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Late-Stage Functionalization of Peptides and Cyclopeptides Using Organozinc Reagents
- and -
Pyrrole Protected 2-Aminoalkylzinc Reagents for the Enantioselective Synthesis of Amino Derivatives

von

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aus

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ERKLÄRUNG

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……

(Marcel Leroux)

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1) "Late-Stage Functionalization of Peptides and Cyclopeptides Using Organozinc Reagents" M. Leroux, T. Vorherr, I. Lewis, M. Schaefer, G. Koch, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 8231.

2) "Pyrrole Protected 2-Aminoalkylzinc Reagents for the Enantioselective Synthesis of Amino-Derivatives" M. Leroux, W.-Y. Huang, Y. Lemke, T. Koller, K. Karaghiosoff, P. Knochel, *manuscript in preparation*.

Für meine Familie und Sina

„Die Wissenschaft fängt eigentlich erst

da an interessant zu werden, wo sie aufhört."

Justus von Liebig

Abbreviations

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
ATR	attenuated total reflection
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Bz	benzoyl
calc.	calculated
Cbz	carboxybenzyl
dba	*trans*,*trans*-dibenzylideneacetone
DCE	1,2-dichloroethane
diglyme	diglycoldimethylether
DMF	*N*,*N*-dimethylformamide
e.g.	*exempli gratia*, for example
EI	electron ionization (MS)
equiv	equivalent(s)
Et	ethyl
EX	electrophile
FG	functional group
GC	gas chromatography
Hal	halogen
Het	undefined heteroaryl substituent
HRMS	high resolution mass spectrometry
i	*iso*
i.e.	*id est*, that is
IR	infrared spectroscopy
J	coupling constant (NMR)
M	mol L^{-1}
MD	molecular dynamics
MDCK	madin darby canine kidney cells assay
Me	methyl
Met	metal
mol%	equiv•10^2
m.p.	melting point
MS	mass spectrometry
NCE	new chemical entity

NMP	*N*-Metyl-2-pyrrolidone
NMR	nuclear magnetic resonance
PAMPA	parallel artificial membrane permeability assay
pc	precursor
PG	protecting group
Ph	phenyl
Piv	pivaloyl
PMDTA	*N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine
ppm	parts per million
Pr	propyl
Py/Pyr	pyridyl
R	undefined organic substituent
SAPSA	solvent-accessible polar surface area
sat.	saturated
SFC	supercritical fluid chromatography
t	*tert*
THF	tetrahydrofuran
tfp	*tri*(2-furanyl)phosphine
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TP	typical procedure
vol	volume
WHO	World Health Organization

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A. INTRODUCTION

1 General Introduction

In 2018, over 18 million new cancer cases and almost 10 million cancer-related deaths were recorded according to the world health organization (WHO).[1] With a steadily rising world population (2019: approx. 7.7 billion)[2] and the increase of life expectation[3], the number of people suffering from the various kinds of cancer is likely to further increase. For this reason, an efficient and fast way to develop new pharmaceutical drugs becomes even more important in future. In general, the process of drug discovery from the very beginning to the drug approval, takes 12 up to 15 years and costs more than one billion dollar.[4] In the beginning of the drug development process, the design and preparation of new chemical entities (NCE) is important. Usually, a lot of NCEs must be synthesized and tested to find only a few (2-5) suitable candidates for the clinical trial phases.[5] To enhance this step, efficient and broadly applicable methods for the synthesis of organic molecules are necessary. Organometallic chemistry has found broad application in the development and production of pharmaceutical compounds.[6] Some of the 200 top-selling drugs[7] are small-molecule pharmaceuticals prepared with at least one step using organometallic reagents. Examples for those compounds (Figure 1) are omeprazole[8] (proton-pump inhibitor), escitalopram[9] (selective serotonin reuptake inhibitor), ezetimibe[10] (cholesterol absorption inhibitor) and sitagliptin[11] (diabetes treatment).

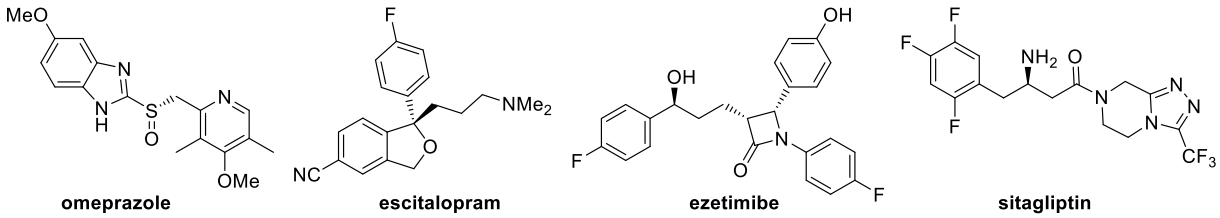

Figure 1: Examples for top-selling drugs synthesized by using organometallic reagents.

Besides small-molecules and proteins, drugs based on bioactive peptides are gaining importance for pharmaceutical application.[12]

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[1] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, A. Jemal, *CA-Cancer J. Clin.* **2018**, *68*, 394.
[2] United Nations, Department of Economic and Social Affairs, Population Division (2019). *World Population Prospects 2019, Online Edition*.
[3] V. Kontis, J. E. Bennett, C. D. Mathers, G. Li, K. Foreman, M. Ezzati, *Lancet* **2017**, *389*, 1323.
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[5] A. A. Ciociola, L. B. Cohen, P. Kulkarni, *Am. J. Gastroenterol.* **2014**, *109*, 620.
[6] M. L. Crawley, B. M. Trost, *Applications of transition metal catalysis in drug discovery and development: an industrial perspective*, John Wiley & Sons, New Jersey, USA, **2012**.
[7] N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348.
[8] U. K. Junggren, S. E. Sjöstrand US-4255431, **1981**.
[9] K. K. Vipin, K. M. Umar, R. B. Narsimha, K. S. Ranjith, D. Ramesh, M. Sivakumaran EP-2017271A1, **2009**.
[10] C. H. V. A. Sasikala, P. Reddy Padi, V. Sunkara, P. Ramayya, P. K. Dubey, V. Bhaskar Rao Uppala, C. Praveen, *Org. Process Res. Dev.* **2009**, *13*, 907.
[11] D. Kim, L. Wang, M. Beconi, G. J. Eiermann, M. H. Fisher, H. He, G. J. Hickey, J. E. Kowalchick, B. Leiting, K. Lyons et al., *J. Med. Chem.* **2005**, *48*, 141.
[12] J. L. Lau, M. K. Dunn, *Bioorg. Med. Chem.* **2018**, *26*, 2700.

Two examples for peptides used for cancer therapy are carfilzomib[13], a selective proteasome inhibitor and leuprorelin[14], a gonadotropin-releasing hormone inhibitor (Figure 2).

Furthermore, cyclopeptides have found useful application[15] as peptidomimetics, since they show increased stability towards proteolysis[16]. One example is the cyclic peptide ciclosporin[17], which is used as immunosuppressant, consisting of eleven amino acids (Figure 2).

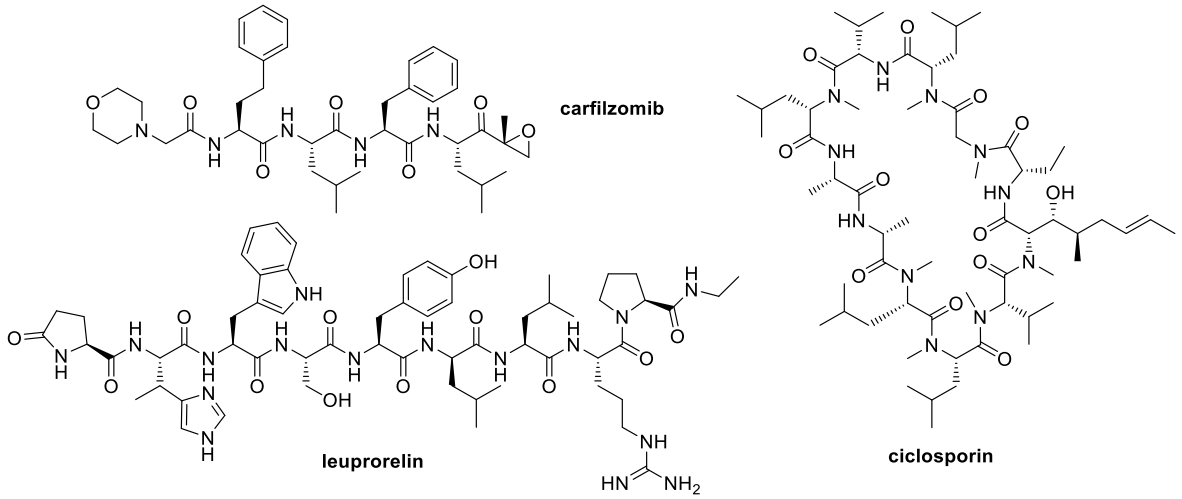

Figure 2: Selected examples for top-selling drugs based on linear and cyclic peptides.

To accelerate the drug development process, the fast preparation of a broad range of NCEs is of importance. Therefore, new efficient methods for the formation of carbon-carbon bonds are needed to further extend the chemical space[18]. Organometallic chemistry and transition-metal catalysis proved to be powerful tools for the preparation of complex and functionalized molecules.[19]

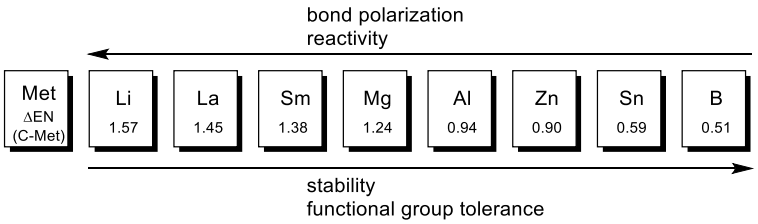

Figure 3: Electronegativity differences of selected metal relative to carbon, calculated with the Pauling scale.[20]

Depending on the purpose, different organometallic regents must be used for organic synthesis. The reagents reactivities and therefore functional group tolerances are varying dependent on the metal.

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[13] D. L. Hughes, *Org. Process Res. Dev.* **2016**, *20*, 2028.
[14] A. N. Balaev, V. N. Osipov, K. A. Okhmanovich, V. E. Fedorov, *Pharm. Chem. J.* **2014**, *48*, 217.
[15] L. Gentilucci, R. de Marco, L. Cerisoli, *Curr. Pharm. Des.* **2010**, *16*, 3185.
[16] a) K.-i. Harada, K. Fujii, T. Shimada, M. Suzuki, H. Sano, K. Adachi, W. W. Carmichael, *Tetrahedron Lett.* **1995**, *36*, 1511; b) A. Napolitano, I. Bruno, P. Rovero, R. Lucas, M. P. Peris, L. Gomez-Paloma, R. Riccio, *Tetrahedron* **2001**, *57*, 6249; c) A. Aneiros, A. Garateix, *J. Chromatogr. B* **2004**, *803*, 41; d) V. Arumugam, M. Venkatesan, S. Ramachandran, U. Sundaresan, *Int. J. Pept. Res. Ther.* **2018**, *24*, 13.
[17] X. Wu, J. L. Stockdill, P. Wang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 4098.
[18] J.-L. Reymond, M. Awale, *ACS Chem. Neurosci.* **2012**, *3*, 649.
[19] M. Schlosser, *Organometallics in Synthesis Third Manual*, John Wiley & Sons, New Jersey, USA, **2013**.
[20] L. Pauling, *J. Am. Chem. Soc.* **1932**, *54*, 3570.

Origin of the diversity of reactivity is the divergent polarization of the carbon-metal bond and which can be ranked by the electronegativity-differences between carbon and the chosen metal (Figure 3).[21] Therefore, polar organolithium reagents show a very high reactivity and have to be handled at low temperatures, whereas less-polar organoboron compounds tends to be more tolerant toward functional groups but are in contrast less reactive. Organozinc reagents are located in the middle of this scale and are a reasonable compromise between reactivity and functional group tolerance.

2 Preparation of Organozinc Reagents

2.1 Overview

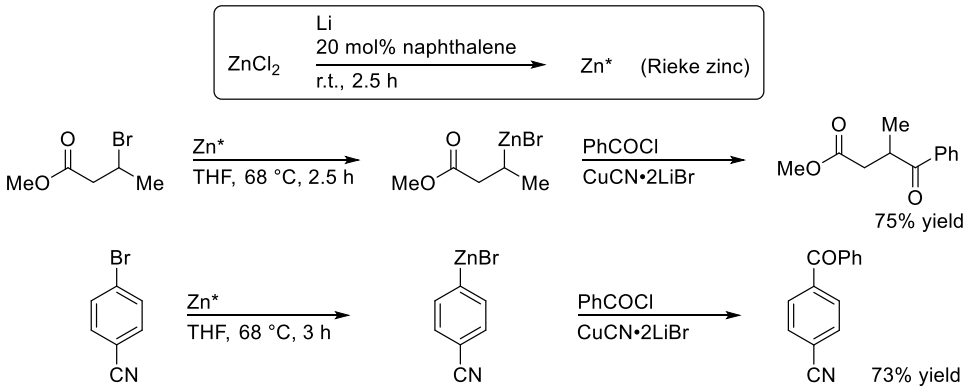
The origin of organozinc chemistry can be traced back to the middle of the 19th century. Frankland discovered diethylzinc as the first organozinc reagent in 1848 by heating ethyl iodide with zinc metal.[22] Until Grignard discovered the convenient synthesis of organomagnesium reagents in 1900[23], organozinc compounds were the only known organometallics for the formation of new carbon-carbon bonds. Although magnesium reagents were more reactive towards various electrophiles and provided higher yields, organozinc compounds still have been used in reactions such as Simons-Smith cyclopropanations[24] or Reformatsky reaction[25]. Since its discovery, organozinc chemistry evolved and many versatile applications have been developed.[26] Organozinc compounds easily undergo a broad range of transmetalation reactions due to the presence of empty low-lying *p*-orbitals which can readily interact with *d*-orbitals of different transition metal salts. These zinc/transition-metal intermediates are highly reactive and can undergo various reactions with electrophiles, while retaining the high functional group tolerance. An important application is the transmetalation reaction to copper or palladium, which allows their use in very efficient cross-coupling reactions.[27] The cross-coupling reaction is a very powerful method in organic chemistry which was awarded with the chemistry Nobel prize in 2010 to Negishi, Heck and Suzuki for their research on this type of C–C bond formation.[28] Especially the work of Negishi involving organozinc reagents provides a versatile pathway to obtain highly functionalized

[21] A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.
[22] E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171
[23] a) V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322; b) V. Grignard, *Ann. Chim.* 1**901**, *24*, 433.
[24] a) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323; b) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256; c) M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **2003**, *125*, 2341.
[25] a) S. Reformatsky, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210; b) R. Moumne, S. Lavielle, P. Karoyan, *J. Org. Chem.* **2006**, *71*, 3332.
[26] P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker in *Organic reactions*, Wiley Online Library, Hoboken, N.J., **2003**, pp. 417–759.
[27] a) P. Knochel, H. Leuser, L.-Z. Cong, S. Perrone, F. F. Kneisel in *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, Germany, **2008**, pp. 251; b) F. H. Lutter, M. S. Hofmayer, J. M. Hammann, V. Malakhov, P. Knochel, *in Organic Reactions*, Vol. 100 (Ed.: S. E. Denmark), John Wiley & Sons, Hoboken,USA, **2019**.
[28] X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 9047.

organic compounds.[29] In the following chapters, the preparation and application will be described in detail.

2.2 Oxidative Insertion

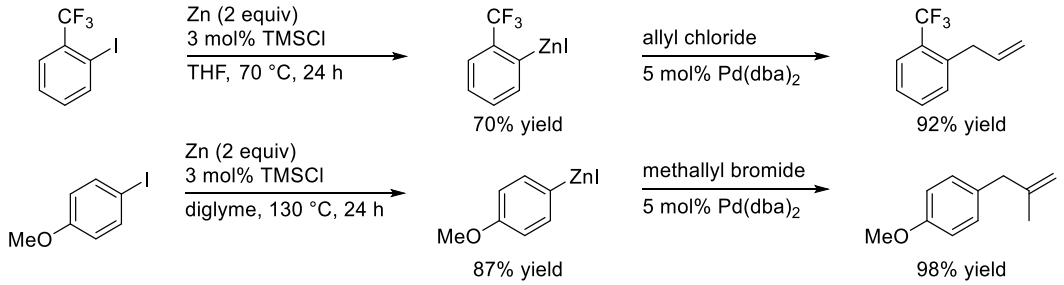
The oxidative insertion of zinc into alkyl iodides, reported by Frankland[22], was the first method used to prepare organozinc reagents. Due to the low reactivity of this metal, the reaction scope was limited to a few alkyl iodides. As a base metal, the surface of elemental zinc is covered with an oxide layer, which reduces the reactivity for metal insertion reactions. Several methods have been developed for the activation of the zinc surface, including HCl washing[30a], treatment with ultrasonic waves[30b], or the addition of 1,2-dibromoethane[30c] or chlorotrimethylsilane[30d]. Another approach to obtain highly active zinc particles is to reduce zinc chloride with sodium or lithium in the presence of naphthalene, as reported by Rieke.[31] With this activated zinc, functionalized alkyl bromides as well as aryl bromides can be converted into the corresponding organozinc reagents and used for trapping reaction with e.g. acyl chlorides (Scheme 1).[32]



Scheme 1: Insertion of Rieke zinc into alkyl and aryl bromides and subsequent transmetalation to copper for acylation reactions leading to functionalized ketones.

However, the highly activated Rieke zinc is not needed for the oxidative insertion into the more reactive carbon-iodide bond (Scheme 2).

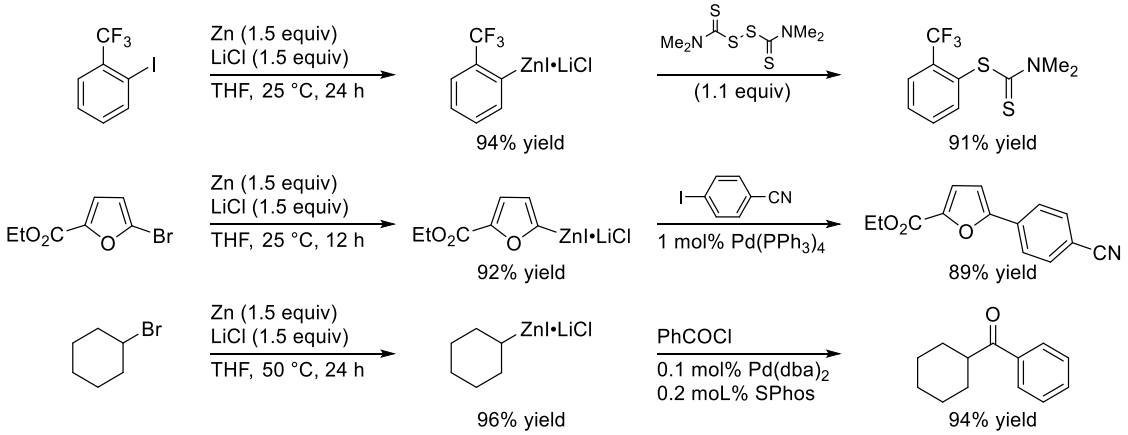
[29] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298 b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; c) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, *2010*, 4343; d) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540.
[30] a) M. S. Newman, F. J. Evans, *J. Am. Chem. Soc.* **1955**, *77*, 946; b) B. H. Han, P. Boudjouk, *J. Org. Chem.* **1982**, *47*, 5030. c) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; d) J. K. Gawroński, *Tetrahedron Lett.* **1984**, *25*, 2605;
[31] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.
[32] a) M. V. Hanson, J. D. Brown, R. D. Rieke, Q.J. Niu, *Tetrahedron Lett.* **1994**, *35*, 7205; b) A. Fürstner, R. Singer, P. Knochel, *Tetrahedron Lett.* **1994**, *35*, 1047.



Scheme 2: Direct insertion of zinc into aryl iodides at elevated temperatures providing organozinc reagents suitable for allylation reactions.33

Whereas the insertion of zinc dust into alkyl iodides proceeds quite fast, the insertion into aryl iodides is slow and requires elevated reaction temperatures. For the examples shown in Scheme 2, zinc dust was activated by chlorotrimethylsilane and reacted with aryl iodides at temperatures of 70 °C up to 130 °C in high boiling ethers to slowly form the corresponding organozinc reagents within 24 h.[33]

The group of Knochel reported a more efficient protocol for the preparation of functionalized organozinc reagents. Thus, previously activated zinc dust and equimolar amounts lithium chloride were used to perform oxidative insertion into aryl- and heteroaryl iodides as well as bromides (Scheme 3). Using this method, corresponding organozinc reagents can be obtained in excellent yield using mild reaction temperatures of 25 °C up to 50 °C with significantly reduced reaction time.[34]



Scheme 3: Preparation of functionalized organozinc reagents by oxidative insertion of zinc dust in the presence of LiCl and trapping reactions with various electrophiles.[34a]

The role of lithium chloride during the oxidative zinc insertion has been further investigated.[35] Based on these investigations, lithium chloride significantly increases the solubility of the formed organozinc compound in THF. Consequently, it promotes the solvation of the formed zinc species from the zinc-metal surface and thus accelerates following surface reactions.

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[33] R. Ikegami, A. Koresawa, T. Shibata, K. Takagi, *J. Org. Chem.* **2003**, *68*, 2195.

[34] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.

[35] C. Feng, D. W. Cunningham, Q. T. Easter, S. A. Blum, *J. Am. Chem. Soc.* **2016**, *138*, 11156.

2.3 Transmetalation

Another approach for the preparation of organozinc reagents, is the transmetalation of more polar metal-reagents with zinc salts. The driving force of this reaction is the formation of the thermodynamically more stable organometallic reagent with a more covalent carbon-metal bond (Figure 4).

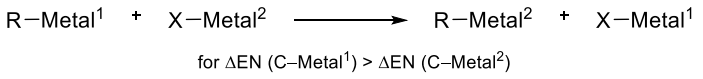
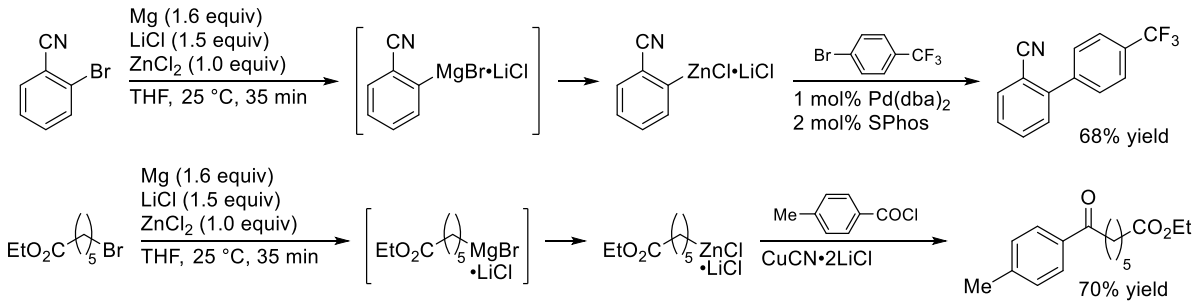


Figure 4: General principle of a transmetalation reaction forming the thermodynamically more stable organometallic compound based on electronegativity.

Many reagents suitable for the transmetalation to zinc are readily available, e.g. organolithium or organomagnesium compounds. This allows the preparation of organozinc reagents which might not be accessible *via* oxidative insertion. The downside of this method is the restricted functional group tolerance due to the increased reactivity of the more polar organometallics.[36]

An elegant way to use both, the advantage of the fast magnesium insertion as well as the tolerance towards functional groups of zinc, was reported by the Knochel group.[37] Magnesium turnings were inserted in the presence of lithium chloride as well as zinc chloride into aryl bromides or alkyl bromides. During the reaction, the *in-situ* generated magnesium species is directly transmetalated by the zinc salts to the corresponding organozinc compound. This method therefore provides an easy access to various reagents whose preparation would be lengthy *via* zinc insertion.



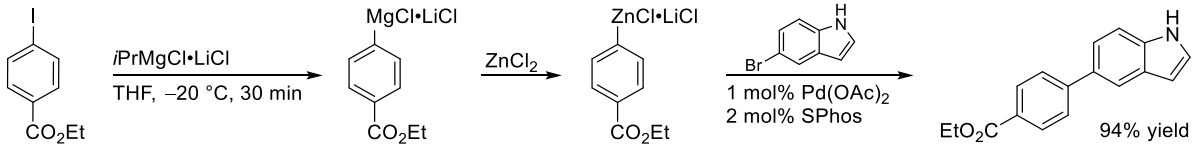
Scheme 4: Oxidative insertion of magnesium into aryl- and alkyl-bromides in the presence of lithium chloride and *in-situ* transmetalation to the corresponding organozinc compounds.[37]

An additional way for the preparation of organozinc reagents is the use of halogen-metal exchange reagents and subsequent transmetalation with zinc salts. In 2004, Knochel reported the lithium complexed exchange reagent *i*PrMgCl•LiCl (also known as "Turbo Grignard"), which enables the preparation of a broad range of aryl- and heteroarylmagnesium reagents from the corresponding aryl

[36] P. Knochel, *Handbook of functionalized organometallics*. *Applications in synthesis*, Wiley-VCH, Weinheim, Germany, **2005**, 261.
[37] a) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; b) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082.

iodides or bromides.[38] Due the high reactivity of these reagents, the exchange reaction can be performed at low temperatures tolerating various functional groups.[39]

In Scheme 5, an example for the iodine-magnesium exchange of ethyl 4-iodobenzoate is displayed, which was performed at –20 °C in 30 min. After subsequent transmetalation with zinc chloride, the resulting organozinc reagent was successfully used for palladium-catalyzed cross-coupling reaction with 5-bromoindole in 94% yield.[40]



Scheme 5: Iodine-magnesium exchange using *i*PrMgCl•LiCl and subsequent transmetalation with zinc chloride providing organozinc reagents for cross-coupling chemistry.[40a]

2.4 Halogen-Metal Exchange

In principle, the halogen-metal exchange is driven by the formation of a more stable organometallic compound (Figure 5).[41] In contrast to magnesium, the exchange reaction of organozinc compounds is more complicated, since the reactivity of mono-organozinc reagents is too low. [42]

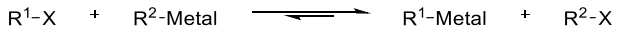
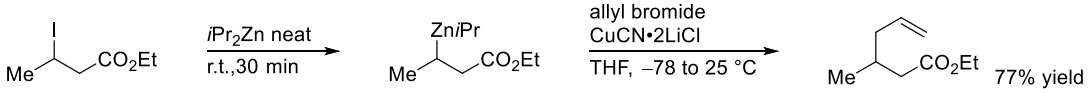


Figure 5: Schematic representation of the halogen-metal exchange reaction.

However, using dialkylzinc reagents, the zinc-iodine exchange can be performed. The solvent free treatment of ethyl 3-iodobutanoate with diisopropylzinc at room temperature provides the mixed organozinc species with can be used after transmetalation to copper, for allylation reactions (Scheme 6).[43] Since the mixed organozinc reagent is formed, both alkyl moieties react with the electrophile. For this reason, the electrophile must be used in excess and thus the separation of both products can be quite difficult.[44]



Scheme 6: Iodine-zinc exchange using diisopropylzinc leading to a mixed zinc species, which readily reacts with copper(I)cyanide and allyl bromide.[43]

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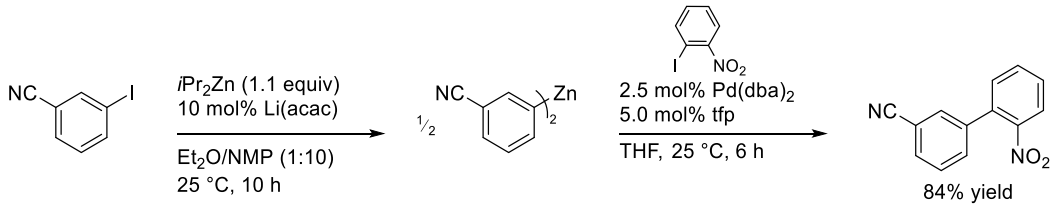
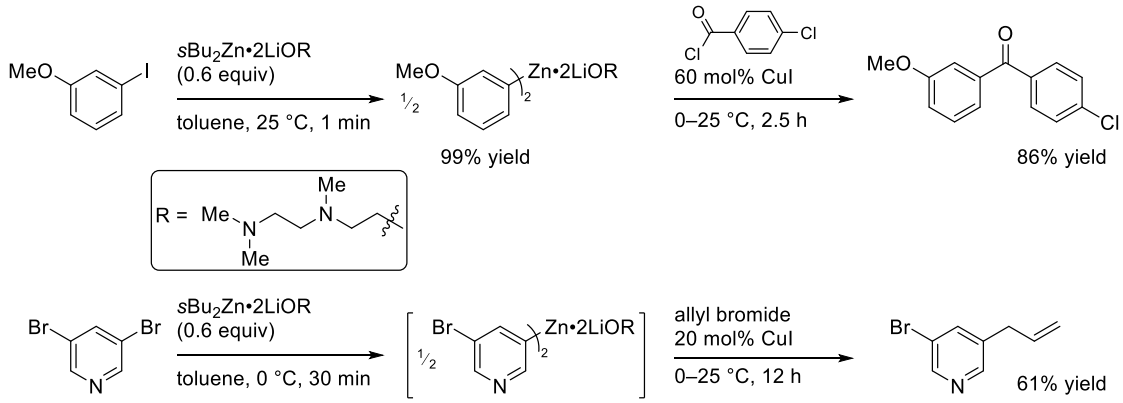
[38] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[39] D. S. Ziegler, B. Wei, P. Knochel, *Chem. Eur. J.* **2019**, *25*, 2695.
[40] a) G. Manolikakes, M. A. Schade, C. M. Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765; b) P. Knochel, M. A. Schade, S. Bernhardt, G. Manolikakes, A. Metzger, F. M. Piller, C. J. Rohbogner, M. Mosrin, *Beilstein J. Org. Chem.* **2011**, *7*, 1261.
[41] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.
[42] M. Balkenhohl, P. Knochel, *Chem. Eur. J.* **2019**.
[43] L. Micouin, P. Knochel, *Synlett* **1997**, *1997*, 327.
[44] P. Knochel, *Handbook of functionalized organometallics*. *Applications in synthesis*, Wiley-VCH, Weinheim, Germany, **2005**, 271.

An improved exchange reaction was described by Knochel *et. al.* in 2004 using diisopropylzinc in the presence of catalytic amounts of lithium acetylacetonate as a promoter for an intermediate ate-complex.[45] Using this procedure, the exchange of 3-iodobenzonitrile can be performed at room temperature within 10 h using a diethyl ether/NMP solvent mixture. The formed bis-arylzinc reagent can be used for a subsequent palladium-catalyzed Negishi cross-coupling with 2-iodonitrobenzene in 84% yield (Scheme 7).



Scheme 7: Preparation of a diarylzinc reagent by a Li(acac)-promoted iodine-zinc exchange using diisopropylzinc and subsequent palladium catalyzed cross-coupling reaction.[45]

Recently, the group of Knochel reported a bimetallic halogen-zinc exchange reagent consisting of bis-*sec*-butylzinc complexed with two lithium alkoxides in toluene.[46] With this reagent, iodine-zinc exchange reactions are possible, even on electron-rich arenes, within minutes at room temperature in almost quantitative yields. Additionally, even bromine-zinc exchange reactions could be performed on aryl- as well as heteroaryl bromides with reaction times of 30 min to 5 h. The resulting bis-arylzinc reagents were successfully applied in transition-metal catalyzed allylation, acylation and cross-coupling reactions (Scheme 8).

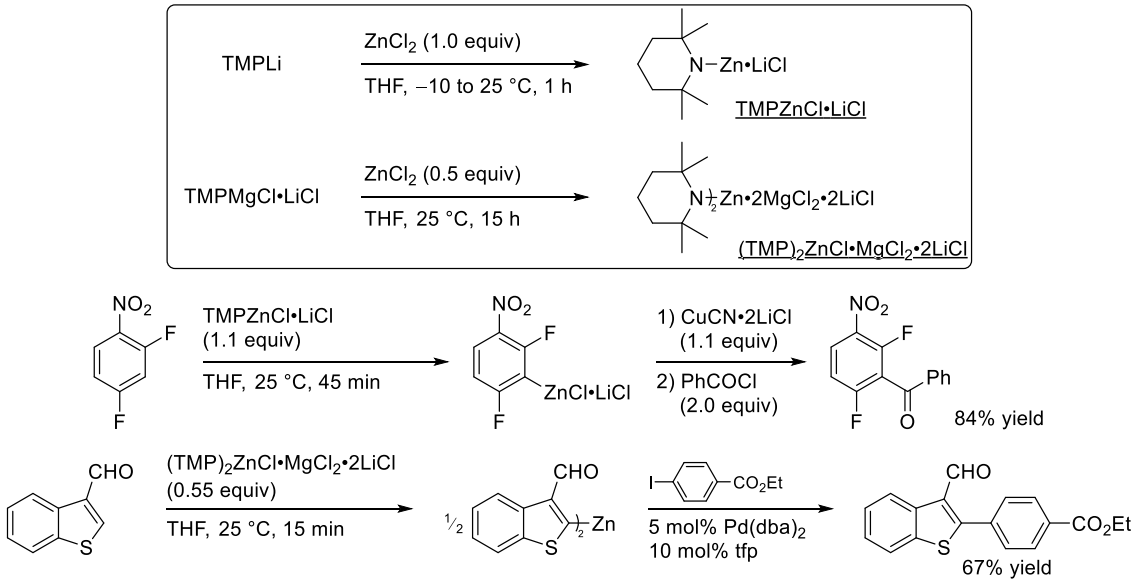


Scheme 8: Iodine-zinc exchange of 3-iodoanisole and bromine-zinc exchange of 3,5-dibromopyridine, using a bimetallic-alkoxide reagent in toluene.[46]

[45] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
[46] M. Balkenhohl, D. S. Ziegler, A. Desaintjean, L. J. Bole, A. R. Kennedy, E. Hevia, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 12898.

2.5 Directed Metalation

Besides oxidative insertion or halogen-metal exchange of halogenated substrates, another approach towards organozinc reagents is possible using metal bases. These reagents allow for the deprotonation of arenes and heteroarenes and thus converts them into the corresponding organometallic compound.[47] The group of Knochel reported the preparation of two different sterically hindered TMP bases.[48] Application of the TMPZn•LiCl[49] base as well as the $(TMP)_2ZnCl•MgCl_2•LiCl$[50] base can provide mild chemoselective deprotonation of various aryl and heteroaryl substrates leading to functionalized organozinc reagents (Scheme 9). These reagents can be used for a variety of reaction with different electrophiles.



Scheme 9: Preparation of mono[49a]- and bis[50a]-TMP-zinc bases and their application in arene metalation.

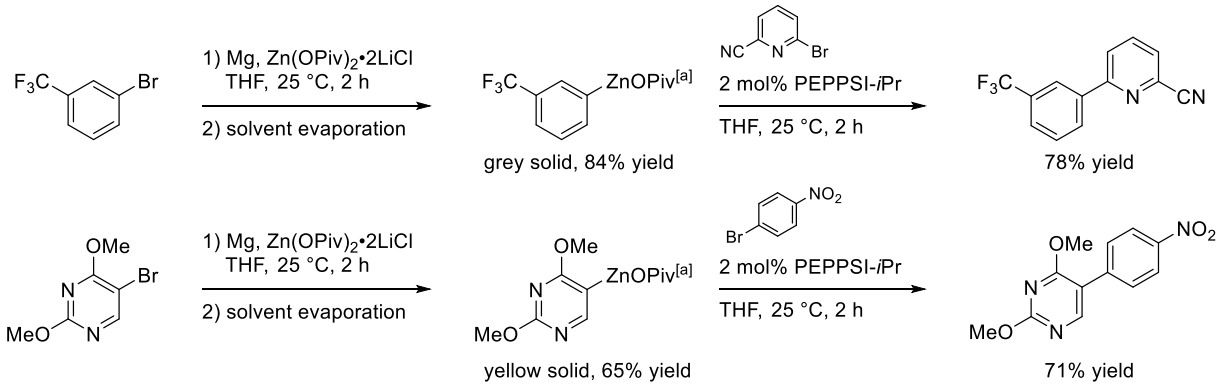
2.6 Zinc Pivalates

The main disadvantage of organozinc reagents is their sensitivity towards moisture, which leads to hydrolysis of the organometallic compound. To overcome this weakness, Knochel *et al.* investigated different salts for complexation. It was found, that the use of readily available zinc pivalate[51] for transmetalation of Grignard reagents leads to solid organozinc compounds, after evaporation of the solvents.[52] These solid organometallics exhibit an improved stability towards moisture from air. Since

[47] J. M. Mallan, R. L. Bebb, *Chem. Rev.* **1969**, *69*, 693.
[48] B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[49] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; c) S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel, *Org. Process Res. Dev.* **2010**, 14, 339;
[50] a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; b) T. Bresser, G. Monzon, M. Mosrin, P. Knochel, *Org. Process Res. Dev.* **2010**, *14,* 1299.
[51] M. Ellwart, Y.-H. Chen, C. P. Tüllmann, V. Malakhov, P. Knochel, *Org. Synth.* **2018**, *95*, 127.
[52] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205; b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed*. **2012**, *51*, 9428; c) J. R. Colombe, S. Bernhardt, C.

these compounds were very stable under argon, they could be stored for future application, while losing only a small percentage of activity over time.

The preparation could be performed, using magnesium for the insertion into the aryl bromides or iodides, while in the presence of zinc pivalate. Various functionalized, solid organozinc reagents could be prepared and used for subsequent reactions with a broad range of electrophiles (Scheme 10).[53]



Scheme 10: Preparation of solid aryl- and heteroarylzinc pivalates and their application in Negishi cross-coupling reactions.[53] [a] complexed, Mg(OPiv)X and LiCl are omitted for clarity.

Due to the presence of different salts in the reaction mixture, the exact structure of the resulting zinc pivalates was hard to determine. Further structural studies performed by Mulvey and Hevia[54] showed that the reagents have the general formula "RZnX•Mg(OPiv)$_2$•nLiCl" (X = Br, I, Cl; n = 1–2). For clarity, the abbreviation RZnOPiv is used in this thesis for this sophisticated structure. It was suggested, that the complexed magnesium pivalate acts as a moisture scavenger which might explain the improved stability.

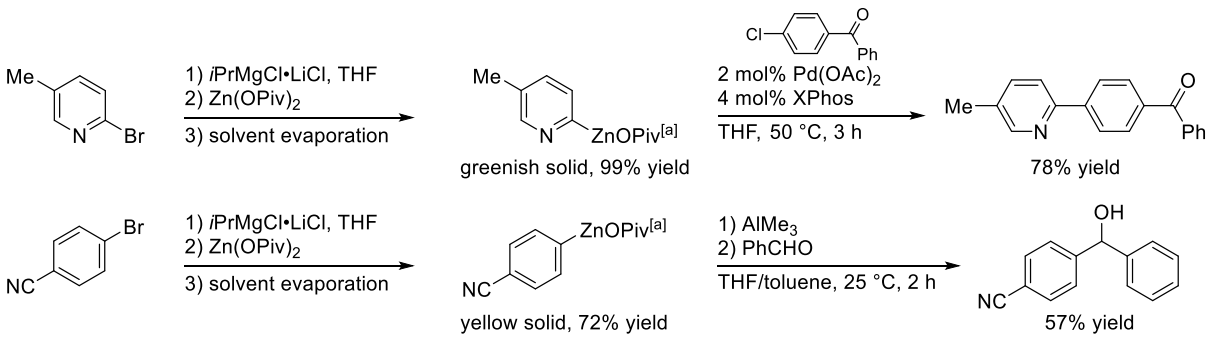
Besides oxidative insertion, halogen-magnesium exchange *via* "Turbo Grignard" with a subsequent transmetalation by zinc pivalate can be used for the preparation. Various functionalized aryl- and heteroarylzinc pivalates can be obtained using this method tolerating all kinds of functional groups. Furthermore, the application in trapping reactions like allylation, cross-coupling or addition to aldehydes using trimethylaluminium can be performed (Scheme 11).[55]

Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754; d) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302; e) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289; f) T. J. Greshock, K. P. Moore, R. T. McClain, A. Bellomo, C. K. Chung, S. D. Dreher, P. S. Kutchukian, Z. Peng, I. W. Davies, P. Vachal, M. Ellwart, S. M. Manolikakes, P. Knochel, P. G. Nantermet, *Angew. Chem. Int. Ed.* **2016**, *55*, 13714.

[53] S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205.

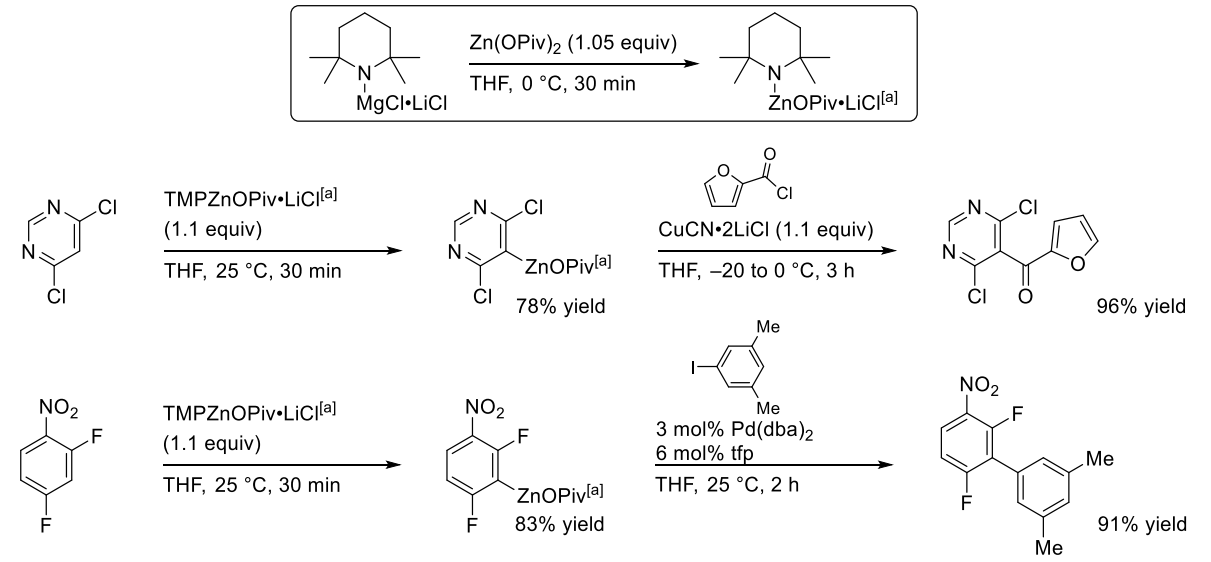
[54] A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, *53*, 2706.

[55] a) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754; b) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289.



Scheme 11: Preparation of organozinc pivalates *via* halogen-metal exchange followed by transmetalation with $Zn(OPiv)_2$ and reactions with various electrophiles.[55] [a] complexed, Mg(OPiv)X and LiCl are omitted for clarity.

In addition, a TMPZnOPiv•LiCl base was described starting from readily available TMPMgCl•LiCl. With this new sterically hindered base, sensitive heterocycles and arenes, bearing various functional groups could selectively be metalated, providing solid zinc pivalates in high yields. These reagents could then be applied in transition-metal-catalyzed reactions with various electrophiles (Scheme 12).[56]



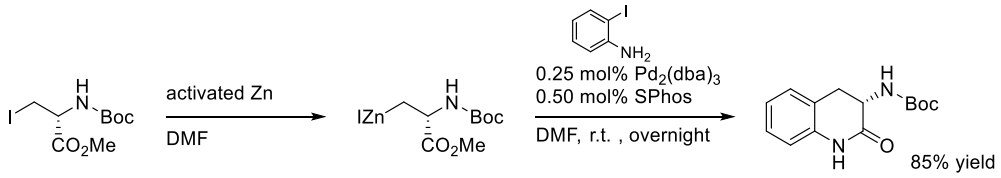
Scheme 12: Preparation of TMPZnOPiv•Mg(OPiv)Cl•LiCl and metalation of aryl- and heteroaryl compounds for subsequent acylation or cross-coupling reactions.[56] [a] complexed, Mg(OPiv)X and LiCl are omitted for clarity

2.7 Chiral Organozinc Reagents

As discussed above, organozinc reagents tolerate a variety of functional groups and display a mild reactivity. They are therefore well suited for the preparation of functionalized alkylzinc reagents containing a chiral center. Jackson has demonstrated the utility of amino acids as precursors for the

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

preparation of chiral serine-derived organozinc reagents and has shown their application for the synthesis of novel amino acids, using Negishi cross-couplings (Scheme 13).[57]

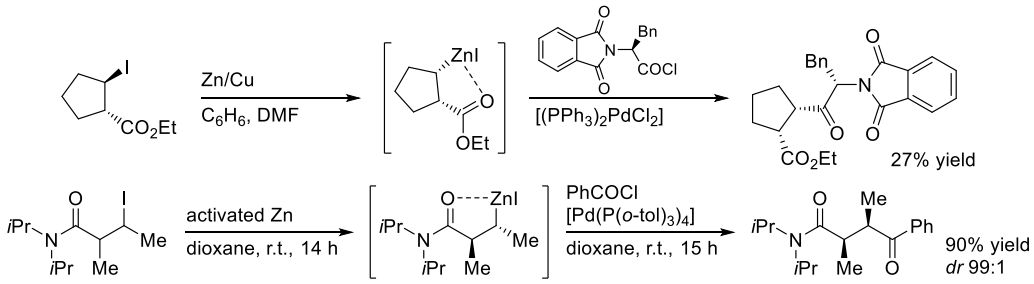


Scheme 13: Preparation of a chiral serine-based alkylzinc reagent and Negishi cross-coupling reaction leading to a chiral lactam.[57b]

The preparation of alkylzinc reagents from secondary alkyl iodides, bearing a protected chiral amino group, was described by Knochel. Due to the assumed radical nature of the zinc insertion, the stereoinformation is usually lost during the reaction. However, in the strained system shown in Scheme **14**, the conversion of the iodide to the corresponding alkylzinc iodide as well as the following copper mediated stannylation, proceeds with full retention of configuration to the *exo* product.[58]

Scheme 14: Preparation of an alkylzinc iodide by oxidative insertion of zinc with retention of configuration and subsequent stannylation leads selectively to the *exo* tin derivative.[58]

Another strategy to obtain alkylzinc reagents with defined stereocenters is an oxygen-zinc chelatization during the insertion reaction. For example, an ester in proximity to the iodide coordinates to the inserting zinc and therefore specifies its configuration. In Scheme 15, two examples for this kind of reaction are displayed.



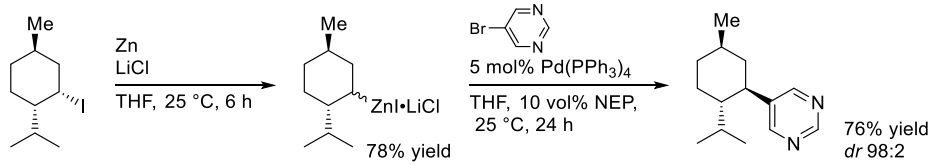
Scheme 15: Preparation of chiral organozinc compounds with defined stereocenters due to oxygen-zinc chelation and following palladium catalyzed reaction with acyl chlorides.[59,60b]

[57] a) J. Ross, F. Dreiocker, M. Schäfer, J. Oomens, A. J. H. M. Meijer, B. T. Pickup, R. F. W. Jackson, *J. Org. Chem.* **2011**, *76*, 1727; b) A. J. Ross, H. L. Lang, R. F. W. Jackson, *J. Org. Chem.* **2010**, *75*, 245; c) T. Carrillo-Marquez, L. Caggiano, R. F. W. Jackson, U. Grabowska, A. Rae, M. J. Tozer, *Org. Biomol. Chem.* **2005**, *3*, 4117; d) H. J. C. Deboves, U. Grabowska, A. Rizzo, R. F. W. Jackson, *J. Chem. Soc., Perkin Trans. 1* **2000**, 4284; e) R. F. W. Jackson, K. James, M. J. Wythes, A. Wood, *J. Chem. Soc., Chem. Commun.* **1989**, 644.

[58] R. Duddu, M. Eckhardt, M. Furlong, H.P. Knoess, S. Berger, P. Knochel, *Tetrahedron* **1994**, *50*, 2415.

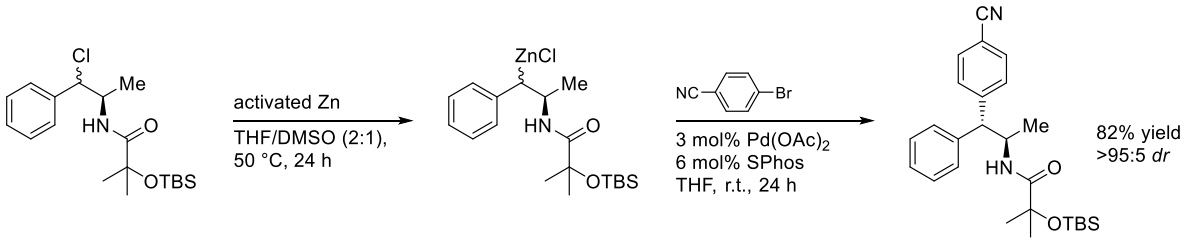
For the cyclopentyl derivative, insertion of the *trans*-iodide leads to the *cis*-complexed zinc reagents, which after palladium-catalyzed acylation also provides the *cis*-ketone.[59] The reaction of the alkyliodide bearing an diisopropyl amide in 3-position also leads to a coordination during the insertion, which causes a diastereoselective acylation with both methyl groups in *cis*-configuration with a diastereomeric ratio of 99:1.[60]

Besides chelatization, thermodynamic and steric effects can also be used to achieve stereoselectivity. In Scheme 16, the stereocenter of the iodide of the menthol derivative racemizes during the oxidative zinc insertion. After transmetalation to a bulky palladium-catalyst, the cross-coupling with 5-bromopyrimidine diastereoselectively leads to the equatorial coupling product due to steric effects.[61]



Scheme 16: Highly diastereoselective Csp^3–Csp^2 Negishi cross-coupling reaction of a 1,2,4-substituted cyclohexylzinc reagent with a heteroaryl bromide, promoted by a bulky palladium catalyst.[62]

The steric effect was also used by the group of Wang. A norephedrine derivative protected with a bulky amino protecting group (Scheme 17) was treated with activated zinc to obtain the corresponding alkylzinc iodide. Following palladium-catalyzed cross-coupling reaction with 4-bromobenzonitrile selectively leads to the *trans*-product with a diastereomeric ratio of >95:5.[62]

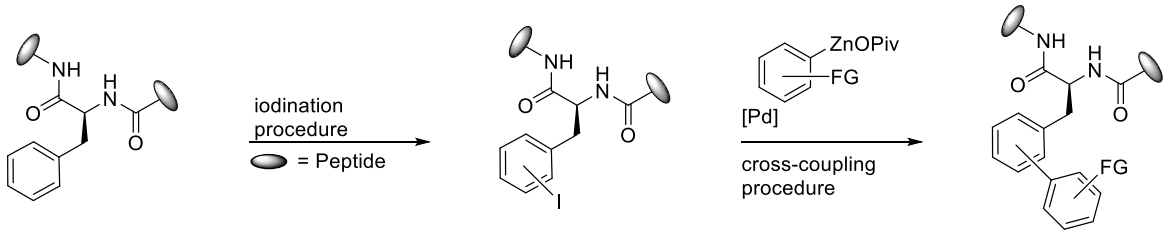


Scheme 17: Preparation of a norephedrine based organozinc reagent with a bulky *N*-protecting group leading to highly diastereoselective Negishi cross-coupling products.[62]

[59] Mitsuya Sakurai, Tadashi Hata, Yuichiro Yabe, *Tetrahedron Lett.* **1993**, *34*, 5939.
[60] a) S. Sakami, T. Houkawa, M. Asaoka, H. Takei, *J. Chem. Soc., Perkin Trans. 1* **1995**, 285; b) T. Houkawa, T. Ueda, S. Sakami, M. Asaoka, H. Takei, *Tetrahedron Lett.* **1996**, *37*, 1045.
[61] T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer, P. Knochel, *Nat. Chem.* **2010**, *2*, 125.
[62] S. Tang, S. Li, D. Zhou, H. Zeng, N. Wang, *Sci. China Chem.* **2013**, *56*, 1293.

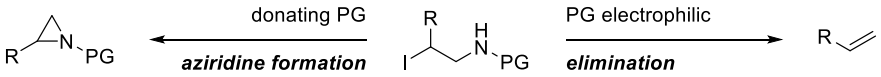
3 Objectives

The late-stage functionalization of peptides and cyclopeptides is an important way to adjust biophysical properties during the drug discovery process. By attaching various moieties e.g. aryl or heteroaryl groups to the peptide side chain, biophysically relevant properties such as solubility or membrane permeability can be altered and further optimized. For this purpose, C-H activations or Suzuki-Miyaura cross-coupling reactions have already been described. Nevertheless, the application of those methods is often limited to a few target-sides and the functionalization scope is restricted. For this reason, a new versatile method for peptide modification with a broad functional group tolerance should be developed. Previous applications of organozinc pivalates in Negishi cross-coupling reactions displayed great tolerance towards functional groups and should therefore be investigated for the late-stage modification of peptides. To use peptides in cross-coupling reactions, a suitable side-chain moiety has to be converted into the corresponding halide. Since iodides have shown very fast reaction rates in cross-coupling reactions, a straightforward and universally applicable procedure for the conversion of a peptide into an iodinated peptide was envisioned (Scheme 18). Finally, a fast cross-coupling protocol has to be found to make the reaction feasible in the presence of peptides containing acidic protons.



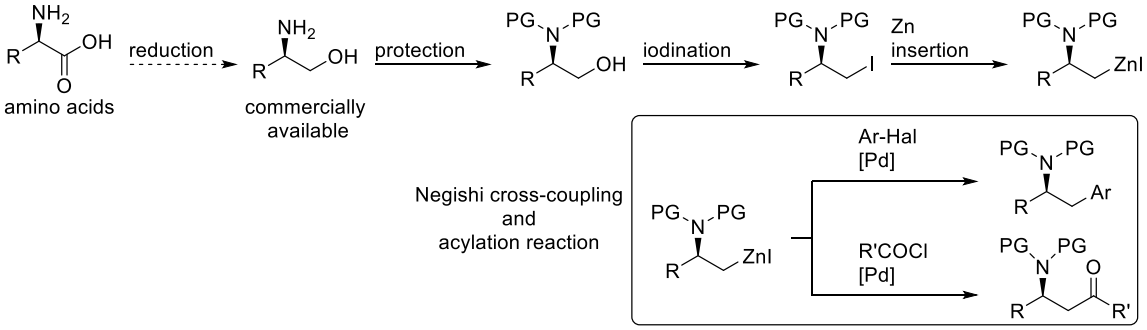
Scheme 18: Schematic representation of the peptide iodination and following late-stage functionalization *via* Negishi cross-coupling.

Furthermore, new chiral alkylzinc reagents containing an amino-group in β-position would be of major interest. Proteinogenic α-amino acids contain a predefined stereo-center and are easily reduced to the corresponding amino-alcohol without loss of optical purity. Therefore, those compounds should be excellent starting materials towards chiral alkylzinc compounds. Since alkylzinc compounds and most of the cross-coupling catalysts are sensitive to free amines, a suitable protecting group is necessary. There are several requirements for an ideal protecting group. It must be inert, insensitive towards nucleophilic organozinc reagents and should not contain acidic protons which might hydrolyze the zinc reagent. Furthermore, it should not promote other unintended reactions: Whereas an electrophilic amino protecting group destabilizes the resulting organozinc reagent and leads to elimination, a donating amino protecting group on the other hand destabilizes the starting iodide derivatives by formation of aziridine, see Scheme 19. Additionally, the removal of the protecting group at the end of the sequence must be feasible while the introduced functional groups as well as the stereocenters remain unchanged.



Scheme 19: Possible side-reactions during the zinc-insertion using inappropriate protecting groups.

Starting from the chiral amino-alcohol, straightforward protection and iodination reaction should provide chiral alkyl iodides which then can be used for oxidative insertion of zinc dust to obtain the corresponding alkylzinc reagents. A valuable addition would be the application of these reagents in following cross-coupling and acylation reactions, which should deliver 1,2-substituted amino-derivatives (Scheme 20).



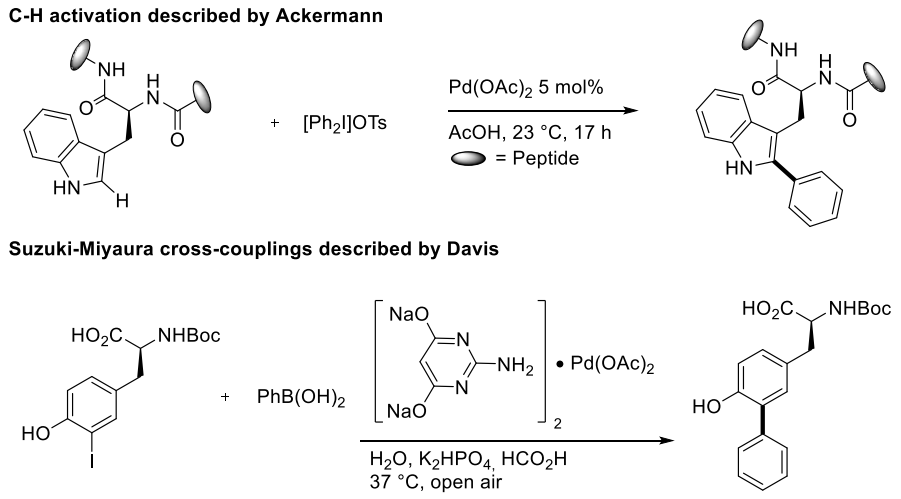
Scheme 20: Schematic representation for the preparation of β-amino alkylzinc reagent starting from chiral amino-alcohols and the subsequent application in Negishi cross-coupling and acylation reactions.

B. RESULTS AND DISCUSSION

1 Late-Stage Functionalization of Peptides and Cyclopeptides Using Organozinc Reagents

1.1 Introduction

The late-stage functionalization of peptides using C-H activation[63] or Suzuki-Miyaura cross-couplings[64] is already known and has found useful application (Scheme 21). For this purpose, various transition metals, such as palladium, nickel, gold, ruthenium and manganese, have been used[65]. However, there is still a strong need to extend the toolbox of peptide modification and to broaden the scope of targets as well as introducible moieties. Therefore, the development of a new universal method using a non-specialized target side and exhibiting a diverse functional group tolerance is necessary. Since organozinc chemistry is known for the high functional group tolerance and mild reaction conditions, it should be well suited for this purpose.[66]



Scheme 21: Palladium catalyzed peptide modifications using C-H arylations with diaryliodonium salts[67] or Suzuki-Miyaura cross-coupling reactions[68].

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[63] a) J. Ruiz-Rodríguez, F. Albericio, R. Lavilla, *Chem. Eur. J.* **2010**, *16*, 1124; b) Z. Ruan, N. Sauermann, E. Manoni, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 3172; c) A. Schischko, H. Ren, N. Kaplaneris, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 1576; d) H. G. Lee, G. Lautrette, B. L. Pentelute, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2017**, *56*, 3177.

[64] G. Espuña, G. Arsequell, G. Valencia, J. Barluenga, J. M. Alvarez-Gutiérrez, A. Ballesteros, J. M. González, *Angew. Chem. Int. Ed.* **2003**, *43*, 325.

[65] a) W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14700; b) S. E. Hooshmand, B. Heidari, R. Sedghi, R. S. Varma, *Green Chem.* **2019**, *21*, 381; c) T. Willemse, W. Schepens, H. Vlijmen, B. Maes, S. Ballet, *Catalysts* **2017**, *7*, 74.

[66] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298 b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340. c) N. Hadei, E. A. B. Kantchev, C. J. O'Brie, M. G. Organ, *Org. Lett.* **2005**, *7*, 3805. d) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, Eur. *J. Org. Chem.* **2010**, *2010*, 4343. e) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540.

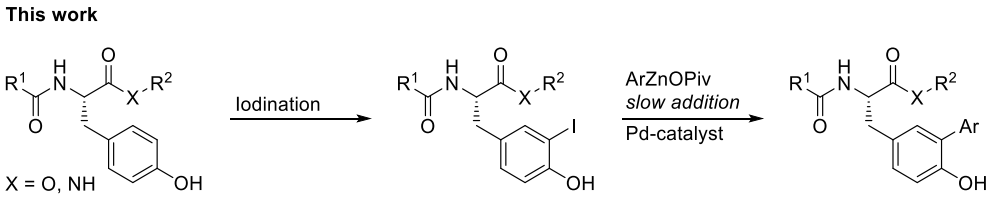
[67] Y. Zhu, M. Bauer, L. Ackermann, *Chem. Eur. J.* **2015**, *21*, 9980.

[68] J. M. Chalker, C. S. C. Wood, B. G. Davis, *J. Am. Chem. Soc.* **2009**, *131*, 16346.

Recently, the group of Knochel reported organozinc reagents using pivalate salts as counterions which display an enhanced air- and moisture stability[69]. They have found broad application in a variety of reactions with all kinds of electrophiles.[70]

Previously, a method for palladium- and nickel-catalyzed cross-coupling reactions has been reported using organozinc halides and electrophiles bearing acidic protons.[71] The fast cross-coupling reaction combined with a slow addition of the zinc reagents allows for the tolerance of sensitive and acidic functional groups.

Herein, a convenient late-stage functionalization of various highly functionalized polypeptides is reported. The procedure consists of a regioselective iodination of a tyrosine containing peptide and a subsequent highly selective palladium-catalyzed cross coupling reaction enabled by the slow addition of various polyfunctional organozinc pivalates (Scheme 22).



Scheme 22: A generalized pathway for the late-stage functionalization of peptides using organozinc pivalates.

1.2 Method Development for Iodination and Negishi Cross-Coupling Based on Tyrosine

A Boc protected *L*-tyrosyl methyl ester was chosen as a model substrate since it contains most of the sensitive functional groups, such as phenolic hydroxyl groups, amides and α-acidic esters. To convert protected amino acid (**2a**) into an eligible cross-coupling electrophile, a selective mono-iodination procedure had to be found. Experiments showed that the use of the oxidation agent Chloramine T combined with sodium iodide[72] proved to be successful to mainly obtain the mono-iodinated tyrosine derivative. To achieve the best results, the oxidant had to be added very slowly *via* a syringe pump at low temperatures (Scheme 23). A screening showed that 1.2 equivalents of the iodination mixture provided the best result in terms of reaction conversion and yield of the mono-iodo tyrosine **3a**. The major by-product was the bis-iodo derivative which had to be separated first by column chromatography

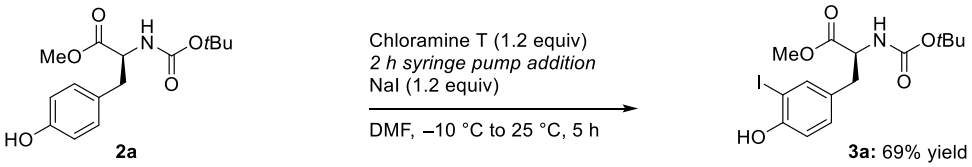
[69] a) A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, *53*, 2706; b) Y.-H. Chen, M. Ellwart, V. Malakhov, P. Knochel, *Synthesis* **2017**, *49*, 3215.

[70] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205. b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9428. c) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289. d) M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10662.

[71] G. Manolikakes, C. Muñoz Hernandez, M. A. Schade, A. Metzger, P. Knochel, *J. Org. Chem.* **2008**, *73*, 8422.

[72] T. Kometani, D. S. Watt, T. Ji, *Tetrahedron Lett.* **1985**, *26*, 2043.

and subsequent RP-HPLC purification. Then, thus obtained iodotyrosyl methyl ester **3a** was used as screening substrate to develop the procedure for the cross-coupling reaction.

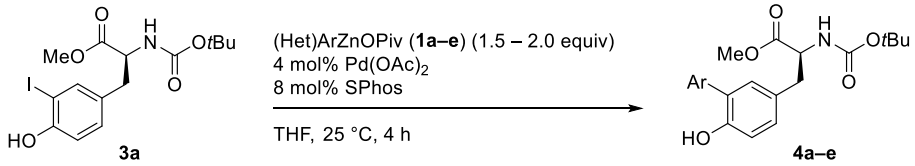


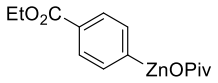
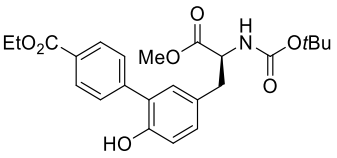
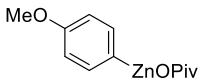
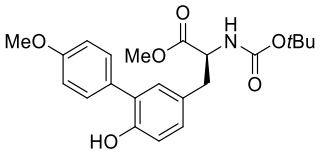
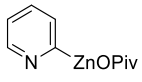
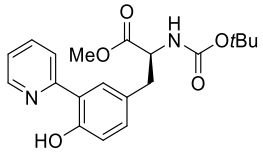
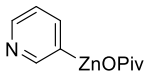
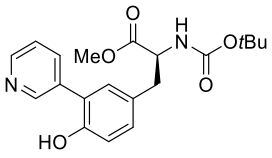
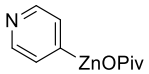
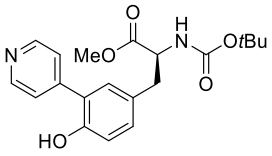
Scheme 23: Regioselective mono-iodination of protected *L*-tyrosine using sodium iodide and Chloramine T.

The first attempts for the Negishi-cross coupling reaction were performed using aryl- and heteroaryl zinc pivalates according to standard literature procedures[73]. A catalytic system of $Pd(OAc)_2$ combined with Buchwald's phosphine ligand SPhos[74] showed the best result in preliminary experiments and was used for the cross-coupling reactions. Since nitrogen can competitively bind as a ligand to palladium as well[75], a slightly increased catalyst loading was necessary. To a pre-stirred mixture of the palladium salt and the ligand in THF, the iodo-tyrosine was added. The corresponding arylzinc pivalates were added dropwise over a period of 1 h *via* syringe pump and the reaction mixture was stirred until full conversion of the electrophile was observed. An electron-rich (**1a**) as well as an electron-poor (**1b**) organozinc pivalate was used for the test cross-coupling reactions of the protected iodo-tyrosine, affording the desired cross-coupling products **4a** and **4b** in 74% and 50% yield. Next, the scope with respect to the arylzinc reagent was examined. Since pyridine residues are interesting moieties for the late-stage functionalization, three different isomeric pyridylzinc pivalates (**1c**–**e**) have been used. To ensure full reaction conversion, the amount of pyridylzinc pivalate was increased to 2.0 equivalents. The three corresponding pyridyl-tyrosine derivatives **4c**–**e** could be obtained in high yields of 73–87% (Table 1).

[73] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205; b) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754; c) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289; d) S. Otsuka, D. Fujino, K. Murakami, H. Yorimitsu, A. Osuka, *Chem. Eur. J.* **2014**, *20*, 13146; e) M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10662.
[74] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.
[75] T. E. Barder, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 12003.

Table 1: Negishi cross-couplings of tyrosine derivative **3a** with aryl- and heteroarylzinc pivalates **1a**–**e**.



Entry	Zinc Pivalate	Product	Yield (%)[a]
1	 **1a**	 **4a**	74
2	 **1b**	 **4b**	50
3	 **1c**	 **4c**	87
4	 **1d**	 **4d**	80
5	 **1e**	 **4e**	73

[a] Yield of the isolated analytically pure product. [b] 1.5 equiv of ArZnOPiv were used. [c] 2.0 equiv of HetArZnOPiv were used.

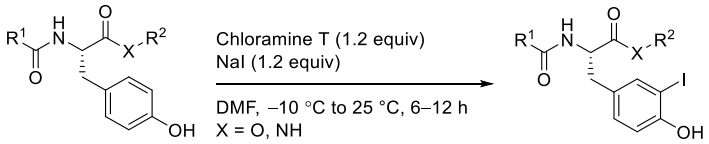
1.3 Iodination of Tyrosine-based Peptides

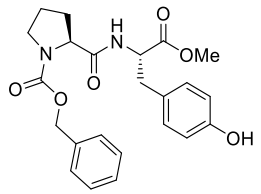
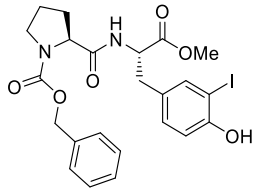
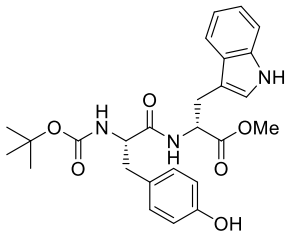
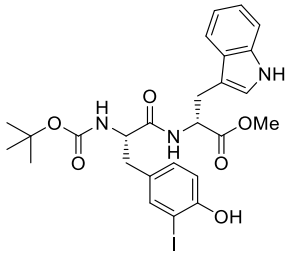
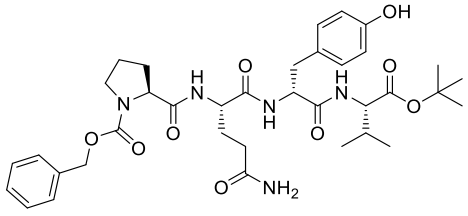
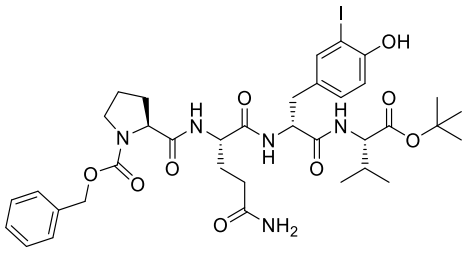
After the successful mono-iodination of the protected tyrosine, the procedure was extended to various small peptides (Table 2)[76]. First, a dipeptide consisting of *N*-Cbz-protected proline and a tyrosyl methyl ester (peptide **2b**) was tested. Using the previously developed reaction conditions, the mono-iodinated dipeptide **3b** was obtained in 79% yield. Furthermore, dipeptide **2c** containing a tryptophan unit was

[76] Peptides were provided by Novartis Pharma AG, Basel, Switzerland. Special thanks to Dr. Guido Koch and Dr. Thomas Vorherr.

iodinated using the same protocol. However, the desired mono-iodo peptide was obtained in only 30% yield, although 24% of the starting material were recovered. It seemed that the indole moiety of the tryptophan is too sensitive towards the oxidation reagent[77] which caused many minor side products and an overall unclean reaction. In addition, increasing the amount of the iodination reagent did not improve the reaction outcome. Further optimization attempts to increase the yield were not successful. A tetrapeptide containing proline, glutamine, tyrosine and valine was also successfully iodinated followed the developed procedure leading to 52% yield of the mono-iodinated peptide **3d**.

Table 2: Mono-iodination of the tyrosine moiety on small peptides using Chloramine T and sodium iodide.



Entry	Peptide	Iodinated peptide	Yield (%)[a]
1	 **2b**	 **3b**	79
2	 **2c**	 **3c**	30[b]
3	 **2d**	 **3d**	52

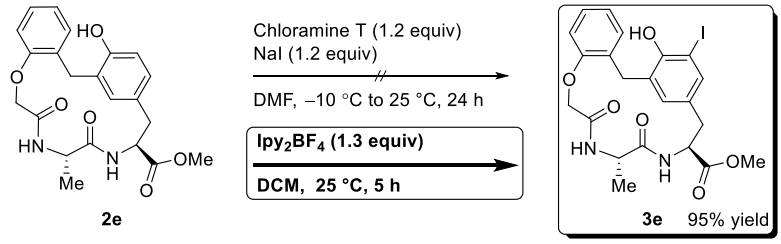
[a] Yield of the isolated analytically pure product. [b] 24% of the starting material were recovered.

In addition to linear peptides, cyclopeptides were investigated because of their high potential for late-stage functionalization due to possible medical applications[78]. Unfortunately, the iodination using the standard procedure did not provide any mono-iodinated product. Since optimization attempts including

[77] G. Mourier, L. Moroder, A. Previero *Z. Naturforsch. B* **1984**, *39*, 101.

[78] a) N. K. Gulavita, S. P. Gunasekera, S. A. Pomponi, E. V. Robinson, *J. Org. Chem.* **1992**, *57*, 1767; b) M. Cebrat, Z. Wieczorek, I. Z. Siemion, *Peptides* **1996**, *17*, 191; c) B. Vera, J. Vicente, A. D. Rodríguez, *J. Nat. Prod.* **2009**, *72*, 1555; d) W.-Y. Fang, R. Dahiya, H.-L. Qin, R. Mourya, S. Maharaj, *Mar. Drugs* **2016**, *14*, 194.

varying the temperature, amount of the reagent and the reaction time were not successful, the use of an alternative method was necessary. It was found that the bis(pyridine)iodonium reagent of Barluenga[79] was perfectly suited for this cyclic peptide. The reaction of the cyclopeptide **2e** with 1.3 equivalents of Barluenga's reagent in DCM led to the iodinated cyclopeptide **3e** in 95% yield within 5 h (Scheme 24).



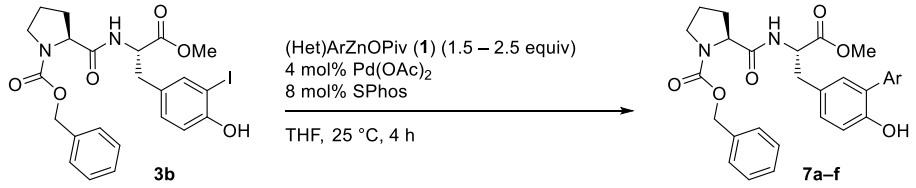
Scheme 24: Iodination of the tyrosine-based cyclopeptide **2e** using Barluenga's reagent.

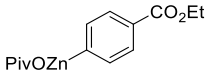
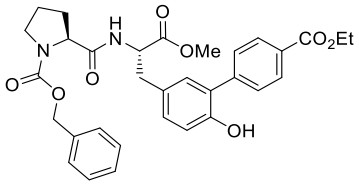
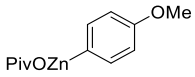
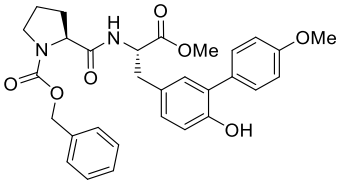
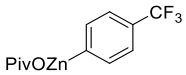
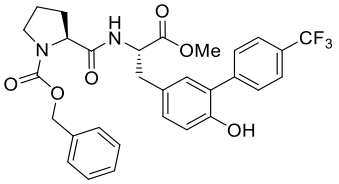
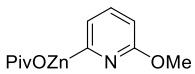
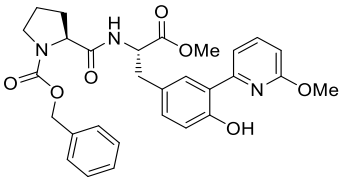
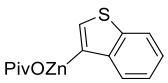
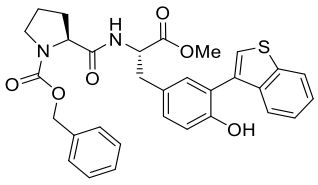
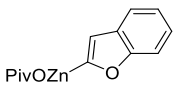
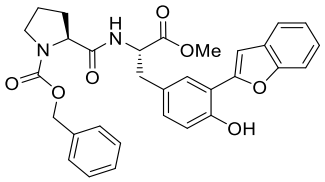
1.4 Negishi Cross-Coupling of Tyrosine based Peptides Using Organozinc Pivalates

With these four iodinated peptides in hand, further investigations on the late-stage functionalization *via* Negishi cross-coupling reaction have been made, using the reaction conditions developed in the preliminary experiments on the protected tyrosine. Therefore, the peptide **3b** was coupled with various aryl and heteroaryl organozinc pivalate in the presence of palladium acetate and SPhos (Table 3). Crucial for this method was again the slow addition of the zinc reagent solution *via* syringe pump over a period of 1 h. The first experiments using 1.5 equivalents of the corresponding organozinc pivalate revealed that the yields were comparable to the ones of the previous cross-couplings. The modified peptide **7a** using an electron deficient zinc pivalate **1a** was obtained in 67% yield (tyrosine derivative: 74% yield) and **7b** using an electron rich zinc species in 48% yield (tyrosine derivative: 50% yield). Applying 1.5 equivalents of the pyridyl zinc pivalate **1g** provided the corresponding peptide **7g** in 61% yield. The experiments showed that no full conversion of the iodo-peptides was achieved during the reaction. Therefore, to obtain a higher yield for the following reaction, the amount of zinc reagent used was increased to 2.5 equiv. Thus, the arylated peptide **7f** using the zinc pivalate **1f** was obtained in a high yield of 80%. To extend the reaction scope to benzene-fused heterocycles, the benzothiophenylzinc **1h** as well as benzofuranylzinc **1i** derivative have been used to obtain the modified peptides **7e** and **7f** in 47% and 87% yield. In conclusion, it was possible to use electron-rich and –poor arylzinc pivalates as well as heteroarylzinc pivalates to prepare the modified peptide **7e**–**f** in 47–87% yield. It was shown that the method developed on the tyrosine test substrate was also suitable for dipeptides.

[79] G. Espuña, G. Arsequell, G. Valencia, J. Barluenga, J. M. Alvarez-Gutiérrez, A. Ballesteros, J. M. González, *Angew. Chem. Int. Ed.* **2003**, *43*, 325.

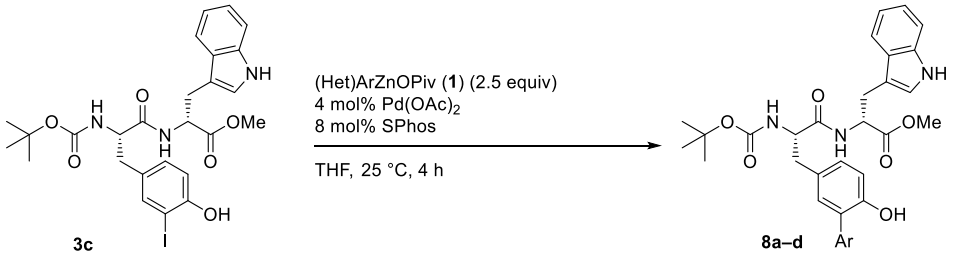
Table 3: Negishi cross-coupling of the dipeptide **3b** with aryl- and heteroarylzinc pivalates of type **1**.

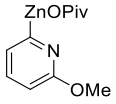
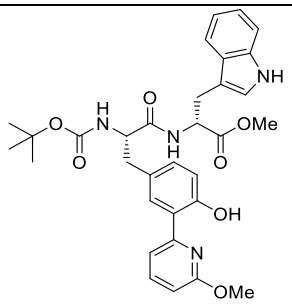
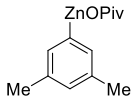
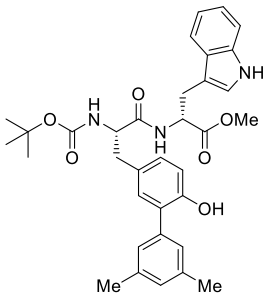
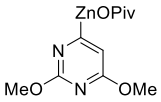
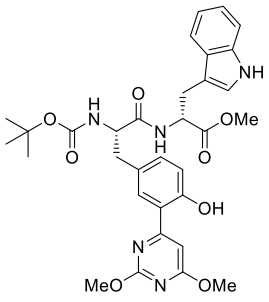
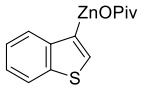
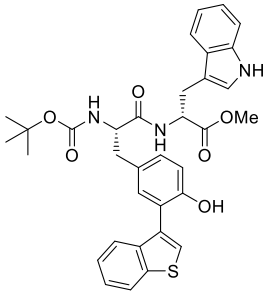


Entry	Zinc Pivalate	Product	Yield (%)[a]
1	 **1a**	 **7a**	67[b]
2	 **1b**	 **7b**	48[b]
3	 **1f**	 **7c**	80[c]
4	 **1g**	 **7d**	61[b]
5	 **1h**	 **7c**	47[c]
6	 **1i**	 **7f**	87[c]

[a] Yield of the isolated analytically pure product. [b] 1.5 equiv of ArZnOPiv were used. [c] 2.5 equiv of ArZnOPiv were used.

Table 4: Negishi cross-coupling reactions of the dipeptide **3c** with aryl- and heteroarylzinc pivalates of type **1**.

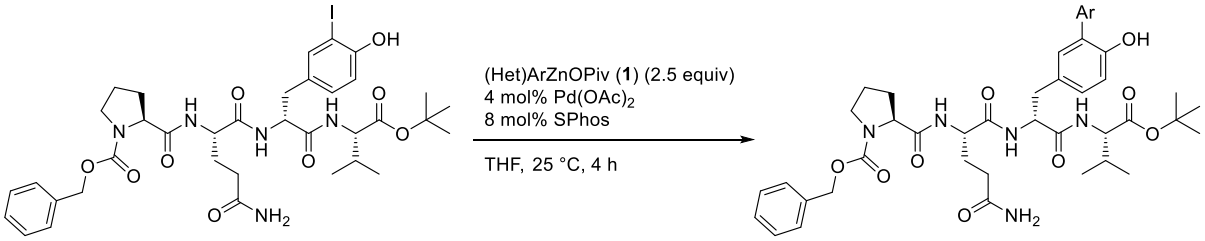


Entry	Zinc Pivalate	Product	Yield (%)[a]
1	 **1g**	 **8a**	92
2	 **1j**	 **8b**	72
3	 **1k**	 **8c**	76
4	 **1h**	 **8d**	38

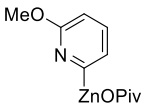
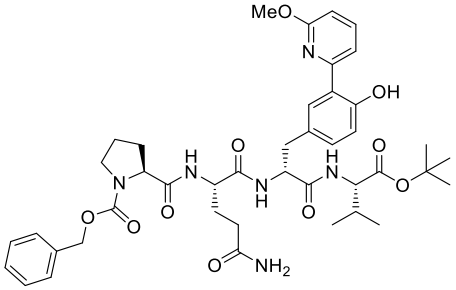
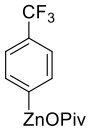
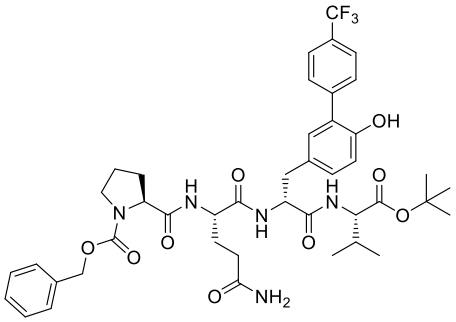
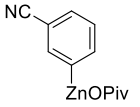
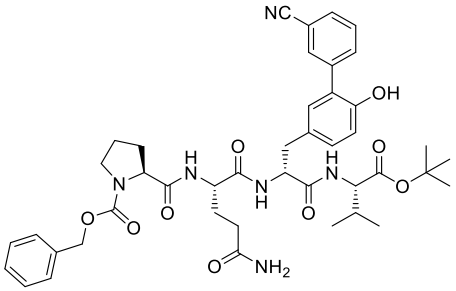
[a] Yield of the isolated analytically pure product.

The experiments were continued with the tryptophan containing peptide **3c**. In contrast to the iodination, the presence of tryptophan did not pose a problem for cross-coupling reactions. Various aryl- as well as heteroarylzinc pivalates were successfully applied to the cross-coupling reaction leading to the modified peptide **8a**–**d** in 38–92% isolated yield (Table 4).

Table 5: Negishi cross-coupling of the tetrapeptide **3d** with aryl- and heteroarylzinc pivalates of type **1**.



3d **9a–c**

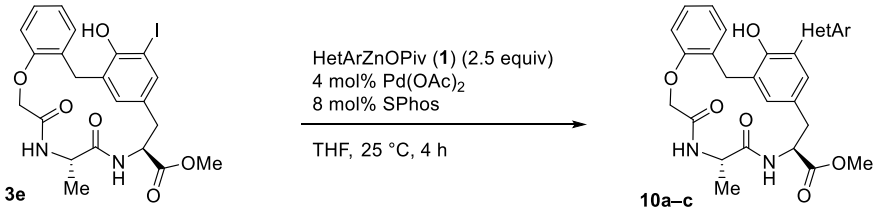
Entry	Zinc Pivalate	Product	Yield (%)[a]
1	 **1g**	 **9a**	50
2	 **1f**	 **9b**	80
3	 **1l**	 **9c**	89

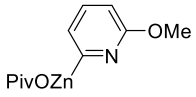
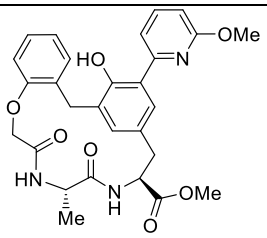
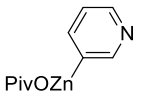
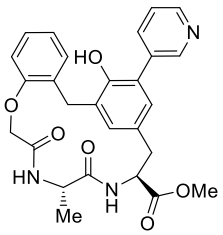
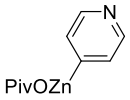
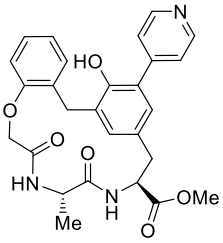
[a] Yield of the isolated analytically pure product.

After the successful Negishi cross-couplings on the previous dipeptides, this method was further extended to a tetrapeptide containing a primary amide from glutamine. The first cross-coupling using

the pyridylzinc derivative **1g** furnished the desired product **9a** in a moderate yield of 50%. In contrast, using the arylzinc pivalates **1f** and **1l** led to the products **9b** and **9c** in high yields between 80% and 89%, respectively (Table 5). Thus, in conclusion, the increased size of the peptide and the presence of the primary amide did not compromise the cross-coupling reaction.

Table 6: Negishi cross-coupling of the cyclopeptide **3e** with heteroarylzinc pivalates of type **1**.



Entry	Zinc Pivalate	Product	Yield (%)[a]
1	 **1g**	 **10a**	82
2	 **1d**	 **10b**	53
3	 **1e**	 **10c**	67

[a] Yield of the isolated analytically pure product.

Additionally, cross-coupling experiments were conducted on the mono-iodinated tyrosine-based cyclopeptide **3e**. As a preliminary test for the following experiments (see 1.6), pyridylzinc pivalates were exclusively used to investigate the feasibility for the late-stage introduction of pyridyl moieties. Three different substituted pyridylzinc reagents were used to check if it is possible to achieve modified cyclopeptides with the pyridyl nitrogen atom in *ortho*-, *meta*- and *para*-position. Therefore, peptide **3e** was used for Negishi cross-coupling reactions with the corresponding zinc reagents **1g, 1d** or **1e** and the modified cyclopeptides **10a–c** were obtained in 53–82% yield (Table 6). It was found that the

performance of the cross-coupling is dependent on the position of the pyridyl nitrogen atom which is displayed in the deviated yields for the 2-, 3- and 4-position products.

1.5 Negishi Cross-Coupling Reactions of Alkylzinc Halides with Tyrosine Derivatives

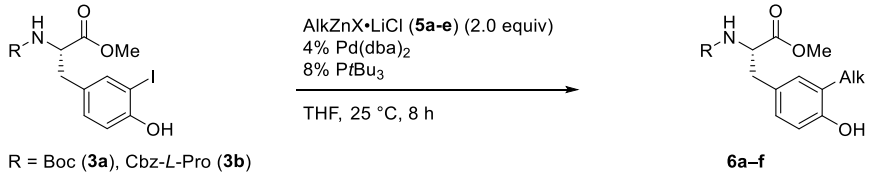
In addition to the aryl and heteroaryl Negishi cross-coupling reactions discussed in the previous chapter, a new method for the coupling of alkylzinc reagents was also investigated.

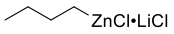
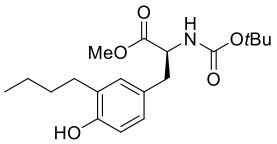
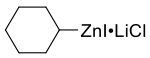
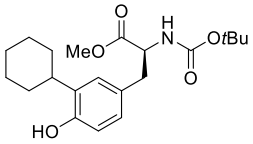
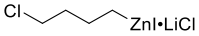
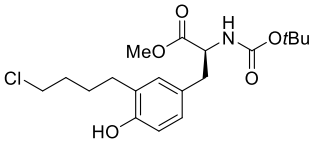
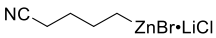
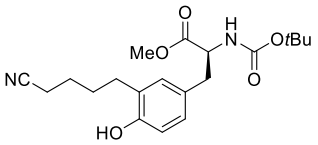
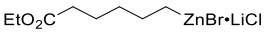
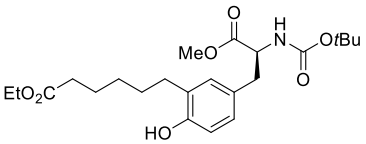
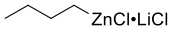
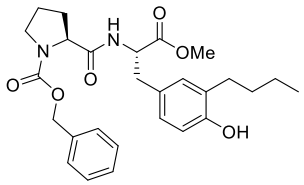
Attempts to extend the cross-coupling to alkylzinc pivalates proved to be difficult and a new optimization study was required. It was found, that zinc organometallics prepared by the direct oxidative insertion of zinc powder in the presence of LiCl were most suitable for a subsequent cross-coupling.[80] The previously used catalytic system (palladium acetate and SPhos) was not suitable for this reaction type and did not provide the desired products. It was found that the catalyst developed by Fu[81] with 4 mol% palladium dibenzylideneacetone ($Pd(dba)_2$) and 8 mol% tri-*tert*-butylphosphine ($PtBu_3$) gave the best results. Thus, the coupling of various functionalized primary and secondary alkylzinc halides (**5a**–**e**) bearing a chloro-, an ester- or a nitrile-function with the iodinated tyrosines **3a** and **3b** led to the modified tyrosines (**6a**–**e**) including the dipeptide **6f** (Table 7) in 48–82% isolated yield. Remarkably, the use of the Fu-catalyst led to relatively fast cross-coupling reactions. Combined with the slow addition of the organozinc reagent, an excellent compatibility with the acidic amides and phenolic protons was achieved.

[80] a) I. Kalvet, T. Sperger, T. Scattolin, G. Magnin, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 7078; b) C. Feng, D. W. Cunningham, Q. T. Easter, S. A. Blum, *J. Am. Chem. Soc.* **2016**, *138*, 11156; c) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082; d) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

[81] C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719.

Table 7: Negishi cross-coupling of tyrosine derivative **3a** and **3b** with alkylzinc halides **5a**–**e**.



Entry	Tyrosine	Alkylzinc reagent	Product	Yield (%)[a]
1	**3a**	 **5a**	 **6a**	82
2	**3a**	 **5b**	 **6b**	71
3	**3a**	 **5c**	 **6c**	72
4	**3a**	 **5d**	 **6d**	58
5	**3a**	 **5e**	 **6e**	48
6	**3b**	 **5a**	 **6f**	61

[a] Yield of the isolated analytically pure product.

1.6 Negishi Cross-Couplings of Iodo-Phenylalanine-based Cyclopeptides with Pyridylzinc Pivalates

The previous experiments have shown that the late-stage functionalization using Negishi cross-coupling in combination with arylzinc pivalates is well suitable for the modification of linear and cyclic tyrosine-based peptides. With this tool in hands, it should be possible to functionalize even large peptides based on similar amino acids used before.

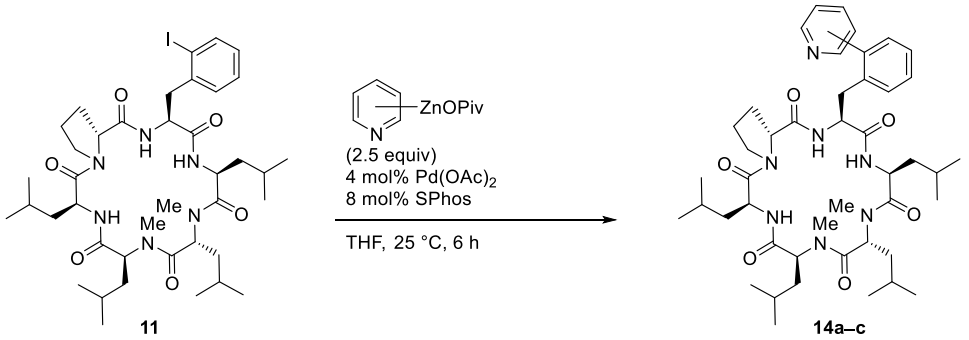
For the following experiments, hexameric-cyclopeptides consisting of three valine-, one proline- and one iodo-phenylalanine-blocks provided by *Novartis*[82] were used. The position of the iodo moiety in the phenylalanine side-chain was varying, so three different cyclopeptides (*ortho*-**11**, *meta*-**12** and *para*-**13**) were used as electrophile. The aim of this study was to introduce a 2-, 3- and 4-pyridyl moiety into each of the three cyclopeptide to get a set of nine different peptide-modifications. Then, the biophysical properties of these products were investigated (see the end of this chapter).

The first experiments were performed on the *ortho*-iodophenylalanine cyclohexapeptide using pyridylzinc pivalates **1c**–**e** and the same reaction conditions as for previous cross-couplings (Table 8).Whereas the 3- and 4- pyridylzinc reagents provided the desired modified peptides **14b** and **14c** in reasonable yield of 62% and 67 respectively, the 2-pyridyl did not provide the coupling product using those conditions. Further optimization experiments showed that increasing the catalyst loading (8 mol% palladium acetate and 16 mol% SPhos) as well as increasing the amount of zinc reagent (3.0 equivalents) and raising the reaction temperature to 60 °C led to the desired product **14a** in a moderate yield of 38% after 24 h (Table 8, Entry 1). As the de-iodinated cyclopeptide was detected as the main side-product, the problem might be the reductive elimination during the cross-coupling cycle[83]. A reason for this phenomenon was not determined, but steric hindrance of the ortho-iodide with the 2-pyridyl residue might play a significant role. Further increasing the amount of catalyst and reagent or a different catalytic system did not provide higher amounts of product but more undesired de-iodination product.

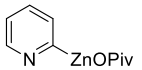
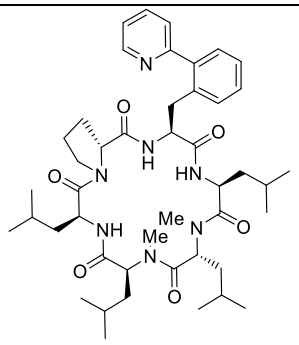
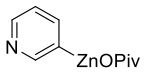
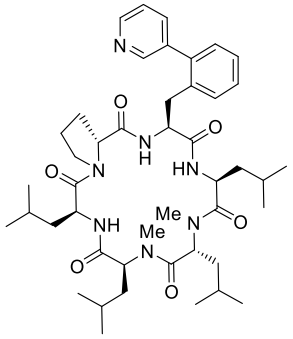
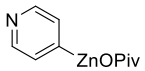
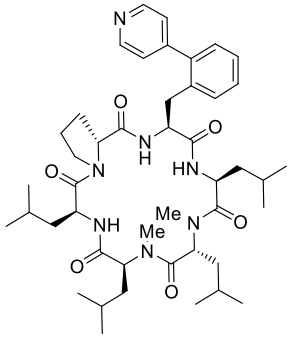
[82] Peptides were provided by Novartis Pharma AG, Basel, Switzerland. Special thanks to Dr. Guido Koch and Dr. Thomas Vorherr.

[83] Q. Liu, Y. Lan, J. Liu, G. Li, Y.-D. Wu, A. Lei, *J. Am. Chem. Soc.* **2009**, *131*, 10201.

Table 8: Negishi cross-coupling of the cyclopeptide **11** with pyridylzinc pivalates **1c**–**e**.



11 **14a–c**

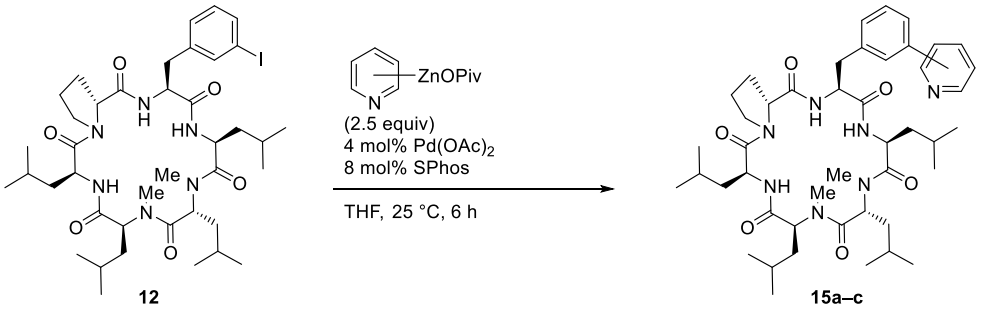
Entry	Zinc Pivalate	Product	Yield (%)[a]
1	 **1c**	 **14a**	38[b]
2	 **1d**	 **14b**	62
3	 **1e**	 **14c**	67

[a] Yield of the isolated analytically pure product. [b] Different reaction conditions were used: 2-pyridylzinc pivalate (3.0 equiv), 8 mol% $Pd(OAc)_2$, 16 mol% SPhos, THF, 60 °C, 24 h.

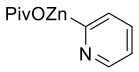
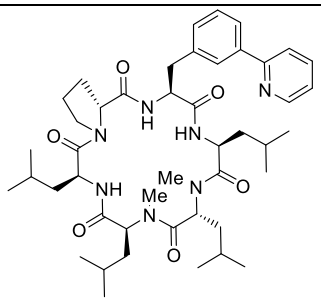
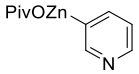
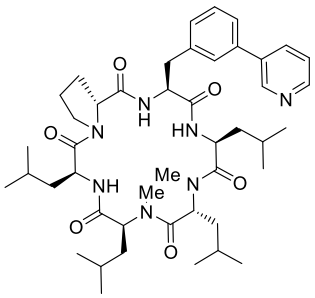
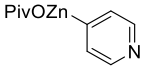
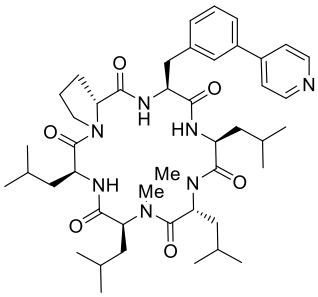
Experiments were continued with the *meta*-iodo cyclopeptide **12**. Applying the standard reaction conditions using the three different substituted pyridylzinc reagents provided the modified *meta*-cyclohexapeptides **15a**–**c** in 62–77% yield (Table 9). For this *meta*-iodo peptide, the 2-pyridylzinc

pivalate coupling led to an even better yield as for the other cross-couplings, which indicates that the zinc reagent was not the reason for the low yields of **14a** but the *ortho*-substituted peptide.

Table 9: Negishi cross-coupling of the cyclopeptide **12** with pyridylzinc pivalates **1c**–**e**.



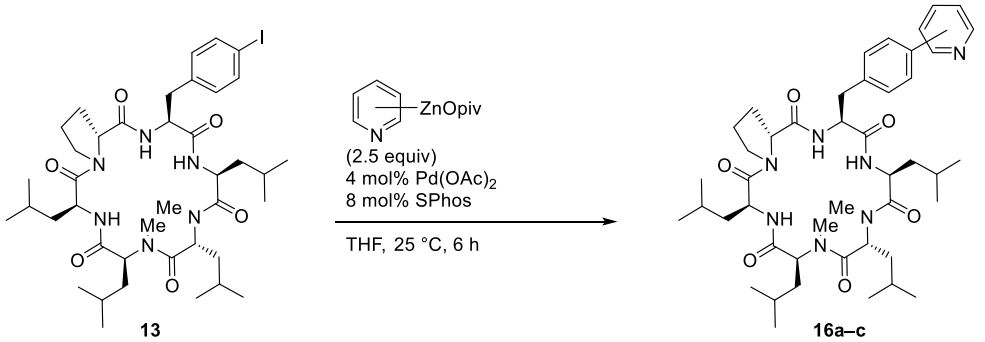
12 **15a–c**

Entry	Zinc Pivalate	Product	Yield (%)[a]
1	 **1c**	 **15a**	72
2	 **1d**	 **15b**	62
3	 **1e**	 **14c**	77

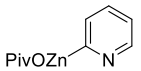
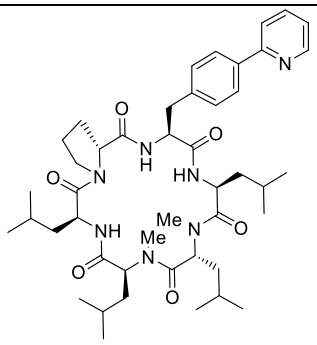
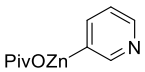
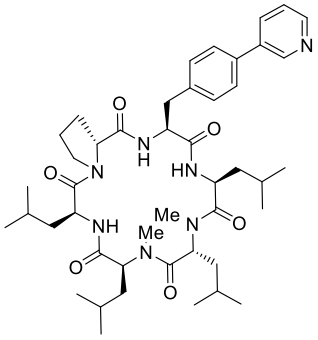
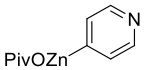
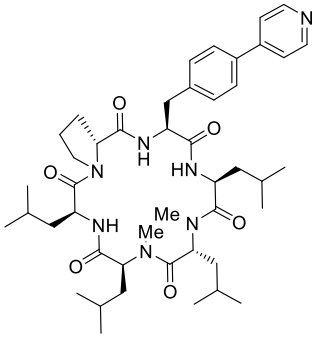
[a] Yield of the isolated analytically pure product.

The last set of cross-coupling reaction was performed using the *para*-iodophenylalanine cyclopeptide **13** and the 2-,3- and 4-pyridylzinc pivalates (**1c**–**e**). After Negishi cross-coupling reactions, the *para*-pyridyl modified cyclopeptides **16a**–**c** were obtained in 62–84% yield (Table 10).

Table 10: Negishi cross-coupling of the cyclopeptide **13** with pyridylzinc pivalates **1c**–**e**.



13 **16a–c**

Entry	Zinc Pivalate	Product	Yield (%)[a]
1			84
	1c	**16a**	
2			62
	1d	**16b**	
3			80
	1e	**16c**	

[a] Yield of the isolated analytically pure product.

This set of nine modified cyclopeptides as well as the three starting iodophenylalanine-cyclopeptides were used for biophysical studies to investigate the influence of the pyridyl-substituents on properties like solubility under physiological conditions, cell-membrane permeability and transport rate through membranes. All measurements and calculations of the biophysical properties were conducted and evaluated by *Novartis Pharma AG.*[84]

The membrane permeability- and solubility-parameters of the cyclopeptides **11**–**16** were compared to the results of *in-silico* calculations. Therefore, the nine cross-coupling products (**14**–**16**) have been submitted for MD (molecular dynamics) simulations followed by calculation of the solvent-accessible polar surface area (abbreviated SAPSA) to result in an *in-silico* assessment regarding their permeability properties in the first instance. Interestingly, different SAPSA values were observed and as expected in the cases, in which the pyridyl moiety is more exposed (*meta* and *para* substituted phenylalanine residues) more polar surface area is accessible. Next, solubility and permeability parameters were assessed. The low solubility measured for the starting materials (**11**–**13**) was improved by the pyridyl core in most of the cases (see Table 11, Entries 4–9 and 12), and on the basis of the PAMPA (Parallel Artificial Membrane Permeability Assay) results, all cyclic peptides display high permeability. However, in the cellular assessment (MDCK; Madin Darby canine kidney cells assay), the position of the pyridyl linkage seemed to be sensitive regarding transport across. As for the *in-silico* analyses, the *para*-phenylalanine substituted analogues showed reduced transport rates.

Table 11: Biophysical properties of the iodo-cyclopeptides and the modified cyclopeptides.[84]

Entry	Peptide	SAPSA (Å^2)	Solubility[b] (µM)	PAMPA	MDCK (10^{-6}cm/s)	SFC (min)
1	**11**	62	< 4	-4.2[b]	n.d. [a]	3.15
2	**12**	74	3	-4.3[b]	n.d. [a]	3.14
3	**13**	75	< 4	-5.4[b]	n.d. [a]	3.23
4	**14a**	76	24	-4.7[c]	n.d. [a]	3.37
5	**14b**	84	46	-4.3[b]	15.7	3.31
6	**14c**	83	52	-4.5[b]	19.3	3.39
7	**15a**	74	21	-4.5[b]	3.3	3.51
8	**15b**	101	26	-4.7[b]	3.2	3.60
9	**15c**	94	31	-4.8[b]	13.6	3.76
10	**16a**	84	9	-4.5[b]	1.4	3.61
11	**16b**	99	< 4	-4.6[b]	2.1	3.72
12	**16c**	106	22	-4.6[b]	2.9	3.89

[a] not determined due to QC or recovery problems. [b] at pH 6.8, [c] at pH 8.0.

[84] Experiments and calculations were performed by Dr. Thomas Vorherr, Dr. Ian Lewis, Dr. Michael Schaefer of the Novartis Pharma AG, Basel.

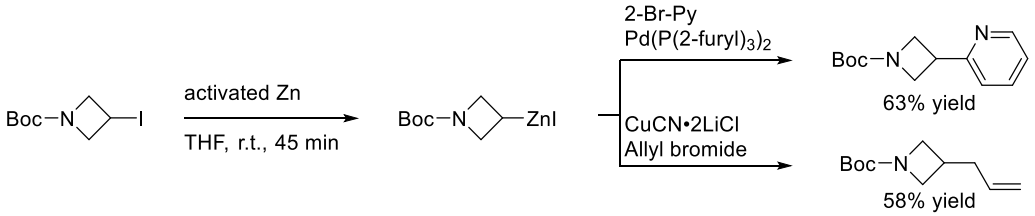
However, this assay reflects the sum of active and passive transport properties, whereas the SFC (supercritical fluid chromatography) method rank-orders only for passive permeability. Nevertheless, the cross-coupling products resulting from *ortho*-phenylalanine substitutions clearly showed a higher passive permeability. This finding was in line with the MD simulations followed by SAPSA calculation of the preferred conformational clusters.[85]

[85] M. Leroux, T. Vorherr, I. Lewis, M. Schaefer, G. Koch, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 8231.

2 Pyrrole Protected 2-Aminoalkylzinc Reagents for the Enantioselective Synthesis of Amino Derivatives

2.1 Introduction

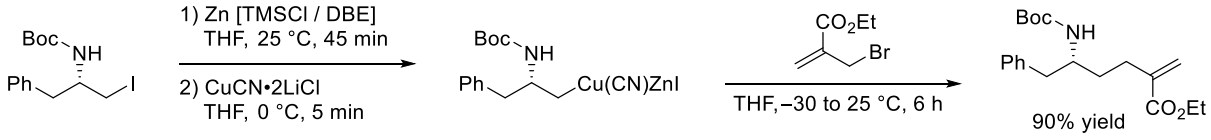
The preparation of organozinc reagents bearing a nitrogen in β-position in cyclic systems was already described in the literature. Using a *N*-Boc protected azetidine, the zinc compound can be easily produced from the corresponding iodide and used in cross-couplings as well as allylation reactions (Scheme 25).



Scheme 25: Preparation of (N-Boc-azetidin-3-yl)zinc(II) iodide and application in cross-coupling and allylation reactions.[86]

In general, the preparation of chiral amino-derivatives is of great synthetic importance in the development of new pharmaceuticals and agrochemicals.[87] A straightforward and fast way to obtain chiral amino-derivatives is the use of enantiopure amino acids as precursors. Since they can be produced industrially by fermentation in big scale without the use of expensive catalysts, they are cheap and therefore excellent suited for this application.[88]

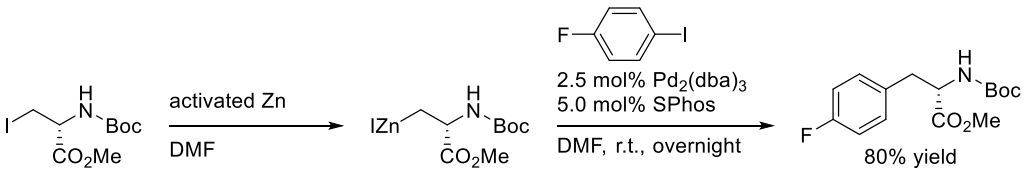
Recently, the group of Knochel already utilized chiral amino-alcohols obtained from amino acids to prepare mixed zinc-copper reagents which were used for various allylation reactions (Scheme 26).[89]



Scheme 26: Preparation of a chiral amino-alcohol based zinc-copper reagent and following reaction with a functionalized allyl bromide.[89]

[86] S. Billotte, *Synlett* **1998**, *1998*, 379.
[87] a) T. C. Nugent, M. El-Shazly, Adv. Synth. Catal. 2010, 352, 753; b) T. C. Nugent, *Chiral Amine Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2010**; c) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Kesseler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788.
[88] a) M. D'Este, M. Alvarado-Morales, I. Angelidaki, *Biotechnol. Adv.* **2018**, *36*, 14; b) N. Tonouchi, H. Ito *Amino Acid Fermentation* (Eds.: A. Yokota, M. Ikeda), Springer Japan, Tokyo, Japan, **2017**, 3–14.
[89] R. Duddu, M. Eckhardt, M. Furlong, H.P. Knoess, S. Berger, P. Knochel, *Tetrahedron* **1994**, *50*, 2415.

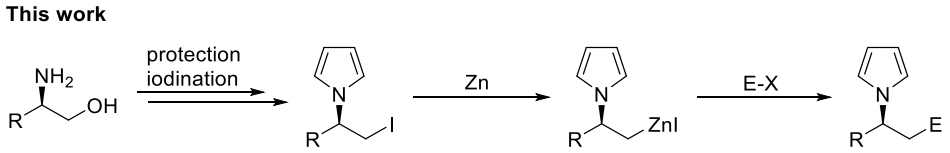
In the approach of Jackson, chiral C- and N-protected amino acids have been converted to alkyl iodides and after oxidative zinc insertion, used for cross-coupling reactions.[90] Especially, starting from serine, side-chain modified amino acid derivatives can be produced, as displayed in Scheme 27.



Scheme 27: Preparation of a chiral amino-acid alkylzinc reagent and its application in a Negishi cross-coupling reaction.[91]

In addition to these approaches, a new method was envisioned to prepare a broad range of chiral amino organozinc reagent starting from readily accessible amino-alcohols to obtain a powerful and universally applicable tool for the synthesis of functionalized amino derivatives.

Herein, a convenient and quite general preparation of chiral pyrrole-protected organozinc reagents and their application in transition-metal catalyzed reactions with electrophiles, bearing various functional groups, is reported (Scheme 28).



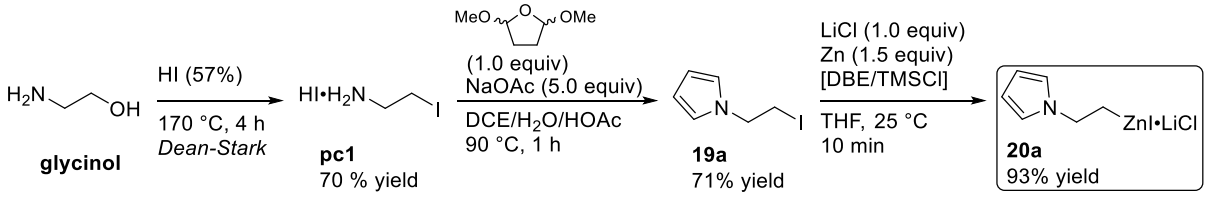
Scheme 28: A new approach towards chiral amino-organozinc reagents using pyrrole as a protecting group.

[90] a) J. Ross, F. Dreiocker, M. Schäfer, J. Oomens, A. J. H. M. Meijer, B. T. Pickup, R. F. W. Jackson, *J. Org. Chem.* **2011**, *76*, 1727; b) T. Carrillo-Marquez, L. Caggiano, R. F. W. Jackson, U. Grabowska, A. Rae, M. J. Tozer, *Org. Biomol. Chem.* **2005**, *3*, 4117; c) H. J. C. Deboves, U. Grabowska, A. Rizzo, R. F. W. Jackson, *J. Chem. Soc., Perkin Trans. 1* **2000**, 4284; d) R. F. W. Jackson, K. James, M. J. Wythes, A. Wood, *J. Chem. Soc., Chem. Commun.* **1989**, 644.

[91] A. J. Ross, H. L. Lang, R. F. W. Jackson, *J. Org. Chem.* **2010**, *75*, 245.

2.2 Proof of Principle for β-Amino Alkylzinc Reagents Starting from Glycinol

Preliminary experiments were performed using glycinol (2-aminoethanol) as test substrate. It was found, that achiral glycinol offers a promising opportunity to obtain the simplest β-iodo-alkyl amine by treating glycinol with hydroiodic acid at high temperatures (**pc1**, Scheme 29). Therefore, this substrate was used for the determination of an amino protecting group compatible with a zinc insertion. Experiments revealed that benzyl-, alkyl-, allyl-, Boc-, phthaloyl- or silyl-protecting groups were not suited for this purpose. It was found that 1*H*-pyrrole is an excellent protecting group for this study which met all requirements. Protection of the amino-group was easily performed by refluxing the β-iodo-alkylamine in 2,5-dimethoxy tetrahydrofuran with sodium acetate and acetic acid in a 1,2-dichloroethane/water mixture for 1 h and provided the desired pyrrole-protected alkyl iodide **19a** in 71% yield (Scheme 29). Zinc powder was suspended in dry THF together with lithium chloride[92] and activated with 1,2-dibromoethane and chlorotrimethylsilane[93] for the oxidative insertion. The previous prepared alkyl iodide was added to this mixture at room temperature and the corresponding organozinc reagent **20a** was obtained in a good yield of 93% after 10 min (Scheme 29). This reagent showed no tendency to undergo elimination reactions and was stable at 25 °C for several days without decomposition.

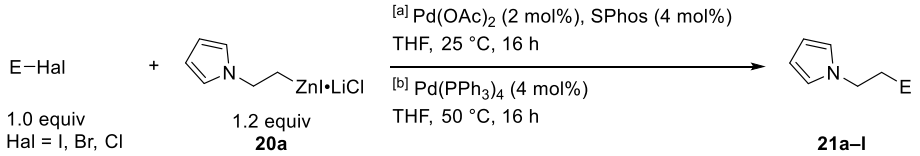


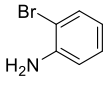
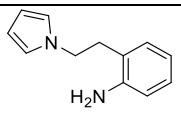
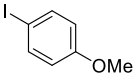
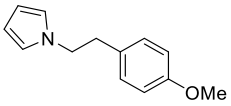
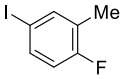
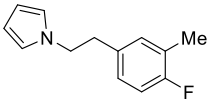
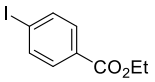
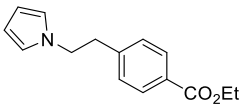
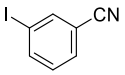
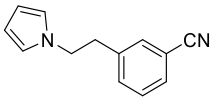
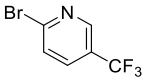
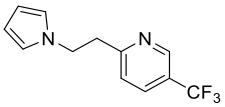
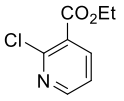
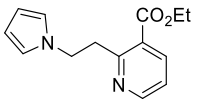
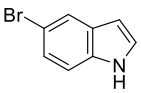
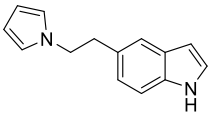
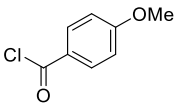
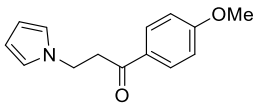
Scheme 29: Preparation of a pyrrole protected organozinc reagent starting from glycinol.

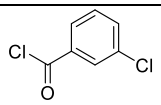
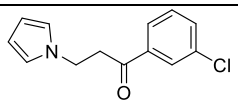
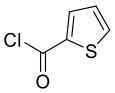
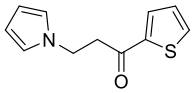
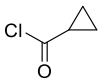
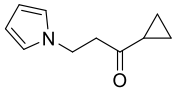
In the next step, this new organozinc reagent was used in a broad range of palladium catalyzed cross-coupling reaction to determine the functional group tolerance. Experiments revealed that the use of 2 mol% $Pd(OAc)_2$ and 4% SPhos[94] provided the best results. Thus, electron-rich as well as electron poor cross-coupling products (**21a**–**e**) were obtained in yields between 85% and 98%. Additionally, it was possible to use heteroaryl halides in this cross-coupling protocol providing the modified heteroaryl compounds **21f**–**h** in 83–95% yield (Table 12). The pyrrole-containing organozinc reagent was also successfully applied in palladium catalyzed acylation reactions. Therefore, the reaction of various acyl chlorides with reagent **20a** in the presence of 4 mol% $Pd(PPh_3)_4$ at 50 °C provided aryl- and heteroarylketones **21i**–**k** as well as a cyclopropyl-ketone **21l** in 73–87% yield (Table 12).

[92] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.
[93] P. Knochel, M. J. Rozema, C. E. Tucker, *Organocopper reagents* (Ed.: R. J. K. Taylor), Oxford University press, Oxford, **1994**, 85.
[94] Y. Yang, N. J. Oldenhuis, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 615.

Table 12: Palladium catalyzed cross-coupling and acylation reactions of the glycinol-based *N*-alkylpyrrolezinc reagent **20a** with (hetero-)aryl halides and acid chlorides.



Entry	Electrophile	Product	Yield (%)[c]
1		 **21a**	98[a]
2		 **21b**	95[a]
3		 **21c**	83[a]
4		 **21d**	97[a]
5		 **21e**	85[a]
6		 **21f**	83[a]
7		 **21g**	95[a]
8		 **21h**	90[a]
9		 **21i**	87[b]

Entry	Electrophile	Product	Yield (%)[c]
10		 **21j**	82[b]
11		 **21k**	73[b]
12		 **21l**	83[b]

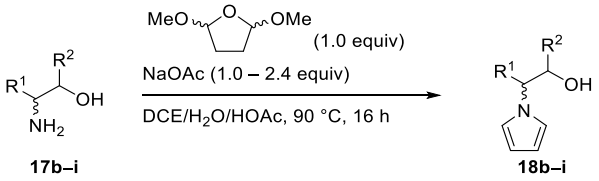
[a] 2 mol% $Pd(OAc)_2$, 4 mol% SPhos, 25 °C, 16 h. [b] 4 mol% $Pd(PPh_3)_4$, 50 °C, 16 h. [c] Yield of analytically pure isolated product.

2.3 Preparation of Pyrrole-protected 2-Amino Alcohols

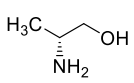
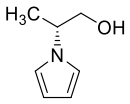
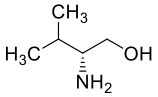
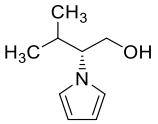
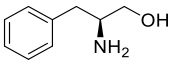
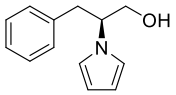
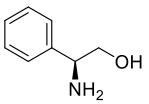
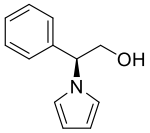
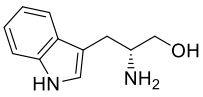
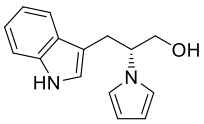
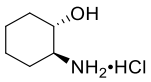
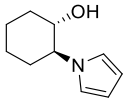
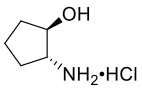
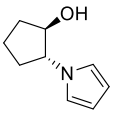
With the proof-of-principle established for glycinol, this method should be extended to commercially available chiral 2-amino alcohols obtained from amino acids (natural *L* or unnatural *D*-enantiomer). Since the iodination conditions using hydroiodic acid were too harsh for most of the amino-alcohols and due to possible racemization of the chiral amino-group, another approach had to be found.

In a newly developed pathway, the optical pure amino-alcohols were first transformed into the corresponding *N*-pyrrolyl-alkyl alcohol using the same procedure as previously for the glycinol derivative and then iodinated afterwards (see chapter 2.4). Thus, the chiral amino-alcohols **17b**–**f** were treated with 2,5-dimethoxytetrahydrofuran and sodium acetate in the presence of acetic acid in a 1,2-dichlorethane/water emulsion at 90 °C for 16 h, providing the pyrrole-derivatives **18b**–**f** in 71–92% yield (Table 13). Additional to these amino acids-based precursors, optical pure cyclic *trans*-2-amino alcohols were used. Applying the same conditions, the 2-aminocyclohexanol **(*S*,*S*)-17h** and the 2-aminocyclopentanol **(*R*,*R*)-17i** were converted to the corresponding pyrrole derivatives **(*S*,*S*)-18h** and **(*R*,*R*)-18i** in 83% and 77% yield with full retention of stereochemistry (Table 13).

Table 13: Preparation of chiral pyrrole-protected 2-amino alcohols of type **18**.



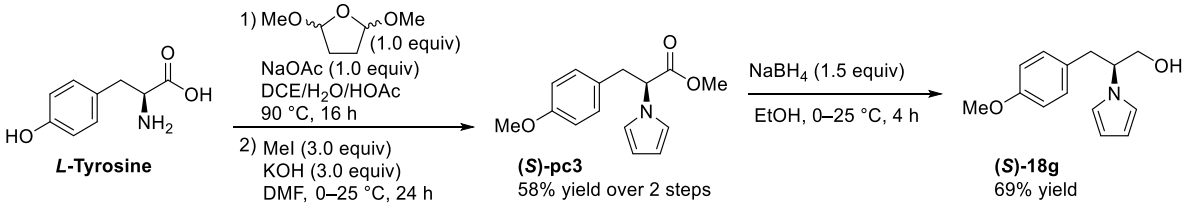
17b–i **18b–i**

Entry	2-Aminoalcohol	Pyrrole Derivative	Yield (%)[a]
1			79[b]
	(*R*)-17b	**(*R*)-18b**	
2			84
	(*R*)-17c	**(*R*)-18c**	
3			85
	(*S*)-17d	**(*S*)-18d**	
4			92
	(*S*)-17e	**(*S*)-18e**	
5			71
	(*R*)-17f	**(*R*)-18f**	
6			83 *d.r.* 99:1
	(*S*,*S*)-17h	**(*S*,*S*)-18h**	
7			77 *d.r.* 99:1
	(*R*,*R*)-17i	**(*R*,*R*)-18i**	

[a] Yield of the isolated analytically pure product. [b] Reaction was finished after 5 h.

Besides these *N*-pyrrolyl-alcohols, a tyrosine-based precursor was also of interest. Since the phenolic hydroxyl group might destabilize the desired organozinc reagent, methylation was necessary. For the reduction with mild reducing agents, the free acid was converted to the methyl ester. Starting from *L*-tyrosine, an easy and straightforward synthesis pathway including pyrrole formation, phenol protection and methyl esterification (**(*S*)-pc3**) was performed in 58% yield over two steps without purification in between: Initially, the pyrrole group was formed using the default method followed by treatment with

methyl iodide and potassium hydroxide to achieve the methoxy group as well as the methyl ester. The methyl ester was then reduced with sodium borohydride to obtain the desired *N*-pyrrolyl-alkyl alcohol **(*S*)-18g** in 69% yield (Scheme 30).

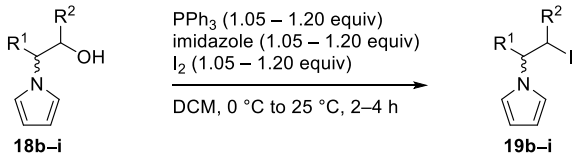


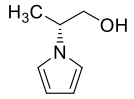
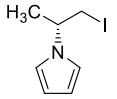
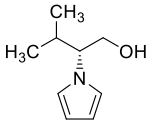
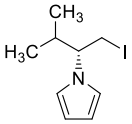
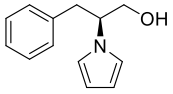
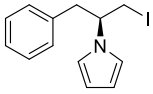
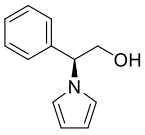
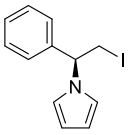
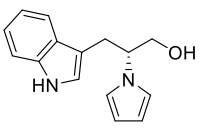
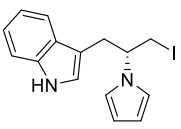
Scheme 30: Preparation of a pyrrole protected 2-aminoalcohol based on *L*-tyrosine.

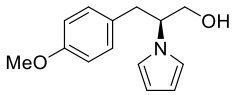
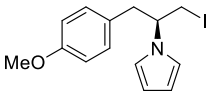
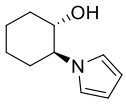
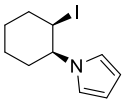
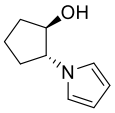
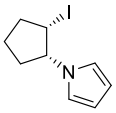
2.4 Preparation of *N*-Pyrrolyl Alkyl Iodides

In the last step of the synthesis, the *N*-pyrrolylalkyl alcohol was converted into the corresponding alkyl iodide.

Table 14: Appel typed iodination of the chiral amino-alcohols **18** providing in the alkyl iodides **19**.



Entry	Pyrrole Derivative	Iodide	Equiv Reagents	Yield (%)[a]
1	 **(*R*)-18b**	 **(*R*)-19b**	1.20	79 *ee* = 99%
2	 **(*R*)-18c**	 **(*R*)-19c**	1.10	84 *ee* = 99%
3	 **(*S*)-18d**	 **(*S*)-19d**	1.10	85 *ee* = 99%
4	 **(*S*)-18e**	 **(*S*)-19e**	1.10	92 *ee* = 99%
5	 **(*R*)-18f**	 **(*R*)-19f**	1.05	71 *ee* = 99%

Entry	Pyrrole Derivative	Iodide	Equiv Reagents	Yield (%)[a]
6	 **(*S*)-18g**	 **(*S*)-19g**	1.05	95 *ee* = 92%
7	 **(*S*,*S*)-18h**	 **(*S*,*R*)-19h**	1.20	76[b,c] *ee* = 99%
8	 **(*R*,*R*)-18i**	 **(*R*,*S*)-19i**	1.10	43[b,c] *ee* = 98%

[a] Yield of the isolated analytically pure product. [b] Reaction was carried out at 50 °C for 16 h. [c] *d.r.* > 99:1.

For this purpose, the *N*-pyrrolyl-alcohols **18b**–**g** were iodinated[95] by treatment of the alcohol with triphenylphosphine, iodine and 1*H*-imidazole in DCM starting from 0 °C to 25 °C within 2–4 h. After purification the resulting alkyl iodides **19b**–**g** were obtained in 71–95% yield (Table 14). For these compounds, the optical purity was determined using chiral HPLC analysis. Alkyl iodides **19b**–**f** display a very high purity with an enantiomeric excess of 99%. This finding proved that the protection and the iodination procedure proceeded without racemization. Notably, for the tyrosine derivative **(*S*)-19g** a decreased optical purity down to 92% *ee* was found which might be caused by the harsh reaction conditions during precursor synthesis.

The cyclic *N*-pyrrolyl alcohols **(*S*,*S*)-18h** and **(*R*,*R*)-18i** could not be iodinated using these reaction conditions. For seeing a conversion of the alcohol, the reaction temperature had to be raised to 50 °C and the reaction time drastically increased to 16 h. Using these modified conditions, the iodinated products **(*S*,*R*)-19h** and **(*R*,*S*)-19i** could be obtained in 76% and 43% yield with inversion of the stereocenter. Due to the elevated temperatures, the elimination reaction was more favored than usual and was observed as main side product for both reactions. The *cis*-conformation of **(*S*,*R*)-19h** was verified by comparing the coupling constants in the ^{1}H-NMR spectrum. For the five-membered alkyl iodide **(*R*,*S*)-19i**, a single crystal could be obtained and following x-ray crystallography analysis confirmed the *cis*-configuration, as displayed in Figure 6.

[95] a) V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5516; b) G. L. Lange, C. Gottardo, *Synth. Commun.* **1990**, *20*, 1473; c) P. J. Garegg, B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866; d) R. Appel, *Angew. Chem. Int. Ed.* **1975**, *14*, 801.

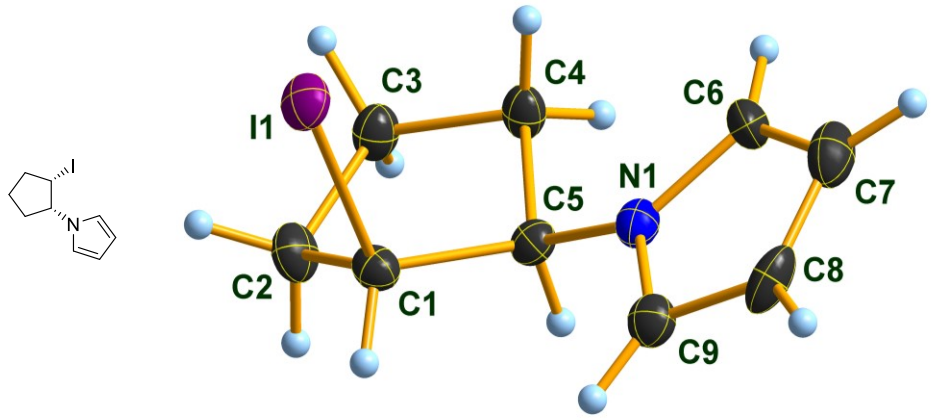
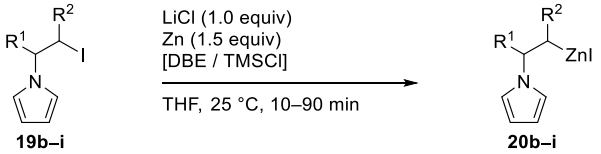


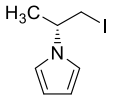
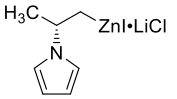
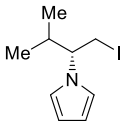
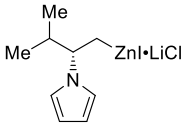
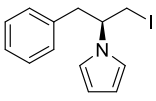
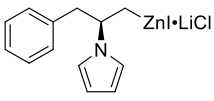
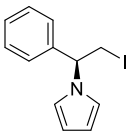
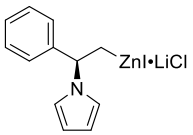
Figure 6: Crystal structure of iodide **(*R*,*S*)-19i** is showing the *cis*-configuration of pyrrole and iodide. Thermal ellipsoids are drawn at 50% probability level.

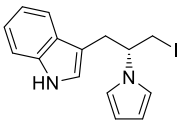
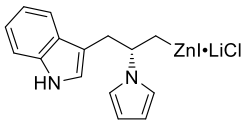
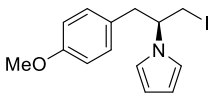
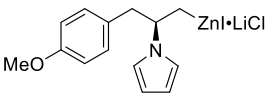
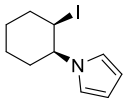
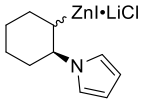
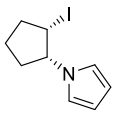
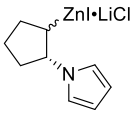
2.5 Oxidative Zinc Insertion of 1,2-substituted *N*-Pyrrolyl-Alkyl Iodides

With the previously prepared *N*-pyrrolyl-alkyl iodides in hand, the preparation of the organozinc reagents was investigated.

Table 15: Preparation of β-amino alkylzinc iodides *via* oxidative insertion of activated zinc dust in the presence of lithium chloride.



Entry	Iodide	Alkylzinc Compound	Time (min)	Yield (%)[a]
1	 **(*R*)-19b**	 **(*R*)-20b**	20	76
2	 **(*R*)-19c**	 **(*R*)-20c**	10	80
3	 **(*S*)-19d**	 **(*S*)-20d**	10	82
4	 **(*S*)-19e**	 **(*S*)-20e**	90	71

Entry	Iodide	Alkylzinc Compound	Time (min)	Yield (%)[a]
5	 **(*R*)-19f**	 **(*R*)-20f**	30	91
6	 **(*S*)-19g**	 **(*S*)-20g**	15	95
7	 **(*S*,*R*)-19h**	 **(*S*)-20h**	10	79
8	 **(*R*,*S*)-19i**	 **(*R*)-20i**	10	96

[a] Yield of the zinc species was determined by titration against iodine in THF.

Using activated zinc dust with lithium chloride in THF at 25 °C afforded the iodides **19b**–**i** (Table 15). For most of the alkyl iodides, the reaction proceeded smoothly with slight heat generation within 10 min to 20 min. For the phenylglycinol- (**(*S*)-19e**) and the tryptophanol-derivative (**(*R*)-19f**) longer reaction times of 90 min and 30 min respectively were necessary to achieve full conversion of the alkyl iodides. Yield determination for the zinc reagents in THF was performed by titration against iodine[96] and measuring the volume which resulted in 71–96% yield of the corresponding reagents **20a**–**i**. Interestingly, the secondary amine of the indole side-chain of the tryptophanol-based iodide **(*R*)-19f** did not lead to hydrolysis or decreased output during the zinc insertion and the resulting reagent did not show tendencies for fast decomposition.

2.6 Negishi Cross-Coupling and Acylation Reactions of Pyrrole-protected Organozinc Reagents

With these eight different chiral pyrrole-protected alkylzinc halides in hand, various transition-metal catalyzed cross-coupling reactions as well as acylation reactions were performed.

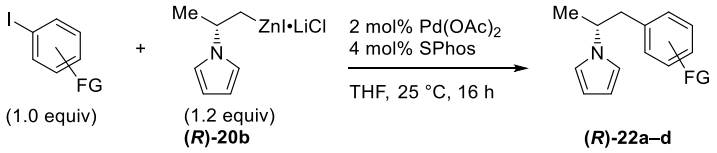
Based on Alaninol

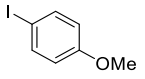
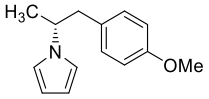
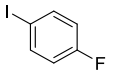
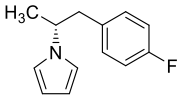
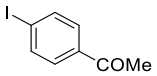
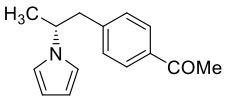
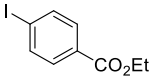
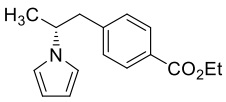
Starting with the alaninol-based reagent, four different cross-coupling reaction were carried out using different electron-rich and –poor electrophiles. The products **(*R*)-22a**–**d** were obtained in 83–99% yield

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

with a high optical purity of >95% ee (Table 16). Thus, the method developed for the achiral glycinol derivative is also applicable for chiral amino-alcohol derivatives without racemization.

Table 16: Cross-coupling reactions using an alaninol based organozinc reagent.



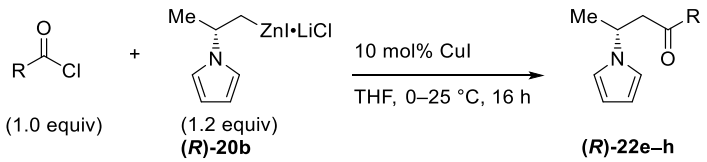
Entry	Electrophile	Product	*ee (%)*	Yield (%)[a]
1		 **(*R*)-22a**	>95	83
2		 **(*R*)-22b**	98	86
3		 **(*R*)-22c**	99	91
4		 **(*R*)-22d**	99	99

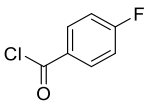
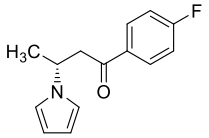
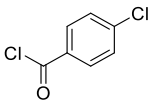
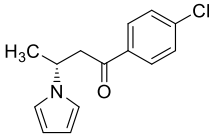
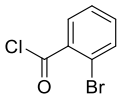
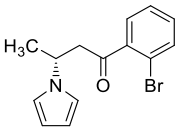
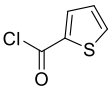
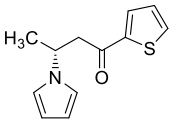
[a] Yield of analytically pure isolated product.

Furthermore, acylation reactions were investigated using the organozinc reagent **(*R*)-20b**. $Pd(PPh_3)_4$ catalyzed acylation reactions were successful for the glycinol derivative. However, using the brominated acid chloride, unintended cross-coupling side-reactions with the aryl bromide occurred. For this reason and to evaluate a cheaper alternative to palladium, copper(I) iodide[97] was used for the reaction of the alaninol-based zinc reagent with acid chlorides. It was found, that using 10 mol% of catalyst at 0 °C provided the aryl- and heteroaryl-ketones **(*R*)-22e**–**h** in acceptable yields between 59% and 79% with high optical purities of 99% *ee* (Table 17).

[97] H.-S. Jung, S.-H. Kim, *Tetrahedron Lett.* **2015**, *56*, 1004.

Table 17: Copper(I) iodide catalyzed acylation reactions of the organozinc reagent **(*R*)-20b** with acid chlorides.



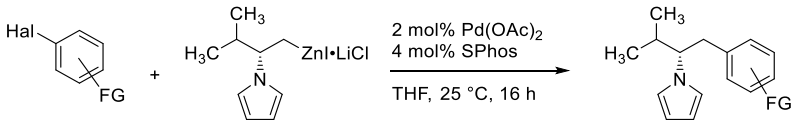
Entry	Electrophile	Product	*ee (%)*	Yield (%)[a]
1		 (*R*)-22e	99	73
2		 (*R*)-22f	99	67
3		 (*R*)-22g	99	79
4		 (*R*)-22h	99	59

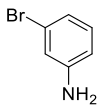
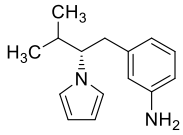
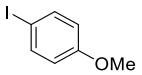
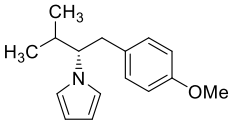
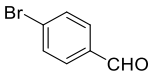
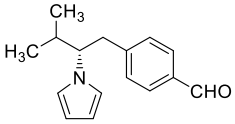
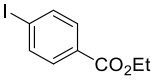
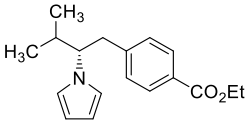
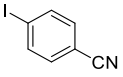
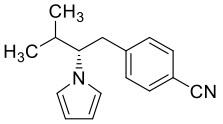
[a] Yield of analytically pure isolated product.

Based on Valinol

The same type of experiment was conducted for the valinol-based organozinc reagents **(*R*)-20c**. For the cross-coupling reaction, different electrophiles bearing sensitive functional groups such as amines, aldehydes or nitriles were tested. The reactions provided the cross-coupling products **(*S*)-23a**–**e** in yields between 86% and 93% (Table 18) while maintaining the high enantiomeric excess of 99% previously measured for the iodide **(*R*)-19c**.

Table 18: Cross-coupling reactions using the valinol-based organozinc reagent **(*R*)-20c**.

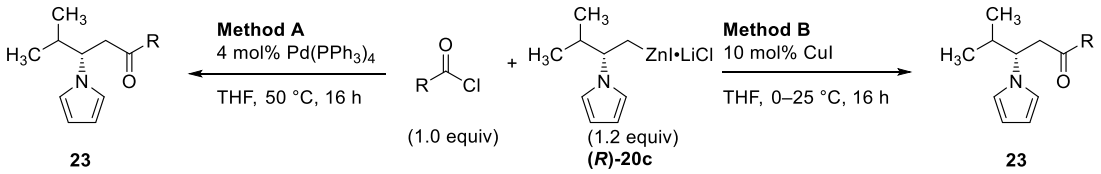


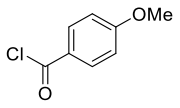
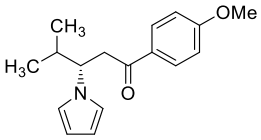
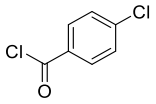
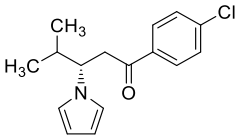
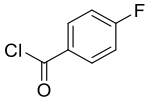
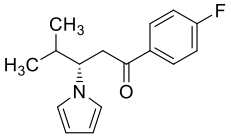
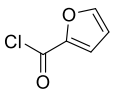
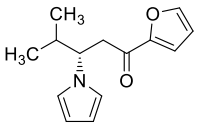
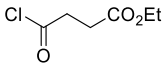
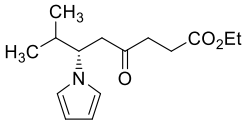
Entry	Electrophile	Product	*ee (%)*	Yield (%)[a]
1		 **(*S*)-23a**	99	93
2		 **(*S*)-23b**	99	89
3		 **(*S*)-23c**	99	86
4		 **(*S*)-23d**	99	88
5		 **(*S*)-23e**	99	93

[a] Yield of analytically pure isolated product.

Additionally, acylation reaction using $Pd(PPh_3)_4$ or copper(I) iodide (for halogen-containing acid chlorides) as catalyst were performed providing aryl- and hetero-aryl ketones **(*S*)-23f**–**i** as well as the alkyl ketone **(*S*)-23j** in 66–85% yield (Table 19). All prepared ketones exhibit a high optical purity with 99% *ee*.

Table 19: Palladium and copper catalyzed acylation reactions using the valinol-based zinc reagent **(*R*)-20a**.



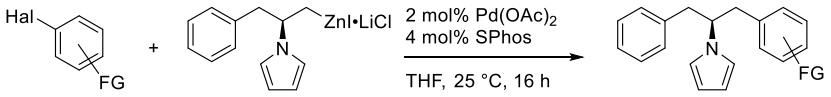
Entry	Electrophile	Product	Method	*ee (%)*	Yield (%)[a]
1		 **(*S*)-23f**	A	99	85
2		 **(*S*)-23g**	B	99	80
3		 **(*S*)-23h**	B	99	70
4		 **(*S*)-23i**	A	99	72
5		 **(*S*)-23j**	A	99	66

[a] Yield of analytically pure isolated product.

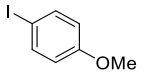
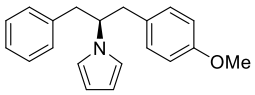
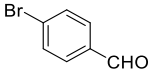
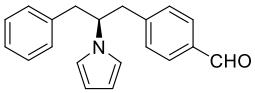
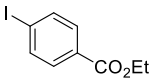
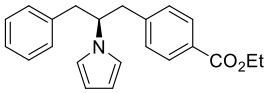
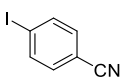
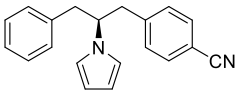
Based on Phenylalaninol

With the organozinc reagent **(*S*)-20d**, derived from *L*-phenylalaninol, the first organometallic of this study containing a benzyl instead of an alkyl residue, palladium catalyzed reactions were investigated. For this purpose, selected electrophiles containing donating as well as withdrawing functional groups were employed for Negishi cross-coupling reaction. The corresponding coupling-products **(*S*)-24a**–**d** were successfully obtained in high yields of 84–96% and high optical purity (Table 20).

Table 20: Cross-coupling reactions using the phenylalaninol-based organozinc reagent **(*S*)-20d**.



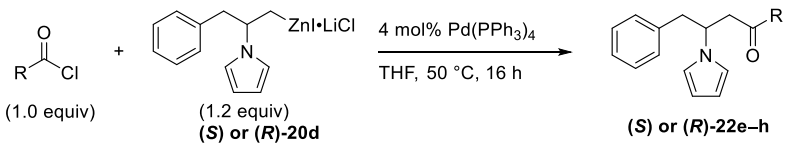
(1.0 equiv) Hal = Br, I | (1.2 equiv) **(*S*)-20d** | **(*S*)-24a–d**

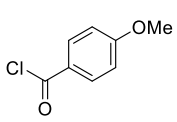
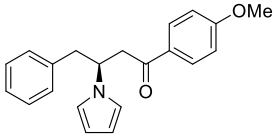
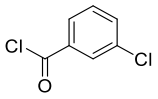
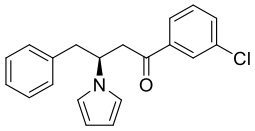
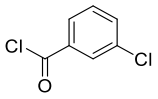
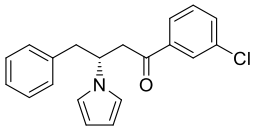
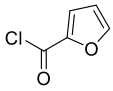
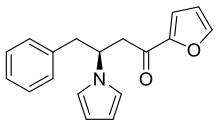
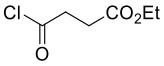
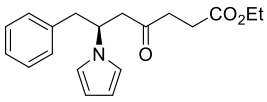
Entry	Electrophile	Product	*ee (%)*	Yield (%)[a]
1		 **(*S*)-24a**	99	84
2		 **(*S*)-24b**	99	91
3		 **(*S*)-24c**	99	96
4		 **(*S*)-24d**	99	94

[a] Yield of analytically pure isolated product.

Next, the reaction scope of this reagent was extended to acylation reactions using $Pd(PPh_3)_4$ as catalyst. The reaction of different aryl- and alkyl-acid chlorides provided the products **(*S*)-24e**–**h** with an enantiomeric excess of 99% and yields between 70% and 85% (Table 21). It was necessary to obtain the opposite enantiomers of ketone **(*S*)-24f** for further experiments. Therefore, the zinc reagent **(*R*)-20d** derived from *D*-phenylalaninol was reacted with 3-chlorobenzoyl chloride providing the ketone **(*R*)-24f** in 82% yield and 99% *ee* (Table 21, Entry 3).

Table 21: Palladium catalyzed acylation reactions using the phenylalaninol-based organozinc reagent **20d**.



Entry	Electrophile	Product	*ee (%)*	Yield (%)[a]
1		 **(*S*)-24e**	99	73
2		 **(*S*)-24f**	99	85
3[b]		 **(*R*)-24f**	99	82[b]
4		 **(*S*)-24g**	99	84
5		 **(*S*)-24h**	99	70

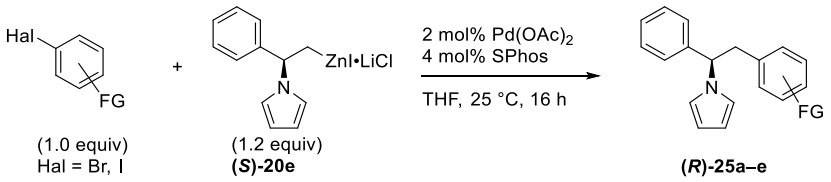
[a] Yield of the isolated analytically pure product. [b] **(*R*)-20d** was used instead of **(*S*)-20d** to obtain the corresponding enantiomer for further experiments.

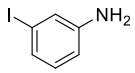
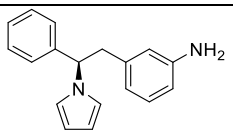
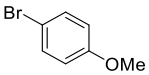
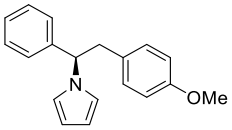
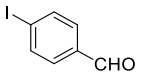
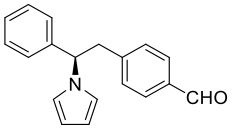
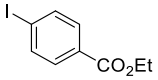
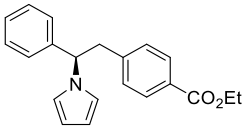
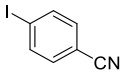
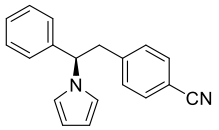
Based on Phenylglycinol

Due to the positive results for the benzyl side-chain containing reagent **20d** the scope for the nucleophilic reagent was extended towards a reagent with a phenyl side-chain. Therefore, the organozinc reagent **(*S*)-20e** derived from the unnatural amino acid α-phenylglycine was prepared. Because of the benzylic position of the chiral pyrrole center, this reagent was most liable to undergo racemization reaction and showed special behavior during the zinc insertion due to the prolonged reaction time. On the other hand, the palladium catalyzed cross-couplings revealed that a broad range of functionalized electrophiles can be applied and the products **(*R*)-25a**–**e** were obtained in 75% to 95% yield (Table 22). Remarkably, even bearing the pyrrole in the sensitive benzylic position, the

optical purity did not decrease during the zinc insertion or the cross-coupling reaction and all products showed an enantiomeric excess of 99%.

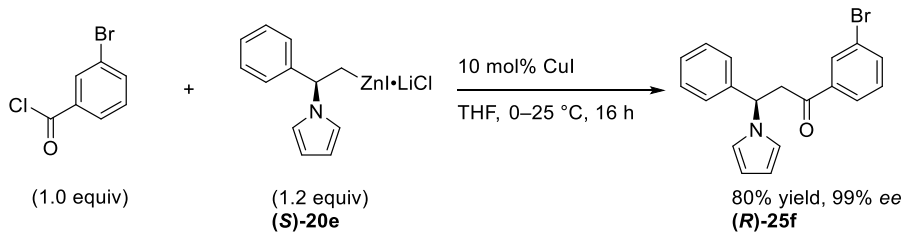
Table 22: Cross-couplings using a phenylglycinol-based organozinc reagent **(*S*)-20e** with different electrophiles.



Entry	Electrophile	Product	*ee (%)*	Yield (%)[a]
1		 **(*R*)-25a**	99	75
2		 **(*R*)-25b**	99	75
3		 **(*R*)-25c**	99	84
4		 **(*R*)-25d**	99	92
5		 **(*R*)-25e**	99	95

[a] Yield of analytically pure isolated product.

To complete this set, one copper(I) iodide acylation was performed using 3-bromobenzoyl chloride combined with **(*S*)-20e** and the ketone **(*R*)-25f** was obtained in 80% yield with 99% *ee* (Scheme 31).

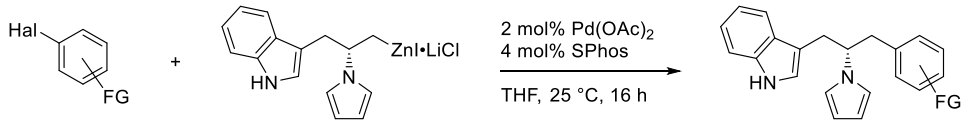


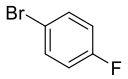
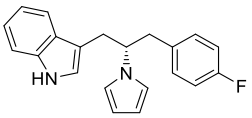
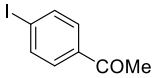
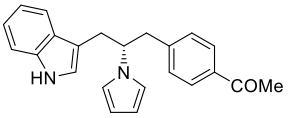
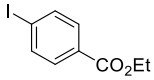
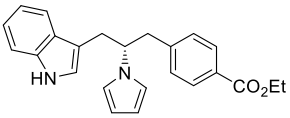
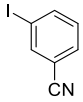
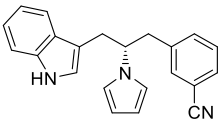
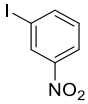
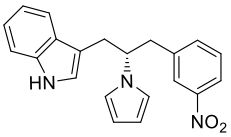
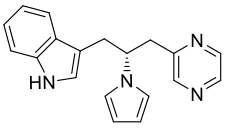
Scheme 31: Copper catalyzed acylation of *N*-alkylzinc pyrrole **(*S*)-20e** with 3-bromobenzoyl chloride.

Based on Tryptophanol

After successfully testing various *N*-pyrrolyl-alkylzinc reagents bearing alkyl, benzyl, or phenyl residues, a more sensitive substrate was tested. Starting from tryptophanol the corresponding iodide was successfully converted into the organozinc reagent while tolerating the –NH group of the indole moiety. Then, this reagent was evaluated for the application in cross-coupling reactions to check its tolerance towards the catalytic system and the electrophiles. For these experiments, even more demanding and sensitive coupling-compounds were chosen containing e.g. ketones, nitriles or nitro groups and a pyrazine scaffold.

Table 23: Cross-coupling reactions using the tryptophanol-based organozinc reagent **(*R*)-20f**.



Entry	Electrophile	Product	*ee (%)*	Yield (%)[a]
1		 **(*S*)-26a**	99	68
2		 **(*S*)-26b**	99	98
3		 **(*S*)-26c**	99	97
4		 **(*S*)-26d**	99	92
5		 **(*S*)-26e**	99	91
6		 **(*R*)-26f**	99	98

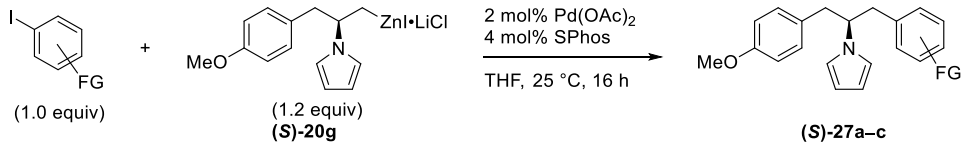
[a] Yield of analytically pure isolated product.

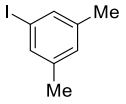
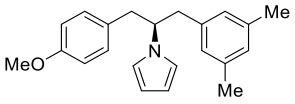
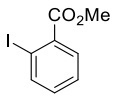
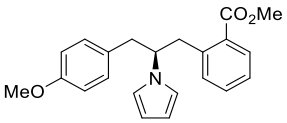
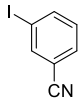
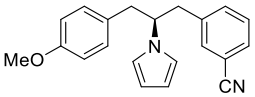
The experiments revealed that the indole-containing reagent was fully tolerating the reaction conditions and the products **26a**–**f** were successfully obtained in 68–98% yield with high enantiomeric excess.

Based on Tyrosinol

In this set of organozinc reagent, the last compound derived from natural amino acids was the protected tyrosinol derivative **(*S*)-20g**. Application in Negishi cross-coupling reactions using palladium acetate and SPhos as catalyst provided the electron-rich and –deficient products **(*S*)-27a**–**c** in excellent yields between 93% and 96% yield (Table 24). Due to the decreased optical purity of the alkyl iodide **(*S*)-19g** (92% *ee*) the cross-coupling products also exhibit a lower enantiomeric excess of 92%.

Table 24: Cross-coupling reactions using the tyrosinol-based organozinc reagent **(*S*)-20g**.

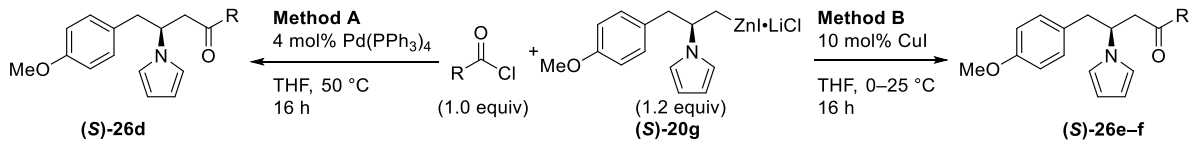


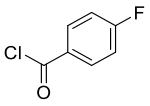
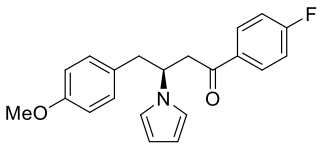
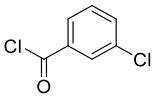
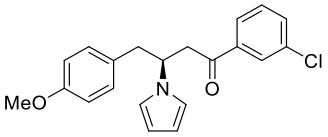
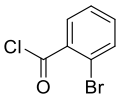
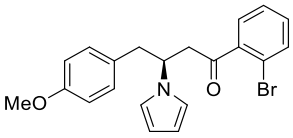
Entry	Electrophile	Product	*ee (%)*	Yield (%)[a]
1		 **(*S*)-27a**	92	95
2		 **(*S*)-27b**	92	96
3		 **(*S*)-27c**	92	93

[a] Yield of analytically pure isolated product.

Conducting acylation reactions with the tyrosinol-based reagent using the previously applied copper and palladium catalyzed methods provided the three different halogenated ketones **(*S*)-27d**–**f** in 75% to 84% yield (Table 25). As shown for the cross-coupling products, the acylation also displayed lower optical purities of 92% *ee* which was caused by the reduced optical purity of the starting *N*-pyrrolylalkyl-iodide.

Table 25: Cooper and palladium acylation reactions using the tyrosinol-based organozinc reagent **(*S*)-20g**.



Entry	Electrophile	Product	Method	*ee (%)*	Yield (%)[a]
1		 **(*S*)-27d**	A	92	78
2		 **(*S*)-27e**	B	92	84
3		 **(*S*)-27f**	B	92	75

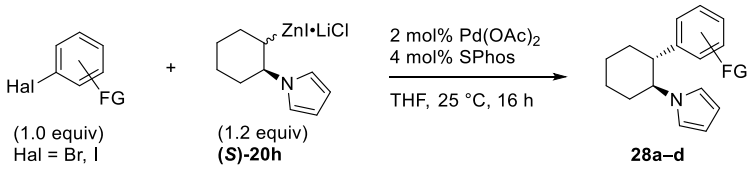
[a] Yield of analytically pure isolated product.

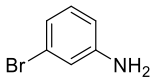
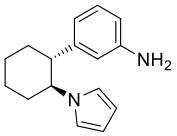
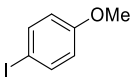
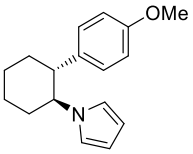
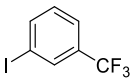
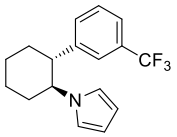
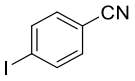
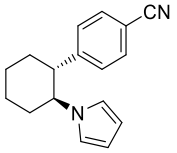
Based on 2-Aminocyclohexanol

In addition to the amino acid based organozinc reagents, the 2-aminocyclohexylzinc derivative was further investigated for cross-coupling reactions. During the zinc insertion of **(*S*,*R*)-19h**, the stereo-information is lost due to the radical insertion mechanism. Using a palladium catalyst with bulky-ligands, the selectivity for the following bond formation can be driven to the sterically less hindered product as already described in the literature.[98] Reaction of the organozinc reagent **(*S*)-20h** using the same procedure as for the previous experiments with different substituted electron-rich and -deficient electrophiles provided the cross-coupling products **28a**–**d** in high yields between 84% and 97% (Table 26). Remarkably, the reactions using the palladium-SPhos catalyst led selectively to the *trans*-product with a diastereomeric ratio of 99:1. The alignment of the pyrrole to the introduced aryl substituent was determined by evaluating the coupling-constants of the involved protons in the ^{1}H-NMR spectrum. The optical purity was determined *via* chiral HPLC and showed an enantiomeric excess of 99% for all products.

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

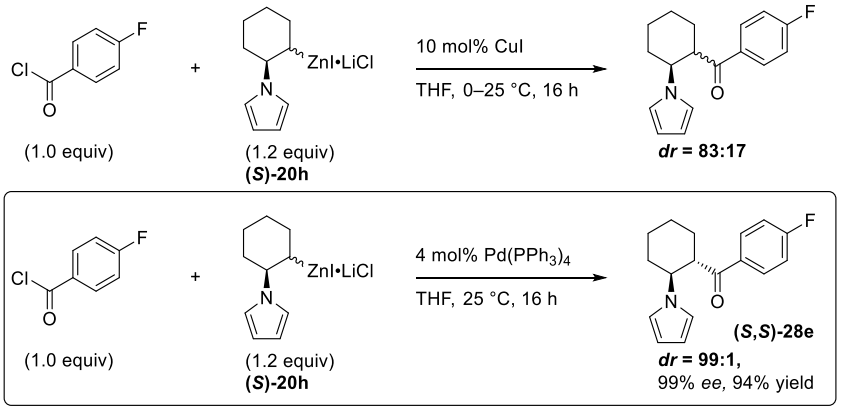
Table 26: Selective cross-coupling reactions using the reagent **(*S*)-20h** leading to the *trans*-products **28a**–**d**.



Entry	Electrophile	Product	*ee (%) / dr*	Yield (%)[a]
1		 **(R,*S*)-28a**	99 / 99:1	92
2		 **(*S,R*)-28b**	99 / 99:1	84
3		 **(*S,R*)-28c**	99 / 99:1	97
4		 **(R,*S*)-28d**	99 / 99:1	96

[a] Yield of analytically pure isolated product.

For the acylation reaction, the choice of the catalyst is crucial for the success of the reaction. Reaction of the organozinc reagent **(*S*)-20h** with 4-fluorobenzoyl chloride and substoichiometric amounts of cooper(I) iodide resulted in the desired product **28e**, but with a ratio of 83% *trans*- to 17% *cis*-isomer. Using catalytic amounts of the bulky $Pd(PPh_3)_4$ catalyst at room temperature, the reaction provided only the *trans*-isomer with a diastereomeric ratio of 99:1 and a yield of 94% (Scheme 32).

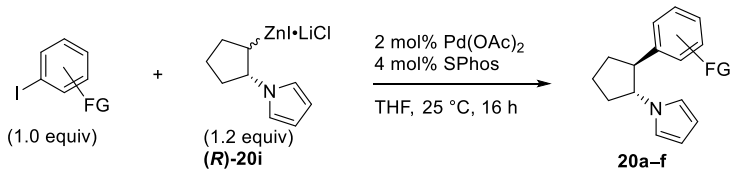


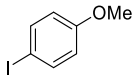
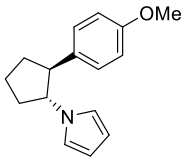
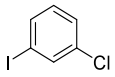
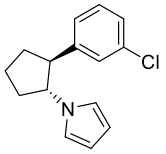
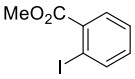
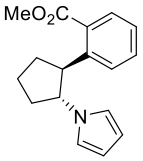
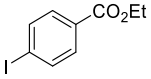
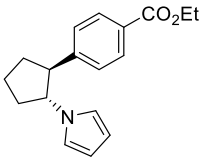
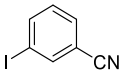
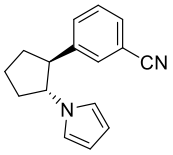
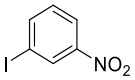
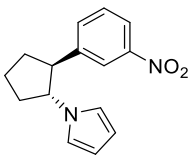
Scheme 32: Copper and palladium catalyzed acylation reaction of **(*S*)-20h** with 4-fluorobenzoyl chloride.

Based on 2-Aminocyclopentanol

Furthermore, the application of a 2-aminocyclopentanol derived reagent for Negishi cross-coupling reactions was investigated. As for the six-membered reagent, the zinc insertion induced a loss of the stereo-configuration of the iodine bearing carbon. Therefore, the palladium catalyst should predefine the position of the introduced aryl moiety.

Table 27: Cross-coupling reactions using a 2-aminocyclopentanol-based organozinc reagent **(*R*)-20i**.



Entry	Electrophile	Product	*ee (%) / dr*	Yield (%)[a]
1		 **(R,*S*)-29a**	99 / 99:1	79
2		 **(*R,S*)-29b**	99 / 99:1	93
3		 **(*S,R*)-29c**	99 / 98:2	85
4		 **(*S,R*)-29d**	99 / 99:1	84
5		 **(*S,R*)-29e**	99 / 99:1	85
6		 **(R,*S*)-29f**	99 / 99:1	75

[a] Yield of analytically pure isolated product.

Experiments showed that the reaction of the organozinc reagent **(*R*)-20i** with different electrophiles bearing electron-donating as well as –withdrawing functional groups using the standard method successfully provided the coupling-products **29a**–**f** in 75% to 93% yield. Interestingly, only one diastereomer was selectively formed and all products exhibit high *dr* and *ee* of 99%. Determining the configuration of the aryl ring *via* NMR analysis was difficult due to the low differences of the coupling constants in five-membered rings. Fortunately, a single-crystal X-ray structure analysis of product **(*S,R*)-29c** could be performed. The structure displayed in Figure 7 shows a *trans* relation between the pyrrole and the aryl residue. Conclusively, the *trans*-configuration in the cyclopentane derivatives is also induced by the catalyst and favored as already determined for the cyclohexane products.

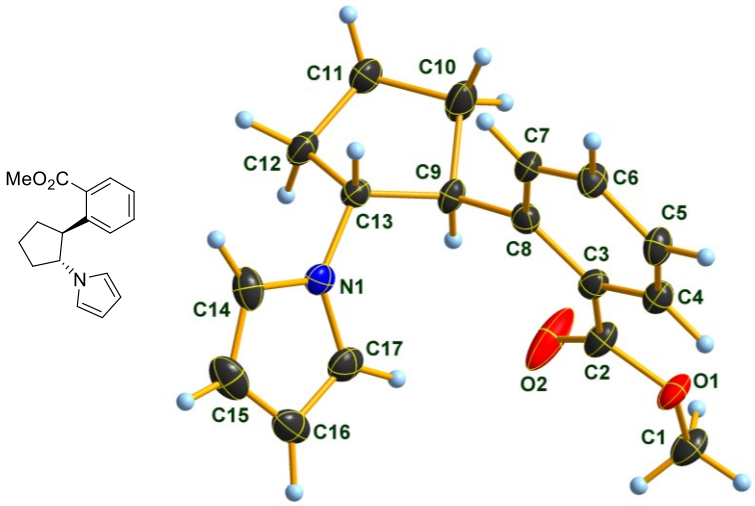


Figure 7: Molecular crystal structure of the cross-coupling product **(*S,R*)-29c** is showing the trans-configuration of pyrrole to the aryl residue. Thermal ellipsoids are drawn at 50% probability level.

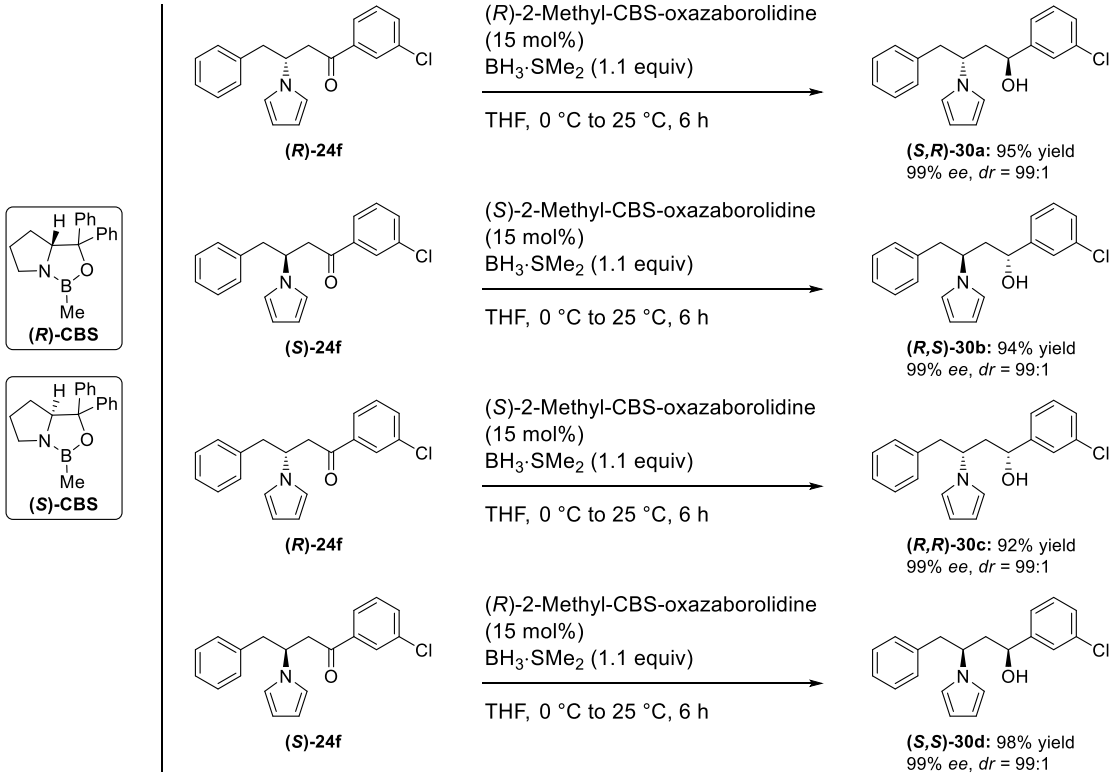
2.7 Selective CBS-Reduction of Chiral Pyrrole-containing Acylation Products

In order to demonstrate the versatility of the methodology, other options to further functionalize and utilize the chiral pyrrole-containing products were investigated. After acylation reaction, chiral ketones in 3-position were obtained which are interesting for selective reduction to generate chiral 1,3-substituted *N*-pyrrolyl-alcohols, which then can be converted to the corresponding amino alcohol. For the asymmetric reduction, the Corey-Bakshi-Shibata[99] protocol was applied. Both enantiomers of the phenylalaninol derived ketone **(*R*)-24f** and **(*S*)-24f** were used with a (*R*)- and (*S*)-CBS catalyst in order to exploit a pathway to all four possible stereoisomers.

For the experiments, the corresponding CBS catalyst was mixed with reducing agent borane dimethylsulfide at 0 °C and the selected ketone was added slowly. After conducting the four desired

[99] a) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986; b) E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, *53*, 2861.

reactions, the chiral alcohols **30a**–**d** were obtained in excellent yields of 92–98% with a diastereomeric ratio of 99:1 and high enantiomeric excess of 99% (Scheme 33).



Scheme 33: Selective CBS reduction of the acylation products **(*R*)-24f** and **(*R*)-24f** provide a pathway to obtain all four configurational isomers.

The absolute configuration of the alcohols was predicted with the CBS-model in first instance. To confirm this assumption, the alcohol **(*R*,*S*)-30d** which was prepared using the (*R*)-CBS catalyst, was esterificated. The (*R*)- as well as the (*S*)-Mosher acid (MTPA) were used to obtain two diastereomers for NMR analysis. With both NMR-spectra of the ester-diastereomers in hand, the chemical shifts were compared and evaluated as reported in the literature[100] (see Appendix). The analysis confirmed the absolute configuration. The conclusion for this system is that (*R*)-CBS catalyst provides the (*S*)-alcohol and *vice versa* (*S*)-CBS catalyst provides the (*R*)-alcohol.

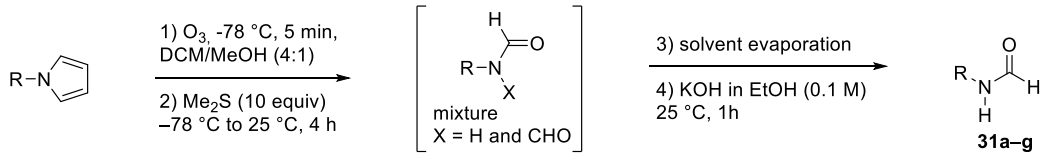
2.8 Deprotection of the Pyrrole-Group Using Ozonolysis

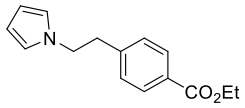
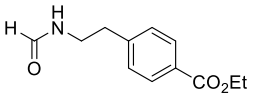
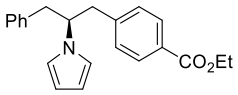
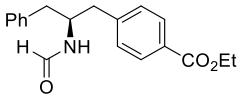
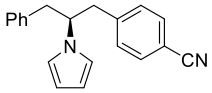
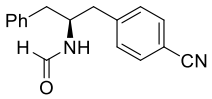
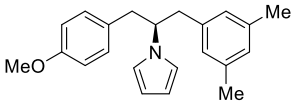
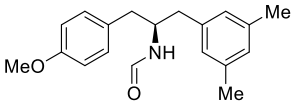
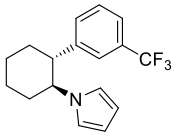
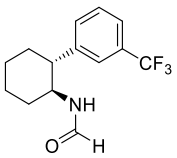
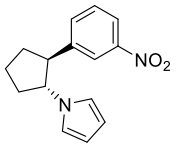
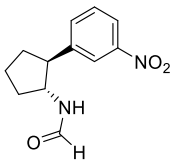
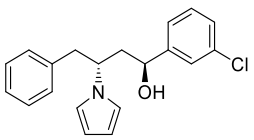
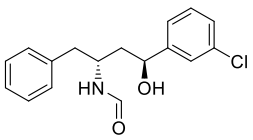
To complete this reaction sequence, it was desired to develop a deprotection procedure for the pyrrole group in the last step. An important aspect for the deprotection reaction was the preservation of the stereocenters. Harsh reaction conditions involving e.g. strong bases or high temperatures might lead to racemization and must be avoided. It was found, that ozonolysis was suitable for the removal of the pyrrole ring. Subsequent reductive work-up of the ozonide should provide the diformylamide product.

[100] a) T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451; b) J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17.

Experiments revealed that the reaction can be performed quickly by treating the pyrrole derivative with ozone-gas at –78 °C in a DCM/methanol mixture for a few minutes. After reductive treatment with methyl sulfide, a mixture of the formamide and the diformylamide was obtained. For obtaining solely the formamide, the mixture was stirred in a diluted potassium hydroxide solution in ethanol for 1 h.

Table 28: Pyrrole deprotection reactions of selected products *via* ozonolysis to the corresponding formamide.



Entry	Functionalized Pyrrole	Deprotection Product	Yield (%)[a]
1	 **21c**	 **31a**	71
2	 (***S***)-**24c**, 99% *ee*	 (***S***)-**31b**, 99% *ee*	74
3	 (***S***)-**24d**, 99% *ee*	 (***S***)-**31c**, 99% *ee*	65
4	 (***S***)-**27a**, 92% *ee*	 (***S***)-**31d**, 92% *ee*	84
5	 (***S,R***)-**28c**, *dr* 99:1, 99% *ee*	 (***S,R***)-**31e**, *dr* 99:1, 99% *ee*	74
6	 (**R,*S***)-**29f**, *dr* 99:1, 99% *ee*	 (***R,S)***-**31f**, *dr* 99:1, 99% *ee*	71
7	 (***S,R***)-**30a**, *dr* 99:1, 99% *ee*	 (***R,S***)-**31g**, *dr* 99:1, 99% *ee*	76

[a] Yield of analytically pure isolated product.

Selected cross-coupling products as well as a CBS-reduced alcohol have been examined for this deprotection strategy and the formamide derivatives **31a**–**g** were obtained in yields between 65% and

84% (Table 28). Remarkably, the stereocenters were not affected by this method and all diastereomeric ratios as well as the enantiomeric excesses were preserved. All formamide products were stable solids and easy to handle.

Two crystal structures could be obtained from single-crystals of the deprotected products. In Figure 8, the molecular structure of **(*S,R*)-31e** is displayed. It confirms the *trans*-configuration of the formamide group to the aryl moiety which was previously determined by NMR studies for the pyrrole derivative **(*S,R*)-28c.**

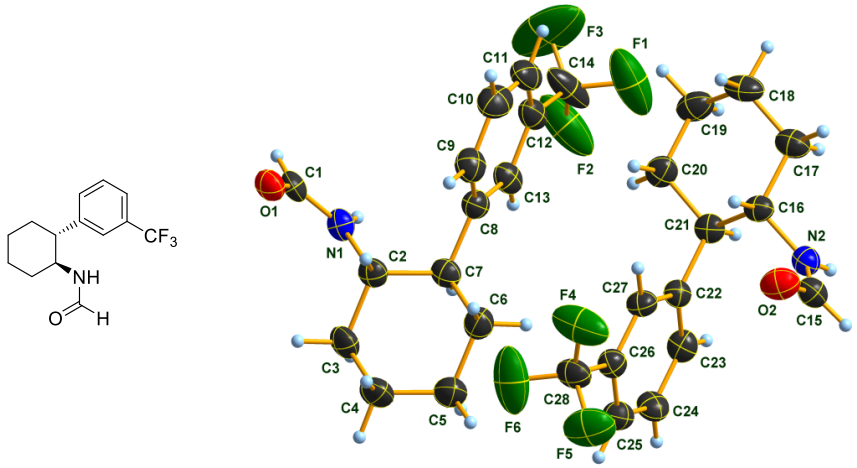


Figure 8: Molecular structure of the deprotected formamide **(*S,R*)-31e** in the crystal is showing the trans-configuration of the formamide and aryl residue. Thermal ellipsoids are drawn at 50% probability level. The fluorine atoms of both CF_3 groups are disordered.

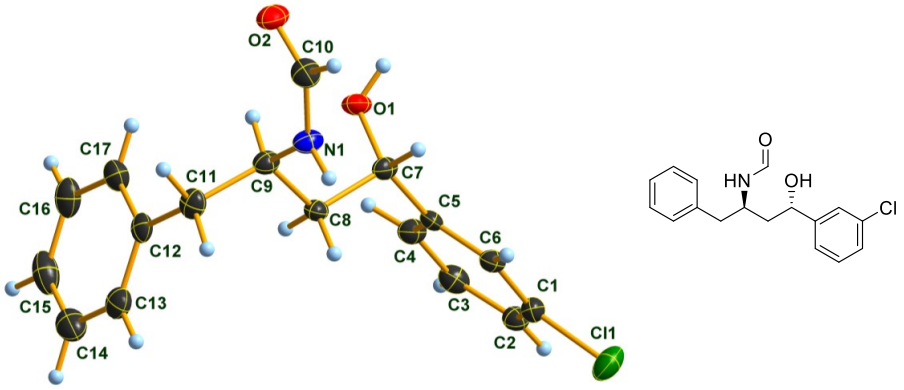


Figure 9: Molecular structure of the deprotected formamide **(*R,S*)-31g** in the crystal is showing the anti-configuration of the formamide and alcohol. Thermal ellipsoids are drawn at 50% probability level.

Figure 9 shows the molecular structure of the deprotected CBS-product **(*R,S*)-31g**. The assumptions made by the Mosher's ester analysis using NMR-spectroscopy for the correlation of the CBS-catalyst to the configuration of the alcohol was also confirmed by this structure, since the *anti*-product was predicted.

3 Summary

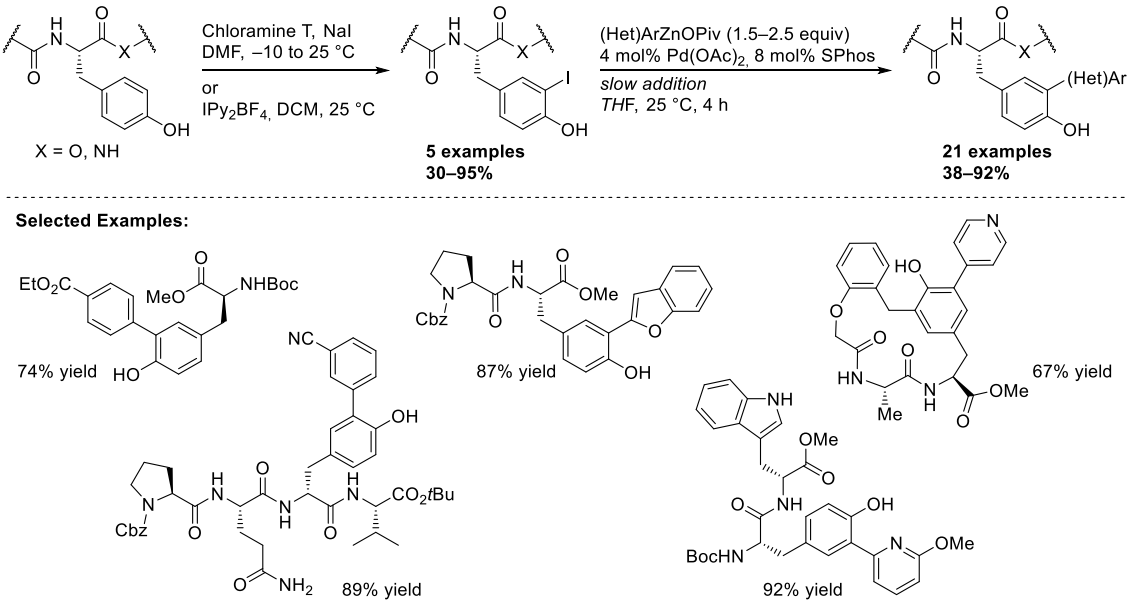
In this thesis, two major subjects were investigated and discussed.

First, the late-stage functionalization of peptides and cyclopeptides was investigated. For this purpose, tyrosine-based peptides were selectively iodinated and subsequently used in Negishi cross-coupling experiments. The use of functionalized aryl- and heteroarylzinc pivalates in presence of a palladium catalyst furnished sidechain arylated peptides tolerating various sensitive and acidic functional groups. Furthermore, iodophenylalanine-containing cyclopeptides were modified *via* cross-couplings of isomeric pyridylzinc pivalates to obtain cyclopeptides with differently linked pyridyl-moieties.

Secondly, a new method was developed for the preparation of chiral β-aminoalkylzinc reagents for the synthesis of functionalized amino-derivatives. Starting from chiral amino alcohols, the amino functions were converted into 1*H*-pyrroles as protecting groups and subsequently the alcohols were converted to the corresponding iodides. After oxidative insertion of zinc powder into these pyrrole-protected alkyl iodides, the resulting organozinc reagents were applied in transition-metal catalyzed Negishi cross-couplings as well as acylation reactions.

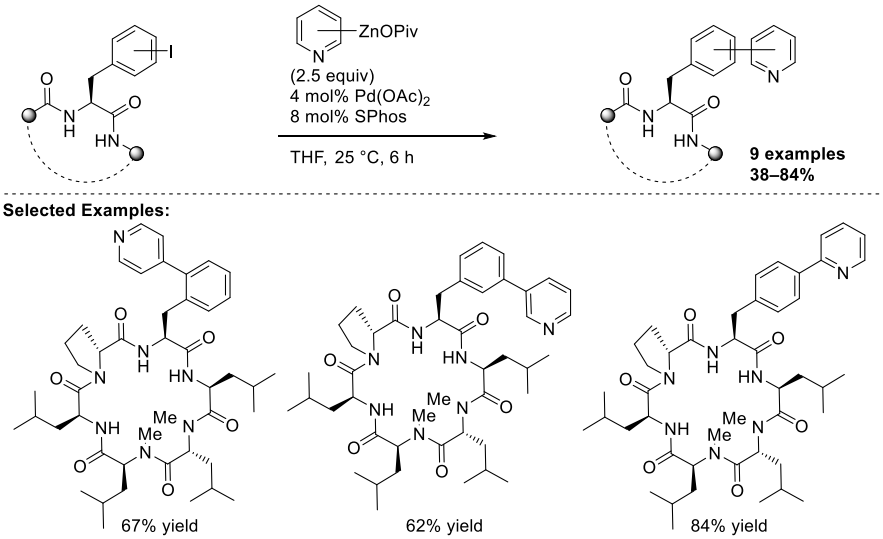
3.1 Late-Stage Functionalization of Peptides and Cyclopeptides using Organozinc Pivalates

A range of tyrosine-containing oligopeptides was selectively iodinated in *ortho*-position to the phenolic hydroxyl group of the tyrosine sidechain using Chloramine T and NaI. Cross-coupling reactions were successfully performed with electron-rich as well as electron-poor aryl- and heteroarylzinc pivalates in the presence of a catalytic system consisting of $Pd(OAc)_2$ and SPhos. Despite a slight excess of organozinc reagent, this protocol showed a high tolerance towards functional groups and provided the functionalized peptides in good yields (Scheme 34).



Scheme 34: Summary of the late-stage functionalization of tyrosine-based peptides.

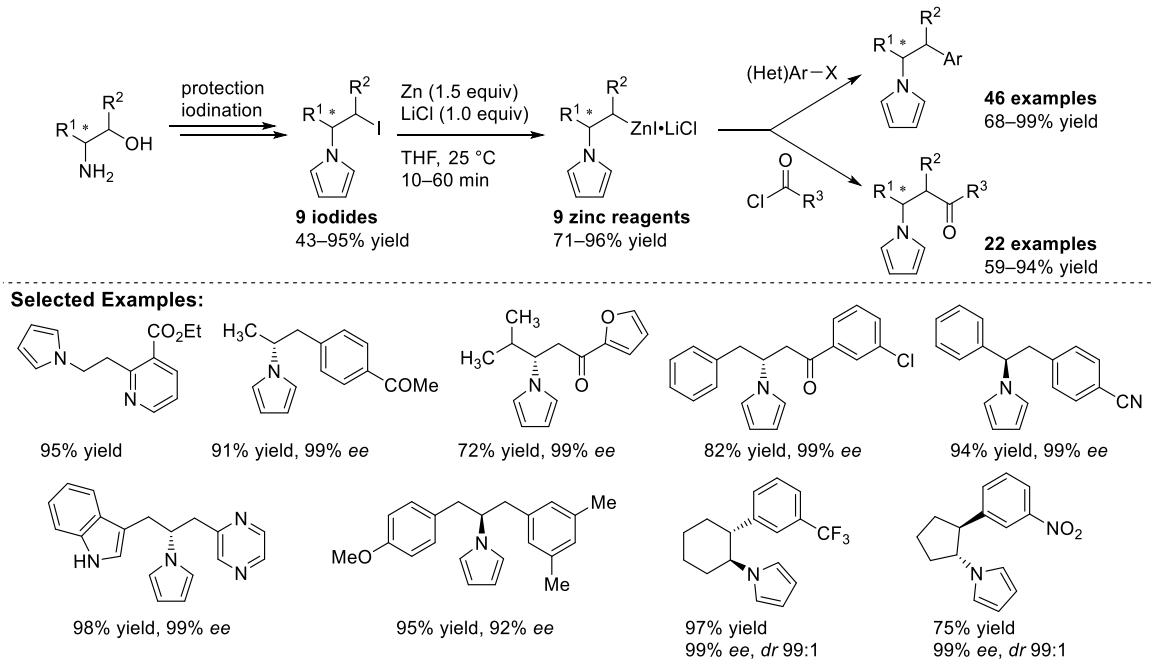
Additionally, the high practicality of this late-stage functionalization was demonstrated by applying it to cyclic hexamer-peptides. Three isomeric cyclopeptides containing *ortho*-, *meta*- and *para*-iodinated phenylalanine sidechains were employed in cross-coupling reactions with 2-, 3- and 4-pyridylzinc pivalates and nine different pyridyl-substituted peptides were successfully obtained (Scheme 35). As a part of a cooperation with *Novartis Pharma AG*, the biophysical properties of these modified compounds were investigated and evaluated regarding solubility as well as cell-membrane permeability.



Scheme 35: Summary of the late-stage functionalization of iodophenylalanine-containing cyclopeptides.

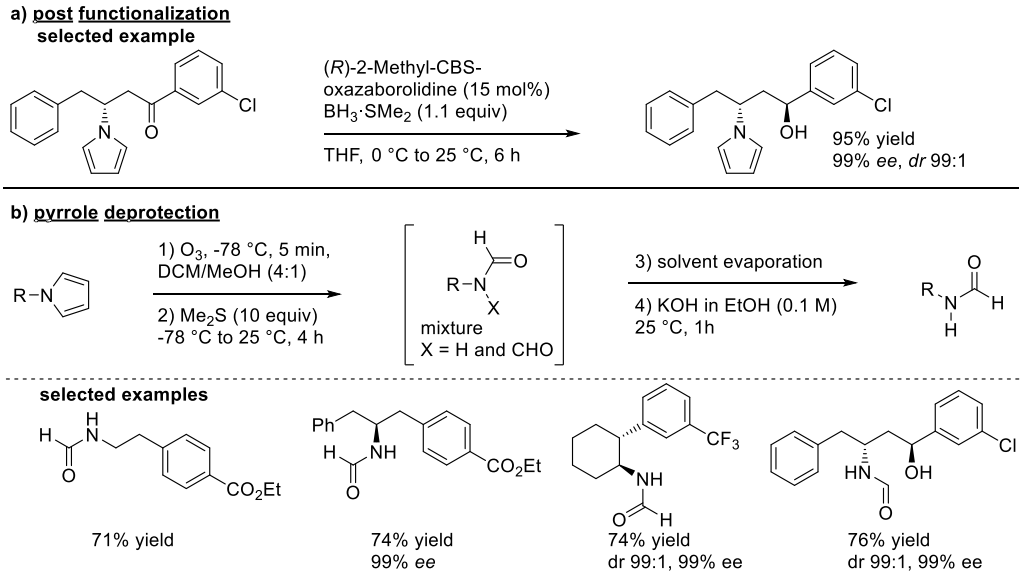
3.2 Pyrrole Protected 2-Aminoalkylzinc Reagents for the Enantioselective Synthesis of Amino Derivatives

Chiral amino-alcohols, mostly derived from natural and unnatural amino acids, were used for the syntheses of chiral organozinc reagents. After pyrrole-protection of the amino-groups and conversion of the alcohols into the corresponding alkyl iodides, various organozinc reagents containing different alkyl, aryl- and heteroaryl-moieties were prepared *via* oxidative zinc insertion. The application of these reagents in Negishi cross-couplings was investigated. Differently substituted electron-poor and -rich electrophiles bearing sensitive groups were successfully deployed in coupling reactions using $Pd(OAc)_2$ and SPhos as catalyst and a broad range of functionalized chiral pyrrole derivatives were obtained. Furthermore, palladium and copper catalyzed acylation experiments were conducted providing various chiral aryl-, heteroaryl- and alkyl-ketones in good yields. The application of β-*N*-pyrrolyl cyclopentyl- and cyclohexylzinc reagents exclusively provided the *trans*-substituted products in an excellent diastereoselectivity. All cross-coupling and acylation products were obtained with full retention of the stereocenters and thus exhibited high optical purity (Scheme 36).



Scheme 36: Summary for the preparation of the 2-aminoalkylzinc reagents and their application.

Additionally, a post-functionalization of acylation products using the asymmetric CBS-reduction was performed to achieve the synthesis of chiral 1,3-amino alcohol derivatives. Thus, two enantiomerically pure ketones were reduced in presence of either the (*R*)- or (*S*)-CBS catalyst resulting in all four possible configurational isomers in excellent yield and high optical purity (Scheme 37a).



Scheme 37: Summary of the post-functionalization and pyrrole deprotection.

Finally, a suitable deprotection method was developed to convert the pyrrole into a viable formamide. Therefore, selected cross-coupling and post-functionalized products were treated with ozone at low temperatures. After reductive and subsequent mild basic work-up, the formamide products were obtained without decay of functional groups or racemization of stereocenters in moderate yields (Scheme 37b).

C. EXPERIMENTAL PART

1 General Considerations

All reactions including organometallic compounds have been carried out using standard *Schlenk*-techniques in flame-dried glassware equipped with rubber septum and magnetic stirring bars under argon. Syringes for transferring anhydrous solvents or reagents were purged with argon prior to use. Yields are referred to isolated yields of compounds with a purity >95% as determined by ^{1}H-NMR (25 °C) or capillary GC.

1.1 Solvents

For the preparation of anhydrous solvents, the crude solvents were first purified by distillation and then dried according to standard methods by distillation from drying agents as stated below and were stored under argon. Non-anhydrous solvents were obtained from commercial sources and used without further purification.

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

DCM was continuously refluxed and freshly distilled from CaH_2 under nitrogen.

Solvents for column chromatography were distilled prior to use.

1.2 Reagents

All reagents and starting materials were obtained from commercial sources and used without further purification unless otherwise stated.

***i*PrMgCl•LiCl** was prepared by careful addition of *i*PrCl (78.5 g, 91.3 mL, 1.00 mol, 1.00 equiv) to a suspension of Mg (26.74 g, 1.10 mol, 1.10 equiv) and LiCl (46.63 g, 1.10 mol, 1.10 equiv) in dry THF (900 mL). The reaction mixture was stirred for 12 h and afterwards the floating particles were filtered. The solution was cannulated into a flame-dried and argon flushed *Schlenk*-flask and the concentration of the active species was determined by titration against I_2 in THF.[101]

Zn(OPiv)$_2$ was prepared by successive addition of zinc oxide (4.07 g, 50 mmol) to a solution of pivalic acid (11.3 g,110 mmol) in toluene (250 mL) and refluxing in a Dean-Stark apparatus for 16 h. The solvent was removed by rotary evaporation and the zinc pivalates then dried under high vacuum.[102]

***n*BuLi** solution in hexane was purchased from Albemarle and the concentration was determined by titration against *N*-benzylbenzamide in THF at −20 °C.[103]

***n*BuMgCl** solution in THF was purchased from *Albemarle* (Frankfurt, Germany) and the concentration was determined by titration with iodine in the presence of LiCl in THF at 0 °C.[101]

[101] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.
[102] M. Ellwart, Y.H. Chen, C.P. Tüllmann, V. Malakov, P. Knochel, *Org. Synth.* **2018**, *95*, 127.
[103] A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281.

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

1.3 Chromatography

Flash column chromatography (FCC) was performed using SiO_2 60 (0.040–0.063 mm, 230–400 mesh ASTM) from *Merck*. Thin layer chromatography (TLC) was performed using aluminum plates covered with SiO_2 (*Merck* 60, F–254). Spots were visualized by UV light irradiation and/or by staining of the TLC plate with one of the solutions below, followed by heating with a heat gun.
$KMnO_4$ (0.3 g), K_2CO_3 (20 g) and KOH (0.3 g) in water (300 mL).
$Ce(SO_4)_2$ (5.0 g), $(NH_4)_6Mo_7O_{24}•4H_2O$ (25 g) and conc. H_2SO_4 (50 mL) in water (450 mL).
Ninhydrin (1.5 g) and acetic acid (3.0 mL) in ethanol (100 mL).

1.4 Preparative RP-HPLC

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

1.5 Analytical data

NMR spectra were recorded on *Bruker* ARX 200, AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in parts-per-million (ppm) relative to the residual solvent peak: $CDCl_3$ (δ_H: 7.26; δ_C: 77.16) or d_6-DMSO (δ_H: 2.50; δ_C: 39.52). For the observation of the observed signal multiplicities, the following abbreviations and combinations thereof were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), m (multiplet) and br (broad). If not otherwise noted, the coupling constants given are either H-H or H-F coupling constants for proton signals and C-F coupling constants for carbon signals. To overcome the rotation barrier of peptide-rotamers, spectra were measured in d_6-DMSO at 80 °C to receive the one averaged set of signals.[104]
Melting points are uncorrected and were measured on a *Büchi* B.540 apparatus.
Infrared spectra were recorded from 4000–650 cm^{-1} on a Perkin Elmer Spectrum BX-59343 instrument. For detection a Smiths Detection DuraSampl IR II Diamond ATR sensor was used. The main absorption peaks are reported in cm^{-1}.

[104] D. X. Hu, P. Grice, S. V. Ley, *J. Org. Chem.* **2012**, *77*, 5198.

Gas chromatography (GC) was performed with instruments of the type Hewlett-Packard 6850 Series II, using a column of the type HP 5 (Hewlett-Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm, film thickness 0.25 µm). The detection was accomplished using a flame ionization detector.

High resolution mass spectra (HRMS) were recorded on a Finnigan MAT 95Q or Finnigan MAT 90 instrument for electron impact ionization (EI). Electron spray ionization (ESI) high resolution mass spectra were measured on a *Thermo Finnigan* LTQ FT Ultra High Performance Mass Spectrometer with a resolution of 100.000 at m/z 400. The spray-capillary voltage of the IonMax ESI-unit is set to 4 kV while the heating-capillary temperature is set to 250 °C.

For the combination of **gas chromatography with mass spectroscopic** detection, a GC–MS of the type *Hewlett-Packard* 6890/MSD 5793 networking was used (column: HP 5–MS, *Hewlett–Packard*; 5% phenylmethylpolysiloxane; length: 15 m, diameter: 0.25 mm, film thickness: 0.25 µm).

LCMS. For reaction/product control and purity determination of polar molecules and peptides, an analytical *Agilent Technologies* 1260 Infinity LC with a binary pump (acetonitrile/water, additive: TFA) and a *Kinetix* EVO C18 5 µm column (length: 150 mm, diameter: 4.6 mm) was used. LC-chromatograms were recorded with a DAD detector (210 nm wavelength, 40 nm bandwidth, ref-wavelength 400 nm, ref-bandwidth 100 nm) combined with a low-mass *Agilent Technologies* 6120 Quadrupole Mass Spectrometer.

Enantiomeric Excess (*ee*) of chiral products were determined *via* chiral HPLC analysis on a *Shimadzu Prominence* 20A HPLC system. For developing a chiral resolution method, different chiral normal phase columns (*Daicel Chemical Industries* Chiralcel OD-H, OJ, OB-H or Chiralpak AS-H, ADH) were tested with *n*-heptane and *i*PrOH as mobile phase (isocratic) using a racemic mixture of the compound. If racemic resolution via chiral hplc was not successful, a chiral GC was used for analysis. Measurements were made on an *Agilent HP* 6890 Series gas chromatograph using a *Varion* capillary column (CP-Chiralsil Dex-CB 25 m, 0.25 m, 0.25 µm) with an average velocity of 45 cm/s.

The **diastereomeric ratio (*dr*)** was determined either by NMR, GC or HPLC analysis.

Specific Rotation $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ values of chiral products were measured in $CHCl_3$ at 20 °C using a wavelength λ = 589 nm and a 1 dm cuvette on a *Anton Paar* MCP *200* instrument. The sample concentration was 0.01 g/mL and the values are reported in °·mL·dm^{-1}·g^{-1}.

1.6 Single Crystal X-Ray Diffraction Studies

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

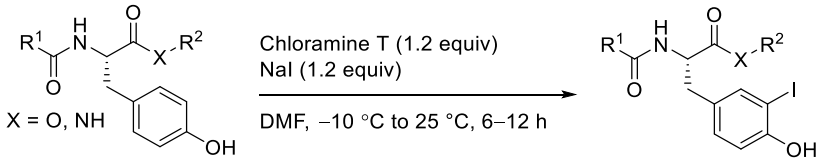
Data collection and data reduction were performed with the CrysAlisPro software.[105] Absorption correction using the multiscan method[105] was applied. The structures were solved with SHELXS-97,[106] refined with SHELXL-97[107] and finally checked using PLATON.[108] The single crystal structures are shown in DIAMOND[109] representation.

[105] Program package CrysAlisPro 1.171.39.46e (Rigaku OD, 2018).
[106] Sheldrick, G. M. SHELXS-97: *Program for Crystal Structure Solution* **1997** University of Göttingen, Germany.
[107] Sheldrick, G. M. SHELXL-97: *Program for the Refinement of Crystal Structures **1997*** University of Göttingen, Germany.
[108] Spek, A. L. PLATON: *A Multipurpose Crystallographic Tool* **1999** Utrecht University, Utrecht, The Netherlands.
[109] DIAMOND, Crystal Impact GbR., Version 3.2i.

2 Late-Stage Functionalization of Peptides and Cyclopeptides using Organozinc Reagents

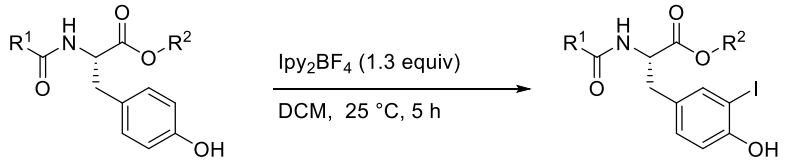
2.1 Typical Procedures (TP1–8)

Typical procedure for the iodination of tyrosine-based peptides (TP1):



A 100 mL round bottom flask, equipped with a magnetic stirring bar and rubber septum, was charged with the corresponding tyrosine containing peptide of type **2** (2.00 mmol, 1.00 equiv), sodium iodide (360 mg, 2.40 mmol, 1.20 equiv) and DMF (10 mL). Chloramine-T trihydrate[110] (676 mg, 2.40 mmol, 1.20 mmol) was dissolved in DMF (4.8 mL) and then added dropwise *via* syringe pump over 2 h at −10 °C. Afterwards, the reaction mixture was stirred additional 3 h at 0 °C before slowly warming up to 25 °C within 1–7 h. The yellow reaction mixture was quenched with water (50 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, DCM/MeOH) and following reversed-phase HPLC-chromatography (MeCN/H_2O).

Typical procedure for the iodination of tyrosine-based peptides (TP2):



A 100 mL round bottom flask equipped with a magnetic stirring bar and rubber septum, was charged with the corresponding tyrosine-based peptide **2e** (2.00 mmol, 1.00 equiv) and freshly distilled dichloromethane (16 mL). Bis(pyridine)iodonium tetrafluoroborate[111] (Ipy_2BF_4; 967 mg, 2.60 mmol, 1.30 equiv) was dissolved in freshly distilled DCM (7.8 mL) and added to the flask over 1 h via syringe pump After additional 4 h of stirring, water (50 mL) was added and the reaction mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *i*hexanes/ethyl acetate or DCM/MeOH) and following reversed-phase HPLC-chromatography (MeCN/H_2O).

[110] T. Kometani, D. S. Watt, T. Ji, *Tetrahedron Lett.* **1985**, *26*, 2043.
[111] G. Espuña, G. Arsequell, G. Valencia, J. Barluenga, J. M. Alvarez-Gutiérrez, A. Ballesteros, J. M. González, *Angew. Chem. Int. Ed.* **2003**, *43*, 325.

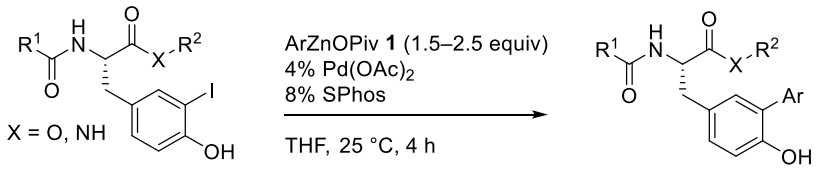
Typical procedure for the preparation of arylzinc pivalates using halogen-metal exchange (TP3)

A dry and argon-flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a rubber septum, was charged with the corresponding aryl halide (1.00 equiv) and freshly distilled THF. The reaction mixture was cooled down to –20 °C before *i*PrMgCl·LiCl (solution in THF, 1.10 equiv) was added dropwise. The solution was stirred at this temperature for a given time until full conversion of the starting material was observed by GC-analysis of hydrolyzed and iodolyzed aliquots. Afterwards, the magnesium species was transmetalated with $Zn(OPiv)_2$ (1.20 equiv) and the resulting arylzinc pivalate solution was titrated with iodine in THF.[112]

Typical procedure for the preparation of arylzinc pivalates using oxidative insertion and transmetalation (TP4)

To a dry and argon-flushed *Schlenk*-tube, fitted with a magnetic stirring bar and a rubber septum, LiCl (1.20 equiv) was added and dried at ca. 450 °C for 5 min under high vacuum using a heat gun. Afterwards, magnesium turnings (1.20 equiv) were added and the solids were suspended with freshly distilled THF. The magnesium turnings were activated by adding trimethylsilyl chloride (TMSCl; 5 mol%) and 1,2-dibromoethane (DBE; 5 mol%) and heating for a short period until the gas evolution stopped. The corresponding aryl halide (1.00 equiv) was added dropwise at 25 °C. and the reaction progress was monitored by GC-analysis of hydrolyzed and iodolyzed aliquots. After full conversion of the starting material, the suspension was filtered with a syringe-filter and transferred in another dry and argon flushed *Schlenk*-tube. $Zn(OPiv)_2$ (1.20 equiv) was added at 0 °C and the suspension was stirred until a clear solution was formed. The concentration was determined by titration with iodine in THF.

Typical procedure for the Negishi cross-coupling reaction of iodotyrosine containing peptides (TP5):



A flame-dried and argon-flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a rubber septum, was charged with $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos[113] (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL). After 10 min of stirring, the corresponding iodotyrosine-peptide of type **3** (0.30 mmol, 1.0 equiv) was added. The arylzinc pivalate solution of type **1** in THF (1.50–2.50 equiv) was added gradually *via* syringe-pump over a period of 1 h. After complete addition, the reaction mixture was stirred for further 3 h. Afterwards, the reaction mixture was quenched

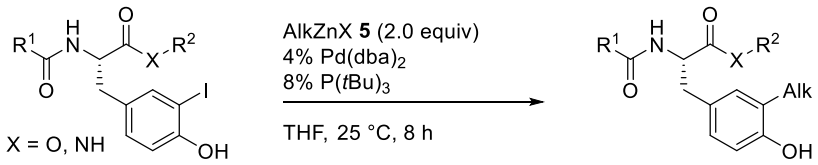
[112] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.
[113] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.

with a sat. aq. NH_4Cl solution (3 mL). The reaction mixture extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *i*hexanes/ethyl acetate), followed by preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$).

Typical procedure for the preparation of alkylzinc halides using an oxidative insertion of zinc dust (TP6)

To a dry and argon-flushed *Schlenk*-tube, fitted with a magnetic stirring bar and a rubber septum, LiCl (1.00–1.50 equiv) was added and dried at ca. 450 °C for 5 min under high vacuum using a heat gun. Afterwards, zinc dust (1.40–2.50 equiv) was added and the solids were suspended in freshly distilled THF. Zinc dust was activated by adding trimethylsilyl chloride (TMSCl; 0.05 equiv) and 1,2-dibromoethane (DBE; 0.05 equiv) and heating for a short period until the gas evolution stopped. The corresponding alkyl halide (1.00 equiv) was added dropwise at 25 °C and reaction progress was monitored by GC-analysis of hydrolyzed and iodolyzed aliquots. After full conversion of the starting material, the suspension was filtered with a syringe-filter and transferred in another dry and argon flushed *Schlenk*-tube. The concentration was determined by titration with iodine in THF.

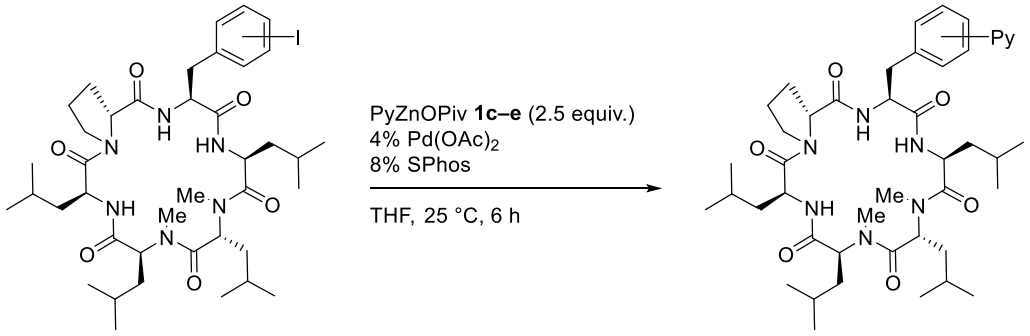
Typical procedure for Negishi cross-coupling reactions of iodotyrosine containing peptides with alkylzinc halides (TP7):



A flame-dried and argon-flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a rubber septum, was charged with $Pd(dba)_2$ (6.90 mg, 12.0 µmol, 4.00 mol%), P*t*Bu$_3$[114] (0.03 mL, 1.00 M in toluene, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL). After 10 min stirring, the corresponding iodotyrosine-peptide of type **3** (0.30 mmol, 1.0 equiv) was added. The corresponding alkylzinc halide solution of type **5** in THF (2.00 equiv) was added gradually via syringe-pump over a period of 1 h. After complete addition, the reaction mixture was stirred for further 7 h. Afterwards, the reaction mixture was quenched with sat. aq. NH_4Cl solution (3 mL). The reaction mixture extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *i*hexanes/ethyl acetate) and following reversed-phase HPLC-chromatography ($MeCN/H_2O$).

[114] C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719.

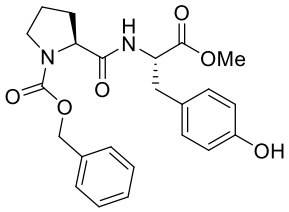
Typical procedure for the Negishi cross-coupling reaction of macrocyclic iodophenylalanine containing peptides (TP8):



A flame-dried and argon-flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a rubber septum, was charged with $Pd(OAc)_2$ (0.72 mg, 3.20 µmol, 4.00 mol%), SPhos[115] (2.63 mg, 6.40 µmol, 8.00 mol%) and freshly distilled THF (0.8 mL). After 10 min stirring, the corresponding macrocyclic iodo-peptide (68.1 mg, 0.08 mmol, 1.0 equiv) was added. The pyridylzinc pivalate solution of type **1** in THF (2.5 equiv) was added gradually *via* syringe-pump over a period of 1 h. After complete addition, the reaction mixture was stirred further for 5 h. Afterwards, the reaction was quenched with a sat. aq. NH_4Cl solution (1 mL). The reaction mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was flushed through a short silica column (10 cm) with MeCN and the crude product was purified *via* reversed-phase HPLC-chromatography.

2.2 Characterization of the Tyrosine containing Peptides

Cbz-*L*-Pro-*L*-Tyr-OMe (2b)



Compound **2b** was obtained from the Novartis archive.[116]

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm): δ = 8.93 (s, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.40 – 7.25 (m, 5H), 7.01 – 6.93 (m, 2H), 6.69 – 6.63 (m, 2H), 5.10 – 4.95 (m, 2H), 4.46 (td, *J* =7.9, 6.1 Hz, 1H), 4.29 – 4.23 (m, 1H), 3.57 (s, 3H), 3.41 (qt, *J* = 10.2, 6.9 Hz, 2H), 2.87 (qd, *J* = 14.0, 7.1 Hz, 2H), 2.16 – 2.01 (m, 1H), 1.85 – 1.72 (m, 3H).

[115] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.
[116] M. Cortes-Clerget, J.-Y. Berthon, I. Krolikiewicz-Renimel, L. Chaisemartin, B. H. Lipshutz, *Green Chem.* **2017**, *19*, 4263.

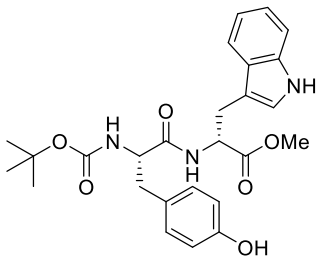
^{13}C-NMR (101 MHz, 80 °C, DMSO-d$_6$, ppm): δ = 171.5, 171.4, 155.7, 153.7, 136.7, 129.4, 127.8, 127.2, 126.8, 126.8, 114.7, 65.6, 59.2, 53.3, 51.2, 46.4, 35.7, 29.9, 22.8.l

HRMS (ESI): m/z calc. for [M+Na; $C_{23}H_{26}N_2NaO_6^+$]: 449.1689; found: 449.1683; m/z calc. for [M+H; $C_{23}H_{27}N_2O_6^+$]: 427.1864; found: 427.1867; calc. for [M-H; $C_{23}H_{25}N_2O_6^-$]: 425.1718; found: 425.1730.

IR (Diamond-ATR, neat): $\nu =$ 3311 (w), 2952 (w), 2360 (w), 2340 (w), 1742 (m), 1693 (s), 1647 (vs), 1614 (m), 1515 (vs), 1411 (s), 1354 (s), 1262 (s), 1210 (s), 1173 (s), 1113 (s), 1028 (w), 985 (m), 826 (m), 766 (m), 744 (m), 697 (m).

M.p. 74.7 °C.

Boc-*L*-Tyr-*D*-Trp-OMe (2c)



Compound **2c** was obtained from the Novartis archive.[117]

^{1}H-NMR (400 MHz, 80 °C, DMSO-d$_6$, ppm): δ = 10.67 (s, 1H), 8.84 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.34 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.07 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.00 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.64 – 6.56 (m, 2H), 6.27 (s, 1H), 4.59 (td, *J* = 7.7, 6.0 Hz, 1H), 4.16 (td, *J* = 8.8, 4.8 Hz, 1H), 3.61 (s, 2H), 3.17 (dd, *J* = 14.6, 5.9 Hz, 1H), 3.07 (dd, *J* = 14.7, 7.7 Hz, 1H), 2.77 (dd, *J* = 13.9, 4.8 Hz, 1H), 2.58 (dd, *J* = 14.0, 9.0 Hz, 1H), 1.32 (s, 9H).

^{13}C-NMR (101 MHz, 80 °C, DMSO-d$_6$, ppm): δ = 171.6, 171.1, 155.4, 154.5, 135.9, 129.6, 127.5, 126.8, 123.3, 120.6, 118.1, 117.6, 114.5, 111.0, 109.0, 77.8, 55.5, 52.7, 51.2, 36.6, 27.7, 27.0.

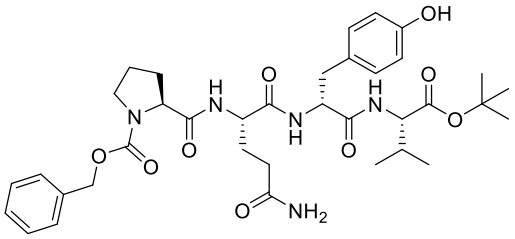
HRMS (ESI): m/z calc. for [M+Na; $C_{26}H_{31}N_3NaO_6^+$]: 504.2111; found: 504.2106; m/z calc. for [M+H; $C_{26}H_{32}N_3O_6^+$]: 482.2286; found: 482.2286; calc. for [M-H; $C_{26}H_{30}N_3O_6^-$]: 480.2140; found: 480.2149.

IR (Diamond-ATR, neat): $\nu =$ 3340 (w), 2964 (vw), 2359 (w), 2332 (w), 1733 (w), 1684 (m), 1655 (vs), 1539 (m), 1517 (s), 1457 (w), 1437 (m), 1366 (w), 1307 (w), 1270 (m), 1242 (m), 1226 (m), 1174 (m), 1166 (s), 1049 (w), 1026 (w), 1012 (w), 825 (w), 811 (w), 745 (m).

M.p. 131.4 °C.

[117] C. J. Chapman, A. Matsuno, C. G. Frost, M. C. Willis, *Chem. Commun.* **2007**, 3903.

Cbz-*L*-Pro-*L*-Glu-*D*-Tyr-*L*-Val-O*t*Bu (2d)



Compound **2d** was obtained from the Novartis archive.[118]

^{1}H-NMR (400 MHz, 80 °C, DMSO-d$_6$, ppm): δ = 8.86 (s, 1H), 7.92 (s, 1H), 7.72 (dd, *J* = 25.3, 8.3 Hz, 2H), 7.41 – 7.24 (m, 5H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.94 – 6.33 (m, 2H), 6.68 – 6.60 (m, 2H), 5.18 – 4.98 (m, 2H), 4.56 (q, *J* = 8.6 Hz, 1H), 4.23 (ddd, *J* = 22.4, 10.9, 5.6 Hz, 2H), 4.05 (dd, *J* = 8.3, 5.9 Hz, 1H), 3.44 (h, *J* = 10.7, 10.1 Hz, 3H), 2.93 (dd, *J* = 13.9, 5.3 Hz, 1H), 2.73 (dd, *J* = 13.9, 8.9 Hz, 1H), 2.18 – 1.93 (m, 3H), 1.92 – 1.75 (m, 4H), 1.68 (dq, *J* = 14.6, 7.6 Hz, 1H), 1.42 (s, 9H), 0.84 (dd, *J* = 6.8, 4.5 Hz, 6H).

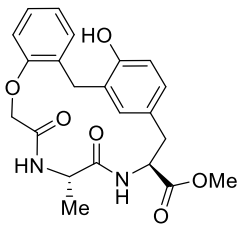
^{13}C-NMR (101 MHz, 80 °C, DMSO-d$_6$, ppm): δ = 173.4, 171.5, 170.7, 170.6, 169.8, 155.5, 153.8, 136.7, 129.6, 127.9, 127.3, 127.2, 127.1, 126.9, 126.8, 114.6, 80.3, 65.6, 59.3, 57.7, 53.9, 52.3, 46.4, 36.8, 31.1, 29.7, 27.4, 23.1, 18.4, 17.6.

HRMS (ESI): m/z calc. for [M+Na; $C_{36}H_{49}N_5NaO_9^+$]: 718.3428; found: 718.3422; m/z calc. for [M+H; $C_{36}H_{50}N_5O_9^+$]: 696.3603; found: 696.3607.

IR (Diamond-ATR, neat): ν = 3287 (w), 2963 (w), 2360 (w), 2334 (w), 1732 (w), 1638 (vs), 1540 (m), 1517 (m), 1448 (m), 1436 (m), 1358 (m), 1274 (m), 1226 (m), 1211 (w), 1171 (m), 1140 (m), 695 (w).

M.p. 160.4 °C.

Methyl (8*S*,11*S*)-1^6-hydroxy-8-methyl-6,9-dioxo-4-oxa-7,10-diaza-1(1,3),3(1,2)-dibenzenacyclododecaphane-11-carboxylate (2e)



Compound **2e** was obtained from the Novartis archive.

^{1}H-NMR (599 MHz, DMSO-d$_6$, ppm): δ = 9.31 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 7.4 Hz, 1.8, 1H), 7.22 – 7.17 (m, 2H), 7.00 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.91 (td, *J* = 7.4, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 4.68 (d, *J* = 14.3 Hz, 1H), 4.52 (d,

[118] M. Amblard, J.-A. Fehrentz, J. Martinez, G. Subra, *Mol. Biotechnol.* **2006**, *33*, 239.

J = 14.2 Hz, 1H), 4.45 (dq, *J* = 8.6, 6.9 Hz, 1H), 4.37 (ddd, *J* = 11.4, 8.3, 3.2 Hz, 1H), 3.97 (d, *J* = 14.4 Hz, 1H), 3.77 (d, *J* = 14.4 Hz, 1H), 3.66 (s, 3H), 2.89 (dd, *J* = 13.7, 3.2 Hz, 1H), 2.69 (dd, *J* = 13.7, 11.1 Hz, 1H), 1.03 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (151 MHz, DMSO-d$_6$, ppm): δ = 172.0, 170.8, 167.6, 155.5, 153.8, 132.0, 131.0, 128.1, 127.5, 127.4, 127.3, 126.3, 120.9, 115.0, 111.2, 66.6, 53.8, 52.0, 46.9, 35.8, 30.3, 16.4.

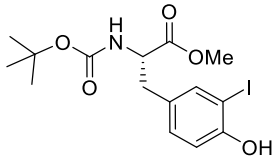
HRMS (ESI): m/z calc. for [M+Na; $C_{22}H_{24}N_2NaO_6^+$]: 435.1532; found: 435.1529; m/z calc. for [M+H; $C_{22}H_{25}N_2O_6^+$]: 413.1707; found: 413.1710; calc. for [M-H; $C_{26}H_{30}N_3O_6^-$]: 411.1562; found: 411.1556.

IR (Diamond-ATR, neat): ν = 3416 (w), 3393 (w), 3209 (w), 3055 (w), 2355 (vw), 1724 (s), 1655 (s), 1566 (m), 1524 (m), 1489 (m), 1438 (s), 1356 (m), 1259 (s), 1230 (s), 1216 (m), 1143 (m), 1114 (s), 1042 (m), 819 (w), 800 (w), 759 (vs), 698 (w), 686 (w).

M.p. 214.7 °C.

2.3 Preparation of Iodotyrosine containing Peptides

Boc-*L*-(ortho-iodo)Tyr-OMe (3a)



According to **TP1**, commercially available Boc-L-tyrosine methyl ester **2a** (591 mg, 2.00 mmol, 1.00 equiv) and sodium iodide (360 mg, 2.40 mmol, 1.20 equiv) were dissolved in DMF (10 mL) and cooled to –10 °C. Chloramine-T trihydrate (676 mg, 2.40 mmol, 1.20 mmol) as solution in DMF (4.8 mL) was added dropwise over 2 h and the suspension was stirred for 3 h. Afterwards, the reaction mixture was warmed to 25 °C and stirred for additional 2 h. The crude product was extracted and purified by flash column chromatography. After final prep-HPLC purification, the title compound **3a** was obtained as white solid (581 mg, 1.38 mmol, 69% yield).

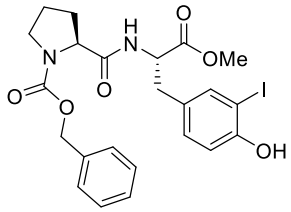
^{1}H-NMR (400 MHz, CDCl$_3$, ppm): δ = 7.42 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.39 (s, 1H), 5.00 (d, *J* = 8.2 Hz, 1H), 4.51 (d, *J* = 7.4 Hz, 1H), 3.72 (s, 3H), 3.03 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.93 (dd, *J* = 13.9, 6.0 Hz, 1H), 1.43 (s, 9H).

^{13}C-NMR (101 MHz, CDCl$_3$, ppm): δ = 172.3, 155.2, 154.2, 139.0, 131.2, 130.3, 115.2, 85.7, 80.3, 54.6, 52.5, 37.1, 28.5.

HRMS (ESI): m/z calc. for [M+H; $C_{15}H_{21}INO_5^+$]: 422.0459; found: 422.0470; calc. for [M-H; $C_{15}H_{21}INO_5^-$]: 420.0313; found: 420.0320.

IR (Diamond-ATR, neat): ν = 3386 (w), 3334 (w), 1713 (m), 1686 (vs), 1605 (w), 1576 (w), 1523 (s), 1508 (s), 1444 (m), 1419 (m), 1395 (w), 1349 (w), 1304 (m), 1289 (m), 1272 (m), 1254 (s), 1219 (m), 1156 (s), 1067 (m), 1027 (m), 993 (m), 828 (m), 810 (m), 759 (w).
M.p. 135.7 °C.

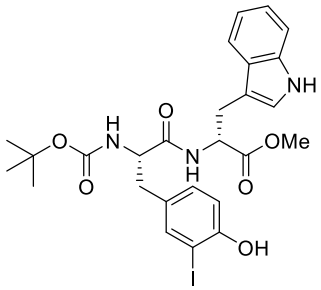
Cbz-*L*-Pro-*L*-(ortho-iodo)Tyr-OMe (3b)



According to **TP1**, tyrosine-peptide **2b** (852 mg, 2.00 mmol, 1.00 equiv) and sodium iodide (360 mg, 2.40 mmol, 1.20 equiv) were dissolved in DMF (10 mL) and cooled to –10 °C. Chloramine-T trihydrate (676 mg, 2.40 mmol, 1.20 mmol) as solution in DMF (4.8 mL), was added dropwise over 2 h and the suspension was stirred for 3 h at this temperature, before warming to 25 °C and stirring additional 6 h. The crude product was extracted and purified by flash column chromatography. After final prep-HPLC purification, the title compound **3b** was obtained as white solid (873 mg, 1.58 mmol, 79% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d$_6$, ppm): δ = 9.82 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 2.1 Hz, 1H), 7.38 – 7.25 (m, 5H), 7.00 (d, *J* = 8.9 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.12 – 4.94 (m, 2H), 4.45 (q, *J* = 7.6 Hz, 1H), 4.24 (dd, *J* = 8.5, 2.8 Hz, 1H), 3.58 (s, 3H), 3.50 – 3.35 (m, 2H), 2.86 (qd, *J* = 14.1, 7.1 Hz, 2H), 2.15 – 2.00 (m, 1H), 1.77 (q, *J* = 7.1, 6.4 Hz, 3H).
^{13}C-NMR (101 MHz, 80 °C DMSO-d$_6$, ppm): δ = 171.5, 171.2, 154.9, 153.7, 138.8, 136.7, 129.7, 129.4, 127.8, 127.2, 126.9, 114.5, 83.7, 65.6, 59.3, 53.1, 51.2, 46.4, 34.9, 22.8.
HRMS (ESI): m/z calc. for [M+Na; $C_{23}H_{25}IN_2NaO_6^+$]: 575.0650; found: 553.0653; m/z calc. for [M+H; $C_{23}H_{26}IN_2O_6^+$]:553.0830; found: 553.0833; calc. for [M-H; $C_{23}H_{24}IN_2O_6^-$]: 551.0685; found: 551.0681.
IR (Diamond-ATR, neat): ν = 3314 (w), 3226 (w), 1746 (m), 1691 (s), 1644 (vs), 1603 (m), 1536 (m), 1502 (m), 1446 (m), 1413 (s), 1351 (s), 1282 (m), 1262 (m), 1210 (s), 1176 (m), 1124 (m), 1088 (w), 1034 (m), 983 (w), 823 (w), 804 (w), 766 (m), 737 (m), 693 (m), 665 (m).
M.p. 165.4 °C.

Boc-*L*-(ortho-iodo)Tyr-*D*-Trp-OMe (3c)



According to **TP1**, tyrosine-peptide **2c** (963 mg, 2.00 mmol, 1.00 equiv) and sodium iodide (360 mg, 2.40 mmol, 1.20 equiv) were dissolved in DMF (10 mL) and cooled to –10 °C. Chloramine-T trihydrate (676 mg, 2.40 mmol, 1.20 mmol) as solution in DMF (4.8 mL), was added dropwise over 2 h and the suspension was stirred for 3 h at this temperature, before warming to 25 °C and stirring additional for 7 h. The crude product was extracted and purified by flash column chromatography. During final prep-HPLC purification, the title compound **3c** was obtained as reddish solid (365 mg, 0.60 mmol, 30% yield) and remaining starting material was recovered (231 mg, 0.48 mmol, 24% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d$_6$, ppm): δ = 10.67 (s, 1H), 9.74 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 2.1 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.34 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.07 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.94 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.39 (s, 1H), 4.60 (td, *J* = 7.7, 6.0 Hz, 1H), 4.15 (td, *J* = 9.2, 4.5 Hz, 1H), 3.61 (s, 3H), 3.18 (ddd, *J* = 14.6, 6.1, 0.8 Hz, 1H), 3.08 (dd, *J* = 15.8, 6.4 Hz, 1H), 2.73 (dd, *J* = 13.9, 4.5 Hz, 1H), 1.31 (s, 9H).

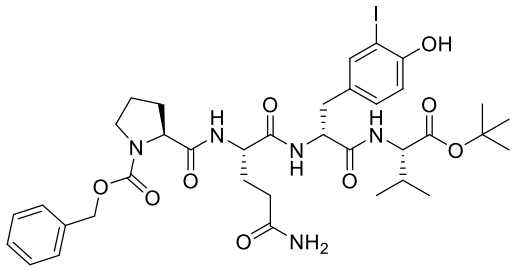
^{13}C-NMR (101 MHz, 80 °C, DMSO-d$_6$, ppm): δ = 171.6, 170.9, 154.6, 154.5, 138.8, 135.9, 130.3, 129.9, 126.8, 123.3, 120.6, 118.1, 117.6, 114.3, 111.0, 109.0, 83.6, 77.8, 55.3, 52.7, 51.3, 36.0, 27.7, 27.1.

HRMS (ESI): m/z calc. for [$C_{26}H_{30}IN_3O_6$]: 607.1179; found: 607.1153; calc. for [M+H; $C_{26}H_{31}IN_3O_6^+$]: 608.1252; found: 608.1261; calc. for [M-H; $C_{26}H_{29}IN_3O_6^-$]: 606.1107; found: 606.1118.

IR (Diamond-ATR, neat): ν = 3414 (m), 3398 (w), 3344 (w), 3310 (w), 1716 (m), 1682 (m), 1659 (vs), 1605 (w), 1519 (s), 1504 (s), 1456 (m), 1438 (m), 1414 (m), 1391 (m), 1365 (m), 1318 (m), 1291 (m), 1253 (m), 1238 (m), 1221 (m), 1193 (m), 1169 (s), 1038 (m), 1011 (m), 825 (w), 743 (s), 691 (w), 664 (w).

M.p. 160.7 °C.

Cbz-*L*-Pro-*L*-Glu-*D*-(ortho-iodo)Tyr-*L*-Val-O*t*Bu (3d)



According to **TP1**, tyrosine-peptide **2d** (1.39 g, 2.00 mmol, 1.00 equiv) and sodium iodide (360 mg, 2.40 mmol, 1.20 equiv) were dissolved in DMF (10 mL) and cooled to –10 °C. Chloramine-T trihydrate (676 mg, 2.40 mmol, 1.20 mmol) as solution in DMF (4.8 mL), was added dropwise over 2 h and the suspension was stirred for 1 h at this temperature, before warming to 25 °C and stirring additional for 2 h. The crude product was extracted and purified by flash column chromatography. After final prep-HPLC purification, the title compound **3d** was obtained as white solid (855 mg, 1.04 mmol, 52% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d$_6$, ppm): δ = 9.75 (s, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.78 (t, *J* = 9.9 Hz, 2H), 7.55 (d, *J* = 2.1 Hz, 1H), 7.42 – 7.25 (m, 5H), 7.03 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.92 – 6.33 (m, 2H), 5.07 (s, 2H), 4.58 (td, *J* = 8.5, 5.4 Hz, 1H), 4.29 – 4.17 (m, 2H), 4.06 (dd, *J* = 8.3, 5.8 Hz, 1H), 3.42 (t, *J* = 8.2 Hz, 2H), 2.90 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.70 (dd, *J* = 13.8, 8.8 Hz, 1H), 2.10 (dq, *J* = 8.1, 4.1 Hz, 1H), 2.07 – 1.94 (m, 3H), 1.90 – 1.75 (m, 4H), 1.70 (p, *J* = 7.6, 7.1 Hz, 1H), 1.42 (s, 9H), 0.84 (t, *J* = 7.0 Hz, 6H).

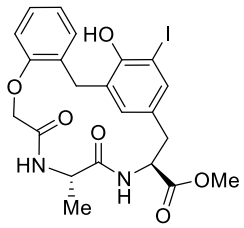
^{13}C-NMR (101 MHz, 80 °C, DMSO-d$_6$, ppm): δ = 173.4, 171.5, 170.6, 170.4, 169.8, 154.7, 153.8, 138.8, 136.7, 129.9, 129.8, 127.9, 127.2, 126.9, 114.4, 83.7, 80.3, 65.6, 59.3, 57.6, 53.6, 52.3, 46.4, 36.4, 31.2, 29.7, 27.4, 23.2, 18.4, 17.6.

HRMS (ESI): m/z calc. for [M+H; $C_{36}H_{49}IN_5O_9^+$]: 822.2569; found: 822.2593; calc. for [M-H; $C_{36}H_{47}IN_5O_9^-$]: 820.2424; found: 820.2426.

IR (Diamond-ATR, neat): ν = 3285 (m), 3199 (w), 2963 (w), 2358 (w), 1737 (w), 1680 (s), 1665 (s), 1631 (vs), 1543 (m), 1508 (m), 1467 (w), 1437 (m), 1418 (m), 1358 (m), 1295 (w), 1278 (m), 1232 (m), 1211 (w), 1164 (m), 1133 (m), 1038 (w), 825 (w), 766 (w), 734 (w), 696 (w), 661 (w).

M.p. 174.5 °C.

Methyl (8*S*,11*S*)-1^6-hydroxy-1^5-iodo-8-methyl-6,9-dioxo-4-oxa-7,10-diaza-1(1,3),3(1,2)-dibenzenacyclododecaphane-11-carboxylate (3e)



According to **TP2**, tyrosine-cyclopeptide **2e** (825 mg, 2.00 mmol, 1.00 equiv) was dissolved in freshly distilled DCM (16 mL). Bis(pyridine)iodonium tetrafluoroborate (967 mg, 2.60 mmol, 1.30 equiv) was dissolved in freshly distilled DCM (8 mL) and added to the reaction mixture within 1 h. After stirring for 4 h, water (50 mL) was added and the crude product was extracted and purified by flash column chromatography. After final prep-HPLC purification, the title compound **3e** was obtained as beige solid (1.02 g, 1.90 mmol, 95% yield).

^{1}H-NMR (400 MHz, DMSO-d$_6$, ppm): δ = 8.93 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.23 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.04 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.92 (td, *J* = 7.6, 1.2 Hz, 1H), 6.89 (d, *J* = 2.1 Hz, 1H), 4.67 (d, *J* = 14.2 Hz, 1H), 4.51 (d, *J* = 14.2, 1H), 4.44 (dd, *J* = 8.8, 7.0 Hz, 1H), 4.36 (ddd, *J* = 11.4, 8.3, 3.2 Hz, 1H), 4.11 (d, *J* = 14.9 Hz, 1H), 3.84 (d, *J* = 14.9 Hz, 1H), 3.66 (s, 3H), 2.90 (dd, *J* = 13.7, 3.2, 1H), 2.65 (dd, *J* = 13.7, 11.3 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (101 MHz, DMSO-d$_6$, ppm): δ = 171.8, 170.9, 167.5, 155.5, 152.5, 136.6, 131.8, 131.3, 131.2, 128.9, 127.8, 127.3, 121.0, 111.5, 88.6, 66.7, 53.7, 52.0, 46.9, 34.9, 31.0, 16.4.

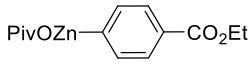
HRMS (ESI): m/z calc. for [M; $C_{22}H_{23}IN_2O_6$]: 538.0601; found: 538.0565; calc. for [M+H; [$C_{22}H_{24}IN_2O_6^+$]: 539.0674; found: 539.0682; calc. for [M-H; $C_{22}H_{22}IN_2O_6^-$]: 537.0528; found: 537.0529.

IR (Diamond-ATR, neat): ν = 3272 (w), 2359 (w), 1751 (s), 1641 (vs), 1552 (m), 1492 (w), 1468 (m), 1448 (m), 1432 (m), 1367 (m), 1286 (w), 1244 (m), 1217 (s), 1146 (m), 1117 (m), 1052 (w), 1042 (w), 994 (w), 938 (w), 915 (w), 807 (w), 749 (s), 719 (m), 706 (m).

M.p. decomposition at 280 °C.

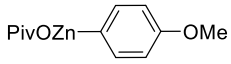
2.4 Preparation of Arylzinc Pivalates

(4-(Ethoxycarbonyl)phenyl)zinc pivalate (1a)



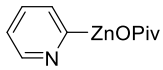
According to **TP3**, ethyl 4-iodobenzoate (4.14 g, 15.0 mmol, 1.00 equiv) was dissolved in 30 mL freshly distilled THF and cooled to –20 °C. *i*PrMgCl·LiCl (15.5 mL, 17.0 mmol, 1.10 equiv, 1.10 M in THF) was added dropwise and the solution stirred for 2 h. $Zn(OPiv)_2$ (4.82 g, 18.0 mmol, 1.20 equiv) was added and the mixture stirred at 25 °C until a clear solution was obtained. The concentration was determined by titration with iodine (0.39 M, 83% yield).[119]

(4-Methoxyphenyl)zinc pivalate (1b)



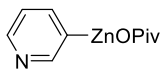
According to **TP3**, 4-iodoansiole (3.51 g, 15.0 mmol, 1.00 equiv) was dissolved in 20 mL freshly distilled THF and cooled to –20 °C. *i*PrMgCl·LiCl (15.5 mL, 17.0 mmol, 1.10 equiv, 1.10 M in THF) was added dropwise and the solution stirred for 2 h. $Zn(OPiv)_2$ (4.82 g, 18.0 mmol, 1.20 equiv) was added and the mixture stirred at 25 °C until a clear solution was obtained. The concentration was determined by titration with iodine (0.55 M, 73% yield). [20]

(Pyridin-2-yl)zinc pivalate (1c)



According to a modified version of **TP3**, *i*PrMgCl·LiCl (3.64 mL, 4.40 mmol, 1.10 equiv, 1.21 M in THF) was cooled to 0 °C and 2-bromopyridine (632 mg, 4.00 mmol, 1.00 equiv) was added dropwise over 15 min. After complete addition, the mixture was stirred for 1 h and again cooled to 0 °C. $Zn(OPiv)_2$ (1.29 g, 4.80 mmol, 1.20 equiv) was added and the mixture stirred at 25 °C until a clear solution was obtained. The concentration was determined by titration with iodine (0.52 M, 67% yield).[120]

(Pyridin-3-yl)zinc pivalate (1d)

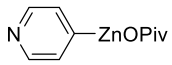


According to **TP3**, 3-bromopyridine (632 mg, 4.00 mmol, 1.00 equiv) was dissolved in 4 mL freshly distilled THF and cooled to 0 °C. *i*PrMgCl·LiCl (3.64 mL, 4.40 mmol, 1.10 equiv, 1.21 M in THF) was

[119] S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289.
[120] J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754.

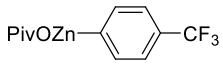
added dropwise and the solution stirred for 2 h. $Zn(OPiv)_2$ (1.29 g, 4.80 mmol, 1.20 equiv) was added and the mixture stirred at 25 °C until a clear solution was obtained. The concentration was determined by titration with iodine (0.42 M, 93% yield).[21]

(Pyridin-4-yl)zinc pivalate (1e)



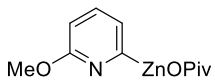
According to **TP3**, 4-iodopyridine (410 mg, 2.00 mmol, 1.00 equiv) was dissolved in 4 mL freshly distilled THF and cooled to –20 °C. *i*PrMgCl·LiCl (1.81 mL, 2.2 mmol, 1.10 equiv, 1.21 M in THF) was added dropwise and the solution stirred for 30 min. $Zn(OPiv)_2$ (643 mg, 2.40 mmol, 1.20 equiv) was added and the mixture stirred at 25 °C until a clear solution was obtained. The concentration was determined by titration with iodine (0.23 M, 76% yield).[23]

(4-(Trifluoromethyl)phenyl)zinc pivalate (1f)



According to **TP4**, LiCl (509 mg, 12.0 mmol, 1.20 equiv) and magnesium turnings (292 mg, 12.0 mmol, 1.20 equiv) were mixed with 10 mL freshly distilled THF and cooled to 0 °C. 4-Bromobenzotrifluoride (509 mg, 10.0 mmol, 1.00 equiv) was added dropwise and the suspension stirred for 4 h. The solution was transferred with a syringe-filter to a fresh *Schlenk*-flask, and $Zn(OPiv)_2$ (3.21 g, 12.0 mmol, 1.20 equiv) was added at 0 °C. After stirring at 25 °C for 15 min, the concentration was determined by titration with iodine (0.69 M, 75% yield). [121]

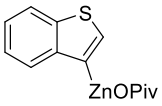
(6-methoxypyridin-2-yl)zinc pivalate (1g)



Under *Schlenk*-conditions, 2-bromo-6-methoxypyridine (2.82 g, 15.0 mmol, 1.00 equiv) was dissolved in 24 mL freshly distilled THF and cooled to –78 °C. *n*BuLi (5.80 mL, 15.0 mmol, 2.60 M in *n*hexane) was added dropwise and the mixture was stirred additional 30 min before $Zn(OPiv)_2$ (4.82 g, 18.0 mmol, 1.20 equiv) was added. After stirring at 25 °C for 1 h, the concentration was determined by titration with iodine (0.24 M, 50% yield).[122]

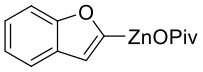
[121] S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289.
[122] J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754.

(Benzo[*b*]thiophen-3-yl)zinc pivalate (1h)



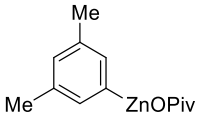
According to **TP3**, 3-bromobenzo[*b*]thiophene (2.13 g, 10.0 mmol, 1.00 equiv) was dissolved in 10 mL freshly distilled THF and cooled to –20 °C. *i*PrMgCl·LiCl (11.0 mL, 11.0 mmol, 1.10 equiv, 1.00 M in THF) was added dropwise and the solution stirred for 1 h. $Zn(OPiv)_2$ (3.21 g, 12.0 mmol, 1.20 equiv) was added and the mixture stirred at 25 °C until a clear solution was obtained. The concentration was determined by titration with iodine (0.46 M, 96% yield).[23]

(Benzofuran-2-yl)zinc pivalate (1i)



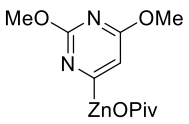
Under *Schlenk*-conditions, 2,3-Benzofuran (355 mg, 3.00 mmol, 1.00 equiv) was dissolved in 6 mL freshly distilled THF and cooled to 0 °C. *n*BuLi (1.09 mL, 3.00 mmol, 2.75 M in *n*hexane) was added dropwise and the mixture was stirred additional 5 min. $Zn(OPiv)_2$ (964 mg, 3.60 mmol, 1.20 equiv) and 4.00 mL freshly distilled THF were added. After stirring at 25 °C for 1 h, the concentration was determined by titration with iodine (0.12 M, 40% yield).[123]

(3,5-dimethylphenyl)zinc pivalate (1j)



According to **TP3**, 1-iodo-3,5-dimethylbenzene (1.16 g, 5.00 mmol, 1.00 equiv) was dissolved in 5 mL freshly distilled THF. *i*PrMgCl·LiCl (5.00 mL, 5.50 mmol, 1.10 equiv, 1.10 M in THF) was added dropwise and the solution stirred for 1 h. $Zn(OPiv)_2$ (643 mg, 2.40 mmol, 1.20 equiv) was added and the mixture stirred until a clear solution was obtained. The concentration was determined by titration with iodine (0.45 M, 99% yield).[124]

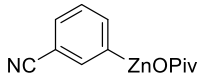
(2,6-dimethoxypyrimidin-4-yl)zinc pivalate (1k)



[123] S. Otsuka, D. Fujino, K. Murakami, H. Yorimitsu, A. Osuka, *Chem. Eur. J.* **2014**, *20*, 13146.
[124] S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289.

According to **TP4**, LiCl (255 mg, 6.00 mmol, 1.20 equiv) and Mg turnings (146 mg, 6.00 mmol, 1.20 equiv) were mixed with 10 mL freshly distilled THF. 5-bromo-2,4-dimethoxypyrimidine (1.10 g, 5.00 mmol, 1.00 equiv) was added dropwise and the suspension stirred for 2 h at 25 °C. The solution was transferred with a syringe-filter to a fresh *Schlenk*-flask and $Zn(OPiv)_2$ (1.61 g, 6.00 mmol, 1.20 equiv) was added at 0 °C. After stirring at 25 °C for 15 min, the concentration was determined by titration with iodine (0.64 M, 65% yield).[25]

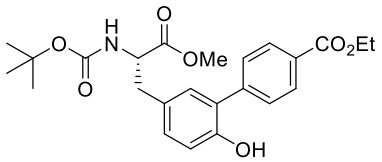
(3-cyanophenyl)zinc pivalate (1l)



According to **TP3**, 3-iodobenzonitrile (458 mg, 2.00 mmol, 1.00 equiv) was dissolved in 2 mL freshly distilled THF and cooled to –30 °C. *i*PrMgCl·LiCl (2.00 mL, 2.20 mmol, 1.10 equiv, 1.10 M in THF) was added dropwise and the solution stirred for 30 min. $Zn(OPiv)_2$ (643 mg, 2.40 mmol, 1.20 equiv) was added and the mixture stirred at 25 °C until a clear solution was obtained. The concentration was determined by titration with iodine (0.44 M, 96% yield).[24]

2.5 Negishi Cross-Coupling reactions of Iodotyrosine with Arylzinc Pivalates

Ethyl (*S*)-5'-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-2'-hydroxy-[1,1'-biphenyl]-4-carboxylate (4a)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before tyrosine-derivate **3a** (126 mg, 0.30 mmol, 1.00 equiv) was added. The arylzinc pivalate solution **1a** in THF (1.15 mL, 0.39 M, 0.45 mmol, 1.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporation, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-derivate **4a** was obtained as colorless solid (99.0 mg, 0.22 mmol, 74% yield).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm) δ = 8.08 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.98 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 5.08 (d, *J* = 8.4 Hz, 1H), 4.56 (dt, *J* = 8.6, 6.0 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 3.09 (dd, *J* = 14.0, 5.7 Hz, 1H), 3.00 (dd, *J* = 14.1, 6.1 Hz, 1H), 1.43 – 1.35 (m, 12H).

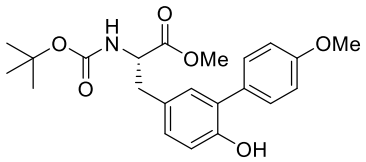
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 172.6, 166.7, 155.3, 152.1, 142.4, 131.4, 130.4, 130.0, 129.4, 129.2, 128.2, 127.4, 116.6, 80.3, 61.2, 54.7, 52.4, 37.6, 28.4, 14.4.

HRMS (ESI): m/z calc. for [M; $C_{24}H_{29}NO_7$]: 443.1944; found: 443.1916; m/z calc. for [M+H; $C_{24}H_{30}NO_7^+$]: 444.2017; found: 444.2021; calc. for [M-H; $C_{24}H_{28}NO_7^-$]: 442.1871; found: 442.1881.

IR (Diamond-ATR, neat): ν = 3357 (w), 2978 (w), 2359 (w), 2340 (w), 1712 (s), 1691 (s), 1608 (m), 1502 (m), 1435 (m), 1399 (m), 1367 (s), 1278 (vs), 1216 (m), 1166 (s), 1103 (m), 1059 (w), 1019 (m), 859 (w), 757 (m), 705 (w), 668 (w).

M.p. 67.8 °C.

Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(6-hydroxy-4'-methoxy-[1,1'-biphenyl]-3-yl)propanoate (4b)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before tyrosine-derivate **3a** (126 mg, 0.30 mmol, 1.00 equiv) was added. The arylzinc pivalate solution **1b** in THF (0.82 mL, 0.55 M, 0.45 mmol, 1.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After purification via preparative reversed-phase HPLC-chromatography (MeCN/H_2O), the modified tyrosine-derivate **4b** was obtained as colorless solid (60.0 mg, 0.15 mmol, 50% yield).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm) δ = 7.39 – 7.36 (m, 2H), 7.02 – 6.98 (m, 2H), 6.96 (d, *J* = 7.6 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.01 (d, *J* = 8.3 Hz, 1H), 4.56 (dt, *J* = 8.6, 5.9 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.08 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.01 (dd, *J* = 14.0, 6.0 Hz, 1H), 1.41 (s, 9H).

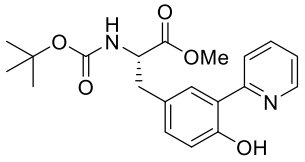
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 172.6, 159.4, 155.3, 151.8, 131.3, 130.3, 129.6, 129.3, 128.1, 128.0, 116.0, 114.7, 80.1, 55.5, 54.7, 52.3, 37.6, 28.4.

HRMS (ESI): m/z calc. for [M; $C_{22}H_{27}NO_6$]: 401.1838; found: 401.1801; m/z calc. for [M+H; $C_{22}H_{28}NO_6^+$]: 402.1911; found: 402.1915; calc. for [M-H; $C_{22}H_{26}NO_6^-$]: 400.1766; found: 400.1768.

IR (Diamond-ATR, neat): ν = 3371 (w), 2975 (w), 2359 (vw), 1742 (m), 1689 (s), 1609 (m), 1516 (s), 1504 (vs), 1437 (m), 1392 (m), 1366 (m), 1277 (s), 1245 (vs), 1176 (s), 1045 (m), 1026 (m), 834 (m), 797 (w), 757 (m).

M.p. 58.3 °C.

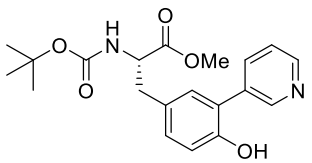
Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-3-(pyridin-2-yl)phenyl) propanoate (4c)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before tyrosine-derivate **3a** (126 mg, 0.30 mmol, 1.00 equiv) was added. The 2-pyridylzinc pivalate solution **1c** in THF (1.15 mL, 0.52 M, 0.60 mmol, 2.00 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After purification via preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-derivate **4c** was obtained as colorless solid (97.0 mg, 0.26 mmol, 87% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 13.85 (s, 1H), 8.53 (dt, *J* = 5.1, 1.4 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.85 (td, *J* = 8.3, 7.8, 1.8 Hz, 1H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.06 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.02 (d, *J* = 8.4 Hz, 1H), 4.59 (dd, *J* = 13.2, 5.7 Hz, 1H), 3.71 (s, 3H), 3.11 (dd, *J* = 14.0, 5.9 Hz, 1H), 3.04 (dd, *J* = 14.1, 6.1 Hz, 1H), 1.41 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 172.6, 159.1, 157.6, 155.2, 145.9, 138.2, 132.6, 127.1, 126.2, 121.8, 119.4, 118.9, 118.7, 80.1, 54.7, 52.4, 37.9, 28.5.
HRMS (ESI): m/z calc. for [M; $C_{20}H_{24}N_2O_5$]: 372.1685; found: 372.1648; m/z calc. for [M+H; $C_{20}H_{25}N_2O_5^+$]: 373.1758; found: 373.17560; calc. for [M-H; $C_{20}H_{23}N_2O_5^-$]: 371.1612; found: 371.1613.
IR (Diamond-ATR, neat): ν = 3352 (w), 2976 (w), 2359 (w), 2341 (w), 1742 (m), 1705 (s), 1594 (s), 1564 (m), 1493 (s), 1485 (s), 1456 (m), 1435 (m), 1391 (m), 1365 (s), 1299 (m), 1270 (s), 1245 (s), 1216 (s), 1160 (vs), 1099 (w), 1057 (m), 1018 (m), 826 (m), 789 (m), 754 (s), 666 (w).
M.p. 164.2 °C.

Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-3-(pyridin-3-yl)phenyl) propanoate (4d)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before tyrosine-

derivate **3a** (126 mg, 0.30 mmol, 1.00 equiv) was added. The 3-pyridylzinc pivalate solution **1d** in THF (1.43 mL, 0.42 M, 0.60 mmol, 2.00 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating the crude product was pre-purified by flash column chromatography. After purification via preparative reversed-phase HPLC-chromatography (MeCN/H_2O), the modified tyrosine-derivate **4d** was obtained as colorless solid (88.0 mg, 0.24 mmol, 80% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 8.88 (s, 1H), 8.50 (dd, *J* = 5.1, 1.6 Hz, 1H), 8.00 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.45 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.03 (s, 1H), 7.00 (d, *J* = 2.1 Hz, 1H), 6.99 (s, 1H), 5.07 (d, *J* = 8.3 Hz, 1H), 4.56 (q, *J* = 5.7 Hz, 1H), 3.71 (s, 3H), 3.09 (dd, *J* = 13.9, 5.8 Hz, 1H), 3.00 (dd, *J* = 14.0, 6.1 Hz, 1H), 1.39 (s, 9H).

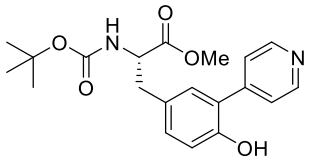
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 172.6, 155.3, 153.3, 148.5, 145.7, 138.4, 135.3, 131.3, 131.0, 128.2, 124.2, 124.0, 117.0, 80.2, 54.7, 52.5, 37.7, 28.4.

HRMS (ESI): m/z calc. for [M; $C_{20}H_{24}N_2O_5$]: 372.1685; found: 372.1647; m/z calc. for [M+H; $C_{20}H_{25}N_2O_5^+$]: 373.1758; found: 373.1757; calc. for [M-H; $C_{20}H_{23}N_2O_5^-$]: 371.1612; found: 371.1611.

IR (Diamond-ATR, neat): ν = 3326 (vw), 2976 (w), 2359 (w), 1741 (m), 1696 (m), 1612 (w), 1573 (w), 1509 (m), 1436 (m), 1405 (m), 1392 (m), 1365 (m), 1287 (m), 1249 (m), 1215 (m), 1161 (s), 1059 (m), 1027 (m), 853 (vw), 823 (w), 749 (vs), 710 (m), 667 (w).

M.p. 132.9 °C.

Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-3-(pyridin-4-yl)phenyl) propanoate (4e)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before tyrosine-derivate **3a** (126 mg, 0.30 mmol, 1.00 equiv) was added. The 4-pyridylzinc pivalate solution **1e** in THF (2.61 mL, 0.23 M, 0.60 mmol, 2.00 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After purification via preparative reversed-phase HPLC-chromatography (MeCN/H_2O), the modified tyrosine-derivate **4e** was obtained as yellow solid (82.0 mg, 0.22 mmol, 73% yield).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm) δ = 8.58 (d, *J* = 5.2 Hz, 2H), 7.63 (d, *J* = 5.2 Hz, 2H), 7.08 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 5.09 (d, *J* = 8.4 Hz, 1H), 4.57

(q, *J* = 6.6 Hz, 1H), 3.72 (s, 3H), 3.10 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.00 (dd, *J* = 14.0, 6.2 Hz, 1H), 1.40 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 172.5, 155.3, 153.7, 148.6, 147.6, 131.3, 131.3, 127.9, 125.3, 124.6, 117.0, 80.3, 54.7, 52.4, 37.7, 28.4.

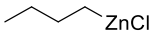
HRMS (ESI): m/z calc. for [M; $C_{20}H_{24}N_2O_5$]: 372.1685; found: 372.1649; m/z calc. for [M+H; $C_{20}H_{25}N_2O_5^+$]: 373.1758; found: 373.1753; calc. for [M-H; $C_{20}H_{23}N_2O_5^-$]: 371.1612; found: 371.1613.

IR (Diamond-ATR, neat): ν = 3344 (w), 2976 (w), 2359 (w), 2341 (w), 1741 (m), 1696 (m), 1601 (m), 1542 (w), 1509 (m), 1435 (m), 1410 (m), 1391 (m), 1365 (m), 1289 (m), 1251 (m), 1215 (s), 1162 (s), 1058 (m), 1007 (m), 832 (m), 806 (w), 751 (vs), 667 (w).

M.p. 129.4 °C.

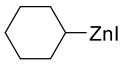
2.6 Preparation of Alkylzinc Halides

*n*Butylzinc(II) chloride (5a)



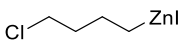
Under *Schlenk*-conditions, *n*BuMgCl (3.23 mL, 5.00 mmol, 1.00 equiv, 1.55 M in THF) was cooled down to 0 °C and $ZnCl_2$ (5.00 mL, 5.00 mmol, 1.00 M in THF, 1.00 equiv) was added. The mixture was stirred at 25 °C for 30 min and then titrated with iodine (0.59 M, 97% yield).[125]

Cyclohexylzinc(II) iodide (5b)



According to **TP6**, LiCl (382 mg, 9.00 mmol. 1.50 equiv) and zinc dust (1.18 g, 18.0 mmol, 2.50 equiv) were suspended in 6 mL freshly distilled THF and activated with TMSCl and DBE. Iodcylcohexan (1.26 g, 6.00 mmol, 1.00 equiv) was added dropwise and the reaction mixture was stirred for 2 h. After filtration, the concentration was determined by titration with iodine (0.79 M, 76% yield).[126]

(4-Chlorobutyl)zinc(II) iodide (5c)

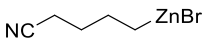


According to **TP6**, LiCl (305 mg, 7.20 mmol. 1.20 equiv) and zinc dust (785 mg, 12.0 mmol, 2.00 equiv) were suspended in 6 mL freshly distilled THF and activated with TMSCl and DBE. 1-Chloro-4-iodobutane (1.31 g, 6.00 mmol, 1.00 equiv) was added dropwise and the reaction mixture

[125] I. Kalvet, T. Sperger, T. Scattolin, G. Magnin, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 7078.
[126] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

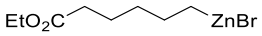
was stirred for 1 h. After filtration, the concentration was determined by titration with iodine (0.84 M, 84% yield).

(4-Cyanobutyl)zinc(II) bromide (5d)



According to **TP6**, LiCl (424 mg, 10.0 mmol. 1.00 equiv) and zinc dust (915 mg, 14.0 mmol, 1.40 equiv) were suspended in 10 mL freshly distilled THF and activated with TMSCl and DBE. 4-Bromobutyronitrile (1.48 g, 10.0 mmol, 1.00 equiv) was added dropwise and the reaction mixture was stirred for 16 h at 50 °C. After filtration, the concentration was determined by titration with iodine (0.86 M, 86% yield).

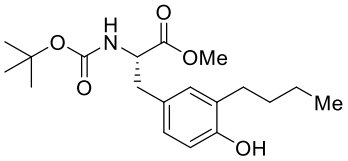
(6-Ethoxy-6-oxohexyl)zinc(II) bromide (5e)



According to **TP6**, LiCl (255 mg, 6.00 mmol. 1.00 equiv) and zinc dust (550 mg, 8.40 mmol, 1.40 equiv) were suspended in 6 mL freshly distilled THF and activated with TMSCl and DBE. Ethyl 6-bromohexanoate (1.34 g, 6.00 mmol, 1.00 equiv) was added dropwise and the reaction mixture was stirred for 50 h at 50 °C. After filtration, the concentration was determined by titration with iodine (0.81 M, 81% yield).

2.7 Negishi Cross-Coupling reactions of Iodotyrosine with Alkylzinc Halides

Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(3-butyl-4-hydroxyphenyl)propanoate (6a)



According to **TP7**, $Pd(dba)_2$ (6.90 mg, 12.0 µmol, 4.00 mol%), P*t*Bu_3 (0.03 mL, 1.00 M in toluene, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before tyrosine-derivate **3a** (126 mg, 0.30 mmol, 1.00 equiv) was added. The butylzinc chloride solution **5a** in THF (1.02 mL, 0.59 M, 0.60 mmol, 2.00 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 7 h. After quenching, extracting and evaporating, the crude product was purified by flash column chromatography. Final purification via preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$) yielded the modified alkyltyrosine-derivate **6a** as colorless solid (88.0 mg, 0.25 mmol, 82% yield).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm) δ = 6.84 (d, *J* = 2.2 Hz, 1H), 6.79 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 1H), 4.97 (d, *J* = 8.4 Hz, 1H), 4.53 (q, *J* = 6.5 Hz, 1H), 3.71 (s, 3H), 2.99 (qd, *J* = 14.0, 5.9 Hz, 2H), 2.56 (t, *J* = 7.8 Hz, 2H), 1.61 – 1.54 (m, 2H), 1.43 (s, 9H), 1.37 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

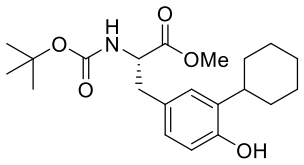
^{13}C-NMR (151 MHz, $CDCl_3$, ppm) δ = 172.7, 155.3, 152.8, 131.2, 128.9, 127.8, 127.7, 115.4, 80.1, 54.7, 52.3, 37.6, 32.0, 29.8, 28.5, 22.7, 14.1.

HRMS (ESI): m/z calc. for [M+Na; $C_{19}H_{29}NNaO_5^+$]: 374.1943; found: 374.1940; calc. for [M-H; $C_{19}H_{28}NO_5^-$]: 350.1973; found: 350.1979.

IR (Diamond-ATR, neat): $\nu =$ 3467 (m), 3371 (w), 2954 (w), 2922 (w), 2854 (w), 2359 (vw), 1739 (s), 1690 (vs), 1526 (s), 1507 (m), 1436 (m), 1361 (s), 1264 (s), 1243 (m), 1218 (s), 1167 (s), 1124 (m), 1052 (s), 1010 (m), 999 (m), 817 (m), 810 (m), 775 (w), 716 (w).

M.p. 87.2 °C.

Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(3-cyclohexyl-4-hydroxyphenyl) propanoate (6b)



According to **TP7**, $Pd(dba)_2$ (6.90 mg, 12.0 µmol, 4.00 mol%), P*t*Bu_3 (0.03 mL, 1.00 M in toluene, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before tyrosine-derivate **3a** (126 mg, 0.30 mmol, 1.00 equiv) was added. The cyclohexylzinc iodide solution **5b** in THF (0.76 mL, 0.79 M, 0.60 mmol, 2.00 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 7 h. After quenching, extracting and evaporating, the crude product was purified by flash column chromatography. Final purification via preparative reversed-phase HPLC-chromatography (MeCN/H_2O) yielded the modified alkyltyrosine-derivate **6b** as colorless solid (79.0 mg, 0.21 mmol, 71% yield).

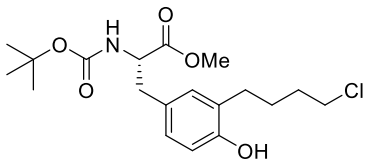
^{1}H-NMR (599 MHz, $CDCl_3$, ppm) δ = 6.88 (d, *J* = 2.2 Hz, 1H), 6.78 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 5.01 – 4.89 (m, 2H), 4.54 (dt, *J* = 8.2, 5.6 Hz, 1H), 3.71 (s, 3H), 3.00 (d, *J* = 5.8 Hz, 2H), 2.78 (tt, *J* = 11.5, 2.9 Hz, 1H), 1.88 – 1.80 (m, 4H), 1.80 – 1.72 (m, 1H), 1.46 – 1.37 (m, 14H), 1.35 – 1.19 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 172.7, 155.2, 152.0, 133.8, 128.1, 128.0, 127.4, 115.5, 80.0, 54.6, 52.4, 37.8, 37.2, 33.3, 33.2, 28.5, 27.1, 26.4.z

HRMS (ESI): m/z calc. for [M+Na; $C_{21}H_{31}NNaO_5^+$]: 400.2100; found: 400.2098; calc. for [M-H; $C_{21}H_{30}NO_5^-$]: 376.2129; found: 376.2139.

IR (Diamond-ATR, neat): ν = 3378 (w), 2977 (w), 2925 (m), 2851 (m), 2359 (w), 1688 (vs), 1610 (w), 1506 (s), 1436 (m), 1392 (m), 1366 (s), 1273 (m), 1250 (s), 1223 (m), 1164 (vs), 1100 (w), 1060 (m), 1022 (w), 910 (w), 823 (w), 733 (m).
M.p. 67.1 °C.

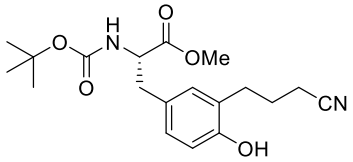
Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(3-(4-chlorobutyl)-4-hydroxyphenyl) propanoate (6c)



According to **TP7**, $Pd(dba)_2$ (6.90 mg, 12.0 µmol, 4.00 mol%), P*t*Bu_3 (0.03 mL, 1.00 M in toluene, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before tyrosine-derivate **3a** (126 mg, 0.30 mmol, 1.00 equiv) was added. The 4-chlorobutylzinc iodide solution **5c** in THF (0.72 mL, 0.84 M, 0.60 mmol, 2.00 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 7 h. After quenching, extracting and evaporating, the crude product was purified by flash column chromatography. Final purification via preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$) yielded the modified alkyltyrosine-derivate **6c** as colorless solid (85.0 mg, 0.22 mmol, 72% yield).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm) δ = 6.84 (d, *J* = 2.2 Hz, 1H), 6.80 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.64 (d, *J* = 8.1, 1H), 5.18 (s, 1H), 4.98 (d, *J* = 8.3 Hz, 1H), 4.53 (q, *J* = 6.7 Hz, 1H), 3.71 (s, 3H), 3.56 (t, *J* = 6.6, 2H), 2.99 (qd, *J* = 13.9, 5.8 Hz, 2H), 2.60 (t, *J* = 7.4 Hz, 2H), 1.86 – 1.78 (m, 2H), 1.74 (p, *J* = 7.2 Hz, 2H), 1.42 (s, 9H).
^{13}C-NMR (151 MHz, $CDCl_3$, ppm) δ = 172.7, 155.3, 152.9, 131.3, 128.2, 128.0, 115.5, 80.2, 54.7, 52.4, 45.1, 45.1, 37.7, 32.3, 29.3, 28.5, 27.1.
HRMS (ESI): m/z calc. for [M+Na; $C_{19}H_{28}ClNNaO_5^+$]: 408.1554; found: 408.1550; calc. for [M-H; $C_{19}H_{27}ClNO_5^-$]: 384.1583; found: 384.1588.
IR (Diamond-ATR, neat): ν = 3417 (m), 3376 (m), 2976 (w), 1725 (s), 1687 (vs), 1609 (w), 1503 (s), 1437 (m), 1367 (m), 1306 (m), 1298 (m), 1267 (s), 1225 (s), 1163 (s), 1110 (m), 1017 (m), 986 (m), 851 (w), 821 (s), 721 (s).
M.p. 103.3 °C.

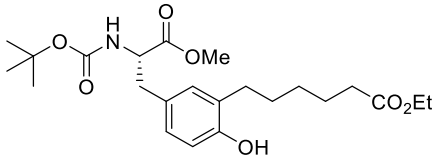
Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(3-(3-cyanopropyl)-4-hydroxyphenyl) propanoate (6d)



According to **TP7**, $Pd(dba)_2$ (6.90 mg, 12.0 µmol, 4.00 mol%), P*t*Bu_3 (0.03 mL, 1.00 M in toluene, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before tyrosine-derivate **3a** (126 mg, 0.30 mmol, 1.00 equiv) was added. The 4-cyanobutylzinc bromide solution **5d** in THF (0.70 mL, 0.86 M, 0.60 mmol, 2.00 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 7 h. After quenching, extracting and evaporating, the crude product was purified by flash column chromatography. Final purification via preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$) yielded the modified alkyltyrosine-derivate **6d** as colorless solid (62.0 mg, 0.17 mmol, 58% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 6.85 – 6.78 (m, 2H), 6.64 (d, *J* = 8.7 Hz, 1H), 5.74 (s, 1H), 5.00 (d, *J* = 8.5 Hz, 1H), 4.53 (q, *J* = 6.1 Hz, 1H), 3.73 (s, 3H), 2.98 (qd, *J* = 14.0, 6.0 Hz, 2H), 2.80 – 2.65 (m, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 1.96 (p, *J* = 7.3 Hz, 2H), 1.42 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 172.7, 155.3, 153.2, 131.6, 128.6, 128.0, 126.4, 120.0, 115.6, 80.3, 54.7, 52.5, 37.6, 29.2, 28.4, 25.5, 16.6.
HRMS (ESI): m/z calc. for [M+Na; $C_{19}H_{26}N_2NaO_5^+$]: 385.1739; found: 385.1737; calc. for [M-H; $C_{19}H_{25}N_2O_5^-$]: 361.1769; found: 361.1776.
IR (Diamond-ATR, neat): $\nu =$ 3366 (m), 2977 (m), 2933 (m), 2360 (m), 2339 (w), 1743 (m), 1711 (s), 1686 (s), 1612 (m), 1510 (s), 1437 (m), 1393 (m), 1366 (s), 1259 (s), 1212 (m), 1164 (vs), 1114 (m), 1060 (m), 1022 (m).
M.p. 94.9 °C.

Ethyl (*S*)-6-(5-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-2-hydroxyphenyl)hexanoate (6e)

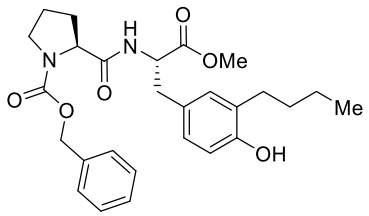


According to **TP7**, $Pd(dba)_2$ (6.90 mg, 12.0 µmol, 4.00 mol%), P*t*Bu_3 (0.03 mL, 1.00 M in toluene, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before tyrosine-derivate **3a** (126 mg, 0.30 mmol, 1.00 equiv) was added. The alkylzinc halide solution **5e** in THF (0.74 mL, 0.81 M, 0.60 mmol, 2.00 equiv) was added dropwise over 1 h and the reaction mixture

stirred at 25 °C for further 7 h. After quenching, extracting and evaporating, the crude product was purified by flash column chromatography. Final purification via preparative reversed-phase HPLC-chromatography (MeCN/H_2O) yielded the modified alkyltyrosine-derivate **6e** as colorless, viscous oil (61.0 mg, 0.14 mmol, 48% yield).

^{1}H-NMR (800 MHz, $CDCl_3$, ppm) δ = 6.82 (d, *J* = 2.1 Hz, 1H), 6.80 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.31 (s, 1H), 4.98 (d, *J* = 8.4 Hz, 1H), 4.52 (dt, *J* = 8.4, 5.8 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 3.04 – 2.91 (m, 2H), 2.56 (dd, *J* = 8.9, 6.6 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.67 (dd, *J* = 9.0, 6.2 Hz, 2H), 1.63 – 1.55 (m, 2H), 1.44 – 1.34 (m, 11H), 1.24 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (201 MHz, $CDCl_3$, ppm) δ = 174.2, 172.7, 155.3, 152.9, 131.2, 128.7, 127.8, 127.8, 115.5, 80.1, 60.4, 54.7, 52.3, 37.6, 34.4, 29.9, 29.5, 29.1, 28.5, 24.8, 14.4.
HRMS (ESI): m/z calc. for [M+Na; $C_{23}H_{35}NNaO_7^+$]: 460.2311; found: 460.2308; calc. for [M-H; $C_{23}H_{34}NO_7^-$]: 436.2341; found: 436.2357.
IR (Diamond-ATR, neat): ν = 3383 (w), 2978 (w), 2934 (m), 2859 (w), 2358 (w), 1732 (s), 1715 (vs), 1611 (w), 1508 (s), 1437 (m), 1392 (m), 1367 (s), 1259 (s), 1205 (s), 1166 (vs), 1114 (w), 1060 (m), 1023 (m), 856 (vw), 822 (w).

Benzyl (*S*)-2-(((*S*)-3-(3-butyl-4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (6f)



According to **TP7**, $Pd(dba)_2$ (6.90 mg, 12.0 µmol, 4.00 mol%), P*t*Bu_3 (0.03 mL, 1.00 M in toluene, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3b** (166 mg, 0.30 mmol, 1.00 equiv) was added. The butylzinc chloride solution **5a** in THF (1.02 mL, 0.59 M, 0.60 mmol, 2.00 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 7 h. After quenching, extracting and evaporating, the crude product was purified by flash column chromatography. Final purification via preparative reversed-phase HPLC-chromatography (MeCN/H_2O) yielded the modified alkyltyrosine-peptide **6f** as colorless solid (87.0 mg, 0.18 mmol, 61% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm) δ = 8.69 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.28 (q, *J* = 7.6, 6.6 Hz, 5H), 6.81 (d, *J* = 2.2 Hz, 1H), 6.75 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 5.01 (d, *J* = 11.3 Hz, 2H), 4.42 (td, *J* = 7.7, 6.3 Hz, 1H), 4.23 (dd, *J* = 8.7, 3.1 Hz, 1H), 3.53 (s, 3H), 3.44 – 3.30 (m, 2H), 2.88 – 2.74 (m, 2H), 2.46 – 2.42 (m, 2H), 2.12 – 1.98 (m, 1H), 1.81 – 1.67 (m, 3H), 1.48 (tt, *J* = 7.8, 6.3 Hz, 2H), 1.33 – 1.22 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, 80 °C, DMSO-d$_6$, ppm) = 171.5, 171.4, 153.7, 153.4, 136.7, 129.9, 128.0, 127.8, 127.1, 126.8, 126.7, 126.6, 114.5, 65.5, 59.3, 53.4, 51.1, 46.4, 35.9, 31.1, 29.9, 28.8, 22.8, 21.5, 13.3.

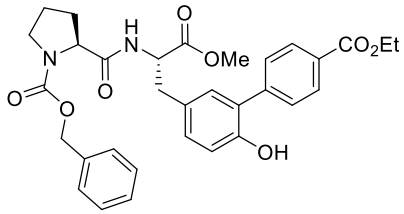
HRMS (ESI): m/z calc. for [M+Na; $C_{27}H_{34}N_2NaO_6^+$]: 505.2315; found: 505.2312; m/z calc. for [M+H; $C_{27}H_{35}N_2O_6^+$]: 483.2490; found: 483.2492; calc. for [M-H; $C_{27}H_{33}N_2O_6^-$]: 481.2344; found: 481.2348.

IR (Diamond-ATR, neat): $\nu =$ 3347 (w), 2951 (w), 1745 (m), 1696 (s), 1648 (vs), 1609 (w), 1538 (m), 1509 (w), 1449 (m), 1409 (s), 1357 (s), 1260 (m), 1206 (s), 1176 (m), 1122 (m), 985 (w), 956 (w), 825 (w), 802 (w), 766 (m), 743 (m), 697 (m).

M.p. 106.7 °C.

2.8 Negishi Cross-Coupling Reactions of Tyrosine containing Peptides with Arylzinc Pivalates

Benzyl (*S*)-2-(((*S*)-3-(4'-(ethoxycarbonyl)-6-hydroxy-[1,1'-biphenyl]-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (7a)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3b** (166 mg, 0.30 mmol, 1.00 equiv) was added. The arylzinc pivalate solution **1a** in THF (1.15 mL, 0.39 M, 0.45 mmol, 1.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **7a** was obtained as colorless solid (116 mg, 0.20 mmol, 67% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d$_6$, ppm) δ = 9.28 (s, 1H), 8.02 – 7.93 (m, 3H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 5H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.02 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.99 (s, 2H), 4.54 (td, *J* = 8.1, 5.8 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.26 (dd, *J* = 8.6, 3.3 Hz, 1H), 3.60 (s, 3H), 3.44 – 3.31 (m, 2H), 3.04 – 2.86 (m, 2H), 2.06 (p, *J* = 8.1, 7.5 Hz, 1H), 1.83 – 1.65 (m, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

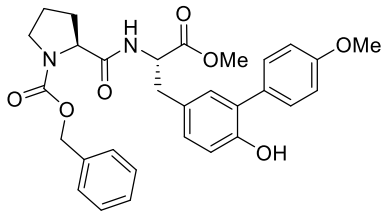
^{13}C-NMR (101 MHz, 80 °C, DMSO-d$_6$, ppm) δ = 171.5, 171.3, 165.3, 153.7, 152.7, 143.1, 136.6, 130.5, 129.4, 128.7, 128.2, 127.8, 127.7, 127.6, 127.1, 126.8, 125.9, 115.9, 65.5, 60.0, 59.3, 53.1, 51.2, 46.4, 35.6, 29.9, 22.8, 13.7

HRMS (ESI): m/z calc. for [M; $C_{32}H_{34}N_2O_8$]: 574.2315; found: 574.2278; m/z calc. for [M+H; $C_{32}H_{35}N_2O_8^+$]: 575.2388; found: 575.2399; calc. for [M-H; $C_{32}H_{33}N_2O_8^-$]: 573.2242; found: 573.2242.

IR (Diamond-ATR, neat): ν = 3334 (w), 2951 (w), 2359 (w), 2341 (w), 1744 (m), 1709 (s), 1697 (s), 1607 (m), 1514 (m), 1432 (m), 1401 (m), 1356 (m), 1312 (m), 1275 (vs), 1231 (m), 1211 (s), 1180 (m), 1110 (m), 1103 (m), 1018 (w), 754 (m), 699 (w).

M.p. 89.6 °C.

Benzyl (*S*)-2-(((*S*)-3-(6-hydroxy-4'-methoxy-[1,1'-biphenyl]-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (7b)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3b** (166 mg, 0.30 mmol, 1.00 equiv) was added. The arylzinc pivalate solution **1b** in THF (0.82 mL, 0.55 M, 0.45 mmol, 1.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography (MeCN/H_2O), the modified tyrosine-peptide **7b** was obtained as colorless solid (75.0 mg, 0.14 mmol, 48% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm) δ = 8.96 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.37 – 7.24 (m, 5H), 7.05 (d, *J* = 2.3 Hz, 1H), 6.96 – 6.89 (m, 3H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.06 – 4.95 (m, 2H), 4.52 (td, *J* = 8.0, 6.0 Hz, 1H), 4.26 (dd, *J* = 8.6, 3.3 Hz, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 3.44 – 3.32 (m, 2H), 2.93 (qd, *J* = 13.9, 7.0 Hz, 2H), 2.15 – 1.99 (m, 1H), 1.84 – 1.66 (m, 3H).

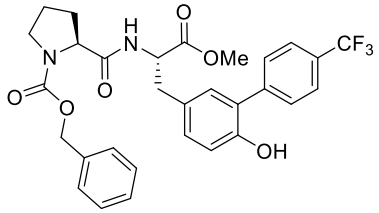
^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm) δ = 171.5, 171.4, 157.8, 153.7, 152.5, 136.6, 130.6, 130.3, 129.6, 127.9, 127.8, 127.3, 127.1, 126.9, 126.8, 115.7, 113.1, 65.5, 59.3, 54.8, 53.2, 51.1, 46.4, 35.7, 29.9, 22.8.

HRMS (ESI): m/z calc. for [M; $C_{30}H_{32}N_2O_7$]: 532.2210; found: 532.2175; m/z calc. for [M+H; $_{30}H_{33}N_2O_7^+$]: 533.2282; found: 533.2287; calc. for [M-H; $C_{30}H_{31}N_2O_7^-$]: 531.2137; found: 531.2140.

IR (Diamond-ATR, neat): ν = 3311 (w), 2951 (w), 2359 (w), 1742 (m), 1694 (s), 1667 (s), 1608 (m), 1517 (s), 1504 (s), 1433 (s), 1417 (s), 1355 (s), 1277 (s), 1244 (vs), 1210 (s), 1177 (vs), 1116 (m), 1027 (m), 987 (w), 834 (m), 797 (w), 751 (m), 697 (m).

M.p. 90.9 °C.

Benzyl (*S*)-2-(((*S*)-3-(6-hydroxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (7c)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3b** (166 mg, 0.30 mmol, 1.00 equiv) was added. The arylzinc pivalate solution **1f** in THF (1.09 mL, 0.69 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **7c** was obtained as colorless solid (137 mg, 0.24 mmol, 80% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm): δ = 9.35 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.22 (m, 5H), 7.14 (d, *J* = 2.3 Hz, 1H), 7.03 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.05 – 4.91 (m, 2H), 4.54 (td, *J* = 8.1, 5.8 Hz, 1H), 4.25 (dd, *J* = 8.6, 3.3 Hz, 1H), 3.59 (s, 3H), 3.43 – 3.31 (m, 2H), 3.05 – 2.87 (m, 2H), 2.13 – 1.99 (m, 1H), 1.82 – 1.64 (m, 3H).

^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm): δ = 171.7, 171.5, 153.8, 152.8, 142.5, 136.7, 130.6, 129.6, 129.4, 127.9, 127.8, 127.2, 126.8 (q, *J* = 31.5 Hz), 126.3, 125.7, 124.3 (q, *J* = 3.9 Hz), 116.0, 65.6, 59.4, 53.2, 51.3, 46.5, 35.7, 30.0, 22.8.

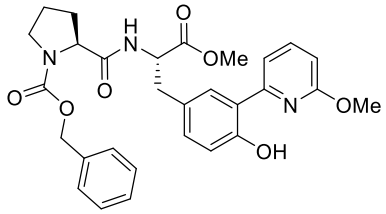
^{19}F-NMR (377 MHz, 80 °C, DMSO-d_6, ppm): δ = –60.9.

HRMS (ESI): m/z calc. for [M; $C_{30}H_{29}F_3N_2O_6$]: 570.1978; found: 570.1951; m/z calc. for [M+H; $C_{30}H_{30}F_3N_2O_6^+$]: 571.2050; found: 571.2059; calc. for [M-H; $C_{30}H_{28}F_3N_2O_6^-$]: 569.1905; found: 569.1912.

IR (Diamond-ATR, neat): ν = 3298 (w), 1742 (w), 1688 (m), 1658 (m), 1611 (w), 1524 (w), 1502 (w), 1414 (m), 1401 (m), 1355 (m), 1323 (vs), 1278 (m), 1210 (m), 1162 (m), 1108 (vs), 1067 (s), 1016 (m), 986 (w), 845 (m), 769 (w), 736 (w), 697 (m).

M.p. 84.8 °C.

Benzyl (*S*)-2-(((*S*)-3-(4-hydroxy-3-(6-methoxypyridin-2-yl)phenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (7d)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3b** (166 mg, 0.30 mmol, 1.00 equiv) was added. The pyridylzinc pivalate solution **1g** in THF/*n*hexane (1.88 mL, 0.24 M, 0.45 mmol, 1.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **7d** was obtained as colorless solid (96.0 mg, 0.18 mmol, 61% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm) δ = 12.52 (s, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.21 (m, 5H), 7.11 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.84 – 6.79 (m, 2H), 5.04 – 4.89 (m, 2H), 4.58 (td, *J* = 8.3, 5.8 Hz, 1H), 4.26 (dd, *J* = 8.7, 3.2 Hz, 1H), 3.94 (s, 3H), 3.61 (s, 3H), 3.47 – 3.32 (m, 2H), 3.06 – 2.90 (m, 2H), 2.08 (q, *J* = 8.4 Hz, 1H), 1.84 – 1.64 (m, 3H).

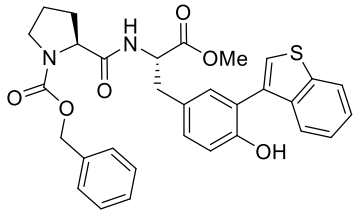
^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm) δ = 171.5, 171.3, 161.5, 156.3, 154.0, 153.7, 140.4, 136.6, 131.3, 127.7, 127.6, 127.2, 127.1, 126.7, 119.1, 117.0, 112.7, 107.8, 65.5, 59.2, 53.2, 53.1, 51.2, 46.4, 35.7, 30.0, 22.7.

HRMS (ESI): m/z calc. for [M; $C_{29}H_{31}N_3O_7$]: 533.2162; found: 533.2112; m/z calc. for [M+H; $C_{29}H_{32}N_3O_7^+$]: 534.2235; found: 534.2237; calc. for [M-H; $C_{29}H_{30}N_3O_7^-$]: 532.2089; found: 532.2077.

IR (Diamond-ATR, neat): ν = 3322 (w), 2951 (w), 2879 (w), 2359 (w), 2340 (w), 1742 (m), 1685 (s), 1597 (s), 1573 (s), 1461 (s), 1415 (s), 1355 (s), 1288 (m), 1264 (vs), 1208 (s), 1178 (m), 1117 (m), 1087 (m), 1026 (m), 807 (m), 751 (s), 697 (m), 668 (w).

M.p. 94.8 °C.

Benzyl (*S*)-2-(((*S*)-3-(3-(benzo[b]thiophen-3-yl)-4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (7e)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3b** (166 mg, 0.30 mmol, 1.00 equiv) was added. The heteroarylzinc pivalate solution **1h** in THF (1.63 mL, 0.46 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **7e** was obtained as colorless solid (78.0 mg, 0.14 mmol, 47% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm) δ = 9.07 (s, 1H), 8.01 – 7.95 (m, 2H), 7.64 – 7.59 (m, 1H), 7.57 (s, 1H), 7.37 – 7.33 (m, 2H), 7.33 – 7.23 (m, 6H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.06 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 4.99 (s, 2H), 4.54 (td, *J* = 8.0, 6.0 Hz, 1H), 4.26 (dd, *J* = 8.6, 3.4 Hz, 1H), 3.59 (s, 3H), 3.43 – 3.30 (m, 2H), 2.96 (qd, *J* = 14.1, 7.1 Hz, 2H), 2.13 – 1.99 (m, 1H), 1.82 – 1.65 (m, 2H).

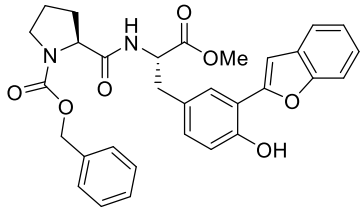
^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm) δ = 171.5, 171.4, 153.7, 153.2, 138.9, 138.1, 136.6, 134.0, 131.2, 129.0, 127.8, 127.1, 127.1, 126.8, 124.2, 123.6, 123.4, 123.1, 122.1, 121.7, 115.6, 65.5, 59.3, 53.2, 51.2, 46.4, 35.6, 30.1, 22.8.

HRMS (ESI): m/z calc. for [M+Na; $C_{31}H_{30}N_2NaO_6S^+$]: 581.1722; found: 581.1722; m/z calc. for [M+H; $C_{31}H_{31}N_2O_6S^+$]: 559.1903; found: 559.1897; calc. for [M-H; $C_{31}H_{29}N_2O_6S^-$]: 557.1752; found: 557.1752.

IR (Diamond-ATR, neat): ν = 3325 (m), 2952 (w), 2359 (w), 2339 (w), 1742 (s), 1695 (vs), 1682 (vs), 1668 (vs), 1609 (w), 1523 (m), 1498 (m), 1418 (vs), 1355 (s), 1243 (m), 1212 (s), 1177 (m), 1115 (m), 986 (w), 819 (w), 759 (vs), 697 (m), 667 (w).

M.p. 96.0 °C.

Benzyl (*S*)-2-(((*S*)-3-(3-(benzofuran-2-yl)-4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (7f)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3b** (166 mg, 0.30 mmol, 1.00 equiv) was added. The heteroarylzinc pivalate solution **1i** in THF/*n*hexane (6.25 mL, 0.12 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography (MeCN/H_2O), the modified tyrosine-peptide **7f** was obtained as colorless solid (141 mg, 0.26 mmol, 87% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d$_6$, ppm) δ = 10.00 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 2.2 Hz, 1H), 7.64 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.35 – 7.20 (m, 7H), 7.04 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 5.01 (s, 2H), 4.53 (td, *J* = 8.0, 6.1 Hz, 1H), 4.26 (dd, *J* = 8.6, 3.2 Hz, 1H), 3.61 (s, 3H), 3.49 – 3.32 (m, 2H), 3.05 – 2.92 (m, 2H), 2.14 – 1.99 (m, 1H), 1.87 – 1.67 (m, 3H).

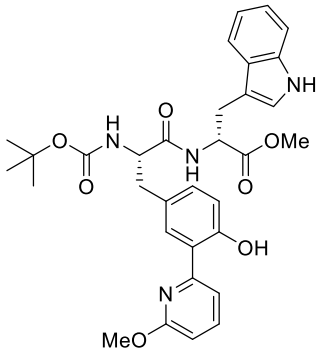
^{13}C-NMR (101 MHz, 80 °C, DMSO-d$_6$, ppm) δ = 171.5, 171.3, 153.7, 153.1, 152.9, 152.1, 136.6, 129.6, 129.0, 127.7, 127.5, 127.1, 126.8, 126.4, 123.6, 122.3, 120.5, 116.2, 115.9, 110.1, 105.0, 65.5, 59.3, 53.3, 51.2, 46.4, 35.7, 30.1, 22.8.

HRMS (ESI): m/z calc. for [M; $C_{31}H_{30}N_2O_7$]: 542.2053; found: 542.2024; m/z calc. for [M+H; $C_{31}H_{31}N_2O_7^+$]: 543.2126; found: 543.2132; calc. for [M-H; $C_{31}H_{29}N_2O_7^-$]: 541.1980; found: 541.1988.

IR (Diamond-ATR, neat): ν = 3278 (w), 2951 (w), 2359 (w), 1741 (m), 1658 (vs), 1650 (s), 1612 (m), 1529 (m), 1511 (s), 1453 (s), 1414 (vs), 1354 (vs), 1300 (m), 1258 (vs), 1208 (s), 1179 (s), 1123 (s), 1088 (m), 1029 (m), 821 (m), 743 (vs), 696 (s).

M.p. 94.4 °C.

Methyl ((*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-3-(6-methoxypyridin-2-yl)phenyl)propanoyl)-*D*-tryptophanate (8a)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3c** (182 mg, 0.30 mmol, 1.00 equiv) was added. The pyridylzinc pivalate solution **1g** in THF/*n*hexane (3.13 mL, 0.24 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **8a** was obtained as colorless solid (165 mg, 0.28 mmol, 92% yield).

^{1}H-NMR (599 MHz, 80 °C, DMSO-d_6, ppm) δ = 12.50 (s, 1H), 10.66 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.87 (dd, *J* = 8.3, 7.7 Hz, 1H), 7.73 (d, *J* = 2.2 Hz, 1H), 7.66 – 7.59 (m, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.34 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.98 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.3, 0.6 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.43 (s, 1H), 4.62 (td, *J* = 7.7, 6.0 Hz, 1H), 4.25 (dd, *J* = 13.1, 8.4 Hz, 1H), 3.94 (s, 3H), 3.61 (s, 3H), 3.19 (dd, *J* = 14.6, 6.0 Hz, 1H), 3.08 (dd, *J* = 14.2, 7.9 Hz, 1H), 2.86 (dd, *J* = 13.9, 4.7 Hz, 1H), 2.66 (dd, *J* = 13.9, 9.5 Hz, 1H), 1.28 (s, 9H).

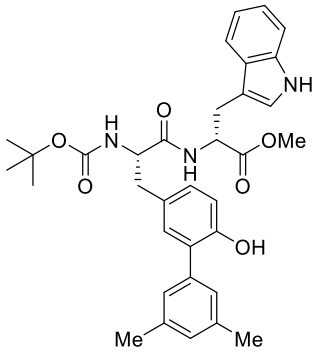
^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm) δ = 171.6, 171.1, 161.6, 156.1, 154.6, 154.3, 140.4, 135.9, 131.6, 128.0, 127.7, 126.8, 123.2, 120.6, 118.9, 118.0, 117.6, 116.8, 112.6, 111.0, 109.0, 107.7, 77.8, 55.4, 53.3, 52.7, 51.3, 36.7, 27.7, 27.1.

HRMS (ESI): m/z calc. for [M+Na; $C_{32}H_{36}N_4NaO_7$]: 611.2482; found: 611.2475; calc. for [M-H; $C_{32}H_{35}N_4O_7^-$]: 587.2511; found: 5877.2517.

IR (Diamond-ATR, neat): ν = 3326 (m), 2976 (w), 2359 (m), 2340 (m), 1734 (m), 1697 (s), 1660 (s), 1598 (s), 1573 (s), 1494 (s), 1460 (vs), 1435 (s), 1391 (m), 1366 (m), 1337 (m), 1288 (m), 1264 (vs), 1210 (s), 1165 (s), 1066 (w), 1024 (m), 809 (m), 746 (s), 668 (w).

M.p. 209.6 °C.

Methyl ((*S*)-2-((tert-butoxycarbonyl)amino)-3-(6-hydroxy-3',5'-dimethyl-[1,1'-biphenyl]-3-yl)propanoyl)-*D*-tryptophanate (8b)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3c** (182 mg, 0.30 mmol, 1.00 equiv) was added. The arylzinc pivalate solution **1j** in THF (1.67 mL, 0.45 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **8b** was obtained as yellowish solid (129 mg, 0.22 mmol, 72% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm): δ = 10.67 (s, 1H), 8.84 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.33 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.13 (d, *J* = 1.6 Hz, 2H), 7.09 (dd, *J* = 6.9, 2.1 Hz, 2H), 7.05 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.98 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.91 (dt, *J* = 1.8, 0.9 Hz, 1H), 6.88 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.40 (s, 1H), 4.60 (q, *J* = 7.5 Hz, 1H), 4.26 – 4.16 (m, 1H), 3.59 (s, 3H), 3.17 (dd, *J* = 14.6, 6.1 Hz, 1H), 3.07 (dd, *J* = 14.6, 7.6 Hz, 1H), 2.81 (dd, *J* = 13.9, 4.6 Hz, 1H), 2.61 (dd, *J* = 13.9, 9.5 Hz, 1H), 2.30 (s, 6H), 1.30 (s, 9H).

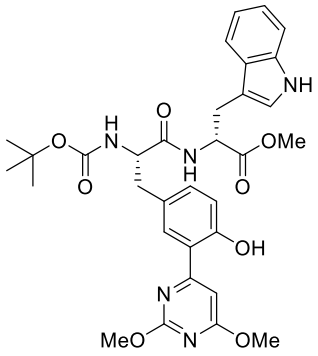
^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm): δ = 171.6, 171.2, 154.5, 152.3, 138.4, 136.1, 135.9, 130.8, 128.5, 128.1, 127.3, 127.3, 126.8, 126.5, 123.2, 120.6, 118.0, 117.6, 115.4, 111.0, 109.0, 77.8, 55.4, 52.7, 51.2, 36.7, 27.7, 27.1, 20.6.

HRMS (ESI): m/z calc. for [M+Na; $C_{34}H_{39}N_3NaO_6^+$]: 608.2731; found: 608.2730; m/z calc. for [M-H; $C_{34}H_{38}N_3O_6^-$]: 584.2766; found: 584.2790.

IR (Diamond-ATR, neat): ν = 3406 (w), 3318 (w), 1691 (m), 1659 (s), 1602 (m), 1509 (s), 1499 (s), 1455 (m), 1439 (m), 1366 (s), 1232 (s), 1161 (vs), 1077 (w), 1048 (m), 1011 (m), 851 (m), 807 (w), 740 (s), 701 (w).

M.p. 111.3 °C.

Methyl ((*S*)-2-((tert-butoxycarbonyl)amino)-3-(3-(2,6-dimethoxypyrimidin-4-yl)-4-hydroxyphenyl)propanoyl)-*D*-tryptophanate (8c)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3c** (182 mg, 0.30 mmol, 1.00 equiv) was added. The pyrimidylzinc pivalate solution **1k** in THF (1.17 mL, 0.64 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **8c** was obtained as beige solid (143 mg, 0.23 mmol, 76% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm): δ = 10.66 (s, 1H), 8.88 (s, 1H), 8.12 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.33 (dt, *J* = 8.1, 0.8 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.06 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.00 – 6.95 (m, 2H), 6.93 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.35 (s, 1H), 4.65 – 4.54 (m, 1H), 4.25 – 4.15 (m, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.59 (s, 3H), 3.16 (dd, *J* = 14.6, 6.0 Hz, 1H), 3.10 – 3.01 (m, 1H), 2.80 (dd, *J* = 14.0, 4.7 Hz, 1H), 2.61 (dd, *J* = 14.0, 9.3 Hz, 1H), 1.30 (s, 9H).

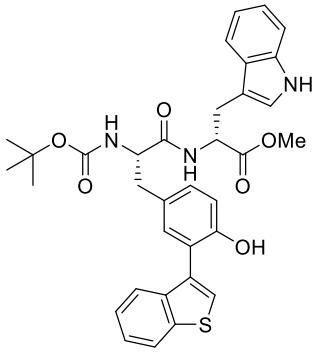
^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm): δ = 171.6, 171.1, 167.8, 163.8, 158.1, 154.6, 153.1, 135.9, 131.5, 129.4, 127.7, 126.8, 123.2, 120.6, 119.4, 118.0, 117.6, 115.0, 113.0, 111.0, 109.0, 77.8, 55.4, 53.9, 53.1, 52.7, 51.2, 36.5, 27.7, 27.1.

HRMS (ESI): m/z calc. for [M+Na; $C_{32}H_{37}N_5NaO_8^+$]: 642.2534; found: 642.2534; m/z calc. for [M+H; $C_{32}H_{38}N_5O_8^+$]: 620.2715; found: 620.2718; calc. for [M-H; $C_{32}H_{36}N_5O_8^-$]: 618.2569; found: 618.2588.

IR (Diamond-ATR, neat): ν = 3324 (w), 2359 (w), 1737 (m), 1690 (m), 1659 (m), 1594 (m), 1560 (m), 1501 (m), 1469 (s), 1392 (s), 1381 (s), 1235 (m), 1163 (s), 1079 (m), 1059 (m), 1014 (s), 801 (m), 742 (m).

M.p. 151.7 °C.

Methyl ((*S*)-3-(3-(benzo[b]thiophen-3-yl)-4-hydroxyphenyl)-2-((tert-butoxycarbonyl)amino)propanoyl)-*D*-tryptophanate (8d)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3c** (182 mg, 0.30 mmol, 1.00 equiv) was added. The heteroarylzinc pivalate solution **1h** in THF (1.53 mL, 0.49 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **8d** was obtained as colorless solid (68.0 mg, 0.11 mmol, 38% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm) δ = 10.64 (s, 1H), 8.98 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.99 – 7.96 (m, 1H), 7.70 – 7.62 (m, 1H), 7.55 (s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.30 (m, 3H), 7.17 (d, *J* = 2.2 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.05 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.38 (s, 1H), 4.60 (td, *J* = 7.6, 6.0 Hz, 1H), 4.29 – 4.19 (m, 1H), 3.58 (s, 3H), 3.17 (dd, *J* = 14.6, 6.1 Hz, 1H), 3.06 (dd, *J* = 14.7, 7.5 Hz, 1H), 2.85 (dd, *J* = 13.9, 4.6 Hz, 1H), 2.63 (dd, *J* = 14.0, 9.5 Hz, 1H), 1.28 (s, 9H).

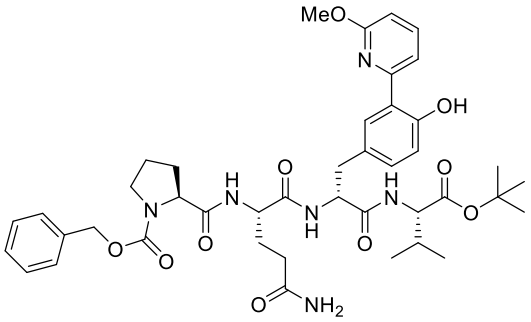
^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm) δ = 171.6, 171.1, 154.6, 153.0, 138.9, 138.2, 135.9, 134.2, 131.4, 129.2, 127.9, 126.8, 124.0, 123.5, 123.4, 123.2, 123.2, 122.1, 121.5, 120.5, 118.0, 117.6, 115.4, 111.0, 109.0, 77.8, 55.5, 52.6, 51.2, 36.6, 27.7, 27.1.

HRMS (ESI): m/z calc. for [M+Na; $C_{34}H_{35}N_3NaO_6S$]: 636.2144; found: 363.2144; m/z calc. for [M+H; $C_{34}H_{36}N_3O_6S^+$]: 614.2319; found: 614.2322; calc. for [M-H; $C_{34}H_{34}N_3O_6S^-$]: 612.2174; found: 612.2177.

IR (Diamond-ATR, neat): ν = 3327 (w), 3007 (w), 2977 (w), 2359 (w), 1731 (m), 1694 (m), 1660 (s), 1610 (w), 1496 (s), 1456 (m), 1434 (m), 1366 (m), 1246 (m), 1215 (m), 1162 (s), 1111 (w), 1059 (w), 1020 (w), 818 (w), 753 (vs), 706 (vw), 667 (w).

M.p. 129.6 °C.

Benzyl (*S*)-2-(((*S*)-5-amino-1-(((*R*)-1-(((*S*)-1-(tert-butoxy)-3-methyl-1-oxobutan-2-yl)amino)-3-(4-hydroxy-3-(6-methoxypyridin-2-yl)phenyl)-1-oxopropan-2-yl)amino)-1,5-dioxopentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (9a)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3d** (247 mg, 0.30 mmol, 1.00 equiv) was added. The pyridylzinc pivalate solution **1g** in THF/*n*hexane (3.13 mL, 0.24 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **9a** was obtained as colorless solid (120 mg, 0.15 mmol, 50% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm): δ = 12.55 (s, 1H), 7.94 – 7.86 (m, 2H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 4.9 Hz, 4H), 7.29 (t, *J* = 4.2 Hz, 1H), 7.16 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.81 (t, *J* = 8.1 Hz, 2H), 6.59 (s, 2H), 5.13 – 4.99 (m, 2H), 4.72 – 4.63 (m, 1H), 4.27 – 4.18 (m, 2H), 4.07 (dd, *J* = 8.3, 5.8 Hz, 1H), 3.95 (s, 3H), 3.49 – 3.36 (m, 2H), 3.07 – 2.99 (m, 2H), 2.84 (dd, *J* = 14.0, 9.0 Hz, 1H), 2.14 – 1.92 (m, 4H), 1.88 – 1.61 (m, 4H), 1.41 (s, 9H), 0.87 – 0.78 (m, 6H).

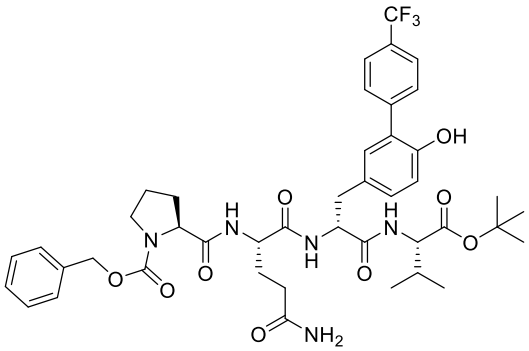
^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm): δ = 173.3, 171.5, 170.6, 170.6, 169.8, 161.5, 156.2, 154.2, 153.8, 140.4, 136.6, 131.6, 127.9, 127.7, 127.6, 127.2, 126.9, 119.0, 117.0, 112.7, 107.7, 80.3, 65.7, 59.4, 57.7, 53.7, 53.3, 52.3, 46.4, 37.0, 37.0, 31.1, 29.7, 27.4, 27.3, 23.0, 18.3, 17.6.

HRMS (ESI): m/z calc. for m/z calc. for [M+H; $C_{42}H_{55}N_6O_{10}^+$]: 803.3974; found: 803.3971; calc. for [M+2H; $C_{42}H_{56}N_6O_{10}^{2+}$]: 804.4047; found: 804.4010.

IR (Diamond-ATR, neat): ν = 3285 (w), 2973 (w), 2359 (m), 2340 (m), 1732 (w), 1699 (m), 1652 (s), 1638 (vs), 1540 (m), 1464 (m), 1419 (m), 1392 (w), 1358 (w), 1337 (w), 1286 (w), 1266 (m), 1210 (w), 1160 (w), 668 (w).

M.p. 175.7 °C.

Benzyl (*S*)-2-(((S)-5-amino-1-(((*R*)-1-(((*S*)-1-(tert-butoxy)-3-methyl-1-oxobutan-2-yl)amino)-3-(6-hydroxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-1-oxopropan-2-yl)amino)-1,5-dioxopentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (9b)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3d** (247 mg, 0.30 mmol, 1.00 equiv) was added. The arylzinc pivalate solution **1f** in THF (1.09 mL, 0.69 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **9b** was obtained as colorless solid (202 mg, 0.24 mmol, 80%).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm): δ = 9.24 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.82 – 7.71 (m, 4H), 7.74 – 7.67 (m, 2H), 7.40 – 7.24 (m, 5H), 7.19 (d, *J* = 2.2 Hz, 1H), 7.07 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.62 (s, 2H), 5.13 – 5.01 (m, 2H), 4.67 (q, *J* = 7.9 Hz, 1H), 4.29 – 4.18 (m, 2H), 4.06 (dd, *J* = 8.4, 5.8 Hz, 1H), 3.50 – 3.37 (m, 2H), 2.99 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.81 (dd, *J* = 13.9, 8.7 Hz, 1H), 2.14 – 2.04 (m, 1H), 2.04 – 1.94 (m, 3H), 1.89 – 1.74 (m, 4H), 1.74 – 1.63 (m, 1H), 1.41 (s, 9H), 0.81 (dd, *J* = 6.8, 5.8 Hz, 6H).

^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm): δ = 173.4, 171.5, 170.6, 170.6, 169.8, 153.8, 152.6, 142.7, 136.7, 130.6, 129.7, 129.3, 128.1, 127.8, 127.2, 126.9, 126.6 (q, *J* = 31.9), 126.3 (q, *J* = 271.8), 126.3, 125.5, 124.4, 124.3, 124.1 (q, *J* = 3.9), 115.8, 80.3, 65.6, 59.4, 57.6, 53.7, 52.3, 46.4, 36.9, 31.1, 29.7, 27.5, 27.4, 23.2, 18.3, 17.6.

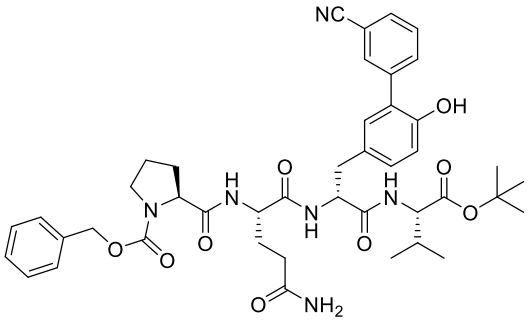
^{19}F-NMR (377 MHz, 80 °C, DMSO-d_6): δ = –60.9.

HRMS (ESI): m/z calc. for [M+Na; $C_{43}H_{52}F_3N_5NaO_9^+$]: 862.3615; found: 862.3614; calc. for [M-H; $C_{43}H_{51}F_3N_5O_9^-$]: 838.3644; found: 838.3667.

IR (Diamond-ATR, neat): ν = 3294 (w), 2969 (w), 1657 (s), 1650 (s), 1618 (m), 1523 (m), 1508 (m), 1424 (m), 1401 (m), 1358 (m), 1325 (vs), 1278 (m), 1215 (m), 1163 (s), 1122 (s), 1068 (m), 1017 (w), 985 (vw), 845 (w), 755 (m), 697 (w).

M.p. 180.2 °C.

Benzyl (*S*)-2-(((*S*)-5-amino-1-(((*R*)-1-(((*S*)-1-(tert-butoxy)-3-methyl-1-oxobutan-2-yl)amino)-3-(3'-cyano-6-hydroxy-[1,1'-biphenyl]-3-yl)-1-oxopropan-2-yl)amino)-1,5-dioxopentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (9c)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3d** (247 mg, 0.30 mmol, 1.00 equiv) was added. The arylzinc pivalate solution **1l** in THF (1.70 mL, 0.44 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **9c** was obtained as colorless solid (215 mg, 0.27 mmol, 89% yield).

^{1}H-NMR (400 MHz, 80 °C, DMSO-d_6, ppm): δ = 9.31 (s, 1H), 7.96 (t, *J* = 1.8 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.70 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.59 (td, *J* = 7.8, 0.6 Hz, 1H), 7.38 – 7.24 (m, 5H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.06 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.81 – 6.30 (m, 2H), 5.07 (s, 2H), 4.69 (q, *J* = 7.7 Hz, 1H), 4.23 (t, *J* = 7.3, 2H), 4.06 (dd, *J* = 8.4, 5.8 Hz, 1H), 3.51 – 3.35 (m, 2H), 2.98 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.81 (dd, *J* = 13.9, 8.7 Hz, 1H), 2.15 – 2.05 (m, 1H), 2.04 – 1.92 (m, 3H), 1.89 – 1.74 (m, 4H), 1.70 (d, *J* = 8.1 Hz, 1H), 1.41 (s, 9H), 0.81 (dd, *J* = 7.7, 6.8 Hz, 6H).

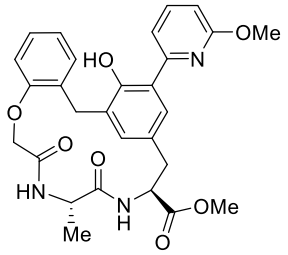
^{13}C-NMR (101 MHz, 80 °C, DMSO-d_6, ppm): δ = 173.4, 171.5, 170.6, 170.6, 169.8, 153.8, 152.5, 139.6, 136.7, 133.5, 132.0, 130.6, 129.8, 129.5, 128.7, 128.2, 127.9, 127.2, 126.9, 124.8, 118.5, 115.8, 110.8, 80.3, 65.7, 59.4, 57.6, 53.6, 52.3, 46.4, 37.0, 36.9, 31.1, 29.7, 27.5, 27.4, 23.0, 18.3, 17.6.

HRMS (ESI): m/z calc. for [M+Na; $C_{43}H_{52}N_6NaO_9^+$]: 819.3688; found: 819.3701; m/z calc. for [M+H; $C_{43}H_{53}N_6O_9^+$]: 797.3869; found 797.3880; m/z calc. for [M-H; $C_{43}H_{51}F_3N_6O_9^-$]: 795.3723; found: 795.3743.

IR (Diamond-ATR, neat): ν = 3288 (w), 2968 (w), 2358 (w), 2228 (w), 1652 (vs), 1538 (m), 1511 (s), 1447 (m), 1418 (m), 1395 (m), 1358 (m), 1310 (m), 1272 (m), 1258 (m), 1213 (m), 1145 (m), 693 (m).

M.p. 129.0 °C.

Methyl (8*S*,11*S*)-16-hydroxy-15-(6-methoxypyridin-2-yl)-8-methyl-6,9-dioxo-4-oxa-7,10-diaza-1(1,3),3(1,2)-dibenzenacyclododecaphane-11-carboxylate (10a)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3e** (162 mg, 0.30 mmol, 1.00 equiv) was added. The pyridylzinc pivalate solution **1g** in THF/*n*hexane (3.13 mL, 0.24 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **10a** was obtained as colorless solid (130 mg, 0.25 mmol, 82% yield).

^{1}H-NMR (400 MHz, DMSO-d_6, ppm): δ = 13.69 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 2.1 Hz, 1H), 7.39 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.22 (td, *J* = 7.9, 7.4, 1.8 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 4.70 (d, *J* = 14.3 Hz, 1H), 4.53 (d, *J* = 14.4 Hz, 1H), 4.51 – 4.46 (m, 1H), 4.46 – 4.41 (m, 1H), 4.08 (d, *J* = 14.6 Hz, 1H), 3.97 (s, 3H), 3.89 (d, *J* = 14.7 Hz, 1H), 3.69 (s, 3H), 3.04 (dd, *J* = 13.7, 3.3 Hz, 1H), 2.74 (dd, *J* = 13.6, 11.4 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H).

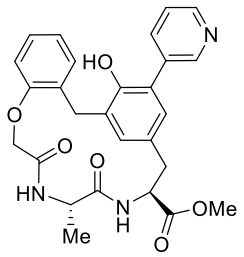
^{13}C-NMR (101 MHz, DMSO-d_6, ppm): δ = 172.0, 171.0, 167.6, 161.5, 155.6, 155.0, 154.6, 141.3, 132.8, 132.0, 128.4, 127.8, 127.7, 127.5, 125.4, 121.0, 118.1, 112.8, 111.4, 108.2, 66.7, 54.0, 53.9, 52.0, 47.0, 35.7, 29.9, 16.4.

HRMS (ESI): m/z calc. for [M+H, $C_{28}H_{30}N_3O_7^+$]: 520.2078. found: 520.2083

IR (Diamond-ATR, neat): ν = 3295 (w), 3276 (w), 1730 (m), 1668 (m), 1650 (vs), 1594 (m), 1545 (s), 1493 (m), 1465 (m), 1451 (s), 1433 (m), 1355 (w), 1302 (m), 1263 (s), 1243 (m), 1198 (s), 1176 (m), 1121 (m), 1103 (m), 1054 (m), 1045 (w), 1034 (m), 999 (m), 923 (w), 828 (m), 810 (m), 745 (s), 736 (s), 692 (m).

M.p. 284.6 °C.

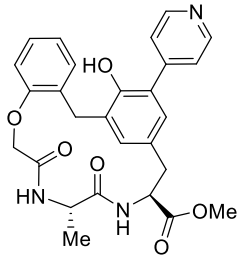
Methyl (8*S*,11*S*)-16-hydroxy-8-methyl-6,9-dioxo-15-(pyridin-3-yl)-4-oxa-7,10-diaza-1(1,3),3(1,2)-dibenzenacyclododecaphane-11-carboxylate (10b)



According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3e** (162 mg, 0.30 mmol, 1.00 equiv) was added. The zinc pivalate solution **1d** in THF (1.79 mL, 0.42 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography (MeCN/H_2O), the modified tyrosine-peptide **10b** was obtained as colorless solid (78 mg, 0.16 mmol, 53% yield).

^{1}H-NMR (400 MHz, DMSO-d_6, ppm): δ = 8.67 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.50 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.87 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.43 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.34 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.26 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.09 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.95 (td, *J* = 7.4, 1.1 Hz, 1H), 6.82 (d, *J* = 2.2 Hz, 1H), 4.75 (d, *J* = 14.2 Hz, 1H), 4.60 – 4.41 (m, 3H), 4.15 (d, *J* = 15.3 Hz, 1H), 3.86 (d, *J* = 15.3 Hz, 1H), 3.66 (s, 3H), 3.01 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.69 (dd, *J* = 13.6, 11.5 Hz, 1H), 1.01 (d, *J* = 7.0 Hz, 3H).
^{13}C-NMR (101 MHz, DMSO-d_6, ppm): δ = 171.9, 171.0, 167.5, 155.6, 150.3, 149.7, 147.6, 136.5, 134.6, 131.8, 130.4, 129.1, 128.9, 128.7, 127.8, 127.3, 126.5, 123.2, 121.0, 111.4, 66.5, 53.5, 52.0, 46.8, 35.8, 30.6, 16.6.
HRMS (ESI): m/z calc. for [M+H, $C_{27}H_{28}N_3O_6^+$]: 490.1973; found: 490.1977.
IR (Diamond-ATR, neat): ν = 3370 (m), 3008 (w), 2930 (w), 1733 (m), 1668 (vs), 1537 (s), 1533 (s), 1492 (m), 1454 (m), 1234 (s), 1217 (s), 1165 (m), 1117 (m), 752 (s).
M.p. 145.0 °C.

Methyl (8*S*,11*S*)-16-hydroxy-8-methyl-6,9-dioxo-15-(pyridin-4-yl)-4-oxa-7,10-diaza-1(1,3),3(1,2)-dibenzenacyclododecaphane-11-carboxylate (10c)

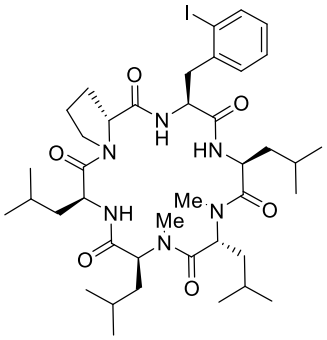


According to **TP5**, $Pd(OAc)_2$ (2.69 mg, 12.0 µmol, 4.00 mol%), SPhos (9.85 mg, 24.0 µmol, 8.00 mol%) and freshly distilled THF (0.6 mL) were mixed and stirred for 10 min, before iodotyrosine-peptide **3e** (162 mg, 0.30 mmol, 1.00 equiv) was added. The zinc pivalate solution **1e** in THF (3.26 mL, 0.23 M, 0.75 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred at 25 °C for further 3 h. After quenching, extracting and evaporating, the crude product was pre-purified by flash column chromatography. After final preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$), the modified tyrosine-peptide **10c** was obtained as colorless solid (98 mg, 0.20 mmol, 67% yield).

^{1}H-NMR (400 MHz, DMSO-d_6, ppm): δ = 8.66 (s, 1H), 8.59 (dd, *J* = 4.4, 1.6 Hz, 2H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.51 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.34 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.26 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.11 – 7.05 (m, 2H), 7.02 (d, *J* = 2.2 Hz, 1H), 6.95 (td, *J* = 7.4, 1.1 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 4.74 (d, *J* = 14.2 Hz, 1H), 4.57 – 4.40 (m, 3H), 4.15 (d, *J* = 15.3 Hz, 1H), 3.86 (d, *J* = 15.3 Hz, 1H), f 3.01 (dd, *J* = 13.7, 3.5 Hz, 1H), 2.69 (dd, *J* = 13.6, 11.5 Hz, 1H), 1.01 (d, *J* = 6.9 Hz, 3H).
^{13}C-NMR (101 MHz, DMSO-d_6, ppm): δ = 171.9, 171.0, 167.5, 155.6, 150.2, 149.3, 146.4, 131.8, 131.1, 129.3, 129.1, 128.5, 127.8, 127.3, 127.1, 124.1, 121.0, 111.5, 66.6, 53.5, 52.0, 46.8, 35.7, 30.5, 16.5.
HRMS (ESI): m/z calc. for [M+H, $C_{27}H_{28}N_3O_6^+$]: 490.1973; found: 490.1976.
IR (Diamond-ATR, neat): ν = 3280 (m), 3075 (w), 2950 (w), 2358 (w), 2340 (w), 1741 (m), 1644 (vs), 1603 (m), 1544 (s), 1493 (m), 1471 (m), 1450 (m), 1410 (w), 1372 (w), 1326 (w), 1281 (m), 1243 (s), 1213 (s), 1116 (m), 1054 (m), 1002 (w), 919 (w), 832 (w), 747 (s), 705 (w), 667 (w).
M.p. 254.8 °C.

2.9 Negishi Cross-Coupling reactions of Iodophenylalanine containing Cyclopeptides with Pyridylzinc Pivalates

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-3-(2-iodobenzyl)-6,9,12,15-tetraisobutyl-8,11-dimethyltetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (11)



Cyclopeptide **11** was prepared by standard methods.[127]

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.80 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.58 (d, *J* = 9.3 Hz, 1H), 7.29 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.24 (td, *J* = 7.5, 1.3 Hz, 1H), 7.04 (d, *J* = 9.3 Hz, 1H), 6.90 (td, *J* = 7.6, 1.7 Hz, 1H), 6.23 (d, *J* = 9.7 Hz, 1H), 5.29 (dd, *J* = 11.7, 4.1 Hz, 1H), 5.13 (dt, *J* = 9.3, 7.2 Hz, 1H), 4.92 – 4.88 (m, 1H), 4.88 – 4.83 (m, 2H), 4.05 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.68 (ddd, *J* = 10.2, 7.5, 5.7 Hz, 1H), 3.54 (dt, *J* = 10.3, 6.9 Hz, 1H), 3.48 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.30 (dd, *J* = 14.4, 8.1 Hz, 1H), 3.23 (s, 3H), 3.01 (s, 3H), 2.21 – 2.12 (m, 1H), 1.99 – 1.89 (m, 3H), 1.89 – 1.82 (m, 2H), 1.79 (dt, *J* = 13.2, 6.7 Hz, 1H), 1.71 (dt, *J* = 14.0, 7.1, 1H), 1.64 – 1.60 (m, 1H), 1.58 – 1.44 (m, 5H), 1.44 – 1.32 (m, 2H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.95 – 0.90 (m, 15H), 0.87 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 174.1, 174.0, 171.3, 170.6, 170.0, 169.4, 140.4, 139.8, 130.7, 128.9, 128.7, 101.9, 61.2, 55.0, 53.8, 52.8, 48.6, 47.9, 47.8, 42.3, 41.6, 40.7, 37.6, 36.3, 31.5, 30.8, 28.1, 25.4, 25.4, 25.3, 25.0, 24.8, 23.7, 23.4, 23.0, 22.9, 22.9, 22.0, 21.3.

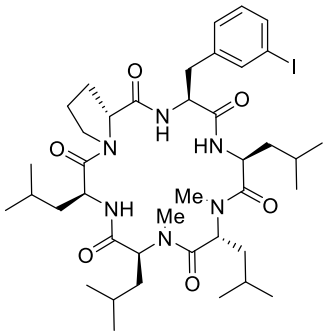
HRMS (ESI): m/z calc. for [M+Na; $C_{40}H_{63}IN_6NaO_6^+$]: 873.3751; found: 873.3759; m/z calc. for [M+H; $C_{40}H_{64}IN_6O_6^+$]: 851.3927; found: 851.3943.

IR (Diamond-ATR, neat): ν = 3302 (w), 2956 (m), 2933 (w), 2871 (w), 1626 (vs), 1516 (m), 1466 (m), 1444 (m), 1386 (w), 1368 (w), 1340 (w), 1322 (w), 1294 (w), 1281 (w), 1238 (w), 1205 (w), 1171 (w), 1128 (w), 1099 (w), 1011 (w), 921 (w), 730 (s).

M.p. 190.4 °C.

[127] T. Vorherr, I. Lewis, J. Berghausen, S. Desrayaud, M. Schaefer, *Int. J. Pept. Res. Ther.* **2018**, *24*, 35.

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-3-(3-iodobenzyl)-6,9,12,15-tetraisobutyl-8,11-dimethyltetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (12)



Cyclopeptide **12** was prepared by standard methods.[128]

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.56 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.51 (d, *J* = 9.3 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 9.4 Hz, 1H), 7.00 (t, *J* = 7.7 Hz, 1H), 6.14 (d, *J* = 9.7 Hz, 1H), 5.28 (dd, *J* = 11.7, 4.1 Hz, 1H), 5.12 (dt, *J* = 9.4, 7.2 Hz, 1H), 4.90 (dt, *J* = 9.6, 7.1 Hz, 1H), 4.86 – 4.77 (m, 2H), 4.03 (dd, *J* = 8.0, 4.6 Hz, 1H), 3.69 (ddd, *J* = 10.4, 7.5, 5.7 Hz, 1H), 3.56 (dt, *J* = 10.4, 7.0 Hz, 1H), 3.29 (dd, *J* = 14.1, 6.7 Hz, 1H), 3.22 (s, 3H), 3.05 – 3.00 (m, 1H), 3.00 (s, 3H), 2.19 (dq, *J* = 12.1, 7.2 Hz, 1H), 2.11 – 2.03 (m, 1H), 2.00 – 1.92 (m, 2H), 1.91 – 1.82 (m, 2H), 1.79 (dt, *J* = 13.4, 6.9 Hz, 1H), 1.69 (dt, *J* = 13.9, 7.2 Hz, 1H), 1.62 – 1.46 (m, 5H), 1.46 – 1.33 (m, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.93 (td, *J* = 6.8, 3.5 Hz, 15H), 0.87 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 174.2, 174.1, 171.4, 170.7, 170.0, 169.2, 139.4, 138.5, 136.3, 130.4, 128.9, 94.8, 61.1, 55.1, 53.3, 52.9, 48.6, 47.9, 47.8, 42.4, 41.4, 38.7, 37.6, 36.5, 36.3, 31.5, 30.8, 28.3, 25.5, 25.4, 25.3, 24.9, 24.8, 23.7, 23.4, 23.0, 23.0, 22.9, 22.0, 21.3.

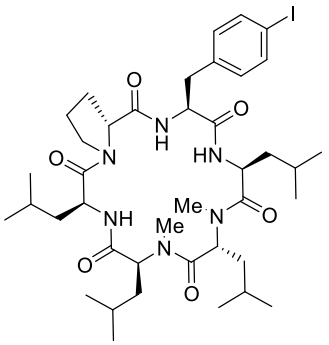
HRMS (ESI): m/z calc. for [M+Na; $C_{40}H_{63}IN_6NaO_6^+$]: 873.3751; found: 873.3755; m/z calc. for [M+H; $C_{40}H_{64}IN_6O_6^+$]: 851.3927; found: 851.3942.

IR (Diamond-ATR, neat): ν = 3298 (w), 2953 (m), 2868 (w), 2359 (w), 2339 (w), 1625 (vs), 1508 (m), 1466 (m), 1445 (m), 1419 (m), 1385 (m), 1366 (w), 1282 (w), 1202 (w), 1170 (w), 1127 (w), 1098 (w), 1065 (w), 772 (w).

M.p. 112.4 °C.

[128] T. Vorherr, I. Lewis, J. Berghausen, S. Desrayaud, M. Schaefer, *Int. J. Pept. Res. Ther.* **2018**, *24*, 35.

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-3-(4-iodobenzyl)-6,9,12,15-tetraisobutyl-8,11-dimethyltetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (13)



Cyclopeptide **13** was prepared by standard methods.[129]

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.61 – 7.57 (m, 2H), 7.50 (d, *J* = 9.4 Hz, 1H), 7.07 (d, *J* = 9.5 Hz, 1H), 6.96 – 6.92 (m, 2H), 6.16 (d, *J* = 9.7 Hz, 1H), 5.28 (dd, *J* = 11.7, 4.1 Hz, 1H), 5.09 (ddd, *J* = 9.4, 7.8, 6.7 Hz, 1H), 4.91 (dt, *J* = 9.6, 7.1 Hz, 1H), 4.85 – 4.78 (m, 2H), 4.02 (dd, *J* = 7.9, 4.6 Hz, 1H), 3.70 (ddd, *J* = 10.4, 7.5, 5.6 Hz, 1H), 3.56 (dt, *J* = 10.4, 7.0 Hz, 1H), 3.28 (dd, *J* = 14.2, 6.7 Hz, 1H), 3.23 (s, 3H), 3.02 (dd, *J* = 9.3, 5.1 Hz, 1H), 3.00 (s, 3H), 2.21 (dp, *J* = 12.3, 7.0 Hz, 1H), 2.09 – 2.02 (m, 3H), 1.99 – 1.91 (m, 2H), 1.91 – 1.76 (m, 3H), 1.64 – 1.46 (m, 5H), 1.45 – 1.31 (m, 2H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.95 – 0.91 (m, 15H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 174.3, 174.1, 171.4, 170.9, 169.9, 169.3, 137.8, 136.5, 131.6, 92.5, 61.1, 55.1, 53.3, 53.1, 48.5, 47.8, 47.8, 42.2, 41.3, 37.6, 36.6, 36.2, 31.5, 30.8, 28.3, 25.5, 25.4, 25.3, 25.0, 24.6, 23.7, 23.3, 23.0, 23.0, 22.9, 22.8, 22.1, 21.2.

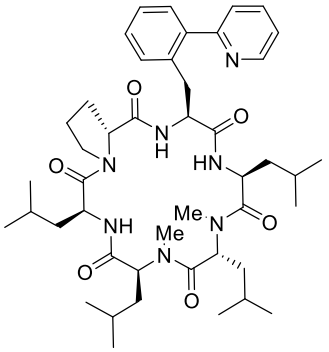
HRMS (ESI): m/z calc. for [M+Na; $C_{40}H_{63}IN_6NaO_6^+$]: 873.3751; found: 873.3752; m/z calc. for [M+H; $C_{40}H_{64}IN_6O_6^+$]: 851.3927; found: 851.4205.

IR (Diamond-ATR, neat): ν = 3521 (vw), 3316 (w), 2953 (w), 2869 (w), 2360 (w), 2339 (w), 1667 (m), 1632 (vs), 1556 (w), 1516 (m), 1447 (m), 1402 (w), 1386 (w), 1367 (w), 1296 (w), 1263 (w), 1235 (w), 1098 (w), 1006 (w), 806 (w), 761 (w).

M.p. 134.5 °C.

[129] T. Vorherr, I. Lewis, J. Berghausen, S. Desrayaud, M. Schaefer, *Int. J. Pept. Res. Ther.* **2018**, *24*, 35.

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-6,9,12,15-tetraisobutyl-8,11-dimethyl-3-(2-(pyridin-2-yl)benzyl)tetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (14a)



According to a modified version of **TP8**, $Pd(OAc)_2$ (1.42 mg, 6.40 µmol, 8.00 mol%) and SPhos (5.26 mg, 12.8 µmol, 16.00 mol%) were dissolved in freshly distilled THF (0.8 mL) and the catalyst mixture was stirred for 10 min. The *ortho*-iodophenylalanine cyclopeptide **11** (68.1 mg, 80.0 µmol, 1.0 equiv) was added and the mixture heated to 60 °C. Afterwards, the 2-pyridylzinc pivalate solution **1c** in THF (0.46 mL, 0.52 M, 0.24 mmol, 3.00 equiv) was added dropwise over 1 h and the reaction stirred for further 23 h at this temperature. After quenching, extracting and evaporating, the crude product was flushed through a silica-plug with acetonitrile. Purification via preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$) yielded the modified cyclopeptide **14a** as colorless solid (24.4 mg, 30.4 µmol, 38% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 10.64 (s, 1H), 8.77 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.88 (s, 1H), 7.76 (d, *J* = 9.5 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.35 – 7.27 (m, 2H), 7.04 (d, *J* = 9.3 Hz, 1H), 5.33 (dd, *J* = 11.7, 4.1 Hz, 1H), 5.04 (ddd, *J* = 9.6, 8.1, 6.3 Hz, 1H), 4.86 (dt, *J* = 9.2, 6.8 Hz, 2H), 4.57 (s, 1H), 4.05 (t, *J* = 6.2 Hz, 1H), 3.56 (ddt, *J* = 22.1, 10.6, 5.5 Hz, 2H), 3.33 (dd, *J* = 13.8, 4.7 Hz, 1H), 3.27 (s, 3H), 3.05 (s, 3H), 2.86 (t, *J* = 13.0 Hz, 1H), 2.36 (s, 2H), 2.08 (p, *J* = 6.6, 5.8 Hz, 1H), 1.98 (ddd, *J* = 14.6, 10.5, 4.2 Hz, 1H), 1.85 (ddd, *J* = 14.8, 9.6, 5.5 Hz, 2H), 1.79 – 1.50 (m, 9H), 1.49 – 1.32 (m, 2H), 1.00 (dd, *J* = 6.5, 5.7 Hz, 6H), 0.97 – 0.93 (m, 6H), 0.93 (d, *J* = 2.1 Hz, 3H), 0.91 – 0.83 (m, 9H).

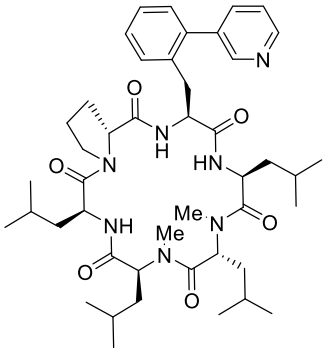
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 174.1, 174.1, 172.2, 170.9, 170.4, 169.8, 159.2, 147.8, 138.1, 136.6, 130.7, 130.0, 129.5, 126.9, 125.2, 122.4, 61.0, 56.0, 55.1, 52.7, 48.8, 47.8, 47.7, 42.1, 41.4, 37.8, 36.2, 33.9, 31.3, 30.9, 29.8, 28.5, 25.4, 25.3, 25.3, 25.1, 24.7, 23.8, 23.3, 23.2, 23.1, 23.0, 22.7, 22.2, 21.3.

HRMS (ESI): calcd. [M+H, $C_{45}H_{68}O_6N_7$]: 802.5226, found: 802.5212; calcd. [M-H, $C_{45}H_{66}O_6N_7$]: 800.5080, found: 800.5086: calcd. [M, $C_{45}H_{67}O_6N_7$]: 801.5153, found: 801.5121.

IR (ATR, cm^{-1}) ν = 3494 (vw), 3304 (w), 2954 (m), 2869 (w), 2360 (vw), 1664 (m), 1627 (vs), 1519 (m), 1470 (m), 1443 (m), 1386 (w), 1367 (w), 1265 (w), 1098 (w), 1024 (vw), 999 (vw), 758 (w).

M.p. 115.4 °C.

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-6,9,12,15-tetraisobutyl-8,11-dimethyl-3-(2-(pyridin-3-yl)benzyl)tetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (14b)



According to **TP8**, $Pd(OAc)_2$ (0.72 mg, 3.20 µmol, 4.00 mol%) and SPhos (2.63 mg, 6.40 µmol, 8.00 mol%) were dissolved in freshly distilled THF (0.8 mL) and the catalyst mixture was stirred for 10 min, before *ortho*-iodophenylalanine cyclopeptide **11** (68.1 mg, 80.0 µmol, 1.0 equiv) was inserted. Afterwards, the 3-pyridylzinc pivalate solution **1d** in THF (0.48 mL, 0.42 M, 0.20 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred for further 5 h. After quenching, extracting and evaporating, the crude product was flushed through a silica-plug with acetonitrile. Purification via preparative reversed-phase HPLC-chromatography (MeCN/H_2O) yielded the modified cyclopeptide **14b** as colorless solid (39.8 mg, 49.6 µmol, 62% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 8.60 (d, *J* = 4.0 Hz, 1H), 8.55 (s, 1H), 7.65 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.45 (d, *J* = 9.4 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.40 – 7.32 (m, 1H), 7.35 – 7.28 (m, 2H), 7.23 – 7.17 (m, 1H), 7.04 (d, *J* = 9.5 Hz, 1H), 5.90 (d, *J* = 9.6 Hz, 1H), 5.27 (dd, *J* = 11.6, 4.0 Hz, 1H), 5.08 (dt, *J* = 8.9, 7.2 Hz, 1H), 4.88 (dt, *J* = 9.3, 7.0 Hz, 1H), 4.79 (dd, *J* = 9.9, 5.5 Hz, 1H), 4.69 (s, 1H), 3.88 – 3.83 (m, 1H), 3.66 (ddd, *J* = 11.4, 7.6, 5.1 Hz, 1H), 3.52 (dt, *J* = 11.2, 6.6 Hz, 1H), 3.38 (dd, *J* = 14.5, 4.7 Hz, 1H), 3.19 (s, 3H), 3.14 (dd, *J* = 14.5, 7.6 Hz, 1H), 2.99 (s, 3H), 2.22 – 1.74 (m, 7H), 1.71 – 1.30 (m, 9H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.95 – 0.88 (m, 18H), 0.86 (d, *J* = 6.5 Hz, 3H).

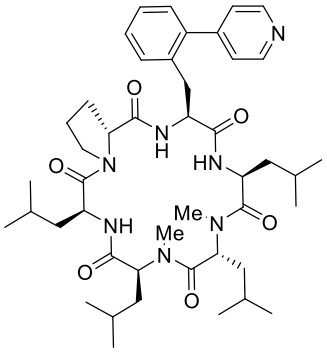
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 174.0, 174.0, 171.1, 170.5, 169.8, 169.3, 149.8, 148.4, 138.7, 137.2, 136.9, 134.8, 130.5, 130.4, 128.6, 127.1, 123.2, 60.9, 54.9, 53.5, 52.8, 48.3, 47.7 (2 C), 42.2, 41.3, 37.5, 36.1, 33.3, 31.3, 30.6, 28.0, 25.3, 25.3, 25.2, 24.8, 24.6, 23.6, 23.2, 22.9, 22.8, 22.7, 22.7, 21.9, 21.1.

HRMS (ESI): calcd. [M+H, $C_{45}H_{68}O_6N_7$]: 802.5226, found: 802.5212; calcd. [M-H, $C_{45}H_{66}O_6N_7$]: 800.5080, found: 800.5098.

IR (ATR, cm^{-1}) ν = 3511 (w), 3303 (w), 2955 (m), 2870 (w), 1629 (vs), 1517 (m), 1468 (m), 1448 (m), 1386 (w), 1367 (w), 1100 (w), 1028 (vw), 1003 (vw), 760 (w), 718 (vw).

M.p. 119.0 °C.

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-6,9,12,15-tetraisobutyl-8,11-dimethyl-3-(2-(pyridin-4-yl)benzyl)tetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (14c)



According to **TP8**, $Pd(OAc)_2$ (0.72 mg, 3.20 µmol, 4.00 mol%) and SPhos (2.63 mg, 6.40 µmol, 8.00 mol%) were dissolved in freshly distilled THF (0.8 mL) and the catalyst mixture was stirred for 10 min, before *ortho*-iodophenylalanine cyclopeptide **11** (68.1 mg, 80.0 µmol, 1.0 equiv) was inserted. Afterwards, the 4-pyridylzinc pivalate solution **1e** in THF (0.87 mL, 0.23 M, 0.20 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred for further 5 h. After quenching, extracting and evaporating, the crude product was flushed through a silica-plug with acetonitrile. Purification via preparative reversed-phase HPLC-chromatography (MeCN/H_2O) yielded the modified cyclopeptide **14c** as colorless solid (43.0 mg, 53.6 µmol, 67% yield).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm) δ = 8.67 (s, 2H), 7.40 (d, *J* = 9.2 Hz, 1H), 7.39 – 7.37 (m, 1H), 7.34 – 7.27 (m, 4H), 7.19 – 7.16 (m, 1H), 7.06 (d, *J* = 9.4 Hz, 1H), 5.97 (d, *J* = 9.7, 1H), 5.27 (dd, *J* = 11.7 Hz, 4.1, 1H), 5.07 (dt, *J* = 9.2, 7.1 Hz, 1H), 4.88 (dt, *J* = 9.5, 7.0 Hz, 1H), 4.79 (dd, *J* = 10.0, 5.4 Hz, 1H), 4.68 (ddd, *J* = 9.9, 8.2, 4.6 Hz, 1H), 3.85 (dd, *J* = 7.7, 4.2 Hz, 1H), 3.68 – 3.63 (m, 1H), 3.52 (dt, *J* = 10.6, 7.0 Hz, 1H), 3.46 (dd, *J* = 14.6, 4.6 Hz, 1H), 3.18 (s, 3H), 3.06 (dd, *J* = 14.7, 8.2 Hz, 1H), 2.98 (s, 3H), 2.20 – 2.11 (m, 1H), 1.94 (ddd, *J* = 14.7, 10.5, 4.2 Hz, 1H), 1.88 – 1.75 (m, 5H), 1.70 – 1.64 (m, 1H), 1.61 – 1.46 (m, 5H), 1.45 – 1.31 (m, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.93 (ddd, *J* = 6.3, 4.8, 2.8 Hz, 15H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H).

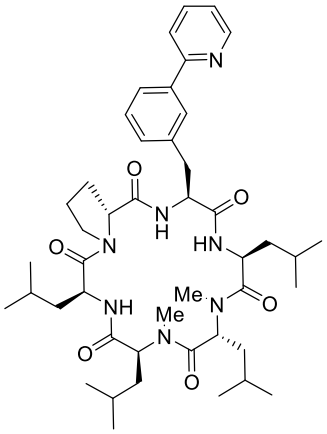
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 174.2, 171.3, 170.5, 170.0, 169.4, 149.8, 139.9, 134.4, 132.8, 130.6, 130.0, 128.8, 127.3, 124.8, 124.7, 60.9, 55.1, 53.6, 53.0, 48.5, 47.8, 47.8, 42.3, 41.4, 37.6, 36.3, 33.7, 31.5, 30.7, 29.8, 28.1, 25.4, 25.3, 25.0, 24.8, 23.7, 23.4, 23.0, 23.0, 22.9, 22.8, 22.0, 21.3.

HRMS (ESI): calcd. [M+H, $C_{45}H_{68}O_6N_7$]: 802.5226, found: 802.5216; calcd. [M-H, $C_{45}H_{66}O_6N_7$]: 800.5080, found: 800.5093.zzz

IR (ATR, cm^{-1}) ν = 3502 (w), 3296 (w), 2955 (m), 2927 (m), 2869 (w), 2360 (vw), 1631 (vs), 1516 (m), 1448 (m), 1386 (w), 1367 (w), 1261 (w), 1098 (w), 802 (w), 763 (w).

M.p. 137.9 °C

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-6,9,12,15-tetraisobutyl-8,11-dimethyl-3-(3-(pyridin-2-yl)benzyl)tetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (15a)



According to **TP8**, $Pd(OAc)_2$ (0.72 mg, 3.20 µmol, 4.00 mol%) and SPhos (2.63 mg, 6.40 µmol, 8.00 mol%) were dissolved in freshly distilled THF (0.8 mL) and the catalyst mixture was stirred for 10 min, before *meta*-iodophenylalanine cyclopeptide **12** (68.1 mg, 80.0 µmol, 1.0 equiv) was inserted. Afterwards, the 2-pyridylzinc pivalate solution **1c** in THF (0.39 mL, 0.52 M, 0.20 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred for further 5 h. After quenching, extracting and evaporating, the crude product was flushed through a silica-plug with acetonitrile. Purification via preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$) yielded the modified cyclopeptide **15a** as colorless solid (46.2 mg, 57.6 µmol, 72% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 8.67 (d, *J* = 4.5 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.81 (s, 1H), 7.78 – 7.70 (m, 2H), 7.54 (d, *J* = 9.4 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.04 (d, *J* = 9.4 Hz, 1H), 6.21 (d, *J* = 9.5 Hz, 1H), 5.29 (dd, *J* = 11.7, 4.1 Hz, 1H), 5.11 (dt, *J* = 9.4, 7.2 Hz, 1H), 4.93 – 4.79 (m, 3H), 4.00 (dd, *J* = 7.9, 4.6 Hz, 1H), 3.68 (ddd, *J* = 10.4, 7.5, 5.7 Hz, 1H), 3.53 (dt, *J* = 10.3, 6.8 Hz, 1H), 3.43 (dd, *J* = 14.1, 6.9 Hz, 1H), 3.24 (s, 3H), 3.20 (dd, *J* = 14.3, 5.1 Hz, 1H), 3.01 (s, 3H), 2.16 (dt, *J* = 11.9, 6.9 Hz, 1H), 2.07 – 1.72 (m, 6H), 1.68 – 1.31 (m, 9H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.92 (dd, *J* = 11.0, 6.3 Hz, 12H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H).

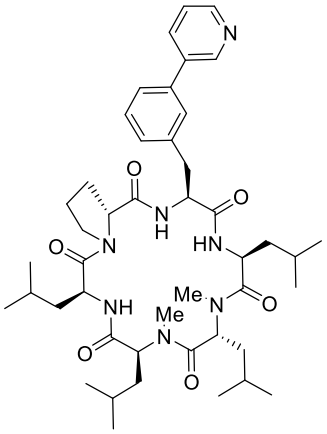
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 174.2, 174.1, 171.2, 171.0, 170.0, 169.6, 157.4, 149.8, 139.9, 137.4, 136.9, 130.2, 129.2, 128.1, 125.8, 122.3, 120.8, 61.1, 55.1, 53.5, 52.9, 48.6, 47.8, 47.8, 42.3, 41.4, 37.7, 37.0, 36.3, 31.5, 30.8, 28.4, 25.4, 25.4, 25.3, 24.9, 24.7, 23.7, 23.4, 23.0, 22.9, 22.9, 22.8, 22.1, 21.3.

HRMS (ESI): calcd. [M+H, $C_{45}H_{68}O_6N_7$]: 802.5226, found: 802.5214; calcd. [M-H, $C_{45}H_{66}O_6N_7$]: 800.5080, found: 800.5089.

IR (ATR, cm^{-1}) ν = 3509 (vw), 3303 (w), 2955 (m), 2930 (w), 2870 (w), 2359 (vw), 2341 (vw), 1629 (vs), 1585 (w), 1518 (m), 1463 (m), 1446 (m), 1386 (w), 1099 (w), 769 (w), 753 (w), 668 (vw).

M.p. 114.9 °C

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-6,9,12,15-tetraisobutyl-8,11-dimethyl-3-(3-(pyridin-3-yl)benzyl)tetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (15b)



According to **TP8**, $Pd(OAc)_2$ (0.72 mg, 3.20 µmol, 4.00 mol%) and SPhos (2.63 mg, 6.40 µmol, 8.00 mol%) were dissolved in freshly distilled THF (0.8 mL) and the catalyst mixture was stirred for 10 min, before *meta*-iodophenylalanine cyclopeptide **12** (68.1 mg, 80.0 µmol, 1.0 equiv) was inserted. Afterwards, the 3-pyridylzinc pivalate solution **1d** in THF (0.48 mL, 0.42 M, 0.20 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred for further 5 h. After quenching, extracting and evaporating, the crude product was flushed through a silica-plug with acetonitrile. Purification via preparative reversed-phase HPLC-chromatography (MeCN/H_2O) yielded the modified cyclopeptide **15b** as colorless solid (39.8 mg, 49.6 µmol, 62% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 8.90 (s, 1H), 8.63 (s, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.57 – 7.44 (m, 4H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 9.3 Hz, 1H), 6.39 (d, *J* = 9.6 Hz, 1H), 5.28 (dd, *J* = 11.6, 4.1 Hz, 1H), 5.10 (q, *J* = 7.7 Hz, 1H), 4.90 (d, *J* = 9.2 Hz, 2H), 4.82 (dd, *J* = 9.8, 5.5 Hz, 1H), 4.05 (s, 1H), 3.69 (d, *J* = 5.9 Hz, 1H), 3.55 (t, *J* = 8.5 Hz, 1H), 3.42 (dd, *J* = 14.1, 6.8 Hz, 1H), 3.23 (s, 3H), 3.22 – 3.16 (m, 1H), 3.00 (s, 3H), 2.23 – 2.11 (m, 1H), 2.06 – 1.71 (m, 6H), 1.68 – 1.29 (m, 9H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.92 (td, *J* = 6.3, 2.7 Hz, 12H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H).

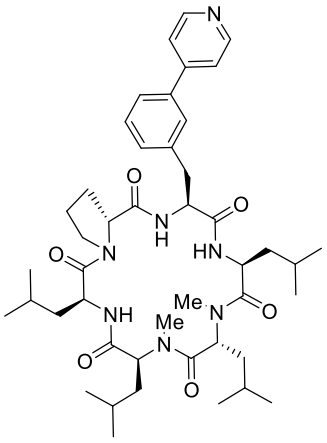
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 174.2, 174.1, 171.4, 170.9, 170.0, 169.4, 146.6, 146.4, 138.3, 137.3, 136.4, 130.0, 129.6, 128.4, 125.9, 124.5, 61.1, 55.1, 53.4, 53.0, 48.6, 47.8 (2 C), 42.3, 41.4, 37.6, 37.0, 36.3, 31.5, 30.8, 29.8, 28.3, 25.4, 25.4, 25.3, 24.9, 24.7, 23.7, 23.4, 23.0, 22.9, 22.9, 22.8, 22.0, 21.3.

HRMS (ESI): calcd. [M+H, $C_{45}H_{68}O_6N_7$]: 802.5226, found: 802.5213; calcd. [M-H, $C_{45}H_{66}O_6N_7$]: 800.5080, found: 800.5094.

IR (ATR, cm^{-1}) $\nu =$ 3502 (w), 3301 (w), 2955 (m), 2870 (w), 2359 (vw), 1629 (vs), 1519 (m), 1467 (m), 1447 (m), 1386 (w), 1367 (w), 1099 (w), 783 (vw), 712 (vw).

M.p. 127.7 °C

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-6,9,12,15-tetraisobutyl-8,11-dimethyl-3-(3-(pyridin-4-yl)benzyl)tetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (15c)



According to **TP8**, $Pd(OAc)_2$ (0.72 mg, 3.20 µmol, 4.00 mol%) and SPhos (2.63 mg, 6.40 µmol, 8.00 mol%) were dissolved in freshly distilled THF (0.8 mL) and the catalyst mixture was stirred for 10 min, before *meta*-iodophenylalanine cyclopeptide **12** (68.1 mg, 80.0 µmol, 1.0 equiv) was inserted. Afterwards, the 4-pyridylzinc pivalate solution **1e** in THF (0.87 mL, 0.23 M, 0.20 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred for further 5 h. After quenching, extracting and evaporating, the crude product was flushed through a silica-plug with acetonitrile. Purification via preparative reversed-phase HPLC-chromatography (MeCN/H_2O) yielded the modified cyclopeptide **15c** as colorless solid (49.4 mg, 61.6 µmol, 77% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 8.71 (s, 2H), 7.78 (s, 2H), 7.59 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 9.8 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 9.4 Hz, 1H), 6.46 (d, *J* = 9.8 Hz, 1H), 5.28 (dd, *J* = 11.7, 4.1 Hz, 1H), 5.15 – 5.06 (m, 1H), 4.98 – 4.87 (m, 2H), 4.81 (dd, *J* = 10.0, 5.4 Hz, 1H), 4.10 – 4.02 (m, 1H), 3.73 – 3.64 (m, 1H), 3.60 – 3.50 (m, 1H), 3.39 (dd, *J* = 14.2, 7.1 Hz, 1H), 3.26 (d, *J* = 5.3 Hz, 1H), 3.23 (s, 3H), 3.00 (s, 3H), 2.24 – 2.11 (m, 1H), 2.06 – 1.72 (m, 6H), 1.69 – 1.31 (m, 9H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.96 – 0.90 (m, 12H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 7.9 Hz, 3H).

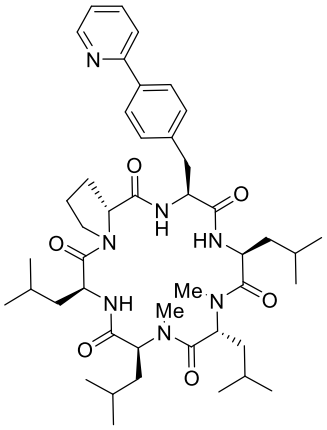
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 174.2, 174.1, 171.6, 170.7, 170.0, 169.3, 146.3 (2 C), 138.8, 136.9, 131.8, 129.8, 128.6, 126.0, 122.9 (2 C), 61.1, 55.1, 53.4, 53.1, 48.6, 47.9, 47.8, 42.5, 41.4, 37.6, 37.2, 36.3, 31.6, 30.8, 29.8, 28.1, 25.5 (2 C), 25.3, 25.0, 24.7, 23.7, 23.4, 23.0 (2 C), 22.9 (2 C), 22.0, 21.3.

HRMS (ESI): calcd. [M+H, $C_{45}H_{68}O_6N_7$]: 802.5226, found: 802.5213; calcd. [M-H, $C_{45}H_{66}O_6N_7$]: 800.5080, found: 800.5087.

IR (ATR, cm^{-1}) ν =3302 (m), 2955 (m), 2930 (m), 2870 (w), 1688 (w), 1665 (m), 1657 (m), 1631 (vs), 1513 (m), 1468 (m), 1461 (m), 1451 (m), 1445 (m), 1099 (w), 790 (vw).

M.p. 135.3 °C

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-6,9,12,15-tetraisobutyl-8,11-dimethyl-3-(4-(pyridin-2-yl)benzyl)tetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (16a)



According to **TP8**, $Pd(OAc)_2$ (0.72 mg, 3.20 µmol, 4.00 mol%) and SPhos (2.63 mg, 6.40 µmol, 8.00 mol%) were dissolved in freshly distilled THF (0.8 mL) and the catalyst mixture was stirred for 10 min, before *para*-iodophenylalanine cyclopeptide **13** (68.1 mg, 80.0 µmol, 1.0 equiv) was inserted. Afterwards, the 2-pyridylzinc pivalate solution **1c** in THF (0.39 mL, 0.52 M, 0.20 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred for further 5 h. After quenching, extracting and evaporating, the crude product was flushed through a silica-plug with acetonitrile. Purification via preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$) yielded the modified cyclopeptide **16a** as colorless solid (53.9 mg, 67.2 µmol, 84% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 8.68 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.75 (ddd, *J* = 8.0, 7.2, 1.8 Hz, 1H), 7.70 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.57 (d, *J* = 9.3 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.22 (ddd, *J* = 7.2, 4.8, 1.3 Hz, 1H), 7.06 (d, *J* = 9.4 Hz, 1H), 6.14 (d, *J* = 9.5 Hz, 1H), 5.30 (dd, *J* = 11.7, 4.1 Hz, 1H), 5.17 – 5.08 (m, 1H), 4.94 – 4.85 (m, 2H), 4.82 (dd, *J* = 9.7, 5.7 Hz, 1H), 4.00 (dd, *J* = 7.8, 4.7 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.59 – 3.52 (m, 1H), 3.41 (dd, *J* = 14.1, 6.7 Hz, 1H), 3.25 (s, 3H), 3.15 (dd, *J* = 14.1, 5.0 Hz, 1H), 3.01 (s, 3H), 2.25 – 2.15 (m, 1H), 2.09 – 1.75 (m, 6H), 1.65 – 1.33 (m, 9H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.98 – 0.90 (m, 15H), 0.88 (d, *J* = 2.4 Hz, 3H), 0.86 (d, *J* = 2.5 Hz, 3H).

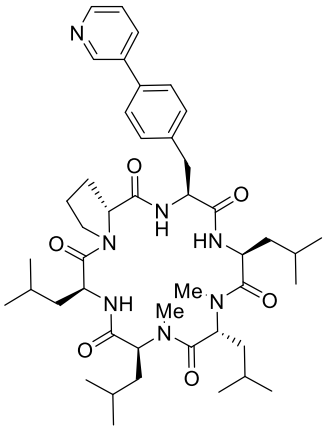
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 174.2, 174.1, 171.2, 170.9, 169.9, 169.6, 157.2, 149.8, 138.3, 137.8, 136.9, 130.0 (2 C), 127.3 (2 C), 122.2, 120.5, 61.1, 55.1, 53.4, 53.0, 48.6, 47.8, 47.8, 42.2, 41.4, 37.7, 36.8, 36.3, 31.5, 30.8, 28.4, 25.5, 25.4, 25.3, 25.0, 24.6, 23.7, 23.4, 23.1, 23.0, 22.9, 22.8, 22.1, 21.3.

HRMS (ESI): calcd. [M+H, $C_{45}H_{68}O_6N_7$]: 802.5226, found: 802.5216; calcd. [M-H, $C_{45}H_{66}O_6N_7$]: 800.5080, found: 800.5091.

IR (ATR, cm^{-1}) $\nu =$ 3498 (vw), 3303 (w), 2955 (m), 2930 (w), 2870 (w), 2359 (w), 1630 (vs), 1589 (w), 1518 (m), 1467 (m), 1446 (m), 1386 (w), 1367 (w), 1098 (w), 776 (w), 668 (vw).

M.p. 130.6°C

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-6,9,12,15-tetraisobutyl-8,11-dimethyl-3-(4-(pyridin-3-yl)benzyl)tetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (16b)



According to **TP8**, $Pd(OAc)_2$ (0.72 mg, 3.20 µmol, 4.00 mol%) and SPhos (2.63 mg, 6.40 µmol, 8.00 mol%) were dissolved in freshly distilled THF (0.8 mL) and the catalyst mixture was stirred for 10 min, before *para*-iodophenylalanine cyclopeptide **13** (68.1 mg, 80.0 µmol, 1.0 equiv) was inserted. Afterwards, the 3-pyridylzinc pivalate solution **1d** in THF (0.48 mL, 0.42 M, 0.20 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred for further 5 h. After quenching, extracting and evaporating, the crude product was flushed through a silica-plug with acetonitrile. Purification via preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$) yielded the modified cyclopeptide **16b** as colorless solid (39.8 mg, 49.6 µmol, 62% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 8.83 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.85 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.52 (d, *J* = 10.0 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.37 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 9.5 Hz, 1H), 6.23 (d, *J* = 9.6 Hz, 1H), 5.30 (dd, *J* = 11.6, 4.1 Hz, 1H), 5.20 – 5.09 (m, 1H), 4.95 – 4.87 (m, 2H), 4.82 (dd, *J* = 9.8, 5.5 Hz, 1H), 4.05 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.75 – 3.67 (m, 1H), 3.57 (dt, *J* = 10.4, 6.9 Hz, 1H), 3.42 (dd, *J* = 14.1, 6.6 Hz, 1H), 3.25 (s, 3H), 3.13 (dd, *J* = 14.1, 4.9 Hz, 1H), 3.01 (s, 3H), 2.22 (dt, *J* = 11.8, 7.0 Hz, 1H), 2.08 (dq, *J* = 11.0, 5.4 Hz, 1H), 2.01 – 1.75 (m, 6H), 1.65 – 1.33 (m, 8H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.98 – 0.92 (m, 12H), 0.92 (d, *J* = 3.1 Hz, 3H), 0.89 (d, *J* = 3.5 Hz, 3H), 0.88 (d, *J* = 3.4 Hz, 3H).

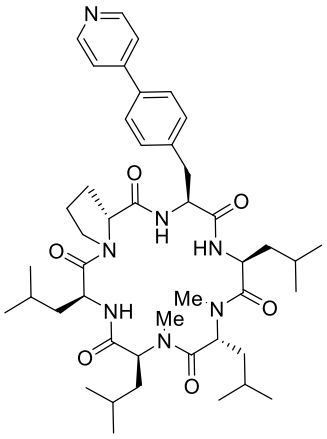
^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 174.2, 174.2, 171.4, 170.8, 170.0, 169.5, 148.6, 148.4, 137.0, 136.7, 136.4, 134.4, 130.4 (2 C), 127.5 (2 C), 123.7, 61.1, 55.1, 53.5, 53.1, 48.6, 47.9, 42.2, 41.4, 37.7, 36.8, 36.3, 31.5, 30.8, 29.8, 28.3, 25.5, 25.4, 25.3, 25.0, 24.6, 23.7, 23.4, 23.1, 23.0, 22.9, 22.9, 22.1, 21.3.

HRMS (ESI): calcd. [M+H, $C_{45}H_{68}O_6N_7$]: 802.5226, found: 802.5215; calcd. [M-H, $C_{45}H_{66}O_6N_7$]: 800.5080, found: 802.5090.

IR (ATR, cm^{-1}) ν = 3509 (w), 3303 (w), 2955 (m), 2930 (w), 2870 (w), 2361 (w), 2339 (w), 1630 (vs), 1519 (m), 1469 (m), 1447 (m), 1367 (w), 1100 (w), 799 (w), 712 (vw).

M.p. 140.6 °C

(3*S*,6*S*,9*R*,12*S*,15*S*,20a*R*)-6,9,12,15-tetraisobutyl-8,11-dimethyl-3-(4-(pyridin-4-yl)benzyl)tetradecahydropyrrolo[1,2-*a*][1,4,7,10,13,16]hexaazacyclooctadecine-1,4,7,10,13,16-hexaone (16c)



According to **TP8**, $Pd(OAc)_2$ (0.72 mg, 3.20 µmol, 4.00 mol%) and SPhos (2.63 mg, 6.40 µmol, 8.00 mol%) were dissolved in freshly distilled THF (0.8 mL) and the catalyst mixture was stirred for 10 min, before *para*-iodophenylalanine cyclopeptide **13** (68.1 mg, 80.0 µmol, 1.0 equiv) was inserted. Afterwards, the 4-pyridylzinc pivalate solution **1e** in THF (0.87 mL, 0.23 M, 0.20 mmol, 2.50 equiv) was added dropwise over 1 h and the reaction mixture stirred for further 5 h. After quenching, extracting and evaporating, the crude product was flushed through a silica-plug with acetonitrile. Purification via preparative reversed-phase HPLC-chromatography ($MeCN/H_2O$) yielded the modified cyclopeptide **16c** as colorless solid (51.3 mg, 64.0 µmol, 80% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ = 8.65 (d, *J* = 5.4 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.54 – 7.47 (m, 3H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 9.5 Hz, 1H), 6.27 (d, *J* = 9.7 Hz, 1H), 5.30 (dd, *J* = 11.7, 4.1 Hz, 1H), 5.13 (q, *J* = 7.8 Hz, 1H), 4.96 – 4.86 (m, 2H), 4.82 (dd, *J* = 9.9, 5.5 Hz, 1H), 4.05 (dd, *J* = 7.0, 3.7 Hz, 1H), 3.69 (q, *J* = 8.2, 6.8 Hz, 1H), 3.56 (dt, *J* = 9.9, 6.6 Hz, 1H), 3.39 (dd, *J* = 14.1, 6.7 Hz, 1H), 3.24 (s, 3H), 3.15 (dd, *J* = 14.1, 4.9 Hz, 1H), 3.00 (s, 3H), 2.16 (s, 6H), 2.13 – 1.74 (m, 4H), 1.68 – 1.32 (m, 7H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.94 (qd, *J* = 6.6, 4.1 Hz, 15H), 0.89 (d, *J* = 2.7 Hz, 3H), 0.87 (d, *J* = 2.5 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm) δ = 174.1, 174.1, 171.3, 170.6, 169.9, 169.3, 150.0, 148.2, 138.2, 136.7, 130.4, 127.2, 121.6, 60.9, 54.9, 53.3, 52.9, 48.4, 47.7, 42.1, 41.2, 37.5, 36.7, 36.1, 31.4, 30.6, 29.7, 28.1, 25.3, 25.3, 25.2, 24.8, 24.5, 23.6, 23.2, 22.9, 22.8, 22.8, 22.7, 21.9, 21.1.

HRMS (ESI): calcd. [M+H, $C_{45}H_{68}O_6N_7$]: 802.5226, found: 802.5211; calcd. [M-H, $C_{45}H_{66}O_6N_7$]: 800.5080, found: 802.5089.

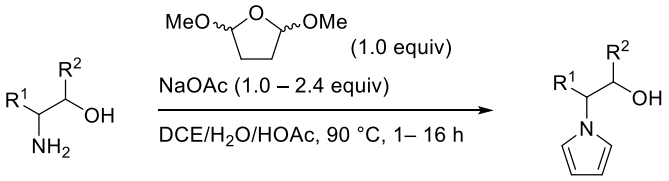
IR (ATR, cm^{-1}) ν = 3510 (w), 3297 (w), 3028 (vw), 2955 (m), 2870 (w), 2360 (w), 1630 (vs), 1600 (w), 1519 (m), 1466 (w), 1447 (m), 1386 (w), 1367 (w), 1099 (w), 997 (vw), 804 (w).

M.p. 141.5 °C

3 Pyrrole Protected 2-Aminoalkylzinc Reagents for the Enantioselective Synthesis of Amino Derivatives

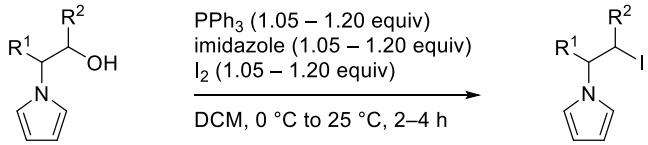
3.1 Typical Procedures (TP9–15)

Typical procedure for the pyrrole protection of β-amino-alcohols (TP9): [130]



In a round-bottom flask equipped with a magnetic stirring bar, the corresponding amino-alcohol (1.00 equiv) and NaOAc·$3H_2O$ (1.00–2.40 equiv) were dissolved in a 1,2-dichloroethane/water mixture (1:1) and acidified with glacial acetic acid. 2,5-Dimethoxytetrahydrofuran (*cis*/*trans* mixture, 1.00 equiv) was added and the two-phase mixture was refluxed at 90 °C under vigorous stirring for 1 h up to 16 h. The reaction was cooled to room temperature and the organic phase was separated. The aqueous phase was extracted three times with EtOAc and the combined organic phases were neutralized with sat. aq. $NaHCO_3$ solution, washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (hexanes/EtOAc, addition of 1% Et_3N) and the corresponding *N*-pyrrolyl-alkyl alcohol was obtained.

Typical procedure for the preparation of *N*-pyrrolyl-alkyl iodides (TP10): [131]

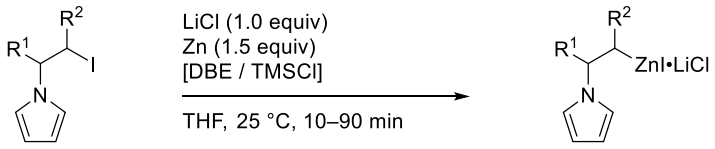


In a dry *Schlenk* flask or tube, PPh_3 (1.05–1.20 equiv) and imidazole (1.05–1.20 equiv) were dissolved in dry DCM and cooled to 0 °C. Iodine (1.05–1.20 equiv) was added in three portions over a period of 10 min. The corresponding *N*-pyrrolyl-alkylalcohol (1.00 equiv) dissolved in dry DCM was added dropwise to the reaction mixture at 0 °C over a period of 30 min. The mixture was stirred for 30 min at this temperature and was then allowed to warm to room temperature and stirred additionally for 1.5 h up to 3 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution, the organic phase was separated and the aqueous phase extracted three times with DCM. The combined organic phases were dried over

[130] a) B. S. Gourlay, P. P. Molesworth, J. H. Ryan, J. A. Smith, *Tetrahedron Lett.* **2006**, *47*, 799; b) C. W. Jefford, de Villedon de Naide, Fabienne, K. Sienkiewicz, *Tetrahedron: Asymmetry* **1996**, *7*, 1069.
[131] a) V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5516; b) G. L. Lange, C. Gottardo, *Synth. Commun.* **1990**, *20*, 1473; c) P. J. Garegg, B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866; d) R. Appel, *Angew. Chem. Int. Ed.* **1975**, *14*, 801.

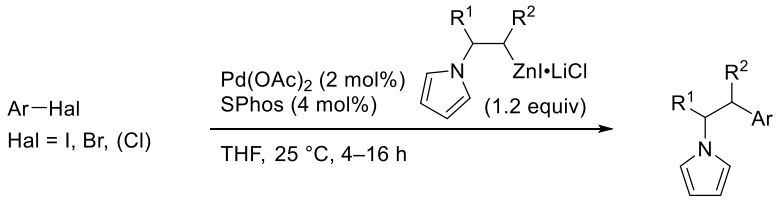
$CaCl_2$ and the solvents evaporated. The crude product was purified *via* flash column chromatography (hexanes/EtOAc, darkness) and the corresponding *N*-pyrrolyl-alkyl iodide was obtained.

Typical procedure for LiCl promoted oxidative zinc insertions (TP11):



Two *Schlenk* tubes, equipped with a magnetic stirring bar, were dried using a heat gun at 630 °C under high vacuum and flushed with argon three times. In one tube, LiCl (1.0 equiv) was added and dried *in vacuo* at 470 °C. Zinc dust (1.5 equiv) was added and dried *in vacuo* at 350 °C. Under argon atmosphere, freshly distilled dry THF was added and the zinc dust was activated using 1,2-dibromoethane (DBE, 5 mol%) and chlorotrimethylsilane (TMSCl, 5 mol%) and the solution was slightly heated until a gas formation started. The tube was placed in a water bath and the alkyl iodide was added dropwise or in small portions. After complete addition of the starting material, the water bath was removed. The reaction progress was monitored by quenching small aliquots with sat. aq. solution NH_4Cl and gas chromatography analysis. After full conversion of the *N*-pyrrolyl-alkyliodide, the solution was passed through a syringe filter and the solution was transferred to the second dry *Schlenk* tube. The concentration of the corresponding *N*-pyrrolyl-alkylzinc iodide was determined by titration against iodine[132] (approx. 30-40 mg) in dry THF (1.5 mL) under argon atmosphere.

Typical procedure for palladium catalyzed cross-couplings (TP12):

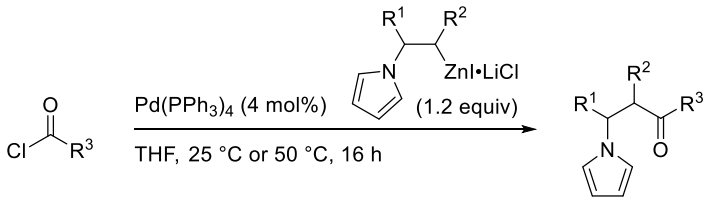


A *Schlenk* tube, equipped with a magnetic stirring bar, was dried using a heat gun at 630 °C under high vacuum and flushed with argon three times. $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos[133] (8.21 mg, 20.0 µmol, 4 mol%) were dissolved in freshly distilled dry THF (1 mL) and stirred for 10 min. The corresponding aryl halide (0.50 mmol, 1.00 equiv) was added and to this mixture, the corresponding *N*-pyrrolyl-alkylzinc iodide in THF (0.60 mmol, 1.20 equiv) was added dropwise. The reaction was stirred upon full conversion of the electrophile and then quenched with sat. aq. NH_4Cl solution (1 mL). The cross-coupling mixture was extracted three times with EtOAc, the combined organic phases dried

[132] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.
[133] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.

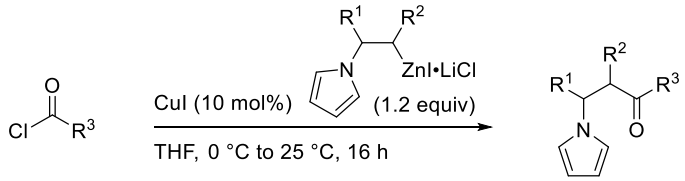
over $MgSO_4$ and the solvent evaporated. After purification *via* flash column chromatography (hexanes/EtOAc) the corresponding cross-coupling product was obtained.

Typical procedure for palladium catalyzed acylation reactions (TP13a): [134]



A *Schlenk* tube equipped, with a magnetic stirring bar, was dried using a heat gun at 630 °C under high vacuum and flushed with argon three times. $Pd(PPh_3)_4$ (23.1 mg, 20.0 µmol, 4 mol%) was dissolved in freshly distilled dry THF (1 mL) and the associated acid chloride (0.50 mmol, 1.00 equiv) was added. The corresponding *N*-pyrrolyl-alkylzinc iodide in THF (0.60 mmol, 1.20 equiv) was added dropwise and the mixture was stirred at room temperature or 50 °C 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (1 mL) and extracted three times with EtOAc. The combined organic phases dried over $MgSO_4$ and the solvent evaporated. Purification *via* flash column chromatography (hexanes/EtOAc) yielded the corresponding acylation product.

Typical procedure for copper(I) iodide catalyzed acylation reactions (TP13b): [135]



A *Schlenk* tube, equipped with a magnetic stirring bar, was dried using a heat gun at 630 °C under high vacuum and flushed with argon three times. CuI (9.52 mg, 0.05 mmol, 10 mol%) was added to a freshly prepared solution of the corresponding *N*-pyrrolyl-alkylzinc iodide (0.60 mmol, 1.20 equiv) at 0 °C and the mixture stirred for 10 min. The associated acid chloride (0.50 mmol, 1.00 equiv) was added dropwise and the reaction was mixture stirred for 1 h at 0 °C. Cooling was removed and stirring was continued at room temperature for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl, extracted three times with EtOAc and the combined organic layers dried over $MgSO_4$. Evaporation of the solvent and flash column chromatography purification (hexanes/EtOAc) yielded the corresponding acylation product.

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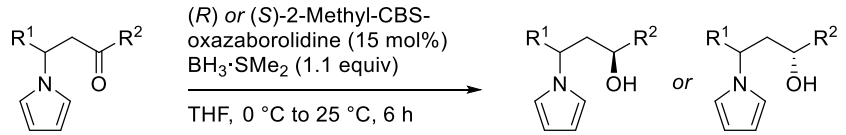
[134] a) D. Haas, D. Sustac-Roman, S. Schwarz, P. Knochel, *Org. Lett.* **2016**, *18*, 6380; b) R. D. Rieke, S.-H. Kim, *Tetrahedron Lett.* **2011**, *52*, 3094; c) E. Negishi, V. Bagheri, S. Chatterjee, F.-T. Luo, J. A. Miller, A.T. Stoll, *Tetrahedron Lett.* **1983**, *24*, 5181.

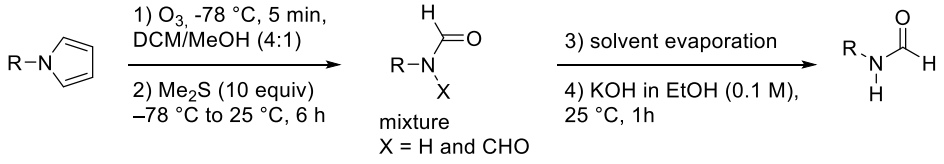
[135] a) H.-S. Jung, S.-H. Kim, *Tetrahedron Lett.* **2015**, *56*, 1004; b) E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1984**, *106*, 3368.

Typical procedure for stereoselective CBS-reduction (TP14): [136]



A *Schlenk* tube, equipped with a magnetic stirring bar, was dried using a heat gun at 630 °C under high vacuum and flushed with argon three times. The enantiopure CBS-catalyst ((*R*)- or (*S*)-2-methyl-CBS-oxazaborolidine, 15 mol-%) was dissolved in freshly distilled dry THF and $BH_3 \cdot SMe_2$ (1.10 equiv) was added slowly at 0 °C. After 10 min of stirring at this temperature, a solution of the corresponding ketone (1.00 equiv) in dry THF was added dropwise to the reaction mixture. Cooling was removed and the reaction mixture was stirred at room temperature until full conversion of the ketone. The reaction was quenched by the slow addition of methanol and the solvents were removed under reduced pressure. The resulting residue was purified using flash column chromatography (hexane/EtOAc, addition of 1% Et_3N) to yield the desired enantioenriched alcohol.

Typical procedure for the pyrrole deprotection reaction *via* ozonolysis (TP15): [137]

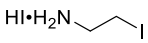


In a two-neck round bottom flask, the corresponding pyrrole derivative (1.0 equiv) was dissolved in a mixture of DCM and methanol (4:1) and cooled to –78 °C. Ozone was passed through the solution (flow approx. 2 L/min) until a blueish color was observed. Excess of ozone was removed by flushing with nitrogen for 10 min. Dimethyl sulfide (10.0 equiv) was added, cooling was removed, and the reaction mixture stirred for additional 6 h. After evaporation of all solvents, the residue was dissolved in KOH in EtOH (0.1 M) and stirred for 1 h. Ethanol was removed under reduced pressure and following purification of the crude product *via* flash column chromatography purification (hexanes/EtOAc, addition of 1% Et_3N, $KMnO_4$ stain) yielded the corresponding mono-formamide containing product.

[136] a) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986; b) E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, *53*, 2861.
[137] a) E. Tokumaru, A. Tengeiji, T. Nakahara, I. Shiina, *Chem. Lett.* **2015**, *44*, 1768; b) C. Kashima, T. Maruyama, Y. Fujioka, K. Harada, *J. Chem. Soc., Perkin Trans. 1* **1989**, 1041.

3.2 Precursor Syntheses

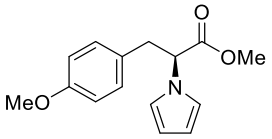
2-Iodoethan-1-amine hydroiodide (pc1)



The desired 2-iodoethan-1-amine hydroiodide was prepared as reported in the literature[138]: To a round bottle flask with 57% hydroiodic acid (44.89 g, 200 mmol, 2.00 equiv) 2-aminoethanol (6.11 g, 100 mmol, 1.00 equiv) was added at 0 °C. The reaction mixture was heated to 170 °C for 4 h. During the reaction, 24 mL of water were removed with a *Dean-Stark* apparatus and a black solid was formed. The reaction mixture was cooled down to room temperature and the residue washed with Et_2O several times. After recrystallization with Et_2O/EtOH the pure product 2-iodoethan-1-amine hydroiodide **pc1** was obtained as colorless salt (20.8 g, 69.6 mmol, 70% yield).

^{1}H-NMR (400 MHz, DMSO-d$_6$, ppm): δ = 7.86 (s, 3H), 3.30 – 3.25 (m, 2H), 3.24 – 3.17 (m, 2H).
^{13}C-NMR (101 MHz, DMSO-d$_6$, ppm): δ = 41.4, -0.7.
IR (Diamond-ATR, neat, cm^{-1}): ν = 2995 (s), 1567 (m), 1552 (s), 1485 (s), 1468 (s), 1436 (s), 1380 (m), 1315 (m), 1225 (m), 1207 (s), 1074 (m), 1058 (s), 1015 (s), 910 (s), 860 (vs), 785 (s).

Methyl (*S*)-3-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)propanoate ((*S*)-pc3)



According to a modified version of **TP9**, *L*-tyrosine (9.06 g, 50.0 mmol, 1.00 equiv) and $NaOAc{\cdot}3H_2O$ (6.80 g, 50.0 mmol, 1.0 equiv) were dissolved in 1,2-dichloroethane (37.5 mL), water (37.5 mL) and glacial acetic acid (12.5 mL). 2,5-dimethoxytetrahydrofuran (6.60 g, 50.0 mmol, 1.00 equiv) was added and the resulting suspension was refluxed under vigorous stirring for 16 h at 90 °C. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3x150 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* to obtain the crude **(*S*)-3-(4-hydroxyphenyl)-2-(1*H*-pyrrol-1-yl)propanoic acid ((*S*)-pc2)**.

Without further purification, the crude product **(*S*)-pc2** was dissolved in DMF (100 mL) and cooled with an ice-bath, before KOH (3.09 g, 55.0 mmol, 1.50 equiv) was added. Iodomethane (4.67 mL, 75.0 mmol, 1.50 equiv) was added dropwise at 0 °C and the reaction mixture was then stirred for 1 h at ambient temperature. This step was repeated: After cooling down to 0 °C, another portion of KOH (3.09 g, 55.0 mmol, 1.50 equiv) and iodomethane (4.67 mL, 75.0 mmol, 1.50 equiv) were added. The resulting mixture was stirred for 24 h at room temperature. After aqueous workup and extraction with ethyl acetate (3x 150 mL), the combined organic layers were washed successively with a saturated LiCl

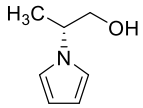
[138] Katchalski, E.; Ishai, D. B. *J. Org. Chem.* **1950**, 15, 1067.

solution (100 mL) and brine (100 mL). The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography to obtain **(*S*)-pc3** as a colorless oil (7.56 g, 29.2 mmol, 58% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.95 – 6.89 (m, 2H), 6.79 – 6.75 (m, 2H), 6.72 (t, *J* = 2.2 Hz, 2H), 6.15 (t, *J* = 2.2 Hz, 2H), 4.70 (dd, *J* = 8.8, 6.5 HZ, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.36 (dd, *J* = 13.9, 6.5 Hz, 1H), 3.20 (dd, *J* = 13.9, 8.8 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 170.8, 158.7, 130.0, 128.4, 120.2, 114.1, 108.8, 63.9, 55.3, 52.7, 38.8
MS (EI, 70 eV, %): *m/z* = 259 (10), 192 (6); 122 (9), 121 (100), 91 (4), 77 (3).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{15}H_{17}NO_3$]: 259.1208; found 259.1200 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2954 (w), 1741 (s), 1612 (m), 1513 (s), 1488 (m), 1464 (w), 1439 (m), 1300 (m), 1283 (m), 1273 (m), 1245 (vs), 1198 (m), 1177 (s), 1164 (s), 1111 (m), 1091 (m), 1072 (m), 1032 (s), 823 (m), 722 (vs).

3.3 Preparation of β-*N*-Pyrrolyl-Alkyl Alcohols

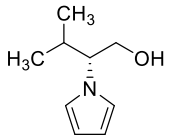
(*R*)-2-(1H-Pyrrol-1-yl)propan-1-ol ((*R*)-18b)



Following **TP9**, the product was synthesized by refluxing a solution of *D*-alaninol **(*R*)-17b** (1.88 g, 25.0 mmol, 1.00 equiv), $NaOAc{\cdot}3H_2O$ (3.40 g, 25.0 mmol, 1.00 equiv) and 2,5-dimethoxytetrahydrofuran (*cis*/*trans* mixture, 3.30 g, 25.0 mmol, 1.00 equiv) in 1,2-dichloroethane (37.5 mL), water (37.5 mL) and glacial acetic acid (12.5 mL) for 5 h. The crude product was purified by flash column to afford **(*R*)-18b** (2.47 g, 19.7 mmol, 79% yield) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.75 (t, *J* = 2.1 Hz, 2H), 6.19 (t, *J* = 2.1 Hz, 2H), 4.17 (quint, *J* = 7.0, 4.6 Hz, 1H), 3.75 – 3.63 (m, 2H), 1.68 (br, 1H), 1.45 (d, *J* = 6.9 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 118.9, 108.4, 67.7, 57.2, 17.5.
MS (EI, 70 eV, %): *m/z* = 125 (52), 94 (100), 93 (13), 78 (22), 68 (12).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_7H_{11}NO$]: 125.0841; found: 125.0836 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3392 (w), 2974 (w), 2936 (w), 2877 (w), 2360 (vw), 1548 (vw), 1490 (m), 1454 (w), 1413 (w), 1387 (w), 1319 (w), 1275 (m), 1089 (m), 1049 (s), 984 (w), 953 (w), 724 (vs).
M.p. 50.3 °C.

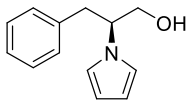
(*R*)-3-Methyl-2-(1*H*-pyrrol-1-yl)butan-1-ol ((*R*)-18c)



Following **TP9**, the product was synthesized by refluxing a solution of *D*-valinol **(*R*)-17c** (2.58 g, 25.0 mmol, 1.00 equiv), $NaOAc \cdot 3H_2O$ (3.40 g, 25.0 mmol, 1.00 equiv) and 2,5-dimethoxytetrahydrofuran (*cis*/*trans* mixture, 3.30 g, 25.0 mmol, 1.00 equiv) in 1,2-dichloroethane (37.5 mL), water (37.5 mL) and glacial acetic acid (12.5 mL) for 16 h. The crude product was purified by flash column chromatography to afford **(*R*)-18c** (3.21 g, 20.9 mmol, 84% yield) as a yellow liquid.

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 6.68 (t, *J* = 2.1 Hz, 2H), 6.17 (t, *J* = 2.2 Hz, 2H), 3.89 (dd, *J* = 11.9, 3.8 Hz, 1H), 3.81 (dd, *J* = 11.7, 8.7 Hz, 1H), 3.58 (td, *J* = 9.0, 3.8 Hz, 1H), 2.02 (dhept, *J* = 9.3, 6.7 Hz, 1H), 1.58 (br, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H).
^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 119.8, 108.3, 68.8, 64.3, 30.8, 20.1, 19.6.
MS (EI, 70 eV, %): *m/z* = 153 (37), 122 (100), 120 (10), 107 (12), 106 (12), 94 (18), 82 (31), 80 (38), 68 (18), 67 (14), 44 (17).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_9H_{15}NO]$: 153.1154; found: 153.1147 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): $\nu =$ 2961 (w), 2874 (w), 1489 (m), 1470 (w), 1413 (w), 1387 (w), 1369 (w), 1275 (m), 1088 (m), 1062 (m), 1019 (m), 970 (w), 931 (w), 856 (vw), 824 (vw), 720 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +21.1.

(*S*)-3-Phenyl-2-(1*H*-pyrrol-1-yl)propan-1-ol ((*S*)-18d)



Following **TP9**, a solution of *L*-phenylalaninol **(*S*)-17d** (3.78 g, 25.0 mmol, 1.00 equiv), $NaOAc \cdot 3H_2O$ (3.40 g, 25.0 mmol, 1.00 equiv) and 2,5-dimethoxytetrahydrofuran (*cis*/*trans* mixture, 3.30 g, 25.0 mmol, 1.00 equiv) in 1,2-dichloroethane (37.5 mL), distilled water (37.5 mL) and glacial acetic acid (12.5 mL) was heated under reflux for 16 h. Purification of the crude product by flash column chromatography afforded **(*S*)-18d** (4.27 g, 21.2 mmol, 85% yield) as a yellow oil.

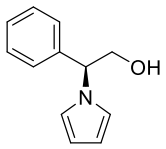
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.33 – 7.19 (m, 3H), 7.09 – 7.05 (m, 2H), 6.73 (t, *J* = 2.1 Hz, 2H), 6.20 (t, *J* = 2.1 Hz, 2H), 4.22 (tt, *J* = 7.3, 5.9 Hz, 1H), 3.83 (d, *J* = 6.0 Hz, 2H), 3.14 – 3.04 (m, 2H), 1.69 (br, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 137.7, 129.0, 128.6, 126.8, 119.3, 108.6, 65.4, 63.6, 38.7.
MS (EI, 70 eV, %): *m/z* = 202 (14), 201 (90), 170 (39), 168 (16), 111 (11), 110 (100), 99 (12), 97 (21), 91 (43), 85 (32), 83 (23), 82 (41), 77 (11), 71 (49), 70 (13), 67 (10), 65 (13), 56 (12), 57 (61), 55 (34), 44 (17), 43 (43), 40 (28).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{13}H_{15}NO$]: 201.1154; found: 201.1150 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3456 (w), 3027 (w), 2939 (w), 2874 (vw), 1733 (vw), 1603 (vw), 1547 (vw), 1489 (m), 1454 (w), 1412 (w), 1330 (w), 1272 (m), 1091 (m), 1063 (m), 1040 (m), 1000 (w), 939 (w), 819 (vw), 722 (vs), 697 (vs).

M.p.: 52.6 °C.

(*S*)-2-Phenyl-2-(1*H*-pyrrol-1-yl)ethan-1-ol ((*S*)-18e)



Following **TP9**, a solution of (*S*)-2-phenylglycinol **(*S*)-17e** (4.11 g, 30.0 mmol, 1.00 equiv), NaOAc·3H_2O (4.08 g, 30.0 mmol, 1.00 equiv) and 2,5-dimethoxytetrahydrofuran (*cis*/*trans* mixture, 3.97 g, 30.0 mmol, 1.00 equiv) in 1,2-dichloroethane (45 mL), distilled water (45 mL) and glacial acetic acid (15 mL) was heated under reflux for 16 h. Purification of the crude product by flash column chromatography afforded **(*S*)-18e** (5.17 g, 27.6 mmol, 92% yield) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.38 – 7.27 (m, 3H), 7.18 – 7.14 (m, 2H), 6.82 (t, *J* = 2.2 Hz, 2H), 6.24 (t, *J* = 2.1 Hz, 2H), 5.26 (dd, *J* = 8.3, 5.1 Hz, 1H), 4.27 – 4.12 (m, 3H), 1.87 (br, 1H).

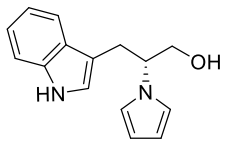
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 138.6, 129.0, 128.2, 126.7, 120.1, 108.9, 65.4, 65.0.

MS (EI, 70 eV, %): *m/z* = 187 (14), 157 (12), 156 (100), 154 (11), 129 (14), 128 (12).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{12}H_{13}NO$]: 187.0997; found: 187.0990 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3275 (m), 2953 (w), 2894 (w), 1491 (m), 1449 (s), 1408 (m), 1326 (m), 1272 (s), 1201 (m), 1095 (m), 1081 (s), 1056 (s), 1029 (vs), 999 (s), 939 (m), 852 (w), 829 (w), 748 (m), 722 (vs), 697 (vs).

(*R*)-3-(1*H*-Indol-3-yl)-2-(1*H*-pyrrol-1-yl)propan-1-ol ((*R*)-18f)



Following **TP9**, a solution of *D*-tryptophanol **(*R*)-17f** (3.81 mmol, 20.0 mmol, 1.00 equiv), NaOAc·3H_2O (3.90 g, 28.7 mmol, 1.44 equiv) and 2,5-dimethoxytetrahydrofuran (*cis*/*trans* mixture, 2.64 g, 20.0 mmol, 1.00 equiv) in 1,2-dichloroethane (40 mL), distilled water (40 mL) and glacial acetic acid (4.1 mL) was heated under reflux for 16 h. Purification of the crude product by flash column chromatography afforded **(*R*)-18f** (3.43 g 14.3 mmol, 71% yield) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.94 (s, 1H), 7.57 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.34 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.76 (t, *J* = 2.0 Hz,

2H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.21 (t, *J* = 2.1 Hz, 2H), 4.31 (dtd, *J* = 7.8, 6.6, 5.3 Hz, 1H), 3.85 (t, *J* = 5.9 Hz, 2H), 3.33 – 3.25 (m, 1H), 3.19 (ddd, *J* = 14.8, 7.8, 0.9 Hz, 1H), 1.66 (t, *J* = 6.3 Hz, 1H).

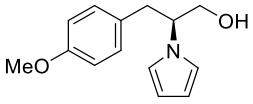
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 136.1, 127.3, 122.6, 122.2, 119.6, 119.4, 118.5, 111.6, 111.3, 108.5, 65.9, 62.5, 28.0.

MS (EI, 70 eV, %): *m/z* = 241 (5), 240 (32), 173 (14), 131 (10), 130 (100).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{15}H_{16}N_2O$]: 240.1263; found: 240.1257 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3402 (m), 2942 (w), 1489 (m), 1456 (m), 1420 (m), 1336 (m), 1271 (m), 1229 (m), 1091 (s), 1065 (m), 1011 (m), 938 (w), 821 (w), 724 (vs).

(*S*)-3-(4-Methoxyphenyl)-2-(1H-pyrrol-1-yl)propan-1-ol ((*S*)-18g)



(*S*)-pc3 (5.78 g, 25.0 mmol, 1.00 equiv) was dissolved in ethanol (50 mL), the resulting solution cooled to 0 °C and $NaBH_4$ (1.42 g, 37.5 mmol, 1.50 equiv) was added in small portions. The mixture was warmed to room temperature and stirred for 4 h, before all solvent were evaporated. The residue was suspended in EtOAc (150 mL), the remaining $NaBH_4$ was quenched with sat. aq. NH_4Cl and the organic phase separated. After washing with sat. aq. $NaHCO_3$ solution and brine, the organic phase was dried over $MgSO_4$, filtered and the solvents removed *in vacuo*. Purification by flash column chromatography yielded the alcohol **(*S*)-18g** as a viscous colorless liquid (4.01 g, 17.26 mmol, 69% yield).[139]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.97 – 6.91 (m, 2H), 6.81 – 6.75 (m, 2H), 6.70 (t, *J* = 2.1 Hz, 2H), 6.17 (t, *J* = 2.1 Hz, 2H), 4.15 (tt, *J* = 7.2, 5.9 Hz, 1H), 3.82 (d, *J* = 5.9 Hz, 2H), 3.77 (s, 3H), 3.02 (s, 1H), 3.00 (d, *J* = 1.6 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.5, 130.0, 129.7, 119.3, 114.0, 108.6, 65.5, 63.8, 55.3, 37.8.

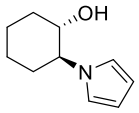
MS (EI, 70 eV, %): *m/z* = 231 (32), 200 (11), 198 (13), 164 (53), 121 (100), 110 (30), 91 (12), 82 (59).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{14}H_{17}O_2N_4$]: 231.1259; found: 231.1253 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm-1): ν = 2836 (w), 1612 (m), 1584 (w), 1511 (s), 1490 (m), 1463 (m), 1328 (w), 1300 (m), 1273 (m), 1243 (vs), 1178 (s), 1091 (m), 1066 (m), 1031 (s), 940 (w), 874 (w), 831 (m), 816 (m), 766 (w), 722 (vs).

[139] J.-E. Joo, K.-Y. Lee, V.-T. Pham, Y.-S. Tian, W.-H. Ham, *Org. Lett.* **2007**, *9*, 3627.

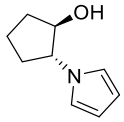
(1*S*,2*S*)-2-(1*H*-Pyrrol-1-yl)cyclohexan-1-ol (*S*,*S*-18h)



According to a modified version of **TP9**, (1*S*,2*S*)-2-aminocyclohexan-1-ol hydrochloride **(*S*,*S*)-17h** (6.07 g, 40.0 mmol, 1.00 equiv) and NaOAc·3H_2O (10.9 g, 80 mmol, 2.00 equiv) were dissolved in a mixture of 1,2-dichloroethane (65 mL), water (65 mL) and glacial acetic acid (21 mL). Then, 2,5-dimethoxytetrahydrofuran (*cis*/*trans* mixture, 5.29 g, 40.0 mmol, 1.00 equiv) was added and the two-phase mixture was stirred vigorously at 90 °C for 16 h. After aqueous workup and purification *via* flash column, **(*S*,*S*)-18h** was obtained as yellowish solid (5.45 g, 33.0 mmol, 83% yield, *d.r.* > 99.1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.74 (t, *J* = 2.2 Hz, 2H), 6.17 (t, *J* = 2.2 Hz, 2H), 3.65 – 3.54 (m, 2H), 2.15 – 1.98 (m, 3H), 1.88 – 1.79 (m, 2H), 1.77 – 1.64 (m, 1H), 1.46 – 1.30 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 119.2, 108.4, 74.3, 65.8, 33.3, 32.4, 25.4, 24.4.
MS (EI, 70 eV, %): *m/z* = 166 (10), 165 (100), 106 (22), 94 (21), 93 (10), 81 (15), 80 (20), 79 (11), 68 (48), 67 (12).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{10}H_{15}NO$]: 165.1154; found: 165.1148 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3466 (w), 2933 (m), 2858 (w), 1668 (vw), 1490 (m), 1450 (m), 1414 (w), 1360 (w), 1274 (s), 1232 (w), 1134 (w), 1088 (s), 1062 (s), 1047 (m), 985 (w), 941 (m), 867 (w), 848 (w), 718 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –2.7.
M.p. 36.4 °C.

(1*R*,2*R*)-2-(1H-Pyrrol-1-yl)cyclopentan-1-ol ((*R*,*R*)-18i)



According to a modified version of **TP9**, (1*R*,2*R*)-2-aminocyclopentan-1-ol hydrochloride **(*R*,*R*)-17i** (2.75 mmol, 20.0 mmol, 1.00 equiv) and NaOAc·3H_2O (6.53 g, 48.0 mmol, 2.40 equiv) were dissolved in a mixture of 1,2-dichloroethane (40 mL), water (40 mL) and glacial acetic acid (3 mL). Then, 2,5-dimethoxytetrahydrofuran (*cis*/*trans* mixture, 2.64 g, 20.0 mmol, 1.00 equiv) was added and the two-phase mixture was stirred vigorously at 90 °C for 16 h. After aqueous workup and purification *via* flash column, **(*R*,*R*)-18i** was obtained as colorless liquid (2.33 g, 15.4 mmol, 77% yield, d.r. >99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.76 (t, *J* = 2.1 Hz, 2H), 6.18 (t, *J* = 2.2 Hz, 2H), 4.17 – 4.03 (m, 2H), 2.43 (d, *J* = 2.4 Hz, 1H), 2.32 – 2.19 (m, 1H), 2.13 – 2.00 (m, 1H), 2.03 – 1.76 (m, 3H), 1.73 – 1.57 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 119.1, 108.2, 78.7, 67.5, 31.6, 29.9, 20.0.

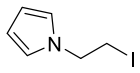
MS (EI, 70 eV, %): *m/z* = 151 (100), 106 (56), 94 (74), 80 (58), 68 (100).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_9H_{13}NO$]: 151.0997; found: 151.0990 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3361 (w), 2962 (w), 2878 (w), 1666 (vw), 1491 (m), 1451 (w), 1418 (w), 1280 (m), 1091 (m), 1064 (m), 1051 (m), 977 (w), 719 (vs).

3.4 Preparation of β-*N*-Pyrrolyl-Alkyl Iodides

1-(2-Iodoethyl)-1*H*-pyrrole (19a)



According to a modified version of **TP9**, 2-iodoethan-1-amine hydroiodide (**pc1**, 5.98 g, 20.0 mmol, 1.00 equiv) and NaOAc·3H_2O (13.6 g, 100 mmol, 5.00 equiv) were dissolved in 10 mL glacial acetic acid. To the reaction mixture 2,5-dimethoxytetrahydrofuran (*cis*/*trans* mixture, 2.91 g, 20.0 mmol, 1.00 equiv) was added and the mixture was refluxed at 90 °C for 1 h. The reaction was quenched with water and neutralized with saturated $NaHCO_3$, extracted with ethyl acetate and the combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by flash column chromatography to yield the alkyl iodide **19a** as a yellowish liquid (3.12 g, 14.1 mmol, 71% yield).[140]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.69 (t, *J* = 2.1, 2H), 6.19 (t, *J* = 2.1 Hz, 2H), 4.25 (t, *J* = 7.5 Hz, 2H), 3.40 (t, *J* =7.5 Hz, 2H).

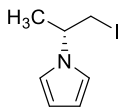
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 120.5, 108.9, 52.0, 3.4.

MS (EI, 70 eV, %): *m/z* = 221 (100), 193 (35), 155 (18), 127 (14), 94 (44), 80 (20).

HRMS (ESI): m/z calc. for [C_6H_8IN]: 220.9701; found: 220.9695 ([M]$^+$).

IR (Diamond-ATR, neat, cm^{-1}): ν = 3098 (vw), 2963 (vw), 2363 (vw), 1556 (w), 1495 (m), 1445 (w), 1418 (w), 1350 (w), 1290 (m), 1276 (s), 1238 (m), 1172 (m), 1087 (s), 1064 (m), 964 (m), 834 (w), 717 (vs).

(*R*)-1-(1-Iodopropan-2-yl)-1H-pyrrole ((*R*)-19b)



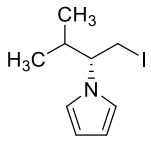
According to **TP10**, a solution of **(*R*)-18b** (2.47 g, 19.7 mmol, 1.00 equiv) in dry DCM (30 mL) was added dropwise to a 0 °C solution of PPh_3 (6.20 g, 23.6 mmol, 1.20 equiv), imidazole (1.61 g, 23.6 mmol, 1.20 equiv) and iodine (6.00 g, 23.6 mmol, 1.20 equiv) in dry DCM (33 mL) over a period of 30 min. The mixture was then allowed to warm to room temperature and stirred for an additional 90 min. After quenching with $Na_2S_2O_3$, extraction with DCM and purification via flash column

[140] Gracia, S.; Cazorla, C.; Métay, E.; Pellet-Rostaing, S.; Lemaire, M. *J. Org. Chem.* **2009**, 74, 3160.

chromatography **(*R*)-19b** (4.23 g, 18.0 mmol, 91% yield, 99.7% ee) was obtained as a faint yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.66 (t, *J* = 2.1 Hz, 2H), 6.18 (t, *J* = 2.1 Hz, 2H), 3.71 – 3.62 (m, 2H), 3.51 – 3.43 (m, 1H), 2.18 – 2.04 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 119.5, 108.0, 67.8, 34.4, 20.3, 19.4, 8.9.
MS (EI, 70 eV, %): *m/z* = 263 (24), 220 (33), 193 (14), 122 (47), 94 (28), 93 (100).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_9H_{14}NI$]: 263.0171; found: 263.0164 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2961 (w), 2872 (w), 1545 (vw), 1487 (m), 1469 (w), 1419 (w), 1387 (w), 1369 (w), 1293 (w), 1272 (m), 1190 (m), 1156 (w), 1087 (m), 1067 (m), 970 (w), 923 (w), 856 (w), 717 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –49.6.

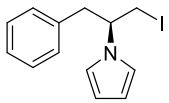
***(R)*-1-(1-Iodo-3-methylbutan-2-yl)-1*H*-pyrrole ((*R*)-19c)**



According to **TP10**, a solution of **(*R*)-18c** (2.30 g, 15.0 mmol, 1.00 equiv) in dry dichloromethane (30 mL) was added dropwise to a 0 °C solution of PPh_3 (4.33 g, 16.5 mmol, 1.10 equiv), imidazole (1.12 g, 16.5 mmol, 1.10 equiv) and iodine (4.19 g, 16.5 mmol, 1.10 equiv) in dry DCM (33 mL) over a period of 30 min. The mixture was then allowed to warm to room temperature and stirred for an additional 90 min. After quenching with sat. aq. $Na_2S_2O_3$ solution, extraction with DCM and purification by flash column chromatography **(*R*)-19c** (3.46 g, 13.1 mmol, 88% yield, 99.5% *ee*) was obtained as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.66 (t, *J* = 2.1 Hz, 2H), 6.18 (t, *J* = 2.1 Hz, 2H), 3.71 – 3.62 (m, 2H), 3.51 – 3.43 (m, 1H), 2.18 – 2.04 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 119.5, 108.0, 67.8, 34.4, 20.3, 19.4, 8.9.
MS (EI, 70 eV, %): *m/z* = 263 (24), 220 (33), 193 (14), 122 (47), 94 (28), 93 (100).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_9H_{14}NI$]: 263.0171; found: 263.0164 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2961 (w), 2872 (w), 1545 (vw), 1487 (m), 1469 (w), 1419 (w), 1387 (w), 1369 (w), 1293 (w), 1272 (m), 1190 (m), 1156 (w), 1087 (m), 1067 (m), 970 (w), 923 (w), 856 (w), 717 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –34.0.

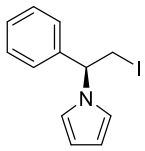
(*S*)-1-(1-Iodo-3-phenylpropan-2-yl)-1*H*-pyrrole ((*S*)-19d)



Following **TP10**, **(*S*)-18d** (4.23 g, 21.0 mmol, 1.00 equiv) in dry DCM (40 mL) was added dropwise to a solution of triphenylphosphine (6.08 g, 23.2 mmol, 1.10 equiv), iodine (5.87 g, 23.1 mmol, 1.10 equiv) and imidazole (1.58 g, 23.1 mmol, 1.10 equiv) in dry DCM (44 mL) at 0 °C over a period of 45 min. The mixture was stirred for another 30 min, allowed to warm to room temperature and stirred for an additional 90 min. Quenching with $Na_2S_2O_3$, extraction with DCM and purification by flash column chromatography afforded **(*S*)-19d** (5.52 g, 17.7 mmol, 84% yield, 99.9% *ee*) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.26 – 7.16 (m, 3H), 7.02 – 6.97 (m, 2H), 6.61 (t, *J* = 2.1 Hz, 2H), 6.14 (t, *J* = 2.2 Hz, 2H), 4.19 (tt, *J* = 7.7, 5.9 Hz, 1H), 3.51 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.42 (dd, *J* = 10.5, 7.6 Hz, 1H), 3.22 (dd, *J* = 13.8, 6.3 Hz, 1H), 3.11 (dd, *J* = 13.7, 7.9 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 137.2, 129.0, 128.7, 127.1, 118.9, 108.5, 62.9, 42.1, 9.5.
MS (EI, 70 eV, %): *m/z* = 311 (24), 220 (84), 117 (14), 115 (16), 93 (100), 91 (26).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{13}H_{14}NI$]: 311.0171; found: 311.0163 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3061 (vw), 3025 (w), 2946 (vw), 1603 (vw), 1545 (vw), 1486 (m), 1453 (w), 1414 (w), 1328 (w), 1273 (m), 1175 (m), 1089 (m), 1069 (m), 1030 (w), 964 (w), 917 (w), 867 (vw), 821 (vw), 719 (vs), 697 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –1.5.

(*S*)-1-(2-Iodo-1-phenylethyl)-1*H*-pyrrole ((*S*)-19e)



Following **TP10**, **(*S*)-18e** (4.68 g, 25.0 mmol, 1.00 equiv) in dry DCM (40 mL) was added dropwise to a solution of triphenylphosphine (7.21 g, 27.5 mmol, 1.10 equiv), iodine (6.98 g, 27.5 mmol, 1.10 equiv) and imidazole (1.87 g, 27.5 mmol, 1.10 equiv) in dry DCM (44 mL) at 0 °C over a period of 30 min. The mixture was stirred for another 30 min, allowed to warm to room temperature and stirred for an additional 3 h. Quenching with $Na_2S_2O_3$, extraction with DCM and purification by flash column chromatography afforded **(*S*)-19e** (5.28 g, 17.8 mmol, 71% yield, 99.8% *ee*) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.40 – 7.32 (m, 3H), 7.23 – 7.17 (m, 2H), 6.78 (t, *J* = 2.1 Hz, 2H), 6.25 (t, *J* = 2.1 Hz, 2H), 5.33 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.86 (dd, *J* = 10.8, 6.1 Hz, 1H), 3.77 (dd, *J* =10.8, 9.5 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 139.6, 129.1, 128.5, 126.5, 119.6, 108.9, 65.2, 6.9.

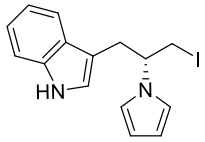
MS (EI, 70 eV, %): *m/z* = 297 (45), 231 (31), 193 (59), 170 (39), 168 (31), 167 (14), 156 (25), 104 (100), 103 (22), 78 (22), 77 (14).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{12}H_{12}NI$]: 297.0014; found: 297.0005 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3059 (vw), 3028 (vw), 1485 (m), 1450 (m), 1423 (w), 1311 (w), 1277 (m), 1175 (m), 1128 (w), 1089 (m), 1068 (m), 1022 (w), 961 (w), 913 (vw), 859 (w), 752 (w), 718 (vs), 695 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +31.2.

(*R*)-3-(3-Iodo-2-(1*H*-pyrrol-1-yl)propyl)-1*H*-indole ((*R*)-19f)



Following **TP10**, **(*R*)-18f** (2.40 g, 10.0 mmol, 1.00 equiv) in dry DCM (20 mL) was added dropwise to a solution of PPh_3 (2.75 g, 10.5 mmol, 1.05 equiv), imidazole (715 mg, 10.5 mmol, 1.05 equiv) and iodine (2.67 g, 10.5 mmol, 1.05 equiv) in dry DCM (21 mL) at 0 °C over a period of 30 min. The mixture was stirred for another 30 min, allowed to warm to room temperature and stirred for an additional 2h. Quenching with $Na_2S_2O_3$, extraction with DCM and purification by flash column chromatography afforded **(*R*)-19f** as a yellowish oil (2.96 g, 8.45 mmol, 84% yield, 99.5% *ee*)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.91 (s, 1H), 7.59 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.37 (dt, *J* = 8.1 Hz, 0.9, 1H), 7.29 – 7.20 (m, 1H), 7.18 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.72 (t, *J* = 2.1 Hz, 2H), 6.69 (d, *J* = 2.4 Hz, 1H), 6.21 (t, *J* = 2.2 Hz, 2H), 4.37 – 4.28 (m, 1H), 3.59 (dd, *J* = 10.4, 5.4 Hz, 1H), 3.49 (dd, *J* = 10.4, 7.4 Hz, 1H), 3.47 (dd, *J* = 14.7, 6.5 Hz, 1H), 3.28 (ddd, *J* = 14.7, 7.7, 0.9 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 136.0, 127.1, 122.9, 122.3, 119.8, 119.0, 118.4, 111.4, 111.1, 108.3, 61.5, 31.6, 10.4.

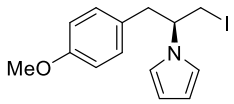
MS (EI, 70 eV, %): *m/z* = 350 (5), 156 (2), 131 (10), 130 (100), 128 (3), 93 (3), 77 (2).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{15}H_{15}IN_2$]: 350.0280; found: 350.0267 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3409 (m), 1487 (m), 1456 (m), 1419 (m), 1336 (m), 1272 (m), 1228 (m), 1177 (m), 1090 (s), 1066 (m), 1010 (m), 918 (w), 809 (w), 721 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +5.7.

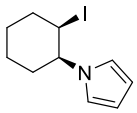
(*S*)-1-(1-Iodo-3-(4-methoxyphenyl)propan-2-yl)-1*H*-pyrrole ((*S*)-19g)



Following **TP10**, **(*S*)-18g** (3.47 g, 15.0 mmol, 1.00 equiv) in dry DCM (30 mL) was added dropwise to a solution of PPh_3 (4.72 g, 18.0 mmol, 1.05 equiv), imidazole (1.23 g, 18.0 mmol, 1.05 equiv) and iodine (4.57 g, 18.0 mmol, 1.05 equiv) in dry DCM (36 mL) at 0 °C over a period of 30 min. The mixture was stirred for another 30 min, allowed to warm to room temperature and stirred for an additional 2 h. Quenching with $Na_2S_2O_3$, extraction with DCM and purification by flash column chromatography afforded **(*S*)-19g** as a colorless oil (4.86 g, 14.3 mmol, 95% yield, 92.0% *ee*)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.94 – 6.89 (m, 2H), 6.82 – 6.76 (m, 2H), 6.63 (t, *J* = 2.1 Hz, 2H), 6.16 (t, *J* = 2.1 Hz, 2H), 4.16 (tt, *J* = 7.7 Hz, 6.1, 1H), 3.78 (s, 3H), 3.53 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.43 (dd, *J* = 10.5, 7.7 Hz, 1H), 3.17 (dd, *J* = 13.9, 6.3 Hz, 1H), 3.07 (dd, *J* = 13.9, 7.8 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.6, 130.0, 129.1, 118.9, 114.1, 108.4, 63.0, 55.3, 41.2, 9.6.
MS (EI, 70 eV, %): *m/z* = 341 (20), 147 (9), 121 (100), 93 (16), 77 (10).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{14}H_{16}INO$]: 341.0277; found: 341.0271 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 1611 (m), 1511 (s), 1487 (m), 1463 (m), 1440 (m), 1301 (m), 1273 (m), 1244 (vs),1177 (s), 1090 (m), 1069 (m), 1032 (s), 963 (w), 934 (w), 817 (m), 810 (m), 719 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –4.4.

1-((1*S*,2*R*)-2-Iodocyclohexyl)-1*H*-pyrrole (*S*,*R*-19h)



Based on a modified version of **TP10**, PPh_3 (4.93 g, 18.8 mmol, 1.20 equiv), imidazole (1.28 g, 18.8 mmol, 1.20 equiv) and iodine (4.77 g, 18.8 g, 1.20 equiv) were dissolved in DCM (30 mL) at 0 °C and stirred for 15 min. A solution of **(*S*,*S*)-18h** (2.60 g, 15.7 mmol, 1.00 equiv) in DCM (38 mL) was added dropwise to the reaction mixture over 30 min. Afterwards, cooling was removed and the reaction heated up to 50 °C for 30 h. After quenching with NaS_2O_3-solution, aqueous workup and purification *via* flash column chromatography, **(*S*,*R*)-19h** was obtained as a colorless oil (3.30 g, 12.0 mmol, 76% yield, 99.8% ee).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.74 (t, *J* = 2.2 Hz, 2H), 6.18 (t, *J* = 2.1 Hz, 2H), 4.90 (tq, *J* = 3.1, 1.5 Hz, 1H), 3.26 (dt, *J* = 11.7, 3.3 Hz, 1H), 2.30 – 2.21 (m, 1H), 2.21 – 2.09 (m, 1H), 2.04 – 1.87 (m, 2H), 1.82 (tt, *J* = 12.7, 3.4 Hz, 1H), 1.70 – 1.61 (m, 1H), 1.58 – 1.43 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 118.5, 108.0, 60.5, 44.4, 35.2, 28.1, 25.4, 21.8.

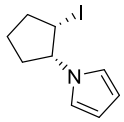
MS (EI, 70 eV, %): *m/z* = 275 (49), 193 (129), 148 (100), 127 (12), 118 (24), 106 (16), 81 (76), 80 (38), 79 (66), 77 (15), 68 (63), 67 (29).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{10}H_{14}IN$]: 275.0171; found: 275.0164 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2936 (m), 2860 (w), 1488 (m), 1445 (w), 1297 (m), 1279 (m), 1256 (m), 1162 (m), 1093 (m), 1055 (w), 998 (m), 956 (m), 834 (w), 714 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –59.4.

1-((1*R*,2*S*)-2-Iodocyclopentyl)-1*H*-pyrrole ((*R*,*S*)-19i)



According to a modified version of **TP10**, PPh_3 (4.32 g, 16.5 mmol, 1.10 equiv) and imidazole (1.12 g, 16.5 mmol, 1.10 equiv) were dissolved in dry DCM (20 mL). Iodine (4.19 g, 16.5 mmol, 1.10 equiv) was added in small portions at 0 °C, followed by the addition of **(*R*,*R*)-18i** (2.27 g, 15.0 mmol, 1.00 equiv) in dry DCM (20 mL) over a period of 30 min. The resulting reaction mixture further stirred for 30 min at room temperature and refluxed at 50 °C for 16 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (75 mL) and diluted with water (75 mL). After extraction with DCM (3x150 mL), the combined organic phases were dried over $MgSO_4$ and the solvent evaporated. Purification by flash column chromatography afforded the title **(*R*,*S*)-19i** compound as white solid (1.67 g, 6.64 mmol, 43% yield, 98.1% *ee*, d.r. >99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.75 (t, *J* = 2.2 Hz, 2H), 6.19 (t, *J* = 2.2 Hz, 2H), 4.63 (td, *J* = 5.0, 3.5 Hz, 1H), 3.83 (ddd, *J* = 9.4, 7.4, 4.9 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.44 – 2.28 (m, 2H), 2.25 – 2.06 (m, 2H), 1.89 – 1.75 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 119.8, 108.1, 63.7, 37.4, 36.0, 27.9, 21.1.

MS (EI, 70 eV, %): *m/z* = 261 (100), 192 (51), 134 (92), 127 (81), 106 (51), 68 (76).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_9H_{12}IN$]: 261.0014; found: 261.0010 ([M]$^+$).

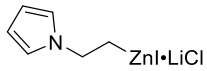
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2959 (m), 2915 (w), 2855 (w), 1492 (m), 1443 (w), 1362 (w), 1337 (m), 1296 (w), 1280 (m), 1261 (s), 1199 (w), 1174 (m), 1100 (s), 1063 (s), 1018 (s), 976 (m), 922 (w), 870 (w), 796 (vs), 727 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +97.5.

M.p. 77.4 °C.

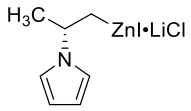
3.5 Preparation of Organozinc Reagents from Chiral β-*N*-Pyrrolyl-Alkyl Iodides

(2-(1*H*-Pyrrol-1-yl)ethyl)zinc(II) iodide (20a)



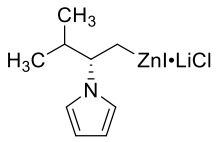
According to **TP11**, LiCl (424 mg, 10.0 mmol, 1.00 equiv) and zinc dust (981 mg, 15.0 mmol, 1.50 equiv) were dried and suspended in freshly distilled dry THF (15 mL). After activation with DBE and TMSCl, the suspension was cooled with a water-bath and **19a** (2.21 g, 10.0 mmol, 1.00 equiv) was added dropwise. After 10 min, the reaction mixture was passed through a syringe filter and a 0.58 M yellow solution of the title compound **20a** was obtained (16.0 mL, 9.28 mmol, 93% yield).

(*R*)-(2-(1H-Pyrrol-1-yl)propyl)zinc(II) iodide ((*R*)-20b)



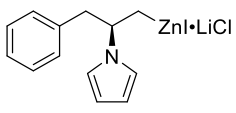
According to **TP11**, LiCl (255 mg, 6.00 mmol, 1.00 equiv) and zinc powder (588 mg, 9.00 mmol, 1.50 equiv) were dried. Dry THF (9.0 mL) was added and the zinc powder was activated using DBE and TMSCl. **(*R*)-19b** (1.41 g, 6.00 mmol, 1.00 equiv) was added dropwise and the reaction mixture was stirred for 20 min. After syringe-filtration **(*R*)-20b** was obtained as a 503 mM yellow solution in THF (9.10 mL, 4.58 mmol, 76% yield).

(*R*)-(3-Methyl-2-(1*H*-pyrrol-1-yl)butyl)zinc(II) iodide ((*R*)-20c)



According to **TP11,** LiCl (170 mg, 4.00 mmol, 1.00 equiv) and zinc powder (392 mg, 6.00 mmol, 1.50 equiv) were dried. Freshly distilled THF (6.0 mL) was added and the zinc powder was activated using DBE and TMSCl. **(*R*)-19c** (1.05 g,4.00 mmol, 1.00 equiv) was added dropwise and the reaction mixture was stirred for 10 min. After syringe-filtration, **(*R*)-20c** was obtained as a 0.52 M yellow solution in THF (6.10 mL, 3.18 mmol, 80% yield).

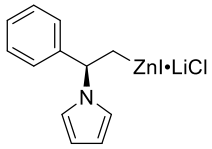
(*S*)-(3-Phenyl-2-(1*H*-pyrrol-1-yl)propyl)zinc(II) iodide ((*S*)-20d)



Following **TP11**, LiCl (340 mg, 8.02 mmol, 1.00 equiv) and zinc dust (785 mg, 12.0 mmol, 1.50 equiv) were dried, suspended in dry THF (12 mL) and activated with DBE and TMSCl. **(*S*)-19d** (2.49 g,

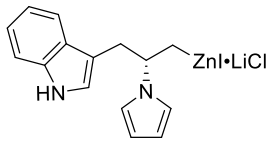
8.00 mmol, 1.00 equiv) was added dropwise. After 10 min, the suspension was filtered with a syringe filter and a 0.50 M yellow solution of **(*S*)-20d** in THF (13.0 mL, 6.52 mmol, 82% yield) was obtained.

(*S*)-(2-Phenyl-2-(1*H*-pyrrol-1-yl)ethyl)zinc(II) iodide ((*S*)-20e)



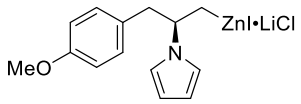
Following **TP11**, LiCl (255 mg, 6.00 mmol, 1.00 equiv) and zinc dust (589 mg, 9.00 mmol, 1.50 equiv) were dried, suspended in dry THF (9 mL) and activated with DBE and TMSCl. **(*S*)-19e** (1.78 g, 6.00 mmol, 1.00 equiv) was added dropwise. After 90 min, the suspension was filtered with a syringe filter and a 0.45 M yellow solution of **(*S*)-20e** in THF (9.50 mL, 4.28 mmol, 71% yield) was obtained.

(*R*)-(3-(1*H*-Indol-3-yl)-2-(1*H*-pyrrol-1-yl)propyl)zinc(II) iodide ((*R*)-20f)



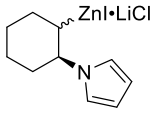
Following **TP11**, LiCl (314 mg, 7.40 mmol, 1.00 equiv) and zinc dust (726 mg, 11.1 mmol, 1.50 equiv) were dried, suspended in dry THF (15 mL) and activated with DBE and TMSCl. **(*R*)-19f** (2.60 g, 7.40 mmol, 1.00 equiv) was added dropwise. After 30 min, the suspension was filtered with a syringe filter and a 0.42 M solution of **(*R*)-20f** in THF (16.0 mL, 6.78 mmol, 91% yield) was obtained.

(*S*)-(3-(4-Methoxyphenyl)-2-(1*H*-pyrrol-1-yl)propyl)zinc(II) iodide ((*S*)-20g)



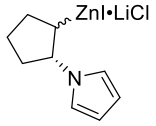
Following **TP11**, LiCl (254 mg, 6.00 mmol, 1.00 equiv) and zinc dust (588 mg, 9.00 mmol, 1.50 equiv) were dried, suspended in dry THF (12 mL) and activated with DBE and TMSCl. **(*S*)-19g** (2.44 g, 6.00 mmol, 1.00 equiv) was added dropwise. After 15 min, the suspension was filtered with a syringe filter and a 0.47 M solution of **(*S*)-20g** in THF (12.0 mL, 5.64 mmol, 95% yield) was obtained.

(*S*)-(2-(1*H*-Pyrrol-1-yl)cyclohexyl)zinc(II) iodide ((*S*)-20h)



According to **TP11,** LiCl (140 mg, 3.30 mmol, 1.00 equiv) and zinc powder (324 mg, 4.95 mmol, 1.50 equiv) were dried. Freshly distilled THF (6.6 mL) was added and the zinc powder was activated using DBE and TMSCl. **(*S*,*R*)-19h** (908 mg, 3.30 mmol, 1.00 equiv) was added dropwise and the reaction mixture was stirred for 10 min. After syringe-filtration, **(*S*)-20h** was obtained as a 0.39 M yellow solution (6.6 mL, 2.60 mmol, 79% yield).

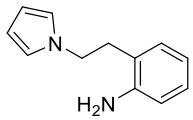
(*R*)-(2-(1H-Pyrrol-1-yl)cyclopentyl)zinc(II) iodide (*R*-20i)



According to **TP11,** LiCl (212 mg, 5.00 mmol, 1.00 equiv) and zinc powder (490 mg, 7.50 mmol, 1.50 equiv) were dried. Freshly distilled THF (10 mL) was added and the zinc powder was activated using DBE and TMSCl. **(*R*,*S*)-19i** (1.31 g, 5.00 mmol, 1.00 equiv) was added dropwise and the reaction mixture was stirred for 10 min. After syringe-filtration, **(*R*)-20i** was obtained as a 0.48 M clear solution (10.0 mL, 4.78 mmol, 96% yield).

3.6 Transition-Metal-Catalyzed Reactions using β-*N*-Pyrrolyl-Alkylzinc Reagents

2-(2-(1*H*-Pyrrol-1-yl)ethyl)aniline (21a)



According to **TP12** a freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 2-bromoaniline (86.0 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The crude product was purified by flash column chromatography to afford **21a** (91 mg, 0.49 mmol, 98% yield) as a brownish liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.12 (t, *J* = 8.0 Hz, 1H), 6.65 (t, *J* = 2.0 Hz, 2H), 6.62 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.09 (d, *J* = 7.6 Hz, 2H), 6.47 (t, *J* = 2.0 Hz,1H), 6.16 (t, *J* = 2.0 Hz,1H), 4.11 (t, *J* = 7.6 Hz, 2H), 3.55 (br, 2H), 2.99 (t, *J* = 7.6 Hz, 2H).

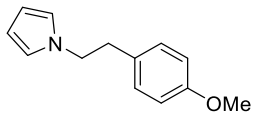
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 145.9, 139.7, 129.5, 120.5, 119.2, 115.7, 113.7, 107.9, 51.0, 38.3.

MS (EI, 70 eV, %): *m/z* = 186 (100), 185 (26), 184 (13), 119 (49), 106 (9), 80 (61).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{12}H_{14}N_2$]: 186.1157; found: 186.1145 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3436 (w), 3356 (w), 2925 (w), 2870 (w), 1618 (s), 1604 (s), 1589 (m), 1495 (s), 1459 (m), 1279 (s), 1168 (m), 1088 (s), 1066 (m), 865 (w), 780 (m), 722 (vs), 691 (s).

1-(4-Methoxyphenethyl)-1*H*-pyrrole (21b)



According to **TP12**, a freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 4-iodoanisole (117 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL). The resulting reaction mixture was stirred for 16 h and quenched with sat. aq. NH_4Cl solution. Extraction with EtOAc and purification by flash column chromatography afforded **21b** (96.0 mg, 0.48 mmol, 95% yield) as a colorless solid.

In a large-scale attempt, the same procedure was carried out using 1.17 g (5.00 mmol, 1.00 equiv) of ethyl 4-iodoanisole and a freshly prepared solution of **20a** (10.3 mL, 0.58 M, 6.00 mmol, 1.20 equiv) with catalytic amounts of $Pd(OAc)_2$ (23.0 mg, 0.10 mmol, 2 mol%) and SPhos (82.0 mg, 0.20 mmol, 4 mol%), yielding 908 mg (4.51 mmol, 90% yield) of **21b**.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.05 – 6.98 (m, 2H), 6.87 – 6.81 (m, 2H), 6.61 (t, *J* = 2.1 Hz, 2H), 6.14 (t, *J* = 1.9, 2H), 4.08 (dd, *J* = 8.0, 6.8 Hz, 2H), 3.81 (s, 3H), 3.01 (t, *J* = 7.4 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.4, 130.6, 129.8, 120.6, 114.0, 108.0, 55.4, 51.5, 37.6.

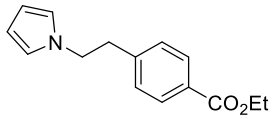
MS (EI, 70 eV, %): *m/z* = 201 (13), 134 (33), 122 (10), 121 (100), 91 (12), 80 (23).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{13}H_{15}NO$]: 201.1154; found: 201.1143 ([M$^+$]).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2929 (w), 2360 (w), 1704 (w), 1613 (m), 1513 (vs), 1500 (m), 1458 (w), 1282 (m), 1247 (s), 1179 (m), 1089 (w), 1035 (m), 824 (w), 724 (s).

M.p. 40.6 °C.

Ethyl 4-(2-(1*H*-pyrrol-1-yl)ethyl)benzoate (21c)



Following **TP12**, ethyl 4-iodobenzoate (138 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) were dissolved in dry THF (1 mL). A freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) was added dropwise and the reaction mixture was stirred for 16 h. After quenching and extraction, the crude product was purified by flash column chromatography to afford **21c** (118 mg, 0.49 mmol, 97% yield) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.99 – 7.92 (m, 2H), 7.16 – 7.11 (m, 2H), 6.57 (t, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

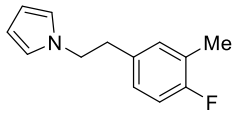
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.6, 143.8, 129.9, 129.0, 128.8, 120.6, 108.3, 61.0, 50.8, 38.5, 14.5.

MS (EI, 70 eV, %): *m/z* = 243 (46), 198 (10), 131 (13), 80 (100).

HRMS (EI, 70 eV): *m/z* calcd. for $[C_{15}H_{17}NO_2]$: 243.1259; found: 243.1245 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2981 (w), 2930 (w), 1713 (s), 1612 (w), 1500 (w), 1416 (w), 1366 (w), 1310 (w), 1276 (vs), 1180 (w), 1105 (m), 1070 (w), 1022 (w), 852 (vw), 767 (w), 726 (m), 706 (w).

1-(4-Fluoro-3-methylphenethyl)-1H-pyrrole (21d)



According to **TP12**, a freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 2-fluoro-5-iodotoulene (118 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL). The reaction mixture was stirred for 16 h and afterwards quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The crude product was purified by flash column chromatography to afford **21d** (84.0 mg, 0.41 mmol, 83% yield) as a colorless liquid.

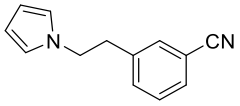
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.98 – 6.87 (m, 3H), 6.64 (t, *J* = 1.6 Hz, 2H), 6.19 (t, *J* = 1.6 Hz, 2H), 4.12 (t, *J* = 7.2 Hz, 2H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.30 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.2 (d, *J* = 244.4 Hz), 133.7 (d, *J* = 4.0 Hz), 131.6 (d, *J* = 5.1 Hz), 127.2 (d, *J* = 7.1 Hz), 124.7 (d, *J* = 17.2 Hz), 120.4, 114.9 (d, *J* = 23.2 Hz), 108.0, 51.2 (d, *J* = 1.0 Hz), 37.5, 14.4 (d, *J* = 4.0 Hz).

^{19}F-NMR (377 MHz, $CDCl_3$, ppm): δ = –120.8.

MS (EI, 70 eV, %): *m/z* = 203 (10), 136 (16), 123 (23), 80 (100), 78 (14).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{13}H_{14}FN$]: 203.1110; found: 203.1097 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2926 (w), 2871 (vw), 1498 (s), 1440 (w), 1359 (w), 1283 (m), 1248 (m), 1210 (m), 1119 (m), 1088 (m), 1069 (w), 969 (w), 817 (m), 758 (w), 718 (vs).

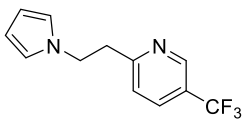
3-(2-(1*H*-Pyrrol-1-yl)ethyl)benzonitrile (21e)



According to **TP12**, 3-iodobenzonitrile (115 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) were dissolved in dry THF (1 mL). A freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) was added dropwise and the reaction mixture stirred for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The crude product was purified by flash column chromatography to afford **21e** as a brownish liquid (83 mg, 0.43 mmol, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.54 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 1.6 Hz, 1H), 7.54 (dt, *J* = 7.6, 1.6 Hz, 1H), 6.55 (t, *J* = 2.0 Hz, 2H), 6.14 (t, *J* = 2.0 Hz, 2H), 4.13 (t, *J* = 7.0 Hz, 2H), 3.09 (t, *J* = 7.0 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 139.8, 133.2, 132.2, 130.4, 129.3, 120.4, 118.7, 112.5, 108.4, 50.5, 37.7.
MS (EI, 70 eV, %): *m/z* = 196 (9), 116 (15), 89 (16), 80 (100), 78 (15).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{13}H_{12}N_2$]: 196.1000; found: 196.0990 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2923 (m), 2853 (w), 2228 (w), 1498 (m), 1460 (w), 1441 (w), 1361 (w), 1281 (m), 1088 (m), 1068 (m), 1023 (w), 969 (w), 916 (w), 796 (m), 722 (vs), 687 (s).

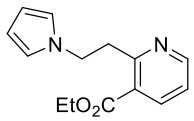
2-(2-(1*H*-Pyrrol-1-yl)ethyl)-5-(trifluoromethyl)pyridine (21f)



According to **TP12**, a freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 2-chloro-5-trifluoromethylpyridine (91.0 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL). The reaction mixture was stirred for 16 h and afterwards quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The crude product was purified by flash column chromatography to afford **21f** (99.0 mg, 0.41 mmol, 82% yield) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.87 (s, 1H), 7.80 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.59 (t, *J* = 2.0 Hz, 2H), 6.12 (t, *J* = 2.0 Hz, 2H), 4.37 (t, *J* = 7.0 Hz, 2H), 3.32 (t, *J* = 7.0 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 162.3 (q, *J* = 1.0 Hz), 146.3 (q, *J* = 4.0 Hz), 133.6 (q, *J* = 4.0 Hz), 124.8 (q, *J* = 33.0 Hz), 123.5 (q, *J* = 273.7 Hz), 123.3, 120.4, 108.3, 48.6, 40.3.
^{19}F-NMR (377 MHz, $CDCl_3$, ppm): δ = –62.3
MS (EI, 70 eV, %): *m/z* = 240 (6), 174 (35), 161 (22), 147 (13), 80 (100), 78 (16), 67 (8).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{12}H_{11}F_3N_2$]: 240.0874; found: 240.0862 ([$M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2931 (w), 1605 (m), 1573 (m), 1498 (w), 1395 (w), 1326 (s), 1282 (m), 1167 (m), 1119 (vs), 1079 (s), 1067 (s), 1031 (w), 1015 (m), 968 (w), 944 (w), 863 (m), 843 (m), 722 (vs).
M.p. 38.5 °C.

Ethyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)nicotinate (21g)



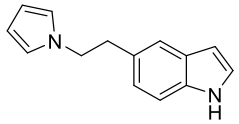
According to **TP12**, a freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 2-chloronicotinate (93.0 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL). The reaction mixture was stirred for 16 h and afterwards quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The crude product was purified by flash column chromatography to afford **21g** (116 mg, 0.48 mmol, 95% yield) as a yellowish solid.

In a large-scale attempt, the same procedure was carried out using 427 mg (2.30 mmol, 1.00 equiv) of ethyl 2-chloronicotinate and a freshly prepared solution of **20a** (4.76 mL, 0.58 M, 2.76 mmol, 1.20 equiv) with catalytic amounts of $Pd(OAc)_2$ (11.0 mg, 46.0 µmol, 2 mol%) and SPhos (38.0 mg, 92.0 µmol, 4 mol%), affording 512 mg (2.10 mmol, 90% yield) of **21g**.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.68 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.21 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.26 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.70 (t, *J* = 2.1 Hz, 2H), 6.11 (t, *J* = 2.1 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.35 – 4.29 (m, 2H), 3.69 – 3.63 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.2, 159.4, 151.9, 138.8, 126.3, 121.6, 120.7, 108.0, 61.7, 49.1, 39.2, 14.4.
MS (EI, 70 eV, %): *m/z* = 245 (15), 244 (100), 215 (61), 199 (21), 197 (27), 178 (77), 171 (57), 170 (10, 169 (26), 165 (11), 150 (46), 148 (11), 132 (16), 104 (10), 93 (20), 80 (49), 78 (10).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{14}H_{16}N_2O_2$]: 244.1212; found: 244.1204 ([M^+]).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3092 (w), 2988 (w), 1715 (vs), 1572 (m), 1501 (w), 1444 (m), 1361 (w), 1282 (m), 1262 (s), 1245 (s), 1235 (s), 1137 (s), 1085 (vs), 1057 (s), 1020 (m), 967 (m), 866 (w), 829 (w), 780 (m), 734 (vs), 707 (s).
M.p. 57.1 °C.

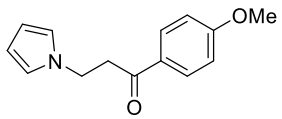
5-(2-(1*H*-Pyrrol-1-yl)ethyl)-1*H*-indole (21h)



According to **TP12**, a freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 5-bromoindole (98.0 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL). The reaction mixture was stirred for 16 h and afterwards quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The crude product was purified by flash column chromatography to afford **21h** (95 mg, 0.45 mmol, 90% yield) as a brownish solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.00 (s, 1H), 7.49 (s, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.19 (t, *J* = 2.8 Hz, 1H), 7.02 (dq, *J* = 8.3, 1.7 Hz, 1H), 6.80 – 6.70 (m, 2H), 6.58 (q, *J* = 2.7 Hz, 1H), 6.33 – 6.13 (m, 2H), 4.25 – 4.17 (m, 1H), 3.45 – 2.87 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 134.7, 129.8, 128.2, 124.7, 123.0, 120.7, 120.4, 111.1, 107.9, 102.3, 52.0, 38.6.
MS (EI, 70 eV, %): *m/z* = 210 (5), 143 (14), 131 (10), 130 (100), 128 (9), 115 (8), 103 (8), 80 (16).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{14}H_{14}N_2]$: 210.1157; found: 210.1146 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3423 (w), 3096 (vw), 2924 (w), 1498 (w), 1472 (w), 1457 (w), 1412 (w), 1336 (w), 1279 (m), 1085 (m), 1063 (m), 965 (w), 892 (w), 819 (w), 800 (m), 762 (m), 720 (vs), 698 (m).
M.p. 88.6 °C.

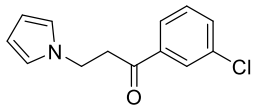
1-(4-Methoxyphenyl)-3-(1*H*-pyrrol-1-yl)propan-1-one (21i)



According to **TP13a**, 4-methoxybenzoyl chloride (85.3 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) with catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The reaction mixture was stirred at 50 °C for 16 h and afterwards quenched with sat. aq. NH_4Cl solution. The crude product was extracted with EtOAc and purified by flash column chromatography. **21i** (113 mg, 0.44 mmol, 87% yield) was obtained as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.92 (d, *J* = 9.2 Hz, 2H), 6.95 (d, *J* = 9.2 Hz, 2H), 6.73 (t, *J* = 2.2 Hz, 2H), 6.16 (t, *J* = 2.2 Hz, 2H), 4.38 (t, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 3.41 (t, *J* = 7.2 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 195.9, 163.7, 130.3, 129.6, 120.7, 113.8, 108.3, 55.5, 44.4, 40.2.
MS (EI, 70 eV, %): *m/z* = 229 (24), 212 (15), 211 (100), 210 (25), 196 (72), 180 (21), 168 (26), 167 (49), 135 (71), 94 (84), 77 (18).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{14}H_{15}NO_2$]: 229.1103; found: 229.1098 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2933 (w), 2839 (vw), 1671 (s), 1598 (vs), 1574 (m), 1509 (m), 1419 (m), 1371 (m), 1313 (m), 1255 (s), 1213 (s), 1167 (vs), 1089 (m), 1025 (s), 982 (m), 834 (s), 722 (vs).

1-(3-Chlorophenyl)-3-(1*H*-pyrrol-1-yl)propan-1-one (21j)

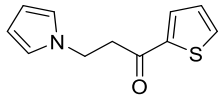


According to **TP13a**, 3-chlorobenzoyl chloride (87.5 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) with catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The mixture was stirred at 50 °C for 16 h and afterwards quenched with sat. aq. NH_4Cl solution. The crude product was extracted with EtOAc and purified by flash column chromatography. **21j** (96 mg, 0.41 mmol, 82% yield) was obtained as an orange oil.

In a large-scale attempt according to a modified version of **TP13b**, the reaction was carried out using 1.75 g (10.0 mmol, 1.00 equiv) of 3-chlorobenzoyl chloride and a freshly prepared solution of **20a** (19.0 mL, 0.58 M, 11.0 mmol, 1.10 equiv) with catalytic amounts of CuI (190 mg, 1.00 mmol, 10 mol%) at 0 °C up to 25 °C. After quenching, extraction and flash column chromatography purification, 1.76 g (7.53 mmol, 75% yield) of **21j** was obtained.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.91 (t, *J* = 2.0 Hz, 1H), 7.80 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.57 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 6.73 (t, *J* = 2.0 Hz, 2H), 6.17 (t, *J* = 2.0 Hz, 2H), 4.39 (t, *J* = 6.8 Hz, 2H), 3.43 (t, *J* = 6.8 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 196.4, 138.0, 135.2, 133.5, 130.2, 128.3, 126.2, 120.8, 108.7, 44.2, 40.8.
MS (EI, 70 eV, %): *m/z* = 233 (11), 180 (3), 139 (16), 111 (27), 94 (100), 80 (32), 67 (12), 53 (11).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{13}H_{12}ClNO$]: 233.0607; found: 233.0602 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3098 (vw), 3065 (vw), 2919 (w), 2850 (vw), 1684 (s), 1570 (m), 1498 (m), 1423 (m), 1370 (m), 1282 (m), 1203 (s), 1088 (m), 1071 (m), 997 (w), 896 (w), 776 (m), 722 (vs), 695 (m), 677 (s).

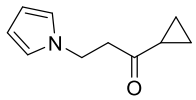
3-(1*H*-Pyrrol-1-yl)-1-(thiophen-2-yl)propan-1-one (21k)



According to **TP13a**, 2-thiophenecarbonyl chloride (73.3 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) with catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The mixture was stirred at 50 °C for 16 h and afterwards quenched with sat. aq. NH_4Cl solution. The crude product was extracted with EtOAc and purified by flash column chromatography. **21k** (75 mg, 0.37 mmol, 73% yield) was obtained as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.66 (s, 1H), 7.65 (q, *J* = 1.1 Hz, 1H), 7.14 – 7.09 (m, 1H), 6.70 (t, *J* = 2.1 Hz, 2H), 6.14 (t, *J* = 2.1 Hz, 2H), 4.36 (t, *J* = 6.9 Hz, 2H), 3.37 (t, *J* = 6.9 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 190.4, 143.8, 134.3, 132.3, 128.4, 120.8, 108.6, 44.4, 41.4.
MS (EI, 70 eV, %): *m/z* = 205 (37), 186 (56), 154 (16), 111 (55), 94 (100), 80 (16).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{11}H_{11}NOS]$: 205.0561; found: 205.0556 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3104 (vw), 3075 (w), 2954 (w), 2905 (w), 1661 (s), 1498 (m), 1438 (w), 1414 (s), 1395 (m), 1364 (m), 1278 (m), 1238 (s), 1219 (m), 1088 (m), 1059 (m), 1040 (m), 961 (w), 928 (m), 894 (m), 841 (m), 825 (m), 732 (s), 709 (vs).
M.p. 60.1 °C.

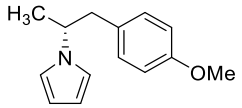
1-Cyclopropyl-3-(1*H*-pyrrol-1-yl)propan-1-one (21l)



According to **TP13a**, cyclopropanecarbonyl chloride (52.3 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **20a** (1.03 mL, 0.58 M, 0.60 mmol, 1.20 equiv) with catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The mixture was stirred at 50 °C for 16 h and afterwards quenched with sat. aq. NH_4Cl solution. The crude product was extracted with EtOAc and purified by flash column chromatography. **21l** (69 mg, 0.42 mmol, 83% yield) was obtained as an orange liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.65 (t, *J* = 2.1 Hz, 2H), 6.13 (t, *J* = 2.1 Hz, 2H), 4.20 (t, *J* = 6.8 Hz, 2H), 3.02 (t, *J* = 6.8 Hz, 2H), 1.87 (tt, *J* = 7.8 Hz, 4.6, 1H), 1.09 – 1.00 (m, 2H), 0.89 (dt, *J* = 7.9, 3.4 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 208.3, 120.7, 108.4, 45.0, 44.1, 21.1, 11.2.
MS (EI, 70 eV, %): *m/z* = 163 (39), 145 (15), 130 (12), 117 (10), 106 (28), 94 (100), 93 (13), 80 (34).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{10}H_{13}NO]$: 163.0997; found: 163.0991 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3098 (vw), 3008 (vw), 2932 (vw), 1694 (s), 1552 (vw), 1499 (m), 1444 (w), 1389 (m), 1282 (m), 1194 (w), 1085 (s), 1067 (m), 1014 (m), 903 (w), 875 (w), 818 (w), 721 (vs).

(*R*)-1-(1-(4-Methoxyphenyl)propan-2-yl)-1*H*-pyrrole ((*R*)-22a)



Following **TP12**, a freshly prepared solution of **(*R*)-20b** (1.52 mL, 394 mM, 0.60 mol, 1.20 equiv) was added dropwise to a solution of 4-iodoanisole (117 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL). The reaction mixture was stirred for 16 h and afterwards quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The crude product was purified by flash column chromatography to obtain **(*R*)-22a** (89.0 mg, 0.41 mmol, 83% yield, >95% *ee*) as a brown liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.91 – 6.88 (m, 2H), 6.82 – 6.78 (m, 2H), 6.66 (t, *J* = 2.0 Hz, 2H), 6.14 (t, *J* = 2.0 Hz, 2H), 4.22 (sextet, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 3.01 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.89 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.48 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.2, 130.3, 130.0, 118.5, 113.7, 107.5, 57.1, 55.2, 44.2, 21.2.

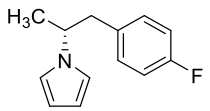
MS (EI, 70 eV, %): *m/z* = 215 (17), 148 (11), 121 (19), 94 (100), 78 (9).

HRMS (EI, 70 eV): *m/z* calcd. for $[C_{14}H_{17}NO]$: 215.1310; found: 215.1306 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2971 (w), 2933 (w), 2834 (w), 1611 (m), 1511 (s), 1489 (m), 1454 (w), 1301 (m), 1269 (m), 1244 (vs), 1178 (m), 1090 (m), 1034 (m), 955 (w), 815 (m), 721 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): -94.6.

(*R*)-1-(1-(4-Fluorophenyl)propan-2-yl)-1*H*-pyrrole ((*R*)-22b)



Following **TP12**, a freshly prepared solution of **(*R*)-20b** (1.52 mL, 394 mM, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 4-fluoroiodobenzene (111 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL). The reaction mixture was stirred for 16 h and afterwards quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The crude product was purified by flash column chromatography to obtain **(*R*)-22b** (87.0 mg, 0.43 mmol, 86% yield, 98.5% *ee*) as a brown liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.96 – 6.88 (m, 4H), 6.63 (t, *J* = 2.0 Hz, 2H), 6.13 (t, *J* = 2.0 Hz, 2H), 4.22 (sextet, *J* = 6.8 Hz, 1H), 3.01 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.93 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.51 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.7 (d, *J* = 245.4 Hz), 133.8 (d, *J* = 3.0 Hz), 130.4 (d, *J* = 8.1 Hz), 118.5, 115.1 (d, *J* = 21.2 Hz), 107.7, 56.9, 44.2, 21.2.

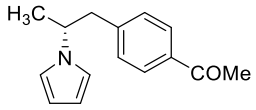
MS (EI, 70 eV, %): *m/z* = 203 (13), 109 (10), 94 (100), 78 (11).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{13}H_{14}FN$]: 203.1110; found: 203.1104 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2975 (w), 2933 (w), 1603 (w), 1509 (vs), 1489 (m), 1452 (w), 1414 (w), 1378 (w), 1320 (w), 1269 (m), 1221 (s), 1158 (w), 1092 (m), 955 (w), 821 (m), 722 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –96.5.

(*R*)-1-(4-(2-(1*H*-Pyrrol-1-yl)propyl)phenyl)ethan-1-one ((*R*)-22c)



Following **TP12**, a freshly prepared solution of **(*R*)-20b** (1.52 mL, 394 mM, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 4-iodoacetophenone (123 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL). The reaction mixture was stirred for 16 h and afterwards quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The crude product was purified by flash column chromatography to obtain **(*R*)-22c** (103 mg, 0.45 mmol, 91% yield, 99.0% *ee*) as a brown liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.84 (d, *J* = 5.2 Hz, 2H), 7.04 (d, *J* = 5.2 Hz, 2H), 6.62 (t, *J* = 1.2 Hz, 2H), 6.13 (t, *J* = 1.2 Hz, 2H), 4.29 (sextet, *J* = 4.4 Hz, 1H), 3.10 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.02 (dd, *J* = 9.2, 4.4 Hz, 1H), 2.59 (s, 3H), 1.53 (d, *J* = 4.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 197.8, 143.8, 135.6, 129.2, 128.4, 118.5, 107.8, 56.6, 45.0, 26.5, 21.5.

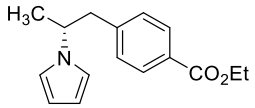
MS (EI, 70 eV, %): *m/z* = 227 (5), 94 (100), 78 (8).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{15}H_{17}NO$]: 227.1310; found: 227.1306 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2974 (w), 2932 (w), 1679 (vs), 1606 (m), 1489 (m), 1413 (m), 1358 (m), 1267 (vs), 1183 (w), 1091 (w), 1018 (w), 956 (m), 847 (w), 814 (w), 724 (s), 695 (w).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –137.2.

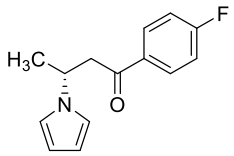
Ethyl (*R*)-4-(2-(1*H*-pyrrol-1-yl)propyl)benzoate ((*R*)-22d)



Following **TP12**, a freshly prepared solution of **(*R*)-20b** (1.38 mL, 0.44 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of ethyl 4-iodobenzoate (138 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL). The reaction mixture was stirred for 16 h and afterwards quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. Flash column chromatography purification of the crude product afforded **(*R*)-22d** (128 mg, 0.49 mmol, 99% yield, 99.0% *ee*) as an orange liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.97 – 7.86 (m, 2H), 7.07 – 6.95 (m, 2H), 6.61 (t, *J* = 2.2, 2H), 6.11 (t, *J* = 2.1, 2H), 4.36 (q, *J* = 7.1, 2H), 4.26 (h, *J* = 6.8, 1H), 3.08 (dd, *J* = 13.4, 7.7, 1H), 3.00 (dd, *J* = 13.5, 6.2, 1H), 1.50 (d, *J* = 6.8, 3H), 1.39 (t, *J* = 7.1, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.6, 143.5, 129.7, 129.1, 128.9, 118.6, 107.9, 61.0, 56.7, 45.2, 21.5, 14.4.
MS (EI, 70 eV, %): *m/z* = 257 (6), 94 (100), 78 (7).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{16}H_{19}NO_2]$: 257.1416; found: 257.1412 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2977 (w), 2934 (w), 1711 (s), 1611 (w), 1489 (w), 1415 (w), 1367 (w), 1310 (w), 1271 (vs), 1178 (m), 1102 (s), 1021 (m), 954 (w), 761 (m), 719 (s), 706 (s).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): −104.9.

(*R*)-1-(4-Fluorophenyl)-3-(1*H*-pyrrol-1-yl)butan-1-one ((*R*)-22e)



According to **TP13b**, catalytic amounts of CuI (9.52 mg, 0.05 mmol, 10 mol%) were added at 0 °C to a freshly prepared solution of **(*R*)-20b** (1.38 mL, 0.44 M, 0.60 mmol, 1.20 equiv). After dropwise addition of 4-fluorobenzoyl chloride (79 mg, 0.50 mmol, 1.00 equiv) the reaction mixture was stirred for 1 h at 0 °C, warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. Flash column chromatography purification of the crude product afforded **(*R*)-22e** (84 mg, 0.36 mmol, 73% yield, 99.7% *ee*) as a yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.96 – 7.90 (m, 2H), 7.16 – 7.10 (m, 2H), 6.78 (t, *J* = 2.0 Hz, 2H), 6.16 (t, *J* = 2.0 Hz, 2H), 4.85 (sextet, *J* = 6.8 Hz, 1H), 3.46 (dd, *J* = 16.8, 6.0 Hz, 1H), 3,28 (dd, *J* = 16.8, 7.2 Hz, 1H), 1.60 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 195.7, 165.9 (d, *J* = 256.5 Hz), 133.1 (d, *J* = 3.0 Hz), 130.6 (d, *J* = 9.1 Hz), 118.5, 115.8 (d, *J* = 22.2 Hz), 108.1, 51.2, 47.0, 21.9.

^{19}F-NMR (376 MHz, $CDCl_3$, ppm): δ = -104.6.

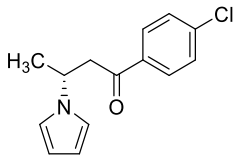
MS (EI, 70 eV, %): *m/z* = 231 (12), 211 (20), 198 (16), 123 (100), 108 (77), 94 (32), 75 (12).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{14}H_{14}FNO$]: 231.1059; found: 231.1053 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): $\nu =$ 3101 (vw), 3066 (vw), 2977 (w), 2935 (vw), 1684 (vs), 1597 (vs), 1506 (m), 1411 (m), 1361 (m), 1322 (w), 1275 (m), 1228 (s), 1203 (m), 1157 (s), 1089 (m), 996 (w), 955 (w), 835 (s), 726 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): −22.3.

(*R*)-1-(4-Chlorophenyl)-3-(1*H*-pyrrol-1-yl)butan-1-one ((*R*)-22f)



According to **TP13b**, catalytic amounts of CuI (9.52 mg, 0.05 mmol, 10 mol%) were added at 0 °C to a freshly prepared solution of **(*R*)-20b** (1.38 mL, 0.44 M, 0.60 mmol, 1.20 equiv). After dropwise addition of 4-chlorobenzoyl chloride (88 mg, 0.50 mmol, 1.00 equiv) the mixture was stirred for 1 h at 0 °C, warmed to room temperature and then stirred for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. Flash column chromatography purification of the crude product afforded **(*R*)-22f** (83 mg, 0.34 mmol, 67% yield, 99.5% *ee*) as a yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.85 – 7.82 (m, 2H), 7.45 – 7.42 (m, 2H), 6.77 (t, *J* = 2.0 Hz, 2H), 6.16 (t, *J* = 2.0 Hz, 2H), 4.85 (sextet, *J* = 6.8 Hz, 1H), 3.46 (dd, *J* = 16.8, 5.6 Hz, 1H), 3,28 (dd, *J* = 16.8, 7.2 Hz, 1H), 1.60 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 196.1, 139.9, 135.0, 129.4, 129.0, 118.5, 108.1, 51.1, 47.0, 21.9.

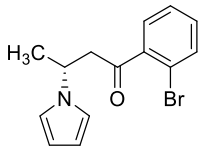
MS (EI, 70 eV, %): *m/z* = 247 (9), 231 (19), 229 (62), 227 (100), 214 (63), 191 (64), 139 (59), 108 (55), 94 (22).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{14}H_{14}ClNO$]: 247.0764; found: 247.0759 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): $\nu =$ 2976 (w), 2934 (vw), 1685 (vs), 1588 (s), 1489 (m), 1400 (m), 1361 (m), 1321 (w), 1289 (m), 1274 (m), 1212 (m), 1203 (m), 1090 (vs), 995 (m), 955 (w), 819 (m), 725 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): −9.5.

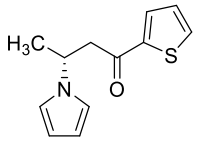
(*R*)-1-(2-Bromophenyl)-3-(1*H*-pyrrol-1-yl)butan-1-one ((*R*)-22g)



According to **TP13b**, catalytic amounts of CuI (9.52 mg, 0.05 mmol, 10 mol%) were added at 0 °C to a freshly prepared solution of **(*R*)-20b** (1.38 mL, 0.44 M, 0.60 mmol, 1.20 equiv). After dropwise addition of 2-bromobenzoyl chloride (110 mg, 0.50 mmol, 1.00 equiv) the reaction mixture was stirred for 1 h at 0 °C, warmed to room temperature and then stirred for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. Flash column chromatography purification of the crude product afforded **(*R*)-22g** (115 mg, 0.39 mmol, 79% yield, 99.6% *ee*) as a yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.57 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.11 (dd, *J* = 7.2, 2.0 Hz, 1H), 6.70 (t, *J* = 2.0 Hz, 2H), 6.11 (t, *J* = 2.0 Hz, 2H), 4.78 (sextet, *J* = 6.8 Hz, 1H), 3.41 (dd, *J* = 17.2, 6.8 Hz, 1H), 3,27 (dd, *J* = 17.2, 6.8 Hz, 1H), 1.56 (d, *J* = 6.8 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 201.4, 141.3, 133.6, 131.8, 128.4, 127.5, 118.6, 118.4, 108.1, 51.3, 51.0, 21.9.
MS (EI, 70 eV, %): *m/z* = 291 (1), 212 (66), 191 (100), 182 (92), 170 (27), 165 (59), 145 (33), 108 (42), 94 (36).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{14}H_{14}BrNO$]: 291.0259; found: 291.0258 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3097 (vw), 3064 (vw), 2975 (w), 2934 (vw), 1696 (m), 1586 (w), 1489 (m), 1427 (m), 1357 (w), 1315 (w), 1290 (m), 1274 (m), 1200 (w), 1088 (m), 1056 (m), 1025 (m), 994 (m), 954 (m), 756 (m), 719 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): −21.5.

(*R*)-3-(1*H*-Pyrrol-1-yl)-1-(thiophen-2-yl)butan-1-one ((*R*)-22h)



According to **TP13b**, catalytic amounts of CuI (9.52 mg, 0.05 mmol, 10 mol%) were added at 0 °C to a freshly prepared solution of **(*R*)-20b** (1.38 mL, 0.44 M, 0.60 mmol, 1.20 equiv). After dropwise addition of 2-thiophenecarbonyl chloride (73.0 mg, 0.5 mmol, 1.00 equiv), the mixture was stirred for 1 h at 0 °C, warmed to room temperature and then stirred for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. Flash column chromatography purification of the crude product afforded **(*R*)-22h** (65 mg, 0.30 mmol, 59% yield, 99.5% *ee*) as a yellowish solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.66 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.65 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.12 (dd, *J* = 4.8, 3.8 Hz, 1H), 6.78 (t, *J* = 2.0 Hz, 2H), 6.15 (t, *J* = 2.0 Hz, 2H), 4.83 (sextet, *J* = 6.8 Hz, 1H), 3.41 (dd, *J* = 16.0, 6.0 Hz, 1H), 3,25 (dd, *J* = 16.0, 7.2 Hz, 1H), 1.60 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 190.2, 144.2, 134.3, 132.3, 128.3, 118.7, 108.2, 51.5, 48.0, 21.9.

MS (EI, 70 eV, %): *m/z* = 219 (26), 210 (100), 199 (89), 186 (92), 111 (86), 108 (78), 94 (29).

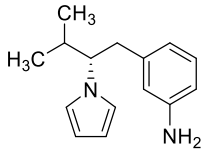
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{12}H_{13}NOS$]: 219.0718; found: 219.0712 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3097 (vw), 2976 (w), 2933 (vw), 1656 (s), 1517 (w), 1489 (w), 1414 (s), 1360 (w), 1318 (w), 1274 (m), 1234 (w), 1222 (w), 1089 (m), 1060 (m), 946 (w), 857 (w), 721 (vs).

M.p.: 44.5 °C.

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): −34.0.

(*S*)-3-(3-Methyl-2-(1*H*-pyrrol-1-yl)butyl)aniline ((*S*)-23a)



According to **TP12**, a freshly prepared solution of **(*R*)-20c** (1.15 mL, 0.52 M, 0.60 mol, 1.20 equiv) was added dropwise to a solution of 3-bromoaniline (86.0 mg, 0.50 mol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and the resulting mixture was stirred for 16 h. After aqueous workup, extraction and flash column chromatography purification, **(*S*)-23a** (106 mg, 0.46 mmol, 93% yield, 99.8% *ee*) was obtained as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.99 (t, *J* = 7.7 Hz, 1H), 6.57 (t, *J* = 2.1 Hz, 2H), 6.49 (ddd, *J* = 7.9, 2.4, 1.0 Hz, 1H), 6.38 (dt, *J* = 7.5, 1.3 Hz, 1H), 6.19 (t, *J* = 2.0 Hz, 1H), 6.08 (t, *J* = 2.1 Hz, 2H), 3.66 (ddd, *J* = 9.7, 7.7, 4.5 Hz, 1H), 3.51 (br, 2H), 3.06 (dd, *J* = 13.8, 4.5 Hz, 1H), 2.89 (dd, *J* = 13.8, 9.7 Hz, 1H), 2.03 (dhept, *J* = 13.4, 6.8 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 146.4, 140.3, 129.2, 119.9, 119.2, 115.7, 113.2, 107.2, 68.5, 40.0, 33.6, 20.7, 18.9.

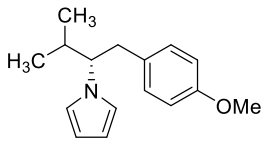
MS (EI, 70 eV, %): *m/z* = 228 (32), 183 (12), 122 (100), 107 (10), 106 (11), 80 (20).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{15}H_{20}N_2$]: 228.1626; found: 228.1620 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3362 (w), 2958 (w), 2925 (w), 2871 (w), 1604 (m), 1590 (m), 1489 (m), 1461 (m), 1411 (w), 1386 (w), 1368 (w), 1290 (m), 1272 (m), 1168 (w), 1086 (m), 1067 (m), 995 (w), 929 (w), 867 (w), 779 (m), 720 (vs), 696 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –101.2.

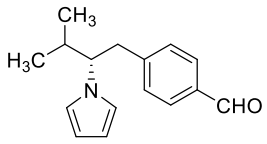
(*S*)-1-(1-(4-Methoxyphenyl)-3-methylbutan-2-yl)-1*H*-pyrrole ((*S*)-23b)



According to **TP12**, a freshly prepared solution of **(*R*)-20c** (1.15 mL, 0.52 M, 0.60 mol, 1.20 equiv) was added dropwise to a solution of 4-iodoanisole (117 mg, 0.50 mol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and the resulting mixture was stirred for 16 h. After aqueous workup, extraction and flash column chromatography purification, **(*S*)-23b** (109 mg, 0.45 mmol, 89% yield, 99.4% *ee*) was obtained as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.84 – 6.79 (m, 2H), 6.76 – 6.70 (m, 2H), 6.55 (t, *J* = 2.1 Hz, 2H), 6.08 (t, *J* = 2.1 Hz, 2H), 3.75 (s, 3H), 3.62 (ddd, *J* = 10.1, 7.9, 4.2 Hz, 1H), 3.11 (dd, *J* = 14.0, 4.2 Hz, 1H), 2.92 (dd, *J* = 14.0, 10.1 Hz, 1H), 2.04 (dhept, *J* = 13.3, 6.8 Hz, 1H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.1, 131.1, 129.7, 119.8, 113.7, 107.3, 68.9, 55.2, 39.1, 33.7, 20.7, 19.1.
MS (EI, 70 eV, %): *m/z* = 243 (10), 122 (100), 121 (18), 80 (20).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{16}H_{21}NO$]: 243.1623; found: 243.1617 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2957 (w), 1612 (w), 1511 (s), 1488 (m), 1465 (m), 1412 (w), 1386 (w), 1368 (w), 1300 (m), 1274 (m), 1243 (s), 1177 (m), 1086 (m), 1068 (w), 1034 (m), 912 (w), 820 (m), 718 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –124.1.

(*S*)-4-(3-Methyl-2-(1*H*-pyrrol-1-yl)butyl)benzaldehyde ((*S*)-23c)



According to **TP12**, a freshly prepared solution of **(*R*)-20c** (1.15 mL, 0.52 M, 0.60 mol, 1.20 equiv) was added dropwise to a solution of 4-bromobenzaldehyd (92.5 mg, 0.50 mol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and the resulting mixture was stirred for 16 h. After aqueous workup, extraction and flash column chromatography purification, **(*S*)-23b** (112 mg, 0.46 mmol, 92% yield, 99.6% *ee*) was obtained as an orange oil.

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 9.92 (s, 1H), 7.78 – 7.61 (m, 2H), 7.11 – 6.98 (m, 2H), 6.50 (t, *J* = 2.1, 2H), 6.05 (t, *J* = 2.2, 2H), 3.65 (ddd, *J* = 10.9, 8.3, 3.8, 1H), 3.24 (dd, *J* = 13.8, 3.7, 1H), 3.02 (dd, *J* = 13.8, 10.8, 1H), 2.13 – 2.03 (m, 1H), 1.11 (s, 2H), 0.80 (d, *J* = 6.7, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 192.1, 146.4, 134.9, 129.9, 129.4, 119.6, 107.7, 68.5, 40.4, 34.2, 20.6, 19.3.z

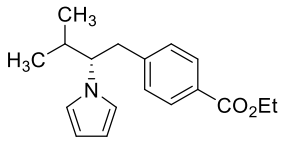
MS (EI, 70 eV, %): *m/z* = 241 (8), 122 (100), 91 (17), 80 (19).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{16}H_{19}NO$]: 241.1467; found: 241.1458 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2961 (w), 2925 (w), 1698 (s), 1605 (s), 1576 (w), 1488 (m), 1469 (w), 1386 (w), 1306 (w), 1274 (m), 1259 (m), 1214 (m), 1168 (m), 1086 (m), 1068 (m), 928 (w), 845 (w), 816 (m), 779 (m), 719 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –180.5.

Ethyl (*S*)-4-(3-methyl-2-(1*H*-pyrrol-1-yl)butyl)benzoate ((*S*)-23d)



According to **TP12**, a freshly prepared solution of **(*R*)-20c** (1.15 mL, 0.52 M, 0.60 mol, 1.20 equiv) was added dropwise to a solution of ethyl 4-iodobenzoate (138 mg, 0.50 mol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and the resulting mixture was stirred for 16 h. After aqueous workup, extraction and flash column chromatography purification, **(*S*)-23d** (126 mg, 0.44 mmol, 88% yield, 99.7% *ee*) was obtained as colorless oil.

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.87 – 7.84 (m, 2H), 6.98 – 6.92 (m, 2H), 6.51 (t, *J* = 2.1 Hz, 2H), 6.05 (t, *J* = 2.1 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.64 (ddd, *J* = 10.6, 8.2, 3.9 Hz, 1H), 3.21 (dd, *J* = 13.8, 3.9 Hz, 1H), 3.00 (dd, *J* = 13.8, 10.6 Hz, 1H), 2.06 (dhept, *J* = 8.2, 6.7 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 166.7, 144.4, 129.6, 128.8, 128.7, 119.7, 107.6, 68.5, 60.9, 40.2, 34.1, 20.6, 19.2, 14.4.

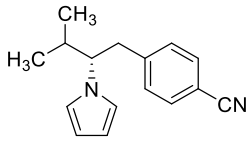
MS (EI, 70 eV, %): *m/z* = 285 (4), 122 (100), 80 (16).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{16}H_{23}NO_2$]: 285.1729; found: 285.1721 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2960 (w), 2873 (w), 1711 (s), 1611 (w), 1488 (w), 1469 (w), 1444 (w), 1416 (w), 1388 (w), 1367 (m), 1271 (vs), 1179 (m), 1100 (s), 1088 (m), 1069 (m), 1021 (m), 929 (w), 873 (w), 764 (m), 720 (s), 704 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –136.1.

(*S*)-4-(3-Methyl-2-(1*H*-pyrrol-1-yl)butyl)benzonitrile ((*S*)-23e)



According to **TP12**, a freshly prepared solution of **(*R*)-20c** (1.15 mL, 0.52 M, 0.60 mol, 1.20 equiv) was added dropwise to a solution of 4-iodobenzonitrile (115 mg, 0.50 mol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and the resulting mixture was stirred for 16 h. After aqueous workup, extraction and flash column chromatography purification, **(*S*)-23e** (111 mg, 0.47 mmol, 93% yield, 99.6% *ee*) was obtained as a yellowish oil.

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.46 – 7.41 (m, 2H), 6.98 – 6.93 (m, 2H), 6.48 (t, *J* = 2.1 Hz, 2H), 6.05 (t, *J* = 2.2 Hz, 2H), 3.59 (ddd, *J* = 11.0, 8.4, 3.6 Hz, 1H), 3.20 (dd, *J* = 13.9, 3.6 Hz, 1H), 2.99 (dd, *J* = 13.9, 10.9 Hz, 1H), 2.08 (dhept, *J* = 8.5, 6.7 Hz, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 144.6, 132.1, 129.5, 119.5, 119.0, 110.4, 107.9, 68.4, 40.4, 34.2, 20.5, 19.3.

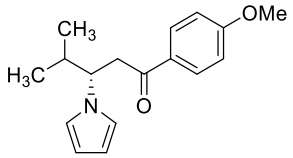
MS (EI, 70 eV, %): *m/z* = 238 (10), 195 (17), 193 (13), 122 (100), 116 (27), 80 (21).

HRMS (EI, 70 eV): *m/z* calcd. for $[C_{16}H_{18}N_2]$: 238.1470; found: 238.1463 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm-1): ν = 2961 (w), 2226 (m), 1607 (w), 1505 (w), 1488 (m), 1470 (w), 1414 (w), 1387 (w), 1369 (w), 1300 (w), 1274 (m), 1259 (m), 1177 (w), 1087 (m), 1068 (m), 1022 (w), 928 (w), 821 (m), 721 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –185.4.

(*S*)-1-(4-Methoxyphenyl)-4-methyl-3-(1*H*-pyrrol-1-yl)pentan-1-one ((*S*)-23f)



According to **TP13a**, 3-methoxybenzoyl chloride (85.3 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*R*)-20c** (1.15 mL, 0.52 M, 0.60 mol, 1.20 equiv) with catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The reaction mixture was stirred at 50 °C for 16 h and quenched with sat. aq. NH_4Cl solution. The crude product was extracted with EtOAc and purified by flash column chromatography. **(*S*)-23f** (116 mg, 0.43 mmol, 85% yield, 99.8% *ee*) was obtained as a yellowish solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.89 – 7.84 (m, 2H), 6.93 – 6.87 (m, 2H), 6.68 (t, *J* = 2.1 Hz, 2H), 6.07 (t, *J* = 2.1 Hz, 2H), 4.39 (td, *J* = 8.0, 5.0 Hz, 1H), 3.86 (s, 3H), 3.47 (dd, *J* = 16.7, 7.9 Hz, 1H), 3.33 (dd, *J* = 16.7, 5.1 Hz, 1H), 2.13 – 1.98 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 195.8, 163.6, 119.7, 113.7, 107.5, 77.3, 77.0, 76.7, 61.7, 55.4, 42.2, 34.1, 20.2, 19.0.

MS (EI, 70 eV, %): *m/z* = 271 (5), 253 (27), 238 (25), 210 (100), 167 (21), 135 (93), 77 (9).

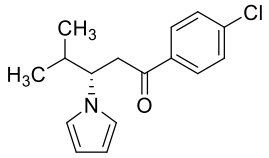
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{17}H_{21}NO_2$]: 271.1572; found: 271.1564 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2963 (m), 2937 (w), 2360 (w), 2340 (w), 1675 (m), 1600 (vs), 1575 (m), 1510 (m), 1489 (m), 1465 (w), 1419 (m), 1359 (w), 1306 (w), 1259 (vs), 1218 (w), 1170 (s), 1088 (w), 1029 (m), 834 (m), 725 (m).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +1.1.

M.p. 50.5 °C.

(*S*)-1-(4-Chlorophenyl)-4-methyl-3-(1*H*-pyrrol-1-yl)pentan-1-one ((*S*)-23g)



According to **TP13b**, a freshly prepared solution of **(*R*)-20c** (1.15 mL, 0.52 M, 0.60 mol, 1.20 equiv) was mixed with catalytic amounts of CuI (9.52 mg, 0.05 mmol, 10 mol%) at 0 °C. 3-Chlorobenzoyl chloride (87.5 mg, 0.50 mmol, 1.00 equiv) was added and the mixture stirred for 1 h at 0 °C before warming to room temperature. The reaction mixture was stirred for 16 h and quenched with sat. aq. NH_4Cl solution. The crude product was extracted with EtOAc and purified by flash column chromatography to obtain **(*S*)-23g** (110 mg, 0.40 mmol, 80% yield, 99.7% *ee*) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.84 – 7.76 (m, 2H), 7.49 – 7.34 (m, 2H), 6.66 (t, *J* = 2.1 Hz, 2H), 6.07 (t, *J* = 2.1 Hz, 2H), 4.35 (td, *J* = 8.3, 4.7 Hz, 1H), 3.49 (dd, *J* = 16.8, 8.2 Hz, 1H), 3.33 (dd, *J* = 16.8, 4.7 Hz, 1H), 2.18 – 1.99 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 196.5, 139.9, 135.3, 129.5, 129.1, 119.8, 107.8, 61.9, 42.7, 34.3, 20.3, 19.2.

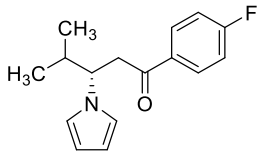
MS (EI, 70 eV, %): *m/z* = 275 (6), 257 (27), 242 (35), 214 (73), 141 (35), 139 (100), 111 (7), 94 (8).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{16}H_{18}ClNO$]: 275.1077; found: 275.1067 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2963 (w), 2874 (w), 1686 (s), 1589 (m), 1488 (m), 1400 (m), 1358 (w), 1274 (m), 1212 (m), 1176 (w), 1089 (s), 1012 (w), 930 (w), 828 (m), 783 (w), 723 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –6.7.

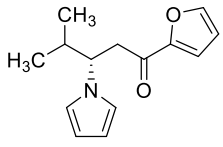
(*S*)-1-(4-Fluorophenyl)-4-methyl-3-(1*H*-pyrrol-1-yl)pentan-1-one ((*S*)-23h)



According to **TP13b**, a freshly prepared solution of **(*R*)-20c** (1.15 mL, 0.52 M, 0.60 mol, 1.20 equiv) was mixed with catalytic amounts of CuI (9.52 mg, 0.05 mmol, 10 mol%) at 0 °C. 4-Fluorobenzoyl chloride (79.3 mg, 0.50 mmol, 1.00 equiv) was added and the mixture stirred for 1 h at 0 °C before warming to room temperature. The reaction mixture was stirred for 16 h and quenched with sat. aq. NH_4Cl solution. The crude product was extracted with EtOAc and purified by flash column chromatography to obtain **(*S*)-23h** (91 mg, 0.35 mmol, 70% yield, 99.4% *ee*) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.97 – 7.77 (m, 2H), 7.16 – 7.05 (m, 2H), 6.67 (t, *J* = 2.1 Hz, 2H), 6.07 (t, *J* = 2.1 Hz, 2H), 4.36 (td, *J* = 8.3, 4.8 Hz, 1H), 3.50 (dd, *J* = 16.8, 8.2 Hz, 1H), 3.33 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.16 – 2.00 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 196.0, 165.9 (d, *J* = 255.1), 133.4 (d, *J* = 3.0), 130.8 (d, *J* = 9.4), 119.8, 115.8 (d, *J* = 21.9), 107.8, 61.9, 42.6, 34.3, 20.3, 19.2.
^{19}F-NMR (377 MHz, $CDCl_3$, ppm): δ = –104.9.
MS (EI, 70 eV, %): *m/z* = 259 (6), 241 (38), 239 (12), 226 (47), 199 (14), 198 (100), 170 (13), 136 (15), 123 (66).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{16}H_{18}FNO$]: 259.1372; found: 259.1363 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2963 (m), 2874 (w), 1684 (s), 1596 (s), 1506 (m), 1489 (m), 1471 (w), 1411 (m), 1388 (w), 1359 (m), 1298 (m), 1274 (s), 1235 (s), 1156 (s), 1088 (m), 1069 (w), 994 (w), 930 (w), 838 (s), 818 (w), 724 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –22.3.

(*S*)-1-(Furan-2-yl)-4-methyl-3-(1*H*-pyrrol-1-yl)pentan-1-one ((*S*)-23i)



According to **TP13a**, 2-furoyl chloride (65.3 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*R*)-20c** (1.15 mL, 0.52 M, 0.60 mol, 1.20 equiv) with catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The reaction mixture was stirred at 50 °C for 16 h and quenched with sat. aq. NH_4Cl solution. The crude product was extracted with EtOAc and purified by flash column chromatography to obtain **(*S*)-23i** (83 mg, 0.36 mmol, 72% yield, 99.9% *ee*) as a pale yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.55 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.12 (dd, *J* = 3.6, 0.8 Hz, 1H), 6.66 (t, *J* = 2.1 Hz, 2H), 6.49 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.06 (t, *J* = 2.1 Hz, 2H), 4.33 (td, *J* = 8.5 Hz, 4.9, 1H), 3.40 (dd, *J* = 16.3, 8.7 Hz, 1H), 3.22 (dd, *J* = 16.3, 4.9 Hz, 1H), 2.18 – 1.95 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 186.6, 152.8, 146.6, 119.8, 117.4, 112.5, 107.7, 61.7, 42.5, 34.3, 20.2, 19.1.

MS (EI, 70 eV, %): *m/z* = 231 (11), 213 (54), 198 (51), 170 (100), 167 (15), 136 (11), 115 (11), 95 (43).

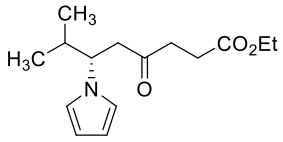
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{14}H_{17}NO_2$]: 231.1259; found: 231.1252 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3123 (w), 3094 (w), 2965 (w), 2880 (w), 1645 (vs), 1490 (w), 1465 (s), 1416 (w), 1397 (m), 1290 (w), 1274 (w), 1164 (w), 1098 (w), 1063 (w), 998 (w), 914 (w), 775 (m), 733 (m).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –4.9.

M.p. 90.5 °C.

Ethyl (*S*)-7-methyl-4-oxo-6-(1*H*-pyrrol-1-yl)octanoate ((*S*)-23j)



According to **TP13a**, ethyl 4-chloro-4-oxobutyrate (82.3 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*R*)-20c** (1.15 mL, 0.52 M, 0.60 mol, 1.20 equiv) with catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The reaction mixture was stirred at 50 °C for 16 h and quenched with sat. aq. NH_4Cl solution. The crude product was extracted with EtOAc and purified by flash column chromatography to obtain **(*S*)-23j** (88 mg, 0.33 mmol, 66% yield, 99.5% *ee*) as an orange liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.62 (t, *J* = 2.2 Hz, 2H), 6.09 (t, *J* = 2.1 Hz, 2H), 4.15 – 4.05 (m, 3H), 2.98 (dd, *J* = 16.1, 9.1 Hz, 1H), 2.88 (dd, *J* = 16.1, 4.7 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.58 – 2.48 (m, 1H), 2.45 – 2.30 (m, 2H), 2.04 – 1.89 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 206.9, 172.8, 119.7, 107.9, 62.1, 60.8, 46.8, 37.9, 34.2, 28.0, 20.1, 19.1, 14.3.206.7, 172.6, 119.5, 107.7, 61.9, 60.6, 46.7, 37.8, 34.0, 27.9, 20.0, 19.0, 14.1.

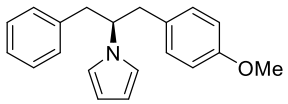
MS (EI, 70 eV, %): *m/z* = 265 (1), 247 (32), 186 (22), 174 (88), 159 (43), 144 (42), 130 (100), 101 (53).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{15}H_{23}NO_3$]: 265.1678; found: 265.1670 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2964 (m), 2934 (w), 2875 (w), 1731 (vs), 1719 (vs), 1489 (m), 1470 (w), 1413 (m), 1371 (m), 1349 (w), 1275 (m), 1195 (m), 1089 (m), 1035 (w), 726 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –71.1.

(*S*)-1-(1-(4-Methoxyphenyl)-3-phenylpropan-2-yl)-1*H*-pyrrole ((*S*)-24a)



According to **TP12**, a freshly prepared solution of **(*S*)-20d** (1.30 mL, 0.47 M, 0.60 mol, 1.20 equiv) was added dropwise to a solution of 4-iodoanisole (118 mg, 0.50 mol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL). The mixture was stirred for 16 h and quenched with sat. aq. NH_4Cl solution. The crude product was extracted with EtOAc and purified by flash column chromatography to afford **(*S*)-24a** (123 mg, 0.42 mmol, 84% yield, 98.8% *ee*) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.27 – 7.16 (m, 3H), 6.99 – 6.94 (m, 2H), 6.88 – 6.83 (m, 2H), 6.80 – 6.75 (m, 2H), 6.55 (t, *J* = 2.1 Hz, 2H), 6.08 (t, *J* = 2.1 Hz, 2H), 4.18 (tt, *J* = 7.8, 6.3 Hz, 1H), 3.77 (s, 3H), 3.13 – 2.98 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.4, 138.4, 130.4, 130.0, 129.0, 128.5, 126.6, 119.1, 113.9, 107.8, 64.0, 55.3, 42.6, 41.8.

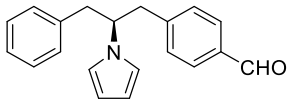
MS (EI, 70 eV, %): *m/z* = 291 (9), 200 (42), 198 (18), 171 (13), 170 (100), 168 (64), 153 (11), 121 (18), 91 (41).

HRMS (EI, 70 eV): *m/z* calcd. for $[C_{20}H_{21}NO]$: 291.1623; found: 291.1617 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3027 (w), 2929 (w), 1611 (w), 1583 (w), 1511 (s), 1488 (m), 1454 (m), 1441 (w), 1411 (w), 1301 (m), 1243 (vs), 1177 (m), 1109 (w), 1089 (m), 1070 (m), 1032 (s), 910 (w), 823 (m), 719 (vs), 698 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +7.8.

(*S*)-4-(3-Phenyl-2-(1*H*-pyrrol-1-yl)propyl)benzaldehyde ((*S*)-24b)



According to **TP12**, a solution of **(*S*)-20d** (1.30 mL, 0.47 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 4-bromo benzaldehyde (82.5 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and the resulting reaction mixture stirred for 16 h. After quenching with sat. aq. NH_4Cl solution and extraction with EtOAc, the crude product was purified by flash column chromatography to afford **(*S*)-24b** (133 mg, 0.46 mmol, 91% yield, 99.8% *ee*) as a dark-orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.89 (s, 1H), 7.69 – 7.64 (m, 2H), 7.24 – 7.13 (m, 3H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.98 – 6.94 (m, 2H), 6.47 (t, *J* = 2.1 Hz, 2H), 6.01 (t, *J* = 2.1 Hz, 2H), 4.19 (tt,

J = 7.8, 6.6 Hz, 1H), 3.13 (dd, *J* = 13.8, 8.0 Hz, 1H), 3.09 (d, *J* = 7.1 Hz, 2H), 3.03 (dd, *J* = 13.7, 6.4 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 192.1, 145.6, 137.9, 135.1, 130.0, 129.6, 129.0, 128.7, 126.9, 119.0, 108.2, 63.5, 43.0, 42.7.

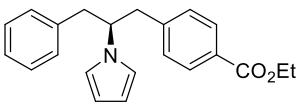
MS (EI, 70 eV, %): *m/z* = 289 (10), 198 (68), 196 (20), 171 (13), 170 (100), 168 (57), 167 (12), 153 (12), 119 (10), 91 (40).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{20}H_{19}NO$]: 289.1467; found: 289.1462 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3027 (w), 2922 (w), 2850 (vw), 2736 (vw), 1694 (s), 1605 (s), 1576 (m), 1488 (m), 1454 (w), 1306 (m), 1267 (m), 1213 (m), 1169 (m), 1089 (m), 1070 (m), 930 (w), 853 (w), 821 (m), 775 (m), 720 (vs), 698 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +49.9.

Ethyl (*S*)-4-(3-phenyl-2-(1*H*-pyrrol-1-yl)propyl)benzoate ((*S*)-24c)



According to **TP12**, a solution of **(*S*)-20d** (1.30 mL, 0.47 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of ethyl 4-iodobenzoate (140 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and the resulting reaction mixture stirred for 16 h. After quenching with sat. aq. NH_4Cl solution and extraction with EtOAc, the crude product was purified by flash column chromatography to afford **(*S*)-24c** (162 mg, 0.49 mmol, 96% yield, 99.9% *ee*) as a yellow oil.

In a large-scale attempt, the same procedure was carried out using 552 mg (2.00 mmol, 1.00 equiv) of ethyl 4-iodobenzoate and a freshly prepared solution of **(*S*)-20d** (4.80 mL, 0.50 M, 2.40 mmol, 1.20 equiv) with catalytic amounts of $Pd(OAc)_2$ (9.00 mg, 40.0 µmol, 2 mol%) and SPhos (33.0 mg, 80.3 µmol, 4 mol%), resulting in a yield of 632 mg **(*S*)-24c** (1.90 mmol, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.94 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.22 (m, 3H), 7.06 – 7.00 (m, 4H), 6.57 (t, *J* = 2.1 Hz, 2H), 6.11 (t, *J* = 2.1 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.28 (quint, *J* = 7.1 Hz, 1H), 3.23 – 3.07 (m, 4H), 1.42 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.6, 143.5, 138.0, 129.7, 128.9, 128.9, 128.9, 128.5, 126.7, 119.0, 108.0, 63.4, 60.9, 42.8, 42.5, 14.4.

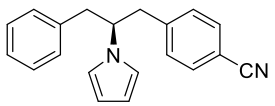
MS (EI, 70 eV, %): *m/z* = 333 (6), 242 (40), 171 (13), 170 (100), 168 (61), 167 (14), 163 (12), 91 (30).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{22}H_{23}NO_2$]: 333.1729; found: 333.1721 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2979 (w), 2928 (w), 1710 (s), 1610 (w), 1575 (vw), 1488 (m), 1454 (w), 1415 (w), 1366 (w), 1311 (w), 1271 (vs), 1178 (m), 1101 (s), 1070 (m), 1021 (m), 932 (w), 850 (w), 752 (m), 720 (s), 698 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +32.4.

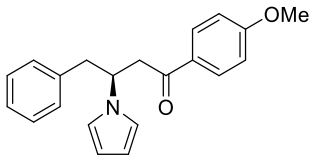
(*S*)-4-(3-Phenyl-2-(1*H*-pyrrol-1-yl)propyl)benzonitrile ((*S*)-24d)



According to **TP12**, the product was synthesized from 4-iodobenzonitrile (458 mg, 2.00 mmol, 1.00 equiv) and a freshly prepared solution of **(*S*)-20d** (4.80 mL, 0.50 M, 2.40 mmol, 1.20 equiv) in the presence of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%). The mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of crude product with EtOAc and flash column chromatography purification afforded **(*S*)-24d** (540 mg, 1.89 mmol, 94% yield, 98.8% *ee*) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.52 – 7.46 (m, 2H), 7.32 – 7.22 (m, 4H), 7.07 – 7.02 (m, 2H), 7.00 – 6.95 (m, 2H), 6.53 (t, *J* = 2.1 Hz, 2H), 6.09 (t, *J* = 2.1 Hz, 2H), 4.22 (tt, *J* = 7.8, 6.5 Hz, 1H), 3.22 (dd, *J* = 13.7, 7.9 Hz, 1H), 3.15 – 3.06 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 143.8, 137.8, 132.2, 129.7, 129.0, 128.7, 126.9, 119.0, 119.0, 110.6, 108.3, 63.4, 43.0, 42.6.
MS (EI, 70 eV, %): *m/z* = 286 (11), 196 (14), 195 (100), 193 (32), 171 (11), 170 (84), 168 (43), 167 (10), 116 (44), 91 (24).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{20}H_{18}N_2]$: 286.1470; found: 286.1465 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm-1): ν = 3062 (vw), 3028 (vw), 2924 (w), 2226 (m), 1733 (vw), 1606 (w), 1488 (m), 1454 (w), 1414 (w), 1267 (m), 1178 (w), 1089 (m), 1070 (m), 931 (w), 846 (w), 826 (m), 755 (m), 721 (vs), 698 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +44.3.

(*S*)-1-(4-Methoxyphenyl)-4-phenyl-3-(1*H*-pyrrol-1-yl)butan-1-one ((*S*)-24e)



Following **TP13a**, the product was synthesized from 4-methoxybenzoyl chloride (85 mg, 0.50 mmol, 1.00 equiv) and freshly prepared solution of **(*S*)-20d** (1.40 mL, 0.42 M, 0.60 mmol, 1.20 equiv) with catalytic amount of $Pd(PPh_3)_4$ (23 mg, 20.0 µmol, 4 mol%). The reaction mixture was stirred at 50 °C for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-24e** (154 mg, 0.48 mmol, 86% yield, 99.9% *ee*) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.95 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.26 (m, 3H), 7.08 (d, *J* = 7.2 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.73 (td, J = 2.0, 1.2 Hz, 2H), 6.16 (td, *J* = 2.0, 1.6 Hz, 2H), 4.95 (quint, *J* = 6.8 Hz, 1H), 3.92 (s, 3H), 3.55 (dd, *J* = 16.8, 6.4 Hz, 1H), 3.43 (dd, *J* = 16.8, 7.0 Hz, 1H), 3.22 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.15 (dd, *J* = 13.6, 8.4 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 195.5, 163.6, 137.8, 126.6, 119.0, 113.7, 107.8, 77.3, 77.0, 76.7, 57.3, 55.4, 43.8, 42.8.

MS (EI, 70 eV, %): *m/z* = 319 (1), 298 (15), 210 (50), 184 (8), 167 (9), 135 (100), 91 (5), 77 (8).

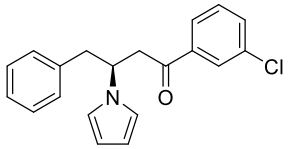
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{21}H_{21}NO_2$]: 319.1572; found: 319.1565 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3027 (w), 2934 (w), 1674 (s), 1600 (vs), 1575 (m), 1510 (m), 1490 (m), 1419 (m), 1360 (w), 1259 (s), 1218 (m), 1171 (s), 1090 (m), 1029 (m), 990 (w), 834 (w), 725 (m), 701 (m).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –31.2.

M.p.: 90.1 °C.

(*S*)-1-(3-Chlorophenyl)-4-phenyl-3-(1*H*-pyrrol-1-yl)butan-1-one ((*S*)-24f)



According to **TP13a**, 3-chlorobenzoyl chloride (88 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*S*)-20d** (1.40 mL, 0.42 M, 0.60 mmol, 1.20 equiv) with catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The reaction mixture was stirred at 50 °C for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-24f** (138 mg, 0.43 mmol, 85% yield, 99.9% *ee*) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.86 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.29 – 7.23 (m, 3H), 7.05 (d, *J* = 7.6 Hz, 2H), 6.69 (td, *J* = 2.0, 1.6 Hz, 2H), 6.12 (td, *J* = 2.0, 1.6 Hz, 2H), 4.90 (quint, *J* = 6.8 Hz, 1H), 3.53 (dd, *J* = 17.2, 6.4 Hz, 1H), 3.43 (dd, *J* = 17.2, 6.4 Hz, 1H), 3.15 (d, *J* = 7.2 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 196.0, 138.3, 137.7, 135.1, 133.4, 130.1, 129.1, 128.6, 128.2, 126.9, 126.2, 119.2, 108.3, 57.3, 44.4, 42.9.

MS (EI, 70 eV, %): *m/z* = 323 (1), 302 (16), 267 (18), 214 (100), 139 (83), 111 (9), 91 (6).

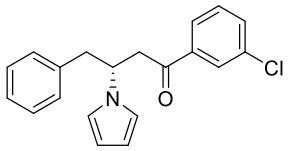
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{20}H_{18}ClNO$]: 323.1077; found: 323.1071 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3063 (w), 3028 (w), 2918 (w), 2360 (s), 2340 (m), 1688 (vs), 1571 (m), 1489 (m), 1420 (m), 1360 (m), 1276 (m), 1256 (m), 1212 (m), 1090 (m), 724 (vs), 700 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –22.5.

M.p.: 66.5 °C.

(*R*)-1-(3-Chlorophenyl)-4-phenyl-3-(1*H*-pyrrol-1-yl)butan-1-one ((*R*)-24f)

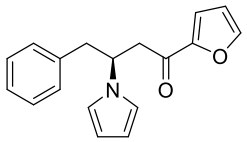


To obtain the (*R*)-enantiomer, the reaction was repeated using the (*R*)-zinc species starting from the *D*-phenylalaninol. The procedure for preparation of the starting materials was done in the same way as for the *L*-phenylalaninol (**18d–20d**).

According to **TP13a**, 3-chlorobenzoyl chloride (88 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*R*)-20d** (1.53 mL, 0.39 M, 0.60 mmol, 1.20 equiv) with catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The reaction mixture was stirred at 50 °C for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product and flash column chromatography purification afforded **(*R*)-24f** (133 mg, 0.41 mmol, 82% yield, 99.9% *ee*) as a white solid.

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +20.9.

(*S*)-1-(Furan-2-yl)-4-phenyl-3-(1*H*-pyrrol-1-yl)butan-1-one ((*S*)-24g)



Following **TP13a**, 2-furoyl chloride (65.0 mg, 0.50 mmol, 1.00 equiv), a freshly prepared solution of **(*S*)-20d** (1.40 mL, 0.42 M, 0.60 mmol, 1.20 equiv) and catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The reaction mixture was stirred at 50 °C for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-24g** (118 mg, 0.42 mmol, 84% yield, 99.8% *ee*) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.26 – 7.19 (m, 3H), 7.14 (d, *J* = 3.6 Hz, 1H), 7.04 – 6.99 (m, 2H), 6.65 (t, *J* = 2.1 Hz, 2H), 6.51 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.08 (t, *J* = 2.1 Hz, 2H), 4.85 (pent, *J* = 7.0 Hz, 1H), 3.42 (dd, *J* = 16.5, 7.1 Hz, 1H), 3.25 (dd, *J* = 16.5, 6.6 Hz, 1H), 3.12 (d, *J* = 7.1 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 186.1, 152.6, 146.7, 137.7, 129.1, 128.5, 126.8, 119.2, 117.5, 112.5, 108.1, 57.2, 44.1, 42.9.

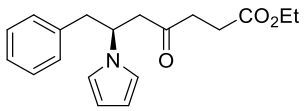
MS (EI, 70 eV, %): *m/z* = 279 (4), 188 (23), 170 (29), 115 (9), 95 (100), 91 (8).

HRMS (EI, 70 eV): *m/z* calcd. for $[C_{18}H_{17}NO_2]$: 279.1259; found: 279.1253 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3124 (w), 3095 (w), 3024 (vw), 1650 (vs), 1561 (w), 1492 (w), 1465 (m), 1397 (m), 1288 (w), 1279 (m), 1162 (w), 1057 (w), 1031 (w), 1002 (w), 917 (w), 774 (m), 737 (m), 697 (m).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –37.5.
M.p.: 120.5 °C.

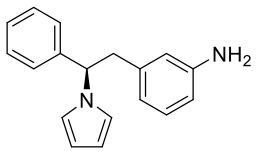
Ethyl (*S*)-4-oxo-7-phenyl-6-(1*H*-pyrrol-1-yl)heptanoate ((*S*)-24h)



Following **TP13a**, ethyl 4-chloro-4-oxobutyrate (82 mg, 0.50 mmol, 1.00 equiv), a freshly prepared solution of **(*S*)-20d** (1.40 mL, 0.42 M, 0.60 mmol, 1.20 equiv) and catalytic amount of $Pd(PPh_3)_4$ (23.0 mg, 20.0 µmol, 4 mol%) were used. The reaction mixture was stirred at 50 °C for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-24h** (110 mg, 0.35 mmol, 70% yield, 99.9% *ee*) as a brownish liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.21 (dddt, *J* = 6.9, 5.2, 3.5, 1.8 Hz, 3H), 7.01 – 6.90 (m, 3H), 6.59 (t, *J* = 2.1 Hz, 2H), 6.08 (t, *J* = 2.1 Hz, 2H), 4.66 (p, *J* = 7.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.03 (d, *J* = 7.1 Hz, 2H), 3.02 (dd, *J* = 16.5, 7.4 Hz, 1H), 2.89 (dd, *J* = 16.6, 6.3 Hz, 1H), 2.71 – 2.39 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 206.3, 172.7, 137.6, 129.1, 128.5, 126.8, 119.1, 108.2, 60.8, 57.3, 48.3, 42.9, 37.9, 27.9, 14.3.
MS (EI, 70 eV, %): *m/z* = 311 (1), 295 (15), 222 (18), 204 (29), 176 (20), 130 (100), 101 (54), 91 (20).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{19}H_{23}NO_3]$: 313.1678; found: 313.1622 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2980 (w), 2926 (w), 1718 (vs), 1490 (m), 1412 (m), 1371 (m), 1350 (m), 1270 (m), 1196 (m), 1092 (m), 1030 (w), 749 (w), 726 (s), 701 (m).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –16.3.

(*R*)-3-(2-Phenyl-2-(1H-pyrrol-1-yl)ethyl)aniline ((*R*)-25a)



According to **TP12**, 3-Bromoaniline (86 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%), SPhos (8.21 mg, 20.0 µmol, 4 mol%) and a freshly prepared solution of **(*S*)-20e** (1.33 mL, 0.45 M, 0.60 mmol, 1.20 equiv) were used. The mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded Purification of the crude product by flash column chromatography afforded **(*R*)-25a** (98 mg, 0.38 mmol, 75% yield, 99.8% *ee*) as a light orange solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.35 – 7.24 (m, 3H), 7.20 – 7.15 (m, 2H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.75 (t, *J* = 2.1 Hz, 2H), 6.53 (ddd, *J* = 7.9, 2.4, 1.0 Hz, 1H), 6.45 (d, *J* = 6.9 Hz, 1H), 6.30 (t, *J* = 2.0 Hz, 1H), 6.16 (t, *J* = 2.1 Hz, 2H), 5.28 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.55 (br, 2H), 3.47 (dd, *J* = 13.8, 8.6 Hz, 1H), 3.34 (dd, *J* = 13.8, 6.5 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 146.5, 141.8, 139.2, 129.4, 128.7, 127.7, 126.7, 119.9, 119.4, 115.9, 113.5, 108.1, 64.8, 42.3.

MS (EI, 70 eV, %): *m/z* = 262 (3), 157 (12), 156 (100), 129 (13), 128 (10).

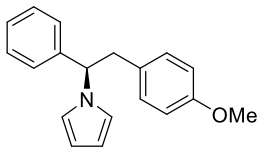
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{18}H_{18}N_2$]: 262.1470; found: 262.1464 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3396 (w), 3313 (w), 3214 (w), 3126 (w), 3023 (w), 1630 (m), 1586 (m), 1486 (m), 1454 (m), 1407 (m), 1322 (w), 1283 (m), 1268 (s), 1164 (w), 1090 (s), 1039 (w), 1025 (w), 981 (w), 949 (w), 906 (w), 870 (w), 775 (m), 727 (s), 693 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –24.2.

M.p.: 81.3 °C.

(*R*)-1-(2-(4-Methoxyphenyl)-1-phenylethyl)-1*H*-pyrrole ((*R*)-25b)



Following **TP12**, 4-iodoanisole (118 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*S*)-20e** (1.33 mL, 0.45 M, 0.60 mmol, 1.20 equiv) were used as starting materials with catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%). Stirring the reaction mixture for 16 h followed by quenching, extraction and purification of the crude product by flash column chromatography afforded **(*R*)-25b** (105 mg, 0.38 mmol, 75% yield, 99.7% *ee*) as a faint yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.32 – 7.22 (m, 4H), 7.18 – 7.13 (m, 2H), 6.92 – 6.86 (m, 2H), 6.77 – 6.73 (m, 2H), 6.72 (t, *J* = 2.1 Hz, 2H), 6.14 (t, *J* = 2.1 Hz, 2H), 5.21 (dd, *J* = 8.6, 6.6 Hz, 1H), 3.76 (s, 3H), 3.48 (dd, *J* = 13.9, 8.6 Hz, 1H), 3.35 (dd, *J* = 13.8, 6.6 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.4, 141.7, 130.1, 130.0, 128.7, 127.8, 126.8, 119.8, 113.9, 108.2, 65.3, 55.3, 41.4.

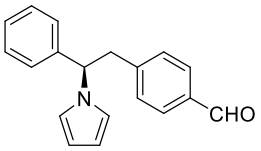
MS (EI, 70 eV, %): *m/z* = 277 (2), 157 (12), 156 (100), 129 (12), 121 (9).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{19}H_{19}NO$]: 277.1467; found: 277.1460 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3029 (vw), 2930 (w), 2834 (vw), 1611 (w), 1584 (w), 1511 (s), 1487 (m), 1451 (m), 1408 (w), 1301 (w), 1244 (s), 1178 (m), 1088 (m), 1031 (m), 972 (w), 910 (w), 820 (m), 756 (m), 720 (vs), 697 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –17.3.

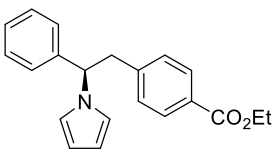
(*R*)-4-(2-Phenyl-2-(1*H*-pyrrol-1-yl)ethyl)benzaldehyde ((*R*)-25c)



According to **TP12**, 4-bromobenzaldehyde (93.0 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*S*)-20e** (1.33 mL, 0.45 M, 0.60 mmol, 1.20 equiv) were used as starting materials with catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) present. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*R*)-25c** (116 mg, 0.42 mmol, 84% yield, 99.4% *ee*) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.95 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.21 – 7.12 (m, 4H), 6.70 (t, *J* = 2.1 Hz, 2H), 6.14 (t, *J* = 2.1 Hz, 2H), 5.29 (dd, *J* = 9.0, 6.4 Hz, 1H), 3.62 (dd, *J* = 13.7, 9.0 Hz, 1H), 3.51 (dd, *J* = 13.7, 6.3 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 192.0, 145.2, 141.0, 135.1, 130.0, 129.7, 128.9, 128.1, 126.6, 119.7, 108.5, 64.5, 42.4.
MS (EI, 70 eV, %): *m/z* = 275 (1), 157 (12), 156 (100), 129 (11).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{19}H_{17}NO]$: 275.1310; found: 275.1305 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2923 (w), 1686 (s), 1602 (s), 1576 (m), 1488 (m), 1451 (m), 1398 (w), 1345 (w), 1308 (m), 1266 (m), 1216 (m), 1201 (m), 1165 (m), 1093 (m), 1078 (m), 1026 (w), 977 (m), 863 (m), 832 (m), 808 (m), 747 (m), 725 (vs), 696 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +1.0.
M.p.: 67.0 °C.

Ethyl (*R*)-4-(2-phenyl-2-(1*H*-pyrrol-1-yl)ethyl)benzoate ((*R*)-25d)



Following **TP12**, ethyl 4-iodobenzoate (140 mg, 0.50 mmol, 1.00 equiv), a freshly prepared solution of **(*S*)-20e** (1.33 mL, 0.45 M, 0.60 mmol, 1.20 equiv) as well as $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%). The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*R*)-25d** (149 mg, 0.47 mmol, 92% yield, 99.9% *ee*) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.93 – 7.86 (m, 2H), 7.35 – 7.22 (m, 3H), 7.20 – 7.13 (m, 2H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.70 (t, *J* = 2.2 Hz, 2H), 6.13 (t, *J* = 2.1 Hz, 2H), 5.27 (dd, *J* = 8.9, 6.4 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.58 (dd, *J* = 13.7, 8.9 Hz, 1H), 3.47 (dd, *J* = 13.7, 6.4 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.6, 143.2, 141.1, 129.8, 129.1, 129.1, 128.8, 128.0, 126.7, 119.7, 108.4, 64.6, 61.0, 42.2, 14.4.

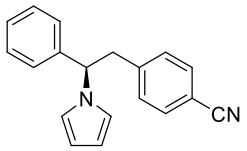
MS (EI, 70 eV, %): *m/z* = 319 (1), 178 (8), 157 (12), 156 (100), 129 (9).

HRMS (EI, 70 eV): *m/z* calcd. for $[C_{21}H_{21}NO_2]$: 319.1572; found: 319.1564 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3030 (vw), 2980 (w), 2931 (vw), 1709 (s), 1611 (w), 1487 (m), 1451 (w), 1416 (w), 1366 (w), 1311 (w), 1272 (vs), 1179 (m), 1102 (s), 1021 (m), 974 (w), 926 (w), 872 (w), 841 (w), 754 (m), 722 (vs), 697 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –7.7.

(*R*)-4-(2-Phenyl-2-(1*H*-pyrrol-1-yl)ethyl)benzonitrile ((*R*)-25e)



According to **TP12**, 4-iodobenzonitrile (115 mg, 0.50 mmol, 1.00 equiv), a freshly prepared solution of **(*S*)-20e** (1.33 mL, 0.45 M, 0.60 mmol, 1.20 equiv) as well as $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%). The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*R*)-25e** (130 mg, 0.48 mmol, 95% yield, 99.7% *ee*) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.53 – 7.47 (m, 2H), 7.37 – 7.26 (m, 3H), 7.21 – 7.16 (m, 2H), 7.10 – 7.05 (m, 2H), 6.68 (t, *J* = 2.1 Hz, 2H), 6.14 (t, *J* = 2.1 Hz, 2H), 5.24 (dd, *J* = 9.2, 6.1 Hz, 1H), 3.59 (dd, *J* = 13.8, 9.2 Hz, 1H), 3.48 (dd, *J* = 13.8, 6.1 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 143.5, 140.7, 132.3, 129.8, 128.9, 128.2, 126.6, 119.7, 118.9, 110.8, 108.7, 64.4, 42.3.

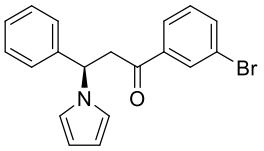
MS (EI, 70 eV, %): *m/z* = 272 (1), 157 (12), 156 (100), 129 (12).

HRMS (EI, 70 eV): *m/z* calcd. for $[C_{19}H_{16}N_2]$: 272.1313; found: 272.1310 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3030 (vw), 2923 (w), 2853 (vw), 2226 (m), 1607 (w), 1486 (m), 1451 (w), 1415 (w), 1265 (m), 1178 (w), 1089 (m), 1071 (m), 1021 (w), 973 (vw), 911 (w), 821 (m), 753 (m), 722 (vs), 698 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +8.3.

(*R*)-1-(3-Bromophenyl)-3-phenyl-3-(1*H*-pyrrol-1-yl)propan-1-one ((*R*)-25f)



According to **TP13b**, a freshly prepared solution of **(*S*)-20e** (1.33 mL, 0.45 M, 0.60 mmol, 1.20 equiv) was mixed with catalytic amounts of CuI (9.52 mg, 0.05 mmol, 10 mol%) at 0 °C. 3-Bromobenzoyl chloride (109 mg, 0.50 mmol, 1.00 equiv) was added and the mixture stirred for 1 h at 0 °C before warming to room temperature. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded a white solid **(*R*)-25f** (142 mg, 0.40 mmol, 80% yield, 99.8% *ee*).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.05 (t, *J* = 1.8 Hz, 1H), 7.85 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.70 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1H), 7.38 – 7.24 (m, 4H), 7.23 – 7.19 (m, 2H), 6.76 (t, *J* = 2.2 Hz, 2H), 6.16 (t, *J* = 2.1 Hz, 2H), 5.95 (t, *J* = 6.9 Hz, 1H), 3.91 (dd, *J* = 17.3, 7.6 Hz, 1H), 3.74 (dd, *J* = 17.3, 6.4 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 195.1, 141.0, 138.3, 136.5, 131.3, 130.5, 129.0, 128.1, 126.7, 126.5, 123.2, 119.9, 108.7, 58.4, 44.9.

MS (EI, 70 eV, %): *m/z* = 353 (2), 337 (36), 336 (14), 335 (38), 334 (14), 256 (22), 254 (38), 185 (85), 183 (86), 180 (16), 171 (12), 170 (100), 157 (17), 155 (17), 127 (13), 103 (16), 76 (15).

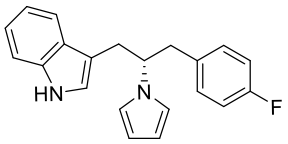
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{19}H_{16}BrNO]$: 353.0415; found: 353.0409 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3095 (vw), 3063 (vw), 3028 (vw), 2922 (w), 1681 (s), 1567 (w), 1488 (m), 1450 (m), 1423 (m), 1368 (w), 1305 (m), 1260 (m), 1203 (m), 1097 (m), 1069 (m), 995 (m), 887 (m), 823 (w), 791 (m), 770 (m), 730 (s), 697 (vs), 671 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –8.2.

M.p.: 118.4 °C.

(*S*)-3-(3-(4-Fluorophenyl)-2-(1H-pyrrol-1-yl)propyl)-1H-indole ((*S*)-26a)



According to **TP12**, 1-bromo-4-fluorobenzene (88.0 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*R*)-20f** (1.43 mL, 0.42 M, 0.60 mmol, 1.20 equiv) were used as starting materials with catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol% present. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-26a** as brownish highly viscous gel (109 mg, 0.34 mmol, 68% yield, 99.4% *ee*).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.90 (s, 1H), 7.46 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.35 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.16 – 7.11 (m, 1H), 6.93 – 6.84 (m, 4H), 6.60 – 6.57 (m, 3H), 6.09 (t, *J* = 2.1 Hz, 2H), 4.27 (tt, *J* = 8.3, 6.0 Hz, 1H), 3.29 (dd, *J* = 14.8, 6.1 Hz, 1H), 3.23 (dd, *J* = 14.9, 8.2 Hz, 1H), 3.12 (dd, *J* = 13.1, 5.0 Hz, 1H), 3.07 (dd, *J* = 13.1, 7.7 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.7 (d, *J* = 244.3 Hz), 136.1, 134.2 (d, *J* = 3.2 Hz), 130.4 (d, *J* = 7.9 Hz), 127.3, 122.7, 122.1, 119.6, 119.1, 118.4, 115.2 (d, *J* = 21.1 Hz), 112.1, 111.3, 107.8, 62.8, 42.2, 32.0.

^{19}F-NMR (377 MHz, $CDCl_3$, ppm): δ = –116.6.

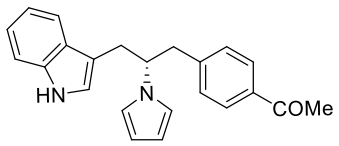
MS (EI, 70 eV, %): *m/z* = 318 (10), 209 (12), 188 (16), 186 (13), 131 (10), 130 (100), 109 (15).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{21}H_{19}FN_2$]: 318.1532; found: 318.1520 ([M]).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3412 (w), 2920 (w), 2852 (w), 1602 (w), 1508 (s), 1490 (m), 1456 (m), 1418 (w), 1356 (w), 1336 (w), 1266 (w), 1220 (s), 1158 (m), 1090 (m), 1070 (w), 1012 (w), 924 (w), 910 (w), 822 (m), 724 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +19.7.

(*S*)-1-(4-(3-(1*H*-Indol-3-yl)-2-(1*H*-pyrrol-1-yl)propyl)phenyl)ethan-1-one ((*S*)-26b)



According to **TP12**, 1-(4-iodophenyl)ethan-1-one (123 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*R*)-20f** (1.43 mL, 0.42 M, 0.60 mmol, 1.20 equiv) were used as starting materials with catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) present. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-26b** as a highly viscous colorless gel (168 mg, 0.49 mmol, 98% yield, 99.4% *ee*).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.00 (s, 1H), 7.83 – 7.77 (m, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.21 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.03 – 6.99 (m, 2H), 6.60 (d, *J* = 2.4 Hz, 1H), 6.59 (t, *J* = 2.1 Hz, 2H), 6.09 (t, *J* = 2.1 Hz, 2H), 4.40 – 4.30 (m, 1H), 3.34 – 3.24 (m, 2H), 3.23 – 3.13 (m, 2H), 2.56 (s, 3H).

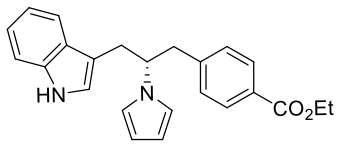
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 198.0, 144.2, 136.1, 135.6, 129.2, 128.6, 127.3, 122.7, 122.1, 119.6, 119.1, 118.4, 111.9, 111.4, 107.9, 62.4, 42.9, 32.3, 26.7.

MS (EI, 70 eV, %): *m/z* = 343 (6), 342 (25), 242 (18), 209 (12), 131 (11), 130 (100), 43 (16).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{23}H_{22}N_2O$]: 342.1732; found: 342.1727 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3378 (w), 3006 (w), 2920 (vw), 1674 (s), 1606 (m), 1572 (w), 1488 (w), 1456 (m), 1414 (m), 1358 (m), 1268 (s), 1216 (m), 1184 (m), 1090 (m), 1070 (m), 1010 (w), 958 (w), 926 (w), 846 (w), 818 (w), 740 (vs), 722 (vs), 666 (m).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –11.2.

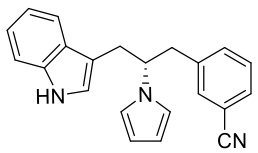
Ethyl (*S*)-4-(3-(1*H*-indol-3-yl)-2-(1*H*-pyrrol-1-yl)propyl)benzoate ((*S*)-26c)



According to **TP12**, ethyl 4-iodobenzoate (138 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*R*)-20f** (1.43 mL, 0.42 M, 0.60 mmol, 1.20 equiv) were used as starting materials with catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) present. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-26c** as a brownish highly viscous gel (180 mg, 0.48 mmol, 97% yield, 99.0% *ee*).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.96 (s, 1H), 7.91 – 7.85 (m, 2H), 7.47 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.35 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 7.03 – 6.95 (m, 2H), 6.59 (d, *J* = 2.3 Hz, 1H), 6.58 (t, *J* = 2.2 Hz, 2H), 6.08 (t, *J* = 2.1 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.44 – 4.29 (m, 1H), 3.33 – 3.22 (m, 2H), 3.22 – 3.11 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.6, 143.7, 136.0, 129.6, 128.9, 128.7, 127.2, 122.6, 122.0, 119.5, 119.0, 118.3, 111.8, 111.2, 107.8, 62.3, 60.9, 42.8, 32.0, 14.3.
MS (EI, 70 eV, %): 373 (8), 372 (26), 242 (30), 209 (17), 163 (6), 130 (100), 43 (17).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{24}H_{24}N_2O_2]$: 372.1838; found: 372.1833 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3386 (w), 2984 (w), 2930 (w), 1704 (s), 1610 (w), 1490 (w), 1456 (m), 1416 (m), 1368 (w), 1312 (m), 1274 (vs), 1228 (m), 1180 (m), 1104 (s), 1090 (s), 1070 (m), 1020 (m), 928 (w), 852 (w), 740 (vs), 722 (vs), 666 (w).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –9.4.

(*S*)-3-(3-(1*H*-Indol-3-yl)-2-(1*H*-pyrrol-1-yl)propyl)benzonitrile ((*S*)-26d)

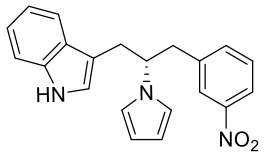


According to **TP12**, 3-iodobenzonitrile (115 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*R*)-20f** (1.43 mL, 0.42 M, 0.60 mmol, 1.20 equiv) were used as starting materials with

catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) present. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-26d** as yellowish highly viscous gel (150 mg, 0.46 mmol, 92% yield, 99.1% *ee*).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.99 (s, 1H), 7.51 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.45 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.29 – 7.19 (m, 2H), 7.18 – 7.12 (m, 2H), 7.04 (dt, *J* = 7.8, 1.5 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.56 (t, *J* = 2.1 Hz, 2H), 6.10 (t, *J* = 2.1 Hz, 2H), 4.35 – 4.23 (m, 1H), 3.30 (d, *J* = 7.2 Hz, 2H), 3.16 (dd, *J* = 13.9, 4.8 Hz, 1H), 3.09 (dd, *J* = 13.9, 9.4 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 139.9, 136.1, 133.5, 132.5, 130.4, 129.1, 127.2, 122.7, 122.3, 119.7, 119.0, 119.0, 118.3, 112.3, 111.7, 111.4, 108.2, 62.3, 42.4, 32.2.
MS (EI, 70 eV, %): 326 (5), 325 (20), 131 (10), 130 (100), 61 (7), 43 (30).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{22}H_{19}N_3]$: 325.1579; found: 325.1574 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3408 (m), 2950 (w), 2922 (w), 2230 (m), 1488 (m), 1458 (m), 1422 (w), 1356 (w), 1336 (w), 1266 (w), 1230 (w), 1090 (m), 1070 (w), 1010 (w), 938 (w), 910 (w), 798 (w), 728 (vs), 692 (m).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –3.6.

(*S*)-3-(3-(3-Nitrophenyl)-2-(1*H*-pyrrol-1-yl)propyl)-1*H*-indole ((*S*)-26e)



According to **TP12**, 1-iodo-3-nitrobenzene (138 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*R*)-20f** (1.43 mL, 0.42 M, 0.60 mmol, 1.20 equiv) were used as starting materials with catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) present. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-26e** as a yellow highly viscous gel (157 mg, 0.45 mmol, 91%, 99.1% *ee*).

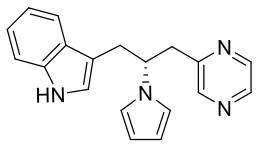
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.02 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 7.97 (s, 1H), 7.78 (t, *J* = 2.0 Hz, 1H), 7.52 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.36 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.10 (dt, *J* = 7.7, 1.4 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.58 (t, *J* = 2.1 Hz, 2H), 6.10 (t, *J* = 2.1 Hz, 2H), 4.40 – 4.29 (m, 1H), 3.35 – 3.30 (m, 2H), 3.24 (dd, *J* = 13.9, 4.8 Hz, 1H), 3.17 (dd, *J* = 13.9, 9.5 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 148.2, 140.4, 136.1, 135.2, 129.2, 127.3, 123.9, 122.8, 122.3, 121.8, 119.7, 119.0, 118.4, 111.8, 111.4, 108.3, 62.3, 42.5, 32.3.
MS (EI, 70 eV, %): 345 (8), 185 (10), 130 (62), 70 (10), 61 (17), 45 (15), 43 (100).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{19}H_{18}N_4$]: 345.1477; found: 345.1472 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3412 (w), 2924 (vw), 1524 (s), 1488 (m), 1456 (m), 1422 (w), 1350 (s), 1266 (w), 1090 (m), 1070 (m), 1010 (w), 928 (w), 816 (w), 804 (w), 724 (vs), 692 (m).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +13.2.

(*R*)-3-(3-(Pyrazin-2-yl)-2-(1*H*-pyrrol-1-yl)propyl)-1*H*-indole ((*R*)-26f)



According to **TP12**, 2-iodopyrazine (103 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*R*)-20f** (1.43 mL, 0.42 M, 0.60 mmol, 1.20 equiv) were used as starting materials with catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) present. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*R*)-26f** as an orange highly viscous gel (148 mg, 0.49 mmol, 98% yield, 99.3% *ee*).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.45 (dd, *J* = 2.6, 1.5 Hz, 1H), 8.35 (d, *J* = 2.6 Hz, 1H), 8.06 (d, *J* = 1.5 Hz, 1H), 8.03 (s, 1H), 7.52 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.32 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.13 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.58 (t, *J* = 2.1 Hz, 2H), 6.06 (t, *J* = 2.1 Hz, 2H), 4.71 (dtd, *J* = 8.9, 7.2, 5.5 Hz, 1H), 3.41 – 3.24 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 154.2, 145.1, 144.1, 142.7, 136.1, 127.4, 122.8, 122.1, 119.6, 119.0, 118.5, 111.8, 111.3, 108.2, 60.6, 42.3, 32.3.

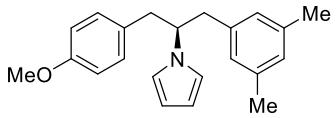
MS (EI, 70 eV, %): 302 (1), 235 (20), 208 (17), 207 (19), 172 (14), 131 (10), 130 (100), 128 (11), 94 (11).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{19}H_{18}N_4$]: 302.1531; found: 302.1522 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3406 (w), 3224 (w), 3056 (w), 2924 (w), 1488 (w), 1456 (m), 1404 (m), 1356 (w), 1336 (w), 1268 (w), 1228 (w), 1132 (w), 1090 (m), 1058 (m), 1018 (m), 926 (w), 826 (w), 738 (vs), 722 (vs), 666 (w).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –6.7.

(*S*)-1-(1-(3,5-Dimethylphenyl)-3-(4-methoxyphenyl)propan-2-yl)-1*H*-pyrrole ((*S*)-27a)



According to **TP12**, 1-iodo-3,5-dimethylbenzene (116 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*S*)-20g** (1.28 mL, 0.47 M, 0.60 mmol, 1.20 equiv) were used as starting materials with catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol,

4 mol% present. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-27a** a colorless liquid (152 mg, 0.48 mmol, 95% yield, 92.5% *ee*)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.88 – 6.83 (m, 3H), 6.80 – 6.75 (m, 2H), 6.61 (s, 2H), 6.58 (t, *J* = 2.1 Hz, 2H), 6.10 (t, *J* = 2.1 Hz, 2H), 4.18 (p, *J* = 7.1 Hz, 1H), 3.78 (s, 3H), 3.10 – 2.94 (m, 4H), 2.27 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.3, 138.2, 137.9, 130.5, 130.0, 128.2, 126.9, 119.1, 113.8, 107.6, 63.9, 55.3, 42.5, 41.5, 21.4.

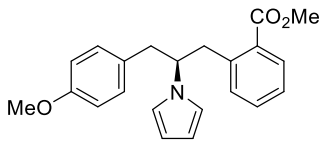
MS (EI, 70 eV, %): *m/z* = 319 (3), 198 (100), 183 (11), 169 (14), 131 (10), 119 (25).

HRMS (EI, 70 eV): *m/z* calcd. for $[C_{22}H_{25}NO]$: 319.1936; found: 319.1928 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3009 (w), 2916 (w), 2835 (w), 1608 (m), 1511 (vs), 1488 (m), 1464 (m), 1441 (m), 1245 (vs), 1178 (m), 1089 (m), 1034 (s), 840 (m), 719 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –16.6.

Methyl (*S*)-2-(3-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)propyl)benzoate ((*S*)-27b)



According to **TP12**, methyl 2-iodobenzoate (131 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*S*)-20g** (1.28 mL, 0.47 M, 0.60 mmol, 1.20 equiv) were used as starting materials with catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) present. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-27b** a colorless liquid (168 mg, 0.48 mmol, 96% yield, 92.5% *ee*).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.92 – 7.85 (m, 1H), 7.31 – 7.19 (m, 2H), 6.92 – 6.85 (m, 2H), 6.82 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.77 – 6.70 (m, 2H), 6.48 (t, *J* = 2.1 Hz, 2H), 6.00 (t, *J* = 2.1 Hz, 2H), 4.28 (dddd, *J* = 10.0, 8.4, 6.0, 4.5 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.65 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.22 (dd, *J* = 13.2, 9.5 Hz, 1H), 3.15 – 3.04 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 168.0, 158.2, 140.3, 132.0, 131.6, 130.9, 130.6, 130.0, 129.4, 126.7, 119.2, 113.7, 107.5, 64.0, 55.3, 52.1, 42.0, 41.5.

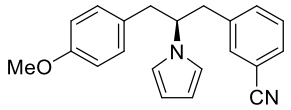
MS (EI, 70 eV, %): *m/z* = 349 (2), 228 (50), 197 (14), 196 (100), 168 (17), 167 (10).

HRMS (EI, 70 eV): *m/z* calcd. for $[C_{22}H_{23}NO_3]$ 349.1678; found: 349.1670 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2951 (w), 1715 (s), 1612 (w), 1512 (s), 1488 (m), 1434 (m), 1294 (m), 1244 (vs), 1178 (m), 1132 (m), 1082 (s), 1034 (m), 963 (w), 819 (m), 748 (m), 720 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +25.8.

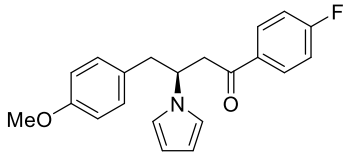
(*S*)-3-(3-(4-Methoxyphenyl)-2-(1*H*-pyrrol-1-yl)propyl)benzonitrile ((*S*)-27c)



According to **TP4**, 3-iodobenzonitrile (115 mg, 0.50 mmol, 1.00 equiv) and a freshly prepared solution of **(*S*)-20g** (1.28 mL, 0.47 M, 0.60 mmol, 1.20 equiv) were used as starting materials with catalytic amounts of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol% present. The reaction mixture was stirred at room temperature for 16 h and quenched sat. aq. NH_4Cl solution. Extraction of the crude product with EtOAc and flash column chromatography purification afforded **(*S*)-27c** a colorless liquid (147 mg, 0.47 mmol, 93% yield, 92.0% *ee*).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.45 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 1.8 Hz, 1H), 7.03 (dt, *J* = 8.0, 1.4 Hz, 1H), 6.95 – 6.90 (m, 2H), 6.82 – 6.77 (m, 2H), 6.50 (t, *J* = 2.1 Hz, 2H), 6.07 (t, *J* = 2.1 Hz, 2H), 4.12 (dddd, *J* = 8.9, 7.8, 6.6, 5.4 Hz, 1H), 3.78 (s, 3H), 3.17 – 2.97 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.5, 139.7, 133.4, 132.5, 130.4, 130.0, 129.8, 129.2, 118.9, 118.9, 114.0, 112.4, 108.3, 77.5, 77.2, 76.8, 63.6, 55.3, 42.0, 41.9.
MS (EI, 70 eV, %): *m/z* = 316 (15), 249 (13), 200 (48), 198 (11), 196 (14), 195 (100), 193 (32), 121 (36), 116 (24).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{21}H_{20}N_2O]$: 316.1576; found: 316.1567 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2935 (w), 2228 (m), 1612 (m), 1583 (w), 1512 (vs), 1487 (m), 1442 (w), 1301 (m), 1244 (vs), 1178 (m), 1090 (m), 1071 (m), 1033 (m), 939 (w), 920 (w), 819 (m), 797 (m), 722 (vs), 691 (s).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +7.3.

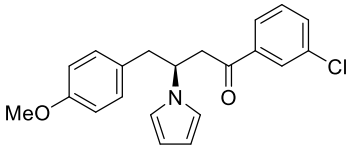
(*S*)-1-(4-Fluorophenyl)-4-(4-methoxyphenyl)-3-(1*H*-pyrrol-1-yl)butan-1-one ((*S*)-27d)



According to **TP13a**, a solution of **(*S*)-20g** (1.28 mL, 0.47 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 4-fluorobenzoyl chloride (79.3 mg, 0.50 mmol, 1.00 equiv) and $Pd(PPh_3)_4$ (23.1 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to afford the title compound **(*S*)-27d** as a colorless solid (131 mg, 0.39 mmol, 78% yield, 92.3% *ee*).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.95 – 7.85 (m, 2H), 7.16 – 7.06 (m, 2H), 6.95 – 6.86 (m, 2H), 6.82 – 6.72 (m, 2H), 6.65 (t, *J* = 2.2 Hz, 2H), 6.09 (t, *J* = 2.1 Hz, 2H), 4.81 (dq, *J* = 7.7, 6.4 Hz, 1H), 3.76 (s, 3H), 3.48 (dd, *J* = 17.0, 6.5 Hz, 1H), 3.35 (dd, *J* = 17.0, 6.6 Hz, 1H), 3.12 – 2.98 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 195.7, 166.0 (d, *J* = 255.4 Hz), 158.5, 133.2 (d, *J* = 3.0 Hz), 130.8 (d, *J* = 9.3 Hz), 130.2, 129.7, 119.2, 115.9 (d, *J* = 22.0 Hz), 113.9, 108.1, 57.5, 55.3, 44.1, 42.0.
^{19}F-NMR (377 MHz, $CDCl_3$, ppm): δ = –105.9.
MS (EI, 70 eV, %): *m/z* = 337 (2), 199 (13), 123 (100), 121 (15).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{21}H_{20}O_2NF$] 337.1478; found: 337.1473 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 1679 (s), 1594 (m), 1510 (m), 1490 (m), 1461 (m), 1371 (m), 1327 (m), 1300 (m), 1278 (m), 1247 (s), 1177 (m), 1159 (m), 1101 (m), 1073 (m), 1053 (w), 1029 (m), 998 (m), 939 (w), 846 (m), 822 (s), 813 (s), 714 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –28.1.
M.p. 81.3 °C.

(*S*)-1-(3-Chlorophenyl)-4-(4-methoxyphenyl)-3-(1*H*-pyrrol-1-yl)butan-1-one ((*S*)-27e)



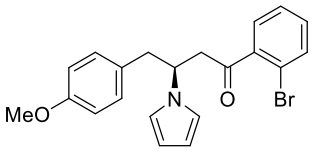
According to **TP13b**, CuI (9.52 mg, 0.05 mmol, 10 mol%) was added to a freshly prepared solution of **(*S*)-20g** (1.28 mL, 0.47 M, 0.60 mmol, 1.20 equiv) at 0 °C and the mixture stirred for 10 min before 3-chlorobenzoyl chloride (87.5 mg, 0.50 mmol, 1.00 equiv) was added dropwise. The reaction mixture stirred for 1 h at 0 °C and stirring was continued afterwards at room temperature for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography and the title compound **(*S*)-27e** was obtained as white solid (148 mg, 0.41 mmol, 84% yield, 92.8% ee).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.83 (t, *J* = 1.9 Hz, 1H), 7.73 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.0, 2.1, 1.0 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 6.96 – 6.87 (m, 2H), 6.81 – 6.71 (m, 2H), 6.66 (t, *J* = 2.1 Hz, 2H), 6.09 (t, *J* = 2.1 Hz, 2H), 4.81 (p, *J* = 6.8 Hz, 1H), 3.77 (s, 3H), 3.48 (dd, *J* = 17.1, 6.6 Hz, 1H), 3.35 (dd, *J* = 17.2, 6.5 Hz, 1H), 3.06 (d, *J* = 7.1 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 196.1, 158.5, 138.2, 135.1, 133.4, 130.2, 130.1, 129.6, 128.2, 126.2, 119.2, 114.0, 108.2, 57.4, 55.3, 44.3, 42.0.
MS (EI, 70 eV, %): *m/z* = 353 (2), 199 (19), 141 (34), 139 (100), 121 (25).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{21}H_{20}ClNO_2$] 353.1183; found: 353.1177 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 1673 (m), 1611 (m), 1513 (s), 1490 (m), 1419 (m), 1360 (w), 1276 (m), 1252 (s), 1210 (m), 1175 (m), 1093 (m), 1032 (m), 830 (m), 811 (m), 786 (s), 740 (m), 715 (vs), 691 (m), 674 (m).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –22.4.

M.p. 86.6 °C.

(*S*)-1-(2-Bromophenyl)-4-(4-methoxyphenyl)-3-(1*H*-pyrrol-1-yl)butan-1-one ((*S*)-27f)



According to **TP13b**, CuI (9.52 mg, 0.05 mmol, 10 mol%) was added to a freshly prepared solution of **(*S*)-20g** (1.28 mL, 0.47 M, 0.60 mmol, 1.20 equiv) at 0 °C and the mixture stirred for 10 min before 2-bromobenzoyl chloride (110 mg, 0.50 mmol, 1.00 equiv) was added dropwise. The reaction mixture stirred for 1 h at 0 °C and stirring was continued afterwards at room temperature for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography and the title compound **(*S*)-27f** was obtained as colorless liquid (149 mg, 0.37 mmol, 75% yield, 92.1% ee).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.61 – 7.52 (m, 1H), 7.35 – 7.22 (m, 2H), 7.10 – 7.01 (m, 1H), 6.94 – 6.85 (m, 2H), 6.81 – 6.73 (m, 2H), 6.58 (t, *J* = 2.1 Hz, 2H), 6.06 (t, *J* = 2.1 Hz, 2H), 4.73 (p, *J* = 7.3 Hz, 1H), 3.77 (s, 3H), 3.47 (dd, *J* = 17.0, 7.6 Hz, 1H), 3.37 (dd, *J* = 17.0, 6.3 Hz, 1H), 3.11 – 2.97 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 201.6, 158.5, 141.4, 133.7, 131.9, 130.2, 129.6, 128.6, 127.6, 119.3, 118.5, 114.0, 108.2, 57.9, 55.3, 48.5, 42.1.

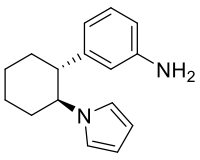
MS (EI, 70 eV, %): *m/z* = 397 (1), 185 (98), 183 (100), 121 (21).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{21}H_{20}BrNO_2$] 397.0677; found: 397.0671 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2935 (w), 1697 (m), 1612 (m), 1586 (w), 1511 (s), 1489 (m), 1465 (m), 1427 (m), 1357 (w), 1244 (vs), 1178 (m), 1110 (w), 1090 (m), 1068 (m), 1030 (s), 990 (m), 923 (w), 820 (m), 755 (m), 721 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –22.1.

(3-((1*R*,2*S*)-2-(1*H*-Pyrrol-1-yl)cyclohexyl)aniline ((*R*,*S*)-28a)



According to **TP12**, a solution of **(*S*)-20h** (1.54 mL, 0.39 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 2-bromoaniline (86.0 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash

column chromatography to afford the title compound **(*R*,*S*)-28a** as a yellow solid (111 mg, 0.46 mmol, 92% yield, 99.7% *ee*, *dr* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.97 (t, *J* = 7.8 Hz, 1H), 6.49 (t, *J* = 2.2 Hz, 2H), 6.48 – 6.43 (m, 3H), 6.31 (t, *J* = 2.0 Hz, 1H), 5.95 (t, *J* = 2.1 Hz, 2H), 3.87 (td, *J* = 11.5, 3.9 Hz, 1H), 3.32 (s, 2H), 2.80 – 2.63 (m, 1H), 2.24 – 2.14 (m, 1H), 2.05 – 1.94 (m, 2H), 1.93 – 1.81 (m, 2H), 1.72 – 1.60 (m, 1H), 1.58 – 1.39 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 146.2, 144.6, 129.1, 119.0, 117.4, 114.3, 113.4, 107.0, 63.8, 51.8, 34.9, 34.1, 26.1.

MS (EI, 70 eV, %): *m/z* = 241 (16), 240 (100), 239 (19), 173 (41), 158 (34), 144 (27), 134 (41), 132 (15), 130 (18), 121 (10), 120 (25), 119 (17), 118 (11), 107 (30), 106 (39), 81 (13), 79 (10).

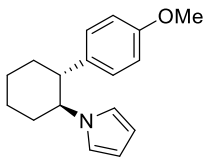
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{16}H_{20}N_2$]: 240.1626; found: 240.1622 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3359 (w), 2929 (s), 2855 (m), 1686 (w), 1607 (s), 1591 (m), 1490 (s), 1460 (m), 1447 (m), 1408 (w), 1272 (s), 1168 (w), 1090 (m), 1066 (m), 932 (w), 861 (w), 780 (m), 721 (vs), 698 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +98.4.

M.p. 88.5 °C.

1-((1*S*,2*R*)-2-(4-Methoxyphenyl)cyclohexyl)-1H-pyrrole ((*S*,*R*)-28b)



According to **TP12**, a solution of **(*S*)-20h** (1.54 mL, 0.39 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 4-iodoanisole (117 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to afford the title compound **(*S*,*R*)-28b** as colorless oil (107 mg, 0.42 mmol, 84% yield, 99.5% *ee*, *dr* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.96 – 6.89 (m, 2H), 6.75 – 6.68 (m, 2H), 6.46 (t, *J* = 2.1 Hz, 2H), 5.94 (t, *J* = 2.1 Hz, 2H), 3.83 (td, *J* = 11.5, 3.9 Hz, 1H), 3.73 (s, 3H), 2.76 (td, *J* = 11.6, 3.5 Hz, 1H), 2.19 (dtd, *J* = 12.8, 4.0, 2.1 Hz, 1H), 2.04 – 1.94 (m, 2H), 1.94 – 1.82 (m, 2H), 1.74 – 1.60 (m, 1H), 1.60 – 1.39 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.0, 135.5, 127.9, 118.9, 113.6, 107.0, 64.3, 55.2, 51.0, 35.0, 34.3, 26.2, 26.2.

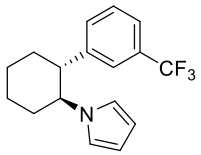
MS (EI, 70 eV, %): *m/z* = 256 (13), 255 (75), 254 (16), 189 (14), 188 (100), 173 (14), 160 (13), 159 (21), 147 (16), 134 (81), 121 (95), 120 (36), 115 (14), 106 (18), 91 (24), 82 (16), 81 (21), 80 (17).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{17}H_{21}NO$]: 255.1623; found: 255.1619 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2929 (m), 2855 (w), 1611 (w), 1512 (s), 1489 (m), 1461 (w), 1446 (m), 1286 (m), 1272 (m), 1247 (s), 1178 (m), 1089 (m), 1066 (w), 1034 (m), 997 (w), 959 (w), 822 (s), 716 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +122.7.

1-((1*S*,2*R*)-2-(3-(Trifluoromethyl)phenyl)cyclohexyl)-1*H*-pyrrole ((*S*,*R*)-28c)



According to a modified version of **TP12**, a solution of **(*S*)-20h** (4.31 mL, 0.39 M, 1.68 mmol, 1.20 equiv) was added dropwise to a solution of 3-iodobenzotrifluoride (381 mg, 1.40 mmol, 1.00 equiv), $Pd(OAc)_2$ (6.29 mg, 28.0 µmol, 2 mol%) and SPhos (23.0 mg, 56.0 µmol, 4 mol%) in dry THF (3 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to afford the title compound **(*S*,*R*)-28c** as a white solid (398 mg, 1.36 mmol, 97% yield, 99.9% *ee*, *dr* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.38 (ddt, *J* = 7.7, 1.8, 1.0 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.13 (dtd, *J* = 7.7, 1.3, 0.7 Hz, 1H), 6.42 (t, *J* = 2.1 Hz, 2H), 5.92 (t, *J* = 2.1 Hz, 2H), 3.86 (td, *J* = 11.4, 3.9 Hz, 1H), 2.88 (ddd, *J* = 12.1, 10.9, 3.5 Hz, 1H), 2.27 – 2.18 (m, 1H), 2.06 – 1.98 (m, 2H), 1.97 – 1.86 (m, 2H), 1.73 (dtd, *J* = 13.8, 12.4, 3.7 Hz, 1H), 1.63 – 1.42 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 144.3, 130.6 (q, *J* = 1.4 Hz), 130.5 (q, *J* = 31.9 Hz), 128.6, 124.3 (q, *J* = 272.3 Hz), 123.7 (q, *J* = 3.8 Hz), 123.4 (q, *J* = 3.9 Hz), 118.8, 107.6, 64.1, 51.9, 34.8, 33.7, 26.1, 26.1.

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -62.6.

MS (EI, 70 eV, %): *m/z* = 294 (19), 192 (100), 292 (25), 211 (14), 185 (11), 29 (), 134 (51), 120 (36), 106 (32), 81 (15), 80 (15), 68 (16).

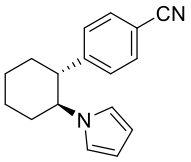
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{17}H_{18}F_3N$]: 293.1391; found: 293.1383 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2942 (w), 2861 (vw), 2358 (vw), 1489 (w), 1449 (w), 1329 (s), 1270 (w), 1195 (w), 1158 (s), 1119 (s), 1090 (s), 1074 (s), 961 (w), 916 (w), 804 (m), 722 (vs), 702 (s), 666 (w).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +45.6.

M.p. 80.9 °C.

4-((1*R*,2*S*)-2-(1*H*-Pyrrol-1-yl)cyclohexyl)benzonitrile ((*R*,*S*)-28d)



According to **TP12**, a solution of **(*S*)-20h** (1.54 mL, 0.39 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 4-iodobenzonitrile (115 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to afford the title compound **(*R*,*S*)-28d** as a yellowish solid (120 mg, 0.48 mmol, 96% yield, 99.8% *ee*, *dr* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.48 – 7.40 (m, 2H), 7.15 – 7.07 (m, 2H), 6.42 (t, *J* = 2.1 Hz, 2H), 5.91 (t, *J* = 2.1, 2H), 3.85 (td, *J* = 11.5, 3.9, 1H), 2.88 (td, *J* = 11.6, 3.5 Hz, 1H), 2.27 – 2.17 (m, 1H), 2.06 – 1.84 (m, 4H), 1.68 (qd, *J* = 12.6, 3.4 Hz, 1H), 1.60 – 1.41 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 148.9, 132.1, 127.9, 119.1, 118.7, 110.4, 107.6, 63.8, 52.2, 34.7, 33.6, 26.0, 25.9.

MS (EI, 70 eV, %): *m/z* = 251 (19), 250 (100), 249 (36), 183 (14), 169 (18), 168 (25), 154 (14), 142 (17), 140 (18), 134 (62), 121 (17), 120 (51), 116 (42), 115 (17), 106 (52), 93 (15), 89 (13), 81 (27), 80 (25), 79 (17), 68 (26), 67 (11).

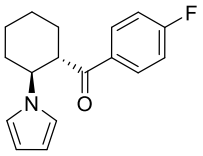
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{17}H_{18}N_2]$: 250.1470; found: 250.1467 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2932 (m), 2857 (w), 2225 (m), 1700 (vw), 1608 (m), 1504 (w), 1489 (m), 1448 (w), 1415 (w), 1300 (w), 1272 (m), 1090 (m), 1066 (w), 959 (w), 911 (vw), 826 (m), 720 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +158.9.

M.p. 94.8 °C.

(1*S*,2*S*)-2-(1*H*-Pyrrol-1-yl)cyclohexyl)(4-fluorophenyl)methanone ((*S*,*S*)-28e)



According to **TP13a**, a solution of **(*S*)-20h** (1.54 mL, 0.39 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 4-fluorobenzoyl chloride (79.3 mg, 0.50 mmol, 1.00 equiv) and $Pd(PPh_3)_4$ (23.1 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to

afford the title compound **(*S*,*S*)-28e** as a colorless solid (128 mg, 0.47 mmol, 94% yield, 99.8% *ee*, *dr* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.80 – 7.73 (m, 2H), 7.06 – 6.99 (m, 2H), 6.65 (t, *J* = 2.1 Hz, 2H), 5.95 (t, *J* = 2.1 Hz, 2H), 4.36 (ddd, *J* = 12.2, 10.6, 4.0 Hz, 1H), 3.68 (ddd, *J* = 11.9, 10.6, 3.6 Hz, 1H), 2.25 – 2.16 (m, 1H), 2.03 – 1.94 (m, 2H), 1.94 – 1.82 (m, 2H), 1.65 – 1.49 (m, 2H), 1.49 – 1.36 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 200.7, 165.84 (d, *J* = 254.9 Hz), 133.09 (d, *J* = 3.0 Hz), 130.64 (d, *J* = 9.3 Hz), 119.1, 115.68 (d, *J* = 21.9 Hz), 107.8, 59.5, 52.2, 33.7, 30.7, 25.5, 25.3.

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -105.3.

MS (EI, 70 eV, %): *m/z* = 123 (50), 148 (100), 149 (10), 175 (31), 271 (28).

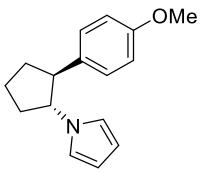
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{17}H_{18}FNO$]: 271.1372; found: 271.1366 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2934 (m), 2858 (w), 1674 (s), 1597 (s), 1506 (m), 1488 (m), 1410 (m), 1377 (w), 1300 (m), 1273 (m), 1234 (s), 1214 (s), 1156 (s), 1090 (m), 1060 (m), 984 (m), 947 (m), 838 (s), 746 (m), 716 (vs), 685 (m).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +45.6.

M.p. 63.2 °C.

1-((1*R*,2*S*)-2-(4-Methoxyphenyl)cyclopentyl)-1*H*-pyrrole ((*R*,*S*)-29a)



According to **TP12**, a solution of **(*R*)-20i** (1.25 mL, 0.48 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 4-iodoanisole (117 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to afford the title compound **(*R*,*S*)-29a** as yellowish solid (95 mg, 0.39 mmol, 79% yield, 99.2% *ee*, *dr* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.05 – 6.97 (m, 2H), 6.87 – 6.78 (m, 2H), 6.65 (t, *J* = 2.2 Hz, 2H), 6.12 (t, *J* = 2.2 Hz, 2H), 4.26 (q, *J* = 8.7 Hz, 1H), 3.79 (s, 3H), 3.19 (td, *J* = 9.8 Hz, 8.0, 1H), 2.45 – 2.31 (m, 1H), 2.25 (ddt, *J* = 12.5, 8.0, 4.2 Hz, 1H), 2.19 – 2.05 (m, 1H), 2.07 – 1.83 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.3, 134.7, 128.1, 119.0, 114.0, 107.8, 77.5, 77.2, 76.8, 67.8, 55.3, 52.5, 33.3, 32.7, 22.8.

MS (EI, 70 eV, %): *m/z* = 241 (5), 159 (10), 174 (100), 143 (19), 121 (10), 106 (6), 91 (5).

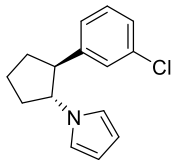
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{16}H_{19}NO$]: 241.1467; found: 241.1462 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2955 (w), 2907 (w), 2876 (w), 1612 (w), 1581 (w), 1514 (s), 1492 (m), 1461 (m), 1421 (w), 1324 (w), 1305 (w), 1278 (s), 1234 (s), 1176 (m), 1108 (w), 1088 (m), 1070 (m), 1026 (s), 982 (w), 825 (s), 722 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –165.1.

M.p. 55.6 °C.

1-((1*R*,2*S*)-2-(3-Chlorophenyl)cyclopentyl)-1*H*-pyrrole ((*R*,*S*)-29b)



According to **TP12**, a solution of **(*R*)-20i** (1.25 mL, 0.48 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 1-chloro-3-iodobenzene (119 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to afford the title compound **(*R*,*S*)-29b** as yellowish oil (114 mg, 0.46 mmol, 93% yield, 99.6% *ee*, *dr* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.22 – 7.12 (m, 2H), 7.09 (qd, *J* = 1.6, 1.0 Hz, 1H), 6.95 – 6.86 (m, 1H), 6.62 (t, *J* = 2.2 Hz, 2H), 6.12 (t, *J* = 2.2 Hz, 2H), 4.28 (dt, *J* = 9.6, 8.5 Hz, 1H), 3.20 (td, *J* = 9.8, 8.0 Hz, 1H), 2.38 (dtd, *J* = 13.2, 8.0, 5.4 Hz, 1H), 2.33 – 2.20 (m, 1H), 2.19 – 2.04 (m, 1H), 2.07 – 1.82 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 144.9, 134.4, 129.9, 127.1, 126.9, 125.7, 119.0, 108.1, 67.6, 53.1, 33.4, 32.6, 22.9.

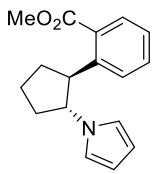
MS (EI, 70 eV, %): *m/z* = 245 (49), 178 (30), 143 (100), 106 (26), 68 (39).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{15}H_{16}ClN$]: 245.0971; found: 245.0966 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2961 (w), 2874 (w), 1596 (w), 1571 (w), 1489 (m), 1477 (m), 1452 (w), 1415 (w), 1325 (w), 1279 (m), 1090 (m), 1067 (m), 978 (w), 782 (m), 718 (vs), 691 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –183.0.

Methyl 2-((1*S*,2*R*)-2-(1*H*-pyrrol-1-yl)cyclopentyl)benzoate ((*S*,*R*)-29c)

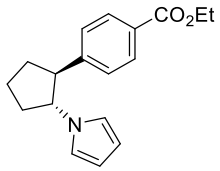


According to **TP12**, a solution of **(*R*)-20i** (1.25 mL, 0.48 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of methyl 2-iodobenzoate (131 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred 16 h.

After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to afford the title compound **(*S*,*R*)-29c** as a white solid (115 mg, 0.43 mmol, 85%, 99.9% *ee*, *d.r.* = 98:2).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.71 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.28 – 7.19 (m, 1H), 6.59 (t, *J* = 2.2 Hz, 2H), 6.04 (t, *J* = 2.2 Hz, 2H), 4.47 (q, *J* = 8.6 Hz, 1H), 4.32 (q, *J* = 9.3 Hz, 1H), 3.80 (s, 3H), 2.45 – 2.31 (m, 2H), 2.16 – 1.88 (m, 3H), 1.86 – 1.74 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 168.4, 144.0, 132.1, 131.1, 130.3, 126.7, 126.2, 119.1, 107.7, 67.2, 52.2, 47.8, 33.7, 33.6, 22.8.
MS (EI, 70 eV, %): *m/z* = 269 (23), 210 (100), 201 (53), 170 (58), 169 (35), 153 (38).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{17}H_{19}NO_2]$: 269.1416; found: 269.1408 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2965 (w), 2948 (w), 2872 (w), 1703 (vs), 1574 (w), 1493 (w), 1430 (m), 1296 (m), 1279 (m), 1237 (vs), 1184 (m), 1128 (m), 1099 (m), 1076 (s), 980 (w), 966 (w), 834 (w), 817 (w), 753 (m), 731 (vs), 709 (s).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –17.2.
M.p. 105.5 °C.

Ethyl 4-((1*S*,2*R*)-2-(1*H*-pyrrol-1-yl)cyclopentyl)benzoate ((*S*,*R*)-29d)



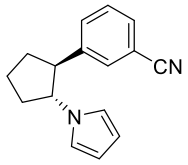
According to **TP12**, a solution of **(*R*)-20i** (1.25 mL, 0.48 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of ethyl 4-iodobenzoate (138 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to afford the title compound **(*S*,*R*)-29d** as colorless liquid (119 mg, 0.42 mmol, 84% yield, 99.3% *ee*, *dr* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.94 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.60 (t, *J* = 2.1 Hz, 2H), 6.09 (t, *J* = 2.1 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.30 (q, *J* = 8.8 Hz, 1H), 3.27 (td, *J* = 9.7, 8.1 Hz, 1H), 2.39 (dtd, *J* = 13.0, 7.9, 5.4 Hz, 1H), 2.28 (ddt, *J* = 12.0, 8.5, 4.7 Hz, 1H), 2.19 – 2.07 (m, 1H), 2.07 – 1.86 (m, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.6, 148.1, 129.9, 128.9, 127.2, 119.0, 108.1, 77.5, 77.2, 76.8, 67.7, 61.0, 53.5, 33.4, 32.5, 22.9, 14.5.
MS (EI, 70 eV, %): *m/z* = 283 (38), 216 (70), 187 (42), 143 (100), 128 (38), 120 (44), 115 (45), 106 (55), 94 (37), 68 (20).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{18}H_{21}NO_2]$: 283.1572; found: 283.1566 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2962 (w), 2876 (w), 1711 (s), 1610 (m), 1490 (m), 1451 (w), 1417 (w), 1367 (w), 1271 (vs), 1181 (m), 1102 (s), 1067 (m), 1020 (m), 978 (w), 852 (w), 770 (m), 720 (s), 705 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –250.6.

3-((1*S*,2*R*)-2-(1*H*-Pyrrol-1-yl)cyclopentyl)benzonitrile ((*S*,*R*)-29e)



According to **TP12**, a solution of **(*R*)-20i** (1.25 mL, 0.48 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 3-iodobenzonitrile (115 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to afford the title compound **(*S*,*R*)-29e** as a white solid (107 mg, 0.45 mmol, 91% yield, 99.8% *ee*, *dr* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.48 (dt, *J* = 7.7 Hz, 1.4, 1H), 7.38 – 7.29 (m, 2H), 7.21 (dt, *J* = 8.0, 1.6 Hz, 1H), 6.59 (t, *J* = 2.1 Hz, 2H), 6.11 (t, *J* = 2.1 Hz, 2H), 4.24 (q, *J* = 8.7 Hz, 1H), 3.24 (td, *J* = 10.1, 7.9 Hz, 1H), 2.45 – 2.34 (m, 1H), 2.33 – 2.23 (m, 1H), 2.20 – 1.82 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 144.1, 131.9, 130.6, 130.4, 129.4, 119.0, 118.9, 112.6, 108.4, 67.6, 52.9, 33.2, 32.0, 22.7.

MS (EI, 70 eV, %): *m/z* = 236 (83), 168 (100), 120 (37), 106 (42), 94 (30), 68 (42).

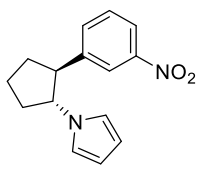
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{15}H_{16}N_2]$: 236.1313; found: 236.1308 ($[M]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2960 (w), 2944 (w), 2873 (w), 2227 (w), 1581 (w), 1492 (m), 1471 (w), 1435 (w), 1408 (w), 1332 (w), 1278 (m), 1098 (m), 1064 (w), 978 (w), 915 (w), 900 (w), 832 (w), 797 (m), 728 (vs), 694 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –199.9.

M.p. 57.7 °C.

1-((1*R*,2*S*)-2-(3-Nitrophenyl)cyclopentyl)-1*H*-pyrrole ((*R*,*S*)-29f)



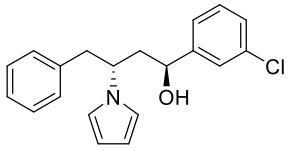
According to **TP12**, a solution of **(*R*)-20i** (1.25 mL, 0.48 M, 0.60 mmol, 1.20 equiv) was added dropwise to a solution of 1-iodo-3-nitrobenzene (125 mg, 0.50 mmol, 1.00 equiv), $Pd(OAc)_2$ (2.25 mg,

10.0 µmol, 2 mol%) and SPhos (8.21 mg, 20.0 µmol, 4 mol%) in dry THF (1 mL) and stirred for 16 h. After quenching with sat. aq. NH_4Cl and extraction with EtOAc, the crude product was purified by flash column chromatography to afford the title compound **(*R*,*S*)-29f** as a yellowish solid (96 mg, 0.37 mmol, 75% yield, 99.6% *ee*, *dr* > 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.05 (ddd, *J* = 8.1, 2.3, 1.1 Hz, 1H), 8.00 (t, *J* = 2.0 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.26 (dt, *J* = 7.7, 1.4 Hz, 1H), 6.61 (t, *J* = 2.2 Hz, 2H), 6.11 (t, *J* = 2.2 Hz, 2H), 4.29 (q, *J* = 8.8 Hz, 1H), 3.33 (td, *J* = 9.9, 7.9 Hz, 1H), 2.48 – 2.36 (m, 1H), 2.32 (ddt, *J* = 11.9, 8.1, 4.4 Hz, 1H), 2.16 (ddd, *J* = 13.3, 8.4, 5.8 Hz, 1H), 2.11 – 1.90 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 148.5, 144.7, 134.0, 129.5, 121.9, 121.7, 118.9, 108.4, 67.7, 53.0, 33.2, 32.2, 22.6.
MS (EI, 70 eV, %): *m/z* = 256 (100), 239 (44), 128 (39), 120 (61), 115 (71), 106 (85), 94 (67), 68 (69).
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{15}H_{16}N_2O_2]$: 256.1212; found: 256.1206 ($[M]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 2952 (w), 2873 (vw), 1528 (m), 1511 (w), 1492 (w), 1346 (m), 1279 (m), 1094 (m), 1069 (w), 896 (vw), 860 (w), 831 (w), 806 (w), 733 (vs), 682 (m).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –162.8.
M.p. 55.8 °C.

3.7 Selective CBS-Reduction of Pyrrole-containing Ketones

(1*S*,3*R*)-1-(3-Chlorophenyl)-4-phenyl-3-(1H-pyrrol-1-yl)butan-1-ol ((*S*,*R*)-30a)



According to **TP14**, (*R*)-2-methyl-CBS-oxazaborolidine (41.6 mg, 0.15 mmol, 15 mol%) was dissolved in freshly distilled THF (3 mL) and the resulting solution was cooled down to 0 °C. $BH_3{\cdot}SMe_2$ (83.6 mg, 1.10 mmol, 1.10 equiv) was added dropwise and the mixture stirred for 15 min. **(*R*)-24f** (323 mg, 1.00 mmol, 1.00 equiv) was dissolved in freshly distilled THF (3 mL) and added to the reaction mixture *via* syringe-pump over a period of 1 h at 0 °C. After complete addition, stirring was continued for 1h at 0 °C and for 2 h at room temperature. The reaction was quenched with methanol, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography to yield **(*S*,*R*)-30a** as a colorless oil (310 mg, 0.95 mmol, 95% yield, 99.9% *ee*, *d.r.* = 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.26 – 7.18 (m, 6H), 7.11 – 7.07 (m, 1H), 6.98 (d, *J* = 1.9 Hz, 1H), 6.98 – 6.95 (m, 1H), 6.68 (t, *J* = 2.1 Hz, 2H), 6.16 (t, *J* = 2.1 Hz, 2H), 4.49 (dddd, *J* = 10.5, 8.4, 6.0, 4.2 Hz, 1H), 4.19 (dd, *J* = 9.6, 3.3 Hz, 1H), 3.08 (dd, *J* = 13.7, 8.4 Hz, 1H), 2.97 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.15 – 2.00 (m, 2H), 1.79 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 146.8, 138.1, 134.5, 129.9, 129.0, 128.5, 127.8, 126.7, 125.8, 123.7, 119.2, 108.2, 70.1, 58.6, 45.3, 43.6.

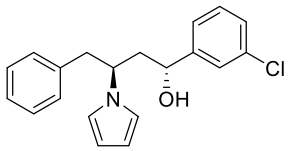
MS (EI, 70 eV, %): *m/z* = 325 (8), 171 (100), 141 (28), 139 (44), 113 (11), 111 (13), 104 (25), 94 (92), 93 (13), 91 (24), 77 (36), 68 (14).

HRMS (EI, 70 eV): *m/z* calcd. for [$C_{20}H_{20}ClNO$]: 325.1233; found: 325.1231.

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3437 (w, br), 3028 (w), 2920 (w), 1598 (w), 1574 (w), 1489 (m), 1477 (w), 1454 (w), 1432 (w), 1416 (m), 1333 (w), 1270 (m), 1202 (w), 1089 (m), 1068 (m), 1057 (m), 1030 (w), 957 (w), 787 (m), 754 (m), 725 (s), 699 (vs).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +33.8.

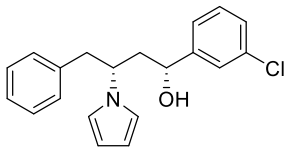
(1*R*,3*S*)-1-(3-Chlorophenyl)-4-phenyl-3-(1*H*-pyrrol-1-yl)butan-1-ol ((*R*,*S*)-30b)



According to **TP14**, (*S*)-2-methyl-CBS-oxazaborolidine (20.8 mg, 0.08 mmol, 15 mol%) was dissolved in freshly distilled THF (1.5 mL) and the resulting solution was cooled down to 0 °C. BH_3·SMe_2 (41.7 mg, 0.55 mmol, 1.10 equiv) was added dropwise and the mixture stirred for 15 min. **(*S*)-24f** (162 mg, 0.50 mmol, 1.00 equiv) was dissolved in freshly distilled THF (1.5 mL) and added to the reaction mixture *via* syringe-pump over a period of 1 h at 0 °C. After complete addition, stirring was continued for 1h at 0 °C and for 2 h at room temperature. The reaction was quenched with methanol, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography to yield **(*S*,*R*)-30b** as a colorless oil (153 mg, 0.47 mmol, 94% yield, 99.7% *ee*, *d.r.* = 99:1).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –43.4.

(1*R*,3*R*)-1-(3-Chlorophenyl)-4-phenyl-3-(1*H*-pyrrol-1-yl)butan-1-ol ((*R*,*R*)-30c)

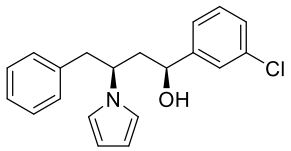


According to **TP14**, (*S*)-2-methyl-CBS-oxazaborolidine (20.8 mg, 0.08 mmol, 15 mol%) was dissolved in freshly distilled THF (1.5 mL) and the resulting solution was cooled down to 0 °C. BH_3·SMe_2 (41.7 mg, 0.55 mmol, 1.10 equiv) was added dropwise and the mixture stirred for 15 min. **(*R*)-24f** (162 mg, 0.50 mmol, 1.00 equiv) was dissolved in freshly distilled THF (1.5 mL) and added to the reaction mixture *via* syringe-pump over a period of 1 h at 0 °C. After complete addition, stirring was continued for 1h at 0 °C and for 2 h at room temperature. The reaction was quenched with methanol,

the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography to yield **(*R*,*R*)-30c** as a colorless oil (150 mg, 0.46 mmol, 92% yield, 99.4% *ee*, *d.r.* = 99:1).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.28 – 7.26 (m, 2H), 7.24 (s, 1H), 7.22 – 7.20 (m, 1H), 7.20 – 7.18 (m, 2H), 7.10 – 7.06 (m, 1H), 6.91 – 6.86 (m, 2H), 6.59 (t, *J* = 2.1 Hz, 2H), 6.15 (t, *J* = 2.1 Hz, 2H), 4.46 (td, *J* = 7.0, 2.1 Hz, 1H), 3.96 – 3.85 (m, 1H), 3.07 – 2.95 (m, 2H), 2.41 (ddd, *J* = 14.2, 9.9, 6.6 Hz, 1H), 2.16 (ddd, *J* = 14.1, 7.3, 4.7 Hz, 1H), 1.74 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 145.6, 137.7, 134.7, 130.0, 129.0, 128.5, 128.3, 126.8, 126.6, 124.7, 119.0, 108.5, 71.9, 59.2, 44.3, 43.6.
MS (EI, 70 eV, %): *m/z* = 325 (7), 234 (13), 172 (11), 171 (91), 141 (25), 139 (39), 111 (11), 104 (19), 94 (100), 93 (11), 91 (22), 77 (34), 68 (12).
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{20}H_{20}ClNO$]: 325.1233; found: 325.1226 ([M]$^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3389 (w, br), 3062 (vw), 3028 (vw), 2948 (w), 2923 (w), 1597 (w), 1574 (w), 1489 (m), 1433 (w), 1328 (w), 1271 (m), 1201 (w), 1089 (m), 1064 (m), 1028 (w), 886 (w), 788 (m), 751 (m), 722 (s), 697 (vs).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): +34.9.

(1*R*,3*S*)-1-(3-Chlorophenyl)-4-phenyl-3-(1*H*-pyrrol-1-yl)butan-1-ol ((*S*,*S*)-30d)



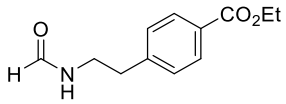
According to **TP14**, (*R*)-2-methyl-CBS-oxazaborolidine (20.8 mg, 0.08 mmol, 15 mol%) was dissolved in freshly distilled THF (1.5 mL) and the resulting solution was cooled down to 0 °C. BH_3·SMe_2 (41.7 mg, 0.55 mmol, 1.10 equiv) was added dropwise and the mixture stirred for 15 min. **(*S*)-24f** (162 mg, 0.50 mmol, 1.00 equiv) was dissolved in freshly distilled THF (1.5 mL) and added to the reaction mixture *via* syringe-pump over a period of 1 h at 0 °C. After complete addition, stirring was continued for 1h at 0 °C and for 2 h at room temperature. The reaction was quenched with methanol, the solvents were removed *in vacuo* and the crude product was purified by flash column chromatography to yield **(*S*,*S*)-30d** as a colorless oil (160 mg, 0.49 mmol, 98% yield, 99.4% *ee*, *d.r.* = 99:1).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –41.6.

3.8 Deprotection of Pyrrole-Derivatives using Ozonolysis

General remark: All deprotected products contain a mono-formamides moiety as a mixture of the *cis* and the *trans* conformation.[141] The NMR values stated are for the major conformer.

Ethyl 4-(2-formamidoethyl)benzoate (31a)



According to **TP15**, **21c** (243 mg, 1.00 mmol, 1.00 equiv) was dissolved in 8 mL DCM and 2 mL methanol and cooled to –78 °C. Ozone was passed through for 5 min followed by nitrogen for 10 min. Dimethyl sulfide (621 mg, 10.0 mmol, 10.0 equiv) was added and the reaction mixture stirred for 6 h at room temperature. After evaporation of the solvents, the residue was stirred for 1 h in 10 mL KOH in ethanol (0.1 M) and afterwards ethanol removed under reduced pressure. The crude product was purified by *via* flash column chromatography purification and the title compound **31a** (158 mg, 0.71 mmol, 71% yield) was obtained as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6, ppm): *major conformer* δ = 8.14 – 8.02 (m, 1H), 7.97 (d, *J* = 1.7 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.42 – 7.32 (m, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.35 (q, *J* = 6.9 Hz, 3H), 2.80 (t, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, DMSO-d_6, ppm): *major conformer* δ = 165.7, 161.1, 145.1, 129.2, 129.1, 127.9, 60.6, 38.3, 35.0, 14.2.

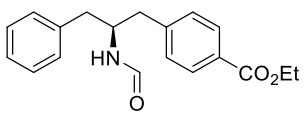
MS (EI, 70 eV, %): *m/z* = 221 (5), 177 (13), 176 (100), 164 (23), 148 (49), 136 (37), 135 (21), 132 (13), 131 (90), 118 (21), 107 (15), 103 (15), 91 (32), 90 (31), 89 (20), 77 (18), 58 (18).

HRMS (ESI): *m/z* calcd. for [M+H, $C_{12}H_{16}NO_3^+$]: 222.1125; found: 222.1124.

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3236 (w), 3055 (w), 2982 (w), 1705 (s), 1685 (w), 1655 (s), 1610 (m), 1541 (m), 1440 (m), 1382 (m), 1364 (m), 1278 (vs), 1241 (s), 1177 (s), 1121 (s), 1105 (s), 1045 (m), 1026 (m), 851 (m), 782 (s), 765 (m), 704 (s).

M.p. 65.5 °C.

Ethyl (*S*)-4-(2-formamido-3-phenylpropyl)benzoate ((*S*)-31b)



According to **TP15**, **(*S*)-24c** (334 mg, 1.00 mmol, 1.00 equiv) was dissolved in 8 mL DCM and 2 mL methanol and cooled to –78 °C. Ozone was passed through for 5 min followed by nitrogen for 10 min. Dimethyl sulfide (621 mg, 10.0 mmol, 10.0 equiv) was added and the reaction mixture stirred for 6 h

[141] M. J. Deetz, J. E. Fahey, B. D. Smith, *J. Phys. Org. Chem.* **2001**, *14*, 463.

at room temperature. After evaporation of the solvents, the residue was stirred for 1 h in 10 mL KOH in ethanol (0.1 M) and afterwards ethanol removed under reduced pressure. The crude product was purified by *via* flash column chromatography purification and the title compound **(*S*)-31b** (230 mg, 0.74 mmol, 74% yield, 99.5% *ee*) was obtained as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): *major conformer* δ = 8.06 – 7.95 (m, 3H), 7.38 – 7.13 (m, 7H), 5.49 (d, *J* = 7.4 Hz, 1H), 4.58 (sext, *J* = 7.3 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.04 – 2.73 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): *major conformer* δ = 166.6, 160.8, 143.2, 137.4, 129.9, 129.5, 129.4, 129.4, 128.7, 126.9, 61.0, 50.3, 40.1, 14.4.

MS (EI, 70 eV, %): *m/z* = 311 (1), 267 (17), 266 (100), 221 (16), 220 (32), 193 (38), 192 (33), 174 (35), 164 (24), 148 (61), 120 (89), 119 (12), 103 (20), 91 (52), 77 (12).

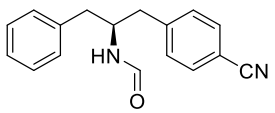
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{19}H_{21}NO_3$]: 311.1521; found: 311.1520 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3272 (w), 3029 (w), 2981 (w), 2928 (w), 2856 (vw), 1712 (s), 1659 (s), 1610 (m), 1496 (w), 1444 (w), 1416 (w), 1386 (m), 1366 (m), 1311 (w), 1273 (vs), 1178 (m), 1103 (s), 1021 (m), 911 (w), 853 (w), 759 (m), 732 (m), 699 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –1.6.

M.p. 127.8 °C.

(*S*)-*N*-(1-(4-Cyanophenyl)-3-phenylpropan-2-yl)formamide ((*S*)-31c)



According to **TP15**, **(*S*)-24d** (286 mg, 1.00 mmol, 1.00 equiv) was dissolved in 8 mL DCM and 2 mL methanol and cooled to –78 °C. Ozone was passed through for 5 min followed by nitrogen for 10 min. Dimethyl sulfide (621 mg, 10.0 mmol, 10.0 equiv) was added and the reaction mixture stirred for 6 h at room temperature. After evaporation of the solvents, the residue was stirred for 1 h in 10 mL KOH in ethanol (0.1 M) and afterwards ethanol removed under reduced pressure. The crude product was purified by *via* flash column chromatography purification and the title compound **(*S*)-31c** (172 mg, 0.74 mmol, 65% yield, 99.9% *ee*) was obtained as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): *major conformer* δ = 8.02 (s, 1H), 7.65 – 7.55 (m, 2H), 7.35 – 7.22 (m, 5H), 7.23 – 7.13 (m, 2H), 5.52 (d, *J* = 6.4 Hz, 1H), 4.56 (sext, *J* = 7.6 Hz, 1H), 3.05 – 2.72 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): *major conformer* δ = 160.8, 143.7, 137.1, 132.4, 130.2, 129.3, 128.8, 127.0, 118.9, 110.6, 50.2, 40.3, 40.2.

MS (EI, 70 eV, %): *m/z* = 264 (1), 220 (16), 219 (100), 218 (15), 173 (42), 148 (32), 145 (69), 128 (29), 120 (62), 117 (11), 116 (19), 103 (17), 91 (50), 89 (14), 77 (15), 65 (15).

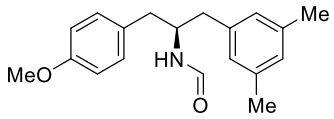
HRMS (EI, 70 eV): *m/z* calcd. for [$C_{17}H_{16}N_2O$]: 264.1263; found: 264.1260 ([M]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3265 (w), 3029 (w), 2923 (w), 2857 (w), 2226 (m), 1661 (vs), 1607 (m), 1540 (m), 1506 (m), 1496 (m), 1454 (m), 1387 (m), 1252 (w), 734 (w), 701 (m).

[α]$_D^{20}$ (CHCl$_3$, °·mL·dm^{-1}·g^{-1}): +1.2.

M.p. 137.6 °C.

(*S*)-*N*-(1-(3,5-Dimethylphenyl)-3-(4-methoxyphenyl)propan-2-yl)formamide ((*S*)-31d)



According to **TP15**, **(*S*)-27a** (160 mg, 0.50 mmol, 1.00 equiv) was dissolved in 4 mL DCM and 1 mL methanol and cooled to –78 °C. Ozone was passed through for 5 min followed by nitrogen for 10 min. Dimethyl sulfide (311 mg, 5.00 mmol, 10.0 equiv) was added and the reaction mixture stirred for 6 h at room temperature. After evaporation of the solvents, the residue was stirred for 1 h in 5 mL KOH in ethanol (0.1 M) and afterwards ethanol removed under reduced pressure. The crude product was purified by *via* flash column chromatography purification and the title compound **(*S*)-31d** (92 mg, 0.31 mmol, 62% yield, 92.0% *ee*) was obtained as a white solid.

^{1}H-NMR (400 MHz, CDCl$_3$, ppm): *major conformer* δ = 8.04 (d, *J* = 1.7 Hz, 1H), 7.16 – 7.09 (m, 2H), 6.89 – 6.70 (m, 5H), 5.37 (d, *J* = 8.4 Hz, 1H), 4.47 (dt, *J* = 8.2, 6.6 Hz, 1H), 3.79 (s, 3H), 2.93 – 2.58 (m, 4H), 2.29 (s, 6H).

^{13}C-NMR (101 MHz, CDCl$_3$, ppm): *major conformer* δ = 160.8, 158.4, 138.1, 137.6, 130.4, 129.7, 128.4, 127.2, 114.0, 55.3, 50.5, 39.7, 38.9, 21.4.

MS (EI, 70 eV, %): *m/z* = 298 (1), 252 (100), 237 (49), 150 (10), 148 (47), 144 (11), 131 (27), 121 (29), 118 (12), 91 (17).

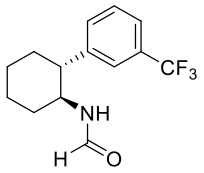
HRMS (EI, 70 eV): *m/z* calcd. for [M+H, $C_{19}H_{24}NO_2^+$]: 298.1802; found: 298.1801 ([M+H]$^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3296 (m), 2951 (w), 2917 (w), 2860 (w), 1659 (vs), 1608 (m), 1539 (m), 1511 (s), 1441 (m), 1385 (m), 1260 (m), 1240 (s), 1176 (m), 1109 (w), 1039 (s), 848 (m), 835 (m), 822 (m), 810 (m), 745 (m), 701 (s).

[α]$_D^{20}$ (CHCl$_3$, °·mL·dm^{-1}·g^{-1}): –1.1.

M.p. 91.3 °C.

***N*-((1*S*,2*R*)-2-(3-(Trifluoromethyl)phenyl)cyclohexyl)formamide ((*S*,*R*)-31e)**



According to **TP15**, **(*S*,*R*)-28c** (147 mg, 0.50 mmol, 1.00 equiv) was dissolved in 4 mL DCM and 1 mL methanol and cooled to –78 °C. Ozone was passed through for 5 min followed by nitrogen for 10 min. Dimethyl sulfide (311 mg, 5.00 mmol, 10.0 equiv) was added and the reaction mixture stirred for 6 h at room temperature. After evaporation of the solvents, the residue was stirred for 1 h in 5 mL KOH in ethanol (0.1 M) and afterwards ethanol removed under reduced pressure. The crude product was purified by *via* flash column chromatography purification and the title compound **(*S*,*R*)-31e** (100 mg, 0.37 mmol 74% yield, 99.8% *ee*, *dr* > 99:1) was obtained as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6, ppm): δ = 7.83 (d, *J* = 9.2, 1H), 7.69 (dd, *J* = 1.9, 0.7, 1H), 7.58 – 7.47 (m, 4H), 3.99 (qd, *J* = 11.1, 4.0, 1H), 2.62 (td, *J* = 11.9, 3.6, 1H), 1.92 – 1.84 (m, 1H), 1.83 – 1.67 (m, 3H), 1.62 – 1.21 (m, 4H).

^{13}C-NMR (101 MHz, DMSO-d_6, ppm): δ = 159.71, 145.61, 131.60, 128.96, 128.68 (q, *J* = 31.2), 124.38 (q, *J* = 272.3), 124.27 (q, *J* = 4.0), 122.83 (q, *J* = 3.9), 49.56, 48.79, 34.22, 33.45, 25.57, 24.81.

^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ = –60.9.

MS (EI, 70 eV, %): *m/z* = 272 (1), 227 (14), 226 (100), 211 (37), 206 (13), 172 (10), 159 (10), 129 (14).

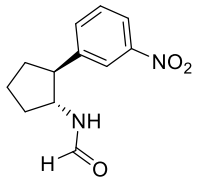
HRMS (EI, 70 eV): *m/z* calcd. for $[C_{14}H_{17}F_3NO]^+$: 272.1257; found: 272.1255 ($[M+H]^+$).

FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3251 (w), 3037 (w), 2936 (m), 2860 (m), 1678 (m), 1651 (s), 1543 (m), 1449 (m), 1384 (m), 1318 (s), 1233 (m), 1160 (s), 1114 (s), 1072 (s), 894 (m), 800 (s), 701 (s), 663 (m).

$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –15.2.

M.p. 89.3 °C

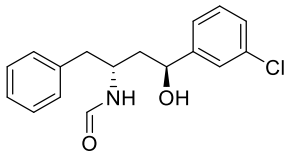
***N*-((1*R*,2*S*)-2-(3-Nitrophenyl)cyclopentyl)formamide ((*R*,*S*)-31f)**



According to **TP15**, **(*R*,*S*)-29f** (128 mg, 0.50 mmol, 1.00 equiv) was dissolved in 4 mL DCM and 1 mL methanol and cooled to –78 °C. Ozone was passed through for 5 min followed by nitrogen for 10 min. Dimethyl sulfide (311 mg, 5.00 mmol, 10.0 equiv) was added and the reaction mixture stirred for 6 h at room temperature. After evaporation of the solvents, the residue was stirred for 1 h in 5 mL KOH in ethanol (0.1 M) and afterwards ethanol removed under reduced pressure. The crude product was purified by *via* flash column chromatography purification and the title compound **(*R*,*S*)-31f** (82.0 mg, 0.35 mmol 71% yield, 99.3% *ee*, *dr* > 99:1) was obtained as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): *major conformer* δ = 8.12 – 8.01 (m, 2H), 8.04 (d, *J* = 1.2 Hz, 1H), 7.62 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.48 (q, *J* = 7.8 Hz, 1H), 5.87 (d, *J* = 8.1 Hz, 1H), 4.42 (p, *J* = 8.6 Hz, 1H), 2.99 (td, *J* = 9.8, 8.0 Hz, 1H), 2.36 – 2.13 (m, 2H), 1.98 – 1.53 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): *major is conformer* δ = 161.1, 148.4, 144.6, 133.5, 129.7, 122.7, 121.9, 56.0, 51.9, 32.9, 32.6, 22.4.
MS (EI, 70 eV, %): *m/z* = 235.1 (1), 189 (68), 172 (100), 142 (27), 128 (19), 115 (37), 107 (44), 77 (14).
HRMS (EI, 70 eV): *m/z* calcd. for$[C_{12}H_{15}N_2O_3]^+$: 235.1077; found: 235.1076 ($[M+H]^+$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3295 (w), 2948 (w), 2869 (w), 1650 (s), 1526 (vs), 1389 (m), 1345 (s), 1095 (w), 890 (w), 811 (w), 735 (m), 689 (m).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –56.6.
M.p. 110.7 °C.

***N*-((2*R*,4*S*)-4-(3-Chlorophenyl)-4-hydroxy-1-phenylbutan-2-yl)formamide ((*R*,*S*)-31g)**

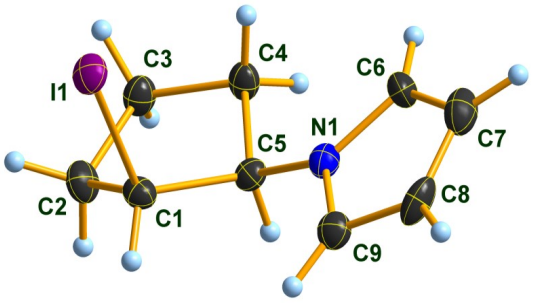


According to **TP15**, **(*S*,*R*)-30a** (244 mg, 0.75 mmol, 1.00 equiv) was dissolved in 12.5 mL DCM and 2.5 mL methanol and cooled to –78 °C. Ozone was passed through for 3 min followed by nitrogen for 5 min. Dimethyl sulfide (466 mg, 7.50 mmol, 10.0 equiv) was added and the reaction mixture stirred for 6 h at room temperature. After evaporation of the solvents, the residue was stirred for 1 h in 8 mL KOH in ethanol (0.1 M) and afterwards ethanol removed under reduced pressure. The crude product was purified by *via* flash column chromatography purification and the title compound **(*R*,*S*)-31g** (173 mg, 0.57 mmol 76% yield, 99% *ee*, *dr* = 99:1) was obtained as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): *major conformer* δ = 8.15 (d, *J* = 1.9 Hz, 1H), 7.33 (t, *J* = 1.7 Hz, 1H), 7.30 (dt, *J* = 8.1, 1.8 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.23 – 7.19 (m, 2H), 7.19 – 7.14 (m, 3H), 5.87 (d, *J* = 8.9 Hz, 1H), 4.64 (dd, *J* = 11.0, 2.5 Hz, 1H), 4.29 (s, 1H), 2.92 (dd, *J* = 14.1, 6.2 Hz, 1H), 2.82 (dd, *J* = 14.1, 7.5 Hz, 1H), 1.87 (ddd, *J* = 14.0, 11.0, 2.8 Hz, 1H), 1.64 (ddd, *J* = 13.9, 10.8, 2.6 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): *major is conformer* δ = 162.4, 146.0, 136.9, 134.4, 129.8, 129.2, 128.9, 127.5, 127.1, 126.0, 123.8, 69.4, 46.6, 44.9, 40.8.
MS (EI, 70 eV, %): *m/z* = 194 (19), 151 (14), 149 (35), 145 (13), 139 (19), 138 (18), 127 (13), 125 (33), 103 (38), 92 (12), 91 (100), 77 (25), 65 (20).
HRMS (ESI): *m/z* calcd. for [M+H; $C_{17}H_{19}ClNO_2^+$]: 304.1099; found: 304.1101 ([M+H]$^+$); calcd. for [M-H; $C_{17}H_{17}ClNO_2^-$]: 302.0953; found: 302.0954 ([M-H]$^-$).
FT-IR (Diamond-ATR, neat, cm^{-1}): ν = 3290 (m, br), 3063 (w), 3029 (w), 2917 (w), 1662 (vs), 1599 (m), 1574 (m), 1541 (m), 1497 (m), 1477 (w), 1454 (m), 1433 (m), 1385 (m), 1079 (w), 787 (m), 700 (s).
$[\alpha]_D^{20}$ ($CHCl_3$, °·mL·dm^{-1}·g^{-1}): –51.8.
M.p. 110.7 °C.

D. APPENDIX

Single Crystal Structure of 1-((1*R*,2*S*)-2-iodocyclopentyl)-1*H*-pyrrole ((*R*,*S*)-19i)

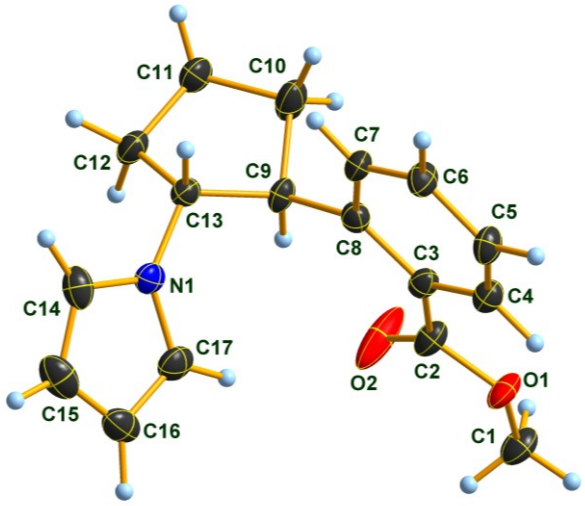


Molecular structure of compound **(*R*,*S*)-19i** in the crystal; thermal ellipsoids are drawn at 50% probability level.

Details for X-ray data collection and structure refinement for compound **(*R*,*S*)-19i.**

	(*R*,*S*)-19i		
Empirical formula	$C_9H_{12}IN$	$\rho_{calcd.}$ [g cm^{-3}]	1.892
Formula mass	261.10	μ [mm^{-1}]	3.430
T[K]	123(2)	*F*(000)	504
Crystal size [mm]	0.20 × 0.15 × 0.03	Θ range [°]	3.10 – 25.24
Crystal description	colorless platelet	Index ranges	$-9 \leq h \leq 9$
Crystal system	orthorhombic		$-14 \leq k \leq 14$
Space group	*P*212121		$-18 \leq l \leq 18$
a [Å]	6.7058(2)	Reflns. collected	18366
b [Å]	10.4137(3)	Reflns. obsd.	2608
c [Å]	13.1287(3)	Reflns. unique	2792 (R_{int} = 0.0444)
α [°]	90.0	R_1, wR_2 (2σ data)	0.0246, 0.0534
β [°]	90.0	R_1, wR_2 (all data)	0.0284, 0.0548
γ [°]	90.0	GOOF on F^2	1.065
V [Å^3]	916.81(4)	Peak/hole [e Å^{-3}]	0.892 / -0.506
Z	4	$\rho_{calcd.}$ [g cm^{-3}]	1.892

Single Crystal Structure of Methyl 2-((1*S*,2*R*)-2-(1*H*-pyrrol-1-yl)cyclopentyl)benzoate ((*S*,*R*)-29c)

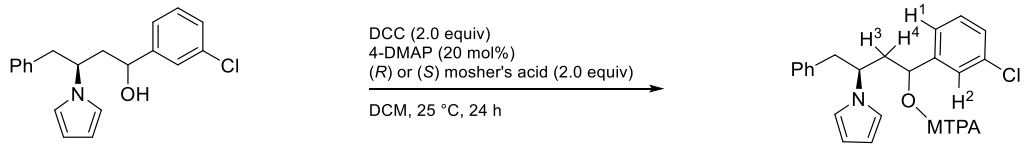


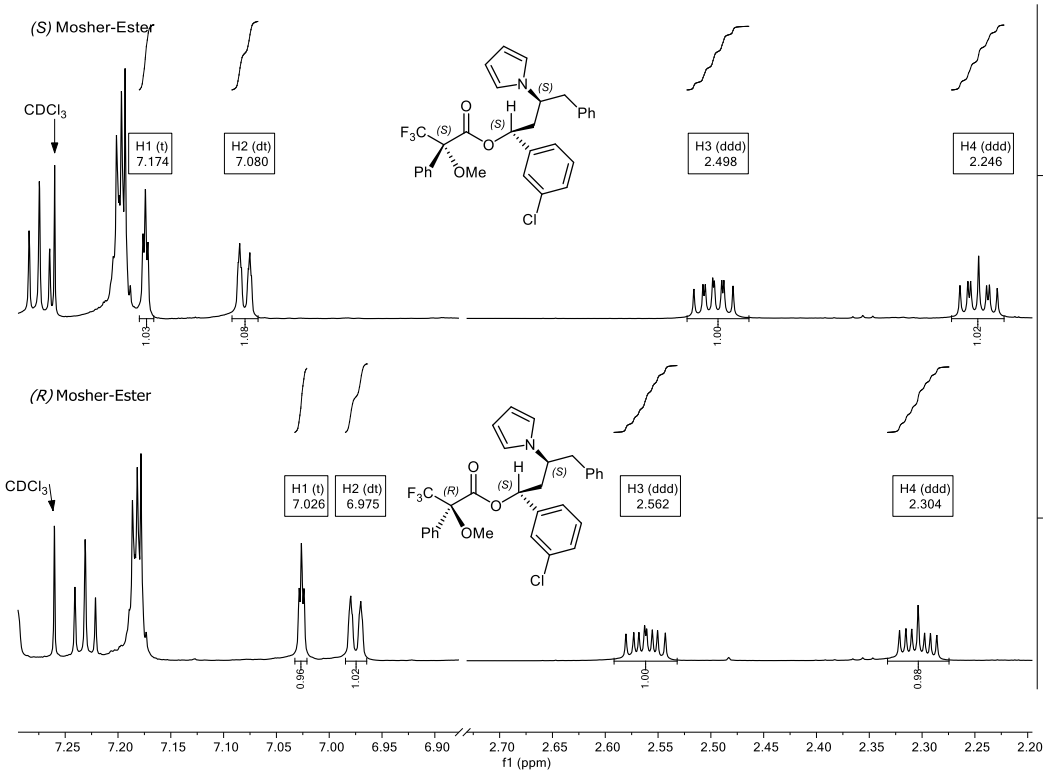
Molecular structure of compound **(*S*,*R*)-29c** in the crystal; thermal ellipsoids are drawn at 50% probability level.

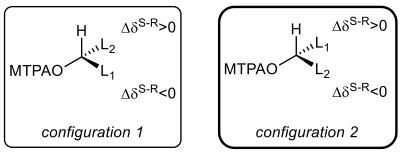
(*S*,*R*)-29c			
Empirical formula	$C_{17}H_{19}NO_2$	$\rho_{calcd.}$ [g cm^{-3}]	1.280
Formula mass	269.33	μ [mm^{-1}]	0.084
T[K]	123(2)	*F*(000)	576
Crystal size [mm]	0.20 × 0.10 × 0.02	Θ range [°]	2.46 – 25.24
Crystal description	colorless block	Index ranges	$-10 \leq h \leq 10$
Crystal system	orthorhombic		$-7 \leq k \leq 11$
Space group	*P*212121		$-19 \leq l \leq 19$
a [Å]	8.9810(8)	Reflns. collected	9514
b [Å]	9.6691(6)	Reflns. obsd.	1723
c [Å]	16.0885(12)	Reflns. unique	2647 (R_{int} = 0.0878)
α [°]	90.0	R_1, wR_2 (2σ data)	0.0581, 0.0802
β [°]	90.0	R_1, wR_2 (all data)	0.1090, 0.0952
γ [°]	90.0	GOOF on F^2	1.005
V [Å^3]	1397.10(18)	Peak/hole [e Å^{-3}]	0.203 / -0.199
Z	4	$\rho_{calcd.}$ [g cm^{-3}]	1.280

Mosher-Ester Analysis of (*R*,*S*)-30d using ^{1}H-NMR spectroscopy

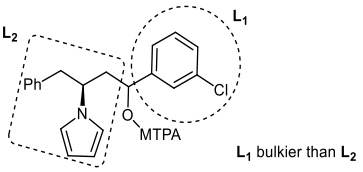
The analysis of the absolute configuration has been performed as reported in the literature[142]:





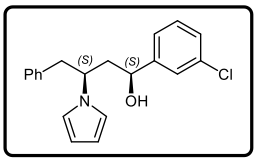


$$\Delta\delta^{S-R} = \delta^{S} - \delta^{R}$$



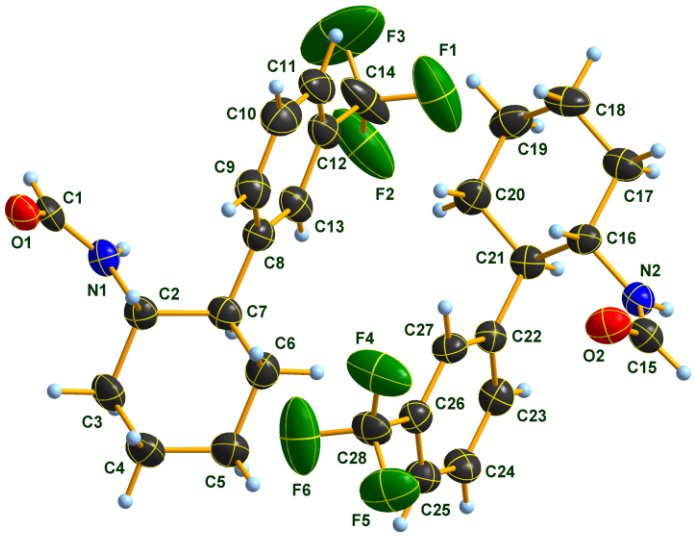
For L_1:	For L_2:
$\Delta\delta\ (H1)^{S-R} = 7.174 - 7.026 = 0.148\ > 0$	$\Delta\delta\ (H3)^{S-R} = 2.498 - 2.562 = -0.064 < 0$
$\Delta\delta\ (H2)^{S-R} = 7.080 - 6.975 = 0.105\ > 0$	$\Delta\delta\ (H4)^{S-R} = 2.246 - 2.304 = -0.058 <\ 0$

According to the $\Delta\delta$ shifts of both ^{1}H-NMR spectra, *configuration 2* fits. The $\Delta\delta$ values for L_1 protons are positive, therefore the L_1 residue must stand back. On the other hand, the $\Delta\delta$ values for the L_2 protons are negative, therefore the L_2 chain must stand in front. In conclusion the alcohol has an absolute (*S*) configuration as draw here:



[142] a) T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451; b) J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17.

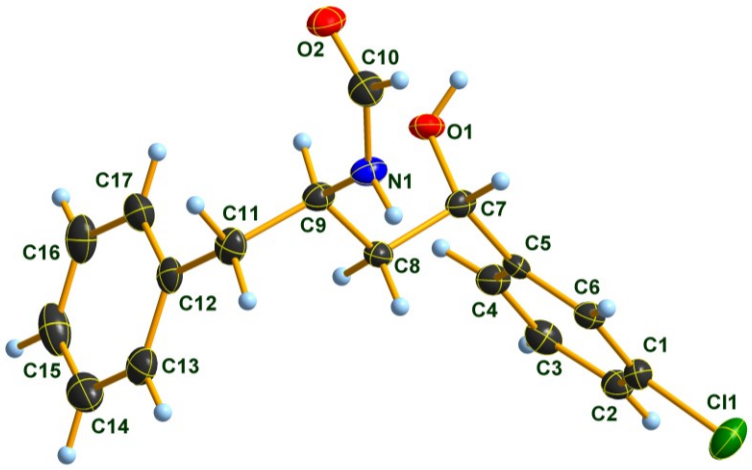
Single Crystal Structure of N-((1*S*,2*R*)-2-(3-(trifluoromethyl)phenyl)cyclohexyl)formamide ((*S*,*R*)-31e)



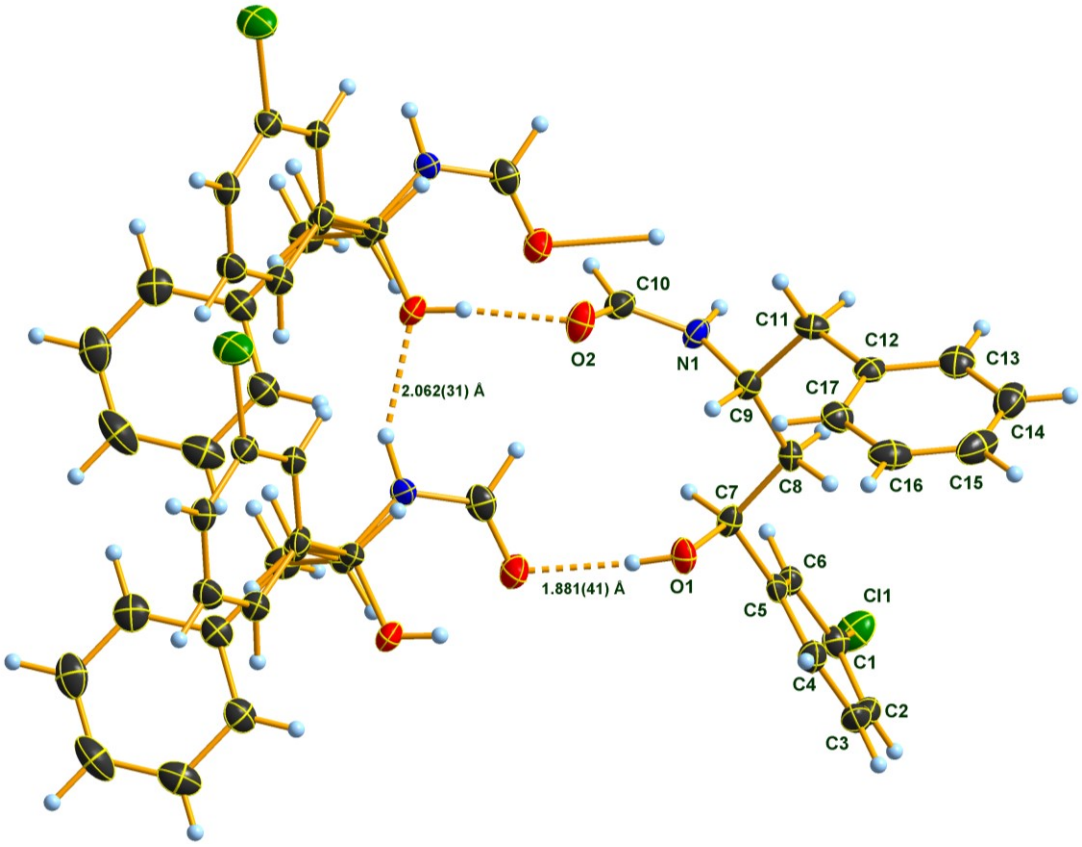
Molecular structure of compound **(*S*,*R*)-31e** in the crystal; thermal ellipsoids are drawn at 50% probability level. The fluorine atoms of both CF_3 groups are disordered. Splitting of the positions of the fluorine atoms did not result in a significant decrease of the R-values.

(*S*,*R*)-31e			
Empirical formula	$C_{14}H_{16}F_3NO$	Z	4
Formula mass	271.28	$\rho_{calcd.}$ [g cm^{-3}]	1.310
T[K]	123(2)	μ [mm^{-1}]	0.110
Crystal size [mm]	0.40 × 0.40 × 0.30	*F*(000)	568
Crystal description	colorless block	Θ range [°]	2.10 – 25.24
Crystal system	monoclinic	Index ranges	$-10 \leq h \leq 12$
Space group	*P*21		$-10 \leq k \leq 10$
a [Å]	9.9214(8)		$-19 \leq l \leq 17$
b [Å]	8.8541(5)	Reflns. collected	9015
c [Å]	16.0010(11)	Reflns. obsd.	3721
α [°]	90.0	Reflns. unique	5163
β [°]	101.894(8)	R_1, wR_2 (2σ data)	0.0626, 0.1358
γ [°]	90.0	R_1, wR_2 (all data)	0.0923, 0.1555
V [Å^3]	1375.43(17)	GOOF on F^2	1.026
		Peak/hole [e Å^{-3}]	0.392 / -0.262

Single Crystal Structure of *N*-((2*R*,4*S*)-4-(3-chlorophenyl)-4-hydroxy-1-phenylbutan-2-yl)formamide ((*R*,*S*)-31g)



Molecular structure of compound **(*R*,*S*)-31g** in the crystal; thermal ellipsoids are drawn at 50% probability level.



Hydrogen bonding in the crystal structure of compound **(*R*,*S*)-31g**; thermal ellipsoids are drawn at 50% probability level. Symmetry codes: -0.5+x, 1.5-y, -z; 0.5+x, 1.5-y, -z.

(*R*,*S*)-31g			
Empirical formula	$C_{17}H_{18}ClNO_2$	Z	4
Formula mass	303.77	$\rho_{calcd.}$ [g cm^{-3}]	1.303
T[K]	123(2)	μ [mm^{-1}]	0.250
Crystal size [mm]	0.40 × 0.05 × 0.05	*F*(000)	640
Crystal description	colorless rod	Θ range [°]	2.24 – 25.24
Crystal system	orthorhombic	Index ranges	$-6 \leq h \leq 7$
Space group	*P*212121		$-17 \leq k \leq 13$
a [Å]	6.0177(5)		$-22 \leq l \leq 18$
b [Å]	14.1572(17)	Reflns. collected	8907
c [Å]	18.1767(18)	Reflns. obsd.	2304
α [°]	90.0	Reflns. unique	3174 (R_{int} = 0.0616)
β [°]	90.0	R_1, wR_2 (2σ data)	0.0482, 0.0455
γ [°]	90.0	R_1, wR_2 (all data)	0.0775, 0.0527
V [Å^3]	1548.5(3)	GOOF on F^2	0.918