Late-Stage Peptide Functionalization by Ruthenium-Catalyzed C–H Arylations and Alkylations

Dissertation

for the award of the degree

“Doctor rerum naturalium”

of the Georg-August-Universität Göttingen

within the doctoral program of chemistry

of the Georg-August University School of Science (GAUSS)

Submitted by

Alexandra Schischko

From Shevchenko, Kazachstan

Göttingen, 2018

Thesis Committee

Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry

Prof. Dr. Dietmar Stalke, Institute of Inorganic Chemistry

Members of the Examination Board

Reviewer: Prof. Dr. Lutz Ackermann, Institute of Organic and Biomolecular Chemistry

Second reviewer: Prof. Dr. Dietmar Stalke, Institute of Inorganic Chemistry

Further Members of the Examination Board

Prof. Dr. Manuel Alcarazo

Dr. Franziska Thomas

Dr. Shoubhik Das

Dr. Alexander Breder

Date of the oral examination: October 24th, 2018

Contents

Acknowledgements

Mein herzlichster Dank geht an meinen Doktorvater Professor Lutz Ackermann für die Möglichkeit, an dieser Arbeit in seinem Arbeitskreis gearbeitet zu haben, und die stete Unterstützung durch wertvolle Gespräche und Ratschläge während dieser Zeit. Das von ihm gestellte Thema war für mich eine Herausforderung, die zu meiner persönlichen und fachlichen Weiterentwicklung beigetragen hat. Die hervorragende Ausstattung des Arbeitskreises gab mir viele Möglichkeiten und Freiheiten. Durch das hochinternationale Kollegium konnte ich mein gesprochenes Englisch verfeinern und viele wertvolle Kontakte und Freundschaften aufbauen. Das schätze ich ungemein.

Professor Dietmar Stalke danke für die Übernahme des Zweitgutachtens. Mein weiterer Dank geht an Professor Manuel Alcarazo, Dr. Franziska Thomas, Dr. Shoubhik Das und Dr. Alexander Breder für die Teilnahme an der Prüfungskommission.

I am very grateful to Jan, Mélanie, Nikos and Torben for the conscientious proofreading of this thesis.

Vielen Dank an Gabi für die Unterstützung in Verwaltungsangelegenheiten. Ebenfalls einen großen Dank an Stefan für die Unterstützung bei technischen Angelegenheiten. Karsten danke ich vielmals für das Management der Laborausstattung und für die Bereitstellung von selbstsynthetisierten Chemikalien und trockenen Lösungsmitteln.

Bei der analytischen Abteilung bedanke ich mich außerordentlich für die Messungen meiner Proben. Insbesondere danke ich Dr. Michael John für die Hilfe bei Strukturaufklärungen.

A huge thanks to the whole working group, especially to the people who worked with me on the same topic, Yingjun, Michaela, Hongjun and Nikos. It was an honor to have worked with you! And, our powerful cooperation was fruitful!

Also, I like to thank my lab mates for the support and the great time we had in and outside the lab, Jie, Korni, Janson, Michaela, Eloisa, Qingqing, Benz, Alex, Wei, Gandeepan, Chuan, Lada, Chris, Matteo, Mo and Ela.

Ganz besonders möchte ich mich bei Alex bedanken, der mir immer zur Seite stand, mich in schlechten Zeiten ermunterte und mich in guten Zeiten bei zahlreichen Unternehmungen mit bester Laune versorgte. Darko, я рада, что встретила тебя. Мы отлично провели время в Геттингене, до следующей встречи в ✱ Берлине! Auch unvergessen bleibt Jonas, den ich trotz der leider nur kurzen Zeit bei uns als Freund gewonnen und geschätzt habe. Daniel, my most beautiful friend, I miss you a lot.

Weiter bin ich sehr froh über und dankbar für das soziale Leben im Arbeitskreis, die Kanutouren, die Fussballturniere, die BBQs, die „Klassenfahrten“, die Weihnachtsfeiern, die Bowlingabende und vielem mehr.

Meinen Freunden danke ich für ihre Unterstützung und für die wundervolle Zeit, die wir zusammen verbringen. Meiner Mama und meinen Brüdern möchte ich danken für den immerwährenden Rückhalt in allen Lebensabschnitten. Ihr wart immer, auch in Abwesenheit, eine wichtige Stütze für mich. Und den liebevollsten Dank an dich, Jan, für alles, womit du mich täglich bescherst, deine verständnisvolle Art, deine Unterstützung, deine Liebe!

List of Abbreviations

2D	two-dimesional
3c-4e	three-center four-electron
δ	chemical shift
λ_{max}	wavelength at maximum intensity
AA	amino acid
Ac	acetyl
Ad	adamantyl
Alk	alkyl
AMLA	ambiphilic metal ligand activation
aq.	aqueous
Ar	aryl
arb.	arbitrary
ATR	attenuated total reflection
BIES	base-assisted intramolecular electrophilic substitution
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BODIPY	boron-dipyrromethene
br	broad
Bu	butyl
Bz	benzoyl
calcd	calculated
cat.	catalytic
Cbz	benzyloxycarbonyl
CMD	concerted metalation-deprotonation
cod	1,5-cyclooctadien
comp.	compound
conc.	concentration
Cp*	pentamethylcyclopentadienyl
C_q	quaternary carbon
Cy	cyclohexyl
d	doublet
DCE	1,2-dichloroethane
DG	directing group

DIC	*N*,*N*'-diisopropylcarbodiimide
DIEA	*N,N*-diisopropylethylamine
DMA	dimethylacetamide
DMEDA	*N*,*N*'-dimethylethylenediamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppm	bis(diphenylphosphino)methane
dr	diastereomeric ratio
dtbpy	4,4'-di-*tert*-butyl-2,2'-dipyridyl
ee	enantiomeric excess
EI	electron ionization
ESI	electrospray ionization
Et	ethyl
equiv	equivalents
Fmoc	9-fluorenylmethoxycarbonyl
FTICR	fourier transform ion cyclotron resonance
GPC	gel permeation chromatography
GVL	γ-valerolactone
Hal	halogen
HASPO	heteroatom-substituted secondary phosphine oxide
HBS	hydrogen bond surrogate
Hex	hexyl
HFIP	hexafluoroisopropanol
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectrometry
i	*iso*
I	intensity
ICK	inhibitory-cysteine knot
IES	internal electrophilic substitution
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazolinium
IntStd	internal standard
IR	infrared
isol.	isolated
J	coupling constant

KIE	kinetic isotope effect
LC-MS	liquid chromatography mass spectrometry
L	ligand
[M]	metal
m	multiplet
m	*meta*
M	molecular weight
m/z	mass to charge ratio
Me	methyl
Mes	2,4,6-trimethylphenyl
m. p.	melting point
MS	mass spectrometry
MTBE	*tert*-butyl methyl ether
MW	microwave
n	*normal*
n. d.	not detectable
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NP	nanoparticle
o	*ortho*
Oct	octyl
Oxyma	ethyl (hydroxyimino)cyanoacetate
p	*para*
p. a.	per analysis
Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
PEG	polyethylene glycol
Pent	pentyl
PG	protecting group
Ph	phenyl
Phth	phthaloyl
Pin	pinacol
Piv	pivalyl
Pr	propyl
PS	polystyrene
PTLC	preparative thin layer chromatography

PTM	posttranslational modification
py	pyridyl
pym	pyrimidyl
q	quartet
R	rest
RCM	ring-closing metathesis
RI	refractive index
RP	reversed phase
s	singlet
S_EAr	electrophilic aromatic substitution
SPO	secondary phosphine oxide
SPPS	solid phase peptide synthesis
SPS	solvent purification system
Su	succinimide
t	triplet
t	time
t-	*tert*-
T	temperature
TBAB	tetrabutylammonium bromide
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIS	triisopropylsilane
TLC	thin layer chromatography
TM	transition metal
tosyl	*para*-toluenesulfonyl
TPPTS	triphenylphosphine tris-(sulfonate)
TRIP	2,4,6-triisopropylphenyl
trityl	triphenylmethyl
Trt	triphenylmethyl
Ts	*para*-toluenesulfonyl
unsat.	unsaturated
UV	ultra violet
VIS	visible

List of the Three Letter Amino Acid Codes

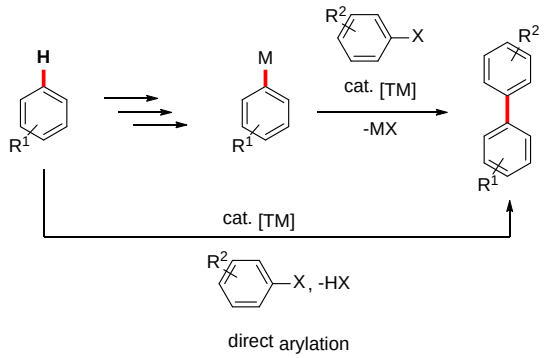
Ala	alanine
Arg	arginine
Asn	aspargine
Asp	aspartic acid
Cys	cysteine
Gln	glutamine
Glu	glutamic acid
Gly	glycine
His	histidine
Ile	isoleucine
Leu	leucine
Lys	lysine
Met	methionine
Phe	phenylalanine
Pro	proline
Ser	serine
Thr	threonine
Trp	tryptophan
Trp^{py}	*N'*-2-pyridyltryptophan
Tyr	tyrosine
Val	valine

1 Introduction

The conservation and sustainable management of resources is one of the main goals in chemical syntheses, which is to be adopted by chemists to increase the awareness for the environment.[1] In 1998, Anastas and Warner defined the "12 Principles of Green Chemistry", which guide the environmentally-benign processes of chemicals production.[2] Besides waste-reduction, avoidance of auxiliaries and temporary derivatizations during a synthesis, minimization of energy consumption and use of innocuous substances, atom- and step-economy, and the catalytic use of reagents rather than the utilization of stoichiometric amounts are fundamental requirements in nowadays syntheses. C–H activation is a tool in organic chemistry that leads contemporary chemical syntheses towards green and sustainable processes.

1.1 C–H Activation

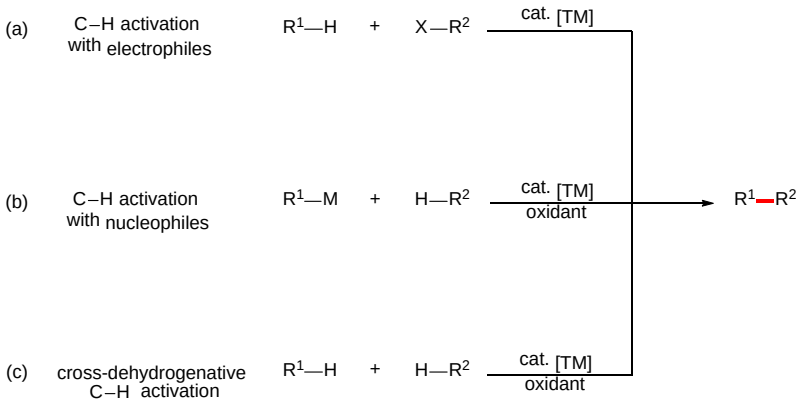
The traditional transition metal-catalyzed cross-coupling of organometallic reagents with organic (pseudo)halides has proven to be a powerful tool,[3] which was recognized with the Nobel Prize for chemistry in 2010. However, in cross-coupling reactions substrates need to be metalated to form the organometallic reagents by usually time-consuming and economically inefficient multi-step transformations (Scheme 1). The handling and storage of those organometallic compounds can be difficult. Additionally, during the cross-coupling reaction stoichiometric amounts of metal salts are formed as undesired by-products. To confront these disadvantages, catalytic C–H activation has been intensely studied in the last years.[4,5]



Scheme 1: Comparison between classical cross-coupling and direct arylation.

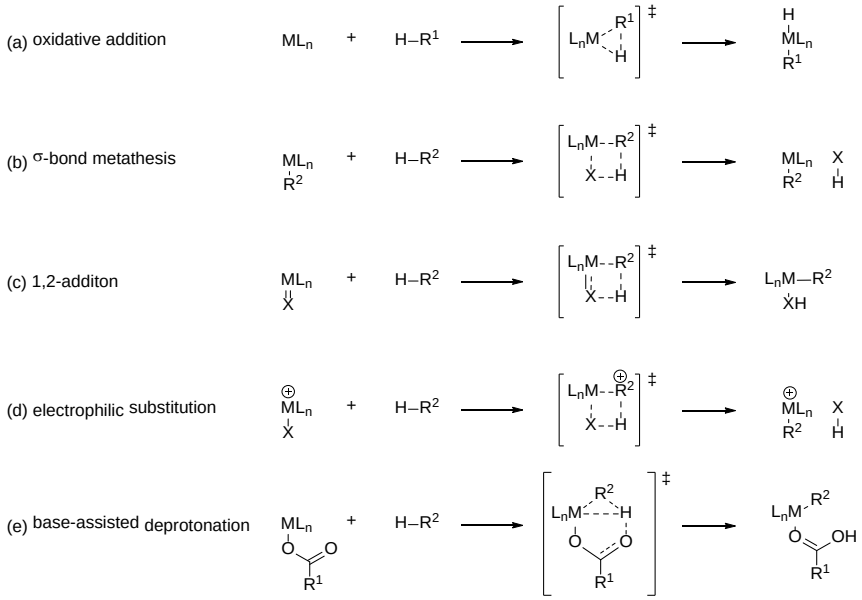
These reactions can be divided into three categories depending on the nature of the coupling partner of the C–H activated substrate (Scheme 2).[5d] The C–H bond can react with an aryl (pseudo)halide as

an electrophile or with an organometallic reagent as a nucleophile. Furthermore, a cross-dehydrogenative coupling reaction is possible. The latter two reaction types require stoichiometric oxidants.

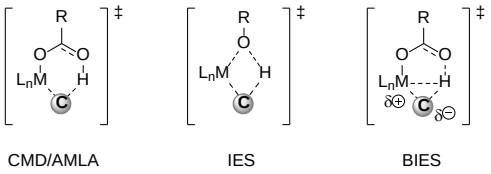


Scheme 2: Comparison of C–H activation strategies.[5d]

The concept of C–H activation implies the direct C–H metalation by the active catalyst.[6] Mechanistic studies mainly displayed five distinct pathways regarding the crucial C–H metalation step (Scheme 3).[7] For electron-rich, low-valent late transition metals, such as iridium, the oxidative addition (a) is often preferred. Since early transition metals with d^0-configuration do usually not undergo an oxidative addition, they can activate the C–H bond via a σ-bond metathesis (b). In a similar pathway the C–H bond is cleaved via a 1,2-addition (c) to an unsaturated TM=X multiple bond. This mechanism is typical for group III to V transition metals. The electrophilic substitution (d), where the transition metal acts as a Lewis acid, commonly occurs with electron-deficient late transition metals, such as palladium(II), platinum(II) or platinum(IV). The base-assisted deprotonation (e) requires a bidentate base, such as a carboxylate or a secondary phosphine oxide (SPO), to form a six- or five-membered transition state, respectively. This mechanism can either be termed concerted metalation-deprotonation (CMD) or ambiphilic metal ligand activation (AMLA, Scheme 4).[8] In the presence of alkoxy ligands transition metals are favored to undergo an internal electrophilic substitution (IES) based on a four-membered transition state. An additional mechanism is the base-assisted intramolecular electrophilic substitution (BIES), which is prevalent for base assistance with electrophilic transition metals.[9]

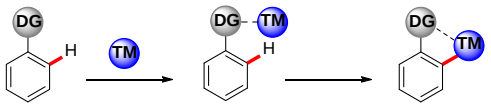


Scheme 3: Pathways for the C–H activation step.

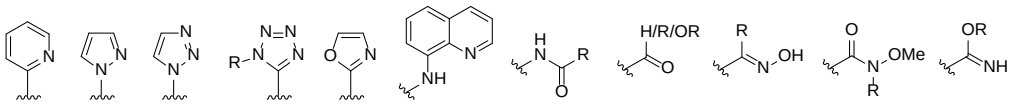


Scheme 4: Base-assisted metalation.

One of the key obstacles for C–H activation reactions is the regioselectivity, since organic molecules usually contain several C–H bonds with almost equal dissociation energies and acidities. This issue can be circumvented by controlling the selectivity through electronic bias, steric hindrance or the incorporation of directing groups.[10] The latter consist of Lewis basic functionalities, which precoordinate to the transition metal, and thus bring it in close proximity to the desired C–H bond (Scheme 5). Today, many different directing groups have been established (Scheme 6).[11]



Scheme 5: Regioselective C–H activation using directing groups. DG: directing group.

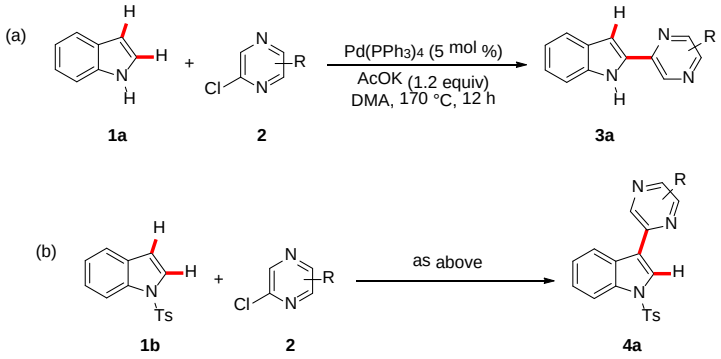


Scheme 6: Frequently used directing groups.

1.1.1 Palladium-Catalyzed C–H Activation of Indoles

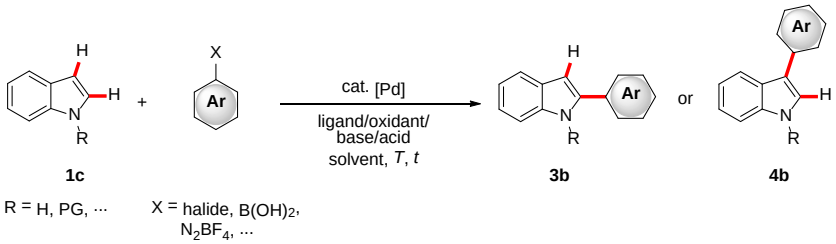
Indole is one of the most ubiquitous nitrogen-heterocycle-containing substructures, appearing in natural compounds, pharmaceuticals as well as industrial products.[12] A vast number of indole-containing compounds is biologically active and therefore the syntheses of a variety of new indoles is of immense importance.[13] Besides traditional synthetic routes, such as the Fischer indole synthesis, the Gassman indole synthesis or the Bischler indole synthesis,[14] through which different indole structures can be achieved, C–H arylation of the indole core structure emerged as a new and efficient way to further diversify indoles.

Early examination of the palladium-catalyzed C–H arylation of indoles by the group of Ohta in 1985 showed a different regioselectivity for electronically different indoles (Scheme 7).[15] While the *NH*-free indole **1a** was arylated with chloropyrazines **2**, affording C2-functionalized indoles **3a**, the tosyl-protected indole **1b** was arylated exclusively in the C3 position. Thus, the electron-withdrawing tosyl group changed the electronics and therefore the C2/C3 site-selectivity of the indole.



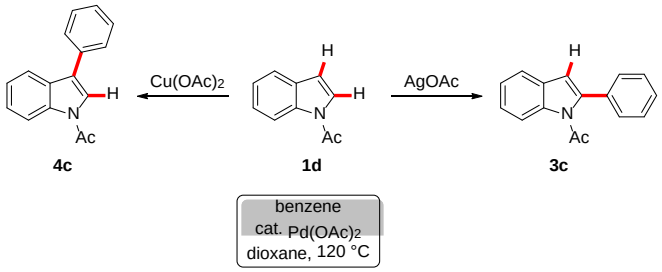
Scheme 7: Divergent regioselectivity of the C–H arylation of indole.[15]

In the past two decades new procedures for the palladium-catalyzed direct C–H arylation of indoles were developed by the groups of Sanford,[16] Sames,[17] Larrosa[18] and Daugulis,[19] among others (Scheme 8). Generally, these reactions suffer from harsh reaction conditions, such as elevated reaction temperatures, the need for strong oxidants, bases or acids. Another issue is the already mentioned site-selectivity between the nitrogen as well as the C2 and C3 positions, which are prone to react prior to the C4–C7 positions. Inspecting the literature, the development of mild reaction conditions and the avoidance of rather toxic reagents becomes apparent. The applied ligands for the palladium-catalysis changed from phosphines,[17,20] to carboxylate-assisted approaches,[17d,21] carboxylates,[18,22] or other non-toxic ligands.[16,23] The choice of the arylating agent varied from previously used iodoarenes,[17,20,24] over bromoarenes[23a,24] and chloroarenes[19,25] to aryl boronic acids[18a] and other arenes, such as benzene,[18b] benzoic acids,[21b] aryl diazo borates,[22a] aryl sulfinates[23b] and diaryliodonium salts.[16,22b] The applied oxidants for the oxidative couplings also varied from toxic and expensive silver[18b,21b] or copper salts[18b,23b] to benign oxygen.[18a,20b]



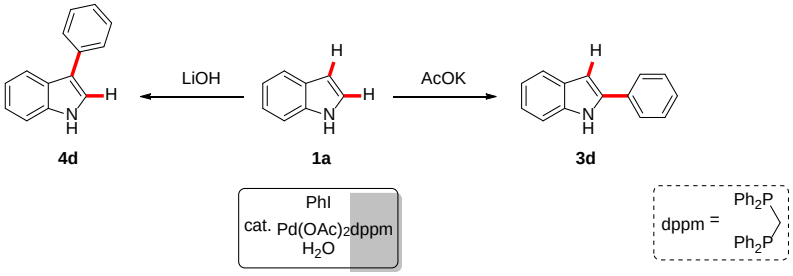
Scheme 8: General palladium-catalyzed arylation of indoles.

These different reaction modes demonstrate the possibilities of tuning the regioselectivity. For example, the work of DeBoef shows an oxidant-controlled switch in the C2/C3 selectivity (Scheme 9).[21a] While the use of silver acetate in the palladium-catalyzed arylation of *N*-acetylindole **1d** with benzene delivered the C2-arylated indole **3c** as the major product, the utilization of copper(II)acetate provided the C3 aryl indole **4c** as the main product. Similar findings were previously shown by Fagnou[22b] and Itahara.[26]



Scheme 9: Oxidant-controlled regioselectivity of the palladium-catalyzed arylation.[21a]

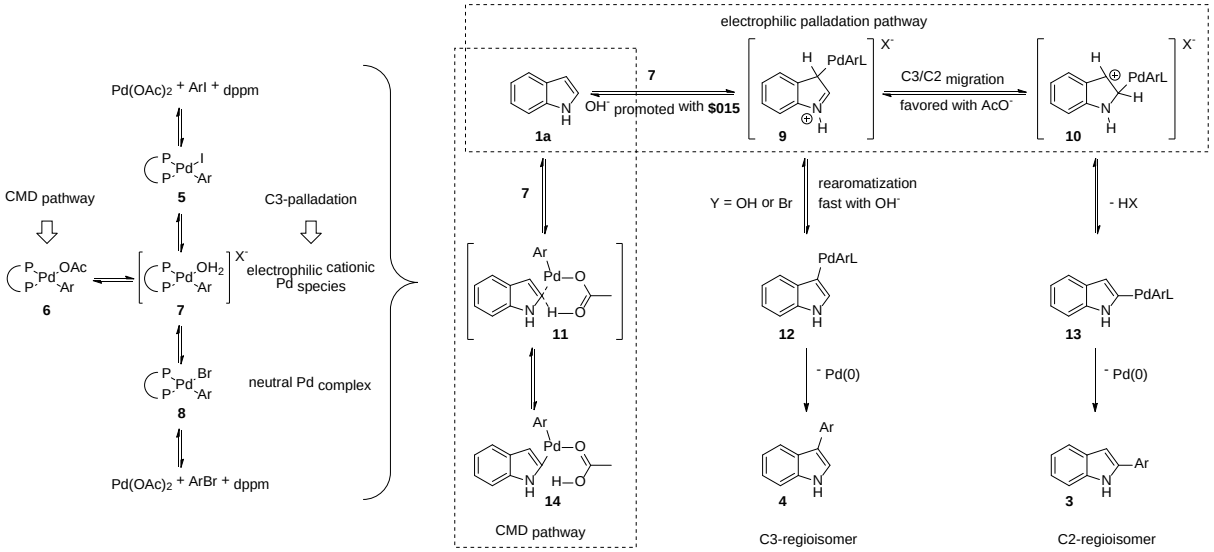
Djakovitch showed a C2/C3-site-selective arylation depending on the base (Scheme 10).[20a] The formation of the C3-arylated product **4d** was preferred when strong hard bases were used, while weak soft bases gave the C2-arylated indole **3d** as the major product.



Scheme 10: Base-controlled site-selectivity of the C–H arylation of indoles.[20a]

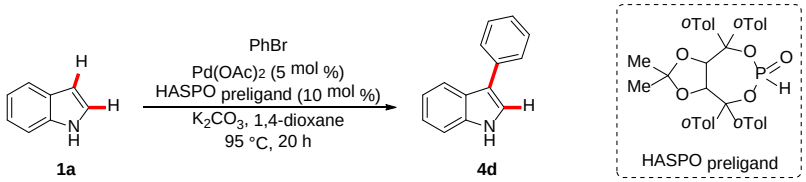
Regarding the mechanism of the palladium-catalyzed C2-arylation of indoles with aryl halides, Djakovitch proposed a palladium(0)/palladium(II) catalytic pathway that is supported by experimental findings (Scheme 11).[20a] The highly electrophilic complex **7** could undergo a C3-palladation to form the complex **9**. From here, two pathways are reasonable: The first starts with a migration from C3 to C2, which is favored in the presence of a weak base. This leads to complex **10**,

which delivers the C2-arylated isomer **3** through formation of the σ-complex **13** and subsequent reductive elimination. The second way is based on a rearomatization, which is facilitated by the presence of a strong base. The deprotonation leads to formation of complex **12** and finally to the C3 regioisomer **4**.



Scheme 11: Proposed mechanistic pathway.[20a]

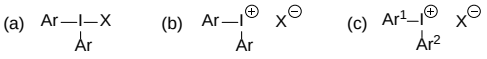
An example for the selective C3–H modification of indoles was demonstrated by the palladium-catalyzed HASPO-assisted arylation of indole **1a** with bromoarenes (Scheme 12).[27] The catalytic system consisted of $Pd(OAc)_2$, a HASPO additive and K_2CO_3 in dioxane. Notably, air-stable HASPO preligands were applied.



Scheme 12: C3-selective arylation of indoles.[27]

1.1.2 Arylations of (Hetero)Arenes with Diaryliodonium Salts

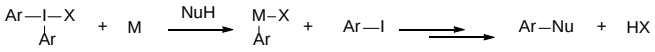
Since diaryliodonium salts were first described by Hartmann and Meyer in 1894,[28] these air- and moisture-stable hypervalent iodine(III) compounds have become readily available and widely used. Structurally, diaryliodonium compounds are usually T-shaped, which is typical for iodine(III) compounds (Scheme 13). The iodine, the apical aryl group and the "counterion" form a three-center four-electron (3c-4e) bond.[29] In solution the degree of dissociation to Ar_2I^+ and X^- depends on both the solvent and the counterion.[30] The dissociated species is considered to maintain the roughly 90° angle of Ar–I^+–Ar as a solvent molecule coordinates instead.[31]



Scheme 13: Structure of Ar_2IX: (a) T-shaped. (b) ionic T-shaped. (c) unsymmetric.

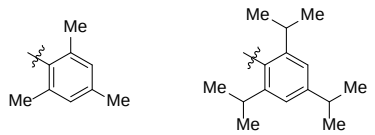
The reactivity of the iodine(III) species is determined by the electrophilic nature of the iodine (Scheme 14). Typically, one aryl group is transferred to the nucleophile and consequently aryl iodide is formed as the stoichiometric leaving group. In nucleophilic aromatic substitutions or cross-coupling reactions neutral leaving groups are more beneficial as compared to anionic leaving groups.[32]

As to the mechanism, it is generally believed that under transition metal-catalysis one aryl group is transferred to the metal to form an aryl metal complex in a high oxidation state. The product is formed through reductive elimination with the nucleophile that has coordinated to the metal either before or after the transfer of the aryl moiety.[33]



Scheme 14: General reaction of Ar_2IX with nucleophiles.

The use of diaryliodonium salts is considered a disadvantage due to the generation of equimolar amounts of aryl iodides, which becomes even more inexpedient when more complex aryls are to be introduced. To circumvent this issue, unsymmetrical diaryliodonium salts have been designed. The idea was to introduce an inexpensive "dummy" aryl moiety that can be wasted as aryl iodide. For this strategy, a high chemoselectivity with respect to the transferred aryl group is of immense importance. For metal-catalyzed reactions, the chemoselectivity is usually guided by the sterics of the aryl moieties. Sterically demanding aryl groups, such as the 2,4,6-trimethylphenyl (mesityl) or 2,4,6-triisopropylphenyl (TRIP), can generally be used as dummy groups (Scheme 15).[33d,34]

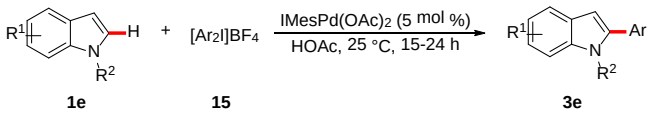


Scheme 15: Common dummy groups.

Due to their high electrophilicity and their leaving group ability, diaryliodonium salts have been applied for various electrophilic arylations, for radical reactions, and for transition metal-catalyzed cross-coupling reactions.[35,36]

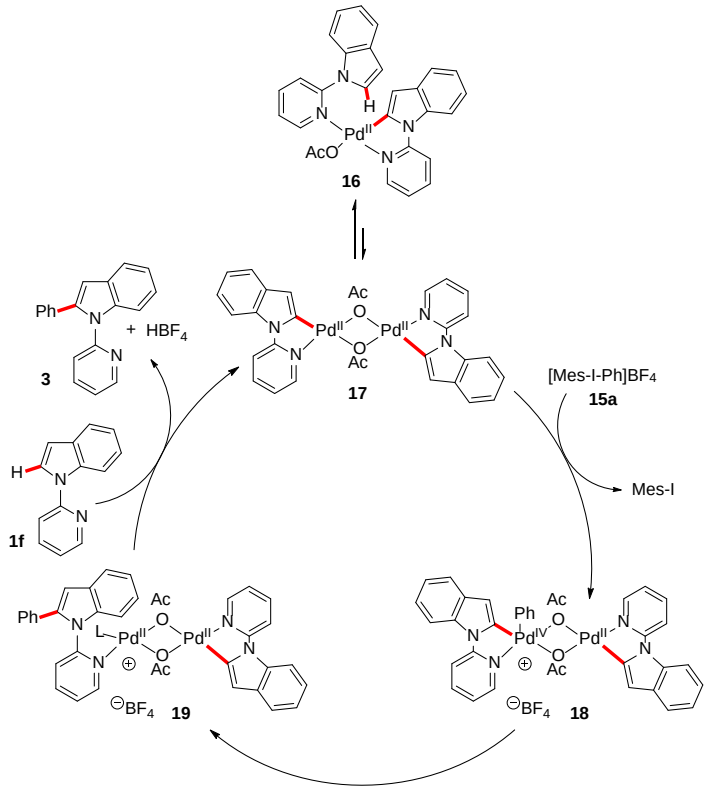
In 2006, Sanford presented the C2-arylation of indole with $[Ph_2I]BF_4$ in the presence of catalytic amounts of $Pd(OAc)_2$ or $IMesPd(OAc)_2$ (Scheme 16).[23c] A catalytic cycle can be proposed according to a previously reported arylation of phenylpyridines under similar conditions (Scheme 17).[33d] A phenyl

group of the mixed diaryliodonium salt is transferred to the palladium dimer complex **17** to form the cationic palladium(II)/palladium(IV) complex **18**. Thereafter, the initial palladium(II)/palladium(II) complex **17** is regenerated by reductive elimination of the product **3** and a subsequent addition of the substrate **1f**.



1e **15** **3e**

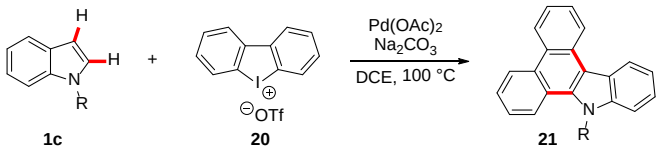
Scheme 16: Palladium-catalyzed arylation with $[Ar_2I]BF_4$.[23c]



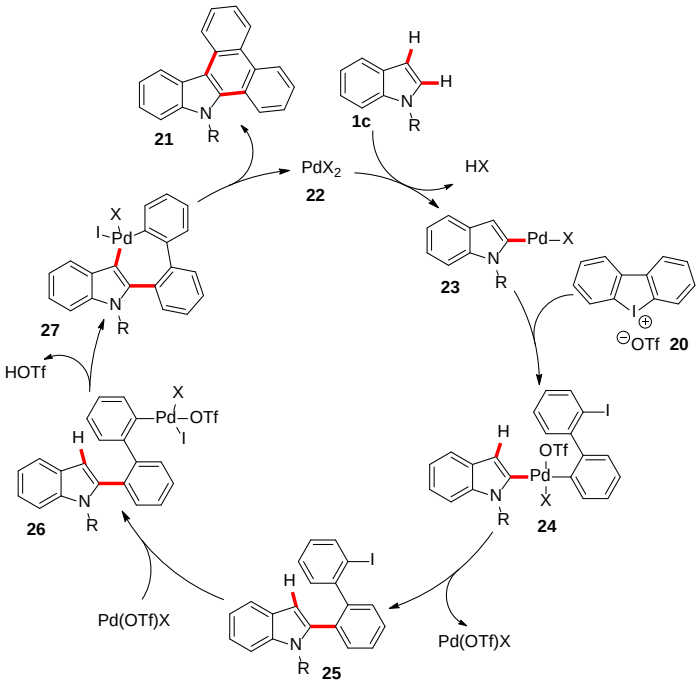
Scheme 17: Catalytic cycle for palladium-catalyzed arylation with $[Ar_2I]BF_4$.[23c]

A more recent publication by Huang in 2014 showed the palladium-catalyzed combined C2,C3-diarylation of indole **1c** with biphenyliodonium triflate **20** to obtain carbazoles **21** (Scheme 18).[37] Sanford's report[23c] and further mechanistic observations[37] indicate a palladium(II)/(IV)-catalytic system, in which the palladated C2 position of the indole first reacts with the biphenyliodonium **20** to give the palladium(IV) complex **24** (Scheme 19). After a reductive elimination to palladium(II) the intermediate **25** is formed. A second oxidative addition of the recycled palladium(II) species to the aryl iodide affords the complex **26**, which is transformed to the complex **27** by C3-palladation to give the final product **21** after reductive elimination. This publication showed an economic way of the

utilization of diaryliodonium salts with a minimized waste-coproduction, which however is only useful when the diannulated carbazole is desired.

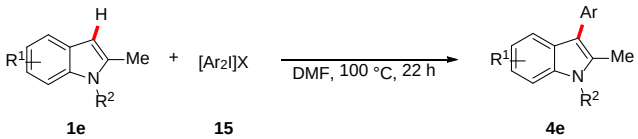


Scheme 18: Palladium-catalyzed C2,C3-diarylation of indoles.[37]



Scheme 19: Mechanism of the palladium-catalyzed C2,C3-diarylation of indoles.[37]

A metal-free approach for the C–H arylation of indoles applying diaryliodonium salts was shown by the Ackermann group (Scheme 20).[38] The reaction of indoles **1e** with diaryliodonium salts **15** proceeded smoothly in DMF at 100 °C. Diaryliodonium triflates, tosylates, tetrafluoroborates as well as trifluoroacetates and hexafluorophosphates were applicable for this reaction. Later this method was applied to peptide modification.[39]

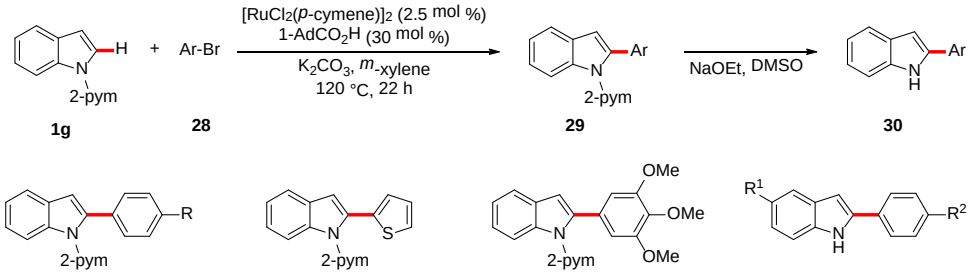


Scheme 20: Metal-free C–H arylation of indoles.[38]

1.2 Ruthenium-Catalyzed C–H Arylations of (Hetero)Aryl Pyridines and Pyrimidines

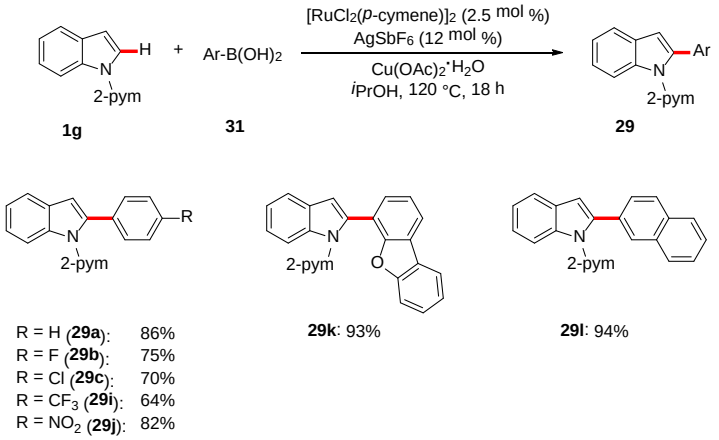
Since the first example of a direct ruthenium-catalyzed C–H arylation of heteroarenes was published by Ackermann in 2011 (Scheme 21),[40] the interest in these transformations has grown. Previous reports on ruthenium-catalyzed arylations focused on the C–H arylation of arenes without heteroatoms and thereby demonstrated the applicability of different directing groups in ruthenium catalysis.[41,42]

The work of Ackermann from 2011 illustrated an efficient way for the C–H arylation of *N*-pyridylated or *N*-pyrimidylated pyrroles and indoles **1g**.[40] Here, $[RuCl_2(p\text{-cymene})]_2$ was used as the precatalyst in combination with catalytic amounts of user- and environment-friendly 1-adamantyl carboxylic acid as the preligand in a basic milieu of K_2CO_3 in *m*-xylene. Aryl bromides **28** as well as chlorides **2** were applied as the arylating agents. Finally, the traceless directing group arylation strategy was accomplished through removal of the directing group from the nitrogen of the indole and pyrrole by reacting the products **29** with sodium ethoxide in DMSO. The substrate scope demonstrated functional group tolerance towards fluoride, chloride, cyanide, ketone, ester, ether, dimethylaniline, as well as thiophene.



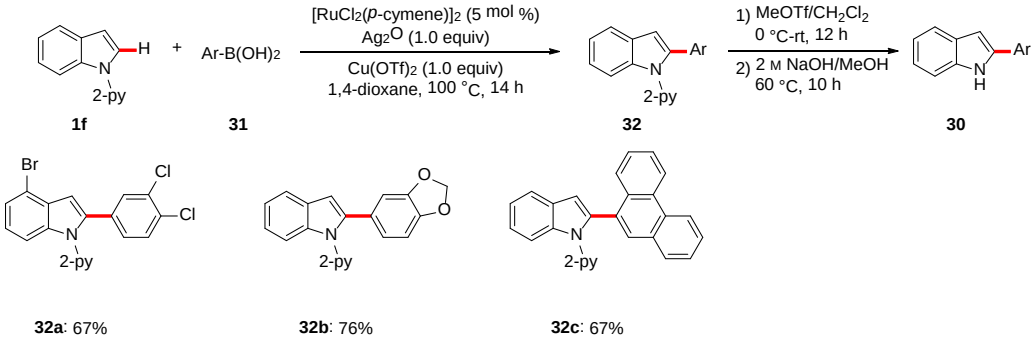
Scheme 21: Ruthenium-catalyzed arylation of indoles with aryl bromides.[40]

In 2014, the group of Pilarski expanded the ruthenium-catalyzed C–H arylation of pyrimidyl indoles **1g** and pyrroles under oxidative conditions using aryl boronic acids **31** as the arylating agents (Scheme 22).[43] The optimized reaction conditions revealed catalytic amounts of $[RuCl_2(p\text{-cymene})]_2$ and $AgSbF_6$ combined with one equivalent of $Cu(OAc)_2 \cdot H_2O$ as the terminal oxidant to be best suitable for this transformation. The reaction proceeded in isopropanol at 120 °C within 18 h.



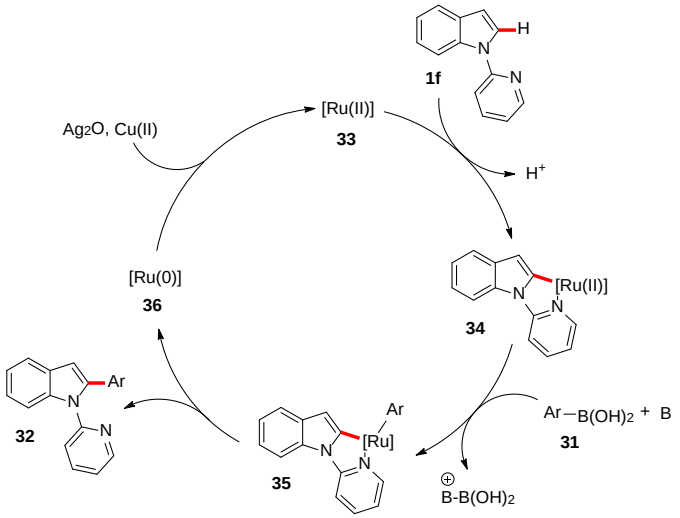
Scheme 22: Ruthenium-catalyzed arylation of indoles with arylboronic acids.[43]

A similar work with indole pyridines **1f** was published by Kapur in 2015 (Scheme 23).[44] In this case, various solvents and oxidants were tested. After optimization of the coupling of indole pyridine **1f** with phenylboronic acids **31**, catalytic amounts of $[RuCl_2(p\text{-cymene})]_2$ with one equivalent of $Cu(OTf)_2$ and Ag_2O in dioxane appeared optimal at 100 °C. The pyridyl directing group could be successfully removed by treatment with MeOTf and subsequently with a base according to a literature procedure.[45]



Scheme 23: Ruthenium-catalyzed arylation of indioles with arylboronic acids.[44]

A plausible catalytic cycle was proposed (Scheme 24). First, a ruthenium(II)-species **33** is coordinated by the pyridyl directing group and activates the C–H bond in the C2 position. Thereafter, transmetalation with the arylboronic acid **31** followed by reductive elimination sets free the C2-arylated indole **32**. Finally, the released ruthenium(0)-species **36** is oxidized to ruthenium(II) **33** by copper(II). Possibly, the role of silver oxide is to facilitate the transmetalation and also to assist the reoxidation step.

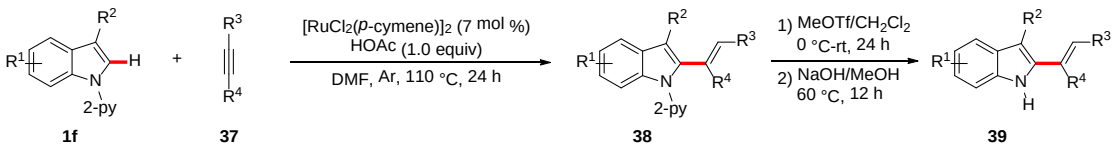


Scheme 24: Mechanism of the ruthenium-catalyzed arylation of indoles.[44]

1.3 Ruthenium-Catalyzed C–H Hydroarylation of Unsaturated C–C Bonds

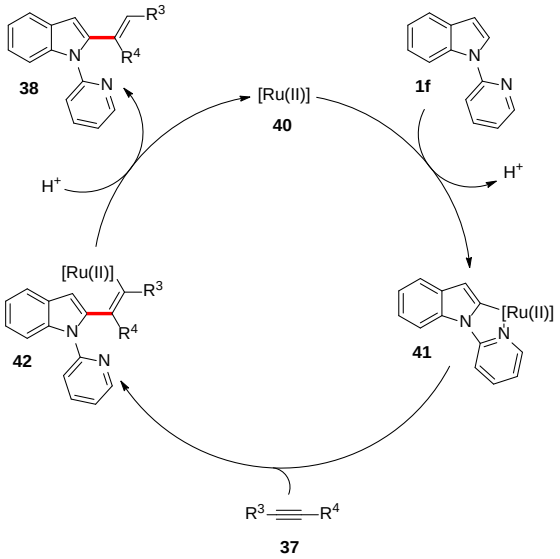
Hydroarylation of arenes is a powerful tool to gain access to alkylarenes.[46] While traditional Friedel-Crafts reactions[47] and additions of organometallic substrates to α,β-unsaturated carbonyl compounds[48] produce stoichiometric amounts of waste salts, hydroarylation features high step- and atom-economy and therefore synthetic efficiency.[49] In recent years, significant progress has been achieved in the field of the addition of unactivated C–H bonds of aryls to unsaturated compounds.[50] For transition metal-catalyzed hydroarylation reactions, different transition metals have been used, such as cobalt,[51] iridium,[52] manganese,[53] rhenium,[54] nickel[55] as well as rhodium[56] and ruthenium,[56d,57] among others.[50]

In 2014, Zeng and coworkers published a ruthenium-catalyzed hydroarylation of alkynes **37** with indoles **1f** (Scheme 25).[57c] The catalyst consisted of $[RuCl_2(p\text{-cymene})]_2$ and one equivalent of acetic acid in DMF at 110 °C. A broad range of alkynes **37** and indole substrates **1f** were coupled to give the desired olefinic products **38**. The *NH*-free indoles **39** were released after the treatment with MeOTf and subsequent addition of base.



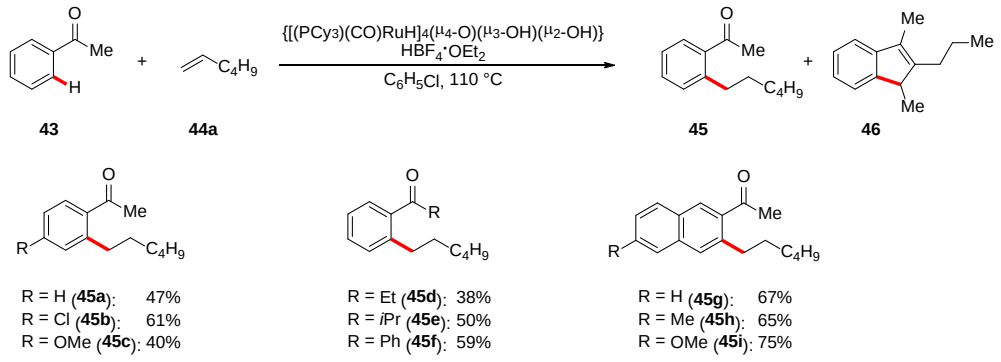
Scheme 25: Ruthenium-catalyzed hydroarylation of alkynes with indoles.[57c]

Mechanistic studies, including H/D exchange experiments and kinetic isotope effect (KIE) studies, gave reason to suggest a catalytic cycle that starts with the coordination of the pyridine to the ruthenium complex **40** followed by an electrophilic activation to obtain complex **41** with a concomitant loss of a proton (Scheme 26). Next, an alkyne **37** inserts into the ruthenium-carbon bond to form complex **42**, which liberates product **38** after protonation.



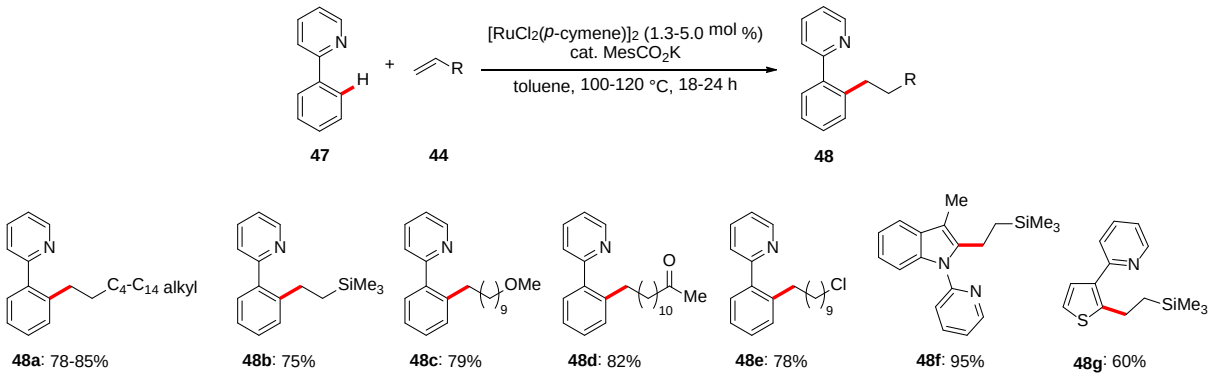
Scheme 26: Catalytic cycle for the ruthenium-catalyzed hydroarylation.[57c]

Activated alkenes, such as α,β-unsaturated carbonyls, vinyl heteroatom compounds, enol and enamine ethers, allenes, and also styrenes, are most likely to perform hydroarylation reactions. However, unactivated olefins are somewhat more challenging substrates. Concerning ruthenium-catalyzed hydroarylations, the use of unactivated alkenes is rare. Regarding recent publications, in 2009 Lee and coworkers showed the ruthenium hydride-catalyzed alkylation of acetophenones **43** with 1-hexene (**44a**, Scheme 27).[57g] An isomerization of the obtained alkyl arenes **45** led to the formation of the byproducts **46**. A similar work was later also demonstrated by the group of Williams.[57f]



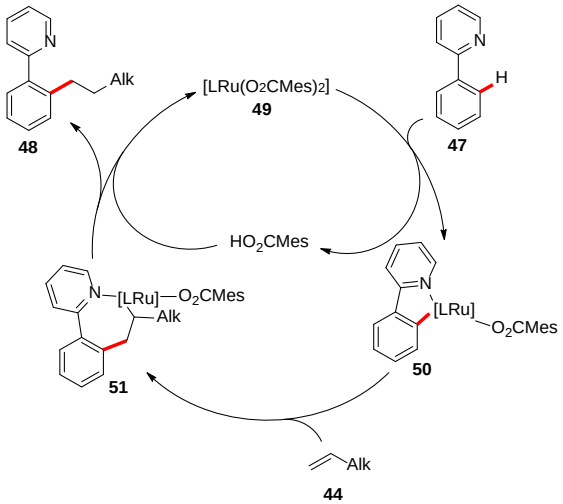
Scheme 27: Ruthenium-catalyzed hydroarylation of unactivated alkenes. Combined yields of both isomers are shown.[57g]

A remarkable report of the alkylation of phenylpyridines **47** with unactivated alkenes **44** was published by Ackermann in 2013 (Scheme 28),[57e] and further examined by Peris.[57b] In this work, a user-friendly, air-stable, carboxylate-assisted ruthenium-catalytic system was used at 100–120 °C in toluene, dioxane or water. The optimized method was extended to indoles and thiophenes, which delivered the corresponding alkylated products **48f** and **48g** in good yields.



Scheme 28: Ruthenium-catalyzed hydroarylation of unactivated alkenes.[57e]

Based on H/D-exchange experiments, competition experiments and previous mechanistic studies, a plausible catalytic cycle was proposed (Scheme 29). After C–H activation of the *ortho*-position, the alkene is hydrometalated to form complex **51**. The reductive elimination, which is probably rate-determining, provides the product **48** and regenerates the catalyst **49**.

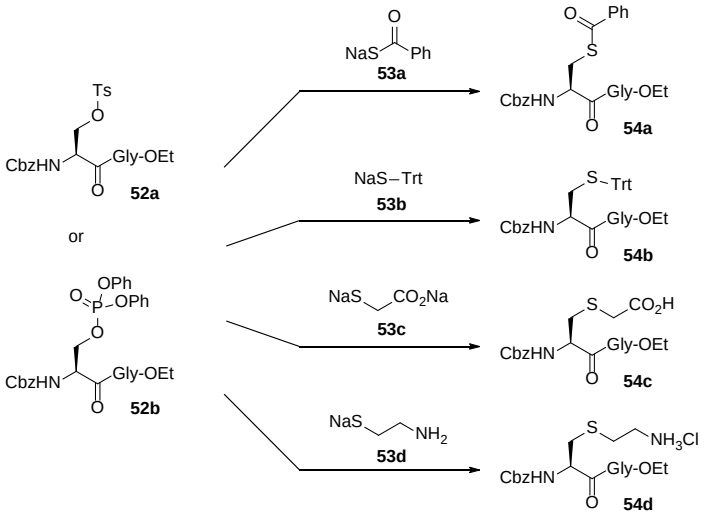


Scheme 29: Catalytic cycle of the ruthenium-catalyzed hydroarylation.

1.4 Chemical Late-Stage Peptide Modification

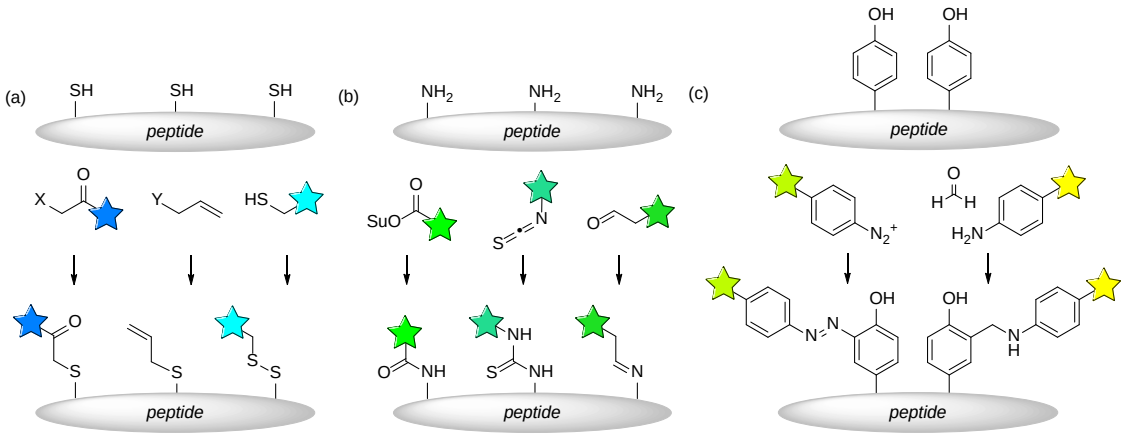
Chemical peptide modification has emerged as a valuable tool for the development of a diversity of new peptides.[58] The present demand for novel peptides is a consequence of the need for probing natural systems, designing therapeutic conjugates and creating new protein constructs. Proteins and peptides containing non-proteinogenic amino acids can have improved pharmacokinetic properties when compared to their natural counterparts.[59] Moreover, peptides are efficient catalysts for selective asymmetric reactions.[60] These peptide modifications are commonly referred to as posttranslational modifications (PTMs), as they are contrived after the actual peptide synthesis, which originally was the translation. However, nowadays, peptide synthesis is realized by automated methodologies, in particular by solid phase peptide synthesis (SPPS). While natural posttranslational modification is precise and diverse, which results in the vast biodiversity found in nature, our possibilities to specifically modify a peptide at a certain site are limited by the chemical transformations that are available. The true challenge is to chemically differentiate between a number of amides, carboxylic acids, amines, alcohols and thiols within a molecule. In order to study cellular processes, it is indispensable to mimic natural posttranslational changes of peptides, including acylation, methylation, phosphorylation, sulfation, ubiquitination and glycosylation, among others. To date, developed methods have primarily focused on the modification of particular peptides and therefore may not be applicable to any other peptide of interest. Consequently, the need for further methods for chemical modifications of peptides continues to persist. The pursued premises are site-selectivity, robustness, mildness and efficiency at temperatures below 40 °C, so as not to disrupt the architecture or function of the peptide or protein. It would be desirable to carry out these modification reactions under biologically ambient conditions, that are 37 °C at a pH of 6–8 in an aqueous media. Moreover, in order to modify peptides within living cells, the modification reactions must exhibit bioorthogonality and biocompatibility, high reaction rates at low substrate concentrations as well as the use of nontoxic reagents.

An early example of a site-selective peptide modification was published in 1965 by Wilchek and coworkers (Scheme 30).[61] They presented the conversion of serine **52** to cysteine **54** by nucleophilic substitution of activated hydroxyl groups, such as tosylates **52a** and phosphoric esters **52b**, with thio-nucleophiles **53**, such as thiolates and thioacylates.



Scheme 30: Conversion of serine to cysteine.[61]

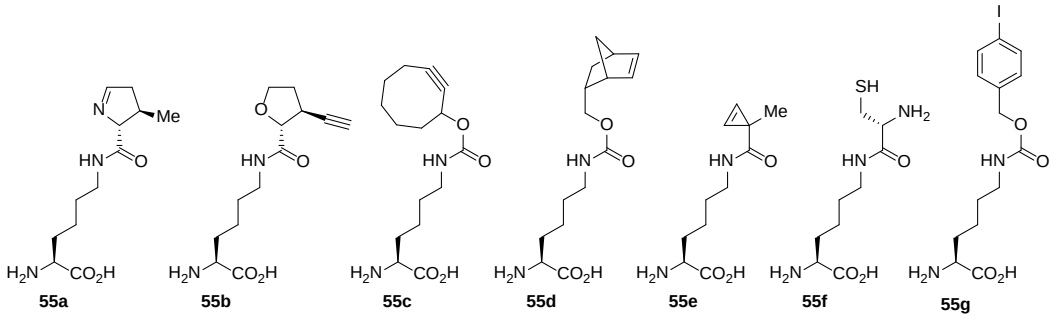
Since then, major development has been achieved and both natural and unnatural amino acid residues were modified. Amongst natural amino acids, functionalized residues have been commonly used, such as lysine, cysteine, tyrosine, threonine and serine (Scheme 31). Amines are likely to undergo reactions with electrophiles, for instance esterifications with activated carbonyls, additions to Michael acceptors, thiocyanates or ketenes, and condensations with carbonyls. Beyond that, even more nucleophilic cysteine is capable of reacting in nucleophilic substitutions of alkyl halides and disulfides, and cysteine can easily be converted to dehydroalanine, which is predestined for conjugate addition reactions.



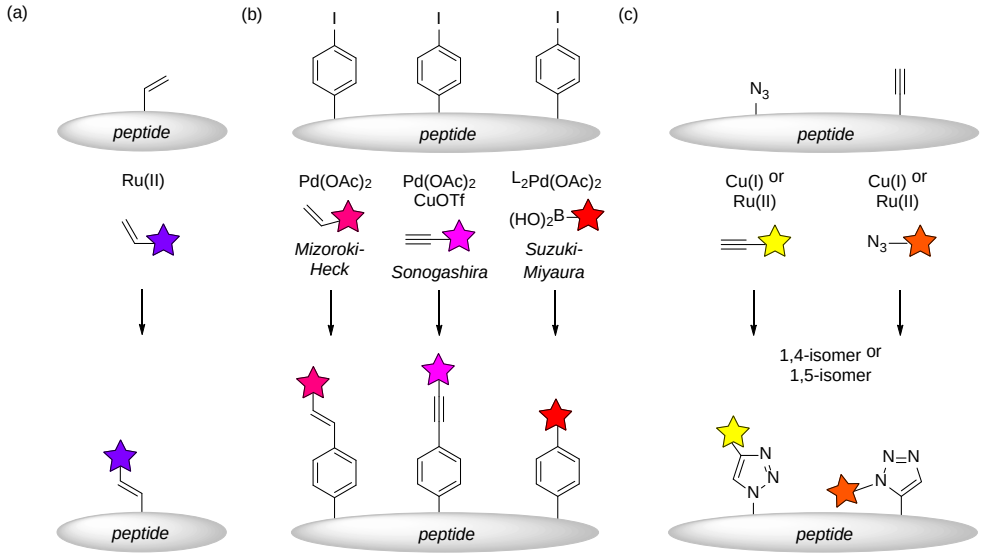
Scheme 31: Examples of peptide modification with (a) cysteine, (b) lysine, and (c) tyrosine.

In addition to transition metal-free approaches, transition metal-catalyzed transformations have been examined.[62] Typically, a “handle” or “tag”, which is supposed to possess a uniquely reactive functional group, is attached to an amino acid or an unnatural amino acid is implemented into the peptide (Scheme 32). This facilitates numerous established transition metal-catalytic reactions,

including click reactions,[63,64] cross-metathesis,[65] and cross-coupling reactions, among which Suzuki-Miyaura[66,67] and Sonogashira[68] reactions have received the most attention (Scheme 33). Successively, some limitations, such as catalyst poisoning and the use of anhydrous solvents, were solved. Air- and moisture-stable as well as environmentally benign catalysts gave rise to mild, efficient and economic procedures.

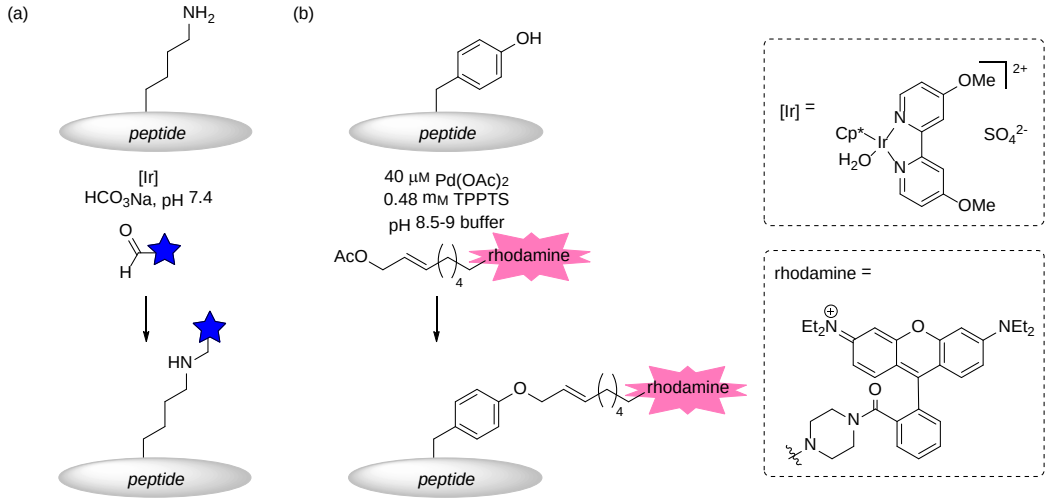


Scheme 32: Examples of genetically encoded lysine-based amino acids for biocompatible reactions.



Scheme 33: Examples of (a) cross-metathesis, (b) cross-coupling and (c) click reactions on peptides.

Early examples focused on the nucleophilic natural amino acids lysine and tyrosine. For example, in 2005 the Francis group published an iridium-Cp*-catalyzed alkylation of lysine with an aldehyde with subsequent reduction of the formed imine by an in situ formed iridium hydride species (Scheme 34a).[69] One year later, the same group reported on the palladium-catalyzed Tsuji-Trost reaction on tyrosine in peptides (Scheme 34b).[70] An in situ formed π-allylpalladium complex, which was generated from allyl acetates or carbamates and $Pd(OAc)_2$/triphenylphosphine tris-(sulfonate) (TPPTS), afforded the selective *O*-alkylation of tyrosine peptides. Rhodamine dyes and lipophilic moieties could thus be introduced into peptides. Further transition metals, such as nickel,[71] iron,[72] copper,[73] cerium,[74] rhodium,[75,76] and gold[77] were also applied for peptide modifications.



Scheme 34: Examples of peptide modifications on (a) lysine and (b) tyrosine.[69,70]

For late-stage modifications of peptides, carbon–carbon bond forming reactions, which can be realized by cross-coupling and cross-metathesis reactions, are amenable and attractive because they are selective and even applicable in living cells.

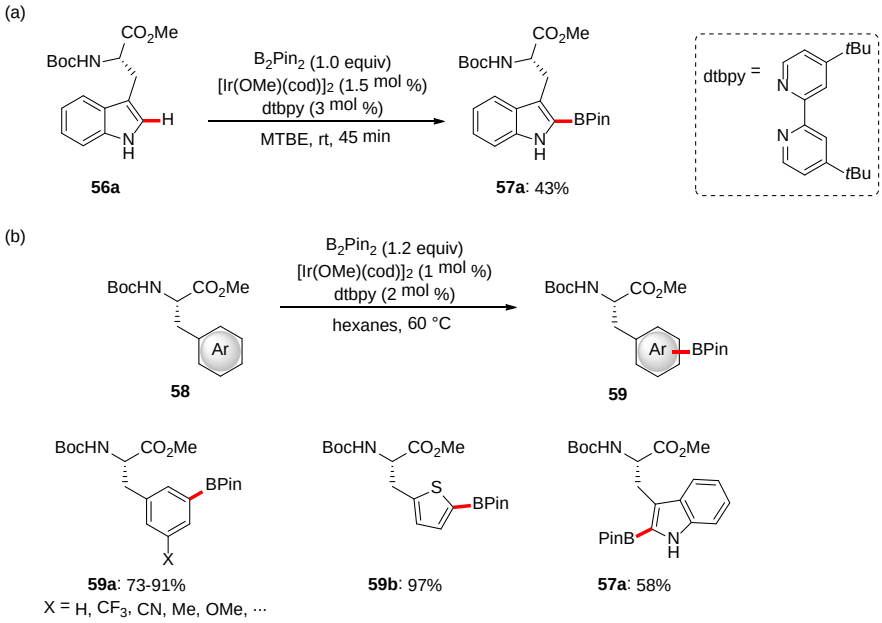
In addition to the described transition metal-catalyzed protocols, approaches that require less prefunctionalization, namely transition metal-catalyzed C–H modification reactions, were developed. Lastly, as on-resin reactions highlight completely new challenges and at the same time reveal completely new advantages, on-resin modification reactions of peptides have also been developed. Along these lines, C–H activation reactions as well as on-resin reactions are described in the following chapters.

1.4.1 C–H-Activation of Peptides

While nature provides a range of elegant modification approaches of peptides, chemical functionalization is still considerably more challenging because many established protocols do not suffice the bio-ambient requirements of peptide modification. Nevertheless, since the first C–H functionalization of peptides was published, significant advances in this area have been made.[78] In contrast to previous functionalization approaches, which relied on nucleophilic functions of the amino acids in a peptide, C–H activation reactions can be performed at otherwise unreactive sites in the presence of more reactive functional groups. In this way, inter alia aliphatic amino acids became interesting for peptide modification reactions.

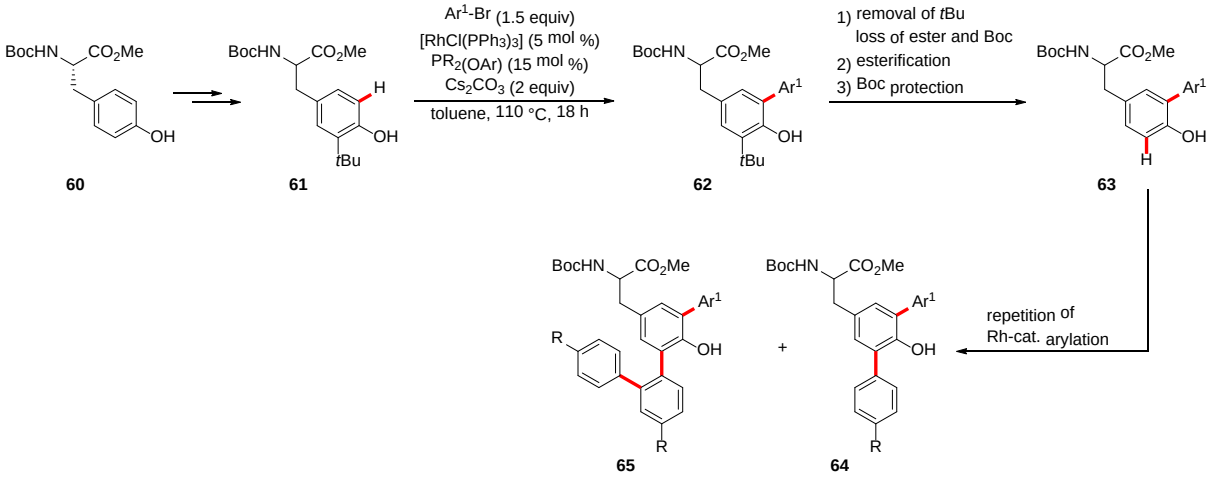
Based on early findings on the iridium-catalyzed C–H borylation of arenes and heteroarenes,[79] the group of Smith and Maleczka showed the application of this regioselective C–H borylation method to the indole moiety of a Boc-protected tryptophan **56a** (Scheme 35a).[80] The authors claim the importance of the Boc protection, as it serves as a directing group. Shortly after this report, James

and coworkers reported on a similar transformation of natural and unnatural amino acids **58** (Scheme 35b).[81]



Scheme 35: Iridium-catalyzed C–H borylation of (a) tryptophan[80] and (b) unnatural amino acids.[81]

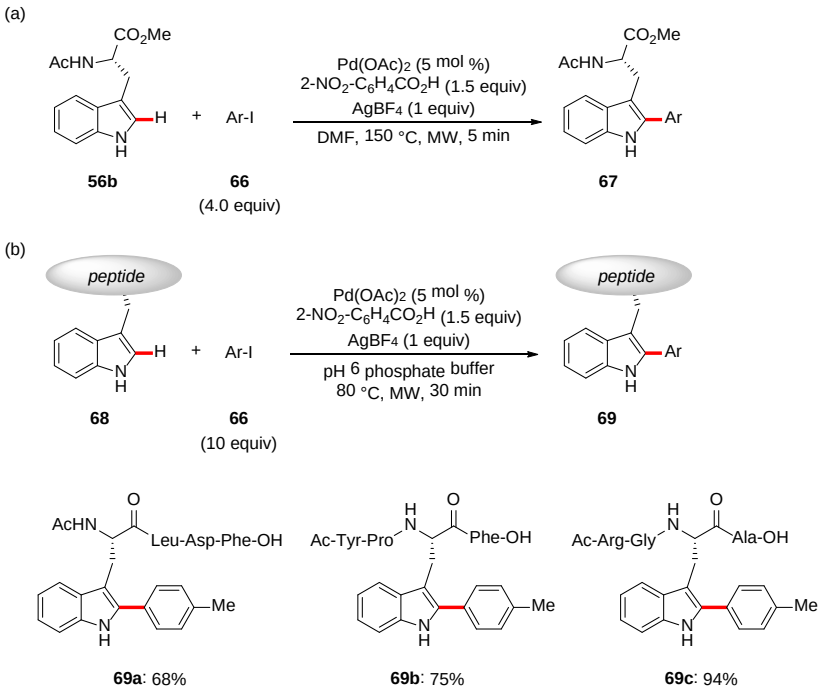
Besides acetoxylation[82] and halogenation[83] reactions, arylation reactions received significant attention, due to the formation of stable carbon–carbon bonds by C–H arylation reactions. Bedford and coworkers published the sequential rhodium-catalyzed twofold C–H *ortho*-arylation of tyrosine (Scheme 36).[84] Prior to the first arylation, a *tert*-butyl protecting group was installed. For the arylation reaction 7.5 mol % [$RhCl(PPh_3)_3$] was used, along with catalytic amounts of a phosphonite ligand, an aryl bromide and two equivalents of Cs_2CO_3 in toluene at 110 °C. After the first arylation and removal of the *tert*-butyl group, the arylation procedure was repeated. This procedure gave rise to novel disubstituted tyrosines **64**. The second arylation resulted in low yields and formation of the side-products **65**. The introduction of the *tert*-butyl group gave a racemic tyrosine, thus the obtained products **64** and **65** were racemic.



Scheme 36: Rhodium-catalyzed sequential C–H diarylation of tyrosine.[84]

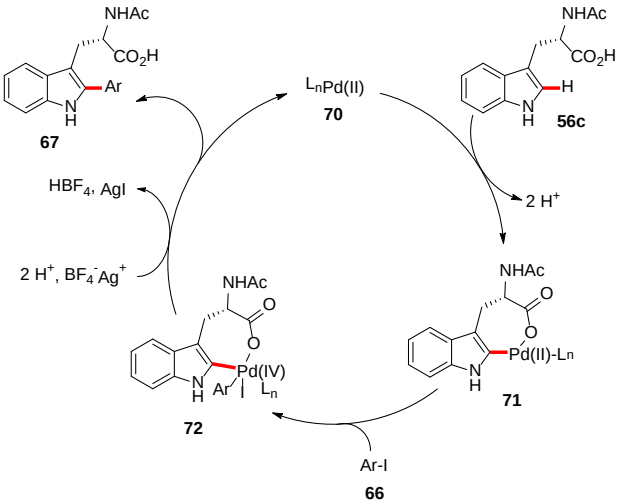
Given the versatility of palladium catalysts, several further palladium-catalyzed C–H arylation methods were developed, including C5 arylation of histidine[85] and C2 arylation of tryptophan.[86] These palladium-catalyzed arylations are similar in two aspects: The use of a palladium(II) catalyst, mostly $Pd(OAc)_2$, and some aryl electrophiles, such as aryl iodides or diaryliodonium salts, or nucleophiles, such as aryl boronic acids. For scavenging the iodide, silver salts were used.

In 2010, the group of Lavilla reported the palladium-catalyzed C–H arylation of tryptophan **56b** using four equivalents of aryl iodides **66**, 5 mol % $Pd(OAc)_2$, 1.5 equivalents of 2-nitrobenzoic acid as the ligand and one equivalent of $AgBF_4$ (Scheme 37).[86b] The reaction was carried out in DMF at 150 °C under microwave irradiation for 5 min. A slightly modified procedure was applied to tryptophan-containing peptides **68**. Here, the relative amount of aryl iodide **66** was increased to ten equivalents and the reaction took place at a pH 6 in phosphate buffer at 80 °C.



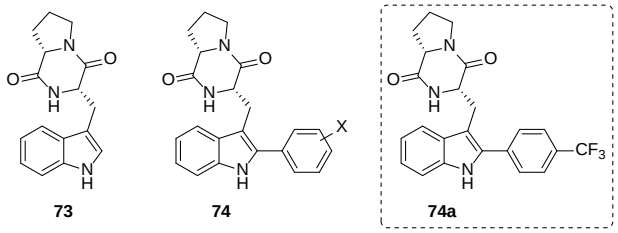
Scheme 37: Palladium-catalyzed C–H arylation of (a) tryptophan and (b) tryptophan peptides.[86b]

The authors considered either a palladium(0)/palladium(II) or a palladium(II)/palladium(IV) catalytic cycle.[86a] In the palladium(II)/palladium(IV) case, the indole undergoes a palladation via a concerted metalation deprotonation mechanism to generate complex **71** (Scheme 38). The following oxidative addition of aryl iodide **66** leads to the palladium(IV) complex **72** from which the silver cation removes the iodide, promoting the reductive elimination of the product **67** and regenerating the palladium(II) catalyst **70**.



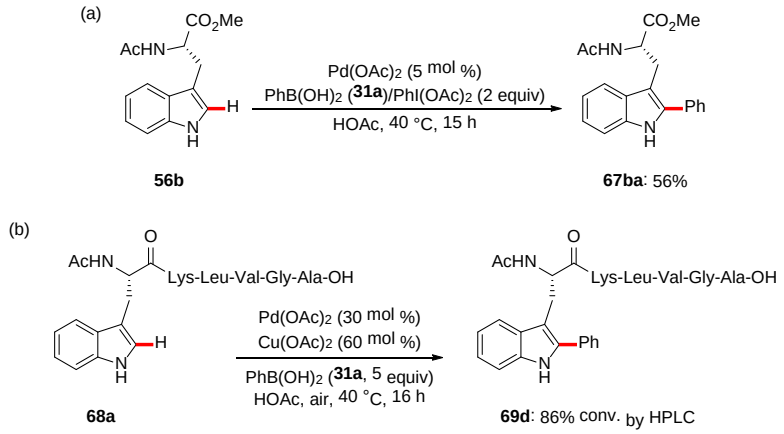
Scheme 38: Catalytic cycle of the palladium-catalyzed C–H arylation.[86a]

Slightly modified reaction conditions were applied to the synthesis of brevianamide F (**73**), a cyclized dipeptide consisting of tryptophan and prolin (Scheme 39). A small library of arylated brevianamide F analogues **74** was assembled regarding different aryl moieties on the indole.[86e] Biological evaluation of the activity of the novel brevianamides **74** revealed *para*-trifluoromethylphenylated diketo-piperazine **74a** to possess higher activity against the tested human cancer cell lines as compared to the natural brevianamide F (**73**). Thus, this finding demonstrated that a change of the indole moiety had a large effect on the bioactivity of this small drug.



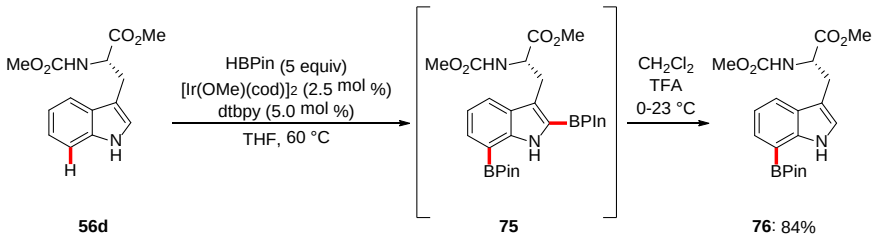
Scheme 39: Brevianamide F and its analogues.[86e]

As the reaction conditions that are required for reaching full conversions are quite harsh and in some cases an epimerization of the stereocenter was observed,[86e] milder methods were desired. Thus, Fairlamb and coworkers published a similar arylation method with improved reaction conditions,[86c] which were peviously developed by Sanford.[23c] Tryptophan **56b** was phenylated using a diphenyliodonium salt, which was in situ generated from $PhB(OH)_2$ and $PhI(OAc)_2$ (Scheme 40a). The reaction was performed in acetic acid at a relatively low temperature of 40 °C for 15 h. When these reaction conditions turned out to be limited to $PhB(OH)_2$ while other arylboronic acids did not yield the desired products, a further optimization revealed that the use of $Cu(OAc)_2$ and air as the oxidant instead of the iodonium compound is more beneficial for reactions on peptides **68** (Scheme 40b). During the reaction, the authors observed the formation of palladium nanoparticles (PdNPs), which they were able to encapsulate with a polymer stabilizer for analysis. Independently synthesized PdNPs were demonstrated to be catalytically active under the given reaction conditions. This finding supports the assumption that a Pd(0)/Pd(II) catalytic cycle prevails.



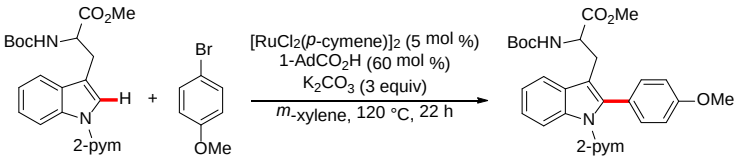
Scheme 40: Palladium-catalyzed C–H arylation of (a) tryptophan and (b) tryptophan peptides.[86c]

In addition to palladium-catalyzed arylation reactions, iridium[87] and ruthenium[40,43] complexes were found to perform C(sp^2)–H bond activation. Loach and coworkers demonstrated the C2,C7-diboronation of the indole of a tryptophan **56d** by applying 2.5 mol % $[Ir(cod)OMe]_2$, 5 mol % of dtbpy as the ligand and five equivalents of pinacolborane as the boron source (Scheme 41). The reaction was performed in THF at 60 °C. Since the C2 position was faster boronated, the excess of pinacolborane was required in order to boronate the C7 position as well. A removal of the boron in the C2 position with TFA in CH_2Cl_2 delivered the C7-boronated indole **76**.



Scheme 41: Iridium-catalyzed C7-boronation of tryptophan.[87]

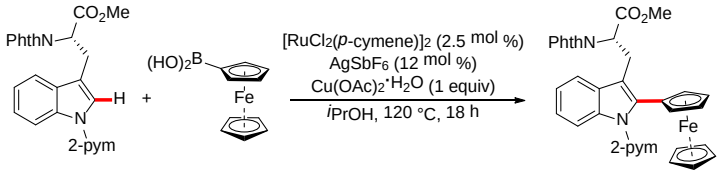
During their studies on the ruthenium-catalyzed arylation of pyrimidyl indoles by the Ackermann group,[40] this method was applied exemplarily to tryptophan **56e** to yield the desired product **67eb** in 41% (Scheme 42). Here, the catalytic system consisted of 5 mol % $[RuCl_2(p\text{-cymene})]_2$ and 60 mol % 1-adamantanecarboxylic acid, combined with three equivalents of K_2CO_3 in *m*-xylene at 120 °C. It is notable that this example was the first non-palladium transition metal-catalyzed direct C–H functionalization of an amino acid.



rac-**56e** **28b** (1.1 equiv) *rac*-**67eb**: 41%

Scheme 42: Ruthenium-catalyzed C–H arylation of tryptophan.[40]

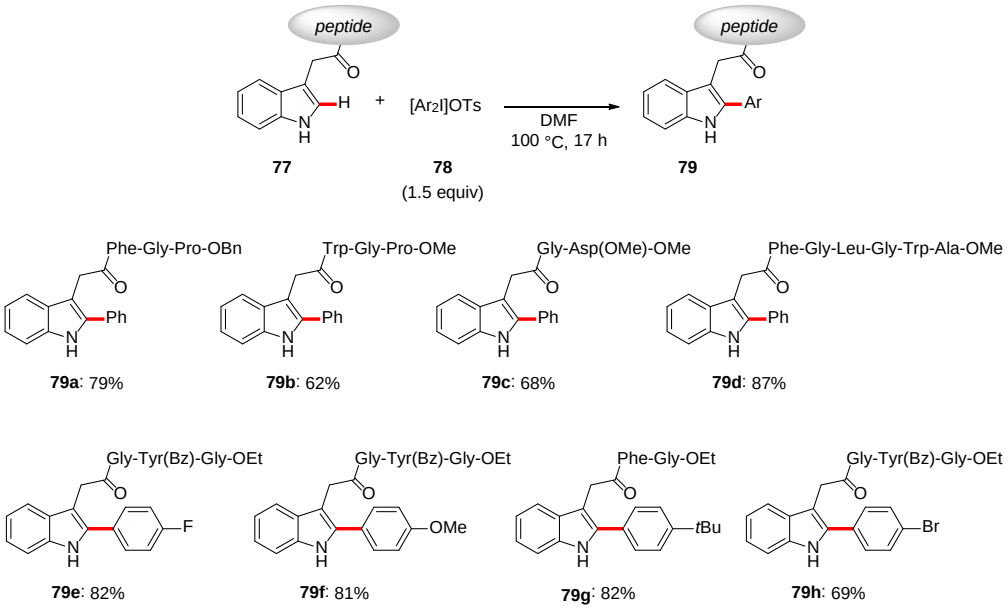
A second example of a ruthenium-catalyzed C2 arylation was presented by Pilarski and coworkers (Scheme 43).[43] In this case four equivalents of ferroceneboronic acid, 2.5 mol % $[RuCl_2(p\text{-cymene})]_2$, 12 mol % $AgSbF_6$ and one equivalent of $Cu(OAc)_2 \cdot H_2O$ were used. The reaction was set up in isopropanol at 120 °C and the product **67fc** was obtained in 76% yield. This example nicely demonstrated a dye labeling of tryptophan, since ferrocene absorbs light in the visible spectral range.



56f **31c** (4 equiv) **67fc**: 76%

Scheme 43: Ruthenium-catalyzed C–H arylation of tryptophan.[43]

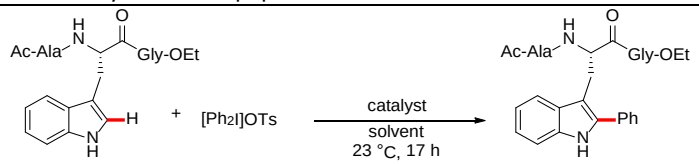
A metal-free approach to C2-arylated peptidomimetics was realized by the group of Ackermann (Scheme 44).[39] The simple catalytic system contained only the two substrates, namely a peptide **77** and a diaryliodonium salt **78**, in DMF. The reaction mixture was heated to 100 °C, delivering peptides **79** in good yields. During the optimization of this reaction, the influence of the diaryliodonium counterion on the product yields became clear. Tosylates **78** turned out to be better suited than tetrafluoroborates, trifluoroacetates or bromides. A range of di- and tripeptides **77** as well as a hexapeptide successfully underwent the transformation with differently-substituted diaryliodonium salts **78**.



Scheme 44: Metal-free C–H arylation of indole peptides.

Under metal-free conditions the indolylacetamide moiety was exclusively arylated, even in the presence of the indole of a tryptophan (Scheme 44). In contrast, under palladium catalysis the tryptophan indole was C–H arylated. The palladium-catalyzed C–H arylation approach developed by the Ackermann group gave rise to arylated peptides **81** using diaryliodonium salts **78** (Table 1).[88] The first optimization approach regarding the C–H arylation of the tripeptide **80a** with 1.5 equivalents of diphenyliodonium tosylate (**78a**) revealed that different copper species combined with various solvents were only able to perform the arylation with unsatisfactory yields of at most 41% (entry 1). The use of palladium as the catalyst gave much better results (entries 2–12). A reaction using 5.0 mol % $Pd(OAc)_2$, $[(MeCN)_2PdCl_2]$ or $Pd(TFA)_2$ as catalysts and either DCE or acetic acid as the solvent, at ambient temperature turned out to be the most suitable conditions by giving the desired product **81aa** in up to 99% yield (entries 4, 5, 10, 11). Lowering the palladium loading to 2.5 or 0.5 mol % still delivered the arylated peptide **81aa** in acceptable yields of 68 and 61%, respectively (entries 6 and 7).

Table 1: Optimization of the C–H arylation of tripeptide **80a**.[a, 88]



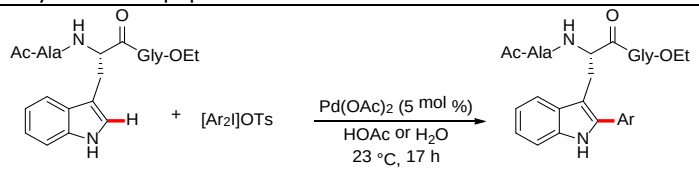
80a **78a** (1.5 equiv) **81aa**

entry	catalyst (5.0 mol %)	solvent	yield
1	Cu(I) or Cu(II)	various	0–41%
2	$Pd(OAc)_2$	DMF	59%
3	$Pd(OAc)_2$	toluene	66%
4	$Pd(OAc)_2$	DCE	85%
5	**$Pd(OAc)_2$**	**HOAc**	**99%**
6	$Pd(OAc)_2$ (2.5 mol %)	HOAc	68%
7	$Pd(OAc)_2$ (0.5 mol %)	HOAc	61%
8	$Pd(OAc)_2$	CF_3CO_2H	39%
9	$PdCl_2$	HOAc	52%
10	$(MeCN)_2PdCl_2$	HOAc	99%
11	$Pd(TFA)_2$	HOAc	99%
12	$Pd(TFA)_2$	CF_3CO_2H	46%

a: Reaction conditions: **80a** (0.20 mmol), **78a** (0.30 mmol), catalyst (5 mol %), solvent (3.0 mL), 23 °C, 17 h.

Using the optimal conditions shown in entry 5, the scope was examined with symmetrical and unsymmetrical diaryliodonium salts, providing the corresponding peptides **81** in high yields (Table 2). Further exploration of this arylation method even allowed the use of water as the reaction medium. Consequently, the scope of the reaction of peptide **80a** with symmetrical diaryliodonium tosylates **78** was reexamined with water instead of the organic solvent, which afforded peptides **81**.

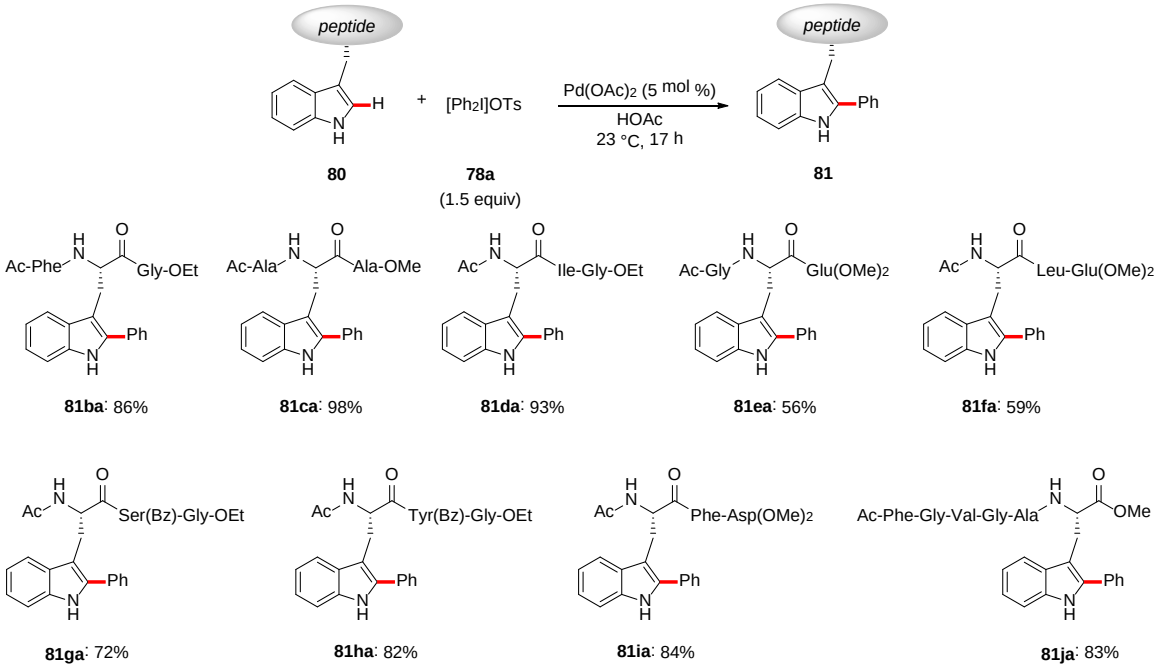
Table 2: Scope of the C–H arylation of tripeptide **80a.**[88]



80a **78** (1.5 equiv) **81**

entry	Ar	compound	yield in HOAc	yield in H_2O
1	C_6H_5 (**78a**)	**81aa**	99%	70%
2	4-$MeOC_6H_4$ (**78b**)	**81ab**	85%	80%
3	2,4-$Me_2C_6H_3$ (**78c**)	**81ac**	51%	71%
4	4-FC_6H_4 (**78d**)	**81ad**	93%	95%
5	4-ClC_6H_4 (**78e**)	**81ae**	94%	64%
6	4-BrC_6H_4 (**78f**)	**81af**	79%	54%

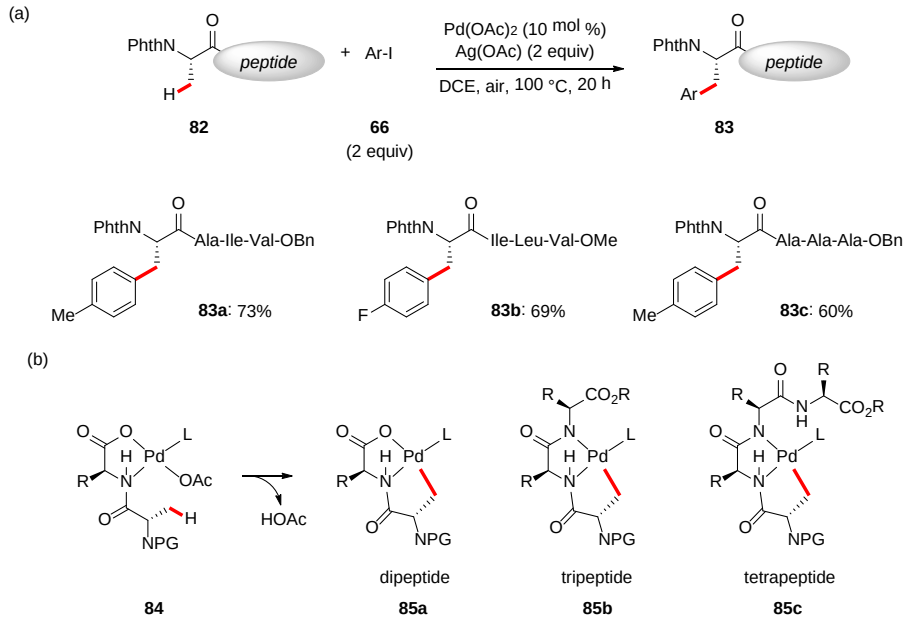
In order to examine the applicability of this method to other peptides, several different tryptophan peptides **80** were submitted to the phenylation with diphenyliodonium tosylate (**78a**) (Scheme 45). Peptides **81** bearing aliphatic and aromatic amino acids as well as methyl ester protected glutamic and aspartic acid and benzoyl protected serine and tyrosine were isolated in good to excellent yields of 56–98%.



Scheme 45: Scope with various tripeptides **80**.[88,89]

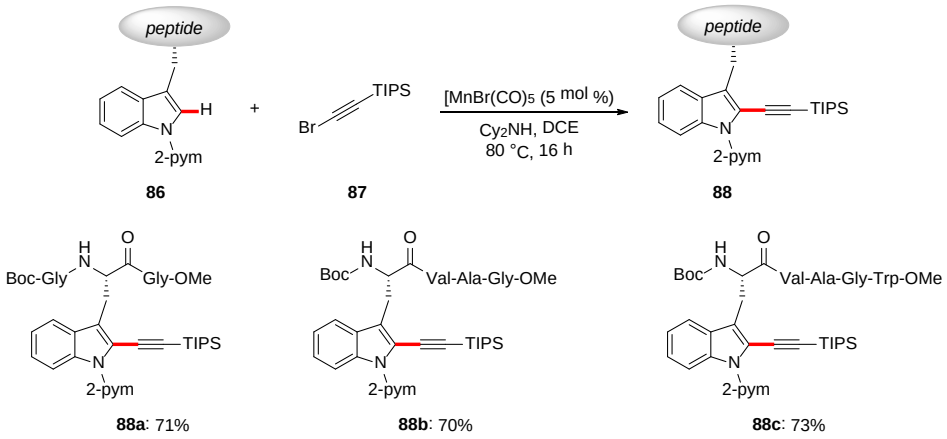
The results for this palladium-catalyzed C–H arylation method set the stage for further examination of this reaction in this thesis.

While the cleavage of the relatively activated C(sp^2)–H bonds was realized straightforward, the activation of the more challenging C(sp^3)–H bonds was also achieved. In their studies on the application of peptides as ligands for palladium-catalyzed C–H activation reactions, the Yu group reported on the arylation and acetoxylation of *N*-terminal alanine in di-, tri- and tetrapeptides **82** (Scheme 46a).[90] With the arylation of alanine, newly substituted phenylalanine peptides **83** were prepared. $Pd(OAc)_2$ was used as the catalyst with no need for additional ligands, since the peptide is believed to take over this role. The proposed complexes **85** show the peptides pincer-like wrapping the palladium (Scheme 46b).



Scheme 46: Palladium-catalyzed C(sp^3)–H arylation of alanine. (a) Scope of the arylation reaction and (b) proposed palladium complexes of the C–H activated peptides.

Moreover, other C–C bond forming reactions were demonstrated recently, such as C–H carbonylation cyclization of valine,[91] diastereoselective arylation of proline[92] as well as arylations of glycine[93] and alkynylation of tryptophan,[94] such as the manganese-catalyzed C–H alkynylation of tryptophan peptides **86** with bromoacetylenes **87** developed by the Ackermann group in 2017 (Scheme 47).[93d]



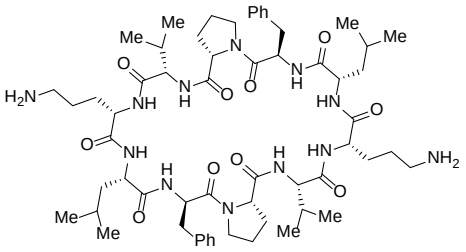
Scheme 47: Manganese-catalyzed C–H alkynylation of peptides.

Another aim of C–H modification reactions on peptides is the formation of carbon-heteroatom bonds. For example, the introduction of ^{18}F can be used for radiolabeling of drug peptides for tracing.[95] So far, selective methods have been developed using a manganese[96] or a palladium[97] catalyst to afford β-fluorinated α-amino acids.

To summarize, while tag and modify strategies are frequently applied to proteins, C–H modification reactions are scarcely used and the proof-of-concept reports that exist today are limited to small peptides. Despite the notable progress over the past decade, there is still much room for improvement.

1.4.2 Chemical Peptide Cyclization including On-Resin Reactions

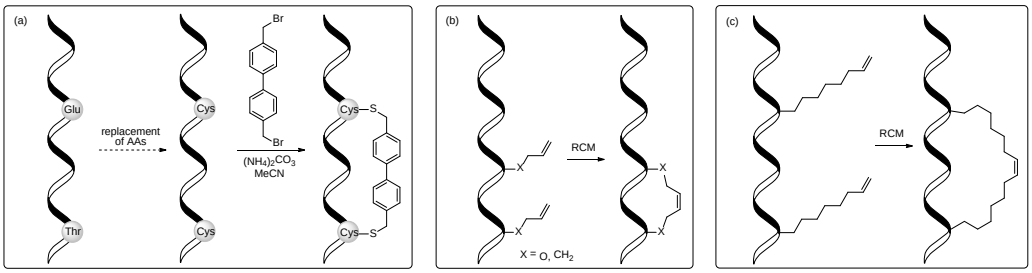
The first bioactive cyclopeptide, gramicidin S (**89**, Scheme 48), was discovered in 1947.[99] Since then, attention for cyclopeptides has been rising and chemical cyclization methods for cyclopeptides[100] and structurally related cyclopeptide alkaloids[101] have been developed. The term cyclopeptide is referred to as any form of cyclized peptide, in particular these are side chain to side chain cycles, backbone cycles, terminus to side chain cycles and backbone cycles containing an inhibitory-cysteine knot (ICK) domain. Naturally occurring peptides are associated with diverse biological activities, such as cytotoxic, antimicrobial and anti-HIV properties. The cyclization of a peptide increases its molecular stability and thus enhances its resistance towards degradation and therefore increases its half-life.[108] This is of particular interest for the development of orally available pharmaceuticals.



89

Scheme 48: Gramicidin S.

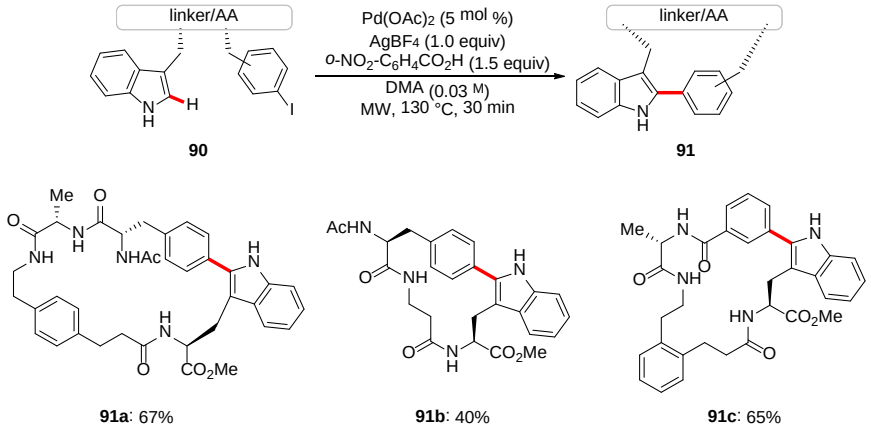
Chemical cyclization of peptides has been realized via hydrocarbon stapling, like click reactions[102] and ring-closing metathesis (RCM),[103] hydrogen bond surrogate (HBS) stapling,[104] intramolecular disulfide formation,[105] peptide grafting[106] and by use of lasso peptides[107] (Scheme 49).



Scheme 49: Examples for peptide helix stabilization by cyclization. (a) Attachment of cysteines to a biaryl. (b) RCM to stabilize one coil. (c) RCM to stabilize two coils.

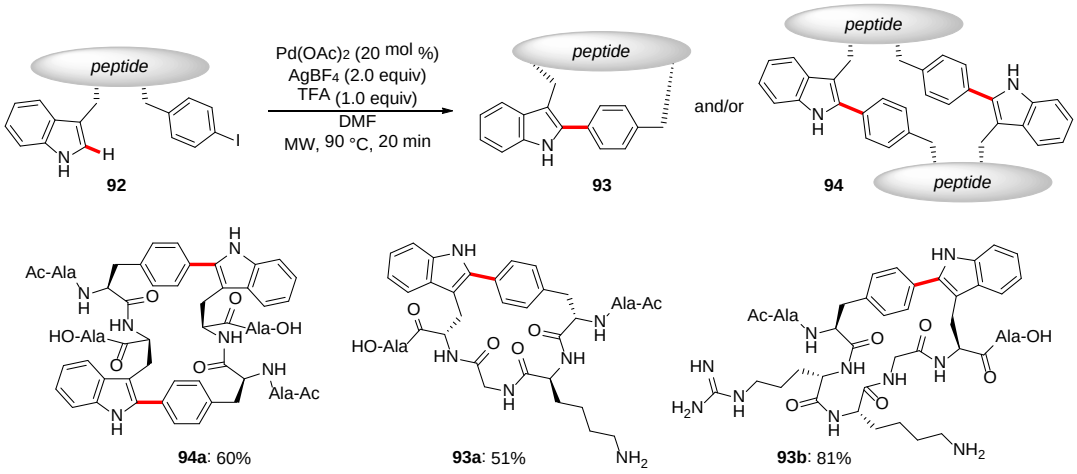
Backbone cyclizations can be achieved on-resin directly after SPPS utilizing resins with certain linkers to cleave the peptide from the resin through the cyclization procedure. Alternatively, certain cleavage procedures based on thioesters allow cyclization in solution.[109,110]

Many cyclization reactions including metatheses, cross-coupling and click reactions, can also be carried out on the solid support.[100e] Additionally, C–H activation methods have been applied for cyclizing peptides.[111] Dong and coworkers used a palladium-catalyzed C–H arylation procedure to connect *para*- or *meta*-iodophenylalanine and tryptophan within a peptide **90** (Scheme 50).[111b] This C–H activation strategy gave rise to peptidomimetics **91**, which contain alkane or alkylarene linkers and amino acids within the newly formed cycle. According to the Ruggli-Ziegler dilution principle, the reactions were performed at a low concentration of 0.03 M.



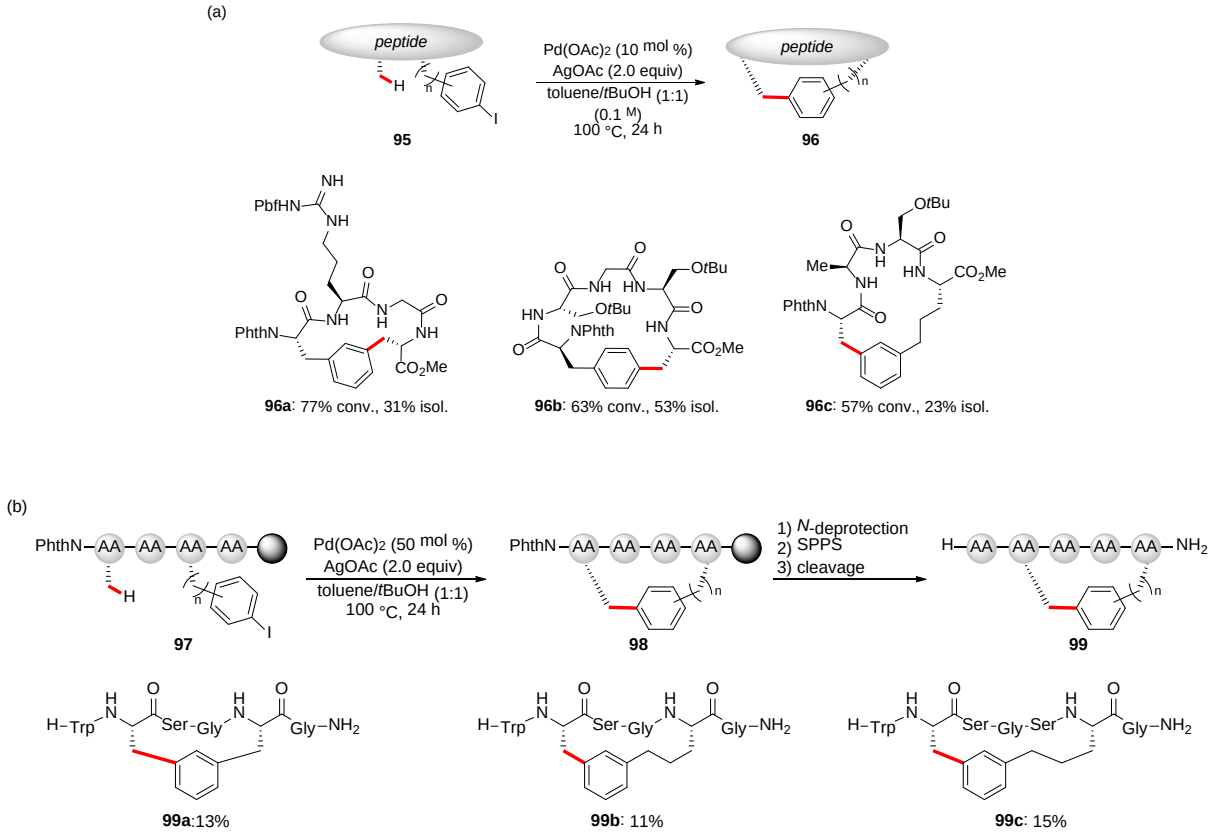
Scheme 50: Cyclization via palladium-catalyzed arylation of tryptophan.

The groups of Lavilla and Albericio demonstrated a palladium-catalyzed cyclic dimer formation of tryptophan-peptides containing an *ortho*-, *meta*- or *para*-iodophenylalanine (Scheme 51).[111a] In order to prevent polymerization, the reactions were carried out at relatively low peptide concentrations of 0.10–0.25 M. Still, for *i*,*i*+1- and *i*,*i*+2-amino acid distance between tryptophan and *para*-iodophenylalanine the formation of dimer **94** was predominant, while for larger peptides with a *i*,*i*+3- and *i*,*i*+4-located tryptophan and *para*-iodophenylalanine mainly the cyclic monopeptides **93** were obtained.



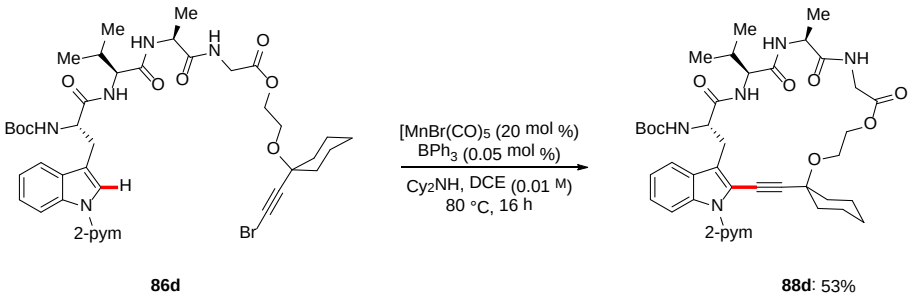
Scheme 51: Cyclization via palladium-catalyzed arylation of tryptophan.[111a]

Furthermore, the work of Albericio showed a palladium-catalyzed C(sp^3)–H arylation of the methyl group of alanine peptides with iodophenylalanine and its derivatives **95** (Scheme 52).[111c] Several cyclic peptides **96** were obtained by this procedure. In addition, this method was demonstrated exemplarily for the cyclization of peptides that were still anchored to the solid support. SPPS was carried out up to the phthalide protected alanine residue that was subjected to the C–H arylation. The cyclization reaction was set up with a higher amount of the catalyst and thereafter, the peptide was prolonged by SPPS, after which a standard cleavage procedure afforded cyclic peptides **99**. On-resin peptide modifications have unbeatable advantages compared to reactions in solution. The purification, which is one major issue in peptide chemistry, is easily done just by washing out all reagents, without any loss of peptide. The reaction can be driven to completion by using a large excess of any reagent without hindering the purification procedure. Additionally, the poor solubility of polar peptides in organic solvents does not need to be of concern. Also no aggregation or jellification can occur. Especially for cyclization reactions, the resin-supported approach is powerful, because no dimers or polymers can be formed, whereas the reaction can be performed at high substrate and catalyst concentrations. This facilitates higher reaction rates as compared to diluted reaction mixtures. The necessary amount of solvent only depends on the swelling properties of the employed resin. After cleavage of the peptide from the resin, the yields depend mainly on the completeness of the cleavage and on the purification procedure.



Scheme 52: Cyclization via palladium-catalyzed arylation of alanine (a) in solution and (b) on-resin.[111c]

The already mentioned manganese-catalyzed C–H alkynylation approach (Scheme 47) was also applied for the cyclization of a peptide (Scheme 53). The bromoalkyne was introduced into the peptide **86d** via an ethyleneglycole moiety at the *C*-terminus. This allowed the formation of the cyclopeptide **88d**.



Scheme 53: Cyclization via manganese-catalyzed C–H alkynylation.

In summary, large advances in peptide and protein modification and functionalization methods have been achieved in recent years. Selective transformations enable specific applications and facilitate biological studies. So far, applications described in the literature range from

✧ labeling via introduction of radioactive or heavy isotopes or fluorophores,

✧ change of solubility via PEGylation,

✧ change of the peptide function via glycosylation, phosphorylation, biotinylation, lipidation, ubiquitination or cyclization

✧ stabilization of the three-dimensional structures to enhance reactivity via cyclization,

✧ ligations to provide access to otherwise non-feasible syntheses of peptides,

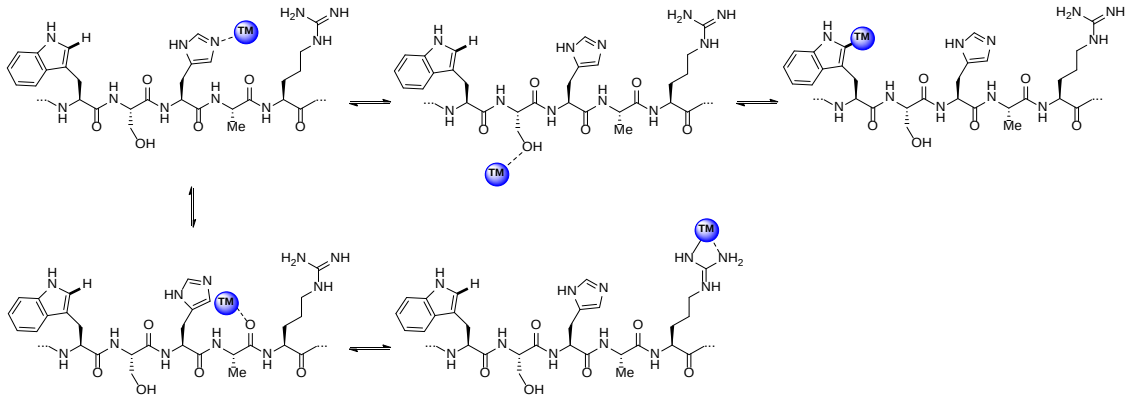
✧ change of properties for oral administration of peptide therapeutics[112] as well as

✧ change of peptide properties to diversify food properties.[113]

Besides biological applications, chemical syntheses also make use of peptide modifications, for example by using peptides as ligands for stereoselective reactions or by mimicking biological systems to facilitate the construction of complex structures.

2 Objectives

C–H activation has emerged as a powerful tool for selective and more efficient chemical syntheses in comparison to previously used strategies. For modification of peptides, reactions relying on the direct C–H cleavage are scarce as different kinds of drawbacks need to be overcome. Many C–H activation procedures require the exclusion of air and water, the use of strong bases, which could racemize the stereocenters of amino acids and/or damage certain functionalities, or the use of strong acids, which could cleave the amide bonds or demolish other functional groups associated with peptides. Another obstacle can be a significantly decreased reaction rate, due to the fact that peptides posses several Lewis basic sites, which increase the possibilities to coordinate and chelate the transition metal at different positions (Scheme 54). This circumstance reduces the probability of coordination to the transition metal in the desired position and therefore results in a less efficient catalysis.



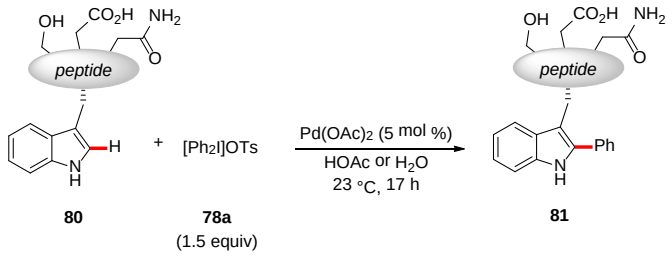
Scheme 54: Examples for coordination of the transition metal at different sites in a peptide.

Regarding the potential of and need for new peptide designs, the goal of this thesis was to develop C–H activation reactions that can be applied to peptides. Tryptophan was the amino acid of choice, because of its relatively low natural abundance and its distinct spectroscopic properties.

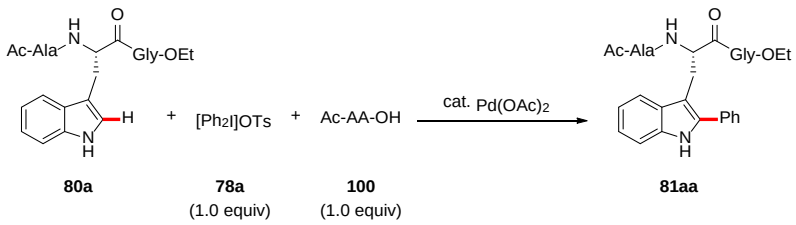
2.1 Palladium-Catalyzed C–H Arylation with Diaryliodonium Salts

Lavilla[86a,b] and Fairlamb[86c,d] presented two approaches for the palladium-catalyzed C2–H arylation of tryptophan peptides using aryl iodides or arylboronic acids as arylating agents. In contrast, in our group, a metal-free C2–H arylation of indole-3-acetamides **77** was developed (Scheme 44).[39] This method has two main advantages, namely transition metal-free reaction conditions and the use of diaryliodonium salts as mild electrophiles. However, this method is limited to peptides bearing an unnatural indole-3-acetamide fragment, as the procedure selectively facilitated the arylation of the

indole-3-acetamide moiety, while no reaction of a tryptophan indole moiety was observed. Based on these findings and the intention to use natural tryptophan peptides directly, a palladium-catalyzed procedure with diaryliodonium salts was developed by Dr. Yingjun Zhu and further examined by Michaela Bauer in our group. In order to extend the scope of this method, its applicability to peptides **80**, which bear amino acids with unprotected functionalities, should be examined (Scheme 55). Moreover, the robustness of this procedure was to be probed further by carrying out the reaction of the tripeptide **80a** with diphenyliodonium tosylate (**78a**) in the presence of one equivalent of an amino acid **100**, which bears further unprotected functional groups (Scheme 56).



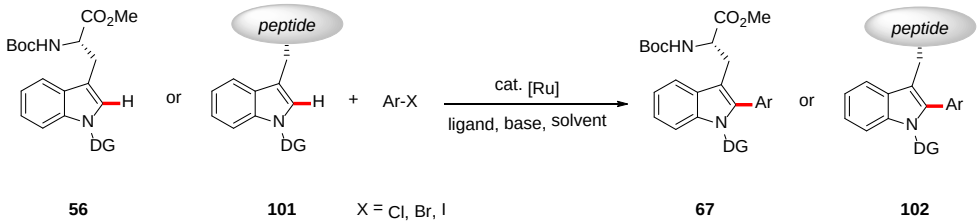
Scheme 55: Palladium-catalyzed C–H arylation of unprotected peptides.



Scheme 56: Palladium-catalyzed arylation of peptide **80a** in the presence of amino acids **100**.

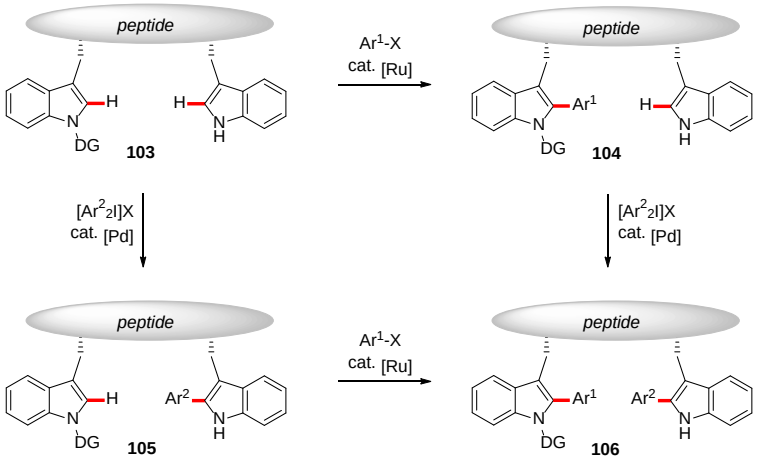
2.2 Ruthenium-Catalyzed C–H Arylation of Tryptophan-Containing Peptides

Despite the advantages and versatility associated with palladium as a catalyst for C–H activation reactions, which are described in chapters 1.1 and 1.4, some drawbacks remain. A reasonable alternative is ruthenium, because it is considerably cheaper than palladium[114] and still capable to perform diverse C–H transformations as described in chapters 1.2–1.4. Based on the example of the ruthenium-catalyzed C–H arylation of pyrimidyl tryptophan *rac*-**56e** with aryl bromide **28b** (Scheme 42),[40] a similar procedure for tryptophans **56** should be developed (Scheme 57). Additionally, the applicability to tryptophan peptides **101** should be explored. While the example shown by our group (Scheme 42)[40] was performed with a racemic substrate *rac*-**56e**, for subsequent studies enantiomeric pure L-tryptophan **56e** should be used to exclude a potential racemization of the tryptophan during the catalytic reaction.



Scheme 57: Ruthenium-catalyzed C–H arylation of tryptophan peptides.

To exploit the contrary reactivities of palladium and ruthenium, peptides **103** containing an *NH*-free tryptophan and one with a directing group were to be submitted to a subsequent selective twofold C–H arylation (Scheme 58).



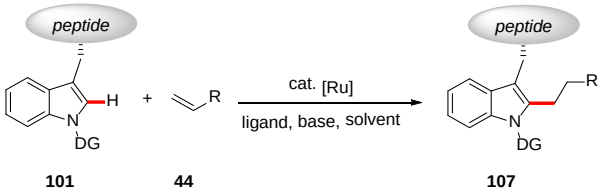
Scheme 58: Sequential twofold C–H arylation of peptides **103**.

2.3 Ruthenium-Catalyzed C–H Alkylation of Tryptophan-Containing Peptides

Among the C–H activation strategies applied for modifications of peptides, arylation reactions have been most extensively studied. The incorporation of an aryl group has certain effects on the substrate, such as a significant change of the fluorescent and absorption properties, as well as a potential change of the three-dimensional structure due to the formation of twisted biaryls in the case of tryptophan, tyrosine and histidine. Contrasting these effects, alkylation of peptides may be used for alternative intentions. For example, the introduction of long aliphatic chains could help to solubilize polar peptides in organic solvents. Furthermore, alkylation might help to prevent precipitation since long aliphatic chains hinder crystal packing.

Since thus far only very few examples for C–H alkylation reactions on peptides are known, our interest arose in developing C–H alkylation methods that are suitable for peptides. Based on the ruthenium-catalyzed hydroarylation procedure published by our group (Scheme 28),[57e] a related

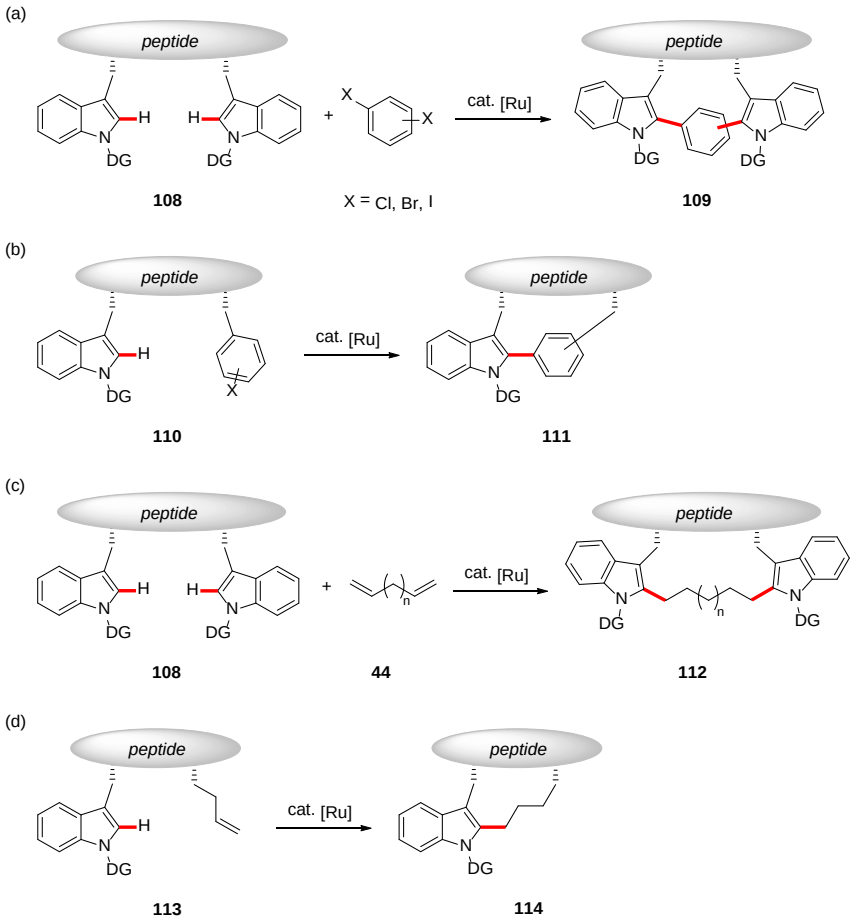
approach for peptides should be feasible (Scheme 59). Analogous to the conversion of phenylpyridines **47** with unactivated alkenes **44** in the presence of a ruthenium catalyst and a carboxylate salt, tryptophan peptides **101** should be able to hydroarylate alkenes **44** to provide alkylated peptides **107.**



Scheme 59: Ruthenium-catalyzed C–H alkylation of tryptophan peptides.

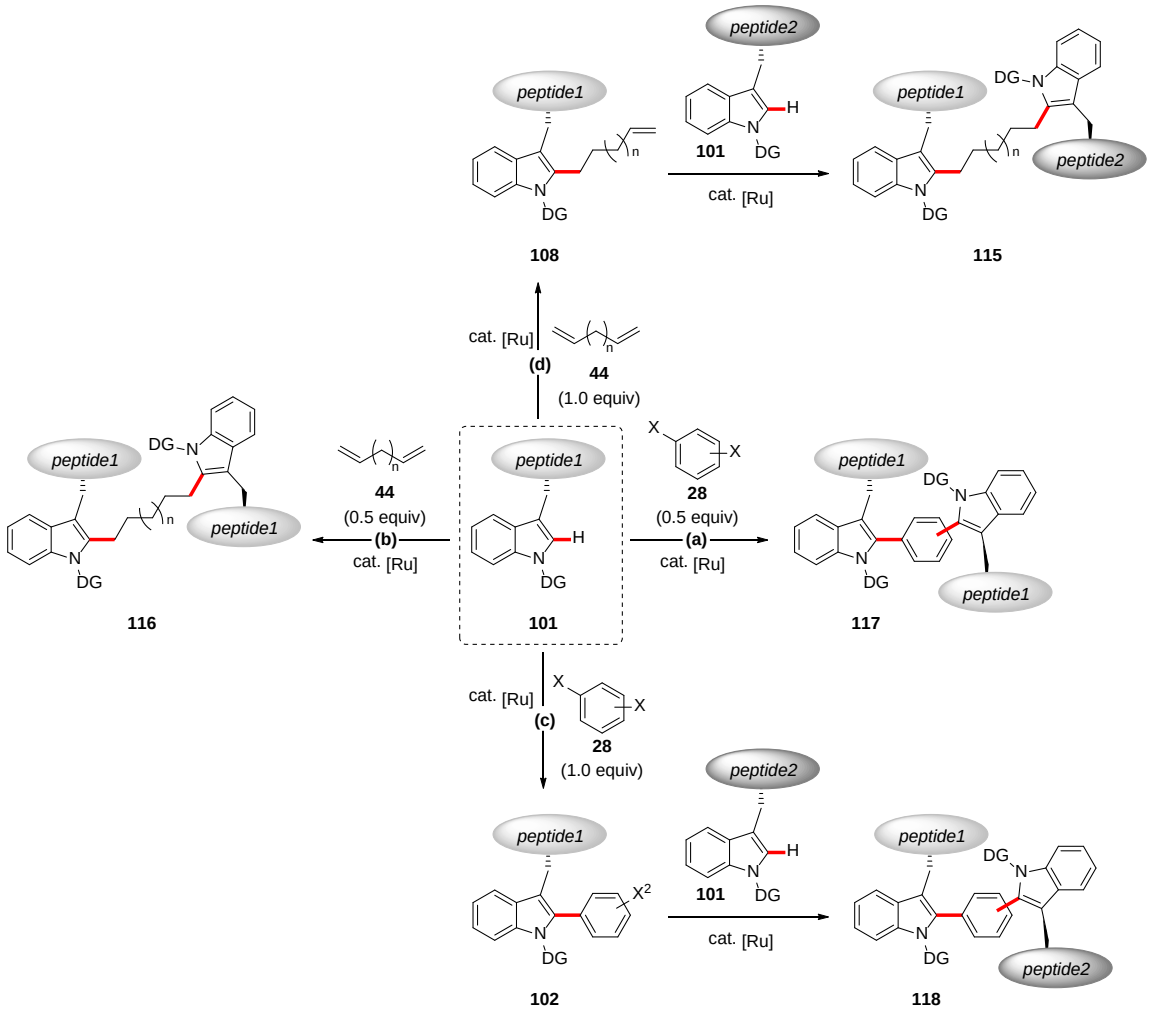
2.4 Applications for the C–H Functionalization Reactions

Among the C–H activation procedures presented in chapters 2.1–2.3, cyclization reactions of peptides had inter alia the highest level of our interest. The importance of chemical cyclization of peptides is described in chapter 1.4.2. Peptides could be cyclized by a C–H arylation strategy using a dihaloarene (Scheme 60 a) to doublearylate a peptide **108**, which contains two tryptophans. Another possibility (b) could be the incorporation of a halogenated phenylalanine into a tryptophan peptide **110**, which could then be cyclized through ruthenium catalysis, leading to cyclopeptides **111**. Additionally, comparable methods based on the hydroarylation procedure presented in chapter 1.3 appeared feasible. A twofold alkylation (c) of peptide **108** with a dialkene **44** would lead to cyclopeptides **112**, while an intramolecular alkylation (d) of tryptophan peptides **113** that contain an amino acid with a terminal alkene, would provide cyclic peptides **114**.



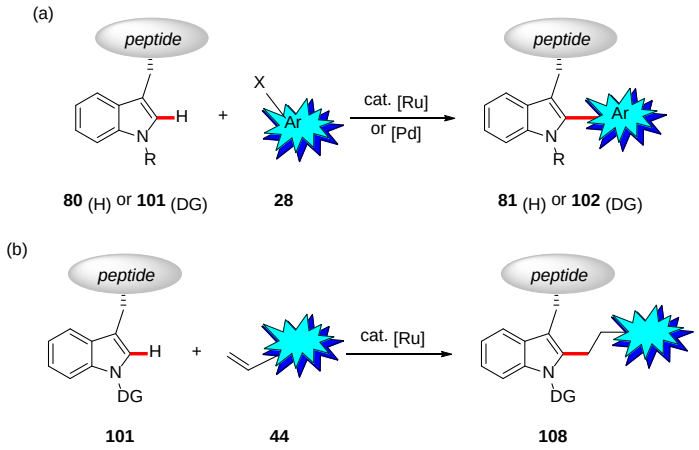
Scheme 60: Peptide cyclization by (a) twofold C–H arylation, (b) intramolecular C–H arylation, (c) twofold hydroarylation and (d) intramolecular hydroarylation.

Another application of interest was the ligation of peptides. Peptide ligation does not only give rise to larger peptides, which otherwise might be difficult to prepare and infeasible to purify, it also allows the construction of new peptide motifs and unusual peptide branchings. Conceivable methods for peptide ligation could be the reaction of a tryptophan peptide **101** with (a) 0.5 equivalents of a dihaloarene **28** or with (b) 0.5 equivalents of a dialkene **44** to provide dimerlike peptides **117** and **116**, respectively (Scheme 61). If peptide **101** underwent a coupling with (c) one equivalent of a dihaloarene **28** or with (d) one equivalent of a dialkene **44**, the corresponding products **102** and **108** would be formed. These could undergo another similar arylation or alkylation reaction with a peptide **101**, which would form the ligation products **118** and **115**.



Scheme 61: Peptide ligation by (a) twofold C–H arylation with identical peptides, (b) twofold C–H arylation with different peptides, (c) twofold hydroarylation with identical peptides and (d) twofold hydroarylation with different peptides.

In addition to the already characteristic spectroscopic properties of tryptophan, another aim of this work was to label peptides, including labeling with fluorescent moieties (Scheme 62). This should be accomplished by (a) C–H arylation of peptides **68** or **101** with highly fluorescent aryl halides **28**, which feature extended conjugated π-systems. This method seems suitable because the arylation itself already extends the π-system of the indole. Moreover, the hydroarylation method (b) using an alkene **44** that is carrying a fluorophore should also be viable.



Scheme 62: Peptide labeling by (a) C–H arylation and (b) hydroarylation.

3 Results and Discussion

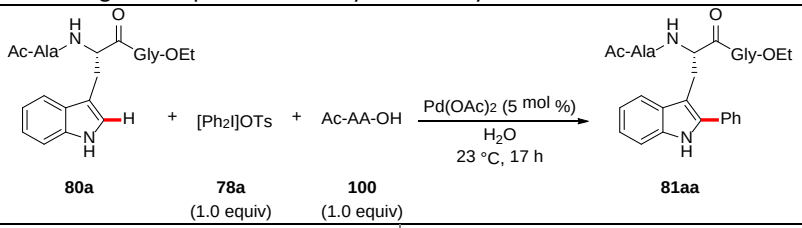
3.1 Palladium-Catalyzed C–H Arylation of Tryptophan-Containing Peptides with Diaryliodonium Salts

Lavilla[86a,b] and Fairlamb[86c,d] have presented palladium-catalyzed procedures for the direct C–H arylation of tryptophan peptides. Nonetheless, in order to obtain high conversions, those methods required a relatively high catalyst loading, an excess of the arylating agent, oxidants and elevated temperatures. In contemplation of the harshness of those reaction conditions, a mild protocol for the direct C–H arylation of tryptophan peptides was developed by our group (Scheme 45).[88]

Since this palladium-catalyzed arylation method was only applied to protected peptides so far, the robustness of this procedure had to be proven by an intermolecular competition screening.[115]

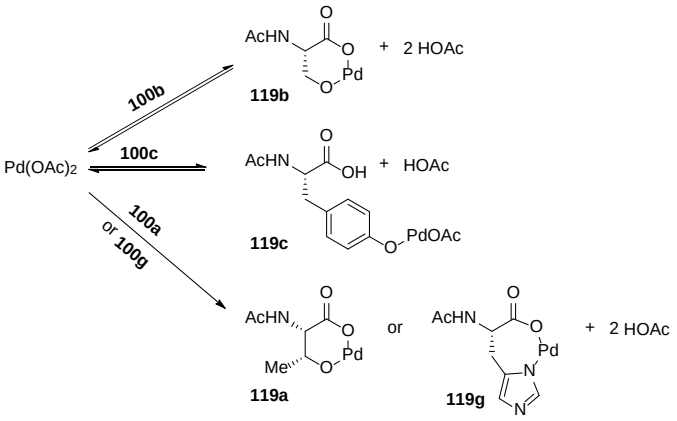
For this purpose peptide **80a** was reacted with one equivalent of diphenyliodonium tosylate (**78a**) in the presence of one equivalent of an acetylated amino acid **100** in water as the reaction medium (Table 3). After 17 h at ambient temperature the product **81aa** was isolated. When no additional amino acid **100** was added, the product **81aa** was isolated with a yield of 68% (entry 1). In the case of free hydroxygroup-containing amino acids as additives, the resulted yield of peptide **81aa** was found to be inconsistent (entries 2–4). While tyrosine **100c** and serine **100b** affected only a slight decrease of the yield, the addition of threonine **100a** shut down the reaction. The reason might be a coordination and binding of the amino acids **100** to palladium, forming catalytically inactive complexes **119** (Scheme 63). The same applies to histidine (entry 8). The addition of free amides **100d** and **100e** caused a slight decrease of the yield. In contrast, the presence of glutamic acid **100f** increased the reaction rate, yielding 80% of product **81aa**. As glutamic acid is diprotic, it can be speculated that protons are involved in the catalytic process and a higher acid concentration has a positive effect on the reaction rate. This finding is in accordance with the previously achieved full conversion of substrate **80a** when using acetic acid as the reaction medium. The reaction with glutamic acid was performed by Dr. Yingjun Zhu (entry 7).

Table 3: Robustness screening for the palladium-catalyzed C–H arylation.[a]



entry	AA	yield	entry	AA	yield
1	-	68%	5	Asn (**100d**)	17%
2	Thr (**100a**)	10%	6	Gln (**100e**)	52%
3	Ser (**100b**)	46%	7	Glu (**100f**)	80%[b]
4	Tyr (**100c**)	60%[b]	8	His (**100g**)	6%

a: Reaction conditions: **80a** (0.20 mmol), **78a** (0.20 mmol), **100** (0.20 mmol), $Pd(OAc)_2$ (5 mol %), H_2O (3.0 mL), 23 °C, 17 h. b: The reaction was performed by Dr. Yingjun Zhu.



Scheme 63: Possible binding of amino acids to palladium.

The desire to use a solvent milder than acetic acid and to achieve full conversions at the same time led to further attempts to optimize the reaction of peptide **80a** with diphenyliodonium tosylate (**78a**). An analysis of the pH course of the reaction in water using a digtal pH meter with a glas electrode placed in the reaction tube showed a pH of 3.2 at the beginning of the reaction (Figure 1). During the first five hours the pH smoothly declined to 1.8, due to the formation of tosylic acid during the reaction. The reaction thus is proposed autocatalyic, because acid accelerates the reaction rate. With these findings in hand, initial additions of acids to the reaction mixture were probed.

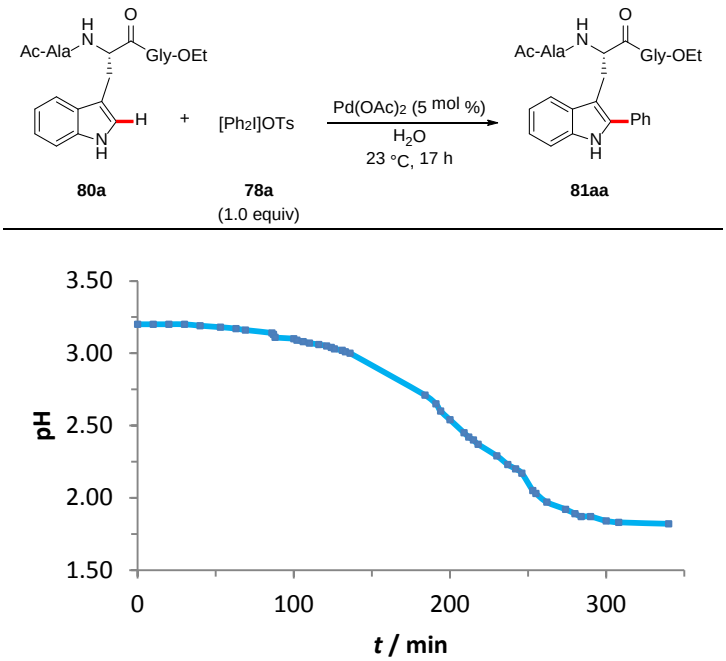
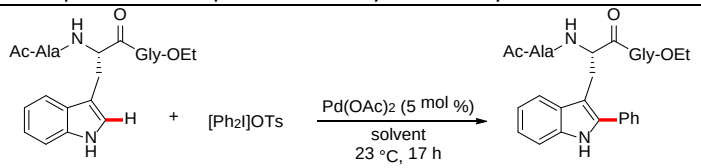


Figure 1: pH curve of the palladium-catalyzed coupling of peptide **80a** with diphenyliodonium tosylate (**78a**).

The addition of two equivalents of acetic acid provided an unsatisfactory result (Table 4, entry 2). As during the reaction of the tosylate salt **78a** tosylic acid is formed, an addition of one equivalent of tosylic acid was probed (entry 3). The resulting yield of 50% was even lower than without the addition of acid (entry 1). For the pH curve has the biggest slope at pH 2.5, it can be assumed, that the reaction rate was highest at this point. Therefore, a phosphate buffer of pH 2.5 as the reaction medium was probed, which gave a disappointing result of 44% yield (entry 4). Because the substrate **78a** is barely dissolvable in water at ambient temperature, the phase transfer catalyst tetrabutylammonium bromide (TBAB) was added (entry 5). This shut down the reaction. A slight excess of 1.5 equivalents of tosylate **78a** increased the yield to 80% (entry 6), but the conversion remained incomplete. Since the optimization attempts did not succeed, for further reactions 1.5 equivalents of the arylating agent **78** and acetic acid or water as the solvent were used.

Table 4: Attempts for further optimization of palladium-catalyzed C–H arylation.[a]



80a **78a** (1.0 equiv) **81aa**

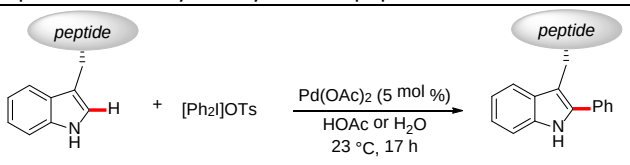
entry	solvent	additive	yield
1	H_2O	-	68%
2	H_2O	HOAc (2 equiv)	77%
3	H_2O	HOTs (1 equiv)	50%
4	phosphate buffer pH 2.5	-	44%
5	H_2O	TBAB (10 mol %)	0%
6	H_2O	-	80%[b]

a: Reaction conditions: **80a** (0.20 mmol), **78a** (0.20 mmol), $Pd(OAc)_2$ (5 mol %), solvent (3.0 mL), 23 °C, 17 h. b: 1.5 equiv **78a** were used.

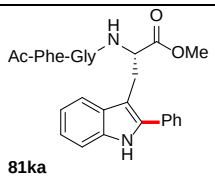
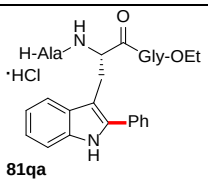
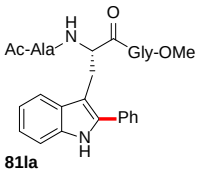
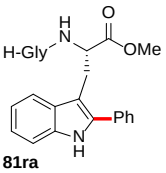
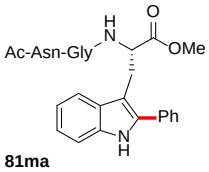
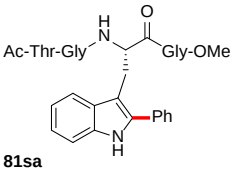
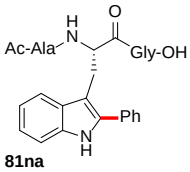
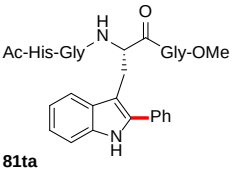
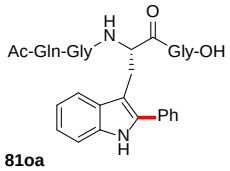
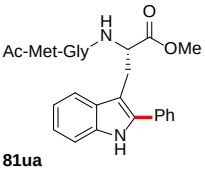
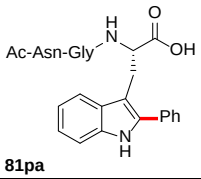
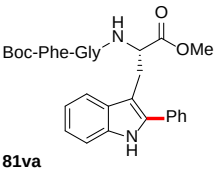
In order to expand the substrate scope shown in scheme 45, peptides **80** were reacted with diphenyliodonium tosylate (**78a**) to yield arylated peptides **81** (Table 5). As expected, fully protected peptides **80k** and **80l** and a free amide bearing peptide **80m** were converted to afford high yields of 52, 96 and 85% when using acetic acid, and slightly reduced yields when using water as the solvent (entries 1–3). Due to the relatively unpolar nature of phenylalanine and its resulting low solubility in water, peptide **80k** was isolated with a low yield of 25% after the reaction in water. Tripeptide **80n** with an unprotected C-terminus was obtained with a high yield when reacted in acetic acid, and a lower yield when water was used (entry 4). The free amide and carboxyic acid containing substrate **80o** was transformed to the product **81oa** in acetic acid in 72% yield (entry 5). The structurally similar peptide **80p** was reacted in water, but afforded only little formation of 20% of product **81pa**, which was determined by ^{1}H NMR measurement (entry 6). Neither free amine hydrochloride salt **80q** nor free amine peptide **80r** were tolerated by this palladium-catalyzed C–H arylation (entries 7 and 8). The products **81qa** and **81ra** were not detected and the corresponding starting materials were reisolated. Tetrapeptides **81s** and **81t** bearing *tert*-butyl and trityl protected threonine and histidine, respectively, were submitted to the catalytic reaction in acetic acid in order to cleave the acid labile protecting groups and thus set free the hydroxyl group and the imidazole during the reaction (entries 9 and 10). In both cases, a complex mixture of several arylated compounds was found, which could not be separated. Methionine-containing substrate **80u** was not converted, likely because thioethers are strong Lewis bases and hence potential poisons to the catalyst (entry 11). For the reason that the synthesis of small peptides, such as the presented tri- and tetrapeptides, is conventionally carried out in solution, which is much cheaper than SPPS, the peptides were assembled stepwise from Boc-protected amino acids. For the synthesis of peptides **80** the *N*-terminal acetylation is the last and

unfortunately relatively low-yielding step. To confront this disadvantageous synthetic step, it is desirable to use Boc-protected peptides directly. Hence, Boc-peptide **80v** was probed in the palladium-catalyzed arylation in acetic acid (entry 12). As expected, the peptide **81va** was partially deprotected and the free amine shut down the reaction, so that no arylated product could be isolated. On the other hand, no deprotection occurred in water. However, due to the low solubility of the unpolar Boc-phenylalanine peptide **80v** and the resulting reduced reaction rate, only 23% yield of product **81va** was obtained.

Table 5: Further scope of the palladium-catalyzed arylation of peptides **80**.



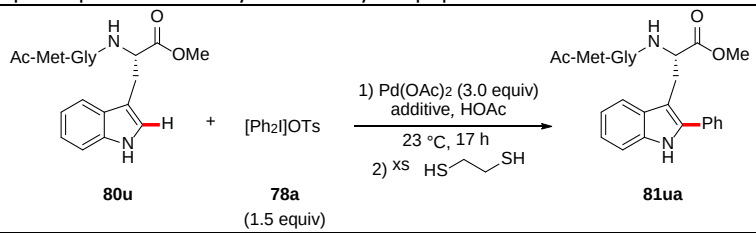
80 **78a** (1.5 equiv) **81**

entry	product	yield	entry	product	yield
1	 **81ka**	25% (H_2O) 52% (HOAc)	7	 **81qa**	0% (H_2O)[c]
2	 **81la**	67% (H_2O) 96% (HOAc)	8	 **81ra**	0% (H_2O)[c]
3	 **81ma**	63% (H_2O) 85% (HOAc)	9	 **81sa**	0% (HOAc)[d]
4	 **81na**	49% (H_2O) 80% (HOAc)	10	 **81ta**	0% (HOAc)[e]
5	 **81oa**	72% (HOAc)	11	 **81ua**	0% (HOAc)
6	 **81pa**	20%[b] (H_2O)	12	 **81va**	23% (H_2O) 0% (HOAc)

a: Reaction conditions: **80** (0.20 mmol), **78a** (0.30 mmol), $Pd(OAc)_2$ (5 mol %), HOAc (3.0 mL) or H_2O (3.0 mL), 23 °C, 17 h. b: The conversion was determined by ^1H NMR (IntStd trimethoxybenzene). c: The reaction was carried out at 40 °C. d: *t*Bu-protected peptide **80s** was used. e: Trityl-protected peptide **80t** was used.

The methionine peptide **80u** possessing a thioether group was anticipated to be challenging, because the thioether is capable to coordinate to palladium irreversibly, and thus stop the catalysis. Further attempts to arylate peptide **80u** were thus done (Table 6) by applying three equivalents of $Pd(OAc)_2$ in order to provide free palladium, while one equivalent is bound to methionine (entry 1). After the reaction no peptide — neither starting material nor product — could be detected in solution. An excess of ethane-1,2-dithiole was added to set free the peptide, but still no peptide could be observed in solution. However, a solid was formed which could not be analyzed by NMR, because it was insoluble in $CDCl_3$ or DMSO-d_6. According to studies regarding the affinity of sulfur to metals, zinc appears to bind sulfur strongest among the probed metals.[116] An addition of zinc might therefore saturate the sulfur and ensure that the palladium stays free to proceed the C–H activation reaction. Nonetheless, neither the addition of three equivalents of elemental zinc nor zinc bromide furnished arylated product **81ua** (entries 2 and 3).

Table 6: Further attempts to palladium-catalyzed C–H arylate peptide **80u**.[a]



80u **78a** (1.5 equiv) **81ua**

entry	additive	yield
1	-	0%
2	Zn (3.0 equiv)	0%
3	$ZnBr_2$ (3.0 equiv)	0%

a: Reaction conditions: **80u** (0.20 mmol), **78a** (0.30 mmol), $Pd(OAc)_2$ (0.60 mmol), additive (0.60 mmol), HOAc (3.0 mL), 23 °C, 17 h.

Overall, these results demonstrated a good compatibility with carboxylic acids and free amides, which are both common functional groups in biological environments. Unfortunately, more sophisticated functional groups, such as hydroxyl groups and amines, imidazoles and thioethers, were not tolerated by the palladium-catalyzed C–H arylation.

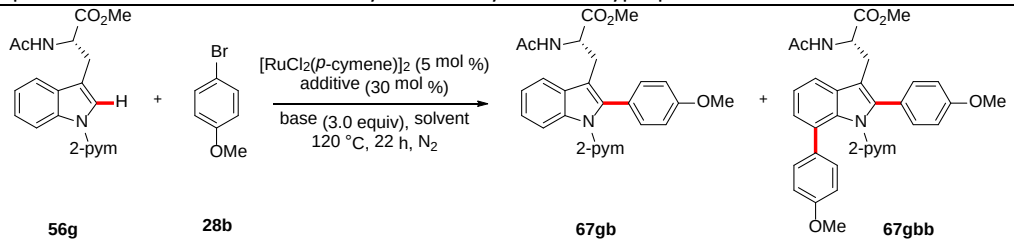
3.2 Ruthenium-Catalyzed C–H Arylation of Tryptophan-Containing Peptides

Based on the ruthenium-catalyzed C–H arylation of indoles with aryl bromides and chlorides developed in our group (Scheme 21),[40] a C–H arylation method should be developed for structurally complex peptides. The tryptophan example that was previously demonstrated was a preliminary result with a racemic amino acid. It afforded the desired tryptophan *rac*-**56e** in an unsatisfactory yield of 41% including impurities (Scheme 42). Although this example proved that this C–H arylation method is in principle applicable to protected tryptophan, further optimization was needed.

3.2.1 Optimization of the Ruthenium-Catalyzed C–H Arylation

First, the result mentioned above was reproduced, which afforded 33% of the isolated pure tryptophan **67eb** (Table 7, entry 1). Additionally, a diarylated byproduct **67ebb** was isolated in 12% yield. Exchanging substrate **56e** with acetylated tryptophan **56g** caused no significant change in the reactivity (entry 2). Therefore, further optimization was done using the cheaper and easier to synthesize tryptophan **56g**. When the reaction was carried out under air instead of a nitrogen atmosphere, no product formation could be observed (entry 3). The use of an aryl iodide **66b** resulted in almost the same yield as with the corresponding bromide **28b** (entry 4). Changing the solvent to *tert*-amyl alcohol, DMSO, DMA, DMF or NMP yielded no product (entries 5–10). In *tert*-amyl alcohol and DMSO a cleavage of the methyl ester of substrate **56g** was observed. Changing the base to CsOPiv or KOAc in *meta*-xylene or NMP did not improve the yield (entries 11–14). An elevated temperature of 140 °C raised the yield of the monoarylated substrate **67gb** to 46% (entry 15), while 14% of the diarylated species **67gbb** was formed. A further increase of the reaction temperature or a prolongation of the reaction time beyond 22 h at 120 °C were discarded as too harsh conditions. One hour at 140 °C under microwave irradiation yielded 21% of the mono- and 11% of the diarylated product (entry 16). Thus, the ratio of the mono- to diarylation considerably worsened. Different carboxylic acids or triphenylphosphine did not greatly improve the yield of the desired product **67gb** (entries 17–21), so that other strategies had to be considered.

Table 7: Optimization of the ruthenium-catalyzed C–H arylation of tryptophan.

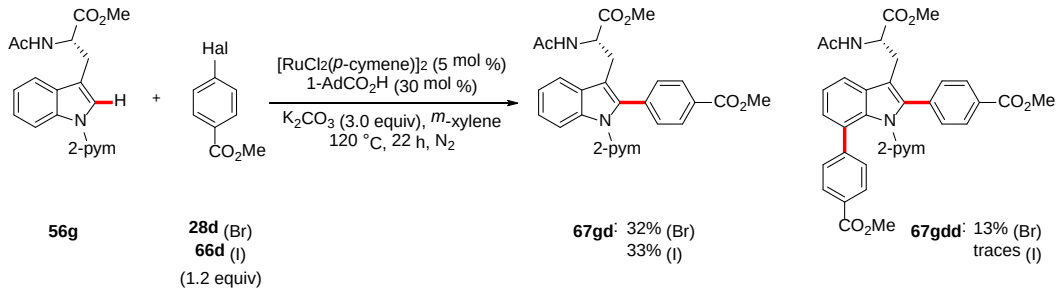


56g **28b** (1.2 equiv)

entry	base	additive	solvent	note	yield **67gb** + **67gbb**/%
1	K_2CO_3	1-AdCO_2H	*m*-xylene	**56e** (Boc)/**67eb** (Boc) instead of **56g** (Ac)/**67gb** (Ac)	33 + 12
2	K_2CO_3	1-AdCO_2H	*m*-xylene	-	33 + 7
3	K_2CO_3	1-AdCO_2H	*m*-xylene	under air	0
4	K_2CO_3	1-AdCO_2H	*m*-xylene	aryl iodide **66b** was used	31 + 9
5	K_2CO_3	1-AdCO_2H	*t*-amyl alcohol	-	0
6	K_2CO_3	1-AdCO_2H	DMSO	-	0
7	K_2CO_3	1-AdCO_2H	DMA	-	0
8	K_2CO_3	1-AdCO_2H	DMF	-	0
9	K_2CO_3	1-AdCO_2H	NMP	-	0
10	K_2CO_3	PPh_3	NMP	-	0
11	CsOPiv	1-AdCO_2H	*m*-xylene	-	14 + 0
12	KOAc	1-AdCO_2H	*m*-xylene	-	traces
13	CsOPiv	1-AdCO_2H	NMP	-	traces
14	KOAc	1-AdCO_2H	NMP	-	10 + 0
15	K_2CO_3	1-AdCO_2H	*m*-xylene	at 140 °C	46 + 14
16	K_2CO_3	1-AdCO_2H	*m*-xylene	1 h at 140 °C under microwave irradiation	21 + 11
17	K_2CO_3	$PhCO_2H$	*m*-xylene	-	11 + 3
18	K_2CO_3	PPh_3	*m*-xylene	-	40 + 0
19	K_2CO_3	MesCO_2H	*m*-xylene	-	5 + 2
20	K_2CO_3	(TRIP)CO_2H	*m*-xylene	-	12 + 3
21	K_2CO_3	Boc-Ile-OH	*m*-xylene	-	13 + 4

a: Reaction conditions: **56g** (0.30 mmol), **28b** (0.36 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), additive (30 mol %), base (0.90 mmol), solvent (3.0 mL), 120 °C, 22 h, N_2.

In order to test if the low conversion was caused by the electron-donating nature of the methoxy group of the aryl halogenides **28b**/**66b**, the electron-deficient aryl halogenides **28d**/**66d** were probed, which posses an electron-withdrawing ester group. The obtained results were comparable to those obtained with aryl halogenides **28b**/**28b** (Scheme 64).

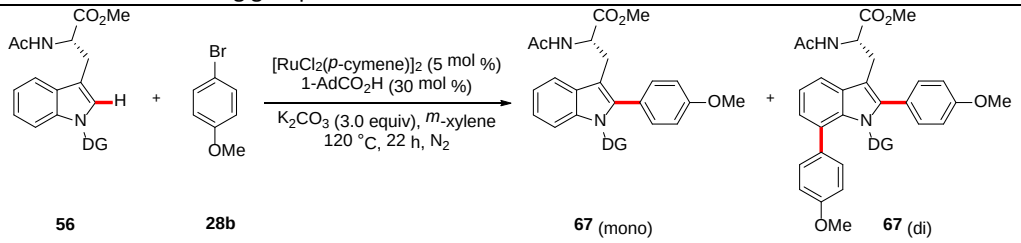


56g **28d** (Br) **66d** (I) (1.2 equiv) **67gd**: 32% (Br) 33% (I) **67gdd**: 13% (Br) traces (I)

Scheme 64: Examination of aryl halogenides **28** and **66**.

Furthermore, the tryptophans **56g**, **56h**, **56i** and **56b** were compared, which were decorated with the directing groups 2-pyrimidyl, 2-pyridyl, a carbamoyl group or no directing group (Table 8). While the carbamoyl group and no directing group showed no conversion (entries 3 and 4), an outstanding result was achieved using 2-pyridine as the directing group, which afforded the arylated product **67hb** in 74% yield along with only 11% of the diarylated byproduct (entry 2). Further optimization was carried out using substrate **56h**.

Table 8: Examination of directing groups.[a]



56 **28b** (1.2 equiv) **67** (mono) **67** (di)

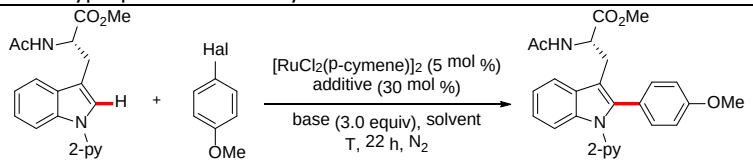
entry	DG	starting material	product	yield mono + di/%
1	2-pym	**56g**	**67gb** + **67gbb**	33 + 7
2	2-py	**56h**	**67hb** + **67hbb**	74 + 11
3	$(CO)NH_2$	**56i**	**67ib**	0
4	H	**56b**	**67bb**	0

a: Reaction conditions: **56** (0.30 mmol), **28b** (0.36 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), 1-$AdCO_2H$ (30 mol %), K_2CO_3 (0.90 mmol), *m*-xylene (3.0 mL), 120 °C, 22 h, N_2.

When the reaction was performed at 120 °C, the conversion was complete, affording 74% yield of the arylated tryptophan **67hb** (Table 9, entry 1). In order to probe if lower reaction temperatures sufficed, the reaction was carried out at 100 and 80 °C, which afforded only incomplete conversions and lower yields (entries 2 and 3), while at 60 °C no conversion was detected (entry 4). The reactivities of different aryl halides were probed by performing the corresponding reactions at 80 °C, so that the conversions were incomplete and a comparison was meaningful. In contrast to the aryl chloride **2b**, which was not reactive, the aryl iodide **66b** delivered a comparable result as the aryl

bromide **28b** (entries 5 and 6). Since previous studies revealed phosphines to be suitable additives for different transition metal-catalyzed transformations, triphenylphosphine and tricyclohexylphosphine were tested, yielding product **67hb** in 66 and 90%, respectively (entries 7 and 8). Notably, no formation of diarylated species could be observed when phosphines were applied.

Table 9: Optimization with tryptophan **56h** and aryl halides.[a]



56h | **66b** (I), **28b** (Br), **2b** (Cl) (1.2 equiv) | **67hb**

entry	Hal	additive	base	solvent	T/°C	yield
1	Br	1-AdCO_2H	K_2CO_3	*m*-xylene	120	74%
2	Br	1-AdCO_2H	K_2CO_3	*m*-xylene	100	53%
3	Br	1-AdCO_2H	K_2CO_3	*m*-xylene	80	26%
4	Br	1-AdCO_2H	K_2CO_3	*m*-xylene	60	0%
5	I	1-AdCO_2H	K_2CO_3	*m*-xylene	80	30%
6	Cl	1-AdCO_2H	K_2CO_3	*m*-xylene	80	0%
7	Br	PPh_3	K_2CO_3	*m*-xylene	120	66%
8	Br	PCy_3	K_2CO_3	*m*-xylene	120	90%

a: Reaction conditions: **56h** (0.30 mmol), aryl halide (0.36 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), additive (30 mol %), base (0.90 mmol), solvent (3.0 mL), 22 h, N_2.

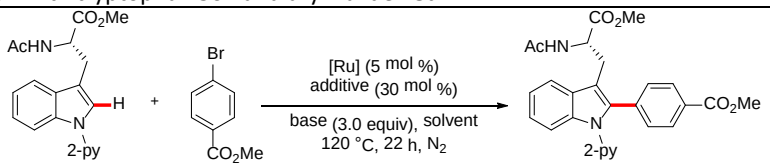
For the reasons that phosphines are relatively toxic and harmful to the environment, and at the same time user-unfriendly as they tend to be oxidized by air oxygen so that a storage under exclusion of air is necessary, the aim was to identify a more environmentally benign and user-friendly additive.

Further optimization was undertaken with the aryl halides **28d** and **66d**, because it was impossible to separate the tryptophan **67hb** from the starting material and the diarylated byproduct by column chromatography on silica, while the GPC purification was rather time-consuming and costly. The product **67hd**, on the other hand, could be purified by column chromatography on silica.

Different combinations of additives, bases and solvents were examined (Table 10).[117] A part of the optimization was performed by Prof. Dr. Hongjun Ren. Among the commonly used benzoic acids and inorganic bases, pentafluorobenzoic acid combined with potassium phosphate revealed to perform the arylation reaction with full conversion, delivering 83% yield of the desired product **67hd** (entry 9). Suitable solvents for this transformation seemed to be the aromatic toluene (entry 19) and *meta*-

xylene (entries 4, 6, 7, 9, 10). Other solvents, such as GVL (entry 5, 13, 14), NMP, DMF, DME and DMA turned out to harm the process (entries 15–18). $RuCl_3 \cdot (H_2O)_n$ and $[RuCl_2(benzene)]_2$ did not perform as well as did $[RuCl_2(p\text{-cymene})]_2$ (entries 20 and 21). With the optimized reaction conditions in hand, the scope of the reaction was explored. Either the combination of 1-adamantanecarboxylic acid and potassium carbonate or pentafluorobenzoic acid and potassium phosphate in *meta*-xylene was used for the following reactions.

Table 10: Optimization with tryptophan **56h** and aryl halide **28d**.[a]



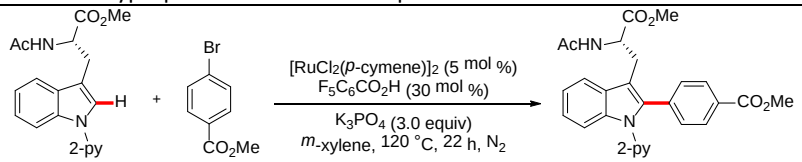
56h **28d** (1.1 equiv) **67hd**

entry	[Ru]	additive	base	solvent	yield
1	$[RuCl_2(p\text{-cymene})]_2$	1-AdCO_2H	KOAc	*m*-xylene	22%[b]
2	$[RuCl_2(p\text{-cymene})]_2$	MesCO_2H	KOAc	*m*-xylene	0%[b]
3	$[RuCl_2(p\text{-cymene})]_2$	-	KOAc	*m*-xylene	0%[b]
4	**$[RuCl_2(p\text{-cymene})]_2$**	**1-AdCO_2H**	**K_2CO_3**	***m*-xylene**	**70%**
5	$[RuCl_2(p\text{-cymene})]_2$	1-AdCO_2H	K_2CO_3	GVL	15%[b]
6	$[RuCl_2(p\text{-cymene})]_2$	$F_5C_6CO_2H$	K_2CO_3	*m*-xylene	69%[b]
7	$[RuCl_2(p\text{-cymene})]_2$	1-AdCO_2H	K_3PO_4	*m*-xylene	64%[b]
8	$[RuCl_2(p\text{-cymene})]_2$	$(3\text{-}F_3CC_6H_4)CO_2H$	K_3PO_4	*m*-xylene	11%
9	**$[RuCl_2(p\text{-cymene})]_2$**	**$F_5C_6CO_2H$**	**K_3PO_4**	***m*-xylene**	**83%**
10	$[RuCl_2(p\text{-cymene})]_2$	$F_5C_6CO_2H$	K_3PO_4	*m*-xylene	78%[c]
11	$[RuCl_2(p\text{-cymene})]_2$	$F_5C_6CO_2H$	K_3PO_4	*m-xylene*	11%[d]
12	$[RuCl_2(p\text{-cymene})]_2$	(TRIP)CO_2H	K_3PO_4	*m*-xylene	35%[b]
13	$[RuCl_2(p\text{-cymene})]_2$	1-AdCO_2H	K_3PO_4	*m*-xylene/GVL (1:1)	20%[b]
14	$[RuCl_2(p\text{-cymene})]_2$	$F_5C_6CO_2H$	K_3PO_4	*m*-xylene/GVL (1:1)	18%[b]
15	$[RuCl_2(p\text{-cymene})]_2$	$F_5C_6CO_2H$	K_3PO_4	NMP	28%
16	$[RuCl_2(p\text{-cymene})]_2$	$F_5C_6CO_2H$	K_3PO_4	DMF	traces
17	$[RuCl_2(p\text{-cymene})]_2$	$F_5C_6CO_2H$	K_3PO_4	DME	34%
18	$[RuCl_2(p\text{-cymene})]_2$	$F_5C_6CO_2H$	K_3PO_4	DMA	16%
19	$[RuCl_2(p\text{-cymene})]_2$	$F_5C_6CO_2H$	K_3PO_4	toluene	59%
20	$RuCl_3 \cdot (H_2O)_n$	$F_5C_6CO_2H$	K_3PO_4	*m*-xylene	0%
21	$[RuCl_2(benzene)]_2$	$F_5C_6CO_2H$	K_3PO_4	*m*-xylene	64%

a: Reaction conditions: **56h** (0.30 mmol), **28d** (0.33 mmol), [Ru] (5 mol %), additive (30 mol %), base (0.90 mmol), solvent (3.0 mL), 120 °C, 22 h, N_2. b: The reaction was performed by Prof. Dr. Hongjun Ren. c: 2.5 mol % $[Ru]_2$ was used. d: 1.0 mol % $[Ru]_2$ was used.

The reactions presented so far were carried out at a tryptophan concentration of $1 \cdot 10^{-1}$ M (Table 11, entry 3). Higher concentrations of $2 \cdot 10^{-1}$ and $5 \cdot 10^{-1}$ M afforded almost quantitative yields of 97 and 94%, respectively (entries 1 and 2), whereas the reaction proceeded slower at lower concentrations and thus the yield dropped to 54% at $2 \cdot 10^{-2}$ M and 9% at $1 \cdot 10^{-2}$ M (entries 4 and 5).

Table 11: Examination of the tryptophan concentration dependence.[a]



56h **28d** (1.1 equiv) **67hd**

entry	**56h** concentration	yield	entry	**56h** concentration	yield
1	$5 \cdot 10^{-1}$ M	94%	4	$2 \cdot 10^{-2}$ M	54%
2	$2 \cdot 10^{-1}$ M	97%	5	$1 \cdot 10^{-2}$ M	9%
3	$1 \cdot 10^{-1}$ M	83%			

a: Reaction conditions: **56h** (0.30 mmol), **28d** (0.33 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $F_5C_6CO_2H$ (30 mol %), K_3PO_4 (0.90 mmol), *m*-xylene (0.6–30.0 mL), 120 °C, 22 h, N_2.

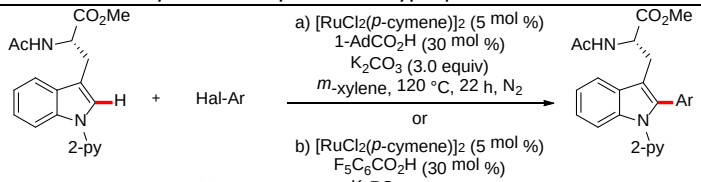
3.2.2 Scope and Limitations of the Ruthenium-Catalyzed Peptide C–H Arylation

Tryptophan **56h** was tested with different aryl bromides **28** and iodides **66** bearing a variety of functional groups (Table 12). A part of this scope was performed by Prof. Dr. Hongjun Ren. The reactions were set up with 5 mol % $[RuCl_2(p\text{-cymene})]_2$ in *meta*-xylene at 120 °C and either 30 mol % 1-adamantylcarboxylic acid and 3.0 equivalents of potassium carbonate (conditions a), or 30 mol % pentafluorobenzoic acid and 3.0 equivalents of potassium phosphate (conditions b) were used. Fortunately, different functional groups were well tolerated by the ruthenium-catalyzed C–H arylation. Products **67** bearing methoxy groups (entries 1 and 3), esters (entries 2 and 4), aniline (entry 5), cyanide (entry 6), fluoride (entry 9), enolizable ketone (entry 10), as well as pyridine (entry 11), ferrocene (entry 12), various polyarenes (entries 13–16) and styrene (entry 21) were thus synthesized in high to excellent yields. It is noteworthy, that in most cases conditions b resulted in higher yields than conditions a. One exception was the pyridyl bromide **28m**, which afforded product **67hm** in 95% yield under conditions a, while only 48% of product **67hm** were isolated using conditions b. The obtained compounds highlighted vast potential for peptide applications. For example, the introduced fluorine in compound **67hk** could serve as a radioactive tracer. Furthermore, the incorporation of chromophores and fluorophores was demonstrated with

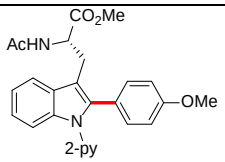
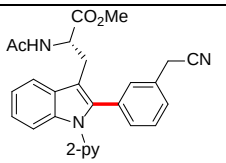
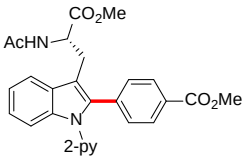
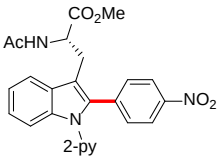
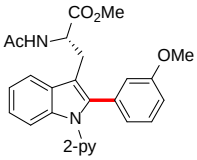
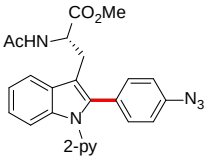
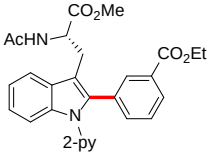
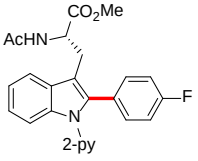
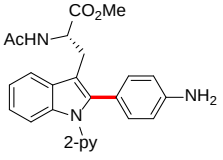
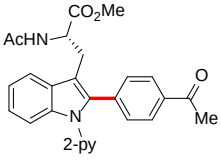
compounds **67hb** and **67hn–67hq**. Additionally, compounds **67hg**, **67hh**, **67hl** and **67hv** can easily undergo further chemical modifications.

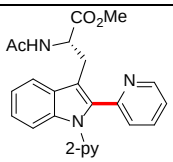
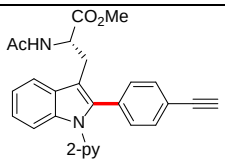
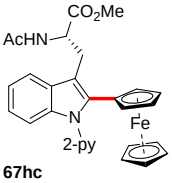
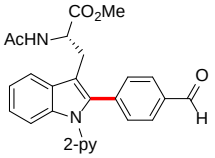
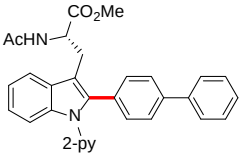
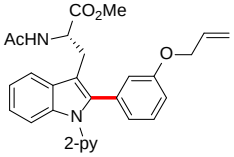
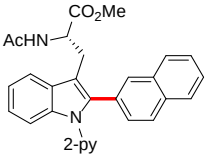
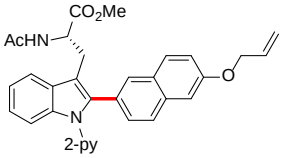
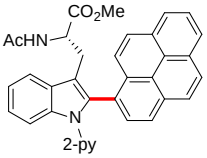
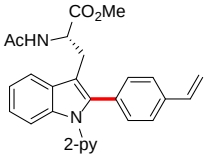
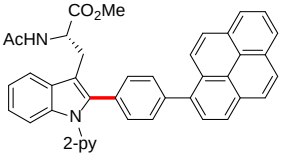
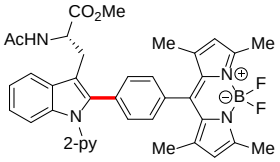
Aryl halides bearing a nitro group (entry 7), an azide (entry 8) or alkyne (entry 17), an aldehyde (entry 18) or an allyloxy group (entries 19 and 20) were not tolerated, which resulted in very little conversions and either no or low yields of the corresponding tryptophans **67**. The formation of products **67ht** and **67hu** were observed by LC-MS, but due to the formation of several byproducts, the purifications was challenging. Unfortunately, the introduction of a BODIPY dye attached to iodobenzene did not work (entry 22).

Table 12: Scope of the ruthenium-catalyzed C–H arylation of tryptophan **56h**.[a]



56h — **28** (Br), **66** (I) (1.1 equiv) — **67**

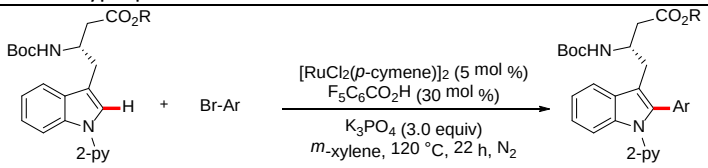
entry	product	yield	entry	product	yield
1	 **67hb**	a) 74% (Br) b) 70% (Br)	6	 **67hh**	b) 75%[b] (Br)
2	 **67hd**	a) 70% (Br) b) 83% (Br)	7	 **67hi**	a) 10% (Br) b) 18% (Br)
3	 **67he**	b) 53% (Br) + 10% di	8	 **67hj**	b) 0% (Br)
4	 **67hf**	b) 66% (Br)	9	 **67hk**	a) 82% (Br) b) 95%[b] (Br)
5	 **67hg**	a) 77% (Br) b) 76% (Br)	10	 **67hl**	b) 76%[b] (Br)

entry	product	yield	entry	product	yield
11	 **67hm**	a) 95% (Br) b) 48% (Br)	17	 **67hr**	b) 0%[b] (Br)
12	 **67hc**	b) 17% (I), 52%[c] (I)	18	 **67hs**	b) 0%[b] (I)
13	 **67hn**	b) 72%[b] (Br)	19	 **67ht**	b) 0% (Br)
14	 **67ho**	a) 56% (Br) b) 87% (Br) + 11% di	20	 **67hu**	b) 25% (Br), 36%[d] (Br)
15	 **67hp**	a) 32% (Br) b) 13% (Br)	21	 **67hv**	b) 74% (Br)
16	 **67hq**	a) 51% (I) b) 74% (Br)	22	 **67hw**	b) 0% (I)

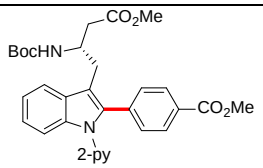
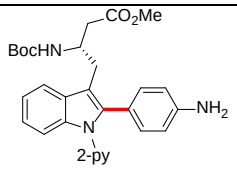
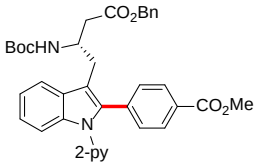
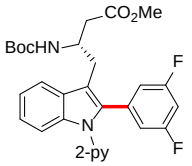
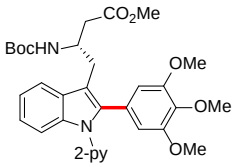
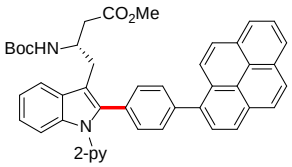
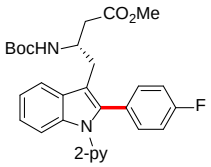
a: Reaction conditions: **56h** (0.30 mmol), **28** or **66** (0.33 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), additive (30 mol %), base (0.90 mmol), *m*-xylene (3.0 mL), 120 °C, 22 h, N_2. b: The reaction was performed by Prof. Dr. Hongjun Ren. c: 20 mol % $[Ru]_2$ and 120 mol % $F_5C_6CO_2H$ were used. d: 10 mol % $[Ru]_2$ and 60 mol % $F_5C_6CO_2H$ were used.

Having established the scope of tryptophan **56h**, β[3]-*homo*-tryptophans **120** were investigated for the ruthenium-catalyzed C–H arylation method (Table 13). Several aryl groups were coupled to β[3]-*homo*-tryptophan **120**, affording arylated products **121** in moderate to excellent yields. Surprisingly, only little amounts of product **121ay** were observed by LC-MS.

Table 13: Scope with β[3]-*homo*-tryptophans **120**.[a]



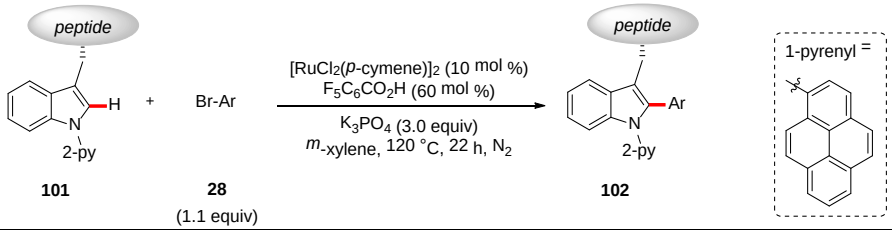
120 **28** (1.1 equiv) **121**

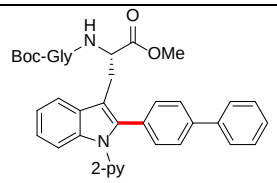
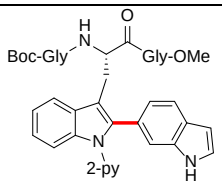
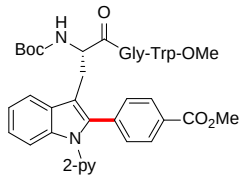
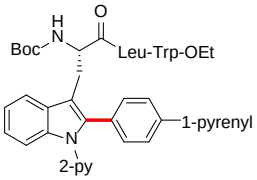
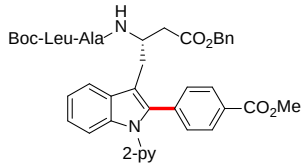
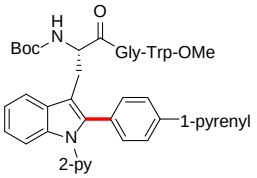
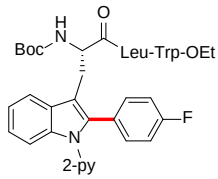
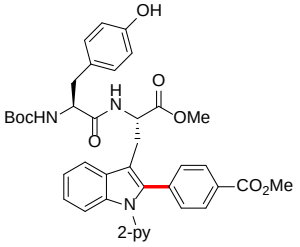
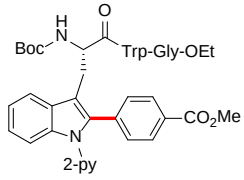
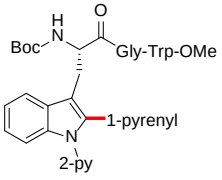
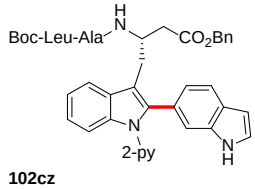
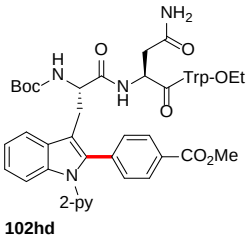
entry	product	yield	entry	product	yield
1	 **121ad**	54%	5	 **121ag**	96%
2	 **121bd**	61%	6	 **121ay**	traces
3	 **121ax**	42%	7	 **121aq**	28%
4	 **121ak**	89%			

a: Reaction conditions: **120** (0.30 mmol), **28** (0.33 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $F_5C_6CO_2H$ (30 mol %), K_3PO_4 (0.90 mmol), *m*-xylene (3.0 mL), 120 °C, 22 h, N_2.

In addition to the examined single tryptophans **56** and **120**, the ruthenium-catalyzed C–H arylation was applied for the diversification of tryptophan peptides **101** (Table 14). Some of these reactions were performed by Prof. Dr. Hongjun Ren. As the peptides showed a lower reactivity than single tryptophans, the catalyst loading was increased to 10 mol %. A range of differently substituted arylated peptides **102** could be synthesized in good yields (entries 1–8). Remarkably, free indole-containing peptides were arylated exclusively on the pyridylated indole moiety (entries 2, 4, 5, 8–10). Also, 6-bromoindole (**28z**) as the coupling partner was well tolerated, providing novel 2,6-biindole structures **102cz** and **102fz** (entries 6 and 7). Due to incomplete conversions and a thereof resulting difficult purification, peptide **102bq** was isolated in a low yield (entries 9). For peptides **102gd**, **102bp** and **102hd** the purification was not successful, although they were the major compounds in the reaction mixtures as determined by LC-MS analysis, so that not even an analytical amount could be isolated (entries 10–12).

Table 14: : Scope of the ruthenium-catalyzed C–H arylation of tryptophan peptides **101**.[a]



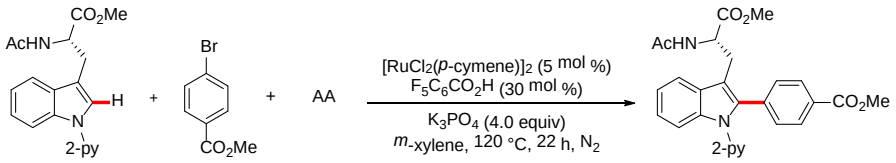
entry	product	yield	entry	product	yield
1	 **102an**	61%[b]	7	 **102fz**	62%
2	 **102bd**	64%	8	 **102dq**	58%
3	 **102cd**	65%	9	 **102bq**	10%
4	 **102dk**	51%	10	 **102gd**	0%
5	 **102ed**	70%	11	 **102bp**	0%
6	 **102cz**	70%	12	 **102hd**	0%

a: Reaction conditions: **101** (50–100 mg), **28** (1.1 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $F_5C_6CO_2H$ (60 mol %), K_3PO_4 (3.0 equiv), *m*-xylene (3.0 mL), 120 °C, 22 h, N_2. b: The reaction was performed by Prof. Dr. Hongjun Ren.

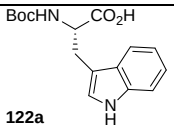
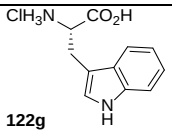
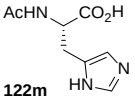
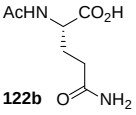
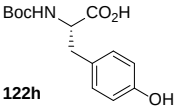
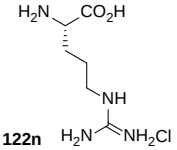
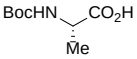
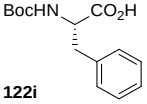
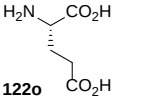
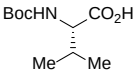
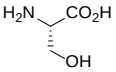
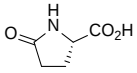
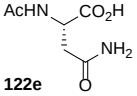
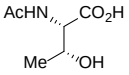
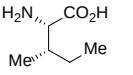
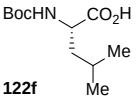
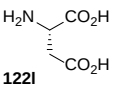
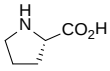
3.2.3 Bioorthogonal Screening of the Ruthenium-Catalyzed C–H Arylation

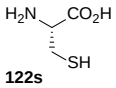
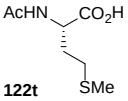
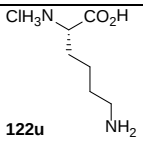
In order to determine, which of the naturally occurring amino acids are tolerated, and thereby demonstrate the chemoselectivity of the developed C–H arylation method, the catalytic reactions were carried out in the presence of one equivalent of an amino acid **122** (Table 15). Some of these test reactions were performed by Nikolaos Kaplaneris. Most of the tested amino acids **122** were well tolerated (entries 1–16) affording tryptophan **67hd** in good yields. In cases of low yields, it is conceivable that the added amino acid irreversibly chelated the ruthenium and thus deactivated the catalyst (entries 17–21). The bioorthogonal screening showed a tolerability of heteroaromatics, such as indoles (entries 1 and 7) and imidazoles (entry 13), aromatics (entries 8 and 9), free amides (entries 2 and 5), free hydroxyl groups (entries 8, 10, 11), aliphatics (entries 3, 4, 6), guanidine (entry 14) as well as free carboxylic acids (entries 1–16). Thiols and thioethers, on the other hand, did shut down the reaction (entries 19 and 20). Free amines were partially tolerated (entries 7, 10, 12, 14, 15), while in some cases free amines or free amines combined with carboxylic acids hindered the reaction (entries 17, 18, 21).

Table 15: Robustness screening for the ruthenium-catalyzed C–H arylation.[a]



56h **28d** (1.1 equiv) **122** (1.0 equiv) **67hd**

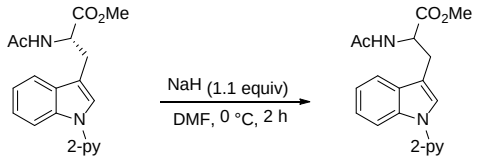
entry	AA	yield	entry	AA	yield	entry	AA	yield
1	 **122a**	81%[b]	7	 **122g**	43%[b]	13	 **122m**	83%
2	 **122b**	59%	8	 **122h**	76%[b]	14	 **122n**	50%
3	 **122c**	79%[b]	9	 **122i**	90%	15	 **122o**	40%
4	 **122d**	89%	10	 **122j**	43%	16	 **122q**	77%[b]
5	 **122e**	95%	11	 **122k**	64%	17	 **122p**	23%
6	 **122f**	75%	12	 **122l**	57%	18	 **122r**	4%

entry	AA	yield	entry	AA	yield	entry	AA	yield
19	 **122s**	0%	20	 **122t**	11%	21	 **122u**	33%[b]

a: Reaction conditions: **56h** (0.30 mmol), **28d** (0.33 mmol), **122** (0.30 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $F_5C_6CO_2H$ (30 mol %), K_3PO_4 (0.90 mmol), *m*-xylene (3.0 mL), 120 °C, 22 h, N_2. b: The reaction was performed by Nikolaos Kaplaneris.

3.2.4 Studies on a Potential Racemization of Tryptophan

The tryptophan **56h** was racemized using NaH in DMF, affording the racemic substrate *rac*-**56h** (Scheme 65). The ruthenium-catalyzed C–H arylation of *rac*-**56h** delivered the racemic products *rac*-**67hd** and *rac*-**67hg**. An HPLC analysis showed that no racemization of the stereocenter occured during the reaction (Figure 2).



56h *rac*-**56h**: 20%

Scheme 65: Probing racemization with tryptophan **56h**.

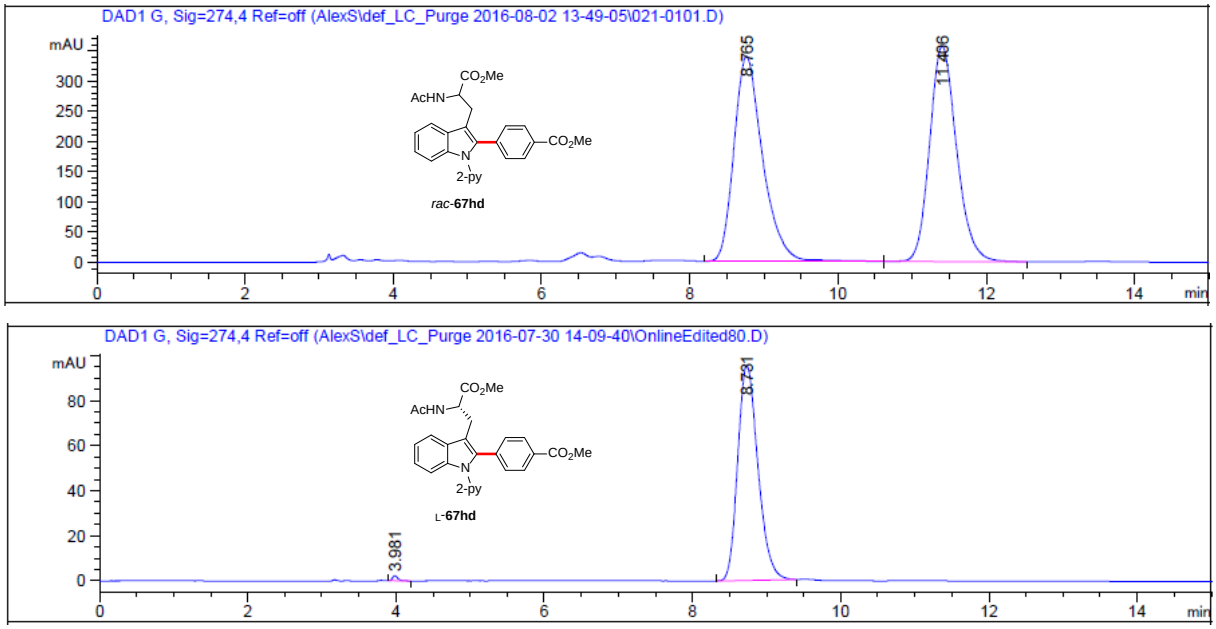


Figure 2: HPLC-chromatograms of the racemic mixture of compound *rac*-**56h** and of isolated product L-**56h**.

Due to the basic free amine of the 4-bromoaniline (**28g**), the product **67hg** partially racemized during the arylation reaction. Compound **67hg** was then isolated with 92%*ee* (Figure 3). A control reaction of tryptophan **56h** with methyl 4-bromobenzoate (**28d**) in the presence of 1.1 equivalents of aniline showed that the product **67hd** was almost fully racemic, since it was obtained with only 10%*ee* (Figure 4).

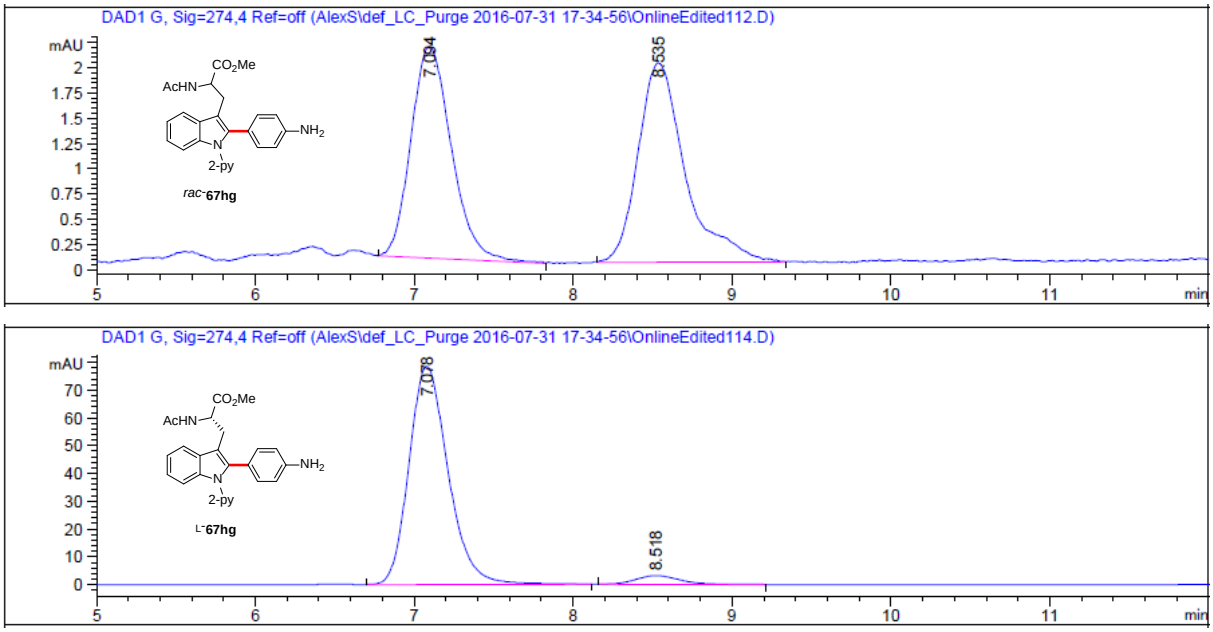


Figure 3: HPLC-chromatograms of racemic mixture of the compound *rac*-**67hg** and of isolated product **67hg**, 92%*ee*.

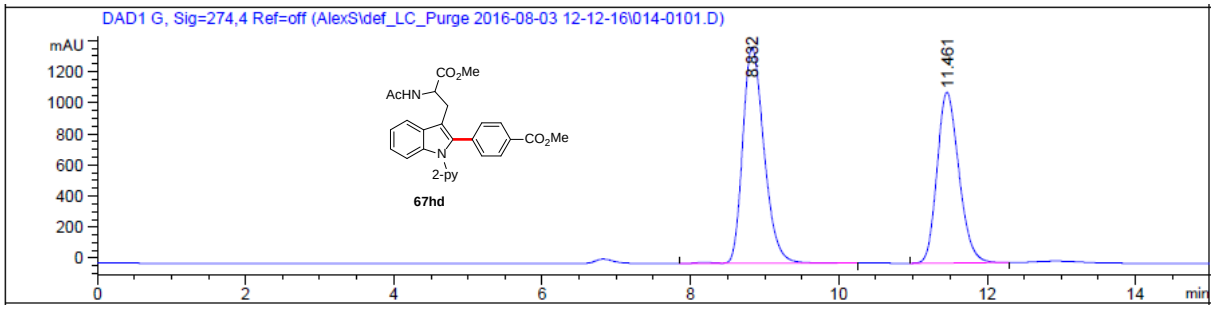


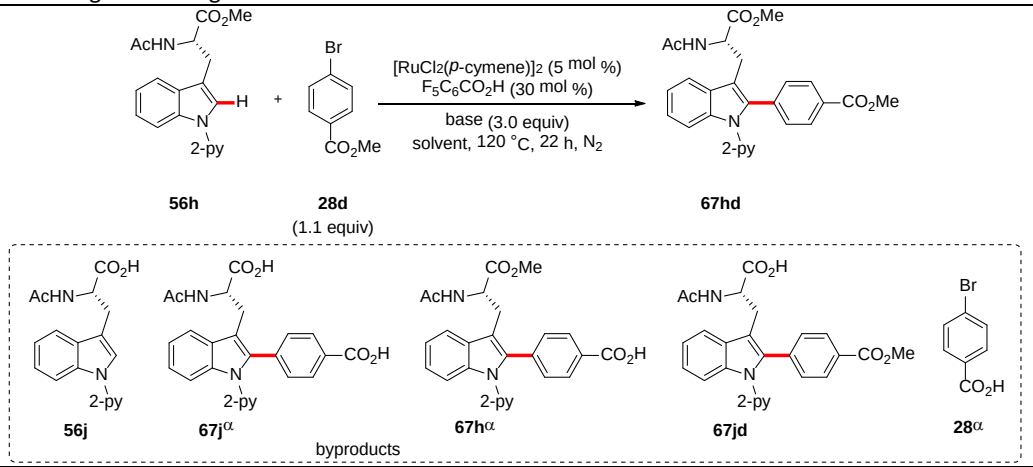
Figure 4: HPLC-chromatogram of the compound **67hd**, 10%*ee*, isolated after the reaction of **56h** with **28d** in the presence of 1.1 equiv aniline.

3.2.5 Ruthenium-Catalyzed C–H Arylation of Tryptophan-Containing Peptides in Water

Having established the ruthenium-catalyzed C–H arylation procedure in an organic solvent under inert atmosphere, we became intrigued by more biocompatible reaction conditions. The necessity for the oxygen-free atmosphere could not be circumvented. Contrary to this, the anhydrous organic solvent could be replaced by water. Initial results of adding water to *meta*-xylene showed the formation of the desired product **67hd** in 39 and 33% yield (Table 16, entries 1 and 2). This drop of

yield was due to the partial saponification of the esters, resulting in a mixture of byproducts, which were detected by LC-MS. In a 1:1 ratio of *meta*-xylene and water as well as in pure water no product **67hd** was formed and only the shown byproducts were observed (entries 3 and 4). Also, mixtures of acetonitrile and water in combination with potassium phosphate or the weaker base potassium carbonate gave the same results (entries 5–7). The change to the organic base triethylamine made the difference, affording 40% of isolated product **67hd** (entry 8). Still, the major part of the compounds hydrolysed. The use of a triethylamine/TFA buffer-like system to avoid hydrolysis did not improve the result (entry 9).

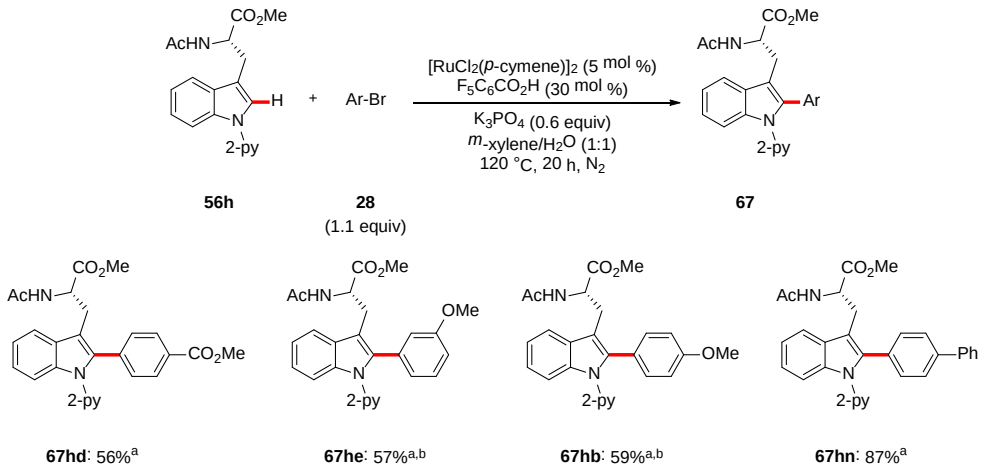
Table 16: Exchange of the organic solvent with water.[a]



entry	base	solvent	yield
1	K_3PO_4	*m*-xylene/H_2O 100:1	39%
2	K_3PO_4	*m*-xylene/H_2O 10:1	33%
3	K_3PO_4	*m*-xylene/H_2O 1:1	0%
4	K_3PO_4	H_2O	0%
5	K_3PO_4	H_2O/MeCN 1:1	0%
6	K_2CO_3	H_2O/MeCN 1:1	0%
7	K_2CO_3	H_2O/MeCN 1:10	0%
8	Et_3N	H_2O/MeCN 10:1	40%
9	Et_3N/TFA 2:1	H_2O/MeCN 10:1	37%

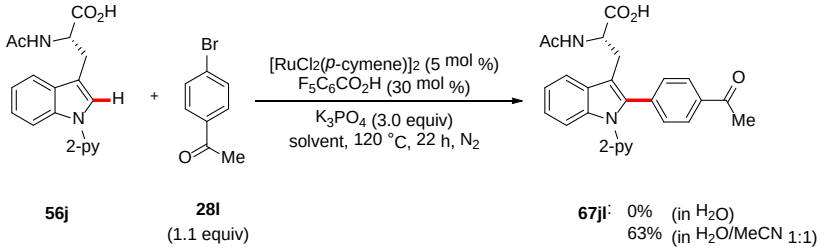
a: Reaction conditions: **56h** (0.30 mmol), **28d** (0.33 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $F_5C_6CO_2H$ (30 mol %), base (3.0 equiv), solvent (3.0 mL), 120 °C, 22 h, N_2.

The reduction of the amount of potassium phosphate to 0.6 equivalents decreased the extent of saponification, so that products **67** were isolated in reasonable yields after reaction in a 1:1 mixture of water and *meta*-xylene (Scheme 66). The reactions shown in scheme 66 were all performed by Nikolaos Kaplaneris.



Scheme 66: Ruthenium-catalyzed C–H arylation in a water-*meta*-xylene mixture. a: The reaction was performed by Nikolaos Kaplaneris. b: 10 mol % catalyst were used.

Next, to circumvent saponifications, free carboxylic acid substrate **56j** was reacted with arene **28l** in water or in a 1:1 mixture of water and acetonitrile (Scheme 67). Due to the poor solubility of the starting materials in water, the conversion was low and no product **67jl** was isolated. The addition of acetonitrile solved this problem and the desired arylated tryptophan **67jl** could be isolated in 63% yield.

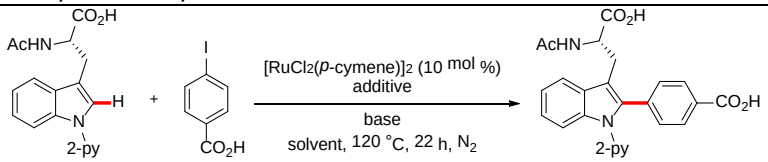


Scheme 67: Ruthenium-catalyzed C–H arylation in water.

To assure full solubility of all substrates used, substrate **56j** was reacted with arene **66α**, which are both soluble in water (Table 17). As all attempts to isolate pure tryptophan **67jα** failed, and thus no calibration of the liquid chromatograms could be recorded, the measured ratios of starting material **56j** to product **67jα** are given. Although these ratios do not correspond to yields of formed product, they indicate an approximate outcome of the reaction and were therefore successfully applied to further reactions.

Using potassium phosphate and pentafluorobenzoic acid in water, the substrate **56j** could not be observed in the LC-MS and only arylated product **67jα** was found (entry 1). The same result was achieved when no additive was added (entry 2). The use of potassium carbonate, potassium acetate or sodium hydroxide without additives indicated incomplete or no conversion (entries 3–5). Similar results were obtained when basic buffers of pH 8–12 were used (entries 6–9).

Table 17: Ruthenium-catalyzed C–H arylation in water.[a]

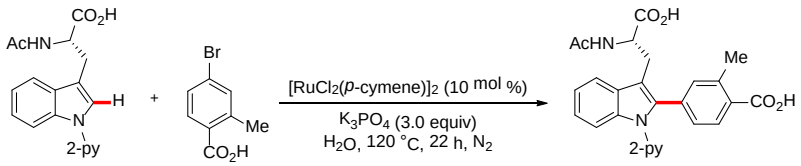


56j **66α** (1.1 equiv) **67jα**

entry	base (equiv)	additive (equiv)	solvent	LC-MS **56j**/**67jα**[b]
1	K_3PO_4 (3.0)	$F_5C_6CO_2H$ (0.6)	H_2O	0:100
2	K_3PO_4 (3.0)	-	H_2O	0:100
3	K_2CO_3 (3.0)	-	H_2O	26:74
4	KOAc (3.0)	-	H_2O	100:0
5	NaOH (2.1)	-	H_2O	29:71
6	-	-	buffer pH 8	100:0
7	-	-	buffer pH 9	100:0
8	-	-	buffer pH 11	57:43
9	-	-	buffer pH 12	27:73

a: Reaction conditions: **56j** (0.30 mmol), **66α** (0.33 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), additive, base, solvent (3.0 mL), 120 °C, 22 h, N_2. b: Product **67jα** could not be isolated.

Due to the unsuccessful purification of product **67jα**, aryl halide **28β** was submitted to the C–H arylation of tryptophan **56j** under the best suitable conditions for the reaction in water (Table 17, entry 2). Water-soluble aryl halide **28β** bearing a carboxylic acid was coupled to tryptophan **56j** in order to give the corresponding arylated product **67jβ** in 61% yield (Scheme 68). The isolated and structurally confirmed compound **67jβ** exemplarily proved the general possibility of the applicability of water as the reaction medium.

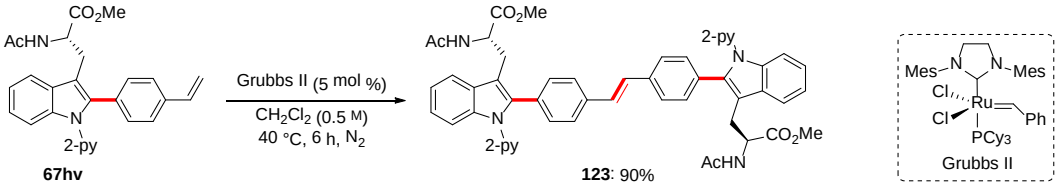


56j **28β** (1.1 equiv) **67jβ**: 61%

Scheme 68: Ruthenium-catalyzed C–H arylation in water.

3.2.6 Ruthenium-Catalyzed Ligation of Tryptophan-Containing Peptides

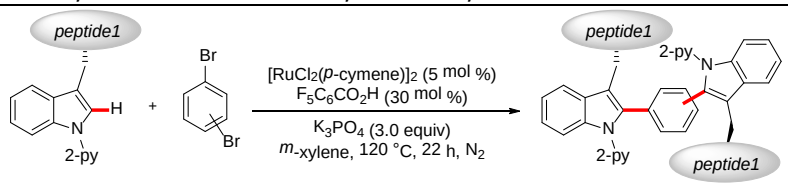
Several different strategies were carried out for the ruthenium-catalyzed ligation of tryptophans **56**, **67** ans **101**. Styrene-containing substrate **67hv** was successfully submitted to a cross-metathesis reaction using the Grubbs II catalyst, delivering the ligation product **123** in 90% yield (Scheme 69). As expected, the *E*-configured product was formed exclusively.

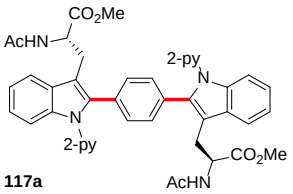
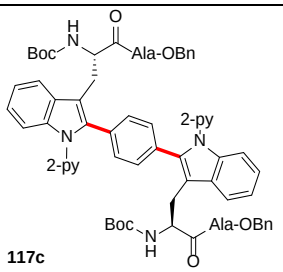
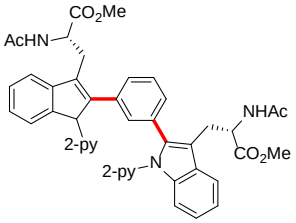
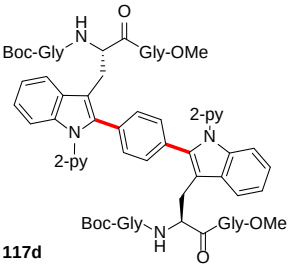


Scheme 69: Ligation of tryptophan **67hv**.

Another double functionalization ligation strategy provided products **117** by the reaction of tryptophans **101** with half an equivalent of 1,4- or 1,3-dibromobenzene **28** (Table 18). Single tryptophans furnished dipeptides **117a** and **117b** in excellent yields (entries 1 and 2). The product **117b** was synthesized by Prof. Dr. Hongjun Ren. Also, tetrapeptide **117c** was synthesized in a very high yield of 79% (entry 3). Due to complications during the purification process, hexapeptide **117d** was obtained in a comparably low yield of 35% (entry 4).

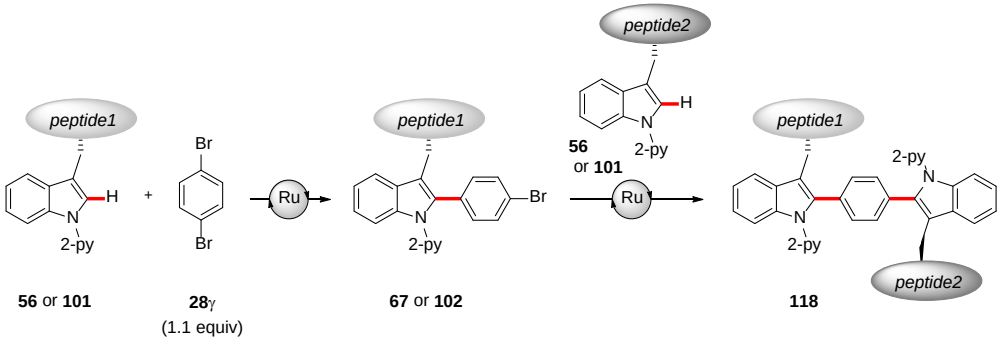
Table 18: Peptide ligation by twofold ruthenium-catalyzed C–H arylation.[a]



entry	product	yield	entry	product	yield
1	 **117a**	91%	3	 **117c**	79%
2	 **117b**	82%[b]	4	 **117d**	35%

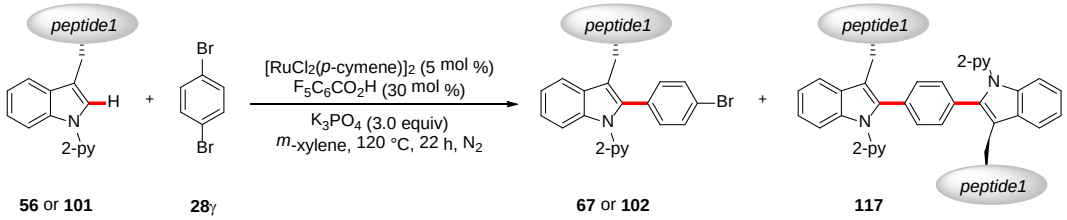
a: Reaction conditions: **101** (50–100 mg), **28** (0.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5–10 mol %), $F_5C_6CO_2H$ (30–60 mol %), K_3PO_4 (3.0 equiv), *m*-xylene (3.0 mL), 120 °C, 22 h, N_2. b: The reaction was performed by Prof. Dr. Hongjun Ren.

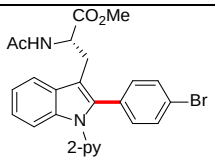
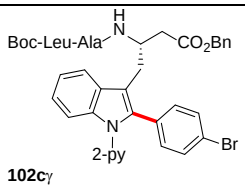
A further ligation approach by twofold C–H arylation was the introduction of a *para*-bromophenyl substituent for a subsequent coupling with a second peptide **56** or **101** in order to provide ligation products **118** (Scheme 70). Although 1.1 equivalents of 1,4-dibromobenzene (**28γ**) were used, the formation of ligation products **117** was also observed, accompanied by a low-yielding generation of the desired bromine-containing peptides **67** and **102** (Table 19). This observation indicated an accelerated reactivity of aryl bromides **67** and **102** as compared to dibromide **28γ**. For the reason of such low yields for the first desired step, this ligation approach was discarded. Moreover, the obtained small amounts of the substrates **67hγ** and **102cγ** were not reacted further with a second peptide **56** or **101**.



Scheme 70: Ligation of two different peptides **56** or **101** by twofold ruthenium-catalyzed C–H arylation.

Table 19: Syntheses of *para*-bromophenyl peptides **67** and **102**.[a]



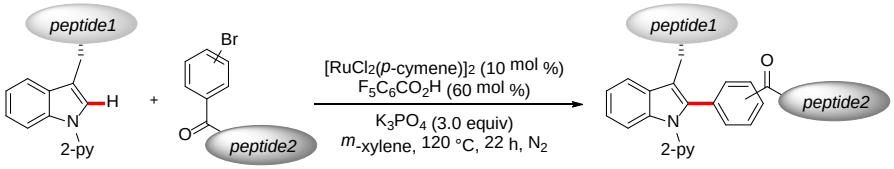
entry	product	yield	entry	product	yield
1	 **67hγ**	17%	2	 **102cγ**	31%

a: Reaction conditions: **56** or **101** (50–100 mg), **28γ** (1.1 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $F_5C_6CO_2H$ (30 mol %), K_3PO_4 (3.0 equiv), *m*-xylene (3.0 mL), 120 °C, 22 h, N_2.

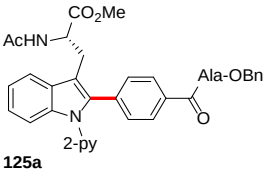
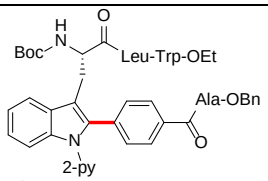
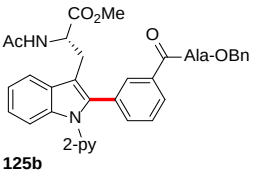
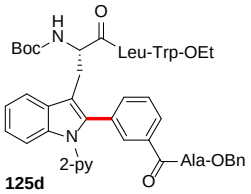
Along with the intention of producing aryl bromide-containing peptides, peptides **124** equipped with an aryl bromide-containing linker were ligated with peptides **56** and **101** in order to provide products **125** (Table 20). The ligation reactions delivering products **125** were all performed by Prof. Dr. Hongjun Ren in our group. Compared to the wasteful and costly preparation of peptides **67hγ** and **102cγ**, *meta*- and *para*-bromophenacylated peptides **124** were easily accessible by application of

standard protection chemistry. Ligation products **125a–d** were formed and isolated in very good yields of 58–68%. *NH*-free indole-containing products **125c** and **125d** once more proved the excellent selectivity of this ruthenium-catalyzed C–H arylation method.

Table 20: Ruthenium-catalyzed C–H ligation of petides **56** or **101** and **124**.[a]

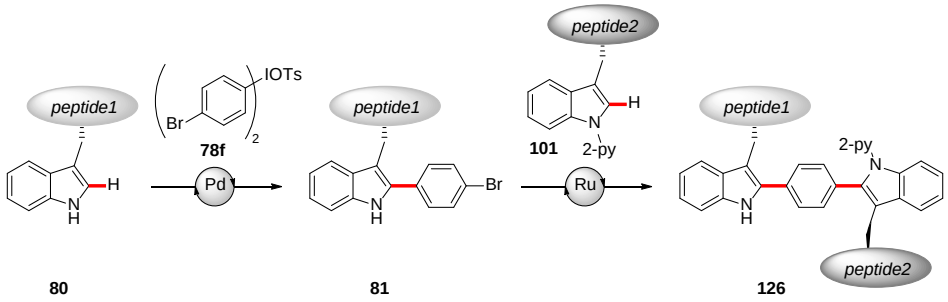


56 or **101** **124** (1.1 equiv) **125**

entry	product	yield	entry	product	yield
1	 **125a**	68%[b]	3	 **125c**	58%[b]
2	 **125b**	58%[b]	4	 **125d**	68%[b]

a: Reaction conditions: **56** or **101** (50–100 mg), **124** (1.1 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $F_5C_6CO_2H$ (60 mol %), K_3PO_4 (3.0 equiv), *m*-xylene (3.0 mL), 120 °C, 22 h, N_2. b: The reaction was performed by Prof. Dr. Hongjun Ren.

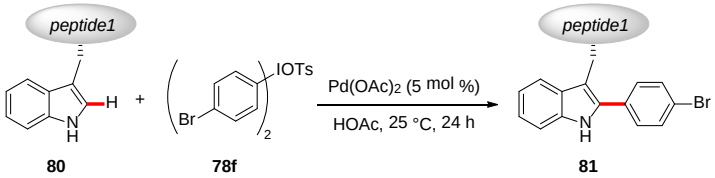
An additional ligation attempt was realized by a sequential multicatalytic C–H arylation combination (Scheme 71). First, palladium-catalysis furnished aryl bromide-containing peptides **81**,[89] (Table 21). The aryl bromide peptides **81af** and **81wf** were obtained with 67 and 57% yield, respectively. Next, these peptides were coupled with peptides **56** or **101** yielding ligation products **126** (Table 22). Thus, tetrapeptide **126a** and β[3]-*homo*-tryptophan hexapeptide **126b** were prepared in good yields of 53 and 56% (entries 1 and 2). Unfortunately, ligation products derived from peptide **81wf** could not be isolated, although the product masses were observed by LC-MS analyses (entries 3 and 4).



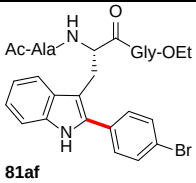
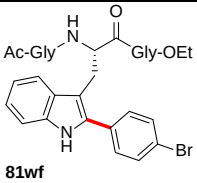
80 **81** **126**

Scheme 71: Ligation by multicatalytic C–H arylation.

Table 21: First step of the multicatalytic C–H arylation approach.[a]

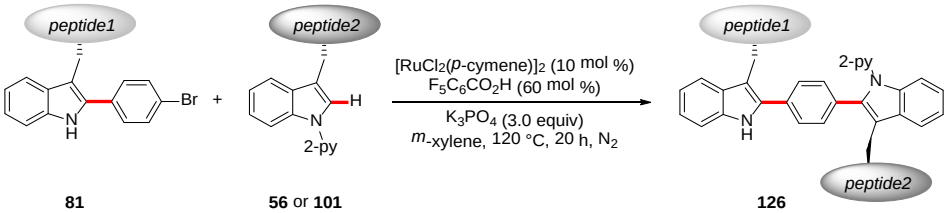


80 **78f** (1.5 equiv) **81**

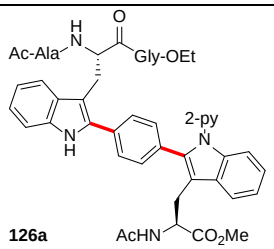
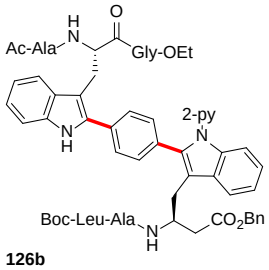
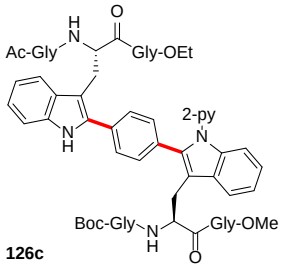
entry	product	yield	entry	product	yield
1	 **81af**	67%	2	 **81wf**	57%

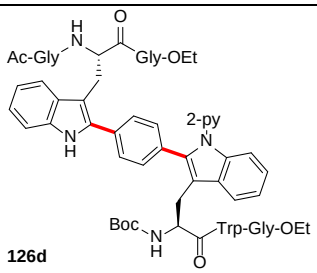
a: Reaction conditions: **80** (0.20 mmol), **78f** (0.30 mmol), $Pd(OAc)_2$ (5 mol %), HOAc (3.0 mL), 25 °C, 24 h.

Table 22: Second step of the multicatalytic C–H arylation approach.[a]



81 **56** or **101** (1.0 equiv) **126**

entry	*peptide1*	*peptide2*	product	yield
1	**81af**	Ac-Trp^{py}-OMe (**56h**)	 **126a**	53%
2	**81af**	Boc-Leu-Ala-β^3*h*Trp^{py}-OBn (**101c**)	 **126b**	56%
3	**81wf**	Boc-Gly-Trp^{py}-Gly-OMe (**101f**)	 **126c**	0%[b]

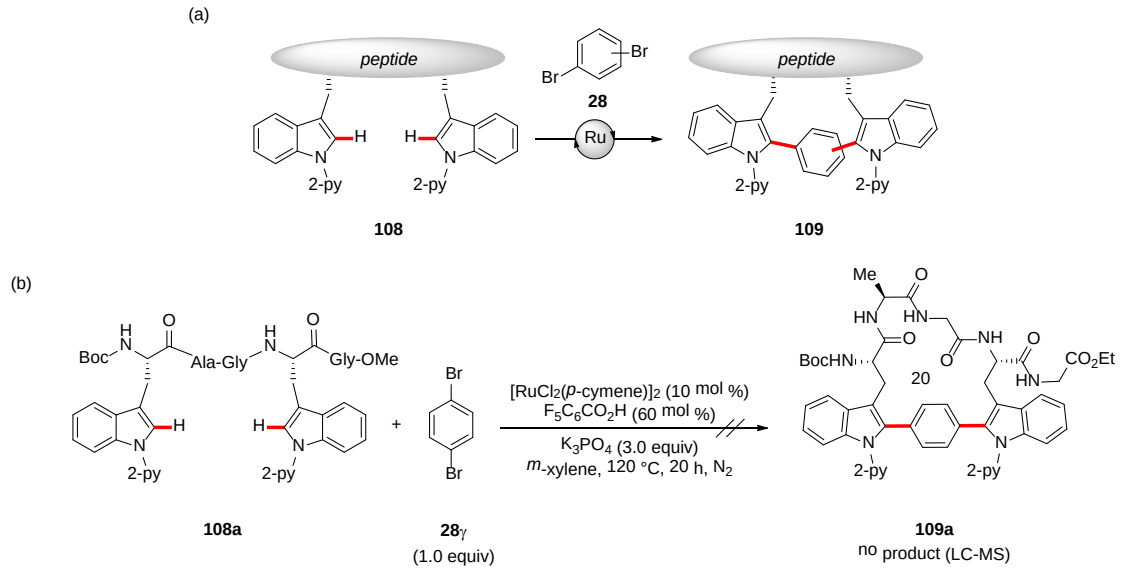
entry	*peptide1*	*peptide2*	product	yield
4	**81wf**	Boc-Trp^{py}-Trp-Gly-OEt (**101e**)	 **126d**	0%[b]

a: Reaction conditions: **81** (20–40 mg), **101** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $F_5C_6CO_2H$ (60 mol %), K_3PO_4 (3.0 equiv), *m*-xylene (1.0 mL), 120 °C, 22 h, N_2. b: LC-MS indicated product formation.

The last two presented ligation approaches, applying bromophenacylated peptides **124** or using the sequential palladium-ruthenium-catalysis, nicely demonstrated the simple accessibility of chemically ligated peptides with a unique branching at the tryptophan moiety.

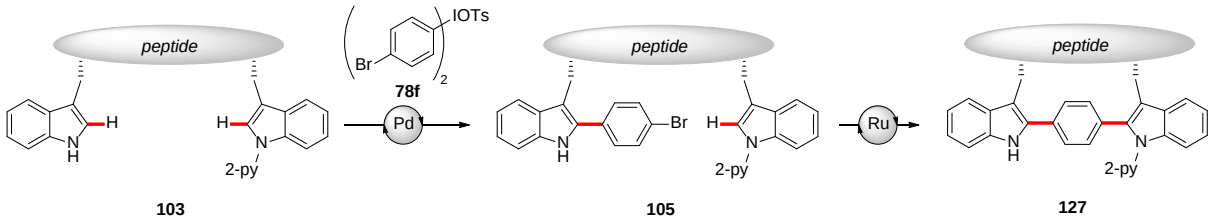
3.2.7 Attempted Ruthenium-Catalyzed Cyclization of Tryptophan-Containing Peptides

The application of the ruthenium-catalyzed C–H arylation method developed in this work should be suitable for the cyclization of peptides **108**, which contain two pyridylated tryptophans. A twofold C–H arylation with an aryl dibromide **28** should afford cyclopeptides **109** (Scheme 72 a). A preliminary attempt was performed by reacting pentapeptide **108a**, bearing tryptophans in an *i*,*i*+3-distance with 1,4-dibromobenzene (**28γ**), under the best suitable conditions using 10 mol % of the ruthenium-catalyst, pentafluorobenzoic acid and potassium phosphate in *meta*-xylene at 120 °C. Unfortunately, an LC-MS analysis of the crude reaction mixture indicated no product formation.



Scheme 72: Ruthenium-catalyzed cyclization of peptides **108**. (a) General approach. (b) Unsuccessful attempt.

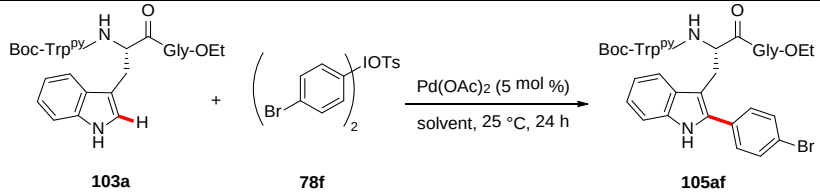
Another intended cyclization approach was the palladium-catalyzed C–H arylation of peptides **103** according to the method discribed in chapter 3.1[89] followed by an intramolecular C–H arylation of a pyridylated tryptophan in order to form cyclic peptides **127** (Scheme 73).



Scheme 73: Cyclization by multicatalytic C–H aylation.

Initially, the first step was examined with the peptide **103a** as the model peptide (Table 23). The concern that the pyridyl group might harm the palladium-catalyzed reaction was confirmed. Although the reaction was carried out in the most suitable solvents sought out for this transformation, namely DCE, DMF, toluene, water and acetic acid, no formation of product **105af** could be detected. Also, no arylation of the pyridylated tryptophan was observed.

Table 23: Palladium-catalyzed C–H arylation of peptide **103a**.[a]



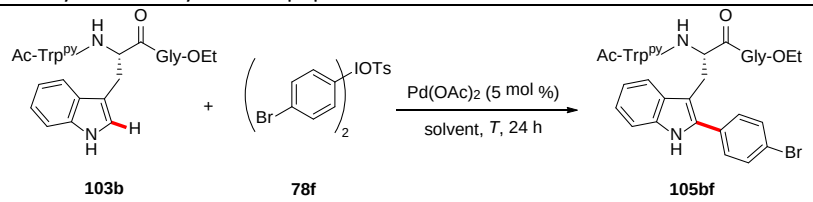
103a + **78f** (1.5 equiv) → **105af**

entry	solvent	yield	entry	solvent	yield
1	DCE	0%	4	H_2O	0%
2	DMF	0%	5	H_2O/HOAc 1:1	0%
3	toluene	0%	6	HOAc	0%

a: Reaction conditions: **103a** (0.10 mmol), **78f** (0.15 mmol), $Pd(OAc)_2$ (5 mol %), solvent (1.0 mL), 25 °C, 24 h.

In order to examine harsher reaction conditions, acetylated peptide **103b** was used (Table 24). No product **105bf** were formed when DCE, DMF, toluene or acetic acid were used as the solvents (entries 1–4). In TFA as the reaction medium, LC-MS analysis gave reason to assume product formation. However, the conversion was low and no product **105bf** was isolated (entry 5). An increase of the reaction temperature to 60 °C resulted in an increased conversion and thus arylated peptide **105bf** was isolated in 35% yield (entry 6). To accomplish full conversion, the reaction was carried out in TFA at 100 °C. After the reaction, neither starting material **103b** nor product **105bf** was detected.

Table 24: Palladium-catalyzed C–H arylation of peptide **103b**.[a]



103b **78f** (1.5 equiv) **105bf**

entry	solvent	*T*/°C	yield	entry	solvent	*T*/°C	yield
1	DCE	25	0%	5	TFA	25	0%[b]
2	DMF	25	0%	6	TFA	60	35%
3	toluene	25	0%	7	TFA	100	0%
4	HOAc	25	0%				

a: Reaction conditions: **103b** (0.05 mmol, 30 mg), **78f** (0.08 mmol), $Pd(OAc)_2$ (5 mol %), solvent (1.0 mL), 25 °C, 24 h.
b: LC-MS indicated product formation.

For the synthesis of cyclopeptides **127**, peptides **103** would need to have a certain minimum backbone length in order to assure sufficient space and flexibility for the formation of the triarylated system of the final products **105**. However, it was deemed as unreasonable to attempt further experiments with longer peptides **103**, because in our experience larger peptides tend to react slower, while peptide **103b**, which is far too small for the intended cyclization, was already isolated in only 35% yield.

3.2.8 Fluorescence Studies of the Arylated Tryptophans

The fluorescence properties of selected C–H arylated tryptophans **67** were examined and compared to the parent unarylated tryptophan **56h**. Initially, 2D-scans of the examined compounds were recorded in order to figure out at which excitation wavelength the maximum emission occurs. The 2D spectra of compound **67hq** is shown exemplarily (Figure 5 a). This highly fluorescent tryptophan showed two emission maxima at excitations with 280 and 350 nm, respectively.

The arylated compounds **67hd**, **67hq**, **67ho** and **67hn** all showed enhanced fluorescence as compared to the native non-arylated compound **56h** (Figure 5 b). The Stokes shift varies from 103 nm for compound **67hn** to 196 nm for compound **67hq** (Table 25).

A fluorine in the *para*-position of the phenyl group in compound **67hk** drastically diminished the fluorescence intensity (Figure 5 c). Futhermore, the ferrocene of compound **67hc** completely quenched the fluorescence.

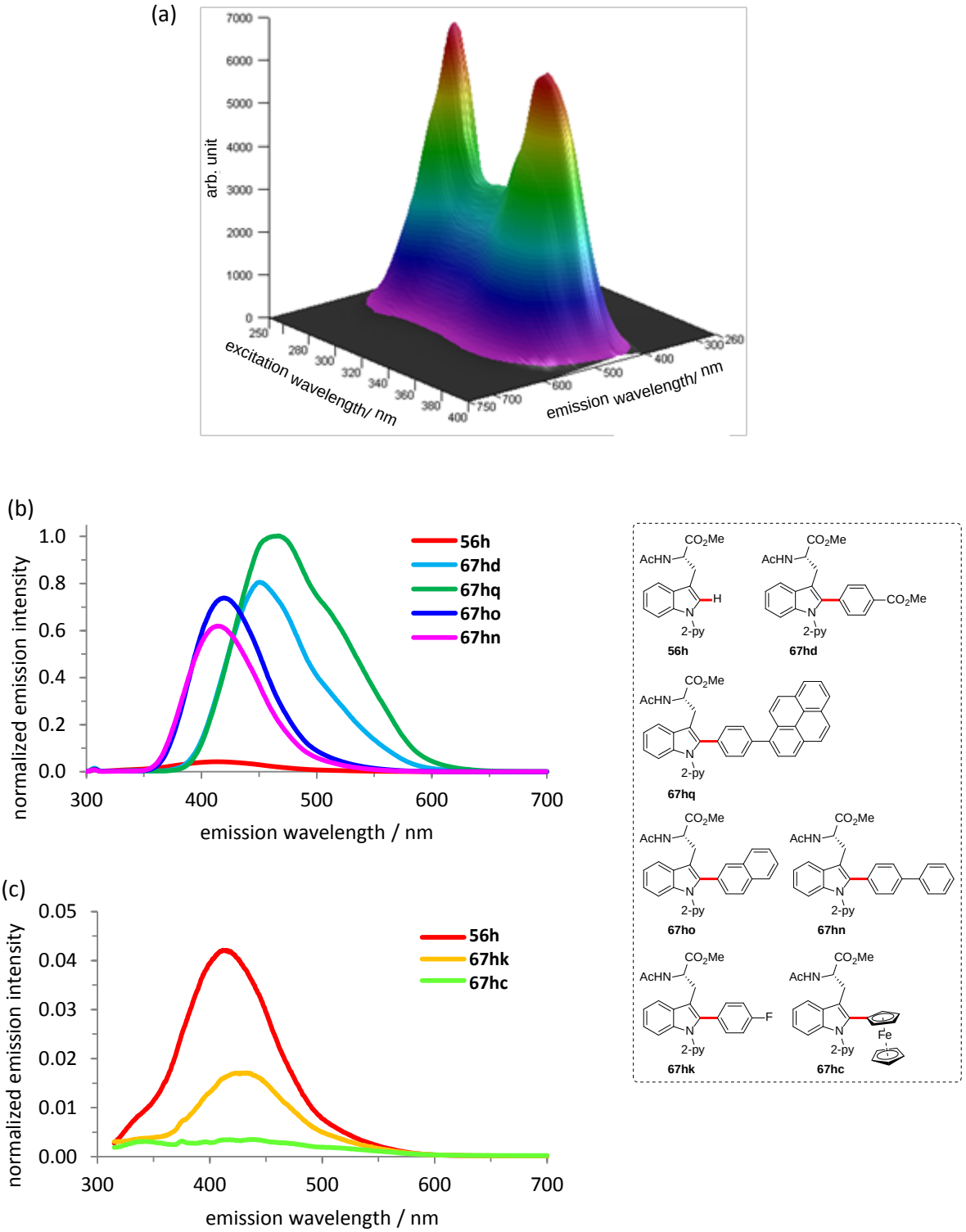


Figure 5: Fluorescent measurements. (a) Excitation-Emission-scan of compound **67hq**. (b) and (c) Emission of selected compounds. All spectra were recorded at a concentration of 1 mg/L. The excitation wavelengths correspond to the λ_{max} values shown in table 25.

Table 25: Fluorescence data.

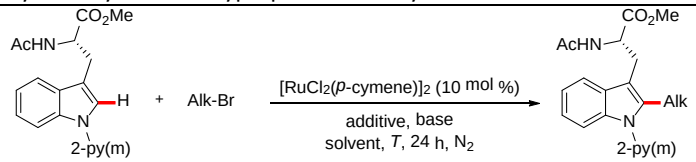
entry	compound	absorption λ_{max}/nm	emission λ_{max}/nm	Stokes shift/nm
1	**56h**	280	412	132
2	**67hd**	320	450	130
3	**67hq**	270	466	196
4	**67ho**	280	419	139
5	**67hn**	311	414	103
6	**67hk**	255	432	177
7	**67hc**	270	n. d.	-

3.3 Ruthenium-Catalyzed C–H Alkylation of Tryptophan-Containing Peptides

Having established C–H arylation methods for the modification of tryptophan-containing peptides **80** and **101**, our interest for alkylation methods for peptides arose. Despite of a widespread research on peptide modification reactions and a few examples of C–H functionalization procedures, C–H alkylation methods for peptides are scarce in literature.

Analogous to the transference of the ruthenium-catalyzed C–H arylation of phenylpyridines to pyrimidylated or pyridylated tryptophans, alkylation methods developed for simple structures such as phenylpyridines should be transferred to tryptophan peptides. Two alkylation strategies were considered: reactions with alkyl halides and hydroarylations of unsaturated compounds. Ruthenium-catalyzed C–H alkylations developed by our group have been successfully applied to phenylpyridines.[118] Similar reaction conditions were tested on the tryptophans **56g** and **56h** (Table 26). A primary, a secondary and a benzylic alkyl bromide were chosen as test substrates for the ruthenium-catalyzed C–H alkylation using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and 1-adamantyl carboxylic acid or mesityl carboxylic acid in combination with a base. Unfortunately, these alkylation reactions did not deliver the desired products. Instead, the starting material **56** was reisolated.

Table 26: Ruthenium-catalyzed alkylation of tryptophan with alkyl bromides.[a]



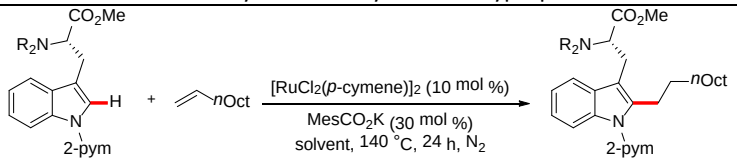
56g (2-pym) **56h** (2-py) **128** **107**

entry	Trp	alkyl bromide	additive	base	solvent	*T*/° C	result
1	**56g**	*n*HexBr (**128a**, 1.2 equiv)	1-AdCO_2H (30 mol %)	K_2CO_3	*m*-xylene	140	n. d.
2	**56g**	CyBr (**128b**, 1.2 equiv)	1-AdCO_2H (30 mol %)	K_2CO_3	*m*-xylene	140	n. d.
3	**56g**	BnBr (**128c**, 1.2 equiv)	1-AdCO_2H (30 mol %)	K_2CO_3	*m*-xylene	140	traces
4	**56h**	*n*HexBr (**128a**, 3.0 equiv)	MesCO_2H (60 mol %)	K_3PO_4	*m*-xylene	120	n. d.
5	**56h**	CyBr (**128b**, 3.0 equiv)	MesCO_2H (60 mol %)	K_3PO_4	*m*-xylene	120	n. d.
6	**56h**	CyBr (**128b**, 3.0 equiv)	MesCO_2H (60 mol %)	K_2CO_3	1,4-dioxane	120	traces

a: Reaction conditions: **56** (0.30 mmol), **128**, [$RuCl_2$(*p*-cymene)]$_2$ (10 mol %), additive, base (3.0 equiv), solvent, 24 h, N_2. n. d.: Product was not detected.

Inspired by the ruthenium-catalyzed alkylation of phenylpyridines using unactivated alkenes, which was developed by our group in 2013 (Scheme 28),[57e] similar reaction conditions were applied to tryptophan **56g**, delivering the alkylated product **107gb** in 38 and 60% when the reaction was carried out at 120 and 140 °C, respectively (Table 27, entries 1 and 2). When Boc- or phthalide-protected tryptophan **56e** or **56f** was used, the yield dropped to 31 and 13%, respectively (entries 3 and 4). Acetylated tryptophan **56g** was most suitable for this transformation, so it was used for the following reactions. Changing the solvent to other aromatic, aliphatic, etheric or alcoholic solvents did not improve the yield (entries 5–13). Moreover, the alcohols 1-butanol and ethylene glycol led to a transesterification of the starting material **56g**. The increase of the amount of additive mesityl carboxylic acid yielded 21% of the alkylated product **107gb** (entry 14). The use of microwave irradiation also did not improve the outcome of the reaction (entries 15 and 16).

Table 27: Optimization of the ruthenium-catalyzed C–H alkylation of tryptophan with unactivated alkenes.[a]



56g (R_2 = H, Ac)
56e (R_2 = H, Boc)
56f (R_2 = Phth)

44b (3.0 equiv)

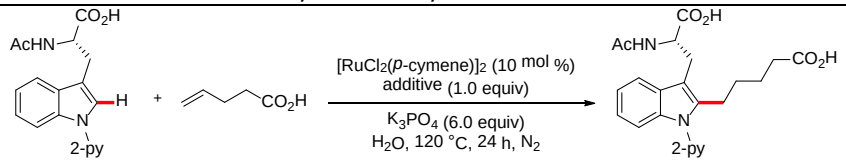
107gb
107eb
107fb

entry	Trp	solvent	note	yield
1	**56g**	toluene	at 120 °C	38%
2	**56g**	toluene	-	60%
3	**56e**	toluene	-	31%
4	**56f**	toluene	-	13%
5	**56g**	*m*-xylene	-	29%
6	**56g**	NMP	-	n. d.
7	**56g**	hexanes	-	24%
8	**56g**	1,4-dioxane	-	8%
9	**56g**	DME	-	10%
10	**56g**	HOAc	-	25%
11	**56g**	1-butanol	-	n. d.[b]
12	**56g**	*n*-octane	-	n. d.
13	**56g**	ethylene glycol	-	n. d.[b]
14	**56g**	toluene	$MesCO_2K$ (2.0 equiv)	21%
15	**56g**	toluene	140 °C, 1 h, MW	traces
16	**56g**	toluene	140 °C, 4 h, MW	traces

a: Reaction conditions: **56** (0.30 mmol), **44b** (0.90 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $MesCO_2K$ (30 mol %), solvent (3.0 mL), 140 °C, 24 h, N_2. b: Transesterification of the tryptophan substrate was observed.

A similar approach was the alkylation of tryptophan **56j** with alkene **44c**, which are both soluble in basic water (Table 28). Different additives were tested for this reaction. When mesityl carboxylic acid or 1-adamantyl carboxylic acid were used (entries 1 and 3), the product mass was detected by the LC-MS analysis. However, due to purification difficulties, alkylated product **107jc** was not isolated. When other additives were used, only traces of the product were observed.

Table 28: Optimization of the ruthenium-catalyzed C–H alkylation in water.[a]



56j **44c** (3.0 equiv) **107jc**

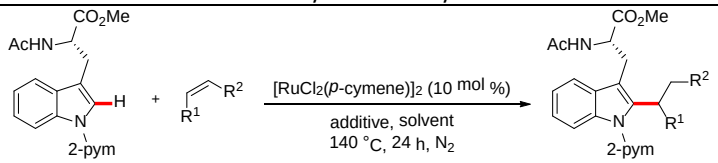
entry	additive	yield	entry	additive	yield
1	$MesCO_2K$	0%[b,c]	5	$(TRIP)CO_2H$	0%
2	$F_5C_6CO_2H$	0%	6	PPh_3	0%
3	$1\text{-}AdCO_2H$	0%[c]	7	HOPiv	0%
4	$(3\text{-}F_3CC_6H_4)CO_2H$	0%	8	-	0%[d]

a: Reaction conditions: **56j** (0.30 mmol), **44c** (0.90 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), additive (0.30 mmol), K_3PO_4 (1.80 mmol), H_2O (3.0 mL), 120 °C, 24 h, N_2. b: No K_3PO_4 was added. c: LC-MS indicated product formation. d: The reaction was set up in acetic acid.

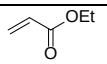
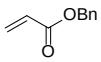
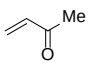
Furthermore, different types of olefins were examined in order to identify suitable alkylating agents for tryptophan peptides (Table 29). Activated olefins were reacted with tryptophan **56g**, applying 10 mol % $[RuCl_2(p\text{-cymene})]_2$ and 30 mol % mesityl carboxylate in toluene at 140 °C (entries 1–11). For these reactions, only in the case of norbornene **136a** the alkylation product **137ga** was isolated with a reasonable yield of 36%. NMR analysis of the product **137ga** showed a 1:1:1:1 mixture of isomers. The reaction with styrene delivered 4% of the corresponding alkylated tryptophan **133ga**.

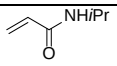
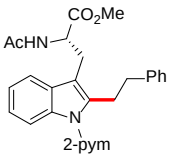
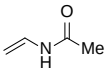
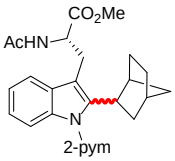
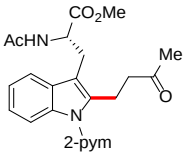
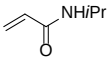
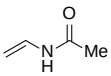
Since under basic conditions the alkylation reactions did not proceed, the substrates **129**–**134** were reacted with tryptophan **56g** in acetic acid (entries 12–16). Interestingly, the desired alkylation products could be isolated in a very high yield of 91% when using methyl vinyl ketone (**130a**) (entry 13). This result set the stage for further optimization reactions with α,β-unsaturated substrates **129**–**131**.

Table 29: Screening of olefins for the ruthenium-catalyzed C–H alkylation.[a]



56g

entry	alkene	additive	solvent	result
1	 **129a**	$MesCO_2K$ (30 mol %)	toluene	n. d.
2	 **129b**	$MesCO_2K$ (30 mol %)	toluene	n. d.
3	 **130a**	$MesCO_2K$ (30 mol %)	toluene	n. d.

entry	alkene	additive	solvent	result
4	 **131a**	$MesCO_2K$ (30 mol %)	toluene	n. d.
5	 **132a**	$MesCO_2K$ (30 mol %)	toluene	 **133ga**: 4%
6	 **134a**	$MesCO_2K$ (30 mol %)	toluene	n. d.
7	 **135a**	$MesCO_2K$ (30 mol %)	toluene	n. d.
8	 **136a**	$MesCO_2K$ (30 mol %)	toluene	 **137ga**: 36%[b]
9	 **138a**	$MesCO_2K$ (30 mol %)	toluene	n. d.
10	 **139a**	$MesCO_2K$ (30 mol %)	toluene	n. d.
11	 **140a**	$MesCO_2K$ (30 mol %)	toluene	n. d.
12	 **129a**	-	HOAc	traces
13	 **130a**	-	HOAc	 **141ga**: 91%
14	 **131a**	-	HOAc	n. d.
15	 **132a**	-	HOAc	traces
16	 **134a**	-	HOAc	n. d.

a: Reaction conditions: **56g** (0.30 mmol), alkene (0.90 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), additive (30 mol %), solvent (3.0 mL), 140 °C, 24 h, N_2. b: A mixture of diastereomers was isolated. n. d.: No alkyl product was detected.

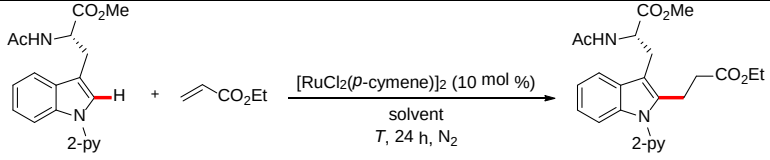
3.3.1 Ruthenium-Catalyzed C–H Alkylation with Acrylates

3.3.1.1 Optimization of the C–H Alkylation

Based on the successful alkylation of tryptophan **56g** with methyl vinyl ketone (**130a**) and the previous finding that pyridylated tryptophans are more reactive than pyrimidylated derivatives, the alkylation of tryptophan **56h** with ethyl acrylate (**129a**) was subsequently optimized (Table 30). A part

of the optimization was performed by Nikolaos Kaplaneris (entry 18). The first attempt was related to the results with vinyl ketone **130a** reacting tryptophan **56h** with 3 equivalents of ethyl acrylate (**129a**) and 10 mol % $[RuCl_2(p\text{-cymene})]_2$ in acetic acid at 120 °C under an atmosphere of nitrogen, resulting in a remarkable yield of 81% (entry 1). At this high temperature, partial transesterification of the methyl and ethyl esters was observed. In order to derive mild reaction conditions, less acidic solvents were tested. However, acetic acid buffers (entries 2 and 3), mixtures of acetic acid and organic solvents or water (entries 4–10) as well as weaker acids (entries 11–16), such as propionic acid, pivalic acid and ammonium chloride, did not improve the yield. A decrease of the reaction temperature to 100 °C increased the yield to 88% (entry 17). A reason could be the reduction of possible side reactions, such as transesterification, Michael addition or polymerization. A further decrease of the reaction temperature to 80 °C combined with an increased concentration of the starting material **56h** of 1.0 M afforded the best achieved yield of 90% (entry 19). Here, no transesterification was observed and the reaction could be easily set up under air. At lower reaction temperatures of 60 and even 38 °C hydroarylation product **142ha** was formed in 80 and 54% yield, respectively (entries 20 and 21). A decrease of the ruthenium catalyst loading to 5.0 mol % still delivered a high yield of 83% at 80 °C, however, the conversion was incomplete (entry 22). Further reduction of the catalyst loading to 2.5 or 1.0 mol % gave unsatisfying results (entries 23 and 24). The tolerance towards water was demonstrated by using a 3:1 or 1:1 mixture of acetic acid and water, affording product **142ha** in good yields of 75 and 60% (entries 25 and 26). To emphasize, the herein developed ruthenium-catalyzed C–H alkylation reaction was successfully performed at a biocompatible temperature of 38 °C in an aqueous acidic medium under air. This is an important prerequisite for possible bioorthogonal applications.

Table 30: Optimization of the ruthenium-catalyzed C–H alkylation with ethyl acrylate (**129a**).[a]



56h **129a** (3.0 equiv) **142ha**

entry	$[Ru]_2$/mol %	solvent	Trp conc./M	*T*/°C	yield
1	10	HOAc	0.3	120	81%
2	10	HOAc/KOAc buffer pH 4.0	0.3	120	traces
3	10	HOAc/KOAc buffer pH 3.7	0.3	120	traces
4	10	GVL/HOAc 1:1	0.3	120	58%
5	10	HOAc/*t*-amyl alcohol 1:9	0.3	120	traces
6	10	$HOAc/H_2O$ 1:9	0.3	120	traces

entry	$[Ru]_2$/mol %	solvent	Trp conc./M	*T*/°C	yield
7	10	HOAc/toluene 1:9	0.3	120	traces
8	10	HOAc/*m*-xylene1:9	0.3	120	traces
9	10	HOAc/*n*-octane 1:9	0.3	120	47%
10	10	HOAc/DME 1:9	0.3	120	traces
11	10	HO_2CEt	0.3	120	35%
12	10	HOPiv	0.3	120	23%
13	10	citric acid/NaOH in H_2O pH 3.5	0.3	120	n. d.
14	10	$KHSO_4$ in H_2O pH 1.6	0.3	120	n. d.
15	10	GVL/NH_4Cl (5 M in H_2O) 1:1	0.3	120	13%
16	10	NH_4Cl (5 M in H_2O)	0.3	120	traces
17	10	HOAc	0.3	100	88%
18	10	HOAc	0.3	80	73%[b,c]
19	**10**	**HOAc**	**1.0**	**80**	**90%[c]**
20	10	HOAc	1.0	60	80%[c]
21	10	HOAc	1.0	38	54%[c]
22	5.0	HOAc	1.0	80	83%[c]
23	2.5	HOAc	1.0	80	28%[c]
24	1.0	HOAc	1.0	80	traces[c]
25	10	HOAc/H_2O 3:1	1.0	80	75%[c]
26	10	HOAc/H_2O 1:1	1.0	80	60%[c]

a: Reaction conditions: **56h** (0.15 mmol), **129a** (0.45 mmol), $[RuCl_2(p\text{-cymene})]_2$ (1.0–10 mol %), solvent (0.15–0.45 mL), 24 h, N_2 or air. b: The reaction was performed by Nikolaos Kaplaneris. c: The reaction was set up under air. n. d.: Product was not detected.

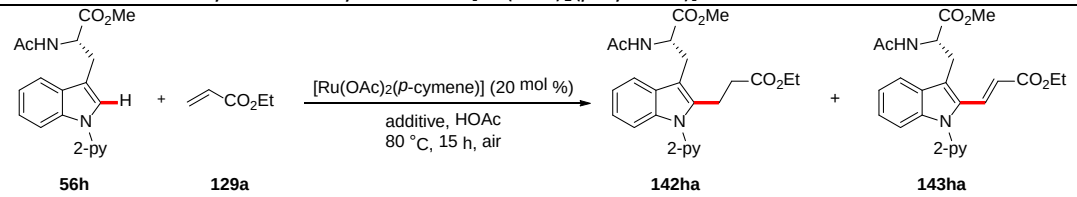
Later experiments showed that under the optimal reaction conditions (entry 19), the conversion was complete after 15 h. All following reactions were therefore stopped after 15 h.

When $[RuCl_2(p\text{-cymene})]_2$ is dissolved in acetic acid, it is prone to exchange its two chloride ligands for two acetates (Scheme 74). This gave reason to assume that the formed $[Ru(OAc)_2(p\text{-cymene})]$ could be the active complex, because the reaction did not proceed without acid. In order to prove this, the reaction was carried out using 10 mol % $[Ru(OAc)_2(p\text{-cymene})]$ instead of $[RuCl_2(p\text{-cymene})]_2$ (Table 31). Unexpectedly, no desired product was formed (entry 1). The addition of 40 mol % HCl afforded 92% of product **142ha**, just as for the optimal reaction conditions (entry 2). In order to prove if the addition of protons is necessary or if the addition of chloride suffices to accomplish the reaction, sodium and potassium chloride were added, respectively (entries 3 and 4). Surprisingly, in these cases the unsaturated product **143ha** was formed in addition to the expected product **142ha**. The conversion was rather low and thus the products were isolated with

unsatisfactory low yields. It is a notable discovery that the electroneutral coupling was switched to an oxidative one only through the addition of sodium or potassium chloride. The following reactions were set up with 40 mol % of the ruthenium catalyst in order to guarantee full conversion. The aim was to push the selectivity completely to the unsaturated product **143ha**. The increase of the amount of sodium chloride to 6.0 equivalents still gave a mixture of products **142ha** and **143ha** (entry 5). Although no starting material **56h** was present anymore, isolation of the products by chromatography afforded only 14 and 8% of the products. When 20 equivalents of sodium chloride were applied, no hydroarylation product **142ha** was detected and only the olefin **143ha** seemed to have been formed (entry 6). Comparable to the previous case, only a small amount of 15% of tryptophan **143ha** was isolated. The elevated amounts of ruthenium or sodium chloride might have caused a precipitation of the tryptophans by being chelated. Attempts to release the tryptophan **143ha** after the reaction and before the chromatography by the addition of propane-1,3-dithiol failed.

Scheme 74: $[RuCl_2(p\text{-cymene})]_2$ in acetic acid.

Table 31: Ruthenium-catalyzed C–H alkylation with $[Ru(OAc)_2(p\text{-cymene})]$.[a]



56h **129a** (3.0 equiv) **142ha** **143ha**

entry	additive	yield **142ha**	yield **143ha**	entry	additive	yield **142ha**	yield **143ha**
1	-	n. d.	n. d.	4	KCl (3.0 equiv)	24%	10%
2	aq. HCl (40 mol %)	92%	n. d.	5	NaCl (6.0 equiv)	14%	8%[b]
3	NaCl (3.0 equiv)	22%	9%	6	NaCl (20 equiv)	n. d.	15%[b]

a: Reaction conditions: **56h** (0.15 mmol), **129a** (0.45 mmol), $[Ru(OAc)_2(p\text{-cymene})]$ (20 mol %), additive, HOAc (0.15 mL), 80 °C, 15 h, air. b: 40 mol % [Ru] were used. n. d.: Product was not detected.

3.3.1.2 Scope with Tryptophan and Acrylates

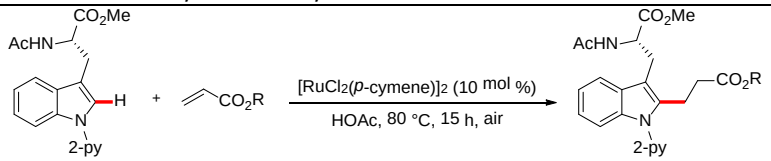
Next, the versatility of the C–H alkylation method was examined (Table 32). Several reactions of this scope were performed by Nikolaos Kaplaneris. Aliphatic, aromatic as well as benzylic acrylates were coupled efficiently to tryptophan **56h**, affording the alkylated products **142** in excellent yields.

Functional groups, such as methoxy, enolizable ketone, cyanide, nitro, chloride, bromide, fluoride as well as styrene, terminal alkene, and hydroxyl were well tolerated. Also, the thioester **142hq** was successfully synthesized, showing tolerance towards thioacrylates. The synthetic approaches for further modifications of the demonstrated spectrum of compounds that are available by this method are widespread. Halogenated compounds could be used for cross-coupling reactions, enolizable ketones for aldol and Grignard additions, olefins for metathesis reactions, cyanides and nitro compounds could be reduced to amines, fluorides could be employed for ^{18}F-labeling and polyaromatics for fluorescence labeling. Another noteworthy functionality is the PEG moiety of substrate **142ht**, which is of high interest because PEGylated peptides promise great potential. PEGylation creates a possibility to tune the solubility of small drugs or peptides.[119] Moreover, PEGylation can assist the self-organization of supramolecular nanostructures and can cause changes of the photoluminescent properties.[120] Furthermore, PEGylation is used for protein conjugation in order to enhance pharmacological and pharmaceutical properties.[121] It is also used for drug delivery[122] and other applications. Last, the natural products menthol and cholesterol were ligated with tryptophan **56h**, providing the products **142hu** and **142hv** in high yields of 62 and 86%.

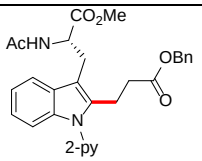
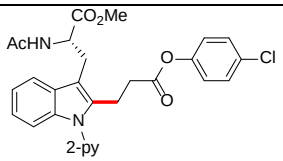
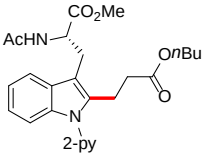
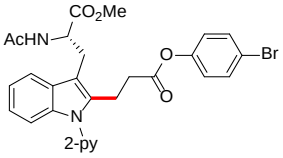
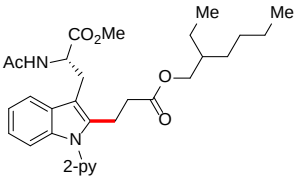
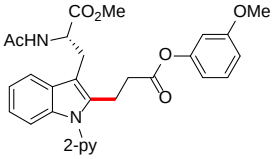
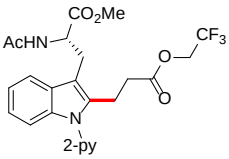
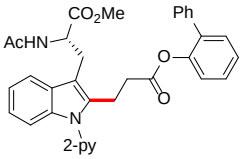
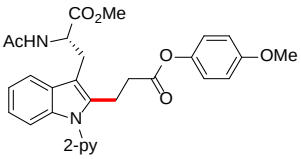
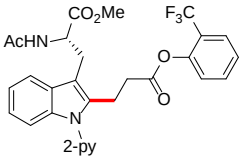
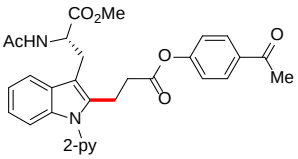
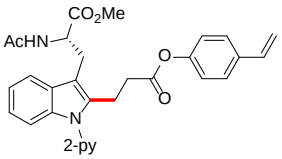
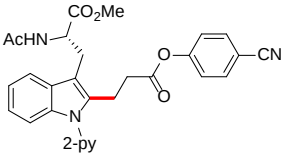
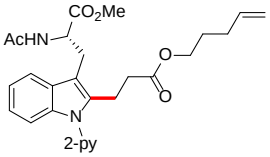
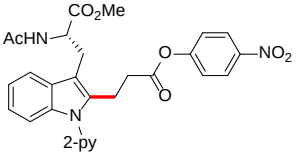
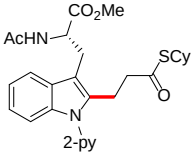
The substrates **142hw** and **142hx** were obtained with rather low yields of 27 and 40%, respectively. The ruthenium-catalyst might insert into the C–I bond causing side reactions. The *tert*-butyl group is sensitive to acid and was therefore cleaved under the reaction conditions.

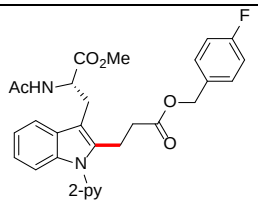
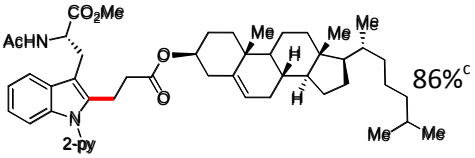
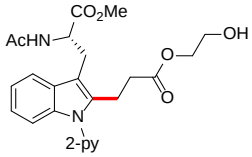
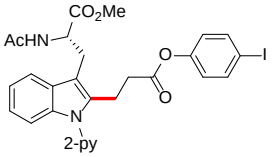
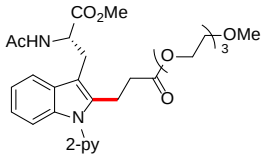
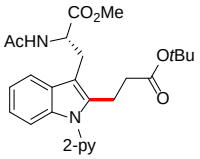
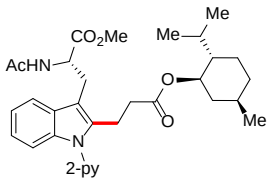
The obtained products illustrate the possibility of the introduction of a variety of diversely decorated molecules with the prospect for subsequent modifications. It is particularly noteworthy, that basically any substrate, that contains a hydroxyl or thiol group, which can be easily converted to the corresponding acrylate, could be applied.

Table 32: Scope of the ruthenium-catalyzed C–H alkylation.[a]



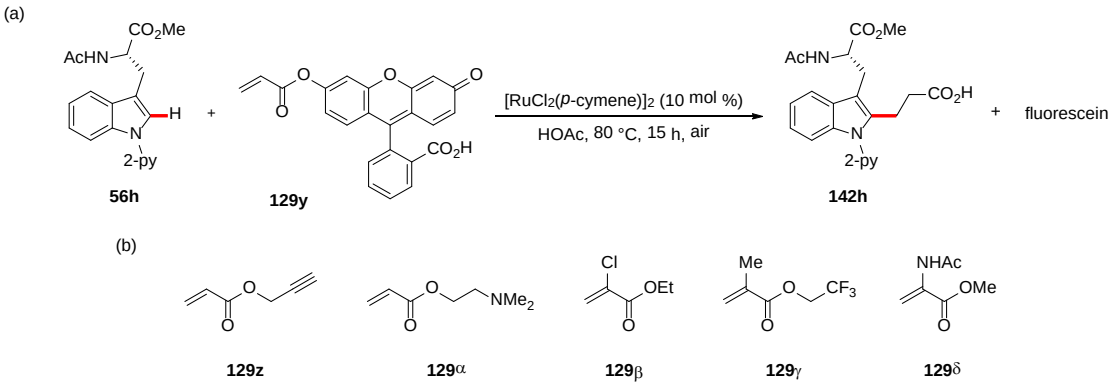
56h **129** (1.5-3.0 equiv) **142**

entry	product	yield	entry	product	yield
1	 **142hb**	89%	9	 **142hj**	64%
2	 **142hc**	90%	10	 **142hk**	72%[b]
3	 **142hd**	74%	11	 **142hl**	72%[b]
4	 **142he**	71%	12	 **142hm**	79%[b]
5	 **142hf**	73%	13	 **142hn**	75%[b]
6	 **142hg**	70%	14	 **142ho**	55%
7	 **142hh**	61%[b]	15	 **142hp**	75%
8	 **142hi**	53%[b]	16	 **142hq**	75%

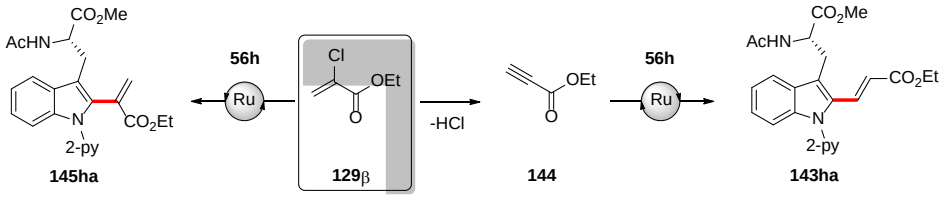
entry	product	yield	entry	product	yield
17	 **142hr**	66%	21	 **142hy** (from cholesterol)	86%[c]
18	 **142hs**	51%	22	 **142hw**	27%[b]
19	 **142ht**	74%	23	 **142hx**	40%
20	 **142hu** (from menthol)	62%			

a: Reaction conditions: **56h** (0.15 mmol), **129** (1.5–3.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), HOAc (0.15 mL), 80 °C, 15 h, air. b: The reaction was performed by Nikolaos Kaplaneris. c: Toluene/HOAc (1:1) was used and the reaction was carried out at 100 °C.

Fluoresceinyl acrylate **129y** was not suitable for this ruthenium-catalyzed C–H alkylation approach (Scheme 75 a). Although the actual C–H alkylation occurred, the acrylic ester was cleaved during the reaction and tryptophan **142h** was observed in the LC-MS spectra, while neither starting meterial **56h** nor desired product **142hy** was detected. Alkyne **129z** and tertiary amine **129α** were not tolerated by the ruthenium catalysis, resulting in no product formation (Scheme 75 b). Also, the α-substituted acrylates **129β** and γ as well as the dehydroalanine **129δ** did not deliver the desired products **142**. For the reaction with acrylate **129β**, the mass of the product **143ha** was observed in the LC-MS (Scheme 76). A possible explanation is the elimination of hydrogen chloride followed by the hydroarylation of the propiolate **144**. Possibly, propiolates **144** would be suitable substrates for this reaction. Another possibility is the direct coupling of the halogenated alkene **129β** affording regioisomer **145ha**, whose molecular weight is the same as that of product **143ha**.

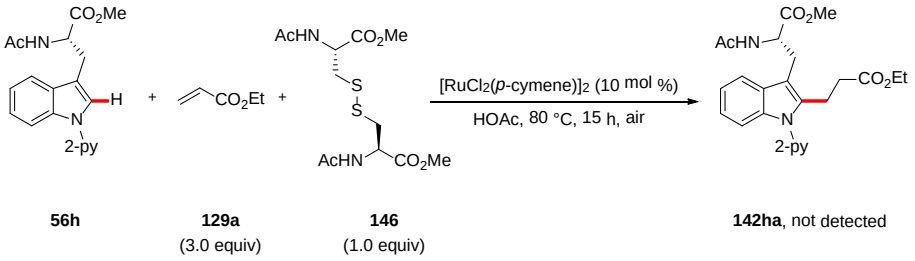


Scheme 75: (a) Coupling with acrylate **129y**. (b) Unsuitable substrates for the ruthenium-catalyzed C–H alkylation.



Scheme 76: Possible ruthenium-catalyzed reactions of acrylate **129β** with tryptophan **56h**.

The tolerance of disulfides was examined by a bioorthogonal test with the disulfide **146** (Scheme 77). The standard reaction of tryptophan **56h** with acrylate **129a** was carried out in the presence of one equivalent of disulfide **146**. No product **142ha** was detected thus showing an intolerance towards disulfides.



Scheme 77: Bioorthogonal test with a disulfide.

3.3.1.3 Studies on a Potential Racemization of Tryptophan

Tryptophan **56h** was partially racemized using a modified literature procedure.[44]

The ruthenium-catalyzed C–H alkylation of *rac*-**56h** yielded partially racemic products *rac*-**142ha**, *rac*-**142hd** and *rac*-**142hu**. HPLC analysis showed that no racemization occurred during the ruthenium-catalyzed C–H alkylation (Figure 7–9).

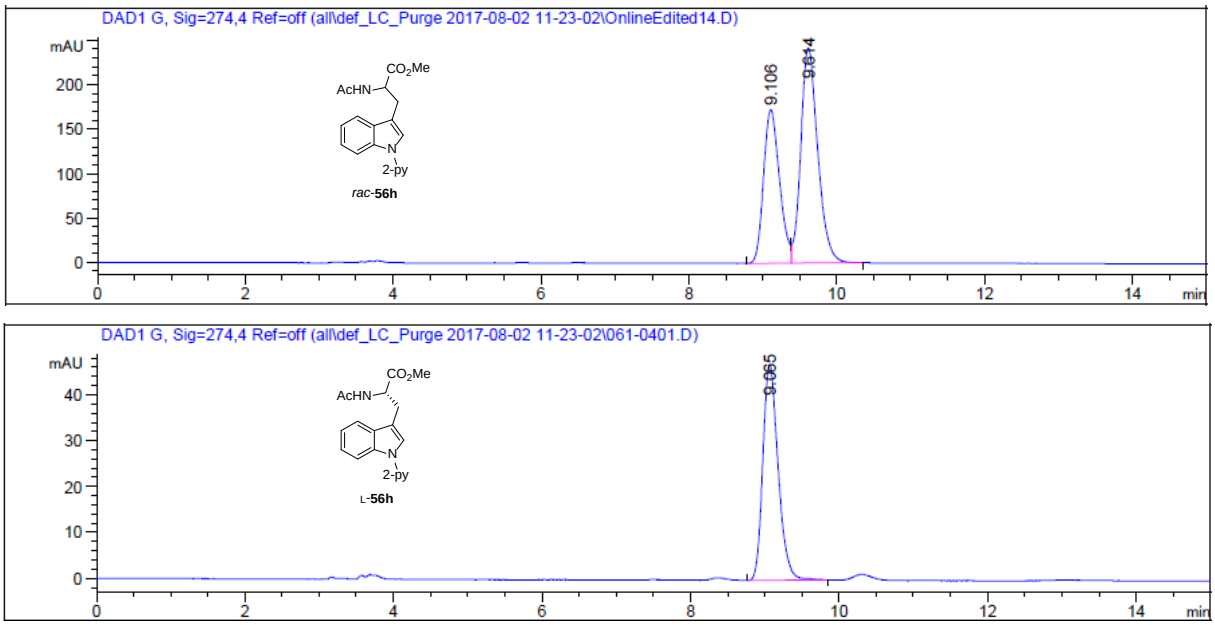


Figure 6: HPLC-Chromatograms of the partially racemic mixture of the compound *rac*-**56h** and of starting material L-**56h**.

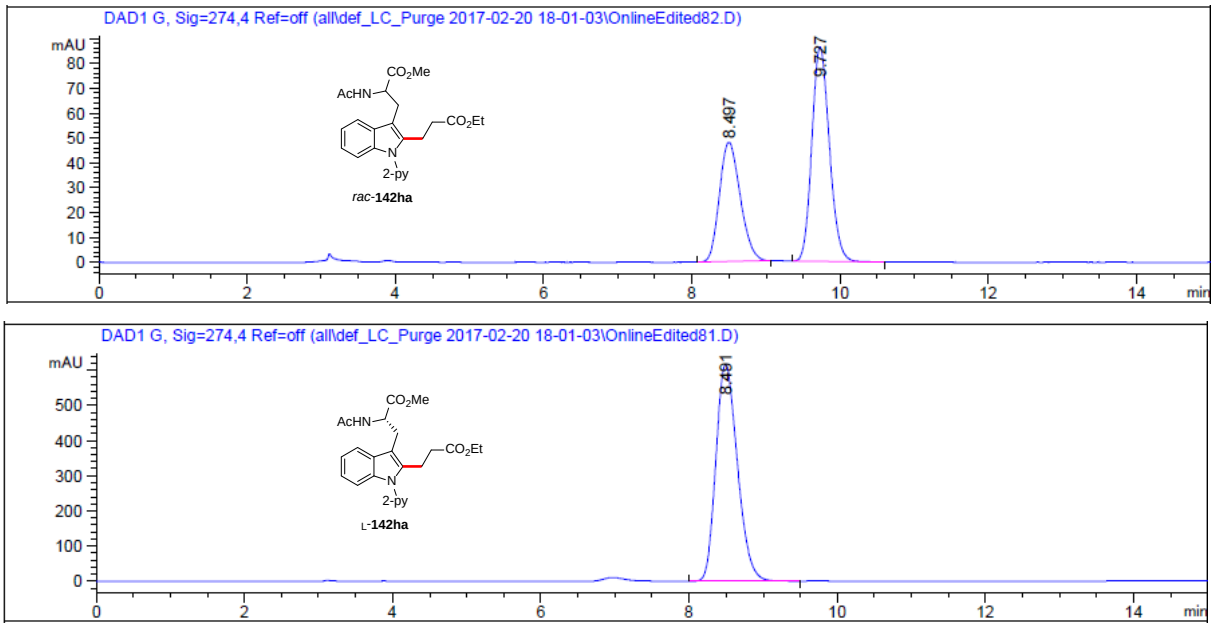


Figure 7: HPLC-Chromatograms of the partially racemic mixture of the compound *rac*-**142ha** and of isolated product L-**142ha**.

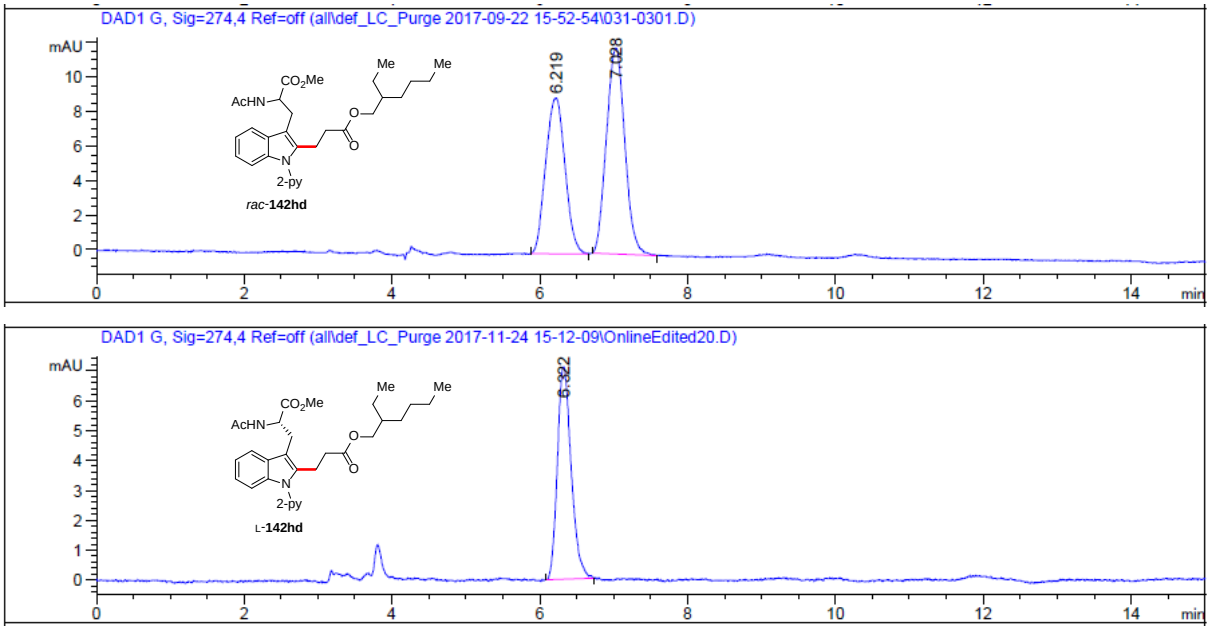


Figure 8: HPLC-Chromatograms of the partially racemic mixture of the compound *rac*-**142hd** and of isolated product L-**142hd**.

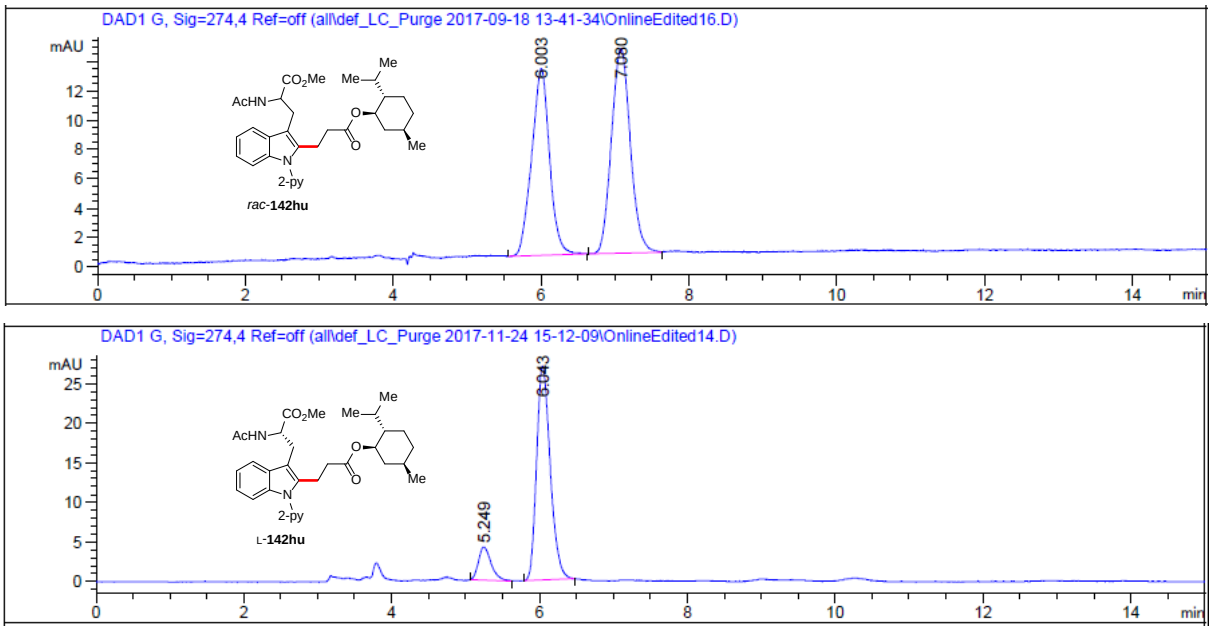


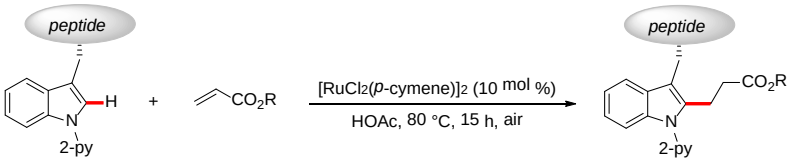
Figure 9: HPLC-Chromatograms of the partially racemic mixture of the compound *rac*-**142hu** and of isolated product L-**142hu**.

3.3.1.4 Scope of the C–H Alkylation of Peptides with Acrylates

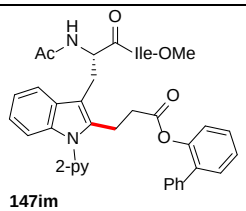
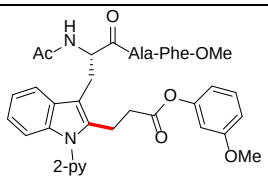
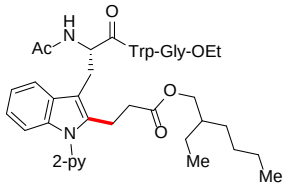
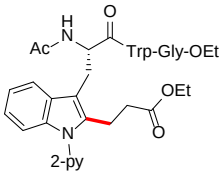
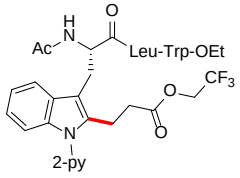
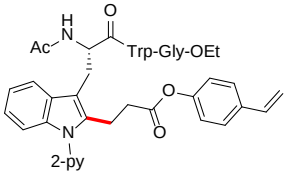
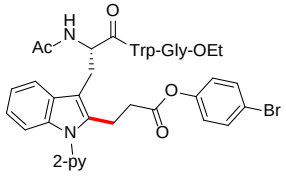
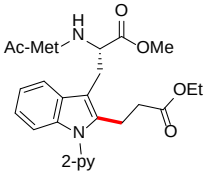
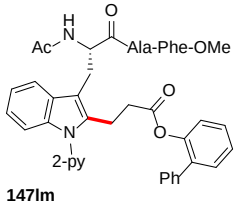
Having explored the scope and limitations of the ruthenium-catalyzed C–H alkylation of single tryptophan, the focus was next shifted to peptides **101** (Table 33). Some reactions were performed by Nikolaos Kaplaneris. Di- and tripeptides **101** were alkylated providing alkylated peptides **147** (entries 1–6). Both aromatic and aliphatic acrylates were applicable and the yields of the isolated compounds **147** vary from 53 to 76%. Due to difficulties regarding the purification, the alkylated

peptide **147ja** was not isolated, although the product mass was detected in the LC-MS analysis, while no starting material **101j** was detectable, which indicated a full conversion. The product **147jo** was also not obtained and in this case, the LC-MS analysis revealed a complex mixture of products. Methionine-containing peptide **147ma** was not formed.

Table 33: Scope of the ruthenium-catalyzed C–H alkylation of peptides **101**.[a]



101 **129** (3.0 equiv) **147**

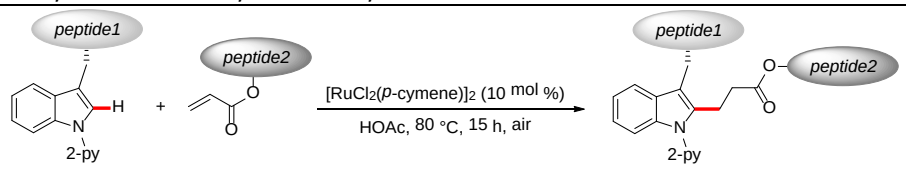
entry	product	yield	entry	product	yield
1	 **147im**	76%[b]	6	 **147ll**	53%[b]
2	 **147jd**	60%	7	 **147ja**	0%[c]
3	 **147kc**	57%	8	 **147jo**	0%[d]
4	 **147jk**	58%	9	 **147ma**	0%
5	 **147lm**	59%[b]			

a: Reaction conditions: **101** (50–100 mg), **129** (1.1–5.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), HOAc (0.1–0.3 mL), 80 °C, 15 h, air. b: The reaction was performed by Nikolaos Kaplaneris. c: LC-MS analysis indicated product formation. d: LC-MS analysis indicated a complex mixture of products.

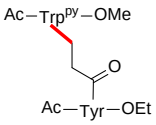
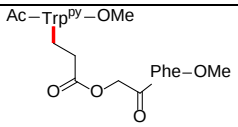
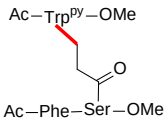
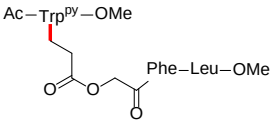
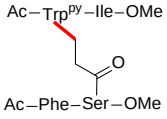
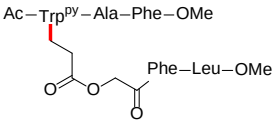
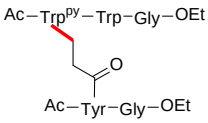
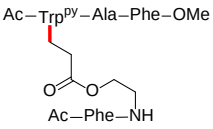
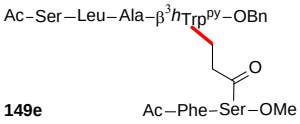
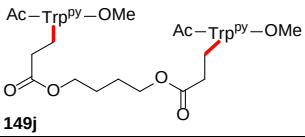
3.3.1.5 C–H Activation Ligation of Peptides

The ruthenium-catalyzed C–H alkylation approach was successfully applied for peptide ligation (Table 34). Ligation products **149** were obtained through the reaction of tryptophan peptides **101** with acryloyl peptides **148**. Some ligation reactions were performed by Nikolaos Kaplaneris. Acrylates of the natural amino acids tyrosine and serine delivered di- to hexapeptides **149a–e** in good yields of 42 to 64%. Furthermore, for peptides that do not contain a hydroxyl group, linkers were used to introduce the acrylate. For the *N*-terminus, 2-hydroxy acetic acid was used, which is incorporated in products **149f–h**, while for the *C*-terminus, 2-aminoethanol was applied, presented in product **149i**. With these two simple linkers any peptides could be used for this ligation method. The last example showed the ligation of two tryptophans **56h**, which were reacted with 0.5 equivalents of a diacrylate, affording product **149j**.

Table 34: Ligation by ruthenium-catalyzed C–H alkylation.[a]

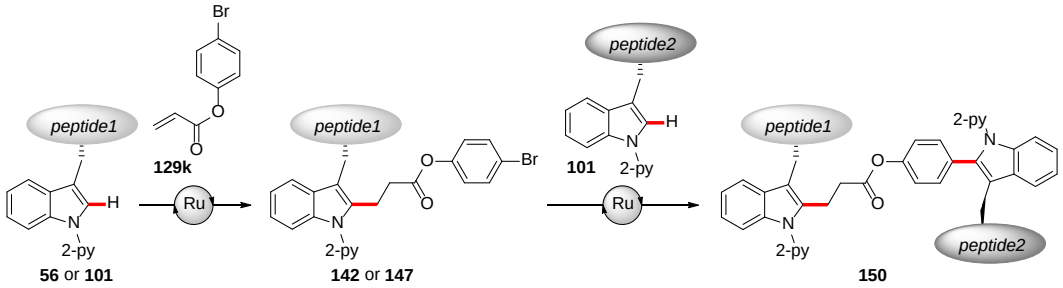


101 **148** (1.1 equiv) **149**

entry	product	yield	entry	product	yield
1	 **149a**	59%[b]	6	 **149f**	67%[c]
2	 **149b**	64%[c]	7	 **149g**	61%[c]
3	 **149c**	56%[c]	8	 **149h**	52%[c]
4	 **149d**	57%[b]	9	 **149i**	52%[c]
5	 **149e**	42%	10	 **149j**	54%

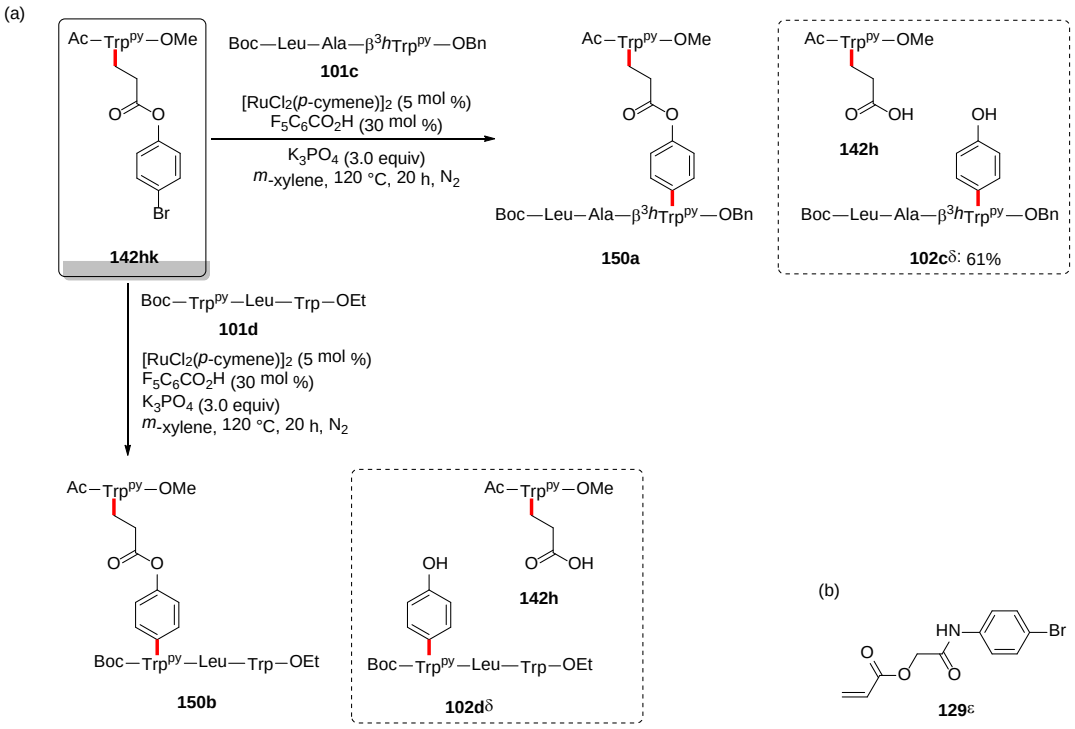
a: Reaction conditions: **101** (50–100 mg), **148** (1.1 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), HOAc (0.1–0.3 mL), 80 °C, 15 h, air. b: The reaction was stopped after 8 h to prevent phenolic ester cleavage. c: The reaction was performed by Nikolaos Kaplaneris.

Next, a combinatorial twofold ruthenium-catalyzed C–H ligation method was sought. The idea was to first alkylate peptides **56** or **101** with the acrylate **129k** followed by the arylation of a second peptide **101** (Scheme 78). The ligation products **150** would consist of two peptides, bridged by a phenol propionate. The first step of this procedure is presented in chapters 3.3.1.2 and 3.3.1.4, providing substrates **142hk** and **147jk**, which should be applied for this approach.



Scheme 78: Ligation through a sequential twofold C–H modification approach.

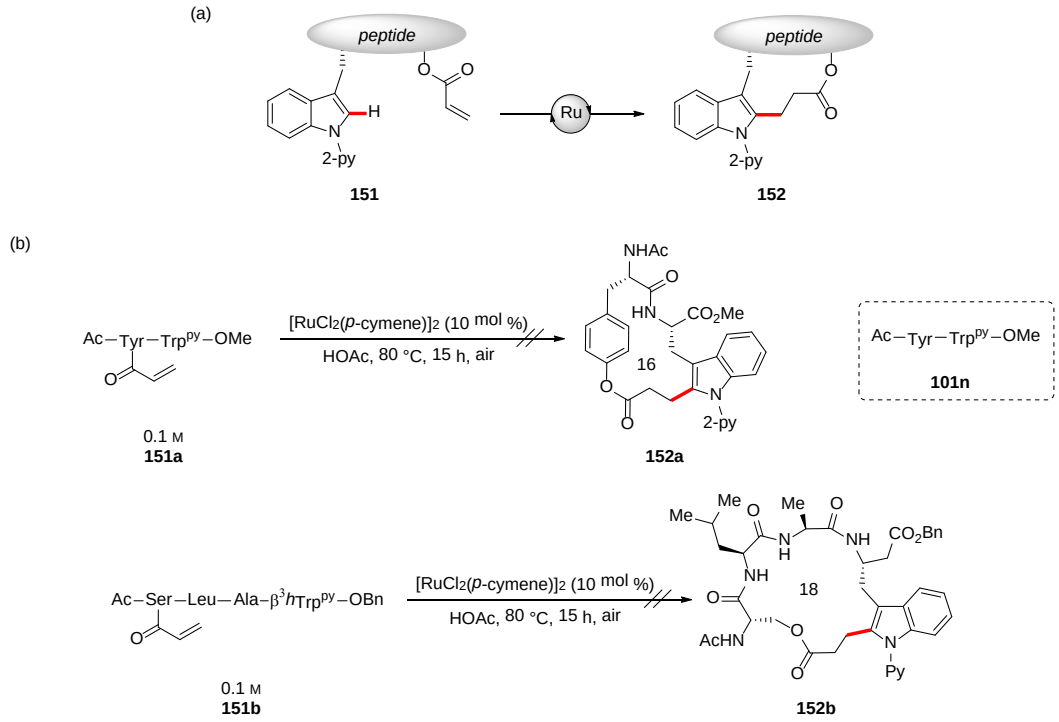
The structurally simpler substrate **142hk** was submitted to the ruthenium-catalyzed C–H arylation reaction to be ligated with two different peptides **101c** and **101d** (Scheme 79). Traces of the ligation products **150a** and **150b** were detected in the LC-MS, however, these peptides could not be isolated. Due to a cleavage of the phenolic ester, tryptophan **142h** and peptides **102cδ** and **102dδ** were found in the LC-MS analysis. In the case of the reaction with peptide **101c** the cleavage product **102cδ** was isolated in 61% yield. On the one hand, these results demonstrate that in principle this ruthenium-catalyzed C–H arylation method works. On the other hand, the choice of the linker was not suitable due to the instability of the phenolic ester under basic reaction conditions. A conceivably more suitable linker might be the acrylate **129ε** consisting of a bromoaniline connected to the acryloyl moiety by 2-hydroxy acetic acid. The more complex substrate **147jk** was not used due to the results, that were obtained with the substrate **142hk**.



Scheme 79: (a) Ligation through ruthenium-catalyzed arylation with bromide **142hk**. (b) Ligation linker **129ε**.

3.3.1.5 Attempted Cyclization of Acryloyl Peptides

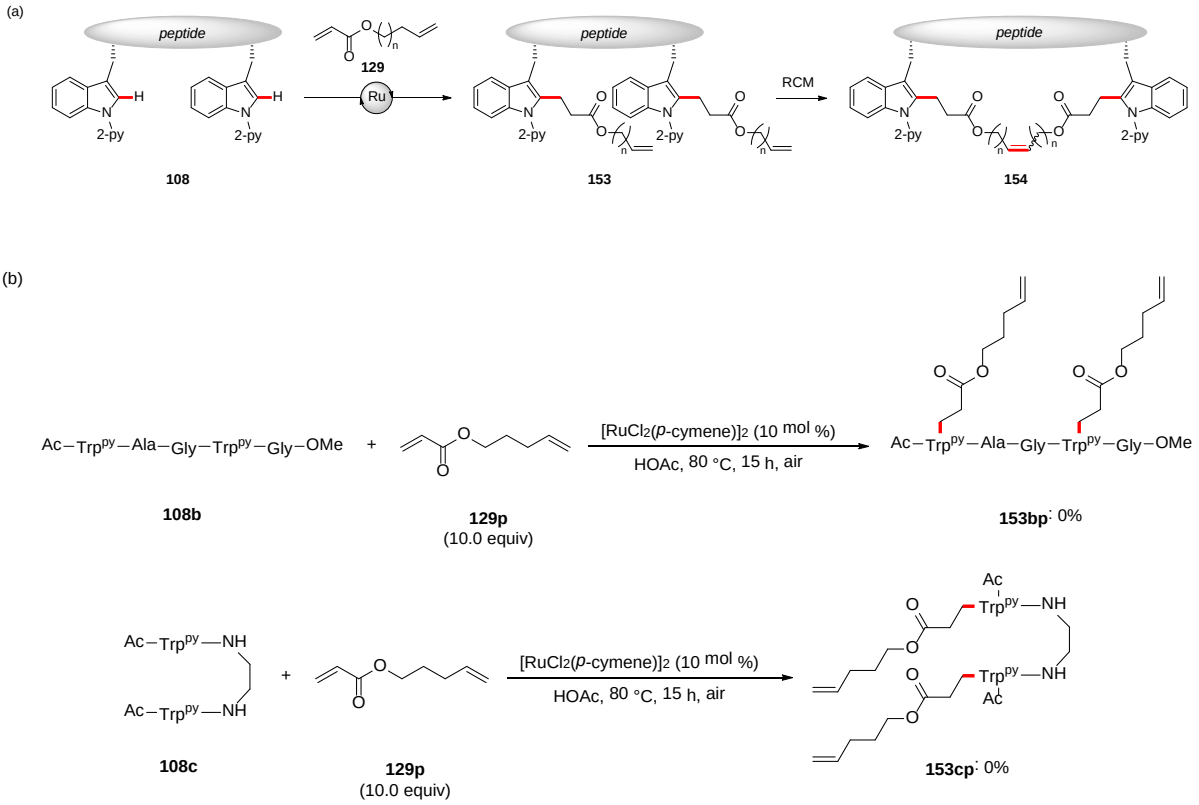
The ruthenium-catalyzed C–H alkylation was attempted in an intramolecular fashion in order to obtain cyclopeptides **152** (Scheme 80). The cyclization reactions were carried out at a concentration of 0.1 M. Unfortunately, neither cyclic peptide **152a** nor **152b** were obtained. In the case of the tyrosine acrylate **151a**, acrylic ester hydrolysis led to peptide **101n**, whose molecular mass was observed in the LC-MS analysis. After the reaction of peptide **151b**, the serine acrylate signals were still present in the NMR spectra and the LC-MS analysis did not indicate the formation of the cyclic peptide **152b**.



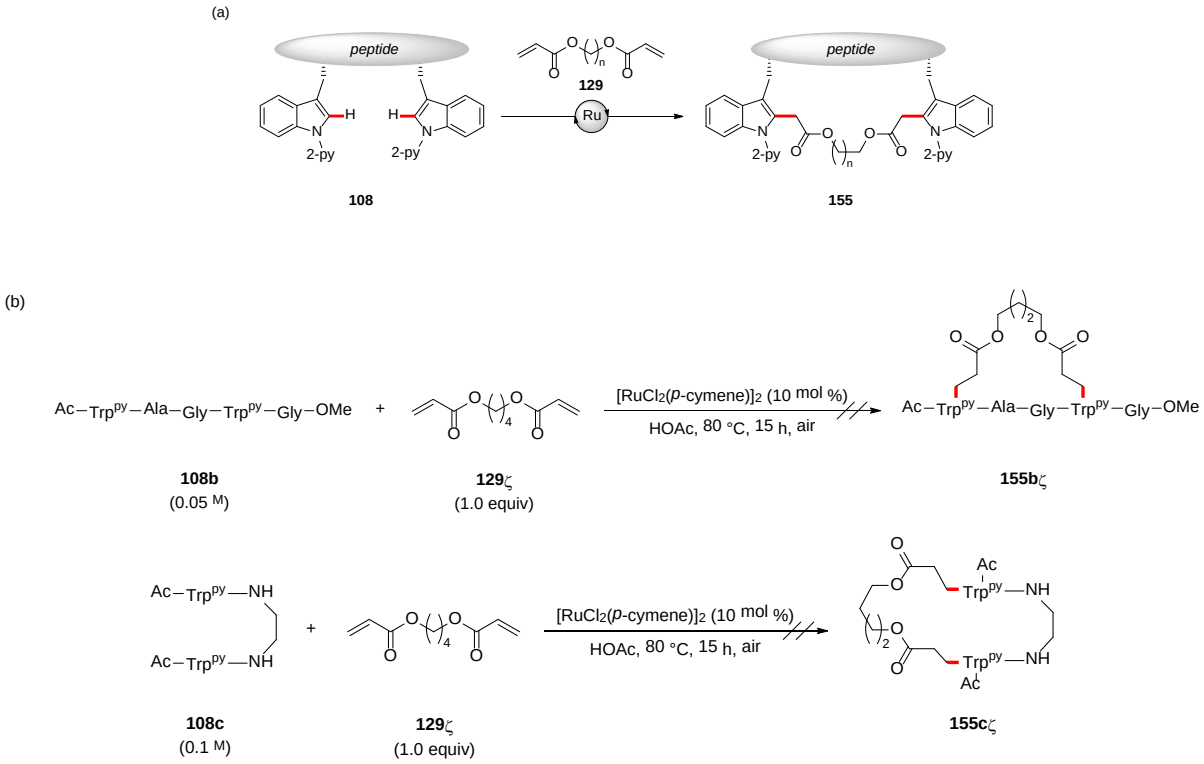
Scheme 80: Ruthenium-catalyzed intramolecular cyclization. (a) General approach. (b) Unsuccessful attempts.

Another attempt to achieve a cyclic peptide was the C–H alkylation of peptides **108** with an acrylate **129**, which contained a terminal alkene. A subsequent RCM reaction would lead to cyclic peptides **154** (Scheme 81). Regrettably, neither dialkene **153bp** nor **153cp** could be isolated due to purification difficulties, such as the non-feasible separation by chromatography.

Last but not least, peptides **108** were submitted to undergo a cyclization by a twofold C–H alkylation with a diacrylate **129** (Scheme 82). Traces of an addition product — cyclic or monoalkylated — were observed in the LC-MS analysis. However, after a prolonged reaction time or at an elevated reaction temperature, no peptide substrates — neither starting materials **108b** and **108c** nor alkylated peptides **153** — could be detected. Possibly, the substrates polymerized after a monoalkylation.



Scheme 81: Ruthenium-catalyzed cyclization by RCM. (a) General approach. (b) Unsuccessful attempts.



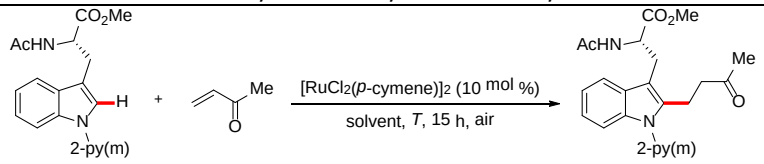
Scheme 82: Ruthenium-catalyzed cyclization with a diacrylate. (a) General approach. (b) Unsuccessful attempts.

3.3.2 Ruthenium-Catalyzed C–H Alkylation with Vinyl Ketones

3.3.2.1 Optimization of the Reaction

Starting from the successful reaction of trytophan **56g** with vinyl ketone **130a** (Table 29, entry 13), the ruthenium-catalyzed C–H alkylation reaction with vinyl ketones was optimized in order to make the reaction conditions as mild as possible (Table 35). Similar to the C–H alkylation method with acrylates **129** the coupling of vinyl ketone **130a** with the pyridylated tryptophan **56h** proceeded better than with the pyrimidylated tryptophan **56g** (entries 1–6). The use of either one percent of acetic acid in water or 10 percent in GVL at a reaction temperature of 80 °C was sufficient to deliver the desired product in excellent yields (entries 7–15). Also, mixtures of weaker acids, such as propionic acid and even ammonium chloride, could be used with GVL, affording the alkylated product **141ha** in excellent yields (entries 16–21). At temperatures lower than 80 °C the yield dropped (entries 22 and 23).

Table 35: Optimization of the ruthenium-catalyzed C–H alkylation with vinyl ketones.[a]



56g (2-pym) **56h** (2-py) | **130a** (3.0 equiv) | **141ga** **141ha**

entry	Trp (0.3 M)	solvent	*T*/°C	yield
1	**56g**	HOAc	140	91%
2	**56g**	HOAc	120	90%
3	**56g**	HOAc	100	81%
4	**56g**	HOAc	80	41%
5	**56g**	HOAc	60	18%
6	**56h**	HOAc	80	98%
7	**56h**	HOAc/H_2O 1:1	80	98%
8	**56h**	HOAc/H_2O 1:9	80	99%
9	**56h**	HOAc/H_2O 1:99	80	98%
10	**56h**	HOAc/GVL 1:1	80	99%
11	**56h**	HOAc/GVL 1:99	80	30%
12	**56h**	HOAc/GVL 5:95	80	73%
13	**56h**	HOAc/GVL 1:9	80	98%
14	**56h**	HOAc/GVL 1:9	70	92%
15	**56h**	HOAc/GVL 1:9	60	23%
16	**56h**	HO_2CEt/GVL 1:9	80	95%
17	**56h**	buffer pH 5	80	traces
18	**56h**	buffer pH 5/GVL	80	traces

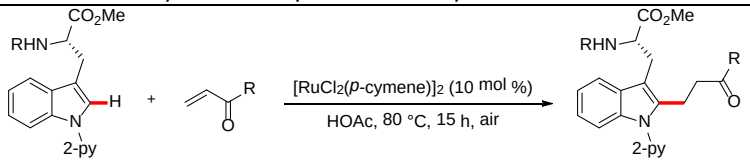
entry	Trp (0.3 M)	solvent	*T*/°C	yield
19	**56h**	NH_4Cl (5 M in H_2O)	80	91%
20	**56h**	NH_4Cl (5 M in H_2O)/GVL 9:1	80	98%
21	**56h**	NH_4Cl (1 M in H_2O)/GVL 9:1	80	96%
22	**56h**	NH_4Cl (5 M in H_2O)/GVL 9:1	60	35%
23	**56h**	NH_4Cl (5 M in H_2O)/GVL 9:1	38	17%

a: Reaction conditions: **56** (0.15 mmol), **130a** (0.45 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), solvent (0.15 mL), 80 °C, 15 h, air.

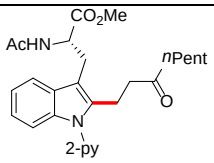
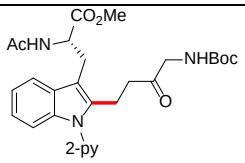
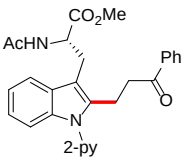
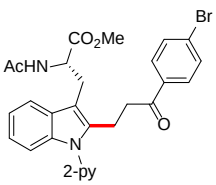
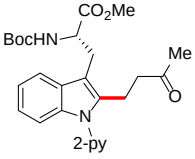
3.3.2.2 Scope with Tryptophan and Vinyl Ketones

The scope of the ruthenium-catalyzed C–H alkylation reaction with vinyl ketones **130** showed the applicability of aliphatic and aromatic vinyl ketones **130**, providing alkyl tryptophans **141** in high yields (Table 36, entries 1–4). Notably, the Boc-containing substrates **141ka** and **141hd** were obtained from the reaction in a 9:1 mixture of water and acetic acid and no deprotection of the Boc-moiety was detected. The bromide-containing tryptophan **141he**, which was intended to be used for peptide ligation similar to substrates **142hk** and **147jk**, was not formed by this C–H alkylation method (entry 5). Instead, the unreacted tryptophan **56h** was reisolated with 78% yield.

Table 36: Scope of the ruthenium-catalyzed C–H alkylation with vinyl ketones.[a]



56k (R = Boc) **56h** (R = Ac) **130** (1.1-3.0 equiv) **141**

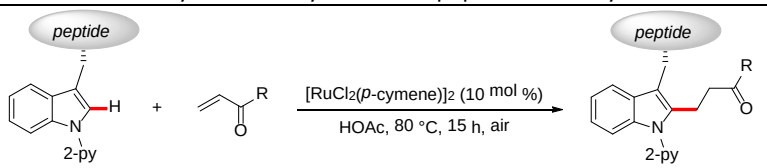
entry	product	yield	entry	product	yield
1	 **141hb**	97%	4	 **141hd**	88%[b]
2	 **141hc**	68%	5	 **141he**	0%
3	 **141ka**	89%[b]			

a: Reaction conditions: **56** (0.15 mmol), **130** (1.1–3.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), HOAc (0.15 mL), 80 °C, 15 h, air. b: The reaction was carried out in H_2O/HOAc 9:1.

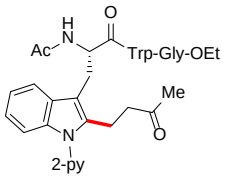
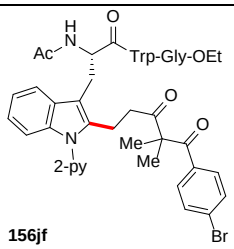
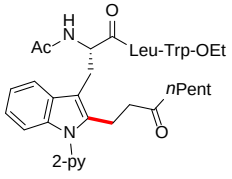
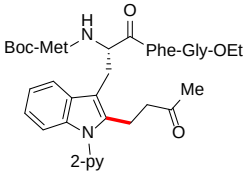
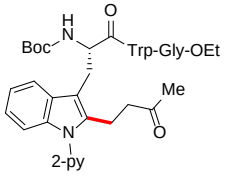
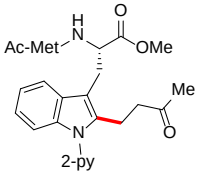
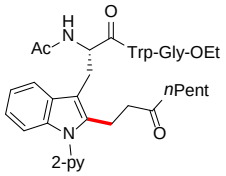
3.3.2.3 Scope with Peptides and Vinyl Ketones

Peptides **101** were successfully alkylated with vinyl ketones **130**, delivering alkylated peptides **156** (Table 37). The examples **156ja**, **156kb** and **156ea** showed an excellent regioselectivity as the pyridylated tryptophan was alkylated exclusively, not affecting the *NH*-free tryptophans. The use of a 9:1 mixture of water and acetic acid allowed the alkylation of the Boc-protected peptides, providing Boc-peptide **156ea**. Alkylated peptides **156jb**, **156jf**, **156oa** and **156ma** were not isolated due to difficulties separating them from the unreacted peptides **101**. In these cases, the target masses were found in the LC-MS chromatograms, indicating product formation. Even the methionine peptides **156oa** and **156ma** were indicated to have been formed.

Table 37: Scope of the ruthenium-catalyzed C–H alkylation with peptides and vinyl ketones.[a]



101 **130** (1.1-5.0 equiv) **156**

entry	product	yield	entry	product	yield
1	 **156ja**	83%	5	 **156jf**	0%[c]
2	 **156kb**	51%	6	 **156oa**	0%[b,c]
3	 **156ea**	56%[b]	7	 **156ma**	0%[c]
4	 **156jb**	0%[c]			

a: Reaction conditions: **101** (50–100 mg), **130** (1.1–5.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), solvent (0.1–0.3 mL), 80 °C, 15 h, air. b: The reaction was carried out in H_2O/HOAc 9:1. c: LC-MS indicated product formation.

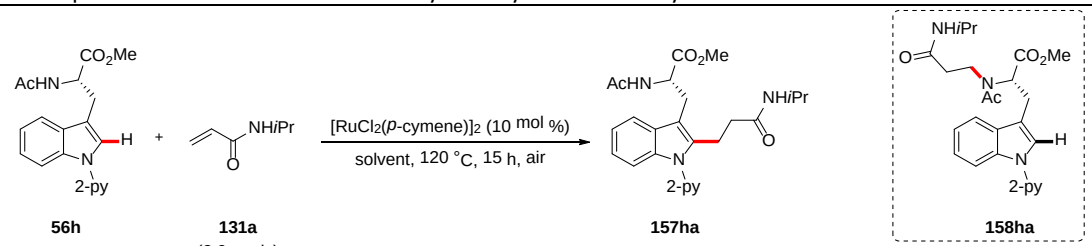
3.3.3 Ruthenium-Catalyzed C–H Alkylation with Acrylamides

Due to the successful alkylation of tryptophan peptides with acrylates and vinyl ketones, acrylamides **131** gained our interest. Several advantages are associated with acrylamides, as they are easily accessible from primary or secondary amines. Regarding peptides, amines are present in every amino acid and thus every peptide could be acrylated to be used for novel ligation or cyclization motifs.

3.3.3.1 Optimization of the Reaction

For the optimization of the hydroarylation of acrylamide **131a** with tryptophan **56h**, similar to the reactions with acrylates and vinyl ketones, 10 mol % $[RuCl_2(p\text{-cymene})]_2$ was used as the catalyst and various acidic solvent mixtures were screened (Table 38). The measured peak area ratios of the substrates **56h** and **157ha** are given as an indicator for the approximate reaction result. In all cases, only small amounts of an alkylated product were formed. For the reactions in acetic acid, hexanes/acetic acid and ethanol/acetic acid (entries 1, 10, 14), the *N*-alkylated product **158ha** was isolated as the sole product in 19, 21 and 47% yield, respectively. As the retention time of all detected alkyl products was identical, the probability for the formation of the C2 product is rather low. For this reason, no further experiments were attempted towards the C2 alkylation of tryptophan with acrylamides **131**.

Table 38: Optimization of the ruthenium-catalyzed alkylation with acrylamide **131a**.[a]



56h **131a** (2.0 equiv) **157ha** **158ha**

entry	solvent	**56h/158ha** (LC-MS)	entry	solvent	**56h/158ha** (LC-MS)
1	HOAc	77:23	10	hexanes/HOAc 9:1	75:25
2	TFA	100:traces	11	1,4-dioxane/HOAc 9:1	100:traces
3	HO_2CH	100:0	12	DME/HOAc 9:1	96:4
4	GVL/HOTf 9:1	100:traces	13	DMF/HOAc 9:1	100:traces
5	GVL/HCl 9:1	88:12	14	EtOH/HOAc 9:1	45:55
6	GVL/HOAc 9:1	88:12	15	DMSO/HOAc 9:1	100:0
7	GVL/NH_4Cl (5 M in H_2O) 9:1	92:8	16	MeCN/HOAc 9:1	80:20
8	*m*-xylene/HOAc 9:1	95:5	17	acetone/HOAc 9:1	80:20
9	NMP/HOAc 9:1	90:10	18	mesitylene/HOAc 9:1	100:0

a: Reaction conditions: **56h** (0.15 mmol), **131a** (0.30 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), solvent (0.15 mL), 120 °C, 15 h, air.

3.4 On-Resin C–H Alkylation of Peptides

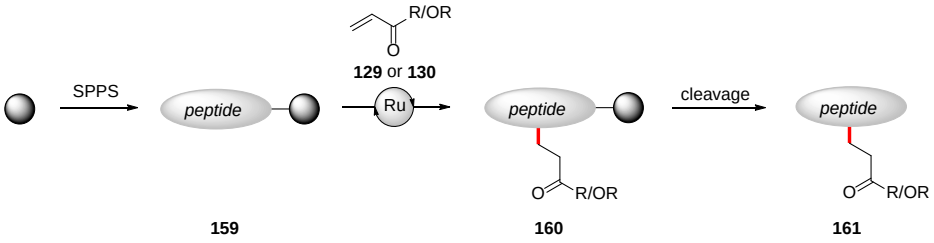
A number of methods for postsynthetic peptide modification has been developed. Although, different kinds of issues have been overcome, a few challenges remain. Some of these are

- ✧ purification of the peptidic products,
- ✧ removal of metal catalyst traces,
- ✧ solubility of peptides in common organic solvents, and
- ✧ aggregation and jellification during the reaction.

To circumvent these problems, the modification reactions can be carried out on peptides bound to a resin. On-resin reactions of peptides have already been used since the first SPPS was developed by Merrifield in 1963.[123] The idea was that a peptide which is chemically bound to a resin, is reacted with a substrate, which afterwards is washed out through a filter without any peptide loss. After the washing, further reactions could be carried out. Finally, when all necessary modifications are finished, the peptide is cleaved from the resin. This solid-phase-supported approach enjoys great reputation due to a wide range of successful applications.

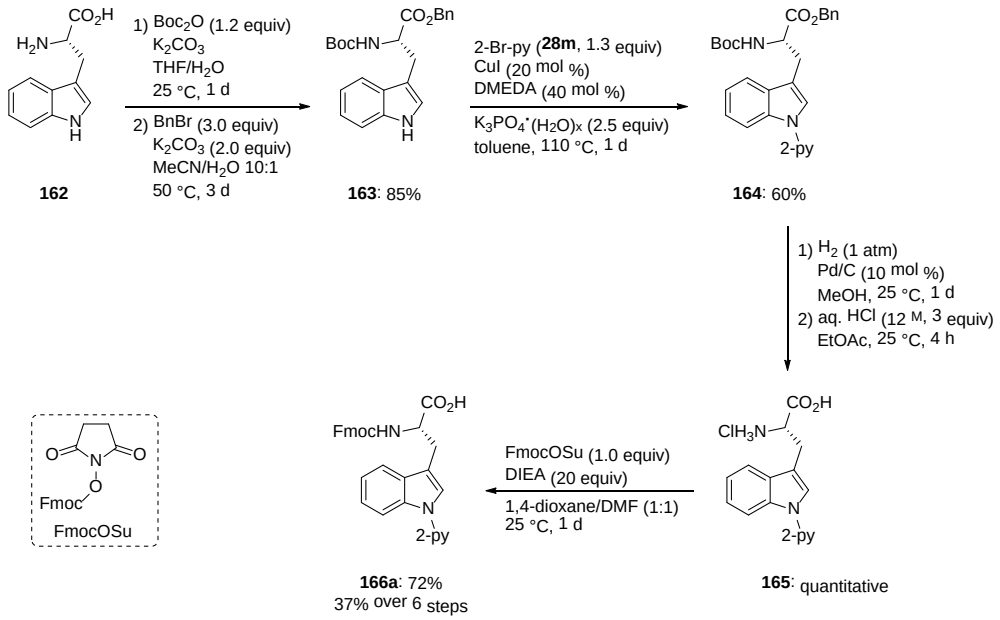
3.4.1 On-Resin C–H Alkylation with Acrylates and Vinyl Ketones

The ruthenium-catalyzed alkylation method described in chapters 3.3.1 and 3.3.2 should be applied to peptides on the solid phase (Scheme 83). Pyridylated tryptophan-containing peptides **159** should be synthesized according to standard procedures of SPPS and afterwards alkylated by the ruthenium-catalyzed alkylation approach in order to deliver alkylated peptides on resin **160**. The cleavage of the peptide from the resin would set free a C–H alkylated peptide **161**.



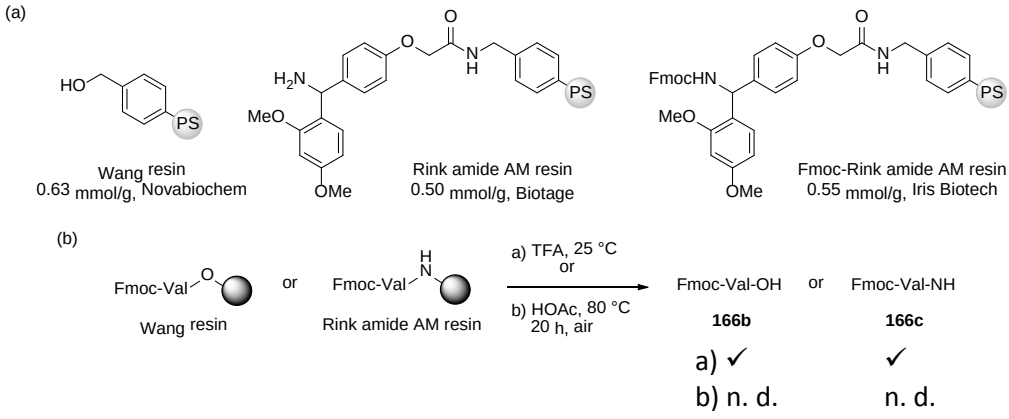
Scheme 83: On-resin ruthenium-catalyzed C–H alkylation of peptides.

For the synthesis of peptides **159**, which contain a pyridylated tryptophan, an Fmoc-protected pyridylated tryptophan was synthesized (Scheme 84). Starting from tryptophan **162**, the amine and the carboxylic acid were protected with base-orthogonal protecting groups. The 2-pyridyl group was introduced via an Ullmann coupling in order to obtain tryptophan **164**. Hydrogenative deprotection of the benzyl ester followed by an acidic cleavage of the Boc-moiety furnished the hydrochloride **165**. The Fmoc-protection was accomplished using FmocOSu in a basic medium. The ready-to-use Fmoc-protected tryptophan **166a** was thus synthesized in 37% overall yield.



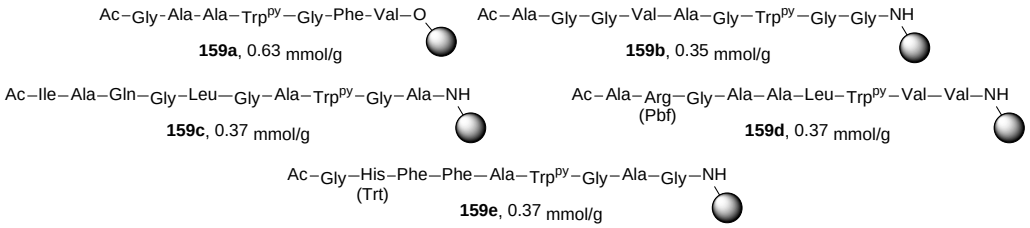
Scheme 84: Synthesis of tryptophan **166a** for the SPPS.

Prior to the ruthenium-catalyzed procedure, the acid stability of the commonly used Rink amide AM and Wang resins was examined (Scheme 85 a). Both Rink amide and Wang resins are commonly applied for the Fmoc SPPS strategy and thus the cleavage is accomplished with acids. An Fmoc-Val Wang resin and an Fmoc-Val Rink amide resin were treated with trifluoroacetic acid at ambient temperature and with acetic acid at 80 °C, respectively. The cleaved Fmoc-amino acids **166b** and **c** were detected by an LC-MS analysis. As expected, the Fmoc-amino acids were cleaved with trifluoroacetic acid. Fortunately, no Fmoc-amino acids were detected in the solution after heating the resins in acetic acid. With this finding, the established conditions for the ruthenium-catalyzed C–H alkylation reactions could be applied. Another advantage of acetic acid as the reaction medium is a swelling of 2.8 mL/g (Wang resin), which is a moderate value as compared to other organic solvents.[124]



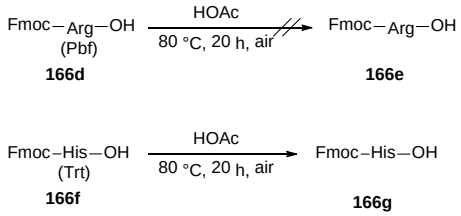
Scheme 85: (a) Resins used. PS: polystyrene. (b) Acid stability test of resins. ✓: Fmoc amino acid was cleaved from resin. n. d.: The Fmoc-amino acid was not detected in solution.

Pyridylated tryptophan-containing peptides **159** with a sequence of up to 10 amino acids were synthesized using automated SPPS (Scheme 86). Peptides **159a** and **159b** contain only aliphatic and aromatic amino acids with no further functionalities, whereas peptides **159c**, **159d** and **159e** were equipped with a free amide of glutamine, a Pbf-protected arginine and a trityl-protected histidine, respectively.



Scheme 86: Peptides **159**.

The acid stability of the Pbf and the trityl protecting groups was tested via heating Fmoc-Arg(Pbf)-OH (**166d**) and Fmoc-His(Trt)-OH (**166f**) in acetic acid (Scheme 87). An LC-MS analysis showed no deprotection of arginine **166d**, whereas histidine **166f** was completely trityl-deprotected.

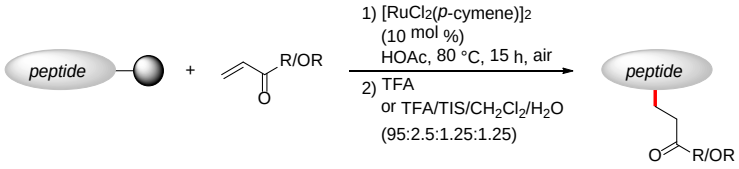


Scheme 87: Acid stability test of protecting groups.

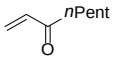
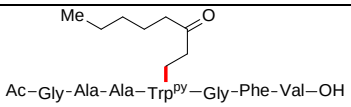
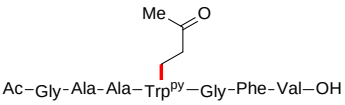
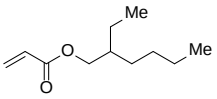
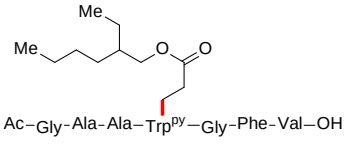
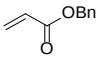
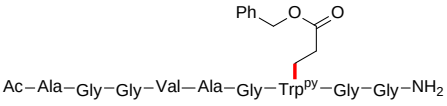
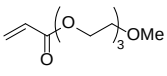
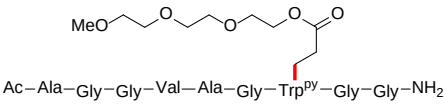
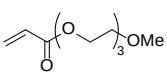
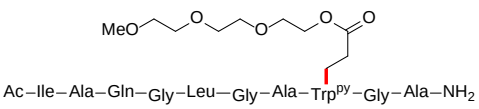
Next, the scope of the ruthenium-catalyzed C–H alkylation was examined. The reactions were set up in 10 mL conical-bottom test tubes without stir bar. 30 µmol of resin **159** was placed in the test tube and 100 µL of a catalyst stock solution were added ($[RuCl_2(p\text{-cymene})]_2$ in HOAc, 18.4 mg/mL, 10 mol %). After the addition of an alkene, the mixture was slightly shaken and then left calm to swell the resin. After 30 min of swelling, a few drops of acetic acid were added if necessary, until the resin was completely covered with solvent. The test tube was fitted with a septum and placed in a glove finger with a stir bar, which allowed for a slight shaking of the reaction mixture in the heating bath. The glove was fixated above the heating bath and the reaction mixture was heated to 80 °C for 15 h. Thereafter, the resin was alternately washed with acetic acid and methanol several times and dried overnight at 40 °C. For the cleavage, the resins were treated with TFA or a mixture of TFA/TIS/CH_2Cl_2/H_2O (95:2.5:1.25:1.25). The cleaved peptides were precipitated from –20 °C cold diethylether and centrifuged three times and finally dried in vacuum.

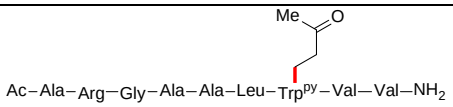
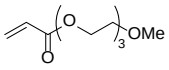
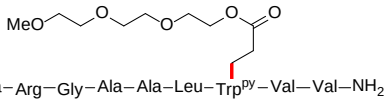
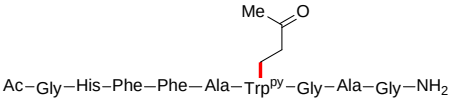
Acrylates and vinyl ketones were applied, delivering alkylated peptides **161** (Table 39). The yields shown refer to the SPPS-alkylation-cleavage-purification sequence and do not only represent the ruthenium-catalyzed step. Peptides **161a**, **161d**, and **161f–h** were isolated in good yields of 43–78%. Peptides **161b**, **161c** and **161e** were observed in the LC-MS, but they could not be purified by crystallization and washings or preparative HPLC. While the protected arginine peptide **159d** was not deprotected during the ruthenium-catalyzed procedure and thus the nucleophilic guanidine was not affected, alkylated peptides **161g** and **161h** were obtained with a selective alkylation of the tryptophan moiety. In contrast, histidine peptide **159e** was deprotected during the alkylation reaction, resulting in the formation of byproducts and a 1:1 mixture of di- and trialkylated peptides was isolated. Probably, one of the imidazole *N*-atoms underwent an aza-Michael addition to form peptides **161j** and **161k** (Scheme 88). A subsequent electrophilic aromatic substitution afforded peptides **161l** and **161m**.

Table 39: Scope of the ruthenium-catalyzed on-resin C–H alkylation.[a]

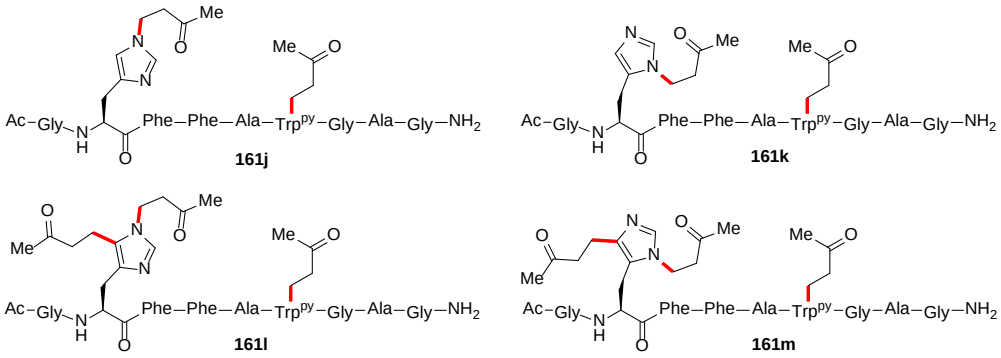


159 **130** (R) or **129** (OR) (5.0 equiv) **161**

entry	peptide	alkene	product	yield
1	**159a**	 **130b**	 **161a**	78%
2	**159a**	 **130a**	 **161b**	n. i.
3	**159a**	 **129d**	 **161c**	n. i.
4	**159b**	 **129b**	 **161d**	69%
5	**159b**	 **129t**	 **161e**	n. i.
6	**159c**	 **129t**	 **161f**	43%

entry	peptide	alkene	product	yield
7	**159d**	 **130a**	 **161g**	71%
8	**159d**	 **129t**	 **161h**	45%
9	**159e**	 **130a**	 **161i**	n. d.

a: Reaction conditions: 1) **159** (30 µmol), **129** or **130** (3.0–10.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), HOAc (30–150 µL), 80 °C, 15 h, air; 2) TFA (3 mL) or TFA/TIS/CH_2Cl_2/H_2O (3 mL, 95:2.5:1.25:1.25), 25 °C, 4 h. n. i.: The product could not be isolated. n. d.: The product was not detected.

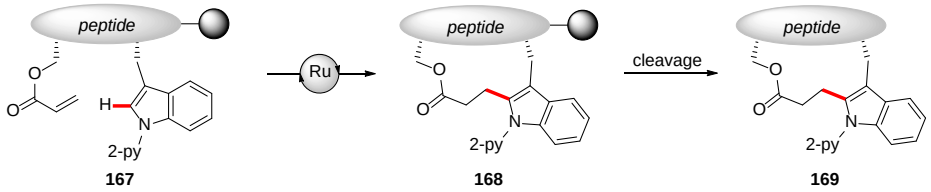


Scheme 88: Possible products for the ruthenium-catalyzed alkylation of peptide **159e**.

To summarize, the ruthenium-catalyzed on-resin C–H alkylation of peptides was highly successful. The developed on-resin modification allowed the efficient and selective introduction of functionalized alkanes as shown in chapter 3.3.1.2. Furthermore, the on-resin procedure allowed the incorporation of side chain-protected amino acids, such as arginine, that would otherwise lead to side reactions. For this on-resin reaction it is possible to use large excess of reagents to drive the reaction to completion without affecting the purification, or to set up the reaction several times without intermediate purification. Remaining reagents can be easily washed out without a loss of product. The reaction can be followed by an LC-MS analysis after cleavage of analytical amounts of the resin. The reaction set up is very simple and bench solvents can be used. The necessary amount of solvent is reduced to the volume needed for swelling the resin, which depends on the properties of the resin used and on the peptide attached to it. With the peptides attached to the solid phase, poor solubility of peptides is not an issue. Moreover, no peptide aggregation or jellification can occur during the reaction.

3.4.2 Attempted Cyclization via On-Resin C–H Alkylation

Having achieved a successful procedure for the ruthenium-catalyzed C–H alkylation of peptides on the solid phase, on-resin cyclization of peptides was investigated. Peptides **167**, containing pyridylated tryptophan and an acrylate moiety, should be cyclized on-resin in order to form peptides **168**, which would set free cyclopeptides **169** after cleavage from the resin (Scheme 89). The acrylic moiety should be introduced via the natural amino acids serine, threonine, tyrosine or cysteine. In addition to the advantages of reactions on the solid phase as described above, cyclization reactions in particular may profit significantly from the on-resin approach, because dimerization and polimerization are efficiently avoided. Therefore, the reaction does not need to be carried out in a highly diluted mixture, which would decrease the reaction rate significantly.



Scheme 89: Ruthenium-catalyzed on-resin cyclization of peptides.

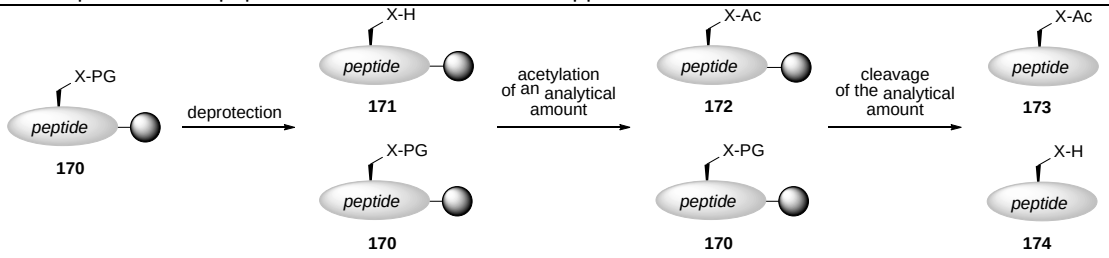
For the synthesis of the acryloyl peptides **167**, peptides **170** from the SPPS needed to be deprotected without cleaving the peptide from the resin (Table 40). The *tert*-butyl protected serine-containing peptides **170a** and **170b** were chosen for the optimization of the deprotection step. After each deprotection procedure, an analytical amount of the resin was acetylated twice, using a 1 M solution of a 1:2 mixture of acetic anhydride and diisopropylethylamine in CH_2Cl_2. After the cleavage of the analytical acetylated sample with TFA at ambient temperature, the ratio of acetylated to free peptide was determined by LC-MS analysis.

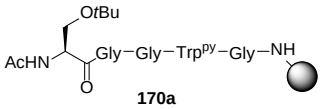
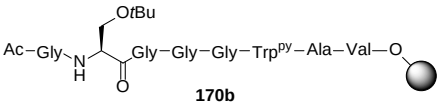
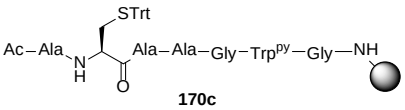
The simplest method for the cleavage of the *tert*-butyl ether would be heating peptides **170a** and **170b** in acetic acid, but, unfortunately, only traces of peptide **170** were deprotected in this way (entries 1a and 2a). Therefore, further literature-known methods using Lewis acids were tested. However, the results were unsatisfactory (entries 1b–e and 2b–f). The $CeCl_3$/NaI procedure was found to be most promising.[125] Indeed, after several repetitions of this procedure, no more hydroxyl-free peptide **174b** was detected. Only acetylated peptide **173b** was present. Hence, the deprotection was complete and hydroxyl-free peptide **174b** was acryloylated using a solution of a 10-fold excess of acryloyl chloride and 20-fold excess of diisopropylethylamine in CH_2Cl_2 affording acryloyl peptide **167b**.

Due to the difficult deprotection of *tert*-butyl ethers, the trityl protected cysteine peptide **170c** was explored instead. Neither 2 N HCl nor HBr in acetic acid at ambient temperature afforded the desired

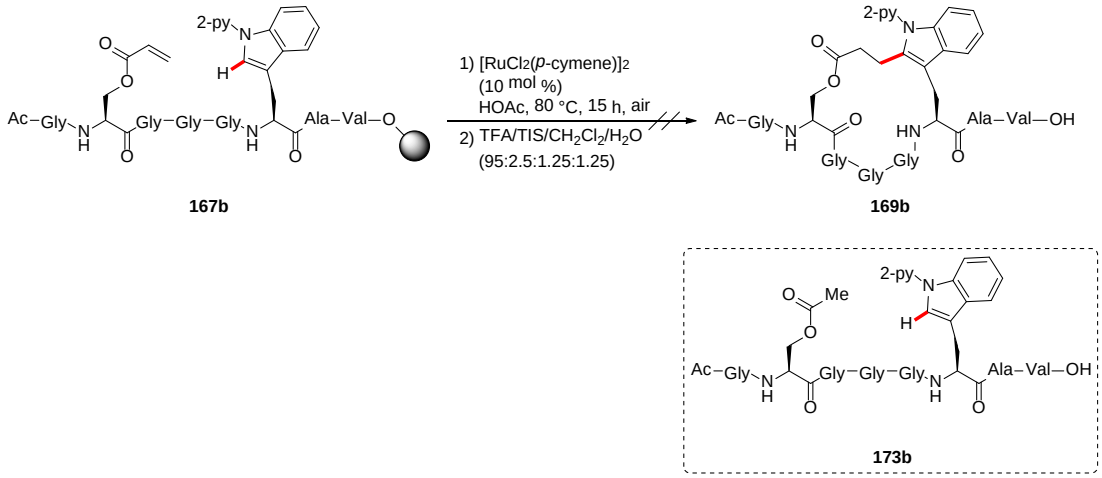
deprotected products (entries 3a and b). Also, LiCl in refluxing methanol, acetic acid at 80 °C and 2 N HBr in acetic acid at 80 °C did not deliver free thiopeptide **171c** (entries 3c–e).

Table 40: Deprotection of peptide side chains on the solid support.



entry	peptide	deprotection procedure	**173**/**174** (LC-MS)
1	 **170a**	a) HOAc, 80 °C, 2 d b) 1) $ZnBr_2$, CH_2Cl_2, 25 °C, 1 d; 2) H_2O c) 1) $ZnBr_2$, $CHCl_3$, 60 °C, 2 d; 2) H_2O d) $CeCl_3 \cdot 7\ H_2O$, NaI, MeCN, 80 °C, 3 d e) 2 × repetition of d)	a) traces b) traces c) traces d) 25:75 e) 49:51
2	 **170b**	a) HOAc, 80 °C, 2 d b) 1) $ZnBr_2$, CH_2Cl_2, 25 °C, 1 d; 2) H_2O c) 2 × repetition of b) d) 1) $ZnBr_2$, $CHCl_3$, 60 °C, 1 d; 2) H_2O e) $CeCl_3 \cdot 7\ H_2O$, NaI, MeCN, 80 °C, 1 d f) 4 × repetition of e)	a) traces b) traces c) 38:62 d) 67:33 e) 79:21 f) 100:0
3	 **170c**	a) 2 N HCl in HOAc, 25 °C, 1 d b) 2 N HBr in HOAc, 25 °C, 1 d c) LiCl in MeOH, 70 °C, 1 d d) HOAc, 80 °C, 1 d e) 2 N HBr in HOAc, 80 °C, 1 d	a) 0:100 b) 0:100 c) 0:100 d) 0:100 e) 0:100

The acrylated peptide **167b** was reacted with 10 mol % $[RuCl_2(p\text{-cymene})]_2$ in acetic acid at 80 °C. The reaction was performed on a 30 µmol scale, which corresponds to 26 mg of peptide **169b**. After the cleavage and crystallization from cold diethylether, only a very small amount of peptide was obtained, which was not sufficient for an NMR analysis. The LC-MS analysis revealed acetylated peptide **173b**. Either the acrylate was transesterificated with acetic acid or the double bond was hydrolyzed. The unexpectedly little amount of peptide might be obtained, because of a partial cleavage of the peptide from the resin during the deprotection procedures. Repeatedly exposing the peptide **170b** to different Lewis acids might have partially cleaved the peptide from the resin. The acetic acid solution did not contain any peptide as confirmed by LC-MS analysis (Table 40, entry 1a). For the experiments with Lewis acids the reaction solutions were not tested.



Scheme 90: Ruthenium-catalyzed on-resin cyclization.

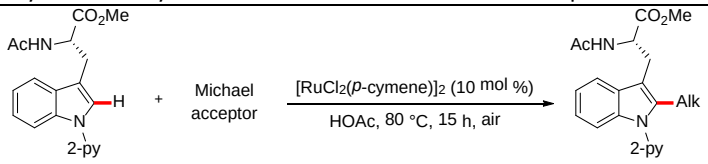
3.5 Miscellaneous C–H Modification Reactions on Tryptophan

3.5.1 Reactions with Miscellaneous Michael Acceptors

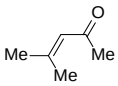
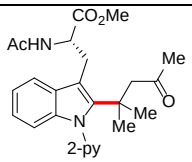
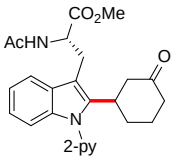
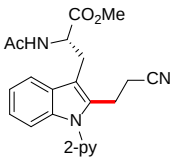
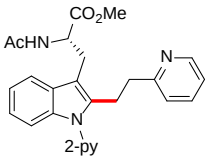
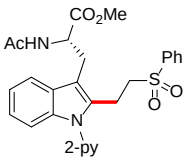
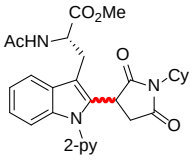
Based on the ruthenium-catalyzed addition of acrylates and vinyl ketones to tryptophan, the scope of unsaturated substrates suitable for this kind of addition should be expanded to further Michael acceptors (Table 41). β-Substituted, α,β-unsaturated ketones **175** and **177**, acrylonitrile **179**, vinylpyridine **181** and vinyl sulfone **183** did not react with tryptophan under the previously developed reaction conditions for the coupling of acrylates and vinyl ketones (entries 1–5).

Maleimide **185** afforded the desired hydroarylation product **186** in 76% yield at 100 °C for 15 h. A reaction temperature of 80 °C led to an incomplete conversion. Due to prochiral sites of the maleimide **185**, a 1:1 mixture of two diastereomers **186** was obtained. This result could be a starting point for a new series of tryptophan modifications. An advantage is the facile accessibility of maleimides from primary amines and maleic anhydride. The question of the stereoselectivity might be solved by substrate-control via more bulky or chiral substituents on the nitrogen of the maleimide or by catalyst-control applying chiral ligands.

Table 41: Ruthenium-catalyzed C–H alkylation with miscellaneous Michael acceptors.[a]



56h

entry	Michael acceptor	product	yield
1	 **175**	 **176**	0%
2	 **177**	 **178**	0%
3	 **179**	 **180**	0%
4	 **181**	 **182**	0%
5	 **183**	 **184**	0%
6	 **185**	 **186**	76%[b]

a: Reaction conditions: **56h** (0.15 mmol), alkene (0.45 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), HOAc (0.15 mL), 80 °C, 15 h, air. b: The reaction was carried out at 100 °C. A 1:1 mixture of two diastereomers was isolated.

3.5.2 Reactions with Various Unsaturated Compounds

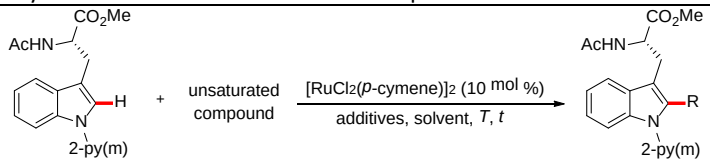
Ruthenium-catalyzed C–H activation with various unsaturated compounds were investigated (Table 42). The reaction conditions were similar to those of comparable reactions found in the literature.[126] Electroneutral and oxidative attempts with terminal or internal alkynes **37a** and **37b**, as

well as with terminal allene **187** and bromostyrene **188** did not succeed (entries 1–5). Either no conversion was observed or complex mixtures of products were obtained.

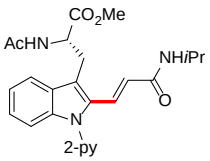
The coupling of acrylamide **131a** under oxidative conditions afforded the alkenylated product **189ha** in 9% yield (entry 6). The reaction conditions were adapted from a similar alkenylation with acrylates.[127] The yield is rather low due to a low conversion of the substrate **56h**, but no byproduct formation was observed. An optimization of these reaction conditions would enable a novel way for C–H alkenylations with acrylamides and/or acrylates.

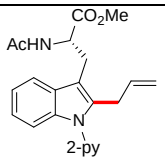
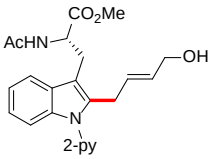
The last two examples demonstrate an S_N2'-type substitution of allyl acetate **190a** and vinyl dioxolanone **192a** to tryptophan **56h** (entries 7 and 8). The corresponding allyl products **191ha** and **193ha** were isolated in 59 and 53% yield, respectively. Recently, a decarboxylative approach using dioxolanone **192a** was also developed in our group using a manganese-catalyzed C–H activation reaction.[128] In this case, the catalytic system consisted of 10 mol % $MnBr(CO)_5$ and 20 mol % sodium acetate in trifluoroethanol at 100 °C. The two successive reactions with acetate **190a** and dioxolanone **192a** under simple reaction conditions using $[RuCl_2(p\text{-cymene})]_2$ in acetic acid at 80 °C can be used as a base for further allylations of tryptophan peptides.

Table 42: Ruthenium-catalyzed reactions with unsaturated compounds.[a]



56g (2-pym)
56h (2-py)

entry	Trp	unsat. comp.	reaction conditions	result
1	**56g**	H—≡—*n*Bu **37a** (2.0 equiv)	HOAc (1.0 equiv), DMF, 120 °C, 2 d, N_2	complex mixture of products[b]
2	**56g**	H—≡—*n*Bu **37a** (2.0 equiv)	$Cu(OAc)_2$ (1.0 equiv), $AgPF_6$ (10 mol %), HFIP, 120 °C, 1 d, N_2	no conversion[c]
3	**56g**	Ph—≡—Ph **37b** (2.0 equiv)	$AgSbF_6$ (40 mol %), HOPiv (5.0 equiv), *i*PrOH, 120 °C, 2 d, N_2	complex mixture of products[b]
4	**56g**	*n*Pent **187** (3.0 equiv)	$MesCO_2K$ (30 mol %), toluene, 120 °C, 1 d, N_2	no conversion[c]
5	**56g**	Br Ph **188** (1.2 equiv)	1-$AdCO_2H$ (30 mol %), K_2CO_3 (3.0 equiv), *m*-xylene, 140 °C, 1 d, N_2	no conversion[c]
6	**56h**	NH*i*Pr **131a** (2.0 equiv)	KPF_6 (20 mol %), $Cu(OAc)_2$ (2.0 equiv), H_2O, 110 °C, 17 h, N_2	 **189ha**: 9%

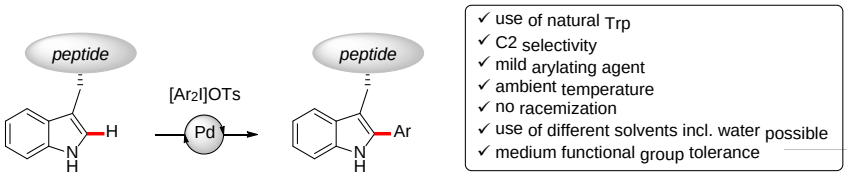
entry	Trp	unsat. comp.	reaction conditions	result
7	**56h**	 **190a** (3.0 equiv)	HOAc, 80 °C, 15 h, air	 **191ha**: 59%
8	**56h**	 **192a** (3.0 equiv)	HOAc, 80 °C, 15 h, air	 **193ha**: 53%

a: Reaction conditions: **56** (0.15 mmol), unsat. comp. (1.2–3.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), additives, solvent. b: Determined by TLC analysis. c: Determined by NMR analysis.

4 Summary and Outlook

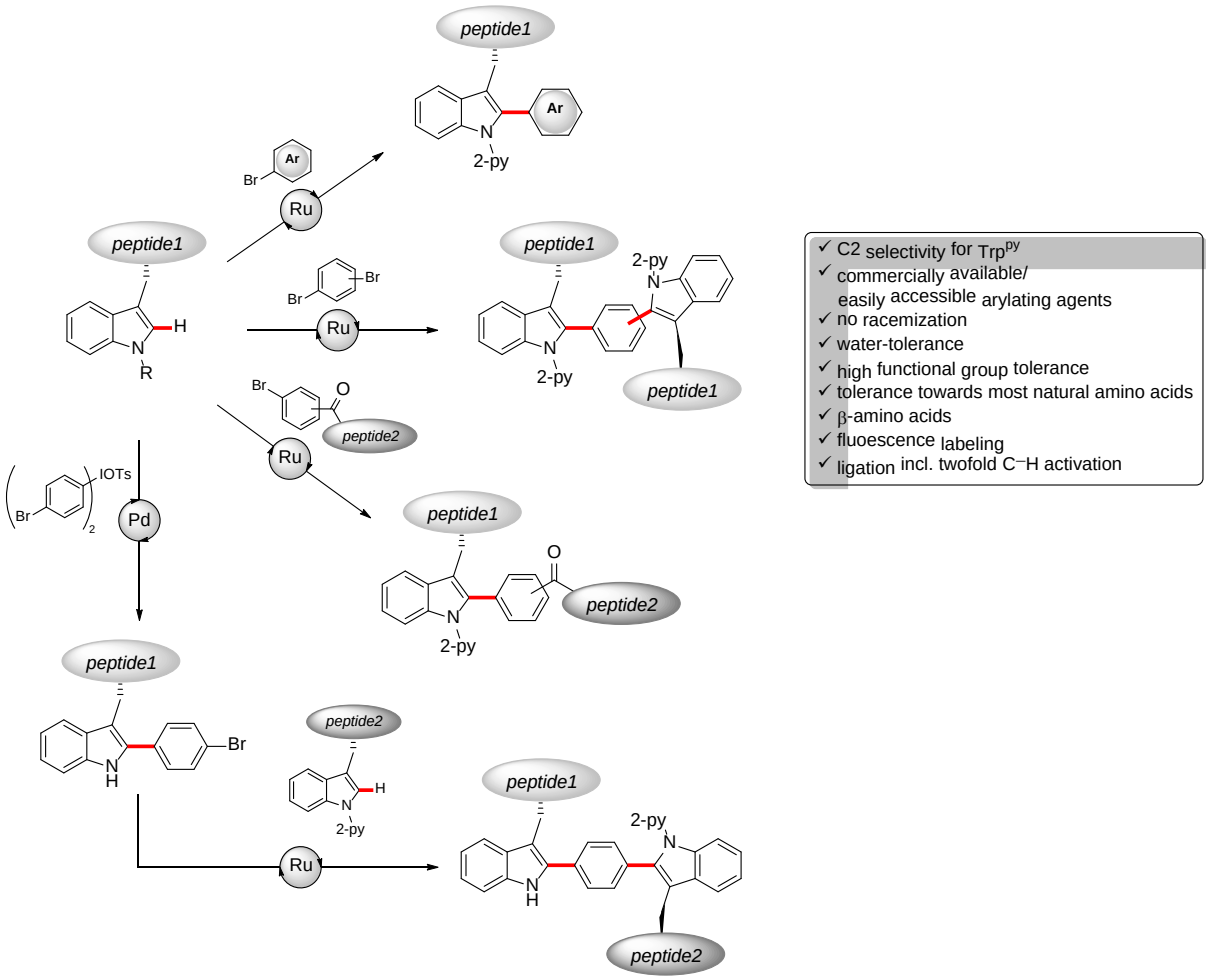
The development of sustainable chemical syntheses for the production of highly functionalized organic molecules, such as drugs, agrochemicals and functional materials, is of great topical importance for academia and industries. C–H activation contributed to an improvement of the strategies used for chemical syntheses, because its step- and atom-economy and the catalytic use of transition metals facilitate short and simple preparations of complex structures. The aim of this work was the development of postsynthetic peptide modification reactions applying C–H activation strategies.

The palladium-catalyzed C–H arylation method was successfully applied to the synthesis of arylated peptides (Scheme 91).[89] Diaryliodonium salts were used as mild arylating agents and $Pd(OAc)_2$ was employed as the catalyst. The use of a variety of solvents, such as DMF, toluene, DCE and acetic acid, was possible. The reaction was shown to be water-tolerant and proceeded selectively at the C2 position of the natural tryptophan in a complex peptide.



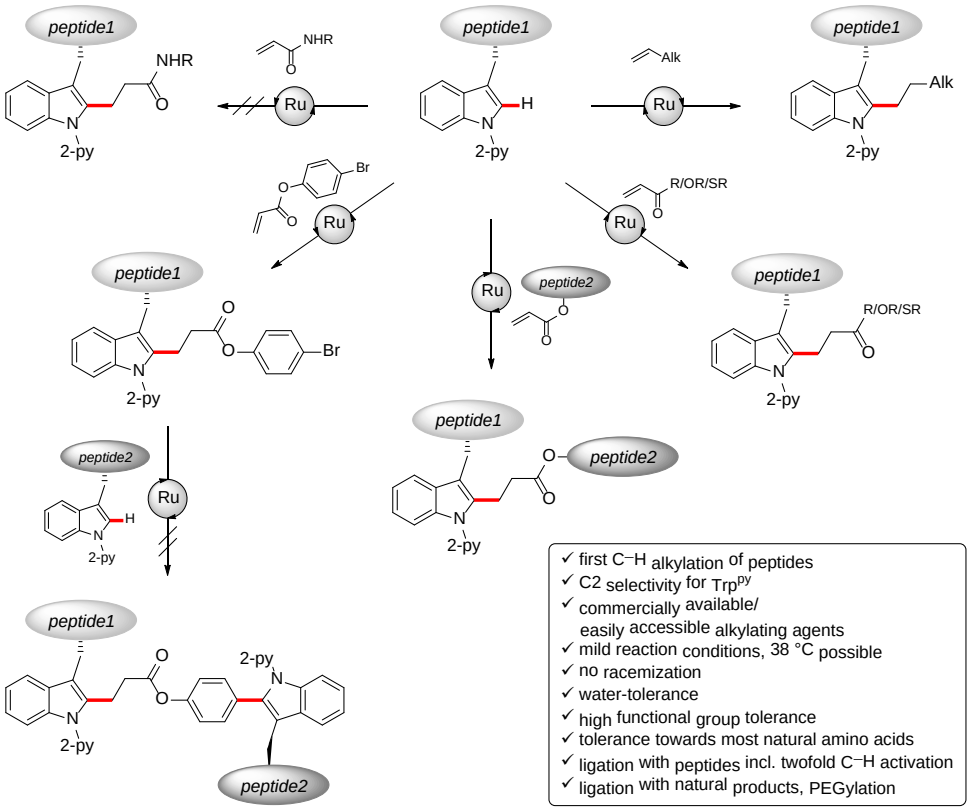
Scheme 91: Palladium-catalyzed C–H arylation of peptides.

Ruthenium as an inexpensive transition metal for C–H activation reactions was explored. The optimized reaction conditions for the C–H arylation of pyridylated tryptophans allowed the introduction of diversely decorated aryl moieties, affording C–H arylated peptides (Scheme 92).[117] A large functional group tolerance was illustrated by the preparation of arylated tryptophans. Also, β^3-*homo*-tryptophans and tryptophan peptides delivered the C–H arylated products. A bioorthogonal test proved the reaction to be tolerant towards almost all natural amino acids. Furthermore, the reaction is water-tolerant and despite of the basic medium, no racemization of the stereocenters of the amino acids was detected. Arylated products with an extended π-system showed enhanced fluorescence properties as compared to the corresponding unarylated compounds. Different modes of ligation were demonstrated including a twofold C–H activation sequence applying palladium- and ruthenium-catalysis, delivering uniquely branched ligation products.



Scheme 92: Ruthenium-catalyzed C–H arylation of peptides.

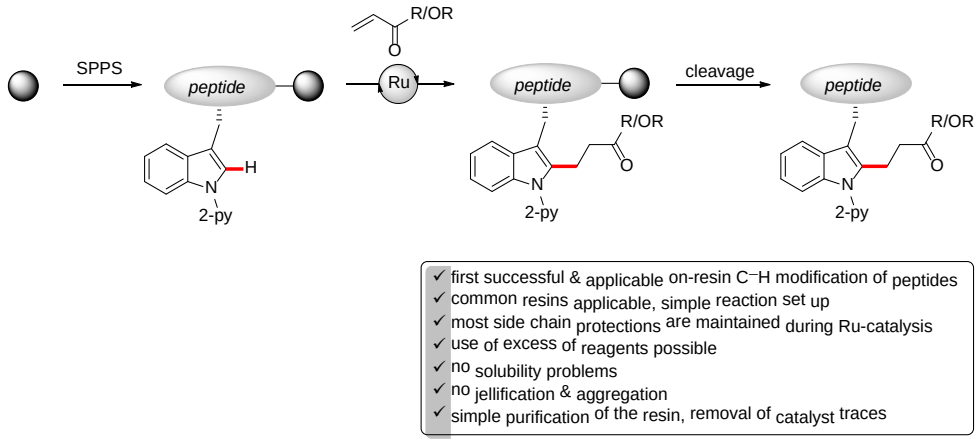
A transition metal-catalyzed C–H alkylation of peptides was achieved through ruthenium-catalysis (Scheme 93). The hydroarylation of unactivated alkenes was shown to be feasible and also the coupling with vinyl ketones, acrylates and thioacrylates proceeded smoothly without noteworthy drawbacks. Furthermore, the acryloyl moiety was introduced into peptides which enabled the ligation of peptides. Another pursued strategy was the introduction of a phenyl bromide-containing acrylate as a linker for a subsequent C–H arylation.



Scheme 93: Ruthenium-catalyzed C–H alkylation of peptides.

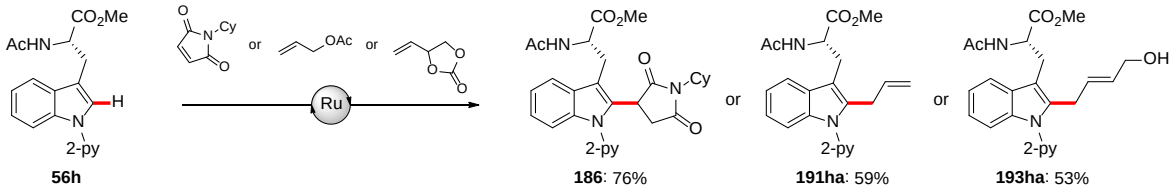
The ruthenium-catalyzed alkylation procedure was successfully extended to peptides on-resin (Scheme 94). This approach possesses all advantages that are generally associated with on-resin procedures. On-resin peptides derived from the SPPS were reacted with acrylates and vinyl ketones in the presence of a ruthenium-catalyst. A cleavage from the resin delivered C–H alkylated peptides and thus, alkylated peptides with up to ten amino acids were prepared this way.

Future work could be the ligation with acryloyl peptides using this on-resin C–H modification method. Also, on-resin cyclizations of peptides should be feasible. Unfortunately, it was not possible to selectively deprotect serine or cysteine on-resin. However, serine with a more acid-labile protecting group, such as a silyl ether, or serine with a free hydroxy group could be incorporated into the peptide in order to enable an on-resin acryloylation. Also, the direct coupling of Fmoc-Ser(acryloyl)-OH during the SPPS could be possible.



Scheme 94: Ruthenium-catalyzed on-resin C–H alkylation of peptides.

Other envisioned ruthenium-catalyzed C–H modification reactions are the hydroarylation with maleimides as well as allylations with allyl acetates and vinyl dioxolanones (Scheme 95). The preliminary individual examples present a starting point for additional research on other alkylation and allylation reactions.



Scheme 95: Further ruthenium-catalyzed C–H modifications of tryptophan.

5 Experimental Part

5.1 General Remarks

Unless otherwise noticed, all reacitons were carried out under an atmosphere of N_2 using pre-dried glassware and standard Schlenk techniques. Yields refer to isolated compounds, estimated to be >95% pure as determined by ^{1}H NMR.

Vacuum

The following pressure was measured using a rotary vane pump RZ6 from Vacuubrand®: 2 mbar (uncorrected value).

Melting Points

Melting points were measured using a Stuart® Melting Point Apparatus SMP3 from Barloworld Scientific. Values are uncorrected.

Chromatography

Analytical thin layer chromatography (TLC) was performed on TLC plates Alugram® Xtra Sil G/UV_{254}, detection was done under UV light at 254 nm. Manual flash column separations were carried out on Merck Geduran Silica 60 (0.063–0.200 mm, 70–230 mesh ASTM). Preparative TLC (PTLC) was carried out on TLC plates pre-coated with aluminium oxide F-254 (type E) or with silica. Recycling preparative HPLC (GPC) was carried out on a JAI® (LC-92XX II Series, injection- and control-valve, UV and RI detector) connected to JAIGEL HH series columns. Chloroform of HPLC grade stabilized with ethanol was employed. HPLC chromatograms were recorded on an Agilent 1290 Infinity using the column CHIRALPAK® IC-3 and hexanes/ethyl acetate (1:1, 1 mL/min, detection at 274 nm). LC-MS chromatograms were recorded on an Agilent 6100s Series Single Quad using the RP column ZORBAX SB-C18, 5 µm. The flow rate was set to 0.5 mL/min, detection at 270 and 290 nm. The methods used are as follows:

Table 43: LC-MS methods.

method length	*t*/min	acetonitrile (0.1% TFA)	water (0.1% TFA)
15 min	0	60	40
	5	100	0
	13	100	0
	15	60	40
22 min	0	60	40
	5	100	0
	20	100	0
	22	60	40

Solvents

Solvents for column chromatography were purified via distillation under reduced pressure prior to their use. Solvents for reactions involving moisture-sensitive reagents were dried, distilled and stored under N_2 according to following standard procedures.[129]

Solvents purified by solvent purification system (SPS-800) from M. Braun: Dichloromethane, tetrahydrofurane, diethylether, dimethylformamide.

Solvents dried and distilled from Na using benzophenone as indicator: Methanol, *tert*-amylalcohol, toluene, *meta*-xylene, hexanes, 1,4-dioxane, 1,2-dimethoxyethane.

Solvents dried and distilled from CaH_2: dichloroethane, dimethylacetamide, dimethylformamide, dimethylsulfoxide, *N*-methyl-2-pyrrolidone, γ-valerolactone.

For synthesis grade solvents for reactions under air were used without further purification: trifluoroacetic acid, acetic acid, propionic acid, all buffer solutions, γ-valerolactone, *tert*-amylalcohol, toluene, *meta*-xylene, 1,2-dimethoxyethane, *n*-octane, hexanes, aq. HCl (12 M).

For peptide synthesis grade solvent for the SPPS: DMF.

Reagents

Chemicals obtained from commercial sources (with a purity >95%) were used without further purification. The following compounds were synthesized according to previously described literature protocols:

Protected amino acids and peptides,[130] homologated tryptophans **120**,[131] *N*-pyridyl tryptophans **56h**, **56j** and **120**,[44] *N*-pyrimidyl tryptophans **56e**, **56f** and **56g**[44] (from 2-Iodopyrimidine),[132] iodonium tosylate **78a**,[133] allyloxyarenes **28x** and **28y**,[134] pyrene **66u**,[135] bromopyrene **28t**,[136] acrylates **129**,[137] thioacrylate **129q**[137] at –88 °C, vinyl ketones **130**,[138] allene **187**,[139] peptides from the SPPS **159**.[140]

The following chemicals were kindly provided by the persons mentioned below:

Karsten Rauch: $[RuCl_2(p\text{-cymene})]_2$, $[Ru(OAc)_2(p\text{-cymene})]$.

Prof. Dr. Lutz Ackermann: Grubbs II.

Michaela Bauer: tosylate **78f**, tryptophan **56e**, iodoferrocene **66c**.

Prof. Dr. Hongjun Ren: bromophenyl pyrene **28q**, peptides **101d** and **108**.

Nikolaos Kaplaneris: tryptophan **142hk**, acryloyl peptide **148b**.

Wei Wang: iodophenyl-BODIPY **66w**.

Dr. Mélanie Lorion: vinyl ketone **130d**.

Dr. Alexander Bechtoldt: acrylates **129b**, **129f**, **129g**, **129j**, **129k**, **129o**, **129p**, **129r**, **129u** and **129v**.

Dr. Ruhuai Mei: Dehydroalanine **129δ**.

NMR

Nuclear magnetic resonance (NMR) spectroscopy was performed at 300, 400, 500 or 600 MHz (^{1}H NMR), 75, 100 or 125 MHz (^{13}C NMR) or 282 MHz, 376 MHz and 471 MHz (^{19}F NMR) on a Varian Inova 600, Varian Inova 500, Bruker Avance III HD 500, Bruker Avance III HD 400, Bruker Avance III 400, Varian VNMRS 300, Bruker Avance 300, Varian Mercury VX 300, Varian Mercury 300, or Bruker Avance III 300 in the solvent indicated. Chemical shifts are reported as δ values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively.

	^{1}H NMR	^{13}C NMR
$CDCl_3$	7.26 ppm	77.16 ppm
DMSO-d_6	2.50 ppm	39.52 ppm
CD_3OD	3.31 ppm	49.00 ppm

For characterization of the observed resonance multiplicities the following abbrevations were applied: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), or analogue representations. The coupling constants *J* are reported in Hertz (Hz).

IR

Infrared spectroscopy (IR) was carried out on a Bruker® Alpha-P ATR spectrometer. Liquid samples were measured as film and solid samples neat. Spectra were recorded in the range from 4000 to 600 cm^{-1}. Analysis of the spectral data were carried out using Opus 6. Absorption is given in wave numbers (cm^{-1}).

MS

Mass spectrometry electron ionization (EI) spectra were measured on a time-of-flight mass spectrometer AccuTOF from JOEL. Electrospray ionization (ESI) mass spectra were recorded on an Io-

Trap mass spectrometer LCQ from Finnigan, a quadropole time-of-flight maXis from Bruker Daltonic or on a time-of-flight mass spectrometer microTOF from Bruker Daltonic. ESI-HRMS spectra were recorded on a Bruker Apex IV or Bruker Daltonic 7T, fourier transform ion cyclotron resonance (FTICR) mass spectrometer. The ratios of mass to charge (m/z) are indicated, intensities relative to the base peak (I = 100) are provided in parentheses.

Fluorescence Spectroscopy

Fluorescence excitation and emission data in solution were recorded on a Jasco® FP-8500 spectrofluorometer. The scan speed was adjusted to 200 nm/min. All compounds were measured at a concentration of 1 mg/L in DMSO.

UV-VIS Spectroscopy

UV-Visible Spectroscopy was performed on a Jasco® V-770 spectrophotometer. A baseline in the appropriate solvent was obtained prior to recording spectra.

Peptide Synthesis and Purification

Peptides for on-resin reactions were synthesized by microwave-assisted solid phase peptide synthesis (SPPS) using hydroxymethyl polystyrene resin (Novabiochem®, 1.2 mmol/g), or Rink-Amide-ChemMatrix® resin (Biotage, 0.50 mmol/g) or Fmoc-Rink-Amide AM resin (Iris Biotech, 0.55 mmol/g). SPPS was carried out in a CEM Liberty Blue™. Amino acids were coupled using Oxyma and DIC in DMF. Deprotection was performed with 20% piperidine in DMF. Cleavage was carried out in BD Discardit™ II 10 mL syringes fitted with a frit. Precipitated peptides were centrifuged with a Heraeus Megafuge 16R from Thermo Scientific™ for 3 min at 9800 rounds/min.

5.2 General Procedures

General procedure A for palladium-catalyzed C–H arylations of peptides with diaryliodonium salts:

A mixture of peptide **80** (0.20 mmol), diphenyliodonium tosylate **78** (0.30 mmol) and $Pd(OAc)_2$ (5.0 mol %) in HOAc (3.0 mL) or H_2O (3.0 mL) was stirred at 25 °C for 17 h. Thereafter, H_2O (5 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by column chromatography or GPC to yield the desired product **81**.

General procedure B1 for ruthenium-catalyzed C–H arylations of tryptophans with aryl halides:

An oven dried Schlenk flask was charged with tryptophan **56** (0.30 mmol), solid aryl halide **28** or **66** (0.33 mmol, 1.1 equiv), $[RuCl_2(p\text{-cymene})]_2$ (9.2 mg, 5.0 mol %), 1-adamantylcarboxylic acid (16.2 mg,

30 mol %) and K_2CO_3 (124 mg, 3.0 equiv) and the flask was evacuated and refilled with N_2 three times. Dry *meta*-xylene (3.0 mL) was added via syringe and the mixture was stirred at 120 °C for 22 h. Liquid aryl halides **28** and **66** were added after the addition of the solvent. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (3.0 mL) and purified by column chromatography, PTLC or GPC to yield products **67**.

General procedure B2 for ruthenium-catalyzed C–H arylations of tryptophans with aryl halides:
An oven dried Schlenk flask was charged with tryptophan **56** or **120** (0.30 mmol), solid aryl halide **28** or **66** (0.33 mmol, 1.1 equiv), $[RuCl_2(p\text{-cymene})]_2$ (9.2 mg, 5.0 mol %), pentafluorobenzoic acid (19.1 mg, 30 mol %) and K_3PO_4 (191 mg, 3.0 equiv) and the flask was evacuated and refilled with N_2 three times. Dry *meta*-xylene (3.0 mL) was added via syringe and the mixture was stirred at 120 °C for 22 h. Liquid aryl halides **28** and **66** were added after the addition of the solvent. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (3.0 mL) and purified by column chromatography, PTLC or GPC to yield products **67** and **121**.

General procedure B3 for ruthenium-catalyzed C–H arylations of peptides with aryl halides:
An oven dried Schlenk flask was charged with peptide **101** (50–100 mg), solid aryl halide **28** (1.1 equiv), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), pentafluorobenzoic acid (60 mol %) and K_3PO_4 (3.0 equiv) and the flask was evacuated and refilled with N_2 three times. Dry *meta*-xylene (3.0 mL) was added via syringe and the mixture was stirred at 120 °C for 22 h. Liquid aryl halides **28** were added after the addition of the solvent. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (3.0 mL) and purified by column chromatography or PTLC to yield products **102**.

General procedure B4 for ruthenium-catalyzed C–H arylations of peptides with dibromobenzenes:
An oven dried Schlenk flask was charged with a peptide **56** or **101** (50–100 mg), dibromobenzene **28** (0.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 or 10 mol %), pentafluorobenzoic acid (30 or 60 mol %) and K_3PO_4 (3.0 equiv) and the flask was evacuated and refilled with N_2 three times. Dry *meta*-xylene (3.0 mL) was added via syringe and the mixture was stirred at 120 °C for 22 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (3.0 mL) and purified by column chromatography or PTLC to yield products **117**.

General procedure C for ruthenium-catalyzed C–H alkylations of tryptophans with unactivated alkenes:

An oven dried Schlenk flask was charged with tryptophan **56** (0.30 mmol), $[RuCl_2(p\text{-cymene})]_2$ (18.4 mg, 10 mol %) and KO_2CMes (18.2 mg, 30 mol %) and the flask was evacuated and refilled with N_2 three times. Dry toluene (1.0 mL) and alkene **44** (3.0 equiv) were added via syringe and the mixture was stirred at 140 °C for 24 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (3.0 mL) and purified by column chromatography to yield products **107**.

General procedure D1 for ruthenium-catalyzed C–H alkylations of tryptophans with alkenes:

A conical-bottom test tube was charged with tryptophan **56** or **120** (0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (9.2 mg, 10 mol %). HOAc (0.15 mL) and acrylate **129** or vinyl ketone **130** (1.3–3.0 equiv) were added. The tube was fitted with a septum and the mixture was stirred at 80 °C for 15 h. After cooling to ambient temperature, the reaction mixture was diluted with toluene (5.0 mL) and purified by column chromatography, PTLC or GPC to yield products **142** and **141**.

General procedure D2 for ruthenium-catalyzed C–H alkylations of peptides with alkenes:

A conical-bottom test tube was charged with peptide **101** (50–100 mg) and $[RuCl_2(p\text{-cymene})]_2$ (10 mol %). HOAc (0.1–0.3 mL) and acrylate **129** or vinyl ketone **130** (1.1–5 equiv) were added. The tube was fitted with a septum and the mixture was stirred at 80 °C for 15 h. After cooling to ambient temperature, the reaction mixture was diluted with toluene (5.0 mL) and purified by column chromatography or PTLC to yield products **147** and **156**.

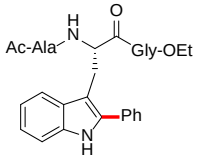
General procedure E for ruthenium-catalyzed on-resin C–H alkylations of peptides:

A 10 mL conical-bottom test tube without a stir bar was charged with a peptide loaded resin **159** (30 µmol) and $[RuCl_2(p\text{-cymene})]_2$ (10 mol %). HOAc (30–150 µL) and acrylate **129** or vinyl ketone **130** (3.0–10.0 equiv) were added. The test tube was fitted with a septum and the mixture was heated to 80 °C for 15 h with slightly shaking of the reaction vial. After cooling to ambient temperature, the mixture was transferred with methanol to a 10 mL syringe equipped with a frit. The resin was washed with HOAc (5×5 mL), MeOH (3×5 mL), HOAc (3×5 mL), MeOH (3×5 mL), and CH_2Cl_2 (5 × 5 mL). After drying overnight at 40 °C, the resin was treated with TFA (3 mL) or TFA/TIS/CH_2Cl_2/H_2O (3 mL, 95:2.5:1.25:1.25) at ambient temperature for 4 h. The cleavage solution was collected and the resin was washed with TFA (3 mL) and HOAc (3×5 mL). The collected washing solution was concentrated under reduced pressure and the peptide was three times precipitated from cold Et_2O (–20 °C, 5 mL), centrifuged and decanted. The obtained solid peptide **161** was dried in vacuum.

5.3 Analytical Data

5.3.1 Analytical Data for Arylated Peptides 81 and 105

Ethyl acetyl-L-alanyl-2-phenyl-L-tryptophylglycinate (81aa)



The general procedure A was followed using peptide **80a** (80.5 mg). Purification by column chromatography (hexanes/EtOAc/MeOH 1:5:0.2) yielded peptide **81aa** as a white solid (95 mg, 99% for the reaction in HOAc and 65 mg, 68% for the reaction in H_2O).

m. p.: 183 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.8 (br s, 1H), 8.31 (dd, *J* = 5.8, 5.8 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.31 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.05 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 6.97 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 4.54 (ddd, *J* = 8.2, 8.2, 4.9 Hz, 1H), 4.25 (dq, *J* = 7.1, 7.1 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.91–3.69 (m, 2H), 3.22–3.09 (m, 1H), 2.97 (dd, *J* = 14.8, 8.4 Hz, 1H), 1.80 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 2H), 1.14 (d, *J* = 7.1 Hz, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.3 (C_q), 171.9 (C_q), 169.5 (C_q), 169.4 (C_q), 135.7 (C_q), 135.4 (C_q), 133.0 (C_q), 129.2 (C_q), 128.4 (CH), 128.3 (CH), 127.6 (CH), 121.7 (CH), 119.6 (CH), 118.8 (CH), 111.2 (CH), 107.8 (C_q), 60.7 (CH_2), 54.1 (CH), 48.8 (CH), 41.3 (CH_2), 28.4 (CH_2), 22.8 (CH_3), 18.2 (CH_3), 14.4 (CH_3).

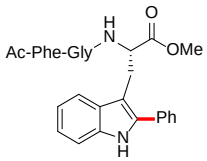
IR (ATR): 3272, 2968, 1732, 1631, 1539, 1449, 1369, 1302, 1241, 1192, 1157, 1026, 736, 699 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 979 (13) $[2M+Na]^+$, 903 (4) $[2M+H]^+$, 501 (100) $[M+Na]^+$, 479 (41) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{31}N_4O_5^+$ 479.2289 $[M+H]^+$, found 479.2900.

The measured data is in accordance with the literature data.[97]

Methyl acetyl-L-phenylalanylglycyl-2-phenyl-L-tryptophanate (81ka)



The general procedure A was followed using peptide **80k** (69.7 mg). Purification by column chromatography (hexanes/EtOAc/MeOH 1:5:0.2) yielded peptide **81ka** as a white solid (42 mg, 52% for the reaction in HOAc and 20 mg, 25% for the reaction in H_2O).

m. p.: 85 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.3 (s, 1H), 8.37–8.30 (m, 1H), 8.26–8.17 (m, 2H), 8.10–8.04 (m, 1H), 7.95–7.92 (m, 2H), 7.68–7.62 (m, 2H), 7.62–58 (m, 2H), 7.53–7.48 (m, 1H), 7.28–7.16 (m, 6H), 4.56–4.46 (m, 1H), 4.45–4.36 (m, 1H), 3.78–3.72 (m, 1H), 3.70–3.62 (m, 1H), 3.16 (s, 3H), 3.04–2.93 (m, 2H), 2.77–2.66 (m, 2H), 1.90 (s, 3H).

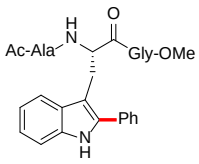
^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.3 (C_q), 172.0 (C_q), 169.7 (C_q), 169.0 (C_q), 138.5 (C_q), 136.3 (C_q), 135.9 (C_q), 133.1 (C_q), 129.5 (CH), 129.1 (CH), 129.1 (C_q), 128.4 (CH), 128.4 (CH), 127.9 (CH), 126.6 (CH), 121.9 (CH), 119.3 (CH), 118.9 (CH), 111.6 (CH), 106.9 (C_q), 54.5 (CH), 53.6 (CH), 52.0 (CH_3), 42.1 (CH_2), 37.8 (CH_2), 27.7 (CH_2), 22.9 (CH_3).

IR (ATR): 3279, 1737, 1644, 1521, 1454, 1436, 1372, 1305, 1279, 1216, 742, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 563 (100) $[M+Na]^+$, 541 (58) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{31}H_{33}N_4O_5^+$ 541.2445 $[M+H]^+$, found 541.2449.

Methyl acetyl-L-alanyl-2-phenyl-L-tryptophylglycinate (81la)



The general procedure A was followed using peptide **80l** (74.9 mg). Purification by column chromatography (hexanes/EtOAc/MeOH 1:5:0.2) yielded peptide **81la** as a colorless solid (85 mg, 96% for the reaction in HOAc and 60 mg, 67% for the reaction in H_2O).

m. p.: 177 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.12 (s, 1H), 8.10 (t, *J* = 5.8 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.73–7.64 (m, 3H), 7.53–7.44 (m, 2H), 7.42–7.30 (m, 2H), 7.09 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 4.66 (q, *J* = 7.2 Hz, 1H), 4.20 (p, *J* = 7.0 Hz, 1H), 3.71 (dd, *J* = 17.3, 5.9 Hz, 1H), 3.65–3.57 (m, 1H), 3.56 (s, 3H), 3.38–3.29 (m, 1H), 3.28 (s, 2H), 3.11 (dd, *J* = 14.4, 6.9 Hz, 1H), 1.79 (s, 3H), 1.08 (d, *J* = 7.1 Hz, 3H).

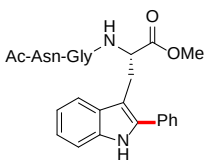
^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.4 (C_q), 171.9 (C_q), 170.2 (C_q), 169.7 (C_q), 136.3 (C_q), 135.8 (C_q), 133.2 (C_q), 129.4 (C_q), 129.0 (CH), 128.6 (CH), 127.7 (CH), 121.8 (CH), 119.6 (CH), 119.0 (CH), 111.4 (CH), 107.9 (C_q), 54.2 (CH), 52.0 (CH_3), 48.8 (CH), 41.1 (CH_2), 28.3 (CH_2), 22.9 (CH_3), 18.2 (CH_3).

IR (ATR): 3270, 2924, 1743, 1631, 1540, 1448, 1369, 1201, 1177, 1010, 744, 698 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 951 (12) $[2M+Na]^+$, 929 (2) $[2M+H]^+$, 487 (100) $[M+Na]^+$, 465 (31) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{29}N_4O_5^+$ 465.2132 $[M+H]^+$, found 465.2137.

Methyl acetyl-L-aspargylglycyl-2-phenyl-L-tryptophanate (81ma)



The general procedure A was followed using peptide **80m** (83.3 mg). Purification by column chromatography (hexanes/EtOAc/MeOH 1:5:1) yielded peptide **81ma** as a colorless solid (86 mg, 85% for the reaction in HOAc and 64 mg, 63% for the reaction in H_2O).

m. p.: 124 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.22 (s, 1H), 8.27 (d, *J* = 7.3 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.97 (dd, *J* = 5.9, 5.9 Hz, 1H), 7.66–7.58 (m, 2H), 7.56–7.48 (m, 3H), 7.42–7.34 (m, 2H), 7.32 (s, 1H), 7.11

(ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.03 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.83 (s, 1H), 4.54–4.46 (m, 2H), 3.68 (dd, *J* = 16.9, 5.7 Hz, 1H), 3.63–3.56 (m, 1H), 3.37 (dd, *J* = 14.5, 8.8 Hz, 1H), 3.29 (s, 3H), 3.22 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.56–2.51 (m, 1H), 2.41 (dd, *J* = 15.5, 7.6 Hz, 1H), 1.84 (s, 3H).

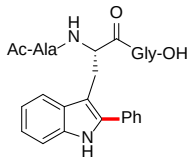
^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.8 (C_q), 171.4 (C_q), 171.3 (C_q), 169.4 (C_q), 168.6 (C_q), 135.8 (C_q), 135.3 (C_q), 132.6 (C_q), 128.6 (CH), 128.6 (C_q), 127.9 (CH), 127.4 (CH), 121.4 (CH), 118.8 (CH), 118.4 (CH), 111.1 (CH), 106.5 (C_q), 53.2 (CH), 51.5 (CH), 49.8 (CH_3), 41.8 (CH_2), 37.1 (CH_2), 27.1 (CH_2), 22.5 (CH_3).

IR (ATR): 3297, 1734, 1651, 1531, 1435, 1412, 1372, 1312, 1217, 744, 698 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 530 (100) $[M+Na]^+$, 508 (19) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{30}N_5O_6^+$ 508.2191 $[M+H]^+$, found 508.2186.

Acetyl-L-alanyl-2-phenyl-L-tryptophylglycine (81na)



The general procedure A was followed using peptide **80n** (75.9 mg). Purification by column chromatography (EtOAc/MeOH 3:1→1:1) yielded peptide **81na** as a colorless solid (72 mg, 80% for the reaction in HOAc and 44 mg, 49% for the reaction in H_2O).

m. p.: 120 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.14 (d, *J* = 2.1 Hz, 1H), 8.53–8.22 (m, 1H), 7.75–7.71 (m, 1H), 771–7.67 (m, 1H), 7.50–7.44 (m, 2H), 7.43–7.38 (m, 1H), 7.38–7.33 (m, 1H), 7.33–7.30 (m, 1H), 7.09–7.03 (m, 1H), 6.99–6.92 (m, 1H), 4.62–4.55 (m, 1H), 4.24 (dddd, *J* = 7.1, 7.1, 7.1, 7.1 Hz, 1H), 3.55–3.43 (m, 1H), 3.40–3.29 (m, 1H), 3.25–3.17 (m, 1H), 3.16–3.06 (m, 1H), 1.80 (s, 3H), 1.11 (d, *J* = 7.1 Hz, 3H).

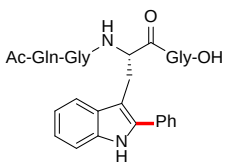
^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.4 (C_q), 172.3 (C_q), 170.2 (C_q), 169.2 (C_q), 136.0 (C_q), 135.2 (C_q), 132.8 (C_q), 129.1 (C_q), 128.6 (CH), 128.1 (CH), 127.2 (CH), 121.4 (CH), 119.3 (CH), 118.6 (CH), 111.0 (CH), 108.1 (C_q), 54.4 (CH), 48.4 (CH), 43.8 (CH_2), 28.0 (CH_2), 22.3 (CH_3), 18.0 (CH_3).

IR (ATR): 3296, 1644, 1599, 1533, 1449, 1396, 1344, 1307, 1262, 1242, 743, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 473 (100) $[M+Na]^+$, 451 (6) $[M+H]^+$, 375 (24).

HR-MS (ESI) *m/z* calcd for $C_{24}H_{26}N_4NaO_5^+$ 473.1795 $[M+Na]^+$, found 473.1774.

Actyl-L-glutamylglycyl-2-phenyl-L-tryptophylglycine (81oa)



The general procedure A was followed using peptide **80o** (50.0 mg) and HOAc. Purification by column chromatography (EtOAc/MeOH 1:1) yielded peptide **81oa** as a white solid (41 mg, 72%).

m. p.: 145 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.20 (s, 1H), 8.42 (dd, *J* = 13.3, 8.6 Hz, 1H), 8.28 (dd, *J* = 7.8, 2.5 Hz, 1H), 8.24–8.18 (m, 1H), 7.74–7.65 (m, 3H), 7.52–7.43 (m, 2H), 7.39–7.25 (m, 4H), 7.07 (dddd, *J* = 7.9, 7.9, 1.1, 1.1 Hz, 1H), 6.99 (dddd, *J* = 7.9, 6.9, 2.7, 1.0 Hz, 1H), 6.74–6.67 (m, 1H), 4.6–4.57 (m, 1H), 4.24–4.17 (m, 1H), 3.88 (br s, 1H), 3.77–3.68 (m, 1H), 3.58–3.48 (m, 1H), 3.44–3.33 (m, 2H), 3.25–3.17 (m, 1H), 3.12–3.05 (m, 1H), 2.15–2.05 (m, 2H), 1.90–1.81 (m, 2H), 1.74 (s, 3H).

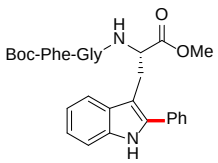
^{13}C NMR (126 MHz, DMSO-d_6): δ = 175.1 (C_q), 173.9 (C_q), 173.9 (C_q), 171.9 (C_q), 171.8 (C_q), 171.7 (C_q), 170.0 (C_q), 169.6 (C_q), 169.5 (C_q), 168.5 (C_q), 168.4 (C_q), 135.9 (C_q), 135.1 (C_q), 135.1 (C_q), 132.8 (C_q), 129.0 (C_q), 129.0 (C_q), 128.6 (CH), 128.0 (CH), 127.2 (CH), 121.3 (CH), 119.1 (CH), 118.6 (CH), 111.0 (CH), 108.0 (C_q), 108.0 (C_q), 54.5 (CH), 52.4 (CH), 43.9 (CH_2), 42.0 (CH_2), 31.5 (CH_2), 27.9 (CH_2), 27.7 (CH_2), 22.5 (CH_3).

IR (ATR): 3269, 1644, 1600, 1539, 1449, 1393, 1343, 1308, 1256, 1241, 743, 698 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1151 (8) $[2M+Na]^+$, 609 (44) $[M–H+2Na]^+$, 587 (100) $[M+Na]^+$, 565 (7) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{32}N_6NaO_7^+$ 587.2225 $[M+Na]^+$, found 587.2218.

Methyl (*tert*-butoxycarbonyl)-L-phenylalanylglycyl-2-phenyl-L-tryptophanate (81va)



The general procedure A was followed using peptide **80v** (104.5 mg) and H_2O. Purification by column chromatography (MTBE/MeOH 100:1) yielded peptide **81va** as a white solid (28 mg, 23%).

m. p.: 125 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.21 (s, 1H), 8.32 (d, *J* = 7.7 Hz, 1H), 8.01 (dd, *J* = 5.7, 5.7 Hz, 1H), 7.65–7.59 (m, 2H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.53–7.47 (m, 2H), 7.42–7.37 (m, 1H), 7.37–7.34 (m, 1H), 7.27–7.22 (m, 5H), 7.20–7.15 (m, 1H), 7.11 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.05–6.99 (m, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.58 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H), 4.20–4.14 (m, 1H), 3.74 (dd, *J* = 16.8, 5.6 Hz, 1H), 3.63 (dd, *J* = 16.8, 5.6 Hz, 1H), 3.36 (dd, *J* = 14.5, 8.4 Hz, 1H), 3.33 (s, 3H), 3.25–3.18 (m, 1H), 2.99 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.76–2.68 (m, 1H), 1.28 (s, 9H).

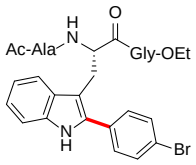
^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.8 (C_q), 171.7 (C_q), 168.5 (C_q), 155.2 (C_q), 135.8 (C_q), 135.4 (C_q), 132.6 (C_q), 129.1 (CH), 128.6 (CH), 128.6 (C_q), 127.9 (CH), 127.9 (CH), 127.4 (CH), 126.0 (CH), 121.4 (CH), 118.8 (CH), 118.4 (CH), 111.1 (CH), 106.4 (C_q), 78.0 (C_q), 55.6 (CH), 53.1 (CH), 51.6 (CH_3), 41.6 (CH_2), 37.3 (CH_2), 28.1 (CH_3), 27.3 (CH_2).

IR (ATR): 3306, 2900, 1739, 1651, 1518, 1455, 1437, 1366, 1248, 1214, 1163, 1019, 741, 699 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 621 (100) $[M+Na]^+$, 599 (52) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{34}H_{38}N_4NaO_6^+$ 621.2684 $[M+Na]^+$, found 621.2661.

Ethyl acetyl-L-alanyl-2-(4-bromophenyl)-L-tryptophyl-glycinate (81af)



The general procedure A was followed using peptide **80a** (81.2 mg), iodonium tosylate **78f** (185 mg) and HOAc. Purification by column chromatography (EtOAc/ THF 9:1) yielded peptide **81af** as a white solid (74 mg, 67%).

m. p.: 191 °C.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.68–7.57 (m, 5H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.13 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.05 (dd, *J* = 7.5, 7.5 Hz, 1H), 4.71 (dd, *J* = 7.3, 7.3 Hz, 1H), 4.19–4.07 (m, 3H), 3.79 (d, *J* = 17.6 Hz, 1H), 3.61 (d, *J* = 17.6 Hz, 1H), 3.51 (dd, *J* = 14.7, 7.3 Hz, 1H), 3.34–3.30 (m, 1H), 1.90 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.2 Hz, 3H).

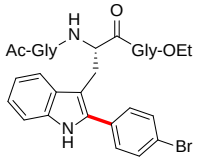
^{13}C NMR (126 MHz, CD_3OD): δ = 174.5 (C_q), 173.6 (C_q), 173.5 (C_q), 170.8 (C_q), 137.7 (C_q), 135.9 (C_q), 133.5 (C_q), 132.8 (CH), 131.0 (CH), 130.4 (C_q), 123.0 (CH), 122.3 (C_q), 120.2 (CH), 119.9 (CH), 112.0 (CH), 108.5 (C_q), 62.3 (CH_2), 55.3 (CH), 50.9 (CH), 42.1 (CH_2), 28.4 (CH_2), 22.4 (CH_3), 17.4 (CH_3), 14.5 (CH_3).

IR (ATR): 3278, 1730, 1629, 1589, 1538, 1452, 1370, 1205, 1006, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1139/1137 (13) $[2M+Na]^+$, 581/579 (100) $[M+Na]^+$, 559/557 (5) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{30}{}^{79}BrN_4O_5{}^+$ 557.1394 $[M+H]^+$, found 557.1375.

Ethyl acetyl-glycyl-2-(4-bromophenyl)-L-tryptophylglycinate (81wf)



The general procedure A was followed using peptide **80w** (100 mg), iodonium tosylate **78f** (204 mg) and HOAc. Purification by column chromatography (EtOAc/ THF 5:2) yielded peptide **81wf** as a white solid (80 mg, 57%).

m. p.: 205 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.23 (s, 1H), 8.36 (dd, *J* = 5.8, 5.8 Hz, 1H), 8.13–8.05 (m, 1H), 7.96 (dd, *J* = 5.7, 5.7 Hz, 1H), 7.72–7.61 (m, 5H), 7.33 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.10 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.00 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 4.74–4.66 (m, 1H), 4.04 (q, *J* = 7.0 Hz, 2H), 3.75–3.68 (m, 2H), 3.62 (dd, *J* = 16.9, 5.7 Hz, 1H), 3.46 (dd, *J* = 16.9, 5.4 Hz, 1H), 3.27 (dd, *J* = 14.4, 6.3 Hz, 1H), 3.04 (dd, *J* = 14.4, 7.5 Hz, 1H), 1.80 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H).

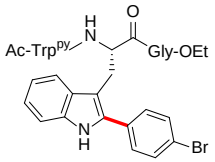
^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.5 (C_q), 169.5 (C_q), 169.4 (C_q), 168.6 (C_q), 136.0 (C_q), 134.1 (C_q), 132.0 (C_q), 131.5 (CH), 130.2 (CH), 128.9 (C_q), 121.7 (CH), 120.6 (C_q), 119.2 (CH), 118.8 (CH), 111.1 (CH), 108.1 (C_q), 60.4 (CH_2), 53.5 (CH), 41.9 (CH_2), 40.8 (CH_2), 28.2 (CH_2), 22.4 (CH_3), 14.0 (CH_3).

IR (ATR): 3294, 1740, 1684, 1624, 1526, 1434, 1202, 1008, 737, 706, 673 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1111/1109 (54) $[2M+Na]^+$, 1088/1086 (7) $[2M+H]^+$, 567/565 (100) $[M+Na]^+$, 545/543 (19) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{28}{}^{79}BrN_4O_5^+$ 543.1236 $[M+H]^+$, found 543.1233.

Ethyl acetyl-1-(2-pyridyl)-L-tryptophyl-2-(4-bromophenyl)-L-tryptophylglycinate (105bf)



The general procedure A was followed using peptide **103b** (30 mg), iodonium tosylate **78f** (46 mg) and TFA at 60 °C. Purification by column chromatography (EtOAc/THF 9:1) yielded peptide **105bf** as a white solid (13 mg, 35%).

m. p.: 164 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.22 (s, 1H), 8.54 (ddd, *J* = 5.0, 2.9, 2.9 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.17–8.10 (m, 1H), 8.03–7.90 (m, 2H), 7.76–7.54 (m, 5H), 7.35–7.32 (m, 1H), 7.28–7.21 (m, 2H), 7.21–7.13 (m, 2H), 7.13–6.97 (m, 1H), 4.70 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 4.63 (ddd, *J* = 8.1, 8.1, 5.3 Hz, 2H), 4.09–3.91 (m, 2H), 3.70–3.61 (m, 1H), 3.56–3.47 (m, 1H), 3.37–3.32 (m, 2H), 3.11–3.04 (m, 1H), 2.92 (dd, *J* = 14.8, 8.5 Hz, 1H), 1.75 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.4 (C_q), 170.9 (C_q), 169.2 (C_q), 169.2 (C_q), 152.0 (C_q), 148.4 (CH), 139.0 (CH), 135.9 (C_q), 134.7 (C_q), 134.2 (C_q), 131.9 (C_q), 131.4 (CH), 130.1 (CH), 129.9 (C_q), 128.8 (C_q), 124.3 (CH), 122.9 (CH), 121.6 (CH), 120.7 (CH), 120.5 (C_q), 119.9 (CH), 119.0 (CH), 118.7 (CH), 114.5 (C_q), 113.9 (CH), 113.7 (CH), 111.0 (CH), 108.0 (C_q), 60.3 (CH_2), 53.7 (CH), 52.8 (CH), 40.7 (CH_2), 28.1 (CH_2), 27.2 (CH_2), 22.5 (CH_3), 13.9 (CH_3).

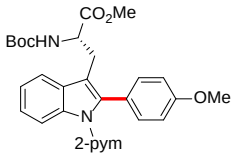
IR (ATR): 3260, 1652, 1592, 1473, 1455, 1437, 1185, 1133, 1010, 800, 745, 720 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 773/771 (100) $[M+Na]^+$, 751/749 (39) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{39}H_{38}{}^{79}BrN_6O_5^+$ 749.2082 $[M+H]^+$, found 749.2070.

5.3.2 Analytical Data for Arylated Tryptophans 67

Methyl *tert*-butoxycarbonyl-1-(2-pyrimidyl)-2-(4-methoxyphenyl)-L-tryptophanate (67eb)



The general procedure B1 was followed using tryptophan **56e** (119 mg) and 4-bromoanisole (**28b**, 62 mg). Purification by column chromatography (hexanes/ EtOAc 1:1) yielded tryptophan **67eb** as a white solid (49 mg, 33%) and diarylated tryptophan **67ebb** as a white solid (18 mg, 12%).

m. p.: 154 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.73 (d, *J* = 4.9 Hz, 2H), 7.96–7.91 (m, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.32 (dd, *J* = 4.8, 4.8 Hz, 1H), 7.26–7.18 (m, 2H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.13–7.09 (dm, *J* = 8.4 Hz, 2H), 6.93–6.88 (dm, *J* = 8.4 Hz, 2H), 4.19 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 3.77 (s, 3H), 3.42 (s, 3H), 3.17 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.08 (dd, *J* = 14.4, 7.8 Hz, 1H), 1.30 (s, 9H).

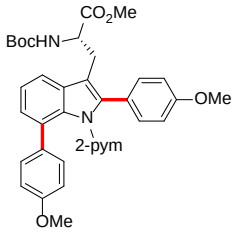
^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.2 (C_q), 158.6 (CH), 158.4 (C_q), 157.0 (C_q), 155.0 (C_q), 137.2 (C_q), 136.0 (C_q), 130.7 (CH), 128.8 (C_q), 124.5 (C_q), 123.0 (CH), 121.3 (CH), 118.9 (CH), 118.3 (CH), 113.5 (CH), 112.9 (C_q), 112.3 (CH), 78.2 (C_q), 55.0 (CH_3), 54.3 (CH), 51.6 (CH_3), 28.0 (CH_3).

IR (ATR): 1974, 1741, 1708, 1561, 1507, 1456, 1421, 1365, 1345, 1244, 1160, 1026, 832, 745 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1027 (43) $[2M+Na]^+$, 1005 (4) $[2M+H]^+$, 525 (100) $[M+Na]^+$, 503 (14) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{30}N_4NaO_5^+$ 525.2108 $[M+H]^+$, found 525.2092.

Methyl *tert*-butoxycarbonyl-1-(2-pyrimidyl)-2,7-di(4-methoxyphenyl)-L-tryptophanate (67ebb)



The general procedure B1 was followed using tryptophan **56e** (119 mg) and 4-bromoanisole (**28b**, 62 mg). Purification by column chromatography (hexanes/ EtOAc 1:1) yielded tryptophan **67eb** as a white solid (49 mg, 33%) and diarylated tryptophan **67ebb** as a white solid (18 mg, 12%).

m. p.: 161 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.25 (d, *J* = 4.8 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.26–7.20 (m, 1H), 7.14–7.08 (m, 1H), 7.07–7.00 (m, 4H), 6.85–6.79 (m, 4H), 6.58–6.52 (m, 2H), 4.21 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.46 (s, 3H), 3.15 (dd, *J* = 14.5, 7.1 Hz, 1H), 3.09 (dd, *J* = 14.4, 8.0 Hz, 1H), 1.31 (s, 9H).

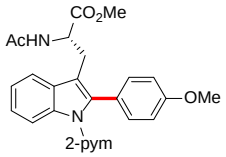
^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.2 (C_q), 170.2 (C_q), 158.7 (C_q), 157.4 (CH), 157.0 (C_q), 155.1 (C_q), 138.8 (C_q), 133.5 (C_q), 131.8 (C_q), 131.7 (CH), 129.2 (C_q), 128.7 (CH), 126.5 (C_q), 124.6 (CH), 123.1 (C_q), 120.4 (CH), 118.9 (CH), 117.7 (CH), 113.3 (CH), 113.2 (CH), 110.6 (C_q), 78.2 (C_q), 55.0 (CH_3), 54.9 (CH_3), 54.4 (CH), 51.6 (CH_3), 28.0 (CH_3), 26.4 (CH_2).

IR (ATR): 2974, 1741, 1708, 1562, 1506, 1417, 1364, 1242, 1161, 1053, 1026, 832, 791, 745 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 631 (100) $[M+Na]^+$, 609 (1) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{35}H_{36}N_4NaO_6^+$ 631.2527 $[M+Na]^+$, found 631.2510.

Methyl acetyl-1-(2-pyrimidyl)-2-(4-methoxyphenyl)-L-tryptophanate (67gb)



The general procedure B1 was followed using tryptophan **56g** (101 mg) and 4-bromoanisole (**28b**, 62 mg). Purification by GPC yielded tryptophan **67gb** as a white solid (44 mg, 33%) and diarylated tryptphan **67gbb** as a white solid (11 mg, 7%).

m. p.: 131 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.73 (dd, *J* = 4.9, 0.6 Hz, 2H), 8.31–8.22 (m, 1H), 7.97–7.89 (m, 1H), 7.69–7.62 (m, 1H), 7.33 (ddd, *J* = 4.8, 4.8, 0.6 Hz, 1H), 7.28–7.17 (m, 2H), 7.15–7.06 (dm, *J* = 8.4 Hz, 2H), 6.95–6.84 (dm, *J* = 8.4 Hz, 2H), 4.50 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H), 3.77 (s, 3H), 3.40 (s, 3H), 3.17 (dd, *J* = 14.2, 7.7 Hz, 1H), 3.08 (dd, *J* = 14.2, 7.1 Hz, 1H), 1.75 (s, 3H).

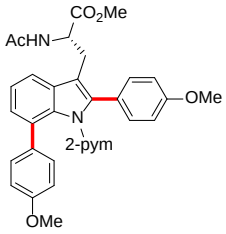
^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.9 (C_q), 169.0 (C_q), 158.6 (CH), 158.4 (C_q), 157.0 (C_q), 137.3 (C_q), 136.0 (C_q), 130.8 (CH), 128.7 (C_q), 124.4 (C_q), 123.1 (CH), 121.4 (CH), 118.8 (CH), 118.3 (CH), 113.5 (CH), 112.6 (C_q), 112.4 (CH), 55.0 (CH_3), 52.6 (CH), 51.6 (CH_3), 26.7 (CH_2), 22.2 (CH_3).

IR (ATR): 3262, 1739, 1653, 1560, 1507, 1455, 1419, 1371, 1344, 1244, 1175, 1026, 833, 745 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 911 (31) $[2M+Na]^+$, 889 (5) $[2M+H]^+$, 467 (100) $[M+Na]^+$, 445 (80) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{25}N_4O_4^+$ 445.1870 $[M+H]^+$, found 445.1870.

Methyl acetyl-1-(2-pyrimidyl)-2,7-di(4-methoxyphenyl)-L-tryptophanate (67gbb)



The general procedure B1 was followed using tryptophan **56g** (101 mg) and 4-bromoanisole (**28b**, 62 mg). Purification by GPC yielded tryptophan **67gb** as a white solid (44 mg, 33%) and diarylated tryptphan **67gbb** as a white solid (11 mg, 7%).

m. p.: 172 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.25 (d, *J* = 4.8 Hz, 2H), 7.67 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.25 (dd, *J* = 7.9, 7.3 Hz, 1H), 7.09–6.96 (m, 4H), 6.85–6.77 (m, 4H), 6.60–6.52 (m, 2H), 4.51 (ddd, *J* = 7.3, 7.3, 7.3 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.44 (s, 3H), 3.21–3.04 (m, 2H), 1.77 (s, 3H).

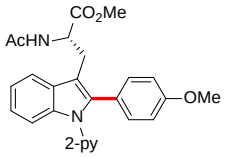
^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.9 (C_q), 169.1 (C_q), 158.7 (C_q), 157.4 (CH), 156.9 (C_q), 139.0 (C_q), 133.6 (C_q), 131.8 (C_q), 131.5 (CH), 129.0 (C_q), 128.7 (CH), 126.6 (C_q), 124.7 (CH), 123.0 (C_q), 120.5 (CH), 118.9 (CH), 117.6 (CH), 113.2 (CH), 113.1 (CH), 110.3 (C_q), 79.13 (C_q), 55.1 (CH_3), 55.0 (CH_3), 52.8 (CH), 51.6 (CH_3), 26.7 (CH_2), 22.4 (CH_3).

IR (ATR): 3255, 1741, 1661, 1515, 1423, 1372, 1345, 1248, 1177, 1023, 830, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1101 (6) $[2M+H]^+$, 573 (31) $[M+Na]^+$, 551 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{32}H_{31}N_4O_5^+$ 551.2289 $[M+H]^+$, found 551.2284.

Methyl acetyl-1-(2-pyridyl)-2-(4-methoxyphenyl)-L-tryptophanate (67hb)



The general procedure B1 was followed using tryptophan **56h** (101 mg) and 4-bromoanisole (**28b**, 62 mg). Purification by GPC yielded tryptophan **67hb** as a white solid (98 mg, 74% and 93 mg, 70% when procedure B2 was followed).

m. p.: 90 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.55 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.64–7.61 (m, 2H), 7.51 (ddd, *J* = 8.1, 7.4, 2.0 Hz, 1H), 7.22–7.17 (m, 2H), 7.16 (dm, *J* = 8.6 Hz, 2H), 7.14–7.12 (m, 1H), 6.84 (dm, *J* = 8.6 Hz, 2H), 6.66 (ddd, *J* = 7.8, 0.9, 0.9 Hz, 1H), 5.79 (d, *J* = 7.8 Hz, 1H), 4.76 (dt, *J* = 7.9, 5.8 Hz, 1H), 3.78 (s, 3H), 3.45 (dd, *J* = 14.7, 5.9 Hz, 1H), 3.40 (dd, *J* = 14.7, 5.9 Hz, 1H), 3.38 (s, 3H), 1.69 (s, 3H).

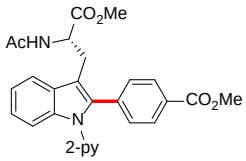
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (C_q), 169.4 (C_q), 159.1 (C_q), 151.6 (C_q), 148.8 (CH), 137.4 (CH), 137.2 (C_q), 136.8 (C_q), 131.6 (CH), 128.7 (C_q), 123.9 (C_q), 123.2 (CH), 121.7 (CH), 121.3 (CH), 121.1 (CH), 118.6 (CH), 114.1 (CH), 111.5 (CH), 110.1 (C_q), 55.3 (CH), 52.7 (CH_3), 52.1 (CH_3), 26.7 (CH_2), 23.0 (CH_3).

IR (ATR): 3053, 2950, 2834, 1739, 1656, 1506, 1455, 1435, 1245, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 466 (100) $[M+Na]^+$, 444 (48) $[M+H]^+$, 313 (6), 250 (5).

HR-MS (ESI) *m/z* calcd for $C_{26}H_{26}N_3O_4^+$ 444.1918 $[M+H]^+$, found 444.1913.

Methyl acetyl-1-(2-pyridyl)-2-(benzoic acid methyl ester-4-yl)-L-tryptophanate (67hd)



The general procedure B1 was followed using tryptophan **56h** (101 mg) and methyl 4-bromobenzoate (**28d**, 71 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hd** as a white solid (99 mg, 70% and 117 mg, 83% when procedure B2 was followed).

m. p.: 100 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.52 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 7.99 (dm, *J* = 8.5 Hz, 2H), 7.67–7.56 (m, 2H), 7.53 (ddd, *J* = 7.8, 1.8, 1.8 Hz, 1H), 7.34 (dm, *J* = 8.5 Hz, 2H), 7.27–7.17 (m, 2H), 7.14 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 6.71 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 5.76 (d, *J* = 7.9 Hz, 1H), 4.79 (dt, *J* = 8.1, 5.7 Hz, 1H), 3.88 (s, 3H), 3.54–3.39 (m, 2H), 3.30 (s, 3H), 1.68 (s, 3H).

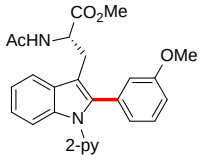
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.8 (C_q), 169.3 (C_q), 166.3 (C_q), 151.2 (C_q), 149.0 (CH), 137.7 (CH), 137.2 (C_q), 136.5 (C_q), 136.2 (C_q), 130.2 (CH), 129.6 (CH), 129.2 (C_q), 128.7 (C_q), 123.8 (CH), 121.6 (CH), 121.6 (CH), 121.3 (CH), 119.1 (CH), 111.6 (C_q), 111.4 (CH), 52.6 (CH), 52.2 (CH_3), 52.1 (CH_3), 26.8 (CH_2), 23.0 (CH_3).

IR (ATR): 3068, 2939, 1740, 1656, 1468, 1455, 1436, 1246, 1176, 744 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 494 (100) $[M+Na]^+$, 472 (26) $[M+H]^+$, 341 (3).

HR-MS (ESI) *m/z* calcd for $C_{27}H_{26}N_3O_5^+$ 472.1867 $[M+H]^+$, found 472.1867.

Methyl acetyl-1-(2-pyridyl)-2-(3-methoxyphenyl)-L-tryptophanate (67he)



The general procedure B2 was followed using tryptophan **56h** (101 mg) and 3-bromoanisole (**28e**, 62 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67he** as a white solid (71 mg, 53%) and diarylated tryptophan **67hee** as a white solid (13 mg, 10%).

m. p.: 88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.70–7.65 (m, 2H), 7.56 (ddd, *J* = 8.1, 7.4, 1.9 Hz, 1H), 7.30–7.22 (m, 3H), 7.18 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H), 6.89–6.83 (m, 2H), 6.81–6.78 (m, 1H), 6.76–6.71 (m, 1H), 5.68 (d, *J* = 7.9 Hz, 1H), 4.85–4.77 (m, 1H), 3.71 (s, 3H), 3.58–3.44 (m, 2H), 3.42 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (C_q), 169.4 (C_q), 159.5 (C_q), 151.6 (C_q), 148.8 (CH), 137.5 (CH), 137.1 (C_q), 137.0 (C_q), 133.0 (C_q), 129.6 (CH), 128.7 (C_q), 123.5 (CH), 122.8 (CH), 121.6 (CH), 121.4

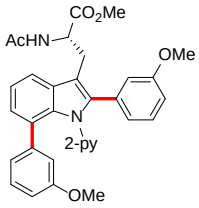
(CH), 121.2 (CH), 118.9 (CH), 115.7 (CH), 113.9 (CH), 111.5 (CH), 110.6 (C_q), 55.3 (CH_3), 52.7 (CH), 52.2 (CH_3), 26.7 (CH_2), 23.0 (CH_3).

IR (ATR): 3053, 2951, 1740, 1658, 1588, 1455, 1434, 1366, 1035, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 443 (6) $[M]^+$, 313 (100), 298 (10), 269 (11), 234 (8), 204 (5).

HR-MS (ESI) *m/z* calcd for $C_{26}H_{26}N_3O_4^+$ 443.1845 $[M]^+$, found 443.1853.

Methyl acetyl-1-(2-pyridyl)-2,7-di(3-methoxyphenyl)-L-tryptophanate (67hee)



The general procedure B2 was followed using tryptophan **56h** (101 mg) and 3-bromoanisole (**28e**, 62 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67he** as a white solid (71 mg, 53%) and diarylated tryptophan **67hee** as a white solid (13 mg, 10%).

m. p.: 110 °C.

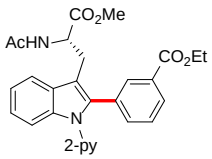
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 7.66 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.29–7.09 (m, 5H), 6.88 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.82 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 6.78–6.70 (m, 2H), 6.70–6.62 (m, 2H), 6.53 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.45 (s, br., 1H), 5.82 (d, *J* = 7.9 Hz, 1H), 4.79 (ddd, *J* = 7.9, 5.7, 5.7 Hz, 1H), 3.60 (s, 3H), 3.59 (s, 3H), 3.52–3.44 (m, 1H), 3.46 (s, 3H), 3.39 (dd, *J* = 14.7, 6.0 Hz, 1H), 1.73 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.2 (C_q), 169.8 (C_q), 159.2 (C_q), 158.5 (C_q), 151.5 (C_q), 147.9 (CH), 141.2 (C_q), 139.3 (C_q), 136.4 (CH), 133.9 (C_q), 132.9 (C_q), 129.6 (C_q), 129.3 (CH), 128.4 (CH), 127.1 (C_q), 125.8 (CH), 123.6 (CH), 123.3 (CH), 121.7 (CH), 121.5 (CH), 120.7 (CH), 118.3 (CH), 116.3 (CH), 114.1 (CH), 113.9 (CH), 112.4 (CH), 109.7 (C_q), 55.3 (CH_3), 55.1 (CH_3), 52.8 (CH), 52.3 (CH_3), 26.7 (CH_2), 23.2 (CH_3).

IR (ATR): 2921, 2852, 1741, 1655, 1584, 1469, 1436, 1410, 1216, 1175, 1036, 782, 743, 700 cm^{-1}.

HR-MS (EI) *m/z* calcd for $C_{33}H_{31}N_3O_5^+$ 549.2264 $[M]^+$, found 549.2279.

Methyl acetyl-1-(2-pyridyl)-2-(benzoic acid ethyl ester-3-yl)-L-tryptophanate (67hf)



The general procedure B2 was followed using tryptophan **56h** (101 mg) and ethyl 3-bromobenzoate (**28f**, 76 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hf** as a white solid (96 mg, 66%).

m. p.: 83 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.53 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.96 (ddd, *J* = 7.2, 1.8, 1.8 Hz, 1H), 7.94–7.92 (m, 1H), 7.67–7.65 (m, 1H), 7.61–7.59 (m, 1H), 7.53 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.41–7.36 (m, 2H), 7.23 (dddd, *J* = 15.0, 7.2, 7.2, 1.2 Hz 2H), 7.14 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 6.74 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 4.80 (dt, *J* = 8.0, 5.8 Hz, 1H), 4.32 (q, *J* = 7.2 Hz,

2H), 3.47 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.42 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.34 (s, 3H), 1.71 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

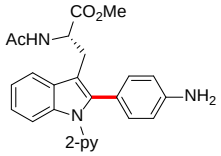
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 (C_q), 169.4 (C_q), 165.7 (C_q), 151.2 (C_q), 149.0 (CH), 137.6 (CH), 137.1 (C_q), 136.3 (C_q), 134.6 (CH), 132.1 (C_q), 131.3 (CH), 130.8 (C_q), 128.8 (CH), 128.6 (C_q), 128.5 (CH), 123.7 (CH), 121.7 (CH), 121.6 (CH), 121.3 (CH), 119.0 (CH), 111.4 (CH), 111.1 (C_q), 61.2 (CH_2), 52.5 (CH), 52.2 (CH_3), 26.8 (CH_2), 23.0 (CH_3), 14.3 (CH_3).

IR (ATR): 3294, 3068, 1715, 1660, 1468, 1455, 1435, 1278, 1244, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 508 (100) $[M+Na]^+$, 486 (34) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{28}N_3O_5^+$ 486.2023 $[M+H]^+$, found 486.2019.

Methyl acetyl-1-(2-pyridyl)-2-(4-anilino)-L-tryptophanate (67hg)



The general procedure B1 was followed using tryptophan **56h** (101 mg) and 4-bromoaniline (**28g**, 57 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hg** as a white solid (99 mg, 77% and 98 mg, 76% when procedure B2 was followed).

m. p.: 189 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.68–7.59 (m, 2H), 7.53 (ddd, *J* = 8.0, 7.4, 2.0 Hz, 1H), 7.24–7.17 (m, 2H), 7.15 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.02 (dm, *J* = 8.6 Hz, 2H), 6.69 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 6.62 (dm, *J* = 8.6 Hz, 2H), 5.67 (d, *J* = 7.7 Hz, 1H), 4.76 (dt, *J* = 7.7, 5.8 Hz, 1H), 3.78 (br s, 2H), 3.49–3.38 (m, 2H), 3.43 (s, 3H), 1.71 (s, 3H).

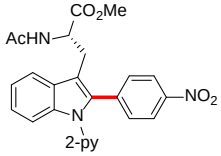
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1 (C_q), 169.5 (C_q), 151.7 (C_q), 148.7 (CH), 146.2 (C_q), 137.8 (C_q), 137.4 (CH), 136.7 (C_q), 131.5 (CH), 128.8 (C_q), 123.0 (CH), 121.8 (CH), 121.2 (C_q), 121.2 (CH), 121.0 (CH), 118.5 (CH), 115.0 (CH), 111.5 (CH), 109.6 (C_q), 52.8 (CH), 52.1 (CH_3), 26.6 (CH_2), 23.0 (CH_3).

IR (ATR): 3449, 3356, 2922, 1734, 1630, 1466, 1456, 1434, 1367, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 451 (69) $[M+Na]^+$, 429 (100) $[M+H]^+$, 298 (6).

HR-MS (ESI) *m/z* calcd for $C_{25}H_{25}N_4O_3^+$ 429.1921 $[M+H]^+$, found 429.1926.

Methyl acetyl-1-(2-pyridyl)-2-(4-nitrophenyl)-L-tryptophanate (67hi)



The general procedure B1 was followed using tryptophan **56h** (101 mg) and 1-bromo-4-nitrobenzene (**28i**, 67 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hi** as a yellow solid (14 mg, 10% and 25 mg, 18% when procedure B2 was followed).

m. p.: 91 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 8.20–8.16 (dm, *J* = 8.5 Hz, 2H), 7.69 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.65 (ddd, *J* = 8.0, 7.5, 1.9 Hz, 1H), 7.61–7.58 (m, 1H), 7.46–7.42 (dm, *J* =

8.5 Hz, 2H), 7.32–7.26 (m, 2H), 7.25–7.20 (m, 1H), 6.88 (dt, *J* = 8.0, 1.0 Hz, 1H), 5.83 (d, *J* = 7.9 Hz, 1H), 4.84 (ddd, *J* = 8.0, 6.6, 5.5 Hz, 1H), 3.54–3.42 (m, 2H), 3.36 (s, 3H), 1.76 (s, 3H).

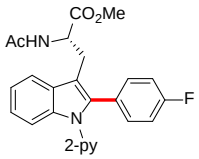
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.2 (C_q), 169.6 (C_q), 151.2 (C_q), 149.6 (CH), 147.0 (C_q), 139.0 (C_q), 138.3 (CH), 137.7 (C_q), 135.2 (C_q), 131.2 (CH), 128.9 (C_q), 124.6 (CH), 123.8 (CH), 122.2 (CH), 121.9 (CH), 121.7 (CH), 119.6 (CH), 112.9 (C_q), 111.6 (CH), 52.8 (CH), 52.4 (CH_3), 27.2 (CH_2), 23.2 (CH_3).

IR (ATR): 2923, 1739, 1657, 1589, 1513, 1468, 1454, 1435, 1340, 1212, 1106, 854, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 939 (10) $[2M+Na]^+$, 917 (1) $[2M+H]^+$, 481 (97) $[M+Na]^+$, 459 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{23}N_4O_5^+$ 459.1663 $[M+H]^+$, found 459.1662.

Methyl acetyl-1-(2-pyridyl)-2-(4-fluorophenyl)-L-tryptophanate (67hk)



The general procedure B1 was followed using tryptophan **56h** (101 mg) and 1-bromo-4-fluorobenzene (**28k**, 58 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hk** as a white solid (106 mg, 82% and 123 mg, 95% when procedure B2 was followed).

m. p.: 102 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59–8.56 (m, 1H), 7.67–7.56 (m, 3H), 7.28–7.22 (m, 4H), 7.21–7.17 (m, 1H), 7.07–7.01 (m, 2H), 6.75–6.71 (m, 1H), 5.74 (d, *J* = 8.0 Hz, 1H), 4.81 (dt, *J* = 8.0, 5.8 Hz, 1H), 3.51–3.39 (m, 2H), 3.38 (s, 3H), 1.74 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (C_q), 169.5 (C_q), 162.3 (d, $^1J_{CF}$ = 248.9 Hz, C_q), 151.4 (C_q), 149.0 (CH), 137.9 (CH), 137.0 (C_q), 136.4 (C_q), 132.3 (d, $^3J_{CF}$ = 8.1 Hz, CH), 128.8 (C_q), 127.9 (d, $^4J_{CF}$ = 3.6 Hz, C_q), 123.6 (CH), 121.8 (CH), 121.7 (CH), 121.4 (CH), 119.0 (CH), 115.7 (d, $^2J_{CF}$ = 21.6 Hz, CH), 111.5 (CH), 110.7 (C_q), 52.6 (CH), 52.2 (CH_3), 26.7 (CH_2), 23.0 (CH_3).

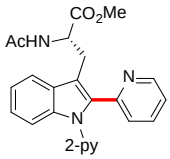
^{19}F NMR (376 MHz, $CDCl_3$): δ = –112.9 (m).

IR (ATR): 3053, 2951, 1740, 1655, 1504, 1468, 1455, 1435, 1156, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 454 (100) $[M+Na]^+$, 432 (24) $[M+H]^+$, 301 (3).

HR-MS (ESI) *m/z* calcd for $C_{25}H_{23}FN_3O_3^+$ 432.1718 $[M+H]^+$, found 432.1711.

Methyl acetyl-1,2-di(2-pyridyl)-L-tryptophanate (67hm)



The general procedure B1 was followed using tryptophan **56h** (101 mg) and 2-bromopyridine (**28m**, 52 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hm** as a white solid (118 mg, 95% and 20 mg, 16% when procedure B2 was followed).

m. p.: 111 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.88 (d, *J* = 4.7 Hz, 1H), 8.72 (ddd, *J* = 5.0, 1.8, 1.0 Hz, 1H), 8.58 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.76–7.66 (m, 2H), 7.61 (ddd, *J* = 8.0, 7.4, 1.9 Hz, 1H), 7.51 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.33–7.22 (m, 3H), 7.20 (ddd, *J* = 7.2, 4.8, 0.9 Hz, 1H), 6.89 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 6.81 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 4.65 (ddd, *J* = 11.0, 4.8, 3.3 Hz, 1H), 3.76 (s, 3H), 3.36 (dd, *J* = 14.1, 3.4 Hz, 1H), 3.17 (dd, *J* = 14.1, 11.0 Hz, 1H), 2.02 (s, 3H).

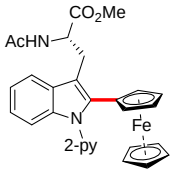
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9 (C_q), 170.4 (C_q), 151.7 (C_q), 150.2 (C_q), 149.2 (CH), 148.6 (CH), 137.8 (CH), 137.7 (C_q), 136.3 (CH), 135.4 (C_q), 128.2 (C_q), 125.9 (CH), 124.6 (CH), 122.3 (CH), 121.7 (CH), 121.6 (CH), 121.4 (CH), 119.4 (CH), 115.0 (C_q), 111.7 (CH), 54.0 (CH), 52.3 (CH_3), 26.1 (CH_2), 22.9 (CH_3).

IR (ATR): 3022, 1746, 1671, 1588, 1551, 1468, 1455, 1434, 1365, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 437 (100) $[M+Na]^+$, 415 (38) $[M+H]^+$, 284 (2), 236 (3).

HR-MS (ESI) *m/z* calcd for $C_{24}H_{23}N_4O_3^+$ 415.1765 $[M+H]^+$, found 415.1763.

Methyl acetyl-1-(2-pyridyl)-2-ferrocenyl-L-tryptophanate (67hc)



The general procedure B2 was followed using tryptophan **56h** (101 mg) and iodoferrocene (**66c**, 140 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hc** as a yellow solid (26 mg, 17% and 81 mg, 52% when procedure B2 was followed and 20 mol % $[Ru]_2$ and 120 mol % $F_5C_6CO_2H$ were used).

m. p.: 128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.68 (ddd, *J* = 8.0, 7.4, 2.0 Hz, 1H), 7.59–7.52 (m, 1H), 7.42–7.36 (m, 1H), 7.27 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 7.19–7.11 (m, 2H), 6.90 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 6.19 (d, *J* = 7.6 Hz, 1H), 4.95 (q, *J* = 7.3 Hz, 1H), 4.29–4.23 (m, 2H), 4.23–4.18 (m, 2H), 3.98 (s, 5H), 3.73 (d, *J* = 7.2 Hz, 2H), 3.59 (s, 3H), 1.95 (s, 3H).

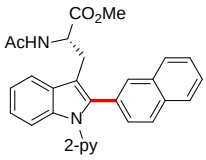
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9 (C_q), 169.6 (C_q), 152.4 (C_q), 149.0 (CH), 137.8 (C_q), 137.6 (CH), 135.1 (C_q), 129.2 (C_q), 122.9 (CH), 122.7 (CH), 122.0 (CH), 121.0 (CH), 117.9 (CH), 110.8 (CH), 110.8 (C_q), 69.7 (CH), 69.6 (CH), 69.5 (CH), 68.4 (CH), 68.3 (CH), 53.3 (CH), 52.4 (CH_3), 29.0 (CH_2), 23.3 (CH_3).

IR (ATR): 3284, 3054, 2952, 1738, 1651, 1468, 1435, 1367, 1208, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 544 (93) $[M+Na]^+$, 522 (100) $[M+H]^+$, 434 (9), 391 (9).

HR-MS (ESI) *m/z* calcd for $C_{29}H_{28}FeN_3O_3^+$ 522.1475 $[M+H]^+$, found 522.1473.

Methyl acetyl-1-(2-pyridyl)-2-(2-naphthyl)-L-tryptophanate (67ho)



The general procedure B1 was followed using tryptophan **56h** (101 mg) and 2-bromonaphthalene (**28o**, 68 mg). Purification by column chromatography (EtOAc)

yielded tryptophan **67ho** as a white solid (78 mg, 56% and 121 mg, 87% when procedure B2 was followed) and diarylated tryptophan **67hoo** was isolated as a white solid (20 mg, 11% when procedure B1 was followed).

m. p.: 113 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.86–7.66 (m, 5H), 7.52 (ddd, *J* = 6.2, 3.4, 3.4 Hz, 1H), 7.45 (ddd, *J* = 8.0, 7.4, 2.0 Hz, 1H), 7.33–7.21 (m, 5H), 7.13 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 6.73 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 5.68 (d, *J* = 8.0 Hz, 1H), 4.82 (dt, *J* = 8.0, 5.7 Hz, 1H), 3.55 (ddd, *J* = 18.6, 14.7, 5.7 Hz, 2H), 3.21 (s, 3H), 1.59 (s, 3H).

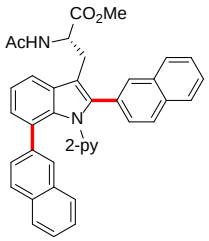
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 (C_q), 169.4 (C_q), 151.5 (C_q), 148.9 (CH), 137.6 (CH), 137.2 (C_q), 137.1 (C_q), 133.1 (C_q), 132.4 (C_q), 129.5 (CH), 129.2 (C_q), 128.8 (C_q), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 126.6 (CH), 126.5 (CH), 123.5 (CH), 121.6 (CH), 121.4 (CH), 121.2 (CH), 118.9 (CH), 111.5 (CH), 111.1 (C_q), 52.7 (CH), 52.0 (CH_3), 26.8 (CH_2), 22.9 (CH_3).

IR (ATR): 3285, 3035, 2939, 1737, 1652, 1468, 1453, 1434, 1367, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 486 (100) $[M+Na]^+$, 464 (49) $[M+H]^+$, 333 (3).

HR-MS (ESI) *m/z* calcd for $C_{29}H_{26}N_3O_3^+$ 464.1969 $[M+H]^+$, found 464.1968.

Methyl acetyl-1-(2-pyridyl)-2,7-di(2-naphthyl)-L-tryptophanate (67hoo)



The general procedure B1 was followed using tryptophan **56h** (101 mg) and 2-bromonaphthalene (**28o**, 68 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67ho** as a white solid (78 mg, 56% and 121 mg, 87% when procedure B2 was followed) and diarylated tryptophan **67hoo** was isolated as a white solid (20 mg, 11% when procedure B1 was followed).

m. p.: 133 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.68 (m, 5H), 7.67–7.59 (m, 2H), 7.59–7.51 (m, 1H), 7.51–7.42 (m, 3H), 7.42–7.27 (m, 5H), 7.19–7.10 (m, 2H), 6.85 (ddd, *J* = 7.6, 7.6, 1.9 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 6.41–6.33 (m, 1H), 5.72 (d, *J* = 7.9 Hz, 1H), 4.84 (ddd, *J* = 8.0, 5.7, 5.7 Hz, 1H), 3.58 (dd, *J* = 14.7, 5.6 Hz, 1H), 3.48 (dd, *J* = 14.7, 5.9 Hz, 1H), 3.29 (s, 3H), 1.67 (s, 3H).

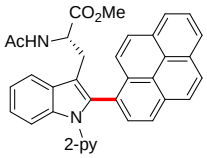
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.3 (C_q), 169.8 (C_q), 151.5 (C_q), 148.0 (CH), 139.5 (C_q), 137.4 (C_q), 136.4 (CH), 134.5 (C_q), 133.1 (C_q), 132.8 (C_q), 132.6 (C_q), 131.7 (C_q), 130.4 (CH), 129.9 (C_q), 129.2 (C_q), 128.2 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.2 (C_q), 127.2 (CH), 126.8 (CH), 126.8 (CH), 126.7 (CH), 126.3 (CH), 125.9 (CH), 125.7 (CH), 123.8 (CH), 121.6 (CH), 120.9 (CH), 118.5 (CH), 110.2 (C_q), 52.9 (CH), 52.2 (CH_3), 26.8 (CH_2), 23.1 (CH_3).

IR (ATR): 2921, 2852, 1737, 1655, 1467, 1436, 1415, 1220, 1196, 1176, 1130, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1201 (2) $[2M+Na]^+$, 1179 (2) $[2M+H]^+$, 612 (31) $[M+Na]^+$, 590 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{39}H_{32}N_3O_3^+$ 590.2438 $[M+H]^+$, found 590.2434.

Methyl acetyl-1-(2-pyridyl)-2-(1-pyrenyl)-L-tryptophanate (67hp)



The general procedure B1 was followed using tryptophan **56h** (101 mg) and 1-bromopyrene (**28p**, 93 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hp** as a white solid (52 mg, 32% and 21 mg, 13% when procedure B2 was followed).

Due to formation of rotamers, the NMR spectra show a double set of signals.

m. p.: 156 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.46 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.43 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.25–8.12 (m, 3H), 8.11–8.00 (m, 10H), 7.97–7.89 (m, 4H), 7.85–7.79 (m, 4H), 7.77–7.74 (m, 1H), 7.38–7.28 (m, 6H), 7.12 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 2H), 6.91 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 6.88 (ddd, *J* = 7.7, 4.9, 1.0 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 6.48 (d, *J* = 8.1 Hz, 1H), 5.47 (d, *J* = 7.8 Hz, 1H), 5.42 (d, *J* = 7.6 Hz, 1H), 4.75–4.67 (m, 2H), 3.55 (dd, *J* = 14.9, 5.2 Hz, 1H), 3.40 (dd, *J* = 14.8, 6.9 Hz, 1H), 3.33 (dd, *J* = 14.8, 5.5 Hz, 1H), 3.25 (dd, *J* = 14.8, 5.5 Hz, 1H), 3.21 (d, *J* = 6.9 Hz, 7H), 1.19 (s, 6H).

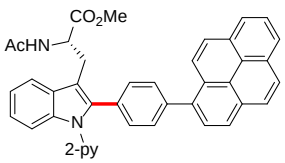
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.1 (C_q), 172.0 (C_q), 169.7 (C_q), 169.5 (C_q), 151.5 (C_q), 151.5 (C_q), 148.9 (CH), 148.9 (CH), 137.6 (CH), 137.3 (CH), 136.2 (C_q), 136.0 (C_q), 131.7 (C_q), 131.6 (C_q), 131.3 (C_q), 131.3 (C_q), 130.9 (C_q), 130.8 (C_q), 130.4 (C_q), 130.4 (C_q), 129.5 (CH), 129.5 (CH), 129.0 (CH), 129.0 (CH), 128.9 (CH), 128.8 (C_q), 128.7 (C_q), 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.5 (CH), 127.5 (CH), 126.6 (CH), 126.5 (CH), 126.4 (C_q), 126.2 (C_q), 125.9 (CH), 125.8 (CH), 125.7 (CH), 125.7 (CH), 124.9 (CH), 124.8 (CH), 124.8 (CH), 124.7 (CH), 124.5 (C_q), 124.4 (C_q), 123.9 (CH), 123.9 (CH), 121.6 (CH), 121.5 (CH), 121.4 (CH), 121.3 (CH), 120.8 (CH), 120.6 (CH), 119.2 (CH), 119.1 (CH), 112.8 (C_q), 112.6 (C_q), 112.1 (CH), 112.0 (CH), 52.7 (CH), 52.6 (CH), 52.2 (CH_3), 52.1 (CH_3), 27.3 (CH_2), 27.0 (CH_2), 22.9 (CH_3), 22.5 (CH_3).

IR (ATR): 2921, 1736, 1654, 1569, 1467, 1455, 1434, 1368, 1212, 849, 723 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1097 (3) $[2M+Na]^+$, 1075 (3) $[2M+H]^+$, 560 (63) $[M+Na]^+$, 538 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{35}H_{28}N_3O_3^+$ 538.2125 $[M+H]^+$, found 538.2128.

Methyl acetyl-1-(2-pyridyl)-2-[4-(1-pyrenyl)phenyl]-L-tryptophanate (67hq)



The general procedure B1 was followed using tryptophan **56h** (101 mg) and 1-(4-iodophenyl)pyrene (**66q**, 133 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hq** as a white solid (94 mg, 51% and 136 mg, 74% when procedure B2 was followed).

m. p.: 123 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 8.24–8.18 (m, 3H), 8.16–8.06 (m, 4H), 8.03 (ddd, *J* = 7.6, 0.8, 0.8 Hz, 1H), 7.96 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.72 (dddd, *J* = 8.3, 2.0, 2.0, 0.9 Hz, 2H), 7.65 (ddd, *J* = 8.1, 7.5, 2.0 Hz, 1H), 7.63 (dm, *J* = 7.8 Hz, 2H), 7.46 (dm, *J* = 7.8 Hz, 2H), 7.32–7.24 (m, 3H), 6.87 (dddd, *J* = 8.1, 0.9, 0.9, 0.9 Hz, 1H), 5.86 (d, *J* = 7.9 Hz, 1H), 4.90 (dt, *J* = 7.9, 5.4 Hz, 1H), 3.66 (dd, *J* = 15.0, 5.4 Hz, 1H), 3.61 (dd, *J* = 15.0, 5.4 Hz, 1H), 3.48 (s, 3H), 1.79 (s, 3H).

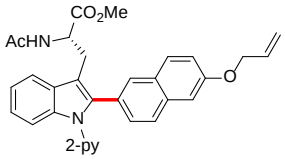
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (C_q), 169.6 (C_q), 151.7 (C_q), 149.1 (CH), 140.8 (C_q), 137.6 (CH), 137.3 (C_q), 137.2 (C_q), 136.6 (C_q), 131.5 (C_q), 130.9 (C_q), 130.8 (CH), 130.8 (C_q), 130.5 (CH), 129.0 (C_q), 128.4 (C_q), 127.8 (CH), 127.6 (CH), 127.4 (CH), 127.4 (CH), 126.1 (CH), 125.3 (CH), 125.0 (C_q), 125.0 (CH), 124.9 (C_q), 124.7 (CH), 124.7 (CH), 123.6 (CH), 121.9 (CH), 121.6 (CH), 121.4 (CH), 119.0 (CH), 111.6 (CH), 110.8 (C_q), 52.7 (CH), 52.2 (CH_3), 26.7 (CH_2), 23.1 (CH_3).

IR (ATR): 3043, 1737, 1660, 1587, 1467, 1454, 1434, 1367, 1210, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 636 (26) $[M+Na]^+$, 614 (33) $[M+H]^+$, 533 (30), 437 (85), 415 (100).

HR-MS (ESI) *m/z* calcd for $C_{41}H_{32}N_3O_3^+$ 614.2438 $[M+H]^+$, found 614.2427.

Methyl acetyl-1-(2-pyridyl)-2-[2-(6-allyloxy)naphthalyl]-L-tryptophanate (67hu)



The general procedure B2 was followed using tryptophan **56h** (101 mg) and 2-(allyloxy)-6-bromonaphthalene (**28u**, 87 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hu** as a white solid (39 mg, 25% and 56 mg, 36% when procedure B2 was followed and 10 mol % $[Ru]_2$ was used).

m. p.: 98 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.78–7.60 (m, 5H), 7.44 (ddd, *J* = 7.8, 7.8, 1.9 Hz, 1H), 7.29–7.16 (m, 4H), 7.12 (ddd, *J* = 5.2, 5.2, 1.9 Hz, 2H), 6.71 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.12 (dddd, *J* = 17.4, 10.5, 5.3, 5.3 Hz, 1H), 5.71 (d, *J* = 7.7 Hz, 1H), 5.53–5.42 (m, 1H), 5.37–5.30 (m, 1H), 4.81 (ddd, *J* = 7.9, 5.6, 5.6 Hz, 1H), 4.65 (ddd, *J* = 5.3, 1.5, 1.5 Hz, 2H), 3.62–3.44 (m, 2H), 3.23 (s, 3H), 1.59 (s, 3H).

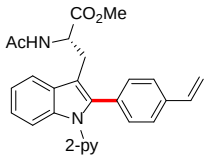
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.0 (C_q), 169.5 (C_q), 157.2 (C_q), 151.7 (C_q), 149.0 (CH), 137.7 (CH), 137.5 (C_q), 137.2 (C_q), 133.8 (C_q), 133.0 (CH), 133.0 (CH), 129.6 (CH), 129.5 (CH), 129.0 (C_q), 128.7 (C_q), 128.4 (CH), 127.1 (CH), 127.0 (C_q), 123.5 (CH), 121.8 (CH), 121.4 (CH), 121.3 (CH), 119.8 (CH), 118.9 (CH), 118.0 (CH_2), 111.7 (CH), 110.9 (C_q), 106.9 (CH), 69.0 (CH_2), 52.8 (CH), 52.1 (CH_3), 26.9 (CH_2), 23.0 (CH_3).

IR (ATR): 3296, 3039, 1735, 1647, 1627, 1606, 1589, 1468, 1455, 1435, 1367, 1204, 993, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1061 (24) $[2M+Na]^+$, 542 (100) $[M+Na]^+$, 520 (59) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{32}H_{30}N_3O_4^+$ 520.2231 $[M+H]^+$, found 520.2228.

Methyl acetyl-1-(2-pyridyl)-2-(4-styryl)-L-tryptophanate (67hv)



The general procedure B2 was followed using tryptophan **56h** (101 mg) and 4-bromostyrene (**28v**, 93 mg). Purification by column chromatography (EtOAc) yielded tryptophan **67hv** as a white solid (96 mg, 74%).

m. p.: 161 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.66–7.58 (m, 2H), 7.51 (ddd, *J* = 7.8, 7.8, 1.9 Hz, 1H), 7.38–7.30 (m, 2H), 7.26–7.09 (m, 6H), 6.72–6.58 (m, 2H), 5.73 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.26 (dd, *J* = 10.9, 0.7 Hz, 1H), 4.78 (ddd, *J* = 8.0, 5.7, 5.7 Hz, 1H), 3.55–3.39 (m, 2H), 3.33 (s, 3H), 1.66 (s, 3H).

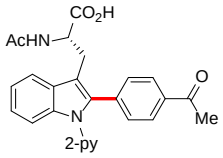
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.0 (C_q), 169.6 (C_q), 151.6 (C_q), 149.0 (CH), 137.7 (CH), 137.2 (C_q), 137.1 (C_q), 137.1 (C_q), 136.1 (CH), 131.2 (C_q), 130.6 (CH), 128.9 (C_q), 126.4 (CH), 123.6 (CH), 121.8 (CH), 121.6 (CH), 121.3 (CH), 119.0 (CH), 114.8 (CH_2), 111.6 (CH), 110.8 (C_q), 52.8 (CH), 52.2 (CH_3), 26.8 (CH_2), 23.1 (CH_3).

IR (ATR): 1734, 1654, 1469, 1456, 1435, 1367, 1212, 728 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 901 (22) $[2M+Na]^+$, 879 (2) $[2M+H]^+$, 462 (100) $[M+Na]^+$, 440 (83) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{27}H_{26}N_3O_3^+$ 440.1969 $[M+H]^+$, found 440.1959.

Acetyl-1-(2-pyridyl)-2-(4-acetylphenyl)-L-tryptophan (67jl)



The general procedure B1 was followed using tryptophan **56j** (48 mg) and 4-bromoacetophenone (**28l**, 32 mg). H_2O/MeCN (1:1, 1.5 mL) was used instead of *m*-xylene. After cooling to ambient temperature, HCl (12 M, 1 mL) was added to the reaction mixture and the water phase was extracted with EtOAc (3×10 mL). The organic layers were combined and the solvent was removed in vacuum. Purification by column chromatography (CH_2Cl_2/HOAc 5:1) yielded tryptophan **67jl** as a white solid (41 mg, 63%).

m. p.: 167 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.52 (d, *J* = 4.6 Hz, 1H), 8.01 (d, *J* = 7.1 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.76 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.29 (dd, *J* = 7.3, 4.8 Hz, 1H), 7.24–7.09 (m, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 4.53–4.33 (m, 1H), 3.27–3.11 (m, 1H), 3.02–2.87 (m, 1H), 2.55 (s, 3H), 1.67 (s, 1H).

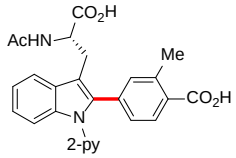
^{13}C NMR (126 MHz, DMSO-d_6): δ = 197.7 (C_q), 168.3 (C_q), 151.6 (C_q), 149.3 (CH), 138.6 (CH), 137.5 (C_q), 137.0 (C_q), 135.7 (C_q), 135.4 (C_q), 130.6 (CH), 129.4 (C_q), 128.2 (CH), 123.3 (CH), 122.1 (CH), 121.7 (CH), 120.9 (CH), 120.8 (CH), 116.6 (C_q), 111.2 (CH), 55.2 (CH), 29.5 (CH_2), 27.1 (CH_3), 23.4 (CH_3).

IR (ATR): 2954, 2924, 2853, 1706, 1469, 1455, 1435, 1365, 1162, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 905 (15) $[2M+Na]^+$, 464 (100) $[M+Na]^+$, 442 (22) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{24}N_3O_4^+$ 442.1767 $[M+H]^+$, found 442.1770.

Acetyl-1-(2-pyridyl)-2-(3-methyl-benzoic acid-4-yl)-L-tryptophan (67jβ)



The general procedure B1 was followed using tryptophan **56j** (48 mg) and 4-bromo-2-methylbenzoic acid (**28β**, 35 mg). After cooling to ambient temperature, HCl (12 M, 1 mL) was added and the solvent was removed in vacuum. Purification by column chromatography (first column EtOAc/THF/HOAc 12:2:1, followed by second column CH_2Cl_2/HOAc 6:1) yielded tryptophan **67jβ** as a white solid (42 mg, 61%).

m. p.: 210 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.55 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.73 (td, *J* = 7.7, 1.9 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.27 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.18–7.09 (m, 4H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.51 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 1H), 3.20 (dd, *J* = 14.2, 5.8 Hz, 1H), 2.96 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.41 (s, 3H), 1.69 (s, 3H).

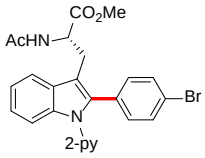
^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.6 (C_q), 168.0 (C_q), 151.3 (C_q), 148.6 (CH), 137.9 (CH), 136.7 (C_q), 136.5 (C_q), 136.3 (C_q), 132.1 (CH), 131.8 (C_q), 128.8 (C_q), 126.8 (CH), 122.4 (CH), 121.4 (CH), 121.3 (CH), 120.2 (CH), 119.9 (CH), 114.2 (C_q), 110.9 (CH), 54.7 (CH), 28.6 (CH_2), 22.7 (CH_3), 21.9 (CH_3).

IR (ATR): 3390, 2918, 2850, 1576, 1469, 1455, 1436, 1394, 1365, 1285, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 937 (13) $[2M+Na]^+$, 480 (100) $[M+Na]^+$, 458 (40) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{24}N_3O_5^+$ 458.1710 $[M+H]^+$, found 458.1708.

Methyl acetyl-1-(2-pyridyl)-2-(4-bromophenyl)-L-tryptophanate (67hγ)



The general procedure B1 was followed using tryptophan **56h** (200 mg) and 1,4-dibromobenzene (**28γ**, 154 mg) in 4 mL *m*-xylene. Purification by column chromatography yielded tryptophan **67hγ** as a white solid (51 mg, 17%).

m. p.: 103 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.57–8.53 (m, 1H), 7.63 (ddd, *J* = 6.9, 1.3, 1.3 Hz, 1H), 7.60–7.55 (m, 2H), 7.44 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.25–7.20 (m, 2H), 7.20–7.16 (m, 1H), 7.13–7.09 (m, 2H), 6.73 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 4.83–4.75 (m, 1H), 3.46 (ddd, *J* = 14.7, 6.1, 1.1 Hz, 1H), 3.41 (ddd, *J* = 14.7, 5.3, 1.1 Hz, 1H), 3.34 (d, *J* = 1.1 Hz, 3H), 1.71 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.2 (C_q), 169.7 (C_q), 151.4 (C_q), 149.3 (CH), 138.1 (CH), 137.3 (C_q), 136.3 (C_q), 132.1 (CH), 132.0 (CH), 131.0 (C_q), 129.0 (C_q), 123.9 (CH), 122.4 (C_q), 121.9 (CH), 121.9 (CH), 121.6 (CH), 119.2 (CH), 111.6 (CH), 111.2 (C_q), 52.7 (CH), 52.3 (CH_3), 26.8 (CH_2), 23.2 (CH_3).

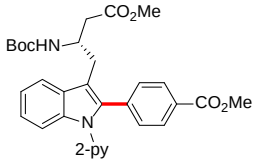
IR (ATR): 2952, 2922, 1740, 1653, 1468, 1454, 1435, 1368, 1212, 1009, 742, 729 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1009/1007 (36) $[2M+Na]^+$, 987/985 (2) $[2M+H]^+$, 516/514 (81) $[M+Na]^+$, 494/492 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{23}{}^{79}BrN_3O_3{}^+$ 492.0917 $[M+H]^+$, found 492.0912.

5.3.3 Analytical Data for Arylated β³-*homo*-Tryptophans 121

Methyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-(benzoic acid methyl ester-4-yl)-β³-*homo*-L-tryptophanate (121ad)



The general procedure B2 was followed using tryptophan **120a** (100 mg) and methyl 4-bromobenzoate (**28d**, 58 mg). Purification by column chromatography (hexanes/EtOAc 1:1) yielded tryptophan **121ad** as a white solid (72 mg, 54%).

m. p.: 96 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.56–8.47 (m, 1H), 7.95 (dm, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 6.5 Hz, 1H), 7.63 (ddd, *J* = 6.9, 2.3, 2.3 Hz, 1H), 7.53 (ddd, *J* = 7.8, 7.8, 1.9 Hz, 1H), 7.31 (dm, *J* = 8.3 Hz, 2H), 7.27–7.19 (m, 2H), 7.13 (dd, *J* = 7.4, 4.9 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.13–5.02 (m, 1H), 4.36–4.22 (m, 1H), 3.89 (s, 3H), 3.37 (s, 3H), 3.28–3.17 (m, 1H), 3.12 (dd, *J* = 13.9, 8.3 Hz, 1H), 2.37–2.19 (m, 2H), 1.34 (s, 9H).

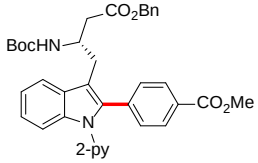
^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5 (C_q), 155.0 (C_q), 151.4 (C_q), 149.0 (CH), 137.6 (CH), 137.4 (C_q), 136.6 (C_q), 135.9 (C_q), 135.2 (C_q), 130.3 (CH), 129.7 (CH), 129.5 (CH), 129.0 (C_q), 128.5 (C_q), 123.8 (CH), 121.4 (CH), 121.4 (CH), 119.8 (CH), 113.8 (C_q), 111.3 (CH), 79.1 (C_q), 52.2 (CH_3), 51.4 (CH_3), 48.0 (CH), 37.0 (CH_2), 29.4 (CH_2), 28.3 (CH_3).

IR (ATR): 2954, 2924, 2853, 1706, 1469, 1455, 1435, 1365, 1162, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 566 (100) $[M+Na]^+$, 544 (62) $[M+H]^+$, 488 (57), 432 (33).

HR-MS (ESI) *m/z* calcd for $C_{31}H_{34}N_3O_6{}^+$ 544.2442 $[M+H]^+$, found 544.2448.

Benzyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-(benzoic acid methyl ester-4-yl)-β³-*homo*-L-tryptophanate (121bd)



The general procedure B2 was followed using tryptophan **120b** (100 mg) and methyl 4-bromobenzoate (**28d**, 58 mg). Purification by column chromatography (hexanes/EtOAc 1:1) yielded tryptophan **121bd** as a white solid (52 mg, 32% and 21 mg, 13% when procedure B2 was followed).

m. p.: 92 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.98–7.92 (m, 2H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.54 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.35–7.29 (m, 4H), 7.29–7.20 (m, 3H), 7.17–7.13 (m, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 5.01 (d, *J* = 9.2 Hz, 1H), 4.93 (d, *J* = 12.3 Hz, 1H), 4.80 (d, *J* =

12.4 Hz, 1H), 4.33 (ddd, *J* = 8.2, 8.2, 3.7 Hz, 1H), 3.90 (s, 3H), 3.26–3.10 (m, 2H), 2.45–2.31 (m, 2H), 1.35 (s, 9H).

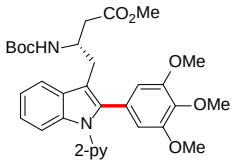
^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.6 (C_q), 166.8 (C_q), 155.2 (C_q), 151.6 (C_q), 149.3 (CH), 137.9 (CH), 137.6 (C_q), 136.9 (C_q), 136.1 (C_q), 135.7 (C_q), 130.5 (CH), 129.8 (CH), 129.3 (C_q), 128.8 (C_q), 128.7 (CH), 128.3 (CH), 128.2 (CH), 124.0 (CH), 121.7 (CH), 121.6 (CH), 120.0 (CH), 114.1 (C_q), 111.5 (CH), 79.3 (C_q), 66.3 (CH_2), 52.4 (CH_3), 48.2 (CH), 37.5 (CH_2), 29.4 (CH_2), 28.4 (CH_3).

IR (ATR): 2979, 1716, 1469, 1455, 1436, 1364, 1275, 1163, 1103, 770, 742, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1261 (2) $[2M+Na]^+$, 1239 (2) $[2M+H]^+$, 642 (100) $[M+Na]^+$, 620 (51) $[M+H]^+$, 564 (45) $[M–Hpy+Na]^+$, 520 (16) $[M–Boc+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{37}H_{38}N_3O_6^+$ 620.2755 $[M+H]^+$, found 620.2752.

Methyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-(3,4,5-trimethoxyphenyl)-β^3-*homo*-L-tryptophanate (121ax)



The general procedure B2 was followed using tryptophan **120a** (100 mg) and 5-bromo-1,2,3-trimethoxybenzene (**28x**, 67 mg). Purification by column chromatography (hexanes/EtOAc 1:1) yielded tryptophan **121ax** as a white solid (67 mg, 48%).

m. p.: 87 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.59 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.81 (d, *J* = 6.7 Hz, 1H), 7.69–7.61 (m, 1H), 7.56 (ddd, *J* = 7.8, 7.8, 2.0 Hz, 1H), 7.30–7.20 (m, 2H), 7.17 (dd, *J* = 7.4, 5.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.46 (s, 2H), 5.18–5.08 (m, 1H), 4.31 (dddd, *J* = 8.8, 7.0, 7.0, 3.8 Hz, 1H), 3.86 (s, 3H), 3.69 (s, 6H), 3.45 (s, 3H), 3.25–3.18 (m, 2H), 2.38–2.33 (m, 2H), 1.38 (s, 9H).

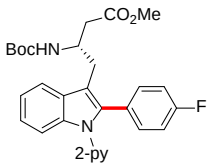
^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.2 (C_q), 153.1 (C_q), 152.1 (C_q), 148.9 (CH), 137.7 (CH), 137.6 (C_q), 137.1 (C_q), 128.7 (C_q), 127.1 (C_q), 123.5 (CH), 121.7 (CH), 121.4 (CH), 119.6 (CH), 112.6 (C_q), 111.5 (CH), 107.9 (CH), 61.1 (CH_3), 56.3 (CH_3), 51.5 (CH), 48.2 (CH_2), 37.2 (CH_2), 28.5 (CH_3).

IR (ATR): 2938, 1704, 1585, 1502, 1457, 1436, 1237, 1163, 1123, 1004, 744 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1173 (32) $[2M+Na]^+$, 1151 (15) $[2M+H]^+$, 598 (100) $[M+Na]^+$, 576 (89) $[M+H]^+$, 520 (84), 476 (31) $[M–Boc+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{32}H_{38}N_3O_7^+$ 576.2704 $[M+H]^+$, found 576.2699.

Methyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-(4-fluorophenyl)-β^3-*homo*-L-tryptophanate (121ak)



The general procedure B2 was followed using tryptophan **120a** (100 mg) and 1-bromo-4-fluorobenzene (**28k**, 47 mg). Purification by column chromatography (hexanes/EtOAc 1:1) yielded tryptophan **121ak** as a white solid (109 mg, 89%).

m. p.: 75 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59–8.54 (m, 1H), 7.86–7.78 (m, 1H), 7.69–7.61 (m, 1H), 7.56 (ddd, *J* = 7.8, 7.8, 1.9 Hz, 1H), 7.30–7.20 (m, 4H), 7.16 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.06–6.97 (m, 2H), 6.75 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.10 (d, *J* = 9.3 Hz, 1H), 4.31 (td, *J* = 9.0, 8.3, 4.2 Hz, 1H), 3.45 (s, 3H), 3.23–3.05 (m, 2H), 2.33 (dd, *J* = 5.4, 3.0 Hz, 2H), 1.38 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.2 (d, $^1J_{CF}$ = 248.1 Hz, C_q), 155.1 (C_q), 151.6 (C_q), 149.0 (CH), 137.6 (CH), 137.1 (C_q), 136.0 (C_q), 132.3 (d, $^3J_{CF}$ = 8.1 Hz, CH), 128.5 (C_q), 128.0 (C_q), 127.9 (d, $^4J_{CF}$ = 3.1 Hz, C_q), 123.5 (CH), 121.5 (CH), 121.4 (CH), 119.6 (CH), 115.5 (d, $^2J_{CF}$ = 21.5 Hz, CH), 112.9 (C_q), 111.3 (CH), 79.1 (C_q), 51.4 (CH), 47.9 (CH_3), 36.9 (CH_2), 29.6 (CH_2), 28.3 (CH_3).

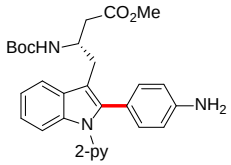
^{19}F NMR (376 MHz, $CDCl_3$): δ = –113.5 (m).

IR (ATR): 2954, 2854, 1706, 1588, 1468, 1455, 1436, 1365, 1158, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 526 (100) $[M+Na]^+$, 504 (28) $[M+H]^+$, 448 (41), 404 (20) $[M–Boc+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{31}FN_3O_4^+$ 504.2293 $[M+H]^+$, found 504.2289.

Methyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-(4-anilino)-β^3-*homo*-L-tryptophanate (121ag)



The general procedure B2 was followed using tryptophan **120a** (100 mg) and 4-bromoaniline (**28g**, 46 mg). Purification by column chromatography (EtOAc) yielded tryptophan **121ag** as a white solid (117 mg, 96%).

m. p.: 95 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.57 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.81–7.67 (m, 1H), 7.68 (dd, *J* = 6.3, 3.1 Hz, 1H), 7.53–7.49 (m, 1H), 7.21 (dm, *J* = 8.4 Hz, 2H), 7.12 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H), 7.01 (dm, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 2H), 5.06 (d, *J* = 8.5 Hz, 1H), 4.29 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.59 (br s, 2H), 3.46 (s, 3H), 3.19–3.07 (m, 2H), 2.32 (d, *J* = 5.6 Hz, 2H), 1.38 (s, 9H).

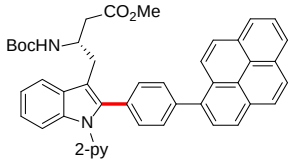
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (C_q), 155.0 (C_q), 151.9 (C_q), 148.6 (CH), 145.6 (C_q), 137.5 (C_q), 137.3 (CH), 136.8 (C_q), 131.5 (CH), 128.7 (C_q), 122.8 (CH), 121.7 (C_q), 121.6 (CH), 121.0 (CH), 120.9 (CH), 119.2 (CH), 115.0 (CH), 111.8 (C_q), 111.4 (CH), 79.0 (C_q), 51.4 (CH), 48.1 (CH_2), 37.3 (CH_2), 29.4 (CH_3), 28.4 (CH_3).

IR (ATR): 3437, 2976, 1698, 1509, 1468, 1455, 1435, 1365, 1047, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 523 (100) $[M+Na]^+$, 501 (41) $[M+H]^+$, 445 (38), 401 (20) $[M–Boc+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{33}N_4O_4^+$ 501.2496 $[M+H]^+$, found 501.2495.

Methyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-[4-(1-pyrenyl)phenyl]-β^3-*homo*-L-tryptophanate (121aq)



The general procedure B2 was followed using tryptophan **120a** (95 mg) and 1-(4-bromophenyl)pyrene (**28q**, 96 mg). Purification by column chromatography (hexanes/EtOAc 1:1) yielded tryptophan **121aq** as a white solid (45 mg, 28%).

m. p.: 84 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.65 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.22 (dd, *J* = 10.0, 7.6 Hz, 2H), 8.20–8.17 (m, 2H), 8.11–8.10 (m, 2H), 8.07 (d, *J* = 9.3 Hz, 1H), 8.03 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.93–7.88 (m, 1H), 7.78–7.73 (m, 1H), 7.65 (ddd, *J* = 7.8, 7.8, 2.1 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.30 (ddd, *J* = 7.2, 6.5, 3.8 Hz, 2H), 7.22 (dd, *J* = 7.5, 4.9 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.23 (d, *J* = 9.1 Hz, 1H), 4.49–4.40 (m, 1H), 3.47 (s, 3H), 3.39–3.28 (m, 2H), 2.47–2.44 (m, 2H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.2 (C_q), 155.3 (C_q), 151.9 (C_q), 149.1 (CH), 140.5 (C_q), 137.6 (CH), 137.4 (C_q), 136.9 (C_q), 131.5 (C_q), 131.0 (C_q), 130.9 (C_q), 130.8 (C_q), 130.7 (CH), 130.6 (CH), 128.8 (C_q), 128.5 (C_q), 127.7 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 126.1 (CH), 125.3 (CH), 125.1 (C_q), 125.0 (CH), 125.0 (CH), 124.9 (C_q), 124.7 (CH), 123.6 (CH), 121.8 (CH), 121.5 (CH), 119.7 (CH), 113.2 (C_q), 111.6 (CH), 79.3 (C_q), 53.6 (CH), 51.6 (CH_3), 37.3 (CH_2), 29.9 (CH_2), 28.6 (CH_3).

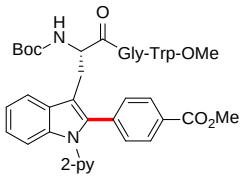
IR (ATR): 2963, 1705, 1468, 1455, 1435, 1364, 1164, 1047, 1019, 844, 780, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1394 (32) $[2M+Na]^+$, 1372 (47) $[2M+H]^+$, 708 (74) $[M+Na]^+$, 686 (100) $[M+H]^+$, 630 (62), 586 (13) $[M–Boc+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{45}H_{40}N_3O_4^+$ 686.3013 $[M+H]^+$, found 686.3017.

5.3.4 Analytical Data for Arylated Peptides 102

Methyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-(benzoic acid methyl ester-4-yl)-L-tryptophylglycyl-L-tryptophanate (102bd)



The general procedure B3 was followed using peptide **101b** (100 mg) and methyl 4-bromobenzoate (**28d**, 37 mg). Purification by column chromatography (EtOAc) yielded peptide **102bd** as a white solid (78 mg, 64%).

m. p.: 121 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.55–8.47 (m, 1H), 7.94 (dm, *J* = 8.4 Hz, 2H), 7.77–7.69 (m, 1H), 7.65–7.51 (m, 2H), 7.51–7.41 (m, 1H), 7.41–7.35 (m, 1H), 7.29 (dm, *J* = 8.4 Hz, 2H), 7.27–7.20 (m, 4H), 7.19–7.08 (m, 2H), 7.03 (ddd, *J* = 9.1, 5.4, 2.6 Hz, 1H), 6.86–6.79 (m, 1H), 6.64–6.56 (m, 1H), 6.50–6.40 (m, 1H), 4.96–4.80 (m, 1H), 4.78–4.68 (m, 1H), 4.44–4.27 (m, 1H), 3.88 (s, 3H), 3.60 (s, 3H), 3.51–3.39 (m, 1H), 3.39–3.27 (m, 2H), 3.27–3.15 (m, 2H), 1.24 (s, 9H).

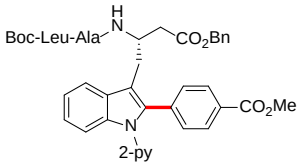
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (C_q), 171.8 (C_q), 166.6 (C_q), 166.1 (C_q), 151.3 (C_q), 149.1 (CH), 138.0 (CH), 137.4 (C_q), 136.2 (C_q), 136.1 (C_q), 134.3 (CH), 131.4 (C_q), 130.3 (CH), 129.8 (CH), 129.4 (C_q), 128.3 (C_q), 128.2 (C_q), 128.2 (C_q), 127.3 (C_q), 124.1 (CH), 123.6 (CH), 123.3 (CH), 122.1 (CH), 121.8 (CH), 121.6 (CH), 119.5 (CH), 118.3 (CH), 114.1 (CH), 111.4 (CH), 109.2 (C_q), 80.4 (C_q), 55.7 (CH), 55.1 (CH), 52.4 (CH_3), 52.2 (CH_3), 43.2 (CH_2), 34.0 (CH_2), 28.2 (CH_3), 27.2 (CH_2).

IR (ATR): 3327, 1714, 1661, 1611, 1513, 1469, 1455, 1436, 1276, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 795 (81) $[M+Na]^+$, 773 (27) $[M+H]^+$, 721 (100).

HR-MS (ESI) *m/z* calcd for $C_{43}H_{45}N_6O_8^+$ 773.3293 $[M+H]^+$, found 773.3281.

Benzyl *tert*-butoxycarbonyl-L-leucyl-L-alanyl-1-(2-pyridyl)-2-(benzoic acid methyl ester-4-yl)-β^3-*homo*-L-tryptophanate (102cd)



The general procedure B3 was followed using peptide **101c** (50 mg) and methyl 4-bromobenzoate (**28d**, 17 mg). Purification by column chromatography (EtOAc) yielded peptide **102cd** as a white solid (39 mg, 65%).

m. p.: 88 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.56 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.97 (dm, *J* = 8.5 Hz, 2H), 7.86–7.84 (m, 1H), 7.67–7.64 (m, 1H), 7.55 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.36 (dm, *J* = 8.5 Hz, 2H), 7.35–7.28 (m, 5H), 7.28–7.22 (m, 4H), 7.16 (dd, *J* = 7.4, 4.9 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.54 (d, *J* = 7.3 Hz, 1H), 5.03 (d, *J* = 7.9 Hz, 1H), 4.94 (d, *J* = 12.4 Hz, 1H), 4.77 (d, *J* = 12.3 Hz, 1H), 4.61 (tt, *J* = 11.5, 4.6 Hz, 1H), 4.26 (tt, *J* = 7.1, 7.1 Hz, 1H), 4.12–4.06 (m, 1H), 3.90 (s, 3H), 3.24 (dd, *J* = 14.2, 5.8 Hz, 1H), 3.15 (dd, *J* = 14.2, 9.0 Hz, 1H), 2.41 (dd, *J* = 16.8, 5.4 Hz, 1H), 2.37 (dd, *J* = 16.8, 5.4 Hz, 1H), 1.27 (s, 9H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 2.2 Hz, 3H), 0.94 (d, *J* = 2.3 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 2H).

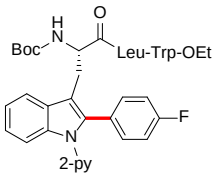
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1 (C_q), 171.1 (C_q), 171.1 (C_q), 166.5 (C_q), 156.8 (C_q), 151.3 (C_q), 149.0 (CH), 137.7 (CH), 137.4 (C_q), 136.5 (C_q), 136.0 (C_q), 135.3 (C_q), 130.3 (CH), 129.6 (CH), 129.5 (C_q), 129.1 (C_q), 128.5 (C_q), 128.4 (CH), 128.1 (CH), 128.0 (CH), 128.0 (CH), 123.9 (CH), 121.7 (CH), 121.5 (CH), 119.6 (CH), 113.4 (C_q), 111.5 (CH), 66.2 (CH_2), 52.2 (CH), 48.9 (CH), 47.0 (CH_3), 41.2 (CH_2), 36.6 (CH_2), 29.0 (CH_2), 28.4 (CH_3), 24.8 (CH_3), 23.1 (CH_3), 21.9 (CH), 18.1 (CH).

IR (ATR): 3315, 2954, 2923, 2853, 1720, 1646, 1468, 1455, 1436, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 826 (100) $[M+Na]^+$, 804 (20) $[M+H]^+$, 752 (20).

HR-MS (ESI) *m/z* calcd for $C_{46}H_{53}N_5O_8Na^+$ 826.3786 $[M+Na]^+$, found 826.3781.

Ethyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-(4-fluorophenyl)-L-tryptophyl-L-leucyl-L-tryptophanate (102dk)



The general procedure B3 was followed using peptide **101d** (100 mg) and 1-bromo-4-fluorobenzene (**28k**, 27 mg). Purification by column chromatography (EtOAc) yielded peptide **102dk** as a white solid (58 mg, 51%).

m. p.: 117 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.64–8.59 (m, 1H), 8.58–8.55 (m, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.59 (ddd, *J* = 7.8, 7.8, 2.0 Hz, 1H), 7.52–7.46 (m, 1H), 7.31–7.20 (m, 6H), 7.19 (dd, *J* = 7.4, 4.8 Hz, 1H), 7.13 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.07 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.02 (ddd, *J* = 8.6, 8.6, 2.9 Hz, 2H), 6.87–6.83 (m, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.68–6.61 (m, 1H), 6.37 (d, *J* = 8.0 Hz, 1H),

4.82–4.75 (m, 1H), 4.58 (d, *J* = 7.7 Hz, 1H), 4.33 (q, *J* = 7.7 Hz, 2H), 4.10 (ddddd, *J* = 18.0, 14.0, 11.1, 7.0, 3.7 Hz, 1H), 3.38 (ddd, *J* = 14.9, 5.9, 2.1 Hz, 1H), 3.31 (dd, *J* = 14.9, 5.3 Hz, 1H), 3.27–3.19 (m, 2H), 1.88 (br s, 1H), 1.55 (dt, *J* = 13.9, 7.2 Hz, 1H), 1.47–1.40 (m, 1H), 1.30 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 2H), 0.81 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (C_q), 171.5 (C_q), 170.7 (C_q), 162.4 (d, $^1J_{CF}$ = 249.0 Hz, C_q), 151.4 (C_q), 149.0 (CH), 137.9 (CH), 137.1 (C_q), 136.7 (C_q), 136.03 (C_q), 136.01 (C_q), 132.4 (d, $^3J_{CF}$ = 8.1 Hz, CH), 128.2 (C_q), 127.6 (d, $^4J_{CF}$ = 3.4 Hz, C_q), 127.4 (C_q), 123.4 (CH), 123.3 (CH), 121.9 (CH), 121.73 (CH), 121.66 (CH), 121.55 (CH), 119.4 (CH), 118.4 (CH), 118.3 (CH), 115.9 (d, $^2J_{CF}$ = 21.6 Hz, CH), 115.7 (CH), 111.30 (CH), 109.4 (C_q), 109.3 (C_q), 80.6 (C_q), 61.5 (CH_2), 52.6 (CH), 52.4 (CH), 51.5 (CH), 40.3 (CH_2), 28.1 (CH_3), 27.4 (CH_2), 26.6 (CH_2), 24.6 (CH), 22.6 (CH_3), 22.3 (CH_3), 14.0 (CH_3).

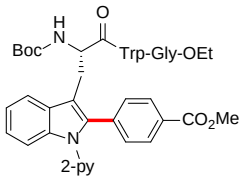
^{19}F NMR (376 MHz, $CDCl_3$): δ = –112.6 (m).

IR (ATR): 3325, 1645, 1505, 1469, 1455, 1436, 1221, 1157, 839, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 825 (100) $[M+Na]^+$, 803 (29) $[M+H]^+$, 789 (20).

HR-MS (ESI) *m/z* calcd for $C_{46}H_{52}N_6O_6F^+$ 803.3927 $[M+H]^+$, found 803.3920.

Ethyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-(benzoic acid methyl ester-4-yl)-L-tryptophyl-L-tryptophylglycinate (102ed)



The general procedure B3 was followed using peptide **101e** (100 mg) and methyl 4-bromobenzoate (**28d**, 36 mg). Purification by column chromatography (EtOAc) yielded peptide **102ed** as a white solid (84 mg, 70%).

m. p.: 137 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.13 (s, 1H), 8.71–8.64 (m, 1H), 7.93 (dm, *J* = 7.8 Hz, 2H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.57 (ddd, *J* = 7.8, 7.8, 2.0 Hz, 1H), 7.37–7.19 (m, 6H), 7.17 (dm, *J* = 7.8 Hz, 2H), 7.11 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.00 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.85–6.78 (m, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.36–6.30 (m, 1H), 6.17 (d, *J* = 7.2 Hz, 1H), 4.45 (q, *J* = 6.6 Hz, 1H), 4.26–4.16 (m, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.89–3.85 (m, 1H), 3.77 (dd, *J* = 17.9, 5.8 Hz, 1H), 3.47 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.28–3.16 (m, 2H), 2.87 (dd, *J* = 15.0, 6.0 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 9H).

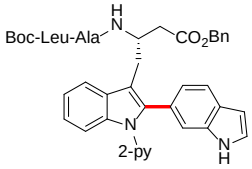
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5 (C_q), 169.3 (C_q), 166.4 (C_q), 155.4 (C_q), 151.2 (C_q), 148.9 (CH), 138.1 (CH), 137.3 (C_q), 136.1 (C_q), 136.0 (C_q), 135.9 (C_q), 130.4 (CH), 130.0 (CH), 129.6 (C_q), 128.4 (C_q), 128.3 (C_q), 127.5 (C_q), 124.3 (CH), 123.4 (CH), 122.0 (CH), 121.8 (CH), 121.8 (CH), 121.7 (CH), 120.1 (CH), 119.5 (CH), 118.1 (CH), 111.9 (C_q), 111.5 (CH), 111.1 (CH), 108.9 (C_q), 80.1 (C_q), 61.1 (CH_2), 55.3 (CH), 53.6 (CH), 52.3 (CH_3), 41.2 (CH_2), 28.3 (CH_3), 27.8 (CH), 26.1 (CH_2), 26.0 (CH_2), 14.1 (CH_3).

IR (ATR): 3341, 1720, 1660, 1469, 1455, 1435, 1366, 1276, 1163, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 809 (100) $[M+H]^+$, 787 (5).

HR-MS (ESI) *m/z* calcd for $C_{44}H_{47}N_6O_8^+$ 809.3269 $[M+H]^+$, found 809.3270.

Benzyl *tert*-butoxycarbonyl-L-leucyl-L-alanyl-1-(2-pyridyl)-2-(6-indolyl)-β^3-*homo*-L-tryptophanate (102cz)



The general procedure B3 was followed using peptide **101c** (50 mg) and 6-bromoindole (**28z**, 16 mg). Purification by column chromatography (1% Et_3N in EtOAc) yielded peptide **102cz** as a white solid (41 mg, 70%).

m. p.: 122 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.21 (s, 1H), 8.51 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.70 (dd, *J* = 15.2, 7.9 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.39–7.32 (m, 2H), 7.32–7.25 (m, 3H), 7.24–7.19 (m, 3H), 7.17 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 7.04 (ddd, *J* = 7.4, 4.8, 1.0 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.72–6.65 (m, 2H), 6.48 (dd, *J* = 2.5, 2.5 Hz, 1H), 6.21 (s, 1H), 4.98 (d, *J* = 8.4 Hz, 1H), 4.89 (d, *J* = 12.3 Hz, 1H), 4.80 (d, *J* = 12.3 Hz, 1H), 4.59–4.51 (m, 1H), 4.10 (tt, *J* = 7.0, 7.0 Hz, 1H), 4.05–3.96 (m, 1H), 3.17 (dd, *J* = 14.4, 6.9 Hz, 1H), 3.06 (dd, *J* = 14.4, 7.3 Hz, 1H), 2.50 (dd, *J* = 16.2, 5.4 Hz, 1H), 2.42 (dd, *J* = 16.3, 6.0 Hz, 1H), 2.09 (br s, 1H), 1.62 (dp, *J* = 19.7, 6.5 Hz, 1H), 1.53 (td, *J* = 11.3, 9.3, 5.0 Hz, 1H), 1.46–1.41 (m, 1H), 1.38 (s, 9H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 6H).

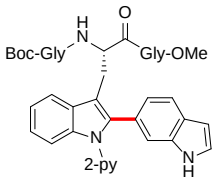
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3 (C_q), 171.2 (C_q), 171.2 (C_q), 155.7 (C_q), 151.9 (C_q), 148.6 (CH), 138.5 (C_q), 137.5 (CH), 136.9 (C_q), 135.8 (C_q), 135.6 (C_q), 128.7 (C_q), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.5 (C_q), 125.8 (CH), 124.7 (C_q), 123.1 (CH), 122.1 (CH), 121.5 (CH), 121.2 (CH), 121.0 (CH), 120.7 (CH), 118.8 (CH), 113.7 (CH), 112.1 (C_q), 111.7 (CH), 102.1 (CH), 80.1 (C_q), 66.2 (CH_2), 53.1 (CH), 48.8 (CH), 47.6 (CH), 40.9 (CH_2), 37.7 (CH_2), 29.0 (CH_2), 28.2 (CH_3), 24.6 (CH), 23.0 (CH_3), 21.7 (CH_3), 18.5 (CH_3).

IR (ATR): 3294, 2955, 1645, 1513, 1468, 1453, 1436, 1366, 1248, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 807 (100) $[M+Na]^+$, 785 (24) $[M+H]^+$, 717 (6).

HR-MS (ESI) *m/z* calcd for $C_{46}H_{53}N_6O_6^+$ 785.4021 $[M+H]^+$, found 785.4021.

Methyl *tert*-butoxycarbonyl-glycyl-1-(2-pyridyl)-2-(6-indolyl)-L-tryptophylglycinate (102fz)



The general procedure B3 was followed using peptide **101f** (50 mg) and 6-bromoindole (**28z**, 21 mg). Purification by column chromatography (1% Et_3N in EtOAc) yielded peptide **102fz** as a white solid (38 mg, 62%).

m. p.: 126 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.35 (s, 1H), 8.49 (dd, *J* = 5.2, 1.9 Hz, 1H), 7.68 (ddd, *J* = 15.4, 7.3, 1.8 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.42 (s, 1H), 7.41–7.35 (m, 1H), 7.20 (ddddd, *J* = 7.1, 7.1, 7.1, 7.1, 1.4 Hz, 2H), 7.14 (dd, *J* = 2.8, 2.8 Hz, 1H), 7.08 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 6.96 (s, 1H), 6.80 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.66 (dd, *J* = 17.2, 8.0 Hz, 2H), 6.46–6.42 (m, 1H), 5.19–5.12 (m, 1H), 4.77 (q, *J* =

7.2 Hz, 1H), 3.83 (dd, *J* = 18.0, 5.7 Hz, 1H), 3.65–3.58 (m, 1H), 3.57 (s, 3H), 3.44–3.36 (m, 3H), 3.30 (dd, *J* = 14.7, 7.2 Hz, 1H), 1.38 (s, 9H).

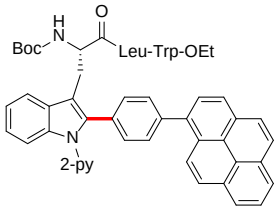
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4 (C_q), 169.8 (C_q), 169.4 (C_q), 156.1 (C_q), 151.9 (C_q), 148.6 (CH), 138.9 (C_q), 137.7 (CH), 137.0 (C_q), 135.8 (C_q), 128.7 (C_q), 127.4 (C_q), 125.8 (CH), 124.5 (C_q), 123.1 (CH), 121.9 (CH), 121.7 (CH), 121.2 (CH), 121.2 (CH), 120.6 (CH), 118.8 (CH), 113.4 (CH), 111.6 (CH), 111.0 (C_q), 102.0 (CH), 80.1 (C_q), 54.1 (CH), 52.2 (CH_3), 43.8 (CH_2), 41.2 (CH_2), 28.2 (CH_3), 27.8 (CH_2).

IR (ATR): 3300, 1747, 1652, 1506, 1469, 1454, 1436, 1365, 1162, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 647 (100) $[M+Na]^+$, 625 (75) $[M+H]^+$, 304 (22).

HR-MS (ESI) *m/z* calcd for $C_{34}H_{37}N_6O_6^+$ 625.2769 $[M+H]^+$, found 625.2766.

Ethyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-[4-(1-pyrenyl)phenyl]-L-tryptophyl-L-leucyl-L-tryptophanate (102dq)



The general procedure B3 was followed using peptide **101d** (100 mg) and 1-(4-bromophenyl)pyrene (**28q**, 55 mg). Purification by column chromatography (EtOAc) yielded peptide **102dq** as a white solid (80 mg, 58%).

m. p.: 120 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.66 (dd, *J* = 5.0, 1.9 Hz, 1H), 8.53 (s, 1H), 8.22 (dd, *J* = 7.6, 1.4 Hz, 2H), 8.17 (d, *J* = 7.5 Hz, 1H), 8.13 (d, *J* = 9.2 Hz, 1H), 8.11 (d, *J* = 1.4 Hz, 2H), 8.05–8.01 (m, 2H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.78 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.68 (ddd, *J* = 7.8, 7.8, 2.0 Hz, 1H), 7.63–7.60 (m, 2H), 7.51–7.47 (m, 3H), 7.30 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.28–7.23 (m, 4H), 7.13–7.10 (m, 1H), 7.08–7.05 (m, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.90–6.86 (m, 1H), 6.69 (d, *J* = 6.0 Hz, 1H), 6.47 (d, *J* = 8.2 Hz, 1H), 4.81 (dt, *J* = 7.8, 5.7 Hz, 1H), 4.75 (d, *J* = 7.6 Hz, 1H), 4.49 (d, *J* = 7.5 Hz, 1H), 4.39 (q, *J* = 7.7 Hz, 1H), 4.10 (qq, *J* = 10.8, 7.1 Hz, 2H), 3.56 (dd, *J* = 14.9, 6.0 Hz, 1H), 3.52–3.45 (m, 1H), 3.32 (dd, *J* = 15.0, 5.1 Hz, 1H), 3.21 (dd, *J* = 14.8, 6.6 Hz, 1H), 1.60 (dt, *J* = 13.9, 7.2 Hz, 1H), 1.50 (dt, *J* = 13.4, 6.6 Hz, 1H), 1.31 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H), 0.82 (d, *J* = 6.2 Hz, 3H).

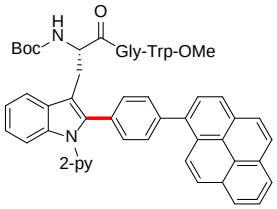
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6 (C_q), 171.4 (C_q), 170.7 (C_q), 155.5 (C_q), 151.6 (C_q), 148.9 (CH), 140.8 (C_q), 137.6 (CH), 137.5 (C_q), 137.3 (C_q), 136.6 (C_q), 136.0 (C_q), 131.4 (C_q), 130.8 (C_q), 130.8 (CH), 130.7 (C_q), 130.5 (CH), 130.4 (C_q), 128.3 (C_q), 128.3 (C_q), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.4 (C_q), 127.3 (CH), 126.0 (CH), 125.2 (CH), 124.9 (C_q), 124.9 (CH), 124.8 (CH), 124.8 (C_q), 124.6 (CH), 123.6 (CH), 123.2 (CH), 121.8 (CH), 121.8 (CH), 121.6 (CH), 121.5 (CH), 119.3 (CH), 119.2 (CH), 118.3 (CH), 111.6 (CH), 111.3 (C_q), 111.2 (CH), 109.4 (C_q), 80.5 (C_q), 61.5 (CH_2), 52.7 (CH), 51.7 (CH), 40.5 (CH_2), 28.2 (CH_3), 27.5 (CH_2), 27.0 (CH_2), 27.0 (CH), 24.7 (CH), 22.6 (CH_3), 22.4 (CH_3), 14.1 (CH_3).

IR (ATR): 3412, 3050, 2958, 1651, 1469, 1455, 1436, 1366, 1021, 740 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1007 (100) $[M+Na]^+$, 985 (26) $[M+H]^+$, 885 (4) $[M–Boc+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{62}H_{61}N_6O_6^+$ 985.4647 $[M+H]^+$, found 985.4625.

Methyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-[4-(1-pyrenyl)phenyl]-L-tryptophylglycyl-L-tryptophanate (102bq)



The general procedure B3 was followed using peptide **101b** (65 mg) and 1-(4-bromophenyl)pyrene (**28q**, 40 mg). Purification by column chromatography (EtOAc) yielded peptide **102bq** as a white solid (10 mg, 10%).

m. p.: 132 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66–8.60 (m, 1H), 8.26–8.19 (m, 2H), 8.19–8.13 (m, 1H), 8.13–8.07 (m, 2H), 8.07–8.00 (m, 2H), 8.00–7.92 (m, 2H), 7.80–7.75 (m, 1H), 7.72–7.65 (m, 2H), 7.62–7.56 (m, 2H), 7.47–7.43 (m, 2H), 7.43–7.39 (m, 1H), 7.31–7.23 (m, 4H), 7.13–7.08 (m, 1H), 7.06–7.02 (m, 1H), 6.98–6.93 (m, 1H), 6.90–6.86 (m, 1H), 4.82–4.73 (m, 1H), 4.56–4.48 (m, 1H), 3.90–3.83 (m, 1H), 3.62 (s, 3H), 3.61–3.57 (m, 1H), 3.50–3.44 (m, 2H), 3.29 (dd, *J* = 15.0, 5.6 Hz, 1H), 3.22 (dd, *J* = 15.0, 5.4 Hz, 1H), 1.36 (s, 9H).

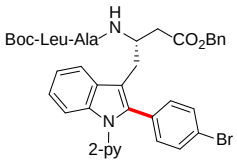
^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2 (C_q), 172.0 (C_q), 168.2 (C_q), 161.1 (C_q), 155.7 (C_q), 149.2 (CH), 141.0 (C_q), 138.0 (CH), 137.4 (C_q), 136.8 (C_q), 136.8 (C_q), 136.2 (C_q), 131.6 (C_q), 131.1 (C_q), 131.0 (CH), 130.9 (C_q), 130.6 (CH), 130.4 (C_q), 130.4 (CH), 128.5 (C_q), 127.9 (CH), 127.7 (CH), 127.7 (CH), 127.7 (CH), 127.5 (CH), 127.4 (C_q), 126.2 (CH), 125.4 (CH), 125.1 (CH), 124.8 (CH), 125.0 (C_q), 123.9 (CH), 123.6 (CH), 122.2 (CH), 122.1 (CH), 121.9 (CH), 121.8 (CH), 121.7 (CH), 119.6 (CH), 119.4 (CH), 118.5 (CH), 109.2 (C_q), 80.6 (C_q), 54.5 (CH), 52.6 (CH_3), 51.5 (CH), 43.5 (CH_2), 28.4 (CH_3), 27.4 (CH_2). 27.2 (CH_2).

IR (ATR): 2958, 2922, 2853, 1713, 1455, 1437, 1259, 1160, 1090, 1013, 846, 794 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 937 (94) $[M+Na]^+$, 915 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{57}H_{51}N_6O_6^+$ 915.3865 $[M+H]^+$, found 915.3858.

Benzyl *tert*-butoxycarbonyl-L-leucyl-L-alanyl-1-(2-pyridyl)-2-(4-bromophenyl)-β^3-*homo*-L-tryptophanate (102cγ)



The general procedure B3 was followed using peptide **101c** (100 mg) and 1,4-dibromobenzene (**28γ**, 39 mg). Purification by column chromatography (EtOAc) yielded peptide **102cγ** as a white solid (38 mg, 31%).

m. p.: 131 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61–8.56 (m, 1H), 7.89–7.82 (m, 1H), 7.80–7.73 (m, 1H), 7.60 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.37–7.28 (m, 7H), 7.25–7.17 (m, 3H), 7.17–7.09 (m, 2H), 6.91 (d, *J* = 8.3, 1H), 5.43 (d, *J* = 8.3 Hz, 1H), 4.98 (d, *J* = 12.2 Hz, 1H), 4.92 (d, *J* = 12.2 Hz, 1H), 4.57–4.45 (m, 1H), 4.44–4.32 (m, 1H), 4.32–4.18 (m, 1H), 3.43–3.29 (m, 1H), 3.16 (dd, *J* = 14.1, 9.9 Hz, 1H), 2.38 (dd, *J* = 16.1,

4.6 Hz, 1H), 2.28–2.12 (m, 1H), 1.84–1.54 (m, 2H), 1.51 (s, 9H), 1.49–1.46 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.3 Hz, 6H).

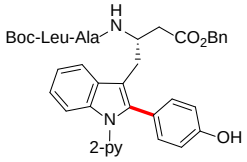
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.7 (C_q), 171.5 (C_q), 171.5 (C_q), 155.8 (C_q), 151.7 (C_q), 149.1 (CH), 137.4 (CH), 137.1 (C_q), 136.3 (C_q), 135.6 (C_q), 131.7 (C_q), 130.4 (CH), 128.9 (C_q), 128.6 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 123.8 (CH), 121.6 (CH), 121.5 (CH), 121.2 (CH), 119.5 (CH), 113.2 (C_q), 111.6 (CH), 79.9 (C_q), 66.4 (CH_2), 53.1 (CH), 49.2 (CH), 46.6 (CH), 41.5 (CH_2), 37.3 (CH_2), 29.8 (CH_2), 28.5 (CH_3), 24.9 (CH), 18.8 (CH_3), 14.2 (CH_3).

IR (ATR): 3288, 2957, 2927, 1647, 1518, 1467, 1454, 1436, 1365, 1163, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 826/824 (1) $[M+H]^+$, 731/729 (92), 726/724 (50) $[M–Boc+H]^+$, 720/718 (100).

HR-MS (ESI) *m/z* calcd for $C_{44}H_{51}{}^{79}BrN_5O_6{}^+$ 824.3017 $[M+H]^+$, found 824.3004.

Benzyl *tert*-butoxycarbonyl-L-leucyl-L-alanyl-1-(2-pyridyl)-2-(4-hydroxyphenyl)-β^3-*homo*-L-tryptophanate (102cδ)



The general procedure D2 was followed using tryptophan **101c** (10.0 mg) and tryptophan **142hk** (10.8 mg). Purification by column chromatography (EtOAc) yielded peptide **102cδ** as a colorless oil (7.5 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59–8.54 (m, 1H), 7.65 (ddd, *J* = 6.8, 5.2, 1.3 Hz, 2H), 7.53 (ddd, *J* = 7.6, 7.6, 1.9 Hz, 1H), 7.36–7.29 (m, 3H), 7.28–7.26 (m, 1H), 7.25–7.16 (m, 2H), 7.14 (ddd, *J* = 5.5, 5.5, 2.8 Hz, 1H), 7.08 (dm, *J* = 8.5 Hz, 2H), 6.78 (dm, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.65 (d, *J* = 7.1 Hz, 1H), 6.12 (d, *J* = 6.5 Hz, 1H), 4.99 (d, *J* = 12.1 Hz, 2H), 4.91 (d, *J* = 12.3 Hz, 1H), 4.55 (ddd, *J* = 8.4, 6.0, 6.0 Hz, 1H), 4.13–4.04 (m, 1H), 3.94–3.86 (m, 1H), 3.30–3.23 (m, 1H), 3.15 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.50 (dd, *J* = 16.2, 5.6 Hz, 1H), 2.41 (dd, *J* = 16.2, 6.3 Hz, 1H), 1.69–1.60 (m, 2H), 1.28–1.23 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.2 (C_q), 171.4 (C_q), 171.4 (C_q), 156.6 (C_q), 156.3 (C_q), 151.7 (C_q), 148.8 (CH), 138.1 (CH), 137.4 (C_q), 137.0 (C_q), 135.7 (C_q), 131.7 (CH), 129.2 (C_q), 128.7 (CH), 128.5 (CH), 128.4 (CH), 123.6 (C_q), 123.4 (CH), 122.1 (CH), 121.6 (CH), 121.4 (CH), 119.0 (CH), 116.5 (CH), 111.7 (CH), 111.5 (C_q), 80.9 (C_q), 66.5 (CH_2), 53.5 (CH), 48.9 (CH), 47.5 (CH), 41.4 (CH_2), 37.6 (CH_2), 29.8 (CH_2), 28.5 (CH_3), 25.0 (CH), 23.2 (CH_3), 21.8 (CH_3), 18.9 (CH_3).

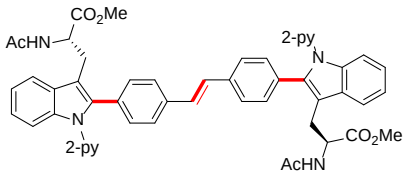
IR (ATR): 3285, 2960, 1715, 1683, 1651, 1510, 1468, 1456, 1436, 1366, 1259, 1163, 1019, 745 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 784 (100) $[M+Na]^+$, 762 (41) $[M+H]^+$, 674 (10), 381 (29).

HR-MS (ESI) *m/z* calcd for $C_{44}H_{52}N_5O_7{}^+$ 762.3861 $[M+H]^+$, found 762.3839.

5.3.5 Analytical Data for Ligated Peptides 123, 117, and 126

(*E*)-1,2-Bis{4-[methyl acetyl-1-(2-pyridyl)-L-tryptophanate]-2-yl}phenylethene (123)



Tryptophan **67hz** (30.0 mg, 68 µmol) and Grubbs II catalyst (2.9 mg, 10 mol %) were stirred in CH_2Cl_2 (0.3 mL) at 40 °C for 6 h under N_2. Purification by column chromatography (EtOAc) yielded peptide **123** as a white solid (26 mg, 90%).

m. p.: 179 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.56 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 2H), 8.30 (d, *J* = 7.8 Hz, 2H), 7.77 (ddd, *J* = 7.8, 7.8, 2.0 Hz, 2H), 7.73–7.66 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 4H), 7.56–7.50 (m, 2H), 7.32 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 4H), 7.23–7.16 (m, 6H), 6.97 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 2H), 4.55 (ddd, *J* = 7.3, 7.3, 7.3 Hz, 2H), 3.41 (s, 6H), 3.36–3.12 (m, 4H), 1.75 (s, 6H).

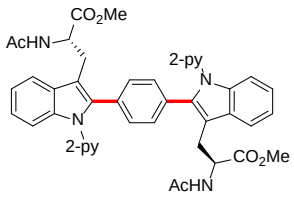
^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.7 (C_q), 168.9 (C_q), 150.8 (C_q), 148.8 (CH), 138.2 (CH), 136.9 (C_q), 136.6 (C_q), 136.1 (C_q), 130.4 (C_q), 130.2 (CH), 128.3 (CH), 128.0 (C_q), 126.2 (CH), 122.8 (CH), 121.9 (CH), 121.5 (CH), 120.6 (CH), 118.8 (CH), 111.4 (C_q), 111.1 (CH), 52.7 (CH), 51.6 (CH_3), 26.8 (CH_2), 22.2 (CH_3).

IR (ATR): 3322, 2924, 1740, 1649, 1532, 1469, 1455, 1435, 1367, 1248, 1223, 781, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1723 (3) $[2M+Na]^+$, 1701 (1) $[2M+H]^+$, 873 (100) $[M+Na]^+$, 851 (73) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{52}H_{47}N_6O_6^+$ 851.3552 $[M+H]^+$, found 851.3551.

1,4-Bis{2-[methyl acetyl-1-(2-pyridyl)]-L-tryptophanate}benzene (117a)



The general procedure B4 was followed using tryptophan **56h** (100 mg), 1,4-dibromobenzene (**28v**, 35 mg) and 5 mol % $[Ru]_2$. Purification by column chromatography (1% Et_3N in EtOAc) yielded peptide **117a** as a white solid (101 mg, 91%).

m. p.: 118 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.53 (ddd, *J* = 5.0, 1.9, 0.8 Hz, 2H), 8.28 (d, *J* = 7.8 Hz, 2H), 7.78 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 2H), 7.72–7.69 (m, 2H), 7.59–7.56 (m, 2H), 7.33 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 2H), 7.23–7.18 (m, 8H), 6.88 (ddd, *J* = 8.1, 1.0, 1.0 Hz, 2H), 4.50 (q, *J* = 7.4 Hz, 2H), 3.41 (s, 6H), 3.26 (dd, *J* = 14.4, 7.4 Hz, 2H), 3.19 (dd, *J* = 14.4, 7.2 Hz, 2H), 1.76 (s, 6H).

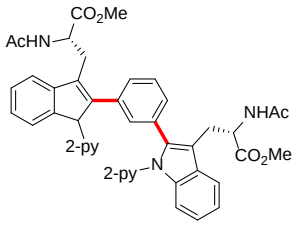
^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.2 (C_q), 169.4 (C_q), 151.1 (C_q), 149.2 (CH), 138.5 (CH), 137.1 (C_q), 137.0 (C_q), 131.1 (C_q), 130.3 (CH), 128.4 (C_q), 123.3 (CH), 122.2 (CH), 121.7 (CH), 121.1 (CH), 119.3 (CH), 112.0 (C_q), 111.7 (CH), 53.1 (CH), 52.1 (CH_3), 27.1 (CH_2), 22.7 (CH_3).

IR (ATR): 3276, 1738, 1651, 1587, 1468, 1454, 1435, 1346, 1035, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 771 (100) $[M+Na]^+$, 749 (13) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{44}H_{41}N_6O_6^+$ 749.3082 $[M+H]^+$, found 749.3076.

1,3-Bis{2-[methyl acetyl-1-(2-pyridyl)]-L-tryptophanate}benzene (117b)



The general procedure B4 was followed using tryptophan **56h** (100 mg), 1,3-dibromobenzene (**28**, 35 mg) and 5 mol % $[Ru]_2$. Purification by column chromatography (1% Et_3N in EtOAc) yielded peptide **117b** as a white solid (91 mg, 82%).

m. p.: 147 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 2H), 7.76–7.73 (m, 2H), 7.69–7.63 (m, 5H), 7.30–7.24 (m, 4H), 7.21 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 2H), 7.14–7.10 (m, 1H), 6.96 (dd, *J* = 7.7, 1.7 Hz, 2H), 6.89–6.86 (m, 2H), 6.50 (d, *J* = 8.1 Hz, 2H), 4.89–4.81 (m, 2H), 3.54 (s, 6H), 3.44 (dd, *J* = 14.4, 6.1 Hz, 2H), 3.30 (dd, *J* = 14.4, 7.3 Hz, 2H), 1.74 (s, 6H).

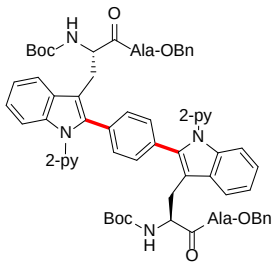
^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0 (C_q), 170.0 (C_q), 151.5 (C_q), 149.1 (CH), 137.7 (CH), 137.2 (C_q), 136.7 (C_q), 132.6 (C_q), 132.2 (CH), 129.9 (CH), 128.4 (C_q), 128.3 (CH), 123.8 (CH), 121.7 (CH), 121.5 (CH), 119.0 (CH), 111.6 (C_q), 111.4 (CH), 52.6 (CH), 52.4 (CH_3), 27.4 (CH_2), 22.8 (CH_3).

IR (ATR): 3278, 1736, 1654, 1588, 1468, 1454, 1434, 1367, 1345, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 771 (100) $[M+Na]^+$, 749 (15) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{44}H_{41}N_6O_6^+$ 749.3082 $[M+H]^+$, found 749.3076.

1,4-Bis({2-[benzyl *tert*-butoxycarbonyl-1-(2-pyridyl)]-L-tryptophyl}-L-alaninate)benzene (117c)



The general procedure B4 was followed using Boc-Trp^{py}-Ala-OBn (**101**, 80 mg), 1,4-dibromobenzene (**28ν**, 17 mg) and 10 mol % $[Ru]_2$. Purification by column chromatography (1% Et_3N in EtOAc) yielded peptide **117c** as a white solid (67 mg, 79%).

m. p.: 105 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 5.1, 2.7 Hz, 2H), 7.76–7.68 (m, 2H), 7.55 (dd, *J* = 7.9, 7.9 Hz, 2H), 7.34–7.20 (m, 16H), 7.20–7.06 (m, 6H), 6.77 (d, 8.2 Hz, 2H), 6.70 (d, 8.2 Hz, 2H), 5.13–5.01 (m, 4H), 5.01–4.94 (m, 2H), 4.44–4.26 (m, 4H), 3.39–3.22 (m, 4H), 1.37–1.17 (m, 24H).

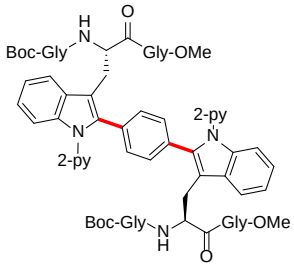
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (C_q), 171.3 (C_q), 155.0 (C_q), 151.5 (C_q), 148.9 (CH), 137.4 (CH), 137.0 (C_q), 136.7 (C_q), 135.4 (C_q), 131.4 (C_q), 130.4 (CH), 128.6 (C_q), 128.5 (CH), 128.1 (CH), 128.0 (CH), 123.6 (CH), 121.4 (CH), 121.4 (CH), 121.1 (CH), 119.1 (CH), 111.6 (CH), 79.7 (C_q), 66.9 (CH_2), 54.3 (CH), 48.2 (CH), 28.2 (CH_3), 18.0 (CH_3).

IR (ATR): 3323, 2923, 1662, 1469, 1454, 1436, 1365, 1153, 742, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1181 (17) $[M+Na]^+$, 1159 (15) $[M+H]^+$, 599 (100).

HR-MS (ESI) *m/z* calcd for $C_{68}H_{71}N_8O_{10}^+$ 1159.5288 $[M+H]^+$, found 1159.5292.

1,4-Bis{[methyl *tert*-butoxycarbonyl-glycyl-1-(2-pyridyl)-L-tryptophan-2-yl]glycinate}benzene (117d)



The general procedure B4 was followed using peptide **101f** (50.0 mg), 1,4-dibromobenzene (**28ν**, 11.6 mg) and 10 mol% $[Ru]_2$. Purification by column chromatography (1% Et_3N in EtOAc) yielded peptide **117d** as a white solid (19 mg, 35%).

m. p.: 133 °C.

^{1}H NMR (600 MHz, CD_3OD): δ = 8.49 (ddd, *J* = 5.0, 1.9, 0.8 Hz, 2H), 7.80 (ddd, *J* = 7.8, 7.8, 1.9 Hz, 4H), 7.51–7.46 (m, 2H), 7.35 (ddd, *J* = 7.6, 5.0, 1.1 Hz, 2H), 7.28–7.27 (m, 4H), 7.25–7.17 (m, 4H), 7.02 (d, *J* = 8.1 Hz, 2H), 4.72–4.66 (m, 2H), 3.81 (d, *J* = 17.5 Hz, 2H), 3.73 (d, *J* = 17.3 Hz, 2H), 3.69–3.66 (m, 2H), 3.65 (s, 6H), 3.59 (d, *J* = 16.8 Hz, 2H), 3.52–3.43 (m, 4H), 1.39 (s, 18H).

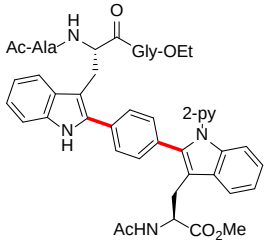
^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.4 (C_q), 171.7 (C_q), 171.3 (C_q), 171.3 (C_q), 152.6 (C_q), 149.7 (CH), 139.9 (CH), 138.7 (C_q), 138.5 (C_q), 132.5 (C_q), 131.6 (CH), 129.9 (C_q), 124.3 (CH), 123.6 (CH), 123.3 (CH), 122.2 (CH), 120.2 (CH), 112.1 (C_q), 80.8 (C_q), 55.1 (CH), 52.6 (CH_3), 44.8 (CH_2), 44.8 (CH_2), 42.0 (CH_2), 28.7 (CH_3).

IR (ATR): 3311, 2928, 1748, 1652, 1515, 1470, 1454, 1436, 1365, 1207, 1162, 780 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1115 (100) $[M+Na]^+$, 1093 (12) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{58}H_{65}N_{10}O_{12}^+$ 1093.4778 $[M+H]^+$, found 1093.4772.

1-{2-[Ethyl (acetyl-L-alanyl)-L-tryptophylglycinate]}-4-{2-[methyl acetyl-1-(2-pyridyl)-L-tryptophanate]}benzene (126a)



The general procedure B3 was followed using peptide **99af** (40 mg) and tryptophan **56h** (36 mg). Purification by column chromatography (1% Et_3N in EtOAc/THF 1:1) yielded peptide **126a** as a white solid (31 mg, 53%).

m. p.: 147 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.21 (s, 1H), 8.58 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.13 (dd, *J* = 5.8, 5.8 Hz, 1H), 7.96 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.80 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.75–7.72 (m, 3H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.58–7.55 (m, 1H), 7.34 (dddd, *J* = 8.6, 7.5, 3.9, 1.5 Hz, 4H), 7.26–7.20 (m, 2H), 7.10 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.03–6.98 (m, 2H), 4.69 (ddd, *J* = 8.4, 7.1, 7.1 Hz, 1H), 4.59 (q, *J* = 7.4 Hz, 1H), 4.25 (dt, *J* = 9.4, 7.1 Hz, 1H), 4.07–3.99 (m, 2H), 3.71 (dd, *J* = 17.3, 5.9 Hz, 1H), 3.58 (dd, *J* = 17.3, 5.6 Hz, 1H), 3.43 (s, 3H), 3.34 (ddd, *J* = 14.4, 11.3, 7.5 Hz, 2H), 3.25 (dd, *J* = 14.4, 6.8 Hz, 1H), 3.12 (dd, *J* = 14.5, 6.8 Hz, 1H), 1.80 (s, 3H), 1.78 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.3 (C_q), 172.1 (C_q), 171.7 (C_q), 169.6 (C_q), 169.6 (C_q), 169.5 (C_q), 151.4 (C_q), 149.4 (CH), 138.7 (CH), 137.4 (C_q), 137.2 (C_q), 136.4 (C_q), 134.7 (C_q), 132.3 (C_q), 130.6

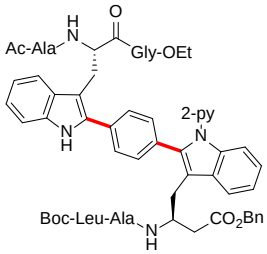
(CH), 130.4 (C_q), 129.4 (C_q), 128.6 (C_q), 128.0 (CH), 123.3 (CH), 122.4 (CH), 122.0 (CH), 121.2 (CH), 119.6 (CH), 119.4 (CH), 119.0 (CH), 112.0 (C_q), 111.7 (CH), 111.4 (CH), 108.5 (C_q), 97.6 (CH), 60.8 (CH_2), 54.2 (CH), 53.4 (CH), 52.2 (CH_3), 48.9 (CH), 41.4 (CH_2), 27.9 (CH_2), 27.3 (CH_2), 22.9 (CH_3), 22.8 (CH_3), 18.7 (CH_3), 14.5 (CH_3).

IR (ATR): 3360, 2927, 2855, 1733, 1645, 1537, 1514, 1455, 1371, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 836 (24) $[M+Na]^+$, 814 (8) $[M+H]^+$, 405 (100).

HR-MS (ESI) *m/z* calcd for $C_{45}H_{48}N_7O_7^+$ 814.3559 $[M+H]^+$, found 814.3547.

1-{2-[Ethyl (acetyl-L-alanyl)-L-tryptophyl-glycinate]}-4-(2-{benzyl [(*tert*-butoxycarbonyl)-L-leucyl-L-alanyl-1-(2-pyridyl)]}-β^3-*homo*-L-tryptophanate)benzene (126b)



The general procedure B3 was followed using peptide **99af** (20 mg) and peptide **101c** (24 mg). Purification by column chromatography (1% Et_3N in EtOAc) yielded peptide **126b** as a white solid (23 mg, 56%).

m. p.: 145 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.19 (s, 1H), 8.57 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.64–7.56 (m, 5H), 7.53 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.35–7.30 (m, 3H), 7.30–7.24 (m, 4H), 7.24–7.18 (m, 5H), 7.18–7.13 (m, 2H), 7.11 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.04 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.85–6.78 (m, 2H), 6.77–6.72 (m, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 5.05 (d, *J* = 7.1 Hz, 1H), 4.97 (s, 2H), 4.65–4.59 (m, 1H), 4.30 (ddd, *J* = 12.9, 6.6, 6.6 Hz, 2H), 4.04 (dddd, *J* = 18.0, 10.9, 7.1, 3.7 Hz, 3H), 3.92–3.84 (m, 1H), 3.77–3.70 (m, 1H), 3.57 (dd, *J* = 15.2, 4.8 Hz, 1H), 3.52–3.42 (m, 2H), 3.42–3.35 (m, 1H), 3.23 (dd, *J* = 14.8, 5.2 Hz, 1H), 2.54 (dd, *J* = 16.3, 5.7 Hz, 1H), 2.32 (dd, *J* = 16.2, 8.1 Hz, 1H), 1.66 (s, 3H), 1.54 (s, 9H), 1.44–1.34 (m, 2H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H), 0.64 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4 (C_q), 171.7 (C_q), 171.5 (C_q), 171.1 (C_q), 170.7 (C_q), 169.9 (C_q), 169.2 (C_q), 161.3 (C_q), 156.0 (C_q), 151.8 (C_q), 149.2 (CH), 137.9 (CH), 137.4 (C_q), 136.3 (C_q), 136.1 (C_q), 135.6 (C_q), 134.4 (C_q), 131.7 (C_q), 131.4 (C_q), 130.3 (CH), 129.7 (C_q), 128.5 (CH), 128.3 (CH), 128.2 (CH), 126.5 (CH), 123.6 (CH), 122.8 (CH), 122.1 (CH), 121.8 (CH), 121.4 (CH), 119.7 (CH), 119.5 (CH), 118.9 (CH), 111.6 (CH), 111.6 (C_q), 111.2 (CH), 107.3 (C_q), 81.3 (C_q), 66.4 (CH_2), 61.1 (CH_2), 53.5 (CH), 53.4 (CH), 49.3 (CH), 48.0 (CH), 47.5 (CH), 41.4 (CH_2), 40.9 (CH_2), 37.4 (CH_2), 29.7 (CH_2), 28.3 (CH_3), 27.2 (CH_2), 24.7 (CH), 23.1 (CH_3), 22.8 (CH_3), 21.1 (CH_3), 19.6 (CH_3), 19.0 (CH_3), 14.0 (CH_3).

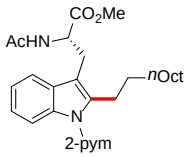
IR (ATR): 3284, 2925, 1722, 1644, 1515, 1469, 1454, 1367, 1162, 1021, 742, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1168 (100) $[M+Na]^+$, 1146 (24) $[M+H]^+$, 542 (21).

HR-MS (ESI) *m/z* calcd for $C_{64}H_{76}N_9O_{11}^+$ 1146.5659 $[M+H]^+$, found 1146.5657.

5.3.6 Analytical Data for Alkylated Tryptophans 107, 133, and 137

Methyl acetyl-1-(2-pyrimidyl)-2-decyl-L-tryptophanate (107gb)



The general procedure C was followed using tryptophan **56g** (101 mg) and 1-decene (**44b**, 126 mg). Purification by column chromatography (hexanes/EtOAc 1:2) yielded tryptophan **107gb** as a colorless oil (55 mg, 38% at 120 °C and 86 mg, 60% when the reaction was carried out at 140 °C).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.93 (d, J = 4.9 Hz, 2H), 8.43 (d, J = 8.0 Hz, 1H), 8.02–7.97 (m, 1H), 7.57–7.52 (m, 1H), 7.44 (dd, J = 4.8, 4.8 Hz, 1H), 7.17–7.12 (m, 2H), 4.54 (ddd, J = 7.5, 7.5, 7.5 Hz, 1H), 3.56 (s, 3H), 3.19 (dd, J = 14.5, 6.9 Hz, 1H), 3.14 (dd, J = 7.4, 7.4 Hz, 1H), 3.12–3.05 (m, 2H), 1.82 (s, 3H), 1.29–1.09 (m, 16H), 0.83 (t, J = 7.1 Hz, 3H).

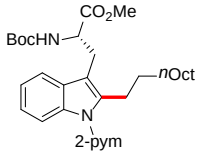
^{13}C NMR (76 MHz, DMSO-d_6): δ = 172.2 (C_q), 169.2 (C_q), 158.8 (CH), 157.2 (C_q), 138.6 (C_q), 135.7 (C_q), 128.7 (C_q), 127.9 (CH), 121.1 (CH), 118.2 (CH), 117.8 (CH), 113.0 (CH), 111.5 (C_q), 52.8 (CH), 51.7 (CH_3), 31.2 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 26.5 (CH_2), 24.8 (CH_2), 22.3 (CH_3), 22.0 (CH_2), 13.8 (CH_3).

IR (ATR): 2923, 2853, 1743, 1654, 1560, 1458, 1420, 1372, 1342, 1209, 1175, 744 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 979 (13) $[2M+Na]^+$, 957 (16) $[2M+H]^+$, 501 (33) $[M+Na]^+$, 479 (100) $[M+H]^+$, 343 (17).

HR-MS (ESI) *m/z* calcd for $C_{28}H_{39}N_4O_3^+$ 479.3017 $[M+H]^+$, found 479.3006.

Methyl *tert*-butoxycarbonyl-1-(2-pyrimidyl)-2-decyl-L-tryptophanate (107eb)



The general procedure C was followed using tryptophan **56e** (60 mg) and 1-decene (**44b**, 63 mg). Purification by column chromatography (hexanes/EtOAc 6:1) yielded tryptophan **107eb** as a colorless oil (25 mg, 31%).

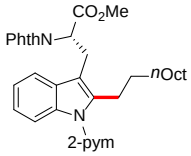
^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.93 (d, J = 4.8 Hz, 2H), 7.99 (ddd, J = 7.1, 3.6, 3.6 Hz, 1H), 7.53 (ddd, J = 7.2, 3.6, 3.6 Hz, 1H), 7.44 (dd, J = 4.8, 4.8 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.19–7.09 (m, 2H), 4.22 (ddd, J = 7.7, 7.7, 7.7 Hz, 1H), 3.59 (s, 3H), 3.23–3.01 (m, 4H), 1.42–1.07 (m, 16H), 0.84 (t, J = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.2 (C_q), 158.6 (CH), 157.0 (C_q), 155.0 (C_q), 138.5 (C_q), 135.5 (C_q), 128.6 (C_q), 122.1 (CH), 121.0 (CH), 118.0 (CH), 117.7 (CH), 112.8v, 111.7 (C_q), 78.1 (C_q), 54.3 (CH), 51.6 (CH_3), 31.1 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 28.5 (CH_2), 28.0 (CH_3), 26.0 (CH_2), 24.8 (CH_2), 22.0 (CH_2), 13.8 (CH_3).

MS (ESI) *m/z* (relative intensity) 1095 (100) $[2M+Na]^+$, 1072 (65) $[2M+H]^+$, 559 (92) $[M+Na]^+$, 537 (77) $[M+H]^+$, 437 (62) $[M–Boc+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{31}H_{45}N_4O_4^+$ 537.3435 $[M+H]^+$, found 537.3436.

Methyl phthaloyl-1-(2-pyrimidyl)-2-decyl-L-tryptophanate (107fb)



The general procedure C was followed using tryptophan **56f** (107 mg) and 1-decene (**44b**, 105 mg). Purification by column chromatography (hexanes/EtOAc 2:1) yielded tryptophan **107fb** as a colorless oil (19 mg, 13%).

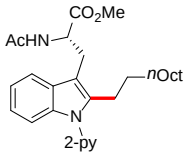
^{1}H NMR (301 MHz, DMSO-d_6): δ = 8.88 (d, *J* = 4.8 Hz, 2H), 7.95–7.88 (m, 1H), 7.83 (s, 3H), 7.54 (dd, *J* = 6.6, 2.0 Hz, 1H), 7.42 (dd, *J* = 4.8, 4.8 Hz, 1H), 7.30–7.23 (m, 1H), 7.15–7.01 (m, 2H), 5.26 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.73 (s, 3H), 3.67–3.48 (m, 4H), 1.21–1.10 (m, 16H), 0.85 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.0 (C_q), 167.0 (C_q), 158.8 (CH), 157.0 (C_q), 138.8 (C_q), 135.7 (C_q), 135.0 (CH), 130.7 (C_q), 128.3 (C_q), 123.4 (CH), 122.4 (CH), 121.2 (CH), 118.3 (CH), 117.7 (CH), 112.8 (CH), 110.8 (C_q), 52.7 (CH), 51.6 (CH_3), 31.2 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 24.8 (CH_2), 23.5 (CH_2), 22.0 (CH_2), 13.9 (CH_3).

MS (ESI) *m/z* (relative intensity) 1155 (10) $[2M+Na]^+$, 589 (100) $[M+Na]^+$, 567 (60) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{34}H_{39}N_4O_4^+$ 567.2966 $[M+H]^+$, found 567.2939.

Methyl acetyl-1-(2-pyridyl)-2-decyl-L-tryptophanate (107hb)

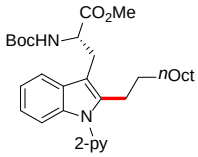


The general procedure C was followed using tryptophan **56h** (107 mg) and 1-decene (**44b**, 105 mg). Purification by column chromatography (hexanes/EtOAc 2:1) yielded tryptophan **107hb** as a colorless oil (19 mg, 13%).

^{1}H NMR (301 MHz, DMSO-d_6): δ = 8.88 (d, *J* = 4.8 Hz, 2H), 7.95–7.88 (m, 1H), 7.85–7.80 (m, 3H), 7.54 (dd, *J* = 6.6, 2.0 Hz, 1H), 7.42 (dd, *J* = 4.8, 4.8 Hz, 1H), 7.30–7.23 (m, 1H), 7.15–7.01 (m, 2H), 5.26 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.73 (s, 3H), 3.67–3.48 (m, 4H), 1.21–1.10 (m, 16H), 0.85 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.0 (C_q), 167.0 (C_q), 158.8 (CH), 157.0 (C_q), 138.8 (C_q), 135.7 (C_q), 135.0 (CH), 130.7 (C_q), 128.3 (C_q), 123.4 (CH), 122.4 (CH), 121.2 (CH), 118.3 (CH), 117.7 (CH), 112.8 (CH), 110.8 (C_q), 52.7 (CH), 51.6 (CH_3), 31.2 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 24.8 (CH_2), 23.5 (CH_2), 22.0 (CH_2), 13.9 (CH_3).

Methyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-decyl-L-tryptophanate (107kb)



The general procedure C was followed using tryptophan **56k** (40 mg) and 1-decene (**44b**, 43 mg). Purification by column chromatography (hexanes/EtOAc 1:1) yielded tryptophan **107kb** as a colorless oil (13 mg, 24%).

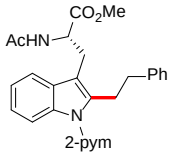
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.89 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.57–7.46 (m, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.33 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.29–7.21 (m, 1H), 7.18–7.05 (m, 2H), 5.13 (d, *J* = 8.2 Hz, 1H), 4.64 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1H), 3.67 (s, 3H), 3.32–3.26 (m, 2H), 2.92–2.84 (m, 2H), 1.34–1.04 (m, 16H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.9 (C_q), 155.2 (C_q), 151.7 (C_q), 149.6 (CH), 139.5 (C_q), 138.3 (CH), 136.8 (C_q), 128.8 (C_q), 122.2 (CH), 122.0 (CH), 121.3 (CH), 120.5 (CH), 118.4 (CH), 109.9 (CH), 108.3 (C_q), 79.9 (C_q), 54.3 (CH), 52.4 (CH_3), 32.1 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.5 (CH_3), 27.8 (CH_2), 24.9 (CH_2), 22.9 (CH_2), 14.3 (CH_3).

MS (ESI) *m/z* (relative intensity) 1093 (50) $[2M+Na]^+$, 1071 (24) $[2M+H]^+$, 558 (100) $[M+Na]^+$, 536 (92) $[M+H]^+$, 436 (36) $[M–Boc+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{32}H_{46}N_3O_4^+$ 536.483 $[M+H]^+$, found 536.3471.

Methyl acetyl-1-(2-pyrimidyl)-2-(1-phenylethane-2-yl)-L-tryptophanate (133ga)



The general procedure C was followed using tryptophan **56g** (101 mg) and styrene (**132a**, 47 mg). Purification by column chromatography (EtOAc) yielded tryptophan **133ga** as a colorless oil (5 mg, 4%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.00 (d, *J* = 4.8 Hz, 2H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.13–8.05 (m, 1H), 7.59–7.52 (m, 1H), 7.49 (dd, *J* = 4.8, 4.8 Hz, 1H), 7.29–7.21 (m, 2H), 7.21–7.09 (m, 5H), 4.58 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H), 3.55 (s, 3H), 3.47–3.32 (m, 2H), 3.14 (dd, *J* = 14.5, 6.7 Hz, 1H), 3.03 (dd, *J* = 14.5, 7.7 Hz, 1H), 2.66 (dd, *J* = 8.1, 8.1 Hz, 2H), 1.81 (s, 3H).

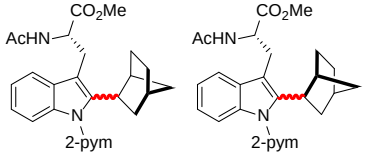
^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.2 (C_q), 169.3 (C_q), 159.0 (CH), 157.2 (C_q), 141.1 (C_q), 137.5 (C_q), 135.6 (C_q), 128.7 (C_q), 128.2 (CH), 128.1 (CH), 125.9 (CH), 122.5 (CH), 121.3 (CH), 118.3 (CH), 117.9 (CH), 113.4 (CH), 112.2 (C_q), 52.7 (CH), 51.8 (CH_3), 35.8 (CH_2), 27.7 (CH_2), 26.4 (CH_2), 22.3 (CH_3).

IR (ATR): 2945, 1738, 1680, 1655, 1576, 1543, 1446, 1374, 1355, 1339, 1276, 1177, 801, 749 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 907 (30) $[2M+Na]^+$, 465 (100) $[M+Na]^+$, 443 (38) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{27}N_4O_3^+$ 433.2078 $[M+H]^+$, found 443.2066.

Methyl acetyl-1-(2-pyrimidyl)-2-(2-norbornyl)-L-tryptophanate (137ga)



The general procedure C was followed using tryptophan **56g** (40 mg) and norbornene (**136a**, 43 mg). Purification by column chromatography (hexanes/EtOAc 1:1) yielded tryptophan **137ga** as a colorless oil (13 mg, 24%).

The NMR spectra show a quadruple set of signals.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.00 (d, *J* = 1.4 Hz, 4H), 8.98 (d, *J* = 1.4 Hz, 4H), 8.55–8.46 (m, 4H), 8.25–8.20 (m, 2H), 7.98–7.90 (m, 4H), 7.88–7.82 (m, 2H), 7.61–7.29 (m, 24H), 7.14–7.04 (m, 8H), 4.64–4.48 (m, 4H), 3.92 (s, 3H), 3.85 (s, 3H), 3.69–3.57 (m, 4H), 3.52 (s, 3H), 3.47–3.30 (m, 4H), 3.42 (s, 3H), 3.28–3.16 (m, 4H), 2.74–2.69 (m, 2H), 2.60–2.56 (m, 2H), 2.22–2.14 (m, 4H), 1.85 (s, 6H), 1.83 (s, 6H), 1.64–1.31 (m, 16H), 1.31–1.01 (m, 16H).

^{13}C NMR (126 MHz,DMSO-d_6): δ = 172.0 (C_q), 171.9 (C_q), 167.0 (C_q), 167.0 (C_q), 165.9 (C_q), 158.9 (CH), 158.9 (CH), 157.3 (C_q), 157.2 (C_q), 155.8 (C_q), 154.6 (C_q), 154.5 (C_q), 140.4 (C_q), 140.4 (C_q), 137.0 (C_q), 136.0 (C_q), 136.0 (C_q), 135.3 (C_q), 135.1 (C_q), 132.2 (CH), 131.0 (CH), 130.6 (CH), 129.1 (C_q), 129.0 (C_q), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.0 (C_q), 126.8 (C_q), 126.4 (C_q), 126.3 (CH), 126.2 (CH), 125.7 (CH), 124.2 (CH), 124.0 (CH), 123.5 (CH), 123.4 (C_q), 122.1 (C_q), 122.0 (CH), 120.4 (CH), 120.3 (CH), 119.0 (CH), 118.9 (CH), 117.8 (CH), 117.7 (CH), 111.0 (CH), 110.6 (CH), 108.9 (C_q), 108.7 (C_q), 106.8 (CH), 106.6 (CH), 53.7 (CH), 53.5 (CH), 52.0 (CH_3), 51.6 (CH_3), 51.5 (CH_3), 40.9 (CH), 40.8 (CH), 40.3 (CH), 38.6 (CH_2), 38.0 (CH_2), 36.9 (CH_2), 36.8 (CH), 35.9 (CH), 30.1 (CH_2), 30.1 (CH_2), 28.3 (CH_2), 28.2 (CH_2), 27.2 (CH_2), 27.0 (CH_2), 22.3 (CH_3), 22.3 (CH_3).

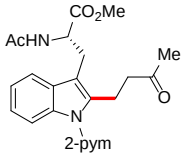
IR (ATR): 3344, 3244, 2917, 1738, 1632, 1510, 1467, 1457, 1435, 1367, 1210, 1179, 837, 746 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 887 (75) $[2M+Na]^+$, 455 (100) $[M+Na]^+$, 433 (13) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{28}N_4NaO_3^+$ 455.2054 $[M+Na]^+$, found 455.2055.

5.3.7 Analytical Data for Alkylated Tryptophans 141

Methyl acetyl-1-(2-pyrimidyl)-2-(butane-3-one-1-yl)-L-tryptophanate (141ga)



The general procedure D1 was followed using tryptophan **56g** (50.8 mg) and but-3-en-2-one (**130a**, 32 mg). Purification by column chromatography (EtOAc) yielded tryptophan **141ga** as a colorless oil (56 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (d, *J* = 4.8 Hz, 2H), 8.24–8.19 (m, 1H), 7.51–7.46 (m, 1H), 7.24–7.17 (m, 2H), 7.15 (dd, *J* = 4.8, 4.8 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 4.92 (ddd, *J* = 7.9, 6.3, 6.3 Hz, 1H), 3.65 (s, 3H), 3.41–3.31 (m, 2H), 3.31–3.21 (m, 2H), 2.76–2.61 (m, 2H), 2.07 (s, 3H), 1.92 (s, 3H).

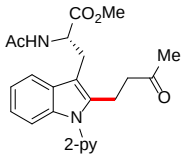
^{13}C NMR (101 MHz, $CDCl_3$): δ = 207.9 (C_q), 172.6 (C_q), 170.2 (C_q), 158.3 (CH), 158.0 (C_q), 137.7 (C_q), 136.4 (C_q), 129.6 (C_q), 123.3 (CH), 122.0 (CH), 118.1 (CH), 117.3 (CH), 115.0 (CH), 112.2 (C_q), 52.7 (CH), 52.5 (CH_3), 43.7 (CH_2), 30.0 (CH_3), 27.1 (CH_2), 23.0 (CH_3), 20.4 (CH_2).

IR (ATR): 3302, 1740, 1709, 1677, 1581, 1561, 1536, 1456, 1423, 1374, 1355, 1339, 1276, 1178, 1125, 801, 749 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 431 (100) $[M+Na]^+$, 409 (27) $[M+H]^+$, 224 (10).

HR-MS (ESI) *m/z* calcd for $C_{22}H_{25}N_4O_4^+$ 409.1870 $[M+H]^+$, found 409.1870.

Methyl acetyl-1-(2-pyridyl)-2-(butane-3-one-1-yl)-L-tryptophanate (141ha)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and but-3-en-2-one (**130a**, 32 mg). Purification by column chromatography (EtOAc) yielded tryptophan **141ha** as a colorless oil (61 mg, 99%).

^{1}H NMR (301 MHz, $CDCl_3$): δ = 8.60 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.88 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1H), 7.54–7.48 (m, 1H), 7.41 (ddd, *J* = 8.0, 0.9, 0.9 Hz, 1H), 7.31 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.27–7.20 (m, 1H), 7.13–7.07 (m, 2H), 6.33 (d, *J* = 7.8 Hz, 1H), 4.91 (ddd, *J* = 7.8, 6.1, 6.1 Hz, 1H), 3.66 (s, 3H), 3.38–3.20 (m, 2H), 3.07 (ddd, *J* = 7.8, 7.8, 2.0 Hz, 2H), 2.54–2.43 (m, 2H), 1.97 (s, 3H), 1.91 (s, 3H).

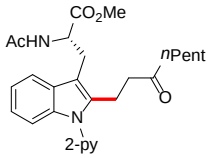
^{13}C NMR (76 MHz, $CDCl_3$): δ = 207.3 (C_q), 172.6 (C_q), 169.9 (C_q), 151.2 (C_q), 149.7 (CH), 138.5 (CH), 137.3 (C_q), 136.7 (C_q), 128.6 (C_q), 122.3 (CH), 122.3 (CH), 120.9 (CH), 120.7 (CH), 118.3 (CH), 109.9 (CH), 109.0 (C_q), 52.8 (CH), 52.3 (CH_3), 42.9 (CH_2), 29.8 (CH_3), 27.0 (CH_2), 23.0 (CH_3), 18.9 (CH_2).

IR (ATR): 3277, 2952, 2926, 1740, 1713, 1655, 1585, 1470, 1459, 1436, 1367, 1218, 1165, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 837 (38) $[2M+Na]^+$, 430 (90) $[M+Na]^+$, 408 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{23}H_{26}N_3O_4^+$ 408.1918 $[M+H]^+$, found 408.1916.

Methyl acetyl-1-(2-pyridyl)-2-(octane-3-one-1-yl)-L-tryptophanate (141hb)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and oct-1-en-3-one (**130b**, 37 mg). Purification by column chromatography (EtOAc) yielded tryptophan **141hb** as a colorless oil (67 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.63 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.92 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1H), 7.56–7.51 (m, 1H), 7.45 (ddd, *J* = 7.9, 0.9, 0.9 Hz, 1H), 7.35 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.29–7.26 (m, 1H), 7.18–7.11 (m, 2H), 6.32 (d, *J* = 7.8 Hz, 1H), 4.95 (ddd, *J* = 7.7, 6.0, 6.0 Hz, 1H), 3.71 (s, 3H), 3.36 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.30 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.16–3.03 (m, 2H), 2.46 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.21 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 2H), 1.95 (s, 3H), 1.48–1.40 (m, 2H), 1.28–1.19 (m, 2H), 1.19–1.10 (m, 2H), 0.84 (dd, *J* = 7.2, 7.2 Hz, 3H).

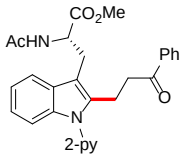
^{13}C NMR (126 MHz, $CDCl_3$): δ = 209.9 (C_q), 172.6 (C_q), 169.9 (C_q), 151.2 (C_q), 149.6 (CH), 138.7 (CH), 137.5 (C_q), 136.7 (C_q), 128.7 (C_q), 122.4 (CH), 122.3 (CH), 121.0 (CH), 120.8 (CH), 118.4 (CH), 110.0 (CH), 109.1 (C_q), 52.8 (CH), 52.4 (CH_3), 42.7 (CH_2), 41.9 (CH_2), 31.2 (CH_2), 27.0 (CH_2), 23.4 (CH_2), 23.1 (CH_3), 22.4 (CH_2), 19.0 (CH_2), 13.9 (CH_3).

IR (ATR): 3290, 2953, 2928, 1742, 1711, 1654, 1585, 1470, 1458, 1436, 1369, 1216, 1130, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 949 (92) $[2M+Na]^+$, 486 (100) $[M+Na]^+$, 464 (26) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{27}H_{34}N_3O_4^+$ 464.2544 $[M+H]^+$, found 464.2541.

Methyl acetyl-1-(2-pyridyl)-2-(2-benzoylethane-1-yl)-L-tryptophanate (141hc)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and 1-phenylprop-2-en-1-one (**130c**, 59 mg). Purification by column chromatography (EtOAc) yielded tryptophan **141hc** as a white solid (48 mg, 68%).

m. p.: 150 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.90 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.81–7.76 (m, 2H), 7.58–7.55 (m, 1H), 7.53 (dddd, *J* = 8.6, 7.1, 1.3, 1.3 Hz, 1H), 7.46 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.40 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.32 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.30–7.27 (m, 1H), 7.18–7.14 (m, 2H), 6.31 (d, *J* = 7.8 Hz, 1H), 4.99 (ddd, *J* = 7.9, 5.9, 5.9 Hz, 1H), 3.71 (s, 3H), 3.40 (dd, *J* = 14.8, 6.1 Hz, 1H), 3.33 (dd, *J* = 14.8, 5.8 Hz, 1H), 3.30–3.20 (m, 2H), 3.16–3.02 (m, 2H), 1.95 (s, 3H).

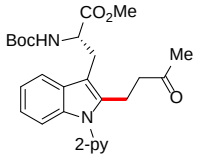
^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.8 (C_q), 172.7 (C_q), 169.9 (C_q), 151.3 (C_q), 149.8 (CH), 138.6 (CH), 137.6 (C_q), 136.8 (C_q), 136.4 (C_q), 133.2 (CH), 128.8 (C_q), 128.6 (CH), 127.9 (CH), 122.4 (CH), 122.4 (CH), 121.1 (CH), 120.8 (CH), 118.4 (CH), 110.0 (CH), 109.1 (C_q), 52.8 (CH), 52.4 (CH_3), 38.3 (CH_2), 27.1 (CH_2), 23.2 (CH_3), 19.5 (CH_2).

IR (ATR): 3334, 3060, 1740, 1674, 1580, 1470, 1458, 1435, 1368, 1206, 740 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 961 (21) $[2M+Na]^+$, 939 (1) $[2M+H]^+$, 492 (100) $[M+Na]^+$, 470 (44) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{28}N_3O_4^+$ 470.2074 $[M+H]^+$, found 470.2074.

Methyl *tert*-butoxycarbonyl-1-(2-pyridyl)-2-(butane-3-one-1-yl)-L-tryptophanate (141ka)



The general procedure D1 was followed using tryptophan **56k** (59.3 mg) and but-3-en-2-one (**130a**, 32 mg) in H_2O/HOAc (9:1, 150 µL). Purification by column chromatography (hexanes/EtOAc 1:2) yielded trytophan **141ka** as a white solid (62 mg, 89%).

m. p.: 87 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.90 (ddd, *J* = 7.4, 2.0 Hz, 1H), 7.57–7.50 (m, 1H), 7.43 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.33 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.30–7.26 (m, 1H), 7.20–7.09 (m, 2H), 5.13 (d, *J* = 8.5 Hz, 1H), 4.64 (ddd, *J* = 6.7, 6.7, 6.7 Hz, 1H), 3.69 (s, 3H), 3.37–3.20 (m, 2H), 3.09 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.62–2.52 (m, 2H), 2.03 (s, 3H), 1.40 (s, 9H).

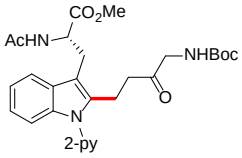
^{13}C NMR (126 MHz, $CDCl_3$): δ = 207.0 (C_q), 172.7 (C_q), 155.0 (C_q), 151.3 (C_q), 149.6 (CH), 138.4 (CH), 137.4 (C_q), 136.7 (C_q), 128.7 (C_q), 122.2 (CH), 122.2 (CH), 121.0 (CH), 120.7 (CH), 118.5 (CH), 109.9 (CH), 109.1 (C_q), 79.8 (C_q), 54.1 (CH), 52.3 (CH_3), 43.4 (CH_2), 29.9 (CH_3), 28.4 (CH_3), 27.7 (CH_2), 19.2 (CH_2).

IR (ATR): 3302, 2928, 1725, 1652, 1586, 1471, 1458, 1436, 1367, 1167, 1020, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 953 (21) $[2M+Na]^+$, 488 (100) $[M+Na]^+$, 466 (24) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{32}N_3O_5^+$ 466.2336 $[M+H]^+$, found 466.2334.

Methyl acetyl-1-(2-pyridyl)-2-(*N*-*tert*-butoxycarbonyl-2-oxo-1-aminobutan-4-yl)-L-tryptophanate (141hd)



The general pyrocedure D1 was followed using tryptophan **56h** (50.6 mg) and *tert*-butyl (2-oxobut-3-en-1-yl)carbamate (**129d**, 30 mg) in H_2O/HOAc (9:1, 150 µL). Purification by column chromatography (EtOAc) yielded trytophan **141hd** as a white solid (68 mg, 88%).

m. p.: 96 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.65–8.60 (m, 1H), 7.92 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1H), 7.54–7.49 (m, 1H), 7.46 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.35 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.30–7.27 (m, 1H), 7.17–7.12 (m, 2H), 6.23 (d, *J* = 8.0 Hz, 1H), 5.19–5.14 (m, 1H), 4.93 (ddd, *J* = 8.1, 6.1, 6.1 Hz, 1H), 3.84 (d, *J* = 5.0 Hz, 2H), 3.68 (s, 3H), 3.34 (dd, *J* = 14.8, 6.5 Hz, 1H), 3.29 (dd, *J* = 14.8, 5.7 Hz, 1H), 3.20–2.08 (m, 2H), 2.54 (dd, *J* = 7.2, 7.2 Hz, 2H), 1.96 (s, 3H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 204.7 (C_q), 172.6 (C_q), 169.9 (C_q), 155.6 (C_q), 151.1 (C_q), 149.8 (CH), 138.7 (CH), 136.8 (C_q), 136.7 (C_q), 128.7 (C_q), 122.5 (CH), 122.4 (CH), 120.9 (CH), 120.9 (CH), 118.4 (CH), 110.1 (CH), 109.3 (C_q), 79.9 (C_q), 52.9 (CH), 52.5 (CH_3), 50.2 (CH_2), 39.4 (CH_2), 28.3 (CH_3), 27.2 (CH_2), 23.2 (CH_3), 19.0 (CH_2).

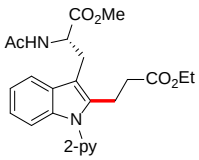
IR (ATR): 3303, 2929, 1732, 1708, 1658, 1524, 1471, 1456, 1436, 1367, 1249, 1218, 1162, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1067 (17) $[2M+Na]^+$, 545 (100) $[M+Na]^+$, 523 (7) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{35}N_4O_6^+$ 523.2551 $[M+H]^+$, found 523.2545.

5.3.8 Analytical Data for Alkylated Tryptophans 142

Methyl acetyl-1-(2-pyridyl)-2-(ethyl propionate-3-yl)-L-tryptophanate (142ha)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and ethyl acrylate (**129a**, 45 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142ha** as a colorless oil (59 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.91 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.59–7.51 (m, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.34 (dd, *J* = 7.2, 5.1 Hz, 1H), 7.30–7.24 (m, 1H), 7.18–7.09 (m, 2H), 6.36 (d, *J* = 7.6 Hz, 1H), 4.96 (ddd, *J* = 7.7, 6.0, 6.0 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 3.38 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.31 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.27–3.13 (m, 2H), 2.29 (ddd, *J* = 9.0, 7.1, 2.5 Hz, 2H), 1.95 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H).

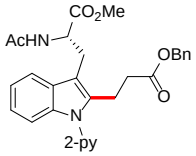
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (C_q), 172.2 (C_q), 169.7 (C_q), 150.9 (C_q), 149.4 (CH), 138.7 (CH), 136.8 (C_q), 136.6 (C_q), 128.5 (C_q), 122.4 (CH), 122.2 (CH), 120.9 (CH), 120.7 (CH), 118.5 (CH), 109.8 (CH), 109.4 (C_q), 60.5 (CH_2), 52.8 (CH), 52.3 (CH_3), 33.7 (CH_2), 27.1 8 (CH_2), 23.1 (CH_3), 20.3 (CH_2), 14.1 (CH_3).

IR (ATR): 2954, 2927, 1731, 1655, 1470, 1459, 1436, 1369, 1176, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 897 (24) $[2M+Na]^+$, 460 (79) $[M+Na]^+$, 438 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{28}N_3O_5^+$ 438.2023 $[M+H]^+$, found 438.2026.

Methyl acetyl-1-(2-pyridyl)-2-(benzyl propionate-3-yl)-L-tryptophanate (142hb)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and benzyl acrylate (**129b**, 36 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hb** as a colorless oil (66 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.90 (ddd, *J* = 8.0, 7.4, 1.9 Hz, 1H), 7.57–7.51 (m, 1H), 7.41 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.33 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.30–7.23 (m, 3H), 7.21–7.12 (m, 4H), 6.27 (d, *J* = 7.8 Hz, 1H), 5.01 (s, 2H), 4.96 (ddd, *J* = 7.8, 6.0, 6.0 Hz, 1H), 3.67 (s, 3H), 3.35 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.32–3.29 (m, 1H), 3.29–3.21 (m, 2H), 2.36 (ddd, *J* = 8.8, 7.0, 2.0 Hz, 2H), 1.94 (s, 3H).

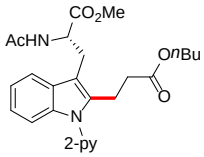
^{13}C NMR (76 MHz, $CDCl_3$): δ = 172.5 (C_q), 172.2 (C_q), 169.9 (C_q), 150.9 (C_q), 149.5 (CH), 138.7 (CH), 136.7 (C_q), 136.6 (C_q), 135.6 (C_q), 128.5 (C_q), 128.4 (CH), 128.1 (CH), 128.0 (CH), 122.5 (CH), 122.3 (CH), 120.9 (CH), 120.8 (CH), 118.5 (CH), 109.9 (CH), 109.5 (C_q), 66.3 (CH_2), 52.7 (CH), 52.3 (CH_3), 33.6 (CH_2), 26.9 (CH_2), 23.0 (CH_3), 20.2 (CH_2).

IR (ATR): 3060, 2951, 1732, 1655, 1470, 1458, 1436, 1212, 1161, 740 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1021 (27) $[2M+Na]^+$, 522 (71) $[M+Na]^+$, 500 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{30}N_3O_5^+$ 500.2180 $[M+H]^+$, found 500.2178.

Methyl acetyl-1-(2-pyridyl)-2-(*n*-butyl propionate-3-yl)-L-tryptophanate (142hc)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and *n*-butyl acrylate (**129c**, 57 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hc** as a colorless oil (62 mg, 90%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.94 (ddd, *J* = 8.0, 7.4, 2.0 Hz, 1H), 7.59–7.52 (m, 1H), 7.48 (ddd, *J* = 8.0, 0.9, 0.9 Hz, 1H), 7.36 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 7.30–7.26 (m, 1H), 7.18–7.10 (m, 2H), 6.32 (d, *J* = 7.8 Hz, 1H), 4.98 (ddd, *J* = 7.8, 6.0, 6.0 Hz, 1H), 3.97 (t, *J* = 6.7 Hz, 2H), 3.72 (s, 3H), 3.44–3.27 (m, 2H), 3.21 (td, *J* = 7.3, 4.5 Hz, 2H), 2.29 (ddd, *J* = 8.9, 7.0, 2.1 Hz, 2H), 1.96 (s, 3H), 1.58–1.43 (m, 2H), 1.35–1.19 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H).

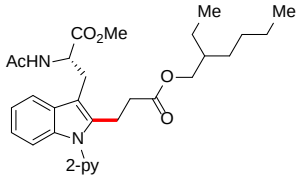
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.5 (C_q), 172.4 (C_q), 169.8 (C_q), 151.0 (C_q), 149.5 (CH), 138.6 (CH), 136.9 (C_q), 136.7 (C_q), 128.6 (C_q), 122.5 (CH), 122.3 (CH), 121.0 (CH), 120.8 (CH), 118.5 (CH), 109.9 (CH), 109.4 (C_q), 64.5 (CH_2), 52.8 (CH), 52.4 (CH_3), 33.8 (CH_2), 30.6 (CH_2), 27.1 (CH_2), 23.2 (CH_3), 20.4 (CH_2), 19.1 (CH_2), 13.7 (CH_3).

IR (ATR): 2957, 2935, 1731, 1655, 1585, 1470, 1459, 1436, 1369, 1174, 1148, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 953 (24) $[2M+Na]^+$, 488 (45) $[M+Na]^+$, 466 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{32}N_3O_5^+$ 466.2336 $[M+H]^+$, found 466.2338.

Methyl acetyl-1-(2-pyridyl)-2-[(2-ethyl)*n*-hexyl propionate-3-yl]-L-tryptophanate (142hd)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and 2-ethylhexyl acrylate (**129d**, 55 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hd** as a colorless oil (58 mg, 74%, dr = 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.65–8.61 (m, 1H), 7.93 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.57–7.52 (m, 1H), 7.47 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.37–7.33 (m, 1H), 7.29–7.25 (m, 1H), 7.18–7.11 (m, 2H), 6.34 (d, *J* = 7.8 Hz, 1H), 4.97 (ddd, *J* = 7.8, 6.0, 6.0 Hz, 1H), 3.93–3.84 (m, 2H), 3.71 (s, 3H), 3.37 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.32 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.27–3.15 (m, 2H), 2.35–2.25 (m, 2H), 1.96 (s, 3H), 1.50–1.43 (m, 1H), 1.29–1.21 (m, 4H), 1.21–1.17 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H).

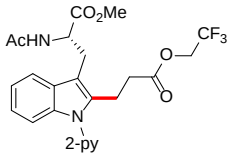
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.5 (C_q), 172.4 (C_q), 169.8 (C_q), 151.0 (C_q), 149.5 (CH), 138.5 (CH), 136.8 (C_q), 136.7 (C_q), 128.6 (C_q), 122.4 (CH), 122.2 (CH), 120.9 (CH), 120.7 (CH), 118.5 (CH), 109.9 (CH), 109.3 (C_q), 67.0 (CH_2), 52.8 (CH), 52.4 (CH_3), 38.6 (CH), 33.7 (CH_2), 30.3 (CH_2), 28.9 (CH_2), 27.1 (CH_2), 23.7 (CH_2), 23.1 (CH_3), 23.0 (CH_2), 20.4 (CH_2), 14.1 (CH_3), 11.0 (CH_3).

IR (ATR): 2957, 2929, 2859, 1732, 1657, 1471, 1459, 1437, 1370, 1173, 1148, 732 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1065 (53) $[2M+Na]^+$, 544 (62) $[M+Na]^+$, 522 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{40}N_3O_5^+$ 522.2962 $[M+H]^+$, found 522.2960.

Methyl acetyl-1-(2-pyridyl)-2-(2,2,2-trifluoroethyl propionate-3-yl)-L-tryptophanate (142he)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and 2,2,2-trifluoroethyl acrylate (**129e**, 46 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142he** as a colorless oil (52 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.92 (ddd, *J* = 7.8, 7.4, 1.9 Hz, 1H), 7.59–7.50 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.35 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.30 (ddd, *J* = 6.0, 3.2, 0.7 Hz, 1H), 7.19–7.12 (m, 2H), 6.19 (d, *J* = 7.8 Hz, 1H), 4.97 (ddd, *J* = 8.0, 5.9, 5.9 Hz, 1H), 4.38 (q, *J* = 8.4 Hz, 2H), 3.69 (s, 3H), 3.38 (dd, *J* = 14.7, 6.3 Hz, 1H), 3.32 (dd, *J* = 14.7. 6.3 Hz, 1H), 3.28–3.11 (m, 2H), 2.55–2.45 (m, 2H), 1.96 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (C_q), 170.7 (C_q), 169.6 (C_q), 151.0 (C_q), 149.6 (CH), 138.5 (CH), 136.6 (C_q), 136.2 (C_q), 128.6 (C_q), 122.7 (q, $^1J_{C\text{-}F}$ =277.5 Hz, CF_3), 122.6 (CH), 122.3 (CH), 120.8 (CH), 120.7 (CH), 118.5 (CH), 110.0 (CH), 109.5 (C_q), 60.3 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, CH_2), 52.9 (CH), 52.4 (CH_3), 33.3 (CH_2), 27.2 (CH_2), 23.2 (CH_3), 20.2 (CH_2).

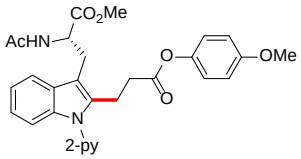
^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.84 (m).

IR (ATR): 3292, 1749, 1652, 1541, 1472, 1459, 1437, 1368, 1267, 1139, 729 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1005 (18) $[2M+Na]^+$, 514 (100) $[M+Na]^+$, 492 (33) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{25}F_3N_3O_5^+$ 492.1741 $[M+H]^+$, found 492.1734.

Methyl acetyl-1-(2-pyridyl)-2-(4-methoxyphenyl propionate-3-yl)-L-tryptophanate (142hf)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and 4-methoxyphenyl acrylate (**129f**, 40 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hf** as a colorless oil (56 mg, 73%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.94 (ddd, *J* = 7.2, 7.2, 1.8 Hz, 1H), 7.60–7.54 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.33–7.29 (m, 1H), 7.19–7.15 (m, 2H), 6.87–6.78 (m, 4H), 6.28 (d, *J* = 7.8 Hz, 1H), 4.98 (ddd, *J* = 8.0, 5.9, 5.9 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.40 (dd, *J* = 15.1, 6.2 Hz, 1H), 3.37–3.31 (m, 2H), 3.31–3.26 (m, 1H), 2.62–2.51 (m, 2H), 1.90 (s, 3H).

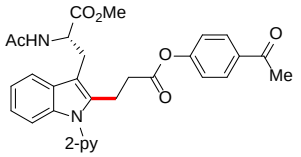
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (C_q), 171.3 (C_q), 169.8 (C_q), 157.1 (C_q), 151.0 (C_q), 149.6 (CH), 143.8 (C_q), 138.6 (CH), 136.7 (C_q), 136.4 (C_q), 128.6 (C_q), 122.5 (CH), 122.3 (CH), 122.1 (CH), 120.9 (CH), 120.8 (CH), 118.5 (CH), 114.3 (CH), 109.9 (CH), 109.6 (C_q), 55.6 (CH_3), 52.8 (CH), 52.4 (CH_3), 33.8 (CH_2), 27.2 (CH_2), 23.1 (CH_3), 20.4 (CH_2).

IR (ATR): 2952, 2927, 1742, 1654, 1505, 1470, 1459, 1436, 1369, 1190, 1135, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1053 (42) $[2M+Na]^+$, 538 (100) $[M+Na]^+$, 516 (71) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{30}N_3O_6^+$ 516.2129 $[M+H]^+$, found 516.2126.

Methyl acetyl-1-(2-pyridyl)-2-(4-acetylphenyl propionate-3-yl)-L-tryptophanate (142hg)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and 4-acetylphenyl acrylate (**129g**, 42 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hg** as a colorless oil (55 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.93 (dm, *J* = 8.7 Hz, 3H), 7.59–7.53 (m, 1H), 7.50 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.40–7.28 (m, 2H), 7.21–7.13 (m, 2H), 7.05 (dm, *J* = 8.7 Hz, 2H), 6.25 (d, *J* = 7.8 Hz, 1H), 4.97 (ddd, *J* = 7.9, 6.0, 6.0 Hz, 1H), 3.68 (s, 3H), 3.48–3.21 (m, 4H), 2.75–2.61 (m, 2H), 2.57 (s, 3H), 1.92 (s, 3H).

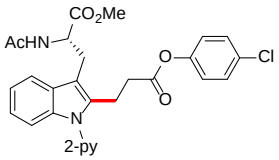
^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.6 (C_q), 172.4 (C_q), 170.3 (C_q), 169.7 (C_q), 154.0 (C_q), 151.0 (C_q), 149.7 (CH), 138.5 (CH), 136.6 (C_q), 136.2 (C_q), 134.6 (C_q), 129.8 (CH), 128.5 (C_q), 122.6 (CH), 122.3 (CH), 121.5 (CH), 120.8 (CH), 120.8 (CH), 118.5 (CH), 110.0 (CH), 109.6 (C_q), 52.9 (CH), 52.4 (CH_3), 34.0 (CH_2), 27.2 (CH_2), 26.6 (CH_3), 23.1 (CH_3), 20.3 (CH_2).

IR (ATR): 2952, 2927, 1745, 1680, 1585, 1471, 1459, 1436, 1265, 1201, 1119, 739 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 550 (100) $[M+Na]^+$, 528 (72) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{30}N_3O_6^+$ 528.2129 $[M+H]^+$, found 528.2136.

Methyl acetyl-1-(2-pyridyl)-2-(4-chlorophenyl propionate-3-yl)-L-tryptophanate (142hj)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and 4-chlorophenyl acrylate (**129j**, 41 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hj** as a white solid (50 mg, 64%).

m. p.: 84 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.94 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.58–7.55 (m, 1H), 7.51 (ddd, *J* = 8.0, 0.9, 0.9 Hz, 1H), 7.36 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.33–7.31 (m, 1H), 7.28 (dm, *J* = 8.8 Hz, 2H), 7.19–7.15 (m, 2H), 6.89 (dm, *J* = 8.8 Hz, 2H), 6.21 (d, *J* = 7.8 Hz, 1H), 4.97 (ddd, *J* = 7.9, 6.0, 6.0 Hz, 1H), 3.69 (s, 3H), 3.39 (dd, *J* = 14.8, 6.4 Hz, 1H), 3.37–3.31 (m, 2H), 3.31–3.26 (m, 1H), 2.67–2.55 (m, 2H), 1.92 (s, 3H).

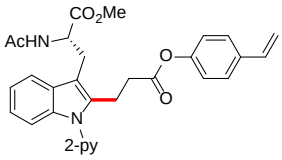
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (C_q), 170.7 (C_q), 169.7 (C_q), 151.1 (C_q), 149.7 (CH), 148.8 (C_q), 138.5 (CH), 136.6 (C_q), 136.3 (C_q), 131.1 (C_q), 129.3 (CH), 128.6 (C_q), 122.7 (CH), 122.6 (CH), 122.3 (CH), 120.8 (CH), 120.8 (CH), 118.5 (CH), 110.0 (CH), 109.6 (C_q), 52.9 (CH), 52.4 (CH_3), 33.9 (CH_2), 27.2 (CH_2), 23.2 (CH_3), 20.4 (CH_2).

IR (ATR): 2953, 2925, 1741, 1654, 1468, 1471, 1459, 1436, 1197, 1133, 1086, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1061 (5) $[2M+Na]^+$, 542 (100) $[M+Na]^+$, 520 (69) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{27}ClN_3O_5^+$ 520.1634 $[M+H]^+$, found 520.1639.

Methyl acetyl-1-(2-pyridyl)-2-(4-styryl propionate-3-yl)-L-tryptophanate (142ho)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and 4-styryl acrylate (**129o**, 34 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142ho** as a white solid (42 mg, 55%).

m. p.: 108 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.94 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.60–7.54 (m, 1H), 7.51 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.37 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 7.35 (dm, *J* = 8.6 Hz, 2H), 7.32–7.29 (m, 1H), 7.19–7.15 (m, 2H), 6.89 (dm, *J* = 8.6 Hz, 2H), 6.66 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.29 (d, *J* = 7.8 Hz, 1H), 5.67 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.22 (dd, *J* = 10.8, 0.8 Hz, 1H), 4.99 (ddd, *J* = 7.8, 5.9, 5.9 Hz, 1H), 3.70 (s, 3H), 3.43–3.26 (m, 4H), 2.64–2.53 (m, 2H), 1.90 (s, 3H).

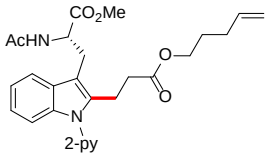
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (C_q), 170.9 (C_q), 169.9 (C_q), 151.1 (C_q), 149.9 (C_q), 149.7 (CH), 138.6 (CH), 136.7 (C_q), 136.4 (C_q), 135.7 (CH), 135.3 (C_q), 128.6 (C_q), 127.0 (CH), 122.6 (CH), 122.3 (CH), 121.4 (CH), 120.9 (CH), 120.8 (CH), 118.5 (CH), 114.0 (CH_2), 110.0 (CH), 109.6 (C_q), 52.9 (CH), 52.5 (CH_3), 33.9 (CH_2), 27.2 (CH_2), 23.1 (CH_3), 20.4 (CH_2).

IR (ATR): 3265, 2934, 1743, 1655, 1586, 1505, 1470, 1459, 1436, 1368, 1197, 1166, 1135, 782, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1045 (100) $[2M+Na]^+$, 534 (99) $[M+Na]^+$, 512 (15) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{30}N_3O_5^+$ 512.2180 $[M+H]^+$, found 512.2172.

Methyl acetyl-1-(2-pyridyl)-2-(5-pent-1-ene propionate-3-yl)-L-tryptophanate (142hp)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and pent-4-en-1-yl acrylate (**129p**, 42 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hp** as a colorless oil (54 mg, 75%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.62–8.66 (m, 1H), 7.92 (ddd, *J* = 8.0, 7.4, 2.0 Hz, 1H), 7.58–7.52 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.31–7.27 (m, 1H), 7.19–7.11 (m, 2H), 6.27 (d, *J* = 7.9 Hz, 1H), 5.74 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 5.00–4.91 (m, 3H), 4.02–3.95 (m, 2H), 3.71 (s, 3H), 3.37 (dd, *J* = 14.9, 6.2 Hz, 1H), 3.32 (dd, *J* = 14.9, 6.2 Hz, 1H), 3.26–3.15 (m, 2H), 2.36–2.26 (m, 2H), 2.05–2.00 (m, 2H), 1.96 (s, 3H), 1.66–1.60 (m, 2H).

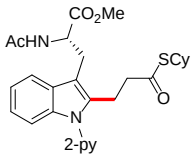
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (C_q), 172.3 (C_q), 169.7 (C_q), 151.0 (C_q), 149.5 (CH), 138.5 (CH), 137.2 (CH), 136.8 (C_q), 136.6 (C_q), 128.5 (C_q), 122.4 (CH), 122.2 (CH), 120.9 (CH), 120.7 (CH), 118.5 (CH), 115.2 (CH_2), 109.9 (CH), 109.4 (C_q), 64.0 (CH_2), 52.8 (CH), 52.4 (CH_3), 33.7 (CH_2), 29.9 (CH_2), 27.7 (CH_2), 27.1 (CH_2), 23.1 (CH_3), 20.3 (CH_2).

IR (ATR): 3274, 2952, 1732, 1655, 1470, 1459, 1436, 1368, 1167, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 977 (6) $[2M+Na]^+$, 500 (91) $[M+Na]^+$, 478 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{27}H_{32}N_3O_5^+$ 478.2336 $[M+H]^+$, found 478.2342.

Methyl acetyl-1-(2-pyridyl)-2-(*S*-cyclohexyl propanethioate-3-yl)-L-tryptophanate (142hq)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and *S*-cyclohexyl prop-2-enethioate (**129q**, 77 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hq** as a white solid (57 mg, 75%).

m. p.: 185 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.94 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.57–7.52 (m, 1H), 7.49 (ddd, *J* = 8.0, 0.9, 0.9 Hz, 1H), 7.36 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H), 7.31–7.27 (m, 1H), 7.17–7.12 (m, 2H), 6.24 (d, *J* = 7.8 Hz, 1H), 4.97 (ddd, *J* = 7.8, 5.9, 5.9 Hz, 1H), 3.71 (s, 3H), 3.45–3.37 (m, 1H), 3.35 (dd, *J* = 14.8, 5.9 Hz, 1H), 3.30 (dd, *J* = 14.8, 5.9 Hz, 1H), 3.27–3.15 (m, 2H), 2.51 (ddd, *J* = 8.6, 6.8, 2.7 Hz, 2H), 1.97 (s, 3H), 1.84–1.78 (m, 2H), 1.67–1.61 (m, 2H), 1.58–1.51 (m, 1H), 1.41–1.18 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.8 (C_q), 172.4 (C_q), 169.7 (C_q), 150.9 (C_q), 149.5 (CH), 138.7 (CH), 136.7 (C_q), 136.5 (C_q), 128.6 (C_q), 122.5 (CH), 122.3 (CH), 120.9 (CH), 120.8 (CH), 118.5 (CH), 109.9

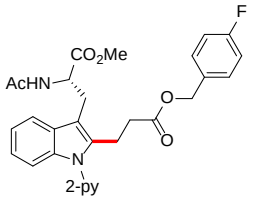
(CH), 109.5 (C_q), 52.8 (CH), 52.5 (CH_3), 43.3 (CH_2), 42.4 (CH), 33.0 (CH_2), 27.1 (CH_2), 25.9 (CH_2), 25.6 (CH_2), 23.2 (CH_3), 21.0 (CH_2).

IR (ATR): 2927, 2852, 1742, 1675, 1470, 1459, 1436, 1369, 740 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1037 (36) $[2M+Na]^+$, 530 (100) $[M+Na]^+$, 508 (11) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{34}N_3O_4S^+$ 508.2265 $[M+H]^+$, found 508.2252.

Methyl acetyl-1-(2-pyridyl)-2-(4-fluorobenzyl propionate-3-yl)-L-tryptophanate (142hr)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and 4-fluorobenzyl acrylate (**129r**, 37 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hr** as a colorless oil (51 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.90 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.56–7.52 (m, 1H), 7.40 (ddd, *J* = 7.9, 1.0, 1.0 Hz, 1H), 7.33 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.29–7.26 (m, 1H), 7.20–7.13 (m, 4H), 6.98–6.90 (m, 2H), 6.25 (d, *J* = 7.8 Hz, 1H), 4.99–4.92 (m, 3H), 3.67 (s, 3H), 3.38–3.28 (m, 2H), 3.28–3.17 (m, 2H), 2.41–2.28 (m, 2H), 1.95 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.6 (C_q), 172.2 (C_q), 169.9 (C_q), 162.6 (d, $^1J_{CF}$ = 247.2 Hz, CF), 151.0 (C_q), 149.6 (CH), 138.7 (CH), 136.7 (C_q), 136.6 (C_q), 131.5 (d, $^4J_{CF}$ = 3.2 Hz, C_q), 130.1 (d, $^3J_{CF}$ = 8.3 Hz, CH), 128.6 (C_q), 122.6 (CH), 122.3 (CH), 121.0 (CH), 120.9 (CH), 118.6 (CH), 115.4 (d, $^2J_{CF}$ = 21.6 Hz, CH), 110.0 (CH), 109.6 (C_q), 65.6 (CH_2), 52.8 (CH), 52.4 (CH_3), 33.6 (CH_2), 27.0 (CH_2), 23.1 (CH_3), 20.3 (CH_2).

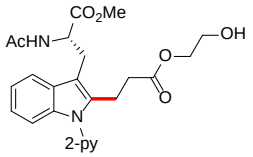
^{19}F NMR (471 MHz, $CDCl_3$): δ = –113.5 (m).

IR (ATR): 2953, 1732, 1656, 1586, 1511, 1471, 1459, 1436, 1370, 1221, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1057 (52) $[2M+Na]^+$, 540 (100) $[M+Na]^+$, 518 (17) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{29}FN_3O_5^+$ 518.2086 $[M+H]^+$, found 518.2081.

Methyl acetyl-1-(2-pyridyl)-2-(2-hydroxyethyl propionate-3-yl)-L-tryptophanate (142hs)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and 2-hydroxyethyl acrylate (**129s**, 34 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hs** as a colorless oil (34 mg, 51%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.47–7.37 (m, 2H), 7.31 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.26–7.18 (m, 1H), 7.13–7.05 (m, 2H), 6.67 (d, *J* = 6.9 Hz, 1H), 4.84 (ddd, *J* = 7.7, 6.2, 6.2 Hz, 1H), 4.03 (ddd, *J* = 5.8, 2.6, 1.5 Hz, 2H), 3.66–3.53 (m, 2H), 3.59 (s, 3H), 3.34–3.25 (m, 2H), 3.25–3.15 (m, 2H), 2.31 (dd, *J* = 7.8, 1.9 Hz, 2H), 1.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (C_q), 172.2 (C_q), 170.3 (C_q), 150.8 (C_q), 149.5 (CH), 138.6 (CH), 136.5 (C_q), 136.5 (C_q), 128.2 (C_q), 122.3 (CH), 122.3 (CH), 120.9 (CH), 120.6 (CH), 118.1 (CH), 109.9

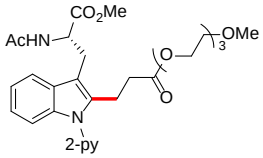
(CH), 109.4 (C_q), 66.3 (CH_2), 60.4 (CH_2), 53.1 (CH), 52.4 (CH_3), 33.9 (CH_2), 27.2 (CH_2), 22.9 (CH_3), 20.5 (CH_2).

IR (ATR): 3292, 2953, 1733, 1654, 1586, 1471, 1458, 1436, 1370, 1223, 1167, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 929 (12) $[2M+Na]^+$, 476 (100) $[M+Na]^+$, 454 (75) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{28}N_3O_6^+$ 454.1973 $[M+H]^+$, found 454.1971.

Methyl acetyl-1-(2-pyridyl)-2-{2-[2-(2-methoxyethoxy)ethoxy]ethyl propionate-3-yl}-L-tryptophanate (142ht)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and 2-[2-(2-methoxyethoxy)ethoxy]ethyl acrylate (**129t**, 49 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142ht** as a colorless oil (62 mg, 74%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.92 (ddd, *J* = 7.5, 7.5, 2.1 Hz 1H), 7.58–7.49 (m, 1H), 7.47 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.34 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.30–7.23 (m, 1H), 7.18–7.09 (m, 2H), 6.35 (d, *J* = 7.7 Hz, 1H), 4.96 (ddd, *J* = 7.8, 6.0, 6.0 Hz, 1H), 4.16–4.10 (m, 2H), 3.70 (s, 3H), 3.63–3.56 (m, 8H), 3.56–3.50 (m, 2H), 3.36 (s, 3H), 3.35–3.31 (m, 2H), 3.28–3.13 (m, 2H), 2.34 (ddd, *J* = 8.7, 6.9, 1.9 Hz, 2H), 1.95 (s, 3H).

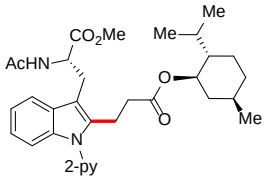
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.5 (C_q), 172.3 (C_q), 169.8 (C_q), 151.1 (C_q), 149.7 (CH), 138.5 (CH), 136.7 (C_q), 136.7 (C_q), 128.5 (C_q), 122.4 (CH), 122.2 (CH), 120.9 (CH), 120.7 (CH), 118.5 (CH), 109.9 (CH), 109.3 (C_q), 71.9 (CH_2), 70.5 (CH_2), 70.5 (CH_2), 70.5 (CH_2), 69.0 (CH_2), 63.7 (CH_2), 59.0 (CH_3), 52.8 (CH), 52.4 (CH_3), 33.6 (CH_2), 27.1 (CH_2), 23.1 (CH_3), 20.3 (CH_2).

IR (ATR): 3289, 2947, 2876, 1733, 1658, 1584, 1568, 1532, 1474, 1459, 1437, 1369, 1177, 1104, 744 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1133 (3) $[2M+Na]^+$, 578 (100) $[M+Na]^+$, 556 (55) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{38}N_3O_8^+$ 556.2653 $[M+H]^+$, found 556.2646.

Methyl acetyl-1-(2-pyridyl)-2-((–)-menthyl propionate-3-yl)-L-tryptophanate (142hu)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and (–)-menthyl acrylate (**129u**, 47 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hu** as a white solid (51 mg, 62%).

m. p.: 84 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 7.93 (ddd, *J* = 8.0, 7.4, 2.0 Hz, 1H), 7.57–7.52 (m, 1H), 7.46 (ddd, *J* = 8.0, 0.9, 0.9 Hz, 1H), 7.35 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.30–7.27 (m, 1H), 7.17–7.11 (m, 2H), 6.30 (d, *J* = 7.7 Hz, 1H), 4.97 (ddd, *J* = 7.8, 5.9, 5.9 Hz, 1H), 4.56 (ddd, *J* = 10.9, 10.9, 4.4 Hz, 1H), 3.72 (s, 3H), 3.37 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.32 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.28–

3.15 (m, 2H), 2.24 (dd, *J* = 7.6, 7.6 Hz, 2H), 1.96 (s, 3H), 1.79 (dddd, *J* = 12.0, 3.9, 3.9, 1.9 Hz, 1H), 1.67–1.52 (m, 3H), 1.39 (ddddd, *J* = 15.2, 8.5, 3.2, 3.2, 3.2 Hz, 1H), 1.29–1.17 (m, 1H), 1.04–0.92 (m, 1H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.82–0.79 (m, 1H), 0.79–0.77 (m, 1H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.62 (d, *J* = 6.9 Hz, 3H).

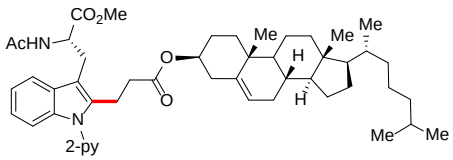
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (C_q), 171.9 (C_q), 151.1 (C_q), 149.5 (CH), 138.4 (CH), 136.8 (C_q), 136.7 (C_q), 130.0 (C_q), 128.6 (C_q), 122.4 (CH), 122.1 (CH), 120.8 (CH), 120.7 (CH), 118.5 (CH), 109.8 (CH), 109.4 (C_q), 74.3 (CH), 52.8 (CH), 52.4 (CH_3), 47.0 (CH), 40.9 (CH_2), 34.2 (CH_2), 33.9 (CH_2), 31.4 (CH), 27.1 (CH_2), 26.4 (CH), 23.7 (CH_2), 23.1 (CH_3), 22.1 (CH_3), 20.8 (CH_3), 20.5 (CH_2), 16.5 (CH_3).

IR (ATR): 2953, 2927, 2868, 1729, 1656, 1471, 1459, 1436, 1369, 1176, 1148, 739 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1117 (49) $[2M+Na]^+$, 570 (69) $[M+Na]^+$, 548 (100) $[M+H]^+$, 410 (11) $[M–menthol+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{32}H_{42}N_3O_5^+$ 548.3119 $[M+H]^+$, found 548.3109.

Methyl acetyl-1-(2-pyridyl)-2-(cholesteryl propionate-3-yl)-L-tryptophanate (142hv)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg), cholesteryl acrylate (**129v**, 98 mg) and a mixture of HOAc (150 µL) and toluene (150 µL) as the solvent. The reaction was carried out at 100 °C. Purification by column chromatography (EtOAc) yielded tryptophan **142hv** as a white solid (100 mg, 86%).

m. p.: 92 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.64 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.92 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.55–7.49 (m, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.34 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 7.27–7.24 (m, 1H), 7.15–7.10 (m, 2H), 6.34 (d, *J* = 7.8 Hz, 1H), 5.31–5.26 (m, 1H), 4.95 (ddd, *J* = 7.8, 6.0, 6.0 Hz, 1H), 4.46 (dddd, *J* = 10.9, 10.9, 6.5, 4.4 Hz, 1H), 3.70 (s, 3H), 3.36 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.30 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.23–3.12 (m, 2H), 2.29–2.17 (m, 2H), 2.17–2.12 (m, 2H), 2.00–1.95 (m, 1H), 1.95–1.89 (m, 1H), 1.93 (s, 3H), 1.84–1.76 (m, 2H), 1.75–1.69 (m, 1H), 1.58–0.95 (m, 21H), 0.94 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.64 (s, 3H).

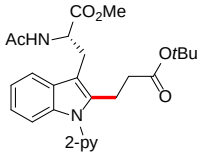
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (C_q), 171.7 (C_q), 170.0 (C_q), 151.1 (C_q), 149.7 (CH), 139.4 (C_q), 138.6 (CH), 137.0 (C_q), 136.7 (C_q), 128.6 (C_q), 122.6 (CH), 122.4 (CH), 122.4 (CH), 121.1 (CH), 120.7 (CH), 118.4 (CH), 109.9 (CH), 109.3 (C_q), 74.2 (CH), 56.7 (CH), 56.2 (CH), 52.9 (CH), 52.5 (CH_3), 50.0 (CH), 42.4 (C_q), 39.8 (CH_2), 39.6 (CH_2), 38.0 (CH_2), 37.0 (CH_2), 36.6 (C_q), 36.2 (CH_2), 35.8 (CH), 34.0 (CH_2), 31.9 (CH_2), 31.9 (CH), 28.3 (CH_2), 28.1 (CH), 27.7 (CH_2), 27.1 (CH_2), 24.3 (CH_2), 23.9 (CH_2), 23.2 (CH_3), 22.9 (CH_3), 22.6 (CH_3), 21.1 (CH_2), 20.4 (CH_2), 19.3 (CH_3), 18.8 (CH_3), 11.9 (CH_3).

IR (ATR): 3294, 2952, 1733, 1647, 1557, 1471, 1458, 1436, 1369, 1202, 1169, 1141, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 800 (100) $[M+Na]^+$, 778 (26) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{49}H_{68}N_3O_5^+$ 778.5153 $[M+H]^+$, found 778.5133.

Methyl acetyl-1-(2-pyridyl)-2-(*tert*-butyl propionate-3-yl)-L-tryptophanate (142hx)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and *tert*-butyl acrylate (**129x**, 57 mg). Purification by column chromatography (EtOAc) yielded tryptophan **142hx** as a colorless oil (28 mg, 40%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.65–8.63 (m, 1H), 7.93 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.56–7.52 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 7.2, 4.8 Hz, 1H), 7.31–7.27 (m, 1H), 7.18–7.11 (m, 3H), 6.27 (d, *J* = 7.8 Hz, 1H), 4.97 (ddd, *J* = 7.9, 6.0. 6.0 Hz, 1H), 3.71 (s, 3H), 3.37 (dd, *J* = 14.8, 6.1 Hz, 1H), 3.33 (dd, *J* = 14.8, 6.1 Hz, 1H), 3.22–3.11 (m, 2H), 2.22–2.12 (m, 2H), 1.96 (s, 3H), 1.33 (s, 9H).

^{13}C NMR (76 MHz, $CDCl_3$): δ = 172.5 (C_q), 171.7 (C_q), 170.0 (C_q), 150.9 (C_q), 149.3 (CH), 139.0 (CH), 137.2 (C_q), 136.7 (C_q), 128.7 (C_q), 122.5 (CH), 122.4 (CH), 121.2 (CH), 120.9 (CH), 118.5 (CH), 109.8 (CH), 109.5 (C_q), 80.5 (C_q), 52.8 (CH), 52.4 (CH_3), 34.9 (CH_2), 27.9 (CH_3), 27.0 (CH_2), 23.1 (CH_3), 20.5 (CH_2).

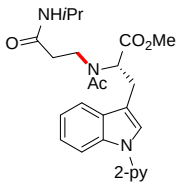
IR (ATR): 3291, 1733, 1646, 1557, 1471, 1458, 1435, 1369, 1203, 1141, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 953 (41) $[2M+Na]^+$, 488 (100) $[M+Na]^+$, 466 (80) $[M+H]^+$, 410 (88) $[M–tBu+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{32}N_3O_5^+$ 466.2336 $[M+H]^+$, found 466.2326.

5.3.9 Analytical Data for Alkylated Tryptophans 158 and 186

Methyl N^α-acetyl-N^α-[3-(isopropylamino)-3-oxopropyl]-1-(2-pyridyl)-L-tryptophanate (158ha)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg) and *N*-isopropylacrylamide (**131a**, 30 mg) in H_2O/HOAc (9:1, 150 µL). Purification by column chromatography (EtOAc) yielded trytophan **158ha** as a white solid (68 mg, 88%).

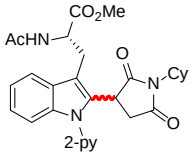
m. p.: 85 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.53–8.48 (m, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.82–7.77 (m, 1H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.28–7.23 (m, 1H), 7.18 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.14 (dd, *J* = 7.4, 4.8 Hz, 1H), 6.31 (d, *J* = 7.9 Hz, 1H), 4.95 (ddd, *J* = 7.9, 5.5, 5.5 Hz, 1H), 4.31 (t, *J* = 6.3 Hz, 2H), 4.08–4.00 (m, 1H), 3.67 (s, 3H), 3.34 (dd, *J* = 14.9, 5.5 Hz, 1H), 3.29 (dd, *J* = 14.9, 5.6 Hz, 1H), 2.42 (t, *J* = 6.3 Hz, 2H), 2.00 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.3 (C_q), 170.8 (C_q), 169.8 (C_q), 152.0 (C_q), 148.6 (CH), 138.9 (CH), 135.3 (C_q), 130.4 (C_q), 124.5 (CH), 123.7 (CH), 121.5 (CH), 120.2 (CH), 119.0 (CH), 114.7 (CH), 113.4 (C_q), 113.1 (CH), 60.9 (CH_2), 52.9 (CH), 52.6 (CH_3), 41.7 (CH), 36.3 (CH_2), 27.7 (CH_2), 23.0 (CH_3), 21.1 (CH_3).

IR (ATR): 3288, 2971, 1737, 1644, 1591, 1542, 1472, 1455, 1437, 1368, 1230, 1037, 742 cm^{-1}.

Methyl acetyl-1-(2-pyridyl)-2-(1-cyclohexylpyrrolidine-2,5-dione-3-yl)-L-tryptophanate (186)



The general procedure D1 was followed using tryptophan **56h** (25.0 mg, 74 µmol) and 1-cyclohexyl-1*H*-pyrrole-2,5-dione (**185**, 20 mg, 0.11 mmol, 1.5 equiv) in 74 µL HOAc at 100 °C. Purification by column chromatography (EtOAc) yielded trytophan **186** as a colorless oil (29 mg, 56 µmol, 76%, dr = 1:1).

Due to formation of two diastereomers, the NMR spectra show a double set of signals.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 8.42 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.91 (ddd, *J* = 7.2, 7.2, 2.0 Hz, 1H), 7.89 (ddd, *J* = 7.2, 7.2, 2.0 Hz, 1H), 7.69–7.65 (m, 1H), 7.56–7.51 (m, 3H), 7.41–7.38 (m, 1H), 7.34–7.31 (m, 1H), 7.31–7.27 (m, 2H), 7.25–7.22 (m, 2H), 7.22–7.15 (m, 3H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.02 (ddd, *J* = 8.5, 6.0, 4.4 Hz, 1H), 4.76 (ddd, *J* = 9.8, 4.8, 4.8 Hz, 1H), 4.46–4.38 (m, 2H), 3.99 (dddd, *J* = 12.3, 12.3, 3.9, 3.9 Hz, 1H), 3.90 (dddd, *J* = 12.3, 12.3, 3.9, 3.9 Hz, 1H), 3.79 (s, 3H), 3.62 (s, 3H), 3.57–3.50 (m, 1H), 3.46 (dd, *J* = 14.8, 4.8 Hz, 1H), 3.20 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.11 (dd, *J* = 14.8, 9.9 Hz, 1H), 3.03 (dd, *J* = 18.0, 6.7 Hz, 1H), 2.95 (dd, *J* = 18.0, 9.7 Hz, 1H), 2.83 (dd, *J* = 18.2, 10.0 Hz, 1H), 2.54 (dd, *J* = 18.2, 6.3 Hz, 1H), 2.20–2.09 (m, 2H), 2.09–1.95 (m, 2H), 2.01 (s, 3H), 1.98 (s, 3H), 1.89–1.77 (m, 4H), 1.68–1.60 (m, 4H), 1.52–1.42 (m, 2H), 1.39–1.23 (m, 4H), 1.23–1.14 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.9 (C_q), 177.9 (C_q), 175.7 (C_q), 175.7 (C_q), 173.0 (C_q), 172.1 (C_q), 171.1 (C_q), 170.6 (C_q), 151.0 (C_q), 150.9 (C_q), 149.5 (CH), 149.4 (CH), 139.0 (CH), 138.9 (CH), 136.6 (C_q), 136.5 (C_q), 131.6 (C_q), 130.2 (C_q), 128.0 (C_q), 127.6 (C_q), 123.9 (CH), 123.7 (CH), 122.3 (CH), 122.3 (CH), 121.5 (CH), 121.2 (CH), 120.6 (CH), 119.9 (CH), 119.1 (CH), 119.1 (CH), 114.4 (C_q), 114.4 (C_q) 110.4 (CH), 110.3 (CH), 53.0 (CH), 52.5 (CH_3), 52.5 (CH_3), 52.2 (CH), 52.1 (CH), 52.0 (CH), 38.3 (CH), 37.8 (CH), 35.8 (CH_2), 34.3 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 28.6 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.8 (CH_2), 25.8 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 23.0 (CH_3), 22.6 (CH_3).

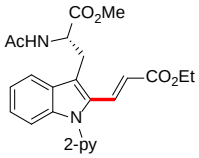
IR (ATR): 3282, 2935, 2856, 1740, 1693, 1583, 1472, 1436, 1397, 1370, 1186, 1141, 735 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1055 (64) $[2M+Na]^+$, 539 (100) $[M+Na]^+$, 517 (7) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{33}N_4O_5^+$ 517.2445 $[M+H]^+$, found 517.2440.

5.3.10 Analytical Data for Olefinated and Allylated Tryptophans 143, 189, 191, and 193

(*E*)-Methyl acetyl-1-(2-pyridyl)-2-(ethyl propenoate-3-yl)-L-tryptophanate (143ha)



The general procedure D1 was followed using tryptophan **56h** (50.6 mg), ethyl acrylate (**129a**, 45 mg), $[Ru(OAc)_2(p\text{-cymene})]_2$ (42 mg) and NaCl (175 mg). Purification by column chromatography (EtOAc) yielded tryptophan **143ha** as a colorless oil (10 mg, 15%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.71 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.91 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.68 (d, *J* = 16.2 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.41 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H), 7.31 (ddd, *J* = 8.9, 8.1, 0.9 Hz, 2H), 7.27–7.24 (m, 1H), 7.19 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.06 (d, *J* = 7.9 Hz, 1H), 5.49 (d, *J* = 16.2 Hz, 1H), 5.02 (ddd, *J* = 7.9, 5.5, 5.5 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 3.56 (d, *J* = 5.5 Hz, 2H), 1.94 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H).

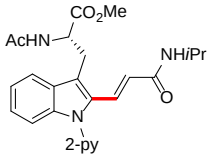
^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.7 (C_q), 169.6 (C_q), 166.5 (C_q), 151.2 (C_q), 149.8 (CH), 139.4 (C_q), 138.7 (CH), 132.0 (C_q), 131.5 (CH), 128.5 (C_q), 125.5 (CH), 123.0 (CH), 122.3 (CH), 121.5 (CH), 119.7 (CH), 119.0 (CH), 118.2 (C_q), 111.0 (CH), 60.6 (CH_2), 52.7 (CH), 52.6 (CH_3), 27.5 (CH_2), 23.2 (CH_3), 14.4 (CH_3).

IR (ATR): 3276, 2956, 2923, 2853, 1737, 1663, 1527, 1469, 1454, 1438, 1369, 1178, 1030, 746 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 893 (34) $[2M+Na]^+$, 458 (53) $[M+Na]^+$, 436 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{26}N_3O_5^+$ 436.1867 $[M+H]^+$, found 436.1857.

(*E*)-Methyl acetyl-1-(2-pyridyl)-2-(isopropylacrylamide-3-yl)-L-tryptophanate (189ha)



A Schlenk flask was charged with tryptophan **56h** (50.0 mg, 148 µmol), isopropylacrylamide (**131a**, 33.5 mg, 296 µmol, 2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (4.5 mg, 7.4 µmol, 5.0 mol %), KPF_6 (5.4 mg, 30 µmol, 20 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (53.8 mg, 296 µmol, 2.0 equiv) and the flask was evacuated and refilled with N_2 three times. H_2O (0.5 mL) was added via syringe and the mixture was stirred at 110 °C for 17 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (3.0 mL) and purified by column chromatography. The product **189ha** was obtained as a white solid (6.0 mg, 13 µmol, 9%).

m. p.: 93 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74–8.63 (m, 1H), 7.90 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.50 (d, *J* = 16.1 Hz, 1H), 7.44 (ddd, *J* = 7.8, 1.4 Hz, 2H), 7.35 (ddd, *J* = 7.7, 3.7, 1.3 Hz, 2H), 7.24–7.12 (m, 2H), 6.67 (d, *J* = 16.1 Hz, 1H), 6.66–6.61 (m, 1H), 6.44 (d, *J* = 7.9 Hz, 1H), 4.87 (ddd, *J* = 9.5, 7.9, 4.7 Hz, 1H), 4.21–4.05 (m, 1H), 3.52–3.30 (m, 2H), 3.41 (s, 3H), 2.05 (s, 3H), 1.21 (d, *J* = 6.5 Hz, 6H).

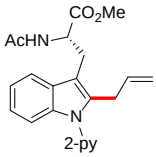
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.8 (C_q), 169.7 (C_q), 165.0 (C_q), 151.0 (C_q), 149.8 (CH), 138.6 (CH), 137.5 (C_q), 133.1 (C_q), 129.0 (C_q), 127.7 (CH), 124.8 (CH), 124.4 (CH), 122.5 (CH), 121.9 (CH), 121.3 (CH), 118.7 (CH), 114.1 (C_q), 111.3 (CH), 53.2 (CH_3), 52.8 (CH), 41.6 (CH), 30.2 (CH_2), 23.6 (CH_3), 23.0 (CH_3), 22.9 (CH_3).

IR (ATR): 3278, 2954, 2924, 1733, 1646, 1556, 1471, 1457, 1436, 1371, 1204, 1170, 1141, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 897 (5) $[2M+Na]^+$, 471 (100) $[M+Na]^+$, 449 (53) $[M+H]^+$, 362 (35).

HR-MS (ESI) *m/z* calcd for $C_{25}H_{29}N_4O_4^+$ 449.2183 $[M+H]^+$, found 449.2188.

Methyl acetyl-1-(2-pyridyl)-2-allyl-L-tryptophanate (191ha)



The general procedure D1 was followed using tryptophan **56h** (25.0 mg, 74 µmol) and allylacetate (**190a**, 22 mg, 0.22 mmol, 3.0 equiv) in 74 µL HOAc. Purification by column chromatography (EtOAc) yielded trytophan **191ha** as a colorless oil (16.4 mg, 59%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.63 (ddd, *J* = 4.9, 1.2, 1.2 Hz, 1H), 7.87 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.55–7.51 (m, 1H), 7.42 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.33–7.28 (m, 2H), 7.17–7.12 (m, 2H), 6.12 (d, *J* = 7.8 Hz, 1H), 5.68 (dddd, *J* = 17.3, 10.1, 5.8, 5.8 Hz, 1H), 4.92 (ddd, *J* = 7.9, 5.9, 5.9 Hz, 1H), 4.83 (dddd, *J* = 10.0, 1.6, 1.6, 1.6 Hz, 1H), 4.72 (dddd, *J* = 17.1, 1.6, 1.6, 1.6 Hz, 1H), 3.70–3.68 (m, 2H), 3.68 (s, 3H), 3.33 (d, *J* = 6.0 Hz, 2H), 1.94 (s, 3H).

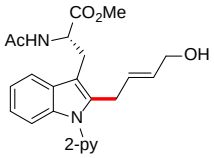
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.6 (C_q), 169.8 (C_q), 151.4 (C_q), 149.5 (CH), 138.3 (CH), 136.9 (C_q), 135.9 (C_q), 135.2 (CH), 128.7 (C_q), 122.5 (CH), 122.3 (CH), 121.4 (CH), 120.8 (CH), 118.4 (CH), 116.1 (CH_2), 110.2 (CH), 109.3 (C_q), 53.0 (CH), 52.6 (CH_3), 29.2 (CH_2), 27.3 (CH_2), 23.4 (CH_3).

IR (ATR): 3276, 2952, 1740, 1655, 1586, 1470, 1458, 1436, 1369, 1222, 1202, 732 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 777 (15) $[2M+Na]^+$, 400 (50) $[M+Na]^+$, 378 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{22}H_{24}N_3O_3^+$ 378.1812 $[M+H]^+$, found 378.1806.

Methyl acetyl-1-(2-pyridyl)-2-((*E*)-but-2-en-1-ol-4-yl)-L-tryptophanate (193ha)



The general procedure D1 was followed using tryptophan **56h** (25.0 mg, 74 µmol) and 4-vinyl-1,3-dioxolan-2-one (**192a**, 25 mg, 0.22 mmol, 3.0 equiv) in 74 µL HOAc. Purification by column chromatography (EtOAc) yielded trytophan **193ha** as a colorless oil (16 mg, 39 µmol, 53%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.67–8.61 (m, 1H), 7.89–7.84 (m, 1H), 7.54–7.47 (m, 1H), 7.44–7.38 (m, 1H), 7.35–7.30 (m, 1H), 7.29–7.27 (m, 1H), 7.16–7.11 (m, 2H), 6.08 (d, *J* = 7.9 Hz, 1H), 5.23 (dddd, *J* = 15.3, 6.1, 6.1, 1.8 Hz, 1H), 5.13–5.04 (m, 1H), 4.91 (ddd, *J* = 8.0, 5.8, 5.8 Hz, 1H), 3.68 (s, 3H), 3.57 (ddd, *J* = 6.1, 1.6, 1.6 Hz, 2H), 3.33 (d, *J* = 5.9 Hz, 2H), 1.94 (s, 3H), 1.42 (dddd, *J* = 6.4, 1.6, 1.6, 1.6 Hz, 2H).

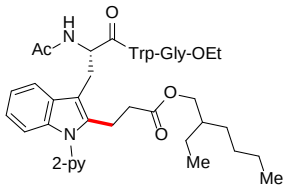
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.6 (C_q), 169.7 (C_q), 151.5 (C_q), 149.5 (CH), 138.2 (CH), 136.9 (CH), 136.9 (CH), 128.7 (C_q), 127.5 (C_q), 126.8 (C_q), 122.4 (CH), 122.3 (CH), 121.5 (CH), 120.7 (CH), 118.3 (CH), 110.2 (CH), 108.7 (C_q), 53.0 (CH), 52.6 (CH_3), 28.2 (CH_2), 27.2 (CH_2), 23.4 (CH_3), 17.9 (CH_2).

MS (ESI) *m/z* (relative intensity) 430 (27) $[M+Na]^+$, 408 (100) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{23}H_{25}N_3O_4^+$ 408.1918 $[M+H]^+$, found 408.1912.

5.3.11 Analytical Data for Alkylated Peptides 147

Ethyl acetyl-1-(2-pyridyl)-2-[(2-ethyl)*n*-hexyl propionate-3-yl]-L-tryptophyl-L-tryptophyl-glycinate (147jd)



The general procedure D2 was followed using peptide **101j** (10.0 mg) and 2-ethylhexyl acrylate (**129d**, 16 mg) in 100 µL HOAc. Purification by PTLC (EtOAc) yielded peptide **147jd** as a colorless oil (7.9 mg, 60%).

^{1}H NMR (500 MHz, CD_3OD): δ = 8.61 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 8.06 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.60–7.57 (m, 1H), 7.55 (ddd, *J* = 7.9, 1.0, 1.0 Hz, 1H), 7.51–7.47 (m, 2H), 7.29 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.18–7.15 (m, 1H), 7.10–7.07 (m, 2H), 7.06 (s, 1H), 7.04 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.94 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.73–4.66 (m, 1H), 4.63–4.59 (m, 1H), 4.11 (ddd, *J* = 7.1. 7.1, 7.1 Hz, 2H), 3.89–3.79 (m, 2H), 3.78–3.67 (m, 2H), 3.26–3.19 (m, 2H), 3.17 (dd, *J* = 7.6, 7.6 Hz, 2H), 3.08 (ddd, *J* = 14.7, 7.1, 3.9 Hz, 2H), 2.34–2.27 (m, 1H), 2.22 (ddd, *J* = 15.9, 7.8, 7.8 Hz, 1H), 1.82 (s, 3H), 1.38 (p, *J* = 6.0 Hz, 1H), 1.22 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.20–1.15 (m, 8H), 0.85 (dd, *J* = 7.1, 7.1 Hz, 3H), 0.77 (dd, *J* = 7.4, 7.4 Hz, 3H).

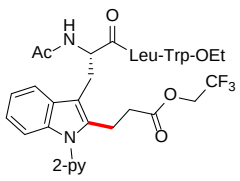
^{13}C NMR (126 MHz, CD_3OD): δ = 174.1 (C_q), 173.5 (C_q), 173.2 (C_q), 173.0 (C_q), 170.7 (C_q), 152.4 (C_q), 150.5 (CH), 140.5 (CH), 138.4 (C_q), 137.8 (C_q), 137.7 (C_q), 129.6 (C_q), 128.8 (C_q), 124.8 (CH), 124.1 (CH), 123.4 (CH), 123.1 (CH), 122.2 (CH), 121.7 (CH), 119.7 (CH), 119.7 (CH), 119.2 (CH), 112.2 (CH), 111.2 (C_q), 110.7 (CH), 110.5 (C_q), 67.9 (CH_2), 62.2 (CH_2), 55.6 (CH), 55.4 (CH), 42.2 (CH_2), 40.1 (CH), 34.5 (CH_2), 31.4 (CH_2), 30.0 (CH_2), 28.7 (CH_2), 27.9 (CH_2), 24.8 (CH_2), 24.0 (CH_2), 22.6 (CH_3), 21.5 (CH_2), 14.5 (CH_3), 14.4 (CH_3), 11.3 (CH_3).

IR (ATR): 2958, 2927, 2858, 1732, 1634, 1583, 1470, 1456, 1436, 1193, 740 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1579 (4) $[2M+Na]^+$, 801 (100) $[M+Na]^+$, 779 (20) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{44}H_{55}N_6O_7^+$ 779.4127 $[M+H]^+$, found 779.4122.

Ethyl *N*-acetyl-1-(2-pyridyl)-2-(2,2,2-trifluoroethyl propionate-3-yl)-L-tryptophyl-L-leucyl-L-tryptophanate (147ke)



The general procedure D2 was followed using peptide **101k** (20.0 mg) and 2,2,2-trifluoroethyl acrylate (**129e**, 24 mg) in 120 µL HOAc. Purification by column chromatography (EtOAc) yielded peptide **147ke** as a white solid (14.1 mg, 57%).

m. p.: 104 °C.

^{1}H NMR (600 MHz, CD_3OD): δ = 8.60 (dd, *J* = 5.1, 1.9 Hz, 1H), 8.00 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.65–7.61 (m, 2H), 7.48–7.43 (m, 2H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.15–7.11 (m, 1H), 7.09–7.03 (m, 4H), 6.97 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.73 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.52 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.44 (ddd, *J* = 8.8, 8.8, 8.8 Hz, 2H), 4.40 (dd, *J* = 9.5, 5.5 Hz, 1H), 4.00 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 2H), 3.25 (dd, *J* =

14.4, 7.6 Hz, 1H), 3.22–3.15 (m, 2H), 3.15–3.07 (m, 3H), 2.48–2.33 (m, 2H), 1.91 (s, 3H), 1.61–1.54 (m, 1H), 1.50–1.38 (m, 2H), 1.06 (dd, *J* = 7.2, 7.2 Hz, 3H), 0.87 (d, *J* = 7.8 Hz, 3H), 0.86 (d, *J* = 7.8 Hz, 3H).

^{13}C NMR (126 MHz, CD_3OD): δ = 173.9 (C_q), 173.3 (C_q), 173.2 (C_q), 172.9 (C_q), 172.1 (C_q), 152.3 (C_q), 150.4 (CH), 140.6 (CH), 138.4 (C_q), 137.9 (C_q), 137.2 (C_q), 129.7 (C_q), 128.6 (C_q), 125.6 (C_q), 124.5 (CH), 124.1 (CH), 123.4 (CH), 123.3 (CH), 122.3 (CH), 121.6 (CH), 119.7 (CH), 119.7 (CH), 119.1 (CH), 112.2 (CH), 111.3 (C_q), 110.7 (CH), 110.4 (C_q), 62.2 (CH_2), 61.0 (CH_2), 55.4 (CH), 55.1 (CH), 52.9 (CH), 42.4 (CH_2), 33.9 (CH_2), 28.4 (CH_2), 28.1 (CH_2), 25.7 (CH), 23.4 (CH_3), 22.6 (CH_3), 22.3 (CH_3), 21.2 (CH_2), 14.3 (CH_3).

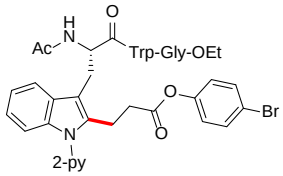
^{19}F NMR (376 MHz, CD_3OD): δ = –75.43 (m).

IR (ATR): 3281, 2930, 1739, 1634, 1458, 1435, 1378, 1281, 1146, 740 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 827 (100) $[M+Na]^+$, 805 (30) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{42}H_{47}F_3N_6O_7^+$ 805.3531 $[M+H]^+$, found 805.3550.

Ethyl *N*-acetyl-1-(2-pyridyl)-2-(4-bromophenyl propionate-3-yl)-L-tryptophyl-L-tryptophyl-glycinate (147jk)



The general procedure D2 was followed using peptide **101j** (20.0 mg) and 4-bromophenyl acrylate (**129k**, 11 mg) in 100 µL HOAc. Purification by PTLC (EtOAc) yielded peptide **147jk** as a white solid (16.4 mg, 58%).

m. p.: 144 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.01 (d, *J* = 6.7 Hz, 1H), 8.73 (ddd, *J* = 4.7, 2.0, 0.8 Hz, 1H), 8.71 (s, 1H), 8.44 (dd, *J* = 5.9, 5.9 Hz, 1H), 8.27–8.21 (m, 1H), 8.21–8.13 (m, 1H), 7.75 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.65–7.53 (m, 4H), 7.38–7.30 (m, 3H), 7.28 (dm, *J* = 8.8 Hz, 2H), 7.21–7.12 (m, 2H), 6.73 (dm, *J* = 8.8 Hz, 2H), 4.89 (ddd, *J* = 12.0, 9.3, 2.3 Hz, 1H), 4.66 (ddd, *J* = 10.5, 6.8, 3.7 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.95–3.81 (m, 2H), 3.51–3.40 (m, 1H), 2.21–3.23 (m, 1H), 3.12–2.80 (m, 5H), 2.15–2.03 (m, 1H), 1.99 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 175.2 (C_q), 172.5 (C_q), 172.0 (C_q), 171.3 (C_q), 170.8 (C_q), 170.0 (C_q), 157.7 (C_q), 151.1 (C_q), 150.3 (CH), 140.1 (CH), 137.0 (C_q), 135.6 (C_q), 135.4 (C_q), 132.4 (CH), 130.9 (C_q), 128.0 (CH), 125.6 (CH), 124.1 (CH), 123.5 (CH), 123.0 (CH), 121.3 (CH), 121.1 (CH), 119.8 (CH), 119.3 (C_q), 119.1 (CH), 118.2 (CH), 116.3 (CH), 111.4 (C_q), 110.5 (CH), 110.0 (C_q), 61.0 (CH_2), 54.9 (CH), 50.8 (CH), 41.4 (CH_2), 37.0 (CH_2), 29.0 (CH_2), 27.7 (CH_2), 23.3 (CH_3), 23.1 (CH_2), 14.6 (CH_3).

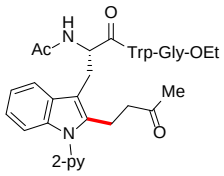
IR (ATR): 3288, 1739, 1641, 1531, 1471, 1458, 1436, 1196, 1123, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1665 (14) $[2M+Na]^+$, 845/843 (100) $[M+Na]^+$, 823/821 (5) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{42}H_{42}{}^{79}BrN_6O_7^+$ 821.2293 $[M+H]^+$, found 821.2283.

5.3.12 Analytical Data for Alkylated Peptides 156

Ethyl acetyl-1-(2-pyridyl)-2-(butane-3-one-1-yl)-L-tryptophyl-L-tryptophyl-glycinate (156ja)



The general procedure D2 was followed using peptide **101j** (40.0 mg) and but-3-en-2-one (**130a**, 14 mg) in 200 µL HOAc. Purification by PTLC (first PTLC with EtOAc/THF 3:2, followed by a second PTLC with MeCN) yielded peptide **156ja** as a white solid (37 mg, 83%).

m. p.: 105 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.60 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 8.03 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.57 (ddd, *J* = 5.7, 3.2, 0.8 Hz, 1H), 7.54–7.44 (m, 3H), 7.29 (ddd, *J* = 8.1, 0.9. 0.9 Hz, 1H), 7.16–6.99 (m, 5H), 6.99–6.89 (m, 1H), 4.67 (ddd, *J* = 11.5, 5.4, 2.0 Hz, 2H), 4.16–4.04 (m, 2H), 3.77–3.70 (m, 2H), 3.27–3.14 (m, 2H), 3.15–2.99 (m, 4H), 2.58–2.38 (m, 2H), 1.94 (s, 3H), 1.82 (s, 3H), 1.25–1.17 (dd, *J* = 7.2, 7.2 Hz, 3H).

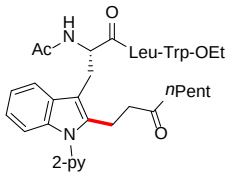
^{13}C NMR (126 MHz, CD_3OD): δ = 210.0 (C_q), 173.6 (C_q), 173.2 (C_q), 173.1 (C_q), 170.8 (C_q), 152.3 (C_q), 150.4 (CH), 140.6 (CH), 138.4 (C_q), 138.3 (C_q), 137.8 (C_q), 129.6 (C_q), 128.7 (C_q), 124.8 (CH), 124.1 (CH), 123.3 (CH), 123.2 (CH), 122.2 (CH), 121.6 (CH), 119.7 (CH), 119.5 (CH), 119.2 (CH), 112.2 (CH), 110.8 (CH), 110.7 (C_q), 110.4 (C_q), 62.3 (CH_2), 55.6 (CH), 55.4 (CH), 43.5 (CH_2), 42.1 (CH_2), 29.8 (CH_3), 28.8 (CH_2), 28.0 (CH_2), 22.6 (CH_3), 20.0 (CH_2), 14.5 (CH_3).

IR (ATR): 3300, 2912, 1740, 1703, 1628, 1539, 1471, 1458, 1437, 1368, 1206, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 687 (100) $[M+Na]^+$, 665 (26) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{37}H_{41}N_6O_6^+$ 665.3082 $[M+H]^+$, found 665.3067.

Ethyl acetyl-1-(2-pyridyl)-2-(octane-3-one-1-yl)-L-tryptophyl-L-leucyl-L-tryptophanate (156kb)



The general procedure D2 was followed using peptide **101k** (15.0 mg) and oct-1-en-3-one (**130b**, 14 mg) in 150 µL HOAc. Purification by PTLC (hexanes/EtOAc 1:4) yielded peptide **156kb** as a colorless oil (9.2 mg, 51%).

^{1}H NMR (500 MHz, CD_3OD): δ = 8.60 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 8.01 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.63 (ddd, *J* = 8.9, 8.0, 0.9 Hz, 2H), 7.49–7.43 (m, 2H), 7.29 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 1H), 7.14–7.09 (m, 1H), 7.09–7.01 (m, 4H), 6.97 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.71 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.55 (dd, *J* = 6.9, 6.9 Hz, 1H), 4.42 (dd, *J* = 9.5, 5.6 Hz, 1H), 4.05–3.98 (m, 2H), 3.27–3.21 (m, 2H), 3.22–3.03 (m, 2H), 3.03–2.97 (m, 2H), 2.51–2.36 (m, 3H), 2.20 (ddd, *J* = 7.3, 7.3, 2.1 Hz, 1H), 1.91 (s, 3H), 1.62–1.15 (m, 9H), 1.08 (dd, *J* = 7.1, 7.1 Hz, 3H), 0.92–0.84 (m, 6H), 0.81 (dd, *J* = 7.3, 7.3 Hz, 3H).

^{13}C NMR (126 MHz, CD_3OD): δ = 212.5 (C_q), 174.2 (C_q), 173.5 (C_q), 173.5 (C_q), 173.1 (C_q), 152.6 (C_q), 150.5 (CH), 140.8 (CH), 138.5 (C_q), 138.4 (C_q), 138.0 (C_q), 129.8 (C_q), 128.7 (C_q), 124.6 (CH), 124.2 (CH), 123.6 (CH), 123.3 (CH), 122.4 (CH), 121.6 (CH), 119.8 (CH), 119.7 (CH), 119.2 (CH), 112.3 (CH),

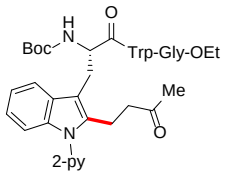
110.9 (C_q), 110.8 (CH), 110.5 (C_q), 62.2 (CH_2), 55.4 (CH), 55.2 (CH), 52.9 (CH), 43.5 (CH_2), 42.5 (CH_2), 42.3 (CH_2), 32.6, (CH_2) 28.3 (CH_2), 28.2 (CH_2), 25.6 (CH), 24.5 (CH_2), 23.5 (CH_2), 23.4 (CH_3), 22.6 (CH_3), 22.2 (CH_3), 20.0 (CH_2), 14.3 (CH_3), 14.3 (CH_3).

IR (ATR): 2955, 2926, 1736, 1711, 1636, 1583, 1566, 1458, 1436, 1369, 1206, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 799 (100) $[M+Na]^+$, 777 (28) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{45}H_{56}N_6O_6^+$ 777.4334 $[M+H]^+$, found 777.4303.

Ethyl (*tert*-butoxycarbonyl)-1-(2-pyridyl)-2-(butane-3-one-1-yl)-L-tryptophyl-L-tryptophyl-glycinate (156ea)



The general procedure D2 was followed using peptide **101e** (50.0 mg) and but-3-en-2-one (**130a**, 16 mg) in 150 µL H_2O/HOAc 9:1. Purification by GPC yielded peptide **156ea** as a colorless oil (31 mg, 56%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.72 (s, 1H), 8.65 (dd, *J* = 4.9, 2.0 Hz, 1H), 7.90 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.61 (dd, *J* = 7.3, 3.4 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.36 (ddd, *J* = 7.8, 4.8, 1.0 Hz, 1H), 7.30–7.27 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.19–7.13 (m, 2H), 7.12–7.05 (m, 2H), 6.91–6.85 (m, 1H), 6.82 (s, 1H), 6.70 (d, *J* = 6.4 Hz, 1H), 6.60–6.52 (m, 1H), 5.03 (d, *J* = 6.3 Hz, 1H), 4.71 (ddd, *J* = 8.1, 5.8, 5.8 Hz, 1H), 4.39 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.85 (dd, *J* = 17.6, 5.7 Hz, 1H), 3.73 (dd, *J* = 17.6, 5.7 Hz, 1H), 3.34–3.26 (m, 2H), 3.17 (dd, *J* = 14.7, 6.7 Hz, 1H), 3.14–3.05 (m, 2H), 2.96 (dd, *J* = 15.2, 6.1 Hz, 1H), 2.48 (dd, *J* = 7.6, 7.6 Hz, 2H), 1.96 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 2H), 1.21 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 207.1 (C_q), 171.6 (C_q), 171.2 (C_q), 169.0 (C_q), 155.5 (C_q), 151.0 (C_q), 149.5 (CH), 138.6 (CH), 137.5 (C_q), 136.7 (C_q), 135.9 (C_q), 128.3 (C_q), 127.3 (C_q), 123.7 (CH), 122.5 (CH), 122.4 (CH), 121.8 (CH), 121.2 (CH), 120.9 (CH), 119.4 (CH), 118.7 (CH), 118.0 (CH), 111.2 (CH), 109.9 (CH), 109.2 (C_q), 109.0 (C_q), 80.2 (C_q), 61.1 (CH_2), 55.4 (CH), 53.7 (CH), 42.9 (CH_2), 41.3 (CH_2), 29.8 (CH_3), 28.0 (CH_3), 27.1 (CH_2), 26.7 (CH_2), 19.0 (CH_2), 14.1 (CH_3).

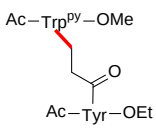
IR (ATR): 3323, 2978, 2919, 1660, 1488, 1471, 1458, 1436, 1365, 1194, 1162, 1019, 739 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1467 (10) $[2M+Na]^+$, 745 (100) $[M+Na]^+$, 723 (39) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{40}H_{47}N_6O_7^+$ 723.3501 $[M+H]^+$, found 723.3493.

5.3.13 Analytical Data for Ligated Peptides 149

Methyl acetyl-1-(2-pyridyl)-2-[*O*-(ethyl acetyl L-phenylalaninate-4-yl) propionate-3-yl]-L-tryptophanate (149a)



The general procedure D2 was followed using tryptophan **56h** (30.0 mg) and tyrosine **148a** (29.9 mg) in 270 µL HOAc. Purification by column chromatography (EtOAc/

MeOH 25:1) yielded peptide **149a** as a white solid (34 mg, 59%).

m. p.: 111 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 5.0, 1.9, 0.8 Hz, 1H), 7.94 (td, *J* = 7.7, 2.0 Hz, 1H), 7.60–7.53 (m, 1H), 7.51 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.37 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.34–7.27 (m, 1H), 7.21–7.13 (m, 2H), 7.06 (dm, *J* = 8.4 Hz, 2H), 6.86 (dm, *J* = 8.4 Hz, 2H), 6.22 (d, *J* = 7.8 Hz, 1H), 5.94 (d, *J* = 7.7 Hz, 1H), 4.97 (ddd, *J* = 7.9, 5.9, 5.9 Hz, 1H), 4.83 (ddd, *J* = 7.8, 5.8, 5.8 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 3.45–3.21 (m, 4H), 3.16–3.02 (m, 2H), 2.64–2.54 (m, 2H), 1.99 (s, 3H), 1.91 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

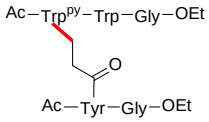
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.6 (C_q), 171.5 (C_q), 171.0 (C_q), 169.9 (C_q), 169.6 (C_q), 151.3 (C_q), 149.8 (CH), 149.6 (C_q), 138.7 (CH), 136.8 (C_q), 136.5 (C_q), 133.7 (C_q), 130.3 (CH), 128.8 (C_q), 122.7 (CH), 122.5 (CH), 121.5 (CH), 121.0 (CH), 121.0 (CH), 118.7 (CH), 110.2 (CH), 109.8 (C_q), 61.8 (CH_2), 53.3 (CH), 53.0 (CH), 52.6 (CH_3), 37.5 (CH_2), 34.1 (CH_2), 27.4 (CH_2), 23.4 (CH_3), 23.3 (CH_3), 20.6 (CH_2), 14.4 (CH_3).

IR (ATR): 3315, 2927, 1750, 1726, 1652, 1544, 1441, 1369, 1202, 1138, 1138, 740 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 665 (100) $[M+Na]^+$, 643 (4) $[M+H]^+$, 528 (47).

HR-MS (ESI) *m/z* calcd for $C_{35}H_{39}N_4O_8^+$ 643.2762 $[M+H]^+$, found 643.2766.

{*N*-acetyl [ethyl-1-(2-pyridyl)-2-{[*N*-acetyl (L-phenylalanineamide-4-yl) propionate-3-yl]}-L-tryptophyl-L-tryptophyl-glycinate]}[N^{ω}-(*O*-ethyl)acetate-2-yl] (149d)



The general procedure D2 was followed using peptide **101j** (10.0 mg) and peptide **148c** (6.7 mg). Purification by PTLC (EtOAc/MeOH 7:1) yielded peptide **149d** as a white solid (9.2 mg, 57%).

m. p.: 93 °C.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.65 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 8.08 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.67–7.58 (m, 2H), 7.52–7.46 (m, 2H), 7.28 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.20 (dm, *J* = 8.6 Hz, 3H), 7.14–7.07 (m, 2H), 7.08–7.01 (m, 2H), 6.94 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.82 (dm, *J* = 8.6 Hz, 2H), 4.69 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.65–4.58 (m, 2H), 4.15 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 2H), 4.10 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 2H), 3.90–3.87 (m, 3H), 3.76–3.66 (m, 2H), 3.28–3.21 (m, 4H), 3.17–3.08 (m, 2H), 3.08–3.01 (m, 2H), 2.84 (dd, *J* = 14.1, 9.2 Hz, 1H), 2.61–2.53 (m, 1H), 2.53–2.44 (m, 1H), 1.87 (s, 3H), 1.78 (s, 3H), 1.24 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.20 (dd, *J* = 7.1, 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3OD): δ = 175.1 (C_q), 174.8 (C_q), 174.4 (C_q), 174.3 (C_q), 174.2 (C_q), 173.8 (C_q), 172.0 (C_q), 171.9 (C_q), 153.5 (C_q), 151.8 (C_q), 151.7 (CH), 141.8 (CH), 139.5 (C_q), 138.9 (C_q), 138.6 (C_q), 137.3 (C_q), 132.2 (CH), 130.7 (C_q), 129.9 (C_q), 125.9 (CH), 125.3 (CH), 124.6 (CH), 124.3 (CH), 123.5 (CH), 123.3 (CH), 122.8 (CH), 120.8 (CH), 120.3 (CH), 117.2 (CH), 113.3 (CH), 112.5 (C_q), 111.9 (CH),

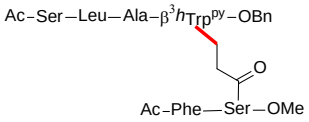
111.6 (C_q), 63.3 (CH_2), 63.3 (CH_2), 56.8 (CH), 56.6 (CH), 56.4 (CH), 43.1 (CH_2), 43.1 (CH_2), 39.1 (CH_2), 35.5 (CH_2), 29.7 (CH_2), 29.0 (CH_2), 23.5 (CH_3), 23.4 (CH_3), 22.3 (CH_2), 15.5 (CH_3), 15.5 (CH_3).

IR (ATR): 3292, 1730, 1669, 1653, 1568, 1472, 1465, 1437, 1372, 1197, 744 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 979 (100) $[M+Na]^+$, 957 (2) $[M+H]^+$, 703 (14).

HR-MS (ESI) *m/z* calcd for $C_{51}H_{56}N_8NaO_{11}^+$ 979.3961 $[M+Na]^+$, found 979.3960.

Benzyl (acetyl-L-serinyl)-L-leucyl-L-alanyl-1-(2-pyridyl)-2-[(methyl (acetyl-L-phenylalanyl)-L-alaninate-3-yl) propionate-3-yl]-β³-*homo*-L-tryptophanate (149e)



The general procedure D2 was followed using peptide Ac-Ser-Leu-Ala-β³*h*Trp^{py}-OBn (**101**, 10.8 mg) and peptide **148b** (11.2 mg) in 50 µL HOAc. Purification by PTLC (first PTLC with EtOAc/MeOH 8:1, followed by a second PTLC with EtOAc/MeOH 10:1) yielded peptide **149e** as a white solid (6.9 mg, 42%).

m. p.: 142 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.65 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.91 (ddd, *J* = 7.7, 7.7, 2.0 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.56 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.46–7.40 (m, 2H), 7.34 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 7.31 (d, *J* = 3.0 Hz, 5H), 7.28–7.21 (m, 2H), 7.21–7.14 (m, 4H), 7.14–7.07 (m, 2H), 6.90 (s, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 5.12–5.06 (m, 2H), 5.04 (ddd, *J* = 8.3, 8.3, 6.0 Hz, 1H), 4.84 (ddd, *J* = 8.7, 4.7, 4.7 Hz, 1H), 4.71–4.65 (m, 1H), 4.56 (dd, *J* = 7.3, 7.3 Hz, 2H), 4.47 (dd, *J* = 11.5, 3.8 Hz, 1H), 4.40–4.34 (m, 1H), 4.26 (dd, *J* = 11.4, 5.4 Hz, 1H), 3.71–3.68 (m, 1H), 3.69 (s, 3H), 3.27–3.22 (m, 1H), 3.22–3.15 (m, 2H), 3.15–3.07 (m, 2H), 3.07–2.98 (m, 2H), 2.93 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.66 (dd, *J* = 16.2, 5.8 Hz, 1H), 2.62–2.57 (dd, *J* = 16.2, 5.8 Hz, 1H), 2.35–2.24 (m, 2H), 1.98 (s, 3H), 1.83 (s, 3H), 1.69–1.64 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 5.7 Hz, 3H), 0.88 (d, *J* = 5.7 Hz, 3H).

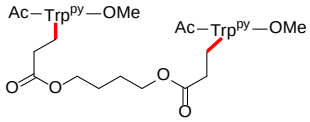
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.6 (C_q), 172.2 (C_q), 172.2 (C_q), 171.6 (C_q), 171.2 (C_q), 170.6 (C_q), 170.3 (C_q), 170.2 (C_q), 169.4 (C_q), 151.2 (C_q), 149.6 (CH), 138.7 (CH), 136.6 (C_q), 136.4 (C_q), 136.4 (C_q), 136.3 (C_q), 135.5 (C_q), 129.2 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 126.7 (CH), 122.4 (CH), 122.3 (CH), 121.0 (CH), 120.8 (CH), 118.7 (CH), 110.7 (C_q), 109.9 (CH), 68.7 (CH_2), 66.6 (CH_2), 63.8 (CH_2), 54.9 (CH), 54.8 (CH), 53.9 (CH), 53.7 (CH), 52.7 (CH), 51.5 (CH_3), 49.0 (CH), 40.4 (CH_2), 38.9 (CH_2), 38.3 (CH_2), 34.0 (CH_2), 29.2 (CH_2), 25.0 (CH), 23.2 (CH_3), 23.2 (CH_3), 23.1 (CH_3), 21.4 (CH_3), 20.7 (CH_2), 18.9 (CH_3).

IR (ATR): 3290, 2938, 1733, 1645, 1531, 1471, 1457, 1437, 1124, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1083 (100) $[M+Na]^+$, 1061 (26) $[M+H]^+$, 550 (60).

HR-MS (ESI) *m/z* calcd for $C_{56}H_{69}N_8O_{13}^+$ 1061.4979 $[M+H]^+$, found 1061.4963.

Butane-1,4-diyl bis[methyl acetyl-1-(2-pyridyl)-2-(propionate-3-yl)-L-tryptophanate] (149j)



The general procedure D2 was followed using tryptophan **56h** (50.6 mg) and butane-1,4-diyl diacrylate (**129ζ**, 15 mg). Purification by column chromatography (EtOAc) yielded peptide **149j** as a white solid (35 mg, 54%).

m. p.: 86 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.62 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 2H), 7.91 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 2H), 7.56–7.53 (m, 2H), 7.45 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 2H), 7.33 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 2H), 7.29–7.27 (m, 2H), 7.16–7.13 (m, 4H), 6.31 (d, *J* = 7.8 Hz, 2H), 4.95 (ddd, *J* = 7.8, 6.0, 6.0 Hz, 2H), 3.96–3.89 (m, 4H), 3.69 (s, 6H), 3.40–3.27 (m, 4H), 3.25–3.12 (m, 4H), 2.31 (ddd, *J* = 8.5, 7.0, 3.1 Hz, 4H), 1.94 (s, 6H), 1.61–1.66 (m, 4H), 1.46–1.51 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.5 (C_q), 172.3 (C_q), 169.8 (C_q), 162.5 (C_q), 151.1 (C_q), 149.6 (CH), 138.5 (CH), 136.7 (C_q), 136.7 (C_q), 128.5 (C_q), 122.4 (CH), 122.3 (CH), 120.9 (CH), 120.7 (CH), 118.4 (CH), 109.9 (CH), 109.3 (C_q), 63.9 (CH_2), 52.8 (CH), 52.4 (CH_3), 33.7 (CH_2), 27.1 (CH_2), 25.1 (CH_2), 23.1 (CH_3), 20.4 (CH_2).

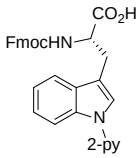
IR (ATR): 2953, 2924, 1731, 1653, 1470, 1459, 1436, 1369, 1167, 740 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 895 (100) $[M+Na]^+$, 873 (71) $[M+H]^+$, 456 (80).

HR-MS (ESI) *m/z* calcd for $C_{48}H_{53}N_6O_{10}^+$ 873.3818 $[M+H]^+$, found 873.3799.

5.3.14 Analytical Data for Tryptophan 166a

***N*$^\alpha$-(9-Fluorenylmethoxycarbonyl)-1-(2-pyridyl)-L-tryptophan (166a)**



A solution of FmocOSu (9-Fluorenylmethyl *N*-succinimidyl carbonate, 1.89 g, 5.6 mmol) in dioxane (20 mL) was added dropwise to a solution of H-Trp^{py}-OH·2HCl (1.98 g, 5.6 mmol) and DIEA (9.7 mL, 56 mmol) in dioxane/DMF (1:1, 500 mL). The mixture was stirred at ambient temperature for 10 h. Then, the solvent was removed in vacuum and the product was purified by column chromatography (2% HOAc in hexanes/EtOAc 1:1). The product **166a** was obtained as a white solid (1.78 g, 63%).

m. p.: 93 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.79 (br s, 1H), 8.54 (dd, *J* = 5.0, 1.8 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 7.94 (ddd, *J* = 9.0, 7.5, 1.9 Hz, 1H), 7.88 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.72–7.58 (m, 4H), 7.40–7.30 (m, 2H), 7.31–7.12 (m, 5H), 4.37 (ddd, *J* = 8.9, 8.9, 4.6 Hz, 1H), 4.25–4.11 (m, 3H), 3.30 (dd, *J* = 14.7, 4.7 Hz, 1H), 3.14 (dd, *J* = 14.7, 9.6 Hz, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 173.1 (C_q), 155.7 (C_q), 151.7 (C_q), 148.3 (CH), 143.5 (C_q), 140.4 (C_q), 138.8 (CH), 134.6 (C_q), 129.5 (C_q), 128.6 (CH), 127.9 (CH), 127.3 (CH), 126.7 (CH), 125.1 (CH),

122.8 (CH), 120.8 (CH), 119.8 (CH), 118.6 (CH), 114.4 (C_q), 113.7 (CH), 113.6 (CH), 65.6 (CH_2), 54.3 (CH), 46.5 (CH), 26.6 (CH_2).

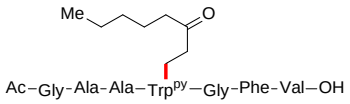
IR (ATR): 1713, 1592, 1472, 1453, 1437, 1318, 1219, 1050, 758, 736 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1029 (30) $[2M+Na]^+$, 1007 (24) $[2M+H]^+$, 526 (100) $[M+Na]^+$, 504 (79) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{31}H_{26}N_3O_4^+$ 504.1918 $[M+H]^+$, found 504.1906.

5.3.15 Analytical Data for Alkylated Peptides 161

(Acetyl glycyl)-L-alanyl-L-alanyl-1-(2-pyridyl)-2-(octane-3-one-1-yl)-L-tryptophyl-glycyl-L-phenyl-alanyl-L-valin (161a)



The general procedure E was followed using resin **159a** (60.0 mg, 0.63 mmol/g, 37.8 µmol) and oct-1-en-3-one (**130b**, 24 mg, 190 mol) in 300 µL HOAc. Purification yielded peptide **161a** as a white solid (28.2 mg, 29.6 µmol, 78%).

^{1}H NMR (500 MHz, CD_3OD): δ = 8.62 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 8.08 (ddd, *J* = 7.7, 7.7, 1.9 Hz, 1H), 7.89 (s, 1H, *NH or OH*), 7.62–7.59 (m, 1H), 7.55 (ddd, *J* = 7.9, 1.0, 1.0 Hz, 1H), 7.49 (ddd, *J* = 7.6, 5.0, 1.1 Hz, 1H), 7.28–7.20 (m, 4H), 7.20–7.14 (m, 2H), 7.13–7.06 (m, 2H), 5.18 (s, 2H, *NH*), 4.64–4.59 (m, 1H), 4.55–4.50 (m, 1H), 4.32–4.23 (m, 2H), 4.19–4.15 (m, 1H), 3.97–3.82 (m, 3H), 3.45–3.36 (m, 1H), 3.26–3.21 (m, 1H), 3.23–3.16 (m, 1H), 3.15–3.06 (m, 1H), 3.01–2.93 (m, 1H), 2.54–2.41 (m, 2H), 2.24 (dd, *J* = 7.3, 7.3 Hz, 2H), 2.16–2.10 (m, 1H), 1.98 (s, 3H), 1.43–1.34 (m, 4H), 1.33 (d, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.23–1.18 (m, 2H), 1.15–1.08 (m, 2H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.82 (t, *J* = 7.0 Hz, 3H).

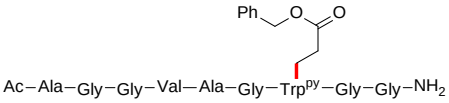
^{13}C NMR (126 MHz, CD_3OD): δ = 212.2 (C_q), 175.6 (C_q), 175.0 (C_q), 174.1 (C_q), 174.0 (C_q), 172.7 (C_q), 172.4 (C_q), 171.4 (C_q), 152.6 (C_q), 150.6 (CH), 140.8 (CH), 138.9 (C_q), 138.5 (C_q), 138.4 (C_q), 131.0 (CH), 130.4 (C_q), 129.8 (CH), 127.6 (CH), 124.2 (CH), 123.4 (CH), 123.3 (CH), 121.8 (CH), 119.6 (CH), 111.1 (C_q), 110.9 (CH), 61.4 (CH), 56.6 (CH), 56.3 (CH), 51.4 (CH), 51.0 (CH), 44.0 (CH_2), 43.6 (CH_2), 43.5 (CH_2), 42.8 (CH_2), 38.5 (CH_2), 32.7 (CH), 32.4 (CH_2), 27.5 (CH_2), 24.6 (CH_2), 23.5 (CH_2), 22.6 (CH_3), 20.2 (CH_2), 20.2 (CH_3), 18.6 (CH_3), 17.6 (CH_3), 17.3 (CH_3), 14.8 (CH_3).

IR (ATR): 3272, 2954, 2926, 1627, 1532, 1451, 1436, 1387, 1370, 1261, 1174, 873, 710 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 974 (100) $[M+Na]^+$, 952 (9) $[M+H]^+$.

HR-MS (ESI) *m/z* calcd for $C_{50}H_{65}N_9NaO_{10}^+$ 974.4747 $[M+Na]^+$, found 974.4730.

(Acetyl L-alanyl)-glycyl-glycyl-L-valinyl-L-alanyl-glycyl-1-(2-pyridyl)-2-(benzyl propionate-3-yl)-L-tryptophyl-glycyl-glycinamide (161d)



The general procedure E was followed using resin **159b** (85.9 mg, 0.35 mmol/g, 30.0 µmol) and benzyl acrylate (**129b**, 15 mg, 90 µmol) in 300 µL HOAc. Purification yielded peptide **161d** as a white solid (21.0 mg, 20.8 µmol, 69%).

^{1}H NMR (500 MHz, DMSO-d$_6$, 70 °C): δ = 8.64–8.61 (m, 1H), 8.13–8.08 (m, 1H), 8.08–8.03 (m, 1H), 8.02–7.72 (m, 8H), 7.66–7.63 (m, 1H), 7.62–7.58 (d, *J* = 9 Hz, 1H), 7.55–7.52 (m, 1H), 7.49–7.46 (m, 1H), 7.19–7.16 (m, 1H), 7.12–7.06 (m, 4H), 6.95–6.80 (br s, 2H), 4.31–4.21 (m, 2H), 4.20–4.14 (m, 1H), 3.81–3.69 (m, 10H), 3.68–3.62 (m, 2H), 3.53 (s, 2H), 3.10–2.97 (m, 2H), 2.45–2.39 (m, 1H), 2.22–2.18 (m, 1H), 2.05–1.97 (m, 1H), 1.86 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H).

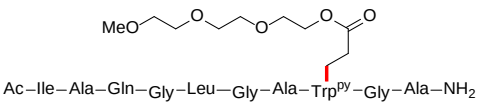
^{13}C NMR (126 MHz, DMSO-d$_6$, 70 °C): δ = 173.2 (C$_q$), 172.9 (C$_q$), 171.2 (C$_q$), 171.2 (C$_q$), 171.1 (C$_q$), 169.8 (C$_q$), 169.6 (C$_q$), 169.5 (C$_q$), 169.3 (C$_q$), 169.0 (C$_q$), 161.4 (CH), 149.3 (CH), 139.0 (CH), 128.7 (CH), 125.9 (CH), 122.6 (CH), 121.6 (CH), 121.2 (CH), 120.0 (CH), 118.5 (CH), 190.7 (CH), 70.2 (CH$_2$), 58.0 (CH), 48.9 (CH), 48.9 (CH), 42.7 (CH$_2$), 42.6 (CH$_2$), 42.4 (CH$_2$), 42.3 (CH$_2$), 42.3 (CH$_2$), 41.5 (CH$_2$), 40.8 (CH$_2$), 31.0 (CH), 30.6 (CH$_2$), 23.0 (CH$_3$), 19.0 (CH$_3$), 18.7 (CH$_2$), 17.9 (CH$_3$), 17.6 (CH$_3$), 17.6 (CH$_3$).

IR (ATR): 3279, 2926, 1648, 1628, 1535, 1422, 1372, 1236, 1024, 672 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1301 (9) [M+Na]$^+$, 1279 (100) [M+H]$^+$.

HR-MS (ESI) *m/z* calcd for $C_{61}H_{95}N_{15}NaO_{15}^+$ 1301.6501 [M+Na]$^+$, found 1301.6487.

(Acetyl L-isoleucyl)-L-alanyl-L-glutaminyl-glycyl-L-leucyl-glycyl-L-alanyl-(1-(2-pyridyl)-2-({2-[2-(2-methoxyethoxy)ethoxy]ethyl} propionate-3-yl)-L-tryptophyl)-glycyl-L-alaninamide (161f)



The general procedure E was followed using resin **159c** (81.0 mg, 0.37 mmol/g, 30.0 µmol) and 2-[2-(2-methoxy-ethoxy)ethoxy]ethyl acrylate (**129t**, 65 mg, 300 µmol) in 300 µL HOAc. Purification yielded peptide **161f** as a white solid (16.5 mg, 12.9 µmol, 43%).

^{1}H NMR (600 MHz, DMSO-d$_6$): δ = 8.64–8.62 (m, 1H, *CH*), 8.21 (dd, *J* = 5.7, 5.7 Hz, 1H, *NH*), 8.18 (dd, *J* = 5.7, 5.7 Hz, 1H, *NH*), 8.10–8.05 (m, 3H, 2*NH*, *CH*), 8.02 (d, *J* = 7.0 Hz, 1H, *NH*), 7.96 (d, *J* = 7.9 Hz, 1H, *NH*), 7.94–7.89 (m, 2H, *NH*), 7.81 (d, *J* = 7.5 Hz, 1H, *NH*), 7.66–7.64 (m, 1H, *CH*), 7.55–7.52 (m, 1H, *CH*), 7.49–7.45 (m, 1H, *CH*), 7.26–7.23 (m, 1H, *NH*), 7.22–7.19 (m, 1H, *NH*), 7.19–7.17 (m, 1H, *CH*), 7.10–7.07 (m, 2H, *CH*), 7.01 (br s, 1H, *NH*), 6.74 (br s, 1H, *NH*), 4.34–4.09 (m, 7H), 3.80–3.64 (m, 6H), 3.55–3.11 (m, 15H), 2.15–2.05 (m, 2H), 1.92–1.82 (m, 1H), 1.85 (s, 3H), 1.77–1.64 (m, 2H), 1.62–1.53 (m, 1H), 1.52–1.36 (m, 3H), 1.29–1.12 (m, 10H), 1.12–1.03 (m, 1H), 0.92–0.76 (m, 12H).

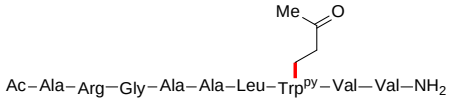
^{13}C NMR (76 MHz, DMSO-d_6): δ = 174.4 (C_q), 174.4 (C_q), 174.0 (C_q), 172.9 (C_q), 172.6 (C_q), 172.3 (C_q), 171.7 (C_q), 171.3 (C_q), 169.7 (C_q), 169.0 (C_q), 169.0 (C_q), 168.5 (C_q), 161.8 (CH), 155.0 (C_q), 152.7 (C_q), 148.9 (CH), 139.7 (CH), 136.0 (C_q), 135.2 (C_q), 130.4 (C_q), 129.3 (CH), 126.6 (CH), 121.4 (CH), 120.4 (CH), 119.4 (CH), 114.8 (C_q), 114.3 (CH), 71.7 (CH_2), 71.6 (CH_2), 70.2 (CH_2), 70.1 (CH_2), 70.0 (CH_2), 69.9 (CH_2), 58.5 (CH_3), 57.4 (CH), 52.8 (CH), 51.6 (CH), 49.0 (CH), 48.7 (CH), 48.5 (CH), 48.4 (CH), 42.6 (CH_2), 42.4 (CH_2), 42.4 (CH_2), 41.2 (CH_2), 41.1 (CH_2), 36.9 (CH), 31.8 (CH_2), 28.4 (CH_2), 24.9 (CH_2), 24.6 (CH), 23.5 (CH_3), 23.0 (CH_3), 22.1 (CH_3), 18.7 (CH_3), 18.3 (CH_3), 18.2 (CH_3), 15.8 (CH_3), 11.5 (CH_3).

IR (ATR): 3290, 2960, 2935, 1652, 1539, 1454, 1412, 1242, 1202, 1132, 1025, 751 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1301 (1) $[M+Na]^+$, 820 (100).

HR-MS (ESI) *m/z* calcd for for $C_{60}H_{90}N_{14}NaO_{17}^+$ 1301.6501 $[M+Na]^+$, found 1301.6477.

(Acetyl L-alanyl)-L-argininyl-glycyl-L-alanyl-L-alanyl-L-leucyl-1-(2-pyridyl)-2-(butane-3-one-1-yl)-L-tryptophyl-L-valinyl-L-valinamide (161g)



The general procedure E was followed using resin **159d** (81.0 mg, 0.37 mmol/g, 30.0 µmol) and but-3-en-2-one (**130a**, 21 mg, 300 µmol) in 300 µL HOAc. Purification yielded peptide **161g** as a white solid (24.0 mg, 21.2 µmol, 71%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.66–8.60 (m, 1H, *CH*), 8.25–7.82 (m, 11H, 10*NH*, *CH*), 7.81–7.60 (m, 4H, 3*NH*, *CH*), 7.56 (d, *J* = 7.5 Hz, 1H, *CH*), 7.52–7.43 (m, 2H, *NH*, *CH*), 7.37–7.21 (m, 2H, 2*NH*), 7.21–7.11 (m, 2H, *NH*, *CH*), 7.11–7.04 (m, 2H, 2*CH*), 7.04–6.98 (m, 2H, 2*NH*), 4.70– 4.60 (m, 1H), 4.40–4.13 (m, 8H), 4.13–4.02 (m, 1H), 3.77–3.64 (m, 2H), 3.23–3.12 (m, 1H), 3.12–3.03 (m, 2H), 3.03–2.91 (m, 3H), 2.48–2.35 (m, 2H), 1.95 (s, 3H), 1.83 (s, 3H), 1.75–1.64 (m, 1H), 1.64–1.41 (m, 5H), 1.41–1.31 (m, 1H), 1.30–1.08 (m, 7H), 1.02–0.94 (m, 3H), 0.92–0.73 (m, 18H).

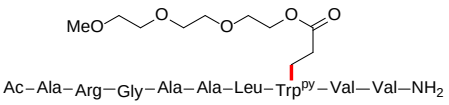
^{13}C NMR (126 MHz, DMSO-d_6): δ = 207.7 (C_q), 173.2 (C_q), 172.4 (C_q), 172.3 (C_q), 172.2 (C_q), 172.1 (C_q), 171.6 (C_q), 171.1 (C_q), 170.9 (C_q), 169.8 (C_q), 168.7 (C_q), 157.1 (C_q), 151.1 (C_q), 150.0 (CH), 139.7 (CH), 137.7 (C_q), 136.7 (C_q), 135.2 (C_q), 128.7 (C_q), 123.2 (CH), 122.3 (CH), 121.8 (CH), 120.5 (CH), 119.3 (CH), 110.3 (CH), 58.1 (CH), 58.0 (CH), 57.9 (CH), 51.8 (CH), 49.0 (CH), 48.8 (CH), 48.7 (CH), 48.5 (CH), 43.2 (CH_2), 42.3 (CH_2), 41.2 (CH_2), 40.9 (CH_2), 31.0 (CH_3), 29.5 (CH_2), 27.6 (CH_2), 25.4 (CH_2), 24.7 (CH), 24.6 (CH), 23.6 (CH_3), 23.5 (CH_3), 23.0 (CH_3), 22.8 (CH_3), 22.2 (CH_3), 22.1 (CH_3), 19.8 (CH_3), 19.2 (CH_2), 18.6 (CH_3), 18.4 (CH_3), 18.3 (CH_3), 13.0 (CH).

IR (ATR): 3277, 2960, 1622, 1519, 1470, 1165, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1152 (2) $[M+Na]^+$, 1130 (85) $[M+H]^+$, 1060 (35), 797 (85), 663 (100).

HR-MS (ESI) *m/z* calcd for $C_{55}H_{84}N_{15}O_{11}^+$ 1130.6469 $[M+H]^+$, found 1130.6461.

(Acetyl L-alanyl)-L-arginyl-glycyl-L-alanyl-L-alanyl-L-leucyl-1-(2-pyridyl)-2-({2-[2-(2-methoxyethoxy)-ethoxy]ethyl} propionate-3-yl)-L-tryptophyl-L-valinyl-L-valinamide (161h)



The general procedure E was followed using resin **159d** (81.0 mg, 0.37 mmol/g, 30.0 µmol) and 2-[2-(2-methoxy-ethoxy)ethoxy]ethyl acrylate (**129t**, 65 mg, 300 µmol) in 300 µL HOAc. Purification yielded peptide **161h** as a white solid (17.2 mg, 13.6 µmol, 45%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.6–8.54 (m, 1H, *CH*), 8.10–7.91 (m, 3H, 2*NH*, *CH*), 7.91–7-78 (m, 3H, 3*NH*), 7.78–7.60 (m, 2H, *NH*, *CH*), 7.60–7.52 (m, 1H, *NH*), 7.52–7.42 (m, 3H, 2*NH*, *CH*), 7.42–7.34 (m, 3H, *NH*, 2*CH*), 7.20–7.05 (m, 2H, *NH*, *CH*), 7.05–6.88 (br s, 3H, 3*NH*), 6.88–6.68 (br s, 1H, *NH*), 4.35–4.15 (m, 7H), 4.15–4.08 (m, 1H), 3.76–3.68 (m, 2H), 3.58–3.32 (m, 12H), 3.24 (s, 3H), 3.16–3.07 (m, 4H), 2.54–2.48 (m, 2H), 2.38–2.32 (m, 2H), 2.08–1.92 (m, 2H), 1.86 (s, 3H), 1.81–1.69 (m, 1H), 1.68–1.56 (m, 2H), 1.56–1.45 (m, 3H), 1.45–1.32 (m, 1H), 1.32–1.16 (m, 9H), 0.92–0.77 (m, 18H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.6 (C_q), 172.3 (C_q), 172.3 (C_q), 171.6 (C_q), 171.6 (C_q), 171.5 (C_q), 171.5 (C_q), 171.4 (C_q), 171.3 (C_q), 170.3 (C_q), 169.2 (C_q), 164.6 (C_q), 156.7 (C_q), 150.5 (C_q), 149.2 (CH), 138.5 (CH), 136.2 (C_q), 128.5 (C_q), 125.7 (CH), 122.3 (CH), 121.0 (CH), 119.7 (CH), 113.6 (CH), 111.7 (C_q), 110.5 (CH), 71.1 (CH_2), 71.0 (CH_2), 69.6 (CH_2), 69.5 (CH_2), 69.5 (CH_2), 69.4 (CH_2), 57.7 (CH_3), 57.7 (CH), 57.3 (CH), 57.3 (CH), 52.1 (CH), 51.2 (CH), 48.4 (CH), 48.2 (CH), 48.1 (CH), 42.1 (CH_2), 41.9 (CH_2), 41.9 (CH_2), 30.9 (CH_2), 30.8 (CH_2), 30.0 (CH), 29.9 (CH), 28.6 (CH_2), 24.6 (CH_2), 24.6 (CH_2), 24.0 (CH), 22.6 (CH_3), 22.2 (CH_3), 22.1 (CH_3), 21.5 (CH_3), 21.5 (CH_3), 18.9 (CH_3), 17.7 (CH_3), 17.7 (CH_3), 17.6 (CH_3), 17.5 (CH_3).

IR (ATR): 3278, 2954, 1618, 1509, 1472, 1094 cm^{-1}.

MS (ESI) m/z (relative intensity) 1278 (5) $[M+H]^+$, 1066 (15), 746 (100) 641 (18).

HR-MS (ESI) m/z calcd for $C_{61}H_{96}N_{15}O_{15}^+$ 1278.7205 $[M+H]^+$, found 1278.7169.

6 Literature

1 M. Essen, J. O. Metzger, E. Schmidt, U. Schneidewind, *Angew. Chem. Int. Ed.* **2002**, *41*, 414–436.

2 a) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2000**, *35*, 686–694; b) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press: Oxford, **1998**.

3 a) *Metal-Catalyzed Cross-Coupling Reactions*, Eds.: F. Diederich, P. J. Stang, Wiley-VCH: New York, **1998**; b) *Transition Metals for Organic Synthesis*, Eds.: M. Beller, C. Bolm, Wiley-VCH: Weinheim, **2004**.

4 *C–H Bond Activation in Organic Synthesis*, Ed.: J. J. Li, CRC Press, Boca Raton, **2015**.

5 a) P. Gandeepan, L. Ackermann, *Chem* **2018**, *4*, 199–222; b) M. M. Lorion, K. Maindan, A. R. Kapdi, L. Ackermann, *Chem. Soc. Rev.* **2017**, *46*, 7399–7420; c) W. Ma, P. Gandeepan, J. Li, L. Ackermann, *Org. Chem. Front.* **2017**, *4*, 1435–1467; d) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826.

6 a) B. Sezen, D. Sames, *What is C–H bond activation* in *Handbook of C–H transformations*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2005**; b) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932.

7 a) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345; b) D. Balcells, E. Clot, E. Eisenstein, *Chem. Rev.* **2010**, *110*, 749–823; c) Y. Boutlada, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820–5831.

8 J. Oxgaard, W. J. Tenn, R. J. Nielsen, R. A. Periana, W. A. Goddard, *Organometallics* **2007**, *26*, 1565–1567.

9 a) H. Wang, M. Moselage, M. J. Gonzalez, L. Ackermann, *ACS Catal.* **2016**, *6*, 2705–2709; b) D. Santrac, S. Cella, W. Wang, L. Ackermann, *Eur. J. Org. Chem.* **2016**, 5429–5436; c) R. Mei, J. Loup, L. Ackermann, *ACS Catal.* **2016**, *6*, 793–797; d) W. Ma, R. Mei, G. Tenti, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 15248–15251; e) D. Zell, M. Bursch, V. Müller, S. Grimme, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 10378–10382.

10 L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35-60.

11 M. R. Yadav, R. K. Rit, M. Shankar, A. K. Sahoo, *Asian J. Org. Chem.* **2015**, *4*, 846–864.

12 a) A. P. Kozikowski, D. Ma, J. Brewer, S. Sun, E. Costa, E. Romeo, A. Guidotti, *J. Med. Chem.* **1993**, *36*, 2908–2920; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2910; c) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013**, *18*, 6620–6662.

13 a) K. Walton, J. P. Berry, *Mar. Drugs* **2016**, 14, 73; b) R. R. Gataullin, *Russ. J. Org. Chem.* **2016**, *52*, 1227–1263; c) Y. Kasaya, K. Hoshi, Y. Terada, A. Nishida, S. Shuto, M. Arisawa, *Eur. J. Org.*

Chem. **2009**, 4606–4613; d) H. Ishikawa, *Yakuga. Zasshi* **2015**, *135*, 383–390; e) S. Lancianesi, A. Palmieri, M. Petrini, *Chem. Rev.* **2014**, *114*, 7108–7149.

14 R. J. Sundberg, in *Comprehensive Heterocyclic Chemistry*, Eds.: A. R. Katritzky, C. W. Rees; Pergamon: Oxford, **1984**; Vol. 4, 313.

15 Y. Akita, A. Inoue, K. Yamamoto, A. Ohta, T. Kurihara, M. Shimizu, *Heterocycles* **1985**, *23*, 2327–2333.

16 N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973.

17 a) B. S. Lane, D. Sames, *Org. Lett.* **2004**, *6*, 2897–2900; b) B. B. Touré, B. S. Lane, D. Sames, *Org. Lett.* **2006**, *8*, 1979–1982; c) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057; d) X. Wang, D. V. Gribkov, D. Sames, *J. Org. Chem.* **2007**, *72*, 1476–1479.

18 a) S. Islam, I. Larrosa, *Chem. Eur. J.* **2013**, *19*, 15093–15096; b) N. Lebrasseur, I. Larrosa, *J. Am. Chem. Soc.* **2008**, *130*, 2926–2927.

19 E. T. Nadres, A. Lazareva, O. Daugulis, *J. Org. Chem.* **2011**, *76*, 471–483.

20 a) L. Joucla, N. Batail, L. Djakovitch, *Adv. Synth. Catal.* **2010**, *352*, 2929–2936; b) S. Chen, Y. Liao, F. Zhao, H. Qi, S. Liu, G.-J. Deng, *Org. Lett.* **2014**, *16*, 1618–1621.

21 a) S. Potavathri, A. S. Dumas, T. A. Dwight, G. R. Naumiec, J. M. Hammann, B. DeBoef, *Tetrahedron Lett.* **2008**, *49*, 4050–4053; b) A. F. P. Biajoli, E. T. da Penha, C. R. D. Correia, *RSC Adv.* **2012**, *2*, 11930–11935; c) Y. Huang, T. Ma, P. Huang, D. Wu, Z. Lin, R. Cao, *ChemCatChem* **2013**, *5*, 1877–1883; d) J. Malmgren, A. Nagendiran, C.-W. Tai, J.-E. Bäckvall, B. Olofsson, *Chem. Eur. J.* **2014**, *20*, 13531–13535.

22 a) J. Zhou, P. Hu, M. Zhang, S. Huang, M. Wang, W. Su, *Chem. Eur. J.* **2010**, *16*, 5876–5881; b) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073.

23 a) L. Wang, W. Yi, C. Cai, *Chem. Commun.* **2011**, *47*, 806–808; b) M. Wu, J. Luo, F. Xiao, S. Zhang, G.-J. Deng, H.-A. Luo, *Adv. Synth. Catal.* **2012**, *354*, 335–340; c) N. S. Nandurkar, M. J. Bhanushali, M. D. Bhor, B. M. Bhanage, *Tetrahedron Lett.* **2008**, *49*, 1045–1048; d) J. Feng, G. Lu, M. Lv, C. Cai, *J. Organomet. Chem.* **2014**, *761*, 28–31.

24 L. Djakovitch, V. Dufaud, R. Zaidia, *Adv. Synth. Catal.* **2006**, *348*, 715–724.

25 L. Ackermann, R. Vicente, R. Born, *Adv. Synth. Catal.* **2008**, *350*, 741-748.

26 T. Itahara, *J. Chem. Soc., Chem. Commun.* **1981**, 254–255.

27 L. Ackermann, S. Barfüßer, *Synlett* **2009**, 808-812.

28 C. Hartmann, V. Meyer, *Chem. Ber.* **1894**, *27*, 426–432.

29 N. W. Alcock, R. M. Countryman, *J. Chem. Soc. Dalton Trans.* **1977**, 217–219.

30 A. Ledwith, S. Al-Kass, D. C. Sherrington, P. Bonner, *Polymer* **1981**, *22*, 143–145.

31 K. Miyamoto, M. Hirobe, M. Saito, M. Shiro, M. Ochiai, *Org. Lett.* **2007**, *9*, 1995–1998.

32 T. Okuyama, T. Takino, T. Sueda, M. Ochiai, *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367.

33 a) A. J. Hickman, M. S. Sanford, *Nature* **2012**, *484*, 177–185; b) A. J. Canty, T. Rodemann, J. H. Ryan in *Robert West AFH*, J. F. Mark (eds) *Advances in Organometallic Chemistry*, Vol. 55. Academic, New York, **2007**, 279; c) N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 11234–11241; d) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331; e) A. J. Canty, A. Ariafard, M. S. Sanford, B. F. Yates, *Organometallics* **2013**, *32*, 544–555; f) E. W. Kalberer, S. R. Whitfield, M. S. Sanford, *J. Mol. Catal. A. Chem.* **2006**, *251*, 108–113; g) B. Chen, X.-L. Hou, Y.-X. Li, Y.-D. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 7668–7671.

34 a) D.-W. Chen, M. Ochiai, *J. Org. Chem.* **1999**, *64*, 6804–6814; b) D.-W. Chen, K. Takai, M. Ochiai, *Tetrahedron Lett.* **1997**, *38*, 8211–8214; c) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174.

35 a) *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*, V. V. Zhdankin, Ed.; John Wiley & Sons: Chichester West Sussex, **2014**; b) *Iodine Chemistry and Applications*, T. Kaiho, Ed.; John Wiley & Sons: Hoboken, **2015**; c) *Arylation with Diaryliodonium Salts*, B. Olofsson; in *Hypervalent Iodine Chemistry. Topics in Current Chemistry*, T. Wirth (eds), Vol 373. Springer, Cham, **2015**.

36 a) D. R. Stuart, *Chem. Eur. J.* **2017**, *23*, 15852–15863; b) K. Aradi, B. L. Tóth, G. L. Tolnai, Z. Novák, *Synlett* **2016**, *27*, 1456–1485; c) D. Kumar, V. Arun, M. Pilania, M. K. Mehra, S. B. Khandagale, *Chemistry & Biology Interface* **2016**, *6*, 270–281.

37 Y. Wu, X. Peng, B. Luo, F. Wu, B. Liu, F. Song, P. Huang, S. Wen, *Org. Biomol. Chem.* **2014**, *12*, 9777–9780.

38 L. Ackermann, M. Dell'Acqua, S. Fenner, R. Vicente, R. Sandmann, *Org. Lett.* **2011**, 13, 2358-2360.

39 Y. Zhu, M. Bauer, J. Ploog, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 13099–13102.

40 L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332–3335.

41 L. Ackermann, R. Vicente, *Top. Curr. Chem.* **2010**, *292*, 211–229.

42 a) M. Seki, *ACS Catal.* **2014**, *4*, 4047−4050; b) R. K. Chinnagolla, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 5246–5249; c) H. Li, W. Wei, Y. Xu, C. Zhanga, X. Wan, *Chem. Commun.* **2011**, *47*, 1497–1499; d) L. Ackermann, R. Born, R. Vicente, *ChemSusChem* **2009**, *2*, 546–549; e) K. Kitazawa, T. Kochi, M. Sato, F. Kakiuchi, *Org. Lett.* **2009**, *11*, 1951–1954; f) S. Oi, R. Funayama, T. Hattori, Y. Inoue, *Tetrahedron* **2008**, *64*, 6051–6059; g) L. Ackermann, R. Born, P. Álvarez-Bercedo, *Angew. Chem. Int. Ed.* **2007**, *46*, 6364–6367; h) L. Ackermann, A. Althammer, R. Born, *Synlett* **2007**, 2833–2836; i) F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 5936–5945; j) S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* **2005**, *70*, 3113–3119; k) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123–3125.

43 C. Sollert, K. Devaraj, A. Orthaber, P. J. Gates, L. T. Pilarski, *Chem. Eur. J.* **2015**, *21*, 5380–5386.

44 V. K. Tiwari, N. Kamal, M. Kapur, *Org. Lett.* **2015**, *17*, 1766–1769.

45 C. K. Jana, S. Grimme, A. Studer, *Chem. Eur. J.* **2009**, *15*, 9078−9084.

46 *Catalytic Hydroarylation of Carbon-Carbon Multiple Bonds,* Eds.: L. G. Habgood, T. B. Gunnoe, L. Ackermann, Wiley-VCH, Weinheim, **2017**.

47 A. G. Olah, A. Molnár, *Hydrocarbon Chemistry*, Wiley-Interscience: New York, **2003**.

48 a) J. D. Hargrave, J. C. Allen, C. G. Frost, *Chem. Asian J.* **2010**, *5*, 386–396; b) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844; c) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169–196.

49 B. M. Trost, *Science* **1991**, *254*, 1471–1477.

50 a) G. E. M. Crisenza, J. F. Bower, *Chem. Lett.* **2016**, *45*, 2–9; b) R. Manikandan, M. Jeganmohan, *Org. Biomol. Chem.* **2015**, *13*, 10420–10436; c) L. Yang, H. Huang, *Chem. Rev.* **2015**, *115*, 3468−3517; d) C. Unaleroglu, B. Temelli, D. I. Tasgin, *Pure Appl. Chem.* **2014**, *86*, 925–932;

51 a) J. Li, Z. Zhang, W. Ma, M. Tang, D. Wang, L.-H. Zoua, *Adv. Synth. Catal.* **2017**, *359*, 1717–1724; b) W. Xu, N. Yoshikai, *Angew. Chem. Int. Ed.* **2016**, *55*, 12731–12735; c) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 2207–2211; d) Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.* **2012**, *51*, 4698–4701; e) L. Ilies, Q. Chen, X. Zeng, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 5221–5223.

52 a) G. E. M. Crisenza, O. O. Sokolova, J. F. Bower, *Angew. Chem. Int. Ed.* **2015**, *54*, 14866–14870; b) J. Kim, S.-W. Park, M.-H. Baik, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 13448−13451; c) T. Shibata, H. Takanoa, *Org. Chem. Front.* **2015**, *2*, 383–387; d) S. Pan, N. Ryu, T. Shibata, *Adv. Synth. Catal.* **2014**, *356*, 929–933; e) T. Shibata, T. Shizuno, *Angew. Chem. Int. Ed.* **2014**, *53*, 5410–5413; f) S. Takebayashi, T. Shibata, *Organometallics* **2012**, *31*, 4114−4117.

53 a) H. Wang, F. Pesciaioli, J. C. A. Oliveira, S. Warratz, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 15063–15067; b) C. Wang, A. Wang, M. Rueping, *Angew. Chem. Int. Ed.* **2017**, *56*, 9935–9938; c) B. Zhou, P. Ma, H. Chen, C. Wang, *Chem. Commun.* **2014**, *50*, 14558–14561.

54 H. Jin, Z. Zhu, N. Jin, J. Xie, Y. Chenga, C. Zhu, *Org. Chem. Front*. **2015**, *2*, 378–382.

55 a) S. Nakanowatari, T. Müller, J. C. A. Oliveira, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 15891–15895; b) G. Vijaykumar, A. Jose, P. K. Vardhanapu, P. Sreejyothi, K. S. Mandal, *Organometallics* **2017**, *36*, 4753−4758; c) Y. Schramm, M. Takeuchi, K. Semba, Y. Nakao, J. F. Hartwig,. *J. Am. Chem. Soc.* **2015**, *137*, 12215−12218; d) J. S. Bair, Y. Schramm, A. G. Sergeev, E. Clot, O. Eisenstein, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 13098−13101; e) W.-C. Lee, C.-H. Wang, Y.-H. Lin, W.-C. Shih, T.-G. Ong, *Org. Lett.* **2013**, *15*, 5358–5361.

56 a) Z. Zhang, M. Tang, S. Han, L. Ackermann, J. Li, *J. Org. Chem.* **2017**, *82*, 664−672; b) Q. Jiang, T. Guo, K. Wua, Z. Yu, *Chem. Commun.* **2016**, *52*, 2913–2915; c) L. Xu, C. Zhang, Y. He, L. Tan, D. Ma, *Angew. Chem. Int. Ed.* **2016**, *55*, 321–325; d) J. Qi, L. Huang, Z. Wang, H. Jiang, *Org. Biomol.*

Chem. **2013**, *11*, 8009–8013; e) L. Yang, B. Qian, H. Huang, *Chem. Eur. J.* **2012**, *18*, 9511–9515; f) L. Huang, Q. Wang, J. Qi, X. Wu, K. Huang, H. Jiang, *Chem. Sci.* **2013**, *4*, 2665–2669; g) J. H. Yoon, Y. J. Park, J. H. Lee, J. Yoo, C.-H. Jun, *Org. Lett.* **2005**, *7*, 2889–2892.

57 a) R. K. Rit, K. Ghosh, R. Mandal, A. K. Sahoo, *J. Org. Chem.* **2016**, *81*, 8552−8560; b) S. Gonell, E. Peris, *ACS Catal.* **2014**, *4*, 2811−2817; c) L. Liang, S. Fu, D. Lin, X.-Q. Zhang, Y. Deng, H. Jiang, W. Zeng, *J. Org. Chem.* **2014**, *79*, 9472−9480; d) M. Schinkel, J. Wallbaum, S. I. Kozhushkov, I. Marek, L. Ackermann, *Org. Lett.* **2013**, *15*, 4482–4484; e) M. Schinkel, I. Marek, L. Ackermann, *Angew. Chem. Int. Ed.* **2013**, *52*, 3977–3980; f) A. J. A. Watson, A. C. Maxwell, J. M. J. Williams, *Org. Lett.* **2010**, *12*, 3856–3859; g) C. S. Yi, D. W. Lee, *Organometallics* **2009**, *28*, 4266–4268; h) F. Kakiuchi, M. Sonoda, T. Tsujimoto, N. Chatani, S. Murai, *Chem. Lett.* **1999**, 1083–1084; i) S. I. Kozhushkov, D. S. Yufit, L. Ackermann, *Org. Lett.* **2008**, *10*, 3409–3412; j) L. Ackermann, S. I. Kozhushkov, D. S. Yufit, *Chem. Eur. J.* **2012**, *18*, 12068-12077.

58 a) J. N. deGruyter, L. R. Malins, P. S. Baran, *Biochemistry* **2017**, *56*, 3863–3873; b) O. Boutureira, G. J. L. Bernardes, *Chem. Rev.* **2015**, *115*, 2174–2195; c) C. D. Spicer, B. G. Davis, *Nat. Commun.* **2014**, *5*, 4740–4753; d) L. Gentilucci, R. De Marco, L. Cerisoli, *Curr. Pharm. Des.* **2010**, *16*, 3185–3203; e) E. Baslé, N. Joubert, M. Pucheault, *Chem. Biol.* **2010**, *17*, 213–227; f) P. Siman, A. Brik, *Org. Biomol. Chem.* **2012**, *10*, 5684–5697; g) S. B. Kent, *Chem. Soc. Rev.* **2009**, *38*, 338−351; h) C. P. R. Hackenberger, D. Schwarzer, *Angew. Chem. Int. Ed.* **2008**, *47*, 10030–10074; i) S. Kotha, K. Lahiri, *Curr. Med. Chem.* **2005**, *12*, 849–875.

59 A. Grauer, B. Konig, *Eur. J. Org. Chem.* **2009**, 5099–6111.

60 a) N. Bogliotti, P. I. Dalko, *Shape- and Site-Selective Asymmetric Reactions*, in *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wiley-VCH Verlag GmbH & Co KGaA, Weinheim, **2007**; b) J. M. Palomo, M. Filice, *Biotechnol. Adv.* **2015**, *33*, 605–613.

61 C. Zioudrou, M. Wilchek, A. Patchornik, *Biochemistry* **1965**, *4*, 1811–1822.

62 a) M. Yang, J. Li, P. R. Chen, *Chem. Soc. Rev.* **2014**, *43*, 6511–6526; b) S. V. Chankeshwara, E. Indrigo, M. Bradley, *Chem. Biol*. **2014**, *21*, 128–135; c) J. M. Chalker, G. J. L. Bernardes, B. G. Davis, *Acc. Chem. Res.* **2011**, *44*, 730–741.

63 a) M. A. Tasdelen, Y. Yagci, *Angew. Chem. Int. Ed.* **2013**, *52*, 5930–5938; b) J. M. Palomo, *Org. Biomol. Chem.* **2012**, *10*, 9309–9318; c) S. S. van Berkel, M. B. van Eldijk, J. C. M. van Hest, *Angew. Chem. Int. Ed.* **2011**, *50*, 8806–8827; d) E. Lallana, R. Riguera, E. Fernandez-Megia, *Angew. Chem. Int. Ed.* **2011**, *50*, 8794–8804.

64 a) C. W. Tornoe, C. Christensen, M Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; b) S. I. van Kasteren, H. B. Kramer, H. H. Jensen, J. S. Campbell, J. Kirkpatrick, N. J. Oldham, D. C. Anthony, B. G. Davis, *Nature* **2007**, *446*, 1105–1109; c) B. K. Raliski, C. A. Howard, D. D. Young, *Bioconjugate Chem.* **2014**, *25*, 1916–1920; d) H. Diaz Velazquez, Y. Ruiz Garcia, M. Vandichel,

A. Madder, F. Verpoort, *Org. Biomol. Chem.* **2014**, *12*, 9350–9356; e) A. Tam, U. Arnold, M. B. Soellner, R. T. Raines, *J. Am. Chem. Soc.* **2007**, *129*, 12670–12671.

65 a) Y. A. Lin, J. M. Chalker, B. G. Davis, *J. Am. Chem. Soc.* **2010**, *132*, 16805–16811; b) Y. A. Lin, J. M. Chalker, B. G. Davis, *ChemBioChem* **2009**, *10*, 959–969; c) Y. A. Lin, J. M. Chalker, N. Floyd, G. J. L. Bernardes, B. G. Davis, *J. Am. Chem. Soc.* **2008**, *130*, 9642–9643; d) Y. A. Lin, O. Boutureira, L. Lercher, B. Bhushan, R. S. Paton, B. G. Davis, *J. Am. Chem. Soc.* **2013**, *135*, 12156–12159.

66 T. Willemse, W. Schepens, H. W. T. van Vlijmen, B. U. W. Maes, S. Ballet, *Catalysts* **2017**, *7*, 74.

67 a) J. M. Chalker, C. S. C. Wood, B. G. Davis, *J. Am. Chem. Soc.* **2009**, *131*, 16346–16347; b) A. Ojida, H. Tsutsumi, N. Kasagi, I. Hamachi, *Tetrahedron Lett.* **2005**, *46*, 3301–3305; c) J. M. Chalker, C. S. C. Wood, B. G. Davis, *J. Am. Chem. Soc.* **2009**, *131*, 16346–16347; d) M. Frese, C. Schnepel, H. Minges, H. Voß, R. Feiner, N. Sewald, *ChemCatChem* **2016**, *8*, 1799–1803.

68 a) J. Li, P. R. Chen, *ChemBioChem* **2012**, *13*, 1728–1731; b) N. Li, R. K. V. Lim, S. Edwardraja, Q. Lin, *J. Am. Chem. Soc.* **2011**, *133*, 15316–15319; c) R. K. V. Lim, N. Li, C. P. Ramil, Q. Lin, *ACS Chem. Biol.* **2014**, *9*, 2139–2148; d) J. Li, S. Lin, J. Wang, S. Jia, M. Yang, Z. Hao, X. Zhang, P. R. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 7330–7338; e) M. J. Corr, S. V. Sharma, C. Pubill-Ulldemolins, R. T. Bown, P. Poirot, D. R. M. Smith, C. Cartmell, A. A. Fayad, R. J. M. Goss, *Chem. Sci.* **2017**, *8*, 2039–2046;

69 J. M. McFarland, M. B. Francis, *J. Am. Chem. Soc.* **2005**, *127*, 13490–13491.

70 S. D. Tilley, M. B. Francis, *J. Am. Chem. Soc.* **2006**, *128*, 1080–1081.

71 a) P. K. Sasmal, C. N. Streu, E. Meggers, *Chem. Commun.* **2013**, *49*, 1581–1587; b) J. M. Antos, M. B. Francis, *Curr. Opin. Chem. Biol.* **2006**, *10*, 253–262.

72 a) A. C. Obermeyer, J. B. Jarman, C. Netirojjanakul, E. Muslemany, M. B. Francis, *Angew. Chem. Int. Ed.* **2014**, *53*, 1057–1061; b) A. C. Obermeyer, J. B. Jarman, M. B. Francis, *J. Am. Chem. Soc*. **2014**, *136*, 9572–9579.

73 A. Ji, W. Ren, H.-W. Ai, *Chem. Commun.* **2014**, *50*, 7469–7472.

74 K. L. Seim, A. C. Obermeyer, M. B. Francis, *J. Am. Chem. Soc.* **2011**, *133*, 16970–16976.

75 D. Gillingham, N. Fei, *Chem. Soc. Rev.* **2013**, *42*, 4918–4931.

76 a) J. M. Antos, M. B. Francis, *J. Am. Chem. Soc.* **2004**, *126*, 10256–10257; b) J. M. Antos, J. M. McFarland, A. T. Iavarone, M. B. Francis, *J. Am. Chem. Soc.* **2009**, *131*, 6301–6308; c) R. Kundu, Z. T. Ball, *Chem. Commun.* **2013**, *49*, 4166–4168.

77 A. O.-Y. Chan, J. L.-L. Tsai, V. K.-Y. Lo, G.-L. Li, M.-K. Wong, C.-M. Che, *Chem. Commun.* **2013**, *49*, 1428–1430.

78 a) W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, in press. b) S. Sengupta, G. Mehta, *Tetrahedron Lett.* **2017**, *58*, 1357–1372; c) A. F. M. Noisier, M. A. Brimble, *Chem. Rev.* **2014**, *114*, 8775–8806.

79 a) J. Y. Cho, M. K. Tse, D. Holmes, R. E. Jr. Maleczka, M. R. III. Smith, *Science* **2002**, *295*, 305–308; b) T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chem. Int. Ed.* **2002**, *41*, 3056–3058; c) T. Ishiyama, J. Takagi, Y. Yonekawa, J. F. Hartwig, N. Miyaura, *Adv. Synth. Catal.* **2003**, *345*, 1103–1106; d) R. E. Jr. Maleczka, F. Shi, D. Holmes, M. R. III. Smith, *J. Am. Chem. Soc.* **2003**, *125*, 7792–7792; e) I. A. I. Mkhalid, D. N. Coventry, D. Albesa-Jove, A. S. Batsanov, J. A. K. Howard, R. N. Perutz, T. B. Marder, *Angew. Chem. Int. Ed.* **2006**, *45*, 489–491; f) T. Kikuchi, Y. Nobuta, J. Umeda, Y. Yamamoto, T. Ishiyama, N. Miyaura, *Tetrahedron* **2008**, *64*, 4967–4971.

80 V. A. Kallepalli, F. Shi, S. Paul, E. N. Onyeozili, R. E. Maleczka, M. R. Smith, *J. Org. Chem.* **2009**, *74*, 9199–9201.

81 F.-M. Meyer, S. Liras, A. Guzman-Perez, C. Perreault, J. Bian, K. James, *Org. Lett.* **2010**, *12*, 3870–3873.

82 C. J. Vickers, T.-S. Mei, J.-Q. Yu, *Org. Lett.* **2010**, *12*, 2511–2513.

83 J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 6452–6455.

84 R. B. Bedford, M. F. Haddow, R. L. Webster, C. J. Mitchell*, Org. Biomol. Chem*. **2009**, *7*, 3119–3127.

85 A. Mahindra, N. Bagra, R. Jain, *J. Org. Chem.* **2013**, *78*, 10954−10959.

86 a) S. Preciado, L. Mendive-Tapia, F. Albericio, R. Lavilla, *J. Org. Chem.* **2013**, *78*, 8129–8135; b) J. Ruiz-Rodríguez, F. Albericio, R. Lavilla, *Chem. Eur. J.* **2010**, *16*, 1124–1127; c) T. J. Williams, A. J. Reay, A. C. Whitwood, I. J. S. Fairlamb, *Chem. Commun*. **2014**, *50*, 3052–3054; d) A. J. Reay, T. J. Williams, I. J. S. Fairlamb, *Org. Biomol. Chem.* **2015**, *13*, 8298–8309; e) S. Preciado, L. Mendive-Tapia, C. Torres-Garcia, R. Zamudio-Vazquez, V. Soto-Cerrato, R. Perez-Tomas, F. Albericio, N. Nicolas, R. Lavilla, *Med. Chem. Commun.* **2013**, *4*, 1171–1174.

87 R. P. Loach, O. S. Fenton, K. Amaike, D. S. Siegel, E. Ozkal, M. Movassaghi, *J. Org. Chem.* **2014**, *79*, 11254–11263.

88 Y. Zhu, *Sustainable Strategies for Site-Selective C–H Functionalizations of N-Heterocycles*, Dissertation, Georg-August-Universität Göttingen **2015**.

89 Y. Zhu, M. Bauer, L. Ackermann, *Chem. Eur. J.* **2015**, *21*, 9980–9983.

90 W. Gong, G. Zhang, T. Liu, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 16940–16946.

91 E. Hernando, J. Villalva, A. M. Martinez, I. Alonso, N. Rodriguez, R. G. Arrayas, J. C. Carretero, *ACS Catal.* **2016**, *6*, 6868–6882.

92 a) B. Mondal, B. Roy, U. Kazmaier, *J. Org. Chem.* **2016**, *81*, 11646–11655; b) X. Wu, D. Zhang, S. Zhou, F. Gao, H. Liu, *Chem. Commun.* **2015**, *51*, 12571–12573.

93 a) L. Zhao, O. Basle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4106–4111; b) S. Zhu, M. Rueping, *Chem. Commun*. **2012**, *48*, 11960–11962; c) X. Jia, Y. Wang, F. Peng, C. Huo, L. Yu, J. Liu, X. Wang, *J. Org. Chem.* **2013**, *78*, 9450–9456; d) Z. Ruan, N. Sauermann, E. Manoni, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 3172–3176.

94 a) J. P. Brand, J. Charpentier, P. Waser, *Angew. Chem. Int. Ed.* **2009**, *48*, 9346–9349; b) G. L. Tolnai, S. Ganss, J. P. Brand, P. Waser, *Org. Lett.* **2013**, *15*, 112–115.

95 S. M. Okarvi, *Eur. J. Nucl. Med.* **2001**, *28*, 929–938.

96 X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker, J. T. Groves, *J. Am. Chem. Soc.* **2014**, *136*, 6842–6845.

97 Q. Zhang, X.-S. Yin, K. Chen, S.-Q. Zhang, B.-F. Shi, *J. Am. Chem. Soc.* **2015**, *137*, 8219–8226.

98 a) M. R. Rella, P. G. Willard, *J. Org. Chem.* **2007**, *72*, 525–531; b) C. Annese, L. D'Accolti, M. De Zotti, C. Fusco, C. Toniolo, P. G. Willard, R. Curci, *J. Org. Chem.* **2010**, *75*, 4812–4816.

99 R. Consden, A. H. Gordon, A. J. P. Martin, R. L. M. Synge, *Biochem. J.* **1947**, *4*, 596–602.

100 a) R.-Y. Zhang, P. Thapa, M. J. Espiritu, V. Menon, J.-P. Bingham, *Bioorg. Med. Chem.* **2018**, *26*, 1135–1150; b) R. Dharanipragada, *Future Med. Chem.* **2013**, *5*, 831–849; c) J. S. Davies, *Amino Acids, Pept. Proteins* **2007**, *36*, 227–286; d) A. D. Pehere, X. Zhang, A. D. Abell, *Aust. J. Chem.* **2016**, *70*, 138–151; e) Z.-M. Wu, S.-Z. Liu, X.-Z. Cheng, W.-Z. Ding, T. Zhu, B. Chen, *Chin. Chem. Lett.* **2016**, *27*, 1731–1739.

101 E. Tuenter, V. Exarchou, S. Apers, L. Pieters, *Phytochem. Rev.* **2017**, *16*, 623–637.

102 a) S. A. Kawamoto, A. Coleska, X. Ran, H. Yi, C.-Y. Yang, S. Wang, *J. Med. Chem.* **2012**, *55*, 1137–1146; b) M. M. Madden, C. I. R. Vera, W. Songa, Q. Lin, *Chem. Commun.* **2009**, 5588–5590.

103 a) H. E. Blackwell, R. H. Grubbs, *Angew. Chem. Int. Ed.* **1998**, *37*, 3281–3284; b) G. Verdine, G. Hilinski, *Drug Discov. Today Technol.* **2012**, *9*, e41–e47; c) Y. Kim, T. Grossmann, G. Verdine, *Nat. Protocols* **2011**, *6*, 761–771.

104 a) A. Patgiri, M. Witten, P. S. Arora, *Org. Biomol. Chem.* **2010**, *8*, 1773–1776; b) A. Patgiri, M. Z. Menzenski, A. B. Mahon, P. S. Arora, *Nat. Protocols* **2010**, *5*, 1857–1865; c) A. Mahon, P. S. Arora, *Chem. Commun*. **2012**, *48*, 1416–1418.

105 a) C. R. Craik, *Methods Enzymol.* **2012**, *50*, 57–74; b) R. J. Clark, J. Jensen, S. T. Nevin, B. P. Callaghan, D. J. Adams, D. J. Craik, *Angew. Chem. Int. Ed.* **2010**, *49*, 6545–6548.

106 a) C. T. Wong, D. K. Rowlands, C. H. Wong, T. W. Lo, G. K. Nguyen, H. Y. Li, J. P. Tam, *Angew. Chem. Int. Ed.* **2012**, *51*, 5620–5624; b) L. Y. Chan, S. Gunasekera, S. T. Henriques, N. F. Worth, S.-J. Le, R. J. Clark, J. H. Campbell, D. J. Craik, N. L. Daly, *Blood* **2011**, *118*, 6709–6717.

107 T. A. Knappe, F. Manzenrieder, C. Mas-Moruno, U. Linne, F. Sasse, H. Kessler, X. Xie, M. A. Marahiel, *Angew. Chem. Int. Ed.* **2011**, *50*, 8714–8717.

108 M. L. Colgrave, D. J. Craik, *Biochemistry* **2004**, *43*, 5965–5975.

109 X. Bu, X. Wu, N. L. J. Ng, C. K. Mak, C. Qin, Z. Guo, *J. Org. Chem*. **2004**, *69*, 2681–2685.

110 J. A. Camarero, B. J. Hackel, J. J. de Yoreo, A. R. Mitchell, *J. Org. Chem.* **2004**, *69*, 4145–4151.

111 a) L. Mendive-Tapia, A. Bertran, J. García, G. Acosta, F. Albericio, R. Lavilla, *Chem. Eur. J.* **2016**, *22*, 13114–13119; b) H. Dong, C. Limberakis, S. Liras, D. Price, K. James, *Chem. Commun.* **2012**, *48*, 11644–11646; c) A. F. M. Noisier, J. García, I. A. Ionut, F. Albericio, *Angew. Chem. Int. Ed.* **2016**, *56*, 314–318; d) D. S. Peters, F. E. Romesberg, P. S. Baran, *J. Am. Chem. Soc*. **2018**, *140*, 2072−2075.

112 S. T. Buckley, F. Hubálek, U. L. Rahbek, *Tissue Barriers* **2016**, *4*, e1156805.

113 F. Van Lancker, A. Adams, N. De Kimpe, *Chem. Rev.* **2011**, *111*, 7876–7903.

114 Average price in august 2018 in $ per Oz: Pd 916, Ru 252. http://www.platinum.matthey.com /prices/price-charts, 09.04.2018.

115 K. D. Collins, F. Glorius, *Acc. Chem. Res.* **2015**, *48*, 619–627.

116 E. V. Britzke, A. F. Kapustinsky, *Z. Anorg. Allg. Chem.* **1933**, *213*, 71–76.

117 A. Schischko, H. Ren, N. Kaplaneris, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 1576–1580.

118 a) L. Ackermann, P. Novák, R. Vicente, N. Hofmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 6045–6048; b) L. Ackermann, N. Hofmann, R. Vicente, *Org. Lett.* **2011**, *13*, 1875–1877; c) N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877−5884.

119 C. Lawatscheck, M. Pickhardt, A. Grafl, K. Linkert, F. Polster, E. Mandelkow, H. G. Börner, *Macromol. Biosci.* **2017**, *17*, 1700109.

120 C. Diaferia, T. Sibillano, D. Altamura, V. Roviello, L. Vitagliano, C. Giannini, G. Morelli, A. Accardo, *Chem. Eur. J.* **2017**, *23*, 14039–14048.

121 a) C. Reichert, G. Borchard, *J. Pharm. Sci.* **2016**, *105*, 386–390; b) F. M. Veronese, *Biomaterials* **2001**, *22*, 405–417.

122 a) M. J. Guichard, T. Leal, R. Vanbever, *Current Opinion in Colloid & Interface Science* **2017**, *31*, 43–50; b) A. Jain, S. K. Jain, *Crit. Rev. Ther. Drug Carrier Syst*. **2008**, *25*, 403–447.

123 R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *38*, 920–924.

124 R. Santini, M. C. Griffith, M. Qi, *Tetrahedron Lett.* **1998**, *39*, 8951–8954.

125 E. Marcantoni, M. Massaccesi, E. Torregiani, *J. Org. Chem.* **2001**, *66*, 4430–4432.

126 C. Bruneau, P. H. Dixneuf, *Top. Organomet. Chem.* **2016**, 137–188.

127 L. Ackermann, L. Wang, R. Wolfram, A. V. Lygin, *Org. Lett.* **2012**, *14*, 728–731.

128 H. Wang, M. Lorion, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 6339–6342.

129 W. L. F. Armarego, C. L. L. Chai, in *Purification of Laboratory Chemicals (Sixth Edition)*, Butterworth-Heinemann, Oxford, **2009**.

130 a) Z.-L. Shen, K. K. K. Goh, C. H. A. Wong, W.-Y. Loo, Y.-S. Yang, J. Lu, T.-P. Loh, *Chem. Commun.* **2012**, *48*, 5856–5858; b) M. N. Kumara, D. C. Gowda, K. S. Rangappa, *Int. J. Chem. Kinet.* **2002**, *34*, 438–444; c) S. M. Voshell, S. J. Lee, M. R. Gagné, *J. Am. Chem. Soc.* **2006**, *128*, 12422–12423.

131 M. R. Linder, S. Steurer, J. Podlech, *Org. Synth.* **2002**, *79*, 154.

132 G. Vlád, I. T. Horváth, *J. Org. Chem.* **2002**, *67*, 6550–6552.

133 a) P. Kazmierczak, L. Skulski, *Synthesis* **1995**, 1027–1032; b) L. Kraszkiewicz, L. Skulski, *Synthesis* **2008**, 2373–2389.

134 S. Rapposelli, S. Cuboni, M. Digiacomo, A. Lucacchini, F. Minutolo, M. L. Trincavelli, A. Balsamo, *Heterocycles* **2008**, *75*, 1467–1477.

135 Samsung Mobile Display Co., Ltd., Patent EP2298741 A1, 2011, column 28.

136 R. H. Mitchell, Y. Chen, J. Zhang, *Org. Prep. Proced. Int.* **1997**, *29*, 715–719.

137 Q. Xiao, Q. He, J. Li, J. Wang, *Org. Lett.* **2015**, *17*, 6090–6093.

138 A. Bugarin, K. D. Jones, B. T. Connell, *Chem. Commun.* **2010**, *46*, 1715–1717.

139 C. Hurtado-Rodrigo, S. Hoehne, M. P. Munos, *Chem. Commun.* **2014**, *50*, 1494–1496.

140 Novabiochem® *Peptide Synthesis*, Merck Millipore, 2014/2015.

Curriculum Vitae

Personal Information

Name:	Alexandra Schischko
Date of birth:	February 16th, 1988
Place of birth:	Shevchenko, Kazachstan
Nationality:	German

Academic Education

8.2014 – Present	**PhD Candidate in Organic Chemistry** Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen Supervisor: Prof. Dr. Lutz Ackermann Thesis: *Late-Stage Peptide Functionalization by Ruthenium-Catalyzed C–H Arylations and Alkylations*
10.2011 – 7.2014	**M. Sc. in Chemistry** Carl-von-Ossietzky-Universität Oldenburg Final grade: 1.56 Master Thesis: *Herstellung von Aminopyridinato-Titan-Katalysatoren für die Hydroaminoalkylierung von Alkenen* Supervisor: Prof. Dr. Sven Doye
10.2008 – 9.2011	**B. Sc. in Chemistry** Carl-von-Ossietzky-Universität Oldenburg Final grade: 2.3 Bachelor Thesis: *Synthese von Hydrazonen und Pyridazin-Derivaten* Supervisor: Prof. Dr. Jens Christoffers

School Education

2000 – 2008	Gymnasium Bad Zwischenahn-Edewecht
1998 – 2000	Orientierungsstufe Edewecht
1997 – 1998	Grundschule Edewecht

Teaching Experience

12.2017 – 1.2018	Supervision of the “MEMO”-Iternship
2014 – 6.2017	Assistant of the practical course “Organisch-Chemisches Praktikum für Lehramtskandidaten und Dipl. Biologen”
2014 – 3.2017	Assistant of the practical course “Chemie für Human- und Zahnmediziner”

Publications

2) A. Schischko, H. Ren, N. Kaplaneris, L. Ackermann, *"Bioorthogonal Diversification of Peptides by Selective Ruthenium(II)-Catalyzed C–H Activation" Angew. Chem. Int. Ed.* **2017**, 56, 1576–1580.

1) J. Dörfler, T. Preuß, A. Schischko, M. Schmidtmann, S. Doye, "*A 2,6-Bis(phenylamino)pyridinato Titanium Catalyst for the Highly Regioselective Hydroaminoalkylation of Styrenes and 1,3-Butadienes*" *Angew. Chem.* **2014**, *126*, 8052–8056; *Angew. Chem. Int. Ed.* **2014**, *53*, 7918–7922.

Conferences

9.2017	International Center for Advanced Studies of Energy Conversion (ICASEC) Summer School, Göttingen, Germany Poster presentation
6.2017	20th European Symposium on Organic Chemistry (ESOC), Cologne, Germany Poster presentation
9. 2016	4. Niedersächsisches Katalyse-Symposium (NiKaS), Braunschweig, Germany Poster presentation
6.2016	8. Göttinger Chemieforum, Göttingen, Germany
10.2014	7. Göttinger Chemieforum, Göttingen, Germany

Erklärung

Hiermit erkläre ich, dass ich die vorliegende Dissertation in dem Zeitraum von August 2014 bis August 2018 am Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen unter Anleitung von Herrn Prof. Dr. Lutz Ackermann selbstständig durchgeführt und keine anderen als die angegebenen Hilfsmittel und Quellen verwendet habe.

Göttingen, den 27.08.2018

_____

Alexandra Schischko