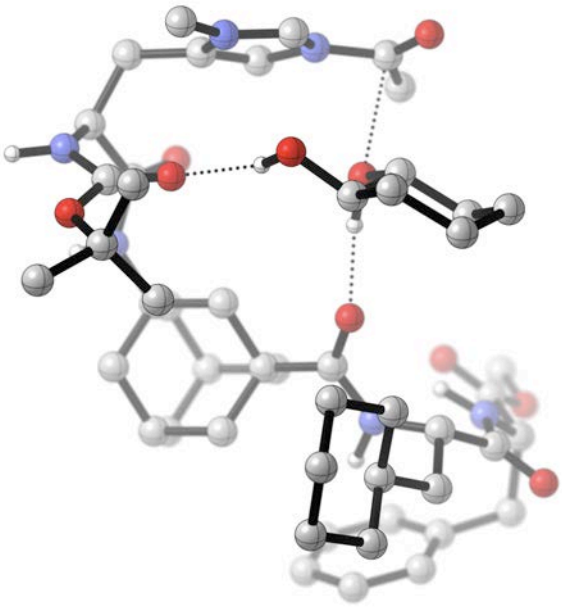
Chasing Selectivity: Peptides as Nucleophilic Catalysts in Enantioselective Electrophile Transfer Reactions



Dissertation zur Erlangung des Doktorgrades
der Naturwissenschaftlichen Fachbereiche
im Fachgebiet Organische Chemie
der Justus-Liebig-Universität Gießen

Vorgelegt von
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aus Werdorf

Gießen 2013

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Für meine Eltern und Christian

„Nur wenige wissen, wie viel man wissen muss, um zu wissen, wie wenig man weiß.”

– Werner Heisenberg –

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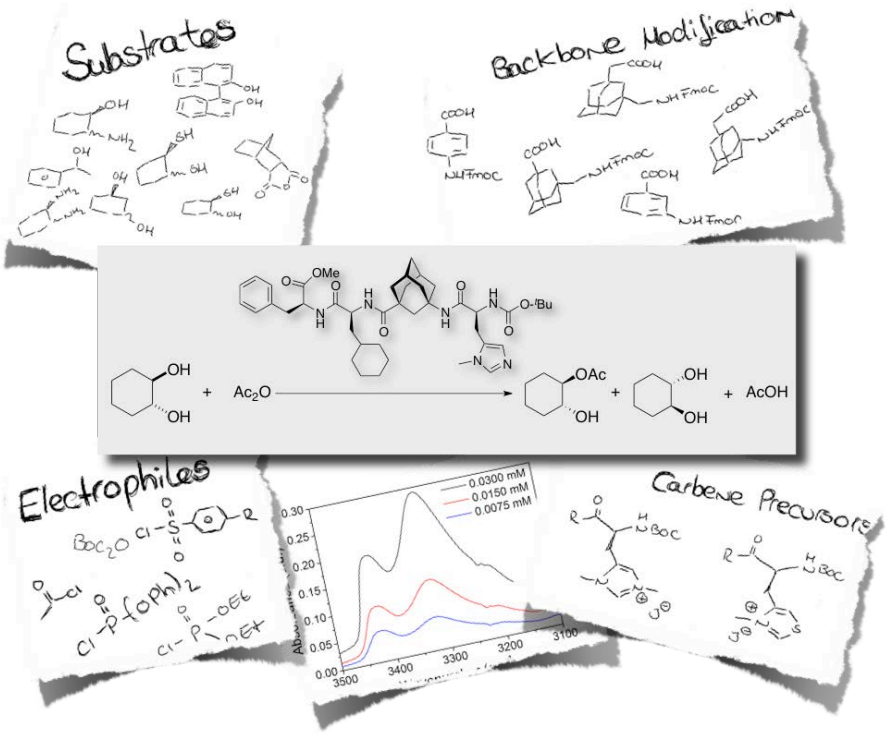
Table of Contents

1. Motivation

Today, there is a high demand for enantiopure building blocks in chemistry and pharmaceutical industry. Additionally to enzymatic approaches, various enantioselective catalysts have been discovered mainly by trial and error processes in the last decade. In 2008 Schreiner *et al.* introduced a highly enantioselective tetrapeptide for the acylative kinetic resolution (KR) of *rac*-cycloalkane-1,2-diols.

This thesis tries to shed some light on the factors that are responsible for the excellent selectivity of Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe in the kinetic resolution (KR) of *rac*-cycloalkane-1,2-diols and may therefore lead to a more rational catalyst design in future. For that reason, all components (substrate, electrophile and catalyst) of the reaction should be individually varied and the influence on the selectivity detected as well as compared to the model system. The modified peptides should also be tested as catalysts in KRs and desymmetrizations of new substrates. The conformation of Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (e.g., *β*-turn) in solution should be investigated by NMR- and IR-spectroscopy, as well as by computational methods.

In a second project we envisioned the modification of the catalytically active Boc-π-methyl histidine amino acid. Methylation of the τ-position of the imidazole moiety should produce *N,N'*-dimethyl histidinium iodide, which can be *in-situ* transformed into a free NHC by base and would offer an easy access to new asymmetric reactions (e.g., benzoin condensations and oxidative esterification).



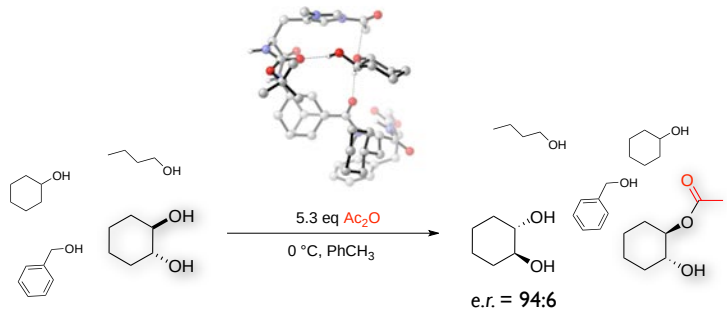
Structure of the doctoral thesis

1. The book chapter “Acylation-type Reactions: Synthesis of Esters *via* Acyl Transfer” for "Volume 6: Heteroatom Manipulation" which is part of “Comprehensive Organic Synthesis 2nd Edition”, is utilized to introduce the topic of enantioselective acyl transfer and to show the state of the art. This work will be published by Elsevier in 2014.

Abstract:

Acyl transfer reactions are one of the most common transformations in organic synthesis as well as in nature. Though many methods (acidic catalysis, basic catalysis and nucleophilic catalysis, e.g., DMAP) for the acylation of alcohols have been known for centuries, asymmetric approaches were just realized in the last 15–20 years. Asymmetric acyl transfer onto alcohols presents a powerful tool for the synthesis of enantiopure substrates, which are important building blocks for the synthesis of natural products, pharmaceuticals and chiral ligands. The introduction explains the differences between kinetic resolution, dynamic kinetic resolution and desymmetrization and shows how the catalytic efficacy of a KR is typically expressed (Kagan’s equation). This article summarizes organocatalysts and metal-complexes capable of an enantioselective acyl transfer. Substrate scope, reaction conditions, selectivities, mechanism, and the accessibility of the catalysts are organized by type of catalyst. The performances of the catalysts are discussed and, if possible, comparisons towards efficiency are made. Additionally, examples for the utilization of chiral acylation catalysts in natural product synthesis are presented in each section.

2. „Lipophilic Oligopeptides for Chemo- and Enantioselective Acyl Transfer Reactions onto Alcohols“ is submitted for publication: *Christian E. Müller,[#] Daniela Zell,[#] Radim Hrdina, Raffael C. Wende, Lukas Wanka, Sören M. M. Schuler, and Peter R. Schreiner*.*



3. Unpublished results.

[#] These authors contributed equally to this work.

Acylation-type Reactions: Synthesis of Esters *via* Acyl Transfer*

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2. General Introduction

Though esterifications were part of daily life over millennia, Carl Wilhelm Scheele in 1782 apparently was the first chemist reporting the acid-catalyzed esterification of organic acids with alcohols.[1,2] In the 19th century chemists like Meyer,[3,4] Berthelot,[5] and Fischer[6] explored the fundamentals of this type of reaction. Today, esterification reactions are some of the most common chemical transformations in nature, in the chemical laboratory, and even in industry (e.g., synthesis of polyesters). Having an increasing demand for enantiomerically pure substrates (e.g., for use as pharmaceuticals, as flavors, as aroma or agricultural chemicals), efficient ways of synthesizing enantiopure products in high yields are required. Optically pure substrates can be obtained by utilizing chromatographic methods, crystallization processes or selective transformations such as kinetic resolution of racemic substrates by acyl transfer; additionally, enantiopure molecules can be prepared by desymmetrization of prochiral molecules. Nature uses enzymes for the selective transfer of acyl groups onto a large variety of substrates. The isolation of specific enzymes led to their application as catalysts for enantioselective acyl-transfer reactions.

This chapter introduces catalysts that are highly effective in the selective acylation of alcohols. Esterification reactions are widely used in this field because acylation agents such as anhydrides are commercially available and because acyl-transfer proceeds under mild reaction conditions utilizing a large variety of catalysts (enzymes, small molecules, metal complexes).

Classic Brønsted acid catalysis is one of the oldest and most popular methods for the esterification of alcohols and therefore will not be discussed in this chapter. This article focuses on new and, in particular, on asymmetric, non-enzymatic approaches for acyl-transfer onto alcohols.

* "Acylation-type Reactions: Synthesis of Esters *via* Acyl Transfer" is a chapter in "Volume 6: Heteroatom Manipulation", which is part of "Comprehensive Organic Synthesis 2nd Edition" edited by G. Morlander, P. Knochel, J. Johnson, K. Mikami, I. Marek, S.-M. Ma & J. Zhang, A. Fürstner, S. Burke, M. C. White, J. Clayden, and C. Welch. This work will be published in 2014 by Elsevier. The use of the book chapter "Acylation-type Reactions: Synthesis of Esters *via* Acyl Transfer" as introduction was permitted by S. Burke.

Depending on the starting material, two principally different acyl transfer processes can occur. The first is to start from a racemic substrate whereby one enantiomer is much more rapidly acylated by a chiral catalyst than the other. Under optimal conditions 50% of enantiopure ester and 50% of enantiopure starting alcohol can be isolated at 50% conversion (kinetic resolution, KR).[7,8] One obvious drawback of this approach is the limitation of the product yield to 50%. The efficiency of a KR can be expressed utilizing Kagan's equation.[9] This method is applicable for reaction following first order kinetics in the absence of nonlinear effects. The selectivity (*S*-value) can be determined using the following approximations:

$$C = \frac{ee}{(ee + ee')}100 \qquad S = \frac{\ln[1 - C(1 + ee')]}{\ln[1 - C(1 - ee')]} \qquad S = \frac{\ln[(1 - C)(1 - ee)]}{\ln[(1 - C)(1 + ee)]}$$

$S = k_{fast}/k_{slow}$

ee = enantiomeric excess predicted for the starting material

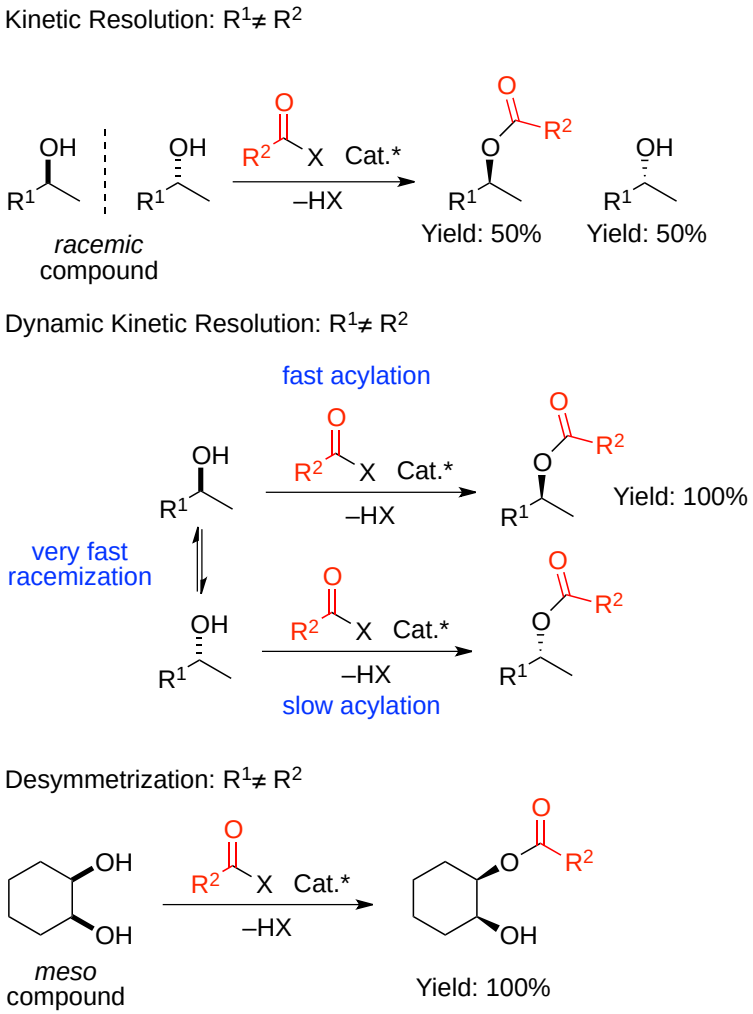
ee ´ = enantiomeric excess predicted for the product

C = conversion

S-values greater than 20 guarantee high enantiomeric excesses for the product as well as the starting material and a conversion close to 50%. *S*-values lower than ten are usually not practically useful in organic syntheses because of incomplete enantiomer separation.

A more efficient way to separate enantiomers is the dynamic version of KR (DKR) as the desired product can then theoretically be isolated in quantitative yield and high *ee*'s. DKR is possible when the starting material racemizes, while the acylated enantiopure product is configurationally stable (Scheme 1). There are many examples for DKR (e. g., Jacobsen's hydrolytic DKR of epoxides[10] and Bäckvall's DKR via acyl transfer onto alcohols[11]) that have been developed in the last 20 years.[12-15]

The desymmetrization of prochiral substrates or *meso*-compounds has become a powerful method in asymmetric synthesis because in theory 100% yield can be obtained (Scheme 1).[16]



(Scheme 1)

Scheme 1

2.1 Synthesis of Esters via Acyl Transfer onto Alcohols

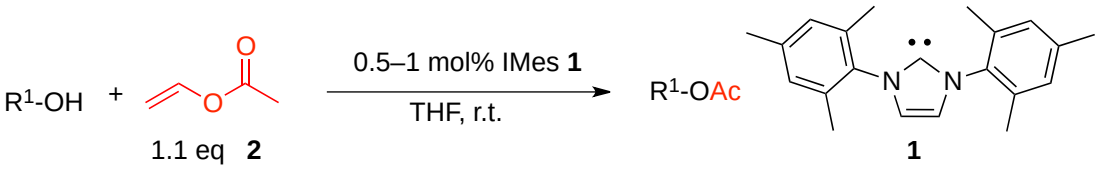
2.1.1 Organocatalytic Synthesis of Esters

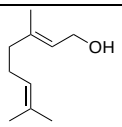
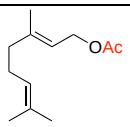
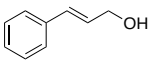
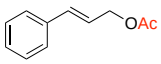
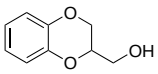
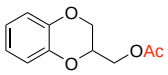
2.1.1.1 *N*-Heterocyclic Carbenes as Catalysts for Acyl Transfer onto Alcohols

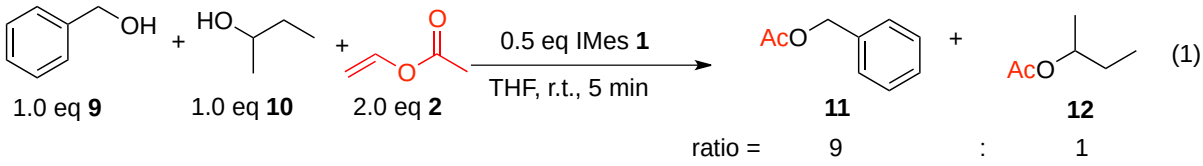
The non-stereoselective synthesis of esters traditionally proceeds via Lewis / Brønsted base or Lewis / Brønsted acid catalysis.[17] A problem of these approaches is the potential cleavage of acid sensitive functional groups such as commonly employed epoxides and acetals. Furthermore, Lewis acid (e.g., $Sc(OTf)_3$, TMSCl, $La(O^iPr)_3$) as well as base catalysts (e.g., phosphines) show low selectivity between primary and secondary alcohols. In 2003 Nolan[18] as well as Hedrick[19] reported almost simultaneously their transesterification

approaches utilizing NHC as catalysts. Nolan and co-workers introduced a catalytic method for synthesizing various esters by using NHC's or their precursor salts and base as catalysts. First they applied their NHC catalyst in the esterification of primary alcohols with vinyl acetate as the acyl source. Almost quantitative yields were obtained even with unsaturated alcohols or alcohols bearing acid sensitive groups (Table 1).[18] In the presence of primary and secondary alcohols in the reaction mixture, acylation of the primary alcohol is clearly favored (Equation 1).

Table 1. Acylation of primary alcohols with IMes **1** as catalyst.

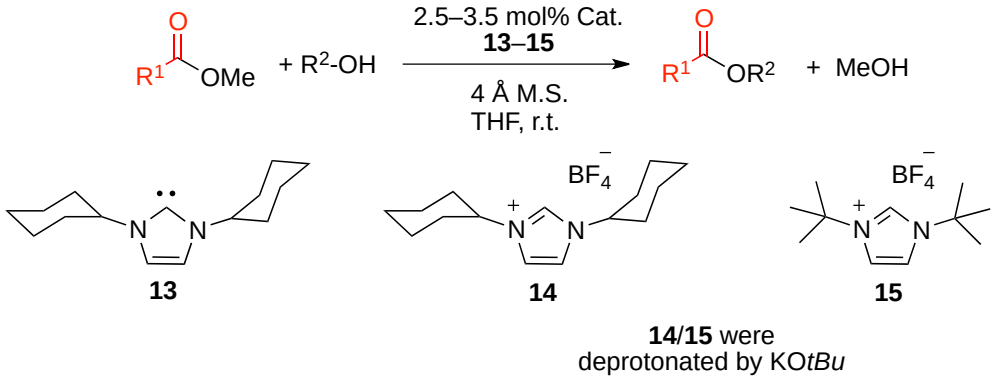


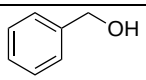
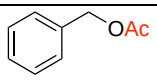
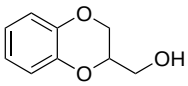
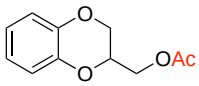
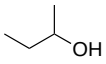
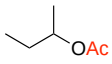
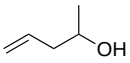
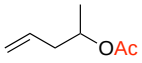
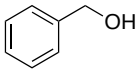
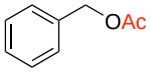
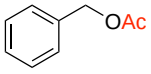
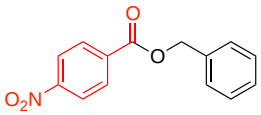
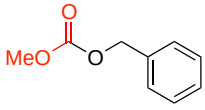
Entry	Alcohol	Product (Ester)	*t* (min)	Yield (%)
1	 **3**	 **4**	60	99
2	 **5**	 **6**	15	96
3	 **7**	 **8**	15	100

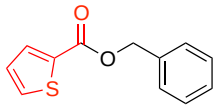


Under slightly modified conditions the transesterification of methyl esters with alcohols is possible (Table 2). Secondary alcohols can be acylated, but the reaction requires higher catalyst loadings (3.5 mol%) due to their lower reactivity. NHC's are air and moisture sensitive and therefore Nolan and co-workers tested the *in situ* generation of the free carbene from a precursor salt by adding base to the reaction mixture. The obtained yields were excellent (up to 100%) even at short reaction times (30 min). The precursor salts for the *in situ* generation of the carbene are commercially available.

Table 2. Transesterification of methyl esters with primary and secondary alcohols mediated by NHC catalysts **13**–**15**.[a]



Entry	Alcohol		Product (Ester)		Cat. (mol%)	*t* (min)	Yield (%)
1		**9**		**11**	**13** (2.5)	60	95
2		**7**		**8**	**13** (2.5)	30	90
3		**10**		**12**	**13** (3.5)	60	92
4		**16**		**17**	**13** (3.5)	60	96
5[d]		**9**		**11**	**14** (3.0)	30	93
6[d]		**9**		**11**	**15** (3.0)	30	100
7[b]		**9**		**18**	**13** (2.5)	15	96
8[c]		**9**		**19**	**13** (2.5)	30	93

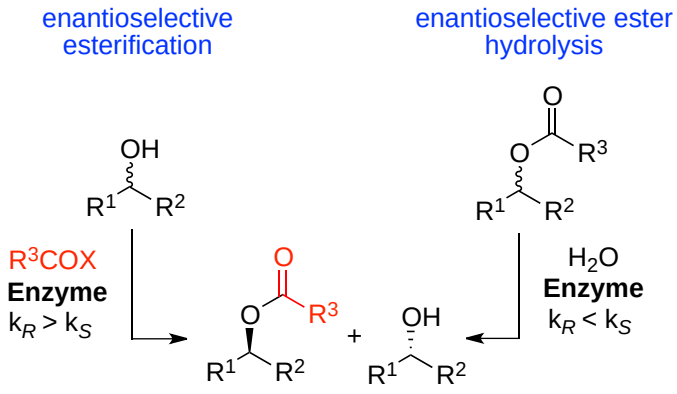
Entry	Alcohol	Product (Ester)	Cat. (mol%)	*t* (min)	Yield (%)
9[b]	**9**	**20** 	**13** (2.5)	15	96

[a] Reaction conditions: 1 mmol alcohol, 1 mL of methyl acetate, 0.5 g 4 Å MS, r.t.. [b] 1.5 mmol alcohol, 1 mmol methyl ester, 1 mL THF, 0.5 g 4 Å MS. [c] 1 mmol alcohol, 1 mmol dimethyl carbonate, 1mL THF. [d] 1 mmol benzyl alcohol, 1 mL methyl acetate, 3 mol% imidazolium salt, 2.5 mol% KO*t*Bu, 0.5 g 4 Å MS, r.t., 30 min.

An advantage of the NHC-catalyzed esterification reactions is that these catalysts display broad functional group tolerance. Esterification of substrates bearing amine, olefin, nitro, ether or thioether functions are feasible. The esterification reactions mediated by NHCs require short reaction times, and excellent yields can be obtained.

2.1.1.2 Asymmetric Acyl Transfer

As mentioned before, acyl transfer is the most common group transfer reaction in organic synthesis. Traditionally, the generation of enantiopure products from racemic alcohols utilizing enzymes was accomplished via selective acyl transfer (esterification) or selective hydrolysis of esters (ester hydrolysis)(Scheme 2).

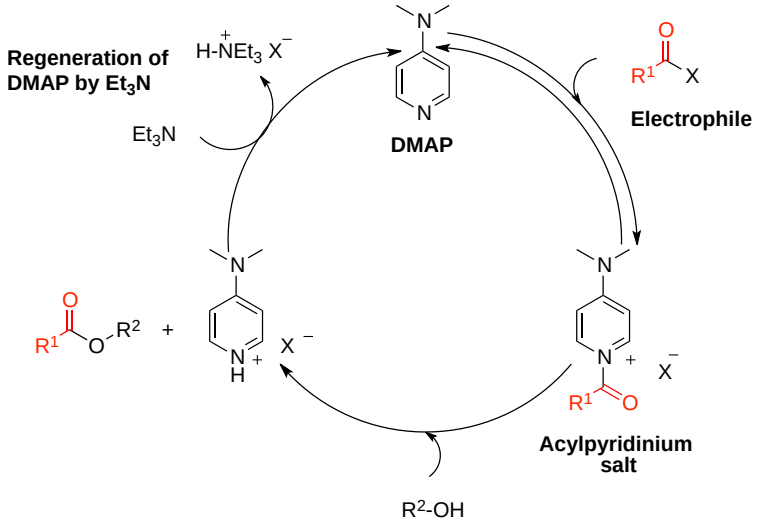


Scheme 2

While enzymes were successfully applied in the enantioselective esterification of various substrate classes and although they give high *S*-values, they do not present the optimal catalysts form a chemist's point of view. One drawback is the accessibility of one enantiomeric form of the enzyme and only one enantiomer of the substrate can be selectively acylated. Furthermore, enzymes cannot be modified easily. Small chiral organic molecules on the other hand can readily be synthesized in both enantiomeric forms, and therefore are capable of resolving both enantiomers in a given reaction. Such organocatalysts are structurally more variable and can be further optimized to improve their selectivity. The first part of the present chapter introduces various types of small organic molecules utilized for stereoselective acyl transfer. The availability of the catalysts, the reaction conditions, the substrate scope, and the selectivities will be discussed and compared to other approaches. Some selected steps in natural product syntheses are presented to demonstrate the practicality of these methods.

2.1.1.2.1 Enantioselective Acyl Transfer Using DMAP-Derivatives

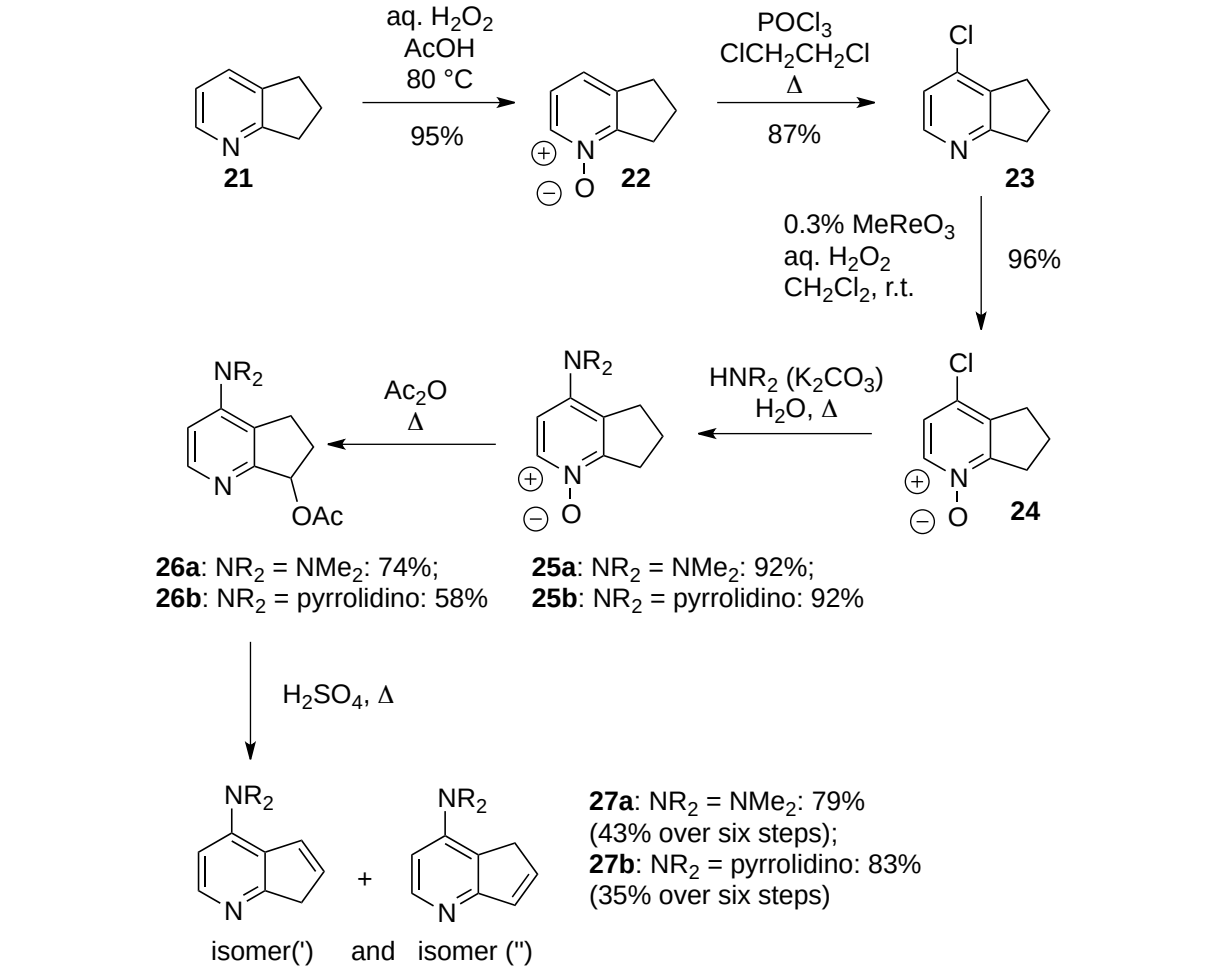
The first achiral acyl transfer onto alcohols utilizing DMAP (4-dimethylaminopyridine) as catalyst and acetic anhydride as acyl source was reported in the late 1960's by Steglich and Höfle.[20] Independently, Litvinenko and Kirichenko found a rate acceleration for the benzoylation of *m*-choloroaniline by adding DMAP instead of pyridine as catalyst.[21] It took nearly 30 years until the first asymmetric approach was introduced by Vedejs and co-workers in 1996.[22] Experimental[23-25] and theoretical[26,27] studies support a nucleophilic mechanism for the DMAP-catalyzed acylation of alcohols. In the first step the nucleophilic nitrogen of the pyridine ring attacks the electrophile (e.g., anhydride or acid halide) and forms an acylpyridinium salt. The reactive intermediate transfers the acyl group onto the alcohol (Scheme 3). Additional base is needed to neutralize the acid that is produced during the acylation process. In some rare examples, additional base is not required, because of the weakness of the generated acid (e.g., acetic acid).[28] Yet, the role of the base is not fully understood, because even in the latter case a rate acceleration is often observed, maybe due assisting by the proton abstraction from the alcohol.[29] Additionally, the rate of the acylation is highly affected by the character of the anion and the solvent.[30,31]

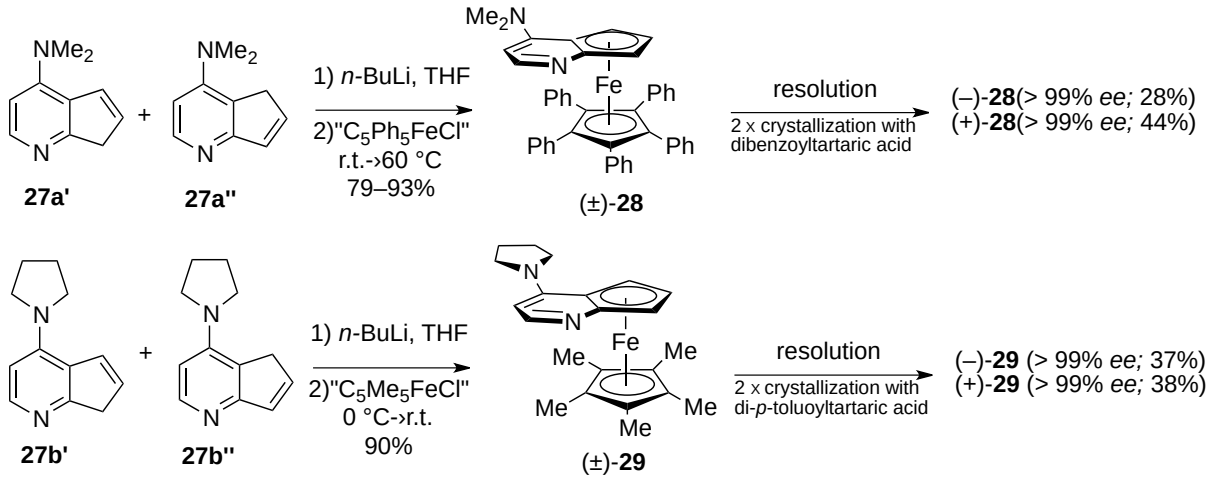


Scheme 3

The first enantioselective approach of Vedejs et al. required 1 eq of "catalyst" and two eq of a Lewis acid in the presence of base. The KR of aryl alkyl alcohols could be achieved with $S \leq 45$.

In 1996 Fu introduced the new planar chiral ferrocenyl-DMAP derivative **28** as a catalyst for the KR of aryl alkyl carbinols. In addition to **28** the same group also synthesized an analogous PPY-based (4-pyrrolidino pyridine) catalyst **29**.[32] Both **28** and **29** are commercially available or can be synthesized in eight steps from readily available starting materials (Scheme 4).[33] These planar-chiral DMAP derivatives are discussed in connection with organocatalytic acyl transfer catalysts, because the nitrogen atom of the DMAP moiety is key. The iron ion of the complex only functions as structure-forming element and supposedly does not influence the activity of the catalyst.



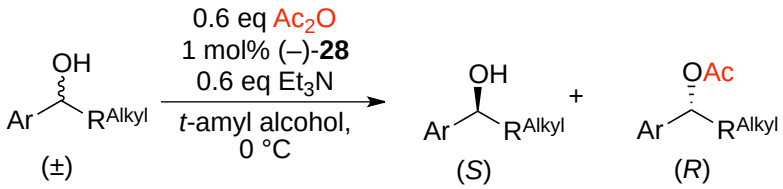


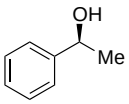
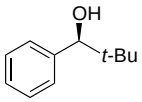
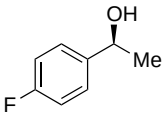
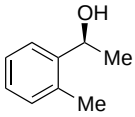
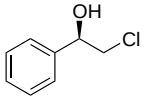
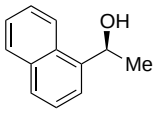
Scheme 4

Catalyst (–)-**28** was successfully applied in the KR of aryl alkyl carbinols (Table 3).[34,35,36] The *ee*'s and *S*-values (32–95) are excellent even at low catalyst loadings of 1

mol% in *t*-amyl alcohol as solvent. In contrast, in Et_2O the selectivities ranged from 12–52 even at a catalyst loading of 2 mol% at room temperature. The *ee*'s provided by catalyst **28** strongly depend on the solvent. The selectivity increased as the steric demand of the alkyl moiety increases. A big advantage of this method is the possible recovery of catalyst (–)-**28**, the low sensitivity of the catalyst towards moisture and oxygen and the absence of chemical by-products. The *S*-values obtained by catalyst **29** were lower and will not be discussed further.

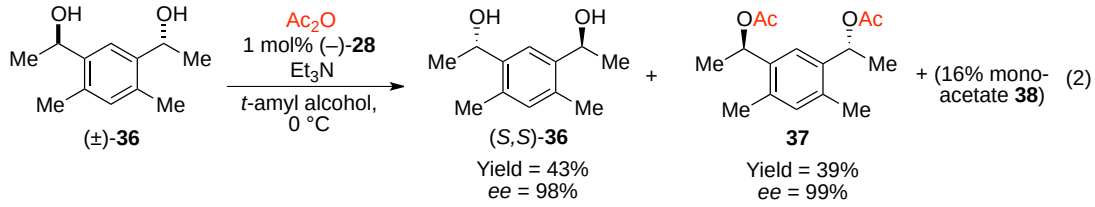
Table 3. Efficiency of catalyst (–)-**28** in the KR of aryl alkyl carbinols.[36]



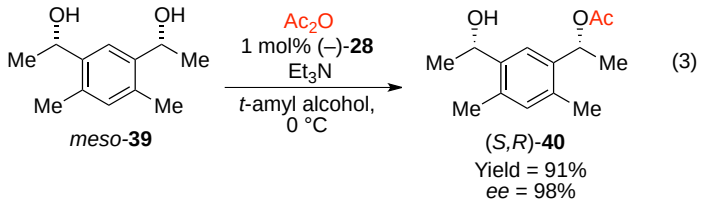
Entry	Unreacted alcohol		Conv. (%)	*ee* (%) of unreacted alcohol	*S*-value
1		**30**	55	99	43
2		**31**	51	96	95
3		**32**	54	99	68
4		**33**	53	99	71
5		**34**	56	98	32
6		**35**	52	95	65

Fu also applied catalyst (–)-**28** in the KR of racemic 1,5-diols as well as in the desymmetrization of *meso*-1,5-diols. In both cases high selectivities could be achieved utilizing the same reaction conditions as for aryl alky alcohols (Equation 2 and 3).[34,35,36]

Kinetic resolution of racemic 1,5-diol 36

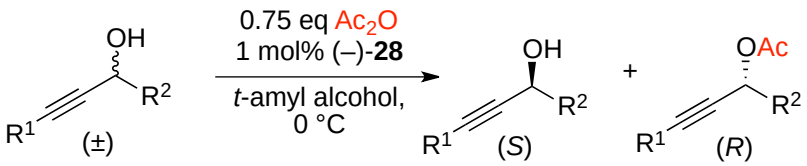


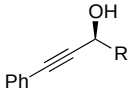
Desymmetrization of *meso*-1,5-diol 39

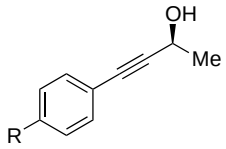
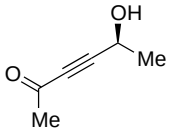
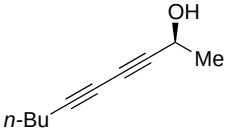
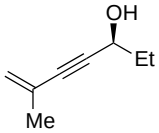


In addition to Birman's amidine catalyst **130** (*S* ≤ 32, Scheme 9 and Table 17), only catalyst (–)-**28** is capable of resolving propargylic alcohols.[37,38] The selectivities are in a range between 3.8 and 20 and therefore synthetically useful. In contrast to aryl alkyl alcohols no additional base was employed, because the acylation of propargylic alcohols occurred under basic conditions in the absence of catalyst. The selectivity for the KR decreases as the steric demand for the alkyl group of the substrate increases (Table 4).[34,35,37]

Table 4. KR of propargylic alcohols by catalyst (–)-**28**.

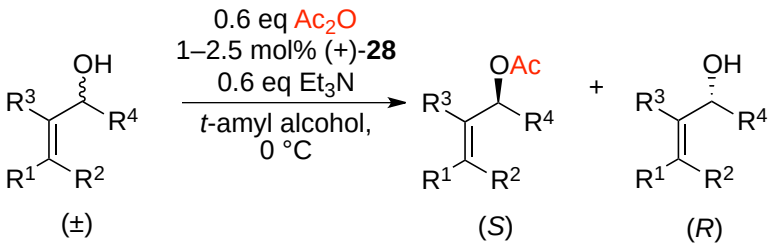


Entry	Unreacted alcohol	R		Conv. (%)	*ee* (%) of unreacted alcohol	*S*-value
1		Me	**41**	58	96	20
2		Et	**42**	58	94	18
3		^{i}Pr	**43**	63	93	11
4		^{t}Bu	**44**	86	95	3.8

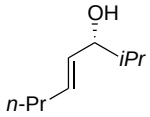
Entry	Unreacted alcohol	R		Conv. (%)	*ee* (%) of unreacted alcohol	*S*-value
5		OMe	**45**	60	94	14
6		CF_3	**46**	71	99	10
7		F	**47**	65	97	13
8		-	**48**	64	95	12
9		-	**49**	66	95	10
10		-	**50**	69	94	7.9

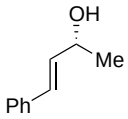
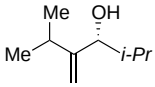
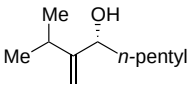
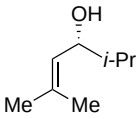
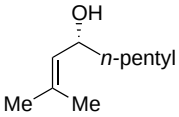
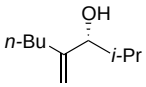
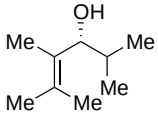
Catalyst (+)-**28** was successfully applied the KR of allylic alcohols. A large variety of substrates can be resolved with good to excellent enantioselectivities (Table 5).[34,35,39]

Table 5. Efficiency of (+)-**28** in the KR of allylic alcohols.

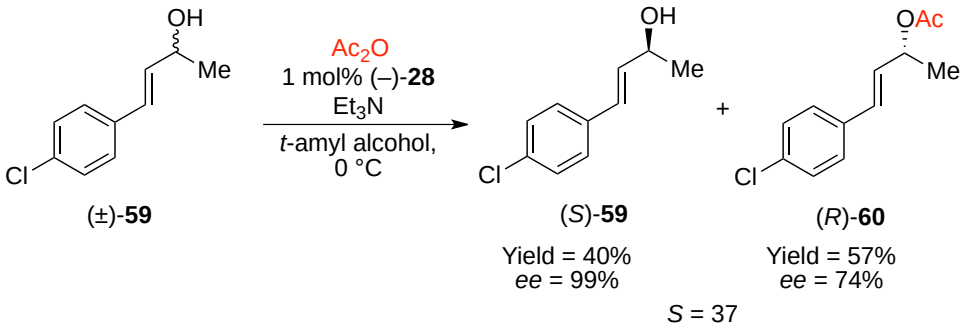


(±) (*S*) (*R*)

Entry	Unreacted alcohol		Conv. (%)	*ee* (%) of alcohol	*S*-value
1		**51**	75	92	5.4

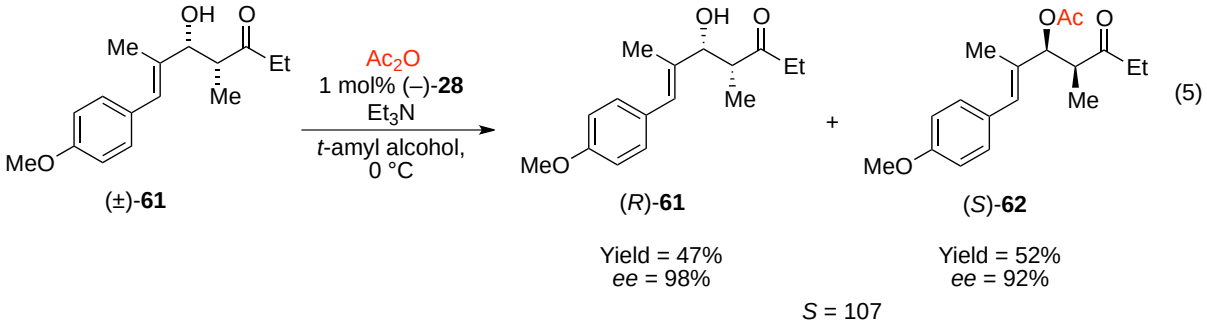
Entry	Unreacted alcohol		Conv. (%)	*ee* (%) of alcohol	*S*-value
2		**52**	54	99	64
3		**53**	63	92	10
4		**54**	77	90	4.7
5		**55**	60	97	18
6		**56**	66	97	12
7		**57**	55	94	25
8		**58**	59	99	29

To illustrate the utility of this selective acyl transfer onto allylic alcohols, Fu applied catalyst (–)-**28** to the KR of allylic alcohols, which serve as key intermediates in natural product syntheses. The KR of a racemic allylic alcohol **59** was achieved with good selectivities ((–)-**59**: *ee* = 99.4%; (+)-**60**: *ee* = 74%)) and high yields ((–)-**59**: Yield = 40%; (+)-**60**: Yield = 57%)). Allylic alcohol (*S*)-(–)-**59** served as a key intermediate in Brenna's total synthesis of (–)-baclofen (Equation 4).[35,39,40]



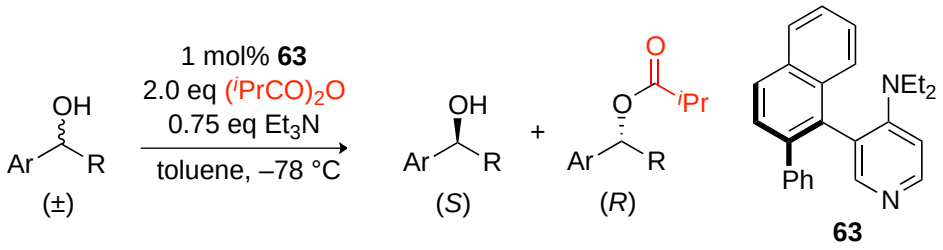
(4)

A second example is the KR of **61** mediated by (–)-**28**. The selectivity realized with Fu's catalyst is higher than that of an aldolase antibody (*ee* = 96%; *S* = 17) utilized by Sinha and Lerner in their total synthesis of epothilone (Equation 5).[35,41] Examples of a small molecule catalyst being superior to an enzymatic approach are rare.



In addition to Fu's planar-chiral DMAP derivative various chiral DMAP- and PPY-catalysts have been developed by other research groups and have been applied in KRs of various substrates. In 1999 Spivey and co-workers employed a chiral DMAP derivative in the KR of a variety of substrates.[34,42,43] Catalyst **63** can be synthesized in seven steps from commercially available 4-pyridone. The selectivities for the KR of secondary alcohols are moderate to good but cannot compete with the selectivities achieved by Fu's catalyst (Table 6).

Table 6. KR of aryl alkyl alcohols mediated by catalyst **63**.

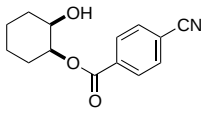
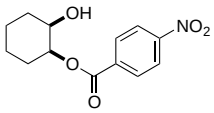
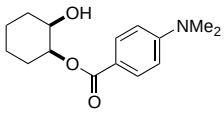
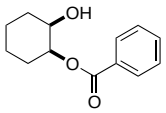
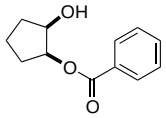
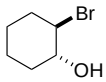
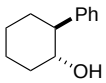
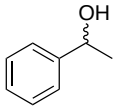
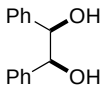
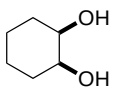


Entry	Ar	R		Conv. (%)	*ee* (%) of alcohol	*ee* (%) of ester	*S*-value
1	1-Nap	Me	**35**	17	19	89	21
2[b]	1-Nap	Me	**35**	22	26	91	29
3	Ph	Me	**30**	39	50	78	13
4	2-Tol	Me	**33**	41	61	86	25
5	Ph	*t*-Bu	**31**	18	19	89	20

[b] Reaction conditions: 1.0 eq $(^{i}PrCO)_2O$

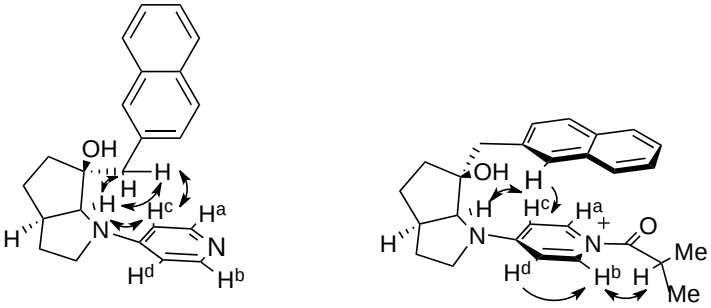
Spivey et al. tested a range of substrates (e.g., monosubstituted cyclic diols, a cyclic *meso*-diol and 2-bromo- and 2-phenylcyclohexanol) under optimized conditions. The best selectivities were observed for monobenzoylated cyclic 1,2-diols (Table 7).[44]

Table 7. Efficiency of catalyst **63** in the KR of various secondary alcohols.[44]

Entry	Substrate		Conv. (%)	*ee* (%) of alcohol	*ee* (%) of ester	*S*-value	Product/ enantiomer
1		**64**	11	8	67	6	(–)/1*R*,2*S*
2		**65**	96	85	39	6	(–)/1*R*,2*S*
3		**66**	18	18	86	16	(–)/1*R*,2*S*
4		**67**	64	98	65	20	(–)/1*R*,2*S*
5		**68**	51	75	73	14	(–)/1*R*,2*S*
6		**69**	54	61	53	6	(–)/1*R*,2*S*
7		**70**	16	14	78	9	(–)/1*R*,2*S*
8		**30**	34	37	71	8	(+)/ *R*
9		**71**	26	-	45	-	(+)/1*S*,2*R*
10		**72**	20	-	78	-	(–)/1*R*,2*S*

Reaction conditions: 2.0 mmol (^{i}PrCO)$_2$O; 0.75 Et_3N; 1 mol% (–)-**63**; –78 °C, 9 h

In 1996 Fuji and Kawabata introduced a 4-PPY-derived chiral catalyst **73**.[34,35,45] On the basis of NMR studies, Fuji and co-workers proposed an "induced fit" mechanism for the acylation of secondary alcohols. They examined **73** and the acylium ion adduct **74** in $CDCl_3$ by ^{1}H-NMR (arrows in Scheme 5 denote the observed NOEs). Catalyst **73** seems to adopt an "open conformation" in which the naphthalene ring and the pyridine ring are separated from each other. In contrast, the naphthalene ring and pyridine ring of **74** are interacting (π-π-stacking) and the catalyst adopts a "closed conformation" (Scheme 5).

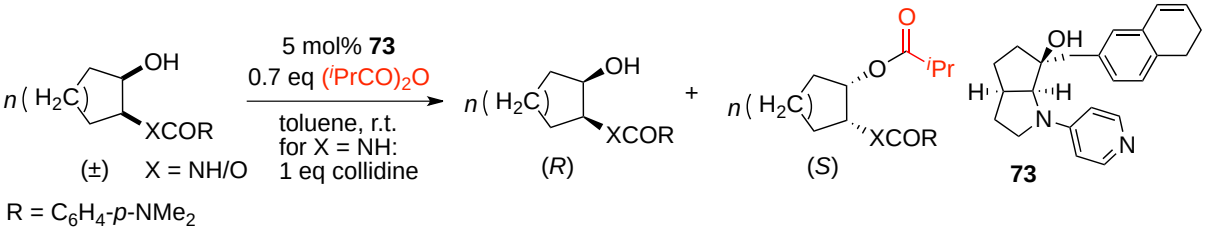


73 (open conformation) **74** (closed conformation)

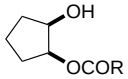
Scheme 5

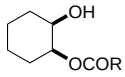
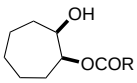
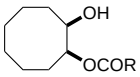
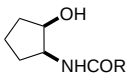
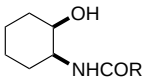
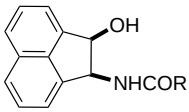
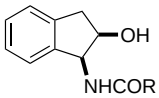
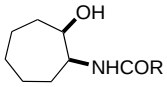
Fuji applied catalyst **73** in the KR of cyclic monobenzoylated 1,2-diols[45] and monobenzoylated 2-aminoalcohols (Table 8).[46] In general, the selectivities for the mono-benzoylated 2-amino alcohols are higher (10–17) than those obtained for the mono-benzoylated 1,2-diols (5.8–10.1). The *S*-value for entry 6 can be increased to 54 by running the reaction at –40 °C.

Table 8. KR of monobenzoylated 1,2-diols and monobenzoylated 2-aminoalcohols mediated by catalyst **73**.

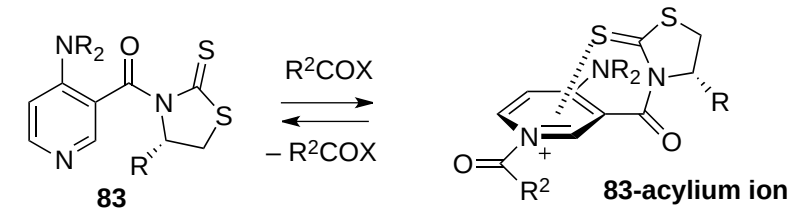


R = C_6H_4-*p*-NMe_2

Entry	Substrate		*t* (h)	Conv. (%)	*ee* (%) of alcohol	*ee* (%) of ester	*S*-value
1		**75**	4	71	97	-	8.3

Entry	Substrate		*t* (h)	Conv. (%)	*ee* (%) of alcohol	*ee* (%) of ester	*S*-value
2		**66**	3	72	99	-	10
3		**76**	4	70	92	-	7
4		**77**	5	73	92	-	6
5		**78**	9	69	99	44	>12
6		**79**	9	58	93	68	17
7		**80**	24	68	99	46	>13
8		**81**	3	64	99	56	17
9		**82**	9	69	97	46	10

In the late 1990's Yamada and his group reported a new acylating catalyst **83**, which undergoes a conformational switch during the acylating step of the catalyst.[34,35,47] They proposed a reaction model that could be confirmed by ^{1}H-NMR measurements, X-ray analysis, and DFT computations.[48] It has been suggested that the selectivities in the KRs of secondary alcohols are due to self-complexation of the acylated catalyst. After the acyl transfer onto the substrate the catalyst adopts its "open conformation" again (Scheme 6).



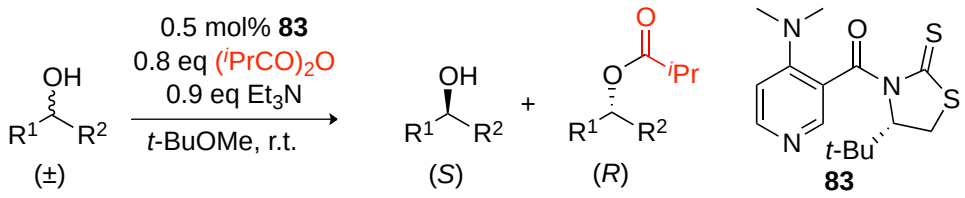
83
"open conformation"

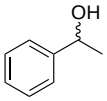
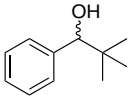
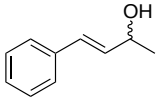
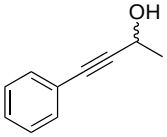
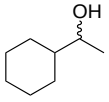
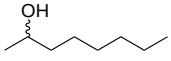
83-acylium ion
"closed conformation"

Scheme 6

Catalyst **83** can readily be prepared from 4-aminonicotinic acid and an auxiliary. Yamada utilized **83** in the KR of secondary alcohols with selectivities ranging from 2.2 to 9.6 (Table 9). High *S*-values were achieved for aryl alkyl alcohols, whereas secondary alkyl alkyl alcohols were resolved with much lower selectivities.[49,50]

Table 9. KR of secondary alcohols with catalyst **83**.

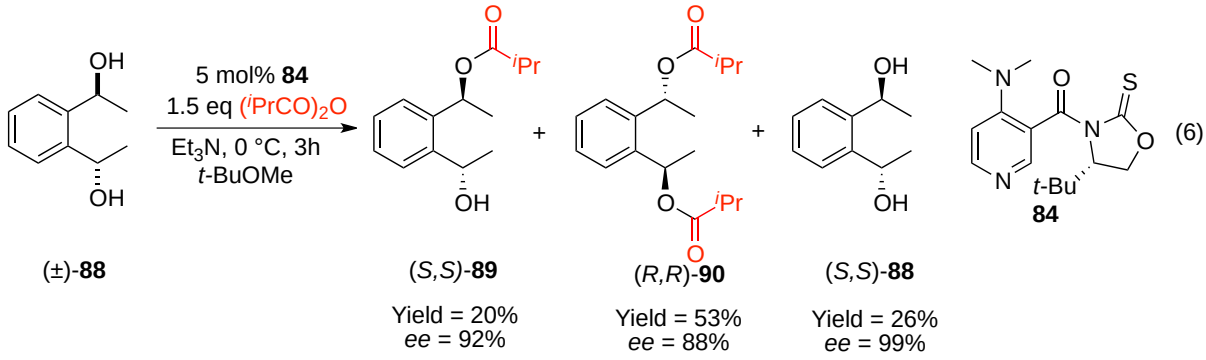


Entry	Substrate		Conv. (%)	*ee* (%) of unreacted alcohol	*S*-value
1		**30**	65	89	7.6
2		**31**	62	88[a]	9.6
3		**85**	65	94[b]	9.8
4		**41**	61	78[b]	6.6
5		**86**	52	31	2.3
6		**87**	48	25	2.2

[a]Reaction time 72 h; [b]Temperature –30 °C; 48 h

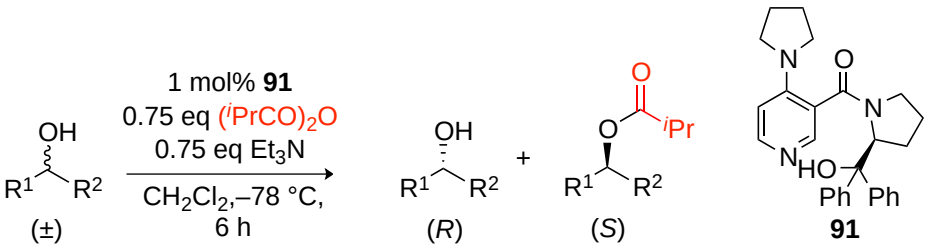
Diols are important building block in organic synthesis and therefore methods for their enantioselective preparation are highly desirable. Catalyst **84** was successfully applied in the KR of racemic 1,4-diol (**88**). While substrates like aryl alkyl alcohols and cyclic *meso* as well as cyclic racemic 1,2- and 1,3-diols are often used as test substrates for

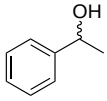
desymmetrizations and KRs mediated by various catalysts and successfully resolved, catalysts for KRs of racemic 1,4-diols are rare (Equation 6).

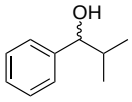
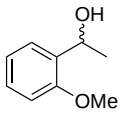
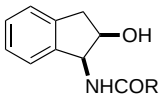
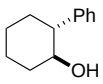
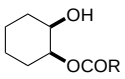


In 2005 Connon and co-workers reported a PPY-derived catalyst **91** that can be easily synthesized in three steps from 3-carboxy-4-chloropyridine without the need for a resolution step.[34,51] The catalyst design was inspired by the "induced fit" concept of Fuji's catalyst **73** and Connon et al. tested catalyst **91** in the KR of various secondary alcohols (Table 10).[52] The selectivities were moderate to good and ranged from 2.3 to 30.0. Good selectivities were achieved for aryl alkyl alcohols and 2-phenylcyclohexanol, whereas *N*-substituted aminoalcohols were poorly resolved. The conversions were low for all examples in Table 10 except of entry 6 because the reactions were stopped after 6 h.

Table 10. Efficiency of catalyst **91** in the KR of various secondary alcohols.

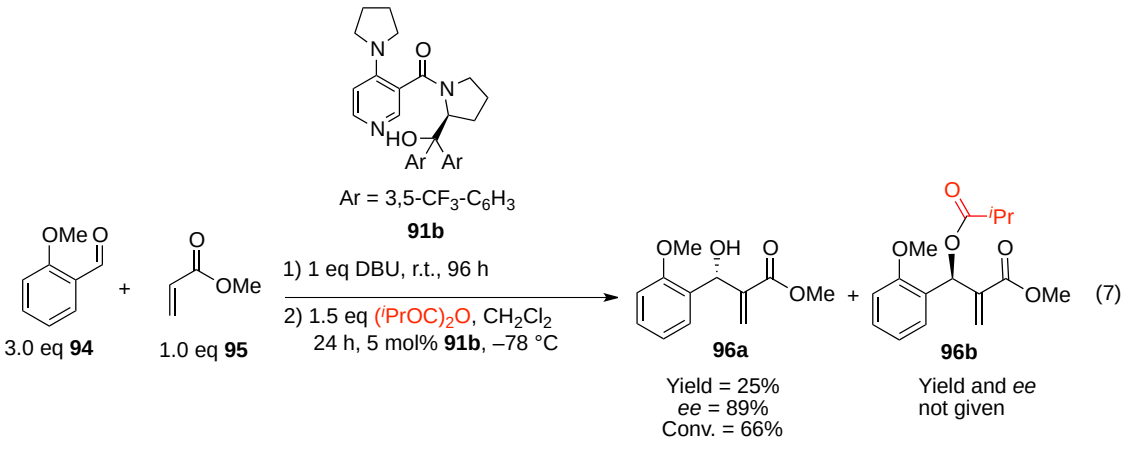


Entry	Substrate		Conv. (%)	*ee* (%) of unreacted alcohol	*S*-value
1		**30**	28	25	6

Entry	Substrate		Conv. (%)	*ee* (%) of unreacted alcohol	*S*-value
2		**92**	19	19	14
3		**93**	18	18	11
4	 R = *p*-Me_2N-C_6H_4	**81**	23	11	2
5		**70**	19	22	30
6[a]	 R = *p*-Me_2N-C_6H_4	**66**	77	>99	20

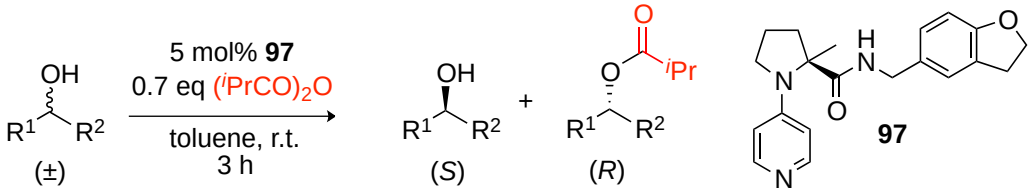
[a] The reaction was stopped after 24 h; The phenyl groups of catalyst **91** were replaced by 3,5-CF_3-C_6H_3-groups.

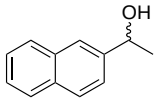
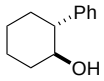
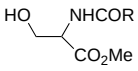
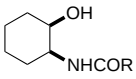
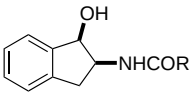
In 2007 Connon and co-workers also applied the slightly modified catalyst **91b** in a one-pot-Baylis-Hillman reaction following an acylative KR.[53] In this process DBU acts as the catalyst for the Baylis-Hillman reaction but does not promote acyl transfer. The enantioselective acylation is mediated by catalyst **91b** (Equation 7).



In 2003 Campbell and co-workers reported readily accessible PPY-derived catalyst **97**.[54] The first step of the synthesis is the nucleophilic substitution of 4-chloropyridine with a-methylproline. The carboxylic acid group of the proline can be functionalized by various amines by standard peptide coupling agents (e.g., HATU). Catalyst **97** was utilized for KRs of secondary alcohols. The selectivities are poor for aryl alkyl alcohols and 2-phenyl cyclohexanol but are good for *N*-substituted amino alcohols (Table 11).

Table 11. KR of various secondary alcohols mediated by catalyst **97**.



Entry	Substrate		Conv. (%)	*ee* (%) of recovered alcohol	*S*-value
1		**98**	74	22	1.4
2		**70**	65	11	1.2
3		**99**	69	99	12.0
4		**79**	59	96	18.8
5		**81**	74	98	8

R = *p*-Me_2N-C_6H_4

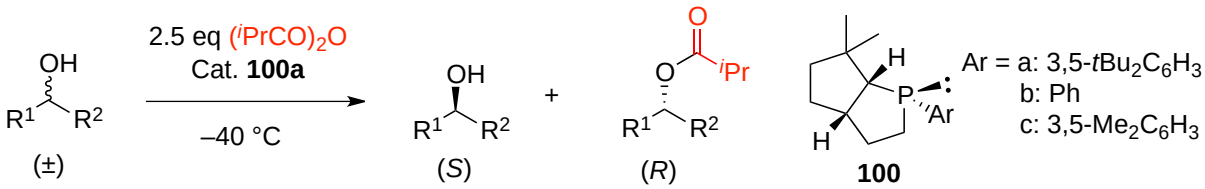
In conclusion, all chiral DMAP- or PPY-derived catalysts are capable of selective acyl transfer. The best results for the KR of aryl alkyl alcohols were obtained by Fu's catalyst **28** with *S*-values in the range of 32–95. The other catalysts resolve aryl alkyl alcohols with selectivities of 13–29 (Spivey **63**), 9.6 (Yamada **83**), 13.5 (Connon **91**) and 1.4 (Campbell **97**). KRs of allylic alcohols, propargylic alcohols, racemic 1,5-diols and the desymmetrization of *meso*-1,5-diols were achieved with catalyst **28** with good to excellent selectivities.

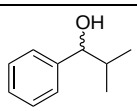
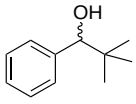
Spivey's catalyst **63** catalyzes KRs of monobenzoylated 1,2-diols with high selectivities under mild conditions. The same substrates can be resolved by Connon's catalyst **91** with excellent selectivities. Catalyst **91** was the first catalyst utilized in a "one-pot" Baylis-Hillman reaction followed by a KR. The selective acyl transfer onto 2-phenyl cyclohexanol mediated by **91** produced high enantiomeric excesses. Good selectivities for the KR of *N*-functionalized 1,2-aminoalcohols were reported for catalysts **73** (Fuji) and catalyst **97** (Campbell). Yamada's catalyst **83** is, to the best of our knowledge, the only chiral DMAP or PPY-derived catalyst capable of transferring an acyl moiety selectively onto racemic cyclic 1,4-diols.

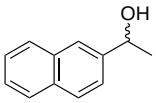
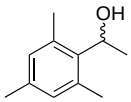
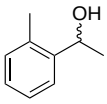
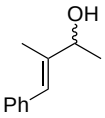
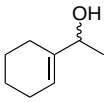
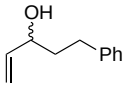
2.1.1.2.2 Phosphine and Phosphinite mediated Enantioselective Acyl Transfer

Vedejs and Driver reported in 1993 the first acylation reaction mediated by tributylphosphines.[55] They compared the catalytic efficiency of DMAP and tributylphosphine in the acylation reaction of alcohols and both catalyst product similar results. The first chiral phosphines were published in 1996 but the selectivities were only moderate.[22] In 1999 Vedejs introduced catalysts **100a-c**, which were successfully employed in the KR of racemic secondary alcohols (Table 12).[34,35,56]

Table 12: KR of racemic secondary alcohols by phosphine catalyst **100a**.

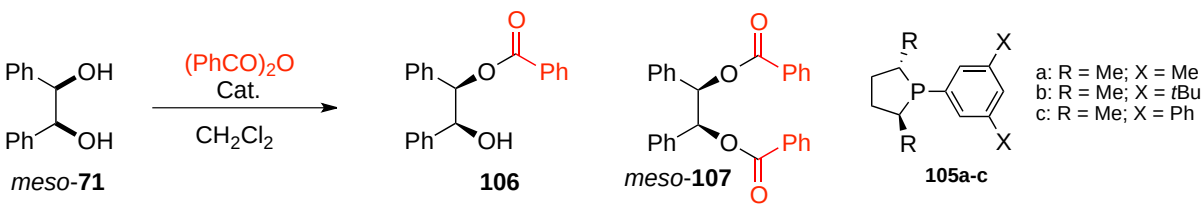


Entry	Substrate		mol% Cat.	Solvent	*ee* (%) alcohol	*ee* (%) ester	Conv. (%)	*S*-value
1		**92**	2.8	Heptane	84	95	47	100
2		**31**	4.9	Heptane	79	93	46	67

Entry	Substrate		mol% Cat.	Solvent	*ee* (%) alcohol	*ee* (%) ester	Conv. (%)	*S*-value
3		**98**	3.9	Heptane	41	97	30	99
4		**101**	12.1	Heptane	79	99	44	369
5		**33**	3.5	Heptane	95	95	50	145
6		**102**	5.0	Toluene	67	82	45	21
7		**103**	5.0	Toluene	90	88	50	49
8		**104**	5.0	Toluene	42	45	48	4

Many other phosphine catalysts were employed in the KR of racemic secondary alcohols, but to date **100a** is the most efficient catalyst for enantioselective acyl transfer in the field of phosphine catalysts. In addition to catalysts **105a-c**, **100a-c** were also capable of transferring acyl moieties onto *meso*-**71**. Phosphine **100b** showed the highest enantiomeric excesses and conversions. The ratio of **106** to *meso*-**107** is 2.6:1, whereas catalyst **105c** gave 87% *ee* and a ratio of 20:1 at 20% conversion (Table 13). The high required catalyst loading of 35–41 mol%, and the low activity of phosphines **105a-c** makes catalyst **100b** preparatively more feasible.[57]

Table 13: Desymmetrization of *meso*-**71** by phosphine catalysts **105a-c** and **100a-b**.

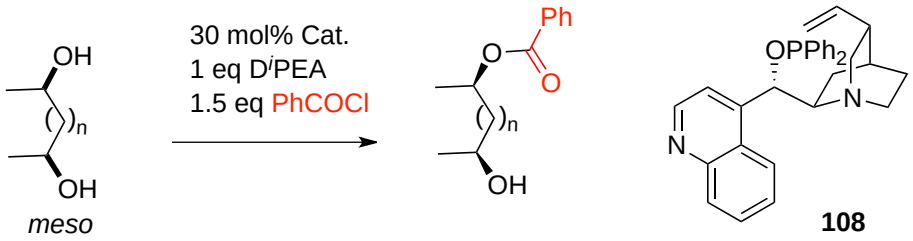


meso-**71** **106** *meso*-**107** **105a-c**

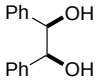
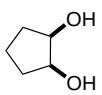
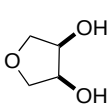
Entry	Cat.	Mol%	*t*	*T* (°C)	Conv. (%)	**106**/**107**	*ee* (%) **106**
1	**105a**	38	4 h	r.t.	20	>20:1	78
2	**105b**	41	1.5 h	r.t.	20	>20:1	87
3	**105c**	35	17 h	r.t.	32	>20:1	87
4	**100a**	4.1	5 min	r.t.	64	5:1	61
5	**100b**	10	22 h	–30	97	2.6:1	94

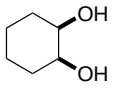
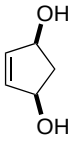
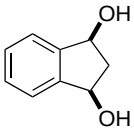
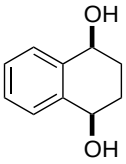
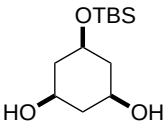
In 2003 Fujimoto and his group used a different approach to design a catalyst with a trivalent phosphorus center.[58] They modified a cinchona alkaloid and synthesized an efficient bifunctional acylation catalyst, which combines a tertiary amino group with a trivalent phosphorus center. The postulated reaction mechanism involves the activation of acyl chloride by the phosphinite moiety while the nitrogen atom of the quinuclidine abstracts a proton of the OH-group. Catalyst **108** was successfully applied in the desymmetrization of *meso*-1,2-, *meso*-1,3- and *meso*-1,4-diols (Table 14).[34,58,59]

Table 14: Desymmetrization of *meso*-1,2-, *meso*-1,3- and *meso*-1,4-diols with catalyst **108**.

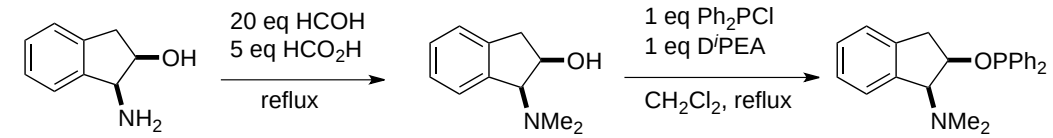


108

Entry	Substrate		*t* (h)	*T* (°C)	Solvent	Yield (%)	*ee* (%)
1		**109**	4.0	–78	EtCN	99	86
2		**71**	1.5	–78	EtCN	98	91
3		**110**	3.5	–78	EtCN	80	93
4		**111**	4.5	–78	EtCN	80	76

Entry	Substrate		*t* (h)	*T* (°C)	Solvent	Yield (%)	*ee* (%)
5		**72**	6.0	–78	EtCN	85	94
6		**112**	4.0	0	CH_2Cl_2	82	81
7		**113**	2.5	0	CH_2Cl_2	71	97
8		**88**	4.0	0	CH_2Cl_2	55	82
9		**114**	6.0	0	CH_2Cl_2	73	70

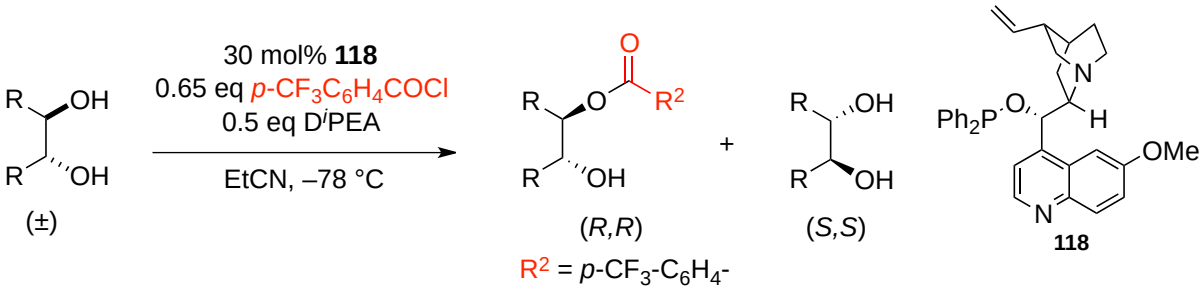
The yields and enantiomeric excesses for all examples were very good. Catalyst **108** can be synthesized readily from cinchonidine in one step. The broad substrate scope for the desymmetrization of diols by **108** and fast access to the catalyst makes **108** preparatively very useful. A drawback might be the high susceptibility of the phosphinite moiety to oxidation and therefore the catalyst needs to be freshly prepared. To solve this problem, Fujimoto et al. published an aminophosphinite catalyst in early 2012. Catalyst **117** can be synthesized in two steps with high yield from commercially available aminoindanols (Scheme 7).[60]

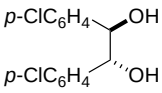
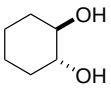
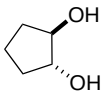
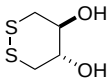
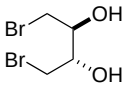


Scheme 7

This catalyst can be isolated and stored under argon in a refrigerator for several months. The selectivities for the desymmetrization of *meso*-1,2-diols (Table 14, entry 1, 2, 5, 8) are comparable to those with catalyst **108**. Consequently, Fujimoto et al. applied catalyst **118** (i.e., catalyst **108** bearing a methoxy group) in the KR of chiral 1,2-diols (Table 15).

Table 15: KR of chiral 1,2-diols with bifunctional catalyst **118**.



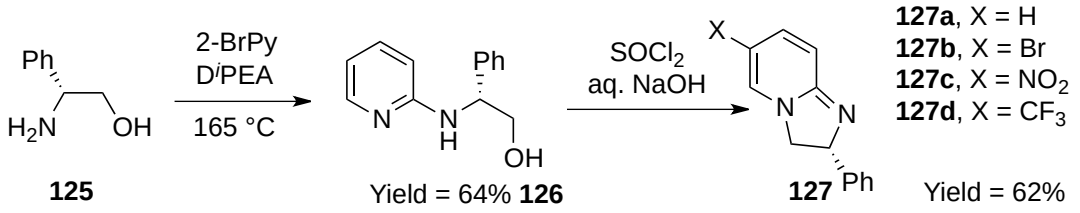
Entry	Substrate		Conv. (%)	*ee* (%) alcohol	*ee* (%) ester	*S*-value
1		**119**	50	99	98	525
2		**120**	51	90	85	38
3		**121**	14	15	89	20
4		**122**	44	63	81	18
5		**123**	41	52	74	11
6		**124**	50	69	68	11

The best selectivities utilizing **108** or **118** were obtained for racemic hydrobenzoin derivatives (*S*-values up to 525), for cyloalkyl-1,2-diols the enantiomeric excesses were good to moderate, while for cyclohexane-1,2-diol the conversion was low. Hence, **118** would be the catalyst of choice for the KR of chiral hydrobenzoin derivatives, whereas Schreiner's catalyst **238** (see Chapter 1.1.1.3.4) is more efficient in the KR of cycloalkane-1,2-diols.

2.1.1.2.3 Amidines and Vicinal Diamines as Catalysts for Enantioselective Acyl Transfer

In 2004 Birman reported the first KR of secondary allylic alcohols utilizing 2,3-dihydroimidazo[1,2-a]pyridines as catalysts.[61,35,34] This structural motif has been known

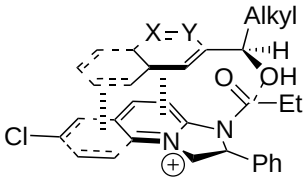
since 1936, but has not been used as a catalytic moiety for acylation reactions. The acyl transfer was proposed[62] to proceed via a nucleophilic mechanism, because Birman obtained the X-ray crystal structure of the *N*-acylated CF_3-PIP hexafluoroantimonate. Catalyst **127a** can be easily synthesized from substituted amino alcohols in two steps and therefore various modifications of **127a** are possible (Scheme 8).[63]



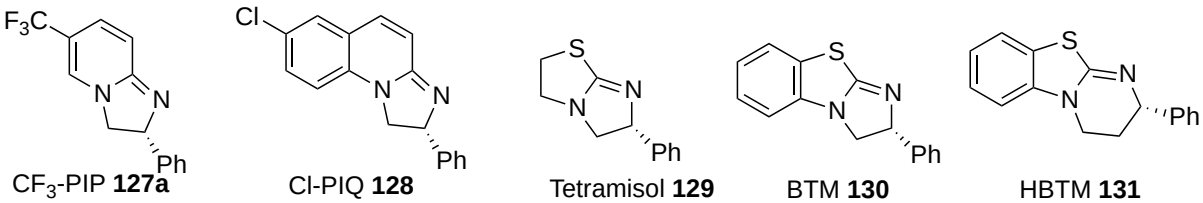
125 Yield = 64% **126** **127** Yield = 62%

Scheme 8

Electron-withdrawing groups in the pyridine ring increase the selectivities and the best *S*-values were achieved by catalyst **127d**. Since the introduction of **127a**-**d** in 2004 Birman and co-workers tested and optimized various amidine catalysts.[61] The replacement of the pyridine moiety by a quinoline moiety (see **127** → **128** or **129** → **130**) improved the performance of the catalysts in the KR of secondary alcohols. Birman et al. proposed additional π-π-interactions as the reason of this observation. Theoretical studies by Houk and co-workers[62] confirmed the importance of the additional aromatic ring for the selectivity of the acyl transfer (Scheme 9).



Proposed TS model for catalyst **127** and **128**

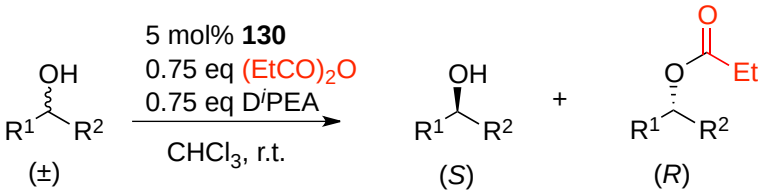


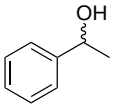
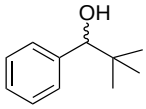
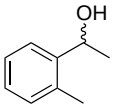
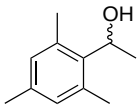
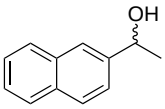
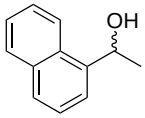
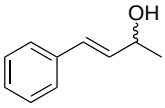
CF_3-PIP **127a** Cl-PIQ **128** Tetramisol **129** BTM **130** HBTM **131**

Scheme 9

Catalyst **130** showed the best results in the KR of secondary aryl alkyl alcohols; the selectivities for all substrates are very high. Even substrates with two bulky moieties (Entry 2) could be resolved with high *S*-values (*S* = 166). One exception was mesityl methyl carbinol (Table 16, Entry 4). In this case poor selectivity of only 2.5 was observed. In contrast, catalyst **127d** is capable of transferring an acyl moiety with a selectivity of *S* = 20 onto mesityl methyl carbinol. The highest *S*-value for this special substrate was obtained with Vedejs' catalyst **100** (*S* = 369).

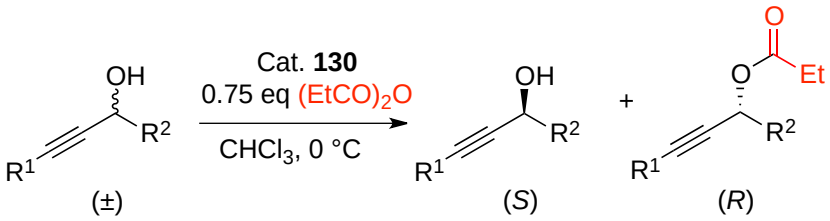
Table 16. Efficiency of catalyst **130** in the KR of aryl alkyl alcohols.

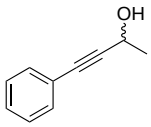
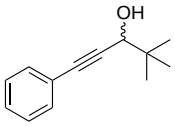
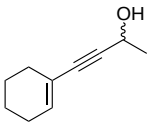
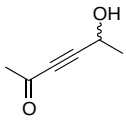
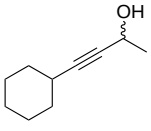
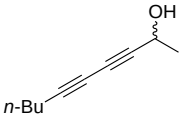


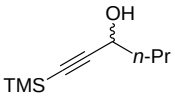
Entry	Substrate		*t* (h)	Conv. (%)	*S*-value
1		**30**	33	49	80
2		**31**	48	51	166
3		**33**	33	50	209
4		**101**	24	20	3
5		**88**	10.5	50	108
6		**35**	8.5	49	128
7		**85**	32	36	23

While there are many nonenzymatic catalysts for the KRs of benzylic or allylic alcohols, the KR of propargylic alcohols was just recently achieved by Fu's planar chiral DMAP-derivative catalyst **28** with selectivities up to 20. Birman and his group applied their catalyst **130** in the KR of various propargylic alcohols as well;[61,64] the selectivities ranged from 5.4 to 32. Although the *S*-values were not as high as in the KR of aryl alkyl alcohols, they are the highest observed by a nonezymatic catalyst for this substrate class to date. In addition to aryl and alkenyl moieties, amidine catalyst **130** is capable of selective acyl transfer onto alkynyl group bearing substrates (Table 17).

Table 17. Efficiency of catalyst **130** in the KR of various propargylic alcohols.

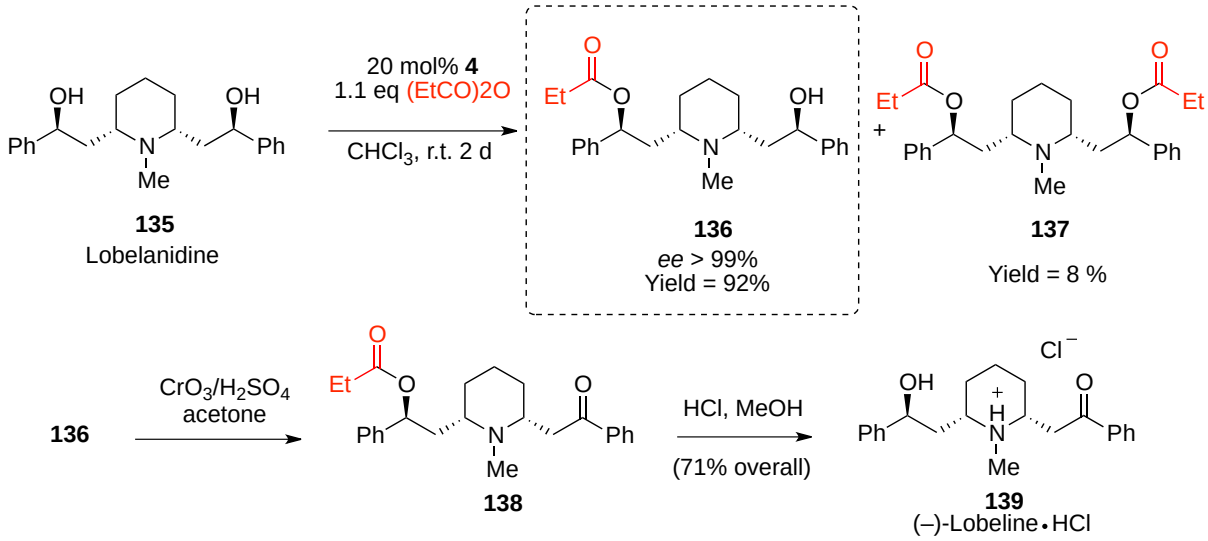


Entry	Substrate		*t* (h)	Conv. (%)	*S*-value
1[a]		**41**	10.5	59	31
2[a]		**44**	10.5	43	10
3[b]		**132**	18	62	27
4[a]		**48**	1.5	55	32
5[c]		**133**	23	60	11
6[a]		**49**	2	52	32

Entry	Substrate		*t* (h)	Conv. (%)	*S*-value
7[c]		**134**	2.5	57	5

[a]Catalyst loading: 4 mol% **130;** [b] 10 mol% **130**, 1.5 eq $(EtCO)_2O$; [c] 10 mol% **130**

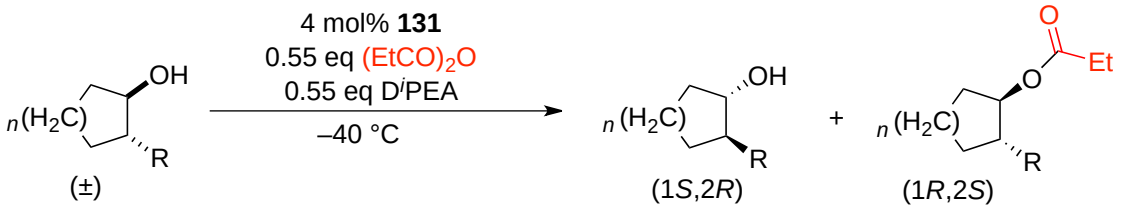
Superficially, it may seem as if new catalysts were synthesized in order to achieve the best possible selectivities in a particular test reaction, but the real motivation often is the synthesis of a catalysts for industrial applications. Hence, test reactions are needed to determine the efficiency of a new catalyst system for asymmetric transformations (e.g., enantioselective acyl transfer). Test reactions offer the possibility to compare selectivities of various catalysts. An example of the utilization of a catalyst in total syntheses of a natural product is shown in Scheme 10. Catalyst **130** was successfully applied in the desymmetrization of lobelanidine. The desymmetrization step proceeds with high conversion and selectivity.[65]

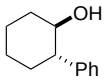
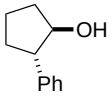
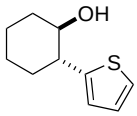
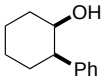
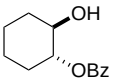
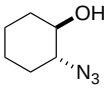


Scheme 10

In 2008 Birman and co-workers extended the substrate scope by using aryl cycloalkanols in the KR mediated by catalyst **131**.[66] Good enantioselectivities were achieved for substrates with aromatic moieties, whereas the *S*-values decreased for substrates containing an $–N_3$ or –OBz group in the 2-position of the alkyl ring.[66]

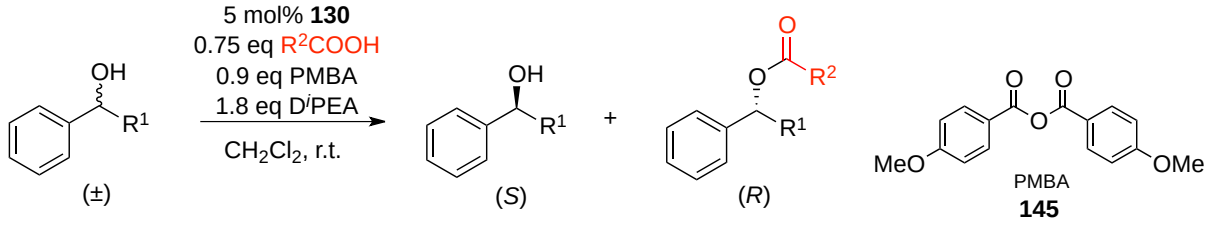
Table 18. KR of aryl cycloalkanols by catalyst **131**.



Entry	Substrate		*t* (h)	Conv. (%)	*S*-value
1		**70**	10	51	107
2		**140**	7	51	66
3		**141**	10	44	44
4		**142**	12	46	28
5		**143**	10	28	5.6
6		**144**	10	26	10

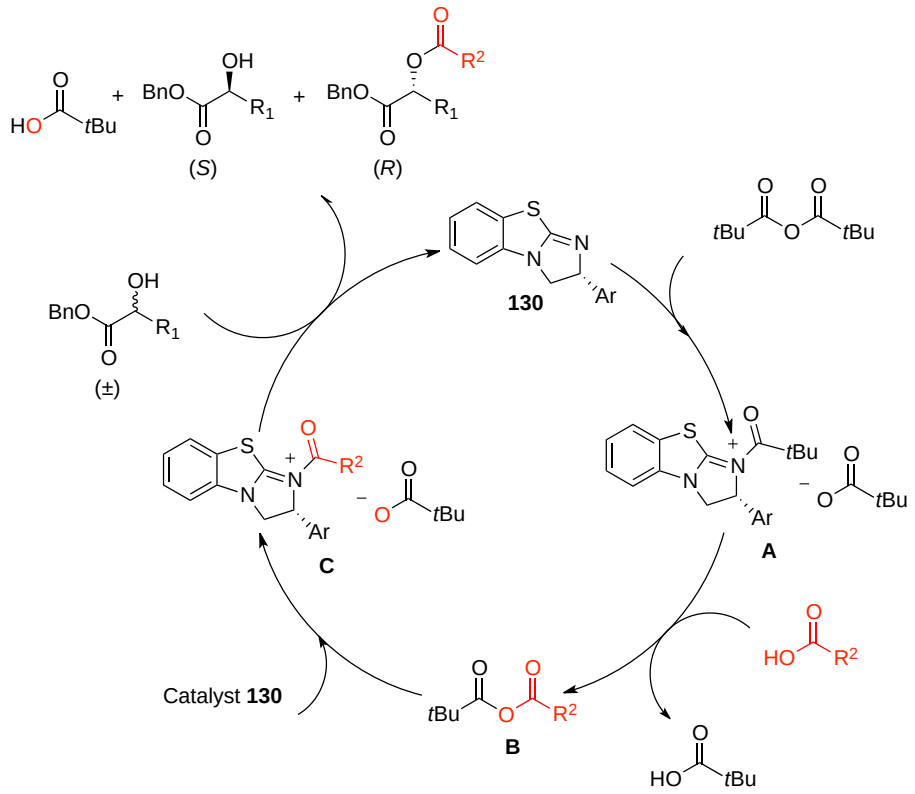
In 2007 Shiina and co-workers reported the KR of secondary benzylic alcohols mediated by catalyst **130**.[67] In contrast to Birman's approach, where anhydrides were used as acyl source, Shiina used carboxylic acids as the acylation agents. The reaction requires benzoic anhydride (PMBA, **145**), which forms a mixed anhydride with the carboxylic acid catalyzed by **130** (Table 19). In fact, the mixed anhydride presents the acyl source (similar to Scheme 11).

Table 19. KR of secondary benzylic alcohols with carboxylic acids catalyzed by **130**.



Entry	R^1		R^2	*ee* (%) alcohol	Yield (%) alcohol	*ee* (%) ester	Yield (%) ester	*S*-value
1	Et	**146**	Et	76	40	89	40	39
2	Et	**146**	$Ph(CH_2)_2$	75	46	90	41	43
3	Et	**146**	$Ph(CH_2)_3$	69	45	90	39	39
4	Et	**146**	$Me_2CH(CH_2)_2$	71	38	83	43	23
5	Et	**146**	CH_2=CH-$(CH_2)_2$	91	38	86	47	42
6	Et	**146**	$MeOCH_2$	38	51	82	32	15
7	Et	**146**	Cy	51	40	76	53	12
8	^{i}Pr	**92**	Et	81	43	90	39	47
9	^{i}Pr	**92**	$Ph(CH_2)_2$	64	53	92	38	46
10	^{t}Bu	**31**	Et	44	67	93	32	42
11	^{t}Bu	**31**	$Ph(CH_2)_2$	58	54	96	36	88

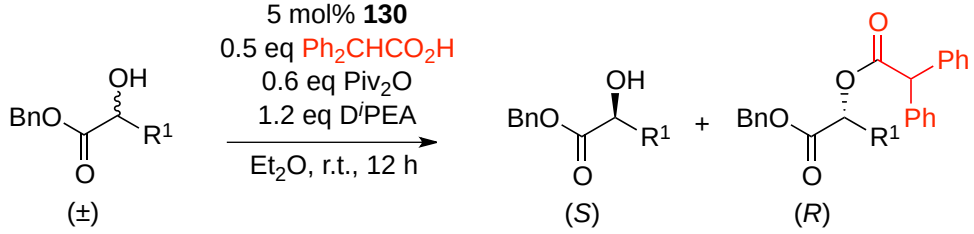
The KR of 2-hydroxyalkanoates can be achieved by using the same mixed anhydride technique. In this case pivalic anhydride is utilized to generate the mixed anhydride catalyzed by (*R*)-benzotetramisol (BTM) **130**. Shiina and his group proposed following catalytic reaction mechanism: pivalic anhydride reacts with BTM and forms acylated species **A**. The carboxylic acid attacks **A** and forms mixed anhydride **B**. BTM activates mixed anhydride **B** and generates a second intermediate **C**, which transfers the acyl moiety (the former carboxylic acid) enantioselectively onto the racemic 2-hydroxyalkanoate (Scheme 11). Schreiner and co-workers reported a similar concept by generating the anhydride *in situ* from carboxylic acids by using substituted carbodiimides as coupling agents. This led to the first enantioselective Steglich esterification.[68] Approaches in which carboxylic acids are directly used as acyl source, are rare because of the need for water removal.



Scheme 11

Shiina and co-workers applied their method to various 2-hydroxyalkanoates and excellent selectivities were observed with catalyst **130** (Table 20). The KR of 2-acyloxyalkanoates with other catalysts is not known and this approach is the first practical method to prepare enantiopure 2-hydroxyalkanoates and 2-acyloxyalkanoates.[69]

Table 20. KR of 2-hydroxyalkanoates utilizing the mixed anhydride method and diphenylacetic acid as the acyl source.

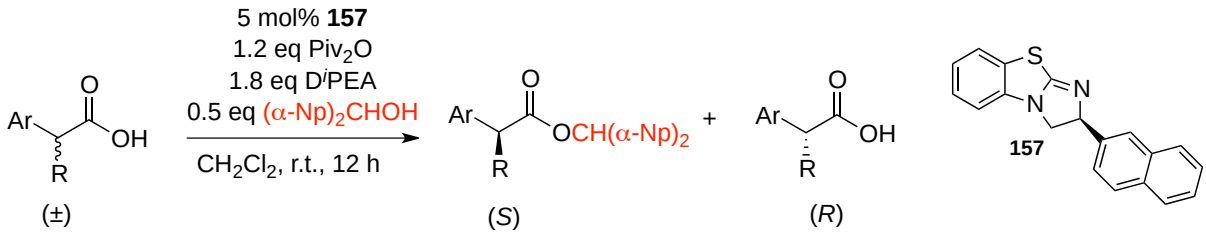


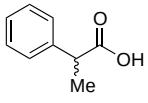
Entry	R^1		*ee* (%) alcohol	Yield (%) alcohol	*ee* (%) ester	Yield (%) ester	*S*-value
1	Me	**147**	82	55	97	44	146

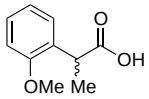
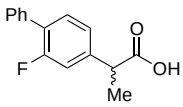
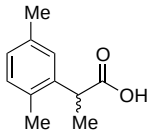
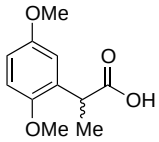
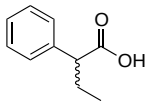
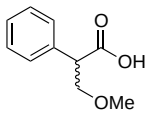
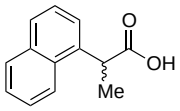
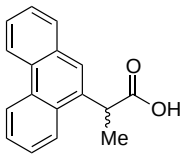
Entry	R^1		*ee* (%) alcohol	Yield (%) alcohol	*ee* (%) ester	Yield (%) ester	*S*-value
2	Et	**148**	94	43	95	46	126
3	*n*Pr	**149**	97	48	95	50	171
4	*i*Pr	**150**	73	50	92	46	53
5	*n*Bu	**151**	88	51	96	47	128
6	*i*Bu	**152**	97	55	94	45	140
7	Cy	**153**	75	53	91	43	47
8	$Ph(CH_2)_2$	**154**	95	47	96	48	202
9	$TBSOCH_2$	**155**	87	50	93	47	80
10	$TBSO(CH_2)_2$	**156**	87	52	96	45	146

Consequently, Shiina and co-workers applied the mixed anhydride method to the KR of chiral carboxylic acids with achiral alcohols.[70] The reaction conditions were similar to those used for the KR of chiral alcohols with achiral acids.[67] The best results were obtained by utilizing bis(α-naphthyl)methanol, catalyst **157**, and pivalic anhydride for the KR of various 2-arylpropanoic acids (Table 21).[71]

Table 21. KR of chiral carboxylic acids with bis(α-naphthyl)methanol mediated by catalyst **157**.



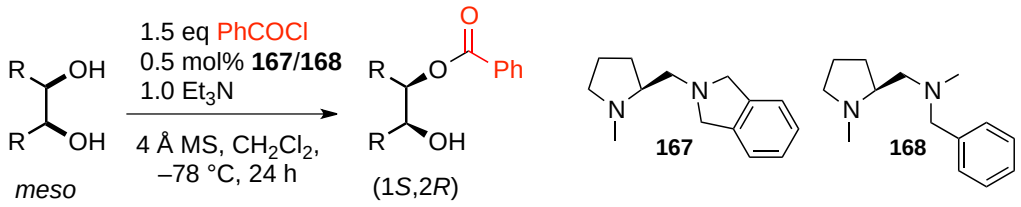
Entry	Substrate		*ee* (%) acid	Yield (%) acid	*ee* (%) ester	Yield (%) ester	*S*-value
1		**158**	59	51	92	45	44

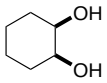
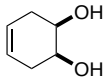
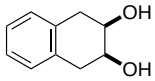
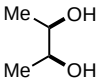
Entry	Substrate		*ee* (%) acid	Yield (%) acid	*ee* (%) ester	Yield (%) ester	*S*-value
2		**159**	73	30	89	48	193
3		**160**	67	42	87	46	29
4		**161**	99.5	43	98	40	484
5		**162**	73	38	98	47	235
6		**163**	46	35	75	45	11
7		**164**	39	47	88	37	24
8		**165**	82	41	96	48	136
9		**166**	86	49	98	48	361

In summary, amidine based catalysts (e.g., **130**, **131**, and **157**) are excellent catalyst for enantioselective acyl transfer reactions. The synthesis of the catalysts can be achieved in a few steps from commercially available starting materials. Various substrates like aryl alkyl alcohols, propargylic alcohols and aryl cycloalkanols can be selectively acylated by **130** and **131**. Shiina employed a mixed anhydride method and extended the substrate scope to 2-hydroxyalkanoates and (chiral) carboxylic acids. A big advantage of of Shiina's and Schreiner's[68] methods is the possibility to use carboxylic acids as acyl equivalents.

In 1998 Oriyama reported the desymmetrization of *meso* alcohols with amine-based catalyst **167** and **168**.[35,72] The proline derived catalysts **167** and **168** showed similar selectivities at low catalyst loadings (0.5 mol%) with acyl chlorides as the acyl source (Table 22). KRs of secondary alcohols with catalyst **167** were also tested and produced *S*-values up to 160 for 2-phenylcyclohexanol at –78 °C.

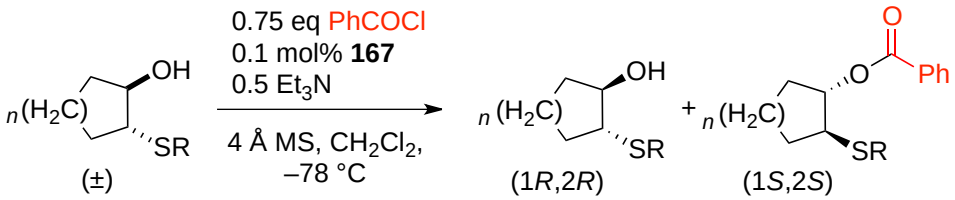
Table 22. Efficiency of catalyst **167** and **168** in the desymmetrizations of *meso* alcohols.

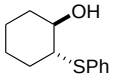
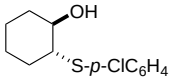
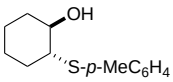
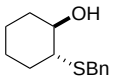
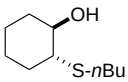
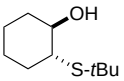
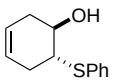
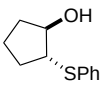
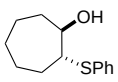
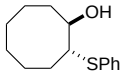
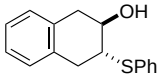


Entry	Substrate		Catalyst	Yield (%) ester	*ee* (%) ester
1		**72**	**167**	62	95
			168	83	96
2		**169**	**167**	78	96
			168	81	90
3		**170**	**167**	89	48
			168	89	66
4		**71**	**167**	68	64
			168	80	60
5		**109**	**167**	80	91
			168	85	94

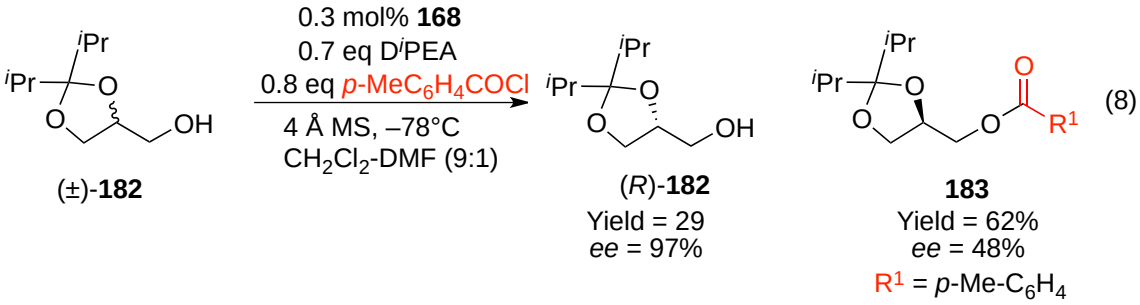
In 2010 Kawamata and Oriyama et al. accomplished the first non-enzymatic KR of racemic cyclic β-hydroxy sulfides. Catalyst **167** catalyzed the acyl transfer with good to excellent selectivities (Table 23). [35,73]

Table 23. Efficiency of catalyst **167** in the KR of β-hydroxy sulfides.

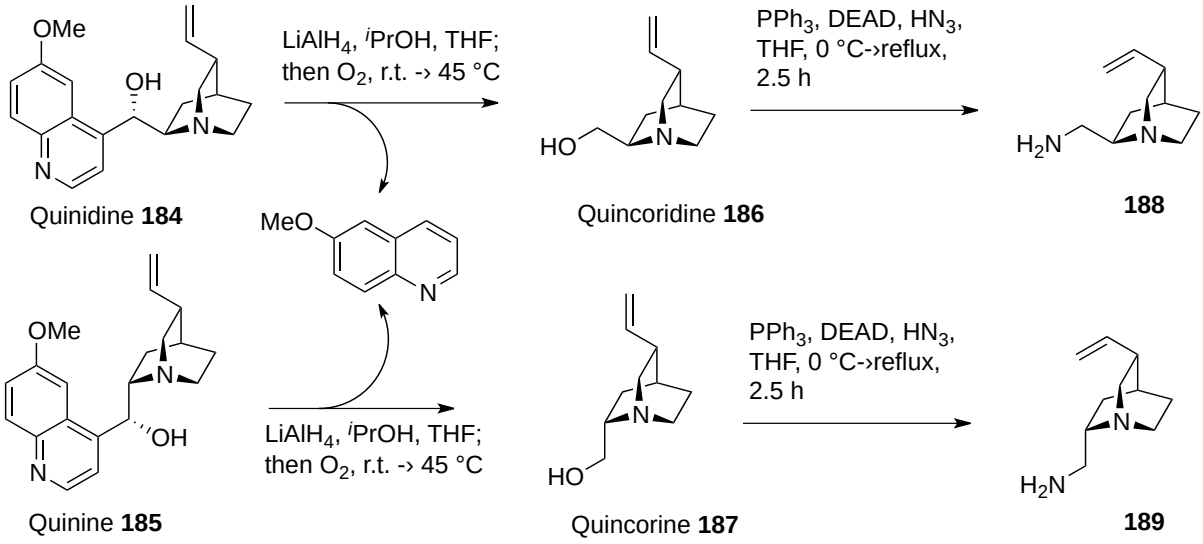


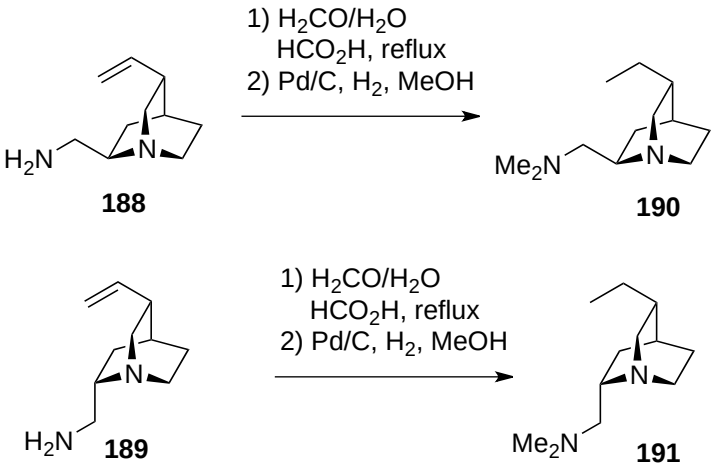
Entry	Substrate		*ee* (%) alcohol	Yield (%) alcohol	*ee* (%) ester	Yield (%) ester	*S*-value
1		**171**	96	49	97	50	280
2		**172**	94	49	98	49	360
3		**173**	97	47	96	49	160
4		**174**	99	48	96	49	160
5		**175**	93	43	92	46	57
6		**176**	73	44	98	42	210
7		**177**	93	47	94	50	160
8		**178**	69	48	68	48	10
9		**179**	97	47	97	48	200
10		**180**	99	48	95	49	160
11		**181**	81	49	86	49	34

Non-enzymatic approaches for the KR of primary alcohols are rare. Oriyama achieved the first KR of a primary alcohol with good selectivities.[74] Primary alcohols are challenging substrates for desymmetrizations or KRs mediated by a small molecule catalyst owing to the fact that no functional group, which is usually required to achieve recognition by a catalyst, is close to the hydroxyl group. Even enzyme-mediated enantioselective acyl transfer onto primary alcohols is rather rare and the selectivities are much lower than those for secondary alcohols. The KR of (±)-**182** with catalyst **168** under optimized conditions is shown in Equation 8.[74]



In 2004 Kündig and co-workers reported the desymmetrization of a *meso*-Cr^0-complex utilizing chiral diamine catalysts **190** and **191**.[35,75] The synthesis of catalysts **190** and **191** can be achieved in four steps starting with quinine or quinidine (Scheme 12).[76]

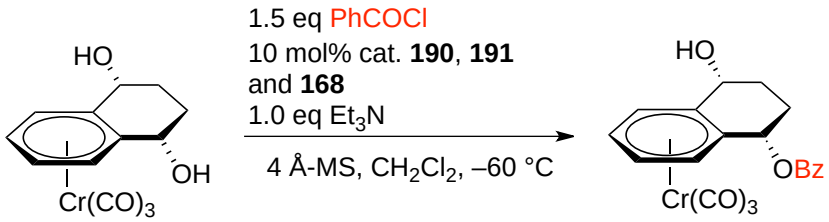




Scheme 12

The selectivities for the desymmetrization of the *meso*-Cr^0-complex are very good. Beside the chiral diamines **190** and **191**, Kündig et al. also tested Oriyama's catalyst **168** under similar reaction conditions' (Table 24).[77]

Table 24. Efficiency of catalysts **168**, **190**, and **191** in the desymmetrization of *meso*-**192**.



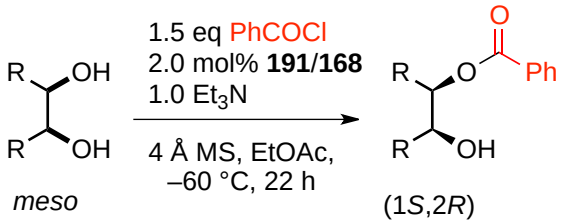
meso-**192** (–)-**193** (shown) or (+)-**193**

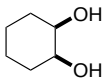
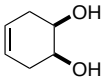
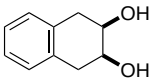
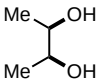
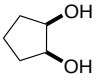
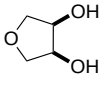
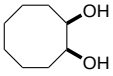
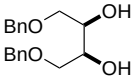
Entry	Cat.	*t* (h)	Yield (%) **193**	*ee* (%) **193**
1	**168**	22	78	95(–)
2	**190**	23	80	94(+)
3	**191**	22	76	99(–)

Consequently, Kündig et al. tested catalyst **191** in the desymmetrization of *meso*-1,2-diols.[76] Oriyama et al. had already successfully applied catalyst **168** to the desymmetrization of the same substrates. Kündig et al. used slightly modified conditions (2 mol% of catalyst **191** instead of 0.5 mol% of **168**; EtOAc as solvent) for his approach. The selectivities achieved by catalyst **191** are comparable to those reported for **168**. Catalyst **191** showed

better results for substrate **72,** whereas catalyst **168** performed better in the desymmetrization of substrates **71** and **169** (Table 25).

Table 25. Efficiency of catalyst **191** in the desymmetrization of *meso*-1,2-diols compared with the results obtained by catalyst **168.**



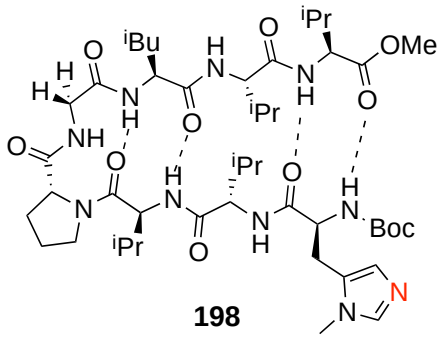
Entry	Substrate		Catalyst	Yield (%) ester	*ee* (%) ester
1		**72**	**191**	92	97
			168	83	96
2		**169**	**191**	79	84
			168	81	90
3		**170**	**191**	65	83
			168	89	66
4		**71**	**191**	82	13
			168	80	60
5		**109**	**191**	82	90
			168	85	94
6		**110**	**191**	87	78
7		**111**	**191**	84	77
8		**194**	**191**	86	77
9		**195**	**191**	51	93

In conclusion, chiral diamines like **167**, **168**, **190**, and **191** are capable catalysts for enantioselective acyl transfer. In particular, *meso*-1,2-diols can be resolved with high selectivities and good yields. Catalyst **168** was also successfully utilized in the KR of β-hydroxy sulfides and a glycerol-derivative bearing a primary alcohol moiety.

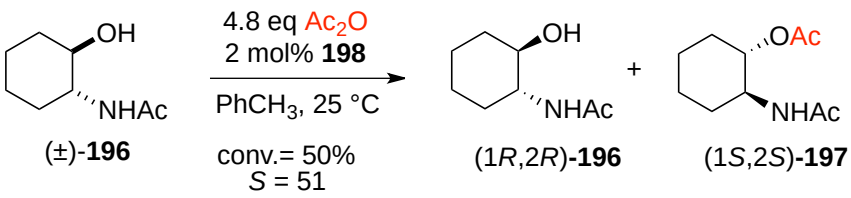
2.1.1.2.4 Enantioselective Acyl Transfer via *N*-Alkylimidazoles

As outlined in the Introduction, enantioselective acylation reactions are widely used in nature. Enzymes are capable of transferring acyl moieties in a highly efficient and chemoselective way. Although enzymes are used as catalysts in enantioselective acylation reactions, scientists were interested in the design of small organocatalysts with comparable properties but advantages such as ease of handling, availability and other reasons.

Miller and co-workers synthesized small peptide-based catalysts containing a nucleophilic moiety to transfer acyl groups onto substrates.[34,35,78,79] The peptide backbone should provide a chiral environment for selective substrate recognition. In this context they discovered a D-Pro-Aib-*β*-turn motif as an excellent scaffold for the synthesis of highly selective catalysts. After optimization of the peptides for the KR of **196** the highest enantioselectivities for the resolution of racemic *trans*-1,2-acetamidocyclohexanol were obtained using peptide **198**. A drawback of this catalyst may be its rather high molecular weight of 946 g·mol^{-1} and the narrow scope for monoprotected 1,2-aminoalcohols.[80]



198

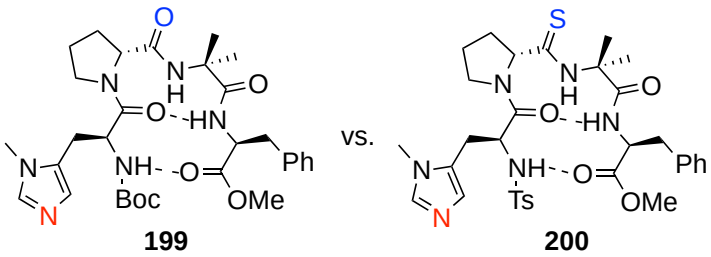


(±)-**196** conv.= 50% *S* = 51 (1*R*,2*R*)-**196** (1*S*,2*S*)-**197**

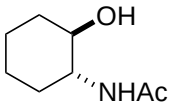
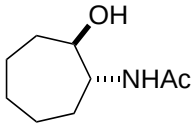
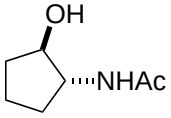
(9)

Qu et al. modified the backbone of Miller's tetrapeptide by introducing a thioamide instead of the amide in the *β*-hairpin-structure[81] and the resulting catalyst **200** was compared with **199** in the KR reaction of **196**; **200** provides a higher *S*-value (Table 26).[81] A possible explanation might be the formation of a more constrained *β*-hairpin structure. Qu succeeded in the synthesis of a smaller, highly efficient catalyst for the KR of **196**, but the substrate scope is still limited to *trans*-1,2-acetamidocycloalkanols.

Table 26: KR of *trans*-1,2-acetamidocycloalkanols with catalyst **199** and **200**.

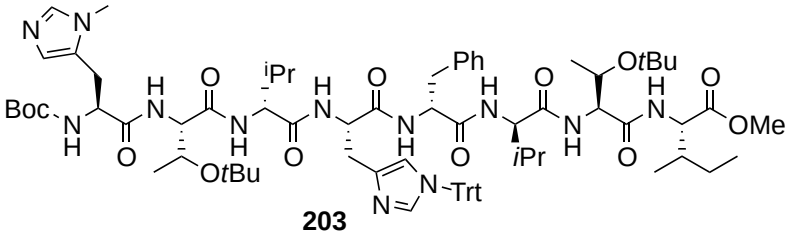


199 **200**

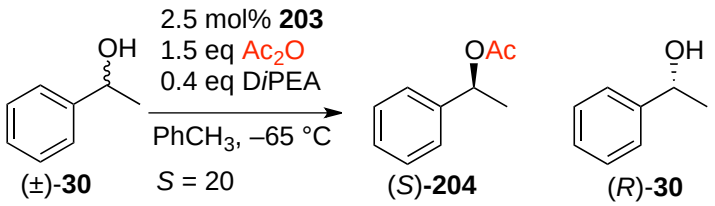
Entry	Substrate		Catalyst	Conv. (%)	*S*-value
1		**196**	**199**	49	28
2			**200**	50	109
3		**201**	**199**	51	17
4			**200**	48	75
5		**202**	**199**	56	6
6			**200**	44	9

A big advantage of peptide catalysts is that they can be easily modified and the synthesis of a great number via SPPS (Solid Phase Peptide Synthesis) is possible in a rather short period of time. A broad range of natural and non-natural amino acids are available and therefore a large number of combinations can be envisaged. Peptide libraries can be prepared and their members tested for various substrates by using, e.g., fluorescence-based

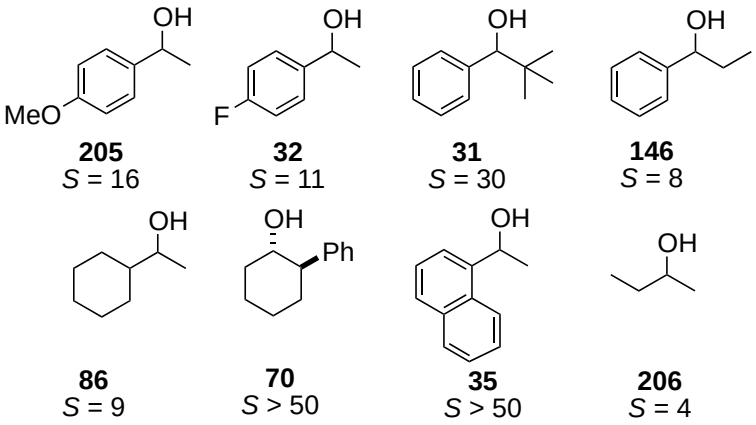
assays for high-throughput identification of active catalysts.[82,83] Miller and co-workers identified peptide **6** as an efficient catalyst for the KR of secondary alcohols by using such a screening method.[82,84]



203



(±)-**30** S = 20 (*S*)-**204** (*R*)-**30** (10)

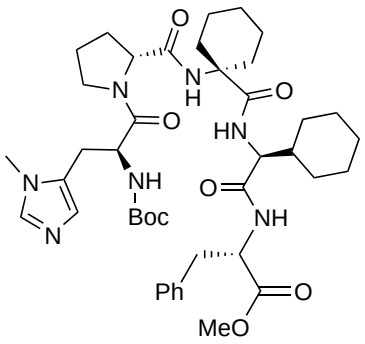


205 S = 16 **32** S = 11 **31** S = 30 **146** S = 8

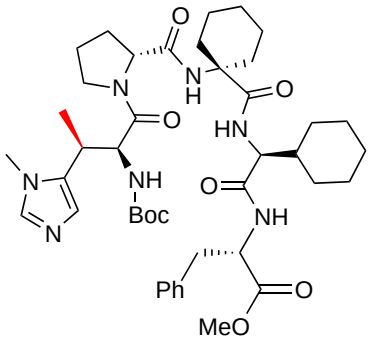
86 S = 9 **70** S > 50 **35** S > 50 **206** S = 4

Equation 10 shows the high selectivity of **203** in the KR of (±)-**30**. In contrast, **203** was less efficient when substrates without an aryl moiety were used. This study shows again the high chemoselectivity of peptide catalysts. While the KR of secondary alcohols especially of *rac*-**30** is widely known and can also accomplished with enzymes, examples for KRs of tertiary alcohols are rare. Even enzyme-catalyzed reactions are not known. Miller et al. achieved the KR of **209**–**212** with moderate to good selectivities. Comparison of the *S*-values generated with catalyst **207**and **208** shows the large effect of small modifications on peptide catalyst systems (Equation 11, Table 27). Simply replacing the π-methyl histidine residue of peptide **207** by a methylated β-methyl-π-methyl histidine moiety increased the selectivity. A reason for this observation may be the restricted rotational freedom around the C^{β}-C^{γ} bond of the β-branched π-methyl histidine moiety. ^{1}H-NMR measurements exhibited

evidence for the restriction of the rotation for the Boc-protected β-methyl-π-methyl histidine, but did not show evidence for restriction of the rotation for the unprotected β-methyl-π-methyl histidine. Hence, Miller proposed that either a remote steric effect or a hydrogen bonding interaction associated to the Boc-group is responsible for the dihedral angle restriction.[79,85]



207



208

(11)

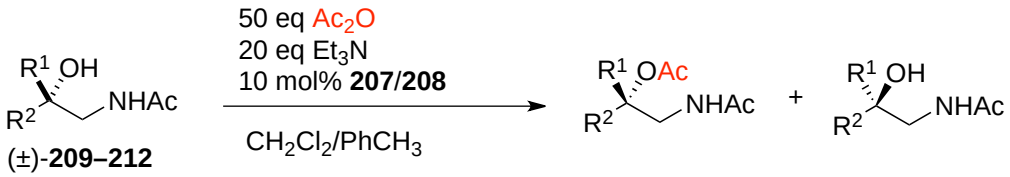
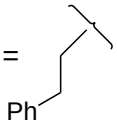
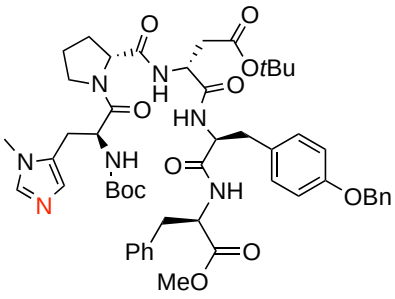


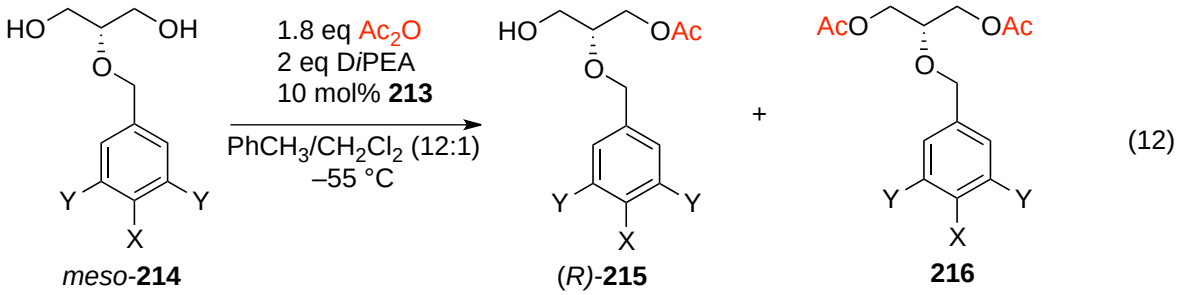
Table 27: Comparison of catalyst **207** and **208** in the KR of tertiary alcohols.

Entry	Substrate		Catalyst	Conv. (%)	*S*-value
1	R^1 = Me	**209**	**207**	33	9
2	R^2 = Cy		**208**	53	>50
3	R^1 = Me	**210**	**207**	39	10
4	R^2 = *p*-NO_2-Ph		**208**	60	24
5	R^1 = Me	**211**	**207**	32	3
6	R^2 = 		**208**	65	18
7	R^1 = CO_2Me	**212**	**207**	21	1.6
8	R^2 = Ph		**208**	43	2.8

The desymmetrization of *meso* compounds has become a powerful tool in asymmetric synthesis. In contrast to KRs, desymmetrization reactions can achieve 100% theoretical yield. Peptide **213,** a modification of **207**, enables the desymmetrization of *meso* glycerol derivative **214**, which presents a formidable challenge.[86] These examples show the manifold applications of small peptide catalysts, because primary, secondary, and tertiary OH-groups can be acylated.



213

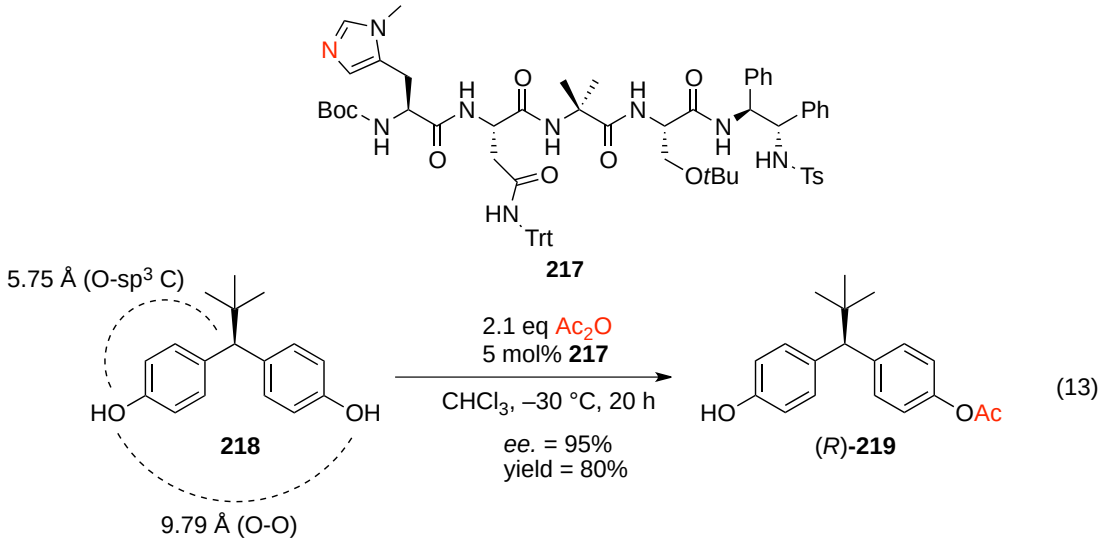


meso-**214** (*R*)-**215** **216**

X = H; Y = H — Yield = 37; *ee.* = 91% — 215/216 ratio = 39:61
X = H; Y = OMe — Yield = 34; *ee.* = 95% — 215/216 ratio = 37/63

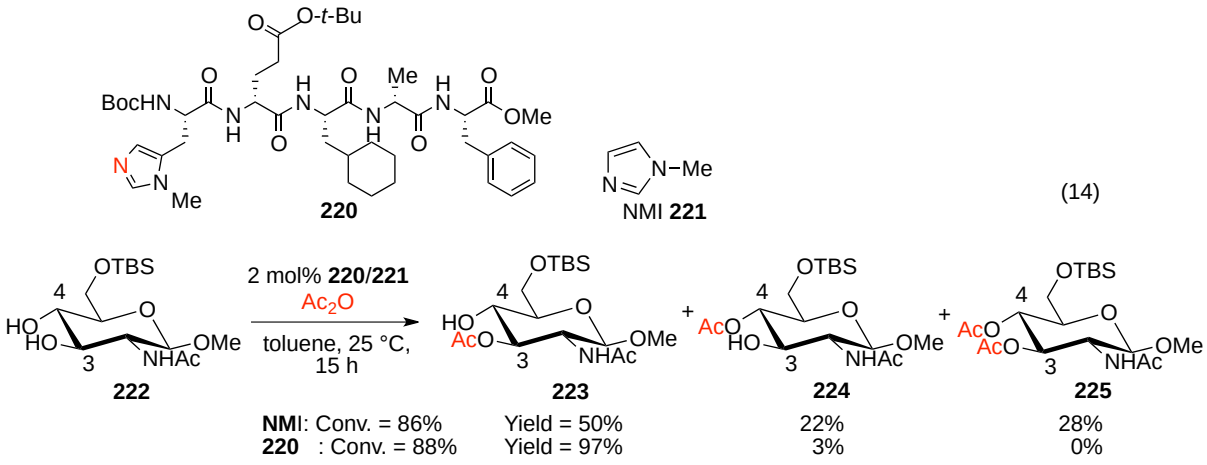
(12)

In 2006 Miller and co-workers found a catalyst that was effective in the enantioselective acylation of substrate **218**. This substrate was challenging because of the large distance between the two OH-groups (almost 10 Å) and also between the OH-group and the prostereogenic center (ca. 6 Å). Enzymes seem to be the best choice to solve such a difficult problem, because their macromolecular structure generates a chiral environment, which provides the potential for enantioselective recognition even if the prostereogenic center and the enantiotopic phenol oxygens of the substrate are far away from each other. In this rare case a chemical method (catalyst **217**) shows better results than enzymatic approaches.[79,87,88]



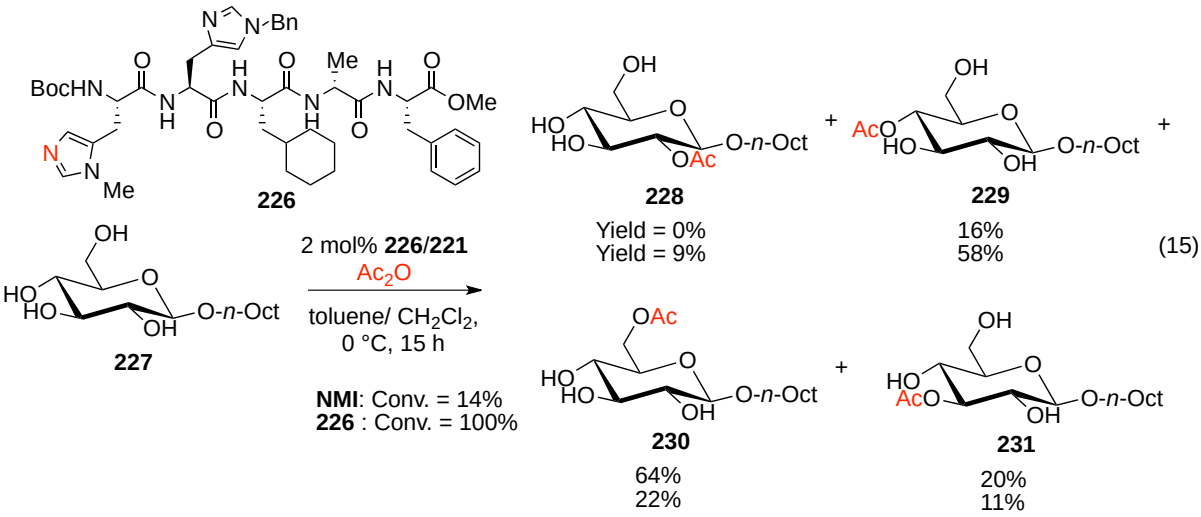
(13)

Site-selective functionalization of substrates containing more than one functional group is synthetically useful but difficult. Hence, enzymatic approaches for chemo- and site-selective transformations are known, but limited to a narrow substrate scope. Miller et al. tested catalyst **220** and *N*-methylimidazole [NMI, (**201**)] in the site-selective acylation of the glucosamine derivative **222**. While achiral NMI produced a mixture of **223**–**225**, catalyst **220** achieved site selective acylation and **223** was obtained in 97% yield as the major product.[79,89]



(14)

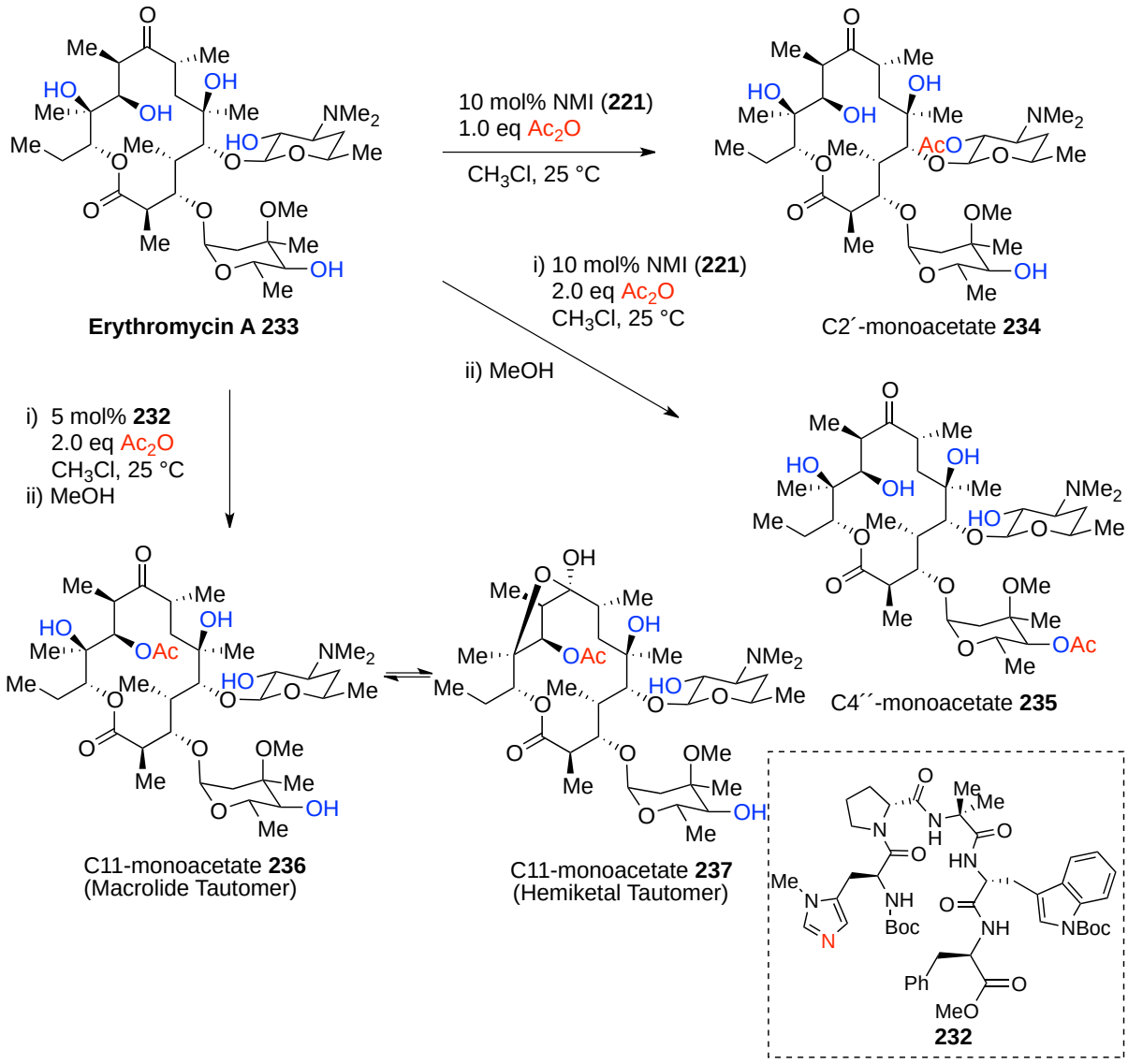
Glucoside **227** was then chosen as a more challenging substrate containing four unprotected OH-groups. NMI **221** as catalyst achieved poor selectivities (three of the four possible products formed) and low conversion (14%). Peptide **226** (a modification of **220**) showed higher activity and provided mono acetate **229** in 58% yield; however, the chemoselectivity was moderate.[79,89]



(15)

Miller and co-workers achieved the selective acylation of a less reactive OH-group in the presence of more reactive OH-groups in erythromycin A (**233**) utilizing pentapeptide **232**.[79,90] The most reactive hydroxyl-group (C2') can be selectively acylated by simply using NMI (**221**) as catalyst and 1 eq of anhydride (product **234**). The next reactive position in the molecule is the C4'' hydroxyl-group. In the presence of 2 eq of anhydride the C2' and C4'' positions were acylated and addition of MeOH selectively cleaved the acetate in the C2' position. Under these conditions **235** is the major product. A triacetate (C2', C4'' and C11 acylated) forms after prolonged reaction time and even after 3 days less than 30% of **233** is converted to **235** and **237** (ratio = 4:1). Tertiary hydroxyl groups do not react under these conditions.

In contrast, peptide **232** is more reactive and a reversal of the inherent selectivity was observed; a ratio of 1:5 of **235** and **237** was estimated by NMR integration. These three examples illustrate on the one hand the potential of small peptides as highly efficient and readily modified catalyst for site-selective natural product synthesis, but on the other hand the complexity and catalyst structure sensitivity for selectively transferring a moiety onto a certain functional group. In order to identify a suitable peptide for the chemoselective transformation (see Equation 14), a peptide library containing 150 peptides was tested, and for transformation shown in Equation 15, a library including 36 peptides was tested.

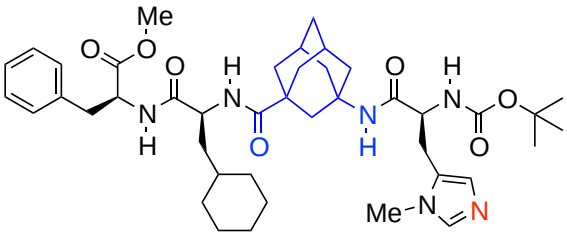


Scheme 13

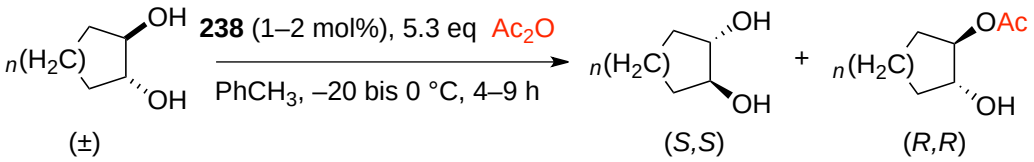
Schreiner and co-workers introduced another approach for the design of peptide catalysts in 2008.[28,35] They did not try to form a stable *β*-hairpin structure by using L-proline/D-proline to generate secondary structure. This approach introduced a rigid and lipophilic non-natural γ-adamantane amino acid as the structure forming building block in peptide catalyst **238**. The KRs of various *trans*-cycloalkane-1,2-diols were realized with *S*-values >50 (Table 28). In this rare case, the efficiency of a small organic catalyst is superior to enzymatic approaches. Various *Pseudomonas* lipases were tested and displayed low activities and poor selectivities in the KR of *trans*-cyclohexan-1,2-diol (**121**).[91] Enantioselective monobenzoylation of the same substrate was accomplished by Cu(II)-bisoxazoline-complexes,[92-94] the obtained selectivities ranged from 14 to 22. Computations by Sunoj and co-workers[95] confirmed the hypothesis of Schreiner et al. that it is not a secondary structure formed by the peptide, but hydrogen bond between a carboxyl group of

the peptide backbone and one hydrogen atom of the diol that is responsible for the observed selectivity. Subsequently, catalyst **238** was utilized in the first enantioselective Steglich esterification protocol.[68] Here, Schreiner and co-workers used carboxylic acids as electrophiles, which react *in situ* with a substituted carbodiimide to form the corresponding anhydride. This method is superior when the chosen anhydride is not stable or not commercially available; the enantioselectivities were high.

Table 28. KR of *trans*-1,2-cycloalkanediols with peptide catalyst **238**.



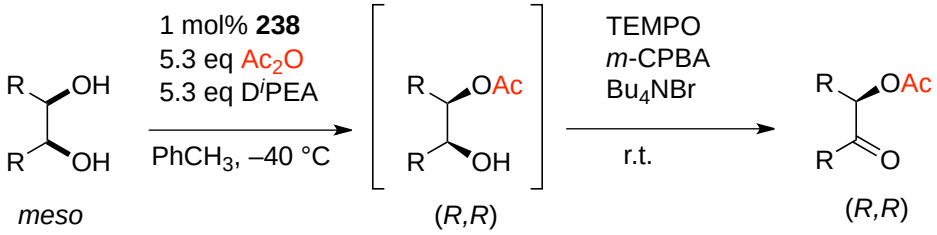
Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (**238**)

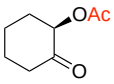
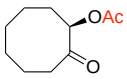


Entry	n		*ee* (%) alcohol	*ee* (%) ester	Yield (%) alcohol	*S*-value
1	1	**122**	>85	49	37	>8
2	2	**121**	>99	78	37	>50
3	3	**239**	>99	79	41	>50
4	4	**240**	>99	85	44	>50

The desymmetrization of *cis*-cycloalkane-1,2-diols (*meso*-diols) was also successfully accomplished by peptide **238** (Table 29).[96] A general drawback of this reaction is the configurationally lability of the monoacylated products via 1,2-acyl migration. Racemization occurs during the work up and lowers the enantiomeric excesses of the isolated products. For this reasons Schreiner et al. devised a protocol for the in situ organocatalytic oxidation of the unacetylated hydroxy function to produce the corresponding α-acetoxy ketones as valuable chiral building blocks.

Table 29. Desymmetrization and direct oxidation of *meso* diols **241–244** under optimized conditions.

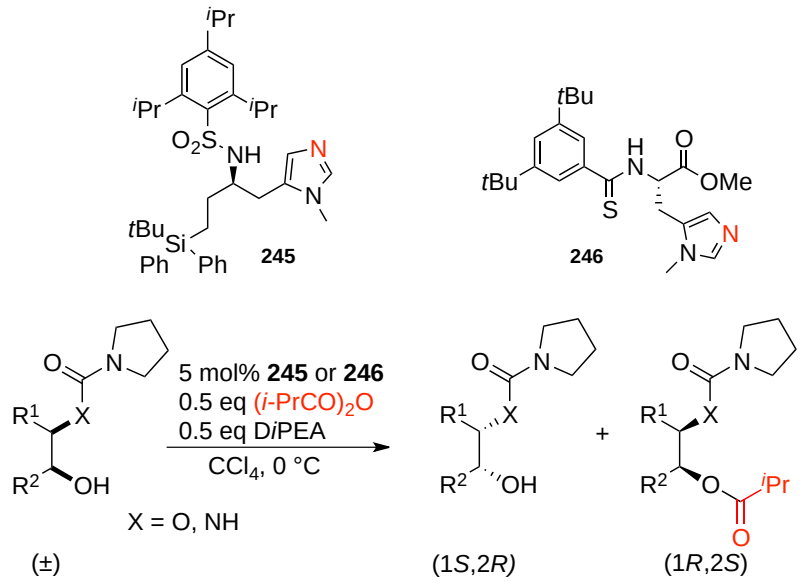


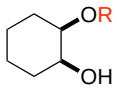
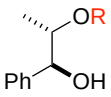
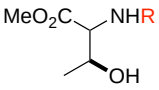
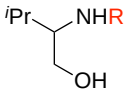
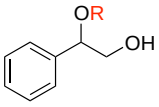
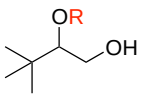
Entry	Product		Yield α-acetoxy ketones (%)	*ee* α-acetoxy alcohol (%)	*ee* α-acetoxy ketones (%)
1		**241**	69	80	64
2		**242**	70	88	88
3		**243**	97	84	94
4		**244**	42	84	81

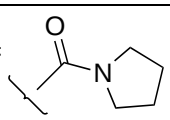
Some enzymatic approaches for the desymmetrization of *meso* cyclohexane-1,2-diol (**72**) are known from the literature. *Pseudomonas* lipase catalyzed this reaction with isopropenyl acetate as the electrophile. An *ee* of 81% was observed and 81% of the product could be isolated.[91] Porcine pancreas lipase catalyzed the desymmetrization of **72** with methyl acetate with an *ee* of 84%.[97] In both cases catalyst **238** can compete with the enzymatic approaches. Organocatalytic methods using chiral 4-pyrrolidinopyridine (PPY) analogues (65% *ee*, 61% conv., isobutyric anhydride), *N,N*-dimethylaminopyridine (DMAP)-based atropisomeric biaryl derivatives (77% *ee* , 20% yield, isobutyric anhydride) or chiral phosphine (67% *ee* , 66% conv., acetic anhydride) led to lower enantioselectivities.

Ishihara at al. (2004)[98,99] as well as Qu and co-workers (2008)[100] followed a non-peptidic biomimetic acylation approach by introducing catalysts **245** and **246**. Both catalysts proved to be highly efficient in the KR of racemic monofunctionalized 1,2-diol and amino alcohols. The only drawback of these reactions is that best selectivities were obtained in CCl_4, which is highly toxic. A variety of substrates is presented in Table 30.[35]

Table 30. Comparison of catalyst **245** with **246** in the KR of various racemic secondary alcohols.



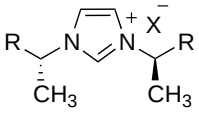
Entry	Substrate		Cat.	Conv. (%)	*ee* (%) alcohol	*ee* (%) ester	*S*-value
1		**247**	**245**	52	97	90	87
			246	52	97	90	80
2		**248**	**245**	47	82	93	68
			246	44	68	86	28
3		**249**	**245**	49	80	82	25
4		**250**	**245**	39	51	80	15
5		**251**	**245**	50	88	86	39
6		**252**	**246**	53	88	76	23
7		**253**	**246**	52	98	88	91

R = 

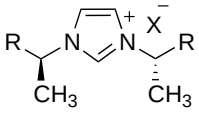
One advantage of peptides or small molecules as catalysts is the possibility to modify them easily, especially because peptides can be readily synthesized via automated SPPS. In all cases the catalysts are highly chemoselective and may therefore serve as catalysts for selective acylation of polyols. Unfortunately, rational catalyst design of oligopeptides, which are capable of specific functionalizations, is difficult as the structures are far too complex to predict their selective recognition abilities of substrates. Peptide libraries and fluorescence-based assays can help identify active peptides for the acylation of substrates, but the preparation and testing of such libraries is time-consuming and a better conceptual understanding of these oligopeptides is highly desirable.

2.1.1.2.5 *N*-Heterocyclic Carbenes as Catalysts for Enantioselective Acyl Transfer

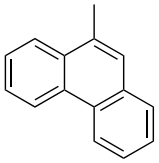
Wanzlick isolated the first NHC-dimer in 1960[101,102] and eight years later the first metal-carbene-complex was synthesized by Öfele.[103] In 1988 G. Bertrand reported the first stable phosphinocarbene.[104] Three years later Arduengo introduced crystalline 1,3-diadamantyl substituted imidazole-2-ylidene.[105] The discovery of this first stable NHC (*N*-heterocyclic carbene) caused a lot of excitement, because carbenes were no longer considered to be short-lived but could be employed as structural motifs with unique properties. Now NHCs are widely used as ligands in organometallic complexes[106] or as organocatalysts.[107] In addition to the utility as catalysts for Umpolung reactions,[108] NHC's are also capable of transferring acyl groups. Bakhtiar and Smith reported the first achiral acyl transfer reactions in 1994 (see Chapter 1.1.1.1 *N*-Heterocyclic Carbenes as Catalysts for Acyl Transfer onto Alcohols).[109] Ten years later, Suzuki and co-workers published the first enantioselective KR mediated by NHCs.[110] Carbenes **254–263** achieved only moderate selectivities ($S \leq 5$) in the KR of *sec.* alcohols.[111] Suzuki et al. proposed the following mechanism.



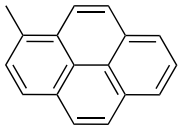
(R,R)-**254**; X = Cl, R = 1-naphthyl
(R,R)-**255**; X = Cl, R = cyclohexyl
(R,R)-**256**; X = Cl, R = phenyl
(R,R)-**257**; X = BF_4, R = 1-naphthyl
(R,R)-**258**; X = BF_4, R = 2-naphthyl
(R,R)-**259**; X = BF_4, R = 9-anthryl
(R,R)-**260**; X = BF_4, R = 1-anthryl
(R,R)-**261**; X = BF_4, R = 1-(2-methoxynaphthyl)
(R,R)-**262**; X = BF_4, R = 1-pyrenyl



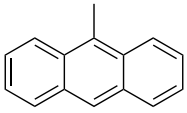
(S,S)-**263**; X = BF_4, R = 9-phenanthryl



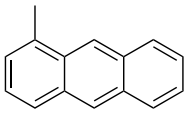
9-phenanthryl



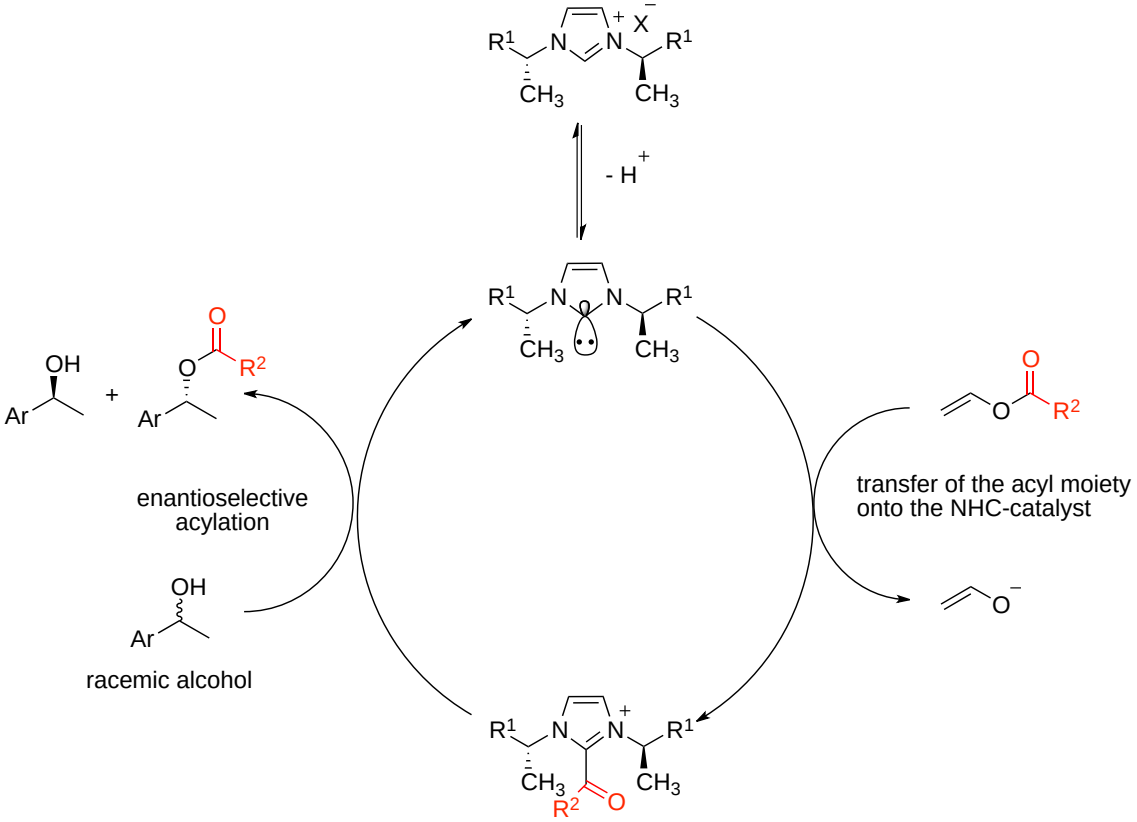
1-pyrenyl



9-anthryl



1-anthryl

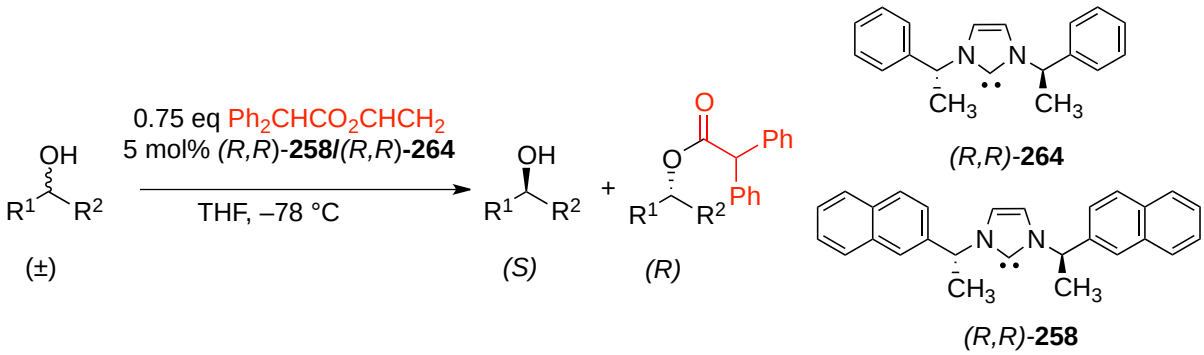


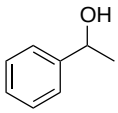
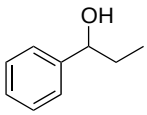
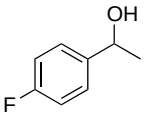
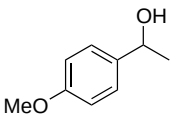
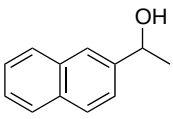
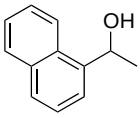
Scheme 14

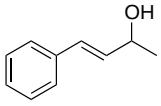
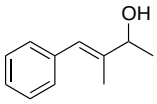
Selective acyl transfer mediated by NHCs seems to proceed via the same nucleophilic catalysis mechanism proposed for DMAP, DMAP-derivatives, *N*-alkyl imidazole-derivatives, amidines, amines, phosphines, and phosphinites (*vide supra*). Instead of a nucleophilic nitrogen or phosphorus atom, the *in situ* generated highly nucleophilic carbene

carbon atom attacks the acyl donor and transfers the acyl moiety onto the alcohol. In addition to the properties of the nucleophile, the selectivity can also be affected by the chemical properties of the acyl source. In 2005 Maruoka et al. increased the enantioselectivity of the acylation process by using vinyl diphenyl acetate as acylating agent.[112] Under optimized conditions a variety of secondary alcohols were acylated (Table 31).

Table 31: Performance of **258** and **264** in the KR of *sec.* alcohols.

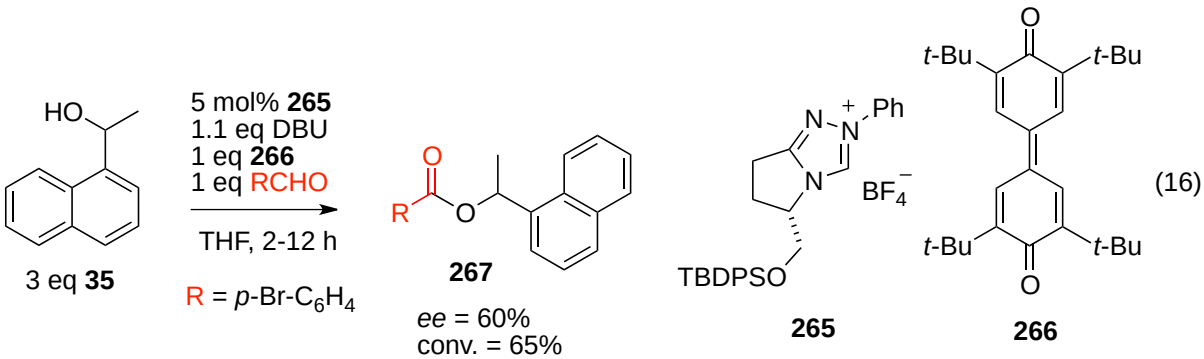


Entry	Substrate		Catalyst	*ee* (%) ester	Yield (%) ester	*S*-value
1		**30**	*(R,R)*-**258**	96	32	80
			(R,R)-**264**	93	33	46
2		**146**	*(R,R)*-**258**	92	33	38
3		**32**	*(R,R)*-**258**	91	39	42
			(R,R)-**264**	90	35	33
4		**205**	*(R,R)*-**258**	94	30	48
5		**98**	*(R,R)*-**258**	95	27	56
			(R,R)-**264**	93	35	46
6		**35**	*(R,R)*-**258**	94	29	47

Entry	Substrate		Catalyst	*ee* (%) ester	Yield (%) ester	*S*-value
7		**85**	*(R,R)*-**264**	84	27	16
8		**102**	*(R,R)*-**264**	87	33	22

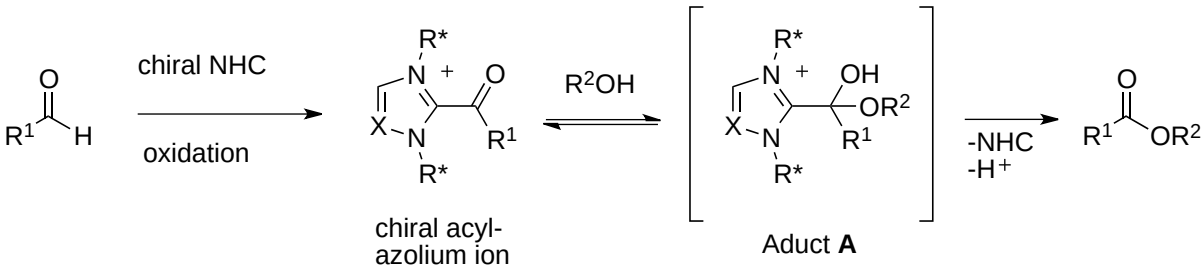
Allylic alcohols as well as aryl alkyl carbinols can be selectively acylated by catalysts **258** and **264**. The selectivity is not affected by electron donating or electron-withdrawing groups on the aromatic ring. In contrast to the KR of allylic *sec.* alcohols catalyzed by DMAP or *N*-alkylimidazole derivatives, no base is needed because vinyl acetates were used as acyl source instead of anhydrides or acyl chlorides. The *S*-values were comparable to the *S*-values achieved by Fu's catalyst **28** (see Chapter 1.1.1.1.1) but the conversions 20% higher on average.

In 2011 Studer and his group published the first KR of *sec.* alcohols by NHC-catalyzed oxidative esterification using aldehydes as the acyl source.[113] They applied an external organic oxidant for their resolution process. Catalyst **265** achieved moderate selectivities in the KR of *sec.* allylic alcohols. Various aromatic *para*-substituted electron-poor aldehydes were tested. Selectivities up to 60 for *para*-bromobenzaldehyde at 65% conversion were obtained. The carbene was generated *in situ* from **265** using DBU as base.



(16)

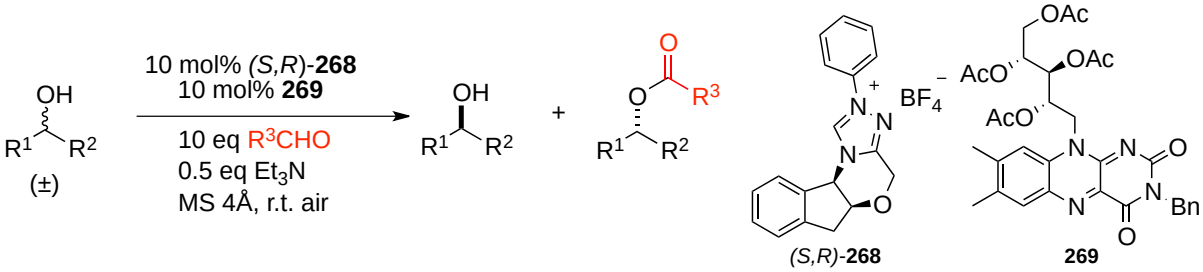
Studer and co-workers proposed following mechanism: In the first step the aldehyde reacts with the NHC and is oxidized by an external oxidation agent (**266**) to form a chiral acyl azolium ion. The alcohol then attacks the acylazolium ion to form adduct **A**. At the end of the process adduct **A** fragments into NHC and the product ester.



Scheme 15

An advantage compared to other KRs is the possibility to use simple aldehydes as acyl source instead of anhydrides, acid chlorides or vinyl acetates. Drawbacks of this approach at present are the low *ee*'s and the necessity of having to use 1 eq of an external oxidizing agent. Yashima and co-workers solved these problems by applying an NHC/flavin system (Table 32).[114] The enantiomeric excesses were still moderate, but only 10 mol% of the oxidant is needed, because it can be regenerated by areobic oxidation.

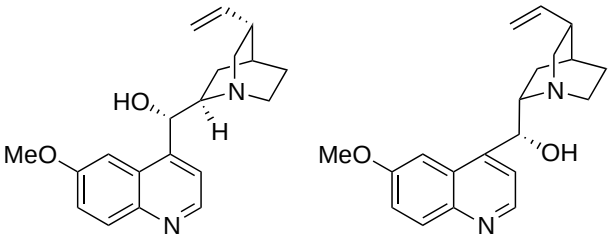
Table 32. Efficiency of a NHC/flavin system in the KR of *sec.* aryl alcohols.



Entry	Alcohol		R^1	R^3	Conv (%)	*ee* (%) alcohol	*S*-value
1		**30**	Ph	Ph	65	43	2.3
2		**35**	1-naphthyl	Ph	55	44	3.2
3		**98**	2-naphthyl	Ph	72	66	3.1
4		**30**	Ph	1-naphthyl	50	32	2.6
5		**30**	Ph	2-naphthyl	47	39	3.7
6		**121**		Ph	62	75	5.6

2.1.1.2.6 Enantioselective Ring Opening of *Meso*-Anhydrides Utilizing Cinchona Alkaloid-Derivatives

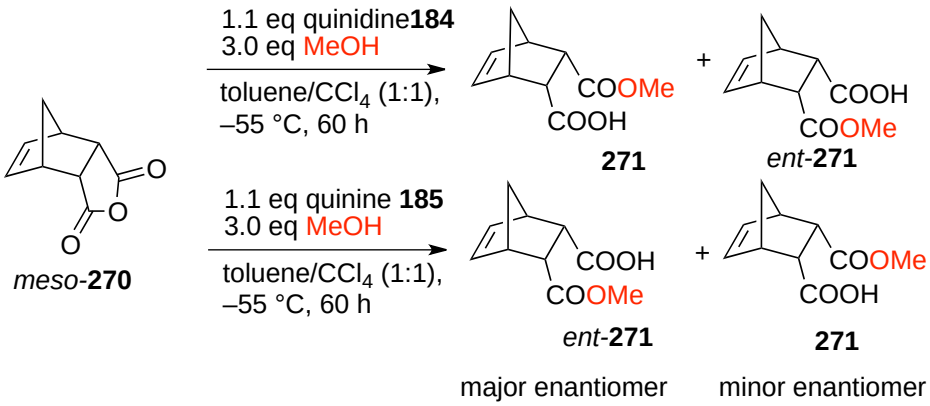
The selective ring opening of *meso* anhydrides[115] mediated by cinchona alkaloids was first reported by Oda in the 1980's.[116] Shortly thereafter, Aitken et al. reported the conversion of a *meso*-anhydride into a lactone mediated by quinine (57%, 76% *ee*).[117,118] In 1999 Bolm and co-workers presented a method for the enantioselective ring opening of bi- and tricyclic *meso* anhydrides by commercially available quinidine (**184**) and quinine (**185**) (Scheme 16).[34,115,119] The desymmetrizations of various cyclic anhydrides utilizing catalysts **184** and **185** proceeded with excellent enantiomeric excesses and high yields (Table 33).

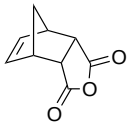


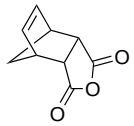
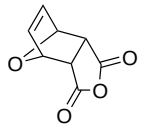
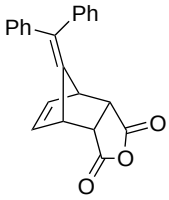
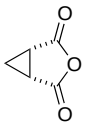
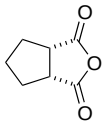
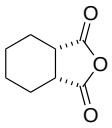
184 (quinidine) **185** (quinine)

Scheme 16

Table 33. Desymmetrization of *meso* anhydrides utilizing commercially available cinchona alkaloid **184** and **185**.



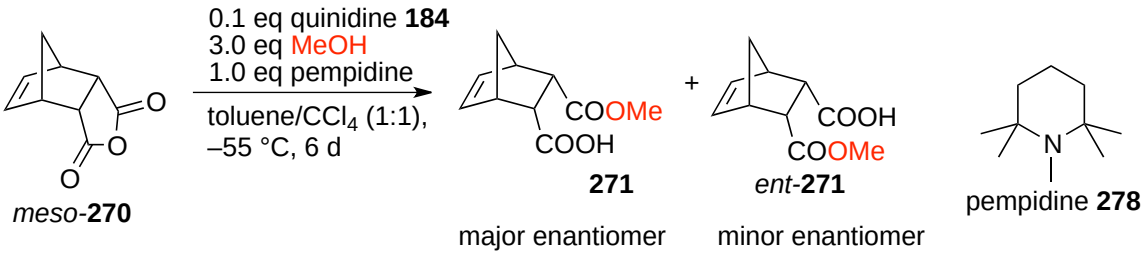
Enty	Substrate		Catalyst	Yield (%) of major enantiomer	*ee* (%) of hemi ester (major enantiomer)
1		**270**	**185**	92	99
2			**184**	98	99

Enty	Substrate		Catalyst	Yield (%) of major enantiomer	*ee* (%) of hemi ester (major enantiomer)
3		**272**	**185**	94	93
4			**184**	96	96
5		**273**	**185**	71	75
6			**184**	61	93
7		**274**	**185**	96	92
8			**184**	95	95
9		**275**	**185**	95	85
10			**184**	96	85
11		**276**	**185**	99	93
12			**184**	97	95
13		**277**	**185**	91	87
14			**184**	98	93

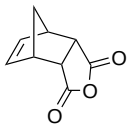
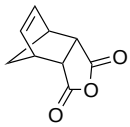
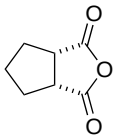
A drawback of this approach is the high “catalyst” loading of 110 mol%, and Bolm et al. investigated the ring opening by catalytic amounts of **184** and **185**.[34,120] They first tested the reaction under optimized conditions with just 10 mol% of quinidine (**184**) without additional base and the reaction stopped at 50% conversion (35% *ee*). Bolm and co-workers proposed following scenario: After the opening of the anhydride by **184** the resulting acid transfers its proton onto the alkaloid, afterwards the protonated alkaloid and the carboxylate of the hemi-ester form an acid-base complex.[121] In addition, the protonated catalyst **184** adopts the open(3)-conformation, which is catalytically active, but less selective.[117,118,122] They tested various auxiliary bases in order to avoid the protonation of **184** and identified pempidine (**278**, Table **34**) as the base, which in combination with **184** showed the highest *ee*. The selectivities and yields were still high (Table 34). A drawback of the method utilizing 10 mol% of **184** is the long reaction time (6 d compared to 60 h) and that pempidine is more

expensive than **184.** Though **184** and pempidine can be recovered, the latter method is not practical.

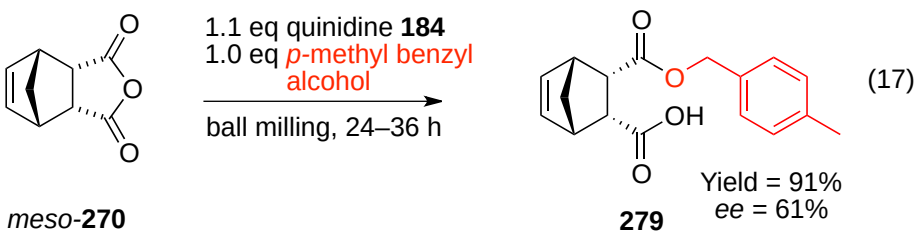
Table 34. Efficiency of catalytic amounts of quinidine in the desymmetrization of *meso* anhydrides.



meso-**270** — **271** major enantiomer — *ent*-**271** minor enantiomer — pempidine **278**

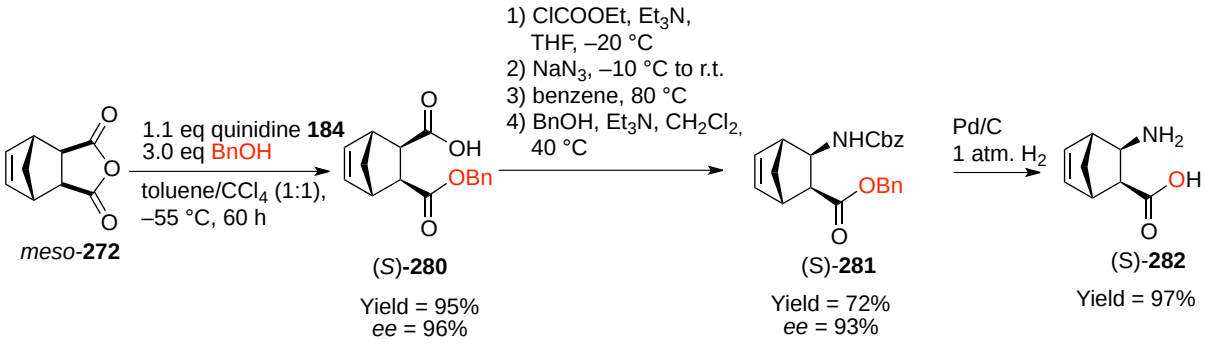
Entry	Substrate		Yield (%) of hemi ester	*ee* (%) of hemi ester
1		**270**	98	90
2		**272**	94	91
3		**276**	96	89

Bolm's group also reported a solvent-free approach under ball milling conditions.[123] Structure **184** (1.1 eq), the solid *meso*-anhydride (1.0 eq), and *p*-methyl benzyl alcohol (1.0 eq) were added to a micro mill and were milled for 24 to 36 h (Equation 17). The achieved selectivities were comparable to the selectivities observed in solution under otherwise similar conditions.



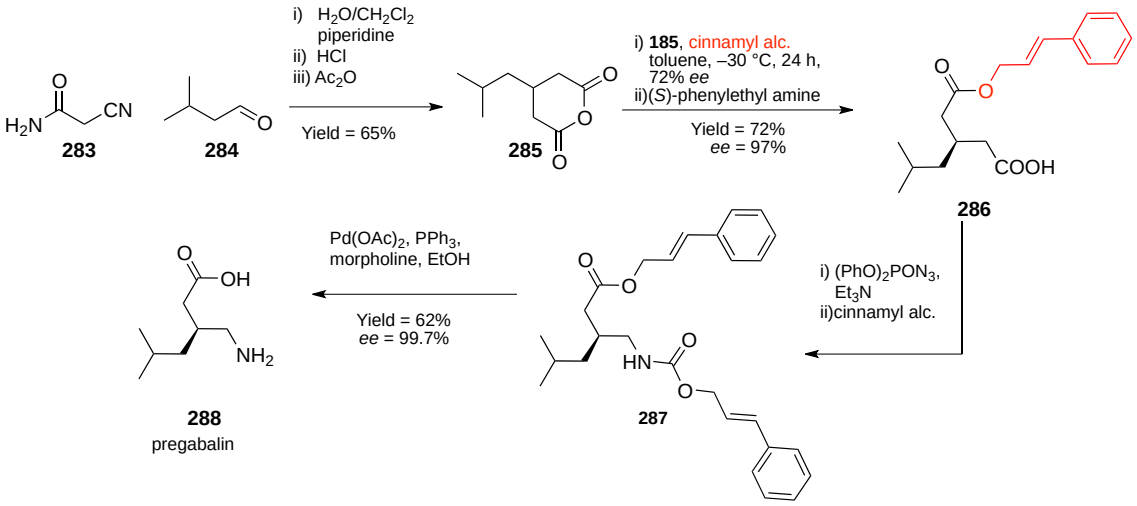
meso-**270** — **279** (17)

The enantiopure hemiesters, generated using **184** or **185**, can be converted to enantiomerically enriched β-amino acids by Curtius degradation followed by hydrogenation (Scheme 17).[34,124]



Scheme 17

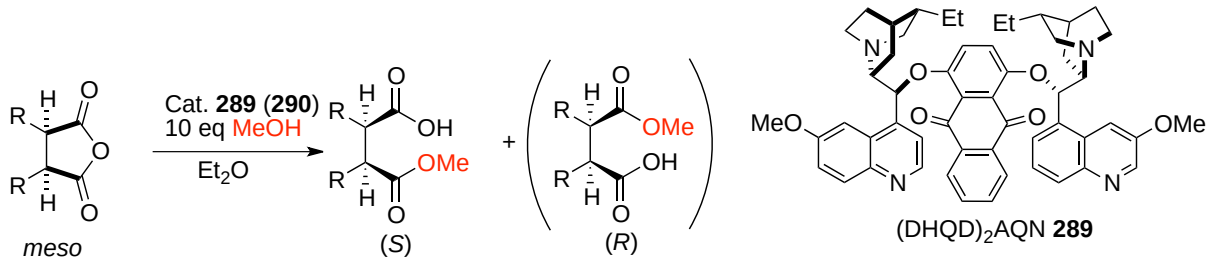
The enantioselective ring opening of *meso* anhydrides introduced by Bolm and his group enabled an improved synthesis of both enantiomers of *trans*-cyclohex-4-ene-1,2-dicarboxylic acid accomplished by Bernardi and co-workers,[125] and the synthesis of enantiopure alicyclic β-amino acids reported by Hamersăk.[126] Furthermore, the enantioselective ring opening of cyclic *meso* anhydrides displays the key step in the enantioselective synthesis of the cyclopentyl core of axinellamines reported by Carreira et al..[127] Hamersăk and his group applied the desymmetrization of *meso* anhydrides mediated by quinine in the synthesis of pregabalin.[128] (*S*)-3-Aminomethyl-5-methylhexanoic acid (pregabalin) was designed as a potential drug for the treatment of epilepsy and neuropatic pain.[129] Bolm's method provided 72% *ee* with cinnamyl alcohol as nucleophile. Further enantiomeric enrichment was achieved by classic salt formation with chiral amines.[128] With the (*S*)-phenylethyl amine salt an *ee* of 97% was achieved.[128] Enantioselective ring opening of *meso* anhydrides presents a powerful tool for the synthesis of enantiopure hemiesters and has been presented as a practical method in *Organic Synthesis*.[130,34]

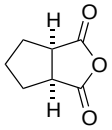


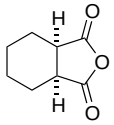
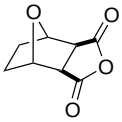
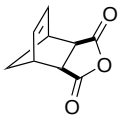
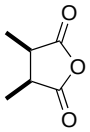
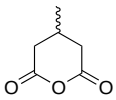
Scheme 18

In 2000 Deng and co-workers applied the commercially available "Sharpless-ligands" $(DHQD)_2AQN$ (**289**) and $(DHQ)_2AQN$ (**290**) in the desymmetrization of cyclic *meso* anhydrides.[131] The selectivities obtained with **289** and **290** were excellent.[34,131,132] The substrate scope ranges from monocyclic to tricyclic *meso* anhydrides. A big advantage of cinchona alkaloid catalysts is the possibility to generate both enantiomers in good yields by choosing the quinidine or quinine-derived catalyst. The catalysts can be quantitatively recovered, which makes this approach synthetically useful (Table 35). Catalyst **290** is not shown but the selectivities are as good as those obtained with **289** (the product (*R*)-hemi ester is the major enantiomer).

Table 35. Efficiency of catalyst **289** and **290** in the desymmetrization of cyclic *meso*-anhydrides.



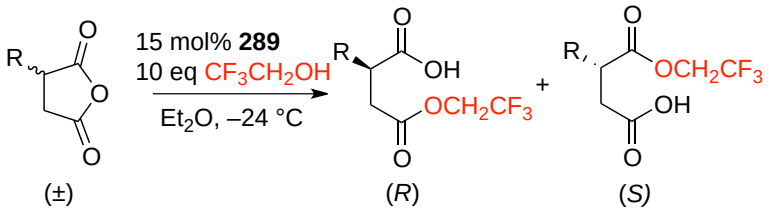
Entry	Substrate		Cat. (mol%)	*T* (°C)	Yield (%)	*ee* (%)
1		**291**	8 (8)	–30	99 (90)	95 (93)

Entry	Substrate		Cat. (mol%)	*T* (°C)	Yield (%)	*ee* (%)
2		**292**	5 (5)	–20	97 (95)	97 (93)
3		**293**	15 (15)	–20	88 (85)	96 (94)
4		**270**	10 (20)	– 30 (–20)	82 (82)	95 (90)
5		**294**	5 (5)	–20	93 (88)	98 (98)
6		**295**	30 (30)	–40 (–35)	70 (56)	91 (82)

The results in parenthesis are obtained with $(DHQ)_2AQN$ as catalyst. The hemiesters were synthesized with the opposite absolute configuration.

Deng performed the parallel KR of racemic 2-aryl and 2-alkyl succinic anhydrides utilizing catalyst **289** (Table 36).[132,133] The best results were obtained with trifluoroethanol as the nucleophile. The yields and selectivities obtained by catalyst **289** were excellent. Parallel KRs of 2-aryl-, as well as 2-alkyl-succinic anhydrides proceeded under mild conditions and the catalyst could be quantitatively recovered.

Table 36. Parallel KR of 2-aryl- and 2-alkyl-succinic anhydrides mediated by catalyst **289**.



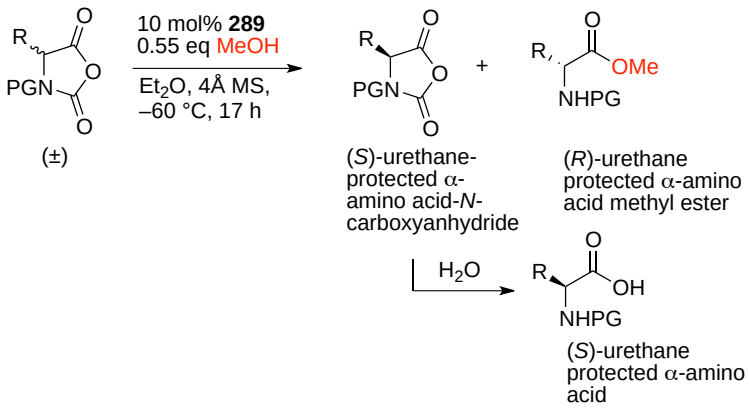
Entry	R		Yield of (*R*)-hemiester (%)	Yield of (*S*)-hemiester (%)	*ee* of (*R*)-hemiester (%)	*ee* of (*S*)-hemiester (%)
1	Me	**296**	41	36	80	93

Entry	R		Yield of (*R*)-hemiester (%)	Yield of (*S*)-hemiester (%)	*ee* of (*R*)-hemiester (%)	*ee* of (*S*)-hemiester (%)
2	Et	**297**	50	38	70	91
3	*n*-Octyl	**298**	41	38	66	98
4	Allyl	**299**	49	40	82	96
5[a]	Ph	**300**	32	44	87	95
6[a]	*m*-MeO-C_6H_4	**301**	30	45	83	96
7[a]	*p*-Cl-C_6H_4	**302**	29	44	76	96

[a] Yields obtained after the conversion of (*R*)-hemiester and (*S*)-hemiester into the β-aryl-γ-lactones.

After Deng and co-workers successfully applied modified cinchona alkaloids in the desymmetrization of cyclic *meso*-anhydrides, and the KR of 2-aryl- and 2-alkyl succinic anhydrides, they were interested in the KR of urethane-protected α-amino acid-*N*-carboxyanhydrides,[134] which can be easily synthesized from racemic amino acids. The reaction generates a carbamate-protected amino ester and the unreacted urethane-protected α-amino acid-*N*-carboxyanhydride enantiomer. The latter can be hydrolyzed to the enantiomerically enriched protected amino acid. The products and the catalyst can be separated through extraction. This approach allows the preparation of enantiomerically enriched protected α-amino acids and the protected α-amino acid esters in high yields and excellent selectivities (Table 37).[34,132,134]

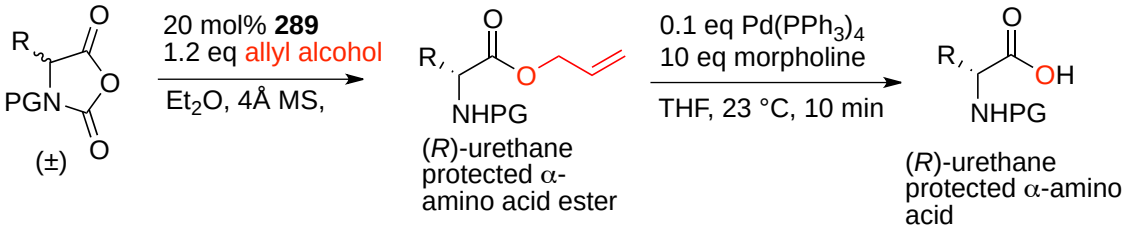
Table 37. KR of urethane-protected α-amino acids-*N*-carboxyanhydrides utilizing catalyst **289**.

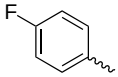
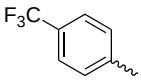
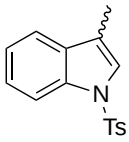


Entry	R	PG		*t* (h)	*T* (°C)	Conv. (%)	*ee* %/ (% Yield) of amino acid ester	*ee* %/ (% Yield) of amino acid	*S*-value
1	$PhCH_2$	Cbz	**303**	17	–60	51	93 (48)	98 (48)	114
2	4-F-$C_6H_4CH_2$	Cbz	**304**	31	–78	50	92 (48)	93 (42)	79
3	$BnOCH_2$	Cbz	**305**	72	–78	52	89 (49)	96 (44)	69
4	$(CH_3)_2CH$	Cbz	**306**	22	0	59	67 (58)	96 (40)	19
5	Ph	Cbz	**307**	16	–78	46	97 (45)	84 (46)	170
6	$PhCH_2$	Fmoc	**308**	46	–78	51	92 (50)	96 (47)	93
7	$PhCH_2$	Boc	**309**	15	–40	59	67 (56)	98 (41)	19
8	$PhCH_2$	Alloc	**310**	15	–60	50	91 (45)	91 (45)	67

As DKR can theoretically produce 100% of product, Deng and his group were interested in converting the KR of urethane protected α-amino acid-*N*-carboxyanhydrides into a dynamic KR (Table 38). The racemization process needs to be faster than the selective transformation of the starting material. Due to this requirement, Deng and co-workers increased the reaction temperature and utilized allyl alcohol in the alcoholysis. The achieved selectivities and yields were high (yield up to 95% and *S* up to 92).[34,132,135]

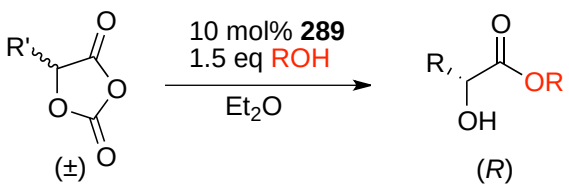
Table 38. Efficiency of **289** in a dynamic KR of urethane protected α-amino acids-*N*-carboxyanhydride using allyl alcohol as nucleophile.

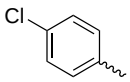
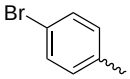
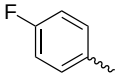
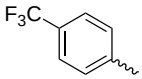
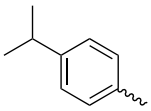
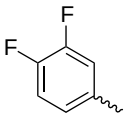
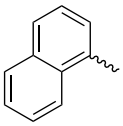
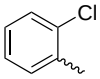
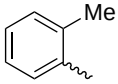


Entry	R	PG		*t* (h)	*T* (°C)	Yield (%) of ester	*ee* (%) of ester	Yield (%) of acid	*ee* (%) of acid
1		Cbz	**307**	1	23	97	91	91	90
2		Cbz	**311**	1	23	96	90	93	90
3		Cbz	**312**	1	23	95	90	88	90
4		Cbz	**313**	2	–30	93	92	93	92
5		Cbz	**314**	0.5	23	98	91	86	89
6		Cbz	**315**	1.5	0	95	90	95	89
7		Fmoc	**316**	1	23	98	90	92	90

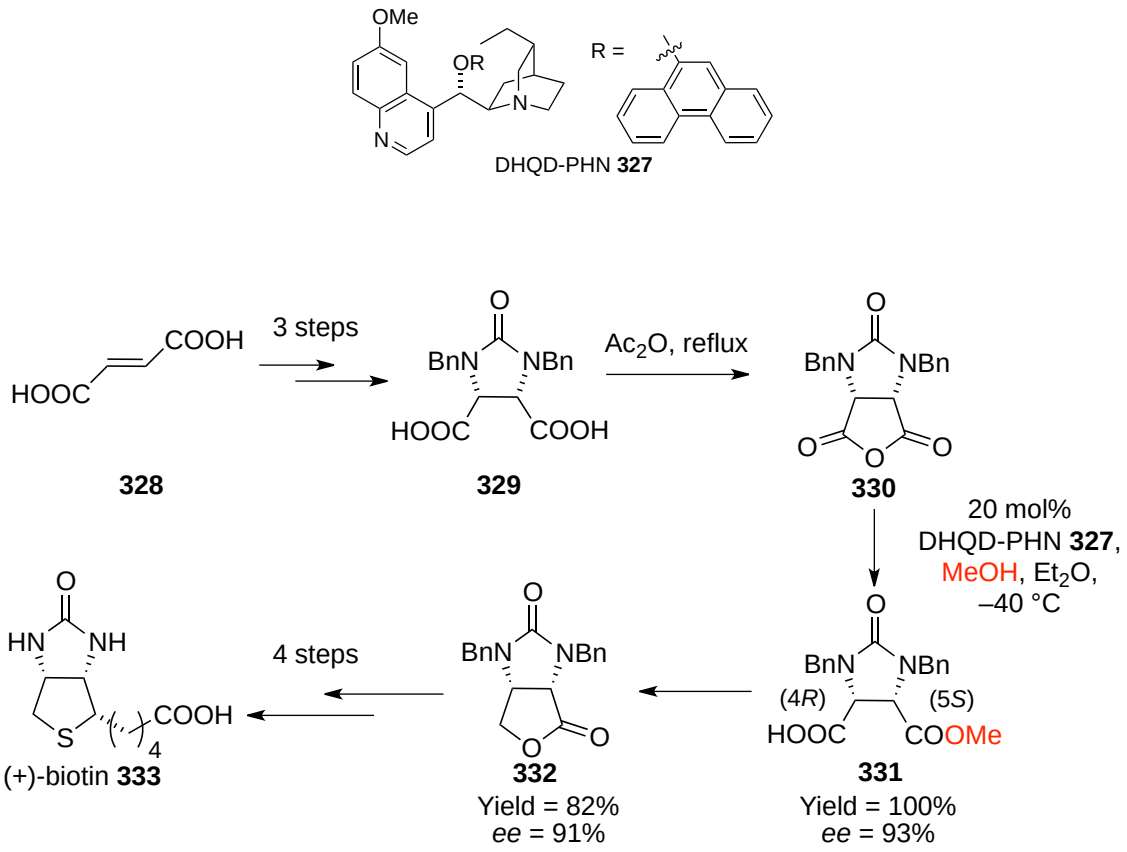
The same strategy afforded the DKR of 5-aryl-1,3-dioxolane-2,4-diones to prepare optically pure α-hydroxy carboxylic acid derivatives in the range of 61–85% yield (Table 39).[136] The enantioselectivities obtained with catalyst **289** were good to excellent for substrates containing aromatic moieties substituted in *para*- or *para* and *meta*-position. In contrast, enantioselectivities decreased for substrates bearing an *ortho*-substituted phenyl group.

Table 39. Dynamic KR of 5-aryl-1,3-dioxolane-2,4-diones mediated by catalyst **289**.



Entry	R'		R-OH	*t* (h)	*T* (°C)	Yield (%) of ester	*ee* (%) of ester
1		**317**	EtOH	24	–78	71	95
2		**318**	EtOH	24	–78	70	96
3		**319**	EtOH	24	–78	80	96
4		**320**	EtOH	24	–78	65	95
5		**321**	EtOH	24	–78	85	93
6		**322**	EtOH	8	–20	68	91
7		**323**	EtOH	24	–78	65	94
8		**324**	^{n}PrOH	14	–40	74	91
9		**325**	EtOH	10	–60	66	62
10		**326**	EtOH	4	–20	61	60

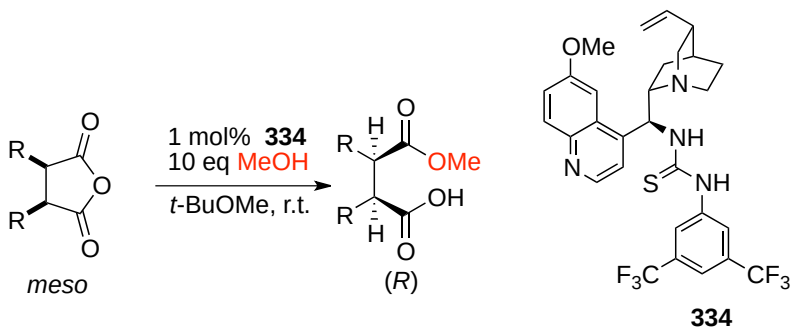
In order to demonstrate the practical utility of their approach, the synthesis of (+)-biotin (333) was chosen as a test sequence. Deng followed the approach of Sternbach and Goldberg and increased the selectivity by utilizing catalyst **327** for the enantioselective ring opening of **330**. High *ee*'s and excellent yields were obtained.[137]

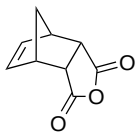
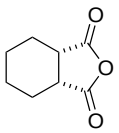
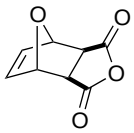
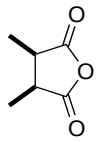
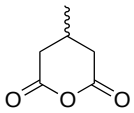


Scheme 19.

In 2008 Connon and co-workers introduced bifunctional cinchona alkaloid/thiourea-derived catalyst **334**[138] and utilized it in the desymmetrization of *meso* or prochiral mono, bi and tricyclic anhydrides at room temperature at low catalyst loadings (1 mol%).[138] They proposed that the thiourea moiety activates the anhydride by hydrogen-bonding while the cinchona moiety promotes general base catalysis. The yields for various substrates range from 93% to 98% and the obtained selectivities were high (Table 40).

Table 40. Desymmetrization of cyclic *meso* anhydrides utilizing bifunctional catalyst **334**.



Entry	Substrate		*t* (h)	Yield (%) of hemi ester	*ee* (%) of hemi ester
1		**270**	100	93	96
2		**277**	30	98	93
3		**273**	130	90	85
4		**335**	14	98	92
5		**295**	18	98	83

The reaction mechanism of selective ring opening of cyclic anhydrides mediated by cinchona alkaloids was widely discussed in the literature.[139] Nucleophilic catalysis or general base catalysis are theoretically possible, but most of the evidence supports the latter mechanism.

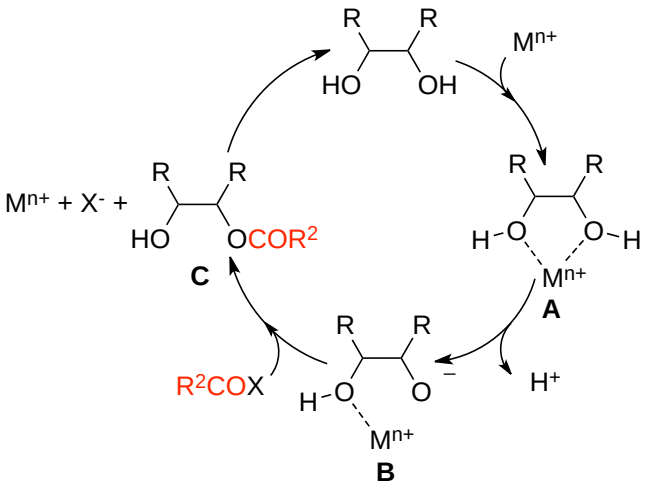
Cinchona alkaloid-derived catalysts are capable of enantioselective ring opening of various cyclic anhydrides, 5-aryl-1,3-dioxolane-2,4-diones,[136] urethane-protected α-amino acid-*N*-carboxyanhydrides,[134] 2-aryl- and 2-alkyl-succinic anhydrides.[133] The selectivities and yields were consistently good to excellent. Deng's DKR is a powerful tool to generate enantioselectively enriched protected α-amino acid esters and protected α-amino acids from racemic α-amino acids. An advantage of the methods introduced by Bolm, Deng, and Connon is the ability to recover the catalysts quantitatively. All catalysts are commercially available or can be easily prepared from available starting materials. In contrast to catalysts **184** and **289**, catalyst **334** gave excellent selectivities in the desymmetrization of cyclic *meso* anhydrides at room temperature and did not require cooling such as needed for **184** (–55 °C) and **289** (–40 °C to –20 °C).

2.1.2 Metal-Complex Mediated Enantioselective Synthesis of Esters

The second part of the article will introduce on the one hand metal complexes, which are capable acyl transfer catalysts and on the other hand complexes that serve as racemization catalysts in order to accomplish DKRs.

2.1.2.1 Cu(II)-Complex Mediated Acylation Reactions

RajanBabu *et al.* introduced an yttrium-salen complex as a catalyst capable of selective acyl transfer onto secondary alcohols.[140] The obtained *S*-values were poor and ranged from 1.5 to 4.8. In 2003 Matsumura and co-workers reported the first synthetically useful KR of vicinal diols mediated by a Cu(II)-ion associated with a chiral (*R,R*)-Ph-box ligand **336**.[94] They proposed a coordination of the 1,2-diol with a metal-ion (M^{n+}) to form a reactive intermediate **A**. In the next step **A** is transformed to a metal alkoxide **B** by a weak base and reacts with an acyl halide to form product **C** (Scheme 20). In contrast to Fu's planar chiral DMAP-ferrocene derived catalyst **28**, in which the iron ion only acts as a structure-forming element, the copper ion of Matsumura's catalyst is involved in the acyl transfer.

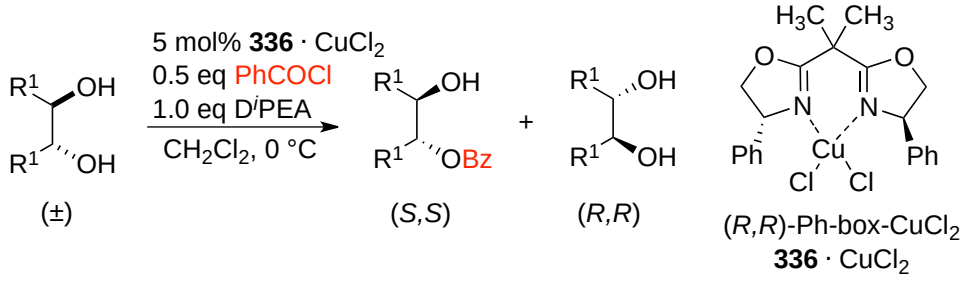


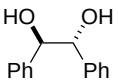
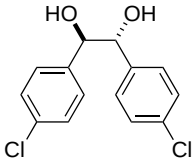
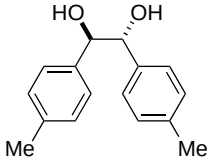
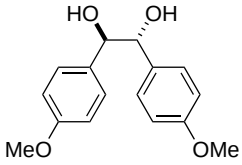
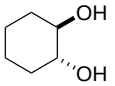
Scheme 20

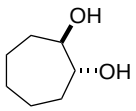
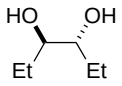
2.1.2.1.1 Kinetic Resolution Utilizing Cu-Complexes

The first applications of catalyst **336**·$CuCl_2$ were in the KR of hydrobenzoin derivatives and racemic cyclic 1,2-diols (Table 41).[94] The Cu-complex gave extraordinary high enantioselectivities for the hydrobenzoins (*S*-value > 645). The selectivities for the cycloalkane 1,2-diols are good, but much lower compared to organocatalytic approaches (e.g., Schreiner's catalyst **238** with *S* >50 for the enantioselective acylation).

Table 41. KR of hydrobenzoins and cyclic 1,2-diols mediated by catalyst **336**·$CuCl_2$.

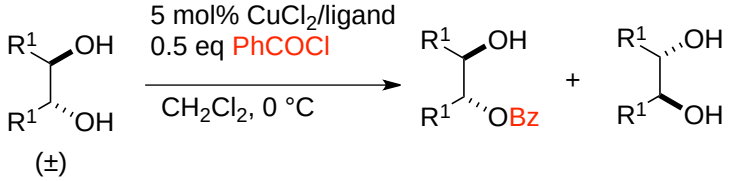


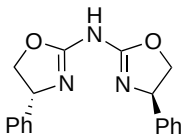
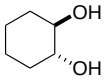
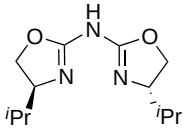
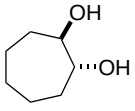
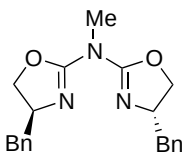
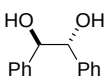
Entry	Substrate		Yield (%) of ester	*ee* (%) of ester	*S*-value
1		**119**	48	>99	>645
2		**120**	48	>99	>645
3		**337**	47	97	183
4		**338**	49	98	356
5		**121**	37	80	14

Entry	Substrate		Yield (%) of ester	*ee* (%) of ester	*S*-value
6		**239**	49	84	28
7		**339**	44	77	14

In 2005 Reiser et al. reported the KRs of racemic 1,2-diols, hydrobenzoin, and α-hydroxycarbonyl compounds mediated by Cu(II)-aza-(bisoxazolines)-complexes (Table 42).[93] The yields and selectivities obtained for the substrates strongly depended on the type of ligand used in the reaction. The yields and selectivities achieved by Reiser's approach for hydrobenzoins and *trans*-cycloheptane-1,2-diol are comparable to those obtained by Matsumura.[93] In contrast, the selectivities for the benzoylation of *trans*-cyclohexane-1,2-diol are higher.

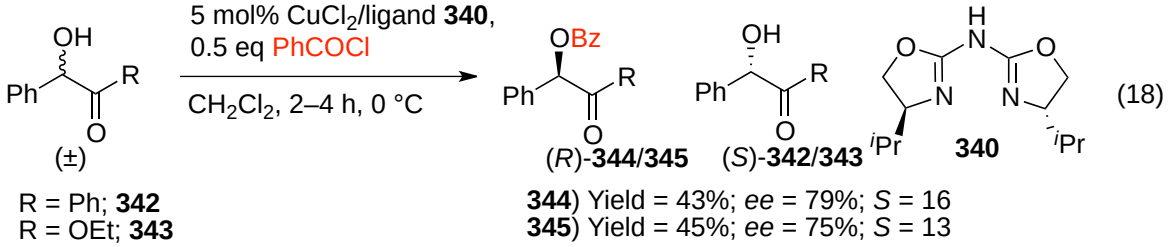
Table 42. Efficiency of Cu(II)-aza-(bisoxazoline)-complexes in the KR of racemic cyclic 1,2-diols and hydrobenzoin.



Entry	Ligand		Substrate		Yield (%) of ester	*ee* (%) of ester	Config.	*S*-value
1[a]		**339**		**121**	46	83	*S,S*	22
2[b]		**340**		**239**	46	82	*R,R*	21
3[a, c]		**341**		**119**	49	99	*R,R*	751

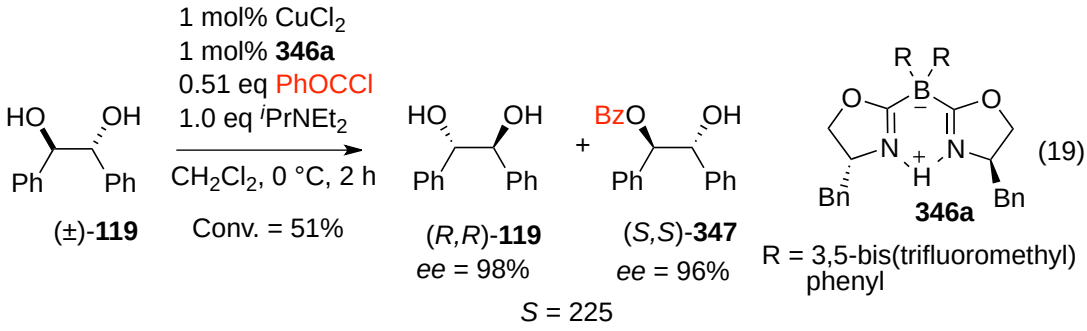
[a] Reaction time = 2 h; [b] reaction time = 3 h; [c] Catalyst loading: 0.5 mol% $CuCl_2$/ligand

Whereas the selectivities for substrates bearing two vicinal hydroxy groups obtained by Cu(II)-complexes (ligands: **339**, **340**, and **341**) were good to excellent, for α-hydroxycarbonyl compounds the achieved selectivities were only moderate (Equation 18).

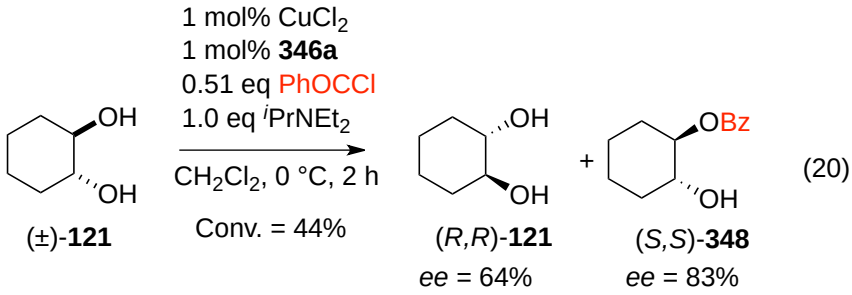


(18)

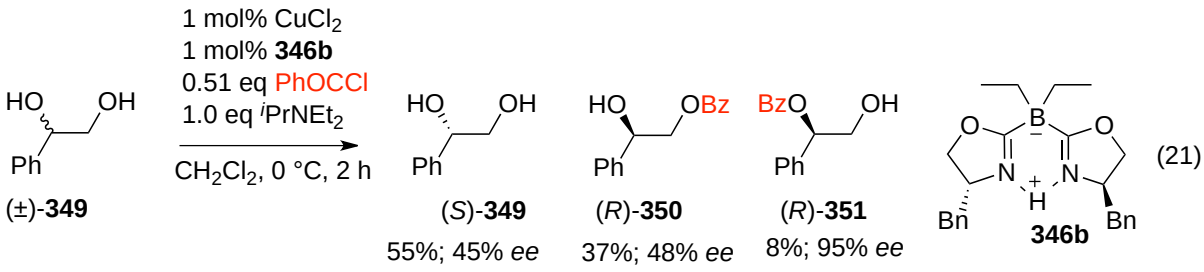
In 2006 Pfaltz and co-workers applied a Cu(II)-ion coordinated to a boron-bridged bisoxazoline (borabox) ligand as catalyst in the KR of racemic hydrobenzoin (Equation 19), cyclohexane-1,2-diol (Equation 20), 1,2-phenylethanediol (Equation 21), and pyridyl alcohols (Table 43).[92]



(19)



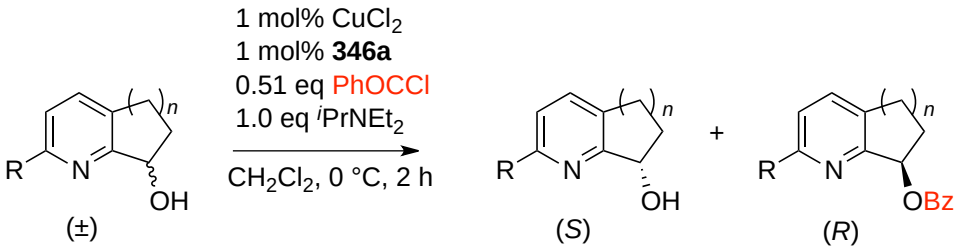
(20)



(21)

The selectivities for hydrobenzoin were excellent even at low catalyst loadings (1 mol%). The results for the borabox ligand **346a** and **346b** are comparable to those obtained with box-ligands (**336**, **339**, **340**, and **341**). Pyridyl alcohols containing a phenyl moiety at the pyridine ring can be resolved with high selectivities by catalyst **346a**.

Table 43. Efficiency of catalyst **346a** in the KR of pyridyl alcohols.

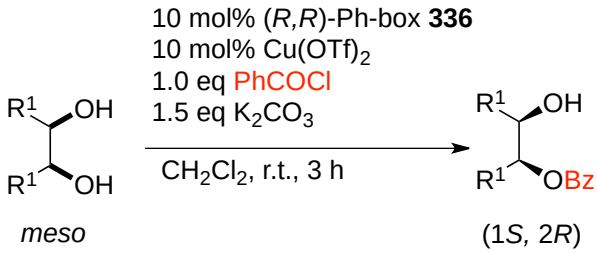


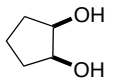
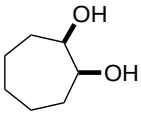
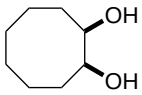
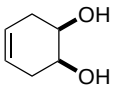
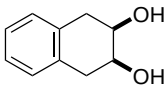
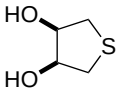
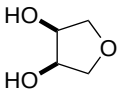
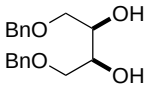
Entry	R	n		Conv. (%)	*ee* (%) of alcohol	*ee* (%) of ester	*S*-value
1	H	1	**352**	46	5	5	1
2	Ph	1	**353**	45	76	91	51
3	H	2	**354**	52	83	76	19
4	Ph	2	**355**	42	70	97	125
5	Cl	2	**356**	47	58	65	8

2.1.2.1.2 Desymmetrization of *Meso*-1,2-diols Mediated by a Cu(II)-complex

Desymmetrization of *meso*-1,2-diols utilizing a copper(II)-ion coordinated by (*R,R*)-Ph-box ligand **336**·$Cu(OTf)_2$ was achieved with moderate to good selectivities (Table 44).[141] A drawback of this method is the high catalyst loading of 10 mol%. Organocatalytic approaches (e.g., Kündig's diamine based catalyst **191**[76] or Oriyama's catalyst **168**[72] mediated the desymmetrization of similar substrates with higher *ee*'s (e.g., substrate **110**; Yield = 87%, *ee* = 78% with cat. **191**).

Table 44. Desymmetrization of *meso*-1,2-diols utilizing catalyst **336**·$Cu(OTf)_2$.

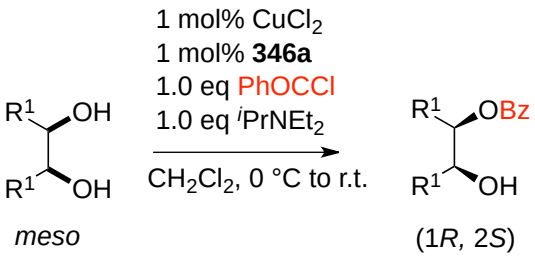


Entry	Substrate		Yield (%)	*ee* (%)
1		**110**	47	3
2		**357**	88	58
3		**194**	85	65
4		**169**	68	93
5		**170**	92	80
6		**358**	63	8
7		**111**	81	racemic
8		**109**	78	97
9		**195**	36	96

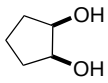
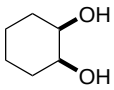
Pfaltz applied the Cu(II)-borabox-derived catalyst **346a** to the desymmetrization of *meso*-1,2-diols and obtained increased selectivities compared to the Cu(II)-(*R*,*R*)-Ph-box catalyst **336**·$Cu(OTf)_2$ (Table 45).[142] The reaction proceeds at low catalyst loadings of 1 mol% and with enantioselectivities up to 94%. The ligands can be synthesized from readily

accessible oxazolines. The borabox ligand structure can be assembled and varied by the reaction of metalated oxazoline with a diaryl or dialkylhaloborane.

Table 45. Efficiency of catalyst **346a** in the desymmetrization of cyclic *meso* diols.

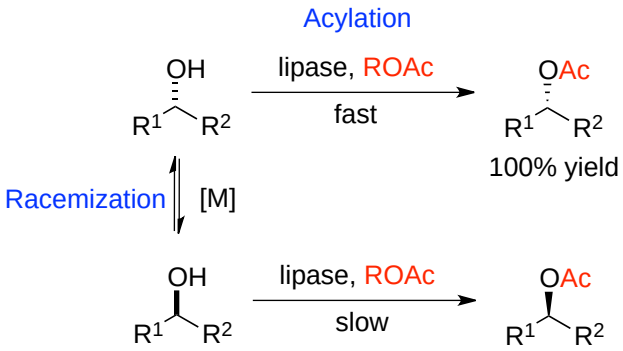


meso (1*R*, 2*S*)

Entry	Substrate		Yield (%)	*ee* (%)
1		**110**	73	76
2		**72**	83	90
3		**109**	65	94

2.1.2.2. Combination of Metal-Complexes and Enzymes in the Dynamic Kinetic Resolutions of Racemic Alcohols

As mentioned in the Introduction the disadvantage of a KR is the limitation to 50% yield for the acylated substrate. Desymmetrizations can produce a theoretical yield of 100%, but they require *meso* or prochiral compounds as starting materials. To overcome the drawback of KR, fast racemization of one of the enantiomeric substrates is needed. In DKR the starting material racemizes, while one enantiomer gets selectively acylated. In a dynamic KR 100% theoretical yield is feasible (Scheme 21).

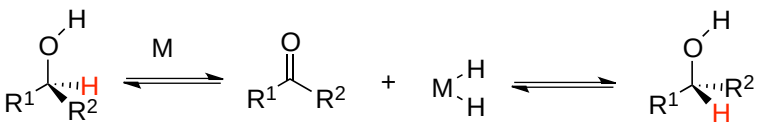


Scheme 21

Examples for DKR utilizing just one catalyst (e.g., a chiral organic molecule, enzymes or metal complexes) are rare. More common is a combination of two catalysts.[15] Possible racemization techniques were categorized by Zwanenburg et al.:[143] base-catalyzed racemization, Schiff base-mediated racemization, acid-catalyzed racemization, enzyme-mediated racemization as well as redox and radical induced racemization processes. Additionally, transition metals are also capable catalysts for the racemization of alcohols. In combination with enzymes usually metal complexes or base are applied to the racemization of the substrate and enzymes provide the enantioselective transfer of the acyl moiety. In the case of the base-catalyzed racemization the substrate scope is mainly limited to molecules bearing an acidic proton at the stereogenic center.[15]

2.1.2.2.1 Dynamic Kinetic Resolution of Alcohols Utilizing Ruthenium-Complexes for Racemization and Enzymes for Selective Acyl Transfer

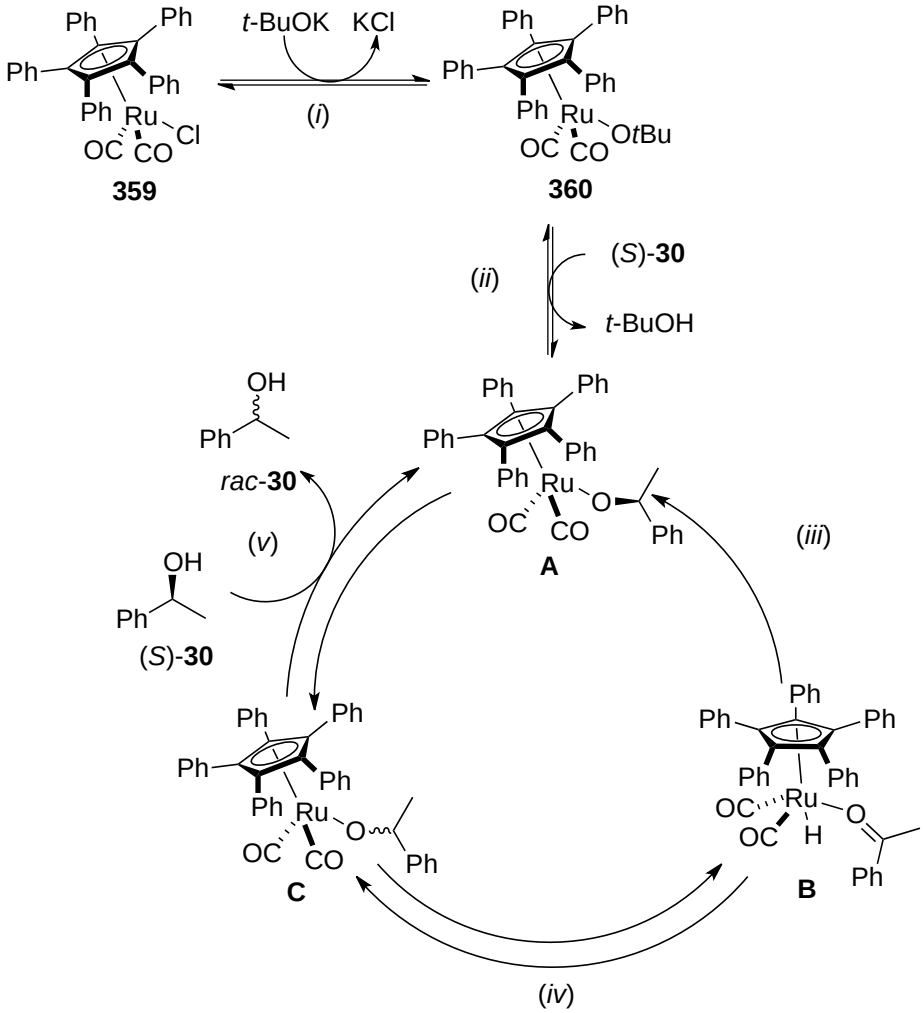
Iridium, rhodium, and ruthenium complexes are known to provide rapid racemization of secondary alcohols via hydrogen transfer, but just a few complexes are compatible with an enzymatic reaction.[15,144,145] It has been proposed that metal hydrides are the reactive intermediates in the hydrogen transfer reaction between metal catalyst and alcohol (Scheme 22).



Scheme 22

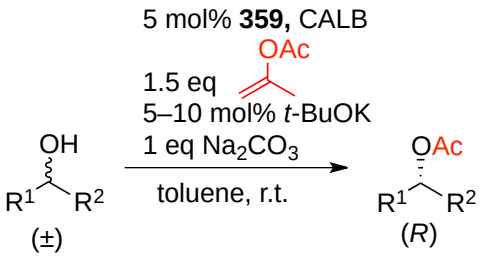
In 1996 Williams and co-workers were the first to use a combination of a rhodium-catalyst and a lipase for the DKR of secondary alcohols.[146] The obtained selectivities were,

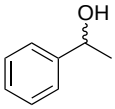
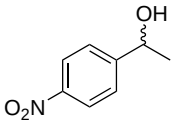
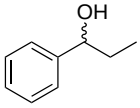
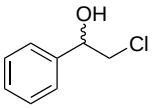
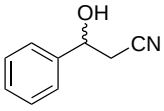
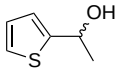
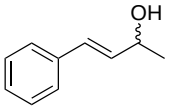
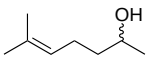
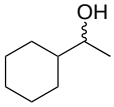
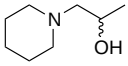
however, moderate. In 1997 Bäckvall et al. reported a DKR of secondary alcohols mediated by a ruthenium catalyst and an immobilized lipase at 70 °C;[11] in 2005 an improved method for the dynamic KR of *sec.* alcohols at room temperature and at short reaction times was published.[147] The observed selectivities and yields were excellent and a wide range of secondary alcohols can be deracemized using this approach (Table 46). They proposed the following ruthenium complex **359** catalyzed racemization mechanism (Scheme 23).

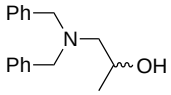


Scheme 23

Table 46. Efficiency of catalyst **359** and CALB (*Candida Antarctica* lipase B) in the DKR of various secondary alcohols.



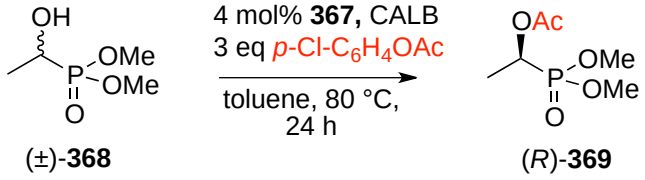
Entry	Substrate		*t* (h)	Yield (%)	*ee* (%)
1		**30**	3	95	>99
2		**361**	20	99	>99
3		**146**	17	92	>99
4		**34**	13	83	>99
5		**362**	6	85	97
6		**363**	6	98	>99
7		**85**	18	89	>99
8		**364**	72	92	98
9		**86**	17	98	>99
10		**365**	5	>99	99

Entry	Substrate		*t* (h)	Yield (%)	*ee* (%)
11		**366**	5	97	97

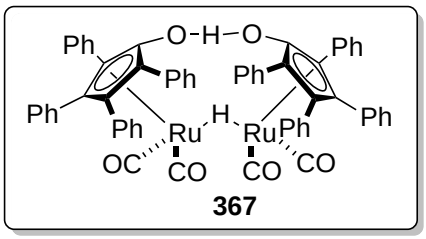
Upscaling issues were addressed for the DKR of racemic 1-phenylethanol **30**.[148] At 1 mol scale, applying 0.05 mol% of ruthenium catalyst **359** and small amounts of enzyme after 20 h at 40 °C, 159 g (97% yield) of (*R*)-1-phenylethanol acetate (99% *ee*) were isolated.[148] The high efficiency was proved by carrying the reaction out at a 10 mol scale. The catalysts loadings of the ruthenium-complex **359** (0.01 mol%) and the biocatalyst were lowered and the reaction was performed in a more highly concentrated reaction mixture. After 21 days 1.43 kg (87% yield) of the product were isolated in excellent enantiomeric purity (97% *ee*).

Bäckvall et al. applied his approach to the DKR of various substrates like α- and β-hydroxyphosphonates (Equations 22, 23)[149] as well as β-azido alcohols (Equation 24).[15,144] The yields and selectivities for the α-hydroxyphosphonate and β-azido alcohol were high and the reactions were carried out under mild reaction conditions. β-Azido alcohols can serve as precursors for the synthesis of enantiopure β-amino alcohols. In the case of β-hydroxyphosphonates keto-byproduct **372** formed. Addition of 2,4-dimethyl-3-pentanol decreased the amount of **372**, but did not increase the amount of product.

Dynamic kinetic resolution of racemic α-hydroxyphosphonates

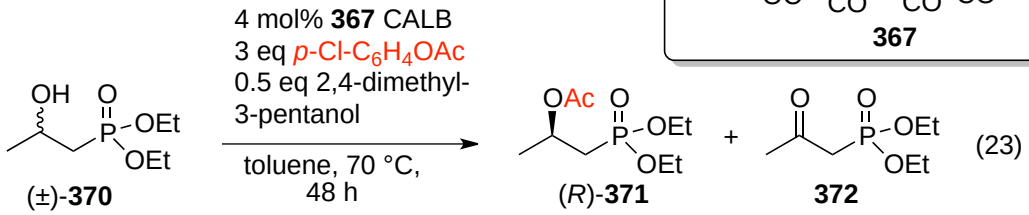


(±)-**368** (*R*)-**369** Yield = 83% *ee* > 99% (22)



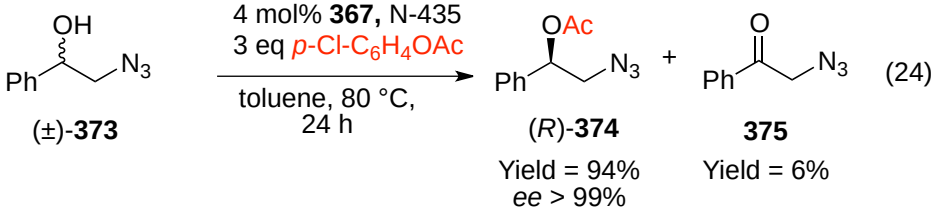
367

Dynamic kinetic resolution of β-hydroxyphosphonates



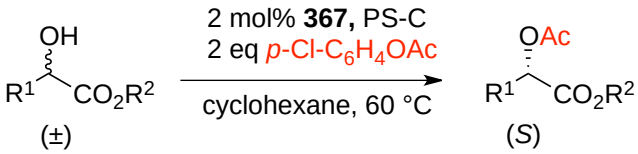
(±)-**370** (*R*)-**371** Yield = 69% *ee* > 99% **372** Yield = 1% (23)

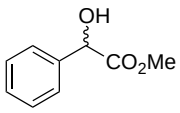
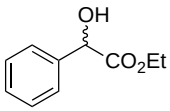
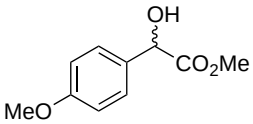
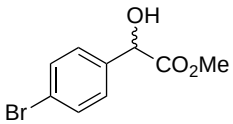
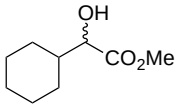
Dynamic kinetic resolution of β-azido alcohols

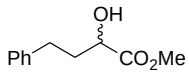
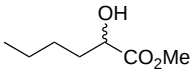


In order to broaden the substrate scope, Bäckvall and co-workers optimized the conditions to afford an efficient DKR of α-hydroxy acid esters.[15,150] The best results were obtained utilizing catalyst **367** and *Pseudomonas cepacia* lipase applying 4-chlorophenyl acetate as acyl donor and cyclohexane as solvent.[150] The selectivities were good and the yields were high for substrates bearing an aryl moiety or a secondary carbon atom in β-position (Table 47). In contrast, the selectivities for substrates with a primary carbon atom in β-position and without aromatic substituent were poor (*ee* = 30; entry 6).

Table 47. Dynamic KR of α-hydroxy acid esters mediated by catalyst **367**and PS-C.

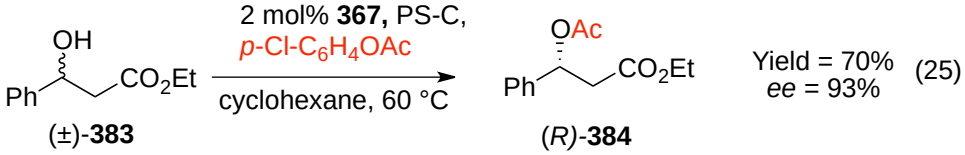


Entry	Substrate		*t* (h)	Yield (%)	*ee* (%)
1		**376**	48	80	94
2		**377**	72	74	96
3		**378**	48	76	94
4		**379**	72	69	98
5		**380**	48	80	98

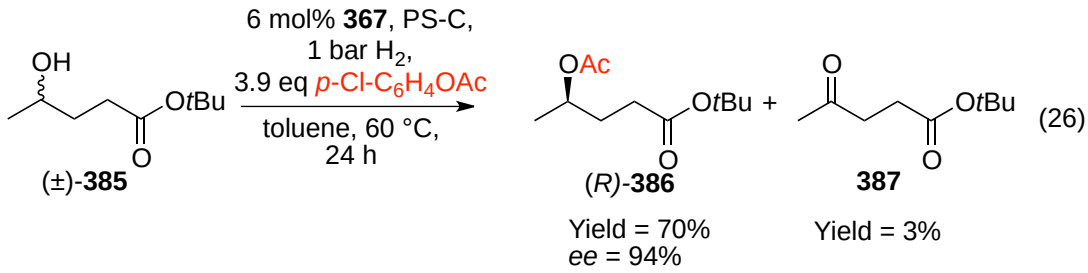
Entry	Substrate		*t* (h)	Yield (%)	*ee* (%)
6		**381**	48	62	30
7		**382**	24	60	80

Subsequently, β-,[151] γ-,[152] and δ-hydroxy acid esters[153] were deracemized. The obtained selectivities were very good and the yields high. For γ- and δ-hydroxy acid esters H_2 as additional hydrogen source improved the yield (Equations 25, 26, and 27).[15]

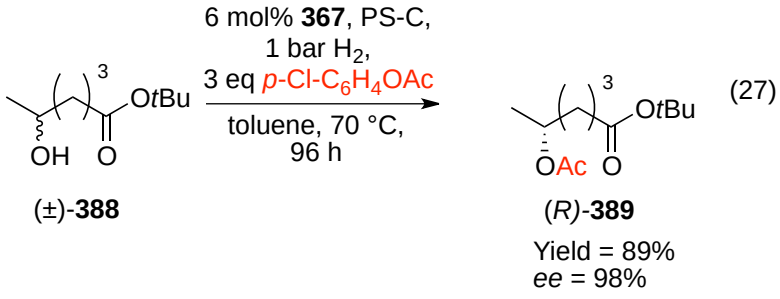
Dynamic kinetic resolution of β-hydroxy acid esters



Dynamic kinetic resolution of γ–hydroxy acid esters

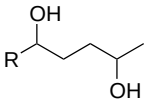
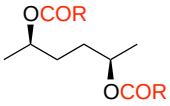
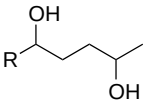
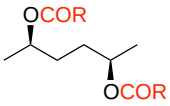
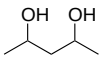
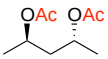
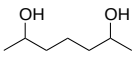
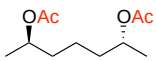
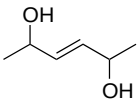
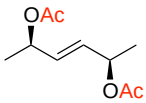
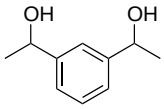
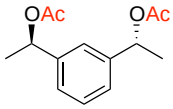
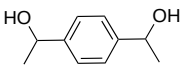
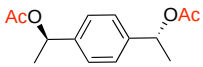
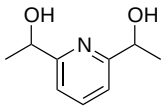
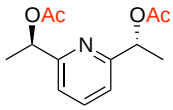


Dynamic kinetic resolution of δ-hydroxy acid esters



Bäckvall and co-workers used their approach for dynamic KRs of 1,3-, 1,4- and 1,5-diols.[15,154] In the case of 1,3-diols an intramolecular acyl transfer produced the undesired *meso* diacetate in 62% yield (Table 48; entry 3); 1,4- and especially 1,5-diols were obtained in good yields and high selectivities. This approach offers advantages compared to KR, because the resolved diols are usually available as a mixture of the racemic and the *meso* forms of the substrates. Hence, the theoretical yield of a KR would be 25% even under optimized reaction conditions.

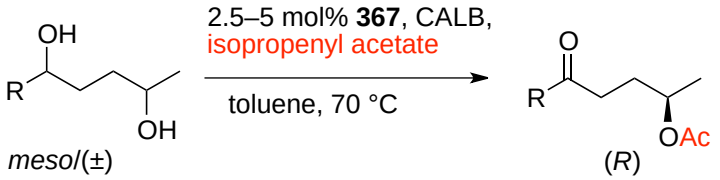
Table 48. Selective acylation of various diols coupled with a ruthenium-complex **367** introduced isomerization.

Entry	Substrate		Product		*t* (h)	Yield (%)	*ee* (%) (*R,R*/*meso*)
1		**390**		**397**	48	63	>99 (86/14)
2		**390**		**398**	1	47	>99 (96/4)
3		**391**		**399**	24	90	>99 (38/62)
4		**392**		**400**	24	63	97 (90/10)
5		**393**		**401**	24	43	>99 (74/26)
6		**394**		**402**	24	76	>99 (98/2)
7		**395**		**403**	24	77	>99 (98/2)
8		**396**		**404**	24	78	>99 (100/0)

Reaction conditions: 4 mol% **367**, 3 eq *p*-chlorophenyl acetate, CALB, toluene.

1,4-Diols can be converted into γ-hydroxy ketones with good selectivities and in high yields also utilizing catalyst **367** and CALB under modified reaction conditions (Table 49).[155] In contrast to the reaction conditions (acyl donor = *p*-chlorophenyl acetate) used to generate acylated 1,4-diols, Bäckvall and co-workers utilized isopropenyl acetate as acyl donor in order to obtain γ-hydroxy ketones as products. In the first step the enzyme acylates the less hindered alcohol function of the diol and acetone forms from isopropenol (keto-enol tautomerism), which is the leaving group of the acylation agent (isopropenyl acetate). Bäckvall proposed that the oxidation of the sterically more hindered OH group of the diol mainly occurs because acetone is reduced more rapidly by the ruthenium complex **367** than the hindered OH-function of the 1,4-diol and therefore the γ-hydroxy ketone accumulates in the system.

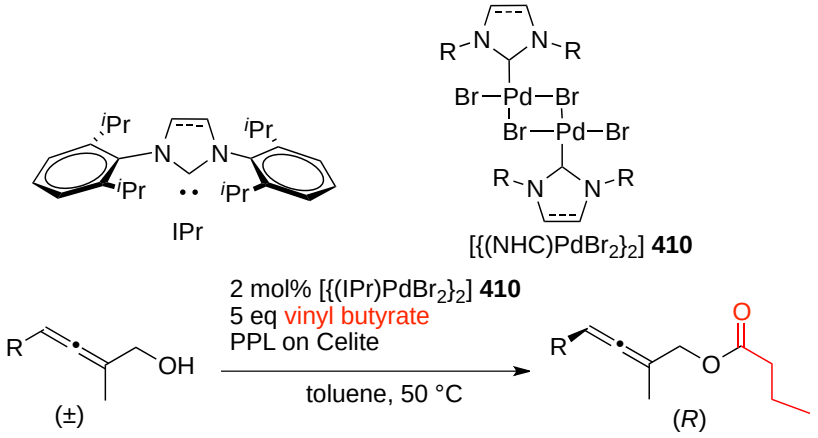
Table 49. Dynamic kinetic asymmetric transformation of 1,4-diols into γ-hydroxy ketones utilizing a ruthenium complex **367** and lipase.



Entry	R		Acyl donor (eq)	*t* (h)	Yield (%)	*ee* (%)
1	Ph	**405**	10	20	75	84
2	*i*-Pr	**406**	20	18	77	89
3	Cy	**407**	20	17	73	90
4	2-naphthyl	**408**	10	18	82	79
5	*p*-F-C_6H_4-	**409**	10	36	75	86

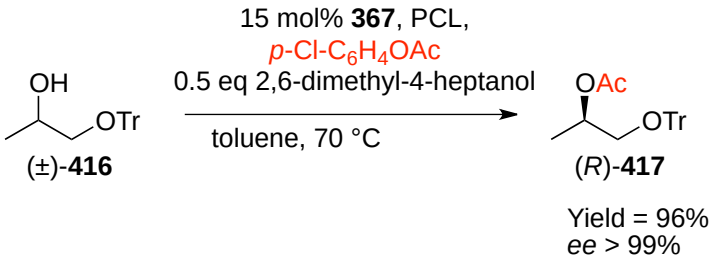
Allenes present a synthetically very useful class of axially chiral compounds.[156] Yet, short synthetic routes for the enantioselective synthesis of axial, helical, and planar chiral allenyl derivatives are rare. Deska and Bäckvall introduced the first DKR of allenols mediated by a palladium complex in combination with the enzyme PPL (porcine pancreatic lipase).[157] The yields are good and the obtained *ee*'s ranged from 66–89% (Table 50). Enantioenrichment of the allenols can be achieved by enzymatic hydrolysis (*ee* = 99%; Yield = 91% for **411**).

Table 50. Efficiency of catalyst **410** and lipase (PPL) in the DKR of allenols.



Entry	R		*t* (h)	Yield (%)	*ee* (%)
1	Ph	**411**	23	81	86
2	3-tolyl	**412**	27	70	89
3	4-chlorophenyl	**413**	24	83	89
4	2-naphthyl	**414**	21	80	87
5	*n*-pentyl	**415**	20	87	66

Park and co-workers used ruthenium catalyst **367** in combination with lipase to deracemize mono-protected 1,2-diols via DKR.[158] A trityl-protected diol acetate was obtained in excellent yield and *ee* = 99% (Equation 28).; 2,4-dimethyl-3-pentanol was added as to avoid the formation of the ketone byproduct.

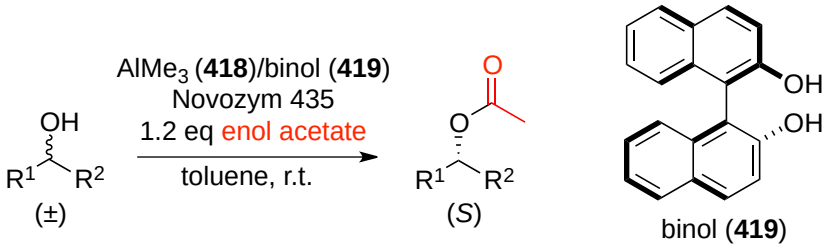


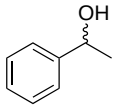
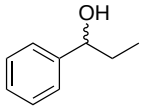
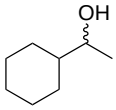
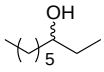
(28)

2.1.2.2.2 Dynamic Kinetic Resolution of Alcohols Utilizing an Aluminum-Complex for Racemization and Enzymes for Selective Acyl Transfer

In 2006 Berkessel and co-workers reported a new system for DKR of secondary alcohols.[159] Instead of an expensive ruthenium-complex for the racemization of the alcohol, Berkessel utilized an in situ generated aluminum complex. The enantioselective acylation of secondary alcohols was mediated by Novozym 435 and good to excellent *ee*'s were obtained (Table 51). The aluminum complex was generated in situ from readily available substrates [e.g., $AlMe_3$ (**418**), binol (**419**)]. The best yields and selectivities were obtained for $AlMe_3$ with binol as ligand. The reported substrate scope is limited to secondary aryl-alkyl and alkyl alcohols.

Table 51. Efficiency of an *in situ* generated $AlMe_3$/binol-complex in combination with Novozym 435 in the dynamic KR of secondary alcohols.



Entry	Substrate		$AlMe_3$ (eq)	*t* (h)	Yield (%)	*ee* (%)
1		**30**	0.1	3	96	96
2		**146**	0.1	18	99	98
3		**86**	0.2	19	97	99
4		**87**	0.2	18	93	80
5		**420**	0.2	18	95	95

DKRs utilizing a ruthenium-complex/aluminum-complex for the racemization of alcohols and a lipase for the selective acyl transfer offer the opportunity to generate enantiomerically enriched products in high yields (100% theoretically yield). A broad substrate scope can be deracemized by these approaches. Tolerating various functional groups (e.g., azides, halides, acid esters, and nitriles) DKR can serve as the key step for synthesizing complex enantiopure substrates (e.g., amino alcohols). The ruthenium complexes **359** and **367** as well as the lipases Novozym 435 and PS-D are commercially available. Catalysts **418**/**419** can be generated *in situ* by mixing commercially available reagents (binol and $AlMe_3$).

Conclusions and Outlook

In the last 20 years various catalyst families for selective acyl transfer have been developed. Today, metal complexes as well as organic molecules still can compete with enzymatic approaches in some asymmetric acylation reactions (e.g., Fu's KR step in the total synthesis of epothilone,[39] Deng's enantioselective ring opening of a *meso*-anhydride in the synthesis of biotin,[137] and Schreiner's KR of cyclic *trans*-1,2 diols[28]). Especially KRs or desymmetrizations of secondary alcohols are excellent entry points for producing stereochemically pure building blocks and many catalyst systems capable of enantioselective acyl transfer in this substrate class have been developed in the last decade. In stark contrast, examples of KRs of primary and tertiary alcohols are rare (see Miller's peptide catalyst for the acylation of a tertiary alcohol[85] and Oriyama's KR of a glycerol derivative[74]) and the identification of new catalysts for these substrate classes would be desirable. Although the identification of new catalysts for enantioselective or site-selective transformations is generally challenging, it still is a highly desirable goal. The examples presented in this chapter show the potential of asymmetric acyl transfer as a tool for the synthesis of enantiopure substrates. All catalysts are highly chemoselective and therefore their substrate scope is limited, yet this limitation offers applications as catalysts for late-key-steps in natural product synthesis. Examples for the successful utilization of small organic catalysts for enantioselective acyl transfer in natural product synthesis were reported by Fu (epothilone, (–)-baclofen), [39] Birman (lobeline),[65] Hamersăk (pregabalin),[128] and Deng (biotin).[137] Miller and co-workers impressively demonstrated the potential of peptide catalysts in the site selective functionalization of substrates containing different OH-groups as present in glucosamines, glucosides,[89] and erythromycin A.[90] Furthermore, peptides represent, to the best of our knowledge, the only catalyst family that was successfully utilized in the selective acyl transfer onto primary, secondary, and tertiary alcohols. These examples give

hope that further investigations may lead to highly chemoselective catalysts capable of selective acylation of a specific OH-group in a polyol like vancomycin. Nature uses enzymes for such complex problems. Hence, the design of a chemoselective catalyst is maybe the biggest challenge in asymmetric synthesis, as enzymes are known to be complex macromolecules displaying secondary, tertiary, and quaternary structure.

The combination of two catalysts is also a powerful tool for asymmetric acyl transfer reactions. Bäckvall et al. showed the practical use of his approach (DKR via combination of Ru-catalyst and enzyme) by performing large-scale experiments (up to 10 mol). The obtained selectivity (*ee* = 97%) and yield (87% = 1.43 kg) for (*R*)-1-phenylethanol acetate were still good on large scale.[148]

To date catalysts are mostly identified through trial and error approaches or by using time consuming screening methods, but the investigation of processes for chemical recognition of the substrate by the catalyst have become more important. In the cases of Birman's amide-based catalysts **127**/**128** and Schreiner's peptide catalyst **238**[95] computations were able to shed some light onto the selective acyl transfer process. While for **127**/**128**[62] π-π interactions seem to be responsible for the chemical recognition and the selective acylation, in peptide **238** hydrogen bonding as well as attractive dispersive interactions between the peptide backbone and the substrate seems responsible of the differentiation between the two enantiomers. Other groups (e.g., Yamada et al., Fuji et al. and Connon et al.) investigated the conformational change of their free catalysts and the acylium ion adduct. All three proposed an "induced fit" process for which NMR-experiments provided some evidence.[45,50,51]

Though the first steps to a better understanding of the acyl transfer as well as the substrate recognition mechanism of the catalyst have been made, we are still far from rational catalyst design. Much more work on the insights of these complex processes will be needed to achieve this goal. Improved computational and analytical methods may prove critical in this endeavor.

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3. Lipophilic Oligopeptides for Chemo- and Enantioselective Acyl Transfer Reactions onto Alcohols

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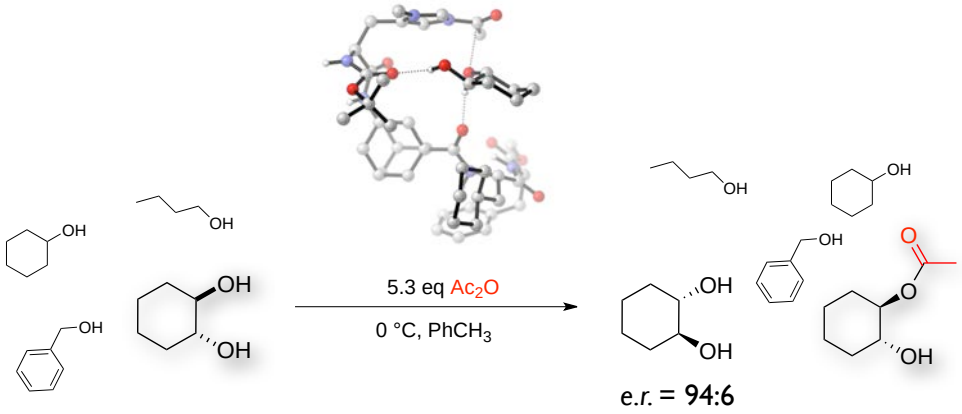


ABSTRACT: In nature enantioselective acylations are performed by enzymes (acylases). Inspired by their extraordinary selectivity we envisioned the synthesis of a small peptidic catalyst for acylative kinetic resolution (KR)/desymmetrization of cyclic *rac*- and *meso*-cycloalkane-1,2-diols. The entire optimization process from the theoretical concept to the final enantioselective catalyst is described and the scope of substrates and electrophiles is presented. Competition experiments with different alcohols and electrophiles were performed to show the full potential of the approach. Additionally we tried to shed some light on the forces responsible for the selectivity utilizing NMR- and IR-spectroscopic methods as well as computations. The catalyst system can be easily modified to a multicatalyst by simply adding other catalytically active amino acids to the peptide backbone and enables the synthesis of chiral and complex molecules from simple starting materials.

[#] These authors contributed equally to this work.

KEYWORDS: Acylation / Alcohols / Desymmetrization / Kinetic Resolution / Organocatalysis / Peptide Catalyst.

Introduction

Enantioselective acylations of chiral or prochiral alcohols are common reactions in nature and in chemistry. Enzymes can be used for the acylative resolution and desymmetrization of a broad range of secondary alcohols (e.g., cyclic *meso*-1,2- and 1,3-diols, 2,5-hexanediols, 1,4-cyclooctanediols and acylation of natural products like vitamin C, alkaloids and hydrocortisone).[1,2,3-5] Though enzymatic acylations are highly chemo- and enantioselective these approaches are often expensive, require stringent reaction conditions, long reaction times, and typically just one enantiomer of the product can be obtained. Also, there is a variety of substrates that cannot be effectively resolved by enzymes (e.g., *trans*-cyclohexane-1,2-diol and primary alcohols).[6] Hence, in the last 20 years various organic and organometallic catalysts (e.g., amidines,[7] vicinal diamines,[8,9] *N*-alkylimidazoles,[10-14] phosphines,[15,16] phosphinites,[17,18] Cu-complexes[19-21] and 4-aminopyridine derivatives[22,23])[24,25] were successfully applied in kinetic resolutions (KRs),[26,27] desymmetrizations,[28] and dynamic kinetic resolutions (DKR)[29,30] of alcohols, amines, and thiols (Figure 1).

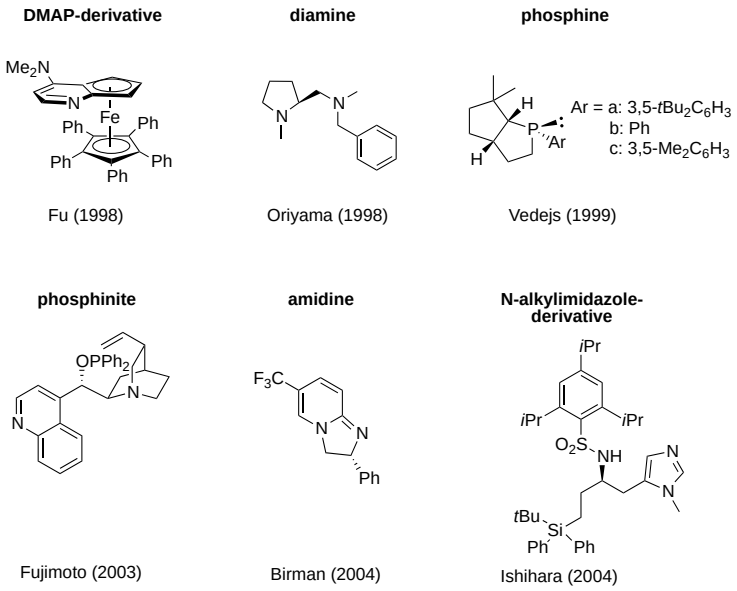


Figure 1. Non-peptidic organocatalysts capable of selective acyl transfer.

The application of short peptides as catalysts for enantioselective transformations has been neglected for a surprisingly long time, though many approaches were inspired by nature.[31,32] Only at the end of the last century chemists realized the capacity of oligopeptides as active catalysts due to their high diversity and their well-established syntheses based on

the coupling of readily available enantiopure amino acids.[31-33] Early prominent examples are the cyclic dipeptides (diketopiperazines) introduced by Inoue in 1981 for the enantioselective hydrocyanation of benzaldehydes[34-38] and the homooligomers of Juliá and Colonna that proved to be highly efficient in epoxidation reactions.[39-42] Remarkably, Wennemers *et al.* discovered that short proline containing oligopeptides display significantly higher reactivity at comparable enantioselectivities in aldol reactions compared to proline itself, which emphasizes the importance of the peptide backbone (Figure 2).[43-45]

Acyl transfer as part of nature's reaction portfolio is one of the most prominent examples for the use of short non-natural peptide catalysts for enantioselective transformations.[24,25,31] In 1998 Miller and coworkers introduced *N*-alkylimidazoles (π-methyl histidine derivatives performed best) containing peptides as acylation catalysts, which proved to be highly selective in various KRs and desymmetrizations.[31,46-49] Especially the KR of racemic *trans*-2-*N*-acetamidocyclohexanol using such peptides was intensively studied and led to the conclusion that a stable yet slightly flexible secondary structure based on intramolecular H-bonding is responsible for the high enantioselectivities (Figure 2).[31,46,49-51] Several attempts were made to improve the selectivities of these peptides by modifying the motifs that are responsible for the formation of a secondary structure (see the peptides of Toniolo[52] and Qu[53] in Figure 2). Though non-peptidic catalysts were successfully utilized in natural product synthesis e.g., epothilone, (–)-baclofen (with Fu's planar chiral ferrocenyl-DMAP derivative),[54] lobeline (with Birman's amidine based catalysts),[55] and biotin (with Deng's modified cinchona alkaloid catalyst),[56] peptidic approaches may offer chemoselective acylations of complex polyols bearing compounds (e.g., vancomycin[57] and erythromycin A[58]) and even carbohydrates.[59] In 2008 our group introduced a highly efficient tetrapeptide catalyst for the KR of *trans*-cycloalkane-1,2-diols *via* acyl transfer (Figure 2).[25,60] In contrast to the established peptide design concepts focusing on secondary structure formation our approach utilizes a highly lipophilic, structurally less flexible, non-natural adamantane γ-amino acid (^{A}Gly in our shorthand notation) in the center of the peptide. We envisioned that the more flexible amino acids at the *N*- and the *C*-terminus of the peptide would form a "dynamic pocket" like an active site in an enzyme and enable selective acyl transfer. The incorporation of additional lipophilic amino acids would allow the use of nonpolar organic solvents.

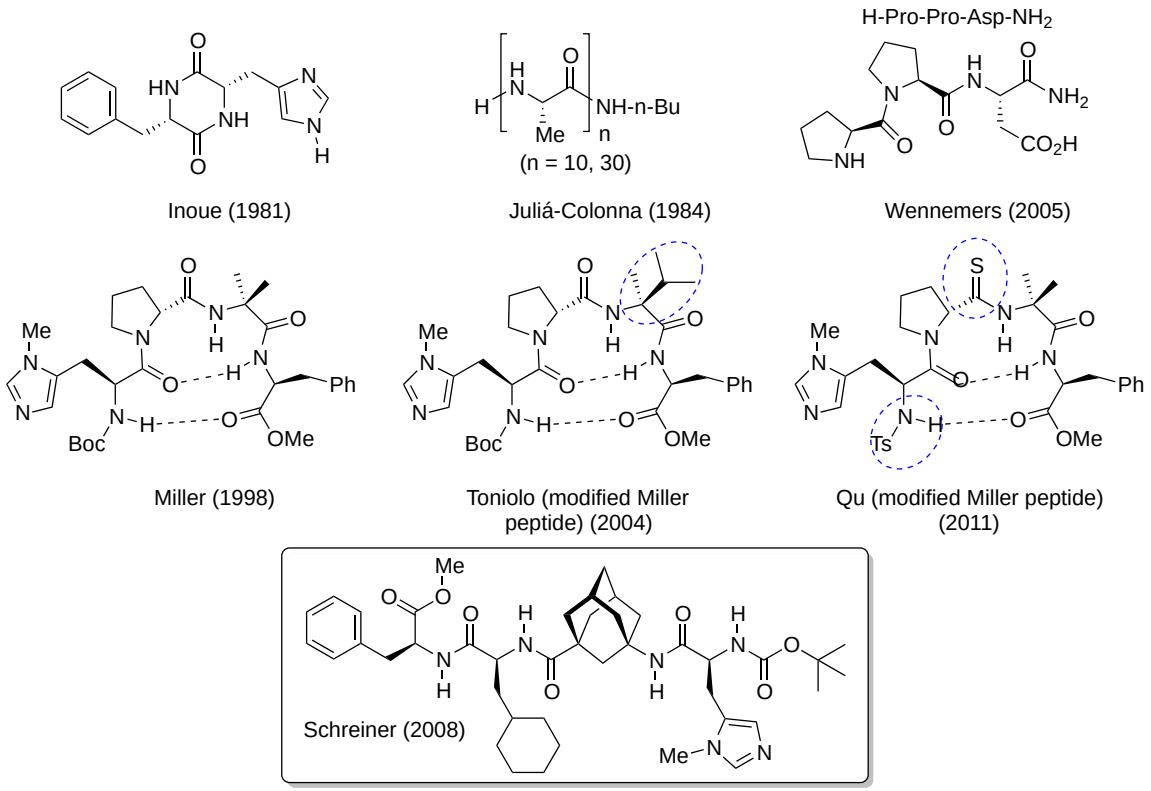


Figure 2. Peptide based catalysts for enantioselective reactions.

The KR of cyclic chiral *trans*-cycloalkane-1,2-diols *via* acyl transfer was chosen as the test reaction, because no synthetically useful approach for this class of substrates was reported. Additionally, natural products bearing vicinal diols are frequently found (e.g., in steroids, flavonoids, carbohydrates, and pharmaceuticals) and therefore a highly chemoselective peptide would be quite useful.[61] Monoacetylation of *trans*-cycloalkane-1,2-diols utilizing enzymes (*Pseudomonas* lipases) displayed low activities as well as selectivities.[6] In the case of metal catalytic approaches for the KR of *trans*-cycloalkane-1,2-diols only selective benzoyl transfer utilizing 0.5 eq of benzoyl chloride were reported by Onomura (2003),[19] Reiser (2005),[20] and Pfaltz (2006).[21,62] All three approaches utilize Cu(II)-complexes containing chiral C_2-symmetric bisoxazolin ligands. The catalyst loading ranged from 5 mol% (Onomura, Reiser) to 1 mol% (Pfaltz) and 1 eq of additional base was added by Pfaltz and Onomura. The obtained *S*-values ranged from 14 to 22[63] and the *ee*'s from 80% to 83% for the product. Selective acyl transfer was not reported. In contrast, our peptide based catalyst achieved a selectivity >50 and an *ee* of >99% for the remaining diol in the acylative KR. Additionally, our approach does not require the addition of a base, because the generated acetic acid (pK_a = 4.74) is comparably weak and in equilibrium with the methylimidazolium ion (pK_a = 7.3)[64] always a small amount of unprotonated catalyst is available. This is one of the rare cases where a chemical method is more efficient than an enzymatic approach.

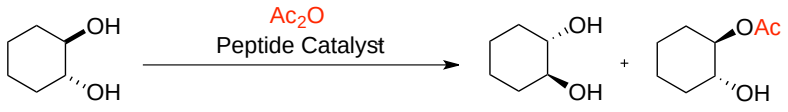
Later the same peptide or similar peptidic catalysts were successfully applied to selective single- and multicatalytic transformations.[25,65-70]

The identification of such highly enantioselective catalysts is still a formidable challenge and mostly relies on trial and error or extensive screening experiments, because the chemical recognition processes of catalyst and substrate are usually hardly predictable.[32] Here we report a full investigation of our oligopeptide catalyst platform including catalyst screenings, substrate scope, chemoselectivity, and present a structural mechanistic model for enantioselective acylations. Additionally, the peptide catalyzed transfer of various other electrophiles to nucleophiles (e.g., alcohols) will be described.

Results and Discussion

Catalyst Screening Using the Acylative KR of *trans*-Cyclohexane-1,2-diol as Test Reaction

A large variety of peptide catalysts was synthesized *via* automated solid phase peptide synthesis (SPPS) using an Fmoc-strategy; additionally, the chosen peptides were prepared in solution in larger quantities utilizing a Boc-strategy. The crude peptides were initially characterized using ESI-MS; purified peptides were characterized by NMR, IR, ESI-MS, and ESI-HRMS (for detailed experimental procedures and analytical data see Experimental and Supplementary Information). All peptide catalysts were tested in the KR of racemic *trans*-cyclohexane-1,2-diol **1** (Scheme 1) with acetic anhydride, but without addition of base. As mentioned in the introduction the KR through acetylation of *rac*-**1** is a formidable challenge[71] and a difficult transformation due the lack of efficient enzymatic, metal-catalyzed, and organocatalytic approaches.[6,72]



(±)-**1** (*S*,*S*)-**1** (*R*,*R*)-**2**

Scheme 1. KR of *trans*-cyclohexane-1,2-diol **1** as test reaction.

We began our research for a new highly lipophilic peptide by using Boc-L-(π-Me)-histidine methylester **3** as a catalyst to determine whether the acyl transfer onto **1** under our chosen reaction conditions (in toluene; no auxiliary base) is generally possible.[73] The ability to perform the KR in a non-polar solvent in the absence of base simplifies the purification of the product. The *ee*'s and yields for our test reaction (Table 1) with **3** were low. Additionally, we

tested **4** introduced by Snapper and Hoveyda in 2006 (**4** showed excellent selectivities in the silylation of racemic and *meso*-1,2-diols) in the acylative KR of *rac*-**1**, but only low selectivity was observed.[74] Our design concept focused on the ^{A}Gly moiety as a sterically demanding and structure determining spacer that should lead to lipophilic peptides soluble in organic solvents. At first we synthesized various tri-, tetra-, and pentapeptides and placed the rigid ^{A}Gly in the center of the molecule. We hoped separating the more flexible amino acids on the *C*- and *N*-terminus of the peptide would enable the formation of a chiral environment (e.g., "a pocket"). All peptides included different catalytically active histidine moieties to identify the most active one: Boc-L-histidine for peptide **5**; Boc-L-(τ-Bzl)-histidine for **7**, **8**, and **9**; and Boc-L-(π-Me)-histidine for **6**, **10**, **11**, and **12** (Figure 3).

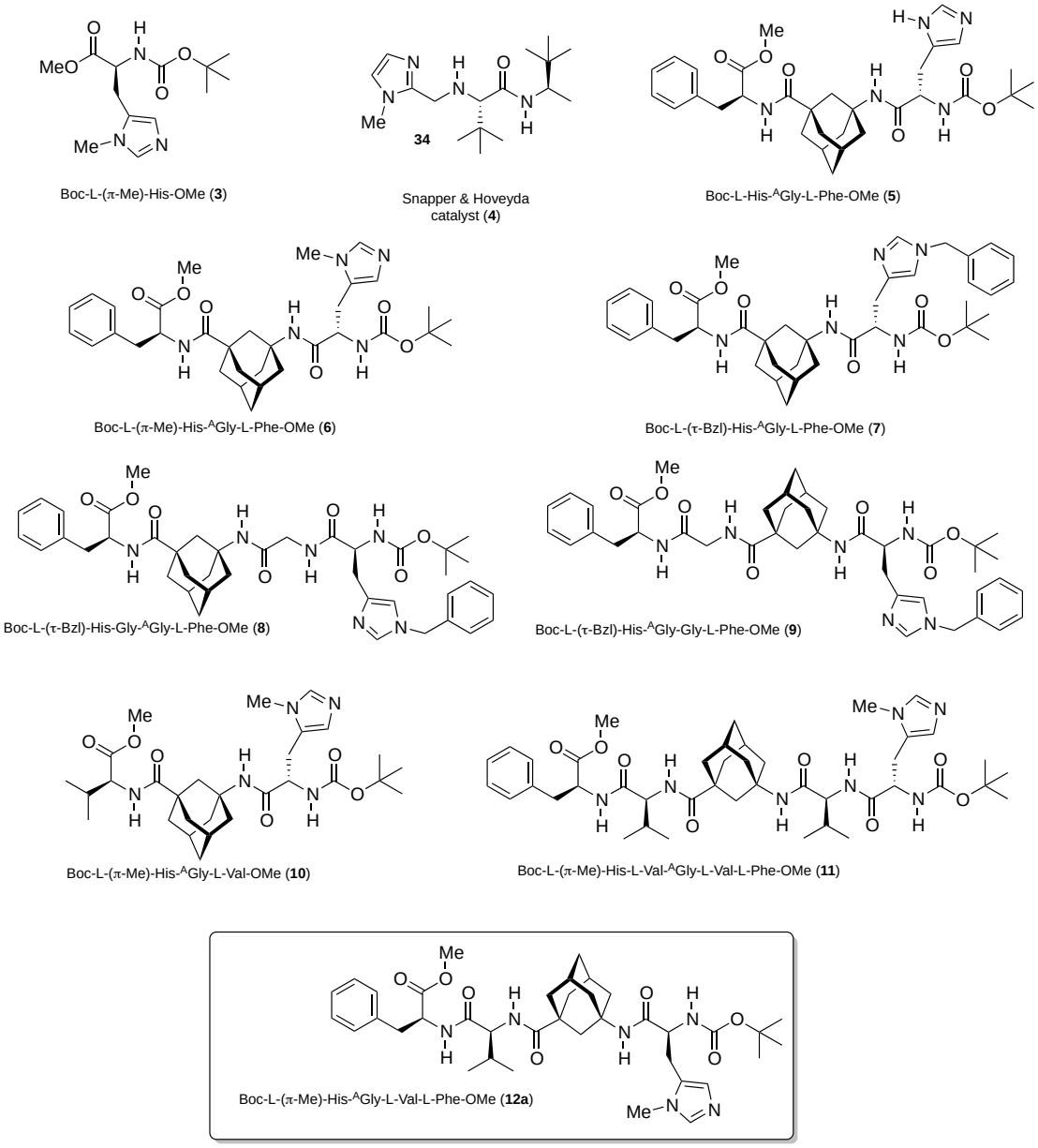


Figure 3. Starting sequences for the search of a selective acyl transfer catalyst.

The results for **3**–**12a** as applied to the KR of *rac*-**1** are summarized in Table 1. A comparison of the tripeptides **5**–**7** having the same peptidic backbone bearing a histidine-(**5**), π-methyl histidine (**6**) and a τ-benzyl-histidine moiety (**7**) shows that Boc-L-(π-Me)-histidine is the catalytically most active histidine derivative. Tripeptidic and tetrapeptidic structures produced high yields but moderate selectivities; pentapeptides showed only low selectivities and activities and were not investigated further. Peptide **12a** was the most selective catalyst and used as model peptide for further modifications.

Table 1. KR of *trans*-diol (±)-**1** with peptide catalysts **3**–**12a**.

entry[a]	cat.	*t* (h)	yield (%)[c] of (*R*, *R*)-**2a**	*er*[d] of (*R*, *R*)-**2a**
1[b]	**3**	15	2	46:54
2[e]	**4**	4	11	44:56
3	**5**	42	4	76:24
4	**6**	18	48	69:31
5	**7**	210	10	54:46
6	**8**	210	10	58:42
7[b]	**9**	210	5	53:47
8[b]	**10**	15	1	75:25
9	**11**	15	7	50:50
10	**12a**	18	43	73:27

[a]All reactions were performed at 0 °C in a mixture of 2.25 mL toluene and 0.85 mL $CHCl_3$ with 1 eq (43.6 mg, 0.375 mmol) of racemic substrate **1**, 0.5 eq of acetic anhydride, and 1 mol% of catalyst. [b]Reaction was performed at –20 °C with 0.1 eq of acetic anhydride. Without catalyst no conversions could be observed. [c,d]Yields and enantiomeric ratios were determined by chiral GC analysis using an internal calibration. [e]Reaction was performed at 0 °C in 4.5 mL toluene with 1 eq of racemic substrate **1** (0.025 mmol, 2.9 mg), 5.3 eq of acetic anhydride, and 2 mol% of catalyst in toluene.

In contrast to enzymes, which often only exist in one enantiomeric form, we readily synthesized *ent*-**12i** (all amino acids D-configured) and, as expected, were able to acetylate *S,S*-**1** with the same selectivity. Switching the positions of L-Val and π-Me-His (**13)** or L-Val and ^{A}Gly (**17**) lowered the selectivities for the KR of *rac*-**1** than **12a**. Hence, it is important that ^{A}Gly is in direct neighborhood to the catalytically active His-moiety.

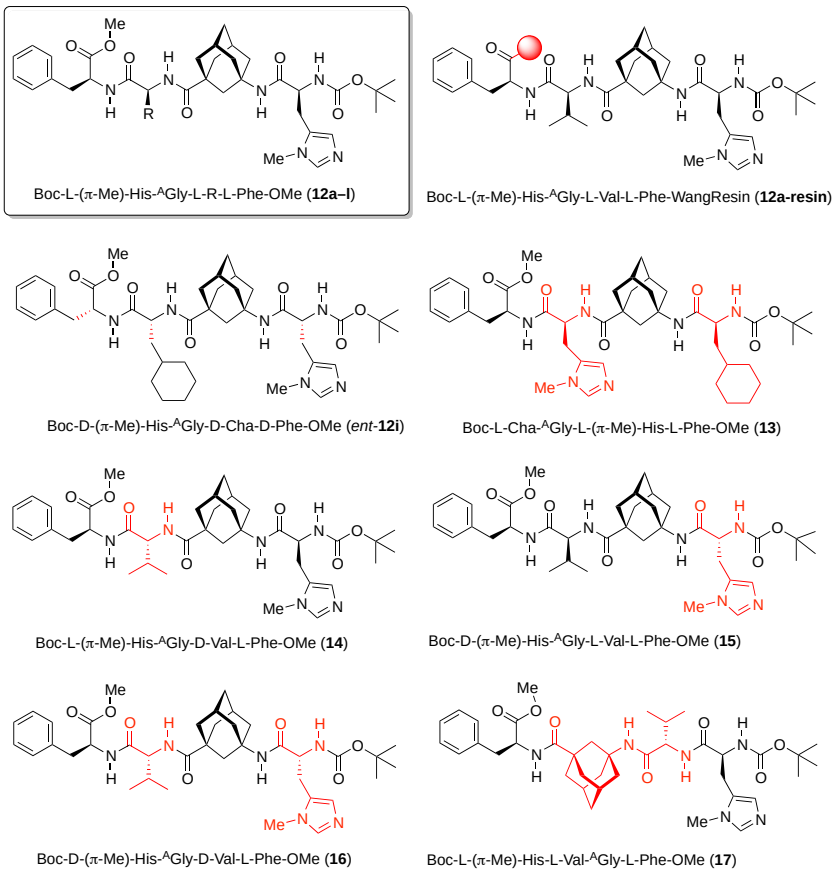


Figure 4. Variation of peptide catalysts; structural changes of the peptides compared to **12** are drawn in red.

Next we focused on changing the configuration of Val, Boc-(π-Me)-His (**14** and **15**) and of both amino acids (**16**). The best *er* values were obtained for peptides containing homoconfigured Val and His amino acids (matched situation for **12a**–**l**, *ent*-**12**, and **16**). The mismatched configuration of either Val or π-Me-His (**14** and **15**) decreases the selectivity for the KR of *rac*-**1** dramatically (Figure 4).

Table 2. Screening of the KR of (±)-**1** with peptide catalysts **12a–l** and **13**–**17**.

entry[a]	cat.	R	yield (%)[c] of (*R*, *R*)-**2a**	*er*[d] of (*R*, *R*)-**2a**
1	**12a**[e]	Val	9.9	85:15
2[b]	**12a-resin** 75	Val	10.2	63:37
3[f]	*ent*-**12i**	Cha	57	12:88
4[f]	**13**	–	35	57:43

entry[a]	cat.	R	yield (%)[c] of (*R*, *R*)-**2a**	*er*[d] of (*R*, *R*)-**2a**
5	**14**	–	9.8	60:40
6	**15**	–	8.1	46:54
7	**16**	–	10.5	21:79
8	**17**	–	5.4	67:33
9	**12b**[e]	^{A}Gly	8.6	67:33
10	**12c**[e]	Leu	10.8	86:14
11	**12d**[e]	Ile	8.1	86:14
12	**12e**[e]	Pro	4.9	75:25
13	**12f**[e]	Ala	4.8	80:20
14	**12g**[e]	Phe	4.9	81:19
15	**12h**[e]	AiB	4.1	71:29
16	**12i**[e]	Cha	8.3	88:12
17	**12j**[e]	Ser	7.5	72:28
18	**12k**[e]	Gly	4.8	70:30
19	**12l**[e]	Tyr	2.8	73:27

[a]All reactions were performed at –20 °C for 15 h in a mixture of toluene and $CHCl_3$ with 1 eq of racemic substrate **1**, 0.1 eq of acetic anhydride, and 1 mol% of catalyst (raw product, after resin cleavage and evaporating of the solvents; without further purification). Without catalyst no conversions were observed. [b] Reaction was performed for 24 h. [c,d] Yields and *er* values were determined by chiral GC analysis using an internal calibration. [e] Results taken from reference 60.[60] [f] All reactions were performed at 0 °C in 4.5 mL toluene with 1 eq of racemic substrate **1** (0.025 mmol, 2.9 mg), 5.3 eq of acetic anhydride, and 2 mol% of catalyst.

The catalytic efficiency of **12a** and the results presented in Table 2 encouraged further variations. Hence, L-Val was replaced by other L-configured amino acids at the *i+2* position (Table 2, **12b**–**12l**). The use of Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (**12i**) as catalyst gave the highest *ee* in the KR of *rac*-**1**. Indeed, **12i** is the most efficient catalyst for the KR of *trans*-cycloalkane-1,2-diols to date.[25,60] Though having identified a capable catalyst for the selective acylation of *rac*-**1** the role of the *C*-terminal amino acid was investigated by using the Boc-L-(π-Me)-His-^{A}Gly-L-Leu-L-R motif (Figure 5) in order to obtain mechanistic insights of the substrate recognition process by the catalyst. The results are summarized in Table 3.

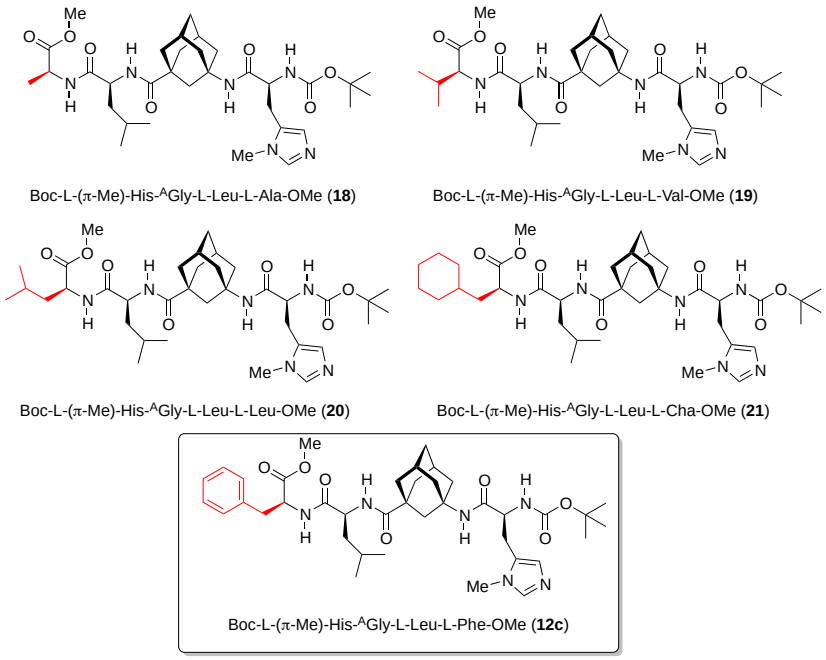


Figure 5. Investigation of the role of the *C*-terminal amino acid.

Table 3. Screening of the KR of (±)-**1** with peptide catalysts **18**–**21** and **12c**.

entry[a]	cat.	yield (%)[b] of (*R*, *R*)-**2a**	*er*[b] of (*R*, *R*)-**2a**
1	**18**	2.0	86:14
2	**19**	1.6	84:16
3	**20**	4.9	87:13
4	**21**	5.1	89:11
5	**12c**	12.7	86:14

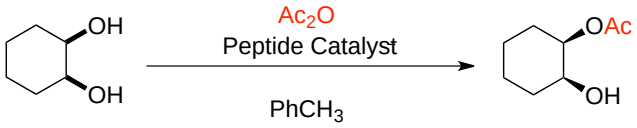
[a]All reactions were performed at –20 °C for 15 h in a mixture of toluene and $CHCl_3$ with 1 eq of racemic substrate **1**, 0.1 eq of acetic anhydride, and 1 mol% of catalyst (raw product, after resin cleavage and evaporating of the solvents; without further purification) **18**–**21** and **12c**. Without catalyst no conversions were observed. [b]Yields and enantiomer ratios were determined by chiral GC analysis using an internal calibration.

Peptide catalyst **21** with *C*-terminal L-Cha proved to be the most selective but generally all tested peptides showed high selectivities. This finding implies that the *C*-terminal amino acid in the tetrapeptide does not strongly affect the selectivity of the peptide.

KR versus Desymmetrization

The KR of *rac*-**1** was achieved with catalyst **12i** under optimized conditions (2 mol% 12i, 5.3 eq Ac_2O, 4.5 mL abs. toluene, 0 °C) with an *ee* of >99% for the starting material at a

conversion of 57%. A general drawback of a KR is the limitation of the theoretical yield to 50%, but in contrast to cyclic *meso*-cycloalkane-1,2-diols no racemization occurs, because the intramolecular acyl transfer yields in the same stereochemistry in the product. Additionally, the benzoylative desymmetrization of *meso*-**22** has successfully been accomplished by chiral diamine[76] and phosphinit-based[18,77] catalysts. Various (π-Me)-histidine derived catalysts were utilized in the desymmetrization of *meso*-cyclohexane-1,2-diol **22** (Scheme 2). We also tested Snapper and Hoveyda's catalyst **4** (highly effective in the desymmetrization of *meso*-1,2-diols *via* silyl-group transfer).[74,78-80]



meso-**22** (*R*,*S*)-**23**

Scheme 2. Desymmetrization of *cis*-cyclohexane-1,2-diol **22** as test reaction.

For the desymmetrizations of *meso*-**22** with **12i** high selectivity was observed. To our surprise Hoveyda's methylimidazole based catalyst **4** (Figure 3) proved to be catalytically inactive at low catalyst loadings (2 mol%) without addition of base (Table 4).[74,78-80] Even at higher catalyst loadings and with added base only moderate selectivities at very low conversions could be achieved. The desymmetrization with **12i** is much faster and slightly more selective with base.

Table 4. Desymmetrization of *meso*-**22** with catalysts **12i** and **4**.

entry[a]	cat.	*t* (h)	*C* (%)[c]	*yield* (%)[c] (*R*, *S*)-**23**	*er* (%)[d] (*R*, *S*)-**23**
1	**12i**	4	42	42	91:9
2	**12i**	24	88	75	87:13
3[b]	**4**	24	–	–	–

[a]All reactions were performed at 0 °C in 4.5 mL toluene with 1 eq of *meso* substrate **22** (0.025 mmol, 2.9 mg), 5.3 eq of acetic anhydride, and 2 mol% of **12i**. Without catalyst there is no conversions. [b] Reaction performed at –20 °C with 20 mol% of **4** and 5.3 eq D*i*PEA. [c]Conversions *C* and yields determined by GC-analysis. [d]*er* values determined by chiral GC analysis.

Model for the Enantioselective Acylation with 12i

The screening of the peptide catalysts identified some of the important structural requirements to produce high enantioselectivities in the acylative KR of *rac*-**1** as reference substrate:

- Tetrapeptides are most selective
- The lipophilic and sterically demanding adamantyl amino acid needs to be located at the *i*+1 position
- Homoconfigured (all three chiral α-amino acids have the same configuration) peptides show the highest selectivities
- The *i*+3 position does not drastically affect the selectivity of the peptide

For a better understanding of the chemical recognition process of the substrate by the catalyst responsible for the selectivity we attempted NMR polarization-transfer and IR studies with **12**. We measured NOE-spectra for the homoconfigured peptide **12a** and the heteroconfigured peptide **14**. Unfortunately, the evaluation and comparison of the NOE-spectra of **12a** and **14** did not produce cross signals that could be assigned to a defined secondary structure for **12a**. Only NOE-signals for the vicinal amino acids were obtained. We also measured the chemical shift dependence of the NH groups in $CDCl_3$ as a function of increasing the d_6-DMSO concentration.[81] In the absence of hydrogen bonds all NH groups should show significant downfield shifts. In the case of **12i**, for (Phe(NH), Val(NH), ^{A}Gly(NH) and π-(Me)-His(NH)) we observed a downfield shift in the range of 0.4–1.4 ppm. This indicates the absence of intramolecular hydrogen-bonds for **12i** in $CDCl_3$ at room temperature.

Another useful method for the identification of intramolecular H-bonding is IR spectroscopy. Gellman has established IR spectroscopy as a tool for the determination of intramolecular amide-amide hydrogen bonds of peptides in CH_2Cl_2.[82] Sharp bands in the N–H stretch region at 3460 – 3450 cm^{-1} were assigned to non-hydrogen bonded N–H, whereas broad bands at 3330 – 3300 cm^{-1} were assigned to internal hydrogen bonds.

We performed IR experiments at various temperatures using a 13 mM solution of **12i** in $CDCl_3$. In order to investigate H-bonding interactions we chose $CDCl_3$ as solvent because of its moderate polarity and high solubility of **12i** in this solvent. In addition, the results of the IR experiments obtained in $CDCl_3$ can be directly compared to those generated by NMR-experiments. At room temperature only one sharp band at 3460–3450 cm^{-1}, assigned to non-hydrogen bonded NH groups, was observed. While reducing the temperature in 10 K steps from 298 K to 233 K a new broad band at 3300 cm^{-1} appeared and the intensity increased as the temperature decreased (see SI). This is an indication for an intramolecular

hydrogen bond at temperatures below 253 K). Up to date we found no evidence for a secondary structure of **12a-l** at r.t. or 0 °C through spectroscopic means (IR, NMR).

We also investigated the possibility of a structure-forming element at the stage of the acylium ion. NMR spectra of the acylium ion were measured at r.t. in $CDCl_3$, but no unusual NOEs indicating a secondary structure were observed. Hence, we utilized a molecular dynamics search for low-lying conformations of the catalyst/acylium ion adduct using the Merck Molecular Force Field (MMFF)[83] and reoptimized the lowest-lying conformation at M06–2X/6–31+G(*d,p*).[84,85] The conformational analysis of the acylium ion of **12i** resulted in a folded structure as the energetically most favored conformation. Irrespective of the starting geometry, the most favorable conformer always placed the cyclohexyl group in **12i** in close proximity to the imidazole/acylium ion adduct (Figure 6, left). We also applied a molecular dynamic search for catalyst/acylium ion adduct and (*R,R*)-**1**. The acylated catalyst **12i** generates a chiral environment around the substrate (Figure 6, middle and right).

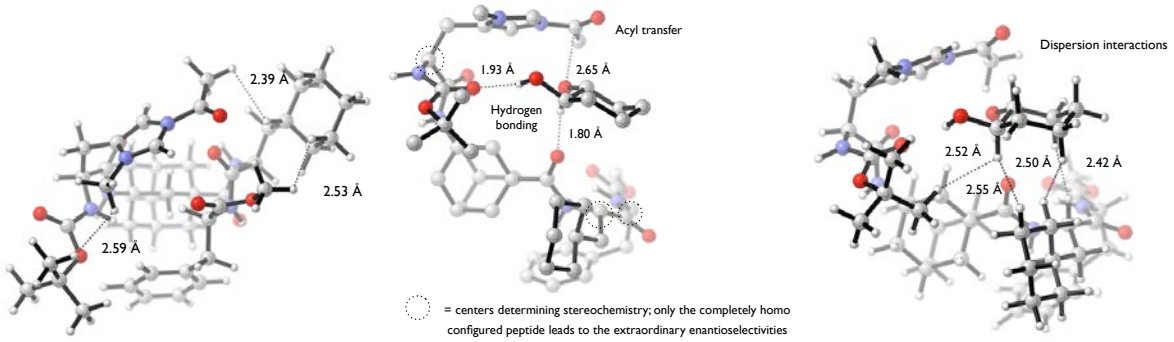


Figure 6. left; M06–2X/6–31+G(*d,p*) reoptimized structure of **12i**;[84,85] middle: M06–2X/6–31+G(*d,p*) reoptimized structure for the enantioselective acylation of *trans*-cycloalkane-1,2-diols in the "pocket" of the acylated catalyst. Hydrogen atoms on the catalyst are omitted for clarity. C gray, N blue, O red.[86] right: Dispersion interactions of substrate and catalyst.

The two geometrically nearest C=O groups apparently provide hydrogen bonding acceptors (Figure 6) needed for chiral recognition of the diols. This arrangement helps rationalize why more hydrophobic R-groups provide higher *ee* values, as they enhance the London dispersion interactions with the substrate (Figure 6, right).[87,88] The model also emphasizes that the ^{A}Gly building block provides a scaffold that separates both ends of the peptide and also holds the centers governing recognition and stereochemistry in place. It seems that *rac*-**1**, as well as the acylium ion adduct have to be present to structure the

"active site" of the peptide by dispersion (Figure 6, right) and hydrogen-bonding interactions in a rather dynamic binding event.

In 2009 Sunoj *et al.* independently performed ONIOM computations at the B3LYP/6-31G(*d*):PM3 level that yielded transition structures for the **12i** catalyzed acyl transfer onto (*R*,*R*)- and (*S*,*S*)-*trans*-cyclohexane-1,2-diol (Figure 7).[89] These computations nicely confirmed our model and the energy difference of 4.5 kcal·mol^{-1} between the two transition states explained the observed high enantioselectivities.

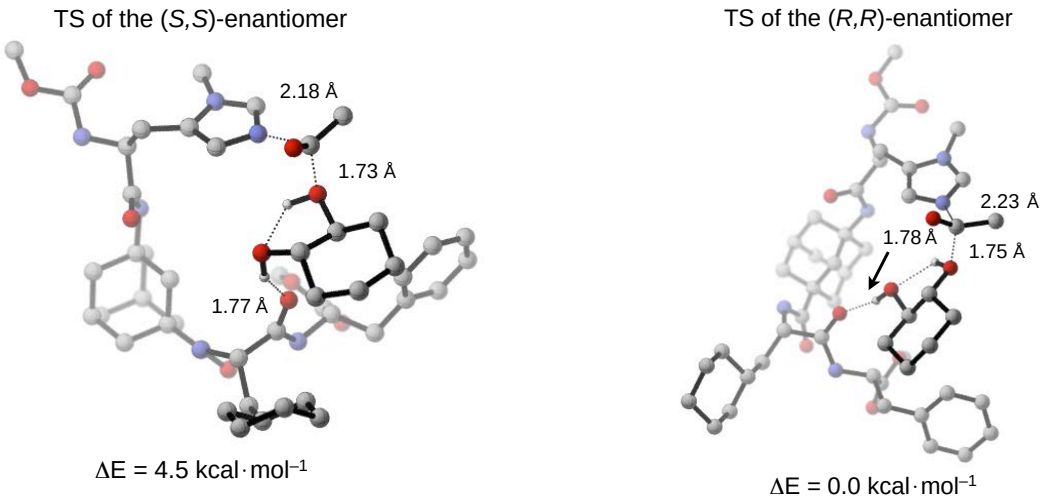
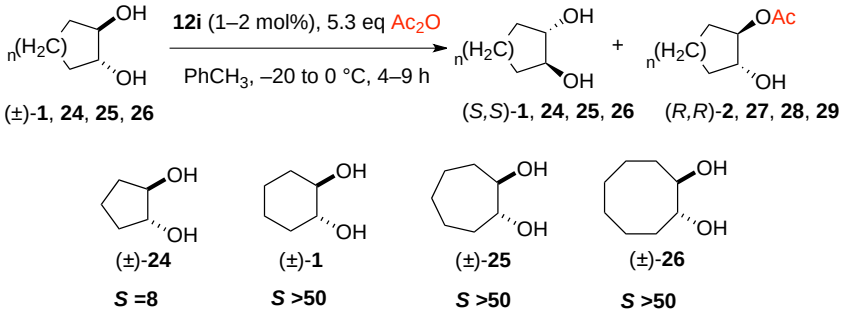


Figure 7. Optimized low-lying transition structures for the acyl transfer catalyzed by **12i** (Moc instead of Boc) to (*1R,2R*)-**1** (left) or to (*1S,2S*)-**1** at ONIOM2(B3LYP/6-31G(*d*):PM3). Only selected hydrogens are shown for clarity. Parts in blue represent the higher (B3LYP) level and the non-framed part the lower (PM3) level in the ONIOM2 partitioning.[86]

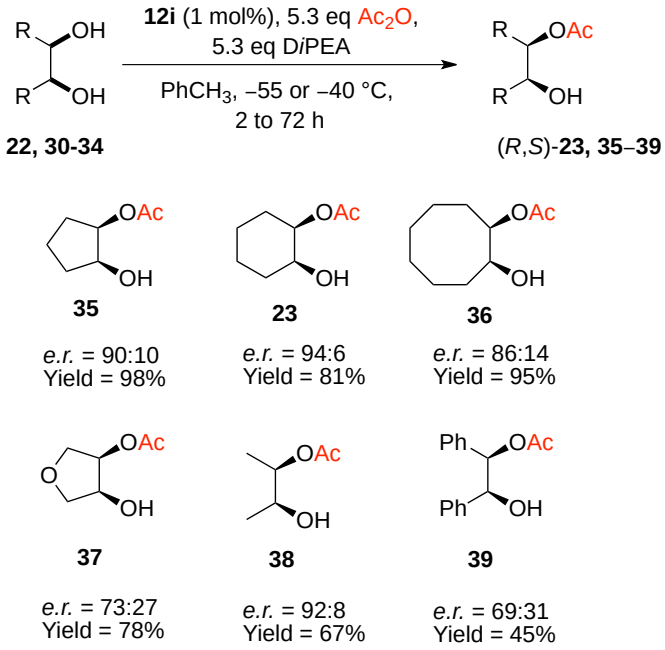
Substrate Scope for Peptide 12i Catalyzed Acylations

We first utilized peptide **12i** in the KR of cyclic *trans*-1,2-diols **24**–**26** and high enantioselectivities were observed. The five-membered ring diol **27** with an *S*-value of 8 proved to be an exception owing to its poor solubility in toluene and the required addition of CH_2Cl_2 (Scheme 3).



Scheme 3. Enantioselective KR of *trans*-cycloalkane-1,2-diols with **12i**.[61]

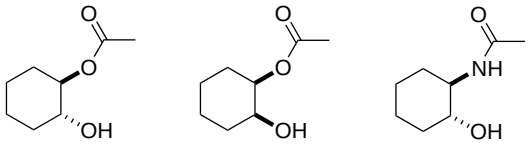
Comparable selectivities were observed for the desymmetrization of *cis*-1,2-diols **22** and **30**–**34** (Scheme 4). Unfortunately, the enantiomerically enriched products are known to racemize easily, e.g., during the workup due to intramolecular acetyl transfer.[90-92] Hence, we decided to oxidize the second OH-group directly after the desymmetrization *in situ* using a one-pot TEMPO catalyzed oxidation protocol.[67] Nevertheless, enantiomeric ratios for the acetylated *meso*-diols **22, 30**–**34** can be readily determined by chiral GC.



Scheme 4. Desymmetrization of *meso*-diols **22, 30**–**34** under optimized conditions.[52]

In contrast to the selective esterification of 1,2-diols (the second OH-group is important as H-bonding donor) other biomimetic approaches mostly require monoacetylated 1,2-diols or monoacetylated 1,2-aminoalcohols to achieve high selectivities.[10-12,14,46] In these cases the additional H-bonding acceptor of the acyl group serves as a docking position. Therefore

acylation catalyst **12i** was tested in the KR of racemic **2**, **23**, and **40** (Figure 8). The latter substrate was successfully used by Miller *et al*.;[31,46,48,50] in our hands Miller's catalyst led to excellent selectivities in the KR of *rac*-**40** (90% *ee* for **40**, 86% *ee* for the diacetylated aminoalcohol, *S* = 41 at *C* = 51%, 24 h at 0 °C)].[60] As expected, **12i** proved to be unselective in these three cases showing the complementarity to Miller's catalyst. Additionally, the inefficient KR of *rac*-**23** was an important finding to show that the diacetylation occurring during the acylative desymmetrization of *meso*-**22** does not affect the selectivity for the monoacetylated product.



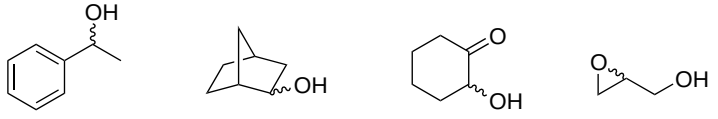
(±)-**2** **C = 4%** ***S* = 1**

(±)-**23** **C = 45%** ***S* = 1**

(±)-**40** **C = 11%** ***S* = 1**

Figure 8. KR of the racemic monoacetylated substrates **2**, **23**, and **40**.

The enantioseparation of racemic secondary monoalcohols is another challenging field for acylative KRs. The KR of racemic 1-phenylethanol **41** *via* organocatalytic acyl transfer is one of the most common test reactions in this area (efficient methods often take advantage of selective π–π-interactions between substrate and catalyst)[24,25,93] and was therefore chosen as a test reaction for **12i** as well. Catalyst **12i** promoted this reaction but showed no enantioselectivity (Figure 9).[94] The KR of other racemic secondary alcohols like *exo*-norborneol **42** and *rac*-**43** *via* acylative KR with catalyst **12i** also led to low selectivities (Figure 9). Catalysts with additional H-bonding donor amino acids serine **12j** and tryptophan **12l** in the *i*+2 position,[60] were tested in the KR of *rac*-**43** but were less efficient than **12i**. Non-enzymatic examples of KR or desymmetrizations of primary alcohols are rare, because no second functional group, which is usually required to achieve chemical recognition by the catalyst, is close to the hydroxyl group.[95,96] As expected the selectivity of **12i** in the KR of racemic **44** was low (Scheme 9), despite significant activity. This finding implicates that the second vicinal OH-group is necessary for the selectivity of the acylation.



(±)-**41** **C = 16%** ***S* = 1**

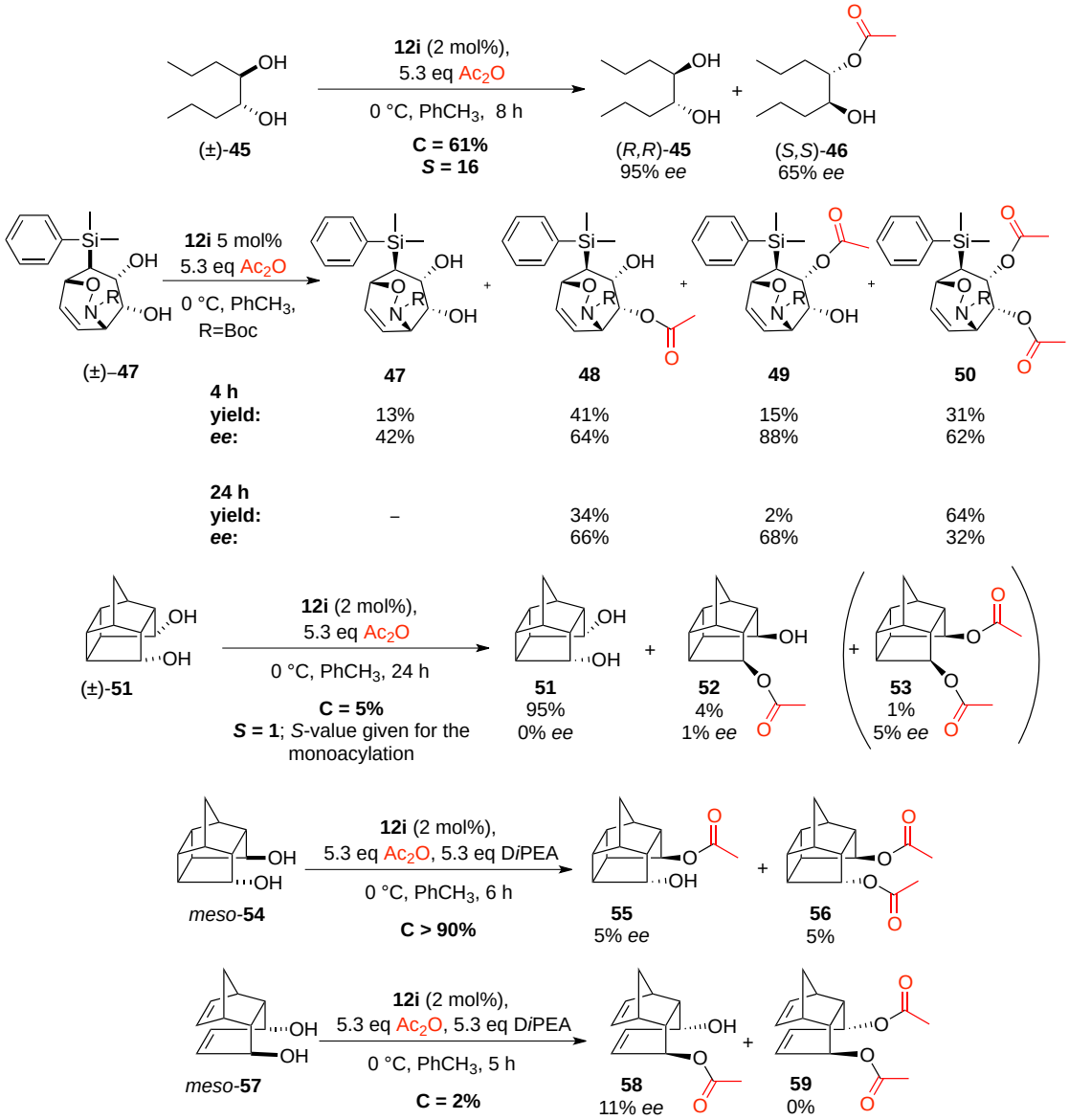
(±)-**42** **C = 22%** ***S* = 1**

(±)-**43** **C = 12%** ***S* = 2**

(±)-**44** **C = 70%** ***S* = 1**

Figure 9. Testing the KR of the racemic monoalcohols **41–44** with catalyst **12i**.

Due to the inefficiency of **12i** in the acylative KR of monoalcohols, a broader range of *meso*- and *rac*-1,2-diols **45**, **47**, **51, 54**, and **57** (Scheme 5) was investigated.



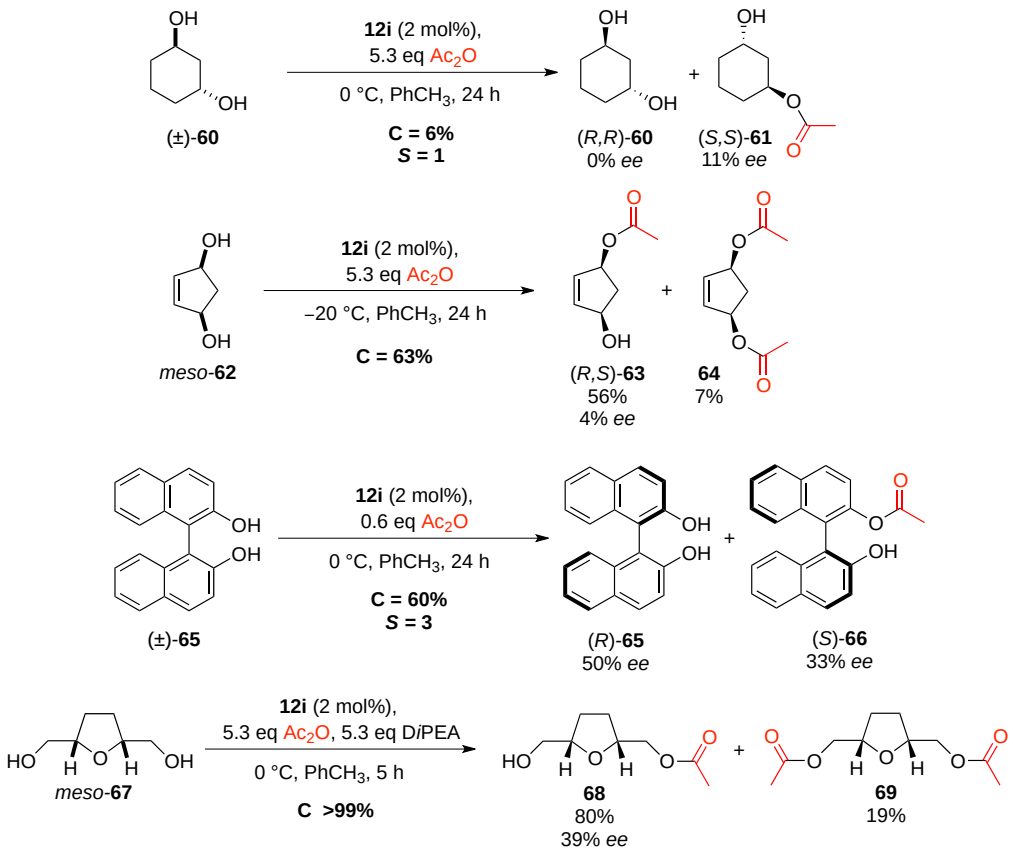
Scheme 5. Testing the KR of the racemic diols **45**, **47**, **51, 54**, and **57** with catalyst **12i**.

Catalyst **12i** showed good performance in the KR of the racemic diol **45** with an *S*-value of 16; apparently **12i** is not only efficient for cyclic vicinal diols but also for the non-cyclic analogues. Landais *et al*. reported an efficient 10-step synthesis of aminocycloheptitols *via* desymmetrization/functionalization of 7-silylcycloheptatrienes. [97] Further functionalization of the 7-silylcycloheptatrienes gave racemic products. Hence, we investigated the selective acetylation of *rac*-**47** by **12i**. The KR of diol *rac*-**47** is rather challenging due to the complex structure (five stereogenic centers) and the possible formation of two product regioisomers **48** and **49**. In principle catalyst **12i** is capable of differentiating between both enantiomeric forms by preferring the acylation of the *R,R*-enantiomer (configuration of the hydroxyl-

groups). The highest *ee*, but a rather low yield (yield = 15%) was observed for the monoacetylated regioisomer **49**. The selectivity for **48** was lower, but the yield was good (yield = 41%) (Scheme 5). We suggest that the high selectivity but lower reactivity of **49** is because of the high steric demand of the dimethylphenylsilyl-group in proximity to the acetylated hydroxyl group. Compared to all other KR experiments we found a large amount of diacetylated product **50**.

In contrast, **12i** proved to be inactive and unselective for **51** and **57** and only moderately active but rather unselective in the desymmetrization experiments with the *meso*-diol **54** (Scheme 5). An explanation might be the rather rigid structure of **51**, **54**, and **57** and the steric demand of the substrates, as well as the absence of intramolecular hydrogen bonds of the diols.

1,3-, 1,4- and 1,5-Diols are also preparatively useful substrates and were therefore tested in the acylative KR with **12i**. Racemic 1,3-diol *rac*-**60** was only poorly resolved and after 24 h only 6% of **61** was observed. Peptide **12i** showed a higher activity for the desymmetrization of *meso*-1,3-diol **62** but provided no selectivity. To our delight, moderate selectivities were achieved in the **12i** catalyzed KR of non-vicinal 1,1′-binaphthyl-2,2′-diol *rac*-**65** (*S* = 3; Scheme 6). Enzymatic[98] and chemical approaches[99] were reported for the resolution of 1,1′-binaphthyl-2,2′-diol *rac*-**65**; the non-enzymatic methods are based on inclusion complexes[100] or salt formation.[101] Both enantiomers can be obtained in high yields and excellent *ee´*s (>99%).[100,102] To the best of our knowledge no catalytic, non-enzymatic approaches for the acylative KR of *rac*-**65** are known to date. This is the first example for catalyst **12i** displaying moderate selectivity for a substrate class different from 1,2-diols (Scheme 6). It is also worth mentioning that the KR of **65** with catalyst **12i** and acetic anhydride proceeded rapidly (4 h) under optimal conditions (5.3 eq Ac_2O, 0 °C) and the diol was completely converted to the corresponding monoacetylated (64%) and diacetylated (36%) products. Therefore the amount of acetic anhydride was reduced to 0.6 eq Ac_2O, which led to a conversion of 43% to **66** after 4 h (stirring over night yielded 60% of **66** with 33% *ee*); only the monoacetylated product was observed. This indicates that the KR of *rac*-**65** is even faster than for our reference diol **1**.



Scheme 6. Efficiency of the KR of **60** and **65** as well as desymmetrization of *meso*-diols **62** and **67** with catalyst **12i**.

Surprisingly, high activity and moderate selectivity was observed for the desymmetrization of 1,5-diol **67**.[103] For an efficient KR or desymmetrization the substrate requires two hydroxyl groups with a proper spatial relationship. It is conceivable that an intramolecular hydrogen bond forms that increases the acidity of the second hydrogen and therefore promotes the acetylation. This might be an explanation for the largely uneven conversions for, e.g., substrates **51** (5%) and **54** (> 90%). While in substrate **54** an intramolecular hydrogen bond is possible, in **51** the two hydroxyl-groups are too far apart.

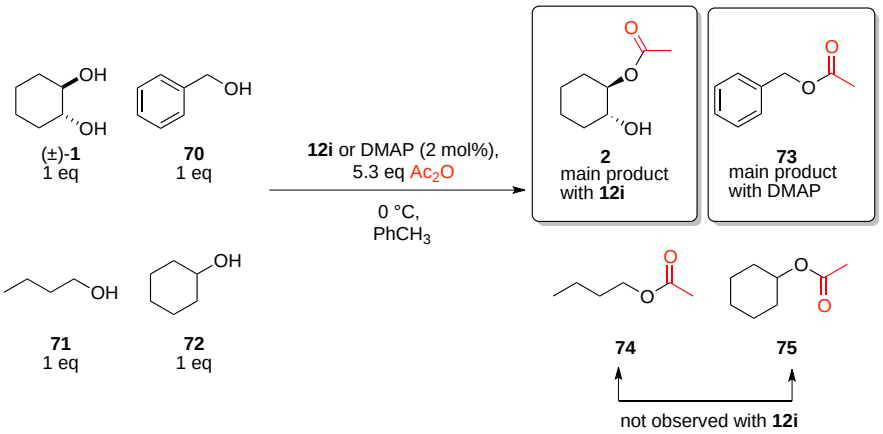
Chemoselectivity of 12i

The outstanding performance of catalyst **12i** for vicinal diols implies high chemoselectivity, which underlines the close relationship to natural catalysts, e.g., enzymes. Of course, high chemoselectivity is often undesirable in synthetic chemistry, which normally strives for broad substrate scope. However, highly chemoselective catalytic processes are interesting for

one-pot reactions, wherein various chemicals are present in the reaction mixture. This is typically the case for domino,[104] tandem,[104,105,106] or cascade[105,106] reactions and becomes even more important for multicatalytic reactions.[65,66,69,70,107] Additionally, this approach could be a useful tool for the site-selective acylation of, e.g., polyols.

We performed competition experiments for the acetylation of chemically different alcohols with **12i** to investigate the chemoselectivity of our best catalyst. For reasons of comparison we performed the same experiments with 4-dimethylaminopyridine (DMAP) in parallel. Initial studies showed that **12i** is capable of transferring acyl groups selectively to the (*R*,*R*)-enantiomer of *trans*-cycloalkane-1,2-diol **1** out of a mixture of alcohols **70**–**72** (Table 5). We used the optimized standard reaction conditions for the KR. The reaction was quenched after 1 h and analyzed by GC. In the presence of **12i** only esters **2** and **73** were observed. Ester **2** proved to be the main product; the *er* of the remaining diol (94% (*S*,*S*)-**1** and 6% (*R*,*R*)-**1**) indicates that indeed (*R*,*R*)-**1** is by far the most reactive compound in the mixture. In contrast, DMAP led to the formation of the esters **2**, **73**, and **74** with **73** being the main product. After 2 h all of the (*R*,*R*)-**1** enantiomer had been acetylated by **12i** and the catalyst showed higher activity towards **70** than to (*S*,*S*)-**1**. The reactivity for the acetylation of (*S*,*S*)-**1** and **72** by **12i** comparable.

Table 5. Yields (*via* GC/MS) of **2**, **73**, **74**, and **75** obtained in the competitive acetylation reaction.

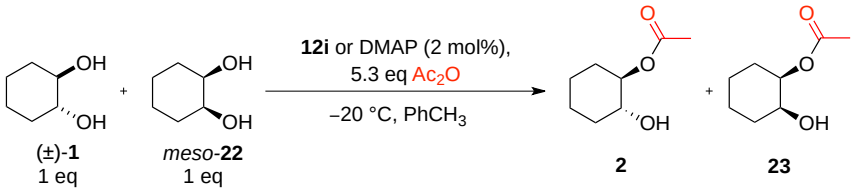


entry	cat.	*t* (h)	yield (%) of **2**	yield (%) of **73**	yield (%) of **74**	yield (%) of **75**
1	**12i**	1	59	traces	-	-
2	**DMAP**	1	traces	22	traces	-
3	**12i**	2	65	15	traces	-

entry	cat.	*t* (h)	yield (%) of **2**	yield (%) of **73**	yield (%) of **74**	yield (%) of **75**
4	**DMAP**	2	31	36	13	-
5	**12i**	5	72	32	traces	-
6	**DMAP**	5	59	68	20	-

Catalyst **12i** can also differentiate between *cis* and *trans*-cyclohexane-1,2-diol; the acetylation of a 1:1 mixture of **1** and **22** resulted in a ratio of 84:16 (**2**/**23**) after 3 h. In contrast, DMAP proved to be less active and showed only a marginal preference for the *trans*-diol. The results for **12i** (Table 6) are remarkable because both diols should have comparable nucleophilicities and differ only in the configuration of the OH-groups. We conclude that stronger hydrogen-bond interactions between (*R*,*R*)-**1** and **12i** compared to (*S*,*S*)-, (*R*,*S*)- and (*S*,*R*)-**1** and the catalyst are responsible for its preferential acetylation. The structure of (*R*,*R*)-**1** seems to fit perfectly into the "pocket" formed by **12i**. This extraordinary high chemo- and enantioselectivity is an astonishing feature for a small molecule.

Table 6. Concurrent and competitive acetylation of *trans*-diol (±)-**1** and *meso*-diol **22** with catalyst **12i** and DMAP.



entry[a]	cat.	*t* (h)	*C* (%) to **2**[b]	*er*[b] **2**	*C* (%) to **23**[b]	ratio **2**:**23**[b]
1	**12i**	1.5	23	94:6	3	87:13
2	DMAP	1.5	5	50:50	4	56:44
3	**12i**	3	31	91:9	6	84:16
4	DMAP	3	9	50:50	7	56:44
5[b]	**12i**	4.5	36	85:15	11	77:23
6[c]	DMAP	4.5	15	50:50	12	55:44
6[c]	**12i**	7.5	38	80:20	15	72:28
7[b]	DMAP	22	20	50:50	16	55:44

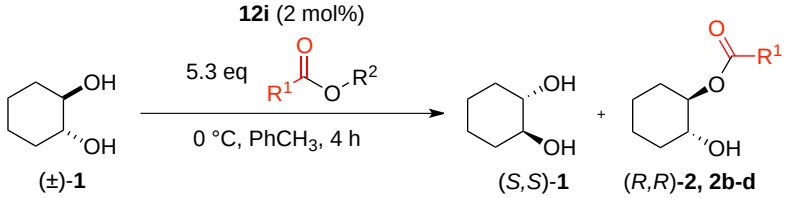
[a]Reactions performed at –20 °C in 4.5 mL toluene with 1 eq of racemic substrate **1** (0.025 mmol, 2.9 mg) and *meso* substrate **22** (0.025 mmol, 2.9 mg), 5.3 eq acetic anhydride, and 2 mol% **12i** or DMAP. Without catalyst no conversions were observed. [b]Conversions *C*, *er* values, and the **2**:**23** ratios were determined by chiral GC analysis.

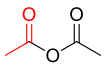
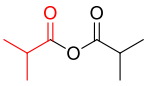
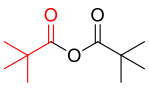
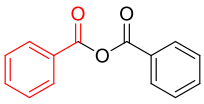
Alternative Electrophiles in Group Transfer Reactions Catalyzed *via* Peptide 12i

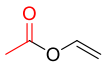
In addition to acetic anhydride we tested a wide range of electrophiles in KRs and desymmetrization experiments. First of all, we investigated the role of the electrophile by determining the activity and selectivity of **12i** in the KR of *rac*-**1** using various acyl donors (Table 7). All anhydrides reacted with 1 to give the corresponding monoesters in good yields; in contrast with vinyl acetate as electrophile (mainly used in combination with enzymes) no conversion was observed. Acetyl chloride provided only 5% of the monoacetylated product after 4 h and resulted in no enantioselectivity neither for the starting material nor for the product (the background reaction led to similar conversions in the same time). The finding that acyl chlorides, though they generally have higher carbonyl reactivities than anhydrides, are less reactive in acetyl transfer reactions catalyzed by the nucleophilic catalysts (DMAP) is common.[108,109] Steglich *et al*. investigated the acetylation of 1-ethinylcyclohexanol with DMAP and found that acetyl chloride reacted three times more slowly than acetic anhydride, though the equilibrium amount of the *N*-acetyl-pyridinium salt is significantly higher.[110] This finding implies that the acetyl-transfer from the *N*-acetyl-DMAP salt onto a hydroxyl-group is highly affected by the counterion of the acylating agent and the auxiliary base.[111] Albert *et al.* also reported the acetylation of 1-propanol with acetyl chloride and acetic anhydride catalyzed by DMAP in the presence of K_2CO_3 and pyridine as auxiliary base.[112] With pyridine, acetyl chloride reacted very rapidly ($t_{1/2}$ = 10 s), whereas acetic anhydride was significantly slower ($t_{1/2}$ = 11 min). In contrast utilizing K_2CO_3, which is insoluble in $CHCl_3$, the reaction rates were reversed (acetyl chloride $t_{1/2}$ = 35 min; acetic anhydride $t_{1/2}$ = 3.2 min). It was proposed that the reactivity can be contributed to the basicity of the generated counterion, which can act as a general base catalyst and deprotonate the nucleophile in the transition state.[113,114] In the presence of a homogeneous base like pyridine, the auxiliary base or the counterion can perform the proton-transfer, whereas the insoluble K_2CO_3 does not take part in the deprotonation. The importance of the counterion was also confirmed by computations utilized by Zipse *et al.* It was found that the counterion and its interaction with the catalytically active *N*-acetyl-pyridinium cation is important for the deprotonation of the substrate.[111,113,114] Additionally, Lutz *et al.* investigated the structure of the *N*-acetyl-DMAP salt by X-ray, NMR- and IR-spectroscopy.[111] Surprisingly no evidence for the formation of a “tight” ion pair for the *N*-acetyl-pyridinium chloride was found, but in the case of *N*-acetyl-pyridinium acetate the analysis of the X-ray data, as well as the computations confirmed a “tight” ion pair. The acetate seems to have hydrogen-bond interactions with the hydrogen at the C2 position of the pyridinium-ring and the hydrogen of the acetyl-group of the *N*-acetyl-moiety at the catalyst.[111] Under our reaction conditions with

no additional base the proton transfer has to be accomplished by the counterion and therefore acetic anhydride reacts faster. With acetyl chloride the catalysts is likely to be protonated by the *in situ* generated hydrogen chloride, but even with additional base (5.3 eq D^{i}PEA) the reaction is much slower and rather unselective. The reaction with acetic or isobutyric anhydride proved to be fast compared to the sterically more hindered benzoic anhydride and pivalic anhydride (Table 7). The use of acetic anhydride and isobutyric anhydride led to high selectivities (S >50 for acetic anhydride, *S* = 41 for isobutyric anhydride), whereas for benzoic anhydride (*S* = 8) and pivalic anhydride (*S* = 5) only moderate selectivities were observed.

Table 7. KR of *trans*-diol (±)-**1** with peptide catalyst **12i** using various acyl donors.

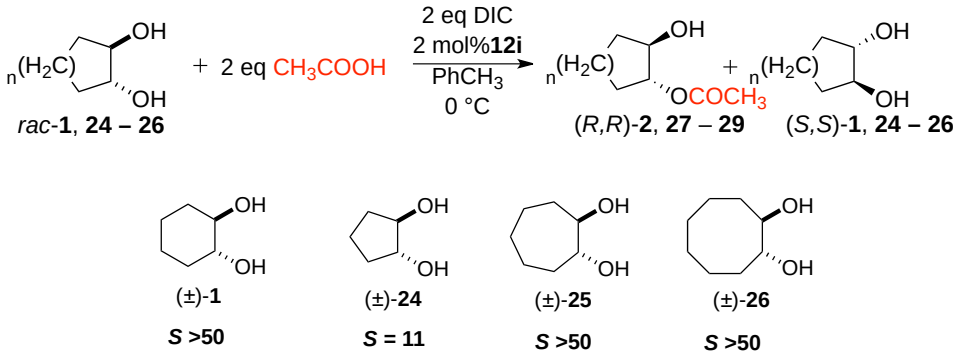


entry[a]	electrophile	ester	*C* (%)[b]	*ee* (%)[c] (*R*, *R*)-**2**	*ee* (%)[c] (*S*, *S*)-**1**	*S*[b]
1		**2**	57	75	>99	>50
2		**2b**	59	71	>99	41
3		**2c**	2	64	2	5
4		**2d**	5	76	4	8
5		**2**	5	–	–	1
6[d]		**2**	27	12	32	2.2

entry[a]	electrophile	ester	*C* (%)[b]	*ee* (%)[c] (*R*, *R*)-**2**	*ee* (%)[c] (*S*, *S*)-**1**	*S* [b]
7		**2**	–	–	–	–

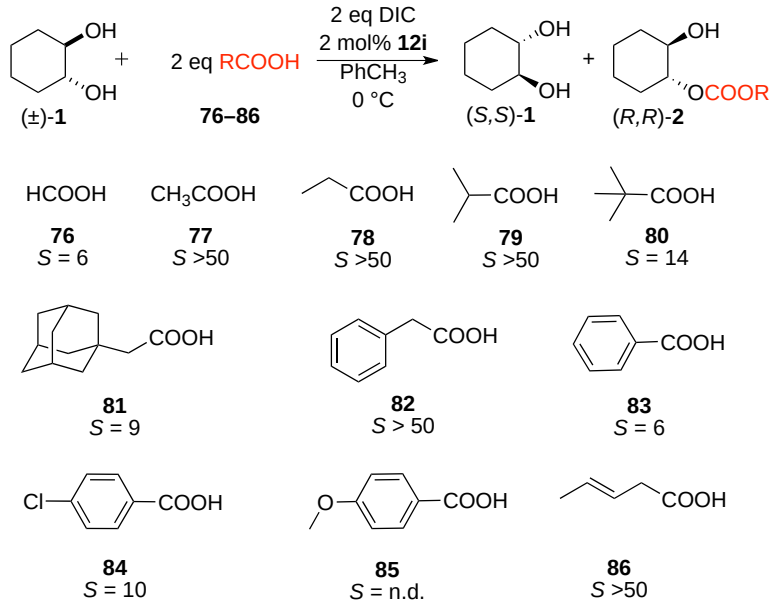
[a]All reactions were performed at 0 °C in 4.5 mL toluene, 1 eq of racemic substrate **1** (0.025 mmol, 2.9 mg), 5.3 eq of the electrophile, and 2 mol% of catalyst (purified *via* HPLC) **12i**. Without catalyst no conversions were observed. [b]*S*-values and conversions determined using the procedure of Kagan and Fiaud.[63] [c]*Ee*-values were determined by chiral GC analysis. [d] The reactions was performed at 0 °C in 4.5 mL toluene, 1 eq of racemic substrate **1** (0.025 mmol, 2.9 mg), 5.3 eq of the electrophile, 2 mol% of catalyst **12i** and 5.3 eq D^{i}PEA.

The direct use of acids as electrophiles in acylation reactions was realized by using peptide **12i** and carbodiimides (DI) for the activation and *in situ* formation of the anhydrides from carboxylic acid precursor. This first enantioselective Steglich esterification protocol[68] was successfully applied to a wide range of acids using *trans*-cycloalkane-1,2-diols **1** and **24**–**26** (Scheme 7) as substrates and is a clear advantage, especially, when the corresponding anhydrides (as, for example, for formic acid) are not stable or not readily available (e.g., phenylacetic acid).



Scheme 7. KR of cyclic *trans*-1,2-diols with acetic acid as electrophile.

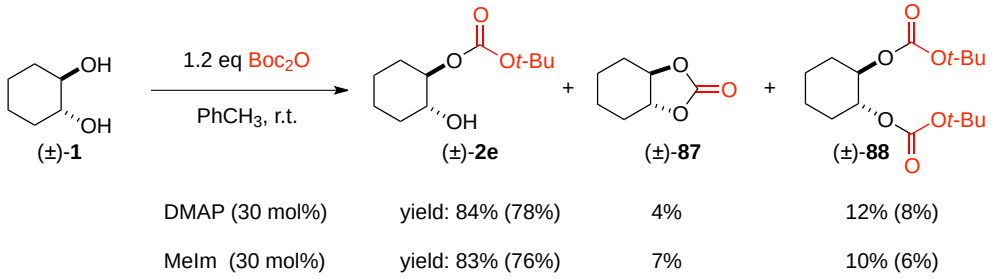
High selectivities and *S*-values >50 were observed for acetic acid **77**, propionic acid **78**, isobutyric acid **79**, phenylacetic acid **82**, and **86**. Accepting lower enantioselectivities and conversions this procedure is also applicable to the acids **76**, **80**, **81**, **83**, and **84** (Scheme 8).[68]



Scheme 8. KR through enantioselective Steglich esterification of *trans*-cyclohexane-1,2-diols **1** using various acids.[69]

The steric demand of the electrophile affects the selectivity as well. KR with acetic acid **77**, propionic acid **78**, isobutyric acid **79** and 3-pentenoic acid **86** catalyzed by **12i** are highly selective, whereas the steric demand for pivalic acid **80** seems to be too high and the selectivity decreases. Higher selectivity was found when the bulky moiety is in the β-position to the acid group (**82**), but a very bulky group like adamantyl (**81**) decreases the selectivity again. The lowest selectivity was observed for benzoic acid (**83**, **84**, and **85**), because of higher stability of the imidazole/benzoylium ion intermediates.

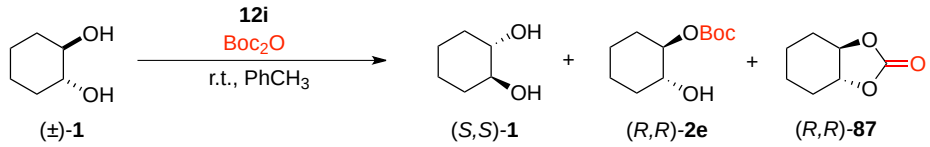
Other electrophiles such as di-*tert*-butyl dicarbonate (Boc_2O), diphenylchlorophosphate and various benzenesulfonyl chlorides were used as electrophiles in the KR of (±)-**1** with **12i**. Miller *et al.* reported the selective sulfonylation (benzenesulfonyl chlorides)[115] and phosphorylation (diphenylchlorophosphate)[31,116,117] mediated by π-(Me)-histidine containing peptides and achieved for the phosphorylation of a *meso*-inositol derivative an *ee* of 98% in 65% yield. The selective sulfonylation of various functionalized *meso*-1,3-diols was accomplished in high yields and good selectivities (yield up to 76%; *er* up to 97:3).[115] The reactivity of Boc_2O towards alcohols and diols in the presence of 4-(dimethylamino)pyridine (DMAP) and *N*-methylimidazole (MeIm) has been reported by Hassner *et al.*[118] The transfer of the Boc-group onto (±)-**1** was tested utilizing 30 mol% DMAP (30 mol% *N*-methylimidazole) and 1.2 eq of Boc_2O (Scheme 9).



Scheme 9. Reaction of DMAP and MeIm with Boc_2O with diol *rac*-**1** leading to *O*-Boc-**2e**, *O,O*-di-Boc-product **88** and the cyclic carbonate **87**. Yields were determined by GC-MS; isolated yields are given in parenthesis.

While the monoacetylated diol (*R,R*)-**2** is the only product of the acylation reaction, the reaction with Boc_2O is more complex and three products were obtained by the DMAP and MeIm catalyzed reaction (Scheme 9). Therefore the KR of (±)-**1** with Boc_2O required optimization (Table 8).

Table 8. KR of *trans*-cyclohexane-1,2-diol **1** with Boc_2O using various reaction conditions.



entry[a]	cat. **12i** (mol%)	*t* (h)	*C* (%)	Boc_2O (eq)	*er* (*S,S*)-**1**[c]	*er* (*R,R*)-**2e**[c]	*er* (*R,R*)-**87**[e]	*S*[d]
1	2	58	30	1	80:20	15:85	17:83	10.3
2	2	58	30	2	64:36	18:82	17:83	6.3
3	2	36	60	5.3	95:5	18:82	22:78	11.7
4	2	16	58	10	83:17	24:76	28:72	6.2
5	5	16	50	5	80:20	20:80	20:80	7.2
6	10	21	54	2	87:13	18:82	-	9.6
7	5	102	50	2	86:14	14:86	-	12.8

entry[a]	cat. **12i** (mol%)	*t* (h)	*C* (%)	Boc_2O (eq)	*er* *(S,S)*-**1**[c]	*er* *(R,R)*-**2e**[c]	*er* *(R,R)*-**87**[e]	*S*[d]
8[b]	10	192	50	2	76:24	24:76	traces	5.2

[a]All reactions performed at room temperature in 4.5 mL dry toluene. [b] This reaction was carried out at 0 °C in 4.5 mL dry toluene. [c] Yields and enantiomer ratios were determined by chiral GC analysis. [d] *S*-values (selectivity factors) determined by the method of Kagan and Fiaud.[63]

In principle, the enantioselective transfer of the Boc-group with **12i** is possible but the reaction requires different conditions compared to the acylation reaction. While the acylation reactions are most efficient using a large excess of Ac_2O (5.3 eq) at low temperature (0 °C), the transfer of the Boc-group works best at room temperature, with 2 eq of Boc_2O and 5 mol% of **12i**. The use of a very large amount of Boc_2O increases the yield of the undesired cyclic carbonate **87**, whereas higher temperatures and higher catalysts loadings decrease the yield of **87**.

The generation of the *O*-Boc protected diol **2e** is catalyzed by **12i**, whereas the formation of the cyclic carbonate **87** only occurs in the presence of a strong base. The reaction mechanism implies that the formation of the *tert*-butoxide during the catalytic cycle probably removes the proton from the second alcohol functionality and therefore promotes cyclization to the cyclic carbonate **87** (Figure 10).[118] Evidence for this proposal comes from the finding that **2e** does not cyclize to **87** in solution even in the presence of catalyst **12i**. In contrast, addition of Boc_2O to the solution gives only the cyclic carbonate **87**.

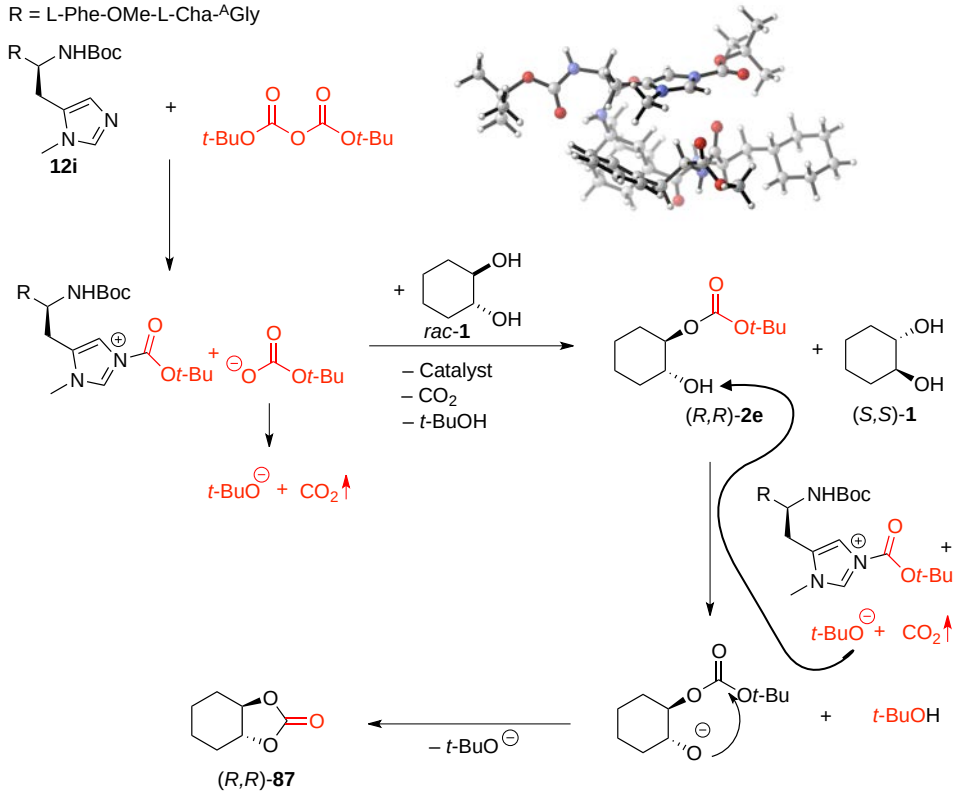


Figure 10. Proposed mechanism of the KR of *trans*-cyclohexane-1,2-diol with Boc_2O and the reoptimized (M06–2X/6–31+G(*d,p*)) structure of the catalyst/*tert*-butoxycarbonylium-adduct.

Using less Boc-anhydride minimized the formation of *tert*-butoxide and the rate of cyclization of **2e** decreased. A catalyst loading of 5 mol% and higher temperature accelerates the reaction and avoids the generation of **87**.

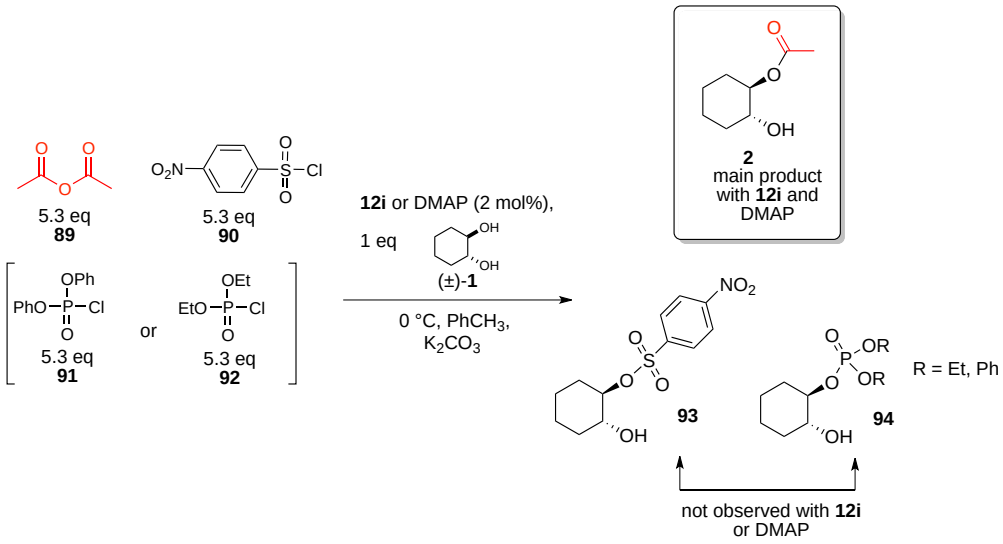
As peptide catalyst **12i** is capable of transferring a variety of acyl anhydrides and Boc-anhydride enantioselectively, we envisioned that the enantioselective transfer of other electrophiles such as diphenylchlorophosphate and various benzenesulfonyl chlorides would also be possible. Although sulfonylation reactions are widely used in organic synthesis, catalytic asymmetric sulfonyl transfer reactions are rare.[72,115] The KR of *trans*-cyclohexane-1,2-diol with various benzenesulfonyl chlorides were therefore examined. Much to our dismay, *p*-Cl- and *p*-CH_3-benzenesulfonyl chlorides gave no reaction while *p*-nitrobenzenesulfonyl chloride unselectively provided 14% of the monosulfonylated-*trans*-1,2-cylohexanediol and 8% of the disulfonylated- *trans*-1,2-cylohexanediol after 24 h at r.t.

Phosphoryl group transfer plays an important role in natural processes like cell signaling pathways. Histidine containing kinases transfer the phosphoryl group to other nucleophiles. Miller *et al.* successfully applied a histidine containing peptide catalyst in the asymmetric phosphorylation of *myo*-Inositol.[31,116,117] The phosphorylation of *trans*-cyclohexane-1,2-diol

mediated by **12i** utilizing $POCl(OPh)_2$ under optimized reaction conditions (10 mol% **12i**, 1 eq $POCl(OPh)_2$, 1 eq Et_3N, r.t., $PhCH_3$) unfortunately, unselectively yielded 32% of the monophosphorylated product.

To test again chemoselectivity (this time for the electrophile), we performed a competition experiment using different electrophiles (Ac_2O, $POCl(OPh)_2$ or $POCl(OEt)_2$ and *p*-NO_2-SO_2Cl) for the functionalization of *rac*-**1**. The progress of the reaction was monitored *via* GC-MS and TLC. For reasons of comparability **12i** and DMAP were used as catalysts in parallel runs (Table 9).

Table 9: Competitive functionalization of *rac*-**1** with **12i** and DMAP.



entry	Cat.	t (h)	C (%)[c]	*er* (%) of **1**[c]	*er* (%) of **2**[c]	*S*
1[a]	**12i**	1	48	85:15	13:87	14
2[b]	**DMAP**	1	16	50:50	50:50	-
3[a]	**12i**	2	50	86:14	14:86	13
4[b]	**DMAP**	2	18	50:50	50:50	-
5[a]	**12i**	3	53	90:10	15:85	14
6[b]	**DMAP**	3	20	50:50	50:50	-
7[d]	**12i**	1	51	93:7	8:92	32

[a] *S*-values and conversions *C* determined using the procedure of Kagan and Fiaud.[63] [b] Conversions were determined by GC-MS analysis. [c] *Er* values were determined by chiral GC analysis. [d] Reaction was performed with 5.3 eq Ac_2O in absence of other electrophiles.

After 1 h **12i** nearly consumed all of (*R*,*R*)-**1** (*C* = 48%). The DMAP catalyzed reaction is slower and only provided 16% yield after 1 h. Under optimized reaction conditions only **2** was observed with both catalysts. K_2CO_3 was used as base to avoid the protonation of the catalyst. The selectivity of the competitive functionalization experiment (*S* = 14) is lower compared to the acylation experiment (*S* = 32), but still good. These results show the capability of **12i** to selectivelly acylate *rac*-**1** in the presence of other electrophiles.

Multicatalytic approaches utilizing a modified peptide backbone of 12i

Oligopeptides are excellent platforms for multicatalysts due to the acessability of various natural and non-natural amino acids bearing different functional groups.[65] Therefore we also tested the selectivity for peptides with a second catalytically active amino acid (Figure 11).

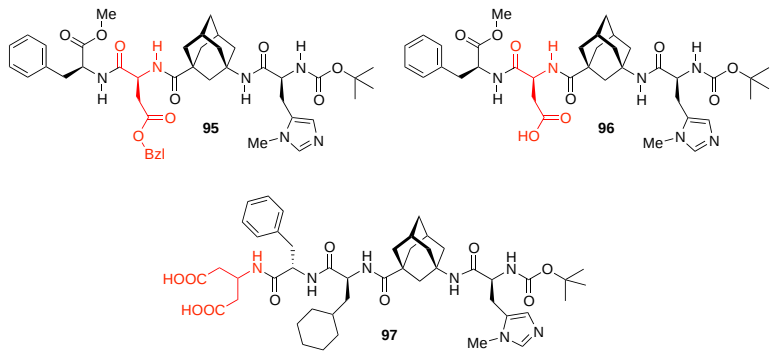


Figure 11. Catalysts **22–24** were synthesized to investigate the influence of a second catalytically active moiety on the selectivity for the KR of *rac*-**1** .

The incorporation of Asp (free carboxylic acid) in the *i*+2 position of the peptide lowered the selectivity of **96** drastically, while the functionalization of the *C*-terminus at the *i*+4 position (**97**) still yielded good *ee*'s. An explanation of this finding may be that the addition of CH_2Cl_2 was required due to poor solubility of **96** in toluene. Additionally, the acidic moiety near the π-Me-His may affect the acyl transfer *via* interacting with the counterion of the acylating agent and however changing the transition state of the selective acyl transfer or by simple intramolecular ion-pairing.[77] Its protected analog **95** in contrast showed a moderate *S*-value (Table 10; entry 1).

Table 10. KR of (±)-**1** with catalysts **95**–**97**.

entry[a]	cat.	*t* (h)	*C* (%)[d]	*ee* (%)[d] (*R*, *R*)-**2a**	*ee* (%)[d] (*S*, *S*)-**1**	*S*[c]
1	**95**	5	56	59	76	9
2[b,e]	**96**	3	45	35	28	3
3[e]	**97**	17	55	60	92	13

[a]All reactions were performed at 0 °C in 4.5 mL toluene with 1 eq of racemic substrate **1** (0.025 mmol, 2.9 mg), 5.3 eq of acetic anhydride, and 2 mol% of **95–97** in toluene. Without catalyst no conversions could be observed. [b]CH_2Cl_2 was added because of the poor solibility of the catalyst. [c]*S*-values and conversions *C* determined using the procedure of Kagan and Fiaud.[64] [d]*Ee* values were determined by chiral GC analysis. [e]Additionally 5.3 eq of $^{i}Pr_2EtN$ were added.

The finding that the amino acid at the *i+3* position of the peptide does not highly affect the selectivity of the KR of *rac*-**1** offered the application of multicatalytic approaches. First attempts were made by replacing the methyl ester *C*-terminus of the peptide by a TEMPO-amide functionality. Hence, the direct oxidation of the rapidly racemizing substrates **38–42** to the configurationally stable α-acetoxy-ketones were enabled (Figure 12). Multicatalyst **96** showed remarkably high oxidation activity and therefore the amount of TEMPO, *m*-CPBA and $^{t}Bu_4NBr$ could be dramatically decreased compared to TEMPO itself (5 mol% vs. 60 mol%; 3.0 eq vs. 8.0 eq and 5 mol% vs. 30 mol%).[67,69]

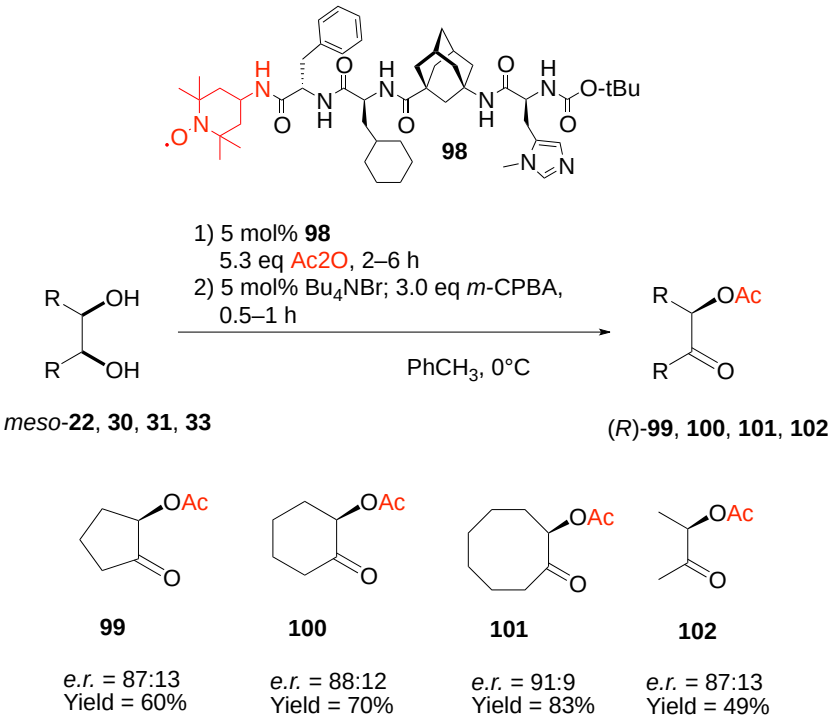
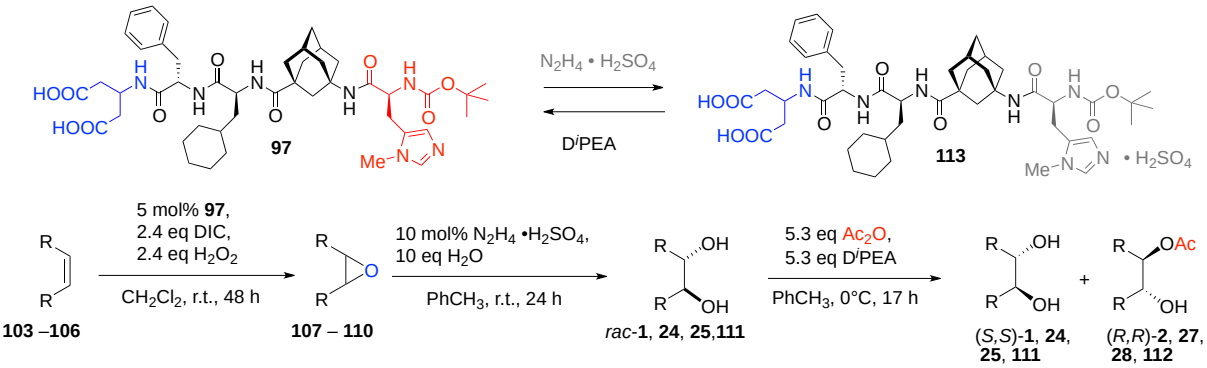


Figure 12. Enantioselective one-pot acylation and oxidation of *meso*-1,2-diols.

One of the most challenging topics in organic chemistry is the synthesis of complex molecules out of simple building blocks in few steps. Hence, we added a β-aspartate moiety (as an epoxidation catalyst) at the *i*+4 position to peptide **12i** and utilized symmetric alkenes as starting materials. The β-aspartate in combination with DIC and H_2O_2 forms the epoxide from the alkene, the addition of hydrazine sulfate forms a salt (**113**) and opens the epoxide to the *trans*-1,2-diol, which finally is selectively acetylated by (π-Me)-histidine.[70]

Table 11: Synthesis of monoacetylated diols from alkenes by a multicatalytic approach.



entry	alkene	Yield (%) of diol	Yield (%) of ester	*ee* (%) of diol	*ee* (%) of ester	S^c
1	**103**	29	26	64	46	5
2	**104**	34	35	92	60	13
3	**105**	19	24	99	68	26
4	**106**	19	21	86	68	14

[a] *S*-values and conversions *C* determined using the procedure of Kagan and Fiaud.[63] [c] *Ee* values were determined by chiral GC analysis.

These two examples show the high potential of multicatalytic approaches and that oligopeptides can serve as excellent platforms for the development of new multicatalysts in future.

Conclusion and Outlook

We identified the highly chemo- and enantioselective peptide catalyst **12i** for acyl transfer onto racemic alkane-1,2-diols. In contrast to common peptide design approaches **12i** does not display a preferred secondary structure but instead recognizes the diols in a dynamic binding event of the acylium cation complex involving hydrogen bonding and dispersion interactions.

Anhydrides proved to be the most efficient acyl source. Hence, we introduced the first enantioselective Steglich esterification utilizing carboxylic acids as acylating agent from

which the anhydrides are generated *in situ*. Competitive experiments for substrates and electrophiles show extraordinary chemoselectivity for cyclic *trans*-alkane-1,2-diols as the substrate and acetic anhydride as the electrophile. Such a narrow substrate scope is usually only observed for enzymes or generally much larger molecules. It is therefore a rather surprising finding that a short oligopeptide such as **12i** mimics the behavior of structures that are typically by orders of magnitude more complex, but with the advantage that both substrate enantiomers can selectively be acetylated.

Such exquisite chemoselectivity is the basis for multicatalytic approaches that are now being realized. These provide high potential for rapidly reaching molecular complexity from simple starting materials in one pot, not requiring protective group chemistry. In the future, we will attempt to directly address specific hydroxyl groups in polyols.

ACKNOWLEDGMENT. This work was supported by the Deutsche Forschungsgemeinschaft (SPP1179) and Alexander-von-Humboldt foundation (fellowship to RH). We thank Christian B. W. Stark (University of Hamburg) for supplying substrate **67** and Yannick Landais (ISM, Université Bordeaux-1) for providing **47**. Additionally we thank J. Romański for the synthesis of **51**, **54** and **57**.

4. Investigation of a Secondary Structure of Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (12i) *via* NMR- and IR-Spectroscopy

Secondary structure plays an important role in the concept introduced by Miller. The use of proline enabled the formation of a *β*-hairpin structure, fixed by two intramolecular hydrogen bonds that seem to be responsible for the selectivity. NMR-titration-, IR- and NOE-experiments were utilized and clear evidence for the existence of the proposed hydrogen bonds was found.[46,48] For the determination of a possible secondary structure of **12i** we utilized the same spectroscopic methods.

A useful method for the identification of intramolecular H-bonding is IR spectroscopy. Gellman has established IR-spectroscopy as a tool for the determination of intramolecular amide-amide hydrogen bonds of peptides in dichloromethane. Sharp signals in the N–H stretching region at 3460 – 3450 cm^{-1} were assigned to non-hydrogen bonded N–H, whereas broad signals at 3330 – 3300 cm^{-1} were assigned to internal hydrogen bonds.[82]

We performed IR-experiments at various temperatures using a 13 mM solution of **12i** in $CDCl_3$. In order to investigate H-bonding interactions we chose $CDCl_3$ as the solvent because of its moderate polarity and the high solubility of **12i**. At r.t. only one sharp signal at 3460–3450 cm^{-1}, assigned to non-hydrogen bonded N–H groups, was observed. While reducing the temperature from 298 K to 233 K in steps of 10 K, a new broad signal at 3300 cm^{-1} appeared, its intensity increasing with decreasing temperatures (Figure 13). This is an indication for an intramolecular hydrogen bond at temperatures below 253 K.

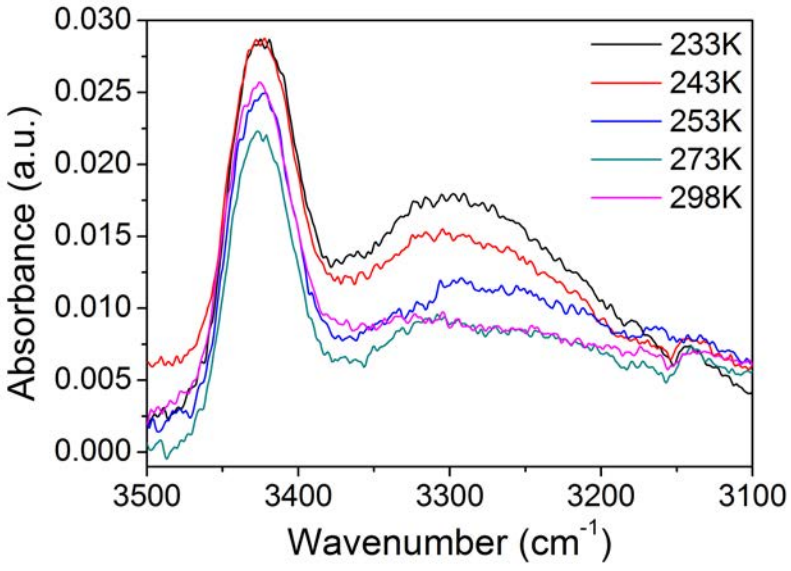


Figure 13: IR-spectra of **12i** in $CDCl_3$ at different temperatures.

We measured NOE-NMR-spectra of the homoconfigured peptide **12i** in d_8-toluene and $CDCl_3$, but only predictable NOE-signals for the vicinal amino acids were obtained. We also measured the chemical shift dependence of the N–H groups in $CDCl_3$ as a function of increasing the d_6-DMSO concentration. In the absence of hydrogen bonds all N–H groups should show significant downfield shifts (Figure 14). In the case of **12i**, we observed a downfield shift in the range of 0.4–1.0 ppm for Phe(NH), Cha(NH), ^{A}Gly(NH) and π-(Me)-His(NH)). This indicates the absence of intramolecular hydrogen bonds for **12i** in $CDCl_3$ at r.t.

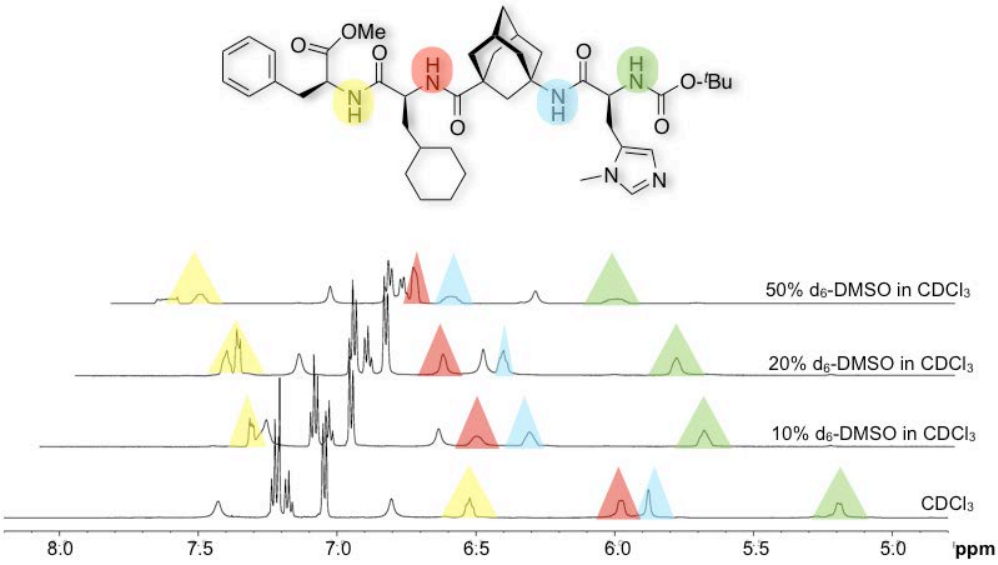


Figure 14: Chemical shifts for the NH-protons of **12i** in $CDCl_3$ at different concentrations of d_6-DMSO.

The selectivity for the KR of **1** utilizing **12i** is highly influenced by the solvent (CH_2Cl_2, S = 9.6; CH_3CN, S = 2.4; $PhCH_3$, S > 50)[60] and therefore the low temperature IR-experiments were repeated in d_8-toluene. Here, in contrast to $CDCl_3$, a broad signal at 3300 cm^{-1} with a higher intensity than the signal at 3450 cm^{-1} was observed at r.t. Unfortunately, no low temperature IR-spectra could be measured because of the low solubility of the peptide **12i** in d_8-toluene. The IR-intensity of hydrogen bond is affected by temperature and their strength decreases with increasing temperature. Hence, we measured an IR-spectrum at 313 K and, as expected, the intensity of the signal assigned to intramolecular hydrogen bonds decreased while the intensity for the signal at 3450 cm^{-1} (indicating free N–H-bonds) increased (Figure 15). These results show the presence of hydrogen bonds in d_8-toluene at r.t. However, this method is not suitable to differentiate between intramolecular and

intermolecular hydrogen bonding. As mentioned before, **12i** is only poorly soluble in d_8-toluene and aggregation of **12i** in a non-polar solvent is possible.

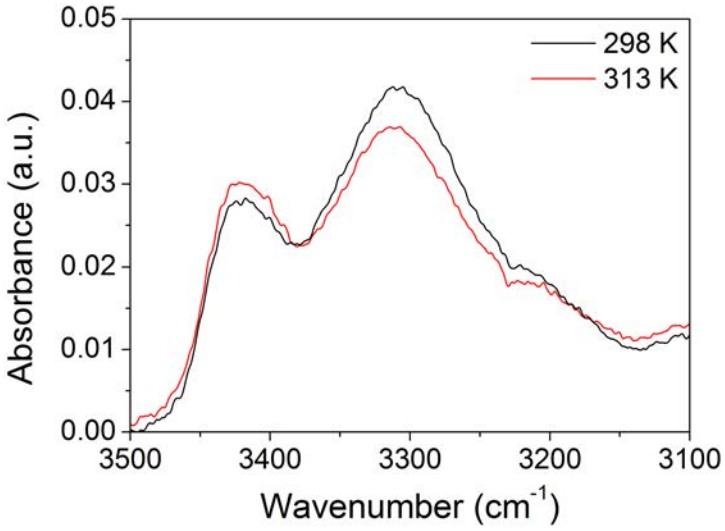


Figure 15: IR-spectra of **12i** in d_8-toluene at different temperatures.

For that reason, we performed IR-measurements at different concentrations. Upon lowering the concentration from 30 mM over 15 mM to 7.5 mM, the intensity of both signals (3450 cm^{-1} and 3300 cm^{-1}) decreased (Figure 16). The loss of intensity for the signals assigned to intramolecular hydrogen bonds is more profound compared to the signal assigned to free N–H-bonds, but the respective signal does not disappear completely. In d_8-toluene a combination of intra- and intermolecular hydrogen bonds seems to be responsible for the high intensity of the signal at 3300 cm^{-1}.

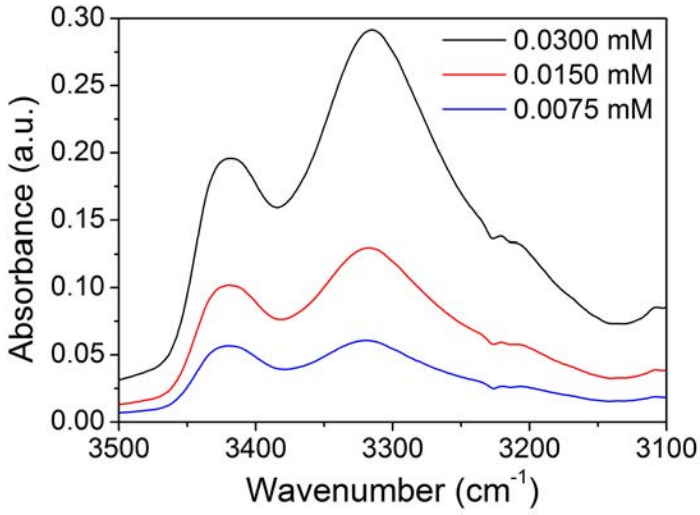


Figure 16: IR-spectra of **12i** in d_8-toluene at different concentrations.

In order to verify this result, chemical shifts of the NH-protons of **12i** (*c* = 26 mM) in d_6-benzene with different concentrations of d_6-DMSO were measured. The NMR-solvent was changed from d_8-toluene to d_6-benzene as for d_6-benzene only one signal is observed at δ = 7.27 ppm in the NMR-spectrum and overlap with shifting NH-protons can be minimized. The addition of 10% of d_6-DMSO induced a downfield shift of 0.5 ppm for His-NH, of 0.15 ppm for Phe-NH and of less than 0.1 ppm for Cha- and ^{A}Gly-NH (Figure 17). The nearly invariant shifts of Cha-NH, Phe-NH and ^{A}Gly-NH indicate hydrogen bonds, but the rigidity of the ^{A}Gly makes hydrogen bonds between Cha-NH and ^{A}Gly-NH with keto-groups of other amino acids unlikely. This finding may be explained by the rather high concentration of **12i** (*c* = 26 mM) and the presence of intermolecular hydrogen bonds due to aggregation in non-polar solvents. Up to date no clear evidence for a secondary structure was found.

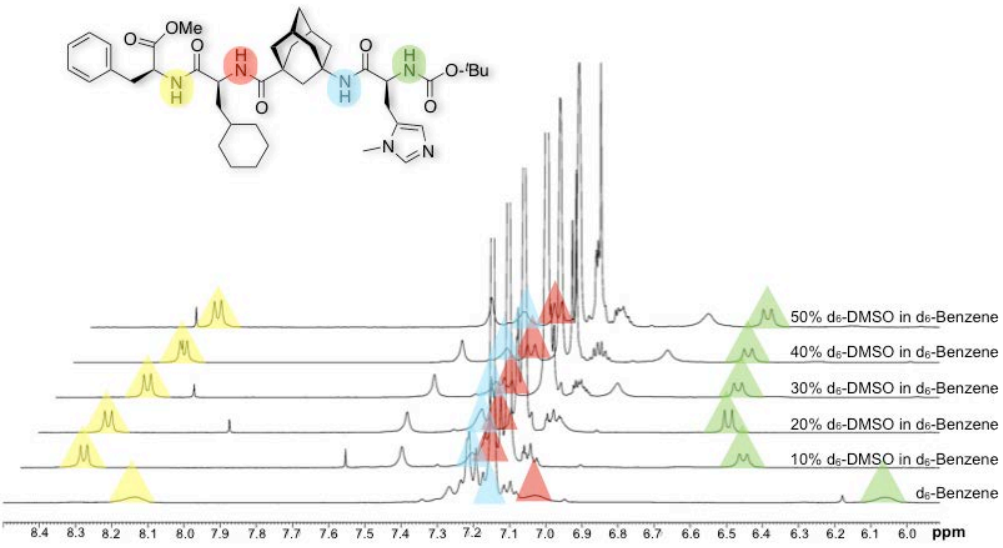


Figure 17: Chemical shifts for the NH-protons of **12i** in d_8-toluene at different concentrations of d_6-DMSO.

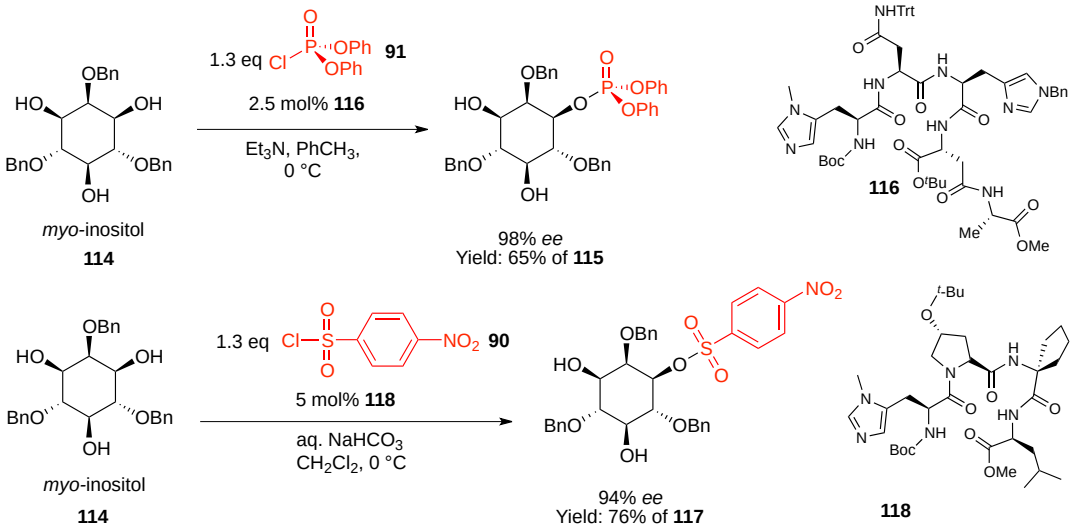
5. Transfer of Different Electrophiles Utilizing Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (12i)

5.1 Asymmetric Phosphorylation- and Sulfonylation-Reactions Mediated by Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (12i)

The KR of *rac*-**1** was tested under standard conditions (2 mol% **12i**, 5.3 eq acylating agent, toluene, 0 °C) utilizing acetyl chloride as the acyl source. It is known from literature that the counterion can have a great influence on both the reaction rate and selectivity. Acetyl chloride provided only 5% of the monoacylated product after 4 h and resulted in no enantioselectivity neither for the starting material nor for the product (the background reaction led to similar conversions in the same time) in the absence of base, because the catalyst gets protonated by the generated HCl. Hence, the KR of *rac*-**1** was repeated under the same conditions adding 5.3 eq D^{i}PEA as homogeneous base to avoid the protonation of the catalytically active π-methyl histidine moiety. Even with base the acyl transfer (AcCl) is much slower and less selective (*C* = 27%; *S* = 2.2) compared to the reaction with Ac_2O, because the background reaction cannot be fully suppressed under these reaction conditions. The finding that acyl chloride, although it has higher carbonyl reactivity than acetic anhydride, is less reactive in acyl transfer reactions catalyzed by the nucleophilic catalysts (DMAP) is very common and is further discussed in the Chapter 3.

As introductorily mentioned **12i** is capable of enantioselective acyl transfer onto *rac*-**1**.[25,60,68] Thus, the selectivity towards phosphoryl- and sulfonyl-transfer was investigated and briefly discussed in Chapter 3. In this chapter the details on these reactions will be described.

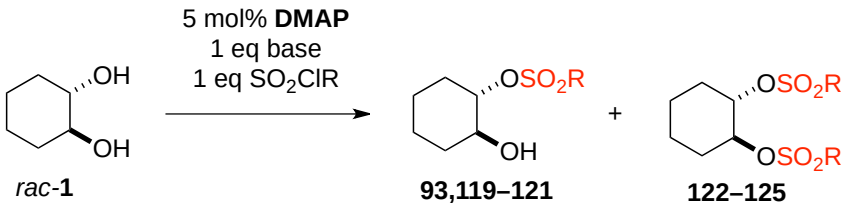
Miller *et al.* reported the selective sulfonylation (benzenesulfonyl chlorides)[115] and phosphorylation (diphenylchlorophosphate)[116,117] utilizing (π-Me)-histidine containing peptides and observed for the phosphorylation of a *meso*-inositol derivative **114** an *ee* of 98% with 65% isolated yield of **115** (Scheme 10). The selective monosulfonylation of various functionalized *meso*-1,3-diols was accomplished in high yields and good selectivities (**117** yield up to 76%; *er* up to 97:3).[115-117]



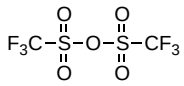
Scheme 10: Selective phosphorylation and sulfonylation of the *meso*-inositol derivative **114** reported by Miller *et al.*

As peptide catalyst **12i** is capable of transferring enantioselectively a variety of acyl-moieties utilizing anhydrides as acyl-source, we envisioned that the enantioselective transfer of other electrophiles such as diphenylchlorophosphate and various benzenesulfonyl chlorides would also be possible. Although sulfonylation reactions are widely used in organic synthesis, catalytic asymmetric sulfonyl-transfer reactions are rare. The sulfonylation of *rac*-**1** with various benzenesulfonyl chlorides was performed and optimized. Unfortunately, for *p*-Cl and *p*-CH_3-benzenesulfonyl chlorides no reaction could be observed (Table 12).
Other sulfonyl-based electrophiles like mesyl chloride and trifluoromethanesulfonic anhydride either reacted without addition of catalyst or various byproducts were observed and were therefore not further tested as sulfonylating agents.

Table 12: Sulfonyl-transfer onto *rac*-**1** mediated by **DMAP** with different bases.

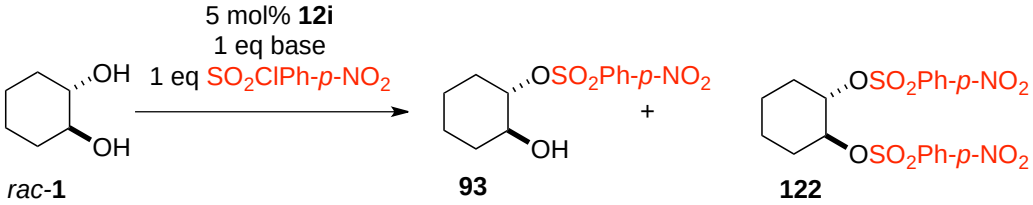


Entry	-R	Base	93, 119–121	122–125
1	-$PhCH_3$	2,6-lutidine	✘	✘
2	-$PhCH_3$	K_2CO_3	✘	✘

Entry	-R	Base	93, 119–121	122–125
3	-PhCl	2,6-lutidine	✘	✘
4	-PhCl	K_2CO_3	✘	✘
5	$-CF_3$	2,6-lutidine	✘	✘
6	$-CF_3$	K_2CO_3	✘	✘
7	$-PhNO_2$	2,6-lutidine	✔	✔
8	$-PhNO_2$	K_2CO_3	✔	traces
9		–	✘	✘

Hence, the reaction conditions for the *p*-nitrophenylsulfonyl-transfer were optimized. D^{i}PEA and 2,6-lutidine were able to catalyze the sulfonyl- transfer and therefore K_2CO_3 was utilized in the KR of *rac*-**1**.

Table 13: Sulfonyl-transfer onto *rac*-**1** mediated by **12i** with different bases.



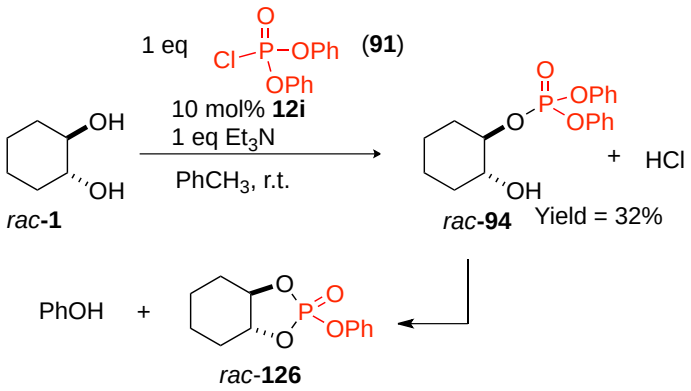
rac-**1** **93** **122**

Entry	Cat.	Base	94	120
1	**12i**	2,6-lutidine	✔	✘
2	–	2,6-lutidine	✔	✘
3	**12i**	D^{i}PEA	✔	✘
4	–	D^{i}PEA	✔	✘
5	**12i**	K_2CO_3	✔	✘
6	–	K_2CO_3	✘	✘

In the case of *p*-nitrobenzenesulfonyl chloride **90**, 14% of monosulfonylated-*trans*-cylohexane-1,2-diol **93** and 8% of disulfonylated-diol **122** were isolated after 24 h at r.t., but no *ee* was detected.

Phosphoryl-group transfer plays an important role in natural processes such as cell signaling pathways. Histidine containing kinases transfer phosphoryl-group to other nucleophiles.

The KR of *rac*-**1** mediated by **12i** utilizing $POCl(OPh)_2$ under optimized reaction conditions (10 mol% **12i**, 1 eq $POCl(OPh)_2$, 1eq Et_3N, r.t., $PhCH_3$) yielded 32% monophosphorylated product (Scheme 11). Unfortunately, no *ee* could be observed.



Scheme 11. KR of *rac*-**1** with diphenylchlorophosphate and catalyst **12i** under optimized conditions using 1 eq of Et_3N as base.

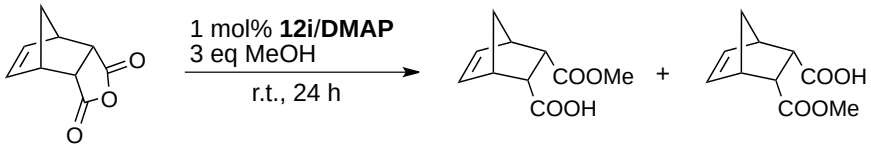
Aside from product **94-Ph,** phenol was detected by GC/MS in all cases. An explanation might be the cyclization of **94-Ph** to **126** (Scheme 11). Unfortunately, **126** could not be isolated. A similar reaction of a monophosphorylated 1,2-diol was reported by Haché.[119]

For further investigations of enantioselective phosphorylation reactions the use of $POCl(OEt)_2$ would be more convenient as no cyclization was observed and **94-Et** could be isolated in good yield (yield = 67%).

5.2 Enantioselective Ring Opening of *Meso*-Anhydrides Mediated by Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (12i)

The enantioselective ring opening of cyclic *meso*-anhydrides utilizing quinine/quinidine was reported by Bolm *et al*. (Introduction: Chapter 2.1.1.2.6).[120-122] Catalyst **12i** is capable of enantioselective acyl transfer onto *rac*-**1** and *meso*-**22** utilizing anhydrides as the acyl source. Hence, we tested **12i** in the enantioselective ring opening of cyclic *meso*-anhydrides. Without catalyst, only traces of hemiesters **128**/*ent*-**128** were observed.

Table 14: Ring opening of *meso*-anhydrides mediated by peptide **12i** under different reaction conditions.

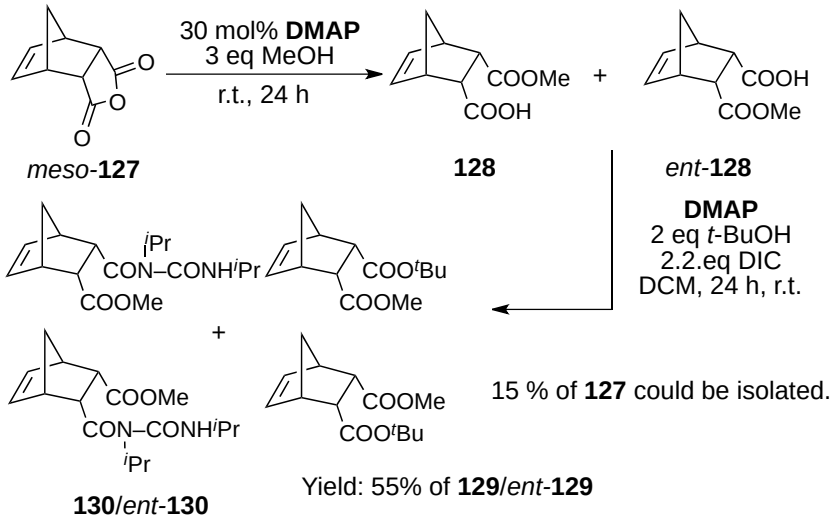


meso-**127** **128** *ent*-**128**

Entry	Cat.	Base	Solvent	*C* (%) to hemiester **128**/*ent*-**128**
1	–	–	toluene	traces
2	**12i**	–	toluene	50
3	**12i**	1 eq DBU	toluene	50
4	**12i**	1 eq MIm	toluene	50
5	**12i**	–	toluene/CCl_4 (1:1)	50
6	**12i**	1 eq Et_3N	toluene	50
7	**DMAP** (30 mol%)	–	toluene	50

Variation of the reaction conditions afforded only 50% of to the hemiester **128**/*ent*-**128** as observed by GC-MS (Table 14). A first hypothesis was that the catalyst is protonated by the generated acid moiety of the hemiester, therefore effectively halting the reaction. Hence, 1 eq of base was added to avoid the protonation of **12i**, but none of the applied bases had any influence on the conversion to the hemiester. This finding was surprising, because Bolm *et al.* reported a catalytic approach (10 mol% quinine, 1 eq base) and observed full conversion to the hemiester **128**/*ent*-**128**.[122] The cyclic *meso*-anhydride **127** and the hemiester **128**/*ent*-**128** seem to equilibrate, which is why we utilized a Steglich esterification to functionalize the second carboxylic group and enforce product formation. Additionally ester **129**/*ent*-**129** can be easily analyzed by chiral GC and is configurationally stable. First, DMAP was used as catalyst to prove the practicability of this reaction sequence. The *in-situ* esterification of the second carboxylic acid worked well and 55% of **129**/*ent*-**129** and only 15% of **127** were

obtained. Additionally 130 mg (0.4 mmol; 15%) of **130**/*ent*-**130** were isolated. The side product was formed because *N*-acylureas were generated during the DIC-induced coupling due to an intramolecular acyl-transfer to the imino moiety, which competed with that to the alcohol.[123] In most cases DMAP is able to suppress this reaction.



Scheme 12: Ring opening of *meso*-**127** with **DMAP** and *in-situ* esterification of the second carboxylic acid *via* Steglich esterification conditions.

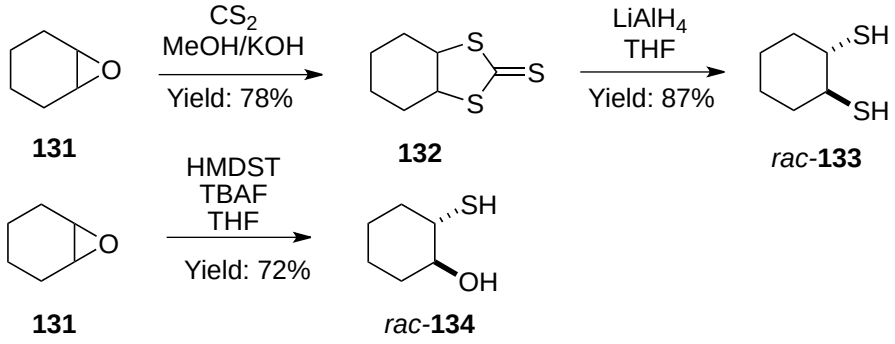
The enantioselective ring opening and direct Steglich esterification was performed under similar conditions utilizing 3 mol% of **12i**. Unfortunately, no selectivity was observed.

6. Exploring the Substrate Scope of Kinetic Resolutions Catalyzed by Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (12i)

Peptide **12i** is capable of a selective acyl transfer onto *rac*-**1** (*S* >50) and *meso*-**22**, whereas the *cis*-diol reacts slower than the *trans*-diol. An explanation might be the formation of an intramolecular hydrogen bond in case of the *trans*-diol, which acidifies the second hydroxyl group and facilitates the acyl-transfer. In order to prove this theory, structural similar substrates like *trans*-cyclohexane-1,2-dithiol, *trans*-2-mercaptocyclohexane-1-ol, *trans*-1,2-diaminocyclohexane and *trans*-2-aminocyclohexane-1-ol were tested.

6.1 Acylative Kinetic Resolution of *trans*-Cyclohexane-1,2-dithiol (133) and *trans*-2-Mercaptocyclohexane-1-ol (134)

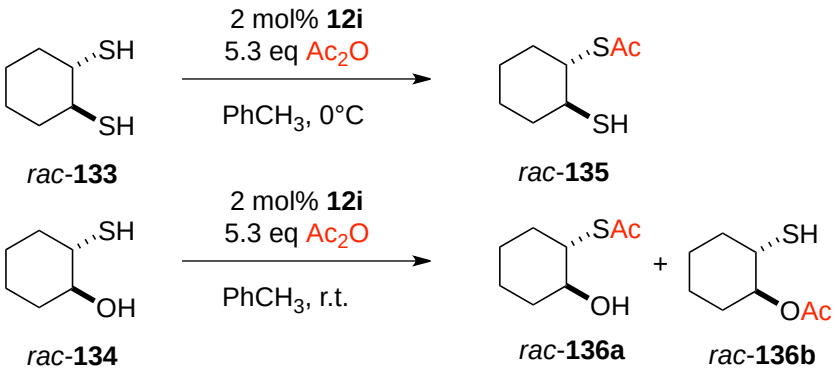
While KRs and desymmetrizations are common methods for the separation of alcohols only a few examples for thiols are known from literature.[124] Compared to *rac*-**1,** thiols are more acidic than alcohols and are not able to form strong hydrogen bonds. Thus, *rac*-**133** and *rac*-**134** should be tested under optimized conditions in the acylative KR mediated by **12i**. We propose that the chemical recognition of **1** by **12i** is mainly based on hydrogen bonding. Therefore, the absence of hydrogen bond acceptors in the substrate may decrease the selectivity. *Rac*-**133** and *rac*-**134** were synthesized following literature procedures.[125-128]



Scheme 13: Synthesis of racemic substrates **133** and **134**.

First, the KR of *trans*-cyclohexane-1,2-dithiol **133** was tested under standard conditions (2 mol% **12i**, 5.3 eq Ac_2O). In the absence of catalyst no acetylation was observed, but even with catalyst **12i** the acetylation of **133** (*C* = 20 % after 5 h) was much slower compared to the acetylation of *rac*-**1** (*C* = 50% after 4 h). An explanation might be that, even though the nucleophilicity of thiols is higher than that of alcohols, it is a "*soft nucleophile*" and prefers the

reaction with "*soft electrophiles*". A C=O group as a "*hard electrophile*" in contrast reacts more likely with "*hard nucleophiles*" like alcohols. Unfortunately, no selectivity was observed.



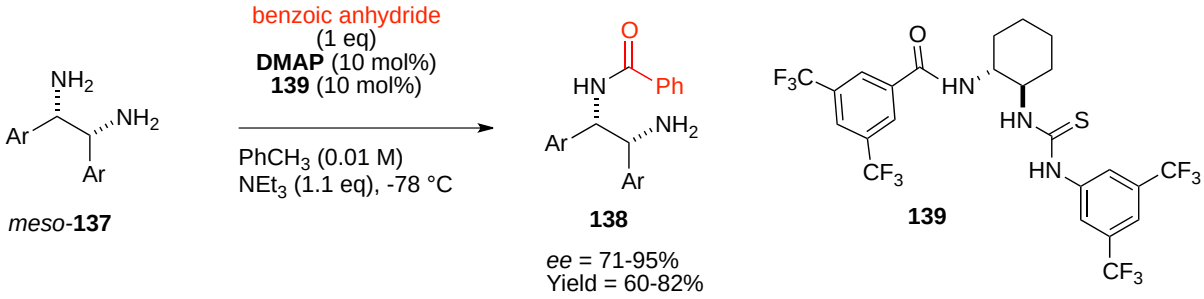
Scheme 14: KR of *rac*-**133** and *rac*-**134** utilizing **12i**.

Trans-2-mercaptocyclohexane-1-ol **134** offers the possibility of hydrogen bonding with **12i** and therefore the interaction should increase. The reaction was carried out at r.t. in order to increase the conversion, but the acetylation of *rac*-**134** was still slow (*C* = 48% after 24 h). For the KR of **134** no selectivity was observed and therefore the acetylated product was not isolated. It seems that both hydroxyl groups of the substrate *rac*-**1** are necessary to generate any *ee* and to increase the reaction rate.

6.2 Acylative Kinetic Resolution of *trans*-1,2-Diaminocyclohexane (140) and *trans*-2-Aminocyclohexane-1-ol (143)

Though amines play an important role in chemistry the examples for acylative KRs or desymmetrizations mediated by small organic catalysts are rare.[25,129,130] A common method for separating the enantiomers of *trans*-1,2-diaminocyclohexane is the salt formation with enantiopure tartaric acid.[131]

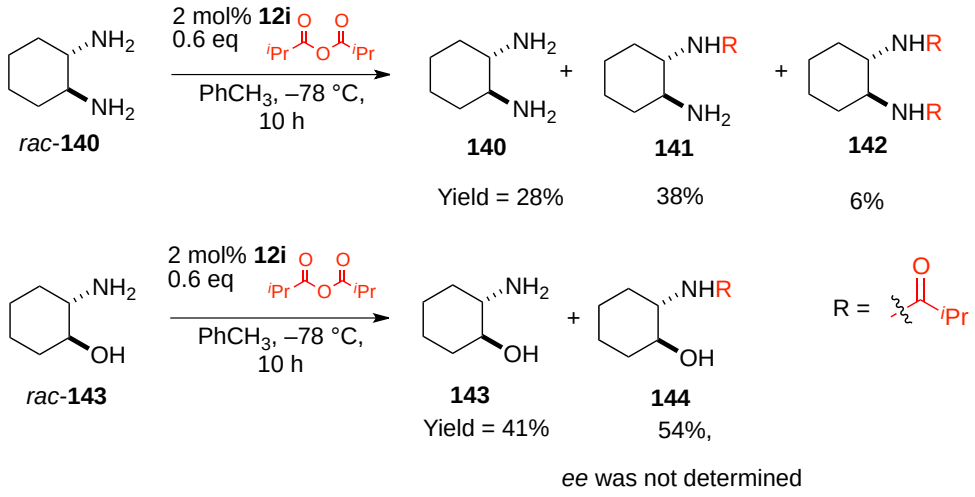
Contrary to thiols, amines can form hydrogen bonds, which yet are weaker compared to those formed by alcohols. For the KR of amines the reaction conditions have to be modified due to the high nucleophilicity of nitrogen. Hence, reactions are usually performed at low temperatures (–78 °C) to avoid non-catalyzed side reactions. Even at –40 °C the non-catalyzed acylation of the amine-groups of *rac*-**140** and *rac*-**143** occurred.



Scheme 15: Desymmetrization of a *vic*-diamine reported by Seidel *et al.*

Seidel *et al.* reported a desymmetrization of the vicinal diamine **137** *via* cooperative catalysis of DMAP and a chiral thiourea catalyst **139** in 2011.[129]

Based on Seidels findings, we tested the KR of *trans*-1,2-diaminocyclohexane *rac*-**140** and *trans*-2-aminocyclohexane-1-ol *rac*-**143** under modified conditions for the KR of *rac*-**1** (–78 °C, 0.5 eq ^{i}butyric anhydride, toluene). The low amount of acylation agent is to avoid complete acylation and to halt the reaction at 50% conversion.



Scheme 16: KR of *rac*-**140** and *rac*-**143** utilizing **12i**.

The separation of the enantiomers of *rac*-**140**, *rac*-**143**, monoacylated *rac*-**141** and monoacylated *rac*-**144** was not possible *via* chiral GC or chiral HPLC. The *ee* was detected by specific optical rotation. For reasons of comparability, the specific optical rotation of monoacylated (*R,R*)-**1** was also measured at the same concentration (25 mg in 1 mL of $CHCl_3$). A specific optical rotation of [α] = (–0.47 ± 0.16) °mL·dm^{-1}·g^{-1} (measured at 22 °C at λ = 589 nm) for **141** was measured for the KR experiment catalyzed by **12i**; for enantiopure **141**, a specific optical rotation of [α]= (–2.71 ± 0.35) °mL·dm^{-1}·g^{-1} (measured at 22 °C at λ = 589 nm) was found. The optical purity can be easily calculated as:

$$optical\ purity[\%] = \frac{[\alpha]1}{[\alpha]2} \cdot 100 = 17.4\ \pm 8.3$$

$[\alpha]1 = \text{measured specific optical rotation}$

$[\alpha]2 = \text{maximal specific optical rotation}$

Horeau showed in 1969 that the ideal proportionality of optical purity and *ee* does not always hold, especially in rather non-polar solvents like $CHCl_3$. The *ee* can hence not be determined exactly.[132]

The specific optical rotation was also measured for **144**, [α] = (–0.300 ± 0.122) °mL·dm^{-1}·g^{-1} (**144** was synthesized by utilizing **12i** as catalyst). The optical purity was not determined.

Unfortunately, only low selectivity was observed for *rac*-**141**, but the error margin for the specific optical rotation and optical purity are quite high. This result implicates the importance of strong hydrogen bonding interactions between **12i** and the substrate, because the selectivity for *rac*-**1** is excellent, whereas the *S*-value of *rac*-**141** is low and no selectivity was observed in the case of *rac*-**133**. Additionally, the low/no *ee* implies that both hydroxyl-groups (hydrogen bond donors) are necessary for the selectivity, because in the KR of *rac*-**134** and *rac*-**144,** no *ee* could be observed. For *rac*-**43** (see Chapter 3, Figure 9), bearing a hydroxyl-group (hydrogen bond donor) vicinal to a keto-group (hydrogen bond acceptor), only low selectivity and activity were observed either.

In future work, less reactive electrophiles (Boc_2O) could be tested. The non-catalyzed mono-Boc-protection of *rac*-**140** was achieved with an excess of **140** at 0 °C (**Boc-141**). Catalyzed reactions at lower temperatures have not yet been conducted.

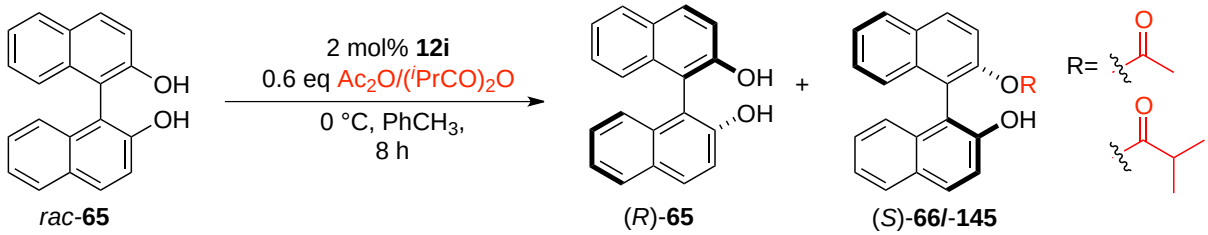
In order to use chiral GC measurements for determining the *ee,* it could be helpful to functionalize the second amine function with highly reactive electrophiles like 1-(trifluoroacetyl)imidazole.

6.3 Acylative Kinetic Resolution of 1,1'-Bi-2,2'-naphthol

The KR of BINOL **65** was tested under standard conditions (5.3 eq Ac_2O, 0 °C) and after 4 h, 64% of monoacylated BINOL **66** and 36% of diacylated BINOL were observed. The high activity of **12i** towards BINOL was unexpected, because usually the reactivity for substrates not bearing two vicinal hydroxyl moieties is low. The reaction conditions were optimized and only 0.6 eq of Ac_2O were used to avoid diacylation.

Under optimized conditions, no diacylated product was observed. Surprisingly, moderate selectivities (*S* = 3) were detected and therefore the influences of temperature and the concentration of isobutyric anhydride on the selectivity were investigated.

Table 15: KR of BINOL **65** utilizing **12i** and $Ac_2O/(^{i}PrCO)_2O$



rac-**65** (*R*)-**65** (*S*)-**66**/**-145**

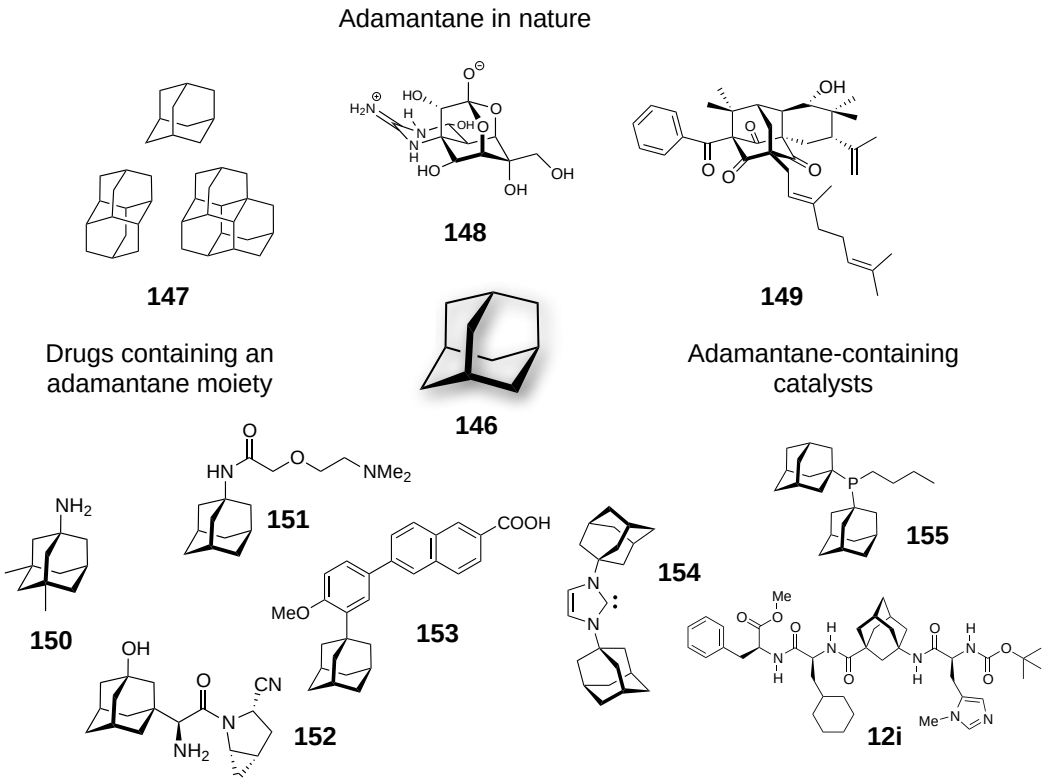
Entry	T (°C)	Anhydride	*C* (%)	*ee* (%) (R)-65	*ee* (%) (*S*)-66/145	*S*-value
1	–70	Ac_2O	56	13.3	17.0	1.5
2	–70	$^{t}Bu_2O$	55	6.5	7.9	1.2
3	–20	Ac_2O	33	28.2	13.9	2.0
4	–20	$^{i}Bu_2O$	58	3.9	5.6	1.1
5	0	Ac_2O	42	39.4	28.4	3.0
6	0	$^{t}Bu_2O$	38	12.4	7.6	1.4
7	25	Ac_2O	46	43.1	37.2	3.6
8	25	$^{t}Bu_2O$	40	21.5	14.3	1.8
9	35	Ac_2O	42	39.8	28.9	3.0
10	35	$^{t}Bu_2O$	42	15.5	11.8	1.5

For Ac_2O and $(^{i}PrCO)_2O$, the best selectivities were achieved at r.t. Higher temperature (35 °C) increased the selectivity, which may be due to decreased hydrogen bonding interactions. In contrast to this finding, lower temperatures do not increase the *S*-values. Usually, lower temperatures increase the selectivity, because weak forces like hydrogen bonding and dispersion interactions become more important. In the KR of *rac*-**1**, the selectivities for $(^{i}PrCO)_2O$ are slightly higher than the selectivities for Ac_2O, but the reaction is slower. In this case the reactivity is comparable, but the higher steric demand of the electrophile probably decreases the *ee*.

7. Synthesis of Adamantane Amino Acids as Building Blocks for Peptidic Catalysts

7.1 Adamantane Cores in Nature, Chemistry and Pharmaceuticals

Adamantane was first isolated from crude petroleum by Landa and Machacek[133] in 1933 and eight years later, Prelog[134] reported the first synthesis. A more practical approach was reported in 1957 by Schleyer (Yield = 12–13%).[135,136] Today, adamantane **146** and its higher analogues (diamandoids) **147** are used in chemistry (e.g. as bulky substituents), pharmaceutical industry (as building block for drugs) and in materials science.[137,138] Diamandoids exhibit remarkable physical properties (e.g., monolayers of functionalized diamondoids show monochromatic electron photoemission).[139]



Scheme 17: Adamantane cores in nature, chemistry and pharmacy.

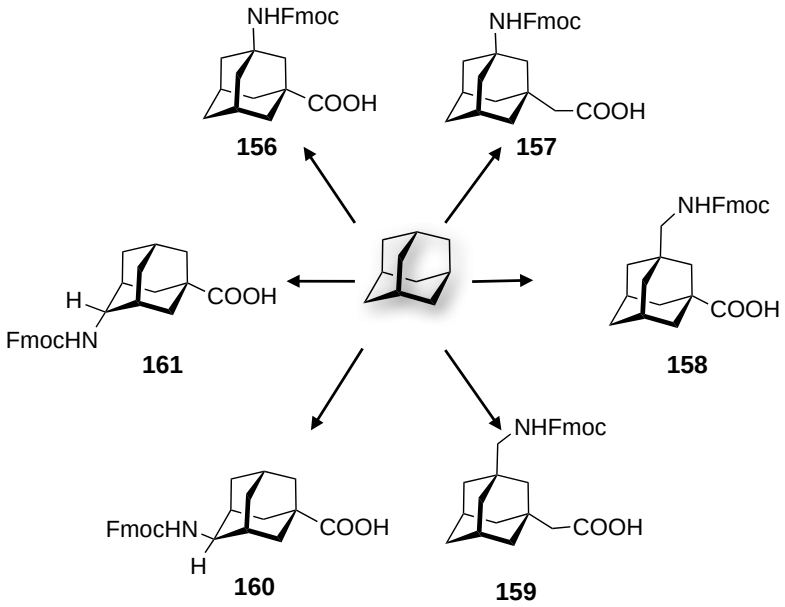
Modified adamantane cores can be found in nature (Scheme 17), e.g., Tetrodotoxin (TTX) **148**, which is one of the strongest known toxins that contains a dioxoadamantane core.[140,141] Adamantane-bearing substances (e.g., Sampsonione I **149**) were also isolated from *Hypercum sampsonii*, a plant being used in traditional chinese medicine.[142,143]

Adamantane-amino-derivatives are known to be active drugs for the treatment of influenza and diseases related to the nervous system.[144] Memantine® (1-amino-3,5-

dimethyladamantane; **150**) plays an important role for combating Alzheimer's disease, Tromantadine (Viru-Merz®; **151**)[145] has anti *Herpes simplex* properties and Saxagliptin (Onglyza®; **152**)[146] was marketed in 2009 for the treatment of type 2 diabetes. Adapalene **153** is used as a drug for the treatment of mild acne.

Additionally, adamantane is a common building block in chemistry. The first stable, crystalline *N*-heterocyclic carbene (NHC) **154** contained two adamantane moieties and was synthesized by Arduengo in 1991.[147] In 1994, Beller *et al.* utilized phosphine **155** successfully as a co-catalyst in a Suzuki coupling reaction.[148] In peptide **12i**, the unnatural adamantane amino acid (^{A}Gly) acts as a rigid spacer between the catalytically active Boc-(π-Me)-histidine moiety while the other amino acids generate a "pocket", in which enantioselective acyl transfer reactions can occur (see Introduction).[60,67,68]

The synthesis of various γ-amino adamantane carboxylic acids was reported by Schreiner *et al*.[149] 1-Aminoadamantane carboxylic acid **156** was successfully incorporated into the highly chemo- and enantioselective acylation catalyst **12i**.[60,149] Hence, we synthesized modified adamantane amino acids as building blocks for peptidic catalysts in order to determine how a more flexible spacer influences the selectivity.



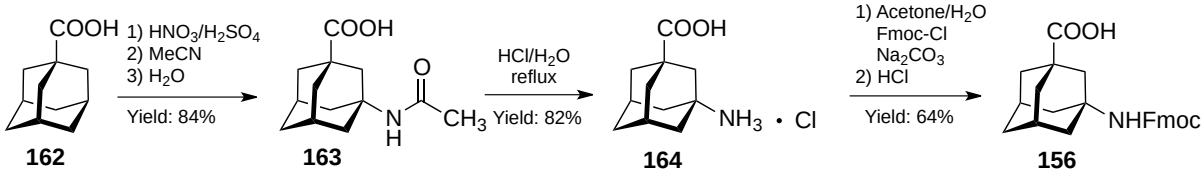
Scheme 18: Modified adamantane amino acids.

In contrast to **156**, the δ-adamantane amino acids **157** and **158** are both elongated (addition of a methylene group). The generation of an ε-adamantane amino acid (**159**) makes an elongation on both substituents necessary. The higher flexibility of **157**, **158**, and **159** incorporated into a peptide may both broaden the substrate scope and enable the comparison of activities and selectivities with the model system. Thus, a better understanding of substrate recognition by **12i** may be achieved. Other interesting

adamantane amino acids are 1,4-substituted **160** and **161** as well as rigid δ-adamantane amino acids.

7.2 Synthesis of 3-[(9-Fluorenyl)methoxycarbonylamino]tricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid (156)

1-Aminoadamantanecarboxylic acid **156** can be easily prepared employing a literature procedure.[149]



162 **163** **164** **156**

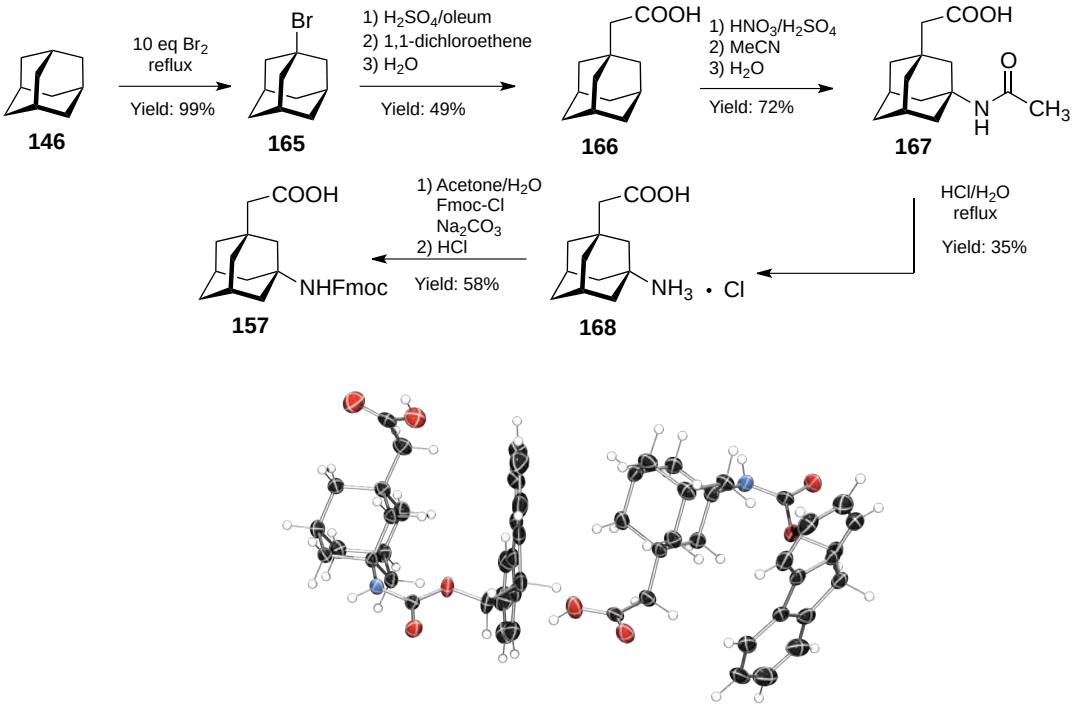
Scheme 19: Synthesis route for the preparation of **156**.

The direct C–H acetamidation of a tertiary carbon atom of adamantane carboxylic acid yielded 90% of pure 3-acetamidoadamantane-1-carboxylic acid. The formation of a radical cation generated by NO_2^+, which is an acceptor in single electron transfer (SET) reactions, is proposed as an intermediate in the acetamidation reaction.[150] The yields for the hydrolysis of **161** (Yield: 85%) and the Fmoc-protection of **162** (Yield: 55%) are comparable to those reported in the literature.[149]

7.3 Synthesis of 1-[(9-Fluorenyl)methoxycarbonylamino]tricyclo[3.3.1.1^{3,7}]decane-3-acetic acid (157)

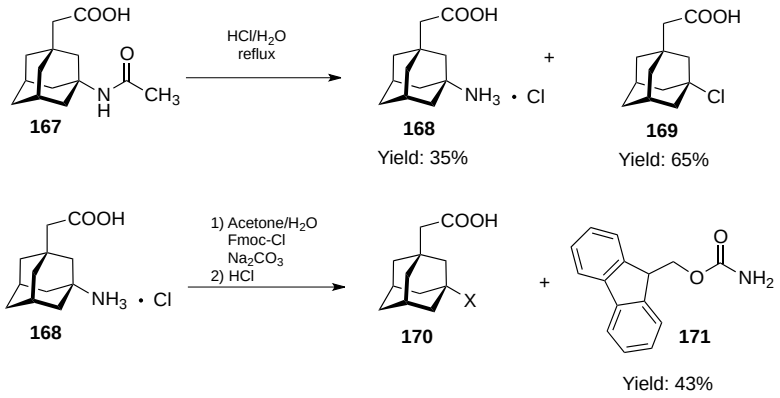
For the synthesis of **157**, we followed a strategy similar to **156**, but starting from adamantane acetic acid instead of **162**. To functionalize adamantane at the tertiary carbon usually halogenated or hydroxylated adamantane precursors[151] are used, because these derivatives are more active towards, e.g., Koch-Haaf[152] and Ritter-type reactions. Hence, the bromination of adamantane was the first step of the sequence. Bromine should be distilled prior to use to avoid multi-bromination due to metal traces.[151,153] Adamantane was dissolved in distilled bromine at 0 °C and afterwards the mixture was refluxed for 1 h. After work up, 1-bromoadamantane was isolated almost quantitatively. For generating the acetic acid moiety **165** was suspended in conc. H_2SO_4 and oleum (20% SO_3) at 0 °C and 1,1-dichloroethene was added. The absence of a Lewis-acid (BF_3) reduced the yield to 50%. For the acetamidation of **166** the same conditions were applied as for **162**, but only 65% of pure product could be isolated. Acidic hydrolysis of **167** in aq. HCl unfortunately yielded only 35% of the desired product **168**, because the formation of 1-chloroadamantane-3-acetic acid **169**

is favored.[151] Chlorinated adamantane carboxylic acid is also a byproduct in the hydrolysis of **163**, but a yield of only 15% is common. Shorter reaction times (1 d) for the hydrolysis of the acetamide **167** did not increase the yield of **168**.



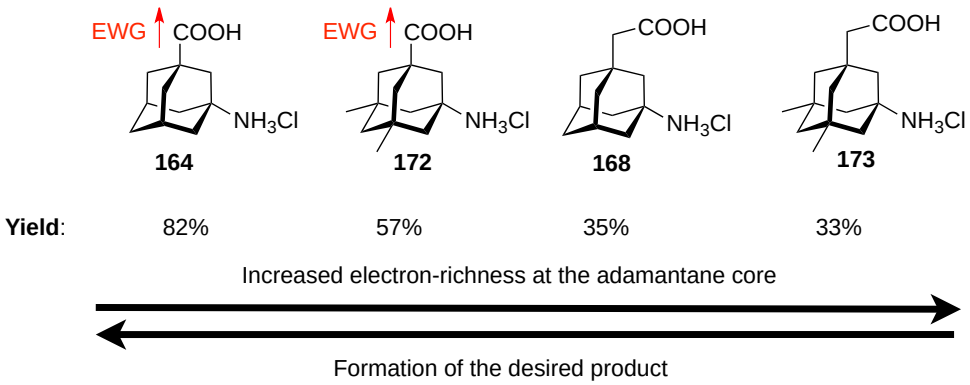
Scheme 20: Synthesis route for the preparation of **157** and its crystal structure (space group: monoclinic).

The Fmoc-protection of **168** yielded a sufficient amount of **157**, but 9-fluorenylmethoxycarbonylamine was observed as a product if the reaction conditions was not strictly adhered to. For the Boc-protection of **168** Boc-NH_2 was also isolated in some cases. Especially the temperature should not rise over 25 °C at all stages of the reaction. This observation is consistent with the higher amount of 1-chloroadamantane-3-acetic acid in the hydrolysis of **167** compared to the yield of 3-chloroadamantane-1-carboxylic acid in the hydrolysis of **163**. Somehow the tendency of substitution of the amide function at the adamantane core is increased for **157** and **167**.



Scheme 21: Distribution of products for the hydrolysis of **167** and the Fmoc-protection of **168**.

Unfortunately, the structure of **170** could not be determined because the colorless solid was insoluble in various solvents (D_2O, d_8-toluene, d_6-DMSO, and $CDCl_3$) and no NMR-spectra could be obtained. The high amount of 3-chloroadamantane-1-carboxylic acid in the hydrolysis may be due to the absence of an electron-withdrawing group at the adamantane unit. The substitution on an electron-poor adamantane core (e.g., 3-acetamidoadamantane-1-carboxylic acid **163**) and, consequently, the formation of an adamantyl-cation, is less favored compared to an electron-rich core (1-acetamidoadamantane-3-acetic acid **167**) due to hyperconjugation with the adamantane C-C σ-bonds. In order to prove this hypothesis, the Fmoc-protection of the dialkylated 1-aminoadamantane-3-acetic acid was utilized as test reaction. The two alkyl-groups at the adamantane should additionally stabilize an adamantyl-cation by hyperconjugation and a higher amount of substitution product should be obtained. Additionally, the yields for the acidic hydrolyses of **164**, **168**, **172** and **173** were compared.

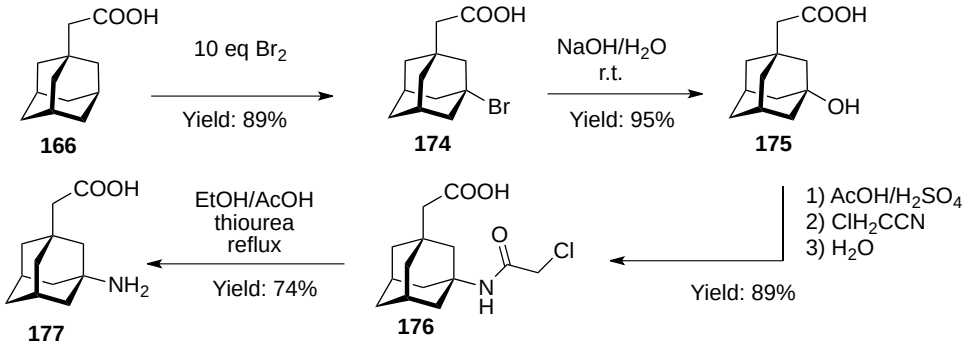


Scheme 22: Comparison of the isolated yields for the hydrolysis products of adamantane cores with different electronic properties.

The results are in accordance with the stability of the proposed intermediate carbocations. The yield of **172** is 28% lower compared to **164**. For electron-poor adamantanes the addition

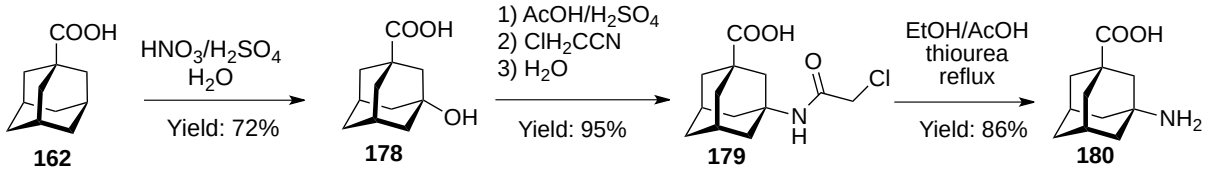
of alkyl-groups decreases the yield of the hydrolysis product drastically. If no electron-withdrawing groups are directly attached to the adamantane core, the influence of the increased hyperconjugation is low (**168** vs. **173**). The Fmoc-protection of **168** yielded 58% of **157** by following the literature procedure, while for **173** only 34% of the product could be isolated.

In order to increase the yield of **168** a slightly modified synthesis route was tested and chloroacetonitrile was used as nucleophile in the acetamidation step (Ritter reaction).[154] The reaction yielded 89% of pure **176**. The hydrolysis of **176** requires milder reaction conditions (AcOH, thiourea *vs.* HCl) and shorter reaction times (10 h *vs.* 3 d) and after work up, 74% of amino acid **177** were isolated. A drawback of this route is that a hydroxyl group at the adamantane is required **(175)** to introduce the chloroacetamide substituent. The hydroxyl group can be easily generated at r.t. by dissolving **174** in a 0.15 M NaOH solution.[155] Two additional steps are necessary, but **174** and **175** can be synthesized in excellent yields and short time. Much to our surprise, **174** could not be utilized for the preparation of **173**. By using the chloroacetonitrile route an overall yield of 56% of pure aminoadamantane acetic acid **177** compared to 23% overall yield for the acetonitrile route.



Scheme 23: Preparation of **177** using chloroacetonitrile for the chloroacetamidation.

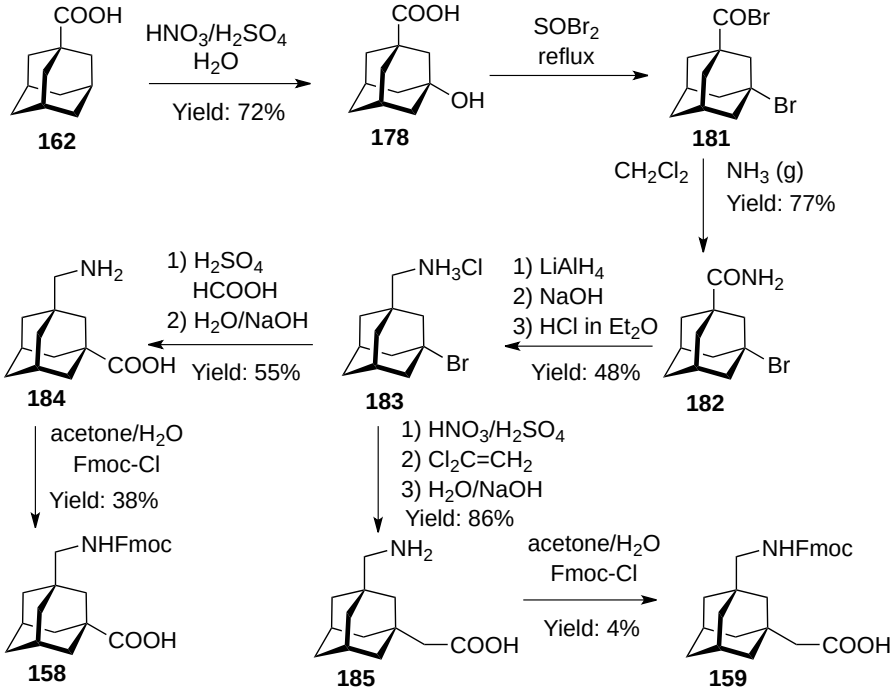
The acetonitrile route was also tested for the synthesis of the free amino acid **180**, but the yields are comparable to the ones obtained by utilizing the direct acetamidation route. Additionally one more step is required for the generation of 3-hydroxyadamantane-1-carboxylic acid and therefore this route is less practically useful.



Scheme 24: Synthesis route for the preparation of **180** using chloroacetonitrile for chloroacetamidation.

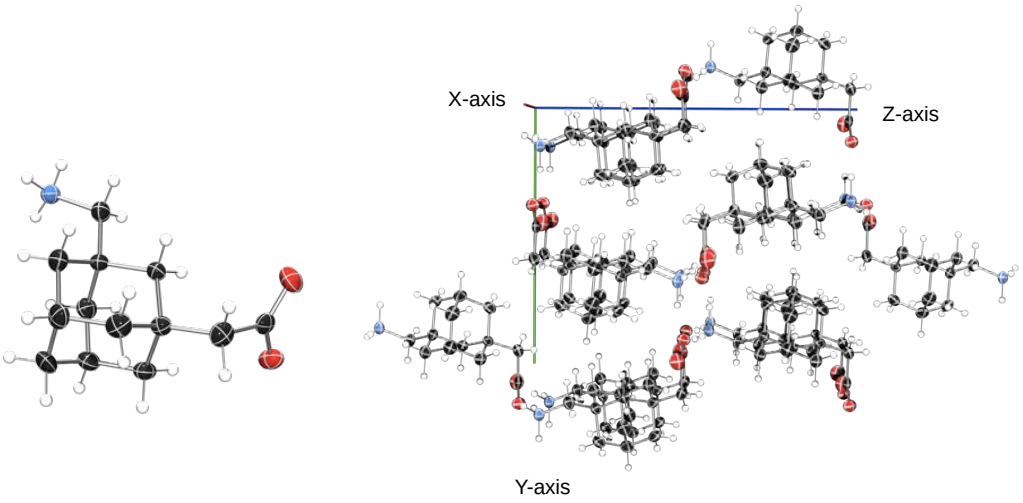
7.4 Syntheses of 3-[(9-Fluorenyl)methoxycarbonylmethylamino]tricyclo[3.3.1.1$^{3.7}$]-decane-1-carboxylic acid (158) and 3-[(9-Fluorenyl)methoxycarbonylmethylamino]-tricyclo[3.3.1.1$^{3.7}$]decane-1-acetic acid (159)

For the synthesis of amino acids **158** and **159** a slightly modified procedure of the synthesis route described by Horvat *et al.* was utilized.[156] In the first step the 3-hydroxyadamantane-1-carboxylic acid **178** was generated. Treatment of **178** with thionylbromide and ammonia gas yielded 77% of **182**. For the reduction of the amide **182** with BH_3·DMS, only 35% of the amine hydrochloride salt **183** could be isolated. This result is in accordance with the yields reported in literature.[156]



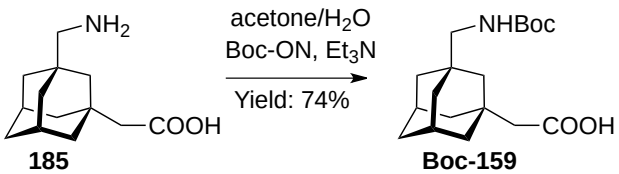
Scheme 25: Synthetic route for the preparation of **158** and **159** (top); crystal structure of **158** (bottom); space group: monoclinic.

Reduction with $LiAlH_4$ did not produce larger amounts of **183**. In both cases, the starting material **182** could be recovered. 1-Bromo-3-methylaminoadamantane hydrochloride **183** can be transformed into **184** by dissolving in H_2SO_4 and adding HCOOH. After neutralization of the reaction mixture, the product precipitates within 3 h. Standard conditions for the Fmoc-protection were applied and **158** could be isolated in 38% yield. In the literature, **185** was not isolated, but directly protected with Boc_2O. The results for the direct Boc-protection of **185** were not reproducible. Hence, **185** was isolated after the neutralization from the reaction mixture.



Scheme 26: Single crystal structure of **185** as zwitterion (left) and crystal packing (right); space group: orthorhombic.

In contrast to the synthesis of **184**, no precipitate was observed after several hours. Hence, the neutralized reaction mixture was stored for 6 d, after which colorless crystals could be isolated. However, the Fmoc-protection with Fmoc-Cl and Fmoc-OSu under standard conditions (acetone/H_2O) did not produce **159**.



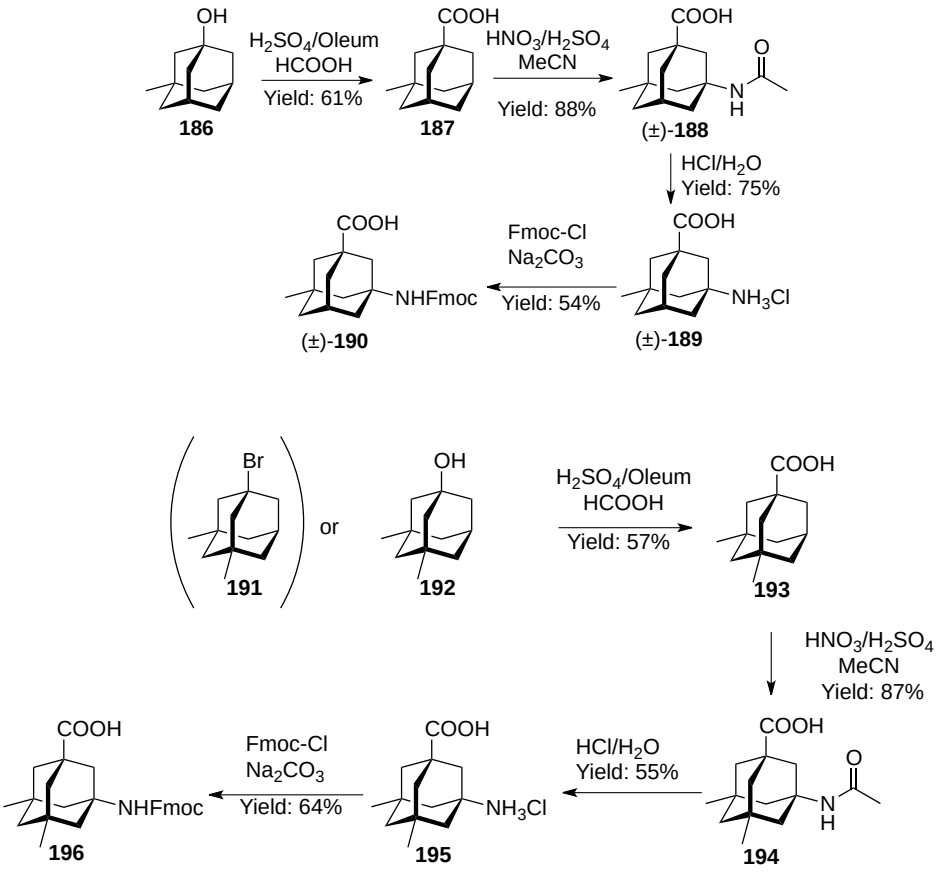
185 **Boc-159**

Scheme 27: Boc-protection of **185** with Boc-ON.

The *in-situ* Boc-protection was not successful, which is why the Boc-protection of isolated **185** was attempted. Using Boc-ON [2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile] as the protecting agent, 3-*tert*-butylcarbonylmethylaminotricyclo[3.3.1.$1^{3,7}$]decane-1-acetic acid **Boc-159** could be isolated in good yield (74%).

7.5 Syntheses of 3-[(9-Fluorenyl)methoxycarbonylmethylamino]-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylic (190) and 3-[(9-Fluorenyl)methoxycarbonylmethylamino]-5-methyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylic (196)

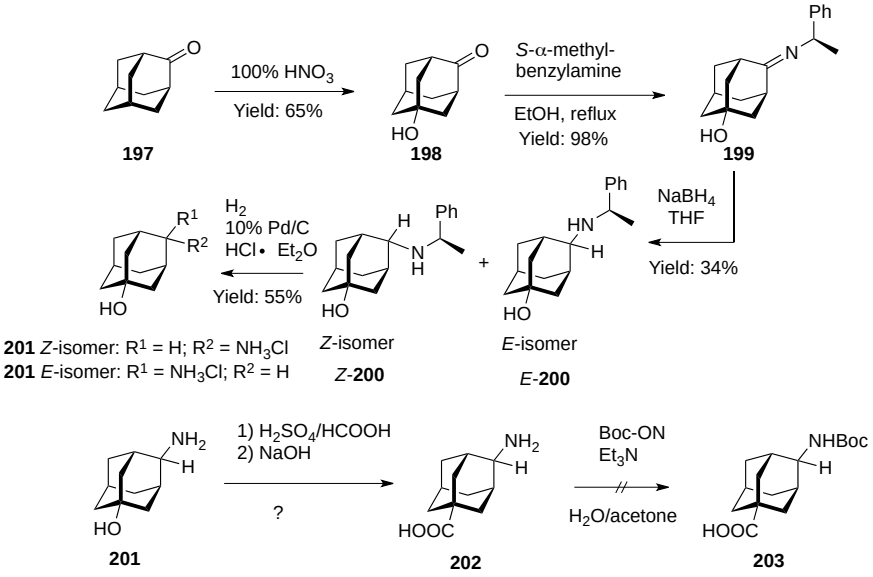
The syntheses of (±)-**190** (for the envisioned application a separation was not necessary) and **196** started from the mono- and dimethylated hydroxyadamantanes **186** and **192**, respectively.[151,157] The direct acetamidation of **187** and **193** produced slightly lower yields as described in literature.[149] For acidic hydrolysis and Fmoc-protection, standard conditions (as mentioned in Scheme 19) were applied.



Scheme 28: Preparation of **(±)-190** and **196**.

7.6 Synthesis of 4-*tert*-Butoxycarbonylmethylaminotricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid (*E*-203) and (*Z*-203)

Hydroxyadamantone **197** was synthesized according to the literature and a comparable yield was isolated.[158] Linders *et al.* reported the synthesis of *E*- and *Z*-**201** in 2006.[159] The introduction of a *N*-benzyl substituent should offer the possibility of an easy HPLC separation. The imine formation and reduction was reproducible, but unfortunately only the *E*-isomers of **200** could be separated *via* HPLC and column chromatography and *Z*-**200** was not obtained. *E*-**200** was debenzylated under standard conditions (PdC/H_2), but even after 2 d only a mixture of **200** and **201** could be isolated. Thus, the reaction mixture was treated with HCl in diethyl ether and **201** precipitated as the hydrochloride. The carboxyl group was introduced under standard conditions (H_2SO_4, HCOOH), but after neutralization of the reaction mixture no adamantane amino acid **202** precipitated after 4 h. A direct Boc-protection with the reaction mixture of **202** was attempted, but no product could be isolated. A reason may be that only a small amount of **201**•HCl was synthesized and the yield of **202** was too low to be isolated.



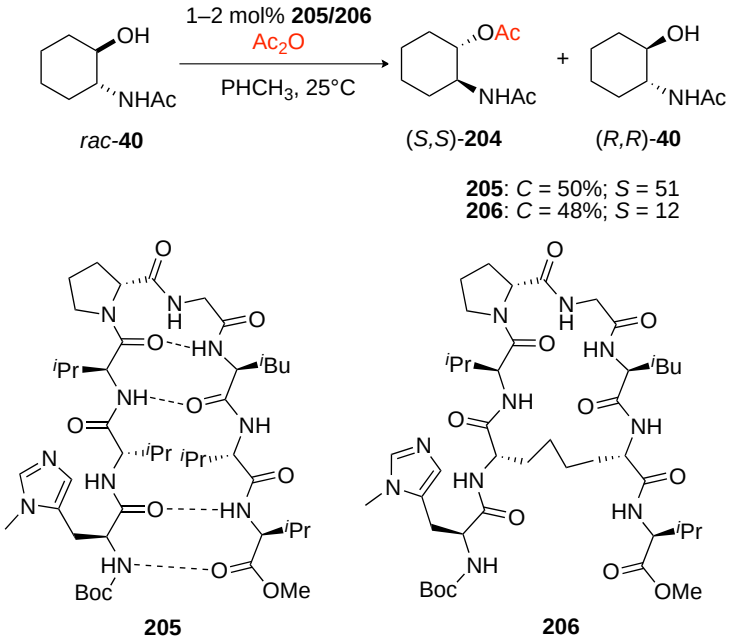
Scheme 29: Synthesis route for the preparation of *E*- and *Z*-**202**

8. Modification of Current Peptide Platform Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (12i)

8.1 Acylative Kinetic Resolution of *trans*-Cyclohexane-1,2-diol with Modified Peptides

As mentioned in Chapter 3, peptide **12i** shows characteristics of a small enzyme, such as high chemo- and enantioselectivities. The substrate scope is limited to 1,2-diols like **1**, **22** and *rac*-**45** and only anhydrides with moderate steric demand are tolerated. We propose that a dynamic binding process in the non-polar solvent toluene accomplishes the chemical recognition of the 1,2-diol **1** by peptide **12i**, because no evidence for a preferred secondary structure was found by NMR- or IR-spectroscopy.

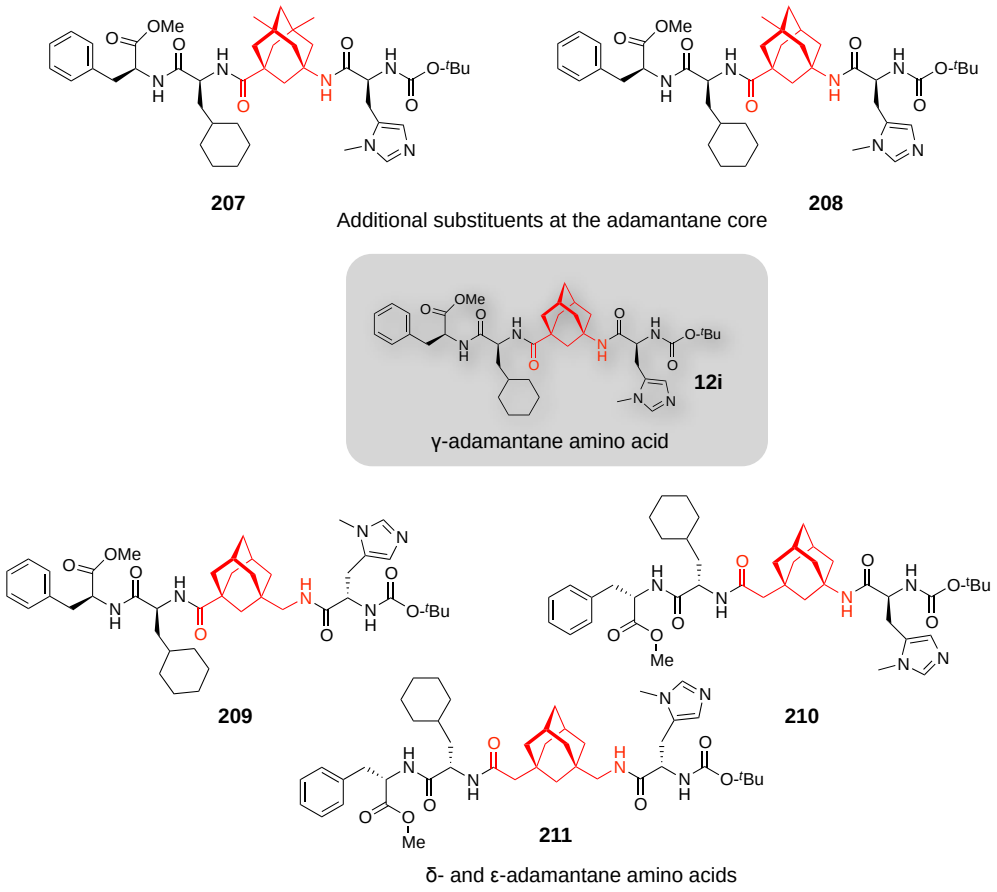
For a better understanding of this catalytic system, the peptide was modified at various positions and the influence of the structural changes was investigated by comparing the selectivities of the modified peptides in the KR of our model substrate *rac*-**1** with the selectivities obtained by **12i**. Miller *et al.* compared the *S*-value of a flexible octapeptide **205**, adopting a proline-induced *β*-hairpin structure stabilized by hydrogen bonding interactions, with octapeptide **206,** in which the secondary structure is determined by a covalent bond (Scheme 30).[48] The less flexible peptide showed a lower selectivity, which implicates that, a modicum of flexibility is necessary for a high *ee*.



Scheme 30: Comparison of the KRs of *rac*-**40** utilizing peptides **205** and **206**.

The flexibility of peptide **12i** was increased by incorporating modified adamantane amino acids (Chapter 7) and methyl groups at the 3- and 3,5-positions of the adamantane core were added to investigate the influence on the structure. Adamantane becomes chiral by

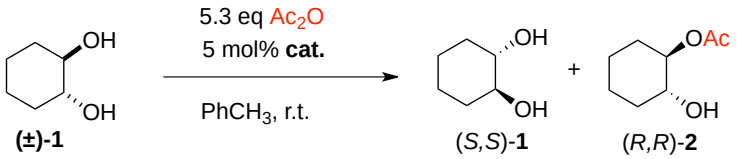
bearing three different substituents, thereby decreasing the selectivity of the KR of *rac*-**1**. Hence, peptide **208** was tested, because the absence of an effect on the selectivity would probably allow immobilization at this position.



Scheme 31: Modified peptides inspired by **12i** incorporating different adamantane amino acids.

The peptides were applied in the KR of *rac*-**1** and their selectivities were compared. Elongation of the adamantane amino acids decreased the selectivity. Although elongation at the *C*-terminus as in **210** has the smallest influence (S = 6.8) relative to **12i** (S > 50), the overall loss of selectivity for all δ- and ε-adamantane amino acids is dramatic. Peptide **209,** which has been elongated at the *N*-terminus, shows only low selectivity (S = 3.2). The most flexible peptide **211** is also the most unselective catalyst (S = 2.9). In contrast, substituents at the adamantane core itself have no pronounced effect on the selectivity, because the peptide backbone, which generates the chiral environment, is not affected. Based on these findings, the immobilization of the catalyst at the adamantane core may be possible without loss of selectivity (see outlook).

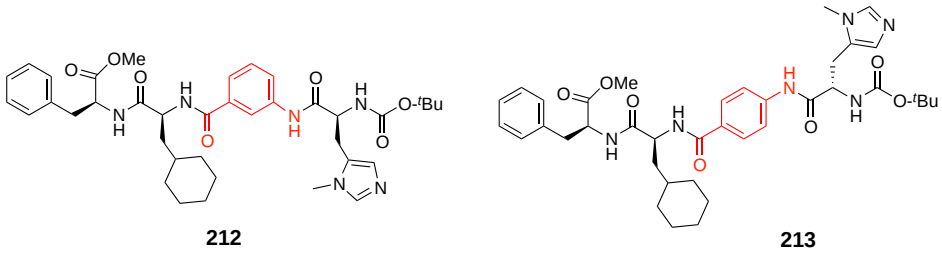
Table 16: KR of *rac*-**1** utilizing modified peptides **207**–**217**.



Entry	Cat.	*t* (h)	*C* (%)[a]	*ee* (%) 1	*ee* (%) 2	*S*-value [a]
1	**12i**	2	54	99	85	>50
2	**207**	2	55	99	78	>50
3	**208**	2	57	99	74	48
4	**209**	5	55	44	36	3.2
5	**210**	2	50	60	58	6.8
6	**211**	5	42	28	38	2.9

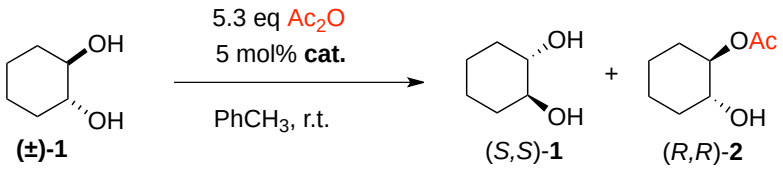
[a] Conversions and *S*-values were determined following the procedure of Kagan and Fiaud.[63]

In the next step, ^{A}Gly was replaced by 3- and 4-aminobenzoic acid (**212**/**213**). The planar aromatic ring may also be able to separate the catalytically active (π-Me)-histidine moiety from the rest of the peptide and generate some kind of catalytically active "pocket". Peptides **212** and **213** were also tested in the KR of *rac*-**1**.



Scheme 32: Modified peptides inspired by **12i** incorporating 3- and- 4-aminobenzoic acid instead of adamantane amino acids at the *i* + *1* position.

Table 17: KR of *rac*-**1** utilizing modified peptides **212** and **213**.



Entry	Cat.	*t* (h)	*C* (%)[a]	*ee* (%) 1	*ee* (%) 2	*S*-value [a]
1	**212**	6	44	32	40	3.1
2	**213**	6	42	20	27	2.1

[a] Conversion and *S*-value were determined following the procedure of Kagan and Fiaud.[63]

^{A}Gly seems to be essential for the selectivity, because with 3- and- 4-aminobenzoic acid as the structure-giving element, only low *ee*-values were detected. Especially **213** was less reactive (only 20% conversion after 3 h) and rather unselective, which may be due to the planar spacer separating the two parts of the peptide chain. Alternatively, the *C*- and *N*-termini of the peptide are too far apart so that no "pocket" is formed. In contrast, 3-aminobenzoic acid (**212**) brings the *C*- and *N*-terminus of the peptide closer together, resulting in increased reactivity and selectivity (S = 3.5) compared to **213**. Again, high flexibility does not lead to high selectivity.

In 2009, Sunoj *et al.* performed ONIOM computations at the B3LYP/6-31G(*d*):PM3 level that yielded transition structures for acyl transfer onto (*R*,*R*)- and (*S*,*S*)-**1** catalyzed by **12i** (Figure 18).[89] These computations confirm our model and the energy difference of 4.5 kcal·mol^{-1} between the two transition states structures nicely explains the observed high enantioselectivities.

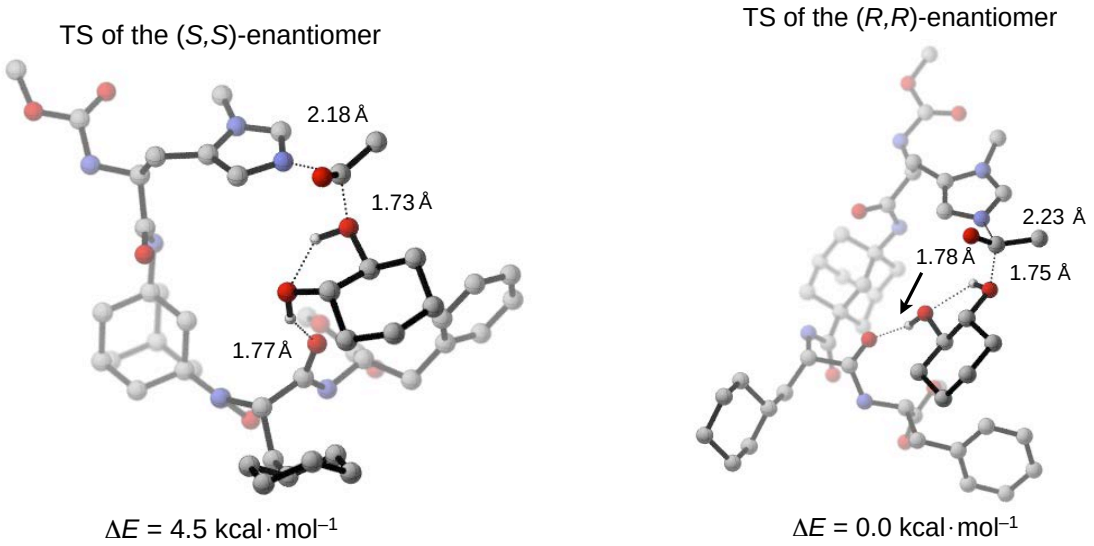
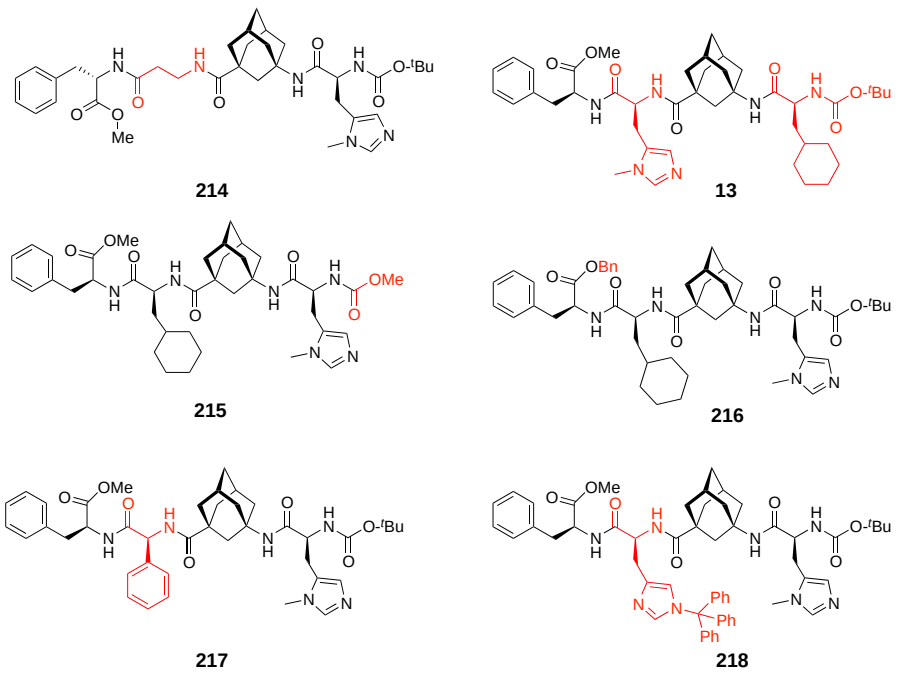


Figure 18. Optimized low-lying transition structures for the acyl transfer catalyzed by **12i** (Moc instead of Boc) to (*1R,2R*)-**1** (left) and to (*1S,2S*)-**1** at ONIOM2(B3LYP/6-31G(d):PM3). Only selected hydrogens are shown for clarity.

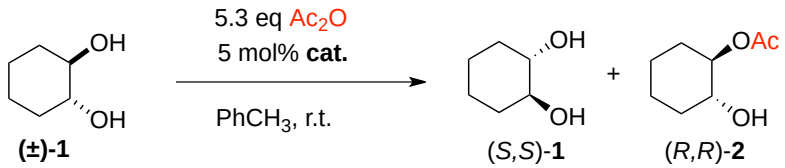
In these computations, the carboxyl group of the cyclohexylalanine moiety seems to be responsible for the hydrogen bonding interaction, which is needed for the recognition of the substrate by the catalyst. Hence, the *i*+2 position (Cha) was replaced by β-alanine (**214**) to shift the carboxyl group and to investigate the possibility of resolving cyclohexane-1,3-diol and other substrates. In peptide **13**, the positions for the catalytically active π-methyl histidine and cyclohexylalanine moieties were changed and the selectivity dropped dramatically to S = 1.5. For the KR of *rac*-**1** utilizing **214**, only a low selectivity of S = 2.5 was observed (Table 18).



Scheme 33: Modified peptides inspired by **12i**.

The influence of the protecting groups at the L-Phe and π-methyl histidine should be investigated and peptides **215** and **216** were synthesized and tested. Additional peptides incorporating amino acids with a high steric demand at the *i* + *2* position (**217** and **218**) were synthesized and tested, but the selectivity was not noticeably affected (Table 18).

Table 18: KR of *rac*-**1** utilizing modified peptides **13** and **214**–**218**.

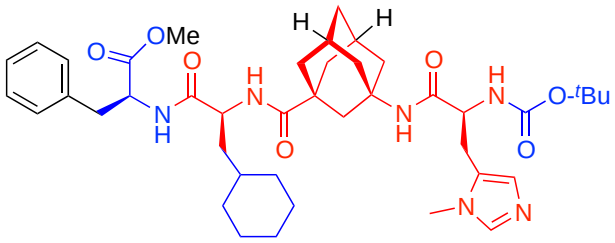


Entry	Cat.	*t* (h)	*C* (%)[a]	*ee* (%) 1	*ee* (%) 2	*S*-value[a]
1	**214**	3	38	28	46	2.5
2	**13**	5	33	8	16	1.5
3	**215**	1	50	88	86	38
4	**216**	2	46	82	94	>50
5	**217**	1	67	99	48	19
6	**218**	2	60	99	64	32

[a] Conversion and *S*-value were determined following the procedure of Kagan and Fiaud.[63]

Modifications of the peptide backbone decreased the selectivity dramatically, whereas additional substituents at the adamantane core, an acetyl group at the π-methyl histidine **215**

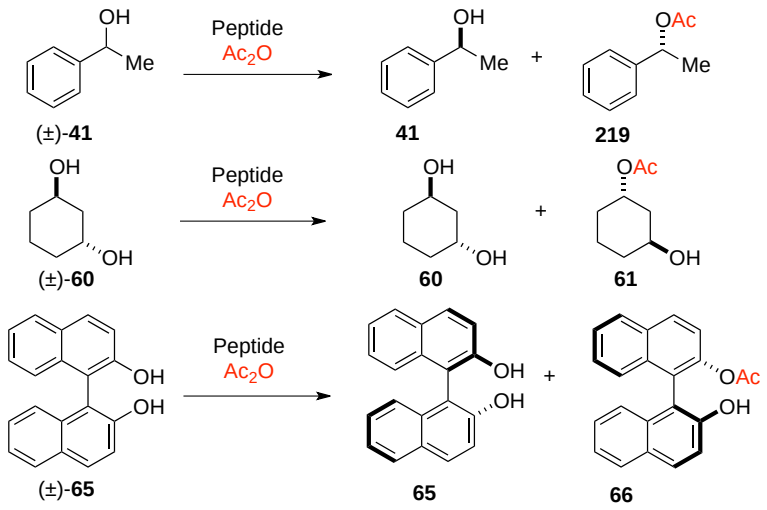
and a Bn– protecting group instead of a Me– group at Phe (**216**) only have a small influence on the *S*-value. Elongation at the *C*-terminus of ^{A}Gly had the lowest impact on the selectivity (*S* = 6.9; **210**), but all modifications at the *N*- or *C*- terminus of the adamantane amino acids decreased the *S*-value to < 10.



Scheme 34: The essential parts of the peptide **12i** for the selectivity are drawn in red, the parts with moderate influence are colored in blue and the black moieties only have a small or negligible effect on the *ee*.

It is no surprise that a catalyst with extraordinarily high selectivity can hardly be fine-tuned to perform even better, but the fact that it influences the system so dramatically is still remarkable. The modified catalysts may be rather unselective in the KR of *rac*-**1**, but new substrates can possibly be resolved.

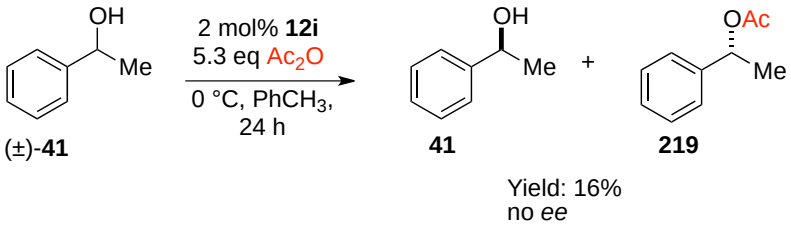
Therefore, we chose three different model reactions: The acylative KR of *rac*-1-phenylethanol, the KR of *rac*-cyclohexane-1,3-diol **60** and the KR of 1,1'-bi-2,2'-naphthol (BINOL) (±)-**65**. The KR of 1-phenylethanol (±)-**41** was chosen as test reaction, because it is one of the most common substrates for acylative KRs (see introduction). The KR protocols for cyclic 1,3-diols are rare, but it contains the same structural features (two hydroxyl groups, cyclohexyl ring) as the resolvable 1,2-diols. Enantiopure BINOL is often used as a ligand or as a building block for chiral Lewis acid catalysts. Enzymatic and chemical approaches were reported for the resolution of 1,1′-binaphthyl-2,2′-diol (±)-**65**. The non-enzymatic methods are based on inclusion complexes or salt formation.[100-102] Both enantiomers can be obtained in high yields and with excellent *ee* (>99%). To the best of our knowledge, no catalytic non-enzymatic approaches for the acylative KR of (±)-**65** are yet known.



Scheme 35: Test reactions for KR mediated by the modified peptides.

8.2 Acylative Kinetic Resolution of *Rac*-1-Phenylethanol (41) Mediated by Modified Peptides

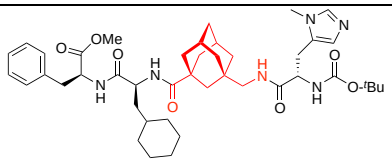
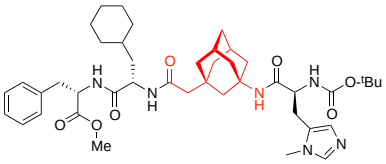
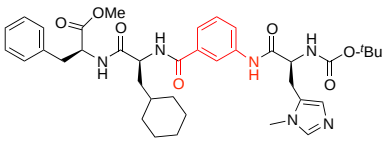
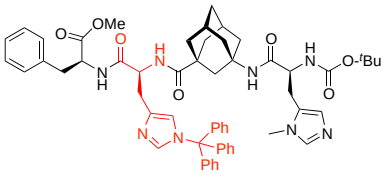
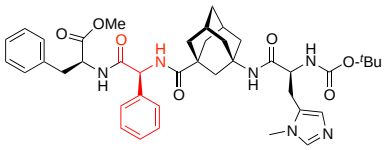
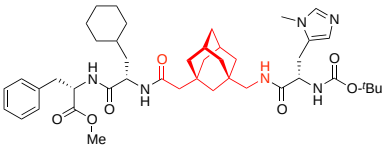
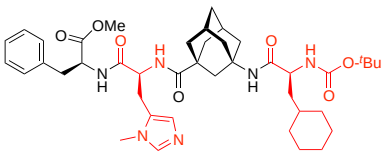
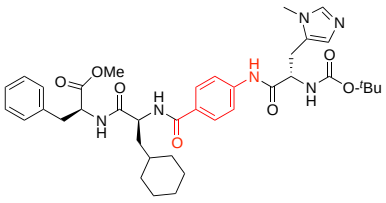
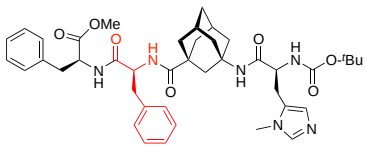
The KR of **41** was tested under standard conditions (2 mol% catalyst, 5.3.eq Ac_2O, toluene) utilizing **12i** as a catalyst. Unfortunately, only 16% of the racemic product could be obtained after 24 h. In contrast to the KR of *rac*-**1** were after 4 h 50% of the product formed, **12i** showed only low reactivity.

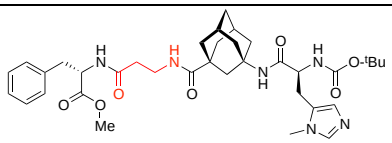


Scheme 36: KR of *rac*-**41** mediated by **12i**.

A reason may be the absence of a second hydroxyl group for hydrogen bonding. Successfully used catalysts in the KR of *rac*-**41** often have aromatic moieties for π-π-interaction. Hence, some other peptides with additional aromatic moieties were synthesized and tested, but all were unselective. Only for **210**, low selectivity was obtained.

Table 19: KR of *rac*-**41** utilizing modified peptides **12g**, **13**, **209**–**213** and **217**–**218**.

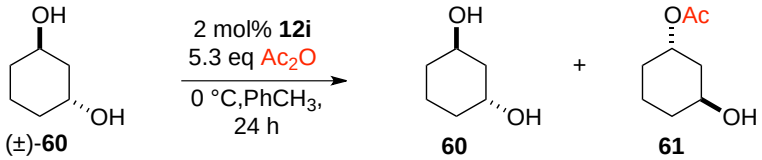
Entry		Cat.	*t* (h)	*C* (%)[a]	*ee* (%) **41**	*ee* (%) **219**	*S*-value[a]
1	**209**		24	50	6	6	1.2
2	**210**		24	50	38	20	2.1
3	**212**		24	50	10	10	1.3
4	**218**		24	✘	0	0	✘
5	**217**		24	62	10	6	1.2
6	**211**		24	50	6	6	1.2
7	**13**		24	42	6	8	1.2
8	**213**		24	50	6	6	1.2
9	**12g**		24	✘	0	0	✘

Entry		Cat.	*t* (h)	*C* (%)[a]	*ee* (%) **41**	*ee* (%) **219**	*S*-value[a]
10	**214**		24	✘	0	0	✘

[a] All yields and *ee* values were determined by chiral GC following the procedure by Kagan and Fiaud.[63]

8.3 Acylative Kinetic Resolution of *Rac*-*Trans*-Cyclohexane-1,3-diol (60) Mediated by Modified Peptides

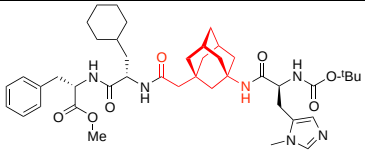
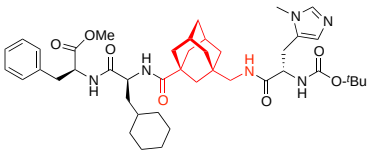
The result for the KR of *trans*-cylohexane-1,3-diol utilizing **12i** is rather disappointing, because only 6% of conversion was detected after 24 h at 0 °C.

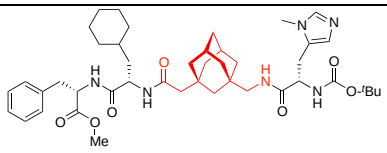
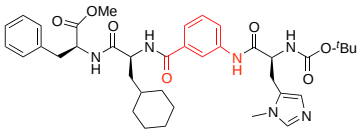
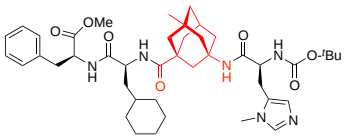
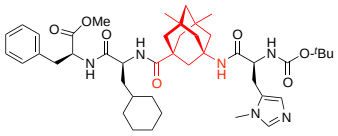
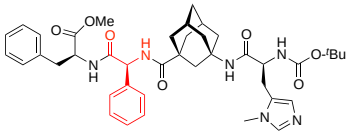
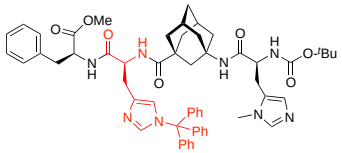
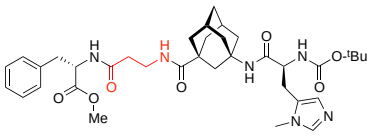


Scheme 37: KR of *rac*-**60** mediated by **12i**.

This finding implicates that the chemical recognition of the peptide and the substrate is low, because the acyl transfer does not occur. Thus, various modified catalysts were tested at r.t. to increase the yield.

Table 20: KR of *rac*-**60** utilizing modified peptides **207–212**, **214**, **217** and **218**.

Entry		Cat.	*t* (h)	*C* (%)[a,b] **60**	*ee* (%) **60**
1	**210**	 3 mol%	3	19	0
2	**209**	 3 mol%	5	10	0

Entry		Cat.	*t* (h)	*C* (%)[a,b]	*ee* (%)
				60	60
3	**211**	 2.5 mol%	5	10	0
4	**212**	 2.5 mol%	6	14	0
5	**208**	 2.5 mol%	7	12	0
6	**207**	 2.5	5	9	0
7	**217**	 2.5 mol%	5	19	0
8	**218**	 2.5 mol%	5	8	0
9	**214**	 5 mol%	2	43	0

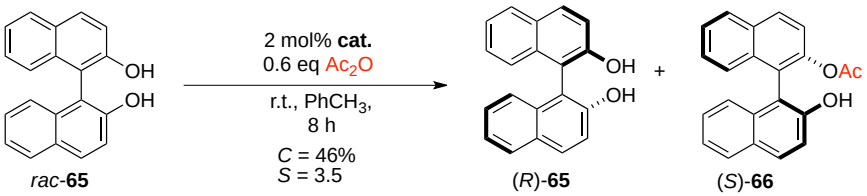
[a] All yields and *ee* values were determined by chiral GC following the procedure by Kagan and Fiaud.[63] [b] All reactions were performed at r.t.

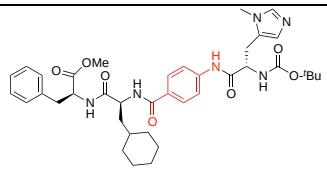
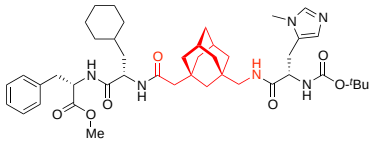
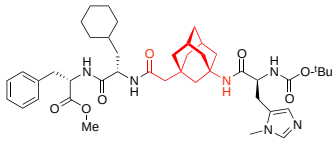
All tested peptides were unselective and the acylation was slow even at r.t. The only exception in terms of reactivity was peptide **214** bearing β-alanine at the *i* + *2* position. For the KR of *rac*-**60**, **12i** and the modified peptides **207–212**, **214**, **217** and **218** were not useful and other amino acid sequences should be tested.

8.4 Acylative Kinetic Resolution of 1,1'-Bi-2,2'-naphthol (65) Mediated by Modified Peptides

For the KR of *rac*-**65**, moderate selectivity was observed using **12i** as catalyst. Unfortunately, the *S*-value could not be increased by lowering the temperature or by using (^{i}PrCO)$_2$O as acyl source. Hence, catalyst **210**, **211** and **213** were tested. We envisioned that the more flexible peptides **210** and **211** maybe increase the selectivity. For both catalysts, only lower selectivities (*S* = 1.3 and 1.5) compared to **12i** (*S* = 3.5) could be observed. Catalyst **213** was unreactive.

Table 21: KR of *rac*-**65** utilizing modified peptides **210, 211** and **213**.



Entry		Cat.	*C* (%)[a]	*ee* (%) 65	*ee* (%) 66	*S*-value[a]
1	**213**		n.d.	✘	✘	✘
2	**211**		16	18	4	1.5
3	**210**		35	9	5	1.3

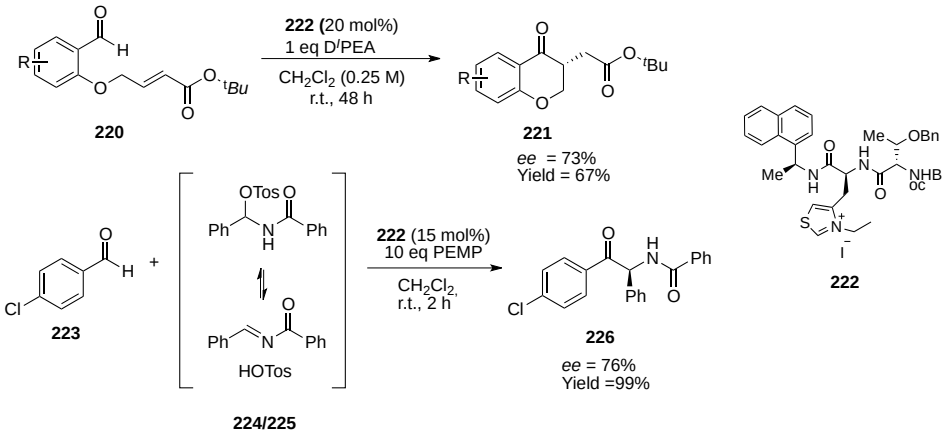
[a] All yields and *ee* values were determined by chiral GC following the procedure by Kagan and Fiaud.[63]

In summary, the best selectivities for the KRs of *rac*-**1** and *rac*-**65** were obtained by peptide **12i** bearing the rigid adamantane amino acid **156**. Only **210** showed some selectivity (*S* = 2.1) in the KR of *rac*-**41**, whereas for **12i**, no selectivity was observed. It seems that a certain degree of rigidity is necessary for high selectivity. Therefore the synthesis and incorporation of *Z*-**202** in a peptide might be promising.

9. NHC-Containing Peptides

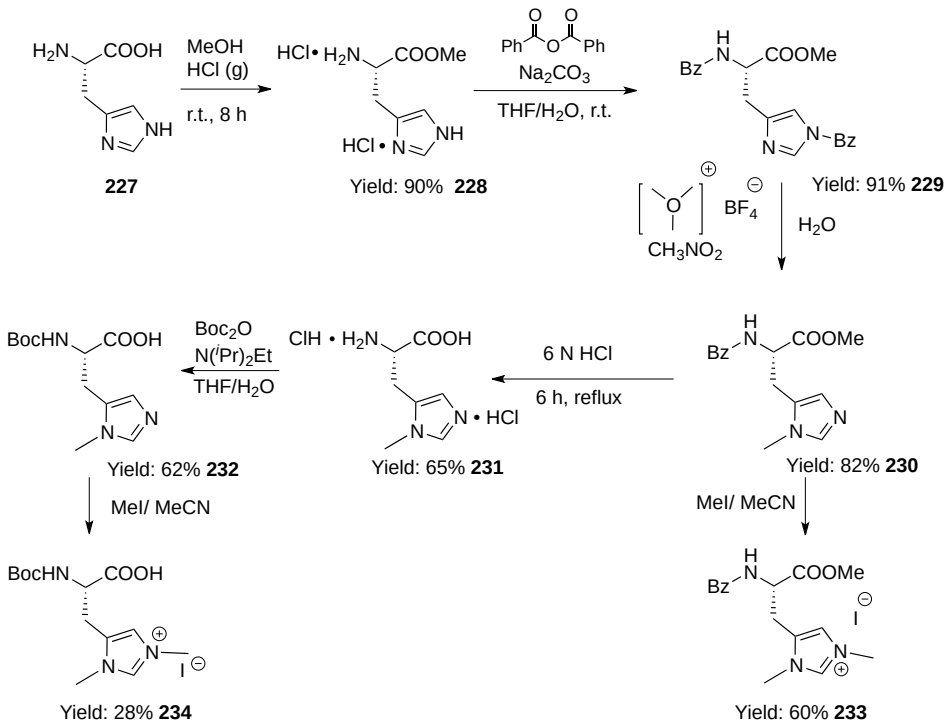
9.1 Syntheses of NHC-Precursor-Containing Peptides and Their Application as Catalyst in Benzoin Condensations

Chiral NHCs are widely utilized in asymmetric benzoin condensations, Stetter reactions and other "*Umpolung* reactions".[160] In 2005 Miller *et al.* were the first to use a peptidic backbone for generating a chiral environment around the carbene.[161,162]



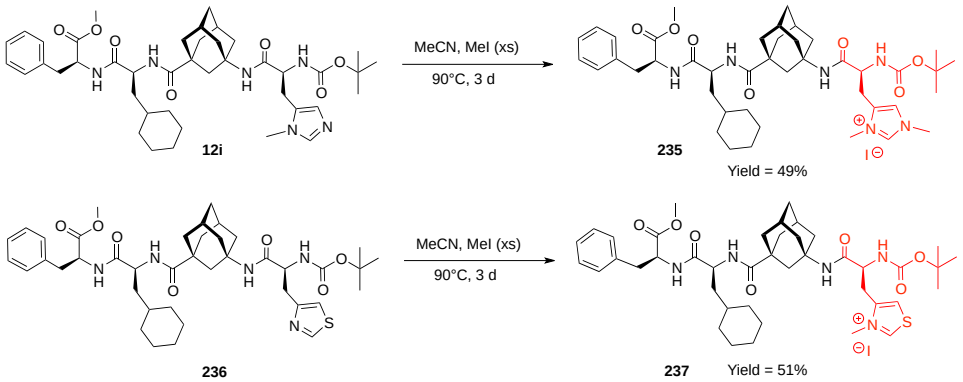
Scheme 38: Carbene induced reactions reported by Miller *et al*.

We envisioned the synthesis of a carbene precursor by simply methylating the second nitogen of the methylimidazole moiety of **12i**. The synthetic pathway was started by methylation of Boc-(π-Me)-histidine utilizing methyl iodide to generate Boc-dimethyl histidinium iodide. The carbene precursor **234** could be isolated in 28% yield. The peptide coupling with **234** was not possible, because of its poor solubility in CH_2Cl_2 (solvent for peptide synthesis in solution) and DMF (solvent for solid phase peptide synthesis (SPPS)).



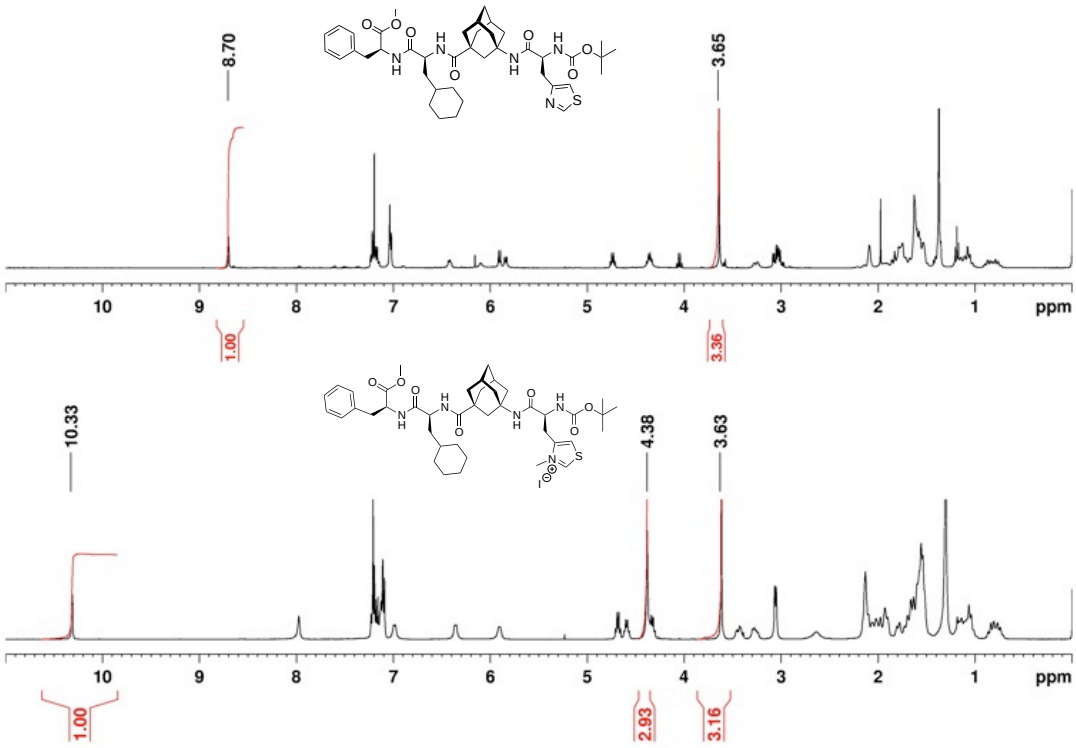
Scheme 39: Synthesis of carbene precursors starting from histidine.

We tried to isolate the free carbene derived from **233** by utilizing Arduengos approach (NaH, THF, DMSO), but no characteristic carbene signal in the ^{13}C-NMR spectrum (expected around 215 ppm) was detected.[163] The result does not confirm that the carbene was not isolated as 1,3-dimethyl-2-ylidenes are unstable towards air and moisture and decompose even at low temperatures. In order to avoid solubility problems of the amino acid salt **234**, the tetrapeptides **12i** and **236** were methylated directly, yielding about 50% of pure **235** and **237**, respectively.



Scheme 40: Synthesis of **235** and **237** *via* direct methylation of tetrapeptides **12i** and **236**.

All efforts to increase the yield of the methylation by utilizing Meerwein's salt, methyl trifluoromethanesulfonate or methyl iodide under microwave conditions were not to avail. In addition to peptide **235** bearing a dimethylimidazolium iodide moiety, the methylthiazolium iodide moiety containing peptide **237** was synthesized, because of the higher acidity. Thiamine, especially thiamine pyrophosphate (TPP), a naturally occurring thiazolium salt, is involved in many enzymatic transformations and cellular processes.[164] The pK_a values for the deprotonation of the *N,N'*-dimethylimidazolium iodide (pK_a = 21.1) and *N*-methylthiazolium iodide (pK_a = 14.5) differ significantly and milder reaction conditions may avoid decomposition of the peptidic backbone.[165]



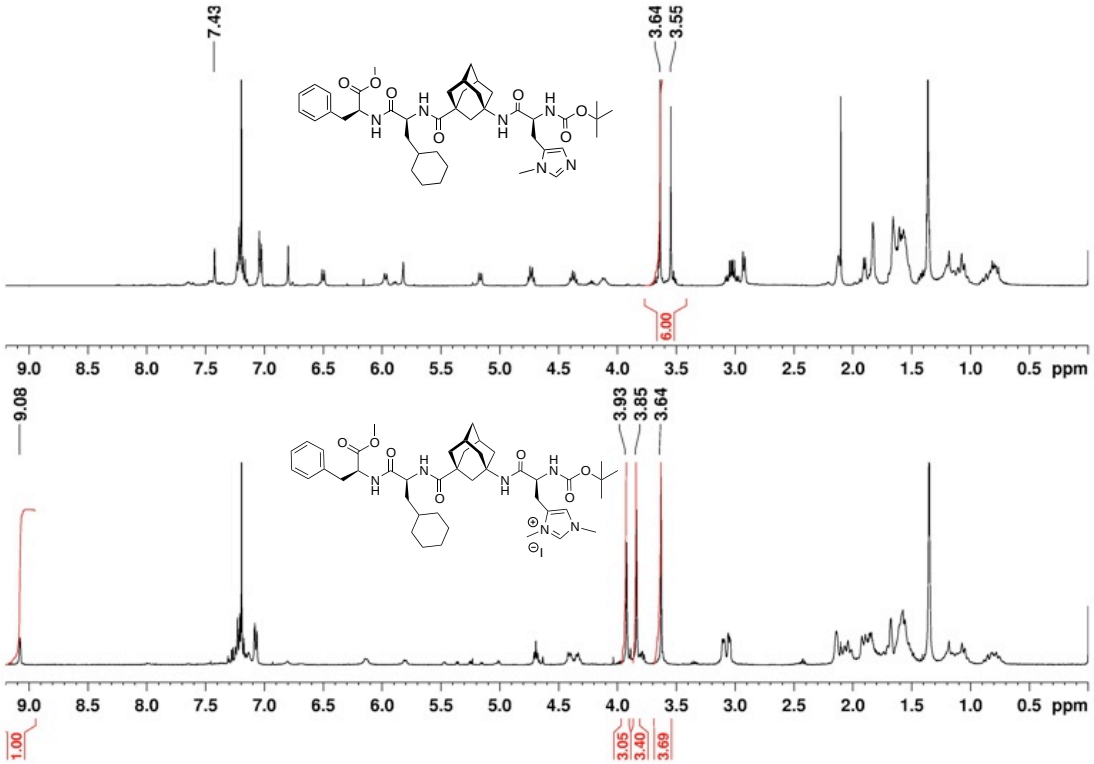
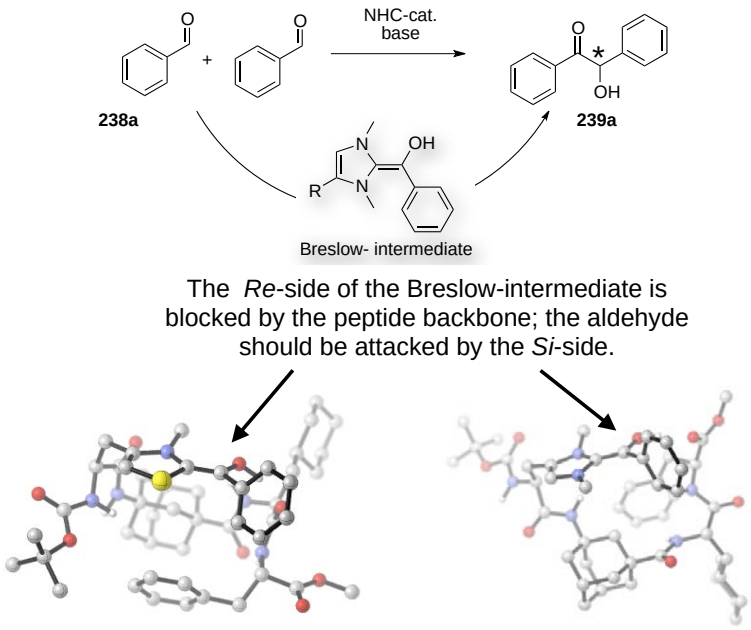


Figure 20: Comparison of the ^{1}H-NMR spectra of **12i/235** and **236/237**.

The benzoin condensation was chosen as test reaction due to the readily available substrates and the broad knowledge of NHCs as catalysts for this type of reaction. Additionally, we utilized a molecular dynamics search for the low-lying conformation of the Breslow intermediates of catalyst **235** and **237**[166,167] The model generated by the MMFF (Merck Molecular Force Field)[83] for the enantioselective acylation of *trans*-cyclohexane-1,2-diol by **12i** helped to rationalize the mechanism and the influence of lipophilic amino acids on the selectivity.



Scheme 41: MMFF-model for the Breslow-intermediate of benzaldehyde and the thiazolylidene (left) and the dimethylimidazolylidene (right). Hydrogen atoms are omitted for clarity.

In both conformations the *Re*-side of the intermediate seems to be blocked by the peptide backbone. Hence, an asymmetric benzoin condensation may be possible. In order to optimize the reaction conditions (base, solvent, temperature), *N,N*-dimethylimidazolium iodide (NDMI) **240** was chosen as small symmetric test catalyst. The reaction conditions for the generation of the free carbene should be comparable for peptide **235** and the small model catalyst **240**.[168] The benzoin condensation of benzaldehyde and **241** was tested in different solvents. THF is the most common solvent for this reaction and 40% of benzoin could be isolated. In toluene, DCM and 1,4-dioxane only traces of benzoin **239a** could be observed. In order to deprotonate **240**, inorganic and organic bases were tested and only with NaH and potassium-*tert*-butoxide benzoin product formation was observed. The deprotonation of *N*-methylthiazolium iodide **242** should be easier due to the higher acidity, but a benzoin condensation could only be achieved with NaH, potassium-*tert*-butoxide and DBU. In the literature, Et_3N is a common base for the *in-situ* generation of thiazolylidenes **243**, but we observed no benzoin condensation by utilizing **242** and Et_3N.[169]

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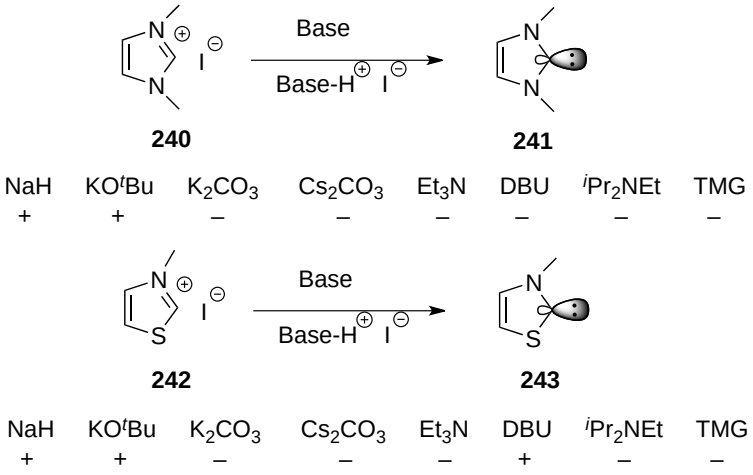
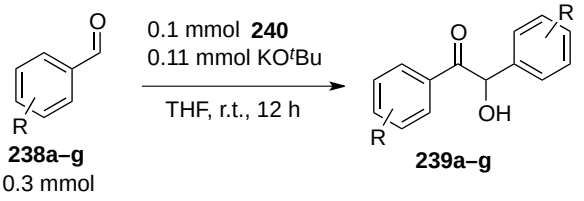


Scheme 42: The deprotonation of **240** and **242** with different bases was tested indirectly by the detection of benzoin **239a**.

Potassium-*tert*-butoxide was applied as the base for further optimizations. The influence of temperature on the benzoin condensation was tested. As expected, the amount of benzoin increased with the temperature (Yield: 65% at 50 °C; 20% at 25 °C). Unfortunately, temperatures over 35 °C are not suitable for asymmetric benzoin condensations, because the structure of the peptide may become too flexible for a chiral induction. At last, we tested various *o*- and *p*-substituted benzaldehydes at optimized reaction conditions (33 mol% *N,N'*-dimethylimidazolium iodide; THF, r.t., 12 h).

Table 22: Benzoin condensation with different aldehydes catalyzed by **240**/KO^{t}Bu.

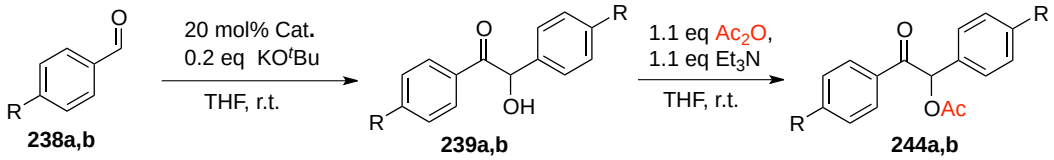


Entry		R	Yield (%)
1	**239a**	H	20[a]
2	**239b**	*p*-F	40[a]
3	**239c**	*p*-CF_3	–
4	**239d**	*p*-MeO	4[b]
5	**239e**	*p*-NO_2	–
6	**239f**	*o*-Cl	15[b]
7	**239g**	*o*-CH_3	23[b]

[a] Isolated product yields; [b] Yields were determined by GC-FID.

The best results were obtained for *p*-fluorobenzaldehyde **238b** and *o*-methylbenzaldehyde **238g**, but again the yields were just moderate. The low yields cannot only be rationalized by a low catalyst activity, but also a possible back reaction (retro-benzoin), which could also have a negative effect on the isolated yields.[170] Retro-benzoin-reactions are usually utilized for the preparation of mixed benzoins. By acylation of the free hydroxyl group of benzoin the equilibrium could be forced to shift to the product side. NHCs are also used as acylation catalysts and therefore, a benzoin-condensation with *in-situ* acylation was tested.

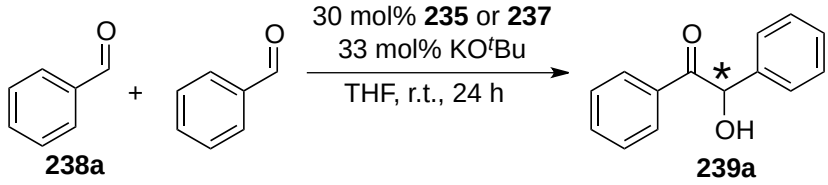
Table 23: Benzoin condensation with *in-situ* acylation catalyzed by **240**/KO^{t}Bu.



238a,b **239a,b** **244a,b**

Entry	Product	Cat.	R	Yield (%)
1	**244a**	**240**	H	70
2	**244b**	**240**	*p*-F	47
3	**244a**	**235**	H	–
4	**244a**	**237**	H	4

The addition of an acylation catalyst (e.g., DMAP) was not necessary due to the acylation abilities of the free carbene. For the benzaldehyde **238a** and *p*-fluorobenzaldehyde **238b**, the yield could be increased utilizing 20 mol% of *N,N'*-dimethylimidazolium iodide **240,** but for peptide **235** and **237** no effect on the yields were observed. Peptides **235** and **237** were tested with a catalyst loading of 30 mol% in the benzoin condensation.



238a **239a**

Boc-L(*N,N*'-Dime-His)I-^{A}Gly-L-Cha-L-Phe-OMe **235** Yield: 5%

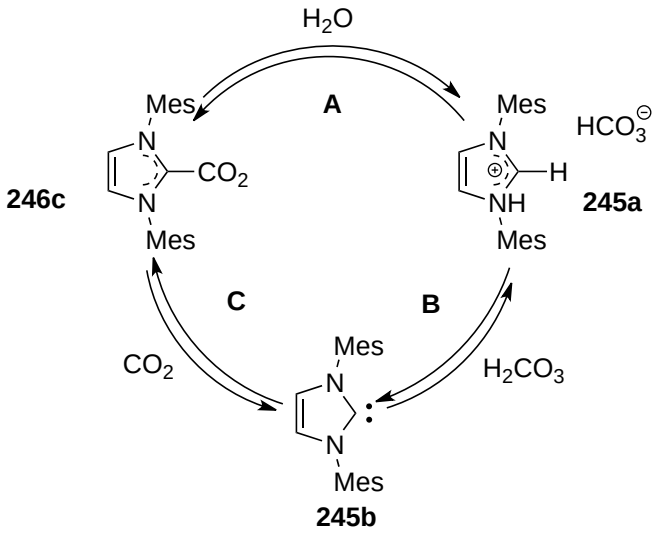
Boc-L(*N*-Me-Taz)I-^{A}Gly-L-Cha-L-Phe-OMe **237** Yield: 20%

Scheme 43: Benzoin condensation catalyzed by **235** and **237** under optimized conditions.

The benzoin condensation utilizing **237** yielded 20% of benzoin and 5% *ee*. A reason for the low yield may be the lower pK_a value (14.5 in DMSO) compared to **235** (21.1 in DMSO).

Prolonging the reaction time to 48 h did not increase the yield. This finding was unexpected due to the fact that other chiral thiazolium-salt-based catalysts achieved quantitative yield in 15 h with 5 mol% catalyst loading and Et_3N as a base.[169] In an intramolecular Stetter reaction, a dipeptide (**222**) with a thiazolium moiety also yielded 60–70% of pure product. A reason for the low yields in the benzoin condensations may be the decomposition of the catalyst by the strong base KO^{t}Bu or by itself (*vide infra*).

The fixation of CO_2 by NHCs is known in the literature.[171,172] While the inner salts are stable and can be used without precautions the CO_2/NHC-adducts are labile in solution and are hence utilized as carbene precursors. Taton *et al.* were able to synthesize an air-stable imidazolium hydrogen carbonate [NHC(H)][HCO_3], which equilibrates in solution with its imidazolium carboxylate, the free carbene and H_2CO_3.[173] The concept was tested by utilizing [IMes(H)][HCO_3] **245a** as catalyst in a benzoin-condensation (20 mol% [IMes(H)][HCO_3], THF, 60 °C) and benzoin was obtained in 88% yield (determined by NMR). A big advantage of the hydrogen carbonate NHC is that no additional base is required for carbene generation.



Scheme 44: Equilibrium of [IMes(H)][HCO_3] in H_2O.

We tested the formation of [IMe(H)][HCO_3] and measured ^{1}H-NMR and ^{13}C-NMR spectra in a mixture of methanol-d_4 and D_2O (Figure 21). While in D_2O the acidic proton could be observed, its peak intensity decreased in methanol-d_4/D_2O. For **245**, no peak was observed due to the rapid exchange with the deuterated solvent on the NMR time scale. In the ^{13}C-NMR spectrum, a signal at 161.4 ppm appeared for **245**, which could be assigned to HCO_3^-. The results are in accordance with those reported in literature.[173]

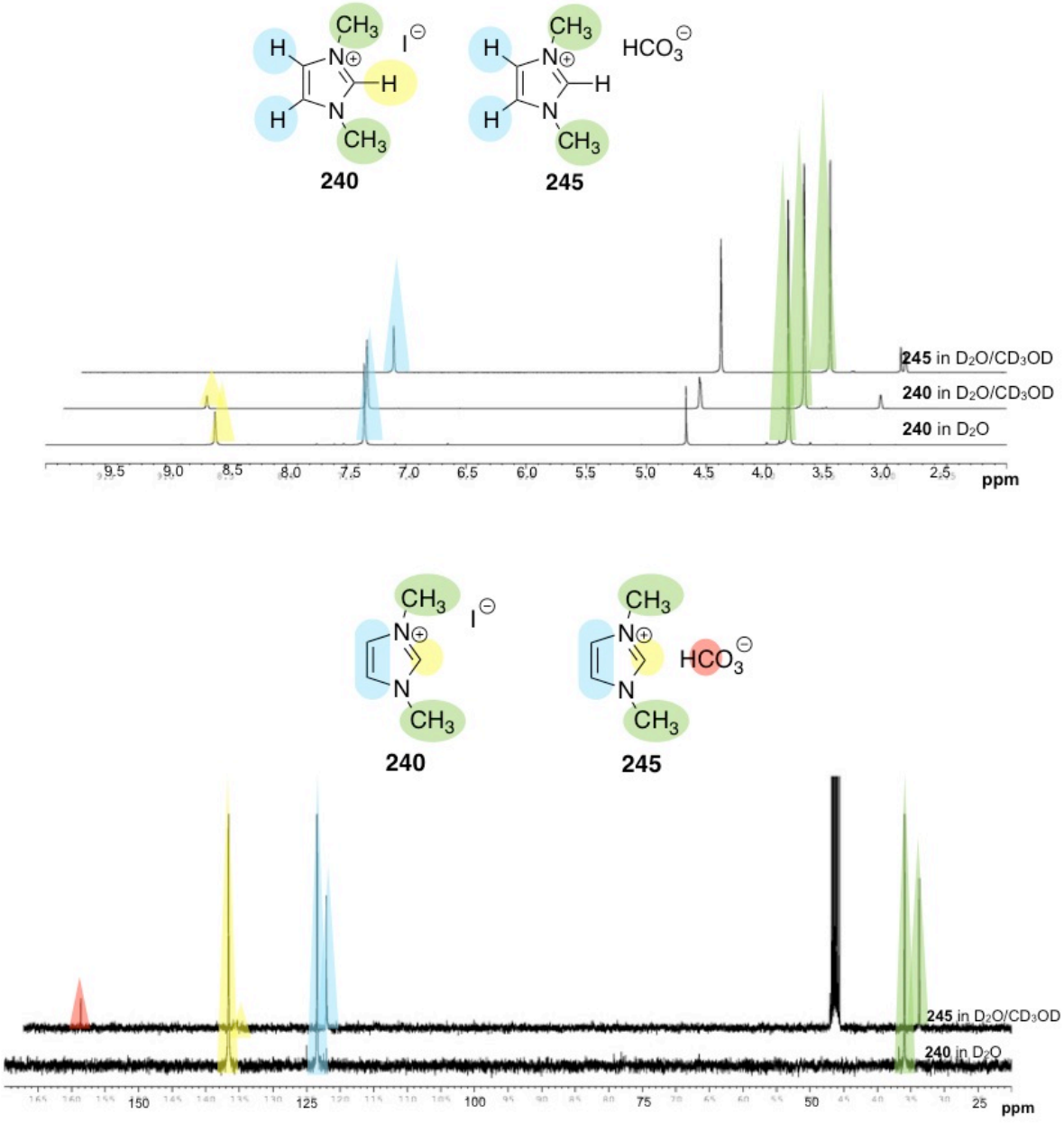
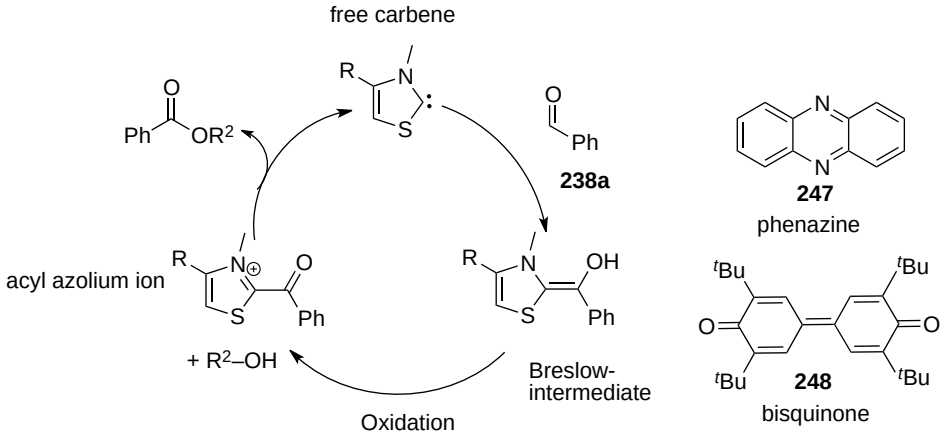


Figure 21: Comparison of the ^{1}H- and ^{13}C-spectra of **240** and **245**.

In contrast to literature reports, no signals indicating a NHC-CO_2-adduct were found. A benzoin condensation under the reaction conditions described in the literature (20 mol% [IMe(H)][HCO_3] , THF, 60°C, 24 h) was performed, but no product was observed.[173] Hence, this concept was not pursued further for peptides **235** and **237**.

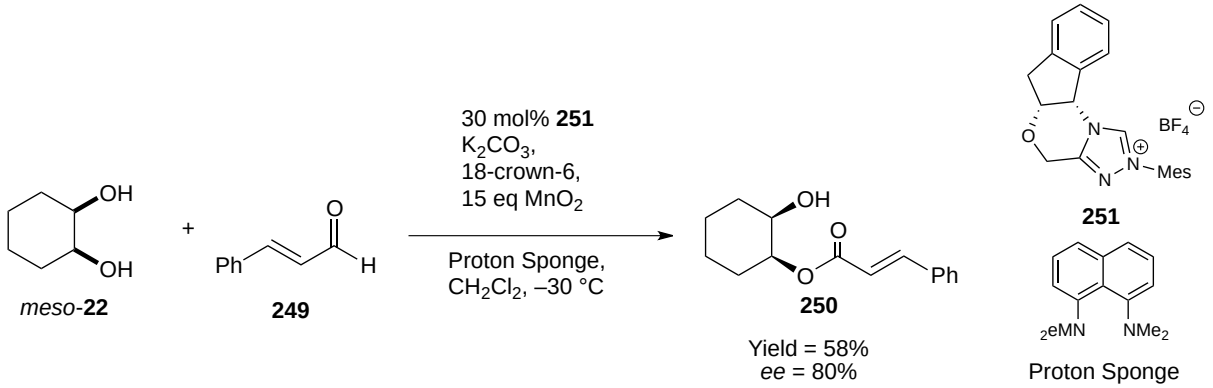
9.2 Oxidative Esterification Reactions Utilizing Peptidic NHCs

NHCs are capable catalysts for oxidative esterifications of alcohols and thioles using aldehydes as the acylating agent.[174-176] For the oxidation an excess of external oxidant or an internal redox reaction is required. It is proposed that, within the presence of a suitable oxidant, the *in-situ*-formed Breslow intermediate can be oxidized to give an acyl azolium ion. The nucleophilic alcohol attacks the acylating agent, generates the ester and regenerates the NHC catalyst.[175-177] Different inorganic substrates like MnO_2 and organic heterocycles can serve as the oxidant (Scheme 38).[178] Only recently, biomimetic two-component organocatalysts with redox-active flavin derived from riboflavin (vitamin B_2) has been reported.[178] Kinetic resolutions and desymmetrizations of alcohols in the context of NHC-catalysis are also known in literature.[174,178,179]



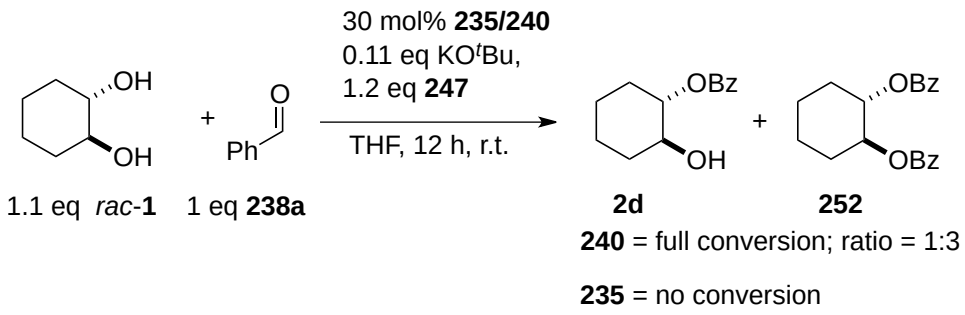
Scheme 45: Proposed mechanism for the oxidative esterification of aldehydes mediated by carbenes.

The asymmetric functionalization of *cis*-cyclohexane-1,2-diol *rac*-**22** was investigated by Scheidt *et al.* and produced **250** in 58% yield and 80% *ee*.[174]



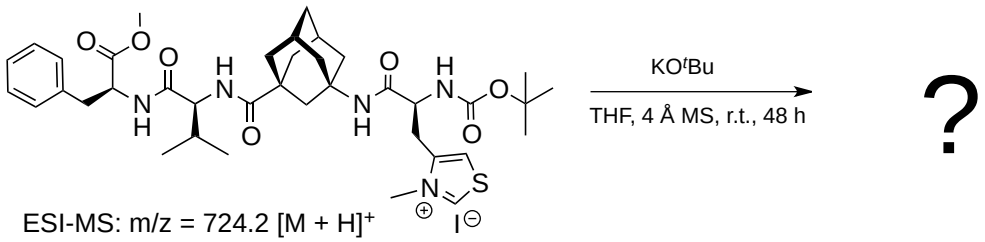
Scheme 46: Oxidative desymmetrization of *meso*-**22**.

The structural similarity between catalyst **12i** and **235** and **237** may enable a selective oxidative esterification of *rac*-**1** using aldehydes as acylating agents. We started with precursor **240** and tested MnO_2 and phenazine **247** as oxidants. MnO_2 yielded only 4% of the monobenzoylated **2d**, whereas by using the organic oxidant phenazine, full conversion and a 1:3 ratio of **2d**:**252** was detected *via* GC after 20 h.



Scheme 47: Oxidative esterification of *rac*-**1** with **235** and **240**.

Peptide **235** showed no conversion under similar reaction conditions. The reaction is possible, but the conditions need to be optimized. The low activity of the peptidic catalysts **235** and **237** in the benzoin condensation and esterification reactions disclose a general reactivity problem of NHCs with a peptidic backbone. Based on this finding, the stability of a peptidic carbene precursor **237-V** under standard conditions (THF, KO^{t}Bu, 4Å MS) was tested.

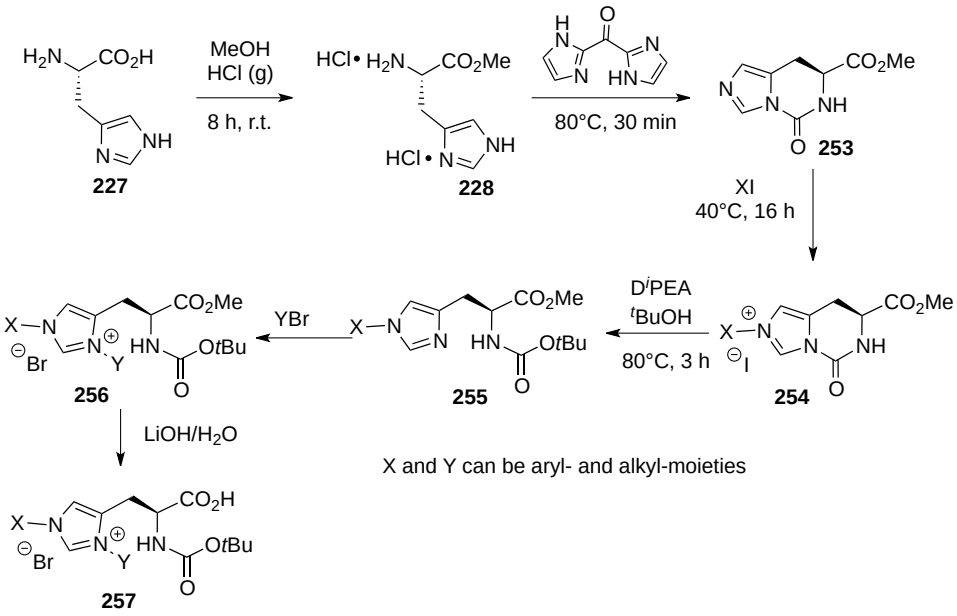


Scheme 50: 237-V before and after the treatment with KO^{t}Bu under the reaction conditions used for the benzoin condensation.

After 48 h, the solvent and the molecular sieve were removed and the residue was dissolved in MeOH. The ESI-MS spectrum did neither show m/z = 724.2, nor an other particular mass. The reisolation of the catalyst was not possible either. Therefore, the decomposition of the catalyst appears to be likely. In contrast, the mass of **12i** (m/z = 761 M+H) could be detected in the ESI-MS spectrum, after stirring the peptide in the presence of KO^{t}Bu in THF for 72 h at

r.t. The decomposition of the peptide seems to be induced by the carbene. Maybe shorter peptides (e.g., tripeptides) should be synthesized and tested in the benzoin condensation, because an intramolecular attack of the carbene is less favored in a shorter peptide.

The decomposing may also be avoided by introducing bulkier substituents at the nitrogen atoms of the histidine imidazole-moiety of histidine. In 2006 Guillen *et al.* reported a synthetic route to various π- and τ-substituted histidinium salts:[180]



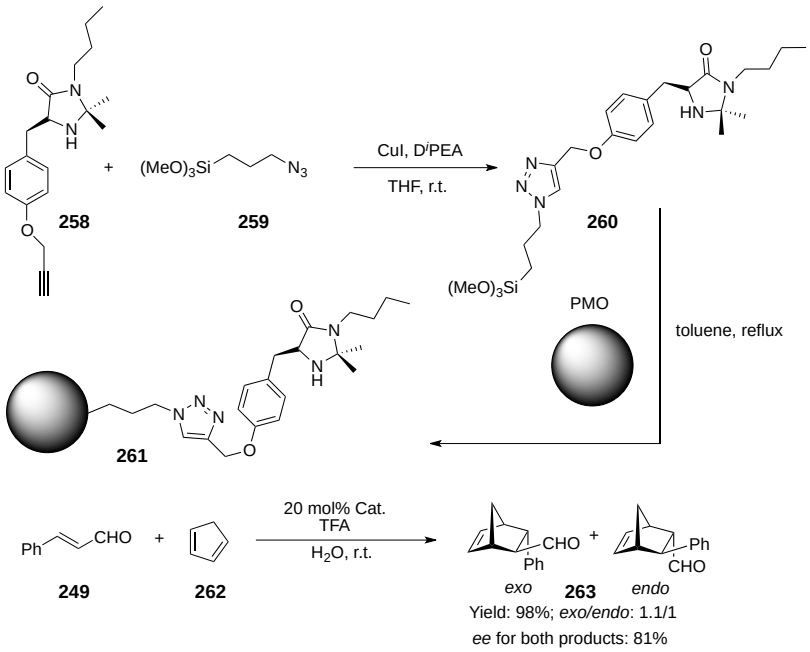
Scheme 51: Synthetic route for the preparation of various π- and τ-substituted histidinium salts.

The higher steric demand of bigger substituents at the NHC may keep the other amino acids at distance, thereby preventing the attack of the nucleophilic carbene at the peptidic backbone.

10. Outlook

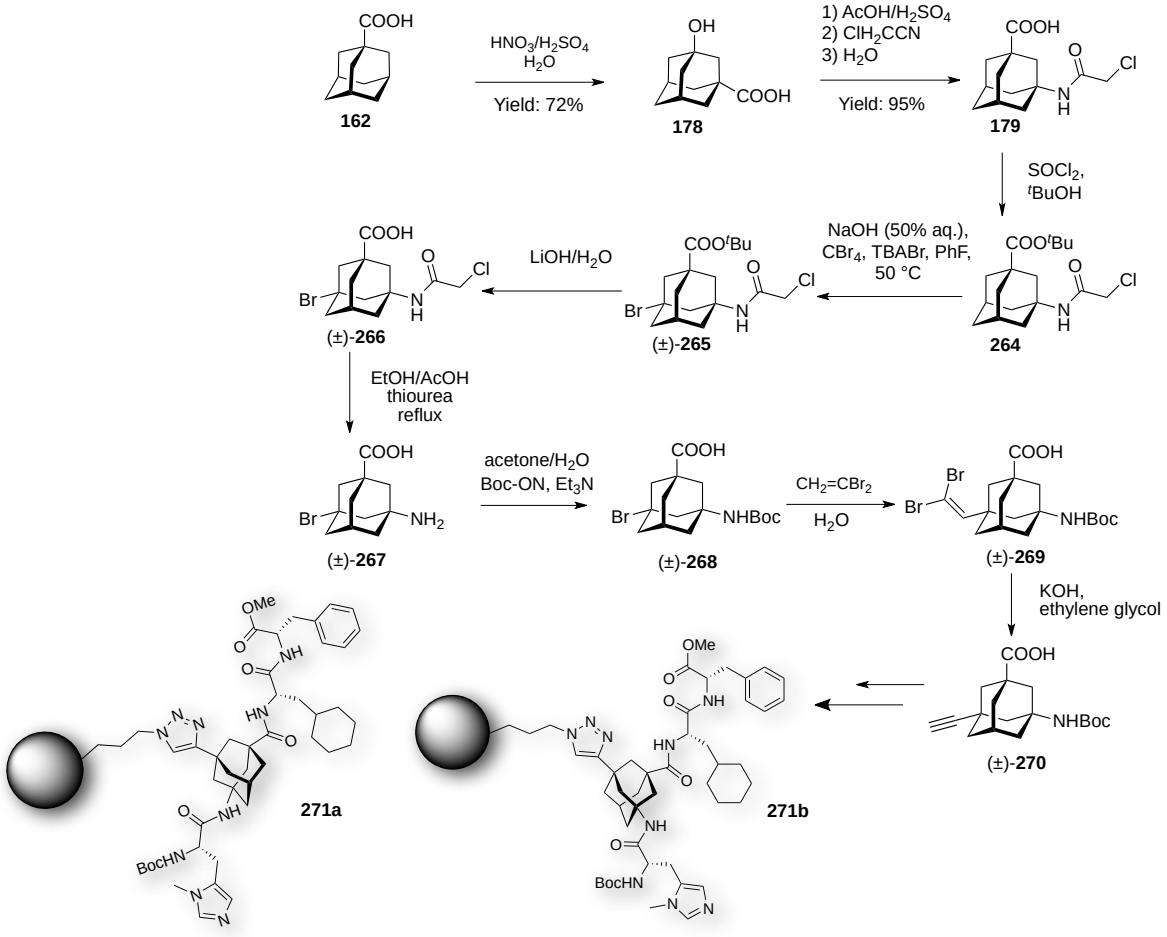
10.1 Immobilization of Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe

Wang *et al.* immobilized MacMillan's catalyst on periodic mesoporous organosilica spheres (PMO)[181] by "click chemistry".[182] The heterogeneous catalyst system showed high activity and selectivity in an asymmetric Diels-Alder reaction. The catalyst could be reused seven times without a significant loss of reactivity.



Scheme 52: MacMillan's immobilized catalyst on PMO (periodic mesoporous organosilica spheres).

The KR of *rac*-**1** was tested with **12a-**resin (the peptide was not cleaved from the resin), but only a low selectivity was observed. Modifications of peptide **12i** at the adamantane core (**207** and **208**) did not decrease the selectivity for the KR of *rac*-**1** drastically and therefore an immobilization at this position might be possible. Unfortunately **207** and **208** were only methylated and therefore it is not known whether bigger substituents at the adamantane core will also not decrease the selectivity. The synthesis of an ^{A}Gly bearing an additional alkine moiety would be necessary. The following synthesis route may be applicable, but unfortunately, nine synthetic steps are required for the Boc-protected amino acid with an additional alkine moiety.[183]

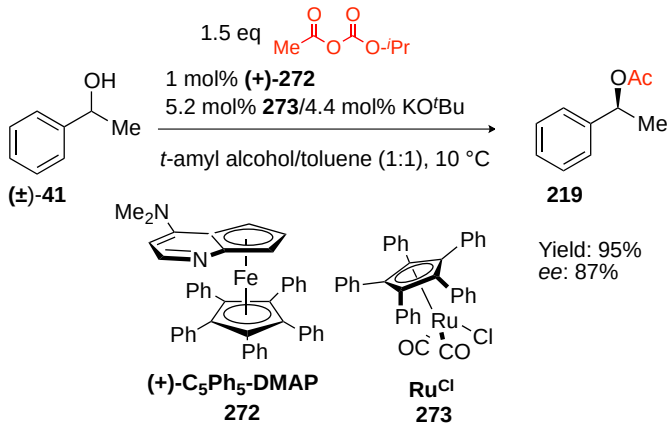


Scheme 53: Synthetic route for the preparation of ^{A}Gly precursor with an additional alkine substituent for “click chemistry”.

The immobilization would yield a mixture of **271a** and **271b** and the effect on the selectivity of the KR of *rac*-**1** can hardly be predicted. However, the inversion of even one stereogenic center at the backbone of **12i** usually has a negative effect on the *ee* (see chapter 3).

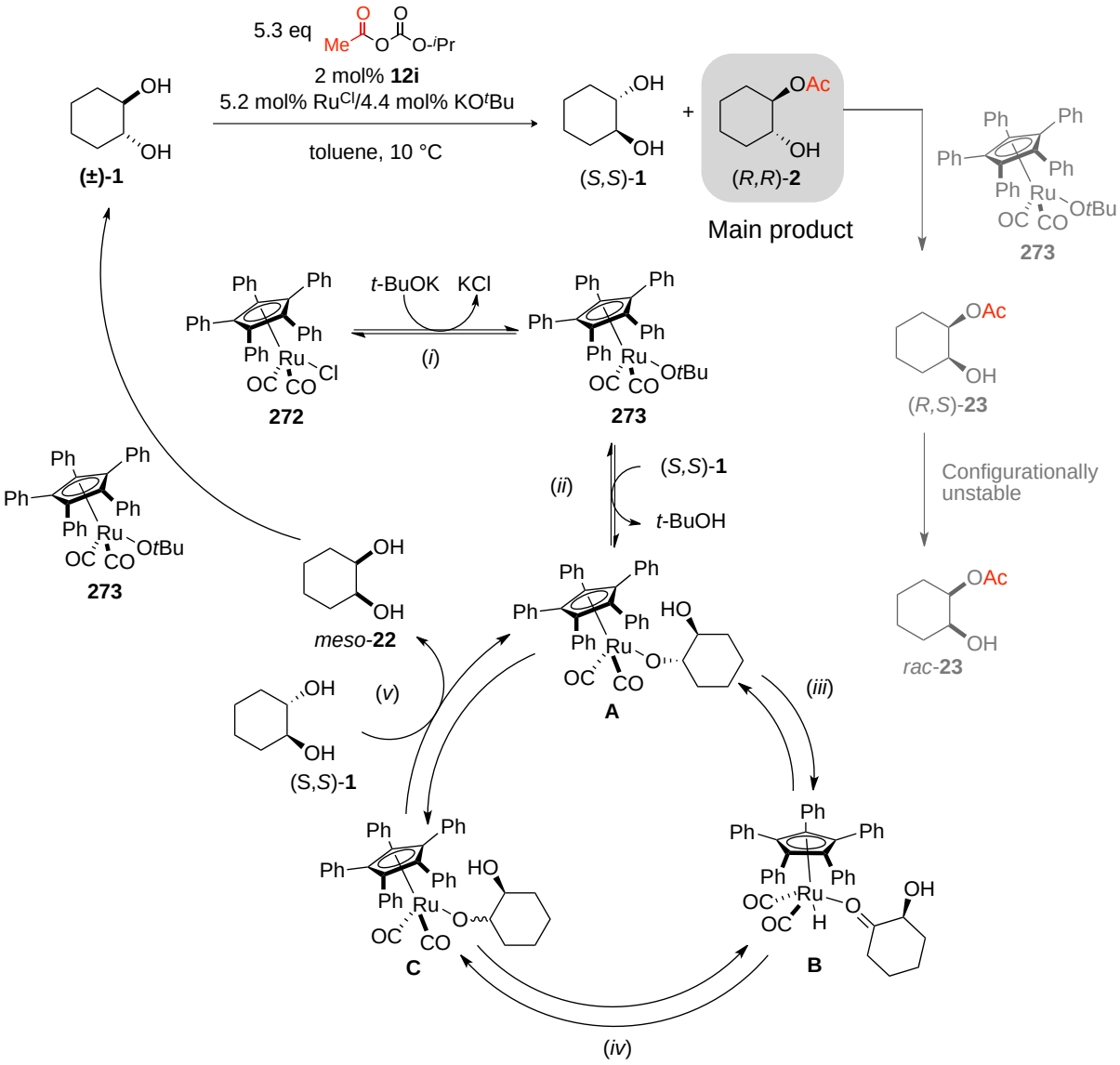
10.2 Dynamic KR of *trans*-Cycolhexane-1,2-diol *via* Combination of Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe and a Metal-Complex

As mentioned introductorily metal complexes are capable of racemizing chiral alcohols. Bäckvall and coworkers successfully combined a ruthenium complex for the racemization with enzymes for selective acyl transfer (see Introduction) and hence increased the possible yield (dynamic KR with a theoretical yield of 100%).[184,185] In 2012, Fu *et al.* reported the dynamic KR of *rac*-phenylethanol under modified conditions utilizing their planar-chiral DMAP-derivative and a racemization catalyst introduced by Bäckvall.[186]



Scheme 55: Dynamic KR of *rac*-**41** utilizing a metal complex for the racemization and an organocatalyst for the enantioselective acyl transfer.

Probably a similar concept could be applied to our catalytic system and the yield of **2** could be increased. In contrast to the system of Fu *et al.*, peptide **12i** shows the highest selectivity towards *rac*-**1**. Hence, both steriogenic centers can be racemized by **273**/**274** and a mixture of, e.g., rac-**1** and *meso*-**1** could be generated. In our case this should not be a problem, because (*R,R*)-**1** reacts much faster than *meso*-**1** and (*S,S)*-**1**, and is therefore the preferentially acetylated substrate. A problem could occur if the reaction of the metal-complex **272** with (*R,R*)-**2** is as fast as the inversion of the steriogenic centers of *meso*-**1**, (*SS*)-**1** and (*RR*)-**1,** because in this case, the enantiopure product may be transformed into (*R,S*)-**2,** which is not configurationally stable and will again racemize to *rac*-***2***.[67] For that reason, this dynamic KR will only work, if the racemization of (*R,R*)-**2** is slow due to a higher steric demand.

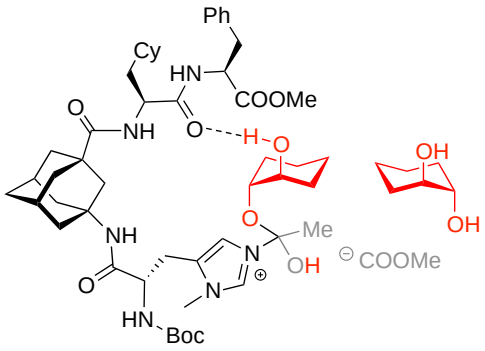


Scheme 56: From KR to DKR: Pro and contra.

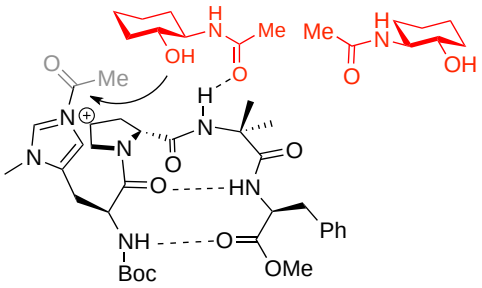
11. Abstract

In 2008/2009, a highly enantioselective tetrapeptide for the kinetic resolution (KR) and desymmetrization of cyclic *rac*- and *meso*-cycloalkane-1,2-diols was introduced by Schreiner *et al.* The conceptual difference between Miller's and Schreiner's approaches is that Miller utilizes amino acids like proline to induce a *β*-turn and generate a secondary peptide structure. The folded structure is fixed by hydrogen bonds and a "pocket" is formed in which enantioselective transformations (e.g., acetylations, sulfonylations and phosphorylations) can occur. In contrast, Schreiner *et al.* use a rigid adamantane amino acid in the middle of the peptide as a rigid spacer to separate both sides of the peptide in order to generate a chiral environment.

Schreiner



Miller



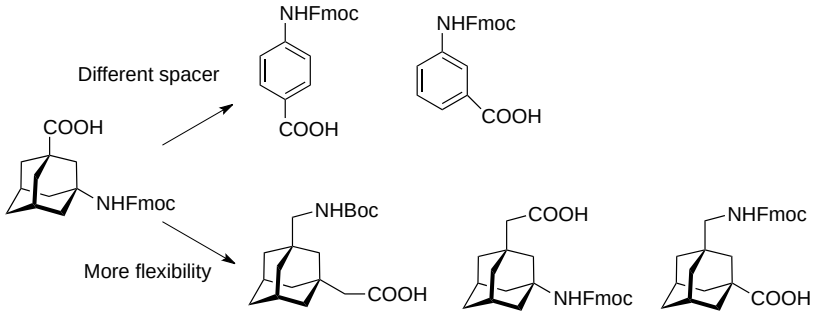
Miller mainly uses screening methods and peptide libraries for the identification of new enantioselective peptides, because catalyst/substrate interactions are hardly predictable due to their high complexity. Thus, rational catalyst design is difficult.

In this thesis, spectroscopic- and computational methods (NMR- and IR-spectroscopy as well as MMFF-computations) have been utilized to shed some light on the interactions (catalyst/substrate) responsible for the selectivity. It has been shown that the solvent highly influences the structure of the catalyst, because in non-polar solvents (e.g., toluene) the peptide has a "tighter" structure and IR-signals at 3300 cm^{-1}, which can be related to hydrogen bonding interactions, whereas no such signals are found at 3300 cm^{-1} in $CDCl_3$ at r.t.

In the second project, Schreiner's catalyst was tested in KR-experiments with different electrophiles (e.g. Boc_2O, AcCl, diphenylchlorophosphate, diethylchlorophosphate and various benzenesulfonylchlorides) to see the influence of the electrophile on the selectivity. It was found that the selectivity depends on the counterion of the electrophile as well as on the electrophile itself. For Ac_2O and Boc_2O, good selectivities could be observed, while sulfonylation-, phosphorylation and acetylation reactions (utilizing AcCl) were unselective.

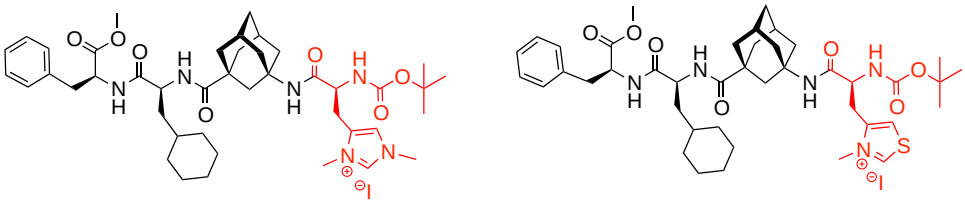
The influence of hydrogen bonding interactions on the selectivity was also tested by using *trans*-1,2-diaminocyclohexane, *trans*-2-aminocyclohexane-1-ol, *trans*-cyclohexane-1,2-dithiol and *trans*-2-mercaptocyclohexane-1-ol as substrates in the KR. For *trans*-cyclohexane-1,2-dithiol, which can only form weak hydrogen bonds to the peptide, and *trans*-2-mercaptocyclohexane-1-ol, which can only form one strong hydrogen bond, some activity, but no selectivity was observed. Strong hydrogen bonding interactions seem to be responsible for the selectivity, because for the structural related amino alcohol, diamine, dithiol and mercoptoalcohol, some activity, but only low (diamine) or no selectivity (dithiol) was found.

The third project dealt with the synthesis of modified adamantane amino acids (AAA), their incorporation into the model peptide and the utilization of the modified peptides in the KR of *trans*-cyclohexane-1,2-diol, *trans*-cyclohexane-1,3-diol, 1-phenylethanol and BINOL.



Unfortunately, all structural changes at the *i + 1* position (more flexible AAAs or 3- and 4-amino benzoic acid), a *β*-amino acid at the *i +2* position decreased the *ee* for the KR of *trans*-cyclohexane-1,2-diol. In contrast, additional substituents at the adamantine core, new aromatic amino acids at the *i +2* position and the replacement of the Boc-group by an acyl moiety only had a low impact on the selectivity. For *trans*-cyclohexane-1,3-diol, no selectivity was observed, while a new peptide showed some selectivity for 1-phenylethanol. For BINOL the best selectivities were observed with the unmodified catalyst.

In the forth section, a novel catalytically active moiety (carbene precursor) was introduced into the standard catalyst.



The synthesis of two different peptides bearing a dimethylimidazolium- or methylthiazolium-salt-group is described. The peptides as well as dimethylimidazolium iodide were tested in benzoin condensations, but in contrast to dimethylimidazolium iodide, only low product yields were observed. Unfortunately, the catalyst decomposes under the reaction conditions utilized for the benzoin condensation. Hence, further investigations will be necessary.

12. Experimental Part

Chemicals

Unless otherwise noted, all chemicals were purchased from Acros Organics, Alfa Aesar, Sigma Aldrich, Merck, Novabiochem, Fluka and TCI in the highest purity grade available. All solvents were distilled prior to use. All aldehydes were freshly distilled. Acetic anhydride, acetyl chloride, diphenylchlorophosphate, diethylchlorophosphate, chloroacetonitrile and *trans*-1,2-diaminocyclohexane were distilled and stored under argon. Potassium *tert*-butylate and K_2CO_3 were dried at 100 °C *in vacuo* and stored under argon. DBU, Et_3N, and D^iPEA were distilled and dried prior to use. All catalytic reactions were carried out under argon atmosphere (99.99%, Messer Griesheim) employing oven- and flame-dried glassware.

Purification of the solvents

All glassware was flame-dried and flushed with argon.

Tetrahydrofuran: THF was stored over KOH for one day. After distillation the solvent was refluxed for several hours under argon with sodium and benzophenone until the solution turned blue. Anhydrous THF was stored over molecular sieve 4 Å under argon.

Toluene: Toluene was refluxed under argon with sodium and benzophenone for several hours until the solution turned blue. Anhydrous toluene was stored over molecular sieve 4 Å under argon.

Methanol: Methanol was refluxed under argon with pieces of magnesia for 3 h. Subsequently, MeOH was distilled off and stored over molecular sieve 3 Å.

NMR

^1H- and ^{13}C-NMR spectra were recorded on Bruker BioSpin Avance II AV600 (600 MHz), AV400 (400 MHz) or AV200 (200 MHz) spectrometers using TMS as an internal standard with chemical shifts given in ppm relative to TMS (δ = 0.00 ppm) or the respective residual solvent peaks. ^1H-NMR data are reported as follows: chemical shifts (multiplicity [ppm], coupling constants [Hz], integration, classification). Multiplicity is recorded as s = singlet, bs = broadened singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet and sept = septet. For ^{13}C-NMR chemical shifts and partial assignments are reported.

ESI-MS

ESI mass spectra were recorded on a Finnigan LCQDuo spectrometer using methanol solutions of the respective compounds.

Column chromatography

Flash column chromatography and filtration were performed using Merck silica gel 60 Å (0.040 – 0.063 mm mesh size).

Thin-layer chromatography

Analytical thin-layer chromatography (TLC) was performed using pre-coated polyester sheets Polygram® SIL G/UV_{254} Machery-Nagel, 0.2 mm silica gel with fluorescent indicator. Visualization was accomplished by irradiation with a UV lamp and/or molybdophosphoric acid solution (5% $H_3[P(Mo_3O_{10})_4]$ in ethanol).

GC-FID

GC analysis was performed utilizing a Hewlett Packard 5890 gas chromatograph combined with flame ionization detection.

HPLC

Chiral, analytical and normal phase HPLC was performed *via* a Spectra SP 8700 equipped with a UV detector (λ = 220 and 254 nm).

Polarimetry:

The specific optical rotation was measured on a Jasco P-2000 spectrometer utilizing a 1mL cell with d = 10 cm.

HR-ESI:

Accurate masses were measured on a Bruker microTOF LC.

The mass accuracy of these measurement is in the range of 5 ppm.

IR:

Low temperature IR experiments:

IR measurements were performed on a Bruker IFS 25 IR spectrometer. We utilized a variable temperature-measuring cell equipped with CaF_2 windows. The solution was filled into the NaF_2 cell (d = 0.1 mm) and cooled to the desired temperature by adding liquid nitrogen. The temperature varied less than 1 K during the process of data acquisition. The spectra (30 scans) were obtained with 2 cm^{-1} resolution. Solvent subtraction was accomplished by utilizing reference spectra obtained at the same temperature as the sample

spectra.

The IR measurements at different concentrations were performer on a Bruker Alpha IR spectrometer. We utilized a KBr cell (d = 0.5 mm)

General procedures

General procedure I: HBTU/HOBt mediated peptide coupling in solution

All peptides were prepared employing standard solid phase peptide synthesis techniques (SPPS), utilizing Fmoc-protected amino acids. HBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) was used as the coupling agent and HOBt (1-hydroxybenzotriazole) as a racemization suppressant. Couplings were performed utilizing two times 2 eq of amino acid, 2 eq HOBt, 2eq HBTU and 4 eq D^{i}PEA in DMF for 30 min.
Fmoc-L-Phe-Wang resin was used as solid support and swollen in DMF for 30 min. prior first Fmoc-cleavage.

General procedure II: Fmoc-cleavage on solid support

Cleavage of *N*-terminal Fmoc-protective groups was accomplished by dissolving the solid phase supported peptide twice in 25% piperidine in DMF (25 min.). Prior the next coupling step the resin was washed five times with DMF, DCM and DMF. For storage, the resin should be washed five times with DMF, DCM and diethyl ether and be kept in a refrigerator until use.

General procedure III: Peptide cleavage from the resin

Peptides were cleaved from their resins as methyl esters by shaking the functionalized resin twice for 2 days with methanol/Et_3N/THF (9 : 1 : 1). The resin was filtered off and washed several times with chloroform. The collected solutions were concentrated under reduced pressure and purified *via* silica flash gel chromatography eluting with chloroform/methanol (95 : 5).

General procedure IV: Fmoc-protection of adamantane amino acids

The adamantane amino acid hydrochlorides and 4.5 equiv. of Na_2CO_3 were suspended in water/acetone (1 : 1). During stirring and cooling in an ice bath, 1.1 equiv. of Fmoc-Cl (9-fluorenylmethyl chloroformate) in acetone were added with an addition funnel. The mixture was stirred at r.t. for about 12 h. Acetone was evaporated under reduced pressure (the temperature of the water bath should not exceed 30 °C) and the mixture poured on ice and

extracted with diethyl ether. The aqueous phase was carefully acidified with conc. HCl (pH ≈ 4) and the precipitate was three times extracted with ethyl acetate. The combined organic phases were washed with water, dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by recrystallization from nitromethane. The protected amino acids were dried in a desiccator over paraffin wax and P_2O_5 under reduced pressure.

General procedure V: Boc-protection of adamantane amino acids

The adamantane amino acid hydrochlorides and 1.0 equiv. NaOH were dissolved in water and refluxed for about 2 h. The adamantane amino acid was filtered off and dried in a desiccator over P_2O_5 under reduced pressure.

The unprotected adamantane amino acid was suspended in water/acetone (1 : 1) and 1.5 eq of triethylamine were added. Then 1.0 eq of Boc-ON (2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile) was added and the reaction mixture was stirred for 24 h. Another 1.0 equiv. of Boc-ON was added and after 24 h the mixture was poured on ice and 0.2 equiv. Na_2CO_3 were added. Acetone was evaporated under reduced pressure (the temperature of the water bath should not exceed 30 °C) and five times extracted with diethyl ether. The aqueous phase was carefully acidified with conc. HCl (pH ≈ 4) and the precipitates were three times extracted with EtOAc. The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated. Drying in a desiccator over paraffin wax and P_2O_5 under reduced pressure yielded the protected amino acids.

General procedure VI: EDC/HOBt mediated peptide coupling in solution

The same equivalents of *N*-protected amino acids or peptide fragments, 1.1 eq of EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), 1.1 eq of HOBt and 1.1 eq of Et_3N were dissolved in DCM and stirred for 12 h at r.t. The reaction mixture was diluted with EtOAc and extracted with 0.5 M citric acid (four times) and saturated $NaHCO_3$-solution. The solvent was removed under reduced pressure and the crude product was dried in a desiccator over paraffin wax and P_2O_5.

General procedure VII: Cleavage of the -O^{t}Bu-protecting group (Boc)

The Boc-protected peptide was dissolved in a solution of HCl in 1,4-dioxane (4.0 M) and stirred for 1 h. The excess of HCl was removed by bubbling argon through the solution. After evaporation of the solvent under reduced pressure the deprotected peptide was coupled without further purification.

General procedure VIII: Methylation of the peptides

100 mg of the tetrapeptide were dissolved in 2 mL acetonitrile and 1 ml of CH_3I was added. The reaction mixture was heated to 90 °C and refluxed for 3 days. After one day 1 mL of CH_3I was added. The solvent was removed under reduced pressure and the crude product was purified *via* column chromatography. Isolated products were characterized by ^{1}H- and ^{13}C-NMR spectroscopy and ESI-MS.

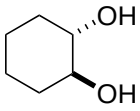
General procedure IX: Synthesis of adamantane amino acid hydrochlorides from their acetamides

The precursor molecules were refluxed in a mixture of conc. hydrochloric acid and water. The hydrochloric acid was removed completely under reduced pressure and the product was dried in a desiccator. The crude hydrochloride was treated with an organic solvent and filtered off *via* suction filtration. Drying in a desiccator over paraffin wax and P_2O_5 under reduced pressure yielded the products.

General procedure X: Enantioselective acylation of chiral alcohols, amino alcohols, dithiols and mercaptoalcohols

0.025 mmol of the alcohol were dissolved in 4.45 mL of dry toluene. 2 mol% of the peptide-catalyst and 13.5 µL (0.1325 mmol) of acetic acid anhydride were added and the mixture was stirred at r.t. or 0 °C. The conversion and enantiomeric excess were determined by chiral GC.

***trans*-Cyclohexane-1,2-diol (1)**



Assay of enantiomeric purity.

Enantiomers of the **1** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250 °C

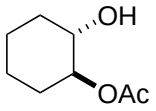
Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100-250 °C, 2 °C/min

Retention times: R_1 = 17.4 min; R_2 = 18.0 min

***trans*-1-Acetoxycyclohexan-2-ol (2a):**



Proof of GC retention times:

Racemic *trans*-cyclohexane-1,2-diol ((±)-**1**) (0.345 g, 3.0 mmol) was treated with acetic anhydride (371 µL, 4 mmol) in the presence of *N,N*-dimethylaminopyridine (0.073 g, 0.6 mmol) in 20 mL DCM and the resulting solution was stirred for 6 h at r.t. DCM was then removed *in vacuo*, and the mono- and diacetylated product were purified *via* silica flash gel chromatography (EtOAc, R_f = 0.70; R_f = 0.81). Isolated racemic **2** was characterized and then subjected to the GC assay described above to verify the origin of the GC signals.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 4.87 – 4.73 (m, 2 H, C*H*OAc), 2.14 – 2.00 (m, 2 H, C*H*) 2.03 (s, 6 H, CH_3), 1.78 – 1.65 (m, 2 H, C*H*), 1.47 – 1.24 (m, 4 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 170.5 (C=O), 73.7, 30.1, 23.4, 21.2.

HR-MS (EI): m/z = 201.114 $[M+H]^+$ (calc. m/z = 201.113)

The NMR data are in accordance with the literature.[60]

Assay of enantiomeric purity.

Enantiomers of **2** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250°C

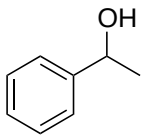
Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100-250 °C, 2 °C/min

Retention times: R_1 = 15.9 min; R_2 = 16.2 min.

(±)-1-Phenylethanol (41)



Assay of enantiomeric purity.

Enantiomers of **41** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).T (Injector + Detector) = 250°C

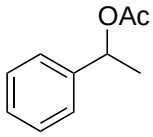
Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100-250 °C, 10 °C/min

Retention times: R_1 = 6.4 min; R_2 = 6.6 min

1-Phenyl-1-acetoxy-ethane (219)



219 was purchased from Sigma Aldrich and used without further purification.

Assay of enantiomeric purity.

Enantiomers of **219** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250°C

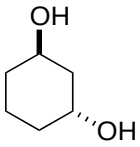
Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100-250 °C, 10 °C/min

Retention times: R_1 = 5.2 min; R_2 = 5.5 min

***trans*-Cyclohexane-1,3-diol (60)**



Assay of enantiomeric purity.

Enantiomers of **60** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDAc column (Macherey Nagel).

T (Injector + Detector) = 250°C

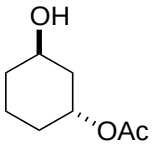
Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 120-250 °C, 5 °C/min

Retention times: R_1 = 26.5 min; R_2 = 27.3 min

***trans*-3-Acetoxy-cyclohexan-1-ol (61):**



Assay of enantiomeric purity.

Enantiomers of monoacetate **61** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250°C

Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 60 °C isothermal for 2 min; then 60–140 °C, 1 °C/min

Retention times: R_1 = 51.1 min; R_2 = 51.9 min

Proof of GC retention times:

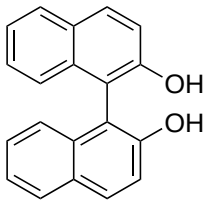
Trans-diol **60** (0.118 g, 1.0 mmol) was treated with acetic anhydride (95 µL, 1.0 mmol) in the presence of DMAP (0.019 g, 0.15 mmol) in 10 mL DCM and the resulting solution was stirred overnight at r.t. DCM was removed *in vacuo*, and the monoacetylated product ((±)-**61**) was purified by silica flash gel chromatography (EtOAc, R_f (**61**) = 0.46). Isolated racemic ((±)-**61**) (0.082 g, 0.7 mmol, 70%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. Additionally 0.035 g (0.18 mmol; 18%) of the diacylated diol **60** (EtOAc, R_f = 0.63) were obtained.

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 5.20 – 5.10 (m, 1 H), 4.03 (sept., 1 H, J = 5.6 Hz), 2.04 (s, 3 H), 1.97–1.37 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 170.5 (C=O), 70.3, 66.9, 38.9, 33.9, 30.1, 21.4, 21.4, 19.1.

The NMR data are in accordance with the literature.[187]

[1,1'-Binaphthalene]-2,2'-diol (Binaphtol) (65):



Racemic [1,1'-binaphthalene]-2,2'-diol (Binaphtol) **65** was purchased from Sigma Aldrich and used without further purification:

Assay of enantiomeric purity.

Enantiomers of diol **65** were separated by using HPLC employing a 25 cm, d = 0.46 cm Chiralpak IB column (Daicel).

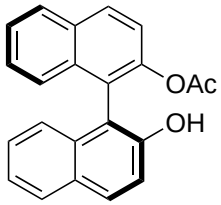
Eluent: Hexane/Isopropanol 95:5

Flow = 1 mL/min

UV-detector λ = 254 nm

Retention times: R_1 = 32.7 min; R_2 = 35.0 min

2'-Hydroxy-[1,1'-binaphthalen]-2-yl acetate (66):



Assay of enantiomeric purity.

Enantiomers of acetate **66** were separated by HPLC employing a 25 cm, d = 0.46 cm Chiralpak IB column (Daicel).

Eluent: Hexane/Isopropanol 95:5

Flow = 1 mL/min

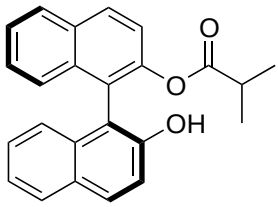
UV-detector λ = 254 nm

Retention times: R_1 = 14.1 min; R_2 = 16.0 min

Proof of GC retention times:

Product **66** was not isolated; a mixture of monoacylated (**66**) and diacylated product were synthesized *via* DMAP catalysis. The products were not separated because the HPLC-signals could be assigned clearly. The NMR data can be found in literature.[189]

2'-Hydroxy-[1,1'-binaphthalen]-2-yl isobutylate (145):



Assay of enantiomeric purity.

Enantiomers of diacetate **145** were separated by using HPLC employing a 25 cm, d = 0.46 cm Chiralpak IB column (Daicel).

Eluent: Hexane/Isopropanol 95:5
Flow = 1 mL/min
UV-detector λ = 254 nm
Retention times: R_1 = 6.6 min; R_2 = 7.3 min

Proof of GC retention times:
Product **70** was not isolated; a mixture of monoacylated (**70**) and **68** was synthesized *via* DMAP catalysis. The products were not separated because the HPLC-signals could be assigned clearly.

General procedure for the KR of *rac*-65 with catalysts 12i, 210, 211 and 213

100 mg (0.35 mmol) **65** and 2 mol% (0,007 mmol) catalyst were dissolved in 65 mL abs. toluene and cooled to a certan temperature. Then 0.5 eq. anhydride (Ac_2O or $(^iPrCO)_2O$) were added and the mixture was stirred for 8 h. The conversion was monitored by TLC ($CHCl_3$; R_f = 0.58 (diacylated product); R_f = 0.5 (**145**); R_f = 0.33 (**65**). The products were not isolated, because the HPLC-signals could be assigned clearly and the *ee* could be determined.

Boc-protection of *rac*-1
Proof of GC retention times using DMAP as catalyst:
Trans-diol **1** (0.58 g, 5.0 mmol) was treated with Boc_2O (1.26 mL, 5.5 mmol) in the presence of DMAP (0.182 g, 1.5 mmol) in 100 mL dry toluene and the resulting solution was stirred overnight at r.t. Toluene was then removed *in vacuo*, and the *O-tert*-butoxylated product ((±)-**2e**), the *O,O*-di-*tert*-butoxylated product ((±)-**88**) and the cyclic carbonate ((±)-**87**) were purified by silica flash gel chromatography (DCM/MeOH (19:1), R_f (**88**) = 0.81; R_f (**87**) = 0.71; R_f (**2e**) = 0.62). Isolated racemic ((±)-**2e**) (0.842 g, 3.9 mmol; 78%; colorless solid) and ((±)-**88**) (0.126 mg, 0.4 mmol, 8%, colorless solid) were characterized and then subjected to the GC assay described to prove the origin of the GC signals. ((±)-**87**) could only be isolated in traces and was therefore synthesized using different reaction conditions. The NMR data for ((±)-**2e**) and ((±)-**90**) are in accordance with the literature.[118]

Proof of GC retention times using *N*-methylimidazole as catalyst:
Trans-diol **1** (0.58 g, 5.0 mmol) was treated with Boc_2O (1.26 mL, 5.5 mmol) in the presence of *N*-methylimidazole (123,2 µL, 1.5 mmol) in 100 mL dry toluene and the resulting solution was stirred overnight at r.t. Toluene was then removed *in vacuo*, and the *O-tert*-butoxylated product ((±)-**2e**), the *O,O*-di-*tert*-butoxylated product ((±)-**88**) and the cyclic carbonate ((±)-**87**) were purified by silica flash gel chromatography (DCM/MeOH (19:1), R_f (**88**) = 0.81; R_f

(**87**) = 0.71; R_f (**2e**) = 0.62). Isolated racemic ((±)-**2e**) (0.821 g, 3.8 mmol; 76%; colorless solid) and ((±)-**88**) (0.94 g, 0.3 mmol; 6%; colorless solid) were characterized and then subjected to the GC assay described to prove the origin of the GC signals. ((±)-**87**) could only be isolated in traces and therefore synthesized using different reaction conditions. The NMR data for ((±)-**2e**) and ((±)-**88**) are in accordance with the literature.[118]

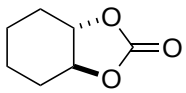
Description of the preparative kinetic resolution experiment of (±)-1 with Boc_2O

Catalyst **12i** (38 mg, 0.05 mmol, 5 mol%) and diol (±)-**1** (116.2 mg, 1 mmol) were dissolved in 160 mL of dry toluene to produce a clear solution. 0.46 mL (2.0 mmol, 2.0 eq) Boc_2O was added and the solution was allowed to stir for 48 h at r.t. The reaction mixture was quenched with 10 mL methanol and then filtered using 40 g silica gel suspended with DCM to remove the catalyst. The solvent was removed under reduced pressure. The crude product was directly purified *via* silica gel column chromatography (DCM/methanol (19:1)). 104.2 mg (0.48 mmol, 48.1%) of **2e** (R_f = 0.62) and 52.1 mg (0.45 mmol, 44%) of **1** (R_f = 0.71) were isolated and directly characterized by chiral GC and NMR spectroscopy.

General procedure: Enantioselective Boc-protection of t*rans*-1,2-cyclohexanediol

2.9 mg (0.025 mmol) of *rac*-**1** were dissolved in 4.45 mL of dry toluene. 1 mol%, 2 mol%, 5 mol% or 10 mol% (0.38 mg, 0.76 mg, 1.9 mg or 3.8 mg) of **12i** and 5.74 µL, 11.49 µL, 28.88 µL or 54.7 (0.025 mmol, 0.05 mmol, 0.1325 mmol or 0.25 mmol) of Boc_2O were added and the mixture was stirred at r.t. The conversion and *ee* were determined by chiral GC.
A stock solution was prepared: 4 mg **12i** in 800 µL of dry toluene.

(3a, 7a)-Hexahydrobenzo-1,3-dioxo-2-one (87)



Proof of GC retention times for the cyclic carbonate 87:

Trans-diol **1** (0.50 g, 4.3 mmol) was treated with Boc_2O (2.94 mL, 12.9 mmol) in the presence of DMAP (0.52 g, 4.3 mmol) in 10 mL of dry acetonitrile and the resulting solution was stirred overnight at r.t. (25 °C). Acetonitrile was then removed *in vacuo*, and the *O,O*-di-*tert*-butoxylated product ((±)-**88**) and the cyclic carbonate ((±)-**87**) were purified by silica flash gel chromatography (hexane/EtOAc (3:1), R_f (**88**) = 0.52; R_f (**87**) = 0.26). Isolated racemic ((±)-**87**) (0.421 g, 3.0 mmol; 70%; colorless solid) and ((±)-**88**) (0.145 mg, 0.46 mmol; 11%; colorless solid) were characterized and then subjected to the GC assay described above to prove the origin of the GC signals.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 3.96 (m, 2 H), 2.19 (m, 2 H), 1.92-1.80 (m, 2 H), 1.69-1.55 (m, 2 H), 1.42-1.29 (m, 2 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 155.1 (C=O), 83.5, 28.2, 23.2.

The NMR data are in accordance with the literature.[118]

Assay of enantiomeric purity.

Enantiomers of the cyclic carbonate **87** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250°C

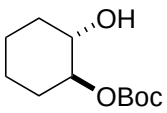
Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100-250 °C, 2 °C/min

Retention times: R_1 = 29.5 min; R_2 = 29.7 min

***tert*-Butyl-2-hydroxycyclohexyl carbonate (2e)**



^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 4.34 (dt, J = 15 Hz, 1 H), 3.57 (dt, J = 15 Hz, 1 H) 2.51 (bs, 1 H), 2.19–2.06 (m, 2 H), 1.76–1.63 (m, 2 H), 1.55 (s, 9 H), 1.42-1.29 (m, 4 H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 153.3 (C=O), 82.1, 80.9, 72.4, 32.7, 29.8, 27.6, 23.7, 23.6.

The NMR data are in accordance with the literature.[118]

Assay of enantiomeric purity.

Enantiomers of the mono *tert*-butoxycarbonylated product **2e** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250°C

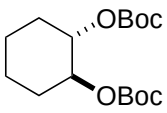
Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100-250 °C, 2 °C/min

Retention times: R_1 = 27.6 min; R_2 = 27.4 min

***tert*-Butylcyclohexane-1,2-diyl dicarbonate (88)**



^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 4.70–4.60 (m, 2 H), 2.19–2.06 (m, 2 H), 1.76–1.63 (m, 2 H), 1.52 (s, 18 H), 1.39-1.23 (m, 4 H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 152.9 (C=O), 82.1, 76.4, 29.9, 27.8, 23.3.
The NMR data are in accordance with the literature.[118]

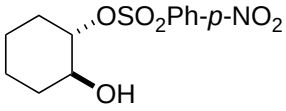
Assay of enantiomeric purity.

Enantiomers of the di-*tert*-butoxycarbonylated product **88** were not separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).
T (Injector + Detector) = 250°C
Splitflow = 80 mL/min
Precolumn pressure = 0.8 bar
Conditions: 100-250 °C, 2 °C/min
Retention times: R_1 = 39.6 min

Sulfonylation of *trans*-1,2-cyclohexanediol using DMAP as catalyst (93)

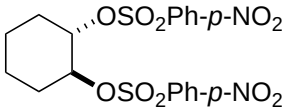
500 mg (4.3 mmol) of *rac*-**1**, 104 mg (20 mol%) of DMAP, 950 mg of (4.3 mmol) 4-nitrobenzenesufonyl chloride and 763 µL of D^{i}PEA were dissolved in 25 mL of dry DCM and stirred for 24 h. The products were purified *via* flash chromatography eluting with ethyl acetate/pentane (3 : 1). 120 mg of **93** (0.4 mmol; 9.3%; R_f = 0.52) and 130 mg of **122** (0.26 mmol; 6.3%; R_f = 0.61) were isolated as yellowish crystals.

***trans*-2-Hydroxycyclohexyl 4-nitrobenzenesulfonate (93)**



^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 8.33 (d, J = 12 Hz, 2 H), 8.08 (d, J = 12 Hz, 2 H), 4.36 (m, 1 H), 3.52 (m, 1 H), 1.99 (t, J = 12 Hz, 2 H), 1.85 (s, 2 H), 1.65 (m, 2 H), 1.43 (m, 1 H), 1.31–1.11 (m, 3 H)
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 150.3, 142.9, 129.1, 124.4, 87.9, 72.0, 32.6, 31.2, 24.0, 23.3.
IR (KBr): v/cm^{-1} = 3538, 2939,1609, 1534, 1351, 1185, 1095, 1076, 981, 926.
HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{12}H_{15}NO_6SNa^+$ 324.0512; Found 324.0513.

***trans*-Cyclohexane-1,2-diyl bis(4-nitrobenzenesulfonate) (122)**



^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 8.29 (d, J = 8 Hz, 4 H), 7.98 (d, J = 8 Hz, 4 H), 4.48 (m, 2 H), 2.04–1.94 (m, 2 H), 1.62–1.55 (m, 2 H), 1.52–1.38 (m, 2 H), 1.28–1.12 (m, 2 H)
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 150.8, 142.4, 129.1, 124.5, 81.3, 31.0, 22.6.

IR (KBr): v/cm^{-1} =2950, 1610, 1538, 1351, 1186, 1094, 977, 919.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{18}N_2O_{10}S_2Na^+$ 509.0295; Found 509.0300.

Assay of enantiomeric purity.

Enantiomers of the monosulfonylated diol **93** were separated by using HPLC employing a 25 cm, d = 0.46 cm Chiralpak IB column (Daicel).

Eluent: Hexane/Isopropanol 90:10

Flow = 0.7 mL/min

UV-detector λ = 254 nm

Retention times: R_1 = 27.8 min; R_2 = 31.9 min

Sulfonylation of *rac*-1 using 12i as catalyst:

116.2 mg (1.0 mmol) of *rac*-**1**, 2 mol% (15.2 mg) of **12i**, 288 mg of 4-nitrobenzenesufonyl chloride were dissolved in 5 mL of dry DCM and 2 mL of a saturated $NaHCO_3$ solution were added. The mixture was stirred for 24 h. The products were purified *via* silica flash gel chromatography eluting with ethyl acetate/pentane (3 : 1). 42 mg (0.13 mmol, 14%) of **93** (R_f = 0.52), 39 mg (0.08 mmol, 8%) of **122** (R_f = 0.61) were isolated. The enantiomeric excess of **1** was determined by chiral GC.

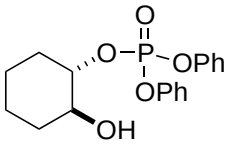
Sulfonylation test reactions

1) 11.6 mg (0,1 mmol) of *rac*-**1** were dissolved in 4.5 mL of dry toluene. 5 mol% (3.8 mg) of **12i**, 12.8 µL (0.11 mmol) of 2,6-lutidine and 20.96 mg (0.11 mmol) of tosyl chloride were added and the mixture was allowed to stir for 24 h. The conversion was determined by TLC using EtOAc/hexane as eluent.

2) 11.6 mg (0,1 mmol) of *rac*-**1** were dissolved in 4.5 mL of dry toluene. 5 mol% (3.8 mg) of **12i**, 12.8 µL (0.11 mmol) of 2,6-lutidine and 21.1 mg (0.11 mmol) of 4-chlorobenzenesulfonyl chloride were added and the mixture was allowed to stir for 24 h. The conversion was determined by TLC using EtOAc/hexane as eluent.

3) 11.6 mg (0,1 mmol) of *rac*-**1** were dissolved in 4.5 mL of dry toluene. 5 mol% (3.8 mg) of **12i**, 12.8 µL (0.11 mmol) of 2,6-lutidine and 18.2 µL (0.11 mmol) of trifluoromethanesulfonic anhydride were added and the mixture was allowed to stir for 24 h. The conversion was determined by TLC using EtOAc/hexane as eluent.

***trans*-2-Hydroxycyclohexyl diphenyl phosphate (94-Ph)**



580 mg (5 mmol) of *rac*-**1**, 0.826 mL (5 mmol) of D^{i}PEA and 183 mg (1.5 mmol) of DMAP were dissolved in dry toluene. 1.035 mL (5 mmol) of diphenylchlorophosphate were added and the mixture was stirred for 12 h at r.t. The solvent was removed under reduced pressure and the crude mixture was purified *via* silica gel chromatography utilizing EtOAc/hexane (3:2) as eluent. 578 mg (1.6 mmol, 33.2%; R_f = 0.35) of a colorless solid were isolated.

The same reaction was accomplished using 22 mg (0.03 mmol) of **12c** as catalyst. The reaction was stopped at a conversion of 50 %. The crude product was purified by preparative HPLC (eluent: TBME/Hexane 60:40; UV-detector λ = 254 nm, E_{max} = 2.56; refractometer; column l = 250 mm, d = 8 mm, LiChrosorb Diol (7 µm, Merck); 70 mg (0.2 mmol; 40%) of a colorless solid were isolated. The product seems to be sensitive towards acids.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.41–7.31 (m, 4 H, H_{Ar} (Phe)), 7.29–7.17 (m, 6 H, H_{Ar} (Phe)), 4.34 (m, 1 H, $H_α$ ($OP(OPh)_2$)), 3.61 (m, 1 H, $H_α$ (OH)), 2.95 (s, 1 H, OH), 2.17–2.09 (m, 1 H), 2.08–2.00 (m, 1 H), 1.77–1.64 (s, 2 H), 1.49–1.40 (m, 1 H), 1.36–1.19 (m, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 150.6, 129.8, 125.5, 120.1, 85.3, 73.3, 32.4, 31.2, 23.9, 23.5.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{21}O_5PNa^+$ 371.1025; Found 371.1019.

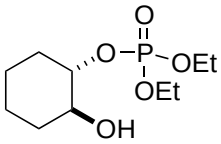
IR (KBr): v/cm^{-1} = 3471.6, 2936.6, 1589.0, 1489.5, 1265.4, 1186.9, 1086.4, 1018.2, 955.4, 774.0.

Assay of enantiomeric purity.

Enantiomers of the mono *tert*-butoxycarbonylated product **94-Ph** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250°C
Splitflow = 80 mL/min
Precolumn pressure = 0.8 bar
Conditions: 140 °C isotherm 13 min
140–250 °C, 2 °C/min
250 °C isotherm 15 min
Retention times: R_1 = 37.5 min; R_2 = 37.9 min (**94-Ph**)
R_1 = 10.4 min; R_2 = 10.9 min (**1**)

***trans*-2-Hydroxycyclohexyl diethyl phosphate (94-Et)**



290 mg (2.5 mmol) of *rac*-**1**, 0.35 mL (2.5 mmol) of D^{i}PEA and 91.6 mg (0.75 mmol) of DMAP were dissolved in dry toluene. 0.36 mL (2.55 mmol) of diethylchlorophosphate were added and the mixture was stirred for 12 h at r.t. The solvent was removed under reduced pressure and the crude mixture was purified *via* Al_2O_3 gel chromatography utilizing acetonitrile as eluent. 425 mg (1.6 mmol, 67%; R_f = 0.49) of a colorless liquid were isolated.

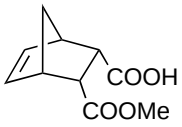
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 4.13–4.01 (q, 4 H, J = 6.8 Hz, O-CH_2-R), 4.00–3.96 (m, 1 H, H_α ($OP(OEt)_2$)), 3.63 (s, 1 H, OH), 3.53–3.47 (m, 1 H, H_α (OH)), 2.14–1.91 (m, 2 H), 1.70–1.58 (m, 2 H), 1.40–1.12 (m, 4 H), 1.32–1.27 (t, 6 H, J = 7.0 Hz, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 83.2, 73.5, 64.1, 32.9 31.7, 24.0, 23.6, 16.1.

IR (Film): v/cm^{-1} = 3404.3, 2938.6, 1453.1, 1258.4, 1028.0.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{10}H_{21}O_5PNa^+$ 275.1022; Found 275.1019.

***(2R,3S)*-3-*endo*-Methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (128)**



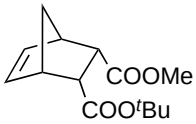
500 mg (3 mmol) of *meso*-**127** were dissolved in 10 mL of dry toluene. 30 mol% (71µL, 0.9 mmol) of methylimidazole and 3 mL of dry methanol were added and stirred for 7 d at r.t. The reaction mixture was concentrated to dryness in *vacuo* and the resulting residue was dissolved in ethyl acetate. The solution was washed with 2 M HCl and dried over Na_2SO_4. The crude product was purified by silica flash gel chromatography eluting with EtOAc (R_f = 0.38). 294 mg (1.5 mmol; 50%) of the product were isolated as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 9.54 (bs, 1 H), 6.24 (m, 1 H), 6.14 (m, 1 H), 3.52 (s, 3 H), 3.23 (dq, J = 10 Hz, 2 H), 3.10 (d, J = 13 Hz, 2 H), 1.41 (td, J = 9 Hz, 1 H), 1.27 (d, J = 9 Hz, 1 H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 178.5, 172.9, 135.7, 134.3, 51.5, 48.8, 48.3, 47.9, 46.5, 46.0

The NMR-data are in accordance with the literature.[122]

2-*tert*-Butyl-3-methyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (129)



507 mg (2.6 mmol) of **128**, 30 mg (0.25 mmol) of DMAP, 1 mL (6.0 mmol) of DIC and 0.5 mL (5.2 mmol) of *tert*-butanol were dissolved in 5 mL of dry DCM and stirred for 1 d at r.t. The precipitates were filtered off and the solution was concentrated to dryness in *vacuo.* The resulting residue was dissolved in DCM and the precipitates were filtered off again. The solution was washed with 0.5 M HCl, $NaHCO_3$ solution and water, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica flash gel chromatography eluting with ethyl acetate/pentane (1 : 1) (R_f = 0.63). 360 mg (1.4 mmol; 55%) of the product were isolated.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.20 (m, 1 H), 5.89 (m, 1 H), 3.57 (s, 3 H), 3.27 (t, J = 4 Hz, 1 H), 3.16 (m, 1 H), 3.00 (m, 1 H), 2.51 (dd, J = 4.8 Hz, 1 H), 1.54 (m, 1 H), 1.39 (s, 9 H), 1.35 (m, 1 H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 174.1, 173.7, 137.8, 135.1, 80.5, 51.9, 48.5, 48.1, 47.9, 47.3, 45.7, 28.2.

GC-MS m/z: $[M]^+$ calcd for $C_{14}H_{20}O_4^{\bullet+}$ 252; Found 252.

Assay of enantiomeric purity.

Enantiomers of the 3-*endo*-Methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-*tert*-butylester were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250°C

Splitflow = 80 mL/min

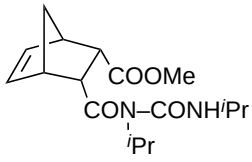
Precolumn pressure = 0.8 bar

Conditions: 110 isotherm (60 min)

110-250 °C, 15 °C/min

Retention times: R_1 = 61.5 min; R_2 = 62.0 min

Methyl-3-(isopropyl(isopropylcarbamyl)carbamyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (130)



Compound **129** was isolated as a byproduct in the synthesis of **128**. The crude product was

purified by silica flash gel chromatography eluting with ethyl acetate/pentane (1 : 1) (R_f = 0.43) and yielded 130 mg (0.4 mmol; 15%) of a colorless product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.25 (bs, 1 H, NH), 6.31 (dd, J = 2.8 Hz, 1 H), 6.15 (dd, J = 2.8 Hz, 1 H), 4.35 (sept, J = 7.0 Hz, 1 H), 3.94 (sept, J = 7.2 Hz, 1 H), 3.57 (s, 3 H), 3.28 (dd, J = 7.2, 2.6 Hz, 1 H), 3.20 (dd, J = 7.2, 2.6 Hz, 1 H), 3.10 (s, 1 H), 2.99 (s, 1 H), 1.40 (d, J = 8 Hz, 1 H), 1.28–1.19 (m, 7 H), 1.36 (q, J = 4.2 Hz, 6 H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 173.9, 154.4, 136.4, 133.4, 52.1, 51.4, 49.2, 48.9, 47.6, 46.8, 45.7, 42.8, 22.6, 22.2, 21.4, 20.1

Competition Experiment with different electrophiles

2.9 mg (0.025 mmol) of *trans*-cyclohexane-1,2-diol **1**, 13.5 µL of (0.1325 mmol) Ac_2O, 27 mg (0.1325 mmol) of 4-nitrobenzenesulfonyl chloride, 19 µL (0.1325 mmol) of $POCl(OEt)_2$ and 80 mg (0.58 mmol) of K_2CO_3 were dissolved in 4.5 mL of abs. toluene and cooled to 0 °C. 2 mol% of peptide **12i** was added and the reaction monitored *via* GC and TLC (the sulfonylated product cannot be detected *via* GC) and chiral GC.

For reasons of comparability the same reaction was run with 2 mol% of DMAP as catalyst.

Assay of product formation:

All signals were detected by GC-FID employing a 30 m 5890_V UP5 (Machery Nagel).

T (Injector + Detector) = 250 °C

Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100 °C – 250 °C, 15 °C/min

Retention times: R = 9.8 min

trans-Cyclohexane-1,2-diol **1**: 6.9 min.

Acylated product **2a**: 8.8 min.

$POCl(OEt)_2$: 6.7 min.

$POCl(OPh)_2$: 15.2 min.

DMAP: 9.5 min.

TLC:

EtOAc = eluent

Rac-**1** R_f = 0.15 n.f.

93 R_f = 0.6 f.

94-Ph R_f = 0.5 f.

94-Et R_f = 0.3 n.f.

2 R_f = 0.6 n.f.

$POCl(OPh)_2$ R_f = 0.7 f.

SO_2ClPh-*p*-NO_2 R_f = 0.65 f.

f. = shows fluorescence

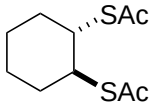
n.f. = shows no fluorescence

The spots were first detected under UV-light and then by phosphomolybdic acid.

Assay of enantiomeric purity.

See *rac*-**1** and **2**.

***trans*-Cyclohexane-1,2-diyl diethanethioate**



^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 3.47 (m, 2 H), 2.25 (s, 6 H), 2.06–1.96 (m, 2 H), 1.66-1.56 (m, 2 H), 1.56–1.44 (m, 2 H), 1.43–1.31 (m, 2 H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 194.6, 46.2, 33.1, 30.5, 24.9.

Assay of enantiomeric purity.

Enantiomers of *trans*-cyclohexane-1,2-diyl diethanethioate

were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250 °C

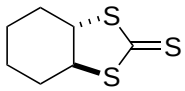
Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100-250 °C, 2 °C/min

Retention times: R_1 = 35.1 min; R_2 = 35.6 min

***trans*- (3a,7a)-Hexahydrobenzo[1,3]dithiole-2-thione (132)**[128]



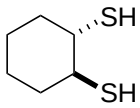
3.5 g (62 mmol) of KOH were dissolved in 15 mL of dry methanol under argon. 5.7 g (74 mmol) of CS_2 were added and the solution stirred for 30 min. Afterwards 2.45 g (25 mmol) cyclohexene oxide were added and the mixture was allowed to stand for 20 h at r.t. The excess CS_2 was distilled off, the yellow crystals separated *via* suction filtration, washed with water and dried in a desiccator under reduced pressure. 3.7 g (19.5 mmol; 78%) of the product were isolated as yellow crystals.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 4.12–3.9 (m, 2 H), 2.19–2.05 (m, 2 H), 1.95–1.81 (m, 2

H) 1.80–1.31 (m, 4 H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 64.53, 29.10, 24.89

***trans*-Cyclohexane-1,2-dithiol (133)**[125]



3.7 g (19.5 mmol) of **133** were dissolved in 25 mL of dry THF, added to a suspension of 1,2 g (31.6 mmol) $LiAlH_4$ in 50 mL of dry THF and the mixture was stirred for 1 h. The suspension was cooled in an ice-bath, 30 mL of water were added and the solution was acidified with 2 M HCl. After extraction with diethyl ether and drying over Na_2SO_4, the solvent was removed under reduced pressure. The crude product was distilled (25 mbar, b.p. = 106 °C) to afford 2.5 g (16.9 mmol; 87%) of the dithiol as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 3.31–2.95 (m, 2 H), 2.61–2.32 (m, 1 H), 2.21–1.95 (m, 2 H), 1.85–1.55 (m, 2 H), 1.45 (m, 1 H) 1.45–1.15 (m, 4 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 48.3, 36.9, 26.45

Assay of enantiomeric purity.

Enantiomers of *trans*-cyclohexane-1,2-diol **133** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDAc column (Macherey Nagel).

T (Injector + Detector) = 250 °C

Splitflow = 80 mL/min

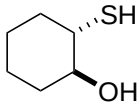
Precolumn pressure = 0.8 bar

Conditions: 100-220 °C, 2 °C/min

220-250 °C, 20 °C/min

Retention times: R_1 = 15.3 min; R_2 = 15.8 min

***trans*-2-Mercaptocyclohexan-1-ol (134)**[127]



To 0.52 mL (5.1 mmol) of **131** and 1.33 g (7.45 mmol) of hexamethyldisilathiane (HMDST) in 0.5 mL of dry THF under argon, 1.3 mL of tetrabutyl ammonium fluoride (TBAF, 1 M solution in THF) were added and the solution was stirred for several minutes at r.t. After the addition of 50% citric acid and additional stirring for 30 min, the reaction mixture was washed with a citric acid-solution, diluted with diethyl ether and dried over Na_2SO_4. The solvent was evaporated. 482 mg (3.6 mmol; 71%) of a colorless liquid were obtained.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 2.71 (m, 2 H), 2.19–2.01 (m, 2 H), 1.95 (m, 2 H), 1.65

(m, 2 H), 1.45–1.21 (m, 4 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 47.36, 36.18, 34.28, 26.30, 24.06

Assay of enantiomeric purity.

Enantiomers of *trans*-2-mercaptocyclohexane-1-ol **134** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250 °C

Splitflow = 80 mL/min

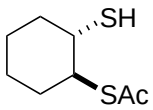
Precolumn pressure = 0.8 bar

Conditions: 100-170 °C, 2 °C/min

170-250 °C, 20 °C/min

Retention times: R_1 = 16.9 min; R_2 = 17.8 min

***trans*- 2-Mercaptocyclohexyl ethanethioate (135)**



Assay of enantiomeric purity.

Enantiomers of **135** could not be separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250 °C

Splitflow = 80 mL/min

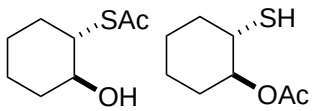
Precolumn pressure = 0.8 bar

Conditions: 100-250 °C, 2 °C/min

Retention times: R_1 = 25.1

The monoacylated product was not isolated because no selectivity for **133** was observed and the signals could be assigned clearly.

***trans*-2-Hydroxycyclohexyl ethanethioate or *trans*-mercaptocyclohexyl acetate (136a/136b)**



Assay of enantiomeric purity.

Enantiomers of **136a/136b** could not be separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel).

T (Injector + Detector) = 250 °C

Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

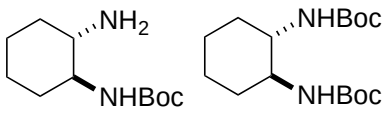
Conditions: 100-170 °C, 2 °C/min

170-250 °C, 20 °C/min

Retention times: R_1 = 27.9 min

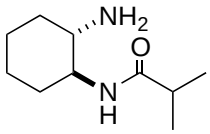
The product was not isolated, because no selectivity for the KR of **134** was observed.

***trans-tert*-Butyl-2-aminocyclohexylcarbamate (Boc-141)**



2.5 mL (20.8 mmol) of *rac*-**140** were dissolved in 13 mL of toluene and cooled to 0 °C in an ice bath. 1.5 g (7.0 mmol) of Boc_2O were dissolved in 13 mL of toluene, added dropwise *via* an addition funnel within 1 h, and the reaction mixture was stirred for 24 h at r.t. 10 mL of H_2O and toluene were added and the layers were separated. The organic layer was concentrated under reduced pressure and the residue was dissolved in 15 mL H_2O and 15 mL of Et_2O and acidified with an HCl solution to pH = 5. The bis-protected amine was extracted with Et_2O. The aqueous phase was adjusted to pH = 10.5 with NaOH-solution and extracted with EtOAc (5 x 15 mL). The organic layers were dried over Na_2SO_4, and then evaporated under reduced pressure to yield 849 mg (4 mmol; 56.6% based on Boc_2O) of the colorless solid monoboc-protected amine and 313 mg (1 mmol, 28% based on Boc_2O) of the diboc-protected amine. The NMR data are in accordance with the literature.[118]

***trans-N*-(2-Aminocyclohexyl)-isobutyramide (141)**



2.5 mL (20.8 mmol) of *rac*-**140** were dissolved in 12.5 mL of DCM and cooled to 0 °C in an ice bath. 1.1 g (7.0 mmol) of $(^{i}PrCO)_2O$ were dissolved in 13 mL of DCM, added drop wise *via* an addition funnel within 1 h, and the reaction mixture was stirred for 16 h at r.t. 10 mL of H_2O and DCM each were added and the layers were separated. The organic layer was concentrated under reduced pressure and the residue was dissolved in 15 mL H_2O and 15 mL DCM and acidified with a HCl solution to pH = 5. The bis-protected amine was extracted with DCM. The aqueous phase was adjusted to pH = 10.5 with a NaOH-solution and extracted with EtOAc (5 x 15 mL). The organic layers were dried over Na_2SO_4, and then evaporated under reduced pressure to yield 405 mg (2.2 mmol; 31% based on $(^{i}PrCO)_2O$) of monoboc-protected amine as a yellowish solid and 608 mg (2.4 mmol; 69% based on

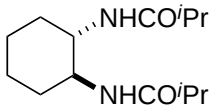
(^{i}PrCO)$_2$O) of the bis-protected amine (colorless solid).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 5.42 (d, 1 H, *J* = 7.7 Hz, NH); 3.51–3.41 (m, 1 H); 2.38–2.24 (m, 2 H); 1.96–1.86 (m, 2 H); 1.81 (s, 2 H); 1.70–1.60 (m, 2 H); 1.32–0.99 (m, 10H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 177.4 (C=O), 55.6, 55.5, 35.9, 35.2, 32.6, 25.1, 25.0, 19.7.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{10}H_{20}N_2ONa^+$ 207.1468; Found 207.1462.

trans-Cyclohexyl-1,2-isobutyramide (142)

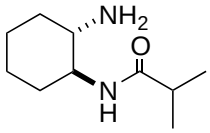


^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.12 (s, 2 H, NH), 3.51–3.41 (m, 2 H, C*H*), 2.38–2.18 (m, 2 H), 1.99–1.88 (m, 2 H), 1.78–1.60 (m, 2 H), 1.32–1.10 (m, 4H), 1.08–0.99 (m, 12 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 177.6 (C=O), 53.4, 35.6, 32.3, 24.7, 19.5.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{14}H_{26}N_2O_2Na^+$ 277.1886; Found 277.1884.

Catalytic acylation of _rac_-140 with (^{i}PrCO)$_2$O at –78 °C



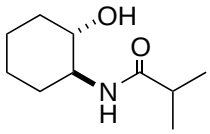
87.5 µL (0.53 mmol) of (^{i}PrCO)$_2$O and 15 mg (2 mol%; 0.02 mmol) of **12i** were dissolved in 160 mL of abs. toluene and cooled to –82°C in an ethylacetate/liquid nitrogen bath. 105 µL (0.875 mmol) of *rac*-**140** were added and the reaction mixture was allowed to stir for 10 h at –82°C. The solvent was removed under reduced pressure and 30 mL of H_2O and 30 mL of DCM were added and the layers were separated. Another 30 mL of H_2O and were added and the aqueous layer was acidified to pH = 5 with a HCl solution. The bis-protected amine was extracted with DCM. The aqueous layer was adjusted to pH = 10.5 with a NaOH-solution and extracted with EtOAc (3 x 30 mL). The organic layers were dried with Na_2SO_4, and then evaporated under reduced pressure to yield 60.7 mg (0.33 mmol; 38%) of the monoboc-protected amine (**141**) as a yellowish solid and 12 mg (0.05 mmol; 6%) of the bis-protected amine (**142**, colorless solid).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 5.42 (d, 1 H, *J* = 7.7 Hz, NH); 3.51–3.41 (m, 1 H); 2.38–2.24 (m, 2 H); 1.96–1.86 (m, 2 H); 1.81 (s, 2 H); 1.70–1.60 (m, 2 H); 1.32–0.99 (m, 10H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 177.4 (C=O), 55.6, 55.5, 35.9, 35.2, 32.6, 25.1, 25.0, 19.7.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{10}H_{20}N_2ONa^+$ 207.1468; Found 207.1462.

***trans-N*-(2-Hydroxycyclohexyl)isobutyramide (144)**



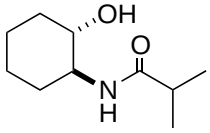
645 mg (5.6 mmol) of *rac*-**143** were dissolved in 20 mL of DCM and cooled to 0°C in an ice bath. 975 (6.16 mmol) of $(^{i}PrCO)_2O$ were added and the mixture was stirred for 40 h at r.t. The solvent was removed under reduced pressure and the crude product was purified *via* silica flash gel column chromatography CH_3Cl/MeOH (10:1). 90% (5 mmol) of a colorless solid were isolated (R_f = 0.3).

^{1}H-NMR (200 MHz, $CDCl_3$): δ/ppm = 5.68 (s, 1 H, NH); 4.18 (bs, 1 H, OH); 3.71–3.44 (m, 1 H, C*H*OH); 3.42–3.18 (m, 1 H, C*H*NH); 2.51–2.29 (quin, 1H, J = 7 Hz, C*H*$(CH_3)_2$); 2.13–1.89 (m, 2 H); 1.79–1.63 (m, 2 H); 1.46–0.99 (m, 10 H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ/ppm = 179.1 (C=O), 75.6, 55.6, 35.6, 34.5, 31.5, 24.6, 24.0, 19.6.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{10}H_{19}NO_2Na^+$ 208.1308; Found 208.1304.

Catalytic acylation of 143 with $(^{i}PrCO)_2O$ at –78 °C



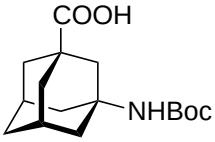
87.5 µL (0.53 mmol) of $(^{i}PrCO)_2O$ and 15 mg (2 mol%; 0.02 mmol) of **12i** were dissolved in 160 mL of abs. toluene and cooled to –82°C in an ethylacetate/liquid nitrogen bath. 100 mg (0.875 mmol) of *rac*-**143** were added and the reaction mixture was allowed to stir for 10 h at –82 °C. The solvent was removed under reduced pressure and the crude product was purified *via* silica flash gel column chromatography CH_3Cl/MeOH (10:1). 90.7 mg (0.47 mmol; 54%) of **144** were isolated (R_f = 0.34) as a colorless solid. Product **143** was isolated by drying the silica gel and subsequent extraction with MeOH. 41.2 mg (0.36 mmol; 41%) of the amino alcohol could be recoverd.

^{1}H-NMR (200 MHz, $CDCl_3$): δ/ppm = 5.68 (s, 1 H, NH); 4.18 (bs, 1 H, OH); 3.71–3.44 (m, 1 H, C*H*OH); 3.42–3.18 (m, 1 H, C*H*NH); 2.51–2.29 (m, 1H, C*H*$(CH_3)_2$); 2.13–1.89 (m, 2 H); 1.79–1.63 (m, 2 H); 1.46–0.99 (m, 10 H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ/ppm = 179.1 (C=O), 75.6, 55.6, 35.6, 34.5, 31.5, 24.6, 24.0, 19.6, 18.9.

Adamantane Amino Acids

3-[(*tert*-Butoxycarbonyl)amino]tricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid (Boc-156)



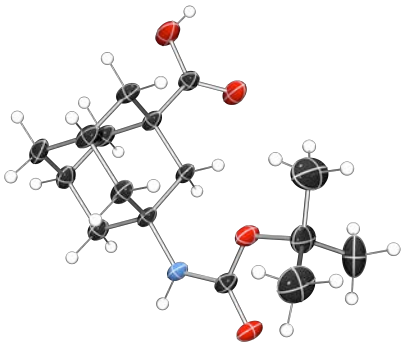
1.0 g (5.1 mmol) of 3-aminoadamantane-1-carboxyclic acid **180** were suspended in 50 mL of H_2O and 50 mL of acetone. 1.1 mL (7.65 mmol) of Et_3N were added. Then, 1.3 g (5.1 mmol) of Boc-ON were added and the reaction mixture was stirred overnight. Another 1.3 g (5.1 mmol) Boc-ON were added and after stirring for 24 h, the reaction mixture was poured over 200 g of crushed ice and 113 mg of Na_2CO_3 were added. After evaporation of acetone, the aqueous layer was extracted with diethyl ether (5 x 50 mL) and acidified to pH=2 by dropwise addition of HCl. A white solid precipitated, which was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (3 x 25 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the remaining solid was dried over P_2O_5 and paraffin wax in a vacuum desiccator. 420 mg (1.4 mmol, 27%) of a colorless solid were obtained.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.11 (bs, 1H, CO_2H); 6.52 (bs, 1 H, NH); 2.10-1.98 (m, 2 H, adamantane), 1.98–1.69 (m, 6 H), 1.69–1.47 (m, 6H), 1.26 (s, 9 H).

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.7 (C=O); 154.3 (C=O); 77.3, 50.1, 42.3, 41.7, 40.5, 37.8, 35.3, 28.5, 28.3.

The NMR data are in accordance with the literature.[149]

Crystallographic data:

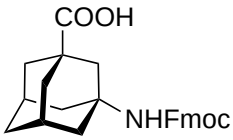


Identification code	shre203p
Empirical formula	$C_{16}H_{25}NO_4$
Formula weight	295.31 g mol^{-1}
Temperature	293(2) K
Wavelength	0.71073 Å

Crystal system, space group	Triclinic	P –1
Unit cell dimensions	a = 6.5642(10) Å	α = 88.685(18) deg.
	b = 9.9774(16) Å	β = 84.354(18) deg.
	c = 12.5043(19) Å	γ = 80.554(18) deg.
Volume	803.9(2) $Å^3$	
Z, Calculated density	4,	1.746 Mg/m^3
Absorption coefficient	0.117 mm^{-1}	
F(000)	464	
Crystal size	1.10 mm x 1.00 mm x 1.50 mm	
Theta range for data collection	2.63 to 28.13 deg.	
Limiting indices	–8 ≤ h ≤ 8, –13 ≤ k ≤ 13, –16 ≤ l ≤ 14	
Reflections collected / unique	7239 / 3546 [R(int) = 0.0514]	
Completeness to theta = 28.13 °		90.3 %
Absorption correction	None	
Refinement method	Full-matrix least-squared on F^2	
Data / restraints / parameter	3546 / 0 / 290	
Goodness-of-fit on F^2	1.388	
Final R indices [I > 2 σ(I)]	R1 = 0.0639	wR2 = 0.1886
R indices (all data)	R1 = 0.0782	wR2 = 0.1964
Largest diff. peak and hole	0.38 and -0.45 e $Å^{-3}$	

The same reaction was also carried using ultrasonic sound due to the poor solubility of the free adamantine amino acid, but the yield did not increase.

3-(9-Fluorenyl)methoxycarbonylaminotricyclo[3.3.1.1$^{3.7}$]decane-1-carboxylic acid (156)



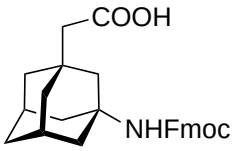
2.317 g (10 mmol) of **164** were dissolved in 120 mL of acetone/water (1/1). The procedure is in accordance with the general procedure IV. During work up, the reaction mixture should not get warmer than 40 °C. The crude product was recrystallized from nitromethane. 2.68 g (6.4 mmol; 64.2%) of a slightly yellowish product were isolated.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.11 (bs, 1H, CO_2H), 7.88 (d, J = 7,6 Hz, 2H), 7.72 (d, J = 7,2 Hz, 2H), 7.41 (t, J = 7,4 Hz, 2H), 7.34 (t, J = 7,6 Hz, 2H), 7.12 (s, 1H, NH), 4.20 (m, 3H), 2.10–1.55 (m, 14 H, adamantane)

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.7 (C=O); 154.3 (C=O); 144.0, 140.7, 127.6, 127.0, 125.2, 120.1, 64.8 (Fmoc-CH_2), 50.2 (C_q), 46.7, 42.3, 41.5, 40.2 (C_q), 37.6, 34.9, 28.2

IR (KBr): v/cm^{-1} = 3315, 3065, 3040, 2911, 2853, 1718, 1675, 1555, 1448, 1263, 1089, 732
The NMR data are in accordance with the literature.[149]

1-(9-Fluorenyl)methoxycarbonylaminotricyclo[3.3.1.1$^{3.7}$]decane-3-methylcarboxylic acid (157)



0.25 g (1 mmol) of **168** were dissolved in 30 mL of acetone/water (1/1). The procedure is in accordance with the general procedure IV. For this synthesis it is important to look carefully after the temperature. During work up, the reaction mixture should not get warmer than 30 °C. The crude product was recrystallized from nitromethane. 0.250 g (0.58 mmol; 58%) of a light yellow product were isolated.

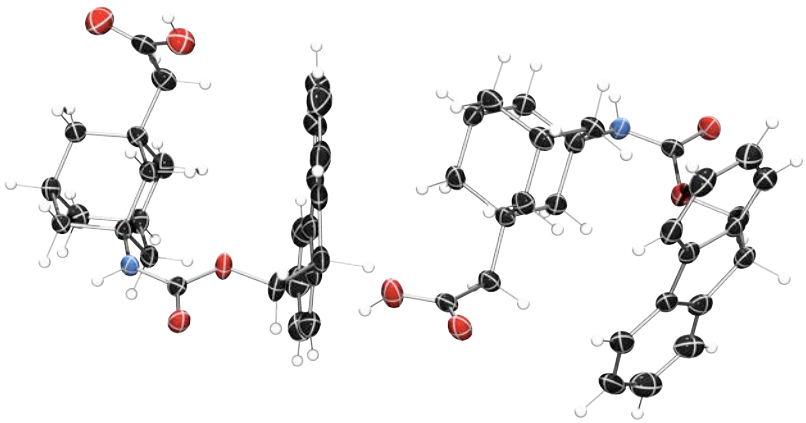
^{1}H-NMR (400 MHz, *d*$_6$-DMSO): δ/ppm = 12.03 (bs, 1H, CO_2H); 7.94 (d, J = 7.6 Hz, 2 H); 7.77 (d, J = 7.2 Hz, 2 H); 7.46 (t, J = 7.5 Hz, 2 H); 7.39 (t, J = 7.6 Hz, 2 H); 7.13 (s, 1H, NH); 4.24 (m, 3H); 2.20–0.96 (m, 16 H, adamantane)

^{13}C-NMR (100 MHz, *d*$_6$-DMSO): δ/ppm = 172.4 (C=O), 154.1 (C=O), 144.1, 140.7, 127.5, 127.0, 125.3, 120.0, 64.8 (Fmoc-CH_2), 50.5 (C_q), 47.7, 46.7, 45.6, 40.7, 40.2, 35.3 (C_q), 33.7, 28.8

IR (KBr): v/cm^{-1} = 3327,3288, 2898, 2853, 1687, 1439, 1333, 742

Elem. Anal.: $C_{27}H_{29}NO_4$ (431.52): calcd. C 75.15, H 6.77, N 3.25; found: C 75.21, H 6.80, N 3.32

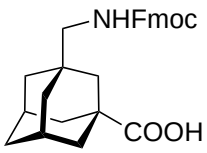
Crystallographic data:



Identification code	shre249p
Empirical formula	$C_{27}H_{29}NO_4$
Formula weight	431.52 g mol^{-1}
Temperature	293(2) K

Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic	P 2_1/c
Unit cell dimensions	a = 8.7479(6) Å	α = 90.0(0) deg.
	b = 16.2356(11) Å	β = 96.257(7) deg.
	c = 31.6541(18) Å	γ = 90.0(0) deg.
Volume	4469.0(5) $Å^3$	
Z, Calculated density	8,	1.283 Mg/m^3
Absorption coefficient	0.086 mm^{-1}	
F(000)	1840	
Crystal size	1.15 mm x 0.95 mm x 0.12 mm	
Theta range for data collection	1.80 to 23.30 deg.	
Limiting indices	–9 ≤ h ≤ 9, –17 ≤ k ≤ 17, –35 ≤ l ≤ 34	
Reflections collected / unique	23490 / 6364 [R(int) = 0.0783]	
Completeness to theta = 23.30 °		98.4 %
Absorption correction	None	
Refinement method	Full-matrix least-squared on F^2	
Data / restraints / parameter	6364 / 0 / 809	
Goodness-of-fit on F2	0.632	
Final R indices [I > 2 σ(I)]	R1 = 0.0404	wR2 = 0.0952
R indices (all data)	R1 = 0.0893	wR2 = 0.1181
Largest diff. peak and hole	0.64 and -0.18 e $Å^{-3}$	

3-(9-Fluorenyl)methoxycarbonylmethylaminotricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid (158)



0.35 g (1.65 mmol) of **184** were dissolved in 40 mL of acetone/water (1/1). The procedure is in accordance with the general procedure IV.

For this synthesis it is important to look carefully after the temperature. During work up, the reaction mixture should not get warmer than 30 °C. The crude product was recrystallized from nitromethane. 0.275 g (0.63 mmol; 38%) of a light yellow product were isolated.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm 12.03 (bs, 1 H), 7.89 (d, J = 6.8 Hz, 2 H), 7.72 (d, J = 8 Hz, 2 H), 7.41 (t, J = 6.0 Hz, 2H); 7.32 (t, J = 6.0 Hz, 2H), 4.28 (m, 3 H), 2.10–1.95 (m, 2 H), 1.83–1.15 (m, 14 H)

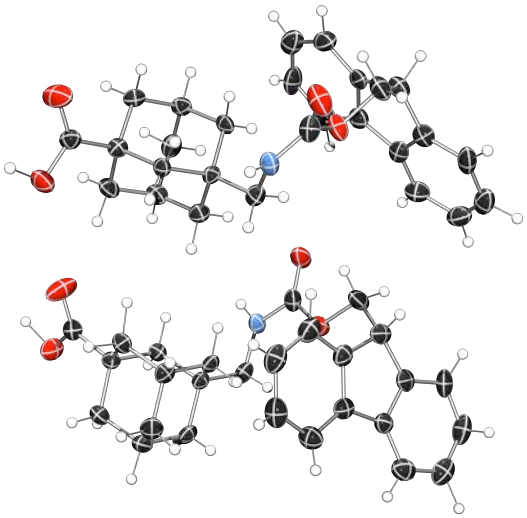
^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 178.4(C=O), 156.6 (C=O), 144.9, 140.7, 140.78,

127.6, 127.0, 125.3, 120.1, 65.1 (Fmoc-CH_2), 51.6 (C_q), 46.8, 41.1, 38.8, 38.1, 35.5, 34.1(C_q), 27.5

IR (KBr): v/cm^{-1} = 3318, 3250, 3098, 2934, 2901, 2848, 1700, 1656, 1553, 1478, 1452, 1213, 1129, 733

Elem. Anal.: $C_{27}H_{29}NO_4$ (431.52): calcd. C 75.15, H 6.77, N 3.25; found: C 75.03, H 6.72, N 3.53

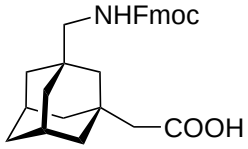
Crystallographic data:



Identification code	shre217p	
Empirical formula	$C_{27}H_{29}NO_4$	
Formula weight	431.52 g mol^{-1}	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic	P –1
Unit cell dimensions	a = 12.9727(27) Å	α = 90.00(0) deg.
	b = 12.1817(17) Å	β = 93.31(2) deg.
	c = 13.8644(24) Å	γ = 90.00(0) deg.
Volume	2187.3(3) $Å^3$	
Z, Calculated density	4,	1.213 Mg/m^3
Absorption coefficient	0.076 mm^{-1}	
F(000)	856	
Crystal size	0.90 mm x 0.15 mm x 1.00 mm	
Theta range for data collection	2.68 to 28.21 deg.	
Limiting indices	–17 ≤ h ≤ 17, –16 ≤ k ≤ 14, –18 ≤ l ≤ 18	
Reflections collected / unique	20039 / 9835 [R(int) = 0.1914]	
Completeness to theta = 27.05 °		91.1 %
Absorption correction	None	

Refinement method	Full-matrix least-squared on F^2	
Data / restraints / parameter	9835 / 0 / 809	
Goodness-of-fit on F2	0.608	
Final R indices [I > 2 σ(I)]	R1 = 0.0603	wR2 = 0.1309
R indices (all data)	R1 = 0.2581	wR2 = 0.2335
Largest diff. peak and hole	0.25 and -0.23 e $Å^{-3}$	

3-(9-Fluorenyl)methoxycarbonylmethyltricyclo[3.3.1.1^{3,7}]decane-1-methylcarboxylic acid (159)



1.0 g (3.7 mmol) of **185** were added to a stirred and cooled (ice bath) mixture of 15 mL conc. sulfuric acid and 0.75 mL conc. nitric acid. Afterwards, 15 mL of 1,1-dichloroethane were added and the reaction mixture was stirred for another 1 h at 0 °C. Stirring was continued overnight at r.t. The solution was poured on ice and extracted with diethyl ether. The aqueous layer was alkalized to pH = 9 with saturated NaOH. 75 mL of acetone and 2.8 g (11 mmol) of Fmoc-Cl were added and the mixture was again stirred overnight.

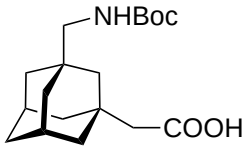
The procedure is in accordance with the general procedure IV. For this synthesis it is important to look carefully after the temperature. During work up, the reaction mixture should not get warmer than 30 °C. Only 0.07g (0.16 mmol; 4%) of a yellowish, highly viscous oil were isolated.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.03 (bs, 1H, CO_2H); 7.77 (d, J = 7,6 Hz, 2 H); 7.61 (d, J = 7,2 Hz, 2 H), 7.42–7.02 (m, 4H); 4.19 (m, 3H); 2.13–0.94 (m, 18 H, adamantane)

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 172.5 (C=O), 156.6 (C=O), 143.6, 140.8, 127.7, 126.6, 125.4, 120.0, 65.3 (Fmoc-CH_2), 51.7 (C_q), 48.3, 47.1, 44.5, 41.5, 38.9 (C_q), 34.7, 32.2, 28.0, 21.2

MS (ESI): *m/z* = 468.2 $[M + Na]^+$; (calc. 468.2)

3-[(*tert*-Butoxycarbonyl)methylamino]tricyclo[3.3.1.1^{3,7}]decane-1-methylcarboxylic acid (Boc-159)



724 mg (3.2 mmol) of **185**, 985.1 mg (4 mmol) Boc-ON (2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile) and 0.5 mL (4.0 mmol) of Et_3N were dissolved in 80 mL of acetone and 80

mL of H_2O and stirred for 18 h at r.t. The reaction mixture was poured on ice and 65 mg of Na_2CO_3 (0.6 mmol) were added. Acetone was removed under reduced pressure and the aqueous solution was extracted with Et_2O. The aqueous layer was acidified to pH = 2 with conc. HCl and extracted with EtOAc (3 x). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. 739.3 mg (2.4 mmol; 74%) of the product were isolated.

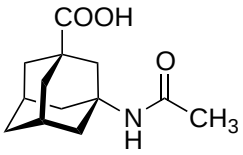
^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 4.55 (bs, 1 H, NH), 2.81–2.72 (m, 2 H), 2.21–1.91 (m, 4 H), 1.68–1.38 (m, 21 H)

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.3 (C=O), 156.4, 79.1, 51.4, 48.2, 44.7, 41.6, 39.2, 36.0, 34.8, 33.0, 28.5, 28.4

MS (ESI): *m/z* = 468.2 $[M + Na]^+$; (calc. 468.2)

The NMR-data are in accordance with the literature.[156]

3-Acetamidotricyclo[3.3.1.1$^{3.7}$]decane-1-carboxylic acid (163)[149]



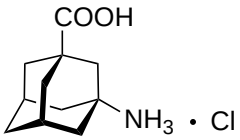
25 g (138.9 mmol) of **162** were suspended in 20 mL of conc. nitric acid and cooled to 0 °C in an ice bath. In the course of 1 h. 150 mL of conc. sulfuric acid were added to the suspension. After stirring for 2 h at 0 °C, 100 mL of acetonitrile were added within 3 h at the same temperature. The reaction mixture was poured on ice, the colorless precipitates collected *via* suction filtration, washed with water and recrystallized from acetic acid/water/acetone (5 : 5 : 2). The product was dried in a desiccator under reduced pressure and 27.82 g (117.2 mmol; 84.4%) of the acetamide were obtained as colorless crystals.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 11.17 (bs, 1H, CO_2H); 7.43 (bs, 1H, NH); 2.08 (m, 2H); 1.98 (s, 2H); 1.85 (m, 4H); 1.76 (s, 3H, CH_3); 1.69 (d, J = 2,8 Hz, 4H); 1.55 (bs, 2H)

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.6 (C=O), 168.8 (C=O), 50.8, 42.1, 41.4, 40.0, 37.6, 35.0, 28.6, 28.5, 23.6.

The NMR-data are in accordance with the literature.

3-Aminotricyclo[3.3.1.1$^{3.7}$]decane-1-carcoxylic acid hydrochloride (164)[149]



23.3 g (98.2 mmol) of **163** were refluxed in 270 mL of conc. HCl and 150 mL of water for 3 d. The crude product was treated with acetone. 18.69g (80.7 mmol; 82.2%) of product were

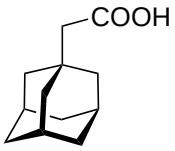
obtained as a colorless solid.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.36 (bs, 1H, CO_2H); 8.33 (bs, 3H, NH_3Cl); 7.37 (t, 1H, J(^{15}NH) =50.6 Hz) 2.15 (m, 2H); 1.88 (m, 2H); 1.76–1.73 (m, 6H); 1.64–1.49 (m, 4H);

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.1 (C=O), 168.8 (C=O), 51.4, 41.5, 41.2, 39.2, 37.2, 34.3, 28.3.

The NMR-data are in accordance with the literature.

Tricyclo[3.3.1.1$^{3.7}$]decane-1-methylcarboxylic acid (166)[155]

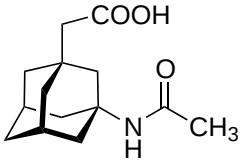


50 g (232 mmol) of **165** were suspended in 550 mL conc. sulfuric acid, which was cooled to 0 °C in an ice bath. While stirring, 100 mL of Oleum (20% SO_3) and afterwards, 44 mL of 1,1-dichloroethene were added. The reaction mixture was stirred for additional 2 h at r.t. and poured on ice. The precipitates were filtered of *via* suction filtration. The crude product was dissolved in a 5%-solution of NaOH at 60-70 °C, the impurities were filtered off and the solution was acidified with conc. HCl (pH = 4-6) to precipitate the methylcarboxylic acid. The product was filtered off *via* suction filtration, washed with water and dried in a desiccator over paraffin wax and P_2O_5 under reduced pressure. 22.6 g (115.5 mmol; 49%) of a colorless solid were isolated.

^{1}H-NMR (200 MHz, d_6-DMSO): δ/ppm = 11.09 (s, 1 H), 2.20-1.77 (m, 5 H), 1.77-1.23 (m, 11 H)

^{13}C-NMR (50 MHz, d_6-DMSO): δ/ppm = 172.0 (C=O), 47.8, 41.4, 35.7, 31.2, 27.6.

1-Acetamidotricyclo[3.3.1.1$^{3.7}$]decane-3-methylcarboxylic acid (167)



12 g (61.9 mmol) of **166** were suspended in 10 mL conc. nitric acid and cooled to 0 °C in an ice bath. Then during 1 h, 64 mL of conc. sulfuric acid were added to the suspension and after 2 h stirring at 0 °C, 44 mL of acetonitrile were added within 3 h at the same temperature. After another 3 h of stirring the reaction mixture was poured on ice. After standing in the refrigerator for 1 d the product was filtered off *via* suction filtration and dried in a desiccator under reduced pressure. 11.10 g (44.6 mmol; 72%) of the acetamide were obtained as colorless crystals.

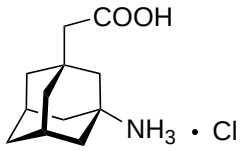
^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 11.71 (bs, 1H, CO_2H); 7.41 (bs, 1H, NH); 2.08–1.95

(m, 6 H); 1.90–1.67 (m, 9 H), 1.59–1.39 (m, 6 H)

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 172.3 (C=O), 168.7 (C=O), 51.4, 47.7, 45.5, 40.8, 40.2, 35.2, 33.6, 28.8, 23.6.

The procedure is in accordance with that reported in literature.[149]

1-Aminotricyclo[3.3.1.1$^{3.7}$]decane-3-methylcarboxylic acid hydrochloride (168)

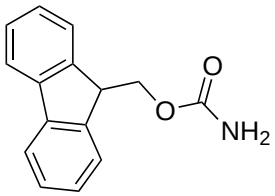


11.1 g (44.2 mmol) of 1-acetamidoadamantane-3-methylcarboxylic acid were refluxed in 80 mL of conc. HCl and 80 mL of water for 1 d. The crude product was treated with acetone. 3.8 g (15.5 mmol; 35%) of the hydrochloride were obtained as a colorless solid.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 11.52 (bs, 1H, CO_2H), 8.20 (t, 1H, J(^{15}NH) =50.6 Hz), 7.37 (bs, 3vH, NH_3Cl), 2.19–2.00 (m, 4 H), 1.80–1.62 (m, 5 H), 1.59–1.39 (m, 5 H).

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 172.3 (C=O), 51.5, 47.3, 44.0, 39.1, 34.5, 33.3, 28.2.

3-(9-Fluorenyl)methoxycarbonylamine (171)



3-(9-Fluorenyl)methoxycarbonylamine was isolated as the main product when the reaction conditions (especially temperature) of the general procedure IV were not kept constant during the Fmoc-protection of **168** .

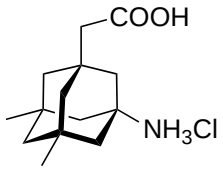
^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 7.94 (d, J = 7.6 Hz, 2 H), 7.77 (d, J = 7.2 Hz, 2 H), 7.46 (t, J = 7.5 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 4.39–4.20 (m, 3H).

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 156.6, 144.0, 140.7, 127.5, 126.7, 125.3, 120.3, 65.0, 46.7.

IR (KBr): v/cm^{-1} = 3427, 3327, 3263, 3205, 3018, 2970, 2900, 1683, 1614, 1424, 1337.

MS (ESI): *m/z* = 262.1 [M + Na]$^{+}$; (calc. 262.1).

1-Amino-5,7-dimethyltricyclo[3.3.1.1$^{3.7}$]decane-3-methylcarboxylic acid hydrochloride (173)

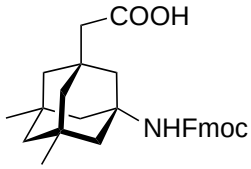


1.55 g (5.5 mmol) of 1-acetamido-5,7-dimethyladamantane-3-methylcarboxylic acid were refluxed in 24 mL of conc. HCl and 12 mL of water for 1 d. The crude product was treated with acetone. 0.506 g (1.8 mmol; 33%) of the product were obtained as a colorless solid.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.12 (bs, 1H, CO_2H), 8.38 (bs, 3H, NH_3Cl), 7.45 (t, 1H, J(^{15}NH) =50.6 Hz), 2.10 (s, 2 H), 1.55 (s, 2 H), 1.38 (m, 4H), 1,21 (m, 4 H), 1.08 (s, 2 H), 0.88 (s, 6 H)

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 172.1 (C=O), 52.8, 48.8, 46.4, 45.1, 42.7, 40.1, 34.7, 32.2, 31.2,

1-(9-Fluorenyl)methoxycarbonylamino-5,7-dimethyltricyclo[3.3.1.1$^{3.7}$]decane-3-methylcarboxylic acid (173-Fmoc)

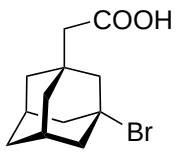


0.25 g (1 mmol) of **173** were dissolved in 12 mL of acetone/water (1/1). The procedure is in accordance with the general procedure IV. During work up, the reaction mixture should not get warmer than 30 °C. 528 mg (0.14 mmol; 34%) of the product were isolated.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.06 (bs, 1H, CO_2H), 7.96 (d, J = 7.6 Hz, 2 H), 7.77 (d, J = 7.2 Hz, 2 H), 7.46 (t, J = 7.5 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.13 (s, 1H, NH), 4.26 (m, 3H), 2.20–0.96 (m, 14 H, adamantane + CH_2), 0.87 (s, 6 H).

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 172.4 (C=O), 154.1 (C=O), 144.1, 140.7, 127.7, 127.0, 125.3, 120.0, 64.9 (Fmoc-CH_2), 52.6, 48.9, 46.6, 46.4, 45.1, 42.7, 40.1, 34.7, 32.2, 31.2.

1-Bromotricyclo[3.3.1.1$^{3.7}$]decane-3-methylcarboxylic acid (174)



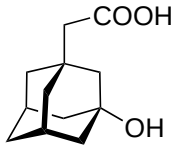
1.0 g (5.1 mmol) of **166** and 3 mL of Br_2 were stirred for 18 h at r.t. and afterwards refluxed for 6 h. The excess of Br_2 was distilled off and the residue was washed with $NaHSO_3$-

solution, the product was filtered off and dried in a desiccator over paraffin wax and P_2O_5. 1.21 g (4.5 mmol; 88%) of the colorless product were isolated.

^{1}H-NMR (400 MHz, *d_6*-DMSO): δ/ppm = 11.99 (bs, 1H, CO_2H), 4.47 (s, 1H), 2.15 (s, 2H), 2.06 (s, 2H), 1.72–1.40 (m, 12 H)

^{13}C-NMR (100 MHz, *d_6*-DMSO): δ/ppm = 172.7, 66.7, 49.6, 47.6, 44.5, 41.0, 35.2, 34.9, 29.8.

1-Hydroxytricyclo[3.3.1.1$^{3.7}$]decane-3-methylcarboxylic acid (175)

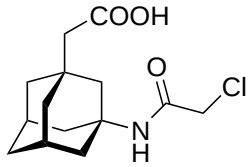


1.21 g (4.4 mmol) of **174** were dissolved in 70 mL of 0.15 M NaOH and the solution was allowed to stand for 20 h. The mixture was acidified with H_2SO_4 and extracted with diethyl ether, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. 0.878 g (4.18 mmol; 95%) of the product were isolated as a colorless solid.

^{1}H-NMR (400 MHz, *d_6*-DMSO): δ/ppm = 11.93 (bs, 1H, CO_2H), 2.31-2.15 (m, 6H), 2.14–2.07 (m, 2H), 2.05 (s, 2H), 1.68–1.50 (m, 6H)

^{13}C-NMR (100 MHz, *d_6*-DMSO): δ/ppm = 172.1, 67.7, 52.9, 48.1, 46.91, 36.8, 34.0, 31.9.

1-Chloroacetamidotricyclo[3.3.1.1$^{3.7}$]decane-3-methylcarboxylic acid (176)[154]



596 mg (2.8 mmol) of **175**, 1.13 g (15 mmol) of chloroacetonitrile and 1.3 mL (22.5 mmol) of acetic acid were mixed and cooled to 0–3 °C in an ice bath. 1.2 mL (22.5 mmol) conc. H_2SO_4 were added dropwise, keeping the temperature below 10 °C. The reaction mixture was stirred for 20 h at r.t. and poured on ice. The precipitates were filtered off, washed with water and dried in a desiccator over paraffin wax and P_2O_5. 668 mg (2.5 mmol; 89%) of the colorless product were isolated.

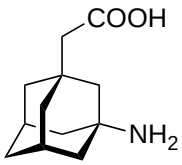
^{1}H-NMR (400 MHz, *d_6*-DMSO): δ/ppm = 8.35 (bs, 1H, CO_2H), 7.61 (s, 1 H, NH), 3.87 (s, 2 H), 2.02–1.82 (m, 4 H), 1.82–1.52 (m, 6 H), 1.52–1.31 (m, 6 H)

^{13}C-NMR (100 MHz, *d_6*-DMSO): δ/ppm = 172.3 (C=O), 164.8 (C=O), 51.8, 47.5, 44.9, 43.41, 40.7, 39.9, 35.1, 33.6, 28.8.

IR (KBr): v/cm^{-1} = 3316, 2911, 2847, 2623, 1696, 1651, 1563, 1447, 1319, 631.

MS (ESI): *m/z* = 308.1 $[M + Na]^+$; (calc. 308.1).

1-Aminotricyclo[3.3.1.1^{3,7}]decane-3-methylcarboxylic acid (177)[154]



629 mg (2.33 mmol) of **176,** 214 mg (2.8 mmol) of thiourea and 0.93 mL of AcOH were refluxed in 5 mL of dry EtOH for 8 h. The solvent was removed under reduced pressure and the crude product was dissolved in H_2O. The mixture was neutralized with NaOH and the precipitates were filtered off. 360 mg (1.7 mmol; 74%) of the colorless solid were isolated.

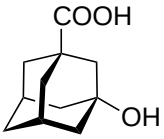
^{1}H-NMR (400 MHz, D_2O): δ/ppm = 1.97–1.90 (m, 2 H), 1.85 (s, 2 H), 1.44–1.21 (m, 12 H)

^{13}C-NMR (100 MHz, D_2O): δ/ppm = 181.3 (C=O), 52.2, 49.6, 47.3, 43.4, 40.8, 35.0, 33.8, 29.1.

IR (KBr): v/cm^{-1} = 2917, 2633, 2229, 1645, 1548, 1394, 1361.

MS (ESI): *m/z* = 210.1 $[M + Na]^+$; (calc. 210.1).

3-Hydroxytricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid (178)[188]

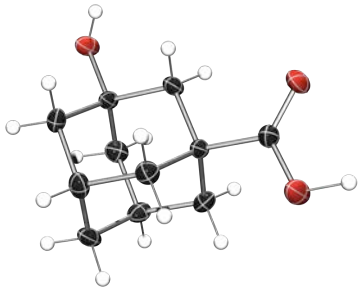


7.21 g (40 mmol) of **162** were suspended in 4 mL of conc. nitric acid at 0 °C. 50 mL of conc. sulfuric acid were added within 2 h at 0 °C. The reaction mixture was stirred for another 3 h and afterwards poured on ice. The colorless precipitates were filtered off *via* suction filtration, washed with water and dried under high vacuum over P_2O_5 in a desiccator. 5.65 g (28.8 mmol; 72%) of the product were isolated.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 5.64 (bs, 2 H, CO_2H and OH), 2.19–2.09 (m, 2 H, adamantane), 1.70–1.41 (m 12 H, adamantane)

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.9 (C=O), 66.4 (C-OH), 46.4, 44.5, 42.4, 37.3, 35.2, 29.6.

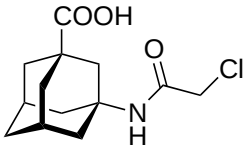
Crystallographic data:



Identification code	shre214p
Empirical formula	$C_{11}H_{16}O_3$

Formula weight	196.24 g mol^{-1}	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic	P $2_1/c$
Unit cell dimensions	a = 6.7002(10) Å	α = 90.000(0) deg.
	b = 20.7848(29) Å	β = 106.002(16) deg.
	c = 7.1773(11) Å	γ = 90.000(0) deg.
Volume	960.80(46) $Å^3$	
Z, Calculated density	4,	1.600 Mg/m^3
Absorption coefficient	0.110 mm^{-1}	
F(000)	524	
Crystal size	0.25 mm x 0.60 mm x 0.15 mm	
Theta range for data collection	3.11 to 27.05 deg.	
Limiting indices	–8 ≤ h ≤ 8, –26 ≤ k ≤ 26, –9 ≤ l ≤ 9	
Reflections collected / unique	7503 / 2056 [R(int) = 0.0625]	
Completeness to theta = 27.05 °		97.3 %
Absorption correction	None	
Refinement method	Full-matrix least-squared on F^2	
Data / restraints / parameter	2056 / 0 / 192	
Goodness-of-fit on F^2	0.812	
Final R indices [I > 2 σ(I)]	R1 = 0.0414	wR2 = 0.1131
R indices (all data)	R1 = 0.0704	wR2 = 0.1295
Largest diff. peak and hole	0.32 and -0.29 e $Å^{-3}$	

3-Chloroacetamidotricyclo[3.3.1.1$^{3.7}$]decane-1-carboxylic acid (179)[154]



492 mg (2.5 mmol) of **178**, 1.13 g (15 mmol) of chloroacetonitrile and 1.2 mL (19.8 mmol) of acetic acid were mixed and cooled to 0-3 °C in an ice bath. 1.2 mL (22.5 mmol) of conc. H_2SO_4 were added dropwise keeping the temperature below 10 °C. The reaction mixture was stirred for 20 h at r.t. and poured on ice. The precipitate was filtered off, washed with water and dried in a desiccator over paraffin wax and P_2O_5. 644 mg (2.37 mmol; 95%) of the colorless product were isolated.

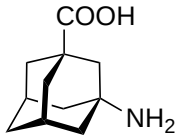
^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.03 (bs, 1H, CO_2H), 7.77 (s, 1 H), 3.95 (s, 2 H, 2.11 (s, 2H), 2.00 (s, 2H), 1.94–1.79 (m, 4H), 1.77–1.64 (m, 4H), 1.57 (s, 2H)

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.9, 165.0, 51.5, 43.1, 41.3, 39.8, 37.8, 34.9,

28.2.

IR (KBr): v/cm^{-1} = 3316, 3092, 2911, 2847, 262, 1696, 1650, 1563, 1447, 1282, 1155, 615

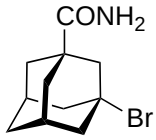
3-Aminotricyclo[3.3.1.1$^{3.7}$]decane-1-carboxylic acid (180)[154]



0.64 g (2.4 mmol) of **179**, 0.23 g (3 mmol) of thiourea and 1 mL of acetic acid were dissolved in 5 mL of ethanol and refluxed for 14 h. To isolate the adamantane amino acid the mixture was evaporated to dryness and afterwards 10 mL of H_2O were added. The solution was acidified with conc. HCl to pH~1 and filtered. The solution was neutralized with a 20% aq. NaOH-solution. The precipitate was filtered off, washed with water and dried in a desiccator over paraffin wax and P_2O_5. 0.448 g (2.1 mmol; 86%) of the free adamantane amino acid were isolated as a colorless solid.

The NMR data are in accordance with the literature.[149]

1-Bromotricyclo[3.3.1.1$^{3.7}$]decane-3-carboxamide (181)[156]

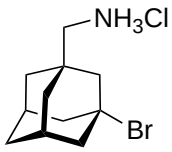


2.6 g (13.3 mmol) of **178** were dissolved in 5 mL of freshly distilled thionyl bromide and heated to 65 °C for 1 h. The excess thionyl bromide was distilled off under reduced pressure. The residue was dissolved in 30 mL of dry DCM and NH_3 gas was bubbled through the solution for about 2 h. The precipitates were filtered off *via* suction filtration and washed with water. The crude product was purified by recrystallization from acetone/cyclohexane (1:1, v/v). 2.82 g (10.9 mmol; 82%) of a colorless product were isolated.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 6.31 (bs 1H, NH_2), 5.77 (bs 1H, NH_2), 2.38 (s, 2 H), 2.31–2.13 (m, 6 H), 1.80 (m, 4 H), 1.64 (m, 2 H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 178.5 ($CONH_2$), 63.4 (C-Br), 49.9, 48.3, 44.8, 37.5, 34.9, 31.7.

1-Bromo-3-(methylamino)tricyclo[3.3.1.1$^{3.7}$]decane hydrochloride (183)[156]



11.0 g (43 mmol) **182** in 100 mL of dry diethyl ether were added to a solution of 3.3 g

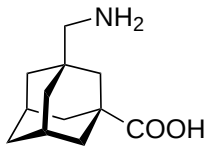
(86 mmol) of $LiAlH_4$ in 200 mL of dry diethyl ether. The suspension was refluxed for 15 h. 12.9 mL of a 4%-NaOH-solution were added, the precipitates were filtered off and the solvent was removed under reduced pressure. The product was precipitated by adding HCl·diethyl ether to the solution. The hydrochloride was filtered off *via* suction filtration and recrystallized from 2-propanol to yield 5.8 g (20.6 mmol; 48%) of the colorless product.

BH_3·DMS can also be used for the reduction.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm 8.12 (bs, 3 H), 2.64 (s, 2 H), 2.39–2.16 (m, 8 H), 1.81–1.55 (m, 6 H))

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 66.7 (C-Br), 50.1, 48.5, 47.6, 44.3, 36.6, 33.8, 31.5

3-(Methylamino)tricyclo[3.3.1.1$^{3.7}$]decane-1-carboxylic acid (184)[156]



0.53 g (1.9 mmol) of **183** were dissolved in 10 mL of conc. H_2SO_4 and the resulting mixture was stirred and cooled in an ice bath. At the same temperature, 1.1 mL of HCOOH was added during 2 h. Stirring was continued for about 1 h and the mixture poured on ice. The solution was neutralized with saturated aqueous NaOH. After about 10 h the product precipitated as colorless crystals. The crude yield was too high because of impurities of inorganic impurities. The crude product was recrystallized from water to yield in 0.223 g (1 mmol; 55%) of the free amino acid.

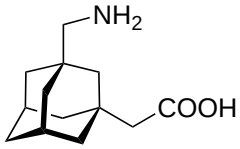
^{1}H-NMR (400 MHz, D_2O): δ/ppm 2.65 (s, 2 H), 2.05 (s, 2 H), 1.92–1.30 (m, 12 H)

^{13}C-NMR (100 MHz, D_2O): δ/ppm = 182.2 (-COOH), 49.9, 40.7, 39.8, 37.5, 37.2, 34.6, 31.8, 27.3

IR (KBr): v/cm^{-1} = 3453, 3047, 2925, 2848, 1713, 1602, 1513, 1203, 1107, 619.

MS (ESI): *m/z* = 210.1 $[M + Na]^+$; (calc. 210.1).

3-Methylaminotricyclo[3.3.1.1$^{3.7}$]decane-1-methylcarboxylic acid (185)



1.0 g (3.7 mmol) of **183** were added to a stirred and cooled (ice bath) mixture of 15 mL conc. sulfuric acid and 0.75 mL of conc. nitric acid. Afterwards 15 mL of 1,1-dichloroethane were added and the reaction mixture was stirred for an additional 1 h at 0 °C and then overnight at r.t. The solution was poured on ice and extracted with diethyl ether. The aqueous layer was

neutralized with a saturated NaOH-solution and some of the solvent was evaporated under reduced pressure. Inorganic salt precipitated after a few days and was filtered off. After another 6 d the product precipitated as colorless crystals. 724 mg (3.3 mmol; 86%) were isolated.

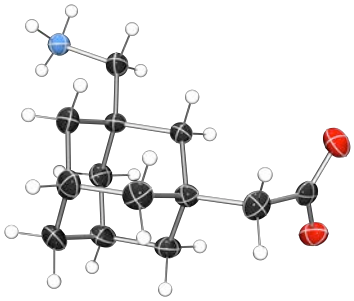
^{1}H-NMR (400 MHz, D_2O): δ/ppm = 2.64 (s, 2 H), 2.02 (m, 4 H), 1.88 (s, 1 H), 1.60–1.22 (m, 11 H)

^{13}C-NMR (100 MHz, D_2O): δ/ppm = 178.5 (C=O); 50.5, 49.9, 43.7, 41.0, 38.1, 34.7, 32.2, 28.1, 21.8

IR (KBr): v/cm^{-1} = 3444, 3033, 2911, 2858, 2619, 1618, 1504, 1390, 683

MS (ESI): *m/z* = 224.0 $[M + H]^+$; (calc. 223.16)

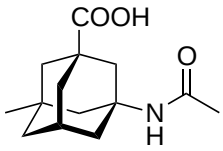
Crystallographic data:



Identification code	shre241p	
Empirical formula	$C_{13}H_{21}NO_2$	
Formula weight	233.31 g mol^{-1}	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic	P 2_1 2_1 2_1
Unit cell dimensions	a = 6.7306(11) Å	α = 90.0(0) deg.
	b = 11.8326(14) Å	β = 90.0(0) deg.
	c = 14.8911(19) Å	γ = 90.0(0) deg.
Volume	1185.93(3) Å^3	
Z, Calculated density	4,	1.245 Mg/m^3
Absorption coefficient	0.083 mm^{-1}	
F(000)	484	
Crystal size	0.60 mm x 0.90 mm x 0.15 mm	
Theta range for data collection	2.74 to 28.18 deg.	
Limiting indices	–8 ≤ h ≤ 8, –13 ≤ k ≤ 15, –19 ≤ l ≤ 19	
Reflections collected / unique	9568 / 2877 [R(int) = 0.0862]	
Completeness to theta = 28.18 °		99.2 %
Absorption correction	None	

Refinement method	Full-matrix least-squared on F^2	
Data / restraints / parameter	2877 / 0 / 229	
Goodness-of-fit on F2	0.633	
Final R indices [I > 2 σ(I)]	R1 = 0.0431	wR2 = 0.0990
R indices (all data)	R1 = 0.0968	wR2 = 0.1301
Largest diff. peak and hole	0.18 and -0.18 e $Å^{-3}$	

3-Acetamido-5-methyltricyclo[3.3.1.1$^{3.7}$]decan-1-carboxylic acid ((±)-188)[149]



The acetamidation of **187** was achieved by the procedure described in the literature.

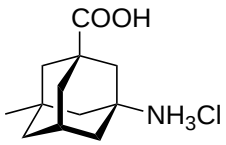
1.46 g (5.8 mmol; 88%) of the product were isolated as a colorless solid.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.12 (bs, 1H, CO_2H); 7.43 (bs, 1H, NH); 2.11 (s, 1H); 1.95–1.87 (m, 2H); 1.87–1.69 (m, 5H); 1.69–1.51 (m, 4 H), 1.48–1.39 (m, 2H), 1.36–1.21 (m, 2H), 0.85 (s, 3 H)

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.6 (C=O), 168.7, 51.6, 46.9, 44.5, 42.1, 42.1, 41.5, 40.1, 37.0, 31.4, 30.0, 28.9, 23.7.

The NMR data are in accordance with the literature.

3-Amino-5-methyltricyclo[3.3.1.1$^{3.7}$]decane-1-carboxylic acid hydrochloride (±)-189



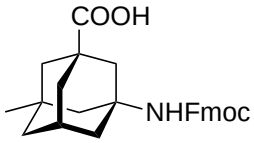
1.46 g (5.8 mmol) of **188** were refluxed in 20 mL of conc. HCl and 9 mL of water for 3 d. The crude product was treated with acetone to remove by-product 3-chloro-5-methyladamantane-1-carboxylic acid. The crude product was treated with acetone. 1.06 g (4.3 mmol; 75%) of the product were obtained as a colorless solid.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.36 (bs, 1H, CO_2H); 8.35 (bs, 3H, NH_3Cl); 7.45 (t, 1H, J(^{15}NH) = 50.6 Hz) 2.21 (s, 1H); 1.92–1.77 (m, 2H); 1.77–1.56 (m, 4H); 1.56-1.44 (m, 2 H), 1.44–1.24 (m, 4H), 0.85 (s, 3 H)

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 176.8 (C=O), 168.8, 51.9, 45.8, 43.9, 42.0, 41.20, 40.4, 38.2, 36.3, 31.5, 29.4, 28.5

The NMR data are in accordance with the literature.[149]

3-(9-Fluorenyl)methoxycarbonylamino-5-methyltricyclo[3.3.1.1$^{3.7}$]decane-1-carboxylic acid (190)



0.25 g (1 mmol) of **189** were dissolved in 30 mL acetone/ water (1/1, v/v). The procedure is in accordance with the general procedure IV. During the whole work up, the reaction mixture should not get warmer than 30 °C. The crude product was recrystallized from nitromethane. 0.230 g (0.54 mmol; 54%) of a colorless solid were isolated.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.13 (bs, 1H, CO_2H), 7.93 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.46 (t, J = 8.0 Hz, 2H), 7.37 (t, J = 7,6 Hz, 2H), 7.20 (s, 1H, NH), 4.24 (m, 3H), 2.24–1.25 (m, 14 H, adamantane), 0.89 (s, 3H, CH_3).

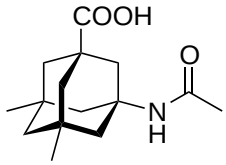
^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.6 (C=O); 154.2 (C=O); 144.0, 140.7, 127.5, 127.0, 125.3, 120.1, 64.8 (Fmoc-CH_2); 50.9 (C_q); 47.0, 46.7, 42.2 (C_q), 42.0, 41.6, 39.5, 37.0, 31.4 (C_q), 29.9, 28.9.

IR (KBr): v/cm^{-1} = 3315, 3065, 3040, 2911, 2853, 1718, 1675, 1555, 1448, 1263, 1089, 732.

Elem. Anal.: $C_{27}H_{29}NO_4$ (431.52): calcd. C 75.15, H 6.77, N 3.25; found: C 75.33, H 6.77, N 3.43.

The NMR data are in accordance with the literature.[149]

3-Acetamido-5,7-dimethyltricyclo[3.3.1.1$^{3.7}$]decane-1-carboxylic acid (194)[149]



The acetamidation of **193** was achieved by the procedure described in literature.

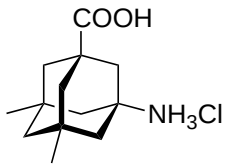
1.25 g (4.7 mmol; 87%) of the product were isolated.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.10 (bs, 1H, CO_2H); 7.43 (bs, 1H, NH); 1.85 (m, 2H); 1.78 (m, 3H); 1.62–1.44 (m, 4 H), 1.46–1.32 (m, 4H), 1.12–1.01 (m, 2H), 0.85 (s, 6 H).

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.7 (C=O), 168.8, 52.4, 49.3, 46.2, 43.9, 42.8, 40.8, 40.1, 38.4, 31.9, 29.6, 23.7.

The NMR data are in accordance with the literature.

3-Amino-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid hydrochloride (195)



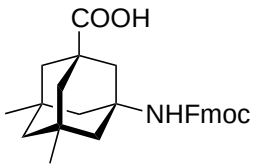
1.25 g (4.7 mmol) of **194** were refluxed in 20 mL of conc. HCl and 9 mL of water for 3 d. Aqueous HCl was removed under reduced pressure. The crude product was treated with acetone to remove by-product 3-chloro-5,7-dimethyladamantane-1-carboxylic acid. 0.69 g (2.7 mmol; 55%) of the product were obtained as a colorless solid.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.36 (bs, 1H, CO_2H), 8.39 (bs, 3H, NH_3Cl), 7.38 (t, 1H, J(^{15}NH) = 50.6 Hz), 1.82–1.77 (m, 2H), 1.52–1.31 (m, 8H), 1.21–1.03 (m, 2 H), 0.85 (s, 6 H).

^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 176.7 (C=O), 52.5, 48.5, 45.0, 43.3, 42.7, 32.1, 29.0.

The NMR data are in accordance with the literature.[149]

3-(9-Fluorenyl)methoxycarbonylamino-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid (196)[149]



0.256 g (0.98 mmol) of **195** were dissolved in 30 mL of acetone/water (1/1, v/v). The procedure is in accordance with the general procedure IV. During the whole work up, the reaction mixture should not get warmer than 30 °C. The crude product was recrystallized from nitromethane. 282 mg (0.63 mmol; 64%) of a colorless solid were isolated.

^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm = 12.11 (bs, 1H, CO_2H), 7.93 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 7,4 Hz, 2H), 7.34 (t, J = 7,6 Hz, 2H), 7.21 (s, 1H, NH), 4.24 (m, 3H), 1.97– 1.78 (m, 2H), 1.68–0.51 (m, 12 H, adamantane), 0.90 (s, 6H, 2X CH_3).

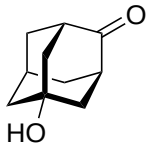
^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm = 177.5 (C=O); 154.2 (C=O); 143.9, 140.7, 127.6, 127.0, 125.3, 120.1, 64.8 (Fmoc-CH_2); 51.7 (C_q); 49.2, 46.7, 46.3, 43.8, 42.8 (C_q), 41.0, 32.00 (C_q), 29.50.

IR (KBr): v/cm^{-1} = 3324,3041, 2940, 2915, 2861, 1694, 1539, 1450, 1273, 1252,1128, 738

Elem. Anal.: $C_{28}H_{31}NO_4$ (445.55): calcd. C 75.48, H 7.01, N 3.14; found: C 75.13, H 7.02, N 3.60.

The NMR data are in accordance with the literature.[149]

5-Hydroxy-2-tricyclo[3.3.1.1$^{3.7}$]decanone (198)[158]

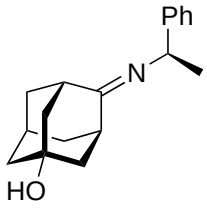


12 g (80 mmol) of **197** were added to 100 mL of 100% nitric acid cooled in an ice bath. The mixture was allowed to stand at r.t. for 3 d and was then heated at 60 °C for 90 min. Nitric acid was distilled off under reduced pressure. 40 mL of water and 15 mL of conc. sulfuric acid were added to the residue and the mixture heated to 60 °C for 1 h. The solution was cooled and extracted with a 2:1 mixture of pentane/diethyl ether. The acidic aqueous layer was neutralized with a saturated NaOH-solution and extracted with chloroform. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was dissolved in DCM, and pentane was added until no more precipitate formed. The product was filtered off *via* suction filtration and dried in a desiccator over paraffin wax and P_2O_5 under reduced pressure to yield 8.64 g (52 mmol; 65%) of the product as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 2.71–2.42 (m, 3 H), 2.24 (d, 1H), 2.17–1.79 (m, 9 H).

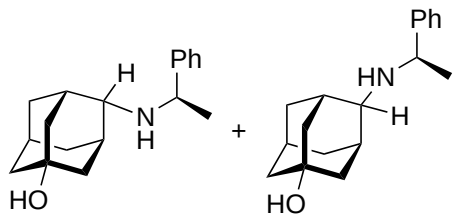
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 216.8 (C=O); 67.1, 46.9, 44.9, 44.1, 38.1, 29.8.

5-(*S*)-α-Methylbenzyliminotricyclo[3.3.1.1$^{3.7}$]decane-2-ol (199)[159]



(*S*)-α-methylbenzylamine (2.54 g, 20 mmol) and **198** (3.32 g, 20 mmol) and were dissolved in 100 mL dry ethanol and refluxed for 64 h in an argon atmosphere. The reaction mixture was concentrated and the crude imine (5.20 g, 98%) was used without purification in the next step.

***E*- + *Z*- 5-(*S*)-α-Methylbenzylaminotricyclo[3.3.1.1$^{3.7}$]decane-2-ol (200)**[159]



Z-isomer E-isomer

5.20 g (19 mmol) of **199** were dissolved in 100 mL of dry THF under argon atmosphere and cooled to 0 °C. 880 mg (24 mmol) of solid sodium borohydride and 4 mL (68 mmol) of acetic

acid were added, and the reaction mixture was stirred at 0 °C for 2h. The reaction mixture was diluted with DCM, and washed with saturated $NaHCO_3$-solution (2 x 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Isomer ***E*-200** was obtained in pure form by chromatography over silica gel using ethyl acetate as the eluent. 1.77 g (7.5 mmol, 34%) of the colorless solid were isolated.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.26–7.18 (m, 4 H), 7.18–7.09 (m, 1 H), 3.75 (q, J = 4 Hz, 1 H), 2.52 (t, 1 H), 2.01–1.94 (m, 2 H), 1.88–1.72 (m, 3 H), 1.65–1.46 (m, 7 H), 1.32–1.17 (m, 5 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 146.1, 128.1, 126.6, 126.4, 67.8, 57.63, 54.8, 45.4, 44.7, 44.4, 34.6, 32.8, 29.9, 29.8, 29.7, 24.8.

Melting point: 105 °C

The obtained data for ***E*-200** are in accordance with the literature. Unfortunately, no pure ***Z*-200** could be isolated *via* silica gel chromatography and HPLC.

HPLC-Method

E-isomer **200** was purified by using HPLC employing a 25 cm, d = 0.46 cm NH_2-phase

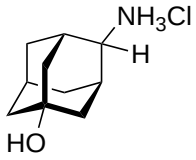
Eluent: TBME/hexane (1:4)

Flow = 5 mL/min

UV-detector λ = 254 nm

Retention times: R_1 = 40 min.

***E*-5-aminotricyclo[3.3.1.1$^{3.7}$]decane-2-ol hydrochloride (201 ·HCl)**[159]



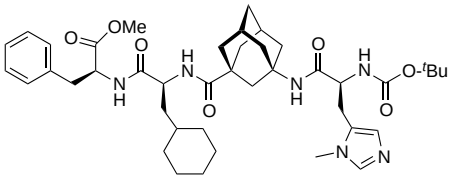
200 mg (0.74 mmol) of ***E*-200** and 30 mg of 10 % Pd/C were suspended in 1 mL of methanol and the mixture was hydrogenated for 72 h. The Pd/C was filtered off, the solvent removed under reduced pressure and the crude product dried in a desiccator over P_5O_{10}. Unfortunately, debenzylation was not complete. The mixture of **201** and **200** was dissolved in Et_2O/MeOH and HCl in Et_2O was added. Product **201·HCl** precipitated and was filtered off. 82 mg (0.4 mmol, 55%) of the hydrochloride were isolated as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 8.21 (s, 3 H, NH_3), 3.21 (s, 1 H, OH), 2.11 (s, 2 H), 2.01 (s, 1 H), 1.91 (d, J = 14 Hz, 2 H), 1.74–1.53 (m, 7 H), 1.37 (d, J = 14 Hz, 2 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 65.1, 53.8, 48.6, 45.1, 43.6, 31.9, 28.8, 28.4.

Peptides:

Boc-L- (π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (12i)



The peptide was synthesized on a solid support using commercially available Fmoc-Phe-Wang resin. 461.5 mg (0.3 mmol) of the preloaded resin was swollen in DMF for 30 min. The Fmoc-cleavage was performed by shaking the resin twice in 25% piperidine in DMF (v/v) for 25 min. The resin was washed five times with DMF, DCM and DMF. Chain elongation was achieved by a double coupling procedure (1 h shaking per coupling step) using Fmoc-Cha-OH (0.237 g, 0.6 mmol), HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol) per coupling step. After washing and cleavage of the Fmoc-group the peptide was elongated using Fmoc-^{A}Gly-OH **154** (0.250 g, 0.6 mmol), coupling agents and the base were used in the same stoichiometric amounts as given above. The peptide was washed again and the protection group was cleaved. For the last double coupling step the reaction time was increased to 2 h. Boc-L-(π-Me)-His-OH (0.121 g, 0.45 mmol), HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol) were used for coupling. The peptide was washed five times with DMF, DCM and diethyl ether and afterwards cleaved from the solid support by shaking it twice for 2 days in methanol/THF and triethylamine (9 : 1 : 1, v/v). The resin was filtered off and washed twice with chloroform. The collected solutions were concentrated under reduced pressure and purified by silica flash gel chromatography eluting with chloroform/methanol (9 : 1), R_f= 0.48.

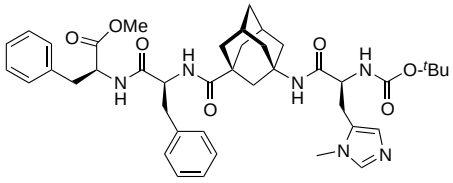
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ppm = 7.40 (s, 1 H, H_{Ar}, CH (His)), 7.24–7.15 (m, 3 H, H_{Ar} (Phe)), 7.10 (d, 2 H, J= 9 Hz, H_{Ar} (Phe)), 6.84 (s, 1 H, H_{Ar}, CH (His)), 6.55 (d, 1 H, J= 12 Hz, NH (Phe)), 6,0 (d, 1 H, J= 9 Hz, NH (Cha)), 5.77 (s, 1 H, NH (^{A}Gly)), 5.18 (d, 1 H, J= 8,4 Hz, NH (His)), 4.8 (q, 1 H, J= 7,2 Hz, $H_α$ (Phe)), 4.4 (q, 1 H, J= 7,2 Hz, $H_α$ (Cha)), 4.16 (s, 1 H, $H_α$ (His)), 3.70 (s, 3 H, OCH_3), 3.60 (s, 3 H, NCH_3), 3.14–3.04 (m, 2 H, Hβ (Phe)), 3.09–2.98 (m, 2 H, Hβ (His)), 2.21-2.17 (m, 2 H, adamantane), 1.93–1,80 (m, 6 H, adamantane + Cha), 1,74–1,58 (m, 12 H, adamantane + Cha), 1,4 (s, 9 H, $C(CH_3)$), 1.31 (t, 1 H, Cha), 1.27–1.09 (m, 4 H, Cha), 0.97–0.80 (m, 2 H, Cha).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ppm = 176.4 (C=O); 171.9 (C=O), 171.6 (C=O), 169.8 (C=O), 155.0 (C=O), 138.2, 135.5, 129.6, 128.8, 128.2 127.2, 126.9, 80.3, 54.5, 53.2, 52.3, 50.7, 42.5, 42.2, 40.4, 40.2, 39.5, 38.3, 38.1, 37.9, 35.1, 34.2, 33.5, 32.7, 31.5, 29.1, 28.3, 26.8, 26.3, 26.1, 26.1.

MS (ESI): *m/z* = 761.5 $[M+H]^+$ (calc. m/z = 761.5); m/z = 783.4 $[M+Na]^+$ (calc. m/z = 783.4); m/z = 1521.3 $[2M+H]^+$ (calc. m/z = 1521.9).

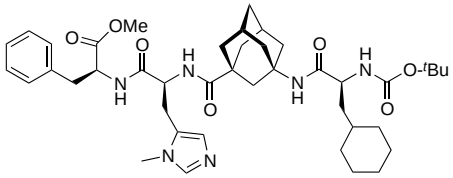
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{42}H_{61}N_6O_7^+$ 761.4596; Found 761.4557.
The NMR data are in accordance with the literature.[60]

Boc-L-(π-Me)-His-^{A} Gly-L-Phe-L-Phe-OMe (12g)[60]



The peptide was synthesized by Dr. Christian. E. Müller. The ESI-MS data are in accordance with the literature.

Boc-L-Cha-^{A}Gly-L-(π-Me)-His-L-Phe-OMe (13)



Solid support: 461.5 mg (0.3 mmol) Fmoc-Phe-Wang resin

1. Double coupling: 117.3 mg (0.3 mmol) Fmoc-(π-Me)-His-OH, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).
2. Double coupling: 250 mg (0.6 mmol) Fmoc-^{A} Gly-OH **154**, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).
3. Double coupling: 271.2 mg (0.6 mmol) Boc-L-Cha-OH·DCHA, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).

Washing: 5X DMF, 5X DCM, 5X DMF
Fmoc-cleavage: 25% piperidine in DMF
Cleavage from the resin: methanol/THF/triethylamine (9 : 1 : 1).
The crude peptide was purified *via* column chromatography utilizing silica flash gel and CH_3Cl/MeOH (10:1: R_f = 0.35). Overall, 136 mg (0.18 mmol; 60%) of the pure peptide were isolated.

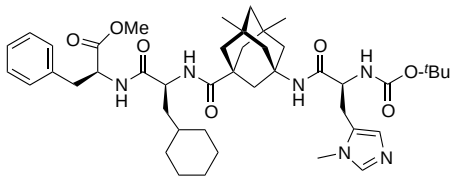
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.58 (s, 1 H, H_{Ar}, CH (His)), 7.25–7.13 (m, 3 H, H_{Ar} (Phe)), 7.00 (d, 2 H, J= 8 Hz, H_{Ar} (Phe)), 6.82 (s, 1 H, H_{Ar}, CH (His)), 6.39 (d, 1 H, J= 8 Hz, NH (Phe)), 5.89 (s, 1 H, NH (Cha)), 4.88 (s, 1 H, NH (^{A}Gly)), 4.65 (q, 1 H, J= 7,2 Hz, $H_α$ (Phe)), 4.51 (q, 1 H, J= 7,2 Hz, $H_α$ (Cha)), 3.98–3.89 (m, 2 H, $H_α$ (His) + NH (His)), 3.64 (s, 3 H, OCH_3), 3.60 (s, 3 H, NCH_3), 3.10–3.01 (m, 1 H, $H_β$ (Phe)), 3.00–2.91 (m, 3 H, $H_β$ (His) + $H_β$ (Phe)), 2.17–2.09 (m, 2 H, adamantane), 2.03–1.78 (m, 7 H, adamantane + Cha), 1.75–1.50 (m, 12 H, adamantane + Cha), 1.38 (s, 9 H, $C(CH_3)$), 1.27–1.01 (m, 4 H, Cha), 0.97–0.74 (m, 2 H, Cha).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 176.7 (C=O); 171.9 (C=O); 171.5 (C=O); 170.2 (C=O); 155.8 (C=O); 137.9, 135.8, 129.1, 128.6, 127.6, 127.1, 77.2, 53.8, 52.5, 52.0, 51.7, 42.6, 42.4, 40.5, 40.3, 39.9, 38.1, 37.9, 37.5, 35.2, 34.1, 33.7, 32.7, 32.0, 39.1, 28.3, 26.6, 26.4, 26.3, 26.1.

MS (ESI): *m/z* = 761.3 $[M+H]^+$ (calc. m/z = 761,5)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{42}H_{61}N_6O_7^+$ 761.4596; Found 761.4575.

Boc-L-(π-Me)-His-5,7-Me$_2$-^{A}Gly-L-Cha-L-Phe-OMe (207)



Solid support: 492.5 mg (0.3 mmol) Fmoc-Phe-Wang resin

1. Double coupling: 235.89 mg (0.6 mmol) Fmoc-L-Cha-OH, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).
2. Double coupling: 200.9 mg (0.45 mmol) **196**, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol)
3. Double coupling: 121.25 mg (0.45 mmol) Boc-L-(π-Me)-histidine, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).

Washing: 5 X DMF, 5 X DCM, 5 X DMF

Fmoc-cleavage: 25% piperidine in DMF.

Cleavage from the resin: methanol/THF/triethylamine (9 : 1 : 1).

The crude peptide was purified *via* column chromatography utilizing silica flash gel and CH_3Cl/MeOH (10:1: R_f = 0.45). Overall, 145 mg (0.2 mmol; 65%) of the pure peptide were isolated.

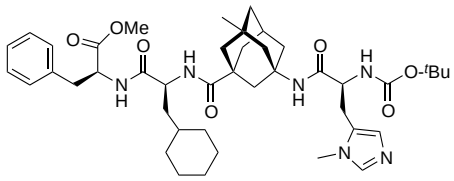
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.53 (s, 1 H, H_{Ar}, CH (His)), 7.26–7.13 (m, 3 H, H_{Ar} (Phe)), 7.03 (d, 2 H, J= 7.2 Hz, H_{Ar} (Phe)), 6.81 (s, 1 H, H_{Ar}, CH (His)), 6.60 (d, 1 H, J= 10 Hz, NH (Phe)), 6.14 (s, 1 H, NH (Cha)), 6.03 (s, 1 H, J = 9 Hz, NH (^{A}Gly)), 5.27 (d, 1 H, J= 8,4 Hz, NH (His)), 4.73 (q, 1 H, J= 7,2 Hz, $H_α$ (Phe)), 4.38 (q, 1 H, J= 7,2 Hz, $H_α$ (Cha)) 4.17 (s, 1 H, $H_α$ (His)), 3.63 (s, 3 H, OCH_3), 3.56 (s, 3 H, NCH_3), 3.10–2.88 (m, 4 H, $H_β$ (Phe) + $H_β$ (His)), 1.88–1.70 (m, 3 H, adamantane), 1.68–0.96(m, 22 H, adamantane + Cha), 1.36 (s, 9 H, $C(CH_3)$), 0.91–0.73 (m, 7 H, CH_3-Ad + Cha).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ppm = 176.2 (C=O); 172.0 (C=O); 171.7 (C=O); 169.8 (C=O); 137.8; 135.8; 129.2; 128.6; 127.2; 127,21; 80.4; 77.2; 53.9; 53.3; 52.6; 52.3; 50.7; 49.5; 46.3, 44.4, 44.3, 43.9, 40.9, 39.6, 37.8, 31.1, 33.4, 32.8, 32.7, 31.8, 29.6, 28.3, 27.0, 26.3, 26.1, 26.1

MS (ESI): *m/z* = 789.4 $[M+H]^+$ (calc. m/z = 789.5)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{44}H_{65}N_6O_7^+$ 789.4909; Found 789.4902.

Boc-L- (π-Me)-His-5-Me-^{A}Gly-L-Cha-L-Phe-OMe (208)



Solid support: 492,5 mg (0.3 mmol) Fmoc-Phe-Wang resin

1. Double coupling: 235.89 mg (0.6 mmol) Fmoc-L-Cha-OH, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).
2. Double coupling: 194.9 mg (0.45 mmol) **190**, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol)
3. Double coupling: 121.25 mg (0.45 mmol) Boc-L-(π-Me)-histidine, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).

Washing: 5X DMF, 5X DCM, 5X DMF

Fmoc-cleavage: 25% piperidine in DMF.

Cleavage from the resin: methanol/THF/triethylamine (9 : 1 : 1).

The crude peptide was purified *via* column chromatography utilizing silica flash gel and CH_3Cl/MeOH (10:1: R_f = 0.45). Overall, 138 mg (0.18 mmol; 62%) of the pure peptide were isolated.

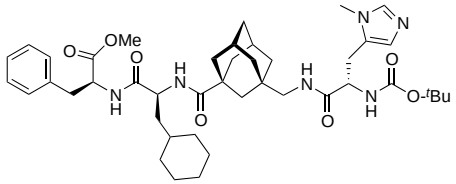
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.53 (s, 1 H, H_{Ar}, CH (His)), 7.25–7.12 (m, 3 H, H_{Ar} (Phe)), 7.04 (d, 2 H, J= 9 Hz, H_{Ar} (Phe)), 6.82 (s, 1 H, H_{Ar}, CH (His)), 6.55 (m, 1 H, NH (Phe)), 6.13 (s, 1 H, NH (Cha)), 6.01 (s, 1 H, NH (^{A}Gly)), 5.28 (s, 1 H, NH (His)), 4.73 (q, 1 H, J= 7,2 Hz, $H_α$ (Phe)), 4.37 (q, 1 H, J= 7,2 Hz, $H_α$ (Cha)), 4.17 (s, 1 H, $H_α$ (His)), 3.63 (s, 3 H, OCH_3), 3.60 (s, 3 H, NCH_3), 3.10–2.87 (m, 4 H, $H_β$ (Phe) + $H_β$ (His)), 2.21–2.09 (m, 1 H, adamantane), 1.93–1.68 (m, 5 H, adamantane + Cha), 1.68–1.47 (m, 9 H, adamantane + Cha), 1.47–1.24 (m, 15 H, C(CH_3) + adamantane), 1.23–0.96 (m, 4 H, Cha), 0.92–0.73 (m, 5 H, CH_3-Ad + Cha).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 176.3 (C=O); 172.0 (C=O); 171.7 (C=O); 169.7(C=O); 137.8; 135.8; 129.2; 128.6; 127.2; 80.5; 77.2; 53.3; 53.2; 52.3; 50.7; 44.9; 43.2; 42.2; 41.5; 39.6; 37.8; 37.6; 37.4; 34.1; 33.4; 32.8; 32.1; 29.9; 29.5; 28.3; 27.0; 26.3; 26.2; 26.0.

MS (ESI): *m/z* = 775.3 $[M+H]^+$ (calc. m/z = 775.5)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{43}H_{63}N_6O_7^+$ 775.4753; Found 775.4742.

Boc-L-(π-Me)-His-MAACA-L-Cha-L-Phe-OMe (209)



Solid support: 461.5 mg (0.3 mmol) Fmoc-Phe-Wang resin

1. Double coupling: 235.89 mg (0.6 mmol) Fmoc-L-Cha-OH, HBTU (0.228 g, 0.6 mmol), $HOBt \cdot H_2O$ (0.092 g, 0.6 mmol), and D^iPEA (0.155 g, 204.1 µL, 1.2 mmol).
2. Double coupling: 193.9 mg (0.45 mmol) **158**, HBTU (0.228 g, 0.6 mmol), $HOBt \cdot H_2O$ (0.092 g, 0.6 mmol), and D^iPEA (0.155 g, 204.1 µL, 1.2 mmol)
3. Double coupling: 121.25 mg (0.45 mmol) Boc-L-(π-Me)-histidine, HBTU (0.228 g, 0.6 mmol), $HOBt \cdot H_2O$ (0.092 g, 0.6 mmol), and D^iPEA (0.155 g, 204.1 µL, 1.2 mmol).

Washing: 5X DMF, 5X DCM, 5X DMF

Fmoc-cleavage: 25% piperidine in DMF

Cleavage from the resin: methanol/THF/triethylamine (9 : 1 : 1).

The crude peptide was purified *via* column chromatography utilizing silica flash gel and CH_3Cl/MeOH (10:1: R_f = 0.45). Overall, 178 mg (0.23 mmol; 76%) of the pure peptide were isolated.

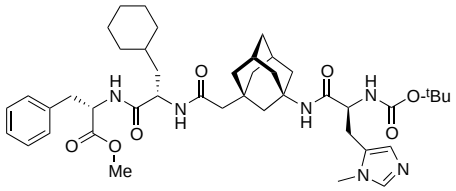
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.37 (s, 1 H, H_{Ar}, CH (His)), 7.24-7.12 (m, 3 H, H_{Ar} (Phe)), 7.03 (d, 2 H, J= 8 Hz, H_{Ar} (Phe)), 6.78 (d, 1 H, J = 7.2 Hz, H_{Ar}, CH (His)), 6.36–6.24 (m, 2 H, NH (Phe) + NH (Cha)), 5.26 (m, 2 H, J = 7.2 Hz, NH (^{A}Gly) + (His)), 4.74 (q, 1 H, J= 7,2 Hz, H_α (Phe)), 4.37 (q, 1 H, J= 7,2 Hz, H_α (Cha)), 4.23 (q, 1 H, J = 6 Hz, H_α (His)), 3.64 (s, 3 H, OCH_3), 3.53 (s, 3 H, NCH_3), 3.12–2.89 (m, 5 H, H_β (Phe) + H_β (Cha)), 2.78–2.74 (m, 1 H), 2.01 (s, 2 H, H_β (His)), 1.71-1.44 (m, 14 H, adamantane), 1.33–0.99 (m, 9 H, adamantane + Cha), 1,34 (s, 9 H, $C(CH_3)$), 0.94-0.71 (m, 2 H, Cha).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 177.1 (C=O); 172.3 (C=O); 172.0 (C=O); 170.9 (C=O); 155.4 (C=O); 138.2; 135.9, 129.3, 128.6, 127.6, 127.1, 80.4, 77.2, 53.2, 52.4, 51.1, 50.5, 41.2, 41.0, 39.2, 39.0, 38.4, 37.8, 35.7, 34.4, 33.5, 32.6, 31.6, 28.4, 28.1, 26.9, 26.4, 26.2, 26.0

MS (ESI): *m/z* = 775.5 $[M+H]^+$ (calc. m/z = 775.5).

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{43}H_{63}N_6O_7^+$ 775.4753; Found 775.4717.

Boc-L-(π-Me)-His-AAMCA-L-Cha-L-Phe-OMe (210)



Solid support: 461.5 mg (0.3 mmol) Fmoc-Phe-Wang resin

1. Double coupling: 235.89 mg (0.6 mmol) Fmoc-L-Cha-OH, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).
2. Double coupling: 258.6 mg (0.6 mmol) **157**, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol)
3. Double coupling: 121.25 mg (0.45 mmol) Boc-L-(π-Me)-histidine, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).

Washing: 5X DMF, 5X DCM, 5X DMF

Fmoc-cleavage: 25% piperidine in DMF

Cleavage from the resin: methanol/THF/triethylamine (9 : 1 : 1).

The crude peptide was purified *via* column chromatography utilizing silica flash gel and CH_3Cl/MeOH (10:1: R_f = 0.45). Overall, 163 mg (0.21 mmol; 70%) of the pure peptide were isolated as a colorless solid.

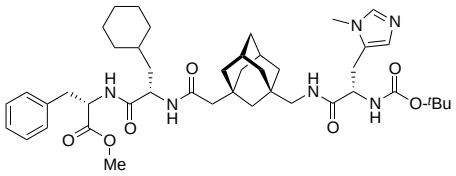
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.36 (s, 1 H, H_{Ar}, CH (His)), 7.24–7.12 (m, 3 H, H_{Ar} (Phe)), 7.04 (d, 2 H, J= 8 Hz, H_{Ar} (Phe)), 6.77 (s, 1 H, H_{Ar}, CH (His)), 6.72 (d, 1 H, J= 12 Hz, NH (Phe)), 6.07 (d, 1 H, J= 9 Hz, NH (Cha)), 5.77 (s, 1 H, NH (^{A}Gly)), 5.20 (d, 1 H, J= 8.4 Hz, NH (His)), 4.73 (q, 1 H, J= 7.2 Hz, $H_α$ (Phe)), 4.38 (q, 1 H, J = 7.2 Hz); 4.09 (m, 1 H, $H_α$ (His)), 3.63 (s, 3 H, OCH_3), 3.53 (s, 3 H, NCH_3), 3.09-2.95 (m, 2 H, $H_β$ (Phe)), 2.90 (d, 2 H), 2.08–2.02 (m, 2 H, adamantane), 1.95–1.80 (m, 4 H, adamantane + Cha), 1.78–1.38 (m, 16 H, adamantane + Cha), 1.35 (s, 9 H, $C(CH_3)$), 1.31 (t, 1 H, Cha),1.27–1.09 (m, 4 H, Cha), 0.94–0.68 (m, 2 H, Cha).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 171.96 (C=O), 171.73 (C=O), 170.65 (C=O), 169.45 (C=O), 155.32 (C=O), 138.10, 135.80, 129.27, 128.55, 127.79, 127.38, 127.09, 80.32, 54.36, 53.32, 52.67, 52.32, 50.90, 50.28, 46.23, 41.05, 40.47, 39.33, 37.84, 35.25; 34.64, 34.00, 33.53, 32.54, 31.49, 29.45, 28.29, 27.00, 26.33, 26.19, 26.01.

MS (ESI): *m/z* = 775.5 $[M+H]^+$ (calc. m/z = 775.5);

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{43}H_{63}N_6O_7^+$ 775.4753; Found 775.4700.

Boc-L- (π-Me)-His-MAAMCA-L-Cha-L-Phe-OMe (211)



All peptide couplings are in accordance with the general procedures VI and VII.

1. HOBt/EDC mediated peptide coupling:

H-Phe-OMe · HCl:	0.269 g (1.250 mmol)
Boc-Cha-OH · $(C_6H_{11})_2NH$:	0.566 g (1.250 mmol)
EDC · HCl:	0.263 g (1.375 mmol)
HOBt:	0.210 g (1.375 mmol)
Et_3N:	0.19 mL (1.375 mmol)
DCM:	8.0 mL

2. Cleavage of the Boc-group with HCl · 1,4-dioxane.

3. HOBt/EDC mediated peptide coupling:

H-Cha-Phe-OMe · HCl:	0.472 g (1.10 mmol)
Boc-181:	0.342 g (1.10 mmol)
EDC · HCl:	0.232 g (1.21 mmol)
HOBt:	0.185 g (1.21 mmol)
Et_3N:	0.17 mL (1.21 mmol)
DCM:	10.0 mL

4. Cleavage of the Boc-group with HCl · 1,4-dioxane.

5. HOBt/EDC mediated peptide coupling:

Boc-MAAMCA-H-Cha-Phe-OMe · HCl:	0.446 g (0.70 mmol)
Boc-π-Me-His-OH:	0.188 g (0.70 mmol)
EDC · HCl:	0.148 g (0.77 mmol)
HOBt:	0.104 g (0.77 mmol)
Et_3N:	0.1 mL (0.77 mmol)
DCM:	8.0 mL

The crude peptide was purified by silica flash gel column chromatography eluating with

$CHCl_3$/MeOH 10:1 (R_f = 0.4) and 209 mg (0.26 mmol; 21%) of the peptide were isolated as a colorless solid.

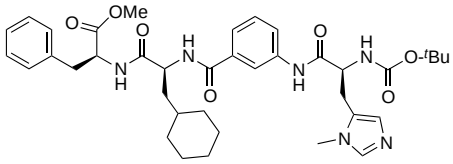
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.43 (s, 1 H, H_{Ar}, CH (His)), 7.26–7.13 (m, 3 H, H_{Ar} (Phe)), 7.03 (d, 2 H, J= 7.2 Hz, H_{Ar} (Phe)), 6.81 (s, 1 H, H_{Ar}, CH (His)), 6.76 (d, 1 H, J= 10 Hz, NH (Phe)), 6.50 (d, 1 H, J= 10 Hz, NH (Cha)), 6.20(s, 1 H, NH (^{A}Gly)), 5.41 (d, 1 H, J= 8,4 Hz, NH (His)), 4.75 (q, 1 H, J= 7,2 Hz, $H_α$ (Phe)), 4.37 (q, 1 H, J= 7,2 Hz, $H_α$ (Cha)), 4.24 (s, 1 H, $H_α$ (His)); 3.63 (s, 3 H, OCH_3); 3.56 (s, 3 H, NCH_3); 3.13–2.74 (m, 4 H, $H_β$ (Phe) + $H_β$ (His)), 2.03–1.83 (m, 4 H, adamantane), 1.72–1.4 (m, 14 H, adamantane + Cha), 1.37 (s, 9 H, $C(CH_3)$), 1.32–0.97 (m, 12 H, Cha + adamantane), 0.97–0.68 (m, 2 H, Cha).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ppm = 172.3 (C=O); 171.8 (C=O); 171.1 (C=O); 170.7 (C=O); 137.9, 135.8, 129.4, 128.6, 127.1, 77.2, 55.32, 52.3, 51.3, 50.7, 44.5, 42.2, 41.5, 39.4, 37.9, 35.8, 34.4, 34.0, 33.6, 33.3, 31.6, 28.3, 26.3, 26.0.

MS (ESI): *m/z* = 789.4 $[M+H]^+$ (calc. m/z = 789.5).

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{44}H_{65}N_6O_7^+$ 789.4909; Found 789.4902.

Boc-L-(π-Me)-His-3-Abz-L-Cha-L-Phe-OMe (212)



Solid support: 461.5 mg (0.3 mmol) Fmoc-Phe-Wang resin

1. Double coupling: 235.85 mg (0.6 mmol) Fmoc-L-Cha-OH, HBTU (0.228 g, 0.6 mmol), $HOBt·H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).
2. Double coupling: 216 mg (0.6 mmol) Fmoc-3-Abz-OH, HBTU (0.228 g, 0.6 mmol), $HOBt·H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol)
3. Double coupling: 121.25 mg (0.45 mmol) Boc-L-(π-Me)-histidine, HBTU (0.228 g, 0.6 mmol), $HOBt·H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).

Washing: 5X DMF, 5X DCM, 5X DMF

Fmoc-cleavage: 25% piperidine in DMF

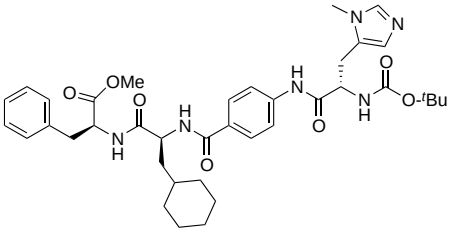
Cleavage from the resin: methanol/THF/triethylamine (9 : 1 : 1).

The crude product was purified *via* silica flash gel column chromatography utilizing CH_3Cl/MeOH (10:1; R_f = 0.4). Overall, 120 mg (0.17 mmol; 57%) of the pure peptide were isolated as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.81 (s, 1 H, H_{Ar}, CH (His)), 7.63–6.88 (m, 12 H, H_{Ar} (Phe) + (Abz) + NH (Phe)+ NH (Cha)), 6,84 (s, 1 H, H_{Ar}, CH (His)), 5.85 (s, 1 H, NH (^{A}Gly)), 4.86–4.55 (m, 3 H, NH (His) + $H_α$ (Phe) + $H_α$ (His)), 3.53 (s, 3 H, OCH_3), 3.49 (s, 3 H, NCH_3), 3.11–2.86 (m, 4 H, $H_β$ (Phe) + $H_β$ (His)), 1.71–1.41 (m, 8 H, adamantane + Cha), 1.30 (s, 9 H, $C(CH_3)$), 1,27–1,09 (m, 4 H, Cha), 0.91–0,69 (m, 2 H, Cha),

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 173.0 (C=O); 172.0 (C=O); 170.4 (C=O); 167.4(C=O); 155.8 (C=O); 138.2; 137.8; 135.9; 134.6, 129.1, 128.4, 128.0, 127.1, 123.4, 123.0, 118.4, 80.6, 54.5, 53.7, 52.2, 51.9, 39.7, 37.8, 34.1, 33.5, 32.7, 31.5, 28.4, 27.3, 26.3, 26.1, 26.0
MS (ESI): *m/z* = 703.3 $[M+H]^+$ (calc. m/z = 703.4); m/z = 725.3 $[M+Na]^+$ (calc. m/z = 725.4).
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{38}H_{51}N_6O_7^+$ 703.3814; Found 703.3765.

Boc-L-(π-Me)-His-4-Abz-L-Cha-L-Phe-OMe (213)

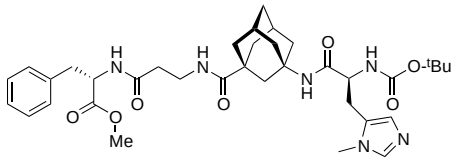


Solid support: 461.5 mg (0.3 mmol) Fmoc-Phe-Wang resin

1. Double coupling: 235.85 mg (0.6 mmol) Fmoc-L-Cha-OH, HBTU (0.228 g, 0.6 mmol), $HOBt{\cdot}H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).
2. Double coupling: 216 mg (0.6 mmol) Fmoc-4-Abz-OH, HBTU (0.228 g, 0.6 mmol), $HOBt{\cdot}H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).
3. Double coupling: 121.25 mg (0.45 mmol) Boc-L-(π-Me)-histidine, HBTU (0.228 g, 0.6 mmol), $HOBt{\cdot}H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).

Washing: 5X DMF, 5X DCM, 5X DMF
Fmoc-cleavage: 25% piperidine in DMF
Cleavage from the resin: methanol/THF/triethylamine (9 : 1 : 1)
The crude product was purified *via* silica flash gel column chromatography utilizing CH_3Cl/MeOH as eluent (10:1; R_f = 0.45). Overall, 112 mg (0.17 mmol; 56%) of the pure peptide were isolated as a colorless solid.
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 8.01 (s, 1 H, H_{Ar}, CH (His)), 7.81 (s, 2 H, H_{Ar} (Abz), 7.43–7.18 (m, 4 H, H_{Ar} (Phe) + (Abz)), 7.18–6.98 (m, 5 H, H_{Ar} (Phe) + (Abz)), 6.93 (s, 1 H, H_{Ar}, CH (His)), 5.62 (s, 1 H, NH (^{A}Gly)), 4.91–4.66 (m, 3 H, NH (His) + H_α (Phe) + H_α (His)), 3.64 (s, 3 H, OCH_3), 3.47 (s, 3 H, NCH_3), 3.17–2.88 (m, 4 H, H_β (Phe) + H_β (His)), 2.17 (s, 1 H), 1.86–1.50 (m, 7 H, Cha), 1.49–1.26 (m, 10 H, $C(CH_3)$ + H (Cha)), 1,27–1,09 (m, 3 H, Cha), 0.91–0,69 (m, 2 H, Cha)
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 174.0 (C=O); 171.6 (C=O); 170.6 (C=O); 166.5(C=O); 155.9 (C=O); 141.3,138.4, 135.9, 129.0, 128.5, 128.3, 126.9, 126.6, 118.9, 80.6, 54.2, 53.9, 52.2, 51.7, 45.9, 39.2, 37.9, 34.1, 33.5, 32.4, 31.3, 29.7, 28.2, 26.8, 26.3, 26.1, 26.0
MS (ESI): *m/z* = 703.3 $[M+H]^+$ (calc. m/z = 703.4); m/z = 725.3 $[M+Na]^+$ (calc. m/z = 725.4).
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{38}H_{51}N_6O_7^+$ 703.3814; Found 703.3760.

Boc-L-(π-Me)-His-^{A}Gly-L-β-Ala-L-Phe-OMe (214)



Solid support: 461.5 mg (0.3 mmol) Fmoc-Phe-Wang resin

1. Double coupling: 185.7 mg (0.6 mmol) Fmoc-β-Ala-OH, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol)
2. Double coupling: 250 mg (0.6 mmol) Fmoc-^{A}Gly-OH, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol)
3. Double coupling: 121.25 mg (0.45 mmol) Boc-L-(π-Me)-histidine, HBTU (0.228 g, 0.6 mmol), HOBt·H_2O (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).

Washing: 5X DMF, 5X DCM, 5X DMF

Fmoc-cleavage: 25% piperidine in DMF

Cleavage from the resin: methanol/THF/triethylamine (9 : 1 : 1)

The crude product was purified *via* silica flash gel column chromatography utilizing CH_3Cl/MeOH as eluent (10:1; R_f = 0.40). Overall, 94 mg (0.14 mmol; 46%) of the pure peptide were isolated as a colorless solid.

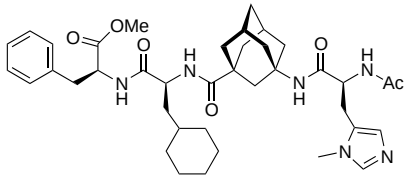
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ppm = 7.63 (s, 1 H, H_{Ar}, CH (His)), 7.26–7.10 (m, 3 H, H_{Ar} (Phe)), 7.05 (d, 2 H, J= 7.2 Hz, H_{Ar} (Phe)), 6.86 (s, 1 H, H_{Ar}, CH (His)), 6.55 (d, 1 H, J= 6 Hz, NH (Phe)), 6.48(d, 1 H, J= 7.6 Hz, NH (β-Ala)), 6.09 (s, 1 H, NH (^{A}Gly)), 5.34 (d, 1 H, J= 7.6 Hz, NH (His)), 4.76 (q, 1 H, J= 6.8 Hz, $H_α$ (Phe)), 4.20–4.12 (m, 1 H, $H_α$ (His)), 3.67 (s, 3 H, OCH_3), 3.60 (s, 3 H, NCH_3), 3,14–3,04 (m, 2 H, Hβ (Phe)), 3.48–3.26 (m, 2 H, β-Ala), 3.12–2.89 (m, 4 H, $H_β$ (His) + (β-Ala)), 2.34–2.27 (m, 2 H, adamantane), 2.13–2.05 (m, 2 H, adamantane), 1.96–1.43 (m, 8 H, adamantane), 1.34 (s, 9 H, $C(CH_3)$).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ppm = 176.7 (C=O); 172.1 (C=O); 171.7 (C=O); 169.5 (C=O); 137.7, 135.9,129.2, 128,6, 127.2, 77.2, 53.4, 52.4,42.6, 42.4, 40.2, 37.9, 37.7, 35.4, 35.1, 31.9, 29.2, 28.2, 26.9.

MS (ESI): *m/z* = 679.3 $[M+H]^+$ (calc. m/z = 679.4).

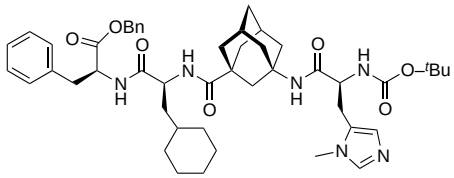
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{36}H_{51}N_6O_7^+$ 679.3814; Found 679.3793.

Ac-L-(π-Me)-His-^{A} Gly-L-Phg-L-Phe-OMe (215)



This peptide was synthesized by M.Sc. Raffael C. Wende. The synthesis can be found in literature.[70]

Boc-L-(π-Me)-His-^{A}Gly-L-Phg-L-Phe-OBn (216)



All peptide couplings are in accordance to the general procedure VI and VII.

1. HOBt/EDC mediated peptide coupling:

H-Phe-OBn · HCl:	0.319 g (1.250 mmol)
Boc-Cha-OH · $(C_6H_{11})_2NH$:	0.566 g (1.250 mmol)
EDC · HCl:	0.263 g (1.375 mmol)
HOBt:	0.210 g (1.375 mmol)
Et_3N:	0.19 mL (1.375 mmol)
DCM:	8.0 mL

2. Cleavage of the Boc-group with HCl · 1,4-dioxane.

3. HOBt/EDC mediated peptide coupling:

H-Cha-Phe-OMe · HCl:	0.472 g (1.10 mmol)
Boc-3-methylaminoadamantan-1-methylcarboxylic acid:	0.313 g (1.10 mmol)
EDC · HCl:	0.232 g (1.21 mmol)
HOBt:	0.185 g (1.21 mmol)
Et_3N:	0.17 mL (1.21 mmol)
DCM:	8.0 mL

4. Cleavage of the Boc-group with HCl · 1,4-dioxane.

5. HOBt/EDC mediated peptide coupling:

Boc-MAAMCA-H-Cha-Phe-OMe · HCl:	0.650 g (0.95mmol)
Boc-(π-Me)-His-OH :	0.269 g (0.95 mmol)
EDC · HCl:	0.382 g (2.00 mmol)
HOBt:	0.270 g (2.00 mmol)
Et_3N:	0.15 mL (2.00 mmol)
DCM:	6.0 mL

The crude peptide was purified by silica flash gel column chromatography eluating with

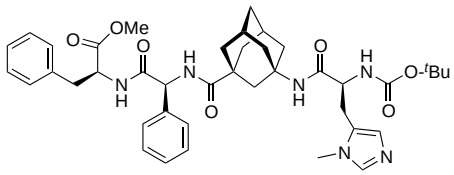
$CHCl_3$/MeOH 10:1 (R_f = 0.4) and 523 mg (0.68 mmol; 54%) of a colorless solid were isolated.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ppm = 7.40 (s, 1 H, H_{Ar}, CH (His)), 7.38–7.32 (m, 3 H, H_{ar} (Phe) + Ph), 7.30–7.23 (m, 5 H, H_{ar} (Phe) + Ph), 7.25–7.19 (m, 2 H, H_{ar} (Phe)),**)**, 6.87 (s, 1 H, H_{Ar}, CH (His)), 6.52 (d, 1 H, J= 12 Hz, NH (Phe)), 6,0 (d, 1 H, J= 9 Hz, NH (Cha)), 5.78 (s, 1 H, NH (^{A}Gly)), 5.18 – 5.08 (m, 3 H, CH_2 + NH (His)), 4.8 (q, 1 H, J= 7,2 Hz, $H_α$ (Phe)), 4.4 (q, 1 H, J= 7,2 Hz, $H_α$ (Cha)), 4.16 (s, 1 H, $H_α$ (His)), 3.60 (s, 3 H, NCH_3), 3.14–3.04 (m, 2 H, Hβ (Phe)), 3.09–2.98 (m, 2 H, Hβ (His)), 2.21-2.17 (m, 2 H, adamantane), 1.93–1,80 (m, 6 H, adamantane + Cha), 1,74–1,58 (m, 12 H, adamantane + Cha), 1,4 (s, 9 H, $C(CH_3)$), 1.31 (t, 1 H, Cha), 1.27–1.09 (m, 4 H, Cha), 0.97–0.80 (m, 2 H, Cha)

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ppm = 176.4 (C=O); 171.9 (C=O), 171.6 (C=O), 169.8 (C=O), 155.0 (C=O), 138.2, 135.5, 135.0, 129.6, 129.0, 128.8, 128.4, 128.2 127.2, 126.9, 80.3, 67.1, 53.2, 52.3, 50.7, 42.5, 42.2, 40.4, 40.2, 39.5, 38.3, 38.1, 37.9, 35.1, 34.2, 33.5, 32.7, 31.5, 29.1, 28.3, 26.8, 26.3, 26.1, 26.1.

MS (ESI): *m/z* = 763.4 $[M+H]^+$ (calc. m/z = 763.4).

Boc-L-(π-Me)-His-^{A} Gly-L-Phg-L-Phe-OMe (217)



Solid support: 461.5 mg (0.3 mmol) Fmoc-Phe-Wang resin

1. Double coupling: 224.42 mg (0.6 mmol) Fmoc-L-Phg-OH, HBTU (0.228 g, 0.6 mmol), $HOBt·H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).
2. Double coupling: 250 mg (0.6 mmol) Fmoc-^{A}Gly-OH **154**, HBTU (0.228 g, 0.6 mmol), $HOBt·H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).
3. Double coupling: 121.25 mg (0.45 mmol) Boc-L-(π-Me)-histidine, HBTU (0.228 g, 0.6 mmol), $HOBt·H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).

Washing: 5X DMF, 5X DCM, 5X DMF

Fmoc-cleavage: 25% piperidine in DMF

Cleavage from the resin: methanol/THF/triethylamine (9 : 1 : 1).

The crude peptide was purified *via* column chromatography utilizing silica flash gel and CH_3Cl/MeOH (10:1: R_f = 0.35). Overall, 224 mg (0.22 mmol; 76%) of the pure peptide were isolated as a colorless solid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ppm = 7.66 (s, 1 H, H_{Ar}, CH (His)), 7.38–7.20 (m, 8 H, H_{Ar} (Phe) + (Phe-Gly)), 7.13–6.97 (m, 2 H, H_{Ar} (Phe)), 6.89 (s, 1 H, H_{Ar}, CH (His)), 6.63 (d, 1 H, J= 7.8 Hz, NH (Phe)), 6.40 (d, 1 H, J= 9 Hz, NH (Phe-Gly)), 6.15 (s, 1 H, NH (^{A}Gly)), 5.44–5.28 (m, 1 H, NH (His)), 4.85 (q, 1 H, J= 7,2 Hz, $H_α$ (Phe)), 4.75 (q, 1 H, J= 7,2 Hz, $H_α$ (Phe-

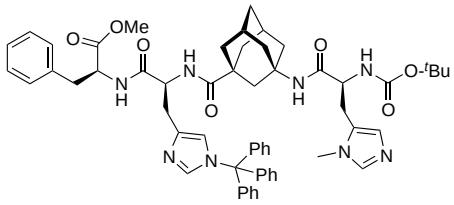
Gly)), 4.23 (s, 1 H, H_α (His)), 3,70 (s, 3 H, OCH_3), 3,60 (s, 3 H, NCH_3), 3.16–2.88 (m, 4 H, H_β (Phe) + H_β (His)), 2.22–2.11 (m, 2 H, adamantane), 2.05–1.46 (m, 12 H, adamantane), 1,4 (s, 9 H, $C(CH_3)$).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ppm = 175.9 (C=O); 171.3 (C=O); 171.2 (C=O); 169.7(C=O); 155.4 (C=O); 137.5; 135.5; 129.16; 129.0, 128.7, 128.4, 127.1, 127.1, 127.0, 80.4, 56.8, 53.7, 53.2, 52.4, 52.3, 42.5, 42.1, 40.2, 38.0, 37.6, 35.1, 31.9, 29.1, 28.3, 27.6, 26.9 25.6.

MS (ESI): *m/z* = 741.3 $[M+H]^+$ (calc. m/z = 741.4)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{41}H_{53}N_6O_7^+$ 741.3970; Found 741.3938.

Boc-L-(π-Me)-His-^{A} Gly-L-His(Trt)-L-Phe-OMe (218)



Solid support: 461,5 mg (0.3 mmol) Fmoc-Phe-Wang resin

1. Double coupling: 371.8 mg (0.6 mmol) Fmoc-L-His(Trt)-OH, HBTU (0.228 g, 0.6 mmol), $HOBt{\cdot}H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol)
2. Double coupling: 250 mg (0.6 mmol) Fmoc-^{A} Gly-OH, HBTU (0.228 g, 0.6 mmol), $HOBt{\cdot}H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol)
3. Double coupling: 121.25 mg (0.45 mmol) Boc-L-(π-Me)-histidine, HBTU (0.228 g, 0.6 mmol), $HOBt{\cdot}H_2O$ (0.092 g, 0.6 mmol), and D^{i}PEA (0.155 g, 204.1 µL, 1.2 mmol).

Washing: 5X DMF, 5X DCM, 5X DMF

Fmoc-cleavage: 25% piperidine in DMF

Cleavage from the resin: methanol/THF/triethylamine (9 : 1 : 1).

The crude peptide was purified *via* column chromatography utilizing silica flash gel and CH_3Cl/MeOH (10:1: R_f = 0.35). Overall, 224 mg (0.22 mmol; 76%) of the pure peptide were isolated as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.99–7.86 (m, 1 H, H_{Ar}, CH (His)), 7,64–7.60 (m, 1 H, H_{Ar} (His)), 7,54 (s, 1 H, H_{Ar} (His)), 7.31 (s, 1 H, H_{Ar}, CH (His)), 7.29–7.19 (m, 9 H, H_{Ar} (Phe)), 7.17–7.07 (m, 3 H, H_{Ar} (Phe)); 7.06–7.00 (m, 6 H, H_{Ar} (Phe)); 6.94–6.88 (m, 2 H, H_{Ar} (Phe)); 6.81 (s, 1 H, NH (Phe), 6.63 (s, 1 H, NH (His)), 5.96 (s, 1 H, NH (^{A}Gly)), 5.24 (d, 1 H, J= 8.4 Hz, NH (His)), 4.69 (q, 1 H, J= 7.6 Hz, H_α (Phe)), 4.56 (q, 1 H, J= 7.6 Hz, H_α (His)), 4.11 (bs, 1 H , H_α (His)), 3.55 (s, 6 H, $OCH_3 + NCH_3$), 3.08–2.76 (m, 6 H, H_β (Phe)) + (His)), 2.21-2.17 (m, 2 H, adamantane), 1.98–1.45 (m, 12 H, adamantane), 1.34 (s, 9 H, $C(CH_3)$).

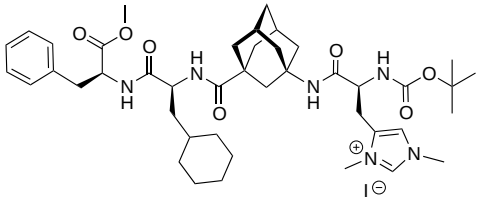
^{13}C-NMR (150 MHz, $CDCl_3$): δ/ppm = 176.8 (C=O); 171.5 (C=O); 170.9 (C=O); 169.4(C=O); 155.2 (C=O); 142.1, 138.1, 137.8, 136.9, 135.9, 129.7, 129.3, 128.5, 128.0, 127.7, 126.9, 126.6, 119.7, 75.4, 54.3, 53.4, 52.9, 52.4, 42.5, 52.4, 42.5, 42.1, 40.1, 40.0, 38.0, 37.8, 35.1,

31.8, 30.3, 29.4, 29.0, 28.3, 26.9

MS (ESI): *m/z* = 987.2 $[M+H]^+$ (calc. m/z = 987.5), m/z =1009.3 $[M+Na]^+$ (calc. m/z = 1009.5).

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{58}H_{67}N_8O_7^+$ 987.5127; Found 987.5054.

Boc-L-(π, τ-Dime-His)I-L-^{A}Gly-L-Cha-L-Phe-OMe (235)



According to the general procedure 100 mg (0.13 mmol) of the tetrapeptide **12i** were methylated. The crude product was purified by silica flash gel column chromatography using DCM/MeOH 4:1 (R_f = 0.2) and 50 mg (0.055 mmol, 39%) of the peptide (pale yellow solid) were obtained.

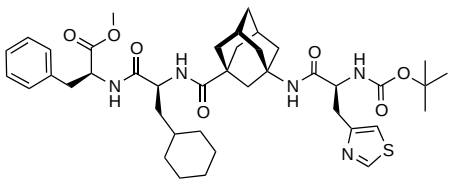
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 9.20 (s, 1 H, C*H*-imidazole (His)), 7.32–7.22 (m, 3 H, H_{Ar} (Phe)), 7.17 (s, 1 H, C*H*-imidazole (His)), 7.15–7.11 (m, 2 H, H_{Ar} (Phe)), 6.92 (s, 1 H, N*H* (His)), 6.69 (d, J = 10.7, 1 H, N*H* (Phe)), 6.17 (d, J = 9, 1 H, N*H* (Cha)), 5.88 (d, J = 8.9, 1 H, N*H* (^{A}Gly)), 4.79–4.76 (m, 1 H, $H_α$ (Phe)), 4.49–4.44 (m, 1 H, $H_α$ (Cha)), 4.44–4.40 (m, 1 H, $H_α$ (His)), 3.99 (s, 3 H, NCH_3), 3.90 (s, 3 H, NCH_3), 3.69 (s, 3 H, OCH_3), 3.21–3.06 (m, 4 H, $H_β$ (Phe) + $H_β$ (His), 2.23–2.07 (m, 6 H, adamantane + Cha), 1.99–1.94 (m, 2 H, adamantane + Cha), 1.86–1.64 (m, 12 H, adamantane + Cha), 1.58–1.50 (m, 1 H, Cha), 1.42 (s, 9 H, C(CH_3)$_3$), 1.25–1.07 (m, 4 H, Cha), 1.06–0.96 (m, 2 H, Cha).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 176.9 (C=O), 172.2 (C=O), 171.75 (C=O), 168.2 (C=O), 136.6, 135.9, 132.3, 129.3, 128.7, 128.4, 127.2, 103.1, 67.4, 67.0, 53.4, 53.2, 52.4, 42.6, 42.2, 40.2, 39.2, 38.3, 38.0, 37.8, 36.6, 34.9, 34.2, 33.5, 32.6, 29.1, 28.3, 27.2, 26.4, 26.1, 26.1, 23.5.

MS (ESI): *m/z* = 775.3 $[M]^+$ (calcd: 775.5).

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{43}H_{63}N_8O_7^+$ 775.4753; Found 775.4717.

Boc-β-(4-Taz)-^{A}Gly-L-Cha-L-Phe-OMe (236)



1. Coupling:

1.08 g (5 mmol) H-L-Phe-OMe·HCl, 2.26 g (5 mmol) Boc-L-Cha-OH·$(C_6H_{11})_2NH$, 0.84 g (5.5 mmol) HOBt·H_2O, 1.06 g (5.5 mmol) EDC ·HCl and 0.75 mL (5.5 mmol) Et_3N in 25 mL DCM.

After evaporation of the solvent, 2.00 g of the dipeptide Boc-L-Cha-L-Phe-OMe were obtained as a colorless solid (4.6 mmol, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.25–7.13 (m, 3 H, H_{Ar} (Phe)), 7.06–7.00 (m, 2 H, H_{Ar} (Phe)), 6.47 (d, J = 7.8, 1 H, N*H* (Phe)), 4.86–4.70 (m, 2 H, N*H* (Cha + H_α (Phe)), 4.13–3.99 (m, 1 H, H_α (Cha)), 3.63 (s, 3 H, OCH_3), 3.04 (dq, J = 6.2 Hz, J = 14.4, 2 H, H_β (Phe)), 1.74–1.47 (m, 6 H, Cha), 1.37 (s, 9 H, C(CH_3)$_3$), 1.29–0.98 (m, 5 H, (Cha)), 0.94–0.72 (m, 2 H, (Cha)).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 172.2 (C=O), 171.6 (C=O), 155.5 (C=O), 135.7 (C_{ar}), 129.3 (C_{ar}), 128.7 (C_{ar}), 127.1 (C_{ar}), 80.0, 53.1, 52.4, 52.2, 39.8, 37.9, 33.9, 33.6, 32.5, 28.2 (C(CH_3)$_3$), 26.3, 26.1, 26.0. **ESI**: m/z = 455.1 $[M + Na]^+$ (calcd: m/z = 455.2).

The Boc-group was cleaved under standard conditions.

2. Coupling:

1.53 g (4.6 mmol) H-L-Cha-L-Phe-OMe·HCl, 1.36 g (4.6 mmol) Boc-L-^{A}Gly-OH, 0.7 g (5.06 mmol) HOBt·H_2O, 0.97 g (5.06 mmol) EDC ·HCl and 0.7 mL (5.06 mmol) Et_3N in 25 mL DCM. After removal of the solvent 2.414 g of the tripeptide Boc-^{A}Gly-L-Cha-L-Phe-OMe were obtained as a colorless solid (3.96 mmol, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.25–7.14 (m, 3 H, H_{Ar} (Phe)), 7.06–7.00 (m, 2 H, H_{Ar} (Phe)), 6.48 (d, J = 6.9 Hz, 1 H, N*H* (Phe)), 5.85 (d, J = 8.0 Hz, 1 H, N*H* (Cha)), 4.74–4.70 (m, 1 H, H_α (Phe)), 4.43–4.34 (m, 2 N*H* (^{A}Gly) + H_α (Cha)), 3.64 (s, 3 H, OCH_3), 3.03 (dq, J = 6.1 Hz, J = 14.3 Hz, 2 H, H_β (Phe)), 2.17–2.08 (m, 2 H, adamantane), 1.92–1.80 (m, 6 H, Cha + adamantane), 1.67–1.52 (m, 12 H, Cha + adamantane), 1.43–1.38 (m, 1 H, Cha), 1.36 (s, 9 H, C(CH_3)$_3$), 1.22–1.03 (m, 5 H, Cha), 0.9–0.72 (m, 2 H, Cha).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 176.6 (C=O), 172.1 (C=O), 171.8 (C=O), 154.5 (C=O), 135.8, 129.2, 128.6, 127.1, 79.0, 53.2, 52.3, 50.8, 50.6, 42.6, 40.9, 39.3, 38.1, 37.8, 35.3, 34.2, 33.5, 32.7, 29.3, 28.5 (C(CH_3)$_3$), 26.3, 26.1, 26.1. **ESI**: m/z = 632.3 $[M + Na]^+$ (calcd: m/z = 632.4), 648.1 $[M + K]^+$ (calcd: m/z = 648.3), 1241.2 $[2 M + Na]^+$ (calcd: m/z = 1241.7).

The Boc-group was cleaved under standard conditions.

3. Coupling:

1.85 g (3.63 mmol) H-^{A}Gly-L-Cha-L-Phe-OMe · HCl, 988 mg (3.63 mmol) Boc-L-Taz-OH, 619 mg (3.99 mmol) EDC·HCl, 539 mg (3.99 mmol) HOBt, 0.5 mL (3.99 mmol) Et_3N in 50 ml DCM. The crude product was purified *via* silica gel column chromatography eluating with DCM/MeOH 10:1 (R_f = 0.3). After evaporation of the solvents under reduced pressure 2.09 g (2.73 mmol, 75%) of the tetrapeptide Boc-L-Taz-^{A}Gly-L-Cha-L-Phe-OMe were isolated as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 8.70 (s, 1 H, C*H* (Taz)), 7.25–7.14 (m, 3 H, H_{Ar} (Phe)), 7.10–7.00 (m, 3 H, H_{Ar} (Phe) + C*H* (Taz)), 6.48–6.38 (m, 1 H, N*H* (Phe)), 6.10 (bs, 1 H,) 5.90 (d, 1 H, J = 9.6 Hz), N*H* (Cha)), 5.84 (d, 1 H, J = 8 Hz, N*H* (Taz)), 4.78–4.68 (m, 1 H, H_α

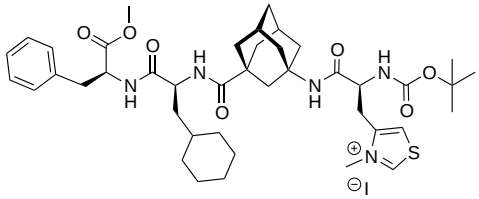
(Phe)), 4.41–4.30 (m, 2 H, H_α (Cha) + N*H* (^{A}Gly)), 3.64 (s, 3 H, OCH_3), 3.63–3.57 (s, 1 H, H_β (Taz)), 3.15–2.94 (m, 4 H, H_β (Phe) + H_β (Taz)), 2.15–2.04 (m, 2 H, adamantane), 1.89–1.72 (m 6 H, Cha + adamantane), 1.66 – 1.53 (m, 13 H, Cha + adamantane), 1.38 (s, 9 H, C(CH_3)), 1.20–1.00 (m, 5 H, Cha), 0.92–0.77 (m, 2 H, Cha).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ppm = 176.4 (C=O); 171.9 (C=O); 171.6 (C=O); 169.8 (C=O); 155.0 (C=O); 138.2; 135.5; 129.6; 128.8; 128.2; 127.2; 127.0; 80.3; 54.5; 53.2; 52.3; 50.7; 42.5; 42.1; 40.4; 40.2; 39.5; 38.3; 38.1; 37.9; 35.1; 34.2; 33.5; 32.7; 31.5; 29.1; 28.3; 26.8; 26.8; 26.3; 26.1

MS (ESI): *m/z* = 786.3 $[M + Na]^+$ (calcd: 786.4), 802.2 $[M + K]^+$ (calcd: 802.4).

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{41}H_{57}N_5O_7SNa^+$ 786.3871; Found 786.3862.

Boc-β-(4-MeTaz)I-^{A}Gly-L-Cha-L-Phe-OMe (237)



According to the general procedure 100 mg (0.13 mmol) of the tetrapeptide **236** were methylated. The crude product was purified by silica flash gel column chromatography using DCM/MeOH 4:1 (R_f = 0.2) and 55 mg (0.06 mmol, 43%) of the peptide (pale yellow solid) were obtained.

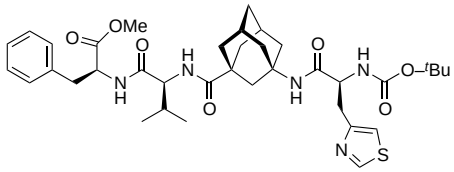
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 10.32 (s, 1 H, C*H*-thiazolyl (Taz)), 7.97 (s, 1 H, C*H*-thiazolyl (Taz)), 7.28–7.15 (m, 3 H, H_{Ar} (Phe)), 7.15–7.08 (m, 3 H, H_{Ar} (Phe + N*H* (Taz)), 6.93 (s, 1 H, N*H* (Phe)), 6.33 (s, 1 H, N*H* (Cha)), 5.92 (s, 1 H, N*H* (^{A}Gly)), 4.73–4.66 (m, 2 H, H_α (Phe)), 4.62–4.56 (m, 1 H, H_α (Cha)), 4.38 (s, 3 H, NCH_3), 4.37–4.30 (m, 1 H, H_α (Taz)), 3.62 (s, 3 H, OCH_3), 3.50–3.38 (m, 1 H, H_β (Taz)), 3.32–3.23 (m, 1 H, H_β (Taz)), 3.11–3.03 (m, 2 H, H_β (Phe)), 2.02–1.88 (m, 8 H, adamantane + Cha), 1.83–1.50 (m, 13 H, adamantane + Cha), 1.31 (s, 9 H, C(CH_3)$_3$), 1.20–1.03 (m, 4 H, Cha) 0.91–0.73 (m, 2 H, Cha).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 177.2 (C=O), 172.6 (C=O), 171.9 (C=O), 168.5 (C=O), 159.1, 155.3, 146.4, 135.9, 129.2, 128.5, 127.0, 123.5, 80.2, 53.2, 52.5, 51.5, 42.5, 42.1, 41.9, 40.3, 40.1, 39.1, 37.9, 37.8, 37.5, 35.0, 34.0, 33.3, 32.5, 31.3, 29.6, 28.3 (C(*C*H$_3$)$_3$), 26.2, 26.0, 25.9.

MS (ESI): *m/z* = 778.3 $[M]^+$ (calcd: m/z = 778.4)

HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{42}H_{60}N_5O_7S^+$ 778.4202; Found 778.4201.

Boc-β-(4-Taz)-^{A}Gly-L-Val-L-Phe-OMe (236-V)



1. Coupling**:**

431 mg (2 mmol) of H-L-Phe-OMe ·HCl, 543 mg (2 mmol) Boc-L-Val-OH, 297 mg (2.2 mmol) of HOBt·H_2O, 421 mg (2.2 mmol) of EDC·HCl and 0.31 mL (2.2 mmol) of Et_3N in 10 mL DCM. After evaporation of the solvent 558 mg (1.47 mmol, 73%) of the dipeptide Boc-L-Val-L-Phe-OMe were obtained as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.34–7.23 (m, 3 H, H_{Ar} (Phe)), 7.15–7.08 (m, 2 H, H_{Ar} (Phe)), 6.43–6.28 (m, 1 H, N*H* (Phe)), 5.09–4.98 (m, 1 H, N*H* (Val)), 4.93–4.84 (m, 1 H, H_{α} (Phe)), 3.96–3.85 (m, 1 H, H_{α} (Val)), 3.72 (s, 3 H, OCH_3), 3.18–3.06 (m, 2 H, H_{β} (Phe)), 2.14–2.04 (m, 1 H, C*H*), 1.46 (s, 9 H, $C(CH_3)_3$), 1.02–0.8 (m, 6 H, CH_3 (Val)).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 171.7 (C=O), 171.2 (C=O), 155.7, 135.7, 129.3, 128.6, 127.2, 79.9, 59.9, 53.1, 52.3, 38.0, 30.9, 28.3 ($C(CH_3)_3$), 19.2, 17.6.

MS (ESI): *m/z* = 401.1 (calcd: m/z = 401.2).

The Boc-group was cleaved under standard conditions.

2. Coupling:

408 mg (1.47 mmol) of H-L-Val-L-Phe-OMe ·HCl, 434 mg (1.47 mmol) of Boc-L-^{A}Gly-OH, 218 mg (1.62 mmol) of HOBt·H_2O, 310 mg (1.62 mmol) of EDC ·HCl and 0.25 mL (1.62 mmol) of Et_3N in 10 mL DCM. After removal of the solvent 611 mg (1.1 mmol, 75%) of the tripeptide Boc-^{A}Gly-L-Val-L-Phe-OMe were obtained as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.32–7.21 (m, 3 H, H_{Ar} (Phe)), 7.12–7.08 (m, 2 H, H_{Ar} (Phe)), 6.40–6.32 (m, 1 H, N*H* (Phe)), 6.20–6.14 (m, 1 H, N*H* (^{A}Gly)), 4.87–4.81 (m, 1 H, N*H* (Val)), 4.49–4.44 (m, 1 H, H_{α}(Phe)), 4.29–4.21 (m, 1 H, H_{α}(Val)), 3.71 (s, 3 H, OCH_3), 3.16–3.05 (m, 2 H, H_{β} (Phe)), 2.25–2.19 (m, 2 H, adamantane), 2.12–2.04 (m, 1 H, C*H*), 2.03–1.99 (m, 2 H, adamantane), 1.96–1.89 (m, 4 H, adamantane), 1.82–1.74 (m, 4 H, adamantane), 1.69–1.59 (m, 2 H, adamantane), 1.43 (s, 9 H, $C(CH_3)_3$), 0.95–0.86 (m, 6 H, CH_3 (Val)).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 176.6 (C=O), 171.6 (C=O), 170.9 (C=O), 135.6, 129.2, 128.7, 127.2, 120.2, 78.9, 57.8, 53.1, 52.3, 50.8, 42.8, 40.9, 38.3, 37.8, 35.3, 31.1, 29.2, 28.5 ($C(CH_3)_3$), 19.1, 18.1.

MS (ESI): *m/z* = 578.3 $[M + Na]^+$ (calcd: m/z = 578.3).

The Boc-group was cleaved under standard conditions.

3. Coupling:

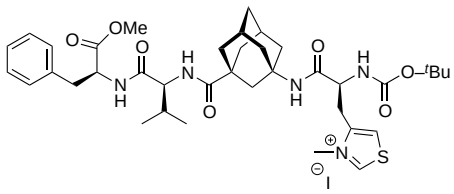
300 mg (0.6 mmol) of H-^{A}Gly-L-Val-L-Phe-OMe·HCl, 147 mg (0.6 mmol) of Boc-L-Taz-OH, 113 mg (0.66 mmol) of EDC·HCl, 80 mg (0.66 mmol) of HOBt, 0.08 ml (0.66 mmol) of Et_3N in 10 mL DCM. The crude product was purified *via* silica gel column chromatography eluting with DCM/MeOH 10:1 (R_f = 0.3). After evaporation of the solvents under reduced pressure 297 mg (0.42 mmol, 42%) of the tetrapeptide Boc-L-Taz-^{A}Gly-L-Val-L-Phe-OMe was isolated as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 8.77 (s, 1 H, C*H*-thiazolyl (Taz)), 7.31 – 7.24 (m, 3 H, H_{Ar} (Phe)), 7.14 – 7.08 (m, 3 H, H_{Ar} + C*H*-thiazolyl (Taz)), 6.37 – 6.28 (m, 1 H, N*H* (Taz)), 6.22 – 6.16 (m, 1 H, N*H* (Phe)), 6.00 – 5.94 (m, 1 H, N*H* (^{A}Gly)), 4.88 – 4.80 (m, 1 H, N*H* (Val)), 4.27 – 4.18 (m, 1 H, $H_α$ (Phe)), 4.16 – 4.08 (m, 1 H, $H_α$ (Val)), 3.77 – 3.60 (m, 4 H, OCH_3 + $H_α$ (Taz)), 3.38 – 3.29 (m, 1 H, $H_β$ (Taz)), 3.19 – 3.06 (m, 3 H, $H_β$ (Phe) + $H_β$ (Taz)), 2.11 – 2.01 (m, 3 H, adamantane), 1.98 – 1.71 (m, 10 H, adamantane + C*H* (Val)), 1.68 – 1.55 (m, 2 H, adamantane), 1.44 (s, 9 H, C(CH_3)$_3$), 0.95 – 0.84 (m, 6 H, CH_3 Val)).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 176.4 (C=O), 141.6 (C=O), 171.2 (C=O), 170.9 (C=O), 170.2 (C=O), 155.5, 153.3, 152.9, 135.5, 130.9, 129.2, 128.8, 128.7, 127.3, 115.9, 80.0, 60.4, 57.8, 54.6, 53.1, 52.3, 51.9, 42.7, 42.4, 40.2, 40.1, 38.2, 38.0, 37.8, 35.1, 35.7, 31.1, 29.1, 28.9, 28.7, 28.3 (C(CH_3)$_3$), 21.1, 19.1, 18.1, 14.2, 14.1.

MS (ESI): *m/z* = 732.3 $[M + Na]^+$ (calcd: m/z = 732.3), m/z = 4114.3 $[2 M + Na]^+$ (calcd: m/z = 1441.7).

Boc-L-(*N*-Me-Taz)I-L-^{A}Gly-L-Val-L-Phe-OMe (237-V)



According to the general procedure 100 mg (0.14 mmol) of the tetrapeptide **236-V** were methylated. The crude product was purified by silica flash gel column chromatography using DCM/MeOH 4:1 (R_f = 0.2) and 296 mg (0.42 mmol, 77%) of the peptide (pale yellow solid) were obtained.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 10.37 (s, 1 H, C*H*-thiazolyl (Taz)), 8.02 (s, 1 H, C*H*-thiazolyl (Taz)), 7.34–7.14 (m, 5 H, H_{ar} (Phe)), 7.14–7.04 (m, 1 H, N*H* (Taz)), 6.60–6.50 (m, 1 H, N*H* (Phe)), 6.04–5.94 (m, 1 H, N*H* (^{A}Gly)), 4.83–4.74 (m, 1 H, N*H* (Val)), 4.73–4.61 (m, 1 H, $H_α$ (Phe)) 4.47 (s, 3 H, NCH_3 (Taz)), 4.26–4.18 (m, 1 H, $H_α$ (Val)), 3.69 (s, 4 H, OCH_3 + $H_α$ (Taz)), 3.56–3.44 (m, 1 H, $H_β$ (Taz)), 3.44–3.31 (m, 1 H, $H_β$ (Taz)), 3.19–3.12 (m, 2 H, $H_β$ (Phe)), 2.67–1.95 (m, 9 H, adamantane), 1.92–1.59 (m, 6 H, adamantane + C*H* (Val)), 1.38

(s, 9 H, C(CH_3)$_3$), 0.96–0.77 (m, 6 H, CH_3 (Val).

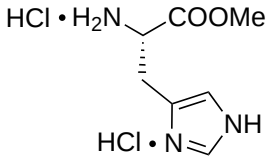
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 172.0 (C=O), 171.8 (C=O), 159.2, 136.0, 129.3, 128.7, 127.2, 53.7, 53.4, 52.55, 42.7, 42.2, 37.5, 30.9, 29.1, 28.4 (C(CH_3)$_3$), 19.1, 18.4.

MS (ESI): *m/z* = 724.3 $[M]^+$ (calcd: m/z = 724.4).

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{38}H_{54}N_5O_7S^+$ 724.3738; Found 724.3740.

Carbene-precursors

L-Histidinedihydrochloride methyl ester (228)

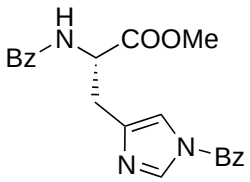


50 g (0.322 mol) of **227** were dissolved in 1 L dry methanol and HCl gas was introduced. A small amount of bubbling should be seen in the gas trap filled with basic solution for about 6 h. The reaction vessel should be monitored all the time. The reaction vessel was sealed and allowed to stir overnight. The product was separated by filtration and washed with water. The product was dried separately in a desiccator over paraffin wax and P_2O_5 under reduced pressure. 67 g (0.28 mol; 86%) of the colorless solid were isolated.

^{1}H-NMR (400 MHz, D_2O): δ/ppm 3.46–3.24 (m, 2H), 3.73 (s, 3H), 4.39 (t, 1H), 7.35 (s, 1H), 8.64 (s, 1H).

^{13}C-NMR (100 MHz, D_2O): δ/ppm 24.5, 51.8, 53.9, 117.9, 126.2, 134.3, 168.9.

L-Dibenzoylhistidine methylester (229)



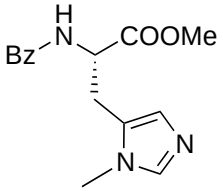
To a solution of 62.0 g (0.256 mol) **228** in 900 mL water, 91.8 g (0.870 mol) of Na_2CO_3 were added. Afterwards 900 mL of THF were added and the transparent solution became opaque. 144.0 g (0.636 mol) of benzoic anhydride were added and allowed to stir. After one hour a second portion of 75 g (0.331 mol) were added and the solution stirred for another 2 h. THF was removed *in vacuo* and 700 mL of DCM were added. The reaction mixture was washed with saturated $NaHCO_3$ solution (three times), citric acid (10%, two times) and brine. The organic layer was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. Diethyl ether (400 mL) were added and the product appeared as a withe solid. The product was separated by filtration and dried under high vacuum over paraffin wax and P_2O_5

in a desiccator. Overall, 82 g (0.21 mol; 85%) of the pure product were isolated as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 3.24–3.10 (m, 2H), 3.67 (s, 3H), 5.04–4.97 (m, 1H), 7.25–8.10 (m, 12H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 171.6, 167.0, 165.9, 139.5, 138.0, 134.5, 133.78, 131.7, 130.5, 129.7, 128.9, 128.4, 127.1, 115.5, 52.5, 29.5.

L-benzoyl methyl histidine methyl ester (230)

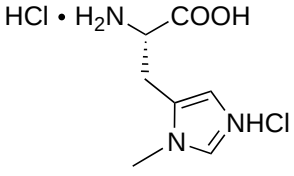


39 g (0.103 mol) of **229** were dissolved in 180 mL of nitromethane and 20 g (0.135 mol) of Meerwein's salt dissolved in 90 mL of nitromethane, were added *via* an addition funnel over 25 min. After 4 h the solvent was removed under reduced pressure to give an orange oil. 500 mL of water were added and the reaction mixture was allowed to stir overnight. The reaction mixture was transferred to a separating funnel and extracted with diethyl ether. The pH of the aqueous layer was adjusted to eight with a saturated $NaHCO_3$ solution, the product extracted with DCM and dried over Na_2SO_4. The solvent was removed and the product dried *in vacuo*. Overall, 23.9 g (83 mmol; 81%) of the colorless solid were obtained.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 3.26 (m, 2H), 3.55 (s, 3H), 3.78 (s, 3H), 5.00 (m, 1H), 6.80 (s, 1H), 7.18–7.94 (m, 7H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 171.6, 167.3, 138.7, 133.6, 132.1, 128.9, 127.7, 126.8, 52.9, 51.8, 31.6, 25.9

L-π-Methylhistidine dihydrochloride (231)



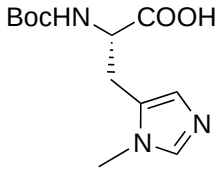
24.5 g (0.0852 mol) of the **230** were dissolved in 1.4 L of 6 M HCl and refluxed for 6–8 h. While cooling a colorless solid precipitated. The reaction mixture was extracted with diethyl ether and the aqueous layer was concentrated to give a yellow oily residue. The crude product was dissolved in warm methanol and diethyl ether was added until the product crystallized. The product was separated by filtration and dried *in vacuo*. Overall, 13.3 g (55.2 mmol; 65%) of the product were isolated.

^{1}H-NMR (400 MHz, D_2O): δ/ppm 3.42–3.13 (m, 2H), 3.73 (s, 3H), 4.20 (t, 1H), 7.31 (s, 1H),

8.58 (s, 1H)

^{13}C-NMR (100 MHz, D_2O): δ/ppm 135.9, 118.7, 51.3, 48.7, 33.2, 23.8

Boc-L-(π-Me)-histidine (232)

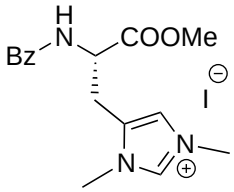


20.47 g (0.0852 mol) of the **231** were dissolved in 615 mL of THF and 615 mL of water. Then, 29.7 mL (0.170 mol) of D^{i}PEA and 46.51 g (0.213 mol) of Boc-anhydride were added and the reaction mixture was allowed to stir at r.t. for 24 h. The solvent was removed in *vacuo* and the crude product was dissolved in 1.5 L $NH_{3(aq)}$ (1.25 M). The solution was washed with DCM and the aqueous layer was concentrated. The colorless solid was dried in *vacuo*. The crude product was then extracted with DCM and filtered off. The solvent was removed under reduced pressure to yield 14.2 g (52.7 mmol; 62%) of a yellowish solid.

^{1}H-NMR (200 MHz, D_2O): δ/ppm 1.26 (s, 9H), 3.02–2.76 (q, 1H), 3.24–3.02 (q, 1H), 3.74 (s, 3H), 4.10 (s, 1H), 7.13 (s, 1H), 8.46 (s, 1H)

^{13}C-NMR (50 MHz, D_2O): δ/ppm 177.1, 157.1, 135.1, 131.4, 118.4, 80.6, 54.3, 33.1, 27.9, 26.8.

L-Benzoyl-*N,N'*-dimethyl histidine methyl ester iodide (233)



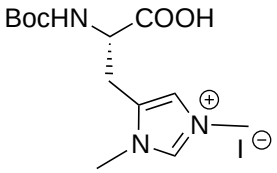
1 g (3.5 mmol) of **230** was dissolved in 5 mL of acetonitrile, then 2 mL of methyl iodide were added and the solution was warmed to 60 °C for 5 h. The excess methyl iodide was distilled off and the solvent was evaporated under reduced pressure. The crude product was purified *via* silica flash gel column chromatography eluting with DCM/methanol (9/1), R_f = 0.32. The product (0.89 g, 2.1 mmol; 60%) was isolated as a yellowish solid.

^{1}H-NMR (400 MHz, D_2O): δ/ppm 3.21–3.41 (m, 2 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 4.86 (m, 1 H), 7.49–7.70 (m, 4 H), 7.87 (m, 1 H), 9.04 (m, 1 H)

^{13}C-NMR (100 MHz, D_2O): δ/ppm 170.8, 166.9, 136.8, 133.8,131.9, 131.3, 128.5, 127.4, 121.4, 52.5, 50.8, 35.8, 33.4, 24.5.

HRMS (ESI-TOF) m/z: $[M+]^+$ calcd for $C_{16}H_{20}N_3O_3^+$ 302.1499; Found 302.1498.

Boc-L-*N,N'*-Dimethylhistidine iodide (234)



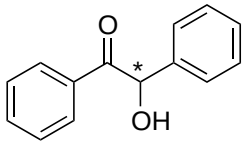
1 g (3.6 mmol) of Boc-L-(π-Me)-histidine **232** was dissolved in 5 mL of DCM, then 2 mL of methyl iodide were added and the mixture was stirred for 1 day at r.t. The crude product was purified *via* silica flash gel column chromatography eluting with ethanol/$NH_{3\ (aq)}$ (7 / 3), R_f = 0.57. 0.42 g (1.0 mmol; 28%) of the product was isolated as a colorless solid.

^{1}H-NMR (400 MHz, D_2O): δ/ppm 1.37 (s, 9H), 2.98 (q, 1H), 3.21 (q, 1H), 3.81 (2 x s, 6H), 4.19 (s, 1H), 7.23 (s, 1H), 8.61 (s, 1H)

^{13}C-NMR (100 MHz, D_2O): δ/ppm 176.6, 157.0, 136.3, 131.9, 121.6, 81.1, 54.1, 35.4, 33.1, 27.5, 26.6.

HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{13}H_{22}N_3O_4^+$ 284.1605; Found 284.1609.

2-Hydroxy-1,2-diphenylethanon (239a)



In a flame-dried vessel under an argon atmosphere, 22 mg of **240** (0.1 mmol, 10 mol%) were dissolved in 3 mL of dry THF at r.t. Subsequently, 11 mg of KO^{t}Bu (0.11 mmol, 11 mol%) were added and the solution was allowed to stir for 30 min. Subsequently, 101 µL of benzaldehyde (1 mmol) were added. After 24 h, the reaction mixture was quenched with 3 mL of a saturated NaCl solution. The organic layer was extracted with dichloromethane and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by silica flash gel column chromatography (EtOAc/hexane, 2:8). Overall, 138 mg (0.65 mmol, 65%) of colorless crystals were obtained. The racemic product was subjected to the HPLC assay to prove the origin of signals.

^{1}H-NMR (200 MHz, $CDCl_3$): δ/ppm = 7.99–7.86 (m, 2 H, H_{Ar}), 7.61–7.47 (m, 1 H, H_{Ar}), 7.46–7.20 (m, 7 H, H_{Ar}), 5.96 (d, J = 5.8 Hz, 1 H, C*H*), 4.56 (d, 1 H, J = 5.8 Hz, O*H*).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 198.9 (C=O), 139.0, 133.9, 133.4, 129.2, 128.7, 128.6, 127.8, 76.2 (*C*H).

ESI: m/z = 235.0 $[M + Na]^+$ (calcd: m/z = 235.1), m/z = 251.0 $[M + K]^+$ (calcd: m/z = 251.3).

1H-NMR-data are in accordance with the data reported from Sigma Aldrich.

Assay of product formation:

Racemic **239a** was detected by GC-FID employing a 30 m 5890_V UP5 (Machery Nagel).

T (Injector + Detector) = 250 °C

Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100 °C – 250 °C, 15 °C/min

Retention times: R = 9.8 min

Assay of enantiomeric purity:

Enantiomers of 2-hydroxy-1,2-diphenylethanon were separated by chiral HPLC employing a Chiralpak IB column (Daicel)

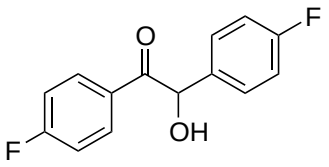
Eluent: Hexane/2-Propanol 95:5

Flow: 1 mL/min

UV-detector: λ = 254 nm and refractometer

Retention times: R_1 = 12.9 min, R_2 = 16.1 min

1,2-Bis(4-Fluorophenyl)-2-hydroxyethanone (239b)



In a flame-dried vessel under an argon atmosphere, 20 mg of **240** (0.1 mmol, 10 mol%) were dissolved in 3 mL of dry THF at r.t. Subsequently, 11 mg of KO^{t}Bu (0.11 mmol, 11 mol%) were added and the solution was allowed to stir for 30 min. Then 107 mL of *p*-fluorobenzaldehyde (1 mmol) were added. After 24 h, the reaction mixture was quenched with 3 mL of a saturated NaCl solution. The organic layer was extracted with dichloromethane and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified *via* column chromatography (EtOAc/hexane, 2:8). 81 mg (0.33 mmol, 33%) of colorless crystals were obtained. The racemic product was subjected to the HPLC assay to prove the origin of signals.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 8.03–7.86 (m, 2 H, H_{Ar}), 7.42–7.23 (m, 2 H, H_{Ar}), 7.18–6.98 (m, 4 H, H_{Ar}), 5.9 (d, J = 5.6, 1 H, C*H*), 4.52 (d, J = 5.2, 1 H, O*H*).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 197.2 (C=O), 167.4 (d, $J_{C-^{19}F}$ = 256), 162.8 (d, $J_{C-^{19}F}$ = 243), 134.8 (d, $J_{C-^{19}F}$ = 4), 131.9 (d, $J_{C-^{19}F}$ = 10), 129.7 (d, $J_{C-^{19}F}$ = 3), 129.6 (d, $J_{C-^{19}F}$ = 8), 116.3 (d, $J_{C-^{19}F}$ = 22, 2 x C), 116.1 (d, $J_{C-^{19}F}$ = 22, 2 x C), 75.4.

ESI: m/z = 277.1 $[M + Na]^+$ (calcd: m/z = 277.1).

The NMR-data are in accordance with the literature.[190]

Assay of product formation:

Racemic **239b** was detected by GC-FID employing a 30 m 5890_V UP5 (Machery Nagel).

T (Injector + Detector) = 250 °C

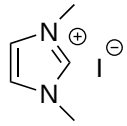
Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100 °C – 250 °C, 15 °C/min

Retention times: R = 9.1 min

_N_-_N_'-Dimethylimidazolium iodide (240)

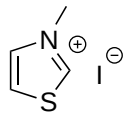


1 mL of *N*-methylimidazole (12.5 mmol) was dissolved in 2 mL of acetonitrile and 1 mL of methyl iodide was added dropwise. The solution was refluxed overnight at 90 °C. The precipitates were filtered off and washed three times with acetonitrile and dried over P_2O_5 and paraffin wax *in vacuo*. Overall, 2.46 g of pale yellow crystals (11 mmol, 88%) could be obtained.

^{1}H-NMR (400 MHz, D_2O): δ/ppm = 8.61 (s, 1 H, C*H*), 7.37 (s, 2 H, C*H*), 3.85 (s, 6 H, CH_3).

^{13}C-NMR (100 MHz, D_2O): δ/ppm = 136.6 (*C*H), 123.4 (2 x *C*H), 35.9 (2 x CH_3).

***N*-Methylthiazolium iodide (242)**



1 mL of *N*-methylimidazole (14 mmol) was dissolved in 2 mL of acetonitrile and 1 mL of methyl iodide was added dropwise. The solution was refluxed overnight at 90 °C. The precipitates were filtered off and washed three times with acetonitrile and dried over P_2O_5 and paraffin wax *in vacuo*. Overall, 2.22 g pale yellow crystals (9.8 mmol, 70%) could be obtained.

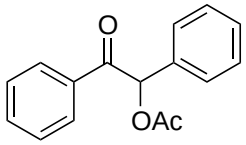
^{1}H-NMR (400 MHz, D_2O): δ/ppm = 8.61 (s, 1 H, C*H*), 7.37 (s, 2 H, C*H*), 3.85 (s, 6 H, CH_3).

^{13}C-NMR (100 MHz, D_2O): δ/ppm = 136.6 (*C*H), 123.4 (2 x *C*H), 35.9 (2 x CH_3).

General procedure for the *in-situ* acylation of benzoin

In a flame-dried vessel under an argon atmosphere, precatalyst **240** (22 mg, 0.1 mmol, 33 mol%) and KO^{t}Bu (11 mg, 0.11 mmol) were degassed for 30 min, suspended in anhydrous THF and stirred for 15 min at r.t. Then, benzaldehyde (30 µL, 0.3 mmol) was added *via* an Eppendorf pipette to the carbene solution. Subsequently, acetic anhydride (36 mL, 1.2 eq.) was added and the solution was stirred for 12 h. After quenching the reaction mixture with water, a GC-FID analysis was performed..

2-Oxo-1,2-diphenylethyl acetate (244a)



Racemic 2-hydroxy-1,2-diphenylethanon (80 mg, 0.38 mmol) were dissolved in 3 mL DCM. Subsequently, 40 µL Ac_2O (0.42 mmol), 4.5 mg DMAP (0.04 mmol, 10 mol%) and 53 µL Et_3N (0.42 mmol) were added and the solution was stirred for 12 h at r.t. (25 °C). The solvent was evaporated under reduced pressure and the acylated product was directly purified *via* silica flash gel column chromatography and eluated with DCM/MeOH 8:2 (R_f = 0.4). 83 mg of 2-Oxo-1,2-diphenylethyl acetate (0.34 mmol, 89%) could be obtained. The racemic product was subjected to the HPLC assay to prove the origin of signals.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.96–7.90 (m, 2 H, H_{Ar}), 7.56–7.45 (m, 3 H, H_{Ar}), 7.44–7.32 (m, 5 H, H_{Ar}), 6.87 (s, 1 H, C*H*), 2.21 (s, 3 H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 193.7 (C=O), 170.5 (C=O), 134.6 (C_{Ar}), 133.6 (C_{Ar}), 133.5 (C_{Ar}), 129.4 (C_{Ar}), 129.2 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (2 x C_{Ar}), 128.6 (2 x C_{Ar}), 77.7 (*C*H), 80.8 (*C*H_3).

The NMR-data are in accordance with the literature.[190]

Assay of product formation:

Racemic **244a** was detected by GC-FID employing a 30 m 5890_V UP5 (Machery Nagel).

T (Injector + Detector) = 250 °C

Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100 °C – 250 °C, 15 °C/min

Retention times: R = 10.9 min.

Assay of enantiomeric purity:

Enantiomers of 2-oxo-1,2-diphenylethyl acetate were separated by chiral HPLC employing a Chiralpak IB column (Daicel)

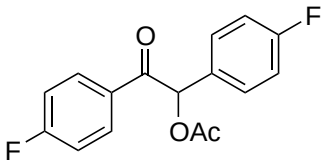
Eluent: Hexane/2-Propanol 95:5

Flow: 1 mL/min

UV-detector: λ = 254 nm and refractomter

Retention times: R_1 = 7.6 min, R_2 = 11.1 min

1,2-Bis(4-fluorophenyl)-2-oxoethyl acetate (244b)



Racemic 1,2-bis(4-fluorophenyl)-2-hydroxyethanone (67 mg, 0.27 mmol) were dissolved in 3 mL of DCM. Subsequently, 28 µL of Ac_2O (0.30 mmol), 3.7 mg of DMAP (0.03 mmol, 10 mol%) and 41 µL triethylamine (0.3 mmol) were added and the solution was stirred for 12 h at r.t. (25 °C). The solvent was evaporated under reduced pressure and the acylated product was directly purified *via* silica flash gel column chromatography and eluated with DCM/MeOH 8:2 (R_f = 0.8). 60 mg of 1,2-bis(4-fluorophenyl)-2-oxoethyl acetate (0.21 mmol, 77%) could be obtained. The racemic product was subjected to the HPLC assay to prove the origin of signals.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 7.92–7.84 (m, 2 H, H_{Ar}), 7.39–7.33 (m, 2 H, H_{Ar}), 7.05–6:95 (m, 4 H, H_{Ar}), 6.72 (s, 1 H, C*H*), 2.13 (s, 3 H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 192.1 (C=O), 170.4 (C=O), 167.2 (d, $J_{C-}{}^{15}{}_F$ = 225), 163.2 (d, $J_{C-}{}^{15}{}_F$ = 248), 131.5 (d, $J_{C-}{}^{15}{}_F$ = 10), 130.8 (d, $J_{C-}{}^{15}{}_F$ = 2.3), 130.5 (d, $J_{C-}{}^{15}{}_F$ = 8.8), 129.3 (d, $J_{C-}{}^{15}{}_F$ = 3), 116.3 (d, $J_{C-}{}^{15}{}_F$ = 22), 116.0 (d, $J_{C-}{}^{15}{}_F$ = 22), 76.6 (*C*H), 20.7 (*C*H_3).

The NMR-data are in accordance with the literature.[190]

Assay of product formation:

Racemic **244b** was detected by GC-FID employing a 30 m 5890_V UP5 (Machery Nagel).

T (Injector + Detector) = 250 °C

Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar

Conditions: 100 °C – 250 °C, 15 °C/min

Retention times: R = 10.3 min

Assay of enantiomeric purity:

Enantiomers of 1,2-bis(4-fluorophenyl)-2-oxoethyl acetate were separated by chiral HPLC employing a Chiralpak IB column (Daicel)

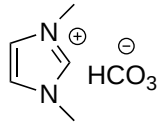
Eluent: Hexane/2-Propanol 95:5

Flow: 1 mL/min

UV-detector: λ = 254 nm and refractomter

Retention times: R_1 = 7.6 min, R_2 = 11.1 min

Synthesis of *N-N'*-Dimethylimidazolium Hydrogen Carbonate (245a)[173]



A mixture of **240** (500 mg, 2.23 mmol) and 1.05 eq. of $KHCO_3$ (25 mg, 0.24 mmol) was dried at 60 °C *in vacuo* for 20 h. 5 mL of dry MeOH were added at r.t. and the resulting suspension was stirred for 48 h. After filtration of the suspension over Celite to remove KCl, the solvent was evaporated *in vacuo* to yield a yellow solid. Trituration of the solid with acetone and drying *in vacuo* yielded 286 mg of *N-N'*-dimethylimidazolium hydrogen carbonate (1.81 mmol, 81%) as a colorless solid.

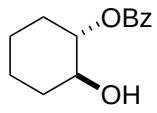
^{1}H-NMR (400 MHz, D_2O): δ/ppm = 7.53 (s, 2 H, C*H*), 3.89 (s, 6 H, 2 x CH_3). The N_2CH and HCO_3^- protons could not be observed due to their rapid exchange with the deuterated solvents on the NMR time scale.

^{13}C-NMR (400 MHz, D_2O): δ/ppm = 161.4 (HCO_3^-), 138.8 (C_q), 124.8 (2 x *C*H), 36.6 (2 X *C*H_3).

Benzoin condensation with 245a as catalyst

N-N'-Dimethylimidazolium hydrogen carbonate (50 mg, 0.31 mmol) and molecular sieve 3 Å were introduced into a Schlenk tube and subjected to vacuum for 30 min. Subsequently, 2 mL of dry THF were added and the solution was stirred for 10 min. Then, 30 mL benzaldehyde (0.3 mmol) were added and the reaction mixture was stirred overnight. After quenching the reaction mixture with water, a GC-FID analysis was performed.

2-Hydroxycyclohexylbenzoate (2d)



Racemic **1** (232 mg, 2.0 mmol) was treated with EDC·HCl (420 mg, 2.2 mmol), Et_3N (310 µL, 2.2 mmol) and benzoic acid (244 mg, 2.2 mmol) in the presence of *N,N'*-dimethylaminopyridine (12 mg, 0.01 mmol, 0.5 mol%) in 10 mL of DCM and stirred for 18 h at r.t. The solvent was removed *in vacuo* and the crude product was purified by silica gel flash chromatography with EtOAc/hexane (1:1), R_f = 0.35. Isolated racemic monobenzoate (206 mg; 0.9 mmol; 45%) was characterized and subjected to the GC assay to prove the origin of signals. Additionally, 91 mg (0.3 mmol; 15%; R_f = 0.5) of the dibenzoylated product **252** were obtained.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm = 8.11–8.03 (m, 2 H, *o*-H_{Ar}), 7.61–7.53 (m, 1 H, *p*-H_{Ar}), 7.47–7.42 (m, 2 H, *m*-H_{Ar}), 4.90–4.81 (m, 1 H, C*H*), 3.80–3.68 (m, 1 H, C*H*), 2.36–2.29 (m, 1 H, OH), 2.21–2.07 (m, 1 H), 1.80–1.72 (m, 2 H), 1.52–1.27 (m, 4 H).

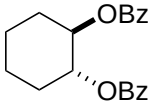
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm = 166.7 (C=O), 133.1 (C_{Ar}), 130.3 (C_{Ar}), 129.7 (2 x C_{Ar}), 128.4 (2 x C_{Ar}), 78.7, 72.8 (*C*-OH), 33.0, 30.0, 23.9, 23.7.
The NMR-data are in accordance with the literature.[68]

Assay of enantiomeric purity:

Enantiomers of **2d** were separated by chiral GC employing a 30 m FS-Hydrodex βTBDAc column (Machery Nagel).
T(Injector + Detector) = 250 °C
Splitflow = 80 mL/min
Precolumn pressure = 0.8 bar
Conditions: 160 °C isothermal
Retention times: R_1 = 84.6 min, R_2 = 86.2 min.

Enantiomers of **2d** were separated by chiral HPLC employing a Chiralpak IC column (Daicel)
Eluent: Hexane/2-Propanol 9:1
Flow: 1 mL/min
UV-detector: λ = 220 nm and refractomter
Retention times: R_1 = 14.6 min, R_2 = 16.2 min

***trans*-Cyclohexyl-1,2-dibenzoate (252)**



^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 8.11–8.03 (m, 4 H, H_{Ar}), 7.51–7.42 (m, 2 H, H_{Ar}), 7.42–7.30 (m, 4 H, H_{Ar}), 5.35–5.22 (m, 2 H, C*H*), 2.31–2.18 (m, 2 H, C*H*), 1.90–1.81 (m, 2 H, *C*H), 2.21–2.07 (m, 1 H), 1.69–1.42 (m, 4 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 166.0 (C=O), 132.9 (C_{Ar}), 130.2 (C_{Ar}), 129.7 (2 x C_{Ar}), 128.2 (C_{Ar}), 74.2 (*C*-OH), 30.2, 23.5.

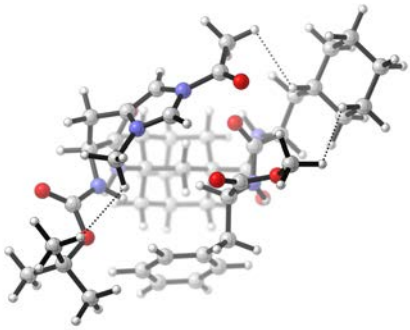
Oxidative Esterification

A flame-dried vessel was charged with **240** or **12i** (10 mmol, 30 mol%), KO^{t}Bu (13 mmol, 11 mol%), **1** (38 mmol, 1.1 eq) and phenazine (0.33 mmol, 1.2 eq.) and degassed for 30 min. 3 mL of dry THF were added and the mixture was stirred for 10 min. Subsequently, benzaldehyde (30 µL, 0.3 mmol) was added *via* an Eppendorf pipette. The reaction mixture was allowed to stir at r.t. for 12 h. After quenching the mixture with water, the product *ee* was determined by chiral GC and chiral HPLC.

Theoretical section

For the molecular dynamics search for low-lying conformations of catalyst/acylium ion adduct, catalyst/*tert*-butoxycarbonylium adduct and catalyst/acylium ion adduct with (*R,R*)-1 we utilized the Merck Molecular Force Field (MMFF).[83] The lowest-lying conformation was reoptimized at the M06-2X/6–31+G(*d,p*) level of theory.[84,85]

Catalyst/acylium ion adduct



6	0.58105	2.61741	-0.38197
6	2.71439	3.89563	-0.23696
6	0.67328	4.68387	1.02144
6	1.93441	5.12634	0.26034
6	-0.22398	3.85138	0.0947
6	1.82293	3.06146	-1.16609
6	-0.62315	4.69848	-1.13073
6	1.41468	3.9226	-2.37348
6	1.52849	5.98949	-0.94189
6	0.64238	5.15702	-1.8773
1	2.31897	4.22944	-2.91331
1	0.79959	3.33318	-3.05833
1	0.34476	5.76061	-2.74117
1	-1.21134	5.56494	-0.80562
1	0.98721	6.87936	-0.59908
1	2.41826	6.33709	-1.48052
1	2.57689	5.70353	0.934
1	3.61535	4.21248	-0.77888
1	3.02554	3.27915	0.61572
1	0.12334	5.56125	1.38256
1	0.9333	4.08132	1.89644
1	0.90091	2.03072	0.49464
1	-1.24275	4.12796	-1.83472
1	-0.03743	1.97293	-1.01857
7	2.56536	1.85605	-1.57022
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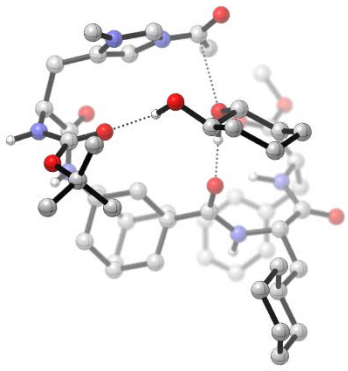
E[M06–2X] = – 2643.9664535

Catalyst/acylium ion adduct with (*R*,*R*)-1



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7	3.45339	-2.17463	2.89643

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1	1.54593	-3.96583	3.90904
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6	4.44719	-1.29754	2.71951
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1	-6.43189	-2.36684	-0.65236
1	-5.54167	-2.38127	-2.95641
1	-5.19754	1.90355	-2.85162
1	-4.91556	-0.24639	-4.06816
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6	1.05531	2.95725	4.3089
6	1.76118	3.91567	3.34466
6	0.6602	1.65801	3.60074
6	2.58583	1.95713	1.99321
8	3.76347	1.34022	1.48192
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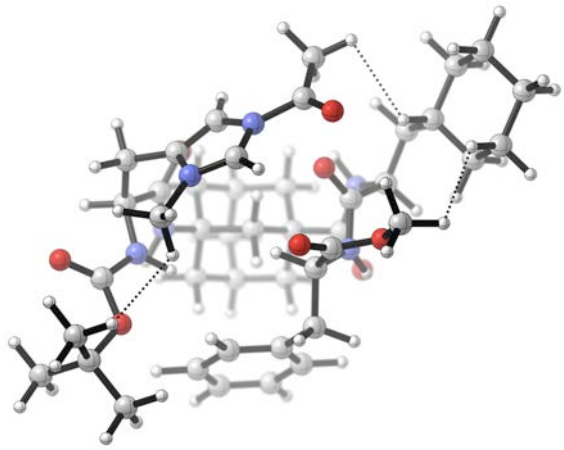
E[M06–2X] = –3030.1604445

Catalyst/tert-butoxycarbonylium ion adduct



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1	3.15571	-1.69968	5.73122

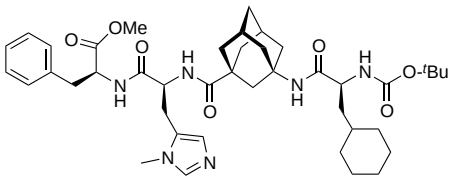
E[M06–2X] = –2837.0691869

References for electronic structure code Gaussian09

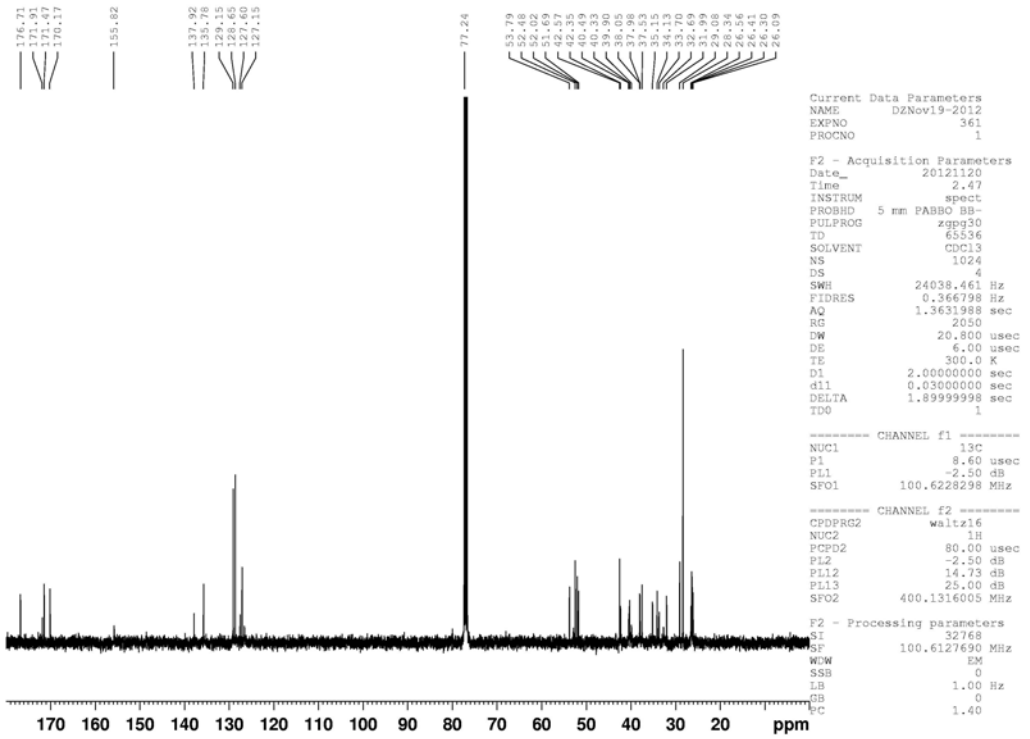
Frisch, M. J.; Trucks, G. W.; Schlegel, H., . B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J., , J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J.; Gaussian09 Revision B.01, Gaussian Inc., Wallingford CT, 2009

NMR-Spectra

Boc-L-Cha-^{A}Gly-L-(π-Me)-His-L-Phe-OMe (13)

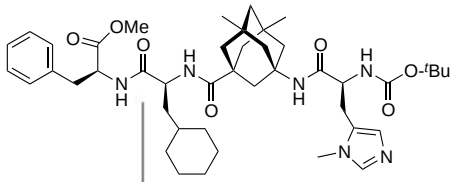



```
Current Data Parameters
NAME        DZNov19-2012
EXPNO                360
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121120
Time                1.46
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           8223.685 Hz
FIDRES        0.125483 Hz
AQ            3.9846387 sec
RG                   181
DW               60.800 usec
DE                6.00 usec
TE               300.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 1H
P1                11.00 usec
PL1               -2.50 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1300335 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                  1.00
```




```
Current Data Parameters
NAME        DZNov19-2012
EXPNO                361
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121120
Time                2.47
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     4
SWH          24038.461 Hz
FIDRES        0.366798 Hz
AQ            1.3631988 sec
RG                  2050
DW               20.800 usec
DE                6.00 usec
TE               300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                13C
P1                8.60 usec
PL1               -2.50 dB
SFO1         100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2            80.00 usec
PL2               -2.50 dB
PL12              14.73 dB
PL13              25.00 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF           100.6127690 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                  1.40
```

Boc-L-(π-Me)-His-5,7-Me$_2$-^{A}Gly-L-Cha-L-Phe-OMe (207)

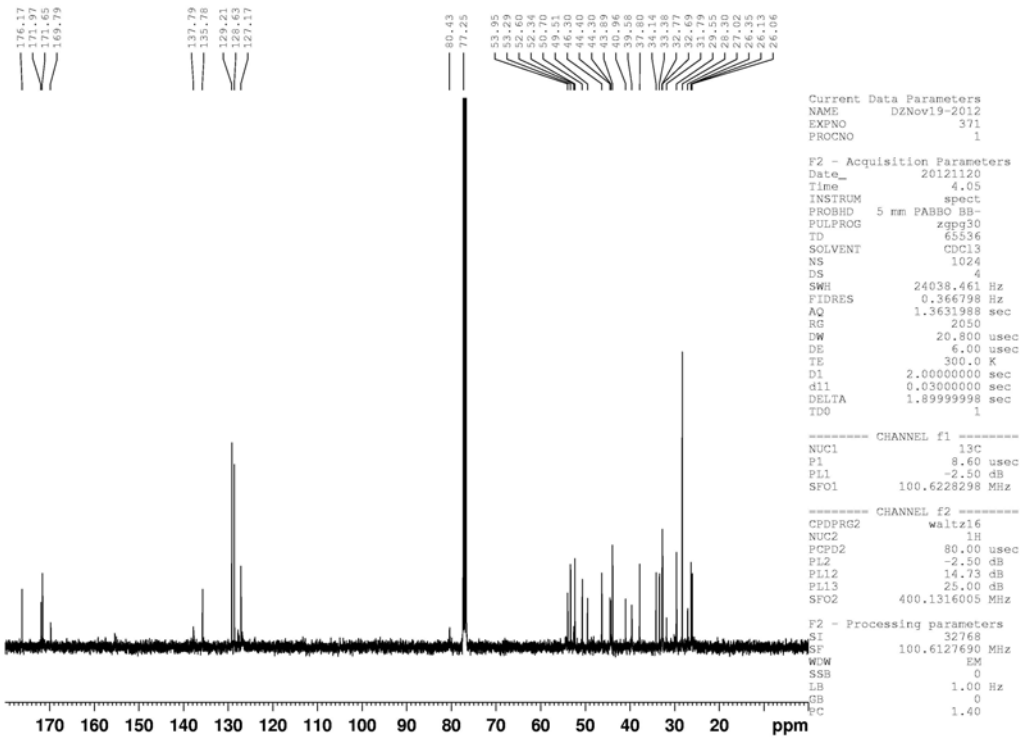


Current Data Parameters
NAME DZNov19-2012
EXPNO 370
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121120
Time 3.05
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 144
DW 60.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 11.00 usec
PL1 -2.50 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300320 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DZNov19-2012
EXPNO 371
PROCNO 1

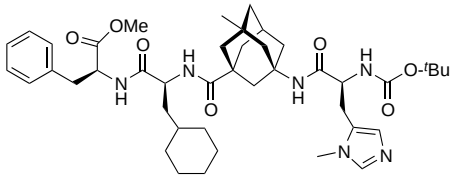
F2 - Acquisition Parameters
Date_ 20121120
Time 4.05
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

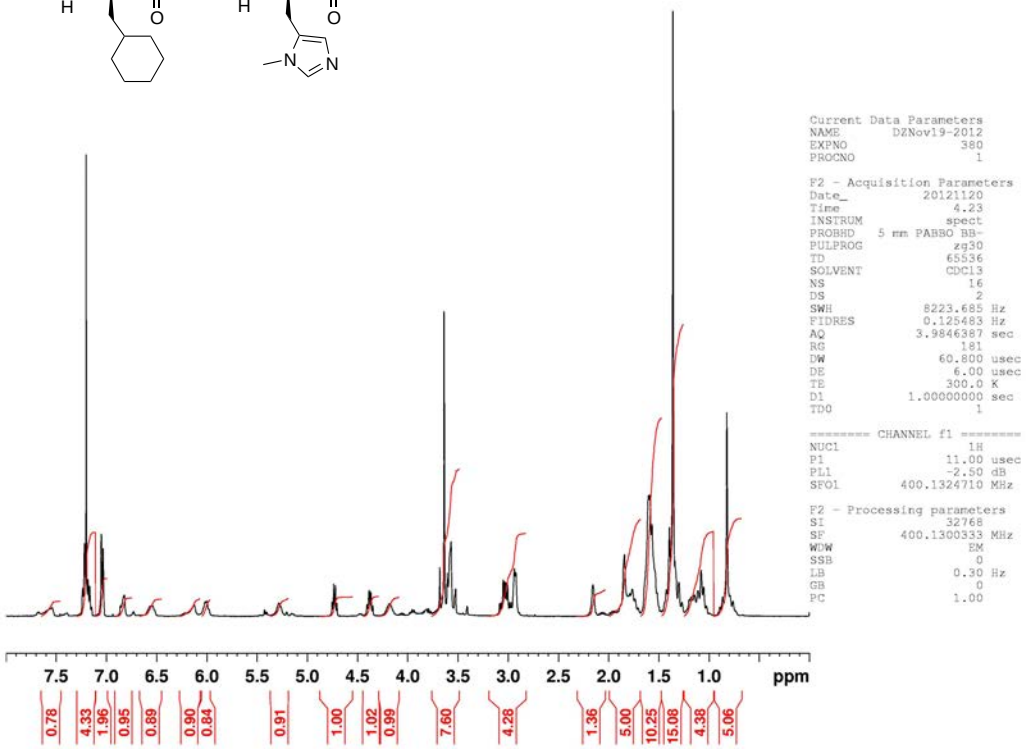
======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 -2.50 dB
SFO1 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.50 dB
PL12 14.73 dB
PL13 25.00 dB
SFO2 400.1316005 MHz

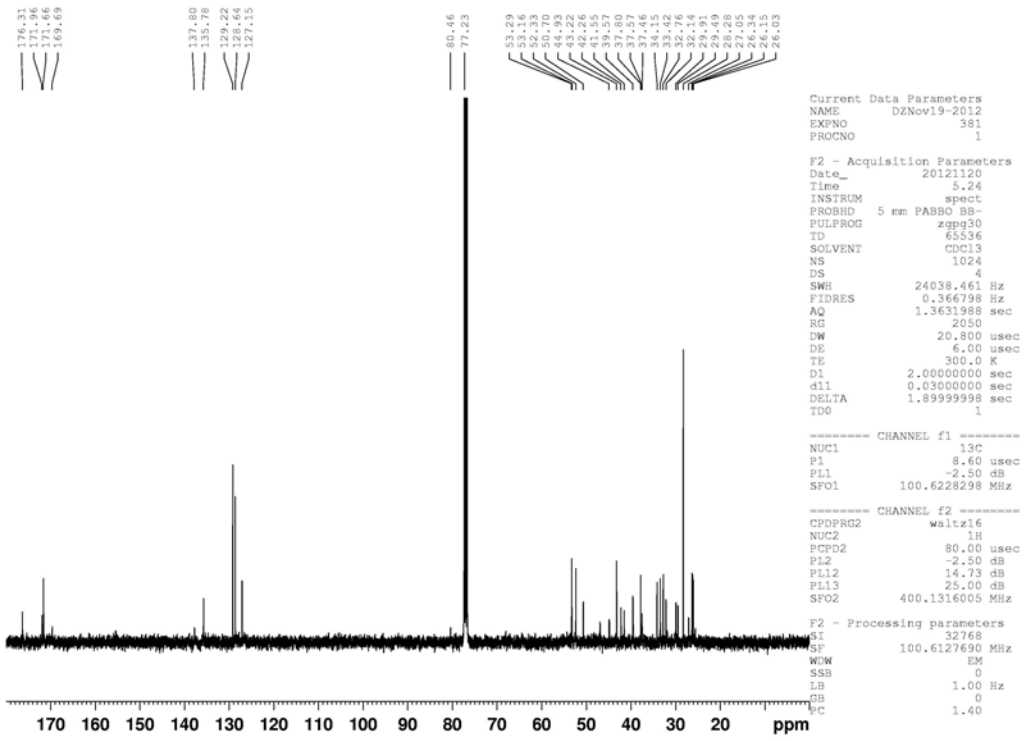
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Boc-L- (π-Me)-His-5-Me-^{A}Gly-L-Cha-L-Phe-OMe (208)



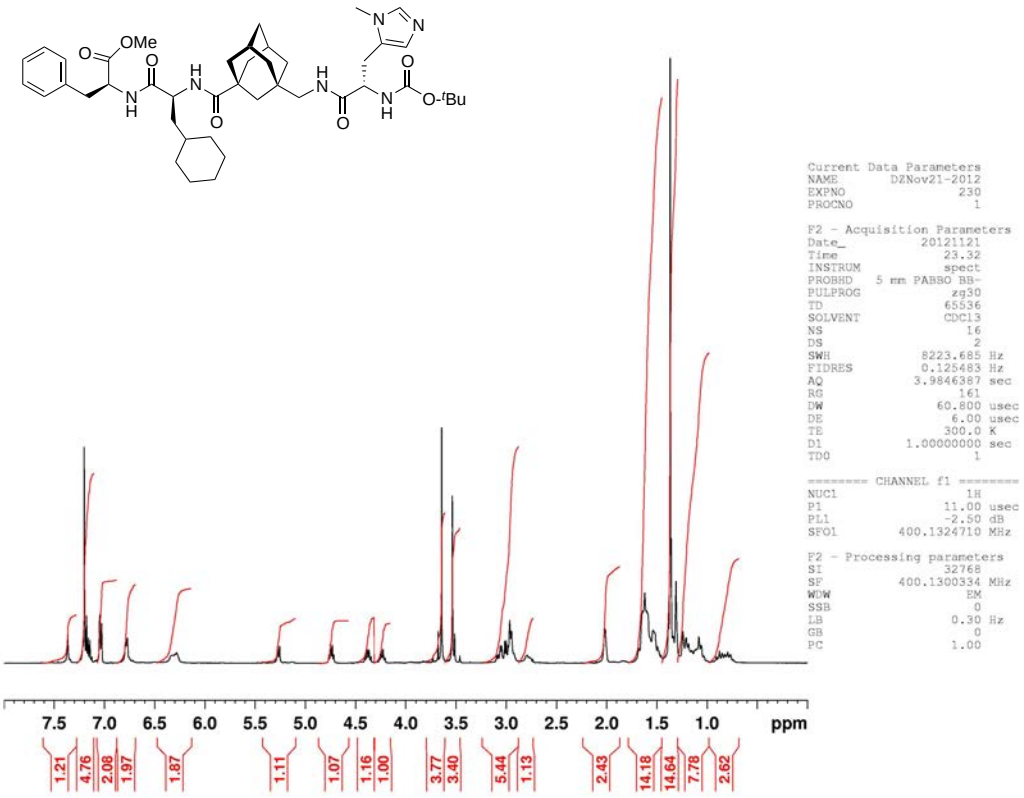


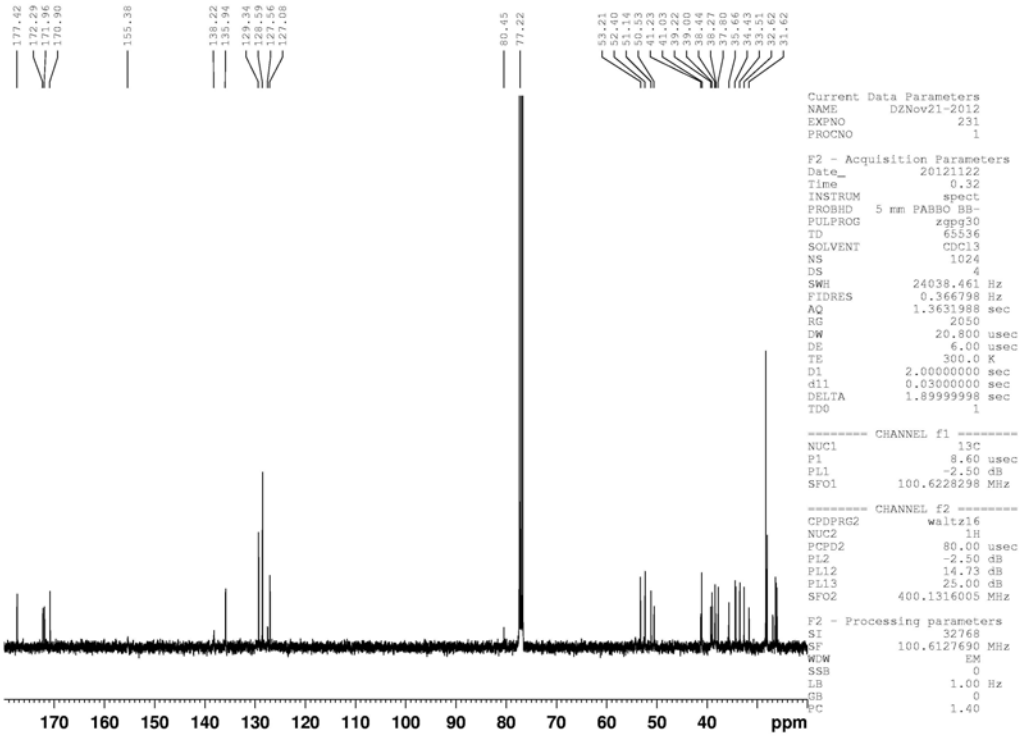

```
Current Data Parameters
NAME                 DZNov19-2012
EXPNO                         380
PROCNO                          1

F2 - Acquisition Parameters
Date_               20121120
Time                    4.23
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      181
DW                   60.800 usec
DE                    6.00 usec
TE                   300.0 K
D1                1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                      1H
P1                    11.00 usec
PL1                   -2.50 dB
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                400.1300333 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```



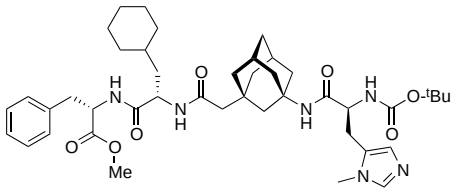

```
Current Data Parameters
NAME                 DZNov19-2012
EXPNO                         381
PROCNO                          1

F2 - Acquisition Parameters
Date_               20121120
Time                    5.24
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     1024
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                     2050
DW                   20.800 usec
DE                    6.00 usec
TE                   300.0 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     13C
P1                    8.60 usec
PL1                  -2.50 dB
SFO1            100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                80.00 usec
PL2                  -2.50 dB
PL12                 14.73 dB
PL13                 25.00 dB
SFO2            400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                100.6127690 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

Boc-L-(π-Me)-His-MAACA-L-Cha-L-Phe-OMe (209)





Boc-L-(π-Me)-His-AAMCA-L-Cha-L-Phe-OMe (210)

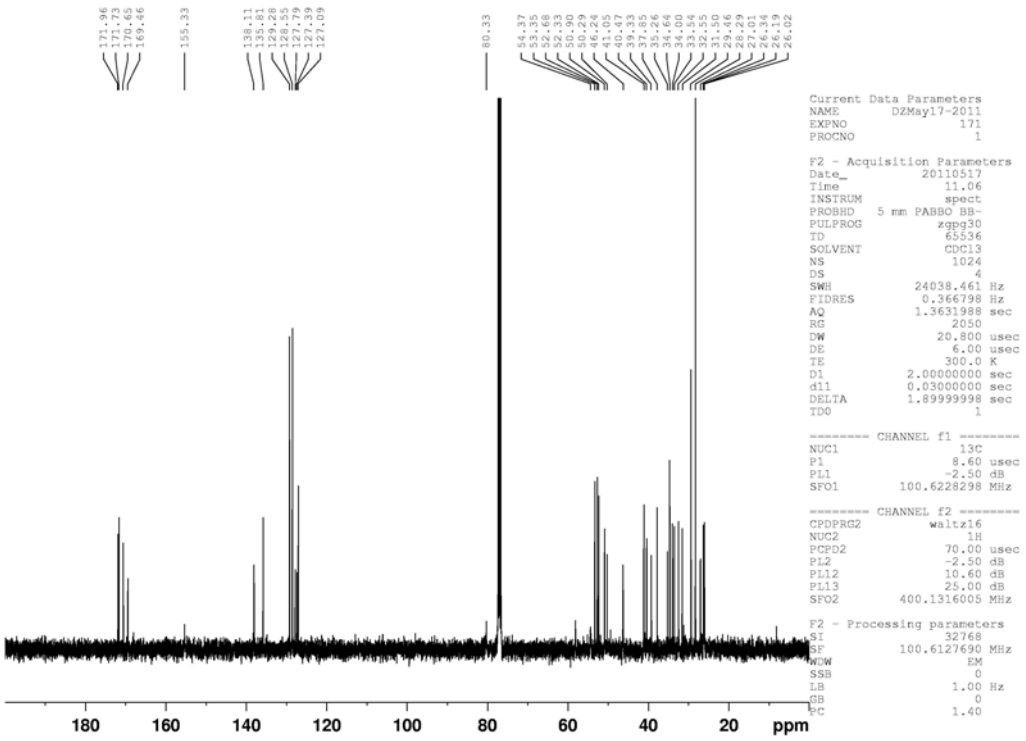


Current Data Parameters
NAME DZMay17-2011
EXPNO 170
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110517
Time 10.41
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 181
DW 60.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 13.60 usec
PL1 -2.50 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300317 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DZMay17-2011
EXPNO 171
PROCNO 1

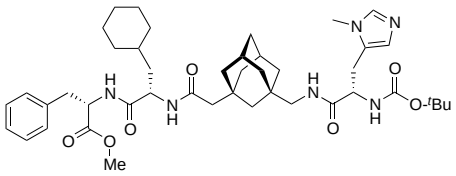
F2 - Acquisition Parameters
Date_ 20110517
Time 11.06
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 -2.50 dB
SFO1 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 70.00 usec
PL2 -2.50 dB
PL12 10.60 dB
PL13 25.00 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Boc-L- (π-Me)-His-MAAMCA-L-Cha-L-Phe-OMe (211)

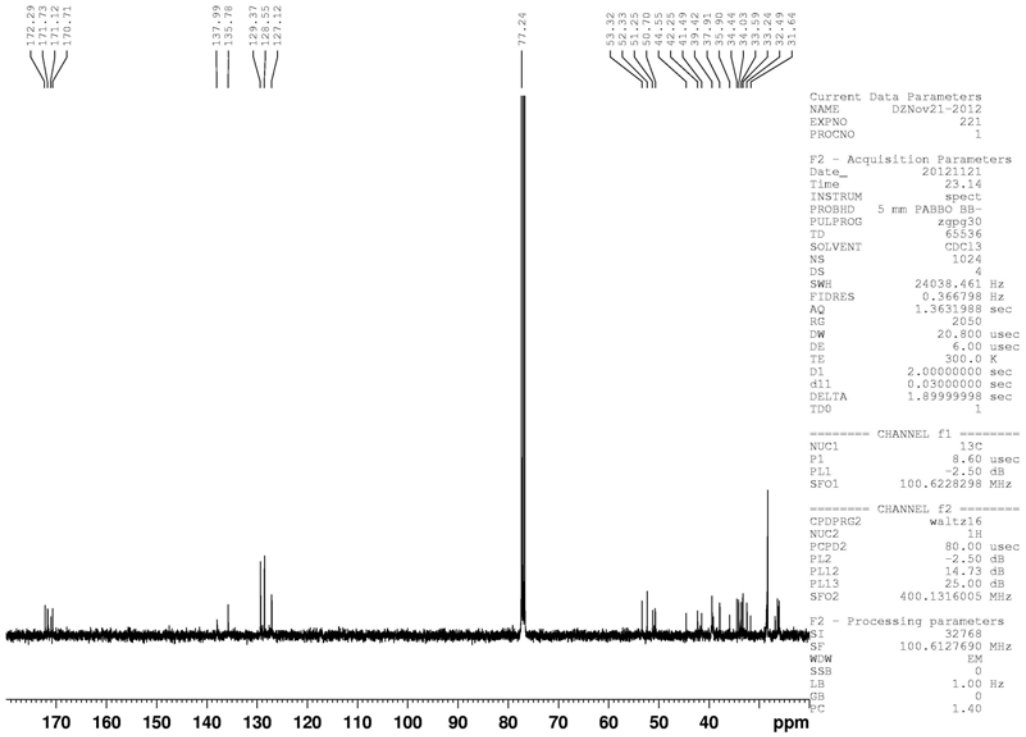


Current Data Parameters
NAME DZNov21-2012
EXPNO 220
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121121
Time 22.13
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 203
DW 60.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 11.00 usec
PL1 -2.50 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300346 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DZNov21-2012
EXPNO 221
PROCNO 1

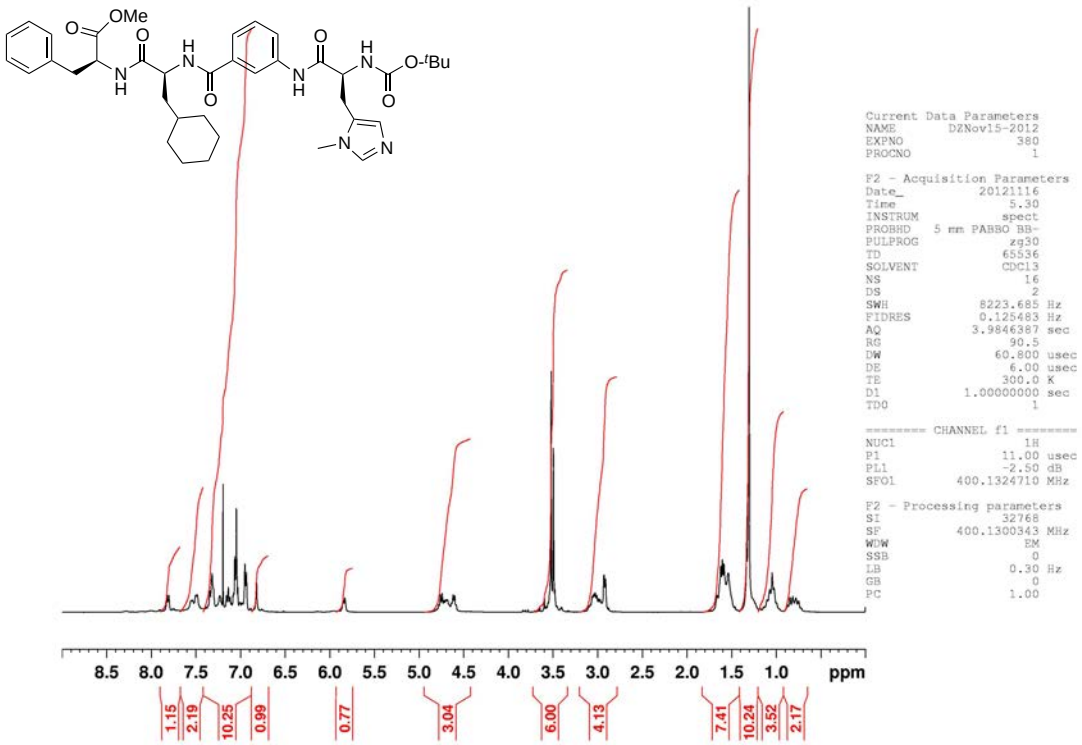
F2 - Acquisition Parameters
Date_ 20121121
Time 23.14
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

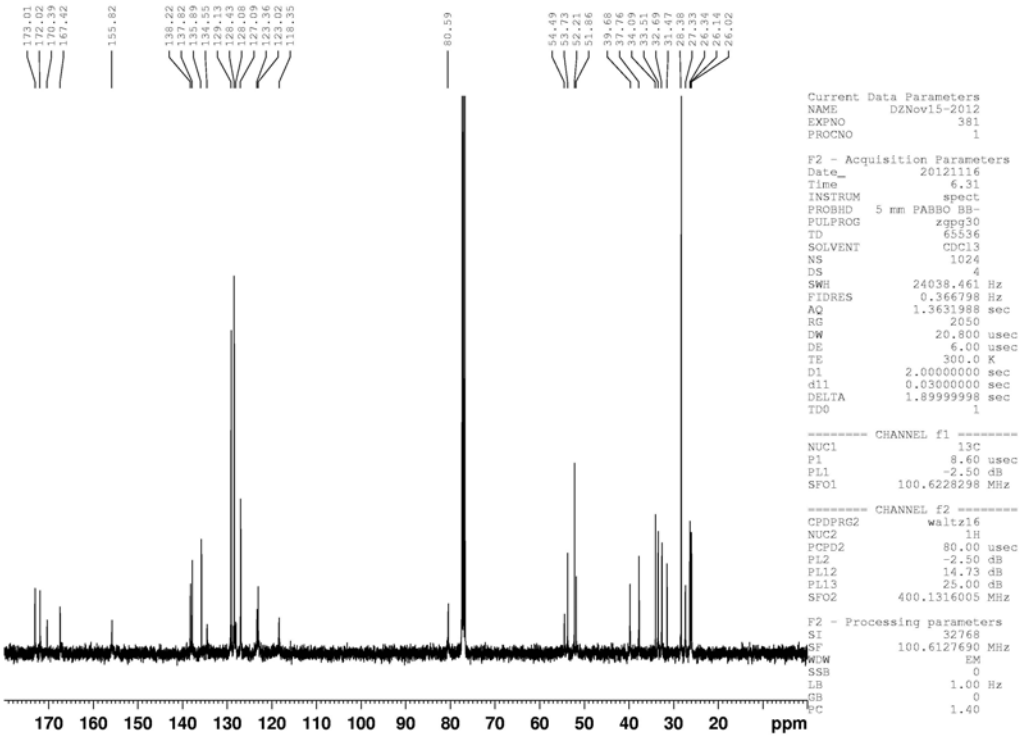
======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 -2.50 dB
SFO1 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.50 dB
PL12 14.73 dB
PL13 25.00 dB
SFO2 400.1316005 MHz

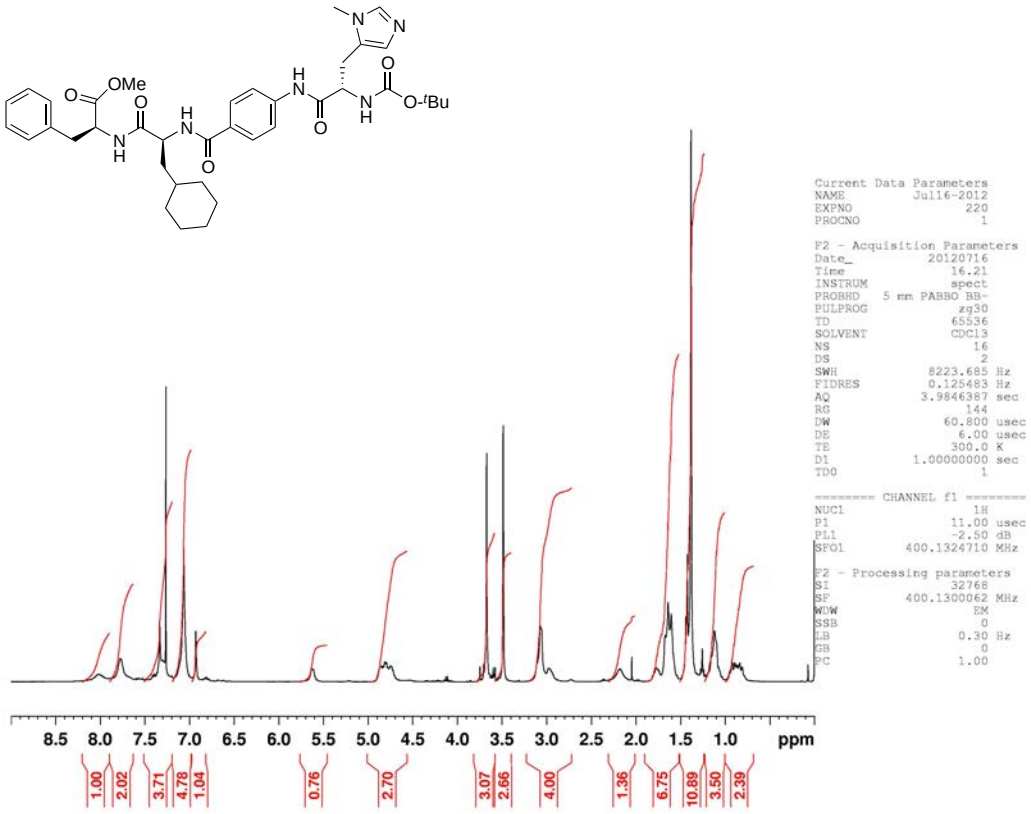
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

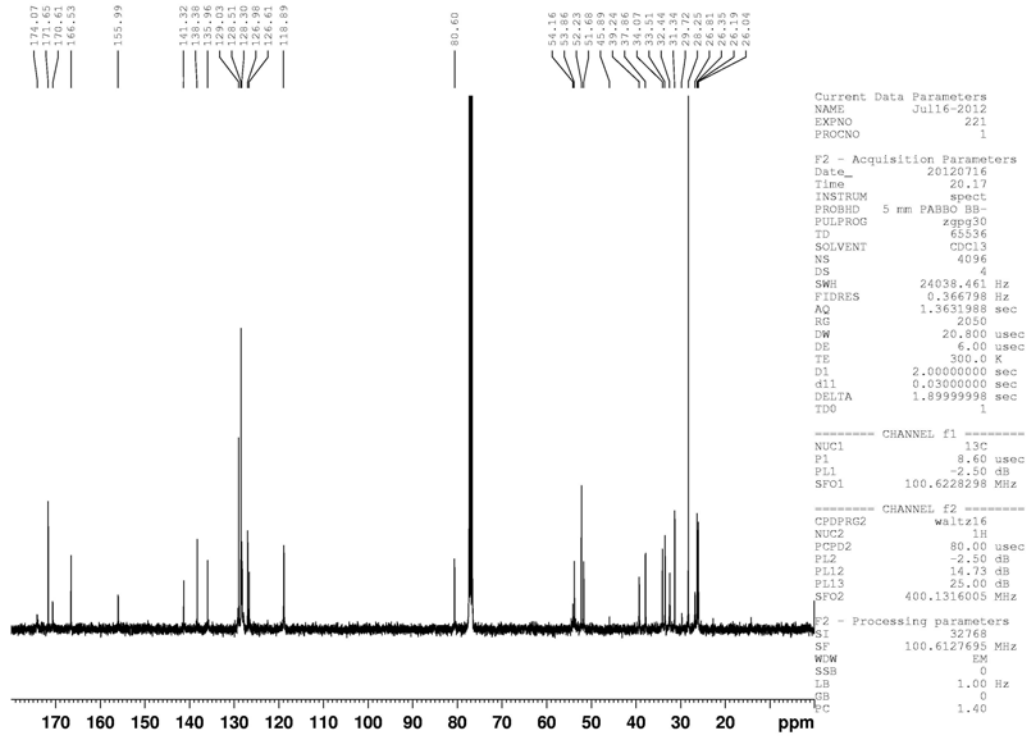
Boc-L-(π-Me)-His-3-Abz-L-Cha-L-Phe-OMe (212)



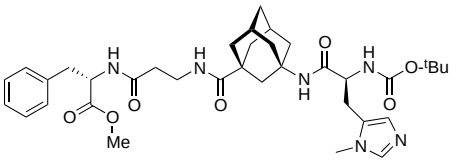


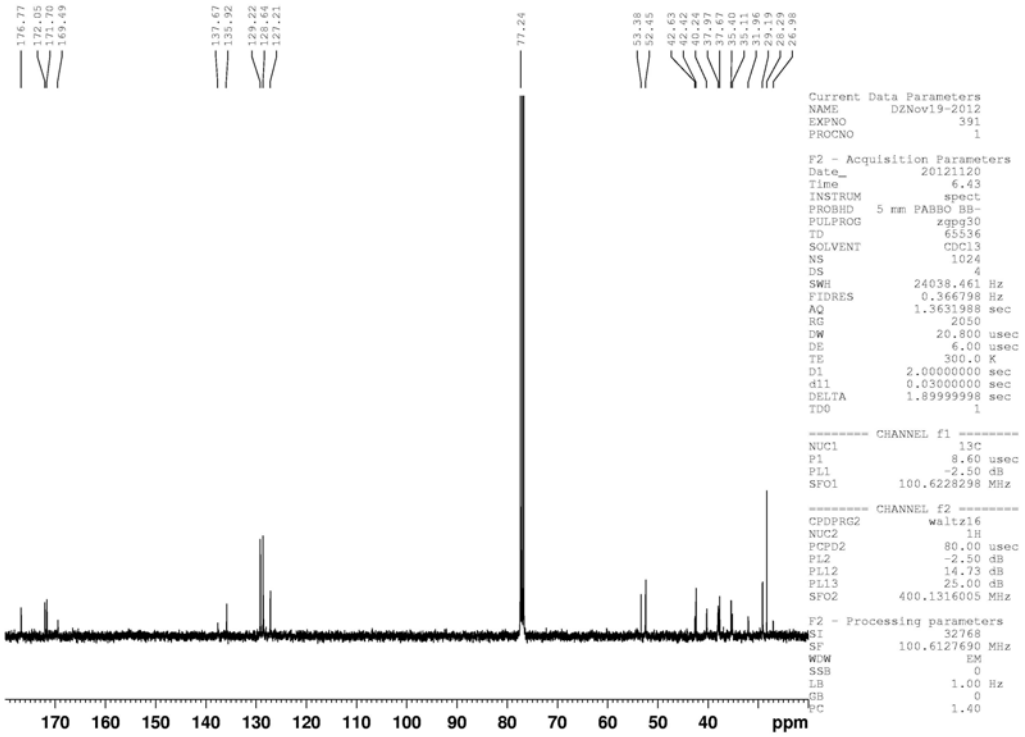
Boc-L-(π-Me)-His-4-Abz-L-Cha-L-Phe-OMe (213)



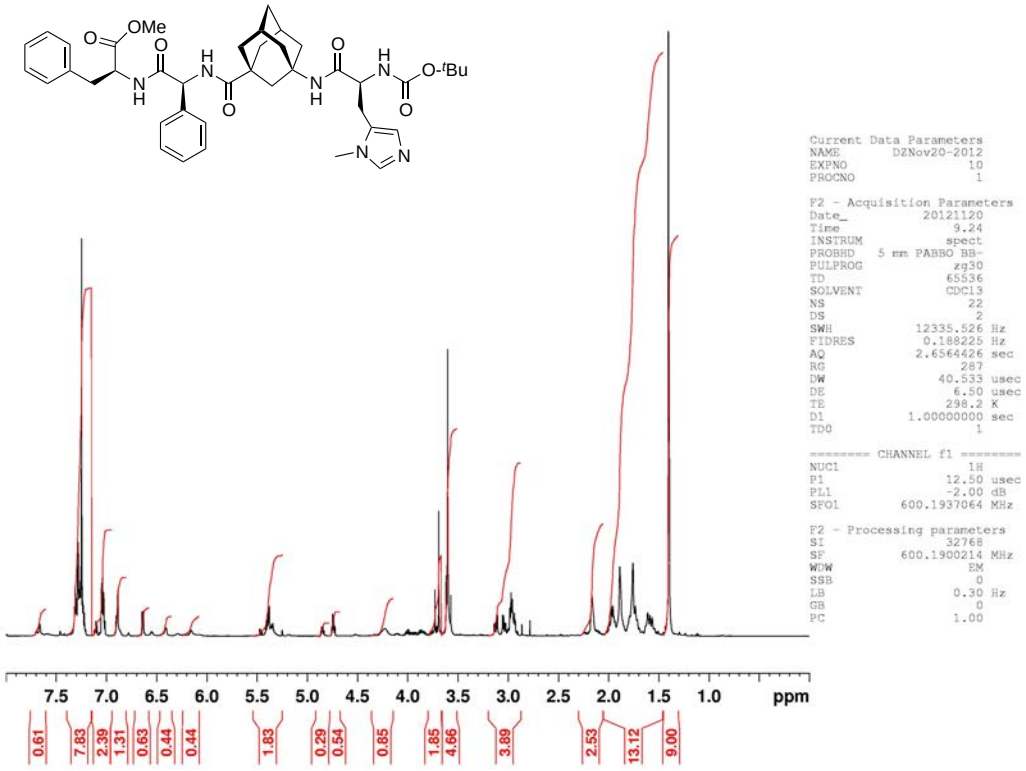


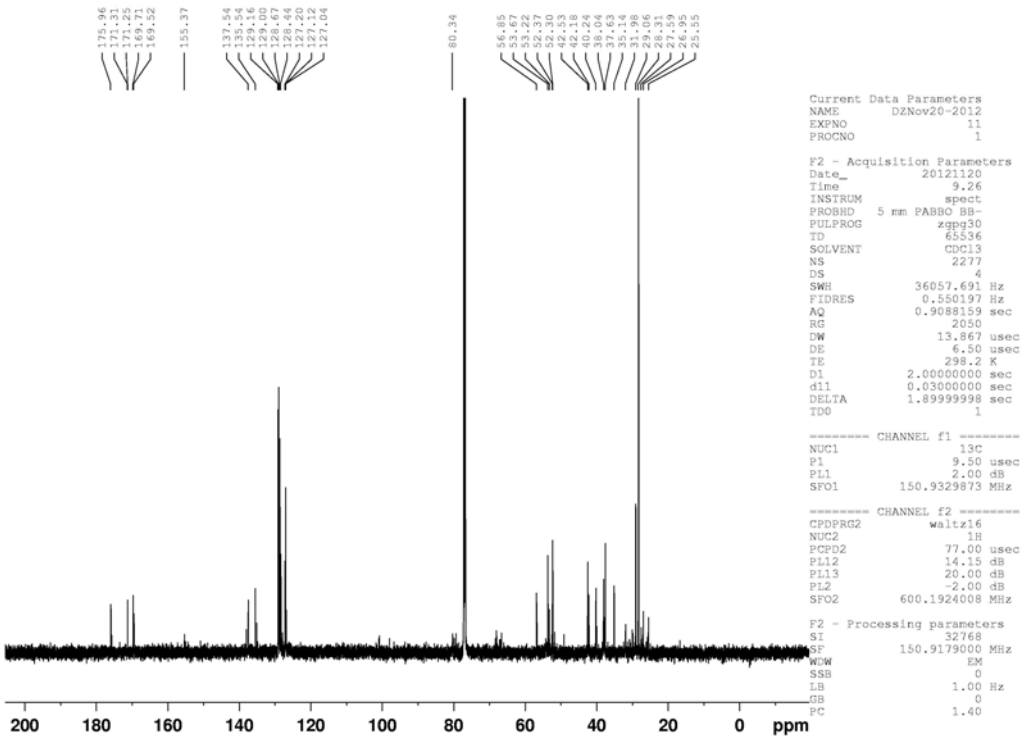
Boc-L-(π-Me)-His-^{A}Gly-L-β-Ala-L-Phe-OMe (214)



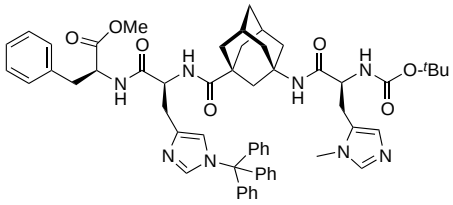


Boc-L-(π-Me)-His-[A]Gly-L-Phg-L-Phe-OMe (217)





Boc-L-(π-Me)-His-[A]Gly-L-His(Trt)-L-Phe-OMe (218)

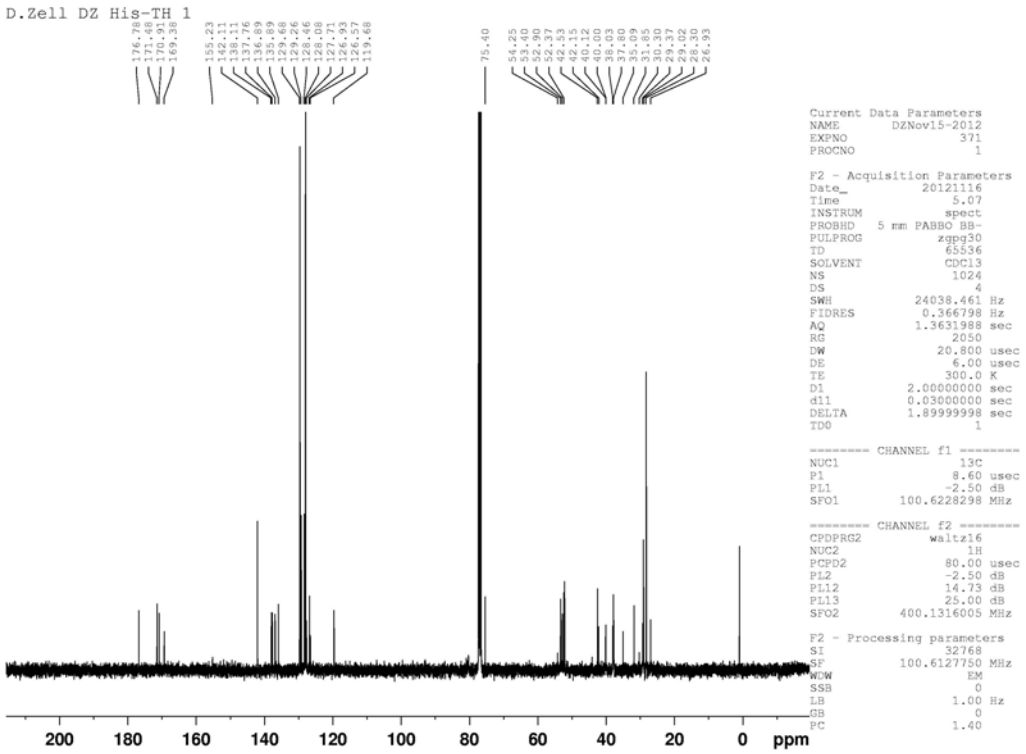


Current Data Parameters
NAME DZNov15-2012
EXPNO 370
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121116
Time 4.07
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 128
DW 60.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 11.00 usec
PL1 -2.50 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300339 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME DZNov15-2012
EXPNO 371
PROCNO 1

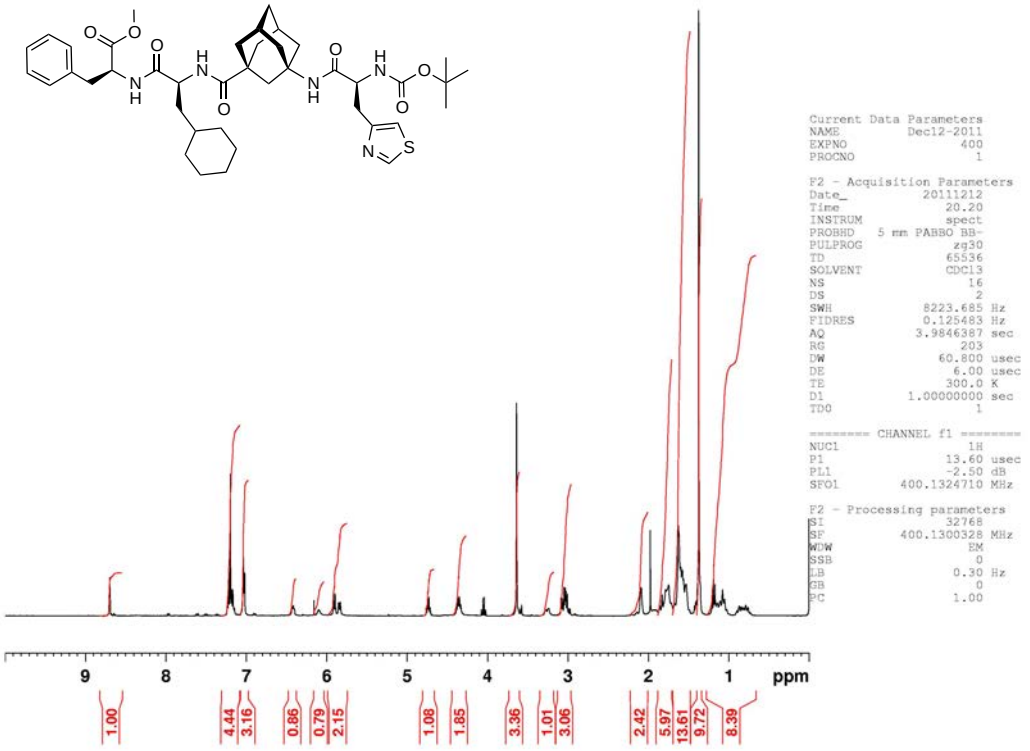
F2 - Acquisition Parameters
Date_ 20121116
Time 5.07
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

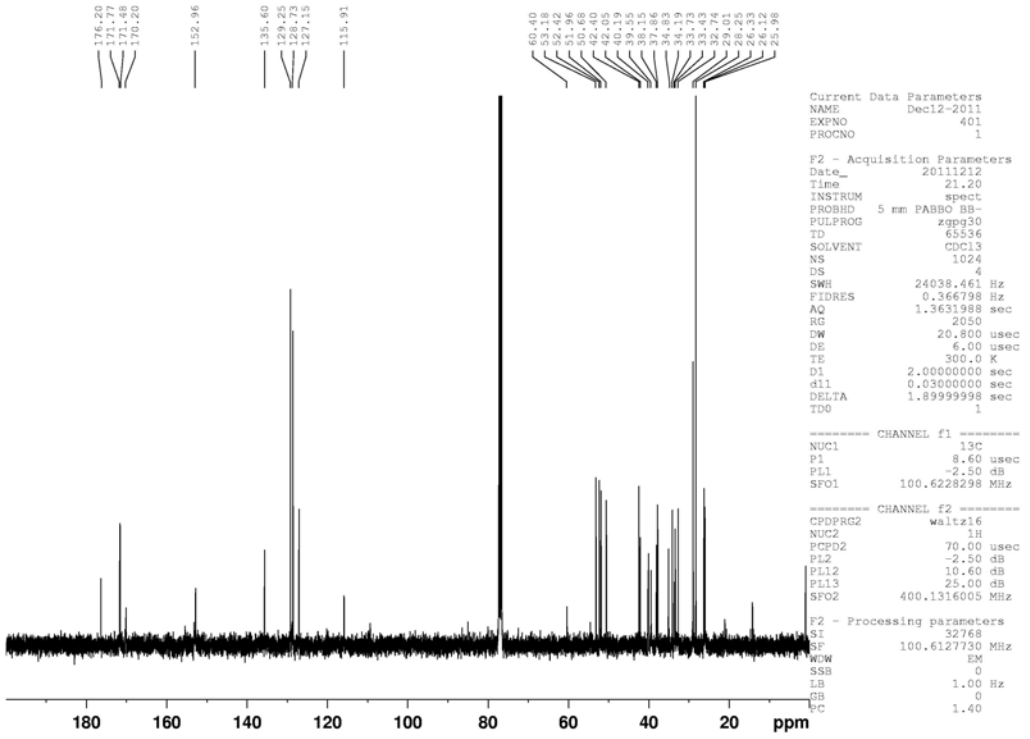
======== CHANNEL f1 ========
NUC1 13C
P1 8.60 usec
PL1 -2.50 dB
SFO1 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.50 dB
PL12 14.73 dB
PL13 25.00 dB
SFO2 400.1316005 MHz

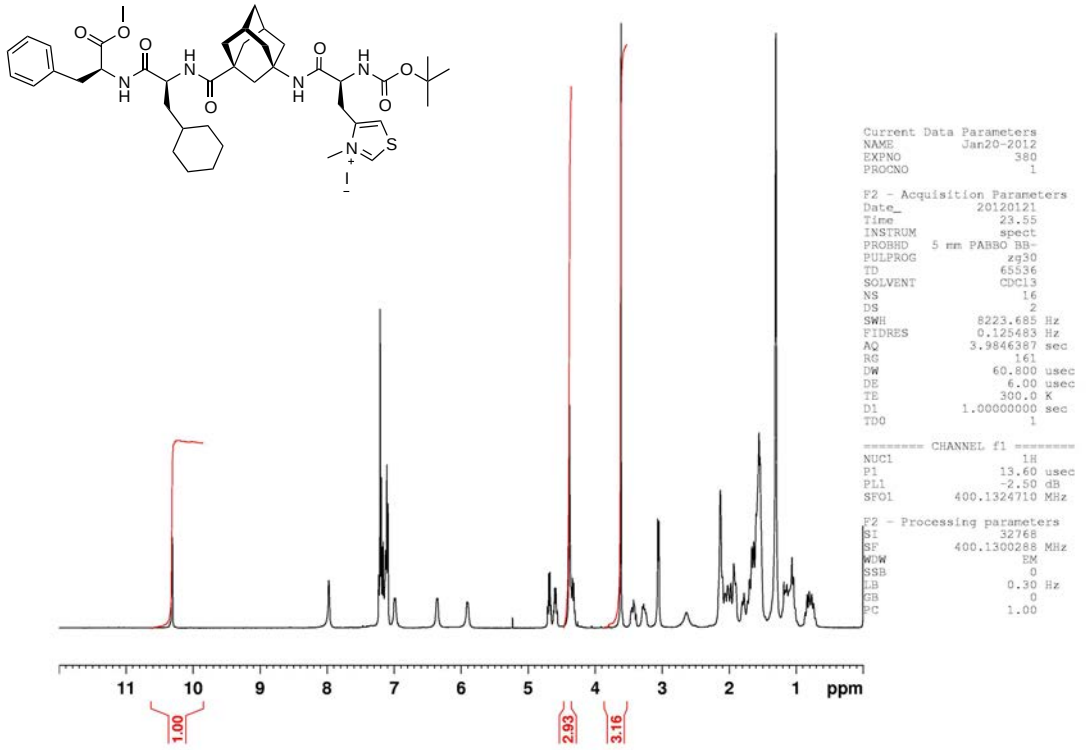
F2 - Processing parameters
SI 32768
SF 100.6127750 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

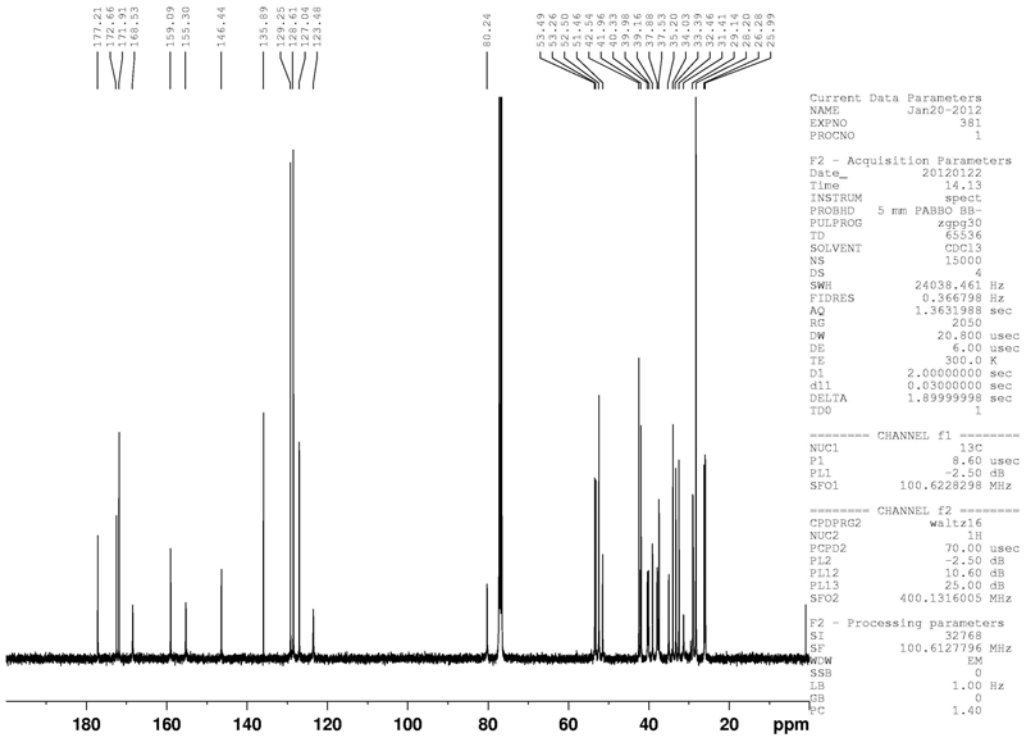
Boc-β-(4-Taz)-^{A}Gly-L-Cha-L-Phe-OMe (236)



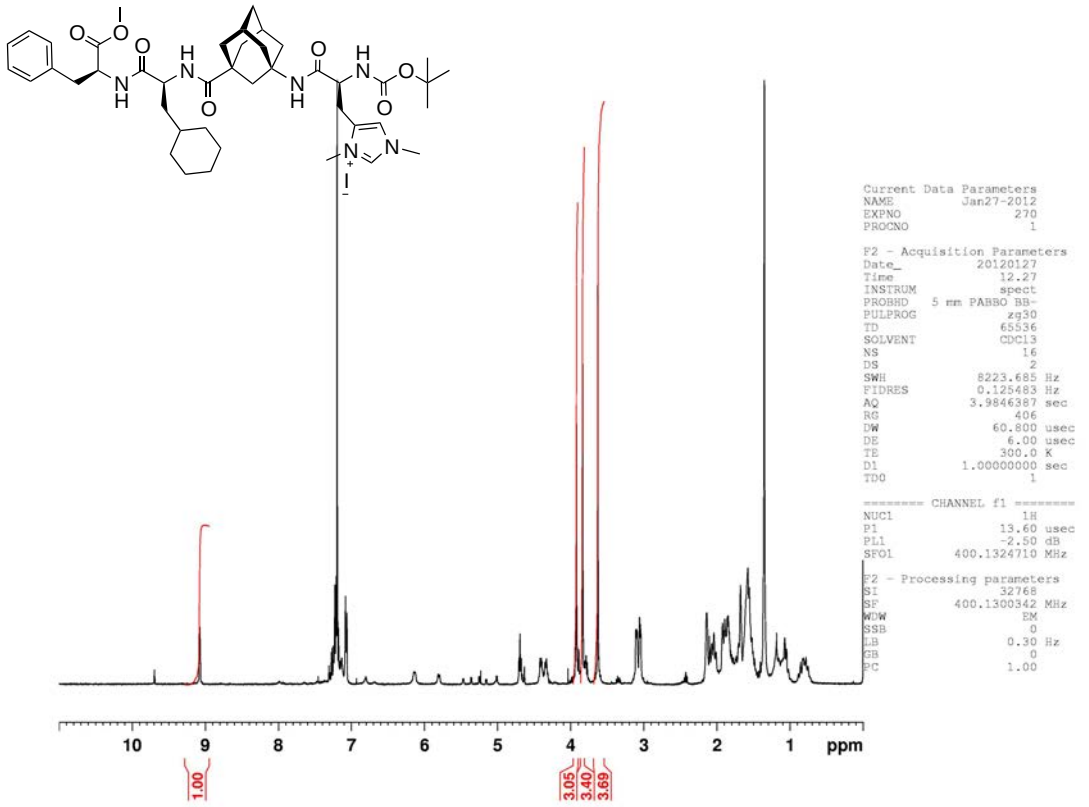


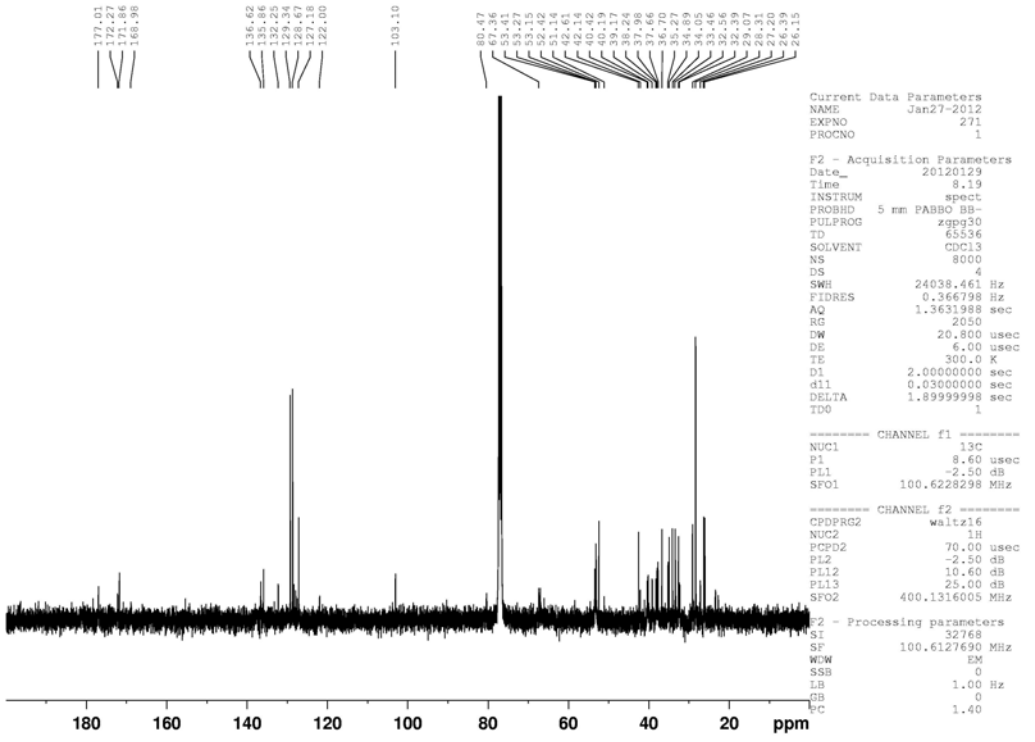
Boc-β-(4-MeTaz)I-^{A}Gly-L-Cha-L-Phe-OMe (237)



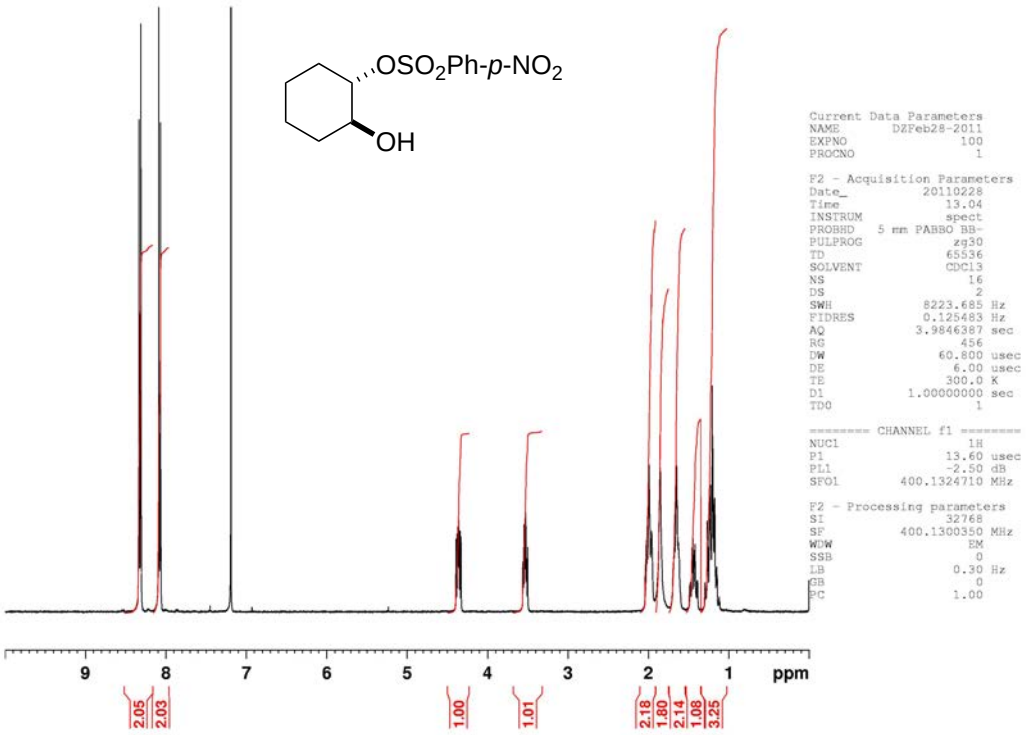


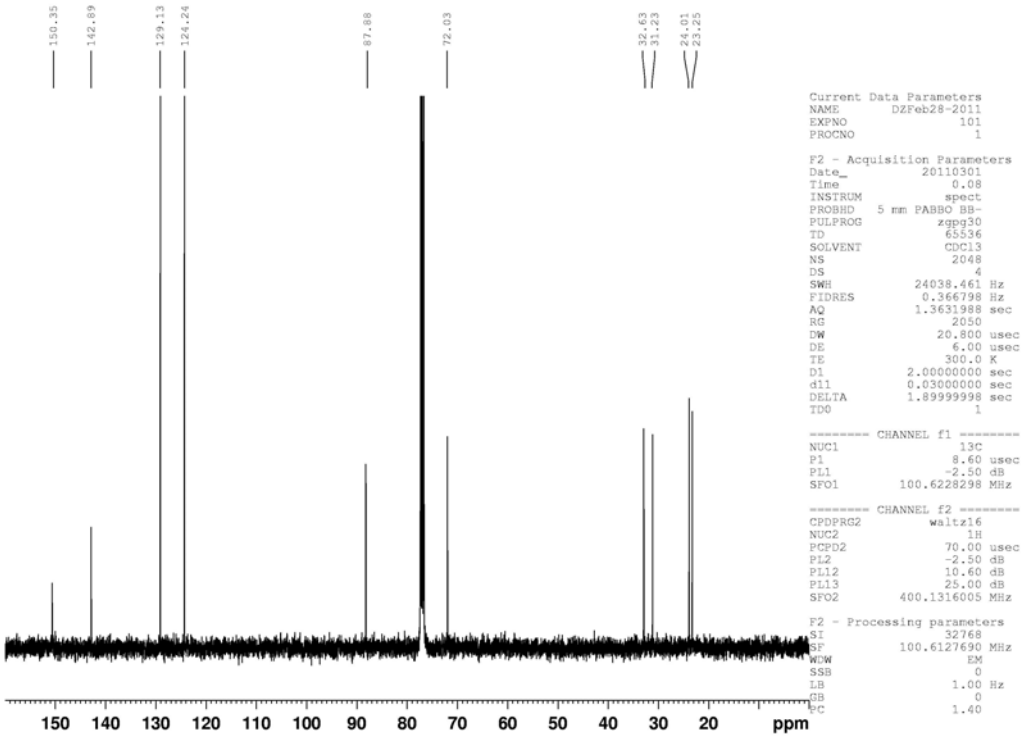
Boc-L-(π, τ-Dime-His)I-L-^{A}Gly-L-Cha-L-Phe-OMe (235)



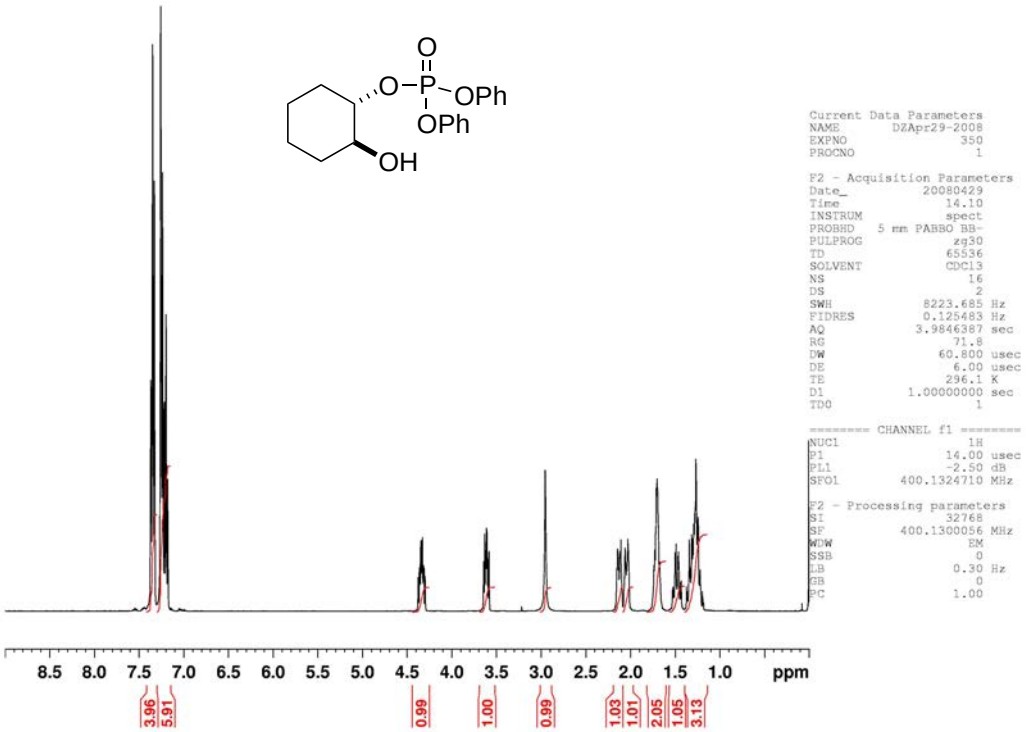


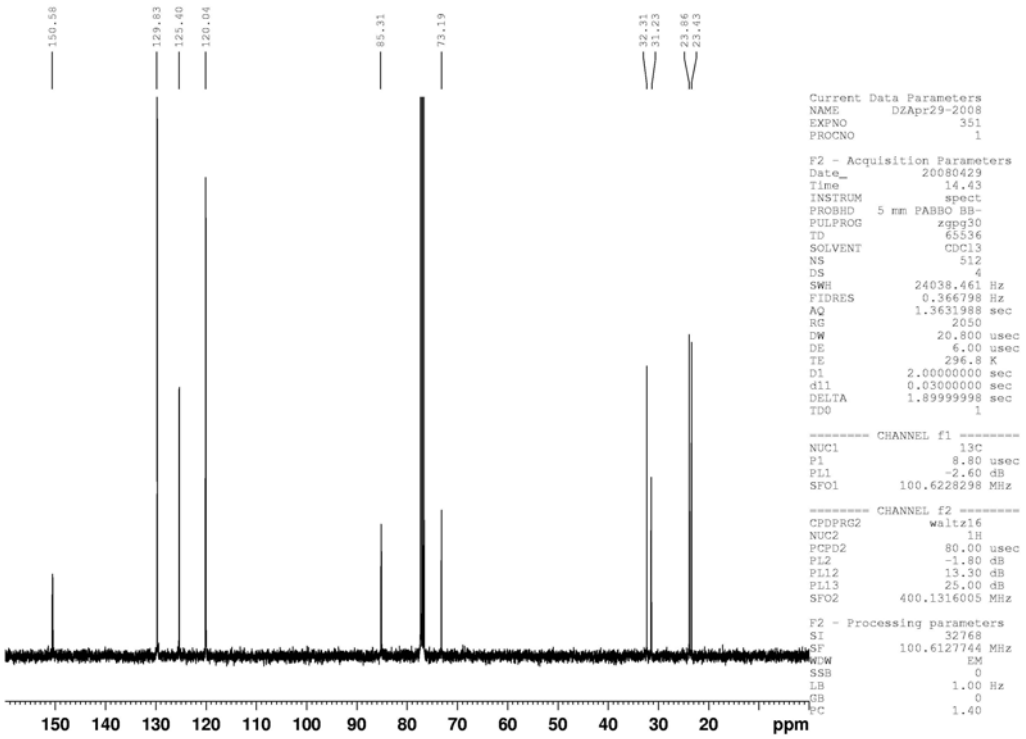
Trans-2-hydroxycyclohexyl 4-nitrobenzenesulfonate (93)



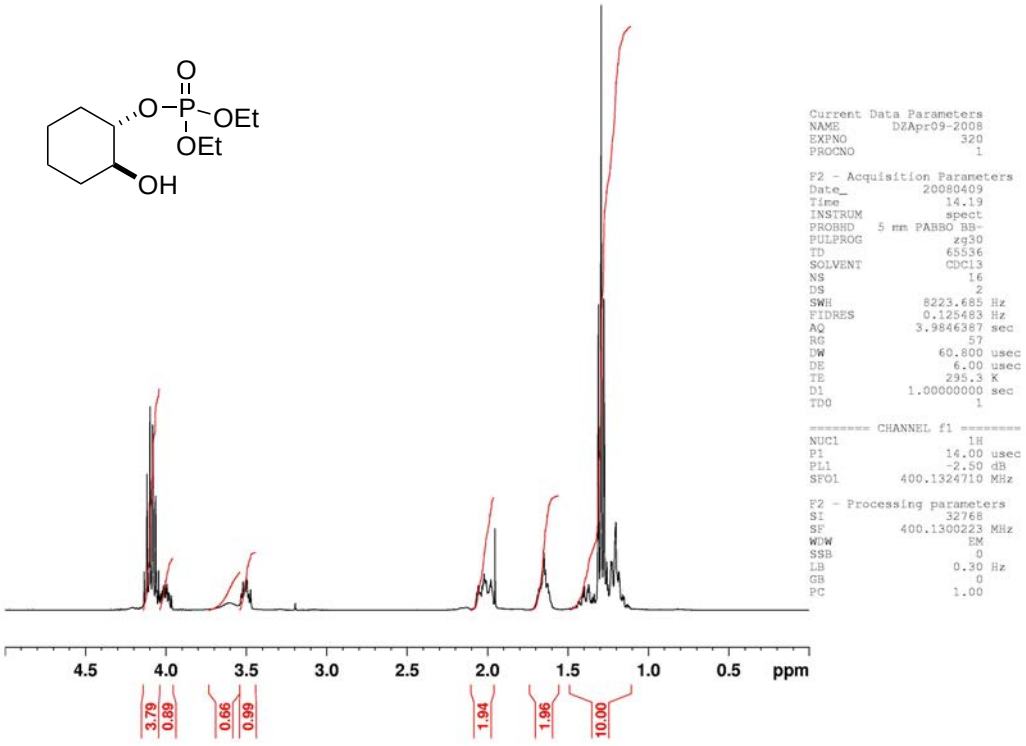


Trans-2-hydroxycyclohexyl diphenyl phosphate (94-Ph):

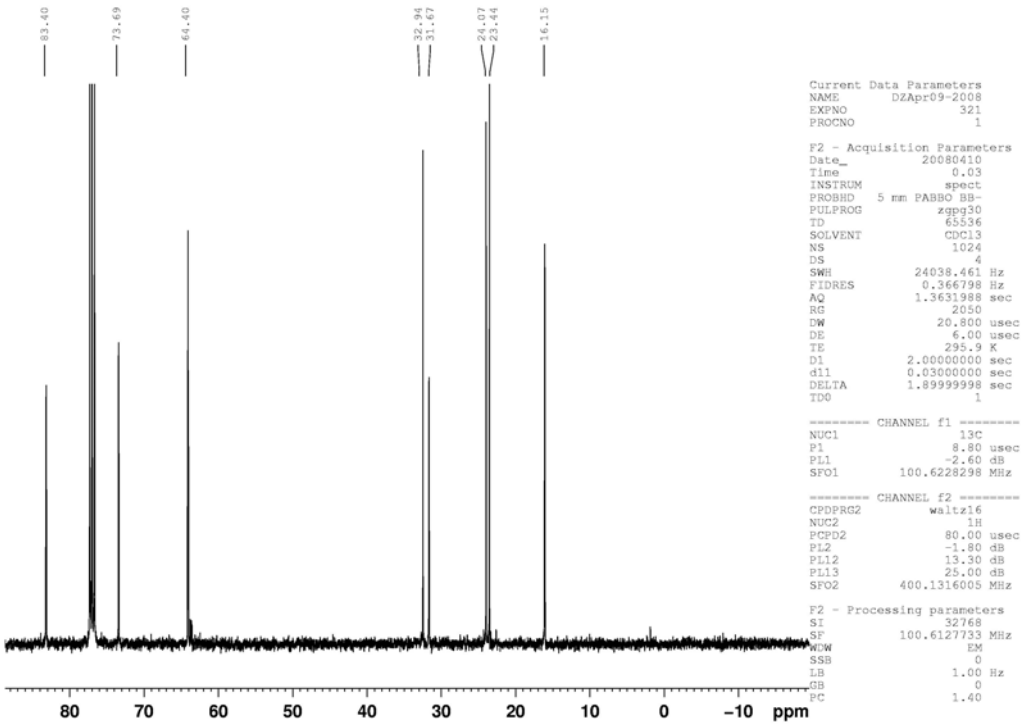




***Trans*-2-hydroxycyclohexyl diethyl phosphate (94-Et):**

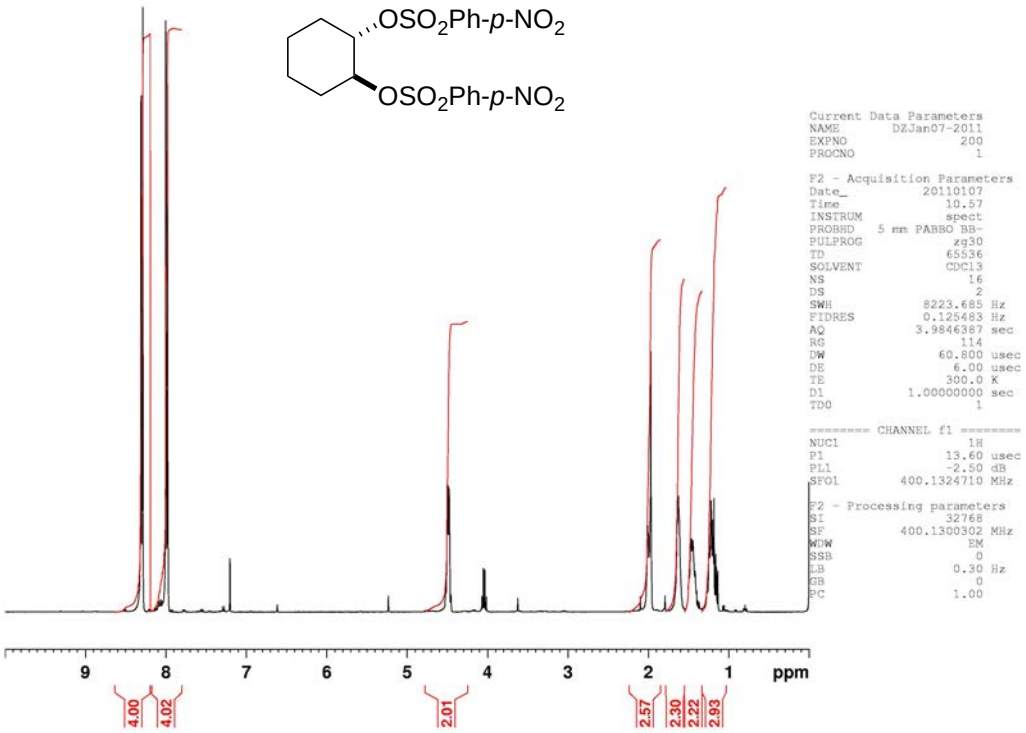


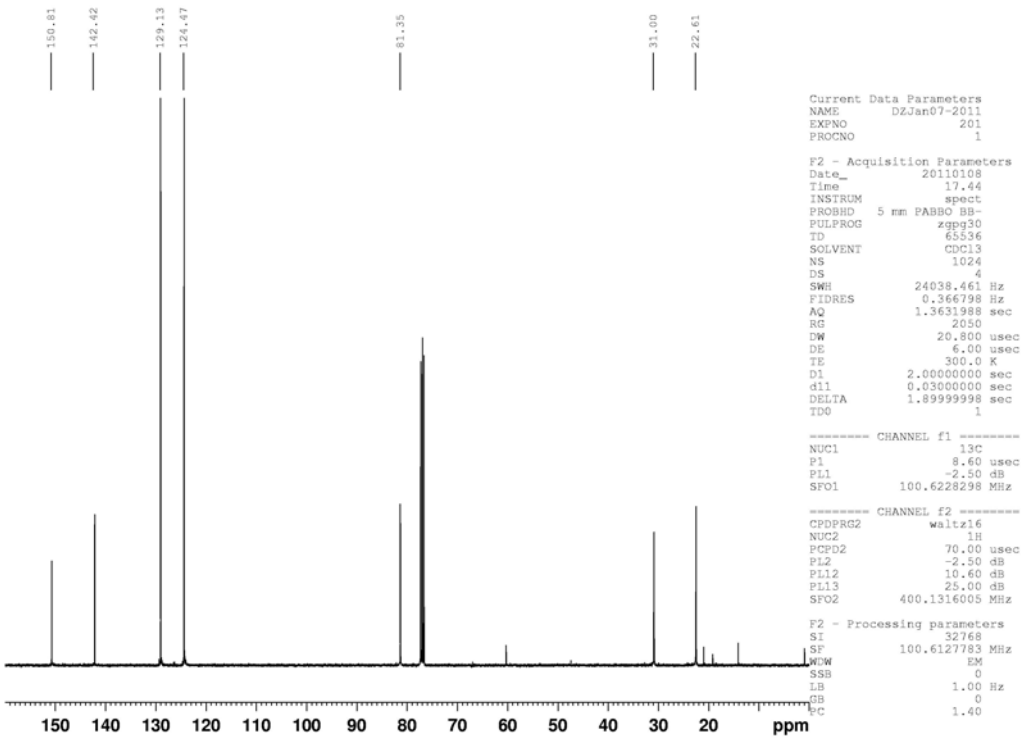

```
Current Data Parameters
NAME          DZApr09-2008
EXPNO                  320
PROCNO                   1

F2 - Acquisition Parameters
Date_           20080409
Time              14.19
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           8223.685 Hz
FIDRES        0.125483 Hz
AQ            3.9846387 sec
RG                  57
DW              60.800 usec
DE               6.00 usec
TE              295.3 K
D1            1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                1H
P1               14.00 usec
PL1              -2.50 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI               32768
SF          400.1300223 MHz
WDW                 EM
SSB                  0
LB              0.30 Hz
GB                   0
PC                1.00
```



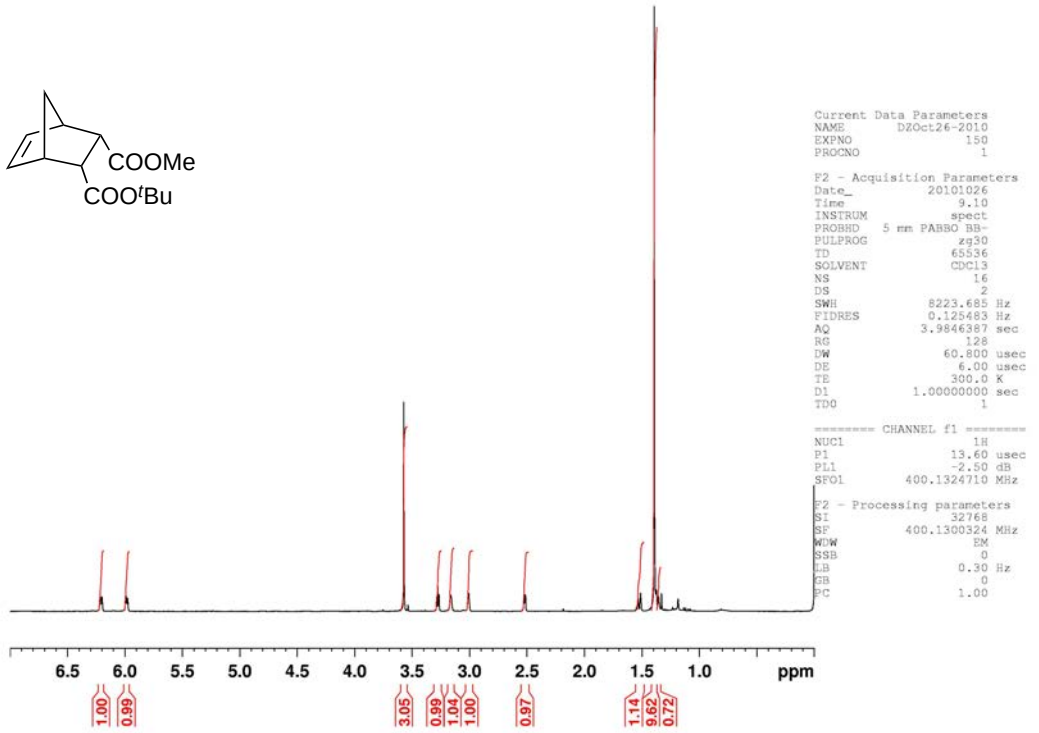

```
Current Data Parameters
NAME          DZApr09-2008
EXPNO                  321
PROCNO                   1

F2 - Acquisition Parameters
Date_           20080410
Time               0.03
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                1024
DS                   4
SWH          24038.461 Hz
FIDRES        0.366798 Hz
AQ            1.3631988 sec
RG                2050
DW              20.800 usec
DE               6.00 usec
TE              295.9 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                13C
P1                8.80 usec
PL1              -2.60 dB
SFO1        100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2            80.00 usec
PL2              -1.80 dB
PL12             13.30 dB
PL13             25.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI               32768
SF          100.6127733 MHz
WDW                 EM
SSB                  0
LB              1.00 Hz
GB                   0
PC                1.40
```

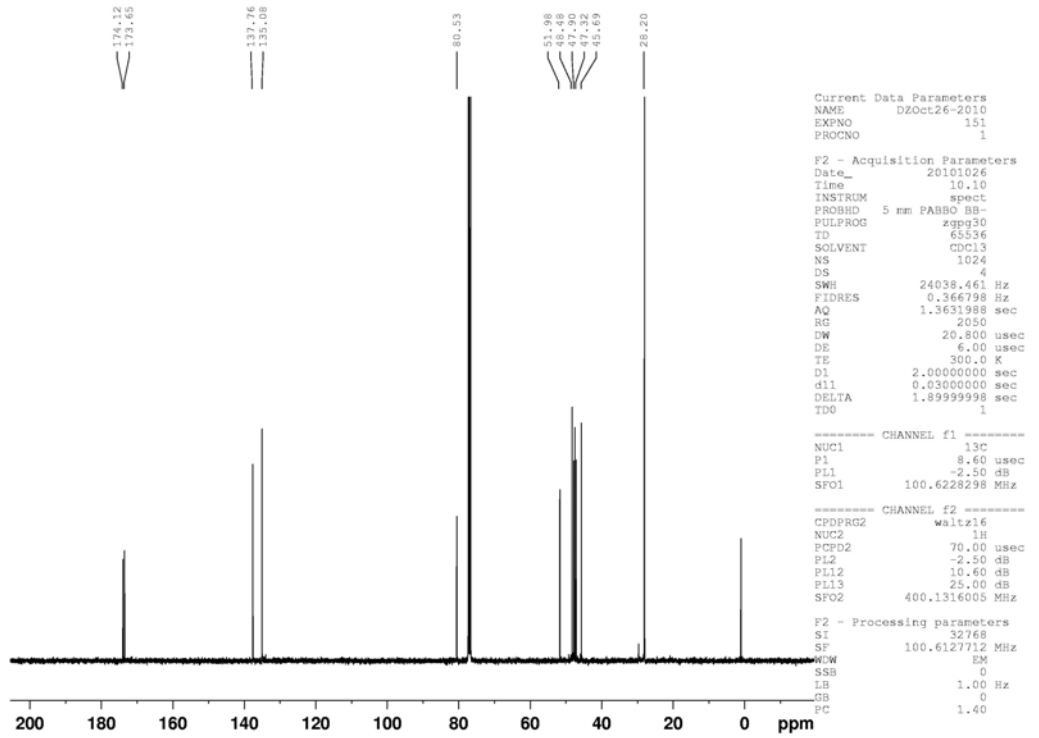
Trans-cyclohexane-1,2-diyl bis(4-nitrobenzenesulfonate) (122)



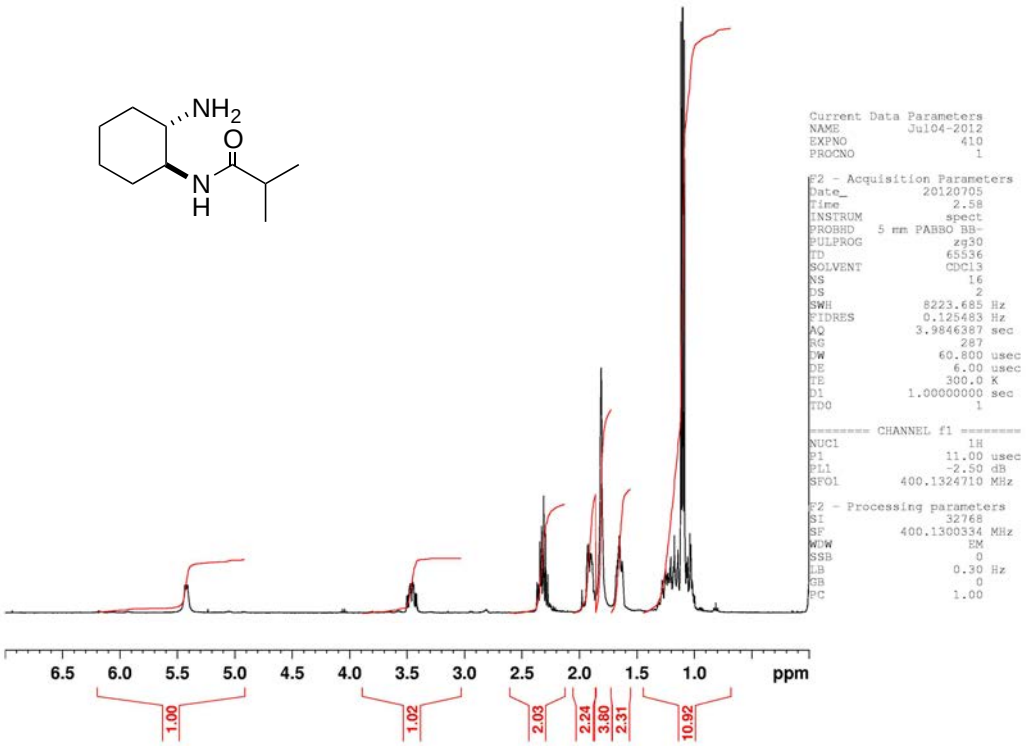


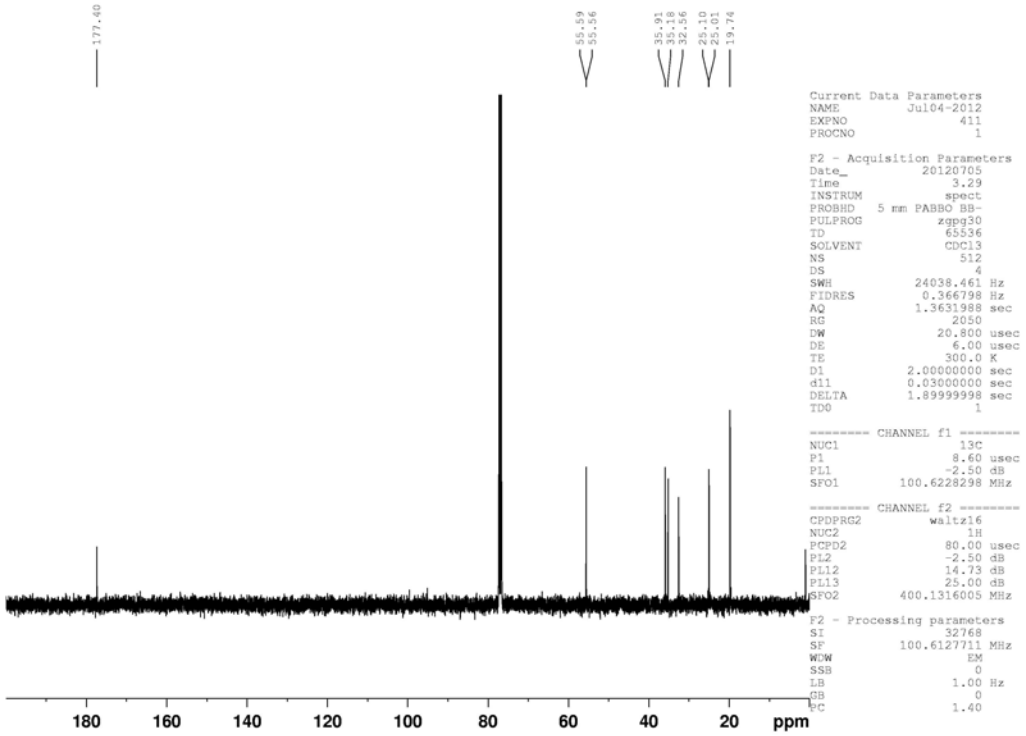
2-*Tert*-butyl 3-methyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (129)



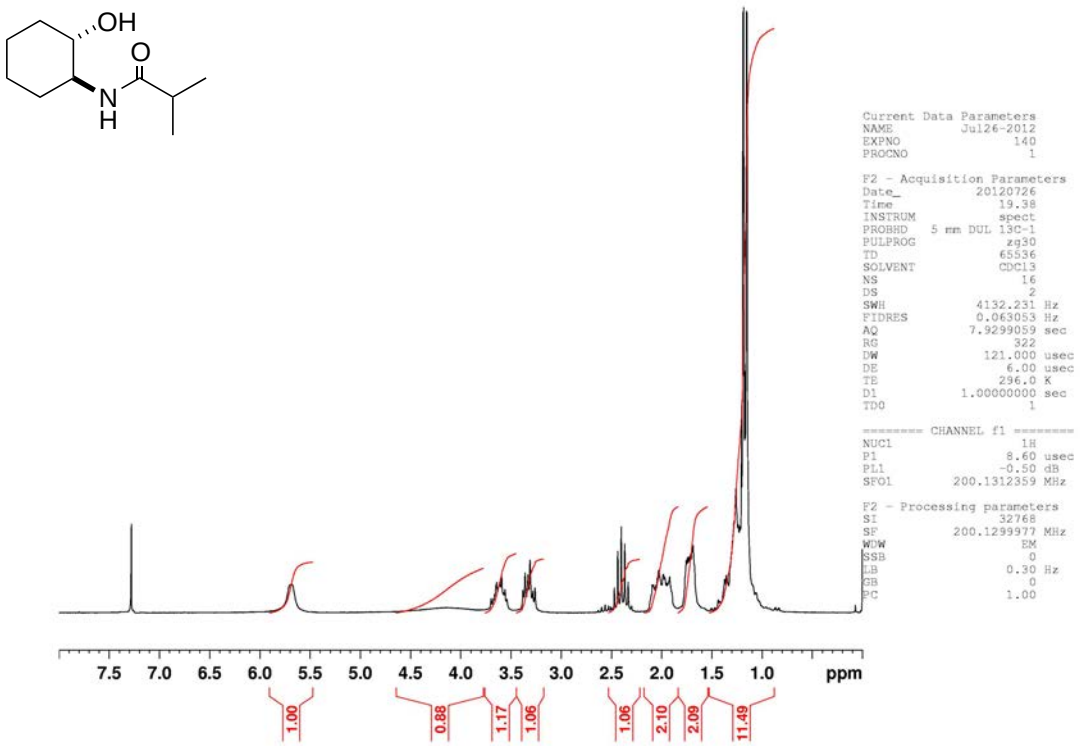


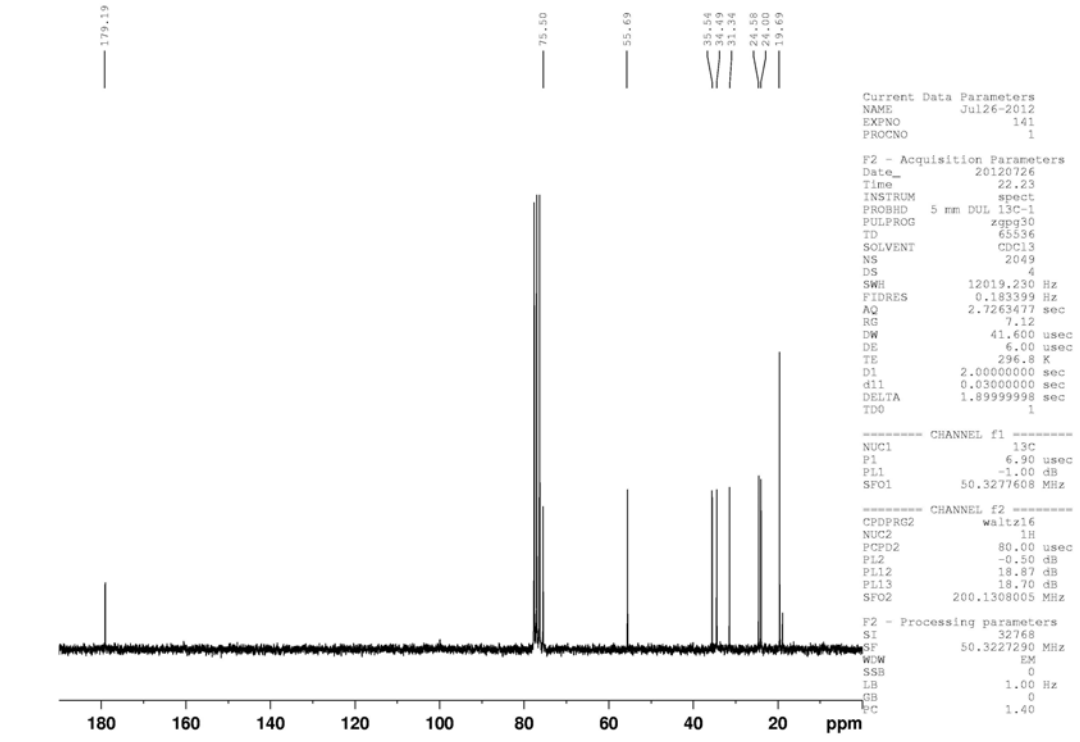
Trans-N-(2-aminocyclohexyl)-isobutyramide (141)



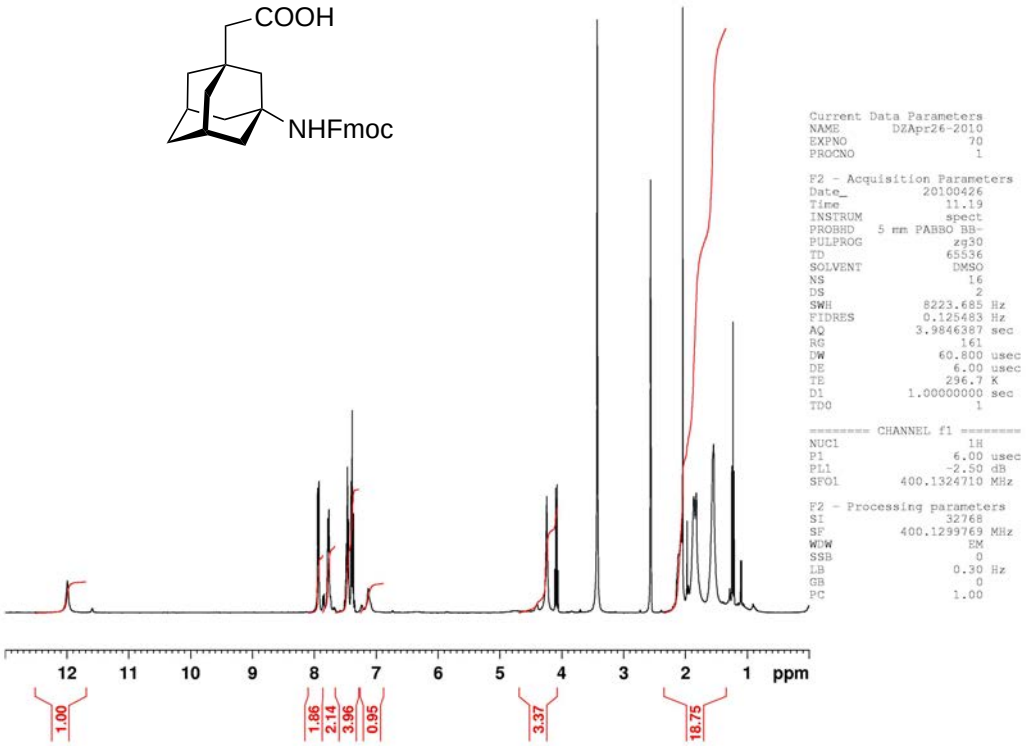


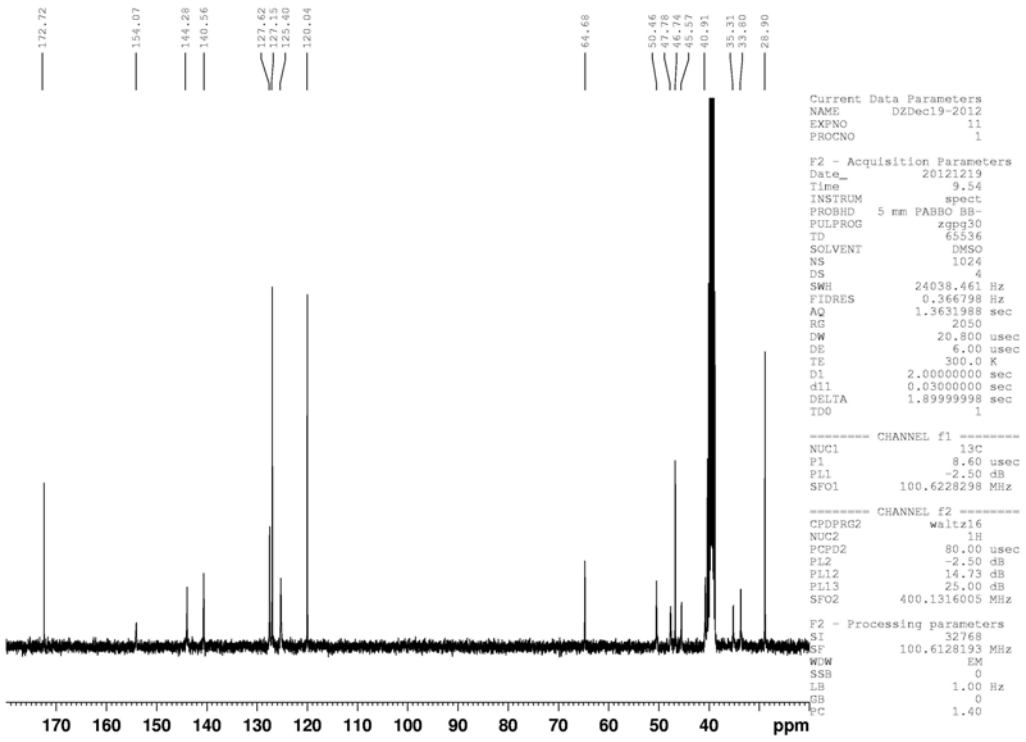
Trans-N-(2-hydroxycyclohexyl)-isobutyramide (144)



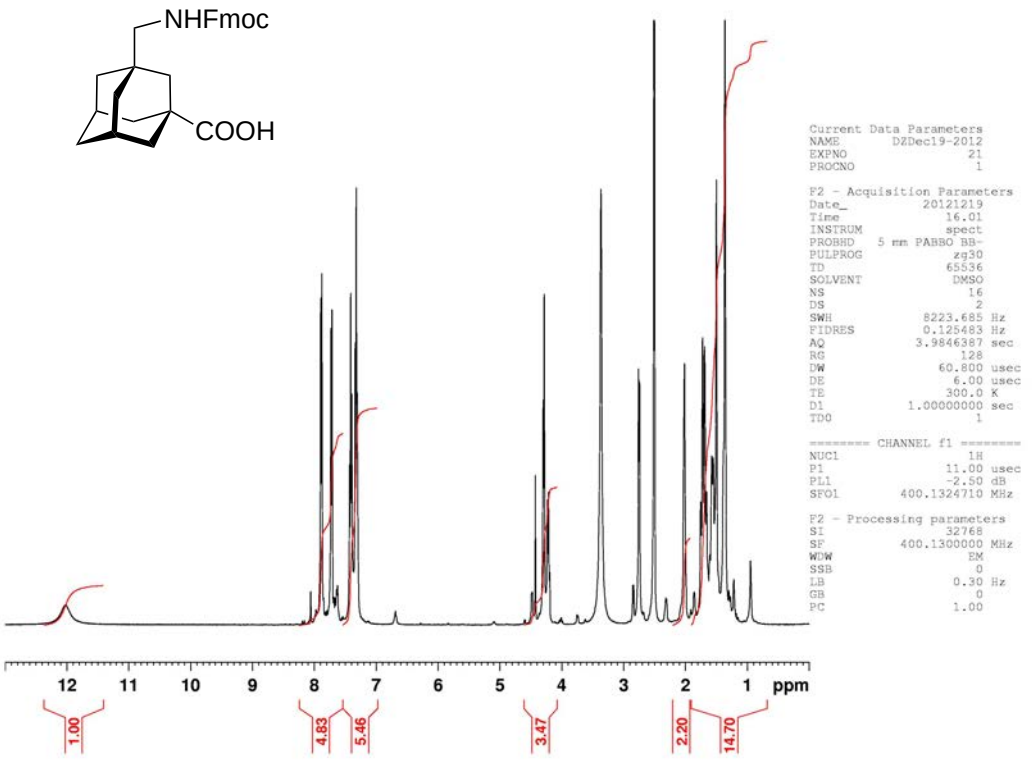


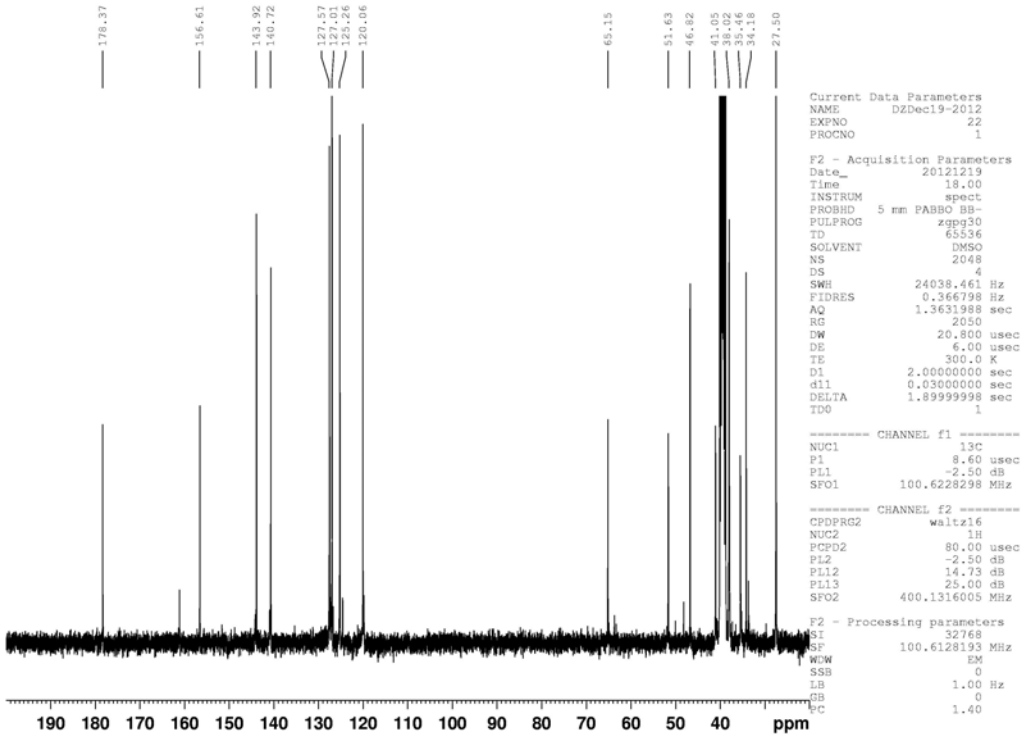
1-(9-Fluorenyl)methoxycarbonylaminotricyclo[3.3.1.1$^{3.7}$]decan-3-methylcarboxylic acid (157)



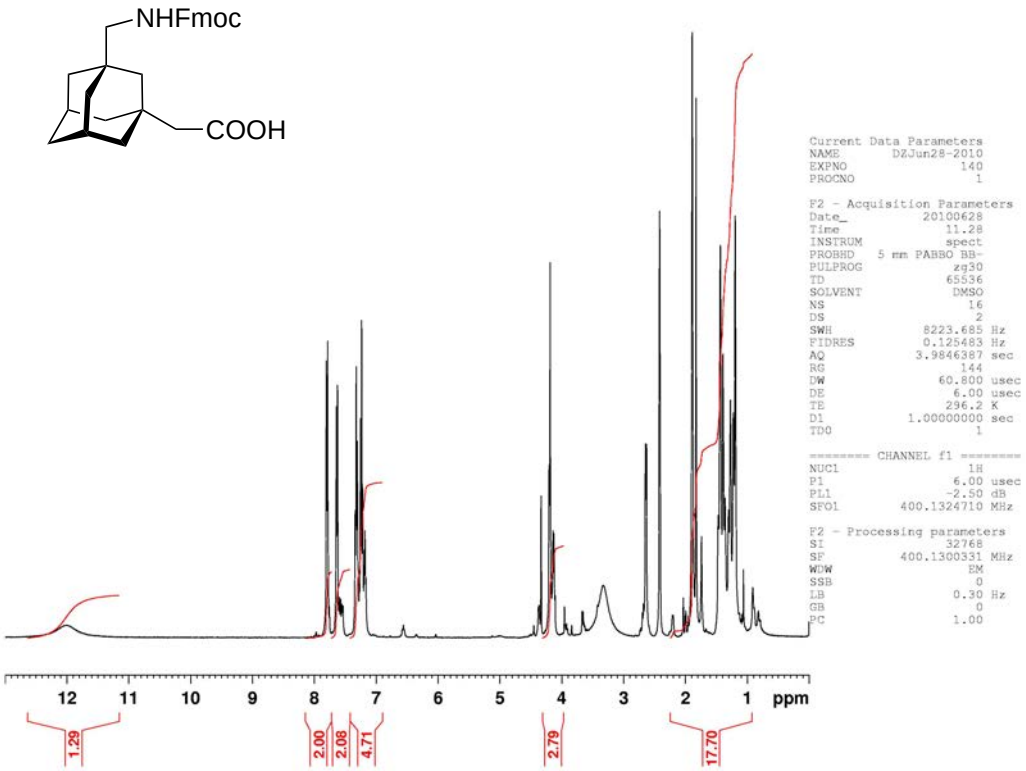


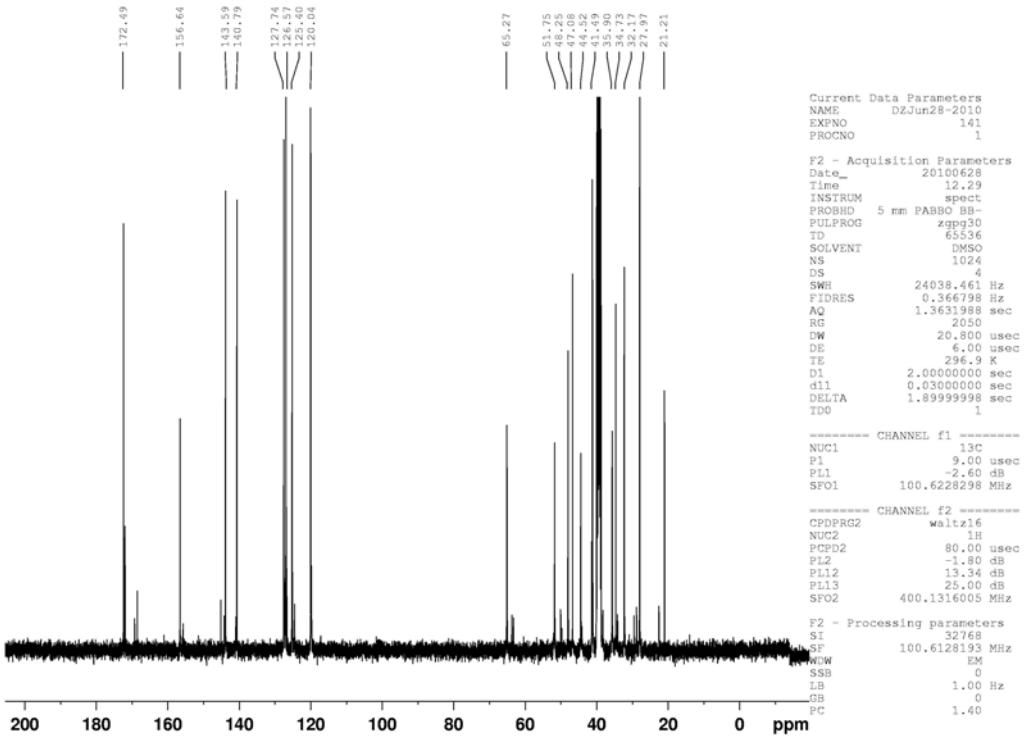
3-(9-Fluorenyl)methoxycarbonylmethylaminotricyclo[3.3.1.1$^{3.7}$]decan-1-carboxylic acid (158)



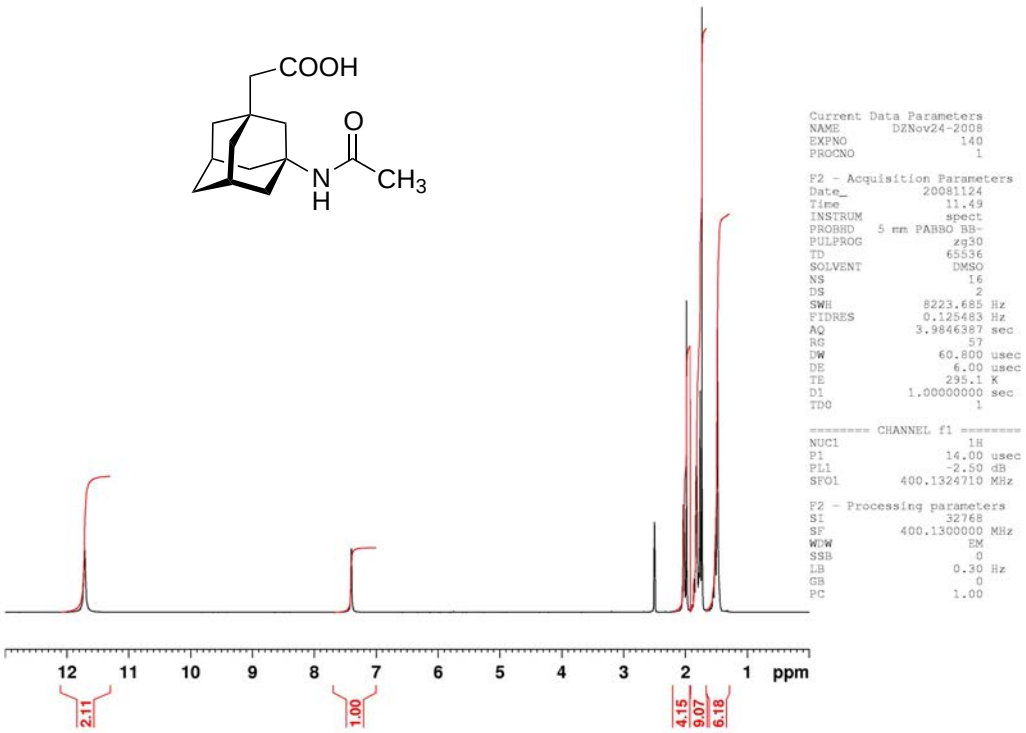


3-(9-Fluorenyl)methoxycarbonylmethyltricyclo[3.3.1.1^{3,7}]decan-1-methylcarboxylic acid (159)

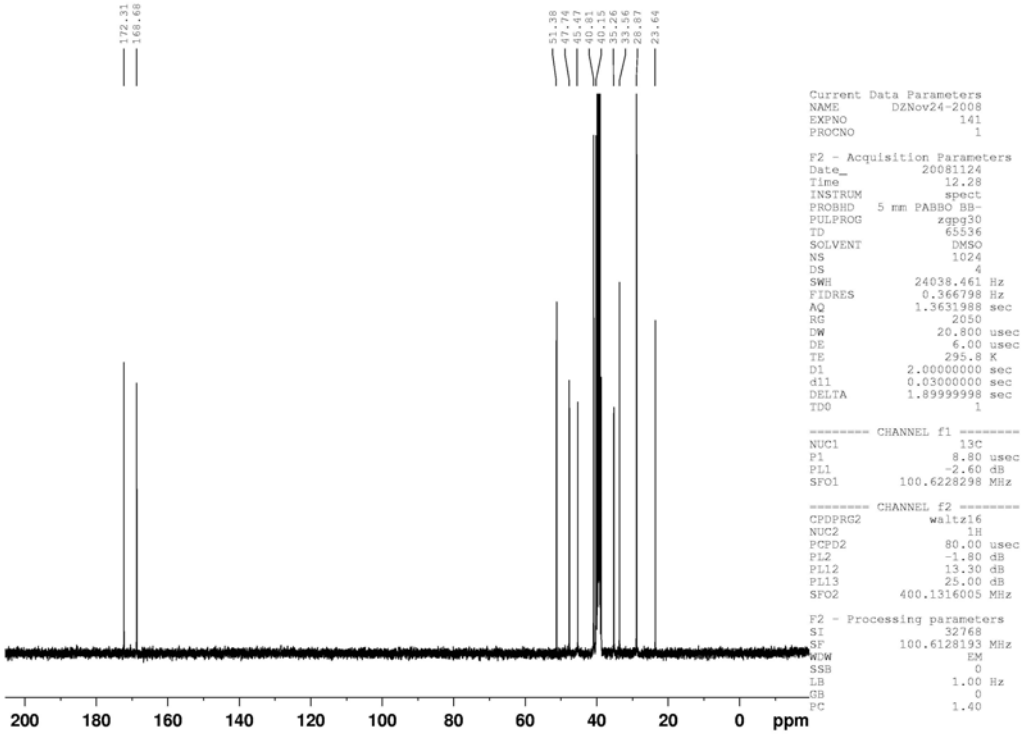




1-Acetamidotricyclo[3.3.1.1^{3,7}]decan-3-methylcarboxylic acid (167)

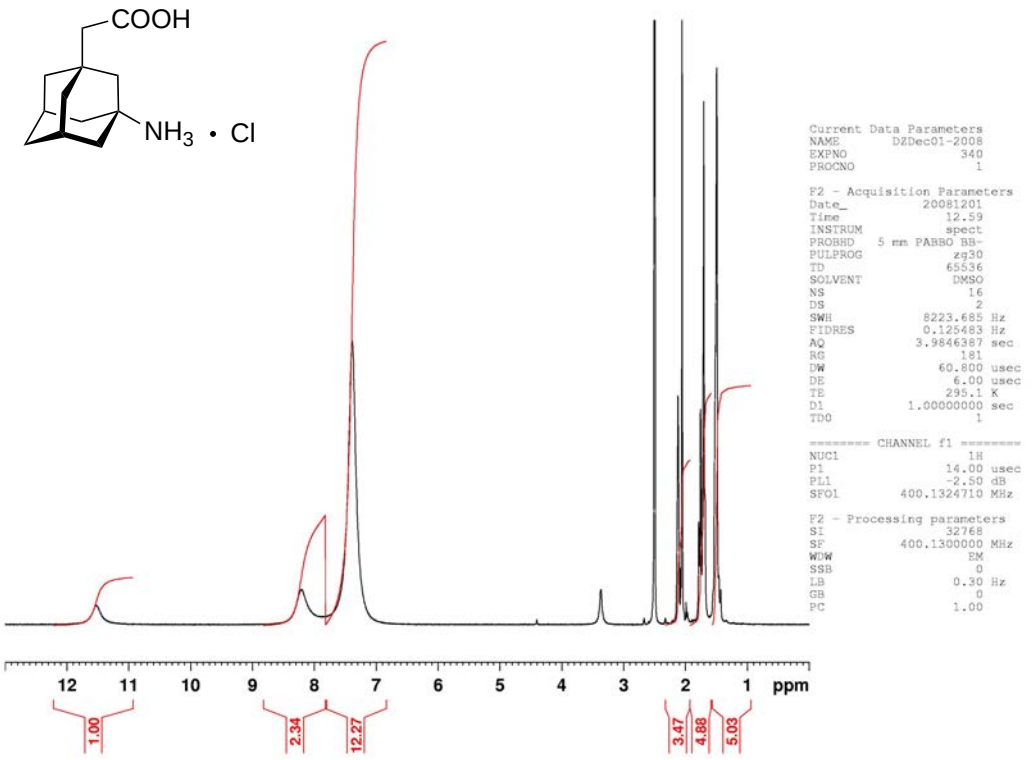


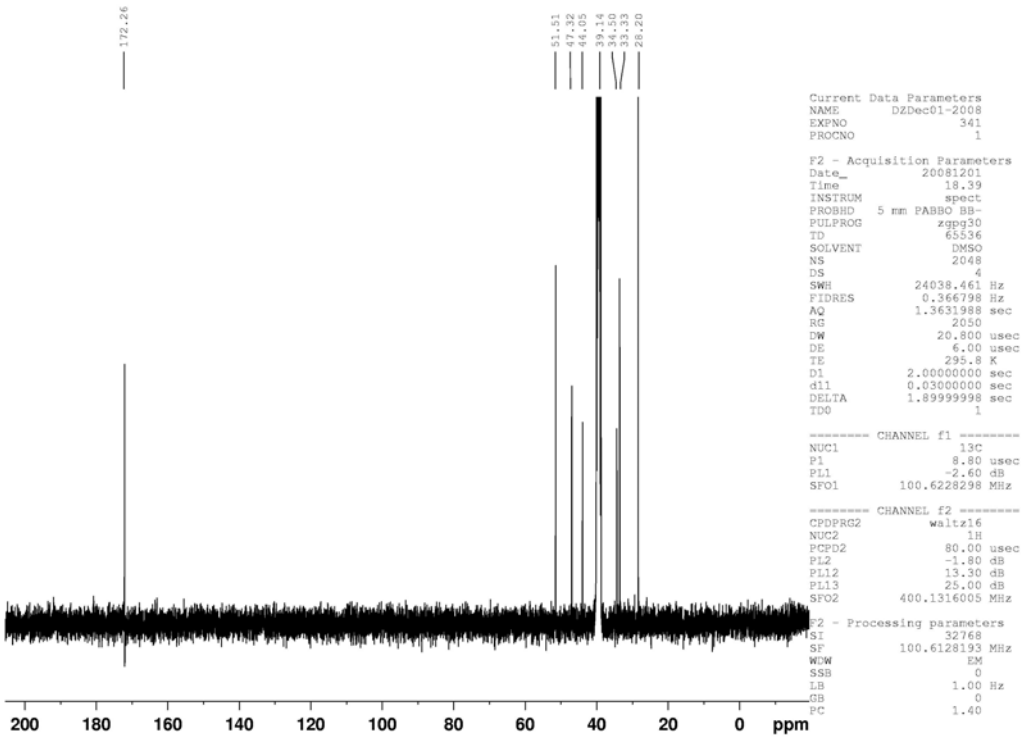

```
Current Data Parameters
NAME                 DZNov24-2008
EXPNO                         140
PROCNO                          1

F2 - Acquisition Parameters
Date_               20081124
Time                   11.49
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                        57
DW                    60.800 usec
DE                     6.00 usec
TE                    295.1 K
D1                  1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     14.00 usec
PL1                    -2.50 dB
SFO1               400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                  400.1300000 MHz
WDW                        EM
SSB                         0
LB                     0.30 Hz
GB                          0
PC                     1.00
```



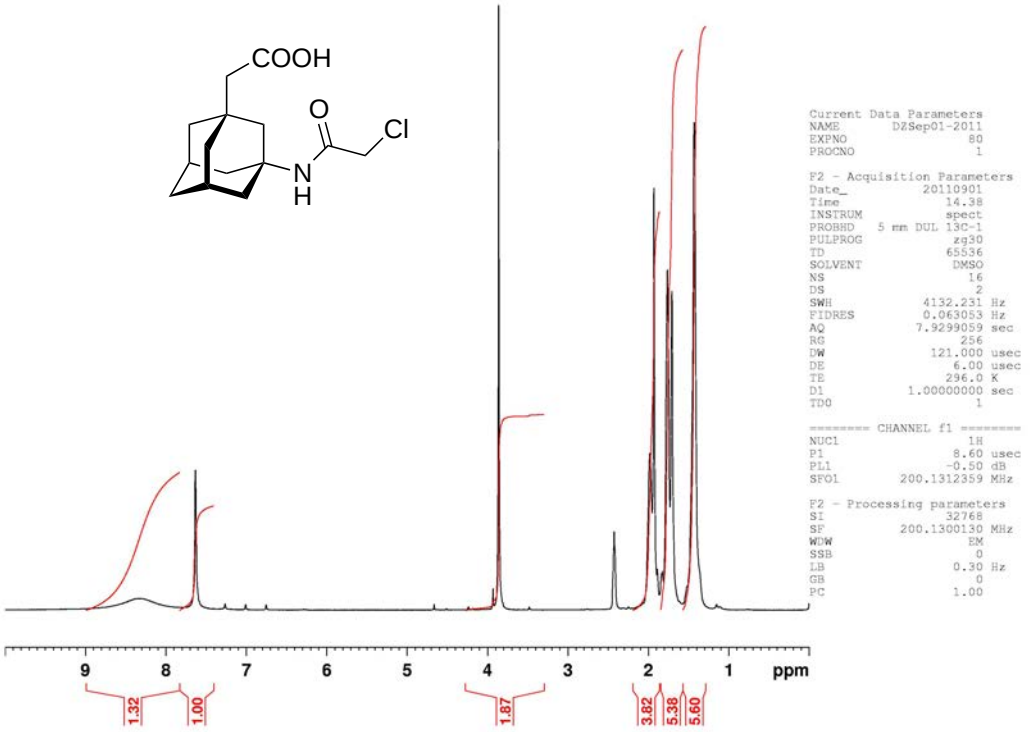

```
Current Data Parameters
NAME                 DZNov24-2008
EXPNO                         141
PROCNO                          1

F2 - Acquisition Parameters
Date_               20081124
Time                   12.28
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                 zgpg30
TD                     65536
SOLVENT                 DMSO
NS                       1024
DS                          4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                       2050
DW                    20.800 usec
DE                     6.00 usec
TE                    295.8 K
D1                  2.00000000 sec
d11                 0.03000000 sec
DELTA               1.89999998 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                      8.80 usec
PL1                    -2.60 dB
SFO1               100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                  80.00 usec
PL2                    -1.80 dB
PL12                   13.30 dB
PL13                   25.00 dB
SFO2               400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                  100.6128193 MHz
WDW                        EM
SSB                         0
LB                     1.00 Hz
GB                          0
PC                     1.40
```

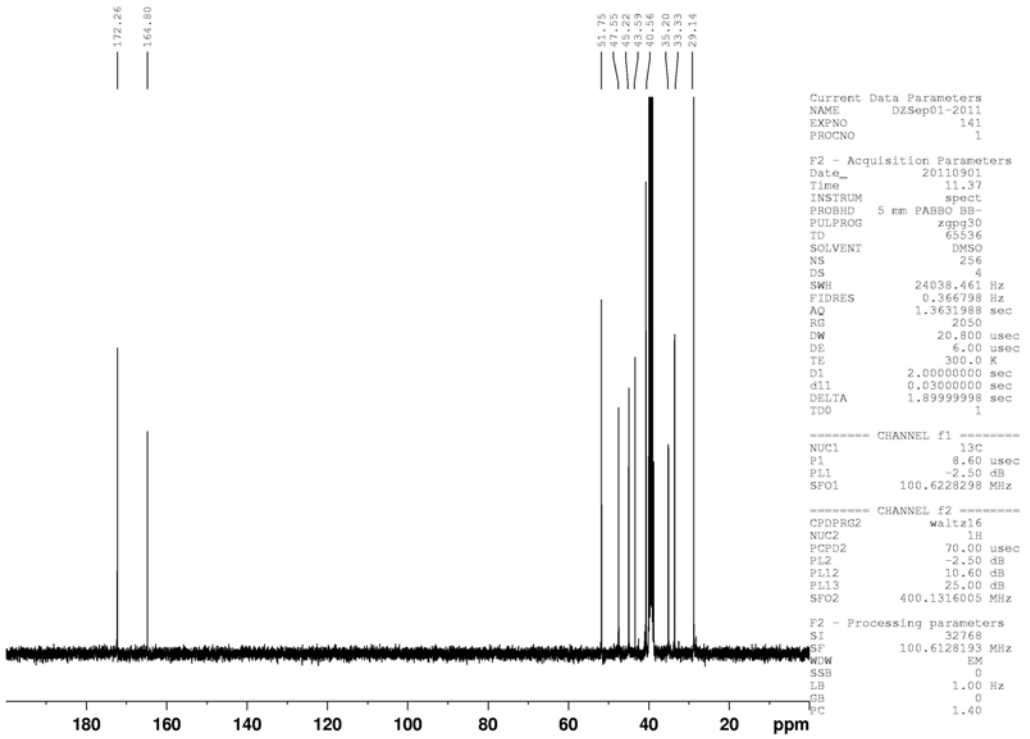
1-Aminotricyclo[3.3.1.1^{3,7}]decan-3-methylcarboxylic acid hydrochloride (168)



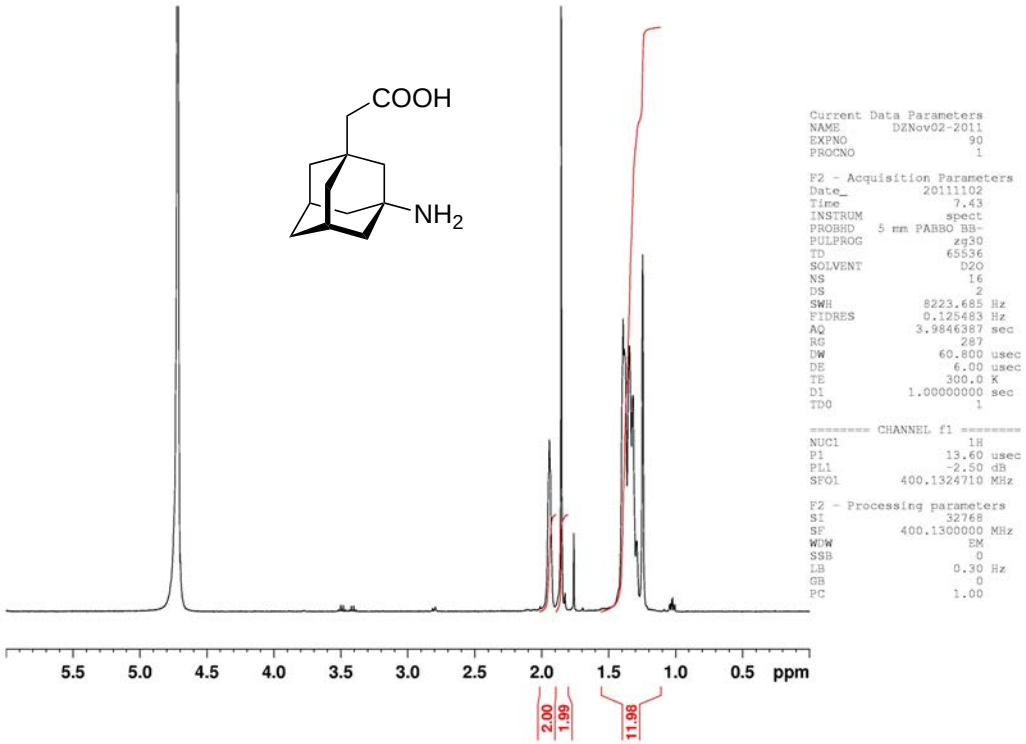


1-Chloroacetamidotricyclo[3.3.1.1$^{3.7}$]decan-3-methylcarboxylic acid (176)

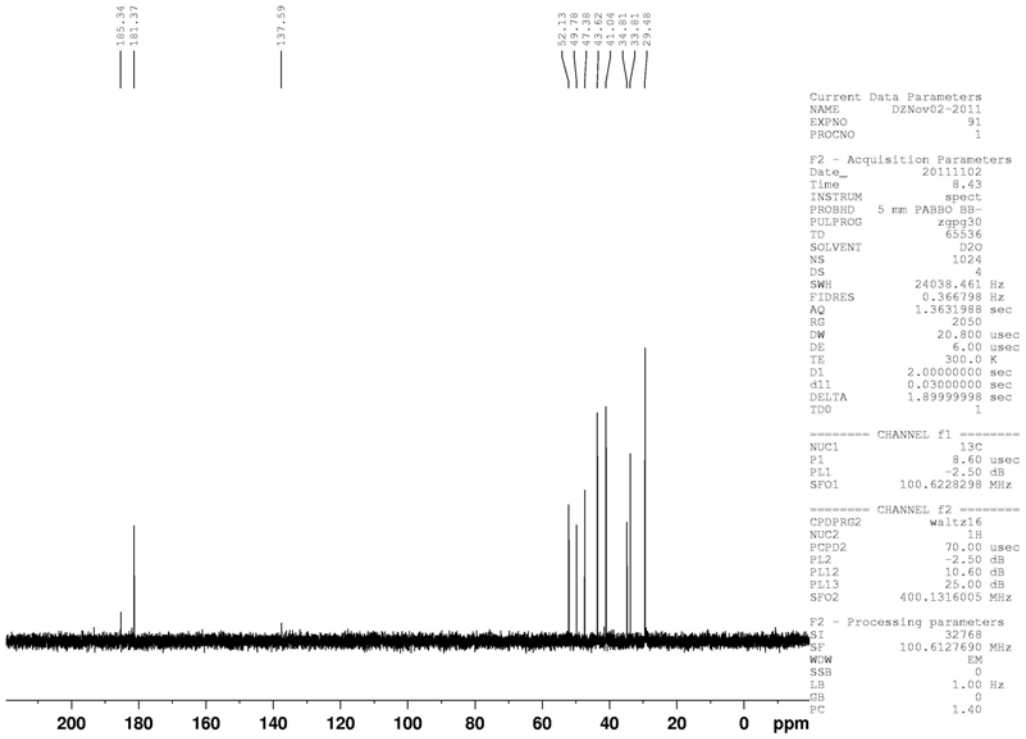




1-Aminotricyclo[3.3.1.1^{3,7}]decan-3-methylcarboxylic acid (177)

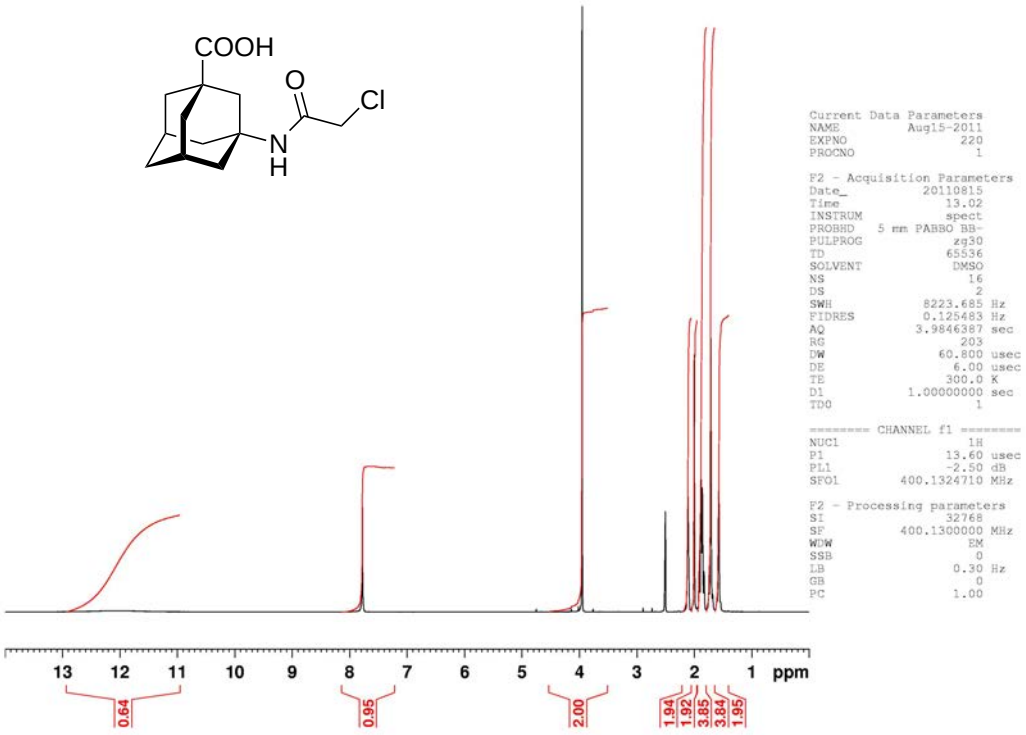



```
Current Data Parameters
NAME          DZNov02-2011
EXPNO                   90
PROCNO                   1

F2 - Acquisition Parameters
Date_              20111102
Time                   7.43
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT                D2O
NS                      16
DS                       2
SWH               8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9846387 sec
RG                     287
DW                  60.800 usec
DE                   6.00 usec
TE                  300.0 K
D1                1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   13.60 usec
PL1                  -2.50 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                   32768
SF              400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```




```
Current Data Parameters
NAME          DZNov02-2011
EXPNO                   91
PROCNO                   1

F2 - Acquisition Parameters
Date_              20111102
Time                   8.43
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT                D2O
NS                    1024
DS                       4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631988 sec
RG                    2050
DW                  20.800 usec
DE                   6.00 usec
TE                  300.0 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    8.60 usec
PL1                  -2.50 dB
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2                70.00 usec
PL2                  -2.50 dB
PL12                 10.60 dB
PL13                 25.00 dB
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF              100.6127690 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

3-Chloroacetamidotricyclo[3.3.1.1$^{3.7}$]decan-1-carboxylic acid (179)




```
Current Data Parameters
NAME          Aug15-2011
EXPNO                220
PROCNO                 1

F2 - Acquisition Parameters
Date_           20110815
Time               13.02
INSTRUM            spect
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PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                   203
DW                60.800 usec
DE                 6.00 usec
TE                300.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.60 usec
PL1                -2.50 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF            400.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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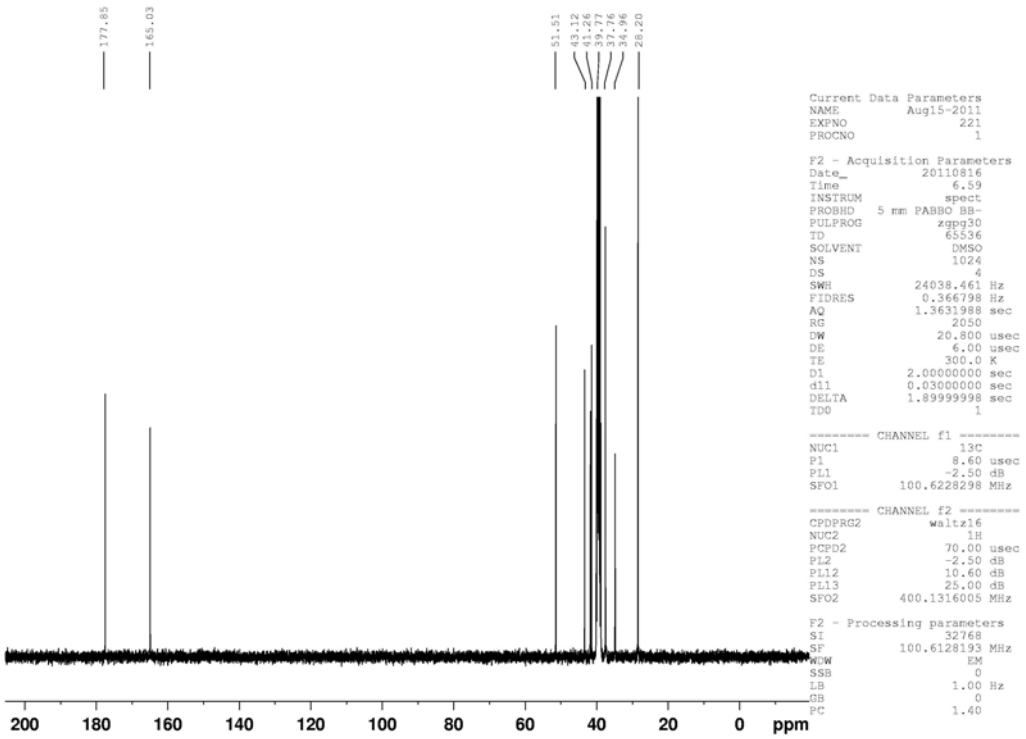


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Current Data Parameters
NAME          Aug15-2011
EXPNO                221
PROCNO                 1

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PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                  1024
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                  2050
DW                20.800 usec
DE                 6.00 usec
TE                300.0 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 8.60 usec
PL1                -2.50 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              70.00 usec
PL2                -2.50 dB
PL12               10.60 dB
PL13               25.00 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
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SF            100.6128193 MHz
WDW                   EM
SSB                    0
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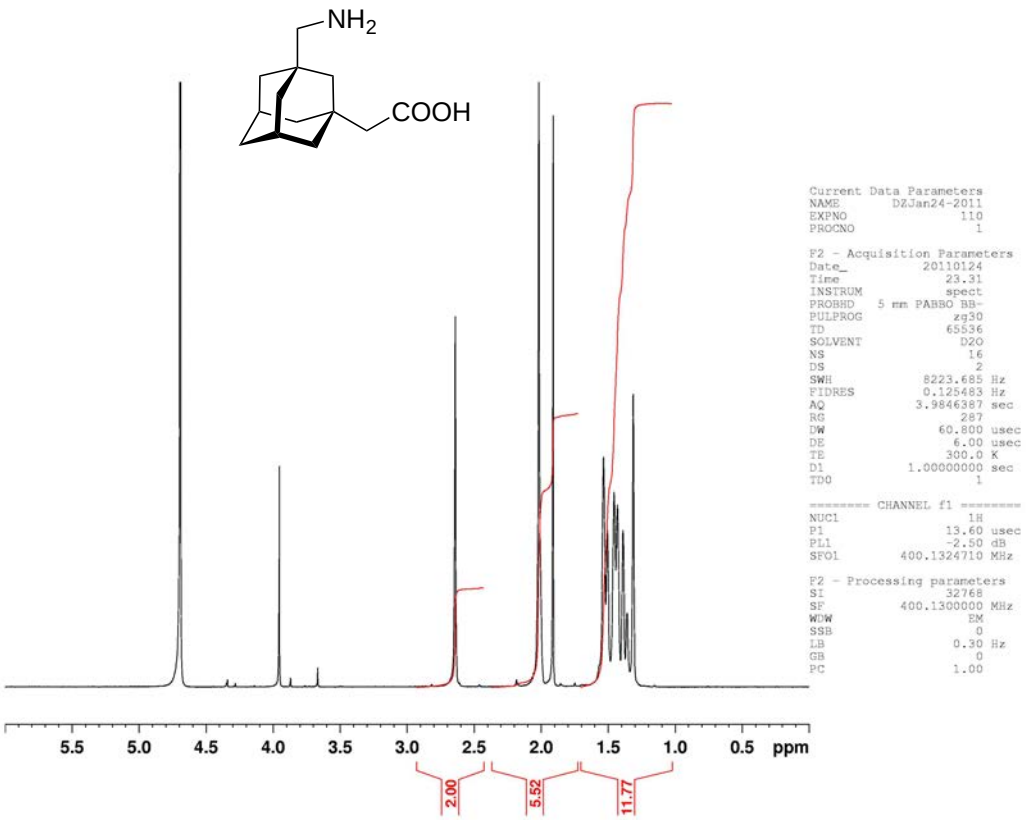
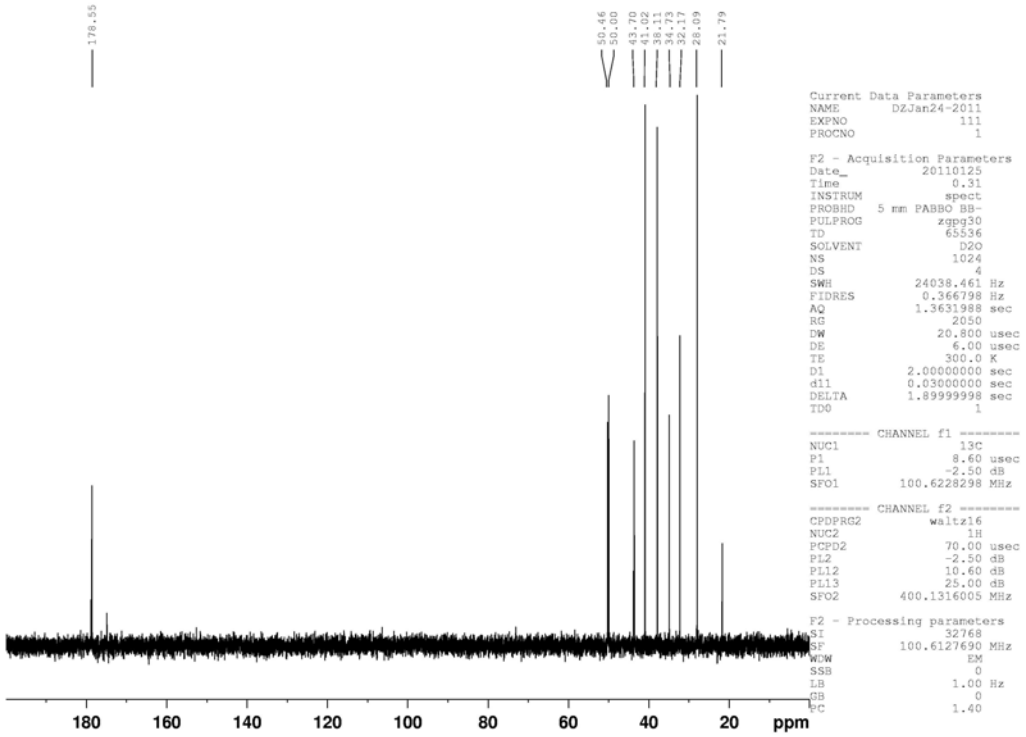
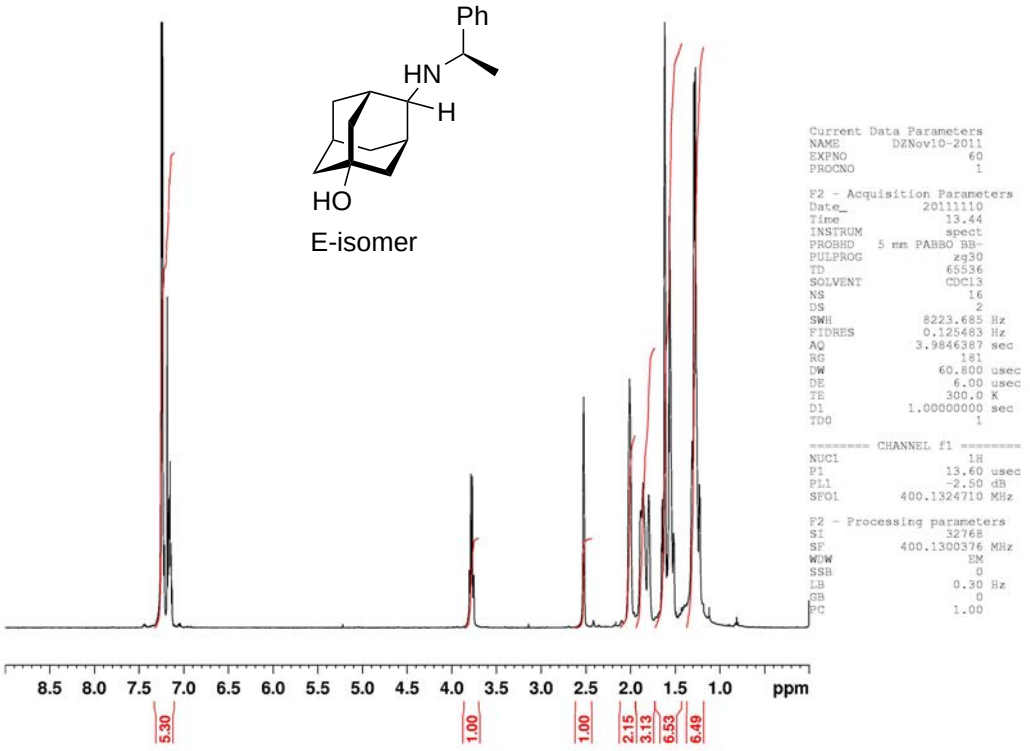
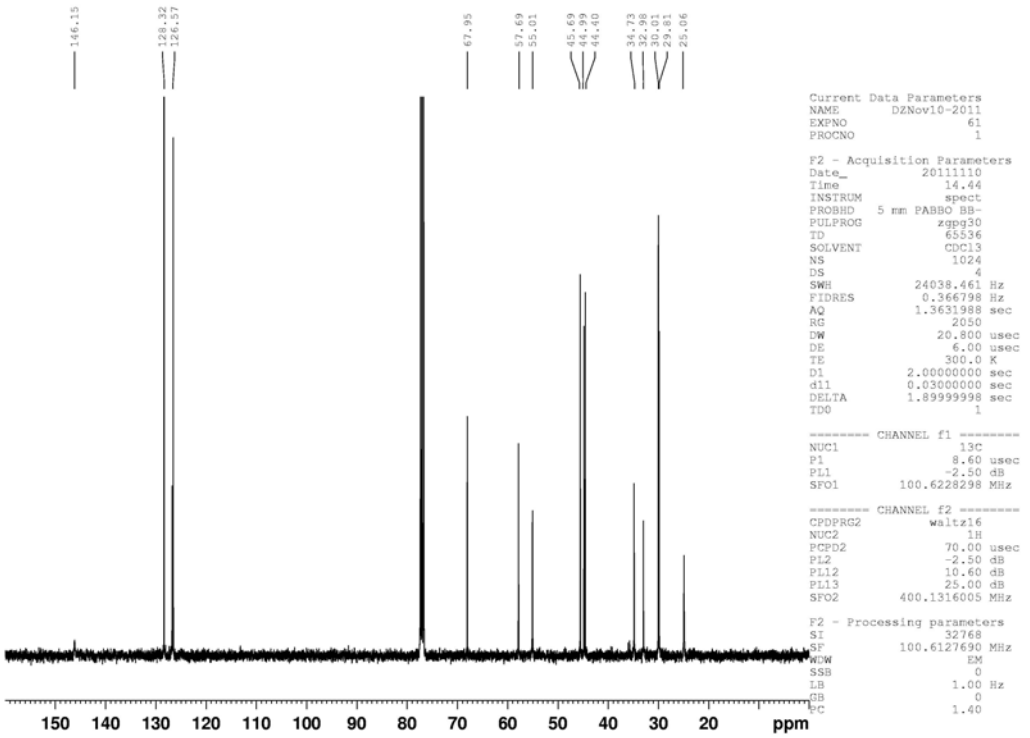
3-Methylaminotricyclo[3.3.1.1^{3,7}]decan-1-methylcarboxylic acid (185)



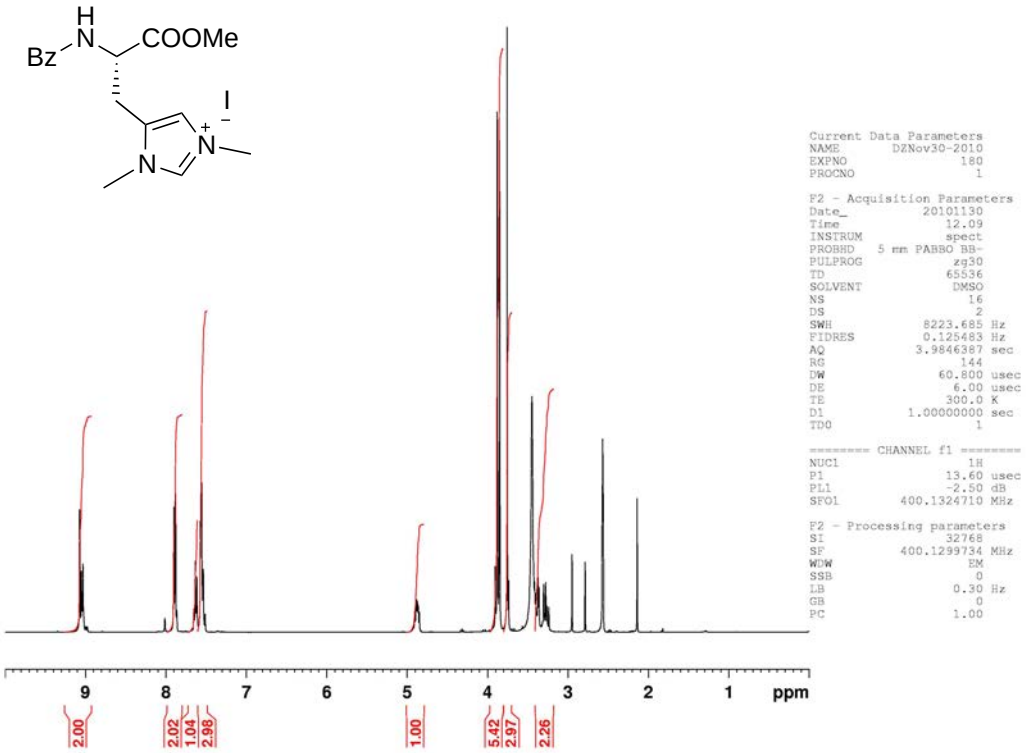


E- 5-S-α-Methylbenzylaminotricyclo[3.3.1.1$^{3.7}$]decane-2-ol (200)





L-Benzoyl-*N,N'*-dimethyl histidine methyl ester iodide (233)

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Current Data Parameters
NAME          DZNov30-2010
EXPNO                  180
PROCNO                   1

F2 - Acquisition Parameters
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Time               12.09
INSTRUM             spect
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PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   16
DS                    2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                  144
DW                60.800 usec
DE                 6.00 usec
TE                300.0 K
D1             1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                13.60 usec
PL1               -2.50 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                32768
SF          400.1299734 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
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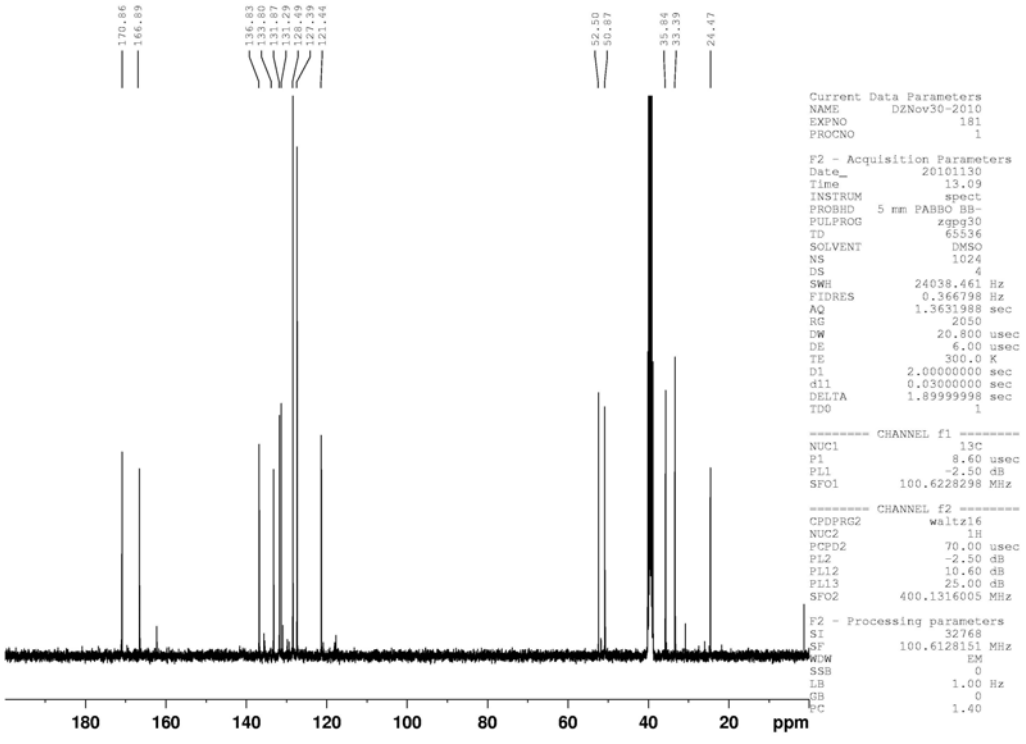


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Current Data Parameters
NAME          DZNov30-2010
EXPNO                  181
PROCNO                   1

F2 - Acquisition Parameters
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Time               13.09
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 1024
DS                    4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3631988 sec
RG                 2050
DW                20.800 usec
DE                 6.00 usec
TE                300.0 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 8.60 usec
PL1               -2.50 dB
SFO1         100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             70.00 usec
PL2               -2.50 dB
PL12              10.60 dB
PL13              25.00 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6128151 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```
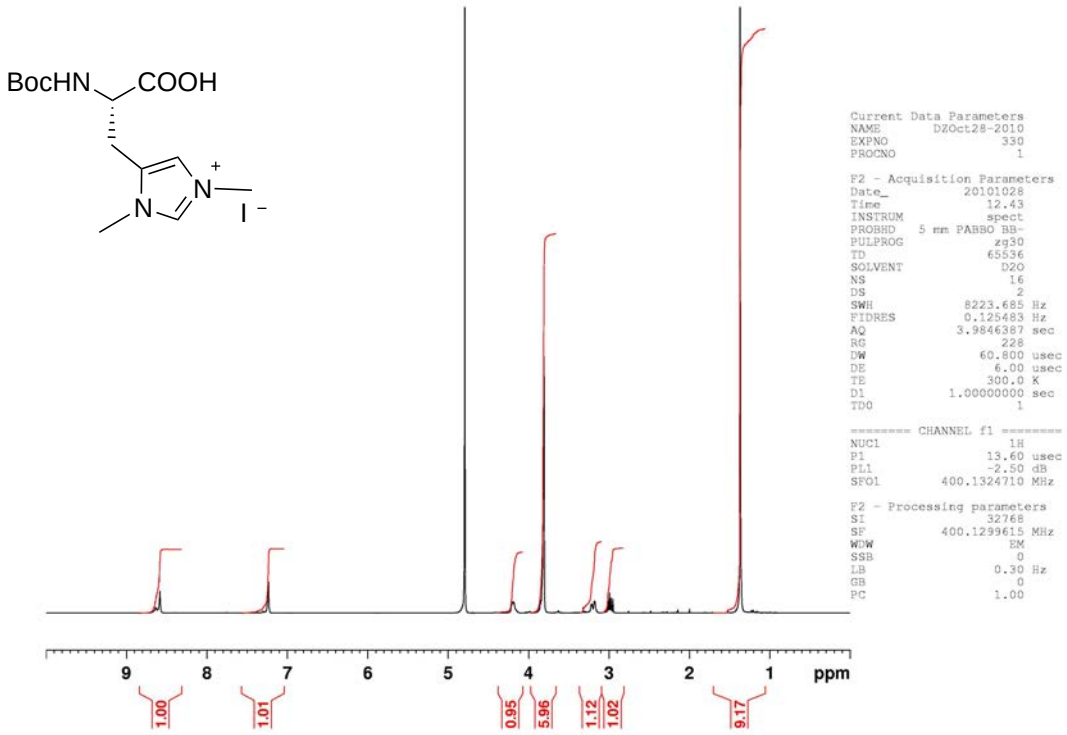
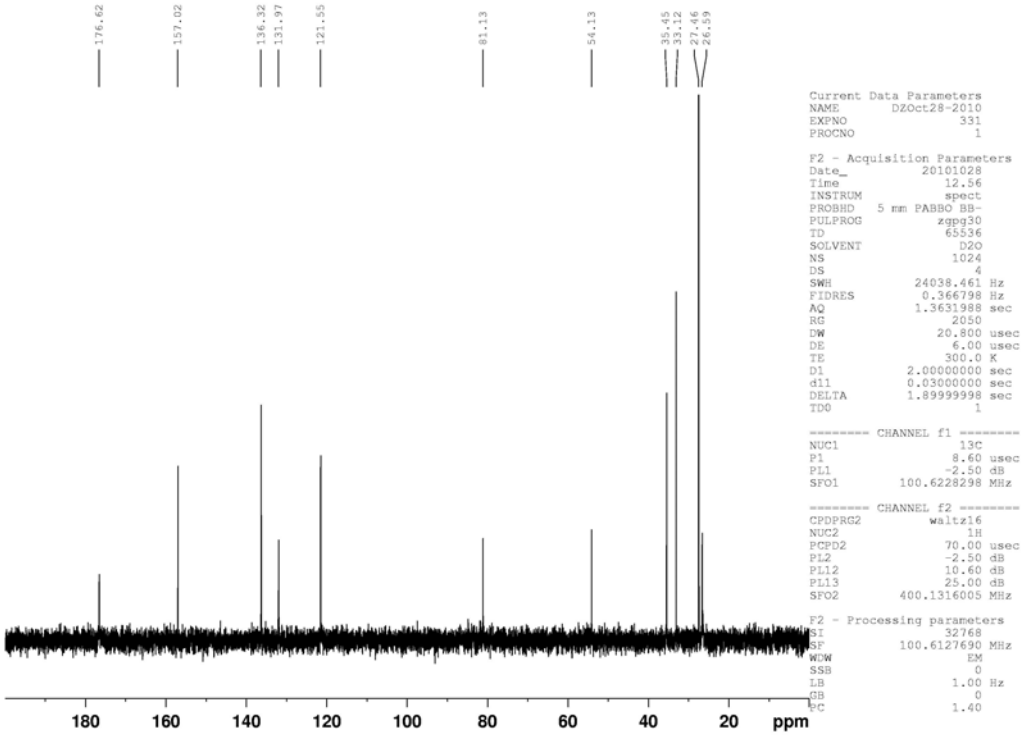
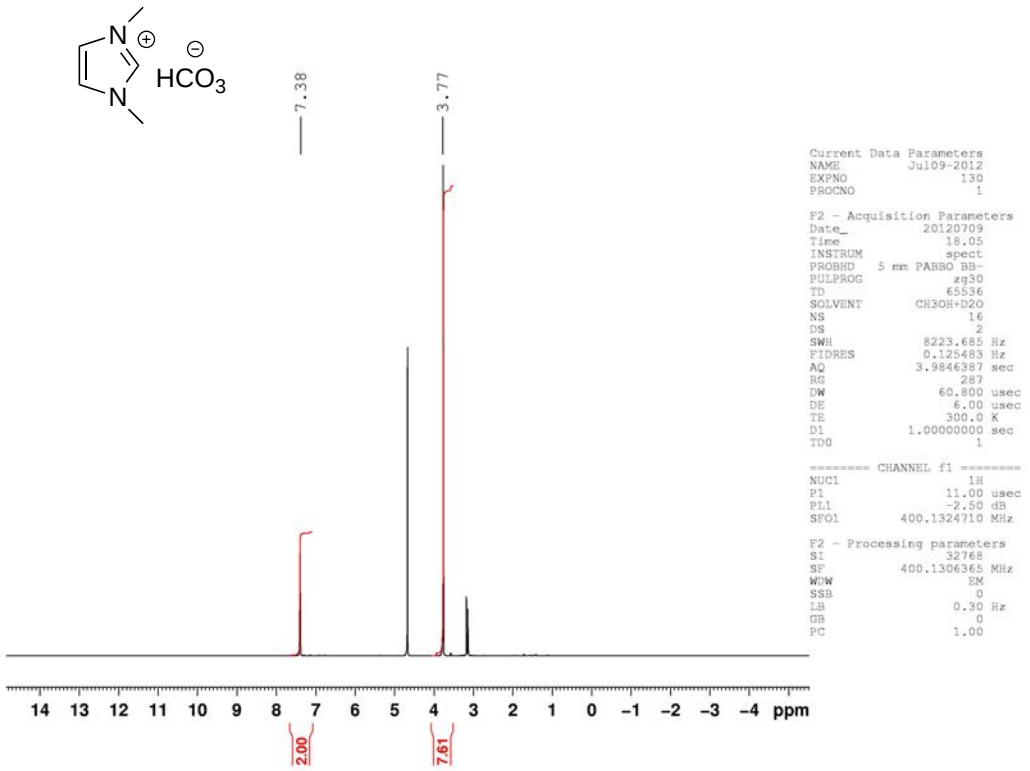
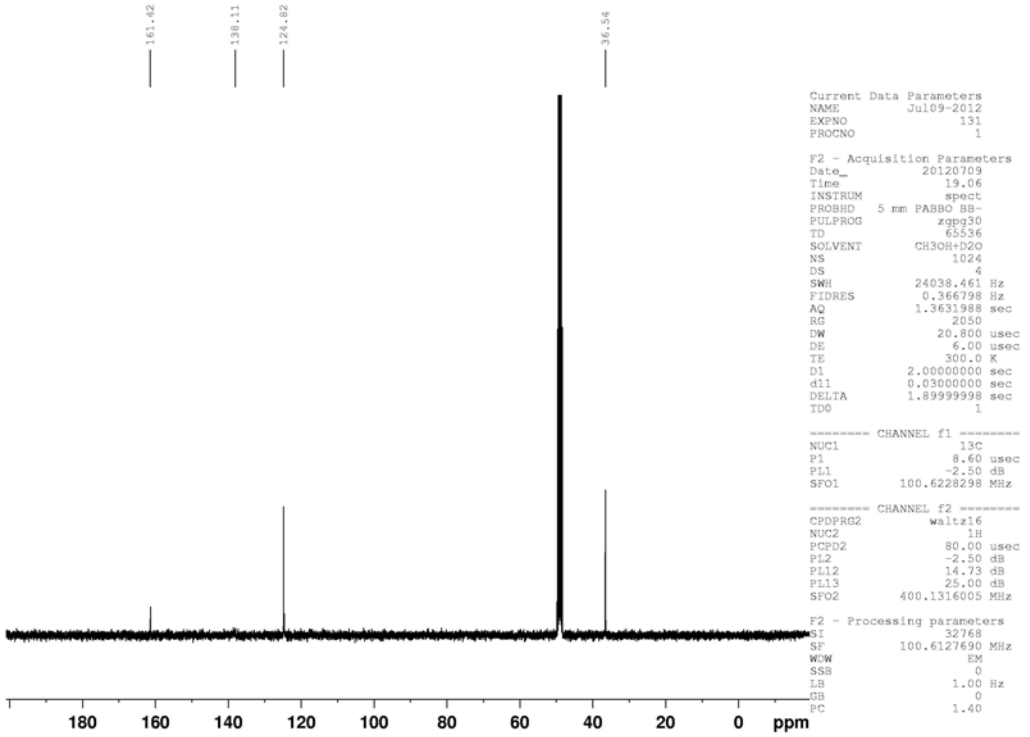

Boc-L-*N,N'*-Dimethylhistidine iodide (234)





N-N'-Dimethylimidazolium Hydrogen Carbonate (245a)





Abbreviations

°C	degree Celcius
Å	Angstrøm
Ar	aromatic
Ac_2O	acetic anhydride
Boc-	*tert*-butoxycarbonyl
BOC-ON	[2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile]
bs	broad singulet
d	doublet
DBU	1,8-diazabicycloundec-7-ene
DCM	dichloromethane
DIC	*N,N'*-diisopropylcarbodiimide
D^iPEA	Diisopropylethylamine
DMAP	*N*-4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EDC · HCl	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
e.g.	for example
eq.	equivalent
ESI	electrospray ionization
Et	ethyl
et al.	et alii (and others)
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FID	flame ionization detector
Fmoc-	9-flourenylmethoxycarbonyl
GC	gas chromatography
h	hour
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
Hz	hertz
KO^tBu	potassium *tert*.-butoxide
Me	methyl
MeI	iodomethane

MeCN	acetonitrile
MeOH	methanol
m	multiplet
mbar	millibar
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
µL	microliter
NaOMe	sodium methanolate
n.d.	not detected
NHC	*N*-heterocyclic carbene
nm	nanometer
NMI	*N*-methylimidazole
NMR	nuclear magnetic resonance
PEMP	pentamethylpiperidine
ppm	parts per million
p-TsOH	p-toluenesulfonic acid
q	quartett
quin	quintett
r.t.	room temperature
s	singlet
sept	septet
sext	sextet
SPPS	solid phase peptide synthesis
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography

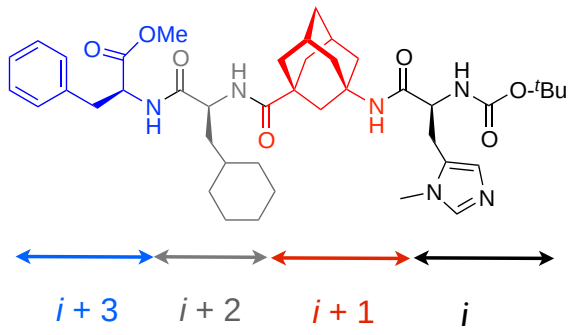
Abreviations of the Amino Acids

Alanine	Ala
β-Alanine	β-Ala
3-Aminobenzoic acid	3-Abz
4-Aminobenzoic acid	4-Abz
2-Aminoisobutyric acid	AiB
Aspartic acid	Asp

Cyclohexylalanine	Cha
Glycine	Gly
τ-benzylhistidine	(τ-Bzl)-His
π-methylhistidine	(π-Me)-His
τ-trityl-histidine	(τ-Trt)-His
Isoleucine	Ile
Leucine	Leu
Phenylalanine	Phe
Phenylglycine	Phg
Proline	Pro
Serine	Ser
Thiazolylalanine	Taz
Tyrosine	Tyr
Valine	Val
γ-Adamantane amino acids	^{A}Gly

Positions of the amino acids in peptides:

Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe



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