Dissertation zur Erlangung des Doktorgrades

der Fakultät für Chemie und Pharmazie

der Ludwig-Maximilians-Universität München

Cobalt-, Iron-, and Nickel-Catalyzed Cross-Coupling Reactions of Zinc and Manganese Organometallics

von

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aus Rosenheim, Deutschland

2020

Erklärung

Diese Dissertation wurde im Sinne von §7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Knochel betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, 8. Februar 2020 ----------

(Ort, Datum) (Maximilian S. Hofmayer)

Dissertation eingereicht am:	13. Januar 2020
1. Gutachter:	Prof. Dr. Paul Knochel
2. Gutachter:	Prof. Dr. Oliver Trapp
Mündliche Prüfung am:	3. Februar 2020

„Im Grunde kehrt alles Große in der Welt auch im Kleinen wieder, wenn man es nur erkennen will."

- Alexander von Humboldt

Meiner Familie

Acknowledgements

This work was carried out from September 2016 to January 2020 under the guidance of Prof. Dr. Paul Knochel at the Faculty of Chemistry and Pharmacy of the Ludwig-Maximilians-Universität, Munich, Germany.

I would like to thank Prof. Dr. Paul Knochel for giving me the opportunity of doing my PhD in his research group and for his guidance and invaluable support throughout the course of my scientific research.

I am very grateful to Prof. Dr. Oliver Trapp for his interest shown in this manuscript by accepting to be my second referee. Thank you Prof. Dr. Konstantin Karaghiosoff for the discussions of NMR spectra, recorded crystal structures and the support throughout my complete studies. I also would like to thank Prof. Dr. Franz Bracher, Dr. Armin Ofial, and Dr. Henry Dube for their support by accepting to be referees.

I want to thank Diana Haas, Jeffrey M. Hammann, Ferdinand H. Lutter, Lucie Grokenberger and Alisa S. Sunagatullina for the fruitful collaboration in our cobalt team. All the interesting discussions and the great ideas to push our projects were really inspirational. I also would like to thank all past and present co-workers of the Knochel group for their kind support and the nice moments we shared together in the lab, at conferences and group activities. Especially thank you Moritz, Juri, Ferdi, Lucie and Alisa, it was an unforgettable time with you and I am grateful for our friendship. Thank you Dr. Vladimir Malakhov, Sophie Hansen, Peter Dowling and Yulia Tsvik for the organization and help in everyday life in the lab and in the office. Thank you Lena Hausner, Pavlos Pelagias, Emanuel Joseph, Lukas Jaschik, Maximilian Bechtel, Arne Stolpmann, Constantin Nuber, Philipp Mauker, Daniel Brösamlen, Matthias Fischer and Aila Rothweiler for your contributions in the course of your bachelor's theses and research internships. You did a great job and I wish you all the best for your future.

Moreover, I would like to thank my friends from Rosenheim and Munich, my sports/climbing partners and my friends from the *Bergwacht München* for the unforgettable moments we share together. You are a highly important part of this work.

I want to thank my whole family for every possible support you gave me over all those years. Above all, thank you Kathi for your unconditional love, patience and believe in me. I am glad that we raise our beloved son Jakob with the same values for life.

Parts of this PhD Thesis have been published in peer-reviewed journals.

1) M. S. Hofmayer, J. M. Hammann, D. Haas, P. Knochel, „Cobalt-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling Reactions of Diarylmanganese Reagents with Secondary Alkyl Iodides“ *Org. Lett.* **2016**, *18*, 6456-6459.
2) M. S. Hofmayer, J. M. Hammann, G. Cahiez, P. Knochel, „Iron-Catalyzed C(sp^2)–C(sp^3) Cross-Coupling Reactions of Di(hetero)arylmanganese Reagents and Primary and Secondary Alkyl Halides“ *Synlett* **2018**, *29*, 65-70.
3) M. S. Hofmayer, F. H. Lutter, L. Grokenberger, J. M. Hammann, P. Knochel, „Practical Ni-Catalyzed Cross-Coupling of Unsaturated Zinc Pivalates with Unsaturated Nonaflates and Triflates“ *Org. Lett.* **2019**, *21*, 36-39.
4) M. S. Hofmayer, A. S. Sunagatullina, D. Brösamlen, P. Mauker, P. Knochel, „Stereoselective Cobalt-Catalyzed Cross-Coupling Reactions of Arylzinc Chlorides with α-Bromolactones and Related Derivatives” *Org. Lett.* **2020***, 22,* 1286-1289.

Parts of this PhD Thesis have been presented at scientific conferences and courses

- OMCOS 20 – 20th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis. July 21-25, 2019 in Heidelberg, Germany. “**Stereoselective Cobalt-Catalyzed Cross-Couplings of α-Bromolactones”**
- ISHC 27 – 27th International Society of Heterocyclic Chemistry Congress. September 1-6, 2019, Kyoto, Japan. “**Stereoselective Cobalt-Catalyzed Cross-Couplings of α-Bromolactones”**
- Boehringer Ingelheim MedChem PhD Course – September 18-20, 2019, Biberach, Germany. “**Transition Metal-Catalyzed Cross-Coupling Reactions”**

List of Abbreviations

acac	acetylacetonate
Alk	alkyl
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
calc.	calculated
conc.	concentrated
δ	chemical shifts in ppm (parts per million)
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*′-dimethylpropyleneurea
EI	electron impact ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
GC	gas chromatography
h	hour
HRMS	high resolution mass spectrometry
*i*Pr	*iso*-propyl
IR	infrared
J	coupling constant (NMR)
M	molarity
m	meta
m.p.	melting point
Me	methyl
MOM	methoxymethyl
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
Piv	pivaloyl
rt	room temperature
sat.	saturated
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
Ts	4-toluenesulfonyl

Table of Contents

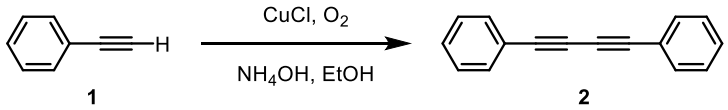
A INTRODUCTION

1 The Development of Transition Metal-Catalyzed Cross-Coupling Reactions

The exploration of transition metal-catalyzed cross-coupling reactions during the last 150 years was complicated by issues regarding the scope and the selectivity as major restrictions.[1] Possible side reactions involve homocoupling, isomerization, β-hydride elimination and functional group intolerance. Pioneering contributions of *Beletskaya*, *Corriu*, *Kumada*, *Kochi*, *Murahashi*, *Sonogashira*, *Stille*, *Trost*, *Tsuji*, *Yamamoto* and overall *Heck*, *Negishi* and *Suzuki* showed, that carbons of all hybridization states can undergo C-C bond forming reactions under palladium catalysis. The development of a vast variety of ligands with different sterical and electronical properties allowed to fine-tune the reactivity and broadened the scope.

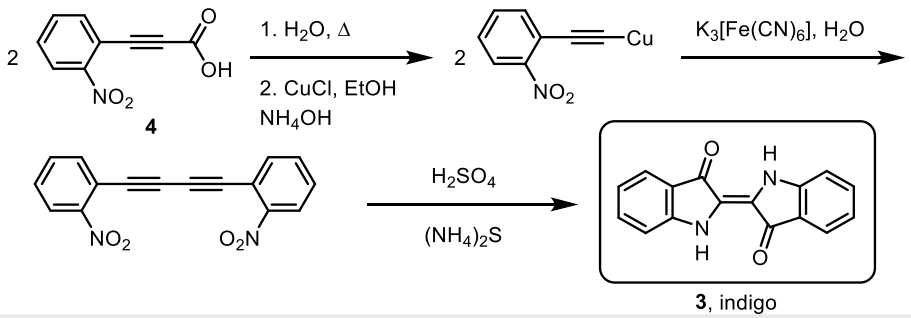
1.1 Early Examples of Carbon-Carbon Bond Formations Involving Transition Metals

The first seminal approaches which formed the basic principles for the development of modern cross-coupling chemistry were reported in the middle of the 19th century. The pioneering work of *Glaser* in 1869 described the homocoupling of phenylacetylene (**1**) in the presence of copper(I) chloride and ammonia in water/ethanol under air, leading to diphenylbutadiyne (**2**, Scheme 1).[2]



Scheme 1. *Glaser* coupling of phenylacetylene (1).

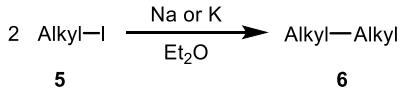
This methodology was utilized by *Baeyer* for a synthesis of indigo (**3**) starting from 2-nitrophenylpropiolic acid (**4**, Scheme 2).[3]



Scheme 2. *Baeyer* synthesis of indigo (3) starting from 2-nitrophenylpropiolic acid (4).

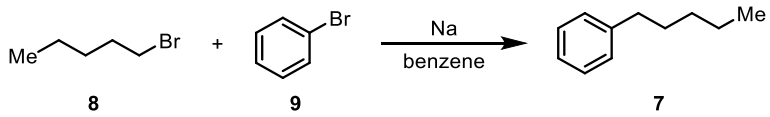
[1] For a review, see: C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus *Angew. Chem., Int. Ed.* **2012**, *51*, 5062-5085.
[2] a) C. Glaser *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422-424. b) C. Glaser *Justus Liebigs Ann. Chem.* **1870**, *154*, 137-171.
[3] A. Baeyer *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 50-56.

In 1855, *Wurtz* described a coupling of alkyl Iodides **5** in the presence of metallic sodium and potassium affording products of type **6** (Scheme 3).[4]



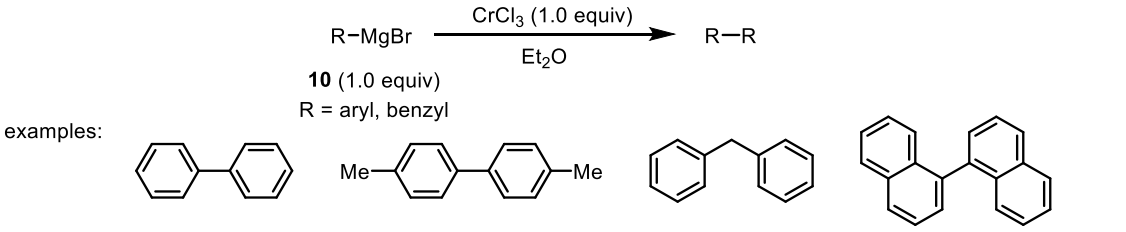
Scheme 3. *Wurtz* coupling of alkyl iodides.

A few years later, *Fittig* and *Tollens* extended this reaction to the formation of alkylated aryl compounds and biaryls starting from alkyl and aryl halides.[5] Thus, pentylbenzene (**7**) was synthesized from bromopentane (**8**) and bromobenzene (**9**) by adding sodium to a solution of the starting materials in benzene (Scheme 4).[5b] The discovery of highly reactive sodium and potassium reagents, led to the development of milder magnesium reagents by *Grignard* in the early 20th century.[6]



Scheme 4. *Fittig* and *Tollens* coupling leading to pentylbenzene (7).

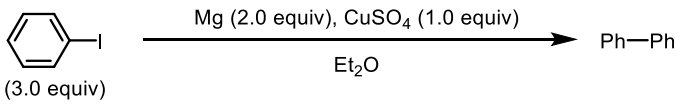
Bennet and *Turner* explored the chromium(III) chloride promoted homocoupling reactions of aryl- and benzylmagnesium reagents of type **10** in 1914 (Scheme 5).[7]



Scheme 5. *Bennet* and *Turner* homocoupling reactions.

Later, in 1919 *Krizewsky* and *Turner* described, that several copper salts are sufficient additives to perform homocoupling reactions with *in situ* generated phenylmagnesium iodide (Scheme 6).[8]

[4] a) A. Wurtz *Ann. Chim. Phys.* **1855**, *44*, 275-312. b) A. Wurtz *Justus Liebigs Ann. Chem.* **1855**, *96*, 364-375.
[5] a) R. Fittig *Justus Liebigs Ann. Chem.* **1862**, *121*, 361-365. b) B. Tollens, R. Fittig *Justus Liebigs Ann. Chem.* **1864**, *131*, 303-323. c) B. Tollens, R. Fittig *Justus Liebigs Ann. Chem.* **1864**, *129*, 369-370.
[6] V. Grignard *C. R. Hebd. Seances Acad. Sci.* **1900**, *130*, 1322-1324.
[7] G. M. Bennett, E. E. Turner *J. Chem. Soc., Trans.* **1914**, *105*, 1057-1062.
[8] J. Krizewsky, E. E. Turner *J. Chem. Soc., Trans.* **1919**, *115*, 559-561.

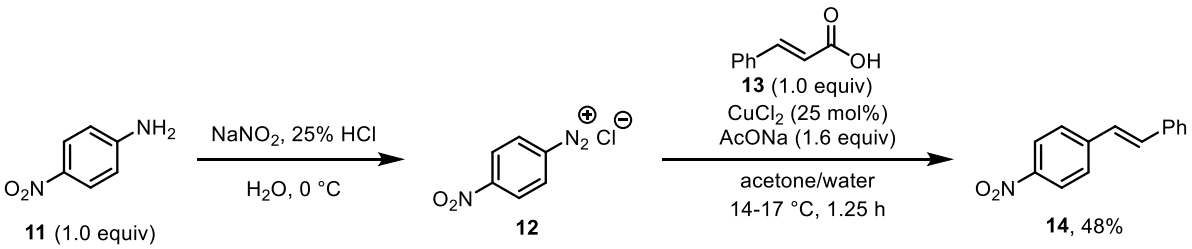


Scheme 6. *Krizewsky* and *Turner* homocoupling.

Although these reactions opened a completely new field for C-C bond formations, they were limited to homocouplings, a small scope or used poorly soluble stoichiometric amounts of metal salts.

1.2 First Selective Transition Metal-Catalyzed Cross-Couplings

An early example for the application of substoichiometric amounts of a metal catalyst was reported by *Job* in 1924, but was barely recognized by the chemistry community.[9] *Job* investigated the effect of nickel(II) chloride on phenylmagnesium bromide in the atmospheres of ethylene, hydrogen, carbon monoxide and other gases. Later in 1939, *Meerwein* described the ability of copper(II) salts to catalyze the first couplings of aryldiazonium salts with substituted alkenes.[10] Thus, 4-nitroaniline (**11**) was transferred into the corresponding aryldiazonium chloride **12** and cross-coupled with cinnamic acid (**13**) under copper catalysis. The product 4-nitrostilbene (**14**) was isolated in 48% yield (Scheme 7).

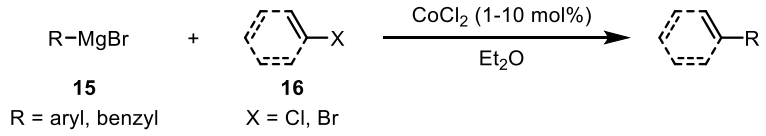


Scheme 7. *Meerwein* copper-catalyzed arylation.

A cross-coupling employing substoichiometric amounts of cobalt(II) chloride as catalyst was explored by *Kharasch* in 1941 (Scheme 8).[11] Aryl- and benzylmagnesium bromides of type **15** underwent efficient coupling reactions with aryl and vinyl halides of type **16**. A selective version based on the chemistry of *Kharasch* was developed over 30 years later by *Kumada*[12] and *Corriu*[13] in 1972. The

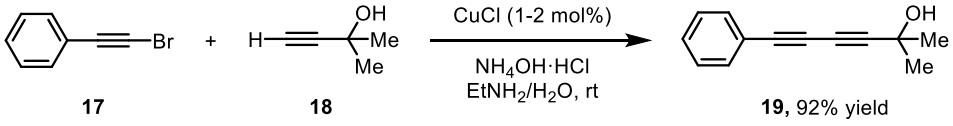
[9] A. Job, R. Reich *C. R. Hebd. Seances Acad. Sci.* **1923**, *177*, 1439-1441.
[10] H. Meerwein, E. Büchner, K. van Emster *J. Prakt. Chem.* **1939**, *152*, 237-266.
[11] a) M. S. Kharasch, E. K. Fields *J. Am. Chem. Soc.* **1941**, *63*, 2316-2320. b) *Grignard Reactions of Nonmetallic Substances* (Eds.: M. S. Kharasch, O. Reinmuth), Prentice-Hall, New York, 1954. c) M. S. Kharasch, C. F. Fuchs *J. Am. Chem. Soc.* **1943**, *65*, 504-507.
[12] a) K. Tamao, K. Sumitani, M. Kumada *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376. b) K. Tamao, Y. Kiso, K. Sumitani, M. Kumada *J. Am. Chem. Soc.* **1972**, *94*, 9268-9269. c) T. Kohei, S. Koji, K. Yoshihisa, Z. Michio, F. Akira, K. Shun-ichi, N. Isao, M. Akio, K. Makoto *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958-1969.
[13] R. J. P. Corriu, J. P. Masse *J. Chem. Soc., Chem. Commun.* **1972**, 144.

cross-coupling of aryl and alkenyl halides with aryl- and alkylmagnesium reagents was catalyzed by adding nickel salts. Herein, the beneficial effect of phospine ligands on the reactivity of the metal was described by *Kumada* and initiated their exploration as ligands in the palladium chemistry.



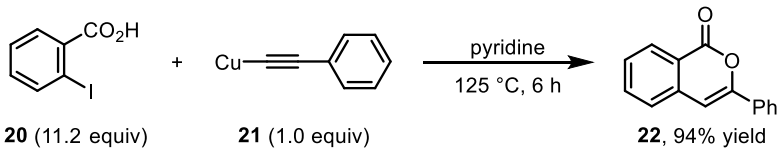
Scheme 8. *Kharasch* cobalt-catalyzed couplings of aryl and benzylmagnesium reagents.

The transition metal-promoted couplings discovered until the middle of the 20th century are fundamental for the coupling chemistry which was developed in the following decades. It was demonstrated, that catalytic amounts of metals salts can be utilized for carbon-carbon bond formations. However, selectivity problems such as the ratio between homocoupling and product, the narrow scope or low functional group tolerance for these reactions represented the major limitations. *Cadiot* and *Chodkiewicz* described a new method to form unsymmetrical sp-sp and sp-sp^2 bonds in 1957 by using aryl and alkynyl halides with alkynylcopper reagents (Scheme 9).[14] Thus, (bromoethynyl)benzene (**17**) and the terminal alkyne **18** gave the bisacetylene **19** in 92% yield by addition of copper(I) chloride.



Scheme 9. *Cadiot-Chodkiewicz* coupling of bromoacetylene 17 and the terminal alkyne 18.

Similarly, *Castro* and *Stephens* cross-coupled sp- and sp^2-carbons in 1963 (Scheme 10).[15] Various functionalized aryl iodides, underwent the reaction with copper acetylides. Thus, 2-iodobenzoic acid (**20**) was coupled with the copper reagent **21** to afford the cyclized isocoumarin **22**.



Scheme 10. *Castro-Stephens* coupling of 2-iodobenzoic acid (20) with copper phenylacetylide (21).

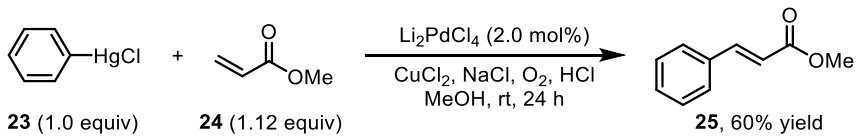
[14] a) W. Chodkiewicz, P. Cadiot *C. R. Hebd. Seances Acad. Sci.* **1955**, *241*, 1055–1057. b) W. Chodkiewicz *Ann. Chim. Paris* **1957**, *2*, 819 – 869. c) P. Cadiot, W. Chodkiewicz, in *Chemistry of Acetylenes* (Ed.: H. G. Viehe), Marcel Dekker, New York, **1969**; pp 597-647.

[15] R. D. Stephens, C. E. Castro *J. Org. Chem.* **1963**, *28*, 3313-3315.

A key for the selective formation of carbon-carbon bonds was elucidated. The combination of an organohalide, an organometallic partner and a transition metal catalyst in stoichiometric or catalytic quantity is required.

1.3 The Discovery of Palladium as Catalyst

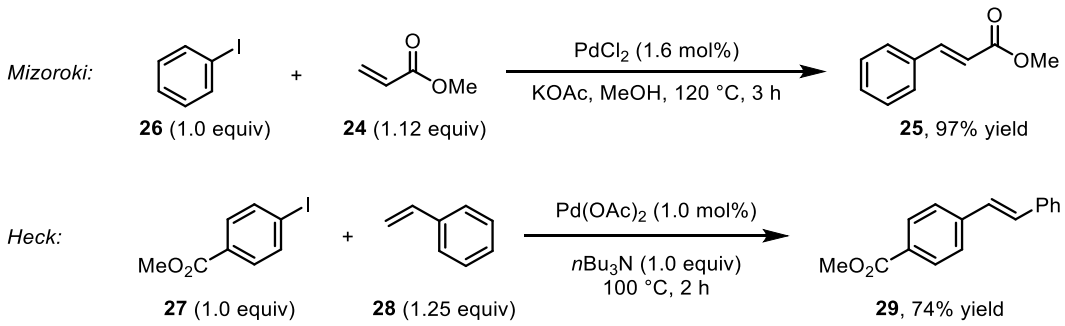
In 1959, the Wacker Chemie GmbH discovered the exceptional activity of palladium in the oxidation of ethylene to acetaldehyde (Wacker oxidation). *Hafner*, the leader of Wacker Chemie's research institute, isolated and characterized a palladium π-allyl complex for the first time.[16] These observations were transferred to the context of cross-couplings by *Heck* and led to one of the most important inventions of the 20th century. In 1968, the coupling of organomercury compounds with alkenes in the presence of a palladium catalyst was reported (Scheme 11).[17] Under reoxidizing conditions, Li_2PdCl_4 readily catalyzes the coupling of phenylmercuric chloride (**23**) and methyl acrylate (**24**) to afford the desired methyl cinnamate (**25**) in 60% yield.



Scheme 11. *Heck's* palladium-catalyzed coupling of organomercury compounds with alkenes.

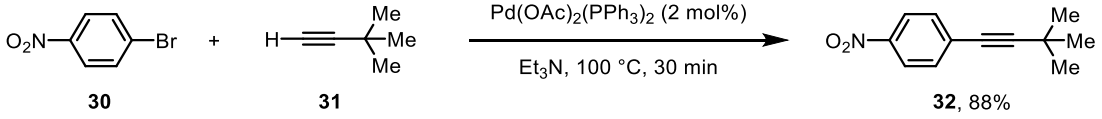
In 1971 and 1972, *Mizoroki*[18] and *Heck*[17a,19] published almost simultaneously that aryl, benzyl and styryl halides can be cross-coupled with alkenes using a palladium(II) catalyst (Scheme 12). Phenyl iodide (**26**) reacts smoothly with methyl acrylate (**24**), leading to methyl cinnamate (**25**) in 97% yield. Similarly, methyl 4-iodobenzoate (**27**) and styrene (**28**) were coupled with palladium(II) acetate as catalyst to furnish 4-carbomethoxy stilbene (**29**) in 74% yield. This procedure is known as the *Mizoroki-Heck*-reaction today.

[16] J. Smidt, W. Hafner *Angew. Chem.* **1959**, *71*, 284-284.
[17] a) R. F. Heck *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526. b) R. F. Heck *J. Am. Chem. Soc.* **1968**, *90*, 5526-5531. c) R. F. Heck *J. Am. Chem. Soc.* **1968**, *90*, 5531-5534. d) R. F. Heck *J. Am. Chem. Soc.* **1968**, *90*, 5535-5538. e) R. F. Heck *J. Am. Chem. Soc.* **1968**, *90*, 5538-5542. f) R. F. Heck *J. Am. Chem. Soc.* **1968**, *90*, 5542-5546. g) R. F. Heck *J. Am. Chem. Soc.* **1968**, *90*, 5546-5548.
[18] a) T. Mizoroki, K. Mori, A. Ozaki *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581-581. b) M. Kunio, M. Tsutomu, O. Atsumu *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1505-1508.
[19] a) H. A. Dieck, R. F. Heck *J. Am. Chem. Soc.* **1974**, *96*, 1133-1136. b) R. F. Heck, J. P. Nolley *J. Org. Chem.* **1972**, *37*, 2320-2322.



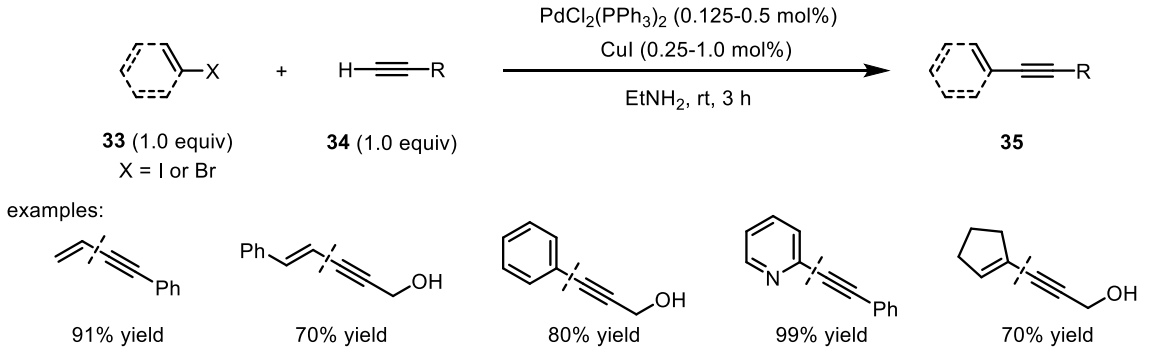
Scheme 12. *Mizuroki's* and *Heck's* first palladium(II) catalyzed cross-coupling reactions of organic halides with alkenes.

Heck reported a palladium-catalyzed coupling of (hetero)aryl and vinyl halides with sp-carbon centers in 1975 (Scheme 13).[20] 4-Bromonitrobenzene (**30**) and *tert*-butylacetylene (**31**) gave the desired alkyne **32** in 88% yield.



Scheme 13. *Heck's* palladium catalyzed coupling of 4-bromonitrobenzene (30) and tert-butylacetylene (31).

Sonogashira extended the possibilities of the palladium-catalyzed cross-couplings of aryl and vinyl halides of type **33** with terminal alkynes of type **34** in 1975 (Scheme 14).[21] By using a copper cocatalyst, the reactions could be performed under exceedingly mild conditions and the desired acetylenes of type **35** were afforded in high to excellent yields.

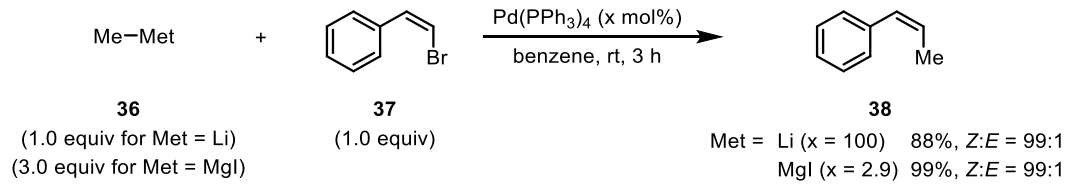


Scheme 14. Sonogashira coupling of vinyl and aryl halides with acetylenes.

Compared to the *Castro-Stephens* cross-coupling (Scheme 10) or the sp^2-sp coupling of *Heck* (Scheme 13), the *Sonogashira* coupling (Scheme 14) can be performed at room temperature with only catalytic

[20] H. A. Dieck, F. R. Heck *J. Organomet. Chem.* **1975**, *93*, 259-263.
[21] K. Sonogashira, Y. Tohda, N. Hagihara *Tetrahedron Lett.* **1975**, *16*, 4467-4470.

amounts of transition metals. Until this time, the coupling of Grignard reagents was predominated by nickel-catalysis.[12, 13] *Murahashi*[22] followed by *Jutand*[23] were the first, who demonstrated that organomagnesium species can undergo palladium-catalyzed carbon-carbon bond formations with alkenyl halides (Scheme 15). Although not catalytically, organolithium reagents were coupled for the first time, which was not possible with nickel salts so far. Organometallic reagents such as **36** could be cross-coupled with (*Z*)-styryl bromide **37** to afford the (*Z*)-product **38** under stereoretention.



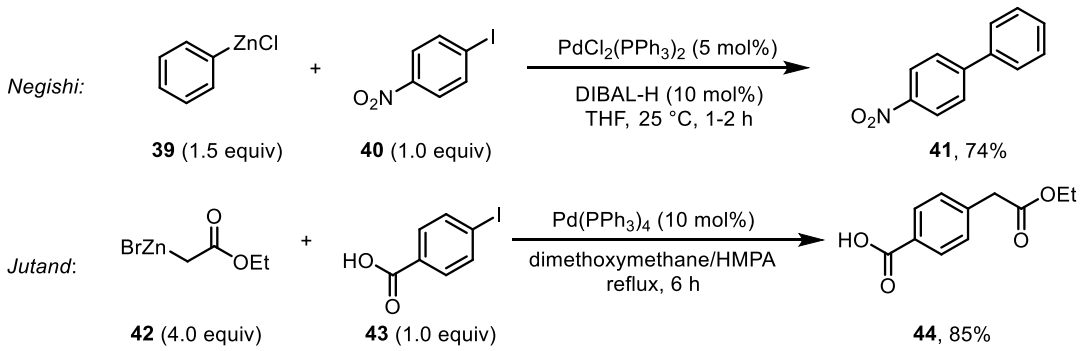
Scheme 15. Palladium-catalyzed *Corriu-Kumada* cross-couplings by *Murahashi*.

However, the limitations of organolithium and –magnesium reagents were obviously the intolerance of sensitive functional groups, due to the anionic character. According to *Snieckus*, the second wave of cross-coupling development began, which is the exploration of the organometallic coupling partner.[1]

1.4 Exploration of Organometallic Reagents as Coupling Partners

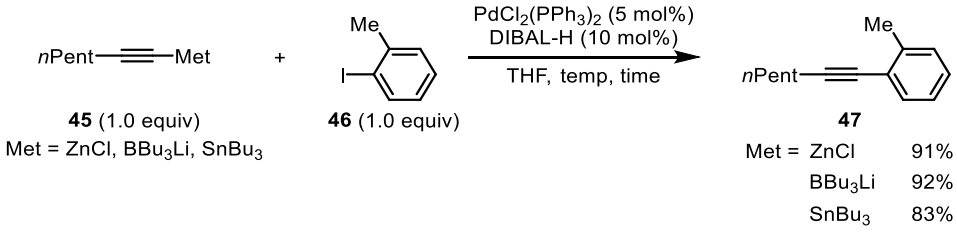
Negishi[24] and *Jutand*[25] reported in 1977, that lithium and magnesium organometallics can be replaced by the much milder organozinc reagents, which undergo palladium-catalyzed cross-couplings with aryl halides (Scheme 16). Phenylzinc chloride (**39**) and 4-iodonitrobenzene (**40**) afforded the biaryl **41** in 74% yield. Similarly, the *Reformatsky* reagent **42** was successfully coupled with 4-iodobenzoic acid (**43**), leading to **44** in 85% yield.

[22] a) S. Murahashi, M. Yamamura, K. Yanagisawa, N. Mita, K. Kondo *J. Org. Chem.* **1979**, *44*, 2408-2417. b) M. Yamamura, I. Moritani, S.-I. Murahashi *J. Organomet. Chem.* **1975**, *91*, C39-C42.
[23] J. F. Fauvarque, A. Jutand *Bull. Soc. Chim. Fr.* **1976**, 765-770.
[24] a) E. Negishi, A. O. King, N. Okukado *J. Org. Chem.* **1977**, *42*, 1821-1823. b) A. O. King, N. Okukado, E.-i. Negishi *J. Chem. Soc., Chem. Commun.* **1977**, 683-684.
[25] J. F. Fauvarque, A. Jutand *J. Organomet. Chem.* **1977**, *132*, C17-C19.



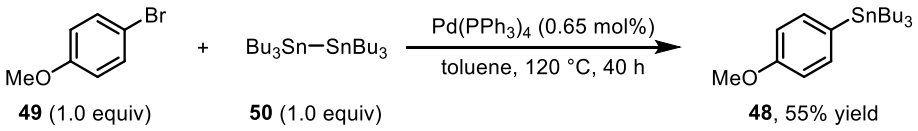
Scheme 16. *Negishi's* and *Jutand's* cross-coupling of organozinc reagents with aryl halides under palladium-catalysis.

Negishi also screened various metal acetylides for their applicability as nucleophilic reagents in Pd-catalyzed cross-coupling reactions (Scheme 17). The metal reagents of type **45**, including boron, tin, and zinc organometallics were efficient coupling partners with 2-iodotoluene (**46**) to afford the alkynylated product **47** in high yields.[26]



Scheme 17. *Negishi's* investigation of other organometallics 45 as coupling partners.

The reactivity of organostannanes under palladium-catalysis was further investigated by *Eaborn*. A procedure to synthesize tributylarylstannanes of type **48** by reacting the corresponding aryl halides, such as **49** with hexabutyldistannane **50** and a palladium(0) catalyst was developed (Scheme 18).[27]

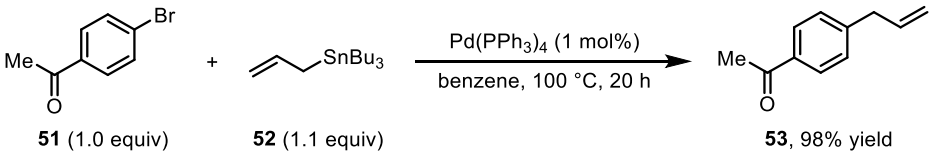


Scheme 18. *Eaborn's* synthesis of trimethylarylstannanes using a palladium(0) catalyst.

Migita demonstrated, that tetrakis(triphenylphosphine)palladium is a sufficient catalyst for the alkylation, arylation and vinylation of acyl chlorides and the allylation of aromatic halides (Scheme

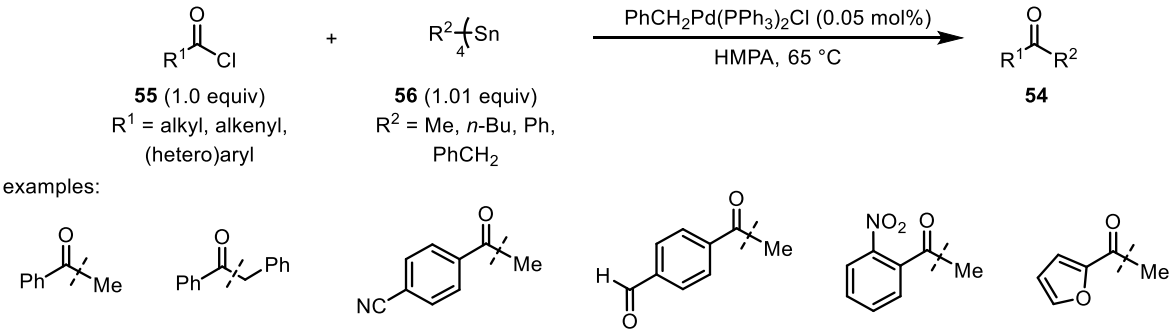
[26] E. Negishi, Aspects of Mechanism and Organometallic Chemistry, (Ed.: J. H. Brewster), Plenum, New York, 1978; pp 285-317.
[27] D. Azarian, S. S. Dua, C. Eaborn, D. R. M. Walton *J. Organomet. Chem.* **1976**, *117*, C55-C57.

19).[28] The keto function of 4-bromoacetophenone (**51**) is well tolerated and the allylation with allyltributylstannane (**52**) under palladium-catalysis leads to the desired product **53** in excellent yield.



Scheme 19. *Migita* allylation of aryl halides with allyltributylstannane (52).

Stille developed versatile and exceedingly mild cross-coupling methodologies in the late 1970s and early 1980s employing organostannanes as metal reagents.[29] An early publication with *Milstein* reported the synthesis of various ketones of type **54** from acyl chlorides **55** and organotin compounds of type **56** (Scheme 20).[30] Various functional groups, such as aldehydes, nitriles and esters were tolerated. Despite the remarkable features of organostannanes, the toxicity of the tin reagents always remained as the major drawback.



Scheme 20. *Stille* palladium-catalyzed acylation reactions of organostannanes.

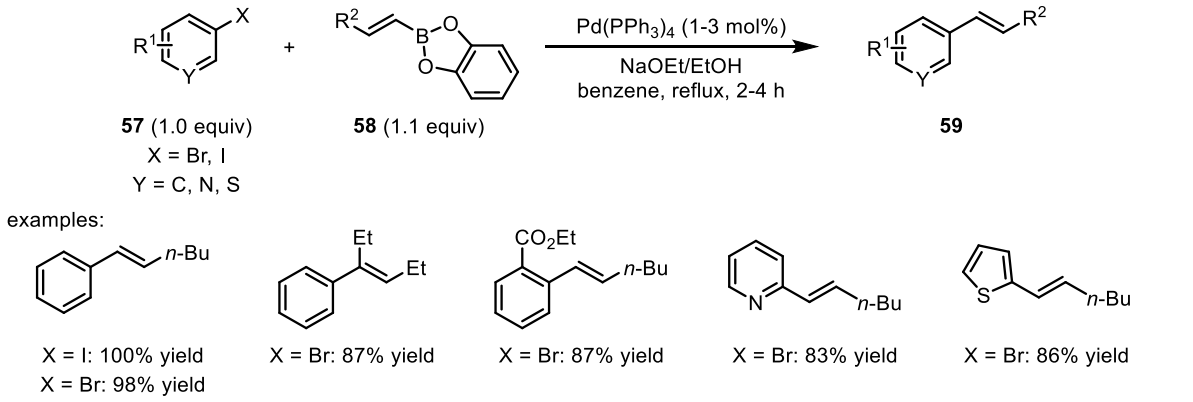
Suzuki and *Miyaura* investigated organoboron reagents as organometallic coupling partners in more detail in 1979 (Scheme 21).[31] (Hetero)aryl bromides and iodides **57** were sufficient coupling partners for simple alkenylboranes of type **58**, leading to the corresponding (*E*)-alkenes of type **59**.

[28] a) M. Kosugi, Y. Shimizu, T. Migita *Chem. Lett.* **1977**, *6*, 1423-1424. b) M. Kosugi, K. Sasazawa, Y. Shimizu, T. Migita *Chem. Lett.* **1977**, *6*, 301-302.

[29] For a reviews on palladium-catalyzed cross-couplings of organotin reagents, see: a) J. K. Stille *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508-524. b) C. Cordovilla, C. Bartolomé, J. M. Martínez-Ilarduya, P. Espinet *ACS Catal.* **2015**, *5*, 3040-3053.

[30] D. Milstein, J. K. Stille *J. Am. Chem. Soc.* **1978**, *100*, 3636-3638.

[31] N. Miyaura, A. Suzuki *J. Chem. Soc., Chem. Commun.* **1979**, 866-867.

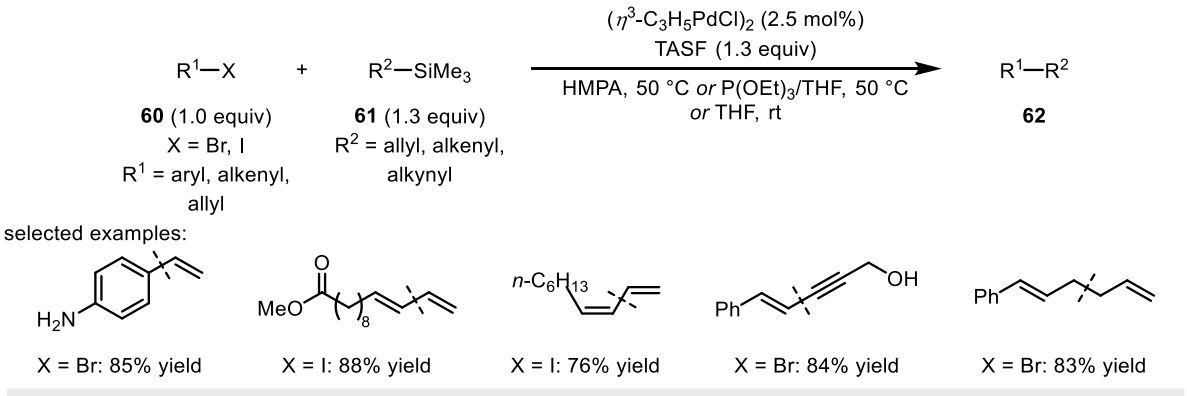


Scheme 21. *Suzuki-Miyaura* cross-coupling of aryl halides 57 with alkenyl boranes 58.

Boron was the remaining metal species identified by *Negishi* (zinc, boron, tin) in the field of palladium-catalyzed cross-couplings. The air- and moisture stability of the starting materials, mild reaction conditions and the generation of inorganic less-toxic byproducts which can easily be removed, made the *Suzuki-Miyaura* coupling an extremely powerful methodology for the formation of carbon-carbon bonds.[32]

Based on publications of *Kumada*[33] and *Hallberg,*[34] the coupling of organic halides **60** with organosilanes **61** under palladium-catalysis was reported by *Hiyama* in 1988 (Scheme 22).[35] TASF (tris(diethylamino)sulfonium difluorotrimethylsilicate) was necessary as a fluorine source to obtain the synthetically useful cross-coupling products **62**. The *Hiyama* coupling-reaction was extended by *DeShong*,[36] *Denmark*,[37] and others in the following decades.

[32] a) N. Miyaura, A. Suzuki *Chem. Rev.* **1995**, *95*, 2457-2483. b) A. Suzuki *J. Organomet. Chem.* **1999**, *576*, 147-168.
[33] J. Yoshida, K. Tamao, H. Yamamoto, T. Kakui, T. Uchida, M. Kumada *Organometallics* **1982**, *1*, 542-549.
[34] A. Hallberg, C. Westerlund *Chem. Lett.* **1982**, *11*, 1993-1994.
[35] a) Y. Hatanaka, T. Hiyama *J. Org. Chem.* **1988**, *53*, 918-920. b) T. Hiyama *J. Organomet. Chem.* **2002**, *653*, 58-61.
[36] a) M. E. Mowery, P. DeShong *J. Org. Chem.* **1999**, *64*, 3266-3270. b) P. DeShong, J. Handy Christopher, E. Mowery Molly *Pure Appl. Chem.* **2000**, *72*, 1655-1658. c) M. E. Mowery, P. DeShong *J. Org. Chem.* **1999**, *64*, 1684-1688.
[37] a) S. E. Denmark, J. Y. Choi *J. Am. Chem. Soc.* **1999**, *121*, 5821-5822. b) S. E. Denmark, C. S. Regens *Acc. Chem. Res.* **2008**, *41*, 1486-1499.



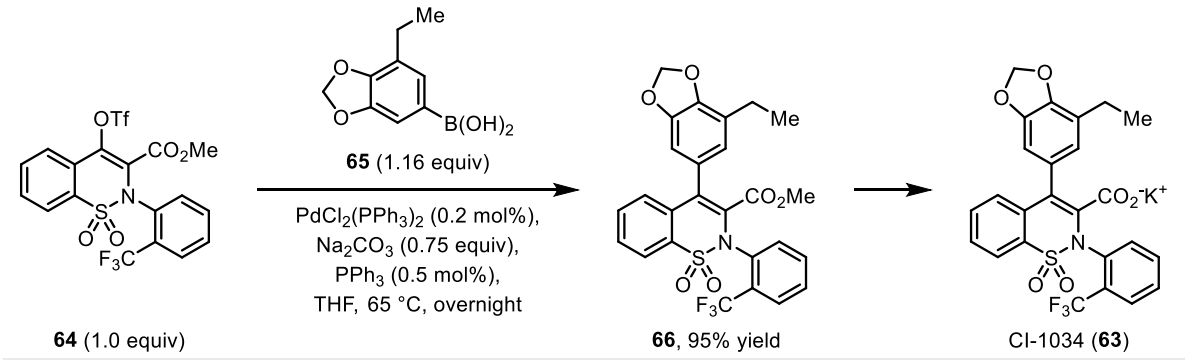
Scheme 22. *Hiyama* coupling of organosilanes.

In the following decades, the fine tuning of these versatile coupling reactions was pursued. Especially the design of sophisticated ligands – to increase functional group tolerance and to broaden the substrate scope – was the key interest of several research groups, such as *Spencer*,[38] *Osborn*,[39] *Milstein*,[40] *Fu*,[41] *Schönebeck*,[42] *Beller*,[43] *Buchwald*,[44] and *Hartwig*[45] to name only a few. The palladium-catalyzed cross-couplings were extended to pseudohalides as electrophiles, including sulfonates such as OMs[46] and OTs,[47] hypervalent iodine species[48] and diazonium salts[49] among others. However, some pseudohalides still stayed subject to nickel-catalysis, due to an unreactive oxidative addition-step for palladium salts.[50]

Palladium-catalyzed cross-couplings have become one of the most powerful methodologies in the toolbox of the synthetic organic chemist. Therefore, these reactions have found plenty of applications in pharmaceutical, agrochemical and natural product synthesis in academia and industry.[51]

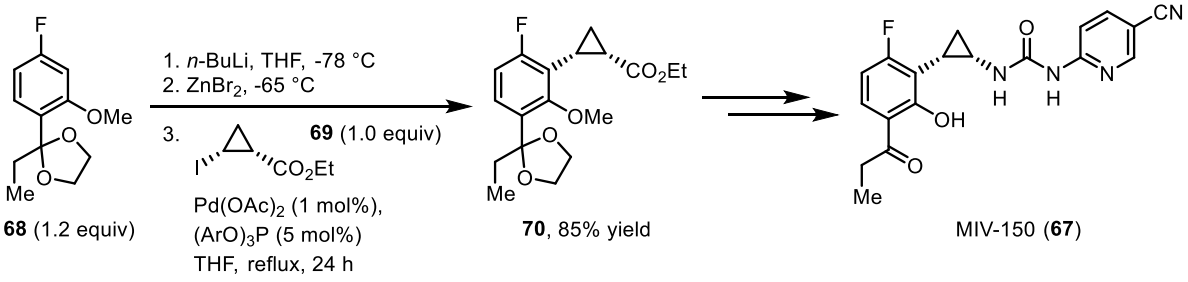
[38] A. Spencer *J. Organomet. Chem.* **1983**, *258*, 101-108.
[39] M. Huser, M.-T. Youinou, J. A. Osborn *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1386-1388.
[40] Y. Ben-David, M. Portnoy, D. Milstein *J. Am. Chem. Soc.* **1989**, *111*, 8742-8744.
[41] a) A. F. Littke, G. C. Fu *Angew. Chem., Int. Ed.* **1998**, *37*, 3387-3388. b) A. F. Littke, C. Dai, G. C. Fu *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028. c) J. H. Kirchhoff, M. R. Netherton, I. D. Hills, G. C. Fu *J. Am. Chem. Soc.* **2002**, *124*, 13662-13663.
[42] F. Proutiere, F. Schoenebeck *Angew. Chem., Int. Ed.* **2011**, *50*, 8192-8195.
[43] A. Zapf, A. Ehrentraut, M. Beller *Angew. Chem., Int. Ed.* **2000**, *39*, 4153-4155.
[44] a) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald *J. Am. Chem. Soc.* **1999**, *121*, 4369-4378. b) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561.
[45] a) Q. Shelby, N. Kataoka, G. Mann, J. Hartwig *J. Am. Chem. Soc.* **2000**, *122*, 10718-10719. b) J. F. Hartwig *Acc. Chem. Res.* **2008**, *41*, 1534-1544.
[46] B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald *J. Am. Chem. Soc.* **2008**, *130*, 13552-13554.
[47] a) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe *J. Am. Chem. Soc.* **2002**, *124*, 4222-4223. b) H. N. Nguyen, X. Huang, S. L. Buchwald *J. Am. Chem. Soc.* **2003**, *125*, 11818-11819.
[48] S.-K. Kang, H.-W. Lee, S.-B. Jang, P.-S. Ho *J. Org. Chem.* **1996**, *61*, 4720-4724.
[49] A. Roglans, A. Pla-Quintana, M. Moreno-Mañas *Chem. Rev.* **2006**, *106*, 4622-4643.
[50] D.-G. Yu, B.-J. Li, Z.-J. Shi *Acc. Chem. Res.* **2010**, *43*, 1486-1495.
[51] For reviews, see: a) C. Torborg, M. Beller *Adv. Synth. Catal.* **2009**, *351*, 3027-3043. b) J. Magano, J. R. Dunetz *Chem. Rev.* **2011**, *111*, 2177-2250. c) A. Biffis, P. Centomo, A. Del Zotto, M. Zecca *Chem. Rev.* **2018**, *118*, 2249-2295.

Pfizer developed a multikilogram synthesis of CI-1034 (**63**) a potent endothelin receptor antagonist, which showed promising effects for the treatment of primary pulmonary hypertension.[52] A *Suzuki*-coupling of triflate **64** and a boronic acid **65** was employed as the key step (Scheme 23). The coupling product **66** was isolated in 95% yield.



Scheme 23. *Suzuki*-coupling as the key step for the synthesis of CI-1034 (63).

A convergent route to MIV-150 (**67**) was performed by *Chiron* (acquired by *Novartis*) on a 0.48 mol scale, using a *Negishi*-coupling as the key step (Scheme 24).[53] MIV-150 (**67**) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type-1 (HIV-1).[53] Thus, the aryl fluoride **68** was metalated by *n*BuLi in THF, transmetalated with $ZnBr_2$ and cross-coupled with the cyclopropyl iodide **69** by using palladium(II) acetate as catalyst and tris(2,4-di-*tert*-butylphenyl) phosphite as ligand. The desired product **70** was isolated by recrystallization in 85% yield. Remarkably, only the *cis*-product **70** was formed in this reaction and no epimerization in the α- or β-position occurred.



Scheme 24. *Negishi*-coupling as the key step for the synthesis of MIV-150.

[52] T. E. Jacks, D. T. Belmont, C. A. Briggs, N. M. Horne, G. D. Kanter, G. L. Karrick, J. J. Krikke, R. J. McCabe, J. G. Mustakis, T. N. Nanninga, G. S. Risedorph, R. E. Seamans, R. Skeean, D. D. Winkle, T. M. Zennie *Org. Process Res. Dev.* **2004**, *8*, 201-212.

[53] S. Cai, M. Dimitroff, T. McKennon, M. Reider, L. Robarge, D. Ryckman, X. Shang, J. Therrien *Org. Process Res. Dev.* **2004**, *8*, 353-359.

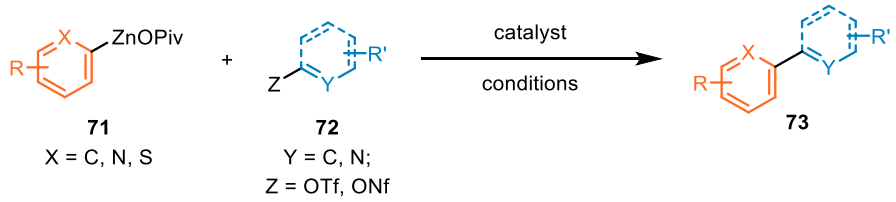
The *Nobel* Prize for *Heck*, *Negishi*, and *Suzuki* in 2010 and a plethora of applications demonstrate the importance of palladium-catalysis in modern cross-coupling based synthetic approaches. Although palladium shows exceptional reactivity patterns and allows a broad variety of transformations, it may not always be the best choice due to several reasons. Mainly, the low earth abundance and the world's high demand for palladium, resulted in an increasing price development.[54] This can be a challenge for the applicability in large scale approaches in the agrochemical and pharmaceutical industry, where cost efficiency is a major requirement. Additionally, reactions that form alkyl-palladium species as intermediates and have hydrogen substituents in the 2-position, often suffer from elimination reactions and undesired side reactions.[55] This is often the case for cross-couplings employing alkyl halides as electrophiles, which limits the scope dramatically.[55] To circumvent these drawbacks it was demonstrated that especially nickel,[56] iron,[57] and cobalt[58] salts can be cheap and environmentally benign alternatives to palladium based approaches.

[54] World market prices for Pd: 51140 EUR/kg; for Co: 32 EUR/kg (retrieved Nov. 2019, http://www.infomine.com).
[55] G. Cahiez, A. Moyeux *Chem. Rev.* **2010**, *110*, 1435-1462.
[56] For reviews on nickel-catalyzed cross-coupling chemistry, see: a) X. Hu *Chemical Science* **2011**, *2*, 1867-1886. b) T. Iwasaki, N. Kambe *Top. Curr. Chem.* **2016**, *374*, 66.
[57] For reviews on iron-catalyzed cross-coupling chemistry, see: a) C. Bolm, J. Legros, J. Le Paih, L. Zani *Chem. Rev.* **2004**, *104*, 6217-6254. b) B. D. Sherry, A. Fürstner *Acc. Chem. Res.* **2008**, *41*, 1500-1511. c) E. Nakamura, T. Hatakeyama, S. Ito, K. Ishizuka, L. Ilies, M. Nakamura *Organic Reactions* **2014**, *83*, 1-210. d) A. Guérinot, J. Cossy *Top. Curr. Chem.* **2016**, *374*, 49. c) A. Piontek, E. Bisz, M. Szostak *Angew. Chem., Int. Ed.* **2018**, *57*, 11116-11128. d) J. D. Sears, P. G. N. Neate, M. L. Neidig *J. Am. Chem. Soc.* **2018**, *140*, 11872-11883.
[58] For reviews on cobalt-catalyzed cross-coupling chemistry, see: a) C. Gosmini, J.-M. Bégouin, A. Moncomble *Chem. Commun.* **2008**, 3221-3233. b) W. Hess, J. Treutwein, G. Hilt *Synthesis* **2008**, 3537-3562. c) P. Knochel, T. Thaler, C. Diene *Isr. J. Chem.* **2010**, *50*, 547-557. d) J. M. Hammann, M. S. Hofmayer, F. H. Lutter, L. Thomas, P. Knochel *Synthesis* **2017**, *49*, 3887-3894.

2 Objectives

Pd-catalysts allow various cross-coupling reactions. However, restrictions and drawbacks as pointed out above can arise with Pd-salts as catalysts and alternatives must be developed. This work aims for the discovery of efficient and economic transition metal-catalyzed cross-coupling reactions to substitute palladium and further extend the scope of these C-C bond forming reactions.

Knochel et al. explored organozinc pivalates as a new class of reagents with unique characteristics.[59] It was demonstrated, that organozinc pivalates of type **71** are excellent coupling reagents using classical electrophiles such as iodides and bromides under Pd- and Co-catalysis.[60] However, the coupling of **71** with pseudohalides, such as triflates and nonaflates of type **72** leading to products of type **73** was still unexplored (Scheme 25). Thus, the first part focused on the development of a cheap and efficient catalyst system, allowing the cross-coupling of a broad range of triflates and nonaflates as electrophiles, with organozinc pivalates as coupling partners.



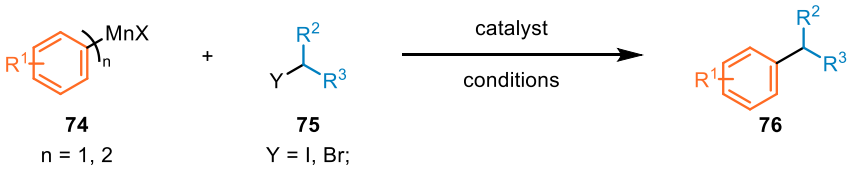
Scheme 25. Cross-coupling of organozinc pivalates 71 with triflates and nonaflates of type 72.

Cross-coupling reactions involving sp^3-carbon centers are often inaccessible for palladium-catalyzed methods, due to β-hydrogen elimination side reactions.[55] Therefore, a coupling-reaction between sp^2-sp^3-carbons, such as the arylation of secondary alkyl halides with earth abundant transition metal-catalysts would be highly favorable. Organomanganese reagents as coupling partners can be a valuable alternative to magnesium organometallics in terms of stability.[86] Additionally, manganese has a low toxicity, is highly earth-abundant and organomanganese reagents can undergo versatile

[59] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel *Angew. Chem., Int. Ed.* **2011**, *50*, 9205-9209. b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel *Angew. Chem., Int. Ed.* **2012**, *51*, 9428-9432. c)C. I. Stathakis, S. M. Manolikakes, P. Knochel *Org. Lett.* **2013**, *15*, 1302-1305. d)A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg *Angew. Chem., Int. Ed.* **2014**, *53*, 2706-2710.

[60] a) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel *Chem. - Eur. J.* **2014**, *20*, 12289-12297. b) M. Ellwart, P. Knochel *Angew. Chem., Int. Ed.* **2015**, *54*, 10662-10665. c) Y.-H. Chen, C. P. Tüllmann, M. Ellwart, P. Knochel *Angew. Chem., Int. Ed.* **2017**, *56*, 9236-9239. d) J. M. Hammann, F. H. Lutter, D. Haas, P. Knochel *Angew. Chem.* **2017**, *129*, 1102-1106. e) J. M. Hammann, L. Thomas, Y.-H. Chen, D. Haas, P. Knochel *Org. Lett.* **2017**, *19*, 3847-3850. f) M. S. Hofmayer, J. M. Hammann, F. H. Lutter, P. Knochel *Synthesis* **2017**, *49*, 3925-3930. g) Y.-H. Chen, S. Graßl, P. Knochel *Angew. Chem., Int. Ed.* **2018**, *57*, 1108-1111. h) J. Li, P. Knochel *Angew. Chem., Int. Ed.* **2018**, *57*, 11436-11440. i) L. Thomas, F. H. Lutter, M. S. Hofmayer, K. Karaghiosoff, P. Knochel *Org. Lett.* **2018**, *20*, 2441-2444. j) F. H. Lutter, L. Grokenberger, M. S. Hofmayer, P. Knochel *Chem. Sci.* **2019**, *10*, 8241-8245.

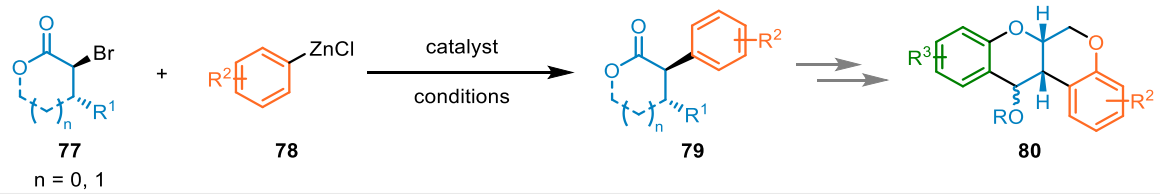
transformations.[61] Thus, the second part focused on the development of coupling reactions involving (hetero)arylmanganese reagents of type **74** with alkyl halides of type **75** leading to the arylated products **76** (Scheme 26).



74 n = 1, 2 **75** Y = I, Br; **76**

Scheme 26. Cross-coupling of organomanganese reagents 74 with alkyl halides of type 75.

The third part aimed for the development of a *trans*-diastereoselective cross-coupling of optically enriched α-bromolactones **77** with arylzinc reagents **78** (Scheme 27). This would allow the formation of optically enriched arylated products **79** as valuable building blocks for total syntheses. The synthetic utility could be demonstrated in the stereoselective preparation of a rotenoid derivative with the core structure **80**.



77 n = 0, 1 **78** **79** **80**

Scheme 27. Stereoselective cross-coupling of α-bromlactones of type 77 with arylzinc reagents 78 and the core-structure of various rotenoids 80.

[61] a) G. Cahiez, C. Duplais, J. Buendia *Chem. Rev.* **2009**, *109*, 1434-1476. b) Z. Peng, P. Knochel *Org. Lett.* **2011**, *13*, 3198-3201. c) A. D. Benischke, A. J. A. Breuillac, A. Moyeux, G. Cahiez, P. Knochel *Synlett* **2016**, *27*, 471-476. d) J. R. Carney, B. R. Dillon, S. P. Thomas *Eur. J. Org. Chem.* **2016**, 3912-3929.

B RESULTS AND DISCUSSION

1 Nickel-Catalyzed Cross-Coupling Reactions of Unsaturated Zinc Pivalates and Unsaturated Nonaflates and Triflates

1.1 Introduction

Organozinc reagents are key intermediates in organic synthesis.[62] Their main features are a high functional group tolerance, low toxicity and a moderate price.[62e] Recently the preparation of organozinc pivalates with enhanced air and moisture stability was reported.[63] These zinc species can be handled in air for several hours without appreciable decomposition.[63] Previously, it was demonstrated that organozinc pivalates are superior reagents for various cross-couplings.[63,64] Functionalized nonaflates and triflates are excellent coupling partners with numerous organometallic reagents and a broad variety of these sulfonates can easily be obtained from the corresponding alcohols and enolates.[65]

However, the nickel-catalyzed reactions of arylzinc reagents with unsaturated triflates and nonaflates lacked of generality.[66]

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[62] a) *Cross-Coupling Reactions, A Practical Guide* (Ed.: N. Miyaura), Springer, Berlin, Germany, **2002**. b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. Meijere, F. Diederich), Wiley-VCH, Weinheim, Germany, **2004**. c) *Modern Drug Synthesis* (Eds.: J. J. Li, D. S. Johnson), Wiley-VCH, Weinheim, Germany, **2010**. d) *Organotransition Metal Chemistry: From Bonding to Catalysis* (Ed.: J. F. Hartwig), University Science Books, Sausalito, CA, **2010**. e) D. Haas, J. M. Hammann, R. Greiner, P. Knochel *ACS Catal.* **2016**, *6*, 1540-1552.

[63] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel *Angew. Chem., Int. Ed.* **2011**, *50*, 9205-9209. b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel *Angew. Chem., Int. Ed.* **2012**, *51*, 9428-9432. c) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel *Org. Lett.* **2013**, *15*, 5754-5757. d) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel *Chem. - Eur. J.* **2014**, *20*, 12289-12297. e) M. Ellwart, P. Knochel *Angew. Chem., Int. Ed.* **2015**, *54*, 10662-10665. f) Y.-H. Chen, C. P. Tüllmann, M. Ellwart, P. Knochel *Angew. Chem., Int. Ed.* **2017**, *56*, 9236-9239.

[64] a) J. M. Hammann, F. H. Lutter, D. Haas, P. Knochel *Angew. Chem., Int. Ed.* **2017**, *56*, 1082-1086. b) J. M. Hammann, L. Thomas, Y.-H. Chen, D. Haas, P. Knochel *Org. Lett.* **2017**, *19*, 3847-3850. c) M. S. Hofmayer, J. M. Hammann, F. H. Lutter, P. Knochel *Synthesis* **2017**, *49*, 3925-3930. d) Y.-H. Chen, S. Graßl, P. Knochel *Angew. Chem., Int. Ed.* **2018**, *57*, 1108-1111. e) J. Li, P. Knochel *Angew. Chem., Int. Ed.* **2018**, *57*, 11436-11440. f) L. Thomas, F. H. Lutter, M. S. Hofmayer, K. Karaghiosoff, P. Knochel *Org. Lett.* **2018**, *20*, 2441-2444. g) C. P. Tüllmann, Y.-H. Chen, R. J. Schuster, P. Knochel *Org. Lett.* **2018**, *20*, 4601-4605.

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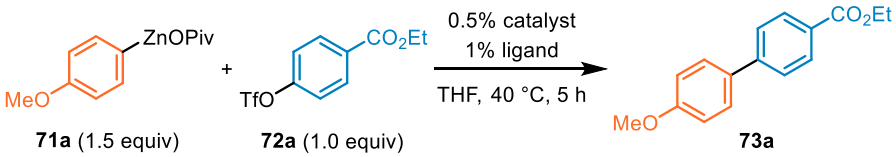
1.2 Nickel-Catalyzed Cross-Coupling Reactions of 4-Anisylzinc and (Hetero)arylzinc Pivalates with Aryl and Alkenyl Triflates and Nonaflates

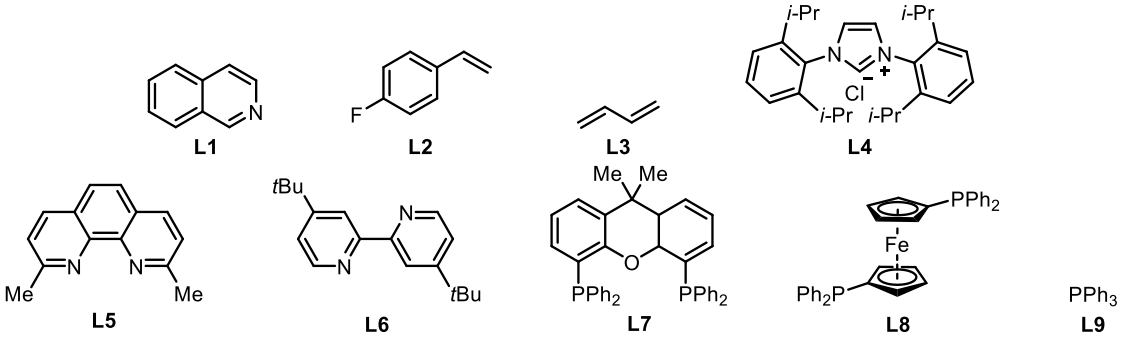
The reaction of 4-anisylzinc pivalate[67] (**71a**) with triflate **72a** was further optimized (Table 1).

Table 1. Reaction conditions optimization of the cross-coupling of arylzinc pivalate 71a with aryl triflate 72a.



71a (1.5 equiv) **72a** (1.0 equiv) **73a**

entry	catalyst	ligand	yield (%)[a]
1	-	-	0
2	$CuCl_2$	-	0
3	$CrCl_2$	-	0
4	$MnCl_2$	-	0
5	$FeCl_2$	-	3
6	$CoCl_2$	-	8
7	$NiCl_2$	-	47
8	$NiCl_2$	**L1**	20
9	$NiCl_2$	**L2**	59
10	$NiCl_2$	**L3**	4
11	$NiCl_2$	**L4**	54
12	$NiCl_2$	**L5**	35
13	$NiCl_2$	**L6**	79
14	$NiCl_2$	**L7**	36
15	$NiCl_2$	**L8**	8
16	$NiCl_2$	**L9**	90 (52)[b] (86)[c]



L1 **L2** **L3** **L4** **L5** **L6** **L7** **L8** **L9**

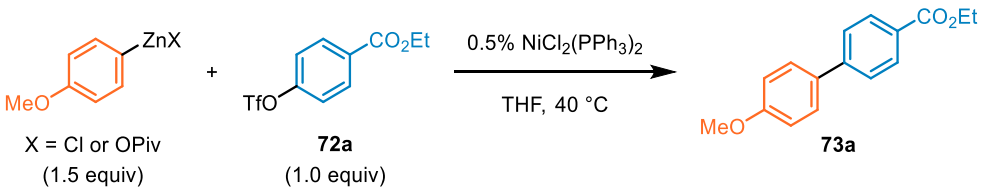
[a]Calibrated GC-yield using undecane as internal standard. [b]Using 4-anisylzinc chloride. [c]Isolated yield of analytically pure product.

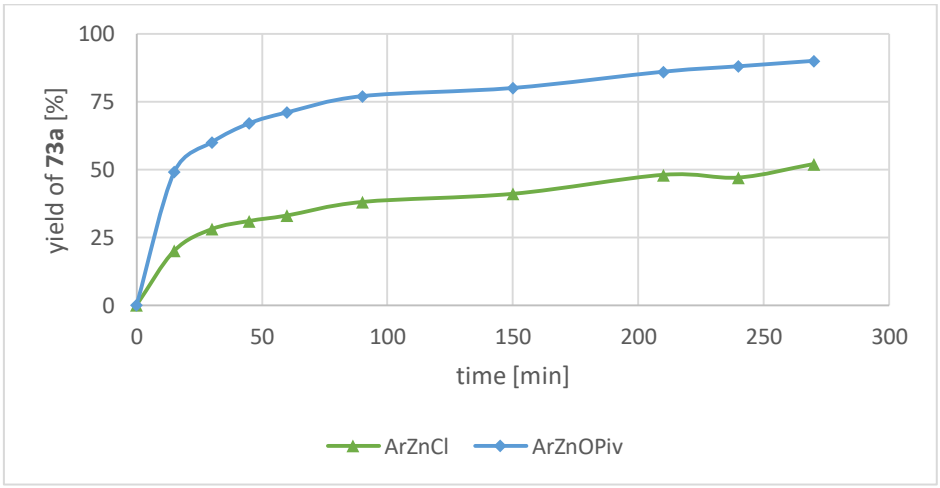
C. Kofink, G. Manolikakes, P. Knochel *Org. Lett.* **2005**, *7*, 4871-4874. h) A. Gavryushin, C. Kofink, G. Manolikakes, P. Knochel *Tetrahedron* **2006**, *62*, 7521-7533. i) L. Melzig, A. Gavryushin, P. Knochel *Org. Lett.* **2007**, *9*, 5529-5532. j) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel *J. Org. Chem.* **2008**, *73*, 7380-7382. k) G. Monzon, P. Knochel *Synlett* **2010**, 304-308. l) A. Pitchaiah, I. T. Hwang, J.-S. Hwang, H. Kim, K.-I. Lee *Synthesis* **2012**, *44*, 1631-1636. m) M. Mastalir, K. Kirchner *Monatsh. Chem.* **2017**, *148*, 105-109. n) C. A. Quesnelle, V. Snieckus *Synthesis* **2018**, *50*, 4395-4412.

[67] NMR experiments and crystallographic data showed, that the structure of these zinc reagents is $RZnX{\cdot}Mg(OPiv)_2{\cdot}LiCl$. However, for the sake of clarity, these reagents were named RZnOPiv; see: A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg *Angew. Chem., Int. Ed.* **2014**, *53*, 2706-2710.

In the absence of a transition metal catalyst, no product formation was observed. $CuCl_2$, $CrCl_2$, $MnCl_2$, $FeCl_2$ and $CoCl_2$ resulted in only poor yields, in contrast to $NiCl_2$, which afforded **73a** in 47% (entries 1-7). To increase the amount of the coupling product, various ligands were added (**L1-9**, entries 8-16).[68] The cheap and commercially available $NiCl_2(PPh_3)_2$ catalyst, led to **73a** in 86% isolated yield. Remarkably, using 4-anisylzinc chloride instead of 4-anisylzinc pivalate (**71a**), resulted in only 52% of product **73a**, showing the superior ability of organozinc pivalates to promote cross-couplings (entry 16).[64a]The variation of solvents showed, that THF was the best solvent when compared to NMP, DMPU, DME, 1,4-dioxane, *t*BuOMe, AcOEt, hexanes and toluene.

The rates of the cross-couplings using 4-anisylzinc chloride and 4-anisylzinc pivalate (**71a**) were compared in detail (Scheme 28). The yield of the product **73a** for each reaction after equal amounts of time was determined. Using the arylzinc pivalate (square data points) leads to a higher rate and a higher overall yield of product **73a**. Using the arylzinc chloride (triangular data points) instead, the reaction rate was significantly lower and led to a decreased overall yield. Longer reaction times did not improve the reaction outcome.



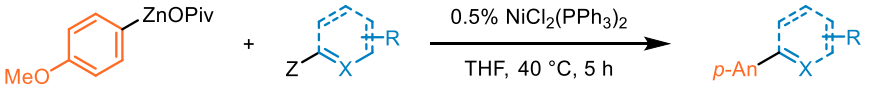


Scheme 28. Rate comparison of 4-anisylzinc chloride (triangles) versus of 4-anisylzinc pivalate 72a (squares) in the cross-coupling with aryl triflate 72a.

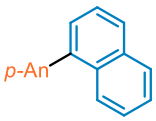
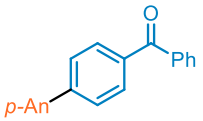
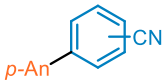
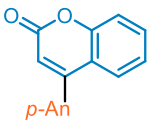
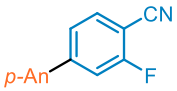
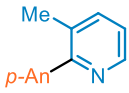
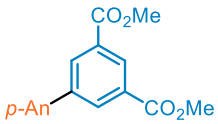
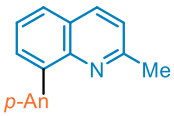
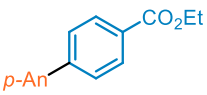
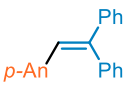
[68] a) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe *J. Am. Chem. Soc.* **2002**, *124*, 4222-4223. b) T. J. Korn, P. Knochel *Angew. Chem., Int. Ed.* **2005**, *44*, 2947-2951. c) T. Hatakeyama, S. Hashimoto, K. Ishizuka, M. Nakamura *J. Am. Chem. Soc.* **2009**, *131*, 11949-11963. d) O. M. Kuzmina, A. K. Steib, J. T. Markiewicz, D. Flubacher, P. Knochel *Angew. Chem., Int. Ed.* **2013**, *52*, 4945-4949. e) S. Z. Tasker, E. A. Standley, T. F. Jamison *Nature* **2014**, *509*, 299-309.

With these optimized conditions in hand, the electrophile scope was further examined. Therefore, 4-anisylzinc pivalate (**71a**) was coupled with various unsaturated triflates and nonaflates (Table 2).[65a,69] The reaction with 1-naphthyl triflate (**72b**) afforded biphenyl **73b** in 87% yield (entry 1). Also, *para*- and *meta*-cyano substituted aryl triflates **72c** and **72d** underwent this cross-coupling with zinc pivalate **71a**, giving **73c** and **73d** in 84% and 71% yield (entry 2). Similarly, the benzonitrile derivative **73e** was obtained in 66% yield (entry 3).

Table 2. Nickel-catalyzed cross-coupling between 4-anisylzinc pivalate (71a) and various (hetero)aryl and alkenyl triflates and nonaflates of type 72.



71a (1.5 equiv) | **72** (1.0 equiv) X = C, N; Z = OTf, ONf | **73** *p*-An = *p*-MeO-C_6H_4

entry	electrophile	product	entry	electrophile	product
1	**72b**; Z = OTf	 **73b**; 87%	6	**72h**; Z = OTf	 **73g**; 66%
2	*m*- : **72c**; Z = OTf *p*- : **72d**; Z = OTf	 *m*- : **73c**; 84% *p*- : **73d**; 71%	7	**72i**; Z = OTf	 **73h**; 95%
3	**72e**; Z = OTf	 **73e**; 66%	8	**72j**; Z = OTf	 **73i**; 87%
4	**72f**; Z = OTf	 **73f**; 87% (86%)[a] (68%)[b]	9	**72k**; Z = ONf	 **73j**; 84%
5	**72g**; Z = ONf	 **73a**; 81%	10	**72l**; Z = ONf	 **73k**; 73%

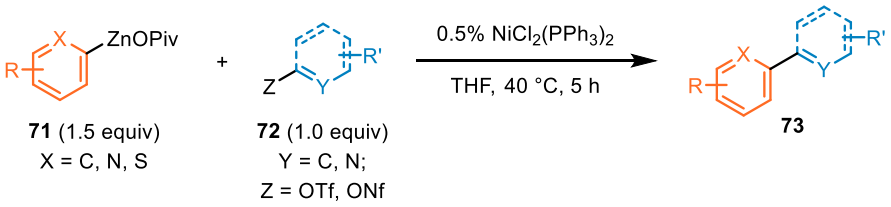
[a] Using **1a** stored as a solid under argon for 8 d. [b] Using 4-anisylzinc chloride.

[69] Triflates and nonaflates were equally efficient substrates in this nickel-catalyzed cross-coupling. These sulfonates afforded the corresponding products in high yields.

Interestingly, ester and ketone moieties were tolerated in this cross-coupling. Thus, the reaction of triflate **72f** and nonaflate **72g** with organozinc reagent **71a**, led to products **73f** and **73a** in 81-87% yield (entries 4 and 5). Using 4-anisylzinc chloride instead of the corresponding arylzinc pivalate **71a** gave **73f** in only 68% yield (entry 4). The *para*-benzophenone triflate **72h** was successfully coupled with arylzinc pivalate **71a**, leading to **73g** in 66% yield (entry 6). Coumarin derivative **73h** was readily obtained by the reaction of **71a** with the heterocyclic triflate **72i** in 95% yield (entry 7). Moreover, pyridyl and quinolyl triflates and nonaflates **72j** and **72k** proved to be good substrates for this cross-coupling. Pyridyl triflate **72j** led to the 2,3-disubstituted pyridine **73i** in 87% yield and quinolyl nonaflate **72k** furnished the quinoline derivative **73j** in 84% yield (entries 8 and 9). Additionally, alkenyl nonaflates were employed in this reaction. Therefore, nonaflate **72l** and zinc pivalate **71a** were cross-coupled, leading to **3k** in 73% yield (entry 10).

Next, the organozinc pivalate scope was examined (Table 3). The coupling of electron rich 3,4,5-trimethoxyphenylzinc pivalate (**71b**) with an electron-poor benzonitrile **72e** and ester derivative **72a** led to the biaryl compounds **73l** and **73m** in 81-85% yield (entries 1 and 2). Furthermore, benzodioxol-5-yl-zinc pivalate (**71c**) reacts with the triflates **72c** and **72j**, furnishing the biphenyls **73n** and **73o** in 85-89% yield (entries 3 and 4). Also, fluorinated arylzinc pivalates can readily be employed in this cross-coupling. Thus, 4-(trifluoromethoxy)phenylzinc pivalate (**71d**) and 4-cyano-substituted aryl triflate **72d** were successfully cross-coupled, leading to biaryl **73p** in 83% yield (entry 5). Similarly, 4-(trifluoromethyl)phenylzinc pivalate (**71e**) reacted with 4-methylquinoline-2-yl nonaflate (**72m**) and 3-cyano-substituted aryl nonaflate **72n**, affording the desired products **73q** and **73r** in 83-91% yield (entries 6 and 7). Using 4-(trifluoromethyl)phenylzinc chloride instead of the corresponding arylzinc pivalate **71e** gave **73r** in only 75% yield (entry 7). Also, the use of electron-poor arylzinc reagents was possible. Thus, 4-cyano-3-fluorophenylzinc pivalate **71f** and (*E*)-4-styrylphenyl triflate (**72o**) led to **73s** in 71% yield (entry 8). Interestingly, couplings between heterocyclic zinc pivalates and heterocyclic triflates could be performed. The coumarin derivative **73t** was obtained in 84% yield, by coupling 3-thienylzinc pivalate **71g** and triflate **72i** (entry 9). Furthermore, *N*-methyl 5-indolylzinc pivalate (**71h**) reacted with triflates **72j** and **72p**, leading to the bis-heterocyclic products **73u** and **73v** in 85-86% yield (entries 10 and 11).

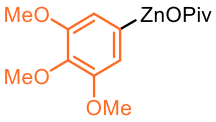
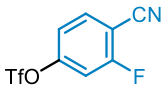
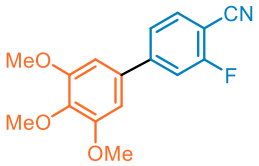
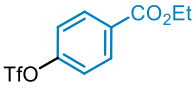
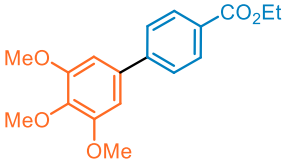
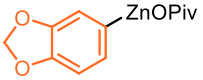
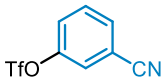
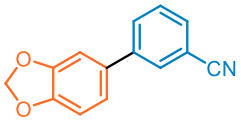
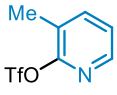
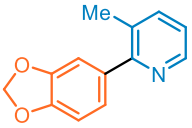
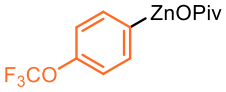
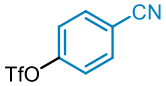
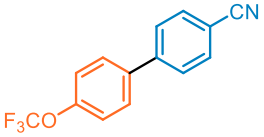
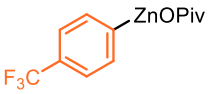
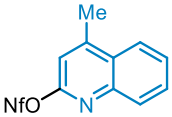
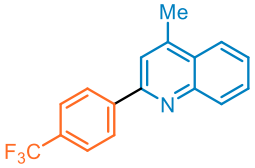
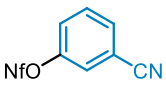
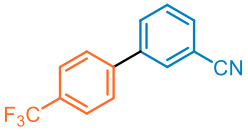
Table 3. Nickel-catalyzed cross-coupling of (hetero)arylzinc pivalates 71b-h with (hetero)aryl triflates and nonaflates of type 72.



71 (1.5 equiv)
X = C, N, S

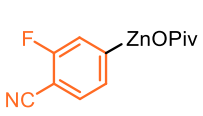
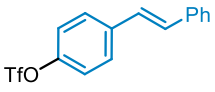
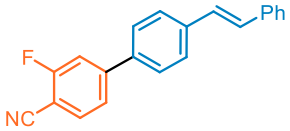
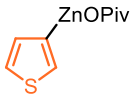
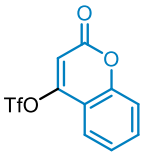
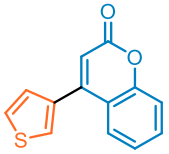
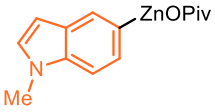
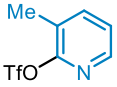
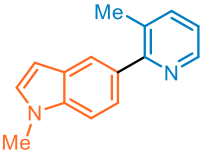
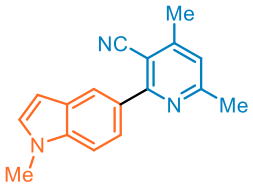
72 (1.0 equiv)
Y = C, N;
Z = OTf, ONf

73

entry	zinc reagent	electrophile	product
1	 **71b**	 **72e**	 **73l**; 85%
2	**71b**	 **72a**	 **73m**; 81%
3	 **71c**	 **72c**	 **73n**; 89%
4	**71c**	 **72j**	 **73o**; 85%
5	 **71d**	 **72d**	 **73p**; 83%
6	 **71e**	 **72m**	 **73q**; 83%
7	**71e**	 **72n**	 **73r**; 91% (75%)[a]

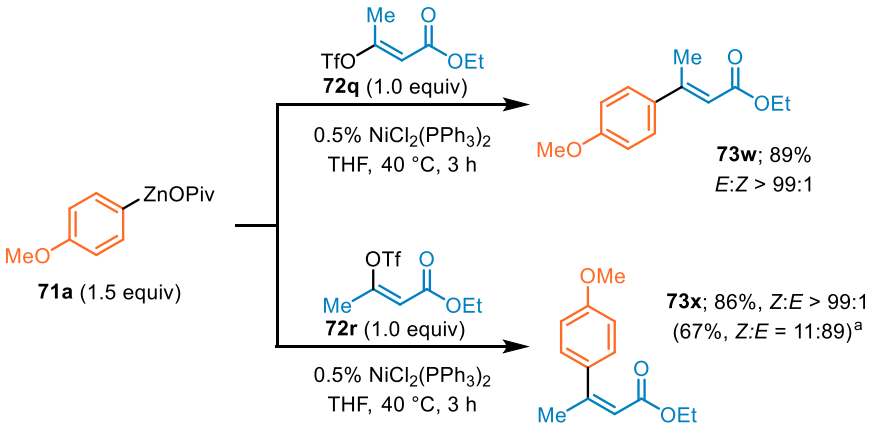
[a] Using 4-anisylzinc chloride.

Table 3. Continued.

8	 **71f**	 **72o**	 **73s**; 71%
9	 **71g**	 **72i**	 **73t**; 84%
10	 **71h**	 **72j**	 **73u**; 86%
11	**71h**	 **72p**	 **73v**; 86%

Additionally, this nickel-catalyzed cross-coupling retained the double bond configuration, using alkenyl triflates as electrophiles (Scheme 29). Thus, the (*E*)-alkenyl triflate[70] of ethyl acetoacetate **72q** underwent a stereoretentive reaction with 4-anisylzinc pivalate (**71a**), affording only *E*-alkene **73w** in 89% yield (*E*/*Z* > 99:1).[71] Similarly, the corresponding (*Z*)-triflate[70] **72r** reacted with arylzinc pivalate **71a** in 86% yield, to give the (*Z*)-acrylate **73x** in high diastereoselectivity (*Z*/*E* > 99:1).[71] Remarkably, using the corresponding organozinc chloride instead of the corresponding arylzinc pivalate **71a**, the reaction proceeds without retention of configuration, leading to the (*E*)-isomer **73w** in only 67% yield (*Z*:*E* = 11:89).

[70] D. Babinski, O. Soltani, D. E. Frantz *Org. Lett.* **2008**, *10*, 2901-2904.
[71] The (*E*)- and the (*Z*)-isomers were verified by NOE-NMR.



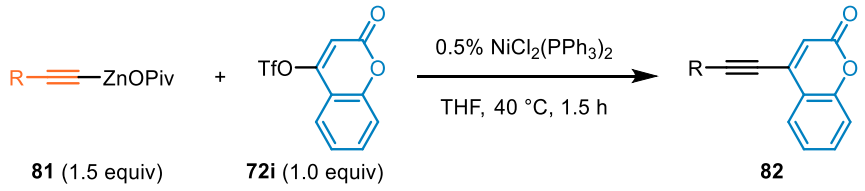
[a]Using 4-anisylzinc chloride.

Scheme 29. Stereoretentive coupling of 4-anisylzinc pivalate (71a) and the alkenyl triflates of ethyl acetoacetate 72q and 72r.

1.3 Nickel-Catalyzed Cross-Coupling Reactions of Alkynylzinc Pivalates with Aryl and Alkenyl Triflates

Remarkably, also alkynylzinc pivalates of type **81** underwent this cross-coupling (Table 4). The reaction of TIPS-ethynylzinc pivalate (**81a**) with triflate **72i** led to **82a** in 97% yield (entry 1). Using the phenyl-substituted alkynylzinc pivalate **81b**, the corresponding alkyne **82b** was obtained in 73% yield (entry 2). Also alkynylzinc pivalate **81c** was cross-coupled with **72i**, providing **82c** in 87% yield (entry 3). Finally, the reaction of (3-chlorophenyl)ethynylzinc pivalate (**81d**) with **72i** gave the desired product **82d** in 93% yield (entry 4).

Table 4. Nickel-catalyzed cross-coupling of alkynylzinc pivalates of type 81 with triflate 72i.



81 (1.5 equiv) **72i** (1.0 equiv) **82**

entry	zinc reagent	product	entry	zinc reagent	product
1	TIPS—≡—ZnOPiv **81a**	**82a**; 97%	3	—≡—ZnOPiv **81c**	**82c**; 87%
2	Ph—≡—ZnOPiv **81b**	**82b**; 73%	4	Cl—≡—ZnOPiv **81d**	**82d**; 93%

2 Cobalt-Catalyzed Cross-Coupling Reactions of Diarylmanganese Reagents with Secondary Alkyl Iodides[72]

2.1 Introduction

Palladium-catalyzed cross-couplings have widely been used.[73] However, cost[74] and toxicity[75] considerations led to the search of alternative transition metal catalysts for cross-coupling reactions. Especially cobalt-catalyzed transformations have shown their synthetic utility.[76] Pioneering work of *Oshima*,[77] *Cahiez*,[78] *Gosmini*,[79] and *Cossy*[80] demonstrated the broad field of applications of cobalt salt catalysis for forming new carbon-carbon bonds.

[72] This project was developed and published in cooperation with Jeffrey M. Hammann, see: M. S. Hofmayer, J. M. Hammann, D. Haas, P. Knochel, *Org. Lett.* **2016**, *18*, 6456 and Jeffrey M. Hammann, PhD Dissertation "Cobalt-Catalyzed Cross-Coupling Reactions" **2017**, LMU Munich.

[73] a) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. Meijere, F. Diederich), Wiley-VCH, Weinheim, Germany, **2004**. b) *Organotransition Metal Chemistry: From Bonding to Catalysis* (Ed.: J. F. Hartwig), University Science Books, Sausalito, CA, **2010**.

[74] World market prices for Pd: 51140 EUR/kg; for Co: 32 EUR/kg (retrieved Nov. 2019, http://www.infomine.com).

[75] *Handbook on the Toxicology of Metals* (Eds.: L. Friberg, G. F. Nordberg, V. B. Vouk), Elsevier, Amsterdam, **1986**.

[76] a) M. Lautens, C. M. Crudden *Organometallics* **1989**, *8*, 2733-2735. b) M. Lautens, W. Tam, C. Sood *J. Org. Chem.* **1993**, *58*, 4513-4515. c) T. Gensch, F. J. R. Klauck, F. Glorius *Angew. Chem., Int. Ed.* **2016**, *55*, 11287-11291. d) A. Lerchen, S. Vásquez-Céspedes, F. Glorius *Angew. Chem., Int. Ed.* **2016**, *55*, 3208-3211.

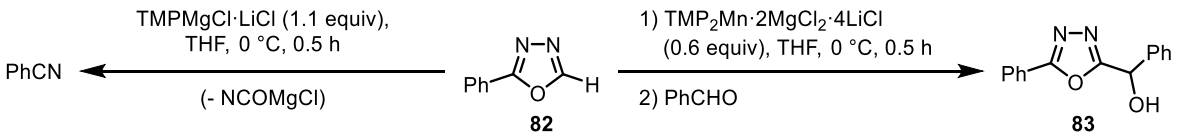
[77] a) Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima *J. Am. Chem. Soc.* **2002**, *124*, 6514-6515. b) H. Ohmiya, H. Yorimitsu, K. Oshima *J. Am. Chem. Soc.* **2006**, *128*, 1886-1889. c) H. Someya, H. Ohmiya, H. Yorimitsu, K. Oshima *Org. Lett.* **2007**, *9*, 1565-1567. d) T. Kobayashi, H. Ohmiya, H. Yorimitsu, K. Oshima *J. Am. Chem. Soc.* **2008**, *130*, 11276-11277. e) K. Murakami, H. Yorimitsu, K. Oshima *Chem. - Eur. J.* **2010**, *16*, 7688-7691.

[78] a) G. Cahiez, H. Avedissian *Tetrahedron Lett.* **1998**, *39*, 6159-6162. b) H. Avedissian, L. Bérillon, G. Cahiez, P. Knochel *Tetrahedron Lett.* **1998**, *39*, 6163-6166. c) G. Cahiez, C. Chaboche, C. Duplais, A. Giulliani, A. Moyeux *Adv. Synth. Catal.* **2008**, *350*, 1484-1488. d) G. Cahiez, C. Chaboche, C. Duplais, A. Moyeux *Org. Lett.* **2009**, *11*, 277-280.

[79] a) I. Kazmierski, M. Bastienne, C. Gosmini, J.-M. Paris, J. Périchon *J. Org. Chem.* **2004**, *69*, 936-942. b) M. Amatore, C. Gosmini, J. Périchon *Eur. J. Org. Chem.* **2005**, 989-992. c) J.-M. Bégouin, C. Gosmini *J. Org. Chem.* **2009**, *74*, 3221-3224. d) X. Qian, A. Auffrant, A. Felouat, C. Gosmini *Angew. Chem., Int. Ed.* **2011**, *50*, 10402-10405. e) A. Moncomble, P. L. Floch, A. Lledos, C. Gosmini *J. Org. Chem.* **2012**, *77*, 5056-5062. f) M. Corpet, X.-Z. Bai, C. Gosmini *Adv. Synth. Catal.* **2014**, *356*, 2937-2942. g) Y. Cai, X. Qian, C. Gosmini *Adv. Synth. Catal.* **2016**, *358*, 2427-2430. h) S. Pal, S. Chowdhury, E. Rozwadowski, A. Auffrant, C. Gosmini *Adv. Synth. Catal.* **2016**, *358*, 2431-2435.

[80] a) L. Nicolas, P. Angibaud, I. Stansfield, P. Bonnet, L. Meerpoel, S. Reymond, J. Cossy *Angew. Chem., Int. Ed.* **2012**, *51*, 11101-11104. b) L. Nicolas, E. Izquierdo, P. Angibaud, I. Stansfield, L. Meerpoel, S. Reymond, J. Cossy *J. Org. Chem.* **2013**, *78*, 11807-11814. c) B. Barré, L. Gonnard, R. Campagne, S. Reymond, J. Marin, P. Ciapetti, M. Brellier, A. Guérinot, J. Cossy *Org. Lett.* **2014**, *16*, 6160-6163. d) L. Gonnard, A. Guérinot, J. Cossy *Chem. - Eur. J.* **2015**, *21*, 12797-12803.

Ackermann[81] and *Yoshikai*[82] also used cobalt complexes for direct C-H activations of various unsaturated systems. Recently, it was reported that cobalt halides are excellent catalysts for the cross-couplings between $C(sp^3)$-$C(sp^2)$,[83] $C(sp^3)$-C(sp)[84] and $C(sp^2)$-$C(sp^2)$[85] centers using magnesium or zinc organometallics. However, these organometallic reagents are not always the best choice for performing C-C bond formations, since homo-couplings are often observed side-reactions. Also, the formation of organomagnesium species leads to the decomposition of sensitive substrates, whereas manganation procedures led to stable nucleophiles (Scheme 30).[86] Studies by *Wunderlich et al.* demonstrated, that organomanganese reagents can be a valuable alternative to magnesium organometallics (Scheme 30). Thus, the directed metalation of phenyloxadiazol **82** with TMPMgCl·LiCl only led to the decomposition of the corresponding organomagnesium intermediate. However, using $TMP_2Mn{\cdot}2MgCl{\cdot}4LiCl$ as base, the stable manganese organometallic could be successfully trapped by benzaldehyde to furnish the secondary alcohol **83**.



Scheme 30. Directed metalation of phenyloxadiazol 82 with a magnesium and manganese TMP-base.

Thus, a new cobalt-catalyzed cross-coupling between secondary alkyl iodides and diarylmanganese reagents was developed.

[81] a) J. Li, L. Ackermann *Angew. Chem., Int. Ed.* **2015**, *54*, 3635-3638. b) J. Li, L. Ackermann *Angew. Chem., Int. Ed.* **2015**, *54*, 8551-8554. c) M. Moselage, N. Sauermann, S. C. Richter, L. Ackermann *Angew. Chem., Int. Ed.* **2015**, *54*, 6352-6355. d) J. Li, M. Tang, L. Zang, X. Zhang, Z. Zhang, L. Ackermann *Org. Lett.* **2016**, *18*, 2742-2745. e) R. Mei, J. Loup, L. Ackermann *ACS Catal.* **2016**, *6*, 793-797. f) H. Wang, M. M. Lorion, L. Ackermann *Angew. Chem., Int. Ed.* **2016**, *55*, 10386-10390. g) H. Wang, M. Moselage, M. J. González, L. Ackermann *ACS Catal.* **2016**, *6*, 2705-2709. h) D. Zell, Q. Bu, M. Feldt, L. Ackermann *Angew. Chem., Int. Ed.* **2016**, *55*, 7408-7412.

[82] a) K. Gao, N. Yoshikai *J. Am. Chem. Soc.* **2011**, *133*, 400-402. b) M.-Y. Jin, N. Yoshikai *J. Org. Chem.* **2011**, *76*, 1972-1978. c) Z. Ding, N. Yoshikai *Angew. Chem., Int. Ed.* **2012**, *51*, 4698-4701. d) B.-H. Tan, J. Dong, N. Yoshikai *Angew. Chem., Int. Ed.* **2012**, *51*, 9610-9614. e) K. Gao, N. Yoshikai *J. Am. Chem. Soc.* **2013**, *135*, 9279-9282. f) B.-H. Tan, N. Yoshikai *Org. Lett.* **2014**, *16*, 3392-3395. g) J. Yang, Y. W. Seto, N. Yoshikai *ACS Catal.* **2015**, *5*, 3054-3057. h) W. Xu, N. Yoshikai *Angew. Chem., Int. Ed.* **2016**, *55*, 12731-12735. i) J. Yan, N. Yoshikai *ACS Catal.* **2016**, *6*, 3738-3742.

[83] a) J. M. Hammann, A. K. Steib, P. Knochel *Org. Lett.* **2014**, *16*, 6500-6503. b) J. M. Hammann, D. Haas, P. Knochel *Angew. Chem., Int. Ed.* **2015**, *54*, 4478-4481. c) J. M. Hammann, D. Haas, A. K. Steib, P. Knochel *Synthesis* **2015**, *47*, 1461-1468. d) A. D. Benischke, I. Knoll, A. Rérat, C. Gosmini, P. Knochel *Chem. Commun.* **2016**, *52*, 3171-3174.

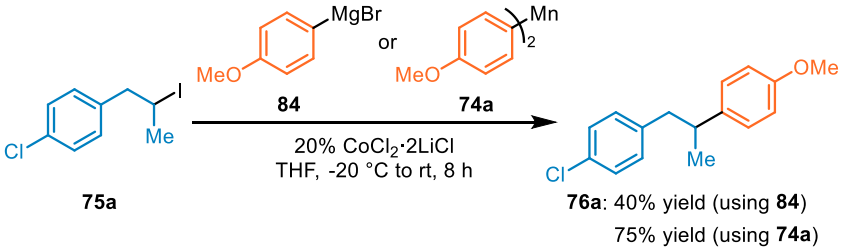
[84] J. M. Hammann, D. Haas, C.-P. Tüllmann, K. Karaghiosoff, P. Knochel *Org. Lett.* **2016**, *18*, 4778-4781.

[85] a) T. J. Korn, G. Cahiez, P. Knochel *Synlett* **2003**, 1892-1894. b) T. J. Korn, M. A. Schade, M. N. Cheemala, S. Wirth, S. A. Guevara, G. Cahiez, P. Knochel *Synthesis* **2006**, 3547-3574. c) T. J. Korn, M. A. Schade, S. Wirth, P. Knochel *Org. Lett.* **2006**, *8*, 725-728. d) A. K. Steib, O. M. Kuzmina, S. Fernandez, D. Flubacher, P. Knochel *J. Am. Chem. Soc.* **2013**, *135*, 15346-15349. e) O. M. Kuzmina, A. K. Steib, S. Fernandez, W. Boudot, J. T. Markiewicz, P. Knochel *Chem. - Eur. J.* **2015**, *21*, 8242-8249. f) D. Haas, J. M. Hammann, F. H. Lutter, P. Knochel *Angew. Chem., Int. Ed.* **2016**, *55*, 3809-3812.

[86] S. H. Wunderlich, M. Kienle, P. Knochel *Angew. Chem., Int. Ed.* **2009**, *48*, 7256-7260.

2.2 Cobalt-Catalyzed Cross-Coupling Reactions of Di(4-anisyl)manganese with Secondary Alkyl Iodides

Preliminary experiments have shown that the cross-coupling between the secondary alkyl iodide **75a** and 4-anisylmagnesium bromide (**84**) proceeds in the presence of 20 mol% $CoCl_2$·2LiCl in THF at -20 °C to 25 °C (8 h) to produce the substitution product **76a** in only 40% yield due to extensive homocoupling side reactions (Scheme 31). However, it was found that by replacing **84** with the corresponding di(4-anisyl)manganese reagent (**74a**) prepared by the transmetalation of **84** with $MnCl_2$·2LiCl[87] (0.5 equiv), the same cross-coupling now produces **76a** in 75% isolated yield (Scheme 31). Remarkably, rearrangement products (branched to unbranched) were not observed during these couplings.[88]



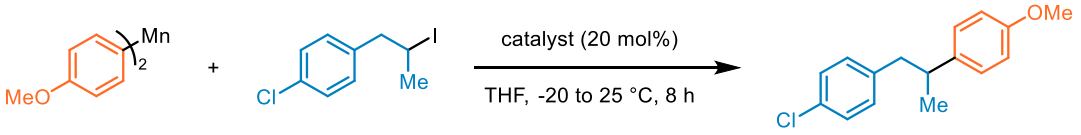
Scheme 31. Cobalt-catalyzed cross-coupling reactions of metal reagents 84 and 74a with alkyl iodide 75a.

Based on these encouraging results, the scope of this cross-coupling was further examined (Table 5). $CoCl_2$·2LiCl was the preferred catalyst since $Co(acac)_2$, $Co(acac)_3$, $CoBr_2$ and $CoCl_2$ gave inferior yields (entries 1-4). The use of 10% $CoCl_2$·2LiCl instead of 20%, reduced the yield of **76a** to 64% (compare entries 5 and 6).

[87] G. Cahiez, *Butyl Manganese Chloride and Related Reagents*, in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: L. Paquette), Wiley, Chichester **1995**; p 925.

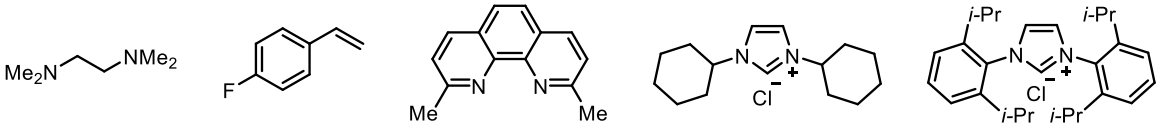
[88] a) K. Tamao, Y. Kiso, K. Sumitani, M. Kumada *J. Am. Chem. Soc.* **1972**, *94*, 9268-9269. b) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu *J. Am. Chem. Soc.* **1984**, *106*, 158-163. c) A. Joshi-Pangu, M. Ganesh, M. R. Biscoe *Org. Lett.* **2011**, *13*, 1218-1221. d) J. T. Binder, C. J. Cordier, G. C. Fu *J. Am. Chem. Soc.* **2012**, *134*, 17003-17006.

Table 5. Reaction conditions optimization of the cross-coupling of alkyl iodide 75a with the manganese reagent 74a.



74a (0.7 equiv) **75a** (1.0 equiv) **76a**

entry	catalyst	ligand[a]	yield (%)[b]
1	$Co(acac)_2$	-	54
2	$Co(acac)_3$	-	82
3	$CoBr_2$	-	73
4	$CoCl_2$	-	79
5	$CoCl_2$·2LiCl	-	83 (75)[c]
6	$CoCl_2$·2LiCl[d]	-	64
7	$CoCl_2$·2LiCl	**L1**	32
8	$CoCl_2$·2LiCl	**L2**	32
9	$CoCl_2$·2LiCl	**L3**	11
10	$CoCl_2$·2LiCl	**L4**	69
11	$CoCl_2$·2LiCl	**L5**	77
12	$PdCl_2$	-	2
13	$CuCl_2$	-	3
14	$CrCl_2$	-	3
15	$NiCl_2$	-	7
16	$FeCl_2$	-	26



L1 **L2** **L3** **L4** **L5**

[a]Using 40% of the ligand [b]Calibrated GC-yield using undecane as internal standard. [c]Isolated yield. [d]Using 10% $CoCl_2$·2LiCl.

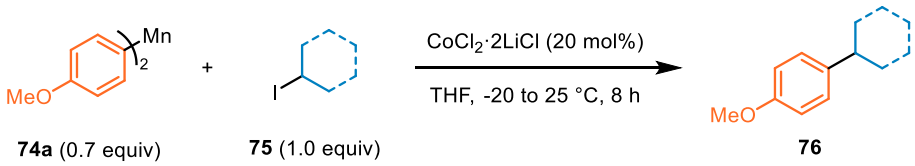
Attempts to improve the reaction outcome by adding ligands such as TMEDA (**L1**),[89] 4-fluorostyrene (**L2**),[90] or neocuproine (**L3**)[84, 91] were not successful (entries 7-9). Also, NHC-ligands **L4** or **L5** were not beneficial for the reaction (entries 10-11). Alternative transition metal salts such as $PdCl_2$, $CuCl_2$, $CrCl_2$, $NiCl_2$ or $FeCl_2$ were inefficient (entries 12-16). A solvent screening showed that THF was the best solvent when compared to NMP, DMPU, DME, 1,4-dioxane and *t*BuOMe.

[89] J. M. Hammann, A. K. Steib, P. Knochel *Org. Lett.* **2014**, *16*, 6500-6503.
[90] a) A. K. Steib, T. Thaler, K. Komeyama, P. Mayer, P. Knochel *Angew. Chem., Int. Ed.* **2011**, *50*, 3303-3307. b) L. R. Jefferies, S. P. Cook *Org. Lett.* **2014**, *16*, 2026-2029. c) L. R. Jefferies, S. R. Weber, S. P. Cook *Synlett* **2015**, *26*, 331-334.
[91] T. Thaler, L.-N. Guo, P. Mayer, P. Knochel *Angew. Chem., Int. Ed.* **2011**, *50*, 2174-2177.

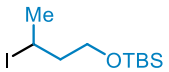
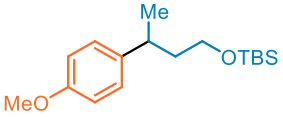
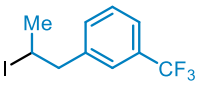
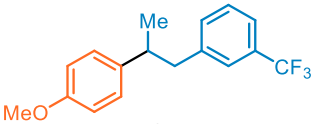
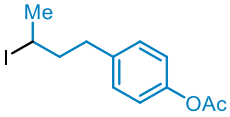
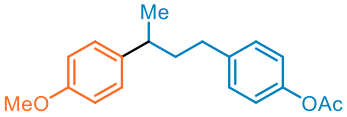
2.1 Cobalt-Catalyzed Cross-Coupling Reactions of Diarylmanganese Reagents with Secondary Alkyl Iodides

These cobalt-catalyzed alkylations proved to be general and the cross-coupling between the dianisylmanganese reagent (**74a**) and various secondary alkyl iodides has been successfully performed (Table 6).[92] Thus, various secondary alkyl iodides bearing a range of various functional groups (OTBS, CF_3, OAc; **75b-d**) reacted with the dianisylmanganese reagent (**74a**) providing the expected products **76b-d** in 73-77% yield (entries 1-3). When the diarylmanganese reagent **74a** reacted with iodide **75b** the coupling-product **76b** was obtained in only 63% yield using $CoCl_2$. In contrast, using THF soluble $CoCl_2$·2LiCl gave **76b** in 73% yield (entry 1). Also, various cyclohexyl iodides underwent the cross-coupling with **74a** yielding the desired arylated products **76e-g** in 75-84% yield. The reaction of **74a** with cyclohexyl iodide (**75e**) gave **76e** in 81% yield using $CoCl_2$ compared to 84% yield when using $CoCl_2$·2LiCl in THF (entry 4). Additionally, this cross-coupling can also be performed with cyclopentyl iodides **75h-i**, leading to the expected products **76h** and **76i** in 59-70% yield (entries 7-8). When a TBSO-substituent was present in the 2-position to the carbon-iodide bond, excellent diastereoselectivities were observed (dr up to 99:1, see entries 6 and 8).

Table 6. Cobalt-catalyzed cross-coupling reactions between various secondary alkyl iodides of type 75 and the diarylmanganese reagent 74a.



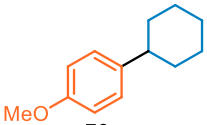
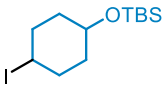
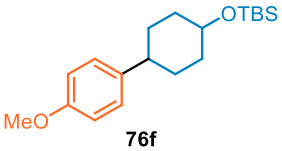
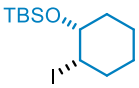
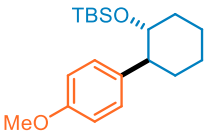
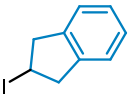
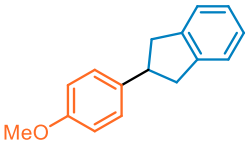
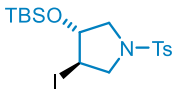
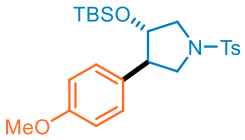
74a (0.7 equiv) **75** (1.0 equiv) **76**

entry	electrophile	product	yield
1	 **75b**	 **76b**	73% (63%)[a]
2	 **75c**	 **76c**	77%
3	 **75d**	 **76d**	75%

[a] 20% $CoCl_2$ was used instead of $CoCl_2$·2LiCl.

[92] Using primary or tertiary alkyl halides did not lead to a good conversion.

Table 6. Continued.

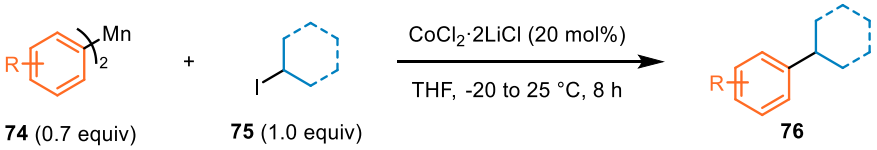
4	 **75e**	 **76e**	84% (81%)[a]
5	 **75f**	 **76f**	75%[b]
6	 **75g**	 **76g**	83%, dr = 99:1
7	 **75h**	 **76h**	70%
8	 **75i**	 **76i**	59%, dr = 95:5

[a] 20% $CoCl_2$ was used instead of $CoCl_2 \cdot 2LiCl$. [b] dr ca. 70:30.

Furthermore, a range of functionalized diarylmanganese reagents could also be readily used in this reaction (Table 7). (*p*-MOMO-$C_6H_4)_2Mn$ (**74b)** reacted smoothly with the alkyl iodides **75c** and **75j**, leading to the arylated products **76j-k** in 75-76% yield (entries 1-2). The coupling of the electron-poor manganese reagent **74c** with **75a** or **75k** afforded the cross-coupling products **76l-m** in 81-87% yield (entries 3-4). Interestingly, the manganese reagents bearing an OBoc- (**74d**) or an OTBS-group (**74e**) were well tolerated and the cross-coupling with **75h** and **75i** (dr = 99:1) led to the desired products **76n-p** in 74-92% yield (entries 5-7). Moreover, the electron-rich diarylmanganese reagent **74f** was readily coupled with the cyclic alkyl iodides **75e** and **75b** to provide the corresponding arylated products **76q-r** in 60-80% yield. Interestingly, using $CoCl_2$ as the catalyst led to dramatically decreased yields for the same reactions affording **76q** ($CoCl_2$: 48%; $CoCl_2 \cdot 2LiCl$: 80%; entry 8) and **76r** ($CoCl_2$: 19%; $CoCl_2 \cdot 2LiCl$: 60%; entry 9). The cross-coupling of **75l** or **75m** with the di(1,3-benzodioxol-5-yl)manganese reagent (**74g**) afforded the arylated compounds **76s-t** in 66-70% yield (entries 10-11). Also, the di(4-methoxy-3,5-dimethylphenyl)manganese reagent (**74h**) was successfully coupled with **75h** and **75i** (dr = 99:1), leading to the desired products **76u-v** in 63-82% yield (entries 12-13). For the diarylmanganese reagents **74e** and **74h** using the protected heterocyclic

iodohydrine **75i** (dr = 99:1) excellent diastereoselectivities were observed (dr = 99:1, entries 7, 13).

Table 7. Cobalt-catalyzed cross-couplings of diarylmanganese reagents of type 74 with secondary alkyl iodides of type 75.



74 (0.7 equiv) **75** (1.0 equiv) **76**

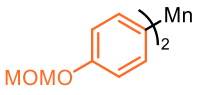
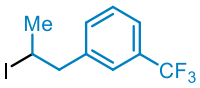
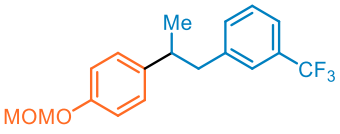
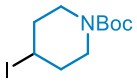
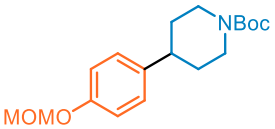
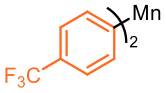
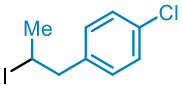
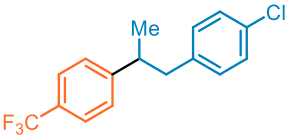
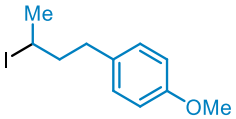
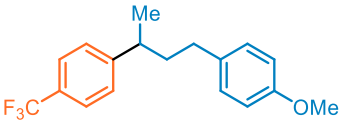
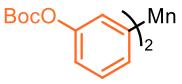
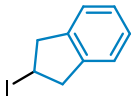
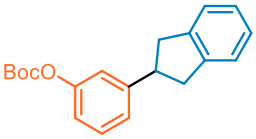
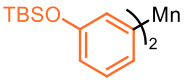
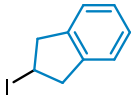
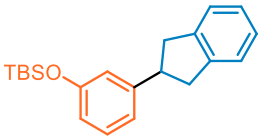
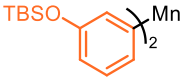
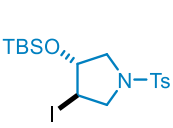
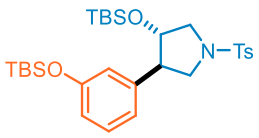
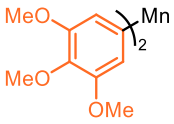
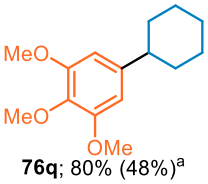
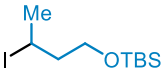
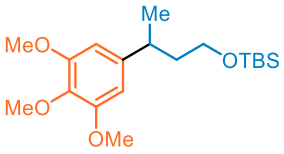
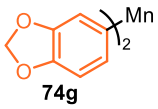
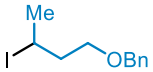
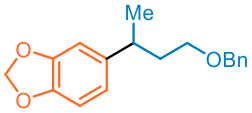
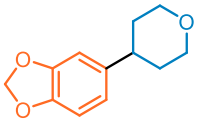
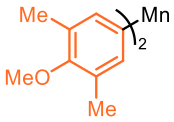
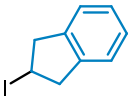
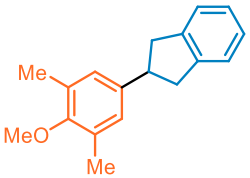
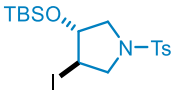
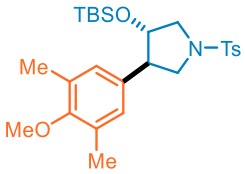
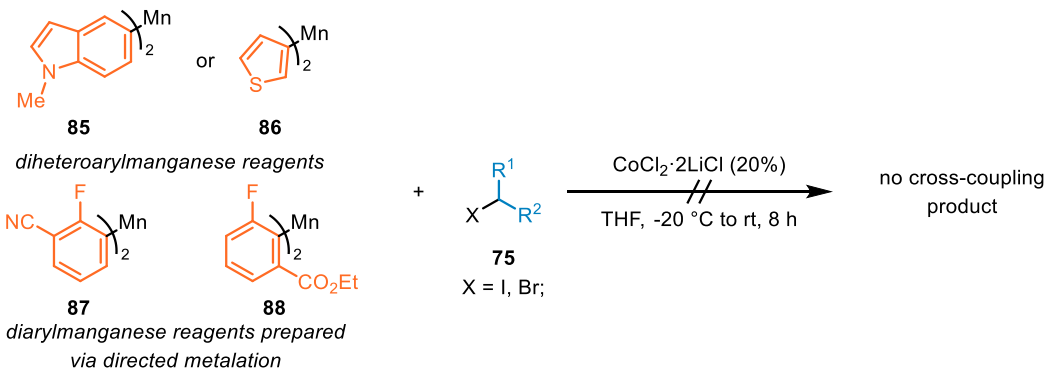
entry	manganese reagent	electrophile	product; yield
1	 **74b**	 **75c**	 **76j**; 76%
2	**74b**	 **75j**	 **76k**; 75%
3	 **74c**	 **75a**	 **76l**; 81%
4	**74c**	 **75k**	 **76m**; 81%
5	 **74d**	 **75h**	 **76n**; 76%
6	 **74e**	 **75h**	 **76o**; 74%
7	 **74h**	 **75i**	 **76p**; 92%; dr = 99:1

Table 7. Continued.

8	 **74f**	 **75e**	 **76q**; 80% (48%)[a]
9	**74f**	 **75b**	 **76r**; 60% (19%)[a]
10	 **74g**	 **75l**	 **76s**; 66%
11	**74g**	 **75m**	 **76t**; 70%
12	 **74h**	 **75h**	 **76u**; 63%
13	**74h**	 **75i**	 **76v**; 82%; dr = 99:1

[a] 20% $CoCl_2$ was used instead of $CoCl_2 \cdot 2LiCl$.

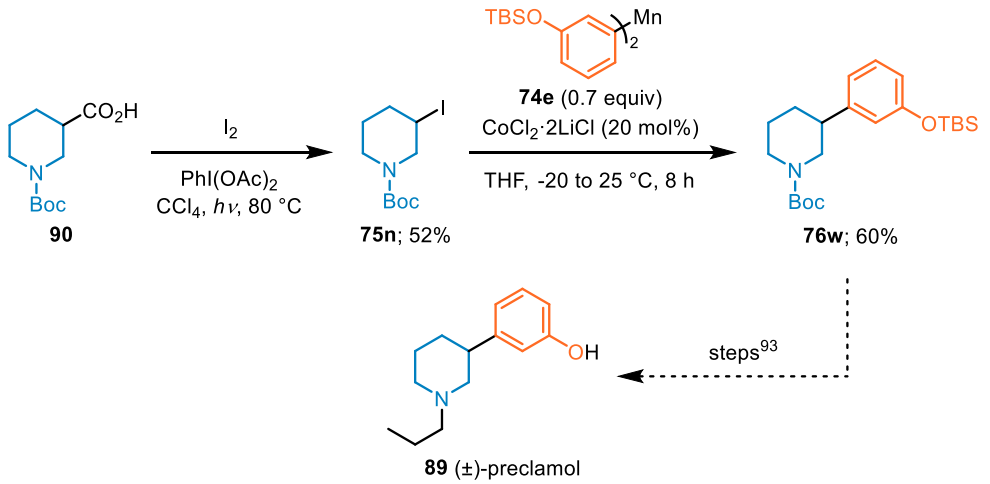
Although, the scope of this reaction is broad and tolerates a variety of functional groups, some limitations occurred (Scheme 32). Experiments using diheteroarylmanganese reagents, such as di(thiophen-3-yl)manganese (**85**) or bis(1-methyl-1*H*-indol-5-yl)manganese (**86**) were performed, but no cross-coupling product was observed. Also, the application of manganese reagents prepared *via* directed metalation, such as **87** and **88** did not lead to product formation.



Scheme 32. Limitations of this methodology.

2.2 Application in the Formal Synthesis of (±)-Preclamol

In order to demonstrate the synthetic utility of this cross-coupling, the protected iodopiperidine **75n** was prepared, which is a key intermediate for the synthesis of (±)-preclamol (**89**).[93] Thus, the commercially available carboxylic acid **90** was converted into the iodide **75n** according to the procedure of *Boto* and coworkers (Scheme 33).[80d, 94] The cobalt-catalyzed cross-coupling with the diarylmanganese reagent **74e** furnished the desired product **76w** in 60% yield.



Scheme 33. Formal synthesis of (±)-preclamol (89).

[93] Gonnard, L.; Guerinot, A.; Cossy, J. *Chem. - Eur. J.* **2015**, *21*, 12797-12803.
[94] A. Boto, R. Hernández, Y. de León, J. R. Murguía, A. Rodriguez-Afonso *Eur. J. Org. Chem.* **2005**, 673-682.

3 Iron-Catalyzed Cross-Coupling Reactions of Di(hetero)arylmanganese Reagents and Primary and Secondary Alkyl Halides

3.1 Introduction

Transition metal catalyzed cross-coupling reactions have found broad application, especially for the synthesis of agrochemicals and pharmaceuticals.[95] In the past, palladium and nickel complexes have frequently been used for such couplings. However, the high price as well as toxicity issues[96] of these catalysts led to the search for alternative transition metals for cross-coupling reactions. Especially, iron is a cheap and environmentally benign alternative for C-C-bond forming reactions, due to its high abundance in the earth's crust. Pioneering work by Fürstner,[97] Cahiez[98] as well as other research groups[99] demonstrated the high potential of iron salts as catalysts in coupling reactions.

[95] a) *Cross-Coupling Reactions, A Practical Guide* (Ed.: N. Miyaura), Springer, Berlin, Germany, **2002**. b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. Meijere, F. Diederich), Wiley-VCH, Weinheim, Germany, **2004**. c) *Modern Drug Synthesis* (Eds.: J. J. Li, D. S. Johnson), Wiley-VCH, Weinheim, Germany, **2010**. d) *Organotransition Metal Chemistry: From Bonding to Catalysis* (Ed.: J. F. Hartwig), University Science Books, Sausalito, CA, **2010**.

[96] a) $LD_{50}(FeCl_2$, rat oral) = 900 mg/kg; $LD_{50}(NiCl_2$, rat oral) = 186 mg/kg. b) K. S. Egorova, V. P. Ananikov *Angew. Chem., Int. Ed.* **2016**, *55*, 12150-12162.

[97] a) A. Fürstner, H. Brunner *Tetrahedron Lett.* **1996**, *37*, 7009-7012. b) A. Fürstner, A. Leitner *Angew. Chem., Int. Ed.* **2002**, *41*, 609-612. c) A. Fürstner, A. Leitner, M. Méndez, H. Krause *J. Am. Chem. Soc.* **2002**, *124*, 13856-13863. d) R. Martin, A. Fürstner *Angew. Chem., Int. Ed.* **2004**, *43*, 3955-3957. e) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner *J. Org. Chem.* **2004**, *69*, 3943-3949. f) B. D. Sherry, A. Fürstner *Acc. Chem. Res.* **2008**, *41*, 1500-1511. g) C.-L. Sun, H. Krause, A. Fürstner *Adv. Synth. Catal.* **2014**, *356*, 1281-1291. h) A. Casitas, H. Krause, R. Goddard, A. Fürstner *Angew. Chem., Int. Ed.* **2015**, *54*, 1521-1526. i) A. Fürstner *ACS Cent. Sci.* **2016**, *2*, 778-789.

[98] a) G. Cahiez, H. Avedissian *Synthesis* **1998**, 1199-1205. b) C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez, P. Knochel *Angew. Chem., Int. Ed.* **2004**, *43*, 2968-2970. c) G. Cahiez, C. Chaboche, F. Mahuteau-Betzer, M. Ahr *Org. Lett.* **2005**, *7*, 1943-1946. d) G. Cahiez, C. Duplais, A. Moyeux *Org. Lett.* **2007**, *9*, 3253-3254. e) G. Cahiez, V. Habiak, C. Duplais, A. Moyeux *Angew. Chem., Int. Ed.* **2007**, *46*, 4364-4366. f) G. Cahiez, A. Moyeux, J. Buendia, C. Duplais *J. Am. Chem. Soc.* **2007**, *129*, 13788-13789. g) G. Cahiez, O. Gager, V. Habiak *Synthesis* **2008**, 2636-2644. h) G. Cahiez, L. Foulgoc, A. Moyeux *Angew. Chem., Int. Ed.* **2009**, *48*, 2969-2972. i) A. D. Benischke, A. J. A. Breuillac, A. Moyeux, G. Cahiez, P. Knochel *Synlett* **2016**, *27*, 471-476.

[99] a) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura *J. Am. Chem. Soc.* **2004**, *126*, 3686-3687. b) M. Nakamura, S. Ito, K. Matsuo, E. Nakamura *Synlett* **2005**, 1794-1798. c) T. Hatakeyama, M. Nakamura *J. Am. Chem. Soc.* **2007**, *129*, 9844-9845. d) T. Hatakeyama, Y. Yoshimoto, T. Gabriel, M. Nakamura *Org. Lett.* **2008**, *10*, 5341-5344. e) S. Ito, Y.-i. Fujiwara, E. Nakamura, M. Nakamura *Org. Lett.* **2009**, *11*, 4306-4309. f) D. Noda, Y. Sunada, T. Hatakeyama, M. Nakamura, H. Nagashima *J. Am. Chem. Soc.* **2009**, *131*, 6078-6079. g) T. Hatakeyama, T. Hashimoto, Y. Kondo, Y. Fujiwara, H. Seike, H. Takaya, Y. Tamada, T. Ono, M. Nakamura *J. Am. Chem. Soc.* **2010**, *132*, 10674-10676. h) E. Nakamura, N. Yoshikai *J. Org. Chem.* **2010**, *75*, 6061-6067. i) Z.-Q. Liu, Y. Zhang, L. Zhao, Z. Li, J. Wang, H. Li, L.-M. Wu *Org. Lett.* **2011**, *13*, 2208-2211. j) O. M. Kuzmina, A. K. Steib, D. Flubacher, P. Knochel *Org. Lett.* **2012**, *14*, 4818-4821. k) Y.-Y. Lin, Y.-J. Wang, C.-H. Lin, J.-H. Cheng, C.-F. Lee *J. Org. Chem.* **2012**, *77*, 6100-6106. l) R. Shang, L. Ilies, A. Matsumoto, E. Nakamura *J. Am. Chem. Soc.* **2013**, *135*, 6030-6032. m) E. Nakamura, T. Hatakeyama, S. Ito, K. Ishizuka, L. Ilies, M. Nakamura *Org. React.* **2014**, *83*, 1-210. n) T. Agrawal, S. P. Cook *Org. Lett.* **2014**, *16*, 5080-5083. o) O. M. Kuzmina, A. K. Steib, A. Moyeux, G. Cahiez, P. Knochel *Synthesis* **2015**, *47*, 1696-1705. p) X. Shang, Z.-Q. Liu *Synthesis* **2015**, *47*, 1706-1708. q) R. Agata, T. Iwamoto, N. Nakagawa, K. Isozaki, T. Hatakeyama, H. Takaya, M. Nakamura *Synthesis* **2015**, *47*, 1733-1740. r) I. Bauer, H.-J. Knölker *Chem. Rev.* **2015**, *115*, 3170-3387. s) R. Greiner, R. Blanc, C. Petermayer, K. Karaghiosoff, P. Knochel *Synlett* **2016**, *27*, 231-236. t) J. Halli, A. E. Schneider, T. Beisel, P. Kramer, A. Shemet, G. Manolikakes *Synthesis* **2017**, *49*, 849-879. u) T. Parchomyk, K. Koszinowski *Synthesis* **2017**, *49*, 3269-3280.

However, most of these reactions use magnesium organometallics as nucleophiles, which are not always the best choice due to their high nucleophilicity. In contrast, the use of organomanganese reagents enables performing coupling reactions under mild conditions.

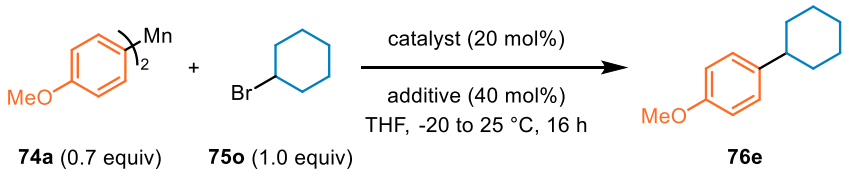
3.2 Iron-Catalyzed Cross-Coupling Reactions of the Di(4-anisyl)manganese Reagent with Alkyl Halides

It was demonstrated that cobalt(II) chloride is an excellent catalyst for the cross-coupling of diarylmanganese reagents with secondary alkyl halides.[100] However, some coupling partners including alkyl bromides as electrophiles and di(hetero)arylmanganese reagents prepared *via* directed metalation were not very efficient and gave only poor yields. Thus, the cross-coupling between cyclohexyl bromide (**75o**) and di(4-anisyl)manganese (**74a**, 0.7 equiv) using 20 mol% $CoCl_2$ gave the desired product **76e** in only 28% yield (Table 8, entry 1). In contrast, different iron salts proved to be more efficient and furnished **76e** in better yields (64-69%, entries 2-4). $FeCl_2$ gave the best results. The addition of amine- (**L1-2**), phosphine- (**L3-4**), phenanthroline- (**L5-6**) and NHC-ligands (**L7**), as well as isoquinoline (**L8**) and 4-fluorostyrene (**L9**), which were beneficial ligands in previous studies,[101] did not improve the reaction outcome (entries 5-13). Remarkably, $CrCl_2$ and $NiBr_2$ were inefficient catalysts for this reaction (entries 14-15). A solvent screening showed that THF led to the best reaction outcome compared to NMP, DME, 1,4-dioxane and *t*BuOMe. Thus, di(4-anisyl)manganese (**74a**) reacted in the presence of 20 mol% $FeCl_2$ in THF at -20 to 25 °C (16 h) to produce the substitution product **76e** in 69% yield (entry 4).

[100] M. S. Hofmayer, J. M. Hammann, D. Haas, P. Knochel *Org. Lett.* **2016**, *18*, 6456-6459.

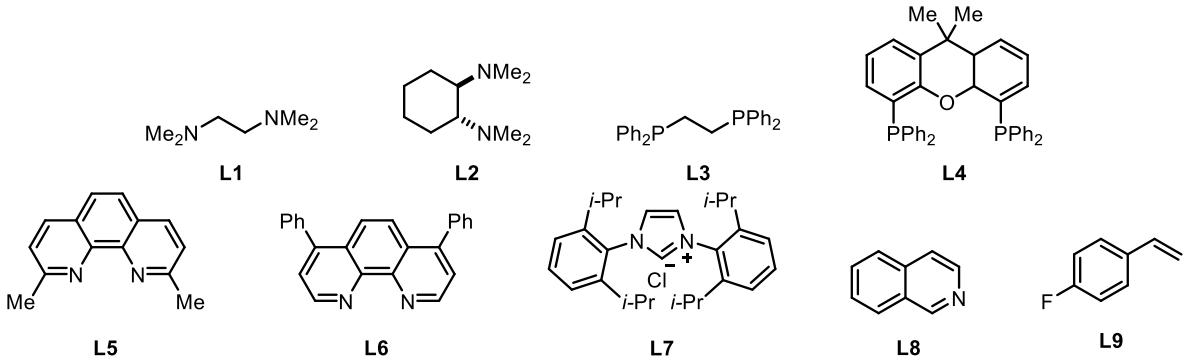
[101] a) T. J. Korn, P. Knochel *Angew. Chem., Int. Ed.* **2005**, *44*, 2947-2951. b) T. J. Korn, M. A. Schade, M. N. Cheemala, S. Wirth, S. A. Guevara, G. Cahiez, P. Knochel *Synthesis* **2006**, 3547-3574. c) T. J. Korn, M. A. Schade, S. Wirth, P. Knochel *Org. Lett.* **2006**, *8*, 725-728. d) S. H. Wunderlich, P. Knochel *Angew. Chem., Int. Ed.* **2009**, *48*, 9717-9720. e) A. K. Steib, T. Thaler, K. Komeyama, P. Mayer, P. Knochel *Angew. Chem., Int. Ed.* **2011**, *50*, 3303-3307. f) O. M. Kuzmina, A. K. Steib, J. T. Markiewicz, D. Flubacher, P. Knochel *Angew. Chem., Int. Ed.* **2013**, *52*, 4945-4949. g) O. M. Kuzmina, A. K. Steib, S. Fernandez, W. Boudot, J. T. Markiewicz, P. Knochel *Chem. - Eur. J.* **2015**, *21*, 8242-8249. h) A. D. Benischke, I. Knoll, A. Rérat, C. Gosmini, P. Knochel *Chem. Commun.* **2016**, *52*, 3171-3174.

Table 8. Reaction conditions optimization of the cross coupling of bromocyclohexane (75o) with the di(4-anisyl)manganese reagent (74a).



74a (0.7 equiv) **75o** (1.0 equiv) **76e**

entry	catalyst	ligand	yield (%)[a]
1	$CoCl_2$	-	28
2	$Fe(acac)_2$	-	64
3	$Fe(acac)_3$	-	66
4	$FeCl_2$	-	69 (63[b])
5	$FeCl_2$	**L1**	64
6	$FeCl_2$	**L2**	56
7	$FeCl_2$	**L3**	66
8	$FeCl_2$	**L4**	62
9	$FeCl_2$	**L5**	62
10	$FeCl_2$	**L6**	63
11	$FeCl_2$	**L7**	58
12	$FeCl_2$	**L8**	56
13	$FeCl_2$	**L9**	54
14	$CrCl_2$	-	0
15	$NiBr_2$	-	5

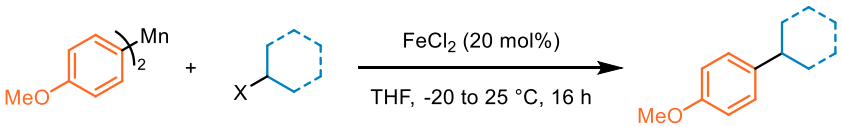


[a]Calibrated GC yield using undecane as internal standard. [b]Isolated yield.

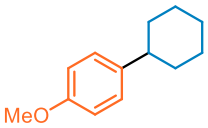
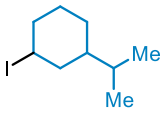
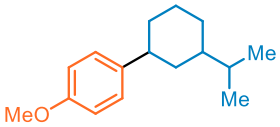
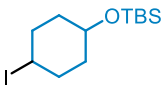
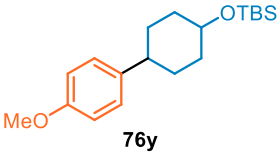
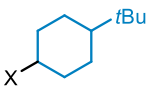
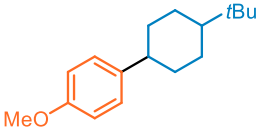
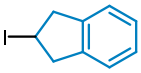
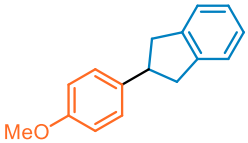
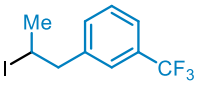
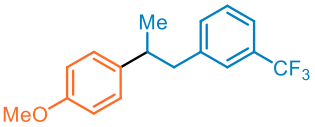
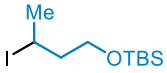
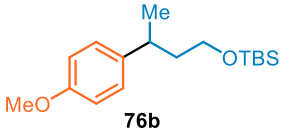
These optimized conditions proved to be general and the cross-couplings of di(4-anisyl)manganese (**74a**) with various primary and secondary alkyl halides of type **75** were successfully performed (Table 9). Thus, a range of cycloalkyl halides were readily employed in this reaction. Cyclohexyl chloride (**75p**), bromide (**75o**) and iodide (**75e**) underwent the cross-coupling with **74a** to afford the desired product **76e** in 32-73% yield (entry 1). The secondary bromides and iodides **75q**, **75f**, **75r-s**, and **76h** bearing an *i*Pr-, OTBS- or a *tert*-butyl-group were also tolerated, leading to the substitution products **76x-z** and **76h** in 43-88% yield (entries 2-5). Furthermore, the functionalized acyclic secondary alkyl iodides **75b-c** and **75t** bearing a CF_3, OTBS or a fluoro substituent, proved to be good substrates, affording the alkylated products **76b-c** and **76aa** in 44-58% yield (entries 6-8). Interestingly, no rearrangement of

branched secondary alkyl groups to the corresponding unbranched secondary alkyl moiety was observed. Additionally, the primary alkyl iodide (3-iodopropyl)benzene (**75u**) coupled smoothly, affording **76ab** in 46% yield (entry 9).

Table 9. Iron-catalyzed cross-coupling reactions between various alkyl halides of type 75 and the diarylmanganese 74a.

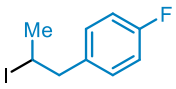
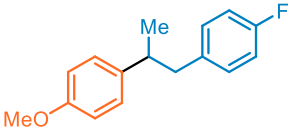
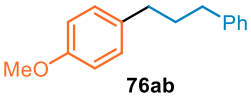


74a (0.7 equiv) **75** (1.0 equiv) X = Cl, Br, I **76**

entry	electrophile	product	yield (starting halide)
1	 **75e,o,p**	 **76e**	32%[a] (**75p**, X = Cl) 63% (**75o**, X = Br) 73% (**75e**, X = I)
2	 **75q**	 **76x**	51%[b]
3	 **75f**	 **76y**	66%[c]
4	 **75r-s**	 **76z**	43%[d] (**75r**, X = Br) 70%[e] (**75s**, X = I)
5	 **75h**	 **76h**	88%
6	 **75c**	 **76c**	52%
7	 **75b**	 **76b**	44%

[a] Calibrated GC yield using undecane as internal standard. [b] Electrophile: *cis*:*trans* ratio: 99:1; product: *cis*:*trans* ratio: 83:17. [c] Electrophile: *cis*:*trans* ratio: 99:1; product: *cis*:*trans* ratio: 75:25. [d] Electrophile: *cis*:*trans* ratio: 75:25; product: *cis*:*trans* ratio: 98:2. [e] Electrophile: *cis*:*trans* ratio: 99:1; product: *cis*:*trans* ratio: 60:40.

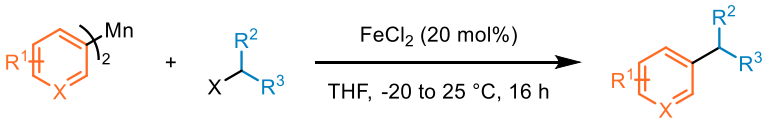
Table 9. Continued.

8	 **75t**	 **76aa**	58%
9	 **75u**	 **76ab**	46%

3.3 Iron-Catalyzed Cross-Coupling Reactions of Di(hetero)arylmanganese Reagents with Alkyl Halides

Furthermore, a range of functionalized diarylmanganese reagents could also be used in this reaction (Table 10). (*p*-MOMO-C_6H_4)$_2$Mn (**74b**) reacted smoothly with the alkyl iodides **75c** and **75j**, leading to the expected products **76j-k** in 46-62% yield (entries 1-2). Interestingly, the diarylmanganese **74d** bearing an OBoc-group was cross-coupled with **75h**, leading to the desired product **76n** in 56% yield (entry 3). The coupling of the electron-poor diarylmanganese **74i** and **74c** with the alkyl halides **75a** and **75k** afforded the cross-coupling products **76ac**, **76ad**, and **76m** in 48-78% yield (entries 4-6).

Table 10. Iron-catalyzed cross-couplings of di(hetero)arylmanganese reagents of type 74 with secondary alkyl bromides and iodides of type 75.



74 (0.7 equiv)
Y = C, N, S

75 (1.0 equiv)
X = Br, I

76

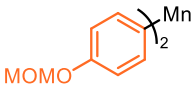
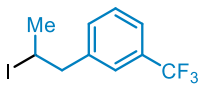
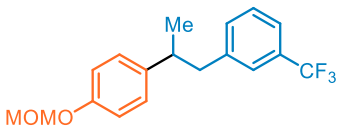
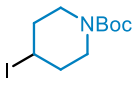
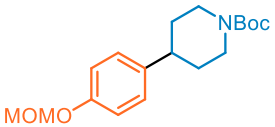
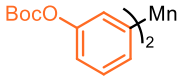
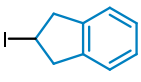
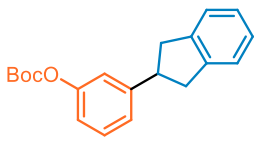
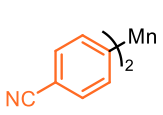
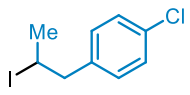
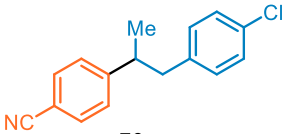
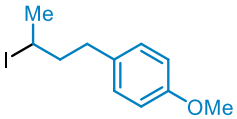
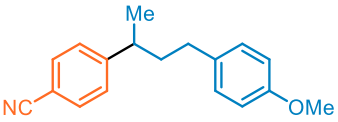
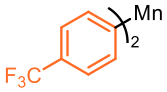
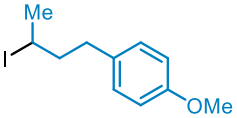
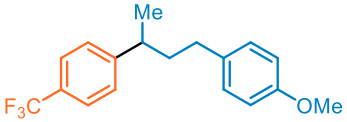
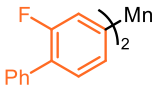
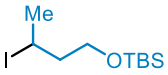
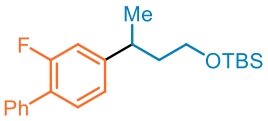
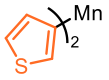
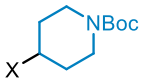
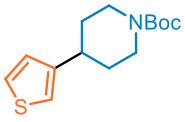
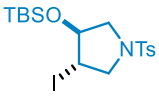
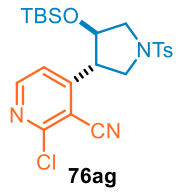
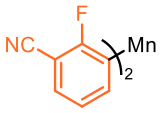
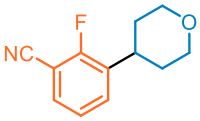
entry	manganese reagent	electrophile	product	yield
1	 **74b**	 **75c**	 **76j**	46%
2	**74b**	 **75j**	 **76k**	62%
3	 **74d**	 **75h**	 **76n**	56%

Table 10. Continued.

4	 **74i**	 **75a**	 **76ac**	57%
5	**74i**	 **75k**	 **76ad**	48%
6	 **74c**	 **75k**	 **76m**	78%
7	 **74j**	 **75b**	 **76ae**	80%
8	 **74k**	 **75v** (X = Br) **75j** (X = I)	 **76af**	82% (using **75v**) 87% (using **75j**)
9	 **74l**	 **75i** (dr = 99:1)	 **76ag**	46% (dr = 99:1)
10	 **74m**	 **75m**	 **76ah**	86%

Also, the diarylmanganese **74j** was successfully coupled with the secondary alkyl iodide **75b**, to give the desired product **76ae** in 80% yield (entry 7). Additionally, heterocyclic diarylmanganese reagents were compatible under these conditions, leading to the expected heterocycles in good yields. Thus, di-(thiophene-3-yl)manganese **74k** coupled smoothly with **75v** or **75j** providing the alkylated thiophene **76af** in 82-87% yield (entry 8). Moreover, diarylmanganese reagents generated *via* directed manganation using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$[86] (0.7 equiv) could also be readily employed. Thus, **74l-m** were cross-coupled with **75i** and **75m**, leading to the corresponding products **76ag** and **76ah** in 46-86% yield (entries 9-10). For the coupling with alkyl iodide **75i** an excellent diastereoselectivity was observed (dr = 99:1).

4 Stereoselective Cobalt-Catalyzed Cross-Coupling Reactions of Arylzinc Chlorides with α-Bromolactones and Related Derivatives[102]

4.1 Introduction

The preparation of chiral agrochemicals and pharmaceuticals requires general and efficient asymmetric syntheses.[103] Recently, several advances involving Pd- and Ni-catalyzed asymmetric carbon-carbon bond formations have been reported.[104] These transition metal-catalyzed asymmetric cross-couplings involve expensive[105] or toxic[106] Ni- or Pd-catalysts. Also, reactions involving alkyl-palladium intermediates are often of limited scope due to β-hydrogen elimination side reactions.[55] It was shown that relatively inexpensive and less toxic $CoCl_2$ can efficiently catalyze cross-couplings.[107] Also, organozinc compounds are excellent nucleophilic reagents for various Co-catalyzed

[102] This project was developed in cooperation with Alisa S. Sunagatullina, see: Alisa S. Sunagatullina, PhD Dissertation, LMU Munich.

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[105] World market prices for Pd: 51140 EUR/kg; for Co: 32 EUR/kg (retrieved Nov. 2019, http://www.infomine.com).

[106] a) *Handbook on the Toxicology of Metals*; Friberg, L.; Nordberg, G. F.; Vouk, V. B., Eds. Elsevier: Amsterdam, 1986; b) Egorova, K. S.; Ananikov, V. P. *Angew. Chem., Int. Ed.* **2016,** *55*, 12150-12162.

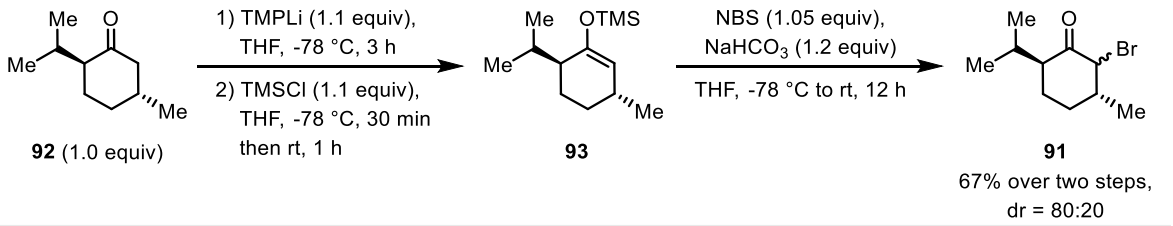
[107] a) Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *Synlett* **2009**, 2931-2934; b) Gülak, S.; Stepanek, O.; Malberg, J.; Rad, B. R.; Kotora, M.; Wolf, R.; Jacobi von Wangelin, A. *Chem. Sci.* **2013,** *4*, 776-784; c) Mao, J.; Liu, F.; Wang, M.; Wu, L.; Zheng, B.; Liu, S.; Zhong, J.; Bian, Q.; Walsh, P. J. *J. Am. Chem. Soc.* **2014,** *136*, 17662-17668; d) Liu, F.; Bian, Q.; Mao, J.; Gao, Z.; Liu, D.; Liu, S.; Wang, X.; Wang, Y.; Wang, M.; Zhong, J. *Tetrahedron: Asymmetry* **2016,** *27*, 663-669; e) Rérat, A.; Michon, C.; Agbossou-Niedercorn, F.; Gosmini, C. *Eur. J. Org. Chem.* **2016,** *2016*, 4554-4560; f) Barde, E.; Guérinot, A.; Cossy, J. *Org. Lett.* **2017,** *19*, 6068-6071; g) Liu, F.; Zhong, J.; Zhou, Y.; Gao, Z.; Walsh, P. J.; Wang, X.; Ma, S.; Hou, S.; Liu, S.; Wang, M.; Wang, M.; Bian, Q. *Chem. - Eur. J.* **2018,** *24*, 2059-2064; h) Thomas, L.; Lutter, F. H.; Hofmayer, M. S.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* **2018,** *20*, 2441-2444; i) Linke, S.; Manolikakès, S. M.; Auffrant, A.; Gosmini, C. *Synthesis* **2018,** *50*, 2595-2600; j) Lutter, F. H.; Graßl, S.; Grokenberger, L.; Hofmayer, M. S.; Chen, Y.-H.; Knochel, P. *ChemCatChem* **2019,** *11*, 5188-5197; k) Sun, X.; Wang, X.; Liu, F.; Gao, Z.; Bian, Q.; Wang, M.; Zhong, J. *Chirality* **2019,** *31*, 682-687; l) Dorval, C.; Dubois, E.; Bourne-Branchu, Y.; Gosmini, C.; Danoun, G. *Adv. Synth. Catal.* **2019,** *361*, 1777-1780; m) Koch, V.; Lorion, M. M.; Barde, E.; Bräse, S.; Cossy, J. *Org. Lett.* **2019,** *21*, 6241-6244; n) Song, T.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2019,** *21*, 603-607.

cross-coupling reactions, as a broad range of sensitive functional groups are tolerated in these organometallics.[108]

Previous experiments demonstrated, that the coupling of organozinc species with cyclic secondary alkyl halides with a substituent in the 2-position can be performed with high *trans*-diastereoselectivity under cobalt-catalysis.[109] Thus, a cross coupling of enantiomerically enriched β-substituted α-bromocarbonyl compounds could lead to the chiral arylation products after a Co-catalyzed cross-coupling with organozinc species.

4.2 Development of Starting Materials

As a starting point the brominated menthone derivative **91** was prepared (Scheme 34).[110] *L*-Menthone (**92**) was deprotonated by TMPLi and trapping with TMSCl gave the silyl enol ether **93**. Subsequent bromination with NBS afforded α-bromo-*L*-menthone **91** in 67% overall yield (dr = 80:20).



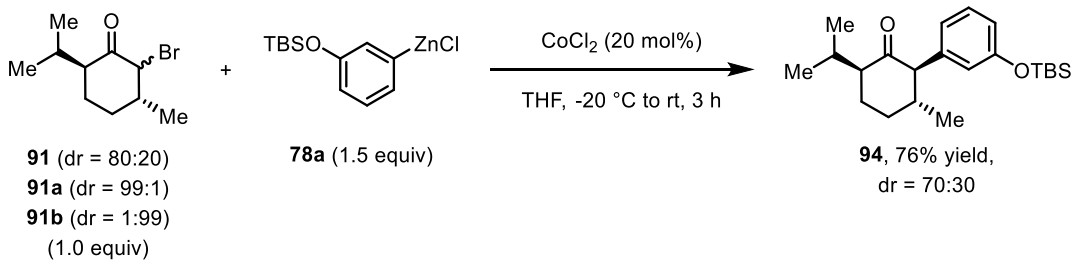
Scheme 34. Synthesis of α-bromo-*L*-menthone 91.

[108] a) Hammann, J. M.; Haas, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2015,** *54*, 4478-4481; b) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. *ACS Catal.* **2016,** *6*, 1540-1552; c) Haas, D.; Hammann, J. M.; Lutter, F. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2016,** *55*, 3809-3812; d) Hammann, J. M.; Hofmayer, M. S.; Lutter, F. H.; Thomas, L.; Knochel, P. *Synthesis* **2017,** *49*, 3887-3894; e) Hammann, J. M.; Lutter, F. H.; Haas, D.; Knochel, P. *Angew. Chem.* **2017,** *129*, 1102-1106; f) Hammann, J. M.; Thomas, L.; Chen, Y.-H.; Haas, D.; Knochel, P. *Org. Lett.* **2017,** *19*, 3847-3850; g) Hofmayer, M. S.; Hammann, J. M.; Lutter, F. H.; Knochel, P. *Synthesis* **2017,** *49*, 3925-3930; h) Li, J.; Knochel, P. *Angew. Chem., Int. Ed.* **2018,** *57*, 11436-11440; i) Balkenhohl, M.; Ziegler, D. S.; Desaintjean, A.; Bole, L. J.; Kennedy, A. R.; Hevia, E.; Knochel, P. *Angew. Chem., Int. Ed.* **2019,** *58*, 12898-12902; j) Graßl, S.; Hamze, C.; Koller, T. J.; Knochel, P. *Chem. - Eur. J.* **2019,** *25*, 3752-3755; k) Lutter, F. H.; Grokenberger, L.; Hofmayer, M. S.; Knochel, P. *Chem. Sci.* **2019,** *10*, 8241-8245; l) Lutter, F. H.; Hofmayer, M. S.; Hammann, J. M.; Malakhov, V.; Knochel, P., Generation and Trapping of Functionalized Aryl- and Heteroarylmagnesium and -Zinc Compounds. in *Organic Reactions*, Denmark, S. E., Ed. 2019; Vol. 100, pp 63-120.

[109] a) J. M. Hammann, D. Haas, P. Knochel *Angew. Chem., Int. Ed.* **2015**, *54*, 4478-4481. b) L. Thomas, F. H. Lutter, M. S. Hofmayer, K. Karaghiosoff, P. Knochel *Org. Lett.* **2018**, *20*, 2441-2444.

[110] Harrowven, D. C.; Pascoe, D. D.; Guy, I. L. *Angew. Chem., Int. Ed.* **2007,** *46*, 425-428.

Preliminary cross-coupling experiments were performed with the α-bromoketone **91** (Scheme 35).

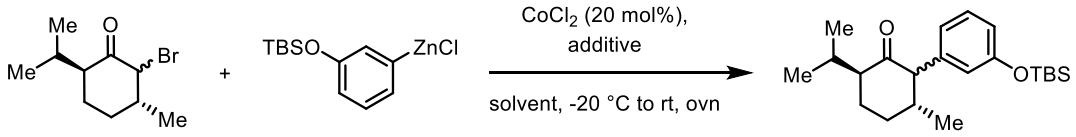


Scheme 35. Cobalt-catalyzed cross-coupling of arylzinc reagent 78a and the diastereomers of bromomenthone 91.

The TBSO-substituted arylzinc chloride **78a** and the menthone derivative **91** (dr = 80:20) led to the desired product **94** with 20% $CoCl_2$ in 76% yield (dr = 70:30). To determine the dependency of the reaction outcome on the diastereomeric ratio of the starting material, the pure diastereomers **91a** and **91b** were subjected to the cross-coupling separately. In each case, the product **94** was formed in the same diastereomeric ratio of 70:30. A ligand and solvent screening was performed to improve the stereoselectivity of this reaction (Table 11). Using *N,N,N',N'*-cyclohexyl-1,2-diamine (**L1**), the bisoxazoline ligand **L2**, and the NHC-ligand **L3** did not lead to significant enhancements of the diastereomeric ratio for product **94** (entries 1-3). In contrast, 40 mol% of triphenylphosphine (**L4**) afforded **94** in 83% yield and a diastereomeric ratio of 85:15 (entry 4). Interestingly, reducing the amount of PPh_3 to 20 mol% led to similar results (entry 5).

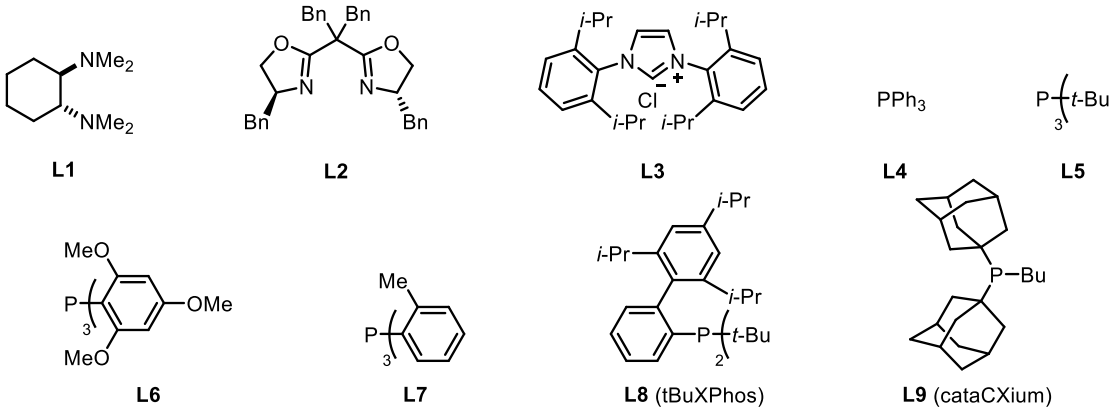
Various trialkyl- or triarylphosphines, such as **L5-9** as additives gave the arylated menthone **94** in decreased yields or decreased diastereomeric purity (entries 6-10). Also, changing the solvent system from THF (entry 5) to acetonitrile, toluene, dioxane, MTBE, NMP, and EtOAc did not improve the reaction outcome (entries 11-16).

Table 11. Additive and solvent screening for the cross-coupling of arylzinc reagent 78a and the bromomenthone 91.



91 (dr = 80:20) (1.0 equiv) | **78a** (1.5 equiv) | **94**

entry	additive	solvent	yield[a]	dr
1	**L1** (20 mol%)	THF	60%	70:30
2	**L2** (20 mol%)	"	77%	75:25
3	**L3** (20 mol%)	"	76%	71:29
4	**L4** (40 mol%)	"	83%	85:15
5	**L4** (20 mol%)	"	82%	85:15
6	**L5** (40 mol%)	"	67%	69:31
7	**L6** (40 mol%)	"	27%	65:35
8	**L7** (40 mol%)	"	85%	72:28
9	**L8** (40 mol%)	"	73%	72:28
10	**L9** (40 mol%)	"	52%	68:32
11	**L4** (20 mol%)	MeCN	48%	74:26
12	"	toluene	80%	76:24
13	"	dioxane	81%	77:23
14	"	tBuOMe	79%	79:21
15	"	NMP	20%	84:16
16	"	EtOAc	79%	79:21



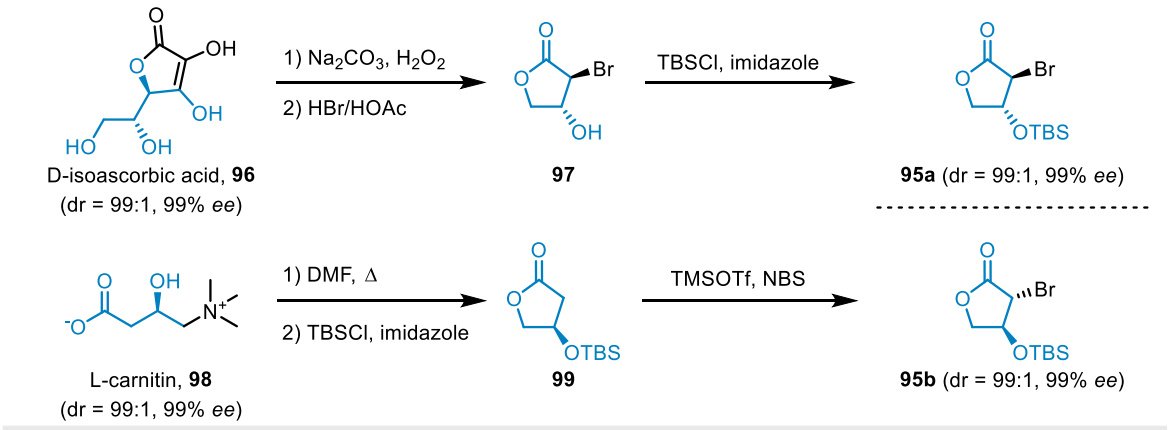
L1 **L2** **L3** **L4** **L5**

L6 **L7** **L8** (tBuXPhos) **L9** (cataCXium)

[a]Calibrated GC yield using undecane as internal standard.

In order to identify starting materials, which afford diastereomerically pure arylation products, two strategies were pursued. First, reducing the conformational degrees of freedom of the starting material possibly forces the selectivity towards one diastereomer in the arylation step. Second, attaching a more bulky group in the β-position, leads to higher steric hindrance and possibly forces the aryl moiety towards the *trans*-isomer. Therefore, a five-membered lactone with a TBSO-substituent in β-position was prepared. The synthesis of α-bromolactone **95a** starts from

D-isoascorbic acid (**96**) as low-cost commercially available precursor (Scheme 36).[111] Deprotonation and oxidation,[112] followed by bromination[113] leads to the α-bromo-β-hydroxylactone **97**. Subsequent TBS protection affords the (3*S*,4*R*)-enantiomer **95a** diastereomerically and enantiomerically pure. The second enantiomer **95b** was synthesized by thermal cyclization of the zwitterion L-carnitine (**98**), followed by TBS-protection affording the intermediate **99**. Selective bromination in α-position led to the desired (3*R*,4*S*)-enantiomer **95b**.



Scheme 36. Synthesis of α-bromolactones 95a-b starting from D-isoascorbic acid (96) and L-carnitine (98).

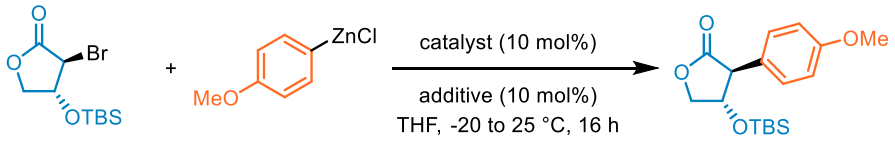
4.3 Stereoselective Cobalt-Catalyzed Cross-Coupling Reactions of Arylzinc Reagents with α-Bromolactones

The chiral α-bromolactone **95a** was then submitted to an arylation using 4-anisylzinc chloride (**78b**). The formation of product **100a** was optimized using various metallic salts (Table 12). Whereas $CuCl_2$, $CrCl_2$, $MnCl_2$, and $FeCl_2$ were not effective catalysts (entries 1-5), $CoCl_2$ gave excellent results compared to $CoBr_2$ or $Co(acac)_2$ (entries 6-8). The addition of a ligand, such as PPh_3 allowed to further improve the yield (entries 9-12).

[111] 5 kg can be purchased for 170 € at Sigma Aldrich (September 2019)
[112] a) N. Cohen, B. L. Banner, A. J. Laurenzano, L. Carozza *Org. Synth.* **1985**, *63*, 127. b) L. L. Wong, R. L. Wong, G. Loh, P. E. W. Tan, S. K. Teoh, S. M. Shaik, P. N. Sharratt, W. Chew, S. T. Tan, D. Wang *Org. Process Res. Dev.* **2012**, *16*, 1003-1012. c) S. R. Borkar, N. Bokolia, I. S. Aidhen, I. A. Khan *Tetrahedron: Asymmetry* **2017**, *28*, 186-195.
[113] a) M. Bols, I. Lundt *Acta Chem. Scand. Ser. B* **1988**, *42*, 67-74. b) C. Falentin, D. Beaupère, G. Demailly, I. Stasik *Tetrahedron* **2008**, *64*, 9989-9991.

These optimized conditions were then applied to the arylation of α-bromolactone **95a** using various arylzinc reagents of type **78** (Table 13). Thus, 4-trifluoromethoxyphenylzinc chloride (**78c**) was cross-coupled with **95a**, leading to the desired α-arylated lactone **100b** in 63% yield (dr = 99:1, 99% *ee*, entry 1). Similarly, the electron-poor organozinc reagent **78d** furnished the 4-trifluorotolyl substituted lactone **100c** in 62% yield (dr = 99:1, 99% *ee*, entry 2).

Table 12. Reaction conditions optimization for the cross-coupling of 4-anisylzinc chloride (78b) with the α-bromolactone 95a.

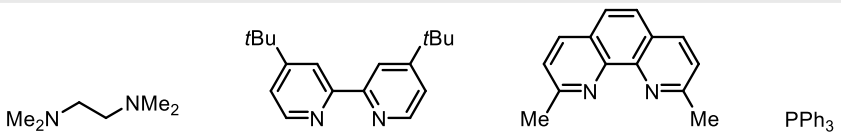


95a (1.0 equiv)
dr = 99:1, 99% *ee*

78b (1.2 equiv)

100a

entry	catalyst	ligand	yield (%)[a]
1	-	-	3
2	$CuCl_2$	-	-
3	$CrCl_2$	-	4
4	$MnCl_2$	-	4
5	$FeCl_2$	-	5
6	$CoCl_2$	-	86 (83)[b]
7	$CoBr_2$	-	77
8	$Co(acac)_2$	-	75
9	$CoCl_2$	**L1**	56
10	$CoCl_2$	**L2**	30
11	$CoCl_2$	**L3**	65
12	**$CoCl_2$**	**L4**	**98 (96)[c]**

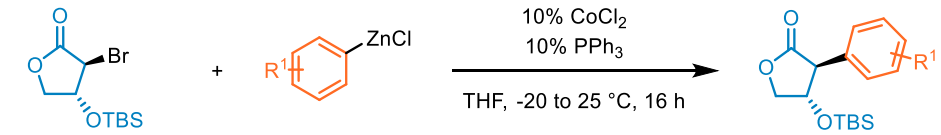


L1 **L2** **L3** **L4**

[a]Calibrated GC yield using undecane as internal standard. [b]99.99% $CoCl_2$ was used. [c]Isolated yield of **100a** (dr = 99:1, 99% *ee*).

Also, the *meta*-substituted arylzinc reagents **78e** and **78a**, bearing a MeS- and a TBSO-group in *meta*-position are satisfactory coupling partners. This afforded the optically pure products **100d** and **100e** in 63-77% yield (dr = 99:1, 99% *ee*, entries 3-4). The arylation of **95a** with (6-methoxynaphthalen-2-yl)zinc chloride (**78f**) and the benzodioxolylzinc reagent **78g** gave the products **100f** and **100g** in 61-84% yield and in excellent stereoselectivity (dr = 99:1, 99% *ee*, entries 5-6). Interestingly, the sterically hindered organozinc chloride **78h**, having a benzyl oxide substituent in the *ortho*-position, was efficiently coupled with α-bromolactone **95a**. The arylated lactone **100h** was obtained in 94% yield; dr = 99:1; 99% *ee* (entry 7).

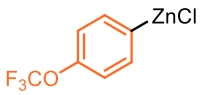
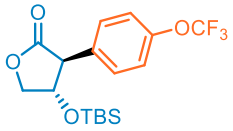
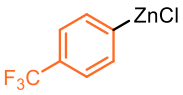
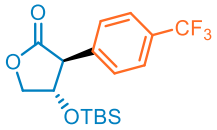
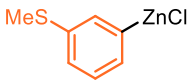
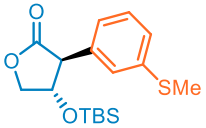
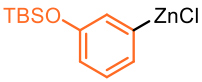
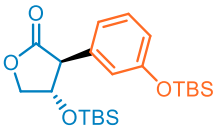
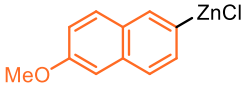
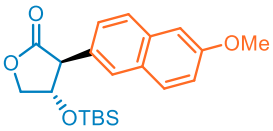
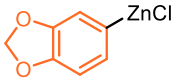
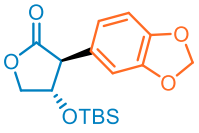
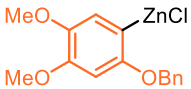
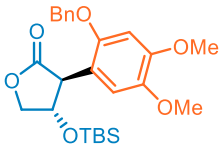
Table 13. Stereoselective cobalt-catalyzed cross-couplings of arylzinc reagents of type 78 with α-bromolactone 95a.



95a (1.0 equiv)
dr = 99:1, 99% *ee*

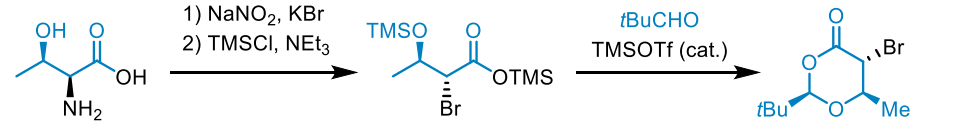
78 (1.2 equiv)

100, 62-94%
dr = 99:1, 99% *ee*

entry	arylzinc reagent	product	yield[a]
1	 **78c**	 **100b**	63%
2	 **78d**	 **100c**	62%
3	 **78e**	 **100d**	63%
4	 **78a**	 **100e**	77%
5	 **78f**	 **100f**	61%
6	 **78g**	 **100g**	84%
7	 **78h**	 **100h**	94%

[a]Isolated yield of analytically pure lactones.

Starting from L-threonine (**101**) and pivalaldehyde, the chiral α-bromolactone **102a** was prepared, bearing a smaller methyl substituent in β-position (Scheme 37).[114] After diazotation, bromination, and TMS-protection of **101**, the bis-trimethylsilylated intermediate **103** can be isolated. The reaction with pivalaldehyde and catalytic TMS-triflate led to the optically enriched protected β-hydroxy ester **102a** in 99% *ee* (2*R*,5*R*,6*R*-substitution). The second enantiomer **102b** (2*S*,5*S*,6*S*-substitution) was synthesized equivalently by simply starting from D-threonine.



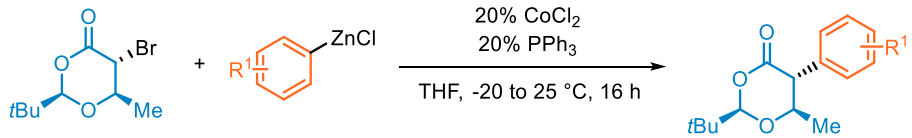
L-threonine, **101** (dr = 99:1, 99% *ee*) — **103** — **102a** (dr = 99:1, 99% *ee*)

Scheme 37. Synthesis of α-bromolactone 102a starting from L-threonine (101).

The cross-coupling of **102a** with various arylzinc reagents of type **78** was performed (Table 3). Thus, 4-anisylzinc chloride **78b** efficiently led to the desired product **104a** in 81% yield (dr = 99:1, 99% *ee*). Similarly, 4-trifluoromethoxyphenylzinc chloride **78c** and the electron-poor trifluoromethyl substituted arylzinc reagent **78d** underwent the coupling affording **104b** and **104c** (dr = 99:1, 99% *ee*) in 61-63% yield (entries 2-3). This C-C bond forming reaction also proceeded well with *meta*-substituted zinc organometallics, such as the TBS-protected phenol **78a** and 3-thioanisylzinc chloride (**78e**). The corresponding arylated esters **104d** and **104e** were obtained in 61-69% yield (dr = 99:1, 99% *ee*, entries 4-5). Methoxynaphthylzinc chloride **78f** and benzodioxolylzinc chloride **78g** stereoselectively arylated the α-bromolactone **102a**, leading to the protected β-hydroxy esters **104f** and **104g** in 73-82% yield (dr = 99:1, 99% *ee*, entries 6-7). Interestingly, the zinc organometallics **78i** and **78j** bearing an ester function in *meta*- and *para*-position were satisfactory coupling partners, leading to **104h** and **104i** in 52-76% yield (entry 8). However, an ester substituent in *para*-position resulted in the loss of stereoselectivity (dr = 50:50). In contrast, the *meta*-carbethoxyphenylzinc chloride **78j** gave the product **104i** in excellent diastereomeric ratio (dr = 99:1). This can be explained by a subsequent base-catalyzed epimerization of the very acidic proton in α-position to the aryl substituent in **104h**.

[114] J. Zimmermann, D. Seebach *Helv. Chim. Acta* **1987**, *70*, 1104-1114.

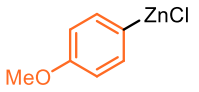
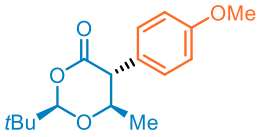
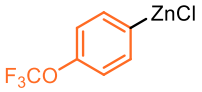
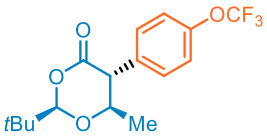
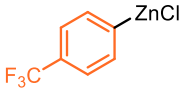
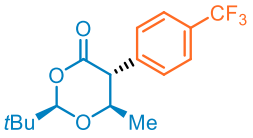
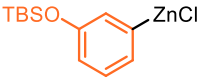
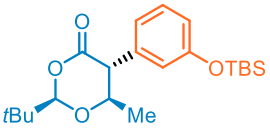
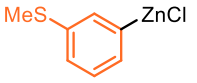
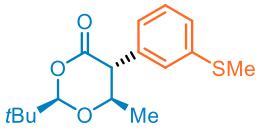
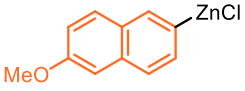
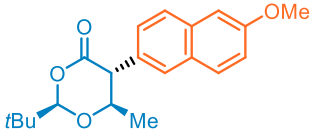
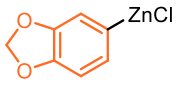
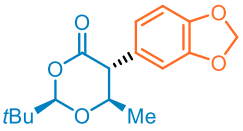
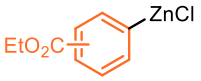
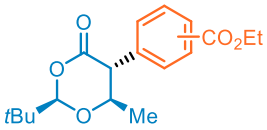
Table 14. Stereoselective cobalt-catalyzed cross-couplings of arylzinc reagents of type 78 with α-bromolactone 102a leading to protected β-hydroxy esters of type 104.



102a (1.0 equiv)
dr = 99:1, 99% *ee*

78 (1.5 equiv)

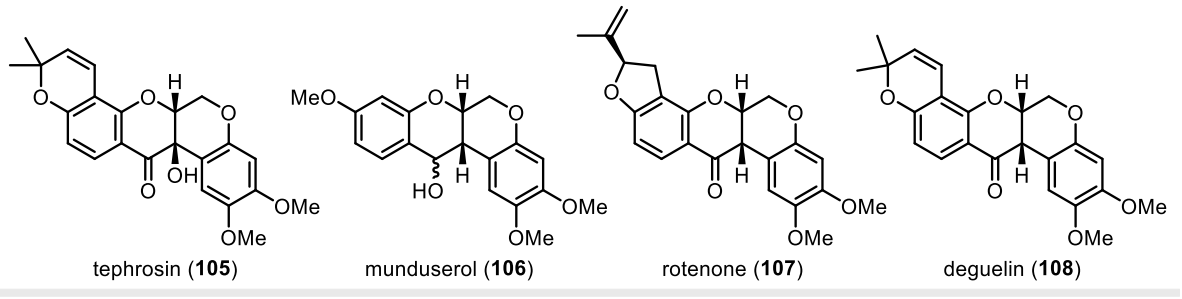
104, 52-82%
dr = 99:1, 99% *ee*

entry	arylzinc reagent	product	yield[a]
1	 **78b**	 **104a**	81%
2	 **78c**	 **104b**	63%
3	 **78d**	 **104c**	61%
4	 **78a**	 **104d**	69%
5	 **78e**	 **104e**	61%
6	 **78f**	 **104f**	82%
7	 **78g**	 **104g**	73%
8	 **78i:** *para* **78j:** *meta*	 **104h:** *para* **104i:** *meta*	*para*: 76%[b] *meta*: 52%

[a]Isolated yield of analytically pure products; [b]dr = 50:50.

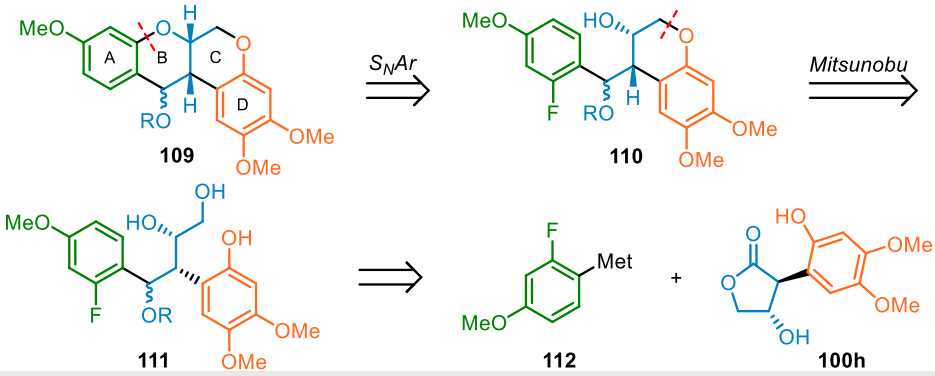
4.4 Total Synthesis of the Artificial Rotenoid Derivative MOM-Protected Munduserol

Many natural and unnatural rotenoids, such as tephrosin (**105**), munduserol (**106**), rotenone (**107**), deguelin (**108**) and various others show considerable antiplasmodial or cytotoxic activities (Scheme 38).[115] These bioactive compounds were the target of several total syntheses.[116]



Scheme 38. Various rotenoids 105-108, bearing the same core scaffold.

The core scaffold consists of four fused six-membered rings A, B, C, D , such as the protected munduserol derivative **109**, which was chosen as the starting point for the retrosynthetic analysis (Scheme 39).



Scheme 39. Retrosynthetic analysis of protected munduserol derivative 109.

[115] a) Fang, N.; Casida, J. E. *Proc. Natl. Acad. Sci.* **1998,** *95*, 3380; b) Fang, N.; Casida, J. E. *J. Agric. Food. Chem.* **1999,** *47*, 2130-2136; c) Yenesew, A.; Derese, S.; Midiwo, J. O.; Oketch-Rabah, H. A.; Lisgarten, J.; Palmer, R.; Heydenreich, M.; Peter, M. G.; Akala, H.; Wangui, J.; Liyala, P.; Waters, N. C. *Phytochemistry* **2003,** *64*, 773-779; d) Ahmed-Belkacem, A.; Macalou, S.; Borrelli, F.; Capasso, R.; Fattorusso, E.; Taglialatela-Scafati, O.; Di Pietro, A. *J. Med. Chem.* **2007,** *50*, 1933-1938; e) Varughese, R. S.; Lam, W. S.-T.; Marican, A. A. b. H.; Viganeshwari, S. H.; Bhave, A. S.; Syn, N. L.; Wang, J.; Wong, A. L.-A.; Kumar, A. P.; Lobie, P. E.; Lee, S. C.; Sethi, G.; Goh, B. C.; Wang, L. *Cancer* **2019,** *125*, 1789-1798.

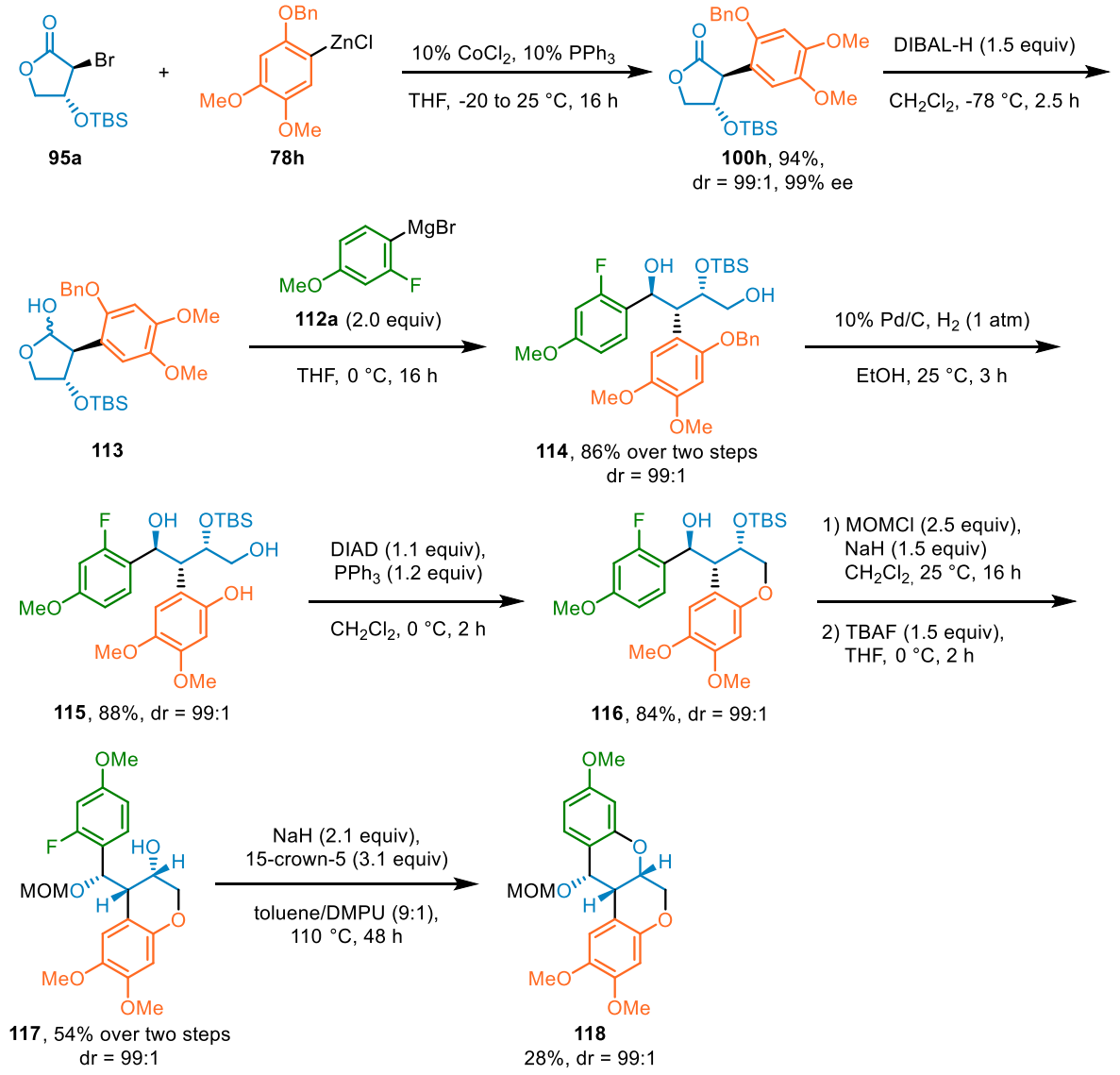
[116] a) Nakatani, N.; Matsui, M. *Agric. Biol. Chem.* **1968,** *32*, 769-772; b) Granados-Covarrubias, E. H.; Maldonado, L. A. *J. Org. Chem.* **2009,** *74*, 5097-5099; c) Nayak, M.; Kim, I. *J. Org. Chem.* **2015,** *80*, 11460-11467; d) Georgiou, K. H.; Pelly, S. C.; de Koning, C. B. *Tetrahedron* **2017,** *73*, 853-858; e) Nakamura, K.; Ohmori, K.; Suzuki, K. *Angew. Chem., Int. Ed.* **2017,** *56*, 182-187; f) Matsuoka, S.; Nakamura, K.; Ohmori, K.; Suzuki, K. *Synthesis* **2019,** *51*, 1139-1156; g) Perveen, S.; Yang, S.; Meng, M.; Xu, W.; Zhang, G.; Fang, X. *Commun. Chem.* **2019,** *2*, 8.

The B-ring could be formed *via* a intramolecular nucleophilic aromatic substitution starting from fluoro-substituted secondary alcohol **110**. The C-ring could be closed by a Mitsunobu-reaction of the aromatic hydroxy group and the primary alcohol in structure **111**. The chiral alcohol **111** could be accessed by opening the optically pure lactone **100h** with a 2-fluoro-4-anisylorganometallic **112**.

Thus , the arylation of α-bromolactone **95a** with arylzinc chloride **78h** under cobalt-catalysis gave **100h** on gram scale in 94% yield and optically pure (dr = 99:1, 99% *ee*, Scheme 40). The arylation product **100h** was reduced by diisobutylaluminum hydride, to furnish lactol **113**. The addition of 2-fluoro-4-methoxyphenylmagnesium bromide (**112a**) led to the ring opening product **114** in 84% yield over two steps. Interestingly, **114** was formed stereoselectively, leading to only a single diastereomer.[117] Palladium catalyzed hydrogenolysis[118] removed the benzyl protecting group on the dimethoxy substituted aryl moiety, affording **115** in 88% yield. The Mitsunobu-reaction using diisopropyl azodicarboxylate and triphenylphosphine, allowed to close the first cycle between the phenol function and the primary alcohol, which led to **116** in 84% yield. Protection of the secondary alcohol with chloromethyl methyl ether and deprotection of the TBS-function by tetrabutylammonium fluoride furnished the secondary alcohol **117** in 54% yield. A combination of sodium hydride and 15-crown-5 ether under heating allowed the intramolecular nucleophilic aromatic substitution and furnished MOM-protected munduserol **118** in 28% yield (dr = 99:1).

[117] For discussions of asymmetric induction in the addition to α,β-substituted aldehydes, see: a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999,** *99*, 1191-1224; b) Evans, D. A.; Cee, V. J.; Siska, S. J. *J. Am. Chem. Soc.* **2006,** *128*, 9433-9441. The stereochemistry was approved by NOE-NMR experiments of the final ring-closed product MOM-protected munduserol derivative (**118**).

[118] Hartung, W. H.; Simonoff, R., Hydrogenolysis of Benzyl Groups Attached to Oxygen, Nitrogen, or Sulfur. in *Organic Reactions*, 1953; pp 263-326.

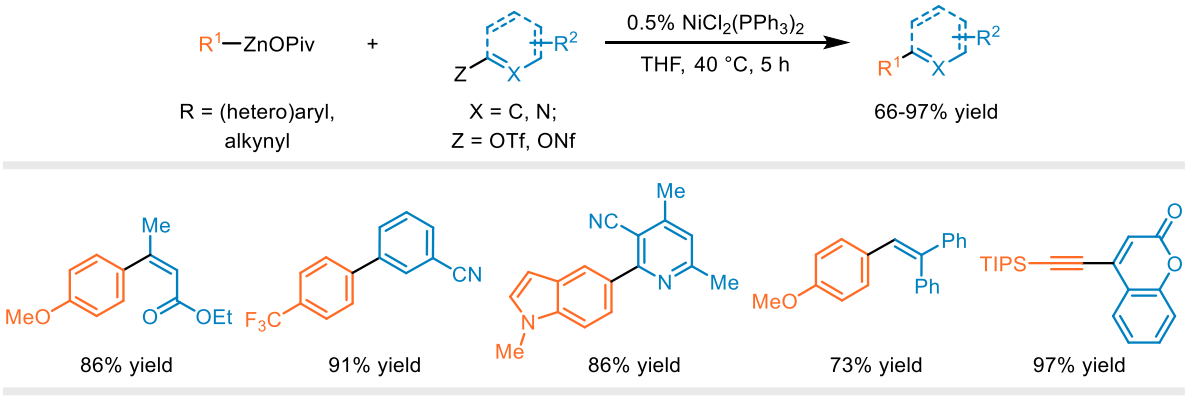


Scheme 40. Total synthesis of MOM-protected munduserol (118)

5 Summary

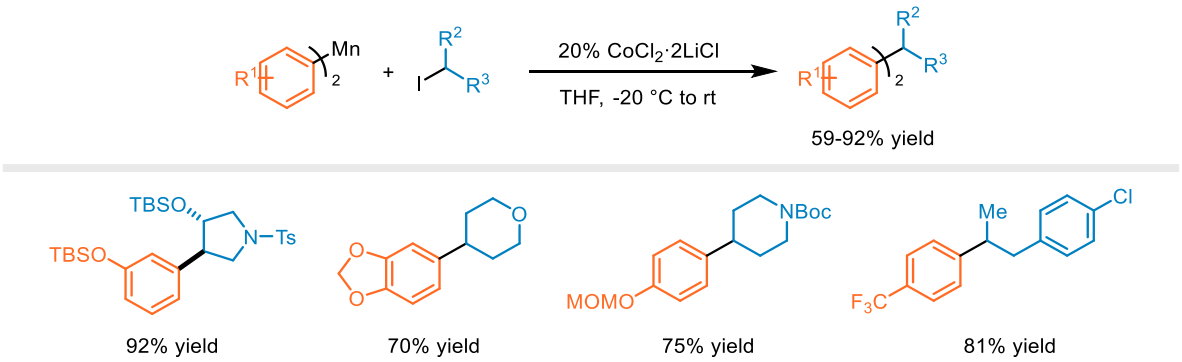
This work focused on the development of new transition metal-catalyzed cross-coupling reactions. A special interest was the utilization of easily accessible starting materials, stable and functional group tolerant organometallics from highly abundant metals and the substitution of expensive palladium catalysts. These requirements were the key features to explore efficient and economic carbon-carbon bond formations as valuable alternatives in the toolbox of organic chemistry.

First, a practical Ni-catalyzed cross-coupling of unsaturated zinc pivalates with unsaturated triflates and nonaflates was developed (Scheme 41). These electrophilic reagents can be easily accessed from the corresponding phenols or enolates. Using (hetero)aryl- and alkynylzinc pivalates as organometallic coupling partners provided the desired products in 66-97% yield. Furthermore, the beneficial effect of organozinc pivalates in comparison to organozinc chlorides was demonstrated, which led to dramatically increased reaction rates. Thus, the coupling products were obtained in significantly higher yields. Also, the catalyst loading of cheap and commercially available $NiCl_2(PPh_3)_2$ was only 0.5 mol%.



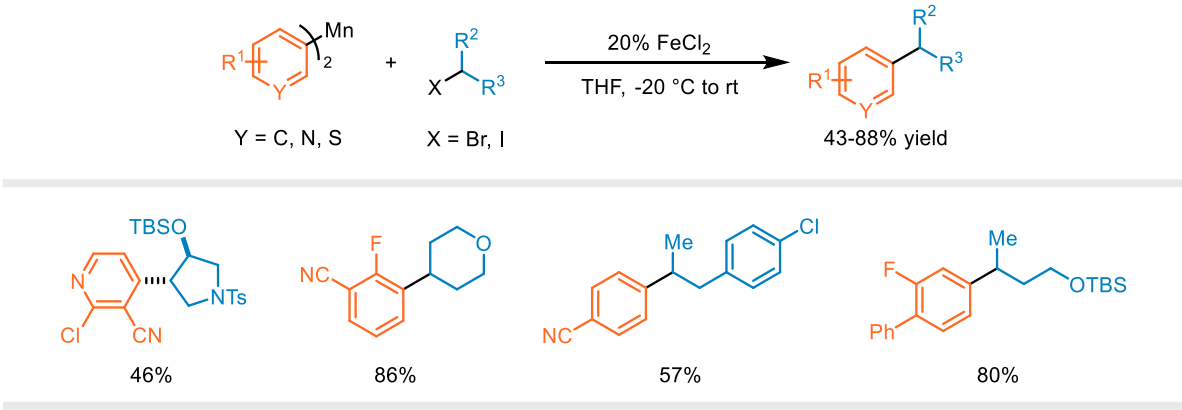
Scheme 41. Nickel-catalyzed cross-coupling of organozinc pivalates with triflates and nonaflates.

The second part focused on the formation of sp^2-sp^3-carbon bonds by using diarylmanganese reagents and secondary alkyl iodides as coupling partners (Scheme 42). The THF-soluble $CoCl_2 \cdot 2LiCl$ as catalyst (20 mol%) led to the alkylated aryls in 59-92% yield under mild conditions (THF, -20 °C to rt). Remarkably, no rearrangement of the secondary alkyl group was observed. Also, this cross-coupling was applied to the preparation of a key intermediate for the synthesis of (±)-preclamol.



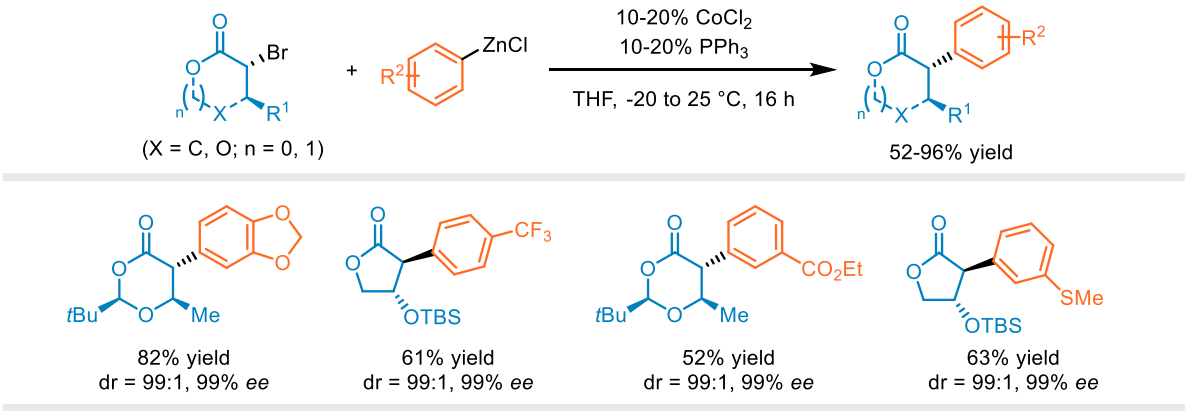
Scheme 42. Cobalt-catalyzed cross-coupling of diarylmanganese reagents with secondary alkyl iodides.

The scope of this reaction was further extended by using $FeCl_2$ as the catalyst (Scheme 43). The formation of sp^2-sp^3-bonds between various alkyl halides and di(hetero)arylmanganese reagents was performed. The alkylated products were obtained in 43-88% yield under mild reaction conditions (THF, -20 °C to rt). Additionally, organometallic reagents prepared *via* directed manganation using $TMP_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ successfully underwent this cross-coupling. High diastereoselectivities were obtained (dr up to 99:1) and rearrangements of secondary alkyl halides to the corresponding unbranched products were not observed.



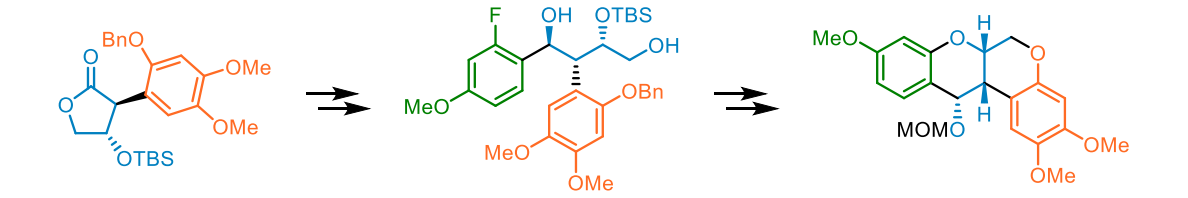
Scheme 43. Iron-catalyzed cross-coupling of di(hetero)arylmanganese reagents with secondary alkyl halides.

The fourth project focused on the stereoselective carbon-carbon bond formation between arylzinc chlorides and chiral α-bromolactones and related derivatives under cobalt-catalysis (Scheme 44). The optically enriched starting materials with substituents in the β-position allowed a highly *trans*-diastereoselective coupling reaction. This led to the chiral arylation products in 52-96% and in excellent stereoselectivity (dr = 99:1, 99% *ee*). In terms of cost efficiency, the cheap and commercially available catalytic system of $CoCl_2$ and PPh_3 was used.



Scheme 44. Stereoselective cobalt-catalyzed cross-coupling of α-bromolactones and arylzinc chlorides.

This cross-coupling reaction was used to prepare an arylated lactone as key intermediate for the stereoselective total synthesis of the artificial rotenoid derivative MOM-protected munduserol (Scheme 45).



Scheme 45. Stereoselective preparation of MOM-protected munduserol starting from an arylated lactone.

C EXPERIMENTAL PART

1 General Considerations

All reactions were performed in flame dried glassware with magnetic stirring under argon atmosphere using *Schlenk* technique. Syringes used to transfer solvents and reagents were purged with argon prior to use. Starting materials were purchased from Sigma Aldrich, TCI, Alfa Aesar, Acros, Apollo Scientific or Fluorochem and were used without further purification.

1.1 Solvents

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

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

DMPU was predried over CaH_2 (4 h) and distilled (bp = 247 °C).

NEt_3 was dried over KOH and distilled.

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

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

Toluene was continuously refluxed and distilled over sodium.

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

1.2 Reagents

***i*PrMgCl·LiCl** was purchased as a 14% solution in THF from Albemarle (Höchst, Germany) and was titrated[119] prior to use.

EtMgBr

A dry and argon-flushed 250 mL *Schlenk*-flask, equipped with a stirring bar and a septum, was charged with magnesium turnings (2.92 g, 120 mmol) in THF (90 mL). Bromoethane (10.8 g, 100 mmol) was added dropwise at 0 °C and the reaction mixture was shortly heated to reflux and again cooled to 0 °C. After stirring for 3 h and allowing to warm to rt, the dark-grey solution was titrated[119] by using a stoichiometric amount of iodine (100 mg) in THF (2 mL) and a concentration of 1.03 M was determined.

[119] Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006,** *45*, 6040-6044.

$Zn(OPiv)_2$

Pivalic acid (20.4 g, 22.6 mL, 200 mmol) was placed in a dry and argon-flushed 500 mL three-necked round bottom flask, equipped with a magnetic stirring bar, a septum, and a pressure equalizer. The mixture was dissolved in dry THF (120 mL), cooled to 0 °C, and a solution of Et_2Zn (13.0 g, 10.8 mL, 105 mmol) in dry THF (120 mL) was added over a period of 30 min under vigorous stirring. Then, the ice-bath was removed and stirring was continued at 25 °C for one additional hour at which point bubbling was ceased (a thick slurry was formed). The solvent was removed *in vacuo* and the solid residue was dried for at least 4 h. $Zn(OPiv)_2$ was obtained in quantitative yield, as a puffy amorphous white solid.

***n*BuLi** was purchased as a solution in hexane from Albemarle (Höchst, Germany) and was titrated prior to use.

$ZnCl_2$ solution in THF (1.0 M)

$ZnCl_2$ (40.9 g, 300 mmol) was placed in a dry and argon-flushed 500 mL *Schlenk*-flask and dried under high vacuum at 150 °C for 4 h. After cooling to 25 °C, anhydrous THF was added until a total volume of 300 mL was reached. The suspension was stirred overnight at 25 °C and after 12 h the salts had completely dissolved. The stirring was stopped and the clear solution was stored over 4 Å MS under argon upon use.

$MnCl_2$ solution in THF (1.0 M)

A dry and argon-flushed 250 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with anhydrous LiCl (140 mmol, 5.94 g) and heated to 150 °C under high vacuum for 5 h. After cooling to rt under vacuum, anhydrous $MnCl_2$ (70.0 mmol, 8.81 g) was added under argon. The *Schlenk*-flask was further heated to 130 °C for 3 h under high vacuum, cooled to 25 °C and charged with dry THF (70 mL). The mixture was stirred for at least 24 h (**covered with aluminum foil**) at rt and the resulting reagent $MnCl_2$·2LiCl (1 M in THF) was obtained as a yellow solution.

$CoCl_2$·2LiCl solution in THF (1.0 M)

LiCl (8.5 g, 200 mmol) was placed in a *Schlenk*-flask and dried under high vacuum at 150 °C for 3 h. After cooling to 25 °C, anhydrous $CoCl_2$ (13.0 g, 100 mmol) was added and the salts were further heated to 130 °C for 5 h under high vacuum. After cooling to 25 °C anhydrous THF (100 mL) was added. The mixture was vigorously stirred until all solids were dissolved and the reagent was obtained as a dark blue solution.

2,2,6,6-Tetramethylpiperidine (**TMPH)** was distilled from CaH_2 under argon prior to use.

TMPMgCl·LiCl

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

$TMP_2Mn·2MgCl_2·4LiCl$

A dry and argon-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with freshly titrated TMPMgCl·LiCl (348 mL, 400 mmol) and cooled to 0 °C. Then, $MnCl_2·2LiCl$ (1 M in THF, 50 mL, 50 mmol) was added over a period of 5 min. The resulting mixture was stirred for 30 min at 0 °C, warmed to rt and stirred for another 3 h. The resulting solution of $TMP_2Mn·2MgCl_2·4LiCl$ was concentrated *in vacuo* and was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.5 M in THF was obtained.

1.3 Purification

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

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

1.4 Analytical Data

NMR spectra were recorded on Varian VXR 400S, Bruker Avance III HD 400 MHz and Bruker AMX 600 instruments. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak of $CHCl_3$ (δ_H = 7.26, δ_C = 77.0) or benzene (δ_H = 7.16, δ_C = 128.1) respectively. For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet), br (broad signal).

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

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

Chiral HPLC (cHPLC) was measured on a *ShimazuHPLC Prominence* with *Daicel Chiracel* columns.

Optical Rotation values were recorded on an *Anton Paar MCP* 500 polarimeter. The specific rotation is calculated as follows:

$$\alpha_{\lambda}^{\varphi} = \frac{\alpha \cdot 100}{c \cdot d}$$

Thereby, the wavelength λ is reported in nm and the measuring temperature φ in °C. α represents the recorded optical rotation, c the concentration of the analyte in 10 mg/mL and d the length of the cuvette in dm. Thus, the specific rotation is given in 10^{-1}·deg·cm^2·g^{-1}. Usage of the sodium D line (λ = 589 nm) is indicated by D instead of the wavelength in nm. The respective concentration as well as the solvent is reported at the relevant section of the experimental section.

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

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

Reactions were monitored by gas chromatography (GC and GC-MS) using an internal standard (undecane) or thin layer chromatography (TLC). Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR (25 °C) and capillary GC analysis.

2 Nickel-Catalyzed Cross-Coupling Reactions of Unsaturated Zinc Pivalates and Unsaturated Nonaflates and Triflates

2.1 Typical Procedures

Typical procedure 1 (TP1) for the preparation of (hetero)arylzinc pivalates by magnesium insertion and transmetalation with $Zn(OPiv)_2$:

A dry and argon flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, was charged with magnesium turnings (1.1 equiv), dry LiCl (1.1 equiv) and dry THF (1 M solution relating to the aryl halide). The aromatic halide (1.0 equiv) was added at 0 °C. The progress of the insertion reaction was monitored by GC-analysis of reaction aliquots quenched with I_2. Upon completion of the insertion, the concentration of the Grignard reagent was determined by titration of I_2. Solid $Zn(OPiv)_2$ (1.0 equiv) was placed in a dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum, THF (2 M relating to $Zn(OPiv)_2$) was added and cooled to 0 °C. The Grignard reagent (1.0 equiv) was added, the solution was allowed to warm to rt and stirred for 1 h. Solvent evaporation affords the solid organozinc pivalate.

Typical procedure 2 (TP2) for the preparation of (hetero)arylzinc pivalates by halogen/magnesium-exchange and transmetalation with $Zn(OPiv)_2$:

A dry and argon flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, was charged with the aryl halide (1.0 equiv) and dry THF (1 M solution relating to the aryl halide). The mixture was cooled to the respective temperature, *i*PrMgCl·LiCl (1.1 equiv) was added dropwise and stirred for the indicated time. The progress of the exchange reaction was monitored by GC-analysis of reaction aliquots quenched with I_2 (for aryl bromides) or H_2O (for aryl iodides). Upon completion of the insertion, the concentration of the Grignard reagent was determined by titration of I_2. Solid $Zn(OPiv)_2$ (1.0 equiv) was placed in a dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum, THF (2 M relating to $Zn(OPiv)_2$) was added and cooled to 0 °C. The Grignard reagent (1.0 equiv) was added, the solution was allowed to warm to rt and stirred for 1 h. Solvent evaporation affords the solid organozinc pivalate.

Typical procedure 3 (TP3) for the preparation of alkynylzinc pivalates by metalation of alkynes using EtMgBr and transmetalation with $Zn(OPiv)_2$:

A dry and argon flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, was charged with the corresponding alkyne (1.0 equiv) and dry THF (2 M solution relating to the alkyne). EtMgBr (1.1 equiv) was added dropwise at rt and the mixture was stirred until a reaction aliquot quenched with I_2 showed full conversion of the starting material. The progress of the metalation was monitored by GC-analysis of reaction aliquots quenched with I_2 in THF. Upon completion, solid $Zn(OPiv)_2$ (1.1 equiv) was added in one portion at 0 °C. The mixture was allowed to warm to rt and stirred for 1 h. Solvent evaporation affords the solid organozinc pivalate.

Typical procedure 4 (TP4) for the preparation of (hetero)aryl triflates:

A dry and argon flushed round-bottomed flask, equipped with a magnetic stirring bar and a septum, was charged with the (hetero)aromatic alcohol (30 mmol, 1.0 equiv), dissolved in NEt_3 (2.0 equiv) and CH_2Cl_2 (50 mL). The mixture was cooled to 0 °C and trifluoromethanesulfonic anhydride (39 mmol, 1.3 equiv) was added dropwise. The reaction was allowed to warm to rt and stirred for 16 h. Sat. aq. NH_4Cl (25 mL) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification on silica yielding the respective triflate.

Typical procedure 5 (TP5) for the preparation of (hetero)aryl nonaflates:

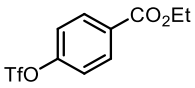
A dry and argon flushed round-bottomed flask, equipped with a magnetic stirring bar and a septum, was charged with the (hetero)aromatic alcohol (30 mmol, 1.0 equiv) and DMAP (5%) and dissolved in NEt_3 (1.3 equiv) and CH_2Cl_2 (50 mL). The mixture was cooled to 0 °C and perfluoro-1-butanesulfonyl fluoride (33 mmol, 1.1 equiv) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 16 h. Sat. aq. NH_4Cl (25 mL) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification on silica yielding the respective nonaflate.

Typical procedure 6 (TP6) for the nickel-catalyzed cross-coupling of unsaturated zinc pivalates with unsaturated nonaflates and triflates

A dry and argon-flushed 20 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with the respective (hetero)aryl or alkenyl triflate or nonaflate (1.0 mmol, 1.0 equiv) and a freshly prepared solution of $NiCl_2(PPh_3)_2$ in THF (1.0 mL, 0.005 mmol, 0.5 mol%) was added. The solution was warmed to 40 °C and the (hetero)aryl or alkynylzinc pivalate dissolved in THF (1.5 mmol, 1.5 equiv, approx. 2 mL) was added under stirring. The reaction was monitored by GC-analysis ($C_{11}H_{24}$ was used as an internal standard). Upon consumption of the starting material, sat. aq. NH_4Cl (5 mL) and EtOAc (5 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with sat. aq. $KHCO_3$ (50 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography purification on silica yielding the respective title compound.

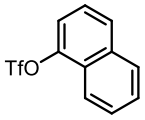
2.2 Preparation of Starting Materials

Ethyl 4-(((trifluoromethyl)sulfonyl)oxy)benzoate (72a)



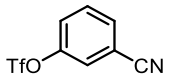
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.15 (d, *J*=8.8, 2H), 7.35 (d, J=8.8, 2H), 4.40 (q, *J*=7.1, 2H), 1.40 (t, *J*=7.1, 3H).

Naphthalen-1-yl trifluoromethanesulfonate (72b)



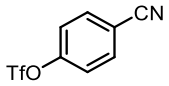
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.10 (d, *J*=8.3, 1H), 7.96 – 7.83 (m, 2H), 7.71 – 7.56 (m, 2H), 7.54 – 7.44 (m, 2H).

3-Cyanophenyl trifluoromethanesulfonate (72c)



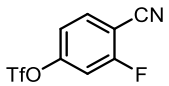
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.72 (d, *J*=7.7, 1H), 7.63 (t, *J*=8.0, 1H), 7.62 – 7.52 (m, 2H).

4-Cyanophenyl trifluoromethanesulfonate (72d)



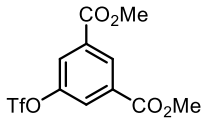
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.84 – 7.76 (m, 2H), 7.46 – 7.39 (m, 2H).

4-Cyano-3-fluorophenyl trifluoromethanesulfonate (72e)



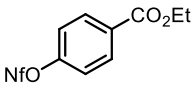
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.79 (dd, *J*=9.0, 6.9, 1H), 7.30 – 7.21 (m, 2H).

Dimethyl 5-(((trifluoromethyl)sulfonyl)oxy)isophthalate (72f)



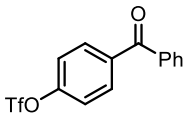
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.71 (s, 1H), 8.11 (s, 2H), 3.98 (s, 6H).

Ethyl 4-(((nonafluorobutyl)sulfonyl)oxy)benzoate (72g)



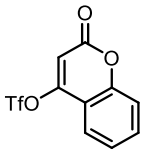
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.15 (d, *J*=8.8, 2H), 7.36 (d, *J*=8.6, 2H), 4.40 (q, *J*=7.1, 2H), 1.40 (t, *J*=7.1, 3H).

4-Benzoylphenyl trifluoromethanesulfonate (72h)



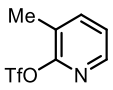
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.95 – 7.88 (m, 2H), 7.83 – 7.77 (m, 2H), 7.69 – 7.60 (m, 1H), 7.55 – 7.48 (m, 2H), 7.44 – 7.38 (m, 2H).

2-Oxo-2*H*-chromen-4-yl trifluoromethanesulfonate (72i)



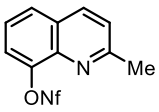
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.70 (t, *J*=7.7, 2H), 7.49 – 7.38 (m, 2H), 6.52 (s, 1H).

3-Methylpyridin-2-yl trifluoromethanesulfonate (72j)



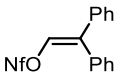
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.20 (dd, *J*=4.8, 1.9, 1H), 7.77 – 7.64 (m, 1H), 7.28 (dd, *J*=7.5, 4.8, 1H), 2.37 (s, 3H).

2-Methylquinolin-8-yl nonafluorobutane-1-sulfonate (72k)



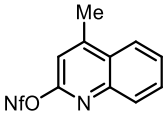
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.09 (d, *J*=8.5, 1H), 7.80 (dd, *J*=8.1, 1.3, 1H), 7.61 – 7.54 (m, 1H), 7.48 (t, *J*=7.9, 1H), 7.39 (d, *J*=8.5, 1H), 2.80 (s, 3H).

2,2-Diphenylvinyl nonafluorobutane-1-sulfonate (72l)



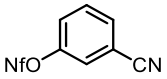
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.36 – 7.25 (m, 6H), 7.22 – 7.15 (m, 4H), 7.02 (s, 1H).

4-Methylquinolin-2-yl nonafluorobutane-1-sulfonate (72m)



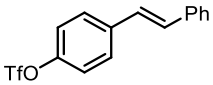
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.96 (t, *J*=9.3, 2H), 7.75 – 7.67 (m, 1H), 7.61 – 7.54 (m, 1H), 7.01 (s, 1H), 2.70 (s, 3H).

3-Cyanophenyl nonafluorobutane-1-sulfonate (72n)



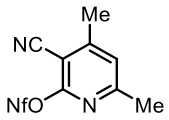
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.72 (dt, *J*=7.6, 1.4, 1H), 7.65 – 7.54 (m, 3H).

(*E*)-4-Styrylphenyl trifluoromethanesulfonate (72o)



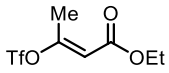
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.62 – 7.56 (m, 2H), 7.56 – 7.51 (m, 2H), 7.44 – 7.36 (m, 2H), 7.35 – 7.25 (m, 3H), 7.14 (d, *J*=16.5, 1H), 7.09 (d, *J*=16.5, 1H).

3-Cyano-4,6-dimethylpyridin-2-yl trifluoromethanesulfonate (72p)



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.19 (s, 1H), 2.59 (s, 3H), 2.58 (s, 3H).

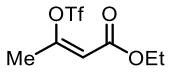
Ethyl (*E*)-3-(((trifluoromethyl)sulfonyl)oxy)but-2-enoate (72q)[70]



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.95 (s, 1H), 4.22 (q, *J*=7.1, 2H), 2.51 (s, 3H), 1.30 (t, *J*=7.1, 3H).

Ethyl (*Z*)-3-(((trifluoromethyl)sulfonyl)oxy)but-2-enoate (72r)[70]

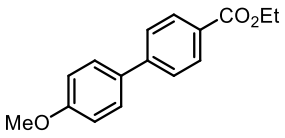
The product was synthesized according to the procedure reported in literature.



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.76 (s, 1H), 4.24 (q, *J*=7.1, 2H), 2.16 (s, 3H), 1.29 (t, *J*=7.1, 3H).

2.3 Nickel-Catalyzed Cross-Coupling Reactions of (Hetero)arylzinc and Alkynylzinc Pivalates with Aryl and Alkenyl Triflates and Nonaflates

Ethyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (73a)



Triflate **71a** as the electrophile:

According to **TP6**, ethyl 4-(((trifluoromethyl)sulfonyl)oxy)benzoate (**72a**, 298 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **73a** as colorless crystals (86%, 220 mg, 0.86 mmol).

Nonaflate **72g** as the electrophile:

According to **TP6**, ethyl 4-(((nonafluorobutyl)sulfonyl)oxy)benzoate (**72g**, 448 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **73a** as colorless crystals (81%, 208 mg, 0.81 mmol).

m.p.: 104 – 106 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.12 – 8.05 (m, 2H), 7.65 – 7.60 (m, 2H), 7.60 – 7.55 (m, 2H), 7.04 – 6.97 (m, 2H), 4.40 (q, *J*=7.1, 2H), 3.86 (s, 3H), 1.41 (t, *J*=7.1, 3H).

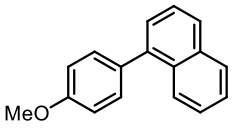
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.7, 160.0, 145.2, 132.6, 130.2, 128.8, 128.5, 126.6, 114.5, 61.0, 55.5, 14.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2968, 2904, 2838, 1704, 1600, 1290, 1270, 1254, 1198, 1182, 1122, 1108, 1036, 1024, 1012, 1000, 828, 770, 718, 698.

MS (EI, 70 eV): *m/z* (%) = 256 (100), 228 (51), 213 (19), 212 (14), 211 (97), 185 (14), 183 (19), 168 (25), 152 (16), 140 (17), 139 (34).

HR-MS (EI, 70 eV): $[C_{16}H_{16}O_3]^{+\bullet}$, calcd.: 256.1094; found: 265.1095.

1-(4-Methoxyphenyl)naphthalene (73b)



According to **TP6**, naphthalen-1-yl trifluoromethanesulfonate (**72b**, 276 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **73b** as colorless crystals (87%, 205 mg, 0.87 mmol).

m.p.: 117 – 118 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.98 – 7.89 (m, 2H), 7.89 – 7.83 (m, 1H), 7.57 – 7.48 (m, 2H), 7.48 – 7.41 (m, 4H), 7.09 – 7.03 (m, 2H), 3.91 (s, 3H).

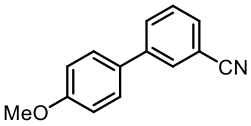
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.1, 140.1, 134.0, 133.3, 132.0, 131.2, 128.4, 127.5, 127.0, 126.2, 126.0, 125.8, 125.5, 113.9, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1608, 1512, 1504, 1496, 1462, 1438, 1394, 1282, 1240, 1208, 1174, 1146, 1106, 1030, 1018, 964, 840, 834, 802, 780.

MS (EI, 70 eV): *m/z* (%) = 234 (100), 233 (13), 219 (35), 203 (21), 202 (10), 191 (34), 190 (32), 189 (62).

HR-MS (EI, 70 eV): $[C_{17}H_{14}O]^{+\bullet}$, calcd.: 234.1039; found: 234.1038

4'-Methoxy-[1,1'-biphenyl]-3-carbonitrile (73c)



According to **TP6**, 3-cyanophenyl trifluoromethanesulfonate (**72c**, 251 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **73c** as yellow oil (84%, 176 mg, 0.84 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.83 – 7.79 (m, 1H), 7.79 – 7.74 (m, 1H), 7.60 – 7.55 (m, 1H), 7.54 – 7.47 (m, 3H), 7.04 – 6.97 (m, 2H), 3.86 (s, 3H).

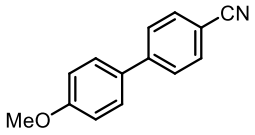
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.1, 142.1, 131.4, 131.1, 130.3, 130.1, 129.6, 128.3, 119.1, 114.7, 113.0, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2936, 2838, 2228, 1608, 1516, 1478, 1464, 1434, 1296, 1268, 1246, 1180, 1048, 1026, 830, 792, 686.

MS (EI, 70 eV): *m/z* (%) = 209 (100), 195 (8), 194 (59), 166 (75), 140 (40), 139 (19), 113 (7).

HR-MS (EI, 70 eV): $[C_{14}H_{11}NO]^{+\bullet}$, calcd.: 209.0835; found: 209.0833.

4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile (73d)



According to **TP6**, 4-cyanophenyl trifluoromethanesulfonate (**72d**, 251 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **73d** as colorless crystals (71%, 149 mg, 0.71 mmol).

m.p.: 111 – 113 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.72 – 7.67 (m, 2H), 7.67 – 7.62 (m, 2H), 7.57 – 7.51 (m, 2H), 7.05 – 6.98 (m, 2H), 3.87 (s, 3H).

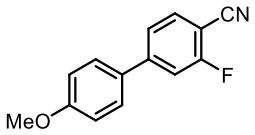
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.4, 145.4, 132.7, 131.7, 128.5, 127.3, 119.2, 114.7, 110.3, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2970, 2868, 2224, 1606, 1492, 1248, 1178, 1118, 1040, 1024, 844, 812.

MS (EI, 70 eV): *m/z* (%) = 209 (100), 194 (50), 166 (66), 164 (9), 140 (38), 139 (14), 113 (7)

HR-MS (EI, 70 eV): $[C_{14}H_{11}NO]^{+\bullet}$, calcd.: 209.0835; found: 209.0833.

3-Fluoro-4'-methoxy-[1,1'-biphenyl]-4-carbonitrile (73e)



According to **TP6**, 4-cyano-3-fluorophenyl trifluoromethanesulfonate (**72e**, 269 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73e** as colorless crystals (66%, 149 mg, 0,66 mmol).

m.p.: 153 – 154 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.6 (dd, *J*=8.1, 6.7, 1H), 7.6 – 7.5 (m, 2H), 7.4 (dd, *J*=8.1, 1.7, 1H), 7.4 (dd, *J*=10.4, 1.6, 1H), 7.1 – 7.0 (m, 2H), 3.9 (s, 3H).

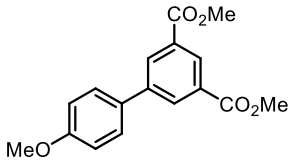
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 163.7 (d, *J*=258.1), 160.8, 148.3 (d, *J*=8.3), 133.8, 130.5 (d, *J*=2.1), 128.5, 122.9 (d, *J*=3.1), 114.8, 114.4, 114.2 (d, *J*=20.2), 99.1 (d, *J*=15.7), 55.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2970, 2868, 2224, 1606, 1492, 1248, 1178, 1118, 1040, 1024, 844, 812.

MS (EI, 70 eV): *m/z* (%) = 227 (100), 212 (39), 185 (8), 184 (66), 158 (39), 157 (8).

HR-MS (EI, 70 eV): $[C_{14}H_{10}FNO]^{+\bullet}$, calcd.: 227.0741; found: 227.0738.

Dimethyl 4'-methoxy-[1,1'-biphenyl]-3,5-dicarboxylate (73f)



According to **TP6**, dimethyl 5-(((trifluoromethyl)sulfonyl)oxy)isophthalate (**72f**, 342 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73f** as colorless crystals (87%, 262 mg, 0.87 mmol).

m.p.: 90 – 92°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.58 (t, *J*=1.6, 1H), 8.40 (d, *J*=1.6, 2H), 7.62 – 7.56 (m, 2H), 7.02 – 6.97 (m, 2H), 3.96 (s, 6H), 3.85 (s, 3H).

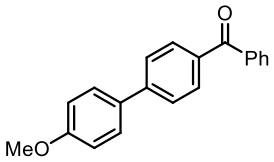
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.4, 160.0, 141.6, 131.8, 131.5, 131.2, 128.8, 128.3, 114.6, 55.5, 52.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2838, 1732, 1716, 1608, 1428, 1338, 1234, 1182, 1130, 1106, 1070, 1028, 998, 970, 830, 754, 726, 718.

MS (EI, 70 eV): *m/z* (%) = 300 (100), 285 (14), 269 (43), 257 (11), 241 (20), 226 (23), 139 (15).

HR-MS (EI, 70 eV): $[C_{17}H_{16}O_5]^{+\bullet}$, calcd.: 300.0992; found: 300.0991.

(4'-Methoxy-[1,1'-biphenyl]-4-yl)(phenyl)methanone (73g)



According to **TP6**, 4-benzoylphenyl trifluoromethanesulfonate (**72h**, 330 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73g** as yellow crystals (66%, 190 mg, 0.66 mmol).

m.p.: 168 – 170 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.91 – 7.86 (m, 2H), 7.86 – 7.81 (m, 2H), 7.70 – 7.65 (m, 2H), 7.63 – 7.56 (m, 3H), 7.54 – 7.47 (m, 2H), 7.06 – 6.98 (m, 2H), 3.87 (s, 3H).

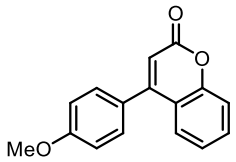
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 196.5, 160.0, 145.0, 138.0, 135.8, 132.5, 132.4, 130.9, 130.1, 128.5, 128.4, 126.5, 114.6, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1646, 1594, 1252, 1200, 1180, 1032, 826, 792, 748, 692, 664.

MS (EI, 70 eV): *m/z* (%) = 289 (17), 288 (75), 212 (16), 211 (100), 183 (17), 168 (19), 152 (12), 140 (13), 139 (26), 77 (10).

HR-MS (EI, 70 eV): $[C_{20}H_{16}O_2]^{+\bullet}$, calcd.: 288.1145; found: 288.1140.

4-(4-Methoxyphenyl)-2*H*-chromen-2-one (73h)



According to **TP6**, 2-oxo-2*H*-chromen-4-yl trifluoromethanesulfonate (**72i**, 294 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73h** as yellowish crystals (95%, 239 mg, 0.95 mmol).

m.p.: 130 – 132°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.58 – 7.49 (m, 2H), 7.44 – 7.35 (m, 3H), 7.26 – 7.18 (m, 1H), 7.07 – 7.00 (m, 2H), 6.32 (s, 1H), 3.88 (s, 3H).

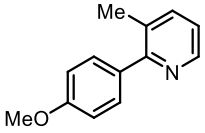
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.9, 160.9, 155.4, 154.3, 131.9, 130.0, 127.5, 127.1, 124.2, 119.2, 117.4, 114.7, 114.4, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3072, 2954, 2930, 2838, 1724, 1682, 1604, 1506, 1450, 1442, 1366, 1254, 1242, 1184, 1176, 1140, 1112, 1028, 928, 886, 830, 772, 752, 710.

MS (EI, 70 eV): *m/z* (%) = 252 (100), 251 (21), 225 (16), 224(98), 221 (11), 210 (11), 209 (75), 181 (34), 153 (16), 152 (50).

HR-MS (EI, 70 eV): $[C_{16}H_{12}O_3]^{+\bullet}$, calcd.: 252.0781; found: 252.0781.

2-(4-Methoxyphenyl)-3-methylpyridine (73i)



According to **TP6**, 3-methylpyridin-2-yl trifluoromethanesulfonate (**72j**, 241 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (7:3) as an eluent to afford **73i** as colorless oil (87%, 173 mg, 0.87 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.53 – 8.47 (m, 1H), 7.57 – 7.51 (m, 1H), 7.51 – 7.45 (m, 2H), 7.12 (dd, *J*=7.6, 4.7, 1H), 7.02 – 6.94 (m, 2H), 3.84 (s, 3H), 2.36 (s, 3H).

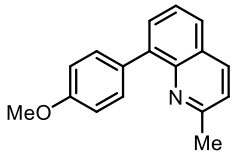
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.5, 158.4, 147.0, 138.6, 133.3, 130.7, 130.4, 121.8, 113.6, 55.4, 20.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1608, 1578, 1513, 1460, 1446, 1440, 1421, 1303, 1294, 1244, 1174, 1118, 1108, 1042, 1024, 1008, 993, 990, 836, 788, 772.

MS (EI, 70 eV): *m/z* (%) = 199 (12), 198 (100), 183 (31), 155 (13), 154 (16).

HR-MS (EI, 70 eV): $[C_{13}H_{12}NO]^{+\bullet}$, calcd.: 198.0912; found: 198.0912 [M^+ -H].

8-(4-methoxyphenyl)-2-methylquinoline (73j)



According to **TP6**, 2-methylquinolin-8-yl nonafluorobutane-1-sulfonate (**72k**, 441 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **73j** as colorless solid (84%, 210 mg, 0.84 mmol).

m.p.: 92 – 93°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.09 (d, *J*=8.4, 1H), 7.84 – 7.76 (m, 2H), 7.74 (ddd, *J*=8.8, 7.6, 1.5, 2H), 7.58 – 7.50 (m, 1H), 7.31 (d, *J*=8.4, 1H), 7.11 – 7.03 (m, 2H), 3.92 (s, 3H), 2.73 (s, 3H).

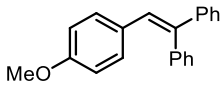
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.1, 158.6, 145.6, 139.5, 136.3, 132.2, 132.1, 130.0, 127.1, 126.9, 125.5, 121.8, 113.4, 55.4, 25.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3014, 2960, 2922, 2839, 1606, 1568, 1507, 1497, 1459, 1452, 1442, 1430, 1331, 1302, 1285, 1246, 1207, 1185, 1177, 1139, 1105, 1031, 1009, 980, 968, 840, 823, 816, 800, 785, 767.

MS (EI, 70 eV): *m/z* (%) = 249 (37), 248 (100), 234 (24), 233 (28), 205 (18), 204 (18), 191 (8).

HR-MS (EI, 70 eV): $[C_{17}H_{14}NO]^{+\bullet}$, calcd.: 248.1070; found: 248.1070 [M^+ -H].

(2-(4-Methoxyphenyl)ethene-1,1-diyl)dibenzene (73k)



According to **TP6**, 2,2-diphenylvinyl nonafluorobutane-1-sulfonate (**72l**, 478 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane as an eluent to afford **73k** as yellowish oil (73%, 210 mg, 0.73 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.39 – 7.25 (m, 8H), 7.25 – 7.20 (m, 2H), 7.00 – 6.94 (m, 2H), 6.93 (s, 1H), 6.72 – 6.63 (m, 2H), 3.76 (s, 3H).

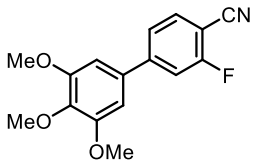
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.5, 143.7, 140.8, 140.7, 130.9, 130.6, 130.2, 128.8, 128.3, 127.8, 127.5, 127.4, 127.3, 113.6, 55.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3054, 3016, 2992, 2951, 2925, 2878, 2853, 2836, 1602, 1574, 1508, 1492, 1463, 1454, 1441, 1415, 1370, 1299, 1248, 1221, 1177, 1152, 1143, 1113, 1079, 1073, 1034, 1009, 999, 943, 877, 832, 814, 806, 780, 767, 752, 733, 714, 700, 690.

MS (EI, 70 eV): *m/z* (%) = 287 (24), 286 (100), 165 (22).

HR-MS (EI, 70 eV): $[C_{21}H_{18}O]^{+\bullet}$, calcd.: 286.1352; found: 286.1353.

3-Fluoro-3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carbonitrile (73l)



According to **TP6**, 4-cyano-3-fluorophenyl trifluoromethanesulfonate (**72e**, 269 mg, 1.0 mmol, 1.0 equiv) reacts with **71b** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (75:25) as an eluent to afford **73l** as colorless crystals (85%, 243 mg, 0.85 mmol).

m.p.: 130 – 132 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.66 (dd, *J*=8.1, 6.7, 1H), 7.44 (dd, *J*=8.1, 1.7, 1H), 7.39 (dd, *J*=10.2, 1.6, 1H), 6.75 (s, 2H), 3.93 (s, 6H), 3.90 (s, 3H).

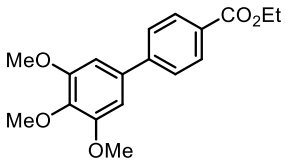
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 163.5 (d, *J*=258.7), 154.0, 148.77 (d, *J*=8.2), 139.4, 133.9 (d, *J*=2.0), 133.8, 123.4 (d, *J*=3.2), 114.9 (d, *J*=20.3), 114.2, 104.7, 99.8 (d, *J*=15.7), 61.1, 56.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2234, 2170, 1620, 1588, 1556, 1492, 1400, 1350, 1256, 1236, 1130, 998, 820, 812, 766.

MS (EI, 70 eV): *m/z* (%) = 287 (100), 272 (77), 244 (49), 229 (40), 214 (29), 212 (44), 201 (26), 184 (45), 158 (99).

HR-MS (EI, 70 eV): $[C_{16}H_{14}FNO_3]^{+\bullet}$, calcd.: 287.0952; found: 287.0944.

Ethyl 3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carboxylate (73m)



According to **TP6**, ethyl 4-(((trifluoromethyl)sulfonyl)oxy)benzoate (**72a**, 298 mg, 1.0 mmol, 1.0 equiv) reacts with **71b** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73m** as colorless oil (81%, 257 mg, 0.81 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.14 – 8.05 (m, 2H), 7.64 – 7.58 (m, 2H), 6.81 (s, 2H), 4.40 (q, *J*=7.1, 2H), 3.94 (s, 6H), 3.90 (s, 3H), 1.42 (t, *J*=7.1, 3H).

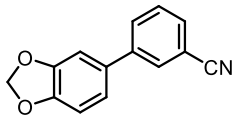
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.6, 153.7, 145.7, 138.5, 136.1, 130.2, 129.4, 127.1, 104.8, 61.1, 61.1, 56.4, 14.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938, 1710, 1588, 1344, 1272, 1242, 1124, 1102, 1078, 1004, 830, 770, 732, 704.

MS (EI, 70 eV): *m/z* (%) = 316 (100) 301 (88), (373 (24), 245 (19), 241 (15), 185 (23), 169 (14), 159 (11).

HR-MS (EI, 70 eV): $[C_{18}H_{20}O_5]^{+\bullet}$, calcd.: 316.1305; found: 316.1300.

3-(Benzo[*d*][1,3]dioxol-5-yl)benzonitrile (73n)



According to **TP6**, 3-cyanophenyl trifluoromethanesulfonate (**72c**, 251 mg, 1.0 mmol, 1.0 equiv) reacts with **71c** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73n** as colorless crystals. (89%, 198 mg, 0.89 mmol).

m.p.: 101 – 103°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.77 (ddd, *J*=2.1, 1.6, 0.6, 1H), 7.72 (ddd, *J*=7.8, 1.9, 1.3, 1H), 7.58 (dt, *J*=7.7, 1.3, 1H), 7.50 (td, *J*=7.8, 0.6, 1H), 7.04 – 7.00 (m, 2H), 6.91 – 6.87 (m, 1H), 6.02 (s, 2H).

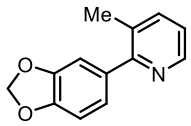
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 148.6, 148.1, 142.2, 133.2, 131.2, 130.4, 130.4, 129.6, 121.0, 118.9, 113.0, 108.9, 107.5, 101.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2235, 1506, 1477, 1453, 1410, 1341, 1274, 1254, 1236, 1232, 1176, 1111, 1035, 934, 914, 908, 900, 847, 815, 802, 786.

MS (EI, 70 eV): *m/z* (%) = 223 (89), 222 (100), 166 (14), 164 (39), 138 (12), 137 (13).

HR-MS (EI, 70 eV): $[C_{14}H_9NO_2]^{+\bullet}$, calcd.: 223.0628 ; found: 223.0625.

2-(Benzo[*d*][1,3]dioxol-5-yl)-3-methylpyridine (73o)



According to **TP6**, 2,2-diphenylvinyl nonafluorobutane-1-sulfonate (**72j,** 241 mg, 1.0 mmol, 1.0 equiv) reacts with **71c** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (7:3) as an eluent to afford **73o** as yellow oil (85%, 181 mg, 0.85 mmol).

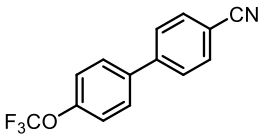
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.50 (dd, *J*=4.8, 1.7, 1H), 7.59 – 7.52 (m, 1H), 7.19 – 7.12 (m, 1H), 7.06 – 6.99 (m, 2H), 6.90 (d, *J*=8.0, 1H), 6.00 (s, 2H), 2.37 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.2, 147.5, 147.4, 147.0, 138.6, 134.8, 130.8, 122.9, 122.0, 109.7, 108.1, 101.2, 20.3.

MS (EI, 70 eV): *m/z* (%) = 212 (100), 182 (10), 154 (35).

HR-MS (EI, 70 eV): $[C_{13}H_{10}NO_2]^{+\bullet}$, calcd.: 212.0706; found: 212.0705 [M^+ -H].

4'-(Trifluoromethoxy)-[1,1'-biphenyl]-4-carbonitrile (73p)



According to **TP6**, 4-cyanophenyl trifluoromethanesulfonate (**72d**, 251 mg, 1.0 mmol, 1.0 equiv) reacts with **71d** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:7) as an eluent to afford **73p** as colorless solid (83%, 217 mg, 0.83 mmol).

m.p.: 50 – 52°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.76 – 7.71 (m, 2H), 7.69 – 7.64 (m, 2H), 7.63 – 7.57 (m, 2H), 7.36 – 7.29 (m, 2H).

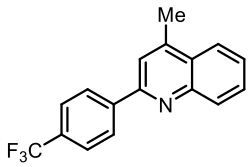
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 149.7 (q, *J*=1.7), 144.3, 138.0, 132.8, 128.8, 127.8, 121.6, 120.6 (q, *J*=257.7), 118.8, 111.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2228, 1606, 1492, 1304, 1290, 1256, 1208, 1166, 1150, 1108, 1022, 1006, 920, 864, 834, 808, 662.

MS (EI, 70 eV): *m/z* (%) = 263 (100), 194 (39), 166 (69), 140 (37), 139 (15), 113 (6).

HR-MS (EI, 70 eV): $[C_{14}H_8F_3NO]^{+\bullet}$, calcd.: 263.0552; found: 263.0552.

4-Methyl-2-(4-(trifluoromethyl)phenyl)quinoline (73q)



According to **TP6**, 4-methylquinolin-2-yl nonafluorobutane-1-sulfonate (**72m**, 441 mg, 1.0 mmol, 1.0 equiv) reacts with **71e** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73q** as yellow oil (83%, 238 mg, 0.83 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.27 (d, *J*=8.1, 2H), 8.18 (d, *J*=8.4, 1H), 8.02 (d, *J*=8.3, 1H), 7.82 – 7.68 (m, 4H), 7.58 (t, *J*=7.6, 1H), 2.79 (s, 3H).

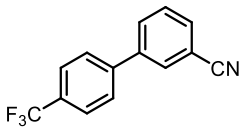
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 155.5, 148.3, 145.5, 143.3 (d, *J*=1.2), 131.1 (q, *J*=32.5), 130.6, 129.8, 127.9, 127.6, 126.7, 125.8 (q, *J*=3.8), 124.4 (q, *J*=272.1), 123.8, 119.7, 19.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1616, 1598, 1551, 1505, 1449, 1418, 1322, 1241, 1234, 1165, 1157, 1143, 1137, 1108, 1077, 1063, 1033, 1015, 951, 905, 878, 866, 841, 787, 768, 758.

MS (EI, 70 eV): *m/z* (%) = 287 (100), 286 (33), 273 (14), 272 (88), 218 (17), 217 (21), 216 (11).

HR-MS (EI, 70 eV): $[C_{17}H_{12}F_3N]^{+\bullet}$, calcd.: 287.0916; found: 287.0912.

4'-(Trifluoromethyl)-[1,1'-biphenyl]-3-carbonitrile (73r)



According to **TP6**, 3-cyanophenyl nonafluorobutane-1-sulfonate (**72n**, 401 mg, 1.0 mmol, 1.0 equiv) reacts with **71e** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73r** as colorless crystals. (91%, 225 mg, 0.91 mmol).

m.p.: 51 – 53°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.86 (t, *J*=1.5, 1H), 7.83 (dt, *J*=7.8, 1.5, 1H), 7.77 – 7.70 (m, 2H), 7.72 – 7.63 (m, 3H), 7.59 (t, *J*=7.8, 1H).

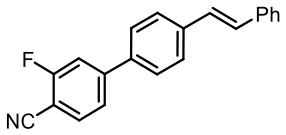
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 142.4, 141.0, 131.7, 130.9, 130.5 (q, *J*=32.7), 130.0, 127.5, 126.2 (q, *J*=3.8), 124.1 (q, *J*=272.1), 118.6, 113.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3072, 2924, 2855, 2231, 1617, 1573, 1480, 1396, 1324, 1165, 1122, 1113, 1070, 1043, 1017, 851, 840, 797.

MS (EI, 70 eV): *m/z* (%) = 247 (100), 228 (11), 228 (9), 197 (10), 177 (12).

HR-MS (EI, 70 eV): $[C_{14}H_8F_3N]^{+\bullet}$, calcd.: 247.0603; found: 247.0600.

(*E*)-3-Fluoro-4'-styryl-[1,1'-biphenyl]-4-carbonitrile (73s)



According to **TP6**, (*E*)-4-styrylphenyl trifluoromethanesulfonate (**72o**, 328 mg, 1.0 mmol, 1.0 equiv) reacts with **71f** (1.5 mmol, 1.5 equiv) prepared according to **TP2**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73s** as colorless solid (71%, 212 mg, 0.71 mmol).

m.p.: 204 – 206 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.68 (dd, *J*=8.1, 6.7, 1H), 7.65 – 7.57 (m, 4H), 7.57 – 7.53 (m, 2H), 7.51 (dd, *J*=8.1, 1.7, 1H), 7.45 (dd, *J*=10.3, 1.6, 1H), 7.43 – 7.36 (m, 2H), 7.33 – 7.27 (m, 1H), 7.21 (d, *J*=16.3, 1H), 7.14 (d, *J*=16.4, 1H).

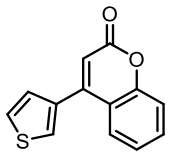
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 163.6 (d, *J*=258.5), 148.1 (d, *J*=8.1), 138.6, 137.0, 136.9 (d, *J*=2.1), 133.9, 130.3, 128.9, 128.2, 127.6, 127.4, 126.8, 123.2 (d, *J*=3.2), 114.6, 114.4, 114.3, 99.8 (d, *J*=15.7).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079, 3022, 2927, 2848, 2231, 1615, 1600, 1575, 1570, 1552, 1487, 1449, 1429, 1404, 1307, 1262, 1213, 1199, 1182, 1118, 1073, 969, 964, 952, 901, 881, 869, 815, 761.

MS (EI, 70 eV): *m/z* (%) = 299 (24), 298 (10), 281 (23), 225 (19), 209 (10), 208 (13), 207 (100), 191 (21), 178 (11), 165 (13).

HR-MS (EI, 70 eV): $[C_{21}H_{14}FN]^{+\bullet}$, calcd.: 299.1105; found: 299.1106.

4-(Thiophen-3-yl)-2*H*-chromen-2-one (73t)



According to **TP6**, 2-oxo-2*H*-chromen-4-yl trifluoromethanesulfonate (**72i**, 294 mg, 1.0 mmol, 1.0 equiv) reacts with **71g** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73t** as yellow solid (84%, 192 mg, 0.84 mmol).

m.p.: 84 – 86 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.70 (dd, *J*=8.0, 1.6, 1H), 7.61 – 7.49 (m, 3H), 7.40 (d, *J*=8.3, 1H), 7.32 – 7.23 (m, 2H), 6.44 (s, 1H).

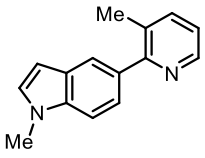
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.0, 154.3, 150.4, 135.9, 132.1, 127.9, 127.2, 126.8, 126.3, 124.4, 119.0, 117.5, 114.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3089, 3078, 1711, 1603, 1560, 1485, 1444, 1413, 1410, 1390, 1385, 1340, 1322, 1274, 1255, 1246, 1207, 1176, 1151, 1140, 1112, 948, 935, 857, 828, 813, 771, 761, 750, 742, 723, 707, 666.

MS (EI, 70 eV): *m/z* (%) = 228 (58), 201 (12), 200 (100), 172 (19), 172 (11), 171 (93).

HR-MS (EI, 70 eV): $[C_{13}H_8O_2S]^{+\bullet}$, calcd.: 228.0240; found: 228.0236.

1-Methyl-5-(3-methylpyridin-2-yl)-1*H*-indole (73u)



According to **TP6**, 3-methylpyridin-2-yl trifluoromethanesulfonate (**72j**, 241 mg, 1.0 mmol, 1.0 equiv) reacts with **71h** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (7:3) as an eluent to afford **73u** as yellow oil (86%, 192 mg, 0.86 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.56 (d, *J*=3.9, 1H), 7.83 – 7.79 (m, 1H), 7.60 – 7.53 (m, 1H), 7.45 (dd, *J*=8.5, 1.6, 1H), 7.39 (d, *J*=8.5, 1H), 7.14 (dd, *J*=7.6, 4.8, 1H), 7.08 (d, *J*=3.1, 1H), 6.55 (d, *J*=3.1, 1H), 3.80 (s, 3H), 2.41 (s, 3H).

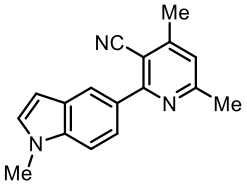
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.0, 146.8, 138.4, 136.4, 132.0, 130.9, 129.4, 128.2, 123.0, 121.6, 121.4, 108.8, 101.5, 32.9, 20.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3046, 2946, 2923, 2817, 1714, 1679, 1616, 1581, 1571, 1563, 1512, 1493, 1458, 1438, 1415, 1378, 1360, 1332, 1297, 1270, 1242, 1222, 1191, 1172, 1151, 1115, 1103, 1079, 1064, 1032, 1006, 992, 887, 788, 760, 747, 718, 660.

MS (EI, 70 eV): *m/z* (%) = 222 (21), 221 (100), 220 (12), 206 (19), 205 (14), 103 (6).

HR-MS (EI, 70 eV): $[C_{15}H_{13}N_2]^{+\bullet}$, calcd.: 221.1073; found: 221.1070 [M^+ -H].

4,6-Dimethyl-2-(1-methyl-1*H*-indol-5-yl)nicotinonitrile (73v)



According to **TP6**, 3-cyano-4,6-dimethylpyridin-2-yl trifluoromethanesulfonate (**72p**, 280 mg, 1.0 mmol, 1.0 equiv) reacts with **71h** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **73v** as colorless crystals (82%, 215 mg, 0.82 mmol).

m.p.: 170 – 172 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.20 – 8.15 (m, 1H), 7.76 (dd, *J*=8.6, 1.8, 1H), 7.42 (d, *J*=8.6, 1H), 7.09 (d, *J*=3.1, 1H), 7.04 (s, 1H), 6.58 (dd, *J*=3.1, 0.8, 1H), 3.82 (s, 3H), 2.64 (s, 3H), 2.58 – 2.56 (m, 3H).

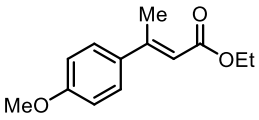
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 162.7, 161.5, 152.4, 137.6, 129.9, 129.4, 128.6, 122.7, 122.4, 121.8, 117.8, 109.3, 105.5, 102.3, 33.1, 25.1, 20.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3084, 2218, 1584, 1544, 1516, 1446, 1428, 1382, 1340, 1326, 1284, 1246, 1092, 882, 866, 812, 780, 762, 734, 726.

MS (EI, 70 eV): *m/z* (%) = 262 (12), 261 (69), 260 (100), 245 (21).

HR-MS (EI, 70 eV): $[C_{17}H_{15}N_3]^{+\bullet}$, calcd.: 261.1260; found: 261.1261.

Ethyl (*E*)-3-(4-methoxyphenyl)but-2-enoate (73w)



According to **TP6**, ethyl (*E*)-3-(((trifluoromethyl)sulfonyl)oxy)but-2-enoate (**72q**, 262 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **73w** as colorless oil (89%, 195 mg, 0.89 mmol).

The E-isomer was verified by NOESY NMR. Z/E > 1/99.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.48 – 7.41 (m, 2H), 6.93 – 6.86 (m, 2H), 6.11 (q, *J*=1.3, 1H), 4.21 (q, *J*=7.1, 2H), 3.82 (s, 3H), 2.56 (d, *J*=1.3, 3H), 1.31 (t, *J*=7.1, 3H).

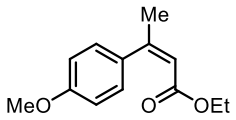
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 167.2, 160.5, 155.0, 134.5, 127.8, 115.5, 113.9, 59.8, 55.4, 17.8, 14.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2980, 2936, 2838, 1706, 1626, 1602, 1574, 1512, 1462, 1440, 1366, 1344, 1288, 1274, 1250, 1152, 1096, 1080, 1030, 872, 828, 808.

MS (EI, 70 eV): *m/z* (%) = 220 (54), 175 (82), 174 (66), 148 (100), 147 (24), 146 (31), 133 (19), 131 (22), 115 (21), 91 (29).

HR-MS (EI, 70 eV): $[C_{13}H_{16}O_3]^{+\bullet}$, calcd.: 220.1094; found: 220.1093.

Ethyl (Z)-3-(4-methoxyphenyl)but-2-enoate (73x)



According to **TP6**, ethyl (*Z*)-3-(((trifluoromethyl)sulfonyl)oxy)but-2-enoate (**72r**, 262 mg, 1.0 mmol, 1.0 equiv) reacts with **71a** (1.5 mmol, 1.5 equiv) prepared according to **TP1**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:7) as an eluent to afford **73x** as yellowish oil (86%, 189 mg, 0.86 mmol).

The Z-isomer was verified by NOESY NMR. Z/E > 99/1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.22 – 7.16 (m, 2H), 6.91 – 6.84 (m, 2H), 5.87 (q, *J*=1.5, 1H), 4.03 (q, *J*=7.1, 2H), 3.82 (s, 3H), 2.17 (d, *J*=1.4, 3H), 1.14 (t, *J*=7.1, 3H).

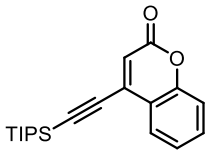
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.3, 159.5, 155.0, 132.8, 128.7, 117.2, 113.4, 59.8, 55.4, 27.2, 14.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2978, 2937, 2906, 2836, 2357, 1717, 1700, 1675, 1652, 1635, 1606, 1575, 1510, 1464, 1456, 1442, 1391, 1387, 1375, 1355, 1290, 1246, 1227, 1155, 1112, 1095, 1080, 1031, 955, 854, 829, 806.

MS (EI, 70 eV): *m/z* (%) = 220 (73), 191 (15), 176 (11), 175 (97), 174 (71), 148 (100), 147 (23), 146 (31), 133 (19), 132 (11), 131 (24), 103 (15), 91 (27).

HR-MS (EI, 70 eV): $[C_{13}H_{16}O_3]^{+\bullet}$, calcd.: 220.1094; found: 220.1092.

4-((Triisopropylsilyl)ethynyl)-2*H*-chromen-2-one (82a)



According to **TP6**, 2-oxo-2*H*-chromen-4-yl trifluoromethanesulfonate (**72i**, 294 mg, 1.0 mmol, 1.0 equiv) reacts with **81a** (1.5 mmol, 1.5 equiv) prepared according to **TP3**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **82a** as colorless solid. (97%, 316 mg, 0.97 mmol).

m.p.: 58 – 60 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.88 (dd, *J*=8.3, 1.6, 1H), 7.55 (ddd, *J*=9.1, 7.4, 1.6, 1H), 7.33 (t, *J*=7.4, 2H), 6.58 (s, 1H), 1.27 – 1.11 (m, 21H).

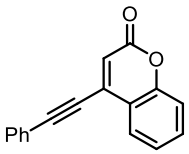
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.3, 153.7, 137.2, 132.3, 126.7, 124.6, 119.5, 118.5, 117.1, 106.8, 99.6, 18.7, 11.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2942, 2891, 2864, 1751, 1727, 1603, 1555, 1485, 1461, 1449, 1361, 1322, 1274, 1249, 1210, 1176, 1146, 1129, 1072, 1059, 1031, 1018, 996, 928, 881, 856, 763, 749, 697, 675, 662.

MS (EI, 70 eV): *m/z* (%) = 301 (40), 283 (85), 255 (51), 245 (91), 231 (70), 227 (100), 213 (88), 161 (70).

HR-MS (EI, 70 eV): $[C_{20}H_{26}O_2Si]^{+\bullet}$, calcd.: 326.1697; found: 326.1692.

4-(Phenylethynyl)-2*H*-chromen-2-one (82b)



According to **TP6**, 2-oxo-2*H*-chromen-4-yl trifluoromethanesulfonate (**72i**, 294 mg, 1.0 mmol, 1.0 equiv) reacts with **81b** (1.5 mmol, 1.5 equiv) prepared according to **TP3**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **82b** as colorless solid (73%, 180 mg, 0.73 mmol).

m.p.: 136 – 137 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.96 (dd, *J*=8.2, 1.6, 1H), 7.68 – 7.62 (m, 2H), 7.57 (ddd, *J*=8.9, 7.5, 1.6, 1H), 7.51 – 7.40 (m, 3H), 7.39 – 7.32 (m, 2H), 6.62 (s, 1H).

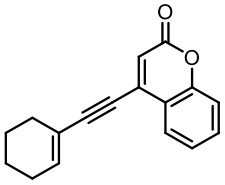
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.3, 153.7, 137.4, 132.4, 132.4, 130.3, 128.8, 126.8, 124.6, 121.3, 118.5, 118.5, 117.2, 102.3, 82.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3065, 3047, 2204, 1750, 1727, 1718, 1688, 1681, 1606, 1593, 1571, 1555, 1487, 1449, 1442, 1439, 1372, 1325, 1282, 1271, 1249, 1189, 1184, 1177, 1172, 1158, 1142, 1125, 1043, 1031, 997, 939, 934, 917, 862, 856, 852, 773, 768, 755, 747, 708, 683, 657.

MS (EI, 70 eV): *m/z* (%) = 246 (100), 219 (14), 218 (84), 190 (15), 189 (99), 188 (17), 187 (19), 163 (15), 95 (21).

HR-MS (EI, 70 eV): $[C_{17}H_{10}O_2]^{+\bullet}$, calcd.: 246.0675; found: 246.0672.

4-(Cyclohex-1-en-1-ylethynyl)-2*H*-chromen-2-one (82c)



According to **TP6**, 2-oxo-2*H*-chromen-4-yl trifluoromethanesulfonate (**72i**, 294 mg, 1.0 mmol, 1.0 equiv) reacts with **81c** (1.5 mmol, 1.5 equiv) prepared according to **TP3**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **82c** as yellowish solid (87%, 218 mg, 0.87 mmol).

m.p.: 114 – 115 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.75 (dd, *J*=8.1, 1.6, 1H), 7.52 – 7.40 (m, 1H), 7.28 – 7.16 (m, 2H), 6.43 – 6.35 (m, 2H), 2.29 – 2.18 (m, 2H), 2.18 – 2.09 (m, 2H), 1.69 – 1.62 (m, 2H), 1.61 – 1.53 (m, 2H).

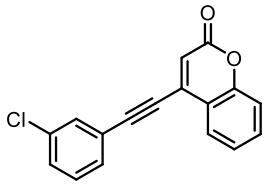
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.5, 153.6, 140.2, 137.8, 132.2, 126.8, 124.4, 119.9, 118.6, 117.6, 117.0, 104.8, 80.8, 28.8, 26.1, 22.1, 21.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2934, 2913, 2875, 2860, 2192, 1713, 1686, 1683, 1651, 1644, 1621, 1600, 1561, 1550, 1486, 1447, 1434, 1425, 1421, 1378, 1352, 1342, 1324, 1279, 1270, 1255, 1244, 1177, 1137, 1120, 1077, 1049, 1028, 932, 918, 863, 854, 841, 777, 762, 753, 707, 668.

MS (EI, 70 eV): *m/z* (%) = 251 (18), 250 (100), 235 (27), 221 (29), 207 (34), 194 (32), 181 (21), 178 (29), 165 (40).

HR-MS (EI, 70 eV): $[C_{17}H_{14}O_2]^{+\bullet}$, calcd.: 250.0988; found: 250.0988

4-((3-Chlorophenyl)ethynyl)-2*H*-chromen-2-one (82d)



According to **TP6**, 2-oxo-2*H*-chromen-4-yl trifluoromethanesulfonate (**72i**, 294 mg, 1.0 mmol, 1.0 equiv) reacts with **81d** (1.5 mmol, 1.5 equiv) prepared according to **TP3**. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **82d** as colorless crystals (93%, 262 mg, 0.93 mmol).

m.p.: 140 – 142 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.92 (dd, *J*=8.3, 1.6, 1H), 7.63 (t, *J*=1.8, 1H), 7.58 (ddd, *J*=9.0, 7.5, 1.6, 1H), 7.52 (dt, *J*=7.5, 1.4, 1H), 7.45 (ddd, *J*=8.1, 2.1, 1.2, 1H), 7.41 – 7.32 (m, 3H), 6.63 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.1, 153.7, 136.9, 134.8, 132.6, 132.1, 130.6, 130.5, 130.1, 126.7, 124.7, 122.9, 119.1, 118.3, 117.2, 100.2, 83.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2215, 1749, 1718, 1674, 1604, 1586, 1565, 1556, 1485, 1472, 1446, 1406, 1374, 1323, 1271, 1257, 1249, 1188, 1174, 1164, 1147, 1126, 1123, 1092, 1079, 1043, 1029, 926, 884, 878, 870, 866, 860, 801, 791, 788, 770, 761, 751, 705, 686, 678, 654.

MS (EI, 70 eV): *m/z* (%) = 282 (32), 280 (100), 254 (25), 252 (75), 245 (24), 189 (96), 188 (28), 187 (49).

HR-MS (EI, 70 eV): $[C_{17}H_9ClO_2]^{+\bullet}$, calcd.: 280.0286; found: 280.0280.

3 Cobalt-Catalyzed Cross-Coupling Reactions of Diarylmanganese Reagents with Secondary Alkyl Iodides

3.1 Typical Procedures

Typical procedure 7 (TP7): Preparation of di(hetero)arylmanganese reagents by magnesium insertion and transmetalation[120]

LiCl (1.2 equiv) was flame dried under high vacuum and allowed to cool to room temperature, then Mg turnings (1.2 equiv) and THF (1 M solution relating to the aryl bromide) were added. The reaction mixture was cooled to 0 °C and the corresponding aryl bromide (1.0 equiv) was added dropwise. The progress of the insertion reaction was monitored by GC-analysis of reaction aliquots quenched with I_2. Then a solution of $MnCl_2 \cdot 2LiCl$ (0.55 equiv, 1 M in THF) was added dropwise at 0 °C and the solution was stirred for 1 h to afford the corresponding diarylmanganese reagent.

Typical procedure 8 (TP8): Preparation of di(hetero)arylmanganese reagents by bromine-magnesium exchange and transmetalation[121]

The corresponding aryl bromide (1.0 equiv) was dissolved in THF (1 M solution relating to the aryl bromide) and the reaction mixture was cooled to the corresponding temperature. Then *i*PrMgCl·LiCl (1.1 equiv) was added dropwise and the reaction was stirred at this temperature until reaction aliquots quenched with I_2 showed full consumption of the starting material. Then a solution of $MnCl_2 \cdot 2LiCl$ (0.55 equiv, 1 M in THF) was added dropwise and the solution was stirred for 1 h before use to afford the corresponding diarylmanganese reagent (ca. 0.5 M in THF).

[120] For magnesium insertion, see: F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel *Chem. - Eur. J.* **2009**, *15*, 7192-7202.

[121] For applications of the bromine-magnesium exchange, see: a) H. Ren, A. Krasovskiy, P. Knochel *Org. Lett.* **2004**, *6*, 4215-4217. b) H. Ren, A. Krasovskiy, P. Knochel *Chem. Commun.* **2005**, 543-545. c) C.-Y. Liu, P. Knochel *Org. Lett.* **2005**, *7*, 2543-2546. d) H. Ren, P. Knochel *Chem. Commun.* **2006**, 726-728. e) P. Sinha, P. Knochel *Synlett* **2006**, 3304-3308. f) C.-Y. Liu, H. Ren, P. Knochel *Org. Lett.* **2006**, *8*, 617-619. g) A. H. Stoll, A. Krasovskiy, P. Knochel *Angew. Chem., Int. Ed.* **2006**, *45*, 606-609. h) F. Kopp, P. Knochel *Synlett* **2007**, *2007*, 0980-0982. i) F. Kopp, S. Wunderlich, P. Knochel *Chem. Commun.* **2007**, 2075-2077. j) W. Lin, L. Chen, P. Knochel *Tetrahedron* **2007**, *63*, 2787-2797. k) C. Despotopoulou, R. C. Bauer, A. Krasovskiy, P. Mayer, J. M. Stryker, P. Knochel *Chem. - Eur. J.* **2008**, *14*, 2499-2506. l) L. Melzig, C. B. Rauhut, P. Knochel *Chem. Commun.* **2009**, 3536-3538. m) C. B. Rauhut, C. Cervino, A. Krasovskiy, P. Knochel *Synlett* **2009**, 67-70.

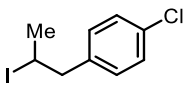
Typical Procedure 9 (TP9): Cobalt-catalyzed cross-coupling of diarylmanganese reagents with secondary alkyl halides

A dry and argon-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with $CoCl_2 \cdot 2LiCl$ (1 M in THF, 0.1 mL, 0.10 mmol, 20 mol%). The secondary alkyl halide (0.50 mmol, 1.0 equiv) and THF (1 mL) were added and the mixture was cooled to -20 °C. The diarylmanganese reagent (0.35 mmol, 0.7 equiv) was added dropwise and the mixture was allowed to warm to rt overnight. A sat. aq. solution of NH_4Cl (5 mL) and EtOAc (5 mL) were added and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvents were evaporated. The residue was subjected to column chromatography purification (SiO_2; *i*hexane:EtOAc) yielding the corresponding title compound.

3.2 Preparation of Starting Materials

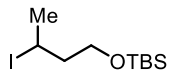
The following starting materials were prepared according to literature procedures with only little deviation.[122] The spectral data of known compounds were in full agreement with the literature.

1-Chloro-4-(2-iodopropyl)benzene (75a)



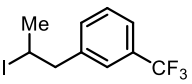
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.31 – 7.27 (m, 2H), 7.14 – 7.10 (m, 2H), 4.29 (dp, *J* = 7.6, 6.8 Hz, 1H), 3.22 (dd, *J* = 14.2, 7.6 Hz, 1H), 3.04 (dd, *J* = 14.2, 7.0 Hz, 1H), 1.90 (d, *J* = 6.8 Hz, 3H).

***tert*-Butyl(3-iodobutoxy)dimethylsilane (75b)[123]**



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.35 (dqd, *J* = 9.5, 6.9, 4.4 Hz, 1H), 3.76 (ddd, *J* = 10.3, 5.7, 4.6 Hz, 1H), 3.65 (ddd, *J* = 10.3, 8.1, 4.8 Hz, 1H), 2.04 – 1.94 (m, 4H), 1.78 (dddd, *J* = 14.6, 8.1, 5.7, 4.4 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

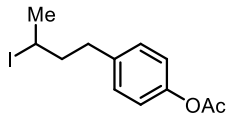
1-(2-Iodopropyl)-3-(trifluoromethyl)benzene (75c)



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ =7.57 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 7.41 – 7.36 (m, 1H), 4.32 (dp, *J* = 7.7, 6.8 Hz, 1H), 3.30 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.13 (dd, *J* = 14.2, 6.9 Hz, 1H), 1.93 (d, *J* = 6.8 Hz, 3H).

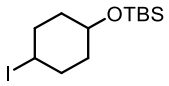
[122] C. W. Cheung, P. Ren, X. Hu *Org. Lett.* **2014**, *16*, 2566-2569.
[123] R. Yefidoff, A. Albeck *Tetrahedron* **2004**, *60*, 8093-8102.

4-(3-Iodobutyl)phenyl acetate (75d)



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.23 – 7.19 (m, 2H), 7.03 – 6.98 (m, 2H), 4.10 (dqd, *J* = 9.2, 6.8, 4.4 Hz, 1H), 2.84 (ddd, *J* = 14.0, 9.0, 5.1 Hz, 1H), 2.69 (ddd, *J* = 13.9, 9.0, 7.0 Hz, 1H), 2.29 (s, 3H), 2.19 – 2.08 (m, 1H), 1.94 (d, *J* = 6.8 Hz, 3H), 1.86 (dddd, *J* = 14.6, 9.0, 7.0, 4.4 Hz, 1H).

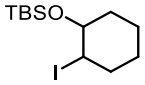
***tert*-Butyl((*cis*-4-iodocyclohexyl)oxy)dimethylsilane (75f)[124]**



dr = 99:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.44 – 4.32 (m, 1H), 3.96 – 3.82 (m, 1H), 2.30 (dtd, *J* = 13.1, 9.0, 3.8 Hz, 2H), 1.97 – 1.87 (m, 2H), 1.72 – 1.62 (m, 2H), 1.63 – 1.52 (m, 2H), 0.90 (s, 9H), 0.04 (s, 6H).

***tert*-Butyl((*cis*-2-iodocyclohexyl)oxy)dimethylsilane (75g)[125]**

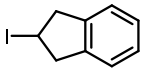


dr = 75:25 (*cis*:*trans*)

^{1}H-NMR (400 MHz, CDCl3, ppm): δ = 4.53 – 4.39 (m, 1H), 3.36 (s br., 1H), 2.32 – 2.20 (m, 1H), 1.96 – 1.84 (m, 1H), 1.79 – 1.60 (m, 3H), 1.57 – 1.30 (m, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H).

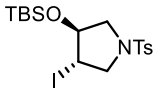
[124] K. Moriya, P. Knochel *Org. Lett.* **2014**, *16*, 924-927.
[125] M. Smietana, V. Gouverneur, C. Mioskowski *Tetrahedron Lett.* **2000**, *41*, 193-195.

2-Iodo-2,3-dihydro-1*H*-indene (75h)[126]



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.28 – 7.23 (m, 2H), 7.23 – 7.18 (m, 2H), 4.71 (tt, *J* = 6.5, 5.0 Hz, 1H), 3.48 (dd, *J* = 16.8, 6.5 Hz, 2H), 3.39 (dd, *J* = 16.8, 5.0 Hz, 2H).

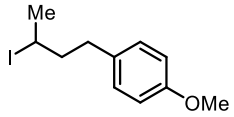
3-((*tert*-Butyldimethylsilyl)oxy)-4-iodo-1-tosylpyrrolidine (75i)[127]



dr = 99:1 (*trans*:*cis*)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.74 – 7.68 (m, 2H), 7.34 – 7.28 (m, 2H), 4.34 (dt, *J* = 4.8, 2.5 Hz, 1H), 3.93 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.88 (dtd, *J* = 5.4, 2.7, 0.8 Hz, 1H), 3.81 (dd, *J* = 10.6, 4.5 Hz, 1H), 3.68 (dd, *J* = 11.1, 2.6 Hz, 1H), 3.17 (ddd, *J* = 10.6, 2.2, 0.9 Hz, 1H), 2.41 (s, 3H), 0.73 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H).

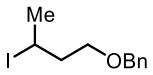
1-(3-Iodobutyl)-4-methoxybenzene (75k)



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.15 – 7.10 (m, 2H), 6.87 – 6.81 (m, 2H), 4.11 (dqd, *J* = 9.1, 6.8, 4.5 Hz, 1H), 3.79 (s, 3H), 2.79 (ddd, *J* = 13.9, 8.8, 5.2 Hz, 1H), 2.64 (ddd, *J* = 13.8, 8.8, 7.0 Hz, 1H), 2.13 (dtd, *J* = 14.2, 8.9, 5.2 Hz, 1H), 1.95 (d, *J* = 6.8 Hz, 3H), 1.84 (dddd, *J* = 14.6, 8.8, 7.1, 4.5 Hz, 1H).

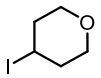
[126] Y. Dai, F. Wu, Z. Zang, H. You, H. Gong *Chem. Eur. J.* **2012**, *18*, 808-812.
[127] J. M. Hammann, D. Haas, A. K. Steib, P. Knochel *Synthesis* **2015**, *47*, 1461-1468.

((3-Iodobutoxy)methyl)benzene (75l)



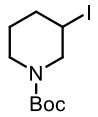
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.39 – 7.27 (m, 5H), 4.64 – 4.44 (m, 2H), 4.39 (dqd, *J*=9.5, 6.9, 4.6, 1H), 3.67 – 3.61 (m, 1H), 3.55 (ddd, *J*=9.6, 8.0, 5.0, 1H), 2.15 – 2.03 (m, 1H), 2.00 – 1.86 (m, 4H).

4-Iodotetrahydro-2H-pyran (75m)



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.45 (tt, *J* = 7.7, 5.5 Hz, 1H), 3.87 – 3.76 (m, 2H), 3.57 – 3.48 (m, 2H), 2.18 – 2.12 (m, 4H).

***tert*-Butyl 3-iodopiperidine-1-carboxylate (75n)[128]**

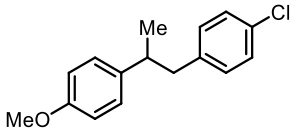


^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.29 – 3.92 (m, 2H), 3.78 (d, *J* = 13.0 Hz, 1H), 3.53 – 3.24 (m, 1H), 3.09 (s, 1H), 2.26 (s, 1H), 2.10 – 1.95 (m, 1H), 1.72 (d, *J* = 13.5 Hz, 1H), 1.57 (s, 1H), 1.46 (s, 9H).

[128] A. Boto, R. Hernández, Y. de León, J. R. Murguía, A. Rodriguez-Afonso *Eur. J. Org. Chem.* **2005**, 673-682.

3.3 Cobalt-Catalyzed Cross-Coupling Reactions of Diarylmanganese Reagents with Secondary Alkyl Iodides

1-Chloro-4-(2-(4-methoxyphenyl)propyl)benzene (76a)



According to **TP9**, 1-chloro-4-(2-iodopropyl)benzene (**75a**, 140 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:1.5) as an eluent to afford **76a** as a colorless solid (75%, 98 mg, 0.38 mmol).

Mp.: 62.2 – 63.5 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.21 – 7.16 (m, 2H), 7.08 – 7.03 (m, 2H), 6.98 – 6.93 (m, 2H), 6.85 – 6.79 (m, 2H), 3.79 (s, 3H), 2.92 (h, *J* = 6.9 Hz, 1H), 2.84 (dd, *J* = 13.3, 7.0 Hz, 1H), 2.74 (dd, *J* = 13.2, 7.6 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 3H).

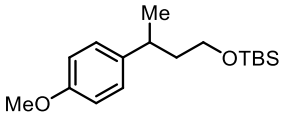
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.0, 139.4, 138.6, 131.7, 130.6, 128.3, 128.0, 113.8, 55.4, 44.7, 41.1, 21.6.

FT-IR (ATR, cm^{-1}): 2956, 2925, 2852, 1513, 1490, 1455, 1440, 1259, 1241, 1177, 1088, 1031, 1008, 829, 814, 806, 798, 698, 656.

MS (EI, 70 eV): m/z (%) = 260 (2), 136 (8), 135 (100), 125 (4), 105 (5), 103 (4), 91 (5), 77 (3).

HR-MS (EI, 70 eV): $[C_{16}H_{17}ClO]^{+\bullet}$, calcd.: 260.0962; found: 260.0952.

***tert*-Butyl(3-(4-methoxyphenyl)butoxy)dimethylsilane (76b)**



According to **TP9**, *tert*-butyl(3-iodobutoxy)dimethylsilane (**75b**, 157 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and

was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76b** as a yellowish oil (73%, 108 mg, 0.37 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.14 – 7.08 (m, 2H), 6.86 – 6.81 (m, 2H), 3.79 (s, 3H), 3.57 – 3.43 (m, 2H), 2.84 (h, *J* = 7.1 Hz, 1H), 1.80 – 1.73 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.00 (d, *J* = 0.8 Hz, 6H).

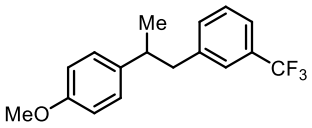
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.9, 139.5, 128.0, 113.8, 61.4, 55.4, 41.5, 35.4, 26.1, 22.7, 18.4, -5.1.

FT-IR (ATR, cm^{-1}): 2953, 2927, 2856, 2834, 1612, 1512, 1462, 1245, 1176, 1095, 1037, 899, 827, 773.

MS (EI, 70 eV): m/z (%) = 237 (100), 165 (20), 135 (22), 97 (20), 89 (56), 85 (42), 84 (31), 83 (29), 71 (49), 69 (32), 57 (89), 55 (29), 44 (25), 43 (46), 41 (28).

HR-MS (EI, 70 eV): $[C_{13}H_{21}O_2Si]^{+\bullet}$, calcd.: 237.1305; found: 237.1314 [M^+-*t*Bu].

1-(2-(4-Methoxyphenyl)propyl)-3-(trifluoromethyl)benzene (76c)



According to **TP9**, 1-(2-iodopropyl)-3-(trifluoromethyl)benzene (**75c**, 157 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **76c** as a colorless oil (77%, 114 mg, 0.39 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.44 – 7.39 (m, 1H), 7.35 – 7.27 (m, 2H), 7.21 – 7.17 (m, 1H), 7.09 – 7.03 (m, 2H), 6.85 – 6.80 (m, 2H), 3.79 (s, 3H), 3.02 – 2.89 (m, 2H), 2.88 – 2.79 (m, 1H), 1.24 (d, *J* = 6.8 Hz, 3H).

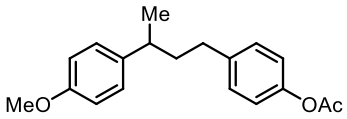
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.2, 141.8, 138.3, 132.7, 130.5 (q, *J* = 31.9 Hz), 128.5, 128.0, 126.0 (q, *J* = 3.9 Hz), 124.4 (q, *J* = 272.2 Hz), 122.8 (q, *J* = 3.9 Hz), 113.9, 55.4, 45.2, 41.0, 21.4.

FT-IR (ATR, cm^{-1}): 2959, 2929, 2836, 2360, 1611, 1512, 1449, 1326, 1245, 1176, 1159, 1118, 1072, 1037, 904, 827, 796, 702, 661.

MS (EI, 70 eV): m/z (%) = 158 (4), 136 (8), 135 (100), 105 (5), 103 (4), 91 (6), 79 (3), 77 (4), 42 (3).

HR-MS (EI, 70 eV): $[C_{17}H_{17}F_3O]^{+\bullet}$, calcd.: 294.1226; found: 294.1232.

4-(3-(4-Methoxyphenyl)butyl)phenyl acetate (76d)



According to **TP9**, 4-(3-iodobutyl)phenyl acetate (**75d**, 159 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **76d** as a colorless oil (75%, 112 mg, 0.37 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.16 – 7.09 (m, 4H), 7.00 – 6.94 (m, 2H), 6.90 – 6.84 (m, 2H), 3.81 (s, 3H), 2.68 (h, *J*=7.1, 1H), 2.49 (td, *J*=7.9, 1.8, 2H), 2.29 (s, 3H), 1.93 – 1.82 (m, 2H), 1.25 (d, *J*=6.9, 3H).

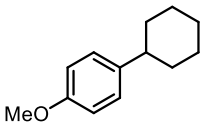
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 169.8, 158.0, 148.7, 140.3, 139.4, 129.4, 128.0, 121.3, 113.9, 55.4, 40.2, 38.8, 33.4, 22.9, 21.3.

FT-IR (ATR, cm^{-1}): 3032, 2995, 2955, 2928, 2866, 2835, 1758, 1610, 1510, 1507, 1368, 1244, 1213, 1189, 1164, 1031, 1017, 1010, 910, 828, 808.

MS (EI, 70 eV): m/z (%) = 299 (4), 298 (22), 256 (14), 148 (5), 136 (10), 135 (100), 121 (8), 107 (12), 105 (4), 91 (5), 77 (5), 43 (8).

HR-MS (EI, 70 eV): $[C_{19}H_{22}O_3]^{+\bullet}$, calcd.: 298.1563; found: 298.1565.

1-Cyclohexyl-4-methoxybenzene (76e)[99a]



According to **TP9**, iodocyclohexane (**75e**, 105 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76e** as a colorless solid (84%, 80 mg, 0.42 mmol).

Mp.: 58.1-58.7 °C

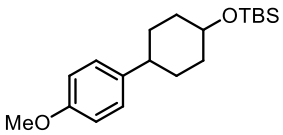
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.17 – 7.11 (m, 2H), 6.87 – 6.82 (m, 2H), 3.79 (s, 3H), 2.46 (ddq, *J*=11.7, 8.7, 3.3, 1H), 1.91 – 1.81 (m, 4H), 1.79 – 1.71 (m, 1H), 1.47 – 1.32 (m, 4H), 1.31 – 1.20 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.8, 140.5, 127.8, 113.8, 55.4, 43.8, 34.9, 27.1, 26.3.

MS (EI, 70 eV): m/z (%) = 190 (56), 147 (97), 121 (34), 111 (36), 97 (59), 95 (47), 85 (51), 84 (93), 83 (45), 71 (65), 69 (68), 57 (100), 55 (74), 43 (71), 42 (62), 39 (72).

HR-MS (EI, 70 eV): $[C_{13}H_{18}O]^{+\bullet}$, calcd.: 190.1352; found: 190.1349.

***tert*-Butyl((4-(4-methoxyphenyl)cyclohexyl)oxy)dimethylsilane (76f)**



According to **TP9**, *tert*-butyl((4-iodocyclohexyl)oxy)dimethylsilane (**75f**, 170 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76f** as a colorless oil (75%, 120 mg, 0.37 mmol).

Signals of both diastereomers are given (dr = 70:30).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.18 – 7.09 (m, 2H), 6.89 – 6.79 (m, 2H), 3.79 (d, *J*=1.9, 3H), 4.09 – 3.58 (m, 1H), 2.51 – 2.38 (m, 1H), 2.03 – 1.72 (m, 4H), 1.64 – 1.37 (m, 4H), 0.92 (s, 9H), 0.07 (s, 6H).

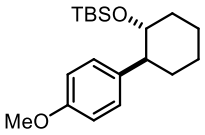
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.9, 157.8, 140.4, 139.2, 127.8, 127.7, 113.8, 113.8, 71.6, 66.0, 55.4, 43.3, 42.8, 36.5, 34.0, 33.1, 28.3, 26.1, 26.0, 18.4, 18.3, -4.4, -4.7.

FT-IR (ATR, cm^{-1}): 2927, 2855, 1612, 1582, 1512, 1471, 1462, 1450, 1441, 1420, 1387, 1375, 1360, 1304, 1281, 1245, 1177, 1117, 1091, 1040, 1019, 1005, 988, 938, 891, 859, 833, 824, 805, 793, 772, 749, 668.

MS (EI, 70 eV): m/z (%) = 263 (18), 189 (8), 188 (50), 187 (100), 173 (5), 134 (15), 121 (17), 75 (39), 73 (8).

HR-MS (EI, 70 eV): $[C_{19}H_{32}O_2Si]^{+\bullet}$, calcd.: 320.2166; found: 320.2168.

tert-Butyl((2-(4-methoxyphenyl)cyclohexyl)oxy)dimethylsilane (76g)



According to **TP9**, *tert*-butyl((*cis*-2-iodocyclohexyl)oxy)dimethylsilane (**75g**, 170 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76g** as a colorless oil (83%, 133 mg, 0.41 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.13 – 7.07 (m, 2H), 6.84 – 6.78 (m, 2H), 3.78 (s, 3H), 3.47 (td, *J*=9.8, 4.5, 1H), 2.39 (ddd, *J*=13.1, 9.6, 3.6, 1H), 2.03 – 1.93 (m, 1H), 1.87 – 1.76 (m, 2H), 1.76 – 1.70 (m, 1H), 1.53 (qd, *J*=13.0, 3.6, 1H), 1.44 – 1.24 (m, 3H), 0.68 (s, 9H), -0.19 (s, 3H), -0.50 (s, 3H).

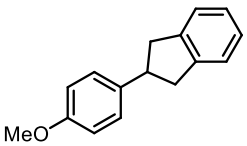
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.1, 137.5, 129.3, 113.5, 76.2, 55.5, 52.2, 36.9, 33.1, 26.3, 25.9, 25.4, 18.0, -4.6, -5.4.

FT-IR (ATR, cm^{-1}): 2926, 2854, 2360, 2341, 1512, 1360, 1244, 1176, 1124, 1090, 1039, 983, 881, 857, 846, 831, 813, 772, 753, 666.

MS (EI, 70 eV): m/z (%) = 305 (1), 265 (6), 264 (22), 263 (100), 189 (12), 187 (7), 165 (7), 121 (33), 75 (33), 73 (12).

HR-MS (EI, 70 eV): $[C_{18}H_{29}O_2Si]^{+\bullet}$, calcd.: 305.1931; found: 305.1936 $[M^+-CH_3]$.

2-(4-Methoxyphenyl)-2,3-dihydro-1*H*-indene (76h)



According to **TP9**, 2-iodo-2,3-dihydro-1*H*-indene (**75h**, 122 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76h** as a colorless oil (70%, 78 mg, 0.35 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.29 – 7.19 (m, 4H), 7.22 – 7.17 (m, 2H), 6.90 – 6.84 (m, 2H), 3.81 (s, 3H), 3.66 (p, *J*=8.6, 1H), 3.33 (dd, *J*=15.4, 8.0, 2H), 3.06 (dd, *J*=15.5, 9.0, 2H).

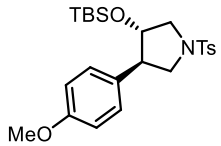
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.1, 143.2, 137.7, 128.1, 126.5, 124.4, 114.0, 55.4, 45.0, 41.2.

FT-IR (ATR, cm^{-1}): 3066, 3019, 2932, 2903, 2833, 1611, 1511, 1482, 1458, 1441, 1243, 1220, 1177, 1034, 825, 741.

MS (EI, 70 eV): m/z (%) = 225 (19), 224 (100), 209 (34), 116 (36), 115 (30), 82 (18), 57 (23), 55 (21), 43 (47), 42 (14).

HR-MS (EI, 70 eV): $[C_{16}H_{16}O]^{+\bullet}$, calcd.: 224.1196; found: 224.1193.

3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-methoxyphenyl)-1-tosylpyrrolidine (76i)



According to **TP9**, 3-((*tert*-butyldimethylsilyl)oxy)4-iodo-1-tosylpyrrolidine (**75i**, 241 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **76i** as a colorless solid (59%, 136 mg, 0.29 mmol).

Signals of the main diastereomer are given (dr = 95:5).

Mp.: 124.3-126.1 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.78 – 7.74 (m, 2H), 7.37 – 7.32 (m, 2H), 7.15 – 7.05 (m, 2H), 6.86 – 6.80 (m, 2H), 4.04 (q, *J*=5.3, 1H), 3.78 (s, 3H), 3.67 – 3.58 (m, 2H), 3.51 (dd, *J*=9.8, 6.2, 1H), 3.10 – 2.97 (m, 2H), 2.45 (s, 3H), 0.71 (s, 9H), -0.16 (s, 3H), -0.21 (s, 3H).

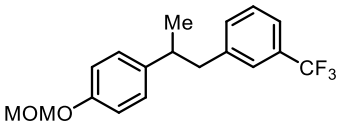
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.9, 143.6, 134.0, 131.2, 129.8, 128.6, 127.7, 114.2, 77.7, 55.4, 54.4, 51.9, 51.5, 25.7, 21.7, 17.9, -4.9, -5.0.

FT-IR (ATR, cm^{-1}): 2953, 2929, 2885, 2856, 1515, 1346, 1250, 1161, 1093, 1034, 834, 778, 666.

MS (EI, 70 eV): m/z (%) = 406 (10), 405 (24), 400 (100), 270 (3), 174 (3), 149 (4), 147 (5), 134 (5), 125 (6), 121 (17), 91 (8), 72 (8), 42 (7).

HR-MS (EI, 70 eV): $[C_{23}H_{32}NO_4SSi]^{+\bullet}$, calcd.: 446.1816; found: 446.1805 $[M^+-CH_3]$.

1-(2-(4-(Methoxymethoxy)phenyl)propyl)-3-(trifluoromethyl)benzene (76j)



According to **TP9**, 1-(2-iodopropyl)-3-(trifluoromethyl)benzene (**75c**, 314 mg, 1 mmol, 1 equiv, in 2 mL THF) reacts with the di(4-(methoxymethoxy)benzene)manganese reagent (**74b**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76j** as a colorless oil (76%, 246 mg, 0.76 mmol).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.42 (d, *J*=7.7, 1H), 7.33 (t, *J*=7.7, 1H), 7.27 (s, 1H), 7.22 (d, *J*=7.6, 1H), 7.08 – 7.03 (m, 2H), 6.98 – 6.93 (m, 2H), 5.15 (s, 2H), 3.48 (s, 3H), 3.02 – 2.88 (m, 2H), 2.87 – 2.79 (m, 1H), 1.24 (d, *J*=6.7, 3H).

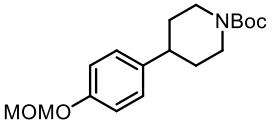
^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 155.8, 141.8, 139.7, 132.7 (d, *J* = 1.2 Hz), 130.5 (q, *J* = 31.9 Hz), 128.6, 128.1, 126.0 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 272.3 Hz), 122.9 (q, *J* = 3.8 Hz), 116.3, 94.7, 56.1, 45.1, 41.1, 21.4.

FT-IR (ATR, cm^{-1}): 2961, 2930, 2899, 1511, 1328, 1314, 1234, 1200, 1152, 1120, 1073, 1019, 999, 921, 831, 796, 702, 661.

MS (EI, 70 eV): m/z (%) = 324 (2), 293 (2), 166 (9), 165 (100), 159 (10), 136 (4), 135 (42), 91 (6), 77 (2), 45 (80).

HR-MS (EI, 70 eV): $[C_{18}H_{19}F_3O_2]^{+\bullet}$, calcd.: 324.1332; found: 324.1334.

***tert*-Butyl 4-(4-(methoxymethoxy)phenyl)piperidine-1-carboxylate (76k)**



According to **TP9**, *tert*-butyl 4-iodopiperidine-1-carboxylate (**75j**, 156 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-(methoxymethoxy)benzene)manganese reagent (**74b**, 0.35 mmol, 0.7 equiv)

prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (10:1) as an eluent to afford **76k** as a colorless solid (75%, 121 mg, 0.38 mmol).

Mp.: 84.8 – 86.6 °C

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.14 – 7.09 (m, 2H), 7.00 – 6.97 (m, 2H), 5.15 (s, 2H), 4.23 (s, 2H), 3.47 (s, 3H), 2.85 – 2.73 (m, 2H), 2.59 (tt, *J* = 12.2, 3.6 Hz, 1H), 1.79 (d, *J* = 12.6 Hz, 2H), 1.63 – 1.54 (m, 2H), 1.48 (s, 9H).

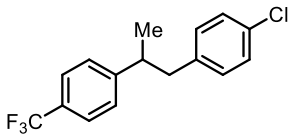
^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 155.8, 155.0, 139.4, 127.8, 116.4, 94.7, 79.5, 56.1, 44.7, 42.1, 33.5, 28.6.

FT-IR (ATR, cm^{-1}): 2974, 2932, 2850, 1687, 1511, 1422, 1365, 1279, 1228, 1198, 1151, 1123, 1106, 1077, 1001, 985, 922, 831, 762.

MS (EI, 70 eV): m/z (%) = 321 (7), 265 (22), 248 (14), 221 (22), 220 (15), 203 (17), 189 (6), 176 (14), 82 (13), 57 (89), 56 (15), 45 (100), 41 (17).

HR-MS (EI, 70 eV): $[C_{18}H_{27}NO_4]^{+\bullet}$, calcd.: 321.1935; found: 321.1931.

1-Chloro-4-(2-(4-(trifluoromethyl)phenyl)propyl)benzene (76l)



According to **TP9**, *tert*-butyl 4-iodopiperidine-1-carboxylate (**75a**, 140 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-(trifluoromethyl)benzene)manganese reagent (**74c**, 0.35 mmol, 0.7 equiv) prepared according to **TP8**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane as an eluent to afford **76l** as a colorless oil (81%, 106 mg, 0.41 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.52 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.22 – 7.17 (m, 2H), 7.00 – 6.93 (m, 2H), 3.04 (h, *J* = 7.1 Hz, 1H), 2.92 – 2.77 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H).

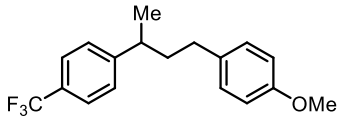
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 150.5 (d, *J* = 1.5 Hz), 138.6, 132.0, 130.5, 128.7 (q, *J* = 30.7 Hz), 128.5, 127.5, 125.4 (q, *J* = 4.0 Hz), 124.4 (q, *J* = 272.0 Hz), 44.2, 41.9, 21.2.

FT-IR (ATR, cm^{-1}): 2964, 2928, 2874, 2856, 1618, 1491, 1322, 1161, 1114, 1105, 1093, 1068, 1014, 834, 801.

MS (EI, 70 eV): m/z (%) = 298 (10), 174 (35), 173 (35), 153 (11), 133 (14), 127 (36), 126 (18), 125 (100), 103 (4), 90 (4), 89 (9), 44 (5), 43 (7).

HR-MS (EI, 70 eV): $[C_{16}H_{14}ClF_3]^{+\bullet}$, calcd.: 298.0731; found: 298.0736.

1-Methoxy-4-(3-(4-(trifluoromethyl)phenyl)butyl)benzene (76m)



According to **TP9**, 1-(3-iodobutyl)-4-methoxybenzene (**75k**, 145 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-(trifluoromethyl)benzene)manganese reagent (**74c**, 0.35 mmol, 0.7 equiv) prepared according to **TP8**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76m** as a colorless oil (87%, 134 mg, 0.43 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.57 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.06 – 7.01 (m, 2H), 6.84 – 6.80 (m, 2H), 3.79 (s, 3H), 2.78 (h, J = 7.1 Hz, 1H), 2.52 – 2.41 (m, 2H), 1.98 – 1.85 (m, 2H), 1.28 (d, J = 6.9 Hz, 3H).

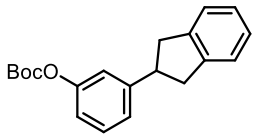
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.9, 151.6 (d, J = 1.5 Hz), 134.2, 129.3, 128.4 (q, J = 32.2 Hz), 127.6, 125.5 (q, J = 4.0 Hz), 124.5 (q, J = 272.0 Hz), 113.9, 55.4, 40.0, 39.5, 33.0, 22.4.

FT-IR (ATR, cm^{-1}): 2958, 2931, 2835, 2360, 2332, 1511, 1323, 1243, 1161, 1115, 1066, 1036, 1016, 837, 820.

MS (EI, 70 eV): m/z (%) = 309 (5), 308 (23), 135 (17), 134 (12), 122 (16), 121 (100), 108 (6), 91 (10), 78 (7), 77 (8), 57 (6).

HR-MS (EI, 70 eV): $[C_{18}H_{19}F_3O]^{+\bullet}$, calcd.: 308.1383; found: 308.1383.

tert-Butyl (3-(2,3-dihydro-1*H*-inden-2-yl)phenyl) carbonate (76n)



According to **TP9**, 2-iodo-2,3-dihydro-1H-indene (**75h**, 122 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3-(BocO)benzene-1-yl)manganese reagent (**74d**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76n** as a colorless oil (76%, 118 mg, 0.38 mmol).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.30 (t, *J* = 7.9 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.21 – 7.14 (m, 3H), 7.12 – 7.10 (m, 1H), 7.03 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H), 3.70 (p, *J* = 8.6 Hz, 1H), 3.36 (dd, *J* = 15.5, 8.2 Hz, 2H), 3.08 (dd, *J* = 15.5, 8.9 Hz, 2H), 1.56 (s, 9H).

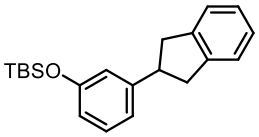
^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 152.1, 151.3, 147.4, 142.8, 129.4, 126.6, 124.5, 124.5, 120.1, 119.2, 83.6, 45.4, 40.9, 27.9.

FT-IR (ATR, cm^{-1}): 2980, 2934, 2907, 2844, 2361, 2332, 1753, 1586, 1369, 1269, 1253, 1232, 1138, 1002, 780, 742, 692.

MS (EI, 70 eV): m/z (%) = 211 (11), 210 (84), 195 (15), 178 (8), 165 (11), 117 (9), 116 (27), 115 (11), 57 (100), 40 (11).

HR-MS (EI, 70 eV): $[C_{20}H_{22}O_3]^{+\bullet}$, calcd.: 310.1563; found: 310.1556.

tert-Butyl(3-(2,3-dihydro-1*H*-inden-2-yl)phenoxy)dimethylsilane (76o)



According to **TP9**, 2-iodo-2,3-dihydro-1H-indene (**75h**, 122 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3-(TBSO)benzene-1-yl)manganese reagent (**74e**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane as eluent to afford **76o** as a colorless oil (74%, 120 mg, 0.37 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.29 – 7.21 (m, 2H), 7.21 – 7.14 (m, 3H), 6.92 – 6.88 (m, 1H), 6.79 (t, *J* = 2.2 Hz, 1H), 6.70 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H), 3.65 (p, *J* = 8.5 Hz, 1H), 3.34 (dd, *J* = 15.5, 8.1 Hz, 2H), 3.07 (dd, *J* = 15.5, 8.8 Hz, 2H), 0.98 (s, 9H), 0.18 (s, 6H).

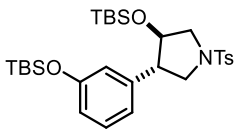
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 155.8, 147.2, 143.1, 129.4, 126.6, 124.4, 120.2, 118.8, 117.9, 45.5, 41.0, 25.9, 18.4, -4.2.

FT-IR (ATR, cm^{-1}): 3069, 3023, 2954, 2930, 2857, 1602, 1584, 1483, 1472, 1278, 1252, 1158, 899, 836, 808, 779, 740, 695.

MS (EI, 70 eV): m/z (%) = 325 (5), 324 (20), 269 (6), 268 (21), 267 (100), 134 (4), 117 (32), 115 (9), 91 (4).

HR-MS (EI, 70 eV): $[C_{21}H_{28}OSi]^{+\bullet}$, calcd.: 324.1904; found: 324.1904.

3-((*tert*-Butyldimethylsilyl)oxy)-4-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-tosylpyrrolidine (76p)



According to **TP9**, 3-((*tert*-butyldimethylsilyl)oxy)4-iodo-1-tosylpyrrolidine (**75i**, 241 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3-(TBSO)benzene-1-yl)manganese reagent (**74e**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as eluent to afford **76p** as a colorless solid (92%, 257 mg, 0.46 mmol).

Mp.: 96.6-97.2 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.79 – 7.73 (m, 2H), 7.37 – 7.32 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.77 – 6.67 (m, 3H), 4.07 (dt, *J* = 5.6 Hz, 1H), 3.67 – 3.59 (m, 2H), 3.50 (dd, *J* = 10.0, 6.6 Hz, 1H), 3.05 (dd, *J* = 10.2, 5.2 Hz, 1H), 2.99 (dt, *J* = 7.8, 6.2 Hz, 1H), 2.45 (s, 3H), 0.98 (s, 9H), 0.72 (s, 9H), 0.18 (s, 6H), -0.16 (s, 3H), -0.21 (s, 3H).

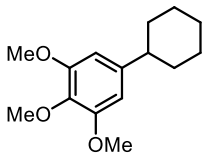
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 156.1, 143.6, 140.7, 133.9, 129.8, 129.8, 127.7, 120.5, 119.3, 119.0, 77.6, 54.5, 52.6, 51.4, 25.8, 25.7, 21.7, 18.4, 17.9, -4.2, -4.9, -5.0.

FT-IR (ATR, cm^{-1}): 2954, 2929, 2886, 2857, 1602, 1585, 1485, 1472, 1463, 1347, 1280, 1252, 1160, 1143, 1093, 1003, 905, 861, 834, 813, 778, 732, 699, 663, 608, 589.

MS (EI, 70 eV): m/z (%) = 507 (4), 506 (19), 505 (33), 504 (100), 224 (8), 149 (3), 91 (3), 73 (4).

HR-MS (EI, 70 eV): $[C_{28}H_{44}NO_4SSi_2]^{+\bullet}$, calcd.: 546.2524; found: 546.2526 $[M^+ -CH_3]$

5-Cyclohexyl-1,2,3-trimethoxybenzene (76q)



According to **TP9**, iodocyclohexane (**75e**, 105 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3,4,5-(trimethoxy)benzene)manganese reagent (**74f**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as eluent to afford **76q** as a colorless oil (80%, 101 mg, 0.40 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.43 (s, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 2.50 – 2.38 (m, 1H), 1.94 – 1.80 (m, 4H), 1.79 – 1.70 (m, 1H), 1.47 – 1.34 (m, 4H), 1.31 – 1.19 (m, 1H).

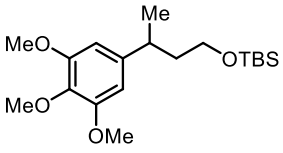
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 153.2, 144.1, 136.2, 103.9, 61.0, 56.2, 45.2, 34.8, 27.0, 26.3.

FT-IR (ATR, cm^{-1}): 2923, 2850, 2363, 2341, 1587, 1508, 1449, 1418, 1330, 1238, 1184, 1133, 1121, 1103, 1009,956, 822, 775, 689.

MS (EI, 70 eV): m/z (%) = 251 (25), 250 (100), 236 (9), 235 (51), 207 (13), 181 (16), 176 (10), 153 (22), 151 (15), 57 (8).

HR-MS (EI, 70 eV): $[C_{15}H_{22}O_3]^{+\bullet}$, calcd.: 250.1563; found: 250.1562.

***tert*-Butyldimethyl(3-(3,4,5-trimethoxyphenyl)butoxy)silane (76r)**



According to **TP9**, *tert*-butyl(3-iodobutoxy)dimethylsilane (**75b**, 157 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3,4,5-(trimethoxy)benzene)manganese reagent (**74f**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column

chromatography on silica using *i*hexane:EtOAc (100:8) as eluent to afford **76r** as a colorless oil (60%, 157 mg, 0.30 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.40 (s, 2H), 3.85 (s, 6H), 3.83 (s, 3H), 3.60 – 3.44 (m, 2H), 2.82 (h, *J* = 7.1 Hz, 1H), 1.77 (q, *J* = 6.8 Hz, 2H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.01 (d, *J* = 2.0 Hz, 6H).

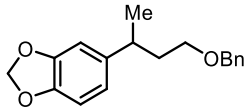
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 153.2, 143.3, 136.3, 104.1, 61.3, 61.0, 56.2, 41.4, 36.7, 26.1, 22.5, 18.4, -5.1.

FT-IR (ATR, cm^{-1}): 2954, 2929, 2856, 1588, 1510, 1459, 1420, 1322, 1236, 1128, 1100, 1010, 982, 899, 832, 811, 773, 664.

MS (EI, 70 eV): m/z (%) = 354 (8), 299 (7), 298 (20), 297 (100), 282 (12), 252 (13), 196 (11), 195 (10), 191 (8), 89 (14), 73 (5).

HR-MS (EI, 70 eV): $[C_{19}H_{34}O_4Si]^{+\bullet}$, calcd.: 354.2226; found: 354.2226.

5-(4-(Benzyloxy)butan-2-yl)benzo[*d*][1,3]dioxole (76s)



According to **TP9**, ((3-iodobutoxy)methyl)benzene (**75l**, 145 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(1,3-benzodioxol-5-yl)manganese reagent (**74g**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:1) as eluent to afford **76s** as a colorless oil (66%, 93 mg, 0.33 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.38 – 7.26 (m, 5H), 6.75 – 6.68 (m, 2H), 6.63 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 4.44 (d, *J* = 2.2 Hz, 2H), 3.45 – 3.29 (m, 2H), 2.86 (dp, *J* = 9.0, 6.9 Hz, 1H), 1.95 – 1.75 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H).

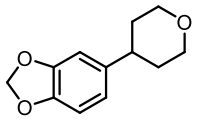
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 147.7, 145.7, 141.1, 138.7, 128.5, 127.8, 127.6, 120.1, 108.2, 107.4, 100.9, 73.1, 68.6, 38.4, 36.5, 22.7.

FT-IR (ATR, cm^{-1}): 3030, 2958, 2926, 2868, 1503, 1486, 1453, 1439, 1363, 1241, 1204, 1189, 1093, 1075, 1060, 1038, 937, 912, 860, 808, 734, 697.

MS (EI, 70 eV): m/z (%) = 285 (11), 284 (65), 192 (52), 176 (21), 163 (30), 150 (30), 149 (100), 135 (27), 119 (19), 91 (88), 65 (18), 43 (20).

HR-MS (EI, 70 eV): $[C_{18}H_{20}O_3]^{+\bullet}$, calcd.: 284.1407; found: 284.1406.

5-(Tetrahydro-2*H*-pyran-4-yl)benzo[*d*][1,3]dioxole (76t)



According to **TP9**, 4-iodotetrahydro-2*H*-pyran (**75m**, 106 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(1,3-benzodioxol-5-yl)manganese reagent (**74g**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as eluent to afford **76t** as a colorless solid (70%, 72 mg, 0.35 mmol).

Mp.: 73.4-74.2 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.76 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H), 6.67 (ddd, *J* = 8.0, 1.8, 0.6 Hz, 1H), 5.93 (s, 2H), 4.08 (td, *J* = 3.0, 0.9 Hz, 1H), 4.06 – 4.03 (m, 1H), 3.54 – 3.46 (m, 2H), 2.68 (tt, *J* = 10.6, 5.3 Hz, 1H), 1.84 – 1.69 (m, 4H).

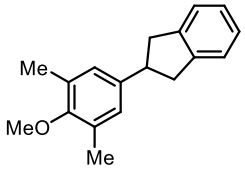
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 147.8, 146.0, 140.2, 119.6, 108.4, 107.4, 101.0, 68.5, 41.5, 34.4.

FT-IR (ATR, cm^{-1}): 2935, 2915, 2841, 1503, 1487, 1440, 1385, 1262, 1247, 1227, 1189, 1129, 1085, 1037, 1020, 980, 930, 911, 875, 806, 776.

MS (EI, 70 eV): m/z (%) = 207 (13), 206 (100), 162 (39), 161 (24), 149 (13), 148 (45), 146 (27), 135 (26), 132 (12), 119 (13), 91 (13), 89 (12).

HR-MS (EI, 70 eV): $[C_{12}H_{14}O_3]^{+\bullet}$, calcd.: 206.0937; found: 206.0934.

2-(4-Methoxy-3,5-dimethylphenyl)-2,3-dihydro-1*H*-indene (76u)



According to **TP9**, 2-iodo-2,3-dihydro-1*H*-indene (**75h**, 122 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(2-methoxy-1,3-dimethylbenzene-5-yl)manganese reagent (**74h**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under

stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as eluent to afford **76u** as a colorless solid (63%, 79 mg, 0.31 mmol).

Mp.: 52.8-54.2 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.26 – 7.21 (m, 2H), 7.22 – 7.16 (m, 2H), 6.97 (s, 2H), 3.73 (s, 3H), 3.60 (p, *J* = 8.8 Hz, 1H), 3.31 (dd, *J* = 15.4, 8.1 Hz, 2H), 3.06 (dd, *J* = 15.6, 9.4 Hz, 2H), 2.28 (s, 6H).

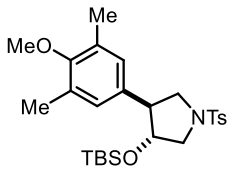
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 155.4, 143.2, 140.7, 130.8, 127.5, 126.5, 124.4, 59.8, 45.2, 41.2, 16.3.

FT-IR (ATR, cm^{-1}): 3020, 2934, 2842, 1482, 1459, 1447, 1436, 1224, 1144, 1015, 870, 763, 741.

MS (EI, 70 eV): m/z (%) = 253 (13), 252 (100), 237 (29), 222 (9), 179 (9), 136 (33), 121 (10).

HR-MS (EI, 70 eV): $[C_{18}H_{20}O]^{+\bullet}$, calcd.: 252.1509; found: 252.1507.

3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-methoxy-3,5-dimethylphenyl)-1-tosylpyrrolidine (76v)



According to **TP9**, 3-((*tert*-butyldimethylsilyl)oxy)4-iodo-1-tosylpyrrolidine (**75i**, 241 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(2-methoxy-1,3-dimethylbenzene-5-yl)manganese reagent (**74h**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as eluent to afford **76v** as a colorless solid (82%, 200 mg, 0.41 mmol).

Mp.: 104.5-106.1 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.81 – 7.72 (m, 2H), 7.38 – 7.32 (m, 2H), 6.77 (s, 2H), 4.03 (q, *J* = 5.4 Hz, 1H), 3.68 (s, 3H), 3.67 – 3.58 (m, 2H), 3.50 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.06 (dd, *J* = 10.2, 5.1 Hz, 1H), 2.94 (dt, *J* = 7.9, 6.1 Hz, 1H), 2.45 (s, 3H), 2.23 (s, 6H), 0.71 (s, 9H), -0.15 (s, 3H), -0.21 (s, 3H).

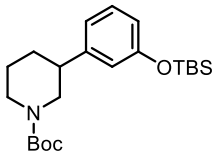
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 156.2, 143.6, 134.4, 134.1, 131.1, 129.8, 127.8, 127.7, 77.6, 59.8, 54.4, 52.0, 51.3, 25.7, 21.7, 18.0, 16.2, -5.0, -5.0.

FT-IR (ATR, cm^{-1}): 2951, 2928, 2886, 1598, 1472, 1346, 1252, 1225, 1160, 1091, 1034, 1009, 868, 835, 811, 777, 733, 665, 594, 580.

MS (EI, 70 eV): m/z (%) = 474 (6), 435 (11), 434 (58), 433 (100), 432 (60), 270 (5), 175 (8), 162 (8), 149 (36), 91 (9), 73 (8).

HR-MS (EI, 70 eV): $[C_{26}H_{39}NO_4SSi]^{+\bullet}$, calcd.: 489.2364; found: 489.2344.

***tert*-butyl 3-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)piperidine-1-carboxylate (76w)**



According to **TP9**, *tert*-butyl 3-iodopiperidine-1-carboxylate (**75n**, 156 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3-(TBSO)benzene-1-yl)manganese reagent (**74e**, 0.35 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as eluent to afford **76w** as a yellowish oil (60%, 116 mg, 0.30 mmol).

^{1}H-NMR (600 MHz, $CDCl_3$, ppm): δ = 7.18 – 7.13 (m, 1H), 6.82 (dt, J = 7.7, 1.4 Hz, 1H), 6.72 – 6.68 (m, 2H), 4.15 (s, 2H), 2.79 – 2.56 (m, 3H), 2.04 – 1.95 (m, 1H), 1.82 – 1.71 (m, 1H), 1.65 – 1.53 (m, 2H), 1.47 (s, 9H), 0.98 (s, 9H), 0.20 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 155.9, 155.0, 145.3, 129.4, 120.2, 119.1, 118.3, 79.6, 60.5, 31.9, 28.7, 25.9, 25.6, 21.2, 18.4, 14.4, -4.2.

FT-IR (ATR, cm^{-1}): 2955, 2930, 2857, 1693, 1602, 1584, 1483, 1473, 1464, 1439, 1417, 1391, 1364, 1280, 1252, 1158, 1148, 1134, 1002, 965, 887, 861, 837, 810, 779, 698.

MS (EI, 70 eV): m/z (%) = 391 (2), 318 (7), 290 (8), 279 (19), 278 (100), 234 (9), 73 (8), 57 (29), 44 (9), 43 (8), 41 (5).

HR-MS (EI, 70 eV): $[C_{22}H_{37}NO_3Si]^{+\bullet}$, calcd.: 391.2537; found: 391.2533.

4 Iron-Catalyzed Cross-Coupling Reactions of Di(hetero)arylmanganese Reagents and Primary and Secondary Alkyl Halides

4.1 Typical Procedures

Typical procedure 10 (TP10): Directed manganation of functionalized aromatics and heteroaromatics using $(TMP)_2Mn\cdot 2MgCl_2\cdot 4LiCl$[86]

In a dry argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, the corresponding starting material (2 mmol) was dissolved in THF (2 mL). This solution was cooled to the given temperature, then $(TMP)_2Mn\cdot 2MgCl_2\cdot 4LiCl$ (0.5 M in THF, 4.8 mL, 2.4 mmol) was added dropwise and stirred at this temperature for the indicated time.

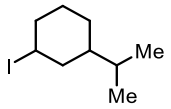
Typical Procedure 11 (TP11): Iron-catalyzed cross-coupling of di(hetero)arylmanganese reagents with alkyl halides

A dry and argon-flushed 20 mL Schlenk tube, equipped with a stirring bar and a septum, was charged with anhydrous $FeCl_2$ (25 mg, 0.20 mmol, 20 mol%). The alkyl halide (1 mmol, 1.0 equiv) and THF (1 mL) were added and the mixture was cooled to -20 °C. The di(hetero)arylmanganese reagent (0.7 mmol, 0.7 equiv) was added dropwise and the mixture was allowed to warm to room temperature overnight. A sat. aq. solution of NH_4Cl (5 mL) and EtOAc (5 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvents were evaporated. The residue was subjected to column chromatography purification (SiO_2; *i*hexane:EtOAc) yielding the corresponding title compound.

4.2 Preparation of Starting Materials

The following starting materials were prepared according to literature procedures with only little deviation.[122] The spectral data of known compounds were in full agreement with the literature.

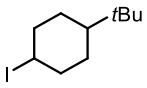
syn-1-Iodo-3-isopropylcyclohexane (75q)



dr = 99:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.93 (t, *J*=3.6, 1H), 2.11 – 1.99 (m, 2H), 1.81 – 1.59 (m, 4H), 1.53 – 1.41 (m, 2H), 1.29 (ddd, *J*=14.5, 10.9, 3.5, 1H), 1.14 – 1.00 (m, 1H), 0.86 (d, *J*=6.8, 6H).

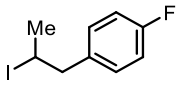
1-(_tert_-Butyl)-4-iodocyclohexane (75s)



dr = 99:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.88 (s, 1H), 2.12 (d, *J*=13.1, 2H), 1.67 – 1.60 (m, 2H), 1.62 – 1.43 (m, 4H), 1.12 – 1.01 (m, 1H), 0.89 (s, 9H).

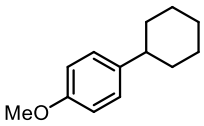
1-Fluoro-4-(2-iodopropyl)benzene (75t)



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.17 – 7.12 (m, 2H), 7.04 – 6.97 (m, 2H), 4.29 (h, *J*=7.0, 1H), 3.22 (dd, *J*=14.2, 7.5, 1H), 3.03 (dd, *J*=14.2, 7.1, 1H), 1.90 (d, *J*=6.8, 3H).

4.3 Iron-Catalyzed Cross-Coupling Reactions of Di(hetero)arylmanganese Reagents and Primary and Secondary Alkyl Halides

1-Cyclohexyl-4-methoxybenzene (76e)[99a]



According to **TP11**, iodocyclohexane (**75e**, 210 mg, 1.0 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76e** as a colorless solid (73%, 139 mg, 0.73 mmol).

Mp.: 58.1-58.7 °C

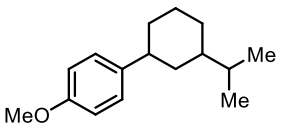
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.17 – 7.11 (m, 2H), 6.87 – 6.82 (m, 2H), 3.79 (s, 3H), 2.46 (ddq, *J*=11.7, 8.7, 3.3, 1H), 1.91 – 1.81 (m, 4H), 1.79 – 1.71 (m, 1H), 1.47 – 1.32 (m, 4H), 1.31 – 1.20 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.8, 140.5, 127.8, 113.8, 55.4, 43.8, 34.9, 27.1, 26.3.

MS (EI, 70 eV): m/z (%) = 190 (56), 147 (97), 121 (34), 111 (36), 97 (59), 95 (47), 85 (51), 84 (93), 83 (45), 71 (65), 69 (68), 57 (100), 55 (74), 43 (71), 42 (62), 39 (72).

HR-MS (EI, 70 eV): $[C_{13}H_{18}O]^{+\bullet}$, calcd.: 190.1352; found: 190.1349.

1-(3-Isopropylcyclohexyl)-4-methoxybenzene (76x)



According to **TP11**, **75q** (252 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76x** as a colorless oil (51%, 119 mg, 0.51 mmol).

The signals of the major diastereomer are given (dr = 83:17).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.19 – 7.12 (m, 2H), 6.90 – 6.83 (m, 2H), 3.80 (s, 3H), 2.48 (tt, *J*=11.7, 3.4, 1H), 1.95 – 1.81 (m, 3H), 1.76 (dtt, *J*=11.6, 3.4, 1.8, 1H), 1.54 – 1.33 (m, 3H), 1.33 – 1.21 (m, 2H), 1.12 (dt, *J*=12.8, 11.8, 1H), 0.90 (dd, *J*=6.8, 3.7, 6H).

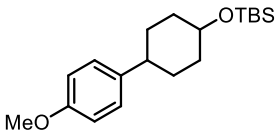
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.8, 140.5, 127.8, 113.8, 55.4, 44.6, 44.0, 38.4, 34.7, 33.2, 29.5, 27.0, 20.0, 19.9.

FT-IR (ATR, cm^{-1}): 2954, 2922, 2852, 1512, 1462, 1444, 1244, 1176, 1038, 824, 806.

MS (EI, 70 eV): m/z (%) = 232 (55), 189 (78), 147 (100), 134 (68), 121 (77).

HR-MS (EI, 70 eV): $[C_{16}H_{24}O]^{+\bullet}$, calcd.: 232.1822; found: 232.1821.

tert-Butyl((4-(4-methoxyphenyl)cyclohexyl)oxy)dimethylsilane (76y)



According to **TP11**, *tert*-butyl((4-iodocyclohexyl)oxy)dimethylsilane (**75f**, 340 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76y** as a colorless oil (66%, 211 mg, 0.66 mmol).

Signals of both diastereomers are given (dr = 75:25).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.18 – 7.09 (m, 2H), 6.89 – 6.79 (m, 2H), 3.79 (d, *J*=1.9, 3H), 4.09 – 3.58 (m, 1H), 2.51 – 2.38 (m, 1H), 2.03 – 1.72 (m, 4H), 1.64 – 1.37 (m, 4H), 0.92 (s, 9H), 0.07 (s, 6H).

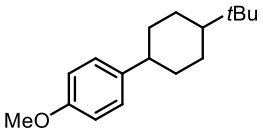
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.9, 157.8, 140.4, 139.2, 127.8, 127.7, 113.8, 113.8, 71.6, 66.0, 55.4, 43.3, 42.8, 36.5, 34.0, 33.1, 28.3, 26.1, 26.0, 18.4, 18.3, -4.4, -4.7.

FT-IR (ATR, cm^{-1}): 2927, 2855, 1612, 1582, 1512, 1471, 1462, 1450, 1441, 1420, 1387, 1375, 1360, 1304, 1281, 1245, 1177, 1117, 1091, 1040, 1019, 1005, 988, 938, 891, 859, 833, 824, 805, 793, 772, 749, 668.

MS (EI, 70 eV): m/z (%) = 263 (18), 188 (50), 187 (100), 121 (17), 75 (39).

HR-MS (EI, 70 eV): $[C_{19}H_{32}O_2Si]^{+\bullet}$, calcd.: 320.2166; found: 320.2168.

1-(4-(*tert*-Butyl)cyclohexyl)-4-methoxybenzene (76z)



According to **TP11**, 1-(*tert*-butyl)-4-iodocyclohexane (**75s**, 266 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76z** as a colorless solid (70%, 172 mg, 0.70 mmol).

Signals of both diastereomers are given (dr = 60:40).

Mp.: 52.0-53.8 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.26 (s, 2H), 7.16 – 7.11 (m, 2H), 6.89 – 6.81 (m, 4H), 3.80 (d, *J*=5.6, 6H), 2.99 (s, 1H), 2.40 (tt, *J*=12.3, 3.4, 1H), 2.26 – 2.14 (m, 2H), 1.98 – 1.84 (m, 5H), 1.81 – 1.70 (m, 1H), 1.61 – 1.53 (m, 2H), 1.47 – 1.33 (m, 2H), 1.25 – 1.01 (m, 6H), 0.85 (d, *J*=32.3, 18H).

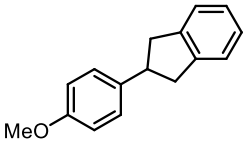
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): 157.8, 157.3, 140.2, 137.4, 128.7, 127.8, 113.8, 113.6, 55.4, 55.4, 48.4, 47.9, 43.8, 35.7, 35.2, 32.8, 32.6, 31.1, 27.9, 27.8, 27.7, 22.8.

FT-IR (ATR, cm^{-1}): 2936, 2852, 1610, 1512, 1482, 1464, 1442, 1364, 1288, 1248, 1180, 1036, 838, 824, 816, 802, 776.

MS (EI, 70 eV): m/z (%) = 246 (65), 147 (100), 121 (38), 57 (40), 55 (21), 44 (29).

HR-MS (EI, 70 eV): $[C_{17}H_{26}O]^{+\bullet}$, calcd.: 246.1979; found: 246.1974.

2-(4-Methoxyphenyl)-2,3-dihydro-1*H*-indene (76h)



According to **TP11**, 2-iodo-2,3-dihydro-1*H*-indene (**75h**, 244 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76h** as colorless oil (88%, 197 mg, 0.88 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.29 – 7.19 (m, 4H), 7.22 – 7.17 (m, 2H), 6.90 – 6.84 (m, 2H), 3.81 (s, 3H), 3.66 (p, *J*=8.6, 1H), 3.33 (dd, *J*=15.4, 8.0, 2H), 3.06 (dd, *J*=15.5, 9.0, 2H).

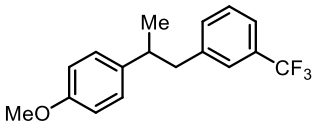
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.1, 143.2, 137.7, 128.1, 126.5, 124.4, 114.0, 55.4, 45.0, 41.2.

FT-IR (ATR, cm^{-1}): 3066, 3019, 2932, 2903, 2833, 1611, 1511, 1482, 1458, 1441, 1243, 1220, 1177, 1034, 825, 741.

MS (EI, 70 eV): m/z (%) = 225 (19), 224 (100), 209 (34), 116 (36), 115 (30).

HR-MS (EI, 70 eV): $[C_{16}H_{16}O]^{+\bullet}$, calcd.: 224.1196; found: 224.1193.

1-(2-(4-Methoxyphenyl)propyl)-3-(trifluoromethyl)benzene (76c)



According to **TP11**, 1-(2-iodopropyl)-3-(trifluoromethyl)benzene (**75c**, 314 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **76c** as a colorless oil (52%, 152 mg, 0.52 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.44 – 7.39 (m, 1H), 7.35 – 7.27 (m, 2H), 7.21 – 7.17 (m, 1H), 7.09 – 7.03 (m, 2H), 6.85 – 6.80 (m, 2H), 3.79 (s, 3H), 3.02 – 2.89 (m, 2H), 2.88 – 2.79 (m, 1H), 1.24 (d, *J* = 6.8 Hz, 3H).

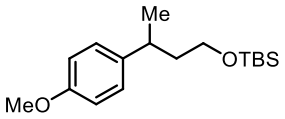
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.2, 141.8, 138.3, 132.7, 130.5 (q, *J* = 31.9 Hz), 128.5, 128.0, 126.0 (q, *J* = 3.9 Hz), 124.4 (q, *J* = 272.2 Hz), 122.8 (q, *J* = 3.9 Hz), 113.9, 55.4, 45.2, 41.0, 21.4.

FT-IR (ATR, cm^{-1}): 2959, 2929, 2836, 2360, 1611, 1512, 1449, 1326, 1245, 1176, 1159, 1118, 1072, 1037, 904, 827, 796, 702, 661.

MS (EI, 70 eV): m/z (%) = 135 (100), 105 (5), 103 (4), 91 (6), 79 (3), 77 (4), 42 (3).

HR-MS (EI, 70 eV): $[C_{17}H_{17}F_3O]^{+\bullet}$, calcd.: 294.1226; found: 294.1232.

***tert*-Butyl(3-(4-methoxyphenyl)butoxy)dimethylsilane (76b)**



According to **TP11**, *tert*-butyl(3-iodobutoxy)dimethylsilane (**75b**, 314 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76b** as a yellowish oil (44%, 130 mg, 0.44 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.14 – 7.08 (m, 2H), 6.86 – 6.81 (m, 2H), 3.79 (s, 3H), 3.57 – 3.43 (m, 2H), 2.84 (h, *J* = 7.1 Hz, 1H), 1.80 – 1.73 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.00 (d, *J* = 0.8 Hz, 6H).

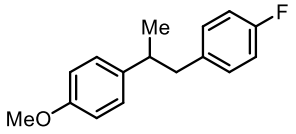
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.9, 139.5, 128.0, 113.8, 61.4, 55.4, 41.5, 35.4, 26.1, 22.7, 18.4, -5.1.

FT-IR (ATR, cm^{-1}): 2953, 2927, 2856, 2834, 1612, 1512, 1462, 1245, 1176, 1095, 1037, 899, 827, 773.

MS (EI, 70 eV): m/z (%) = 237 (100), 89 (56), 85 (42), 84 (31), 71 (49), 69 (32), 57 (89), 43 (46).

HR-MS (EI, 70 eV): $[C_{13}H_{21}O_2Si]^{+\bullet}$, calcd.: 237.1305; found: 237.1314 [M^+-*t*Bu].

1-Fluoro-4-(2-(4-methoxyphenyl)propyl)benzene (76aa)



According to **TP11**, 1-fluoro-4-(2-iodopropyl)benzene (**75t**, 264 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was

worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76aa** as colorless solid (58%, 142 mg, 0.58 mmol).

Mp.: 42.2-43.4 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.09 – 7.03 (m, 2H), 7.02 – 6.96 (m, 2H), 6.94 – 6.87 (m, 2H), 6.85 – 6.80 (m, 2H), 3.79 (s, 3H), 2.88 (ddd, *J*=29.2, 13.7, 7.0, 2H), 2.74 (dd, *J*=13.2, 7.6, 1H), 1.23 (d, *J*=6.8, 3H).

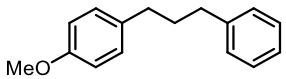
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): 161.41 (d, *J*=243.2), 158.00, 138.77, 136.58, 130.58 (d, *J*=7.7), 128.05, 114.90 (d, *J*=21.0), 113.81, 55.37, 44.55, 41.27, 21.50.

FT-IR (ATR, cm^{-1}): 2950, 2922, 1504, 1466, 1454, 1442, 1262, 1236, 1220, 1180, 1156, 1114, 1102, 1036, 1010, 830, 816, 726, 714.

MS (EI, 70 eV): m/z (%) = 244 (2), 135 (100), 119 (2), 109 (3), 105 (7), 103 (3).

HR-MS (EI, 70 eV): $[C_{16}H_{17}FO]^{+\bullet}$, calcd.: 244.1258; found: 244.1278.

1-Methoxy-4-(3-phenylpropyl)benzene (76ab)



According to **TP11**, (3-iodopropyl)benzene (**75u**, 246 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-anisyl)manganese reagent (**74a**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76ab** as colorless oil (46%, 103 mg, 0.46 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.34 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 7.16 – 7.11 (m, 2H), 6.89 – 6.84 (m, 2H), 3.81 (s, 3H), 2.65 (dt, *J*=17.0, 7.7, 4H), 2.02 – 1.91 (m, 2H).

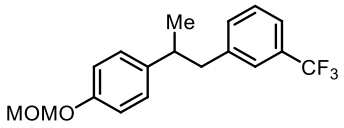
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): 157.9, 142.5, 134.5, 129.4, 128.6, 128.4, 125.8, 113.9, 55.4, 35.5, 34.6, 33.3.

FT-IR (ATR, cm^{-1}): 3026, 2934, 2856, 2834, 1612, 1584, 1510, 1496, 1462, 1454, 1442, 1300, 1242, 1176, 1106, 1036, 826, 808, 742, 698.

MS (EI, 70 eV): m/z (%) = 226 (41), 134 (18), 121 (100), 91 (20), 78 (6), 77 (9).

HR-MS (EI, 70 eV): $[C_{16}H_{18}O]^{+\bullet}$, calcd.: 226.1353; found: 226.1351.

1-(2-(4-(Methoxymethoxy)phenyl)propyl)-3-(trifluoromethyl)benzene (76j)



According to **TP11**, 1-(2-iodopropyl)-3-(trifluoromethyl)benzene (**75c**, 314 mg, 1 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-(methoxymethoxy)benzene)manganese reagent (**74b**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The mixture was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76j** as a colorless oil (46%, 148 mg, 0.46 mmol).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.42 (d, *J*=7.7, 1H), 7.33 (t, *J*=7.7, 1H), 7.27 (s, 1H), 7.22 (d, *J*=7.6, 1H), 7.08 – 7.03 (m, 2H), 6.98 – 6.93 (m, 2H), 5.15 (s, 2H), 3.48 (s, 3H), 3.02 – 2.88 (m, 2H), 2.87 – 2.79 (m, 1H), 1.24 (d, *J*=6.7, 3H).

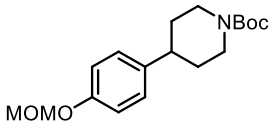
^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 155.8, 141.8, 139.7, 132.7 (d, *J* = 1.2 Hz), 130.5 (q, *J* = 31.9 Hz), 128.6, 128.1, 126.0 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 272.3 Hz), 122.9 (q, *J* = 3.8 Hz), 116.3, 94.7, 56.1, 45.1, 41.1, 21.4.

FT-IR (ATR, cm^{-1}): 2961, 2930, 2899, 1511, 1328, 1314, 1234, 1200, 1152, 1120, 1073, 1019, 999, 921, 831, 796, 702, 661.

MS (EI, 70 eV): m/z (%) = 324 (2), 165 (100), 159 (10), 135 (42), 45 (80).

HR-MS (EI, 70 eV): $[C_{18}H_{19}F_3O_2]^{+\bullet}$, calcd.: 324.1332; found: 324.1334.

tert-Butyl 4-(4-(methoxymethoxy)phenyl)piperidine-1-carboxylate (76k)



According to **TP11**, *tert*-butyl 4-iodopiperidine-1-carboxylate (**75j**, 311 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-(methoxymethoxy)benzene)manganese reagent (**74v**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (10:1) as an eluent to afford **76k** as a colorless solid (62%, 198 mg, 0.62 mmol).

Mp.: 84.8 – 86.6 °C

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.14 – 7.09 (m, 2H), 7.00 – 6.97 (m, 2H), 5.15 (s, 2H), 4.23 (s, 2H), 3.47 (s, 3H), 2.85 – 2.73 (m, 2H), 2.59 (tt, J = 12.2, 3.6 Hz, 1H), 1.79 (d, J = 12.6 Hz, 2H), 1.63 – 1.54 (m, 2H), 1.48 (s, 9H).

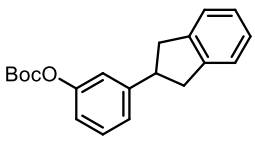
^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 155.8, 155.0, 139.4, 127.8, 116.4, 94.7, 79.5, 56.1, 44.7, 42.1, 33.5, 28.6.

FT-IR (ATR, cm^{-1}): 2974, 2932, 2850, 1687, 1511, 1422, 1365, 1279, 1228, 1198, 1151, 1123, 1106, 1077, 1001, 985, 922, 831, 762.

MS (EI, 70 eV): m/z (%) = 321 (7), 265 (22), 221 (22), 203 (17), 57 (89), 45 (100).

HR-MS (EI, 70 eV): $[C_{18}H_{27}NO_4]^{+\bullet}$, calcd.: 321.1935; found: 321.1931.

tert-Butyl (3-(2,3-dihydro-1*H*-inden-2-yl)phenyl) carbonate (76n)



According to **TP11**, 2-iodo-2,3-dihydro-1*H*-indene (**75h**, 244 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(3-(BocO)benzene-1-yl)manganese reagent (**74d**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76n** as a colorless oil (56%, 175 mg, 0.56 mmol).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.30 (t, *J* = 7.9 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.21 – 7.14 (m, 3H), 7.12 – 7.10 (m, 1H), 7.03 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H), 3.70 (p, *J* = 8.6 Hz, 1H), 3.36 (dd, *J* = 15.5, 8.2 Hz, 2H), 3.08 (dd, *J* = 15.5, 8.9 Hz, 2H), 1.56 (s, 9H).

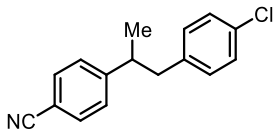
^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 152.1, 151.3, 147.4, 142.8, 129.4, 126.6, 124.5, 124.5, 120.1, 119.2, 83.6, 45.4, 40.9, 27.9.

FT-IR (ATR, cm^{-1}): 2980, 2934, 2907, 2844, 2361, 2332, 1753, 1586, 1369, 1269, 1253, 1232, 1138, 1002, 780, 742, 692.

MS (EI, 70 eV): m/z (%) = 211 (11), 210 (84), 116 (27), 115 (11), 57 (100), 40 (11).

HR-MS (EI, 70 eV): $[C_{20}H_{22}O_3]^{+\bullet}$, calcd.: 310.1564; found: 310.1556.

4-(1-(4-Chlorophenyl)propan-2-yl)benzonitrile (76ac)



According to **TP11**, 1-chloro-4-(2-iodopropyl)benzene (**75a**, 281 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-cyanophenyl)manganese reagent (**74i**, 0.7 mmol, 0.7 equiv) prepared according to **TP8** (exchange at 0 °C for 2 h), at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **76ac** as yellowish solid (57%, 147 mg, 0.57 mmol).

Mp.: 58.0-59.0 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.57 – 7.53 (m, 2H), 7.23 – 7.16 (m, 4H), 6.94 – 6.90 (m, 2H), 3.03 (h, *J*=7.1, 1H), 2.89 – 2.75 (m, 2H), 1.28 (d, *J*=6.9, 3H).

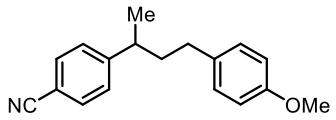
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): 151.9, 138.2, 132.4, 132.1, 130.5, 128.5, 128.1, 119.1, 110.2, 44.0, 42.2, 21.0.

FT-IR (ATR, cm^{-1}): 2960, 2926, 2856, 2222, 1606, 1504, 1490, 1456, 1408, 1370, 1108, 1088, 1014, 832, 802, 766, 728.

MS (EI, 70 eV): m/z (%) = 255 (10), 130 (25), 127 (29), 125 (100).

HR-MS (EI, 70 eV): $[C_{16}H_{14}ClN]^{+\bullet}$, calcd.: 255.0810; found: 255.0811.

4-(4-(4-Methoxyphenyl)butan-2-yl)benzonitrile (76ad)



According to **TP11**, 1-(3-iodobutyl)-4-methoxybenzene (**75k**, 290 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-cyanophenyl)manganese reagent (**74i**, 0.7 mmol, 0.7 equiv) prepared according to **TP8** (exchange at 0 °C for 2 h), at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:5) as an eluent to afford **76ad** as yellow oil (48%, 127 mg, 0.48 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.62 – 7.57 (m, 2H), 7.32 – 7.27 (m, 2H), 7.06 – 6.99 (m, 2H), 6.84 – 6.78 (m, 2H), 3.78 (s, 3H), 2.77 (h, *J*=7.0, 1H), 2.53 – 2.36 (m, 2H), 1.89 (dt, *J*=8.4, 7.4, 2H), 1.27 (d, *J*=6.9, 3H).

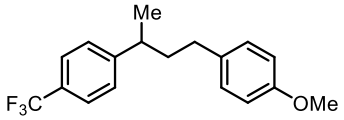
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): 158.0, 153.2, 133.9, 132.4, 129.3, 128.1, 119.2, 113.9, 110.0, 55.4, 39.8, 39.7, 32.9, 22.1.

FT-IR (ATR, cm^{-1}): 2958, 2928, 2856, 2226, 1608, 1512, 1456, 1442, 1416, 1300, 1242, 1176, 1118, 1036, 1018, 832, 820, 750, 702.

MS (EI, 70 eV): m/z (%) = 265 (37), 121 (100), 108 (6), 91 (7), 77 (8).

HR-MS (EI, 70 eV): $[C_{18}H_{19}NO]^{+\bullet}$, calcd.: 265.1462; found: 265.1460.

1-Methoxy-4-(3-(4-(trifluoromethyl)phenyl)butyl)benzene (76m)



According to **TP11**, 1-(3-iodobutyl)-4-methoxybenzene (**75k**, 290 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(4-(trifluoromethyl)benzene)manganese reagent (**74c**, 0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76m** as a colorless oil (78%, 242 mg, 0.78 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.57 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.06 – 7.01 (m, 2H), 6.84 – 6.80 (m, 2H), 3.79 (s, 3H), 2.78 (h, *J* = 7.1 Hz, 1H), 2.52 – 2.41 (m, 2H), 1.98 – 1.85 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 3H).

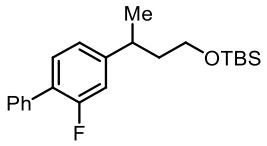
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.9, 151.6 (d, *J* = 1.5 Hz), 134.2, 129.3, 128.4 (q, *J* = 32.2 Hz), 127.6, 125.5 (q, *J* = 4.0 Hz), 124.5 (q, *J* = 272.0 Hz), 113.9, 55.4, 40.0, 39.5, 33.0, 22.4.

FT-IR (ATR, cm^{-1}): 2958, 2931, 2835, 2360, 2332, 1511, 1323, 1243, 1161, 1115, 1066, 1036, 1016, 837, 820.

MS (EI, 70 eV): m/z (%) = 308 (23), 135 (17), 134 (12), 122 (16), 121 (100), 91 (10).

HR-MS (EI, 70 eV): $[C_{18}H_{19}F_3O]^{+\bullet}$, calcd.: 308.1383; found: 308.1383.

***tert*-Butyl(3-(2-fluoro-[1,1'-biphenyl]-4-yl)butoxy)dimethylsilane (76ae)**



According to **TP11**, *tert*-butyl(3-iodobutoxy)dimethylsilane (**75b**, 314 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with **74j** (0.7 mmol, 0.7 equiv) prepared according to **TP7**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:4) as an eluent to afford **76ae** as colorless oil (80%, 288 mg, 0.80 mmol).

^{1}H-NMR (600 MHz, $CDCl_3$, ppm): 7.57 – 7.54 (m, 2H), 7.46 – 7.42 (m, 2H), 7.38 – 7.34 (m, 2H), 7.05 (dd, *J*=7.8, 1.7, 1H), 7.00 (dd, *J*=12.0, 1.7, 1H), 3.59 (dt, *J*=10.2, 6.2, 1H), 3.52 (dt, *J*=10.2, 6.7, 1H), 2.95 (h, *J*=7.1, 1H), 1.82 (dt, *J*=7.1, 6.3, 2H), 1.29 (d, *J*=7.0, 3H), 0.90 (s, 9H), 0.03 (d, *J*=1.5, 6H).

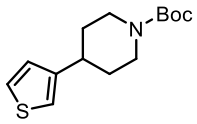
^{13}C-NMR (150 MHz, $CDCl_3$, ppm): 159.9 (d, *J*=247.4), 149.3 (d, *J*=6.7), 136.1, 130.6, 129.1, 128.5, 127.5, 126.5 (d, *J*=13.4), 123.3, 114.7 (d, *J*=22.6), 61.1, 41.1, 35.9, 26.1, 22.2, 18.4, -5.2.

FT-IR (ATR, cm^{-1}): 2956, 2928, 2856, 1484, 1472, 1462, 1418, 1254, 1098, 1076, 1010, 980, 900, 870, 832, 810, 774, 766, 724, 696.

MS (EI, 70 eV): m/z (%) = 302 (22), 301 (100), 207 (22), 179 (77), 165 (35).

HR-MS (EI, 70 eV): $[C_{21}H_{28}FOSi]^{+\bullet}$, calcd.: 343.1888; found: 343.1872 $[M^{+}\text{-}CH_3]$.

tert-Butyl 4-(thiophen-3-yl)piperidine-1-carboxylate (76af)



According to **TP11**, **75j** (311 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with the di(thiophene-3-yl)manganese reagent (**74k**, 0.7 mmol, 0.7 equiv) prepared according to **TP8** (exchange at 0 to 25 °C for 16 h). The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:2) as an eluent to afford **76af** as yellowish oil (87%, 233 mg, 0.87 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.27 (dd, *J*=5.0, 2.9, 1H), 6.98 (dd, *J*=5.0, 1.4, 1H), 6.96 – 6.95 (m, 1H), 4.20 (s, 2H), 2.89 – 2.70 (m, 3H), 1.96 – 1.87 (m, 2H), 1.57 (qd, *J*=12.5, 4.2, 2H), 1.47 (s, 9H).

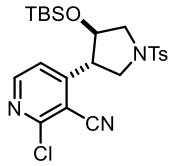
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): 155.0, 146.9, 126.8, 125.6, 119.1, 79.6, 37.9, 33.1, 28.6, 28.6.

FT-IR (ATR, cm^{-1}): 2974, 2932, 2852, 1686, 1478, 1466, 1446, 1420, 1392, 1364, 1292, 1274, 1236, 1158, 1116, 1080, 1018, 992, 940, 874, 850, 834, 776, 724.

MS (EI, 70 eV): m/z (%) = 267 (23), 211 (80), 196 (45), 194 (36), 57 (100), 43 (32).

HR-MS (EI, 70 eV): $[C_{14}H_{21}NO_2S]^{+\bullet}$, calcd.: 267.1288; found: 267.1281.

4-(_trans_-4-((_tert_-Butyldimethylsilyl)oxy)-1-tosylpyrrolidin-3-yl)-2-chloronicotinonitrile (76ag)



According to **TP11**, **75i** (481 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with **74l** (0.7 mmol, 0.7 equiv) prepared according to **TP10** (directed metalation at 0 °C for 2 h), at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (8:2) as an eluent to afford **76ag** as colorless solid (46%, 224 mg, 0.46 mmol).

Only one diastereomer was observed as product (dr = 99:1).

Mp.: 152.9-154.7

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 8.54 (d, *J*=5.3, 1H), 7.77 – 7.72 (m, 2H), 7.48 (d, *J*=5.3, 1H), 7.37 (d, *J*=8.0, 2H), 4.22 (dt, *J*=5.0, 3.9, 1H), 3.70 – 3.59 (m, 3H), 3.51 (dt, *J*=6.5, 4.3, 1H), 3.04 (dd, *J*=10.6, 3.8, 1H), 2.46 (s, 3H), 0.68 (s, 9H), -0.08 (d, *J*=8.2, 6H).

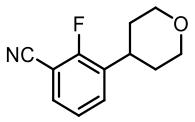
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): 156.0, 153.8, 153.0, 144.3, 133.0, 130.1, 127.7, 120.1, 113.7, 111.3, 54.5, 51.0, 50.4, 29.8, 25.5, 21.7, 17.7, -4.8, -4.9.

FT-IR (ATR, cm^{-1}): 2952, 2926, 2854, 1580, 1540, 1476, 1456, 1376, 1344, 1326, 1262, 1256, 1210, 1184, 1156, 1136, 1096, 1032, 1016, 1004, 952, 910, 864, 850, 840, 826, 808, 776, 708, 680, 664.

MS (EI, 70 eV): m/z (%) = 437 (10), 436 (40), 435 (23), 434 (100), 91 (19).

HR-MS (EI, 70 eV): $[C_{22}H_{27}ClN_3O_3SSi]^{+\bullet}$, calcd.: 476.1225; found: 476.1215 $[M^+ - CH_3]$.

2-Fluoro-3-(tetrahydro-2H-pyran-4-yl)benzonitrile (76ah)



According to **TP11**, 4-iodotetrahydro-2*H*-pyran (**75m**, 212 mg, 1.0 mmol, 1.0 equiv, in 1 mL THF) reacts with **74m** (0.7 mmol, 0.7 equiv) prepared according to **TP10** (directed metalation at 0 °C for 2 h), at -20 °C. The solution was allowed to warm to room temperature under stirring for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (8:2) as an eluent to afford **76ah** as colorless solid (86%, 177 mg, 0.86 mmol).

Mp.: 98.8-100-7 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.50 (m, 2H), 7.23 (t, *J*=7.8, 1H), 4.12 – 4.06 (m, 2H), 3.57 (td, *J*=11.7, 2.4, 2H), 3.17 (tt, *J*=11.9, 4.1, 1H), 1.83 (qd, *J*=12.5, 11.9, 4.4, 2H), 1.77 – 1.72 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): 161.0 (d, *J*=257.4), 133.9 (d, *J*=13.3), 132.7 (d, *J*=5.7), 131.2, 124.9 (d, *J*=4.2), 114.2, 101.6 (d, *J*=16.8), 68.0, 34.3, 32.2.

FT-IR (ATR, cm^{-1}): 2940, 2922, 2850, 2234, 1614, 1582, 1460, 1388, 1366, 1304, 1278, 1272, 1260, 1246, 1234, 1204, 1188, 1174, 1122, 1080, 1026, 1016, 974, 948, 908, 858, 826, 800, 736, 700.

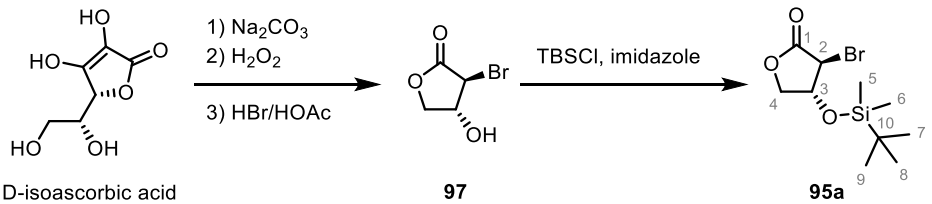
MS (EI, 70 eV): m/z (%) = 205 (44), 161 (79), 160 (49), 147 (100), 134 (46).

HR-MS (EI, 70 eV): $[C_{12}H_{12}FNO]^{+\bullet}$, calcd.: 205.0898; found: 205.0898.

5 Stereoselective Cobalt-Catalyzed Cross-Coupling Reactions of Arylzinc Chlorides with α-Bromolactones and Related Derivatives

5.1 Preparation of α-Bromolactones

(3*S*,4*R*)-3-Bromo-4-((*tert*-butyldimethylsilyl)oxy)dihydrofuran-2(3*H*)-one (95a)



D-isoascorbic acid **96** — **97** — **95a**

D-Isoascorbic acid (**96**, 200 g, 1.14 mol, 1.00 equiv) was dissolved in water (1.5 L). The solution was cooled to 0 °C and Na_2CO_3 (168 g, 1.59 mol, 1.40 equiv) was added in portions. The reaction mixture was allowed to warm to rt, stirred for 30 min and cooled to 0 °C again. Hydrogen peroxide (33% in water, 400 mL, 3.98 mol, 3.50 equiv) was added very slowly in small portions. The mixture was slowly heated to 55 °C and stirred for 40 min. After cooling to 0 °C, activated charcoal (25.0 g) was added, the mixture was heated to 70 °C for 1 h and the hot suspension was filtered over celite. The filtrate was acidified to pH = 1 with concentrated hydrochloric acid (ca. 170 mL) and the water was removed on a rotatory evaporator. The resulting residue was extracted by refluxing in EtOAc (6 x 900 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue containing the crude chiral dihydroxylactone (128 g, 1.09 mol, 96% yield) as a yellowish oil was used in the next step without further purification.[129]

Hydrobromic acid (33% in glacial acetic acid, 420 mL) was cooled to 0 °C and added to the residue containing the dihydroxylactone. The mixture was allowed to warm to rt and was stirred for 2 h. Methanol (500 mL) was added over 3 h using a dropping funnel and the mixture was stirred at rt overnight. The volatiles were removed under reduced pressure and the resulting suspension was extracted with EtOAc (3 x 250 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 6:4) to afford the α-bromo-β-hydroxylactone **97** as brownish oil (54.0 g, 300 mmol, 26% yield over two steps).[130]

The α-bromo-β-hydroxylactone **97** (54.0 g, 300 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (500 mL) and cooled to 0 °C. Imidazole (26.6 g, 390 mmol, 1.30 equiv) and DMAP (367 mg, 3 mmol, 1 mol%)

[129] a) N. Cohen, B. L. Banner, A. J. Laurenzano, L. Carozza *Org. Synth.* **1985**, *63*, 127. b) L. L. Wong, R. L. Wong, G. Loh, P. E. W. Tan, S. K. Teoh, S. M. Shaik, P. N. Sharratt, W. Chew, S. T. Tan, D. Wang *Org. Process Res. Dev.* **2012**, *16*, 1003-1012. c) S. R. Borkar, N. Bokolia, I. S. Aidhen, I. A. Khan *Tetrahedron: Asymmetry* **2017**, *28*, 186-195.
[130] a) M. Bols, I. Lundt *Acta Chem. Scand. Ser. B* **1988**, *42*, 67-74. b) C. Falentin, D. Beaupère, G. Demailly, I. Stasik *Tetrahedron* **2008**, *64*, 9989-9991.

were added and TBSCl (58.8 g, 390 mmol, 1.30 equiv) dissolved in CH_2Cl_2 (200 mL) was added dropwise over 30 min. The mixture was allowed to warm to rt and was stirred overnight, was washed with sat. aq. $NaHCO_3$ (300 mL) and water (300 mL). The organic layer was dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 100:2.5) to afford the protected α-bromolactone **95a** as colorless solid (52.0 g, 176 mmol, 59% yield, dr = 99:1, 99% *ee*).

m.p.: 39 – 40 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.60 (dd, *J* = 9.7, 2.4 Hz, 1H, H-4), 4.51 (td, *J* = 4.3, 2.3 Hz, 1H, H-3), 4.19 (dd, *J* = 9.7, 2.2 Hz, 1H, H-4'), 4.04 (d, *J* = 2.5 Hz, 1H, H-2), 0.88 (s, 9H, H-7-9), 0.12 (d, *J* = 5.7 Hz, 6H, H-5-6).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 171.8 (C-1), 75.4 (C-3), 74.1 (C-4), 41.8 (C-2), 25.7 (C-7-9), 18.0 (C-10), -4.6 (C-5/6), -4.8 (C-5/6).

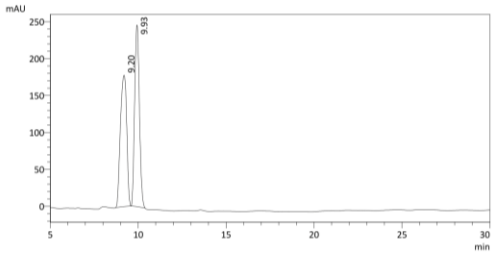
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 2928, 2893, 2884, 2857, 1781, 1747, 1470, 1462, 1373, 1367, 1360, 1346, 1259, 1251, 1231, 1193, 1170, 1103, 1057, 997, 987, 937, 906, 875, 838, 824, 807, 780, 765, 713, 671, 663.

MS (EI, 70 eV): *m/z* (%) = 159 (12), 158 (12), 119 (13), 118 (32), 117 (100), 103 (10), 89 (23), 75 (30), 73 (24), 59 (16), 57 (35), 45 (12), 41 (20).

HR-MS (EI, 70 eV): $[C_6H_{10}BrO_3Si]^{+\bullet}$ = $[M - C(CH_3)_3]^{+\bullet}$, calcd.: 236.9577; found: 236.9575.

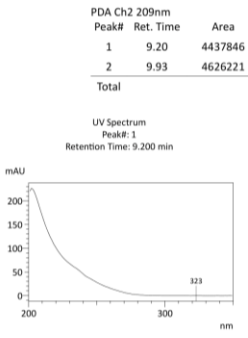
cHPLC: Chiracel OD-H; heptane: *i*PrOH = 99.5:0.5; 1 mL·min^{-1}; 209 nm; R_f(3*S*,4*R*) = 9.2 min; R_f(3*R*-4*S*) = 9.9 min.

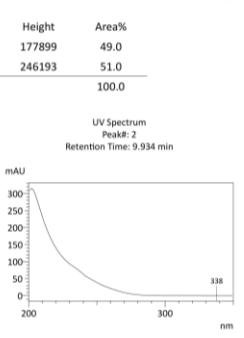
Optical Rotation: $\alpha_D^{20} = -35.2°$ (c = 1.0, $CHCl_3$).

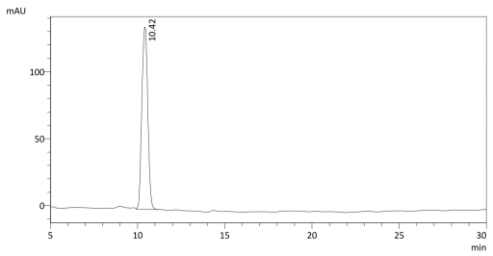


PDA Ch2 209nm

Peak#	Ret. Time	Area	Height	Area%
1	9.20	4437846	177899	49.0
2	9.93	4626221	246193	51.0
Total				100.0

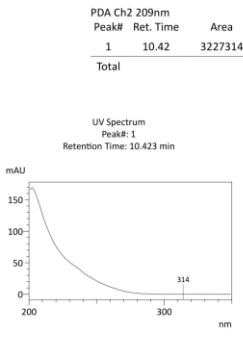




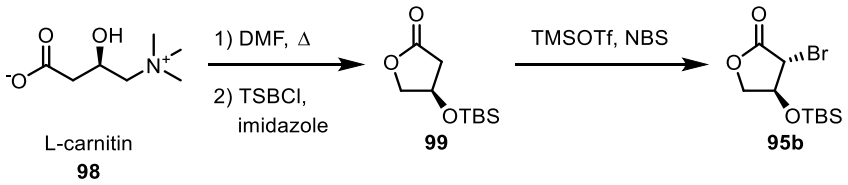


PDA Ch2 209nm

Peak#	Ret. Time	Area	Height	Area%
1	10.42	3227314	136222	100.0
Total				100.0



(3*R*,4*S*)-3-Bromo-4-((*tert*-butyldimethylsilyl)oxy)dihydrofuran-2(3*H*)-one (95b)



L-carnitine (**98**, 3.22 g, 20.0 mmol, 1.0 equiv) was dissolved in DMF (32 mL). The mixture was heated to 150 °C for 16 h, cooled to room temperature and DMF was evaporated under reduced pressure. Sat. aq. NH_4Cl (10 mL) was added and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with 10% aq. LiCl (25 mL) and brine (25 mL), dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 7:3) to afford the chiral β-hydroxylactone (561 mg, 5.50 mmol, 28% yield).

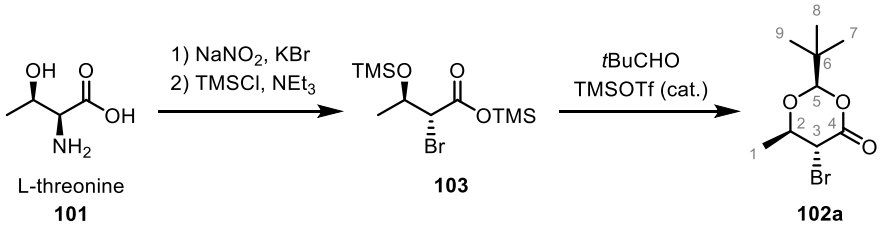
The β-hydroxylactone (561 mg, 5.50 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (11 mL), DMF (8 µL) and NEt_3 (0.92 mL, 6.60 mmol, 1.20 equiv) were added. The mixture was cooled to 0 °C. TBSCl (995 mg, 6.60 mmol, 1.20 equiv) was added and allowed to warm to rt overnight. Sat. aq. NH_4Cl (10 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 7:3) to afford the β-OTBS-substituted lactone **99** (1.18 g, 5.47 mmol, 99% yield).

Lactone **99** (1.18 g, 5.47 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (30 mL) and NEt_3 (4.67 mL, 32.8 mmol, 6.00 equiv) was added. The mixture was cooled to 0 °C and TMSOTf (3.0 mL, 16.4 mmol, 3.0 equiv) was added and stirring was continued for 30 min. *N*-Bromosuccinimide (1.49 g, 8.20 mmol, 1.50 equiv) was dissolved in CH_2Cl_2 (15 mL) and the solution was added to the reaction mixture dropwise. Stirring was continued for 1 h, sat. aq. Na_2CO_3 (20 mL) and water (20 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 100:3) to afford the α-bromolactone **95b** as colorless solid (983 mg, 3.34 mmol, 61% yield, dr = 99:1, 99% *ee*).

The analytical data is identical to the (3*S*,4*R*)-enantiomer **95a.**

Optical Rotation: $\alpha_D^{20} = +35.4°$ (c = 1.0, $CHCl_3$).

(2*R*,5*R*,6*R*)-5-Bromo-2-(*tert*-butyl)-6-methyl-1,3-dioxan-4-one (102a)[114]



L-threonine **101** | **103** | **102a**

L-threonine (**101**, 20.0 g, 168 mmol, 1.00 equiv) and KBr (31.0 g, 260 mmol, 1.50 equiv) were dissolved in water (300 mL) and conc. H_2SO_4 (50 mL) was added. The solution was cooled to -12 °C and $NaNO_2$ (18.8 g, 272 mmol, 1.60 equiv) dissolved in water (60 mL) was added dropwise over 2 h. The mixture was allowed to warm to rt, stirred overnight and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude viscous oil containing the α-bromo acid (22.0 g, 120 mmol) was dissolved in CH_2Cl_2 (150 mL), cooled to 0 °C, and NEt_3 (36.8 mL, 264 mmol, 2.20 equiv) and TMSCl (33.5 mL, 264 mmol, 2.20 equiv) were added. The mixture was allowed to warm to rt and was stirred for 3 d. Pentane (100 mL) was added, the salts were removed by filtration and the filtrate was evaporated to dryness. Pentane (150 mL) was added again, the salts were removed by filtration and the filtrate was evaporated to dryness. The crude product **103** (32.8 g, 100 mmol, 60% yield over two steps) was clean enough for the following transformation.

The TMS-protected compound **103** (32.8 g, 100 mmol, 1.0 equiv) and pivalaldehyde (8.44 g, 98.0 mmol, 0.98 equiv) were dissolved in CH_2Cl_2 (220 mL) and the solution was cooled to -78 °C. TMSOTf (0.54 mL, 3 mol%) was added and stirring at -78 °C was continued overnight. Pyridine (0.8 mL, 10.0 mmol, 0.10 equiv) was added, the mixture was allowed to warm to rt and washed with sat. aq. $NaHCO_3$ (30 mL). The organic layer was dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 9:1) to afford the chiral (*R*)-α-bromolactone **102a** (6.87 g, 27.4 mmol, 27% yield) as colorless solid.

m.p.: 49 – 51 °C.

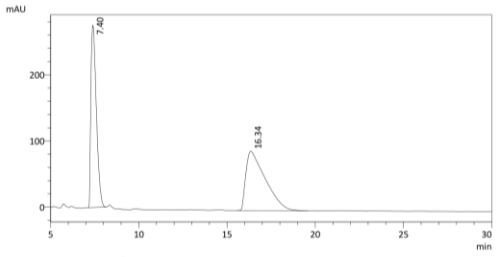
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.00 (s, 1H, H-5), 4.31 (d, *J* = 2.2 Hz, 1H, H-3), 3.88 (qd, *J* = 6.1, 2.2 Hz, 1H, H-2), 1.40 (d, *J* = 6.1 Hz, 3H, H-1), 1.01 (s, 9H, H-7-9).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 165.4 (C-4), 110.0 (C-5), 72.1 (C-2), 46.1 (C-3), 35.7 (C-6), 24.0 (C-7-9), 19.1 (C-1).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2979, 2938, 2878, 1716, 1706, 1701, 1685, 1670, 1654, 1647, 1636, 1458, 1374, 1281, 1168, 1126, 1084, 1028, 941, 853.

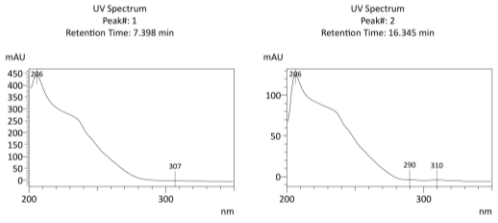
cHPLC: Chiracel OJ-H; heptane:*i*PrOH = 95:5; 1 mL·min^{-1}; 230 nm; R_f(*R**) = 7.4 min; R_f(*S**) = 16.3 min.

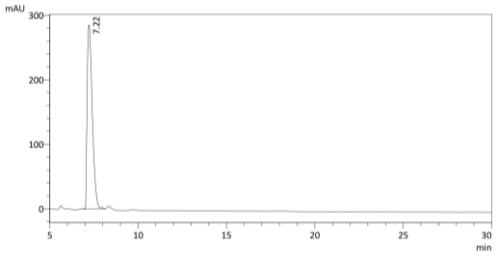
Optical Rotation: $\alpha_D^{20} = -14.2°$ (c = 1.0, $CHCl_3$).



PDA Ch2 230nm

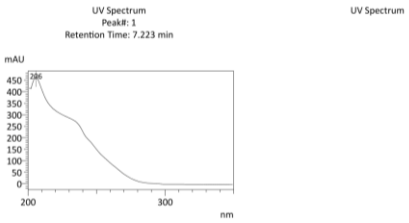
Peak#	Ret. Time	Area	Height	Area%
1	7.40	5933223	275159	46.4
2	16.34	6856051	89713	53.6
Total				100.0





PDA Ch2 230nm

Peak#	Ret. Time	Area	Height	Area%
1	7.22	5741116	285611	100.0
Total				100.0



(2*S*,5*S*,6*S*)-5-Bromo-2-(*tert*-butyl)-6-methyl-1,3-dioxan-4-one (102b)

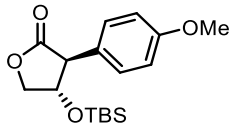
The (*S*)-enantiomer **102b** was synthesized by using D-threonine as starting material.

The analytical data is identical to the other (*R*)-enantiomer **102a**.

Optical Rotation: $\alpha_D^{20} = +15.8°$ (c = 1.0, $CHCl_3$).

5.2 Stereoselective Cobalt-Catalyzed Cross-Coupling Reactions of Arylzinc Reagents with α-Bromolactones

Typical Procedure 1 (TP12) for the cobalt-catalyzed cross-couplings of arylzinc reagents with α-bromolactones: Synthesis of (3*S*,4*S*)-4-((tert-butyldimethylsilyl)oxy)-3-(4-methoxyphenyl)-dihydrofuran-2(3H)-one (100a)



A dry and argon flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, was charged with magnesium turnings (291 mg, 12.0 mmol, 1.20 equiv), dry LiCl (508 mg, 12.0 mmol, 1.20 equiv) and dry THF (1 M solution relating to the aryl halide, 10 mL). 4-Bromoanisole (1.87 g, 10.0 mmol, 1.00 equiv) was added dropwise at 0 °C. The progress of the magnesium insertion was monitored by GC-analysis of reaction aliquots quenched with I_2. Upon completion of the insertion (2 h), the concentration of the Grignard reagent was determined by titration[4] of I_2 in THF (c = 0.82 M).

Solid $ZnCl_2$ (681 mg, 5.00 mmol, 1.00 equiv) was placed in a dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum and dried under vacuum at 250 °C for 5 min. After cooling to rt under vacuum, an argon atmosphere was applied and THF (1 M according to $ZnCl_2$, 5 mL) was added. The Grignard reagent (6.1 mL, 5.00 mmol, 1.00 equiv) was added at 0 °C, the solution was allowed to warm to rt and stirred for 15 min. The concentration of 4-anisylzinc chloride **78b** was determined by titration[119] of I_2 (c = 0.43 M).

A dry and argon-flushed 20 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with $CoCl_2$ (6.5 mg, 0.050 mmol, 10 mol%). The solid was flame dried under high vacuum for 5 min. After cooling to rt, PPh_3 (13 mg, 0.050 mmol, 10 mol%) and the α-bromolactone **95a** (148 mg, 0.500 mmol, 1.00 equiv) was added. The mixture was dissolved in THF (1 mL) and cooled to -20 °C. 4-Anisylzinc chloride **78b** (1.4 mL, 0.600 mmol, 1.20 equiv) was added and the mixture was allowed to warm to rt overnight. The reaction was monitored by GC-analysis ($C_{11}H_{24}$ was used as an internal standard) and TLC. Upon consumption of the starting material, sat. aq. NH_4Cl (5 mL) and EtOAc (5 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **100a** as colorless solid (131 mg, 0.406 mmol, 81% yield, dr = 99:1, 99% *ee*).

m.p.: 56 – 58 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.16 – 7.02 (m, 2H), 6.97 – 6.73 (m, 2H), 4.44 (dd, *J* = 5.9, 2.4 Hz, 2H), 4.11 – 3.97 (m, 1H), 3.80 (s, 3H), 3.64 (d, *J* = 6.1 Hz, 1H), 0.83 (s, 9H), -0.07 (s, 3H), -0.12 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 175.8, 159.4, 129.5, 126.6, 114.6, 76.3, 72.6, 55.4, 55.0, 25.7, 18.0, -4.8, -4.9.

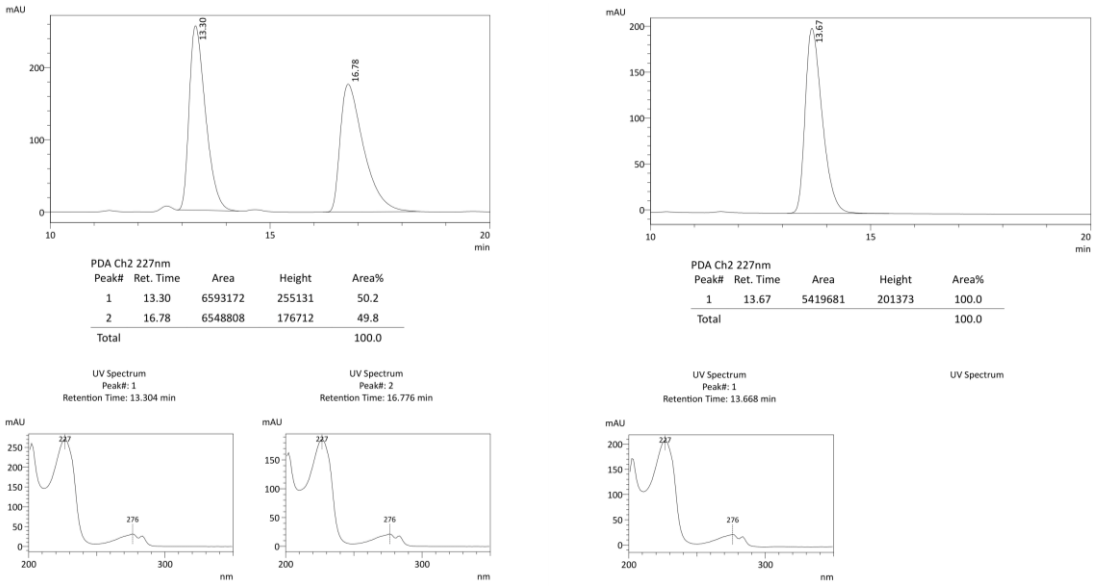
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2997, 2953, 2930, 2856, 1785, 1613, 1515, 1473, 1465, 1345, 1249, 1221, 1177, 1144, 1122, 1109, 1091, 1072, 1023, 1011, 942, 915, 838, 826, 816, 778, 675.

MS (EI, 70 eV): *m/z* (%) = 237 (13), 190 (26), 162 (20), 133 (68), 121 (40), 117 (14), 89 (10), 77 (11), 75 (100), 45 (10), 44 (11), 43 (66).

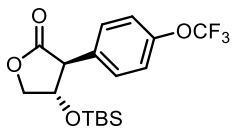
HR-MS (EI, 70 eV): $[C_{17}H_{26}O_4Si]^{+\bullet}$, calcd.: 322.1595; found: 322.1607.

cHPLC: Chiracel OD-H; heptane: *i*PrOH = 98:2; 1 mL·min^{-1}; 227 nm; R_f(*S**) = 13.3 min; R_f(*R**) = 16.8 min.

Optical Rotation: $\alpha_D^{20} = -36.6°$ (c = 1.0, $CHCl_3$).



(3*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(4-(trifluoromethoxy)phenyl)dihydrofuran-2(3*H*)-one (100b)



According to **TP12**, α-bromolactone **95a** (148 mg, 0.500 mmol, 1.00 equiv) was treated with 4-trifluoromethoxyphenylzinc chloride **78c** (0.600 mmol, 1.20 equiv). The crude product was purified

by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **100b** as colorless solid (63% yield, dr = 99:1, 99% *ee*, 119 mg, 0.316 mmol).

m.p.: 57 – 58 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.25 (d, *J* = 2.2 Hz, 4H), 4.56 – 4.31 (m, 2H), 4.21 – 3.97 (m, 1H), 3.79 – 3.57 (m, 1H), 0.82 (s, 9H), -0.08 (s, 3H), -0.15 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 174.7, 149.0, 133.4, 130.1, 121.7, 120.8 (q, *J* = 257.5 Hz), 76.2, 72.4, 54.9, 25.6, 18.0, -4.9.

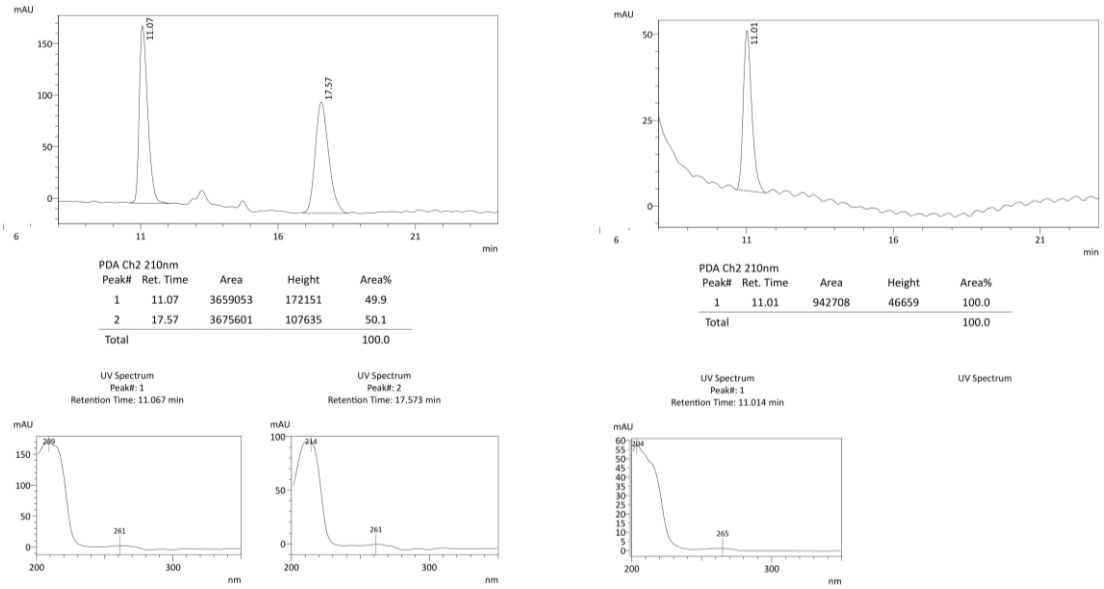
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2932, 2860, 1786, 1510, 1472, 1464, 1390, 1254, 1214, 1154, 1126, 1070, 1028, 1004, 922, 836, 778, 674.

MS (EI, 70 eV): *m/z* (%) = 290 (31), 244 (38), 216 (18), 188 (14), 187 (97), 174 (31), 118 (14), 117 (100), 101 (11), 89 (11), 75 (84), 73 (11), 61 (16), 43 (52).

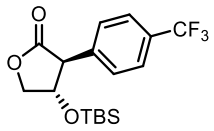
HR-MS (EI, 70 eV): $[C_{17}H_{23}O_4F_3Si]^{+\bullet}$, calcd.: 376.1312; found: 376.1311.

cHPLC: Chiracel OD-H; heptane: *i*PrOH = 98:2; 1 mL·min^{-1}; 210 nm; R_f(*S**) = 11.1 min; R_f(*R**) = 17.6 min.

Optical Rotation: $\alpha_D^{20} = -11.0°$ (c = 1.0, $CHCl_3$).



(3*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one (100c)



According to **TP12**, α-bromolactone **95a** (148 mg, 0.500 mmol, 1.00 equiv) was coupled with 4-trifluoromethylphenylzinc chloride **78d** (0.600 mmol, 1.20 equiv). The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:8) as an eluent to afford **100c** as yellowish solid (62% yield, dr = 99:1, 99% *ee*, 112 mg, 0.310 mmol).

m.p.: 61 – 63 °C.

^{1}H-NMR (400 MHz, benzene-D$_6$, ppm): δ = 7.32 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 3.93 – 3.70 (m, 2H), 3.47 (dd, *J* = 8.6, 7.0 Hz, 1H), 3.15 (d, *J* = 8.1 Hz, 1H), 0.74 (s, 9H), -0.36 (s, 3H), -0.45 (s, 3H).

^{13}C-NMR (101 MHz, benzene-D$_6$, ppm): δ = 173.0, 139.5, 130.1 (q, *J* = 32.4 Hz), 129.4, 125.8 (q, *J* = 3.9 Hz), 124.8 (q, *J* = 272.1 Hz), 75.7, 71.4, 54.8, 25.6, 17.8, -5.1, -5.2.

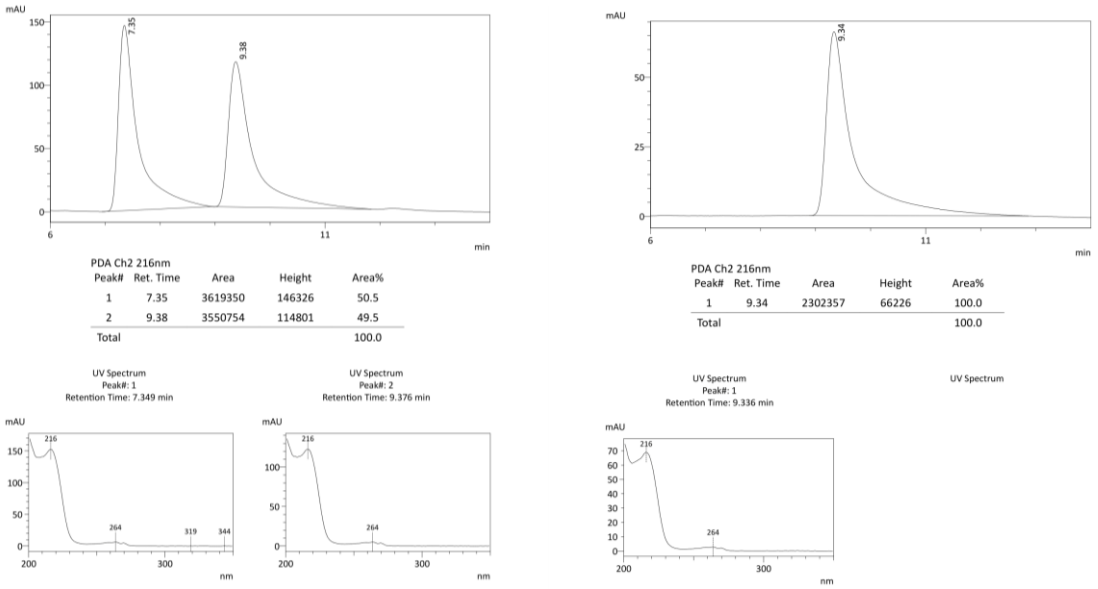
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952, 2932, 2858, 1795, 1621, 1469, 1325, 1257, 1224, 1155, 1136, 1125, 1111, 1068, 1012, 923, 836, 784, 765, 702, 674.

MS (EI, 70 eV): *m/z* (%) = 245 (8), 228 (5), 171 (15), 151 (5), 118 (7), 117 (100), 89 (6), 75 (28), 73 (7), 43 (18).

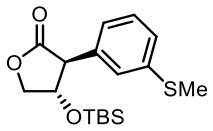
HR-MS (EI, 70 eV): $[C_{17}H_{23}F_3O_3Si]^{+\bullet}$, calcd.: 360.1363; found: 360.1344.

cHPLC: Chiracel AD-H; heptane: *i*PrOH = 98:2; 1 mL·min^{-1}; 216 nm; R_f(*S**) = 9.3 min; R_f(*R**) = 7.4 min.

Optical Rotation: $\alpha_D^{20} = -24°$ (c = 1.0, $CHCl_3$).



(3*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-(methylthio)phenyl)dihydrofuran-2(3*H*)-one (100d)



According to **TP12**, α-bromolactone **95a** (148 mg, 0.500 mmol, 1.00 equiv) was coupled with 3-thioanisylzinc chloride **78e** (0.600 mmol, 1.20 equiv). The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **100d** as colorless solid (63% yield, dr = 99:1, 99% *ee*, 107 mg, 0.316 mmol).

m.p.: 109 – 110 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.29 (t, *J* = 7.7 Hz, 1H), 7.20 (ddd, *J* = 7.9, 1.9, 1.1 Hz, 1H), 7.08 (t, *J* = 1.9 Hz, 1H), 6.97 (dt, *J* = 7.5, 1.5 Hz, 1H), 4.49 – 4.35 (m, 2H), 4.15 – 4.01 (m, 1H), 3.70 – 3.62 (m, 1H), 2.47 (s, 3H), 0.84 (s, 9H), -0.07 (s, 3H), -0.12 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 175.1, 139.6, 135.3, 129.5, 126.6, 126.1, 124.9, 76.1, 72.7, 55.5, 25.7, 18.0, 15.9, -4.8, -4.9.

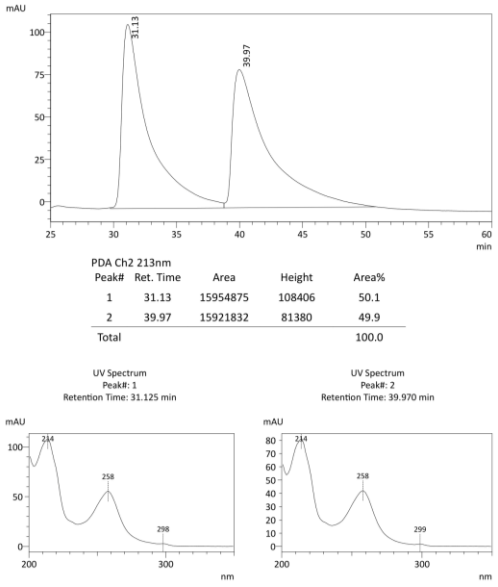
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2928, 2858, 1792, 1592, 1574, 1468, 1416, 1350, 1262, 1252, 1226, 1180, 1152, 1126, 1086, 1070, 1014, 928, 868, 860, 836, 794, 780, 744, 696, 682, 674.

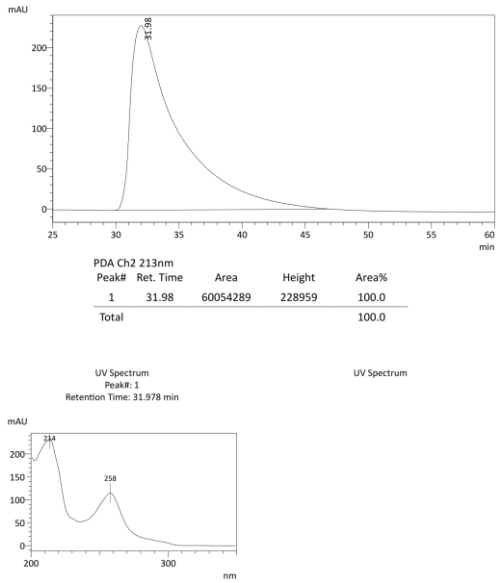
MS (EI, 70 eV): *m/z* (%) = 207 (13), 206 (100), 150 (14), 149 (74), 134 (17), 117 (29), 115 (11), 102 (21), 75 (78).

HR-MS (EI, 70 eV): $[C_{17}H_{26}O_3SSi]^{+\bullet}$, calcd.: 338.1366; found: 338.1376.

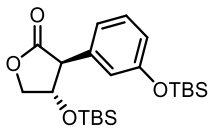
cHPLC: Chiracel AD-H; heptane: *i*PrOH = 99.5:0.5; 1 mL·min^{-1}; 213 nm; R_f(*S**) = 31.1 min; R_f(*R**) = 40.0 min.

Optical Rotation: $\alpha_D^{20} = -23.6°$ (c = 1.0, $CHCl_3$).





(3*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)dihydrofuran-2(3*H*)-one (100e)



According to **TP12**, α-bromolactone **95a** (148 mg, 0.500 mmol, 1.00 equiv) was coupled with arylzinc reagent **78a** (0.600 mmol, 1.20 equiv). The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **100e** as yellow oil (77% yield, dr = 99:1, 99% *ee*, 163 mg, 0.386 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.22 (t, *J* = 7.9 Hz, 1H), 6.83 – 6.75 (m, 2H), 6.68 (t, *J* = 2.1 Hz, 1H), 4.52 – 4.40 (m, 2H), 4.14 – 4.03 (m, 1H), 3.64 (d, *J* = 5.7 Hz, 1H), 0.98 (s, 9H), 0.84 (s, 9H), 0.19 (s, 6H), -0.06 (s, 3H), -0.09 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 175.4, 156.3, 136.0, 130.1, 121.3, 120.3, 119.7, 76.3, 72.8, 55.6, 25.8, 25.7, 18.3, 18.0, -4.3, -4.8, -4.9.

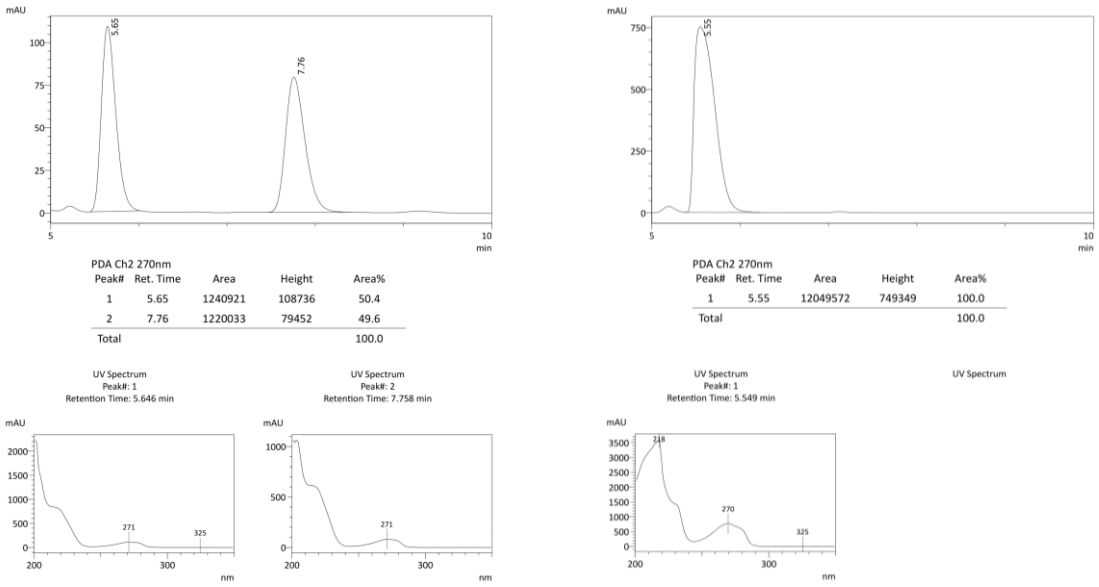
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955, 2930, 2891, 2858, 1786, 1774, 1603, 1586, 1487, 1472, 1464, 1438, 1279, 1253, 1237, 1160, 1121, 1028, 1002, 908, 870, 837, 808, 779, 722, 694.

MS (EI, 70 eV): *m/z* (%) = 365 (39), 337 (60), 278 (25), 277 (62), 233 (100), 159 (63), 117 (88).

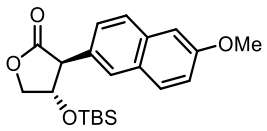
HR-MS (EI, 70 eV): $[C_{22}H_{38}O_4Si_2]^{+\bullet}$, calcd.: 422.2303; found: 422,2313.

cHPLC: Chiracel OD-H; heptane: *i*PrOH = 98:2; 1 mL·min^{-1}; 270 nm; R_f(*S**) = 5.6 min; R_f(*R**) = 7.8 min.

Optical Rotation: $\alpha_D^{20} = -13.4°$ (c = 1.0, $CHCl_3$).



(3*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(6-methoxynaphthalen-2-yl)dihydrofuran-2(3*H*)-one (100f)



According to **TP12**, α-bromolactone **95a** (148 mg, 0.500 mmol, 1.00 equiv) was coupled with (6-methoxynaphthalen-2-yl)zinc chloride **78f** (0.600 mmol, 1.20 equiv). The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **100f** as colorless solid (61% yield, dr = 99:1, 99% *ee*, 113 mg, 0.303 mmol).

m.p.: 136 – 137 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.76 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.20 – 7.09 (m, 2H), 4.61 – 4.44 (m, 2H), 4.13 (dd, *J* = 8.9, 5.7 Hz, 1H), 3.92 (s, 3H), 3.84 (d, *J* = 6.4 Hz, 1H), 0.84 (s, 9H), -0.08 (s, 3H), -0.14 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 175.7, 158.0, 134.1, 129.5, 129.4, 129.0, 127.9, 127.5, 126.3, 119.5, 105.7, 76.2, 72.9, 55.7, 55.4, 25.7, 18.0, -4.7, -4.9.

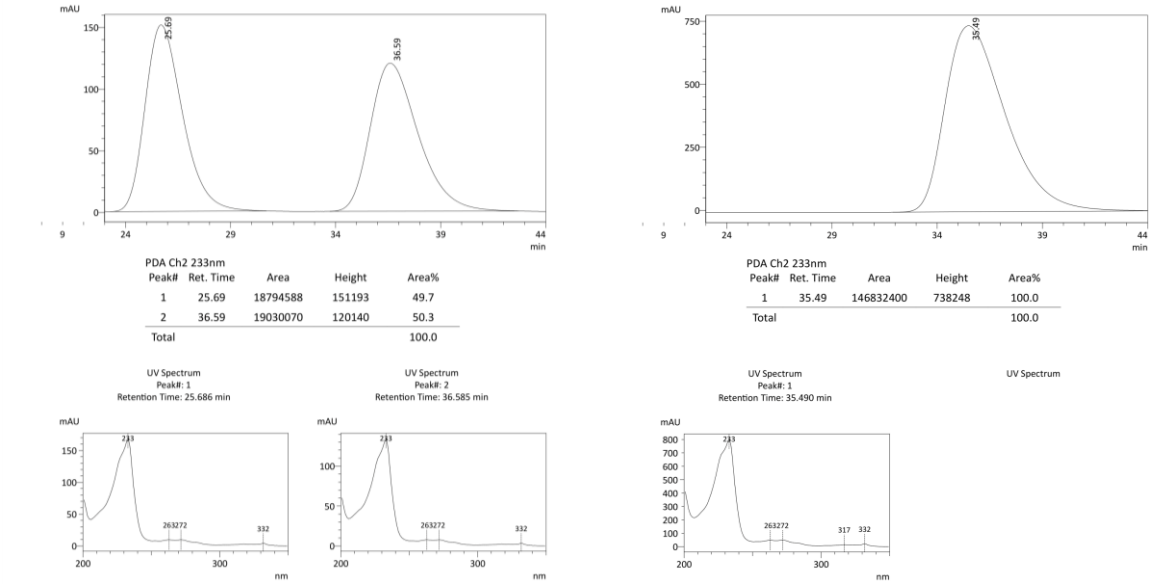
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2928, 2856, 1792, 1608, 1508, 1488, 1468, 1422, 1402, 1392, 1346, 1274, 1262, 1252, 1238, 1228, 1192, 1182, 1154, 1134, 1086, 1072, 1028, 1018, 1002, 974, 928, 906, 888, 860, 848, 834, 814, 782, 738, 704, 686, 670.

MS (EI, 70 eV): *m/z* (%) = 372 (17), 316 (2), 315 (7), 314 (23), 288 (4), 287 (18), 240 (24), 171 (100).

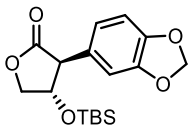
HR-MS (EI, 70 eV): $[C_{21}H_{28}O_4Si]^{+\bullet}$, calcd.: 372.1751; found: 372.1747.

cHPLC: Chiracel OJ-H; heptane: *i*PrOH = 98:2; 1 mL·min^{-1}; 233 nm; R_f(*S**) = 36.6 min; R_f(*R**) = 25.7 min.

Optical Rotation: $\alpha_D^{20} = -39.9°$ (c = 1.0, EtOAc).



(3*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(benzo[*d*][1,3]dioxol-5-yl)dihydrofuran-2(3*H*)-one (100g)



According to **TP12**, α-bromolactone **95a** (148 mg, 0.500 mmol, 1.00 equiv) was coupled with benzodioxolylzinc chloride **78g** (0.600 mmol, 1.20 equiv). The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (100:8) as an eluent to afford **100g** as colorless solid (84% yield, dr = 99:1, 99% *ee*, 141 mg, 0.419 mmol).

m.p.: 75 – 77 °C.

^{1}H-NMR (400 MHz, benzene-D$_6$, ppm): δ = 6.71 – 6.54 (m, 2H), 6.47 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.35 – 5.18 (m, 2H), 3.96 (dt, *J* = 7.6, 6.6 Hz, 1H), 3.84 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.51 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.19 (d, *J* = 7.8 Hz, 1H), 0.77 (s, 9H), -0.29 (s, 3H), -0.31 (s, 3H).

^{13}C-NMR (101 MHz, benzene-D$_6$, ppm): δ = 174.0, 148.6, 147.7, 129.1, 122.5, 109.1, 108.6, 101.2, 76.0, 71.5, 55.0, 25.7, 17.9, -5.0, -5.1.

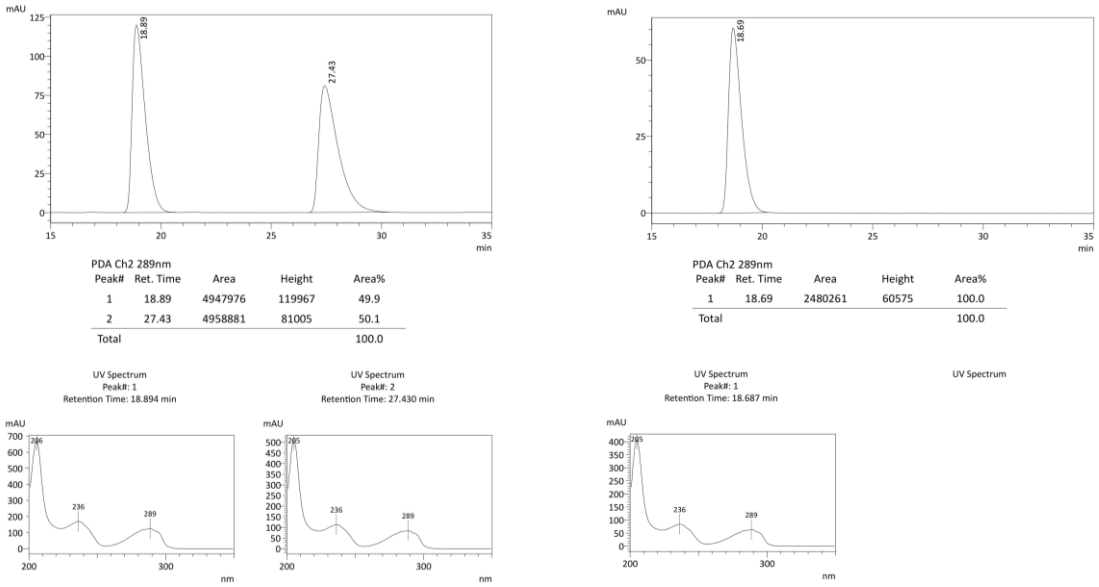
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955, 2927, 2857, 2359, 2332, 1760, 1605, 1508, 1471, 1444, 1379, 1359, 1269, 1252, 1237, 1164, 1095, 1063, 1044, 996, 932, 913, 888, 826, 775, 723, 681, 666.

MS (EI, 70 eV): *m/z* (%) = 251 (30), 204 (12), 162 (21), 147 (25), 135 (100), 117 (41), 89 (14), 75 (48), 73 (13), 43 (19).

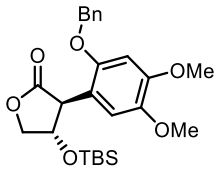
HR-MS (EI, 70 eV): $[C_{17}H_{24}O_5Si]^{+\bullet}$, calcd.: 336.1388; found: 336.1388.

cHPLC: Chiracel OD-H; heptane: *i*PrOH = 99:1; 1 mL·min^{-1}; 289 nm; R$_f$(*S**) = 18.9 min; R$_f$(*R**) = 27.4 min.

Optical Rotation: $\alpha_D^{20} = -28.9°$ (c = 1.0, CHCl$_3$).



(3*S*,4*S*)-3-(2-(Benzyloxy)-4,5-dimethoxyphenyl)-4-((*tert*-butyldimethylsilyl)oxy)dihydrofuran-2(3*H*)-one (100h)



According to **TP12**, α-bromolactone **95a** (2.50 g, 8.46 mmol, 1.00 equiv) was coupled with arylzinc reagent **78h** (10.2 mmol, 1.20 equiv). The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (8:2) as an eluent to afford **100h** as yellow solid. (94% yield, dr = 99:1, 99% *ee*, 3.65 g, 7.96 mmol).

m.p.: 83 – 85 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.47 – 7.32 (m, 5H), 6.71 (s, 1H), 6.63 (s, 1H), 5.06 (q, *J* = 11.4 Hz, 2H), 4.68 (td, *J* = 6.8, 6.3 Hz, 1H), 4.29 (dd, *J* = 9.0, 6.9 Hz, 1H), 3.97 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.60 (d, *J* = 6.8 Hz, 1H), 0.81 (s, 9H), -0.12 (s, 3H), -0.17 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 176.1, 150.5, 149.6, 143.3, 136.6, 128.7, 128.2, 127.8, 115.3, 115.3, 99.3, 74.2, 73.2, 71.6, 56.7, 56.3, 53.1, 25.7, 18.0, -4.8, -5.0.

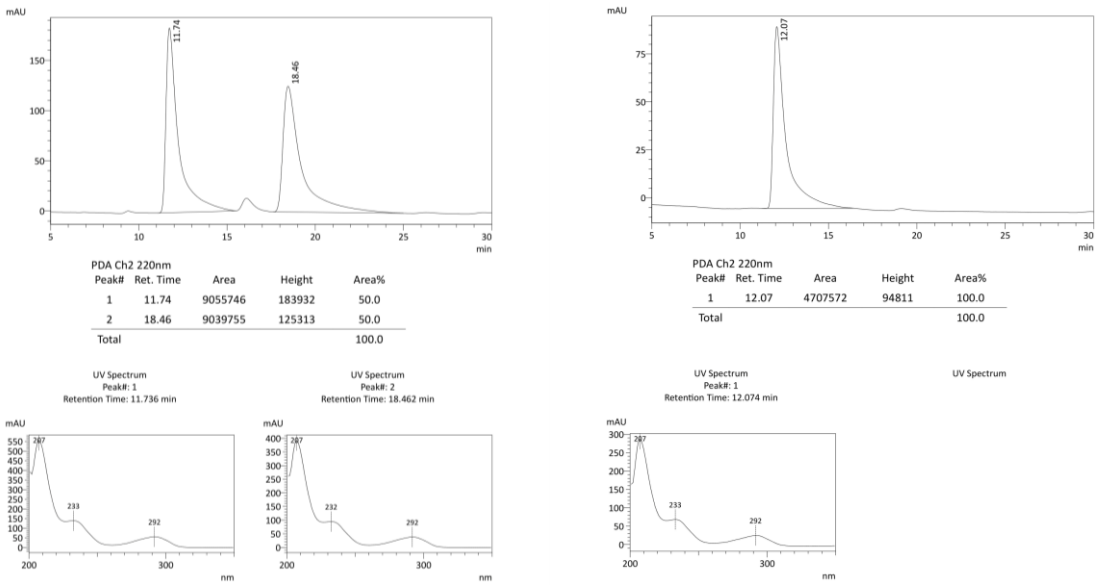
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952, 2929, 2897, 2886, 2855, 1779, 1612, 1511, 1463, 1450, 1400, 1388, 1338, 1251, 1223, 1195, 1152, 1117, 1071, 1021, 933, 882, 836, 815, 780, 758, 733, 697, 683, 672.

MS (EI, 70 eV): *m/z* (%) = 326 (28), 235 (51), 207 (13), 179 (11), 91 (100), 75 (42), 73 (17).

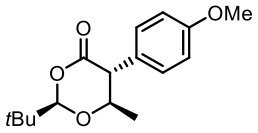
HR-MS (EI, 70 eV): $[C_{25}H_{34}O_6Si]^{+\bullet}$, calcd.: 458.2119; found: 458.2116.

cHPLC: Chiracel AD-H; heptane: *i*PrOH = 95:5; 1 mL·min^{-1}; 220 nm; R_f(*S**) = 11.7 min; R_f(*R**) = 18.5 min.

Optical Rotation: $\alpha_D^{20} = -44.7°$ (c = 1.0, $CHCl_3$).



(2*R*,5*R*,6*R*)-2-(*tert*-Butyl)-5-(4-methoxyphenyl)-6-methyl-1,3-dioxan-4-one (104a)



According to **TP12**, α-bromolactone **102a** (126 mg, 0.500 mmol, 1.00 equiv) was coupled with 4-anisylzinc chloride **78b** (0.750 mmol, 1.50 equiv) using $CoCl_2$ (13 mg, 0.100 mmol, 20 mol%) and PPh_3 (26 mg, 0.100 mmol, 20 mol%) as catalytic system. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **104a** as colorless solid (81% yield, dr = 99:1, 97% *ee*, 113 mg, 0.405 mmol).

m.p.: 68 – 70 °C.

^{1}H-NMR (400 MHz, benzene-D$_6$, ppm): δ = 6.88 – 6.78 (m, 2H), 6.78 – 6.69 (m, 2H), 4.78 (s, 1H), 3.53 (dq, *J* = 10.5, 6.0 Hz, 1H), 3.30 (s, 3H), 3.12 (d, *J* = 10.7 Hz, 1H), 1.04 (s, 9H), 0.90 (d, *J* = 6.0 Hz, 3H).

^{13}C-NMR (101 MHz, benzene-D$_6$, ppm): δ = 168.5, 159.6, 130.7, 114.5, 108.2, 77.3, 55.5, 54.8, 35.5, 24.1, 19.3.

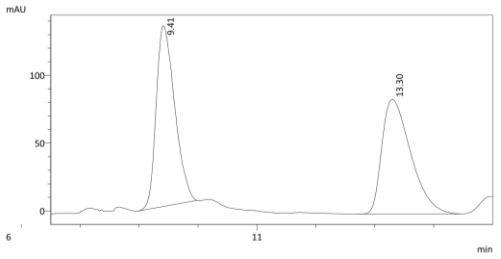
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 2907, 2838, 1736, 1616, 1519, 1484, 1461, 1409, 1345, 1271, 1209, 1177, 1152, 1120, 1081, 1026, 992, 970, 924, 881, 830, 762.

MS (EI, 70 eV): *m/z* (%) = 193 (47), 165 (32), 149 (28), 148 (100), 147 (45), 133 (17), 121 (14), 91 (15), 77 (16), 57 (17), 43 (13), 41 (15).

HR-MS (EI, 70 eV): $[C_{16}H_{22}O_4]^{+\bullet}$, calcd.: 278.1513; found: 278.1514.

cHPLC: Chiracel OJ-H; heptane: *i*PrOH = 9:1; 1 mL·min^{-1}; 222 nm; R_f(*R**) = 13.3 min; R_f(*S**) = 9.4 min.

Optical Rotation: $\alpha_D^{20} = +29.4°$ (c = 1.0, EtOAc).



PDA Ch2 274nm

Peak#	Ret. Time	Area	Height	Area%
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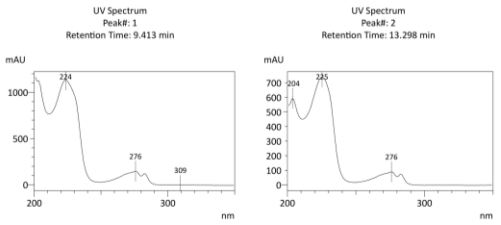
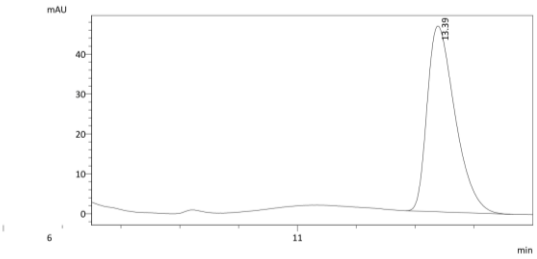
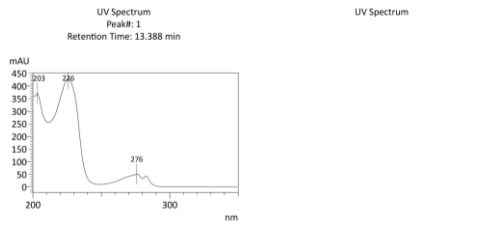
2	13.30	2876097	84521	49.6
Total				100.0



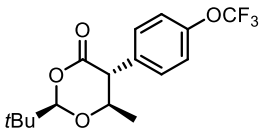


PDA Ch2 274nm

Peak#	Ret. Time	Area	Height	Area%
1	13.39	1535728	46600	100.0
Total				100.0



(2*R*,5*R*,6*R*)-2-(*tert*-Butyl)-6-methyl-5-(4-(trifluoromethoxy)phenyl)-1,3-dioxan-4-one (104b)



According to **TP12**, α-bromolactone **102a** (126 mg, 0.500 mmol, 1.00 equiv) was coupled with 4-trifluoromethoxyphenylzinc chloride **78c** (0.750 mmol, 1.50 equiv) using $CoCl_2$ (13 mg, 0.100 mmol, 20 mol%) and PPh_3 (26 mg, 0.100 mmol, 20 mol%) as catalytic system. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **104b** as colorless solid. (63% yield, dr = 99:1, 99% *ee*, 105 mg, 0.316 mmol).

m.p.: 64 – 67 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.21 (s, 4H), 5.15 (s, 1H), 3.99 (dq, *J* = 10.5, 6.0 Hz, 1H), 3.50 (d, *J* = 10.6 Hz, 1H), 1.23 (d, *J* = 6.1 Hz, 3H), 1.03 (s, 9H).

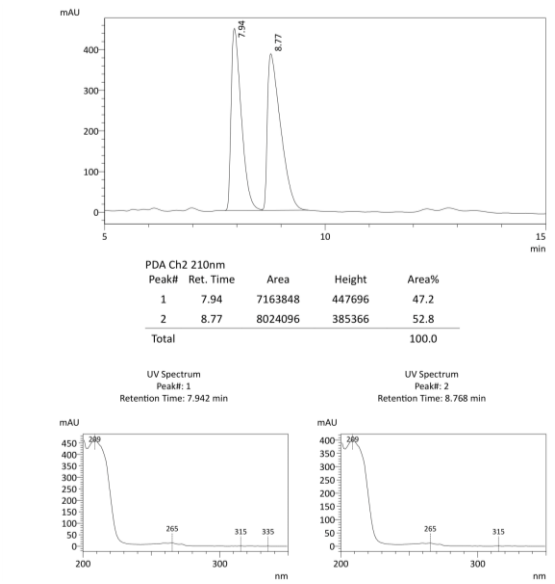
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 169.6, 148.9 (q, *J* = 1.9 Hz), 134.2, 130.8, 121.6, 120.5 (q, *J* = 257.5 Hz), 109.1, 77.0, 55.5, 35.5, 24.0, 19.6.

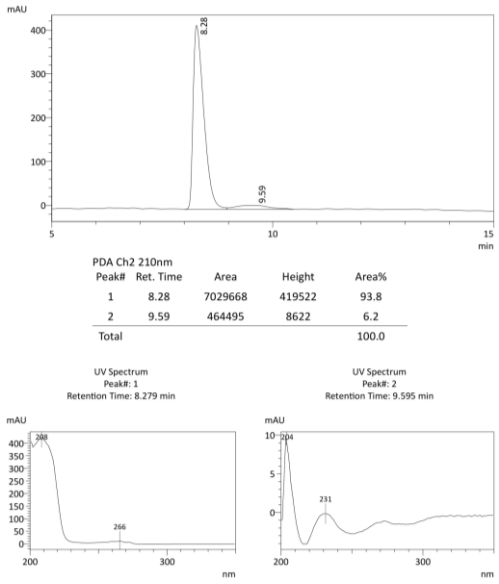
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974, 2966, 2876, 1738, 1512, 1486, 1366, 1344, 1258, 1208, 1150, 1114, 1088, 1030, 1020, 992, 966, 938, 922, 884, 844, 804, 762.

HR-MS: Fragmentation: $[C_{10}H_{10}O_2F_3]^{+\bullet}$ = M – $[C_6H_9O_2]^{+\bullet}$, calcd.: 219.0633; found: 219.0625.

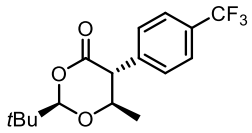
cHPLC: Chiracel OD-H; heptane: *i*PrOH = 98:2; 1 mL·min^{-1}; 210 nm; R_f(*R**) = 7.9 min; R_f(*S**) = 8.7 min.

Optical Rotation: $\alpha_D^{20} = -3.3°$ (c = 1.0, $CHCl_3$).





(2*R*,5*R*,6*R*)-2-(*tert*-Butyl)-6-methyl-5-(4-(trifluoromethyl)phenyl)-1,3-dioxan-4-one (104c)



According to **TP12**, α-bromolactone **102a** (126 mg, 0.500 mmol, 1.00 equiv) was coupled with 4-trifluoromethylphenylzinc chloride **78d** (0.750 mmol, 1.50 equiv) using $CoCl_2$ (13 mg, 0.100 mmol, 20 mol%) and PPh_3 (26 mg, 0.100 mmol, 20 mol%) as catalytic system. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **104c** as colorless crystals. (61% yield, dr = 99:1, 99% *ee*, 97 mg, 0.307 mmol).

m.p.: 90 – 94 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.83 – 7.55 (m, 2H), 7.51 – 7.14 (m, 2H), 5.17 (s, 1H), 4.03 (dq, *J* = 10.6, 6.0 Hz, 1H), 3.56 (d, *J* = 10.6 Hz, 1H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.03 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 169.3, 139.4 (d, *J* = 1.5 Hz), 130.3 (q, *J* = 32.6 Hz), 129.8, 126.1 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.1 Hz), 109.2, 76.8, 55.9, 35.5, 24.0, 19.5.

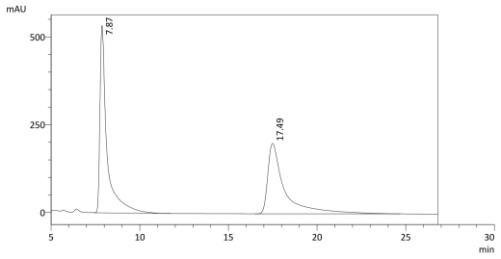
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2967, 2919, 2875, 2359, 2341, 1733, 1619, 1484, 1452, 1366, 1322, 1283, 1214, 1165, 1128, 1117, 1066, 1020, 992, 964, 884, 830, 760, 685.

MS (EI, 70 eV): *m/z* (%) = 214 (3), 213 (31), 203 (31), 187 (11), 186 (100), 185 (22), 158 (13), 117 (52), 115 (11).

HR-MS (EI, 70 eV): Fragmentation: $[C_{10}H_{10}OF_3]^{+\bullet}$ = M – $[C_6H_9O_2]^{+\bullet}$, calcd.: 203.0684; found: 203.0677.

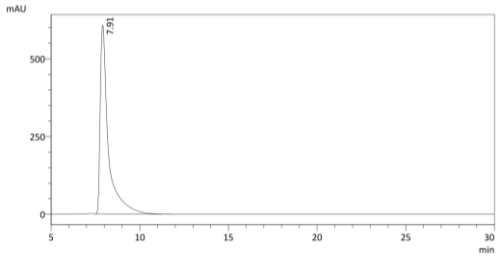
cHPLC: Chiracel AD-H; heptane: *i*PrOH = 70:30; 1 mL·min^{-1}; 215 nm; R_f(*R**) = 7.9 min; R_f(*S**) = 17.5 min.

Optical Rotation: $\alpha_D^{20} = +24.0°$ (c = 1.0, $CHCl_3$).



PDA Ch2 215nm

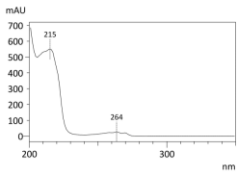
Peak#	Ret. Time	Area	Height	Area%
1	7.87	14704038	533512	52.5
2	17.49	13304145	200563	47.5
Total				100.0



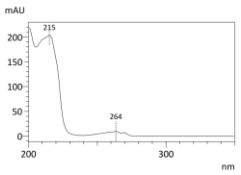
PDA Ch2 321nm

Peak#	Ret. Time	Area	Height	Area%
1	7.91	19233363	607030	100.0
Total				100.0

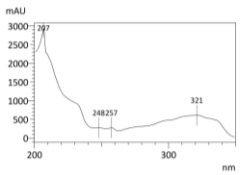
UV Spectrum
Peak#: 1
Retention Time: 7.872 min



UV Spectrum
Peak#: 2
Retention Time: 17.490 min

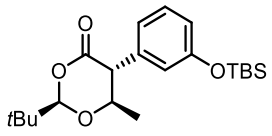


UV Spectrum
Peak#: 1
Retention Time: 7.908 min



UV Spectrum

(2*R*,5*R*,6*R*)-2-(*tert*-Butyl)-5-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-6-methyl-1,3-dioxan-4-one (104d)



According to **TP12**, α-bromolactone **102a** (126 mg, 0.500 mmol, 1.00 equiv) was coupled with arylzinc reagent **78a** (0.750 mmol, 1.50 equiv) using $CoCl_2$ (13 mg, 0.100 mmol, 20 mol%) and PPh_3 (26 mg, 0.100 mmol, 20 mol%) as catalytic system. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (95:5) as an eluent to afford **104d** as colorless solid (69% yield, dr = 99:1, 99% *ee*, 131 mg, 0.346 mmol).

m.p.: 62 – 63 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.20 (t, *J* = 7.9 Hz, 1H), 6.85 – 6.69 (m, 2H), 6.64 (t, *J* = 2.1 Hz, 1H), 5.14 (s, 1H), 3.98 (dq, *J* = 10.4, 6.0 Hz, 1H), 3.41 (d, *J* = 10.6 Hz, 1H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.03 (s, 9H), 0.98 (s, 9H), 0.19 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 169.9, 156.1, 136.9, 130.1, 122.2, 121.2, 119.5, 108.9, 77.2, 56.1, 35.5, 25.8, 24.1, 19.6, 18.3, -4.2, -4.3.

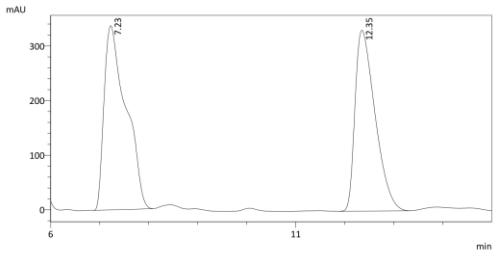
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 2931, 2859, 1732, 1602, 1585, 1485, 1473, 1458, 1446, 1342, 1274, 1253, 1236, 1217, 1151, 1114, 1030, 1002, 993, 982, 961, 939, 926, 874, 860, 837, 804, 783, 758, 728, 699.

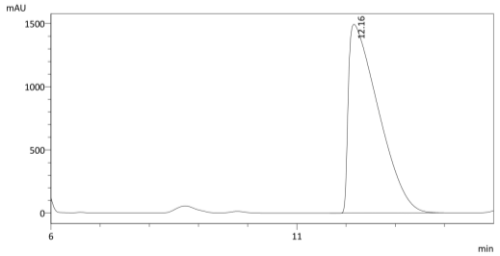
MS (EI, 70 eV): *m/z* (%) = 378 (5), 293 (8), 248 (18), 192 (24), 191 (100), 73 (8).

HR-MS (EI, 70 eV): $[C_{21}H_{34}O_4Si]^{+\bullet}$, calcd.: 378.2221; found: 378.2212.

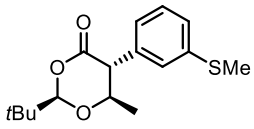
cHPLC: Chiracel OD-H; heptane: *i*PrOH = 99.5:0.5; 1 mL·min^{-1}; 218 nm; R_f(*R**) = 7.2 min; R_f(*S**) = 12.3 min.

Optical Rotation: $\alpha_D^{20} = -0.9°$ (c = 1.0, $CHCl_3$).





(2*R*,5*R*,6*R*)-2-(*tert*-Butyl)-6-methyl-5-(3-(methylthio)phenyl)-1,3-dioxan-4-one (104e)



According to **TP12**, α-bromolactone **102a** (126 mg, 0.500 mmol, 1.00 equiv) was coupled with 3-thioanisylzinc chloride **78e** (0.750 mmol, 1.50 equiv) using $CoCl_2$ (13 mg, 0.100 mmol, 20 mol%) and PPh_3 (26 mg, 0.100 mmol, 20 mol%) as catalytic system. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **104e** as colorless solid (61% yield, dr = 99:1, 99% *ee*, 90 mg, 0.306 mmol).

m.p.: 56 – 57 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.28 (t, *J* = 7.7 Hz, 1H), 7.19 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.05 (t, *J* = 1.8 Hz, 1H), 6.94 (dt, *J* = 7.6, 1.4 Hz, 1H), 5.15 (s, 1H), 4.01 (dq, *J* = 10.6, 6.1 Hz, 1H), 3.44 (d, *J* = 10.6 Hz, 1H), 2.47 (s, 3H), 1.23 (d, *J* = 6.1 Hz, 3H), 1.03 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 169.7, 139.6, 136.2, 129.5, 127.4, 126.0, 125.9, 109.0, 77.1, 56.1, 35.5, 24.1, 19.6, 15.9.

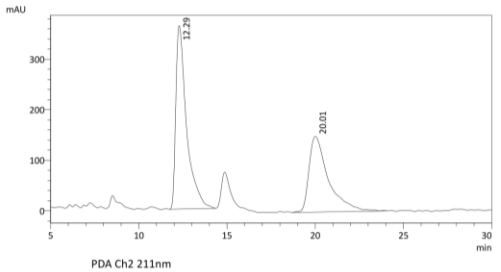
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2978, 2962, 2872, 1738, 1592, 1574, 1482, 1440, 1422, 1410, 1378, 1366, 1342, 1278, 1234, 1212, 1150, 1112, 1086, 1030, 992, 968, 938, 926, 914, 780, 760, 738, 696.

MS (EI, 70 eV): *m/z* (%) = 294 (6), 181 (19), 165 (11), 164 (100), 163 (13), 117 (60), 115 (15).

HR-MS (EI, 70 eV): $[C_{16}H_{22}O_3S]^{+\bullet}$, calcd.: 294.1284; found: 294.1281.

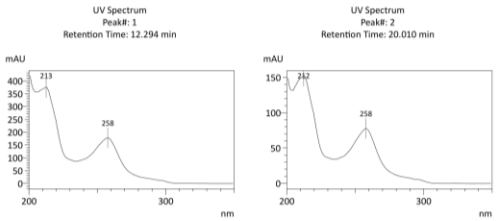
cHPLC: Chiracel OJ-H; heptane: *i*PrOH = 98:2; 1 mL·min^{-1}; 211 nm; R_f(*S**) = 12.29 min; R_f(*R**) = 20.01 min.

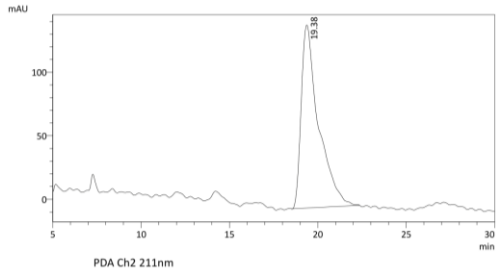
Optical Rotation: $\alpha_D^{20} = +4.3°$ (c = 1.0, $CHCl_3$).



PDA Ch2 211nm

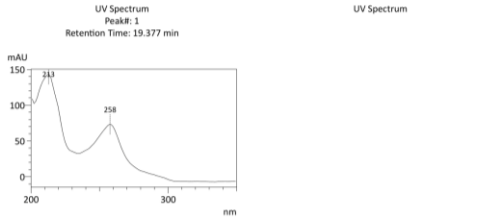
Peak#	Ret. Time	Area	Height	Area%
1	12.29	15392013	362969	57.4
2	20.01	11427046	150066	42.6
Total				100.0



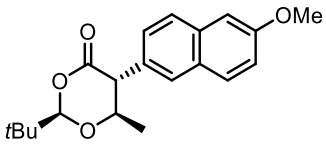


PDA Ch2 211nm

Peak#	Ret. Time	Area	Height	Area%
1	19.38	9829367	144048	100.0
Total				100.0



(2*R*,5*R*,6*R*)-2-(*tert*-Butyl)-5-(6-methoxynaphthalen-2-yl)-6-methyl-1,3-dioxan-4-one (104f)



According to **TP12**, α-bromolactone **102a** (126 mg, 0.500 mmol, 1.00nequiv) was coupled with (6-methoxynaphthalen-2-yl)zinc chloride **78f** (0.750 mmol, 1.50 equiv) using $CoCl_2$ (13 mg, 0.100

mmol, 20 mol%) and PPh_3 (26 mg, 0.100 mmol, 20 mol%) as catalytic system. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **104f** as colorless solid (82% yield, dr = 99:1, 99% *ee*, 134 mg, 0.408 mmol).

m.p.: 199 – 200 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.74 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.60 (d, *J* = 1.8 Hz, 1H), 7.23 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.16 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.12 (d, *J* = 2.5 Hz, 1H), 5.22 (s, 1H), 4.26 – 4.02 (m, 1H), 3.91 (s, 3H), 3.62 (d, *J* = 10.6 Hz, 1H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.06 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 170.2, 158.0, 134.1, 130.6, 129.3, 129.0, 128.6, 127.8, 126.9, 119.4, 109.0, 105.7, 77.2, 56.2, 55.4, 35.5, 24.1, 19.6.

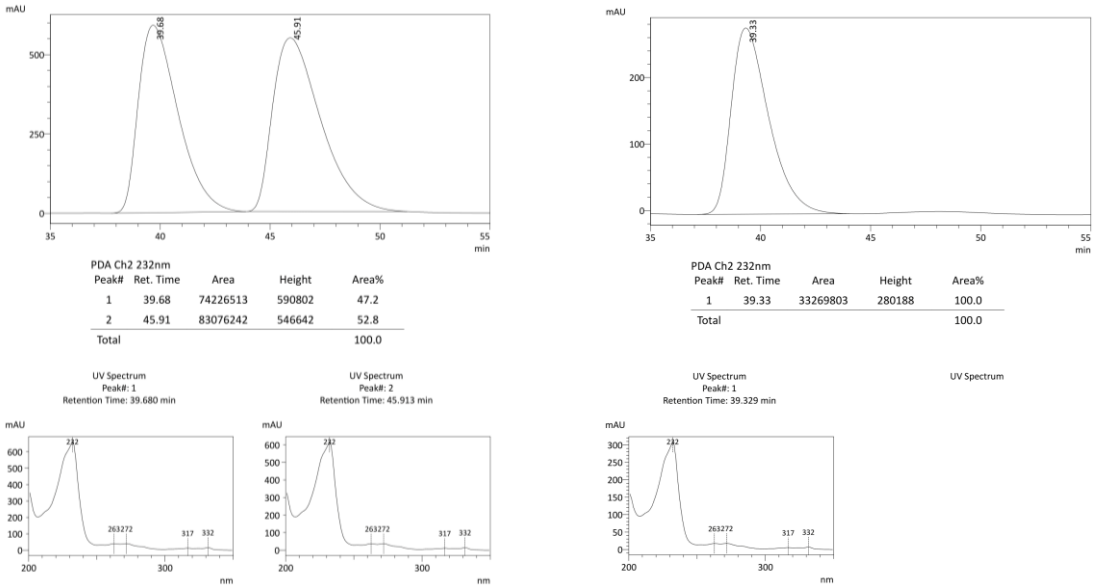
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962, 2906, 2874, 1730, 1630, 1606, 1484, 1462, 1394, 1378, 1364, 1342, 1266, 1234, 1218, 1204, 1176, 1162, 1142, 1110, 1080, 1026, 992, 980, 960, 946, 936, 922, 900, 882, 846, 826, 812, 756, 736, 718, 668.

MS (EI, 70 eV): *m/z* (%) = 328 (37), 243 (47), 215 (27), 199 (56), 198 (100), 155 (24).

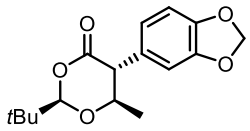
HR-MS (EI, 70 eV): $[C_{20}H_{24}O_4]^{+\bullet}$, calcd.: 328.1669; found: 328.1668.

cHPLC: Chiracel OJ-H; heptane: *i*PrOH = 98:2; 1 mL·min^{-1}; 232 nm; R_f(*R**) = 39.7 min; R_f(*S**) = 45.9 min.

Optical Rotation: $\alpha_D^{20} = +64.2°$ (c = 1.0, EtOAc).



(2*R*,5*R*,6*R*)-5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(*tert*-butyl)-6-methyl-1,3-dioxan-4-one (104g)



According to **TP12**, α-bromolactone **102a** (126 mg, 0.500 mmol, 1.0 equiv) was coupled with benzodioxolylzinc chloride **78g** (0.750 mmol, 1.5 equiv) using $CoCl_2$ (13 mg, 0.100 mmol, 20 mol%) and PPh_3 (26 mg, 0.100 mmol, 20 mol%) as catalytic system. The crude product was purified by column chromatography on silica using *i*hexane:EtOAc (9:1) as an eluent to afford **104g** as colorless oil (73% yield, dr = 99:1, 99% *ee*, 107 mg, 0.366 mmol).

^{1}H-NMR (400 MHz, benzene-D$_6$, ppm): δ = 6.58 (d, *J* = 7.9 Hz, 1H), 6.48 (d, *J* = 1.8 Hz, 1H), 6.29 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.29 (dd, *J* = 13.0, 1.4 Hz, 2H), 4.71 (s, 1H), 3.44 (dq, *J* = 10.5, 6.0 Hz, 1H), 3.00 (d, *J* = 10.7 Hz, 1H), 1.02 (s, 9H), 0.86 (d, *J* = 6.1 Hz, 3H).

^{13}C-NMR (101 MHz, benzene-D$_6$, ppm): δ = 168.2, 148.4, 147.6, 129.9, 123.2, 109.8, 108.6, 108.1, 101.2, 77.1, 55.9, 35.4, 24.1, 19.3.

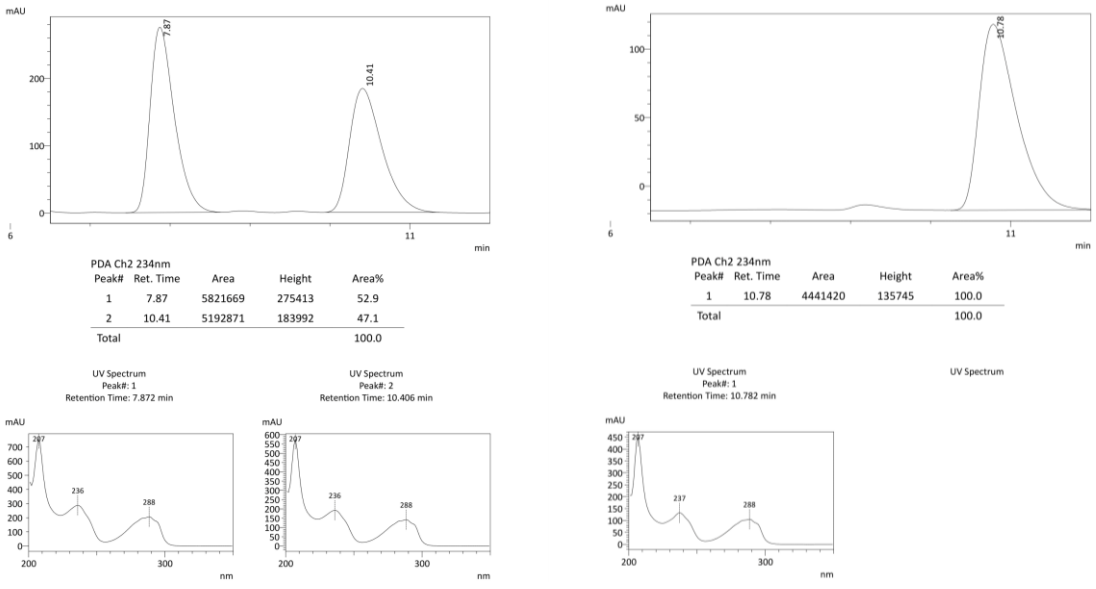
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2978, 2962, 2906, 2874, 1738, 1506, 1486, 1464, 1444, 1410, 1378, 1366, 1340, 1278, 1246, 1228, 1212, 1152, 1112, 1084, 1030, 992, 968, 930, 806, 762, 734.

MS (EI, 70 eV): *m/z* (%) = 292 (7), 207 (17), 163 (11), 162 (100), 43 (32).

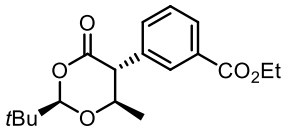
HR-MS (EI, 70 eV): [$C_{16}H_{20}O_5$], calcd.: 292.1305; found: 292.1298.

cHPLC: Chiracel OJ-H; heptane: *i*PrOH = 9:1; 1 mL·min^{-1}; 234 nm; R_f(*R**) = 10.4 min; R_f(*S**) = 7.9 min.

Optical Rotation: $\alpha_D^{20} = +13.4°$ (c = 1.0, $CHCl_3$).



Ethyl 3-((2*R*,4*R*,5*R*)-2-(*tert*-butyl)-4-methyl-6-oxo-1,3-dioxan-5-yl)benzoate (104i)



A dry and argon flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, was charged with ethyl 3-iodobenzoate (207 mg, 0.750 mmol, 1.00 equiv) and dry THF (1.5 mL). The mixture was cooled to -20°C, *i*-PrMgCl·LiCl (0.50 mL, 0.825 mmol, 1.10 equiv) was added dropwise and stirred for 30 min. Solid $ZnCl_2$ (0.750 mmol, 1.00 equiv) was placed in a dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum and dried under vacuum at 250 °C for 5 min. After cooling to rt under vacuum, an argon atmosphere was applied and THF (1.5 mL) was added. The solution was added to the Grignard reagent at -20 °C. The mixture containing arylzinc reagent **78j** was allowed to warm to rt and stirred for 15 min .

A dry and argon-flushed 20 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with $CoCl_2$ (13 mg, 0.100 mmol, 20 mol%). The solid was flame dried under high vacuum for 5 min. After cooling to rt, PPh_3 (26 mg, 0.100 mmol, 20 mol%) and the α-bromolactone **102a** (126 mg, 0.500 mmol, 1.00 equiv) was added. The mixture was dissolved in THF (1 mL) and cooled to -20 °C. The freshly prepared organozinc chloride **78j** was added and the mixture was allowed to warm to rt overnight. Sat. aq. NH_4Cl (5 mL) and EtOAc (5 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification on using *i*hexane:EtOAc (9:1) as an eluent to afford **104i** as colorless oil (52% yield, dr = 99:1, 83 mg, 0.259 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.99 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.86 (t, *J* = 1.8 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.37 (dt, *J* = 7.7, 1.6 Hz, 1H), 5.18 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.06 (dq, *J* = 10.6, 6.1 Hz, 1H), 3.53 (d, *J* = 10.7 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.03 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 169.6, 166.2, 135.8, 133.8, 131.3, 130.2, 129.2, 129.2, 109.0, 76.9, 61.3, 55.9, 35.5, 24.0, 19.5, 14.4.

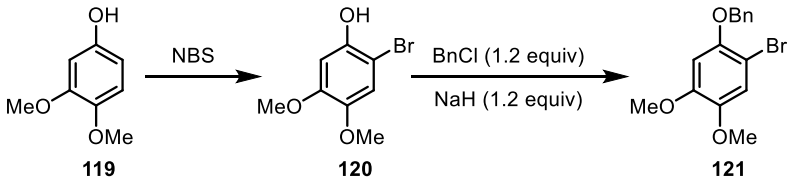
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2980, 2964, 2938, 2906, 2874, 1734, 1716, 1367, 1343, 1283, 1236, 1213, 1189, 1150, 1107, 1084, 1029, 993, 970, 912, 764, 751, 729, 705, 695.

MS (EI, 70 eV): *m/z* (%) = 275 (20), 235 (24), 217 (18), 191 (32), 190 (100), 162 (17), 161 (46), 145 (87), 117 (41), 115 (30), 91 (23), 57 (21).

HR-MS (EI, 70 eV): $[C_{18}H_{23}O_5]^{+\bullet}$ = $[M\text{-}H]^{+\bullet}$, calcd.: 319.1545; found: 319.1547.

5.3 Total Synthesis of the Rotenoid Derivative MOM-Protected Munduserol

1-(Benzyloxy)-2-bromo-4,5-dimethoxybenzene



119 **120** **121**

3,4-Dimethoxyphenol (**119**, 5.00 g, 32.4 mmol, 1.00 equiv) was dissolved in freshly distilled CH_2Cl_2 (60 mL) and cooled to 0 °C. *N*-Bromosuccinimide (5.77 g, 32.4 mmol, 1.00 equiv) was added slowly, the reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction was stopped by adding sodium thiosulfate (15 mL), a sat. sol. of NH_4Cl (15 mL) and water (15 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 8:2). 2-Bromo-4,5-dimethoxyphenol (**120**) was isolated as a brown solid (4.78 g, 20.5 mmol, 63% yield).

2-Bromo-4,5-dimethoxyphenol (**120**, 4.78 g, 20.5 mmol, 1.00 equiv) was dissolved in THF (40mL). The solution was cooled to 0 °C and sodium hydride (60% in paraffin oil, 1.07 g, 26.7 mmol, 1.30 equiv) was added slowly. The reaction mixture was allowed to warm to rt and stirred for 30 min. Benzyl bromide (3.65 mL, 30.8 mmol, 1.50 equiv) was added and the mixture was refluxed at 80 °C overnight. Water (100 mL) was added and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 9:1). 1-(Benzyloxy)-2-bromo-4,5-dimethoxybenzene (**121**) was isolated as a as yellowish solid (5.51 g, 17.1 mmol, 83% yield).

m.p.: 80 – 81 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56 – 7.44 (m, 2H), 7.44 – 7.36 (m, 2H), 7.36 – 7.30 (m, 1H), 7.04 (s, 1H), 6.56 (s, 1H), 5.10 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H).

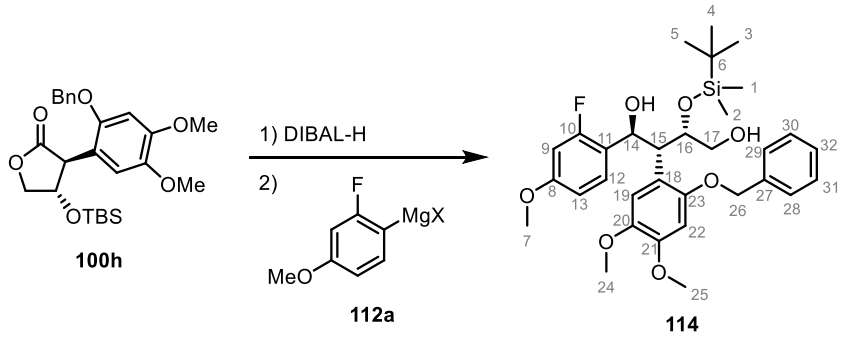
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 149.4, 148.9, 144.4, 136.8, 128.7, 128.2, 127.5, 116.1, 102.6, 101.6, 72.7, 56.6, 56.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3084, 2998, 2969, 2952, 2934, 2920, 2909, 2899, 2877, 2845, 1580, 1503, 1462, 1455, 1445, 1437, 1392, 1373, 1331, 1276, 1264, 1247, 1211, 1199, 1186, 1168, 1164, 1119, 1083, 1045, 1033, 1027, 1011, 997, 975, 966, 922, 843, 817, 804, 759, 727, 700.

MS (EI, 70 eV): *m/z* (%) = 324 (16), 322 (17), 244 (11), 243 (71), 233 (44), 231 (43), 211 (10), 205 (42), 203 (41), 190 (17), 188 (17), 175 (11), 173 (11), 91 (100).

HR-MS (EI, 70 eV): $[C_{15}H_{15}BrO_3]^{+\bullet}$, calcd.: 322.0199; found: 322.0197.

(1*S*,2*R*,3*S*)-2-(2-(Benzyloxy)-4,5-dimethoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)-1-(2-fluoro-4-methoxyphenyl)butane-1,4-diol (114)



A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with the chiral arylated lactone **100h** (3.45 g, 7.52 mmol, 1.00 equiv) and dry CH_2Cl_2 (40 mL) was added. The solution was cooled to -78 °C and a solution of diisobutylaluminum hydride (1.0 M in CH_2Cl_2, 11.3 mL, 11.3 mmol, 1.50 equiv) was added dropwise to the reaction. Upon disappearance of the starting material (TLC, after 2.5 h) the reaction was quenched with sat. aq. Rochelle's salt (10 mL) and EtOAc (10 mL) and allowed to warm to rt and stirred for another 30 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (5 x 20 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue containing the corresponding lactol **113** was used without further purification for the next step.

The crude lactol **113** was dissolved in THF (8 mL) and slowly added to the arylmagnesium reagent **112a** (19.5 mL, 15.0 mmol, 2.00 equiv) at 0 °C. The mixture was allowed to warm to rt and stirred for 16 h. Sat. aq. NH_4Cl (15 mL) and EtOAc (15 mL) was added. The layers were separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 7:3) to afford the alcohol **114** as a foamy solid (3.80 g, 6.49 mmol, 86% yield over two steps).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.39 – 7.33 (m, 2H, H-12, H-19), 7.30 (d, *J* = 7.6 Hz, 2H, H-27-28), 7.20 (dd, *J* = 7.5 Hz, 2H, H-29-30), 7.11 (t, *J* = 7.4 Hz, 1H, H-31), 6.50 (dd, *J* = 8.6, 2.4 Hz, 1H, H-13), 6.25 (dd, *J* = 12.1, 2.5 Hz, 1H, H-9), 6.15 (s, 1H, H-22), 5.66 (d, *J* = 10.6 Hz, 1H, H-14), 4.81 (dd, *J* = 5.7, 2.8 Hz, 1H, H-16), 4.62 (d, *J* = 11.7 Hz, 1H, H-26'), 4.51 (d, *J* = 11.8 Hz, 1H, H-26), 4.15 (dd, *J* = 10.5, 2.6 Hz, 1H, H-15), 3.82 (s, 3H, H-25), 3.68 (dd, *J* = 11.1, 5.6 Hz, 1H, H-17'), 3.46 (dd, *J* = 11.2, 7.9 Hz, 1H, H-17),

3.23 (s, 3H, H-24), 3.00 (s, 3H, H-7), 2.54 (s, 1H, OH), 1.04 (s, 9H, H-3-4), 0.32 (s, 3H, H-1/2), 0.16 (s, 3H, H-1/2).

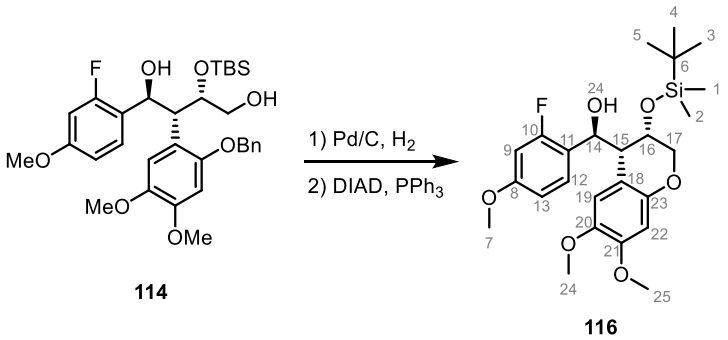
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.2 (d, *J* = 244.5 Hz, C-10), 160.4 (d, *J* = 11.0 Hz, C-8), 150.9 (C-23), 149.1 (C-20), 144.5 (C-21), 137.6 (C-27), 129.4 (d, *J* = 6.4 Hz, C-12), 129.0 (C-30-31), 127.8 (C-32), 127.6 (C-28-29), 123.7 (d, *J* = 13.9 Hz, C-11), 118.5 (C-18), 116.1 (C-19), 111.0 (d, *J* = 2.9 Hz, C-13), 100.7 (d, *J* = 26.9 Hz, C-9), 100.0 (C-22), 73.0 (C-16), 72.1 (C-26), 66.9 (C-14), 65.6 (C-17), 56.5 (C-25), 55.5 (C-24), 54.8 (C-7), 45.3 (C-15), 26.3 (C-3-5), 18.5 (C-6), -4.4 (d, *J* = 38.2 Hz, C-1-2).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3489, 2953, 2932, 2855, 1737, 1624, 1613, 1587, 1507, 1484, 1464, 1444, 1401, 1374, 1360, 1313, 1248, 1214, 1191, 1153, 1106, 1092, 1033, 1025, 973, 948, 920, 889, 859, 830, 812, 775, 735, 696, 667.

HR-MS (EI, 70 eV): $[C_{32}H_{43}FO_7Si]^{+\bullet}$, calcd.: 586.2762; found: 586.2760.

Optical Rotation: $\alpha_D^{20} = +13.4°$ (c = 1.0, $CHCl_3$).

(*S*)-((3*S*,4*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-6,7-dimethoxychroman-4-yl)(2-fluoro-4-methoxyphenyl)methanol (116)



A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with the benzyl protected alcohol **114** (2.76 g, 4.70 mmol, 1.00 equiv). Pd/C (10 mol%) and dry ethanol (30 mL) was added. H_2 was bubbled through the mixture for 1 min at rt. The reaction was stirred under H_2 (1 atm.) for 3 h until full consumption of the starting material was observed *via* TLC. The reaction was filtered over celite and rinsed with EtOAc (100 mL). The solution was dried over Na_2SO_4, the solvents were evaporated under reduced pressure and the residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 1:1) to afford the deprotected product **115** as a colorless solid (2.06 g, 4.15 mmol, 88% yield).

A dry and argon flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, was charged with the aromatic alcohol (2.00 g, 4.04 mmol, 1.00 equiv) and PPh_3 (1.27 g, 4.85 mmol, 1.20 equiv). The mixture was dissolved in CH_2Cl_2 (16 mL) and cooled to 0 °C. Diisopropyl azodicarboxylate (2.34 mL, 4.45 mmol, 1.10 equiv) was added and stirring was continued for 2 h until full consumption

of the starting material was observed *via* TLC. The reaction was warmed to rt and sat. aq. NH_4Cl (5 mL) and CH_2Cl_2 (5 mL) were added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 7:3) to afford product **116** as a yellowish oil (2.57 g, 5.37 mmol, 84% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.46 (t, *J* = 8.6 Hz, 1H, H-12), 6.97 (s, 1H, H-24), 6.67 (dd, *J* = 8.9, 2.6 Hz, 1H, H-13), 6.66 (s, 1H, H-19), 6.53 (dd, *J* = 12.4, 2.5 Hz, 1H, H-9), 6.47 (s, 1H, H-22), 5.51 (d, *J* = 10.1 Hz, 1H, H-14), 4.51 (dt, *J* = 8.0, 6.7 Hz, 1H, H-16), 4.21 (dd, *J* = 8.8, 6.9 Hz, 1H, H-17'), 3.93 (dd, *J* = 8.7, 6.3 Hz, 1H, H-17), 3.78 (s, 3H, H-24), 3.77 (s, 3H, H-25), 3.74 (s, 3H, H-7), 3.64 (dd, *J* = 10.1, 8.0 Hz, 1H, H-15), 0.89 (s, 9H, H-3-5), 0.02 (d, *J* = 15.9 Hz, 6H, H-1-2).

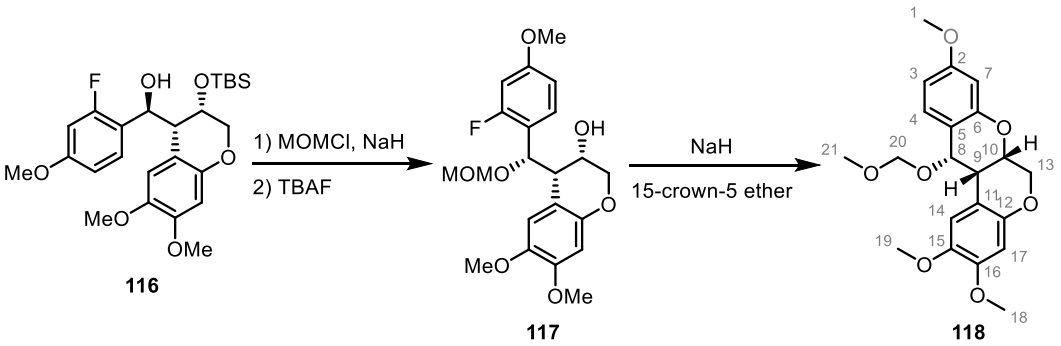
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.3 (d, *J* = 246.1 Hz, C-10), 160.9 (d, *J* = 11.4 Hz, C-8), 149.7 (C-23), 148.8 (C-21), 142.8 (C-20), 129.1 (d, *J* = 5.7 Hz, C-12), 118.5 (d, *J* = 13.0 Hz, C-11), 114.4 (C-15), 110.7 (d, *J* = 2.9 Hz, C-13), 110.3 (C-19), 101.8 (C-22), 101.3 (d, *J* = 26.2 Hz, C-9), 80.4 (C-16), 74.8 (C-14), 73.5 (C-17), 56.5 (C-24), 55.9 (C-25), 55.6 (C-7), 54.3 (C-15), 25.8 (C-3-5), 18.0 (C-6), -4.8 (d, *J* = 40.4 Hz, C-1-2).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3323, 2980, 2969, 2954, 2934, 2883, 2856, 1709, 1626, 1588, 1510, 1465, 1451, 1417, 1374, 1311, 1229, 1203, 1180, 1153, 1106, 1076, 1043, 1029, 1006, 948, 933, 897, 833, 812, 775, 729, 671.

HR-MS (EI, 70 eV): $[C_{25}H_{35}FO_6Si]^{+\bullet}$, calcd.: 478.2181; found: 478.2181.

Optical Rotation: $\alpha_D^{20} = +28°$ (c = 1.0, $CHCl_3$).

MOM-Protected Munduserol (118)



The benzylic alcohol **116** (1.10 g, 2.31 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (5 mL) and the mixture was cooled to 0 °C. NaH (184 mg, 7.67 mmol, 2.00 equiv) was added, stirring at 0 °C was continued for 30 min and chloromethyl methyl ether (0.44 mL, 5.78 mmol, 2.50 equiv) was added. The reaction was allowed to warm to 25 °C and stirred overnight. Sat. aq. NH_4Cl (15 mL) and CH_2Cl_2 (20 mL) were added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 8:2) to afford the MOM- and TBS-protected compound (1.01 g, 1.92 mmol, 84% yield). This intermediate was dissolved in THF (8 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 2.88 mL, 2.88 mmol, 1.50 equiv) was added, and the mixture was stirred for 2 h. Sat. aq. NH_4Cl (20 mL) and EtOAc (20 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to column chromatography purification (silica, *i*hexane:EtOAc 3:7) to afford **117** as a yellowish oil (502 mg, 1.23 mmol, 64% yield). A dry and argon flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, was charged with the alcohol **117** (37 mg, 0.091 mmol, 1.00 equiv), toluene (4.5 mL) and DMPU (0.5 mL). 15-crown-5 ether (38 µL, 0.191 mmol, 2.10 equiv) and NaH (60% in paraffin oil, 12 mg, 0.282 mmol, 3.10 equiv) were added and the mixture was heated to 110 °C for 48 h. The mixture was allowed to cool to rt and sat. aq. NH_4Cl (2 mL) and EtOAc (2 mL) were added. The layers were separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was subjected to preparative thin-layer chromatography purification (silica, *i*hexane:EtOAc 5:5) to afford the rotenoid derivative **118** as a yellow oil (10 mg, 0.026 mmol, 28% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.17 (s, 1H, H-14), 7.02 (d, *J* = 8.1 Hz, 1H, H-4), 6.81 (s, 1H, H-17), 6.44 (d, *J* = 2.4 Hz, 1H, H-7), 6.42 (dd, *J* = 8.1, 2.4 Hz, 1H, H-3), 5.21 (d, *J* = 6.9 Hz, 1H, H-20), 5.18 (d, *J* = 6.9 Hz, 1H, H-20'), 5.05 (s, 1H, H-8), 4.84 (d, *J* = 3.3 Hz, 1H, H-10), 4.22 (d, *J* = 10.6 Hz, 1H, H-13), 3.98

(dd, *J* = 10.6, 3.5 Hz, 1H, H-13'), 3.96 (s, 1H, H-9), 3.88 (s, 3H, H-18), 3.86 (s, 3H, H-19), 3.78 (s, 3H, H-1), 3.50 (s, 3H, H-21).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.4 (C-2), 154.3 (C-6), 149.6 (C-12), 148.9 (C-16), 144.4 (C-15), 127.6 (C-4), 120.6 (C-5), 117.9 (C-11), 111.1 (C-14), 106.0 (C-3), 101.9 (C-7), 100.2 (C-17), 95.5 (C-20), 81.6 (C-10), 77.2 (C-8), 73.5 (C-13), 56.8 (C-19), 56.3 (C-21), 56.2 (C-18), 55.5 (C-1), 43.2 (C-9).

NOE-NMR shows a proximity of H-8 and H-9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2935, 2840, 1623, 1587, 1508, 1465, 1444, 1314, 1272, 1210, 1189, 1148, 1122, 1106, 1092, 1068, 1050, 1008, 949, 921, 833, 790, 752, 666.

HR-MS (EI, 70 eV): $[C_{21}H_{25}O_7]^{+\bullet}$ = $[M+H]^{+\bullet}$, calcd.: 389.1600; found: 389.1601.

Optical Rotation: $\alpha_D^{20} = -18°$ (c = 1.0, $CHCl_3$).