Tandem Hydroformylation / Fischer Indolization

– Synthesis of Biologically Relevant Indoles under Hydroformylation Conditions –

Dissertation

zur

Erlangung des akademischen Grades eines
Doktors der Naturwissenschaften
(Dr. rer. nat.)

des Fachbereichs Chemie der Universität Dortmund

vorgelegt von

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aus Iserlohn

Dortmund, 2005

ACKNOWLEDGEMENT

I gratefully thank the following persons:

Prof. Dr. P. Eilbracht	for the chance to work in his research group, the interesting research topic, his support in many situations and the trust in my skills
Prof. Dr. H. Waldmann	for agreeing to act as a co-referee to this thesis
Prof. Dr. P. Eilbracht, PD Dr. B. Plietker, PD Dr. B. Schmidt, Dr. G. Angelovski, Dr. F. Koç, Dr. A. Schmidt, Dr. K. Müller	for many discussions, suggestions and ideas
Dr. G. Angelovski	for his cooperation with "Macrocyclic Bishydrazones as Metal Sensors"
PD Dr. R. Breinbauer, M. Mentel	for their wonderful cooperation with "Tandem Hydroformylation / Fischer Indolization on Solid Phase"
Ms. P. Linnepe (fka: Köhling)	for letting me play in her playground
Prof. Dr. Costisella, Ms. Danzmann, Ms. Marzian, Ms. Vornweg, Ms. Eichhorn, Mr. Hüfner, Mr. Urschel, Mr. Köpke, Ms, A. Bokelmann, Mr. Lausecker.	for collecting analytical data
Ms. A. Biernat, Ms. N. Bisek, Mr. K. Fischer, Mr. J. Liebich and Mr. N.M. Neisius (I really appreciated your support and without your commitment I would not be able to present many results.)	for supporting me as a lab student
Ms. A. Schick and Mr. O. Gerbersmann	for supporting me as research apprentices
Ms. R. Lawniczek	for supporting me as a trainee lab assistant
Ms. S. Lessing, Ms. S. Kuhl, Dr. Albert, Dr. Hillgärtner	for administrative support
Ms. M. Rak	for proof-reading this thesis
My lovely girlfriend Ariane	for sweetening my life in the past 18 months. (I'm looking forward to the following years!)
„The Rosis"	for supporting me in difficult situations and letting me be part of their family

In memoriam:

HEIDI SCHMIDT († 2003)

HANS-WERNER SCHMIDT († 1995)

To my brother for his courage and his never ending support

GENERAL COMMENTS

The following work has been done in the period from August 2001 until July 2005 at the Faculty of Chemistry, University of Dortmund, under the supervision of Prof. Dr. Peter Eilbracht.

Abbreviations in this thesis are used according to the recommendations of IUPAC and IUBMB. They are defined at their first appearance in the text, except common abbreviations such NMR, HPLC or THF.

The results presented in this thesis are already published or will be published as follows:

Ø Chapter 2 "*Synthesis of Primary and Secondary Tryptamines*"

- Köhling, P.; Schmidt, A.M.; Eilbracht, P.; *Org. Lett .* **2003**, *5*, 3213-3216.

- Schmidt A.M.; Eilbracht, P.; *Org. Biomol. Chem.* **2005**, *3*, 2333-2343.

Ø Chapter 3:"*Synthesis of Tertiary Tryptamines*"

- Schmidt, A.M.; Eilbracht, P.; *J. Org. Chem.* **2005**, *70*, 5528-5535.

- Köhling, P.; Schmidt, A.M.; Eilbracht, P.; *Org. Biomol. Chem.* **2005**, in preparation.

Ø Chapter 4:"*Functionalization of Tryptamines under Hydroformylation Conditions*"

- Schmidt, A.M.; Eilbracht, P.; *Adv. Synth. Catal.* **2005**, in preparation.

Ø Chapter 6:"*Synthesis of Macrocyclic Bishydrazones and Their Application as Metal Sensors*"

- Schmidt, A.M.; Angelovski, G.; Eilbracht, P.; **2005**, in preparation.

Ø Chapter 8:"*Tandem Hydroformylation / Fischer Indole Synthesis on Solid Phase*"

- Mentel, M; Schmidt, A.M.; Breinbauer, R.; Eilbracht, P.; **2005**, in preparation.

TABLE OF CONTENTS

1 INTRODUCTION AND AIMS OF THE PROJECT

1.1 RELEVANCE OF INDOLES AND THEIR SYNTHESIS

Tryptamines are involved in various different biological processes. Serotonin for example, is a neurotransmitter and influences the human nervous system. It controls the state of mind, affects the circadian rhythm, sexual urge and body temperature and seems to play a key role in neurological disorders like migraines. Tailored serotonin type tryptamines are therapeutically used to influence these systems by addressing the responsible receptors selectively. Recent contributions in migraine drug development clearly demonstrate that not only extended substituents in 5-position are required to achieve high selectivities towards subtypes of the serotonin receptor family, but also sophisticated amine moieties in the 3-position as well as a defined distance by which this amine is attached to the indole core (Scheme 1)[1].

Scheme 1: Recent developments in migraine therapy[2].
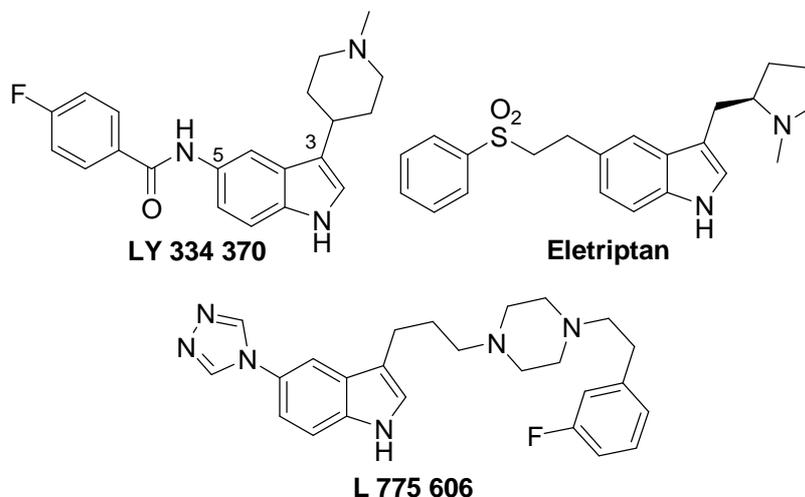
From a synthetic chemist's point of view these and additional features of indole type pharmaceuticals are interesting, such as the occurrence of branching in the *a*- and *b*-positions with respect to the indole core, or stereochemical issues as well as the fact that the side chain nitrogen might be embedded in a cyclic system such as piperidines, pyrrolidines or

[1] For reviews on migraine therapy see: *a*) Schaible, H.-G.; Ebersberger, A.; *PharmIUZ* **2002**, *31*, 452-457. *b*) Limmroth, V.; *PharmIUZ* **2002**, *31*, 458-461. *c*) Gurrath, M.; *PharmIUZ* **2002**, *31*, 470-478. Link, A.; Link, B.; *PharmIUZ* **2002**, *31*, 486-493.

[2] *a*) Johnson, K.W.; Schaus, J.M.; Durkin, M.M.; Audia, J.E.; Kaldor, S.W.; Flaugh, M.E.; Adham, N.; Zgombick, J.M.; Cohen, M.L.; Branchek, T.A.; Phebus, L.A.; *NeuroReport* **1997**, *8*, 2237-2240. *b*) Harding, V. D.; Macrae, R.J.; Ogilvie, R.J.; *PCT Int. Appl.* **1996**, WO9606842A1. *c*) MacLeod, A.M.; Street, L. J.; Reeve, A.J.; Jelley, R.A.; Sternfeld, F.; Beer, M.S.; Stanton, J.A.; Watt, A.P.; Rathbone, D.; Matassa, V.G.; *J. Med. Chem.* **1997**, *22*, 3501-3503.

piperazines. All these features demand synthetic strategies which give convenient and fast access to highly diverse libraries of tryptamines and their homologues. Therefore, it would be preferable to have a general protocol allowing the synthesis of these compounds with simultaneous variations in all important positions. A modular approach with high diversity desires fusion of all building blocks in a late synthetic step with flexible determination of the chain length and the substitution pattern in the side chain. Such a convergent strategy should preferably include the construction of the indole core, with all necessary building blocks (amine moiety, side chain fragment, properly substituted aromatic indole precursor) being easily available in large amounts in prior synthetic steps (Scheme 2).

Scheme 2: Modular approach to tryptamines.
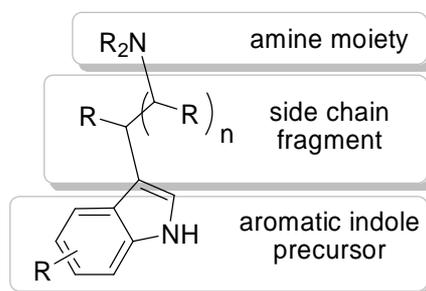
FISCHER's and the LAROCK's method are the most common for the preparation of indoles. In LAROCK's indole synthesis *o*-halo anilines are connected with a functionalized alkyne under palladium catalysis[3] (Scheme 3).

Scheme 3: Basic principle of the Larock indole synthesis.
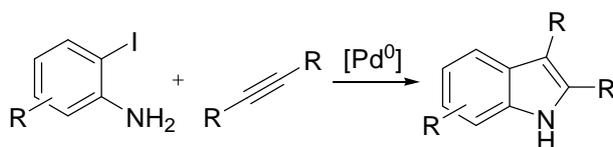
Synthesis of additionally substituted *o*-halo anilines, however, requires further steps and is not always easily achieved. Similarly the alkyne unit may require laborious synthetic procedures. If the final product bears additional substituents on the six-membered ring of the indole core, the substituted *o*-halo anilines subjected to the LAROCK synthesis can cause steric hindrance. Similarly, obtaining the starting materials for FISCHER's indole synthesis can be

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[3] *a*) Larock, R.C.; Yum, E.K. *J. Am. Chem. Soc*. **1991**, *113*, 6689. *b*) Larock, R.C.; Yum, E.K.; Refvik, M.D. *J. Org. Chem*. **1998**, *63*, 7652.

laborious. Here, carbonyl compounds are reacted with aryl hydrazines under acid catalysis[4] (Scheme 4).

Scheme 4: Basic principle of The Fischer indole synthesis.
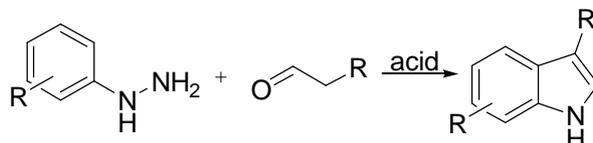
While a number of different approaches have been reported for the synthesis of substituted aryl hydrazines (the degree of substitution is reduced by one as compared to the aryl halide required for a LAROCK synthesis of the same compound), synthesis of the carbonyl compound very often requires a large number of simple functional group transformations (e.g. homologization of the carbon chain, reduction, oxidation). If aldehydes are needed for the indolization step, these have to be protected as acetals, aminals, enol ethers or bisulfite adducts in order to prevent aldol condensation and oligomerization under the harsh conditions of the FISCHER indole synthesis. In some cases the use of masked carbonyl compounds like in the JAPP-KLINGEMANN modification is useful. Here *b*-ketoesters are reacted with aryl diazonium salts to give aryl hydrazones after cleavage of acetic acid. The same hydrazone can be obtained upon condensation of the corresponding *a*-keto ester with aromatic hydrazines.

Scheme 5: Use of Ketoesters as masked aldehydes in indole syntheses.

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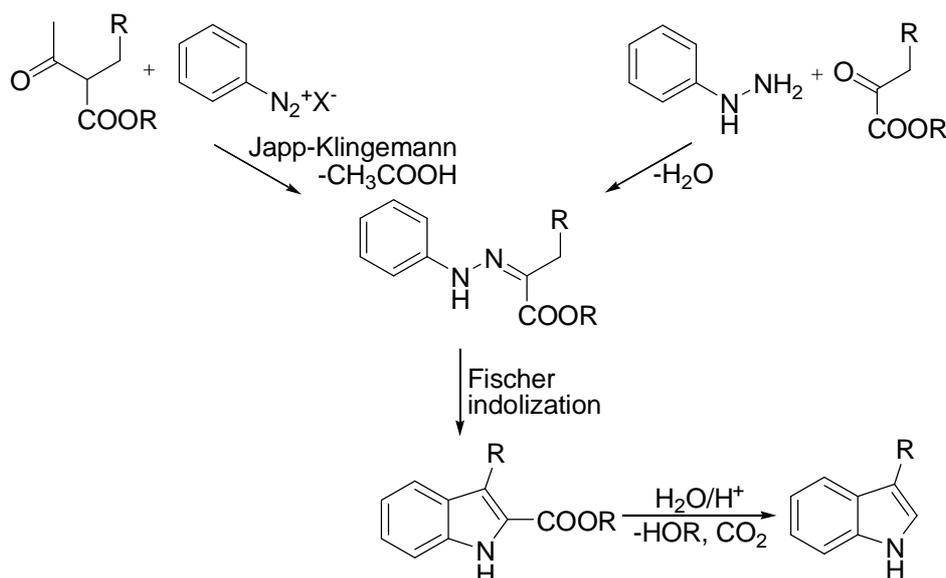
[4] *a*) Robinson, B.; *Chem. Rev.* **1963**, *3*, 373. *b*) Ishii, H.; *Acc. Chem. Res.* **1981**, *14*, 233-247. *c*) Robinson, B.; *"The Fischer Indole Synthesis"*; Wiley, New York, **1982**. *d*) Hughes, D. L.; *Org. Prep. Proceed. Int.* **1993**, *25*, 607-632. *e*) Gribble, G. W.; *J. Chem. Soc., Perkin Trans.* 1 **2000**, 1045.

FISCHER indolization of this hydrazone gives the indole-2-carboxylic acid ester which decarboxylates after hydrolysis, giving indoles without a substituent at the 2-position[5]. In summary, both, the *a*-keto ester as well as the *b*-ketoester, serve as masked aldehydes (Scheme 5). These methodologies require additional steps and reagents and may hamper a general application with broad diversity as demanded for an ideal synthesis[6] and the medicinal chemist's needs.

1.2 HYDROFORMYLATION

A chain elongating *in situ* synthesis of aldehydes might be an alternative to the above described methods. The hydroformylation of olefins is a well known and reliable method for the synthesis of aldehydes and has been used in industrial processes[7]. But although the aldehyde functionality offers a wide range of further transformations, only a few examples are reported in which hydroformylation is used in a multi-step synthesis of fine chemicals. Obviously the homologization of the carbon skeleton by one carbon atom is not efficient enough and is only useful for simple steps at the very beginning of a synthesis. If the hydroformylation could be combined with methodologies for the derivatization of the aldehyde group to one step, the hydroformylation may become an even more attractive tool in the synthesis of fine chemicals.

In the past few decades, a number of so called tandem reactions or reaction sequences under hydroformylation conditions have been reported[8]. The hydroformylation of terminal diarylethenes in the presence of primary and secondary amines affords direct access to pharmacologically active 3,3-diarylpropylamines. This tandem reaction consists of hydroformylation and reductive amination. Rhodium catalyzes the hydroformylation of the olefin as well as the hydrogenation of the enamine which results from the condensation of the aldehyde with the secondary amine (Scheme 6)[9].

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[5] For recent examples see: Heinrich, T.; Böttcher, H.; Gericke, R.; Bartoszyk, G.D.; Anzali, S.; Seyfried, C.A.; Greiner, H.E.; van Amsterdam, C.; *J. Med. Chem.* **2004**, *47*, 4684-4692.

[6] Wender, P.A.; Handy, S.T.; Wright, D.L.; *Chemistry & Industry* **1997**, 765-769.

[7] Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W.; *J. Mol. Catal. A* **1995**, *104*, 17.

[8] *a*) Eilbracht, P; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A.; *Chem. Rev.* **1999**, *99*, 3329-3366. *b*) Schmidt, A.M.; Eilbracht, P; in *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*; (Beller, M.; Bolm, C.), 2nd ed., Wiley-VCH, Weinheim, **2004**, 57-111. *c*) Schmidt, A.M.; Eilbracht, P.; in Topics in Organometallic Chemistry; (Beller, M.), Springer Verlag, New York, **2005**, in preparation.

[9] Rische, T.; Eilbracht, P.; *Tetrahedron* **1999**, *55,* 1915-1920.

Scheme 6: Hydroaminomethylation in the synthesis of pharmaceuticals.
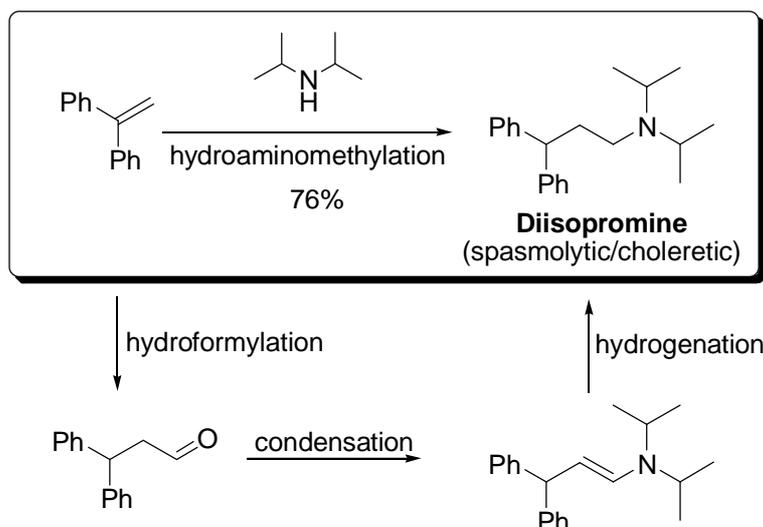
Among all tandem hydroformylation sequences, methods in which the aldehyde functionality is used for the formation of additional *C-C*-bonds seem to be the most attractive. The tandem enolboration / hydroformylation / aldol addition may act as a good example. Here, hydroformylation of an unsaturated carbonyl compound is combined with an aldol reaction. The boron enolate is generated in a previous step from the unsaturated carbonyl, a boron halide and triethylamine. This boron enolate is hydroformylated selectively at the terminal double bond. The resulting aldehyde undergoes an aldol reaction with the boron enolate *in situ* with transfer of the boron enolate's configuration to the aldol product, resulting in good to excellent diastereoselectivities (Scheme 7).

Scheme 7: Tandem enolboration/hydroformylation/aldol reaction.
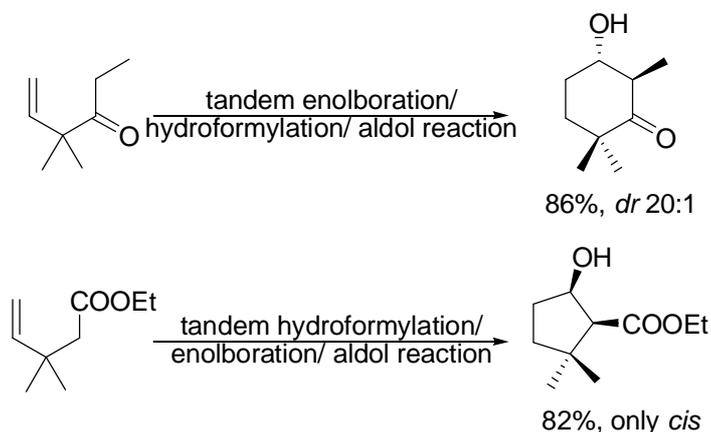
Very recently this methodology has been used for a diastereoselective synthesis of the A-ring of forskolin (Scheme 8)[10].

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[10] Keränen M.D.; Eilbracht P.; *Org. Biomol. Chem.* **2004**, *2*, 1688-1690.

**Scheme 8: Synthesis of the A-ring of forskolin via tandem
enolboration/hydroformylation/aldol reaction.**

82%, 2.5:1 *dr*

Forskolin
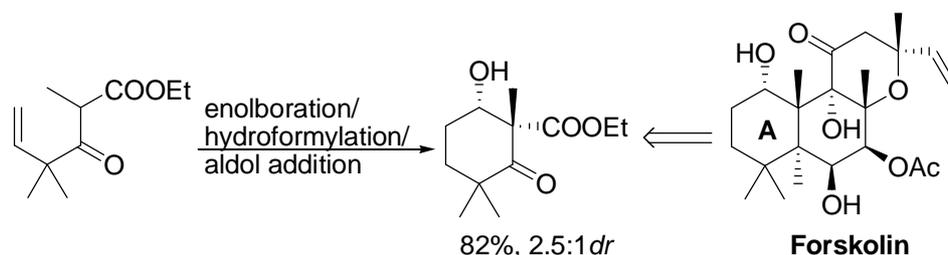
1.3 HYDROFORMYLATION AND INDOLE SYNTHESIS

Surprisingly, only few examples are described in which the hydroformylation has been used to generate aldehydes required for indole syntheses. Thus, hydroformylation of styrene type anilines, derived from a HECK reaction of *o*-halo anilines, gives tryptamines in fair yields. Here, the olefinic bond is regioselectively hydroformylated, and the resulting aldehyde condenses intramolecularly with the amine to give 3-substituted indoles (Scheme 9)[11].

Scheme 9: Tandem hydroformylation/enamine formation in the synthesis of tryptamines

CO/H_2 (1:1), 21 bar
$HRh(CO)(PPh_3)_3/PPh_3$
toluene, 70h, 70°C
32-73%

X = Br, I
R = Hal, OMe, CH$_3$, CF$_3$

R' = N(Boc)$_2$, OH, NHTs
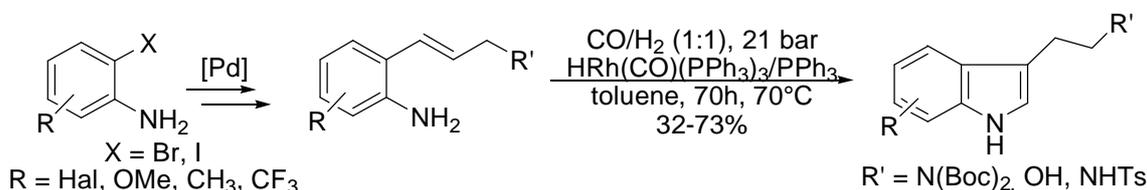
o-Nitrostyrenes can also be converted with this method, as the nitro group is reduced under hydroformylation conditions[12]. This approach is then comparable with the indole syntheses of REISSERT[13], SUGASAWA[14] and BATCHO and LEIMGRUBER[15].

More recently SELWOOD *et al.* have used the hydroformylation for the synthesis of migraine drug 4991W93 to control the relative configuration of the final product, albeit with poor regioselectivity (Scheme 10)[16].

[11] Dong, Y.; Busacca, C. A.; *J. Org. Chem.* **1997**, *62*, 6464-6465.
[12] Ucciani, E.; Bonfand, A.; *Chem. Commun.* **1981**, 82.
[13] Cannon, J. G*.; J. Med. Chem.*, **1981**, *24*, 238.
[14] Douglas, A.W.; *Tetrahedron Letters* **1994**, *35*, 6807.
[15] Siu, J.; Baxendale, I.R.; Ley, S.V.; *Org. Biomol. Chem.* **2004**, *2*, 160-167.
[16] Jandu, K.S; Barrett, V.; Brockwell, M.; Cambridge, D.; Farrant, D.R.; Foster, C.; Giles, H.; Glen, R.C.; Hill, A.P.; Hobbs, H.; Honey, A.; Martin, G.R.; Salmon, J.; Smith, D.; Wollard, P.; Selwood, D.L.; *J. Med. Chem.* **2001**, *44*, 681-693.

Scheme 10: Hydroformylation in indole syntheses: Control of relative configuration.

4991W93
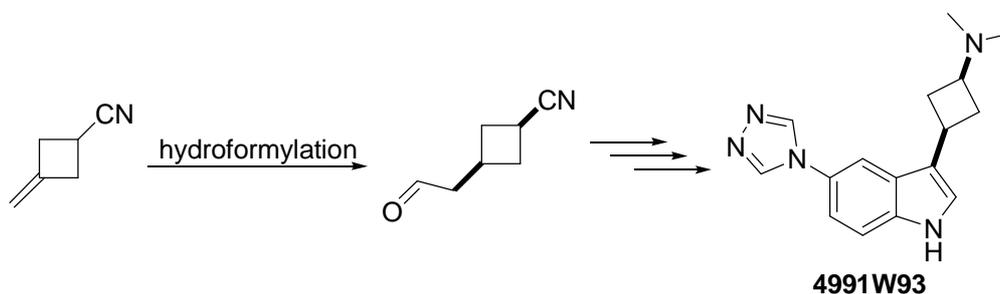
SHELDON *et al.* have published the synthesis of melatonin via regioselective hydroformylation of *N*-allyl acetamide followed by FISCHER indole synthesis (Scheme 11)[17].

Scheme 11: Synthesis of melatonin via hydroformylation followed by Fischer indole synthesis.
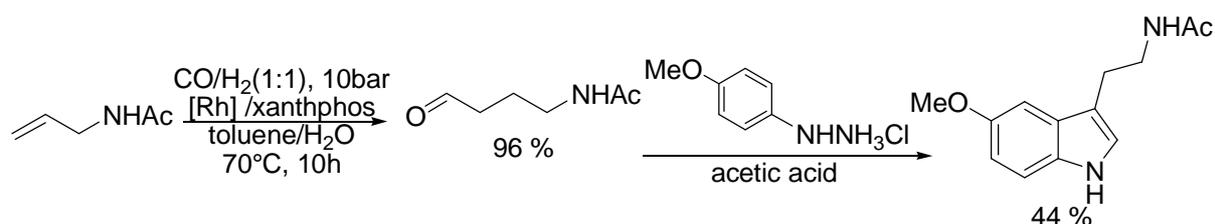
In 2001, KÖHLING was able to demonstrate that, both, the hydroformylation and the FISCHER indolization can be combined to a new tandem reaction[18]. While the chain elongating hydroformylation is used to synthesize the aldehyde *in situ* from an olefin, reducing functional group transformations to a minimum, the presence of an aryl hydrazine and a BRØNSTED acid allows direct conversion to the indole.

Scheme 12: Basic principle of the tandem hydroformylation / Fischer indole synthesis.

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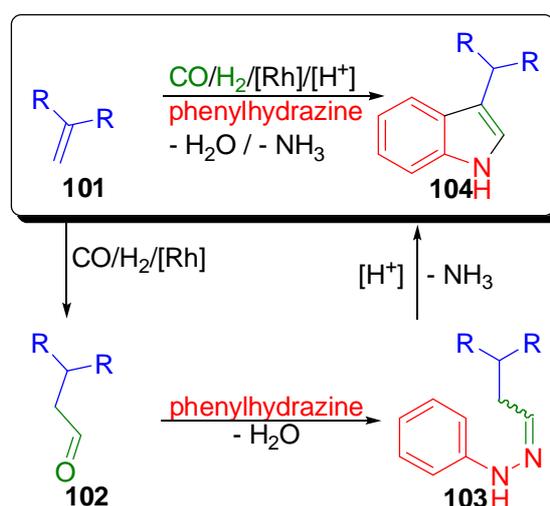
[17] Verspui, G.; Elbertse, G.; Sheldon, F. A.; Hacking, M. A. P. J.; Sheldon, R. A.; *Chem. Commun.* **2000**, 1363.

[18] Köhling, P.; *Diploma Thesis* **2001**, University of Dortmund.

Thus, this tandem reaction includes three steps: hydroformylation of an olefin **101**, condensation of aldehyde **102** with an aryl hydrazine to an aryl hydrazone **103** and finally BRØNSTED acid mediated [3,3]-sigmatropic Diaza-COPE rearrangement and cyclization to indole **104** (Scheme 12). The fact that aldehydes as well as hydrazones are intermediates in this tandem reaction and do not have to be isolated clearly saves time and resources. A series of simple indole derivatives, including tryptophols and tryptamines, have been synthesized with this innovative methodology, starting from easily available olefins and phenylhydrazine (Scheme 13). However, yields need to be improved for more complex structures.

Scheme 13: First examples of tandem hydroformylation / Fischer indole synthesis.
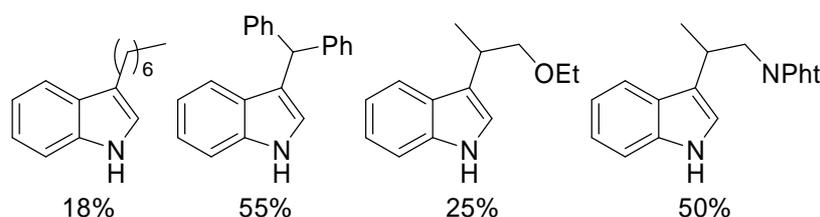
1.4 AIM OF THE PROJECT

Encouraged by these initial results the scope and limitations of this new tandem reaction should be clarified. While tryptophols, 2,3-disubstituted indoles and bisindoles will be discussed in a parallel work[19], this work shall concentrate on the following topics:

- Ø Improvement of the existing protocol in order to

- Ø develop a modular approach towards biologically and pharmaceutically relevant tryptamines and homologues under

- Ø consideration of all necessary biological valances (i.e. substitution pattern at the indole core, type of amine moiety, length of side chain in 3-position, substituents in the side chain).

- Ø Application towards recent drug candidates and

- Ø synthesis of substance libraries for biological evaluations.

In this context

- Ø the tandem reaction and its singular steps shall be investigated intensively starting with basic model aminoolefins with respect to

  - • stability of nitrogen protecting groups and

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[19] Köhling, P.; *Dissertation* **2005**, University of Dortmund.

- different sources of aryl hydrazines.

Ø Furthermore, the tandem reaction shall be optimized with respect to

- chemoselectivity of the tandem reaction,

- regioselectivity of the hydroformylation and of the indolization and

- stereoselectivity of the hydroformylation.

Ø These optimized conditions shall be applied towards more complex substrates such as highly functionalized tryptamine derivatives of pharmacological relevance.

Ø The tandem reaction shall be transferred from solution to solid phase to allow automated, combinatorial access to substance libraries.

2 SYNTHESIS OF PRIMARY AND SECONDARY TRYPTAMINES

To achieve high chemoselectivities for the overall tandem process, it is important that all individual steps work as selectively as possible and all reagents and reactants required as well as all intermediates are compatible and do not affect each other. To ensure this, investigations are started with optimizations of each step, i.e. hydroformylation of aminoolefins, hydroformylation in the presence of hydrazines, FISCHER indolization of aryl hydrazones and finally the complete tandem hydroformylation / FISCHER indole synthesis.

2.1 HYDROFORMYLATION IN THE PRESENCE OF HYDRAZINES

It is well known that hydroformylations can be conducted in the presence of amines. While tertiary amines increase the hydrogenation activity of rhodium based hydroformylation catalysts giving alcohols exclusively[20], primary and secondary amines condense with the aldehyde followed by hydrogenation of the resulting imines or enamines to amines in an overall hydroaminomethylation[21]. In 1999, RISCHE conducted hydroformylations in the presence of aliphatic hydrazines in order to show whether hydrazines behave similarly. In fact, the hydroformylation of styrene (**201**) in the presence of *N,N*-disubstituted hydrazines (**202**) gave the hydrazones (**203**) in excellent yields. No hydrogenation product of the aldehyde or the hydrazone was observed whereas imines are usually reduced under harsh hydroformylation conditions. Obviously, the hydrazine does not enhance the hydrogenation activity of the catalyst and, on the other hand, protects the aldehyde against reduction. Only after prolonged reaction times, could the hydrogenated product **204** be selectively obtained as a result of a hydroaminomethylation. If the styrene (**201b**) was used in a two-fold excess, unsymmetrically substituted alkyl hydrazine **205** was obtained as a 2:1 adduct (Scheme 14).[21]

If this hydroformylation / hydrazone formation shall be applied to the synthesis of tryptamine derivatives, allylic amines have to be used. Since hydroformylation of terminal olefins typically results in a mixture of linear and branched aldehydes, disubstituted terminal olefins like *N*-ethyl-*N*-methallylic amine (**206**) are preferably investigated. Such olefins undergo regioselective hydroformylation to form linear aldehydes and make use of *n*-directing ligands obsolete. To prevent hydrogenation of the starting olefin, high carbon monoxide partial pressures are chosen in order to support the rate determining carbon monoxide insertion.

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[20] *a*) Kaneda, K.; Yasumura, M.; Hiraki, M.; Imanaka, T.; Teransihi, S. *Chem. Lett.* **1981**, 1763. *b*) Kaneda, K.; Imanaka, T.; Teranishi, S. *Chem. Lett.* **1983**, 1465.
[21] Rische, T.; *Dissertation* **1999**, University of Dortmund.

Scheme 14: Hydroformylation in the presence of alkyl hydrazines.

203a R_1=H, R_2=$(CH_2CH_2O)_2$ 84%
203b R_1=R_2=CH_3 96%

201a R=H
201b R=CH_3

204
81%
R_1=H, R_2=$(CH_2CH_2O)_2$

205
85%
R_1=CH_3, R_2=$(CH_2CH_2O)_2$

cond.[21]: i) 1equiv. **201**, 1equiv. **202**, 1mol% [Rh(cod)Cl]$_2$, dioxane, 90bar
CO, 20bar H$_2$, 18h, 110°C ii) like i) but 3d; iii) like i) but 5d.
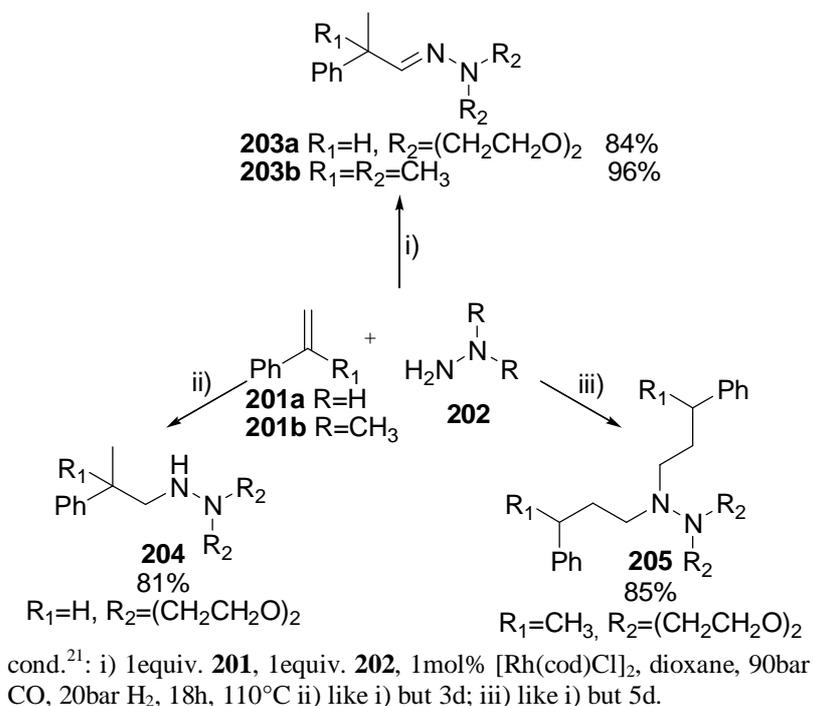
Hydroformylation of **206** indeed gives the desired aryl hydrazone **207**, but neither are inter-
nor intramolecular reductive amination products of the aldehyde observed (Scheme 15).
However, approximately 10% of lactam **208** is obtained as a byproduct.

**Scheme 15: Hydroformylation of secondary
aminoolefins.**

207   **208**
~90   :   10

209

210
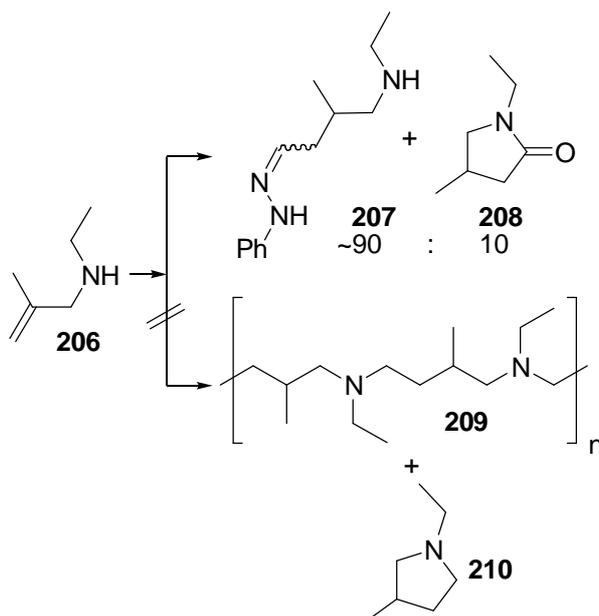
cond.: 1equiv. **206**, 1equiv. phenylhydrazine, 0.3mol%
Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 68h, 100°C.

Obviously, the rhodium acyl species partially tends toward intramolecular nucleophilic
addition of the secondary amine and the formation of lactam **208**, instead of hydrogenolysis to

form the aldehyde. This behavior has previously been reported for allylic amines and could be suppressed with the use of supercritical carbon dioxide ($scCO_2$) as a solvent and as an intermediate protecting group[22].

In order to avoid formation of the lactam as a side product, protection of the allylic amine is necessary. In fact methallylic phthalimide (**211a**) is regioselectively hydroformylated in quantitative yields to give aldehyde **212** and its hydroformylation in the presence of phenylhydrazine yields the corresponding hydrazone **213** as a mixture of *E/Z*-isomers in excellent yields (Scheme 16).

Scheme 16: Hydroformylation and hydroformylation/hydrazone formation of methallyic phthalimide.
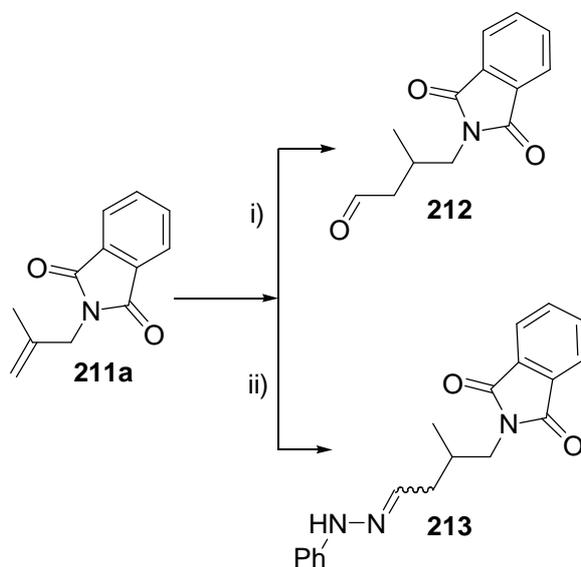
cond.: i) 1eq **211a**, 0.3mol% Rh(acac)(CO)$_2$, THF, 50bar CO, 10bar H_2, 20h, 100°C; ii) like a) but with phenylhydrazine 68h.

After three days reaction time[23] at higher temperatures no hydrogenation of the hydrazone bond can be observed, so that aryl hydrazones seem to be of higher stability against hydrogenation than their alkyl analogues. Thus, the hydrazones obtained from

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[22] Wittmann, K.; Wisniewski, W.; Mynott, R.; Leitner, W.; Kranemann, C.L.; Rische, T.; Eilbracht, P.; Kluwer, S.; Ernsting, J.M.; Elsevier, C.J.; *Chem. Eur. J.* **2001**, *7*, 4584-4589.

[23] It turned out, that the hydroformylation of olefins in the presence of aromatic hydrazines is 2 times slower than in their absence. Turn-Over-Frequency (TOF) for the single hydroformylation was calculated as TOF≈5.4 h^{-1} (determined from a linear fit of a concentration-time plot for the hydroformylation of 114a). Turn-Over-Frequency (TOF) for the hydroformylation in the presence of phenylhydrazine was calculated as TOF≈2.6 h^{-1} (determined from a linear fit of a concentration-time plot for the hydroformylation of **211a** in the presence of phenylhydrazine). These low TOFs result from the use of magnetically stirred pressure vessels. In a pressure vessel with a motor stirrer hydroformylation is up to ten times faster.

hydroformylation reactions are of high purity[24]. Apparently, hydrazines do not alter the chemoselectivity of the hydroformylation catalysts [Rh(cod)Cl]$_2$ and Rh(acac)(CO)$_2$.

2.2 INDOLIZATION OF ARYL HYDRAZONES

After having found conditions for a highly selective synthesis of hydrazones under hydroformylation conditions, the conditions for the FISCHER indolization are optimized. These must be compatible with the hydroformylation step which, therefore, has to be conducted in the same solvent as used for indolization. Furthermore, it is important, that the hydroformylation is not hampered by the addition of acids. The latter can only be tested in a tandem reaction, since olefins can oligomerize and aldehydes can undergo aldol reactions in the presence of acids. Therefore, the FISCHER indolization is optimized by testing different solvents and acids[25]. Most common systems for FISCHER indole synthesis are H$_2$SO$_4$ in alcohols such as methanol or ethanol. Indeed, there are examples, where hydroformylation of alkenes has also been carried out in alcoholic solution. However, using these solvents, depending on the reaction conditions, the intermediate rhodium acyl species can be trapped by the alcohol to give esters[26], or the aldehyde suffers nucleophilic attack by the alcohols to yield acetals[27]. Since acetals are used as protected aldehydes in FISCHER indole synthesis, the use of alcoholic solvents in the hydroformylation step is an option and would support the principle of low stationary aldehyde concentrations. Surprisingly, hydrazone **213** does not lead to indolization in the presence of 4 wt% H$_2$SO$_4$, neither in methanol nor in ethanol. Only less polar solvents like refluxing THF or toluene, which are also very common in hydroformylation chemistry, allow satisfying conversions.

In a next step, different acids are tested, concentrating on commercially available and inexpensive acids. In order to find even minor differences in the acids activity, only one equivalent of each acid is used, the reaction is stopped after two hours and the conversion is estimated by NMR. In this screening, acids from pKa = 5 to pKa = -8, i.e. acetic acid, formic

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[24] Beller *et al.* have simultaneously found that hydrazones can be obtained upon hydroformylation of olefins in the presence of hydrazines. For further details see *a*) Ahmed, M.; Jackstell, R.; Seayad, A.M.; Klein, H.; Beller, M.; *Tetrahedron Lett.* **2004**, *45*, 869-873.

[25] Beller *et al.* have simultaneously found that a tandem hydroformylation / indolization can be performed with Lewis acids such as ZnCl$_2$ instead of Brønsted acids. For further details see Ahmed, M.; Jackstell, R.; Seayad, A.M.; Klein, H.; Beller, M.; *Tetrahedron Lett.* **2004**, *45*, 869-873.

[26] Hakkaku, K.; Sakakibara, Y.; *Jap. Pat. Appl.* **2000**, JP2000143587.

[27] *a*) Bohnen, H. W.; Cornils, B.; *Adv. Catal.* **2002**, *47*, 1-64. *b*) Cornils, B.: *J. Mol. Catal. A-Chem.* **1999**, 143, 1-10. *c*) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W.; *J. Mol. Catal. A-Chem.* **1995**, *104*, 17-85. *d*) Cornils, B.; Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem.* **1994,** *106,* 2219, *Angew. Chem. Int. Ed. Engl.* **1994**, *33,* 2144. *e*) Cornils, B.; Herrmann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds,* VCH: Weinheim **1996**. (f) van Leeuwen, P. W. N. M.; Claver, C. (Eds.) *Rhodium Catalyzed Hydroformylation* Kluwer Academic Publishers, Dordrecht, **2000**.

acid, phosphorous acid, trichloroacetic acid, trifluoroacetic acid, nitric acid, *p*-toluene sulfonic acid (PTSA), H_2SO_4 and hydrochloric acid, are used. A good indication for the starting reaction is the precipitation of ammonium salts from the non-polar solvent. Among all acids, H_2SO_4 as well as PTSA show the best results, leading to full conversion. Obviously the combination of a less polar solvent with at least one equivalent of a strong acid provides a fast and selective conversion of the aryl hydrazones to the desired tryptamines. The high conversions observed within the two hours reaction time are especially encouraging. A slow hydroformylation step, together with a fast condensation and a fast indolization help to keep concentrations of aldehyde and hydrazone low, so that both do not undergo intermolecular acid mediated side reactions.

2.3 Different Sources of Aryl Hydrazines

In the next step the optimized conditions for each step are combined into a tandem reaction and different sources of aromatic hydrazines are tested.

2.3.1 Commercially Available Aryl Hydrazines

Tandem hydroformylation / Fischer indolization of methallylic phthalimide (**211a**) with phenylhydrazine (**214a**) in the presence of one equivalent of PTSA give the desired tryptamine in 60% isolated yield (Table 1). Here the tosylation of the indole nitrogen helps to separate the product from impurities. Obviously, the tandem reaction does not proceed with a selectivity as high as for the single steps. Nevertheless, simple substituents are tolerated, e.g. the *tert.*-butyl group which can be found in a number of *in vitro* serotonin receptor antagonists.

Table 1: Use of commercially available aryl hydrazines in the tandem hydroformylation / Fischer indolization with subsequent tosylation of the indole nitrogen.

entry	hydrazine 214	yield 215
1	**214a** (R=H)	60% (**215a**; R=H)
2	**214b** (R=Cl)	53% (**215b**; R=Cl)
3	**214c** (R=*tert.*-butyl)	48% (**215c**; R=*tert.*-butyl)

cond.: 1equiv. **211a**, 1equiv. **214**, 1mol% [Rh(cod)Cl]$_2$, 50bar CO, 10bar H$_2$, 1equiv. PTSA, 3d, 100°C; then 1equiv. tosylchloride, 50wt% NaOH in H$_2$O, toluene, 20h, rt.

2.3.2 BENZHYDRYLIDENE PROTECTED ARYL HYDRAZINES

In mixing all reagents in non-polar solvents like toluene or THF, a precipitation is observed due to protonation of the aryl hydrazine. Therefore solubility problems might be responsible for the decrease in selectivity. An appropriate protection of the basic hydrazine on the other hand, must allow the conversion of the aldehyde, thus only acid sensitive protecting groups are of interest. BUCHWALD *et al.* have demonstrated that benzhydrylidene protected aryl hydrazines undergo high yielding FISCHER indolization in the presence of carbonyl compounds under acidic conditions[28]. The benzophenone hydrazone itself cannot cyclize to form an indole, it can only transcondense with a second carbonyl compound allowing FISCHER indolization. Benzhydrylidene protected aryl hydrazines are either obtained from commercially available aryl hydrazines or by palladium catalyzed amination of aryl halides with benzophenone hydrazone (Scheme 17).

Scheme 17: Different access to benzhydrylidene protected aromatic hydrazines.
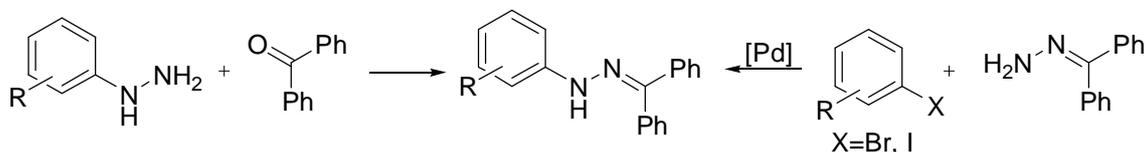
Indeed, the use of protected hydrazines increases the selectivity as well as the yield of the tandem reaction making a consecutive tosylation of the indole nitrogen obsolete. In using this methodology, substituted tryptamines are isolated with up to 83% yield (Table 2). Remarkably, aryl bromides are tolerable although they are known to undergo oxidative addition with rhodium (I) complexes[29] leading to defunctionalization of the aryl bromides. In some cases bromo substituents are even cleaved without a transition metal catalyst under the conditions of FISCHER indolization. On the other hand, bromo substituted indoles are valuable starting materials for further derivatization (e.g. palladium catalyzed cross coupling methodologies of 5-bromo-indole[30]). Therefore, tandem hydroformylation / FISCHER indole synthesis offers a convenient pathway to bromo substituted tryptamine derivatives from easily available starting material.

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[28] *a*) Wagaw, S.; Yang, B. H.; Buchwald, S. L.; *J. Am. Chem. Soc.* **1998**, *120*, 6621-6622. *b*) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *121*, 10251-10263.

[29] Ishiyama, T.; Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 12043-12044.

[30] Blatcher, P.; Carter, M.; Hornby, R.; Owen, M.R.; *PCT Int. Appl.* **1995**, WO9509166.

Table 2: Tandem hydroformylation / Fischer indolization of benzhydrylidene protected aryl hydrazines.
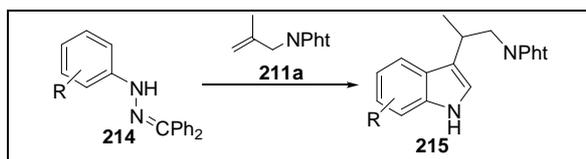
entry	hydrazine **214**	yield **215**
1	**214d** (R=H)	83% (**215d**; R=H)
2	**214e** (R=4-F)	47% (**215e**; R=5-F)
3	**214f** (R=4-Cl)	78% (**215f**; R=5-Cl)
4	**214g** (R=4-Br)	50% (**215g**; R=5-Br)
5	**214h** (R=2-CH$_3$)	48% (**215h**; R=7-CH$_3$)
6	**214i** (R=2-Cl)	42% (**215i**; R=7-Cl)

cond.: 1equiv. **211a**, 1equiv. **214**, 1mol% [Rh(cod)Cl]$_2$, 50bar CO, 10bar H$_2$, 1equiv. PTSA, 3d, 100°C.

2.3.3 a-Boc Protected Aryl Hydrazines

In 2004, Cho *et al.* have successfully applied a-Boc aryl hydrazines in Fischer indolization and obtained indoles with very high purity[31]. Therefore, **214j** is tested as a substrate for the tandem hydroformylation / Fischer indole synthesis. Here, the reaction has to be conducted in a stepwise manner with subsequent addition of acid. Since the Boc group is stable under hydroformylation conditions, a-Boc protected aryl hydrazones can be obtained in quantitative yields. Tandem hydroformylation / Fischer indolization of **214j** gives the protected serotonin analogue **215j**[32] in nearly quantitative yields without the need for further purification. A number of different aryl hydrazines, synthesized using Buchwald's optimized conditions of the copper(I) catalyzed *N*-arylation of amides (Goldberg reaction, Scheme 18)[33] and their non-protected analogues are compared with respect to their reactivity towards tandem hydroformylation / Fischer indole synthesis.

Scheme 18: Principle of the Goldberg reaction.
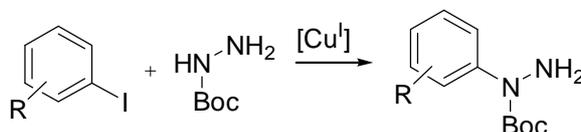
[31] Lim, Y.-K.; Cho, C.-G.; *Tetrahedron Lett.* **2004**, *45*, 1857-1859.
[32] Kenton, R.E; Dudlettes, S.D.; Shulgin, A.T.; *Biological Psychiatry* **1980**, *15*, 349-352.
[33] Wolter, M.; Klapars, A.; Buchwald, S.; *Org. Lett.* **2001**, *3* , 3803-3805.

Only the *p*-methoxy phenylhydrazine **214j** gives a clearly increased yield (Scheme 19) whereas *a*-Boc protected phenylhydrazine **214k** gives only 38% of indole **215d**. 4-Bromo substituted *a*-Boc protected phenylhydrazine **214l** gives 50% of indole **215g**.

Scheme 19: Tandem hydroformylation / Fischer indole synthesis of *a*-Boc protected aromatic hydrazines.

214j: R=OMe
214k: R=H
214l: R=Br

215j: R=OMe (95%)
215d: R=H (38%)
215g: R=Br (50%)

cond.: 1eq **211a**, 1eq **214**, 1mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 68h; 120°C, then 4wt% H$_2$SO$_4$/THF, 2h, 80°C.
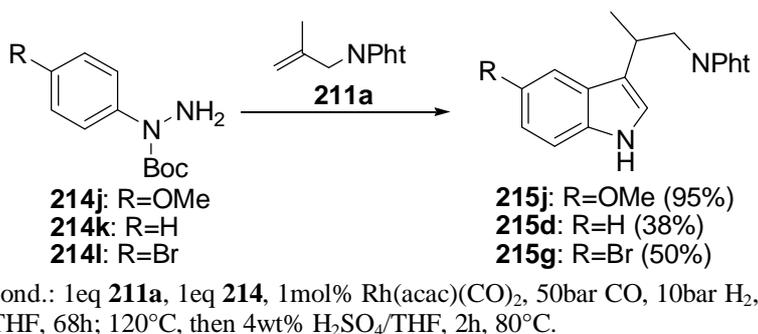
2.4 STABILITY OF NITROGEN PROTECTING GROUPS

In order to compare the stability of different protecting groups under tandem hydroformylation / FISCHER indole synthesis various methallylic amines are *N*-protected with phthalimide, acetyl, benzoyl, tosyl and ethyloxycarbonyl groups and converted in a stepwise manner. While the hydrazone formation under hydroformylation conditions in all cases gives excellent yields, the FISCHER indolization disclosed differences: The phthalimide has already been proven to be stable under the selected conditions. Also the tosylate and the benzamide give good yields of the desired tryptamides. The acetyl group, however, gives a slightly decreased yield.

Table 3: Nitrogen protecting groups in the tandem hydroformylation / Fischer indolization.

entry	olefin **211**	yield **215**
1	**211b** (R$_1$=Et, R$_2$=Ts)	94% (**215k**)
2	**211c** (R$_1$=Et, R$_2$=Bz)	85% (**215l**)
3	**211d** (R^1=Et, R$_2$=Ac)	61% (**215m**)
4	**211e** (R^1=Et, R$_2$=Eoc)	58% (**215n**)

cond.: 1equiv. **211**, 1equiv. **215a**, 1mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 68h, 120°C, then 4wt% H$_2$SO$_4$/THF, 2h, 80°C.

Not surprisingly, the Boc group is cleaved under FISCHER indolization conditions, but with a simple switch from *tert.*-butyloxycarbonyl to an ethyloxycarbonyl group the protected

tryptamine is obtained in 58% yield. Thus, all protecting groups chosen are tolerated under the reaction conditions (Table 3).

2.5 APPLICATIONS OF THE HYDROFORMYLATION / FISCHER INDOLIZATION

Having a reliable protocol in hand, the hydroformylation / indolization sequence was applied in the synthesis of pharmacologically active compounds. Scheme 20 illustrates the importance of *a*-branched tryptamides which become more and more interesting for pharmaceutical applications. LY 156735, for example, has recently been discovered as a drug against sleeping disorders[34]. As shown above, this substitution pattern of the side chain can be obtained by the use of disubstituted terminal olefins in the tandem hydroformylation / FISCHER indole synthesis.

Scheme 20: *a*-branched tryptamines as pharmaceuticals.
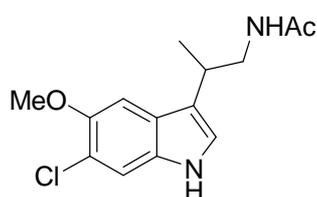
LY 156735

Besides compounds with linear or branched aliphatic side chains, tryptamine analogues with additional cyclic units, such as 3-piperidyl indoles, have been recognized as important pharmacophores in the last decade. The most prominent example is the *N*-phenylindole sertindole.

Scheme 21: Sertindole and its optimized lead structure.
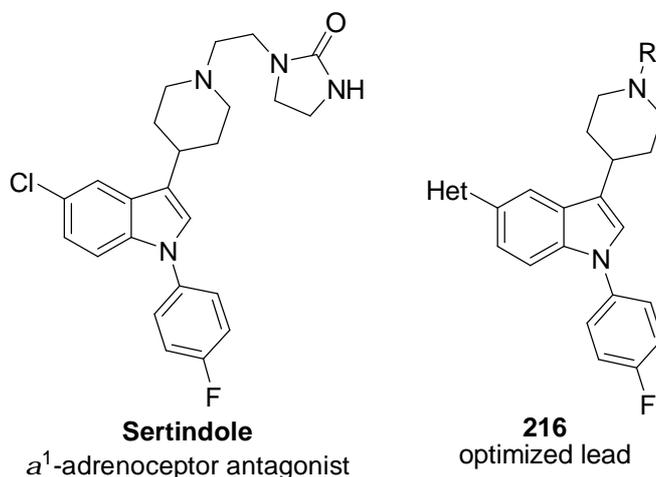
Sertindole
a[1]-adrenoceptor antagonist

216
optimized lead

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[34] Flaugh, M.E.; *Eur. Pat. Appl.* **1995**, EP 655243 A2.

Sertindole blocks diverse dopamine and serotonin receptors, predominantly inhibiting the a^1-adrenoceptor. It is used for the treatment of schizophrenia, helping to reduce typical side effects of classical neuroleptica like clozapin, risperidon or olanzapin (attention deficit disorder, apathy or social withdrawal)[35]. In 2002, ANDERSEN *et al.* optimized the structure of sertindole and increased the selectivity towards the a^1-adrenoceptor by variation of the substituents in 5-position of the indole and of the piperidyl nitrogen. The replacement of the chloro substituent by heterocyclic substituents in **216** especially helps to increase this selectivity[36]. In most cases, these substituents can be introduced via palladium catalysis starting from intermediate 5-bromo-indole **218**. Tandem hydroformylation / FISCHER indole synthesis is a useful method for the synthesis of **218** starting from easily available olefin **217** via conversion with commercially available 4-bromo-phenylhydrazine **214m** to give indole **218** in 39% yield. Copper catalyzed *N*-arylation with 4-iodo-fluoro-benzene leads to the intermediate **219**, which is thus conveniently obtainable in only two steps, increasing the earlier reported yield (11%) of a 4-step synthesis that started with 5-bromo indole (Scheme 22)[36].

Scheme 22: Synthesis of the intermediate for sertindole analogues.
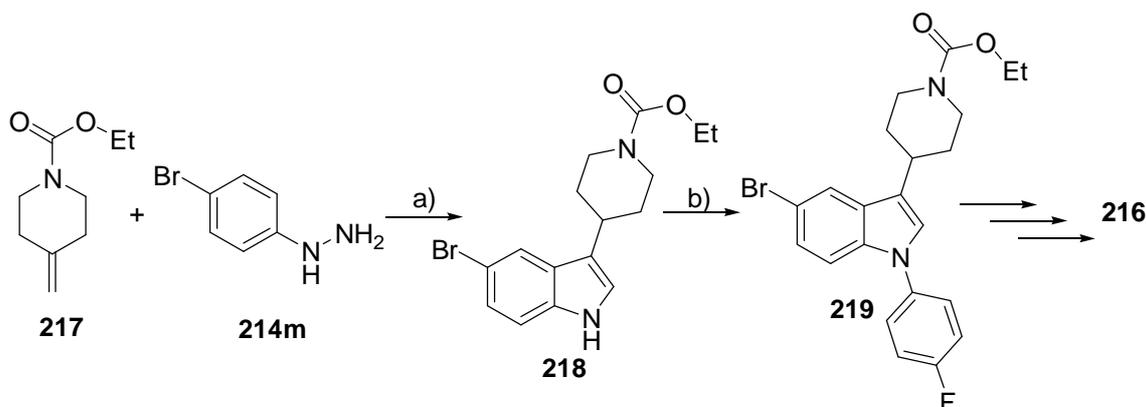
cond.: a) 1equiv. **217**, 1equiv. **214m**, 0.3mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 68h, 120°C then 4wt% H$_2$SO$_4$/THF, 2h, 80°C, 39%. b) 1.2equiv. 4-fluoro-iodobenzene, 2.1equiv. K$_3$PO$_4$*7H$_2$O, 5mol% CuI, 20mol% *N,N'*-dimethylethylendiamine, toluene, 24h, 110°C, 100%.

2.6 *N*-SELECTIVE TANDEM HYDROFORMYLATION / FISCHER INDOLIZATION

2.6.1 *N*-SELECTIVE HYDROFORMYLATION OF ALLYLIC AMIDES

So far the use of disubstituted terminal olefins leads to indoles with branched chains in a 3-position. Most of the biologically active tryptamines however, are tryptamines with a non-branched side chain. Here, the hydroformylation / indolization sequence requires

[35] Arnt, J.; Skarsfeldt, T.; *Neuropsychopharmacology* **1998**, *18*, 2539-2544.
[36] Balle, T.; Perregaard, J.; Ramirez, M.T.; Larsen, A.K.; Søby, K.K.; Liljefors, T.; Andersen, K.; *J. Med. Chem.* **2003**, *46*, 265-283.

monosubstituted olefins. While ligand free hydroformylation of terminal disubstituted olefins regioselectively gives *n*-aldehydes, ligand free hydroformylation of monosubstituted olefins leads to a mixture of *n*- and *iso*-aldehydes. *n*-Selectivity is increased by the use of bidentate ligands such as the biphosphite BIPHEPHOS or the biphosphane XANTPHOS. Both ligands lead to high *n*-selectivities if simple olefins like 1-hexene or 1-octene are used. With functionalized olefins however, the *n*-selectivity decreases dramatically. In tandem hydroformylation / FISCHER indole synthesis protected amino olefins have to be used. The nature of the protecting group strongly affects the *n/iso*-selectivity. Not only may donor groups attached to the olefin compete with the catalyst ligand, but also aryl hydrazines may act as ligands since amines in general coordinate to the metal center and influence the performance of the hydroformylation. For an investigation of the *n/iso*-selectivity, allylic phthalimide (**220a**) is hydroformylated with use of $Rh(acac)(CO)_2$/biphephos in a 1:4 ratio. Here, only a 2:1 mixture of *n/iso*-aldehydes is obtained. As an alternative XANTPHOS is tested, giving higher *n/iso*-ratios in hydroformylation of functionalized olefins. Indeed, the use of Rh/xantphos (1:5) gives the *n*-aldehyde with 81% selectivity. Increasing the catalyst/ligand ratio to 1:10 results only in a marginal enhancement of the *n*-selectivity (85%) (Table 4). To test the influence of the protecting group towards *n/iso*-selectivity, several protected allylic amines are hydroformylated with a $Rh(acac)(CO)_2$/xantphos system (1:5) at 70°C. In contrast to the hydroformylation of disubstituted terminal olefins, a lower carbon monoxide partial pressure is chosen to ensure that carbon monoxide does not displace XANTPHOS from the catalytically active rhodium complex. Although under these conditions all hydroformylation experiments proceed with complete olefin conversion, aldehydes can only be detected as the minor product. Instead, 2-hydroxy pyrrolidines (**223**) are formed in nearly quantitative yield via intramolecular attack of the carbonyl group by the protected primary amine. JACKSON *et al.* found a similar behavior[37]. Since only the *n*-aldehydes can cyclize, this isomer is removed from the hydroformylation equilibrium, shifting the product distribution towards the *n*-aldehyde selectively (Scheme 23).

Consequently, by use of protected secondary allylic amines, this consecutive reaction can be suppressed and the *n*-aldehydes are obtained with high yields and selectivities. Among the amides tested, three different types can be recognized.

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[37] *a*) Teoh, E.; Campi, E. M.;, Jackson, W. R.; *Chem. Commun.* **2002**, 978-979. *b*) Teoh, E.; Campi, E. M.; Jackson, W. R. N.; Robinson, A. J. *New J. Chem.* **2003**, *27*, 387-394.

Scheme 23: Hydroformylation of protected primary amines and consecutive cyclization.

220b-d
b = Ac
c = Boc
d = Ts

n-aldehyde **221a-c** *iso*-aldehyde **222a-c**

a = Ac
b = Boc
c = Ts

223a-c
quant.
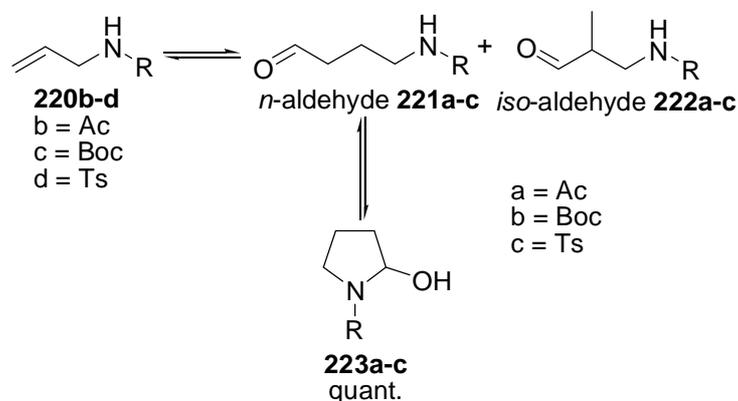
cond.: 1equiv. **220**, 0.3mol% Rh(acac)(CO)$_2$, 1.5mol% XANTPHOS,
10bar CO, 10bar H$_2$, THF, 20h, 70°C.

Those containing two carbonyl groups give the lowest *n/iso*-ratios. Here a precoordination of the catalyst is more probable than in substrates with only one carbonyl group. The allylic acetamide **220f** for example gives an *n/iso*-ratio of 12:1. Ethyloxycarbonyl protected *N*-ethyl allyl amine **220g** gives the highest *n/iso*-selectivity of approximately 14:1, with an optimum of the catalyst ligand ratio at 1:10. Higher catalyst ligand ratios give no further enhancement of the *n*-selectivity in the case of allylic phthalimide.

Table 4: Regioselectivity of the hydroformylation of allylic amines in dependence from the protecting group.

entry	olefin **220**	XANTPHOS : [Rh]	221/222[a),b)]	
1	**220a** (R$_1$=R$_2$=Pht)	5 : 1	4:1	**221a/222a**
		10 : 1	6:1	
2	**220e** (R$_1$=Et, R$_2$=Ts)	5 : 1	6:1	**221e/222e**
		10 : 1	6:1	
3	**220f** (R$_1$=Et, R$_2$=Ac)	5 : 1	11:1	**221f/222f**
		10 : 1	12:1	
4	**220g** (R$_1$=Et, R$_2$=Eoc)	5 : 1	13:1	**221g/222g**
		10 : 1	14:1	

cond.: 1equiv. **220**, 0.3mol% Rh(acac)(CO)$_2$, XANTPHOS (see table), 10bar CO, 10bar H$_2$, THF, 20h, 70°C. [a)] determined by ^{1}H-NMR of the crude reaction mixture. [b)] full conversion.

2.6.2 INFLUENCE OF ARYL HYDRAZINES ON *N*-SELECTIVE HYDROFORMYLATION

In order to study the influence of hydrazines on the *n/iso*-selectivity of the rhodium/xantphos catalyst, hydroformylation of protected allylic amines is conducted in the

presence of phenylhydrazine. From the results compiled in Table 5 it can be concluded that aromatic hydrazines are not competing with the *n*-directing XANTPHOS. Therefore aryl hydrazones are obtained with a high degree of *n*-selectivity starting from protected allylic amines.

Table 5: Tandem hydroformylation / hydrazone formation of allylic amines in dependence from the protecting group.

entry	olefin **220**	XANTPHOS : [Rh]	224/225[a),b]	
1	**220a** ($R_1 = R_2 = $Pht)	5 : 1 10 : 1	1:1 6:1	**224a/225a**
2	**220e** ($R_1 = $Et, $R_2 = $Ts)	5 : 1 10 : 1	3:1 6:1	**224b/225b**
3	**220f** ($R_1 = $Et, $R_2 = $Ac)	5 : 1 10 : 1	11:1 12:1	**224c/225c**

cond.: 1equiv. **220**, 1equiv. **214a**, 0.3mol% Rh(acac)(CO)$_2$, XANTPHOS (see table), 10bar CO, 10bar H$_2$, THF, 68h, 70°C. [a]determined by ^{1}H-NMR of the crude reaction mixture. [b]full conversion.

2.6.3 APPLICATION OF *N*-SELECTIVE HYDROFORMYLATION / INDOLIZATION

In using the optimized conditions of the tandem hydroformylation / indolization procedure, olefin **220j** gives the methyl ester of the plant growth regulator 3-indole butanoic acid (IBA, **226**) in 91% isolated yield (Scheme 24). Hydrazone formation and indolization proceed smoothly after addition of dilute H$_2$SO$_4$.

Scheme 24: Synthesis of the plant growth regulator IBA.
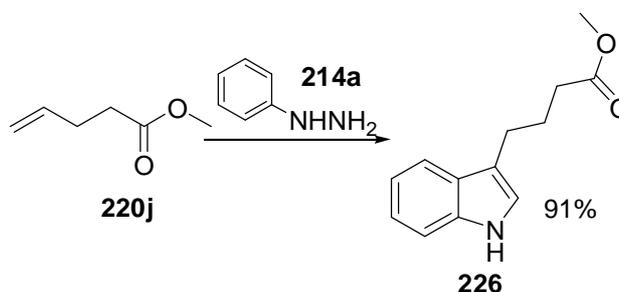
cond.: [a] 1equiv. **220j**, 1equiv. **214a**, 0.3mol% Rh(acac)(CO)$_2$, 3mol% XANTPHOS, 10bar CO, 10bar H$_2$, 68h, 70°C [b] 4wt% H$_2$SO$_4$/THF, 2h, 80°C.

If allylic amides and homoallylic amides are subjected to the same conditions, tryptamines and homotryptamines are obtained in good yields. All protecting groups are tolerated and as

expected from the results described above, strong electron withdrawing protecting groups give the best yields (Table 6).

Table 6: Tandem hydroformylation / Fischer indole synthesis of non-branched tryptamines and homologues.
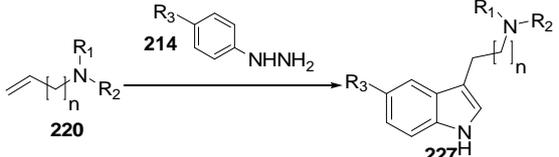
entry	olefin **220**	hydrazine **214**	yield **227**
1	**220c** (n=1, R_1=H, R_2=Ts)	**214a**	**227a**, 59%
2	**220a** (n=1, R_1=R_2=Pht)	**214a**	**227b**, 51%
3	**220a** (n=1, R_1=R_2=Pht)	**214j**	**227c**, 80%
4	**220e** (n=1, R_1=Et, R_2=Ts)	**214a**	**227d**, 81%
5	**220f** (n=1, R_1=Et, R_2=Ac)	**214a**	**227e**, 59%
6	**220h** (n=2, R_1=Et, R_2=Ts)	**214a**	**227f**, 58%
7	**220g** (n=1, R_1=Et, R_2=Eoc)	**214a**	**227g**, 51%
8	**220j** (n=1, R_1=Et, R_2=Bz)	**214a**	**227h**, 32%
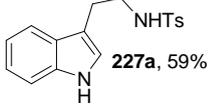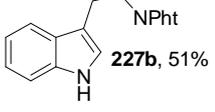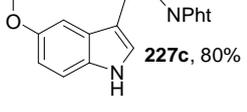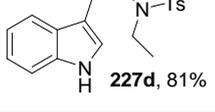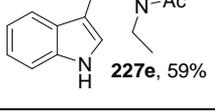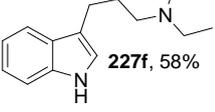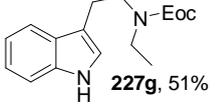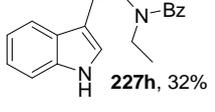
cond.: a) 1equiv. **214**, 1equiv. **220**, 0.3mol% Rh(acac)(CO)$_2$, 3mol% XANTPHOS, 10bar CO, 10bar H$_2$, 68h, 70°C b) 4wt% H$_2$SO$_4$/THF, 2h, 80°C.

It is noteworthy that tandem hydroformylation / FISCHER indole synthesis of **220h** gives tosylated homotryptamine **227f** in good yields. Application of *a*-Boc protected *p*-methoxy phenylhydrazine **214j** yields the 5-methoxy-tryptamine **227c** in excellent yields. Here, no further purification is required.

2.7 INTERIM CONCLUSION

In this chapter the optimization towards the synthesis of protected primary and secondary tryptamines starting from allylic amides is described.

Ø Two different protocols have been developed:

- *First generation protocol.* The hydroformylation of allylic amides is conducted in the presence of an appropriate aromatic hydrazine in unpolar solvents such as THF. Commercially available aryl hydrazines as well as *a*-Boc protected aryl hydrazines can be used. Indolization is started by subsequent addition of acid to this reaction mixture. Here H_2SO_4 turned out to be the acid of choice.

- *Second generation protocol.* The hydroformylation of allylic amides is conducted in the presence of an appropriate aromatic hydrazine and PTSA. If commercially available hydrazines are used, subsequent tosylation helps to purify the indole from by-products. The selectivity of this tandem reaction can be increased by the use of benzhydrylidene protected aryl hydrazines.

Ø Aryl hydrazones can be obtained from a hydroformylation of olefins in the presence of aryl hydrazines in almost quantitative yields. These hydrazones might be useful intermediates for other applications, such as [2+3]-cycloadditions.

Ø *n*-selective hydroformylation can be achieved with the use of XANTPHOS. Aromatic hydrazines do not compete with the ligand for the catalyst and do not hamper the *n*-selectivity.

Ø Several basic applications have been presented, such as the synthesis of the serotonin analogues **215j** and **227c**, the methyl ester of the plant growth regulator IBA (**226**) and of **219**, a valuable intermediate in the synthesis of sertindole analogues.

3 SYNTHESIS OF TERTIARY TRYPTAMINES

Many therapeutically relevant tryptamines contain tertiary amine moieties. In the preceding chapter the application of the tandem hydroformylation / indolization towards primary and secondary tryptamines is described. Here, the tandem reaction of protected primary and secondary allylic and homoallylic amines was preferably conducted in non-polar solvents such as toluene or THF. In order to obtain tryptamines with tertiary amine moieties, tertiary aminoolefins have to be used. Surprisingly, the previously developed protocols fail with this type of substrates. Several reasons might be responsible:

Ø More nucleophilic tertiary amines might be protonated in the presence of acid and precipitate from the non-polar reaction mixture. Precipitation of aryl hydrazine salts is responsible for a lower selectivity earlier. Therefore, benzhydrylidene protected hydrazines are used. The same enrichment of salts might hamper the tandem protocol applied to tertiary amines.

Ø Rhodium catalysts exhibit double bond isomerization activity. It has been reported, that allylic amines isomerize to enamines under rhodium catalysis at mild temperatures[38]. It is also well known, that enamines are easily hydrogenated under hydroformylation conditions in an overall hydroaminomethylation[8]. Such isomerization / hydrogenation processes would lead to a loss of olefin.

Ø It is well documented that the hydrogenation activity of rhodium catalysts is increased in the presence of catalytic amounts of tertiary amines[39]. In using amino olefins, the tertiary amines, as part of the substrate, are present in high excess relative to the catalyst. Therefore, hydrogenation of the olefin can result in loss of starting material while consecutive hydrogenation of the hydroformylation product leads to the corresponding alcohol or hydrazine.

Ø Furthermore, tertiary amines acting as bases can induce aldol condensation reactions of the aldehydes as a side-reaction.

Therefore, a new set of conditions has to be developed for tertiary aminoolefins by conducting the tandem reaction stepwise, and optimization of each single step.

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[38] Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; *J. Am. Chem. Soc.* **1984**, *106*, 5208-5217.

[39] *a*) Kaneda, K.; Yasumura, M.; Hiraki, M.; Imanaka, T.; Teransihi, S. *Chem. Lett.* **1981**, 1763. *b*) Kaneda, K.; Imanaka, T.; Teranishi, S. *Chem. Lett.* **1983**, 1465.

3.1 HYDROFORMYLATION IN THE PRESENCE OF ARYL HYDRAZINES

As expected, hydroformylation of *N*-allylic, *N,N*-dimethyl amine (**301a**) and of 4-methylene, *N*-methyl piperidine (**301l**) does not give any aminoaldehyde even if XANTPHOS is added. If, however, hydroformylation of the same allylic amines is conducted in the presence of phenylhydrazine (**302a**), the expected aryl hydrazones **303** can be isolated in almost quantitative yields (Table 7). No purification is needed, so the products can be used for indolization directly. Under the chosen conditions, electron withdrawing as well as electron donating substituents at the aryl hydrazine are tolerated. Even nitro groups that are prone to catalytic hydrogenation are stable under the selected conditions[40]. It is also important to mention that the use of Rh/xantphos grants high *n*-selectivity in the hydroformylation of terminal monosubstituted amino olefins.

Table 7: Tandem hydroformylation / hydrazone formation of tertiary allylic amines.

entry	olefin **301**	hydrazine **302**	yield **303**
1	**301a** ($R_1=CH_3$)	**302a** ($R_2=H$)	quant. (**303a**)
2	**301b** ($R_1=(CH_2)_5$)	**302a** ($R_2=H$)	97% (**303b**)
3	**301b** ($R_1=(CH_2)_5$)	**302b** ($R_2=OMe$)	93% (**303c**)
4	**301a** ($R_1=CH_3$)	**302c** ($R_2=CN$)	90% (**303d**)
5	**301b** ($R_1=(CH_2)_5$)	**302d** ($R_2=NO_2$)	80% (**303e**)

cond.: 1equiv. **301**, 1equiv. **302**, 0.3mol% Rh(acac)(CO)$_2$, 1.5mol% XANTPHOS, 10bar CO, 10bar H$_2$, THF, 3d, 70°C.

In all cases, hydrogenation products are not observed neither of the olefin nor the aldehyde which is immediately trapped by the hydrazine. Also the aryl hydrazone double bond is not hydrogenated, presumably due to higher stability of aryl hydrazones towards hydrogenation as compared to the aldehyde precursors. In summary, the hydrazone group acts as an efficient protecting group for aldehydes against hydrogenation and aldol reactions. In contrast to other protecting groups, the phenylhydrazone is a building block for the final indole product at the same time.

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[40] Nitro groups can be reduced under harsh hydroformylation conditions allowing to be used as aniline precursors in hydroaminomethylations. Rische, T.; *Dissertation* **1999**, University of Dortmund.

3.2   FISCHER INDOLIZATION

3.2.1   TRYPTAMINES WITH LINEAR SIDE CHAINS

While the hydroformylation described above is performed in THF, FISCHER indolization requires a more polar solvent in order to prevent precipitation of salts formed by protonation of the amino and/or hydrazine/hydrazone groups. Alcohols are common solvents in FISCHER indole syntheses. However, indolization of **303a** in ethanol gives tryptamine **304a** only in an unselective conversion with poor yields. Reaction in methanol does not lead to any improvements, while in aqueous H_2SO_4, fast and highly selective conversion towards indole **304a** is found with quantitative yields. Surprisingly this method proceeds with such a high degree of selectivity that a purification of the reaction product is obsolete. If after a hydroformylation of the amino olefin in the presence of an aryl hydrazine the solvent is removed and the remaining aryl hydrazone is taken up in aqueous H_2SO_4 for the final indolization, a combination of these two steps seems to be a suitable protocol for the synthesis of tryptamines directly from olefins. The reliability of this first generation protocol is tested with a number of different allylic and homoallylic amines and the results are compiled in Table 8.

Table 8: Tandem hydroformylation / Fischer indole synthesis of tertiary allylic amines.

entry	olefin **301**	yield **304**	entry	olefin **301**	yield **304**
1	**301a**	**304a** quant.	2	**301b**	**304b** 97%
3	**301c**	**304c**[a] 96%	4	**301d**	**304d** 94%
5	**301e**	**304e** 91%	6	**301f**	**304f** 91%

cond.: i) 1equiv. **301**, 1equiv. **302a**, 0.3mol% Rh(acac)(CO)$_2$, 1.5mol% XANTPHOS, 10bar CO, 10bar H$_2$, THF, 3d, 70°C. ii) 4wt% H$_2$SO$_4$, 2h, 100°C. Yield is given for the tandem reaction starting with the olefin. [a]precipitated as hydrochloride salt.

Without exception, all indoles are obtained in excellent yields and no products stemming from *iso*-aldehydes are detected. Thus, Rh/xantphos is a powerful hydroformylation catalyst for the regioselective conversion of amino olefins and, in contrast to other observations[41], the positive effect of the ligand is not suppressed in the presence of the amine and hydrazine units. The stability of the carbamate protecting group in **304d** and **304f** is also surprising. After removal of this group the nitrogen can be activated for further derivatization as required for target molecules such as pharmaceutical compound L 775 606. While tryptamine **304a** is known as a prominent structural element in many biologically active indole derivatives, tryptamines with the nitrogen as part of a cyclic moiety are garnering more and more interest. The piperazin moiety especially seems to be very attractive for pharmaceutical use. The structural element of **304c** for example, is found in the antipsychotic oxypertine (Scheme 25). For targets of this type, it is important to prove that both, allylic piperazines as well as homoallylic piperazines, are tolerated under the used conditions, allowing the attachment of amines at varying distances to different indole cores. In general, allylation and homoallylation of amines proceed with excellent yields, thus allowing a modular approach using the method described above.

Scheme 25: Piperazine units in pharmaceutically relevant tryptamines.

Oxypertine
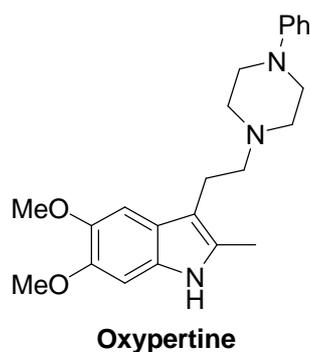
3.2.2 TRYPTAMINES WITH BRANCHED SIDE CHAINS

Apart from tryptamine analogues with linear side chains as prepared above, derivatives with branched side chains have also come into the focus of medicinal chemistry. In the past few years, the first examples of such branched tryptamines possessing pharmacologically interesting properties have been developed. The *a*-branched tryptamine LY 156735 for

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[41] Angelovski, G.; Eilbracht, P.; *Tetrahedron* **2003**, *41*, 8265-8274.

example, is a melatonin agonist, which helps to alleviate the symptoms of jet lag and which enhances readaptation of desynchronized circadian rhythms to a new time zone[42].

Scheme 26: Pharmaceutically relevant tryptamines with branches in the side chain.

LY 156735   *b*-carboline derivatives
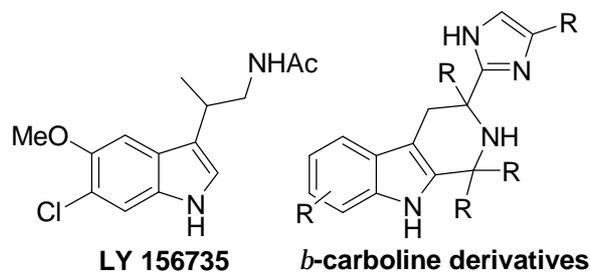
Tryptamines with branches at the *b*-carbon as found in various *b*-carboline derivatives (Scheme 26) act as potential drugs against depression anxiety. Most of the known *b*-branched tryptamines are tryptophan derivatives and can be synthesized starting from this essential amino acid. Therefore, not surprisingly, only a few examples of *b*-branched tryptamines are reported with substituents not possessing the oxidation level of carboxylic groups or with substituents not obtainable from carboxylic groups. Obviously there is a need for a method that allows fast access to branched tryptamines as well. The tandem hydroformylation / FISCHER indolization can be such a method. If branched olefins are used instead of linear olefins, tryptamines and homotryptamines with branches in the side chain can be obtained.

In chapter 2, it has already been demonstrated that *a*-branched tryptamines can be obtained by using terminally disubstituted olefins like methallyic amines which can easily be prepared by simple allylation with methallyic chloride. The allylic amines required for the synthesis of *b*-branched tryptamines are obviously less conveniently obtained and in addition, they bear a stereogenic center. Simple allylation of amines may fail due to poor regioselectivity and problems to control the configuration of the newly formed stereocenter, if it is required. A well-described method to synthesize chiral allylic amines is the OVERMAN rearrangement of allylic trihaloacetimidates, giving protected primary amines[43]. After deprotection and alkylation the tertiary chiral amine **301g** can be obtained as a racemate. An alternative method to obtain chiral allylic amines has been published in 2001 by TAKEUCHI *et al.*[44]. Here regioselective allylic amination of allylic carbonates and acetates has been achieved with a Ir/P(OPh)$_3$ catalyst. In 2002, HARTWIG published the first regio- and enantioselective allylic

[42] Nickelsen, T.; Samel, A.; Vejvoda, M.; Wenzel, J.; Smith, B.; Gerzer, R.; *Chronobiol Int.*,**2002**, *5*, 915-936.
[43] Overman, L.E.; *J. Am. Chem. Soc.* **1974**, *96*, 597.
[44] Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N.; *J. Am. Chem. Soc.* **2001**, *123*, 9525-9534.

amination[45]. With this methodology, a large number of different allylic amines is accessible, such as **301h**, with varying amine functionalities as well as alkyl, homoaryl and heteroaryl substituents tolerable at the stereocenter. Using these methods (OVERMAN rearrangement, allylic amination) for selected examples followed by the tandem hydroformylation / FISCHER indole procedure *b*-branched indoles are obtained in good to excellent yields (Table 9).While the allylic amination proceeds with high enantiomeric excesses, the stereocenter may epimerize during a tandem hydroformylation / FISCHER indolization via reversible double bond isomerization either by the transition metal catalyst or the acid. The tryptamines obtained from enantiomerically pure allylic amines however, reveal complete retention of chirality under hydroformylation conditions.

Table 9: Tandem hydroformylation / Fischer indolization of branched allylic amines.

entry	olefin **301**	yield **304**
1	**301g**	**304g** 85%
2	*rac*-**301h**	*rac*-**304h** 54%[a]
3	(+)-**301h** (96%*ee*)	(+)-**304h** 54%[a], 95%*ee*[a,b]
4	(-)-**301h** (96%*ee*)	(-)-**304h** 54%[a], 95%*ee*[a,b]

cond.: i) 1equiv. **301**, 1equiv. **302a**, 1mol% Rh(acac)(CO)$_2$, 5mol% XANTPHOS , 10bar CO, 10bar H$_2$, THF, 3d, 80°C. ii) 4wt% H$_2$SO$_4$, 2h, 100°C. Yield is given for the tandem reaction starting with the olefin. [a] average of all reactions with 201h, [b] Determined by HPLC with a Daicel Chiracel OJ.

[45] Ohmura, T.; Hartwig, J.F.; *J. Am. Chem. Soc.* **2002**, *124*, 15164-15165.

This combination of iridium catalyzed enantioselective allylic amination and tandem hydroformylation / FISCHER indole synthesis, in contrast to other methods reported, gives fast access to *b*-branched tryptamines which can not be derived from tryptophan and therefore allows access to a new class of tryptamine derivatives for biological screenings.

3.2.3 INDOLIZATION UNDER REARRANGEMENT

In contrast to the use of branched olefins the use of internal olefins is another option to place substituents on the olefin. If, for example, cinnamyl piperidine (**301i**) as a styrene type olefin is used, hydroformylation takes place preferably in benzyl position. Regioselectivity can be improved by the additional use of the biphosphite ligand BIPHEPHOS. Hydroformylation of **301i** and condensation leads to hydrazone **306**. After a [3,3]-sigmatropic rearrangement and cyclization, intermediate **308** is formed which rearranges to gain aromaticity. In this case, the aromatic ring migrates into the 2-position exclusively, forming the selective 5-HT$_{2A}$ antagonist 2-phenyl-trpytamine **304i** in 60% yield (Scheme 27).

Scheme 27: Hydroformylation / Fischer indolization of internal olefins – Synthesis of 2-aryl tryptamines.
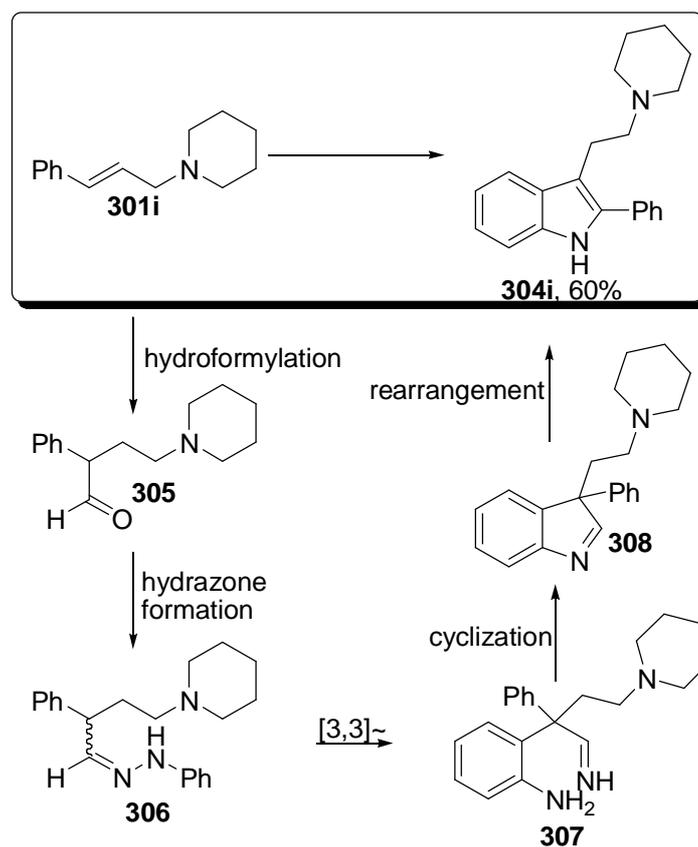
cond.: i) 1equiv. **301i**, 1equiv. **302a**, 0.5mol% Rh(acac)(CO)$_2$, 10mol% XANTPHOS , 10bar CO, 10bar H$_2$, THF, 3d, 100°C. ii) 4wt% H$_2$SO$_4$, 2h, 100°C. Yield is given for the tandem reaction starting with the olefin.

This combination of aryl migration and tandem hydroformylation / FISCHER indole reaction is not limited to allylic amines and might therefore be a valuable tool for the synthesis of drug candidates possessing an aryl moiety in the 2-position like the examples in Scheme 28 [46].
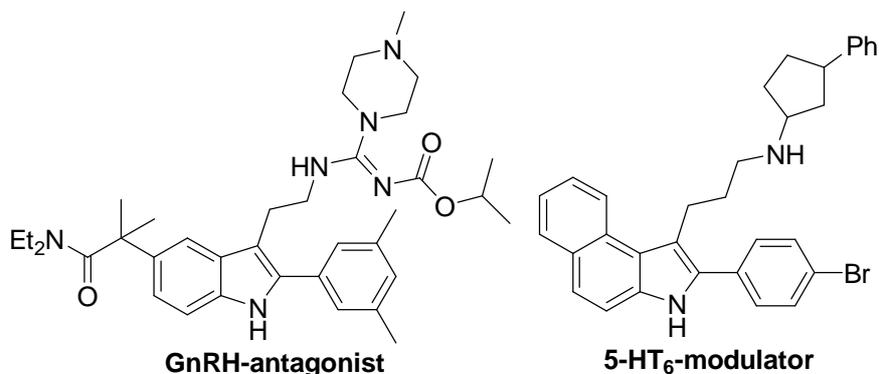
Scheme 28: Pharmaceutically relevant 2-aryl tryptamines.

GnRH-antagonist   **5-HT$_6$-modulator**

3.2.4 HOMOTRYPTAMINES WITH BRANCHED SIDE CHAINS

In using the same protocol with branched homoallylic amines, branched homotryptamines are achieved. The required amines are easily obtained via a combination of MANNICH reaction and WITTIG olefination, by carbomagnezation or by simple BARBIER type reactions.

Scheme 29: Pharmaceutically relevant branched homotryptamine.

Naratriptan
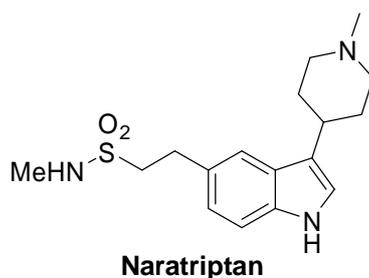
A number of different methods have been published to control absolute configuration of the stereocenters in BARBIER type reactions. The homoallylic moiety can also be embedded in an exocyclic olefin. If 4-methylene-piperidines are used, 3-(*N*-methyl piperdiyl)-indoles are obtained containing an important structural element for active agents like anti-migraine drug L 775 606 or naratriptan (Scheme 29). As it can be seen from Table 10 most homotryptamines can be obtained in good to excellent yields. Halide substituents are tolerated allowing further derivatization with common cross coupling methodologies. With this respect, substrate **204o** may act as a valuable intermediate for the synthesis of naratriptan.

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[46] Köhling, P.; Schmidt, A.M.; Eilbracht, P.; *Org. Biomol. Chem.* **2005**, in preparation.

Table 10: Tandem hydroformylation / Fischer indolization towards branched homotryptamines.

Entry	olefin 301	hydrazine 302	yield 304	Entry	olefin 301	hydrazine 302	yield 304
1	301j	302a (R=H)	304j 41%[a]	2	301k	302a (R=H)	304k 51%[a]
3	301l	302a (R=H)	304l 81%[b]	4	301m	302a (R=H)	304m 78%[c]
5	301m	302e (R=F)	304n 65%[c]	6	301m	302f (R=Cl)	304o 85%[c]
7	301m	302g (R=Br)	304p quant.[c]	8	301m	302h (R=CH$_3$)	304q 66%[c]
9	301m	302b (R=OCH$_3$)	304r 85%[c]				

cond.: [a] i) 1equiv. 301, 1equiv. 302, 1mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 3d, 120°C. ii) 4wt% H$_2$SO$_4$, 2h, 100°C. Yield is given for the tandem reaction starting with the olefin; [b] i) 1equiv. 301, 1equiv. 302, 0.3mol% Rh(acac)(CO)$_2$, 1.5mol% XANTPHOS, 10bar CO, 10bar H$_2$, THF, 3d, 70°C. ii) 4wt% H$_2$SO$_4$, 2h, 100°C. Yield is given for the tandem reaction starting with the olefin; [c] i) 1equiv. 301, 1equiv. 302, 0.3mol% Rh(acac)(CO)$_2$, 50 bar CO, 10 bar H$_2$, THF, 3d, 100°C. ii) 4wt% H$_2$SO$_4$, 2h, 100°C. Yield is given for the tandem reaction starting with the olefin.

3.3 TANDEM REACTION IN WATER

In conclusion, this first generation protocol for tandem hydroformylation / FISCHER indole synthesis gives fast and convenient access to a large number of differently substituted tryptamines with tertiary amine moieties. However, this protocol requires a change of solvent to complete the procedure, although there is no need for a purification of the aryl hydrazones. Therefore, it is desirable to develop an advanced protocol that allows direct access to tryptamine derivatives from amino olefins. This requires a solvent with good solubility for all reagents and reactants. While alcoholic solvents have failed in test reactions, it turned out that

water is the solvent of choice, since H_2SO_4 in water allows a smooth conversion of the aryl hydrazones to tryptamines. Solubility of the rhodium based hydroformylation catalyst in water and even in aqueous H_2SO_4 can be achieved in using sulfonated ligands such as TPPTS or the analogous derivative **309** of XANTPHOS (Scheme 30).

Scheme 30: Water soluble ligands for the second generation protocol in water.
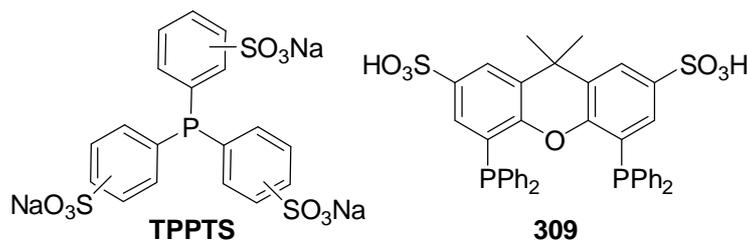
With respect to the pharmacological relevance of 3-piperidyl indoles this modification was tested with allylic and homoallylic substrates mostly containing the piperidyl or the piperazinyl moiety with rhodium/TPPTS or rrhodium/**309** in aqueous H_2SO_4. As shown in Table 11, tandem hydroformylation / FISCHER indole synthesis in water gives, in all cases, excellent results. For 3-piperidyl-indoles (entries 1-4) no further purification is required. It is worth to mention that sensitive bromo substituents are maintained, even at prolonged reaction times, during which the aryl halide is treated with mineral acid under harsh conditions. Clearly, regioselective tandem hydroformylation / FISCHER indole synthesis in water is not limited to disubstituted terminal olefins as the substrate. Conversion of allylic and homoallylic amines also gives good to excellent yields of the desired tryptamine analogues. High regioselectivities can also be achieved with sulfonated xantphos **309**.

Table 11: Tandem hydroformylation / Fischer indolization in water.

entry	olefin **301**	hydrazine **302**	yield **304**
1	**301m**	**302a** (R=4-H)	**304m** 80%[b]
2	**301m**	**302e** (R=4-F)[a]	**304n** 95%[b]
3	**301m**	**302f** (R=4-Cl)[a]	**304o** quant.[b]
4	**301m**	**302g** (R=4-Br)[a]	**304p** 96%[b]
5	**301m**	**302h** (R=2-Cl)[a]	**304s** 96%[b]
6	**301d**	**302a** (R=4-H)	**304d** quant.[c]
7	**301e**	**302a** (R=4-H)	**304e** 50%[c]
8	**301l**	**302a** (R=4-H)	**304l** quant.[c]

cond.: [a] hydrochlorides were used directly; [b] 1equiv. **301**, 1equiv. **302**, 0.3mol% Rh(acac)(CO)$_2$, 1.5mol% TPPTS, 50bar CO, 10bar H$_2$, 4wt% H$_2$SO$_4$, 3d, 100°C; [c] 2equiv. **301**, 1equiv. **302**, 0.3mol% Rh(acac)(CO)$_2$, 3mol% **305**, 10bar CO, 10bar H$_2$, 4wt% H$_2$SO$_4$, 3d, 100°C.

3.4 APPLICATION – SYNTHESIS OF MIGRAINE DRUGS

In further experiments, both protocols for tandem hydroformylation / FISCHER indole were tested in the synthesis of the three anti-migraine drugs LY 334 370, L 775 606 and LY 349 950. The results are given in Table 12. While for entry 1&3 the second generation protocol gives no significant improvement, the tandem reaction in water gives LY 334 370 (entry 2) in almost quantitative yield, making further purifications not necessary. In all cases, overall yields improved, and the number of required steps is reduced compared to already described syntheses.

Table 12: Synthesis of migraine drugs via tandem hydroformylation / Fischer indolization.

entry	olefin **301**	hydrazine **302**	yield **304**
1	**301a**	**302i**	LY 349 950 44%[a]
2	**301m**	**302i**	LY 334 370 95%[b]
3	**301n**	**302j**	L 775 606 51%[a]

cond.: [a] i) 1equiv. **301**, 1equiv. **302**, 1mol% Rh(acac)(CO)$_2$, 5mol% XANTPHOS, 10bar CO, 10bar H$_2$, THF, 3d, 70°C. ii) 4wt% H$_2$SO$_4$, 2h, 100°C. Yield is given for the tandem reaction starting with the olefin; [b] 1equiv. **301**, 1equiv. **302**, 0.3mol% Rh(acac)(CO)$_2$, 1.5mol% TPPTS, 50 bar CO, 10 bar H$_2$, 4wt% H$_2$SO$_4$, 3d, 100°C.

Although syntheses of the required aryl hydrazines have been reported[47,48], it turned out to be hard to obtain the products with sufficient purity. Obviously the classical approach of aniline diazotation and reduction of the resulting diazonium salts with bisulfites or tin dichloride, suffers from low selectivity. Furthermore, purification of aryl hydrazines is hard to manage. Therefore, the GOLDBERG reaction was used to synthesize the required hydrazines

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[47] Xu, Y.-C.; Johnson, K.W.; Phebus, L.A.; Cohen, M.; Nelson, D.L.; Schenck, K.; Walker, C.D.; Fritz, J.E.; Kaldor, S.W.; LeTourneau, M.E.; Murff, R.E.; Zgombick, J.M.; Calligaro, D.O.; Audia, J.E.; Schaus, J.M.; *J. Med. Chem.* **2001**, *24*, 4031-4034.

[48] Sternfeld, F.; Guiblin, A.R.; Jelley, R.A.; Matassa, V.G.; Reeve, A.J.; Hunt, P.A.; Beer, M.S.; Heald, A.; Stanton, J.A.; Sohal, B.; Watt, A.P.; Street, L.J; *J. Med. Chem.* **1999**, *4*, 677-690.

starting from the corresponding aryl iodides under copper catalysis in good yields. The *a*-Boc protected aryl hydrazines are not prone to oxidation and can be easily purified by LC. Under FISCHER indolization conditions, the Boc group is removed to give the desired products in medium to excellent yields. Neither hydrolysis of the amide bonds in LY 334 950 and LY 334 370 nor hydrogenation of the imine-enamine pattern in L 775 606 is observed.

3.5 INTERIM CONCLUSION

Ø In almost every case, aryl hydrazones can be obtained in quantitative yields with high purity upon hydroformylation of aminoolefins in the presence of aromatic hydrazines.

Ø The hydrazone group protects the aminoaldehyde from undesired consecutive reactions such as hydrogenation or aldol reaction. Therefore the hydrazone acts as an efficient and productive protecting group at the same time being part of the final indole product.

Ø Stereogenic centers within the olefin are configuratively stable. Thus, no double bond migration is involved which might lead to thermodynamically more stable enamines.

Ø Two different protocols for the tandem hydroformylation / FISCHER indolization towards tryptamines with tertiary amine moieties have been developed:

- *First generation protocol.* The hydroformylation of aminoolefins is conducted in the presence of aryl hydrazines or *a*-Boc aryl hydrazines in THF. After evaporation of the solvent the remaining hydrazone is indolized in aqueous H_2SO_4.

- *Second generation protocol.* The hydroformylation of aminoolefins is conducted in the presence of aryl hydrazines, hydrazine hydrochlorides or *a*-Boc protected hydrazines in aqueous H_2SO_4 giving tryptamines directly. Water solubility of the catalyst can be achieved by the use of water soluble ligands such as TPPTS or SulfoXANTPHOS. Water is benign and therefore environmentally friendly.

Ø With both protocols, tryptamines and homotryptamines with linear and branched side chains can be obtained in excellent yields and in many cases without further purification.

Ø The combination of modern olefin and hydrazine syntheses with the tandem hydroformylation / FISCHER indolization is a modular approach that allows fast and convenient access towards tryptamines and analogues with high diversity in all

important positions (i.e. substituents on the indole ring, type of amine moiety, length of the side chain, substituents in the side chain).

Ø Even under harsh conditions, useful substituents, such as bromine, are tolerated, offering fast access to valuable intermediates for the synthesis of pharmaceuticals.

Ø Both protocols can be used for the total synthesis of migraine drugs. Here yields of up to 95% are observed.

4 FUNCTIONALIZATION OF TRYPTAMINES UNDER HYDROFORMYLATION CONDITIONS

In the past few years a number of tryptamines and homotryptamines bearing more sophisticated substituents at the amine moiety have been patented as potential drugs for the treatment of completely different medical conditions. Here especially, the substituents on the amine moiety seem to play a key role for the selectivity towards these different receptor families. A selection of such compounds is compiled in Scheme 31.

Scheme 31: Selected examples for recent pharmaceutically active tryptamines.

401
LDL-r regulator
(GSK, 2002)

402
D$_4$ antagonist
(Lundbeck, 2001)

403
CCR5 antagonist
(GSK, 1999)

404
CCR2B antagonist
(GSK, 2002)

Serotonin reuptake inhibitor
(Lundbeck, 2001)

Melanocortin receptor modulator
(Melacure Therapeutics, 2001)

MCH antagonist
(Pharmacopeia, 2001)
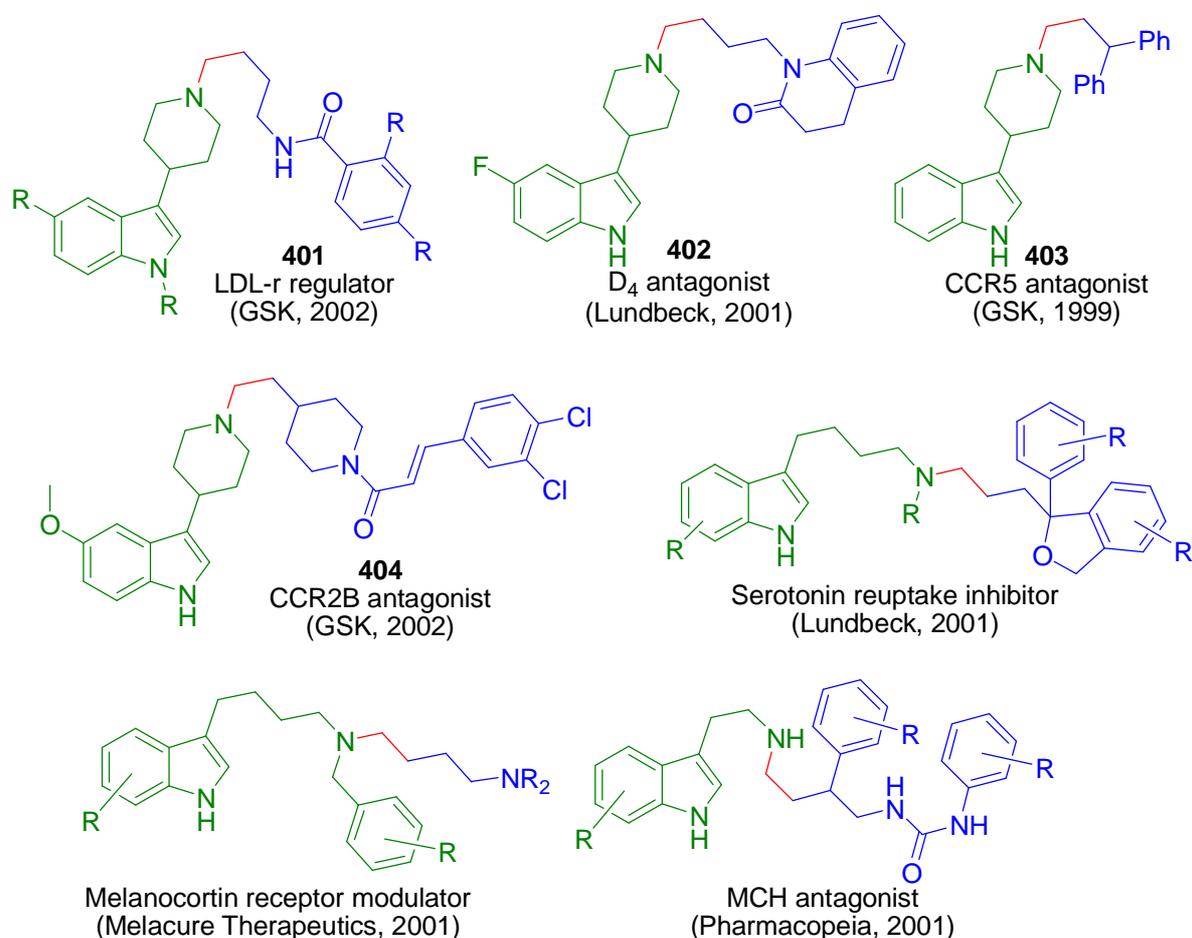
All these compounds can be obtained from simple tryptamines and homologues by alkylation or reductive amination with an aldehyde. In using the hydroaminomethylation, the synthesis of the required aldehyde via hydroformylation can be combined with the reductive amination to a one step procedure. Thus, starting with appropriate olefins (blue), tryptamines (green) and CO/H$_2$ (red), the pharmaceuticals in Scheme 31 may be accessible in only one step. The required tryptamines can also be synthesized efficiently under hydroformylation conditions as described in the previous chapters. In summary, a total synthesis of such

sophisticated tryptamine drugs might be achieved in a few steps using two different tandem hydroformylation sequences. Although primary or secondary tryptamines with aliphatic side chains in the 3-position derived from tandem hydroformylation / FISCHER indolization can be used in hydroaminomethylations in order to attach further substituents on the amine moieties, in this chapter 3-piperidyl indole drugs **401-404** (Scheme 31) are synthesized exclusively, representing pharmaceuticals for the treatment of important medical conditions. The compounds with the general structure **401** for example are LDL-receptor regulators and can be used for the treatment of an imbalance of low density lipoprotein cholesterol (LDL), which is responsible for a number of cardiovascular diseases, such as atherosclerosis, pancreatitis or non-insulin dependent diabetes mellitus (NIDDM)[49]. Substance **402** has a strong affinity towards the dopamine 4 (D_4) receptor. This antagonist can be used for the treatment of certain psychiatric and neurological disorders, in particular psychoses[50]. Compound **403** is a ligand that binds to the chemokine receptor 5 (CCR5). This receptor is involved in many medical conditions such as asthma or atopic disorders (e.g. atopic dermatitis or allergies). Therefore, substances that modulate this receptor might be used for the prevention or treatment of such diseases[51]. Compound **404** is a member of a class of MCP-1 (CCR2b) receptor antagonists. They inhibit MCP-1 stimulated chemotaxis in monocytes and can be used in the treatment of diseases with a clear inflammatory component, such as atherosclerosis, multiple sclerosis and AIDS[49a].

Furthermore, in the synthesis of the selected drugs **401-404** different types of olefins have to be used for the hydroaminomethylation step. Therefore different reaction conditions are presented and will be discussed in detail within this chapter.

4.1   SYNTHESIS OF THE 3-PIPERIDYL INDOLES

Syntheses of the required 3-piperidyl indoles have already been published. In many cases, this core is built up by electrophilic substitution of appropriately substituted indoles (**407**) which have to be synthesized previously (Scheme 32). After elimination of water, the resulting double bond is hydrogenated. This hydrogenation seems to be problematic since a selective differentiation of the conjugated double bonds is hard to manage. Poor yields (around 50%) are obtained for this ostensibly simple transformation reducing the overall

[49] *a)* Bouillot, A.M.J.; Bombrun, A.; Dumaitre, B.A.; Gosmini, R.L.M.; *PCT. Int. Appl.* **2002**, WO2002055496. *b)* Bouillot, A.M.J.; Dumaitre, B.A.; *PCT. Int. Appl.* **2004**, WO2004006923. *c)* Bouillot, A.M.J.; Dumaitre, B.A., *PCT. Int. Appl.* **2004**, WO2004006922.

[50] Bang-Andersen, B.; Felding, J.; Kehler, J.; Andersen, K.; *PCT. Int. Appl.* **2001**, WO2001096328.

[51] Bondell, W.E.; Chan, J.; Porter, R.A. *PCT. Int. Appl.* **1999**, WO1999017773.

yield. Tandem hydroformylation / FISCHER indolization can be an attractive alternative since simple functional group transformations are replaced by skeleton building steps.

Scheme 32: Comparison of syntheses towards 3-piperidyl indoles.

classical approach

tandem hydroformylation / Fischer indole synthesis
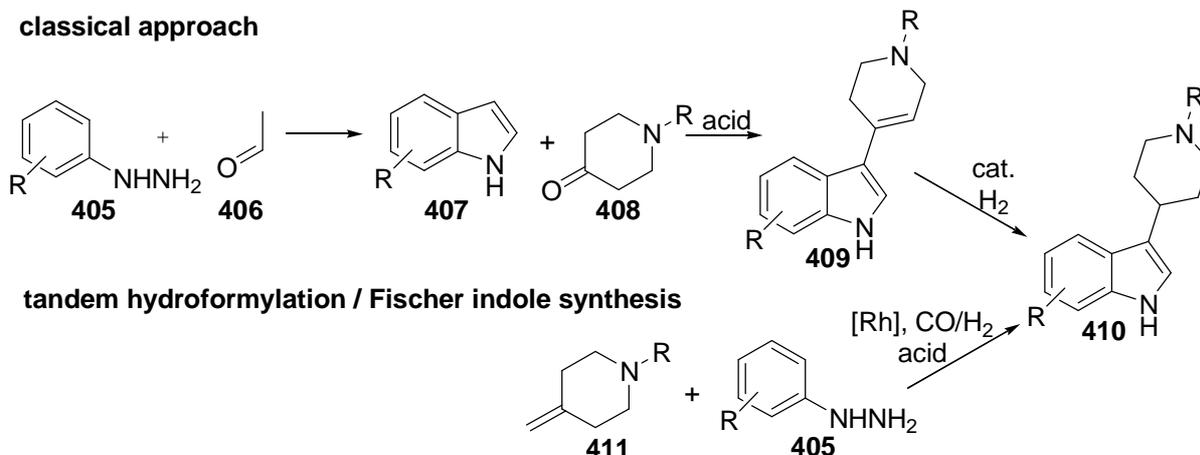
Since for further derivatization a secondary piperidyl indole is required, it would be desirable to subject secondary aminoolefins to the hydroformylation / FISCHER indole sequence directly.

Scheme 33: Attempts to synthesize secondary tryptamines under hydroformylation conditions.
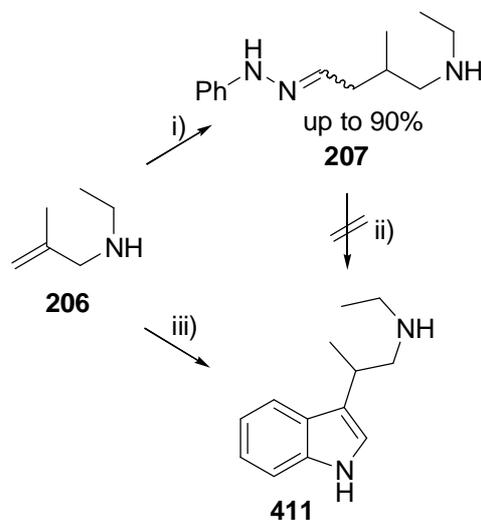
cond.: i) 1equiv. **206**, 1equiv. **302a**, 0.3mol% $Rh(acac)(CO)_2$, 50bar CO, 10bar H_2, THF, 100°C, 3d, 90%. ii) 1equiv. **207**, 4wt% H_2SO_4/THF, 80°C, 2h, 0%. iii) 1equiv. **206**, 1equiv. **302a**, 0.3mol% $Rh(acac)(CO)_2$, 1.5mol% TPPTS, 50bar CO, 10bar H_2, 4wt% H_2SO_4, 68h, 60%.

Although the secondary aminoolefin **206** gives the corresponding hydrazone **207** with up to 90% selectivity upon hydroformylation in the presence of phenylhydrazine, indolization of **207** in aqueous H_2SO_4 as well as 4wt% H_2SO_4 in DMF fails (Scheme 33). Even the second

generation protocol (tandem hydroformylation / FISCHER indole synthesis in water) gives hydrazone **207** in 60% yield. No indole formation is observed.

Therefore, protected primary and secondary aminoolefins, as described in chapter 2, have to be used. The ethyl carbamate group is stable under the conditions of this protocol and can be cleaved off under basic conditions very easily. **412a** can be obtained from ethyl 4-methylenepiperidine-1-carboxylate via simple WITTIG olefination in 81% yield. In order to find the ideal hydrazine source, both protocols for the tandem hydroformylation / FISCHER indolization are tested in the synthesis of the intermediate 3-piperidyl indoles. If benzhydrylidene protected aryl hydrazine **413a** is used with **412a** in the second generation protocol only 20% of the desired indole **414a** is obtained. If in contrast, the free phenylhydrazine is subjected to the first generation protocol, **414a** is isolated in 56% yield. The use of *a*-Boc phenylhydrazine (**413c**) gives only a small improvement of the yield allowing 61% of **414a** to be isolated (Table 13).

Table 13: Different hydrazines sources for the synthesis of 3-piperidyl indoles.

entry	hydrazine **413**	yield **414a**
1	**413a**	20%[a]
2	**413b**	56%[b]
3	**413c**	61%[b]
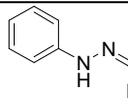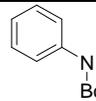
cond.: [a]1equiv. **412a**, 1equiv. **413**, 1equiv. PTSA, 0.3mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 100°C, 3d; [b]1equiv. **412a**, 1equiv. **413**, 0.3mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 68h, then 4wt% H$_2$SO$_4$/THF, 80°C, 2h.

In the same manner, tandem hydroformylation / FISCHER indole synthesis of **412a** with 4-fluoro phenylhydrazine carbamic acid tert-butyl ester (**413d**) gives indole **414b** in 38%. It seems that the fluoro substituent reduces electron density in the aromatic system and that the

key step of the FISCHER indolization, the [3,3]-sigmatropic Diaza-Cope rearrangement, is therefore hampered. In contrast, the use of **413e**, bearing an electron pushing substituent, in the tandem hydroformylation / FISCHER indolization with **412a** gives the desired indole **414c** in 70% isolated yield (Table 14).

Table 14: Synthesis of 3-piperidyl indoles.
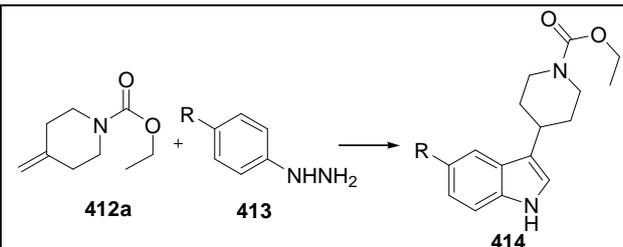
entry	hydrazine **413**	yield **414**
1	**413d** (R=F)	38% (**414b**; R=F)
2	**413e** (R=OCH$_3$)	70% (**414c**; R=OCH$_3$)

cond.: 1equiv. **412a**, 1equiv. **413**, 0.3mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 68h, then 4wt% H$_2$SO$_4$/THF, 80°C, 2h.

Deprotection of **414a**-**d** was in all cases conducted with 20wt% NaOH-solution in ethanol, giving the deprotected products **415** in almost quantitative yields without further purification needed.

Table 15: Deprotection of 3-piperdiyl indoles.
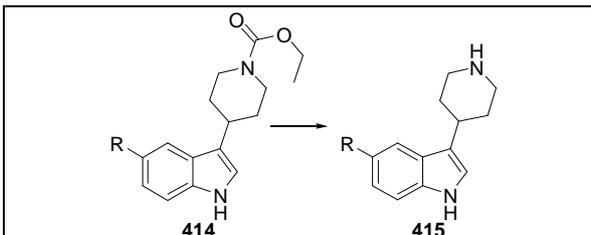
entry	indole **414**	yield **415**
1	**414a** (R=H)	96% (**415a**; R=H)
2	**414b** (R=F)	100% (**415b**; R=F)
3	**414c** (R=OCH$_3$)	100% (**415c**; R=OCH$_3$)

cond.: 1equiv. **414**, 20wt% NaOH, EtOH, 20h 100°C.

4.2 FUNCTIONALIZATION OF 3-PIPERIDYL INDOLES VIA HYDROAMINOMETHYLATION

For the synthesis of compounds **401**-**404** different types of olefins have to be used in the hydroaminomethylation step. Hydroformylation of allylic amides as required for **401** and **402** usually gives mixtures of *n*- and *iso*-aldehydes. Therefore the use of *n*-directing ligands like BIPHEPHOS or XANTPHOS is necessary. In 2003, BELLER *et al.* developed a protocol for

an *n*-selective hydroaminomethylation of simple olefins[52], but if functionalized olefins are used, the *n*-selectivity is reduced in many cases due to precoordination of the catalyst to the functional groups within the olefin. In the case of allylic amides, the catalyst may precoordinate to the amide oxygen and one edge of the double bond simultaneously giving a favored six membered cyclic transition state in a 6-exo-*trig* fashion (Scheme 34).

Scheme 34: Mechanisms for the control of the regioselectivity of the hydroformylation.
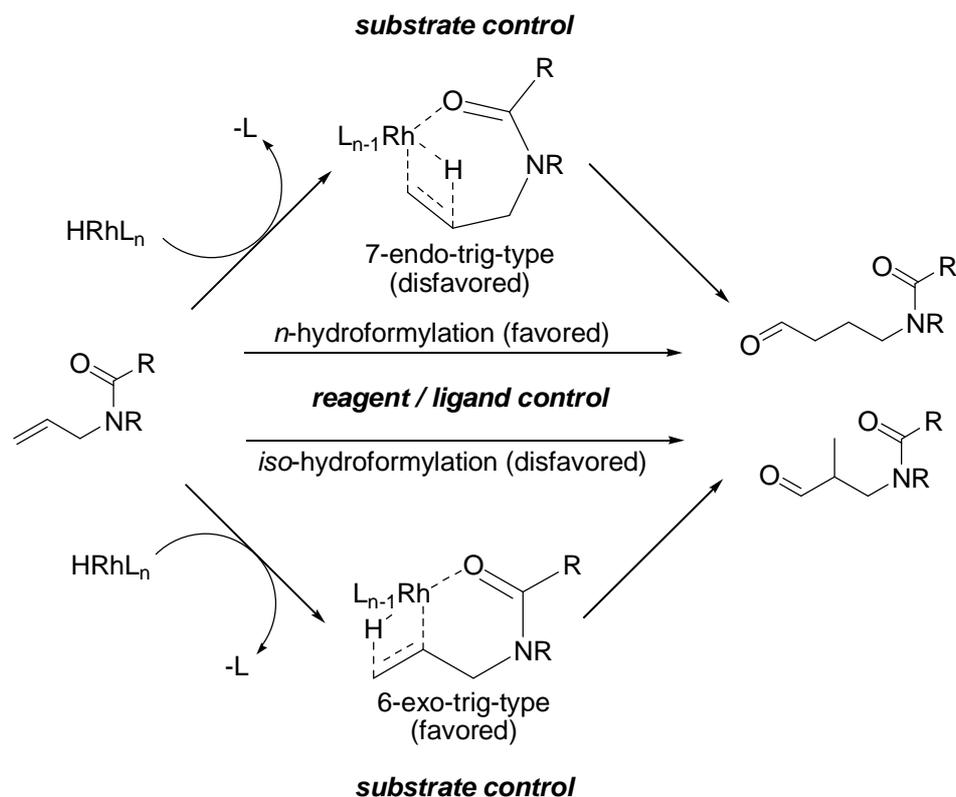
This results in an increased amount of *iso*-product. To suppress this substrate control, the ligand to catalyst ratio has to be increased compared to the original BELLER conditions. Hydroaminomethylation of allylic benzamide **412b** gives the formal analogue **401b** of LDL-receptor regulators **401** in 57% isolated yield. NMR of the crude product indicates *n*-selective hydroaminomethylation. It is also important to mention that only the piperidyl nitrogen is functionalized, no hydroaminomethylation of the indole nitrogen can be observed. Thus, a protection of this nitrogen prior to the conversion is not necessary. In Scheme 35 the total synthesis of **401**'s analogue **401b** is presented.

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[52] Ahmed, M.; Seayad, A.M.; Jackstell, R.; Beller, M.; *J. Am. Chem. Soc.* **2003**, *125*, 10311-10318.

Scheme 35: Synthesis of the analogue of the LDL-receptor regulator 401.

cond.: i) 1equiv. **412a**, 1equiv. **413c**, 0.3mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 120°C, 68h; then 4wt%H$_2$SO$_4$ / THF, 80°C, 2h, 61%; ii) 20wt% NaOH / EtOH, 100°C, 18h, 96%; iii) 1equiv. allylic benzamide (**412b**), 1mol% [Rh(cod)BF$_4$]$_2$, 10mol% XANTPHOS, 10bar CO, 50bar H$_2$, MeOH/toluene (1:1), 125°C, 3d, 57%.

In a comparable experiment functionalization of **415b** with 1-allyl-3,4-dihydroquinolin-2(1H)-one (**412c**) in a regioselective hydroaminomethylation gives D$_4$-receptor antagonist **402** in 49% isolated yield. As well as in the synthesis of **401b** the optimized hydroaminomethylation conditions lead to an *n*-selective reaction (Scheme 36).

Scheme 36: Synthesis of a D$_4$-antagonist.

cond.: i) 1equiv. **412a**, 1equiv. **409d**, 0.3mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 120°C, 68h; then 4wt% H$_2$SO$_4$ / THF, 80°C, 2h, 38%; ii) 20wt% NaOH / EtOH, 100°C, 18h, 100%; iii) 1equiv. **412c**, 1mol% [Rh(cod)BF$_4$]$_2$, 1mol% XANTPHOS, 10bar CO, 50bar H$_2$, MeOH/toluene (1:1), 125°C, 3d, 49%.

The CCR5 modulator **403** has the same 3-piperidyl indole core as LDL-receptor antagonist **401**, but in contrast **403** contains a 3,3-diaryl propyl amine unit. Such units can be synthesized by hydroaminomethylation of 1,1-diarylethenes. Due to steric and electronic reasons, such olefins require harsh conditions for hydroformylation. However, under these harsh conditions the oxidative addition of hydrogen to the intermediate rhodium alkyl species and reductive elimination of the hydrogenated olefin is faster than the rate determining CO-insertion. In 1999, RISCHE developed a protocol that allows chemoselective hydroaminomethylation of 1,1-diarylethenes [53]. Here the addition of PBu$_3$ is crucial, since this phosphane ligand reduces the catalyst's hydrogenation activity. At high temperature and with a high carbon monoxide partial pressure, pharmacologically active 3,3-diarylethenes can be obtained in excellent

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[53] Rische, T.; Eilbracht, P.; *Tetrahedron* **1999**, *55*, 1915-1920.

yields. The same protocol can be applied in the synthesis of **403** giving a 57% of this CCR5 receptor antagonist (Scheme 37).

Scheme 37: Synthesis of a CCR5-modulator.

cond.: i) 1equiv. **412a**, 1equiv. **413c**, 0.3mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 120°C, 68h; then 4wt% H$_2$SO$_4$ / THF, 80°C, 2h, 61%; ii) 20wt% NaOH / EtOH, 100°C, 18h, 100%; iii) 1equiv. 1,1-diphenylethane (**412d**), 5mol% [Rh(cod)Cl]$_2$, 15mol% PBu$_3$, 90bar CO, 10bar H$_2$, dioxane, 130°C, 3d, 57%.

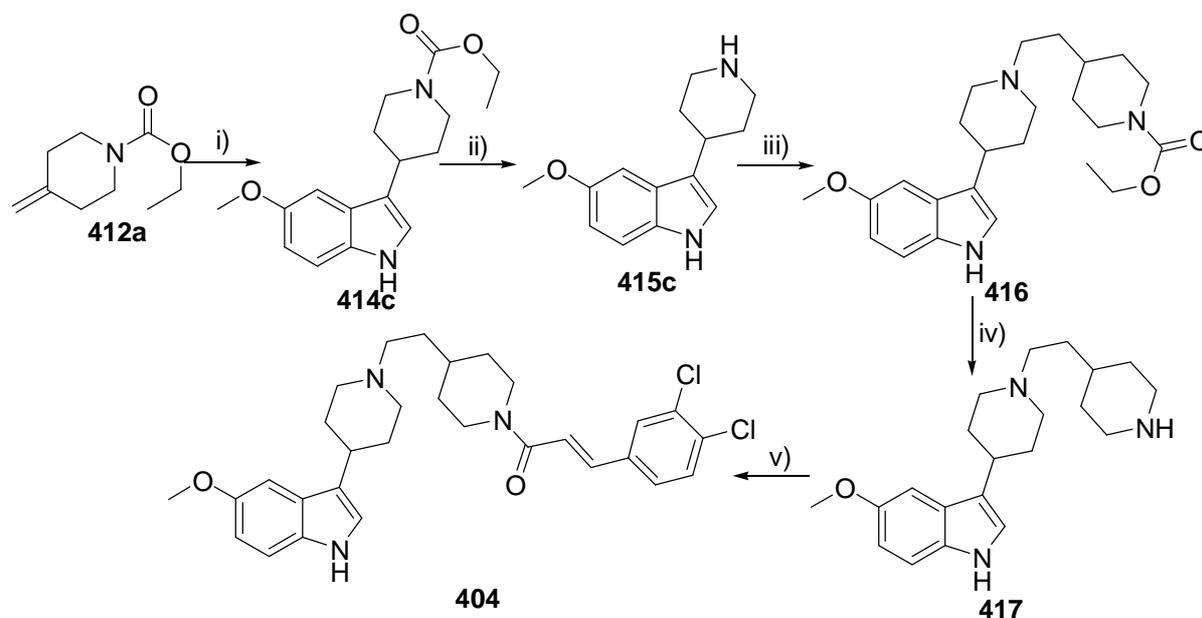In the synthesis of **404** olefin **412a** is used twice. It is used for the initial tandem hydroformylation / FISCHER indolization and it is used to attach the second piperidyl ring to the first via hydroaminomethylation to give **416** in 55% yield.

Scheme 38: Synthesis of a CCR2b-modulator.

cond.: i) 1equiv **412a**, 1equiv. **413e**, 0.3mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 120°C, 68h; then 4wt% H$_2$SO$_4$ / THF, 80°C, 2h, 70%; ii) 20wt% NaOH / EtOH, 100°C, 18h, 100%; iii) 1equiv. **412a**, 1mol% [Rh(cod)Cl]$_2$, 50bar CO, 10bar H$_2$, dioxane, 130°C, 3d, 55% iv) 20wt% NaOH, EtOH, 100°C, 20h, 98% v) 3,4-dichlorocinnamylacid, DCC, DMAP, THF, 24h, 62%.

The additional use of ligands is not necessary since hydroformylation of terminal disubstituted olefins proceeds with a high degree of regioselectivity. Further quantitative deprotection (**417**) allows the 3,4-dichlorocinnamyl acid moiety to be attached under carbodiimide mediation in 62% yield giving the anti-HIV drug **404** (Scheme 38).

4.3 INTERIM CONCLUSION

In this chapter a new synthetic approach towards highly functionalized tryptamines and homologues is developed and is applied towards the synthesis of four 3-piperidyl indole drugs (**401**-**404**).

Ø This innovative and efficient approach consists of 3 steps:

- The tandem hydroformylation / FISCHER indolization is used to synthesize the required indole amines. In contrast to published syntheses 3-piperidyl indoles are obtained in one step with up to 70% yield. Simple functional group transformations are replaced by skeleton building steps.

- Deprotection of the resulting indoles and activation for the final step in all cases gives almost quantitative yields.

- The hydroaminomethylation allows a highly selective and salt free attachment of required substituents on the amine moiety. Adjustment of the hydroaminomethylation conditions allows the use of different types of olefins. A previous protection of the indole nitrogen is not required.

Ø This modular approach is characterized by a high degree of diversity since substituents in all relevant positions can be varied.

Ø All building blocks are commercially available or can be obtained in a few steps.

5 INTRAMOLECULAR TANDEM HYDROFORMYLATION / FISCHER INDOLIZATION

The tandem hydroformylation / FISCHER indole synthesis has so far been applied to the synthesis of 5- or 7-substituted tryptamines and analogues due to their biological relevance. But many naturally occurring indole derivatives and indole drugs possess additional substituents in the 4-position including 3,4-ring annelations. The structures in Scheme 39 may act as representative examples. Psilocybin is reported to enter the central nervous system and causes powerful psychotomimetic effects[54] and (-)-indolactam V is a protein kinase C modulator[55].

Scheme 39: Examples of biologically relevant 4-substituted indoles.

Psilocybin   **(-)-Indolactam V**
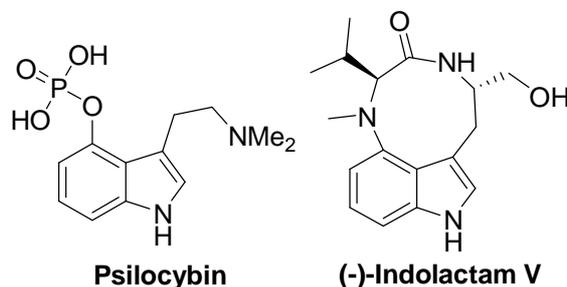
Synthesis of 4-substituted indoles either starts with a simple indole bearing appropriate substituents in the required positions, or the indole core is built up selectively. To achieve a regioselective indole formation, appropriately substituted precursors defining the substitution pattern within the final product are often used.

Scheme 40: Synthesis of psilocin via Larock indole synthesis.
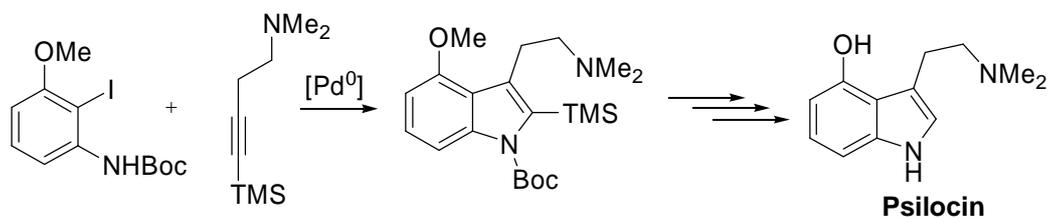
Psilocin

In the LAROCK indole synthesis, for example, *o*-halo-anilines are reacted with alkynes under palladium catalysis. SCAMMELLS *et al.* have used this method to obtain psilocin, which is a

[54] *a*) Stoll, A.; Troxler, F.; Peyer, J.; Hofmann, A. *Helv. Chim. Acta* **1955**, *38*, 1452. *b*) Hofmann, A. *Experientia* **1958**, *14*, 107. *c*) Hofmann,A.; Heim, R.; Brack, A.; Kobel, H.; Frey, A.; Ott, H.; Petrzilka, T.; Troxler,F. *Helv. Chim. Acta* **1959**, *42*, 1557. *d*) Troxler, F.; Seemann, F.; Hofmann,A. *Helv. Chim. Acta* **1959**, *42*, 2073. *e*) Downing, D. F. *Quart. Rev.(London)* **1962**, *16*, 133. *f*) Hofmann, A. *Bull. Narc.* **1971**, *23*, 3. *g*) Brimblecombe, R. W.; Pinder, R. M. *Hallucinogenic Agents*; Wright-Scientechnica: Bristol, UK, 1975; pp 106-108.
[55] Kazanietz, M. G.; Areces, L. B.; Bahador, A.; Mischak, H.; Goodnight, J.; Mushinski, J. F.; Blumberg, P. M. *Mol. Pharmacol.* **1993**, *44*, 298.

metabolite of psilocybin, in 69% isolated yield starting from a 1,2,3-trisubstituted aryl iodide (Scheme 40)[56]. But even the synthesis of such starting compounds is sometimes problematic since the bulky iodide has to be placed in between two substituents.

4-Substituted indoles are also synthesized via the FISCHER indole reaction, although the key step, the [3,3]-sigmatropic rearrangement proceeds with poor regioselectivity. While involvement of the *ortho*-carbon in the cyclic transition state leads to the desired product, a transition state that contains the *ortho'*-carbon gives the undesired 6-substituted indole. If a 1:1 mixture of both regioisomers is not obtained, the indole with substitution in the 6-position is favored due to steric reasons (Scheme 41).

Scheme 41: Regioselectivity in the Fischer indole synthesis.
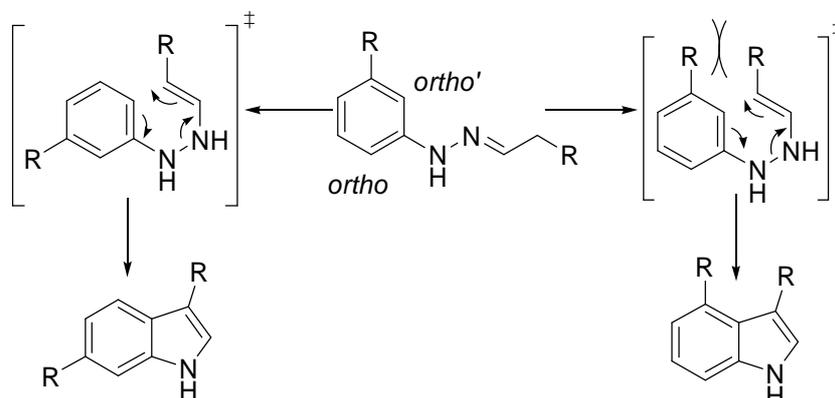
If 3,4-annelated indoles have to be synthesized, such as indolactams (Scheme 39), the additional ring can be closed in an appropriately substituted indole, or the indole may be formed through intramolecular and regioselective indolization from the appropriate macrocyclic hydrazone.

Scheme 42: Retro synthetic analysis of indolactam-V.

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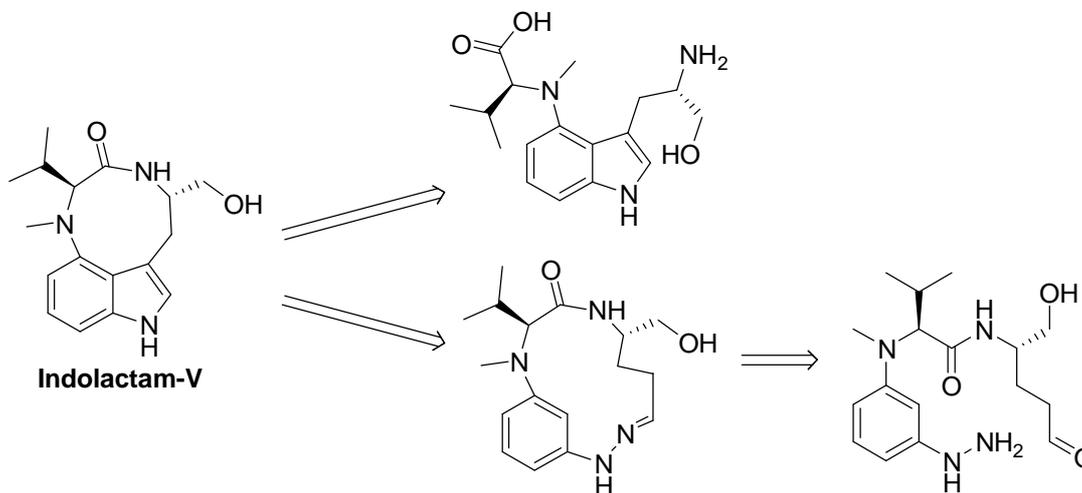
[56] Gathergood, N.; Scammells, P.J.; *Org. Lett.* **2003**, *5*, 921-923.

In both cases ultra high dilution techniques, which are generally limited to small scale reactions, will be required to avoid intermolecular reactions in the ring closing step. This ring closing step is in the first case an intramolecular peptide bond formation, while in the second case an intermolecular condensation of the aldehyde with the hydrazine group has to take place (Scheme 42). An *in situ* formation of the aldehyde via hydroformylation might ensure low concentrations of the intermediate aldehyde as an alternative to high dilution techniques. As long as the hydroformylation is slower than the consecutive reaction (intramolecular condensation and indolization) the aldehyde is not enriched in the reaction mixture, and intermolecular reactions might be suppressed without using ultra high dilution techniques. Apart from the synthesis of 3,4-annelated indoles, this method might also be useful for the synthesis of 4-substituted tryptamines, such as psilocin, if the additional ring contains a cleavable tether (Scheme 43).

Scheme 43: Concept for an intramolecular tandem hydroformylation / Fischer indole synthesis.
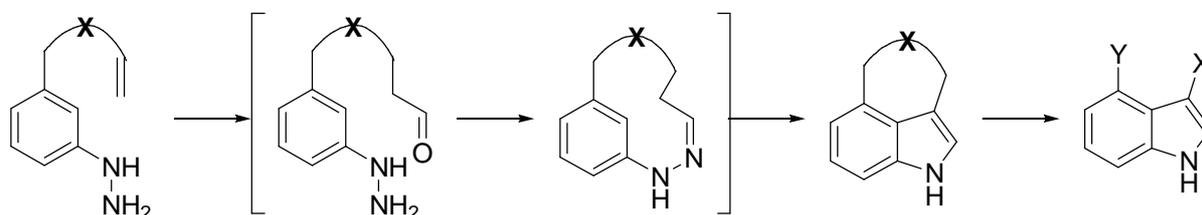
In this chapter preliminary investigations on an intramolecular tandem hydroformylation / FISCHER indolization are presented.

5.1 INTRAMOLECULAR CONDENSATION AND INDOLIZATION

Since the classical synthesis of functionalized aryl hydrazines is in many cases problematic, it is advantageous to start with a commercially available hydrazine and attach the olefinic moiety to the aromatic ring. To achieve high selectivities, the hydrazine group has to be protected first. The benzhydrylidene group turned out to be very effective since the protected hydrazines are stable against oxidation and can be purified by flash chromatography. In addition, benzhydrylidene protected aryl hydrazines can be subjected to a FISCHER indole reaction without previous deprotection as demonstrated earlier. While benzophenone can not undergo tautomerization, transcondensation with an aldehyde proceeds under the acidic FISCHER conditions followed by indolization. Furthermore, the use of protected aryl hydrazines seems to improve the selectivity of the tandem reaction (see above). Condensation of commercially available 3-hydrazino-benzoic acid (**501**) with benzophenone gives the protected hydrazine **502** in 54% yield. The olefin moiety can be introduced under carbodiimide mediation giving the desired test substrate **503** in 76% yield. This substrate is

then subjected to the tandem hydroformylation / FISCHER indole synthesis using the standard protocol with 10 wt% concentration and 0.5 wt% concentration of the substrate to simulate high dilution. In both cases NMR does not show any indole product. Instead, benzophenone was detected as the major compound of a mixture of products. This indicates that the hydroformylation leads to an aldehyde which then transcondenses intermolecularly and sets the benzophenone free (Scheme 44).

Scheme 44: Synthesis of a benzhydrylidene protected test substrate.
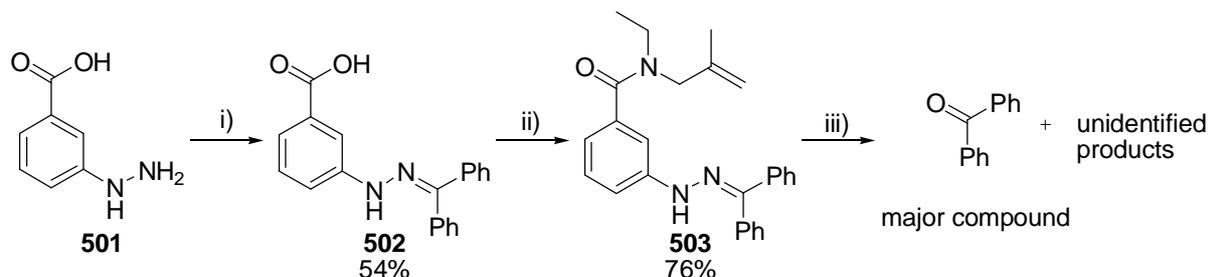
cond.: i) 1equiv. **501**, 1equiv. benzophenone, EtOH/H$_2$O, 20h, 80°C, 54%. ii) 1equiv. *N*-ethyl-*N*-methallylic amine, 1.1equiv. DCC, 5mol% DMAP, CH$_2$Cl$_2$, 20h, rt, 76%. iiia) 1equiv. PTSA, 1mol% [Rh(cod)Cl]$_2$, 20bar CO, 20bar H$_2$, THF (10wt% olefin), 120°C, 39h. iiib) 1equiv. PTSA, 1mol% [Rh(cod)Cl]$_2$, 10bar CO, 10bar H$_2$, THF (0.5wt% olefin), 100°C, 68h.

To give evidence to this assumption and to exclude the problems of single steps of the tandem reaction, the sequence is conducted stepwise. Hydroformylation of **503** in the absence of acid gave the desired aldehyde **504** in 83% isolated yield (Scheme 45).

Scheme 45: Hydroformylation of 402.
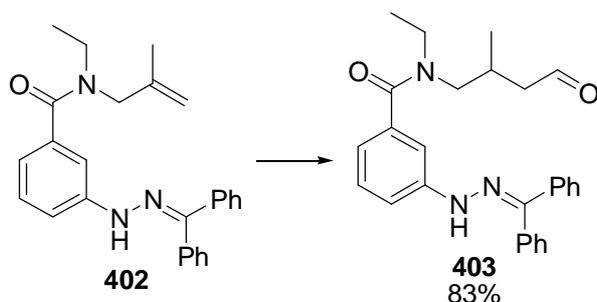
cond.: 1equiv. **402**, 1mol% [Rh(cod)Cl]$_2$, 50bar CO, 10bar H$_2$, THF (1wt% olefin), 120°C, 7h, 83%.

This aldehyde is then subjected to an indolization in high dilution and the reaction is monitored with TLC. With one equivalent of PTSA, no reaction is observed. The reaction is conducted with 5 and 10 equivalents of acid to increase acid concentration. In both cases, the formation of benzophenone is observed, but neither condensation nor indolization are witnessed (Table 16).

Table 16: Intramolecular Fischer indole synthesis.

entry	equiv of PTSA	result
1	1	no conversion
2	5	formation of benzophenone, no hydrazone formation
3	10	formation of benzophenone, no hydrazone formation

cond.: 1equiv. **504**, PTSA (see table), dioxane (0.5wt% olefin), 100°C.

The disfavored ring size of the desired 11-membered cyclic hydrazone might be an explanation. Elongation of the olefinic side chain is achieved by the STEGLICH esterification of **502** with *w*-pentenol (**506a**) and *w*-undecenol (**506b**). Hydroformylation gives aldehydes **508a** and **508b** in 32% and 87% yield. Intramolecular condensation might lead to cyclic hydrazones with a ring size of 13 and 19, but again no intramolecular hydrazone formation can be observed. Only cleavage of the benzophenone hydrazone is detected (Scheme 46).
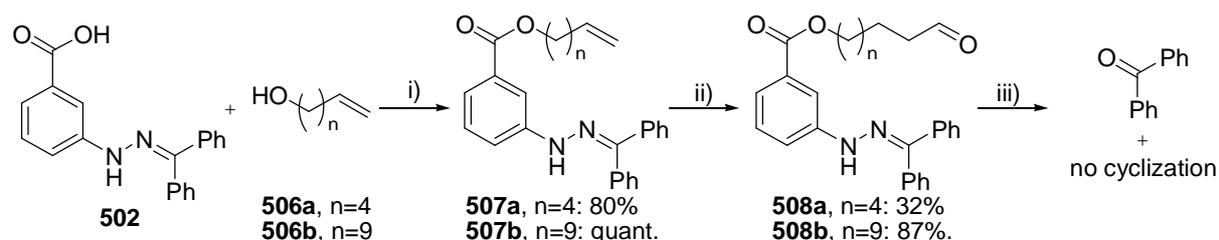
Scheme 46: Synthesis of a benzhydrylidene protected test substrate with prolonged olefinic side chain.

cond.: i) 1equiv. **502**, 1equiv. **506**, 1.1equiv. DCC, 5mol% DMAP, CH_2Cl_2, rt, 18h. ii) 1equiv. **507**, 1mol% $Rh(acac)(CO)_2$, 10mol% BIPHEPHOS 10bar CO, 10bar H_2, THF (10wt% olefin), 60°C, 5h. iii) 1equiv. **508**, 10equiv. H_2SO_4, dioxane (20mmol/ml), 100°C.

Although the hydrazone formation is catalyzed by acids, the presence of PTSA may hamper the hydrazone formation since protonated hydrazines possess a lower nucleophilicity. Therefore, it would be desirable to allow condensation under neutral or less acidic conditions. Two options might be viable: (1) The simplest way is to condense 3-hydrazino-benzoic acid (**501**) with the oxo-aldehyde of *w*-undecenol (**509**). Ring closure might then be achieved with established methods of macrolactonization. While the condensation gives the hydrazone **510** in 58% yield, macrolactonization failed. Different sets of reaction conditions are tested, such as the STEGLICH esterification or the MITSUNOBU reaction. In both cases no product could be

isolated. It could not be clarified, if the reaction fails, or if the enolizable hydrazone decomposes during flash chromatography (Scheme 47).

Scheme 47: Synthesis of a meta-cyclophaneic hydrazone via macrolactonization.
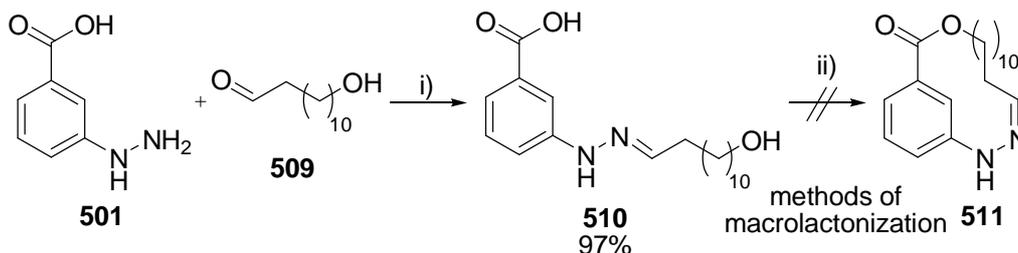

cond.: i) 1equiv. **501**, 1equiv. **509**, THF, rt, 18h, 97%. iia) 1equiv. **510**, 10equiv. DCC, 50mol% DMAP, THF (<1mmol/l). iib) 1equiv. **511**, 2equiv. PPh$_3$, 1.5equiv. DEAD, toluene (2mmol/l).

(2) Since the presence of acid is crucial for the transcondensation step, the benzophenone group has to be cleaved off in a prior step. Deprotection of benzhydrylidene protected amines is achieved by palladium catalyzed hydrogenolysis[57] or by acidic hydrolysis[58]. Both conditions may lead to undesired side reactions such as hydrogenation of the olefinic bond, cleavage of the *N-N*-bond or hydrolysis of the ester group. Therefore, other methods for the introduction of the hydrazine group have to be used. The GOLDBERG reaction offers an alternative. Alkylation of *m*-iodo-phenol (**512**) with undecenyl iodide (**513**) followed by copper(I) mediated *N*-arylation gives the *a*-Boc-protected hydrazine **515** in fair yields. The *b*-nitrogen is now available for an electrophilic attack by the aldehyde. No acid is needed for a cleavage of a protecting group or for the condensation. Indeed, hydroformylation of **515** results in the desired condensation product with excellent yield. This hydrazone is then subjected to the standard indolization conditions with a substrate concentration of 5mmol/l to suppress intermolecular reactions (Scheme 48). Surprisingly, 20% of indolization product **517** was obtained as an approx. 1:1 mixture of *n/iso*-regioisomers and as the only indole product. Obviously, the intramolecular indolization gives regioselective indolization, but with unexpected regioselectivity. Nevertheless, conversion was unselective. Although a long alkenyl chain has been selected, **516** might not easily reach a conformation which is required for the transition state of the indolization. This transition state can either be planar, if a pseudo aromatic transition state is assumed, or can be of chair-type conformation, if the rearrangement is interpreted as an electrophilic aromatic substitution.

[57] Barrett, A.G.M.; Seefeld, M.A.; White, A.J.P.; Williams, D.J.; *J. Org. Chem.* **1996**, *61*, 2677-2685.

[58] *a*) Kaepplinger, C.; Beckert, R.; *Syn. Lett.* **2001**, *7*, 1188-1190. *b*) Hicks, F.; Gou, D.M.; Marchese, S.; Martel, L.J.; Necula, A.; Bennetti, R.; Silva, R.A.; *PCT Int. Appl.* **2004**, WO2004000218.

Scheme 48: First intramolecular tandem hydroformylation / Fischer indolization.
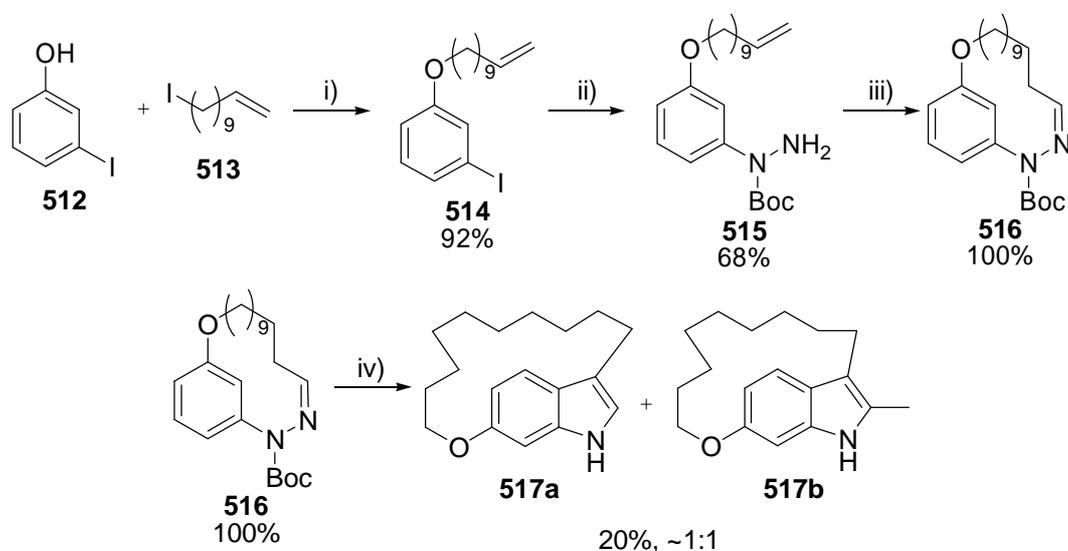
cond.: i) 1.05equiv. **512**, 1equiv. **513**, 1.1equiv. K_2CO_3, 10mol% 18-crown[6], THF, reflux, 18h, 92%. ii) 1equiv. **514**, 1.2equiv. *tert.*-butylcarbazate, 1.4equiv. Cs_2CO_3, 5mol% CuI, 20mol% 1,10-phenantroline, DMF, 21h, 80°C, 68%. iii) 1equiv. **515**, 4mol% Rh(acac)(CO)$_2$, 20mol% XANTPHOS, THF (5mmol/l), 10bar CO, 10bar H_2, 18h, 100°C, 100%. iv) 1eq **516**, 4wt% H_2SO_4/THF (5mmol/l), 18h, 80°C.

A higher flexibility of the intermediate hydrazone **516** can be achieved by enlarging the ring size. One option is to elongate the alkenyl chain which is attached to the aryl halide.

Scheme 49: Use of spacers in the intramolecular indolization.
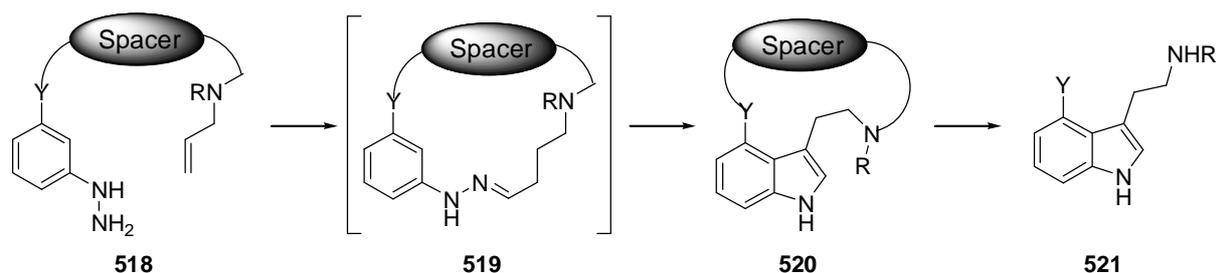
For the synthesis of the 4-substituted tryptamine derivative for example, this means that a spacer has to be introduced between the amine moiety and the substituent in the 4-position. This spacer is either part of the desired structure or acts as an auxiliary group that must be cleaved off after synthesis.

5.2 INTERMOLECULAR CONDENSATION AND INTRAMOLECULAR INDOLIZATION

The most atom economic spacer might be the hydrazone itself in a macrocyclic bishydrazone as illustrated in Scheme 50.

Scheme 50: Hydrazones as spacers.
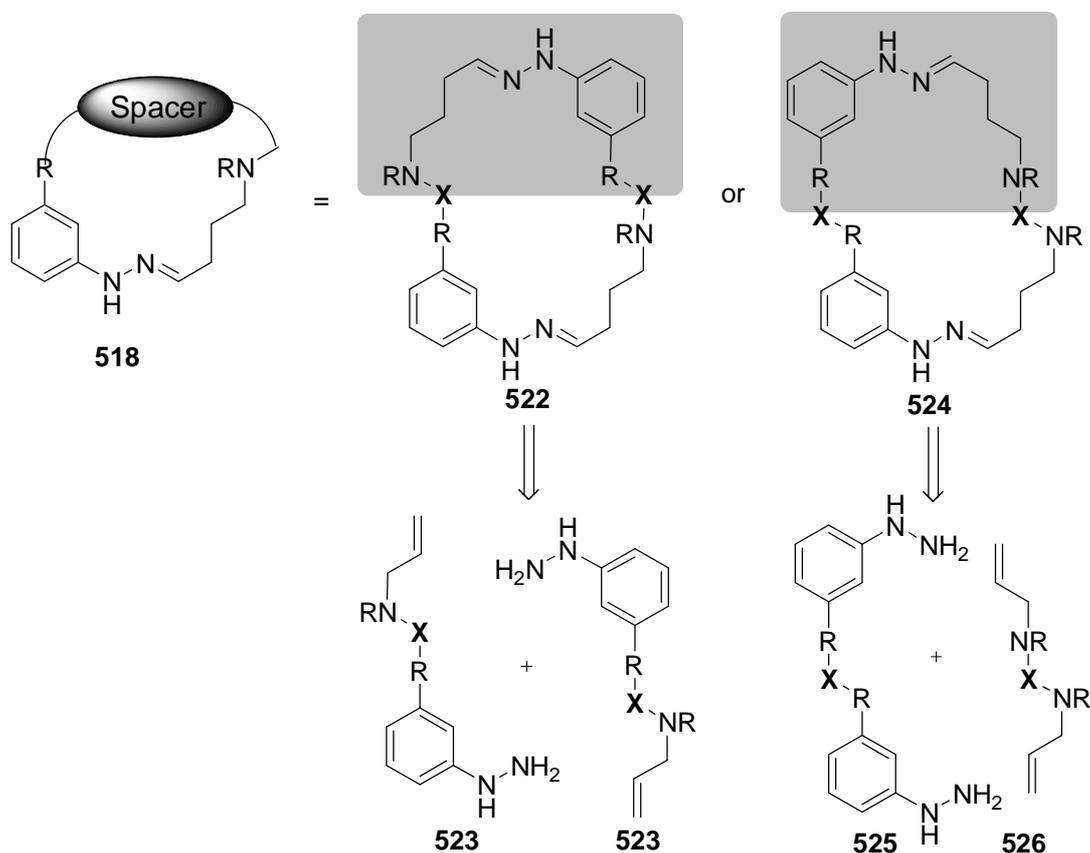
Here two different orientations are possible:

Ø Each amine moiety is linked with the substituent in the 4-position of the aromatic ring or

Ø both amine moieties and both aryl hydrazine moieties are connected with appropriate linkers.

Since the hydrazone bond is formed during hydroformylation, **522** may be synthesized from one single olefin (**523**), which has to give a 1:1 adduct selectively. But compound **523** contains both functionalities and, as demonstrated above, such a hydrazinoolefin undergoes selective intramolecular condensation.

Scheme 51: Synthesis of a symmetric bishydrazine via Goldberg reaction.

527	**528a**: n=4	**529a**: n=4 (97%)	**530a**: n=4 (84%)
	528b: n=10	**529b**: n=10 (87%)	**530b**: n=10 (77%)
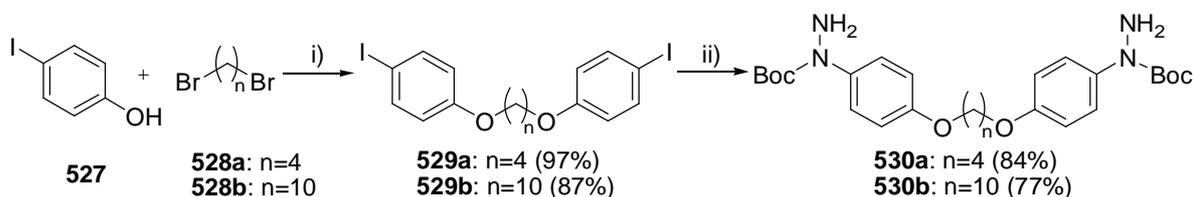
cond.: i) 2.2equiv. **527**, 1equiv. **528**, 2.5equiv. K_2CO_3, 10mol% 18-crown[6], THF, reflux, 20h. ii) 1equiv. **529**, 2.4equiv. *tert.*-butyl carbazate, 2mol% CuI, 22mol% 1,10-phenantroline, 2.8equiv. Cs_2CO_3, DMF, 80°C, 21h.

In contrast, macrocycle **524** may be synthesized from bishydrazine **525** and bisolefin **526**. As mentioned previously, hydroformylation is an excellent tool to convert bisolefins and bisamines to macrocyclic amines in an overall hydroaminomethylation. This methodology might also be helpful for the synthesis of macrocyclic bishydrazones. The required bishydrazines can be synthesized via copper (I) mediated *N*-Arylation exclusively. The classical approach of diazotation and reduction of the resulting diazonium salt fails due to the formation of azo-compounds. The previously used BUCHWALD-HARTWIG amination with benzophenone hydrazone does not give a selective product. Here oligomerization or intramolecular *N*-arylation occurs. Only the GOLDBERG reaction gives the desired product selectively since mono-*N*-arylation occurs only on the more acidic carbamate nitrogen.

To prove whether macrocyclic bishydrazones can be obtained upon hydroformylation / hydrazone formation and whether these macrocycles can be indolized, *p*-substituted hydrazines are synthesized. Indolization of the resulting hydrazone would then lead to one single regioisomer in contrast to the use of the *m*-substituted hydrazines. Thus, two different bishydrazines are synthesized in two steps and in good yields (Scheme 51).

Scheme 52: Configuratively consistent formation of (E)-hydrazones.
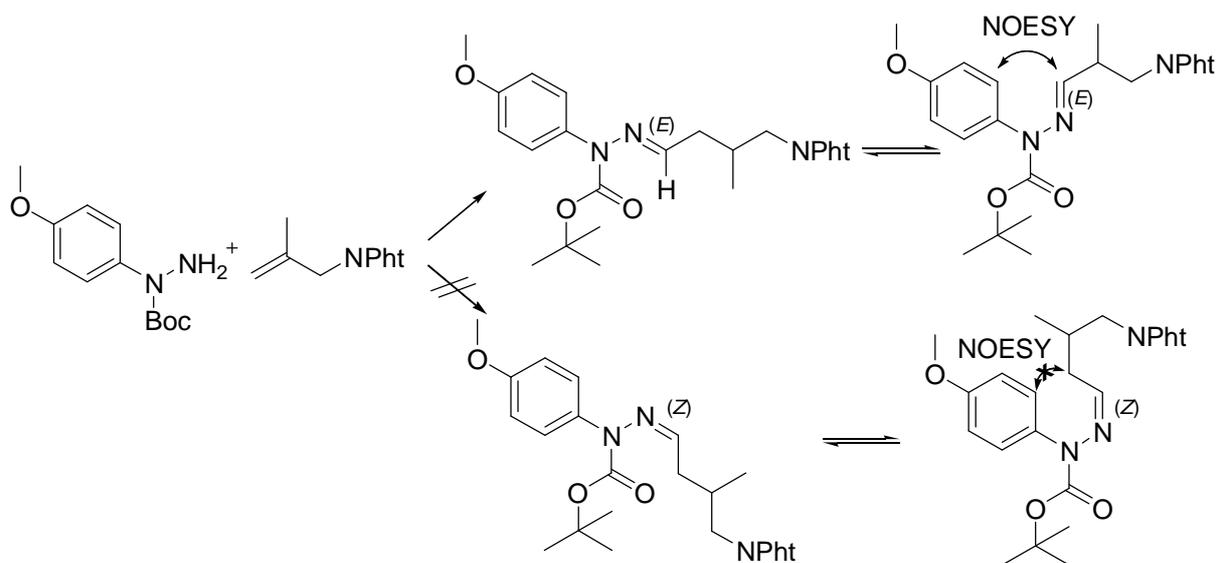
Similar to the synthesis of **215j** the Boc group will stay on the hydrazine during the hydroformylation and will be cleaved off in the indolization step. This is advantageous since *a*-Boc protected hydrazines as well as their hydrazones are stable against oxidation and can be chromatographed. In addition, the *a*-Boc protected hydrazines give (*E*)-configured hydrazones exclusively, as the hydrazone required for the synthesis of **215j** clearly demonstrates (Scheme 52). Thus the use of *a*-Boc protected hydrazines allows a stereospecific formation of the macrocycles and simplifies characterization.

The bisolefin is obtained in two steps starting with ethyl 4-methylenepiperidine-1-carboxylate (**412a**). Deprotection followed by conversion with oxalyl chloride gives a symmetric olefin which can be hydroformylated regioselectively. The symmetry of the resulting aldehydes is important to prevent formation of different regioisomeric macrocycles.

Scheme 53: Synthesis of a symmetric bisolefin.

412a   **532**   **533**

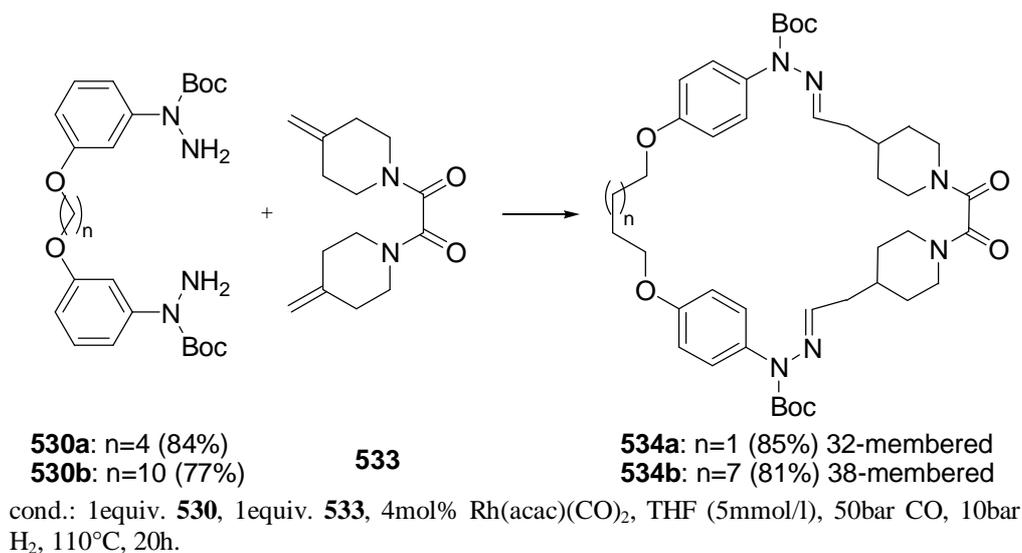cond.: i) 1equiv. **412a**, glycol/NaOH (50wt% in H$_2$O), 80°C, 18h, 44%. ii) 2.1equiv. **532**, 1equiv. oxalyl chloride, 2.1equiv. NEt$_3$, 5mol% DMAP, THF, rt, 1h, 68%.
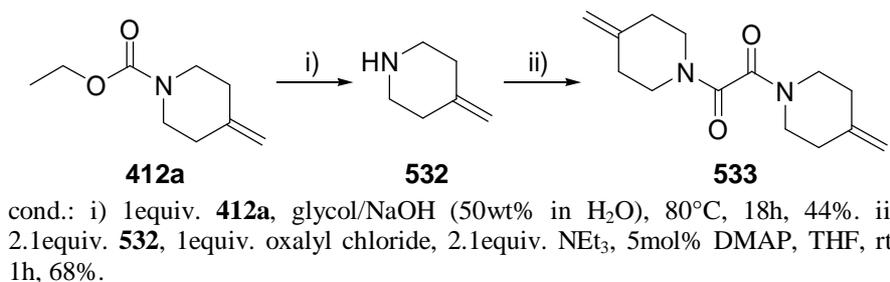
Both, bisolefin **533** and bishydrazines **530a**,**b**, have been subjected to the hydroformylation with a concentration of 5mmol/l of each starting compound. This concentration is much higher than typically used for high dilution techniques. The reason is the *in situ* formation of the reactive aldehyde compound which is trapped by the hydrazone instantly.

Scheme 54: Synthesis of macrocyclic bishydrazones via hydroformylation / hydrazone formation.

530a: n=4 (84%)   **533**   **534a**: n=1 (85%) 32-membered
530b: n=10 (77%)   **534b**: n=7 (81%) 38-membered

cond.: 1equiv. **530**, 1equiv. **533**, 4mol% Rh(acac)(CO)$_2$, THF (5mmol/l), 50bar CO, 10bar H$_2$, 110°C, 20h.

Therefore the concentration of the bisaldehyde is much lower than 5mmol/l, and at no time are concentrations reached which are high enough for side reactions, such as oligomerization, to occur. This allows the conduction of reactions in a 500mg scale in a 250ml PARR pressure vessel. In both cases, the macrocycles can be obtained with excellent yields. These high yields have been explained with a template effect of the rhodium catalyst[41]. These macrocycles are subjected to the same indolization conditions as **516** was subjected to. Although the macrocycles should be flexible enough to reach the required transition states, only traces of

indolization product are determined by HPLC/MS. A successful intramolecular indolization may need a different set of conditions as developed for tryptamines and tryptamides. Therefore an intense and laborious screening of conditions, including solvents and acids, seems to be reasonable and may be part of further investigations. An alternative application of macrocyclic bishydrazones is described in the following chapter.

5.3 INTERIM CONCLUSION

In this chapter preliminary results towards the first successful intramolecular Fischer indole synthesis are presented.

Ø Two different strategies have been investigated:

- An intramolecular condensation under hydroformylation conditions of an olefin bearing a hydrazine group followed by subsequent indolization under pseudo high dilution conditions. This strategy results in a 20% yield of the 6-substituted indole as the only regioisomer.

- Intermolecular condensation under hydroformylation conditions of symmetric bisolefins with symmetric bishydrazines gives macrocyclic bishydrazones in excellent yields. Subsequent indolization gives a very unselective conversion where no indole products were isolated.

Ø In both cases, the intermediate hydrazines are synthesized via the GOLDBERG reaction giving *a*-Boc protected hydrazines as stable hydrazine compounds. The classical approach of diazotation and reduction as well as the synthesis of benzhydrylidene protected hydrazines via BUCHWALD-HARTWIG amination fail.

Ø The Boc group is crucial for the isolation of the macrocycles since the macrocyclic bishydrazones are stable against oxidation and can easily be purified with chromatographic methods.

Ø The presence of the Boc-group also leads to the configuratively consistent formation of the stereogenic hydrazone double bond. Due to hydrogen bonding between the Boc-carbonyl and the hydrazone CH-group, only the (*E*)-isomers are formed.

6 SYNTHESIS OF MACROCYCLIC BISHYDRAZONES AND THEIR APPLICATION AS METAL SENSORS

In this chapter an alternative application for the previously described macrocycles **534a** and **534b** will be presented. ANGELOVSKI demonstrated in 2004 that azamacrocycles derived from tandem hydroformylation sequences are valuable substrates for the recognition of metals and chiral material via fluorescence spectroscopy. In this manner, **601** was used for the detection of zinc and cobalt ions while **602** was used for the differentiation of enantiomeric pairs of chiral amines, such as *a*-phenyl ethylamine (Scheme 55)[59].

Scheme 55: Macrocycles for fluorescence sensing derived from hydroaminomethylations.


601   **602**
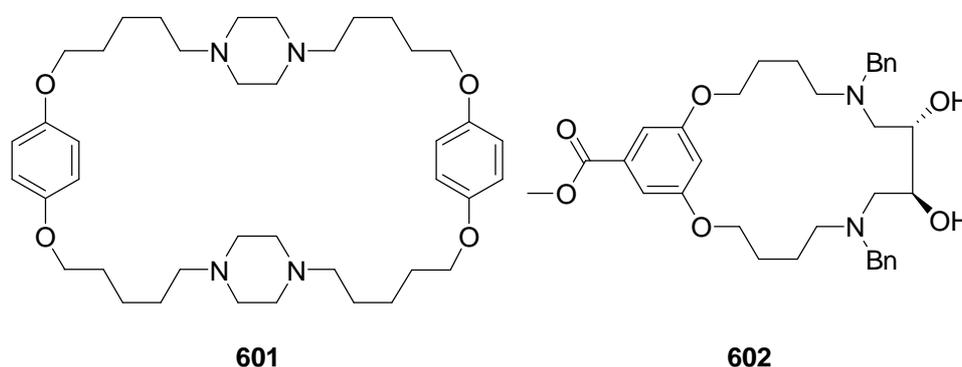
Fluorescence spectroscopy is based on the fact that UV active molecules, such as aromatic compounds, absorb light of a defined wavelength. Absorbance of energy results in an excitation of the molecule which relaxes via different mechanisms such as vibration, emission of sound, solvent interactions, internal conversion or emission of light. The emission of light from electronically excited molecules is called luminescence. Depending on the type of excited state the light is emitted from, it can be differentiated between phosphorescence (from triplet excited states) and fluorescence (from singlet excited states). The latter can be observed as a bathochromic shifted and inverted absorption spectrum with a fluorometer (Scheme 56)[60]. In contrast to UV spectroscopy, fluorescence spectroscopy is a direct measurement of the emitted light and is therefore more sensitive than the measurement of absorbance (usually measured as difference spectra between the light, which is sent to the sample and the emitted light). Thus fluorescence spectroscopy is attractive for the examination of sample material with *nano*-molar to *micro*-molar concentrations. In addition, fluorescence spectroscopy gives access to additional valuable data such as quantum yield and fluorescence lifetime.

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[59] Angelovski, G.; *Dissertation* **2004**, University of Dortmund
[60] Lakowicz, J.R.; *Principles of Fluorescence Spectroscopy*, 2nd ed., Kluwer Academic/Plenum Publishers, New York, **1999**.

Scheme 56: Principle of fluorescence.[60]
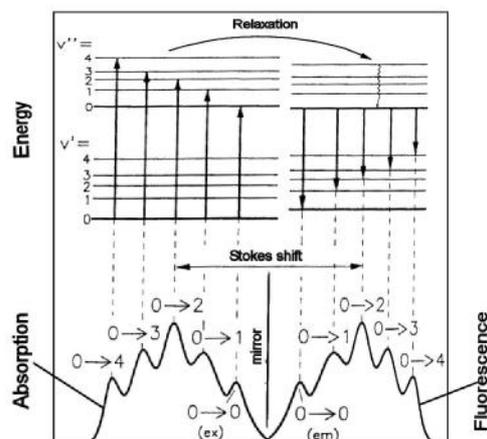
The intensity of a fluorescence spectrum is strongly depending on the presence of other compounds, such as solvents or metals. Interactions between such compounds and the fluorophore can either enhance fluorescence intensity or decrease its intensity (quenching). In the latter case, the excited molecule relaxes faster since the energy is transferred to the additional compound due to collision or complexation. This change of fluorescence intensity can be used analytically for the detection of certain compounds with fluorescence sensors.

Scheme 57: Setup of ideal fluorescence sensors. [60]
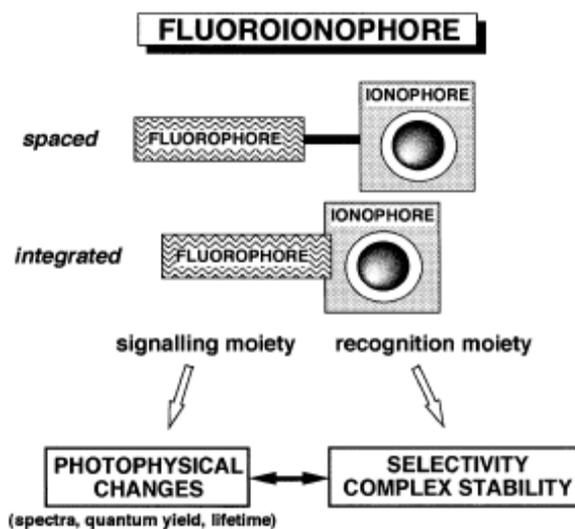
A selective fluorescence sensor consists of two essential parts:

Ø Preferably large aromatic systems are used as signaling units that emit light after excitation.

Ø Recognition units should interact with the analyte (e.g. a metal) selectively and intensely to observe a strong and specific enhancement or quenching of fluorescence.

Both units can either be integrated or can be linked via a spacer (Scheme 57). It is well documented that hydrazones can complex metal ions such as vanadium[61], iron[62], palladium[63], copper[64] or lithium[65]. The hydrazone moiety can either be embedded in a cyclic system or can be part of an acyclic ligand, but only in a few cases have hydrazones been used as a recognition unit for fluorophores[66]. Macrocycle **534** may act as a metal sensing fluorophore. While the hydrazone moieties are possible coordination sides, the aromatic systems may only be poor signaling units due to their small size. Large aromatic systems such as binaphthyl systems are even better signaling units. Therefore an additional macrocycle is synthesized. Starting with bishydrazine **530a** and bisolefin **603** macrocycle **604** can be obtained with almost quantitative yield (Scheme 58).

Scheme 58: Synthesis of 503 via tandem hydroformylation / hydrazone formation.

604: (97%) 32-membered
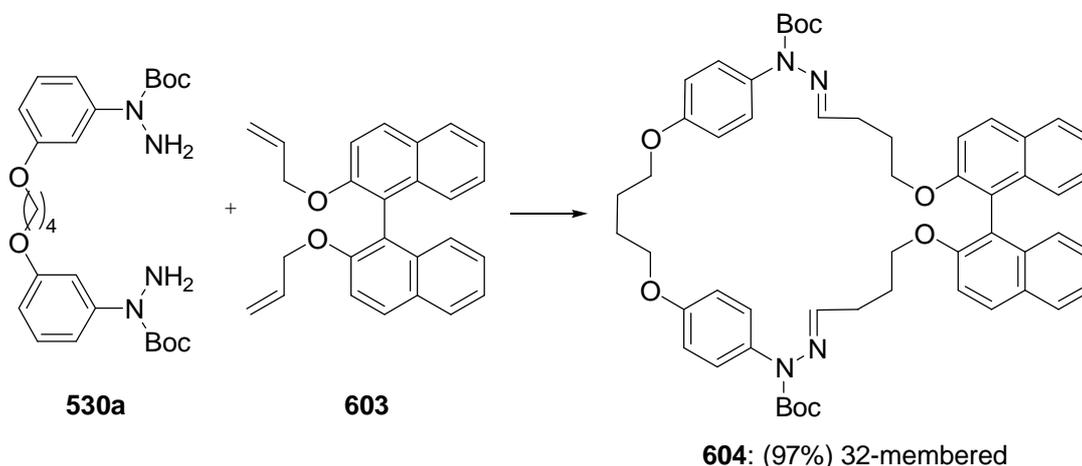
cond.: 1equiv. **530a**, 1equiv. **603**, 4mol% Rh(acac)(CO)$_2$, 20mol% XANTPHOS, THF (5mmol/l), 10bar CO, 10bar H$_2$, 100°C, 20h.

Fluorescence spectra are recorded with 308nm as the excitation wavelength. The obtained spectra are compared with those upon addition of one and two equivalents of different metal salts. After addition of one equivalent of V(II) salt, the fluorescence of **604** for example, is quenched to 50% of the original intensity. The addition of a second equivalent gives additional quenching of 46% (Scheme 59). A similar behavior can be observed after addition of Fe(III) salt (37% quenching with 1eq. and 33% after 2equiv.).

[61] Aggerwall, R.C.; Singh, B.; *Transition Met. Chem.* **1976**, 1, 275.

[62] Rastogi, D.K.; Dua, S.K.; Rana, V.B.; Sahni, S.K.; *J. Inorg. Nucl. Chem.* **1978**, *40*, 1323-1326.

[63] Natile, G.; Cattalini, L.; Gasparrini, F.; *J. Chem. Soc., Chem. Commun.* **1977**, 89.

[64] Iskander, M.F.; El-Sayed, L.; Saddeck, S.; *Transition Met. Chem.* **1981**, *6*, 27.

[65] Ahlbrecht, H.; Dueber, E.O.; Enders, D.; Eichenauer, H.; Weuster, P.; *Tetrahedron Lett.* **1978**, 3691.

[66] Taniguchi, H.; Tsuge, K.; Nakano, S.;J. *Pharm. Soc. Jpn* **1974**, *94*, 759-765.

Scheme 59: Quenching of fluorescence intensity upon addition of vanadium(II) and iron(III) salts.
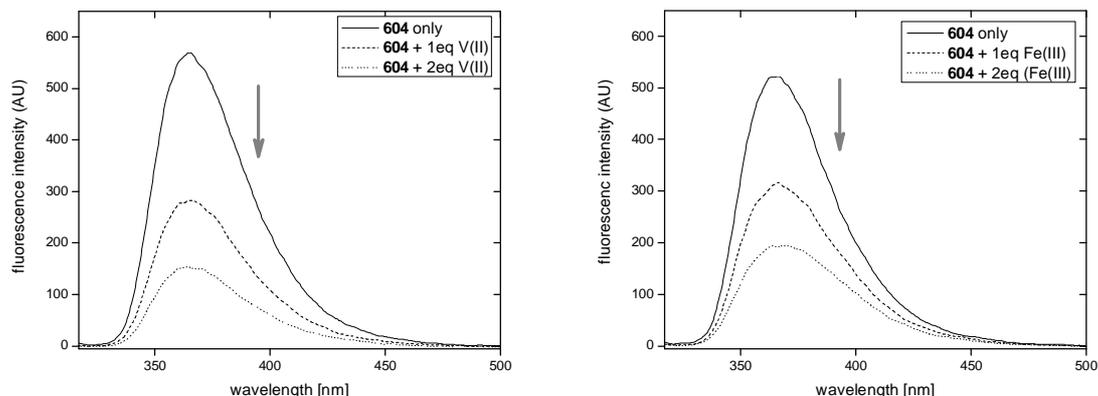
cond.: 1equiv. **604** (30µmol/l in acetonitrile) I_{ex}=305nm, 25°C. a) 1-2equiv. V(acac)$_2$ b) 1-2equiv. FeCl$_3$.

The results of an intense metal screening are compiled in Scheme 60 using the STERN-VOLMER equation [1].

$$\frac{I_0}{I} = 1 + k \cdot c_{quencher}$$

[1]

In Scheme 60 a selectivity towards vandium(II), chromium(III), iron(III) and rhodium(I) is disclosed. All four metals are known to prefer octahedral complexes. The quenching in the presence of rhodium(I) might support the hypothesis that the hydroformylation catalyst acts as a template in the synthesis of the macrocycles.

**Scheme 60: Screening of different metal salts in fluorescence measurements.**
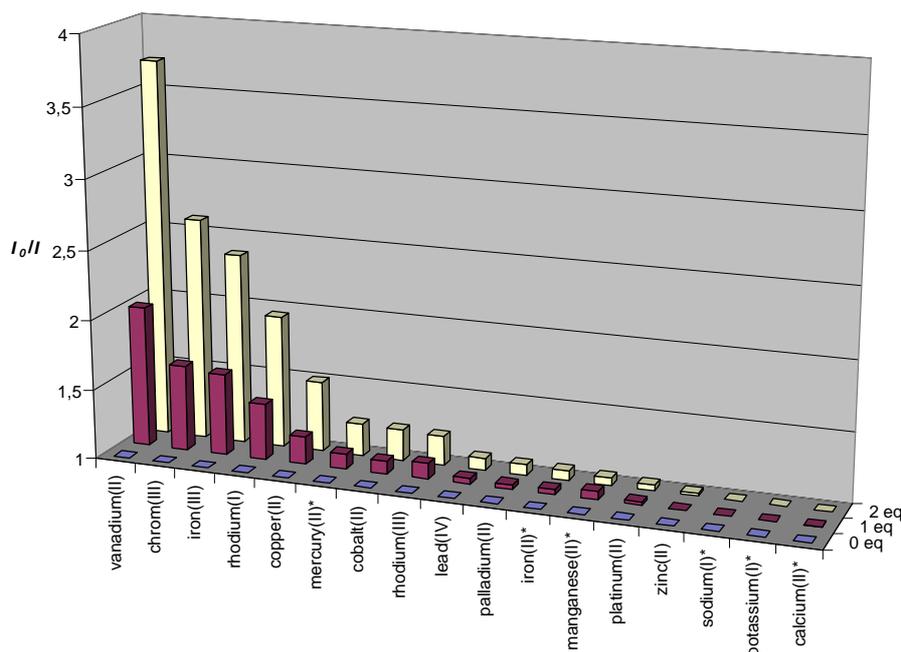
cond.: 1equiv. **604** (30µmol/l in acetonitrile), 1-2equiv. metal salts, I_{ex}=305nm, 25°C.

In contrast, metals that usually give distorted octahedral complexes show weaker quenching, and metals with different complex geometry show no effect at all.

A comparison of the three macrocycles (**534a**, **534b** and **604**) shows a clear dependency of fluorescence quenching from the ring size (Scheme 61). While quenching is the weakest with the biggest ring (**534b**), quenching can be increased by a reduction of ring size. This result suggests that the ring of **534b** is probably too big for a strong complexation or chelation of the metal ions. Although **604** has the same ring size as **534a**, quenching of **604** is in between quenching of **534a** and **534b**. But in contrast to the latter, **604** contains a binaphthyl unit which may spread the macrocycle's conformation and its bite angle, allowing improved chelation of metal ions. Only in the case of vanadium(II) does the behavior of **604** differ from **534**. Here, the quenching of fluorescence is much higher compared to the quenching of fluorescence of **534**. This may be explained by the additional coordination to the extra oxygens.

Although the macrocycles seem to be good ligands for vanadium(II) and chromium(III), the interaction with iron(III) is deemed to be the most promising for further applications.

Scheme 61: Comparison of different macrocycles.
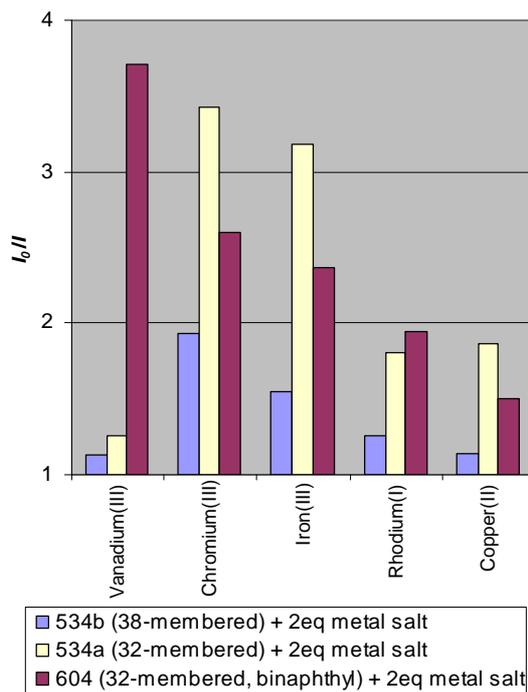
cond.: l_{ex}=305nm, 25°C a) 1equiv. **534b** (10μmol/l in acetonitrile). b) 1equiv. **534b** (30μmol/l in acetonitrile). c) 1equiv. **604** (30μmol/l in acetonitrile).

The determination of iron in blood serum and other body fluid samples is important for the study, diagnosis, and treatment of nutritional and metabolic diseases that cause low or high

iron levels. Iron metabolism disorders have been found to cause iron-deficiency anemia and hemochromatosis, which might ultimately result in liver cancer, liver cirrhosis, arthritis, diabetes, or heart failure[67]. Recent studies have linked late-onset neurodegenerative disorders such as Parkinson´s disease to elevated iron levels[68]. The analysis of iron levels in blood serum and cell extracts is crucial for the diagnosis and treatment of cancer because high amounts of iron are found during tumor cell proliferation. Iron also plays a role in important infectious diseases such as malaria[69]. Since iron is involved in biological redox processes, cycling between the most stable oxidation states of iron (iron(II) and iron(III)) it might be desirable to differentiate between these two oxidation states. A comparison of fluorescence quenching of **604** in the presence of iron(II) and iron(III) clearly demonstrates a selectivity of **604** towards iron(III). The STERN-VOLMER plot in Scheme 62 shows that fluorescence intensity of **604** is almost stable upon addition of 2 equivalents of iron(II), while addition of iron(III) leads to quenching.

Scheme 62: Comparison of fluorescence quenching upon addition of iron(II) and iron(III).
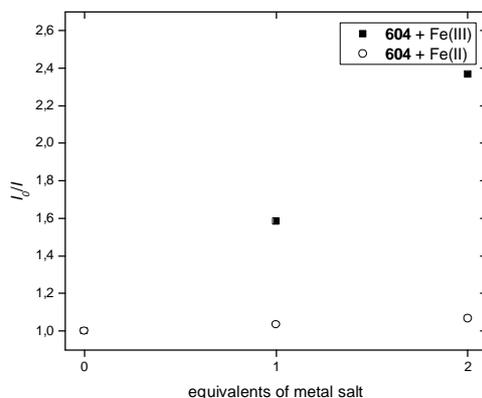
cond.: 1equiv. **604**, (30µmol/l in acetonitrile), 1-2equiv. metal salts, I_{ex}=305nm, 25°C.

The intensity of fluorescence and the rate of relaxation processes, such as quenching, are strongly depending on the solvent which is used. Polar solvents undergo stronger interactions with the fluorophore, depopulating its excitation state faster[60]. So far fluorescence experiments are performed in acetonitrile, but since most biological samples are dissolved in

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[67] a) Trinder, D.; Macey, D. J.; Olynyk, J. K.; *Int. J. Mol. Med.* **2000**, *6*, 607–612. b) Burkitt, M. J.; Milne, L.; Raafat, A.; *Clin. Sci.* **2001**, *100*, 239–247. c) Brugnara, C.; *Clin. Chem.* **2003**, *49*, 1573–1578. d) Leong, W.; Loennerdal, B.; *J. Nutr.* **2004**, *134*, 1–4.

[68] a) Bharath, S.; Hsu, M.; Kaur, D.; Rajagopalan, S.;Andersen, J. K.; *Biochem. Pharmacol.*; **2002**, *64*, 1037–1048. b) Beard, J.; *J. Nutr.* **2003**, *133*, 1468S–1472S.

[69] a) ONeill, P. M.; Bray, P. G.; Hawley, S. R.; Ward, S. A.;Park, B. K.; *Pharmacol. Ther.* **1998**, *77*, 29–58. b) Blauer,G.; Akkawi, M.; Fleischhacker, W.; Hiessboeck, R.; *Chirality* **1998**, *10*, 556–563. c) Egan, T. J.; Hunter, R.; Kaschula, C. H.; Marques, H. M.; Misplon, A.; Walden, J.; *J. Med. Chem.* **2000**, *43*, 283–291.

water, fluorescence quenching of **604** upon addition of iron(III) is also tested in a 1:1 mixture of water/acetonitrile. Although changes in this solvent mixture are less drastic, fluorescence quenching to 10% of the original fluorescence intensity can be achieved by addition of 20 equivalents of iron(III) (Scheme 63).

Scheme 63: Obliteration of fluorescence activity upon addition of iron(III).
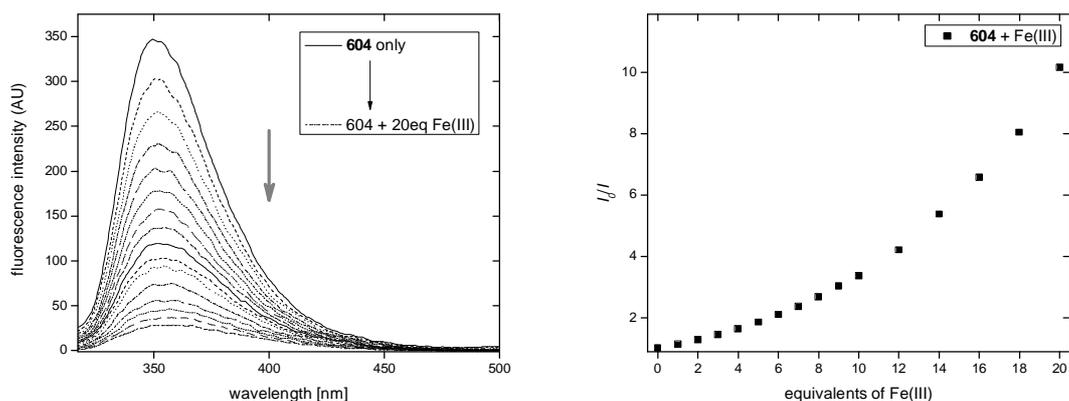
cond.: 1equiv. **503** (30µmol/l in acetonitrile/H$_2$O (1:1)), 1-20equiv metal salts, I_{ex}=305nm, 25°C.

At higher concentrations of iron(III), a deviation of fluorescence quenching from the linear dependency can be observed. This can be explained with a shifted equilibrium between free ligand **604** and an iron/**604** complex towards the complex. While at low concentrations the complex has such a short lifetime, that quenching can be referred to a collision of metal and ligand (collisional or dynamic quenching), the higher concentrations result in more stable complexes (static quenching) and therefore in increased quenching.

**Scheme 64: Fluorescence quenching with iron(III)
and additional electrolytes.**
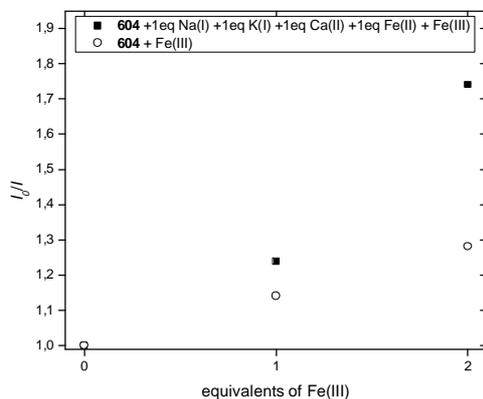
cond.: 1equiv. **604** (30µmol/l in acetonitrile/H$_2$O (1:1)), 1-2equiv. metal salts, I_{ex}=305nm, 25°C.

A similar result is illustrated in Scheme 64. Body fluids usually contain other salts, such as sodium, potassium and calcium salts. Therefore fluorescence measurements have also been conducted in the presence of one equivalent of each salt in water/acetonitrile (1:1). Although all used salts show no quenching at all upon addition to the fluorophore **604**, fluorescence quenching in the presence of iron(III), sodium, potassium, calcium and iron(II) is higher than in the absence of these additional salts. This can also be explained with a higher part of static quenching since the salts increase the complex's lifetime.

6.1   INTERIM CONCLUSION

The synthesis of macrocyclic bishydrazones via tandem hydroformylation of bisolefins in the presence of bishydrazones is described.

Ø   The rhodium catalyst acts as a template for the condensation giving excellent yields under pseudo high dilution conditions.

Ø   Different metals salts are screened for their interaction with the macrocycles via fluorescence spectroscopy. Although none of the investigated macrocycles is designed for metal detection or for fluorescence spectroscopy, the screening disclosed a good fluorescence activity and a remarkable selectivity of the macrocycles towards vanadium, chromium and iron.

Ø   The determination of iron levels might be interesting for medicinal applications since iron(II) is differentiated from iron(III) which is involved in many biological processes. Quenching of fluorescence to 10% of its original intensity can be achieved upon addition of only 20 equivalents. Even in water, the fluorescence is quenched in the presence of iron(III). In the presence of other salts, contained in biological samples, fluorescence quenching is enhanced.

7 INITIAL INVESTIGATIONS TOWARDS ASYMMETRIC TANDEM HYDROFORMYLATION / FISCHER INDOLE SYNTHESIS

In the previous chapters, many examples are presented in which disubstituted terminal olefins have been used to achieve a high regioselectivity in the hydroformylation step without the use of *n*-directing ligands. On the other hand, tryptamines with branched side chains have become interesting substrates for medicinal purposes, as LY 156 735 demonstrates (Scheme 65)[34].

Scheme 65: Example of a pharmaceutically relevant chiral a-branched tryptamine

LY 156735
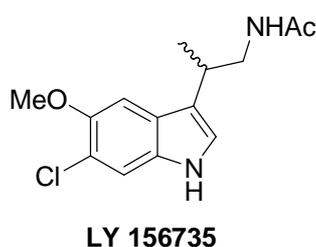
The use of such prochiral olefins in the tandem hydroformylation / FISCHER indolization results in chiral tryptamines (Scheme 66).

Scheme 66: Use of prochiral olefins in the tandem hydroformylation / Fischer indole synthesis.
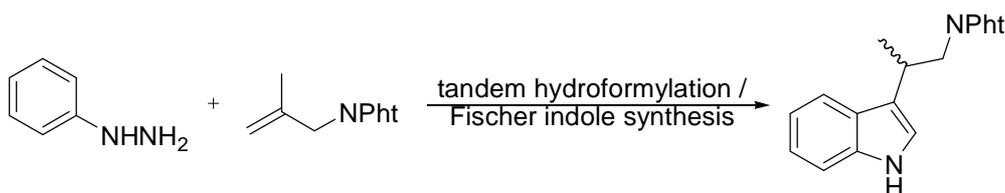

A control of the configuration of this new stereogenic center during the tandem reaction would be desirable. In general, there exist two different strategies for asymmetric hydroformylations:

(1) *Reagent controlled asymmetric hydroformylation.* Here, hydroformylation catalysts are modified with chiral ligands. Hydroformylation of 2-methoxy-6-vinylnaphthalene, for example, with a Pt/(-)-bppm system gives the diethyl acetal of the corresponding aldehyde required for the analgesic naproxen (Scheme 67)[70]. The *in situ* protection is required to conserve the enantiomeric excess since the aldehyde undergoes tautomeric epimerization.

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[70] *a*) Gladiali, S.; Bayon, J. C.; Claver, C. *Tetrahedron: Asymmetry,* **1995**, *6*, 1453-1474. *b*) Eilbracht, P. in *Methoden der Organischen Chemie* (Houben-Weyl) Vol. E 21c: *Stereoselective Synthesis* (Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, Eds.), Thieme: Stuttgart, **1995**, 2488-2733. *c*) Agbossou, F.;

Scheme 67: Enantioselective hydroformylation with *a*-induction.
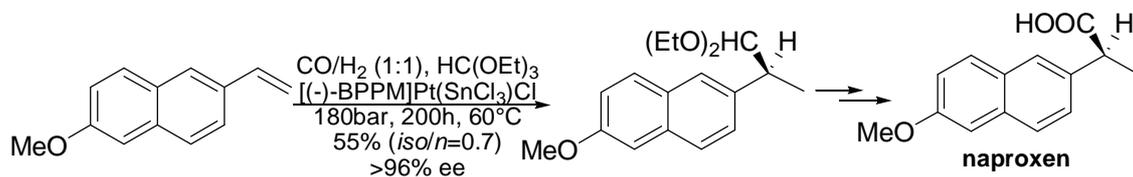
In contrast to asymmetric hydroformylation with induction of stereocenters in *a*-position to the aldehyde, the hydroformylation of disubstituted terminal olefins gives stereocenters in *b*-position (*b*-induction). The best enantiomeric excess so far, can be observed in the asymmetric hydroformylation of dimethyl itaconate, albeit with poor chemoselectivity (Scheme 68)[71].

Scheme 68: Enantioselective hydroformylation with *b*-induction.

[Pt]	83.6% *ee* 19% yield	-- --	51.4% *ee* 73% yield
[Rh]	*rac* 6% yield	9.1% *ee* 80% yield	*rac* 11% yield
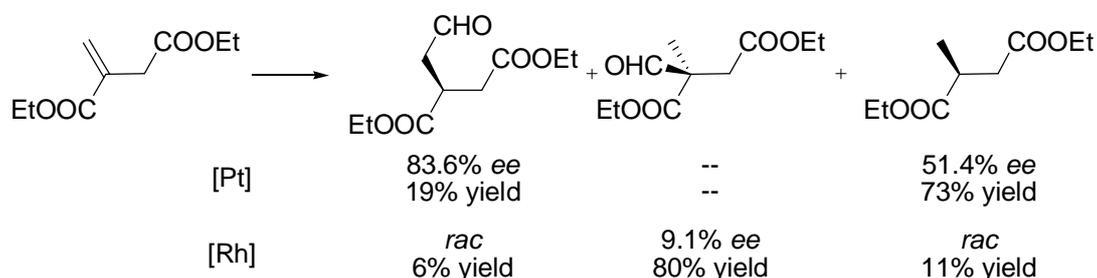
Apart from this special case, hydroformylation of other disubstituted terminal olefins gives lower enantioselectivity. In 2000, Buß conducted asymmetric hydroformylations in the presence of amines to establish an asymmetric hydroaminomethylation. Independent from the type of olefin and from the type of stereochemical induction, enantioselectivities of the hydroaminomethylation are much smaller compared to the enantioselectivities of the hydroformylation. Even if enantiomerically enriched aldehydes are subjected to a rhodium catalyzed reductive amination, epimerization can be observed (Scheme 69)[72]. As a conclusion, sufficient enantioselectivity in the hydroformylation of disubstituted terminal olefins with *b*-induction is still not achievable, especially in the presence of nitrogen nucleophiles.
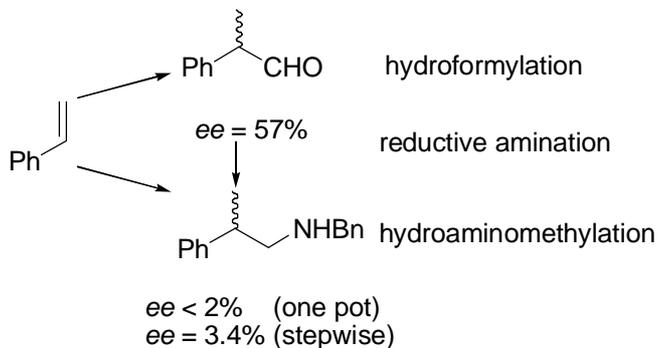
Carpentier, J.-F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485-2506. *d*) Breit, B.; Seiche, W.; *Synthesis* **2001**, 1-36. *e*) Breit, B.; *Accounts Chem. Res.* **2003**, *36*, 264-275.
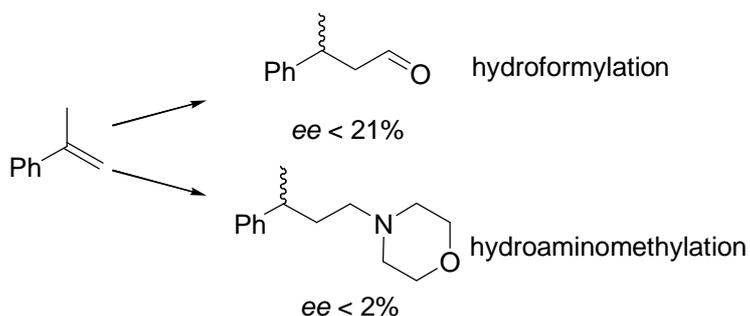[71] Gladiali, S.; Pinna, L.; *Tetrahedron Asymmetry* **1991**, *2*, 623.
[72] Buß, C.; *Dissertation* **1999**, University Dortmund.

Scheme 69: Attempts towards enantioselective hydroaminomethylation.
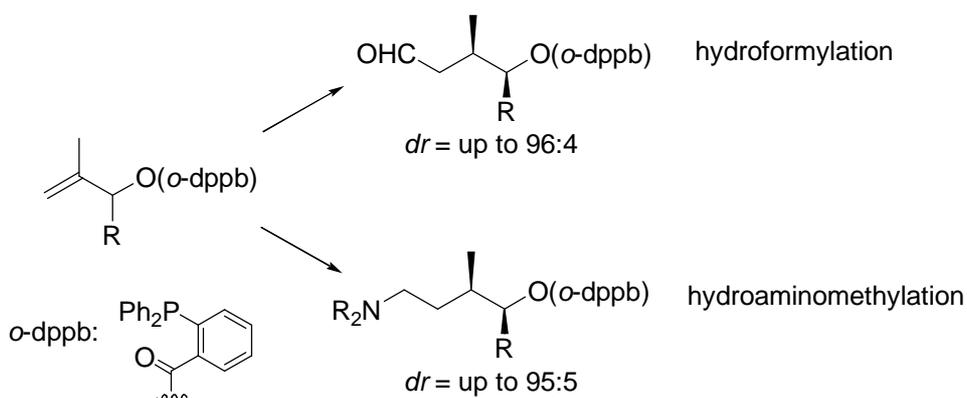
a-**induction:**

Ph CHO   hydroformylation

ee = 57%   reductive amination

Ph NHBn   hydroaminomethylation

ee < 2%   (one pot)
ee = 3.4% (stepwise)

b-**induction:**

Ph O   hydroformylation

ee < 21%

Ph N O   hydroaminomethylation

ee < 2%

(2) *Substrate controlled asymmetric hydroformylation.* An alternative to reagent controlled enantioselective hydroformylation is the substrate controlled diastereoselective hydroformylation. In 1997, BREIT published the first diastereoselective hydroformylation of chiral methallylic alcohol.

Scheme 70: Diastereoselective hydroformylation using a catalyst directing auxiliary.

OHC O(*o*-dppb)   hydroformylation
        R
dr = up to 96:4

O(*o*-dppb)
R

o-dppb: Ph$_2$P

R$_2$N O(*o*-dppb)   hydroaminomethylation
              R
dr = up to 95:5

In this approach the auxiliary *ortho*-diphenylphosphino benzoic acid (*o*-dppb) is appended to the alcohol group helping the catalyst to differentiate between the two diastereotopic faces of the double bond. Hydroformylation gives then the corresponding aldehydes with good

diastereoselectivities (Scheme 70)[73]. Even in the presence of primary and secondary amines, good diastereoselectivities are obtained for the diastereomeric secondary and tertiary amines upon hydroaminomethylation (Scheme 70). BREIT's strategy might also be useful for the stereoselective synthesis of branched tryptamines since the hydroformylation is the stereo discriminating step in the tandem reaction. Substrate controlled hydroformylation of a chiral methallylic amine bearing the *o*-DPPB-group might lead to the corresponding aldehyde with high diastereomeric excesses. This aldehyde should undergo condensation with the present aromatic hydrazine *in situ*. After addition of acid, this hydrazone should give the indole, conserving the diastereomeric ratio (Scheme 71).

Scheme 71: Principle of a diastereoselective tandem hydroformylation / Fischer indole synthesis.
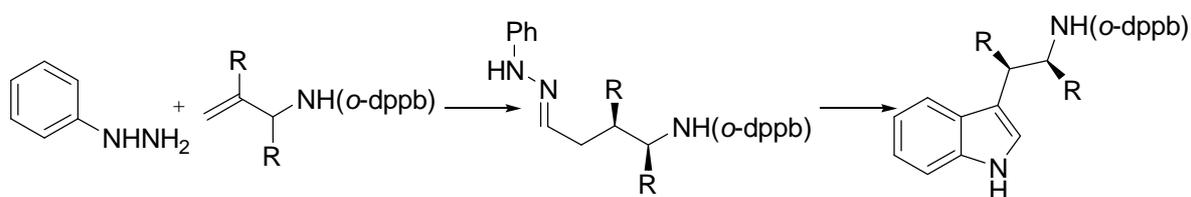
The fact that the aromatic hydrazine does not compete with the diphenylphosphino group is one condition for the high diastereoselectivities in the hydroformylation step. Another condition is that this protocol can be transferred from chiral allylic alcohols to chiral allylic amines. A change from an ester group to an amide group may result in the formation of rotamers, giving an additional stereogenic center which can affect the conformation of the two diastereomeric cyclic transition states dramatically.

7.1 SYNTHESIS OF A TEST SUBSTRATE VIA OVERMAN REARRANGEMENT

To investigate both aspects, chiral methallylic amine **701** is synthesized via OVERMAN rearrangement. Attachment of the auxiliary gives the test substrate **702** in quantitative yield. The hydroformylation is conducted in a non-polar, non-coordinating solvent such as benzene, without the addition of ligand to support the active direction of the catalyst by the auxiliary. Under these conditions low conversion of **702** towards the aldehyde **703** is observed. Conversion can be increased upon addition of P(OPh)$_3$ according to BREIT's conditions[73]. In this case, preferred formation of the aldehyde **703** can be observed accompanied with *N,O*-hemiacetal **704**. This behavior has been observed previously[37]. Since the cyclization of the diastereomeric aldehydes may precede with different reaction rates, and since

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[73] *a*) Breit, B.; Heckmann, G.; Zahn, S.K.; *Chemistry* **2003**, *9*, 425-434. *b*) Breit, B.; Dauber, M.; Harms, K.; *Chemistry* **1999**, *5*, 2819-2827. c) Breit, B.; *Tetrahedron Lett.* **1998**, *39*, 5163-5166. *d*) Breit, B.; *Eur. J. Org. Chem.* **1998**, *6*, 1123-1134. *e*) Breit, B.; Zahn, S.K.; *Tetrahedron Lett.* **1998**, *39*, 1901-1904. *f*) Breit, B.; *Chem. Commun.* **1997**, *6*, 591-592. *g*) Breit, *B.*; *Angew. Chem. Int. Ed.* **1996**, *35*, 2835-2837.

hydroformylation is reversible, the observed diastereomeric ratio of 92:8 may not be representative for the diastereoselectivity of the hydroformylation. The cyclization may be prevented by an *in situ* protection of the aldehyde or alkylation of the *NH*-group. Unlike the synthesis of naproxene, the addition of triethyl orthoformiate does not lead to the corresponding acetal **705** (Scheme 67). While subsequent alkylation of **702** turns out to be difficult, reductive amination of olefin **701** with acetaldehyde followed by attachment of the auxiliary is unselective (Scheme 72).

**Scheme 72: Diastereoselective hydroformylation of prochiral allylic amines.**
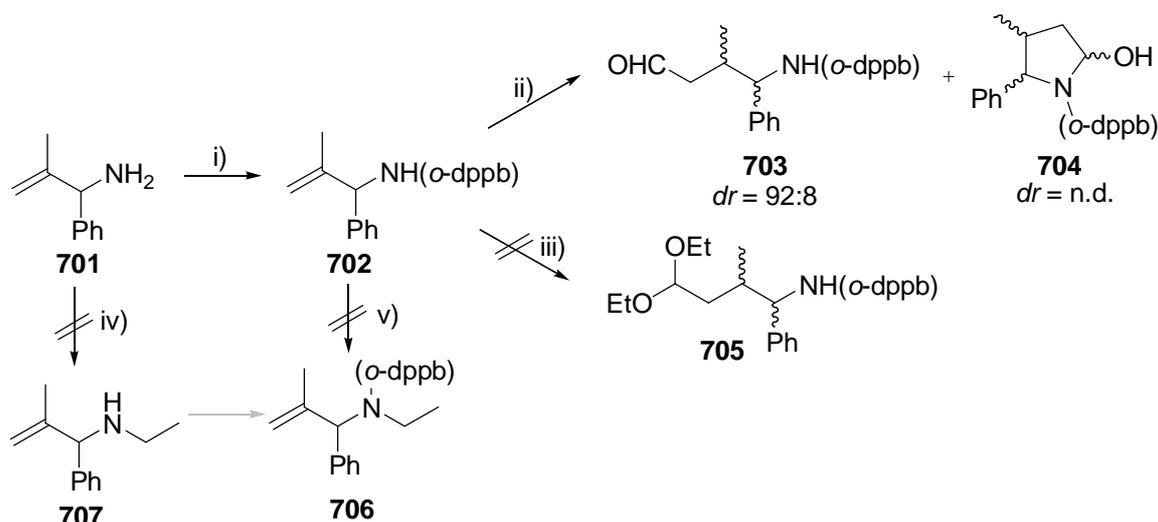
cond.: i) 1equiv. **701**, 1equiv. *o*-diphenylphosphino benzoic acid, 1.1equiv. DCC, 5mol% DMAP, CH$_2$Cl$_2$, rt, 24h, 45%. ii) 1equiv. **702**, 0.7mol% Rh(acac)(CO)$_2$, 2.8mol% P(OPh$_3$)$_3$, 10bar H$_2$, 10bar CO, benzene, 90°C, 20h. iii) 1equiv. **702**, 1equiv. HC(OEt)$_3$, 0.7mol% Rh(acac)(CO)$_2$, 2.8mol% P(OPh$_3$)$_3$, benzene, 80°C, 20h. iv) 1equiv. **702**, 10equiv. bromoethane, 5mol% 18-crown[6], 2.5equiv. K$_2$CO$_3$, acetonitrile, 100°C, 12h. v) 1equiv. **701**, 1equiv. acetaldehyde, THF, rt, 20min, then 0.3equiv. LiAlH$_4$, THF, 80°C, 2h.

7.2 SYNTHESIS OF A TEST SUBSTRATE VIA ALLYLIC AMINATION

Unfortunately, OVERMAN rearrangement gives access to only primary chiral allylic amines. Therefore, an alternative method has to be used to synthesize secondary chiral allylic amines.

**Scheme 73: Allylic amination.**
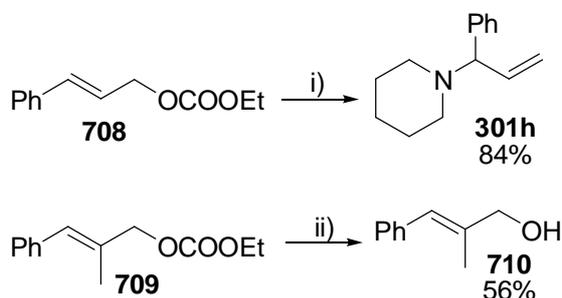
cond.: i) 1equiv. **708**, 3equiv. piperidine, 2mol% [Ir(cod)Cl]$_2$, 8mol% P(OPh)$_3$, EtOH, 80°C, 2h, 84%. ii) 1equiv. **709**, 3equiv. hexylamine, 2mol% [Ir(cod)Cl]$_2$, 8mol% P(OPh)$_3$, EtOH, 80°C, 2h, 56%.

Iridium catalyzed allylic amination of cinnamyl carbonate **708** has already been used for the enantioselective synthesis of chiral allylic amine **301h** in this thesis and might also work here. To synthesize a prochiral, olefin *a*-methyl cinnamyl carbonate (**709**) is subjected to the allylic amination. In contrast to previous experiments, this reaction results in cleavage of the carbonate as the major product (Scheme 73). Although the mechanism of the iridium catalyzed allylic amination is so far not completely investigated, the following mechanistic considerations are assumed in analogy to the palladium catalyzed allylic substitution as a working hypothesis[74].

Allylic substitutions usually proceed via an allyl metal complex formed by *S_N2'-anti-*substitution of the leaving group by the catalyst. In the presence of electron withdrawing ligands, such as P(OPh)$_3$, the resulting *s*-allyl complex **711a** rearranges via the *p*-allyl complex **711b** to the *s'*-allyl complex **711c** which is attacked by the nucleophile *anti* to the catalyst giving the branched isomer preferably (Scheme 74).

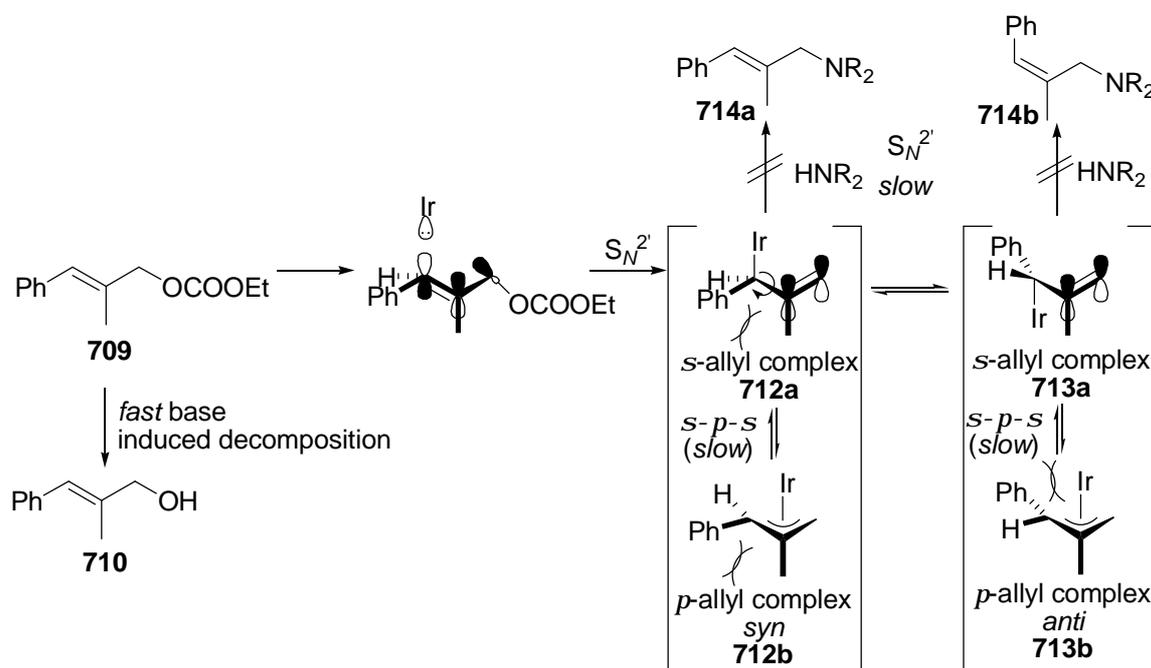**Scheme 74: Mechanism of the iridium catalyzed allylic amination of cinnamyl carbonates.**
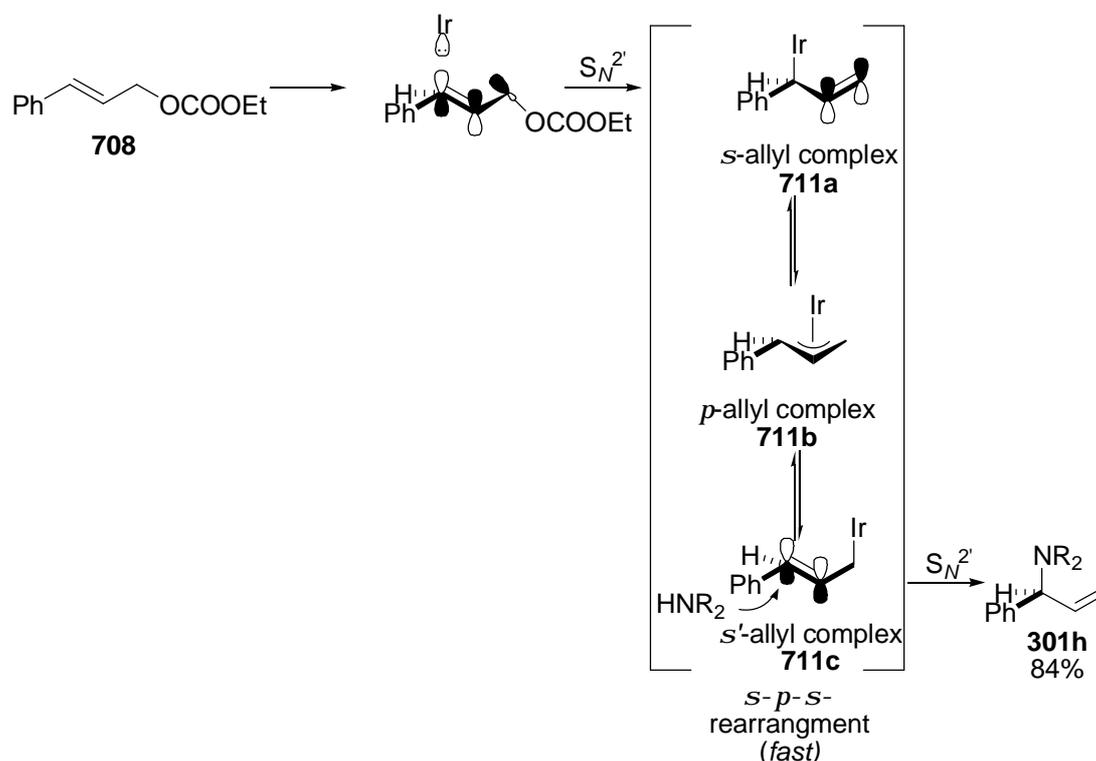
cond.: 1equiv. **631**, 3equiv. piperidine, 2mol% [Ir(cod)Cl]$_2$, 8mol% P(OPh)$_3$, EtOH, 80°C, 2h, 84%.

In the case of *a*-methyl cinnamyl carbonate (**709**), *s*-*p*-*s*-rearrangement of *s*-complex **712a** to *p*-complex **712c** may be kinetically hindered by increased *syn*-periplanar repulsion of

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[74] For a review on Palladium catalyzed allylation reactions see: Trost, B.M.; Lee, C.; in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ojima, I. eds.), Wiley-VCH, New York, **2000**, 593-650.

the methyl and the phenyl substituent. If an S_N2'-*anti* substitution takes place, it may proceed from *s*-complex **712a** to give **714a** or from *s*-complex **713a** to give **714b**. Here however, the alcohol **634** is formed as the major product via base induced decomposition of the starting material. This suggests that S_N2' might, in this special case, be slower than the product decomposition. Steric repulsions within both *s*-complexes may not result in a conformation in which the iridium catalyst is *anti*-periplanar to the incoming nucleophile, reducing the S_N2' reaction rate by far (Scheme 75).

Scheme 75: Mechanism of the iridium catalyzed allylic amination of cinnamyl carbonates.

cond.: 1equiv. **709**, 3equiv. hexylamine, 2mol% [Ir(cod)Cl]$_2$, 8mol% P(OPh)$_3$, EtOH, 80°C, 2h, 56%.

However, if carbonate **715** is subjected to the allylic amination, **717** can be isolated in quantitative yield as the only regioisomer.

Scheme 76: Mechanism of the iridium catalyzed allylic amination of cyclic allylic carbonates.
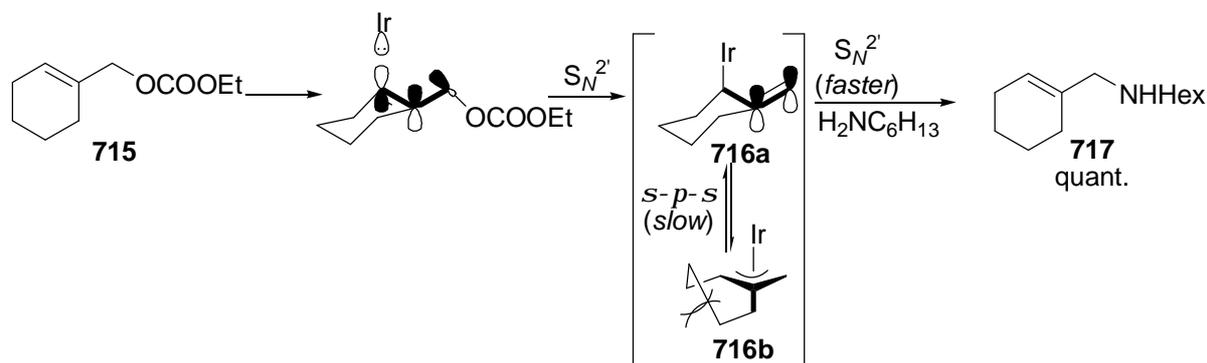
cond.: 1equiv. **715**, 3equiv. hexylamine, 2mol% [Ir(cod)Cl]$_2$, 8mol% P(OPh)$_3$, EtOH, 80°C, 2h, 100%.

The fact that the amine replaces the carbonate on the same carbon atom is known as the memory effect of iridium (Scheme 76)[75]. Here *s*-*p*-rearrangement may be hampered by an increased steric repulsion between the two ring-CH_2-groups in *p*-complex **716b**, therefore, S_N2' proceeds from the initially formed *s*-complex giving the linear amine. Consequently, regioisomeric carbonate **718** has been subjected to the allylic amination resulting in the desired regioisomeric allylic amine **719** in 92% yield (Scheme 77).

**Scheme 77: Synthesis of a chiral and
prochiral allylic amine.**

cond.: 1equiv. **718**, 3equiv. hexylamine,
2mol% [Ir(cod)Cl]$_2$, 8mol% P(OPh)$_3$,
EtOH, 80°C, 2h, 92%.
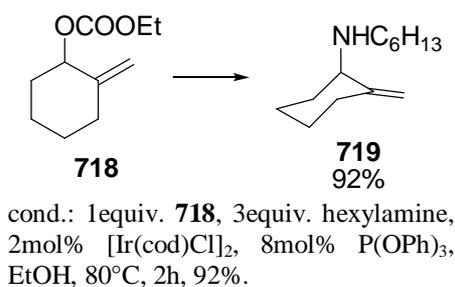
Obviously iridium catalyzed allylic amination can proceed via two different ways. If a fast *s*-*p*-*s*-rearrangement is possible, nucleophilic attack takes place preferably at the higher substituted carbon atom. Although TAKEUCHI supposes that electronic reasons are responsible[76] similar to palladium catalyzed allylations[77], a preference of *s*-complex **711c** appears to be reasonable due to steric pressure. S_N2'-substitution gives then the branched product preferably. In contrast, if a fast *s*-*p*-*s*-rearrangement is hindered, either by the *syn*-periplanar interactions or interactions between the catalyst and bulky substituents in the *anti*-*p*-allyl-iridium complex, the *s*-complex undergoes S_N2'-*anti*-substitution, giving a product in which the leaving group and the nucleophile are placed at the same carbon atom (*memory effect*).

Upon having a secondary chiral allylic amine *o*-DPPB was attached to this substrate using the STEGLICH protocol giving substrate **720** together with an olefinic by-product.

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[75] Faller, J.W.; Sarnatopoulos, N.; *Organometallics* **2004**, *23*, 2179-2185.

[76] *a*) Takeuchi, R.; Kashio, M.; *J. Am. Chem. Soc.* **1998**, *120*, 8647-8655. *b*) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N.; *J. Am. Chem. Soc.* **2001**, *123*, 9525-9534.

[77] Åkermark, B.; Hansson, S.; Krakenberger, B.; Vitagliano, A.; Zetterberg, K.; *Organometallics* **1984**, *3*, 679-682.

**Scheme 78: Steglich amidation towards a test substrate.**
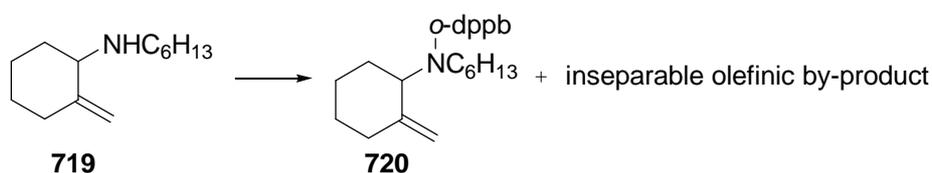
cond.: 1equiv. **719**, 1equiv. *o*-diphenylphosphino benzoic acid, 1.1equiv. DCC, 5mol% DMAP, CH$_2$Cl$_2$, rt, 12h.

7.3 STEREOSELECTIVE HYDROFORMYLATION / FISCHER INDOLIZATION

Since this byproduct can not be separated from the desired olefin, the starting material for carbonate **718** is used for further studies on the influence of aromatic hydrazines on the diastereoselectivity. Hydroformylation of **721** has already been investigated by CRUDDEN in 2002, and a basic diastereoselectivity was observed depending from the alcohol protecting group used. Nevertheless, in all cases the diastereoselectivity does not exceed a 6:1 ratio in favor of the *trans* product (Scheme 79)[78].

Scheme 79: Diastereoselective hydroformylation of protected 2-methylene cyclohexanols.
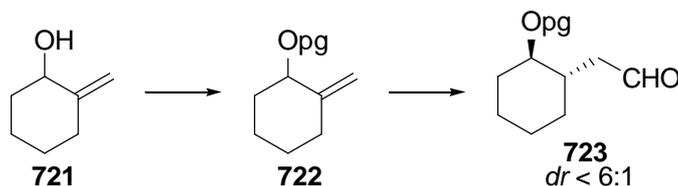
Carbodiimide mediated attachment of *o*-DPPB to **721** gives substrate **724** in quantitative yields. Hydroformylation is conducted without addition of ligand in benzene at low temperature giving aldehyde **649** with excellent diastereoselectivity (*dr* > 95:5). The NMR shows a chemical shift of the aldehyde group that corresponds with that of the *trans* isomer (Scheme 80).

Scheme 80: Diastereoselective hydroformylation using Breit's protocol.
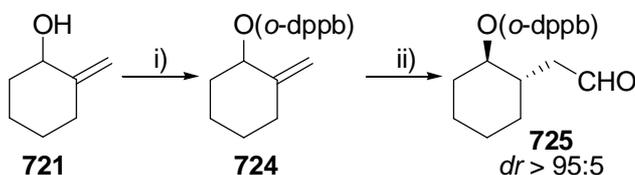
cond.: i) 1equiv. **721**, 1equiv. *o*-diphenylphosphino benzoic acid, 1.1equiv. DCC, 5mol% DMAP, CH$_2$Cl$_2$, rt, 48h, 100%. ii) 1equiv. **724**, 3mol% Rh(acac)(CO)$_2$, 30bar H$_2$, 30bar CO, 40°C, 20h.

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[78] Ren, L.; Crudden, C.M.; *J. Org. Chem.* **2002**, *67*, 1746-1750.

To test the influence of hydrazines on the diastereoselectivity, hydroformylation is conducted in the presence of an aromatic hydrazine. Since the presence of an additional stereogenic center would hamper the determination of the diastereomeric ratio, *a*-Boc protected *p*-methoxy phenylhydrazine **214j** is used. Hydrogen bonding between the Boc-carbonyl group and the hydrazone-CH group is responsible for the selective formation of the (*E*)-hydrazone. Tandem hydroformylation / hydrazone formation gives hydrazone **726** with no loss of diastereoselectivity compared to the hydroformylation (Scheme 81).

Scheme 81: Diastereoselective tandem hydroformylation / Fischer indole synthesis.
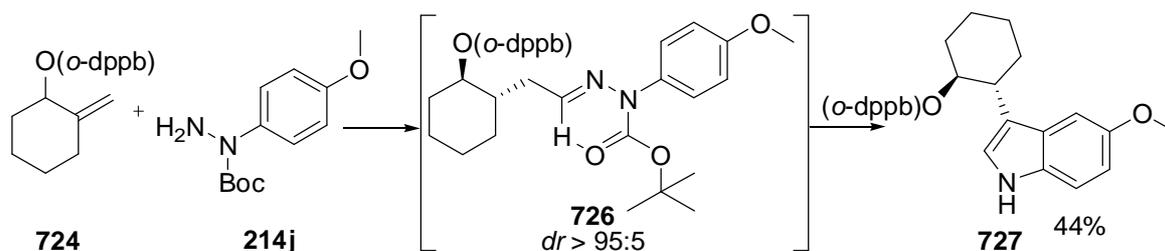
cond.: i) 1equiv. **724**, 1equiv. **214j**, 3mol% Rh(acac)(CO)$_2$, 30bar CO, 30bar H$_2$, THF, 100°C, 20h, 76%. ii) 1equiv. **650**, 4wt% H$_2$SO$_4$ in THF, 80°C, 2h, 44%.

Subsequent indolization of **726** gives the desired indole in 44% yield as a first example of a stereoselective tandem hydroformylation / FISCHER indole synthesis. During acid mediated indolization, the diphenyl phosphino group is partially oxidized to the phosphane oxide which could not be isolated, lowering the isolated yield of indole **727**. Though comparable substrates may easily be achieved by electrophilic substitution of indole **728** with cyclohexene oxide **729**. If further substituents are present on the cyclohexane ring, as required for hapalindole Q, epoxide opening would not precede regioselectively. Here diastereoselective tandem hydroformylation / FISCHER indole synthesis of **731** might be an attractive alternative (Scheme 82).

Scheme 82: Comparison with electrophilic substitution of indoles with epoxides.
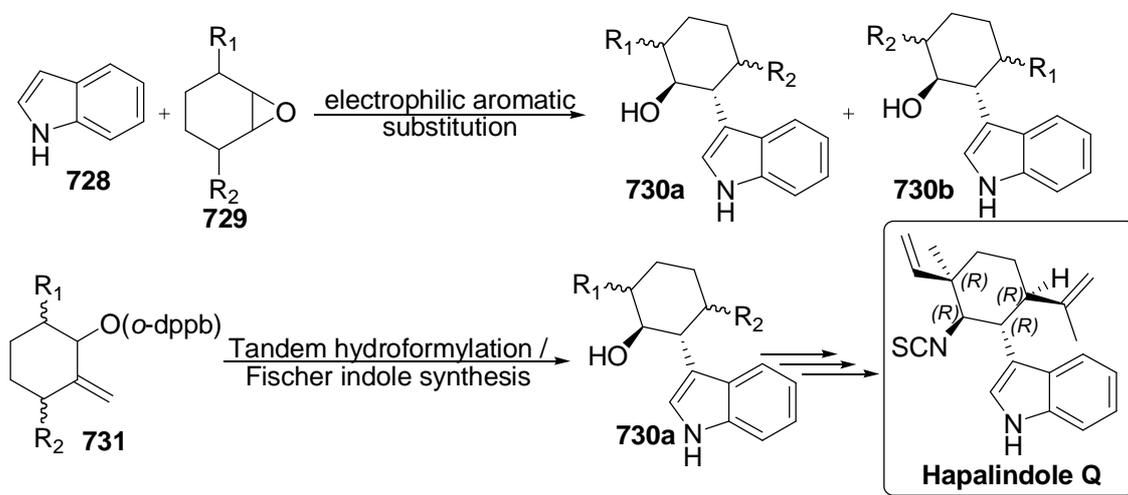
7.4 INTERIM CONCLUSION

In this chapter, the first asymmetric tandem hydroformylation / FISCHER indole synthesis has been described.

Ø Due to a lack of enantioselective hydroformylation catalysts for b-induction of stereocenters, BREIT's protocol for a diastereoselective hydroformylation of methallylic alcohols is used. *Ortho*-diphenylphosphino benzoic acid acts as an auxiliary that directs the hydroformylation catalyst to one diastereotopic faces of the double bond preferably.

Ø Even in the presence of aromatic hydrazines high diastereoselectivities are obtained upon tandem hydroformylation / hydrazone formation.

Ø It couldn't be clarified completely if BREIT's strategy can be transferred to chiral allylic amines, but initial results suggest that even here high diastereoselectivities can be expected.

Ø This methodology might be synthetically valuable for the stereoselective approach towards an intermediate for the total synthesis of hapalindole Q.

Ø Insight into the regioselectivity of the iridium catalyzed allylic amination is given in the context of the synthesis of chiral allylic amines.

Ø If a p-allyl-iridium-complex can be formed, the catalyst evades steric hindrance, giving the branched amination product upon S_N2'-*anti*-substitution.

Ø If the formation of this p-allyl-complex is hindered by steric interaction of substituents amination does not precede formally as an allylic substitution giving linear or branched products depending on the starting material (*memory effect*).

8 Tandem Hydroformylation / Fischer Indole Synthesis on Solid Phase

The discovery of new pharmaceuticals is one of the most challenging issues in medicinal chemistry. This search has been revolutionized in the early 1990's by the introduction of automated, polymer supported, combinatorial chemistry. Nowadays, the search for new pharmacologically active compounds can be described as a two-step process in which a library of compounds with as much diversity as possible is synthesized, starting with a defined set of reactants (Scheme 83). The compounds in this library can differ in their substitution pattern, in their absolute or relative configuration or even in their scaffold. A primary screening on a special target discovers a possible lead structure, which is then optimized in a second combinatorial approach.[79] In many cases, these compounds contain privileged structures, such as benzodiazepines, quinolones or indoles.

**Scheme 83. Solid phase supported two step process for the development of new lead structures.**
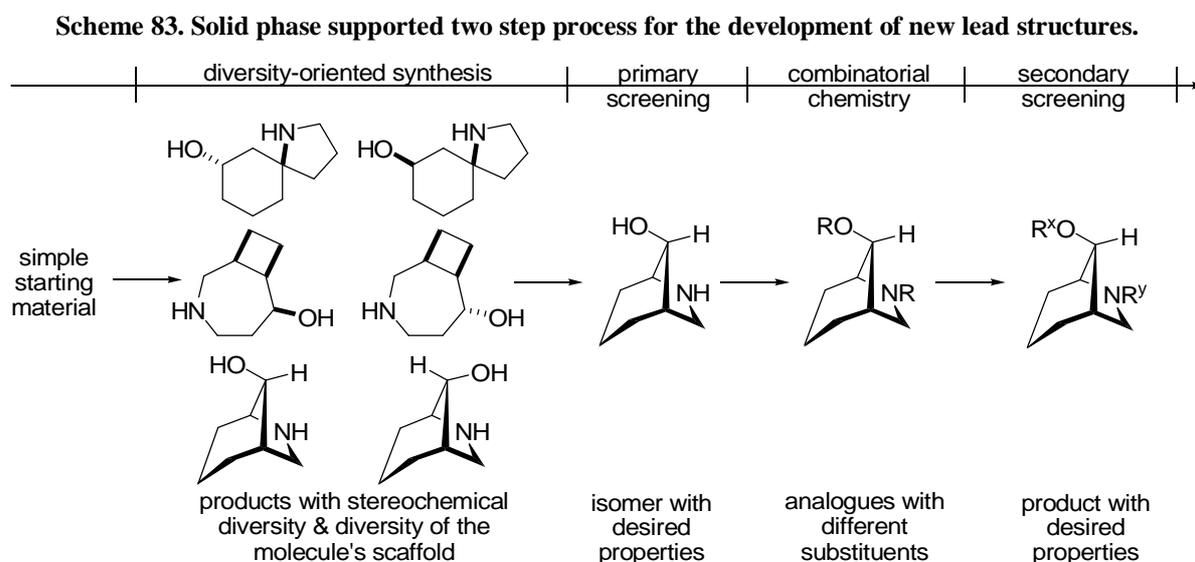
In the previous chapters it has been demonstrated, that the tandem hydroformylation / FISCHER indole synthesis is a powerful synthetic tool for the synthesis of indoles with unusual substitution patterns as well as pharmaceuticals. Considering all experiments, including the work of KÖHLING[18,19], the tandem hydroformylation / FISCHER indolization might also be a very attractive tool for the discovery of new pharmaceuticals. In using different olefins and aromatic hydrazines, not only the substitution pattern of the indole can be varied, but the diversity of the molecule's scaffold can be achieved if the indolization incorporates an additional rearrangement as in the use of internal olefins. Here, the intermediate indolenine rearranges to give the aromatic indole. But with an appropriate set of reaction conditions, the

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[79] Schreiber, S.L.; Burke, M.D.; *Angew. Chem.* **2004**, *116*, 48-60.

indolenine can either be isolated or hydrogenated to give spiro-indolines. Therefore, tandem hydroformylation / FISCHER indole synthesis can be used to create substrate controlled diversity as well as reagent controlled diversity of the molecule's scaffold. Furthermore, the indoles derived from this tandem reaction are ideal intermediates for a WITCOP-WINTERFELDT-oxidation[80] which gives direct access to *g*-quinolones. This consecutive reaction together with a previous tandem hydroformylation / FISCHER indole synthesis in a split-pool approach may give convenient access to a highly diverse library of potentially pharmaceutically active compounds (Scheme 84).

Scheme 84: Structural elements that can be accessed by tandem hydroformylation / Fischer indole synthesis.

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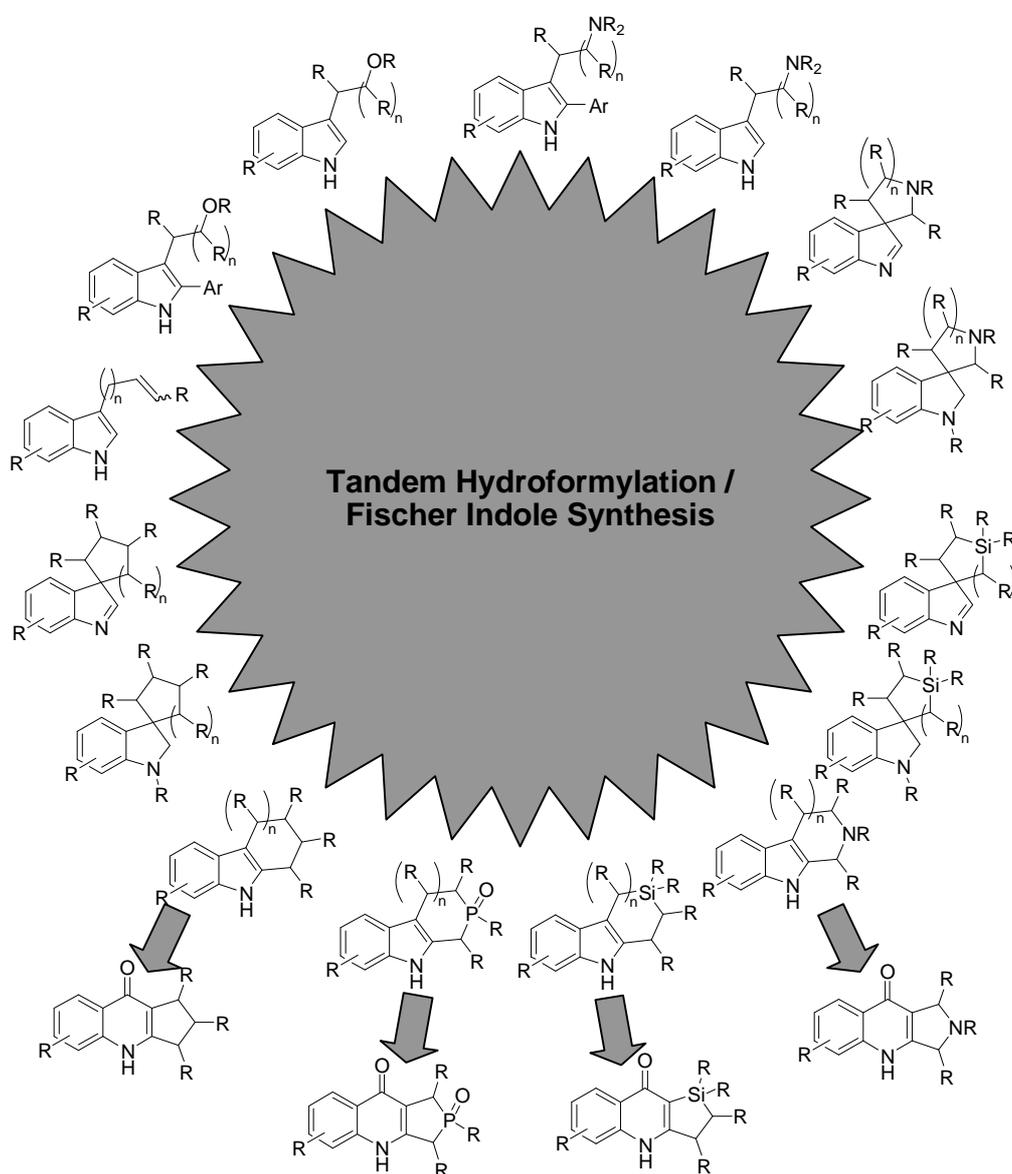
[80] *a*) Jiang, W.; Zhang, X.; Sui, Z. *Org. Lett.* **2003**, 5, 43. *b*) Zhang, X.; Jiang, W.; Sui, Z. Asymmetric total syntheses of quinolactacin A and B through an improved Winterfeldt Oxidation. *Abstracts of Papers*; 224th ACS National Meeting, Boston, MA, 18-22 Aug, 2002; American Chemical Society: Washington, DC, **2002**.

A necessity for the use of this new tandem reaction for the identification of new leads is its transfer from solution to solid phase in order to allow automated combinatorial synthesis. In this chapter, initial investigations for the tandem hydroformylation / FISCHER indole synthesis on polymer support are compiled.

In this context, it has to be focused on the hydroformylation process to allow

Ø small scale parallel synthesis

Ø on polymer support

Ø under a pressurized atmosphere,

as well as on the polymer's design to ensure

Ø a high yielding linkage of the substrate to the polymer,

Ø stability of the linker under the reductive hydroformylation conditions and the harsh and acidic FISCHER indolization conditions,

Ø orthogonal and selective cleavage of the indole product.

8.1 HYDROFORMYLATION ON SOLID PHASE

In the past decade several hydroformylations and tandem reactions under hydroformylation conditions have been transferred from solution to solid phase. Special attention must be paid to the apparatus in which the hydroformylation experiment is conducted in. High reaction rates can only be expected if the gas phase and solution phase are mixed intensively. For this purpose special stirrers were designed as shown in Figure 1.

Figure 1: Parr autoclave with special stirrer for extensive mixing of liquid and gas phase.
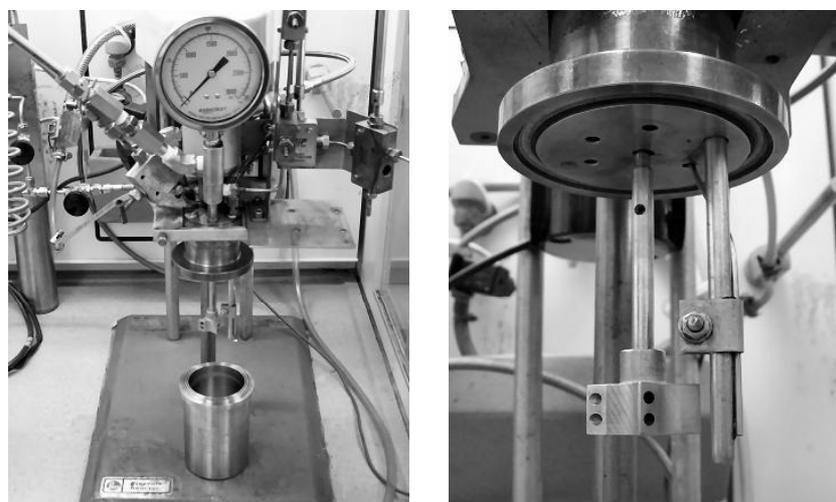
On the other hand, KOÇ experienced that polymer beads are destroyed by such stirrers due to shear stress. Therefore, magnetically stirred or shaken reaction vessels are preferred with

prolongation of the reaction time as a consequence. However, even magnetic stir bars can pulverize polymer beads if the resin gets between the stir bar and the bottom of the reaction vessel. In 1997, TAKAHASHI *et al.* used a Multipin™ system for the hydroformylation in a solid phase approach towards muscone. Hydroformylation was conducted on a polystyrene resin with a 4-hydroxy-phenyl-sulfonylchloride modified trityl linker.[81] While the trityl group can easily be cleaved after hydroformylation, the 4-hydroxy-phenyl sulfonate acts as a leaving group for consecutive alkylations (Scheme 85).

Scheme 85: Hydroformylation of unsaturated alcohols on a modified trityl linked resin.
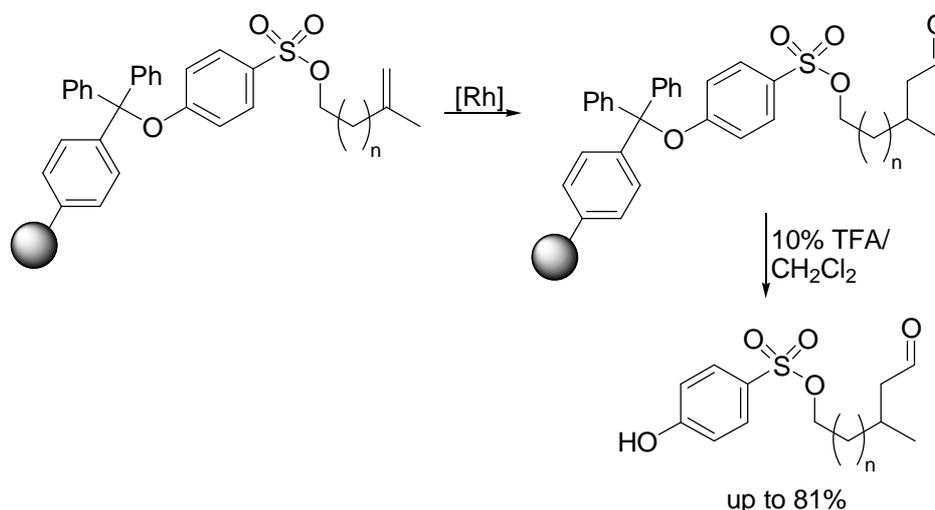
In 2003, MARCHETTI has modified a glass vial for hydroformylation on solid phase. Here, the reaction area is separated from the stirring area with a sintered glass filter and a basket in which the resin is placed (Figure 1). With this method MARCHETTI conducted a series of hydroformylations and tandem reactions under hydroformylation conditions, such as a hydroaminomethylation and a hydroformylation / PICTET-SPENGLER reaction, of different trityl linked olefins.[82]

Figure 2: Glass vial for solid phase synthesis in autoclaves.
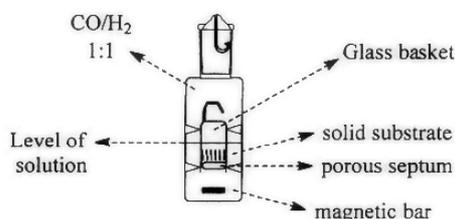
[81] *a*) Takahashi, T.; Machida, K.; Kido, Y.; Nagashima, K.; Ebata, S.; Doi, T.; *Chem. Lett.* **1997**, 1291-1292. *b*) Takahashi, T.; Ebata, S.; Doi, T.; *Tetrahedron Lett.* **1998**, 1369-1372.
[82] *a*) Dessole, G.; Marchetti, M.; Taddei, M.; *J. Comb. Chem.* **2003**, *5*, 198-200. *b*) Marchetti, M.; Botteghi, C.; Paganelli, S.; Taddei, M.; *Adv. Synth. Catal.* **2003**, *345*, 1229-1236.

Very recently KOÇ used an intermolecular hydroaminomethylation on Wang resin to build up dendrons for dendrimer synthesis in a slowly stirred Parr autoclave (Scheme 86).[83]

Scheme 86: Dendrimer synthesis on solid phase.
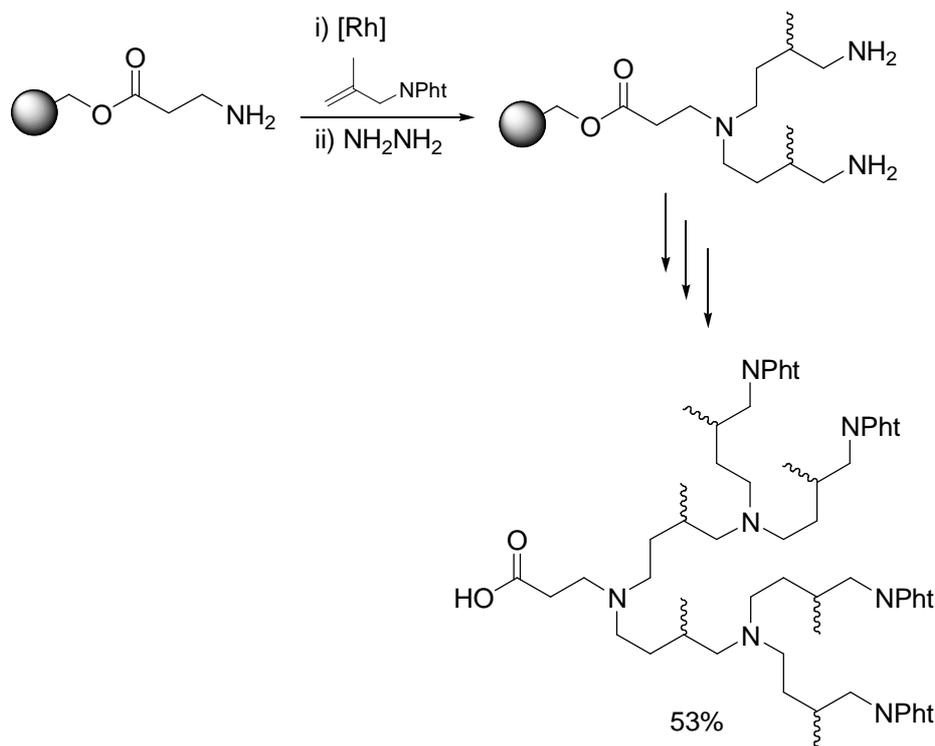
8.2 FISCHER INDOLE SYNTHESES ON SOLID PHASE

Due to the importance of the indole ring in biological and medicinal chemistry, many approaches towards a polymer supported FISCHER indole synthesis have been reported.

Scheme 87: Chapman's Fischer indole synthesis on solid phase.
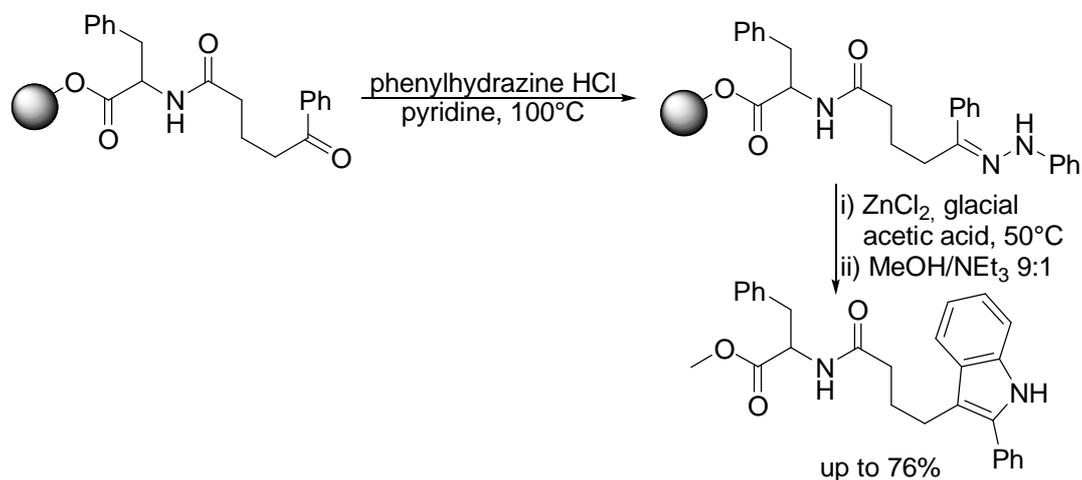
In 1997, CHAPMAN *et al.* synthesized 2-aryl indoles from a HMBA linked 4-benzoylbutyric acid on a polyethyleneglycol modified polystyrene (PS) resin and various aromatic

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[83] Koç, F.; *Dissertation* **2004**, University of Dortmund.

hydrazines.[84] The FISCHER indolization was mediated by $ZnCl_2$ in glacial acetic acid (Scheme 87). While the solid phase synthesis of similar compounds using a safety catch linker failed due to an intramolecular substitution of the sulfonamide by the hydrazone *NH*-group, the use of a carbamate linker on a hydroxymethylated polystyrene resin afforded the desired 2-aryl indoles (Scheme 88).[85]

Scheme 88: Fischer indole synthesis on solid phase using a carbamate linker.

60%, 95% purity
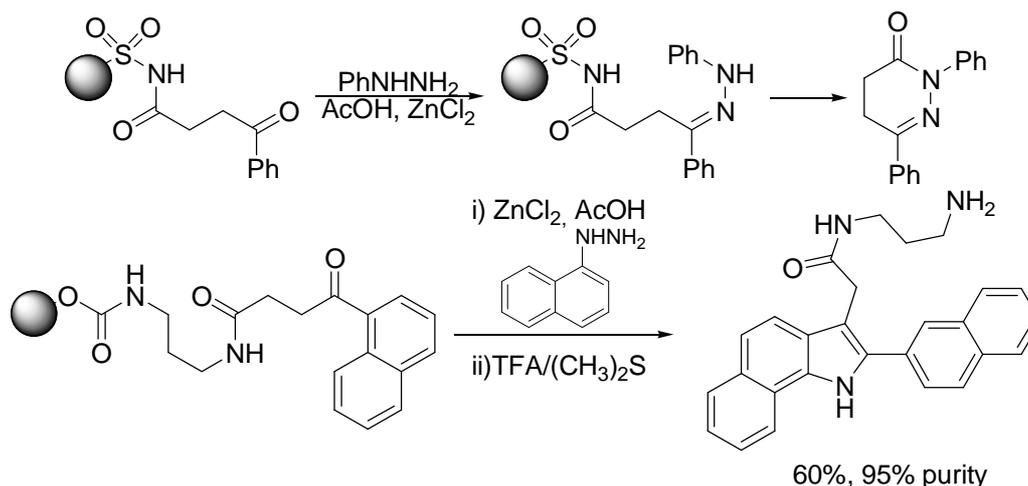
A traceless FISCHER indole synthesis has been developed by WALDMANN.[86] Here, in contrast to previous examples, the aromatic hydrazine is linked to the resin. The hydrazine can be bound to an aldehyde functionalized resin as a hydrazone. In the presence of a carbonyl compound and an acid, this hydrazone is cleaved by transcondensation and the resulting hydrazone undergoes indolization in solution (Scheme 89). This approach can be compared to the BUCHWALD-HARTWIG modification of the FISCHER indole synthesis (see above).

Scheme 89: Waldmann' approach of traceless Fischer indole synthesis.

4-100%
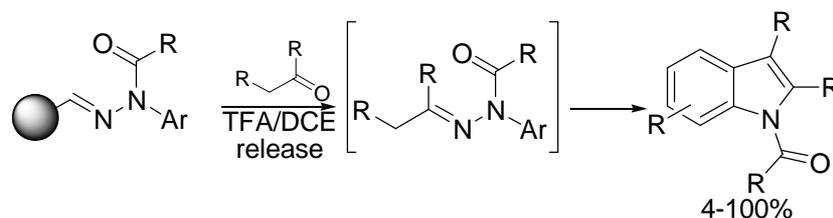
As an alternative, the aromatic hydrazine can be bound via an alkyl spacer. Condensation with a carbonyl gives an ene-hydrazine on solid phase, which is cleaved from the resin upon acid mediated indolization (Scheme 90).

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[84] Hutchins, S.M.; Chapman, K.T.; *Tetrahedron Lett.* **1997**, *37*, 4869-4872.

[85] Yang, L.; *Tetrahedron Lett.* **2000**, 6981-6984.

[86] *a*) Rosenbaum, C.; Baumhof, P.; Mazitschek, R.; Müller, O.; Giannis, A.; Waldmann, H.; *Angew. Chem. Int. Ed.* **2004**, *43*, 224-228. *b*) Rosenbaum, C.; Katzka, C.; Marzinik, A.; Waldmann, H.; *Chem. Commun.* **2003**, 1822-1823.

Scheme 90: Waldmann' approach of traceless Fischer indole synthesis.

6-41%
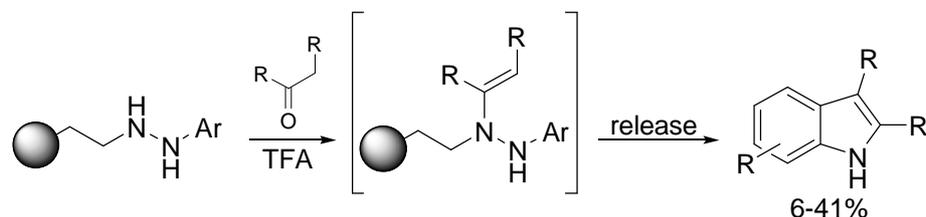
JEONG has used the traceless ELLMANN silicon linker to synthesize indoles and the required hydrazines on a Tentagel S NH$_2$ resin.[87] Indolization is mediated with ZnCl$_2$ in acetic acid, while the silyl linker is cleaved with TFA (Scheme 91).
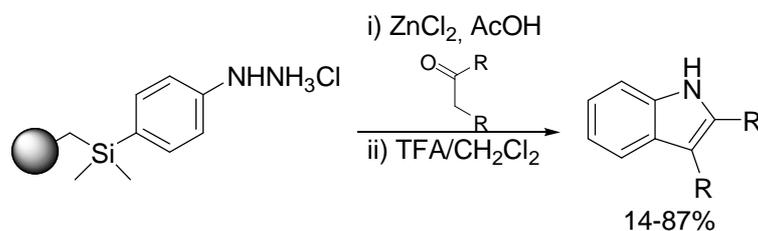
Scheme 91: Ellmann silicon linker in Fischer indole synthesis.

14-87%

Very recently BREINBAUER applied the sulfonamide linker on a polystyrene resin to the FISCHER indole synthesis of 2,3-anellated indoles as well as spiro-indolines starting with polymer bound 4-piperidone. Cleavage of this linker can be achieved with Li-biphenylide (Scheme 92).[88]

Scheme 92: Acid stable sulfonyl chloride PS resin for Fischer indole synthesis on solid phase.
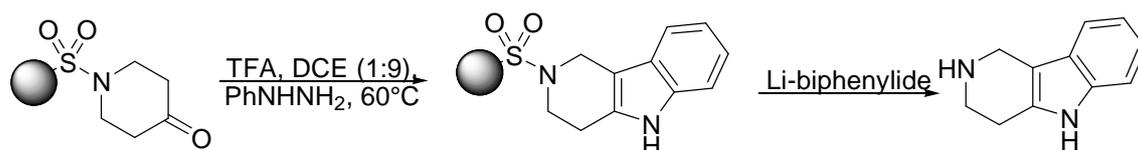
Except this last work and the initial work of CHAPMAN, all linkers, that have been used for FISCHER indole synthesis are acid labile. Here, milder acidic conditions are required for the indolization step to prevent the products or intermediates from being released too early. Therefore, low yields are observed in many cases. Since good results in the tandem hydroformylation / FISCHER indole synthesis with tosylated allylic amines have been observed in solution, the sulfonamide linker seems to be the most promising linker for the tandem hydroformylation / FISCHER indole synthesis on polymer support.

The following results are collected in cooperation with MATTHIAS MENTEL and DR. ROLF BREINBAUER.

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[87] Mun, H.S.; Ham, W.H.; Jeong, J.H.; *J. Comb. Chem.* **2005**, *7*, 130-135.
[88] Mentel, M,; Breinbauer, R.; *in preparation.*

8.3 HYDROFORMYLATION OF SULFONAMIDE LINKED AMINOOLEFINS

Starting with simple aminoolefins linked to the sulfonamide resin, the single steps for the tandem reaction shall be optimized first. Three different aminoolefins are linked to the polystyrene sulfonylchloride resin (**802**) (Scheme 93). On the other hand, disubstituted, terminal olefins require harsher hydroformylation conditions. In contrast, *N*-methyl allylic amine can be hydroformylated under milder conditions with or without control of the regioselectivity. 4-Methylene piperidine and *N*-ethyl-methallylic-amine give linear aldehydes without addition of *n*-directing ligands. **802**-**804** are hydroformylated in a slowly stirred Parr autoclave applying the same conditions Koç has used for the hydroaminomethylation on solid phase. Since the resulting aldehydes do not tolerate the conditions required for the cleavage of the sulfonamide linker, aldehyde loadings are determined using the FmPh-method (Scheme 94)[89].

Scheme 93: Hydroformylation of different olefins on solid phase.
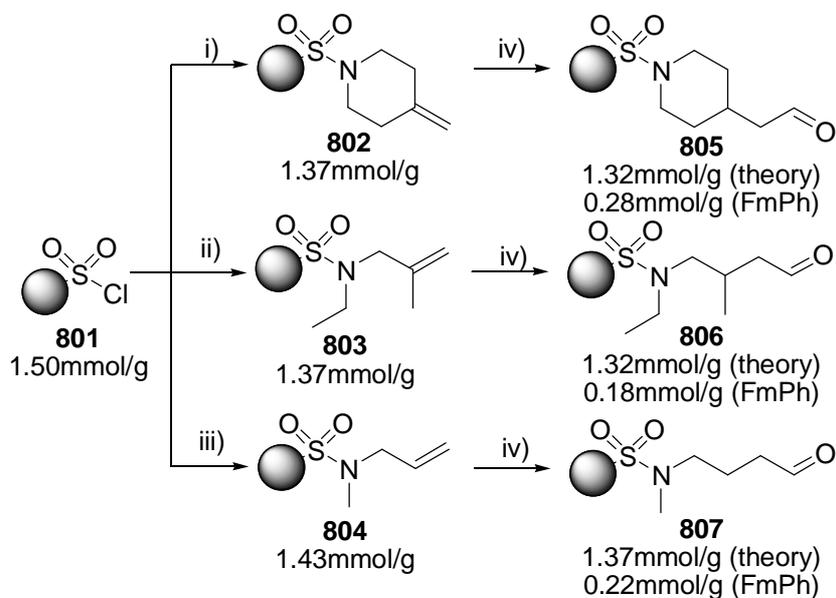
cond.: i) 1equiv. **801**, 5equiv. 4-methylene piperidine, THF/pyridine (1:1), rt, 20h. ii) 1equiv. **801**, 5equiv. *N*-ethyl methallylic amine, CH₂Cl₂/pyridine, rt, 24h. iii) 1equiv. **801**, 5equiv. *N*-methyl allylic amine, pyridine, 60°C, 2h. iv) 1equiv olefin, 20mol% Rh(acac)(CO)₂, 50bar CO, 10bar H₂, THF, 80°C, 2d.

This method was developed by BARANY in 2004, and is a convenient tool for the on-bead analysis of aldehyde loadings. Here the fluorenylmethyl ester of 4-hydrazinobenzoic acid (FmPh, **808**) is reacted with the aldehyde (**805**) to give aromatic hydrazone **809**.

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[89] Shannon, S.K.; Barany, G.; *J. Org. Chem.* **2004**, *69*, 4586-4594.

Scheme 94: On-bead analysis of aldehyde loadings – the FmPh-method.
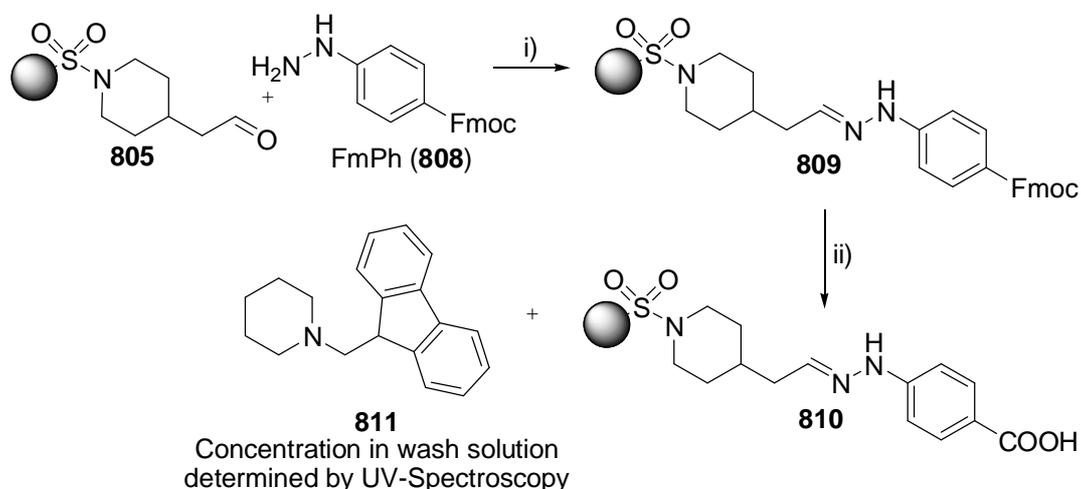
cond.: i) 1equiv. **805**, 3equiv. **808**, 3equiv. DIPEA, DMF/trimethyl orthoformiate (1:1), 80°C, 30min; ii) DMF/piperidine (1:1), rt, 30min.

After washing and upon addition of piperidine in DMF, the fluorenylmethylester is cleaved and the resin is washed properly. The washing solution is collected and the concentration of the fluorenylpiperidine (**811**), and therefore the aldehyde's loading, is analyzed via UV-spectroscopy. The determined loadings, compiled in Scheme 93, are much smaller than the theoretical loadings of the starting olefin. Three reasons are imaginable:

Ø Since there is no direct method to determine olefin loadings, the conversion of the sulfonamide formation is assumed to be quantitative. If attachment of the aminoolefin proceeds not in quantitative yields, the loading with olefin, and therefore, with the aldehyde is much smaller.

Ø The conditions KOÇ has found might not be ideal for the hydroformylation of allylic and homoallylic sulfonamides, causing incomplete conversion.

Ø The FmPh-method may fail with aldehydes derived upon olefin hydroformylation.

In order to exclude problems with the linkage of the aminoolefin to solid phase, *N*-methyl allylic amine is reacted with a spacer to give sulfonamide **813** in solution. This spacer is then placed on aminomethylated polystyrene resin (**812**) under reliable carbodiimide mediation. The obtained olefin is hydroformylated under KOÇ's conditions and the aldehyde loading is determined with the FmPh-method. Again the aldehyde loading is much smaller than the theoretical loading. For a comparison, olefin **814** was ozonolysized to give *a*-aminoaldehyde **81**6 with slightly higher loadings than for the hydroformylation aldehyde. These loadings, however, are still smaller than the theory would let to expect (Scheme 95). To prove the

reliability of Koç's conditions, undecenoic acid, attached to Wang resin (**817**), is hydroformylated.

Scheme 95: Comparison of hydroformylation and ozonolysis.
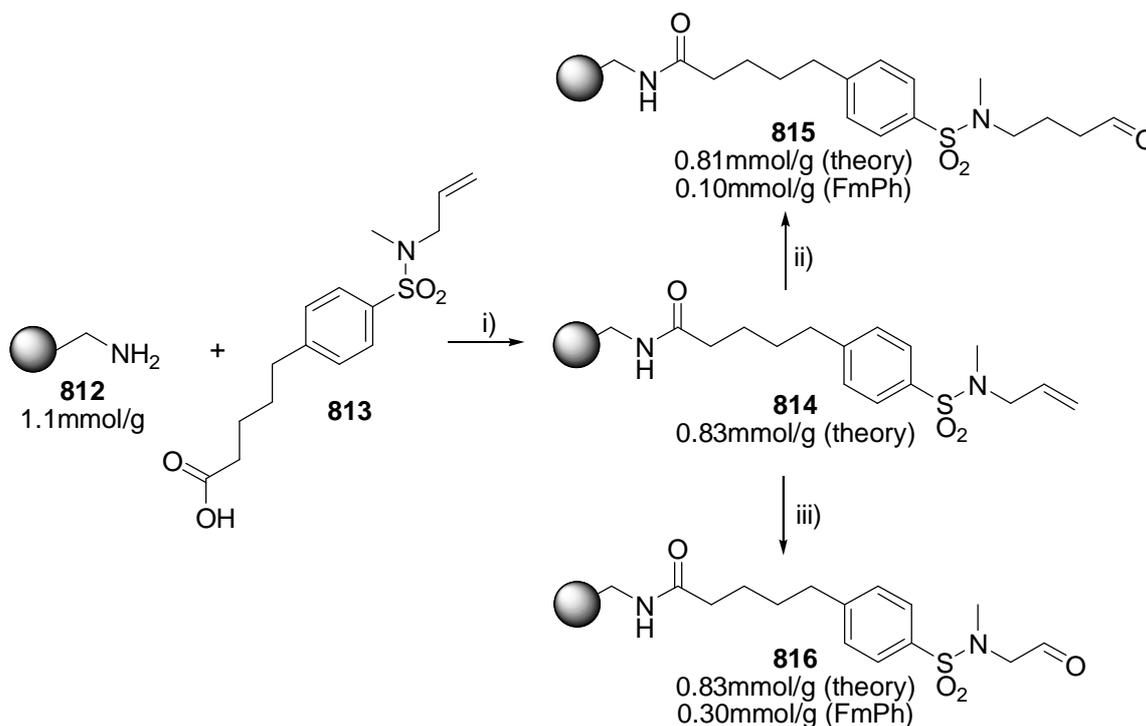
cond.: i) 1equiv. **812**, 5equiv. **813**, 3equiv. DIC, 3equiv. HOBt, 3equiv. NEt$_3$, CH$_2$Cl$_2$, rt, 12h. ii)1equiv. **814**, 20mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 80°C, 5d. iii) O$_3$, CH$_2$Cl$_2$, -78°C, 10min, then 5equiv. PPh$_3$, rt, 12h.

The aldehyde loading is determined with the FmPh-method on the one hand and on the other hand the resulting aldehyde **818** is cleaved off with TFA. While the aldehyde loading was 0.21mmol/g according to the FmPh-method the pure hydroformylation product could be isolated with 87% yield corresponding with an aldehyde loading of 0.84mmol/g (Scheme 96).

Scheme 96: Reliability of the FmPh method.
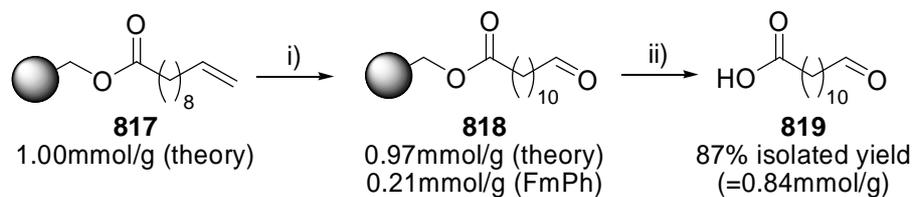
cond.: i) 1equiv. **817**, 20mol% Rh(acac)(CO)$_2$, 10bar CO, 10bar H$_2$, THF, 80°C, 20h. ii) TFA/CH$_2$Cl$_2$ (1:1), rt, 20min, (3x).

Surprisingly, the FmPh-method does not seem to be a reliable method for the control of the hydroformylation's conversion. However, it can be assumed, that the hydroformylation is reliable either on Wang resin or on PS sulfonylchloride resin. To give evidence to this assumption, olefin **820** is hydroformylated followed by cleavage of the Wang linker.

Scheme 97: Hydroformylation of 4-methylene piperidines on sulfonamide PS resin.

820
0.87mmol/g (theory)

821
0.85mmol/g (theory)

822
100% isolated yield
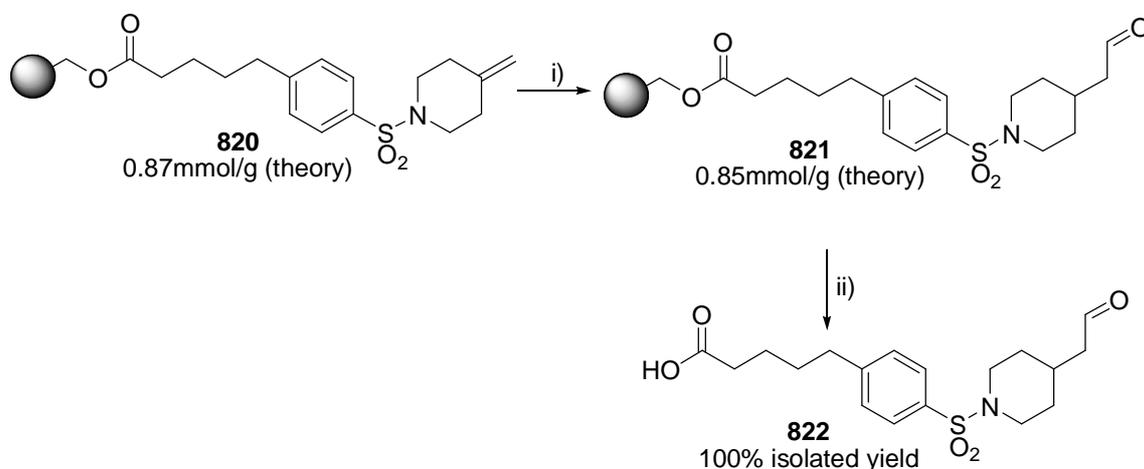
cond.: i) 1equiv. **820**, 20mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 80°C, 44h. ii) TFA/CH$_2$Cl$_2$ (1:1), rt, 20min, (3x).

Aldehyde **822** was isolated in quantitative yield and with high purity upon treatment of the resin with TFA (Scheme 97).

8.4 TANDEM HYDROFORMYLATION / HYDRAZONE FORMATION OF SULFONAMIDE LINKED AMINOOLEFINS

Upon having found conditions for a selective hydroformylation of sulfonamide linked aminoolefins, olefin **820** is subjected to a tandem hydroformylation / hydrazone formation. Based on KOÇ's conditions, the hydroformylation is conducted in the presence of 10 equivalents of phenylhydrazine. After cleavage of the product, a complex mixture is obtained. One can expect that the acidic cleavage conditions may initialize indolization of the hydrazone, but neither indoles nor hydrazones can be detected. If the hydrazone is formed, it might be hydrolyzed during release of the product or the hydrazone is oxidized.

Figure 3: Conical glass vials for parallel synthesis on solid phase in autoclaves.

On the other hand, hydrazone formation might be hampered by the large amount of solvent needed in a Parr autoclave resulting in low hydrazine concentrations. In using magnetically stirred conical glass vials as illustrated in Figure 3 the amount of solvent can be reduced from 80ml to 2ml. The fact that only the cone end of the magnetic stir bar touches the bottom of the flask is crucial to minimize mechanical stress to the polymer beads. Since several flasks can be placed in one autoclave, this method allows parallel synthesis.

While the stability of the resulting hydrazones against oxidation can be improved by replacing unprotected aromatic hydrazines by a-Boc protected aromatic hydrazines, a partial indolization of the hydrazone is prevented by using a base labile linker such as the HMBA linker in olefin **823**. Tandem hydroformylation / hydrazone formation followed by cleavage of the HMBA linker under mild basic conditions gives the desired hydrazone **825** in 23% yield but most importantly with high purity (Scheme 98). This high purity is deemed to indicate a selective hydrazone formation under hydroformylation conditions. Although the amount of rhodium catalyst was increased compared to the reactions in solution, neither side reactions such as aldehyde or olefin hydrogenation nor a consecutive hydrogenation of the hydrazone is observed. The low yield might be caused by an incomplete cleavage of the product but harsher conditions such as sodium methanolat in methanol may affect the hydrazone or Boc group.

Scheme 98: Tandem hydroformylation / hydrazone formation on solid phase.
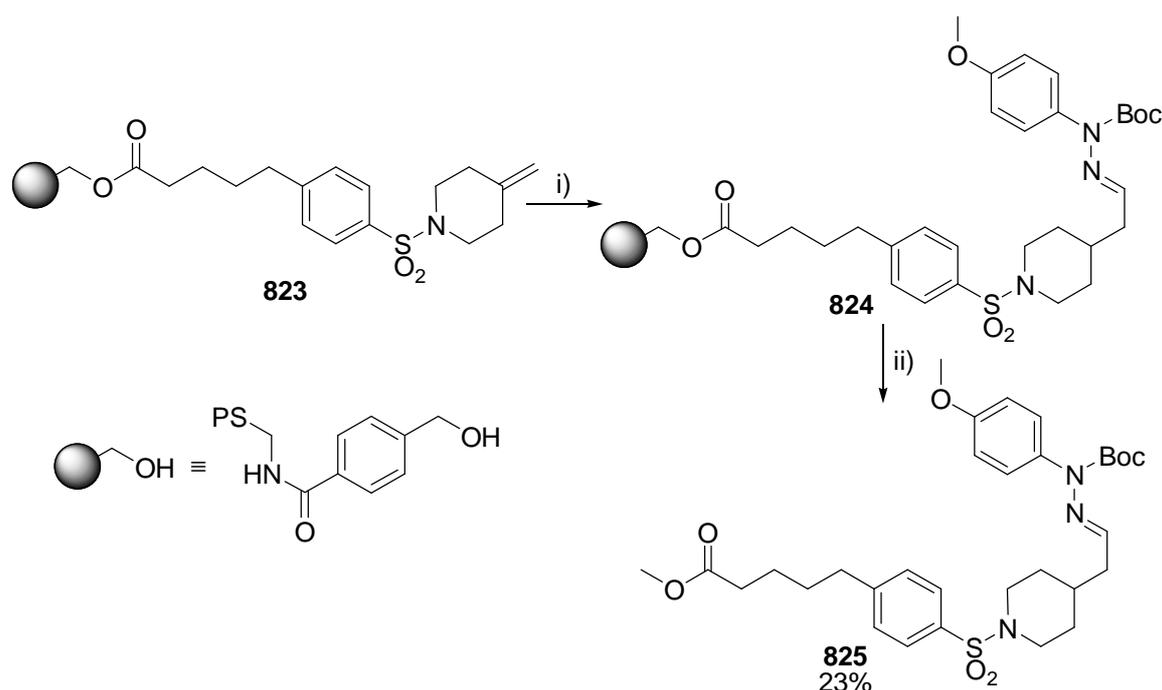
cond.: i) 1equiv. **823**, 10equiv. **214j**, 20mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 80°C, 44h. ii) 1equiv. **824**, dioxane/DIPEA/MeOH (5:4:1), 80°C, 12h.

8.5 TANDEM HYDROFORMYLATION / FISCHER INDOLIZATION OF SULFONAMIDE LINKED AMINOOLEFINS

Two different options for the tandem hydroformylation / FISCHER indolization on polymer support exist:

Ø *First generation protocol for non-polar olefins.* Here the hydroformylation of a polymer bound olefin is conducted in the presence of an aromatic hydrazine. After washing of the resin the hydrazone is indolized in a separate step.

Ø *Second generation protocol for unpolar olefins.* The hydroformylation is conducted in the presence of benzhydrylidene protected hydrazines and PTSA.

8.5.1 FIRST GENERATION PROTOCOL

Since H_2SO_4 in THF turned out to be ideal for reactions in solution, substrate **825** is subjected to the same conditions. After a low yielding cleavage, however, no indole can be isolated. It seems that the indolization conditions are too harsh and induce early cleavage of the HMBA linker.

Scheme 99: Stepwise hydroformylation / hydrazone formation / indolization.
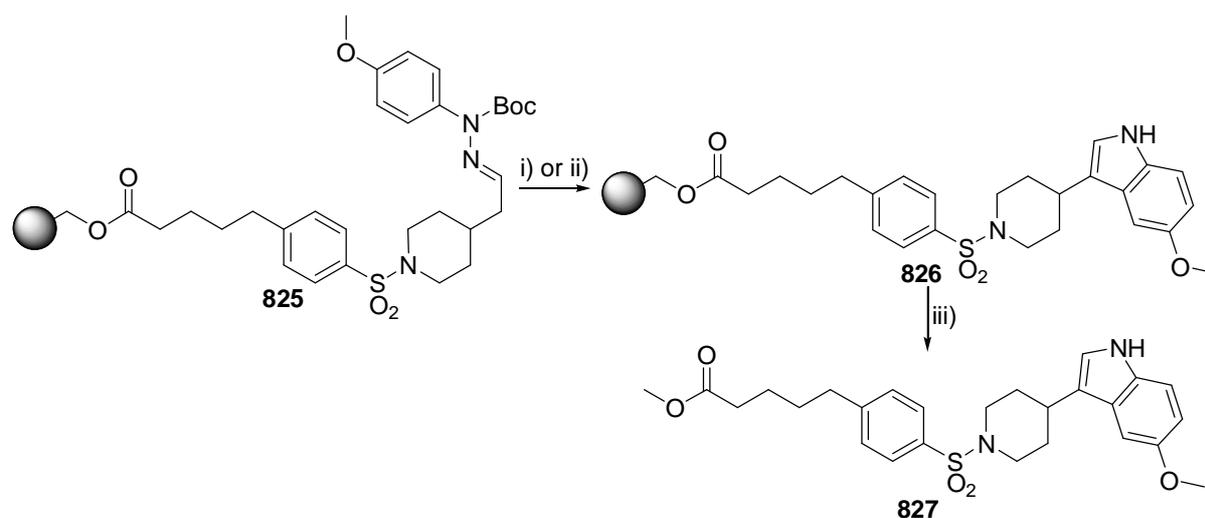
cond.: i) 1equiv. **825**, 4wt% H_2SO_4/THF, 80°C 2h. ii) 1eq **826**, dioxane/TEA/MeOH (5:4:1), 80°C, 12h.

Thus, WALDMANN's conditions, TFA/DCE (1:9), are tested. Although the HMBA linker seems to be stable, no indole product is observed. With TFA/DCE (1:1) neither indole nor any other reasonable product can be isolated from solid phase. Instead, the washing solution contains at least four different products, including the desired indole as the free acid. Obviously the HMBA linker is cleaved during treatment with TFA at 100°C. This clearly demonstrates once more the necessity for an acid stable linker for FISCHER indole synthesis. Therefore, further investigations are made on PS sulfonylamide resin **803**, which is

hydroformylated in the presence of phenylhydrazine (**214a**) and *a*-Boc protected *p*-methoxy-phenylhydrazine (**214j**).

Scheme 100: First generation protocol for the tandem hydroformylation / Fischer indolization on solid phase.
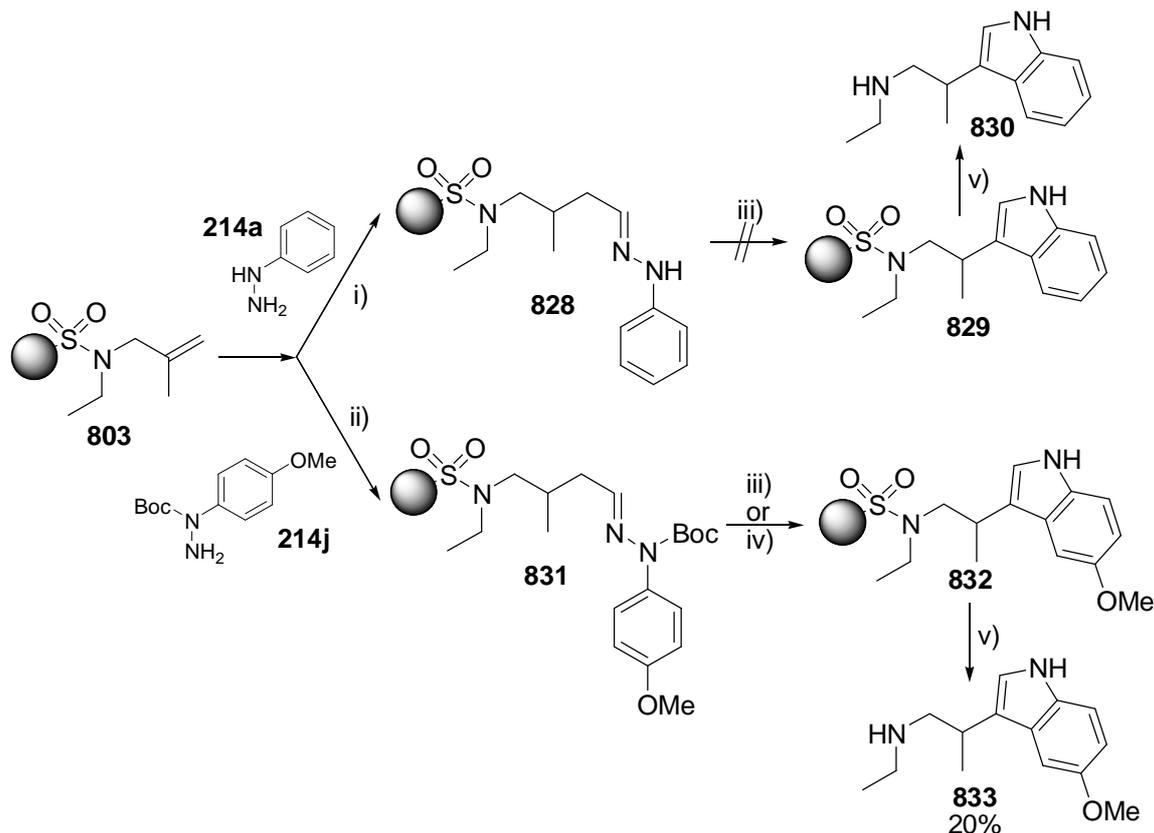
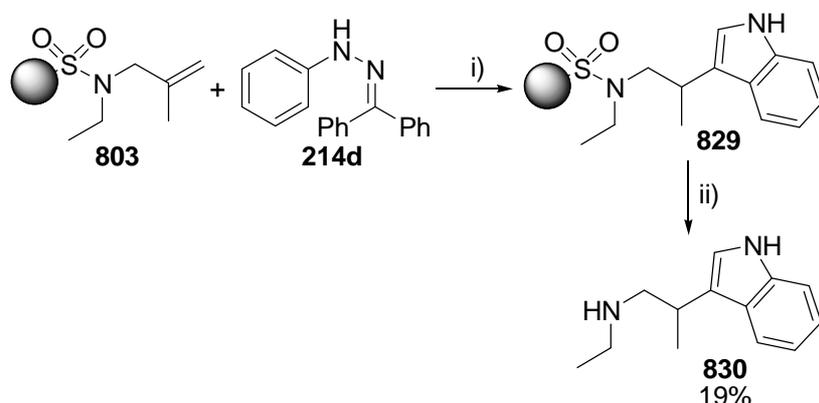cond.: i) 1equiv. **803**, 10equiv. **214a**, 20mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 80°C, 44h. ii) 1equiv. **803**, 10equiv. **214j**, 20mol% Rh(acac)(CO)$_2$, 50bar CO, 10bar H$_2$, THF, 80°C, 44h. iii) 1equiv. hydrazone, TFA/DCE (1:1), 10°C, 18h; iv) 1equiv. **831**, 10equiv. ZnCl$_2$, THF, 100°C, 17h or 1equiv. **831**, 10equiv. BF$_3$*Et$_2$O, CH$_2$Cl$_2$, AcOH (1:1), 65°C, 12h. v) 1equiv. indole, 10equiv. Li-biphenylide (1M in THF), 0°C, 2h.

Both hydrazones are reacted with TFA/DCE (1:1), but under no circumstances can the desired indole be isolated upon cleavage with Li-biphenylide. An intensive screening of reaction conditions discloses that BF$_3$*Et$_2$O in CH$_2$Cl$_2$/AcOH (1:1) and ZnCl$_2$ in THF give smooth indolization of **831**, but further optimizations are needed to suppress the formation of an unidentified by-product

8.5.2 SECOND GENERATION PROTOCOL

An alternative and improvement of this stepwise approach is the second generation protocol. Here, olefins are hydroformylated in the presence of benzhydrylidene protected hydrazines and PTSA to allow direct access to tryptamines in high yields and with high selectivity. To test if this protocol can be transferred from solution to solid phase, olefin **803** is subjected to this tandem reaction using 10 equivalents of hydrazine and 5 equivalents of PTSA.

**Scheme 101: Second generation protocol for the tandem
hydroformylation / Fischer indolization on solid phase.**

cond.: i) 1equiv. **803**, 10equiv. **214d**, 5equiv. PTSA, 20mol% Rh(acac)(CO)$_2$,
50bar CO, 10bar H$_2$, THF, 80°C, 44h. ii) 1equiv. **829**, 10equiv. Li-
biphenylide (1M in THF), 0°C, 2h.

The desired indole can be isolated in 19% yield from a very selective reaction. This then, is the first example of a successful tandem hydroformylation / FISCHER indole synthesis on solid support.

8.6 INTERIM CONCLUSION

In this chapter the first tandem hydroformylation / FISCHER indole synthesis on solid phase is developed. In this context the following features were investigated:

Ø *Hydroformylation process.* It turned out, that the use of conical glass vials is reasonable, in order to

- combine a fast hydroformylation with a minimized mechanical stress to the polymer beads,

- and to allow the simultaneous conduction of different reactions in one pressure vessel (parallel synthesis).

Ø *Tandem hydroformylation / hydrazone formation.* The first hydrazone formation under hydroformylation conditions on solid phase is presented.

- The use of PS HMBA resin is appropriate since the mild basic conditions for a product release do not affect the hydrazone's stability.

- *a*-Boc protected aromatic hydrazines derived via the GOLDBERG reaction are suitable hydrazine sources and do not undergo oxidation during the hydrazone formation or the cleavage of the HMBA linker.

Ø *Tandem hydroformylation / Fischer indole synthesis.* The basis for the synthesis of substance libraries via tandem hydroformylation / FISCHER indolization is established. Since the HMBA linker is not acid stable under harsh indolization conditions, the PS sulfonylchloride resin turned out to be appropriate for the synthesis of tryptamine derivatives. Two protocols have been developed:

- *First generation protocol.* Here the hydroformylation of a polymer bound olefin is conducted in the presence of aromatic hydrazines, preferably an *a*-Boc protected hydrazine. Subsequent indolization is achieved upon treatment with $ZnCl_2$ or BF_3*Et_2O in acetic acid/CH_2Cl_2.

- *Second generation protocol.* Hydroformylation of a polymer bound olefin in the presence of benzhydrylidene protected hydrazines and PTSA results in selective indole formation.

9 SUMMARY AND OUTLOOK

9.1 SUMMARY

Tandem hydroformylation / FISCHER indole synthesis has proved to be a diversity oriented synthetic tool for the fast and convenient synthesis of biologically relevant tryptamines and homologues. In this new tandem reaction, the hydroformylation of aminoolefins is conducted in the presence of aromatic hydrazines and BRØNSTEDT acids to give tryptamines in one pot (Scheme 102).

Scheme 102: Principle of the tandem hydroformylation / Fischer indole synthesis.
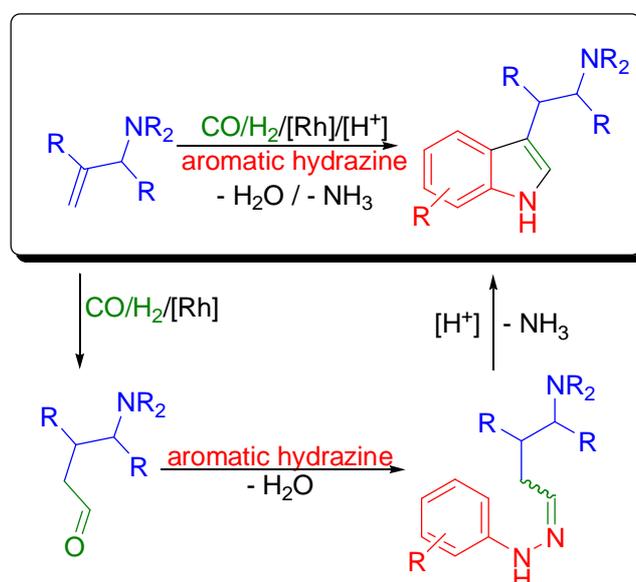
In contrast to the classical protocol, this new approach makes a previous synthesis of aldehydes, followed by their protection as acetals, aminales, bisulfite adducts or enol ethers, obsolete. Instead olefins are converted to aldehydes *in situ*, trapped as aryl hydrazones *in situ* and are indolized to tryptamines instantly. Thus, simple functional group transformations are replaced by *C-C*-bond forming steps in a one pot procedure that saves time and resources. Therefore, this approach may be an attractive alternative production process, especially since olefins can be used as a different source of starting material, circumventing patented production processes.

Starting with appropriate amines, aminoolefins can be synthesized with different state-of-the-art methods (substitution, allylation, WITTIG olefination, BARBIER reaction, carbomagnezation, etc.), allowing high diversity in the chain length and the substitution pattern of the aminoolefins. Independently from these different types of olefins, tandem

hydroformylation / FISCHER indole synthesis is a reliable tool to yield the corresponding indoles (Scheme 103).

Scheme 103: Combination of modern syntheses of aminoolefins with the tandem hydroformylation / Fischer indole synthesis as a highly diversity oriented approach towards tryptamines and homologues.

Tryptamines

Homotryptamines
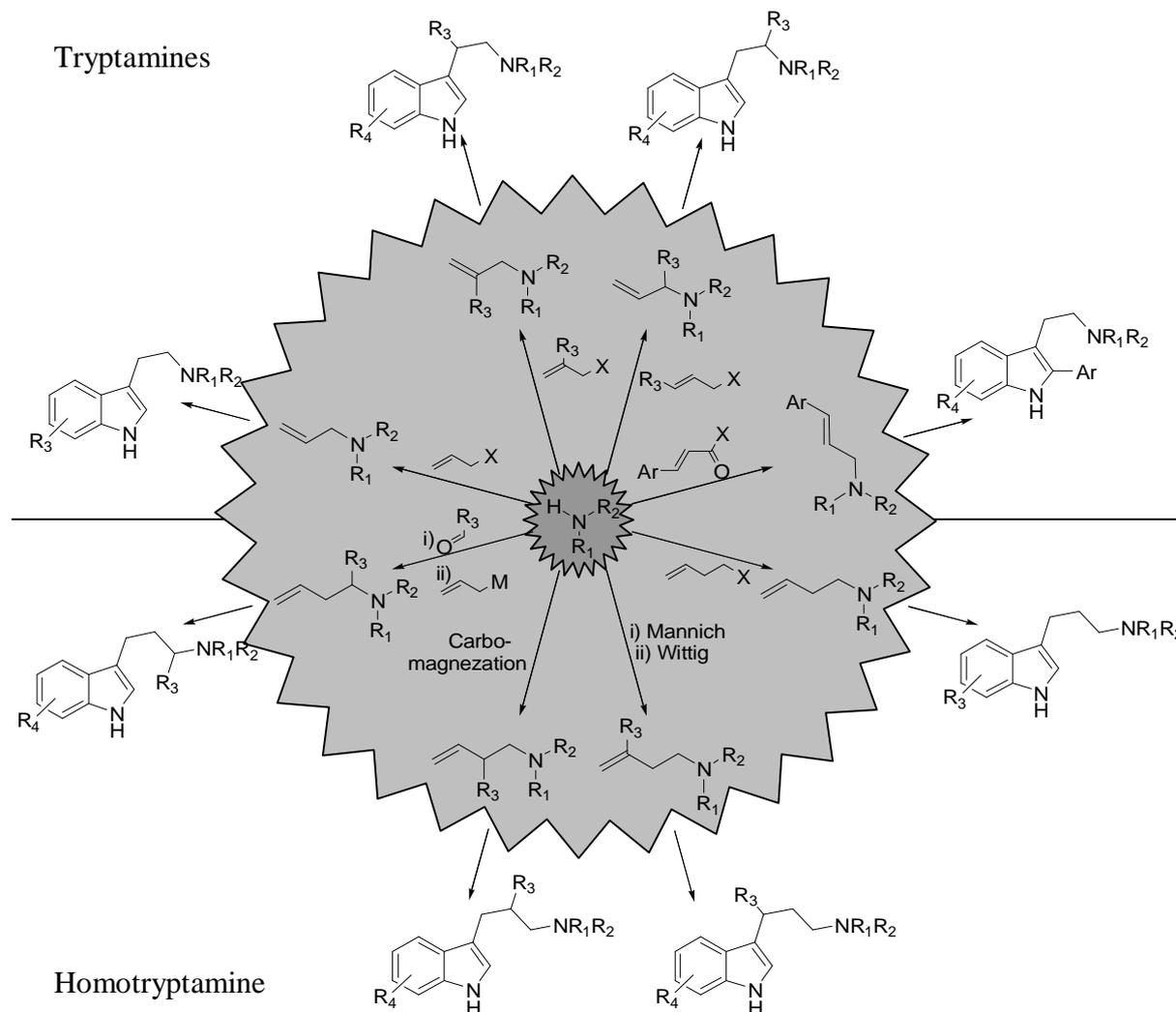
Depending on the nature of the aminoolefin, different conditions have been developed. Non-polar olefins, especially protected primary and secondary aminoolefins, require a non-polar reaction medium. Here the use of THF/H_2SO_4 turned out to be the best system.

Scheme 104: Tandem hydroformylation / Fischer indole synthesis of non-polar olefins.

Key intermediate for a^1-adrenoceptorantagonists 36%

**Serotonin analogue** 95%
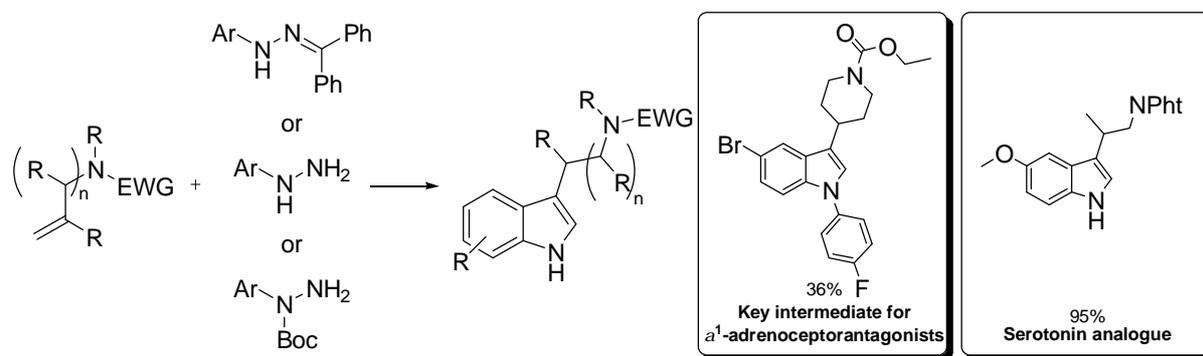
The highest selectivity can be observed, if benzhydrylidene protected aromatic hydrazines, derived from BUCHWALD-HARTWIG amination, are subjected to this tandem reaction. Other sources, such as non-protected hydrazines as well as a-Boc protected hydrazines derived from a GOLDBERG reaction, give satisfying yields too (Scheme 104).

Polar aminoolefins, such as tertiary aminoolefins, require a very polar medium. Here aqueous H_2SO_4 is used. Solubility of the rhodium hydroformylation catalyst is achieved by addition of sulfonated phosphane ligands, such as trisulfonated triphenylphosphane (TPPTS) or disulfonated XANTPHOS (SulfoXANTPHOS), the latter giving high n-selectivities. Commercially available hydrazine hydrochlorides as well as synthesized a-Boc protected aromatic hydrazines can be used. the latter is the option of choice for the synthesis of migraine drugs (Scheme 105).

Scheme 105: Tandem hydroformylation / Fischer indole synthesis of polar olefins.

Migraine drug LY 334 370 95%

Migraine Drug L 775 606 51%
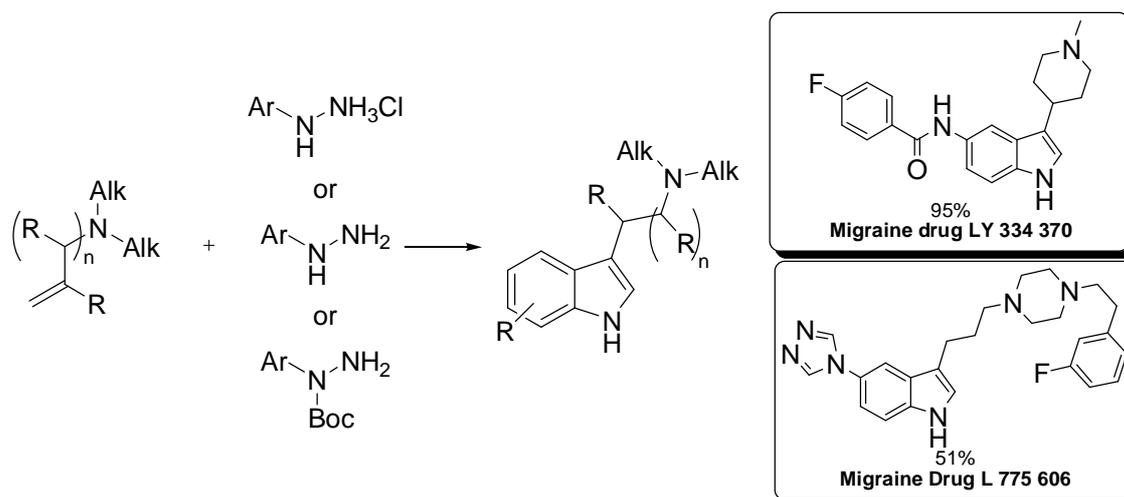
Even stereochemical issues can be incorporated: Either the aminoolefins includes stereochemical information or prochiral olefins are used resulting in the formation of an additional stereocenter.

**Scheme 106: Use of chiral allylic amines with transfer of the
absolute configuration to the indole.**

96% *ee*

54%, 95% *ee*
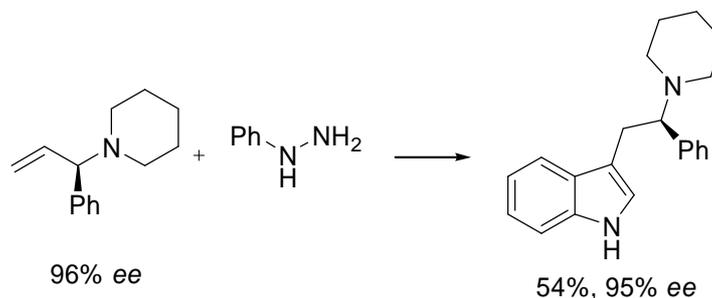
In using chiral allylic amines, no epimerization due to double bond migration either by the rhodium catalyst or by the acid is observed, giving full retention of absolute configuration (Scheme 106).

If disubstituted terminal olefins are used, the relative configuration of the stereocenter in *b*-position in relation to the aldehyde group can be controlled applying BREIT's protocol of substrate directed hydroformylation to this new tandem sequence (Scheme 107).

**Scheme 107: Diastereoselective tandem hydroformylation / Fischer
indole synthesis.**

44%, *dr* > 95:5
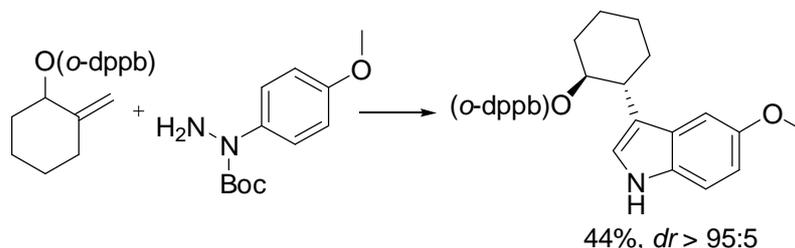
Even regioselectivity problems in the classical indolization of the *meta*-substituted aromatic hydrazines can be overcome by the first intramolecular FISCHER indole synthesis yielding the 6-substituted indole as the only regioisomer and being an illustrative example for the synergy of this tandem reaction (Scheme 108).

**Scheme 108: Regioselective tandem hydroformylation / Fischer
indole synthesis.**

20%, ~1:1
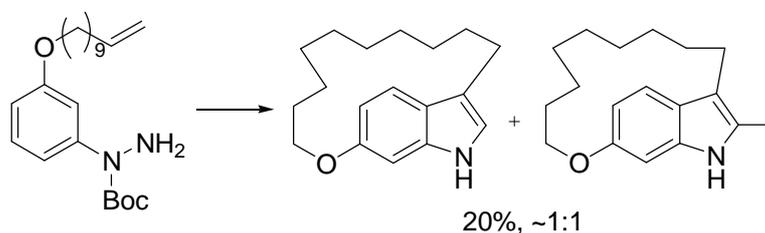
After deprotection, primary and secondary tryptamines and homologues derived from a tandem hydroformylation / FISCHER indolization can be subjected to hydroaminomethylation. This rhodium catalyzed tandem reaction consists of hydroformylation and reductive

- 113 -

amination and allows further, highly selective functionalization towards tryptamines drugs. The combination of these two tandem reactions under hydroformylation conditions gives unusually convenient access to highly functionalized 3-piperidyl indole drugs (Scheme 109).

Scheme 109: Combination of tandem hydroformylation / Fischer indole synthesis and hydroaminomethylation in a fast synthesis of highly functionalized tryptamines.
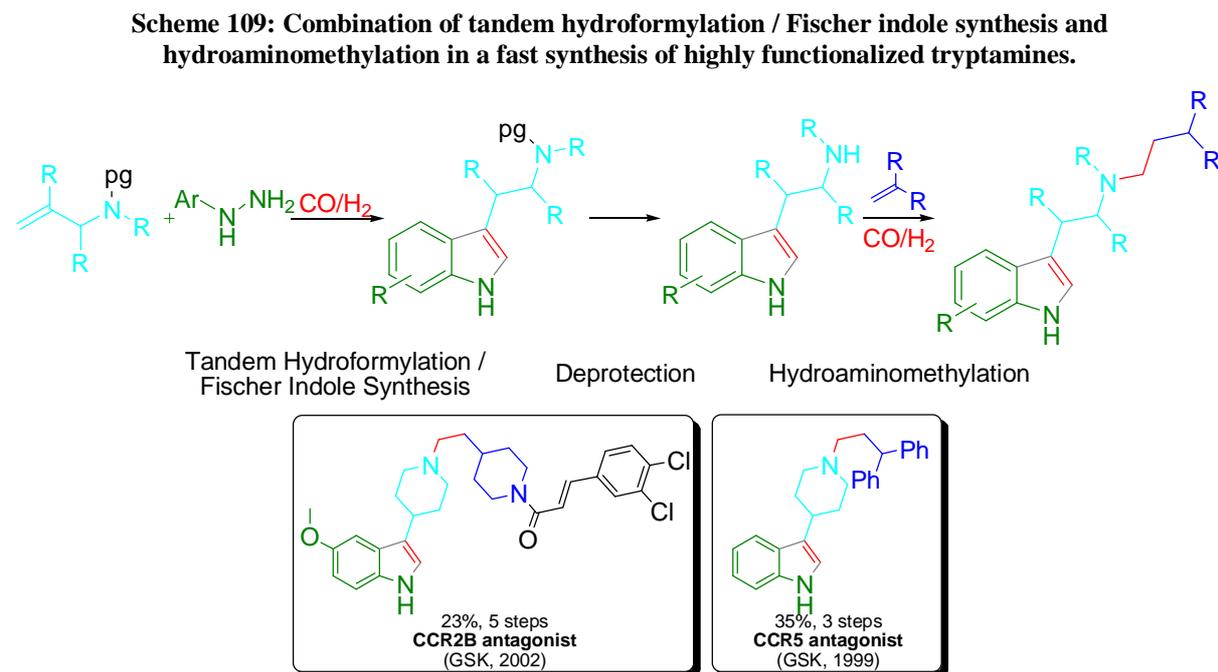
The automated combinatorial synthesis on solid support is a key technology for the development of new pharmaceuticals. The tandem hydroformylation / FISCHER indole synthesis can be an attractive tool for the combinatorial synthesis of highly diverse indole libraries, since this tandem reaction is successfully transferred from solution to solid phase, using a polystyrene sulfonylchloride resin (Scheme 110).

Scheme 110: Tandem hydroformylation / Fischer indole synthesis on solid phase,
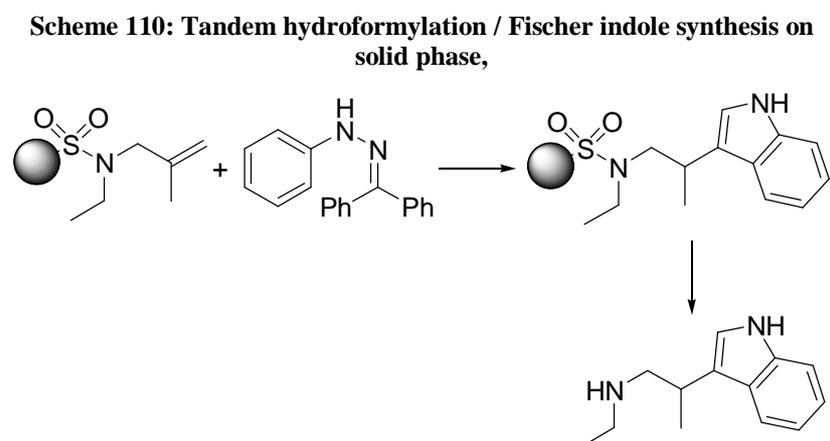
If the hydroformylation of olefins is conducted in the presence of aromatic hydrazines but in the absence of acid, aromatic hydrazones are obtained in almost quantitative yields and can be subjected to highly selective subsequent indolization. Side reactions or consecutive reactions such as hydrogenation could not be observed in any case. Substituents that are prone to catalytic hydrogenation turned out to be stable as well as the aromatic hydrazones group itself, quite in contrary to the analogue alkyl hydrazones or the corresponding aldehydes. In contrast to aminoaldehydes, aminohydrazones derived from aldehydes *in situ* do not undergo consecutive base induced aldol reactions. In conclusion the aromatic hydrazone can be interpreted as a productive protecting group unless it is to be part of the final product. This tandem hydroformylation / hydrazone formation can be used for the synthesis of macrocyclic bishydrazones in extraordinary high yields (Scheme 111).

Scheme 111: Synthesis of macrocyclic bishydrazones under hydroformylation conditions.
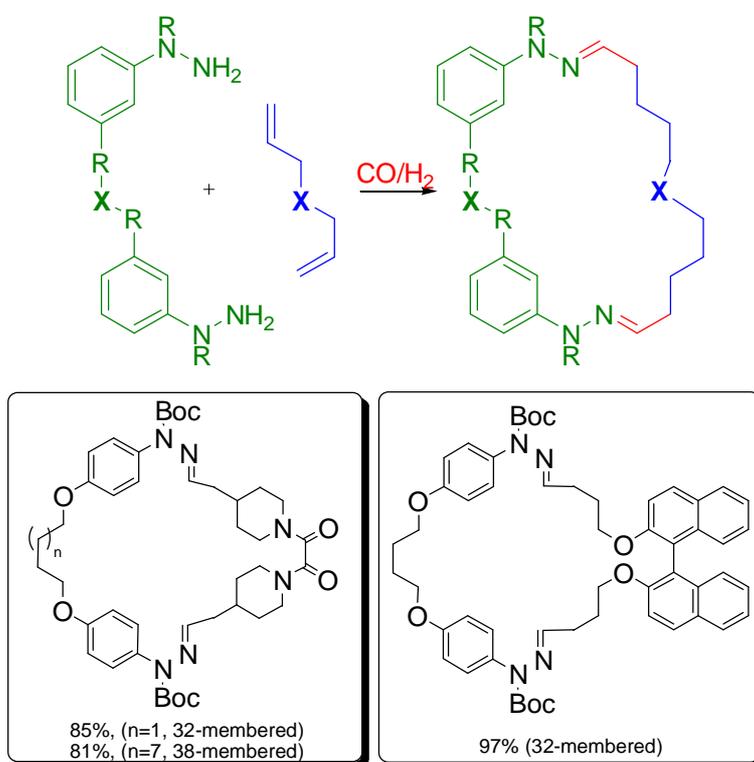
Scheme 112: Metal screening of fluorescence quenching of macrocyclic bishydrazones.
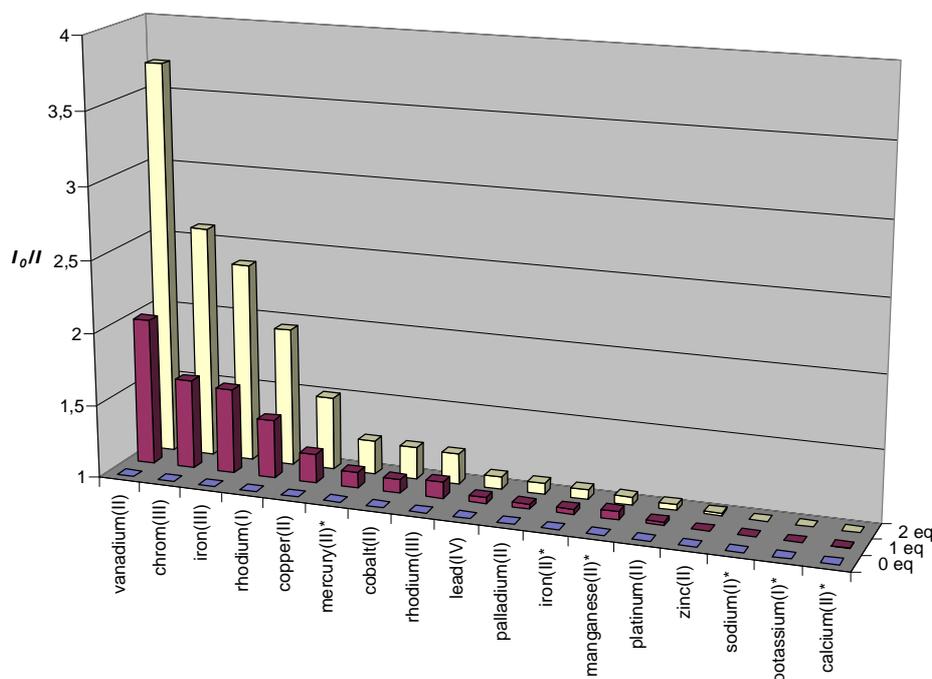
Although these compounds do not undergo selective indolization upon acid addition, these macrocycles represent a new class of macrocycles that show some unexpected selectivity towards metals in the quenching of their fluorescence activity. Besides strong interactions with vanadium(II) and chromium(III), the interaction with iron(III) salts may be interesting for medicinal and environmental applications (Scheme 112).

9.2 OUTLOOK

With the optimized protocols that have been developed in this project, the tandem reaction is now ready for advanced applications:

Ø Although there is still need for further optimizations to increase the yield of the polymer supported tandem hydroformylation / FISCHER indolization, it becomes apparent that this tandem reaction is an appropriate tool for the synthesis of substance libraries. In forthcoming investigations the following issues should be considered:

- The synthesis of starting material should be incorporated. For example ring-closing metathesis for the synthesis of dihydropyrroles, which are needed for *b*-carbolines, or allylic aminations for the synthesis of chiral allylic amines as needed for *b*-branched tryptamines (Scheme 113).

- Tandem hydroformylation / FISCHER indole synthesis must not be the final step in a synthesis on solid phase. Consecutive reactions such as PICTET-SPENGLER

reactions especially of chiral tryptamines to *b*-carbolines and their WITKOP-WINTERFELDT oxidation to *g*-quinolones increase the substance library's diversity (Scheme 113).

Scheme 113: Tandem hydroformylation / Fischer indole synthesis for the synthesis of *b*-carbolines and *g*-quinolones on solid phase.
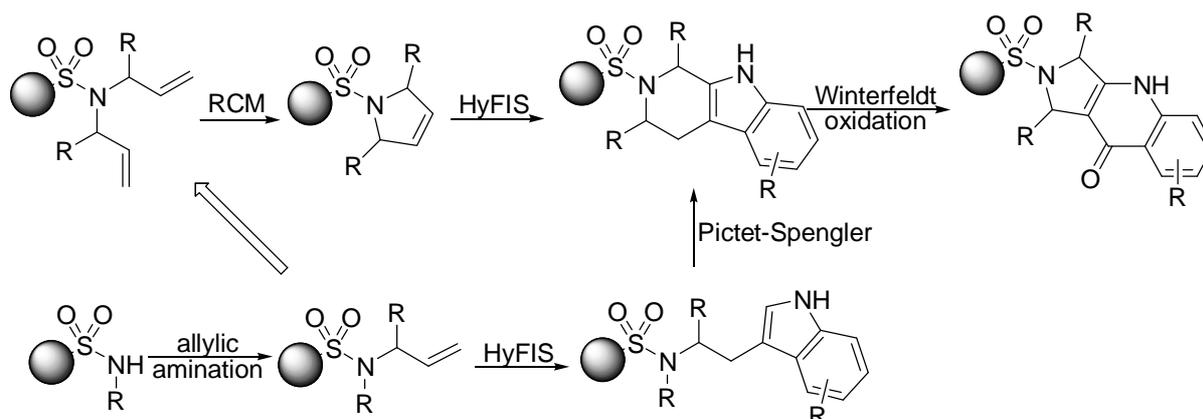
- If the tandem hydroformylation / FISCHER indole synthesis is to be incorporated in a multi step synthesis of indole and quinolone derivatives, on-bead analysis of the tandem reaction's conversion is crucial. Besides instrumental analysis such as magic angle spinning NMR, methods based on the derivatization are important, such as the FmPh-method for the determination of aldehyde loadings. The fact, that the *b*-nitrogen of the aromatic hydrazone is eliminated during indolization as ammonia might be of help if the *b*-nitrogen is labeled with an UV-active signaling unit. This signaling unit is not allowed to hamper the condensation with the carbonyl or the indolization of the resulting hydrazone (Scheme 114).

Scheme 114: On-bead analysis of the conversion of the Fischer indole synthesis.
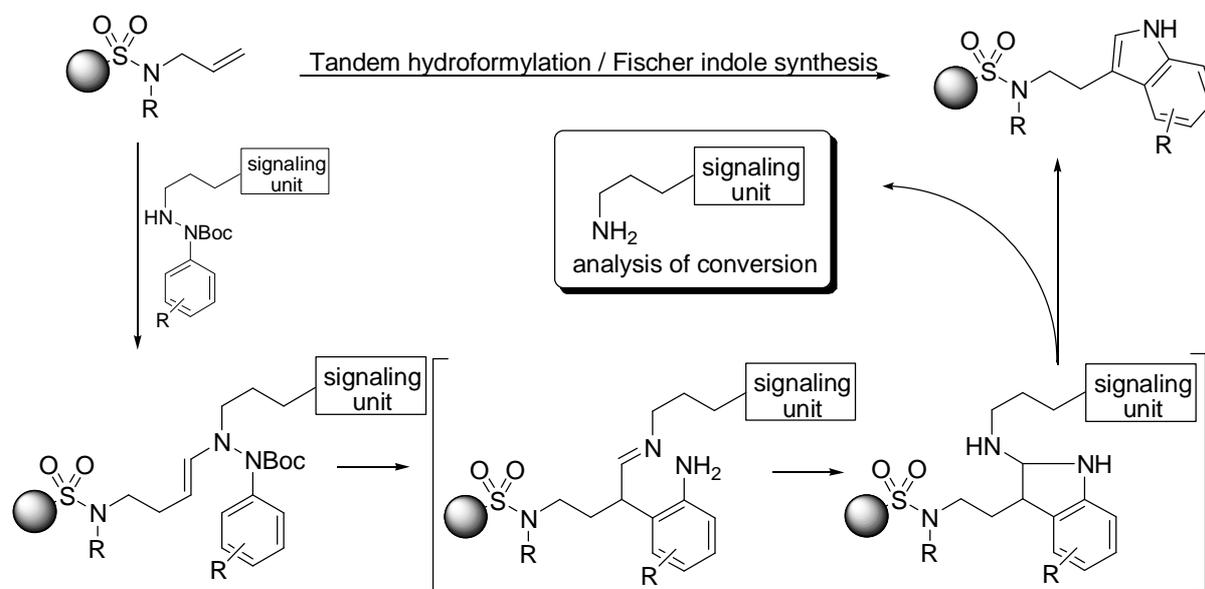
- Thus, this signaling unit should be attached via an alkyl chain. Here the tandem hydroformylation / hydrazone formation might be of help if the reaction is conducted under more forcing conditions that allow consecutive hydrogenation of the hydrazone. However, other methods such as simple alkylation may also be appropriate. Condensation with a carbonyl on solid phase then gives an ene-hydrazine, which undergoes sigmatropic rearrangement followed by elimination of labeled ammonia whose concentration, and therefore, the indolization's conversion might be determined by UV-spectroscopy without need for cleavage of the indole or its derivatization (Scheme 115).

Scheme 115: Synthesis of labeled aromatic hydrazines under hydroformylation conditions for on-bead analysis of the Fischer indolization's conversion.
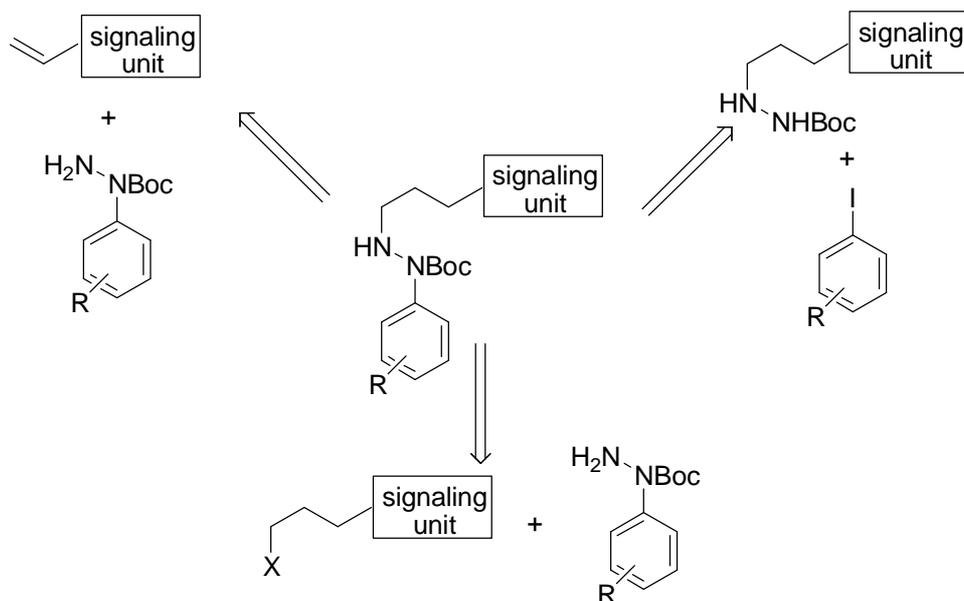
- If the reduction of aromatic hydrazones derived upon tandem hydroformylation / hydrazone formation can undergo subsequent hydrogenation under forcing hydroformylation conditions, this might also be an interesting option to attach aromatic hydrazine to solid phase. This method would be an improvement of WALDMANN's traceless FISCHER indole synthesis on solid phase. Here, the hydrazine was reacted with an aldehyde resin, followed by reduction of the hydrazone with BH$_3$/THF, still being problematic but the only method for a selective reduction without cleavage of the *N-N*-bond.

**Scheme 116: Attachment of aromatic hydrazines to olefin functionalized resins under hydroformylation conditions.**
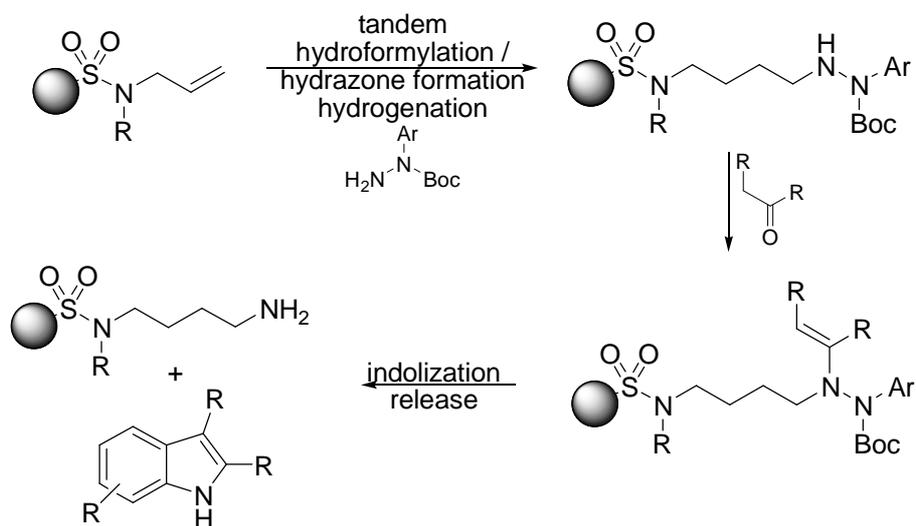
Based on the positive experience with the PS sulfonylchloride resin, simple allylic alcohols of amines might be attached. Hydroformylation / hydrazone formation / hydrogenation might give a polymer bound hydrazine, which is ready for FISCHER indole synthesis (Scheme 116).

Ø Many natural products contain the indole core as the privileged structure. Hapalindoles for example might be synthesized using the intermolecular & diastereoselective tandem hydroformylation / FISCHER indole synthesis. On the other hand, indolactams might be achieved from the intramolecular tandem reaction.

Ø The patented production processes for tryptamine drugs contain, in many cases, necessary, but low yielding, functional group transformation or indolizations towards intermediate 3-alkyl indoles. The tandem hydroformylation / FISCHER indole synthesis might be an alternative since functional group transformations are reduced to a minimum and aminoolefins can be obtained in broad variety. On the other hand production costs will come into the focus. Here the rhodium catalyst will determine the large part of the production costs. Therefore, optimizations towards replacement of rhodium by cobalt, or towards a reduction of the amount of the catalyst seem to be important. Alternatively, 2-phase-techniques or immobilization of the rhodium catalyst might allow reusing this expensive catalyst several times without loss of activity.

Ø The combination of other formylation reactions with the FISCHER indole synthesis might give interesting products:

- *Hydroformylation of epoxides.* The hydroformylation of expoxides has been developed in 1978 and allows the stereoselective synthesis of aldols.

Scheme 117: Tandem epoxides-hydroformylation / Fischer indole synthesis.
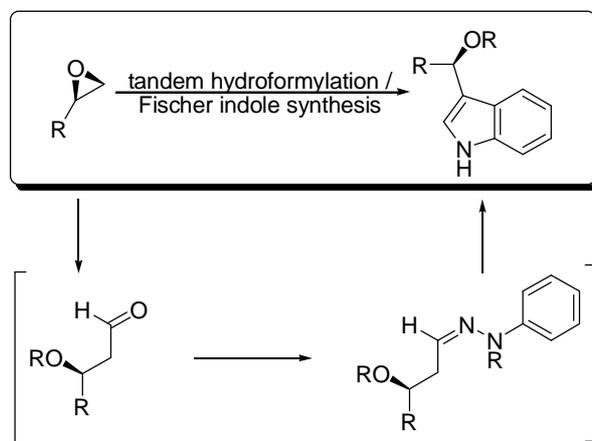
Implementation in a tandem reaction might give Tryptamines with hydroxyl functionality in the *a*-position relative to the indole core (Scheme 117).

- *Silylformylation of Olefines.* The same product would be achieved in a tandem silylformylation / FISCHER indole synthesis of olefins, followed by TAMAO oxidation of the resulting *a*-silyl-tryptamine. In contrast, desilylation in the presence of electrophils or HIYAMA coupling reactions might give access to indoles with sophisticated branches (Scheme 118).

Scheme 118: Tandem silylformylation / Fischer indole synthesis and synthetic options.
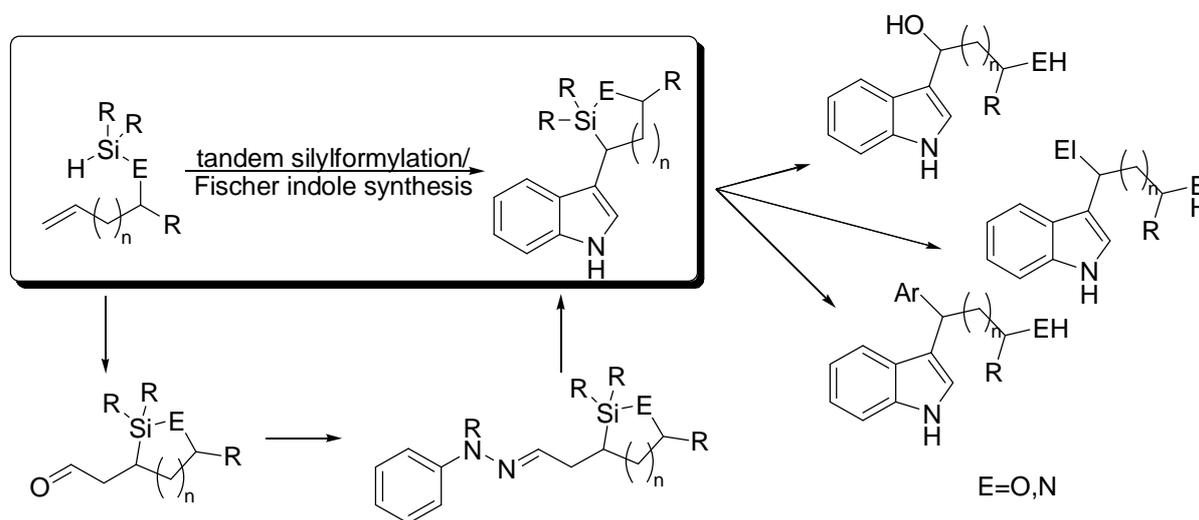
Ø Macrocyclic bisarylhydrazones are proven to be interesting fluorophores for metal sensing. Base on the results compiled in chapter 6, the structure of the presented macrocycles should be optimized with respect to their fluorescence activity and their absorption wavelength. This might be achieved by introducing larger aromatic systems close to the hydrazone group. Here, the GOLDBERG reaction seems to be appropriate for a broad variation of Ar^2.

Scheme 119: Synthesis of fluorescent active hydrazones.

E=C, S=O Ar_1=phenyl, dansyl Ar_2=phenyl, naphthyl, antracenyl
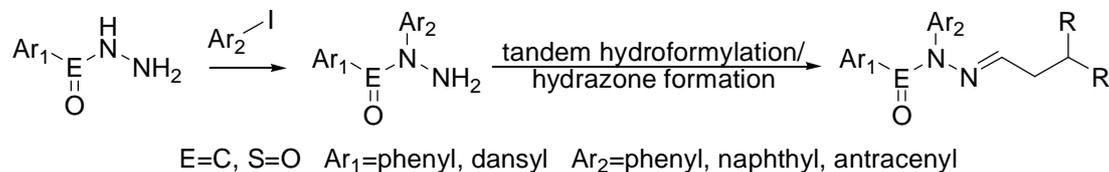
10 EXPERIMENTAL SECTION

10.1 MATERIALS

All reagents and solvents were dried and purified before use by the usual procedures. Rh(acac)(CO)$_2$, XANTPHOS and P(OPh)$_3$ were purchased. Cinnamyl carbonat[90], [Rh(cod)Cl]$_2$[91], [Rh(cod)BF$_4$]$_2$[92], [Ir(cod)Cl]$_2$[93], BIPHEPHOS[94], TPPTS[95], 9,9-dimethyl-4,5-bis(diphenylphosphino)-9H-xanthene-2,7-disulfonic acid[96], *O,O'*-(*R*)-(1,1'-Dinaphthyl-2,2'-diyl)-*N,N'*-di-(*R,R*)-1-phenylethylphosphoramidite[97] and *O,O'*-(*S*)-(1,1'-Dinaphthyl-2,2'-diyl)-*N,N'*-di-(*S*,S)-1-phenylethylphosphoramidite[97] were prepared according to the published method. All aromatic hydrazines and all olefins were purchased unless mentioned otherwise. *N*-Allyl, *N*-ethylamides (**127e-127g**) were synthesized by allylation of the corresponding secondary amides. All *N*-ethylamides required were prepared by the reaction of EtNH$_2$ with the corresponding acid chloride in the presence of NEt$_3$ and DMAP. All other protected allylic amines (**114b-114e**, **127b-127d**) were synthesized by the reaction of the corresponding allylic amines with the corresponding acid chlorides in the presence of NEt$_3$ and DMAP. 2-(2-Methyl-allyl)-isoindole-1,3-dione (**114a**) and 2-allyl-isoindole-1,3-dione (**127a**) were synthesized according to published methods[98]. Allylic amines **301b-301d** were synthesized by allylation of the corresponding amines. Homoallylic amines **310e** and **301f** were prepared by homoallylation of the corresponding amines with 4-bromobutene. Benzhydrylidene protected aryl hydrazines[99,100] and *N*-Boc-arylhydrazines[101] were prepared according to published methods. 2,2'-Bis(allyloxy)-1,1'-binaphthyl (**502**) was donated by GORAN ANGELOVSKI. Polystyrene resins **802**, **803**, **804**, **820** and **823** were donated by MATTHIAS MENTEL.

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10.2 GENERAL METHODS

^{1}H-NMR and ^{13}C-NMR spectra were measured on a BRUKER Advance DRX 400 spectrometer or a BRUKER Advance DRX 500 spectrometer using $CHCl_3$ or CH_2Cl_2 as internal standard. All samples were dissolved in $CDCl_3$. IR spectra were measured on a NICOLET Impact 400D FT-IR spectrometer. Column chromatography was carried out on 70-230 mesh silica gel (MACHEREY-NAGEL;silicagel 60). Optical rotation was determined on a PERKIN Elmer 341. Elemental analyses were performed on a LECO CHNS-932. High resolution mass analyses were performed on a JEOL JMS-SX 102A. Fluorescence measurements were performed on a SPEX Fluoromax-3 spectrofluorometer (JOBINYVON, Edison, NJ, USA) in a 1ml quartz cuvette (HELLMA). Reaction under pressure were carried out in a magnetically stirred BERGHOF type A (250ml, 4 glass vials a 20ml) pressure vessel, a comparable house made autoclave (100ml) or in a PARR autoclave.

10.3 EXPERIMENTS IN CHAPTER 2

10.3.1 GENERAL PROCEDURE FOR THE HYDROFORMYLATION

4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-butyraldehyde (221a/222a). A typical procedure is described. 2-Allyl-isoindole-1,3-dione (86 mg, 0.50 mmol), $Rh(acac)(CO)_2$ (0.38 mg, 0.30 mol%) and XANTPHOS (see table entries) were dissolved in anhydrous THF (0.78 g, 10 wt% olefin), filled in an autoclave and pressurized with 10bar H_2 and 10bar CO. After stirring for 20 hours at 70°C the solvent was removed and the crude product (containing *n*- and *iso*-regioisomers) was analyzed by NMR. *n*-regioisomer: ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.95 (t, 2H, J = 7.2 Hz, CH_2); 2.48 (t, 2H, J = 7.2 Hz, CH_2); 3.67 (t, 2H, J = 7.0 Hz, CH_2); 7.67 (d, 2H, J = 5.2 Hz, 2xCH); 7.77 (d, 2H, J = 5.2 Hz, 2xCH); 9.71 (bs, 1H, CH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) d = 21.0 (CH_2); 37.0 (CH_2); 40.9 (CH_2); 123.1 (2xCH); 131.9 (2xC); 133.9 (2xCH); 168.2 (2xC); 200.8 (CH). *Characteristic data for the iso*-regioisomer: ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.11 (d, 3H, J = 7.2 Hz, CH_3); 2.84 (sext*, 1H, J = 6.7 Hz, CH); 3.76 (dd, 1H, J = 6.5 Hz, J = 14.2 Hz, C*H*H); 3.97 (dd, 1H, J = 7.1Hz, J = 14.2 Hz, CH*H*); 9.68 (d, 1H, J = 1.0 Hz, CH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) d = 11.5 (CH_3); 38.0 (CH_2); 45.7 (CH); 123.3 (2xCH); 134.0 (2xCH); 202.1 (CH). Analytical data fits with literature[102].

3-Methyl-4-(1,3-dioxoisoindolin-2-yl)butanal (212). The general procedure was followed with 2-(2-methylallyl)isoindoline-1,3-dione (1.00 g, 5.00 mmol), $Rh(acac)(CO)_2$ (4.0 mg,

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[102] Delugo, G.; Faedda, G.; Gladiali, S.; *J. Organomet. Chem.* **1984**, *268*, 167-174.

0.3 mol-%), 10 bar H_2 and 50 bar CO. After stirring for 20 hours at 100°C the solvent is removed to give 3-methyl-4-(1,3-dioxoisoindolin-2-yl)butanal (1.16 g, 100 %) without further purification. Analytical data fits with literature[103].

N-Ethyl-4-methyl-N-(4-oxo-butyl)-benzenesulfonamide (221e/222e). The general procedure was followed with N-allyl-N-ethyl-4-methyl-benzenesulfonamide (222 mg, 0.93 mmol), Rh(acac)(CO)$_2$ (0.72 mg, 0.30 mol%) and XANTPHOS (see table entries) to give a mixture of n-aldehyde and iso-aldehyde, which was analyzed by NMR. n-regioisomer: ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.06 (t, 3H, J = 7.3 Hz, CH$_3$); 1.84 (p, 2H, J = 7.0 Hz, CH$_2$); 2.38 (s, 3H, CH$_3$); 2.55 (t, 2H, J = 7.3 Hz, CH$_2$); 3.10 (t, 2H, J = 7.0 Hz, CH$_2$); 3.17 (q, 2H, J = 7.0 Hz, CH$_2$); 7.25 (d, 2H, J = 8.3 Hz, 2xCH); 7.63 (d, 2H, J = 8.3 Hz, 2xCH); 9.76 (bs, 1H, CH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 13.9 (CH$_3$); 21.1 (CH$_2$); 21.4 (CH$_3$); 40.6 (CH$_2$); 43.0 (CH$_2$); 46.6 (CH$_2$); 127.0 (2xCH); 129.7 (2xCH); 136.8 (C); 143.2 (C); 201.5 (CH). *Characteristic data for the iso-regioisomer:* ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.03 (t, 3H, J = 7.3 Hz, CH$_3$); 1.14 (d, 3H, J = 7.3 Hz, CH$_3$); 2.37 (s, 3H, CH$_3$); 2.78 (m, 1H, CH); 3.10 (t, 2H, J = 7.0 Hz, CH$_2$); 3.17 (q, 2H, J = 7.0 Hz, CH$_2$); 7.19 (d, 2H, J = 8.3 Hz, 2xCH); 7.77 (d, 2H, J = 8.3 Hz, 2xCH); 9.67 (d, 1H, J = 1.8 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 12.0 (CH$_3$); 13.9 (CH$_3$); 21.4 (CH$_3$); 43.9 (CH$_2$); 46.1 (CH); 48.1 (CH$_2$); 127.2 (2xCH); 129.7 (2xCH); 136.8 (C); 143.2 (C). (CH) not detectable. IR: $\tilde{n}$ [cm^{-1}] = 2935 (s); 2727 (m); 1724 (vs); 1596 (s); 1336 (vs); 1157 (vs); 1089 (vs); 730 (vs); 549 (vs). HRMS found [M+H]$^+$ 270.1190, C$_{13}$H$_{19}$NO$_3$S requires [M+H]$^+$, 270.1164.

N-Ethyl-N-(4-oxo-butyl)-acetamide (221f/222f). The general procedure was followed with N-allyl-N-ethyl-4-methyl-acetamide (162 mg, 1.27 mmol), Rh(acac)(CO)$_2$ (0.98 mg, 0.30 mol%) and XANTPHOS (see table entries) to give a mixture of n-aldehyde and iso-aldehyde, which was analyzed by NMR. n-regioisomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.03, 0.96 (2t, 3H, J = 7.2 Hz, CH$_3$); 1.71 (m, 2H, CH$_2$); 1.93, 1.94 (2s, 3H, CH$_3$); 2.33, 2.38 (2t, 2H, J = 7.0 Hz, CH$_2$); 3.10-3.24 (4H, 2xCH$_2$); 9.62, 9.65 (2bs, 1H, CH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 13.7, 12.7 (CH$_3$); 20.1, 21.0 (CH$_2$); 21.1, 21.2 (CH$_3$); 43.0, 40.9 (CH$_2$); 44.0, 40.1 (CH$_2$); 47.1 (CH$_2$); 170.0 (C); 201.5, 200.6 (CH). *Characteristic data for the iso-regioisomer:* ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 2.59, 2.64 (2m, 1H, CH); 3.51, 3.54 (2d, 2H, J = 8.5 Hz, CH$_2$); 9.48, 9.59 (2d, 1H, J = 1.8 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 11.6 (CH$_3$); 45.8 (CH); 46.1 (CH$_2$); 202.9 (CH). IR: $\tilde{n}$ [cm^{-1}] = 2935 (s); 2726 (m); 1722

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[103] Ahman, J.; Somfai, P.; *Tetrahedron* **1992**, *48*, 9537-9544.

(vs); 1644 (vs); 1459 (s); 1425 (vs); 1376 (s); 1278 (s); 1035 (m); 794 (m). HRMS found $[M+H]^+$ 158.1210, $C_8H_{15}NO_2$ requires $[M+H]^+$, 158.1181.

Ethyl-(4-oxo-butyl)-carbamic acid ethyl ester (221g/222g). The general procedure was followed with allyl-ethyl-carbamic acid ethyl ester (84 mg, 0.53 mmol), $Rh(acac)(CO)_2$ (0.41 mg, 0.30 mol%) and XANTPHOS (see table entries) to give a mixture of *n*-aldehyde and *iso*-aldehyde, which was analyzed by NMR. *n*-regioisomer: ^{1}H-NMR: $(CDCl_3, 500$ MHz) $d = 1.04$ (t, 3H, $J = 7.0$ Hz, CH_3); 1.17 (t, 3H, $J = 7.0$ Hz, CH_3); 1.78 (t, 2H, $J = 7.1$ Hz, CH_2); 2.40 (m, 2H, CH_2); 3.19 (bs, 4H, $2xCH_2$); 4.05 (q, 2H, $J = 7.0$ Hz, CH_2); 9.70 (bs, 1H, CH). ^{13}C-NMR: $(CDCl_3, 125$ MHz) $d = 13.9, 13.6 (CH_3)$; 14.5 (CH_3); 20.8 (CH_2); 40.9 (CH_2); 41.6 (CH_2); 45.9, 45.2 (CH_2); 60.9 (CH_2); 201.5 (CH). (C) not detectable. *Characteristic data for the iso*-regioisomer: ^{1}H-NMR: $(CDCl_3, 500$ MHz) $d = 9.59$ (d, 1H, $J = 2.0$ Hz, CH). ^{13}C-NMR: $(CDCl_3, 125$ MHz) $d = 11.6 (CH_3)$. IR: $\tilde{n}$ $[cm^{-1}] = 2977$ (s); 2933 (m); 2722 (w); 1697 (vs); 1479 (s); 1425 (s); 1276 (s); 1189 (s); 1147 (m); 1074 (m); 1025 (m); 771 (m). HRMS found $[M+H]^+$ 188.1290, $C_9H_{18}NO_3$ requires $[M+H]^+$, 188.1287.

10.3.2 GENERAL PROCEDURE FOR THE TANDEM HYDROFORMYLATION / HYDRAZONE FORMATION

2-[4-(Phenyl-hydrazono)-butyl]-isoindole-1,3-dione (224a/225a). A typical procedure is described. 2-Allyl-isoindole-1,3-dione (967 mg, 5.17 mmol), phenylhydrazine (557 mg, 5.17 mmol), $Rh(acac)(CO)_2$ (0.38 mg, 0.30 mol%) and XANTPHOS (see table entries) were dissolved in anhydrous THF (8.70 g, 10 wt% olefin), filled in an autoclave and pressurized with 10bar H_2 and 10bar CO. After stirring for 68 hours at 70°C the solvent was removed and the crude product (containing *n*- and *iso*-regioisomers) was analyzed by NMR. Analytical data was obtained from an inseparable mixture of *E/Z* & *n/iso*-isomers. *n*-regioisomer: ^{1}H-NMR: $(CDCl_3, 500$ MHz) $d = 1.96$ (m, 2H, $J = 7.2$ Hz, CH_2); 2.36, 2.27 (dt, 2H, $J = 5.2$ Hz, $J = 7.5$ Hz, CH_2); 3.78 (t, 2H, $J = 7.0$ Hz, CH_2); 6.77, 6.82 (dd, 1H, $J = 7.2$ Hz, $J = 7.5$ Hz, CH); 6.91, 7.01 (d, 2H, $J = 7.5$ Hz, 2xCH); 7.05, 6.45 (t, 1H, $J = 5.2$ Hz, CH); 7.18 (dd, 1H, $J = 8.5$ Hz, $J = 8.5$ Hz, 2xCH); 7.23 (s, 1H, NH); 7.65 (d, 2H, $J = 5.3$ Hz, 2xCH); 7.81 (d, 2H, $J = 5.3$ Hz, 2xCH). ^{13}C-NMR: $(CDCl_3, 125$ MHz) $d = 25.6 (CH_2)$; 29.5 (CH_2); 37.4 (CH_2); 112.3 (2xCH); 119.4 (CH); 123.2 (2xCH); 129.0 (CH); 129.1 (CH); 132.0 (2xC); 133.9 (2xCH); 139.2, 141.6 (CH); 144.9 (C); 168.4 (2xC). *Characteristic data for the iso*-regioisomer: ^{1}H-NMR: $(CDCl_3, 500$ MHz) $d = 1.17$ (d, 3H, $J = 7.0$ Hz, CH_3); 2.96 (m, 1H, $J = 7.0$ Hz, CH); 6.35 (d, 1H, $J = 6.5$ Hz, CH); 7.47 (s, 1H, NH); 7.71-7.73 (2H, $2xCH_2$); 7.86-7.88 (2H, 2xCH). ^{13}C-NMR: $(CDCl_3, 125$ MHz) $d = 16.0 (CH_3)$; 36.2 (CH); 112.9

(2xCH); 120.1 (CH); 123.5 (2xCH). IR: $\tilde{n}$ [cm^{-1}] = 3315 (s); 2966 (s); 1770 (vs); 1722 (vs); 1600 (s); 1398 (s); 1259 (s); 1066 (m); 750 (m); 723 (m). HRMS found [M]$^+$ 307.1349, $C_{18}H_{17}N_3O_2$ requires [M]$^+$, 307.1321.

N-Ethyl-4-methyl-N-[4-(phenyl-hydrazono)-butyl]-benzenesulfonamide (224b/225b). The general procedure was followed with *N*-allyl-*N*-ethyl-4-methyl-benzenesulfonamide (349 mg, 1.46 mmol), phenylhydrazine (158 mg, 1.46 mmol), Rh(acac)(CO)$_2$ (1.13 mg, 0.30 mol%) and XANTPHOS (see table entries) to give an inseparable mixture of *E/Z* & *n/iso*-isomers, which was analyzed by NMR. *n*-regioisomer: ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.08 (t, 3H, J = 7.1 Hz, CH$_3$); 2.29 (dt, 2H, J = 5.1 Hz, J = 7.3 Hz, CH$_2$); 2.37 (s, 3H, CH$_3$); 3.13-3.23 (4H, 2xCH$_2$); 6.78 (dd, 1H, J = 7.3 Hz, J = 8.3 Hz, CH); 6.93 (d, 2H, J = 9.5 Hz, 2xCH); 7.17, 6.65 (t, 1H, J = 5.1 Hz, CH); 7.19 (dd, 2H, J = 7.3 Hz, J = 8.3 Hz, 2xCH); 7.23 (s, 1H, NH); 7.24 (d, 2H, J = 8.2 Hz, 2xCH); 7.65 (d, 2H, J = 8.2 Hz, 2xCH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 14.0 (CH$_3$); 21.4 (CH$_3$); 26.0 (CH$_2$); 29.1 (CH$_2$); 42.9 (CH$_2$); 47.0 (CH$_2$); 112.4, 112.9 (2xCH); 119.4, 120.0 (CH); 127.0 (2xCH); 129.1 (2xCH); 129.6 (2xCH); 136.9 (C); 139.6, 142.2 (CH); 143.0 (C); 145.3 (C). *Characteristic data for the iso-regioisomer:* ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.11 (d, 3H, J = 7.0 Hz, CH$_3$); 2.76 (m, 1H, J = 7.0 Hz, CH); 3.09 (dd, 1H, J = 6.8 Hz, J = 13.8 Hz, C*H*H); 3.30 (dd, 1H, J = 8.5 Hz, J = 13.8 Hz, CH*H*); 6.24 (d, 1H, J = 7.3 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 16.2 (CH$_3$); 35.6 (CH); 43.2 (CH$_2$); 51.4 (CH$_2$); 115.1 (2xCH); 136.5 (C); 139.1 (CH). IR: $\tilde{n}$ [cm^{-1}] = 3399 (m); 2923 (m); 2856 (m); 1598 (m); 1455 (m); 1332 (m); 1153 (s); 1089 (m); 742 (m). HRMS found [M]$^+$ 359.1689, $C_{19}H_{25}N_3O_2S$ requires [M]$^+$ 359.1667.

N-Ethyl-N-[4-(phenyl-hydrazono)-butyl]-acetamide (224c/225c). The general procedure was followed with *N*-allyl-*N*-ethyl-4-acetamide (276 mg, 2.17 mmol), phenylhydrazine (235 mg, 2.17 mmol), Rh(acac)(CO)$_2$ (1.68 mg, 0.30 mol%) and XANTPHOS (see table entries) to give an inseparable mixture of *E/Z* & *n/iso*-isomers, which was analyzed by NMR. *n*-regioisomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.15, 1.10 (t, 3H, J = 7.1 Hz, CH$_3$); 1.79 (m, 2H, J = 7.8 Hz, CH$_2$); 2.07, 2.08 (s, 3H, CH$_3$); 2.27 (dt, 2H, J = 5.2 Hz, J = 7.2 Hz, CH$_2$); 3.29 (t, 2H, J = 7.2 Hz, CH$_2$); 3.36 (q, 2H, J = 7.2 Hz, CH$_2$); 6.78 (dd, 1H, J = 7.5 Hz, J = 8.0 Hz, CH); 6.95 (d, 2H, J = 8.0 Hz, 2xCH); 7.05, 6.45 (t, 1H, J = 5.2 Hz, CH); 7.20 (dd, 2H, J = 7.2 Hz, J = 7.5 Hz, 2xCH); 7.53, 7.67 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 13.9, 12.8 (CH$_3$); 21.3 (CH$_3$); 24.9, 25.6 (CH$_2$); 29.4, 29.0 (CH$_2$); 43.3, 40.3 (CH$_2$); 44.6, 47.6 (CH$_2$); 112.3 (2xCH); 119.1, 119.4 (CH); 129.0, 129.1 (2xCH); 140.1, 138.9 (CH); 145.4 (C); 170.0 (C). *Characteristic data for the iso-regioisomer:* ^{1}H-NMR: (CDCl$_3$, 500 MHz)

d = 2.77 (m, 1H, J = 6.7 Hz, CH); 3.16 (dd, 1H, J = 6.2 Hz, J = 13.7 Hz, C*H*H); 3.63 (dd, 1H, J = 9.3 Hz, J = 13.7 Hz, CH*H*); 6.19 (d, 1H, J = 6.7 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 16.1 (CH$_3$); 35.8 (CH); 143.0 (CH). HRMS found [M]$^+$ 247.1702, C$_{14}$H$_{21}$N$_3$O requires [M]$^+$ 247.1685.

2-[2-Methyl-4-(phenyl-hydrazono)-butyl]-isoindole-1,3-dione (213). The general procedure was followed with 2-(2-methylallyl)-isoindoline-1,3-dione (3.131 mg, 15.56 mmol), phenylhydrazine (1.682 mg, 15.56 mmol), Rh(acac)(CO)$_2$ (40 mg, 1.0 mol%), 10bar H$_2$ and 50bar CO. After stirring for 68 hours at 100°C the solvent was removed and the crude product, containing an inseparable mixture of *E*/*Z* isomers, was analyzed by NMR. ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 0.98, 1.05 (d, 3H, J = 6.6 Hz, CH$_3$); 2.18-2.37 (3H, CH$_2$, CH); 3.56 (dd, 1H, J = 7.0 Hz, J = 13.7 Hz, C*H*H); 3.63 (dd, 1H, J = 6.7 Hz, J = 13.7 Hz, CH*H*); 6.76, 6.82 (dd, 1H, J = 8.0 Hz, J = 8.0 Hz, CH); 6.90, 7.00 (d, 2H, J = 8.3 Hz, CH); 7.02 (t, 1H, J = 5.0 Hz, CH); 7.16, 7.20 (dd, 2H, J = 8.0 Hz, J = 8.3 Hz, 2xCH); 7.32, 7.44 (s, 1H, NH); 7.64, 7.67 (d, 2H, J = 5.5 Hz, 2xCH); 7.77, 7.80 (d, 2H, J = 5.5 Hz, 2xCH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 17.8, 18.0 (CH$_3$); 31.0, 31.1 (CH); 36.9 (CH$_2$); 43.5 (CH$_2$); 112.3, 112.9 (2xCH); 119.3 (CH); 123.1 (2xCH); 129.0 (2xCH); 131.8 (2xC); 133.8, 134.0 (2xCH); 138.6, 138.3 (CH); 145.1 (C); 168.5 (2xC). IR: $\tilde{n}$ [cm^{-1}] = 3315 (s); 2964 (vs); 2873 (s); 1772 (vs); 1600 (s); 1497 (vs); 1257 (vs); 1058 (s); 912 (s). HRMS found [M]$^+$ 321.1472, C$_{19}$H$_{19}$N$_3$O$_2$ requires [M]$^+$ 321.1477.

10.3.3 GENERAL PROCEDURE FOR THE TANDEM HYDROFORMYLATION / FISCHER INDOLE SYNTHESIS FOLLOWED BY TOSYLATION OF THE CRUDE PRODUCT

2-{2-[1-(Toluene-4-sulfonyl)-1H-indol-3-yl]-propyl}-isoindole-1,3-dione (215a). A typical procedure is described. 2-(2-methylallyl)isoindoline-1,3-dione (0.66 g, 3.3 mmol), phenylhydrazine (0.36 g, 3.3 mmol), Rh(acac)(CO)$_2$ (16 mg , 1 mol%) and PTSA (0.63 g, 3.3 mmol) were dissolved in anhydrous toluene (12g), filled in an autoclave and pressurized with 10bar H$_2$ and 10bar CO. After stirring for 2 days at 120°C the mixture was poured into a suspension of Bu$_4$NHSO$_4$ (0.1 g) in toluene (15 ml) and NaOH (10 g, 50wt% in water). Tosylchloride (0.69 g, 3.6 mmol) in toluene (15 ml) was dropped to the mixture within 10 minutes. After stirring for 1 hour the layers were separated and the organic layer was extracted 3 times with EtOAc. The solvent was evaporated and the residue was purified by flash chromatography on silica to give 2-{2-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-propyl}-isoindole-1,3-dione (0.91 g, 60%) ^{1}H-NMR: (CDCl$_3$, 400MHz) d = 1.24 (d, 3H, J = 7.0 Hz, CH$_3$), 2.16 (s, 3H, CH$_3$), 3.43 (m, 1H, CH), 3.64 (dd, 1H, J = 8.9 Hz, J = 13.8 Hz, C*H*H), 3.88

(dd, 1H, J = 6.1 Hz, J = 13.8 Hz, C*H*H), 7.03 (d, 1H, J = 8.3 Hz, CH), 7.09-7.22 (2H, 2xCH), 7.38 (s, 1H, CH), 7.56 – 7.68 (8H, 8xCH), 7.84 (d, 1H, J = 8.3 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 100MHz) d = 17.7 (CH$_3$), 21.3 (CH$_3$), 29.9 (CH), 43.4 (CH$_2$), 113.5 (CH), 119.7 (CH), 122.2 (2xCH), 123.0 (2xCH), 124.6 (CH), 124.7 (C), 126.6 (2xCH), 127.7 (CH), 129.6 (2xCH), 130.0 (C), 131.7 (C), 133.8 (2xCH), 135.0 (2xC), 144.6 (C), 168.2 (2xC, C not observed. IR: $\tilde{n}$ [cm^{-1}] = 2966 (s), 2933 (s), 1770 (vs), 1718 (vs), 1398 (vs), 1184 (vs), 1132 (vs), 717 (vs), 671 (vs). MS (EI, 70eV): m/z (%) = 458 (M$^+$, 22), 298 (100), 200 (25), 160 (51), 155 (60), 106 (31), 91 (91). HRMS found M$^+$ 458.1314, C$_{26}$H$_{22}$N$_2$O$_4$S requires M$^+$, 458.1300. Elementary analysis found C 67.30%, H 4.60%, N 5.90%, C$_{26}$H$_{22}$N$_2$O$_4$S requires C 68.11%, H 4.84%, N 6.11%.

2-{2-[5-Chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-propyl}-isoindole-1,3-dione

(215b). The general procedure was followed with 2-(2-methylallyl)isoindoline-1,3-dione (1.3 g, 6.5 mmol), 4-chloro-phenylhydrazine (0.92 g, 6.5 mmol), [Rh(cod)Cl]$_2$ (32 mg, 1 mol%) and PTSA (1.23 g, 6.5 mmol) to give 2-{2-[5-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-propyl}-isoindole-1,3-dione (0.82 g, 53 %). ^{1}H-NMR: (CDCl$_3$, 500MHz) d = 1.37 (d, 3H, J = 7.0 Hz, CH$_3$), 2.35 (s, 3H, CH$_3$), 3.52 (m, 1H, CH), 3.78 (dd, 1H, J = 8.6 Hz, J = 13.6 Hz, C*H*H), 3.98 (dd, 1H, J = 6.4 Hz, J = 13.6 Hz, CH*H*), 7.21 (d, 1H, J = 8.2 Hz, CH), 7.26 (d, 1H, J = 8.7 Hz, CH), 7.52 (s, 1H, CH), 7.69 (s, 1H, CH), 7.73-7.75 (4H, 4xCH), 7.83-7.88 (4H, 4xCH). ^{13}C-NMR: (CDCl$_3$, 125MHz) d = 17.9 (CH$_3$), 21.5 (CH$_3$), 29.9 (CH), 43.5 (CH$_2$), 114.7 (CH), 119.5 (CH), 123.3 (2xCH), 124.3 (C), 125.0 (CH), 126.7 (2xCH), 129.0 (CH), 129.1 (C), 129.9 (2xCH), 131.4 (C), 131.8 (C), 133.5 (C), 134.0 (2xCH), 145.0 (2xC), 168.3 (2xC), C not observed.

2-{2-[5-t-Butyl-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-propyl}-isoindole-1,3-dione

(215c). The general procedure was followed with 2-(2-methylallyl)isoindoline-1,3-dione (0.27 g, 1.3 mmol), 4-*tert*-butyl-phenylhydrazine (0.22 g, 1.3 mmol), Rh(acac)(CO)$_2$ (14 mg, 1 mol%) and PTSA (0.25 g, 1.3 mmol) to give of 2-{2-[5-*t*-butyl-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-propyl}-isoindole-1,3-dione (0.32 g, 48 %). ^{1}H-NMR: (CDCl$_3$, 400MHz) d = 1.20 (s, 9H, 3xCH$_3$), 1.26 (d, 3H, J = 6.8 Hz, CH$_3$), 2.15 (s, 3H, CH$_3$), 3.44 (m, 1H, CH), 3.64 (dd, 1H, J = 8.5 Hz, J = 13.5 Hz, C*H*H), 3.86 (dd, 1H, J = 6.2 Hz, J = 13.5 Hz, CH*H*), 7.03 (d, 2H, J = 8.6 Hz, 2xCH) 7.23 (d, 1H, J = 8.8 Hz, CH), 7.54 (s, 1H, CH), 7.53-7.55 (2H, 2xCH), 7.62-7.67 (4H, CH), 7.66 (d, 2H, J = 8.6 Hz, 2xCH). ^{13}C-NMR: (CDCl$_3$, 100MHz) d = 17.7 (CH$_3$), 21.3 (CH$_3$), 26.7 (C), 29.7 (CH), 31.5 (3xCH$_3$), 43.6 (CH$_2$), 112.9 (CH), 115.6 (CH), 122.1 (CH), 122.6 (CH) 123.0 (2xCH), 124.9 (C), 126.6 (2xCH), 129.6 (2xCH), 129.9 (C),

131.7 (2xC), 133.0 (C), 133.8 (2xCH), 135.2 (C), 144.4 (C), 146.1 (C), 168.5 (2xC). IR: $\tilde{n}$ [cm^{-1}] = 2962 (s), 2870 (m), 1772 (s), 1713 (vs), 1398 (vs), 1398 (vs), 1369 (vs), 1173 (vs). HRMS found M$^+$, 514.1946, $C_{30}H_{30}SN_2O_4$ requires M$^+$, 514.1926. Elementary analysis found C 69.10%, H 5.70%, N 5.40%, $C_{30}H_{30}SN_2O_4$ requires C 70.02%, H 5.88%, N 5.44%.

10.3.4 GENERAL PROCEDURE FOR THE TANDEM HYDROFORMYLATION / FISCHER INDOLE SYNTHESIS USING BENZHYDRYLIDENE PROTECTED ARYL HYDRAZINES

2-[2-(1H-Indol-3-yl)-propyl]-isoindole-1,3-dione (215d). A typical procedure is described. 2-(2-methylallyl)isoindoline-1,3-dione (1.32 g, 6.60 mmol), *N*-benzhydrylidene-*N'*-phenylhydrazine (1.79 g, 6.60 mmol), [Rh(cod)Cl]$_2$ (32 mg, 1 mol% and PTSA (1.25 g, 6.60 mmol) were dissolved in anhydrous THF (11 g, 10 wt% olefin), filled in an autoclave and pressurized with 10bar H$_2$ and 10bar CO. After stirring for 3 days at 100°C the mixture was filtered through a pad of alumina and the solvent was evaporated to give the crude product (3.16g). 1.06g crude product were purified by flash chromatography on silica to give 2-[2-(1H-indol-3-yl)-propyl]-isoindole-1,3-dione (0.56 g, 83%). ^{1}H-NMR: (CDCl$_3$, 400MHz) *d* = 1.44 (d, 3H, *J* = 7.0 Hz, CH$_3$), 3.73 (m, 1H, CH), 3.87 (dd, 1H, *J* = 9.0 Hz, *J* = 13.3 Hz, CH$_2$), 4.09 (dd, 1H, *J* = 6.3 Hz, *J* = 13.3 Hz, CH$_2$), 7.13-7.24 (3H, 3xCH), 7.37 (d, 1H, J = 8.0 Hz, CH), 7.70-7.87 (5H, 5xCH), 8.31 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100MHz) *d* = 18.4 (CH$_3$), 30.0 (CH), 44,5 (CH$_2$), 111.1 (CH), 118.3 (C), 119.1 (CH), 119.2 (CH), 120.6 (CH), 121.9 (2xCH), 123.0 (2xCH), 126.7 (C), 131.9 (C), 133.8 (CH), 136.2 (2xC), 168.6 (2xC). IR: $\tilde{n}$ [cm^{-1}] = 3406 (s), 2962 (m), 2931 (m), 1770 (vs), 1712 (vs), 1398 (vs), 1034 (s), 714 (vs). HRMS found M$^+$, 304.1219, $C_{19}H_{16}N_2O_2$ requires M$^+$, 304.1212.

2-(2-(5-fluoro-1H-indol-3-yl)propyl)isoindoline-1,3-dione (215e). The general procedure was followed with 2-(2-methylallyl)isoindoline-1,3-dione (0.62 g, 3.1 mmol), *N*-benzhydrylidene-*N'*-(4-fluoro-phenyl)-hydrazine (0.90 g, 3.1 mmol), Rh(acac)(CO)$_2$ (8 mg, 1 mol%) and PTSA (0.59 g, 3.1 mmol) to give 2-[2-(5-fluoro-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (0.47 g, 47 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) *d* = 1.37 (d, 3H, J = 7.0 Hz, CH$_3$); 3.59 (m, 1H, J = 7.0 Hz, CH); 3.79 (dd, 1H, J = 8.7 Hz, J = 13.5 Hz, CHH); 3.97 (dd, 1H, J = 6.7 Hz, J = 13.5 Hz, CHH); 6.88 (dd, 1H, J = 9.0 Hz, J = 9.0 Hz, CH); 7.13 (s, 1H, CH); 7.23 (dd, 1H, J = 9.0 Hz, J = 9.0 Hz, CH); 7.41 (d, 1H, J = 9.7 Hz, CH); 7.67-7.69 (2H, 2xCH); 7.78-7.80 (2H, 2xCH); 8.10 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) *d* = 18.4 (CH$_3$); 30.0 (CH); 44.4 (CH$_2$); 104.1 (d, 1C, J_{C-F} = 23 Hz, CH); 110.3 (d, 1C, J_{C-F} = 25 Hz, CH); 111.7 (d, 1C, J_{C-F} = 10 Hz, CH); 116.2 (C); 118.7 (C); 122.3 (CH); 123.1 (2xCH); 132.0 (2xC); 133.9 (2xCH); 157.7 (d, 1C, J_{C-F} = 234 Hz, C); 168.6 (2xC). IR: $\tilde{n}$ [cm^{-1}] = 3392 (m);

2964 (w); 2933 (w); 1770 (w); 1708 (vs); 1486 (s); 1398 (vs); 1153 (m); 1033 (m). HRMS found M$^+$, 323.1145, $C_{19}H_{15}FN_2O_2$ requires M$^+$, 323.1118. Elementary analysis found C 70.38%, H 5.02%, N 8.30%, $C_{19}H_{15}FN_2O_2$ requires C 70.80%, H 4.69%, N 8.69%.

2-[2-(5-Chloro-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (215f). The general procedure was followed with 2-(2-methylallyl)isoindoline-1,3-dione (0.92 g, 4.6 mmol), *N*-benzhydrylidene-*N'*-(4-chloro-phenyl)-hydrazine (1.40 g, 4.6 mmol), [Rh(cod)Cl]$_2$ (22 mg, 1 mol%) and PTSA (0.87 g, 4.6 mmol) to give 2-[2-(5-chloro-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (0.58 g, 78 %). ^{1}H-NMR: (CDCl$_3$, 400MHz) *d* = 1.41 (d, 3H, *J* = 7.0 Hz, CH$_3$), 3.63 (m, 1H, CH), 3.8 (dd, 1H, *J* = 8.3 Hz, *J* = 13.6 Hz, C*H*H), 4.00 (dd, 1H, *J* = 6.8 Hz, *J* = 13.6 Hz, CH*H*), 7.09 (d, 1H, *J* = 8.2 Hz, CH), 7.14 (s, 1H CH), 7.24 (m, 1H, CH), 7.69-7.72 (3H, 3xCH), 7.81-7.83 (2H, 2xCH), 8.31 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100MHz) *d* = 18.4 (CH$_3$), 29.9 (CH), 44.5 (CH$_2$), 112.12 (CH), 118.24 (C), 118.5 (CH), 122.0 (CH), 122.2 (CH), 123.1 (2xCH), 125.0 (C), 128.0 (C), 131.8 (C), 133.9 (2xCH), 134.5 (2xC), 168.6 (2xC). IR: $\tilde{n}$ [cm^{-1}] = 3383 (m), 2964 (w), 2360 (w), 1765 (s), 1705 (vs), 1466 (s), 1429 (s), 1398 (vs), 1032 (s), 717 (s). HRMS found M$^+$, 338.0802, $C_{19}H_{15}N_2O_2Cl$ requires M$^+$, 338.0822. Elementary analysis found C 66.90%, H 4.35%, N 8.10%, $C_{19}H_{15}N_2O_2Cl$ requires C 67.36%, H 4.46%, N 8.27%.

2-[2-(5-Bromo-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (215g). The general procedure was followed with 2-(2-methylallyl)isoindoline-1,3-dione (0.79 g, 3.9 mmol), *N*-benzhydrylidene-*N'*-(4-bromo-phenyl)-hydrazine (1.38 g, 3.9 mmol), [Rh(cod)Cl]$_2$ (19 mg, 1 mol%) and PTSA (0.74 g, 3.9 mmol) to give 2-[2-(5-bromo-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (0.74 g, 50 %). ^{1}H-NMR: (CDCl$_3$, 400MHz) *d* = 1.36 (d, 3H, *J* = 6.9 Hz, CH$_3$), 3.58 (m, 1H, CH), 3.79 (dd, 1H, *J* = 8.7 Hz, *J* = 13.8 Hz, C*H*H), 3.94 (dd, 1H, *J* = 6.2 Hz, *J* = 13.8 Hz, CH*H*), 7.08-7.16 (3H, 3xCH), 7.65-7.81 (5H, 5xCH), 8.27 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100MHz) *d* = 18.4 (CH$_3$), 29.8 (CH), 44.5 (CH$_2$), 112.6 (CH), 112.6 (C), 118.2 (C), 121.6 (CH), 121.8 (CH), 123.1 (2xCH), 124.8 (CH), 128.6 (C), 131.8 (C), 133.9 (2xCH), 134.8 (2xC), 168.5 (2xC). IR: $\tilde{n}$ [cm^{-1}] = 3377 (s), 1770 (s), 1716 (vs), 1466 (s), 1433 (s), 1398 (vs), 1354 (s), 1034 (s), 795 (s), 715 (vs). HRMS found M$^+$, 382.0280, $C_{19}H_{15}BrN_2O_2$ requires M, 382.0317. Elementary analysis found C 59.75%, H 3.95%, N 7.35%, $C_{19}H_{15}BrN_2O_2$ requires C 59.55%, H 3.95%, N 7.31%.

2-[2-(7-Methyl-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (215h). The general procedure was followed with 2-(2-methylallyl)isoindoline-1,3-dione (0.95 g, 4.7 mmol), *N*-benzhydrylidene-*N'*-*o*-tolyl-hydrazine (1.35 g, 4.7 mmol), [Rh(cod)Cl]$_2$ (23 mg, 1 mol%) and

PTSA (0.90 g, 4.7 mmol) to give 2-[2-(7-Methyl-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (0.72 g, 48 %). ^{1}H-NMR: (CDCl$_3$, 400MHz) d = 1.38 (d, 3H, J = 7.0 Hz, CH$_3$), 2.45 (s, 3H, CH$_3$), 3.68 (m, 1H, CH), 3.81 (dd, 1H, J = 8.9 Hz, J = 13.7 Hz, CHH), 4.05 (dd, 1H, J = 6.4 Hz, J = 13.7 Hz, CHH), 6.96-7.11 (3H, 3xCH), 7.66-7.82 (5H, 5xCH), 8.07 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100MHz) d = 16.5 (CH$_3$), 18.5 (CH$_3$), 30.2 (CH), 44.5 (CH$_2$), 116.9 (CH), 118.9 (C), 119.6 (CH), 120.2 (CH), 120.3 (C), 122.5 (CH), 123.1 (2xCH), 126.3 (C), 132.0 (C), 133.8 (2xCH), 135.8 (2xC), 168.6 (2xC). IR: $\tilde{n}$ [cm^{-1}] = 3402 (s), 1770 (s), 1716 (vs), 1466 (s), 1458 (s), 1433 (s), 1398 (vs), 1034 (s), 714 (vs). HRMS found M$^+$, 318.1395, C$_{20}$H$_{18}$N$_2$O$_2$ require M$^+$, 318.1368. Elementary analysis found C 75.30%, H 5.80%, N 8.20%, C$_{20}$H$_{18}$N$_2$O$_2$ requires C 75.45%, H 5.70%, N 8.80%.

2-[2-(7-Chloro-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (215i). The general procedure was followed with 2-(2-methylallyl)isoindoline-1,3-dione (0.93 g, 4.6 mmol), N-benzhydrylidene-N'-(2-chloro-phenyl)-hydrazine (1.41 g, 4.6 mmol), [Rh(cod)Cl]$_2$ (23 mg, 1 mol%) and PTSA (0.87 g, 4.6 mmol) to give 2-[2-(7-chloro-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (0.21 g, 42 %). ^{1}H-NMR: (CDCl$_3$, 400MHz) d = 1.38 (d, 3H, J = 7.0 Hz, CH$_3$), 3.63 (m, 1H, CH), 3.80 (dd, 1H, J = 8.8 Hz , J = 13.8 Hz, CHH), 4.00 (dd, 1H, J = 6.5 Hz, J = 13.8 Hz, CHH), 7.00 (dd, 1H, J = 7.8 Hz, CH), 7.15 (s, 1H CH), 7.65-7.70 (4H, 4xCH), 7.78-7.82 (2H, 2xCH), 8.38 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100MHz) d = 18.4 (CH$_3$), 30.2 (CH), 44.4 (CH$_2$), 116.5 (C), 117.8 (CH), 119.5 (C), 120.1 (CH), 121.3 (2xCH), 123.1 (2xCH), 128.3 (C), 131.9 (2xC), 133.5 (C), 133.9 (2xCH), 168.6 (2xC). IR: $\tilde{n}$ [cm^{-1}] = 3381(m), 1765 (m), 1705 (vs), 1398 (m), 1032 (m), 893 (m), 717 (m). HRMS found M$^+$, 338.0844, C$_{19}$H$_{15}$ClN$_2$O$_2$ requires M, 338.0822. Elementary analysis found C 67.43%, H 4.07%, N 8.10%, C$_{19}$H$_{15}$ClN$_2$O$_2$ requires C 67.36%, H 4.46%, N 8.27%.

10.3.5 GENERAL PROCEDURE FOR THE TANDEM HYDROFORMYLATION / FISCHER IINDOLE SYNTHESIS WITH SUBSEQUENT ADDITION OF ACID

2-[2-(5-Methoxy-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (215j). A typical procedure is described. 2-(2-Methylallyl)isoindoline-1,3-dione (301 mg, 1.50 mmol), a-Boc-1-(4-methoxyphenyl)hydrazine (356 mg, 1.50 mmol) and Rh(acac)(CO)$_2$ (1.16 mg , 0.03 mol%) were dissolved in anhydrous THF (2.71 g, 10 wt% olefin), filled in an autoclave and pressurized with 10bar H$_2$ and 50bar CO. After stirring for 3 days at 120°C the mixture was poured into H$_2$SO$_4$ (15 ml, 4 wt% in THF) and the resulting mixture was stirred for additional 2h under reflux. NH$_3$ (10 ml, 30 wt% in water) was added and the mixture was extracted 3 times with EtOAc. The solvent was evaporated and the residue was chromatographed

(EtOAc, cyclohexane, silica) to give 2-[2-(5-Methoxy-1H-indol-3-yl)-propyl]-isoindole-1,3-dione (462 mg, 95%). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.38 (d, 3H, J = 7.0 Hz, CH$_3$); 3.60 (m, 1H, J = 7.0 Hz, CH); 3.78 (dd, 1H, J = 9.0 Hz, J = 13.6 Hz, CHH); 3.85 (s, 3H, CH$_3$); 4.01 (dd, 1H, J = 6.2 Hz, J = 13.6 Hz, CHH); 6.79 (d, 1H, J = 8.7 Hz, CH); 7.07 (s, 1H, CH); 7.19 (d, 1H, J = 8.7 Hz, CH); 7.27 (s, 1H, CH); 7.66 (d, 2H, J = 5.4 Hz, 2xCH); 7.78 (d, 2H, J = 5.4 Hz, 2xCH); 8.26 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125MHz) d = 18.2 (CH$_3$); 30.0 (CH); 44.5 (CH$_2$); 55.7 (CH$_3$); 100.6 (CH); 111.9 (CH); 112.3 (CH); 118.1 (C); 121.3 (CH); 123.0 (2xCH); 127.2 (C); 131.3 (C); 131.9 (2xC); 133.8 (2xCH); 153.8 (C); 168.6 (2xC). IR: $\tilde{n}$ [cm^{-1}] = 3399 (m); 1770 (m); 1700 (vs); 1484 (s); 1428 (m); 1398 (s); 1376 (m); 1216 (s); 1157 (m); 1037 (s); 713 (s). HRMS found [M]$^+$ 334.1299, C$_{20}$H$_{18}$N$_2$O$_3$ requires [M]$^+$ 334.1318. Elementary analysis found C 71.64%, H 5.38%, N 8.11%, C$_{20}$H$_{18}$N$_2$O$_3$ requires C 71.84%, H 5.43%, N 8.38%.

N-Ethyl-N-[2-(1H-indol-3-yl)-propyl]-4-methyl-benzenesulfonamide (215k). The general procedure was followed with *N*-ethyl-4-methyl-*N*-(2-methyl-allyl)-benzenesulfonamide (0.71 g, 2.8 mmol), phenylhydrazine (0.30 g, 2.8 mmol) and Rh(acac)(CO)$_2$ (2.2 mg, 0.3 mol%) to give *N*-ethyl-*N*-[2-(1H-indol-3-yl)-propyl]-4-methyl-benzenesulfonamide (0.94 g, 94 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.11 (t, 3H, J = 7.3 Hz, CH$_3$); 1.50 (d, 3H, J = 6.5 Hz, CH$_3$); 2.43 (s, 3H, CH$_3$); 3.29 (q, 2H, J = 7.3 Hz, CH$_2$); 3.40-3.47 (3H, CH$_2$, CH); 7.07 (s, 1H, CH); 7.15 (dd, 1H, J = 7.0 Hz, J = 8.1 Hz, CH); 7.22 (dd, 1H, J = 7.0 Hz, J = 8.1 Hz, CH); 7.28 (d, 2H, J = 8.0 Hz, 2xCH); 7.40 (d, 1H, J = 8.1 Hz, CH); 7.68 (d, 1H, J = 8.1 Hz, CH); 7.72 (d, 2H, J = 8.0 Hz, 2xCH); 8.46 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 13.6 (CH$_3$); 18.2 (CH$_3$); 21.3 (CH$_3$); 30.2 (CH); 43.3 (CH$_2$); 54.0 (CH$_2$); 111.3 (CH); 118.2 (C); 118.6 (CH); 119.0 (CH); 121.0 (CH); 121.7 (CH); 126.4 (C); 127.0 (2xCH); 129.5 (2xCH); 136.3 (C); 136.9 (C); 142.9 (C). IR: $\tilde{n}$ [cm^{-1}] = 3398 (s); 2972 (s); 2931 (s); 1599 (s); 1456 (s); 1329 (s); 1153 (m); 741 (m). HRMS found [M]$^+$ 356.1584, C$_{20}$H$_{24}$N$_2$O$_2$S requires [M]$^+$ 356.1558.

N-Ethyl-N-[2-(1H-indol-3-yl)-propyl]-benzamide (215l). The general procedure was followed with *N*-ethyl-4-methyl-*N*-(2-methyl-allyl)-benzamide (0.66 g, 3.3 mmol), phenylhydrazine (0.35 g, 3.3 mmol) and Rh(acac)(CO)$_2$ (2.5 mg, 0.3 mol%) to give *N*-ethyl-*N*-[2-(1H-indol-3-yl)-propyl]-benzamide (0.82 g, 85 %). ^{1}H-NMR: (C$_2$D$_2$Cl$_4$, 400 MHz, 80°C) d = 1.06-1.20 (3H, CH$_3$); 1.43 (d, 3H, J = 6.5 Hz, CH$_3$); 3.30-3.79 (5H, 2xCH$_2$, CH); 7.00 (s, 1H, CH); 7.10 (dd, 1H, J = 7.5 Hz, J = 7.3 Hz, CH); 7.20 (t, 1H, J = 8.0 Hz, J = 7.0 Hz,); 7.27-7.29 (2H, 2xCH); 7.35-7.53 (5H, 5xCH); 8.21 (bs, 1H, NH). ^{13}C-NMR:

(CDCl$_3$, 100 MHz) d = 13.5, 12.5 (CH$_3$); 18.8, 17.8 (CH$_3$); 28.9, 30.4 (CH); 44.0, 39.9 (CH$_2$); 50.6, 54.7 (CH$_2$); 111.3, 114.9 (CH); 118.4, 117.1 (C); 118.7, 118.3 (CH); 120.8, 121.0 (CH); 121.3 (CH); 126.1, 126.5 (2xCH); 126.8 (C); 128.2, 128.7 (2xCH); 128.9, 129.0 (CH); 136.3 (C); 137.1, 136.9 (C); 171.9 (C). IR: $\tilde{n}$ [cm^{-1}] = 3188 (s); 2972 (s); 2931 (s); 1633 (s); 1456 (s); 1381 (s); 1105 (m); 739 (s).

N-Ethyl-N-[2-(1H-indol-3-yl)-propyl]-acetamide (215m). The general procedure was followed with N-ethyl-4-methyl-N-(2-methyl-allyl)-acetamide (0.58 g, 4.1 mmol), phenylhydrazine (0.44 g, 4.1 mmol) and Rh(acac)(CO)$_2$ (3.2 mg, 0.3 mol%) to give N-ethyl-N-[2-(1H-indol-3-yl)-propyl]-acetamide (0.61 g, 61 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.01, 1.10 (t, 3H, J = 7.1 Hz, CH$_3$); 1.33, 1.41 (d, 3H, J = 6.9 Hz, CH$_3$); 2.06, 1.95 (s, 3H, CH$_3$); 2.97-3.12 (2H, CH$_2$); 3.36-3.55 (2H, CH$_2$); 3.73 (m, 1H, CH); 6.98, 6.95 (s, 1H, CH); 7.08, 7.03 (d, 1H, J = 8.0 Hz, CH); 7.15, 7.11 (d, 1H, J = 8.0 Hz, CH); 7.32, 7.34 (d, 1H, J = 8.0 Hz, CH); 7.66, 7.57 (d, 1H, J = 8.0 Hz, CH); 8.81, 9.01 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 13.5, 12.5 (CH$_3$); 18.6, 18.1 (CH$_3$); 21.4, 21.6 (CH$_3$); 29.2, 30.9 (CH); 43.7, 40.7 (CH$_2$); 51.9, 54.7 (CH$_2$); 111.2, 111.5 (CH); 118.8, 118.5 (CH); 119.0, 117.7 (C); 119.1, 119.4 (CH); 121.0, 120.6 (CH); 121.5, 121.7 (CH); 126.9, 126.2 (C); 136.5, 136.3 (C); 170.6, 170.5 (C). IR: $\tilde{n}$ [cm^{-1}] = 3271 (s); 2970 (s); 2931 (s); 1631 (s); 1458 (s); 1379 (s); 1033 (m); 742 (s). HRMS found [M+H]$^+$ 245.1682, C$_{15}$H$_{20}$N$_2$O requires [M+H]$^+$ 245.1654.

Ethyl-[2-(1H-indol-3-yl)-propyl]-carbamic acid ethyl ester (215n). The general procedure was followed with ethyl-(2-methyl-allyl)-carbamic acid ethyl ester (0.62 g, 3.6 mmol), phenylhydrazine (0.39 g, 3.6 mmol) and Rh(acac)(CO)$_2$ (2.8 mg, 0.3 mol%) to give ethyl-[2-(1H-indol-3-yl)-propyl]-carbamic acid ethyl ester (0.58 g, 58 %). ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.03-1.13 (3H, CH$_3$); 1.28 (t, 3H, J = 7.1 Hz, CH$_3$); 1.39 (bs, 3H, CH$_3$); 3.23-3.72 (5H, 2xCH$_2$, CH); 4.15-4.20 (2H, CH$_2$); 7.01, 6.98 (s, 1H, CH); 7.12 (dd, 1H, J = 7.3 Hz, J = 7.3 Hz, CH); 7.19 (dd, 1H, J = 7.3 Hz, J = 7.7 Hz, CH); 7.35 (d, 1H, J = 7.7 Hz, CH); 7.69 (bs, 1H, CH); 8.38 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 12.9, 13.4 (CH$_3$); 14.6 (CH$_3$); 18.4, 18.1 (CH$_3$); 29.9, 30.7 (CH); 42.3, 42.8 (CH$_2$); 52.9, 53.5 (CH$_2$); 61.0 (CH$_2$); 110.6 (C); 111.3, 111.2 (CH); 119.0 (2xCH); 119.2 (C); 120.6 (CH); 121.8 (CH); 136.5 (C); 154.7 (C). IR: $\tilde{n}$ [cm^{-1}] = 3315 (vs); 2973 (s); 2886 (s); 1683 (vs); 1484 (s); 1380 (m); 1172 (s); 1074 (m); 771 (m). HRMS found [M]$^+$ 274.1652, C$_{16}$H$_{22}$N$_2$O$_2$ requires [M]$^+$ 274.1682.

Ethyl 4-(5-bromo-1H-indol-3-yl)piperidine-1-carboxylate (218). The general procedure was followed with ethyl 4-methylenepiperidine-1-carboxylate (1.75 g, 10.3 mmol),

4-bromo-phenylhydrazine (1.93 g, 10.3 mmol) and Rh(acac)(CO)$_2$ (11 mg, 0.3 mol%) to give ethyl 4-(5-bromo-1H-indol-3-yl)piperidine-1-carboxylate (1.93 g, 39 %).^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.29 (t, 3H, J = 7.2 Hz, CH$_3$); 1.63 (q, 2H, J = 11.7 Hz, CH$_2$); 2.00 (d, 2H, J = 13.7 Hz, CH$_2$); 2.92 (t, 3H, J = 11.7 Hz, CH$_2$); 4.17 (q, 2H, J = 7.2 Hz, CH$_2$); 4.28 (bs, 2H, CH$_2$); 6.92 (s, 1H, CH); 7.20 (d, 1H, J = 8.5 Hz, CH); 7.25 (d, 1H, J = 8.5 Hz, CH); 7.73 (s, 1H, CH); 8.56 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 14.7 (CH$_3$); 32.6 (2xCH$_2$); 33.4 (CH); 44.4 (2xCH$_2$); 61.3 (CH$_2$); 112.3 (C); 112.7 (CH); 120.2 (C); 121.0 (CH); 121.4 (CH); 124.6 (CH); 128.2 (C); 135.0 (C); 155.6 (C).

Ethyl 4-(5-bromo-1-(4-fluorophenyl)-1H-indol-3-yl)piperidine-1-carboxylate (219). CuI (5.35 mg, 5 mol%), *N,N'*-dimethyl-ethylen-diamine (20.2 mg, 20 mol%), K$_3$PO$_4$*7H$_2$O (399 mg, 1.18 mmol) 4-fluoro-iodo-benzene (150 mg, 0.67 mmol) and **125** (197 mg, 0.56 mmol) were dissolved in toluene (1M). After stirring for 24h at 110°C the mixture was poured into EtOAc and filtered through a pad of silica. The solvent was removed to give ethyl 4-(5-bromo-1-(4-fluorophenyl)-1H-indol-3-yl)piperidine-1-carboxylate (250 mg, 100 %) without further purification. ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.28 (t, 3H, J = 7.2 Hz, CH$_3$); 1.67 (q, 2H, J = 9.7 Hz, CH$_2$); 2.04 (d, 2H, J = 13.7 Hz, CH$_2$); 2.97 (q, 3H, J = 12.0 Hz, CH$_2$, CH); 4.16 (q, 2H, J = 7.2 Hz, CH$_2$); 4.30 (bs, 2H, CH$_2$); 7.03 (s, 1H, CH); 7.17 (dd, 2H, J = 8.6Hz, J = 9.0 Hz, 2xCH); 7.27 (bs, 2H, 2xCH); 7.37 (dd, 2H, J = 8.6, J = 9.0 Hz, 2xCH); 7.78 (s, 1H, CH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 14.6 (CH$_3$); 32.5 (2xCH$_2$); 33.3 (CH); 44.3 (2xCH$_2$); 61.1 (CH$_2$); 111.8 (CH); 113.01 (C); 116.4 (d, 2C, J = 23 Hz, 2xCH); 121.3 (C); 124.8 (CH); 125.3 (CH); 125.9 (d, 2C, J = 10 Hz, 2xCH); 129.3 (C); 135.1 (d, 1C, J = 36 Hz, C); 155.5 (C); 161.0 (d, 1C, J = 248 Hz, C). IR: $\tilde{n}$ [cm^{-1}] = 2929 (m); 2850 (m); 1693 (vs); 1511 (vs); 1457 (vs); 1442 (s); 1382 (m); 1213 (vs); 1120 (s); 840 (s); 788 (s). HRMS found [M]$^+$ 444.0864, C$_{22}$H$_{22}$BrFN$_2$O$_2$ requires [M]$^+$ 444.0849.

10.3.6 GENERAL PROCEDURE FOR THE REGIOSELECTIVE TANDEM HYDROFORMYLATION / FISCHER INDOLE SYNTHESIS

Methyl 4-(1H-indol-3-yl)butanoate (226). A typical procedure is described. Methyl pent-4-enoate (263 mg, 2.30 mmol), phenylhydrazine (249 mg, 2.30 mmol), Rh(acac)(CO)$_2$ (1.78 mg , 0.3 mol%) and XANTPHOS (40.0 mg, 3 mol%) were dissolved in anhydrous THF (2.36 g, 10 wt% olefin), filled in an autoclave and pressurized with 10bar H$_2$ and 10bar CO. After stirring for 3 days at 70°C the mixture was poured into H$_2$SO$_4$ (15 ml, 4 wt% in THF) and the resulting mixture was stirred for additional 2h under reflux. NH$_3$ (10 ml, 30 wt% in water) was added and the mixture was extracted 3 times with EtOAc. The solvent was

evaporaterd and the residue was chromatographed (EtOAc/cyclohexane, silica) to give methyl 4-(1H-indol-3-yl)butanoate (455 mg, 91%). Analytical data fits with literature[104].

N-[2-(1H-Indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide (227a). The general procedure was followed with N-allyl-4-methyl-benzenesulfonamide (336 mg, 1.59 mmol), phenylhydrazine (172 mg, 1.59 mmol), Rh(acac)(CO)$_2$ (1.23 mg, 0.30 mol%) and XANTPHOS (28 mg, 3 mol%) to give N-[2-(1H-Indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide (295 mg, 59 %). Analytical data fits with literature[105].

2-[2-(1H-Indol-3-yl)-ethyl]-isoindole-1,3-dione (227b). The general procedure was followed with 2-allyl-isoindole-1,3-dione (322 mg, 1.72 mmol), phenylhydrazine (186 mg, 1.72 mmol), Rh(acac)(CO)$_2$ (0.13 mg, 0.30 mol%) and XANTPHOS (29.9 mg, 3 mol%) to give 2-[2-(1H-indol-3-yl)-ethyl]-isoindole-1,3-dione (255 mg, 51 %). Analytical data was obtained from the mixture of *n/iso*-isomers. *n*-regioisomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 3.17 (dd, 2H, J = 7.5 Hz, J = 8.1 Hz, CH$_2$); 4.02 (dd, 2H, J = 7.5 Hz, J = 8.1 Hz, CH$_2$); 7.08 (s, 1H, CH); 7.13 (dd, 1H, J = 7.3 Hz, J = 8.1 Hz, CH); 7.19 (dd, 1H, J = 7.3 Hz, J = 8.1 Hz, CH); 7.34 (d, 1H, J = 8.1 Hz, CH); 7.50 (d, 1H, J = 7.0 Hz, CH); 7.75 (d, 1H, J = 7.3 Hz, CH); 7.66 (d, 2H, J = 5.5 Hz, 2xCH); 8.11 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 24.4 (CH$_2$); 38.5 (CH$_2$); 111.1 (CH); 112.9 (C); 118.8 (CH); 119.4 (CH); 122.0 (CH); 123.1 (2xCH); 127.3 (2xC); 132.4 (C); 133.6 (2xCH); 136.2 (2xC); 168.3 (2xC). *Characteristic data for the iso*-regioisomer (structure confirmed with 1D-NOESY): ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 2.44 (s, 3H, CH$_3$); 4.97 (s, 2H, CH$_2$); 7.07 (dd, 1H, J = 7.0 Hz, J = 7.0 Hz, CH); 7.15 (dd, 1H, J = 7.0 Hz, J = 7.0 Hz, CH); 7.28 (d, 1H, J = 7.0 Hz, CH); 7.50 (d, 1H, J = 7.0 Hz, CH); 7.66 (d, 2H, J = 5.5 Hz, 2xCH); 7.8 (d, 2H, J = 5.5 Hz, 2xCH); 8.56 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 8.3 (CH$_3$); 32.6 (CH$_2$); 110.1 (C); 110.8 (CH); 119.0 (CH); 119.2 (CH); 122.5 (CH); 123.4 (2xCH); 128.2 (C); 128.9 (C); 131.9 (2xC); 134.1 (2xCH); 135.6 (C); 168.4 (2xC). HRMS found [M]$^+$ 290.1068, C$_{18}$H$_{14}$N$_2$O$_2$ requires [M]$^+$ 290.1055.

2-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-isoindole-1,3-dione (227c). The general procedure was followed with 2-allyl-isoindole-1,3-dione (292 mg, 1.56 mmol), *a*-Boc-1-(4-methoxyphenyl) hydrazine (372 mg, 1.56 mmol), Rh(acac)(CO)$_2$ (0.12 mg, 0.30 mol%)

[104] Perregaard, J.; Moltzen, E.K.; Meier, E.; Sanchez, C.; *J. Med. Chem.* **1995**, *38*, 1998-2008.
[105] Onistschenko, A.; Stamm, H.; *Chem. Ber.* **1989**, *122*, 2397-2398.

and XANTPHOS (27.1 mg, 3 mol%) to give 2-[2-(5-Methoxy-1H-indol-3-yl)-ethyl]-isoindole-1,3-dione (400 mg, 80 %). Analytical data fits with literature[106].

N-Ethyl-N-[2-(1H-indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide (227d). The general procedure was followed with N-allyl-N-ethyl-4-methyl-benzenesulfonamide (349 mg, 1.46 mmol), phenylhydrazine (158 mg, 1.46 mmol), Rh(acac)(CO)$_2$ (1.13 mg, 0.30 mol%) and XANTPHOS (25 mg, 3 mol%) to give N-ethyl-N-[2-(1H-indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide (405 mg, 81 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.14 (t, 3H, J = 7.2 Hz, CH$_3$); 2.38 (s, 3H, CH$_3$); 3.03 (dd, 2H, J = 7.7 Hz, J = 8.3 Hz, CH$_2$); 3.29 (q, 2H, J = 7.2 Hz, CH$_2$); 3.41 (dd, 2H, J = 7.7 Hz, J = 8.3 Hz, CH$_2$); 7.01 (s, 1H, CH); 7.10 (dd, 1H, J = 7.5 Hz, J = 8.0 Hz, CH); 7.16 (dd, 1H, J = 7.5 Hz, J = 8.2 Hz, CH); 7.24 (d, 2H, J = 8.2 Hz, 2xCH); 7.35 (d, 1H, J = 8.2 Hz, CH); 7.57 (d, 1H, J = 8.0 Hz, CH); 7.69 (d, 2H, J = 8.2 Hz, 2xCH); 8.41 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 14.8 (CH$_3$); 21.3 (CH$_3$); 25.4 (CH$_2$); 43.0 (CH$_2$); 48.1 (CH$_2$); 111.3 (CH); 112.1 (C); 118.3 (CH); 119.1 (CH); 121.7 (CH); 122.2 (CH); 127.0 (2xCH); 129.5 (2xCH); 129.6 (C); 136.9 (C); 142.9 (C). IR: $\tilde{n}$ [cm^{-1}] = 3399 (s); 2954 (s); 2923 (vs); 2856 (s); 1455 (vs); 1332 (s); 1153 (s). HRMS found [M]$^+$ 342.1415, C$_{19}$H$_{22}$N$_2$O$_2$S requires [M]$^+$ 342.1402.

N-Ethyl-N-[2-(1H-indol-3-yl)-ethyl]-acetamide (227e). The general procedure was followed with N-allyl-N-ethyl-4-acetamide (276 mg, 2.17 mmol), phenylhydrazine (235 mg, 2.17 mmol), Rh(acac)(CO)$_2$ (1.68 mg, 0.30 mol%) and XANTPHOS (18.8 mg, 3 mol%) to give N-ethyl-N-[2-(1H-indol-3-yl)-ethyl]-acetamide (295 mg, 59 %). Analytical data fits with literature[107].

N-Ethyl-N-[3-(1H-indol-3-yl)-propyl]-4-methyl-benzenesulfonamide (227f). The general procedure was followed with N-but-3-enyl-N-ethyl-4-methyl-benzenesulfonamide (355 mg, 1.40 mmol), phenylhydrazine (152 mg, 1.40 mmol), Rh(acac)(CO)$_2$ (1.09 mg, 0.30 mol%) and XANTPHOS (12.2 mg, 3 mol%) to give N-ethyl-N-[3-(1H-indol-3-yl)-propyl]-4-methyl-benzenesulfonamide (290 mg, 58 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.09 (t, 3H, J = 7.2 Hz, CH$_3$); 1.94 (m, 2H, J = 7.5 Hz, CH$_2$); 2.39 (s, 3H, CH$_3$); 2.76 (t, 2H, J = 7.5 Hz, CH$_2$); 3.20-3.24 (4H, 2xCH$_2$); 7.00 (s, 1H, CH); 7.10 (dd, 1H, J = 7.5 Hz, J = 7.5 Hz, CH); 7.18 (dd, 1H, J = 7.2 Hz, J = 8.0 Hz, CH); 7.23 (d, 2H, J = 8.1 Hz, 2xCH); 7.35 (d, 1H, J = 8.0 Hz, CH); 7.53 (d, 1H, J = 8.0 Hz, CH); 7.65 (d, 2H, J = 8.1 Hz, 2xCH); 8.14 (s, 1H,

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NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 14.0 (CH$_3$); 21.4 (CH$_3$); 22.1 (CH$_2$); 28.7 (CH$_2$); 42.6 (CH$_2$); 47.2 (CH$_2$); 111.1 (CH); 115.1 (C); 118.6 (CH); 119.0 (CH); 121.5 (CH); 121.8 (CH); 127.0 (2xCH); 127.3 (C); 129.5 (2xCH); 136.3 (C); 137.0 (C); 142.9 (C). IR: $\tilde{n}$ [cm^{-1}] = 3403 (s); 2935 (s); 1455 (vs); 1336 (vs); 1305 (vs); 1184 (s); 1155 (vs); 1089 (vs); 742 (vs); 715 (s); 551 (s). HRMS found [M]$^+$ 356.1569, C$_{20}$H$_{24}$N$_2$O$_2$S requires [M]$^+$ 356.1558.

Ethyl-[2-(1H-indol-3-yl)-ethyl]-carbamic acid ethyl ester (227g) The general procedure was followed with allyl-ethyl-carbamic acid ethyl ester (302 mg, 1.92 mmol), phenylhydrazine (208 mg, 1.92 mmol), Rh(acac)(CO)$_2$ (1.49 mg, 0.30 mol%) and XANTPHOS (33.3 mg, 3 mol%) to give ethyl-[2-(1H-indol-3-yl)-ethyl]-carbamic acid ethyl ester (255 mg, 51 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) δ = 1.12 (bs, 3H, CH$_3$); 1.27 (bs, 3H, CH$_3$); 3.01 (bs, 2H, CH$_2$); 3.32, 3.27 (2bs, 2H, CH$_2$); 3.53 (bs, 2H, CH$_2$); 4.14, 4.16 (2bs, 2H, CH$_2$); 6.99 (s, 1H, CH); 7.13 (dd, 1H, J = 7.2 Hz, J = 7.2 Hz, CH); 7.19 (dd, 1H, J = 7.7 Hz, J = 7.2 Hz, CH); 7.35 (d, 1H, J = 7.7 Hz, CH); 7.65 (bs, 1H, CH); 8.27 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) δ = 13.4, 13.9 (CH$_3$); 14.7 (CH$_3$); 24.9, 24.3 (CH$_2$); 26.9 (CH$_2$); 42.3 (CH$_2$); 47.3, 48.1 (CH$_2$); 61.0 (CH$_3$); 111.1 (CH); 113.2 (C); 118.7 (CH); 119.2 (CH); 121.9 (2xCH); 127.4 (C); 136.3 (C); 156.3 (C). IR: $\tilde{n}$ [cm^{-1}] = 3318 (vs); 2977 (vs); 1697 (vs); 1486 (vs); 1280 (vs); 1193 (vs); 1095 (s); 1012 (s); 742 (s). HRMS found [M]$^+$ 260.1490, C$_{15}$H$_{20}$N$_2$O$_2$ requires [M]$^+$ 260.1525.

N-Ethyl-N-[2-(1H-indol-3-yl)-ethyl]-benzamide (227h). The general procedure was followed with *N*-allyl-*N*-ethyl-benzamide (324 mg, 1.71 mmol), phenylhydrazine (185 mg, 1.71 mmol), Rh(acac)(CO)$_2$ (1.32 mg, 0.30 mol%) and XANTPHOS (29.7 mg, 3 mol%) to give N-ethyl-N-[2-(1H-indol-3-yl)-ethyl]-benzamide (160 mg, 32). ^{1}H-NMR: (CDCl$_3$, 500 MHz) δ = 1.27 (bs, 3H, CH$_3$); 2.94, 3.19 (2xbs, 2H, CH$_2$); 3.20, 3.51 (2xbs, 2H, CH$_2$); 3.67, 3.81 (2bs, 2H, CH$_2$); 6.83-7.78 (10H, 10xCH); 8.24 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) δ = 25.0, 23.4 (CH$_2$); 44.3, 39.9 (CH$_2$); 45.6, 49.3 (CH$_2$); 111.2 (CH); 118.8 (CH); 119.3 (CH); 126.3 (2xCH); 126.3 (2xCH); 128.4 (2xCH); 129.1, 129.0 (CH); 137.1, 136.2 (C). IR: $\tilde{n}$ [cm^{-1}] = 3181 (s); 2929 (s); 1606 (vs); 1596 (vs); 1467 (m); 1455 (s); 1319 (m); 748 (s). HRMS found [M]$^+$ 292.1539, C$_{19}$H$_{20}$N$_2$O requires [M]$^+$ 292.1575.

10.4 EXPERIMENTS IN CHAPTER 3

10.4.1 SYNTHESIS OF AMINOOLEFINES

N,N-Diethyl-1-phenylprop-2-en-1-amine (301g). NaH (431 mg, 10.7 mmol) was suspended in dry Et_2O (60 ml). A solution of cinnamyl alcohol (14.5 g, 107 mmol) in dry Et_2O (20 ml) was added dropwise followed by 2,2,2 trichloroacetonitrile (15.6 g, 107 mmol) at -10°C. The solvent was removed and the residue was taken up in MeOH/pentane (200 ml, 0.25wt% MeOH in pentane). The mixture was filtered through a pad of alumina and the solvent was removed to give cinnamyl 2,2,2-trichloroacetimidate (30.0 g, 100 %), which was used for the next step without purification. Cinnamyl 2,2,2-trichloroacetimidate (30.0 g, 107 mmol) in xylene (500 ml) was stirred over night under reflux. The solvent was removed to give 2,2,2-trichloro-N-(1-phenylallyl)acetamide (30.0 g, 100 %) without the need for purification. 2,2,2-Trichloro-N-(1-phenylallyl)acetamide (30.0 g, 107 mmol) in EtOH (100 ml) and NaOH solution (6M, 150 ml) was stirred for 40h at ambient temperature. The mixture was extracted with Et_2O. The solvent was removed and the residue was taken up in HCl-saturated Et_2O (100 ml). Filtration gave 1-phenylprop-2-en-1-amine hydrochloride (11.6 g, 64 %), which was not purified for the next step. 1-Phenylprop-2-en-1-amine hydrochloride (1.02 g, 6.0 mmol), EtBr (6.44 g, 60 mmol), 18-crown[6] (85 mg, 5 mol%) and K_2CO_3 (2.08 g, 15 mmol) in dry CH_3CN (30 ml) were stirred for 12h under reflux. The mixture was filtered through a pad of alumina and the solvent was removed to give N,N-diethyl-1-phenylprop-2-en-1-amine (1.0 g, 89 %) without further purification. ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.00 (t, 6H, J = 7.1 Hz, 2xCH$_3$); 2.54-2.63 (4H, 2xCH$_2$); 4.15 (d, 1H, J = 8.7 Hz, CH); 5.15 (d, 1H, J = 10.2 Hz, C*H*H); 5.20 (d, 1H, J = 17.2 Hz, CH*H*); 5.97 (ddt, 1H, J = 8.0 Hz, J = 10.2 Hz, J = 17.2 Hz, CH); 7.25 (d, 1H, J = 7.2 Hz, CH); 7.32 (dd, 2H, J = 7.2 Hz, J = 7.5 Hz, 2xCH); 7.40 (d, 2H, J = 7.4 Hz, 2xCH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) d = 11.6 (2xCH$_3$); 42.9 (2xCH$_2$); 69.4 (CH); 116.0 (CH$_2$); 126.7 (CH); 127.8 (2xCH); 128.2 (2xCH); 139.5 (CH); 143.1 (C). IR: $\tilde{n}$ [cm^{-1}] = 2969 (s); 2871 (m); 2815 (m); 1450 (s); 1382 (m); 1110 (s); 997 (m); 919 (s); 755 (m); 732 (s); 700 (s).

rac-1-(1-Phenylallyl)piperidine (rac-301h). Cinnamyl ethyl carbonate (2.56 g, 12.4 mmol), piperidine (7.68 g, 37.3 mmol), [Ir(cod)Cl]$_2$ (167 mg, 2 mol%) and P(OPh)$_3$ (290 mg, 8 mol%) in dry EtOH (25 ml) were stirred for 2h under reflux. The solvent was

evaporated and the residue was chromatographed (silica, 2.5 vol% EtOAc in cyclohexane) to give *rac*-1-(1-phenylallyl)piperidine (2.02 g, 81 %). Analytical data fits with literature[108].

(-)-1-(1-Phenylallyl)piperidine ((-)-301h). Cinnamyl ethyl carbonate (2.56 g, 12.4 mmol), piperidine (7.68 g, 37.3 mmol), [Ir(cod)Cl]$_2$ (167 mg, 2 mol%) and *O,O'*-(*R*)-(1,1'-dinaphthyl-2,2'-diyl)-*N,N'*-di-(*R,R*)-1-phenylethylphosphoramidite (134 mg, 2 mol%) in dry THF (12 ml) were stirred over night at ambient temperature. The solvent was evaporated and the residue was chromatographed (silica, 2.5 vol% EtOAc in cyclohexane) to give *(-)*-1-(1-phenylallyl)piperidine (2.38 g, 95 %, 96 %*ee*[109]). Analytical data fits with literature[108].

(+)-1-(1-Phenylallyl)piperidine ((-)-301h). Cinnamyl ethyl carbonate (2.56 g, 12.4 mmol), piperidine (7.68 g, 37.3 mmol), [Ir(cod)Cl]$_2$ (167 mg, 2 mol%) and *O,O'*-(*S*)-(1,1'-dinaphthyl-2,2'-diyl)-*N,N'*-di-(*S,S*)-1-phenylethylphosphoramidite (134 mg, 2 mol%) in dry THF (12 ml) were stirred over night at ambient temperature. The solvent was evaporated and the residue was chromatographed (silica, 2.5 vol% EtOAc in cyclohexane) to give *(+)*-1-(1-phenylallyl)piperidine (2.38 g, 95 %, 96 %*ee*[109]). Analytical data fits with literature[108].

1-Cinnamylpiperidine (301i). Piperdine (7.91 g, 93 mmol), NEt$_3$ (10.3 g, 102 mmol) and DMAP (567 mg, 5 mol%) were dissolved in dry THF (100 ml). To this solution cinnamylchloride (15.5 g, 93 mmol) was added dropwise at 0°C and the resulting mixture was stirred for 3h at ambient temperatures. The precipitate was removed by filtration and the solvent was evaporated to give (*E*)-3-phenyl-1-(piperidin-1-yl)prop-2-en-1-one (18.9 g, 94 %) which is used for the next step without purification. LiAlH$_4$ (1.74 g, 46 mmol) was suspended in dry Et$_2$O (100 ml) and (*E*)-3-phenyl-1-(piperidin-1-yl)prop-2-en-1-one (18.0 g, 84 mmol) in dry Et$_2$O (50 ml) was added carefully. After stirring overnight at ambient temperatures the mixture was quenched with cool water until gas formation was not witnessed anymore. The precipitate was separated by filtration and the solvent was evaporated. The residue was purified by chromatography (silica, cyclohexane, EtOAc, NEt$_3$) to give 1-cinnamylpiperidine (6.55 g, 39%). Analytical data fits with literature[110].

1-(3-Phenylbut-3-enyl)piperidine (301j). Acetophenone (27.6 g, 230 mmol), piperidine (19.6 g, 230 mmol) and paraformaldehyde (35.2 g, 391 mmol) in dry EtOH (50 ml) were stirred for 1h under reflux. Hydrochloric acid (0.5 ml) was added and the mixture was filtered. The filtrate was concentrated and the product was colleted by filtration. The crude product was recrystallized from EtOH to give 1-phenyl-3-(piperidin-1-yl)propan-1-one (15.9 g,

[108] Ohmura, T.; Hartwig, J.F.; *J. Am. Chem. Soc.* **2002**, *124*, 15164-15165.
[109] Determined by HPLC with a Daicel Chiracel OJ
[110] Katritzky, A.R.; Yao, J.; Qi, M.; *J. Org. Chem.* **1998**, *63*, 5232-5234.

32 %). Methyl triphenyl phosphonium bromide (28.6 g, 80.2 mmol) was suspended in dry THF (300 ml). At 0°C n-butyllithium solution (2.5M in hexane, 32 ml) was added and the mixture was stirred for 1h at ambient temperature. 1-Phenyl-3-(piperidin-1-yl)propan-1-one (15.8 g, 72.9 mmol) was added and the mixture was stirred for an additional hour. The solvent was evaporated and the crude product was distilled (75°C, $2 \cdot 10^{-2}$ mbar) to give 1-(3-phenylbut-3-enyl)piperidine (8.61 g, 55 %). ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.41 (bs, 2H, CH$_2$); 1.55-1.60 (4H, 2xCH$_2$); 2.40-2.44 (6H, 3xCH$_2$); 2.71 (dd, 2H, J = 8.0 Hz, J = 8.0 Hz, CH$_2$); 5.07 (s, 1H, CHH); 5.29 (s, 1H, CHH); 7.24 (dd, 1H, J = 7.2 Hz, J = 7.2 Hz, CH); 7.30 (dd, 2H, J = 7.2 Hz, J = 7.7 Hz, 2xCH); 7.40 (d, 2H, J = 7.7 Hz, 2xCH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 24.4 (CH$_2$); 26.0 (2xCH$_2$); 32.9 (CH$_2$); 54.6 (2xCH$_2$); 58.7 (CH$_2$); 112.9 (CH$_2$); 126.0 (2xCH); 127.3 (CH); 128.2 (2xCH); 141.0 (C); 146.8 (C). IR: $\tilde{n}$ [cm^{-1}] = 2933 (vs); 2852 (s); 2798 (s); 1442 (s); 1155 (s); 1122 (s); 892 (s); 775 (s); 703 (s); 412 (vs); 404 (vs). HRMS found [M+H]$^+$ 216.1776, C$_{15}$H$_{21}$N$_2$ requires [M+H]$^+$, 216.1752. Elementary analysis found C 83.13%, H 9.88%, N 6.20%, C$_{15}$H$_{21}$N$_2$ requires C 83.67%, H 9.83%, N 6.50%.

N,N-Diethyl-3-methyl-1-phenylbut-3-en-1-amine (301k). A solution of benzaldehyde (79.7 g, 750 mmol) in Et$_2$O (250 ml) was added to a solution of EtNH$_2$ (33.8 g, 750 mmol) in Et$_2$O (250 ml) at 0°C. MgSO$_4$ (50 g) was added and the mixture was stirred for 1h at ambient temperature followed by filtration. The solvent was removed and the residue was distilled (86°C, 10 mbar) to give N-benzylideneethanamine (78.8 g, 79 %). At 0°C a solution of methallylic chloride (10.8 g, 119 mmol) and N-benzylideneethanamine (10.6 g, 79 mmol) in dry THF (50 ml) was added to a suspension of zinc dust (10.4 g, 158 mmol) in dry THF (100 ml). The mixture was stirred for 4h at ambient temperature and was then filtered through a sintered glass filter. Saturated ammonium hydrochloride solution was added to the filtrate and the pH was adjusted to 10 with NaOH solution. The mixture was extracted with EtOAc and the solvent was removed to give N-ethyl-3-methyl-1-phenylbut-3-en-1-amine (15.0 g, 100 %). A suspension of N-ethyl-3-methyl-1-phenylbut-3-en-1-amine (4.4 g, 23 mmol), EtBr (3.8 g, 35 mmol) and K$_2$CO$_3$ (4.8 g, 35 mmol) in dry CH$_3$CN (25 ml) was stirred for 12h under reflux. The mixture was filtered through a pad of alumina. The solvent was removed and the residue was chromatographed (silica, EtOAc, cyclohexane, NEt$_3$) to give N,N-diethyl-3-methyl-1-phenylbut-3-en-1-amine (3.84 g, 77 %). ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.06 (t, 6H, J = 7.1 Hz, 2xCH$_3$); 1.70 (s, 3H, CH$_3$); 2.33-2.73 (6H, 3xCH$_2$); 3.94 (dd, 1H, J = 5.8 Hz, J = 5.8 Hz, CH); 4.63 (s, 1H, CHH); 4.71 (s, 1H, CHH); 7.24-7.34 (5H, 5xCH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 13.0 (2xCH$_3$); 22.5 (CH$_3$); 40.5 (CH$_2$); 43.0 (2xCH$_2$); 62.2 (CH); 112.3 (CH$_2$); 126.6 (CH); 127.6 (2xCH); 128.5 (2xCH); 140.8 (C); 143.3 (C). IR: $\tilde{n}$ [cm^{-1}] =

3025 (m); 2967 (vs); 2813 (s); 1646 (m); 1492 (m); 1373 (s); 1295 (m); 1201 (m); 1029 (m); 887 (s); 700 (vs) Elementary analysis found C 82.20%, H 10.68%, N 6.10%, $C_{15}H_{23}N$ requires C 82.89%, H 10.67%, N 6.44%.

N,N-Diethyl-1-phenylbut-3-en-1-amine (301l). A solution of benzaldehyde (79.7 g, 750 mmol) in Et_2O (250 ml) was added to a solution of $EtNH_2$ (33.8 g, 750 mmol) in Et_2O (250 ml) at 0°C. $MgSO_4$ (50 g) was added and the mixture was stirred for 1h at ambient temperature. The mixture was filtered, the solvent was removed and the residue was distilled (86°C, 10 mbar) to give N-benzylideneethanamine (78.8 g, 79 %). At 0°C a solution of allylic bromide (15.5 g, 128 mmol) and N-benzylideneethanamine (11.4 g, 85.6 mmol) in dry THF (50 ml) is added to a suspension of zinc dust (10.4 g, 158 mmol) in dry THF (100 ml). The mixture was stirred for 4h at ambient temperature and was then filtered through a sintered glass filter. Saturated NH_4Cl solution was added to the filtrate and the pH was adjusted to 10 with NaOH. The mixture was extracted with EtOAc and the solvent was removed to give N-ethyl-1-phenylbut-3-en-1-amine (15.0 g, 100 %) without further purification. A suspension of N-ethyl-1-phenylbut-3-en-1-amine (5.0 g, 29 mmol), EtBr (4.6 g, 43 mmol) and K_2CO_3 (5.9 g, 43 mmol) in dry CH_3CN (25 ml) was stirred for 12h under reflux. The mixture was filtered through a pad of alumina and the solvent was removed to give N,N-diethyl-1-phenylbut-3-en-1-amine (4.38 g, 76 %) without further purification. ^{1}H-NMR: ($CDCl_3$, 400 MHz) d = 1.02 (t, 6H, J = 7.1 Hz, 2xCH_3); 2.37-2.70 (6H, 3xCH_2); 3.72 (dd, 1H, J = 5.7 Hz, J = 5.7 Hz, CH); 4.92 (d, 1H, J = 10.3 Hz, CHH); 4.99 (d, 1H, J = 17.1 Hz, CHH); 5.66 (ddt, 1H, J = 7.0 Hz, J = 10.3 Hz, J = 17.1 Hz, CH); 7.22-7.32 (5H, 5xCH). ^{13}C-NMR: ($CDCl_3$, 100 MHz) d = 12.5 (2xCH_3); 37.0 (CH_2); 42.9 (2xCH_2); 64.3 (CH); 115.9 (CH_2); 126.6 (CH); 127.8 (2xCH); 128.5 (2xCH); 126.4 (CH); 141.2 (C). IR: $\tilde{n}$ [cm^{-1}] = 2969 (s); 2813 (m); 1639 (w); 1452 (m); 1382 (m); 1199 (m); 995 (w); 765 (w). Elementary analysis found C 82.53%, H 10.87%, N 6.84%, $C_{14}H_{21}N$ requires C 82.70%, H 10.41%, N 6.89%.

1-Methyl-4-methylene-piperidine (301m). NaH (11.9 g, 297 mmol) is suspended in dry DMSO (100 ml) and is stirred for 45 min at 75 °C. The solution is cooled to 0°C. To this mixture a solution of methyl-triphenyl-phosphonium bromide (106 g, 297 mmol) in dry DMSO (200 ml) is added and is stirred for 10min at ambient temperature. 1-Methyl-piperidin-4-one (30.5 g, 270 mmol) was added and the mixture was stirred for 30 min at ambient temperature. The product was distilled directly from the reaction mixture (bp:

75 °C/100 mbar) to obtain 1-methyl-4-methylene-piperidine (25.3 g, 84%). Analytical data fits with literature[111].

10.4.2 TANDEM HYDROFORMYLATION / HYDRAZONE FORMATION

Dimethyl-[4-(phenyl-hydrazono)-butyl]-amine (303a). In a typical procedure *N,N*-dimethylprop-2-en-1-amine (679 mg, 7.97 mmol), phenylhydrazine (862 mg, 7.97 mmol), Rh(acac)(CO)$_2$ (6.2 mg, 0.3 mol%) and XANTPHOS (69 mg, 0.15 mol%) in anhydrous THF (6.1 g, 10 wt% olefin) were filled in an autoclave. The autoclave was pressurized with 10bar H$_2$ and 10bar CO. After stirring for 68 hours (The reaction is stirred magnetically. With a stirrer that mixes gas phase and liquid phase intensively, the reaction time can be reduced by far to our experience) at 70°C the solvent was removed to give dimethyl-[4-(phenyl-hydrazono)-butyl]-amine (1.64 g, 100 %) without further purification. Analytical data was obtained from an inseparable mixture of *E/Z* isomers. ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.69-1.72 (2H, CH$_2$); 2.22 (s, 3H, CH$_3$); 2.28-2.33 (4H, 2xCH$_2$); 6.52-6.81 (1H, CH); 6.97-7.03 (3H, 3xCH); 7.20-7.23 (2H, 2xCH). Major isomer: ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 23.6 (CH$_2$); 29.8 (CH$_2$); 44.8 (2xCH$_3$); 56.4 (CH$_2$); 112.2 (2xCH); 118.8 (CH$_2$); 128.8 (2xCH); 140.6 (CH); 146.1 (C). Minor isomer: ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 23.6 (CH$_2$); 24.8 (CH$_2$); 45.3 (2xCH$_3$); 58.9 (CH$_2$); 112.2 (2xCH); 119.0 (CH$_2$); 128.8 (2xCH); 140.1 (CH); 145.3 (C). IR: $\tilde{n}$ [cm^{-1}] = 2943 (vs), 2779 (s), 1603 (vs), 1496 (vs), 1259 (vs), 1115 (s), 750 (vs), 694 (vs). HRMS found M$^+$ 205.1580, C$_{12}$H$_{19}$N$_3$ requires M$^+$, 205.1579. Elementary analysis found C 69.67%, H 9.14%, N 19.72%, C$_{12}$H$_{19}$N$_3$ requires C 70.20%, H 9.33%, N 20.47%.

N-Phenyl-N'-(4-piperidin-1-yl-butylidene)-hydrazine (303b). The general procedure for the tandem hydroformylation / hydrazone formation was followed with 1-allyl-piperidine (823 mg, 6.57 mmol), phenylhydrazine (710 mg, 6.57 mmol), Rh(acac)(CO)$_2$ (5 mg, 0.3 mol%) and XANTPHOS (57 mg, 0.15 mol%) to give N-phenyl-N'-(4-piperidin-1-yl-butylidene)-hydrazine (1.57 g, 97 %) without further purification. Analytical data was obtained from the inseparable mixture of *E/Z* isomers. ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.09-1.16 (2H, CH$_2$); 1.45-1.74(7H, 3xCH$_2$, CH); 2.28-2.36 (7H, 3xCH$_2$, CH); 6.52-7.36 (7H, 6xCH, NH). Major isomer: ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 22.9 (CH$_2$); 24.0 (CH$_2$); 24.2 (CH$_2$); 25.7 (2xCH$_2$); 54.3 (2xCH$_2$); 58.5 (CH$_2$); 112.2 (2xCH); 119.0 (CH); 128.9 (2xCH); 140.7 (CH); 145.3 (C). Minor isomer: ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 23.4 (CH$_2$); 24.2 (CH$_2$); 24.8 (CH$_2$); 25.6 (2xCH$_2$); 54.0 (2xCH$_2$); 56.7 (CH$_2$); 112.6 (2xCH); 119.3 (CH);

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[111] Della, E.W.; Smith, P.A.; *J. Org. Chem.* **1999**, *64*, 1798-1806.

128.9 (2xCH); 140.6 (CH); 145.4 (C). IR: $\tilde{n}$ [cm^{-1}] = 2935 (vs), 2779 (s), 1601 (vs), 1496 (vs), 1257 (vs), 1115 (s), 748 (vs), 694 (vs). HRMS found [M+H]$^+$ 246.1987, C$_{15}$H$_{25}$N$_3$ requires [M+H]$^+$, 246.1970.

N-(4-Methoxy-phenyl)-N'-(4-piperidin-1-yl-butylidene)-hydrazine (303c). The general procedure for the tandem hydroformylation / hydrazone formation was followed with 1-allyl-piperidine (485 mg, 3.87 mmol), 4-methoxy-phenylhydrazine (538 mg, 3.87 mmol), Rh(acac)(CO)$_2$ (3 mg, 0.3 mol%) and XANTPHOS (34 mg, 0.15 mol%) to give N-(4-Methoxy-phenyl)-N'-(4-piperidin-1-yl-butylidene)-hydrazine (989 mg, 93 %) without further purification. Analytical data was obtained from the inseparable mixture of E/Z isomers. Major isomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.43 (bs, 2H, CH$_2$); 1.55-1.60 (4H, 2xCH$_2$); 1.71-1.76 (2H, CH$_2$); 2.25-2.38 (8H, 4xCH$_2$); 3.74 (s, 3H, CH$_3$); 6.79 (d, 2H, J = 9.0 Hz, 2xCH); 6.91 (d, 2H, J = 9.0 Hz, 2xCH); 7.04 (t, 1H, J = 5.2 Hz, CH); 8.10 (bs, 1H, NH). Minor isomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.43 (bs, 2H, CH$_2$); 1.55-1.60 (4H, 2xCH$_2$); 1.71-1.76 (2H, CH$_2$); 2.25-2.38 (8H, 4xCH$_2$); 3.75 (s, 3H, CH$_3$); 6.48 (t, 1H, J = 6.0 Hz, CH); 6.81 (d, 2H, J = 9.0 Hz, 2xCH); 6.99 (d, 2H, J = 9.0 Hz, 2xCH); 8.10 (bs, 1H, NH). Major isomer: ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 23.2 (CH$_2$); 24.4 (CH$_2$); 25.9 (2xCH$_2$); 30.3 (CH$_2$); 54.6 (2xCH$_2$); 55.7 (CH$_3$); 58.8 (CH$_2$); 114.0 (2xCH); 114.7 (2xCH); 139.6 (C); 140.7 (CH); 153.5 (C). Minor isomer: ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 23.7 (CH$_2$); 24.3 (CH$_2$); 25.8 (2xCH$_2$); 30.3 (CH$_2$); 54.3 (2xCH$_2$); 55.7 (CH$_3$); 57.2 (CH$_2$); 114.2 (2xCH); 114.6 (2xCH); 140.0 (C); 140.1 (CH); 153.5 (C). IR: $\tilde{n}$ [cm^{-1}] = 3307 (s), 2935 (vs), 2767 (s), 1514 (vs), 1234 (vs), 1115 (s), 823 (vs). HRMS found M$^+$ 275.1994 C$_{16}$H$_{25}$N$_3$O requires M$^+$, 275.1998.

4-[N'-(4-Dimethylamino-butylidene)-hydrazino]-benzonitrile (303d). The general procedure for the tandem hydroformylation / hydrazone formation was followed with N,N-dimethylprop-2-en-1-amine (399 mg, 4.69 mmol), 4-cyano-phenylhydrazine (624 mg, 4.69 mmol), Rh(acac)(CO)$_2$ (3.6 mg, 0.3 mol%) and XANTPHOS (41 mg, 0.15 mol%) to give 4-[N'-(4-dimethylamino-butylidene)-hydrazino]-benzonitrile (973 mg, 90 %) without further purification. Analytical data was obtained from the inseparable mixture of E/Z isomers. Major isomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.69-1.78 (2H, CH$_2$); 2.21-2.39 (10H, CH$_3$, 2xCH$_2$); 6.64 (t, 1H, J = 6.9 Hz, CH); 6.97 (d, 2H, J = 8.7 Hz, 2xCH); 7.45 (d, 2H, J = 8.7 Hz, 2xCH); 10.5 (bs, 1H, NH). Minor isomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.69-1.78 (2H, CH$_2$); 2.21-2.39 (10H, CH$_3$, 2xCH$_2$); 6.97 (d, 2H, J = 8.7 Hz, 2xCH); 7.16 (t, 1H, J = 5.2 Hz, CH); 7.45 (d, 2H, J = 8.7 Hz, 2xCH); 7.80 (bs, 1H, NH). Major isomer: ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 23.5 (CH$_2$); 30.0 (CH$_2$); 44.8 (2xCH$_3$); 56.0 (CH$_2$); 100.4

(C); 112.2 (2xCH); 120.4 (C); 133.6 (2xCH); 143.3 (CH); 149.7 (C). Minor isomer: ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 24.1 (CH$_2$); 24.8 (CH$_2$); 45.4 (2xCH$_3$); 59.0 (CH$_2$); 101.1 (C); 112.1 (2xCH); 120.1 (C); 133.5 (2xCH); 143.6 (CH); 148.4 (C). IR: $\tilde{n}$ [cm^{-1}] = 3284 (s), 2945 (vs), 2820 (s), 2218 (vs), 1612 (s), 1533 (vs), 1271 (vs), 1167 (s), 833 (vs). HRMS found M$^+$ 230.1558 C$_{13}$H$_{18}$N$_4$ requires M$^+$, 230.1531.

N-(4-Nitro-phenyl)-N′-(4-piperidin-1-yl-butylidene)-hydrazine (303e). The general procedure for the tandem hydroformylation / hydrazone formation was followed with 1-allyl-piperidine (458 mg, 3.66 mmol), 4-nitro-phenylhydrazine (560 mg, 3.66 mmol), Rh(acac)(CO)$_2$ (2.8 mg, 0.3 mol%) and XANTPHOS (32 mg, 0.15 mol%) to give N-(4-nitro-phenyl)-N'-(4-piperidin-1-yl-butylidene)-hydrazine (845 mg, 80 %) without further purification. Analytical data was obtained from the inseparable mixture of E/Z isomers. Major isomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.37-1.44 (2H, CH$_2$); 1.53-1.58 (4H, 2xCH$_2$); 1.71-1.80 (2H, CH$_2$); 2.24-2.38 (8H, 4xCH$_2$); 7.04 (d, 2H, J = 9.5 Hz, 2xCH); 7.20 (t, 1H, J = 5.2 Hz, CH); 8.09 (d, 2H, J = 9.5 Hz, 2xCH); 9.75 (bs, 1H, NH). Minor isomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.48-1.52 (2H, CH$_2$); 1.60-1.64 (4H, 2xCH$_2$); 1.71-1.80 (2H, CH$_2$); 2.24-2.38 (8H, 4xCH$_2$); 6.70 (t, 1H, J = 6.7 Hz, CH); 6.95 (d, 2H, J = 9.4 Hz, 2xCH); 7.98 (bs, 1H, NH); 8.11 (d, 2H, J = 9.4 Hz, 2xCH). Major isomer: ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 24.0 (CH$_2$); 24.4 (2xCH$_2$); 26.0 (2xCH$_2$); 30.3 (CH$_2$); 54.0 (CH$_2$); 58.7 (CH$_2$); 111.6 (2xCH); 126.2 (2xCH); 136.9 (C); 145.1 (CH); 151.1 (C). Minor isomer: ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 24.0 (CH$_2$); 24.3 (2xCH$_2$); 25.6 (2xCH$_2$); 30.3 (CH$_2$); 54.6 (CH$_2$); 56.1 (CH$_2$); 111.1 (2xCH); 126.0 (2xCH); 136.9 (C); 145.4 (CH); 150.1 (C). IR: $\tilde{n}$ [cm^{-1}] = 3294 (s), 2935 (vs), 2802 (s), 1604 (s), 1504 (vs), 1274 (vs), 1109 (s), 841 (vs). HRMS found [M+H]$^+$ 291.1790 C$_{15}$H$_{22}$N$_4$O$_2$ requires M$^+$, 291.1821.

10.4.3 FIRST GENERATION PROTOCOL OF TANDEM HYDROFORMYLATION / FISCHER INDOLE SYNTHESIS

[2-(1H-Indol-3-yl)-ethyl]-dimethyl-amine (304a). In a typical procedure N,N-dimethylprop-2-en-1-amine (679 mg, 7.97 mmol), phenylhydrazine (862 mg, 7.97 mmol), Rh(acac)(CO)$_2$ (6 mg , 0.3 mol%) and XANTPHOS (69 mg, 1.5 mol%) in anhydrous THF (6.1 g, 10 wt% olefin) were filled in an autoclave. The autoclave was pressurized with 10bar H$_2$ and 10bar CO. After stirring for 3 days (The reaction is stirred magnetically. With a stirrer that mixes gas phase and liquid phase intensively, the reaction time can be reduced by far to our experience) at 70°C the solvent was evaporated and the residue was taken up in H$_2$SO$_4$ (30 ml, 4 wt% in water). After stirring the mixture for 2h

under reflux NH_3 (10 ml, 30 wt% in water) was added and the mixture was extracted with EtOAc. The solvent was evaporated to give [2-(1H-indol-3-yl)-ethyl]-dimethyl-amine (1.5 g, 100%) without further purification. Analytical data fits with literature[112].

3-(2-Piperidin-1-yl-ethyl)-1H-indole (304b). The first generation protocol was followed with 1-allyl-piperidine (823 mg, 6.57 mmol), phenylhydrazine (710 mg, 6.57 mmol), Rh(acac)(CO)$_2$ (5 mg, 0.3 mol%) and XANTPHOS (57 mg, 3 mol%) to give 3-(2-piperidin-1-yl-ethyl)-1H-indole (1.45 g, 97 %) without further purification. Analytical data fits with literature[113].

3-[2-(4-Phenyl-piperazin-1-yl)-ethyl]-1H-indole hydrochloride (304c). The first generation protocol was followed with 1-allyl-4-phenyl-piperazine (994 mg, 4.91 mmol), phenylhydrazine (531 mg, 4.91 mmol), Rh(acac)(CO)$_2$ (3.8 mg, 0.3 mol%) and XANTPHOS (42.6 mg, 3 mol%). The crude product was taken up in dry THF (10 ml) and HCl (20 ml, saturated in Et$_2$O) was added dropwise. The precipitate was collected by filtration giving 3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-1H-indole hydrochloride (1.44 g, 96 %). ^{1}H-NMR: (DMSO-d6, 500 MHz) d = 3.20-3.22 (8H, 4xCH$_2$); 3.66-3.68 (2H, CH$_2$); 3.81-3.84 (2H, CH$_2$); 6.86 (dd, 1H, J = 7.5 Hz, J = 7.5 Hz, CH); 7.00-7.03 (3H, 3xCH); 7.09 (dd, 1H, J = 7.5 Hz, J = 7.5 Hz, CH); 7.23-7.26 (4H, 3xCH, NH); 7.36 (d, 1H, J = 7.5 Hz, CH); 7.66 (d, 1H, J = 7.5 Hz, CH); 11.03 (s, 1H, NH); 11.48 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 19.5 (CH$_2$); 45.5 (2xCH$_2$); 50.5 (2xCH$_2$); 55.5 (CH$_2$); 109.2 (C); 111.6 (CH); 114.5 (CH); 116.06 (2xCH); 118.5 (CH); 120.1 (CH); 121.3 (CH); 123.2 (CH); 126.7 (C); 129.2 (2xCH); 136.3 (C); 149.6 (C). IR: $\tilde{n}$ [cm^{-1}] = 3415 (s); 3216 (s); 2427 (s); 1596 (s); 1494 (s); 1457 (vs); 1436 (s); 754 (vs); 692 (s). HRMS found [M]$^+$ 305.1868 C$_{20}$H$_{23}$N$_3$ requires M$^+$, 305.1892.

Ethyl 4-(2-(1H-indol-3-yl)ethyl)piperazine-1-carboxylate (304d). The first generation protocol was followed with 4-allyl-piperazine-1-carboxylic acid ethyl ester (329 mg, 1.66 mmol), Phenylhydrazine (179 mg, 1.66 mmol), Rh(acac)(CO)$_2$ (1.3 mg, 0.3 mol%) and XANTPHOS (14.4 mg, 3 mol%). The crude product was purified by chromatography (silica, EtOAc, cyclohexane, NEt$_3$) to give Ethyl 4-(2-(1H-indol-3-yl)ethyl)piperazine-1-carboxylate (468 mg, 94 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.27 (t, 3H, J = 7.0 Hz, CH$_3$); 2.52 (bs, 4H, 2xCH$_2$); 2.71 (t, 2H, J = 8.0 Hz, CH$_2$); 2.97 (t, 2H, J = 8.0 Hz, CH$_2$); 3.54 (bs, 4H, 2xCH$_2$); 4.15 (q, 2H, J = 7.0 Hz, CH$_2$); 7.00 (s, 1H, CH); 7.11 (dd, 1H, J = 7.1 Hz, J = 7.7 Hz, CH);

[112] Grina, J.A.; Ratcliff, M.R.; Stermitz, F.R.; *J. Org. Chem.* **1982**, *47*, 2648-2651.
[113] Lounasmaa, M.; Jokela, R.; *Tetrahedron* **1989**, *45*, 3975-3992.

7.18 (dd, 1H, J = 7.1 Hz, J = 8.0 Hz, CH); 7.33 (d, 1H, J = 8.0 Hz, CH); 7.60 (d, 1H, J = 7.7 Hz, CH); 8.34 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 14.6 (CH$_3$); 22.7 (CH$_2$); 43.6 (2xCH$_2$); 52.8 (2zCH$_2$); 59.1 (CH$_2$); 61.3 (CH$_2$); 111.1 (CH); 113.9 (C); 118.6 (CH); 119.1 (CH); 121.5 (CH); 121.8 (CH); 127.4 (C); 136.2 (C); 155.5 (C). IR: $\tilde{n}$ [cm^{-1}] = 3268 (w); 2979 (m); 2809 (m); 2485 (w); 1714 (s); 1481 (m); 767 (w). HRMS found [M+H]$^+$ 302.1847 C$_{17}$H$_{23}$N$_3$O$_2$ requires [M+H]$^+$, 302.1869.

3-(3-(piperidin-1-yl)propyl)-1H-indole (304e). The first generation protocol was followed with 1-(but-3-enyl)piperidine (574 mg, 4.13 mmol), phenylhydrazine (446 mg, 4.13 mmol), Rh(acac)(CO)$_2$ (3.2 mg, 0.3 mol%) and XANTPHOS (35.8 mg, 3 mol%) to give 3-(3-(piperidin-1-yl)propyl)-1H-indole (908 mg, 91 %) without further purification. ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.42 (bs, 2H, CH$_2$); 1.56-16.2 (4H, 2xCH$_2$); 1.89-1.97 (2H, CH$_2$); 2.39-2.43 (bs, 6H, 3xCH$_2$); 2.75 (t, 2H, J = 7.6 Hz, CH$_2$); 6.92 (s, 1H, CH); 7.08 (dd, 1H, J = 7.0 Hz, J = 7.8 Hz, CH); 7.16 (dd, 1H, J = 7.0 Hz, J = 8.1 Hz, CH); 7.31 (d, 1H, J = 8.1 Hz, CH); 7.59 (d, 1H, J = 7.8 Hz, CH); 8.37 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 23.1 (CH$_2$); 24.4 (CH$_2$); 25.9 (2xCH$_2$); 27.3 (CH$_2$); 54.9 (2xCH$_2$); 59.3 (CH$_2$); 111.0 (CH); 116.3 (C); 118.9 (CH); 121.1 (CH); 121.7 (CH); 127.5 (C); 136.3 (C). IR: $\tilde{n}$ [cm^{-1}] = 3218 (s); 2944 (vs); 2937 (vs); 2805 (s); 1455 (s); 1106 (vs); 781 (s); 732 (vs). HRMS found [M]$^+$ 242.1784 C$_{16}$H$_{22}$N$_2$ requires M$^+$, 242.1783.

Ethyl 4-(3-(1H-indol-3-yl)propyl)piperazine-1-carboxylate (304f). The first generation protocol was followed with ethyl 4-(but-3-enyl)piperazine-1-carboxylate (337 mg, 1.59 mmol), phenylhydrazine (172 mg, 1.59 mmol), Rh(acac)(CO)$_2$ (1.2 mg, 0.3 mol%) and XANTPHOS (13.8 mg, 3 mol%) to give ethyl 4-(3-(1H-indol-3-yl)propyl)piperazine-1-carboxylate (455 mg, 91 %) without further purification. ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.27 (t, 3H, J = 7.0 Hz, CH$_3$); 1.88-1.94 (2H, CH$_2$); 2.40-2.45 (6H, 3xCH$_2$); 2.78 (t, 2H, J = 7.5 Hz, CH2); 3.51 (bs, 4H, 2xCH$_2$); 4.16 (q, 2H, J = 7.0 Hz, CH$_2$); 6.93 (s, 1H, CH); 7.10 (dd, 1H, J = 7.2 Hz, J = 7.5 Hz, CH); 7.17 (dd, 1H, J = 7.5 Hz, J = 8.0 Hz, CH); 7.31 (d, 1H, J = 8.0 Hz, CH); 7.60 (d, 1H, J = 7.2 Hz, CH); 8.61 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 16.2 (CH$_3$); 24.4 (CH$_2$); 28.7 (CH$_2$); 45.2 (2xCH$_2$); 54.4 (2xCH$_2$); 59.8 (CH$_2$); 62.8 (CH$_2$); 112.7 (CH); 117.4 (C); 120.4 (2xCH); 122.8 (CH); 123.2 (CH); 129.0 (C); 137.9 (C); 157.1 (C). IR: $\tilde{n}$ [cm^{-1}] = 3324 (s); 2935 (s); 2809 (s); 1700 (vs); 1434 (vs); 1243 (vs); 1128 (vs); 740 (vs). HRMS found [M]$^+$ 315.1970 C$_{18}$H$_{25}$N$_3$O$_2$ requires M$^+$, 315.1947.

N,N-diethyl-2-(1H-indol-3-yl)-1-phenylethanamine (304g). The first generation protocol was followed with N,N-diethyl-1-phenylprop-2-en-1-amine (250 mg, 1.32 mmol),

phenylhydrazine (142 mg, 1.32 mmol), Rh(acac)(CO)$_2$ (0.34 mg, 1 mol%) and XANTPHOS (38 mg, 5 mol%). The crude product was purified by chromatography (silica, EtOAc, cyclohexane, NEt$_3$) to give *N*,*N*-diethyl-2-(1H-indol-3-yl)-1-phenylethanamine (327 mg, 85 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) *d* = 1.06-1.11 (6H, 2xCH$_3$); 2.50-2.55 (2H, CH$_2$); 2.78-2.84 (2H, CH$_2$); 3.18 (d, 1H, *J* = 9.9 Hz, CH*H*); 3.46 (d, 1H, *J* = 14.5 Hz, C*H*H); 4.10 (dd, 1H, *J* = 9.9 Hz, *J* = 14.5 Hz, CH); 6.56 (s, 1H, CH); 7.10-7.28 (8H, 8xCH); 7.61 (d, 1H, *J* = 7.7 Hz, CH); 7.99 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) *d* = 12.8 (2xCH$_3$); 28.3 (CH$_2$); 43.4 (2xCH$_2$); 64.8 (CH); 110.9 (CH); 113.7 (C); 118.6 (CH); 118.9 (CH); 121.5 (CH); 122.5 (CH); 126.5 (CH); 127.6 (2xCH); 127.8 (C); 128.8 (2xCH); 135.9 (C); 141.9 (C). IR: $\tilde{n}$ [cm^{-1}] = 3419 (m); 2967 (s); 1492 (m); 1455 (s); 740 (s); 700 (s). HRMS found [M+H]$^+$ 293.1986 C$_{20}$H$_{25}$N$_2$ requires [M+H]$^+$, 293.1939.

3-(2-Phenyl-2-(piperidin-1-yl)ethyl)-1H-indole ((*rac*)-304h). The first generation protocol was followed with *rac*-1-(1-phenylallyl)piperidine (661 mg, 3.3 mmol), phenylhydrazine (355 mg, 3.3 mmol), Rh(acac)(CO)$_2$ (8.5 mg, 1 mol%) and XANTPHOS (95 mg, 5 mol%). The crude product was purified by chromatography (silica, EtOAc, cyclohexane, NEt$_3$) to give 3-(2-phenyl-2-(piperidin-1-yl)ethyl)-1H-indole (540 mg, 54 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) *d* = 1.44 (bs, 2H, CH$_2$); 1.65 (bs, 4H, 2xCH$_2$); 2.57 (bs, 4H, 2xCH$_2$); 3.26 (d, 1H, *J* = 9.7 Hz, C*H*H); 3.54 (d, 1H, *J* = 4.5 Hz, CH*H*); 3.80 (dd, 1H, *J* = 4.5 Hz, *J* = 9.7 Hz, CH); 6.59 (s, 1H, CH); 7.13 (dd, 1H, *J* = 7.2 Hz, *J* = 7.7 Hz, CH); 7.18 (dd, 1H, *J* = 7.2 Hz, *J* = 7.7 Hz, CH); 7.24-7.30 (6H, 6xCH); 7.63 (d, 1H, *J* = 7.7 Hz, CH); 8.17 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) *d* = 26.2 (CH$_2$); 27.9 (2xCH$_2$); 29.8 (CH$_2$); 53.0 (2xCH$_2$); 72.4 (CH); 112.5 (CH); 115.0 (C); 120.2 (CH); 120.4 (CH); 123.0 (CH); 124.1 (CH); 128.3 (CH); 129.2 (2xCH); 129.3 (C); 130.5 (2xCH); 137.4 (C); 141.9 (C). IR: $\tilde{n}$ [cm^{-1}] = 3426 (s); 2929 (s); 2852 (s); 2798 (s); 1602 (s); 1492 (s); 1469 (s); 1454 (s); 1093 (s); 1068 (m); 1033 (m); 910 (s); 738 (s). HRMS found [M+H]$^+$ 305.2037 C$_{21}$H$_{25}$N$_2$ requires [M+H]$^+$, 305.2056.

3-((+)-2-Phenyl-2-(piperidin-1-yl)ethyl)-1H-indole ((+)-304h). The title compound was obtained with 95 %*ee*[109]. ^{1}H-NMR: (CDCl$_3$, 500 MHz) *d* = 1.44 (bs, 2H, CH$_2$); 1.65 (bs, 4H, 2xCH$_2$); 2.57 (bs, 4H, 2xCH$_2$); 3.26 (d, 1H, *J* = 9.7 Hz, C*H*H); 3.54 (d, 1H, *J* = 4.5 Hz, CH*H*); 3.80 (dd, 1H, *J* = 4.5 Hz, *J* = 9.7 Hz, CH); 6.59 (s, 1H, CH); 7.13 (dd, 1H, *J* = 7.2 Hz, *J* = 7.7 Hz, CH); 7.18 (dd, 1H, *J* = 7.2 Hz, *J* = 7.7 Hz, CH); 7.24-7.30 (6H, 6xCH); 7.63 (d, 1H, *J* = 7.7 Hz, CH); 8.17 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) *d* = 26.2 (CH$_2$); 27.9 (2xCH$_2$); 29.8 (CH$_2$); 53.0 (2xCH$_2$); 72.4 (CH); 112.5 (CH); 115.0 (C); 120.2 (CH); 120.4

(CH); 123.0 (CH); 124.1 (CH); 128.3 (CH); 129.2 (2xCH); 129.3 (C); 130.5 (2xCH); 137.4 (C); 141.9 (C). $[a]$ = +59.6° (c=1.00, CH_2Cl_2).

3-((-)-2-Phenyl-2-(piperidin-1-yl)ethyl)-1H-indole ((-)-304h). The title compound was obtained with 95 %ee[109]. ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.44 (bs, 2H, CH_2); 1.65 (bs, 4H, 2xCH_2); 2.57 (bs, 4H, 2xCH_2); 3.26 (d, 1H, J = 9.7 Hz, CHH); 3.54 (d, 1H, J = 4.5 Hz, CHH); 3.80 (dd, 1H, J = 4.5 Hz, J = 9.7 Hz, CH); 6.59 (s, 1H, CH); 7.13 (dd, 1H, J = 7.2 Hz, J = 7.7 Hz, CH); 7.18 (dd, 1H, J = 7.2 Hz, J = 7.7 Hz, CH); 7.24-7.30 (6H, 6xCH); 7.63 (d, 1H, J = 7.7 Hz, CH); 8.17 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) d = 26.2 (CH_2); 27.9 (2xCH_2); 29.8 (CH_2); 53.0 (2xCH_2); 72.4 (CH); 112.5 (CH); 115.0 (C); 120.2 (CH); 120.4 (CH); 123.0 (CH); 124.1 (CH); 128.3 (CH); 129.2 (2xCH); 129.3 (C); 130.5 (2xCH); 137.4 (C); 141.9 (C).

2-phenyl-3-(2-(piperidin-1-yl)ethyl)-1H-indole (304i). The first generation protocol was followed with 1-cinnamylpiperdine (313 mg, 1.56 mmol), phenylhydrazine (168 mg, 1.56 mmol), Rh(acac)$(CO)_2$ (2 mg, 0.5 mol%) and BIPHEPHOS (122 mg, 10 mol%). The crude product was purified by chromatography (silica, cyclohexane, EtOAc, NEt_3) to give 2-phenyl-3-(2-(piperidin-1-yl)ethyl)-1H-indole (300 mg, 60%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.46 (bs, 2H, CH_2); 1.63 (bs, 4H, 2xCH_2); 2.52 (bs, 4H, 2xCH_2); 2.68 (t, 2H, J = 8.5 Hz, CH_2); 3.12 (t, 2H, J = 8.5 Hz, CH_2); 7.14 (dd, 1H, J = 7.1 Hz, J = 7.0 Hz, CH); 7.20 (dd, 1H, J = 7.1 Hz, J = 7.7 Hz, CH); 7.34-7.37 (2H, 2xCH); 7.44 (dd, 2H, J = 8.0 Hz, J = 8.0 Hz, 2xCH); 7.56 (d, 2H, J = 8.0 Hz, 2xCH); 7.65 (d, 1H, J = 8.0 Hz, CH); 8.31 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) d = 22.1 (CH_2); 24.4 (CH_2); 25.9 (2xCH_2); 54.6 (2xCH_2); 60.0 (CH_2); 110.8 (CH); 111.2 (C); 119.1 (CH); 119.5 (CH); 122.2 (CH); 127.5 (CH); 127.9 (2xCH); 128.8 (2xCH); 129.2 (C); 133.2 (C); 134.7 (C); 135.9 (C). Substitution pattern on indole ring confirmed by 1D-NOESY and gCOSY. IR: $\tilde{n}$ [cm^{-1}] = 3405 (m) 2931 (s), 1602 (s), 1456 (s), 1261 (s), 1101 (s), 739 (vs), 696 (vs). HRMS found [M+H]$^+$ 305.1991 $C_{21}H_{27}N_2$ requires [M+H]$^+$, 305.1974.

3-(1-Phenyl-3-(piperidin-1-yl)propyl)-1H-indole (304j). The first generation protocol was followed with 1-(3-phenylbut-3-enyl)piperidine (676 mg, 3.14 mmol), phenylhydrazine (340 mg, 3.14 mg) and Rh(acac)$(CO)_2$ (8.1 mg, 1 mol%). The crude product was purified by chromatography (silica, EtOAc, cyclohexane, NEt_3) to give 3-(1-phenyl-3-(piperidin-1-yl)propyl)-1H-indole (414 mg, 41 %). ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.45 (s, 2H, CH_2); 1.60 (s, 4H, 2xCH_2); 2.21-2.45 (8H, 4xCH_2); 4.22 (t, 1H, J = 7.1 Hz, CH); 7.01 (dd, 1H, J = 7.2 Hz, J = 8.0 Hz, CH); 7.03 (s, 1H, CH); 7.13 (d, 1H, J = 8.2 Hz, CH); 7.17 (d, 1H,

J = 8.2 Hz, CH); 7.25 (dd, 2H, J = 7.2 Hz, J = 7.5 Hz, 2xCH); 7.30-7.32 (3H, 3xCH); 7.46 (d, 1H, J = 8.0 Hz, CH); 8.38 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 24.5 (CH$_2$); 26.0 (2xCH$_2$); 33.3 (CH$_2$); 41.0 (CH); 54.7 (2xCH$_2$); 57.9 (CH$_2$); 111.0 (CH); 119.1 (CH); 119.4 (CH); 120.1 (C); 121.0 (CH); 121.8 (CH); 125.9 (CH); 127.0 (C); 127.8 (2xCH); 128.2 (2xCH); 136.5 (C); 145.3 (C). IR: $\tilde{n}$ [cm^{-1}] = 3399 (s); 2952 (m); 1666 (s); 1650 (s); 1529 (vs); 1471 (s); 1274 (s); 1095 (s); 835 (m); 804 (s). HRMS found [M+H]$^+$ 318.2097 C$_{22}$H$_{25}$N$_2$ requires [M+H]$^+$, 318.2098.

N,N-Diethyl-3-(1H-indol-3-yl)-1-phenylbutan-1-amine (304k). The first generation protocol was followed with N,N-diethyl-3-methyl-1-phenylbut-3-en-1-amine (678 mg, 3.12 mmol), Phenylhydrazine (337 mg, 3.12 mmol) and Rh(acac)(CO)$_2$ (8 mg, 1 mol%). The crude product was purified by chromatography (silica, EtOAc, cyclohexane, NEt$_3$) to give N,N-diethyl-3-(1H-indol-3-yl)-1-phenylbutan-1-amine (511 mg, 51 %). Analytical data was obtained from the inseparable mixture of diastereomers: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.03, 1.10 (t, 6H, J = 7.0 Hz, 2xCH$_3$); 1.41, 1.45 (d, 3H, J = 6.8 Hz, CH$_3$); 2.07-2.25 (1H, CH); 2.33-2.43, 2.69-2.80 (4H, 2xCH$_2$); 2.54-2.61, 2.96-3.05 (2H, CH$_2$); 3.77, 3.93 (dd, 1H, J = 5.8 Hz, J = 9.0 Hz, CH); 6.91 (s, 1H, CH); 7.12-7.64 (9H, *9xCH*); 8.36, 8.44 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 12.8, 12.9 (2xCH$_3$); 20.6, 22.5 (CH$_3$); 27.5, 27.9 (CH); 40.0, 40.7 (CH$_2$); 43.0, 43.2 (2xCH$_2$); 61.8, 62.3 (CH); 111.0, 111.1 (CH); 118.6 (CH); 119.2, 119.3 (CH); 119.9, 120.3 (CH); 121.4 (CH); 122.6 (C); 126.5 (C); 126.6, 126.8 (CH); 127.7, 127.8 (2xCH); 128.7, 128.9 (2xCH); 136.3, 136.4 (C); 140.8, 141.0 (C). IR: $\tilde{n}$ [cm^{-1}] = 3419 (s); 2058 (m); 2965 (s); 1670 (m); 1600 (m); 1492 (s); 1455 (s); 1226 (m); 908 (s); 736 (vs). HRMS found [M]$^+$ 320.2277 C$_{22}$H$_{28}$N$_2$ requires [M]$^+$, 320.2253.

N,N-Diethyl-3-(1H-indol-3-yl)-1-phenylpropan-1-amine (304l). The first generation protocol was followed with N,N-diethyl-1-phenylbut-3-en-1-amine (332 mg, 1.63 mmol), phenylhydrazine (176 mg, 1.63 mmol), Rh(acac)(CO)$_2$ (1.3 mg, 0.3 mol%) and XANTPHOS (14 mg, 1.5 mol%). The crude product was purified by chromatography (silica, EtOAc, cyclohexane, NEt$_3$) to give N,N-diethyl-3-(1H-indol-3-yl)-1-phenylpropan-1-amine (403 mg, 81 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.06 (t, 6H, J = 7.0 Hz, 2xCH$_3$); 2.15-2.23 (1H, C*H*H); 2.38-2.45 (3H, CH$_2$,CH*H*); 2.59-2.68 (1H, C*H*H); 2.71-2.77 (3H, CH$_2$, CH*H*); 3.81 (dd, 1H, J = 8.5 Hz, J = 8.7 Hz, CH); 6.92 (s, 1H, CH); 7.12 (dd, 1H, J = 7.0 Hz, J = 7.7 Hz, CH); 7.21 (dd, 1H, J = 7.0 Hz, J = 8.0 Hz, CH); 7.31-7.40 (6H, 6xCH); 7.56 (d, 1H, J = 7.7 Hz, CH); 8.08 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 12.8 (2xCH$_3$); 22.4 (CH$_2$); 33.2 (CH$_2$); 43.2 (2xCH$_2$); 64.3 (CH); 111.0 (CH); 116.6 (C); 118.9 (2xCH); 121.0

(CH); 121.7 (CH); 126.8 (CH); 127.5 (C); 127.9 (2xCH); 128.7 (2xCH); 136.3 (C); 141.4 (C). IR: $\tilde{n}$ [cm^{-1}] = 3419 (s); 2967 (vs); 2929 (s); 2869 (s); 1455 (vs); 740 (vs); 701 (s). HRMS found [M]$^+$ 306.2128 $C_{21}H_{26}N_2$ requires [M]$^+$, 306.2098.

3-(1-Methylpiperidin-4-yl)-1H-indole (304m). The first generation protocol was followed with 1-methyl-4-methylene-piperidine (519 mg, 4.67 mmol), phenylhydrazine (505 mg, 4.67 mmol) and Rh(acac)(CO)$_2$ (3.6 mg, 0.3 mol%) to give 3-(1-methylpiperidin-4-yl)-1H-indole (781 mg, 78 %) without further purification. ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.86 (dt, 2H, J = 11.8 Hz, J = 12.7 Hz, CH$_2$); 2.05-2.06 (2H, CH$_2$); 2.15 (t, 2H, J = 11.8 Hz, CH$_2$); 2.36 (s, 3H, CH$_3$); 2.82 (t, 1H, J = 11.8 Hz, CH); 3.00 (d, 2H, J = 11.8 Hz, CH$_2$); 6.91 (s, 1H, CH); 7.09 (dd, 1H, J = 6.8 Hz, J = 7.0 Hz, CH); 7.17 (dd, 1H, J = 7.0 Hz, J = 8.0 Hz, CH); 7.32 (d, 1H, J = 8.0 Hz, CH); 7.65 (d, 1H, J = 8.0 Hz, CH); 8.72 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 32.8 (CH); 32.9 (2xCH$_2$); 46.5 (CH$_3$); 56.3 (2xCH$_2$); 111.2 (CH); 118.8 (CH); 119.0 (CH); 119.8 (CH); 120.9 (C); 121.7 (CH); 126.5 (C); 136.4 (C). IR: $\tilde{n}$ [cm^{-1}] = 3147 (m); 2935 (s); 2921 (s); 2844 (m); 2782 (s); 1457 (s); 1276 (s); 1222 (m); 1110 (m); 989 (s); 732 (vs). HRMS found [M]$^+$ 214.1490 $C_{14}H_{18}N_2$ requires [M]$^+$, 214.1470.

5-Fluoro-3-(1-methylpiperidin-4-yl)-1H-indole (304n). The first generation protocol was followed with 1-methyl-4-methylene-piperidine (479 mg, 4.3 mmol), 4-fluoro phenylhydrazine (543 mg, 4.3 mmol) and Rh(acac)(CO)$_2$ (3.3 mg, 0.3 mol%) to give 5-fluoro-3-(1-methylpiperidin-4-yl)-1H-indole (653 mg, 65 %) without further purification. ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.80 (dt, 2H, J = 12.3 Hz, J = 13.1 Hz, CH$_2$); 2.02 (d, 2H, J = 12.1 Hz, CH$_2$); 2.13 (t, 2H, J = 12.1 Hz, CH$_2$); 2.34 (s, 3H, CH$_3$); 2.73 (t, 1H, J = 12.1 Hz, CH); 2.98 (d, 2H, J = 11.5 Hz, CH$_2$); 6.90 (dd, 1H, J = 9.0 Hz, J = 9.0 Hz, CH); 6.98 (s, 1H, CH); 7.23-7.27 (2H, 2xCH); 8.60 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 32.7 (CH); 32.8 (2xCH$_2$); 46.4 (CH$_3$); 56.2 (2xCH$_2$); 103.8 (d, 1C, $J_{C\text{-}F}$ = 23 Hz, CH); 110.1 (d, 1C, $J_{C\text{-}F}$ = 26 Hz, CH); 111.7 (CH); 121.2 (C); 121.6 (CH); 132.9 (C); 157.4 (d, 1C, $J_{C\text{-}F}$ = 234 Hz, C). IR: $\tilde{n}$ [cm^{-1}] = 3102 (s); 3045 (s); 2942 (vs); 2929 (vs); 2884 (s); 2794 (vs); 1465 (vs); 1274 (s); 1170 (vs); 939 (vs); 790 (s); 757 (s). HRMS found [M]$^+$ 232.1405 $C_{14}H_{17}FN_2$ requires [M]$^+$, 232.1375.

5-Chloro-3-(1-methylpiperidin-4-yl)-1H-indole (304o). The first generation protocol was followed with 1-methyl-4-methylene-piperidine (643 mg, 5.78 mmol), 4-chloro-phenylhydrazine (825 mg, 5.78 mmol) and Rh(acac)(CO)$_2$ (4.7 mg, 0.3 mol%) to give 5-chloro-3-(1-methylpiperidin-4-yl)-1H-indole (1.21 g, 85 %) without further purification. ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.85 (dt, 2H, J = 12.1 Hz, J = 12.7 Hz, CH$_2$); 2.10 (d, 2H,

$J = 12.7$ Hz, CH$_2$); 2.14 (t, 2H, $J = 11.7$ Hz, CH$_2$); 2.37 (s, 3H, CH$_3$); 2.77 (t, 1H, $J = 12.1$ Hz, CH); 3.00 (d, 2H, $J = 11.7$ Hz, CH$_2$); 7.00 (s, 1H, CH); 7.16 (d, 1H, $J = 8.5$ Hz, CH); 7.28 (d, 1H, $J = 8.5$ Hz, CH); 7.63 (s, 1H, CH); 8.27 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) $d = 32.8$ (CH); 33.0 (2xCH$_2$); 46.5 (CH$_3$); 56.3 (2xCH$_2$); 112.1 (C); 112.1 (CH); 118.6 (CH); 121.1 (CH); 122.1 (C); 122.1 (CH); 124.8 (C); 125.5 (C); 127.8 (C). IR: $\tilde{n}$ [cm^{-1}] = 3087 (s); 2964 (s); 2917 (vs); 2771 (s); 1494 (s); 1378 (m); 1274 (s); 1122 (s); 1064 (s); 790 (s); 732 (vs). HRMS found [M]$^+$ 248.1059 C$_{14}$H$_{17}$ClN$_2$ requires [M]$^+$, 248.1080.

5-Bromo-3-(1-methylpiperidin-4-yl)-1H-indole (304p). The first generation protocol was followed with 1-methyl-4-methylene-piperidine (569 mg, 5.12 mmol), 4-bromo-phenylhydrazine (957 mg, 5.12 mmol) and Rh(acac)(CO)$_2$ (4 mg, 0.3 mol%) to give 5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole (1.50 g, 100 %) without further purification. ^{1}H-NMR: (CDCl$_3$, 400 MHz) $d = 1.82$ (dt, 2H, $J = 12.1$ Hz, $J = 12.6$ Hz, CH$_2$); 1.98-2.02 (2H, 2xCH$_2$); 2.12 (t, 2H, $J = 12.1$ Hz, CH$_2$); 2.34 (s, 3H, CH$_3$); 2.73 (t, 1H, $J = 12.1$ Hz, CH); 2.97 (d, 2H, $J = 11.6$ Hz, CH$_2$); 6.92 (s, 1H, CH); 7.18-7.21 (2H, 2xCH); 7.74 (s, 1H, CH); 8.64 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) $d = 31.7$ (CH); 31.9 (2xCH$_2$); 45.4 (CH$_3$); 55.3 (2xCH$_2$); 111.2 (C); 11.7 (CH); 119.8 (C); 120.1 (CH); 120.6 (CH); 123.5 (CH); 127.4 (C); 134.0 (C). IR: $\tilde{n}$ [cm^{-1}] = 2938 (vs); 2786 (vs); 1452 (vs); 1276 (s); 1128 (s); 796 (s); 769 (s). HRMS found [M]$^+$ 292.0547 C$_{14}$H$_{17}$BrN$_2$ requires [M]$^+$, 292.0575.

5-Methyl-3-(1-methylpiperidin-4-yl)-1H-indole (304q). The first generation protocol was followed with 1-methyl-4-methylene-piperidine (487 mg, 4.38 mmol), 4-methyl-phenylhydrazine (535 mg, 4.38 mmol) and Rh(acac)(CO)$_2$ (3.4 mg, 0.3 mol%) to give 5-methyl-3-(1-methylpiperidin-4-yl)-1H-indole (656 mg, 66 %) without further purification. ^{1}H-NMR: (CDCl$_3$, 400 MHz) $d = 1.87$ (dt, 2H, $J = 11.8$ Hz, $J = 12.5$ Hz, CH$_2$); 2.03 (d, 2H, $J = 12.5$ Hz, CH$_2$); 2.15 (t, 2H, $J = 11.8$ Hz, CH$_2$); 2.35 (s, 3H, CH$_3$); 2.45 (s, 3H, CH$_3$); 2.78 (t, 1H, $J = 11.8$ Hz, CH); 3.00 (d, 2H, $J = 11.8$ Hz, CH$_2$); 6.89 (s, 1H, CH); 6.99 (d, 1H, $J = 8.3$ Hz, CH); 7.22 (d, 1H, $J = 8.3$ Hz, CH); 7.43 (s, 1H, CH); 8.26 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) $d = 21.5$ (CH$_3$); 32.9 (2xCH$_2$); 37.2 (CH); 46.5 (CH$_3$); 56.4 (2xCH$_2$); 110.9 (CH); 118.7 (CH); 119.9 (CH); 120.5 (C); 123.4 (CH); 126.8 (C); 128.1 (C); 134.7 (C). IR: $\tilde{n}$ [cm^{-1}] = 2937 (vs); 2690 (s); 1467 (s); 1376 (s); 1274 (s); 1124 (s); 792 (vs); 630 (s). HRMS found [M]$^+$ 228.1626 C$_{15}$H$_{20}$N$_2$ requires [M]$^+$, 228.1627.

5-Methoxy-3-(1-methylpiperidin-4-yl)-1H-indole (304r). The first generation protocol was followed with 1-methyl-4-methylene-piperidine (455 mg, 4.09 mmol), 4-methoxy-phenylhydrazine (565 mg, 4.09 mmol) and Rh(acac)(CO)$_2$ (3.2 mg, 0.3 mol%) to give 3-(1-

methylpiperidin-4-yl)-1H-indole (845 mg, 85 %) without further purification. ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.84 (dt, 2H, J = 12.1 Hz, J = 12.8 Hz, CH$_2$); 2.02 (d, 2H, J = 12.1 Hz, CH$_2$); 2.14 (t, 2H, J = 12.1 Hz, CH$_2$); 2.34 (s, 3H, CH$_3$); 2.75 (t, 1H, J = 12.1 Hz, CH); 2.99 (d, 2H, J = 11.5 Hz, CH$_2$); 3.84 (s, 3H, CH$_3$); 6.84 (d, 1H, J = 8.8 Hz, CH); 6.91 (s, 1H, CH); 7.05 (s, 1H, CH); 7.21 (d, 1H, J = 8.8 Hz, CH); 8.34 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 32.8 (2xCH$_2$); 37.3 (CH); 46.4 (CH$_3$); 56.0 (CH$_3$); 56.3 (2xCH$_2$); 101.0 (CH); 111.9 (2xCH); 120.6 (CH); 120.7 (C); 126.9 (C); 131.6 (C). IR: $\tilde{n}$ [cm^{-1}] = 3141 (s); 2935 (vs); 2830 (vs); 1511 (vs); 1448 (vs); 1276 (vs); 1213 (s); 1056 (s); 792 (s). HRMS found [M+H]$^+$ 245.1672 C$_{15}$H$_{21}$N$_2$O requires [M+H]$^+$, 245.1654.

10.4.4 SECOND GENERATION PROTOCOL FOR THE TANDEM HYDROFORMYLATION / FISCHER INDOLE SYNTHESIS IN WATER

3-(1-Methylpiperidin-4-yl)-1H-indole (304m). In a typical experiment 1-methyl-4-methylenepiperidine (259 mg, 2.33 mmol), phenylhydrazine (252 mg, 2.33 mmol), Rh(acac)(CO)$_2$ (1.8 mg , 0.3 mol%) and TPPTS (20 mg, 1.5 mol%) in H$_2$SO$_4$ (9.3 g, 4 wt% in water, 2.5 wt% olefin) were filled in an autoclave. The autoclave was pressurized with 10bar H$_2$ and 50bar CO. After stirring for 3 days (The reaction is stirred magnetically. With a stirrer that mixes gas phase and liquid phase intensively, the reaction time can be reduced by far to our experience) at 100°C NH$_3$ (10 ml, 30 wt% in water) was added and the mixture was extracted with EtOAc. The solvent was evaporated to give 3-(1-methylpiperidin-4-yl)-1H-indole (400 mg, 80%) without further purification.

5-Fluoro-3-(1-methylpiperidin-4-yl)-1H-indole (304n). The second generation protocol was followed with 1-methyl-4-methylene-piperidine (239 mg, 2.15 mmol), 4-fluoro phenylhydrazine hydrochloride (350 mg, 2.15 mmol), Rh(acac)(CO)$_2$ (1.7 mg, 0.3 mol%) and TPPTS (18 mg, 1.5 mol%) to give 5-fluoro-3-(1-methylpiperidin-4-yl)-1H-indole (477 mg, 95 %) without further purification.

5-Chloro-3-(1-methylpiperidin-4-yl)-1H-indole (304o). The second generation protocol was followed with 1-methyl-4-methylene-piperidine (223 mg, 2.01 mmol), 4-chloro-phenylhydrazine hydrochloride (360 mg, 2.01 mmol), Rh(acac)(CO)$_2$ (1.6 mg, 0.3 mol%) and TPPTS (17 mg, 1.5 mol%) to give 5-chloro-3-(1-methylpiperidin-4-yl)-1H-indole (500 mg, 100 %) without further purification.

5-Bromo-3-(1-methylpiperidin-4-yl)-1H-indole (304p). The second generation protocol was followed with 1-methyl-4-methylene-piperidine (190 mg, 1.71 mmol), 4-bromo-

phenylhydrazine hydrochloride (381 mg, 1.71 mmol), Rh(acac)(CO)$_2$ (1.3 mg, 0.3 mol%) and TPPTS (14.5 mg, 1.5 mol%) to give 5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole (479 g, 96 %) without further purification.

7-Chloro-3-(1-methylpiperidin-4-yl)-1H-indole (304s). The second generation protocol was followed with 1-methyl-4-methylene-piperidine (223 mg, 2.01 mmol), 2-chloro-phenylhydrazine hydrochloride (360 mg, 2.01 mmol), Rh(acac)(CO)$_2$ (1.5 mg, 0.3 mol%) and TPPTS (17 mg, 1.5 mol%) to give 7-chloro-3-(1-methylpiperidin-4-yl)-1H-indole (480 g, 96 %) without further purification. ^{1}H-NMR: (CDCl$_3$, 500 MHz) $d = 1.87$ (dt, 2H, $J = 12.2$ Hz, $J = 12.7$ Hz, CH$_2$); 2.05 (d, 2H, $J = 12.7$ Hz, CH$_2$); 2.14 (t, 2H, $J = 11.7$ Hz, CH$_2$); 2.36 (s, 3H, CH$_3$); 2.79 (t, 1H, $J = 11.7$ Hz, CH); 3.00 (d, 2H, $J = 11.7$ Hz, CH$_2$); 6.99 (s, 1H, CH); 7.02 (dd, 1H, $J = 7.7$ Hz, $J = 8.0$ Hz, CH); 7.17 (d, 1H, $J = 7.7$ Hz, CH); 7.54 (d, 1H, $J = 8.0$ Hz, CH); 8.68 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) $d = 32.9$ (2xCH$_2$); 33.0 (CH); 46.5 (CH$_3$); 56.3 (2xCH$_2$); 116.7 (C); 117.7 (CH); 119.7 (CH); 120.5 (CH); 121.1 (CH); 122.3 (C); 128.2 (C); 133.6 (C). IR: $\tilde{n}$ [cm^{-1}] = 3045 (s); 2942 (s); 2848 (s); 2794 (vs); 2742 (s); 1   469 (m); 1444 (s); 1199 (s); 1116 (s); 775 (s). HRMS found [M]$^+$ 248.1088 C$_{14}$H$_{17}$ClN$_2$O requires [M]$^+$, 248.1080.

Ethyl 4-(2-(1H-indol-3-yl)ethyl)piperazine-1-carboxylate (304d). The second generation protocol was followed with 4-allyl-piperazine-1-carboxylic acid ethyl ester (638 mg, 3.2 mmol), phenylhydrazine (174 mg, 1.6 mmol), Rh(acac)(CO)$_2$ (1.3 mg, 0.3 mol%) and SULFOXANTPHOS (36 mg, 3 mol%). The crude product was purified by chromatography (silica, EtOAc, cyclohexane, NEt$_3$) to give ethyl 4-(2-(1H-indol-3-yl)ethyl)piperazine-1-carboxylate (485 mg, 100 %).

3-(3-(Piperidin-1-yl)propyl)-1H-indole (304e). The second generation protocol was followed with 1-(but-3-enyl)piperidine (574 mg, 4.13 mmol), phenylhydrazine (223 mg, 2.06 mmol), Rh(acac)(CO)$_2$ (1.6 mg, 0.3 mol%) and SULFOXANTPHOS (46 mg, 3 mol%). The crude product was purified by chromatography (silica, EtOAc, cyclohexane, NEt$_3$) to give 3-(3-(piperidin-1-yl)propyl)-1H-indole (249 mg, 50 %).

***N*,*N*-Diethyl-3-(1H-indol-3-yl)-1-phenylpropan-1-amine (304l).** The second generation protocol was followed with *N*,*N*-diethyl-1-phenylbut-3-en-1-amine (664 mg, 3.26 mmol), phenylhydrazine (176 mg, 1.63 mmol), Rh(acac)(CO)$_2$ (1.3 mg, 0.3 mol%) and SULFOXANTPHOS (36 mg, 3 mol%). The crude product was purified by chromatography (silica, EtOAc, cyclohexane, NEt$_3$) to give *N*,*N*-diethyl-3-(1H-indol-3-yl)-1-phenylpropan-1-amine (500 mg, 100 %).

10.4.5 SYNTHESIS OF LY 349 950 & 334 370

N-[4-(4-Fluoro-benzoylamino)-phenyl]-hydrazinecarboxylic acid tert-butyl ester (302i). At 0°C 4-fluorobenzoyl chloride (7.0 g, 44 mmol) was added dropwise to solution of 4-iodo-anilin (9.6 g, 44 mmol), DMAP (270 mg, 5 mol%) and NEt$_3$ (4.9 g, 48 mmol) in dry THF (100 ml). The mixture was stirred for 1h at ambient temperature. The precipitate was filtered off and the solvent was removed to give 4-fluoro-*N*-(4-iodo-phenyl)-benzamide (14.8 g, 99 %), which was subjected to the next step without purification. A suspension of 4-Fluoro-*N*-(4-iodo-phenyl)-benzamide (7.4 g, 22 mmol), hydrazinecarboxylic acid tert-butyl ester (3.4 g, 26 mmol), CuI (207 mg, 5 mol%), 1,10-phenantroline (391 mg, 10 mol%) and Cs$_2$CO$_3$ (9.9 g, 30 mmol) in dry DMF (21 ml) was stirred for 68h at 80°C. The mixture was poured into EtOAc (100 ml) and the solids were separated by filtration through a pad of silica. The solvent was removed and the residue was purified by chromatography (silica, cyclohexane, CH$_2$Cl$_2$, NEt$_3$) to give *N*-[4-(4-fluoro-benzoylamino)-phenyl]-hydrazinecarboxylic acid tert-butyl ester (5.7 g, 78 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) *d* = 1.47 (s, 9H, 3xCH$_3$); 4.40 (s, 2H, NH$_2$); 7.04 (dd, 2H, J = 8.5 Hz, J = 8.5 Hz, 2xCH); 7.38 (d, 2H, J = 8.7 Hz, 2xCH); 7.54 (d, 2H, J = 8.7 Hz, 2xCH); 7.82 (dd, 2H, J = 8.5 Hz, J = 8.5 Hz, 2xCH); 8.32 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) *d* = 28.3 (3xCH$_3$); 81.8 (C); 115.5 (d, 2C, J_{C-F} = 21 Hz, 2xCH); 120.3 (2xCH); 123.9 (2xCH); 129.5 (d, 2C, J_{C-F} = 8 Hz, 2xCH); 131.0 (d, 1C, J_{C-F} = 4 Hz, C); 134.5 (C); 139.6 (C); 155.1 (C); 164.7 (d, 1C, J_{C-F} = 253 Hz, C); 164.8 (C). IR: $\tilde{n}$ [cm^{-1}] = 3367 (s); 2981 (s); 2931 (s); 1691 (s); 1592 (vs); 1525 (vs); 1413 (vs); 1311 (vs); 1232 (vs); 1149 (vs); 1039 (vs); 836 (vs); 759 (vs). HRMS found [M]$^+$ 345.1484, C$_{18}$H$_{20}$FN$_3$O$_3$ requires [M]$^+$, 345.1489. Elementary analysis found C 62.16%, H 5.80%, N 12.03 C$_{18}$H$_{20}$FN$_3$O$_3$ requires C 62.20%, H 5.84%, N 12.17.

N-[3-(2-Dimethylamino-ethyl)-1H-indol-5-yl]-4-fluoro-benzamide (LY 349 950). The first generation protocol is followed with *N,N*-Dimethylprop-2-en-1-amine (262 mg, 3.1 mmol), *N*-[4-(4-Fluoro-benzoylamino)-phenyl]-hydrazinecarboxylic acid tert-butyl ester (1.06 g, 3.1 mmol), Rh(acac)(CO)2 (8 mg, 1 mol%) and XANTPHOS (89 mg, 5 mol%). The crude product is purified by chromatography (silica, CH$_2$Cl$_2$, cyclohexane, NEt$_3$) to give *N*-[3-(2-Dimethylamino-ethyl)-1H-indol-5-yl]-4-fluoro-benzamide (440 mg, 44 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) *d* = 2.30 (s, 6H, 2xCH$_3$); 2.62 (t, 2H, J = 8.0 Hz, CH$_2$); 2.87 (t, 2H, J = 8.0 Hz, CH$_2$); 6.94 (s, 1H, CH); 7.11 (dd, 2H, J = 8.7 Hz, J = 8.2 Hz, 2xCH); 7.20 (d, 1H, J = 8.7 Hz, CH); 7.26 (s, 1H, CH); 7.81 (s, 1H, CH); 7.90 (bs, 2H, 2xCH); 8.13 (s, 1H, NH); 8.59 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) *d* = 23.4 (CH$_2$); 45.3 (2xCH$_3$); 60.0 (CH$_2$); 114.0 (CH); 111.6 (CH); 114.2 (C); 115.6 (d, 2C, J_{C-F} = 21 Hz, 2xCH); 116.9 (CH); 122.8

(CH); 127.6 (C); 129.4 (d, 2C, J_{C-F} = 8 Hz, 2xCH); 129.7 (C); 131.4 (C); 134.0 (C); 163.7 (C); 165.3 (d, 1C, J_{C-F} = 251 Hz, C). IR: $\tilde{n}$ [cm^{-1}] = 3291 (s); 2942 (m); 2823 (m); 1644 (vs); 1602 (vs); 1540 (s); 1481 (vs); 1330 (m); 1232 (s); 1159 (s); 850 (s); 796 (m). HRMS found [M+H]$^+$ 326.1689 $C_{19}H_{20}FN_3O$ requires [M+H]$^+$, 326.1709.

4-Fluoro-*N*-[3-(1-methyl-piperidin-4-yl)-1H-indol-5-yl]-benzamide (**LY 334 370**). The second generation protocol is followed with 1-Methyl-4-methylene-piperidine (158 mg, 1.42 mmol), *N*-[4-(4-Fluoro-benzoylamino)-phenyl]-hydrazinecarboxylic acid tert-butyl ester (491 mg, 1.42 mmol), Rh(acac)(CO)2 (3.7 mg, 1 mol%) and TPPTS (40 mg, 5 mol%) to give 4-Fluoro-*N*-[3-(1-methyl-piperidin-4-yl)-1H-indol-5-yl]-benzamide (474 mg, 95 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) *d* = 1.68 (q, 2H, *J* = 11.8 Hz, 2xCH$_2$); 1.86 (d, 2H, *J* = 11.2 Hz, CH$_2$); 1.96 (t, 2H, *J* = 11.7 Hz, CH$_2$); 2.23 (s, 3H, CH$_3$); 2.60 (t, 1H, *J* = 11.0 Hz, CH); 2.82 (d, 2H, *J* = 9.7 Hz, CH$_2$); 6.71 (s, 1H, CH); 6.98 (bs, 2H, 2xCH); 7.11 (d, 1H, *J* = 8.3 Hz, CH); 7.18 (d, 1H, *J* = 8.3 Hz, CH); 7.84 (bs, 2H, 2xCH); 7.88 (s, 1H, CH); 8.61 (bs, 1H, NH); 9.27 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) *d* = 32.4 (CH); 32.5 (2xCH$_2$); 46.1 (CH$_3$); 56.0 (2xCH$_2$); 111.5 (CH); 112.2 (CH); 115.4 (d, 2C, J_{C-F} = 21 Hz, 2xCH$_2$); 116.8 (CH); 120.6 (C); 121.1 (CH); 126.6 (C); 129.3 (C); 129.4 (d, 2C, J_{C-F} = 8 Hz, 2xCH); 131.2 (C); 134.2 (C); 164.5 (d, 1C, *J* = 251 Hz, CC); 165.3 (C). IR: $\tilde{n}$ [cm^{-1}] = 3291 (s); 2933 (s); 2850 (m); 1646 (vs); 1602 (s); 1540 (s); 1481 (vs); 1328 (m); 1232 (s); 1159 (s); 850 (s); 796 (m). HRMS found [M]$^+$ 351.1729 $C_{21}H_{22}FN_3O$ requires [M]$^+$, 351.1711.

10.4.6 SYNTHESIS OF L 775 606

1-But-3-enyl-4-[2-(3-fluoro-phenyl)-ethyl]-piperazine (**301n**). (3-Fluoro-phenyl)-acetic acid (10.0 g, 64.9 mmol) in dry THF (150 ml) was dropped to a suspension of LiAlH$_4$ (4.92 g, 130 mmol) in dry THF (150 ml) at 0°C. The mixture was stirred for 3h under reflux. At 0°C KOH (2.28 g) in water (9 ml) was added dropwise. The resulting suspension was stirred for 15min under reflux. The precipitate was filtered off, washed with THF (50 ml) and dried over MgSO$_4$. The solvent was removed to give 2-(3-fluoro-phenyl)-ethanol (8.97 g, 99 %) without further purification. At 0°C Br$_2$ (13.9 g, 86.9 mmol) was added dropwise to a solution of triphenyl-phosphane (22.8 g, 86.9 mmol) and imidazole (5.91 g, 86.9 mmol) in dry CH$_2$Cl$_2$ (60 ml) followed by 2-(3-fluoro-phenyl)-ethanol (8.70 g, 62.0 mmol) in dry CH$_2$Cl$_2$ (20 ml). The mixture was stirred for 1h at ambient temperature and was washed consecutively with saturated NaS2O3 solution (10 ml) and saturated NaCl solution (10 ml). The organic layer was dried over MgSO$_4$ and the solvent was removed. The residue was filtered through a pad of silica (cyclohexane / Et$_2$O 5:1) and the solvent was removed to give 1-(2-bromo-ethyl)-3-

fluoro-benzene (11.3 g, 89 %) without the need for further purification. 1-(2-Bromo-ethyl)-3-fluoro-benzene (4.71 g, 23.2 mmol) was added dropwise to a refluxing suspension of piperazine-1-carboxylic acid ethyl ester (4.41 g, 27.8 mmol) and K_2CO_3 (4.89 g, 35.4 mmol) in dry CH_3CN (10 ml). The mixture was stirred for 12h under reflux and was then filtrated through a pad of alumina. The solvent was removed to give 4-[2-(3-fluoro-phenyl)-ethyl]-piperazine-1-carboxylic acid ethyl ester (5.53 g, 85 %), which was subjected to the next step without purification. 4-[2-(3-Fluoro-phenyl)-ethyl]-piperazine-1-carboxylic acid ethyl ester (5.20 g, 18.5 mmol) in NaOH (20 wt% in water, 50 ml) and EtOH (50 ml was stirred for 12h under reflux. The mixture was extracted with EtOAc (3x100 ml). The organic layer was dried over $MgSO_4$ and the solvent was removed to give 1-[2-(3-fluoro-phenyl)-ethyl]-piperazine (3.80 g, 99 %) without purification. 4-Bromo-but-1-ene (0.9 g, 6.9 mmol) was added dropwise to a refluxing suspension of 1-[2-(3-fluoro-phenyl)-ethyl]-piperazine (1.2 g, 5.7 mmol) and K_2CO_3 (1.2 g, 8.6 mmol) in dry CH_3CN (10 ml). The mixture was stirred for 12h under reflux and was then filtrated through a pad of alumina. The solvent was removed to give 1-but-3-enyl-4-[2-(3-fluoro-phenyl)-ethyl]-piperazine (1.49 g, 99 %). without further purification ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 2.21-2.25 (2H, CH_2); 2.40 (dd, 2H, J = 7.2 Hz, J = 8.5 Hz, CH_2); 2.52 (bs, 8H, 4xCH_2); 2.56 (dd, 2H, J = 7.6 Hz, J = 8.7 Hz, CH_2); 2.76 (dd, 2H, J = 7.6 Hz, J = 8.7 Hz, CH_2); 4.97 (d, 1H, J = 10.2 Hz, CHH); 5.03 (d, 1H, J = 17.2 Hz, CHH); 5.77 (ddt, 1H, J = 6.8 Hz, J = 10.2 Hz, J = 17.2 Hz, CH); 6.83-6.89 (2H, 2xCH); 6.93 (d, 1H, J = 7.5 Hz, CH); 7.19 (dd, 1H, J = 7.5 Hz, J = 7.5 Hz, CH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) d = 31.3 (CH_2); 33.3 (CH_2); 53.0 (4xCH_2); 57.9 (CH_2); 60.0 (CH_2); 112.8 (d, 1C, $J_{C\text{-}F}$ = 21 Hz, CH); 115.4 (d, 1C, $J_{C\text{-}F}$ = 21 Hz, CH); 115.6 (CH_2); 124.3 (d, 1C, $J_{C\text{-}F}$ = 4 Hz, CH); 129.7 (d, 1C, $J_{C\text{-}F}$ = 8 Hz, CH); 136.4 (CH); 142.8 (d, 1C, $J_{C\text{-}F}$ = 8 Hz, C); 162.8 (d, 1C, $J_{C\text{-}F}$ = 246 Hz, C). IR: $\tilde{n}$ [cm^{-1}] = 2938 (s); 2807 (s); 1616 (m); 1589 (s); 1488 (s); 1461 (s); 1251 (s); 1159 (s); 1010 (m); 912 (m); 781 (m).

N-(4-[1,2,4]Triazol-4-yl-phenyl)-hydrazinecarboxylic acid tert-butyl ester (302j). At 0°C NEt_3 (14.0 g, 139 mmol) followed by TMS-Cl (31.9 g, 294 mmol) were added dropwise to a suspension of 4-iodo-anilin (4.31 g, 19.6 mmol) and *sym*-diformylhydrazine (4.35 g, 49.4 mmol) in dry pyridine (200 ml). The mixture was stirred for 12h under reflux. The solvent was removed and the residue was taken up in water (200 ml). The precipitate was filtered off and dried *in vacuo* to give pure 4-(4-iodo-phenyl)-4H-[1,2,4]triazole (3.70 g, 70 %). A suspension of 4-(4-iodo-phenyl)-4H-[1,2,4]triazole (4.50 g, 16.6 mmol), hydrazinecarboxylic acid tert-butyl ester (2.76 g, 20.9 mmol), CuI (35.0 mg, 1 mol%), 9,10-phenantroline (313 mg, 10 mol%) and Cs_2CO_3 (7.92 g, 24.3 mmol) in dry DMF (18 ml) was

stirred for 68h at 80°C. Then the mixture was poured into EtOAc (100 ml) and the solids were separated by filtration through a pad of silica. The solvent was removed and the residue was purified by chromatography (silica, cyclohexane, CH_2Cl_2, NEt_3) to give N-(4-[1,2,4]triazol-4-yl-phenyl)-hydrazinecarboxylic acid tert-butyl ester (2.29 g, 48 %). ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.51 (s, 9H, $3xCH_3$); 4.43 (s, 2H, NH_2); 7.28 (d, 2H, J = 8.8 Hz, 2xCH); 7.71 (d, 2H, J = 8.8 Hz, 2xCH); 8.41 (s, 2H, 2xCH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) d = 28.2 ($3xCH_3$); 82.7 (C); 122.0 (2xCH); 123.9 (2xCH); 129.4 (C); 130.2 (2xCH); 143.8 (C); 154.5 (C). IR: $\tilde{n}$ [cm^{-1}] = 3324 (s); 3108 (s); 2985 (s); 1693 (vs); 1612 (s); 1525 (vs); 1369 (vs); 1288 (vs); 1157 (vs); 836 (vs). HRMS found $[M+H]^+$ 276.1470, $C_{13}H_{17}N_5O_2$ requires $[M+H]^+$, 276.1460. Elementary analysis found C 56.36%, H 6.27%, N 25.31 $C_{13}H_{17}N_5O_2$ requires C 56.71%, H 6.22%, N 25.44%.

3-(3-{4-[2-(3-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-propyl)-5-[1,2,4]triazol-4-yl-1H-indole (L 775 606). The first generation protocol is followed with 1-But-3-enyl-4-[2-(3-fluoro-phenyl)-ethyl]-piperazine (455 mg, 1.7 mmol), N-(4-[1,2,4]Triazol-4-yl-phenyl)-hydrazinecarboxylic acid tert-butyl ester (477 mg, 1.7 mmol), Rh(acac)(CO)2 (4.5 mg, 1 mol%) and XANTPHOS (50 mg, 5 mol%). The crude product is purified by chromatography (silica, CH_2Cl_2, EtOH, NEt_3) to give 3-(3-{4-[2-(3-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-propyl)-5-[1,2,4]triazol-4-yl-1H-indole (382 mg, 51 %). ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.27 (t, 2H, J = 7.2 Hz, CH_2); 1.41 (t, 2H, J = 7.2 Hz, CH_2); 1.89 (p, 2H, J = 7.5 Hz, CH_2); 2.44 (t, 2H, J = 7.5 Hz, CH_2); 2.55-2.58 (4H, $2xCH_2$); 2.74-2.78 (6H, $3xCH_2$); 6.84 (d, 1H, J = 8.5 Hz, CH); 6.88 (d, 1H, J = 8.5 Hz, CH); 6.94 (d, 1H, J = 7.5 Hz, CH); 7.05 (d, 1H, J = 8.5 Hz, CH); 7.14 (s, 1H, CH); 7.19 (d, 1H, J = 7.5 Hz, CH); 7.47 (d, 1H, J = 8.5 Hz, CH); 7.52 (s, 1H, CH); 8.44 (s, 2H, 2xCH); 9.51 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) d = 22.6 (CH_2); 27.0 (CH_2); 33.0 (CH_2); 52.8 ($2xCH_2$); 53.0 ($2xCH_2$); 58.0 (CH_2); 59.7 (CH_2); 112.6 (CH); 112.6 (d, 1C, J_{C-F} = 21 Hz, CH); 113.2 (CH); 115.4 (d, 1C, J_{C-F} = 19 Hz, CH); 116.4 (C); 116.5 (CH); 124.3 (CH); 125.8 (C); 127.9 (C); 128.1 (d, 1C, J_{C-F} = 11 Hz, CH); 129.7 (d, 1C, J_{C-F} = 8 Hz, CH); 136.1 (C); 142.5 (2xCH); 142.8 (d, 1C, J_{C-F} = 6 Hz, C); 162.6 (d, 1C, J_{C-F} = 246 Hz, C). IR: $\tilde{n}$ [cm^{-1}] = 3126 (s); 2940 (vs); 2811 (vs); 2773 (s); 1616 (s); 1587 (vs); 1488 (vs); 1448 (vs); 1267 (s); 1249 (vs); 1157 (s); 1139 (vs); 1093 (vs); 784 (s); 730 (vs).

10.5 EXPERIMENTS IN CHAPTER 4

10.5.1 SYNTHESIS OF 401B

Ethyl 4-(1H-indol-3-yl)piperidine-1-carboxylate (414a). The general procedure for the tandem hydroformylation / Fischer indole synthesis with subsequent addition of acid (see 10.3.5) was followed with ethyl 4-methylenepiperidine-1-carboxylate (621 mg, 3.67 mmol), phenylhydrazine (397 mg, 3.67 mmol), $Rh(acac)(CO)_2$ (2.84 mg , 0.3 mol%), 10bar H_2 and 50bar CO in anhydrous THF (5.59 g, 10 wt% olefin) (3d, 120°C). The crude product was purified by flash chromatography on silica to give ethyl 4-(1H-indol-3-yl)piperidine-1-carboxylate (557 mg, 56%). ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.36 (t, 3H, J = 7.1 Hz, CH_3); 1.73 (q, 2H, J = 11.1 Hz, CH_2); 2.09 (d, 2H, J = 15.2 Hz, CH_2); 3.00-3.07 (3H, CH, CH_2); 4.26 (q, 2H, J = 7.1 Hz, CH_2); 4.37 (bs, 2H, CH_2); 6.92 (s, 1H, CH); 7.17 (dd, 1H, J = 7.0 Hz, J = 8.0 Hz, CH); 7.25 (dd, 1H, J = 7.0 Hz, J = 8.2 Hz, CH); 7.38 (d, 1H, J = 8.2 Hz, CH); 7.69 (d, 1H, J = 8.0 Hz, CH); 8.64 (s, 1H, NH). ^{13}C-NMR: ($CDCl_3$, 125 MHz) d = 14.6 (CH_3); 32.5 (2xCH_2); 33.4 (CH); 44.4 (2xCH_2); 61.2 (CH_2); 111.2 (CH); 118.7 (CH); 118.8 (CH); 119.8 (CH); 120.2 (C); 121.6 (CH); 126.2 (C); 136.3 (C); 155.6 (C).

3-(piperidin-4-yl)-1H-indole (415a). Ethyl 4-(1H-indol-3-yl)piperidine-1-carboxylate (400 mg, 1.47 mmol) in EtOH (10 ml) and NaOH (20 wt%, 10 g) was stirred under reflux over night. After extraction of the product with EtOAc the solvent was evaporated to give 3-(piperidin-4-yl)-1H-indole (282 mg, 96 %). ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.26 (bs, 1H, CH); 1.55 (bs, 2H, CH_2); 1.85 (bs, 2H, CH_2); 2.64 (bs, 2H, CH_2); 3.00 (bs, 2H, CH_2); 7.00-7.03 (3H, *3xCH*); 7.31 (bs, 1H, CH); 7.53 (bs, 1H, CH); 10.76 (bs, 1H, NH). ^{13}C-NMR: (dmso-d^6, 125 MHz) d = 32.8 (CH); 33.8 (2xCH_2); 46.6 (2xCH_2); 111.4 (CH); 118.0 (CH); 118.6 (CH); 120.4 (CH); 120.8 (CH); 126.2 (C); 136.4 (C). (C) not observed.

N-(4-(4-(1H-indol-3-yl)piperidin-1-yl)butyl)benzamide (401b). 3-(piperidin-4-yl)-1H-indole (129 mg, 0.80 mmol), *N*-allyl benzamide (129 mg, 0.80 mmol), $[Rh(cod)_2]BF_4$ (3.24 mg , 1 mol%) and XANTPHOS (46.2 mg, 10 mol%) were dissolved in a mixture of anhydrous toluene and anhydrous MeOH (2.45 g, 5 wt% olefin), filled in an autoclave and pressurized with 50bar H_2 and 10bar CO. After stirring for 3d at 125°C the solvent was evaporated and the residue was purified by chromatography (silica, cyclohexane, CH_2Cl_2, NEt$_3$) to give *N*-(4-(4-(1H-indol-3-yl)piperidin-1-yl)butyl)benzamide (170 mg, 57 %). ^{1}H-NMR: ($CDCl_3$, 500 MHz) d = 1.52-1.54 (4H, 2xCH_2); 1.64 (q, 2H, J = 12.3 Hz, CH_2); 1.87 (d, 2H, J = 12.8 Hz, CH_2); 1.96 (t, 2H, J = 11.8 Hz, CH_2); 2.29 (t, 2H, J = 6.8 Hz, CH_2); 2.67

(t, 1H, $J = 11.8$ Hz, CH); 2.90 (d, 2H, $J = 11.5$ Hz, CH$_2$); 3.09 (2d, 1H, $J = 5.8$ Hz, $J = 5.8$ Hz, NH); 3.31 (dt, 2H, $J = 6.5$ Hz, $J = 5.8$ Hz, CH$_2$); 6.78 (s, 1H, CH); 6.90 (dd, 1H, $J = 7.0$ Hz, $J = 6.8$ Hz, CH); 6.99 (dd, 1H, $J = 8.0$ Hz, $J = 7.0$ Hz, CH); 7.21 (d, 1H, $J = 8.0$ Hz, CH); 7.24-7.27 (1H, CH); 7.28 (s, 1H, CH); 7.31 (d, 1H, $J = 7.3$ Hz, CH); 7.45 (d, 1H, $J = 8.0$ Hz, CH); 7.66-7.68 (2H, 2xCH); 9.28 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) $d = 24.3$ (CH$_2$); 27.2 (CH$_2$); 32.6 (2xCH$_2$); 33.2 (CH); 39.5 (CH$_2$); 54.0 (2xCH$_2$); 58.1 (CH$_2$); 111.1 (CH); 118.2 (CH); 118.5 (CH); 119.7 (CH); 120.2 (C); 121.0 (CH); 126.2 (C); 126.8 (2xCH); 128.0 (2xCH); 130.7 (CH); 134.7 (C); 136.2 (C); 167.4 (C). IR: $\tilde{n}$ [cm^{-1}] = 3268 (m); 2927 (m); 2856 (m); 1637 (s); 1540 (m); 1452 (m); 1376 (m); 1309 (m). HRMS found [M]$^+$ 375.2319, C$_{24}$H$_{29}$N$_3$O requires 375.2328.

10.5.2 SYNTHESIS OF 402

Ethyl 4-(5-fluoro-1H-indol-3-yl)piperidine-1-carboxylate (414b). The general procedure for the tandem hydroformylation / Fischer indole synthesis with subsequent addition of acid (see 10.3.5) was followed with ethyl 4-methylenepiperidine-1-carboxylate (816 mg, 4.82 mmol), *N*-(4-fluoro-phenyl)-hydrazine carboxylic acid tert-butyl ester (1.09 g, 4.82 mmol), Rh(acac)(CO)$_2$ (12.4 mg , 1 mol%), 10bar H$_2$ and 50bar CO in anhydrous THF (7.34 g, 10 wt% olefin).The crude product was purified by flash chromatography on silica to give ethyl 4-(5-fluoro-1H-indol-3-yl)piperidine-1-carboxylate (538 mg, 38%). ^{1}H-NMR: (CDCl$_3$, 500 MHz) $d = 1.29$ (t, 3H, $J = 7.1$ Hz, CH$_3$); 1.64-1.66 (2H, CH$_2$); 2.03 (d, 2H, $J = 13.2$ Hz, CH$_2$); 2.91-2.95 (3H, CH, CH$_2$); 4.17 (q, 2H, $J = 7.1$ Hz, CH$_2$); 4.28 (bs, 1H, CH); 6.94 (dd, 1H, $J = 9.0$ Hz, $J = 9.0$ Hz, CH); 6.99 (s, 1H, CH); 7.27 (s, 1H, CH); 7.28 (d, 1H, $J = 9.0$ Hz, CH); 8.22 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) $d = 14.7$ (CH$_3$); 32.6 (2xCH$_2$); 33.6 (CH); 44.4 (2xCH$_2$); 61.3 (CH$_2$); 103.8 (d, 1C, $J_{C-F} = 23$ Hz, CH); 110.3 (d, 1C, $J_{C-F} = 27$ Hz, CH); 111.8 (d, 1C, $J_{C-F} = 10$ Hz, CH); 120.9 (d, 1C, $J_{C-F} = 4$ Hz, C); 121.5 (CH); 126.7 (d, 1C, $J_{C-F} = 10$ Hz, C); 132.9 (C); 155.7 (C); 157.5 (d, 1C, $J_{C-F} = 234$ Hz, C).

5-fluoro-3-(piperidin-4-yl)-1H-indole (415b). Ethyl 4-(5-fluoro-1H-indol-3-yl)piperidine-1-carboxylate (537 mg, 1.85 mmol) in EtOH (10 ml) and NaOH (20 wt%, 10 g) was stirred under reflux over night. After extraction of the product with EtOAc the solvent was evaporated to give 5-fluoro-3-(piperidin-4-yl)-1H-indole (404 mg, 100 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) $d = 1.52$ (q, 2H, $J = 12.0$ Hz, CH$_2$); 1.80 (d, 2H, $J = 12.0$ Hz, CH$_2$); 2.60 (t, 2H, $J = 12.0$ Hz, CH$_2$); 2.75 (t, 1H, $J = 11.7$ Hz, CH); 2.97 (d, 2H, $J = 11.7$ Hz, CH$_2$); 3.32 (bs, 1H, NH); 6.84 (dd, 1H, $J = 9.0$ Hz, $J = 9.2$ Hz, CH); 7.09 (s, 1H, CH); 7.25-7.28 (2H, 2xCH); 10.87 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) $d = 33.5$ (CH); 33.5 (2xCH$_2$); 46.4

(2xCH$_2$); 103.2 (d, 1C, J_{C-F} = 23 Hz, CH); 108.8 (d, 1C, J_{C-F} = 27 Hz, CH); 112.2 (d, 1C, J = 10 Hz, CH); 120.6 (C); 122.7 (CH); 126.3 (d, 1C, J_{C-F} = 10 Hz, C); 133.1 (C); 156.4 (d, 1C, J = 230 Hz, C).

1-allyl-3,4-dihydroquinolin-2(1H)-one (412c). NaH (1.61 g, 40 mmol, 60 wt% in mineral oil) was suspended in anhydrous THF (25 ml). 3,4-dihydroquinolin-2(1H)-one (1.03 g, 6.98 mmol) was added followed by allylic bromide (16.6 g, 137 mmol). After stirring the mixture over night at ambient temperature H$_2$O (25 ml) was added and the mixture was extracted with EtOAc. The solvent was evaporated to give 1-allyl-3,4-dihydroquinolin-2(1H)-one (1.14 g, 87 %). ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 2.67 (dd, 2H, J = 7.9 Hz, J = 9.3 Hz, CH$_2$); 2.91 (dd, 2H, J = 7.9 Hz, J = 9.3 Hz, CH$_2$); 4.55 (d, 2H, J = 4.9 Hz, CH$_2$); 5.14 (d, 1H, J = 17.8 Hz, C*H*H); 5.17 (d, 1H, J = 11.3 Hz, CH*H*); 5.88 (ddt, 1H, J = 4.9 Hz, J = 11.3 Hz, J = 17.8 Hz, CH); 6.98 (d, 2H, J = 7.8 Hz, 2xCH); 7.15 (d, 1H, J = 7.8 Hz, CH); 7.20 (dd, 1H, J = 6.0 Hz, J = 6.8 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 25.4 (CH$_2$); 31.7 (CH$_2$); 45.0 (CH$_2$); 115.3 (CH); 116.2 (CH$_2$); 122.7 (CH); 126.2 (C); 127.3 (CH); 127.7 (CH); 132.6 (CH); 139.8 (C); 169.9 (C). IR: $\tilde{n}$ [cm^{-1}] = 3081 (w); 2927 (w); 2246 (w); 1681 (vs); 1602 (s); 1461 (s); 1376 (vs); 1186 (s); 756 (s). HRMS found [M]$^+$ 187.1027, C$_{12}$H$_{13}$NO requires 187.1057.

1-(4-(4-(5-fluoro-1H-indol-3-yl)piperidin-1-yl)butyl)-3,4-dihydroquinolin-2(1H)-one (402). 5-Fluoro-3-(piperidin-4-yl)-1H-indole (156 mg, 0.72 mmol), 1-allyl-3,4-dihydroquinolin-2(1H)-one (134 mg, 0.72 mmol), [Rh(cod)$_2$]BF$_4$ (2.90 mg , 1 mol%) and XANTPHOS (41.4 mg, 10 mol%) were dissolved in a mixture of anhydrous toluene and anhydrous MeOH (2.54 g, 5 wt% olefin), filled in an autoclave and pressurized with 50bar H$_2$ and 10bar CO. After stirring for 3d at 125°C the solvent was evaporated and the residue was purified by chromatography (silica, cyclohexane, CH$_2$Cl$_2$, NEt$_3$) to give 1-(4-(4-(5-fluoro-1H-indol-3-yl)piperidin-1-yl)butyl)-3,4-dihydroquinolin-2(1H)-one (147 mg, 49 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.63-1.70 (4H, CH$_2$); 1.80 (q, 2H, J = 11.7 Hz, CH$_2$); 2.01 (d, 2H, J = 12.5 Hz, CH$_2$); 2.14 (t, 2H, J = 11.0 Hz, CH$_2$); 2.46 (t, 2H, J = 6.8 Hz, CH$_2$); 2.63 (t, 2H, J = 7.2 Hz, CH$_2$); 2.75 (t, 1H, J = 11.7 Hz, CH$_2$); 2.87 (t, 2H, J = 7.2 Hz, CH$_2$); 3.05 (d, 2H, J = 11.0 Hz, CH$_2$); 3.97 (t, 2H, J = 7.0 Hz, CH$_2$); 6.87 (dd, 1H, J = 8.7 Hz, J = 7.5 Hz, CH); 6.98 (bs, 2H, 2xCH); 7.06 (d, 1H, J = 8.2 Hz, CH); 7.14 (d, 1H, J = 8.2 Hz, CH); 7.22-7.25 (3H, 3xCH); 8.97 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 23.9 (CH$_2$); 25.0 (CH$_2$); 25.5 (CH$_2$); 31.8 (CH$_2$); 32.6 (2xCH$_2$); 33.3 (CH); 47.2 (CH$_2$); 54.1 (2xCH$_2$); 58.2 (CH$_2$); 103.6 (d, 1C, J_{C-F} = 24 Hz, CH); 109.8 (d, 1C, J_{C-F} = 26 Hz, CH); 111.8 (d, 1C, J_{C-F} = 10 Hz,

CH); 114.9 (CH); 120.9 (C); 121.7 (CH); 122.7 (CH); 126.7 (d, 1C, J_{C-F} = 10 Hz, C); 127.4 (CH); 127.9 (CH); 132.9 (C); 139.4 (C); 157.3 (d, 1C, J_{C-F} = 234 Hz, C); 170.2 (C). IR: $\tilde{n}$ [cm^{-1}] = 3467 (w); 3052 (s); 2985 (s); 2942 (s); 2304 (m); 1664 (s); 1602 (s); 1461 (s); 1384 (s); 1265 (vs). HRMS found [M+H]$^+$ 420.2440, $C_{26}H_{30}FN_3O$ requires 420.2429.

10.5.3 SYNTHESIS OF 403

3-(1-(3,3-diphenylpropyl)piperidin-4-yl)-1H-indole (403). 3-(Piperidin-4-yl)-1H-indole (254 mg, 1.27 mmol), diphenylethene (343 mg, 1.90 mmol), [Rh(cod)Cl]$_2$ (31.2 mg, 5 mol%) and tributyl phosphane (38.5 mg, 15 mol%) were dissolved in anhydrous dioxane (3.08 g, 10 wt% olefin), filled in an autoclave and pressurized with 10bar H$_2$ and 90bar CO. After stirring for 3d at 130°C the solvent was evaporated and the residue was purified by chromatography (silica, cyclohexane, CH$_2$Cl$_2$, NEt$_3$) to give 3-(1-(3,3-diphenylpropyl) piperidin-4-yl)-1H-indole (283 mg, 57 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.91 (q, 2H, J = 11.9 Hz, CH$_2$); 2.12 (d, 2H, J = 12.5 Hz, CH$_2$); 2.19 (t, 2H, J = 11.5 Hz, CH$_2$); 2.38-2.44 (4H, 2xCH$_2$); 2.90 (t, 1H, J = 11.9 Hz, CH); 3.11 (d, 2H, J = 11.0 Hz, CH$_2$); 4.07 (t, 1H, J = 6.7 Hz, CH); 6.94 (s, 1H, CH); 7.17 (dd, 1H, J = 7.5 Hz, J = 7.5 Hz, CH); 7.23-7.26 (1H, CH); 7.33-7.36 (11H, 11xCH); 7.72 (d, 1H, J = 8.0 Hz, CH); 8.69 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 32.8 (CH$_2$); 32.9 (2xCH$_2$); 33.4 (CH); 49.3 (CH); 54.4 (2xCH$_2$); 57.4 (CH$_2$); 111.2 (CH); 118.7 (CH); 118.9 (CH); 119.7 (CH); 121.0 (C); 121.5 (CH); 126.0 (2xCH); 126.5 (C); 127.5 (4xCH); 128.3 (4xCH); 136.3 (C); 144.8 (3xC). IR: $\tilde{n}$ [cm^{-1}] = 3424 (m); 3058 (m); 3025 (m); 2929 (vs); 2769 (m); 1598 (m); 1492 (s); 1450 (vs); 1128 (s); 765 (s). HRMS found [M]$^+$ 394.2425, $C_{28}H_{30}N_2$ requires [M]$^+$ 394.2441.

10.5.4 SYNTHESIS OF 404

Ethyl 4-(5-methoxy-1H-indol-3-yl)piperidine-1-carboxylate (414c). The general procedure for the tandem hydroformylation / Fischer indole synthesis with subsequent addition of acid (see 10.3.5) was followed with ethyl 4-methylenepiperidine-1-carboxylate (2.795 g, 16.5 mmol), 1-(4-methoxyphenyl)hydrazine (2.285 g, 16.5 mmol), Rh(acac)(CO)$_2$ (42.9 mg, 1 mol%), 10bar H$_2$ and 50bar CO in anhydrous THF (22.38 g, 10 wt% olefin)The crude product was purified by flash chromatography on silica to give ethyl 4-(5-methoxy-1H-indol-3-yl)piperidine-1-carboxylate (3.475 mg, 70%). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.29 (t, 3H, J = 7.1 Hz, CH$_3$); 1.66 (d, 2H, J = 11.0 Hz, CH$_2$); 2.05 (d, 2H, J = 12.2 Hz, CH$_2$); 2.96 (t, 2H, J = 11.7 Hz, CH$_2$); 3.88 (s, 3H, CH$_3$); 4.18 (q, 2H, J = 7.1 Hz, CH$_2$); 4.30 (bs, 2H, CH$_2$); 6.87 (d, 1H, J = 8.7 Hz, CH); 6.92 (s, 1H, CH); 7.06 (s, 1H, CH); 7.25 (d, 1H,

$J = 8.7$ Hz, CH); 8.20 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) $d = 14.7$ (CH$_3$); 32.6 (2xCH$_2$); 33.5 (CH); 44.5 (2xCH$_2$); 56.0 (CH$_3$); 61.2 (CH$_2$); 101.0 (CH); 111.9 (2xCH); 120.3 (C); 120.6 (CH); 126.7 (C); 131.6 (C); 153.7 (C); 155.7 (C).

5-Methoxy-3-(piperidin-4-yl)-1H-indole (415c). Ethyl 4-(5-methoxy-1H-indol-3-yl)piperidine-1-carboxylate (3.41 g, 11.3 mmol) in EtOH (50 ml) and NaOH (20 wt%, 50 g) is stirred under reflux over night. After extraction of the product with EtOAc the solvent was evaporated to give 5-methoxy-3-(piperidin-4-yl)-1H-indole (2.6 g, 100 %). ^{1}H-NMR: (dmso-d^6, x00 MHz) $d = 1.90$ (d, 2H, $J = 11.8$ Hz, CH$_2$); 2.80 (t, 2H, $J = 10.8$ Hz, CH$_2$); 3.14 (d, 2H, $J = 12.1$ Hz, CH$_2$); 3.71 (s, 3H, CH$_3$); 4.50 (bs, 4H, CH, CH$_2$, NH); 6.66 (d, 1H, $J = 8.6$ Hz, CH); 6.99 (s, 1H, CH); 7.03 (s, 1H, CH); 7.19 (d, 1H, $J = 8.6$ Hz, CH); 10.7 (s, 1H, NH). ^{13}C-NMR: (dmso-d^6, 100 MHz) $d = 31.0$ (3xCH$_2$); 32.3 (CH); 44.7 (2xCH$_2$); 55.6 (CH$_3$); 100.7 (CH); 111.1 (CH); 112.2 (CH); 118.9 (C); 121.5 (CH); 126.4 (C); 131.7 (C); 152.9 (C).

Ethyl 4-(2-(4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl)ethyl)piperidine-1-carboxylate (416). Ethyl 4-methylenepiperidine-1-carboxylate (1.76 g, 10.4 mmol), 5-methoxy-3-(piperidin-4-yl)-1H-indole (2.40 g, 10.4 mmol) and [Rh(cod)Cl]$_2$ (51.3 mg , 1 mol%) were dissolved in a mixture of anhydrous toluene and anhydrous MeOH (33.4 g, 10 wt% olefin), filled in an autoclave and pressurized with 10bar H$_2$ and 50bar CO. After stirring for 3d at 120°C the solvent was evaporated and the residue wais purified by flash chromatography on silica to give ethyl 4-(2-(4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl)ethyl)piperidine-1-carboxylate (2.38 mg, 55%). ^{1}H-NMR: (CDCl$_3$, 500 MHz) $d = 1.13$ (q, 2H, $J = 12.6$ Hz, CH$_2$); 1.25 (t, 3H, $J = 7.0$ Hz, CH$_3$); 1.39-1.52 (3H, CH$_2$, CH); 1.66 (d, 2H, $J = 12.3$ Hz, CH$_2$); 1.80 (q, 2H, $J = 12.1$ Hz, CH$_2$); 2.03 (d, 2H, $J = 11.0$ Hz, CH$_2$); 2.11 (t, 2H, $J = 11.8$ Hz, CH$_2$); 2.35 (t, 1H, $J = 11.5$ Hz, CH); 2.42 (t, 2H, $J = 7.5$ Hz, CH$_2$); 2.68-281 (4H, 2xCH$_2$); 3.06 (d, 2H, $J = 11.5$ Hz, CH$_2$); 3.82 (s, 3H, CH$_3$); 4.12 (q, 2H, $J = 7.0$ Hz, CH$_2$); 6.81 (d, 1H, $J = 8.8$ Hz, CH); 6.88 (s, 1H, CH); 7.04 (s, 1H, CH); 7.18 (d, 1H, CH); 8.87 (s, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) $d = 14.5$ (CH$_3$); 32.0 (CH$_2$); 32.8 (2xCH$_2$); 33.4 (CH); 33.5 (CH$_2$); 33.5 (CH$_2$); 34.4 (CH); 43.8 (CH$_2$); 49.3 (CH$_2$); 54.4 (2xCH$_2$); 55.8 (CH$_3$); 56.4 (CH$_2$); 61.0 (CH$_2$); 100.8 (CH); 111.5 (CH); 111.8 (CH); 120.5 (C); 120.6 (CH); 126.7 (C); 131.5 (C); 153.3 (C); 155.4 (C).

5-Methoxy-3-(1-(2-(piperidin-4-yl)ethyl)piperidin-4-yl)-1H-indole (417). Ethyl-4-(2-(4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl)ethyl)piperidine-1-carboxylate (2.39 g, 5.77 mmol) in EtOH (25 ml) and NaOH (20 wt%, 25 g) was stirred under reflux over night. After extraction of the product with EtOAc the solvent was evaporated to give 5-methoxy-3-

(1-(2-(piperidin-4-yl)ethyl)piperidin-4-yl)-1H-indole (1.93 g, 98 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.41-1.49 (4H, 2xCH$_2$); 1.76-1.81 (3H, CH$_2$, CH); 2.01-2.12 (4H, 2xCH$_2$); 2.39-2.43 (2H, CH$_2$); 2.70 (t, 2H, J = 12 Hz, CH$_2$); 2.77 (q, 2H, J = 8 Hz, CH$_2$); 2.86-2.89 (1H, CH); 3.00-3.08 (2H, CH$_2$); 3.24-3.27 (2H, CH$_2$); 3.83 (s, 3H, CH$_3$); 6.43 (bs, 1H, NH); 6.81 (d, 1H, J = 8.5 Hz, CH); 6.91 (s, 1H, CH); 7.04 (s, 1H, CH); 7.21 (d, 1H, J = 8.5 Hz, CH); 8.47 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 30.6 (2xCH$_2$); 32.6 (CH$_2$); 32.8 (2xCH$_2$); 33.4 (CH); 33.5 (CH); 44.9 (2xCH$_2$); 54.4 (2xCH$_2$); 56.0 (CH$_3$); 56.2 (CH$_2$); 101.2 (CH); 111.9 (2xCH); 120.6 (CH); 126.9 (C); 131.6 (C); 153.5 (C).

(E)-3-(3,4-dichlorophenyl)-1-(4-(2-(4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl)ethyl)piperidin-1-yl)prop-2-en-1-one (404). 3,4-dichlorocinnamyl acid (576 mg, 2.65 mmol) and DMAP (16 mg, 5 mol%) were dissolved in anhydrous THF (5 ml). A solution of DCC (603 mg, 2.92 mmol) and 5-methoxy-3-(1-(2-(piperidin-4-yl)ethyl)piperidin-4-yl)-1H-indole (907 mg, 2.65 mmol) in anhydrous THF (5 ml) was added at 0°C. After stirring the mixture over night at ambient temperature the solvent was evaporated and the residue was purified by chromatography to give (E)-3-(3,4-dichlorophenyl)-1-(4-(2-(4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl)ethyl)piperidin-1-yl)prop-2-en-1-one (890 mg, 62 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.18-1.21 (2H, CH$_2$); 1.52 (q, 2H, J = 7.5 Hz, CH$_2$); 1.55 (bs, 1H, CH); 1.80 (d, 2H, J = 9.7 Hz, CH$_2$); 2.03 (d, 2H, J = 12.0 Hz, CH$_2$); 2.11 (t, 2H, J = 11.3 Hz, CH$_2$); 2.42 (t, 2H, J = 7.3 Hz, CH$_2$); 2.67 (t, 1H, J = 11.5 Hz, CHH); 2.76 (q, 2H, J = 11.8 Hz, CH$_2$); 3.04 (d, 2H, J = 10.7 Hz, CH$_2$); 3.09 (t, 1H, J = 12.0 Hz, CHH); 3.84 (s, 3H, CH$_3$); 4.04 (d, 1H, J = 12.0 Hz, CHH); 4.66 (d, 1H, J = 11.7 Hz, CHH); 6.82 (d, 1H, J = 8.7 Hz, CH); 6.87 (d, 1H, J = 15.5 Hz, CH); 6.93 (s, 1H, CH); 7.05 (s, 1H, CH); 7.22 (d, 1H, J = 8.7 Hz, CH); 7.29 (d, 1H, J = 8.2 Hz, CH); 7.40 (d, 1H, J = 8.2 Hz, CH); 7.50 (d, 1H, J = 15.5 Hz, CH); 7.57 (s, 1H, CH); 8.56 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 31.9 (CH$_2$); 32.8 (2xCH$_2$); 33.1 (CH); 33.4 (2xCH$_2$); 34.7 (CH); 42.3 (CH$_2$); 46.2 (CH$_2$); 54.5 (2xCH$_2$); 56.0 (CH$_3$); 56.4 (CH$_2$); 101.1 (CH); 111.7 (CH); 111.9 (CH); 119.5 (CH); 120.7 (CH); 126.9 (CH); 128.9 (CH); 130.6 (CH); 131.6 (C); 132.9 (C); 133.1 (C); 135.4 (C); 139.6 (CH); 153.5 (C); 164.6 (C). IR: $\tilde{n}$ [cm^{-1}] = 3424 (s); 2929 (s); 2850 (m); 1646 (vs); 1598 (s); 1473 (vs); 1448 (s); 1209 (s); 1029 (m); 977 (m). HRMS found [M]$^+$ 539.2108, C$_{30}$H$_{35}$Cl$_2$N$_3$O$_2$ requires 539.2109.

10.6 EXPERIMENTS IN CHAPTER 5

3-(2-(diphenylmethylene)hydrazinyl)benzoic acid (502). 3-Hydrazino-benzoic acid (4.47 g, 23.7 mmol) and benzophenone (4.32 g, 23.7 mmol) were dissolved in H$_2$O/EtOH

(140 ml, 9:5) and stirred at 80°C. Upon completion of the reaction the mixture was cooled and the precipitate was collected by filtration to give 3-(2-(diphenylmethylene)hydrazinyl)benzoic acid (4.08 g, 54 %). ^{1}H-NMR: (dmso-d^6, 500 MHz) d = 7.26-7.37 (7H, 7xCH_2); 7.45 (d, 2H, J = 7.2 Hz, 2xCH_2); 7.53 (dd, 2H, J = 7.4 Hz, J = 9.7 Hz, 2xCH_2); 7.58 (dd, 2H, J = 7.4 Hz, J = 7.2 Hz, 2xCH_2); 7.86 (s, 1H, CH); 9.17 (s, 1H, NH); 12.8 (bs, 1H, OH). ^{13}C-NMR: (dmso-d^6, 125 MHz) d = 114.1, 114.0 (CH); 117.1, 117.0 (CH); 120.1 (CH); 126.1 (2xCH); 127.9 (CH); 128.3 (2xCH); 129.1 (4xCH); 129.5 (2xCH); 131.4 (C); 133.1 (C); 138.7 (C); 143.9 (C); 145.7 (C); 167.7 (C). Elementary analysis found C 76.10%, H 4.90%, N 8.60%, $C_{20}H_{16}N_2O_2$ requires C 75.93%, H 5.10%, N 8.85%.

3-(2-(diphenylmethylene)hydrazinyl)-*N*-ethyl-*N*-(2-methylallyl)benzamide (503). *N*-Ethyl-2-methylprop-2-en-1-amine (2.12 g, 21 mmol), DMAP (522 mg, 5 mol%) and 3-(2-(diphenylmethylene)hydrazinyl)benzoic acid (6.77 g, 21 mmol) were dissolved in anhydrous CH_2Cl_2 (20 ml). DCC (4.85 g, 23.5 mmol) in anhydrous CH_2Cl_2 (10 ml) was added at 0°C and the mixture was stirred for 20 h at ambient temperature. The solvent was evaporated and the residue was taken up in Et_2O. After filtration the solvent was evaporated and the residue was chromatographed (silica, cyclohexane, EtOAc) to give 3-(2-(diphenylmethylene)hydrazinyl)-*N*-ethyl-*N*-(2-methylallyl)benzamide (6.54 g, 76 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.25, 1.13 (2bs, 3H, CH_3); 1.67, 1.83 (2bs, 3H, CH_3); 3.56, 3.32 (2bs, 2H, CH_2); 3.84, 4.18 (2s, 2H, CH_2); 4.93-5.01 (2H, CH_2); 6.90-7.17 (3H, 3xCH); 7.26-7.38 (6H, 6xCH); 7.55-7.64 (6H, 6xCH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 12.0 (CH_3); 20.0 (CH_3); 39.6, 42.6 (CH_2); 54.2, 48.8 (CH_2); 111.1 (CH); 112.2 (CH_2); 113.7 (CH); 117.7 (CH); 126.5 (2xCH); 128.1 (2xCH); 129.0 (3xCH); 129.1 (CH); 129.7 (3xCH); 132.5 (C); 138.1 (C); 171.7 (C). Elementary analysis found C 77.10%, H 6.80%, N 10.00%, $C_{26}H_{27}N_3O$ requires C 78.65%, H 6.85%, N 10.57%.

3-(2-(diphenylmethylene)hydrazinyl)-*N*-ethyl-*N*-(3-formyl-2-methylpropyl)benzamide (504). 3-(2-(Diphenylmethylene)hydrazinyl)-*N*-ethyl-*N*-(2-methylallyl)benzamide (930 mg, 2.34 mmol) and [Rh(cod)Cl]$_2$ (12 mg, 1 mol%) were dissolved in anhydrous THF (92 g, 1 wt% olefin), filled in an autoclave and pressurized with 10bar H_2 and 50bar CO. After stirring for 7 h at 120°C the solvent was removed and the residue was purified by chromatography (silica, cyclohexane, EtOAc) to give 3-(2-(diphenylmethylene)hydrazinyl)-*N*-ethyl-*N*-(3-formyl-2-methylpropyl)benzamide (834 mg, 83 %). ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.04 (bs, 3H, CH_3); 1.17 (bs, 3H, CH_3); 2.25-2.33 (2H, CH_2); 2.45-3.48 (2H, CH_2); 3.32-3.48 (4H, 2xCH_2); 6.83 (d, 1H, J = 10 Hz, CH); 7.10 (s, 1H, CH); 7.14 (bs, 1H,

CH); 7.28-7.40 (6H, 6xCH); 7.56-7.65 (5H, 5xCH); 9.80 (s, 1H, CH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 13.8, 12.0 (CH$_3$); 18.1, 20.9 (CH$_3$); 26.6 (CH$_3$); 36.2 (CH$_2$); 44.0 (CH$_2$); 49.2 (CH$_2$); 110.8 (CH); 113.6 (CH); 117.4 (CH); 126.5 (2xCH); 128.2 (2xCH); 129.0 (3xCH); 129.3 (CH); 129.7 (3xCH); 132.5 (C); 137.8 (C); 138.0 (C); 144.7 (C); 176.3 (C); 202.1 (CH).

Hex-5-enyl 3-(2-(diphenylmethylene)hydrazinyl)benzoate (507a). 5-Hexenol (251 mg, 2.51 mmol), DMAP (15 mg, 5 mol%) and 3-(2-(diphenylmethylene)hydrazinyl)benzoic acid (794 mg, 2.51 mmol) were dissolved in anhydrous CH$_2$Cl$_2$ (4 ml). DCC (570 mg, 2.76 mmol) in anhydrous CH$_2$Cl$_2$ (1 ml) was added at 0°C and the mixture was stirred for 20 h at ambient temperature. The solvent was evaporated and the residue was taken up in Et$_2$O. After filtration the solvent was evaporated and the residue was chromatographed (silica, cyclohexane, EtOAc) to give hex-5-enyl 3-(2-(diphenylmethylene)hydrazinyl)benzoate (795 mg, 80 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.56 (p, 2H, J = 7.5 Hz, CH$_2$); 1.78 (p, 2H, J = 6.5 Hz, CH$_2$); 2.13 (q, 2H, J = 7.1 Hz, CH$_2$); 4.31 (t, 2H, J = 6.5 Hz, CH$_2$); 4.98 (d, 1H, J = 10.2 Hz, CHH); 5.04 (d, 1H, J = 17.2 Hz, CHH); 5.82 (ddt, 1H, J = 6.5 Hz, J = 10.2 Hz, J = 17.2 Hz, CH); 7.30-7.82 (5H, 14xCH, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 25.2 (CH$_2$); 28.1 (CH$_2$); 33.3 (CH$_2$); 64.8 (CH$_2$); 113.8 (CH); 114.8 (CH$_2$); 117.1 (CH); 120.9 (CH); 126.5 (2xCH); 128.2 (4xCH); 129.0 (CH); 129.2 (CH); 129.3 (CH); 129.7 (CH); 130.0 (2xCH); 132.4 (CH); 132.5 (C); 137.5 (C); 138.0 (C); 144.7 (C); 166.7 (C). HRMS found M$^+$ 398.1963, C$_{26}$H$_{26}$N$_2$O$_2$ requires M$^+$, 398.1932.

Undec-10-enyl 3-(2-(diphenylmethylene)hydrazinyl)benzoate (507b). 11-Undecenol (2.73 g, 16.0 mmol), DMAP (98 mg, 5 mol%) and 3-(2-(diphenylmethylene)hydrazinyl) benzoic acid (5.06 g, 16.0 mmol) were dissolved in anhydrous CH$_2$Cl$_2$ (20 ml). DCC (3.63 g, 17.6 mmol) in anhydrous CH$_2$Cl$_2$ (10 ml) was added at 0°C. The mixture was stirred for 20 h ambient temperature. The solvent was evaporated and the residue was taken up in Et$_2$O. After filtration the solvent was evaporated and the residue was chromatographed (silica, cyclohexane, EtOAc) to give undec-10-enyl 3-(2-(diphenylmethylene)hydrazinyl)benzoate (7.49 g, 100 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.29-1-46 (12H, 6xCH$_2$); 1.75-1.80 (2H, CH$_2$); 2.05 (q, 2H, J = 7.0 Hz, CH$_2$); 4.31 (t, 2H, J = 6.7 Hz, CH$_2$); 4.95 (d, 1H, J = 11.2 Hz, CHH); 5.02 (d, 1H, J = 17.2 Hz, CHH); 5.82 (ddt, 1H, J = 6.7 Hz, J = 11.2 Hz, J = 17.2 Hz, CH); 7.30-7.83 (15H, 15xCH, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 25.9 (CH$_2$); 28.7 (CH$_2$); 28.8 (CH$_2$); 29.0 (CH$_2$); 29.2 (CH$_2$); 29.3 (CH$_2$); 29.4 (CH$_2$); 33.7 (CH$_2$); 65.0 (CH$_2$); 113.8 (CH); 114.1 (CH$_2$); 117.0 (CH); 120.9 (CH); 126.5 (2xCH); 128.1 (4xCH); 128.9 (CH); 129.2 (CH); 129.3 (CH); 129.7 (CH); 130.0 (CH); 131.3 (C); 132.5 (C); 138.0 (C); 144.7 (C);

144.9 (C); 166.7 (C). IR: $\tilde{n}$ [cm^{-1}] = 3332 (s); 3060 (s); 2937 (vs); 2854 (vs); 2123 (vs); 1722 (vs); 1606 (vs); 1590 (vs); 1444 (vs); 1294 (s); 1226 (vs); 1105 (s); 754 (vs). HRMS found M$^+$ 468.2757, $C_{31}H_{36}N_2O_2$ requires M$^+$, 468.2737. Elementary analysis found C 79.10%, H 7.80%, N 5.50%, $C_{31}H_{36}N_2O_2$ requires C 79.45%, H 7.74%, N 5.98%.

6-formylhexyl 3-(2-(diphenylmethylene)hydrazinyl)benzoate (508a). Hex-5-enyl 3-(2-(diphenylmethylene)hydrazinyl)benzoate (735 mg, 1.84 mol), Rh(acac)(CO)$_2$ (5 mg, 1 mol%) and BIPHEPHOS (145 mg, 10 mol%) were dissolved in anhydrous THF (5.87 g, 10 wt% olefin), filled in an autoclave and pressurized with 10bar H$_2$ and 10bar CO. After stirring for 5 h at 60°C the solvent was removed and the residue was purified by chromatography (silica, cyclohexane, EtOAc) to give 6-formylhexyl 3-(2-(diphenylmethylene)hydrazinyl)benzoate (252 mg, 32 %) as an inseparable mixture of *n*/*iso*-aldehyde, which was analyzed with NMR. ^{1}H-NMR: (CDCl$_3$, 400 MHz) *d* = 1.42-1.82 (8H, 4xCH$_2$); 2.42 (t, 2H, *J* = 7.0 Hz, CH$_2$); 4.31 (q, 2H, *J* = 6.5 Hz, CH$_2$); 7.30-7.81 (15H, 14xCH, NH); 9.73 (t, 1H, *J* = 1.8 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) *d* = 21.8 (CH$_2$); 28.4 (CH$_2$); 28.7 (CH$_2$); 43.7 (CH$_2$); 64.8 (CH$_2$); 113.8 (CH); 117.1 (CH); 120.9 (CH); 126.5 (2xCH); 128.1 (2xCH); 128.2 (CH); 129.0 (2xCH); 129.2 (CH); 129.3 (CH); 129.7 (CH); 131.1 (C); 132.3 (CH); 132.5 (C); 138.0 (C); 144.7 (C); 166.8 (C); 202.6 (CH). Characteristic data for the *iso*-regioisomer: ^{1}H-NMR: (CDCl$_3$, 400 MHz) *d* = 1.11 (d, 3H, *J* = 7.0 Hz, CH$_3$); 2.36 (m, 1H, *J* = 7.0 Hz, CH); 9.60 (d, 1H, *J* = 1.8 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) *d* = 13.3 (CH$_3$); 25.8 (CH$_2$); 28.6 (CH$_2$); 29.9 (CH$_2$); 46.1 (CH); 204.8 (CH).

11-formylundecyl 3-(2-(diphenylmethylene)hydrazinyl)benzoate (508b). Undec-10-enyl 3-(2-(diphenylmethylene)hydrazinyl)benzoate (7.52 g, 16.0 mol), Rh(acac)(CO)$_2$ (4 mg, 0.1 mol%) and BIPHEPHOS (63 mg, 1 mol%) were dissolved in anhydrous THF (150 g), filled in an autoclave and pressurized with 10bar H$_2$ and 10bar CO. After stirring for 20 h at 40°C the solvent was removed and the residue was purified by chromatography (silica, cyclohexane, EtOAc) to give 11-formylundecyl 3-(2-(diphenylmethylene)hydrazinyl) benzoate (6.92 g, 87 %) as an inseparable mixture of *n*/*iso*-aldehyde, which was analyzed by NMR. ^{1}H-NMR: (CDCl$_3$, 400 MHz) *d* = 1.26-1.91 (18H, 9xCH$_2$); 2.37 (t, 2H, *J* = 7.3 Hz, CH$_2$); 4.27 (t, 2H, *J* = 6.8 Hz, CH$_2$); 7.24-7.78 (15H, 14xCH, NH); 9.70 (t, 1H, *J* = 1.8 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) *d* = 21.9 (CH$_2$); 28.6 (CH$_2$); 29.1 (CH$_2$); 29.2 (CH$_2$); 29.2 (CH$_2$); 29.3 (CH$_2$); 29.3 (CH$_2$); 29.4 (CH$_2$); 30.3 (CH$_2$); 43.7 (CH$_2$); 64.9 (CH$_2$); 113.7 (CH); 117.0 (CH); 120.8 (CH); 126.4 (2xCH); 128.1 (3xCH); 128.1 (CH); 128.9 (3xCH); 129.1 (CH); 129.2 (CH); 129.6 (3xCH); 129.9 (CH); 131.2 (C); 132.3 (CH); 132.4 (C); 137.9 (C);

144.6 (C); 144.9 (C); 166.6 (C); 202.7 (CH). Characteristic data for the iso-regioisomer: ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.05 (d, 3H, J = 7.0 Hz, CH$_3$); 2.28 (m, 1H, J = 7.0 Hz, CH); 9.57 (d, 1H, J = 2.0 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 13.2 (CH$_3$); 34.8 (CH$_2$); 46.1 (CH); 205.2 (CH).

3-(2-(dodecylidene-12-ol)-hydrazinyl)benzoic acid (510). 12-Hydroxydodecanal (2.99 g, 14.9 mmol) and 3-hydrazino benzoic acid (1.63 g, 14.9 mmol) were stirred in anhydrous THF (50 ml) for 1h at 60°C follows by filtration through a sintered glass filter. The solvent was evaporated to give 3-(2-(dodecylidene-12-ol)-hydrazinyl)benzoic acid (4.83 g, 97 %). ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.23 (bs, 16H, 8xCH$_2$); 1.48-1.54 (4H, 2xCH$_2$); 3.60 (t, 2H, J = 6.6 Hz, CH$_2$); 6.51-7.61 (8H, 5xCH, 2xOH, NH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 25.5 (CH$_2$); 26.9 (CH$_2$); 29.1 (CH$_2$); 29.3 (2xCH$_2$); 29.4 (2xCH$_2$); 29.5 (CH$_2$); 32.0 (CH$_2$); 32.5 (CH$_2$); 62.8 (CH$_2$); 113.7 (CH); 117.3 (CH); 120.8 (CH); 129.2 (CH); 130.5 (C); 142.5 (CH); 142.6 (C); 171.0 (C). IR: $\tilde{n}$ [cm^{-1}] = 3297 (s); 2927 (vs); 2854 (vs); 2624 (m); 1693 (vs); 1606 (vs); 1490 (m); 1463 (s); 1303 (s); 1108 (s); 1054 (s); 885 (s). HRMS found M$^+$ 334.2267, C$_{19}$H$_{30}$N$_2$O$_3$ requires M$^+$, 334.2278. Elementary analysis found C 67.51%, H 9.54%, N 8.72%, C$_{19}$H$_{30}$N$_2$O$_3$ requires C 68.23%, H 9.04%, N 8.38%.

11-iodoundec-1-ene (513). Triphenyl phosphane (32.7 g, 125 mmol) and imidazole (8.50 g, 125 mmol) were dissolved in anhydrous CH$_2$Cl$_2$ (250 ml). At 0°C iodine (31.7 mmol, 125 mmol) was added in portions. 11-Undecenol (15.2 g, 89 mmol) was added and the mixture was stirred for 1 h. The mixture was washed with Na$_2$S$_2$O$_3$ (100 ml, saturated in H$_2$O) and the solvent was evaporated. The residue was taken up in pentane (200 ml) and was filtered followed by evaporation of the solvent to give 11-iodoundec-1-ene (24.6 g, 98 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.27 (bs, 8H, 4xCH$_2$); 1.36 (bs, 4H, 2xCH$_2$); 1.80 (p, 2H, J = 7.2 Hz, CH$_2$); 2.02 (q, 2H, J = 7.0 Hz, CH$_2$); 3.16 (t, 2H, J = 7.0 Hz, CH$_2$); 4.91 (d, 1H, J = 10.2 Hz, CHH); 4.96 (d, 1H, J = 17.2 Hz, CHH); 5.78 (ddt, 1H, J = 6.7 Hz, J = 10.2 Hz, J = 17.2 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 7.1 (CH$_2$); 28.5 (CH$_2$); 28.8 (CH$_2$); 29.0 (CH$_2$); 29.3 (2xCH$_2$); 30.4 (CH$_2$); 33.5 (CH$_2$); 33.7 (CH$_2$); 114.1 (CH$_2$); 139.1 (CH).

1-iodo-3-(undec-10-enyloxy)benzene (514). 3-Iodo-phenol (1.86 g, 8.46 mmol), 11-iodoundec-1-ene (2.26 g, 8.06 mmol), K$_2$CO$_3$ (1.23 g, 8.86 mmol) and 18-crown[6] (213 mg, 10 mol%) were stirred in anhydrous THF (25 ml) for 20h under reflux. The solvent was evaporated and the residue was taken up in H$_2$O and CH$_2$Cl$_2$. The organic layer was washed with NaOH (1N in H$_2$O). The solvent was evaporated to give 1-iodo-3-(undec-10-enyloxy)benzene (2.75 g, 92 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.33-1.48 (12H,

6xCH$_2$); 1.78 (p, 2H, J = 7.2 Hz, CH$_2$); 2.08 (q, 2H, J = 6.7 Hz, CH$_2$); 3.91 (t, 2H, J = 6.5 Hz, CH$_2$); 4.97 (d, 1H, J = 10.2 Hz, CHH); 5.03 (d, 1H, J = 17.2 Hz, CHH); 5.84 (ddt, 1H, J = 6.7 Hz, J = 10.2 Hz, J = 17.2 Hz, CH); 6.86 (d, 1H, J = 8.2 Hz, CH); 6.98 (dd, 1H, J = 8.2 Hz, J = 8.2 Hz, CH); 7.26-7.28 (2H, 2xCH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 25.9 (CH$_2$); 28.8 (CH$_2$); 29.0 (CH$_2$); 29.1 (CH$_2$); 29.2 (CH$_2$); 29.3 (CH$_2$); 29.4 (CH$_2$); 33.7 (CH$_2$); 70.5 (CH$_2$); 94.3 (C); 114.0 (CH); 114.1 (CH$_2$); 123.5 (CH); 129.4 (CH); 130.5 (CH); 138.9 (CH); 159.6 (C).

1-(3-(undec-10-enyloxy)phenyl)hydrazine carboxylic acid tert-butyl ester (515). 1-iodo-3-(undec-10-enyloxy)benzene (2.19 g, 58.8 mmol), hydrazine carboxylic acid tert-butyl ester (1.05 g, 7.97 mmol), CuI (63 mg, 5 mol%), 1,10-phenantroline (239 mg, 10 mol%) and Cs$_2$CO$_3$ (3.03 g, 9.3 mmol) were stirred in dry DMF (7 ml) for 21 h at 80°C. Then the mixture was poured into EtOAc (30 ml) and was filtered through a pad of silica. The solvent was removed and the residue was purified by chromatography (silica, cyclohexane, CH$_2$Cl$_2$, NEt$_3$) to give 1-(3-(undec-10-enyloxy)phenyl)hydrazine carboxylic acid tert-butyl ester (1.51 g, 68 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.29-1.35 (12H, 6xCH$_2$); 1.50 (s, 9H, 3xCH$_3$); 1.75 (p, 2H, J = 7.0 Hz, CH$_2$); 2.03 (q, 2H, J = 7.0 Hz, CH$_2$); 3.92 (t, 2H, J = 6.5 Hz, CH$_2$); 4.41 (s, 2H, NH$_2$); 4.92 (d, 1H, J = 10.2 Hz, CHH); 4.98 (d, 1H, J = 17.1 Hz, CHH); 5.79 (ddt, 1H, J = 7.0 Hz, J = 10.2 Hz, J = 17.1 Hz, CH); 6.64 (d, 1H, J = 8.3 Hz, CH); 7.03-7.05 (2H, 2xCH); 7.16 (dd, 1H, J = 7.5 Hz, J = 7.8 Hz, CH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 25.9 (CH$_2$); 28.2 (3xCH$_3$); 28.8 (CH$_2$); 29.0 (CH$_2$); 29.2 (CH$_2$); 29.3 (CH$_2$); 29.3 (CH$_2$); 29.4 (CH$_2$); 33.7 (CH$_2$); 67.9 (CH$_2$); 81.6 (C); 109-7 (CH); 110.7 (CH); 114.0 (CH$_2$); 115.4 (CH); 128.5 (CH); 139.1 (CH); 144.1 (C); 155.0 (C); 159.0 (C). IR: $\tilde{n}$ [cm^{-1}] = 3338 (w); 3075 (w); 2975 (s); 2927 (vs); 2854 (s); 1698 (vs); 1602 (vs); 1367 (vs); 1336 (vs); 1280 (s); 1255 (s); 1220 (s); 1164 (vs). HRMS found M$^+$ 376.2749, C$_{22}$H$_{36}$N$_2$O$_3$ requires M$^+$, 376.2772. Elementary analysis found C 70.70%, H 9.60%, N 7.37%, C$_{22}$H$_{36}$N$_2$O$_3$ requires C 70.18%, H 9.64%, N 7.44%.

Preperation of 517. 1-(3-(undec-10-enyloxy)phenyl)hydrazinecarboxylic acid tert-butyl ester (300 mg, 0.80 mmol), Rh(acac)(CO)$_2$ (8.43 mg, 4 mol%) and XANTPHOS (64 mg, 20 mol%) in anhydrous THF were filled in an autoclave, pressurized with 10bar CO and 10bar H$_2$ and were stirred for 68h at 100°C. The solvent was removed and the residue was purified by flash chromatography (silica, CH$_2$Cl$_2$, i-PrOH) to give **415** (310 mg, 100 %). **415** (301 mg, 0.74 mmol) was dissolved in H$_2$SO$_4$ (150 g, 4 wt% in THF) and was stirred for 2h under reflux. After addition of NH$_3$ the mixture was extracted with EtOAc, the solvent was remove and the residue was purified by *prep*HPLC to give the title compound (41 mg, 20 %)

as a mixture of *n/iso*-regioisomers. Major isomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 0.46-1.27 (10H, 5xCH$_2$); 1.45-1.53 (4H, 2xCH$_2$); 1.66-1.92 (2H, CH$_2$); 2.57 (dt, 1H, J = 3.7 Hz, J = 14.3 Hz, C*H*H); 2.99 (dt, 1H, J = 5.0 Hz, J = 14.3 Hz, CH*H*); 4.19-4.30 (2H, CH$_2$); 6.87 (s, 1H, CH); 6.92 (d, 1H, J = 8.7 Hz, CH); 6.99 (s, 1H, CH); 7.55 (d, 1H, J = 8.7 Hz, CH); 7.74 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 25.3 (4xCH$_2$); 26.7 (2xCH$_2$); 27.4 (2xCH$_2$); 28.9 (2xCH$_2$); 71.2 (2xCH$_2$); 103.0 (CH); 112.9 (CH); 120.7 (CH); 121.4 (CH). Minor isomer: ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 0.17 (bs, 1H, C*H*H); 0.55 (bs, 1H,CH*H*); 0.66-0.72 (4H, 2xCH$_2$); 1.02-1.72 (11H, CH$_3$, 4xCH$_2$); 2.46 (dt, 1H, J = 5.0 Hz, J = 19.0 Hz, C*H*H); 2.98 (dt, 1H, J = 5.0 Hz, J = 14.2 Hz, CH*H*); 3.79 (dt, 12H, J = 8.7 Hz, J = 11.5 Hz, C*H*H); 4.28 (dt, 1H, J = 11.5 Hz, J = 11.7 Hz, CH*H*); 6.80 (d, 1H, J = 8.5 Hz, CH); 7.03 (s, 1H, CH); 7.36 (d, 1H, J = 8.5 Hz, CH); 7.58 (bs, 1H, NH). ESI/MS: 277 [M+H]$^+$.

1-(4-(4-Iodophenoxy)butoxy)-4-iodobenzene (529a). 4-Iodophenol (4.41 g, 20.0 mmol), 1,4-dibromobutane (1.97 g, 9.11 mmol), K$_2$CO$_3$ (3.15 g, 22.8 mmol) and 18-crown[6] (243 mg, 10 mol%) were stirred in anhydrous THF (100 ml) under reflux for 20h. The solvent was evaporated and the residue was taken up in H$_2$O (100 ml) and CH$_2$Cl$_2$ (100 ml). The organic layer was washed with NaOH (1N in H$_2$O) and the solvent was evaporated to give 1-(4-(4-iodophenoxy)butoxy)-4-iodobenzene (4.35 g, 97 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.94 (t, 4H, J = 5.5 Hz, 2xCH$_2$); 3.98 (t, 4H, J = 5.5 Hz, 2xCH$_2$); 6.66 (d, 4H, J = 9.0 Hz, 4xCH); 7.53 (d, 4H, J = 9.0 Hz, 4xCH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 25.8 (2xCH$_2$); 67.5 (2xCH$_2$); 82.6 (2xC); 116.9 (4xCH); 138.2 (4xCH); 158.8 (2xC). HRMS found M$^+$ 493.9266, C$_{16}$H$_{16}$I$_2$O$_2$ requires M$^+$, 493.9292.

1-(10-(4-Iodophenoxy)decyloxy)-4-iodobenzene (529b). 4-Iodophenol (3.77 g, 17.1 mmol), 1,10-dibromodecane (2.33 g, 7.78 mmol), K$_2$CO$_3$ (2.69 g, 19.5 mmol) and 18-crown[6] (212 mg, 10 mol%) were stirred in anhydrous THF (100 ml) under reflux for 20 h. The solvent was evaporated and the residue was taken up in H$_2$O (100 ml) and CH$_2$Cl$_2$ (100 ml). The organic layer was washed with NaOH (1N in H$_2$O) and the solvent was evaporated to give 1-(10-(4-iodophenoxy)decyloxy)-4-iodobenzene (3.90 g, 87 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.31-1.35 (8H, 4xCH$_2$); 1.42-1.44 (4H, 2xCH$_2$); 1.75 (dt, 4H, J = 6.7 Hz, J = 8.0 Hz, 2xCH$_2$); 3.90 (t, 4H, J = 6.7 Hz, 2xCH$_2$); 6.66 (d, 4H, J = 9.0 Hz, 4xCH); 7.53 (d, 4H, J = 9.0 Hz, 4xCH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 25.9 (2xCH$_2$); 29.1 (2xCH$_2$); 29.3 (2xCH$_2$); 29.4 (2xCH$_2$); 68.1 (2xCH$_2$); 82.4 (2xC); 116.9 (4xCH); 138.1 (4xCH); 159.0 (2xC).

4-(4-(4-(Hydrazinecarboxylic acid tert-butyl ester)phenoxy)butoxy) benzenhydrazine carboxylic acid tert-butyl ester (530a). 1-(4-(4-Iodophenoxy)butoxy)-4-iodobenzene (2.95 g, 5.97 mmol), hydrazine carboxylic acid tert-butyl ester (1.89 g, 14.3 mmol), CuI (23 mg, 2 mol%), 1,10-phenantroline (238 mg, 22 mol%) and Cs_2CO_3 (5.45 g, 16.7 mmol) were stirred in dry DMF (6 ml) for 21 h at 80°C. Then the mixture was poured into EtOAc (30 ml) and was filtered through a pad of silica. The solvent was removed and the residue was purified by chromatography (silica, cyclohexane, CH_2Cl_2, NEt_3) to give 4-(4-(4-(hydrazinecarboxylic acid tert-butyl ester) phenoxy) butoxy) benzenhydrazine carboxylic acid tert-butyl ester (2.52 g, 84 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.47 (s, 18H, 6xCH$_3$); 1.95 (t, 4H, J = 5.2 Hz, 2xCH$_2$); 4.00 (bs, 4H, 2xCH$_2$); 4.43 (bs, 4H, 2xNH$_2$); 6.83 (d, 4H, J = 8.7 Hz, 4xCH); 7.28 (d, 4H, J = 8.7 Hz, 4xCH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 25.9 (2xCH$_2$); 28.3 (6xCH$_3$); 67.6 (2xCH$_2$); 81.3 (2xC); 114.0 (4xCH); 125.2 (4xCH); 136.3 (2xC); 156.2 (2xC). Elementary analysis found C 62.32%, H 7.50%, N 10.88%, $C_{26}H_{38}N_4O_6$ requires C 62.13%, H 7.62%, N 11.15%.

4-(4-(4-(Hydrazinecarboxylic acid tert-butyl ester) phenoxy) decoxy) benzenhydrazine carboxylic acid tert-butyl ester (530b). 1-(10-(4-Iodophenoxy)decyloxy)-4-iodobenzene (3.69 g, 6.39 mmol), hydrazine carboxylic acid tert-butyl ester (2.03 g, 15.3 mmol), CuI (150 mg, 12.5 mol%), 1,10-phenantroline (238 mg, 25 mol%) and Cs_2CO_3 (5.83 g, 17.9 mmol) were stirred in dry DMF (6 ml) for 21 h at 80°C. Then the mixture was poured into EtOAc (30 ml) and was filtered through a pad of silica. The solvent was removed and the residue was purified by chromatography (silica, cyclohexane, CH_2Cl_2, NEt_3) to give 4-(4-(4-(hydrazine carboxylic acid tert-butyl ester) phenoxy) decoxy) benzenhydrazine carboxylic acid tert-butyl ester (2.90 g, 77 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.32 (bs, 8H, 4xCH$_2$); 1.42-1.46 (4H, 2xCH$_2$); 1.46 (s, 18H, 6xCH$_3$); 1.75 (dt, 4H, J = 7.2 Hz, J = 7.7 Hz, 2xCH$_2$); 3.92 (t, 4H, J = 6.5 Hz, 2xCH$_2$); 4.38 (bs, 4H, 2xNH$_2$); 6.81 (d, 4H, J = 9.0 Hz, 4xCH); 7.27 (d, 4H, J = 9.0 Hz, 4xCH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 25.9 (2xCH$_2$); 28.3 (6xCH$_3$); 29.2 (2xCH$_2$); 29.3 (2xCH$_2$); 29.4 (2xCH$_2$); 68.1 (2xCH$_2$); 81.2 (2xC); 114.0 (4xCH); 125.2 (4xCH); 136.1 (2xC); 156.4 (2xC). Elementary analysis found C 65.50%, H 8.77%, N 9.50%, $C_{32}H_{50}N_4O_6$ requires C 65.50%, H 8.59%, N 9.55%.

4-Methylenepiperidine (532). Ethyl 4-methylenepiperidine-1-carboxylate (14.8 g, 87.5 mmol) was stirred in glycol (75 ml) and NaOH (50 wt% in H_2O, 80 g) under reflux over night. The product was extracted with Et_2O and the organic layer was washed with H_2O. The solvent was removed and the residue was distilled to give 4-methylenepiperidine (3.78 g,

44 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.75 (bs, 1H, NH); 2.04 (dd, 4H, J = 7.2 Hz, J = 7.7 Hz, 2xCH$_2$); 2.71 (dd, 4H, J = 7.2 Hz, J = 7.7 Hz, 2xCH$_2$); 4.51 (s, 2H, CH$_2$).

1,2-Bis(4-methylenepiperidin-1-yl)ethane-1,2-dione (533). 4-Methylenepiperidine (2.10 g, 21.2 mmol), NEt$_3$ (1.19 g, 11.1 mmol) and DMAP (65 mg, 5 mol%) were dissolved in anhydrous THF (25 ml) and oxalylchloride (1.28 g, 10.1 mmol) was added dropwise at 0°C. The mixture was stirred for 1h at ambient temperature. The precipitate was removed by filtration and the solvent was evaporated to give 1,2-bis(4-methylenepiperidin-1-yl)ethane-1,2-dione (1.70 g, 68 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 2.27 (dd, 4H, J = 5.8 Hz, J = 6.0 Hz, 2xCH$_2$); 3.39 (dd, 2H, J = 5.8 Hz, J = 6.0 Hz, CH$_2$); 3.63 (dd, 2H, J = 5.8 Hz, J = 6.0 Hz, CH$_2$); 4.82 (d, 2H, J = 4.3 Hz, CH$_2$). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 33.9 (2xCH$_2$); 34.9 (2xCH$_2$); 42.4 (2xCH$_2$); 47.6 (2xCH$_2$); 110.6 (2xCH$_2$); 143.6 (2xC); 163.4 (2xC). IR: $\tilde{n}$ [cm^{-1}] = 3461 (w); 3076 (s); 2937 (vs); 1617 (vs); 1498 (vs); 1440 (vs); 1274 (vs); 1180 (s); 1070 (vs); 985 (vs); 889 (vs). Elementary analysis found C 66.91%, H 8.40%, N 11.17%, C$_{14}$H$_{20}$N$_2$O$_2$ requires C 67.71%, H 8.12%, N 11.28%.

Preparation of 534a. 1,2-Bis(4-methylenepiperidin-1-yl)ethane-1,2-dione (160 mg, 0.65 mmol), 4-(4-(4-(hydrazinecarboxylic acid tert-butyl ester) phenoxy) butoxy) benzenhydrazine carboxylic acid tert-butyl ester (324 mg, 0.65 mmol) and Rh(acac)(CO)$_2$ (6.6 mg, 4 mol%) were dissolved in anhydrous THF (129 ml), filled in an autoclave and pressurized with 50bar CO and 10bar H$_2$. The mixture was stirred at 110°C for 20h. The solvent was removed and the residue was purified by flash chromatography (silica, CH$_2$Cl$_2$/EtOH 9:1) to give **433a** (425 mg, 85 %). ^{1}H-NMR: (CDCl$_3$, 400 MHz) d = 1.17 (bs, 4H, 2xCH$_2$); 1.37 (s, 18H, 9xCH$_3$); 1.69 (bs, 4H, 2xCH$_2$); 1.72 (bs, 2H, 2xCH); 1.90-1.99 (4H, 2xCH$_2$); 2.23 (bs, 4H, 2xCH$_2$); 2.61 (bs, 2H, CH$_2$); 3.00 (bs, 2H, 2xCH$_2$); 3.50 (bs, 2H, CH$_2$); 4.05 (bs, 4H, 2xCH$_2$); 4.40 (bs, 2H, 2xCH$_2$); 6.84 (bs, 2H, 2xCH); 6.95 (s, 8H, 8xCH). ^{13}C-NMR: (CDCl$_3$, 100 MHz) d = 26.9 (2xCH$_2$); 29.1 (6xCH$_3$); 32.3 (2xCH$_2$); 33.2 (2xCH$_2$); 35.3 (2xCH); 40.0 (2xCH$_2$); 41.8 (2xCH$_2$); 47.2 (2xCH$_2$); 68.9 (2xCH$_2$); 82.1 (2xC); 116.4 (4xCH); 130.8 (2xC); 130.9 (4xCH); 145.0 (2xCH); 153.7 (2xC); 159.6 (2xC); 164.1 (2xC). ESI/MS: 797 [M+Na]$^+$; 775 [M+H]$^+$; 719 [M-*tert.*-Bu+H]$^+$; 697 [M-Boc+Na]$^+$; 597 [M-2Boc+Na]$^+$; 575 [M-2Boc+H]$^+$.

Preparation of 534b. 1,2-Bis(4-methylenepiperidin-1-yl)ethane-1,2-dione (145 mg, 0.58 mmol), 4-(4-(4-(hydrazine carboxylic acid tert-butyl ester) phenoxy) decoxy) benzenhydrazine carboxylic acid tert-butyl ester (341 mg, 0.58 mmol) and Rh(acac)(CO)$_2$ (6 mg, 4 mol%) were dissolved in anhydrous THF (116 ml), filled in an autoclave and

pressurized with 50bar CO and 10bar H_2. The mixture was stirred at 110°C for 20h. The solvent was removed and the residue was purified by flash chromatography (silica, CH_2Cl_2/EtOH 9:1) to give **534b** (407 mg, 81 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 0.64-1.11 (46H, 14xCH_2, 6xCH_3); 1.55 (bs, 2H, 2xCH); 1.90-2.01 (2H, CH_2); 2.28-2.42 (2H, CH_2); 2.84 (bs, 2H, CH_2); 3.26 (t, 4H, J = 6.4 Hz, 2xCH_2); 3.73 (bs, 2H, CH_2); 5.88 (bs, 2H, 2xCH); 6.25 (s, 8H, 8xCH. ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 29.1 (4xCH_2); 31.3 (6xCH_3); 32.3 (4xCH_2); 32.5 (4xCH_2); 34.4 (CH_2); 35.4 (CH_2); 40.3 (2xCH); 44.0 (2xCH_2); 49.3 (2xCH_2); 71.4 (2xCH_2); 84.2 (2xC); 118.6 (4xCH); 132.5 (2xC); 133.0 (4xCH); 147.2 (2xCH); 155.9 (2xC); 161.9 (2xC); 166.2 (2xC). ESI/MS: 881 [M+Na]$^+$; 659 [M-2Boc+H]$^+$.

10.7 EXPERIMENTS IN CHAPTER 6

Preparation of 604. 2,2'-Bis(allyloxy)-1,1'-binaphthyl (205 mg, 0.56 mmol), 4-(4-(4-(hydrazinecarboxylic acid tert-butyl ester) phenoxy) butoxy) benzenhydrazine carboxylic acid tert-butyl ester (281 mg, 0.56 mmol), Rh(acac)(CO)$_2$ (5.9 mg, 4 mol%) and XANTPHOS (65 mg, 20 mol%) were dissolved in anhydrous THF (112 ml), filled in an autoclave and pressurized with 10bar CO and 10bar H_2. The mixture was stirred at 100°C for 20h. The solvent was removed and the residue was purified by flash chromatography (silica, CH_2Cl_2/EtOH 9:1) to give **604** (483 mg, 97 %). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.35-1.91 (30H, 6xCH_2, 6xCH_3); 3.88-3.95 (8H, 4xCH_2); 6.32 (t, 2H, J = 5.2 Hz, 2xCH); 6.90 (s, 8H, 8xCH); 7.05 (d, 2H, J = 8.5 Hz, 2xCH); 7.10 (dd, 2H, J = 6.5 Hz, J = 8.5 Hz, 2xCH); 7.24 (dd, 2H, J = 6.5 Hz, J = 8.0 Hz, 2xCH); 7.33 (d, 2H, J = 9.2 Hz, 2xCH); 7.79 (d, 2H, J = 8.0 Hz, 2xCH); 7.87 (d, 2H, J = 9.2 Hz, 2xCH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 26.2 (2xCH_2); 28.2 (6xCH_3); 28.7 (2xCH_2); 29.2 (2xCH_2); 68.2 (2xCH_2); 68.9 (2xCH_2); 115.3 (4xCH); 115.9 (2xCH); 120.2 (2xC); 123.5 (2xCH); 125.3 (2xCH); 126.0 (2xCH); 127.7 (2xCH); 129.1 (2xCH); 129.2 (2xC); 129.6 (2xC); 130.1 (4xCH); 133.6 (2xC); 145.8 (2xCH); 153.0 (2xC); 154.1 (2xC); 158.8 (2xC).

10.8 EXPERIMENTS IN CHAPTER 7

2-(diphenylphosphino)-*N*-(2-methyl-1-phenylallyl)benzamide (702). LiAlH$_4$ (4.67 g, 123 mmol) was suspended in dry THF (100 ml). A solution of (*E*)-2-methyl-3-phenylacrylic acid (24.9 g, 154 mmol) in dry THF (50 ml) was added dropwise and the resulting mixture was stirred over night at ambient temperatures. At 0°C water was added carefully, until hydrogen production stops. The slurry was dissolved by subsequent addition ofH$_2$SO$_4$ and the solution was extracted with EtOAc to give (*E*)-2-methyl-3-phenylprop-2-en-1-ol (22.7 g,

100 %) without further purification. NaH (314 mg, 10 mol%) was suspended in dry Et_2O (60 ml) and (*E*)-2-methyl-3-phenylprop-2-en-1-ol (11.7 g, 78.6 mmol) in dry Et2O (20 ml) was added within 10 min. At -10°C trichloroacetonitrile (11.4 g, 78.6 mmol) was added dropwise and the resulting mixture was stirred for 15 min at 0°C. The solvent was removed and the residue was dissolved in pentane (200 ml with 0.5 ml MeOH). The solution was decanted from the remaining solid and the solvent was evaporated to give (*E*)-2-methyl-3-phenylallyl 2,2,2-trichloroacetimidate (19.6 g, 85 %) without further purification. A solution of (*E*)-2-methyl-3-phenylallyl 2,2,2-trichloroacetimidate (16.5 g, 56.6 mmol) in xylene (500 ml) was stirred over night under reflux. The solvent was removed to give 2,2,2-trichloro-*N*-(2-methyl-1-phenylallyl)acetamide (16.5 g, 100 %) without further purification. A solution of 2,2,2-trichloro-*N*-(2-methyl-1-phenylallyl)acetamide in EtOH (100 ml) and NaOH (150 ml, 8N in H_2O) was stirred at ambient temperatures for 40 h. The mixture was extracted and the solution was saturated with HCl-gas. The precipitate was collected by filtration to give 2-methyl-1-phenylprop-2-en-1-amine hydrochloride (5.25 g, 55). A solution of 2-methyl-1-phenylprop-2-en-1-amine (422 mg, 2.3 mmol) and DCC (521 mg, 2.53 mmol) in anhydrous CH_2Cl_2 (2 ml) was added to a solution of 2-(diphenylphosphino)benzoic acid (703 mg, 2.3 mmol) and DMAP (14 mg, 5 mol%) in CH_2Cl_2 (2 ml). After stirring over night at ambient temperatures the solvent was evaporated and the residue was taken up in Et_2O. The solvent was removed *in vacuo* after filtration through a sintered glass filter and the residue was purified by chromatography (silica, cyclohexane, EtOAc) to give 2-(diphenylphosphino)-*N*-(2-methyl-1-phenylallyl)benzamide (450 mg, 45%). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.65 (s, 3H, CH$_3$); 4.99 (s, 1H, C*H*H); 5.07 (s, 1H, CH*H*); 5.59 (d, 1H, J = 7.5 Hz, CH); 6.51 (bs, 1H, NH); 7.00 (bs, 1H, CH); 7.19-7.40 (17H, 17xCH); 7.70 (bs, 1H, CH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 20.2 (CH$_3$); 59.2 (CH); 111.9 (CH$_2$); 127.3 (4xCH); 128.5 (9xCH); 130.1 (1xCH); 133.6 (4xCH); 134.2 (CH); 135.4 (C); 136.7 (2xC); 139.6 (2xC); 141.6 (C); 143.6 (2xC); 167.8 (C). ^{31}P-NMR (CDCl$_3$, 80Hz) d = -10.02 (s, 1P, PAr$_3$). HRMS found [M]$^+$ 436.1847, C$_{29}$H$_{26}$NOP requires [M+H]$^+$ 436.1864.

(*E*)-2-methyl-3-phenylprop-2-en-1-ol (710). (*E*)-Ethyl 2-methyl-3-phenylallyl carbonate (952 mg, 4.32 mmol), hexylamine (1.31 g, 12.97 mmol), P(OPh)$_3$ (101 mg, 8 mol%) and [Ir(cod)Cl]$_2$ (58 mmol, 2 mol%) in dry EtOH (10 ml) were stirred for 2 h under reflux. The solvent was removed *in vacuo* and the residue was purified by chromatography (silica,

2.5 vol% EtOAc in cyclohexane) to give (*E*)-2-methyl-3-phenylprop-2-en-1-ol (555 mg, 56 %). Analytical data fits with the literature[114].

1-(cyclohexenylmethyl)piperidine (717). Cyclohexenylmethyl ethyl carbonate (205 mg, 1.1 mmol), piperidine (285 mg, 3.4 mmol), P(OPh)$_3$ (26 mg, 8 mol%) and [Ir(cod)Cl]$_2$ (15 mmol, 2 mol%) in dry EtOH (2 ml) were stirred for 2 h under reflux. The solvent was removed *in vacuo* to give 1-(cyclohexenylmethyl)piperidine (100 %*, 40 % conversion).^{1}H-NMR: (CDCl$_3$, 500 MHz) *d* = 1.40-1.62 (18H, 9xCH$_2$); 2.83 (s, 2H, CH$_2$); 5.56 (s, 1H, CH).^{13}C-NMR: (CDCl$_3$, 125 MHz) *d* = 22.2 (2xCH$_2$); 22.7 (CH$_2$); 24.1 (CH$_2$); 25.0 (CH$_2$); 25.1 (CH$_2$); 27.4 (CH$_2$); 54.2 (2xCH$_2$); 66.2 (CH$_2$); 129.2 (CH); 132.3 (C).

_N_-hexyl-2-methylenecyclohexanamine (719). Ethyl 2-methylenecyclohexyl carbonate (1.47 g, 7.7 mmol), hexylamine (2.33 g, 23.0 mmol), P(OPh)$_3$ (180 mg, 8 mol%) and [Ir(cod)Cl]$_2$ (103 mmol, 2 mol%) in dry EtOH (15 ml) were stirred for 24 h under reflux. The solvent was removed and the residue was purified by chromatography (silica, 2.5 vol% EtOAc in cyclohexane) to give *N*-hexyl-2-methylenecyclohexanamine (1.14 g, 73 %, 80 % conversion).^{1}H-NMR: (CDCl$_3$, 500 MHz) *d* = 0.81 (bs, 3H, CH$_3$); 1.15-1.92 (16H, 8xCH$_2$); 2.20 (bs, 1H, CH); 2.46-2.49 (2H, CH$_2$); 4.65 (s, 2H, CH$_2$). ^{13}C-NMR: (CDCl$_3$, 125 MHz) *d* = 13.9 (CH$_3$); 22.5 (CH$_2$); 23.4 (CH$_2$); 27.0 (CH$_2$); 28.3 (CH$_2$); 30.2 (CH$_2$); 31.7 (CH$_2$); 33.4 (CH$_2$); 34.7 (CH$_2$); 47.4 (CH$_2$); 60.6 (CH); 105.7 (CH$_2$); 150.8 (C).

2-methylenecyclohexyl 2-(diphenylphosphino)benzoate (724). A solution of 2-methylenecyclohexanol (161 mg, 1.4 mmol) and DCC (323 mg, 1.6 mmol) in anhydrous CH$_2$Cl$_2$ (2 ml) was added to a solution of 2-(diphenylphosphino)benzoic acid (436 mg, 1.4 mmol) and DMAP (9 mg, 5 mol%) in CH$_2$Cl$_2$ (4 ml). After stirring over night at ambient temperatures the solvent was evaporated and the residue was taken up in Et$_2$O. The solvent was removed *in vacuo* after filtration through a sintered glass filter and the residue was purified by chromatography (silica, cyclohexane, EtOAc) to give 2-methylenecyclohexyl 2-(diphenylphosphino)benzoate (570 mg, 100%). ^{1}H-NMR: (CDCl$_3$, 500 MHz) *d* = 1.47-2.41 (8H, 4xCH$_2$); 4.75 (s, 1H, C*H*H); 4.84 (s, 1H, CH*H*); 5.34-5.40 (1H, CH); 6.91-6.97 (1H, CH); 7.26-7.42 (12H, 12CH); 8-09-8.16 (1H, CH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) *d* = 23.3 (CH$_2$); 27.4 (CH$_2$); 33.2 (CH$_2$); 33.5 (CH$_2$); 75.2 (CH); 107.6 (CH$_2$); 128.2 (CH); 128.4-128.5 (6xCH); 130.5 (CH); 131.8 (CH); 133.8 (2xCH); 134.0 (CH); 134.3 (CH); 138.1 (2xC); 140.5 (C); 146.3 (2xC); 165.7 (C). ^{31}P-NMR (CDCl$_3$, 80Hz) *d* = -3.93 (s, 1P, PAr$_3$).

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[114] Lee, D.-Y.; Moon, C.W.; Jun, C.-H.; *J. Org. Chem.* **2002**, *67*, 3945-3948.

(1,2-*trans*)-2-(2-oxoethyl)cyclohexyl 2-(diphenylphosphino)benzoate (725). A solution of 2-methylenecyclohexyl 2-(diphenylphosphino)benzoate (27 mg, 0.07 mmol) and Rh(acac)(CO)$_2$ (0.4 mg, 3 mol%) in dry benzene (350 mg) was filled in autoclave, was pressurized with CO (30 bar) and H$_2$ (30 bar) and was stirred for 68 h at 40°C. The solvent was evaporated and the residue was analyzed by NMR. ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.55-2.10 (10H, 5xCH$_2$); 2.42 (bs, 1H, CH); 4.65 (bs, 1H, CH); 6.90 (s, 1H, CH); 7.26-7.68 (12H, 12xCH); 8.02 (s, 1H, CH); 9.57 (s, 1H, CH). ^{31}P-NMR (CDCl$_3$, 80Hz) d = -3.73 (s, 1P, PAr$_3$).

(1,2-*trans*)-2-(5-methoxy-1H-indol-3-yl)cyclohexyl 2-(diphenylphosphino)benzoate (727). A solution of 2-methylenecyclohexyl 2-(diphenylphosphino)benzoate (308 mg, 0.77 mmol), *tert*-butyl 1-(4-methoxyphenyl)hydrazinecarboxylate (183 mg, 0.77 mmol), Rh(acac)(CO)$_2$ (6 mg, 3 mol%) in dry THF (3.8 g) was filled in autoclave, was pressurized with CO (30 bar) and H$_2$ (30 bar) and was stirred for 68 h at 40°C. The solvent was evaporated and the residue was taken up in H$_2$SO$_4$ (4 wt% in dry THF, 15 ml) and was stirred for 2 h under reflux. Ammonia (30 wt% in H$_2$O, 5 ml) was added and the mixture was extracted with EtOAc. The solvent was removed and the 219 mg of the residue was purified by chromatography (silica, cyclohexane, EtOAc) to give (1,2-trans)-2-(5-methoxy-1H-indol-3-yl)cyclohexyl 2-(diphenylphosphino)benzoate (44 %, 105 mg) as the only diastereomer. ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.59-2.17 (8H, 8xCH$_2$); 3.07 (dt, 1H, J = 4.0 Hz[115], J = 10.8 Hz, CH); 3.84 (s, 3H, CH$_3$); 5.16 (dt, 1H, J = 4.0 Hz[115], J = 9.3 Hz, CH); 6.84 (s, 3H, 3xCH); 7.11 (s, 1H, CH); 7.16-7.31 (11H, 11xCH); 7.53-7.59 (2H, 2xCH); 7.73 (bs, 1H, CH); 7.87 (bs, 1H, NH). ^{13}C-NMR: (CDCl$_3$, 125 MHz) d = 24.6 (CH$_2$); 25.7 (CH$_2$); 32.0 (CH$_2$); 33.2 (CH$_2$); 39.8 (CH); 55.9 (CH$_3$); 77.4 (CH); 101.2 (CH); 111.7 (CH); 111.8 (CH); 117.9 (C); 121.1 (CH); 127.7 (C); 127.9 (CH); 128.3 (5xCH); 128.4 (CH); 130.3 (CH); 131.2 (C); 131.4 (CH); 133.8 (2xCH); 133.9 (2xCH); 134.0 (CH); 134.9 (C); 138.2 (2xC); 140.0 (C); 153.7 (C); 166.5 (C). ^{31}P-NMR (CDCl$_3$, 80Hz) d = -4.16 (s, 1P, PAr$_3$).

10.9 EXPERIMENTS IN CHAPTER 8

10.9.1 HYDROFORMYLATION ON POLYMER SUPPORT

Polymer supported synthesis of 12-oxododecanoic acid (819) on PS Wang resin. Wangresin (500 mg, 1.1 mmol/g) undecenoic acid (304 mg, 1.65 mmol), DIPCDI (208 mg,

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[115] Coupling constant is characteristic for the *trans*-diastereomer. See Garden, S.J.; Silva, R.B. ; Pinto, A.C.; *Tetrahedron* **2002**, *58*, 8399–8412 for coupling constants of the *cis*- and the *trans*-isomer of 3-(2-hydroxycyclohexyl)-indole.

1.65 mmol), DMAP (10 mg, 5 mol%) and DMF (3 ml) were placed in a syringe and were shaken for 24h at ambient temperatures. The solvent was removed and the resin was washed consecutively with DMF, (5x), CH_2Cl_2 (5x), DMF (5x), CH_2Cl_2 (5x), Et_2O (5x), MeOH (5x) and Et_2O (5x). The resin was dried *in vacuo*. This resin (52 mg, 1.00 mmol/g), Rh(acac)(CO)$_2$ (3 mg, 11 µmol) and dry THF (80 ml) were placed in a PARR autoclave. The vessel was pressurized with CO (10 bar) and H_2 (10 bar) and the mixture was stirred carefully for 20h at 80°C. The resin was collected by filtration and was washed consecutively with THF (3x10 ml), THF/pentane (1:1, 3x10 ml) and pentane (3x10 ml) followed by drying *in vacuo*. This aldehyde resin (30 mg, 0.97 mmol/g) was shaken with TFA/CH_2Cl_2 (1:1, 3x10ml) for 20min at ambient temperature. The organic solutions were collected and the solvent and TFA were removed *in vacuo* to give 12-oxododecanoic acid (3.53 mg, 87%). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 0.85-1.27 (16H, 8xCH_2); 1.61 (bs, 2H, CH_2); 2.33 (bs, 2H, CH_2); 9.74 (bs, 1H, CH).

Polymer supported synthesis of 5-(4-(4-(2-oxoethyl)piperidin-1-ylsulfonyl) phenyl) pentanoic acid (822) on PS Wang resin. Resin **820** (30.6 mg, 0.87 mmol/g), Rh (acac)(CO)$_2$ (13.0 mg, 52 µmol) and dry THF (80 ml) were placed in a PARR autoclave. The vessel was pressurized with CO (50 bar) and H_2 (10 bar) and the mixture was stirred carefully for 20h at 80°C. The resin was collected by filtration and was washed consecutively with THF (3x10 ml), THF/pentane (1:1, 3x10 ml) and pentane (3x10 ml) followed by drying *in vacuo*. This aldehyde resin (31.4 mg, 0.85 mmol/g) was shaken with TFA/CH_2Cl_2 (1:1, 3x10ml) for 20min at ambient temperature. The organic solutions were collected and the solvent and TFA were removed *in vacuo* to give 5-(4-(4-(2-oxoethyl)piperidin-1-ylsulfonyl) phenyl) pentanoic acid (9.8 mg, 100%). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.67 (bs, 7H, 3xCH_2, CH); 2.26 (t, 2H, J = 11.6 Hz, CH_2); 2.36 (s, 4H, 2xCH_2); 2.69 (s, 2H, CH_2); 3.12 (s, 2H, CH_2); 3.75 (d, 1H, J = 10.8 Hz, CH_2); 7.31 (d, 2H, J = 7.6 Hz, 2xCH); 7.62 (d, 2H, J = 7.6 Hz, 2xCH); 9.70 (s, 1H, CH); 11.57 (bs, 1H, OH).

10.9.2 TANDEM HYDROFORMYLATION / HYDRAZONE FORMATION ON POLYMER SUPPORT.

Polymer supported synthesis of (*E*)-tert-butyl 2-(2-(1-(4-(5-methoxy-5-oxopentyl) phenylsulfonyl) piperidin-4-yl) ethylidene)-1-(4-methoxyphenyl) hydrazinecarboxylate (825) on PS HMBA resin. Resin **823** (30 mg, 0.73 mmol/g (theory)), Rh(acac)(CO)$_2$ (0.87 mg, 20 mol%), *tert*-butyl 1-(4-methoxyphenyl)hydrazinecarboxylate (52 mg, 219µmol) and dry THF (2 ml) in a conical glass vial were placed in a BERGHOF autoclave. The vessel

was pressurized with CO (50 bar) and H_2 (10 bar) and the mixture was magnetically stirred for 44h at 80°C. The resin was collected by filtration and was washed consecutively with THF (3x10 ml), THF/MeOH (1:1, 3x10 ml) and MeOH (3x10 ml) followed by drying *in vacuo*. The hydrazone resin (35.5 mg, 0.62 mmol/g) was stirred in dioxane/DIPEA/MeOH (5:4:1, 3ml) for 12h at 80°C. The resin was filtered and washed with THF (3x10 ml), THF/MeOH (1:1, 3x10 ml) and MeOH (3x10 ml). The solvent was removed *in vacuo* to give (*E*)-tert-butyl 2-(2-(1-(4-(5-methoxy-5-oxopentyl) phenylsulfonyl) piperidin-4-yl) ethylidene)-1-(4-methoxyphenyl) hydrazinecarboxylate (3 mg, 23%). ^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.32-1.52 (9H, 4xCH$_2$, CH); 1.40 (s, 9H, 3xCH$_3$) 2.19 (t, 2H, J = 6.0 Hz, CH$_2$); 2.33 (bs, 2H, CH$_2$); 2.69 (bs, 2H, CH$_2$); 2.92-3.07 (2H, CH$_2$); 3.66 (s, 3H, CH$_3$); 3.68 (bs, 2H, CH$_2$); 3.82 (s, 3H, CH$_3$); 6.55 (t, 1H, J = 5.5 Hz, CH); 6.93 (s, 4H, 4xCH); 7.30 (d, 2H, J = 8.4 Hz, 2xCH); 7.62 (d, 2H, J = 8.4 Hz, 2xCH). ESI/MS: 624 [M+Na]$^+$.

### 10.9.3 TANDEM HYDROFORMYLATION / FISCHER INDOLIZATION ON POLYMER SUPPORT

Polymer supported synthesis of *N*-ethyl-2-(5-methoxy-1H-indol-3-yl)propan-1-amine (833) on PS sulfonylchloride resin. Resin **803** (51 mg, 1.37 mmol/g), Rh(acac)(CO)$_2$ (3.58 mg, 20 mol%), *tert*-butyl 1-(4-methoxyphenyl)hydrazinecarboxylate (165 mg, 694μmol) and dry THF (2 ml) in a conical glass vial were placed in a BERGHOF autoclave. The vessel was pressurized with CO (50 bar) and H_2 (10 bar) and the mixture was magnetically stirred for 44h at 80°C. The resin was collected by filtration and was washed consecutively with THF (3x10 ml), THF/MeOH (1:1, 3x10 ml) and MeOH (3x10 ml) followed by drying *in vacuo*. The hydrazone resin (68 mg, 1.02 mmol/g), BF$_3$*Et$_2$O (99 mg, 694 µmol) and molecular sieves (4Å) were stirred in dry CH$_2$Cl$_2$/AcOH (1:1, 2 ml) for 17h at 65°C. The resin was filtered, washed with CH$_2$Cl$_2$ (3x10 ml), CH$_2$Cl$_2$/MeOH (1:1, 3x10 ml) and MeOH (3x10 ml) and dried *in vacuo* to give indole resin (57 mg, 1.16 mmol/g). This resin (57 mg, 1.16 mmol/g) and Li-biphenylide in THF (694μmol) were stirred in dry THF (2ml) for 2h at 0°C. The mixture was quenched with water (100μl) and the resin was separated by filtration. The resin was washed with THF/H$_2$O (1:1, 2x2ml) and THF/HCl (2N in water, 1:1, 2x2ml). THF was removed *in vacuo* and the residue was taken up in EtOAc. The organic layers were separated and were washed with HCl (1N in water, 1x). The collected aqueous layers were washed with EtOAc (2x) and the pH was adjusted to pH=11. The aqueous layer was extracted with EtOAc (3x). The solvent was removed to give *N*-ethyl-2-(5-methoxy-1H-indol-3-yl)propan-1-amine (3 mg, 20%). ESI/MS: 232 [M+H]$^+$.

Polymer supported synthesis of *N*-ethyl-2-(1H-indol-3-yl)propan-1-amine (830) on PS sulfonylchloride resin. Resin **803** (51 mg, 1.37 mmol/g), Rh(acac)(CO)$_2$ (3.62 mg, 20 mol%), 1-(diphenylmethylene)-2-phenylhydrazine (190 mg, 700µmol), PTSA (66 mg, 350µmol) and dry THF (2 ml) in a conical glass vial were placed in a BERGHOF autoclave. The vessel was pressurized with CO (50 bar) and H$_2$ (10 bar) and the mixture was magnetically stirred for 44h at 80°C. The resin was collected by filtration and was washed consecutively with THF (3x10 ml), THF/MeOH (1:1, 3x10 ml) and MeOH (3x10 ml) followed by drying *in vacuo*. This resin (58mg, 1.20 mmol/g) and Li-biphenylide (in THF, 696µmol) were stirred in dry THF (2ml) for 2h at 0°C. The mixture was quenched with water (100µl) and the resin was separated by filtration. The resin was washed with THF/H$_2$O (1:1, 2x2ml) and THF/HCl (2N in water, 1:1, 2x2ml). THF was removed *in vacuo* and the residue was taken up in EtOAc. The organic layers were separated and were washed with HCl (1N in water, 1x). The collected aqueous layers were washed with EtOAc (2x) and the pH was adjusted to pH=11. The aqueous layer was extracted with EtOAc (3x). The solvent was removed to give *N*-ethyl-2-(5-methoxy-1H-indol-3-yl)propan-1-amine (3 mg, 21%).
^{1}H-NMR: (CDCl$_3$, 500 MHz) d = 1.20 (t, 3H, J = 7.2 Hz, CH$_3$); 1.47 (d, 3H, J = 7.0 Hz, CH$_3$); 2.92 (bs, 2H, CH$_2$); 3.14 (dd, 1H, J = 9.0 Hz, J = 10.6 Hz, C*H*H); 3.27 (dd, 1H, J = 8.5 Hz, J = 10.6 Hz, CH*H*); 3.41 (m, 1H, J = 7.0 Hz, CH); 5.20 (bs, 1H, NH); 7.05 (dd, 1H, J = 7.6 Hz, J = 7.7 Hz, CH); 7.14 (dd, 1H, J = 7.6 Hz, J = 8.0 Hz, CH); 7.18 (s, 1H, CH); 7.39 (d, 1H, J = 7.7 Hz, CH); 7.64 (d, 1H, J = 8.0 Hz, CH). NH not detected. ESI/MS: 203 [M+H]$^+$.

ZUSAMMENFASSUNG

In dieser Arbeit wurde gezeigt, dass die Tandem Hydroformylierung / FISCHER Indolsynthese ein geeignetes Werkzeug für die diversitätsorientierte Synthese biologisch relevanter Tryptamine und ihrer Homologe ist. Bei dieser neuen Tandemreaktion wird die Hydroformylierung von Aminoolefinen in Gegenwart aromatischer Hydrazine und von BRØNSTEDT-Säuren durchgeführt und man erhält Tryptamine in einem Schritt (Abbildung 1).

**Abbildung 1: Prinzip der Tandem Hydroformylierung / Fischer Indolsynthese.**
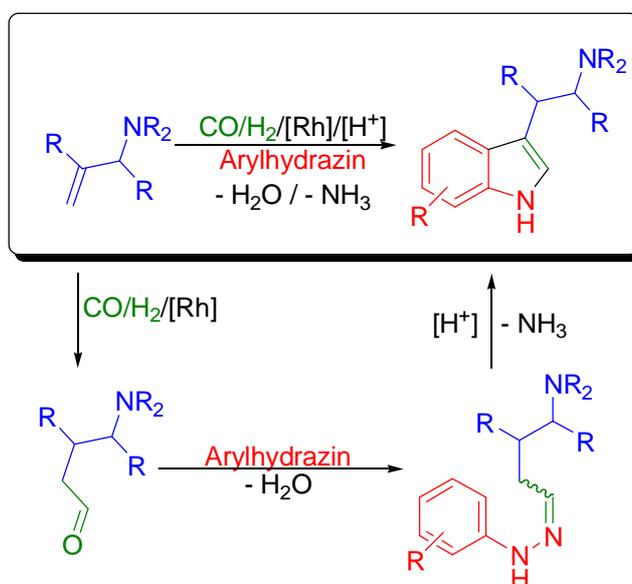
Im Gegensatz zum klassischen Protokoll, entfällt eine vorherige Synthese des benötigten Aldehyds, gefolgt von dessen Umsetzung zu einem als Acetal, Aminal, Bisulfitaddukt oder Enolether geschützten Aldehyd. Stattdessen werden Olefine *in situ* in Aldehyde umgewandelt, als Hydrazone abgefangen und sofort zu Tryptaminen indolisiert. Daher wird die simple Umformung funktioneller Gruppen durch kettenaufbauende Schritte in einem Einschrittverfahren ersetzt, das Zeit und Ressourcen einspart. Dieser Zugangsweg ist eine attraktive Alternative für bestehende Produktionsprozesse, da mit der Verwendung von Olefinen als alternative Rohstoffbasis, der Verfahrenspatentschutz umgangen werden könnte.

Ausgehend von geeigneten Aminen können Aminoolefine mit verschiedenen Methoden hergestellt werden, die als Stand der Technik zu bezeichnen sind (z.B. Substitution, Allylierung, WITTIG-Olefinierung, BARBIER-Reaktion, Carbomagnesierung, etc.). Dabei können alle biologisch wichtigen Valenzen, wie die Kettenlänge der Seitenkette und das Substitutionsmuster dieser Seitenkette, berücksichtigt werden und die daraus resultierenden

Aminoolefine lassen sich der Tandem Hydroformylierung / FISCHER Indolsynthese als verlässliches Werkzeug für die Synthese von Tryptaminen zuführen (Abbildung 2).

Abbildung 2: Kombination moderner Synthesemethoden für Aminoolefin emit der Tandem Hydroformylierung / Fischer Indolsynthese als diversitätsorientierterZugang zu Tryptaminen.
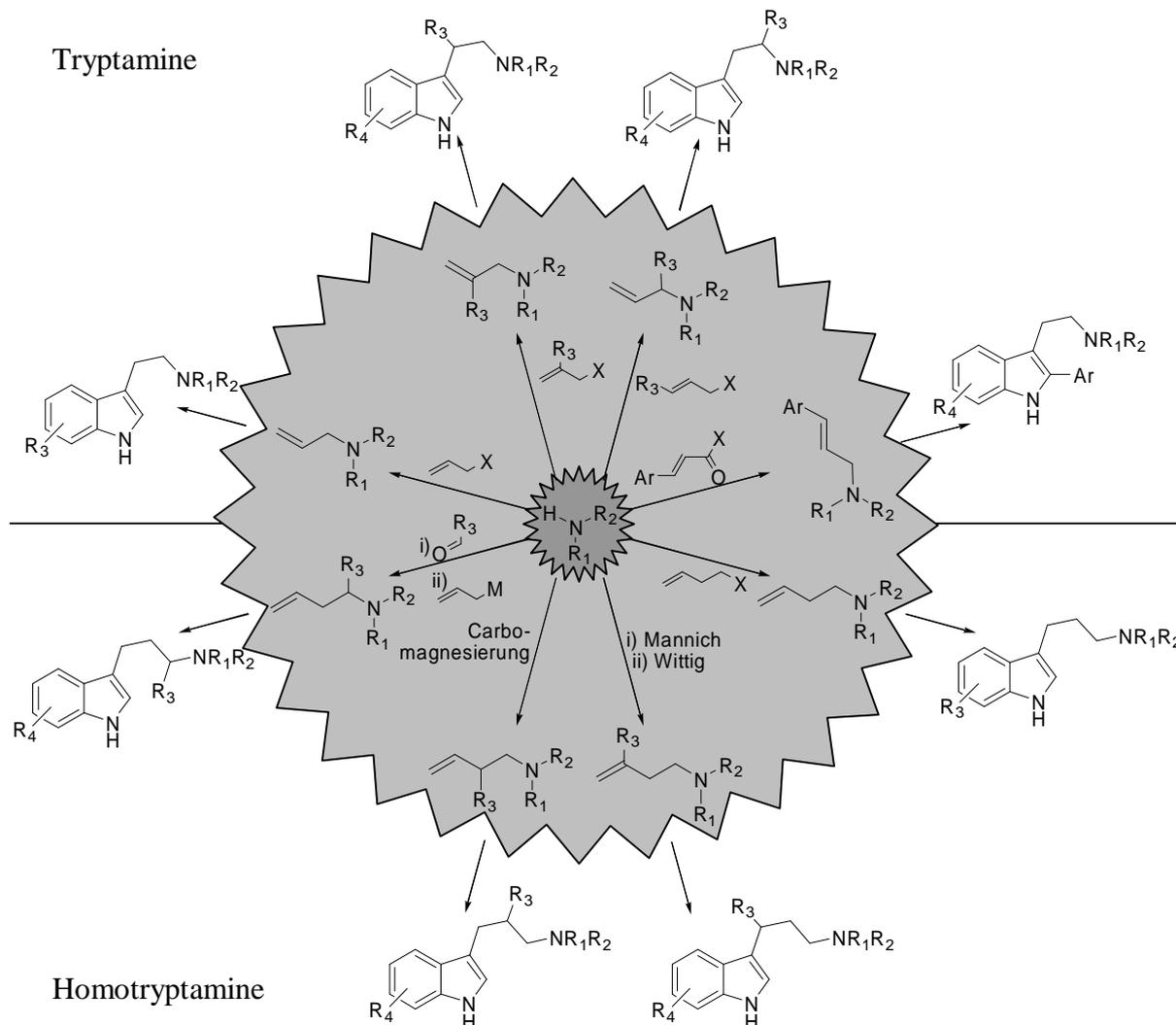

Dabei sind in Abhängigkeit vom Typ des verwendeten Olefins unterschiedliche Reaktionsbedingungen entwickelt worden. Unpolare Olefine, insbesondere geschützte primäre und sekundäre Aminoolefine benötigen ein unpolares Reaktionsmedium. Hier hat sich die Verwendung von Schwefelsäure in THF als am besten geeignetes System herausgestellt. Die höchste Selektivität kann beobachtet werden, durch BUCHWALD-HARTWIG-Aminierung gewinnbare Benzyhdryliden geschützte aromatische Hydrazine eingesetzt werden. Aber auch andere Hydrazinquellen, wie ungeschützte Hydrazine und a-Boc-geschützte Hydrazine, geben zufrieden stellende Ausbeuten (Abbildung 3).

Abbildung 3: Tandem Hydroformylierung / Fischer Indolsynthese unpolarer Olefine.
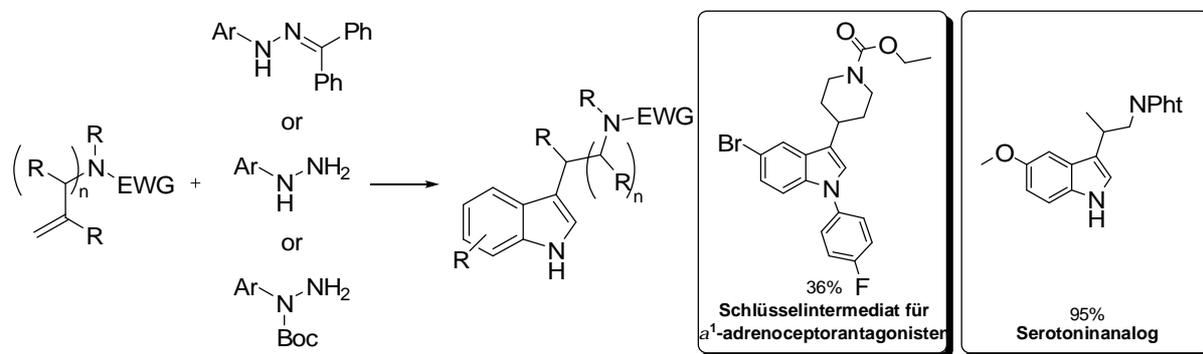

Im Fall polarer Aminoolefine, wie z.B. tertiäre Aminoolefine, die ein sehr polares Reaktionsmedium benötigen, wird wässrige Schwefelsäure verwendet. Eine hohe Löslichkeit des Hydroformylierungskatalysators kann durch den Zusatz sulfonierter Phosphanliganden, wie trisulfoniertes Triphenylphosphan (TPPTS) oder disulfoniertes XANTPHOS (sulfoXANTPHOS) erreicht werden, wobei letzterer hohe *n*-Selektivitäten bei der regioselektiven Hydroformylierung gibt. Kommerziell erhältliche Hydrazin-Hydrochloride können genauso eingesetzt werden, wie *a*-Boc geschützte Hydrazine. Insbesondere bei der Synthese von Wirkstoffen zur Migränebehandlung haben sich letztere als besonders geeignet erwiesen (Abbildung 4).

Abbildung 4: Tandem Hydroformylierung / Fischer Indolsynthese polarer Olefine.
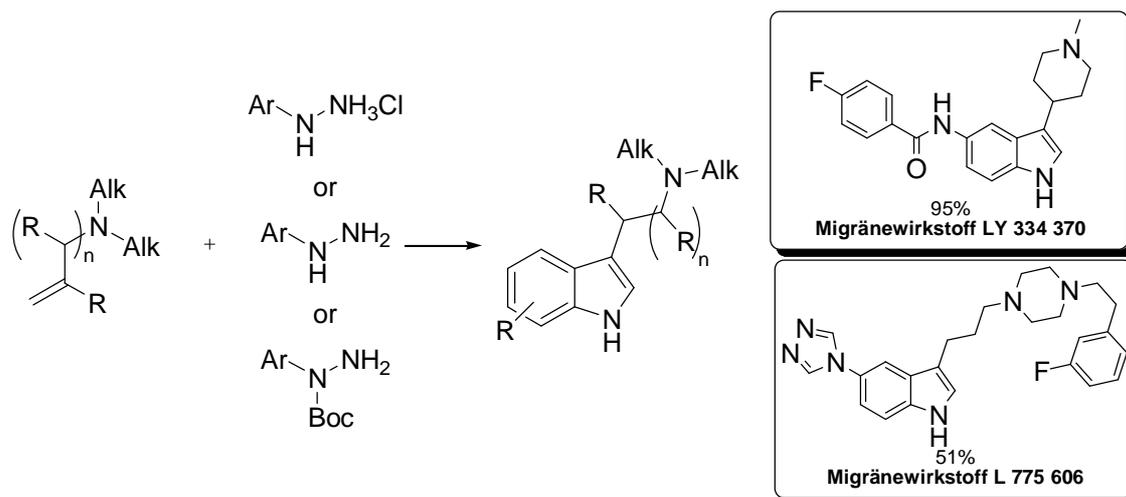
Sogar stereochemische Aspekte können berücksichtigt werden. Entweder kann das einzusetzende Aminoolefin bereits stereochemische Information in sich tragen, oder es werden prochirale Olefine eingesetzt, die ein neues Stereozentrum während der Tandemreaktion bilden.

Abbildung 5: Verwendung chiraler Allylamine unter Erhalt der Absolutkonfiguration.

96% *ee*

54%, 95% *ee*
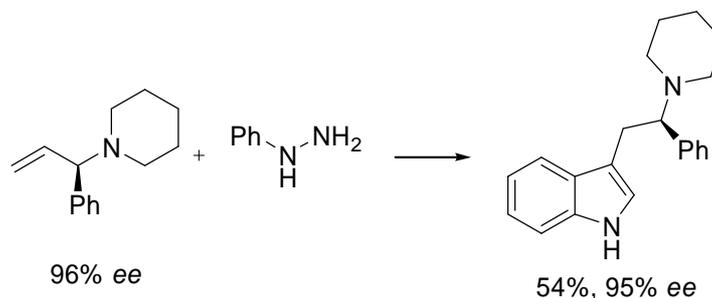
Werden chirale Allylamine verwendet, so wird keine Epimerisierung durch Doppelbindungsverschiebung beobachtet und die Absolutkonfiguration bleibt erhalten (Abbildung 5).

Werden jedoch disubstituierte, terminale Olefine eingesetzt, so kann die Relativkonfiguration des Stereozentrums in *b*-Position bezüglich des Aldehyds kontrolliert werden, indem BREIT's Protokoll zur substratgesteuerten Hydroformylierung auf diese neue Tandemreaktion übertragen wurdet (Abbildung 6).

Abbildung 6: Diastereoselektive Tandem Hydroformylierung / Fischer Indolsynthese.

44%, *dr* > 95:5
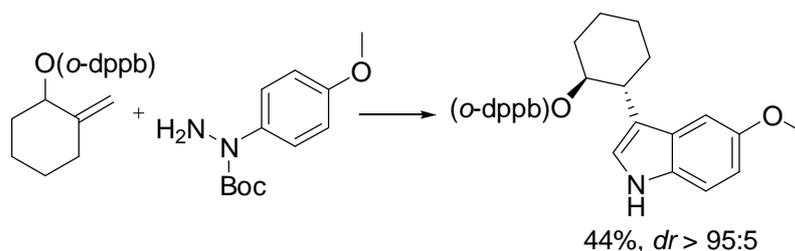
Selbst Probleme mit der Regioselektivität der klassischen FISCHER Indolsynthese *meta*-substituierter aromatischer Hydrazine lassen sich durch die erste erfolgreiche intramolekulare FISCHER Indolsynthese überwinden. Hierbei wird ausschließlich das 6-substituierte Indole erhalten (Abbildung 7).

Abbildung 7: Regioselektive Tandem Hydroformylierung / Fischer Indolsynthese.

20%, ~1:1
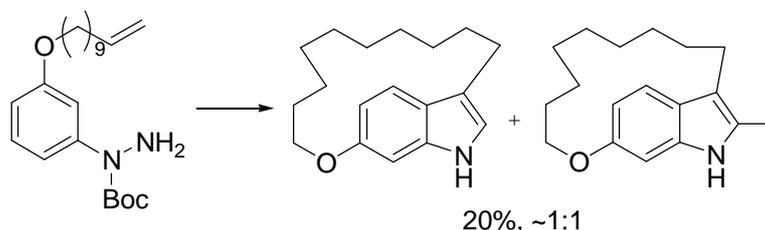
Primäre und sekundäre Tryptamine und ihre Homologe, die durch Tandem Hydroformylierung / Fischer Indolsynthese gewonnen worden sind, sind geeignete Substrate

für eine Hydroaminomethylierung. Diese Rhodium katalysierte Tandemreaktion, bestehend aus Hydroformylierung und reduktiver Aminierung, erlaubt eine zusätzliche Funktionalisierung des Tryptaminstickstoffes und somit die Synthese komplexerer Wirkstoffe zu erhalten. Die Kombination dieser beiden Tandemreaktionen stellt einen ungewöhnlichen schnellen und effizienten Zugang zu 3-Piperidylindolwirkstoffen dar (Abbildung 8).

Abbildung 8: Kombination von Tandem Hydroformylierung / Fischer Indolsynthese und Hydroaminomethylierung in einer effizienten Synthese hoch-funktionalisierter Tryptamine.
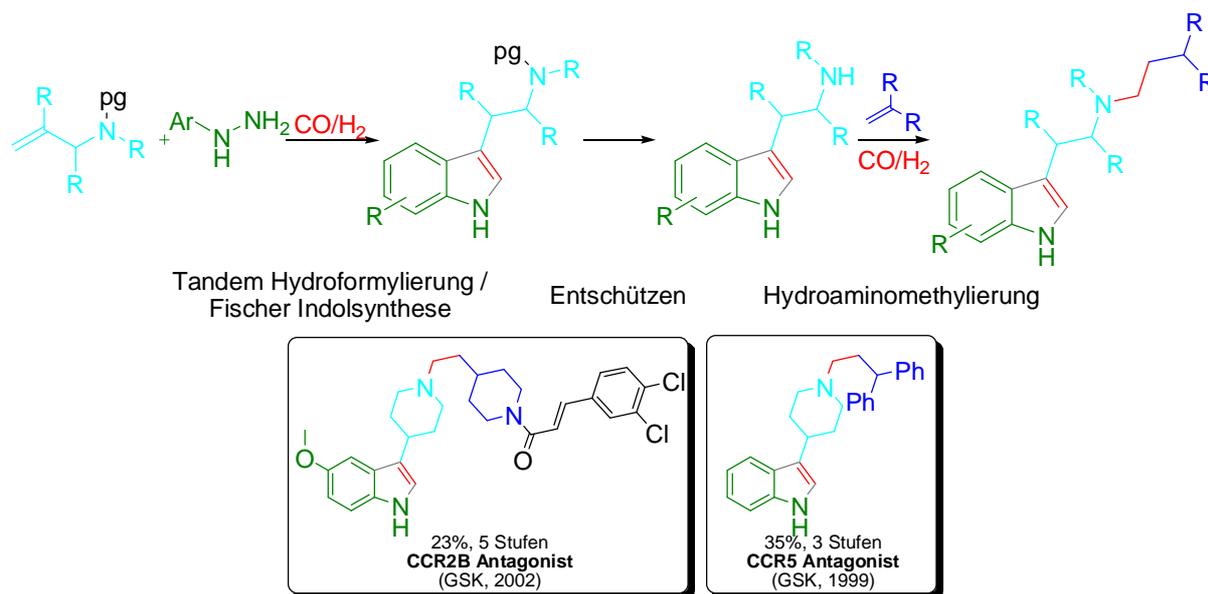
Die automatisierte kombinatorische Synthese an der festen Phase ist eine Schlüsseltechnologie für die Entwicklung neuer Wirkstoffe. Durch die Übertragung der Tandem Hydroformylierung / FISCHER Indolsynthese von Lösung an die feste Phase unter Verwendung von Polystyrolsulfonylchlorid-Harz kann diese Tandemreaktion ein attraktives Werkzeug für die kombinatorische und diversitätsorientierte Synthese von Indolbibliotheken sein (Abbildung 9).

Abbildung 9: Tandem Hydroformylierung / Fischer Indolsynthese an der festen Phase.
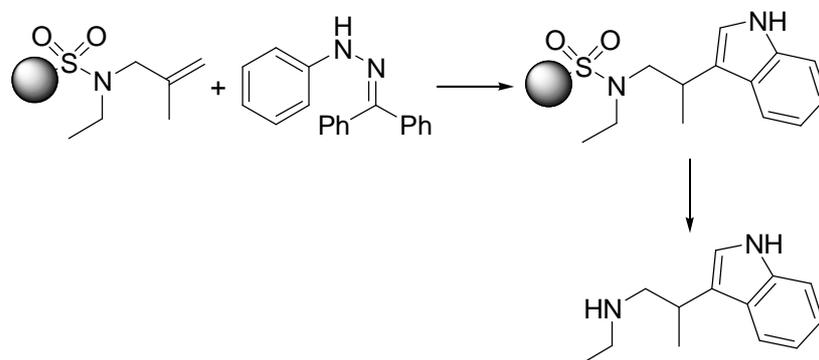
Wird die Hydroformylierung in Anwesenheit aromatischer Hydrazine aber ohne Säure durchgeführt, so können Arylhydrazone in meist quantitativer Ausbeute erhalten werden. Folgereaktionen wie Hydrierung können nicht beobachtet werden. Substituenten, die katalytisch hydriert werden könnten, bleiben genauso erhalten, wie die Hydrazondoppelbindung. Diese erhöhte Stabilität der Arylhydrazone gegenüber katalytischer Hydrierung steht im klaren Gegensatz zum Verhalten von Aminoaldehyden und Alkylhydrazonen, die beide unter Hydroformylierungsbedingungen zum Alkohol bzw. zum Hydrazine hydriert werden können. Zusammenfassend kann die Hydrazongruppe als produktive Schutzgruppe für Aldehyde interpretiert werden, solange diese Schutzgruppe, wie bei der FISCHER Indolsynthese, Teil des Produktes ist. Die Tandem Hydroformylierung / Hydrazonbildung kann genutzt werden um makrocyclische Bishydrazone in außergewöhnlich hohen Ausbeuten zu gewinnen (Abbildung 10).

Abbildung 10: Synthese makrocyclischer Bishydrazone unter Hydroformylierungsbedingungen.
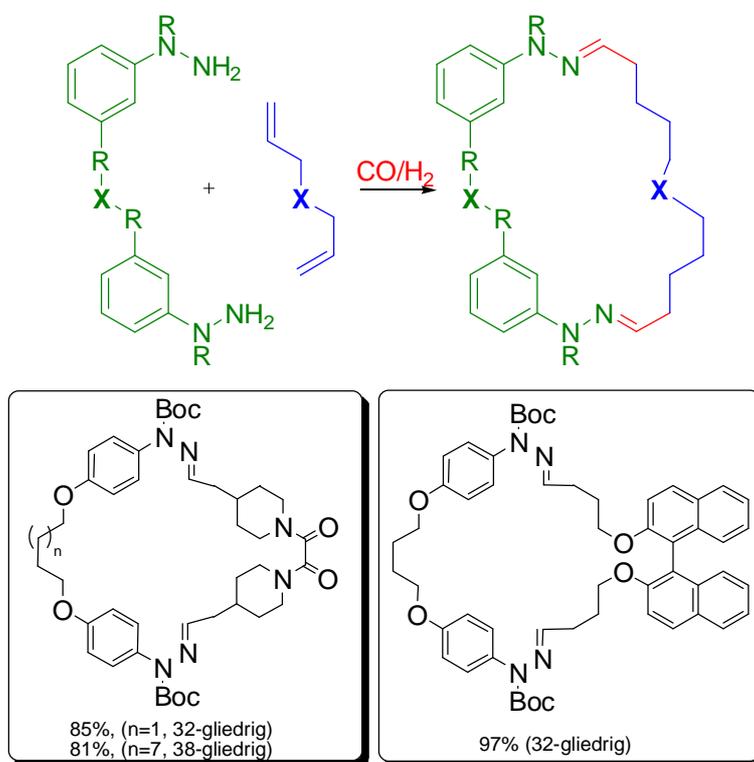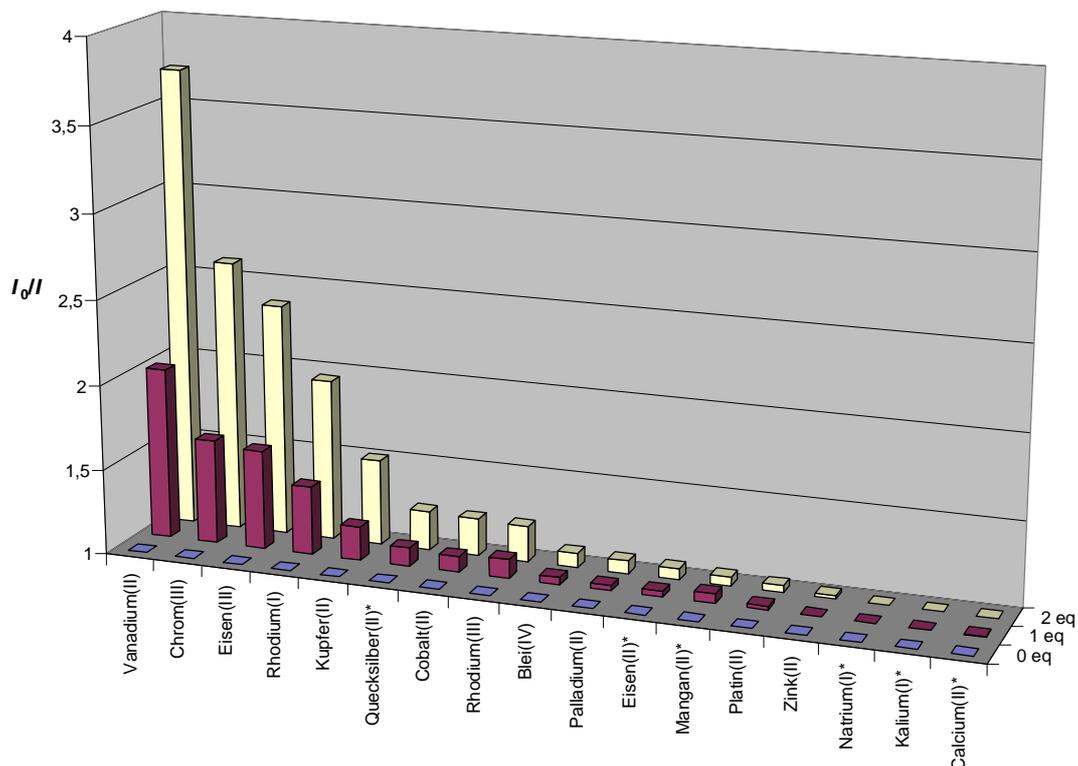
Abbildung 11: Metallscreening auf das Quenchen der Fluoreszenzaktivität makrocyclischer Bishydrazone.

Obwohl diese Makrozyklen nicht selektiv indolisieren, repräsentieren sie eine neue Substratklasse, die eine unerwartete Selektivität bzgl. einiger Metalle beim Quenchen ihrer Fluoreszenzaktivität zeigen. Neben starken Wechselwirkungen mit Vanadium(II) und Chrom(III) scheinen die Wechselwirkungen mit Eisen(III)salzen die interessantsten für Anwendungen in der Diagnostik oder der Schadstoffanalyse zu sein. (Abbildung 11).