheim, Germany **2000**. (b) A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665.

salts change the regioselectivity for the reaction of allylic magnesium reagents.[117] Y. Yamamoto et al. reported that the reaction of allylic tin reagents with aldehydes provided a regioreversed addition in the presence of $AlCl_3 \cdot i$-PrOH.[118] In the reported reactions, these changes in selectivity are rationalized by transmetallations to the corresponding metal species. However transmetallation from zinc to boron is unlikely and therefore, $BF_3 \cdot OEt_2$ is more likely to influence the reaction mechanism *via* a coordinative effect.[56b,49]



Scheme 25: Allylic and benzylic reactivity observed for the reaction of (3,5-dimethylisoxazol-4-yl)methylzinc chloride (**63**) with 3,4-dichlorobenzaldehyde (**65a**) providing products **66a** and **67a**. Diastereomeric ratios and regioselectivities were determined by ^{1}H-NMR of the crude reaction mixture after filtration through silica. [a] 25 °C, 4 h, [b] –60 °C to 25 °C, 12 h.

The diastereoselectivity was also influenced by the addition of Lewis acid. The addition of $LaCl_3 \cdot 2LiCl$ and $MgCl_2$ provided a significant increase in the diastereoselectivity (dr = 96:4 and dr = 94:6, respectively, Scheme 25) compared to the dr = 61:39 in the absence of Lewis acid. In the presence of $Sc(OTf)_3$, only a marginal increase in dr = 74:26 was observed. However, addition of $MnCl_2 \cdot 2LiCl$ provided a slight decrease in diastereoselectivity (dr = 53:47). It is reported in the literature that Lewis acid mediated reactions of allylic organometallics exhibit an entirely different stereochemistry than in the absence of Lewis acids.[56b,49] Y. Yamamoto observed that the addition of Lewis acids influenced both the stereo- and regioselectivity of the reaction of organotin reagents with aldehydes. He proposed that upon the addition of $BF_3 \cdot OEt_2$ an acyclic transition state is formed, where the Lewis acid $BF_3 \cdot OEt_2$ coordinates to the oxygen of the aldehyde, preventing the formation of a chairlike transition state (Scheme 4). The exact influence of the Lewis acid is difficult to determine, since an excess of Lewis acid (2 equiv.) was used, and there are several potential coordination

[117] (a) T. E. Stanberry, M. J. Darmon, H. A. Fry, S. R. Lenox, *J. Org. Chem.* **1976**, *41*, 2052. (b) F. Derguini-Boumechal, R. Lorne, G. Linstrumelle, *Tetrahedron Lett.* **1977**, 1181. (c) G. Linstrumelle, R. Lorne, H. P. Dang, *Tetrahedron Lett.* **1978**, 4069.
[118] Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, K. Maruyama, *Tetrahedron* **1984**, *40*, 2239.

sites for the Lewis acid on both reacrion partners, the isoxazolemethylzinc chloride (N(1), O(3) or methylzinc chloride) and the aldehyde. However, the opposing effects on the selectivity, observed by the addition of different Lewis acids indicate that different reaction pathways are possible. The formation of allylic product in the absence of additional Lewis acids can be explained by a Zimmerman-Traxler like transition state of type **A** (Figure 14). However, aggregates of the organometallic species might hamper the formation of this six membered ring, and a competing acyclic reaction mechanism could therefore explain the lower diastereoselectivity. The addition of Lewis acid might influence the reaction by breaking up the aggregation and thereby favour a cyclic transition state **B**, this might influence the dr (Figure 14). A further possible transition state structure **C** proceeds trough a five membered ring by coordination of the Lewis acid by *O*(2) (Figure 14).

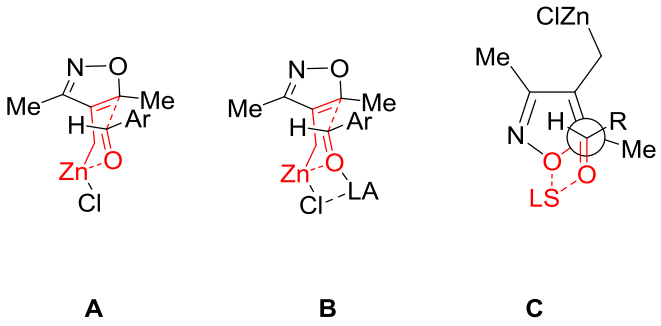


Figure 14: Possible transition states for the reaction of the heterocyclic zinc reagent **63** with aldehyde **65**.

Furthermore, $MgCl_2$ and $LaCl_3 \cdot 2LiCl$ proved to be the most suitable Lewis acids for the reaction in the allylic position, providing the best diastereomeric ratios and regioselectivities (dr = 94:6, **66a**:**67a** = 94:6 and dr = 96:4, **66a**:**67a** = 98:2, respectively). Therefore, the influence of the amount of $MgCl_2$ on the diastereoselectivity ratios was studied in detail (Figure 15). Interestingly, it was observed that the addition of low amounts of Lewis acids (0.1 – 0.4 equiv.) provided a decrease in diastereoselectivity with a minimum around 0.3 to 0.4 equiv. $MgCl_2$ (dr = 44:66), while the addition of further Lewis acid caused an increase in diastereoselectivity. Upon the addition of 0.5 – 1.0 equiv., the ratio increase up to 91:9 was observed, while further addition of $MgCl_2$ provided only an insignificant increase of the diastereomeric ratio, reaching a plateau at around 1.5 equiv. (**66a**:**67a** = 94:6). The progression of the curve could leads to the assumption of a change of the reaction mechanism, which may be explaind by different coordination states of the substrate at different $MgCl_2$ concentrations.

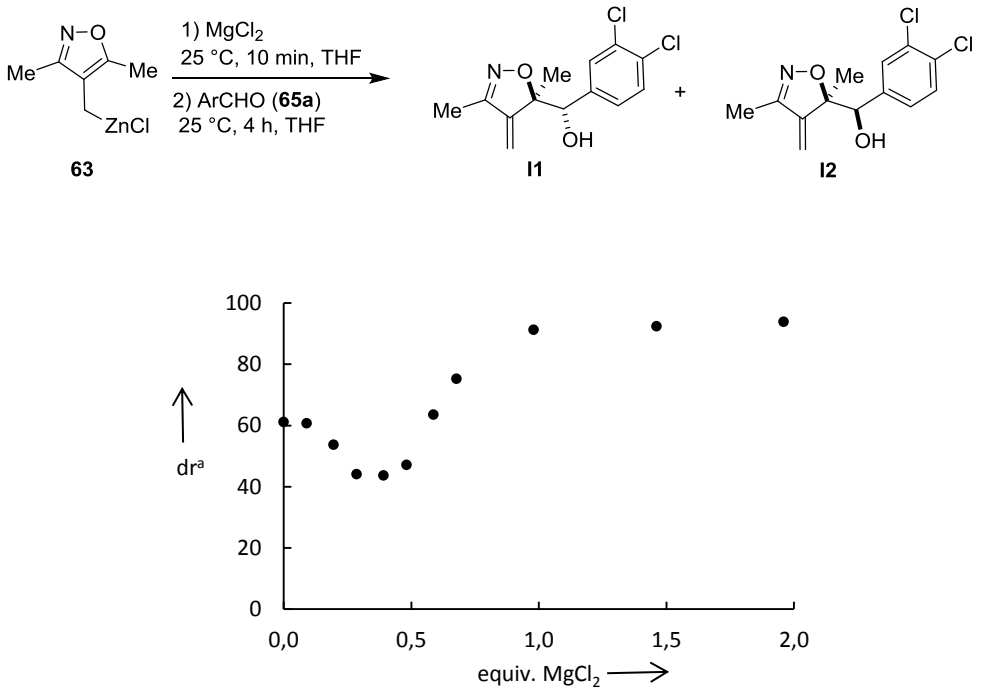


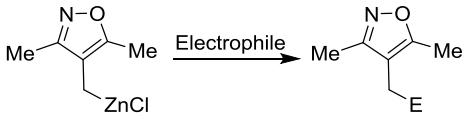
Figure 15. Observed diastereomeric ratio dependent on the molar ratio of $MgCl_2$. [a]Diastereomeric ratios were determined by ^{1}H-NMR of the crude reaction mixture, after filtration through silica.

5.3 Scope of the Reaction in the Benzylic Position

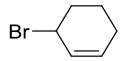
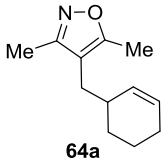
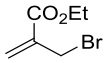
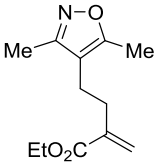
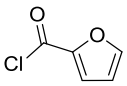
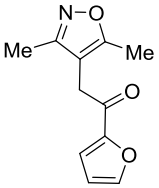
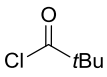
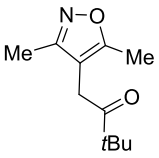
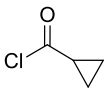
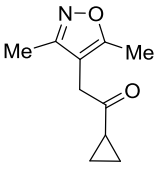
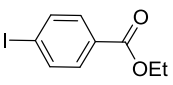
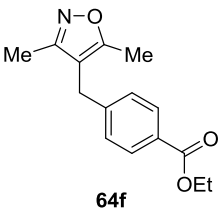
The scope of the benzylic reactivity was tested with representative electrophiles such as allylic halides or acid chlorides in the presence of CuCN·2LiCl.[119] Pd-catalyzed *Negishi* cross-couplings were performed using the palladium catalyst PEPPSI-*iPr*[120] (Table 10). Thus, transmetallation of **63** with CuCN·2LiCl (1 equiv., –40 °C, 30 min), and subsequent reaction with allylic bromides such as 3-bromocyclohexene or ethyl-2-(bromomethyl)acrylate[121] (1.0 equiv., 25 °C, 6 h) provided the isoxazoles **64a**,**b** in 73 and 77% yield (Table 10, entries 1-2). Similarly, copper(I)-mediated acylation with aromatic or aliphatic acid chlorides (1.0 equiv., –40 °C to –20 °C, 24 h) gave the expected ketones **64c-e** (74-81%, Table 10, entries 3-5). Likewise, Pd-catalyzed *Negishi* cross-coupling[24a,85] with aryl iodides in the presence of PEPPSI-*iPr* (1 mol %, 25 °C, 24 h) furnished the expected coupling-products **64f-i** (65 to 85%, Table 10, entries 6-9). The benzylic reactivity of zinc reagent **63** with aldehydes **65a**, **65b** and **65d** in the presence of BF_3·OEt_2 provided isoxazoles **67a-c** in 55-65% yield (Table 10, entries 10-12).

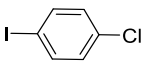
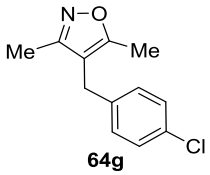
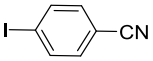
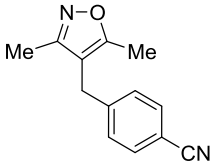
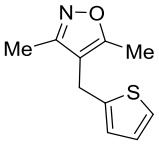
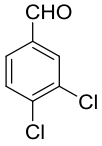
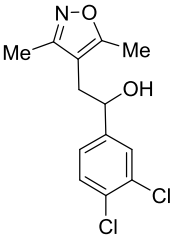
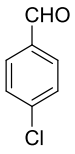
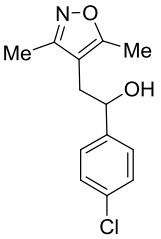
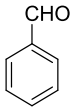
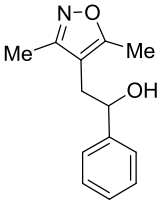
[119] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[120] PEPPSI-iPr = ([1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride)
[121] J. Villieras, M. Rambaud, *Synthesis* **1982**, 924.

Table 10. Reaction of the Heterocyclic Zinc Reagent **63** with Electrophiles Leading to Substituted Isoxazoles of Type **64** and **67**.



63 **64a-i, 67a-c**

Entry	Electrophile (E)	Product	Yield (%)[a]
1		 **64a**	73[b]
2		 **64b**	77[b]
3		 **64c**	81[c]
4		 **64d**	74[c]
5		 **64e**	84[c]
6		 **64f**	87[d]

Entry	Electrophile (E)	Product	Yield (%)[a]
7		 **64g**	85[d]
8		 **64h**	65[d]
9		 **64i**	71[d]
10	 **4a**	 **67a**	55[e]
11	 **4d**	 **67b**	65[e]
12	 **4b**	 **67c**	62[e]

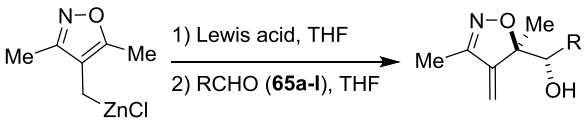
[a] Isolated yield of analytically pure product. [b] Using stoichiometric CuCN•2LiCl (–40 °C 10 min, 25 °C, 6 h). [c] Using stoichiometric CuCN•2LiCl (–40 °C to –10 °C, 24 h). [d] Using PEPPSI *i*Pr (1 mol%, 25 °C, 12 h to 24 h) [e] BF_3•OEt_2, 25 °C, 4 h.

5.4 Scope of the Reaction in the Allylic Position

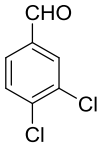
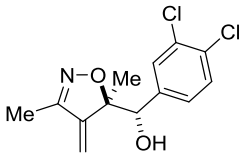
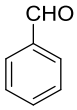
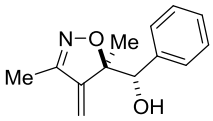
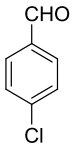
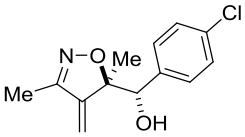
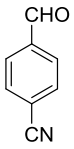
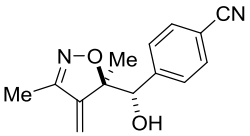
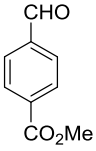
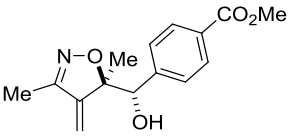
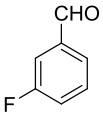
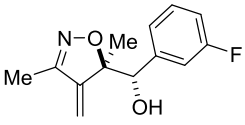
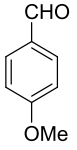
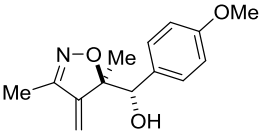
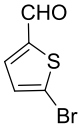
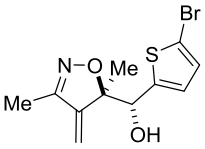
The Lewis acid-accelerated reaction of the heterobenzylic organometallic reagent **63** was performed with various aromatic aldehydes **65b**-**h**, affording a range of stereocontrolled products of type **66** (Table 11). As optimised conditions for these addition reactions, $LaCl_3 \cdot 2LiCl$ (2 equiv., –60 °C to 25 °C, 24 h)[122] or $MgCl_2$ (2 equiv., 25 °C, 4 h) was used. Reaction of **63** with benzaldehyde (**65b**) provided the 4-methylene isoxazoline derivative **66b** in a diastereomeric ratio of 95:5 (Table 11, entry 2). When electron-deficient aromatic aldehydes, such as *p*-chlorobenzaldehyde (**65c**), *p*-formylbenzonitrile (**65d**), methyl *p*-formylbenzoate (**65e**) or *m*-fluorobenzaldehyde (**65f**) were added to zinc reagent **63**, the corresponding alcohols **66d-f** were obtained in 79-96% yield (dr = 93:7 to 96:4, entries 3-6). The reaction with electron-rich *p*-anisaldehyde **65g** provided the product **66g** with dr = 95:5 (entry 7). Electron-rich heteroaromatic 5-bromothiophene-2-carbaldehyde **65h** gave the alcohol **66h** in a diastereomeric ratio of 93:7 (92%, entry 8). Correlating the diastereomeric ratios with Hammett's substituent constants δ[123] showed that the electronic properties of aromatic aldehydes have no direct influence on the diastereoselectivity.[124] In all cases, the reaction occurs predominantly at the allylic and not at the benzylic position, forming a new carbon-carbon bond at C3, providing the dearomatized exo-methylene products **66a-h** (Table 11). It was further attempted to expand the scope of the reaction of zinc reagent **63** with aliphatic aldehydes (Table 11, enteies 9-12). The resulting products **66i-l** were obtained in modest yield (33-58%) and variable diastereoselectivity of 93:7 to 67:33 (entries 9-12, Table 11). Competing aldol-condensation reactions could explain the lower yields. In comparison to aromatic aldehydes, the diastereoselectivities were more variable and higher dr values were only obtained with α-branched aldehydes (**65k** and **65l**).

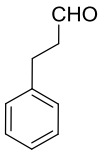
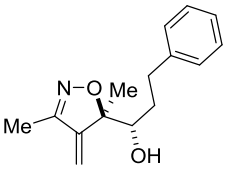
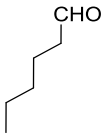
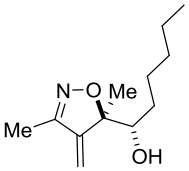
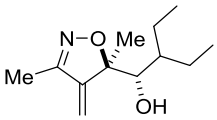
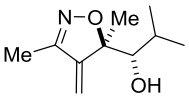
[122] The reaction with $LaCl_3$ was optimized by Dr. Coura Diene (Ludwig-Maximilians-Universtät München).
[123] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*,165.
[124] For further details see experimental part 7.15.13.

Table 11. 4-Methylene Isoxazoline Derivatives of Type **66** Obtained by the Addition of Zinc Reagent **63** to Aldehydes **65a-l**.



63 **66a-l**

Entry	Aldehyde	Products	Yield/Diastereoselectivity (%/dr)
1	 **65a**	 **66a**	92[a]/96:4; 73[b]/94:6
2	 **65b**	 **66b**	91[a]/95:5; 67[b]/95:5
3	 **65c**	 **66c**	92[a]/96:4; 81[b]/95:5
4	 **65d**	 **66d**	96[a]/94:6 82[b]/94:6
5	 **65e**	 **66e**	94[a]/ 95:5 79[b]/93:7
6	 **65f**	 **66f**	87[a]/ 95:5
7	 **65g**	 **66g**	86[a]/ 95:5 84[b]/ 95:5
8	 **65h**	 **66h**	92[a]/93:7

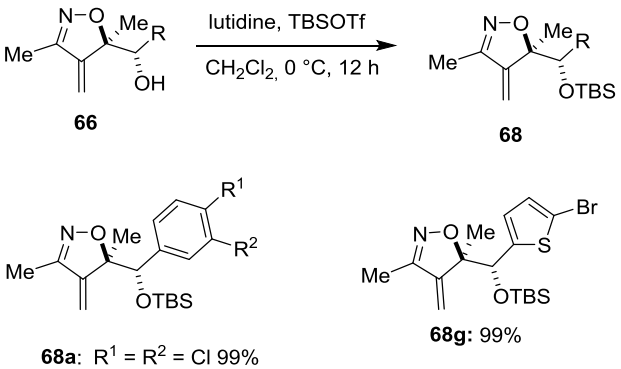
Entry	Aldehyde	Products	Yield/Diastereoselectivity (%/dr)
9	 **65i**	 **66i**	58[b]/ 61:39
10	 **65j**	 **66j**	41[b]/ 67:33
11	 **65k**	 **66k**	33[b]/ 93:7
12	 **65l**	 **66l**	38[b]/ 79:21

[a] $LaCl_3 \cdot 2LiCl$ (2.0 equiv., -60 °C to 25 °C, 24 h), [b] $MgCl_2$ (2.0 equiv., 25 °C, 4 h-6 h).

5.5 Transformation of the Isoxazolines

5.5.1 Transformation to the Homoallyl Alcohols

The 4-methylene isoxazoline derivatives (**66a-e, 66g-h**) were protected as TBS-ethers by the treatment with TBSOTf (2.2 equiv., 0 °C to 25 °C) in 2,6-lutidine (2.5 equiv., 0 °C, CH_2Cl_2), to obtain the isoxazolines **68a-g** in 72% to 99% yield (Scheme 26). The desired Baylis-Hillman products bearing a *β*-quaternary center and a *γ*-hydroxyl function of type **69a-g** are obtained by a reductive cleavage of the N-O bond of isoxazolines **68a-g**. Such reductions of N-O bonds are commonly performed using catalytic hydrogenations,[125] reactions with transition metals in a low oxidation state,[126] reducing metals,[127] or other reductive conditions.[128]

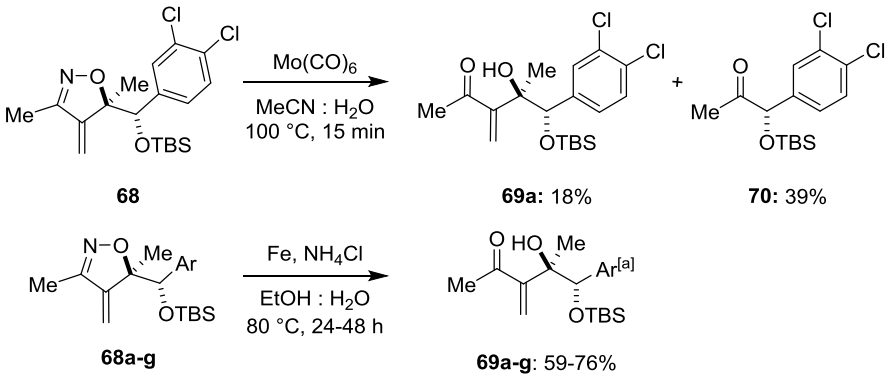


Scheme 26. TBS protection of 4-methylene isoxazoline derivatives.

All attempts for N-O bond cleavage by catalytic hydrogenation were unsuccessful due to a competing reduction of the conjugated olefin. Reduction of the TBS-protected isoxazoline of type **68** with $Mo(CO)_6$ (1-2 h, 80 °C) in acetonitrile:H_2O (10:1)[126c] provided the

[125] (a) D. P. Curran, *J. Am. Chem. Soc.* **1982**, *104*, 4024. (b) D. P. Curran, *J. Am. Chem. Soc.* **1983**, *105*, 5826. (c) K. B. G. Trossell, *Tetrahedron* **1985**, *41*, 5569.
[126] (a) M. Nitta, T. Kobayashi, *J. Chem. Soc. Chem. Commun.* **1982**, 877; (b) N. B. Das, K. B. G. Trossell, *Tetrahedron*, **1983**, *39*, 2247. (c) P. B. Baraldi, A. Barco, S. Benetti, S. Manfredini, D. Simoni, *Synthesis* **1987**, 276. (d) J. W. Bode, E. M. Carreira, *Org. Lett* **2001**, *3*, 1587. (e) J. W. Bode, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 3611. *1949.* (f) Bode, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 3611. (g) D. H. Churykau, V. G. Zinovich, O. G. Kulinkovich *Synlett* **2004**, 11, 1949.
[127] (a) D. Jiang, Y. Chen, *J. Org. Chem.* **2008**, *73*, 9181. (b) I. Karpaviciene, R. Lapinskaite, A. Brukstus, I. Cikotiene, *Synlett*, **2012**, *23*, *381*.
[128] (a) H. Lund, *Acta Chem. Scand.* **1959**, *13*, 249 (b) I. Surov, H. Lund, *Acta Chem Scand.* **1986**, *40*, 831 (c) V. F. Caetono, F. W. J. Demnitz, F. B. Diniz, R. M. Mariz, M. Navorro, *Tetrahedron Lett.* **2003**, *44*, 8217.

corresponding *β*-hydroxy-carbonyl derivatives of type **69** in low yields, since a competing retroaldol reaction occurred, leading to the formation of ketone **70** (Scheme 27).

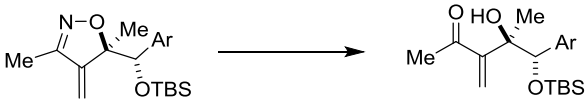


Scheme 27. Reductive N-O bond cleavage of TBS-protected isoxazoline **68a-g** with $Mo(CO)_6$ or Fe and NH_4Cl providing racemic *β*-hydroxy carbonyls **69a-g**. [a] For Ar see Table 12.

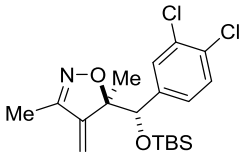
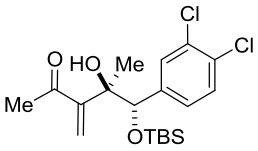
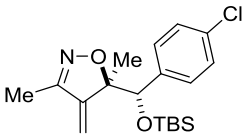
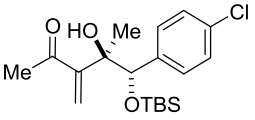
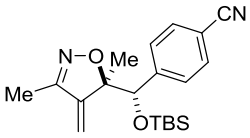
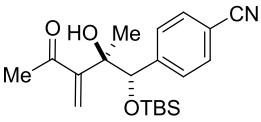
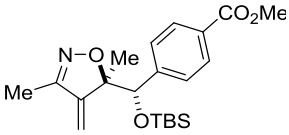
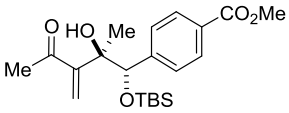
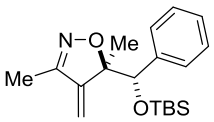
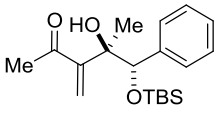
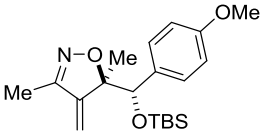
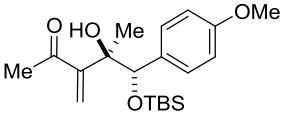
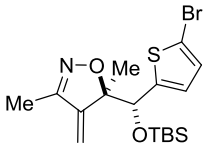
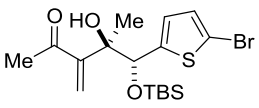
Recently, the reduction of isoxazolines to conjugated *β*-hydroxy-carbonyls was performed with iron and ammonium chloride in the presence of water.[129] Following this protocol, full conversion to the desired *β*-hydroxyl ketones could be achieved (Scheme 27). Thus, when isoxazolines **68a-g** were heated to reflux with a suspension of Fe (5 equiv.), NH_4Cl (5 equiv.) in EtOH:H_2O (1:1) for 12 h-48 h, *β*-hydroxyl carbonyls **69a-g** were obtained in 59-76% yield (Table 12). These products are analogous to those obtained by the Baylis-Hillman reaction.[130]

[129] (a) D. Jiang, Y. Chen, *J. Org. Chem.* **2008**, *73*, 9181. (b) B. Han, X.-L. Yang, R. Fang, W. Yu, C. Wang, X.Y. Duan, S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 8816.
[130] (a) A. B. Baylis, M. E. D. Hillman Acrylic compounds. De215113, **1972**, 16. (b) D. Basavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev.* **2010**, *110*, 5447.

Table 12: Products Obtained by Reductive N-O bond Cleavage of 4-Methyleneisoxazoline Derivatives



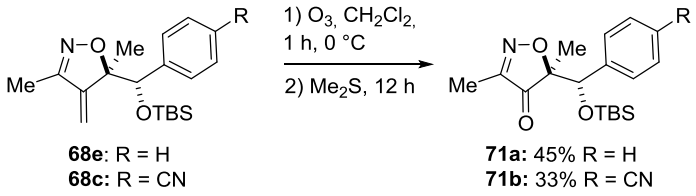
68a-g **69a-g**

Entry	Substrate	Product	Yield[a]
1	 **68a**	 **69a**	60[b], 18[c]
2	 **68b**	 **69b**	76[b]
3	 **68c**	 **69c**	75[b]
4	 **68d**	 **69d**	71[b]
5	 **68e**	 **69e**	68[b]
6	 **68f**	 **69f**	59[b]
7	 **68g**	 **69g**	69[b], 28[c]

[a] Analyticalylly pure product. [b] Fe, NH_4Cl, $EtOH/H_2O$ (80 °C, 12 h-48 h) [c] $Mo(CO)_6$, $MeCN/H_2O$ (80 °C, 1-2 h).

5.5.2 Transformation of Isoxazolines by Ozonolysis

The obtained isoxazole can be easily converted to the ketone by ozonolysis.



68e: R = H
68c: R = CN

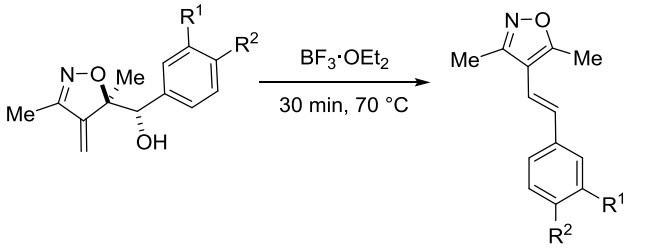
71a: 45% R = H
71b: 33% R = CN

Scheme 28: Ozonolysis of isoxazoles **68e** and **68c**, to the corresponding ketones **71a** and **71b**.

Ozonolysis of the obtained products **68e** and **68c** was performed under standard conditions in dichloromethane at 0 °C. Products **71a-b** were obtained in moderate yields of 33-45% after purification (Scheme 28).

5.5.3 Transformation of Isoxazolines by Acid Mediated Rearrangement

When the isoxazoles **66c** and **66f** were heated in the presence of $BF_3 \cdot OEt_2$ or H_2SO_4, the stereochemistry was lost forming the rearrangement product **72a-b** in moderate yield (Scheme 29).



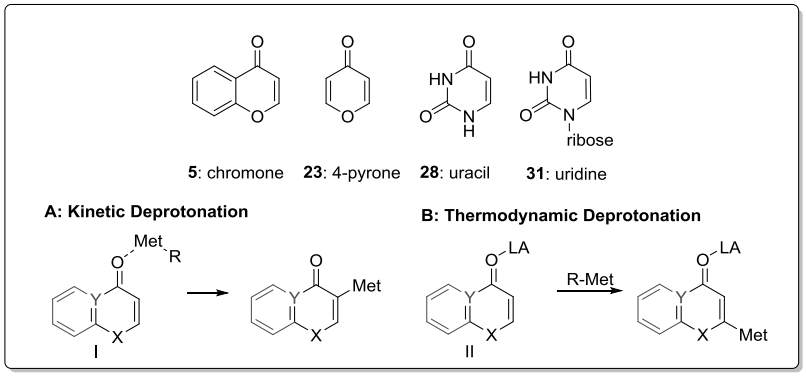
66f: R^1 = F, R^2 = H
66c: R^1 = H, R^2 = Cl

72a: 62% R^1 = F, R^2 = H
72b: 52% R^1 = H, R^2 = Cl

Scheme 29: Acid mediated rearrangement of isoxazoline **66f** and **66c**.

6 Summary

6.1 Lewis Acid Triggered Selective Metallation of Chromone, 4-Pyrone, Uracil and Uridine



Scheme 30: Concept for the regioselective metallation of chromone, 4-pyrone, uracil and uridine.

In summary a method was developed for the regioselective metallation of chromone (**5**), 4-pyrone (**23**), uracil (**28**) and uridine (**31**), by thermodynamic or kinetic deprotonation (Scheme 30). Theoretical calculations showed that the thermodynamically most acidic hydrogen of these molecules is attached to C(2), however the most basic heteroatom of these heterocycles is the carbonyl oxygen. It was considered that the C(4) carbonyl functions as a directing metallation group (DMG-group).[35] Coordination of the metal base (TMPZnCl·LiCl or TMPMgCl·LiCl) leads to the formation of complex **I** after metallation, the kinetic product is obtained (A, Scheme 30). In the presence of a stronger Lewis acid than the metallating base, complexation of this Lewis acid will preferentially occur with the carbonyl group (**II**). In this case, the thermodynamic C(2)-metallated heterocycle is obtained after deprotonation (B, Scheme 30). Trapping of the metallated species with various electrophiles easily allows the functionalization of the corresponding heterocycles. With this new concept, a range of C(3) and C(2) substituted chromones, pyrones, and C(5) and C(6) substituted uracils and uridines were prepared (Figure 16).

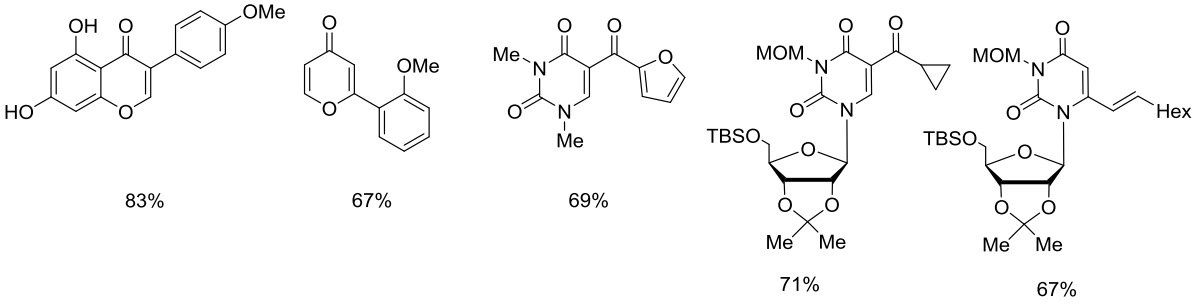
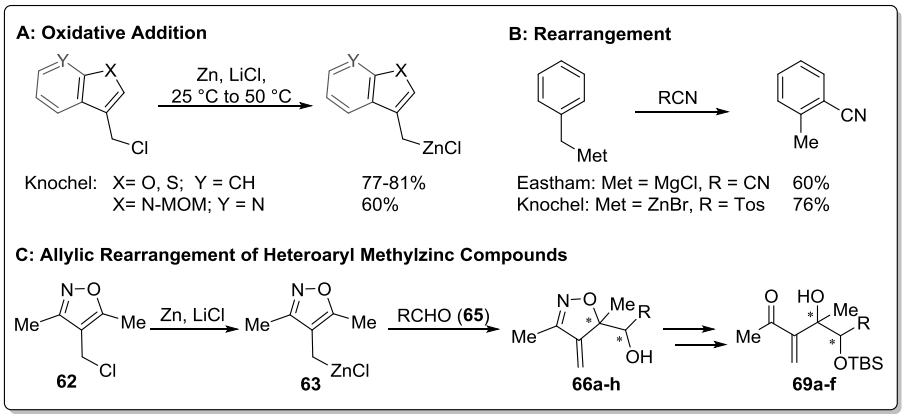


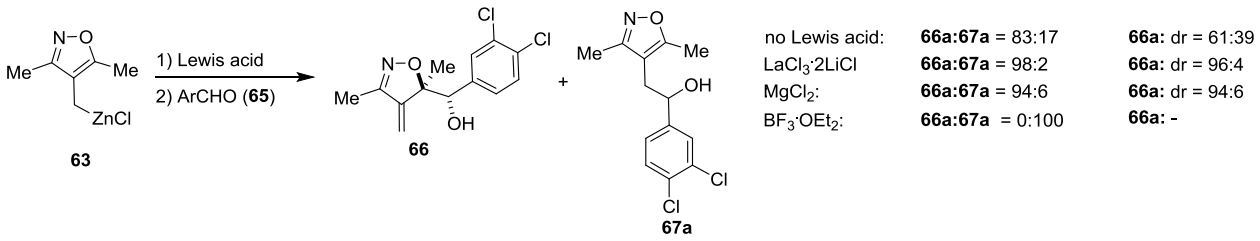
Figure 16: Regioselective functionalization of chromone (**5**), 4-pyrone (**23**), uracil (**34**) and uridine (**40**).

6.2 Influence of Lewis Acids on the Regio- and Diastereoselectivity of Isoxazole Methylzinc Compounds with Aldehydes



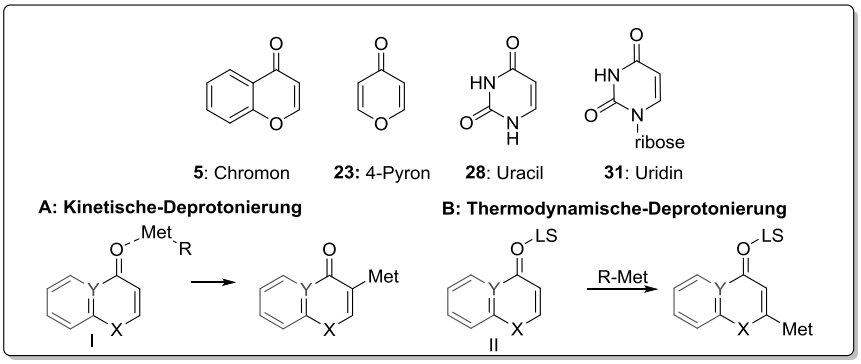
Scheme 31: Concept of allylic rearrangement of heteroaryl methylzinc compounds.

Based on recent results for the easy accessibility of heteroaryl methylzinc (A, Scheme 31) and the allylic reactivity of benzylic zinc reagents (B, Scheme 31), a method was developed for the allylic rearrangement of isoxazolemethyl zinc compounds (C, Scheme 31), subsequent ring opening of the obtained isoxazolines provided *β*-hydroxy carbonyls. In the absence of additional Lewis acid, the zinc reagent (**63**) reacted predominantly *via* an allylic rearrangement providing the dearomatized exo-methylene product (**66a**) in a diastereomeric ratio (dr) of 61:39. Since Lewis acids are known to activate aldehydes by complexation, the influence of Lewis acids was examined (Scheme 32). This study showed that the addition of Lewis acids influences both regioselectivity and diastereoselectivity, and therefore, a change in the reaction mechanism is postulated. The formation of allylic addition product **66a** increased when $LaCl_3 \cdot 2LiCl$ or $MgCl_2$ were added. Both improvements in the regioselectivity and diastereoselectivity were rationalized by a six-membered chair-like Zimmerman-Traxler transition state. The reaction proceeded exclusively at the benzylic position when $BF_3 \cdot OEt_2$ was added. The Lewis-acid-accelerated reaction of the heterobenzylic organometallic reagent **63** was performed with various aromatic aldehydes affording a range of stereocontrolled products **66a-h** in excellent yields (67-92%) and diastereoselectivities (dr = 96:4 to 93:7). The resulting isoxazolines provide, after reductive ring opening, *β*-hydroxy carbonyls of type **69a-f** in moderate yields (60-76%).



Scheme 32: Influence of Lewis acid on the regio- and diastereoselectivity of the reaction from isoxazole methylzinc compounds with aldehydes.

6.3 Einfluss von Lewissäuren auf die Regioselektive Metallierung von Chromon, 4-Pyron, Uracil und Uridin



Schema 33: Metallierungskonzept für die regioselektive Metallierung von Chromon, 4-Pyron, Uracil und Uridin.

Es wurde eine Methode zur regioselektiven Metallierung von Chromon (**5**), 4-Pyron (**23**), Uracil (**28**) und Uridin (**31**) in den Positionen C(2) oder C(3) entwickelt (Schema 33). Theoretischen Rechnungen zufolge, befindet sich bei den genannten Systemen das thermodynamisch acideste Proton in Position C(2), während das Heteroatom mit der höchsten Basizität der Sauerstoff der Carbonylgruppe ist. Es wurde postuliert, dass die Carbonylgruppe in C(4) als dirigierende Gruppe (DMG)[35] fungiert und die stärkste Lewissäure (LS) in Lösung komplexiert. Die Koordination der Carbonylgruppe an die Metallbase (TMPZnCl·LiCl oder TMPMgCl·LiCl) führt zur Bildung eines Komplexes I, wodurch das kinetische Produkt erhalten wird (A, Schema 33). In Gegenwart einer stärkeren Lewissäure ($MgCl_2$) als die metallierende Base (TMPZnCl·LiCl), wird die Bildung eines Komplexes II vermutet, und das erwartete thermodynamische Metallierungsprodukt erhalten (B, Schema 33). Die Anwendung des Konzeptes auf diverse Heterozyklen ermöglicht eine selektive Metallierung in den Positionen C(2) bzw. C(3). Die Reaktion der metallierten Verbindung mit verschiedenen Elektrophilen ermöglicht eine vielseitige Funktionalisierung der Heterozyklen (Abbildung 17).

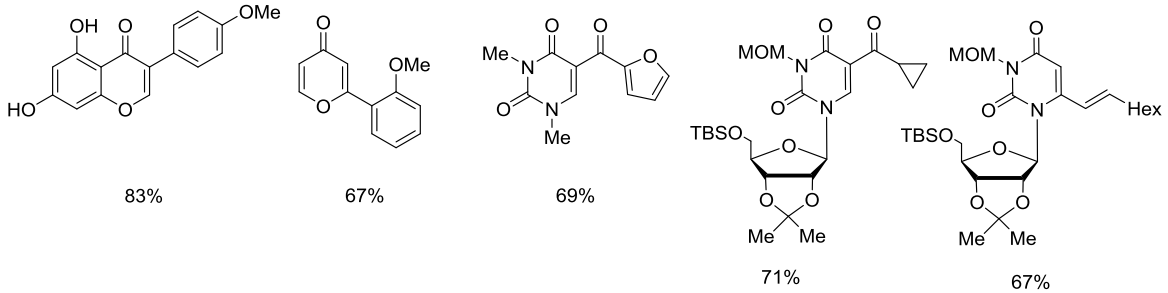
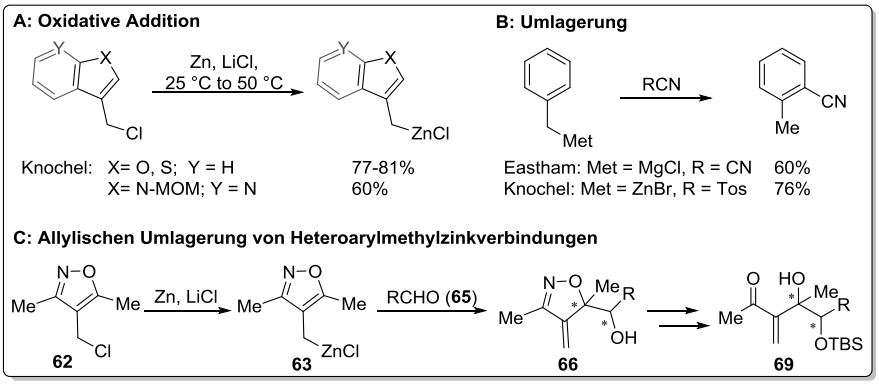


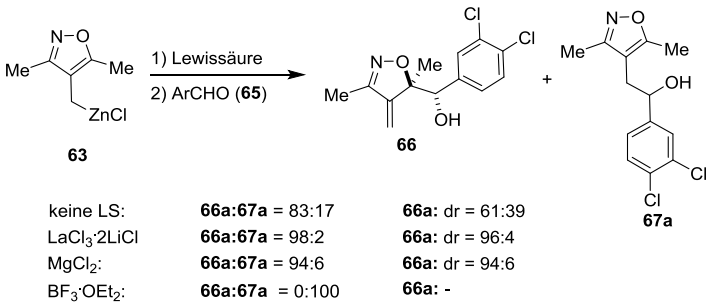
Abbildung 17: Regioselektive Funktionalisierung von Chromon (**5**), 4-Pyron (**23**), Uracil (**34**) and Uridin (**40**).

6.4 Einfluss von Lewissäuren auf die Regio- and Diastereoselektivität von Isoxazolmethylzink Verbindungen



Schema 34: Konzept der Allylischen Umlagerung von Heteroarylmethylzinkverbindungen.

Basierend auf der Synthesemethode zur Darstellung von Heteroaryl-methylzinkverbindungen (A, Schema 34),[111c] und der allylischen Umlagerungen von benzylischen Organometallverbindungen (B, Schema 34),[110] wurde die allylische Addition der Isoxazolmethylzink Verbindung **63** mit Carbonylverbindungen (**65**) untersucht, da die erhaltenen Isoxazoline (**66**) durch Ringöffnung in *β*-Hydroxycarbonyle (**69**) überführt werden können (C, Schema 34). Die Reaktion der Zinkverbindung **63** mit 3,4-Dichlorbenzaldehyd (**65a**) führte zur Bildung der Produkte **66a** und **67a** in einem Regioisomerenverhältnis von 83:17 (Schema 35). Somit verläuft die Reaktion vorwiegend über eine allylische Umlagerung unter Bildung des dearomatisierten *exo*-Methylen-Produkts (**66a**) in einem Diastereomerenverhältnis (dr) von 61:39. Aldehyde werden durch Kompexierung mit Lewissäuren aktiviert, deshalb wurde der Einfluss verschiedener Lewissäuren auf die Reaktion untersucht (Schema 35). In Gegenwart der Lewissäuren $LaCl_3 \cdot 2LiCl$ (2 Äquiv.) oder $MgCl_2$ (2 Äquiv.) wird sowohl die Bildung des allylischen Additionsproduktes (**66a**) verstärkt als auch die Diastereoselektivität verbessert. Diese Verbesserung der Regio- und Diastereoselektivität wird durch das Auflösen von Aggregaten und der dadurch erleichterten Bildung eines sechsgliedrigen Zimmerman-Traxler Übergangszustandes erklärt. In Gegenwart der Lewissäure $BF_3 \cdot OEt_2$ (2 Äquiv.) wird nur das benzylische Produkt (**67a**) erhalten. Wir vermuten, dass die Koordination von $BF_3 \cdot OEt_2$ an den Aldehyd die Bildung eines zyklischen Übergangszustandes verhindert, und somit die Regioselektivität der Reaktion beeinflusst. Die durch Lewissäure beschleunigte Reaktion der heterobenzylischen organometallischen Verbindung (**63**) wurde an einer Vielzahl von Aldehyden untersucht. Die erhaltenen Isoxazoline wurden durch reduktive Ringöffnung in *β*-Hydroxycarbonyle überführt.



Scheme 35: Einfluss von Lewissäuren auf die Regio- und Diastereoselektivität von benzylischen Umlagerungen.

7 Experimental Procedures and Analytical Data

7.1 General

All reactions are carried out under argon atmosphere in flame-dried glassware. Syringes which are used to transfer anhydrous solvents or reagents are purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be pure as determined by ^{1}H-NMR (25 °C) and capillary GC. The products are prepared corresponding to known literature procedures. The analytical data for known compounds match the literature data. The stereochemistry of new compounds was determined by 2D-NMR experiments (COESY, HSQC, HMBC).

7.2 Solvents

Solvents were dried according to standard procedures by distillation over drying agents and stored under argon.

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

DMF was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

EtOH was treated with phthalic anhydride (25 g/L) and sodium, heated to reflux for 6 h and distilled.

Pyridine was dried over KOH and distilled.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

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

NEt_3 was dried over KOH and distilled.

Solvents for column chromatography were distilled on a rotary evaporator prior to use.

7.3 Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. TMP-H, liquid aldehydes and acid chlorides are distilled prior to use.

***i*-PrMgCl·LiCl** solution in THF was purchased from Rockwood Lithium.

***n*-BuLi** solution in hexane was purchased from Rockwood Lithium.
$LaCl_3$·2LiCl solution in THF was purchased from Rockwood Lithium.

7.3.1 Preparation of the Reagent TMPMgCl·LiCl (1)

A dry and nitrogen-flushed 500 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with *i*PrMgCl·LiCl (1.31 M in THF, 229 mL, 300 mmol). Then, TMP-H (52 mL, 306 mmol, 1.02 equiv.) was added and the mixture was stirred until gas evolution ceases (48 h). The solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

7.3.2 Preparation of the Reagent TMPZnCl·LiCl (3)

A dry and argon flushed 250 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum was charged with freshly distilled TMP-H (10.2 mL, 60 mmol) dissolved in THF (60 mL). This solution was cooled to −40 °C and *n*-BuLi (2.4 M in hexane, 25 mL, 60 mmol) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm slowly to –10 °C for 1 h. $ZnCl_2$ (1.0 M in THF, 66 mL, 66 mmol) was dropwise added and the resulting solution was stirred for 30 min at –10 °C, then for further 30 min at 25 °C. The solvents are removed under vacuum affording a yellowish solid. Freshly distilled THF was slowly added under vigorous stirring until the salts are completely dissolved. The freshly prepared TMPZnCl·LiCl solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

7.3.3 Preparation of the Reagent $TMP_2Zn·2MgCl_2·2LiCl$ (4)

A flame-dried and nitrogen-flushed 500 mL *Schlenk*-flask, equipped with a magnetic stirring bar and rubber septum, was charged with a solution of TMPMgCl·LiCl (348 mL, 400 mmol) and cooled to 0 °C. Then, $ZnCl_2$ (1.0 M in THF, 200 mL, 200 mmol, 0.5 equiv.) was added over a period of 15 min. After stirring this mixture for 12 h at 25 °C, $TMP_2Zn·2MgCl_2·2LiCl$ was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

7.3.4 Preparation of CuCN·2LiCl solution

A 250 mL *Schlenk*-flask, equipped with a magnetic stirring bar and rubber septum, was charged with CuCN (80.0 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g). The mixture is heated under vacuum at 140 °C for 5 h. After cooling to 25 °C, 80 mL dryTHF were added and stirring was continued until the salts were dissolved, providing a 1.0 M solution.

7.3.5 Preparation of ZnCl solution

A 250 mL *Schlenk*-flask, equipped with a magnetic stirring bar and rubber septum, was charged with $ZnCl_2$ (100 mmol, 136 g). The mixture is heated under vacuum at 140 °C for 5 h. After cooling to 25 °C, 100 mL dry THF were added and stirring was continued until the salt was dissolved, providing a 1.0 M solution.

7.4 Content determination of organometallic reagents

Organozinc and organomagnesium reagents were titrated with I_2 in a 0.5 M LiCl solution in dry THF at 0 °C. Color change from brown to colourles indicated the end of the titration.

Organolithium reagents were titrated with dry 2-propanol against 1,10-phenanthroline in THF. Color change from red to colourles indicated the end of the titration.

TMPMgCl·LiCl, TMPZnCl·LiCl, and **$TMP_2Zn·2MgCl_2·2LiCl$** was titrated against benzoic acid (122 mg, 1 mmol) using (4-phenylazo)diphenylamine (3 mg) as indicator in 1 mL dry THF at 0 °C. Color change from yellow to dark violet indicated the end of the titration.

7.5 Analytical Data

^{1}H-NMR and ^{13}C-NMR spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to tetramethylsilane. The following abbreviations were used to characterize signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) as well as br (broadened).

Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with

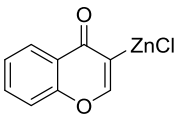
an ionization energy of 70 eV. For coupled gas chromatography / mass spectrometry, a HEWLETT-PACKARD HP 6890 /
MSD 5973 GC/MS system was used. Molecular fragments are reported starting at a relative intensity of 10%.

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 DuraSamplIR II Diamond ATR sensor was used. Wavenumbers are reported in cm-1 starting at an absorption of
10%.

Melting points (mp) were determined on a BÜCHI B-540 melting point apparatus and are uncorrected. Compounds decomposing upon melting are indicated by (decomp.).

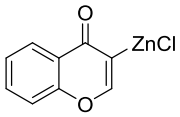
7.6 General procedures

7.6.1 TP 1a: Preparation of C(3) Zincated Chromone (6) on 50 mmol Scale



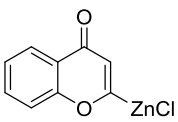
A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with chromone (**5**, 7.31 g, 50 mmol) in dry THF (50 mL). The base TMPZnCl·LiCl (**3**, 1.2 equiv.) was added dropwise at 0 °C over 30 min., through an addition funnel. The reaction mixture was warmed to 25 °C and stirred for additional 7 h. The completion of the metallation was checked by GC-analysis of reaction aliquots quenched with iodine indicating a regioselectivity of C(3):C(2) = 98:2 and 98% conversion.

7.6.2 TP 1b: Preparation of C(3) Zincated Chromone (6) on 2 mmol Scale



A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum is charged with chromone (**5**, 2.0 mmol) in dry THF (2 mL). The base TMPZnCl·LiCl (**3**, 1.2 equiv.) is added dropwise at 25 °C and the reaction mixture is stirred for the given time. The completion of the metallation is checked by GC-analysis of reaction aliquots quenched with iodine indicating a regioselectivity of C(3):C(2)=97:3 and full conversion. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture is quenched with sat. aq. NH_4Cl solution and extracted with EtOAc (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

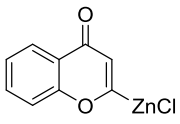
7.6.3 TP 2a: Preparation of C(2) Zincated Chromone (8) on 50 mmol Scale



A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with chromone (**5**, 7.31 g, 50 mmol) and dry $MgCl_2$ (0.4 M in THF, 250 mL) at 0 °C. The base TMPZnCl·LiCl (**3**, 1.2 equiv.) was added dropwise at −5 °C over 30 min., through an addition funnel. The reaction mixture was warmed to 0 °C and stirred for additional 2 h. The completion of the

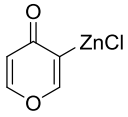
metallation was checked by GC-analysis of reaction aliquots quenched with iodine indicating a regioselectivity of C(2):C(3)=92:8 and full conversion.

7.6.4 TP 2b: Preparation of C(2) Zincated Chromone (8) on 2 mmol Scale



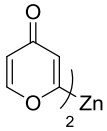
A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum is charged with chromone (**5**, 2.0 mmol) and dry $MgCl_2$ (0.4 M in THF). The base TMPZnCl·LiCl (**3**, 1.2 equiv.) is added dropwise at 0 °C and the reaction mixture is stirred for the given time. The completion of the metallation is checked by GC-analysis of reaction aliquots quenched with iodine indicating a regioselectivity of C(2):C(3)=97:3 and full conversion. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture is quenched with sat. aq. NH_4Cl solution and extracted with EtOAc (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

7.6.5 TP 3: Preparation of C(3) Zincated Pyran (24)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum is charged pyrone (**23**, 1 mL, 0.5 M in THF). The base TMPZnCl·LiCl (**3**, 1.2 equiv.) is added at 0 °C, and the reaction stirred for 2 h. The completion of the metallation was checked by TLC of reaction aliquots quenched with iodine. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture is quenched with sat. aq. NH_4Cl solution and extracted with EtOAc (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

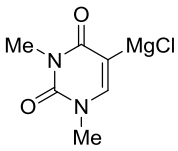
7.6.6 TP 4: Preparation of C(2) Zincated Pyran (26)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged pyrone (**23**, 1 mL, 0.5 M in THF). The base $TMP_2Zn·2LiCl·2MgCl_2$ (**4**, 0.6 equiv.) was added dropwise at −35 °C and the

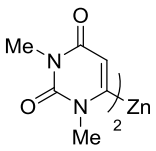
reaction mixture was stirred for 2 h. The completion of the metallation was checked by TLC of reaction aliquots quenched with iodine. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

7.6.7 TP5: Preparation of C(5)-Metallated 1,3-dimethyluracil (35) with TMPMgCl·LiCl (1)



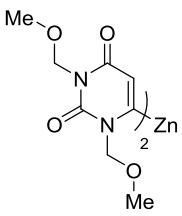
A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with 1,3-dimethyluracil (**34**, 280 mg, 2.0 mmol) in dry THF (2 mL). The base TMPMgCl·LiCl (**1**, 1.2 equiv.) was added dropwise at −40 °C and the reaction mixture was stirred for 4 h. The completion of the metallation is checked by GC-analysis of reaction aliquots quenched with iodine indicating a regioselectivity of C(5):C(6) = 95:5. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NaCl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

7.6.8 TP6: Preparation of C(6)-Metallated 1,3-dimethyluracil (37) with $TMP_2Zn·2LiCl·2MgCl_2$ (4)



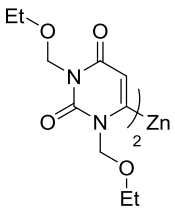
A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with 1,3-dimethyluracil (**34**, 280 mg, 2.0 mmol) in dry THF (2 mL). The base $TMP_2Zn·2LiCl·2MgCl_2$ (**4**, 0.6 equiv.) was added dropwise at −30 °C and the reaction mixture was stirred for 2 days. The completion of the metallation is checked by GC-analysis of reaction aliquots quenched with iodine indicating a regioselectivity of C(5):C(6) = 4:96. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

7.6.9 TP7: Preparation of C(6)-Metallated 1,3-dimethoxymethyluracil (44) with $TMP_2Zn·2LiCl·2MgCl_2$ (4)



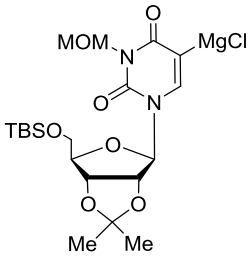
A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with 1,3-dimethoxymethyluracil (**40**, 529 mg, 2.0 mmol) in dry THF (2 mL). The base $TMP_2Zn·2LiCl·2MgCl_2$ (4, 0.6 equiv.) was added dropwise at −30 °C and the reaction mixture was stirred for 48 h. The completion of the metallation was checked by GC-analysis of reaction aliquots quenched with iodine, indicating a regioselectivity of C(5):C(6) = 0:100. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

7.6.10 TP8: Preparation of C(6)-Metallated 1,3-diethylmethyluracil (45) with $TMP_2Zn·2LiCl·2MgCl_2$ (4)



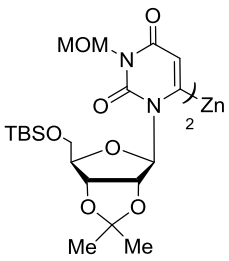
A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with 1,3-dieethoxymthylmethyluracil (**41**, 585 mg, 2.0 mmol) in dry THF (2 mL). The base $TMP_2Zn·2LiCl·2MgCl_2$ (4, 0.6 equiv.) was added dropwise at −30 °C and the reaction mixture was stirred for 48 h. The completion of the metallation was checked by GC-analysis of reaction aliquots quenched with iodine, indicating a regioselectivity of C(5):C(6) = 0:100. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

7.6.11 TP9: Preparation of C(5)-Metallated Protected Uridine (48) with TMPMgCl·LiCl (1)



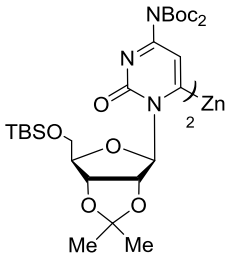
A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with protected uridine (**47**, 0.5 mL, 0.5 M in THF). The base TMPMgCl·LiCl (**1**, 1.2 equiv.) was added dropwise at −40 °C and the reaction mixture was stirred for 24 h. The completion of the metallation was checked by TLC of reaction aliquots quenched with iodine. A regioselectivity of C(5):C(6) = 2:98 was observed. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture was quenched sat. aq. NaCl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

7.6.12 TP10: Preparation of C(6)-Metallated Protected Uridine (60) with $TMP_2Zn·2LiCl·2MgCl_2$ (4):



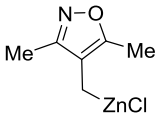
A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with protected uridine (**47**, 0.5 mL, 0.5 M in THF). The base $TMP_2Zn·2LiCl·2MgCl_2$ (**4**, 0.6 equiv.) was added dropwise at −30 °C and the reaction mixture was stirred for 2 days. The completion of the metallation was checked by TLC of reaction aliquots quenched with iodine. A regioselectivity of C(5):C(6) = 97:3 was observed. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) solution and extracted with EtOAc (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

7.6.13 TP11: Preparation of C(6)-Metallated Cytidine (58) with $TMP_2Zn·2LiCl·2MgCl_2$ (4):



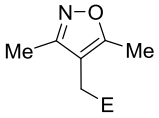
A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with protected cytidine (**57**, 0.5 M in THF). The base $TMP_2Zn·2LiCl·2MgCl_2$ (4, 0.6 equiv.) was added dropwise at −30 °C and the reaction mixture was stirred for 4 h. The completion of the metallation was checked by TLC of reaction aliquots quenched with iodine. Subsequent reactions with electrophiles are carried out under the indicated conditions. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

7.6.14 TP12: Preparation of ((3,5-Dimethylisoxazol-4-yl)methyl)zinc(II) Chloride (63)



In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, zinc dust (490 mg, 12.5 mmol, 1.2 equiv.) and LiCl (318 mg, 12.5 mmol, 1.2 equiv.) were dried under vacuum with a heat gun for 15 min. After cooling to room temperature, THF (10 mL) and 1,2-dibromoethane (5 drops) were added, and the reaction mixture was heated under reflux for 5 seconds. 5 drops of TMSCl were added to the suspension, and the reaction mixture was heated under reflux for 5 seconds. After cooling to room temperature, 4-(chloromethyl)-3,5-dimethylisoxazole (**62**, 713 mg, 10 mmol) was added dropwise and the resulting mixture was heated to 50 °C for 1 day. The solution was titrated at 0 °C prior to use with iodine, showing a yield of 80-85%. Larger scale reactions (30 mmol) provided higher concentrations of up to 90%.

7.6.15 TP12a-12d: Reaction of ((3,5-Dimethylisoxazol-4-yl)methyl)zinc(II) Chloride (63) in the Benzylic Position



TP12a:

The freshly prepared zinc reagent (**63**) was cooled to -40 °C, CuCN·2LiCl (1 M solution in THF) was added and the reaction mixture was stirred for 30 min. Allylation

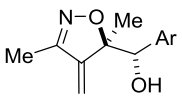
was achieved by adding allylbromide (1 equiv.) at −40 °C, stirring at −40 °C for 10 min and 6 h at 25 °C. Upon completion, the reaction was cooled down to −60 °C and quenched with methanol (1 equiv.). Aqueous NaCl was added, and the resulting mixture was extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

TP12b: The freshly prepared zinc reagent (**63**, 1 equiv.) was cooled to −40 °C, CuCN·2LiCl (1 M solution in THF,) was added and the reaction mixture was stirred for 30 min. Acylation was achieved by acid chloride (1 equiv.) at −40 °C, and warming up to −20 °C for 24 h. Upon completion the reaction was cooled down to −60 °C and quenched with methanol (1 equiv.). Aqueous NaCl was added and the resulting mixture was extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

TP12c: The freshly prepared zinc reagent (**63**, 1 equiv.) reacted in a *Negishi* cross-coupling reaction with aryl iodides (1 equiv.) in the presence of PEPPSI-*i*Pr (1 mol %) for 24 h at 25 °C. Upon completion, the reaction was cooled down to −60 °C and quenched with methanol (1 equiv.). Aqueous NaCl was added and the resulting mixture was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

TP12d: In a dry and Argon flushed Schlenk-flask, was added zinc reagent **63** (1 equiv.) and BF_3 (2 equiv., 50 % in Et_2O) at 25 °C. After stirring for 10 min, the aldehyde (1 equiv., 1 M in THF) was added. The reaction was stirred for 4 h. Upon completion the reaction was cooled to −60 °C and quenched with methanol (1 equiv.). Aqueous NaCl was added and the resulting mixture was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

7.6.16 TP 13a-b: Reaction of ((3,5-Dimethylisoxazol-4-yl)methyl)zinc(II) Chloride (63) in the Allylic Position

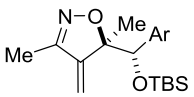


TP13a: In a dry and Argon flushed Schlenk-flask, was added zinc reagent **63** (1 equiv.) and $LaCl_3$·2LiCl (2 equiv., 0.5 M in THF) at -60 °C. After stirring for 10 min, the aldehyde (1.0, 1.5 or 2.0 equiv., 1 M in THF) was added. The reaction was stirred for 1 h at −60 °C, and slowly warmed to room temperature for 24 h. Upon completion, the reaction was cooled down to −60 °C and quenched with methanol (1 equiv.). Aqueous

NaCl was added and the resulting mixture was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

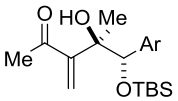
TP13b: In a dry and Argon flushed Schlenk-flask, *was* added zinc reagent **63** (1 equiv.) and $MgCl_2$ (2 equiv., 0.4 M in THF) at 25 °C. After stirring for 10 min, the aldehyde (1 equiv., 1 M in THF) was added. The reaction was stirred for 4 h. Upon completion, the reaction was cooled down to −60 °C and quenched with methanol (1 equiv.). Aqueous NaCl was added and the resulting mixture was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

7.6.17 TP 14: Preperation of TBS-Protected Isoxazolines 68



TP14: To a solution of alcohol **66** (1 equiv., 0.1 M CH_2Cl_2) was added dropwise 2,6-lutidine (2.5 equiv.) at 0 °C. TBSOTf (2.2 equiv.) was added, and the reaction mixture was slowly warmed to room temperature. Completion of the reaction was checked using TLC. Upon completion, the resulting mixture was cooled back to 0 °C and slowly quenched with aq. NH_4Cl. After warming to room temperature, the layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with sat. aq. NaCl, dried over $MgSO_4$ filtered and concentrated *in vacuo*.

7.6.18 TP15a-b: Reductive N-O Bond Cleavage of the Obtained Isoxazolines



TP15a: To a refluxing solution of isoxazoline **68** and NH_4Cl (10 equiv.) in ethanol:H_2O (1:1) was added Fe powder (10 equiv.) under nitrogen. The solution was heated to 80 °C for 1-3 days. Completion of the reaction was checked using TLC. If not noted differently, crude ^{1}H-NMR analysis confirmed full conversion of the reaction. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc and filtered through Celite®. The resulting solid was washed with CH_2Cl_2 and EtOAc

TP15b: Isoxazoline **68** (1 equiv.) and $Mo(CO)_6$ (2 equiv.) was dissolved in MeCN:H_2O (10:1) and heated at 80 °C, in a pressure vial. The reaction conversion was monitored by TLC. Upon compleation, the reaction was cooled to room temperature and filtered trough Celite® and the solids were washed with EtOAc:*i*-hexane (8:2). After filtration, the solvent was removed *in vacuo.*

7.7 Preparation of Chromone Derivatives 7b-d, 9a-c

7.7.1 NMR Experments

7.7.1.1 ^{1}H-NMR-Spectra of C(3) Zincated Chromone in THF at varying temperatures

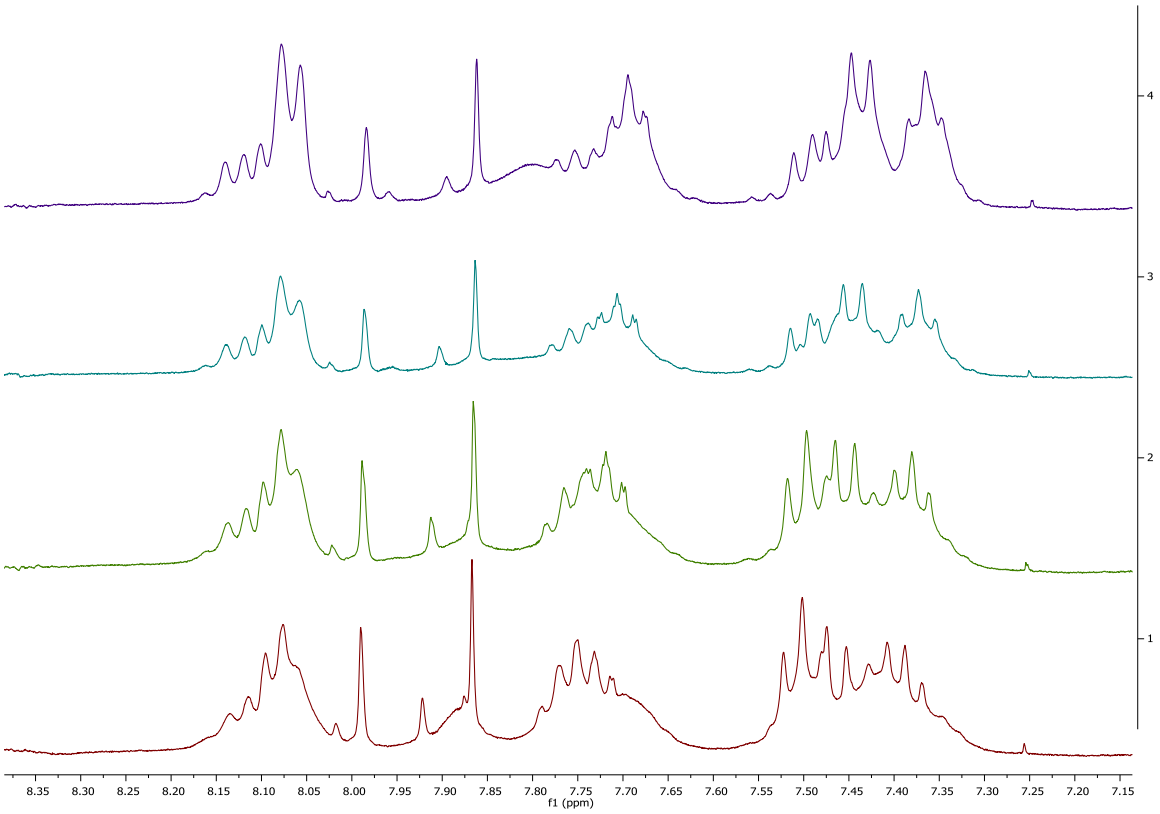
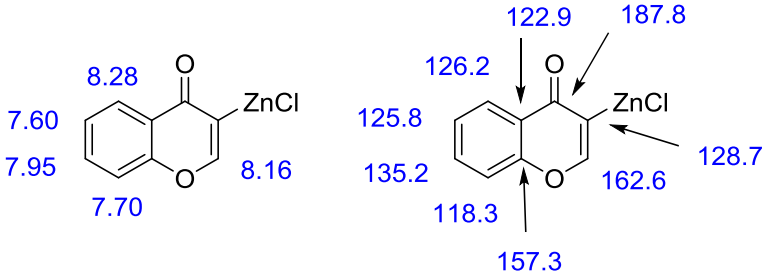


Figure 18: ^{1}H-NMR of crude reaction mixture of chromone (**5**) treated with TMPZnCl·LiCl (3, 1.2 equiv.), measured at varying temperatures (1) 25 °C, (2) 35 °C, (3) 45 °C (4) 55 °C.

7.7.1.2 NMR-Spectra of C(3) Zincated Chromone in THF after the addition of $ZnCl_2$

A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum is charged with chromone (**5**, 2.0 mmol) in dry THF-*d8* (2 mL). The base TMPZnCl·LiCl (**4**, 1.2 equiv. in THF-*d8*) is added dropwise at 25 °C and the reaction mixture is stirred for 30 min. Completion of the metalation is checked by GC-analysis of reaction aliquots quenched with iodine. After completion $ZnCl_2$ (1.0 M in THF-*d8*, 4 mL, 4 mmol) was added, and the solvent was partially



removed. The solution was cannulated into a dry and argon flushed NMR-tube. The C(3) zincated chromone was characterized by 1H, 13C, COSY, HSQC, and HSBC spectra which confirms its identity.

^{1}H NMR (400 MHz, THF-*d*8) δ = 8.28 (d, *J* = 7.04 Hz, 1H), 8.16 (s, 1H), 7.95 (t, *J* = 7.70, 1H), 7.70 (d, *J* = 8.79, 1H), 7.60 (t, *J* = 7.29 Hz, 1H).

^{13}C NMR (400 MHz, THF-*d*8) δ = 187.8, 162.6, 157.3, 135.2, 128.7, 126.2, 125.8, 122.9, 118.3.

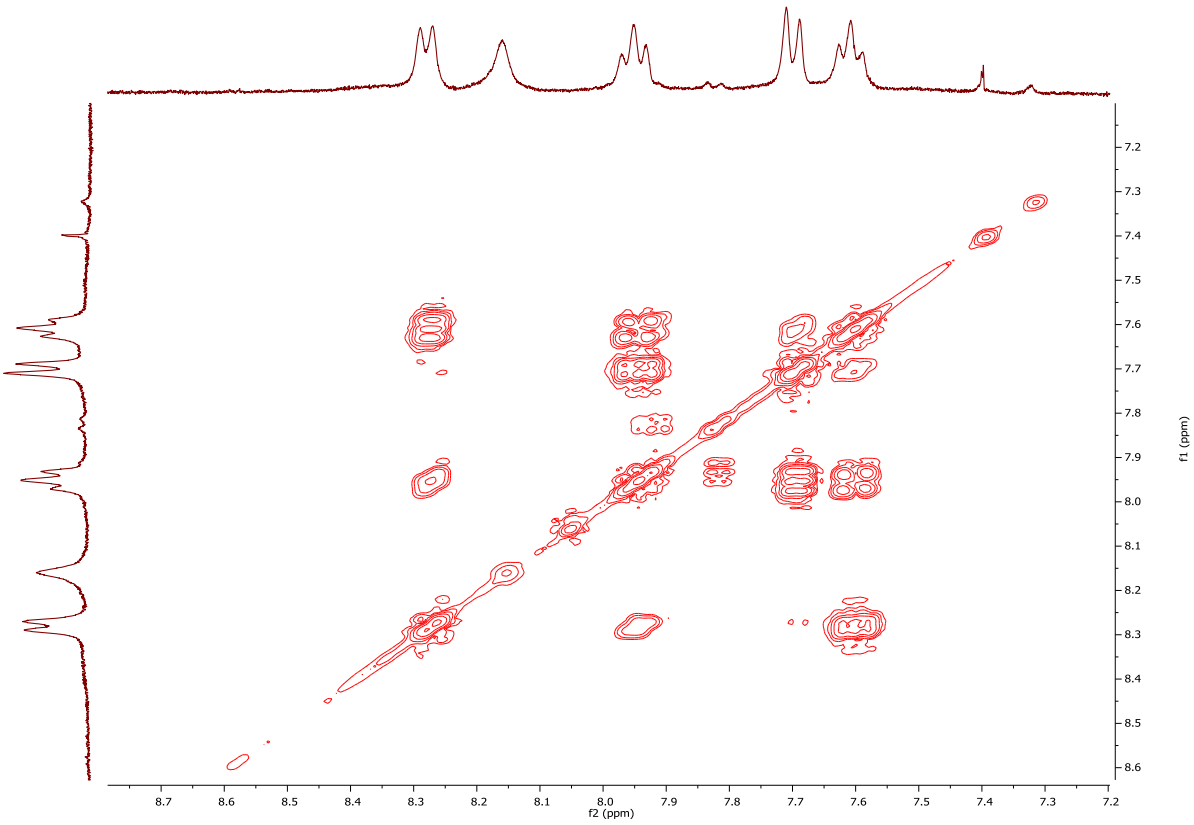


Figure 19: The COSY NMR of C(3) zicated Chromone in THF, after the addition of $ZnCl_2$ (2 equiv.)

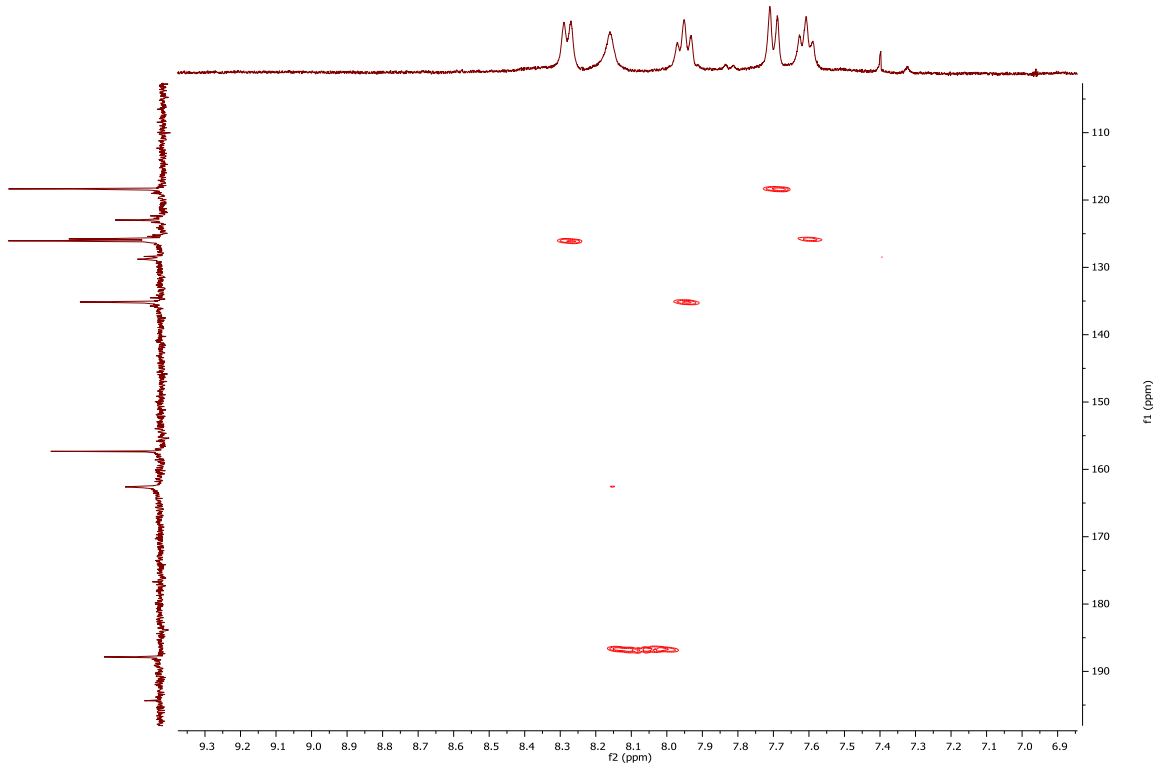


Figure 20: The HSQC-NMR of C(3) zicated Chromone in THF, after the addition of $ZnCl_2$ (2 equiv.)

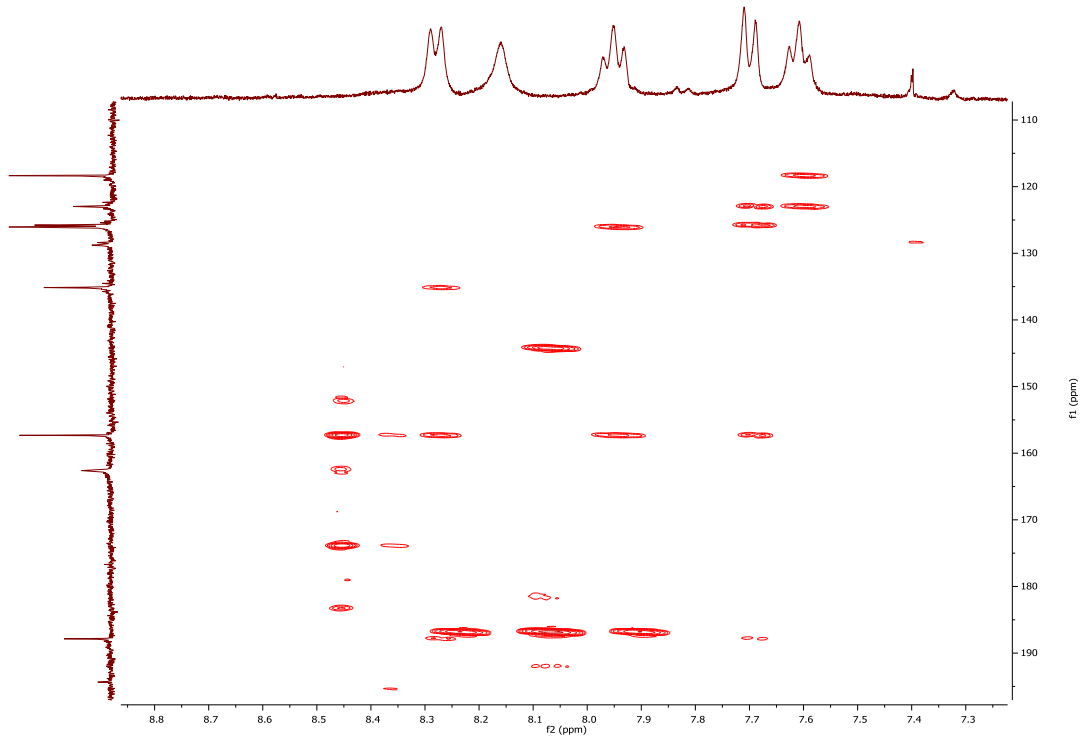
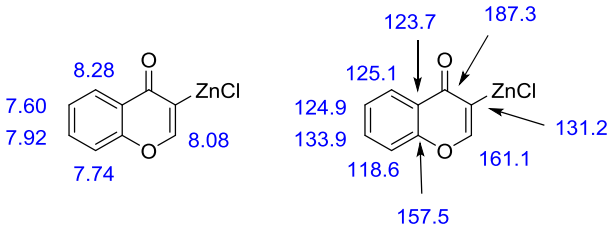


Figure 21: The HMBC-NMR of C(3) zicated Chromone in THF, after the addition of $ZnCl_2$ (2 equiv.)

7.7.1.3 NMR-Spectra C(3) Zincated Chromone in Dioxane



A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum is charged with chromone (**5**, 2.0 mmol) in dry THF (2 mL). The base TMPZnCl·LiCl (**4**; 1.2 equiv. in THF) is added dropwise at 25 °C and the reaction mixture is stirred for 30 min. Completion of the metalation is checked by GC-analysis of reaction aliquots quenched with iodine. After completion the solvent is removed and the crude residue is redesolved in dioxane. The solution was cannulated into a dry and argon flushed NMR-tube. The C(3) zincated chromone was characterized by ^{1}H, ^{13}C, COSY, HSQC, and HSBC spectra which confirms its identity.

^{1}H NMR (400 MHz, Dioxane) δ = 8.28 (d, J = 7.70 Hz, 1H), 8.08 (s, 1H), 7.92 (t, J = 7.48 Hz, 1 H), 7.74 (d, J = 8.57, 1H), 7.60 (t, J = 7.55 Hz, 1H).

^{13}C NMR (400 MHz, Dioxane) δ = 187.3, 161.1, 157.5, 133.9, 131.2, 125.1, 124.9 123.7, 118.6.

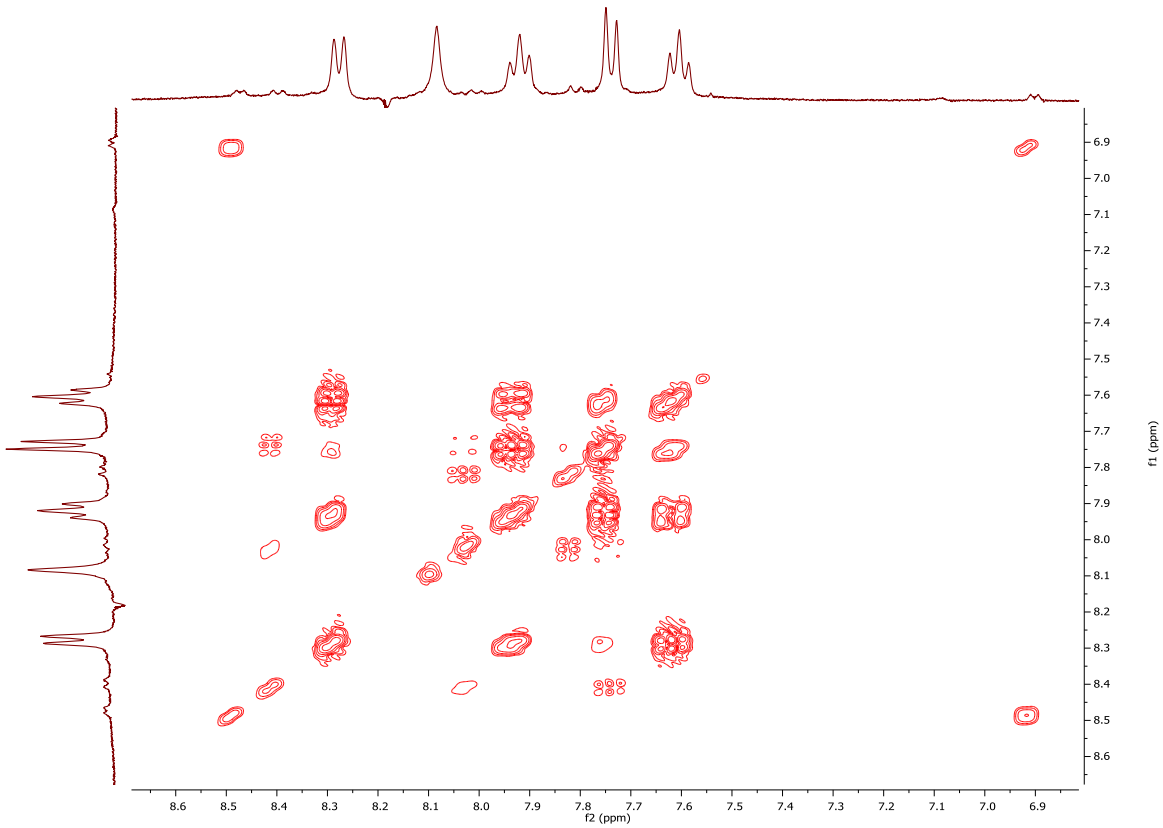


Figure 22: The COSY-NMR of C(3) zicated Chromone in Dioxane

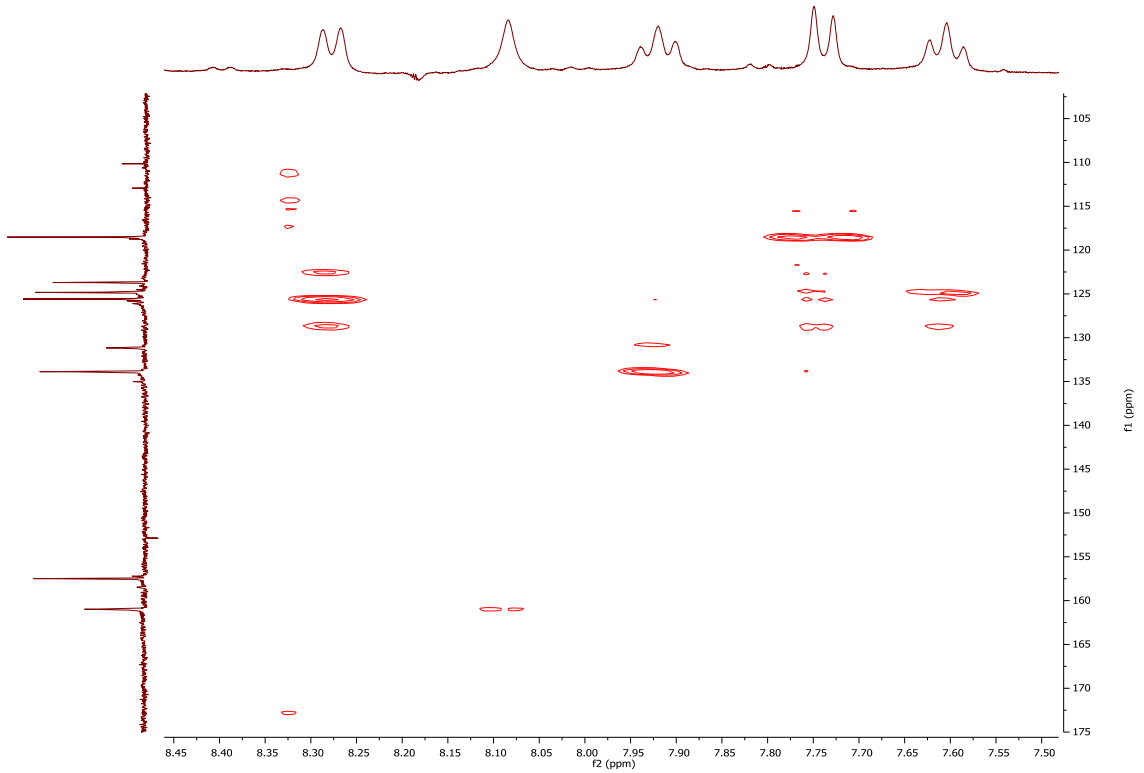


Figure 23: The HSQC-NMR of C(3) zicated Chromone in Dioxane

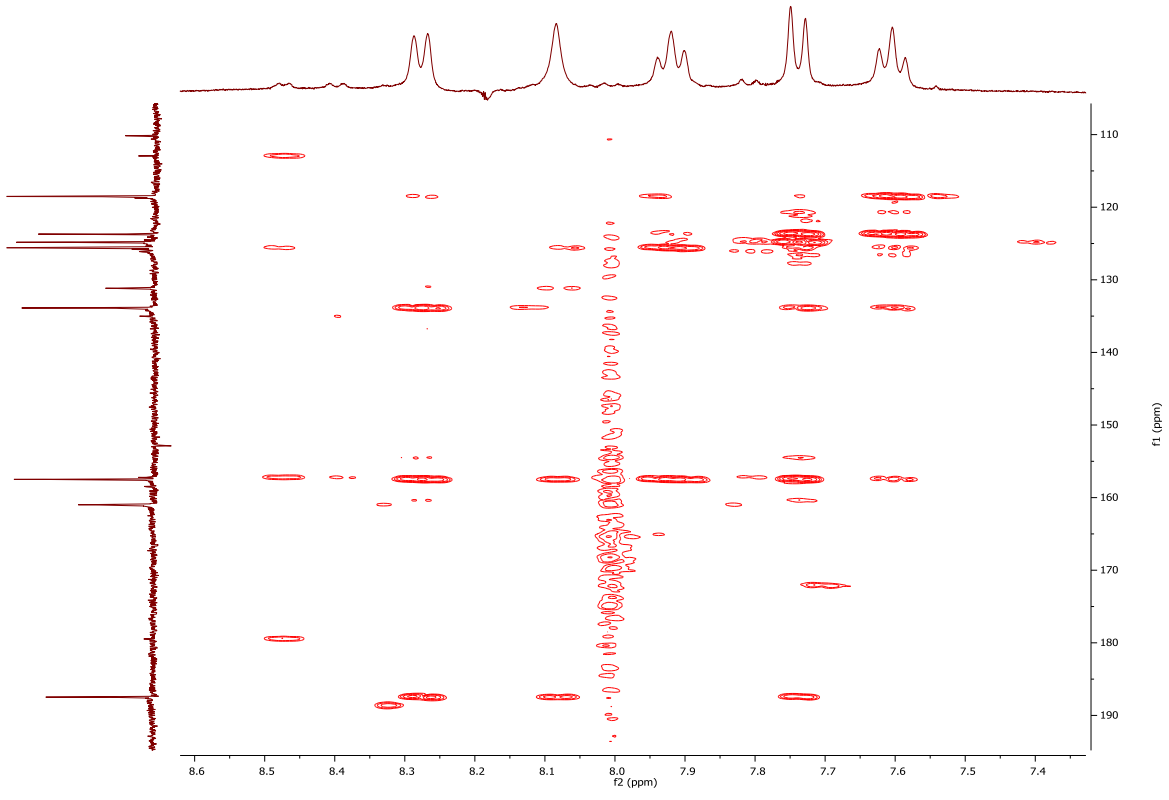
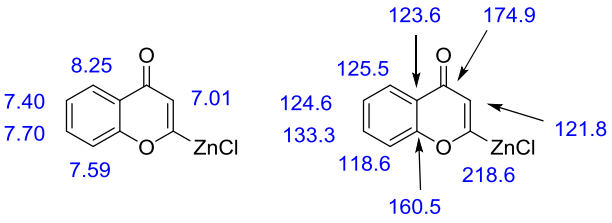


Figure 24: The HMBC-NMR of C(3) zicated Chromone in Dioxane

7.7.1.4 NMR-Spectra of C(2) Zincated Chromone in



A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum is charged with chromone (**5**, 2.0 mmol) in dry THF (2 mL). The base $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ (5, 0.55 equiv.) is added dropwise at -30 °C and the reaction mixture is stirred for 1 h. The completion of the metalation is checked by GC-analysis of reaction aliquots quenched with iodine. After completion the solvent was removed and the crude residue was dissolved in Dioxane. The solution was cannulated into a dry and argon flushed NMR-tube. The C(3) zincated chromone was characterized by 1H, 13C, COSY, HSQC, and HSBC spectra which confirms its identity.

^{1}H NMR (400 MHz, Dioxane) δ = 8.25 (1H), 7.70 (1H), 7.59 (1H), 7.40 (1H), 7.01 (1H).
^{13}C NMR (400 MHz, Dioxane) δ = 218.6, 174.9, 160.5, 133.3, 125.5, 124.6, 123.6, 121.8, 118.6.

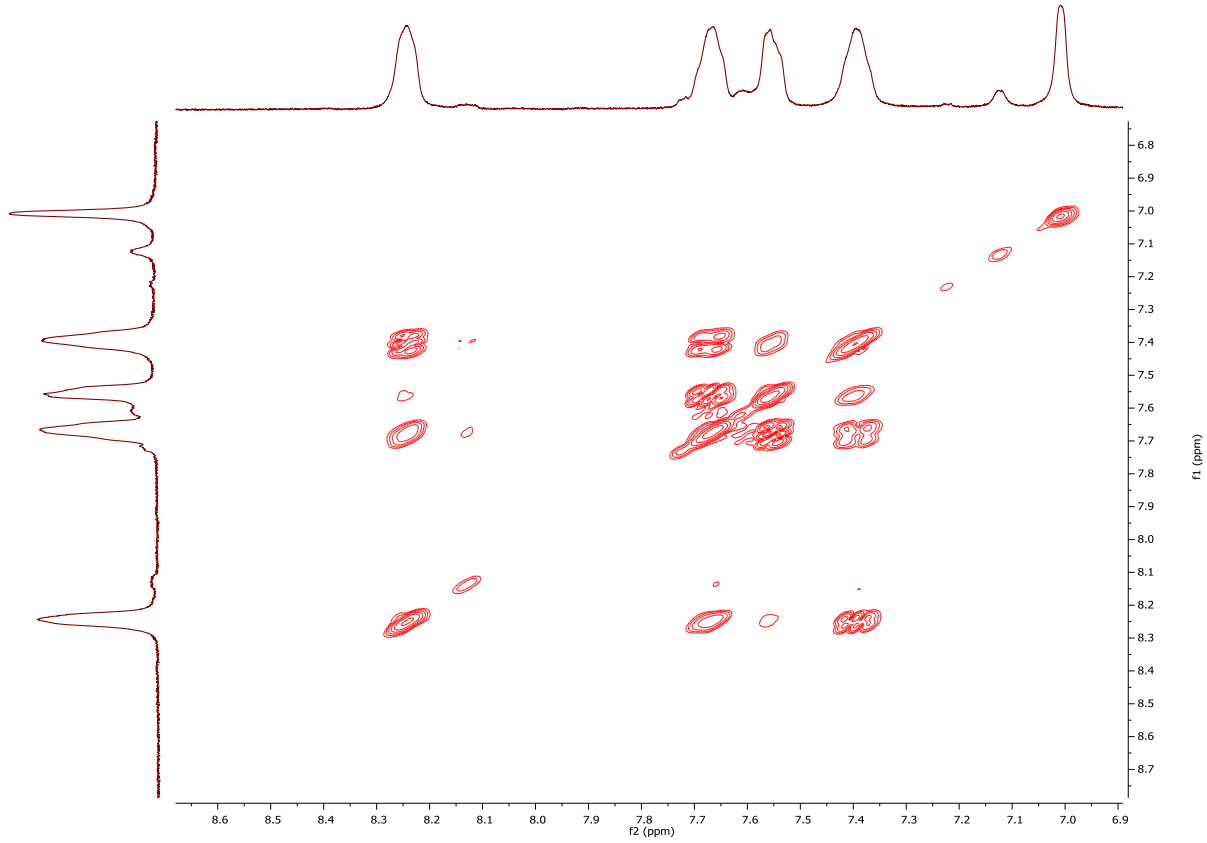


Figure 25: The COSY-NMR of C(2) zicated Chromone in THF, after the addition of $ZnCl_2$ (2 equiv.).

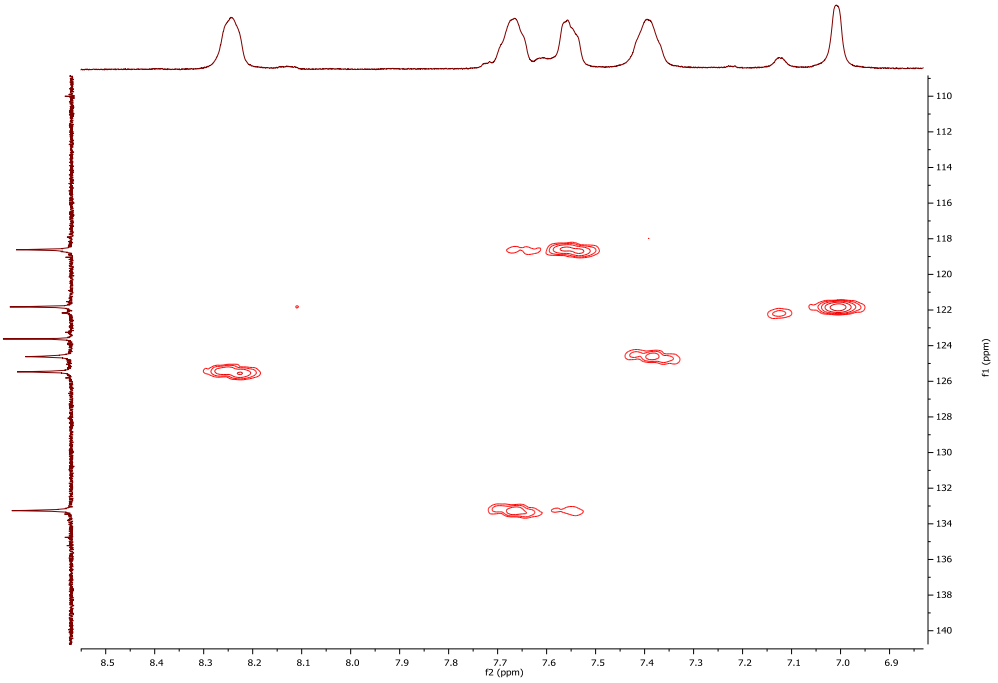


Figure 26: The HSQC-NMR of C(2) zicated Chromone in THF, after the addition of $ZnCl_2$ (2 equiv.).

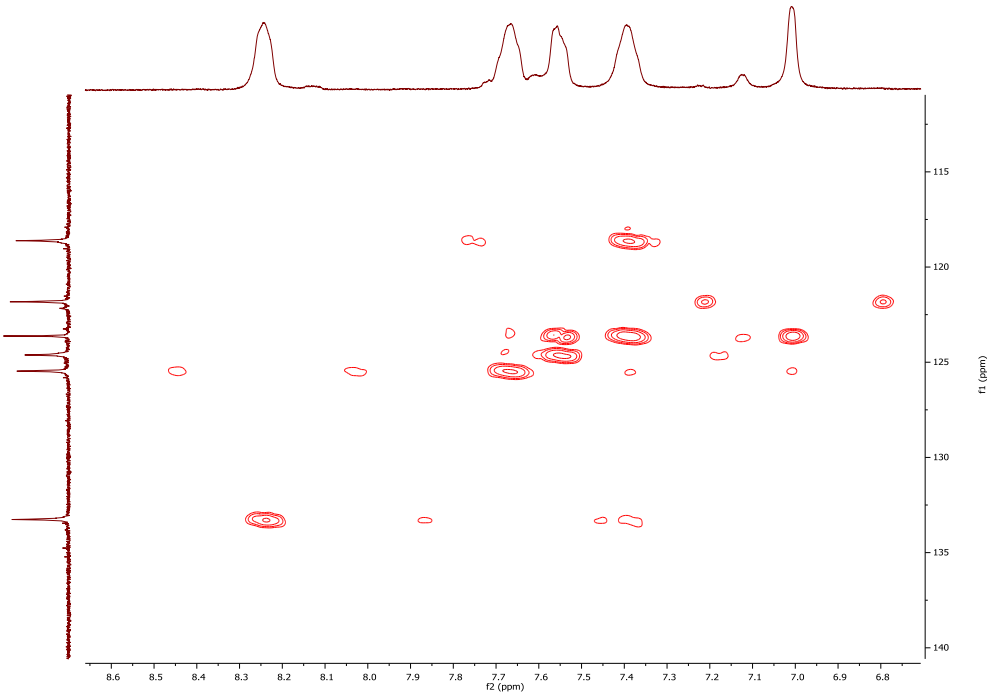
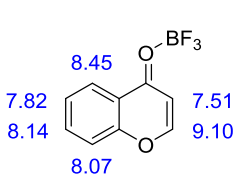
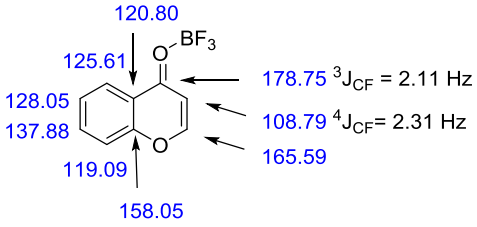


Figure 27: The HMBC-NMR of C(2) zicated Chromone in THF, after the addition of $ZnCl_2$ (2 equiv.).

7.7.1.5 NMR-Spectra of BF_3 Complexes of Chromone THF





A dry and argon flushed NMR-tube is charged with chromone (**5**, 0.5 mmol) and dissolved in dry THF-*d8* (0.5 mL). To the solution is added $BF_3{\cdot}OEt_2$ (1 mmol).

^{1}H NMR (MHz, THF) δ = 7.51 (d, J = 7.51 Hz, 1H), 7.82 (t, J = 8.14 Hz, 1H), 8.07 (d, 8.17 Hz 1H), 8.14 (t, J =7.91 Hz), 8.45 (d, J = 8.14 Hz, 1H), 9.10 (d. J = 5.72 Hz, 1H).
^{13}C NMR (400 MHz, THF) δ = 108.79 (q, $^4J_{CF}$ = 2.31) 119.09 (s, 1C), 120.80 (s, 1C), 125.61 (s, 1C),128.05 (s, 1C), 137.88 (s, 1C), 158.05 (s, 1H), 178.75 (q, $^3J_{CF}$ = 2.11).

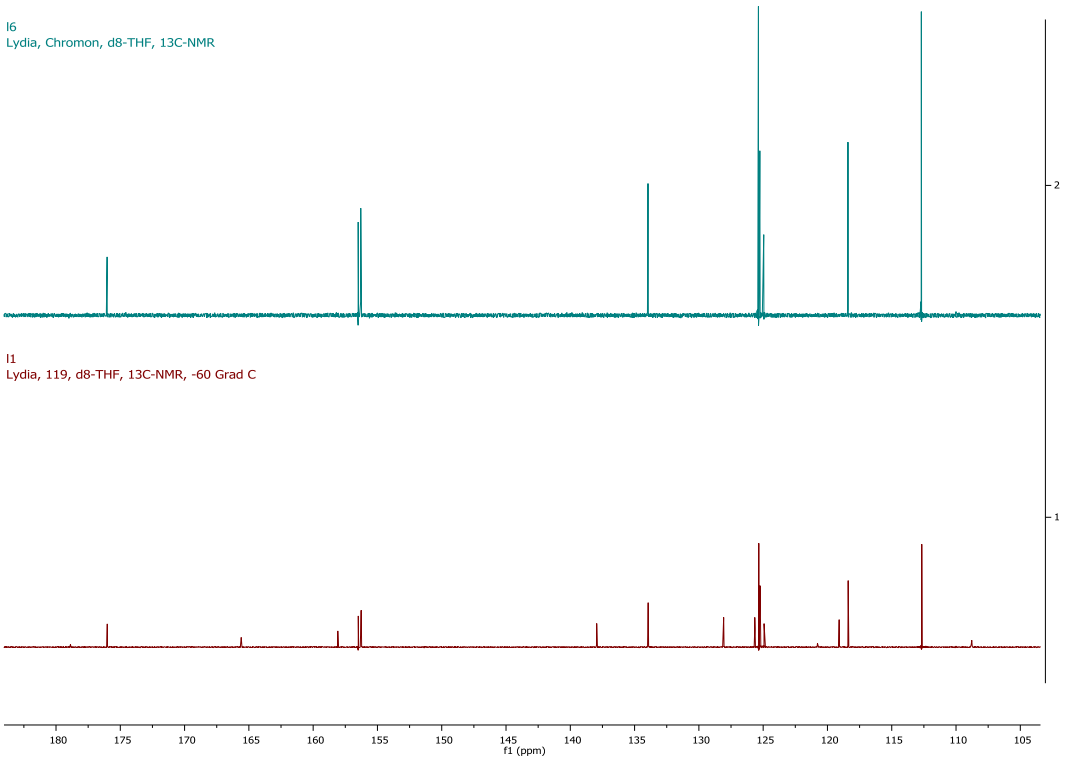


Figure 28: The ^{13}C-NMR of a solution of Chromone and $BF_3{\cdot}OEt_2$ in THF at varying temperatures confirm the coordination of the carbonyl group to Lewis acid BF_3: 1) ^{13}C-NMR Spectra at -60 °C 2) ^{13}C-NMR Spectra at -60 °C.

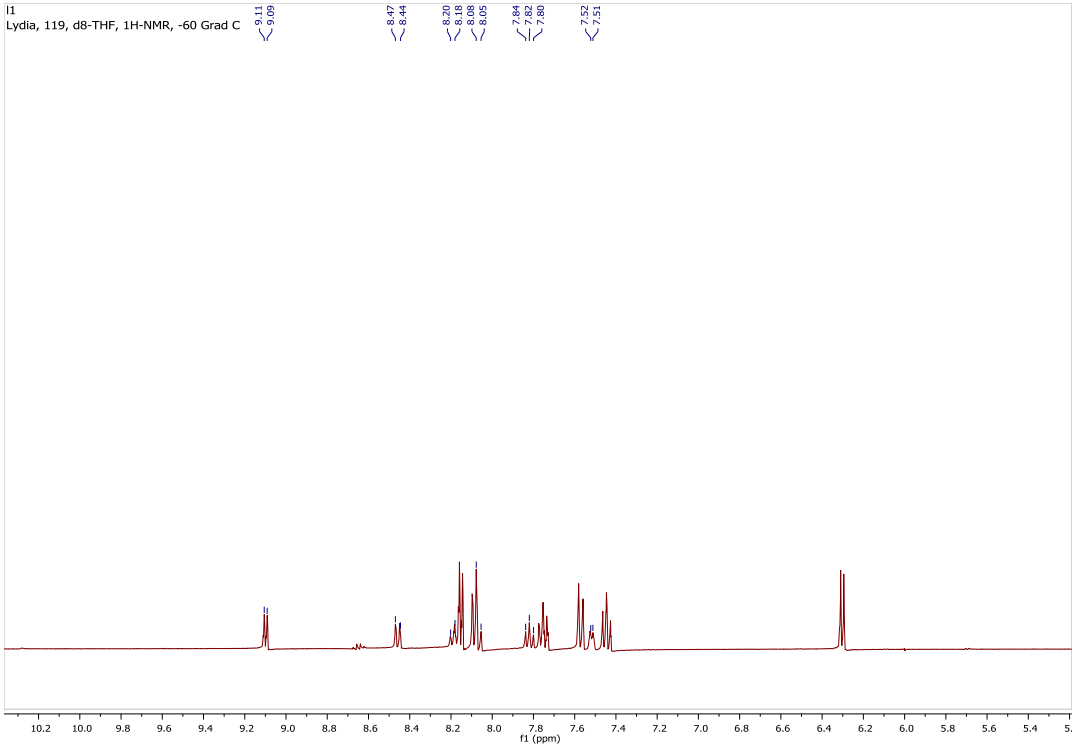
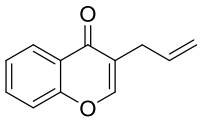


Figure 29: The ^{1}H-NMR of a solution of Chromone and $BF_3{\cdot}OEt_2$ (2.8 equiv.) in THF at -60 °C.

7.7.2 Preparation of 3-Allyl-4H-chromen-4-one (7b) on 50 mmol Scale.



The C(3) zincated chromone (**6**, 50 mmol) was prepared according to **TP1a**, cooled to −50 °C, and CuCN·2LiCl (60 mL, 1.0 M solution in THF, 60 mmol, 1.2 equiv.) was added through an addition funnel over 30 minutes. After further 30 min. of stirring at the same temperature, allyl bromide (7.26 g, 60 mmol, 1.2 equiv.) was added, and the resulting mixture was warmed up to 25 °C and stirred at 25 °C for 12 h. The reaction mixture was then cooled to −10 °C and quenched with MeOH (10 mL). Then NH_4Cl/NH_3 (50 mL, 2 M in H_2O) was added and the resulting mixture was stirred for 2 h at 25 °C. The solution was extracted with CH_2Cl_2 (3 × 300 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:*i*-hexane 1:10) furnished the compound **7b** (8.43 g, 45 mmol, 91%) as a yellow oil.

HRMS (EI) for $C_{12}H_{10}O_2$: calcd. 186.0681 (M^+); found 186.0657.

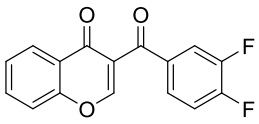
^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.20 (dd, *J*=6.63, 1.11 Hz, 2 H), 5.01 - 5.14 (m, 2 H), 5.71 - 6.02 (m, 1 H) 7.27 - 7.44 (m, 2 H), 7.51 - 7.64 (m, 1 H), 7.69 (s, 1 H), 8.18 (dd, *J*=8.02, 1.66 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 29.6, 117.1, 118.0, 123.0, 123.8, 124.9, 125.9, 133.3, 134.6, 152.6, 156.4, 177.3.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3077 (w), 3068 (w), 3017 (vw), 2970 (w), 2941 (vw), 2900 (w), 1632 (s), 1608 (s), 1573 (m), 1464 (s), 1429 (m), 1398 (s), 1353 (s), 1321 (m), 1297 (m), 1282 (m), 1264 (w), 1226 (w), 1210 (m), 1181 (m), 1156 (s), 1141 (s), 1111 (m), 1027 (w), 1005 (m), 961 (m), 924 (s), 909 (s), 896 (s), 868 (w), 846 (s), 802 (m), 769 (s), 756 (vs), 712 (m), 690 (s).

m.p.: 34 - 36 °C

7.7.3 Preparation of 3-(3,4-difluorobenzoyl)-4H-chromen-4-one (7c)



The C(3) zincated chromone (**6**, 50 mmol) was prepared according to **TP1a**, cooled to −50 °C, and CuCN·2LiCl (60 mL, 1.0 M solution in THF, 60 mmol, 1.2 equiv.) was added through an addition funnel over 30 min. After further 1 h of stirring at the same temperature, 3,4-difluorobenzoyl chloride (10.6 g, 60 mmol, 1.2 equiv.) was added, and the resulting mixture was warmed up to 25 °C over 12 h. The reaction mixture was stirred for additional 36 h until GC analysis indicated full conversion. The reaction mixture was then cooled to −40 °C and quenched with MeOH (10 mL). Then NH_4Cl/NH_3 (50 mL, 2M in H_2O) solution was added and the resulting mixture was stirred for 2 h at 25 °C. The solution was extracted with CH_2Cl_2 (3 × 300 mL), the combined organic extracts were washed with sat. aq. Na_2CO_3 (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The obtained solid was washed with cold Et_2O, the remaining solid is recrystallized from hot acetone. The compound **7c** was obtained in 60% yield (8.61 g, 30 mmol) as a pale orange solid.

HRMS (EI) for $C_{16}H_8F_2O_3$: calcd 286.04415 (M^+); found 286.0445.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.13 - 7.32 (m, 1 H), 7.44 - 7.60 (m, 2 H), 7.60 - 7.67 (m, 1 H), 7.67 - 7.89 (m, 2 H), 8.26 (dd, *J*=7.46, 1.66 Hz, 1 H), 8.34 (s, 1 H).

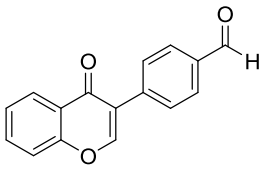
^{13}C NMR (75 MHz, $CDCl_3$) δ = 117.2, 117.4, 118.4, 118.7 (*d,d* , *J*=18.23, 1.68), 124.6, 124.9, 126.3, 126.4, 126.9 (*d,d J*=7.57, 3.65), 134.2 (*d,d*, *J*=4.77, 3.65), 134.6, 159.4 (*dd*, *J*= 266.47, 12.90), 153.9 (*dd*, *J*=273.48, 12.90), 156.0, 159.2, 174.5, 189.5.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1665 (m), 1652 (m), 1645 (m), 1615 (m), 1604 (w), 1596 (w), 1563 (w), 1515 (m), 1464 (m), 1434 (m), 1384 (w), 1348 (w), 1338 (w), 1317 (m), 1299 (m), 1282 (m), 1273 (w), 1234 (w), 1213 (w), 1194 (w), 1172 (w), 1151 (w), 1128 (w), 1110 (m), 1099

(w), 996 (w), 929 (w), 908 (w), 856 (m), 829 (m), 797 (w), 771 (m), 762 (vs), 757 (s), 729 (m), 701 (w), 686 (w), 656 (m).

m.p.: 190 - 191 °C

7.7.4 Preparation of 4-(4-oxo-4H-chromen-3-yl)benzaldehyde (7d)



The C(3) zincated chromone (6, 50 mmol) was prepared according to **TP1a**, warmed to 25 °C and reacted with bromobenzaldehyde (11.1 g, 60 mmol, 1.2 equiv.) in the presence of $Pd(PPh_3)_4$ (0.558 g, 1 mol %) for 18 h. The reaction mixture was then cooled to −10 °C and quenched with MeOH (10 mL). Then sat. aq. NH_4Cl (50 mL) was added and the resulting mixture was stirred for 2 h at 25 °C. The solution was extracted with CH_2Cl_2 (3 × 300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The obtained solid was recrystallized from CH_2Cl_2:heptane. When no more pure product crystallized the remaining mother liquid was concentrated and purified by column chromatography (*i*-hexane:EtOAc 9.5:0.5 to 8:2). Compound **7d** was obtained in 84 % yield (10.4 g, 42 mmol) as a yellow solid.

HRMS (EI) for $C_{16}H_{10}O_3$: calcd. 249.05572 (M^+); found 249.0549.

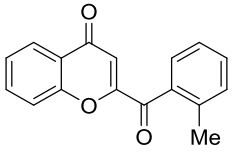
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43 - 7.56 (m, 2 H), 7.68 - 7.77 (m, 1 H), 7.79 (d, *J*=8.29 Hz, 2 H), 7.97 (d, *J*=8.29 Hz, 2 H), 8.12 (s, 1 H), 8.33 (d, *J*=9.68 Hz, 1 H), 10.07 (s, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ = 118.1, 124.3, 124.4, 125.6, 126.4, 129.4, 129.8, 134.00, 135.9, 138.2, 153.7, 156.1, 175.7, 191.8.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = cm-1 (intensity), 1699 (m), 1695 (m), 1630 (m), 1615 (m), 1598 (m), 1558 (m), 1458 (m), 1369 (m), 1357 (m), 1289 (m), 1230 (m), 1214 (m), 1171 (m), 1115 (m), 1047 (m), 1014 (m), 1014 (m), 897 (m), 888 (m), 857 (m), 831 (s), 824 (s), 764 (vs).

m.p.: 198 - 200 °C

7.7.5 Preparation of 2-(2-methylbenzoyl)-4H-chromen-4-one (9b)



The C(2) zincated chromone (**8**, 50 mmol) was prepared according to **TP2a,** cooled to −50 °C and CuCN·2LiCl (60 mL, 1 M solution in THF, 60 mmol, 1.2 equiv.) was added, through an addition funnel over 30 minutes. After further 1 h of stirring at the same temperature, 2-

methylbenzoyl chloride (9.24 g, 60 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at −40 °C for 1 h before it was warmed slowly to 25 °C over 12 h. The reaction mixture was then cooled to −40 °C and quenched with MeOH (10 mL). Then NH_4Cl/NH_3 (50 mL, 2 M in H_2O) was added and the resulting mixture was stirred for 2 h at 25 °C. The solution was extracted with CH_2Cl_2 (3 × 300 mL), the combined organic extracts were washed with sat. aq. Na_2CO_3 (50 mL) dried over anhydrous Na_2SO_4, filtration and concentrated *in vacuo*. The obtained solid was washed with EtOH and the filtrate was concentrated *in vacuo*. The obtained solid was recrystallized from CH_2Cl_2/heptane. When no more pure product crystallized the remaining mother liquid was concentrated and purified by column chromatography (CH_2Cl_2). The compound **9b** was obtained in 60 % yield (10.7 g, 40 mmol, 81%) as an orange solid.

HRMS (EI) for $C_{17}H_{12}O_3$: calcd 265.08647 (M+H); found. 265.08589.

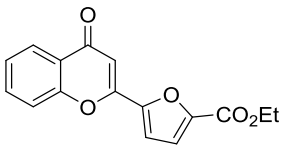
^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.46 (s, 3 H), 6.79 (s, 1 H), 7.20 - 7.40 (m, 2 H), 7.40 - 7.54 (m, 3 H), 7.58 (dd, *J*=8.57, 1.11 Hz, 1 H), 7.75 (ddd, *J*=8.57, 6.91, 1.66 Hz, 1 H), 8.22 (dd, *J*=7.88, 1.80 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 20.1, 115.8, 118.8, 124.5, 125.5, 125.8, 125.9, 129.4, 131.6, 132.1, 134.9, 134.9, 138.4, 155.9, 157.6, 178.6, 190.7.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1679 (m), 1648 (s), 1615 (m), 1598 (m), 1569 (m), 1487 (w), 1469 (m), 1456 (m), 1387 (m), 1377 (s), 1330 (w), 1303 (m), 1288 (w), 1255 (m), 1239 (s), 1214 (m), 1158 (m), 1145 (w), 1130 (m), 1092 (m), 1083 (w), 1039 (w), 1027 (m), 977 (m), 869 (s), 853 (m), 843 (m), 797 (m), 778 (vs), 756 (s), 740 (vs), 729 (s), 712 (m), 668 (s).

m.p.: 95 °C

7.7.6 Preparation of ethyl 5-(4-oxo-4H-chromen-2-yl)furan-2-carboxylate (9c)



The obtained C(2) zincated chromone (**8**, 50 mmol) was prepared according to **TP2b,** warmed to 25 °C and reacted with ethyl 5-bromofuran-2-carboxylate (13.1 g, 60 mmol, 1.2 equiv.) in the presence of $Pd(dba)_2$ (565 mg, 2 mol %) and tfp (465 mg, 4 mol %) for 25 h. The reaction mixture was then cooled to 0 °C and quenched with MeOH (10 mL). Then sat. aq. NH_4Cl (50 mL) is added and the resulting mixture was stirred for 2 h at 25 °C. The solution was extracted with CH_2Cl_2 (3 × 300 mL), the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The obtained crude product

was recrystallized from hot acetone. Compound **9c** was obtained in 62 % yield (8.88 g, 31 mmol) as a gray solid.

HRMS (EI) for $C_{16}H_{12}O_5$: calcd 284.06847 (M^+); found 284.0666.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.41 (t, *J*=7.05 Hz, 3 H), 4.41 (q, *J*=7.10 Hz, 2 H), 6.91 (s, 1 H), 7.14 - 7.21 (m, 1 H), 7.30 (d, *J*=3.32 Hz, 1 H), 7.42 (t, *J*=7.60 Hz, 1 H), 7.51 (d, *J*=7.46 Hz, 1 H), 7.61 - 7.77 (m, 1 H), 8.21 (dd, *J*=7.88, 1.80 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.3, 61.6, 107.4, 113.6, 118.0, 119.0, 124.3, 125.5 125.8, 134.0, 146.8, 148.8, 153.8, 155.8, 158.00, 177.5.

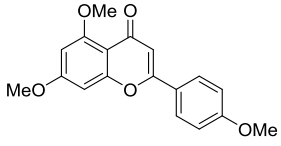
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3149 (w), 3111 (w), 3096 (w), 3054 (w), 3045 (w), 2977 (w), 1723 (s), 1636 (s), 1607 (s), 1577 (m), 1557 (m), 1503 (w), 1475 (m), 1468 (s), 1413 (s), 1371 (s), 1362 (s), 1332 (m), 1287 (s), 1256 (m), 1250 (m), 1227 (s), 1152 (s), 1131 (s), 1116 (m), 1074 (m), 1059 (m), 1025 (m), 1016 (s), 962 (m), 885 (s), 878 (s), 869 (m), 842 (s), 823 (s), 820 (s), 784 (vs), 763 (s), 755 (vs), 733 (m), 703 (m), 672 (s).

m.p.: 120-151 °C

7.8 Natural Product Synthesis

7.8.1 Preparation of 5,7,4'-tetramethoxyflavone (12, TMF)

A dry and argon flushed 10 mL Schlenk-flask equipped with a magnetic stirring bar, and a septum was charged with 5,7-dimethoxy chromone (**11,** 206 mg, 1 mmol) and dissolved in THF (1mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0.6 M in THF, 0.6 mmol, 1.2 equiv.) was added. The reaction was stirred for 30 min and completion of the metallation was checked by TLC of reaction aliquots quenched with I_2 in dry THF. After complete metallation the organozinc reagent reacted in a *Negishi* cross-coupling within 30 min at 25 °C after the addition of *p*-iodanisole (279 mg, 1.2 mmol), $Pd(dba)_2$ (22 mg, 4 mol%) and P(2-furyl)$_3$ (19 mg, 8 mol%). After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (12 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (EtOAc:*i*-hexane 1:10) afforded the desired product **12** (229 mg, 0.73 mmol) as a geay solid in 73%yield.



HRMS (EI) for $C_{18}H_{16}O_5$: calcd. 312.0998; found 312.0987.

MS (70 eV, EI) (m/z)(%): 313 (18), 312 (100), 311 (58), 283(29), 282(11), 281(19), 266 (30), 142 (17), 132 (22).

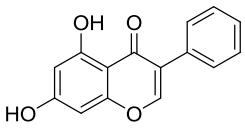
^{1}H NMR (400 MHz, acetone) δ = 3.87 (s, 3 H) 3.89 (s, 3 H) 3.94 (s, 3 H) 6.47 (d, *J*=2.34 Hz, 1 H) 6.49 (s, 1 H) 6.76 (d, *J*=2.34 Hz, 1 H) 7.09 (m, *J*=8.77 Hz, 2 H) 7.95 (m, *J*=8.97 Hz, 2 H)

^{13}C NMR (101 MHz, acetone) δ = 54.98, 55.37, 55.50, 93.02, 95.91, 107.01, 108.89, 114.31, 123.73, 127.53, 159.67, 159.99, 160.89, 162.18, 163.99, 175.44.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2930 (w), 2836 (VW), 2361 (w), 2341 (VW), 1642 (s), 1603 (s), 1595 (s), 1567 (m), 1511 (m), 1489 (m), 1467 (m), 1450 (m), 1419 (m), 1386 (w), 1348 (s), 1295 (w), 1255 (s), 1214 (s), 1194 (s), 1170 (m), 1162 (s), 1120 (s), 1110 (m), 1100 (m), 1055 (m), 1031 (m), 951 (w), 907 (w), 830 (vs), 811 (w), 798 (m), 770 (m), 726 (w), 696 (w), 674 (w), 654 (w).

m.p.: 155 - 157 °C

7.8.2 Preparation of Isochrysin 17



A dry and argon flushed 10 mL Schlenk-flask equipped with a magnetic stirring bar, and a septum was charged with 5,7-bis((triisopropylsilyl)oxy)-chromenone (**11**, 490 mg, 1 mmol) dissolved in THF (1 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0.6 M in THF, 0.6 mmol, 1.2 equiv.) was added at -20 °C. The reaction was stirred for 30 min and completion of the metallation was checked by TLC of reaction aliquots quenched with I_2 in dry THF. After complete metallation the organozinc reagent reacted in a *Negishi* cross-coupling within 1 h at 25 °C after the addition of iodobenzole (280 mg, 1.0 mmol), $Pd(dba)_2$ (22 mg, 4 mol%) and P(2-furyl)$_3$ (18 mg, 8 mol%). After complete conversion, TBAF (624 mg, 2.4 equiv.) was added, and the reaction mixture was stirred for 20 min. The obtained reaction mixture was quenched with sat. aq. NaCl (10 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc:*i*-hexane 1:10) afforded **17** (227mg, 0. 89 mmol, 89%) as a colorless solid.

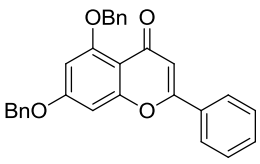
HRMS (EI) for $C_{15}H_{10}O_4$: calcd. 254.05791; found 244.0568.

MS (70 eV, EI) (m/z)(%): 255 (16), 254 (100), 253 (39), 124 (16).

^{1}H NMR (400 MHz, acetone) δ = 6.28 (s, 1 H), 6.43 (s, 1 H), 7.37 (s, 2 H), 7.44 (s, 1 H), 7.60 (d, *J*=6.85 Hz, 2 H), 8.22 (s, 1 H), 12.94 (s, 1H).

^{13}C NMR (101 MHz, acetone) δ = 93.67, 99.06, 105.28, 123.24, 127.97, 128.14, 129.02, 131.22, 154.24, 158.13, 163.02, 164.17, 180.42.

7.8.3 Preparation of benzyl protected chrysin (21)



A dry and argon flushed 10 mL Schlenk-flask equipped with a magnetic stirring bar, and a septum was charged with 5,7-bis(benzyloxy)-chromenone (**18**, 200 mg, 0.55 mmol) and dissolved in THF (1 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.91 mL, 0.73 M in THF, 0.66 mmol) was added at −30 °C. The reaction was stirred for 1 h and completion of the metallation was checked by TLC of reaction aliquots quenched with I_2 in dry THF. After complete metallation the organozinc reagent (**20**) reacted in a *Negishi* cross-coupling within 1 h at 25 °C after the addition of iodo benzene (135 mg, 0.66 mmol), $Pd(dba)_2$ (7 mg, 2 mol%) and P(2-furyl)$_3$

(5 mg, 4 mol%). After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc:*i*-hexane 3:7) afforded **21** (173 mg, 0.40 mmol, 72%) as a colorless solid.

HRMS (ESI) for $C_{29}H_{22}O_4$: calcd. 434.4826 ($M+H^+$); found 435.1592.

^{1}H NMR (400 MHz, acetone-*d6*) δ = 5.27 (s, 4 H), 6.64 (s, 1 H), 6.71 (d, *J* = 2.15 Hz, 1 H), 6.93 (d, *J* = 2.15 Hz, 1 H), 7.28 - 7.47 (m, 6 H), 7.48 - 7.60 (m, 5 H), 7.72 (d, *J* = 7.43 Hz, 2 H), 7.96 - 8.07 (m, 2 H).

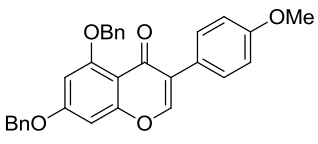
^{13}C NMR (75 MHz, acetone-*d6*) δ = 70.22, 70.27, 94.50, 98.23, 108.58, 109.56, 125.86, 126.69, 127.30, 127.81, 128.10, 128.20, 128.50, 128.95, 131.11, 131.66, 136.45, 137.20, 159.67, 159.70, 160.10, 163.14, 175.49.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3061 (w), 3026 (w), 2955 (w), 2921 (w), 2853 (w), 2361 (w), 2341 (w), 1644 (s), 1625 (m), 1605 (s), 1576 (m), 1560 (w), 1550 (w), 1495 (m), 1488 (m), 1450 (m), 1370 (m), 1346 (s), 1297 (m), 1262 (m), 1212 (m), 1166 (s), 1124 (s), 1100 (s), 1078 (m), 1054 (m), 1028 (m), 1010 (s), 976 (m), 908 (m), 882 (m), 846 (m), 836 (m), 816 (s), 803 (m), 756 (vs), 730 (s), 696 (vs), 689 (vs), 667 (s).

m.p.: 155-156 °C

Lit. ^{1}H NMR[131]

7.8.4 Preparation of benzyl protected biochanine A (20)



A dry and argon flushed 10 mL Schlenk-flask equipped with a magnetic stirring bar, and a septum was charged with 5,7-bis(benzyloxy)-chromenone (**18**, 100 mg, 0.28 mmol) dissolved in THF (1 mL). TMPZnCl·LiCl (**3**, 0.4 mL, 1.4 M in THF, 0.6 mmol) was added. The reaction was stirred for 30 min and completion of the metallation was checked by TLC of reaction aliquots quenched with I_2 in dry THF. After complete metallation the organozinc reagent (**19**) reacted in a *Negishi* cross-coupling within 1 h at 25 °C after the addition of *p*-iodanisole (78 mg, 0.34 mmol), $Pd(dba)_2$ (7 mg, 4 mol%) and P(2-furyl)$_3$ (5 mg, 8 mol%). After complete conversion, the reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous

[131] S. T. Caldwell, H. M. Petersson, L. J. Farrugia, W. Mullen, A. Crozierb, R. C. Hartleya, *Tetrahedron* **2006**, *62*, 7257.

Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc:*i*-hexane 1:10) afforded the desired product **20 (**123 mg, 0.26 mmol, 95%) as a colorless solid.

HRMS (EI) for $C_{30}H_{24}O_5$: calcd. 464.1624 (M^+); found 264.1614.

MS (70 eV, EI) *m/z* (%): 465 (32), 464 (100), 374 (23), 373 (32), 358 (12), 91 (70), 43 (17).

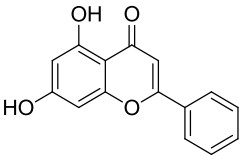
^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.83 (s, 3 H), 5.10 (s, 2 H), 5.22 (s, 2 H), 6.52 (d, *J*=3.59 Hz, 2 H), 6.95 (d, *J*=8.57 Hz, 2 H), 7.18 - 7.53 (m, 10 H), 7.59 (d, *J*=7.46 Hz, 2 H), 7.74 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 55.31, 70.47, 70.81, 94.04, 98.30, 110.54, 113.85, 124.44, 126.19, 126.75, 127.60, 127.63, 128.42, 128.57, 128.75, 130.44, 135.68, 136.28, 149.99, 159.49, 159.82, 160.26, 162.70, 175.19.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3079 (vw), 3067 (vw), 3031 (vw), 3006 (w), 2905 (vw), 2869 (vw), 2846 (vw), 2361 (w), 2342 (w), 1654 (s), 1646 (s), 1614 (vs), 1583 (m), 1570 (m), 1511 (m), 1498 (m), 1449 (m), 1434 (m), 1376 (m), 1364 (m), 1302 (m), 1290 (s), 1258 (s), 1248 (s), 1215 (s), 1200 (m), 1190 (m), 1174 (s), 1164 (s), 1109 (w), 1086 (s), 1071 (s), 1066 (s), 1028 (m), 984 (m), 892 (w), 878 (m), 840 (s), 824 (s), 802 (m), 793 (m), 774 (w), 741 (s), 731 (vs), 694 (s).

m.p.: 157-160 °C

7.8.5 Preparation of Crysin (16)



A suspension of **21** (43 mg, 0.1 mmol) in EtOH (10 mL) was treated with 20% $Pd(OH)_2$/C (7 mg) under a flow of hydrogen for 12 h at 25 °C. Completion of the reaction was checked by TLC. The reaction mixture was then filtered trough Celite and eluted with EtOH. The filtrate was concentrated *in vacuo*. Purification by flash column chromatography (EtOAc:*i*-hexane, 1:9 to 3:7) furnished crysin (**16**, 21 mg, 83%) as a colorless solid.

HRMS (EI) for $C_{15}H_{10}O_4$: calcd. 254.0579 (M^+); found 254.0576.

MS (70 eV, EI) *m/z* (%):255 (21), 254 (100), 253 (10), 226 (17), 152 (21), 124 (14).

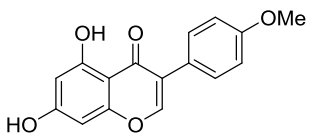
^{1}H NMR (400 MHz, acetone-*d6*) δ = 6.28 (d, *J*=2.14 Hz, 1 H), 6.58 (d, *J*=2.14 Hz, 1 H), 6.79 (s, 1 H), 7.47 - 7.69 (m, 3 H), 8.07 (dd, *J*=7.99, 1.75 Hz, 2 H), 9.71 (s, 1 H), 12.90 (s, 1 H).

^{13}C NMR (101 MHz, acetone-*d6*) δ = 93.95, 98.96, 104.66, 105.27, 126.33, 129.07, 131.36, 131.78, 158.01, 162.48, 163.77, 164.20, 182.22.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3081 (w), 3010 (w), 2925 (w), 2856 (w), 2712 (w), 2634 (w), 2361 (vw), 2349 (vw), 2253 (vw), 2210 (vw), 2044 (vw), 2017 (vw), 1646 (s), 1608 (s), 1578 (m), 1555 (m), 1498 (s), 1448 (s), 1425 (m), 1352 (vs), 1313 (m), 1273 (m), 1247 (m), 1188 (w), 1168 (vs), 1157 (s), 1120 (m), 1103 (m), 1077 (w), 1031 (m), 1026 (m), 999 (w), 977 (w), 908 (m), 840 (m), 807 (s), 782 (m), 748 (m), 732 (m), 693 (m), 674 (m).

Lit. **^{1}H NMR**[132]

7.8.6 Preparation of Biochanin A (14)



A suspension of **20** (50 mg, 0.1 mmol) in EtOAc (10 mL) was treated with 20% $Pd(OH)_2$/C (7 mg) under a flow of hydrogen for 48 h at 25 °C. Completion of the reaction was checked by TLC. The reaction mixture was then filtered trough Celite and eluted with EtOH. The filtrate was concentrated *in vacuo*. Purification by flash column chromatography (*i*-hexane:EtOAc, 1:9 to 3:7) furnished Biochanin A (**14**, 25 mg, 88%) as a colorless solid.

HRMS (EI) for $C_{16}H_{12}O_5$: calcd. 284.0685 (M^+); found 284.0669.

MS (70 eV, EI) *m/z* (%):285 (13), 284 (100), 132.0547 (11).

^{1}H NMR (400 MHz, acetone-d6) δ =3.84 (s, 3 H), 6.29 (dd, *J*=2.14, 1.17 Hz, 1 H), 6.41 (dd, *J*=2.15, 1.37 Hz, 2 H), 7.00 (d, *J*=8.97 Hz, 2 H), 7.55 (d, *J*=8.97 Hz, 2 H), 8.20 (d, *J*=1.17 Hz, 1 H), 13.01 (s, 1H).

^{13}C NMR (101 MHz, acetone-d6) δ = 54.67, 93.60, 98.85, 105.23, 113.60, 122.94, 123.29, 130.17, 153.52, 158.14, 159.76, 162.71, 163.97, 180.56.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3338 (m), 3286 (w), 3088 (w), 3042 (w), 2923 (w), 2853 (w), 2361 (w), 2341 (w), 1652 (s), 1613 (s), 1601 (m), 1571 (s), 1505 (m), 1488 (m), 1447 (s), 1407 (m), 1386 (m), 1361 (m), 1330 (m), 1290 (m), 1276 (m), 1253 (s), 1207 (m), 1173 (vs), 1153 (s), 1060 (m), 1046 (vs), 1021 (s), 988 (s), 934 (m), 909 (m), 877 (m), 836 (s), 813 (vs), 796 (s), 754 (s), 697 (vs), 674 (m), 668 (m).

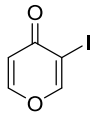
Lit. **^{1}H NMR**[133]

[132] T. Itoh, M. Ninomiya, M. Yasud, K. Koshikawa, Y. Deyashiki, Y. Nozawa, Y. Akao, M. Koketsu, *Bioorg. Med. Chem.* **2009**, *17*, 5374.

[133] J. M. Hastings, M. K. Hadden, and B. S. J. Blagg, *J. Org. Chem.* **2008**, *73*, 369.

7.9 4-Pyrone Derivatives 25a-d, 27a-c

7.9.1 Preparation of 3-iodo-4*H*-pyran-4-one (25a)



To a solution of γ-pyrone (**23**, 1 mL, 0.5 M in THF, 0.5 mmol) was added TMPZnCl·LiCl (**3**, 0.5 mL, 1.2 M in THF, 0.6 mmol, 1.2 equiv.) at 0 °C. The reaction mixture was stirred for 2 h according to **TP3** and reacted with iodine (0.7 mL, 1 M in THF, 0.7 mmol, 1.4 equiv.). The regioselectivity of of the metallation is checked by ^{1}H-NMR indicating C(3):C(2) = 98:2. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 3:7) furnishing compound **25a** (89 mg, 0.40 mmol, 80%) as a yellowish solid.

HRMS (EI) for $C_5H_3IO_2$: calcd. 221.9806 (M^+); found 221.9176.

MS (70 eV, EI) *m/z* (%): 221 (100), 151 (13), 126 (7), 52 (11).

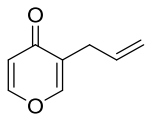
^{1}H NMR (300MHz, $CDCl_3$) δ = 6.40 (d, *J*=5.68 Hz, 1 H), 7.76 (dd, *J*=5.73, 0.96 Hz, 1 H), 8.18 (d, *J*=1.01 Hz, 1 H).

^{13}C NMR (75MHz, $CDCl_3$) δ = 93.83, 114.27, 155.21, 158.04, 173.41.

IR (ATM): $\tilde{\nu}$ (cm^{-1}) = 3099 (vw), 3069 (vw), 1744 (vw), 1685 (w), 1632 (vs), 1609 (m), 1539 (vw), 1399 (w), 1360 (w), 1310 (s), 120-5 (w), 1088 (w), 1027 (m), 945 (m), 911 (vw), 894 (w), 832 (m).

m.p.: 73 - 75 °C

7.9.2 Preparation of 3-allyl-4*H*-pyran-4-one (25b)



To a solution of γ-pyrone (**23**, 1 mL, 0.5 M in THF, 0.5 mmol) was added TMPZnCl·LiCl (**3**, 0.5 mL, 1.2 M in THF, 0.6 mmol, 1.2 equiv.) at 0 °C. The reaction mixture was stirred for 2 h according to **TP3**. The freshly prepared zinc reagent **24** was cooled to −40 °C, CuCN·2LiCl (1 M solution in THF, 0.7 mL, 0.7 mmol, 1.4 equiv.) was added and the reaction mixture was stirred for 30 min. Allylation was achieved by adding allyl bromide (84 mg, 0.7 mmol, 1.4 equiv.) at −40 °C, stirring at −40 °C for 5 min and 1 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 4:6) furnishing compound **25b** (44 mg, 0.32 mmol, 65%) as a yellowish solid.

HRMS (EI) for $C_8H_8O_2$: calcd. 136.1479 (M^+); found 136.0520.

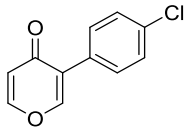
MS (70 eV, EI) *m/z* (%): 136 (100), 137 (11), 135 (43), 121 (88), 108 (12), 107 (21), 91 (11), 79 (35), 53 (15), 77 (18), 71 (57), 67 (59), 66 (45), 65 (48), 63(13).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.02 - 3.17 (m, 2 H), 5.08 (ddd, *J*=1.54, 1.06, 0.87 Hz, 1 H), 5.10 - 5.16 (m, 1 H), 5.76 - 5.97 (m, 1 H), 6.31 (dd, *J*=5.75, 0.61 Hz, 1 H), 7.54 - 7.64 (m, 1 H), 7.69 (dt, *J*=5.76, 0.94 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 29.39, 116.57, 117.47, 128.82, 133.86, 152.52, 155.10, 177.88.

IR (ATM): $\tilde{\nu}$ (cm^{-1}) = 3460 (w), 3078 (w), 2979 (vw), 2911 (vw), 1710 (w), 1645 (vs), 1605 (s), 1427 (m), 1386 (w), 1364 (w), 1322 (s), 1287 (w), 1224 (m), 1149 (m), 1132 (m), 1124 (m), 984 (m), 915 (m), 855 (m), 836 (s), 780 (w), 741 (w), 655 (m).

7.9.3 Preparation of 3-(4-chlorophenyl)-4*H*-pyran-4-one (25c)



To a solution of γ-pyrone (**23**, 1 mL, 0.5 M in THF, 0.5 mmol) was added TMPZnCl·LiCl (**3**, 0.5 mL, 1.2 M in THF, 0.6 mmol, 1.2 equiv.) at 0 °C. The reaction mixture was stirred for 2 h according to **TP3**. The zinc reagent **24** reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (6 mg, 2 mol%), $P(2\text{-furyl})_3$ (5 mg, 4 mol%) and 1-chloro-4-iodobenzene (166 mg, 0.7 mmol, 1.4 equiv.) within 1 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 4:6) yielding compound **25c** (94 mg, 0.45 mmol, 90%) as a colorless liquid.

HRMS (EI) for $C_{11}H_7ClO_2$: calcd. 206.6251 (M^+); found 206.0129.

MS (70 eV, EI) *m/z* (%): 208 (18), 206 (69), 136 (100), 115 (14), 101 (16), 89 (11), 74 (11), 44 (15), 43(14), 43 (15).

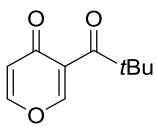
^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.45 (d, *J*=5.81 Hz, 1 H), 7.38 (m, 2 H), 7.44 (m, 2 H), 7.75 (dd, *J*=5.81, 1.11 Hz, 1 H), 7.87 (d, *J*=1.11 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ =117.99, 128.71, 129.45, 129.54, 129.94, 134.58, 152.83, 154.79, 176.43.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3086 (w), 3055 (w), 1673 (w), 1644 (vs), 1611 (s), 1595 (s), 1571 (w), 1558 (w), 1489 (m), 1427 (m), 1399 (m), 1365 (m), 1331 (m), 1302 (w), 1270 (s), 1192 (m), 1107 (w), 1089 (s), 1012 (s), 948 (s), 909 (w), 904 (w), 896 (w), 858 (m), 851 (w), 838 (s), 824 (m), 811 (m), 756 (w), 747 (m), 712 (w).

m.p.: 115 - 116 °C.

7.9.4 Preparation of 3-allyl-4*H*-pyran-4-one (25d)



To a solution of γ-pyrone (**23**, 1 mL, 0.5 M in THF, 0.5 mmol) was added TMPZnCl·LiCl (**3**, 0.5 mL, 1.2 M in THF, 0.6 mmol, 1.2 equiv.) at 0 °C. The reaction mixture was stirred for 2 h according to **TP3**. The zinc reagent **24** was treated with CuCN·2LiCl (0.7 mL, 1 M solution in THF, 0.7 mmol, 1.4 equiv.) for 30 min at −60 °C. Acylation was achieved by adding pivaloyl chloride (84 mg, 0.7 mmol, 1.4 equiv.) at −40 °C and warming up to −4 °C. The reaction mixture was stirred at −4 °C until completion of the reaction. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 4:6) yielding compound **25d** (55 mg, 0.3 mmol, 61%) as a yellow liquid.

HRMS (EI) for $C_{10}H_{12}O_3$: calcd. 180.2005 (M^+); found 180.0784.

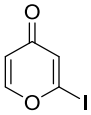
MS (70 eV, EI) *m/z* (%):124 (39), 123 (13), 96 (100), 57 (13), 52 (11), 41 (12).

^{1}H NMR (300 MHz, $CDCl_3$) δ =1.24 (s, 9 H), 6.40 (d, *J*=5.85 Hz, 1 H), 7.69 - 7.74 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ =26.05, 44.89, 118.63, 132.54, 153.11, 155.00, 175.08, 207.46.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3078 (vw), 3073 (vw), 2974 (w), 2937 (vw), 2869 (vw), 1708 (vs), 1651 (s), 1609 (w), 1598 (m), 1559 (w), 1479 (w), 1418 (m), 1360 (s), 1322 (m), 1221 (s), 1155 (m), 1092 (w), 1036 (w), 989 (m), 923 (m), 860 (m), 841 (m), 810 (w).

7.9.5 Preparation of 2-iodo-4*H*-pyran-4-one 27a



To a solution of γ-pyrone (**23**, 1 mL, 0.5 M in THF, 0.5 mmol) was added $TMP_2ZnCl·MgCl_2·2LiCl$ (**4**, 0.5 mL, 0.6 M in THF, 0.3 mmol, 0.6 equiv.) at −35 °C. The reaction mixture was stirred for 2 h according to **TP4** and reacted with iodine (0.7 mL, 1 M in THF, 0.7 mmol, 1.4 equiv.). The regioselectivity of of the metallation is checked by ^{1}H-NMR indicating C(3):C(2) = 1:15. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 3:7) furnishing compound **27a** (53 mg, 0.24, 48%) as a green liquid.

HRMS (EI) for $C_5H_3IO_2$: calcd. 221.9177 (M^+); found 221.9175.

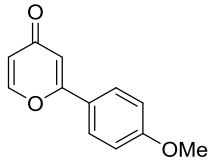
^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.35 (dd, *J*=5.94, 2.35 Hz, 1 H), 6.84 (d, *J*=2.21 Hz, 1 H), 7.67 (d, *J*=5.81 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 117.30, 119.09, 130.00, 156.85, 175.76.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3415 (w), 3089 (w), 2977 (m), 2928 (m), 2850 (w), 1661 (s), 1633 (s), 1575 (s), 1490 (m), 1441 (s), 1401 (s), 1370 (s), 1334 (s), 1288 (s), 1254 (vs), 1226 (vs), 1196

(vs), 1175 (vs), 1162 (s), 1126 (s), 1093 (s), 1071 (s), 1046 (s), 1018 (s), 940 (m), 930 (m), 891 (m), 861 (m), 839 (m), 834 (m), 801 (s), 687 (m).

7.9.6 Preparation of 2-(4-methoxyphenyl)-4*H*-pyran-4-one (27b)



To a solution of γ-pyrone (**23**, 1 mL, 0.5 M in THF, 0.5 mmol) was added $TMP_2ZnCl{\cdot}MgCl_2{\cdot}2LiCl$ (**4**, 0.5 mL, 0.6 M in THF, 0.3 mmol, 0.6 equiv.) at −35 °C. The reaction mixture was stirred for 2 h according to **TP4.** The zinc reagent reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (6 mg, 2 mol%), P(2-furyl)$_3$ (5 mg, 4 mol%) and 1-iodo-4-methoxybenzene (140 mg, 0.7 mmol, 1.4 equiv.) within 12 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 3:7) furnishing compound **27b** (58 mg, 0.29 mmol, 56%) as a yellow liquid.

HRMS (EI) for $C_{12}H_{10}O_3$: calcd. 202.0629 (M^+); found 202.0629.

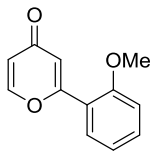
^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.84 (s, 3 H), 6.32 (dd, *J*=5.94, 2.35 Hz, 1 H), 6.66 (d, *J*=2.49 Hz, 1 H), 6.96 (m, 2 H), 7.68 (m, 2 H), 7.78 (d, *J*=5.81 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 55.45, 110.87, 114.44, 116.83, 123.40, 127.42, 154.54, 162.20, 163.94, 179.16.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3069 (w), 2956 (m), 2922 (m), 2836 (m), 1642 (s), 1602 (s), 1593 (s), 1575 (s), 1563 (m), 1508 (s), 1445 (m), 1427 (s), 1411 (s), 1362 (s), 1303 (m), 1260 (s), 1231 (s), 1221 (s), 1197 (m), 1180 (s), 1123 (m), 1029 (s), 1016 (s), 1007 (m), 930 (s), 864 (s), 842 (s), 814 (vs), 797 (s), 732 (m), 712 (m).

Lit. **^{1}H NMR**[134]

7.9.7 Preparation of 2-(2-methoxyphenyl)-4*H*-pyran-4-one (27c)



To a solution of γ-pyrone (**23**, 1 mL, 0.5 M in THF, 0.5 mmol) was added $TMP_2ZnCl{\cdot}MgCl_2{\cdot}2LiCl$ (**4**, 0.5 mL, 0.6 M in THF, 0.3 mmol, 0.6 equiv.) at −35 °C. The reaction mixture was stirred for 2 h according to **TP4.** The zinc reagent reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (6 mg, 2 mol%), P(2-furyl)$_3$ (5 mg, 4 mol%) and 1-iodo-2-methoxybenzene (140 mg, 0.7 mmol, 1.4 equiv.) within

[134] R. C. Barcelos, J. C. Pastre, V. Caixeta, D. B. Vendramini-Costa, J. E. de Carvalho, R. A. Pilli, *Bioorg. Med. Chem.* **2012**, 20, 3635.

12 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:i-hexane 4:6) yielding compound **27c** (68 mg, 0.34 mmol, 67%) as a colorless solid.

HRMS (EI) for $C_{12}H_{10}O_3$: calcd 202.06299; found 202.0628.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.86 (s, 3 H), 6.32 (dd, *J*=5.94, 2.63 Hz, 1 H), 6.90 - 7.13 (m, 3 H), 7.34 - 7.50 (m, 1 H), 7.66 (dd, *J*=7.74, 1.66 Hz, 1 H), 7.80 (d, *J*=5.81 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 55.58, 111.68, 116.56, 117.35, 120.03, 120.67, 128.81, 132.30, 155.06, 157.59, 161.37, 179.62.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3460 (w), 3078 (vw), 2943 (vw), 2840 (vw), 1636 (vs), 1591 (s), 1580 (m), 1561 (m), 1492 (m), 1464 (m), 1454 (m), 1436 (m), 1414 (m), 1361 (m), 1289 (m), 1249 (m), 1227 (m), 1181 (w), 1173 (w), 1128 (m), 1058 (w), 1020 (m), 1008 (m), 927 (s), 872 (m), 826 (w), 796 (w), 757 (m), 722 (w).

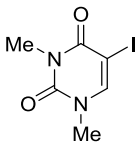
m.p.: 59 - 61 °C

Lit. **^{1}H NMR**: [135]

[135] (a) V. Rukachaisirikul, S. Kannai, S. Klaiklay, S. Phongpaichit, J.Sakayaroj, *Tetrahedron*, **2013**, *69*, 6981. (b) J. Toda, T. Saitoh, T. Oyama, Y. Horiguchi, T. Sano, *Heterocycles* **1996**, *43*, 2457.

7.10 Uracil Derivatives 36a-c, 38a-e, 43 a-d, 46a-d

7.10.1 Preparation of 5-Iodo-1,3-dimethyluracil (36a)



To a solution of 1,3-dimethyluracil (**34**, 140 mg, 1.0 mmol) in THF (1 mL) was added TMPMgCl·LiCl (**1**, 1 mL, 1.2 M in THF, 1.2 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5** and reacted with iodine (1.2 mL, 1 M in THF, 1.2 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 3:7:0.05) furnishing compound **36a** (191 mg, mmol, 0.72 mmol, 72%) as a colorless solid.

HRMS (ESI) for $C_6H_7IN_2O_2$: calcd. 266.0365 (M^+); found 265.9548.

MS (70 eV, EI) *m/z* (%): 266 (100), 208 (13), 167 (19).

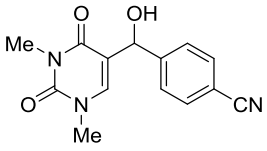
^{1}H-NMR (300 MHz, DMSO-d_6) δ = 3.19 (s, 3 H), 3.28 (s, 3 H), 8.23 (s, 1 H).

^{13}C-NMR (75 MHz, DMSO-d_6) δ = 29.22, 36.87, 66.69, 149.44, 151.60, 160.74.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3068 (w), 3050 (w), 2955 (w), 1688 (s), 1634 (s), 1616 (s), 1509 (m), 1475 (m), 1441 (s), 1425 (m), 1391 (m), 1352 (m), 1340 (s), 1262 (m), 1222 (m), 1143 (m), 1070 (w), 1011 (m), 957 (m), 944 (s), 814 (m), 752 (vs).

m.p.: 227 - 229 °C

7.10.2 Preparation of 4-((1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(hydroxy)methyl)benzonitrile (36b)



To a solution of 1,3-dimethyluracil (**34**, 280 mg, 2.0 mmol) in THF (2 mL) was added TMPMgCl·LiCl (2 mL, 1.2 M in THF, 2.4 mmol) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5** and reacted with *p*-cyanobenzaldehyde (314 mg, 1.2 equiv., 2.4 mmol) at 25 °C within 2 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:EtOH 1:9:0.5) furnishing compound **36b** (378 mg, 1.4 mmol, 70%) as a yellow solid.

HRMS (ESI) for $C_{14}H_{13}N_3O_2$: calcd. 271.2713 (M^+); found 271.0952.

MS (70 eV, EI) *m/z* (%): 272 (15), 271 (100), 270 (28), 248 (68), 247 (30), 167 (37), 156 (10), 141 (22), 140 (26), 129 (26), 42 (60).

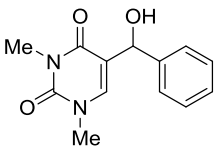
^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 3.30 (s, 3 H) 3.36 (s, 3 H) 5.75 (s, 1 H) 7.02 (s, 1 H) 7.59 (m, 4 H).

^{13}C-NMR: (75 MHz, $CDCl_3$) δ = 27.87, 37.27, 69.50, 111.64, 114.94, 118.61, 127.18, 132.32, 140.35, 146.63, 151.18, 163.04.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3486 (w), 3062 (w), 2953 (w), 2927 (w), 2886 (w), 2858 (w), 2233 (m), 1698 (s), 1655 (s), 1622 (vs), 1608 (s), 1503 (m), 1484 (m), 1457 (m), 1438 (m), 1404 (m), 1388 (m), 1363 (m), 1346 (s), 1312 (m), 1236 (m), 1213 (m), 1186 (m), 1175 (m), 1163 (s), 1088 (m), 1045 (m), 1027 (s), 1014 (m), 976 (m), 958 (m), 924 (m), 865 (m), 850 (m), 830 (s), 797 (s), 780 (m), 763 (m), 754 (s), 722 (m), 682 (m), 656 (m).

m.p.: 205 - 207 °C.

7.10.3 Preparation of 5-(hydroxy(phenyl)methyl)-1,3-dimethyluracil (36c)



To a solution of 1,3-dimethyluracil (**34**, 140 mg, 1.0 mmol) in THF (1 mL) was added TMPMgCl·LiCl (**1**, 1 mL, 1.2 M in THF, 1.2 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5** and reacted with benzaldehyde (124 mg, 1.2 mmol, 1.2 equiv.) at 25 °C for 2 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:EtOH 1:9:0.5 furnishing compound **36c** (182 mg, 0.74 mmol, 74%) as a colorless oil.

HRMS (ESI) for $C_{13}H_{14}N_2O_3$: calcd. 246.2619 (M^+); found 246.0998.

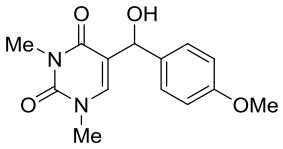
MS (70 eV, EI) *m/z* (%): 247 (14), 246 (100), 229 (11), 228 (37), 227 (19), 199 (15), 169 (25), 167 (24), 143 (14), 141 (10), 105 (11), 77 (11).

^{1}H-NMR (400 MHz, MeOH-d_4) δ = 3.23 (s, 3 H), 3.37 (s, 3 H), 5.68 (s, 1 H), 7.15 - 7.25 (m, 1 H), 7.25 - 7.33 (m, 2 H), 7.34 - 7.45 (m, 2 H), 7.51 (d, *J*=0.98 Hz, 1 H).

^{13}C-NMR (100 MHz, MeOH-d_4) δ = 26.67, 35.97, 68.65, 116.07, 126.39, 127.10, 127.82, 140.89, 142.55, 151.74, 162.81.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3415 (w), 3062 (vw), 3029 (vw), 2953 (w), 2925 (w), 1694 (s), 1653 (vs), 1625 (vs), 1557 (m), 1511 (w), 1482 (s), 1452 (s), 1397 (m), 1367 (m), 1339 (s), 1240 (m), 1171 (m), 1083 (m), 1058 (m), 1033 (m), 1021 (m), 1002 (m), 967 (w), 915 (m), 830 (m), 795 (w), 763 (s), 755 (s), 729 (m), 715 (s), 698 (s), 674 (m), 665 (m).

7.10.4 Preparation of 5-(hydroxy(4-methoxyphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (36d)



To a solution of 1,3-dimethyluracil (**34**, 280 mg, 2.0 mmol) in THF (2 mL) was added TMPMgCl·LiCl (**1**, 2 mL, 1.2 M in THF, 2.4 mmol) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5** and reacted with *p*-methoxybenzaldehyde (326 mg, 1.2 equiv., 2.4 mmol) at 25 °C for 2 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:EtOH 1:9:0.5) furnishing the compound **36d** (259 mg, 0.97 mmol, 48%) as a colorless oil.

HRMS (EI) for $C_{14}H_{16}N_2O_4$: calcd. 276.2878 (M^+); found 276.1104.

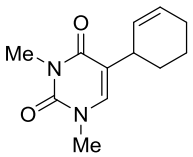
MS (70 eV, EI) *m/z* (%): 276 (100), 240 (62), 158 (46), 140 (70), 137 (31), 77 (30), 42 (60).

^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 3.21 (s, 3 H), 3.25 (d, *J*=2.73 Hz, 3 H), 3.73 (d, *J*=2.92 Hz, 3 H), 5.60 (d, *J*=2.53 Hz, 1 H), 6.69 - 6.85 (m, 2 H), 6.92 (s, 1 H), 7.16 - 7.31 (m, 2 H).

^{13}C-NMR: (101 MHz, $CDCl_3$) δ =27.76, 37.10, 55.22, 69.40, 113.82, 116.23, 127.75, 133.02, 140.03, 151.36, 159.16, 163.21.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3424 (w), 3068 (vw), 3000 (vw), 2955 (w), 2838 (vw), 1696 (s), 1655 (vs), 1629 (vs), 1586 (m), 1510 (s), 1481 (s), 1456 (s), 1367 (m), 1339 (m), 1302 (m), 1244 (s), 1171 (s), 1110 (m), 1085 (m), 1059 (m), 1027 (s), 966 (w), 920 (m), 833 (s), 792 (m), 758 (s), 732 (s), 699 (m).

7.10.5 Preparation of 5-(cyclohex-2-en-1-yl)-1,3-dimethyluracil (36e)



To a solution of 1,3-dimethyluracil (**34**, 280 mg, 2.0 mmol) in THF (1 mL) was added TMPMgCl·LiCl (**1**, 2 mL, 2.4 M in THF, 2.4 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5.** To the freshly prepared magnesium reagent was added CuCN·2LiCl (1 M solution in THF, 2.4 mL, 2.4 mmol, 1.2 equiv.) and the reaction mixture was stirred for 30 min at −40 °C. Allylation was achieved by adding 3-bromocyclohexene (644 mg, 4.0 mmol, 2 equiv.) at −40 °C, stirring at −40 °C for 10 min and 1 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:9:0.05 to 3:7:0.05) furnishing the compound **36e** (248 mg, 1.13 mmol, 56%) as a yellow solid.

HRMS (EI) for $C_{12}H_{16}N_2O_2$: calcd. 220.2676; found 220.1200 (M^+).

MS (70 eV, EI) *m/z* (%): 220 (63), 217 (26), 166 (48), 127 (23), 81 (23), 57 (27), 55 (23), 46 (39), 45 (100), 44 (94).

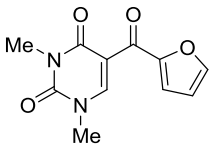
^{1}H-NMR (400 MHz, MeOH-d_4) δ = 1.44 - 1.55 (m, 1 H), 1.54 – 1.57 (m, 2H), 1.76 - 1.93 (m, 1 H), 1.94 - 2.07 (m, 2 H), 3.27 (s, 3 H), 3.36 (s, 3 H), 3.39 (td, *J*=5.82, 3.03 Hz, 1 H), 5.44 - 5.57 (m, 1 H), 5.82 - 5.94 (m, 1 H), 7.17 (s, 1 H).

^{13}C-NMR (101 MHz, MeOH-d_4) δ = 19.44, 24.64, 26.92, 28.06, 32.47, 35.80, 116.24, 127.21, 129.59, 140.88, 151.75, 163.62.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3063 (w), 3019 (w), 2919 (w), 2864 (w), 2854 (w), 2834 (w), 1692 (s), 1657 (vs), 1637 (vs), 1572 (w), 1509 (w), 1452 (s), 1428 (s), 1372 (m), 1341 (s), 1308 (w), 1296 (w), 1288 (w), 1248 (w), 1235 (m), 1221 (m), 1189 (w), 1173 (m), 1154 (w), 1132 (w), 1089 (m), 1058 (w), 1026 (m), 999 (w), 990 (w), 975 (m), 948 (m), 931 (w), 918 (w), 893 (w), 883 (m), 862 (w), 853 (w), 821 (w), 785 (m), 767 (m), 752 (s), 738 (s), 726 (s), 674 (m).

m.p.: 74 – 76 °C

7.10.6 Preparation of 5-(furan-2-carbonyl)-1,3-dimethyluracil (36f)



To a solution of 1,3-dimethyluracil (**34**, 350 mg, 2.5 mmol) in THF (1 mL) was added TMPMgCl·LiCl (**1**, 2.5 mL, 1.2 M in THF, 2.5 mmol, 1 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5**. To the freshly prepared magnesium reagent was added CuCN·2LiCl (2.5 mL, 1 M solution in THF, 2.5 mmol, 1 equiv.) and the reaction mixture was stirred for 30 min. Acylation was achieved by adding furoyl chloride (393 mg, 2.4 mmol) at −40 °C and warming up to −10 °C within 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:9:0.05 to 3:7:0.05) furnishing compound **36f** (391, 1.7 mmol, 66%) as a colorless solid.

HRMS (ESI) for $C_{11}H_{10}N_2O_4$: calcd. 234.2110, found 234.0623.

^{1}H NMR (400 MHz, DMSO-d_6) δ =3.17 (s, 3 H), 3.37 (s, 3 H), 6.71 (dd, *J*=3.61, 1.66 Hz, 1 H), 7.38 (dd, *J*=3.70, 0.78 Hz, 1 H), 8.01 (dd, *J*=1.75, 0.78 Hz, 1 H), 8.28 (s, 1 H).

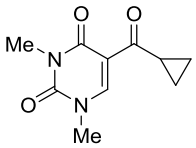
^{13}C NMR (101 MHz, DMSO-d_6) δ = 28.06, 37.40, 111.31, 112.95, 121.38, 148.63, 149.14, 151.31, 152.03, 160.41, 177.02.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3142.00 (w), 3129.00 (w), 3097.00 (w), 2952.00 (w), 1706.00 (m), 1695.00 (m), 1658.00 (s), 1647.00 (s), 1600.00 (m), 1554.00 (m), 1520.00 (w), 1470.00 (m), 1458.00 (m), 1437.00 (s), 1401.00 (m), 1390.00 (s), 1364.00 (s), 1297.00 (s), 1243.00 (m),

1208.00 (m), 1167.00 (m), 1121.00 (m), 1097.00 (m), 1041.00 (s), 998.00 (m), 940.00 (s), 923.00 (m), 893.00 (m), 881.00 (s), 863.00 (m), 818.00 (s), 787.00 (s), 773.00 (s), 753.00 (vs), 697.00 (m), 683.00 (s).

m.p.: 139 - 140°C

7.10.7 Preparation of 5-(cyclopropanecarbonyl)-1,3-dimethyluracil (36g)



To a solution of 1,3-dimethyluracil (**34**, 140 mg, 1.0 mmol) in THF (1 mL) was added TMPMgCl·LiCl (**1**, 1 mL, 1.2 M in THF, 1.2 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5**. To the freshly prepared magnesium reagent was added CuCN·2LiCl (1.2 mL, 1 M solution in THF, 1.2 mmol) and the reaction mixture was stirred for 30 min. Acylation was achieved by adding cyclopropanecarbonyl chloride (125 mg, 1.2 mmol, 1.2 equiv.) at -40 °C and warming up to -20 °C within 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:9:0.05 to 3:7:0.05) furnishing compound **36g** (148 mg, mmol, 0.71 mmol, 71%) as a colorless solid.

HRMS (ESI) for $C_{10}H_{12}N_2O_3$: calcd. 208.2139, found 208.2139.

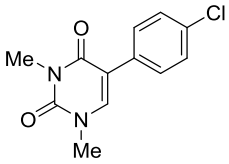
^{1}H NMR (400 MHz, acetone) δ = 0.88 - 0.94 (m, 2 H), 0.94 - 1.00 (m, 2 H), 3.27 (s, 3 H), 3.30 - 3.43 (m, 1 H), 3.52 (s, 3 H), 8.25 (s, 1 H).

^{13}C NMR (101 MHz, acetone) δ = 11.06, 18.37, 27.18, 36.88, 110.84, 149.81, 149.82, 161.37, 196.07.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3103.00 (vw), 3057.00 (w), 3006.00 (w), 2958.00 (w), 1704.00 (m), 1659.00 (m), 1644.00 (s), 1594.00 (s), 1516.00 (m), 1476.00 (m), 1442.00 (s), 1424.00 (m), 1417.00 (m), 1391.00 (m), 1351.00 (m), 1338.00 (s), 1197.00 (m), 1186.00 (m), 1119.00 (m), 1086.00 (m), 1071.00 (m), 1064.00 (w), 1047.00 (m), 1030.00 (m), 996.00 (s), 987.00 (s), 972.00 (m), 887.00 (s), 778.00 (vs), 758.00 (vs), 693.00 (m), 665.00 (m).

m.p.: 154 - 156 °C

7.10.8 Preparation of 5-(4-chlorophenyl)-1,3-dimethyluracil (36h)



To a solution of 1,3-dimethyluracil (**34**, 140 mg, 1.0 mmol) in THF (1 mL) was added TMPMgCl·LiCl (**1**, 1 mL, 1.2 M in THF, 1.2 mmol,

1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5**, transmetalated to the corresponding zinc reagent by adding $ZnCl_2$ (1.2 mL, 1 M solution in THF, 2.4 mmol, 1.2 equiv.) and reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (11 mg, 2 mol%), P(2-furyl)$_3$ (9 mg, 4 mol%)[136] and *p*-chloro-iodobenzene (285 mg , 1.2 mmol) at 25 °C for 2 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:9:0.05 to 3:7:0.05) furnishing compound **36h** (195 mg, 0.78 mmol, 78%) as a colorless solid.

HRMS (EI) for $C_{12}H_{11}ClN_2O_2$: calcd. 250.6809 (M^+); found 250.0499.

MS (70 eV, EI) *m/z* (%): 252 (30), 251 (12), 250 (100), 193 (22), 154 (12), 151 (38).

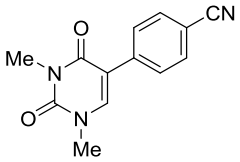
^{1}H-NMR (300 MHz, DMSO-d_6) δ = 3.22 (s, 3 H), 3.37 (s, 3 H), 7.43 (m, *J*=8.57 Hz, 2 H), 7.60 (m, *J*=8.85 Hz, 2 H), 8.03 (s, 1 H).

^{13}C-NMR (75 MHz, DMSO-d_6) δ = 28.22, 36.99, 110.53, 128.49, 130.07, 132.11, 132.84, 143.39, 151.32, 162.05.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2945 (w), 2922 (m), 2852 (w), 1692 (s), 1644 (vs), 1488 (m), 1451 (s), 1404 (m), 1357 (s), 1290 (m), 1210 (m), 1124 (m), 1115 (m), 1094 (m), 1006 (m), 970 (m), 932 (m), 842 (s), 835 (s), 822 (s), 774 (s), 753 (vs), 720 (m), 704 (m).

m.p.: 171 - 173 °C

7.10.9 Preparation of 4-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)benzonitrile (36i)



To a solution of 1,3-dimethyluracil (**34**, 280 mg, 2.0 mmol) in THF (2 mL) was added TMPMgCl·LiCl (**1**, 2 mL, 2.4 M in THF, 2.4 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5**. The freshly prepared magnesium reagent was transmetalated to the corresponding zinc reagent by adding $ZnCl_2$ (2.4 mL, 1 M solution in THF, 2.4 mmol, 1.2 equiv.) and reacted in a *Negishi* cross-coupling reaction by adding $Pd(OAc)_2$ (9 mg, 2%), XantPhos (46 mg, 4%) and *p*-bromobenzonitrile (436 mg, 2.4 mmol, 1.2 equiv.) at 50 °C for 3 days. The crude product was purified by flash column chromatography (SiO_2,

EtOAc:*i*-hexane:Et_3N 1:9:0.05 to 3:7:0.05) furnishing compound **36i** (375 mg, 1.5 mmol, 78%) as a yellow solid.

HRMS (EI) for $C_{13}H_{11}N_3O_2$: calcd. 241.2453 (M^+); found 241.0843.

MS (70 eV, EI) *m/z* (%): 242 (15), 241 (100), 184 (20), 183 (60), 127 (18), 115 (13), 41 (60).

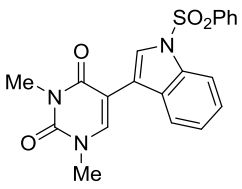
^{1}H-NMR (400 MHz, DMSO-d_6) δ = 3.25 (s, 3 H), 3.41 (s, 3 H), 7.84 (m, 4 H), 8.22 (s, 1 H).

^{13}C-NMR (101 MHz, DMSO-d_6) δ = 28.30, 37.21, 109.78, 109.91, 119.41, 128.81, 132.46, 139.04, 144.82, 151.26, 161.85.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3106 (w), 3076 (w), 3005 (w), 2954 (w), 2225 (m), 1706 (s), 1648 (vs), 1606 (s), 1508 (m), 1480 (s), 1451 (s), 1428 (s), 1409 (s), 1395 (m), 1366 (m), 1345 (s), 1321 (m), 1295 (m), 1265 (m), 1200 (m), 1186 (m), 1117 (m), 1004 (m), 968 (m), 916 (s), 840 (s), 832 (m), 770 (m), 753 (s), 737 (s), 704 (m), 687 (m).

m.p.: 213 - 215 °C

7.10.10 Preparation of 1,3-dimethyl-5-(1-(phenylsulfonyl)-1H-indol-3-yl)uracil (36j)



To a solution of 1,3-dimethyluracil (**34**, 280 mg, 2.0 mmol) in THF (2 mL) was added TMPMgCl·LiCl (**1**, 2 mL, 1.2 M in THF, 2.4 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5**, transmetalated to the corresponding zinc reagent by adding $ZnCl_2$ (2.4 mL, 1 M solution in THF, 2.4 mmol, 1.2 equiv.) and reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (22 mg, 2 mol%), P(2-furyl)$_3$ (19 mg, 4 mol%) and 3-iodo-1-(phenylsulfonyl)-indole (920 mg , 2.4 mmol, 1.2 equiv.) at 25 °C for 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:1:0.01 furnishing compound **36j** (578 mg, 1.46 mmol, 73%) as a colorless solid.

HRMS (EI) for $C_{20}H_{17}N_3O_4S$: calcd. 395.4317 (M^+); found 395.0930.

MS (70 eV, EI) *m/z* (%): 396 (9), 395 (41), 255 (18), 254 (100), 197 (39), 156 (22), 128 (12).

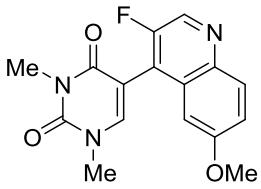
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.43 (s, 3 H), 3.49 (s, 3 H), 7.24 - 7.28 (m, 1 H), 7.31 - 7.36 (m, 1 H), 7.40 - 7.46 (m, 2 H), 7.50 - 7.56 (m, 3 H), 7.90 - 7.94 (m, 2 H), 8.01 (s, 1 H), 8.03 (d, *J*=8.14 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 28.35, 37.30, 106.82, 113.81, 114.01, 120.07, 123.56, 124.95, 125.56, 126.87, 128.84, 129.34, 133.94, 134.84, 137.97, 140.09, 151.12, 162.00.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3170 (vw), 3091 (vw), 3065 (vw), 2955 (vw), 2923 (vw), 2851 (vw), 1699 (s), 1653 (s), 1578 (w), 1546 (w), 1485 (w), 1456 (m), 1446 (s), 1428 (w), 1405 (vw), 1362 (m), 1353 (s), 1332 (m), 1312 (w), 1264 (w), 1209 (m), 1183 (m), 1171 (s), 1162 (s), 1141 (s), 1115 (s), 1100 (m), 1083 (m), 1032 (w), 1026 (w), 1021 (w), 1004 (m), 976 (m), 942 (w), 930 (w), 907 (m), 859 (w), 847 (w), 823 (w), 816 (m), 772 (m), 752 (s), 742 (vs), 726 (vs), 709 (w), 685 (s), 663 (s).

m.p.: 108 °C

7.10.11 Preparation of 5-(3-fluoro-6-methoxyquinolin-4-yl)-1,3-dimethyluracil (36k)



To a solution of 1,3-dimethyluracil (**34**, 280 mg, 2.0 mmol) in THF (2 mL) was added TMPMgCl·LiCl (**1**, 2 mL, 1.2 M in THF, 2.4 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5**. The magnesium reagent was transmetalated to the corresponding zinc reagent by adding $ZnCl_2$ (2.4 mL, 1 M solution in THF, 2.4 mmol, 1.2 equiv.) and reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (22 mg, 2 mol%), $P(2\text{-furyl})_3$ (19 mg, 4 mol%) and 3-fluoro-4-iodo-6-methoxyquinoline (727 mg, 2.4 mmol, 1.2 equiv.) at 25 °C for 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:1:0.01 furnishing compound **36k** (358 mg, 1.14 mmol, 56%) as a colorless solid.

MS (70 eV, EI) *m/z* (%): 316 (18), 315 (100), 314 (27), 300 (17), 272 (10).

HRMS (EI) for $C_{16}H_{14}FN_3O_3$: calcd. 315.2991 (M^+); found 315.1015.

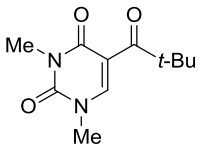
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.45 (s, 3 H), 3.50 (s, 3 H), 3.85 (s, 3 H), 6.85 (d, *J*=2.73 Hz, 1 H), 7.32 (dd, *J*=9.16, 2.73 Hz, 1 H), 7.35 (s, 1 H), 8.01 (d, *J*=9.16 Hz, 1 H), 8.68 (s, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 28.41, 37.40, 55.64, 103.25 (d, *J*= 5.37 Hz), 104.16, (s, 1 C) 120.63 (d, *J*= 2.69 Hz), 121.60 (d, *J*=12.76 Hz), 129.37, 131.52, 138.25 (d, *J*=28.79 Hz), 141.67, 143.76 (d, *J*=1.15 Hz), 151.51, 154.43 (d, *J*=255 Hz), 158.89, 161.07.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3341 (vw), 3106 (vw), 2952 (w), 2842 (w), 1701 (m), 1649 (vs), 1621 (s), 1510 (m), 1476 (m), 1447 (m), 1432 (s), 1393 (m), 1377 (m), 1356 (m), 1344 (s), 1299 (m), 1259 (w), 1227 (s), 1196 (s), 1162 (m), 1130 (s), 1091 (s), 1059 (m), 1029 (m), 1013 (s), 964 (m), 931 (m), 921 (m), 881 (m), 846 (m), 834 (s), 804 (s), 790 (s), 777 (m), 758 (vs), 713 (m), 694 (m), 656 (m).

m.p.: 208 - 210 °C.

7.10.12 Preparation of 1,3-Dimethyl-5-pivaloyluracil (36l)



To a solution of 1,3-dimethyluracil (**34**, 140 mg, 1.0 mmol) in THF (1 mL) was added TMPMgCl·LiCl (**1**, 1 mL, 1.2 M in THF, 1.2 mmol) at −40 °C. The reaction mixture was stirred for 24 h according to **TP5**. To the freshly prepared magnesium reagent was added CuCN·2LiCl (1.2 mL, 1 M solution in THF, 1.2 mmol, 1.2 equiv.) and the reaction mixture was stirred for 30 min. Acylation was achieved by adding pivaloyl chloride (145 mg, 1.2 mmol, 1.2 equiv.) at −40 °C and warming up to −20 °C within 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:9:0.05 to 3:7:0.05) furnishing the compound **36l** (187 mg, 0.83 mmol, 83%) as a colorless solid.

HRMS (EI) for $C_{11}H_{16}N_2O_3$: calcd. 224.2563 (M^+); found 224.1157.

MS (70 eV, EI) *m/z* (%): 167 (28), 167 (100), 140 (34), 57 (13), 42 (66), 40 (16).

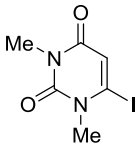
^{1}H-NMR (300 MHz, DMSO-d_6) δ = 1.17 (s, 9 H), 3.17 (s, 3 H), 3.33 (s, 3 H), 7.95 (s, 1 H).

^{13}C-NMR (75 MHz, DMSO-d_6) δ = 26.66, 28.08, 37.19, 44.46, 113.99, 146.33, 151.31, 160.79, 206.09.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3067 (w), 2963 (w), 2926 (w), 2872 (w), 1777 (w), 1705 (s), 1651 (vs), 1609 (s), 1520 (m), 1478 (m), 1443 (s), 1390 (m), 1356 (s), 1342 (s), 1284 (m), 1221 (m), 1179 (m), 1049 (m), 1026 (w), 986 (s), 967 (s), 941 (m), 934 (m), 846 (m), 794 (m), 785 (m), 760 (s), 738 (m), 663 (w).

m.p.: 103 - 105 °C

7.10.13 Preparation of 6-Iodo-1,3-dimethyluracil (38a)



38a was prepared according to **TP6** from 1,3-dimethyluracil (**34**, 140 mg, 1.0 mmol) dissolved in THF (1.0 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0.71 M in THF, 0.7 mmol, 0.7 equiv.) was added at −30 °C to the solution, stirred for 48 h and reacted with iodine (1.2 mL, 1 M in THF, 1.2 mmol). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:9:0.5) yielding compound **38a** (216 mg, 0.81 mmol, 81%) as a colorless solid.

HRMS (EI) for $C_6H_7IN_2O_2$: calcd. 266.0365 (M^+); found 265, 9536.

MS (70 eV, EI) *m/z* (%): 267 (6), 266 (95), 83 (4), 82 (100), 57 (6), 54 (8), 52 (6).

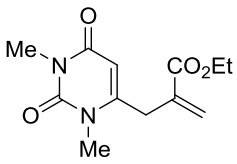
^{1}H-NMR (300 MHz, DMSO-d_6) δ = 3.10 (s, 3 H), 3.52 (s, 3 H), 6.41 (s, 1 H).

^{13}C-NMR (75 MHz, DMSO-d_6) δ = 28.24, 41.68, 112.99, 116.97, 149.99, 161.23.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3092.00 (m), 1684.00 (s), 1652.00 (s), 1647.00 (s), 1631.00 (vs), 1617.00 (s), 1576.00 (s), 1429.00 (s), 1423.00 (vs), 1377.00 (s), 1353.00 (s), 1282.00 (m), 1232.00 (m), 1228.00 (m), 1205.00 (m), 1158.00 (m), 1109.00 (m), 1056.00 (w), 1007.00 (m), 951.00 (m), 845.00 (m), 831.00 (m), 751.00 (vs), 691.00 (m)

m.p.: 183 - 184 °C.

7.10.14 Preparation of ethyl 2-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl)acrylate (38b)



38b was prepared from 1,3-dimethyluracil (**34**, 140 mg, 1.0 mmol) dissolved in THF (1 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0. 71 M in THF, 0.7 mmol, 0.7 equiv.) was added at −30 °C to the solution, according to **TP6** and stirred for 48 h. The freshly prepared zinc reagent was transmetalated to copper by adding CuCN·2LiCl (1.2 mL, 1 M solution in THF 1.2 mmol, 1.2 equiv.) and stirring for 30 min. Allylation was achieved by adding ethyl 2-(bromomethyl)acrylate (231 mg, 1.2 mmol) at −40 °C, stirring for 10 min at –40 °C and 1 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:10: to EtOAc:*i*-hexane 3:7) providing compound **38b** (175 mg, 0.69 mmol, 69%) as a colorless solid.

HRMS (EI) for $C_{12}H_{16}N_2O_4$: calcd. 252.2664 (M^+); found 252.1104.

MS (70 eV, EI) *m/z* (%): 252 (38), 223 (65), 179 (86), 150 (26), 149 (21), 122 (40), 94 (32), 82 (60), 46 (37).

^{1}H-NMR (300 MHz, DMSO-d_6) δ = 1.21 (t, *J*=7.05 Hz, 3 H), 3.14 (s, 3 H), 3.25 (s, 3 H), 3.57 (s, 2 H), 4.16 (q, *J*=7 Hz, 2 H), 5.47 (s, 1 H), 5.73 (d, *J*=0.55 Hz, 1 H), 6.28 (d, *J*=0.55 Hz, 1 H).

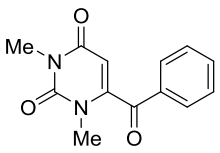
^{13}C-NMR (75 MHz, DMSO-d_6) δ =14.43, 27.92, 31.76, 34.42, 61.35, 100.79, 128.52, 135.64, 152.50, 153.49, 161.94, 165.81.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3111 (vw), 3000 (w), 2970 (w), 2939 (w), 1711 (s), 1690 (vs), 1647 (vs), 1630 (s), 1624 (s), 1467 (s), 1445 (s), 1433 (s), 1412 (m), 1407 (m), 1388 (s), 1367 (m), 1337 (s), 1307 (m), 1237 (s), 1211 (m), 1172 (s), 1148 (s), 1096 (m), 1015 (m), 993 (m), 982

(s), 957 (m), 933 (m), 897 (m), 879 (m), 858 (m), 835 (s), 829 (s), 825 (s), 790 (m), 754 (vs), 664 (m).

m.p.: 67 - 68 °C

7.10.15 Preparation of 6-benzoyl-1,3-dimethyluracil (38c)



38c was prepared from 1,3-dimethyluracil (**34**, 140 mg, 1.0 mmol) dissolved in THF (1 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0.7 M in THF, 0.7 mmol, 0.7 equiv.) was added to the solution at −30 °C according to **TP6** and stirred for 48 h. The freshly prepared zinc reagent was transmetalated to copper by adding CuCN·2LiCl (1 M solution in THF, 1.2 mL, 1.2 mmol, 1.2 equiv.) and stirring for 30 min. Acylation was achieved by adding benzoyl chloride (168 mg, 1.2 mmol) at −40 °C and warming up to −8 °C within 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:9:0.5 to 3:7:0.5) providing compound **38c** (204 mg, 0.84 mmol, 84%) as a colorless oil.

HRMS (EI) for $C_{13}H_{12}N_2O_3$: calcd. 244.2460 (M^+); found 244.0845.

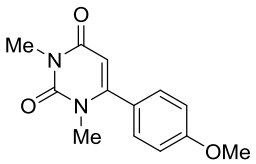
MS (70 eV, EI) *m/z* (%): 244 (62), 216 (37), 215 (42), 159 (19), 158 (21), 105 (100), 82 (81), 77 (63).

^{1}H-NMR (300 MHz, DMSO-d_6) δ = 3.09 (s, 3 H), 3.21 (s, 3 H), 5.85 (s, 1 H), 7.46 - 7.70 (m, 2 H), 7.70 - 7.89 (m, 1 H), 7.92 - 8.13 (m, 2 H).

^{13}C-NMR (75 MHz, DMSO-d_6) δ = 28.09, 33.72, 100.86, 129.77, 130.68, 134.27, 136.01, 150.28, 151.93, 162.07, 189.50.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3706 (vw), 3086 (vw), 3064 (vw), 2954 (vw), 1705 (s), 1651 (vs), 1594 (s), 1580 (m), 1519 (w), 1476 (m), 1446 (s), 1432 (s), 1399 (m), 1364 (s), 1312 (m), 1252 (s), 1210 (m), 1180 (m), 1159 (m), 1073 (w), 1053 (w), 1024 (w), 994 (m), 914 (m), 844 (m), 827 (m), 805 (m), 758 (s), 726 (s), 699 (s), 687 (s), 668 (s).

7.10.16 Preparation of 6-(4-methoxyphenyl)-1,3-dimethyluracil (38d)



38d was prepared according to **TP6** from 1,3-dimethyluracil (**34**, 140 mg, 1.0 mmol) dissolved in THF (1.0 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0.71 M in THF, 0.7 mmol, 0.7 equiv.) was added to the solution at −30 °C and stirred for 48 h. The zinc reagent reacted in a *Negishi* cross-coupling reaction by adding

$Pd(dba)_2$ (22 mg, 2 mol%), P(2-furyl)$_3$ (19 mg, 4 mol%) and *p*-methoxyiodobenzene (280 mg, 1.2 mmol) within 2 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 2:8:0.5) yielding compound **38d** (207 mg, 0.84 mmol, 84%) as a colorless solid.

HRMS (EI) for $C_{13}H_{14}N_2O_3$: calcd. 246.2619 (M^+); found 246.0996.

MS (70 eV, EI) *m/z* (%): 247 (16), 246 (100), 245 (85), 188 (26), 160 (11), 133 (11).

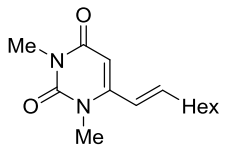
^{1}H-NMR (400 MHz, MeOH-d_4) δ = 3.19 (s, 3 H), 3.29 (s, 3 H), 3.82 (s, 3 H), 5.59 (s, 1 H), 7.01 (m, *J*=8.80 Hz, 2 H), 7.34 (m, *J*=8.80 Hz, 2 H).

^{13}C-NMR (101 MHz, MeOH-d_4) δ = 26.96, 33.84, 54.59, 101.00, 113.91, 125.34, 129.28, 152.64, 155.84, 161.21, 163.24.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954 (w), 2923 (w), 2869 (w), 2846 (w), 1699 (m), 1687 (s), 1645 (vs), 1603 (s), 1570 (m), 1514 (s), 1443 (s), 1429 (s), 1414 (s), 1391 (m), 1368 (s), 1299 (m), 1254 (s), 1226 (m), 1206 (m), 1178 (s), 1164 (m), 1151 (m), 1119 (m), 1027 (s), 1015 (m), 1010 (m), 1001 (s), 846 (s), 839 (s), 813 (vs), 791 (m), 761 (vs), 738 (m), 716 (m), 704 (m), 699 (m), 688 (m), 659 (m).

m.p.: 88 – 89 °C

7.10.17 Preparation of (E)-1,3-dimethyl-6-(3-oct-1-en) uracil (38e)



38e was prepared according to **TP6** from 1,3-dimethyluracil (**34**, 140 mg, 1.0 mmol) dissolved in THF (1.0 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0.71 M in THF, 0.7 mmol, 0.74 equiv.) was added to the solution at −30 °C and stirred for 48 h. The zinc reagent reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (11 mg, 4 mol%), P(2-furyl)$_3$ (9.5 mg, 2 mol%) and (141 mg, 0.59 mmol, 1.2 equiv.) within 2 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 2:8:0.5) yielding compound **38e** (185 mg, 0.74 mmol, 74%) as a colorless oil.

HRMS (EI) for $C_{13}H_{14}N_2O_3$: calcd. 250.168 (M^+), found 250.1683.

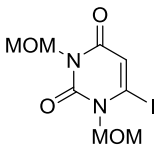
MS (70 eV, EI) *m/z* (%): 250 (60), 207 (12), 194 (13), 193 (100), 180 (11), 167 (30).

^{1}H-NMR (400 MHz, MeOH-d_4) δ =6.33 (m, 1H), 6.13 (m, 1H), 5.74 (s, 1H), 3.37 (s, 3H), 3.32 (s, 3H), 2.21 (m, 2H), 1.57-1.18 (m, 8H), 0.96-0.76 (m, 3H).

^{13}C-NMR (101 MHz, MeOH-d_4) δ =162.69, 152.35, 152.07, 142.13, 121.29, 98.42, 32.92, 32.25, 31.48, 28.69, 28.33, 27.84, 22.47, 14.09.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3063 (w), 3019 (w), 2919 (w), 2864 (w), 2854 (w), 2834 (w), 1692 (s), 1657 (vs), 1637 (vs), 1572 (w), 1509 (w), 1452 (s), 1428 (s), 1372 (m), 1341 (s), 1308 (w), 1296 (w), 1288 (w), 1248 (w), 1235 (m), 1221 (m), 1189 (w), 1173 (m), 1154 (w), 1132 (w), 1089 (m), 1058 (w), 1026 (m), 999 (w), 990 (w), 975 (m), 948 (m), 931 (w), 918 (w), 893 (w), 883 (m), 862 (w), 853 (w), 821 (w), 785 (m), 767 (m), 752 (s), 738 (s), 726 (s), 674 (m).
m.p.: 67 - 68 °C

7.10.18 Preparation of 6-iodo-1,3-bis(methoxymethyl)uracil (43a)



To a solution of 1,3-bis(methoxymethyl) uracil (**40**, 400 mg, 2 mmol) was added $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1.7 mL, 0.71 M in THF, 1.2 mmol) at −30 °C. The reaction mixture was stirred for 48 h according to **TP7** and reacted with iodine (2.4 mL, 1 M in THF, 2.4 mmol). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:9:0.05) yielding compound **43a** (457 mg, 1.40 mmol, 70%) as a yellow solid.

HRMS (EI) for $C_8H_{11}IN_2O_4$: calcd. 326.0884 (M^+); found 325.9749.

MS (70 eV, EI) *m/z* (%): 326 (4), 311 (8), 296 (10), 283 (33), 251 (6), 222 (9), 86 (5), 56 (5), 45 (100).

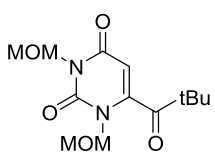
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 3.39 (s, 3 H), 3.41 (s, 3 H), 5.30 (s, 2 H), 5.43 (s, 2 H), 6.49 (s, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 57.14, 57.93, 72.59, 82.52, 110.67, 116.25, 149.93, 160.56.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2958 (vw), 2935 (vw), 2834 (vw), 1706 (m), 1650 (vs), 1576 (m), 1436 (m), 1419 (s), 1402 (m), 1371 (s), 1350 (m), 1330 (m), 1303 (w), 1248 (w), 1194 (m), 1181 (m), 1156 (m), 1100 (s), 1087 (s), 1018 (m), 983 (m), 926 (m), 913 (s), 817 (s), 772 (s), 724 (m), 671 (s).

m.p.:90 - 92 °C

7.10.19 Preparation of 1,3-bis(methoxymethyl)-6-pivaloylpyrimidine-2,4(1H,3H)-dione (43b)



To a solution of 1,3-bis(methoxymethyl) uracil (**40**, 800 mg, 4 mmol) was added $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, .4 mL, 0. 71 M in THF, 2.4 mmol, 2.4 equiv.) at –30 °C. The reaction mixture was stirred for 48 h according to

TP7. The zinc reagent **44** was treated with CuCN·2LiCl (4.8 mL, 1 M solution in THF, 4.8 mmol, 1.2 equiv.) for 30 min at −40 °C. Acylation was achieved by adding pivaloyl chloride (576 mg, 4.8 mmol) at −40 °C and warming up to −10 °C over 12 h. The reaction mixture was stirred at −10 °C until completion of the reaction. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N) yielding compound **43b** (778 mg, 2.7 mmol, 68%) as a yellow liquid.

HRMS (EI) for $C_{13}H_{20}N_2O_5$: calcd. 284.3083 (M^+); found 284.1360.

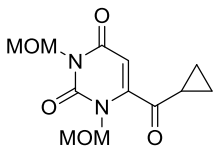
MS (70 eV, EI) *m/z* (%): 252 (9), 241 (11), 209 (8), 140 (6), 138 (18), 73 (8), 57 (25), 45 (100).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.28 (d, *J*=1.11 Hz, 9 H), 3.31 (d, *J*=1.11 Hz, 3 H), 3.43 (d, *J*=1.11 Hz, 3 H), 5.17 (d, *J*=1.11 Hz, 2 H), 5.35 (d, *J*=1.11 Hz, 2 H), 5.77 (d, *J*=0.83 Hz, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 27.49, 44.71, 56.74, 57.94, 72.25, 74.72, 100.04, 148.98, 151.67, 161.56, 205.3.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2972 (w), 2832 (vw), 1720 (m), 1696 (m), 1665 (vs), 1617 (m), 1447 (s), 1414 (m), 1383 (m), 1366 (m), 1335 (s), 1252 (w), 1226 (w), 1196 (m), 1171 (m), 1150 (m), 1086 (vs), 1039 (m), 1023 (w), 986 (m), 915 (s), 844 (m), 828 (m), 799 (w), 779 (m), 767 (m), 739 (w), 683 (w).

7.10.20 Preparation of 6-(cyclopropanecarbonyl)-1,3-bis(methoxymethyl)pyrimidine-2,4(1H,3H)-dione (43c)



To a solution of 1,3-bis(methoxymethyl) uracil (**40**, 100 mg, 0.5 mmol) was added $TMP_2Zn·2MgCl_2·2LiCl$ (**4**, 0.5 mL, 0.71 M in THF, 0.3 mmol, 0.6 equiv.) at −30 °C. The reaction mixture was stirred for 48 h according to **TP7.** The zinc reagent **44** was treated with CuCN·2LiCl (0.6 mL, 1 M solution in THF, 0.6 mmol, 1.2 equiv.) for 30 min at −40 °C. Acylation was achieved by adding cyclopropaneyl chloride (62 mg, 0.6 mmol, 1.2 equiv.) at −40 °C and warming up to –10 °C over 12 h. The reaction mixture was stirred at –10 °C until completion of the reaction. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N) yielding compound **43c** (61 mg, 0.23 mmol, 45%) as a yellow liquid.

HRMS (EI) for $C_{12}H_{16}N_2O_5$: calcd. 268.2658 (M^+); found 268.1057.

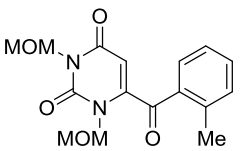
MS (70 eV, EI) *m/z* (%): 238 (6), 237 (4), 236 (10), 225 (7), 180 (5), 164 (15), 150 (4), 69 (12), 45 (100).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.10 - 1.24 (m, 2 H), 1.24 - 1.37 (m, 2 H), 2.16 - 2.37 (m, 1 H), 3.32 (s, 3 H), 3.46 (s, 3 H), 5.36 (s, 2 H), 5.40 (s, 2 H), 6.13 (s, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 13.76, 20.81, 56.57, 57.98, 72.33, 74.75, 103.35, 150.09, 151.69, 161.92, 197.34.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3092 (vw), 2941 (w), 2831 (vw), 1720 (m), 1665 (vs), 1619 (m), 1450 (m), 1415 (m), 1373 (s), 1335 (s), 1250 (w), 1195 (m), 1172 (m), 1158 (m), 1085 (s), 1030 (m), 989 (m), 948 (s), 916 (s), 884 (m), 843 (m), 828 (m), 768 (m), 758 (m), 740 (m), 697 (m).

7.10.21 Preparation of 1,3-bis(methoxymethyl)-6-(2-methylbenzoyl)pyrimidine-2,4(1H,3H)-dione (43d)



To a solution of 1,3-bis(methoxymethyl) uracil (**40**, 100 mg, 0.5 mmol) was added $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.4 mL, 0. 71 M in THF, 0.3 mmol, 0.6 equiv.) at –30 °C. The reaction mixture was stirred for 48 h according to **TP7**. The zinc reagent **44** was treated with CuCN·2LiCl (0.6 mL, 1 M solution in THF, 0.6 mmol) for 30 min at −40 °C. Acylation was achieved by adding 2-methylbenzoyl chloride (93 mg, 0.6 mmol) at −40 °C and warming up to −10 °C over 12 h. The reaction mixture was stirred at −10 °C until completion of the reaction. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N) yielding compound **43d** (114 mg, 0.36 mmol, 72%) as a yellow liquid.

HRMS (EI) for $C_{16}H_{18}N_2O_5$: calcd. 318.3245 (M^+); found 318.1207.

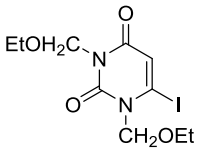
MS (70 eV, EI) *m/z* (%): 286 (26), 231 (17), 214 (36), 199 (14), 119 (42), 105 (12), 91 (36), 65(12), 45 (100).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.60 (s, 3 H), 3.28 (s, 3 H), 3.49 (s, 3 H), 5.40 (s, 2 H), 5.42 (s, 2 H), 5.76 (s, 1 H), 7.27 - 7.38 (m, 2 H), 7.53 (dd, *J*=19.77, 7.60 Hz, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 21.15, 56.53, 58.06, 72.37, 74.89, 104.99, 125.72, 132.06, 132.32, 133.34, 133.57, 141.13, 149.75, 151.77, 161.70, 189.92.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3089 (vw), 2937 (w), 2830 (vw), 1718 (m), 1664 (vs), 1619 (m), 1600 (m), 1570 (w), 1486 (w), 1450 (s), 1413 (m), 1381 (m), 1335 (s), 1303 (w), 1287 (w), 1241 (s), 1194 (m), 1168 (m), 1146 (m), 1131 (w), 1088 (s), 1065 (m), 982 (m), 917 (s), 901 (s), 832 (m), 801 (w), 782 (m), 767 (m), 741 (s), 685 (m), 666 (m).

7.10.22 Preparation of 1,3-bis(ethoxymethyl)-6-iodopyrimidine-2,4(1H,3H)-dione (46a)



To a solution of 1,3-bis(ethoxymethyl) uracil (**41**, 66 mg, 0.29 mmol) was added $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0. 35 M in THF, 0.35 mmol, 1.2 equiv.) at −30 °C. The reaction mixture was stirred for 48 h according to **TP8** and reacted with iodine (0.35 mL, 1 M in THF, 0.35 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:10:0.05) yielding compound **46a** (83 mg, 0.23 mmol, 81%) as a colorless liquid.

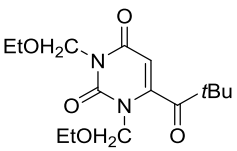
HRMS (ESI) $C_{10}H_{15}IN_2O_4$: calcd. 354.14447 (M^+); found 354.0322.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.22 (m, 6 H), 3.41 - 3.77 (m, 4 H), 5.38 (s, 2 H), 5.50 (s, 2 H), 6.52 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 15.02, 15.16, 65.21, 66.03, 71.16, 81.09, 110.63, 116.32, 149.96, 160.69,

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3065 (w), 2975 (w), 2932 (w), 2884 (w), 1709 (m), 1653 (vs), 1587 (m), 1485 (w), 1437 (m), 1425 (s), 1377 (s), 1348 (m), 1337 (m), 1308 (m), 1242 (m), 1186 (m), 1161 (m), 1099 (s), 1083 (vs), 1024 (m), 1014 (m), 1007 (m), 981 (s), 928 (m), 865 (m), 838 (m), 817 (m), 773 (s), 725 (m), 676 (m).

7.10.23 Preparation of 1,3-Bis(ethoxymethyl)-6-pivaloylpyrimidine-2,4(1H,3H)-dione (46b)



To a solution of 1,3-bis(ethoxymethyl) uracil (**41**, 66 mg, 0.29 mmol) was added $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0. 35 M in THF, 0.35 mmol, 1.2 equiv.) at −30 °C. The reaction mixture was stirred for 48 h according to **TP8.** The freshly prepared zinc reagent was transmetalated to copper by adding CuCN·2LiCl (1 M solution in THF, 0.35 mL, 0.35 mmol, 1.2 equiv.) and stirring for 30 min. Acylation was achieved by adding pivaloyl chloride (36 mg, 0.3 mmol, 1.0 equiv.) at −40 °C and warming up to −10 °C over 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 9:1:0.05) yielding compound **46b** (74 mg, 0.24 mmol, 82%) as a colorless liquid.

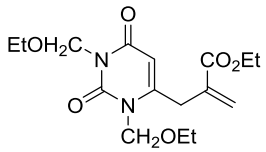
HRMS (ESI) for $C_{15}H_{24}N_2O_5Na^+$: calcd. 335.35522 (M+Na); found 335.15745.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.18 (q, *J*=7.00 Hz, 6 H), 1.29 (s, 9 H), 3.54 (q, *J*=6.91 Hz, 2 H), 3.64 (q, *J*=7.00 Hz, 2 H), 5.21 (s, 2 H), 5.38 (s, 2 H), 5.75 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.59, 15.12, 27.55, 44.63, 65.08, 65.98, 70.81, 73.14, 100.05, 149.16, 151.69, 161.59, 205.59.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2976 (w), 2935 (w), 2878 (vw), 1721 (m), 1671 (vs), 1616 (w), 1445 (m), 1418 (w), 1395 (w), 1381 (w), 1367 (w), 1336 (m), 1238 (w), 1186 (w), 1153 (w), 1094 (m), 985 (w), 920 (w), 843 (w), 829 (w), 801 (vw), 768 (w).

7.10.24 Preparation of Ethyl 2-((1,3-bis(ethoxymethyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl)acrylate (46c)



To a solution of 1,3-bis(ethoxymethyl) uracil (**41**, 66 mg, 0.29 mmol) was added $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0. 35 M in THF, 0.35 mmol, 1.2 equiv.) at −30 °C. The reaction mixture was stirred for 48 h according to **TP8**. The freshly prepared zinc reagent was transmetalated to copper by adding CuCN·2LiCl (1 M solution in THF, 0.35 mL, 0.35 mmol, 1.2 equiv.) and stirring for 30 min. Allylation was achieved by adding 2-(bromomethyl)acrylate (68 mg, 0.35 mmol, 1.2 equiv.) at –40 °C, stirring for 10 min at −40 °C and 1 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 9:1:0.05) yielding compound **46c** (66 mg, 0.19 mmol, 67%) as a colorless liquid.

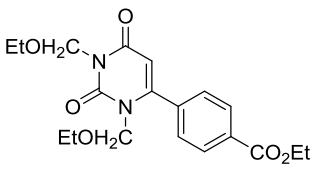
HRMS (ESI) for $C_{16}H_{24}N_2O_6Na^+$: calcd. 363.36522 (M+Na); found 353.15217.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.18 (t, *J*=7.05, 1.94 Hz, 3 H), 1.19 (t, *J*= 7.15 Hz, 3 H), 1.28 (t, *J*=7.05 Hz, 3 H), 3.44 - 3.74 (m, 6 H), 4.20 (q, *J*=7.19 Hz, 2 H), 5.33 (s, 2 H), 5.37 (s, 2 H), 5.55 (s, 1 H), 5.67 (s, 1 H), 6.40 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.08, 14.98, 15.14, 33.56, 61.41, 64.99, 65.82, 70.72, 73.30, 102.41, 128.66, 135.18, 152.78, 153.44, 161.98, 165.52.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3540 (vw), 2977 (w), 2932 (w), 2907 (w), 2877 (vw), 1710 (s), 1664 (vs), 1444 (s), 1368 (m), 1351 (m), 1284 (m), 1245 (m), 1220 (m), 1150 (m), 1090 (vs), 1072 (s), 1024 (s), 979 (m), 880 (m), 843 (m), 823 (m), 773 (m).

7.10.25 Preparation of Ethyl 4-(1,3-bis(ethoxymethyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)benzoate (46d)



To a solution of 1,3-bis(ethoxymethyl) uracil (**41**, 66 mg, 0.29 mmol) was added $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1 mL, 0. 35 M in THF, 0.35 mmol, 1.2 equiv.) at −30 °C according to **TP8**. The zinc reagent reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (11 mg, mol%), $P(2\text{-furyl})_3$ (8 mg, mol%) and ethyl-*p*-iodobenzoate (91 mg, 0.35 mmol, 1.2 equiv.) within 12 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 2:8:0.05) yielding compound **46d** (88 mg, 0.23 mmol, 81%) as a colorless liquid.

HRMS (ESI) for $C_{19}H_{24}N_2O_6Na^+$: calcd. 399.39822 (M+Na); found 399.152123.

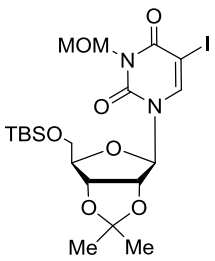
^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.12 (t, *J*=7.04 Hz, 3 H), 1.19 (t, *J*=7.04 Hz, 3 H), 1.37 (t, *J*=7.14 Hz, 3 H), 3.52 (q, *J*=7.04 Hz, 2 H), 3.68 (q, *J*=7.04 Hz, 2 H), 4.37 (q, *J*=7.24 Hz, 2 H), 4.96 (s, 2 H), 5.42 (s, 2 H), 5.66 (s, 1 H), 7.53 (d, *J*=8.22 Hz, 2 H), 8.10 (d, *J*=8.02 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 14.24, 15.03, 15.16, 61.38, 65.20, 65.93, 70.78, 74.70, 103.82, 128.39, 129.69, 132.23, 136.63, 152.50, 154.42, 161.69, 165.50.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2976 (w), 2929 (vw), 2900 (vw), 2878 (vw), 1716 (s), 1671 (vs), 1606 (w), 1441 (m), 1404 (w), 1383 (w), 1367 (w), 1347 (w), 1274 (m), 1231 (w), 1180 (w), 1159 (w), 1101 (m), 1024 (w), 986 (w), 947 (w), 866 (w), 830 (w), 778 (w), 711 (w).

7.11 Uridine Derivatives 49a-n and 51a-f

7.11.1 Preparation of Uridine Derivative 49a



To a solution of uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol) was added TMPMgCl·LiCl (**1**, 0.40 mL, 1.1 M in THF, 0.45 mmol, 1.8 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9** and reacted with iodine (110 mg, 0.45 mmol) for 30 min. The crude product was purified by flash column chromatography (SiO_2, EtOAc:i-hexane/NEt_3 2:8:0.05) furnishing the compound **49a** (99 mg, 0.17 mmol, 70%) as a yellow liquid.

HRMS (EI) for $C_{20}H_{33}IN_2O_7Si$: calcd. 553.0867 (M-Me); found 553.0856.

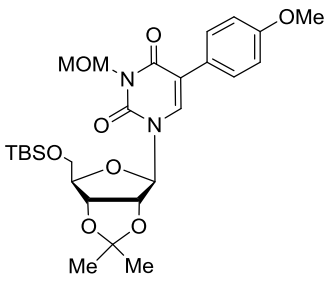
MS (70 eV, EI) *m/z* (%): 511 (100), 451 (20) 339 (84), 309 (20), 307 (20), 277 (44), 229 (42), 171 (65), 143 (34), 129 (75).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.11 (d, J=0.83 Hz, 6 H), 0.89 - 0.91 (m, 9 H), 1.36 (s, 3 H), 1.58 (s, 3 H), 3.43 (s, 3 H), 3.76 - 3.82 (m, 1 H), 3.89 - 3.95 (m, 1 H), 4.41 - 4.45 (m, 1 H), 4.69 - 4.75 (m, 2 H), 5.38 - 5.47 (m, 2 H), 5.83 (d, J=1.94 Hz, 1 H), 7.97 (s, 1 H).

^{13}C-NMR (75 MHz, CDCl3) δ = -5.40, -5.06, 18.38, 25.21, 26.00, 27.18, 58.15, 63.53, 67.76, 73.47, 80.90, 85.86, 87.22, 94.41, 113.83, 143.59, 150.63, 159.80.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3459 (vw),2953 (w), 2929 (w), 2856 (w), 2228 (w), 1713 (m), 1661 (s), 1608 (w), 1503 (w), 1459 (s), 1408 (w), 1382 (m), 1373 (m), 1361 (m), 1254 (m), 1212 (m), 1157 (m), 1126 (m), 1083 (s), 1068 (s), 1018 (m), 969 (m), 939 (w), 916 (m), 833 (vs), 815 (s), 778 (s), 730 (s), 686 (w), 675 (m), 665 (m).

7.11.2 Preparation of Uridine Derivative 49b



To a solution of uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol) was added TMPMgCl·LiCl (**1**, 0.27 mL, 1.1 M in THF, 0.30 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9**. The magnesium reagent was transmetallated to the corresponding zinc reagent by adding $ZnCl_2$ (0.38 mL, 1 M solution in THF, 0.38 mmol, 1.5 equiv.) and stirring for 30 min at −40 °C. The zinc reagent reacted in a *Negishi* cross-coupling reaction by adding

$Pd(dba)_2$ (11 mg, 8 mol%), P(2-furyl)$_3$ (9 mg, 15 mol%) and 4-iodoanisole (88 mg, 0.38 mmol, 1.5 equiv.) at 25 °C for 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:i-hexane/ NEt_3 2:8:0.05) furnishing compound **49b** (111 mg, 0.20 mmol, 81%) as a colorless solid.

HRMS (EI) for $C_{27}H_{40}N_2O_8Si$: calcd. 548.7006 (M^+); found 548.2553.

MS (70 eV, EI) *m/z* (%): 548 (27), 492 (29), 491 (96), 319 (95), 287 (28), 257 (21), 230 (30).

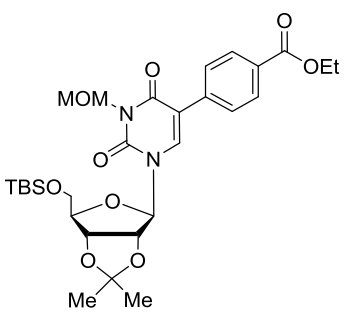
^{1}H-NMR (400 MHz, $CDCl_3$) δ = -0.11 (s, 3 H), -0.04 (s, 3 H), 0.76 (s, 9 H), 1.35 (s, 3 H), 1.58 (s, 3 H), 3.45 (s, 3 H), 3.75 - 3.89 (m, 2 H), 3.79 (s, 3 H), 4.35 (q, *J*=2.73 Hz, 1 H), 4.73 (dd, *J*=6.24, 2.73 Hz, 1 H), 4.83 (dd, *J*=6.24, 2.73 Hz, 1 H), 5.43 (q, *J*=9.55 Hz, 2 H), 5.88 (d, *J*=2.73 Hz, 1 H), 6.88 (m, 2 H), 7.38 (m, 2 H), 7.56 (s, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = -5.64, -5.56, 18.25, 25.29, 25.79, 27.21, 55.32, 58.01, 63.51, 72.31, 80.80, 85.41, 87.08, 94.19, 113.87, 113.91, 114.24, 125.19, 129.66, 135.90, 150.60, 159.39, 162.08.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2987 (w), 2952 (w), 2930 (w), 2856 (w), 1712 (m), 1658 (s), 1609 (m), 1576 (w), 1514 (m), 1453 (m), 1413 (w), 1382 (m), 1373 (m), 1290 (m), 1247 (s), 1212 (m), 1179 (m), 1157 (m), 1126 (m), 1080 (s), 1032 (s), 1005 (m), 970 (m), 918 (m), 831 (vs), 812 (m), 795 (m), 779 (s), 760 (m), 733 (s), 701 (m), 679 (w), 666 (m).

m.p.: 112-113 °C

7.11.3 Preparation of Uridine Derivative 94c



To a solution of uridine derivate **47** (1 mL, 0.5 M in THF, 0.5 mmol) was added TMPMgCl·LiCl (**1**, 0.6 mL, 1.0 M in THF, 0.6 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9.** The magnesium reagent was transmetalated to the corresponding zinc reagent by adding $ZnCl_2$ (0.6 mL, 1 M solution in THF, 0.6 mmol, 1.2 equiv.) and stirring for 30 min at −40 °C. The zinc reagent reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (11 mg, 8 mol%), P(2-furyl)$_3$ (9 mg, 12 mol%) and ethyl-p-iodobenzoate (165 mg, 0.6 mmol, 1.2 equiv.) at 25 °C for 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 2:8:0.05) furnishing compound **49c** (192 mg, 0.32 mmol, 66%) as a colorless liquid.

HRMS (EI) for $C_{29}H_{42}N_2O_9Si$: calcd. 575.2425 (M-Me); found 575.2412.

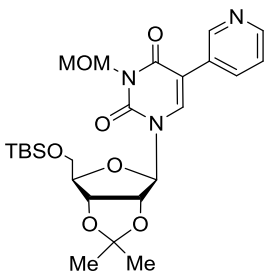
MS (70 eV, EI) *m/z* (%): 534 (33), 533 (100), 475 (15), 362 (19), 361 (75), 329 (21), 299 (19), 229 (18), 171 (35), 143 (17), 129 (67).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = -0.16 (s, 3 H), -0.07 (s, 3 H), 0.72 (s, 9 H), 1.35 (s, 3 H), 1.37 (t, *J*=7.12 Hz, 3 H), 1.58 (s, 3 H), 3.45 (s, 3 H), 3.44 - 3.89 (m, 2 H), 4.36 (q, *J*=7.02 Hz, 2 H), 4.42 (q, *J*=2.53 Hz, 1 H), 4.71 (dd, *J*=6.14, 2.24 Hz, 1 H), 4.82 (dd, *J*=6.34, 2.63 Hz, 1 H), 5.43 (q, *J*=9.55 Hz, 2 H), 5.86 (d, *J*=2.73 Hz, 1 H), 7.56 (d, *J*=8.58 Hz, 2 H), 7.74 (s, 1 H), 8.02 (d, *J*=8.58 Hz, 2 H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = -5.68, -5.59, 14.30, 18.19, 25.21, 25.72, 27.16, 58.06, 60.98, 63.58, 72.33, 80.93, 85.79, 87.44, 94.77, 113.15, 113.82, 128.14, 129.61, 129.65, 137.40, 137.50, 150.47, 161.49, 166.25.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2981 (w), 2953 (w), 2931 (w), 2856 (w), 1711 (s), 1660 (vs), 1608 (m), 1567 (vw), 1513 (w), 1453 (s), 1410 (m), 1382 (m), 1369 (m), 1268 (vs), 1212 (m), 1183 (m), 1157 (m), 1124 (s), 1099 (vs), 1081 (vs), 1021 (s), 1006 (m), 969 (m), 917 (m), 857 (s), 833 (vs), 814 (m), 786 (s), 776 (s), 759 (m), 729 (s), 709 (m), 664 (m).

7.11.4 Preparation of Uridine Derivative 49d



To a solution of uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol) was added TMPMgCl·LiCl (**1**, 0.40 mL, 1.1 M in THF, 0.45 mmol, 1.8 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9.** The magnesium reagent was transmetalated to the corresponding zinc reagent by adding $ZnCl_2$ (0.6 mL, 1 M solution in THF, 0.6 mmol, 1.2 equiv.) and stirring for 30 min at −40 °C. The zinc reagent reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (11 mg, 8 mol%), P(2-furyl)$_3$ (9 mg, 12 mol%) and 3-iodopyridine (61 mg, 0.3 mmol) for 30 min. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing compound **49d** (95 mg, 0.18 mmol, 73%) as a yellow liquid.

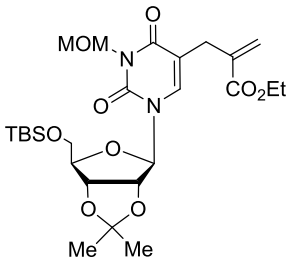
HRMS (ESI) for $C_{25}H_{37}N_3O_7Si$ calcd 520.2474 ($M+H^+$); found 520.2468.

^{1}H NMR (300 MHz, $CDCl_3$) δ = -0.14 (s, 3 H), -0.06 (s, 3 H), 0.72 (s, 9 H), 1.35 (s, 3 H) 1.58 (s, 3 H) 3.45 (s, 3 H), 3.69 - 3.82 (m, 1 H), 3.82 - 3.96 (m, 1 H), 4.40 (q, *J*=2.49 Hz, 1 H), 4.71 (dd, *J*=6.08, 2.49 Hz, 1 H), 4.80 (dd, *J*=6.08, 2.76 Hz, 1 H), 5.36 - 5.50 (m, 2 H), 5.89 (d, *J*=2.76 Hz, 1 H), 7.22 - 7.33 (m, 1 H), 7.75 (s, 1 H), 7.90 (dt, *J*=8.02, 1.94 Hz, 1 H), 8.54 (dd, *J*=4.70, 1.66 Hz, 1 H), 8.61 (d, *J*=1.93 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = -5.67, -5.61, 18.16, 25.23, 25.67, 27.17, 58.06, 63.52, 72.36, 80.84, 85.72, 87.29, 94.46, 111.06, 113.90, 123.05, 129.09, 136.20, 136.94, 148.59, 148.99, 150.49,161.61.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2986 (w), 2953 (w), 2932 (w), 2893 (w), 2857 (w), 1714 (m), 1661 (vs), 1454 (s), 1414 (w), 1383 (m), 1374 (m), 1362 (m), 1292 (m), 1256 (m), 1212 (m), 1185 (w), 1157 (m), 1125 (m), 1083 (s), 1006 (w), 970 (m), 919 (w), 835 (s), 814 (m), 779 (s), 712 (m).

7.11.5 Preperation of Uridine Derivative 49e



To a solution of uridine derivate **47** (1 mL, 0.5 M in THF, 0.5 mmol) was added TMPMgCl·LiCl (**1**, 0.8 mL, 1.1 M in THF, 0.45 mmol, 1.8 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9**. The freshly prepared magnesium reagent was transmetalated to the corresponding copper reagent by adding CuCN·2LiCl (1 M solution in THF, 0.60 mL, 0.60 mmol, 1.2 equiv.) and stirring for 30 min. Allylation was achieved by adding ethyl 2-(bromomethyl)acrylate (84 mg, 0.6 mmol, 1.2 equiv.) at −40 °C, stirring for 10 min at −40 °C and 1 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing compound **49e** reacted(238 mg, 0.43 mmol, 86%) as a colorless liquid.

HRMS (EI) for $C_{26}H_{42}N_2O_9Si$: calcd. 554.7052; found 539.2412 (M-Me).

MS (70 eV, EI) *m/z* (%): .539. (11), 498 (30), 497 (100), 326 (21), 325 (94), 293 (28), 263 (22), 229 (13), 171 (36), 143 (13), 129 (42), 117 (14).

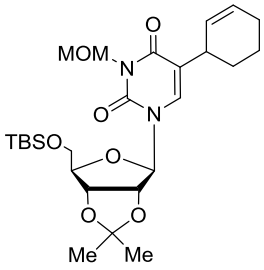
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.01 (3 H), 0.02 (3H), 0.82 (s, 9 H), 1.24 (t, *J*=7.12 Hz, 3 H), 1.30 (s, 3 H), 1.52 (s, 3 H), 3.17 - 3.35 (m, 2 H), 3.37 (s, 3 H), 3.67 - 3.89 (m, 2 H), 4.14 (q, *J*=7.15 Hz, 2 H), 4.20 - 4.30 (m, 1 H), 4.70 (dd, *J*=6.34, 3.02 Hz, 1 H), 4.79 (dd, *J*=6.24, 2.73 Hz, 1 H), 5.19 - 5.37 (m, 2 H), 5.65 (d, *J*=1.36 Hz, 1 H), 5.72 (d, *J*=2.73 Hz, 1 H), 6.19 (d, *J*=1.17 Hz, 1 H), 7.37 (s, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = -5.50, -5.41, 14.15, 18.29, 25.29, 25.82, 27.18, 29.60, 57.85, 60.75, 63.54, 72.05, 80.89, 84.98, 87.16, 94.34, 110.62, 113.88, 127.03, 136.90, 138.05, 150.69, 162.64, 166.36.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2981 (w), 2953 (w), 2931 (w), 2856 (w), 1711 (s), 1666 (vs), 1456 (m), 1371 (m), 1326 (w), 1279 (m), 1253 (m), 1209 (m), 1183 (m), 1176 (m), 1156 (m), 1134 (s),

1083 (vs), 1028 (s), 1006 (m), 975 (m), 940 (m), 919 (m), 870 (m), 834 (vs), 815 (s), 776 (s), 733 (m), 677 (m), 666 (m).

7.11.6 Preparation of Uridine Derivative 49f



To a solution of uridine derivate **47** (1 mL, 0.5 M in THF, 0.5 mmol) was added TMPMgCl·LiCl (**1**, 0.8 mL, 1.1 M in THF, 0.88 mmol, 1.8 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9**. The freshly prepared magnesium reagent was transmetalated to the corresponding copper reagent by adding CuCN·2LiCl (1 M solution in THF, 0.60 mL, 0.60 mmol, 1.2 equiv.) and stirring for 30 min. Allylation was achieved by adding 3-bromocyclohex-1-ene (97 mg, 0.6 mmol) at −40 °C, stirring for 10 min at −40 °C and 1 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing the compound **49f** as a diastereomeric mixture 48:42 (158 mg, 0.30 mmol, 60%) as a colorless liquid.

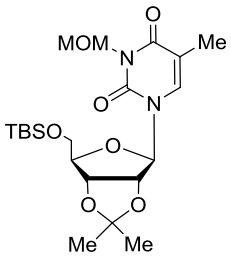
HRMS (EI) for $C_{26}H_{42}N_2O_7Si$ calcd. 522.7064; found 507.2517(M-Me).

^{1}H NMR (300 MHz, $CDCl_3$) δ = -0.03, -0-04 (s, 3 H), 0.05, 0.05 (s, 3 H) 0.86, 0.87 (s, 9 H) 1.34, 1.34, (s, 3H), 1.55, 1.55* (s, 3 H), 1.48-1.67, 1.48-1.67 * (m, 3 H) 1.88 - 2.03, 1.88 - 2.03* (m, 3 H) 3.43, 3.43* (s, 3 H), 3.45-3.50, 3.45 - 3.50* (m, 1 H), 3.73 - 3.84, 3.73 - 3.84* (m, 2 H), 4.19 - 4.24, 4.24 - 4.28 (m, 1 H), 4.73-4.78, 4.73-4.78* (m, 1 H), 4.94 - 4.98, 4.94 - 4.98* (m, 1 H), 5.34, 5.34 (m, 2 H), 5.45-5.49*, 5.49-5.52 (m, 1 H), 5.62 (d, *J*=2.49 Hz, 1 H), 5.91 - 5.95*, 5.88 - 5.92 (m., 1 H), 7.04*, 7.09 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = -5.44, -5.38 (s, 1 C), -5.33, -5.30 (s, 1 C), 18.33, 18.39 (s, 1 C), 19.64, 19.80 (s, 1 C), 24.97*, 24.99 (s, 1 C), 25.33, 25.40* (s, 1 C), 25.87, 25.90* (s, 1 C) 27.16, 27.21* (s, 1 C), 28.13, 28.17* (s, 1 C) 32.68, 32.79* (s, 1 C), 57.92, 57.92* (s, 1 C), 63.66*, 63.74 (s, 1 C), 72.08, 72.11* (s, 1 C), 81.17*, 81.25 (s, 1 C), 84.37*, 84.81 (s, 1 C), 87.76*, 87.86 (s, 1 C), 95.61*, 95.71 (s, 1 C), 113.88, 114.04* (s, 1 C), 117.28, 117.55* (s, 1 C), 127.19, 127.25* (s, 1 C), 130.42*, 130.53 (s, 1 C), 137.26, 137.56* (s, 1 C) 150.58*, 150.62 (s, 1 C) 162.59, 162.60* (s, 1 C).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2928 (m), 2856 (w), 1713 (m), 1662 (vs), 1453 (m), 1381 (m), 1372 (m), 1361 (m), 1256 (m), 1210 (m), 1183 (w), 1158 (m), 1128 (m), 1083 (vs), 1005 (m), 972 (m), 938 (w), 916 (m), 873 (m), 834 (vs), 815 (m), 776 (s), 758 (m), 729 (s), 662 (m).

7.11.7 Preparation of Uridine Derivative 49g



To a solution of uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol) was added TMPMgCl·LiCl (**1**, 0.40 mL, 1.1 M in THF, 0.45 mmol, 1.8 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9**. The freshly prepared magnesium reagent was transmetallated to the corresponding copper reagent by adding CuCN·2LiCl (1 M solution in THF, 0.35 mL, 0.35 mmol) and stirring for 30 min. MeI was added at −40 °C and warmed to 25 °C within 6 h, and stirred for further 48 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing compound **49g** (35 mg, 0.08 mmol, 31%) as a yellow liquid.

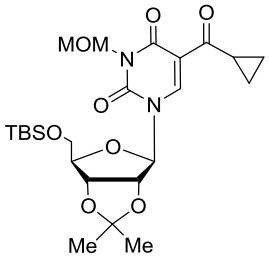
HRMS (ESI) for $C_{21}H_{37}N_2O_7Si^+$ calcd. 457,61845 ($M+H^+$); found 457.23609.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 0.07 (d, *J*=6.31 Hz, 6 H), 0.88 (s, 9 H), 1.34 (s, 3 H), 1.57 (s, 3 H), 1.92 (s, 3 H), 3.42 (s, 3 H), 3.78 (d, *J*=11.53, 1 H), 3.90 (d, *J*=11.53 Hz, 1 H), 4.30 (s, 1 H), 4.73 (s, 2 H), 5.28 - 5.48 (m, 2 H), 5.87 (s, 1 H), 7.32 (s, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$) δ = -5.49, -5.39, 13.22, 18.32, 25.33, 25.84, 27.24, 57.85, 63.37, 72.09, 80.54, 85.19, 86.51, 93.16, 109.85, 113.99, 135.01, 150.99, 163.45.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2988 (w), 2952 (m), 2929 (m), 2858 (w), 1714 (m), 1671 (vs), 1462 (m), 1383 (w), 1372 (m), 1364 (w), 1278 (m), 1254 (m), 1214 (m), 1184 (w), 1157 (w), 1127 (m), 1090 (s), 1035 (w), 974 (w), 918 (w), 859 (m), 836 (s), 774 (m).

7.11.8 Preparation of Uridine Derivative 49h



49h was prepared according to **TP9** from uridine derivate (**47**, 0.5 mL, 0.5 M in THF, 0.25 mmol). To the solution was added TMPMgCl·LiCl (1, 0.27 mL, 1.1 M in THF, 0.30 mmol, 1.2 equiv.) at −40 °C and the solution was stirred for 24 h. The magnesium reagent was treated with CuCN·2LiCl (0.3 mL, 1 M solution in THF, 0.3 mmol, 1.2 equiv.) for 30 min at −40 °C. Acylation was achieved by adding cyclopropanecarbonyl chloride (31 mg, 0.3 mmol) at −40 °C and warming up to −10 °C within 12 h. The reaction mixture was stirred at −10 °C until completion of the reaction. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 2:8:0.05) furnishing compound **49h** (91 mg, 0.18 mmol, 71%) as a colorless liquid.

HRMS (EI) for $C_{24}H_{39}N_2O_8Si$: calcd. 510.6526; found 511.2464 (M^+).

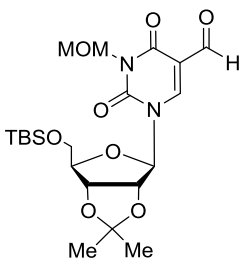
MS (70 eV, EI) *m/z* (%): .454 (26), 453 (100), 395 (11), 282 (12), 281 (57), 251 (12), 249 (15), 229 (12), 249 (15), 229 (12), 219 (21), 171 (33), 143 (16), 129 (25), 117 (13).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.04 (s, 3 H), 0.02 (s, 3 H), 0.80 (s, 9H), 0.97-1.03 (m, 2 H), 1.14-1.18 (m, 2 H), 1.36 (s, 3 H), 1.58 (s, 3 H), 3.29 (tt, *J*=7.84, 4.60 Hz, 1 H), 3.46 (s, 3 H), 3.77 (dd, *J*=11.61, 3.04 Hz, 1 H), 3.87 (dd, *J*=11.61, 3.04 Hz, 1 H), 4.48 - 4.59 (m, 1 H), 4.71 (dd, *J*=5.94, 1.52 Hz, 1 H), 4.83 (dd, *J*=5.94, 2.35 Hz, 1 H), 5.42 (q, *J*=9.40 Hz, 2 H), 5.75 (d, *J*=2.49 Hz, 1 H), 8.45 (s, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = -5.81, -5.56, 12.70, 18.23, 19.41, 25.05, 25.76, 27.05, 58.04, 63.84, 72.17, 81.59, 86.43, 88.39, 96.52, 111.53, 113.45, 145.65, 150.50, 161.12, 196.77.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2987 (w), 2951 (w), 2931 (w), 2856 (w), 1720 (m), 1678 (vs), 1659 (s), 1594 (m), 1453 (s), 1410 (m), 1384 (s), 1362 (m), 1351 (m), 1321 (m), 1288 (m), 1272 (m), 1252 (m), 1212 (m), 1158 (m), 1122 (s), 1090 (vs), 1053 (s), 1021 (m), 990 (m), 969 (m), 919 (m), 872 (m), 860 (m), 833 (vs), 814 (m), 780 (s).

7.11.9 Preparation of Uridine Derivative 49i



To a solution of uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol) was added TMPMgCl·LiCl (**1**, 0.40 mL, 1.1 M in THF, 0.45 mmol, 1.8 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9**. The freshly prepared magnesium reagent was treated with morpholine-4-carbaldehyde (34 mg, 0.29 mmol) at −40 °C and the reaction mixture was allowed to warm up to 25 °C over 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing compound **49i** (38 mg, 0.08 mmol, 32%) as a yellow liquid.

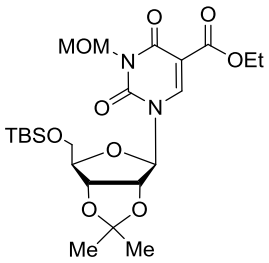
HRMS (ESI) for $C_{21}H_{35}N_2O_8Si^+$ calcd. 471,60145 ($M+H^+$); found 471.21543.

^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.06 (s, 3 H), 0.00 (s, 3 H), 0.76 (s, 9 H), 1.33 (s, 3 H), 1.55 (s, 3 H), 3.41 (s, 3 H), 3.75 (dd, *J*=11.74, 2.45 Hz, 1 H), 3.94 (dd, *J*=11.98, 1.96 Hz, 1 H), 4.55 (s, 1 H), 4.67 (dd, *J*=5.87, 1.22 Hz, 1 H), 4.75 (dd, *J*=5.87, 2.45 Hz, 1 H), 5.22 - 5.48 (m, 2 H), 5.74 (d, *J*=2.45 Hz, 1 H), 8.39 (s, 1 H), 10.00 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = -5.73, -5.42, 18.29, 25.08, 25.82, 27.11, 58.21, 63.84, 71.91, 81.59, 86.58, 88.44, 96.49, 109.78, 113.58, 144.40, 150.38, 161.73, 186.50.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2985(w), 2953 (w), 2933 (w), 2884 (w), 2858 (w), 1727 (m), 1697 (s), 1672 (vs), 1605 (s), 1462 (s), 1421 (w), 1382 (m), 1359 (m), 1280 (m), 1256 (m), 1213 (m), 1184 (w), 1158 (w), 1092 (s), 1008 (w), 969 (m), 918 (w), 860 (m), 836 (s), 778 (s).

7.11.10 Preparation of Uridine Derivative 49j



To a solution of uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol) was added TMPMgCl·LiCl (**1**, 0.40 mL, 1.1 M in THF, 0.45 mmol, 1.8 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9** and reacted with ethyl cyanoformate (30 mg, 0.3 mmol, 1.2 equiv.) at −40 °C and subsequent warming up to −10 °C for 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing compound **49j** (57 mg, 0.11 mmol, 44%) as a yellow liquid.

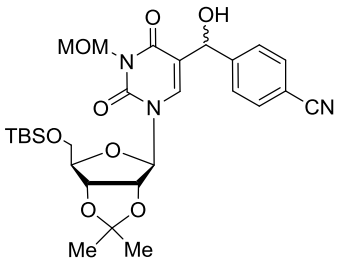
HRMS (ESI) for $C_{23}H_{39}N_2O_9Si^+$: calcd. 515.65445 ($M+H^+$); found 515.2424.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.02 (s, 3 H), 0.03 (s, 3 H), 0.80 (s, 9 H), 1.34 (t, *J*= 7.19. 3 H), 1.36 (s, 3 H), 1.57 (s, 3 H), 3.43 (s, 3 H), 3.73 - 3.84 (m, 1 H), 3.87 - 3.96 (m, 1 H), 4.19 - 4.39 (m, 2 H), 4.55 (s, 1 H), 4.71 (d, *J*=6.08 Hz, 1 H), 4.84 (dd, *J*=5.81, 2.21 Hz, 1 H), 5.37 (q, *J*=9.40 Hz, 2 H), 5.72 (d, *J*=1.94 Hz, 1 H), 8.49 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$ δ = -5.78, -5.59, 14.30, 18.21, 25.03, 25.70, 27.03, 58.12, 61.25, 63.88, 72.10, 81.57, 86.39, 88.47, 96.61, 103.93, 113.45, 146.66, 150.37, 158.80, 163.04.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2986.00 (w), 2966.00 (w), 2949.00 (m), 2934.00 (m), 2857.00 (w), 1752.00 (s), 1735.00 (s), 1728.00 (s), 1709.00 (vs), 1675.00 (vs), 1624.00 (m), 1532.00 (w), 1454.00 (s), 1373.00 (s), 1365.00 (m), 1355.00 (m), 1266.00 (s), 1227.00 (s), 1217.00 (s), 1188.00 (m), 1158.00 (m), 1123.00 (s), 1091.00 (vs), 1029.00 (m), 970.00 (m), 918.00 (w), 861.00 (m), 835.00 (s), 797.00 (m), 778.00 (m).

7.11.11 Preparation of Uridine Derivative 49k



To a solution of uridine derivate **47** (1 mL, 0.5 M in THF, 0.50 mmol) was added TMPMgCl·LiCl (**1**, 0.6 mL, 1.0 M in THF, 0.3 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9**. The magnesium reagent was reagent with 4-(hydroxymethyl)benzonitrile (79 mg, 0.6 mmol, 1.2 equiv.) at −40 °C, stirring for 10 min at −40 °C and 1 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 2:8:0.05) furnishing compound **49k** (212 mg, 0.37 mmol, 74%) as a 1:1 diastereomeric mixture.

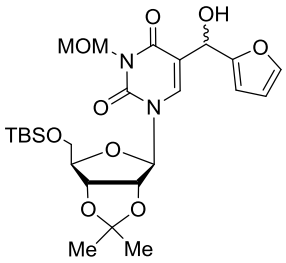
HRMS (EI) for $C_{27}H_{36}N_3O_8Si$: calcd 558,68355 (M-Me), found 558.2268.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.06, 0.07 (s, 3H), 0.07, 0.08 (s, 3H), 0.87. 0.87 (s, 9H), 1.36 (s, 3 H), 1.57 (s, 3 H), 3.40, 3.41 (s, 3 H), 3.74 - 3.81 (m, 2 H), 4.32 - 4.35 (m, 1 H), 4.70 - 4.74 (m, 1 H), 4.78 (s, 1 H), 4.84, 4.86 (d, *J*= 2.49, 1 H), 5.26 - 5.38 (m, 2 H), 5.62*, 5.72 (s, 1H), 5.67, 5.70* (d, *J*=2.49 Hz, 1 H), 7.42*, 7.40 (d, *J*= 7.42, 7.40, 1H), 7.46-7.47, 7.49-7.50 (m, 1H), 7.52-7.53, 7.55-7.56 (m, 1H), 7.64-7.64 (m, 2H),

^{13}C NMR (75 MHz, $CDCl_3$) δ = -5.48, -5.42 (s, 1 C), -5.35, -5.30 (s, 1 C), 18.30, 18.31 (s, 1 C), 25.27 (s, 1 C), 25.86 (s, 1 C), 27.16 (s, 1 C), 58.05, 58.07 (s, 1 C), 63.60, 64.19 (s, 1 C), 69.89, 70.65 (s, 1 C) ,72.02 (s, 1 C), 80.95, 81.07 (s, 1 C) 85.17, 85.22 (s, 1 C), 87.55, 87.62 (s, 1 C) 95.20*, 95.31 (s, 1 C), 111.72, 111.81 (s, 1 C) 113.95, 114.03 (s, 1 C) 114.45, 114.75 (s, 1 C) 118.58, 118.60* (s, 1 C), 126.99, 127.22 (s, 1 C), 132.29, 132.31 (s, 1 C), 137.28, 137.46 (s, 1 C), 146.37, 146.57 (s, 1 C). 150.19, 150.27* (s, 1 C) 162.54, 162.69* (s, 1 C).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3454.00 (w), 2988.00 (w), 2952.00 (w), 2931.00 (w), 2856.00 (w), 2228.00 (w), 1713.00 (m), 1662.00 (vs), 1608.00 (w), 1503.00 (w), 1460.00 (s), 1410.00 (w), 1373.00 (m), 1361.00 (m), 1254.00 (m), 1213.00 (m), 1157.00 (m), 1126.00 (m), 1085.00 (vs), 1019.00 (m), 972.00 (m), 940.00 (w), 918.00 (w), 835.00 (vs), 816.00 (m), 780.00 (s).

7.11.12 Preparation of Uridine Derivative 49l



To a solution of uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol) was added TMPMgCl·LiCl (**1**, 0.3 mL, 1.0 M in THF, 0.30 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9**. The magnesium reagent reacted with furan-2-carbaldehyde (29 mg, 0.30 mmol, 1.2 equiv.) for 10 min at −40 °C and 12 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 2:8:0.05) furnishing the compound **49l** (58 mg, 0.11 mmol, 43%) as a as a 1:1 diastereomeric mixture.

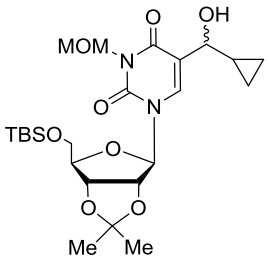
HRMS (ESI) for $C_{25}H_{37}N_2O_8Si^+$: calcd 521,23137 (M-OH), found 521.23093.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.00 (d, 3 H), 0.02 (d, 3 H), 0.81 (s, 9 H) 1.31 (s, 3 H) 1.53 (s, 3 H) 3.38, 3.38 (s, *3* H), 3.71 - 3.75 (m, 2 H), 4.28-4.31 (m, 1 H) 4.68, 4.67 (dd, *J*=6.36, *J*=2.69 Hz, 1 H), 4.80-4.83 (m, 1 H), 5.31 (q, *J*=9.54 Hz, 2 H), 5.63*, 5.59 (s, 1H), 5.70, 5.67 (d, *J*= 5.69, *J*= 5.66, 1 H), 6.29-6.33 (m, 2 H), 7.32-7.34 (m, 1H), 7.41, 7.44* (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = -5.53, -5.48 (s, 1 C), -5.34, 5.37 (s, 1 C), 18.33, 18.36 (s, 1 C), 25.29, 25.31 (s, 1 C), 25.87, 25.90 (s, 1 C), 27.19, 27.22 (s, 1 C), 58.05, 58.07 (s, 1 C), 63.63 (s, 1 C), 65.11*, 65.55 (s, 1 C) 71.99 (s, 1 C), 81.14 (s, 1 C) 85.31, 85.43 (s, 1 C) 87.50, 87.76 (s, 1 C), 95.04*, 95.37 (s, 1 C) 107.56, 107.60 (s, 1 C) 110.60, 110.62 (s, 1 C) 112.78, 112.93* (s, 1 C) 113.88, 113.93 (s, 1 C) 137.60, 137.75, (s, 1 C) 142.34 (s, 1 C) 150.40, 150.46* (s, 1 C) 153.51, 153.56 (s, 1 C) 162.69*, 162.90 (s, 1 C).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = cm-1 (Intensity), 2954.00 (w), 2931.00 (m), 2857.00 (w), 2362.00 (w), 2342.00 (VW), 1761.00 (w), 1715.00 (m), 1669.00 (vs), 1616.00 (w), 1461.00 (s), 1374.00 (m), 1362.00 (m), 1257.00 (m), 1214.00 (m), 1184.00 (w), 1158.00 (m), 1091.00 (s), 1009.00 (m), 971.00 (w), 918.00 (w), 837.00 (s), 816.00 (w), 780.00 (m), 668.00 (w).

7.11.13 Preparation of Uridine Derivative 49m



To a solution of uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol) was added TMPMgCl·LiCl (**1**, 0.3 mL, 1.0 M in THF, 0.3 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9**. The magnesium reagent reacted with cyclopropanecarbaldehyde (21 mg, 0.3 mmol, 1.2 equiv.) at –40 °C, and subsequently stirred for 10 min at –40 °C and 12 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 2:8:0.05) furnishing compound **49m** (38 mg, 0.07 mmol, 30%) as a diastereomeric mixture 1:1.

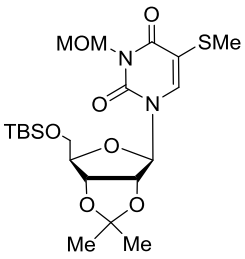
HRMS (ESI) for $C_{24}H_{40}N_2NaO_8Si$: calcd. 535,24461 ($M+Na^+$), found 535.24502.

^{1}H NMR (300 MHz, $CDCl_3$) δ = -0.00, (s, 3 H), 0.01 (s, 3 H), 0.22 - 0.30, 0.47 - 0.54 (m, 2 H) 0.40 - 0.46, 0.56 - 0.63 (m, 2 H), 0.81 (s, 9 H), 1.09 - 1.18 (m , 1 H), 1.31, (s, 3H) 1.52 (s, 3 H), 3.39 (s, 3 H), 3.71 – 3.73*, 3.81-3.82 (m, 2 H), 3.74-3.80 (m 1 H), 4.26-4.29 (m, 1 H), 4.68, 4.69* (d, *J*=2.93 Hz, 1 H), 4.81*, 4.83 (d, *J*=2.45 Hz, 1 H), 5.28 - 5.35 (m, 2 H), 5.68, 5.70* (d, *J*=2.45 Hz, 1 H), 7.47, 7.51* (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = -5.42, -5.39 (s, 1 C) -5.31, -5.26 (s, 1 C), 2.80, 2.85* (s, 1 C) 3.63*, 3.71 (s, 1 C) 15.70, 15.94* (s, 1 C) 18.36, 18.39* (s, 1 C), 25.33 (s, 1 C), 25.90, 25.93 (s, 3 C), 27.22 (s, 1 C), 58.04, 58.06* (s, 1 C), 63.63 (s, 1 C), 72.09 (s, 1 C) 72.59*, 73.27 (s, 1 C), 80.98, 81.00 (s, 1 C), 85.15, 85.19 (s, 1 C), 87.44, 87.60 (s, 1 C), 94.90*, 95.15 (s, 1 C), 114.02, 114.04 (s, 1 C), 115.41, 115.54* (s, 1 C), 136.31*, 136.41 (s, 1 C) 150.49, 150.54* (s, 1 C), 163.29, 163.33* (s, 1 C).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = cm-1 (Intensity), 3483.00 (VW), 3082.00 (VW), 2989.00 (w), 2953.00 (w), 2931.00 (w), 2857.00 (w), 2361.00 (VW), 2340.00 (VW), 1713.00 (m), 1663.00 (vs), 1458.00 (s), 1382.00 (m), 1373.00 (m), 1362.00 (m), 1255.00 (m), 1213.00 (m), 1158.00 (m), 1129.00 (m), 1085.00 (vs), 1031.00 (m), 970.00 (m), 920.00 (m), 870.00 (m), 835.00 (vs), 779.00 (s).

7.11.14 Preparation of Uridine Derivative 49n



To a solution of uridine derivate **47** (2 mL, 0.5 M in THF, 1 mmol) was added TMPMgCl·LiCl (**1**, 1.2 mL, 1.0 M in THF, 1.2 mmol, 1.2 equiv.) at −40 °C. The reaction mixture was stirred for 24 h according to **TP9**. The magnesium reagent reacted with dimethyl disulfide (113 mg, 1.2 mmol, 1.2 equiv.) at −40 °C and reacted 1 h at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 2:8:0.05) furnishing compound **49n** (206 mg, 0.42 mmol, 42%).

HRMS (ESI) for $C_{21}H_{36}N_2NaO_7SSi^+$: calcd. 511.19047 ($M+Na^+$); found 511.19910.

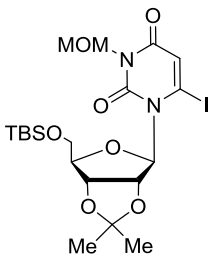
^{1}H NMR (300 MHz, $CDCl_3$) δ = -0.04 (s, 3 H), -0.10 (s, 3 H), 0.72 - 1.06 (m, 9 H), 1.29 - 1.47 (m, 3 H), 1.52 - 1.64 (m, 3 H), 2.23 - 2.37 (m, 3 H), 3.31 - 3.50 (m, 3 H), 3.72 - 3.86 (m, 1 H), 3.86 - 4.00 (m, 1 H), 4.28 - 4.47 (m, 1 H), 4.62 - 4.81 (m, 2 H), 5.27 - 5.49 (m, 2 H), 5.85 (d, *J*=1.38 Hz, 1 H), 7.82 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = -5.52, -5.33, 17.25, 18.35, 25.26, 25.92, 27.21, 58.06, 63.50, 72.61, 80.82, 85.51, 86.98, 93.96, 109.05, 113.91, 140.40, 150.70, 161.38.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2980.00 (w), 2954.00 (m), 2929.00 (m), 2856.00 (w), 1752.00 (s), 1735.00 (s), 1728.00 (s), 1709.00 (vs), 1675.00 (vs), 1624.00 (m), 1454.00 (s), 1373.00 (s), 1365.00 (m),

1355.00 (m), 1266.00 (s), 1227.00 (s), 1217.00 (s), 1188.00 (m), 1158.00 (m), 1123.00 (s), 1091.00 (vs), 1029.00 (m), 970.00 (m), 918.00 (w), 861.00 (m), 835.00 (s), 797.00 (m), 778.00 (m).

7.11.15 Preparation of Uridine Derivative 51a



51 was prepared according to **TP10** from uridine derivate (**47**, 1 mL, 0.25 M in THF, 0.25 mmol). $TMP_2Zn·2MgCl_2·2LiCl$ (**4**, 0.42 mL, 0.71 M in THF, 0.30 mmol, 1.2 equiv.) was added to the solution at −30 °C, stirred for 72 h and reacted with iodine (127 mg, 0.5 mmol) for 30 min. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing compound **51a** (135 mg, 0.24 mmol, 95%) as a colorless liquid.

HRMS (ESI) for $C_{20}H_{33}IN_2O_7Si$: calcd. 568.4752; found 553.0868 ($M-Me^+$).

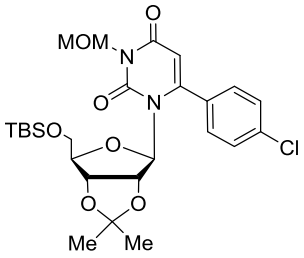
MS (70 eV, EI) *m/z* (%): 511 (17), 542 (12), 385 (17), 340 (16), 339 (100), 309 (13), 276 (20), 229 (26), 213 (17), 170 (34), 142 (19), 129 (36).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.34 (s, 3 H), 1.56 (s, 3 H), 3.42 (s, 3 H), 3.77 - 3.82 (m, 2 H), 4.14 - 4.21 (m, 1 H), 4.86 (dd, J=6.36, 4.42 Hz, 1 H), 5.20 (dd, J=6.50, 1.24 Hz, 1 H), 5.28 (s, 2 H), 6.09 (d, J=1.11 Hz, 1 H), 6.51 (s, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = -5.27, -5.25, 18.47, 25.42, 25.94, 27.24, 58.01, 63.98, 72.31, 81.96, 84.45, 89.81, 102.58, 112.28, 113.80, 116.43, 148.04, 160.52.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2986 (w), 2952 (w), 2929 (w), 2884 (w), 2855 (w), 1719 (m), 1665 (vs), 1584 (m), 1435 (m), 1424 (m), 1372 (m), 1363 (m), 1347 (m), 1332 (m), 1252 (m), 1207 (m), 1196 (m), 1156 (m), 1131 (m), 1082 (vs), 1064 (s), 1005 (m), 948 (m), 917 (m), 876 (s), 833 (vs), 816 (s), 770 (s), 673 (m), 662 (m).

7.11.16 Preparation of Uridine Derivative 51b



51b was prepared according to **TP10** from uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.42 mL, 0.71 M in THF, 0.30 mmol, 1.2 equiv.) was added to the solution at −30 °C, stirred for 72 h and reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (11 mg, 8 mol%), $P(2\text{-furyl})_3$ (9 mg, 15 mol%) and 1-chloro-4-iodobenzene (90 mg, 0.38 mmol) at 25 °C for 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 2:8:0.05) furnishing the compound **51b** (116 mg, 0.21 mmol, 84%) as a yellow liquid.

HRMS (ESI) for $C_{26}H_{37}ClN_2O_7Si$: calcd. 553.1197 (M^+); found 553.2152.

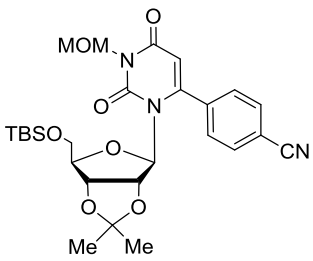
MS (70 eV, EI) *m/z* (%): 495 (15), 325 (35), 324 (18), 323 (100), 293 (10), 171 (16).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.06 (s, 6 H), 0.90 (s, 9 H), 1.29 (s, 3 H), 1.39 (s, 3 H), 3.47 (s, 3 H), 3.82 - 3.86 (m, 2 H), 4.02 - 4.08 (m, 1 H), 4.84 (dd, J=6.36, 4.42 Hz, 1 H), 5.21 (dd, J=6.50, 1.52 Hz, 1 H), 5.37 (s, 2 H), 5.43 (d, J=1.38 Hz, 1 H), 5.66 (s, 1 H), 7.40 - 7.51 (m, 4 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = -5.24, -5.22, 18.44, 25.36, 25.91, 27.09, 57.99, 64.14, 71.95, 82.07, 84.06, 89.32, 93.60, 103.85, 113.62, 129.41, 129.60, 130.87, 136.98, 151.12, 153.98, 161.64.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2987 (vw), 2952 (w), 2929 (w), 2884 (w), 2855 (w), 1717 (m), 1671 (vs), 1621 (w), 1493 (w), 1471 (w), 1440 (m), 1405 (m), 1383 (m), 1372 (m), 1357 (m), 1252 (m), 1208 (m), 1159 (w), 1140 (m), 1088 (vs), 1067 (s), 1015 (m), 969 (w), 954 (m), 901 (m), 868 (m), 834 (vs), 774 (s), 729 (s), 681 (w), 667 (m), 663 (w).

7.11.17 Preparation of Uridine Derivative 51c



51c was prepared according to **TP10** from uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.42 mL, 0.71 M in THF, 0.30 mmol, 1.2 equiv.) was added to the solution at −30 °C, stirred for 72 h and reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (11 mg, 8 mol%), $P(2\text{-furyl})_3$ (9 mg, 15 mol%) and 4-iodobenzonitrile (69 mg, 0.30 mmol) at 25 °C for 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 3:7:0.05) furnishing the compound **51c** (94 mg, 0.17 mmol, 69%) as a colorless liquid.

HRMS (ESI) for $C_{27}H_{37}N_3O_7Si$: calcd. 543.6841($M\text{-}H^+$); found 542.2323.

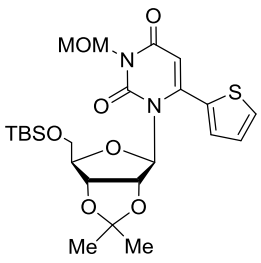
MS (70 eV, EI) *m/z* (%): 486 (16), 428 (10), 315 (20), 314 (100), 284 (11), 252 (13).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.04 (s, 6 H), 0.88 (s, 9 H), 1.27 (s, 3 H), 1.36 (s, 3 H), 3.46 (s, 3 H), 3.80 - 3.82 (m, 2 H), 4 - 4.05 (m, 1 H), 4.82 (dd, *J*=6.43, 4.48 Hz, 1 H), 5.20 (dd, *J*=6.43, 1.36 Hz, 1 H), 5.27 (d, *J*=1.56 Hz, 1 H), 5.35 (s, 2 H), 5.66 (s, 1 H), 7.61 (br. s., 2 H), 7.78 - 7.81 (m, 2 H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = -5.24, -5.24, 18.43, 25.31, 25.89, 27.05, 58.06, 64.03, 72.00, 81.96, 83.95, 89.44, 93.77, 104.31, 113.71, 114.68, 117.65, 129.03, 132.84, 136.69, 150.89, 152.99, 161.34.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2952 (w), 2931 (w), 2856 (w), 1718 (m), 1671 (vs), 1624 (w), 1605 (w), 1504 (w), 1471 (w), 1441 (m), 1406 (m), 1387 (m), 1384 (m), 1373 (m), 1356 (m), 1270 (w), 1253 (m), 1207 (m), 1159 (w), 1140 (m), 1084 (s), 1067 (s), 1021 (m), 1006 (m), 970 (w), 952 (m), 939 (w), 916 (m), 901 (m), 868 (m), 833 (vs), 816 (m), 775 (s), 731 (s), 684 (w), 664 (m).

7.11.18 Preparation of Uridine Derivative 51d



51d was prepared according to **TP10** from uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.42 mL, 0.71 M in THF, 0.30 mmol, 1.2 equiv.) was added to the solution at −30 °C, stirred for 72 h and reacted in a *Negishi* cross-coupling reaction by adding $Pd(dba)_2$ (11 mg, 8 mol%), $P(2\text{-furyl})_3$ (9 mg, 15 mol%) and 2-iodothiophen (63 mg, 0.30 mmol) at 25 °C for 12 h. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 2:8:0.05) furnishing the compound **51d** (127 mg, 0.25 mmol, 99%) as an orange liquid.

HRMS (ESI) for $C_{24}H_{36}N_2O_7SSi$: calcd. 524.6023 (M^+); found 524.1998.

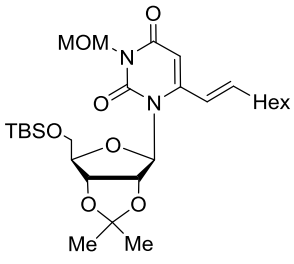
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.04 (s, 3H), 0.05 (s, 3 H), 0.88 (s, 9 H), 1.30 (s, 3 H), 1.42 (s, 3 H), 3.45 (s, 3 H), 3.81 - 3.87 (m, 2 H), 4.08 - 4.13 (m, 1 H), 4.86 (dd, *J*=6.43, 4.29 Hz, 1 H), 5.22 (dd, *J*=6.43, 1.36 Hz, 1 H), 5.35 (s, 2 H), 5.83 (d, *J*=1.36 Hz, 1 H), 5.84 (s, 1 H), 7.15 (dd, *J*=5.17, 3.61 Hz, 1 H), 7.47 (dd, *J*=3.70, 1.17 Hz, 1 H), 7.51 (dd, *J*=5.07, 1.17 Hz, 1 H).

^{13}C-NMR (101 MHz, CDCl3) δ = -5.25, -5.21, 18.45, 25.40, 25.92, 27.11, 57.95, 64.22, 71.93, 82.15, 84.28, 89.54, 93.41, 104.44, 113.50, 128.18, 129.21, 130.47, 132.39, 148.24, 151.18, 161.53.

MS (70 eV, EI) *m/z* (%): 467 (9), 409 (6), 297 (8), 296 (16), 295 (100), 232 (8), 177 (7), 171 (7), 129 (13).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3092 (vw), 2951 (w), 2929 (w), 2855 (w), 1716 (m), 1668 (vs), 1610 (m), 1519 (vw), 1471 (w), 1438 (m), 1403 (w), 1383 (m), 1372 (m), 1359 (m), 1345 (m), 1253 (m), 1208 (m), 1159 (m), 1134 (m), 1083 (s), 1067 (s), 1006 (m), 971 (w), 944 (m), 916 (m), 877 (m), 865 (m), 834 (vs), 773 (s), 755 (m), 729 (s), 709 (s), 681 (m), 666 (m).

7.11.19 Preparation of Uridine Derivative 51e



51e was prepared according to **TP10** from uridine derivate **47** (0.25 mL, 0.5 M in THF, 0.12 mmol). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.19 mL, 0.71 M in THF, 0.14 mmol, 1.2 equiv.) was added to the solution at −30 °C, stirred for 72 h and reacted in a *Negishi* cross-coupling reaction by adding $Pd(PPh_3)_4$ (11.5 mg, 4 mol%) and (*E*)-1-iodooct-1-ene (60 mg, 0.25 mmol) at 25 °C for 12 h. The crude product was

purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 2:8:0.05) furnishing the compound **51e** (107 mg, 0.19 mmol, 76%) as a yellow liquid.

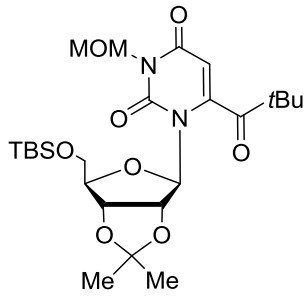
HRMS (ESI) for $C_{28}H_{49}N_2O_7Si^+$: calcd 553.79145; found 553.33017.

^{1}H-NMR (600 Hz, $CDCl_3$) δ = 0.04 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H), 0.90 (s, 3 H), 1.29 - 1.32 (m, 4 H), 1.33 (s, 3 H), 1.45 - 1.49 (m, 2 H), 1.53 (s, 3 H), 1.58 (m., 2 H), 2.23 - 2.27 (m , 2 H), 3.43 (s, 3 H), 3.77 - 3.85 (m, 2 H), 4.15 (dt, *J*=7.20, 4.77 Hz, 1 H), 4.87 (dd, *J*=6.31, 4.39 Hz, 1 H), 5.22 (dd, *J*=6.45, 1.24 Hz, 1 H), 5.31 (s, 2 H), 5.71 (s, 1 H), 5.74 (s, 1 H), 6.20 - 6.27 (m, 1 H), 6.27 - 6.40 (m, 1 H).

^{13}C-NMR (MHz, $CDCl_3$) δ = -5.27, -5.26, 14.04, 18.49, 22.55, 25.40, 25.94, 27.22, 28.31, 28.74, 31.55, 32.95, 57.79, 64.17, 71.78, 81.96, 84.09, 89.47, 92.84, 100.50, 113.55, 121.22, 143.11, 151.09, 152.97, 162.35.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954 (w), 2929 (m), 2856 (w), 1717 (m), 1673 (vs), 1616 (w), 1444 (m), 1382 (m), 1372 (m), 1360 (m), 1254 (w), 1210 (w), 1159 (w), 1138 (w), 1090 (m), 1009 (w), 974 (w), 940 (w), 916 (w), 872 (w), 838 (m), 776 (w).

7.11.20 Preparation of Uridine Derivative 51f



51f was prepared according to **TP10** from uridine derivate **47** (0.5 mL, 0.5 M in THF, 0.25 mmol). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.42 mL, 0.7 M in THF, 0.30 mmol, 1.2 equiv.) was added to the solution at −30 °C and was stirred for 72 h. The zinc reagent was treated with CuCN·2LiCl (0.3 mL, 1 M solution in THF, 0.3 mmol, 1.2 equiv.) for 30 min at −40 °C. Acylation was achieved by adding pivaloyl chloride (36 mg, 0.3 mmol) at −40 °C and warming up to 0 °C within 12 h. The reaction mixture was stirred at 0 °C until completion of the reaction. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing compound **51f** (128 mg, 0.24 mmol, 99%) as a colorless liquid.

HRMS (EI) for $C_{25}H_{42}N_2O_8Si$: calcd. 526.6951; found 511.2476 (M-Me^+).

MS (70 eV, EI) *m/z* (%): 411 (7), 298 (15), 297 (100), 265 (9), 235 (9), 170 (11) 129 (12).

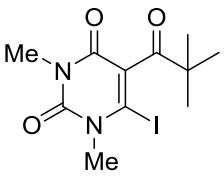
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.03 (s, 6 H), 0.87 (s, 9 H), 1.31 (s, 12 H), 1.49 (s, 3 H), 3.44 (s, 3 H), 3.72 - 3.86 (m, 2 H), 4.09 - 4.18 (m, 1 H), 4.81 (dd, *J*=6.63, 4.15 Hz, 1 H), 5.09 (d, *J*=1.38 Hz, 1 H), 5.19 (dd, *J*=6.36, 1.66 Hz, 1 H), 5.26 - 5.38 (m, 2 H), 5.56 (s, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = -5.33, -5.31, 18.37, 25.37, 25.85, 26.70, 27.16, 45.26, 58.03, 63.64, 71.93, 81.94, 84.17, 89.49, 95.59, 98.66, 113.90, 150.23, 151.48, 161.50, 205.39.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2955 (w), 2932 (w), 2856 (w), 1724 (m), 1704 (m), 1674 (vs), 1617 (w), 1479 (w), 1471 (w), 1446 (m), 1406 (w), 1390 (m), 1383 (m), 1371 (m), 1355 (m), 1252 (m), 1207 (m), 1178 (w), 1158 (w), 1137 (m), 1084 (s), 1065 (s), 1006 (m), 945 (m), 916 (m), 888 (m), 868 (m), 834 (vs), 816 (m), 798 (m), 773 (s), 731 (s), 669 (w).

7.12 Preperation of 5,6-Disubstituited Uracils and Uridines, 52-57

7.12.1 Preperation of 5,6-Disubstituited Uracil 52



To a solution of 6-iodo-1,3-dimethyl-5-pivaloyl uracil (**36l**, 123 mg, 0.54 mmol) in THF (1 mL) was added TMPMgCl·LiCl (**1**, 1.2 M in THF, m 0.75 mL, 0.9 mmol) at −40 °C. The reaction mixture was stirred for 24 h. Upon full conversion, iodine (1.2 M in THF, 0.75 mL, 0.9 mmol) was added and the reaction was stirred at 25 °C for 1 h. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) extracted with CH_2Cl_2 (3 × 20 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 1:1:0.01) furnishing compound **52** (70 mg, 0.20 mmol, 36%) as a colorless solid.

HRMS (EI) for $C_{11}H_{15}IN_2O$: calc. 350.0128 (M^+); found 350.0140.

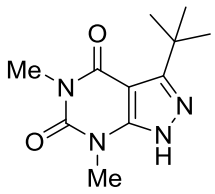
MS (EI, 70 eV) m/z (%): 350.01 (100), 351.02 (13), 352.02 (8)

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 3.73 (s, 3H), 3.33 (s, 3H), 1.34 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 207.30, 165.17, 148.98, 124.19, 112.68, 45.09, 34.69, 27.99, 27.42.

m.p.: 151-153 °C

7.12.2 Preperation of Pyrazole 54



To a solution of 6-Iodo-1,3-dimethyl-5-pivaloyl uracil (**52**, 1 M in DMF, 0.1 mL) was added N_2H_4 (1 M in THF, 0.15 mL, 0.15 mmol, 1.5 equiv.). The reaction mixture was stirred for 1 h at 60 °C. Upon completion, the reaction was quenched with sat. aq. NaCl (10 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 2:8:0.05 furnishing compound **54** (21 mg, 0.09 mmol, 87%) as a colorless solid.

HRMS (EI) for $C_{11}H_{15}IN_3$: calc. 236.1273 (M^+); found 236.1216.

MS (EI, 70 eV) m/z (%): 237 (13), 236 (81), 235 (23), 222 (16), 221 (100), 137 (13)

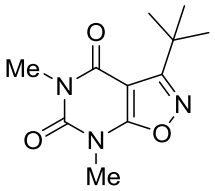
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 10.21 (s, 1H), 3.52 (s, 3H), 3.40 (s, 3H), 1.53(s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 158.86, 155.42, 152.47, 152.00, 97.26, 32.71, 29.74, 28.14, 27.85.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3222.00 (m), 3165.00 (w), 3129.00 (w), 3073.00 (w), 3042.00 (w), 2988.00 (w), 2965.00 (m), 2919.00 (w), 2876.00 (w), 2854.00 (w), 1706.00 (s), 1661.00 (s), 1596.00 (vs), 1522.00 (s), 1492.00 (m), 1436.00 (m), 1426.00 (s), 1417.00 (m), 1405.00 (m), 1367.00 (m), 1351.00 (m), 1307.00 (s), 1294.00 (s), 1241.00 (s), 1010.00 (s), 981.00 (s), 925.00 (s), 786.00 (m), 774.00 (m), 743.00 (s), 708.00 (s).

m.p.: 255-257 °C

7.12.3 Preparation of Isoxazole 55



To a solution of 6-Iodo-1,3-dimethyl-5-pivaloyl uracil (**52**, 1 M in DMF, 0.1 mL, 0,1 mmol) was added $NH_2OH{\cdot}HCl$ (9 mg, 0.13 mmol, 1.3 equiv.). The reaction mixture was stirred for 1 h at 60 °C. Upon completion, the reaction was quenched with sat. aq. NaCl (10 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane:Et_3N 2:8:0.05 furnishing compound **55** (13 mg, 0.05 mmol, 55%) as a colorless solid.

HRMS (EI) for $C_{11}H_{15}N_3O_3$: calc. 237.1113 (M^+); found 236.1066.

MS (EI, 70 eV) m/z (%): 237 (40), 222 (79), 196 (12), 195 (33), 182 (23), 181 (50), 126 (12), 125 (14), 124 (42), 67 (812), 58 (34), 57 (90), 56 (16), 55 (14), 53 (14), 43 (36).

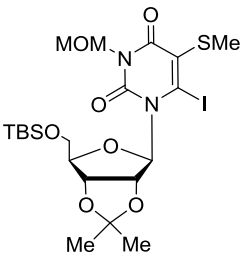
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 3.49 (s, 3H), 3.37 (s, 3H), 1.52(s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 185.76, 158.77, 155.01, 151.02, 97.98, 35.38, 30.29, 28.31, 27.10.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2976.00 (w), 2930.00 (w), 2874.00 (w), 2857.00 (w), 2361.00 (w), 2340.00 (w), 1724.00 (s), 1673.00 (vs), 1613.00 (vs), 1551.00 (m), 1497.00 (m), 1424.00 (s), 1372.00 (m), 1362.00 (s), 1302.00 (s), 1272.00 (s), 1250.00 (m), 1182.00 (m), 1012.00 (s), 786.00 (s), 742.00 (vs).

m.p.: 230-232 °C

7.12.4 Preparation of 5,6-Disubstituited Uridine 53



To a solution of Uridine derivate **49n** (1 mL, 0.50 M in THF, 0.50 mmol) was added TMPMgCl·2LiCl (**1**, 0.6 mL, 1.0 M in THF, 0.30 mmol, 1.2 equiv.) at −20 °C. The reaction mixture was stirred for 20 min. The magnesium reagent reacted with iodine (0.6 mL, 1.0 M in THF, 0.30 mmol, 1.2 equiv.) at −20 °C, stirring for 10 min at –20 °C and 10 min at 25 °C. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/ NEt_3 2:8:0.05) furnishing the compound **53** (267 mg, 0.43 mmol, 87%) as a yellow liquid.

HRMS (ESI) for $C_{20}H_{32}IN_2O_7SSi^-$ calcd 599,53302 (M-Me); found 599.04743.

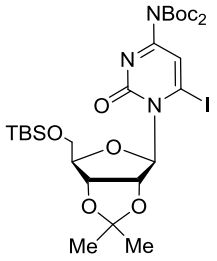
^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.04 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H), 1.34 (s, 3 H), 1.55 (s, 3 H), 2.38 (s, 3 H), 3.43 (s, 3 H), 3.70 - 3.89 (m, 2 H), 4.01 - 4.22 (m, 1 H), 4.86 (dd, *J*=6.53, 4.39 Hz, 1 H), 5.18 (dd, *J*=6.53, 1.27 Hz, 1 H), 5.33 (s, 2 H), 6.40 (d, *J*=1.36 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = -5.26, -5.24, 17.94, 18.48, 25.42, 25.95, 27.23, 58.25, 63.99, 73.24, 82.00, 84.66, 89.89, 105.07, 113.81, 120.75, 126.49, 148.46, 157.30.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3469 (w), 2987 (w), 2952 (w), 2928 (m), 2856 (w), 1715 (s), 1661 (vs), 1531 (s), 1434 (m), 1422 (s), 1372 (s), 1358 (s), 1258 (m), 1209 (s), 1187 (m), 1158 (m), 1138 (m), 1089 (vs), 1065 (vs), 970 (s), 958 (s), 919 (m), 878 (s), 864 (s), 835 (s), 808 (s), 766 (vs), 665 (s).

7.13 Cytidine Derivatives 59a-d

7.13.1 Preparation of Cytidine Derivative 59a



Compound **59a** was prepared according to **TP10** from cytidine derivate **57** (1.00 mL, 0.20 M in THF, 0.20 mmol). To the solution $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.50 mL, 0.5 M in THF, 0.25 mmol, 1.2 equiv.) was added at −30 °C and subsequently stirred for 4 h. The obtained zinc species **58** reacted with iodine (63 mg, 0.25 mmol) for 30 min. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing the compound **59a** (95 mg, 0.12 mmol, 61%) as a colorless liquid.

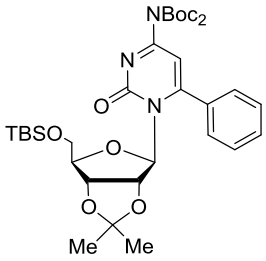
HRMS (ESI) for $C_{28}H_{47}IN_3O_9Si$: calcd. 724.2126; found 724.2122.

^{1}H NMR (400 MHz, acetone) δ = 0.02 (s, *J*=1.17, 3 H), 0.02 (s, *J*=1.17, 3 H), 0.87 (s, 9 H), 1.32 (s, 3 H), 1.50 (s, 3 H), 1.54 (s, 18 H), 3.83 (d, *J*=1.17 Hz, 1 H), 3.85 (s, 1 H), 4.16 (td, *J*=6.55, 3.72 Hz, 1 H), 4.87 (dd, *J*=6.36, 3.81 Hz, 1 H), 5.26 (dd, *J*=6.46, 1.17 Hz, 1 H), 6.23 (d, *J*=0.98 Hz, 1 H), 7.65 (s, 1 H),

^{13}C NMR (101 MHz, acetone) δ = -5.96, -5.82, 17.99, 24.51, 25.39, 26.54, 26.89, 64.06, 82.90, 84.41, 84.82, 90.89, 102.96, 109.83, 112.79, 118.26, 149.04, 151.53, 161.29,

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3426.00 (w), 3265.00 (w), 2977.00 (w), 2934.00 (w), 1710.00 (s), 1638 (vs), 1549 (m), 1495 (m), 1421 (m), 1369 (s), 1273 (s), 1254 (s), 1146 (vs), 1102 (s), 1065 (s), 1043 (m), 1013 (m), 868 (m), 803 (m), 767 (m), 734 (w), 661 (w).

7.13.2 Preparation of Cytidine Derivative 59b



Compound **59b** was prepared according to **TP10** from cytidine derivate **57** (0.50 mL, 0.20 M in THF, 0.10 mmol). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.16 mL, 0.72 M in THF, 0.11 mmol, 1.1 equiv.) was added to the solution at −30 °C, and subsequently stirred for 4 h. The obtained zinc species **58** reacted with iodobenzene (24 mg, 0.12 mmol, 1.2 equiv.) for 30 min. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing compound **57b** (29 mg, 0.04 mmol, 43%) as a colorless liquid.

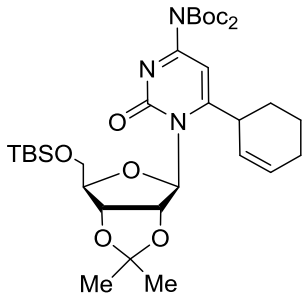
HRMS (ESI) for $C_{34}H_{52}N_3O_9Si^+$:calcd. 674,34673; found 674.34650.

^{1}H NMR (300 MHz, acetone-*d6*) δ = 0.07 (s, 3 H), 0.07 (s, 3 H), 0.91 (s, 9 H), 1.27 (s, 3 H), 1.32 (s, 3 H), 1.57 (s, 18 H), 3.91 (s, 1 H,) 3.94 (s, 1 H), 4.01 - 4.12 (m, 1 H), 4.88 (dd, *J*=6.36, 3.87 Hz, 1 H), 5.28 (dd, *J*=6.50, 1.24 Hz, 1 H), 5.63 (s, 1 H), 6.91 (s, 1 H), 7.62 (s, 5 H).

^{13}C NMR (75 MHz, acetone-*d6*) δ = -5.90, -5.78, 18.02, 24.44, 25.40, 26.40, 26.95, 64.25, 83.10, 84.20, 84.53, 90.57, 93.94, 97.52, 112.56, 128.47, 128.97, 130.65, 133.58, 149.38, 153.93, 160.71, 161.62.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2980 (w), 2952 (w), 2932 (w), 2929 (w), 2887 (w), 2856 (w), 1781 (m), 1745 (s), 1685 (s), 1608 (m), 1596 (m), 1574 (w), 1537 (m), 1492 (w), 1467 (w), 1461 (w), 1413 (m), 1395 (m), 1370 (m), 1308 (vs), 1284 (m), 1251 (s), 1209 (m), 1159 (s), 1131 (vs), 1092 (m), 1057 (m), 1033 (w), 973 (w), 879 (w), 837 (m), 816 (w), 789 (w), 776 (m), 701 (w).

7.13.3 Preparation of Cytidine Derivative 59c



Compound **59c** was prepared according to **TP10** from cytidine derivate **57** (1.00 mL, 0.20 M in THF, 0.20 mmol). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.32 mL, 0.72 M in THF, 0.23 mmol, 1.1 equiv.) was added to the solution at −30 °C, stirred for 4 h. The zinc reagent **58** was treated with CuCN·2LiCl (0.3 mL, 1 M solution in THF, 0.3 mmol, 1.5 equiv.) for 30 min at −40 °C. Acylation was achieved by adding bromocyclohex-1-ene (48 mg, 0.23 mmol, 1.1 equiv.) at −40 °C and warming up to 0 °C. The reaction mixture was stirred at 0 °C until completion. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing compound **59c** (70 mg, 0.10 mmol, 52%, dr = 91:19) as a colorless liquid.

HRMS (ESI) for $C_{34}H_{56}N_3O_9Si^+$: calcd. 678.37803 ($M+H^+$), found 678.37798.

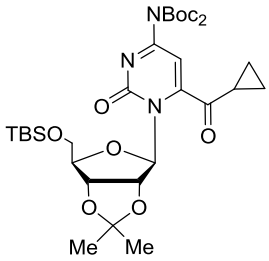
Major isomer: **^{1}H NMR** (400 MHz, Acetone) δ = = 0.00 (s, 3 H), 0.01 (s, 3 H), 0.86 (9 H), 1.31 (s, 3 H), 1.48 (s, 3 H), 1.53 (s, 18 H), 1.68 - 1.73 (m, 3 H), 2.07 - 2.12 (m, 3 H), 3.77 - 3.79 (m, 1 H), 3.84 (d, *J*=3.18 Hz, 1 H), 3.86 (d, *J*=1.96 Hz, 1 H), 4.10 - 4.13 (m, 1 H), 4.86 (dd, *J*=6.48, 3.79 Hz, 1 H), 5.29 (dd, *J*=6.48, 1.10 Hz, 1 H), 5.64 - 5.68 (m, 1 H), 5.98 (m, 1 H), 6.03 - 6.07 (m, 1 H), 6.87 (m, 1 H).

Major isomer: **^{13}C NMR** (101 MHz, acetone) δ = -5.9 (1 C, $^{1}J_{SiC}$ = 56.9), -5.8 (1 C, $^{1}J_{SiC}$ = 56.9), 0.89 (3 C), 18.0 (l C), 19.6 (1 C), 24.6 (1 C), 24.8 (1 C), 27.0 (6 C), 28.8 (1 C), 25.4 (1 C), 26.6 (1 C), 37.7 (1 C), 64.2 (1 C), 83.2 (1 C), 84.3 (1 C), 84.4 (2 C), 90.5 (1 C), 92.0 (1 C), 95.7 (1 C), 112.8 (1 C), 125.4 (1 C); 149.5 (2 C), 131.0 (1 C), 154.4 (1 C), 162.1 (1 C), 164.8 (1 C).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2979 (w), 2930 (w), 2856 (w), 1779 (m), 1743 (s), 1716 (m), 1680 (s), 1603 (m), 1538 (m), 1472 (w), 1460 (w), 1420 (m), 1394 (m), 1381 (m), 1369 (s), 1300 (s), 1248 (s), 1209 (m), 1156 (s), 1133 (vs), 1098 (s), 1084 (s), 1054 (s), 1047 (s), 975 (m), 937 (m), 876 (m), 835 (vs), 815 (m), 789 (m), 776 (s), 727 (m).

7.13.4 Preparation of Cytidine Derivative 59d

Compound **59d** was prepared according to **TP10** from cytidine derivate **57** (1 mL, 0.20 M in THF, 0.20 mmol). To the solution was added $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.32 mL, 0.72 M in THF, 0.23 mmol, 1.1 equiv.) at −30 °C and subsequently stirred for 4 h. The zinc reagent **60** was treated with CuCN·2LiCl (0.3 mL, 1 M solution in THF, 0.3 mmol, 1.5 equiv.) for 30 min at −40 °C. Acylation was achieved by adding cyclopropanecarbonyl chloride (31 mg, 0.3 mmol, 1.5 equiv.) at −40 °C and warming up to 0 °C within 12 h. The reaction mixture was stirred at 0 °C until completion. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane/NEt_3 2:8:0.05) furnishing compound **69d** (69 mg, 0.10 mmol, 52%) as a colorless liquid.



HRMS (ESI) for $C_{32}H_{51}N_3O_{10}Si^+$: calcd 666,86345; found 666.3414 (M^+-Me).

^{1}H NMR (400 MHz, acetone) δ = 0.00 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9 H), 1.21 - 1.33 (m, 4 H), 1,27 (s, 3H), 1.44 (s, 3 H), 1.52 (s, 18 H), 2.33 - 2.59 (m, 1 H), 3.78 - 3.86 (m, 2 H), 4.06-4.10 (m, 1 H), 4.78 (dd, *J*=6.48, 4.03 Hz, 1 H), 5.22 (dd, *J*=6.60, 1.22 Hz, 1 H), 5.72 (d, *J*=1.22 Hz, 1 H), 7.11 (s, 1 H).

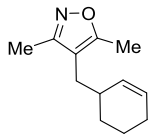
^{13}C NMR (101 MHz, acetone) δ = -5.93, -5.80, 13.39, 13.97, 18.04, 21.64, 24.66, 25.43, 26.61, 26.95, 63.94, 82.67, 84.47, 84.93, 90.09, 94.74, 94.77, 113.11, 149.21, 153.07, 156.96, 162.34, 197.93.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2980.00 (w),2955 (w),2932 (w),2856 (w),1782 (m),1745 (s),1689 (s),1604 (m),1540 (w),1472 (w),1461 (w),1426 (w),1383 (m),1371 (s),1349 (w),1311

(vs),1251 (s),1210 (m),1157 (s),1128 (vs),1083 (s),1062 (m),1026 (m),1005 (w),967 (w),876 (w),838 (s),815 (m),779 (m).

7.14 Regioselective Reaction of Zinc Species 63 with Various Electrophiles at the Benzylic Position 64a-i

7.14.1 Preparation of 4-(Cyclohex-2-en-1-ylmethyl)-3,5-dimethylisoxazole (64a)



Compound **64a** was prepared according to **TP12a** from zinc species **63** (1 mmol, 0.4 M in THF), CuCN·2LiCl (1.2 mmol, 1 M in THF, 1.2 equiv.) and 3-bromocyclohex-1-ene (160 mg, 1 mmol, 1 equiv.). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:9) furnishing product **64a** (139 mg, 0.73 mmol, 73%) as a colorless oil.

HRMS (EI) for $C_{12}H_{17}NO$: calcd 191.1310 (M^+); found 191.1342.

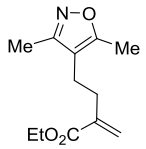
MS (EI, 70eV), m/z(%): 191 (8), 176 (14), 148 (21), 112 (18), 111 (16), 110 (82).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 - 1.23 (m, 1 H), 1.38 - 1.55 (m, 1 H), 1.59 - 1.74 (m, 2 H), 1.94 (d, *J*=2.49 Hz, 2 H), 2.15 (d, *J*=2.49 Hz, 3 H), 2.10 – 2.31 (m, 3 H), 2.24 (d, *J*=2.21 Hz, 3 H), 5.43 (d, *J*=9.95 Hz, 1 H), 5.58 - 5.74 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.28, 11.05, 21.01, 25.22, 28.75, 28.85, 35.61, 112.06, 127.98, 130.35, 159.71, 165.12.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3232, 3026, 2925, 2857, 2843, 1735, 1670, 1636, 1448, 1422, 1260, 1193, 891, 742, 721, 693.

7.14.2 Preparation of Ethyl 4-(3,5-dimethylisoxazol-4-yl)-2-methylenebutanoate (64b)



64b was prepared according to **TP12a** from zinc species **63** (1 mmol, 0.4 M in THF), CuCN·2LiCl (1.2 mmol, 1 M in THF, 1.2 equiv.) and 2-(bromomethyl)acrylate (191 mg, 1 mmol, 1 equiv.). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:9) furnishing product **64b** (171 mg, 0.77 mmol, 77%) as a colorless oil.

HRMS (EI) for $C_{12}H_{17}NO_3$: calcd 223.1208 (M^+); found 223.1203.

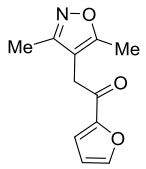
MS (EI, 70eV), m/z(%): 223 (5), 111 (10), 110 (100), 68 (58).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J*=7.05 Hz, 3 H), 2.16 (s, 3 H), 2.22 (s, 3 H), 2.32 - 2.47 (m, 4 H), 4.16 (q, *J*=7.00 Hz, 2 H), 5.44 (d, *J*=1.11 Hz, 1 H), 6.10 (d, *J*=1.38 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.04, 10.79, 14.14, 21.60, 32.40, 60.68, 112.56, 125.91, 139.44, 159.49, 164.95, 166.68.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2983, 2964, 2931, 2872, 1710, 1631, 1447, 1425, 1369, 1324 , 1302, 1253, 1193, 1142, 1056, 1025, 947, 890, 861, 818, 750, 735, 693, 661.

7.14.3 Preparation of 2-(3,5-Dimethylisoxazol-4-yl)-1-(furan-2-yl)ethan-1-one (64c)



64c was prepared according to **TP12b** from zinc species **63** (0.8 mmol, 0.4 M in THF)**,** CuCN·2LiCl (0.95 mmol, 1 M in THF, 1.2 equiv.) and 2-furoyl chloride (104 mg, 0.8 mmol, 1 equiv.). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:9) furnishing product **64c** (133 mg, 0.64 mmol, 81%) as a colorless solid.

HRMS (EI) for $C_{11}H_{11}NO_3$: calcd. 205.0739 (M^+); found 205.0741.

MS (EI, 70eV), m/z(%): 205 (22), 163 (17), 162 (61), 110 (23), 95 (100).

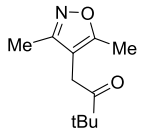
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14 (d, *J*=1.38 Hz, 3 H), 2.27 (d, *J*=1.11 Hz, 3 H), 3.79 (s, 2 H), 6.51-6.53 (m, 1 H), 7.20 (d, *J*=3.59 Hz, 1 H), 7.57 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.22, 11.09, 32.14, 106.85, 112.62, 117.54, 146.63, 152.03, 159.89, 166.50, 184.65.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) =3144, 3122, 3114, 3095, 2962, 2928, 2849, 1735, 1646, 1561, 1460, 1454, 1422, 1392, 1332, 1281, 1259, 1238, 1200, 1191, 1163, 1084, 1071, 1040, 994, 915, 880, 785, 777, 745, 695, 682.

m.p.: 89-91 °C

7.14.4 Preparation of 64d



1-(3,5-Dimethylisoxazol-4-yl)-3,3-dimethylbutan-2-one (**64d**) was prepared according to **TP12b** from zinc species **63** (0.8 mmol, 0.4 M in THF), CuCN·2LiCl (0.95 mmol, 1 M in THF, 1.2 equiv.) and pivaloyl chloride (0.96 mg, 0.8 mmol, 1 equiv.). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:9) furnishing product **64d** (116 mg, 0.54 mmol, 74%) as a colorless solid.

HRMS (EI) for $C_{11}H_{17}NO_2$: calcd 195.1259 (M^+); found 195.1302.

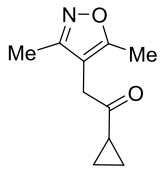
MS (EI, 70eV), m/z(%): 139 (11), 110 (10), 68 (16), 57 (100).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 2.07 (d, *J*=1.38 Hz, 3 H), 2.21 (s, 3 H), 3.45 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ =10.17, 11.02, 26.38, 20.11, 44.20, 107.67, 159.74, 166.94, 211.09.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3014, 2890, 1698, 1649, 1454, 1444, 1428, 1411, 1378, 1317, 1263, 1217, 1200, 1187, 1097, 1075, 1043, 1025, 925, 893, 883, 813, 791, 746, 740, 681.

7.14.5 Preparation of 1-Cyclopropyl-2-(3,5-dimethylisoxazol-4-yl)ethan-1-one (64e)



64e was prepared according to **TP12b** from zinc species **63** (0.8 mmol, 0.4 M in THF), CuCN·2LiCl (0.95 mmol, 1 M in THF, 1.2 equiv.) and cyclopropanecarbonyl chloride (83 mg, 0.8 mmol, 1 equiv.). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:9) furnishing the products **64e** (121 mg, 0.67 mmol, 84%) as a colorless solid.

HRMS (EI) for $C_{10}H_{13}NO_2$: calcd179.0946 (M^+); found 179.0934.

MS (EI, 70eV), m/z(%): 179 (6), 137 (9), 136 (32), 110 (11).

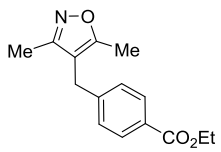
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 - 0.92 (m, 2 H), 0.92 - 1.03 (m, 2 H), 1.84-1.91 (m, 1H), 2.09 (d, *J*=1.11 Hz, 3 H), 2.24 (d, *J*=0.83 Hz, 3 H), 3.47 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.12, 10.99, 11.31, 19.83, 37.09, 107.40, 159.71, 166.10, 206.26.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2965, 2934, 2916, 2870, 1707, 1644, 1479, 1455, 1427, 1410, 1395, 1366, 1328, 1265, 1221, 1197, 1064, 1005, 936, 887, 810, 746, 719, 671.

m.p.: 52-54 °C

7.14.6 Preparation of Ethyl 4-((3,5-dimethylisoxazol-4-yl)methyl)benzoate (64f)



64f was prepared according to **TP12c** from zinc species **63** (1.0 mmol, 0.4 M in THF) ethyl-p-iodobenzoate and (248 mg, 0.9 mmol, 0.9 equiv.) in the presence of PEPPSI-iPr (5 mg, 1 mol %). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:9) furnishing product **64f** (203 mg, 0.78 mmol, 87%) as a yellow oil.

HRMS (EI) for $C_{15}H_{17}NO_3$: calcd 259.1208 (M^+), found: 259.1207

MS (EI, 70eV), m/z(%):260 (18), 259 (100), 258 (36), 231 (30), 230 (69), 216 (20), 215 (14), 214 (87), 189 (20), 188 (29), 187 (10), 186 (56), 149 (18), 145 (21), 144 (28), 143 (10), 131 (13), 115 (15), 103 (12), 102 (12), 77 (11), 43 (41).

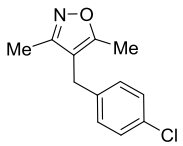
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, *J*=7.06 Hz, 3 H), 2.08 (s, 3 H), 2.32 (s, 3 H), 3.74 (s, 2 H), 4.38 (q, *J*=7.02 Hz, 2 H), 7.18 (d, *J*=8.17 Hz, 2 H), 7.98 (d, *J*=8.17 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ =10.29, 11.03, 14.32, 28.23, 60.93, 111.63, 128.02, 128.93, 129.91, 143.98, 159.78, 165.65, 166.33.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2987, 1705, 1610, 1478, 1449, 1416, 1365, 1278, 1179, 1124, 1107, 1020, 880, 743, 730.

7.14.7 Preparation of 4-(4-Chlorobenzyl)-3,5-dimethylisoxazole (64g)

64g was prepared according to **TP12c** from zinc species **63** (0.8 mmol, 0.4 M in THF) and 1-chloro-4-iodobenzene (190 mg, 0.8 mmol, 1 equiv.) in the presence of PEPPSI-iPr (5 mg, 1 mol %). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:9) furnishing product **64g** (151 mg, 0.68 mmol, 85%) as a yellow oil.



HRMS (EI) for $C_{12}H_{12}ClNO_2$: calcd 221.0607 (M^+); found 221.0608.

MS (EI, 70eV), m/z(%): 223 (28), 222 (10), 221 (100), 220 (18), 186 (30), 180 (11), 179 (13), 178 (36), 167 (11), 165 (49).

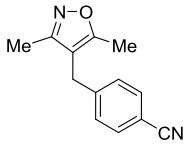
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3 H), 2.29 (s, 3 H), 3.63 (s, 2 H), 7.02 (d, *J*=8.29 Hz, 2 H), 7.24 (d, *J*=8.57 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.27, 10.99, 27.53, 111.86, 128.71, 129.33, 132.25, 137.23, 159.76, 165.51.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3030, 2991, 2962, 2925, 2846, 1639, 1489, 1422, 1406, 1257, 1198, 1186, 1089, 1039, 1014, 901, 887, 804, 758.50, 741, 695.

7.14.8 Preparation of 4-((3,5-Dimethylisoxazol-4-yl)methyl)benzonitrile (64h)

64h was prepared according to **TP12c** from zinc species **63** (0.8 mmol, 0.4 M in THF) and 4-iodobenzonitrile (183 mg, 0.8 mmol, 1 equiv.) in the presence of PEPPSI-*iPr* (5 mg, 1 mol %). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:9) furnishing product **64h**



(110 mg, 0.52 mmol, 65%) as a yellow oil.

HRMS (EI) for $C_{12}H_{12}ClNO_2$: calcd 212.0947 (M^+); found 212.0936.

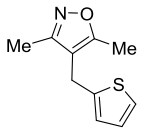
MS (EI, 70eV), m/z(%): 213 (10), 212 8100), 211 (31), 170 (24), 169 (60), 156 (49), 155 (11), 140 (10), 128 (32).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3 H), 2.28 (s, 3 H), 3.72 (s, 2 H), 7.19 (d, *J*=8.57 Hz, 2 H), 7.54 (d, 8.57 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.24, 11.01, 28.25, 110.49, 111.02, 118.65, 128.80, 132.42, 144.40, 159.57, 165.87.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2961, 2922, 2854, 2224, 1639, 1606, 1501, 1448, 1421, 1411, 1260, 1200, 1187, 1176, 1117, 1039, 902, 884, 844, 820, 767, 742, 721, 697, 661.

7.14.9 Preparation of 3,5-Dimethyl-4-(thiophen-2-ylmethyl)isoxazole (64i)



64i was prepared according to **TP12c** from zinc species **63** (0.8 mmol, 0.4 M in THF) and 2-iodothiophene (167 mg, 0.8 mmol, 1 equiv.) in the presence of PEPPSI-*iPr* (5 mg, 1 mol %). The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:9) furnishing product **64i** (110 mg, 0.57 mmol, 71%) as a yellow oil.

HRMS (ESI) for $C_{12}H_{12}ClNO_2$: calcd 194.06341(M^+); found194.06336.

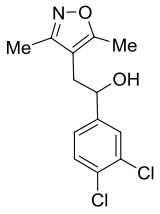
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 2.32 (s, 3 H), 3.83 (s, 2 H), 6.66 - 6.76 (m, 1 H), 6.90 (dd, *J*=5.11, 3.46 Hz, 1 H), 7.13 (dd, *J*=5.25, 1.11 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.12, 10.94, 22.76, 112.33, 123.97, 124.60, 126.89, 142.21, 159.57, 165.41.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3115, 3074, 2995, 2967, 2921, 1638, 1450, 1422, 1307, 1261, 1192, 1138, 1076, 1034, 1010, 886, 849, 827, 759, 741, 691.

7.15 Benzylic Addition of Zinc Species 1 to Aldehydes forming Products 67a-c

7.15.1 Preparation of 1-(3,4-Dichlorophenyl)-2-(3,5-dimethylisoxazol-4-yl)ethan-1-ol (67a)



67a was prepared according to **TP12d** from zinc reagent **63** (0.42 mmol, 0.42 M in THF, 1 equiv.), $BF_3 \cdot OEt_2$ (0.21 mL, 0.84 mmol, 50% in Et_2O, 2 equiv.), and 3,4-dichlorobenzaldehyde (0.42 mL, 0.42 mmol, 1 M in THF, 1 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **67a** as a colorless solid (66 mg, 0.23 mmol, 55%).

HRMS (EI) for $C_{13}H_{13}Cl_2NO_2$: calcd 286.15200 ($M+H^+$); found 286.0384.

MS (EI): 288 (1), 286 (1), 176 (60), 175 (11), 174 (100), 172 (24), 148 (28), 146 (49), 144 (16).

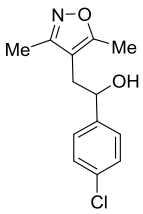
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3 H) 2.13 (s, 3 H) 2.65 (d, *J*=6.38 Hz, 2 H) 4.74 (t, *J*=6.38 Hz, 1 H) 7.05 - 7.10 (m, 1 H) 7.37 - 7.42 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.12, 10.91, 32.37, 72.66, 109.32, 125.15, 127.76, 130.39, 131.65, 132.65, 143.76, 159.90, 166.65.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3296, 1636, 1467, 1455, 1420, 1391, 1380, 1335, 1257, 1191, 1128, 1076, 1051, 1029, 974, 912, 903, 883, 854, 825, 777, 745, 703, 684, 678.

m.p.: 131 °C

7.15.2 Preparation of 1-(4-Chlorophenyl)-2-(3,5-dimethylisoxazol-4-yl)ethan-1-ol (67b)



67b was prepared according to **TP12d** from zinc reagent **63** (0.80 mmol, 0.4 M in THF, 1 equiv.), $BF_3 \cdot OEt_2$ (0.42 mL, 1.6 mmol, 50% in Et_2O, 2 equiv.), and 4-dichlorobenzaldehyde (0.80 mL, 0.8 mmol, 1 M in THF, 1 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **67b** as a colorless oil (132 mg, 0.52 mmol, 65%).

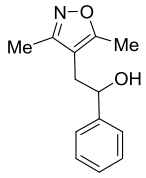
HRMS (EI) for $C_{13}H_{15}ClNO_2$: calcd 252.07858 ($M+H^+$), found 252.07834.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H), 2.07 (s, 3 H), 2.68, 4.76 (ABX, δ_A=2.67, δ_B=2.64, δ_x=4.76, J_{AB}= 14.38 Hz, J_{AX}= 6.36 Hz, J_{BX}= 6.30 Hz, 2H), 2.92 (s, 1 H), 7.09 - 7.22 (m, 2 H), 7.22 - 7.39 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.01, 10.79, 32.41, 73.15, 109.56, 127.22, 128.54, 133.43, 142.04, 160.06, 166.60.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) =3326, 2924, 1636, 1490, 1455, 1422, 1404, 1371, 1338, 1308, 1259, 1239, 1191, 1105, 1088, 1074, 1051, 1013, 972, 901, 862, 852, 818, 756, 745, 712, 679.

7.15.3 Preparation of 2-(3,5-Dimethylisoxazol-4-yl)-1-phenylethan-1-ol (67c)



67c was prepared according to **TP12d** from zinc reagent **63** (0.80 mmol, 0.4 M in THF, 1 equiv.), $BF_3{\cdot}OEt_2$ (0.42 mL, 1.6 mmol, 50% in Et_2O, 2 equiv.), and benzaldehyde (0.80 mL, 0.8 mmol, 1 M in THF, 1 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **67c** as a colorless oil (108 mg, 0.50 mmol, 62%).

HRMS (EI) for $C_{13}H_{15}NO_2$: 218,1181 ($M+H^+$); found 218.1206.

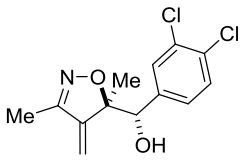
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.95 (s, 3 H), 1.99 (s, 3 H) 2.58-2.77, 4.73 (ABX, δ_A=2.69, δ_B= 2.65, δ_x= 4.73, J_{AB}= 14.47 Hz, J_{AX}= 6.23 Hz, J_{BX}= 6.41 Hz, 2H), 3.04 (s, 1 H), 7.04 - 7.49 (m, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.91, 10.66, 32.43, 73.88, 109.75, 125.86, 127.75, 128.43, 143.49, 160.22, 166.56.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3373, 3092, 3066, 3029, 2925, 2859, 1744, 1720, 1689, 1634, 1493, 1452, 1423, 1328, 1260, 1193, 1093, 1060, 1026, 909, 890, 842, 760, 737, 699, 679.

7.16 Allylic Addition of Zinc Species 1 with Aldehydes 66a-l

7.16.1 Preparation of (S)-(3,4-Dichlorophenyl)((R)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)methanol (66a)



66a was prepared according to **TP13a** from zinc reagent **63** (1.5 mmol, 1.5 equiv.), $LaCl_3 \cdot 2LiCl$ (2.00 mmol, 0.5 M in THF, 2 equiv.), and 3,4-dichlorobenzaldehyde (1.0 mmol, 1.0 mL, 1 M in THF, 0.66 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **66a** as a white solid (263 mg, 0.92 mmol, 92%, dr= 96:4).

66a could also be prepared according to **TP13b** from zinc reagent **63** (0.3 mmol) to produce the title compound in 73% yield (dr= 94:6).

HRMS (EI) for $C_{13}H_{14}Cl2NO_2$: calcd 286.0323 ($M+H^+$), found 286.0370.

MS (EI, 70 eV): m/z (%) = 178 (4), 175 (73), 173 (54), 145 (21), 111 (98), 96 (24), 83 “0), 82 (21), 75 (22), 70 (100), 68 (79), 55 (17), 43 (56).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.97 (s, 3 H), 2.92 (s, 1 H), 4.63 (s, 1 H), 4.69 (s, 1 H), 5.31 (s, 1 H), 7.14 - 7.33 (m, 1 H), 7.33 - 7.55 (m, 2 H).

^{13}C NMR (101 MHz, acetone d6): δ = 8.67, 21.25, 75.93, 88.31, 108.31, 128.09, 129.19, 129.99, 130.42, 130.60, 141.45, 152.42, 154.12.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) =3268, 2983, 2955, 2924, 2852, 2722, 2677, 2339, 1723, 1644, 1589, 1564, 1469, 1452, 1416, 1395, 1384, 1372, 1296, 1251, 1199, 1130, 1073, 1030, 909, 889, 855, 821, 752, 744.

m.p.: 86 - 96 °C

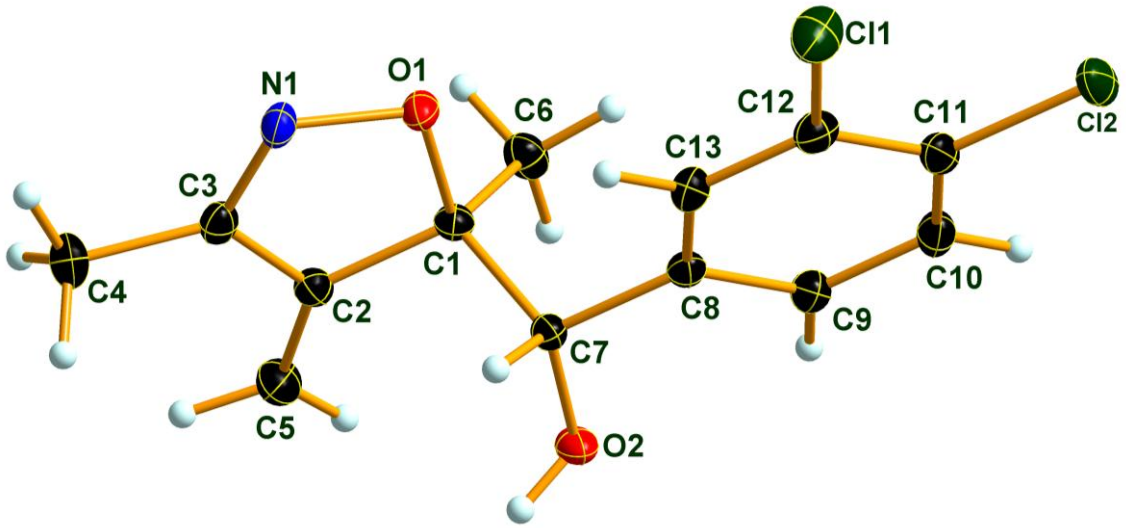


Figure 38: Molecular structure of compound **66a** in the crystal, DIAMOND representation, thermal ellipsoids are drawn at 50% probability level.

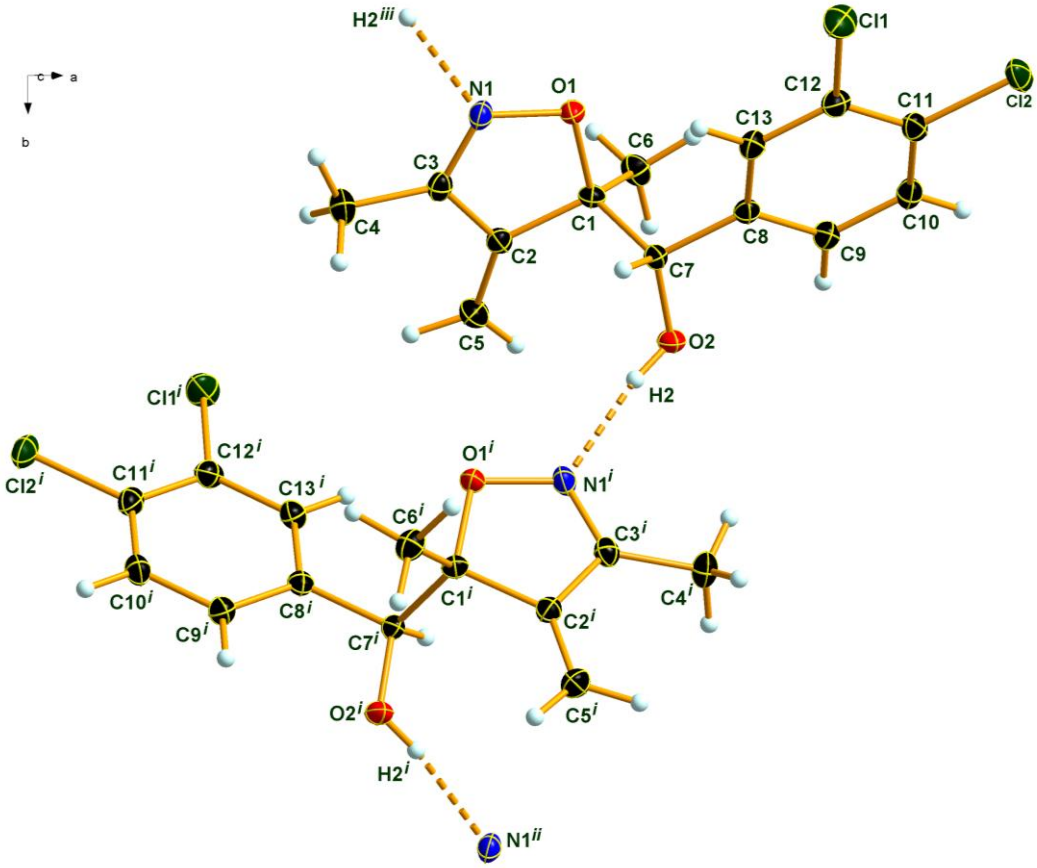


Figure 39: Crystal structure of compound **66a**, chains formed by O-H···N hydrogen bonds, O-H 0.83(2) Å, H···N 1.98(2) Å, O···N 2.798(2) Å, O-H-N 172(2)°, DIAMOND representation, thermal ellipsoids are drawn at 50% probability level; symmetry codes: *i*) 1-x, 0.5+y, 0.5-z; *ii*) x, 1+y, z; *iii*) 1-x, -0.5+y, 0.5-z.

Table 13: Details for X-ray data collection and structure refinement for compound **66a**.

Empirical formula	$C_{13}H_{13}Cl_2NO_2$
Formula mass	286.14
T [K]	100(2)
Crystal size [mm]	0.384 × 0.247 × 0.088
Crystal description	colorless block
Space group	*P*21/*c*
a [Å]	10.5625(3)
b [Å]	10.6780(3)
c [Å]	11.7851(4)
β [°]	92.663(3)
V [Å^3]	1327.76(7)
Z	4
ρ_{calcd} [g cm^{-3}]	1.431
μ [mm^{-1}]	0.481
F(000)	592
Θ range [°]	4.19 – 30.03
Index ranges	$-6 \leq h \leq 6$
	$-17 \leq k \leq 14$
	$-36 \leq l \leq 37$
Reflns. collected	13283
Reflns. obsd.	3100
Reflns. unique	3867
	(R_{int} = 0.0388)
R_1, wR_2 (2σ data)	0.0370, 0.0824
R_1, wR_2 (all data)	0.0521, 0.0910
GOOF on F^2	1.044
Peak/hole [e Å^{-3}]	0.396, -0.330

Single crystals of compound **66a**, suitable for X-ray diffraction, were obtained by slow evaporation of CH_2Cl_2 solutions at ambient temperature. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer

equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å). Data collection was performed with the CrysAlis CCD software;[137] CrysAlis RED software[138] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[139] was applied. The structures were solved with SHELXS-97,[140] refined with SHELXL-97[141] and finally checked using PLATON.[142] Details for data collection and structure refinement are summarized in Table 1.

CCDC 993119 contains supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 13: Molecular structure of compound **66a** in the crystal; selected atom distances (in Å).

Cl1 – C12	1.737(2)	C2 – C3	1.459(2)
Cl2 – C11	1.736(2)	C3 – C4	1.488(2)
O1 – N1	1.418(2)	C7 – C8	1.516(2)
O1 – C1	1.467(2)	C8 – C13	1.394(2)
O2 – C7	1.414(2)	C8 – C9	1.397(2)
N1 – C3	1.289(2)	C9 – C10	1.388(2)
C1 – C6	1.520(2)	C10 – C11	1.388(2)
C1 – C7	1.564(2)	C11 – C12	1.394(2)
C1 – C2	1.505(2)	C12 – C13	1.389(2)
C2 – C5	1.333(2)		

Table 14. Molecular structure of compound **66a** in the crystal; selected bond angles (in °).

N1 – O1 – C1	109.0(1)	C1 – C7 – C8	112.8(1)

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

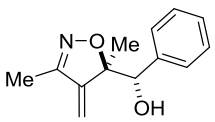
O1 – N1 – C3	109.9(1)	O2 – C7 – C1	108.5(1)
O1 – C1 – C2	103.3(1)	C7 – C8 – C9	121.2(1)
O1 – C1 – C6	108.9(1)	C7 – C8 – C13	120.0(1)
C2 – C1 – C6	114.5(1)	C9 – C8 – C13	118.9(1)
C2 – C1 – C7	109.6(1)	C8 – C9 – C10	120.7(1)
O1 – C1 – C7	107.0(1)	C9 – C10 – C11	120.1(1)
C6 – C1 – C7	112.9(1)	Cl2 – C11 – C12	121.0(1)
C1 – C2 – C5	129.4(1)	C10 – C11 – C12	119.6(1)
C3 – C2 – C5	126.2(1)	Cl2 – C11 – C10	119.4(1)
C1 – C2 – C3	104.5(1)	Cl1 – C12 – C11	120.8(1)
N1 – C3 – C4	121.6(1)	C11 – C12 – C13	120.3(1)
C2 – C3 – C4	125.9(1)	Cl1 – C12 – C13	118.9(1)
N1 – C3 – C2	112.6(1)	C8 – C13 – C12	120.5(1)
O2 – C7 – C8	109.2(1)		

Table 15. Molecular structure of compound **66a** in the crystal; selected torsion angles (in °).

N1 – O1 – C1 – C2	9.1(1)	C5 – C2 – C3 – N1	-174.0(2)
N1 – O1 – C1 – C6	131.2(1)	C5 – C2 – C3 – C4	5.8(2)
N1 – O1 – C1 – C7	-106.5(1)	O2 – C7 – C8 – C9	20.0(2)
C1 – O1 – N1 – C3	-6.0(2)	O2 – C7 – C8 – C13	-159.2(1)
O1 – N1 – C3 – C2	-0.1(2)	C1 – C7 – C8 – C9	-100.8(2)
O1 – N1 – C3 – C4	-179.9(1)	C1 – C7 – C8 – C13	80.1(2)
O1 – C1 – C2 – C3	-8.8(1)	C7 – C8 – C9 – C10	-180.0(2)
O1 – C1 – C2 – C5	171.1(2)	C13 – C8 – C9 – C10	-0.8(2)
C6 – C1 – C2 – C3	-127.0(1)	C7 – C8 – C13 – C12	179.7(1)
C6 – C1 – C2 – C5	52.9(2)	C9 – C8 – C13 – C12	0.6(2)
C7 – C1 – C2 – C3	105.0(1)	C8 – C9 – C10 – C11	0.4(2)
C7 – C1 – C2 – C5	-75.2(2)	C9 – C10 – C11 – Cl2	180.0(1)
O1 – C1 – C7 – O2	176.6(1)	C9 – C10 – C11 – C12	0.2(2)
O1 – C1 – C7 – C8	-62.2(1)	Cl2 – C11 – C12 – Cl1	-0.8(2)
C2 – C1 – C7 – O2	65.3(1)	Cl2 – C11 – C12 – C13	179.8(1)
C2 – C1 – C7 – C8	-173.6(1)	C10 – C11 – C12 – Cl1	178.9(1)

C6 – C1 – C7 – O2	-63.6(1)	C10 – C11 – C12 – C13	-0.5(2)
C6 – C1 – C7 – C8	57.5(2)	Cl1 – C12 – C13 – C8	-179.3(1)
C1 – C2 – C3 – N1	5.9(2)	C11 – C12 – C13 – C8	0.1(2)
C1 – C2 – C3 – C4	-174.4(1)		

7.16.2 Preparation of (S)-((R)-3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)(phenyl)methanol (66b)



66b was prepared according to **TP13a** from zinc reagent **63** (17.3 mmol, 0.4 M in THF, 1.5 equiv.), $LaCl_3 \cdot 2LiCl$ (23 mmol, 0.5 M in THF, 2 equiv.), and benzaldehyde (11.5 mmol, 11.5 mL, 1 M in THF, 0.66 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **66b** as a white solid (2.28 g, 10.53 mmol, 91%, dr= 95:5).

66b could also be prepared according to **TP13b** from zinc reagent **63** (0.4 mmol) to produce the title compound in 67% yield (dr= 95:5).

HRMS (EI) for $C_{13}H_{17}NO_2$: calcd 218.1181($M+H^+$), found 218.1190.

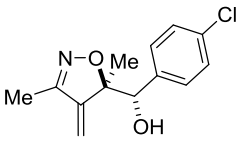
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 1.97 (s, 3 H), 2.60 (s, 1 H), 4.59 (s, 1 H), 4.75 (s, 1 H), 5.28 (s, 1 H), 7.31 - 7.37 (m, 5 H)

^{13}C NMR (100 MHz, acetone-d6): δ = 155.64, 150.13, 137.08, 128.06, 127.81, 127.56, 109.85, 89.35, 78.18, 23.12, 9.71.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3345, 3100, 3063, 3026, 2991, 2982, 2955, 2924, 2853, 1819, 1725, 1641, 1602, 1491, 1453, 1429, 1415, 1398, 1372, 1326, 1234, 1219, 1179, 1092, 1080, 1055, 907, 877, 809, 788, 733.

m.p.: 107 - 110 °C

7.16.3 Preparation of (S)-(4-Chlorophenyl)((R)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)methanol (66c)



66c was prepared according to **TP13a** from zinc reagent **63** (16 mmol, 0.4 M in THF, 1.5 equiv.), $LaCl_3 \cdot 2LiCl$ (21 mmol, 0.5 M in THF, 2 equiv.), and 4-chlorobenzaldehyde (10.7 mol, 1 M in THF, 0.66 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **66c** as a white solid (2.48 g, 9.88 mmol, 92%, dr= 96:4).

66c could also be prepared according to **TP13b** from zinc reagent **63** (0.21 mmol) to produce the title compound in 81% yield (dr= 95:5).

HRMS (EI) for $C_{13}H_{14}ClNO_2$: calcd 251.0713 (M^+), found 252.0778.

MS (EI, 70 eV): m/z (%)= 205 (53), 139 (34), 111 (39), 110 (26), 82 (31), 77 (100), 68 (43), 55 (12), 43 (33).

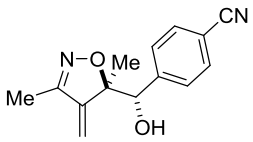
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 3 H), 1.96 (s, 3 H), 2.69 (s, 1 H), 4.59 (s, 1 H), 4.68 (s, 1 H), 5.27 (s, 1 H), 7.28 (s, 4 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 9.72, 22.84, 77.46, 89.05, 109.96, 127.76, 129.12, 133.86, 135.59, 150.07, 155.66.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3353, 3097, 3017, 2989, 2925, 2897, 1804, 1790, 1738, 1643, 1593, 1489, 1436, 1402, 1370, 1314, 1289, 1238, 1186, 1086, 1063 1013, 898, 835, 808, 761.

m.p.:111 - 113 °C

7.16.4 4-((S)-((R)-3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)(hydroxy)methyl)benzonitrile (66d)



66d was prepared according to **TP13a** from zinc reagent **63** (22 mmol, 0.4 M in THF, 1.5 equiv.), $LaCl_3 \cdot 2LiCl$ (30 mmol, 0.5 M in THF, 2 equiv.), and 4-formylbenzonitrile (15 mmol, 1 M in THF, 0.67 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **66d** as a white solid (3.49 g, 14.4 mmol, 96%, dr= 94:6).

66d could also be prepared according to **TP13b** from zinc reagent **63** (0.21 mmol) to produce the title compound in 82% yield (dr= 94:6).

HRMS (EI) for $C_{14}H_{14}N_2O_2$: calcd 243.1133 ($M+H^+$), found 343.1055.

MS (EI, 70 eV): m/z (%) = 243 (2), 220 (6), 205 (22), 140 (8), 133 (6), 132 (72), 110 (82), 104 (68), 82 (35), 77 (45), 70 841), 69 (24), 68 (100), 55 (13), 51 (12), 43 (58).

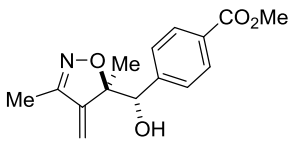
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3 H), 1.95 (s, 3 H), 2.93 (d, *J*=3.59 Hz, 1 H), 4.70 (m, 2 H), 5.30 (s, 1 H), 7.48 (m, 2 H), 7.60 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.69, 22.29, 77.18, 88.68, 110.01, 111.76, 118.71, 128.56, 131.35, 142.87, 150.42, 155.55.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3348, 3095, 2992, 2927, 2900,1707, 1688, 1643, 1609, 1592, 1489, 1447, 1437, 1403, 1373, 1308, 1242, 1201, 1189, 1086, 1067, 1014, 912, 894, 843, 836, 822, 809, 761, 742.

m.p.: 95 - 98 °C

7.16.5 Methyl 4-((S)-((R)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl) (hydroxy)methyl) benzoate (66e)



66e was prepared according to **TP13a** from zinc reagent **63** (22.5 mmol, 0.4 M in THF, 1.5 equiv.), $LaCl_3 \cdot 2LiCl$ (30 mmol, 0.5 M in THF, 2 equiv.), and methyl 4-formylbenzoate (15 mmol, 1 M in THF, 0.66 equiv.). Purification by flash chromatography (*i*-Hexane:EtOAc 8:2) furnishing **66e** as a white solid (3.893 g, 14 mmol, 94%, dr= 95:5).

66e could also be prepared according to **TP13b** from zinc reagent 63 (0.21 mmol) to produce the title compound in 79% yield (dr= 93:7).

HRMS (EI) for $C_{15}H_{17}NO_4$: calcd 276.1235 ($M+H^+$), found 276.1232.

MS (EI, 70 eV): m/z (%): 245 (6), 244 (29), 164 (100), 134 821), 128 (5), 121 (6), 110 (81), 106 (32), 96 (27), 77 (49), 68 (43), 59 (26), 42 (25).

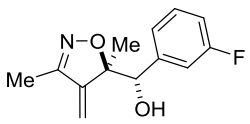
^{1}H NMR (300 MHz, $CDCl_3$): δ =1.40 (s, 3 H), 1.95 (s, 3 H), 2.79 (d, *J*=3.87 Hz, 1 H), 3.91 (s, 3 H), 4.57 (s, 1 H), 4.76 (d, *J*=3.59 Hz, 1 H), 5.27 (s, 1 H), 7.42 (m, 2 H), 7.98 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.70, 22.87, 52.14, 77.75, 89.01, 110.04, 127.82, 128.79, 129.79, 142.18, 150.02, 155.68, 166.90.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3351, 21991, 2945, 2923, 1726, 1640, 1611, 1438, 1406, 1309, 1272, 1259, 1189, 1178, 1102, 1088, 1016, 961, 918, 898, 858, 803, 781, 737.

m.p.: 80 - 82 °C

7.16.6 Preparation of (S)-((R)-3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)(3-fluorophenyl)methanol (66f):



66f was prepared according to **TP13a** from zinc reagent **63** (1.5 mmol, 0.4 M in THF, 1.5 equiv.), $LaCl_3 \cdot 2LiCl$ (2 mmol, 0.5 M in THF, 2 equiv.), and 3-fluorobenzaldehyde (1 mmol, 1 M in THF, 0.66 equiv.). Purification by flash hromatography (*i*-hexane:EtOAc 8:2) furnishing **66f** as a white solid (205 mg, 0.87 mmol, 87%, dr= 95:5).

HRMS (EI) for $C_{13}H_{14}FNO_2$: calcd 236.1086 ($M+H^+$); found 236.1111.

MS (EI, 70 eV): m/z (%) = 236 824), 218 (7), 176 (8), 133 (7), 125 815), 123 830), 112 (36), 110 (30), 97 (47), 95 (38), 82 (72), 77 (28), 70 (15), 68 (100), 55 (18).

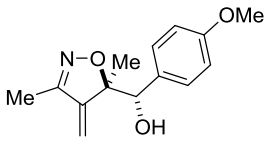
^{1}H NMR (400 MHz, $CDCl_3$): δ =1.37 (s, 3H), 1.93 (s, 3H), 3.07 (d, *J*= 3.70, 1H), 4.63 (d, *J*=0.70, 1H), 4.67 (d *J*= 3.31, 1H), 5.28 (d, *J*= 0.78, 1H), 6.94-9.99 (m, 1H), 7.04-7.07 (m, 1H), 7.09-7.11 (m, 1H), 7.22- 7.28 (m, 1H).

^{13}C NMR (101 MHz, acetone-d6): δ = 8.68, 21.43, 76.51, 88.49, 108.11, 113.78 (d, *J*= 21.41), 114.69 (d, *J*= 22.19), 123.99, 128.68 (d, J= 8.17), 143.27 (d, J= 7.01), 152.43, 154.06, 162.07 (d, J= 242).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3460, 3092, 2987, 2964, 2918, 1645, 1613, 1587, 1485, 1449, 1438, 1412, 1396, 1370, 1287, 1253, 1233, 1159, 1136, 1114, 1078, 1052, 1038, 1015, 970, 917, 906, 898, 884, 873, 863, 794, 760, 741, 726, 708, 692, 676.

m.p.:96 - 97 °C

7.16.7 Preparation of (S)-((R)-3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)(4-methoxyphenyl)methanol (66g)



66g was prepared according to **TP13a** from zinc reagent **63** (17 mmol, 0.4 M in THF, 1.5 equiv.), $LaCl_3$·2LiCl (23 mmol, 0.5 M in THF, 2 equiv.), and *p*-anisaldehyde (11.5 mmol, 1 equiv., 1 M in THF). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **66g** as a white solid (2.44 g, 9.8 mmol, 86%, dr= 95:5).

66g could also be prepared according to **TP13b** from zinc reagent **63** (0.3 mmol) to produce the title compound in 84% yield (dr= 95:5).

HRMS (EI) for $C_{14}H_{18}NO_3$: calcd 248.1286 ($M+H^+$); found 248.1289.

MS (EI, 70 eV): m/z (%): 248 (3), 230 (5), 138 (39), 135 (100), 122 (7), 112 (6), 111 (30), 109 (62), 92 (13), 83 (11), 82 (16), 77 (49), 68 (27), 66 (17), 65 (11), 43 (23).

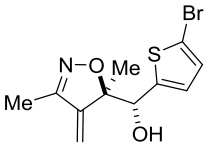
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.96 (s, 3 H), 2.54 (d, *J*=3.59 Hz, 1 H), 3.80 (s, 3 H), 4.58 (s, 1 H), 4.69 (d, *J*=3.32 Hz, 1 H), 5.26 (s, 1 H), 6.83-6.86 (m, 2 H), 7.15 - 7.34 (d, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.70, 23.17, 55.21, 77.86, 89.48, 109.73, 112.97, 128.88, 129.18, 150.14, 155.62, 159.39.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3346, 2971, 2933, 2840, 1683, 1683, 1639, 1609, 1579, 113, 1440, 1401, 1368, 1314, 1302, 1244, 1183, 1171, 1120, 1086, 1063, 1031, 908, 838, 819, 775, 760.

m.p.: 103 °C

7.16.8 Preparation of (R)-(5-Bromothiophen-2-yl)((R)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl) methanol (66h)



66h was prepared according to **TP13a** from zinc reagent **63** (17 mmol, 0.4 M in THF, 1.5 equiv.), $LaCl_3 \cdot 2LiCl$ (22.6 mmol, 0.50 M in THF, 2 equiv.), and 5-bromothiophene-2-carbaldehyde (11.3 mmol, 1 M in THF, 0.66 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **66h** as a white solid (3.14 g, 10.4 mmol, 92%, dr= 93:7).

HRMS (EI) for $C_{11}H_{12}BrNO_2S$: calcd 301.9850 ($M+H^+$), found 301.9858.

MS (EI, 70 eV): m/z (%)= 301 (1), 193 (34), 111 (100), 110 (21), 84 (75), 83 (16), 81 (15), 70 (31), 68 (22), 55 (5), 42 (8).

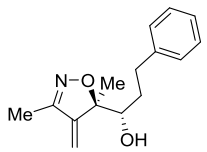
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3 H), 1.99 (s, 3 H), 2.80 (d, *J*=4.70 Hz, 1 H), 4.79 (d, *J*=3.87 Hz, 1 H), 4.89 (s, 1 H), 5.32 (s, 1 H), 6.78 (d, *J*=3.87 Hz, 1 H), 6.91 (d, *J*=3.87 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.72, 22.38, 75.02, 88.56, 109.93, 112.00, 125.93, 129.13, 142.56, 150.45, 155.54.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 32466, 2925, 2849, 1641, 1442, 1400, 1371, 1312, 1252, 1148, 1118, 1070, 1054, 1014, 969, 909, 874, 849, 804, 760, 749.

m.p.: 117 - 118 °C

7.16.9 Preparation of (S)-1-((R)-3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)-3-phenylpropan-1-ol (66i)



66i was prepared according to **TP13b** from zinc reagent **63** (1.35 mmol, 0.45 M in THF, 1 equiv.), $MgCl_2$ (2.7 mmol, 0.4 M in THF, 2 equiv.), 3-phenylpropanal and (1.35 mmol, 1 M in THF, 1 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **66i** as a colorless oil (193 mg, 0.79 mmol, 58%, dr= 39:61).

HRMS (ESI) for $C_{15}H_{20}NO_2$: cacd 246,14940 ($M+H^+$); found 346.14868.

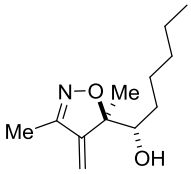
Major isomer **^{1}H NMR** (MHz, $CDCl_3$): δ = 1.39 (s, 3H), 1.59-1.81 (m, 1H), 1.83-1.94 (m, 1H), 2.00 (s, 3H), 2.58-2.67 (m, 1H), 2.56 (s, 1H), 2.88 -2.95 (m, 1H), 3.41-3.47 (m, 1H), 5.02 (s, 1H), 5.27 (s, 1H), 7.16-7.20 (m, 3H), 7.24-7.28 (m, 2H). Minor isomer **^{1}H NMR** (MHz, $CDCl_3$): δ = 1.39 (s, 3H), 1.59-1.81 (m, 1H), 1.83-1.94 (m,1H), 2.00 (s, 3H), 2.44 (s,

1H), 2.58-2.67 (m, 1H), 2.88 -2.95 (1H), 3.47-3.50 (m, 1H), 5.11 (s, 1H), 5.29 (s.1 H), 7.14-7.17 (m, 3H), 7.24-7.28 (m, 2H).

Major isomer **^{13}C NMR** (MHz, $CDCl_3$): δ =9.86, 22.64, 31.83, 32.54, 75.80, 89.53, 108.23, 125.98, 128.49, 128.62, 141.93, 152.05, 155.13. Minor isomer **^{13}C NMR** (MHz, $CDCl_3$): δ = 9.86, 22.37, 32.05, 32.40, 75.45, 89.18, 108.40, 125.98, 128.50, 128.63, 141.93, 152.05, 155.31.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3411, 3092, 3062, 3024, 2989, 2954, 2924, 2860, 1715, 1640, 1602, 1495, 1453, 1396, 1378, 1309, 1263, 1177, 1151, 1062, 1044, 1030, 1012, 895, 820, 743, 728, 698, 675.

7.16.10 (S)-1-((R)-3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)hexan-1-ol (66j)



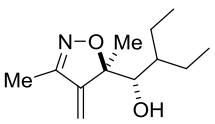
66j was prepared according to **TP13b** from zinc reagent **63** (1.35 mmol, 0.45 M in THF, 1 equiv.), $MgCl_2$ (2.7 mmol, 0.4 M in THF, 2 equiv.), and hexanal (1.35 mmol, 1 M in THF, 1 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **66j** as a colorless oil (117 mg, 0.55 mmol, 41%, dr = 33:67).

HRMS (ESI) for $C_{12}H_{22}NO_2$: calcd 212.16505 ($M+H^+$), found 212.1645.

Major isomer **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 0.82 - 0.90 (m, 3 H), 1.22-1.33 (m, 6 H) 1.40 (s, 3 H), 1.50-1.60 (m, 2 H), 2.02 (s, 3H), 3.38-3.46 (m, 1 H), 5.06 (d, *J*=0.83 Hz, 1 H), 5.30 (d, *J*=0.83 Hz, 1 H). Minor isomer **^{1}H NMR** (300 MHz, $CDCl_3$) 0.82 - 0.90 (m, 3 H), 1.24 (m, 6H), 1.37 (s, 3H), 1.49-1.60 (m, 2H), 2.02 (s, 3 H), 3.36 - 3.47 (m, 1 H), 5.06 (d, *J*=0.83 Hz, 1 H) 5.30 (d, *J*=0.84 Hz, 1 H).

Major isomer **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 9.76, 14.02, 22.50, 22.58, 25.96, 29.73, 31.68, 76.45, 89.49, 107.95, 151.98, 155.08. Minor isomer **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 9.76, 14.02, 21.99, 22.59, 25.75, 29.96, 31.70, 76.08, 89.17, 107.98, 152.14, 155.21.

7.16.11 Preparation of ((S)-1-((R)-3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)-2-ethylbutan-1-ol (66k)



66k was prepared according to **TP13b** from zinc reagent **63** (1.35 mmol, 0.45 M in THF, 1 equiv.), $MgCl_2$ (2.7 mmol, 0.4 M in THF, 2 equiv.), and 2-ethylbutanal (1.35 mmol, 1 M in THF, 1 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **66k** as a colorless oil (93 mg, 0.44 mmol 33%, dr= 7:93).

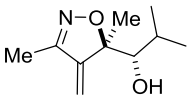
HRMS (ESI) for $C_{12}H_{22}NO_2$: calcd 212,1650 ($M+H^+$), found 212.16451.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.84 (t, *J*=7.33 Hz, 6 H), 1.03-1.10 (m, 1 H), 1.20-1.14, (m, 1 H), 1.28 - 1.37, (m, 2 H) ,1.46 (s, 3 H), 1.56 - 1.68 (m, 1 H), 2.00 (s, 4 H), 3.33 (s, 1H), 5.98 (s, 1 H), 5.25 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 9.81, 11.52, 12.23, 20.72, 23.73, 24.35, 42.37, 77.05, 90.29, 107.52, 153.25, 154.85.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3426, 2959, 2930, 2873, 1640, 1462, 1395, 1379, 1138, 1098, 1048, 1013, 981, 895, 856, 783, 734, 705, 674.

7.16.12 Preparation of ((S)-1-((R)-3,5-Dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)-2-methylpropan-1-ol (66l):



66l was prepared according to **TP13b** from zinc reagent **63** (1.35 mmol, 0.45 M in THF, 1 equiv.), $MgCl_2$ (2.7 mmol, 0.4 M in THF, 2 equiv.), and isobutyraldehyde (1.35 mmol, 1 M in THF, 1 equiv.). Purification by flash chromatography (*i*-hexane:EtOAc 8:2) furnishing **66l** as a colorless oil (94 mg, 0.51 mmol, 38%, dr=21:79).

HRMS (ESI) for $C_{10}H_{18}NO_2$: cacd 184.13375 ($M+H^+$), found 184.13317.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.91 (d, *J*=6.63 Hz, 3 H), 0.98 (d, *J*=6.91 Hz, 3 H), 1.46 (s, 3 H), 1.75 - 1.88 (m, 1 H), 1.90 (s, 1 H), 2.01 (s, 3 H), 3.15 (dd, *J*=8.43, 3.73 Hz, 1 H), 5.05 (s, 1 H), 5.30 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 9.86, 16.90, 22.24, 23.80, 29.24, 80.26, 89.89, 107.69, 153.16, 154.79.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3411, 2958, 2928, 2871, 1640, 1470, 1450, 1440, 1415, 1393, 1367, 1349, 1260, 1168, 1138, 1129, 1098, 1037, 1013, 982, 895, 735, 706, 674.

7.16.13 Hammett-Plot for Isoxazolines Established for $LaCl_3$•2LiCl Accelerated Addition of Zinc Reagent 1 with Substituted Benzaldehydes 4.

Table 16							
isoxazolines	*m-*	*p-*	σ_m	σ_p	$\Sigma\,\sigma$	*dr*	
66a	Cl	Cl	0,37	0,23	0,6	96	24,00
66b		H	0	0	0	95	19,00
66c		Cl		0,23	0,23	94	15,67
66d		CN		0,66	0,66	94	15,67
66e		COOMe		0,45	0,45	95	19,00
66f	F		0,34		0,34	95	19,00
66g		OMe		-0,27	-0,27	95	19,00

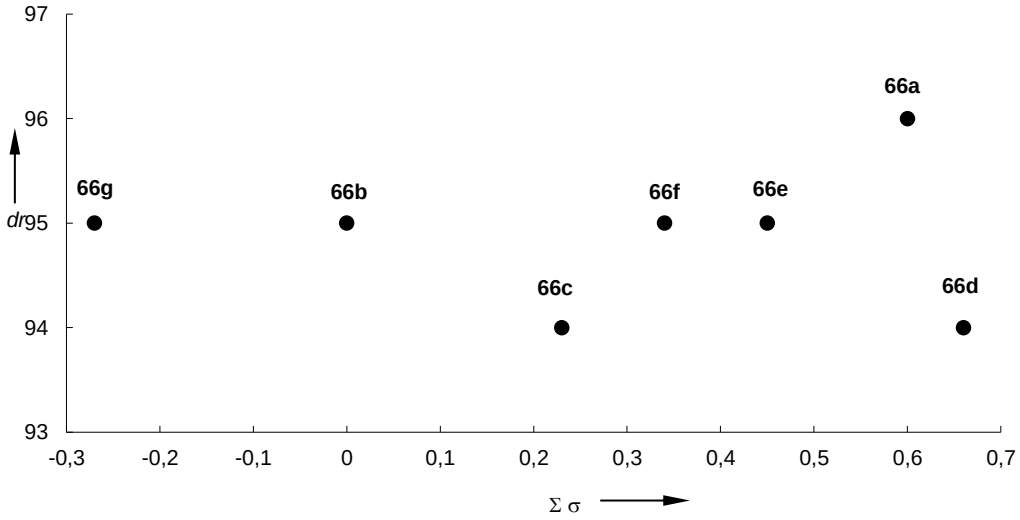
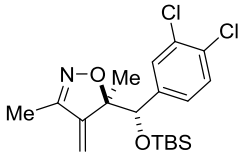


Figure 13: Hammett-plot for isoxazolines established for $LaCl_3$•2LiCl accelerated addition of zinc reagent 1 with substituted benzaldehydes **65**.

7.17 TBS Protection of Isoxazolines 68a-g

7.17.1 Preparation of (R)-5-((S)-((Tert-butyldimethylsilyl)oxy)(3,4-dichlorophenyl)methyl)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazole (68a)



68a was prepared according to **TP14** from **66a** (286 mg, 1 mmol) 0.1 M in CH_2Cl_2, 2,6-lutidine (0.29 mL, 2.5 equiv.) and TBSOTf (0.50 mL, 2.2 mmol, 2.2 equiv.). Flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:10) furnishing compound **68a** (397 mg, 0.99 mmol, 99%) as a colorless solid.

HRMS (EI) for $C_{19}H_{27}Cl_2NO_2Si$: calcd 289.0320 (M-TBS), found 289.0395.

MS (EI, 70 eV): m/z (%) = 347 (5), 327 (12), 291 (55), 289 (100), 197 (10), 75 813), 73 (27), 69 (5), 57 (8), 43 85).

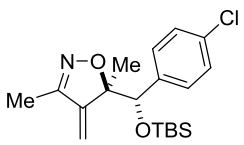
^{1}H NMR (400 MHz, acetone-d6): δ = ppm -0.20 (s, 3 H), 0.07 (s, 3 H), 0.88 (s, 9 H), 1.34 (s, 3 H), 1.85 (s, 3 H), 4.69 (s, 1 H), 5.08 (s, 1 H), 5.41 (s, 1 H), 7.31 - 7.40 (m, 1 H), 7.49 (d, *J*=8.41 Hz, 1 H), 7.57 (d, *J*=1.76 Hz, 1 H).

^{13}C NMR (101 MHz, acetone-d6): δ = ppm -5.77, -5.54, 8.69, 17.76, 21.66, 25.26, 77.61, 88.45, 108.58, 128.32, 129.27, 130.33, 130.61, 130.77, 140.80, 151.62, 154.05.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2952, 2926, 2887, 2833, 1470, 1437, 1416, 1394, 1366, 1366, 1360, 1347, 1260, 1252, 1201, 1154, 1130, 1116, 1089, 1071, 1032, 1012, 1004, 948, 938, 876, 849, 834, 778, 741, 734, 721, 706, 675.

m.p.:75.8 - 76.2 °C

7.17.2 Preparation of (R)-5-((S)-((*tert*-Butyldimethylsilyl)oxy)(4-chlorophenyl)methyl)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazole (68b)



68b was prepared according to **TP14** from **66c** (332 mg, 1.3 mmol) 0.1 M in CH_2Cl_2, 2,6-lutidine (0.37 mL, 3.2 mmol, 2.5 equiv.) and TBSOTf (0.66 mL, 2.9 mmol, 2.2 equiv.). Flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:10) furnishing compound **68b** (424 mg, 1.2 mmol, 89%) as a colorless oil

HRMS (EI) for $C_{19}H_{28}ClNO_2Si$: calcd 366.1656 ($M+H^+$), found 366.1439.

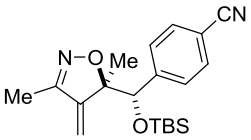
MS (EI, 70eV), m/z(%): 310 (15), 308 (41), 257 (100), 256 (46), 255 (32).

^{1}H NMR (300 MHz, $CDCl_3$): δ = -0.25 (s, 3 H), 0.01 (s, 3 H), 0.86 (s, 9 H), 1.29 (s, 3 H), 1.93 (s, 3 H), 4.48 (s, 1 H), 4.88 (s, 1 H), 5.26 (s, 1 H), 7.26 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.06, -4.81, 9.68, 18.11, 21.74, 25.78, 78.02, 88.72, 108.81, 127.49, 129.48, 133.44, 137.97, 151.49, 154.54.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 658, 667, 672, 688, 697, 707, 731, 757, 776, 817, 834, 856, 884, 897, 938, 1006, 1014, 1035, 1087, 1108, 1145, 1148, 1159, 1192, 1251, 1361, 1371, 1406, 1452, 1462, 1471, 1490, 1596, 1642, 2856, 2883, 2893, 2929, 2955.

7.17.3 Preparation of 4-((S)-((*tert*-Butyldimethylsilyl)oxy)((R)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)methyl)benzonitrile (68c)



68c was prepared according to **TP14** from **66d** (299 mg, 1.23 mmol) 0.1 M in CH_2Cl_2, 2,6-lutidine (0.36 mL, 3.1 mmol, 2.5 equiv.) and TBSOTf (0.62 mL, 2.7 mmol, 2.2 equiv.). Flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:10) furnishing compound **68c** (427 mg, 1.20 mmol, 97%) as colorless oil.

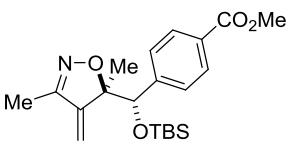
HRMS (ESI) for $C_{20}H_{28}N_2O_2Si$: calcd 356.1920 ($M+H^+$), found 357.1993.

^{1}H NMR (300 MHz, $CDCl_3$): δ = -0.30 (s, 3 H), -0.02 (s, 3 H), 0.83 (s, 9 H), 1.27 (s, 3 H), 1.88 (s, 3 H), 4.47 (s, 1 H), 4.94 (s, 1 H), 5.27 (s, 1 H), 7.42 - 7.49 (m, 2 H), 7.49 - 7.58 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.06, -4.83, 9.62, 18.05, 21.39, 25.74, 77.98, 88.40, 109.19, 111.50, 118.75, 128.90, 131.10, 145.02, 151.48, 154.57.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 662, 673, 728, 778, 835, 855, 890, 908, 938, 1006, 1013, 1019, 1078, 1093, 1115, 1122, 1158, 1200, 1253, 1259, 1361, 1372, 1396, 1410, 1437, 1452, 1463, 1472, 1502, 1609, 2230, 2856, 2883, 2928, 2955.

7.17.4 Preparation of methyl 4-((S)-((*tert*-butyldimethylsilyl)oxy)((R)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazol-5-yl)methyl)benzoate (68d)



68d was prepared according to **TP14** from **66e** (302 mg, 1.1 mmol) 0.1 M in CH_2Cl_2, 2,6-lutidine (0.31 mL, 2.6 mmol, 2.5 equiv.) and TBSOTf (0.50 mL, 2.2 mmol, 2.0 equiv.). Flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:10) furnishes compound **66d** (310 mg, 0.80 mmol, 72%) as a colorless oil.

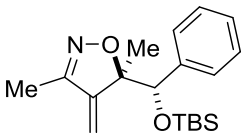
HRMS (ESI) for $C_{21}H_{31}NO_4Si$: calcd 390.2100 ($M+H^+$), found 390.2097.

^{1}H NMR (300 MHz, $CDCl_3$): δ = -0.28 (s, 3 H), -0.01 (s, 3 H), 0.83 (s, 9 H), 1.28 (s, 3 H), 1.90 (s, 3 H), 3.87 (s, 3 H), 4.54 (s, 1 H), 4.87 (s, 1 H), 5.26 (s, 1 H), 7.40 (d, *J*=8.57 Hz, 2 H), 7.94 (d, *J*=8.57 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.08, -4.88, 9.64, 18.09, 21.76, 25.75, 51.98, 78.35, 88.66, 108.92, 128.20, 128.58, 129.49, 144.64, 151.41, 154.53, 166.96.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 657, 670, 684, 701, 707, 730, 776, 814, 834, 854, 859, 890, 939, 966, 1006, 1013, 1019, 1035, 1089, 1110, 1159, 1176, 1191, 1252, 1257, 1275, 1309, 1347, 1361, 1371, 1397, 1414, 1435, 1462, 1472, 1611, 1642, 1721, 2856, 2893, 2929, 2952.

7.17.5 (R)-5-((S)-((*tert*-Butyldimethylsilyl)oxy)(phenyl)methyl)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazole (68e)



68e was prepared according to **TP14** from **66b** (207 mg, 0.95 mmol) 0.1 M in CH_2Cl_2, 2,6-lutidine (0.21 mL, 1.8 mmol, 2.5 equiv.) and TBSOTf (0.47 mL, 2.1 mmol, 2.2 equiv.). Flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:10) furnishes compound **68e** (309 mg, 0.93 mmol, 98%) as a colorless oil.

HRMS (EI) for $C_{19}H_{29}NO_2Si$: calcd 316.1732 (M-Me), found 316.1725.

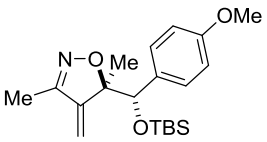
MS (EI, 70eV), m/z(%): 316 (6), 295 815), 274 (95), 222 (100), 200 (32).

^{1}H NMR (300 MHz, $CDCl_3$): δ = -0.25 (s, 3 H), 0.01 (s, 3 H), 0.86 (s, 9 H), 1.30 (s, 3 H), 1.94 (s, 3 H), 4.55 (s, 1 H), 4.84 (s, 1 H), 5.26 (s, 1 H), 7.18 - 7.40 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.07, -4.86, 9.70, 18.13, 22.03, 25.80, 78.68, 88.99, 108.69, 127.22, 127.63, 128.19, 139.27, 151.44, 154.51.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 668, 683, 699, 712, 727, 775, 817, 833, 856, 881, 899, 939, 949, 1006, 1011, 1029, 1065, 1082, 1095, 1145, 1159, 1175, 1193, 1218, 1250, 1351, 1361, 1370, 1390, 1397, 1411, 1452, 1462, 1472, 1493, 1512, 1641, 2856, 2883, 2891, 2928, 2955.

7.17.6 Preparation of (R)-5-((S)-((tert-butyldimethylsilyl)oxy)(4-methoxyphenyl)methyl)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazole (68f)



68f was prepared according to **TP14** from **66g** (1.13 g, 4.6 mmol) 0.1 M in CH_2Cl_2, 2,6-lutidine (1.36 mL, 11.7 mmol, 2.5 equiv.) and TBSOTf (2.32 mL, 10.2 mmol, 2.2 equiv.). Flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:10) furnishes compound **68f** (1.45 g, 4.02 mmol, 87%) as a colorless oil.

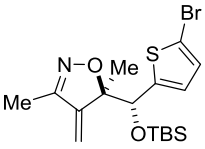
HRMS (ESI) for $C_{20}H_{31}NO_3Si$: calcd 362.2151 ($M+H^+$); found 362.12148.

^{1}H NMR (300 MHz, $CDCl_3$): δ = -0.25 (s, 3 H), 0.00 (s, 3 H), 0.85 (s, 9 H), 1.28 (s, 3 H), 1.93 (s, 3 H), 3.79 (s, 3 H), 4.49 (s, 1 H), 4.83 (s, 1 H), 5.24 (s, 1 H), 6.80 (d, *J*=8.57 Hz, 2 H), 7.23 (d, *J*=8.85 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.09, -4.83, 9.70, 18.13, 22.05, 25.81, 55.10, 78.31, 89.16, 108.52, 112.61, 129.22, 131.46, 151.50, 154.48, 159.06.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 664, 672, 681, 690, 696, 707, 716, 732, 749, 776, 791, 834, 858, 883, 899, 938, 949, 1006, 1011, 1035, 1077, 1087, 1112, 1172, 1197, 1246, 1280, 1302, 1314, 1360, 1370, 1397, 1410, 1441, 1463, 1471, 1511, 1584, 1611, 1641, 2856, 2883, 2893, 2928, 2955.

7.17.7 Preparation of (R)-5-((R)-(5-Bromothiophen-2-yl)((tert-butyldimethylsilyl)oxy)methyl)-3,5-dimethyl-4-methylene-4,5-dihydroisoxazole (68g)



68g was prepared according to **TP14** from **66h** (409 mg, 1.35 mmol) 0.1 м in CH_2Cl_2, 2,6-lutidine (0.39 mL, 3.3 mmol, 2.5 equiv.) and TBSOTf (0.68 mL, 3 mmol, 2.2 equiv.). Flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:10) furnishes compound **68g** (555 mg, 1.33 mmol, 99%) as a colorless oil.

HRMS (ESI) for $C_{17}H_{26}BrNO_2SSi$: calcd 416.0715 ($M+H^+$); found 416.0712.

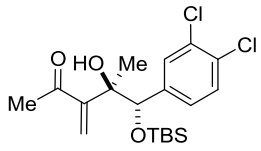
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 3 H), 0.02 (s, 3 H), 0.89 (s, 9 H), 1.36 (s, 3 H), 1.98 (s, 3 H), 4.65 (s, 1 H), 4.98 (s, 1 H), 5.31 (s, 1 H), 6.72 (d, *J*=3.87 Hz, 1 H), 6.88 (d, *J*=3.59 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.01, -4.97, 9.74, 18.09, 21.60, 25.76, 75.47, 88.44, 109.34, 111.56, 125.72, 128.85, 144.96, 151.05, 154.71.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 665, 673, 701, 712, 735, 753, 777, 815, 835, 893, 939, 969, 1006, 1011, 1041, 1054, 1077, 1083, 1116, 1159, 1208, 1251, 1275, 1345, 1361, 1371, 1390, 1397, 1415, 1437, 1462, 1471, 1642, 2856, 2883, 2927, 2955.

7.18 Reduction of TBS-Protected Isoxazoline to the Corresponding β-Hydroxy carbonyl Derivatives 69a-g .

7.18.1 Preparation of (4R,5S)-5-((*tert*-Butyldimethylsilyl)oxy)-5-(3,4-dichlorophenyl)-4-hydroxy-4-methyl-3-methylenepentan-2-one (69a)



69a was prepared according to **TP15a** from a suspension of **68a** (150 mg, 0.37 mmol) and NH_4Cl (153 mg, 3 mmol, 10 equiv.) in EtOH:H_2O (1:1, 30 mL) and Fe powder (165 mg, 3 mmol, 10 equiv.). The reaction mixture was heated at 80 °C for 3 days. The crude product was worked up according to **TP15a** and purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 0.01-9.99) furnishing compound **69a** (90 mg, 0.22 mmol, 60%) as a colorless solid.

69a could also be prepared according to **TP15b** from **68a** (1 mmol), to produce the compound in 18% yield.

HRMS (ESI) for $C_{19}H_{28}Cl_2O_3Si$: calcd 401.1106 (M-H); found 401.1113.

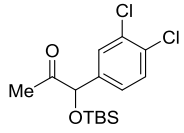
^{1}H NMR (400 MHz, $CDCl_3$): δ = -0.24 (s, 3 H), 0.03 (s, 3 H), 0.71 - 0.93 (s, 9 H), 1.38 (s, 3 H), 2.27 (s, 3 H), 3.82 (s, 1 H), 5.01 (s, 1 H), 5.97 (s, 1 H), 5.98 (s, 1 H), 6.96 - 7.09 (m, 1 H), 7.23 - 7.32 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = -5.10, -4.61, 18.03, 24.75, 25.75, 27.46, 77.07, 77.08, 127.11, 128.42, 129.28, 129.63, 131.13, 131.43, 141.41, 149.91, 201.41.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 670, 699, 712, 731, 776, 793, 817, 835, 864, 909, 939, 956, 972, 1005, 1029, 1055, 1072, 1085, 1129, 1136, 1153, 1203, 1219, 1251, 1258, 1293, 1360, 1389, 1453, 1463, 1471, 1494, 1614, 1671, 1713, 2856, 2893, 2928, 2953.

7.18.2 1-((tert-Butyldimethylsilyl)oxy)-1-(3,4-dichlorophenyl)propan-2-one (70)

70 was formed as the byproduct in the reaction **68a** (400 mg, 1 mmol) and $Mo(CO)_6$ (258 mg, 2 mmol) in MeCN:H_2O (17 mL, 10:1) at 80 °C. The crude product was worked up according **TP15b** and purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:9) furnishing compound **70** (129 mg, 0.39 mmol, 39%) as a colorless solid.



HRMS (ESI) for $C_{15}H_{22}Cl_2O_2Si$: calcd 331.0693 (M-H), found 331.0695.

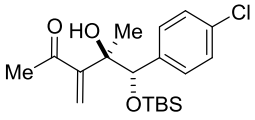
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.09 (s, 3 H), 0.95 (s, 9 H), 2.11 (s, 3 H), 4.96 (s, 1 H), 7.25-7.27 (m, 1H), 7.40-7.43 (m, 1 H), 7.53 - 7.53 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = -5.19, -4.97, 18.16, 23.96, 25.67, 80.02, 125.07, 127.72, 130.49, 132.17, 132.76, 138.86, 208.21.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3354, 2989, 2923, 2895, 2853, 1489, 1448, 1400, 1369, 1086, 1062, 1013, 897, 834, 808, 760, 695, 674.

m.p.: 111 - 113 °C

7.18.3 Preparation of (4R,5S)-5-((*tert*-Butyldimethylsilyl)oxy)-5-(4-chlorophenyl)-4-hydroxy-4-methyl-3-methylenepentan-2-one (69b)



69b was prepared according to **TP15a** from a suspension of **68b** (36 mg, 0.1 mmol) and NH_4Cl (53 mg, 1 mmol, 10 equiv.) in EtOH:H_2O (1:1, 10 mL) and Fe powder (55 mg, 1 mmol, 10 equiv.). The reaction mixture was heated at 80 °C for 1 day. The crude product was worked up according to **TP15a** and purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:10) furnishing compound **69b** (28 mg, 0.07 mmol, 76%) as a colorless solid.

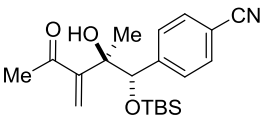
69b could also be prepared according to **TP15b** from **68b** (0.1 mmol), to produce the title compound in 32% yield.

HRMS (ESI) for $C_{19}H_{29}ClO_3Si$: calcd 367.1501 (M-H); found 367.1504.

^{1}H NMR (599 MHz, $CDCl_3$): δ = -0.26 (s, 3 H), 0.03 (s, 3 H), 0.87 (s, 9 H), 1.40 (s, 3 H), 2.25 (s, 3 H), 3.91 (s, 1 H), 5.03 (s, 1 H), 5.93 (s, 1H), 5.95 (s, 1 H), 7.07 - 7.22 (m, 4 H).**^{13}C NMR** (151 MHz, $CDCl_3$): δ = -5.11, -4.64, 18.06, 25.02, 25.78, 27.50, 77.23, 77.69, 127.49, 127.99, 129.10, 133.00, 139.51, 150.13, 201.33.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 672, 700, 742, 776, 834, 866, 913, 939, 956, 967, 1006, 1015, 1060, 1252, 1296, 1361, 1401, 1407, 1463, 1472, 1491, 1598, 1673, 2858, 2886, 2911, 2954, 3547.00 .

7.18.4 Preparation 4-((1S,2R)-1-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-2-methyl-3-methylene-4-oxopentyl)benzonitrile (69c):



69c was prepared according to **TP15a** from a suspension of **68c** (36 mg, 0.1 mmol) and NH_4Cl (53 mg, 1 mmol, 10 equiv.) in EtOH:H_2O (1:1, 10 mL) and Fe powder (55 mg, 1 mmol, 10 equiv.). The reaction mixture was refluxed for 2 days. The crude product was worked up according to **TP15a** and purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 0.5:10) furnishing compound **69c** (27 mg, 0.07 mmol, 75%) as a colorless solid.

HRMS (ESI) for $C_{20}H_{29}NO_3Si$: calcd 358,1843 (M-H), found 358.1843.

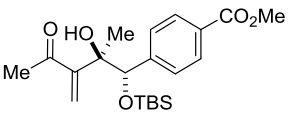
^{1}H NMR (300 MHz, acetone-d6): δ = -0.21 (s, 3 H), 0.08 (s, 3 H), 0.90 (s, 9 H), 1.44 (s, 3 H), 2.30 (s, 3 H), 4.34 (s, 1 H), 5.26 (s, 1 H), 5.91 (s, 1 H), 6.04 (s, 1 H), 7.44 (d, *J*=8.57 Hz, 2 H), 7.63 (d, *J*=8.02 Hz, 2 H).

^{13}C NMR (75 MHz, acetone-d6): δ = -4.75, -4.36, 18.82, 25.59, 26.25, 28.08, 77.63, 78.71, 111.70, 119.54, 128.60, 129.94, 131.81, 148.10, 151.82, 201.94.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 670, 682, 702, 744, 777, 795, 822, 834, 858, 874, 912, 938, 963, 978, 1003, 1022, 1068, 1085, 1126, 1182, 1204, 1252, 1258, 1273, 1301, 1361, 1392, 1408, 1420, 1451, 1463, 1471, 1508, 1611, 1664, 2228, 2858, 2930, 2952, 3536.

MP: 82.5 - 83 °C

7.18.5 methyl 4-((1S,2R)-1-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methyl-3-methylene-4-oxopentyl)benzoate (69d)



69d was prepared according to **TP15a** from a suspension of **68d** (39 mg, 0.1 mmol), NH_4Cl (53 mg, 1 mmol, 10 equiv.) and Fe powder (55 mg, 0.1 mmol, 10 equiv.) in EtOH:H_2O (1:1, 10 mL). The reaction mixture was heated at 80 °C for 3 day. The crude product was worked up according to **TP15a** and purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 0.01:9.99) furnishing the compound **69d** (28 mg, 0.07 mmol, 71%) as a colorless solid.

69d could also be prepared according to **TP15b** from **68d** (0.1 mmol), to produce the title compound in 27% yield.

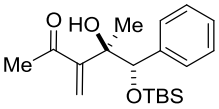
HRMS (ESI) for $C_{21}H_{32}O_5Si$: calcd 392.5613 (M^+); found 392.1977.

^{1}H NMR (400 MHz, $CDCl_3$): δ = -0.27 (s, 3 H), 0.04 (s, 3 H), 0.86 (s, 9 H), 1.41 (s, 3 H), 2.24 (s, 3 H), 3.88 (s, 3 H), 3.93 (s, 1 H), 5.11 (s, 1 H), 5.90 (s. 1H), 5.92 (s, 1H), 7.27 (d, *J*=8.85 Hz, 2 H) 7.89 (d, *J*=8.29 Hz, 2 H)

^{13}C NMR (400 MHz, $CDCl_3$): δ = -5.11, -4.69, 18.07, 25.06, 25.76, 27.47, 51.98, 77.20, 78.03, 127.79, 128.01, 128.62, 129.13, 146.27, 150.03, 167.06, 201.29.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 657, 671, 687, 699, 712, 726, 775, 793, 816, 836, 862, 913, 939, 956, 969, 1005, 1019, 1063, 1108, 1136, 1156, 1177, 1191, 1218, 1252, 1259, 1274, 1360, 1390, 1397, 1419, 1435, 1463, 1472, 1611, 1672, 1721, 2856, 2883, 2929, 2952, 3541.

7.18.6 Preparation of (4R,5S)-5-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-4-methyl -3-methylene-5-phenylpentan-2-one (69e)



69e was prepared according to **TP15a** from a suspension of **68e** (165 mg, 0.50 mmol), NH_4Cl (265 mg, 5 mmol, 10 equiv.) and Fe powder (275 mg, 5 mmol, 10 equiv.) in EtOH:H2O (1:1, 50 mL). The reaction mixture was heated at 80 °C for 2 days. The crude product was worked up according to TP5a and purified by flash column chromatography (SiO2, EtOA/*i*-hexane 0.10:9.90) furnishing compound **69e** (114 mg, 0.34 mmol, 68%) as a colorless solid.

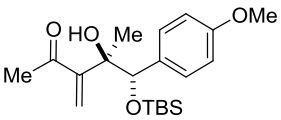
HRMS (ESI) for $C_{19}H_{30}O_3Si$: calcd 333,1891 (M-H), found 333.1891.

^{1}H NMR (400 MHz, CDCl3): δ = -0.27 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 1.41 (s, 3 H), 2.24 (s, 3 H), 4.04 (s, 1 H), 5.03 (s, 1 H), 5.89 (s, 1 H), 5.91 (s, 1 H), 7.19 (s, 5 H).

^{13}C NMR (101 MHz, CDCl3): δ = -5.13, -4.70, 18.10, 25.15, 25.80, 27.53, 77.46, 78.56, 127.26, 127.28, 127.51, 127.80, 140.85, 150.34, 201.42.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 657, 671, 684, 687, 699, 726, 775, 793, 816, 836, 862, 913, 939, 957, 969, 1005, 1019, 1062, 1109, 1136, 1156, 1177, 1192, 1252, 1259, 1275, 1361, 1390, 1419, 1435, 1463, 1471, 1611, 1672, 1721, 2856, 2885., 2929, 2952, 3541.

7.18.7 (4R,5S)-5-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-5-(4-methoxyphenyl)-4-methyl-3-methylenepentan-2-one (69f)



69f was prepared according to **TP15a** from a suspension of **68f** (333 mg, 0.92 mmol) and NH_4Cl (530 mg, 10 mmol, 10 equiv.) in

EtOH:H_2O (1:1, 100 mL) and Fe powder (550 mg, 10 mmol, 10 equiv.). The reaction mixture was heated at 80 °C for 1 day. The crude product was worked up according to **TP15a** and purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 0.5:10) furnishing compound **69f** (198 mg, 0.54 mmol, 59%) as a colorless oil.

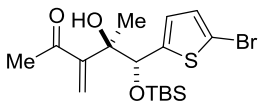
HRMS (ESI) for $C_{20}H_{32}O_4Si$: calcd 364.2070 (M^+); found 364.2031.

^{1}H NMR (300 MHz, $CDCl_3$): δ = -0.27 (s, 3 H), 0.02 (s, 3 H), 0.86 (s, 9 H), 1.40 (s, 3 H), 2.22 (s, 3 H), 3.76 (s, 3 H), 3.99 (s, 1 H), 4.98 (s, 1 H), 5.88 (s, 1 H), 5.92 (s, 1 H), 6.71- 7.74 (m, 2 H), 7.08- 7.11 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = ppm -5.13, -4.65, 18.09, 25.26, 25.81, 27.51, 55.02, 77.55, 78.12, 112.62, 127.30, 128.87, 133.11, 150.51, 158.74, 201.34.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 671, 746, 777, 834, 867, 956, 1006, 1037, 1056, 1174, 1245, 1295, 1360, 1391, 1463, 1471, 1512, 1586, 1612, 1674, 2857, 2887, 2931, 2954, 3000, 3546.

7.18.8 (4R,5R)-5-(5-Bromothiophen-2-yl)-5-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-methyl-3-methylenepentan-2-one (69g)



69g was prepared according to **TP15a** from a suspension of **68g** (42 mg, 0.1 mmol) and NH_4Cl (53 mg, 1 mmol, 10 equiv.) in EtOH:H_2O (1:1, 10 mL) was added Fe powder (55 mg, 1 mmol, 10 equiv.). The reaction mixture was heated at 80 °C for 2 days. The crude product was worked up according to **TP** and purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 0.5:10) furnishing the compound **69g** (29 mg, 0.07 mmol, 69%) as a colorless solid.

69g could also be prepared according to **TP15a** from **68g** (0.1 mmol), to produce the title compound in 28% yield.

HRMS (ESI) for $C_{17}H_{27}BrO_3SSi$: calcd 419.4490 ($M+H^+$); found 419.0728.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.14 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.44 (s, 3 H), 2.23 (s, 3 H), 3.58 (s, 1 H), 5.35 (s, 1 H), 6.00 (s, 1 H), 6.17 (s, 1 H), 6.46 (d, *J*=3.87 Hz, 1 H), 6.76 (d, *J*=3.87 Hz, 1 H).

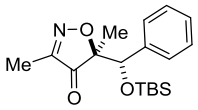
^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.14, -4.90, 18.07, 25.28, 25.74, 27.43, 75.16, 76.93, 112.03, 125.86, 127.85, 128.09, 145.88, 149.70, 200.62.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 665, 742, 780, 807, 833, 862, 906, 967, 1004, 1065, 1141, 1176, 1212, 1251, 1298, 1361, 1399, 1438, 1470, 1615, 1622, 1662, 2853, 2926, 2953, 3476.

MP 69 - 70 °C

7.19 Ozonolysis of TBS-Protected Isoxazoline to the Ketons 71a-71b

7.19.1 (S)-5-((S)-((tert-butyldimethylsilyl)oxy)(phenyl)methyl)-3,5-dimethylisoxazol-4(5H)-one (71a)



71a was prepared from a solution of **68e** (260 mg, 0.78 mmol) in CH_2Cl_2 (15 mL) at 0 °C. A O_3/O_2 mixture was passed through the solution for 1 h. Completion of the reaction was checked using TLC. Upon completion, Me_2S (0.1 mL) was added and the reaction mixtrure was stirred for further 12 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:10) furnishing the compound **71a** (117 mg, 0.35 mmol, 45 %) as a colorless liquid.

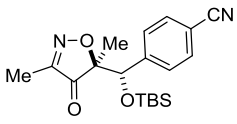
^{1}H NMR (200 MHz, $CDCl_3$) δ = -0.22 (s, 3 H), 0.05 (s, 3 H), 0.84 (s, 9 H), 1.33 (s, 3 H), 1.88 (s, 3 H), 4.78 (s, 1 H), 7.26 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = -5.33, -4.90, 7.78, 18.07, 18.63, 25.59, 78.63, 86.87, 127.65, 127.72, 128.35, 137.95, 153.68, 204.71.

HRMS (EI) for $C_{15}H_{17}N_2O_3Si$: calcd 301.10134, found 301.997 (M-*t*-Bu)

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2955, 2928, 2885, 2857, 1738, 1585, 1471, 1454, 1388, 1361, 1258, 1095, 1070, 1029, 1005, 983, 939, 909, 853, 847, 775, 745, 698, 672.

7.19.2 Preparation of 4-((S)-((tert-butyldimethylsilyl)oxy)((S)-3,5-dimethyl-4-oxo-4,5-dihydroisoxazol-5-yl)methyl)benzonitrile (71b)



71b was prepared from a solution of **68c** (100 mg, 0.28 mmol) in CH_2Cl_2 (15 mL) at 0 °C. A O_3/O_2 mixture was passed through the solution for 1 h. Completion of the reaction was checked using TLC. Upon completion, Me_2S (0.1 mL) was added and the reaction mixtrure was stirred for further 12 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 1:10) furnishing the compound **71b** (33 mg, 0.09 mmol, 33 %) as a colorless liquide.

HRMS (EI) for $C_{14}H_{18}O_3N_1Si$: calcd. 276.1061, found 276.1063.

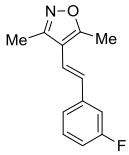
^{1}H NMR (300 MHz, $CDCl_3$) δ = -0.22 (s, 3 H), 0.07 (s, 3 H), 0.84 (s, 9 H), 1.32 (s, 3 H), 1.91 (s, 3 H), 4.81 (s, 1 H), 7.39 (m, *J*=8.02 Hz, 2 H), 7.60 (m, *J*=8.29 Hz, 2 H).

^{13}C NMR (75 MHz $CDCl_3$) δ = -5.27, -4.92, 7.85, 18.02, 18.57, 25.53, 77.71, 86.13, 112.38, 118.51, 128.39, 131.68, 143.28, 153.80, 204.28.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2958, 2929, 2888, 2871, 2227, 1734, 1608, 1582, 1502, 1469, 1437, 1411, 1385, 1361, 1260, 1252, 1197, 1119, 1096, 1016, 1005, 982, 905, 852, 837, 831, 790, 779, 767, 732, 702, 676.

7.20 Acid Mediated Rearrangement of TBS-Protected Isoxazoline 72a-72b

7.20.1 Preparation of (E)-4-(3-fluorostyryl)-3,5-dimethylisoxazole 72a



To **66f** (1 M in THF, 1 mL, 1 mmol) was added BF_3 OEt_2 (5 mL) at 25 °C. The reaction was wormed to 80 °C for 30 min. Completion of the reaction was checked using TLC. Upon completion, the resulting mixture was cooled back to 25 °C and slowly quenched with aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with aqueous NaCl, dried over $MgSO_4$ filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 0/10 to 1/10) furnishing the compound **72a** as a colorless solid (135 mg, 0.62 mmol, 62% yield)

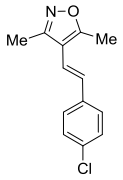
HRMS (EI) for $C_{13}H_{12}FNO$**:** calcd 217,09029, found 217.0885.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.41 (s, 3 H), 2.50 (s, 3 H), 6.72 - 6.75 (m, 2 H), 6.92 - 6.99 (m, 1 H), 7.12 - 7.23 (m, 2 H), 7.27 - 7.36 (m, 1 H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 11.59, 11.89, 112.39 (d, 21.88 Hz, 1C), 112.70, 114.50 (d, 21.50 Hz, 1 C), 117.88, 122.05 (d, 2.69 Hz, 1C), 128.71 (d, 2.6 Hz, 1 C), 130.28 (d, 18.45 Hz, 1C), 139.35 (d, 7.68Hz, 1 C), 158.23, 163.18 (d, 245.68), 166.11.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3046, 2977, 2931, 2839, 1655, 1610, 1602, 1579, 1486, 1446, 1426, 1380, 1371, 1315, 1266, 1242, 1208, 1145, 1039, 955, 938, 890, 875, 771, 751, 733, 692, 670.

7.20.2 Preparation of (E)-4-(4-chlorostyryl)-3,5-dimethylisoxazole 72b



To **66c** (1 M in THF, 1 mL, 1 mmol) and BF_3 OEt_2 (5 mL) at 25 °C, the reaction was wormed to 80 °C for 30 min. Completion of the reaction was checked using TLC. Upon completion, the resulting mixture was cooled back to 25 °C and slowly quenched with aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with aqueous NaCl, dried over $MgSO_4$ filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, EtOAc:*i*-hexane 0/10 to 1/10) furnishing the compound **72a** as a colorless solid **72a** (121 mg, 0.52 mmol, 52% yield)

HRMS (ESI) for $C_{13}H_{13}NCl$**:** calcd 234.0680, found 234.0681 ($M+H^+$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.40 (s, 3 H), 2.49 (s, 3 H), 6.71 (s, 2 H), 7.35 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.62, 11.91,112.80,117.14, 127.25, 128.60, 128.88, 133.32, 135.68, 158.22, 165.94.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3012, 2968, 2928, 2854, 1649, 1597, 1489, 1447, 1424, 1404, 1379, 1317, 1293, 1260, 1221, 1195, 1181, 1106, 1088, 1035, 1011, 959, 951, 886, 862, 853, 808, 784, 774, 761,743 ,710, 679, 667.