Tandem Reaction Sequences under Hydroformylation Conditions
-Syntheses of Indoles and Tetrahydro-β-Carbolines-

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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Dortmund, 2008
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Tag der mündlichen Prüfung:
Acknowledgement

The following work took place in the time from July 2005 until May 2008 at the Faculty of Chemistry, University of Dortmund, under supervision of Prof. Dr. Peter Eilbracht.

I gratefully thank Prof. Dr. Peter Eilbracht for the chance to work in his research group, for the interesting research topic and for giving me the opportunity to conduct this research in complete freedom while always been there when encouragement and support were needed.

I wish to thank Prof. Dr. Norbert Krause for agreeing to act as a co referee to this thesis. Dr. Horst Hillgärtner, is acknowledged for agreeing to be the member of my PhD committee and for the administrative support.

I would like to thank Prof. Dr. B. Plietker for use of his HPLC instruments and Prof. Dr. B. Costissela, Ms. S. Marzian, Mr. A. Bruckmeyer and Mr. W. Hiller for collecting analytical data.

Mr. A. Farwick and Mr. J. Liebich who supported me as diploma students and Ms. K. Dogan, who supported me in the course of her research towards master in chemistry, are gratefully acknowledged, without their commitment I would not be able to present many results.

Special thanks I owe to Mr. T. Rothenbücher, and Mr. M. A. Subhani, for many interesting discussions and for making the office a nice place to work in.

I wish to thank Dr. S. Nave, Dr. N. Susnjar-Hearley, Dr. V. K. Srivastava, Mr. Y. Berezhanskyy, Dr. S. Chercheja, Dr. R. Kedar and Ms. Z. Krausova (Alexandrová), for many interesting discussions and viewpoints shared and for making my time in Dortmund memorable experience.

Dr. S. Nadakudity is gratefully acknowledged for proof reading this thesis. I also wish to thank Ms. S. Lessing and Ms. K. Weber for their exceptional organizational support. Many thanks are due to all other members of the Eilbracht workgroup for their friendship, nice working atmosphere and constant exchange of ideas.

On the end, I would like to thank my mother and my brother for their support and understanding.

Most importantly, I thank my dear wife Aleksandra for giving us our little angel and for her understanding and support, which made all of this possible.
In memoriam:
Petar Bondzić (1951-2004†)
To Andjela and Aleksandra
### List of Abbreviations and Symbols

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>Acetylacetonato</td>
</tr>
<tr>
<td>APT</td>
<td>Attached proton test</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxy carbonyl</td>
</tr>
<tr>
<td>cod</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphor sulphonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>Days</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-Diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DPPB</td>
<td>1,4-diphenylphosphino butane</td>
</tr>
<tr>
<td>DPPE</td>
<td>1,2-diphenylphosphino ethane</td>
</tr>
<tr>
<td>DPPF</td>
<td>1,1'-diphenylphosphino ferrocene</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact</td>
</tr>
<tr>
<td>Eoc</td>
<td>Ethyloxycarbonyl</td>
</tr>
<tr>
<td>Equiv</td>
<td>Equivalents</td>
</tr>
<tr>
<td>ESI</td>
<td>Electron spray ionisation</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast atom bombardment</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>Hours</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>L</td>
<td>Ligand</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium hexamethyl disylazide</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>MTBE</td>
<td>Methyl tert-butyl ether</td>
</tr>
<tr>
<td>n.d.</td>
<td>not determined</td>
</tr>
<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
</tbody>
</table>
o  ortho
p  para
PG  Protecting group
Ph  Phenyl
Pht  Phthaloyl
PTSA  para-Toluene sulfonic acid
Pyr  pyridyl
rt  room temperature
\(t\)-Bu  \textit{tert}-butyl
TBD  1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TFA  Trifluoro acetic acid
THF  Tetrahydrofuran
Tlc  Thin layer chromatography
TPPTS  Triphenylphosphan-tris-sulfonat
XANTPHOS  4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
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7 Zusammenfusung
1 Introduction and Aims of the Project

1.1 Relevance of Indoles and Indole as Privileged Structure

The indole framework is one of the most frequently found structural motifs in natural products and pharmaceutically active compounds.\(^1\) For instance, indole core is a key substructure in the amino acid tryptophan \(1\) (and is present in the multitude of molecules containing this amino acid). This bicycle is also very frequently found in physiologically active compounds, melatonin \(2\) and serotonin \(3\) being examples. The latter one is acting as a neurotransmitter in the central nervous system, regulating functions of the cardiovascular and gastrointestinal systems. It is also often found in hallucinogenic substances such as psilocin \(4\), as well as in many other naturally occurring molecules (Figure 1).

\[ \text{Figure 1. Structures of naturally occurring indoles: tryptophan, melatonin and serotonin} \]

\[ \text{N} \quad \text{H} \quad \text{HN} \quad \text{O} \quad \text{MeO} \quad \text{Melatonin} \]

\[ \text{N} \quad \text{H} \quad \text{NH}_2 \quad \text{HO} \quad \text{Serotonin} \]

\[ \text{N} \quad \text{H} \quad \text{NH}_2 \quad \text{COOH} \quad \text{Tryptophan} \]

\[ \text{OH} \quad \text{N} \quad \text{4} \quad \text{Psilocin} \]

Owing to the great structural diversity of biologically active indoles, literature even entitles it as the most important structural class in drug discovery. The indole ring systems have become an important structural components in many pharmaceutical agents, some examples being sertindole \(5\), which affects dopaminergic system and is used for the treatment of schizophrenia, or nonsteroidal anti-inflammatory drugs indomethacin \(6\) and ondansetron \(7\) (Figure 2).\(^2\)


Furthermore, chiral indole compounds mostly derived from the amino acid tryptophan are also used as catalysts. One example is the chiral Lewis acid 8 developed by Corey for stereoselective Diels-Alder reactions (Figure 3). Tryptophan itself is for instance used as organo-catalyst in Mannich and Mannich type reactions.4

Among indole derivatives, those with a tryptamine scaffold (3-aminoethyl indole) are particularly important compounds and many of these are known to be synthetic medicines and physiologically active substances (serotonin, melatonin, psilocin, etc.). Tryptamines and tryptamides are referred to as “privileged structures” owing to their binding ability to many different types of receptors with high affinity.6

Serotonin (5-hydroxy tryptamine, 5-HT, Figure 1, 3), is a biogenic amine neurotransmitter with diverse physiological actions in both the central and peripheral nervous systems, and operates through various distinct membrane receptors. Up to date fourteen different human serotonin (5-HT) receptors have been cloned and organized into seven distinct subclasses (5HT_1-5HT_7). Among these subtypes, the 5HT_1B and 5HT_1D receptors have attracted considerable attention as putative targets for novel antimigraine drugs, leading to the development of 5HT_1B/1D receptor selective agonist sumatriptan (GR43175) which has been followed to the market by a series of other “tripptans” such as naratriptan 10, zolmitriptan 11, rizatriptan and others (Figure 4).

**Figure 4.** Recently marketed serotonin receptor agonists

![Diagram of serotonin receptor agonists: Sumatriptan (9), Naratriptan (10), Zolmitriptan (11)]

However, neither sumatriptan nor number of related compounds in use distinguishes significantly between these two subtypes in their binding activities which is required in order to prevent side effects associated with commercial medicaments.

In the past few years, it was found that in addition to appropriate substituents at C5, more sophisticated amine moieties have to be attached with varying distances at C3 of indole core in order to achieve discrimination between subtypes of the serotonin receptor family. From a synthetic chemist’s point of view, these and additional features such as the occurrence of branching in the α and β-positions as well as stereochemical issues are important. Such branched tryptamines possessing pharmacologically interesting properties have recently been developed as well. Indole core is as well present as a substructure in a vast number of more

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complex compounds, one of very important classes being tetrahydro β-carbolines (THBC’s, Figure 5).

**Figure 5.** β-carboline and tetrahydro-β-carboline frameworks

[β-carboline](#) [Tetrahydro β-carboline](#)

This ring system is present in numerous natural and synthetic organic compounds, many of which display useful and interesting biological activities. The reported effects of this class of compounds comprise antineoplastic (tubulin binding),\(^{10}\) anticonvulsive, hypnotic and anxiolytic (benzodiazepine receptor ligands),\(^{11}\) antiviral,\(^{12}\) antiplasmodial activity\(^{13}\) and others. Some representative examples of biologically active natural products possessing THBC framework are depicted on Figure 6. Ajmaline 12 was isolated from *Rauwolfia serpentina* and exhibits important cardiovascular effect.\(^{14}\) Suaveoline 13 was isolated from the trunk bark of *Rauwolfia suaveolens* S. while fungal metabolite Fumitremorgin C 14 was isolated from *Penicillium* and *Aspergillus* genera and exhibits tremorgenic activity (Figure 6).\(^{15}\)

**Figure 6.** Naturally occurring tetrahydro-β-carbolines


Due to these important applications new methods for indole synthesis and functionalization continue to attract attention.\textsuperscript{16}

1.2 Syntheses of Indoles and Tetrahydro-β-Carbolines

1.2.1 Syntheses of Indoles

Due to afore mentioned diversity of the indole ring systems, synthesis has always been a challenge. Key factors including starting material availability, functional group tolerance and substitution pattern often decide whether or not a particular synthetic method is suitable for a desired target. Furthermore, mild synthetic methods that provide rapid assembly of the indole ring and are atom economical are desirable. Miscellaneous elegant approaches were developed for the synthesis of indoles among which Fischer’s and the Larock’s method are the most commonly used for the preparation of functionalized indoles. Heteroannulation approach in the synthesis of indoles combining 2-haloanilines and 2-aminophenols with either terminal or internal alkynes has been achieved by a number of transition metal catalyzed processes. In Larock’s method $\text{o}$-iodoanilines and disubstituted alkynes are used as substrates in the Pd catalyzed process to give 2,3-disubstituted indoles (Scheme 1).\textsuperscript{17}

\begin{center}
\textbf{Scheme 1.} The Larock indole synthesis
\end{center}

Important features of this reaction are the wide variety of suitable disubstituted alkynes that can be used as coupling partners as well as the high regioselectivity of the reaction. However, alkyne coupling partner is required in excess (1.5-2 equiv) and for volatile alkynes multiple equivalents are needed to achieve high yields. Synthesis of additionally substituted


o-halo anilines may however require further steps and is not always easily achieved. Similarly, the alkyne unit may require laborious synthetic procedures. Fischer indole synthesis is another important method developed as early as 1883 and up to date remained an extremely useful and important method for the synthesis of a variety of indole intermediates and biologically active compounds. Over 100 years after the initial discovery, the Fischer indole synthesis is still the most commonly employed method for the preparation of indoles. It can be regarded as the acid promoted cyclization of an arylhydrazone of aldehyde or ketone (Scheme 2).

Scheme 2. Basic principle of The Fischer indole synthesis

In many cases, the indolization reaction is carried out by simply heating the ketone or aldehyde and the arylhydrazone with the appropriate acid or acid catalyst without isolation of the hydrazone intermediate. Wide range of functional groups around the aromatic ring is compatible with conditions of Fischer indolization. The degree of substitution of aryl hydrazines required for Fischer method is reduced by one as compared to the arylhalide required for a Larock synthesis of the same compound. However use of carbonyl compounds is often connected with side reactions such as aldol reaction or aldehyde oligomerization under the harsh conditions of the Fischer indole synthesis. It is therefore often required for these to be protected as acetals, aminals, enol ethers or bisulfite adducts. Use of masked aldehyde functionalities such as α-keto esters has been reported as well. However, methods that allow formation of aldehyde in situ in the presence of phenyl hydrazines have been developed recently. Hydrazone formation then prevents unwanted side reactions and indolization is readily carried out by the addition of the appropriate acid (vide infra).

1.2.2 Syntheses of Tetrahydro-β-carbolines

Traditional strategies for the synthesis of functionalized variants of this “privileged” moiety have relied largely upon cyclocondensation of an appropriately substituted

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tryptophan or tryptamine derivatives with carbonyl compounds under aprotic or acidic conditions (Pictet-Spengler reaction).\textsuperscript{20} In general the Pictet-Spengler (PS) reaction comprises of an acid catalized cyclocondensation of the \(\beta\)-arylethyl amine derivatives with aldehydes or ketones involving iminium ion intermediates (Scheme 3).

\textbf{Scheme 3. Classical Pictet-Spengler reaction}

With the advent of asymmetric stereocontrol,\textsuperscript{21} the importance of this method for the synthesis of the tetrahydro-\(\beta\)-carboline core has rapidly increased culminating in enantioselective and diastereoselective preparations of this type of compound. Using a number of diastereoselective substrate-controlled Pictet-Spengler cyclizations lead to useful chiral building blocks for alkaloid syntheses.\textsuperscript{22} Recently, Jacobsen\textsuperscript{23} and List\textsuperscript{24} have independently reported examples of highly enantioselective catalytic Pictet-Spengler reactions providing ready access to a range of substituted tetrahydro-\(\beta\)-carbolines in high enantiomeric excesses.

\textbf{1.3 Aims of the Project}

As already noted Fischer indole synthesis is one of the most important methods for the synthesis of indole containing molecules and its improvements has been an objective of numerous efforts of synthetic chemists during decades. One of the most recent

\begin{itemize}
  \item \textsuperscript{21} (a) Czerwinski, K. M.; Cook, J. M. Stereochemical Control of the Pictet-Spengler Reaction in the Natural Product Synthesis; Pearson, W., Ed.; JAI Press: Greenwich, CT, 1996; Vol 3, p. 217.
  \item \textsuperscript{23} Taylor, M. S.; Jacobsen, E. N. \textit{J. Am. Chem. Soc.} \textbf{2004}, 126, 10558.
\end{itemize}
improvements involves *in situ* formation of aldehyde component from the olefinic starting materials, using regioselective Rh catalyzed hydroformylation reaction. This process if performed in the presence of aromatic hydrazines allows one step synthesis of indoles from olefins (vide infra) in a reaction sequence known as tandem hydroformylation / Fischer indole synthesis. The aim of this work was to improve and extend synthetic pathways to chiral branched tryptamines, tryptamides, tryptophanes and their homologues using tandem hydroformylation / Fischer indole synthesis sequence (Scheme 4).

**Scheme 4.** Tandem hydroformylation / Fischer indole synthesis sequence

Due to their medicinal and pharmacological relevance desired structures shall be synthesised as enantiopure molecules if possible. Structures with varying distances between indole core and amine functionality are primary targets for the synthesis due to their biological relevance. Since multiple stereocenters are not generated during hydroformylation step, enantiopure starting materials should be synthesized via method that allows flexible access to both antipodes as well as introduction of diverse substituents and multiple stereocenters in one step. Optimization of reaction conditions with special regard to stability of the nitrogen protecting groups as well as preservation of chiral information especially in tryptophan derivatives possessing acidic α protons at chiral center would be an issue of special concern.

Next, application of olefins as the precursors of the electrophilic component in the Pictet-Spengler reaction should be investigated. *In situ* hydroformylation of the olefin in the presence of indole nucleophiles (i.e. tryptamine, tryptophane, etc.) should yield in the tetrahydro-β-carboline structures (Scheme 5). The feasibility of tandem hydroformylation / Pictet-Spengler reaction for the synthesis of tetrahydro-β-carbolines shall be tested and optimized.
Scheme 5. Tandem hydroformylation/Pictet-Spengler reaction

The scope and limitations of this tandem reaction should be clarified; the tandem reaction shall be investigated starting with basic model olefins with respect to chemoselectivities and regioselectivities of all single steps involved in this sequence. Possible side reactions shall be minimized. Aprotic as well as protic conditions for this reaction are to be investigated.

Next, the tandem hydroformylation / Fischer indole synthesis sequence shall be applied for the synthesis of tetrahydro-β-carbolines. When using cyclic olefins in the tandem hydroformylation / Fischer indole synthesis sequence intermediate 3,3 spiroindoleninium cations are formed (vide infra), these species rearrange to give carbazole type molecules. If this cyclic olefin is containing nitrogen embedded in the ring tetrahydro-β-carbolines are obtained. This alternative and highly modular approach for the synthesis of biologically and pharmacologically relevant tetrahydro-β-carbolines under hydroformylation conditions involving Fischer indole synthesis should be investigated. THBC structures possessing substituents that can not be introduced via classical approaches such as Pictet-Spengler reaction and those containing substituents in positions that are unavailable via those classical approaches are of special interest. Use of enantiopure substituted cyclic aminoolefins in the tandem hydroformylation / Fischer indole synthesis sequence shall grant access to enantiopure functionalized THBCs (Scheme 6).

Scheme 6. Tandem hydroformylation / Fischer indole synthesis approach in the synthesis of tetrahydro-β-carbolines
Enantiopure starting materials shall be synthesized via method that allows flexible variation of substituents R as well as access to both antipodes which consequently allows synthesis of both enantiomers of final molecule. The tandem reaction and its single steps shall be investigated starting with basic model cyclic aminoolefins with respect to stability of nitrogen protecting groups and different sources of aryl hydrazines. Furthermore, the tandem reaction shall be optimized with respect to chemoselectivity of the tandem reaction and regioselectivity of the hydroformylation and the indolization steps respectively. These optimized conditions shall be applied towards sophisticated substrates of possible pharmacological relevance considering all necessary biological valances (i.e. substitution pattern at the indole core as well as type of substituents with special regard on their electronic and steric properties).

1.4 Hydroformylation in Tandem Sequences

Hydroformylation of the olefins represents highly efficient and atom economical, "green" method for the synthesis of the aldehydes required as the building blocks in many synthetic processes. Subsequent reactions involving thus formed aldehyde comprise Fischer indole synthesis and Pictet-Spengler reaction as well as many other reactions. In situ formation of aldehydes and their subsequent trapping by the suitable nucleophiles represents foundation for all tandem reactions performed under hydroformylation conditions.

1.4.1 Rh Catalyzed Hydroformylation

Since O. Roelen discovered hydroformylation (Oxo – Synthese) in 1937,\textsuperscript{25} by accident due to a breakdown of a high pressure reactor at the Ruhrchemie AG, this process has witnessed continual growth and the worldwide production capacity reached $6.6 \times 10^6$ tons in 1995. This makes hydroformylation one of the most important industrial reactions. Formally, this chemical reaction involves the addition of a formyl group (CHO) and a hydrogen atom to a carbon-carbon double bond (Scheme 7).

The first investigations toward rhodium catalyzed hydroformylation were carried out at the end of the 1950’s. The synthesis and the spectroscopic characterization of rhodium hydride complexes containing triphenylphosphine by Wilkinson et al.\textsuperscript{26} and their use in the hydrogenation and hydroformylation processes opened the way to the research on phosphine modified rhodium catalysts. Enormous amount of research done in this area led to catalyst systems with improved regioselectivity towards linear products as well as to enantioselective hydroformylations.

However, although 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 more attractive tool in the synthesis of more complex molecules. These combinations of multiple reactions proceeding consecutively in predictable manner are called tandem reactions.

The term “tandem reaction” refers to the synthetic strategies that involve sequential use of different reactions or catalysts with minimum workup, or change in conditions. Multiple catalysts and/or steps operating consecutively could circumvent the time and yield losses associated with the isolation and purification of intermediates in the multistep sequences. Tandem reactions constitute a significant challenge for synthetic chemists and give them a number of opportunities to improve chemical transformations. In the past few decades, a number of so called tandem reactions or sequential reactions under hydroformylation conditions have been reported.\textsuperscript{27}

1.4.2 Tandem Hydroformylation / Aldol Reaction

Among all tandem hydroformylation sequences, the most attractive are those in which the aldehyde functionality is used for the formation of additional C-C bonds. Aldehydes generated in the hydroformylation reaction in the presence of silyl enol ethers, enamines or enolates undergo consecutive aldol reaction. Thus the unsaturated silyl enol ethers such as 16 are undergoing selective hydroformylation at the monosubstituted double bond followed by an intramolecular Mukaiyama type aldol addition to give the silylated aldol adducts 17 in good yields and with complete transfer of the silyl fragment to the carbinol oxygen (Scheme 8).28

Scheme 8. Mukaiyama type aldol addition under hydroformylation conditions

The tandem enolboration / hydroformylation / aldol addition is another example of the aldol reaction under hydroformylation conditions. This cascade reaction allows regio- and diastereoselective construction of carbocycles bearing highly-functionalised quaternary carbon centers.29 Both intra- and intermolecular aldol reactions following hydroformylation are reported. Recently, enantioselective organocatalyzed aldol reactions under hydroformylation conditions were reported.30

1.4.3 Tandem Hydroformylation / Wittig Reaction

Consecutive hydroformylation / Wittig reaction is one of the last reported consecutive reactions involving hydroformylation.31 The reaction is limited to stabilized ylides, because non stabilized ylides are too basic and induce rhodium inactivation. Under hydroformylation conditions and in the presence of Ph$_3$P=CHCOR, compound 18 leads to the oxo derivative 19. The process involves a sequence of reactions that includes initial hydroformylation to give the aldehyde 20 in a stereoselective way, Wittig olefination to give the trans conjugated

alkene 21 and hydrogenation (Scheme 9). Disubstituted ylides (i.e. PPh$_3$=C(Me)COR) do not undergo hydrogenation and in consequence $\alpha$, $\beta$-unsaturated ketones or esters are obtained. Ylides including the ester function provide low yields. The stereoselectivity of the process is determined by the chelating (directing) group o-DPPB, and stereochemistries all-syn, anti-syn, and all-anti can be obtained.

Scheme 9. Tandem hydroformylation / Wittig reaction

\[
\begin{align*}
0.7 \text{ mol\% } & [\text{RhH(CO)(PPh$_3$)$_3$}, \\
\text{CO/H$_2$}=10/10 \text{ bar}, 90 ^\circ \text{C} & \quad \text{Ph$_3$P=}CHCOR, \text{ yields up to 82\%,} \\
\text{dr from } 90/10 \text{ to } 98/2
\end{align*}
\]

1.4.4 Indole Syntheses under Hydroformylation Conditions

Until recently, only a few examples were described in which the hydroformylation has been used to generate aldehydes required for the indole syntheses. Hydroformylation of styrene type anilines 23, derived from a Heck reaction of o-halo anilines 22, gives tryptamines in fair yields. Here, the olefinic bond of 23 is regioselectively hydroformylated, and the resulting aldehyde condenses intramolecularly with the amine to give 3-substituted indole 24 (Scheme 10).

Scheme 10. Tandem hydroformylation / enamine formation in the synthesis of tryptamines

\[
\begin{align*}
X = \text{Br, I} \\
R = \text{H, OMe, CH$_3$, CF$_3$}
\end{align*}
\]

In 2000, Sheldon et al. have published the synthesis of melatonin 26 via regioselective hydroformylation of N-allyl acetamide 25 followed by Fischer indole synthesis (Scheme 11).

Scheme 11. Scheldon synthesis of melatonin

In 2001, Köhling demonstrated that, both, the hydroformylation and the Fischer indolization can be combined to a new tandem reaction. The general reaction pathway involves hydroformylation to generate the aldehyde in situ from an olefin. Presence of an aryl hydrazine allows formation of the hydrazone intermediate which undergoes Fischer indolization catalyzed by in situ present Bronsted acid yielding the desired indole (Scheme 12).

Scheme 12. Tandem hydroformylation / Fischer indole synthesis approach

Eilbracht and Schmidt were able to perform tandem hydroformylation / Fischer indole synthesis sequence in water. Using the water soluble TPPTS as ligand, it was possible to

---

perform the whole reaction sequence in aqueous sulphuric acid. The antimigraine drug candidate LY334370 28 was prepared in one pot synthesis sequence in excellent yield. The use of α-Boc protected aryl hydrazine 27 increased the selectivity of the reaction and allowed introduction of substituents at the phenyl ring of the indole moiety (Scheme 13).

Scheme 13. One pot synthesis of LY 334 370

The hydroformylation / Fischer indole synthesis might be especially interesting from a large scale preparative viewpoint. Low catalyst loadings and environmentally harmless solvents can be used, which accompanied with good yields makes promising perspective for industrial use.

Standard hydroformylation / Fischer indolization reactions do not create chiral information. In order to obtain chiral tryptamines and tryptamides, enantiopure amino olefins have to be used. These in turn, are easily obtained via transition metal catalyzed asymmetric allylic substitutions. In the next chapter short overview on Ir catalyzed allylic substitution reactions is given. These were broadly used throughout work described in this thesis.

1.4.5 Tetrahydro-β-carboline Syntheses under Hydroformylation Conditions

Hydroformylation have only scarcely been used for the synthesis of aldehydes required for the preparation of tetrahydro-β-carbolines via Pictet-Spengler reaction. Tandem hydroformylation / Pictet-Spengler reaction have been used by Taddei et al. for the synthesis of tetrahydro-β-carbolines on the solid phase.36 Tandem hydroformylation / Fischer indolization besides its role in the preparation of indoles has been applied for the synthesis of tetrahydro-β-carboline as well. Cyclic

36 Dessole, G.; Marchetti, M.; Taddei, M. J. Comb. Chem. 2003, 5, 198-200
aminoolefin 29 was hydroformylated in the presence of phenylhydrazine. After subsequent acidic indolization intermediate spiroindoleninium cation 30 undergoes rearrangement to give tetrahydro-β-carboline structure 31 in excellent yield (Scheme 14).\textsuperscript{37} The product of formal retro Mannich reaction was obtained exclusively.

**Scheme 14.** Tandem hydroformylation / Fischer indolization in the synthesis of the tetrahydro-β-carboline 31

\[
\begin{align*}
\text{NTs} \quad \text{CO/H}_2 = 50/20 \text{ bar} \\
\text{[Rh(acac)(CO)}_2] \quad \text{PhNHNNH}_2 \\
\text{CO/H}_2 = 50/20 \text{ bar} \\
\text{100°C, 3d, THF} \\
\text{1) PhNHNNH}_2 \\
\text{[Rh(acac)(CO)}_2] \\
\text{CO/H}_2 = 50/20 \text{ bar} \\
\text{100°C, 3d, THF} \\
\text{2) 4w% H}_2\text{SO}_4 \\
\text{THF reflux 2h} \\
\end{align*}
\]

However, when carbocyclic and cyclic silyl olefins 32 were used in this sequence γ-carbolines 34 were obtained i.e. exclusive rearrangement of β carbon of intermediate spiroindoleninium cations 33 has occurred (Scheme 15).\textsuperscript{37}

**Scheme 15.** Use of carbocyclic and silyl olefins in the synthesis of carbazoles

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{(X=C; R}_1=\text{OH, R}_2=\text{CH}_2\text{OBn)} \\
\text{(X=C; R}_1=\text{OH, R}_2=\text{tert-Bu)} \\
\text{(X=Si; R}_1, \text{R}_2=\text{Ph)} \\
\end{align*}
\]

1 eq. Phenylhydrazin, 0.5 mol% Rh(acac)(CO)\textsubscript{2}, 1 eq. PTSA, 50/10 bar CO/H\textsubscript{2}, 100 °C, 3 d

28-39%

It is noteworthy to mention that when 6, 7 or 8 membered carbocyclic olefins were used in this sequence, intermediate spiroindoleninium structures were trapped by hydrogenation under applied hydroformylation conditions.\textsuperscript{37} It was possible to control outcome of the reaction to some extent by control of partial pressures of CO and H\textsubscript{2}. Higher partial pressures of H\textsubscript{2} favored reduction of intermediate spiroindoleninium cation. However, when 5 membered cycloolefins were used as substrates it was observed that spiroindolenines could not be trapped by simply increasing partial pressure of H\textsubscript{2} as in case of higher olefins.

1.4.6 Tandem Hydroformylation / Reductive Amination

Another important group of tandem reactions under hydroformylation conditions that are performed in the presence of heteroatom nucleophiles (amines) are reductive aminations, so called “hydroaminomethylation” reactions. The hydroaminomethylation of alkenes was originally discovered by Reppe \(^{38}\) and consists of the hydroformylation of an alkene, followed by reaction of the intermediate aldehyde with a primary or secondary amine to form an imine or enamine, and a final hydrogenation to give a secondary or tertiary amine. For example the hydroformylation of terminal diarylethenes \(^{35}\) in the presence of amines \(^{36}\) grants direct access to pharmacologically active 3,3-diarylpropylamines \(^{37}\) (Scheme 16).\(^ {39}\) Rhodium catalyzed the hydroformylation of the olefin as well as the hydrogenation of the enamine \(^{39}\) which is obtained from the condensation of the aldehyde \(^{38}\) with the secondary amine.

**Scheme 16. Hydroaminomethylation reaction**

Besides intermolecular processes these reactions are occurring intramolecularly as well. Unsaturated amines or amides \(^{40}\) under hydroformylation conditions undergo intramolecular ring closure. The catalytic cycle of the hydroformylation offers two reaction pathways of the metal acyl intermediate \(^{41}\) leading to lactams \(^{42}\) on one hand or cyclic amines \(^{43}\) on the

---


other (Scheme 17). The generation of the lactams 42 proceeds via cleavage of the rhodium-acyl species 41 by the nitrogen atom, which presumably is precoordinated to the metal. Cyclic amines of type 43 are obtained from unsaturated amines if the metal acyl intermediate as an alternative undergoes hydrogenolysis by reaction with hydrogen. The aldehyde thus generated is following the hydroaminomethylation sequence to give 43. The chemoselectivities of these reactions are controllable to some extent by the ratio of syngas and/or the chosen catalyst and ligand.40

Scheme 17. Intramolecular hydroaminomethylation reaction

1.5 Transition Metal Catalyzed Allylic Substitutions

As already noted, starting materials required for the synthesis of the tryptamines with varying lengths of side chains, containing multiple stereocenters (see Figure 7), can successfully be prepared via transition metal catalyzed allylic substitution reactions. This methodology was used as well for the preparation of precursors required for the synthesis of tetrahydro-β-carbolines via tandem hydroformylation / Fischer indole synthesis (see Scheme 6).

Figure 7. Examples of desired starting materials and final structures available through combination of Ir catalyzed allylic substitution with tandem hydroformylation / Fischer indole synthesis

Due to their wide use in this thesis, asymmetric allylic substitutions will be shortly overviewed in this chapter. Allylic substitutions are one of the most important transition metal catalyzed reactions for C-C and C-Heteroatom bond formation. Pd catalyzed allylic alkylation of sodium dimethylmalonate was introduced for the first time in 1965 by Tsuji, followed by the first enantioselective version by Trost in 1977. Allylic alkylations with dialkylmalonates as well as with other nucleophiles have been intensively studied and good yields and high enantioselectivities can now be obtained via proper combination of a transition metal and a chiral ligand. Over the past few years research has been focused on finding the catalyst which favors the formation of branched chiral products in the

---

substitution reactions of the allylic substrates 44 or 45. Simple cinnamyl substrates do not lead to chiral products 46 with palladium catalysts because substitution occurs at the less substituted allylic terminus (Scheme 18).

Scheme 18. Possible products of transition metal catalyzed allylic substitution reaction

Unlike the palladium catalyst,\(^{44}\) some transition metals such as platinum,\(^{45}\) rhodium,\(^{46}\) ruthenium,\(^{47}\) molybdenum,\(^{48}\) tungsten,\(^{49}\) and iridium promote the allylic alkylation at the more substituted terminus of the allylic substrate. However with Mo or W based catalysts only substrates with \(R = \text{aryl}\) are giving high levels of both regio- and enantioselectivity towards branched product, while the substitutions catalyzed by Ru or Rh are suitable for use with chiral branched allylic alcohol derivatives of type 45.

1.5.1 Iridium Catalyzed Allylic Substitution Reactions

The first studies towards iridium catalyzed allylic substitution were conducted by Takeuchi in 1997.\(^{50}\) He used allylic carbonates and acetates as substrates and sodium dimethylmalonate as nucleophile. Catalytic amounts of [Ir(cod)Cl]\(_2\) and triphenylphosphite catalyzed the allylic substitution (Scheme 19). Branched to linear ratios of up to 99/1 were


reached. Especially promising were the short reaction times and very good yields of the reactions. Takeuchi noted that in case of enantiopure substrates of type 45 and soft nucleophiles retention of configuration is observed.

Scheme 19. First Iridium catalyzed allylic substitution reactions

The first enantioselective iridium catalyzed allylic alkylation was published in the same year by Helmchen. As ligands, chiral phosphinooxazolines 48 with differently substituted aryl moieties were used. It was found that electron withdrawing substituents furnished good yields, high enantioselectivities and regioselectivities towards branched product, although their steric demands had to be small. Ligand 48b was therefore found to be most suitable (Scheme 20).

Scheme 20. First enantioselective allylic alkylation reaction

---

In 2001 Takeuchi et al.\textsuperscript{52} performed the first Ir catalyzed allylicamination and obtained branched allylic amines in excellent regioselectivities. Here, regioselective allylicamination of allylic carbonates and acetates has been achieved with an Ir/P(O\textsubscript{Ph})\textsubscript{3} catalyst. Phosphoramidite ligand \textbf{L1} originally developed by Feringa for the copper catalyzed 1,4-additions of dialkylzinc reagents,\textsuperscript{53} was introduced in 2002 by Hartwig \textit{et al.} to a iridium catalyzed allylic aminations, good to very good yields and excellent enantioselectivities were obtained with all tested substrates (Scheme 21).\textsuperscript{54}

**Scheme 21.** First enantioselective Ir catalyzed allylic amination

These results prompted several research groups to start investigations towards mechanistic aspects of this catalytic system. It was discovered that simple stirring of [Ir(cod)Cl]\textsubscript{2} with ligand \textbf{L1} gives the square planar complex 49, which is however catalytically not active in allylic substitution reactions (Scheme 22).\textsuperscript{55} Nevertheless, the addition of a sufficiently basic amine leads to the cyclometalation of the phosphoramidite ligand at the methyl group of the amino substituent. Subsequent elimination of hydrochloric acid and coordination of a second phosphoramidite ligand generates a trigonal bipyramidal structure 50. Dissociation of the second monodentate phosphoramidite ligand then generates the active catalyst 51. Reactions using this activated catalyst proceeded significantly faster and allowed lower catalyst loadings to be used.\textsuperscript{56} In subsequent studies Hartwig developed procedures for preforming of the active catalyst using DABCO or propylamine as additives. At room temperature, the

required cyclometalation of complex 49 requires hours, therefore reactions without activation of the catalyst prior to addition of the reagents occur with an induction period and without full concentration of the active catalyst.

**Scheme 22.** Formation of the active catalyst

Eventhough yields and selectivities appeared to be similar when using a non-preformed catalyst system, Hartwig could show that due to the long induction period the reaction rates were significantly lower. The reaction of benzylamine with the carbonate derived from (E)-2-hexen-1-ol without activation of the catalyst required 10 h to proceed to completion, while the reaction with initial activation with propylamine occurred within 2 h. Mainly all assumptions about the mechanism of the Ir catalyzed allylic aminations were based on Pd catalyzed allylations. Pd-catalyzed allylic substitution reactions occur by oxidative addition of an allylic ester, followed by attack of the nucleophile on the allyl intermediate. The identity of each species on the palladium-catalyzed reaction pathway has been determined, and the rates of individual steps of the catalytic cycle have been measured. The connection

between the mechanisms of iridium- and palladium-catalyzed processes has been made recently. Hartwig and Markovic were able to isolate resting state of the catalyst 53. The kinetic data on the catalytic process lead to the unexpected conclusion that reaction of the Ir(I) species with the allylic esters is endergonic and reversible (Scheme 23).

**Scheme 23.** Mechanism of Ir catalyzed allylic substitution reaction

Proposed catalytic cycle resembles one accepted for the Pd catalyzed allylation reactions.

In 2004 Alexakis et al.\(^{60}\) introduced even more efficient class of phosphoramidite type ligands: ortho substituted ligands (Figure 8), with these ligands higher selectivities and shorter reaction times were achieved.

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It was initially thought that orthomethoxy group on the phenyl ring has a role in coordinating to metal center and therefore influencing on selectivity and rate of reaction. However, proofs for this could not be observed, additionally it was found that ligands possessing ortho methyl groups such as L4 and L5 are even better in terms of rate and selectivity of the reaction (Scheme 24).\textsuperscript{61} It is now accepted that the substituents on phenyl ring enhance the dissociation of ligand L from complex 50 making formation of active complex easier.

Scheme 24. Application of ortho substituted ligands in Ir catalyzed allylic substitution reaction

In 2005 Hartwig et al. showed that phosphoramidite ligands with single resolved stereocenter are equally efficient as their precedents with two stereocenters (Scheme 25).\textsuperscript{62}

Due to the excellent regioselectivities towards branched products which makes Ir complementary method to palladium catalyzed allylic aminations and due to excellent enantioselectivities this method has witnessed considerable research efforts directed towards extension of scope of reaction as well as attempts towards application in the synthesis of more complex molecules. Reactions of ketone enolates and amines as nucleophiles with allylic carbonates proceeded in excellent yields and enantioselectivities. In addition various O-alkylating agents such as phenolates can be used for allylic etherifications as well as aryl zinc reagents for allylic arylation.

Since allylic esters are typically prepared from allylic alcohols, the use of allylic alcohols in asymmetric allylic substitution would streamline synthetic sequences and would be more atom economic. The poor leaving group ability of a hydroxyl group causes the substitution of allylic alcohols typically to require high temperatures, neat conditions or an activator. However, in the presence of Ti, Ta or Nb alkoxides in stoichiometric amounts allylic aminations proceed in good yields and high regio- and enantio-selectivities. In the presence of catalytic amounts of BPh₃ reactions with aromatic anilines proceed in same manner (Scheme 26).
Scheme 26. Ir catalyzed allylic aminations with allylic alcohols

Ir catalyzed intramolecular allylic substitution, as well as combination of intermolecular Ir catalyzed allylic substitution with ring closing metathesis reaction has allowed asymmetric syntheses of various carbo- and hetero-cycles. A combination of Ir catalyzed allylic substitutions with ring closing metathesis (RCM) has been recently applied for the preparation of some biologically active compounds like (S)-nicotine and prostaglandin analogue TEI-9826. Similarly, 2,5-disubstituted-2,5-dihydropyrroles were prepared by Helmchen’s group in excellent regio- and diastereoselectivities (Scheme 27). The primary amine was synthesized via Ir catalyzed allylic amination with N$_2$N-diacylamines as ammonia equivalents followed by subsequent deprotection of acyl moieties.

Scheme 27. Synthesis of 2,5-disubstituted dihydropyroles via combination of allylic amination and RCM

---

1.5.2 Ir Catalyzed Allylic Alkylations with Unsymmetric Nucleophiles

Iridium catalyzed allylic alkylation using symmetric nucleophiles (e.g. dimethylmalonates) has been studied by several research groups and a variety of substrates can be alkylated with enantiomeric excesses that are quite generally higher than 90% ee (vide supra). However, the use of unsymmetrical nucleophiles is a far more challenging task since not only regio- and enantioselectivity have to be controlled, but also diastereoselectivity has to be taken into account in order to obtain desired stereoisomers 57 or 58 in excess (Scheme 28).

**Scheme 28.** Possible products in transition metal catalyzed allylic alkylation with unsymmetric nucleophiles

Linear product 56 and branched 57 and 58 can be selectively obtained depending on the transition metal applied.

In 2003 Takemoto *et al.* published an elegant approach towards β-substituted α-amino acids using iridium catalyzed allylic alkylation as key step.\(^{70}\) Iridium catalyzed allylic alkylation favoured the branched diastereomeric products 61 and 62. Diastereoselectivity was influenced by the type of base and counter cation used. Both diastereomers were synthesized in excess depending on reaction conditions and with high enantioselectivities using \(t\)-butyl glycinate 60 and ligand 63 (Scheme 29).

---

Scheme 29. Diastereoselective allylic alkylation of benzophenone glycinate

\[
\begin{align*}
\text{Ph} \underset{\text{P(O)(OEt)}_2}{\text{OP}} & \quad \text{Ph} \underset{\text{CO}_2\text{Bu}}{\text{N}} \\
\text{SEt} & \quad \text{Ph} \underset{\text{CO}_2\text{Bu}}{\text{N}} \\
\text{Ph} \ & \quad \text{Ph} \ \\
\end{align*}
\]

\[\text{[Ir(cod)Cl]_2} \quad 63, \text{ solvent} \]

\[
\begin{align*}
\text{R} & \quad \text{reaction conditions} & \text{yield, %} & \text{ratio} & \text{ee, %} \\
\text{Ph} & \quad \text{LiN(SiMe}_3)_2, \text{ THF} & 71 & 70/30 & 97/\text{nd} \\
\text{Ph} & \quad \text{solid KOH, toluene} & 82 & 12/88 & 56/92 \\
\text{p-} & \quad \text{LiN(SiMe}_3)_2, \text{ THF} & 78 & 12/88 & 56/92 \\
\text{CF}_3 & \quad \text{solid KOH, toluene} & 78 & 10/90 & 93/94 \\
\text{C}_6\text{H}_4 & & & & \\
\end{align*}
\]

The stereochemical course of the reaction can be explained as follows (Scheme 30). Initially, two \(\pi\)-allyl complexes 64 and 65 (\(\sigma\)-allyl complexes could not be excluded) would be formed predominantly by attack of the iridium(I)-ligand 63 complex on the allylic substrate 59. However, the complex 65 should be disfavored due to the steric interaction between the ethylthio group of the ligand and the phenyl group of 59. Therefore, the nucleophilic attack of the enolate of 60 at the allylic carbon \(\text{trans}\) to the phosphorus atom would give the chiral products 61 and 62 with high enantioselectivity. Different behavior of the bases might be attributed to the geometry of the enolate of 60.

Scheme 30. Stereochemical course of reaction
Namely, it was assumed that the use of KOH as a base would give the $E$-enolate 66 predominantly, but, in contrast, the $Z$-enolate 67 would be formed with use of LiN(SiMe$_3$)$_2$ as a base.\textsuperscript{71} Length of the linker to sulphide group proved to be crucial for good enantioselectivities of reaction, since six membered transition state was assumed to be essential for high enantioselectivities. Ligands possessing longer chains or bulkier groups than ethyl on the other side of chain gave lower ee’s. Additionally Takemoto was able to make several interesting observations. The substitution pattern of the chiral ligand did not influence the diastereoselectivity of reaction at all. The use of chiral phase transfer catalyst, which should influence the enolate geometry of the nucleophile, also failed to improve the ratio of 61/62. In contrast the type of ester moiety had drastic influence on the diastereoselectivity. When using the corresponding methyl ester of 57 diastereoselectivities were significantly lower, albeit the enantioselectivity of the reaction was not affected. Therefore stereodifferentiation of the enantiotopic faces of the allyl-metal complex coordinated by chiral ligand 63 is highly independent of the nucleophiles employed.

2 Syntheses of Tryptamines, Tryptophanes and Homologues

Schmidt and Eilbracht have recently reported on the synthesis of various branched tryptamine and tryptamide analogues involving tandem hydroformylation / Fischer indole synthesis sequence.\textsuperscript{35,72} This convergent method allowed introduction of various substituents in all pharmacologically relevant positions of the indole core. We wanted to concentrate on the side chains of these molecules i.e. formally, substituents in position 3. We used tandem hydroformylation / Fischer indolization strategy for the preparation of enantiopure tryptamines, tryptophanes and their homologues with different complexities and lengths of side chain which is as already mentioned (vide supra) very important issue in regard to biological activity of these types of molecules. Required olefinic starting materials are synthesized via efficient enantioselective Ir catalyzed substitution reactions (Scheme 31).

Scheme 31. Envisaged synthetic pathway for the synthesis of tryptamine analogues

2.1 Synthesis of Enantiopure Tertiary Tryptamines and Tryptamides

Most of the known β-branched tryptamines are tryptophan derivatives and can be synthesized starting from this essential amino acid. Therefore, not surprisingly, only a few examples of β-branched tryptamines are reported with substituents not possessing the oxidation level of carboxylic group or with substituents not obtainable from carboxylic group of tryptophane. Powerful method for the synthesis of this type of indole molecules is tandem hydroformylation / Fischer indole synthesis sequence. The chiral branched allylic amines required are synthesized via Ir catalyzed allylic amination of allylic carbonates. After hydroformylation in the presence of the phenyl hydrazines and subsequent indolization tryptamines and tryptamides bearing substituents other than those obtainable from tryptophan carboxylic group could be prepared (Scheme 32).

Scheme 32. Envisaged reaction pathway for the synthesis of branched tryptamines and tryptamides

2.1.1 Synthesis of Allylic Amines via Ir Catalyzed Allylic Amination Reaction

Although vast number of approaches is available for the enantioselective synthesis of allylic and homoallylic amines, in the last couple of years Ir catalyzed allylic aminations emerged as one of the most powerful and most convenient methods for their synthesis. With this methodology, a large number of different allylic amines is accessible. Our reactions were run using conditions previously described,\(^{73}\) i.e. the catalyst was prepared by \textit{in situ} activation of \([\text{Ir(cod)Cl}]_2\) and ligands \textbf{L1} or \textbf{L3} with the propyl amine, in dry THF. In the test reaction of cinnamyl carbonate \textbf{68a} and benzylamine, ligand \textbf{L1} (Table 1, Entry 1) gave product \textbf{70a} in 56% yield and 90% ee, while ligand \textbf{L3} gave product \textbf{70a} in 76% yield and 94% ee, proving to be the ligand of choice for this reaction (Table 1, Entry 2).

Table 1. Ir catalyzed allylic aminations of various allylic carbonates 68, with amines 69

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>Amine, 69</th>
<th>Ligand</th>
<th>Time (h)</th>
<th>Yieldb, 70 (%)</th>
<th>ee%c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (68a)</td>
<td>benzylamine</td>
<td>L1</td>
<td>1.5</td>
<td>90/10</td>
<td>58 (70a)</td>
</tr>
<tr>
<td>2</td>
<td>Ph (68a)</td>
<td>benzylamine</td>
<td>L3</td>
<td>0.25</td>
<td>92/8</td>
<td>76 (70a)</td>
</tr>
<tr>
<td>3</td>
<td>Ph (68a)</td>
<td>benzylamine</td>
<td>entL3</td>
<td>0.5</td>
<td>96/4</td>
<td>75 (70a)</td>
</tr>
<tr>
<td>4</td>
<td>Ph (68a)</td>
<td>cyclohexylamine</td>
<td>L3</td>
<td>46</td>
<td>94/6</td>
<td>74 (70a)</td>
</tr>
<tr>
<td>5</td>
<td>Ph (68a)</td>
<td>morpholine</td>
<td>L3</td>
<td>16</td>
<td>95/5</td>
<td>82 (70c)</td>
</tr>
<tr>
<td>6</td>
<td>Ph (68a)</td>
<td>phthalimide</td>
<td>L3</td>
<td>12</td>
<td>98/2</td>
<td>66 (70d)</td>
</tr>
<tr>
<td>7</td>
<td>Ph (68a)</td>
<td>pyrrolidine</td>
<td>L3</td>
<td>0.5</td>
<td>95/5</td>
<td>73 (70e)</td>
</tr>
<tr>
<td>8</td>
<td>2-MeOPh (68b)</td>
<td>diethylamine</td>
<td>L3</td>
<td>18</td>
<td>96/4</td>
<td>62 (70f)</td>
</tr>
<tr>
<td>9</td>
<td>4-MeOPh (68c)</td>
<td>piperidine</td>
<td>L3</td>
<td>46</td>
<td>91/9</td>
<td>91 (70g)</td>
</tr>
<tr>
<td>10</td>
<td>2-furyl (68d)</td>
<td>morpholine</td>
<td>L3</td>
<td>20</td>
<td>95/5</td>
<td>81 (70h)</td>
</tr>
<tr>
<td>11</td>
<td>3-Purydyl (68e)</td>
<td>piperidine</td>
<td>L3</td>
<td>0.5</td>
<td>96/4</td>
<td>85 (70i)</td>
</tr>
<tr>
<td>12</td>
<td>Et (68f)</td>
<td>benzylamine</td>
<td>L3</td>
<td>5</td>
<td>91/9</td>
<td>62 (70j)</td>
</tr>
<tr>
<td>13</td>
<td>Pr (68g)</td>
<td>benzylamine</td>
<td>L3</td>
<td>2</td>
<td>89/11</td>
<td>60 (70k)</td>
</tr>
<tr>
<td>14</td>
<td>aPr (68g)</td>
<td>aniline</td>
<td>L3</td>
<td>46</td>
<td>95/5</td>
<td>77 (70l)</td>
</tr>
</tbody>
</table>

a Method A: In THF at 50 °C, The ratio of 68:69:[Ir(cod)Cl]:[L3] = 100:150:1:2, b Ratio determined by 1H-NMR of crude reaction mixture, c Yield of isolated product after column chromatography, d Determined by chiral HPLC, e Not Determined

Reactions with all other substrates were run with ligand L3 and good yields and excellent enantioselectivities were obtained in all cases with allylic carbonates bearing sp3 as well as sp2 substituents (Table 1). Ent-L3 gave comparable yield and enantioselectivity as L3 but product 70a with opposite configuration at chiral center was obtained (Table 1, Entry 3). Not only amines are good nucleophiles for this reaction, phthalimide as well gave product 70d in 66% yield and 98% ee in reaction with cinnamyl carbonate 68a (Table 1, Entry 6). Various other carbonates and amines were combined demonstrating the versatility of this approach for the synthesis of starting materials for tandem hydroformylation / Fischer indole...
synthesis. Absolute configurations of 70a and 70d were determined by comparison of optical rotation data of isolated compounds with literature values of known compounds.

Phenyl, substituted phenyl as well as alkyl rests present in starting carbonates 68a-g are generating substituents in the β position of the final tryptamine molecule, as already mentioned introducing these substituents by other methods is extremely difficult. Aromatic pyridyl and furyl substituents can be introduced in the tryptophane molecule starting from carboxylic group but this requires multiple steps and is associated with serious drawbacks.

It is already mentioned that under hydroformylation conditions primary and secondary amines are undergoing intramolecular "hydroaminomethylation" reaction. Schmidt observed that under hydroformylation conditions allylic amides 72 are completely consumed, but aldehydes 73 and 74 were only detected as the minor product (Scheme 33).

Instead, 2-hydroxy pyrrolidines 75 are formed in nearly quantitative yield. Consequently, by use of protected secondary allylic amines, this consecutive reaction can be suppressed and the n-aldehydes can be obtained with high yields and selectivities. Jackson et al. found a similar behavior.

Scheme 33. Intramolecular cyclization of secondary allylic amines under hydroformylation conditions

\[
\begin{align*}
\text{cond.:} & \quad 1\text{eq.} \ 72, \ 0.3\text{mol}\% \ \text{Rh(acac)(CO)}_2, \ 1.5\text{mol}\% \ \text{XANTPHOS}, \\
& \quad 10\text{bar CO}, \ 10\text{bar H}_2, \ \text{THF}, \ 20\text{h}, \ 70^\circ\text{C}.
\end{align*}
\]

Due to these observations secondary allylic amines obtained from the amination reaction of carbonates with primary amines had to be protected. Substrates 70a, b and 70j-l (Table 2) were protected with acetyl group and in all cases good yields of acetylation products were

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obtained. Acetyl group is stable under hydroformylation conditions and is desirable in the potentially bioactive molecules as it is increasing lipophilicity of the parent molecules.

Table 2. Protection of primary amines prior to hydroformylation

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70a</td>
<td>88 (R)</td>
</tr>
<tr>
<td>2</td>
<td>70a</td>
<td>85 (S)</td>
</tr>
<tr>
<td>3</td>
<td>70b</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>70j</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>70k</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>70l</td>
<td>76</td>
</tr>
</tbody>
</table>

2.1.2 \textit{N}-selective Hydroformylation of Allylic Amines and Amides

Having tertiary allylic amines in hands, attention was turned towards optimization of hydroformylation of the chosen substrates. Hydroformylation of tertiary allylic amines however can be associated with some serious side reactions such as rhodium catalysts promoted isomerisation of allylic amines to enamines at mild temperatures,\textsuperscript{76} the enamines formed are easily hydrogenated under hydroformylation conditions in a sequence known as hydroaminomethylation. It is also well known that the hydrogenation activity of rhodium catalysts is increased in the presence of catalytic amounts of tertiary amines.\textsuperscript{77} In using amino olefins, the tertiary amines, as part of the substrate, are present in high excess relative to the catalyst. Furthermore, tertiary amines acting as bases can induce aldol condensation reactions of the aldehydes as a side-reaction. However all these possible side reactions are avoided when hydroformylation of olefins is performed in the presence of phenyl hydrazines.\textsuperscript{34} Hydrazines are trapping the aldehyde formed and protecting it from possible


side reactions. The role of phenyl hydrazines is therefore dual as they are building blocks for the final molecule but at the same time they are acting as protecting group for the aldehyde moiety.

For our desired indole structures it is crucial to have \textit{n}-aldehydes in highest possible percent in reaction mixture. \textit{Iso}-aldehydes are giving another type of indole structures, namely 2,3 disubstituted indoles. These structures if present might be hampering isolation of desired product from the reaction mixture. It is well known that ligand free hydroformylation of terminal disubstituted olefins regioselectively gives \textit{n}-aldehydes, however, ligand free hydroformylation of monosubstituted olefins leads to a mixtures of \textit{n}- and \textit{iso}-aldehydes. \textit{N}-selectivity is increased by the use of bidentate ligands such as the biphosphite BIPHEPHOS 77 or the biphosphine XANTPHOS, 78 (Figure 9).

\textbf{Figure 9.} Ligands for \textit{n}-selective hydroformylations

![Ligands for \textit{n}-selective hydroformylations](image)

Both ligands lead to high \textit{n}-selectivities if simple olefins like 1-hexene or 1-octene are used. With functionalized olefins however, the \textit{n}-selectivity decreases dramatically. The nature of the protecting group strongly affects \textit{n}/\textit{iso} selectivity. Additionally \textit{N}-donor groups attached to the olefin may compete with ligand for the catalyst, altering its activity. It has been established previously that XANTPHOS is giving best \textit{n}/\textit{iso} selectivities in tandem hydroformylation / Fischer indolization sequence. Ratios of Rh / XANTPHOS of 1/10 were sufficient to achieve high selectivities towards the desired \textit{n}-aldehydes.\textsuperscript{35} To test the influence of the protecting group and substrate structure on the \textit{n}/\textit{iso}-selectivity, several protected allylic amines are hydroformylated with a Rh(acac)(CO)\textsubscript{2} / XANTPHOS system in 1:10 ratio (Table 3). Here lower carbon monoxide partial pressures were chosen to ensure that carbon monoxide does not displace XANTPHOS from the catalytically active rhodium complex.
Among the compounds tested, three different types can be recognized (Table 3). Those containing two carbonyl groups are known to give lower \(n/\text{iso}\) ratios. Here a precoordination of the catalyst is more probable than in substrates with only one carbonyl group. The allylic acetamide 76a was hydroformylated under conditions involving 1 mol% Rh(acac)(CO)\(_2\), 10 mol% XANTPHOS, 10/10bar CO/H\(_2\), at 80°C in THF, however after 2 days of reaction only 45% of substrate was converted to aldehyde although in high \(n/\text{iso}\) ratio of 95/5 (Table 3, Entry 1), after 3 days 80% conversion of substrate was achieved maintaining high ratio of \(n/\text{iso}\) isomers (Table 3, Entry 2). In order to achieve full conversion 76a was submitted to the same reaction conditions with increased temperature to 90 °C which after 3 days yielded in full conversion of aldehyde and in 98/2 ratio of \(n/\text{iso}\) isomers (Table 3, Entry 3). Under same conditions tertiary amine 70e (Table 3, Entry 4) is fully converted to \(n\)-aldehyde exclusively. Allylic phthalimide 70d under the same conditions was converted more than 95% and gave as well high \(n/\text{iso}\)-selectivity of 96/4 (Table 3, Entry 5). Reactions run in DCM appeared to be faster, yielding in full conversions at lower temperatures (compare Entries 4 and 5, Table 3) or in shorter reaction times (compare entries 6 and 7, Table 3). In no case significant amounts of side reaction products.

---

Table 3. Optimization of hydroformylation of allylic amines, amides and imides

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>[Rh] : XANTPHOS</th>
<th>CO/H(_2) bar</th>
<th>Time / d</th>
<th>Temp / °C</th>
<th>Solvent</th>
<th>Conv.(^{a}) / %</th>
<th>Ratio(^{a})</th>
<th>79:80</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76a</td>
<td>1 : 10</td>
<td>10/10</td>
<td>2</td>
<td>80</td>
<td>THF</td>
<td>45</td>
<td>95/5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>76a</td>
<td>1 : 10</td>
<td>10/10</td>
<td>3</td>
<td>80</td>
<td>THF</td>
<td>80</td>
<td>98/2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>76a</td>
<td>1 : 10</td>
<td>10/10</td>
<td>3</td>
<td>90</td>
<td>THF</td>
<td>100</td>
<td>98/2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>76e</td>
<td>1 : 10</td>
<td>10/10</td>
<td>3</td>
<td>90</td>
<td>THF</td>
<td>100</td>
<td>100:0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>70e</td>
<td>1 : 10</td>
<td>50/10</td>
<td>3</td>
<td>80</td>
<td>DCM</td>
<td>100</td>
<td>95/5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>70d</td>
<td>1 : 10</td>
<td>10/10</td>
<td>3</td>
<td>90</td>
<td>THF</td>
<td>&gt;95</td>
<td>96/4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>70d</td>
<td>1 : 10</td>
<td>10/10</td>
<td>3</td>
<td>80</td>
<td>DCM</td>
<td>100</td>
<td>93:7</td>
<td></td>
</tr>
</tbody>
</table>

conditions: 1equiv substrate, 1 mol% Rh(acac)(CO)\(_2\), 10 mol% XANTPHOS, CO/H\(_2\) (see table), THF, Time and temperature (see table), \(^{a}\)Determined by \(^{1}\)H-NMR of the crude reaction mixture.
were observed. Even in absence of phenylhydrazine hydroformylation gave aldehydes exclusively in high \( n/iso \) ratios. Due to the somewhat higher selectivity towards \( n \)-products when hydroformylation is performed in THF, although at the expense of longer reaction times all tandem reactions were performed in THF as a solvent (see below). It is known that subsequent acid promoted indolizations are giving highest yields in THF, this as well contributed to the selection of THF as a solvent of choice for our reaction sequence.

### 2.1.3 Tandem Reaction towards Synthesis of \( \beta \)-branched Tertiary Tryptamines and Tryptamides

Since hydroformylation of olefins is not affected by the presence of aryl hydrazines it can be expected that optimized conditions for hydroformylation can be transferred to the tandem sequence without negative effects on yield or selectivity or reaction. Tertiary amines obtained were submitted to optimized hydroformylation conditions in the presence of aryl hydrazines. Reaction conditions involved 1 mol\% Rh(acac)(CO)\(_2\), 10 mol\% XANTPHOS, 10 bar CO and 10 bar H\(_2\) gas pressure at 90 °C. Indolization was subsequently performed in 4w\% H\(_2\)SO\(_4\) (Table 4). This protocol involving tandem hydroformylation / hydrazone formation with subsequent indolization in the presence of acid was proven to be superior to the protocol where Brønsted acid (mainly PTSA) is added directly in reaction vessel during hydroformylation.\(^{34}\)
Table 4. Tandem hydroformylation / Fischer indolization in the synthesis of tryptamines and tryptamides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Product</th>
<th>Yield, (\text{ee}%)</th>
<th>Entry</th>
<th>Olefin</th>
<th>Product</th>
<th>Yield, (\text{ee}%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76a, 76b</td>
<td>(\text{Ph, Ac, Bn})</td>
<td>62%, (R) 92% ee</td>
<td>8</td>
<td>70d, 70e</td>
<td>(\text{Ph, R_2, R_3})</td>
<td>67%, (R) ((+)(-81a))</td>
</tr>
<tr>
<td>2</td>
<td>76b</td>
<td>(\text{Ph, Ac, Bn})</td>
<td>65%, (S) 97% ee</td>
<td>9</td>
<td>70f, 70g</td>
<td>(\text{2-MeOPh, Et, Ph})</td>
<td>33%, (--)(-81j))</td>
</tr>
<tr>
<td>3</td>
<td>76c</td>
<td>(\text{Ph, Ac, Cy})</td>
<td>45%, ((+)(-81e))</td>
<td>10</td>
<td>70h, 70i</td>
<td>(\text{2-furyl, Morpholine})</td>
<td>56% (811)</td>
</tr>
<tr>
<td>4</td>
<td>76d</td>
<td>(\text{Et, Ac, Bn})</td>
<td>59%, (81d)</td>
<td>11</td>
<td>70j</td>
<td>(\text{Et, Ac, Ph})</td>
<td>66%, (--)(-81f))</td>
</tr>
<tr>
<td>5</td>
<td>76e</td>
<td>(\text{Ph, Ac, Bn})</td>
<td>52%, (--)(-81g))</td>
<td>13</td>
<td>70l</td>
<td>(\text{3-pyr, R_3, R_2})</td>
<td>41% (81m)</td>
</tr>
</tbody>
</table>

All indolizations are performed in 4w\% H\textsubscript{2}SO\textsubscript{4} under reflux for 2h unless otherwise stated.\(^\dagger\) Isolated yield after column chromatography; \(^\dagger\) Determined by chiral HPLC columns; \(^\dagger\) Indolization performed in toluene with 4eq of ZnCl\textsubscript{2}.
While allylic amination proceeds with high ee's, the stereocenter may epimerize during a tandem hydroformylation / Fischer indolization via reversible double bond isomerisation catalyzed either by the transition metal catalyst or the acid. The tryptamines and tryptamides \( \text{81} \) obtained from enantiomerically pure allylic amines and amides, however, reveal complete retention of enantiopurity (Table 4, Entries 1, 2, 5 and 7). In all cases hydroformylation led to the complete conversion of olefin into aldehyde, subsequent indolizations in 4w\% \( \text{H}_2\text{SO}_4 \) gave moderate to good yields in all cases except in entry 13 where protic acid led to the precipitation of the pyridinium salts of the hydrazone formed. In this case indolization in the presence of aprotic acid i.e. 4eq of \( \text{ZnCl}_2 \) in refluxing toluene for 12h gave 41\% yield of the product \( \text{81m} \). Allylic amides in general gave slightly higher yields of products probably due to the lowered basicity of the nitrogen present in side chain of tryptamides (Nb), which eased isolation of the product and prevented tailing on \( \text{SiO}_2 \) columns (Table 4, Entries 1-6, 8). On the contrary amines with alkyl groups on the Nb nitrogen were isolated in lower yields due to the higher basicity which during chromatography induced increased tailing and stacking on the columns of \( \text{SiO}_2 \). Absolute configurations, where available, were determined by ascribing absolute configurations of starting material to final tryptamine molecule.

In summary, combination of iridium catalyzed enantioselective allylic amination and tandem hydroformylation / Fischer indole synthesis, in contrast to other methods reported, gives fast access to \( \beta \)-branched tryptamines which can not be derived from tryptophan and allows ready access to a new class of tryptamine derivatives for biological screenings.

### 2.2 Synthesis of \( \beta \)-branched Homotryptophanes

#### 2.2.1 Ir Catalyzed Allylic Substitutions of Benzophenone Glycinates

Using the same protocol with branched homoallylic amines, branched homotryptophanes were synthesized. For the synthesis of homoallylic amines Ir catalyzed allylic alkylation of allylic carbonates \( \text{68} \) with benzophenone glycinate \( \text{82} \) was envisaged. These allyl glycines (\( \text{83+84} \)) after hydroformylation in presence of the phenyl hydrazines and indolization should yield in homotryptophane structures \( \text{85} \) (Scheme 34).
As already mentioned, iridium catalyzed allylic substitutions of symmetric nucleophiles (e.g. sodium dimethylmalonate) and 3-substituted allylic alcohol derivatives are very well established reactions. On the contrary, Ir catalyzed allylic alkylations of benzophenone glycinate 82 are only scarce in the literature. Benzophenone glycinate has some advantageous properties for our purposes: benzophenone group is stable under hydroformylation conditions but under conditions of subsequent indolization which include reflux for 2h in 4 w% H₂SO₄, this group is cleaved allowing synthesis of primary β-branched tryptophanes (Scheme 34). Test substrate 68a in the presence of ligands L1 and L3 was submitted to various reaction conditions which are known to give different stereochemical outcomes, yields and selectivities were then compared (Table 5).

Table 5. Ir catalyzed allylic substitution of 82 and 68a under various reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand, reaction conditions</th>
<th>reaction time</th>
<th>yield, %a</th>
<th>Ratiob</th>
<th>eec</th>
<th>83a 84a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L3, 0.2 equiv DABCO, THF, 50°C</td>
<td>16h</td>
<td>87</td>
<td>87</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>L1, LiN(SiMe₃)₂ THF, -78°C to rt</td>
<td>3h</td>
<td>80</td>
<td>70:30</td>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>L3, LiN(SiMe₃)₂ THF, -78°C to rt</td>
<td>3h</td>
<td>84</td>
<td>75:25</td>
<td>87</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>L3, solid KOH, THF, rt</td>
<td>5h</td>
<td>65</td>
<td>40/60</td>
<td>91</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>“cyclometalated” catalyst 50</td>
<td>7d</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>

*a Yield of isolated product after column chromatography; b Determined by isolation after column chromatography; c Determined by HPLC on chiral column.
First, standard established protocol for the allylic aminations using 20 mol% DABCO for preactivation of the catalyst in the presence of ligand L3 was applied (Table 5, Entry 1). Under these conditions after 16 hours complete conversion was achieved and the products were isolated in 87 % overall yield. Both, syn and anti stereoisomers were separately isolated in approximately 3/2 ratio in favour of syn isomer 83a. Both isomers showed excellent ee values of 97% and 95 %ee respectively. In contrast to the method used by Take moto which required 10 mol% of metal catalyst and 20 mol% of ligand 63, here, only 2 mol% of catalyst and 4 mol% of ligand L3 had to be used to achieve reasonable reaction times. Preforming of the enolate at -78 °C using LHMDS as a base and adding preformed enolate to the mixture of catalyst, ligand and carbonate gave 80% and 84 % yield of products respectively for ligands L1 and L3. Approximately 4/1 ratio of syn/anti, was observed in both cases. As expected ligand L3 gave higher ee’s of products 83a and 84a than ligand L1 (Table 5, entries 2 and 3). Complete conversion of starting material was observed after 3h, but surprisingly in this case ee values were lower as compared to salt free conditions (Table 5, Entry 1). Preforming of the enolate with KOH at room temperature and adding preformed enolate to the mixture of catalyst, ligand L3 and carbonate gave approximately 2/3 ratio of syn/anti products with good enantioselectivity of 83a (Table 5, Entry 4). Under these conditions products were isolated in 65% overall yield which is somewhat lower value as compared to other tested conditions.

These results are in accordance with Takemoto’s observation that diastereoselectivity is controlled by the geometry of enolate formed and not by the chiral ligand, i.e. reaction performed under kinetic control (small counterion, low temperature) is favouring the formation of Z enolate and syn product while thermodynamic control (bigger counterion, room temperature) is favouring the formation of E enolate and anti product. However, in no case high stereoselectivities were observed, they ranged from 4/1 in favour of syn isomer (Table 5, Entry 3) to 2/3 in favour of anti isomer (Table 5, Entry 4). These poor regioselectivities can most probably be ascribed to the sterically undemanding ester group applied.

However, even base free allylic substitutions are well known for palladium catalyzed allylic substitutions using carbonates as substrates. The general mechanism involves coordination of the carbonate to the metal center and subsequent loss of CO₂. Dissociation of the metal bound alkoxide will then normally provide a sufficiently basic species, which will

act as base during the reaction. Interestingly, when the active ‘‘cyclometalated’’ catalyst 50 obtained by activation with excess propylamine,71 was applied for alkylation reaction without additional base no conversion was observed even after several days of reaction time. Apparently unlike our initial thoughts the use of DABCO in substoichiometric amounts is crucial for success of this procedure. Besides its role in catalyst activation DABCO is most probably taking part in deprotonation of 82 making it sufficiently nucleophilic for alkylation reactions. Enantioselectivities obtained in test reactions were very promising, and showed high potential of phosphoramidite type ligands in the Ir catalyzed allylic substitution reactions. Despite somewhat longer reaction times when using salt free conditions (i.e. DABCO as a base) due to the best enantioselectivities of both diastereoisomers and due to the lack of higher diastereodifferentiation with other methods, these conditions were chosen to be used with various allylic carbonates 68b-f (Table 6).

![Image of chemical reaction]

**Table 6. Ir- Catalyzed Allylic Substitution of 79 with Various Substrates 67b-f**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>Conditions,*</th>
<th>yield, %b</th>
<th>Ratio°</th>
<th>ee, %d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-MeOPh (68b)</td>
<td>A, L3</td>
<td>82</td>
<td>70/30</td>
<td>91 (83b)</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOPh (68c)</td>
<td>A, L3</td>
<td>97</td>
<td>56/44</td>
<td>94 (83c)</td>
</tr>
<tr>
<td>3</td>
<td>4-MeOPh (68c)</td>
<td>B, L1</td>
<td>55</td>
<td>62/38</td>
<td>67 (83c)</td>
</tr>
<tr>
<td>4</td>
<td>2-furyl (68d)</td>
<td>A, L3</td>
<td>69</td>
<td>60/40</td>
<td>95 (83d)</td>
</tr>
<tr>
<td>5</td>
<td>3-pyridyl (68e)</td>
<td>A, L3</td>
<td>72</td>
<td>65/35</td>
<td>92 (83e)</td>
</tr>
<tr>
<td>6</td>
<td>n-C2H5 (68f)</td>
<td>A, L3</td>
<td>65</td>
<td>75/25</td>
<td>nd (83f)</td>
</tr>
</tbody>
</table>
| 7     | H (68h) | A, L3 | 28 (83h) | / | / | /

* Method A: In THF at 50 °C, The ratio of 68: 82: DABCO: [Ir(cod)Cl]2: (Ra, Rc, Rc)-L3 was 100: 100: 20: 2:4. Method B: In THF at 0 °C The ratio of 68: 82: LiN(SiMe3)2: [Ir(cod)Cl]2: L1 was 150: 100: 150: 2: 4; ° Yield of isolated product after column chromatography; ° Determined by isolation of both isomers; d Determined by HPLC on chiral column.

All tested substrates gave good yields and excellent enantioselectivities. Syn isomer was obtained in excess in all cases, although with poor diastereoselectivities. Substrates 68c-e possessing p-MeO-Ph, furyl or pyridyl groups reapectively, yielded in approximately 60/40 ratios of syn/anti isomers (Table 6, Entries 2, 4 and 5), substrate 68b possessing o-MeO-Ph group, however, gave slightly higher ratio of syn isomer of 70/30 (Table 6, Entry 1),
surprisingly substrate 68f possessing Et group gave 75/25 ratio of syn/anti diastereoisomers with good enantiomeric excess of syn isomer, ee of anti isomer was not determined (Table 6, Entry 6). p-MeO-cinnamyl carbonate 68c was submitted to conditions which involved preforming the enolate with LiHMDS in presence of ligand L1 yielding in 55% overall yield of products with low enantioselectivity (Table 6, Entry 2) once more proving the superiority of ligand L3 and salt free conditions (Table 6, Entry 3). In reaction of 68h with 82 only one stereocenter is formed, product was isolated in rather poor yield of 28 %, which can be partly ascribed to higher volatility of allylcarbonate (Table 6, Entry 7).

Absolute configuration of isolated diastereoisomers was determined by transforming ethyl ester 83a into methyl ester and by comparing optical rotation data of 86a with literature data. Absolute configuration was determined to be as shown on scheme 35. Absolute configurations of other substrates can be ascribed by analogy.

**Scheme 35. Determination of absolute configuration**

![Scheme 35](image)

In an attempt to introduce nitrogen protecting group that is stable under the acidic indolization conditions and that would yield in tertiary tryptophanes which are as well interesting compounds from medicinal point of view, ethyl glycinate was protected with the phthaloyl group to give compound 87. Phthaloyl group is stable under acidic indolization conditions. However, standard procedure used for alkylations with benzophenone protected glycine 82 proved unsuccessful with Pht protected glycine ethyl ester 87. Preforming of the enolate with LiHMDS and adding it to the solution of the carbonate and catalyst led to the intensive coloration of the reaction mixture but even after prolonged reaction times no product could be observed, this was as well the case when the salt free conditions using DABCO as a base were applied (Scheme 36).
2.2.2 Hydroformylation and Indolization of Allyl Benzophenone Glycinates

Since it proved difficult to separate sufficient amounts of diastereoisomers for indole synthesis reaction, diastereomeric mixture of allyl glycineses 83a+84a containing 62/38 ratio of these two was submitted to same conditions used for the synthesis of branched tryptamines and tryptamides involving 1 mol% Rh(acac)(CO)$_2$, 10 mol% XANTPHOS, in THF at 90 °C for 3 days. After 3 days the olefin was hydroformylated with only 45% conversion, which resulted in 22% yield of desired indole after indolization. In order to achieve full conversion of the olefin, reaction time was prolonged to 5 days leaving other variables the same and each step of the sequence was separately performed and examined. After 5 days of hydroformylation full conversion of olefin was observed, with a ratio of n/iso aldehyde of 95/5 as determined by $^1$H-NMR of crude reaction mixture. To a solution of aldehyde 1 equiv phenyl hydrazine was added and after 2 h of reaction full conversion towards hydrazone 88 was achieved, subsequent indolization with 4 w % H$_2$SO$_4$ yielded in satisfactory 57% of indole 85a (Scheme 37). This test reaction showed that aldehyde hydroformylation is the key step for obtaining good yields and once full conversion of aldehyde is achieved remaining steps are proceeding without any major influences on the overall yield of the reaction. Ratio of isomers in the indole mixture was the same as in the starting material, approximately 60/40 implying that even at reflux temperatures in diluted H$_2$SO$_4$ racemization can not be observed.
With these newly established conditions substrates 83a+84a and 83f+84f were submitted to tandem sequence yielding in primary β-branched homotryptophanes. Products were isolated in moderate yields as mixtures of diastereoisomers (Scheme 38). It is noteworthy to mention that substrate 83a+84a gave slightly higher yield in tandem process than when every step was performed separately.

Attempted hydroformylation / hydrazone formation reactions with subsequent indolization with Lewis acids, which should preserve benzophenone group of 83a+84a, and in turn yield in tertiary tryptophane 89 were unsuccessful, after 24 hours of reflux with 4 equiv of ZnCl₂ in toluene only starting hydrazone was quantitatively recovered. Attempted indolization

with BF$_3$ was unsuccessful as well, hydrazone was completely recovered even after prolonged reaction times (Scheme 39).

**Scheme 39.** Lewis acid promoted indolizations

![Scheme 39](image)

**indolization conditions:**

1. a) 4 eq ZnCl$_2$, toluene, reflux 24h
2. b) 2 eq BF$_3$•Et$_2$O, THF, rt then reflux 12h

In summary, we have shown that Ir catalyzed alkylation reactions in combination with tandem hydroformylation / Fischer indolization are representing a powerful strategy for the synthesis of branched homotryptophanes. Starting materials were obtained in high enantiomeric purities however their separation on large scale was not successful. In order to make this procedure more synthetically useful it would be necessary to use single enantiopure diastereoisomers in this sequence in order to get access to enantiopure homotryptophane derivatives.
2.3 Synthesis of Longer Chain Tryptophanes

2.3.1 Ir Catalyzed Allylic Alkylation of Cyanoacetates

Ir catalyzed allylic alkylation of allylic carbonates 68 with cyanoacetates 90 was applied in the synthesis of required starting materials 91. Nitrile group of cyanoacetates is planned to be used as masked amine functionality. These substrates after hydroformylation, indolization and selective reduction of nitrile moiety should yield in primary tryptophane homologues 93 (Scheme 40).

Scheme 40. Envisaged pathway for the synthesis of longer chain tryptophanes

As noted by Takemoto albeit influencing diastereoselectivity the ester functionality does not affect the enantioselectivity of the reaction. Therefore stereodifferentiation of the enantiotopic faces of the allyl-metal complex coordinated by chiral ligands should be highly independent of the nucleophiles employed. Based on this rationale it was expected that similar enantioselectivities will be obtained with the cyanoacetate nucleophiles as with benzophenone protected glycinate. Since there are no precedents for the Ir catalyzed allylic alkylations with cyanoacetates as nucleophiles in the literature, optimisation of reaction conditions was required. We focused on allylic alkylations using t-butyl cyanoacetate as nucleophile hoping that the sterically more demanding t-butyl group of 90a would both increase diastereodifferentiation and ease the separation of diastereomers (Table 7). Allylic carbonate 68a was chosen as test substrate.
Salt free conditions involving use of 20 mol% of DABCO as well as kinetic and thermodynamic conditions for enolate formation were tested (Table 7), in all cases products were obtained but stereoselectivities were rather poor considering the fact that bulky ester group was used, only approximately 1/1 ratios of diastereoisomers were observed in all cases. Nevertheless ratio depended on the applied base so that Li base and kinetic conditions (Table 7, Entry 1) gave opposite diastereoisomer from KOH or NaOH under thermodynamic conditions (Table 7, Entries 2 and 3). In all cases yields were moderate ranging from 42-76%. One reason for poor diastereoselectivities could be low steric demand of the nitrile group, which results in unselective enolate formation. In the case of benzophenone glycinate large benzhydrylidene group should favour the E enolate to a larger extent when a sterically demanding counter cation is used. Similarly selective formation of the Z enolate might be hampered by the fact, that the nitrile moiety is unable to sufficiently coordinate the small lithium ion. Another reason for the loss of stereochemical information might be due to racemization under the reaction conditions. Methylene protons of cyanoacetates are more acidic than those of benzophenone glycinites, abstraction of the methylene proton and subsequent reprotonation would presumably produce a 50:50 mixture of both diastereoisomers. This observation was supported by the fact that under base free conditions using previously activated catalyst 50 (by the propyl amine activation method) on the contrary to the benzophenone glycinites, reaction proceeds with moderate yield (Table 7, Entry 5) although after longer reaction time of 5 days. This result is showing that most probably the methoxide released is sufficiently basic to deprotonate substrate and make it

<table>
<thead>
<tr>
<th>entry</th>
<th>Base, conditions</th>
<th>Reaxn.time</th>
<th>dr&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield, %&lt;sup&gt;b&lt;/sup&gt;&lt;sub&gt;91a&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiHMDS, THF, -78°C to rt</td>
<td>3h</td>
<td>62/38</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>solid KOH, THF, rt</td>
<td>16h</td>
<td>43/57</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>solid NaOH, THF, rt</td>
<td>6h</td>
<td>45/55</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>DABCO, THF, 50 °C</td>
<td>18h</td>
<td>57/43</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>“cyclometalated” catalyst 50</td>
<td>5 days</td>
<td>52/48</td>
<td>42</td>
</tr>
</tbody>
</table>

<sup>a</sup> Diastereomeric ratio determined by NMR of crude reaction mixture, <sup>b</sup> Yield of isolated product after column chromatography.
more nucleophilic. Unfortunately we were not able to separate diastereoisomers of the obtained products and consequently we could not determine ee values of syn and anti isomers.

We next focused on the allylic alkylation of various carbonates with cyanacettes 90a and 90b as nucleophiles using DABCO as a base which although somewhat slower compared to other bases gave best yields in test reactions. Several reactions were set up first utilizing 90b as nucleophile (Table 8, entries 1-5). The diastereoselectivities determined and yields are summarized in table 8. All reactions gave approximately 1/1 ratios of stereoisomers in moderate to good yields.

Table 8. Ir catalyzed allylic alkylation of 90a and 90b with 68

<table>
<thead>
<tr>
<th>entry</th>
<th>R,</th>
<th>R′</th>
<th>method</th>
<th>Time</th>
<th>dr. ratio</th>
<th>Yield, % (91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>A</td>
<td>16</td>
<td>50:50</td>
<td>65 (91b)</td>
</tr>
<tr>
<td>2</td>
<td>4-MeO-Ph</td>
<td>Me</td>
<td>A</td>
<td>12</td>
<td>50:50</td>
<td>70 (91c)</td>
</tr>
<tr>
<td>3</td>
<td>2-furyl</td>
<td>Me</td>
<td>A</td>
<td>3</td>
<td>55:45</td>
<td>47 (91d)</td>
</tr>
<tr>
<td>4</td>
<td>3-puridyl</td>
<td>Me</td>
<td>A</td>
<td>45</td>
<td>50:50</td>
<td>50 (91e)</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>Me</td>
<td>A</td>
<td>48</td>
<td>/</td>
<td>27 (91f)</td>
</tr>
<tr>
<td>6</td>
<td>tBu</td>
<td>H</td>
<td>A</td>
<td>48</td>
<td>/</td>
<td>47 (91g)</td>
</tr>
<tr>
<td>7</td>
<td>2-MeO-Ph</td>
<td>tBu</td>
<td>B</td>
<td>20</td>
<td>70/30</td>
<td>70 (91h)</td>
</tr>
<tr>
<td>8</td>
<td>2-MeO-Ph</td>
<td>tBu</td>
<td>B</td>
<td>6d</td>
<td>68/32</td>
<td>35 (91h)</td>
</tr>
<tr>
<td>9</td>
<td>3-puridyl</td>
<td>tBu</td>
<td>A</td>
<td>48</td>
<td>52/48</td>
<td>60 (91i)</td>
</tr>
</tbody>
</table>

- Method A: In THF at 50 °C. The ratio of 68: 90: DABCO: [Ir(cod)Cl]2: (Ra, Rc, Rc)-L3 was 100: 100: 20: 2: 4, THF, 50 °C; Method B: The ratio of 68: 90: 50 : was 100: 100: 4, THF, 50 °C. Determined by 1H-NMR of crude reaction mixture; Yield of isolated product after column chromatography.

We next turned attention on the cyanacetae 90a, (Table 8, entries 6-9) The reactions with this nucleophile however showed that the benzhydrylidene protecting group and its steric demand seem to be vital for obtaining significant diastereomeric induction. Due to its sp hybridisation and the resulting shape the nitrile group is especially small and it might be unsuitable for this kind of diastereoselective reaction. However, all compounds were obtained in moderate to good yields showing the viability of this approach. Diastereomeric ratios were determined by 1H-NMR of crude reaction mixtures. Disappointingly regardless of substrate used, only slightly improved
diastereoselectivities were observed as compared to methyl ester. In the reaction with the
orthomethoxy substituted cinnamyl carbonate 68b (Table 8, Entry 7) slightly improved
diastereoselectivity of 70/30 was observed. To test if DABCO is responsible for this result
the preformed catalyst 50 and no external base was used. Here, the same diastereoselectivity
was observed, albeit in this case the reaction rate and yield were lower (Table 8, Entry 8).
Obviously DABCO is not solely controlling the diastereoselectivity, instead a substrate
controlled diastereoselectivity might be apparent. Most probably due to the steric
compression caused by the methoxy substituent of the substrate one of the isomeric enolates
(E or Z) of 90a is reacting faster with 68b. Enolate reacting faster is removed from E/Z
equilibrium hence causing shifting of the reaction further in the same direction i.e. higher
preference towards formation of one of the two possible diastereoisomers is observed. Since
diastereoisomers could not be separated in any case we decided to use mixtures of
diastereoisomers for hydroformylation / Fischer indole reactions and try to separate both
diastereomers in later stages of the synthesis.

2.3.2 Hydroformylation and Indolization of Allyl Cyanoacetates

Hydroformylation of the homoallylic nitriles 91 proved to be difficult and initial test
reactions using standard conditions for hydroformylation of homoallylic amines (1 mol%
Rh(acac)(CO)₂, 10 mol% XANTPHOS, 1eq PHNHNH₂, 10/10 bar pressure of CO/H₂, 90
°C, THF, 5d, followed by indolization with 4 wt% H₂SO₄) on the allylic cycanoacetate 91a
did not yield the desired indole. Therefore we tested all steps of the reaction separately.
Performing the reaction in the absence of phenylhydrazine with the same substrate under the
same conditions revealed that only 20% of olefin was converted under these conditions,
therefore we increased temperature to 110 °C since longer reaction times than 5 days are to
the authors experience highly inconvenient and impractical. After 5 days complete
conversion of olefin 91a was observed. Hydrazone formation was then carried out under
atmospheric pressure at room temperature. After indolization under standard conditions the
desired indole 91a was isolated in 39 % yield. This test experiment once more demonstrated
that conversion of the olefin is the decisive factor for the success of reaction. After the new
conditions were established other substrates were submitted to these conditions, Table 9
summarizes the synthesized indoles, which were all obtained as mixtures of diastereomers.
2 SYNTHESSES OF TRYPTAMINES, TRYPTOPHANES AND HOMOLOGUES

Table 9. Syntheses of idoles from homoallylnitriles

\[
\begin{align*}
\text{entry} & \quad R^1 & \quad R^2 & \quad \text{Yield} \ %,^a \quad 92 \\
1 & \quad \text{Ph} & \quad \text{Me} & \quad 39 \ (92a) \\
2 & \quad 4\text{-MeO-Ph} & \quad \text{Me} & \quad 66 \ (92b) \\
3 & \quad \text{Ph} & \quad \text{tBu} & \quad 60 \ (92c) \\
4 & \quad 2\text{-MeO-Ph} & \quad \text{tBu} & \quad 37 \ (92d) \\
5 & \quad \text{H} & \quad \text{tBu} & \quad 57 \ (92e) \\
\end{align*}
\]

\(^a\text{Yield of isolated product after column chromatography.}\)

It is noteworthy to mention that hydroformylation conditions as well as subsequent acidic indolization conditions did not influence the diastereomeric ratios of obtained products which were the same as in the starting materials. In general products are obtained moderate to good yields, however separation of diastereomers would be necessary in order to increase the synthetic use of this pathway.

2.3.3 Reduction of Nitrile Group

For the reduction of nitrile group few different conditions were tested including LiAlH\(_4\) in THF and Pd/C under H\(_2\) atmosphere but in all cases inseparable mixtures of products were observed. Catalytic hydrogenation however, using Raney-Co as a catalyst in stoichiometric amount under 40 bar pressure of H\(_2\) selectively reduced nitrile functionality and furnished quantitative yield of desired products (Scheme 41).
2.3.4 Double Alkylation of Allyl Methylcarbonate and Synthesis of Bisindole 95

Notably, in allylic alkylations with allyl carbonate (Table 8, Entries 5 and 6) double alkylation was observed when performing the reaction with DABCO as a catalyst. Compounds 94a and 94b were isolated in an addition to the monoalkylation products 91f and 91g (Scheme 42). Tert-butylycyanooacetate 90a gave almost doubled yield of desired monoalkylation product compared to methylcyanooacetate 90b but both gave similar yield of double alkylation product 94. No reaction conditions that entirely favour double alkylation product have been developed, although it seems that higher temperature and excess of base are shifting the reaction towards the bisubstituted product. For all other carbonates no double alkylation could be observed.

Double alkylation product 94b was converted into bisindole 95 in the reaction with the 2 equivalents of phenylhydrazine (Scheme 43). Bisindole was obtained in very good yield of 68%.
Scheme 43. Synthesis of bisindole 95 from the double alkylation product 94b

Conditions: 1 mol-% Rh(acac)(CO)$_2$, 10 mol-% Xantphos, 2 equiv Phenylhydrazin, 10 bar CO, 10 bar H$_2$, THF, 5 d, 100°C then H$_2$SO$_4$, 2h, 80°C.

In summary, this convergent, one-pot strategy allowed synthesis of various functionalized indoles. Combination of Ir catalyzed allylic substitutions and tandem hydroformylation / Fischer indole synthesis sequence gave completely new insight in the synthesis of tryptamines, tryptophanes and homologues. Variabilities of the possible reactants are high, which allows flexible determination of the substitution pattern in final products. Regioselectivity of the tandem reaction was effectively controlled with the use of the biphosphine ligand XANTPHOS. Finally we have given several examples for the application of this tandem sequence demonstrating that this approach may be valuable for the synthesis of substance libraries with high diversity.

2.3.5 Allyl Glycinates in the Synthesis of Pipecolic Acid Derivatives

Compounds 83+84 obtained from Ir catalyzed allylic alkylation reactions with benzophenone glycinates can be used as starting materials for the synthesis of pipecolic acid derivatives 97. Reaction sequence involves deprotection of 83+84 and subsequent hydroformylation of amine 96 which after intramolecular hydroaminomethylation reaction should yield in pipecolic acid derivatives 97 (Scheme 44).

Scheme 44. Retrosynthetic pathway for the synthesis of pipecolic acid derivatives 97
While deprotection of substrates 83+84 to give 96a-c proceeded in good yields, subsequent hydroformylation in presence of 1 mol% Rh catalyst and 10 mol% of ligand XANTPHOS at 80 °C in THF for 3 days gave inseparable mixtures of products in all cases (Scheme 45).

**Scheme 45.** Deprotection and hydroformylation of allyl glycines

Further optimizations of reaction conditions in regard of applied catalyst, ligand, solvent and pressures of CO/H\(_2\) should be done in order to selectively obtain desired structures. Protection of primary amino group in form of carbamate as performed by Ojima et al.\(^8\) in their synthesis of pipecolic acid derivatives via hydroformylation intramolecular cyclization sequence, would be one of the solutions to minimize side reactions and obtain high yields of desired products.

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3 Tandem Hydroformylation / Pictet-Spengler Reaction

Although classical Pictet-Spengler (PS) reaction is well established as a method of choice for construction of tetrahydro-β-carboline (THBC) frameworks, original strategy has been modified over the past decades, allowing N-acyl, N-sulfinyl and N-sulfonyl β-arylethylamines to be used as nucleophilic components.\(^8^1\) On the other hand, masked ketones, aldehydes and aldehyde equivalents such as acetals, ketals, enol ethers, thioortho esters, oxazines and oxazolidines\(^8^2\) as well as acetylene sulfoxides, enamines, azalactones, and perhydro-1,3-heterocycles\(^8^3\) have been applied as electrophilic components. Olefins, however have rarely been used as precursors of electrophilic component in the Pictet-Spengler reaction.

3.1 Tandem Reaction under Aprotic Conditions

Possibility of combining Rh catalyzed olefin hydroformylation reaction and the PS reaction into a tandem reaction sequence, involving olefins as precursors of electrophilic component was explored by Taddei et al. They used this sequence for solid phase synthesis of carbolines.\(^3^6\) However, completely new set of reaction conditions had to be developed in order to achieve application of this reaction sequence in solution. While the hydroformylation reaction in the presence of rhodium catalyst would be used to synthesize the aldehyde \textit{in situ} from an olefin 99, reducing functional group transformations to a minimum, the presence of β-arylethyl amine 98 (and a Brønsted acid


allows direct conversion to a Schiff base 100 which then subsequently cyclizes to form tetrahydro-β-carboline ring system 101 (Scheme 46).

**Scheme 46.** Tandem hydroformylation / Pictet Spengler reaction

This methodology allows introduction of various substituents at C₁ without the need of costly aldehyde components, high concentrations of aldehyde component in the mixture are avoided due to the slow hydroformylation step, causing that competitive aldehyde self-condensation reaction which may result in low yields is avoided.⁸⁴ Thus some of the primary limitations of the conventional Pictet-Spengler reaction are overcome. To achieve high yields of desired product high chemoselectivities would be required in each step of tandem process. Therefore, 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. Hydroformylations of olefins in the presence of amines are yielding in different products, primary and secondary amines are condensing with the aldehydes followed by hydrogenation of the resulting imines or enamines to amines in an overall hydroaminomethylation. It is also known that the rhodium acyl species are partially undergoing nucleophilic addition of the amine to form the amide, instead of hydrogenolysis to form the aldehyde.⁸⁵ Hence, a tandem synthesis of tetrahydro-β-carbolines under hydroformylation conditions according to the above described limitations has to consist of efficient hydroformylation step leading exclusively to aldehyde. This without isolation or side reactions must condense under the same reaction conditions with β-arylethyl amine to form imine so that reduction and self condensation of aldehydes are avoided. Intermediate imine must cyclize fast in order to avoid reduction which leads to hydroaminomethylation product.

Since hydroformylation of terminal olefins usually results in a mixture of linear and branched aldehydes, disubstituted terminal olefins like 1,1′ diphenylethylene or cyclic olefins are preferably investigated. The former undergo regioselective hydroformylation to form linear aldehydes and make use of n-directing ligands obsolete, and the latter are symmetric compounds and may yield in only one aldehyde structure. To prevent hydrogenation of the starting olefin, and/or intermediate Schiff base high carbon monoxide partial pressures are chosen in order to support the rate determining carbon monoxide insertion.

It is well known that tryptophan methylester undergoes Pictet-Spengler reaction with aldehydes in aprotic conditions, the conversion of later and cyclopentene as electrophile precursor under hydroformylation conditions was chosen as a model reaction. Cyclopentene is a cheap and readily available olefin, hydroformylation of cyclopentene is well known and described, conditions usually include temperatures of 40-80 °C and pressures of 40-80 bar of syngas for 1-3 days depending on tandem sequence involved, in the presence of 0.5-1 mol% of rhodium catalyst.

When cyclopentene was mixed with (S)-tryptophan methylester in toluene, which is most commonly used as solvent in conventional PS reactions and is also very convenient solvent for hydroformylation reactions, and submitted to the hydroformylation in the presence of 1 mol % of Rh(acac)(CO)₂ at 80 °C and at 30/10 bar of CO/H₂ pressure two different products were isolated (Table 10, Entry 1). Surprisingly no Pictet-Spengler product was observed, only byproducts 105 and 106 were isolated, which arouse from mono and double hydroaminomethylation reactions respectively. Obviously, reduction of intermediate Schiff base 109 is faster than electrophilic attack of imine to aromatic ring of indole, (Scheme 47, pathways b and d). Same products were isolated in reaction with cyclohexene (Table 10, Entry 2) although this olefin requires higher temperature for reaction to proceed as compared to cyclopentene. Apparently, in toluene only reduction products were obtained. On the contrary, when reaction was performed in more polar solvents such as CH₂Cl₂, THF or MeOH, we were able to isolate the Pictet-Spengler products 103, cis and 104, trans in all cases. When mixture of cyclopentene and (S)-tryptophan methylester 102 was hydroformylated in CH₂Cl₂, 103 and 104 were isolated in relative ratios of approximately 1/1 and overall yield of 73 % accompanied with four additional byproducts 105, 106, 107 and 108 (Table 10, entry 6), even in this case reduction of intermediate Schiff bases represents significant problem, formation of two new byproducts 107, and 108 is observed in addition to 105 and 106 which were observed before.
Table 10. Tandem hydroformylation / Pictet-Spengler reaction under aprotic conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>Cond</th>
<th>Solvent</th>
<th>Olefin 99 (n)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>Ratio&lt;sup&gt;2&lt;/sup&gt; 103/104</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>Toluene</td>
<td>1</td>
<td>65</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>Toluene</td>
<td>2</td>
<td>60</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>THF</td>
<td>1</td>
<td>45</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>THF</td>
<td>1</td>
<td>47/53</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>MeOH</td>
<td>1</td>
<td>50/50</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>CH₂Cl₂</td>
<td>1</td>
<td>48/52</td>
<td>3</td>
<td>7</td>
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<tr>
<td>7</td>
<td>B</td>
<td>CH₂Cl₂</td>
<td>1</td>
<td>79</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>CH₂Cl₂</td>
<td>1</td>
<td>51/49</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>D</td>
<td>CH₂Cl₂</td>
<td>2</td>
<td>45/55</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>B</td>
<td>CH₂Cl₂</td>
<td>3</td>
<td>44/56</td>
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<td>0</td>
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<td>CH₂Cl₂</td>
<td>4</td>
<td>43</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions A: 1 mol% of Rh(acac)(CO)₂, 30 bar CO, 10 bar H₂, 80 °C, 3d; Method B: 1 mol% of Rh(acac)(CO)₂, 50 bar CO, 10 bar H₂, 80 °C, 3d; Method C: 1 mol% of Rh(acac)(CO)₂, 70 bar CO, 10 bar H₂, 80 °C, 3d; D: 1 mol% of [Rh(COD)Cl]₂, 50 bar CO, 10 bar H₂, 120 °C, 3d.<br><sup>b</sup> Yield of isolated product after column chromatography; <sup>2</sup> ratio based on isolated products after column chromatography.

Formation of 106 and 107 can be explained as depicted (Scheme 47, pathways c and d), monoalkylated tryptophan methylester 105 reacts with another molecule of aldehyde giving Schiff base 110 which undergoes hydrogenation yielding in 106 or cyclization giving 107. While it is clear for 106 that it arises from 105, 107 can be formed in the hydroaminomethylation sequence starting from 104 as well. To test which of this pathways is actually occurring control experiments were set. Pure 103, 104 and 105 were
independently submitted to the hydroformylation conditions in the presence of cyclopentene and only 105 yielded in 47% of 107 accompanied with dihydroaminomethylation product 106 in 22% yield. Compounds 103 and 104 gave no product of hydroaminomethylation presumably due to high steric hindrance of piperidine ring nitrogen (Nb). Based on these observation direct formation of 107 from 103 or 104 can be ruled out.

Scheme 47. Tandem hydroformylation / Pictet-Spengler reaction and formation of side products

It is noteworthy to mention that 107 is isolated exclusively as trans isomer. The formation of the trans isomer in this case is kinetically and thermodynamically favored, and can be explained by a Felkin-Ahn–like attack of the E-iminium from the face opposite to the ester group (Figure 10). Cook et al. have shown that if Nb nitrogen of tryptophan esters is monoprotected with sterically demanding Bn or Cbz groups and as such submitted to conventional PS reaction trans adducts will be formed exclusively. Apparently methylcyclopentyl group of 105 creates enough steric congestion so that iminium attack is following Felkin-Ahn rule and hence yields exclusively in trans isomer of 107 when reacted with second molecule of aldehyde.
Byproduct 108 was only observed when CH_2Cl_2 was used as solvent and CH_2 fragment which inserts between iminium carbon and indole position 1 originates most probably from the solvent. Same reactants in THF under the same conditions gave rise only to Pictet-Spengler products in 45 % yield (Table 10, entry 3). Lower yield compared to the CH_2Cl_2 is due to the incomplete conversion of 80% in this case. Prolonged reaction time of 4 days allowed full conversion of olefin and increased yield of 103 and 104 to some extent but also yielded in reduction product 105 (Table 10, Entry 4).

It is known that aldehydes can undergo nucleophilic attack by the alcohols to yield acetals. Since acetals are used as protected aldehydes in PS reaction, the use of alcohols as solvents in the hydroformylation step is an option and would support the principle of low stationary aldehyde concentrations. To our surprise when we attempted this reaction in MeOH only 15 % overall yield of Pictet-Spengler adducts were isolated accompanied with 105 as a main product in 48 % yield, (Table 10, Entry 5). Up to now it was obvious that polarity of solvent plays a crucial role in distribution of products in this reaction, while in unpolar solvent, such as toluene, reduction of intermediate Schiff base is favoured, in more polar solvents that stabilize cationic intermediate and promote electrophilic attack, rate of cyclization is by far higher than that of reduction.

Best yields of 103 and 104 were obtained in CH_2Cl_2, thus this solvent was chosen for further optimization of reaction conditions. In order to lower the extent of reduction, carbon monoxide pressure and CO/H_2 ratio was increased to 50/10 and 70/10 bar (Table 10, Entries 7 and 8 respectively) while 50/10 ratio gave 79 % yield of 103 and 104 and lower yields of

---

byproducts, ratio of 70/10 gave lower yields of Pictet-Spengler adducts, therefore operating pressure of 50 bar CO and 10 bar H₂ was chosen. Few different substrates were reacted under these conditions and results are summarized in (Table 10, Entries 9-11). In the reaction of cycloheptene under the same conditions (Table 10, Entry 10) 103 and 104 are obtained in lower yields than in case of 1 or 2 carbons smaller carbocycles. Surprisingly when cyclooctene was reacted no Pictet-Spengler products were observed, main product was that of mono hydroaminomethylation reaction 105 obtained in 43 % yield (Table 10, Entry 11). Trend from cyclopentene to cyclooctene can be observed: yield of Pictet-Spengler products lowers until finally reaches zero. This is most probably connected with steric hindrance of formed aldehydes i.e. higher sterical hindrance lowers the rate of cyclization and hence reduction becomes more competitive reaction exclusively yielding in hydroaminomethylation product. This trend can be observed as well when trans stilbene 111 and 1,1’ diphenylethylene 112 are reacted with 102 (Scheme 48). Former having one Ph group in α position and one in β position gives lower yield of PS product 113 accompanied with mono hydroaminomethylated by-product 114, while later having two Ph groups in β position of aldehyde due to lower steric compression gives Pictet-Spengler product 115 in higher yield as a mixture of inseparable diastereoisomers accompanied by-product 116 as well, however in lower yield as compared to trans stilbene.

**Scheme 48.** Tandem hydroformylation / Pictet-Spengler reaction of noncyclic olefins

![Scheme 48](image-url)
3.2 Tandem Hydroformylation / Pictet-Spengler Reaction under Protic Conditions

These optimized conditions were applied in the Pictet-Spengler reaction of tryptamine. PS reactions of tryptamine often require harsher conditions than their tryptophan counterparts, this is due to the absence of the inductively electron-withdrawing carbonyl group in tryptophan and thus lower pKa values of tryptamine based Schiff bases. Tryptamine imines are significantly less reactive towards electrophilic attack, and hence the presence of Brønsted acid is required in order for reaction to proceed. Brønsted acids such as sulphuric acid (1equiv), trifluoroacetic acid (TFA) (1equiv), p-toluenesulphonic acid (pTsOH) (1equiv), and camphorsulphonic acid (CSA) (1equiv) (Table 11, Entries 1-4) were tested in reaction of tryptamine 98 and cyclopentene under optimized conditions, Lewis acids ZnCl₂ and BF₃ (Table 11, Entries 5 and 6) were tested as well. All reactions were carried out at the identical conditions for 72 hours and yields of product 101a were determined by isolation. Best results are obtained with CSA, while p-TsOH gave lower yields of desired product while sulphuric and trifluoroacetic acid gave mainly mixtures of byproducts. Lewis acids gave no product at all (Table 11).

Table 11. Testing different acids in tandem hydroformylation / Pictet-Spengler reaction of tryptamine

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂SO₄</td>
<td>80</td>
<td>72</td>
<td>/</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>80</td>
<td>72</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>pTsOH</td>
<td>80</td>
<td>72</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>CSA</td>
<td>80</td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>ZnCl₂</td>
<td>100</td>
<td>72</td>
<td>/</td>
</tr>
<tr>
<td>6</td>
<td>BF₃</td>
<td>100</td>
<td>72</td>
<td>/</td>
</tr>
</tbody>
</table>

a Yield of isolated product after column chromatography.
Conditions optimized for tryptophan methylester, with addition of 1 equiv of CSA were applied in the reaction of tryptamine with selected olefins (Table 12). Although in these reactions formation of byproducts of similar structure as in aprotic version was observed, their isolation proved to be very difficult. It was possible to separate main product from byproducts in each case but not to separate byproducts from each other. Only in the case of protected methallylic amines (Table 12, Entries 7, 8) product of elimination of N residue was isolated (Scheme 49). Surprisingly and in the contrary to the aprotic conditions Pictet-Spengler product from cyclooctene was isolated in fair yield (Table 12, Entry 4).

**Table 12.** Tandem hydroformylation / Pictet-Spengler reaction of tryptamine and selected olefins under protic conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Alkene Conversion (%)</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>80</td>
<td>72</td>
<td>&gt;99</td>
<td>65 (101a)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>110</td>
<td>80</td>
<td>&gt;95</td>
<td>46 (101b)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>80</td>
<td>68</td>
<td>&gt;99</td>
<td>68 (101c)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>80</td>
<td>72</td>
<td>&gt;99</td>
<td>59 (101d)</td>
</tr>
<tr>
<td>5</td>
<td>Ph Ph</td>
<td>110</td>
<td>72</td>
<td>&gt;95</td>
<td>64 (101e)</td>
</tr>
<tr>
<td>6</td>
<td>Ph Ph</td>
<td>110</td>
<td>72</td>
<td>&gt;99</td>
<td>49 (101f)</td>
</tr>
<tr>
<td>7</td>
<td>N(Et)Ts</td>
<td>110</td>
<td>72</td>
<td>&gt;99</td>
<td>74 (101g)</td>
</tr>
<tr>
<td>8</td>
<td>NPht</td>
<td>110</td>
<td>72</td>
<td>&gt;99</td>
<td>82 (101h)</td>
</tr>
<tr>
<td>9</td>
<td>OBn</td>
<td>110</td>
<td>72</td>
<td>&gt;99</td>
<td>51 (101i)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were conducted at room temperature on a 1 mmol scale in THF(10ml) with a relative mol ratio of tryptamine/olefin/catalyst of 100/100/1; 1 mol% of Rh(acac)(CO)<sub>2</sub>, 1 equiv CSA, 50 bar CO, 10 bar H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>;<sup>b</sup> Determined by analysis of <sup>1</sup>H spectra of crude reaction mixture;<sup>c</sup> Yield of isolated product after column chromatography
All other substrates gave moderate to good yields in presence of 1 equiv of camphorsulphonic acid. 1,1 disubstituted substrates as well as hindered internal olefins such as stilbene (Table 12, Entry 5) are requiring harsher conditions for hydroformylation, therefore temperature of 110 °C for 3 days was applied. Temperature of 80° C in the hydroformylation of 1,1 diphenylethylene gave only 20 % conversion of olefin and product in the 8 % yield. Same substrate at 110 °C after 3 days was almost quantitatively consumed and yielded product in quite fair yield of 64 % (Table 12, Entry 5). Cyclohexene and methallylic amines require harsher conditions as well, temperatures of 110°C were applied in order to achieve full conversion of olefin (Table 12, Entries 2 and 7-9). Yields of products varied from moderate 46% for cyclohexane to very good 74% and 82 % for methallylic amines respectively (Table 12, Entries 7 and 8). Methallylic alcohol (Table 12, Entry 9) required harsher conditions for hydroformylation as well, product was isolated in moderate 51% yield.

**Scheme 49.** Byproduct isolated after tandem hydroformylation / Pictet-Spengler reaction with tertiary methallylic amines

![Diagram](image_url)

3.3 Witkop-Winterfeldt Oxidation of Tetrahydro-β-carbolines

In the early 1950s Witkop described in a series of papers that oxidation of indoles with a variety of oxidation reagents leads to the formation of quinolones. The mechanism of this reaction involves the oxidative cleavage of the 2,3-double bond of the indole moiety (Witkop oxidation) followed by a Camps cyclization forming the quinolone ring. Winterfeldt identified conditions which allowed a one pot Witkop oxidation / Camps cyclization sequence and applied this strategy for the synthesis of pyrrolo[2,3-c]quinolones starting from
1,2,3,4-tetrahydro-β-carbolines.\(^87\) In general γ-quinolones are representing a class of biologically active molecules.\(^88\)

We used synthesized THBCs as substrates for Witkop-Winterfeldt oxidation. Prior to oxidation, Nb nitrogen atoms of tetrahydro-β-carbolines 101a and 101e were protected with benzyl group to give 118 and 120 and then were submitted to standard Witkop-Winterfeldt conditions to yield γ-quinolones 119 and 121 in fair yields (Scheme 50).

**Scheme 50.** Witkop-Winterfeldt oxidation of THBCs

![Scheme 50](image)

Benzyl protected 118 was as well submitted to ozonolysis reaction, this should result in the oxidative cleavage of 2,3 double bond of indole core without subsequent Camps cyclization and yield in macrocyclic structure 122. However, depending on the method of reduction of intermediate ozonide, γ-quinolone 119 may also be expected (Scheme 51). Nevertheless, ozonolysis gave no desired products. Mixture of inseparable compounds was observed. Further optimizations of reaction conditions should be done in order to obtain macrocyclic structure 122 as main product.

**Scheme 51.** Ozonolysis of 118

---


When phenethyl amine 123 was used as nucleophile in tandem hydroformylation / Pictet-Spengler reaction under the optimized conditions gave only hydroaminomethylation products 124 and 125 in reactions with cyclopentene and 1,1 diphenylethylene (Scheme 52). This is most probably due to the lower nucleophilicity of phenyl ring compared to indole nucleus causing that reduction of intermediate iminium ion is faster in this case than cyclization to form tetrahydroisoquinoline structures.

**Scheme 52.** Attempted tandem hydroformylation / Pictet-Spengler reaction with phenethylamine

In conclusion we have demonstrated that this reaction sequence can be applied in the synthesis of various THBCs involving both aprotic and protic conditions, problem with formation of reduction byproducts still remains. However, yields of tetrahydro-β-carbolines are synthetically useful in most of the cases. Tandem hydroformylation / Pictet-Spengler reaction allowed syntheses of tetrahydro-β-carbolines starting exclusively from cyclic- and 1,1-disubstituted terminal olefins but proved inapplicable when more sensitive substrates were applied, this hampered preparations of more complex carboline structures. Due to this drawbacks alternative method for the synthesis of tetrahydro-β-carbolines involving tandem hydroformylation / Fischer indole synthesis was thoroughly investigated. This convenient method for the synthesis of the indole core containing molecules should allow introduction
of various substituents that are unavailable via tandem hydroformylation / Pictet-Spengler reaction and allow placing of substituents in positions unavailable via classical approaches.
4 Tetrahydro-β-carbolines via Tandem Hydroformylation / Fischer Indole Synthesis

Despite the wide scope of the Pictet-Spengler condensation and its continuous development, it turns out to be less applicable when 3- or 4-substituted THBC systems are targeted. In these cases syntheses of appropriate α or β substituted tryptamine precursors are required, which can be very laborious and time-demanding process especially when enantiomerically pure molecules are desired.

Lately, for the synthesis of enantiopure 4-substituted THBCs attention has been focused on the asymmetric functionalization of the indole core, involving Pd-catalyzed intramolecular allylic alkylations of 2-indolyl carbonates or acetates, or intramolecular Lewis acid catalyzed Friedel-Crafts type functionalisations of indoles. While these examples take advantage of the relatively nucleophilic 3-position of the indole nucleus to add electrophiles via both Lewis acid and transition metal catalyzed intramolecular alkylations, there are comparatively few methods for the synthesis of enantiopure 3-functionalized THBCs. Most of the known 3-substituted THBCs are tryptophan derivatives and are synthesized via Pictet-Spengler reaction starting from this essential amino acid. Therefore, not surprisingly, only a few examples of 3-substituted tetrahydro-β-carbolines are reported with substituents not possessing the oxidation level of carboxylic group or with substituents not obtainable via number of simple functional group transformations of carboxylic group of tryptophan. Lack of the versatile methods for the synthesis of THBCs having particular kind of substituents in positions which are not easily accessible by PS reaction has prompted us to test possibility of synthesizing these molecules via tandem hydroformylation / Fischer indole synthesis sequence. Recently use of carbo- or heterocyclic olefins in tandem hydroformylation / Fischer indole synthesis sequence yielding carbazoles, β-sila carbazoles and β-carboline has been reported. If performing this reaction with substituted N-containing heterocyclic olefins formations of substituted carbolines should be expected (Scheme 53).


We envisaged use of this strategy for the synthesis of enantiopure substituted carboline derivatives starting from enantiopure 2-substituted 2,5 dihydropyrroles 128 (Scheme 54). These substrates are possessing two available positions for the hydroformylation, and can yield in two regioisomeric aldehydes, which condense with aromatic hydrazine giving hydrazones 129 and 130. In the presence of acid each of the two hydrazones formed undergoes [3, 3] sigmatropic rearrangement to give two pairs of diastereoisomeric cationic spiroindoleninium intermediates 131 and 132. Two rearrangement pathways of these species are possible and four different carbolines can be expected depending on the preference of rearrangement. However, we assumed that only retro Mannich type products 133 and 135 (highlighted, Scheme 54) will be formed exclusively due to the higher stability of carbocation in α position to nitrogen and hence its higher preference towards migration.37 Spiroindoleninium intermediates 131 and 132 are believed to be involved as intermediates in Pictet-Spengler reaction as well, they are formed after endo attack of position 3 of indole to iminium ion. It is noteworthy to mention that preference of migration in Pictet-Spengler reaction is directed towards β and not γ carbolines such as 134 and 136. This was in accordance with our expectations for the rearrangement of 131 and 132 in our envisaged sequence. Retention of chiral information during rearrangement was expected as well (Scheme 54).
**Scheme 54.** Tandem hydroformylation / Fischer indole synthesis sequence in the synthesis of THBCs

4.1 Synthesis of Enantiopure 2-Substituted 2,5 Dihydropyrroles

2-substituted 2,5-dihydropyrroles were synthesized via Ir catalyzed allylic amination / ring closing metathesis strategy (Table 13). Since under hydroformylation conditions primary and secondary amines are undergoing hydroaminomethylation reaction use of N-protected starting materials is required. Electron withdrawing protecting groups were required in order to ease ring closing metathesis reaction.
Table 13. Enantioselective synthesis of 2-substituted 2,5-dihydropyrroles

\[
\begin{align*}
\text{R} & \quad \text{CO}_2\text{Me} \\
\text{68} & \\
\text{PG-N}^+ & \quad \text{HN-} \\
\text{128} & \\
\text{L3, DABCO, 50 °C, THF} & \\
\rightarrow & \\
\text{HN-} & \quad \text{R} \\
\text{137} & \\
\text{PG-N}^+ & \quad \text{R} \\
\text{139} & \\
\text{CIPG, Et}_3\text{N, DMAP, THF} & \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R.</th>
<th>Ligad</th>
<th>Time (h)\textsuperscript{b}</th>
<th>137/138\textsuperscript{c}</th>
<th>Yield, 137, (%)\textsuperscript{d}</th>
<th>ee %</th>
<th>PG</th>
<th>Yield, 139 (%)\textsuperscript{a}</th>
<th>Yield, 128 (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>L3</td>
<td>20</td>
<td>95/5</td>
<td>137a (76)</td>
<td>96</td>
<td>Eoc</td>
<td>139a (87)</td>
<td>128a (92)</td>
</tr>
<tr>
<td>2</td>
<td>o-MeO-Ph</td>
<td>L3</td>
<td>24</td>
<td>96/4</td>
<td>137b (48)</td>
<td>nd</td>
<td>Ts</td>
<td>139b (86)</td>
<td>128b (95)</td>
</tr>
<tr>
<td>3</td>
<td>p-MeOPh</td>
<td>L3</td>
<td>18</td>
<td>95/5</td>
<td>137c (74)</td>
<td>95</td>
<td>Ts</td>
<td>139c (81)</td>
<td>128c (89)</td>
</tr>
<tr>
<td>4</td>
<td>p-Cl-Ph</td>
<td>L3</td>
<td>24</td>
<td>93/7</td>
<td>137d (78)</td>
<td>91</td>
<td>Ts</td>
<td>139d (91)</td>
<td>128d (93)</td>
</tr>
<tr>
<td>5</td>
<td>p-CF\textsubscript{3}-Ph</td>
<td>L3</td>
<td>48</td>
<td>92/8</td>
<td>137e (75)</td>
<td>nd</td>
<td>Ts</td>
<td>139e (92)</td>
<td>128e (90)</td>
</tr>
<tr>
<td>6</td>
<td>Et\textsuperscript{e}</td>
<td>L3</td>
<td>24</td>
<td>94/6</td>
<td>137f (75)</td>
<td>98</td>
<td>Ts</td>
<td>139f (88)</td>
<td>128f (91)</td>
</tr>
<tr>
<td>7</td>
<td>&quot;Pr\textsuperscript{e}</td>
<td>L3</td>
<td>24</td>
<td>95/5</td>
<td>137g (75)</td>
<td>97</td>
<td>Ts</td>
<td>139g (68)</td>
<td>128g (85)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Tosilated in situ due to high volatility; \textsuperscript{b}Reaction time; \textsuperscript{c}Branched to linear ratio determined by \textsuperscript{1}H NMR spectroscopy; \textsuperscript{d}Yield of isolated product; \textsuperscript{e}Not isolated, protected in situ.

Ir catalyzed reactions were run using previously optimized procedure for the allylic aminations i.e. the catalyst was prepared by in situ activation of [Ir(cod)Cl\textsubscript{2} and ligand L3 with the base DABCO, in dry THF. Good yields and enantioselectivities were obtained with all tested allylic carbonates bearing sp\textsuperscript{3} as well as sp\textsuperscript{2} substituents, possessing electron withdrawing and electron donating groups (Table 13). Amines bearing an aliphatic group R (Table 13, Entries 6 and 7) had to be protected in situ due to high volatility. Prior to ring closing metathesis reaction all amines were protected with Ts or Eoc groups (Table 13). These reactions proceeded in good yields in all cases. After protection tertiary amines were submitted to metathesis reaction using Grubbs I catalyst, all desired products were isolated in excellent yields after 24 h.
4.2 Synthesis of 3,4 Dehydro 2-Substituted Piperidines

Six membered 2-substituted 3,4 dehydro piperidine 143 was synthesized via allylic amination / ring closing metathesis sequence using homoallylamine in amination step instead of allyl amine. Allylic aminations with homoallylic amine proceeded in good yields and in high enantioselectivities with various allylic carbonates (Table 14).

Table 14. Allylic amination of allylic carbonates with homoallylic amine

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>ligand</th>
<th>Time (h)</th>
<th>140/141, b/l</th>
<th>Yield, 140 (%)</th>
<th>Ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>L3</td>
<td>48</td>
<td>96/4</td>
<td>140a (74)</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>p-MeOPh</td>
<td>L3</td>
<td>48</td>
<td>95/5</td>
<td>140b (78)</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>2-Furyl</td>
<td>L3</td>
<td>4</td>
<td>94/6</td>
<td>140c (70)</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>3-Purydyl</td>
<td>L3</td>
<td>24</td>
<td>97/3</td>
<td>140d (81)</td>
<td>97</td>
</tr>
</tbody>
</table>

*a Reaction time; ** Branched to linear ratio determined by 1H NMR spectroscopy; *Yield of isolated product after column chromatography; *d Determined by HPLC on chiral column; *nd not determined

Amine 140b was protected with Eoc group to give 142 and submitted to ring closing metathesis reaction to give 143 in 95% yield (Scheme 55).

Scheme 55. Synthesis of 3,4 dehydropiperidine 143

These six membered substrates are possible precursors for interesting, new type of carboline molecules possessing 7 membered ring attached to indole core.
With required starting materials in hands, we could start the investigation on the distribution of reaction products in the tandem sequence. First, reaction conditions had to be optimized.

4.3 Optimization of Reaction Conditions Towards Synthesis of THBCs

Stepwise procedure involving tandem hydroformylation / hydrazone formation using 1 mol% Rh(acac)(CO)$_2$ under 50/10 bar CO/H$_2$ pressure in THF at 100 °C for 3 days with subsequent indolization in 4 w % H$_2$SO$_4$ have been applied for the test reaction with substrate 128b. Here, higher partial pressures of CO were chosen in order to prevent possible hydrogenation of intermediate spiroindolinenium species. Unmodified Rh catalyst which was expected to unselectively hydroformylate both available positions of substrate, yielded in only two THBC products 133a and 135a, out of four possible, in good yield of 87% and ratio of 1/1.3 in favour of 135a (Scheme 56). 1-substituted carborne 133a was isolated as racemate while 3-substituted 135a retained enantiopurity of the substrate.

Scheme 56. Tandem hydroformylation/Fischer indole synthesis in the synthesis of functionalized THBCs

Both products originated from the rearrangement of carbons situated between pyrrole N atom and quaternary center of spiroindolenine intermediates 131 and 132 i.e. the products of formal retro Mannich reaction / Pictet-Spengler cyclization were obtained exclusively, no rearrangement of β carbon was observed as was the case with carbocyclic and cyclic silyl olefins yielding in γ-carboline structures (see Scheme 15).

Since rearrangement showed high selectivity towards retro Mannich type products i.e. main product is β not γ carboline, and since decisive factor whether 1- or 3-substituted THBC would be formed is hydroformylation step (Scheme 57), it was necessary to

---

Scheme 57. Dependence of product distribution on hydroformylated position of substrate

regioselectively hydroformylate olefin in order to shift distribution of reaction products towards desired 3-substituted THBCs. This was achieved via modifications of rhodium catalyst with various phosphine and phosphite ligands (Table 15). Reaction with monophosphine ligand PPh$_3$ modified catalyst (Table 15, Entry 1), gave good yield of 85% and ratio of products of 1/2.7 in favour of 135a. Rh catalyst modified with diphosphine ligands such as DPPF and BINAP, (Table 15, Entries 2 and 4) yielded in no aldehyde at all, while DPPB (Table 15, Entry 3) gave 30% conversion of olefin and only 22% yield of products.

Table 15. Testing of ligands in tandem hydroformylation / THBC synthesis

<table>
<thead>
<tr>
<th>entry</th>
<th>Ligand</th>
<th>Olefin conv., %$^a$</th>
<th>yield, %$^b$</th>
<th>Ratio$^c$</th>
<th>ee, %$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>133a + 135a</td>
<td>133a : 135a</td>
<td>133a</td>
</tr>
<tr>
<td>1</td>
<td>PPh$_3$</td>
<td>full</td>
<td>85</td>
<td>1:2.7</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>DPPF</td>
<td>0</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>3</td>
<td>DPPB</td>
<td>30</td>
<td>22</td>
<td>1:1.3</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>BINAP</td>
<td>0</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>5</td>
<td>XANTPHOS</td>
<td>full</td>
<td>37</td>
<td>1:5.2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>P(OPh)$_3$</td>
<td>full</td>
<td>72</td>
<td>1:1.6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>BIPHEPHOS</td>
<td>full</td>
<td>81</td>
<td>1:1.4</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Determined by 1H-NMR of crude reaction mixture $^b$ Isolated yield after column chromatography; $^c$ based on isolated product; $^d$ Determined by HPLC on chiral column.
Bulky diphosphine ligand XANTPHOS (Table 15, Entry 5) commonly used for \( n \) selective hydroformylations of terminal olefins gave the best ratio of 133a/135a stating 1/5.2 but in poor yield of 37 %. Phosphite ligand P(OPh)\(_3\) (Table 15, Entry 6) provided moderate yield and had low influence on regioselectivity of hydroformylation, bulky diphosphite ligand BIPHEPHOS (Table 15, Entry 7) which is as well used for \( n \) selective hydroformylations of terminal olefins had almost no effect on regioselectivity with ratio of 1/1.4 in favour of 133a and yield of 81 %. In summary PPh\(_3\) appeared to be the best compromise between yield and selectivity of hydroformylation step and hence this ligand was chosen for further reactions. In all cases 1-substituted THBC 133a was isolated as racemate while 3-substituted 135a retained enantio purity of starting material. Possible explanations for this behaviour are offered in the next chapter.

Piperidine 143 was as well submitted to these standard conditions for tandem hydroformylation / Fischer indol synthesis, however mixture of inseparable products was obtained. Complex mixture of products can actually be expected based on mechanistic considerations of rearrangement pathways of intermediate spiroindoleninium cations 144 and 145 (Scheme 58). It is clear that 144 will have preference towards exclusive formation of 146, while 145 may give 147 and 148 with approximately same probability since there is no driving force for selective rearrangement of this spiroindoleninium specie towards one of the possible products.

Scheme 58. Possible products in tandem hydroformylation / Fischer indolization of piperidine 133

As already mentioned when 6, 7 or 8 membered cyclic olefins are used, intermediate spiroindolenine structures can as well be trapped by hydrogenation under hydroformylation conditions.\(^{37}\) This further complicates possible outcome of the reaction with
dehydropiperidines of type 143, although degree of reduction can be controlled to some extent by control of partial pressures of CO and H₂.

Due to the all mentioned drawbacks of envisaged protocol when using six membered cyclic olefins further optimizations of reaction conditions would be necessary in order to obtain desired products exclusively. Since it proved difficult to isolate products of rearrangement in these cases further investigation was focused to five membered systems exclusively.

### 4.4 Mechanistic Insight

Few ambiguities exist about the mechanism by which spiroindoleninium cation undergoes transformation to carboline molecule, nevertheless, few possible explanations are offered that seem to be viable. Possible rearrangement pathways of enantiopure spiroindoleninium cation 149 are shown on scheme 59. The first proposed mechanistic pathway involves Wagner-Meerwein's like 1,2 shift which proceeds in a suprafacial fashion⁹² leading to the preservation of stereochemical information in the final molecule giving 151. The second mechanistic pathway proposed by Danishevsky⁹¹c involves retro Mannich reaction of 149 to give 150 followed by subsequent Pictet-Spengler cyclization of 150 proceeding via attack of position 2 of indole core to iminium ion. This pathway therefore results in racemization due to the free rotation in the ring opened intermediate 150, allowing statistical distribution of final product and hence yielding in 151rac (Scheme 59).

---

**Scheme 59.** Possible reaction pathways of indoleninium intermediate

---

Some reports, however, are suggesting that attack on the iminium ion of 150 would presumably occur from position 3 of indole core (Scheme 60). This makes Danyshefsky pathway obsolete, and as well causes racemization of 149 due to the equilibrium between 149 and 150 that is established in that case. Racemization of 149 then subsequently leads to the racemization of 151.

Scheme 60. Attack from position 3 of indole core on iminium ion and intramolecular trapping of formed spiroindoleninium cation in the total synthesis of aspidophytine.

As 1-substituted THBC is isolated as racemate which complies with involvement of retro Mannich pathway, it can be assumed based on the discussion presented above that this pathway takes part in the rearrangement sequence and not Wagner-Meerwein’s 1,2 shift. However, that would most probably be premature conclusion since there is another factor that has to be taken into consideration, and that is acid catalyzed racemization of 1-substituted THBCs. Racemization of 1-substituted THBCs under acidic conditions is well documented and presumably occurs via C1-Nb bond scission (Scheme 61). This means that even if Wagner-Meerwein’s 1,2 shift is occurring, final carboline would be isolated as racemate since acidic conditions were used in the course of rearrangement. Therefore at this

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point we can not say with certainty that retro Mannich pathway is responsible for racemization.

Scheme 61. Mechanism of the acid induced racemization of chiral 1-substituted THBCs

To sort out the possibility of acid catalyzed racemization, stepwise procedure involving thermally induced indolization was attempted but unfortunately gave no product (Table 16, Entry 2). Lewis acid catalyzed indolization gave desired products in significantly lower yields but again 1-substituted THBC was isolated as racemate (Table 16, Entry 3).

Table 16. Testing of different indolization conditions in tandem hydroformylation / THBC synthesis

<table>
<thead>
<tr>
<th>entry</th>
<th>Ligand</th>
<th>Olefin conv., %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Indoliz. Method&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield, %&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Ratio&lt;sup&gt;d&lt;/sup&gt;</th>
<th>ee, %&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>/</td>
<td>full</td>
<td>A</td>
<td>87</td>
<td>1:1.3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>/</td>
<td>full</td>
<td>B</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>3</td>
<td>/</td>
<td>full</td>
<td>C</td>
<td>35</td>
<td>1:1.3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>/</td>
<td>65</td>
<td>D</td>
<td>32</td>
<td>1:1.2</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H-NMR of crude reaction mixture; <sup>b</sup> Method A: 4 w % H<sub>2</sub>SO<sub>4</sub>, THF, 60 °C; method B: ethyleneglycol, 180 °C, 24h; method C: 4eq ZnCl<sub>2</sub>, toluol, 120 °C, method D: tandem reaction with 1eq PTSA; <sup>c</sup> Isolated yield after column chromatography; <sup>d</sup> Based on isolated product; <sup>e</sup> Determined by HPLC on chiral column.
Stability of product towards racemization in acidic conditions can be tested independently if enantiopure 1-substituted THBC is submitted to conditions used for indolization, but unfortunately we were not able to separate enantiomers of 1-substituted THBCs on preparative scale. It is noteworthy to mention that when reaction was performed in the presence of 1 eq PTSA added in reaction mixture i.e. one step procedure is performed, comparable results to stepwise procedure were obtained in terms of ee’s of isolated products although yield was drastically lowered (Table 16, Entry 4). In order to finally make discrimination between retro Mannich pathway and 1,2-shift, crossover experiment with internal, symmetric allylic amines 152 and 153 was performed (Scheme 62). It is known that acyclic internal olefins are undergoing to the same type of rearrangement as cyclic ones. These substrates should clearly have the same preference towards formation of Mannich type products, however, they have additional possibility of forming crossover products.

These substrates were submitted to the same reaction conditions as cyclic aminoolefin 128b. A crossover experiment indicated that the rearrangement occurs intramolecularly, no crossover products were observed in the crude reaction mixture, meaning that retro Mannich pathway is not favored. Although due to general difficulties in analysis of the crude mixtures after hydroformylation / indolization procedures, these experiments should be performed with more different substrates in order to establish conclusions with more certainty. Nevertheless, now it can be speculated with a little more certainty that the reaction occurs via 1, 2 shift and that most probably racemization is post rearrangement event i.e. acid present in the mixture as indolization promotor causes racemization of the 1-substituted

Scheme 62. Crossover experiment with internal allylic amines
tetrahydro-β-carboline. 3-substituted carboline is obtained from the intermediate whose stereocenter is not influenced by any of the possible reaction pathways therefore it stays intact.

4.5 Synthesis of Various Substituted THBCs

Next, attention was turned to the scope of the reaction (Table 17). Several pyrroles containing various alkyl or aromatic substituents were tested in optimized conditions in the presence of unsubstituted phenyl hydrazine (Table 17, Entries 1-8). In all cases 3-substituted THBC was the main product. Pyrroles containing both electron donating and electron withdrawing aromatic substituents were tested. The regioselectivities of products ranged from 1/1.4 to 1/5.5 in favor of 135. Tosyl protected pyrrole 128a gave better yields of products under applied conditions than its Eoc protected counterpart 128b (Table 17, Entries 1 and 2), hence Ts protected substrates were used in further reactions. Electron donating substituents on the substrate are shifting regioselectivity towards 3-substituted product giving 1/5.2 - 5.5 ratios in favor of 135 (Table 17, Entries 3 and 4) while electron withdrawing one gave 1/1.4 ratio in favor of 135 (Table 17, Entry 6).

**Table 17. Synthesis of THBCs from substrates 109**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>PG</th>
<th>R₁</th>
<th>yield, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee, %&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (128a)</td>
<td>Ts</td>
<td>H</td>
<td>85</td>
<td>1.2.7</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Ph (128b)</td>
<td>Eoc</td>
<td>H</td>
<td>63</td>
<td>1.2.1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>o-MeO-Ph (128c)</td>
<td>Ts</td>
<td>H</td>
<td>71</td>
<td>1.5.2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>p-MeO-Ph (128d)</td>
<td>Ts</td>
<td>H</td>
<td>76</td>
<td>1.5.5</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>p-Cl-Ph (128e)</td>
<td>Ts</td>
<td>H</td>
<td>74</td>
<td>1.2.4</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>p-CF₃-Ph (128f)</td>
<td>Ts</td>
<td>H</td>
<td>58</td>
<td>1.4</td>
<td>nd&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Et (128g)</td>
<td>Ts</td>
<td>H</td>
<td>65</td>
<td>1.3.3</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Pr (128h)</td>
<td>Ts</td>
<td>H</td>
<td>69</td>
<td>1.3.6</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after column chromatography; <sup>b</sup> Determined by isolation; <sup>c</sup> Determined by HPLC on chiral column; <sup>d</sup> Ratio not determined;
Substrates 128g and 128h having alkyl substituents Et and Pr gave 65 and 69 % yield of products respectively and ratios of 133/135 of 1: 3.3 and 1:3.6 (Table 17, Entries 7 and 8). 3-substituted product retained enantiopurity of starting material in all cases while 1-substituted product was obtained as racemate, in all cases as well.

Recently, Buchwald et al. have demonstrated that benzhydrylidene protected aryl hydrazines 154 undergo high yielding Fischer indolization in the presence of carbonyl compounds under acidic conditions. Benzhydrylidene protected aryl hydrazines can be prepared either via protection of phenylhydrazines with benzophenone group or via Pd mediated amination of aryl halides (Scheme 63).

Feasibility of these substrates was tested in our tandem sequence. Various ly substituted phenylhydrazones 154 can be used which consequently allows introduction of various substitutents in the indole part of the molecule (Table 18).

### Table 18. Synthesis of tetrahydro-β-carbolines from benzophenone protected phenyl hydrazones

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>PG</th>
<th>R1</th>
<th>Olefin yield, %a</th>
<th>Ratiob</th>
<th>ee, %c</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Ph</td>
<td>Ts</td>
<td>α-Me</td>
<td>45</td>
<td>ndf</td>
<td>/</td>
</tr>
<tr>
<td>10</td>
<td>Ph</td>
<td>Ts</td>
<td>p-Cl</td>
<td>41</td>
<td>1.4:4</td>
<td>0 (133j)</td>
</tr>
<tr>
<td>11</td>
<td>Ph</td>
<td>Ts</td>
<td>p-MeO</td>
<td>46</td>
<td>ndf</td>
<td>/</td>
</tr>
</tbody>
</table>

a Isolated yield after column chromatography; b Determined by isolation; c Determined by HPLC on chiral column; dRatio not determined, only product 135 was isolated;

Since the benzhydrylidene group is stable under hydroformylation conditions, here the reaction has to be conducted in the presence of Brønsted acid added to reaction mixture. Acid present cleaves protecting group during the course of reaction thus releasing free hydrazine for condensation with aldehyde. Hence, reactions were run with 1eq of PTSA added in reaction mixture. Tandem reaction with benzhydrylidene protected hydrazines gave lower yields under the same reaction conditions than its stepwise counterpart with unprotected hydrazines. Same migration tendency was observed as with unprotected hydrazines. Presence of substituents in the indole part of the molecule is important from the biological point of view, for instance 5-MeO substituent is present in many bioactive THBCs while presence of 5-Cl substituent allows further derivatizations of indole core via coupling reactions.

In 2004, Cho et al. have applied $\alpha$-Boc aryl hydrazines 155 in Fischer indolization and obtained indoles with very high purity.95 $\alpha$-Boc aryl hydrazines, were synthesized using Buchwald’s optimized conditions of the copper(I) catalyzed $N$-arylation of amides (Goldberg reaction, Scheme 64).96

**Scheme 64.** Synthesis of t-Boc protected phenyl hydrazines via Goldberg Reaction

\[
\begin{array}{c}
\text{Substrate 156} \\
\text{obtained via Goldberg reaction} \\
\text{was tested in the tandem hydroformylation /} \\
\text{Fischer indole synthesis in the reaction with 128b} \\
\text{(Scheme 65). Here, the reaction was} \\
\text{conducted in a stepwise manner with subsequent addition of acid. Boc group is stable under} \\
\text{hydroformylation conditions, and primary amine functionality is free for condensation with} \\
\text{phenyl hydrazines, therefore $\alpha$-Boc protected aryl hydrazones can be obtained in quantitative} \\
\text{yields. After acidic indolization product 157 was obtained in moderate yield of 38\%.} \\
\text{Apparently, benzhydrylidene or $\alpha$-Boc protected hydrazines are giving lower yields in this} \\
\text{reaction sequence. However presence of heterocyclic moieties in the position 5 of the indole} \\
\text{core is very important and was found to be crucial for biological activities in various kinds of} \\
\text{biological assays.}^1
\end{array}
\]

Scheme 65. Application of α-Boc protected aryl hydrazines in tandem sequence

Highly convergent approach for the synthesis of 157 is illustrated in scheme 66. Presynthesized functionalized building blocks are assembled in last step, making this method highly desirable for the combinatorial library syntheses.

Scheme 66. Retrosynthetic pathway for the synthesis of 157
4.6 Synthesis of 1,3 Disubstituted Tetrahydro-β-Carboline 165

In order to synthesize 1,3-disubstituted tetrahydro-β-carbolines 159 it was necessary to synthesize 2,5-disubstituted pyrroles 158 (Scheme 67).

Scheme 67. Envisaged retrosynthetic pathway for the synthesis of 1,3-disubstituted tetrahydro-β-carbolines

This was achieved by modified procedure of Helmchen et al.\textsuperscript{69c} Ir catalyzed allylic amination of cinnamyl carbonate 68a with phtalimide in the presence of ligand L3 gave allylimide 160 in 66% yield and 98% ee as R enantiomer (Scheme 68). After deprotection of 160, primary amine 161 was obtained in 90% yield. This amine was further mono protected with Ts group to give 162. Alternative method for the synthesis of 162 would involve direct amination with TsNH\textsubscript{2}, however due to the low acidity of protons attached to the sulphonamido group of TsNH\textsubscript{2} this substrate was not successfully used in amination reactions so far. If appropriate conditions for aminations with TsNH\textsubscript{2} can be found, synthesis of 162 can then be achieved in one step. Aminations with \textit{p}-nosylamide are however, known and they proceed in high yields and enantioselectivities.\textsuperscript{69i} Unfortunately nitro group of \textit{p}-NsNH\textsubscript{2} is not compatible with hydroformylation conditions since anilines are obtained due to the reduction reaction under harsh hydroformylation conditions.\textsuperscript{97}

\textsuperscript{97} Rische, T.; \textit{Dissertation} 1999, University of Dortmund.
Scheme 68. Synthesis of 2,5 disubstituted dihydropyrroles via Ir catalyzed allylic amination / ring closing metathesis sequence

Allylic amine 162 was used as nucleophile for next Ir catalyzed amination reaction with cinnamyl carbonate 68a in the presence of ligand L3 to yield 163 as a 90/10 trans/cis mixture of diastereomers (Scheme 69). After separation of diastereomers and ring closing metathesis pyrrole 164 was isolated in 89 % yield as single diastereoisomer possessing R, R configuration at stereo centers (Scheme 68). It is noteworthy to mention that 162 was converted into Li anion to promote reaction since salt free conditions using DABCO activation of catalyst gave no product. Unprotected pyrrole that is obtained by Helmchen procedure (Scheme 29) could not be used under hydroformylation conditions since it can undergo intermolecular hydroaminomethylation reaction and since protection of such pyrrole is prevented by steric hindrance of bulky Ph groups. Pyrrole 164 was submitted to standard reaction conditions in a stepwise manner in the presence of phenylhydrazine to give 165 in 71 % yield and in excellent ee of 98%. Symmetric pyrrole 164 circumvents problems with regioselectivity of hydroformylation, so that single carboline product is obtained. This methodology can be used for synthesis of variously substituted substrates of type 164 either with same or different substituents in positions 2 and 5 of pyrrole ring granting access to various interesting THBC structures.

In summary, this convergent, one-pot strategy offers a convenient approach towards functionalized THBCs. Modularity and variability of the reactants are high, highly functionalized building blocks are assembled in a last synthetic step allowing simultaneous
variations and flexible determination of the substitution pattern in final products. Reaction sequence depends on two factors, the regioselective hydroformylation to yield desired aldehyde and the selective migration of one of the two available substituents. For both factors clear tendencies were observed.
5 Summary and Outlook

5.1 Summary

Tandem hydroformylation / Fischer indole synthesis in combination with enantioselective Ir catalyzed allylic substitution reactions proved to be powerful method for the preparation of tryptamines, tryptophanes and their homologues. Starting with appropriate substrates it was possible to introduce side chains of varying complexities and lengths in position 3 of the desired indole structures.

Using amines as nucleophiles in the enantioselective Ir catalyzed allylic amination reaction simple chiral allylic amines were synthesized in high yields and with excellent enantioselectivities. These after hydroformylation / Fischer Indolization sequence granted access to various tryptamines and tryptamides (Scheme 69). 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 69. Access to chiral tryptamines and tryptamides

When benzophenone glycinates were used as substrates in the enantioselective Ir catalyzed allylic substitution reactions with allyl carbonates, allyl glycine derivatives were obtained. These are suitable substrates for the synthesis of homotryptophane framework containing molecules. Using phosphoramidite ligands for the first time with this nucleophile high yields and enantioselectivities of final products were achieved (Scheme 70). Low catalyst and ligand loadings and mild reaction conditions were accompanied with reasonable reaction times, good yields and excellent ee values in all cases. All this makes phosphoramidite ligands the ligands of choice for this reaction.
Scheme 70. Enentioselective synthesis of allyl glycinates

Allylated benzophenone glycinates were synthesized as starting materials for the hydroformylation / Fischer indolization sequence. They allowed access to primary homotryptophane derivatives in good yields. Deprotection of benzophenone group is taking place in parallel with indolization under acidic conditions (Scheme 71).

Scheme 71. Synthesis of primary homotryptophane derivatives

Finally in order to achieve further homologization of the carbon chain at position 3 of indole core, cyanoacetates were used as substrates for Ir catalyzed allylic substitution reaction. Here, nitrile group is used as masked amino functionality. Alkylations of allylic carbonates with cyanoacetates proceeded in good yields (Scheme 72).

Scheme 72. Synthesis of allylated cyanoacetates
Synthesized cyanoacetates were submitted to tandem hydroformylation / Fischer indole synthesis sequence to give indoles in moderate yields. After reduction of nitrile functionality primary amine moiety was obtained to give tryptophane homologues with four carbons in side chain (Scheme 73).

**Scheme 73.** Synthesis of longer chin tryptophane analogues

In summary, tandem hydroformylation / Fischer indole synthesis sequence proved to be very efficient tool for the syntheses of various types of functionalized indoles, from simple tryptamines to complex tryptophane homologues bearing multiple stereocenters.

Scope of tandem processes that can be performed under hydroformylation conditions has been expanded to the tandem hydroformylation / Pictet-Spengler reactions. Importance of this approach lies in the fact that it allows fast and convenient access to pharmacologically important annulated indole systems known as tetrahydro-β-carbolines. Tandem hydroformylation / Pictet-Spengler reaction was performed in the solution for the first time. Reactions run under aprotic conditions using tryptophane methyl ester as a nucleophilic component and carbocyclic olefins as aldehyde precursors allowed access to cis and trans THBCs in good yields and ratios of approximately 1 : 1 in all cases (Scheme 74).

**Scheme 74.** Tandem hydroformylation / Pictet-Spengler reaction under aprotic conditions
This reaction under protic conditions i.e. in the presence of Brønsted acid and tryptamine as a nucleophilic component and various carbocyclic, methallylic amines and methallylic alcohols as precursors of electrophilic component under optimized conditions proceeded in good yields although with detectable formation of byproducts that lowered the yield of reaction and that could not be completely suppressed (Scheme 75).

Scheme 75. Tandem hydroformylation / Pictet-Spengler reaction under protic conditions

Tandem hydroformylation / Pictet-Spengler reaction allowed syntheses of tetrahydro-β-carbolines starting from symmetric cyclic- and 1,1′ disubstituted terminal olefins but proved impotent when more sensitive substrates like terminal olefins bearing stereocenters were applied, this hampered the preparations of more complex carboline structures. Due to this drawback, alternative method for the synthesis of tetrahydro-β-carbolines involving tandem hydroformylation / Fischer indole synthesis has been investigated. This powerful methodology has been applied for the synthesis of tetrahydro-β-carbolines possessing substituents that were not available via tandem hydroformylation / Pictet-Spengler reaction. These substituents were as well quite generally introduced in positions that are unavailable via classical approaches. Use of enantiopure 2-substituted 2,5 dihydropyrroles (previously synthesized via allylic amination / ring closing metathesis approach) in the hydroformylation / Fischer indole synthesis sequence yielded in the tetrahydro-β-carboline structures in good yields and moderate selectivities (Scheme 76).
Here, 3-substituted products retained enantiopurity of substrate while 1-substituted were isolated as racemates in all cases. Distribution of 1- and 3-substituted products depended solely on the regioselectivity of hydroformylation step which was controlled to some extent with phosphine ligand modified Rh catalysts.

Use of benzophenone protected phenylhydrazones allowed introduction of substituents in the positions 5-7 of indole core. Here reactions were run with the Brønsted acid present in the reaction mixture. This allowed deprotection of benzophenone group in situ and its subsequent condensation with aldehyde formed in the hydroformylation step from olefin. Here, 3-substituted THBCs were obtained in excess as in the case when unprotected hydrazines were used, although yields were lower with these hydrazones (Scheme 77).

$p$-MeO group present in position 5 of indole core has important medicinal repercussions, while presence of halogenide in this position allows further derivatizations of these molecules via cross coupling techniques.

**Scheme 76.** Synthesis of tetrahydro-β-carbolines via tandem hydroformylation / Fischer indole synthesis

**Scheme 77.** Use of benzophenone protected hydrazones in the synthesis of tetrahydro-β-carbolines
Use of α-Boc protected hydrazines synthesized via Goldberg reaction proved beneficial for introduction of more sophisticated moieties in the position 5 of the indole core, e.g. heterocyclic triazole unit was introduced with help of these hydrazines (Scheme 78). Use of these hydrazines however resulted in lower yields of final products.

**Scheme 78.** Use of α-Boc protected hydrazines in the synthesis of THBCs via tandem hydroformylation / Fischer indole synthesis sequence

Using 2,5 disubstituted pyrrole as a substrate for tandem hydroformylation / Fischer indolization allowed preparation of 1,3-disubstituted tetrahydro-β-carboline in high enantiopurity (Scheme 79).

**Scheme 79.** Synthesis of 1,3 disubstituted tetrahydro-β-carbolines
In summary, efficient modular synthesis of functionalized enantiopure THBCs starting from enantiopure cyclic aminoolesfins has been achieved. Good yields of final products and moderate to good regioselectivities of hydroformylation were achieved.

5.2 Outlook

Based on the results presented in this thesis various options may be possible for further extension of the scope of tandem hydroformylation / Fischer indole synthesis sequence in the preparation of the tetrahydro-\(\beta\)-carbolines. This protocol may also be used for the synthesis of tetracyclic systems \textbf{168} and \textbf{171} (Scheme 80) via intramolecular trapping of the spiroindolenine intermediates \textbf{167} and \textbf{170} either with carbon or oxygen nucleophiles present in the starting pyroles. This approach has been used by Corey in total synthesis of the Aspidophytine (see Scheme 60). However problem of selectivity of hydroformylation would still be present.

\textbf{Scheme 80.} Possible approach to tetracyclic indoline structures involving trapping of intermediate spiroindoleninium cation
To avoid problems with regioselectivity of hydroformylation and in order to get access to pentacyclic annulated indolines, substrates 172 and 175 can be used, after initial hydroformylation, intramolecular trapping of spiroindolenine carbocations 173 and 176 would give access to rather complex structures 174 and 177 (Scheme 81).

Scheme 81. Tandem hydroformylation / Fischer indolization in the synthesis of pentacyclic indoline systems

Tandem hydroformylation / Fischer indolization approach for the synthesis of THBCs can be transferred to the solid phase making this highly convergent method even more attractive for the combinatorial libraries syntheses. Sulphonated polystyrene resins have already been used in the syntheses of indoles under hydroformylation conditions on solid phase (Scheme 82).70

Scheme 82. Tandem hydroformylation / Fischer indolization on solid phase
Few alternative approaches for the synthesis of the tetrahydro-β-carbolines on solid phase under hydroformylation conditions would be possible. Attaching enantiopure amines to the resin would give 182, after ring closing metathesis on the solid phase and subsequent hydroformylation / indolization sequence 184 would be obtained, which after cleavage can yield in THBCs, alternatively, Winterfeldt oxidation of 184 on solid phase would be an option for access to γ-quinolones (Scheme 83).

Scheme 83. Prospectives in solid phase approaches towards indoles and THBCs

An alternative approach might include allylic amination on solid phase starting from 186 or attaching of already preformed amines to the resin both options giving 187, subsequent hydroformylation / indolization sequence would yield in indoles 188. These can be cleaved or submitted to Pictet-Spengler reaction under hydroformylation conditions to yield in the
1,3 disubstituted THBCs \textbf{184, 187} can be as well submitted to another allylic amination which leads to the synthesis of \textbf{184} by the set of reactions already described above. These highly diversified approaches can give access to the vast number of THBC structures that are not available by other methods.

Enantiopure tertiary tryptamides \textbf{81}, obtained from tandem hydroformylation / Fischer indole synthesis of allylic amides after deprotection can be submitted to the acyl Pictet-Spengler reaction to give stereo defined 1,3 disubstituted THBCs \textbf{189}. Pictet-Spengler reaction can be used for the further derivatizations of the tryptophane homologues \textbf{93} as well, granting access to the indole structures \textbf{190} hardly obtainable by other methods possessing annulated 7 or 8 membered rings (Scheme 84). Here an option of submitting starting materials to Pictet-Spengler reaction under hydroformylation conditions would lead to further diversification of reaction pathways and to the increase in substance library diversity.

\textbf{Scheme 84.} Pictet-Spengler reaction of tryptamides and tryptophane homologues
6 Experimental Section

6.1 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 CDCl$_3$ as solvent with CHCl$_3$ as internal standard. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants are given in Hertz (Hz). The proton spectra are reported as follows δ/ppm (multiplicity, number of protons, coupling constant J/Hz). Two dimensional spectra (COSY, HSQC, HMBC) were used where appropriate to aid the assignments in $^1$H and $^{13}$C spectra. High resolution mass analyses were performed on a Jeol JMS-SX 102A. IR spectra were measured on a Nicolet Impact 400D FT-IR spectrometer. IR spectra were recorded as films on NACl or KBr plates or for solids pressed with KBr. The peak intensities are defined as very strong (vs), strong (s), medium (m) or weak (w). Optical rotations were measured on a Perkin-Elmer 341 polarimeter in a 10 cm cell in the stated solvent; [α]$_D$ values are given in 10$^{-1}$deg.cm$^2$g$^{-1}$ (concentration c given as g/100 mL). Enantiomeric excesses were determined by analytical HPLC, Hewlet-Packard 1050 series chromatograph using a CHIRALCELL OD-H (250x4.6 mm), CHIRALCELL OJ-H (250x4.6 mm) and CHIRALPAK AD (250x4.6 mm) columns as noted. Column chromatography was carried out on 70–230 mesh silica gel (Macherey–Nagel; silicagel 60) using Cyclohexane/EA, Cyclohexane/MTBE or CH$_2$Cl$_2$/MeOH as eluents.

6.2 Materials

All Ir catalyzed reactions were conducted using standard Schlenk techniques. THF was distilled from sodium-benzophenone ketyl under nitrogen, CH$_2$Cl$_2$ was distilled from CaH$_2$ under nitrogen. All other solvents were purchased and used as received. [Ir(cod)Cl]$_2$, O,O'-[(1,1'-Dinaphthyl-2,2'-diyl)-N,N'-di-(R,R)-1 phenylethylphosphoramidite [(Ra,RC,RC)-L1], [(Ra,RC,RC)-L3], [(Sa,SC,SC)-entL3], were prepared according to published procedures. Rh(acac)(CO)$_2$ was purchased. Allylic carbonates (68a – 68f) were synthesized

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by the reaction of corresponding allylic alcohols with methyl chloroformate in the presence of pyridine. (E)-4-methoxycinnamyl alcohol, (E)-2-methoxycinnamyl alcohol, and (E)-3-(2-furanyl)-2-propen-1-ol were prepared by the NaBH₄/CeCl₃ reduction of corresponding aldehydes. (E)-4-chlorocinnamyl alcohol,¹⁰⁰ (E)-4-trifluoromethylcinnamyl alcohol,¹⁰⁰ (E)-3-(pyridin-3-yl)prop-2-en-1-ol were prepared according to published procedure. (E)-cinnamyl alcohol, (E)-2-hexen-1-ol, (E)-2-penten-1-ol, 2-methoxycinnamaldehyde, (E)-3-(2-furyl)acrolein, (Aldrich Chemicals Co.), (E)-4-methoxycinnamaldehyde (TCI), (Alfa Aesar) were purchased and used without further purification.

6.3 Experiments in Chapter 2

General Procedure for iridium catalysed allylic aminations

Catalyst activation with propylamine.

\[[\text{Ir(cod)Cl}]_2 \text{(0.04 mmol)} \text{ and phosphoramidite ligand (L1 or L3) (0.08 mmol.)} \text{ were diluted in 0.3 ml of dry THF and 0.3 ml propylamine and the mixture was stirred under argon stream at 50 °C for 20 min. After this time all volatiles were evaporated. The yellow solid was diluted in 4ml of dry THF to generate a stock solution of the activated catalyst. Amine (1.2 mmol) was added to 1 ml of the stock solution of the catalyst (1 mol% catalyst). Carbonate (1 mmol) was added via syringe and the reaction was stirred at room temperature until the carbonate was fully converted (TLC analysis). The volatile materials were evaporated and the ratio of regioisomers (branched to linear b/l) was determined by $^1$H – NMR of the crude mixture. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate or cyclohexane/MTBE) to give the desired product.}\]

Benzyl-(1-phenyl-allyl)-amine (Table 1, Entry 1), (70a)

The general procedure for allylic aminations was followed with \[[\text{Ir(cod)Cl}]_2 \text{(6.7 mg, 0.01 mmol)} \text{ ligand L1 (9 mg, 0.02 mmol), cinnamyl methyl carbonate (192 mg, 1 mmol.) and benzylamine (214 mg, 2 mmol). The reaction was conducted at room temperature for 1.5 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 90/10. The mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 4/1) to give the title compound (129 mg, 58 %) as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 90 % [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99.6/0.4; flow rate = 1 ml/min; detection wavelength = 254 nm; TR = 13.4 (-), 17.5 (+) min]. (R) configuration, $[\alpha]_D^{20} = -2.5 \text{ (c = 0.84, CHCl}_3\text{)}$; (Table 1, Entry 2), (70a) The general
procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (6.7 mg, 0.01 mmol), ligand L3 (11.4 mg, 0.02 mmol), cinnamyl methyl carbonate (192 mg, 1 mmol) and benzylamine (214 mg, 2 mmol). The reaction was conducted at room temperature for 0.25 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 92/8. The mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 4/1) to give the title compound (170 mg, 76%) as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 94% [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99.6/0.4; flow rate = 1 ml/min; detection wavelength = 254 nm; TR = 13.4 (-), 17.5 (+) min]. (R) configuration, $[^{[20]}D]_D = -2.6$ (c = 1.100, CHCl$_3$); (Table 1, Entry 3), (70a) The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (6.7 mg, 0.01 mmol), ligand entL3 (11.4 mg, 0.02 mmol), cinnamyl methyl carbonate (192 mg, 1 mmol) and benzylamine (214 mg, 2 mmol). The reaction was conducted at room temperature for 0.5 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 96/4. The mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 4/1) to give the title compound (168 mg, 75%) as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 97% [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99.6/0.4; flow rate = 1 ml/min; detection wavelength = 254 nm; TR = 13.4 (-), 17.5 (+) min]. (S) configuration, $[^{[20]}D]_D = +2.8$ (c = 1.35, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.40-7.20 (m, 10H), 5.95 (ddd, 1H, $J = 7.3$ Hz, $J = 10.1$ Hz, $J = 17.2$ Hz), 5.22 (d, 1H, $J = 17.1$ Hz), 5.12 (d, 1H, $J = 10.2$ Hz), 4.22 (d, 1H, $J = 7.1$ Hz), 3.73 (d, 2H, $J = 3.1$ Hz), 1.85 (bs, 1H). $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 142.9,141.1, 140.8, 128.5, 128.3, 128.2, 127.3, 127.2, 126.9, 115.2, 65.0, 51.2; Analytical data fits with literature.102

$N$-(1-phenylallyl)cyclohexanamine (Table 1, Entry 4), (70b) The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (13 mg, 0.02 mmol), ligand L3 (23 mg, 0.04 mmol), cinnamyl methyl carbonate (384 mg, 2 mmol) and cyclohexylamine (218 mg, 2.4 mmol). The reaction was conducted at room temperature for 46 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 94/6. The mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 6/1) to give the

title compound (319 mg, 74 %) as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 97% [Diaceel Chiralcel OJ (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 98/2; flow rate = 0.3 mL/min; detection wavelength = 215 nm; TR = 14.6 (+), 15.3 (-) min]. \([\alpha]_D^{20} = -14.3 \, (c = 0.700, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) ppm 7.32 (d, \(J = 4.33 \text{ Hz}, 1\)H), 7.25-7.20 (m, 1H), 5.92 (ddd, \(J = 17.18, 10.12, 7.13 \text{ Hz}, 1\)H), 5.15 (d, \(J = 17.10 \text{ Hz}, 1\)H), 5.07 (d, \(J = 10.10 \text{ Hz}, 1\)H), 4.38 (d, \(J = 7.11 \text{ Hz}, 1\)H), 2.35-2.45 (m, 1H), 1.94 (d, \(J = 12.79 \text{ Hz}, 1\)H), 1.84 (d, \(J = 12.69 \text{ Hz}, 1\)H), 1.64-1.74 (m, 2H), 1.52-1.61 (m, 1H), 1.32 (br, 1H), 1.11 (m, 5H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta \) ppm 143.4 (C), 141.6 (CH), 128.4 (CH), 127.2 (CH), 126.9 (CH), 114.5 (CH\(_2\)), 62.3 (CH), 53.4 (CH), 34.0 (CH\(_2\)), 33.7 (CH\(_2\)), 26.2 (CH\(_2\)), 25.1 (CH\(_2\)), 25.05 (CH\(_2\)); HRMS: m/z (FAB) calc for C\(_{15}\)H\(_{21}\)N (M\(^+\)) 215.1675, found 215.1634; IR(film): \(\nu \) [cm\(^{-1}\)] = 3061(w), 3025(w), 2925(s), 2851(s), 1450(s), 1115(m), 700(s); 4-(1-phenylallyl)morpholine (Table 1, Entry 5), (70c) The general procedure for allylic aminations was followed with [Ir(cod)Cl\(_2\)] \(7 \text{ mg, 0.01 mmol}\), ligand L\(_3\) \(11 \text{ mg, 0.02 mmol}\), cinnamyl methyl carbonate (180 mg, 0.93 mmol) and morpholine (105 mg, 1.2 mmol). The reaction was conducted at room temperature for 16 h. \(^1\)H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 95/5. The mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 6/1) to give the title compound (155 mg, 82 %) as colourless oil. HPLC analysis indicated that the enantiomeric excess of the product was 94% [Diaceel Chiralcel OJ (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 98.4/1.6; flow rate = 1 mL/min; detection wavelength = 215 nm; TR = 6.7 (+), 7.5 (-) min]. \([\alpha]_D^{20} = -94 \, (c = 1.022, \text{CHCl}_3)\); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta \) ppm 7.34-7.27 (m, 4H), 7.24-7.20 (m, 1H), 5.89 (ddd, 1H, \(J = 9.5 \text{ Hz}, J = 9.5 \text{ Hz}, J = 17.3 \text{ Hz}\)), 5.22 (d, 1H, \(J = 17.0 \text{ Hz}\)), 5.09 (dd, 1H, \(J = 1.1 \text{ Hz}, J = 10.1 \text{ Hz}\)), 3.67 (t, 4H, \(J = 4.6 \text{ Hz}\)), 3.60 (d, 1H, \(J = 8.8 \text{ Hz}\)), 2.46 (bs, 2H), 2.34-2.28 (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta \) ppm 147.6 (s, 1C), 140.1 (s, 1C), 129.1 (s, 1C), 117.0 (s, 1C), 114.9 (s, 1C), 113.2 (s, 1C), 55.6 (s, 1C), 38.0 (s, 1C), 19.1 (s, 1C), 13.9 (s, 1C). Analytical data fits with literature.\(^{102}\)
2-((R)-1-phenylallyl)isoindoline-1,3-dione (Table 1, Entry 6), (70d)

The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (13 mg, 0.02 mmol), ligand L$_3$ (23 mg, 0.04 mmol), cinnamyl methyl carbonate (384 mg, 2 mmol) and phthalimide (441 mg, 3 mmol). The reaction was conducted at room temperature for 12 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 98/2. The mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 6/1) to give the title compound (347 mg, 66%) as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 98% [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 7.7 (+), 8.8 (-) min]. $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.82 (dd, 1H, $J$ = 3.0 Hz, $J$ = 5.4 Hz), 7.68 (dd, 1H, $J$ = 3.0 Hz, $J$ = 5.4 Hz), 7.46 (d, 1H, $J$ = 7.5 Hz), 7.34 (dd, 1H, $J$ = 7.4 Hz, $J$ = 7.4 Hz), 7.27 (dd, 1H, $J$ = 7.2 Hz, $J$ = 7.2 Hz), 6.67 (ddd, 1H, $J$ = 7.2 Hz, $J$ = 17.2 Hz), 5.29 (d, 1H, $J$ = 10.2 Hz), 5.36 (d, 1H, $J$ = 17.1 Hz); $^{13}$C NMR (101 MHz, CDCl$_3$ δ ppm 167.6, 138.4, 134.0, 133.9, 131.8, 128.4, 127.7, 127.6, 123.2, 119.0, 56.7; Analytical data fits with literature.$^{103}$

1-(1-phenylallyl)pyrrolidine (Table 1, Entry 7), (70e)

The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (7 mg, 0.01 mmol), ligand L$_3$ (12 mg, 0.02 mmol), cinnamyl methyl carbonate (192 mg, 1 mmol) and pyrrolidine (86 mg, 1.2 mmol). The reaction was conducted at room temperature for 0.5 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 95/5. The mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 4/1) to give the title compound (136 mg, 73%) as colourless oil. HPLC analysis indicated that the enantiomeric excess of the product was 98% [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99.6/0.4; flow rate = 0.4 mL/min; detection wavelength = 215 nm; TR = 13.0 (-), 15.2 (+) min]. $[\alpha]_{D}^{20}$ = -1.1 (c = 1.000, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.35-7.27 (m, 4H), 7.24-7.19 (m, 1H), 6.02 (ddd, 1H, $J$ = 9.0 Hz, $J$ = 9.8 Hz, $J$ = 17.1 Hz), 5.19 (d, 1H, $J$ = 17.0 Hz), 4.99 (dd, 1H, $J$ = 1.2 Hz, $J$ = 10.1 Hz), 3.57 (d, 1H, $J$ = 8.6 Hz), 2.52-2.46 (m, 2H), 2.39-2.33 (m, 2H), 1.78-1.71 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$, 125 MHz) δ ppm 167.6, 138.4, 134.0, 133.9, 131.8, 128.4, 127.7, 127.6, 123.2, 119.0, 56.7; Analytical data fits with literature.$^{103}$

CDCl$_3$ $\delta$ ppm 143.2 (s, 1C), 141.5 (s, 1C), 128.4 (s, 1C), 127.6 (s, 1C), 127.0 (s, 1C), 114.8 (s, 1C), 75.2 (s, 1C), 52.9 (s, 1C), 23.3 (s, 1C). Analytical data fits with literature.$^{102}$

$N,N$-diethyl-1-(2-methoxyphenyl)prop-2-en-1-amine (Table 1, Entry 8), (70f)

The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (11 mg, 0.015 mmol), ligand L$_3$ (17 mg, 0.030 mmol, 0.02 equiv.), (E)-3-(2-methoxyphenyl)allyl methyl carbonate (335 mg, 1.5 mmol) and diethylamine (79 mg, 1.8 mmol). The reaction was conducted at room temperature for 18 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 96/4. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 3/1) to give the title compound (205 mg, 62 %) as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 91% [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99.6/0.4; flow rate = 1 mL/min; detection wavelength = 215 nm; TR = 7.2 (-), 8.0 (+) min]. $[\alpha]_D^{20}$ = -73.0 (c = 1.004, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.47 (dd, $J = 7.57, 1.39$ Hz, 1H), 7.23-7.16 (m, 1H), 6.95 (t, $J = 7.40, 7.40$ Hz, 1H), 6.86 (d, $J = 8.19$ Hz, 1H), 5.91 (ddd, $J = 17.38, 9.82, 8.76$ Hz, 1H), 5.22 (dd, $J = 17.04, 0.90$ Hz, 1H), 4.99 (dd, $J = 10.04, 1.59$ Hz, 1H), 4.67 (d, $J = 8.50$ Hz, 1H), 3.82 (s, 3H), 2.68-2.53 (m, 4H), 0.97 (t, $J = 7.08, 7.08$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 157.1 (C), 140.8 (CH), 131.0 (C), 128.5 (CH), 127.4 (CH), 120.6 (CH), 114.5 (CH$_2$), 110.8 (CH), 61.1 (CH), 55.5 (CH), 42.6 (2xCH$_2$), 10.8 (2xCH$_3$); HRMS: m/z (FAB) calc for C$_{14}$H$_{21}$NO (M$^+$) 219.1623, found 219.1621. IR(film): $\nu$ [cm$^{-1}$] = 3076 (w), 2968 (s), 2943 (s), 2871 (m), 2834 (m), 1488 (s), 1464 (s), 1239 (s), 754 (s).

$N$-1-(1-(4-methoxyphenyl)allyl)piperidine (Table 1, Entry 9), (70g)

The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (26 mg, 0.04 mmol), ligand L$_3$ (45 mg, 0.08 mmol), (E)-3-(4-methoxyphenyl)allyl methyl carbonate (888 mg, 4 mmol) and piperidine (374 mg, 4.4 mmol). The reaction was conducted at room temperature for 46 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 91/9. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate/triethylamine = 3/1/0.01) to give the title compound (863 mg, 91 %) as yellowish solid. HPLC analysis indicated that the enantiomeric excess of the
product was 94% [Diacel Chiralcel OD-H (0.46 cm × 25 cm, 5 µm); heptane/2-propanol = 99.6/0.4; flow rate = 0.5 mL/min; detection wavelength = 230 nm; TR = 16.1 (-), 17.8 (+) min]. \([\alpha]_D^{20} = -102.5\) (c = 1.012, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.37-1.45 (m, 2H), 1.50-1.59 (m, 4H), 2.33-2.20 (m, 2H), 2.36-2.48 (m, 2H), 3.61 (d, \(J = 8.59\) Hz, 1H), 3.79 (s, 3H), 5.06 (d, \(J = 10.09\) Hz, 1H), 5.15 (d, \(J = 17.40\) Hz, 1H) 5.94 (ddd, \(J = 17.40, 10.09, 8.59\) Hz, 1H), 6.85 (d, \(J = 8.60\) Hz, 2H), 7.24 (d, \(J = 8.60\) Hz, 2H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 158.6 (C), 140.73 (CH), 134.5 (C), 129.07 (2xCH), 115.64 (CH\(_2\)), 113.84 (2xCH), 74.8 (CH), 55.3 (CH\(_3\)), 52.6 (2xCH\(_2\)), 26.3 (2xCH\(_2\)), 24.8 (CH\(_2\)); HRMS: m/z (FAB) calc for C\(_{14}\)H\(_{21}\)NO (M\(^+\)) 231.1623, found 231.1625; IR(KBr): \(\nu\) [cm\(^{-1}\)] = 2963 (s), 2934 (s), 2851 (m), 2783 (s), 2744 (m), 2169 (m), 1501 (s), 1452 (m), 1122 (vs), 1004 (vs), 925 (s).

4-(1-Furan-2-yl-allyl)-morpholine (Table 1, Entry 10), (70h)

The general procedure for allylic aminations was followed with [Ir(cod)Cl]\(_2\) (13.5 mg, 0.02 mmol), ligand L\(_3\) (23 mg, 0.04 mmol), (E)-3-Furan-2-yl-prop-2-en-1-ol methyl carbonate (365 mg, 2 mmol.) and morpholine (350 mg, 4 mmol). The reaction was conducted at room temperature for 20 h. \(^1\)H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 95/5. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (313 mg, 81 %) as yellowish oil.

Enantiomers could not be separated on any of available columns. \([\alpha]_D^{20} = -54.5\) (c = 0.915, CHCl\(_3\)); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) ppm 7.37 (s, 1H), 6.30 (m, 1H), 6.00 (ddd, 1H, J=3.0Hz), 6.00 (ddd, 1H, J=8.5Hz, J=10.0Hz, J=18.0Hz), 5.25 (m, 2H), 3.89 (d, 1H, J=8.2Hz),3.69 (t, 4H, J=4.7Hz), 2.50 (m, 2H) ppm 2.35 (m, 2H); \(^1\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 135.4, 118.7, 110.1, 108.2, 67.4, 67.2, 51.2; HRMS: m/z (FAB) calc for C\(_{11}\)H\(_{15}\)NO\(_2\) (M\(^+\)) 193.1103, found 193.1077; IR(film): \(\nu\) [cm\(^{-1}\)] = 3106 (w), 3080 (w), 2955 (s), 2863 (s), 2810 (s), 1641 (w), 1497 (m), 1457 (m), 1310 (m), 1122 (vs), 1004 (vs), 925 (s).

3-(1-Piperidin-1-yl-allyl)-pyridine (Table 1, Entry 11), (70i)

The general procedure for allylic aminations was followed with [Ir(cod)Cl]\(_2\) (13.5 mg, 0.02 mmol), ligand L\(_3\) (23 mg, 0.04 mmol), (E)-3-Pyridin-3-yl-prop-2-en-1-ol methyl carbonate (396 mg, 2 mmol.) and piperidine (340 mg, 4 mmol). The reaction was conducted at room temperature for 0.5 h. \(^1\)H
NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 96/4. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 1/1) to give the title compound (345 mg, 85 %) as colourless oil. HPLC analysis indicated that the enantiomeric excess of the product was 99 % [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 ml/min; detection wavelength = 254 nm; TR = 6.9 (-), 8.0 (+) min]. \([\alpha]^{20}_D = -65 \text{ (c = 1.060, CHCl}_3\); 

\(\text{H-NMR (CDCl}_3, 400 \text{ MHz}) \delta \text{ ppm 8.52 (s, 1H), 8.44 (d, 1H, } J = 4.6 \text{ Hz), 7.64 (d, 1H, } J = 7.8 \text{ Hz), 7.21 (dd, 1H, } J = 4.8 \text{ Hz, } J = 7.8 \text{ Hz), 5.92-5.83 (m, 1H), 5.18 (d, 1H, } J = 17.1 \text{ Hz), 5.11 (d, 1H, } J = 10.1 \text{ Hz), 3.71 (d, 1H, } J = 8.6 \text{ Hz), 2.41-2.22 (m, 4H), 1.55-1.49 (m, 4H), 1.41-1.36 (m, 2H); }^{13}\text{C-NMR (CDCl}_3, 100 \text{ MHz}) \delta \text{ ppm 149.7, 148.3, 139.0, 137.6, 135.3, 123.3, 116.9, 72.6, 52.2, 26.1, 24.5; HRMS: m/z (ESI) calc for C}_{13}\text{H}_{19}\text{N}_2 (M+H^+) 203.15428, found 203.15425; IR(film): } \nu [\text{cm}^{-1}] = 3461 (m), 2942 (vs), 2843 (vs), 2784 (vs), 2751 (vs), 2357 (w), 1845 (w), 1653 (m), 1574 (vs), 1418 (vs), 1313 (s), 1109 (vs), 991 (vs), 925 (vs).

**Benzyl-(1-ethyl-allyl)-amine (Table 1, Entry 12), (70j)**

The general procedure for allylic aminations was followed with [Ir(cod)Cl]_2 (13.5 mg, 0.02 mmol), ligand L3 (23 mg, 0.04 mmol), (E)- Pent-2-en-1-ol methyl carbonate (290 mg, 2 mmol.) and benzylamine (430 mg, 4 mmol). The reaction was conducted at room temperature for 5 h. \(\text{H-NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 91/9. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 5/1) to give the title compound (218 mg, 62 %) as colourless oil. HPLC analysis indicated that the enantiomeric excess of the product was 98 % [Diacel Chiralcel OJ (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99/1; flow rate = 1 ml/min; detection wavelength = 254 nm; TR = 7.8 (-), 8.6 (+) min]. \([\alpha]^{20}_D = -2.5 \text{ (c = 1.040, CHCl}_3\); 

\(\text{H-NMR (CDCl}_3, 400 \text{ MHz}) \delta \text{ ppm 7.32-7.28 (m, 4H), 7.25-7.20 (m, 1H), 5.60 (ddd, 1H, } J = 8.3 \text{ Hz, } J = 10.2 \text{ Hz, } J = 17.3 \text{ Hz), 5.16-5.07 (m, 2H), 3.82 (d, 1H, } J = 13.2 \text{ Hz), 3.64 (d, 1H, } J = 13.2 \text{ Hz), 2.93 (dd, 1H, } J = 7.9 \text{ Hz, } J = 13.5 \text{ Hz), 1.59-1.39 (m, 3H), 0.87 (t, 3H, } J = 7.5 \text{ Hz); }^{13}\text{C-NMR (CDCl}_3, 100 \text{ MHz}) \delta \text{ ppm 141.0, 140.7, 128.3, 128.1, 126.8, 116.3, 62.8, 51.21, 28.4, 10.3; HRMS: m/z (FAB) calc for C}_{13}\text{H}_{19}\text{N} (M^+) 189.1517, found 189.1525; IR(film): } \nu [\text{cm}^{-1}] = 3060 (m), 2962 (m), 2935 (m), 1451 (s), 1390 (m), 1102 (s), 912 (vs), 708 (vs).
Benzyl-(1-propyl-allyl)-amine (Table 1, Entry 13), (70k)

The general procedure for allylic aminations was followed with \([\text{Ir(cod)Cl}]_2\) (6.7 mg, 0.01 mmol), ligand \(L_3\) (11.4 mg, 0.02 mmol), (E)- Hex-2-en-1-ol methyl carbonate (145 mg, 1 mmol) and benzylamine (214 mg, 2 mmol). The reaction was conducted at room temperature for 2 h. \(^1\text{H}\) NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 89/11. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 4/1) to give the title compound (114 mg, 60 %) as colourless oil. HPLC analysis indicated that the enantiomeric excess of the product was 94% [Diacel Chiralcel OJ (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99/1; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 7.2 (-), 8.1 (+) min]. \([\alpha]_{D}^{20} = -1.0\) (c = 1.072, CHCl\(_3\)); \(^1\text{H}\)-NMR (CDCl\(_3\), 400 MHz) \(\delta\) ppm 7.32-7.28 (m, 4H), 7.25-7.20 (m, 1H), 5.61 (ddd, 1H, \(J = 8.3\) Hz, \(J = 10.2\) Hz, \(J = 17.2\) Hz), 5.15-5.06 (m, 2H), 3.82 (d, 1H, \(J = 13.1\) Hz), 3.63 (d, 1H, \(J = 13.2\) Hz), 3.01 (dd, 1H, \(J = 7.7\) Hz, \(J = 13.7\) Hz), 1.48-1.22 (m, 5H), 0.88 (t, 1H, \(J = 7.2\) Hz). \(^{13}\text{C}\)-NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 141.4, 140.7, 128.3, 128.1, 126.7, 115.9, 60.9, 51.2, 37.9, 19.1, 14.0; Analytical data fits with literature.\(^{102}\)

\(N\)-(hex-1-en-3-yl)aniline (Table 1, Entry 14), (70l)

The general procedure for allylic amination was followed with \([\text{Ir(cod)Cl}]_2\) (28 mg, 0.04 mmol), ligand \(L_3\) (45 mg, 0.02 mmol), (E)-hex-2-enyl methyl carbonate (318 mg, 2 mmol) and aniline (204 mg, 2.2 mmol). The reaction was conducted at room temperature for 46 h. \(^1\text{H}\) NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 95/5. The mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 20/1) to give the title compound (271 mg, 77 %) as colourless oil. HPLC analysis indicated that the enantiomeric excess of the product was 91% [Diacel Chiralcel OJ (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99.6/0.4; flow rate = 1 mL/min; detection wavelength = 215 nm; TR = 7.2 (-), 8.0 (+) min]. \([\alpha]_{D}^{20} = -7.044\) (c = 0.530, CHCl\(_3\)); \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.15 (t, \(J = 7.89, 7.89\) Hz, 2H), 6.67 (t, \(J = 7.30, 7.30\) Hz, 1H), 6.60 (d, \(J = 7.77\) Hz, 2H), 5.74 (ddd, \(J = 16.75, 10.28, 6.19\) Hz, 1H), 5.21 (d, \(J = 17.21\) Hz, 1H), 5.11 (d, \(J = 10.29\) Hz, 1H), 3.81 (q, \(J = 6.44, 6.42, 6.42\) Hz, 1H), 3.70 (bs, 1H), 1.63-1.53 (m, 2H), 1.50-1.38 (m, 2H), 0.95 (t, \(J = 7.26, 7.26\) Hz, 3H); \(^{13}\text{C}\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) ppm 147.6 (C), 140.1 (CH), 129.1 (CH),
117.0 (CH), 114.9 (CH$_2$), 113.2 (CH), 55.6 (CH), 38.0 (CH$_2$), 19.1 (CH$_2$), 14.0 (CH$_3$); Analytical data fits with literature.$^{104}$

**General Procedure for Acetylation of the Secondary Amines:**

To a stirred solution of amine (1 equiv.) in 10 ml of dry CH$_2$Cl$_2$ was added DMAP (0.05 equiv.) and dry triethylamine (3 equiv.) and the mixture was degassed under argon atmosphere using an ultrasound bath. Reaction mixture was cooled down to 0 °C and acetyl chloride (2 equiv.) was added dropwise via syringe. The mixture was allowed to stir at room temperature until amine was fully converted as determined by TLC. After completion of the reaction solvent was evaporated and 10 ml of diethylether were added. The formed suspension was filtered through sintered glass filter, and the volatiles removed *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate or cyclohexane/MTBE) to give the desired product.

*N*-benzyl-*N*-(1-phenylallyl)acetamide (Table 2, Entry 1), (76a), (R-(-)).

The general procedure was followed with *N*-benzyl-1-phenylprop-2-en-1-amine (447 mg, 2.0 mmol), DMAP (12 mg, 0.1 mmol), triethylamine (607 mg, 0.79 ml, 6.0 mmol) and acetyl chloride (314 mg, 0.285 ml, 4.0 mmol) in 10 ml of CH$_2$Cl$_2$. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 4/1) to give the title compound (467 mg, 88 %) as viscous colourless oil. $^{[\alpha]}_D^{20} = -44.6$ (c = 1.60, CHCl$_3$); (Table 2, Entry 2), (76b), (S-(+)). The general procedure was followed with *N*-benzyl-1-phenylprop-2-en-1-amine (447 mg, 2.0 mmol), DMAP (12 mg, 0.1 mmol), triethylamine (607 mg, 0.79 ml, 6.0 mmol) and acetyl chloride (314 mg, 0.285 ml, 4.0 mmol) in 10 ml of CH$_2$Cl$_2$. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 4/1) to give the title compound (452 mg, 85 %) as viscous colourless oil. $^{[\alpha]}_D^{20} = +46.2$ (c = 1.12, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.37-7.18 (m, 8 H), 7.05 (d, 2 H, $J = 7.0$ Hz), 6.48, 5.54, (2d, 1 H, $J = 4.6$ Hz, $J = 6.8$ Hz), 6.01 (ddd, 1H, $J = 6.9$ Hz, $J = 10.3$ Hz, $J = 17.3$ Hz), 5.33-5.11 (m, 2 H), 4.75-4.35 (m, 2 H), 2.23, 2.07 (s, 3 H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 171.8 (s, C), 139.2 (s, C), 137.9 (s, C), 135.2, 135.0 (d, CH), 128.7, 128.6,

128.1, 127.9, 127.7, 127.1, 126.7, 126.1 (10d, CH), 119.2, 118.8 (t, CH2), 64.7, 60.1 (d, CH), 49.4, 47.5 (t, CH2), 22.6, 22.5 (q, CH3); HRMS: m/z (ESI) calc for C_{18}H_{20}NO (M+H^+) 266.15394, found 266.15400; IR(film): ν [cm⁻¹] = 3060 (m), 3021 (m), 2929 (m), 1943 (w), 1818 (w), 1648 (vs), 1497 (s), 1418 (vs), 1260 (m), 1188 (m), 918 (m).

\(N\)-cyclohexyl-\(N\)-(1-phenylallyl)acetamide (Table 2, Entry 3), (76c)

The general procedure was followed with \(N\)-(1-phenylallyl)cyclohexanamine (193mg, 0.896mmol), DMAP (5 mg, 0.041 mmol), triethylamine (145 mg, 2.79 mmol) and acetylchloride (145 mg, 1.86 mmol) in 10 ml of CH₂Cl₂.

The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 2/1) to give the title compound (213 mg, 92 %) as viscous yellowish oil. \(^1\)H NMR (400 MHz, CDCl₃) δ ppm 7.42-7.14 (m, 10H), 6.62-6.45 (m, 1H), 6.34-6.14 (m, 1H), 5.44 (d, 1H, \(J = 10.05\) Hz), 5.39-5.15 (m, 4H), 5.03 (bs, 1H), 4.10 (bs, 1H), 3.61 (t, 1H, \(J = 11.1\) Hz), 2.17 (s, 1H), 1.99-1.44 (m, 18H), 1.86 (s, 3H), 1.68 (s, 3H), 1.40-1.00 (m, 6H), \(^13\)C NMR (101 MHz, CDCl₃) δ ppm 171.1, 169.3, 140.5, 140.1, 137.5, 136.1, 128.4, 127.9, 127.2, 126.8, 126.5, 126.3, 118.7, 117.3, 60.9, 60.6, 59.2, 55.3, 32.5, 32.0, 31.0, 30.4, 26.1, 26.0, 24.7, 23.4; HRMS: m/z (FAB) calc for C_{17}H_{23}NO (M⁺) 257.1780, found 257.1787; IR(film): ν [cm⁻¹] = 3028 (w), 2929 (s), 2853 (s), 1644 (s), 1449 (s), 1427 (s), 699 (s);

\(N\)-Benzyl-\(N\)-(1-ethyl-allyl)-acetamide (Table 2, Entry 4), (76d)

The general procedure was followed with \(N\)-benzylpent-1-en-3-amine (315 mg, 1.80 mmol), DMAP (11 mg, 0.089 mmol), triethylamine (547 mg, 0.72 ml, 5.4 mmol) and acetylchloride (283 mg, 0.26 ml, 3.6 mmol) in 10 ml of CH₂Cl₂.

The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 4/1) to give the title compound (293 mg, 75 %) as viscous colourless oil. \([\alpha]_{D}^{20} = -48.7\ (c = 1.634\ CHCl₃); \(^1\)H-NMR (CDCl₃, 400 MHz) δ ppm 7.30 (t, 1H, \(J = 7.3\) Hz), 7.26-7.15 (m, 4H), 5.73 (dddd, 1H, \(J = 6.4\) Hz, \(J = 10.4\) Hz, \(J = 16.7\) Hz, \(J = 23.4\) Hz), 5.17-5.06 (m, 2H), 4.95 (dd, 1H, \(J = 7.1\) Hz, \(J = 14.3\) Hz), 4.68 (d, 1H, \(J = 15.4\) Hz), 4.43 (s, 1H), 4.31 (d, 1H, \(J = 15.4\) Hz), 4.12 (dd, 1H, \(J = 6.6\) Hz, \(J = 12.9\) Hz), 2.20, 2.00 (s, 3H), 1.58 ( p, 2H, \(J = 7.3\) Hz), 0.81 (dt, 3H, \(J = 7.3\) Hz, \(J = 24.8\) Hz). \(^13\)C-NMR (CDCl₃, 100 MHz) δ ppm 171.6, 139.2, 138.1, 136.6, 136.4, 128.6, 128.1, 127.6, 127.1, 126.6, 126.1, 117.6, 116.6, 62.8, 58.3, 48.4, 45.4, 25.6, 24.6, 22.5, 22.3, 11.0, 10.9; HRMS: m/z (FAB)
calc for C_{14}H_{20}NO (M^{+}) 218.15394, found 218.15381; IR(film): υ [cm^{-1}] = 2968 (s), 2929 (m), 2876 (m), 1753 (m), 1641 (vs), 1457 (s), 1411 (s), 1254 (w), 1208 (m), 925 (s), 728 (s).

**N-benzyl-N-(hex-1-en-3-yl)acetamide (Table 2, Entry 5), (76e)**

The general procedure was followed with N-benzylhex-1-en-3-amine (294 mg, 1.55 mmol), DMAP (9.5 mg, 0.078 mmol), triethylamine (471 mg, 0.62 ml, 4.65 mmol) and acetylchloride (243 mg, 0.22 ml, 3.10 mmol) in 10 ml of CH_2Cl_2. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 4/1) to give the title compound (280 mg, 78%) as colourless oil. 

$\alpha\text{D}^{20} = -41.5$ (c = 0.836, CHCl_3); 1H-NMR (CDCl_3, 400 MHz) δ ppm 7.33 (t, 2H, J = 7.5 Hz), 7.26 (d, 2H, J = 7.9 Hz), 7.20 (d, 1H, J = 7.9 Hz), 5.73 (dddd, 1H, J = 6.3 Hz, J = 10.4 Hz, J = 16.8 Hz, J = 27.6 Hz), 5.18-5.01 (m, 2.5H), 4.72 (d, 0.5 H, J = 15.4 Hz), 4.43 (d, 1H, J = 1.7 Hz), 4.28 (d, 0.5H, J = 15.4 Hz), 4.24-4.20 (m, 0.5H), 2.20, 2.00 (s, 3H), 1.58-1.50 (m, 2H), 1.32-1.12 (m, 2H), 0.84, 0.73 (t, 1H, J = 7.3 Hz); 13C-NMR (CDCl_3, 100 MHz) δ ppm 171.6 (s, C), 139.2, 138.1 (s, C), 136.9, 136.7 (d, CH), 128.6, 128.2, 127.6, 127.1, 126.7, 126.1 (6d, CH), 117.4, 116.5 (t, CH_2), 60.9, 56.6 (d, CH), 48.5, 45.5 (t, CH_2), 34.6, 33.7 (t, CH_2), 22.5, 22.3 (q, CH_3), 19.6 (t, CH_2), 13.9, 13.6 (q, CH_3); HRMS: m/z (ESI) calc for C_{14}H_{22}NO (M+H^{+}) 232.16959, found 232.16945; IR(film): υ [cm^{-1}] = 2955 (s), 2922 (s), 2870 (m), 1955 (w), 1648 (vs), 1420 (w), 978 (m).

**N-Phenyl-N-(1-propyl-allyl)-acetamide (Table 2, Entry 6), (76f)**

The general procedure was followed with N-(hex-1-en-3-yl)aniline (203 mg, 1.16 mmol), DMAP (7 mg, 0.058 mmol), triethylamine (352 mg, 0.46 ml, 3.48 mmol) and acetylchloride (180 mg, 0.163 ml, 2.30 mmol) in 10 ml of CH_2Cl_2. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 4/1) to give the title compound (192 mg, 76%) as viscous colourless oil. $\alpha\text{D}^{20} = -12.7$ (c = 0.937, CHCl_3); 1H NMR (400 MHz, CDCl_3) δ ppm 7.42-7.30 (m, 3H), 7.08 (d, J = 6.82 Hz, 2H), 5.66-5.52 (m, 1H), 5.22-5.12 (m, 2H), 5.08 (d, J = 10.26 Hz, 1H), 1.73 (s, 3H), 1.57-1.42 (m, 1H), 1.41-1.27 (m, 3H), 0.88 (t, J = 7.00 Hz, 3H); 13C NMR (101 MHz, CDCl_3) δ ppm 170.0 (C), 139.9 (C), 137.2 (CH), 129.9 (CH), 129.1 (CH), 128.0 (CH), 117.4 (CH_2), 57.3 (CH), 34.2 (CH_2), 23.3 (CH_3), 19.5 (CH_2), 13.8 (CH_3); HRMS: m/z (ESI) calc for C_{14}H_{20}NO (M+H^{+}) 218.15394, found 218.15381;
6 Experimental Section

IR(film): $\nu$ [cm$^{-1}$] = 3063 (w), 2958 (s), 2931 (s), 2872 (s), 1660 (s), 1594 (s), 1494 (s), 1382 (s), 1313 (s), 702 (s);

**General procedure for hydroformylation / Fischer indole synthesis reactions with subsequent addition of Bronsted acid. General procedure A**

In a thick walled sample vial containing PTFE septum Rhodium(I)(acac)(CO)$_2$ (0.01 equiv.), XANTPHOS (0.1 equiv.), phenylhydrazine (1 equiv.) and olefin (1 equiv.) were dissolved in dry THF (5 mL). The vial was placed in a pressure vessel, flushed with argon and pressurized with 10 bar H$_2$ and 10 bar CO. The reaction mixture was stirred for 5 days at 80 °C. A 4 wt. % solution of H$_2$SO$_4$ in THF (5 mL) was slowly added and the resulting mixture was refluxed for 3 hours. Reaction was quenched with ammonia solution (30% in water) and the aqueous phase was extracted with 4x10 mL DCM. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and volatiles were removed in vacuo. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate or cyclohexane/MTBE) to give the desired product.

**General procedure for hydroformylation / Fischer indole synthesis reactions with subsequent addition of Lewis acid. General procedure B**

In a thick walled sample vial containing PTFE septum olefin (1 equiv.), phenylhydrazine (1 equiv.), Rhodium(I)(acac)(CO)$_2$ (0.01 equiv.) and XANTPHOS (0.1 equiv.) were dissolved in dry THF (5 mL). The vial was placed in a pressure vessel, flushed with argon and pressurized with 10 bar H$_2$ and 10 bar CO. The reaction mixture was stirred for 5 days at 80 °C. After completion of the reaction volatiles were removed in vacuo, residue was dissolved in toluol (10 mL) and ZnCl$_2$ (4 eq) was added and the resulting mixture was refluxed for 12 hours. Reaction mixture was diluted with water and the aqueous phase was extracted with 4x10 mL DCM. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and volatiles were removed in vacuo. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate or cyclohexane/MTBE) to give the desired product.
**N-Benzyl-N-[2-(1H-indol-3-yl)-1-phenyl-ethyl]-acetamide (Table 3, Entry 1), (81a), (R- (+))**

The general procedure A was followed with N-Benzyl-N-(1-phenyl-allyl)-acetamide (335 mg, 1.26 mmol), phenylhydrazine (136 mg, 1.26 mmol), Rh(acac)(CO)$_2$ (4.5 mg, 0.013 mmol) and XANTPHOS (73 mg, 0.13 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE/triethylamine = 1/1/0.1) to give (288 mg, 62 % yield) of the title compound as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 92 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 2 ml/min; detection wavelength = 254 nm; TR = 11.3 (+), 14.2 (-) min]. $[\alpha]_{D}^{20} = +2.1$ (c = 1.800, CHCl$_3$); (Table 3, Entry 2), (81b), (S-(-))

The general procedure A was followed with N-Benzyl-N-(1-phenyl-allyl)-acetamide (265 mg, 1.0 mmol), phenylhydrazine (109 mg, 1.26 mmol), Rh(acac)(CO)$_2$ (4 mg, 0.01 mmol) and XANTPHOS (60 mg, 0.1 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE/triethylamine = 1/1/0.1) to give (240 mg, 65 % yield) of the title compound as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 97 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 2 ml/min; detection wavelength = 254 nm; TR = 11.2 (+), 14.3 (-) min]. $[\alpha]_{D}^{20} = -2.0$ (c = 1.800, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 8.25, 8.16 (2 bs, 1 H, NH), 7.85-7.07 (m, 13 H, 13 x CH), 6.91 (d, 1 H, J = 4.5 Hz, CH), 6.97, 6.47 (2 s, 1 H, CH), 6.36, 5.38 (dd, 1H, 1H, J = 4.9 Hz, J = 9.3 Hz, J = 7.8 Hz, CH), 4.45, 4.29 (2 d, 1 H, J = 17.6 Hz, CH$_2$), 4.73, 4.21 (2 d, 1 H, J = 15.0 Hz, J = 14.9 Hz, CH), 3.48-3.31 (m, 2 H, CH$_2$), 2.02, 1.82, (2 s, 3 H, CH$_3$); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 172.1 (s, C), 142.4 (s, C), 139.9 (s, C), 137.9 (s, C), 131.8, 131.7, 128.8, 128.6, 128.5, 128.1, 127.7, 127.4 (2 d, CH), 127.3, 127.1, 126.8, 126.3 (s, C), 122.6, 122.2, 122.0, 119.7, 119.4, 118.8, 118.1 (2 d, CH), 112.5 (s, C), 111.6, 111.1 (2 d, CH), 62.0, 57.1 (2 d, CH), 49.0, 45.9 (2 t, CH$_2$), 27.8, 27.1 (2 t, CH$_2$), 23.0, 22.2 (2 q, CH$_3$); HRMS: m/z (FAB) calc for C$_{25}$H$_{25}$N$_2$O (M+H$^+$) 369.1967, found 369.2004; IR(film): ν [cm$^{-1}$] = 3419 (w), 3273 (m), 3029 (w), 2925 (w), 1630 (s), 1495 (m), 1455 (m), 1421 (m), 1360 (w), 1336 (w), 1028 (w), 981 (w), 743 (s), 699 (s), 542 (w);
N-(2-(1H-indol-3-yl)-1-phenylethyl)-N-cyclohexylacetamide, (Table 3, Entry 3), (81c)

The general procedure A was followed with N-cyclohexyl-N-(1-phenylallyl)acetamide (100 mg, 0.39 mmol), phenylhydrazine (42 mg, 0.39 mmol), Rh(acac)(CO)₂ (1 mg, 0.004 mmol) and XANTPHOS (22 mg, 0.038 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 1/2) to give (64 mg, 45 % yield) of the title compound as yellow oil. [α]²⁰D = +46.4 (c = 0.507, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ ppm 8.49 (s, 1H), 8.23 (s, 1H), 7.71 (d, 1H, J = 7.36 Hz), 7.58 (d, 1H, J = 7.73 Hz), 7.49 (d, 2H, J = 7.43 Hz), 7.44 (d, 2H, J = 7.29 Hz), 7.41-7.24 (m, 8H), 7.24-7.09 (m, 4H), 6.94 (d, 2H, J = 23.79 Hz), 5.20 (dd, 1H, J = 7.79 Hz, J = 5.35 Hz), 3.81 (dd, 1H, J = 11.52 Hz, J = 6.95 Hz), 3.70-3.54 (m, 2H), 3.31 (dd, 2H, J = 14.79 Hz, J = 8.77 Hz), 2.18 (s, 3H), 1.78 (s, 3H), 1.70-1.43 (m, 10H), 1.41-1.00 (m, 6H), 1.00-0.70 (m, 4H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 170.9, 170.8 (2xC), 139.8 (2xC), 136.1 (2xC), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.2 (C), 126.6 (CH), 123.0, 122.9 (2xCH), 122.0 (CH), 121.6 (CH), 119.4 (CH), 119.1 (CH), 118.5 (CH), 118.0 (CH), 111.6 (C), 111.5 (CH), 111.2 (CH), 56.6 (CH), 32.2 (CH₂), 30.4 (CH₂), 29.2 (CH₂), 26.7 (CH₂), 26.4 (CH₂), 26.3 (CH₂), 26.1 (CH₂), 25.3 (CH₂), 25.2 (CH₂), 24.2 (CH₃), 23.9 (CH₃); HRMS: m/z (HPLC-ESI) calc for C₂₄H₂₉N₂O (M+H⁺) 361.2274, found 361.2268; IR(film): ν [cm⁻¹] = 3279 (s), 3058 (s), 2930 (s), 2853 (s), 1719 (m), 1633 (s), 1494 (s), 1454 (s), 1380 (s), 1366 (s), 1316 (s), 909 (s), 738 (s), 699 (s), 646 (m);

N-Benzyl-N-[1-(1H-indol-3-ylmethyl)-propyl]-acetamide, (Table 3, Entry 4), (81d)

The general procedure A was followed with N-Benzyl-N-(1-ethylallyl)-acetamide (245 mg, 1.13 mmol), phenylhydrazine (122 mg, 1.13 mmol), Rh(acac)(CO)₂ (4.7 mg, 0.011 mmol) and XANTPHOS (65.4 mg, 0.113 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate/triethylamine = 1/1/0.1) to give (214 mg, 59 % yield) of the title compound as brownish oil. [α]²⁰D = -54.4 (c = 1.02, CHCl₃); ¹H-NMR (CDCl₃, 400 MHz) δ ppm 8.77, 8.69 (2 bs, 1H), 7.53, 7.47 (2 d, 1H, J = 7.8 Hz), 7.38-7.04 (m, 8H), 6.99, 6.66 (2 s, 1H), 4.71, 4.55 (2 d, 1H, J = 15.4 Hz), 4.33 (dd, 1H, J = 17.4 Hz, J = 43.0 Hz), 4.02 -3.95, 3.07-3.02 (2 m, 1H), 2.95-2.85 (m, 2H), 2.05-1.81 (2 s, 1H), 1.70-1.59 (m, 2H), 0.92-0.80 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 172.2 (s, C), 139.3 (s, C), 137.8, 136.1 (2s, C), 127.5, 126.9 (2s, C), 128.5, 128.2, 127.9, 127.1, 126.7,
126.3, 122.9, 122.4, 121.7, 121.5, 119.2, 118.9, 118.5, 117.8 (14d, 7xCH), 112.6, 111.4 (2s, C), 111.5, 111.1 (2d, CH), 61.8 (d, CH), 43.9 (t, CH\textsubscript{2}), 29.4, 28.4 (2t, CH\textsubscript{2}), 26.4, 25.2 (2 t, CH\textsubscript{2}), 22.9, 22.0 (2q, CH\textsubscript{3}), 11.4, 11.3 (2q, CH\textsubscript{3}); HRMS: m/z (ESI) calc for C\textsubscript{21}H\textsubscript{25}N\textsubscript{2}O (M+H\textsuperscript{+}) 321.19614, found 321.19619; IR(film): ν [cm\textsuperscript{-1}] =3412 (m), 3280 (bs), 2955 (s), 2925 (s), 2860 (s), 1495 (m), 1440 (m), 1333 (m), 1305 (m), 1240 (m), 1160 (w), 1106 (m), 974 (m), 742 (s).

**N-Benzyl-N-[1-(1H-indol-3-ylmethyl)-butyl]-acetamide, (Table 3, Entry 5), (81e)**

The general procedure A was followed with N-Benzyl-N-(1-propyl-allyl)-acetamide (405 mg, 1.75 mmol), phenylhydrazine (190 mg, 1.75 mmol), Rh(acac)(CO)\textsubscript{2} (6.3 mg, 0.017 mmol) and XANTPHOS (101 mg, 0.17 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE/triethylamine = 1/1/0.1) to give (445 mg, 76 % yield) of the title compound as yellow oil. HPLC analysis indicated that the enantiomeric excess of the product was 91 % [Diacel Chiralcel OD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1.5 ml/min; detection wavelength = 254 nm; TR = 17.0 (-), 19.5 (+) min]. [$\alpha$]\textsubscript{D}\textsuperscript{20} = + 26.2 (c = 0.992, CHCl\textsubscript{3}); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) δ ppm 8.69, 8.61 (2 bs, 1H, NH), 7.53, 7.46 (2d, 1H, J = 7.8 Hz, CH), 7.40-7.04 (m, 8H, 8 x CH), 7.02, 6.67 (2 d, 1H, J = 1.8 Hz, J = 2.1 Hz, CH), 4.79, 4.47 (2 d, 1H, J = 15.3 Hz, CH\textsubscript{H}), 4.38, 4.32 (2d, 1H, J = 17.4 Hz, CH\textsubscript{H}), 4.10-4.02, 3.08-3.01 (m, 1H, CH), 2.94-2.84 (m, 2H, CH\textsubscript{2}), 2.04, 1.77 (2 s, 3H, CH\textsubscript{3}), 1.61-1.51 (m, 2H, CH\textsubscript{2}), 1.32-1.20 (m, 2H, CH\textsubscript{2}), 0.81, 0.74 (2 t, 3H, J = 7.3 Hz, CH\textsubscript{3}); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 100 MHz) δ ppm 172.2 (s, C), 139.7 (s, C), 136.3, 128.7, 128.4, 128.2 (s, C), 127.8, 127.3, 126.9, 126.5, 123.0 (s, C), 122.5, 122.2, 121.9, 119.6, 119.3, 118.9 (d, CH), 118.1 (d, CH), 113.0 (s, C), 111.6, 111.2 (2 d, CH), 60.1 (d, CH), 46.0 (t, CH\textsubscript{2}), 35.9, 34.7 (2 t, CH\textsubscript{2}), 29.8, 28.9 (2 t, CH\textsubscript{2}), 23.2, 22.2 (2 q, CH\textsubscript{3}), 20.3, 20.1, (2 t, CH\textsubscript{2}), 14.1, 13.9 (2 q, CH\textsubscript{3}); HRMS: m/z (FAB) calc for C\textsubscript{22}H\textsubscript{27}N\textsubscript{2}O (M+H\textsuperscript{+}) 335.2123, found 335.2129; IR(film): ν [cm\textsuperscript{-1}] = 3412 (m), 3296 (bs), 2955 (s), 2925 (s), 2870 (s), 1560 (s), 1495 (m), 1456 (m), 1340 (m), 1299 (m), 1237 (m), 1162 (w), 1106 (m), 974 (m), 879 (w), 742 (s).
The general procedure A was followed with \(N\)-(hex-1-en-3-yl)-\(N\)-phenylacetamide (100 mg, 0.46 mmol), phenylhydrazine (50 mg, 0.46 mmol), Rh(acac)(CO)\(_2\) (1.5 mg, 0.006 mmol) and XANTPHOS (32 mg, 0.055 mmol). The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/MTBE = 1/1) to give (99 mg, 66 % yield) of the title compound as brown oil. \([\alpha]^{20}_D = -47.2\) (c = 0.46, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) ppm 8.27 (bs, 1H), 7.52-7.28 (m, 5H), 7.23-7.17 (m, 2H), 7.08-7.12 (m, 1H), 5.33 (s, 1H), 2.87 (dd, 1H, \(J = 15.44\) Hz, \(J = 9.11\) Hz), 2.73 (dd, 1H, \(J = 15.53\) Hz, \(J = 5.91\) Hz), 1.74 (s, 3H), 1.59-1.44 (m, 4H), 0.93 (t, 3H, \(J = 7.05\) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) ppm 171.1 (C), 139.5 (C), 136.2 (C), 129.2 (CH), 129.0 (CH), 128.1 (CH), 127.6 (C), 122.2 (CH), 121.8 (CH), 119.2 (CH), 118.7 (CH), 113.2 (C), 111.0 (CH), 60.5 (CH), 35.2 (CH\(_2\)), 29.1 (CH\(_2\)), 23.7 (CH\(_3\)), 20.0 (CH\(_2\)), 14.0 (CH\(_3\)); HRMS: \(m/z\) (ESI) calc for C\(_{21}\)H\(_{25}\)N\(_2\)O (M+H\(^+\)) 321.1961, found 321.1962; IR(film): \(\nu\) [cm\(^{-1}\)] = 3291 (s), 2957(s), 2928(s), 2870 (m), 1633 (s), 1593 (s), 1494 (s), 1394 (s), 740 (s), 703 (s).

The general procedure A was followed with 4-(1-phenylallyl)morpholine (150 mg, 0.738 mmol), phenylhydrazine (80 mg, 0.738 mmol), Rh(acac)(CO)\(_2\) (1.92 mg, 0.007 mmol) and XANTPHOS (43 mg, 0.07 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE/triethylamine = 1/1/0.1) to give (119 mg, 52 % yield) of the title compound as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 97 % [Diacel Chiralcel OD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 2 ml/min; detection wavelength = 254 nm; TR = 16.2 (+), 18.2 (-) min]. \([\alpha]^{20}_D = -41.6\) (c = 1.35, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.88 (bs, 1H), 7.55 (d, 1H, \(J = 7.9\) Hz), 7.14-7.34 (m, 7H), 7.10 (t, 1H, \(J = 7.4\) Hz), 6.56 (d, 1H, \(J = 2.5\) Hz), 3.74 (t, 4H, \(J = 4.6\) Hz), 3.64 (dd, 1H, \(J = 4.8\) Hz, \(J = 9.6\) Hz), 2.51-2.55 (m, 2H), 3.50 (dd, 1H, \(J = 4.5\) Hz, \(J = 14.4\) Hz), 3.08 (dd, 1H, \(J = 9.6\) Hz, \(J = 14.3\) Hz), 2.61-2.66 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 140.8 (C). 136.0 (C), 128.9 (CH), 128.0 (CH), 127.8 (C), 127.1 (CH), 122.7 (CH), 121.8 (CH), 119.2 (CH), 118.7 (CH), 113.2 (C), 111.1 (CH), 71.0 (CH), 67.5 (CH\(_2\)), 51.5 (CH\(_2\)), 28.6 (CH\(_2\)); HRMS: \(m/z\) (FAB) calc for C\(_{20}\)H\(_{23}\)N\(_2\)O (M+H\(^+\)) 307.1810, found 307.1805; IR(film): \(\nu\) [cm\(^{-1}\)] = 3396 (m), 3012
(m), 3027 (w), 2954 (s), 2853 (s), 2810 (s), 1599 (s), 1500 (s), 1452 (s), 1272 (s), 1116 (s), 1068 (m), 876 (m), 742 (s), 703 (s).

2-(2-(1H-indol-3-yl)-1-phenylethyl)isoindoline-1,3-dione, (Table 3, Entry 8), (81h)

The general procedure A was followed with phthalimide (300 mg, 2 mmol), phenylhydrazine (220 mg, 2 mmol), Rh(acac)(CO)$_2$ (5.2 mg, 0.02 mmol) and Xanthphos (120 mg, 0.2 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate/ = 2/1) to give (491 mg, 67 % yield) of the title compound as yellowish oil. $[\alpha]^{20}_{D}=+112.5$ (c = 0.810, CHCl3); $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 8.05 (s, 1H), 7.72-7.63 (m, 4H), 7.54 (dd, 2H, $J$ = 3.1 Hz, $J$ = 5.3 Hz), 7.37 (t, 2H, $J$ = 7.4 Hz), 7.31 (d, 1H, $J$ = 7.2 Hz), 7.23 (d, 1H, $J$ = 7.1 Hz), 7.16-7.08 (m, 2H), 6.92 (s, 1H), 5.85 (dd, 1H, $J$ = 6.0 Hz, $J$ = 10.4 Hz), 4.19 (dd, 1H, $J$ = 10.5 Hz, $J$ = 14.9 Hz), 3.70 (dd, 1H, $J$ = 6.0 Hz, $J$ = 14.9 Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 168.3, 139.6, 136.0, 133.7, 131.6, 128.5, 128.0, 127.8, 127.2, 122.9, 122.4, 121.8, 119.3, 118.5, 112.0, 111.0, 54.9, 27.1; HRMS: m/z (ESI) calc for C$_{24}$H$_{19}$N$_2$O$_2$ (M+H$^+$) 367.1410, found 367.14410; IR(film): $\nu$ [cm$^{-1}$] = 3441 (w), 3054 (w), 2929 (w), 1757 (w), 1707 (s), 1398 (m), 1352 (s), 1319 (m), 1102 (m), 715 (s).

3-(2-phenyl-2-(pyrrolidin-1-yl)ethyl)-1H-indole, (Table 3, Entry 9), (81i)

The general procedure A was followed with 1-(1-phenylallyl)pyrrolidine (100 mg, 0.533 mmol), phenylhydrazine (58 mg, 0.533 mmol), Rh(acac)(CO)$_2$ (1.55 mg, 0.006 mmol) and XANTPHOS (36 mg, 0.062 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE/triethylamine = 1/1/0.1) to give (73 mg, 47 % yield) of the title compound as brown oil. HPLC analysis indicated that the enantiomeric excess of the product was 98 % [Diacel Chiralcel OD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 2 ml/min; detection wavelength = 254 nm; TR = 7.1 (-), 9.2 (+) min]. $[\alpha]^{20}_{D}=-112.9$ (c = 1.00, CHCl3); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.98 (bs, 1H), 7.54 (d, 1H, $J$ = 7.9 Hz), 7.27 (d, 1H, $J$ = 7.8 Hz), 7.07-7.21 (m, 6 H), 6.40 (d, 1H, $J$ = 2.1 Hz), 4.48 (dd, $J$ = 3.9 Hz, $J$ = 10.4 Hz, 1H), 3.58 (dd, $J$ = 3.6 Hz, $J$ = 13.8 Hz, 1 H), 3.11 (dd, 1H, $J$ = 10.5 Hz, $J$ = 14.0 Hz), 2.77-2.79 (m, 2 H), 2.54-
2.57 (m, 2 H), 1.79-1.85 (m, 4 H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ ppm 143.1 (s, C), 136.0 (s, C), 128.5 (2 d, CH), 128.0 (2 d, CH), 127.8 (s, C), 127.1 (d, CH), 122.9 (d, CH), 121.7 (d, CH), 119.2 (d, CH), 118.9 (d, CH), 112.9 (s, C), 111.0 (d, CH), 71.8 (d, CH), 53.3 (2 t, CH2), 32.0 (t, CH2), 23.4 (2 t, CH2); HRMS: m/z (FAB) calc for C$_{20}$H$_{23}$N$_2$ (M+H$^+$) 291.1861, found 291.1846; IR(film): $\nu$ [cm$^{-1}$] = 3478 (m), 3424 (m), 2969 (m), 2794 (m), 1731 (m), 1492 (m), 1455 (s), 1372 (m), 1046 (m), 915 (w), 889 (w), 702 (s).

$N,N$-diethyl-2-((1H-indol-3-yl)-1-(2-methoxyphenyl)ethanamine, (Table 3, Entry 10), (81j)

The general procedure A was followed with $N,N$-diethyl-1-(2-methoxyphenyl)prop-2-en-1-amine (150 mg, 0.68 mmol), phenylhydrazine (74 mg, 0.68 mmol), Rh(acac)(CO)$_2$ (1.78 mg, 0.0068 mmol) and XANTPHOS (40 mg, 0.068 mmol, 0.1 equiv.). The crude reaction mixture was purified by column chromatography on silica gel (DCM/MeOH/triethylamine = 10/1/0.1) to give (74 mg, 33 % yield) of the title compound as brown solid. $\left[\alpha\right]_D^{20} = -20.45$ (c = 1.700, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm, 7.79 (bs, 1H), 7.61 (d, 1H, $J = 7.66$ Hz), 7.45 (d, 1H, $J = 7.33$ Hz), 7.25 (d, 1H, $J = 6.49$ Hz), 7.19-7.03 (m, 1H), 6.92 (t, 1H, $J = 7.41$ Hz), 6.74 (d, 1H, $J = 8.13$ Hz), 6.67 (s, 1H), 4.77 (dd, 1H, $J = 9.52$ Hz, $J = 5.33$ Hz), 3.48 (s, 1H), 3.38 (dd, 1H, $J = 14.52$ Hz, $J = 5.19$ Hz), 3.14 (dd, 1H, $J = 14.47$ Hz, $J = 9.65$ Hz), 2.79 (qd, 1H, $J = 14.18$, $J = 7.14$ Hz, 7.13 Hz), 2.50 (qd, 1H, $J = 13.49$ Hz, $J = 6.79$ Hz, $J = 6.79$ Hz), 1.06 (t, 1H, $J = 7.05$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 158.1 (C), 135.8 (C), 128.5 (CH), 128.0 (CH), 127.4 (CH), 122.1 (CH), 121.4 (CH), 120.1 (CH), 118.8 (2xCH), 114.0 (C) 110.7 (2xCH), 55.8 (CH), 55.3 (CH$_3$), 43.4 (CH$_2$), 28.5 (CH$_2$), 12.8 (CH$_3$); HRMS: m/z (FAB) calc for C$_{21}$H$_{26}$N$_2$O (M+H$^+$) 322.2045, found 323.2098; IR(film): $\nu$ [cm$^{-1}$] = 3450 (s), 2975 (s), 1615 (s), 1510 (s), 1410 (s), 1255 (s), 1178 (s), 1035 (s), 747 (s);

3-(2-(4-methoxyphenyl)-2-(piperidin-1-yl)ethyl)-1H-indole, (Table 3, Entry 11), (81k)

The general procedure A was followed with N-1-((1-(4-Methoxyphenyl) allyl) piperidin (150 mg, 0.64 mmol), Phenylhydrazin (70 mg, 0.64 mmol), Rh(acac)(CO)$_2$ (1.71 mg, 0.006 mmol) and XANTPHOS (37 mg, 0.06 mmol).

The crude reaction mixture was purified by column chromatography on silica gel
(cyclohexane/MTBE = 1/1) to give (116 mg, 50 % yield) of the title compound as white solid. \([\alpha]_D^{20} = -25.45 \) (c = 1.700, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) ppm 7.81 (bs, 1H), 7.60 (d, 1H, \(J = 7.61 \) Hz), 7.32-7.24 (m, 1H), 7.18-7.05 (m, 4H), 6.79 (d, 2H, \(J = 8.43 \) Hz), 6.62 (s, 1H), 3.77 (s, 3H), 3.77-3.75 (m, 1H), 3.46 (dd, 1H, \(J = 15.34, J = 5.16 \) Hz), 3.24-3.14 (m, 1H), 2.50 (bs, 4H), 1.61 (bs, 4H), 1.39 (bs, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 159.2 (C), 135.8 (C), 129.8 (2xCH), 129.8 (C), 128.0 (CH), 127.7 (C), 122.5 (CH), 121.3 (CH), 118.7 (CH), 113.4 (C), 112.9 (2xCH), 110.9 (CH), 69.9 (CH), 55.5 (CH3), 51.3 (CH2), 29.6 (CH2), 28.2 (CH2), 26.3 (2xCH2), 24.6 (CH2); HRMS: m/z (ESI) calc for \(C_{22}H_{27}N_2O\) (M+H\(^+\)) 335.2118, found 335.2118; IR(KBr): \(\nu \text{[cm}^{-1}\] = 3444 (s), 2956 (s), 1609 (s), 1515 (s), 1457 (s), 1403 (s), 1255 (s), 1181 (s), 1027 (s), 747 (s);

3-(2-Furan-2-yl-2-morpholin-4-yl-ethyl)-1H-indole, (Table 3, Entry 12), (81l)

The general procedure A was followed with 4-(1-Furan-2-yl-allyl)-morpholine (315 mg, 1.63 mmol), phenylhydrazine (176 mg, 1.63 mmol), Rh(acac)(CO)\(_2\) (5.8 mg, 0.016 mmol) and XANTPHOS (94 mg, 0.16 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE/triethylamine = 1/1/0.1) to give (270 mg, 56 % yield) of the title compound as brown oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) ppm 7.98 (s, 1H), 7.56 (d, 1H, \(J = 7.8 \) Hz), 7.37 (s, 1H), 7.28 (d, 1H, \(J = 8.0 \) Hz), 7.12 (dt, 2H, \(J = 7.2 \) Hz, \(J = 25.3 \) Hz), 6.76 (s, 1H), 6.24 (dd, 1H, \(J = 2.0 \) Hz, \(J = 2.7 \) Hz), 6.04 (d, 1H, \(J = 3.1 \) Hz), 3.85 (t, 1H, \(J = 7.4 \) Hz), 3.73 (m, 4H), 3.31 (d, 2H, \(J = 7.4 \) Hz), 2.57 (ddt, 2H, \(J = 4.9 \) Hz, \(J = 10.9 \) Hz, \(J = 15.6 \) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 153.6, 141.7, 136.0, 127.7, 122.4, 121.9, 119.3, 118.7, 113.1, 111.2, 109.9, 108.9, 67.4, 63.7, 50.5, 26.4; HRMS: m/z (ESI) calc for \(C_{18}H_{21}N_2O_2\) (M+H\(^+\)) 297.15975, found 297.15973; IR(film): \(\nu \text{[cm}^{-1}\] = 3444 (s), 2956 (s), 1609 (s), 1515 (s), 1457 (m), 1395 (s), 1245 (s), 1181 (s), 910 (s), 747 (s);

3-(2-Piperidin-1-yl-2-pyridin-3-yl-ethyl)-1H-indole, (Table 3, Entry 13), (81m)

The general procedure B was followed with 3-(1-Piperidin-1-yl-allyl)-pyridine (264 mg, 1.30 mmol), phenylhydrazine (141 mg, 1.30 mmol), Rh(acac)(CO)\(_2\) (4.7 mg, 0.013 mmol) and XANTPHOS (75 mg, 0.13 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE/triethylamine = 1/1/0.1) to
give (162 mg, 41 % yield) of the title compound as brown solid. \([\alpha]_D^{20} = -42.6\) (c = 1.21, CHCl₃); ¹H-NMR (CDCl₃, 400 MHz) δ ppm 8.40-8.35 (m, 2H), 7.88 (bs, 1H), 7.55-7.48 (m, 2H), 7.26 (d, 1H, J = 8.1 Hz), 7.15-7.10 (m, 2H), 7.06 (t, 1H, J = 7.3 Hz), 6.63 (d, 1H, J = 1.5 Hz), 3.77 (dd, 1H, J = 4.3 Hz, J = 9.5 Hz), 3.47 (dd, 1H, J = 3.0 Hz, J = 14.0 Hz), 3.14 (dd, 1H, J = 10.3 Hz, J = 14.0 Hz), 2.48 (bs, 4H), 1.70-1.55 (m, 4H), 1.42-1.36 (m, 2H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 150.2, 148.2, 136.0, 135.9, 134.5, 127.4, 122.9, 122.5, 121.8, 119.1, 118.5, 112.6, 111.0, 68.3, 51.4, 27.9, 26.1, 24.45; HRMS: m/z (ESI) calc for C₂₀H₂₄N₃ (M+H⁺) 306.19647, found 306.19616; IR(film): ν [cm⁻¹] = 3467 (w), 3165 (m), 2922 (vs), 2843 (s), 1720 (s), 1615 (s), 1589 (s), 1464 (vs), 1365 (m), 1249 (s), 1088 (s), 741 (vs).

General Procedures for iridium catalyzed Allylic Alkylations.

**Catalyst activation with DABCO. General procedure A**

In a schlenck tube [Ir(cod)Cl]₂ (0.02 equiv.), phosphoramidite ligand L₃ (0.04 equiv.) and DABCO (0.2 equiv.) were dissolved in dry THF (1 ml/mmol) and stirred under argon atmosphere at 50 °C for 2 hours. Carbonate (1 equiv.) was added in one portion and the mixture was stirred for another 20 minutes. Nucleophile (Cyanoacetate) was added and the mixture was stirred at 50 °C until TLC showed full conversion. The reaction was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂. Collected organic extracts were dried over MgSO₄, filtered and volatiles were evaporated in vacuo. The ratio of diastereoisomers (sin/anti) was determined by ¹H – NMR of the crude reaction mixture. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate or cyclohexane/MTBE) to give the desired product.

**Catalyst activation with propylamine. General procedure B**

[Ir(cod)Cl]₂ (0.08 mmol) and phosphoramidite ligand L₃ (0.16 mmol.) were diluted in 1 ml of dry THF, 0.3 ml propylamine were added and the mixture was stirred under argon stream at 50 °C for 20 min. After this time all volatiles were evaporated. The yellow solid was diluted in 4ml of dry THF to generate a stock solution of the activated catalyst. Amine (1.2 mmol) was added to 1 ml of the stock solution of the catalyst (2 mol% catalyst). Carbonate (1 mmol) was added in one portion and the reaction was stirred at room temperature until TLC showed full conversion. The volatile materials were evaporated and the ratio of
diastereoisomers (sin/anti) was determined by $^1$H – NMR of the crude reaction mixture. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate or cyclohexane/MTBE) to give the desired product.

**LiHMDS as a base. General procedure C**

$[\text{Ir}(\text{cod})\text{Cl}]_2$ (0.02 mmol, 0.02 equiv.), phosphoramidite ligand $L_3$ (0.04 mmol, 0.04 equiv.) and carbonate (1 mmol, 1 equiv.) were dissolved in dry THF (1mL) and stirred under argon atmosphere at r.t. for 15 minutes. In a separate flask solution of cyanoacetate or benzophenone protected glycine ethyl ester (1.1 mmol, 1.1 equiv.) in dry THF (2 mL) was cooled to -78°C. LiHMDS (1.1 mmol, 1.1 equiv.) was added dropwise via syringe and solution was stirred for 30 minutes at -78°C. The solution containing lithium enolate was added dropwise to a solution containing carbonate and catalyst cooled to -78 °C. The reaction mixture was allowed to warm up to room temperature and was stirred until TLC showed full conversion. Reaction mixture was quenched with 20 mL of sat. NH$_4$Cl solution, extracted with CH$_2$Cl$_2$ (4x10mL), washed with brine, dried over MgSO$_4$, filtered and evaporated. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE) to give the desired product.

**KOH or NaOH as a base. General procedure D**

$[\text{Ir}(\text{cod})\text{Cl}]_2$ (0.02 mmol, 0.02 equiv.), and phosphoramidite ligand $L_3$ (0.04 mmol, 0.08 equiv.) were dissolved in 1 mL of dry THF and stirred under argon atmosphere at r.t. for 15 min.. In a separate flask cyanoacetate or benzophenone protected glycine ethyl ester (1.1 mmol, 1.1 equiv.), KOH (1.1 mmol, 1.1 equiv.) or NaOH (1.1 mmol, 1.1 equiv.) and Bu$_4$NHSO$_4$ (0.1 mmol, 0.1 equiv.) were suspended in dry THF and stirred vigorously for 30 minutes at 0 °C. The solution containing the catalyst was cooled to 0 °C and carbonate (1 mmol, 1 equiv.) was added dropwise via syringe, suspension containing the enolate was subsequently added and the reaction mixture was allowed to warm to room temperature. The reaction was conducted at r.t until TLC showed full conversion. Reaction mixture was quenched with 20 mL of sat. NH$_4$Cl solution, extracted with CH$_2$Cl$_2$ (4x10mL), washed with brine dried over MgSO$_4$, filtered and evaporated. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE) to give the desired product.
(2S,3R)-ethyl 2-(diphenylmethyleneamino)-3-phenylpent-4-enoate (83a),
(2R,3R)-ethyl 2-(diphenylmethyleneamino)-3-phenylpent-4-enoate (84a).

(Table 5, Entry 1) The general procedure A was followed with cinnamyl methylcarbonate (96 mg, 0.5 mmol), N-(Diphenylmethylene)glycin ethyl ester (150 mg, 0.55 mmol), [Ir(cod)Cl]_2 (7 mg, 0.01 mmol), ligand L3 (11 mg, 0.02 mmol) and DABCO (12 mg, 0.1 mmol) in dry THF (3 mL). The reaction was conducted at 50 °C for 16 hours. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =25/1) to give (103 mg, 54 % yield) of the 83a and (63 mg, 33 % yield) of the 84a. 83a: [α]_D^{20} = -175.4 (c = 0.960, CHCl_3); HPLC analysis indicated that the enantiomeric excess of the product was 97 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 5 min. (-), 5.9 min (+)]; 84a: [α]_D^{20} = +168.7 (c = 1.230, CHCl_3); HPLC analysis indicated that the enantiomeric excess of the product was 95 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 4.8 (-), 7.1 (+) min].

(Table 5, Entry 2) The general procedure C was followed with cinnamyl methylcarbonate (96 mg, 0.5 mmol), N-(Diphenylmethylene)glycin ethyl ester (150 mg, 0.55 mmol), [Ir(cod)Cl]_2 (7 mg, 0.01 mmol), ligand L1 (11 mg, 0.02 mmol) and LiHMDS (0.5 ml, 1M solution in THF) in dry THF (3 mL). The reaction was conducted at r.t. for 3h. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =25/1) to give (107 mg, 56 % yield) of the 83a and (46 mg, 24 % yield) of the 84a. 83a: [α]_D^{20} = -89.6 (c = 0.742, CHCl_3); HPLC analysis indicated that the enantiomeric excess of the product was 65 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 5.0 (-), 5.9 min (+)]; 84a: [α]_D^{20} = +119.6 (c = 0.945, CHCl_3); HPLC analysis indicated that the enantiomeric excess of the product was 62 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 4.7 (-), 7.1 min (+)].

(Table 5, Entry 3) By a similar procedure as above in the presence of ligand L3 cinnamyl methylcarbonate (96 mg, 0.5 mmol) was transformed into (121 mg, 63 % yield) of the 83a and (40 mg, 21 % yield) of the 84a. The reaction was conducted at r.t. for 3h. 83a: [α]_D^{20} = -172.4 (c = 0.560, CHCl_3); HPLC analysis indicated that the enantiomeric excess of the
product was 87% [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 5.0 (-), 5.9 (min (+)).

84a: ee not determined.

(Table 5, Entry 4) The general procedure D was followed with cinnamyl methylcarbonate (96 mg, 0.5 mmol), N-(Diphenylmethylene)glycin ethyl ester (150 mg, 0.55 mmol), [Ir(cod)Cl]₂ (7 mg, 0.01 mmol), ligand L₃ (11 mg, 0.02 mmol) and DABCO (12 mg, 0.1 mmol) in dry THF (3 mL). The reaction was conducted at 50 °C for 5 hours. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =25/1) to give (50 mg, 26% yield) of the 83a and (75 mg, 39% yield) of the 84a. 83a: [α]D²⁰ = -170.5 (c = 0.89, CHCl₃); HPLC analysis indicated that the enantiomeric excess of the product was 91% [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 5.0 (-), 5.8 (+) min]. 84a: ee not determined.

83a: ¹H-NMR (CDCl₃, 400 MHz) δ ppm 7.64 (d, 2H, J = 7.2 Hz), 7.42-7.30 (m, 6H), 7.24-7.10 (m, 5H), 6.79 (d, 2H, J = 6.2 Hz), 6.32 (ddd, 1H, J = 8.9 Hz, J = 13.5 Hz, J = 16.9 Hz), 5.22-5.16 (m, 2H), 4.35 (d, 1H, J = 6.0 Hz), 4.17-4.02 (m, 3H), 1.12 (t, 3H, J = 7.1 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 171.1, 170.8, 140.9, 139.5, 137.4, 136.2, 130.3, 128.9, 128.5, 128.4, 128.2, 127.9, 127.7, 126.6, 117.4, 70.6, 60.8, 53.7, 14.1; HRMS: m/z (ESI) calc for C₂₆H₂₆NO₂ (M+H⁺) 384.19581, found 384.19616; IR(film): ν [cm⁻¹] = 3054 (m), 2981 (s), 2922 (vs), 2850 (s), 1963 (w), 1878 (w), 1733 (vs), 1615 (s), 1444 (s), 1240 (s), 1024 (s), 703 (s).

84a: ¹H-NMR (CDCl₃, 400 MHz) δ ppm 7.43 (d, 2H, J = 7.3 Hz), 7.29 (m, 4H), 7.26-7.07 (m, 7H), 6.71 (d, 2H, J = 3.8 Hz), 6.32 (ddd, 1H, J = 8.9 Hz, J = 10.1 Hz, J = 17.3 Hz), 5.11 (d, 1H, J = 17.1 Hz), 5.05 (d, 1H, J = 10.2 Hz), 4.33 (d, 1H, J = 9.1 Hz), 4.22-4.08 (m, 3H), 1.59 (t, 3H, J = 7.1 Hz); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 171.1, 170.9, 140.3, 139.6, 137.5, 135.9, 130.1, 128.9, 128.6, 128.2, 128.0, 127.8, 126.6, 116.9, 70.9, 60.9, 54.1, 14.2; HRMS: m/z (ESI) calc for C₂₆H₂₆NO₂ (M+H⁺) 384.19581, found 384.19630; IR(film): ν [cm⁻¹] = 3050 (m), 2985 (s), 2922 (vs), 2850 (s), 1960 (w), 1876 (w), 1730 (vs), 1615 (s), 1448 (s), 1240 (s), 1120 (s), 1024 (s), 703 (s).
(2S,3R)-ethyl 2-(diphenylmethyleneamino)-3-(2-methoxyphenyl)pent-4-enoate, (83b), (2R,3R)-ethyl 2-(diphenylmethyleneamino)-3-(2-methoxyphenyl)pent-4-enoate, (84b), (Table 6, Entry 1).

The general procedure A was followed with (E)-3-(2-methoxyphenyl)allyl methyl carbonate (111 mg, 0.5 mmol), N-(Diphenylmethylene)glycin ethyl ester (150 mg, 0.55 mmol), [Ir(cod)Cl]_2 (7 mg, 0.01 mmol), ligand L3 (11 mg, 0.02 mmol) and DABCO (12 mg, 0.1 mmol) in dry THF (3 mL). The reaction was conducted at 50 °C for 48 hours. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =20/1) to give (118 mg, 57 % yield) of the 83b and (52 mg, 25 % yield) of the 84b.

83b: \[\alpha^D_{20} = -170.5 \text{ (c = 0.89, CHCl}_3\text{)}\]; HPLC analysis indicated that the enantiomeric excess of the product was 91 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 98/2; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 7.6 (-), 8.3 (+) min]. ^1H-NMR (CDCl_3, 400 MHz) \(\delta\) ppm 7.58 (d, 2H, \(J = 7.2 \text{ Hz}\)), 7.37-7.25 (m, 6H), 7.12 (t, 2H, \(J = 7.9 \text{ Hz}\)), 6.79 (t, 1H, \(J = 7.3 \text{ Hz}\)), 6.71-6.65 (m, 3H), 6.42 (dt, 1H, \(J = 9.6\text{Hz}, J = 17.3 \text{ Hz}\)), 5.22 (d, 1H, \(J = 17.3 \text{ Hz}\)), 5.17 (dd, 1H, \(J = 1.1 \text{ Hz}, J = 10.2 \text{ Hz}\)), 4.54 (d, 1H, \(J = 5.5 \text{ Hz}\)), 4.47 (dd, 1H, \(J = 5.6 \text{ Hz}, J = 8.7 \text{ Hz}\)), 4.17-4.00 (m, 2H), 3.50 (s, 3H), 1.13 (t, 3H, \(J = 7.1 \text{ Hz}\)); ^13C-NMR (CDCl_3, 100 MHz) \(\delta\) ppm 171.3, 170.8, 156.7, 139.6, 136.7, 136.4, 130.1, 129.6, 129.2, 128.8, 128.1, 127.9, 127.9, 127.5, 120.1, 117.5, 110.3, 67.8, 60.6, 54.9, 47.6, 14.1; HRMS: m/z (ESI) calc for C_{27}H_{28}NO_3 (M+H^+) 414.20637, found 414.20594; IR(film): \(\nu\) [cm\(^{-1}\)] = 3073 (m), 2968 (s), 2929 (s), 2830 (m), 2265 (m), 1746 (vs), 1661 (s), 1635 (vs), 1490 (vs), 1457 (s), 1420 (s), 1326 (m), 1286 (m), 1155 (m), 1024 (m), 912 (s), 754 (vs), 689 (vs).

84b: \[\alpha^D_{20} = -136.5 \text{ (c = 1.15, CHCl}_3\text{)}\]; ee not determined; ^1H-NMR (CDCl_3, 400 MHz) \(\delta\) ppm 7.41-7.33 (m, 5H), 7.29 (t, 2H, \(J = 7.5 \text{ Hz}\)), 7.13-7.05 (m, 2H,), 6.85-6.77 (m , 2H), 6.69 (d, 1H, \(J = 8.1 \text{ Hz}\)), 6.11 (dt, 1H, \(J = 9.8\text{Hz}, J = 18.3 \text{ Hz}\)), 5.13 (d, 1H, \(J = 17.1 \text{ Hz}\)), 5.01 (d, 1H, \(J = 10.1 \text{ Hz}\)), 4.62 (d, 1H, \(J = 9.4 \text{ Hz}\)), 4.44 (t, 1H, \(J = 9.0 \text{ Hz}\)), 4.27-4.10 (m, 2H), 3.56 (s, 3H), 1.25 (t, 3H, \(J = 7.2 \text{ Hz}\)); ^13C-NMR (CDCl_3, 100 MHz) \(\delta\) ppm 171.5, 170.4, 157.0, 140.1, 137.0, 136.0, 130.2, 129.9, 128.9, 128.5, 128.5, 127.9, 127.7, 127.6, 120.2, 116.7, 110.3, 69.3, 60.7, 54.8, 49.9, 14.2; HRMS: m/z (ESI) calc for C_{27}H_{28}NO_3 (M+H^+) 414.20637, found 414.20602; IR(film): \(\nu\) [cm\(^{-1}\)] = 3070 (m), 2954 (s),
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2929 (s), 2834 (m), 2265 (m), 1743 (vs), 1485 (vs), 1420 (s), 1320 (m), 1155 (m), 1024 (m), 912 (s), 754 (vs), 696 (vs).

(2S,3R)-ethyl 2-(diphenylmethyleneamino)-3-(4-methoxyphenyl)pent-4-enoate, \( (83c) \), (2R,3R)-ethyl 2-(diphenylmethyleneamino)-3-(4-methoxyphenyl)pent-4-enoate, \( (84c) \), (Table 6, Entry 2) The general procedure A was followed with \((E)\)-3-(4-methoxyphenyl)allyl methyl carbonate (111 mg, 0.5 mmol), \( N\)-(Diphenylmethylene)glycin ethyl ester (150 mg, 0.55 mmol), \([\text{Ir(cod)}\text{Cl}]_2\) (7 mg, 0.01 mmol), ligand \( \text{L3} \) (11 mg, 0.02 mmol) and DABCO (12 mg, 0.1 mmol) in dry THF (3 mL). The reaction was conducted at 50 °C for 48 hours. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =20/1) to give (110 mg, 54 % yield) of the \( 83c \) and (89 mg, 43 % yield) of the \( 84c \). \( 83c: \ [\alpha]_{D}^{20} = -145.2 \) (c = 0.515, CHCl₃); HPLC analysis indicated that the enantiomeric excess of the product was 94 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 6.1 (-), 7.9 min (+)]. \( 84c: \ [\alpha]_{D}^{20} = +84.3 \) (c = 0.865, CHCl₃); HPLC analysis indicated that the enantiomeric excess of the product was 91 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 6.2 (-), 7.9 (+) min].

(Entry 3) The general procedure C was followed with \((E)\)-3-(4-methoxyphenyl)allyl methyl carbonate (96 mg, 0.5 mmol), \( N\)-(Diphenylmethylene)glycin ethyl ester (150 mg, 0.55 mmol), \([\text{Ir(cod)}\text{Cl}]_2\) (7 mg, 0.01 mmol), ligand \( \text{L1} \) (11 mg, 0.02 mmol) and LiHMDS (0.5 ml, 1M solution in THF) in dry THF (3 mL). The reaction was conducted at r.t. for 3h. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =20/1) to give (74 mg, 36 % yield) of the \( 83c \) and (39 mg, 19 % yield) of the \( 84c \). \( 83c: \ [\alpha]_{D}^{20} = -93.7 \) (c = 1.10, CHCl₃); HPLC analysis indicated that the enantiomeric excess of the product was 67 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 6.1 (-), 7.9 min (+)]. \( 84c: \ [\alpha]_{D}^{20} = +46.2 \) (c = 0.645, CHCl₃); HPLC analysis indicated that the enantiomeric excess of the product was 62 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 6.2 (-), 7.9 (+) min].
**83c:** $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.61 (d, 2H, $J = 7.3$ Hz), 7.40-7.27 (m, 6H), 7.01 (d, 2H, $J = 8.6$ Hz), 6.81 (d, 2H, $J = 6.0$ Hz), 6.73 (d, 1H, $J = 8.6$ Hz), 6.28-6.17 (m, 1H), 5.16-5.08 (m, 2H), 4.28 (d, 1H, $J = 6.2$ Hz), 4.10-3.99 (m, 3H), 3.73 (s, 3H), 1.10 (t, 3H, $J = 7.1$ Hz), $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 171.0, 170.9, 158.2, 137.7, 136.3, 132.9, 130.3, 129.5, 128.9, 128.4, 128.3, 127.9, 127.8, 117.0, 113.6, 70.8, 60.8, 55.2, 52.8, 14.1; HRMS: m/z (ESI) calc for C$_{27}$H$_{28}$NO$_3$ (M+H$^+$) 414.20637, found 414.20568; IR(film): ν [cm$^{-1}$] = 3050 (s), 2975 (s), 2929 (s), 1920 (w), 1872 (w), 1740 (vs), 1621 (vs), 1510 (vs), 1444 (s), 1240 (s), 1120 (s), 1030 (s), 918 (s), 695 (m);

**84c:** $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.45 (d, 1H, $J = 7.3$ Hz), 7.40-7.29 (m, 4H), 7.26-7.21 (m, 2H), 7.03 (d, 2H, $J = 8.6$ Hz), 6.78-6.71 (m, 4H), 5.93 (ddd, 1H, $J = 8.6$ Hz, $J = 10.1$ Hz, $J = 17.3$ Hz), 5.08 (d, 1H, $J = 17.1$ Hz), 5.02 (d, 1H, $J = 10.3$ Hz), 4.29 (d, 1H, $J = 8.9$ Hz), 4.20-4.03 (m, 3H), 3.74 (s, 3H), 1.23 (t, 3H, $J = 7.1$ Hz), $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 171.7, 171.1, 158.2, 137.8, 136.0, 132.4, 130.1, 129.8, 128.9, 128.5, 128.2, 128.0, 127.8, 116.5, 113.5, 70.9, 60.8, 55.2, 53.2, 14.2; HRMS: m/z (ESI) calc for C$_{27}$H$_{28}$NO$_3$ (M+H$^+$) 414.20637, found 414.20600; IR(film): ν [cm$^{-1}$] = 3045 (s), 2972 (s), 2929 (s), 1920 (w), 1830 (w), 1733 (vs), 1620 (vs), 1510 (vs), 1444 (s), 1220 (s), 1060 (s), 1030 (s), 918 (s), 695 (m);

(2S,3R)-ethyl 2-(diphenylmethyleneamino)-3-(2-furyl)pent-4-enoate, (83d)
(2R,3R)-ethyl 2-(diphenylmethyleneamino)-3-(2-furyl)pent-4-enoate, (84d)

(Table 6, Entry 4) The general procedure A was followed with (E)-3-furan-2-yl-prop-2-en-1-ol methyl carbonate (91 mg, 0.5 mmol), N-(diphenylmethylene)glycin ethyl ester (150 mg, 0.55 mmol), [Ir(cod)Cl]$_2$ (7 mg, 0.01 mmol), ligand L3 (11 mg, 0.02 mmol) and DABCO (12 mg, 0.1 mmol) in dry THF (3 mL). The reaction was conducted at 50 °C for 48 hours. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =20/1) to give (76 mg, 41 % yield) of the 83d and (52 mg, 28 % yield) of the 84d.

**83d:** $[\alpha]_{D}^{20} = -128.5$ (c = 0.92, CHCl$_3$); HPLC analysis indicated that the enantiomeric excess of the product was 95 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 5.9 (-), 7.0 min (+)]; $^1$H-
NMR (CDCl$_3$, 400 MHz) $\delta$ 7.59 (d, 2H, $J = 7.3$ Hz), 7.41-7.34 (m, 4H), 7.32-7.26 (m, 2H), 7.22 (s, 1H), 6.96 (d, 1H, $J = 3.6$ Hz), 6.27-6.17 (m, 2H), 6.01 (d, 1H, $J = 3.0$ Hz), 5.27-5.20 (m, 2H), 4.45 (d, 1H, $J = 5.4$ Hz), 4.22 (dd, 1H, $J = 5.6$ Hz, $J = 8.7$ Hz), 4.19-4.07 (m, 2H), 1.19 (t, 3H, $J = 7.1$ Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 171.5, 170.6, 154.1, 141.1, 139.6, 136.2, 134.7, 130.3, 128.9, 128.6, 128.3, 127.9, 118.3, 110.2, 106.5, 68.5, 60.9, 47.5, 14.1; HRMS: m/z (ESI) calc for C$_{24}$H$_{24}$NO$_3$ (M+H$^+$) 374.17507, found 374.17511; IR(film): $\nu$ [cm$^{-1}$] = 3385 (w), 3080 (w), 3054 (w), 2981 (m), 2922 (w), 2340 (m), 1738 (vs), 1659 (s), 1444 (s), 1254 (s), 1180 (m), 1142 (m), 932 (s), 702 (vs).

84d: $\left[\alpha\right]_D^{20} = +34.4$ (c = 0.742, CHCl$_3$); HPLC analysis indicated that the enantiomeric excess of the product was 94 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 5.1 (-), 7.3 min (+)]; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.52 (d, 1H, $J = 7.4$ Hz), 7.41-7.22 (m, 4H), 6.93 (d, 2H, $J = 4.4$ Hz), 6.25 (s, 1H), 6.17 (d, 1H, $J = 2.7$ Hz), 5.88 (td, 1H, $J = 18.3$ Hz), 5.14 (d, 1H, $J = 17.1$ Hz), 5.09 (d, 1H, $J = 10.2$ Hz), 4.35 (d, 1H, $J = 8.1$ Hz), 4.24 (t, 1H, $J = 8.3$ Hz), 4.16 (q, 2H, $J = 7.1$ Hz), 1.23 (t, 3H, $J = 7.1$ Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 171.4, 170.6, 153.4, 141.2, 139.6, 135.9, 134.9, 130.3, 128.9, 128.6, 128.4, 128.0, 127.9, 117.8, 110.2, 107.3, 69.1, 60.9, 47.6, 14.2; HRMS: m/z (ESI) calc for C$_{24}$H$_{24}$NO$_3$ (M+H$^+$) 374.17507, found 374.17516; IR(film): $\nu$ [cm$^{-1}$] = 3380 (w), 3080 (w), 3054 (w), 2981 (m), 2922 (w), 2340 (m), 1738 (vs), 1659 (s), 1444 (s), 1254 (s), 1180 (m), 1142 (m), 932 (s), 702 (s).

(2S,3R)-ethyl 2-(diphenylmethyleneamino)-3-(3-pyridyl)pent-4-enoate, (83e)
(2R,3R)-ethyl 2-(diphenylmethyleneamino)-3-(3-pyridyl)pent-4-enoate, (84e)

(Table 6, Entry 5) The general procedure A was followed with (E)-3-pyridin-3-yl-prop-2-en-1-ol methyl carbonate (100 mg, 0.5 mmol), N-(diphenylmethyleneglycin ethyl ester (150 mg, 0.55 mmol), [Ir(cod)Cl]$_2$ (7 mg, 0.01 mmol), ligand L3 (11 mg, 0.02 mmol) and DABCO (12 mg, 0.1 mmol) in dry THF (3 mL). The reaction was conducted at 50 °C for 48 hours. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =20/1) to give (90 mg, 47 % yield) of the 83e and (48 mg, 25 % yield) of the 84e.
enantiomeric excess of the product was 92\% [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 \( \mu \)m); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 7.9 (major), 10.1 (minor) min]. \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \( \delta \) ppm 8.43-8.35 (m, 2H), 7.61 (d, 2H, \( J = 7.3 \) Hz), 7.44 (d, 2H, \( J = 7.9 \) Hz), 7.40-7.22 (m, 7H), 7.12 (dd, 1H, \( J = 4.8 \) Hz, \( J = 7.7 \) Hz), 6.78 (d, 2H, \( J = 6.1 \) Hz), 6.30 (ddd, 1H, \( J = 8.7 \) Hz, \( J = 10.1 \) Hz, \( J = 17.3 \) Hz), 5.23-5.13 (m, 2H), 4.30 (d, 1H, \( J = 5.8 \) Hz), 4.17-4.01 (m, 3H), 1.12 (t, 3H, \( J = 7.1 \) Hz); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \( \delta \) ppm 171.9, 170.8, 150.9, 142.6, 139.6, 136.2, 136.6, 136.0, 135.5, 130.9, 128.8, 128.5, 128.3, 128.0, 127.5, 123.5, 118.8, 70.9, 61.6, 50.8, 14.7; HRMS: \( m/z \) (ESI) calc for C\(_{25}\)H\(_{25}\)N\(_2\)O\(_2\) (M+H\(^+\)) 385.19105, found 385.19128; IR(film): \( \nu \) [cm\(^{-1}\)] = 3375 (w), 3080 (w), 2988 (m), 2922 (m), 2850 (m), 1740 (vs), 1575 (s), 1444 (s), 1273 (s), 1175 (m), 1017 (m), 925 (s), 695 (vs).

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\((2S,3R)\)-ethyl 2-(diphenylmethyleneamino)-3-(ethyl)pent-4-enoate, (83f)

\((2R,3R)\)-ethyl 2-(diphenylmethyleneamino)-3-(ethyl)pent-4-enoate, (84f)

(Table 6, Entry 6) The general procedure A was followed with methyl (E)-pent-2-enyl carbonate (77 mg, 0.5 mmol), \( N \)-(Diphenylmethylene)glycin ethyl ester (150 mg, 0.55 mmol), [Ir(cod)Cl]\(_2\) (7 mg, 0.01 mmol), ligand L\(_3\) (11 mg, 0.02 mmol) and DABCO (12 mg, 0.1 mmol) in dry THF (3 mL). The reaction was conducted at 50 °C for 48 hours. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =20/1) to give (79 mg, 47 \% yield) of the \(83f\) and (30 mg, 18 \% yield) of the \(84f\).
83f: $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.63 (d, 2H, $J = 7.2$ Hz), 7.45-7.34 (m, 4H), 7.30 (t, 2H, $J = 7.3$ Hz), 7.12 (dd, 2H, $J = 2.6$ Hz, $J = 6.4$ Hz), 5.91 (dt, 1H, $J = 9.9$ Hz, $J = 17.1$ Hz), 5.14-5.08 (m, 2H), 4.15 (ddt, 2H, $J = 3.6$ Hz, $J = 7.2$ Hz, $J = 10.6$ Hz), 4.04 (d, 1H, $J = 4.6$ Hz), 2.63-2.59 (m, 1H), 1.34-1.20 (m, 5H), 0.77 (t, 3H, $J = 7.4$ Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 171.7, 170.5, 139.7, 138.7, 136.6, 130.2, 128.9, 128.5, 128.4, 127.9, 127.9, 116.9, 69.2, 60.6, 50.1, 24.5, 14.3, 11.8; HRMS: m/z (ESI) calc for C$_{22}$H$_{26}$NO$_2$ (M+H$^+$) 336.19581, found 336.19591; IR(film): ν [cm$^{-1}$] = 3054 (m), 2968 (s), 2929 (s), 2863 (s), 2364 (w), 1976 (w), 1904 (w), 1733 (vs), 1621 (s), 1528 (m), 1451 (s), 1372 (m), 1319 (w), 1260 (m), 1030 (m), 912 (s), 695 (s).

84f: $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.63 (d, 2H, $J = 7.3$ Hz), 7.44-7.34 (m, 4H), 7.31 (t, 2H, $J = 7.3$ Hz), 7.11 (dd, 2H, $J = 2.7$ Hz, $J = 6.4$ Hz), 5.45 (dt, 1H, $J = 9.8$ Hz, $J = 17.3$ Hz), 5.07-4.98 (m, 2H), 4.12 (q, 2H, $J = 7.1$ Hz), 3.94 (d, 1H, $J = 7.4$ Hz), 2.72-2.62 (m, 1H), 1.66-1.46 (m, 2H), 1.22 (t, 3H, $J = 7.1$ Hz), 0.80 (t, 3H, $J = 7.4$ Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 171.5, 170.9, 139.6, 138.4, 136.4, 130.3, 128.9, 128.6, 128.4, 127.9, 127.9, 117.2, 70.1, 60.6, 49.9, 23.3, 14.3, 11.7; HRMS: m/z (ESI) calc for C$_{22}$H$_{26}$NO$_2$ (M+H$^+$) 336.19581, found 336.19595; IR(film): ν [cm$^{-1}$] = 2965 (s), 2931 (s), 2863 (s), 2320 (w), 1976 (w), 1904 (w), 1825 (w), 1730 (vs), 1625 (s), 1515 (m), 1451 (s), 1372 (m), 1319 (w), 1260 (m), 1030 (m), 925 (s), 695 (s).

ethyl 2-(diphenylmethyleneamino)pent-4-enoate, 83h), (Table 6, Entry 7).

The general procedure A was followed with allyl methylcarbonate (60 mg, 0.5 mmol), $N$-(Diphenylmethylene)glycin ethyl ester (150 mg, 0.55 mmol), [Ir(cod)Cl]$_2$ (7 mg, 0.01 mmol), racemic ligand L3 (11 mg, 0.02 mmol) and DABCO (12 mg, 0.1 mmol) in dry THF (3 mL). The reaction was conducted at 50 °C for 48 hours. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =15/1) to give the title compound (43 mg, 28%) as colourless oil. $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.62 (d, 2H, $J = 7.2$ Hz), 7.45-7.28 (m, 6H), 7.18-7.11 (m, 2H), 5.67 (tdd, 1H, $J = 7.2$ Hz, $J = 10.0$ Hz, $J = 17.2$ Hz), 5.05 (d, 1H, $J = 17.1$ Hz), 5.00 (d, 1H, $J = 10.1$ Hz), 4.20-4.08 (m, 3H), 2.64 (tq, 2H, $J = 6.9$ Hz, $J = 14.0$ Hz), 1.24 (t, 3H, $J = 7.1$ Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 171.8, 170.58, 139.5, 136.4, 134.3,
130.3, 128.8, 128.6, 128.4, 127.9, 127.9, 117.6, 65.3, 60.9, 38.19, 14.2. Analytical data fits with literature.\textsuperscript{105}

$(2S,3R)$-methyl 2-(diphenylmethyleneamino)-3-phenylpent-4-enoate (86a)

To a 20 ml of 1% $\text{K}_2\text{CO}_3$ solution in methanol was added $(2S,3S)$-ethyl 2-(diphenylmethyleneamino)-3-phenylpent-4-enoate (83a), 50 mg (0.13 mmol), and after 1h of stirring at room temperature, methanol was removed and the crude rest was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate =15/1) to give the title compound (40 mg, 89%) as colourless oil.

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\left[\alpha\right]_{20}^{20} = -175 \text{ (c = 1.12, CHCl}_3\right); \text{ } ^{1}\text{H-NMR (CDCl}_3, 400 MHz) \delta \text{ ppm 7.45-7.09 (m, 13H), 6.70 (s, 2H), 5.98 (ddd, 2H, } J = 8.9, J = 10.4, J = 17.4 \text{ Hz), 5.13 (d, 1H, } J = 17.4 \text{ Hz), 5.07 (d, 1H, } J = 10.4 \text{ Hz), 4.39 (d, 1H, } J = 8.9 \text{ Hz), 4.13 (dd, 1H, } J = 8.9, 8.9 \text{ Hz), 3.72 (s, 3H); } ^{13}\text{C-NMR (CDCl}_3, 100 MHz) \delta \text{ ppm 171.8, 171.3, 140.3, 139.7, 137.4, 135.9, 130.5, 128.9, 128.8 (2C), 128.3, 128.2, 128.1, 127.9, 126.8, 116.9, 71.4, 54.4, 52.3. Analytical data fits with literature.}\textsuperscript{70}

2-Amino-4-(1H-indol-3-yl)-3-phenyl-butyric acid ethyl ester (85a)

The general procedure A was followed with ethyl 2-(diphenylmethyleneamino)-3-phenylpent-4-enoate (83a+84a) (655 mg, 1.7 mmol), phenylhydrazine (186 mg, 1.7 mmol), Rh(acac)(CO)$_2$ (4.4 mg, 0.017 mmol) and XANTPHOS (65 mg, 0.17 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate/triethylamine = 1/2/0.1) to give (334 mg, 61 % yield) of the title compound as yellow oil. \textsuperscript{1}H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 8.22, 8.12 (2s, 1H), 7.65, 7.61 (2d, 1H, $J = 7.7$ Hz), 7.30-7.14 (m, 8H), 6.78, 6.67 (2s, 1H), 4.16-4.06, 4.02-3.92, 3.88-3.80 (3m, 2H), 3.73 (d, 1H, $J = 4.9$ Hz), 3.57, 3.50-3.34 (dd, m 2H, $J = 7.3$ Hz, $J = 12.8$ Hz). 3.17 (td, 1H, $J = 7.7$ Hz, $J = 14.6$ Hz), 1.81 (bs, 2H), 1.22, 1.06 (2t, 1H, $J = 7.1$ Hz). $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 175.2, 174.5 (2xC), 141.5, 140.2 (2xC), 136.0, 135.9 (2xC), 128.5, 128.4 (2xC), 128.2, 128.1 (2xC), 127.5, 127.4 (2xC), 126.9, 126.7 (2xC), 122.6, 122.4 (2xC), 121.6, 121.5 (2xC), 119.0, 118.9 (2xC), 118.7, 118.6 (2xC), 113.5, 113.3 (2xC), 111.0, 110.9 (2xC), 60.8, 60.7(2xCH$_2$), 59.2, 57.7 (2xC), 50.0, 49.3 (2xC), 27.9,

26.0 (2xCH₂), 14.1, 13.8 (2xCH₃). HRMS: m/z (ESI) calc for C₂₀H₂₃N₂O₂ (M+H⁺) 323.17540, found 323.17553;

2-Amino-3-(1H-indol-3-ylmethyl)-pentanoic acid ethyl ester (85b)

The general procedure A was followed with ethyl 2-(diphenylmethyleneamino)-3-(ethyl)pent-4-enoate (83f+84f) (735 mg, 2.2 mmol), phenylhydrazine (239 mg, 2.2 mmol), Rh(acac)(CO)₂ (5.7 mg, 0.022 mmol) and XANTPHOS (85 mg, 0.17 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate/triethylamine = 1/2/0.1) to give (278 mg, 46 % yield) of the title compound as yellow oil. 

1H-NMR (CDCl₃, 400 MHz) δ ppm 8.35, 8.29 (2s, 1H), 7.65, 7.58 (2d, 1H, J = 7.8 Hz), 7.31 (d, 1H, J = 7.8 Hz), 7.12 (dt, 2H, J = 7.2 Hz, J = 27.7 Hz), 7.00, 6.93 (2s, 1H), 4.05 (dq, 1H, J = 7.2 Hz, J = 10.9 Hz), 3.86 (dq, 1H, J = 7.2 Hz, J = 10.9 Hz), 3.60, 3.48 (2d, 1H, J = 2.7 Hz), 2.84, 2.73 (2t, 1H, J = 8.1 Hz), 2.27-2.19 (m, 1H), 1.59 (bs, 2H), 1.54-1.35 (m, 2H), 1.17 (t, 3H, J = 7.1 Hz), 0.97 (t, 3H, J = 7.5 Hz); 13C-NMR (CDCl₃, 100 MHz) δ ppm 175.9, 136.3, 127.6, 122.7, 121.6, 118.9, 113.8, 111.0, 60.7, 55.3, 44.0, 25.1, 23.7, 14.0, 11.9; HRMS: m/z (ESI) calc for C₂₀H₂₃N₂O₂ (M+H⁺) 275.17540, found 275.17548; IR(film): ν [cm⁻¹] = 3389 (bs), 3251 (bs), 2948 (s), 2863 (s), 1733 (vs), 1477 (s), 1227 (s), 1188 (s), 1024 (m).

tert-butyl 2-cyano-3-phenylpent-4-enoate, (91a),

(Table 8, Entry 1) The general procedure C was followed with [Ir(cod)Cl]₂ (13 mg, 0.02 mmol), ligand L₃ (23 mg, 0.04 mmol), cinnamyl methylcarbonate (192 mg, 1 mmol), t-butyl cyanoacetate (155 mg, 1.1 mmol, 0.16 mL) and LiHMDS (184 mg, 1.1 mmol, 1.1 mL, 1.1 equiv.). The reaction was conducted at room temperature for 3h. 1H-NMR of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 65/35. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 18/1) to give the title compound (168 mg, 65 %) as yellow oil.

(Table 8, Entry 2) The general procedure D was followed with [Ir(cod)Cl]₂ (13 mg, 0.02 mmol), ligand L₃ (23 mg, 0.04 mmol), cinnamyl methylcarbonate (192 mg, 1 mmol), t-butyl cyanoacetate (155 mg, 1.1 mmol, 0.16 mL 1.1 equiv.), KOH (62 mg, 1.1 mmol) and Bu₄NHSO₄ (16 mg, 0.2 mmol). The reaction was conducted at r.t. for 16 h. 1H-NMR of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 43/57. The
crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 18/1) to give the title compound (160 mg, 62%) as yellow oil.

(Table 8, Entry 3) The general procedure D was followed with [Ir(cod)Cl]₂ (13 mg, 0.02 mmol), ligand L₃ (23 mg, 0.04 mmol), cinnamyl methyl carbonate (192 mg, 1 mmol), t-butyl cyanoacetate (155 mg, 1.1 mmol, 0.16 mL), NaOH (44 mg, 1.1 mmol) and Bu₄NHSO₄ (16 mg, 0.2 mmol). The reaction was conducted at r.t. for 12 h. 1H-NMR of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 45/55. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 18/1) to give the title compound (155 mg, 60%) as yellow oil.

(Table 8, Entry 4) The general procedure C was followed with [Ir(cod)Cl]₂ (13 mg, 0.02 mmol), ligand L₃ (23 mg, 0.04 mmol), cinnamyl methylcarbonate (192 mg, 1 mmol), t-butyl cyanoacetate (155 mg, 1.1 mmol, 0.16 mL) and DABCO (23 mg, 0.2 mmol). The reaction was conducted at 50 °C for 18 h. 1H-NMR of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 57/43. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 18/1) to give the title compound (196 mg, 76%) as yellow oil.

(Table 8, Entry 5) The general procedure B for allylic alkylations was followed with [Ir(cod)Cl]₂ (15 mg, 0.02 mmol), ligand L₃ (19 mg, 0.04 mmol), cinnamyl methylcarbonate (192 mg, 1 mmol), t-butyl cyanoacetate (155 mg, 1.1 mmol, 0.16 mL). The reaction mixture was stirred at r.t. for 5 days. 1H-NMR of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 52/48. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE=9/1) to give the title compound (108 mg, 42%) as yellow oil.

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\begin{align*}
\text{N} & \text{C} \\
\text{O} & \text{O'Bu}
\end{align*}
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\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{)} \delta \text{ ppm 7.39-7.26 (m, 10H), 6.21-6.04 (m, 2H), 5.27 (td, 4H, } J = 16.72 \text{ Hz, } J = 11.22 \text{ Hz, } J = 11.22 \text{ Hz), 4.00 (dt, 2H, } J = 7.60, J = 7.53, J = 2.79 \text{ Hz), 3.77 (d, 1H, } J = 7.52 \text{ Hz), 3.71 (d, 1H, } J = 7.16 \text{ Hz), 1.37 (s, 9H), 1.36 (s, 9H); } ^{13}\text{C NMR (101 MHz, CDCl}_3\text{)} \delta \text{ ppm 163.7 (C), 163.6 (C), 138.4 (C), 137.8 (C), 136.2 (CH), 135.0 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 119.0 (CH₂), 118.0 (CH₂), 115.7 (C), 115.7 (C), 84.2 (C), 84.1 (C), 49.9 (CH), 49.6 (CH), 27.6 (CH₃), 27.6 (CH₃); HRMS: m/z (HPLC-ESI) calc for C₁₆H₂₀N₂O₂ (M+H⁺) 258.1489, found 258.1490; IR(film): ν [cm⁻¹] =3080 (m), 3021 (m), 2956 (s), 2240 (m), 1750 (vs), 1640 (m), 1615 (m), 1491 (m), 1435 (s), 1260 (s), 1124 (w), 1029 (m), 918 (s), 843 (w), 726 (m), 702 (m).}
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Methyl 2-cyano-3-phenylpent-4-enoate, (91b) (Table 8, Entry 1),

The general procedure A was followed with cinnamyl methylcarbonate (300 mg, 1.56 mmol, 1 equiv.), methylcyanoacetate (185 mg, 1.87 mmol, 1.2 equiv.), [Ir(cod)Cl]_2 (21 mg, 0.03 mmol, 0.02 equiv.), ligand L3 (35 mg, 0.06 mmol, 0.04 equiv.) and DABCO (35 mg, 0.31 mmol, 0.2 equiv.) in dry THF (4 mL). The reaction was conducted at 50 °C for 16 hours. 1H-NMR of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 50/50. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 5/1) to give the title compound (219 mg, 65 %) as colourless oil. 

1H NMR (400 MHz, CDCl_3) δ ppm 7.38-7.28 (m, 5 H), 6.23-6.07 (m, 1 H), 5.34-5.24 (m, 2 H), 4.06 (dd, 1H, J = 8.0 Hz, J = 16.8 Hz), 3.89, 3.83 (2 d, 1H, J = 6.3 Hz, J = 7.4 Hz), 3.73 (s, 3H), 3.71 (s, 3 H); 13C NMR (100 MHz, CDCl_3) δ ppm 165.5 (2xC), 138.5, 137.7 (C), 136.0, 134.6 (CH), 129.1 (2xCH), 128.3, 128.1 (CH), 128.1, 127.7 (CH), 119.5,118.3 (CH2), 115.3 (2xC), 53.6, 53.5 (CH), 49.7 (2xCH3), 44.5, 44.0 (CH); HRMS: m/z (FAB) calc for C_{13}H_{14}NO_2 (M^+) 216.1025, found 216.1024; IR (film): v [cm^{-1}] = 3086 (m ), 3032 (s), 2956 (s), 2249 (m), 1755 (s), 1640 (m), 1602 (m), 1495 (m), 1435 (s), 1259 (s), 1124 (w), 1029 (m), 929 (s), 843 (w), 726 (m), 702 (m), 671 (w).

Methyl 2-cyano-3-(4-methoxyphenyl)pent-4-enoate (91c), (Table 8, Entry 2),

The general procedure A was followed with (E)-3-(4-methoxyphenyl)allyl methyl carbonate (300 mg, 1.35 mmol, 1 equiv.), cyanoacetate (160 mg, 1.62 mmol, 0.14 mL 1.2 equiv.), [Ir(cod)Cl]_2 (24 mg, 0.027 mmol, 0.02 equiv.), ligand L3 (31 mg, 0.054 mmol, 0.04 equiv.) and DABCO (30 mg, 0.27 mmol, 0.2 equiv) in 4 mL dry THF. The reaction was conducted at 50 °C for 12 hours. 1H-NMR of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 50/50. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 5/1) to give the title compound (232 mg, 70 %) as yellow oil. 

1H NMR (500 MHz, CDCl_3) δ ppm 7.24-7.20 (m, 1H), 6.90-6.86 (m, 1H), 6.12 (dddd, 1H, J = 17.75 Hz, J = 17.16 Hz, J = 10.32 Hz, J = 7.88 Hz), 5.27 (td, 1H, J = 24.60 Hz, J = 12.53 Hz), 4.02 (dd, 1H, J = 14.22 Hz, J = 6.90 Hz), 3.87-3.84 (m, 1H), 3.79 (s, 1H), 3.78 (d, 1H , J = 6.46 Hz), 3.72 (s, 1H), 3.71 (s, 1H); 13C NMR (125 MHz, CDCl_3) δ ppm 165.4, 164.3 (C), 159.3, 159.2 (C), 136.1, 134.8 (CH), 130.3, 129.5 (C), 129.1, 128.7 (CH), 118.9, 117.7
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(CH2), 115.3, 115.2 (C), 114.3, 114.2 (CH), 55.2, 55.2 (CH3), 53.3, 53.3 (CH3), 48.9, 48.7 (CH), 45.0, 44.0 (CH). HRMS: m/z (EI) calc for C14H15NO3 (M+) 245.1046, found 245.1029; IR(film): ν [cm⁻¹] = 3461 (w), 3008 (m), 2955 (s), 2830 (s), 2364 (m), 2252 (m), 2068 (w), 1766 (vs), 1608 (vs), 1516 (s), 1431 (s), 1306 (m), 1273 (m), 1030 (s), 833 (s).

Methyl 2-cyano-3-(furan-2-yl)pent-4-enoate (91d), (Table 8, Entry 3)

The general procedure A was followed with (E)-3-(furan-2-yl)allyl methyl carbonate (300 mg, 1.65 mmol, 1 equiv.), methylcyanoacetate (195 mg, 1.98 mmol, 1.2 equiv.), [Ir(cod)Cl]2 (30 mg, 0.033 mmol, 0.02 equiv.), ligand L3 (38 mg, 0.066 mmol, 0.04 equiv.) and DABCO (37 mg, 0.33 mmol, 0.2 equiv.) in dry THF (4 mL). The reaction was conducted at 50 °C for 3 hours. 1H-NMR of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 55/45. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 5/1) to give the title compound (158 mg, 47 %) as light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.38-7.40 (m, 2H), 6.36-6.33 (m, 2H), 6.28 (d, 1H, J = 3.21 Hz), 6.24 (d, 1H, J = 3.18 Hz), 6.11-5.97 (m, 2H), 5.35 (ddd, 4H, J = 14.26 Hz, J = 8.53 Hz, J = 4.96 Hz), 4.22-4.14 (m, 2H), 4.06 (d, 1H, J = 5.36 Hz), 3.88 (d, 1H, J = 6.35 Hz), 3.79 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ ppm 165.0 (2xC), 151.0, 150.6 (C), 142.6, 142.5 (CH), 132.9, 131.6 (CH), 120.9, 119.7 (CH₂), 114.7, 114.6 (C), 110.6, 110.5 (CH), 107.9, 107.7 (CH), 53.5 (2xCH₃), 43.7, 43.6 (CH), 42.4, 42.3 (CH). HRMS: m/z (FAB) calc for C₁₁H₁₁NO₃ (M⁺) 205.0739, found 205.0762; IR(film): ν [cm⁻¹] = 2962 (w), 2909 (m), 2850 (w), 2357 (w), 2245 (w), 1753 (vs), 1648 (w), 1503 (w), 1434 (m), 1267 (s), 1004 (m).938 (m).

Methyl 2-cyano-3-(pyridin-3-yl)pent-4-enoate (mixture of diastereomers), (91e), (Table 8, Entry 4)

The general procedure A was followed with (E)-methyl 3-(pyridin-3-yl)allyl carbonate (200 mg, 1.04 mmol, 1 equiv.), cyanoacetate (112 mg, 1.14 mmol, 0.1 mL 1.1 equiv.), [Ir(cod)Cl]₂ (14 mg, 0.020 mmol, 0.02 equiv.), ligand L₃ (24 mg, 0.042 mmol, 0.04 equiv.) and DABCO (23 mg, 0.207 mmol, 0.2 equiv.) in 2 mL dry THF. The reaction was conducted at 50 °C for 45 hours. 1H-NMR of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 50/50. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 1/2) to give the title compound (108 mg, 148
mg, 45 %) as yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ ppm 8.58-8.54 (m, 3H), 8.52 (d, 1H, $J = 1.61$ Hz), 7.75-7.70 (m, 1H), 7.70-7.67 (m, 1H), 7.35-7.28 (m, 2H), 6.20-6.04 (m, 2H), 5.33 (ddd, 4H, $J = 31.21$ Hz, $J = 16.46$ Hz, $J = 9.99$ Hz), 4.14-4.09 (m, 2H), 3.93 (d, 1H, 1.6 Hz), 3.82 (d, 1H, 6.18 Hz), 3.75 (s, 3H), 3.72 (s, 3H); 13C NMR (101 MHz, CDCl$_3$) δ ppm 164.8 (2xC), 149.6 (2xCH), 149.4, 149.2 (CH), 135.4, 135.0 (CH), 134.7 (CH), 134.0 (C), 133.4 (CH), 133.2 (C), 123.7 (2xCH), 120.4, 119.2 (CH$_2$), 114.7 (2xC), 53.7, 53.6 (CH$_3$), 46.9, 46.6 (CH), 43.9, 43.4 (CH); HRMS: m/z (EI) calc for C$_{12}$H$_{12}$N$_2$O$_2$ (M$^+$) 216.0893, found 216.0897; IR (film): ν [cm$^{-1}$] = 3474 (w), 3072 (m), 2962 (m), 2922 (w), 2259 (m), 1753 (vs), 1628 (m), 1582 (m), 1431 (s), 1247 (vs), 1194 (m), 1024 (m), 925 (s).

**Methyl 2-cyanopent-4-enoate (Table 8, Entry 5), (91f)**

The general procedure A for allylic alkylations was followed with [Ir(cod)Cl]$_2$ (17 mg, 0.019 mmol), ligand L3 (19 mg, 0.033 mmol), DABCO (21 mg, 0.187 mmol), allyl methylcarbonate (85 mg, 0.723 mmol) and methyl cyanoacetate (135 mg, 1.36 mmol). The reaction mixture was stirred at 50°C for 3 days. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE=9/1) to give 27 mg (0.194 mmol, 27% yield) of the title compound as colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 5.81 (tdd, 1H, $J = 17.1$ Hz, $J = 10.1$ Hz, $J = 7.01$ Hz), 5.30-5.20 (m, 2H), 3.81 (s, 3H), 3.58 (dd, 1H, $J = 7.16$ Hz, $J = 6.38$ Hz), 2.74-2.63 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 166.0 (C), 131.2 (CH), 120.1 (CH$_2$), 116.0 (C), 53.5 (CH$_3$), 37.3 (CH), 33.8 (CH$_2$); HRMS: m/z (EI) calc for C$_7$H$_9$NO (M$^+$) 139.0633, found 139.0615; IR (film): ν [cm$^{-1}$] = 3474 (w), 3072 (m), 2962 (m), 2922 (w), 2259 (m), 1753 (vs), 1628 (m), 1574 (m), 1431 (s), 1247 (vs), 1194 (m), 1024 (m), 925 (s).

**tert-butyl 2-cyanopent-4-enoate, (91g), (Table 8, Entry 6)**

The general procedure A was followed with [Ir(cod)Cl]$_2$ (25 mg, 0.037), ligand L3 (39 mg, 0.068 mmol), DABCO (38 mg, 0.344 mmol) allyl carbonate (186 mg, 1.6 mmol) and t-butyl cyanoacetate (260 mg, 1.85 mmol), in dry THF (3 mL). The reaction was stirred at 50 °C for 48h. After standard workup crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 16:1) to give the title compound (138 mg, 47 %) as
colourless oil. \([\alpha]_D^{20} = +0.9 (c = \text{0.937}, \text{CHCl}_3);^1\text{H} \text{NMR (400 MHz, CDCl}_3) \delta \text{ppm} 5.87-5.75 (m, 1H), 5.24 (t, 2H, \(J = 12.17\) Hz), 3.46 (t, 1H, \(J = 6.72\) Hz), 2.65 (t, 2H, \(J = 6.74\)Hz), 1.49 (s, 9H); \(^{13}\text{C} \text{NMR (101 MHz, CDCl}_3) \delta \text{ppm} 164.4 \text{ (C), 131.5 (CH), 119.8 (CH}_2, 116.4 \text{ (C), 84.2 (C), 38.4 (CH), 33.9 (CH}_2, 27.8 (3xCH}_3)).\text{Analytical data fits with literature}^{106}

**Tert-butyl 2-cyano-3-(2-methoxyphenyl)pent-4-enoate, (91h),**

(Table 8, Entry 7) The general procedure A was followed with \([\text{Ir(cod)}\text{Cl}]_2 (30 \text{ mg, 0.045 mmol, 0.02 equiv.}), \text{ligand L3} (49 \text{ mg, 0.09 mmol, 0.04 equiv.}), \text{DABCO} (114 \text{ mg, 1.02 mmol, 0.45 equiv.}), (E)-3-(2-methoxyphenyl)allyl methyl carbonate (500 mg, 2.25 mmol, 1 equiv.) and \text{t-butyl cyanoacetate} (349 mg, 2.47 mmol, 1.1 equiv.). The mixture was stirred at 50 °C for 20 hours. \(1\text{H-NMR} \) of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 70/30. The crude reaction mixture was purified by flash column chromatography using cyclohexane/MTBE (10:1) as eluent to afford title compound (407 mg, 70% yield) as yellow oil.

(Table 8, Entry 8) The general procedure B was followed with \([\text{Ir(cod)}\text{Cl}]_2 (30 \text{ mg, 0.045 mmol, 0.02 equiv}), \text{ligand L3} (49 \text{ mg, 0.09 mmol, 0.04 equiv.}), (E)-3-(2-methoxyphenyl)allyl methyl carbonate (445 mg, 2.0 mmol, 1 equiv) and \text{t-butyl cyanoacetate} (300 mg, 2.0 mmol, 1.1 equiv.). The mixture was stirred at 50 °C for 6 days. \(1\text{H-NMR} \) of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 68/32. The crude reaction mixture was purified by flash column chromatography using cyclohexane/MTBE (10:1) as eluent to afford title compound (180 mg, 35% yield) as yellow oil.

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^1\text{H} \text{NMR (400 MHz, CDCl}_3) \delta \text{ppm} 7.30-7.21 (m, 4H), 6.98-6.84 (m, 2H), 6.29-6.07 (m, 2H), 5.30 (dd, 1H, \(J = 13.61\) Hz, \(J = 7.31\) Hz), 5.20 (dd, 1H, \(J = 13.49\) Hz, \(J = 9.31\) Hz), 4.32-4.22 (m, 1H), 4.05 (dd, 1H, \(J = 14.97\) Hz, \(J = 8.10\) Hz), 3.86 (s, 3H), 3.85 (s, 3H), 1.40 (s, 9H),1.35 (s, 9H); \(^{13}\text{C} \text{NMR (100 MHz, CDCl}_3) \delta \text{ppm} 164.2, 164.1 \text{ (C), 156.8, 156.5 (C), 135.3, 134.2 (CH), 129.2 (2xCH), 129.0, 128.9 (2xCH), 120.8 (2xCH), 118.9, 118.1 (2xCH}_2, 116.2, 116.1 (C), 110.9, 110.6 (2xCH), 83.7, 83.6 (C), 55.3 (2xCH}_3), 45.8, 45.5 (2xCH), 42.8, 42.7 (2xCH), 27.6 (6xCH}_3). \text{HRMS: m/z (ESI) calc for C}_{17}\text{H}_{21}\text{NO}_3 (\text{M+H}^+) 287.15214, \text{found 287.15221}; \text{IR(film): v [cm}^{-1}] = 3474 (w), 3073 (m), 2981 (s), 2935 (m), 2239 (m), 1740 (vs), 1589 (s), 1490 (s), 1450 (s), 1234 /s), 1135 (vs), 1017 (s), 938 (s), 835 (s).

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**Experimental Section**

**tert-butyl 2-cyano-3-(pyridin-3-yl)pent-4-enoate, (91i), (Table 8, Entry 9)**

The general procedure A was followed with (E)-methyl 3-(pyridin-3-yl)allyl carbonate (200 mg, 1.04 mmol, 1 equiv.), t-butyl cyanoacetate (175 mg, 1.24 mmol, 0.18 mL 1.2 equiv.), [Ir(cod)Cl]₂ (14 mg, 0.020 mmol, 0.02 equiv.), ligand L₃ (23 mg, 0.04 mmol, 0.04 equiv.) and DABCO (23 mg, 0.207 mmol, 0.2 equiv.) in 1 mL dry THF. The reaction was conducted at 50 °C for 48 hours. ¹H-NMR of the crude reaction mixture indicated the ratio of diastereoisomers (syn/anti) to be 52/48. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 3/2) to give the title compound (133 mg, 60 %) as yellow oil. ¹H NMR (500 MHz, CDCl₃) δ ppm 8.58-8.53 (m, 1H), 7.78-7.74 (m, 1H), 7.68-7.65 (m, 1H), 7.31 (td, 1H, J = 7.95 Hz, J = 5.05 Hz, J = 5.05 Hz), 6.17-6.05 (m, 1H), 5.37 (d, 1H, J = 10.30 Hz), 5.35-5.24 (m, 1H), 4.06 (dt, 1H, J = 7.51 Hz, J = 12.5 Hz, J = 7.3 Hz, J = 7.3 Hz, J = 8.0 Hz), 7.44 (dd, 1H, J = 1.4 Hz, J = 6.7 Hz), 7.40-7.13 (m, 6H), 7.03, 6.91 (2 d, 1H, J = 7.3 Hz, J = 7.6 Hz), 7.12, 6.89 (2d, 1H, J = 2.3 Hz, J = 1.7 Hz), 4.01 (dd, 1H, J = 5.9 Hz, J = 12.5 Hz), 3.78-3.72 (m, 1H), 3.91, 3.82, 3.55,3.37 (4 s, 3H), 3.52-3.31 (m, 1H), 2.80-2.38 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 163.2 (2xC), 149.8 (CH), 149.4 (2xCH), 149.2 (CH), 135.4, 135.1 (CH), 135.1 (CH), 134.1 (C), 133.8 (CH), 133.4 (C), 123.5 (2xCH), 119.9, 118.9 (CH₂), 115.2 (2xC), 84.7, 84.6 (C), 47.1, 46.6 (CH), 44.6, 44.2 (CH), 27.5 (6x CH₃); HRMS: m/z (HPLC-ESI) calc for C₁₅H₁₉N₂O₂ (M+H⁺) 259.1441, found 259.1441; IR(film): ν [cm⁻¹] = 3435 (w), 2988 (s), 2929 (m), 2252 (m), 2200 (m), 1864 (w), 1740 (vs), 1648 (w), 1569 (m), 1483 (s), 1424 (s), 1378 (s), 1268 (s), 1142 (s), 918 (s).

**methyl 2-cyano-4-(1H-indol-3-yl)-3-phenylbutanoate, (92a), (Table 9, Entry 1)**

The general procedure was followed with methyl-2-cyano-3-phenylpent-4-enoate (300 mg, 1.4 mmol), phenylhydrazine (151 mg, 1.4 mmol), Rh(acac)(CO)₂ (3.2 mg, 0.014 mmol) and XANTPHOS (73 mg, 0.14 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 2/1) to give (174 mg, 39 % yield) of the title compound as yellow oil; ¹H NMR (500 MHz, CDCl₃) δ ppm 8.18, 8.03 (2 bs, 1 H), 7.68, 7.59 (2d, 1H, J = 7.9 Hz, J = 8.0 Hz), 7.44 (dd, 1H, J = 1.4 Hz, J = 6.7 Hz), 7.40-7.13 (m, 6H), 7.03, 6.91 (2 d, 1H, J = 7.3 Hz, J = 7.6 Hz), 7.12, 6.89 (2d, 1H, J = 2.3 Hz, J = 1.7 Hz), 4.01 (dd, 1H, J = 5.9 Hz, J = 12.5 Hz), 3.78-3.72 (m, 1H), 3.91, 3.82, 3.55,3.37 (4 s, 3H), 3.52-3.31 (m, 1H), 2.80-2.38 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 166.3 (s, C), 144.3 (s, C), 139.1, 129.3, 128.9, 128.6, 128.2, 128.1, 128.0, 127.8 (s, C), 127.1,123.8,123.3,122.5 (s, C), 122.2, 121.1,
119.7, 119.3 (2 d, CH), 118.9, 118.8 (2 d, CH), 115.7, 115.6, 113.3 (2 s, C), 112.1, 111.7 (2 s, C), 111.5, 111.3 (2 d, CH), 54.1, 53.2, 53.1, 52.4 (4 q, CH3), 46.0, 44.4 (2 d, CH), 46.1, 43.3 (2 d, CH), 29.7, 28.5, 27.6, 25.9 (4 t, CH2); HRMS: m/z (FAB) calc for C_{20}H_{19}N_{2}O_{2} (M+H') 319.1447, found 319.1490; IR(film): \nu [\text{cm}^{-1}] = 3415 (m), 3060 (m), 2922 (m), 2863 (m), 2245 (w), 1746 (vs), 1503 (m), 1457 (s), 1267 (m), 1017 (m), 741 (vs).

**methyl 2-cyano-4-(1H-indol-3-yl)-3-(4-methoxyphenyl)butanoate, (92b), (Table 9, Entry 2)**

The general procedure A was followed with methyl 2-cyano-3-(4-methoxyphenyl)pent-4-enoate (200 mg, 0.8 mmol), phenylhydrazine (86 mg, 0.8 mmol), Rh(acac)(CO)\(_2\) (2.16 mg, 0.008 mmol) and XANTPHOS (47 mg, 0.08 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 2/1) to give (189 mg, 66 % yield) of the title compound as yellow oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) ppm 8.15 (s, 1H), 8.01 (s, 1H), 7.68 (d, 1H, \(J = 7.88\) Hz), 7.60 (d, 1H, \(J = 7.84\) Hz), 7.41-7.31 (m, 4H), 7.29-7.08 (m, 8H), 6.94-6.83 (m, 6H), 3.81 (s, 3H), 3.81-3.74 (m, 4H), 3.79 (s, 3H), 3.57 (s, 3H), 3.47 (dd, 1H, \(J = 14.70\) Hz, \(J = 7.56\) Hz), 3.43-3.36 (m, 2H), 3.40 (s, 3H), 3.30 (dd, 1H, \(J = 14.71\) Hz, \(J = 5.96\) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) ppm 166.2, 165.6 (2xCH), 159.3, 159.1 (2xCH), 136.4, 136.1 (2xCH), 131.9, 130.9 (2xCH), 129.9, 128.7 (2xCH), 127.2, 127.0 (2xCH), 123.0, 123.5 (2xCH), 122.3, 122.0 (2xCH), 119.7, 119.5 (2xCH), 118.7, 118.6 (2xCH), 116.0, 115.5 (2xCH), 114.1, 114.1 (2xCH), 112.1, 111.7 (2xCH), 111.3, 111.1 (2xCH), 55.2 (2xCH\(_3\)), 53.1, 52.9 (2xCH\(_3\)), 45.2, 45.2 (2xCH), 44.4, 43.3 (2xCH), 29.7, 28.4 (2xCH\(_2\)); HRMS: m/z (HPLC-ESI) calc for C_{21}H_{21}N_{2}O_{3} (M+H') 349.15467, found 349.15465; IR(film): \nu [\text{cm}^{-1}] = 3446 (m), 2910 (s), 2835 (s), 2215 (m), 1733 (vs), 1502 (m), 1455 (s), 1255 (vs), 1010 (m), 740 (vs).

**tert-butyl 2-cyano-4-(1H-indol-3-yl)-3-phenylbutanoate, (92c), (Table 9, Entry 3),**

The general procedure was followed with tert-butyl 2-cyano-3-phenylpent-4-enoate (53b) (106 mg, 0.41 mmol), phenylhydrazine (55 mg, 0.8 mmol), Rh(acac)(CO)\(_2\) (1.07 mg, 0.004 mmol) and XANTPHOS (23 mg, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 2/1) to give (88 mg, 60 % yield) of the title compound as yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 8.07 (bs, 1H), 7.90 (bs, 1H), 8.07 (bs, 1H), 7.90 (bs, 1H).
7.68 (d, 1H, J = 7.76 Hz), 7.56 (d, 1H, J = 7.82 Hz), 7.47 (d, 2H, J = 7.25 Hz), 7.40-7.05 (m, 16H), 3.79-3.67 (m, 4H), 3.51-3.25 (m, 4H), 1.27 (s, 9H), 1.23 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ ppm 164.7 (C), 164.5 (C), 128.5 (CH), 128.5 (CH), 128.2 (2xCH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 122.3 (CH), 122.0 (CH), 119.4 (CH), 119.7 (CH), 118.7 (2xCH), 116.6 (C), 116.1 (C), 112.1 (2xC), 111.3 (CH), 111.1 (CH), 83.8 (C), 46.3 (CH), 46.0 (CH), 45.0 (CH), 43.7 (CH), 30.1 (CH$_2$), 28.8 (CH$_2$), 27.5 (6xCH$_3$). IR(film): ν [cm$^{-1}$] = 3420 (m), 3070 (s), 2922 (s), 2233 (m), 1737 (vs), 1602 (w), 1508 (m), 1455 (s), 1261 (s), 1017 (m), 741 (vs).

**tert-butyl 2-cyano-4-(1H-indol-3-yl)-3-(2-methoxyphenyl)butanoate, (92d), (Table 9, Entry 4),**

The general procedure was followed with tert-butyl 2-cyano-3-(2-methoxyphenyl)pent-4-enoate (200 mg, 0.69 mmol), phenyldihydrazine (75 mg, 0.69 mmol), Rh(acac)(CO)$_2$ (1.96 mg, 0.007 mmol) and XANTPHOS (41 mg, 0.069 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 2/1) to give (101 mg, 37 % yield) of the title compound as brown oil; $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 8.11 (s, 1H), 7.95 (s, 1H), 7.74 (d, 1H, J = 7.71 Hz), 7.60 (d, 7H, J = 7.74 Hz), 7.52 (d, 7H, J = 7.52 Hz), 7.37 (d, 1H, J = 7.68 Hz), 7.32-7.04 (m, 1H), 6.98-6.76 (m, 1H), 4.30 (td, 1H, J = 9.59 Hz, J = 6.41 Hz), 4.21-4.11 (m, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.31-3.18 (m, 2H), 3.47-3.33 (m, 2H), 1.24 (s, 18H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 164.8, 164.5 (2xC), 157.1, 157.0 (2xC), 136.3, 136.0 (2xC), 129.2 (CH), 128.5, 128.42 (2xC), 128.2 (C), 128.0 (CH), 127.5, 127.4 (2xC), 127.2 (C), 123.0, 122.9 (2xC), 122.0, 121.8 (2xC), 120.6, 120.4 (2xC), 119.4, 119.2 (2xC), 118.8, 118.7 (2xC), 116.8 (2xC), 112.4, 112.4 (2xC), 111.2, 111.0 (2xC), 110.6, 110.5 (2xC), 83.4, 83.4 (2xC), 55.4, 55.3 (2xC), 43.6, 42.3 (2xC), 40.9 (CH), 38.9 (CH), 29.5 (CH$_2$), 27.4 (6xCH$_3$), 26.8(CH$_2$). IR(film): ν [cm$^{-1}$] = 3440 (m), 3080 (s), 2922 (s), 2233 (m), 1733 (vs), 1605 (w), 1510 (m), 1455 (s), 1245 (vs), 1012(m), 741 (vs).
** tert-butyl 2-cyano-4-(1H-indol-3-yl)butanoate, ( Table 9, Entry 5), (92e)**

The general procedure was followed with tert-butyl 2-cyanohe5-enoate (300 mg, 1.54 mmol), phenylhydrazine (166 mg, 1.54 mmol), Rh(acac)(CO)₂ (3.52 mg, 0.015 mmol) and XANTPHOS (80 mg, 0.154 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 3/1) to give (251 mg, 57 % yield) of the title compound as yellow oil;

**1H-NMR** (CDCl₃, 400 MHz) δ ppm 8.22 (s, 1H), 7.63 (d, 1H, J = 7.8 Hz), 7.37 (d, 1H, J = 8.0 Hz), 7.19 (dt, 2H, J = 7.2 Hz, J = 14.9 Hz), 7.03 (s, 1H), 3.43 (dd, 1H, J = 6.1 Hz, J = 8.4 Hz), 3.02 (tq, 1H, J = 7.4 Hz, J = 14.9 Hz), 2.40-2.34 (m, 1H), 1.50 (s, 9H);

**13C-NMR** (CDCl₃, 100 MHz) δ ppm 165.1, 136.3, 126.9, 122.2, 122.0, 119.3, 118.4, 116.9, 112.9, 111.2, 83.9, 37.8, 30.1, 27.6, 22.2; HRMS: m/z (FAB) calc for C₁₇H₂₀N₂O₂ (M⁺) 284.1520, found 284.1515; IR(film): v [cm⁻¹] = 3415 (s), 2975 (m), 2935 (m), 2252 (w), 1733 (vs), 1457 (s), 1365 (s), 1155 (vs), 748 (s).

**General procedure for reduction of α-cyanoacetate indoles**

In a reaction vial containing PTFE septum cyano indole (40-50 mg, 1 equivalent) and Raney-Co (100-200 mg, qualitative superstoichiometric amount), were dissolved in 3 ml of MeOH and subsequently 4 ml of water was added. Reaction mixture was placed in an autoclave and pressurized with 40 bar of H₂. The reaction was vigorously stirred at 90 °C for 5h. After autoclave is cooled down to room temperature reaction mixture is filtered through sintered glass filter, filer was washed with 50 ml of MeOH and volatiles were removed under reduced pressure to give desired compound without further purification.

**methyl 2-(aminomethyl)-4-(1H-indol-3-yl)-3-phenylbutanoate, (93a)**

The general procedure was followed with methyl 2-cyano-4-(1H-indol-3-yl)-3-phenylbutanoate (40 mg, 0.13mmol) and 100 mg of Raney-Co. The crude reaction mixture was filtered through sintered glass filter to yield title compound (42 mg, 100 % yield) without further purification. 

**1H NMR** (500 MHz, CDCl₃) δ ppm 8.93, 8.03 (2 bs,1 H, NH), 7.60-7.47 (m, 1H), 7.40-7.08 (m, 6H), 7.04 (d, 1H, J = 7.7 Hz), 6.90 (t, 1H, J = 7.3 Hz), 6.71, 6.49 (2d, 1H, J = 2.1 Hz, J = 1.9 Hz), 4.00, 3.81 (2m, 1 H), 3.90, 3.78, 3.63, 3.46 (4 s, 3 H), 3.38-2.95 (m, 2H), 3.28-3.25, 2.93-2.91 (2 m, 1 H), 2.76-2.32- (m, 2 H);

**13C NMR** (125 MHz, CDCl₃) δ ppm 167.4 (d, C),145.2 (d, C), 135.9, 154
129.3, 128.9, 128.8, 128.7, 128.5, 128.4, 128.1, 127.8 (d, C ), 127.6, 126.7 (d, C ), 122.8, 122.5, 121.9, 121.7 (2 d, CH ), 121.0, 119.3, 118.8 (d, CH ), 113.3(d, CH ), 112.6, 112.4, 111.6, 111.2 (2 s, C ), 54.0, 53.5, 53.1, 52.3 (4 q, CH3 ), 48.7, 47.4 (2t, CH2 ), 45.9 (d, CH ) , 46.4, 43.1 (2 d, CH ), 30.2, 27.6, 26.9, 25.9 (4 t, CH2); HRMS: m/z (FAB) calc for C_{20}H_{23}N_{2}O_{2} (M+H^+) 323.1760, found 323.1800; IR(film): \nu [cm^{-1}] =3440-2955 (vs), 2063 (w), 1731 (vs), 1440 (s), 1241 (s), 1142 (s), 1010 (vs).

2-aminomethyl-4-(1H-indol-3-yl)-butyric acid tert-butyl ester, (93b)

The general procedure was followed with tert-butyl 2-cyano-4-(1H-indol-3-yl)butanoate (50 mg, 0.18 mmol) and 150 mg of Raney-Co (3 wt. equiv.). The crude reaction mixture was filtered through sintered glass filter to yield title compound (46 mg, 90 % yield) without further purification; \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) \delta ppm 8.41 (s, 1H), 7.53 (d, 1H, J = 7.6 Hz), 7.30 (d, 1H, J = 7.8 Hz), 7.10 (dt, 2H, J = 6.9 Hz, J = 27.9 Hz), 6.99 (s, 1H), 5.22 (bs, 2H), 2.98 (d, 2H, J = 40.3 Hz), 2.80-2.56 (m, 3H), 2.06-1.80 (m, 3H), 1.43 (s, 9H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 100 MHz) \delta ppm 173.9, 136.2, 127.2, 121.9, 121.7, 118.9, 118.6, 114.8, 111.3, 81.5, 46.1, 42.0, 30.1, 28.0, 22.3; HRMS: m/z (ESI) calc for C\textsubscript{17}H\textsubscript{25}N\textsubscript{2}O\textsubscript{2} (M+H\textsuperscript{+}) 289.19105, found 289.19062; IR(film): \nu [cm\textsuperscript{-1}] = 3395-2988 (vs), 2055 (w), 1720 (vs), 1641 (s), 1444 (s), 1273 (m ), 1142 (s), 741 (vs).

methyl 2-allyl-2-cyanopent-4-enoate (94a)

During the synthesis of 91f following the general procedure A for allylic alkylation with [Ir(cod)Cl\textsubscript{2}](17 mg, 0.019 mmol), ligand L3 (19 mg, 0.033 mmol), DABCO (21 mg, 0.187 mmol), allyl methylcarbonate (85 mg, 0.723 mmol) and methylcyanoacetate (135 mg, 1.36 mmol) 94a was isolated as a byproduct. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexan/MTBE=9/1) to give (21 mg, 21% yield) of the title compound as colourless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta ppm 5.80 (ddd, 2H J = 17.01 Hz, J = 14.85 Hz, J =7.31 Hz), 5.28-5.20 (m, 4H), 3.79 (s, 3H), 2.65 (dd, 2H, J = 13.83, J = 7.40 Hz), 2.55 (dd, 2H, J = 13.80 Hz, J =7.23 Hz); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta ppm 168.5 (C), 130.4 (2xCH), 121.0 (2xCH\textsubscript{2}), 118.3 (C), 53.3 (CH\textsubscript{3}), 49.3 (C), 40.6 (CH\textsubscript{2}); HRMS: m/z (ESI) calc for C\textsubscript{10}H\textsubscript{13}NO\textsubscript{2} (M+H\textsuperscript{+}) 179.09463, found 179.09450; IR(film): \nu [cm\textsuperscript{-1}] =3075
During the synthesis of 91g following the general procedure A with [Ir(cod)Cl]2 (25 mg, 0.037), ligand L3 (39 mg, 0.068 mmol), DABCO (38 mg, 0.344 mmol), allylcarbonate (186 mg, 1.6 mmol) and t-butyl cyanooacetate (225 mg, 1.60 mmol), in dry THF (3 mL). 94b was isolated as a byproduct. Crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/MTBE = 16/1) to give the title compound (71 mg, 20 %) as colourless oil. 1H NMR (400 MHz, CDCl3) δ ppm 5.76 (tdd, 1H, J = 14.71 Hz, J = 9.59 Hz, J = 7.28 Hz), 5.24-5.11 (m, 1H), 2.55 (dd, 1H, J = 13.87 Hz, J = 7.47 Hz), 2.44 (dd, 1H, J = 13.83 Hz, J = 7.11 Hz), 1.42 (s, 1H); 13C NMR (100 MHz, CDCl3) δ ppm 166.5 (C), 130.5 (2xCH), 120.4 (2xCH2), 118.5 (C), 49.5 (C), 40.5 (2xCH2), 33.7 (C), 27.6 (CH3); HRMS: m/z (ESI) calc for C13H19NO2 (M+H+) 222.14886, found 222.14890; IR(film): ν [cm⁻¹] = 3080 (w), 2968 (m), 2922 (m), 2239 (w), 1727 (vs), 1641 (m), 1365 (s), 1254 (s), 1148 (vs), 918 (m).

The general procedure was followed with tert-butyl 2-allyl-2-cyanopent-4-enoate (280 mg, 1.26 mmol), phenylhydrazine (276 mg, 2.52 mmol), Rh(acac)(CO)2 (3.3 mg, 0.013 mmol) and XANTPHOS (50 mg, 0.13 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate = 3/1) to give (368 mg, 68 % yield) of the title compound as yellow oil; 1H-NMR (CDCl3, 400 MHz) δ ppm 8.01 (s, 2H), 7.61 (d, 2H, J = 7.8 Hz), 7.34 (d, 2H, J = 8.0 Hz), 7.16 (dt, 4H, J = 7.2 Hz, J = 26.4 Hz), 6.99 (s, 2H), 3.08 (td, 2H, J = 4.7 Hz, J = 13.4 Hz), 2.85 (td, 2H, J = 4.8 Hz, J = 13.4 Hz), 2.38 (td, 2H, J = 4.9 Hz, J = 12.9 Hz), 2.13 (td, 2H, J = 4.6 Hz, J = 13.0 Hz), 1.54 (s, 9H); 13C-NMR (CDCl3, 100 MHz) δ ppm 168.0, 136.3, 127.0, 122.1, 121.5, 119.6, 119.4, 118.6, 114.2, 111.2, 84.2, 50.7, 38.2, 27.8, 21.4; HRMS: m/z (ESI) calc for C27H29N3O2 (M+H+) 428.23325, found 428.23328; IR(film): ν [cm⁻¹] = 3415 (s), 3060 (w), 2975 (s), 2742 (s), 2856 (m), 2245 (w), 1727 (vs), 1464 (s), 1267 (s), 1148 (s), 735 (vs).
General procedure for deprotection of benzophenone imines

To a stirred solution of imine (1 equiv.) in 1:1 THF/water solution (6 mL/mmol) hydroxylamine hydrochloride (3 equiv.) was added. The mixture was stirred for three hours at room temperature and the solvent was removed under reduced pressure. The crude material was then treated with 1 N HCl and washed with ethylacetate. The aqueous phase was neutralized using 1 N NaOH and extracted with DCM. Collected organic extracts were dried over MgSO₄ and the solvent was removed under reduced pressure to give desired product.

Ethyl 2-aminopent-4-enoate, (96a)

The general procedure was followed with ethyl 2-(diphenylmethyleneamino)pent-4-enoate (160 mg, 0.52 mmol) and hydroxylamine hydrochloric acid (108 mg, 1.56 mmol) to give the title compound 47 mg (63%) as yellowish oil. ¹H NMR (500 MHz, CDCl₃) δ ppm 5.74 (tdd, J = 17.22, 10.16, 7.20, 7.20 Hz, 1H), 5.13 (dd, J = 13.14, 6.15 Hz, 2H), 4.17 (ttdd, J = 10.73, 7.26, 7.26, 3.61, 3.61 Hz, 2H), 3.52 (dd, J = 7.00, 5.23 Hz, 1H), 2.54-2.44 (m, 1H), 2.37 (td, J = 14.03, 7.18, 7.18 Hz, 1H), 1.86 (d, J = 6.44 Hz, 1H), 1.27 (t, J = 7.14, 7.14 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ ppm 169.6 (C), 134.9 (CH), 120.1 (CH2), 62.4 (CH2), 55.3 (CH), 40.6 (CH2), 15.7 (CH3). Analytical data fits with literature.

2-Amino-3-phenyl-pent-4-enolic acid ethyl ester, (96b)

The general procedure was followed with ethyl 2-(diphenylmethyleneamino)-3-phenylpent-4-enoate (355 mg, 0.93 mmol) and hydroxylamine hydrochloric acid (195 mg, 2.78 mmol) to give ethyl 2-amino-3-phenylpent-4-enoate (113 mg, 56 %) as yellowish oil. ¹H-NMR (CDCl₃, 400 MHz) δ ppm 7.36-7.28 (m, 4H), 7.24 (dd, J = 7.1 Hz, J = 12.3 Hz, 6H), 6.12 (ddddd, J = 8.7 Hz, J = 17.3 Hz, J = 17.5 Hz, J = 17.5 Hz, 2H), 5.24-5.18 (m, 2H), 5.14 (dd, J = 6.2 Hz, J = 13.0 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.00 (q, J = 7.1 Hz, 2H), 3.76-3.70 (m, 2H), 3.62-3.58 (m, 2H), 1.50 (s, 4H), 1.25 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H); ¹³C-NMR...
NMR (CDCl₃, 400 MHz) δ ppm 174.1, 174.0, 140.5, 139.7, 137.7, 136.6, 128.6, 128.4, 128.2, 128.0, 127.1, 126.8, 118.1, 116.7, 60.7 (2C), 59.3 (2C), 55.1 (2C), 14.2, 13.9; HRMS: m/z (FAB) calc for C₁₃H₁₉NO₂ (M+H⁺) 220.1338, found 220.1331;

2-Amino-3-(4-methoxy-phenyl)-pent-4-enoic acid ethylester, (96c)

The general procedure was followed with ethyl 2-(diphenylmethyleneamino)-3-(4-methoxyphenyl)pent-4-enoate (422 mg, 1.02 mmol) and hydroxylaminehydrochloric acid (651 mg, 3.06 mmol) to give ethyl 2-amino-3-(4-methoxyphenyl)pent-4-enoate (175 mg, 69 %) as yellow oil. ¹H-NMR (CDCl₃, 400 MHz) δ ppm 7.15 (dd, J = 8.6 Hz, J = 12.8 Hz, 4H), 6.85 (dd, J = 8.2 Hz, J = 8.2 Hz, 4H), 6.10-6.06 (m, 2H), 5.23-5.18 (m, 2H), 5.13-5.10 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.01 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.70 (dd, J = 7.8 Hz, J = 7.8 Hz), 3.56 (td, J = 5.5 Hz, J = 10.9 Hz, 2H), 1.77 (s, 4H), 1.25 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H); ¹³C-NMR (CDCl₃, 400 MHz) δ ppm 174.0 (2C), 158.4, 138.0, 136.9, 132.5, 131.6, 129.3, 129.0, 117.9, 116.5, 114.1, 113.9, 60.8, 60.7, 59.3, 55.2 (2C), 54.1 (2C), 14.2, 14.0; HRMS: m/z (FAB) calc for C₁₄H₂₀NO₃ (M+H⁺) 250.1443, found 250.1438;
6.4 Experiments in Chapter 3

General procedure for tandem hydroformylation / Pictet-Spengler reaction under aprotic conditions

In a thick walled sample vial containing PTFE septum (S)-Triptophanmethylester (1 equiv.), olefin (1 equiv.) and Rh(acac)(CO)$_2$ (0.01 equiv.) were dissolved in dry solvent (8 mL). The vial was placed in a pressure vessel, flushed with argon and pressurized with 50 bar CO and 10 bar H$_2$. The reaction mixture was stirred for 3 days at designated temperature. Volatiles were removed under reduced pressure and the crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexan/ethylacetat) to give the desired product.

**a:** (1S,3S)-methyl 1-cyclopentyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate. (Table 10, Entry 7)

The general procedure was followed with (S)-tryptophane methylester (218 mg, 1 mmol), cyclopenten (68 mg, 1 mmol) and Rh(acac)(CO)$_2$ (3.6 mg, 0.01 mmol) in 8 ml of DCM under 50 bar CO and 10 bar H$_2$ at 80 °C for 72 h (Table 1, entry 7). The crude reaction mixture was purified by flash column chromatography on silica gel (Cyclohexan/Ethylacetat = 6/1) to give 113 mg (38 %) of a, 119 mg (40 %) of b, 9 mg, (2.5 %) of c; 3 mg ( 1 %) of d and 19 mg (5 %) of e.

**a:** $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.97 (s, 1H), 7.48 (d, 1H, $J$ = 7.6Hz), 7.30 (d, 1H, $J$ = 7.9 Hz), 7.12 (dt, 2H, $J$ = 7.0 Hz, $J$ = 20.1 Hz), 4.10 (d, 1H, $J$ = 6.4 Hz), 3.81 (s, 3H), 3.74 (dd, 1H, $J$ = 4.1Hz, $J$ = 11.2 Hz), 3.12 (ddd, 1H, $J$ = 1.5 Hz, $J$ = 4.0 Hz, $J$ = 14.9 Hz), 2.86-2.76 (m, 1H), 2.28 (q, 1H, $J$ = 8.0 Hz), 2.02-1.93 (m, 1H), 1.80-1.36 (m, 8H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 173.7, 135.8, 135.6, 126.9, 121.5, 119.4, 117.8, 110.7, 108.4, 56.7, 56.4, 52.1, 44.3, 29.2, 28.5, 25.9, 25.4; HRMS: m/z (ESI) calc for C$_{18}$H$_{23}$N$_2$O$_2$ (M+H$^+$) 299.17540, found 299.17489; IR(film): v [cm$^{-1}$] = 3402 (s), 3060 (w), 2955 (s), 2863 (s), 1740 (vs), 1457 (s), 1359 (m), 1181 (m), 741 (m).

**b:** (1R,3S)-methyl 1-cyclopentyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate.

$^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.86 (s, 1H), 7.48 (d, 1H, $J$ = 7.6 Hz), 7.28 (d, 1H, $J$ = 7.8 Hz), 7.12 (dt, 2H, $J$ = 6.7 Hz, $J$ = 14.7 Hz),
4.06-3.98 (m, 2H), 3.73 (s, 3H), 3.11 (dd, 1H, J = 5.1 Hz, J = 15.3 Hz), 2.99 (dd, 1H, J = 7.3 Hz, J = 15.2 Hz), 2.36 (bs, 1H), 2.21 (dd, 1H, J = 9.1 Hz, J = 17.2 Hz), 1.94-1.80 (m, 2H), 1.78-1.36 (m, 6H); 13C-NMR (CDCl3, 100 MHz) δ ppm 174.3, 135.7, 135.4, 126.9, 121.5, 119.2, 117.9, 110.6, 107.1, 55.1, 52.7, 52.0, 45.2, 30.2, 29.9, 25.6, 24.9, 24.7; HRMS: m/z (ESI) calc for C18H23N2O2 (M+H+) 299.17540, found 299.17489; IR(film): ν [cm⁻¹] = 3395 (m), 3054 (w), 2995 (s), 1727 (vs), 1444 (s), 1319 (m), 1260 (m), 1221 (m), 741 (s).

c: (1R,3S)-methyl 1-cyclopentyl-2-(cyclopentylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate.

1H-NMR (CDCl3, 400 MHz) δ ppm 7.82 (s, 1H), 7.54 (d, 1H, J = 7.7 Hz), 7.32 (d, 1H, J = 8.0 Hz), 7.15 (dt, 2H, J = 7.0 Hz, J = 14.9 Hz), 4.05 (dd, 1H, J = 4.6 Hz, J = 11.5 Hz), 3.80 (s, 3H), 3.50 (d, 1H, J = 9.5 Hz), 3.11 (dd, 1H, J = 11.6 Hz, J = 15.8 Hz), 2.82 (dd, 1H, J = 4.6 Hz, J = 15.9 Hz), 2.44 (dd, 1H, J = 4.0 Hz, J = 12.7 Hz), 2.25-2.02 (m, 4H), 1.96-1.20 (m, 14H), 1.01-0.84 (m, 1H). 13C-NMR (CDCl3, 100 MHz) δ ppm 173.8, 135.8, 135.3, 126.9, 121.5, 119.4, 118.1, 110.6, 107.5, 62.0, 57.1, 53.8, 51.7, 45.5, 38.1, 31.7, 31.1, 30.7, 30.4, 25.5, 25.3, 24.9, 24.3, 19.5; HRMS: m/z (ESI) calc for C24H32N2O2 (M+H⁺) 381.25366, found 381.25362; IR(film): ν [cm⁻¹] = 3395 (m), 2935 (s), 2870 (s), 1740 (vs), 1575 (m), 1451 (s), 1260 (w), 1083 (w), 748 (s).

d: (S)-methyl 2-(cyclopentylmethylamino)-3-(1H-indol-3-yl)propanoate.

1H-NMR (CDCl3, 400 MHz) δ ppm 8.71 (s, 1H), 7.62 (d, 1H, J = 7.8 Hz), 7.29 (d, 1H, J = 8.0 Hz), 7.14 (dt, 2H, J = 7.1 Hz, J = 14.7 Hz), 6.96 (s, 1H), 3.67 (t, 1H, J = 6.8 Hz), 3.64 (s, 3H), 3.17 (qd, 2H, J = 6.7 Hz, J = 14.3 Hz), 2.50 (ddd, 2H, J = 7.3 Hz, J = 10.9 Hz, J = 17.8 Hz), 1.96 (dt, 1H, J = 7.6 Hz, J = 15.1 Hz), 1.76 (bs, 1H), 1.74-1.62 (m, 2H), 1.58-1.42 (m, 4H), 1.14-1.00 (m, 2H). 13C-NMR (CDCl3, 100 MHz) δ ppm 175.4, 136.1, 127.2, 122.9, 121.7, 119.1, 118.4, 111.1, 110.6, 62.3, 53.9, 51.5, 39.8, 30.6, 30.5, 29.1, 25.1; HRMS: m/z (ESI) calc for C18H24N2O2 (M+H⁺) 301.1905, found 301.19067. IR (film): ν [cm⁻¹] = 3152 (m), 2942 (m), 2916 (m), 2863 (m), 2364 (w), 1740 (vs)1457 (s), 1431 (s), 1325 (s), 1221 (m), 1135 (m), 735 (s).
**e:** (S)-methyl 2-(bis(cyclopentylmethyl)amino)-3-(1H-indol-3-yl)propanoate.

\[
{^1}H-NMR (CDCl_3, 400 MHz) \delta \text{ ppm } 8.00 (s, 1H), 7.57 (d, 1H, } J = 7.7 \text{ Hz), 7.32 (d, 1H, } J = 7.9 \text{ Hz), 7.13 (dt, 2H, } J = 7.1 \text{ Hz, } J = 23.4 \text{ Hz), 7.00 (s, 1H), 3.74 (dd, 1H, } J = 4.4 \text{ Hz, } J = 9.7 \text{ Hz), 3.57 (s, 3H), 3.26 (dd, 1H, } J = 10.0 \text{ Hz, } J = 14.1 \text{ Hz), 2.92 (dd, 1H, } J = 3.8 \text{ Hz, } J = 14.1 \text{ Hz), 2.52-2.34 (m, 4H), 2.09-1.97 (m, 2H), 1.72-1.42 (m, 12H), 1.36-1.18 (m, 2H), 1.15-1.04 (m, 2H). \]

\[
{^{13}}C-NMR (CDCl_3, 100 MHz) \delta \text{ ppm } 173.2, 136.1, 127.5, 122.7, 121.8, 119.2, 118.5, 118.9, 112.7, 111.1, 63.3, 56.7, 50.7, 38.2, 30.8, 30.7, 25.5, 25.1, 25.1; \]

HRMS: m/z (ESI) calc for C_{24}H_{35}N_2O_2 (M+H^+) 383.26931, found 383.26895. IR(film): \nu [\text{cm}^{-1}] = 3415 (m), 2948 (s), 2856 (s), 1733 (vs), 1457 (s), 1162 (m), 735 (s).

**a:** (1S,3S)-methyl 1-cyclohexyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate. (Table 10, Entry 9)

The general procedure was followed with (S)-tryptophane methylester (218 mg, 1 mmol), cyclohexen (82 mg, 1 mmol) and Rh(acac)(CO)$_2$ (3.6 mg, 0.01 mmol) in 10 ml of DCM under 50 bar CO and 10 bar H$_2$ at 100 °C for 72 h (Table 1, entry 9). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexan/ethylacetat = 6/1) to give 87 mg (28 %) of a, 109 mg (35 %) of b, 21 mg (5.1 %) of c, 3 mg (1 %) of d, 45 mg (11 %) of e and 15 mg (4.8 %) of f.

\[
a: \quad {^1}H-NMR (CDCl_3, 400 MHz) \delta \text{ ppm } 7.92 (s, 1H), 7.47 (d, 1H, } J = 7.6 \text{ Hz), 7.31 (d, 1H, } J = 7.9 \text{ Hz), 7.12 (dt, 2H, } J = 7.1 \text{ Hz, } J = 14.6 \text{ Hz), 4.14 (d, 1H, } J = 1.6 \text{ Hz), 3.81 (s, 1H), 3.73 (dd, 1H, } J = 4.0 \text{ Hz, } J = 11.1 \text{ Hz), 3.10 (ddd, 1H, } J = 1.3 \text{ Hz, } J = 3.6 \text{ Hz, } J = 14.6 \text{ Hz), 2.82-2.73 (m, 1H), 2.42 (bs, 1H), 1.88-1.64 (m, 6H), 1.50-1.10 (m, 5H); \]

\[
{^{13}}C-NMR (CDCl_3, 100 MHz) \delta \text{ ppm } 173.8, 135.9, 134.7, 127.1, 121.5, 119.4, 117.8, 110.7, 108.9, 57.6, 56.4, 52.1, 42.3, 29.7, 26.8, 26.5, 26.3, 25.9; \]

Analytical data fits with literature$^{108}$

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b: (1R,3S)-methyl 1-cyclohexyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate.

\[
\begin{align*}
(1R,3S)-methyl & \\
& 1-cyclohexyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate.
\end{align*}
\]

\[\text{1H-NMR (CDCl}_3, 400 MHz) \delta \text{ ppm 7.81 (s, 1H), 7.50 (d, 1H, } J = 7.6 \text{ Hz), 7.31 (d, 1H, } J = 7.9 \text{ Hz), 7.13 (dt, 2H, } J = 6.7 \text{ Hz, } J = 14.9 \text{ Hz), 4.06 (d, 1H, } J = 5.0 \text{ Hz), 4.02 (dd, 1H, } J = 5.6 \text{ Hz, } J = 6.6 \text{ Hz), 3.73 (s, 3H), 3.05 (qd, 2H, } J = 6.5 \text{ Hz, } J = 15.7 \text{ Hz, } J = 44.4 \text{ Hz), 2.21 (bs, 1H), 1.85-1.62 (m, 6H), 1.36-1.12 (m, 5H); } \text{13C-NMR (CDCl}_3, 100 MHz) \delta \text{ ppm 174.5, 135.7, 134.5, 127.0, 121.5, 119.3, 117.9, 110.6, 107.7, 55.2, 53.3, 52.0, 43.1, 30.2, 28.4, 26.5, 26.4, 26.3, 24.9. Analytical data fits with literature.}\]

c: (1R,3S)-methyl 1-cyclohexyl-2-(cyclohexylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate.

\[
(1R,3S)-methyl & \\
& 1-cyclohexyl-2-(cyclohexylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate.
\end{align*}
\]

\[\text{1H-NMR (CDCl}_3, 400 MHz) \delta \text{ ppm 7.73 (s, 1H), 7.52 (d, 1H, } J = 7.6 \text{ Hz), 7.30 (d, 1H, } J = 7.9 \text{ Hz), 7.12 (td, 2H, } J = 7.1 \text{ Hz, } J = 22.1 \text{ Hz), 4.00 (dd, 1H, } J = 4.8 \text{ Hz, } J = 10.5 \text{ Hz), 3.74 (s, 3H), 3.39 (d, 1H, } J = 8.5 \text{ Hz), 3.09 (dd, 1H, } J = 10.6 \text{ Hz, } J = 15.8 \text{ Hz), 2.82 (dd, 1H, } J = 4.8 \text{ Hz, } J = 15.9 \text{ Hz), 2.36 (d, 1H, } J = 12.8 \text{ Hz), 2.26-2.12 (m, 3H), 1.94-1.60 (m, 9H), 1.40-1.00 (m, 9H), 0.83-0.70 (m, 2H); } \text{13C-NMR (CDCl}_3, 100 MHz) \delta \text{ ppm 173.8, 135.7, 134.5, 126.9, 121.4, 119.3, 118.0, 110.5, 107.8, 63.2, 57.2, 55.9, 51.7, 42.0, 36.6, 31.6, 31.4, 30.9, 30.7, 26.9, 26.8, 26.5, 26.4, 26.3, 26.2, 26.1, 20.1. HRMS: m\text{/z (ESI) calc for } C_{26}H_{37}N_2O_2 \text{ (M+H\textsuperscript{+}) 409.28496, found 409.28483. IR(film): } \nu [\text{cm}^{-1}] = 3454 (w), 2916 (s), 2850 (s), 1740 (vs), 1451 (s), 1260 (m), 1076 (m), 741 (vs).} \]

d: (S)-methyl 2-(cyclohexylmethylamino)-3-(1H-indol-3-yl)propanoate.

\[
(1R,3S)-methyl & \\
& 1-cyclohexyl-2-(cyclohexylmethylamino)-3-(1H-indol-3-yl)propanoate.
\end{align*}
\]

\[\text{1H-NMR (CDCl}_3, 400 MHz) \delta \text{ ppm 7.73 (s, 1H), 7.52 (d, 1H, } J = 7.6 \text{ Hz), 7.30 (d, 1H, } J = 7.9 \text{ Hz), 7.12 (td, 2H, } J = 7.1 \text{ Hz, } J = 22.1 \text{ Hz), 4.00 (dd, 1H, } J = 4.8 \text{ Hz, } J = 10.5 \text{ Hz), 3.74 (s, 3H), 3.39 (d, 1H, } J = 8.5 \text{ Hz), 3.09 (dd, 1H, } J = 10.6 \text{ Hz, } J = 15.8 \text{ Hz), 2.82 (dd, 1H, } J = 4.8 \text{ Hz, } J = 15.9 \text{ Hz), 2.36 (d, 1H, } J = 12.8 \text{ Hz), 2.26-2.12 (m, 3H), 1.94-1.60 (m, 9H), 1.40-1.00 (m, 9H), 0.83-0.70 (m, 2H); } \text{13C-NMR (CDCl}_3, 100 MHz) \delta \text{ ppm 175.4, 136.0, 127.1, 122.9, 121.6, 118.9, 118.4, 111.1, 110.4, 62.1, 54.7, 51.5, 37.7, 31.01, 30.9, 29.0, 26.3, 25.7, 25.6; HRMS: m\text{/z (ESI) calc for } C_{19}H_{27}N_2O_2 \text{ (M+H\textsuperscript{+}) 315.20670, found 315.20630. IR(film): } \nu [\text{cm}^{-1}] = 3421 (w), 2916 (s), 2850 (s), 1740 (vs), 1451 (s), 1260 (m), 1076 (m), 741 (vs).} \]
6 EXPERIMENTAL SECTION

e: (S)-methyl 2-(bis(cyclohexylmethyl)amino)-3-(1H-indol-3-yl)propanoate.

\[\text{CO}_2\text{Me}\]

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 8.01 (s, 1H), 7.57 (d, 1H, $J = 7.7$ Hz), 7.32 (d, 1H, $J = 8.0$ Hz), 7.14 (dt, 2H, $J = 7.0$ Hz, $J = 22.0$ Hz), 6.97 (d, 1H, $J = 1.9$ Hz), 3.69 (dd, 1H, $J = 4.2$ Hz, $J = 10.1$ Hz), 3.57 (s, 3H), 3.26 (dd, 1H, $J = 10.1$ Hz, $J = 14.1$ Hz), 2.92 (dd, 1H, $J = 4.0$ Hz, $J = 14.1$ Hz), 2.40 (dd, 2H, $J = 9.1$ Hz, $J = 12.9$ Hz), 2.28 (dd, 2H, $J = 5.2$ Hz, $J = 12.9$ Hz), 1.92 (d, 2H, $J = 12.7$ Hz), 1.75-1.61 (m, 8H), 1.43-1.33 (m, 2H), 1.28-1.09 (m, 6H), 0.90-0.75 (m, 4H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 173.2, 136.2, 127.4, 122.6, 121.1, 119.2, 118.4, 112.7, 111.1, 63.4, 58.5, 50.7, 36.2, 31.6, 26.9, 26.2, 26.1, 25.6. HRMS: m/z (ESI) calc for C$_{26}$H$_{39}$N$_2$O$_2$ (M+H$^+$) 411.30061, found 411.30012. IR (film): $\nu$ [cm$^{-1}$] = 3415 (m), 2935 (vs), 2850 (vs), 1740 (vs), 1451 (s), 1352 (w), 1221 (w), 741 (s).

f: (S)-methyl 2-(cyclohexylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate.

\[\text{CO}_2\text{Me}\]

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.76 (s, 1H), 7.45 (d, 1H, $J = 7.4$ Hz), 7.26 (d, 1H, $J = 7.8$ Hz), 7.09 (tt, 2H, $J = 6.7$ Hz, $J = 13.6$ Hz), 4.13 (d, 1H, $J = 15.1$ Hz), 3.90 (d, 1H, $J = 15.1$ Hz), 3.84 (dd, 1H, $J = 4.1$ Hz, $J = 5.9$ Hz), 3.62 (s, 3H), 3.12 (qd, 2H, $J = 4.9$ Hz, $J = 15.5$ Hz), 2.57 (ddd, 2H, $J = 7.1$ Hz, $J = 12.8$ Hz, $J = 20.7$ Hz), 1.87 (d, 1H, $J = 12.7$ Hz), 1.76-1.60 (m, 4H), 1.59-1.47 (m, 1H), 1.30-1.11 (m, 3H), 0.94-0.80 (m, 2H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 173.5, 136.0, 131.9, 127.1, 121.3, 119.2, 117.8, 110.6, 106.2, 61.3, 60.3, 51.4, 46.8, 36.2, 31.6, 26.8, 26.1, 26.0, 23.7; HRMS: m/z (ESI) calc for C$_{20}$H$_{27}$N$_2$O$_2$ (M+H$^+$) 327.20670, found 327.20631; IR (film): $\nu$ [cm$^{-1}$] = 3395 (s), 2935 (s), 2837 (s), 1733 (s), 1628 (w), 1451 (s), 1352 (w), 1221 (w), 741 (s).

a: (1S,3S)-methyl 1-cycloheptyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Table 10, Entry 10)

The general procedure was followed with (S)-tryptophane methylester (218 mg, 1 mmol), cycloheptene (97 mg, 1 mmol) and Rh(acac)(CO)$_2$ (3.6 mg, 0.01 mmol) in 10 ml of DCM under 50 bar CO and 10 bar H$_2$ at 80 °C for 72 h. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexan/ethylacetat = 10/1) to give 101 mg (31 %) of a, 130 mg (40 %) of b and 72 mg (22 %) of c.
**a:** $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.88 (s, 1H), 7.47 (d, 1H, $J$ = 7.6 Hz), 7.32 (d, 1H, $J$ = 7.8 Hz), 7.12 (dt, 2H, $J$ = 7.2 Hz, $J$ = 21.0 Hz), 4.19 (s, 1H), 3.81 (s, 3H), 3.72 (dd, 1H, $J$ = 4.0 Hz, $J$ = 11.1 Hz), 3.10 (dd, 1H, $J$ = 2.5 Hz, $J$ = 14.8 Hz), 2.82-2.72 (m, 1H), 2.05-1.96 (m, 2H), 1.83-1.71 (m, 2H), 1.70-1.28 (m, 12H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 173.8, 135.9, 135.1, 127.2, 121.6, 119.4, 117.8, 1.7, 109.3, 59.2, 56.4, 52.1, 43.3, 31.6, 28.7, 28.1, 27.8, 27.5, 27.5, 25.9; HRMS: m/z (ESI) calc for C$_{20}$H$_{27}$N$_2$O$_2$ (M+H$^+$) 327.20670, found 327.20607; IR(film): ν [cm$^{-1}$] = 3375 (m), 3054 (w), 2922 (s), 1733 (vs), 1464 (s), 1325 (m), 1260 (s), 1214 (m), 754 (m).

**b:** (IR,3S)-methyl 1-cycloheptyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate.

$^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.76 (s, 1H), 7.48 (d, 1H, $J$ = 7.5 Hz), 7.29 (d, 1H, $J$ = 7.8 Hz), 7.11 (dt, 2H, $J$ = 7.1 Hz, $J$ = 20.0 Hz), 4.28 (s, 1H), 4.02 (t, 1H, $J$ = 5.0 Hz), 3.65 (s, 3H), 3.15-3.06 (m, 2H), 2.01-1.92 (m, 2H), 1.91-1.71 (m, 2H), 1.70-1.23 (m, 12H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 174.7, 135.8, 134.4, 127.1, 121.6, 121.5, 119.5, 119.3, 117.9, 117.9, 110.7, 110.6, 108.0, 55.6, 53.9, 51.9, 44.7, 31.8, 29.2, 28.2, 27.8, 27.6, 27.3, 24.2; HRMS: m/z (ESI) calc for C$_{20}$H$_{27}$N$_2$O$_2$ (M+H$^+$) 327.20670, found 327.20607; IR(film): ν [cm$^{-1}$] = 3389 (m), 2929 (s), 2850 (s), 1733 (vs), 1621 (w), 1451 (s), 1339 (m), 1267 (m), 1017 (w), 735 (s).

**c:** (S)-methyl 2-(cycloheptylmethylamino)-3-(1H-indol-3-yl)propanoate.

$^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 8.27 (s, 1H), 7.60 (d, 1H, $J$ = 7.8 Hz), 7.31 (d, 1H, $J$ = 8.0 Hz), 7.13 (dt, 1H, $J$ = 7.2 Hz, $J$ = 25.8 Hz), 7.00 (d, 1H, $J$ = 1.5 Hz), 3.61 (s, 3H), 3.59 (t, 1H, $J$ = 6.7 Hz), 3.13 (qd, 2H, $J$ = 6.7 Hz, $J$ = 14.4 Hz), 2.36 (ddd, 2H, $J$ = 6.8 Hz, $J$ = 11.2 Hz, $J$ = 43.8 Hz), 1.75-1.20 (m, 12H), 1.07 (dd, 2H, $J$ = 10.2 Hz, $J$ = 21.4 Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 175.6, 136.1, 127.4, 122.7, 121.9, 119.3, 118.7, 111.2, 111.1, 62.3, 55.2, 51.6, 39.5, 32.5, 32.3, 29.2, 28.4, 28.4, 26.4, 26.4; HRMS: m/z (ESI) calc for C$_{20}$H$_{27}$N$_2$O$_2$ (M+H$^+$) 329.22235, found 329.22250; IR(film): ν [cm$^{-1}$] = 3408 (m), 2922 (s), 2843 (s), 1733 (vs), 1457 (s), 1352 (m), 1267 (m), 1241 (m), 741 (s).
(S)-methyl 2-(cyclooctylmethylamino)-3-(1H-indol-3-yl)propanoate (Table 10, Entry 11).

The general procedure was followed with (S)-tryptophane methylester (218 mg, 1 mmol), cyclooctene (110 mg, 1 mmol) and Rh(acac)(CO)$_2$ (3.6 mg, 0.01 mmol) in 10 ml of DCM under 50 bar CO and 10 bar H$_2$ at 80 °C for 72 h (Table 1, entry 11).

The crude reaction mixture was purified by flash column chromatography on silica gel (Cyclohexan/Ethylacetat = 10/1) to give 147 mg (43 %) of title compound as brownish oil.

$^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 8.29 (s, 1H), 7.60 (d, 1H, J=7.8Hz), 7.31 (d, 1H, J=8.0Hz), 7.13 (dt, 2H, J=7.1Hz, J=26.3Hz), 7.01 (d, 1H, J=1.8Hz), 3.61 (s, 3H), 3.58 (d, 1H, J=6.7Hz), 3.13 (qd, 2H, J=6.7Hz, J=14.4Hz), 2.40 (dd, 1H, J=7.1Hz, J=11.2Hz), 2.27 (dd, 1H, J=6.4Hz, J=11.1Hz), 2.05-1.80 (m, 2H), 1.65-1.27 (m, 12H), 1.22-1.09 (m, 2H);

$^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 175.5, 136.1, 127.3, 122.8, 121.9, 119.3, 118.7, 111.2, 111.1, 62.3, 55.6, 51.6, 37.5, 30.8, 30.5, 29.2, 26.9, 26.3, 25.5, 25.3; HRMS: m/z (ESI) calc for C$_{21}$H$_{31}$N$_2$O$_2$ (M+H$^+$) 343.23801, found 343.23755; IR(film): ν [cm$^{-1}$] = 3402 (m), 2922 (s), 2850 (s), 2364 (w), 1733 (vs), 1451 (s), 1345 (m), 1194 (m), 1010 (w), 748 (s).

(1S,3S)-methyl 2,3,4,9-tetrahydro-1-((S)-1,2-diphenylethyl)-1H-pyrido[3,4-b]indole-3-carboxylate, (113)

The general procedure was followed with (S)-tryptophane methylester (218 mg, 1 mmol), trans-stilbene (180 mg, 1 mmol) and Rh(acac)(CO)$_2$ (3.6 mg, 0.01 mmol) in 8 ml of DCM.

The crude reaction mixture was purified by flash column chromatography on silica gel (Cyclohexan/Ethylacetat = 10/1) to give 138 mg (34 %) of a and 136 mg (33 %) b, and 169 mg (41 %) of c.

a: $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.66 (bs, 1H), 7.46 (d, 1H, J = 6.5 Hz), 7.35-6.95 (m, 11H), 6.88 (d, 2H, J = 6.7 Hz), 4.54 (d, 1H, J = 7.3 Hz), 3.83 (s, 3H), 3.76 (dd, 1H, J = 3.9 Hz, J = 11.2 Hz), 3.35 (dd, 1H, J = 3.3 Hz, J = 13.5 Hz), 3.25-3.05 (m, 3H), 2.92-2.82 (m, 2H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 173.6, 141.3, 139.8, 135.3, 134.3, 129.0, 128.9, 128.8, 127.9, 127.4, 126.6, 125.7, 121.8, 119.4, 117.9, 110.8, 109.4, 57.7, 56.5, 53.0, 52.2, 37.6, 25.9; HRMS: m/z (ESI) calc for C$_{27}$H$_{27}$N$_2$O$_2$ (M+H$^+$) 411.20670, found 411.20665; IR(film): ν [cm$^{-1}$] = 3415 (m), 2922 (s), 2843 (s), 1700 (vs), 1654 (vs), 1457 (s), 1352 (m), 1260 (vs), 1037 (m), 754 (s).
(1R,3S)-methyl 2,3,4,9-tetrahydro-1-((R)-1,2-diphenylethyl)-1H-pyrido[3,4-b]indole-3-carboxylate, (113)

**b:** $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.55 (s, 1H), 7.43 (d, 1H, J=8.0Hz), 7.40-7.0 (m, 11H), 6.93 (d, 2H, J=6.8Hz), 4.47 (d, 1H, J=9.2Hz), 4.02 (dd, 1H, J=5.1Hz, J=8.3Hz), 3.76 (s, 3H), 3.54 (dd, 1H, J=3.5Hz, J=13.6Hz), 3.19 (td, 1H, J=3.7Hz, J=13.6Hz), 3.13 (dd, 1H, J=4.9Hz, J=15.4Hz), 3.04-2.90 (m, 2H), 2.11 (bs, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 174.3, 142.1, 140.3, 135.6, 134.5, 129.2, 129.0, 128.9, 128.1, 127.3, 126.6, 125.8, 121.8, 119.3, 118.0, 110.7, 108.1, 55.9, 53.1, 52.5, 52.3, 39.1, 25.7; HRMS: m/z (ESI) calc for C$_{27}$H$_{27}$N$_2$O$_2$ (M+H$^+$) 411.20670, found 411.20676; IR(film): ν [cm$^{-1}$] = 3435 (m), 2922 (s), 2847 (s), 1720 (vs), 1624 (vs), 1457 (s), 1352 (m), 1267 (vs), 1024 (w), 728 (s).

(S)-methyl 2-(2,3-diphenylpropylamino)-3-(1H-indol-3-yl)propanoate, (113)

**c:** $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 8.04, 7.97 (2s, 1H), 7.54 (t, 1H, J = 6.9 Hz), 7.28 (dd, 1H, J = 4.2 Hz, J = 8.0 Hz), 7.22-7.06 (m, 8H), 7.03 (d, 1H, J = 6.9 Hz), 6.98 (t, 1H, J = 6.7 Hz), 6.89 (d, 1H, J = 6.5 Hz), 6.82, 6.72 (2d, 1H, J = 1.7 Hz), 3.62-3.50 (m, 4H), 3.13 (dd, 0.5H, J = 5.4 Hz, J = 14.4 Hz), 3.08-2.70 (m, 6H), 2.64 (dd, 0.5H, J = 7.9 Hz, J = 10.9 Hz). $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 175.0, 174.9, 142.8, 142.5, 140.0, 139.9, 136.1, 136.0, 129.0, 128.9, 128.3, 128.2, 128.0, 127.9, 127.7, 127.7, 127.3, 127.1, 126.4, 126.3, 125.8, 125.7, 122.8, 122.6, 122.0, 121.9, 119.3, 118.6, 118.6, 111.1, 111.1, 111.0, 110.9, 77.3, 77.0, 76.7, 62.1, 62.0, 52.9, 52.3, 51.7, 51.6, 47.7, 47.6, 41.2, 40.6, 29.2, 28.7; HRMS: m/z (ESI) calc for C$_{27}$H$_{29}$N$_2$O$_2$ (M+H$^+$) 413.22235, found 413.22195; IR(film): ν [cm$^{-1}$] = 3428 (m), 3034 (m), 2922 (m), 2850 (m), 2370 (w), 1937 (w), 1733 (vs), 1464 (s), 1208 (m), 741 (s), 659 (s).

(S)-methyl 2,3,4,9-tetrahydro-1-(2,2-diphenylethyl)-1H-pyrido[3,4-b]indole-3-carboxylate, (115)

The general procedure was followed with (S)-tryptophane methylester (218 mg, 1 mmol), 1,1’-diphenylethylene (180 mg, 1 mmol) and Rh(acac)(CO)$_2$ (3.6 mg, 0.01 mmol) in 8 ml of DCM. The crude reaction mixture was purified by flash column chromatography on silica gel (Cyclohexan/Ethylacetat = 10/1) to give 275 mg (67 %) of 115 and 72 mg (17 %) of 116. $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.56 (s, 1H), 7.46 (s, 1H), 7.44 (d, 2H, J = 7.7 Hz), 7.38-7.04 (m, 26H), 4.42-4.34 (m, 2H), 4.10-4.00 (m, 2H),
3.91 (dd, 1H, J = 4.9 Hz, J = 9.1 Hz), 3.78 (s, 3H), 3.73 (s, 3H), 3.63 (dd, 1H, J = 4.2 Hz, J = 11.1 Hz), 3.06 (dd, 2H, J = 4.5 Hz, J = 15.3 Hz), 2.80 (dd, 2H, J = 10.2 Hz, J = 14.6 Hz), 2.74-2.66 (m, 1H), 2.48-2.41 (m, 2H), 2.35 (ddd, 1H, J = 4.7 Hz, J = 9.0 Hz, J = 13.7 Hz), 1.82 (bs, 2H); 13C-NMR (CDCl$_3$, 100 MHz) δ ppm 174.1, 173.6, 144.6, 144.5, 144.3, 143.6, 135.9, 135.7, 135.5, 135.3, 128.7, 128.8, 128.6, 128.5, 128.2, 127.7, 127.6, 127.1, 126.9, 126.7, 126.6, 126.3, 121.8, 119.6, 119.5, 117.9, 110.7, 110.7, 108., 107.2, 56.4, 52.1, 52.0, 51.9, 51.1, 48.6, 47.8, 47.4, 41.4, 41.3, 25.9, 25.6; HRMS: m/z (ESI) calc for C$_{27}$H$_{27}$N$_2$O$_2$ (M+H$^+$) 411.20670, found 411.20654; IR(film): ν [cm$^{-1}$] = 3054 (m), 2916 (m), 2850 (m), 1950 (w), 1815 (w), 1733 (vs), 1680 (s) 1490 (s), 1425 (s), 1345 (m), 1260 (vs), 1010 (m), 754 (s), 708 (s).

(S)-methyl 2-(3,3-diphenylpropylamino)-3-(1H-indol-3-yl)propanoate, (116)

In a thick walled sample vial containing PTFE septum tryptamine (1 equiv.), olefin (1 equiv.), Rh(acac)(CO)$_2$ (0.01 equiv.), and Brønsted acid (1 equiv.) were dissolved in dry solvent (8 mL). The vial was placed in a pressure vessel, flushed with argon and pressurized with 50 bar CO and 10 bar H$_2$. The reaction mixture was stirred for 3 days at 80 °C or 110 °C. Reaction was quenched with ammonia solution (30% in water) and the aqueous phase was extracted with 4x10 mL DCM. The combined organic layers were washed with brine,
dried over MgSO$_4$, filtered and volatiles were removed in vacuo. The crude reaction mixture was purified by column chromatography on silica gel (DCM/MeOH) to give the desired product.

1-Cyclopentyl-2,3,4,9-tetrahydro-1H-b-carboline, (101a), (Table 12, Entry 1)

The general procedure was followed with tryptamine (160 mg, 1 mmol), cyclopenten (68 mg, 1 mmol), Rh(acac)(CO)$_2$ (3.6 mg, 0.01 mmol) and camphor sulphonic acid (218 mg, 1 mmol) in 8 ml of DCM. The crude reaction mixture was purified by column chromatography on silica gel (DCM/MeOH) to give (156 mg, 65 % yield) of the title compound as yellowish oil; $^1$H-NMR (CDCl$_3$, 500 MHz) δ ppm 7.99 (s, 1H), 7.50 (d, 1H, $J$ = 7.7 Hz), 7.32 (d, 1H, $J$ = 7.9 Hz), 7.14 (dt, 2H, $J$ = 7.3 Hz, $J$ = 26.4 Hz), 3.93 (d, 1H, $J$ = 7.4 Hz), 3.37 (dt, 1H, $J$ = 4.7 Hz, $J$ = 12.5 Hz), 3.06-3.00 (m, 1H), 2.82-2.72 (m, 2H), 2.41 (bs, 1H), 2.27 (q, 1H, $J$ = 7.4 Hz), 2.00-1.92 (m, 1H), 1.84 (ddt, 1H, $J$ = 3.7 Hz, $J$ = 7.6 Hz, $J$ = 11.5 Hz), 1.79-1.50 (m, 6H), 1.38 (dd, 1H, $J$ = 8.6 Hz, $J$ = 12.4 Hz, $J$ = 17.7 Hz); $^{13}$C-NMR (CDCl$_3$, 125 MHz) δ ppm 135.9, 135.5, 127.2, 121.4, 119.2, 117.9, 110.6, 109.1, 56.9, 44.4, 42.3, 29.8, 29.3, 25.8, 25.2, 22.5; HRMS: m/z (FAB) calc for C$_{16}$H$_{21}$N$_2$ (M+H$^+$) 241.1699, found 241.1686; IR(film): ν [cm$^{-1}$] = 3421 (m), 3224 (m), 3047 (m), 2955 (m), 2581 (w), 2475 (w), 1667 (m), 1646 (s), 1418 (s), 1300 (s), 1254 (s), 1004 (m), 741 (vs).

1-Cyclohexyl-2,3,4,9-tetrahydro-1H-b-carboline, (101b), (Table 12, Entry 2)

The general procedure was followed with tryptamine (160 mg, 1 mmol), cyclohexen (82 mg, 1 mmol), Rh(acac)(CO)$_2$ (3.6 mg, 0.01 mmol) and camphorsulphonic acid (218 mg, 1 mmol) in 8 ml of DCM at 110 °C for 72 h. The crude reaction mixture was purified by flash column chromatography on silica gel (DCM/MeOH/triethylamine = 20/1/0.1) to give (117 mg, 46 % yield) of the title compound as brown oil; $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.81 (s, 1H), 7.39 (d, 1H, $J$ = 7.6 Hz), 7.22 (d, 1H, $J$ = 7.8 Hz), 7.02 (dt, 2H, $J$ = 7.1 Hz, $J$ = 14.9 Hz), 3.89 (s, 1H), 3.27 (dt, 1H, $J$ = 4.3 Hz, $J$ = 12.5 Hz), 2.92-2.83 (m, 1H), 2.70-2.56 (m, 2H), 1.80-1.00 (m, 11H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 135.5, 135.2, 127.5, 121.3,
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119.2, 117.9, 110.6, 109.9, 57.7, 43.0, 42.2, 30.2, 27.5, 26.9, 26.8, 26.4, 26.5, 22.7. Analytical data fits with literature.\textsuperscript{109}

1-Cycloheptyl-2,3,4,9-tetrahydro-1H-b-carboline, (101c), (Table 12, Entry 3)

The general procedure was followed with tryptamine (160 mg, 1 mmol), cyclohepten (96 mg, 1 mmol), Rh(acac)(CO)\textsubscript{2} (3.6 mg, 0.01 mmol) and camphorsulphonic acid (218 mg, 1 mmol) in 8 ml of DCM. The crude reaction mixture was purified by flash column chromatography on silica gel (DCM/MeOH/triethylamine = 20/1/0.1) to give (182 mg, 68 \% yield) of the title compound as brown oil; \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) $\delta$ ppm 7.89 (s, 1H), 7.48 (d, 1H, $J$ = 7.6 Hz), 7.31 (d, 1H, $J$ = 7.9 Hz), 7.12 (dt, 2H, $J$ = 7.3 Hz, $J$ = 25.2 Hz), 4.10 (s, 1H), 3.40 (ddd, 1H, $J$ = 1.8 Hz, $J$ = 4.5 Hz, $J$ = 12.0 Hz), 2.94 (ddd, 1H, $J$ = 5.0 Hz, $J$ = 10.1 Hz, $J$ = 12.5 Hz), 2.80-2.64 (m, 2H), 2.16 (bs, 1H), 2.02-1.93 (m, 1H), 1.84-1.28 (m, 12H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 100 MHz) $\delta$ ppm 135.6, 135.3, 127.5, 121.3, 119.2, 117.9, 110.6, 110.3, 59.3, 43.6, 43.3, 32.0, 28.7, 28.2, 27.7, 27.5, 22.6; HRMS: m/z (FAB) calc for C\textsubscript{18}H\textsubscript{25}N\textsubscript{2} (M+H\textsuperscript{+}) 269.2012, found 269.1997; IR(film): $\nu$ [cm\textsuperscript{-1}] = 3415 (m), 3283 (m), 2935 (m), 2364 (w), 1917 (w), 1674 (s), 1608 (s), 1464 (s), 1319 (m), 1201 (m), 991 (m), 748 (s).

1-Cyclooctyl-2,3,4,9-tetrahydro-1H-b-carboline, (101d), (Table 12, Entry 4)

The general procedure was followed with tryptamine (160 mg, 1 mmol), cycloocten (110 mg, 1 mmol), Rh(acac)(CO)\textsubscript{2} (3.6 mg, 0.01 mmol) and camphorsulphonic acid (218 mg, 1 mmol) in 8 ml of DCM. The crude reaction mixture was purified by flash column chromatography on silica gel (DCM/MeOH/triethylamine = 20/1/0.1) to give (166 mg, 59 \% yield) of the title compound as brown oil; \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) $\delta$ ppm 8.04 (s, 1H) ppm 7.51 (d, 1H, $J$ = 7.6 Hz), 7.33 (d, 1H, $J$ = 7.8 Hz), 7.15 (dt, 2H, $J$ = 6.9 Hz, $J$ = 20.2 Hz), 4.08 (s, 1H), 3.42 (ddd, 1H, $J$ = 2.0 Hz, $J$ = 4.5 Hz, $J$ = 12.0 Hz), 2.95 (ddd, 1H, $J$ = 5.0 Hz, $J$ = 10.0 Hz, $J$ = 12.5 Hz), 2.83-2.68 (m, 2H), 2.24-2.02 (m, 1H), 1.86-1.30 (m, 14H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 100 MHz) $\delta$ ppm 135.6, 135.3, 127.4, 121.2, 119.1, 117.8, 110.6, 110.4, 60.1, 43.5, 41.2, 31.7, 27.9, 27.4, 26.6, 25.6, 25.5, 22.6; HRMS: m/z (FAB) calc for C\textsubscript{19}H\textsubscript{25}N\textsubscript{2} (M-H\textsuperscript{+}) 281.2023, found 281.1996; IR(film): $\nu$ [cm\textsuperscript{-1}] = 3415 (m), 3283 (m), 2935 (m), 2364 (w), 1917 (w), 1674 (s), 1608 (s), 1464 (s), 1319 (m), 1201 (m), 991 (m), 748 (s).

The general procedure was followed with tryptamine (160 mg, 1 mmol), 1,1'-diphenylethen (180 mg, 1 mmol), Rh(acac)(CO)$_2$ (3.6 mg, 0.01 mmol) and camphorsulphonic acid (218 mg, 1 mmol) in 8 ml of DCM. The crude reaction mixture was purified by flash column chromatography on silica gel (DCM/MeOH/triethylamine = 10/1/0.1) to give (229 mg, 64 % yield) of the title compound as white solid; $^1$H-NMR (DMSO D$_6$, 400 MHz) δ ppm 10.78 (s, 1H), 7.53 (d, 2H, $J = 7.3$ Hz), 7.37-7.30 (m, 6H), 7.26 (t, 2H, $J = 7.7$ Hz), 7.19 (t, 1H, $J = 7.4$ Hz), 7.13 (t, 1H, $J = 7.3$ Hz), 7.02 (t, 1H, $J = 8.0$ Hz), 6.93 (t, 1H, $J = 7.4$ Hz), 4.51 (dd, 1H, $J = 3.3$ Hz, $J = 12.0$ Hz), 3.68 (d, 1H, $J = 10.7$ Hz), 3.41 (bs, 1H), 3.12 (dt, 1H, $J = 4.8$ Hz, $J = 12.6$ Hz), 3.00-2.93 (m, 1H), 2.76 (ddd, 1H, $J = 5.0$ Hz, $J = 7.4$ Hz, $J = 12.6$ Hz), 2.62-2.49 (m, 2H), 2.03-1.94 (m, 1H); $^{13}$C-NMR (DMSO D$_6$, 100 MHz) δ ppm 146.1, 143.7, 137.3, 135.5, 128.3, 128.2, 128.1, 127.3, 127.1, 126.0, 125.7, 120.2, 118.0, 117.2, 110.7, 107.2, 49.7, 46.4, 41.4, 39.5, 22.4; HRMS: m/z (FAB) calc for C$_{25}$H$_{25}$N$_2$ (M+H$^+$) 353.2012, found 353.2032; IR(film): ν [cm$^{-1}$] = 3375 (m), 2929 (m), 2909 (m), 1602 (w), 1490 (s), 1464 (m), 1345 (m), 1313 (w), 1120 (s), 1010 (m), 741 (vs).
C_{25}H_{25}N_2 (M+H\textsuperscript{+}) 353.2012, found 353.2011; IR(film): ν [cm\textsuperscript{-1}] = 3421 (m), 3290 (w), 3054 (m), 2962 (s), 2922 (s), 2344 (w9, 1871 (w), 1700 (m), 1602 (m), 1541 (vs), 1267 (m), 1102 (m), 1004 (m), 740 (vs).

N-Ethyl-4-methyl-N-[2-methyl-3-(2,3,4,9-tetrahydro-1H-b-carbolin-1-yl)-propyl]-benzene sulfonamide, (101g), (Table 12, Entry 7)

The general procedure was followed with tryptamine (160 mg, 1 mmol), N-Ethyl-4-methyl-N-(2-methyl-allyl)-benzenesulfonamide (253 mg, 1 mmol), Rh(acac)(CO)\textsubscript{2} (3.6 mg, 0.01 mmol) and camphor sulphonnic acid (218 mg, 1 mmol) in 8 ml of DCM. The crude reaction mixture was purified by flash column chromatography on silica gel (DCM/MeOH/triethylamine = 9/1/0.1) to give (315 mg, 74 % yield) of the title compound as yellowish oil. $^1$H-NMR (CDCl\textsubscript{3}, 400 MHz) δ ppm 8.37 (s, 1H), 7.66 (d, 2H, $J = 8.1$ Hz), 7.45 (d, 1H, $J = 7.6$ Hz), 7.32 (d, 1H, $J = 7.9$ Hz), 7.24 (d, 2H, $J = 8.0$ Hz), 7.09 (dt, 2H, $J = 7.1$ Hz, $J = 14.6$ Hz), 4.16 (d, 1H, $J = 5.2$ Hz), 3.31-3.12 (m, 4H), 3.00 (td, 1H, $J = 6.3$ Hz, $J = 12.9$ Hz), 2.83 (dd, 1H, $J = 7.2$ Hz, $J = 13.7$ Hz), 2.73-2.67 (m, 2H), 2.37 (s, 3H), 2.24-2.15 (m, 1H), 1.94 (bs, 1H), 1.81 (ddd, 1H, $J = 4.4$ Hz, $J = 9.3$ Hz, $J = 13.8$ Hz), 1.64-1.59 (m, 1H), 1.01 (dd, 6H, $J = 6.9$ Hz, $J = 16.4$ Hz); $^{13}$C-NMR (CDCl\textsubscript{3}, 100 MHz) δ ppm 143.2, 136.9, 136.3, 135.7, 129.6, 127.4, 127.1, 121.4, 119.2, 117.9, 110.9, 108.8, 53.8, 49.9, 43.3, 42.1, 39.1, 28.8, 22.8, 21.4, 18.0, 13.4; HRMS: m/z (FAB) calc for C_{24}H_{32}N_3O_2S (M+H\textsuperscript{+}) 426.2215, found 426.2224; IR(film): ν [cm\textsuperscript{-1}] = 3380 (s), 2925 (s), 1448 (vs), 1132 (vs), 1080 (m), 745 (s).

2-[2-Methyl-3-(2,3,4,9-tetrahydro-1H-b-carbolin-1-yl)-propyl]-isoindole-1,3-dione, (101h), (Table 12, Entry 8)

The general procedure was followed with tryptamine (160 mg, 1 mmol), 2-(2-Methyl-allyl)-isoindole-1,3-dione (201 mg, 1 mmol), Rh(acac)(CO)\textsubscript{2} (3.6 mg, 0.01 mmol) and camphor sulphonic acid (218 mg, 1 mmol) in 8 ml of DCM. The crude reaction mixture was purified by flash column chromatography on silica gel (DCM/MeOH/triethylamine = 9/1/0.1) to give (307 mg, 82 % yield) of the title compound as yellow solid. $^1$H-NMR (CDCl\textsubscript{3}, 500 MHz) δ ppm 8.99, 8.64 (2s, 1H), 7.86 (dq, 2H, $J = 3.0$ Hz, $J = 5.4$ Hz, $J = 13.0$ Hz), 7.71 (ddd, 2H, $J = 3.0$ Hz, $J = 5.5$ Hz, $J = 8.4$ Hz), 7.47 (d, 1H, $J = 7.7$ Hz), 7.39 (dd,
1H, J = 8.0 Hz, J = 12.6 Hz), 7.15 (ddd, 1H, J = 1.5 Hz, J = 3.2 Hz, J = 9.2 Hz), 7.08 (t, 1H, J = 7.4 Hz), 4.25, 4.20 (dd, J = 3.0 Hz, J = 9.0 Hz; t, J = 7.4 Hz, 1H), 3.77 (d, 1H, J = 5.2 Hz), 3.71 (dd, 1H, J = 5.6 Hz, J = 13.7 Hz), 3.58 (dd, 1H, J = 8.8 Hz, J = 13.7 Hz), 3.30-3.26 (m, 1H), 3.09-3.01 (m, 1H), 2.72 (t, 2H, J = 5.7 Hz), 2.40-2.31 (m, 1H), 2.12 (bs, 1H), 1.85-1.70, 1.60-1.54 (2m, 1H), 1.01 (d, 3H, J = 6.8 Hz); 13C-NMR (CDCl3, 100 MHz) δ ppm 169.3, 168.7, 136.4, 135.8, 135.7, 133.9, 131.8, 127.2, 123.2, 121.3, 121.2, 119.0, 117.8, 110.9, 110.8, 108.6, 50.3, 49.4, 43.6, 42.4, 41.4, 41.254, 40.2, 40.1, 30.5, 29.6, 22.7, 19.3, 18.2; HRMS: m/z (ESI) calc for C23H24N2O3 (M+H +) 374.18630, found 374.18575; IR(film): ν [cm⁻¹] = 3395(s), 3054 (m), 2942 (s), 1772 (vs), 1713 (vs), 1621 (w), 1470 (s), 1267 (m), 1043 (vs), 748 (vs).

1-(3-Benzoyloxy-2-methyl-propyl)-2,3,4,9-tetrahydro-1H-b-carboline, (101i), (Table 12, Entry 9)

The general procedure was followed with tryptamine (160 mg, 1 mmol), (2-Methyl-allyloxymethyl)-benzene (162 mg, 1 mmol), Rh(acac)(CO)2 (3.6 mg, 0.01 mmol) and camphor sulphonicacid (218 mg, 1 mmol) in 8 ml of DCM. The crude reaction mixture was purified by flash column chromatography on silica gel (DCM/MeOH/triethylamine = 10/1/0.1) to give (171 mg, 51 % yield) of the title compound as yellow oil; 1H-NMR (CDCl3, 400 MHz) δ ppm 8.64 (s, 1H), 7.45 (d, 1H, J = 7.4 Hz), 7.37-7.26 (m, 5H), 7.12-7.02 (m, 1H), 4.53 (d, 1H, J = 1.1 Hz) ppm 4.25 (t, 1H, J = 6.9 Hz), 3.48 (dd, 1H, J = 4.1 Hz, J = 9.0 Hz), 3.39 (t, 1H, J = 8.7 Hz), 3.32-3.25 (m, 1H), 3.09-3.01 (m, 1H), 2.75-2.60 (m, 3H), 2.17-2.08 (m, 1H), 1.82 (td, 2H, J = 3.1 Hz, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz); 13C-NMR (CDCl3, 100 MHz) δ ppm 137.8, 136.2, 135.4, 128.5, 127.8, 127.3, 121.2, 118.9, 117.8, 110.7, 108.1, 76.8, 73.4, 50.1, 41.2, 40.6, 30.3, 22.5, 17.9; HRMS: m/z (FAB) calc for C22H26N2O (M+H +) 355.2118, found 355.2095; IR(film): ν [cm⁻¹] = 3395(s), 3054 (m), 2942 (s), 1772 (vs), 1713 (vs), 1621 (w), 1470 (s), 1267 (m), 1043 (vs), 748 (vs).

2,3,4,9-tetrahydro-1-isobutyl-1H-pyrido[3,4-b]indole, (117)

This compound was obtained as a byproduct in the syntheses of the 101 g-i, in the yields of 10-15%. 1H-NMR (CDCl3, 400 MHz) δ ppm 7.89 (s, 1H), 7.49 (d, 1H, J = 7.5 Hz), 7.27 (d, 1H, J = 7.8 Hz), 7.12 (ddd, 2H, J = 7.1 Hz, J = 14.2 Hz, J = 14.8 Hz), 4.10 (dd, 1H, J = 6.1 Hz, J = 7.7 Hz), 3.34 (dt, 1H, J = 4.6 Hz, J = 12.7 Hz), 3.02 (ddd, 1H, J = 4.5 Hz, J = 7.9 Hz, J = 14.8 Hz), 2.870 (m), 1713 (m), 1621 (m), 1451 (m), 1109 (s), 735 (s).
2.80-2.68 (m, 2H), 2.05-1.90 (m, 1H), 1.73 (bs, 1H), 1.64-1.54 (m, 2H), 1.01 (dd, 6H, J = 6.6 Hz, J = 12.1 Hz), $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 136.7, 135.5, 127.5, 121.3, 119.2, 117.9, 110.6, 108.6, 50.4, 44.3, 42.4, 24.5, 23.8, 22.7, 21.6. Analytical data fits with literature.$^{110}$

2-Benzyl-1-cyclopentyl-2, 3, 4, 9-tetrahydro-1H-b-carboline, (118)

1-Cyclopentyl-2,3,4,9-tetrahydro-1H-b-carboline (480 mg, 2 mmol), Et$_3$N (202 mg, 0.26 mL, 2 mmol) and benzylbromide (342 mg, 0.24 mL, 2 mmol) were dissolved in dry DMF (4 ml) and the mixture was stirred under argon stream at room temperature for 1h. After this time reaction mixture was diluted with water and extracted with 4x10 ml DCM. Collected organic extracts were washed with brine, dried over MgSO$_4$, filtered and evaporated. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate= 9/1) to give the title compound (562 mg, 85 % yield) as yellow oil; $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.68 (s, 1H), 7.55 (d, 1H, J = 7.6 Hz), 7.40-7.22 (m, 6H), 7.16 (dt, 2H, J = 7.3 Hz, J = 26.4 Hz), 3.81 (d, 1H, J = 13.4 Hz), 3.64 (d, 1H, J = 13.4 Hz), 3.35 (ddd, 1H, J = 5.2 Hz, J = 11.6 Hz, J = 13.6 Hz), 3.27 (d, 1H, J = 9.7 Hz), 3.07 (dd, 1H, J = 5.8 Hz, J = 13.9 Hz), 3.03-2.93 (m, 1H), 2.54 (dd, 1H, J = 5.0 Hz, J = 15.8 Hz), 2.29-2.18 (m, 1H), 2.24 (q, 1H, J = 7.4 Hz ), 1.83-1.42 (m, 4H), 1.39-1.22 (m, 2H), 0.92-0.8 (m, 2H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 140.0, 135.5, 135.4, 129.0, 128.0, 127.2, 126.8, 121.3, 119.2, 118.0, 110.6, 107.2, 61.6, 57.1, 45.8, 43.6, 31.4, 31.1, 25.4, 24.3, 16.9; HRMS: m/z (FAB) calc for C$_{23}$H$_{27}$N$_2$ (M+H$^+$) 331.2169, found 331.2189; IR(film): ν [cm$^{-1}$] = 3419(m), 2917(m), 1539(vs), 1452(s), 1321(s), 1142(s), 808 (s).

2-Benzyl-3-cyclopentyl-1,2,3,4-tetrahydro-pyrrolo[3,4-b]quinolin-9-one, (119)

2-benzyl-1-cyclopentyl-2, 3, 4, 9-tetrahydro-1H-b-carboline (120 mg, 0.34 mmol) and KOBu (76 mg, 0.68 mmol) were dissolved in 12 ml of DMF. Oxygen was bubbled through reaction mixture for 5h at room temperature. After this time reaction mixture was diluted with water and extracted with 4x10 ml DCM. Collected organic extracts were washed with brine, dried over MgSO$_4$, filtered and evaporated. The crude reaction mixture

was purified by column chromatography on silica gel (cyclohexane/ethylacetate= 9/1) to give the title compound (63 mg, 54 % yield) as yellowish solid; \(^1\text{H}-\text{NMR} (\text{DMSO D}_6, 400 \text{ MHz}) \delta \text{ ppm} \ 11.80 \ (s, 1\text{H}), \ 8.07 \ (d, 1\text{H}, J = 8.0 \text{ Hz}), \ 7.63-7.56 \ (m, 2\text{H}), \ 7.40-7.31 \ (m, 4\text{H}), \ 7.29-7.20 \ (m, 2\text{H}), \ 4.34 \ (s, 1\text{H}), \ 3.99 \ (d, 1\text{H}, J = 13.8 \text{ Hz}), \ 3.94 \ (dd, 1\text{H}, J = 2.4 \text{ Hz}, J = 13.5 \text{ Hz}), \ 3.75 \ (d, 1\text{H}, J = 13.8 \text{ Hz}), \ 3.49 \ (d, 1\text{H}, J = 13.4 \text{ Hz}), \ 2.45-2.37 \ (m, 1\text{H}), \ 1.70-1.22 \ (m, 8\text{H}); \ ^{13}\text{C}-\text{NMR} (\text{DMSO D}_6, 100 \text{ MHz}) \delta \text{ ppm} \ 173.1, \ 152.5, \ 140.5, \ 139.7, \ 130.9, \ 128.2, \ 128.1, \ 126.8, \ 125.0, \ 124.6, \ 122.6, \ 118.2, \ 115.8, \ 70.2, \ 61.9, \ 56.6, \ 43.9, \ 28.42, \ 25.9, \ 25.2, \ 24.4; \text{HRMS: m/z (FAB) calc for C}_{23}\text{H}_{25}\text{N}_{2}\text{O (M+H\textsuperscript{+}) 345.1961, found 345.1941; IR(film): v [cm}^{-1} = 3441 (m), 3067 (w), 2942 (m), 2870 (w), 2784 (w), 1621 (s), 1562 (s), 1503 (vs), 1365 (m), 754 (m), 721 (m).}

**2-Benzyl-1-(2,2-diphenyl-ethyl)-2,3,4,9-tetrahydro-1H-b-carboline, (120)***

\[
\begin{align*}
\text{N} & \quad \text{NBn} \\
\text{N} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{H} & \quad \text{H}
\end{align*}
\]

1-(2,2-Diphenyl-ethyl)-2,3,4,9-tetrahydro-1H-b-carboline (250 mg, 0.71 mmol), Et\(_3\)N (79 mg, 104 µL, 0.78 mmol) and benzylbromid (133 mg, 93 µL, 0.78 mmol) were dissolved in dry DMF (4 ml) and the mixture was stirred under argon stream at room temperature for 2h. After this time reaction mixture was diluted with water and extracted with 4x10 ml DCM. Collected organic extracts were washed with brine, dried over MgSO\(_4\), filtered and evaporated. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate= 9/1) to give the title compound (280 mg, 88 % yield) as yellow oil; \(^1\text{H}-\text{NMR} (\text{CDCl}_3, 400 \text{ MHz}) \delta \text{ ppm} \ 7.60 \ (d, 1\text{H}, J = 7.3 \text{ Hz}), \ 7.50-7.18 \ (m, 17\text{H}), \ 7.15 \ (d, 2\text{H}, J = 7.1 \text{ Hz}), \ 4.44 \ (dd, 1\text{H}, J = 4.4 \text{ Hz}, J = 10.5 \text{ Hz}), \ 3.87 \ (d, 1\text{H}, J = 13.2 \text{ Hz}), \ 3.69-3.62 \ (m, 2\text{H}), \ 3.35 \ (ddd, 1\text{H}, J = 4.8 \text{ Hz}, J = 11.7 \text{ Hz}, J = 13.9 \text{ Hz}), \ 3.13 \ (dd, 1\text{H}, J = 5.2 \text{ Hz}, J = 13.9 \text{ Hz}), \ 3.06-2.95 \ (m, 1\text{H}), \ 2.70-2.55 \ (m, 2\text{H}), \ 2.50-2.42 \ (m, 1\text{H}); \ ^{13}\text{C}-\text{NMR} (\text{CDCl}_3, 100 \text{ MHz}) \delta \text{ ppm} \ 144.9, \ 144.8, \ 139.7, \ 135.6, \ 134.9, \ 129.2, \ 128.6, \ 128.4, \ 128.3, \ 128.2, \ 127.7, \ 127.2, \ 127.0, \ 126.2, \ 126.0, \ 121.4, \ 119.2, \ 117.9, \ 110.6, \ 107.4, \ 57.2, \ 54.4, \ 47.8, \ 42.9, \ 41.7, \ 16.8; \text{HRMS: m/z (FAB) calc for C}_{32}\text{H}_{31}\text{N}_{2}\text{ (M+H\textsuperscript{+}) 443.2482, found 443.2501; IR(film): v [cm}^{-1} = 3248 (m), 3054 (m), 3021 (m), 2935 (m), 2364 (w), 1963 (w), 1864 (w), 1694 (m), 1503 (s), 1444 (s), 1339 (m), 1116 (m), 1004 (m), 741 (vs), 695 (vs).}
2-Benzyl-3-(2, 2-diphenyl-ethyl)-1,2,3,4-tetrahydro-quinolin-9-one, (121)

2-Benzyl-1-(2,2-diphenyl-ethyl)-2,3,4,9-tetrahydro-1H-b-carboline (110 mg, 0.25 mmol) and KOtBu (56 mg, 0.50 mmol) were dissolved in 10 ml of DMF. Oxygen was bubbled through reaction mixture for 5h at room temperature. After this time reaction mixture was diluted with water and extracted with 4x10 ml DCM. Collected organic extracts were washed with brine, dried over MgSO₄, filtered and evaporated. The crude reaction mixture was purified by column chromatography on silica gel (DCM/MeOH = 20/1) to give the title compound (55 mg, 48 % yield) as white solid; ¹H-NMR (DMSO D₆, 400 MHz) δ ppm 11.66 (s, 1H), 7.98 (d, 1H, J = 7.8 Hz), 7.60-7.02 (m, 17H), 6.86 (t, 1H, J = 6.8 Hz), 4.42 (s, 1H), 4.18 (s, 1H), 3.84 (t, 2H, J = 14.8 Hz), 3.51 (d, 1H, J = 13.1 Hz), 3.40 (d, 1H, J = 13.0 Hz), 2.81-2.72 (m, 1H), 2.45-2.36 (m, 1H); ¹³C-NMR (DMSO D₆, 100 MHz) δ ppm 172.9, 152.0, 145.2, 144.6, 140.3, 139.2, 130.8, 128.5, 128.4, 128.2, 127.9, 127.7, 127.5, 126.9, 126.0, 125.6, 125.02, 124.5, 122.5, 118.1, 115.5, 66.6, 59.3, 54.9, 46.7, 38.2; HRMS: m/z (FAB) calc for C₃₂H₂₉N₂O (M+H⁺) 457.2274, found 457.2273; IR(film): ν [cm⁻¹] = 3435 (m), 2364 (vs), 2331 (s), 1621 (m), 1569 (m), 1490 (m), 761 (w), 659 (m).

N-(cyclopentylmethyl)-2-phenylethylamine, (124)

The general procedure was followed with phenethylamine (120 mg, 1 mmol), cyclopentene (70 mg, 1 mmol), Rh(acac)(CO)₂ (3.6 mg, 0.01 mmol) and camphor sulphonicacid (218 mg, 1 mmol) in 8 ml of DCM. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 10/1) to give (109 mg, 54 % yield) of the title compound as yellow oil; ¹H-NMR (CDCl₃, 400 MHz) δ ppm 7.30-7.23 (m, 2H), 7.21-7.15 (m, 3H), 2.85 (qd, 4H, J = 2.0 Hz, J = 8.7 Hz), 2.56 (d, 2H, J = 7.2 Hz), 2.25 (bs, 1H), 1.99 ( pd, 1H, J = 7.7 Hz, J = 15.3 Hz), 1.77-1.68 (m, 2H), 1.60-1.44 (m, 4H), 1.15-1.05 (m, 2H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 139.8, 128.6, 128.4, 126.4, 126.1, 55.4, 51.3, 39.8, 36.0, 30.8, 25.2.

N-phenethyl-3,3-diphenylpropan-1-amine, (125)

The general procedure was followed with phenethylamine (120 mg, 1 mmol), 1,1’-diphenylethylene (180 mg, 1 mmol), Rh(acac)(CO)₂ (3.6 mg, 0.01 mmol) and camphor sulphonicacid
(218 mg, 1 mmol) in 8 ml of DCM. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 10/1) to give (179 mg, 57 % yield) of the title compound as yellow oil; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.29-7.12 (m, 15H), 3.93 (t, 1H, $J = 7.8$Hz), 2.86-2.73 (m, 4H), 2.59 (t, 1H, $J = 7.7$Hz), 2.24 (q, 1H, $J = 7.7$Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 144.5, 139.6, 128.7, 128.4, 127.7, 126.2, 50.8, 48.9, 47.9, 35.9, 35.3.

6.5 Experiments in Chapter 4

**General Procedure for the Enantioselective Iridium Catalysed Allylic Amination.**

[Ir(cod)Cl]$_2$ (0.01 equiv.), phosphoramidite ligand L3 (0.02 equiv.) and DABCO (0.1 equiv.) were dissolved in dry THF (1 ml) and the mixture was stirred under argon stream at 50 °C for 2h. After this time carbonate (1 equiv.) was added to reaction mixture and allowed to stir for 15 min. Then amine (1.5-2.0 equiv.) was added and the reaction was stirred at 50 °C until the carbonate was fully converted as determined by TLC analysis. The volatile materials were evaporated and the ratio of regioisomers (branched to linear, b/l) was determined by $^1$H – NMR of the crude mixture. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate) to give the desired product.

(R)-N-allyl-1-phenylprop-2-en-1-amine, (137a), (Table 13, Entry 1).

The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (13.5 mg, 0.02 mmol), ligand L2 (22 mg, 0.04 mmol), DABCO (23 mg, 0.2 mmol), cinnamyl methyl carbonate (385 mg, 2.0 mmol) and allylamine (171 mg, 225µl, 3.0 mmol). The reaction was conducted at 50 °C for 20 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 96/4. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (263 mg, 76 %) as colourless oil. HPLC analysis indicated that the enantiomeric excess of the product was 96 % [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99.6/0.4; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 7.4 (-), 8.3 (+) min]. $[\alpha]_D^{20} = -13.6$ (c =0.1050, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.33 (4, 1H), 7.24 (ddd, 1H, $J = 2.8$ Hz, $J = 5.8$ Hz, $J = 8.5$ Hz), 5.91 (dt, 2H, $J = 7.2$ Hz, $J = 17.1$ Hz), 5.21 (d, 1H, $J = 17.3$ Hz), 5.11 (m, 3H), 4.22 (d, 1H, $J = 7.1$ Hz), 3.18 (m, 2H), 1.46 (s, 1H); $^{13}$C-NMR (CDCl$_3$, 100
MHz) δ ppm 142.9, 141.0, 136.9, 128.7, 127.4, 127.3, 116.1, 115.2, 65.3, 50.0. Analytical data fits with literature.\textsuperscript{111}

\textit{N-allyl-1-(2-methoxyphenyl)prop-2-en-1-amine, (137b), (Table 13, Entry 2).}

The general procedure for allylic aminations was followed with [Ir(cod)Cl\(_2\)] (13.5 mg, 0.02 mmol) ligand L\(_3\) (22 mg, 0.040 mmol), DABCO (23 mg, 0.2 mmol), (\textit{E})-2-methoxycinnamyl methyl carbonate (445 mg, 2.0 mmol) and allylamine (171 mg, 225µl, 3.0 mmol). The reaction was conducted at 50 °C for 24 h. \(^1\)H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 96/4. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 3/1) to give the title compound (195 mg, 48 %) as yellowish oil. \([\alpha]\textsubscript{D}\textsuperscript{20} = +14.1 (c = 0.780, CHCl\(_3\)); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) δ ppm 7.27 (d, 1H, \(J = 7.5\) Hz), 7.21 (t, 1H, \(J = 7.4\) Hz), 6.92 (t, 1H, \(J = 7.4\) Hz), 6.85 (d, 1H, \(J = 8.2\) Hz), 6.03-5.86 (m, 2H), 5.15 (dd, 2H, \(J = 9.9\) Hz, \(J = 17.2\) Hz), 5.10-5.02 (m, 2H), 4.53 (d, 1H, \(J = 6.9\) Hz), 3.81 (s, 3H), 3.16 (qd, 2H, \(J = 6.0\) Hz, \(J = 13.9\) Hz), 1.90 (bs, 1H); \(^13\)C-NMR (CDCl\(_3\), 100 MHz) δ ppm 157.0, 139.8, 136.9, 130.6, 128.1, 128.0, 120.8, 115.7, 114.9, 110.7, 59.6, 55.3, 50.0; HRMS: m/z (FAB) calc. for C\(_{13}\)H\(_{18}\)NO (M+H\(^+\)) 204.1383, found 204.1395; IR(film): ν [cm\(^{-1}\)] = 3343 (w), 2929(m), 2830( s), 1602(s), 1490( s), 1460(s), 1247(s), 925(s), 748(s), 735(s).

\textit{N-allyl-1-(4-methoxyphenyl)prop-2-en-1-amine, (137c), (Table 13, Entry 3).}

The general procedure for allylic aminations was followed with [Ir(cod)Cl\(_2\)] (13.5 mg, 0.02 mmol) ligand L\(_3\) (22 mg, 0.040 mmol), DABCO (23 mg, 0.2 mmol), (\textit{E})-4-methoxycinnamyl methyl carbonate (445 mg, 2.0 mmol) and allylamine (171 mg, 225µl, 3.0 mmol). The reaction was conducted at 50 °C for 20 h. \(^1\)H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 96/4. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 3/1) to give the title compound (299 mg, 74 %) as yellowish oil. HPLC analysis of the Eoc protected derivative of amine indicated that the enantiomeric excess of the product was 92 % [Diacel

Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 98/2; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 9.9 (-), 10.8 (+) min. $[\alpha]_{D}^{20} = -7.2$ (c = 1.12, CHCl$_3$);

$^{1}$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.23 (d, 2H, $J = 8.6$ Hz), 6.85 (d, 2H, $J = 8.6$ Hz), 5.89 (ddd, 2H, $J = 3.3$ Hz, $J = 7.0$ Hz, $J = 10.2$ Hz), 5.15 (dd, 2H), 5.07 (d, 2H, $J = 10.2$ Hz), 4.16 (d, 1H, $J = 7.1$ Hz), 3.77 (s, 3H), 3.16 (m, 2H), 1.41 (bs, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 158.7, 141.0, 136.8, 134.8, 128.3, 115.9, 114.8, 113.9, 64.5, 55.2, 49.9; HRMS: m/z (FAB) calc. for C$_{13}$H$_{18}$NO (M+H$^+$) 204.1383, found 204.1366; IR(film): $\nu$ [cm$^{-1}$] = 3316 (w), 2935(m), 2830(s), 1602(s), 1503(s), 1444(s), 1240(s), 1030(s), 965(s).

$N$-allyl-1-(4-chlorophenyl)prop-2-en-1-amine, (137d), (Table 13, Entry 4).

The general procedure for allylic aminations was followed with [Ir(cod)Cl$_2$] (27 mg, 0.04 mmol) ligand L$_3$ (44 mg, 0.08 mmol), DABCO (46 mg, 0.4 mmol), (E)-4-chlorocynnamyl methyl carbonate (907 mg, 4.0 mmol) and allylamine (342 mg, 450 µl, 6.0 mmol). The reaction was conducted at 50 °C for 20 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 93/7. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (650 mg, 78 %) as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 91% [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99/1; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 3.7 (+), 5.6 (-) min. $[\alpha]_{D}^{20} = -20.3$ (c = 2.2, CHCl$_3$);

$^{1}$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.27 (s, 4H), 5.86 (ddd, 2H, $J = 6.0$Hz, $J = 10.0$Hz, $J = 17.0$Hz), 5.22-5.12 (m, 2H), 5.09 (dd, 2H, $J = 5.6$Hz, $J = 15.7$Hz), 4.19 (d, 1H, $J = 7.1$Hz), 3.21-3.09 (m, 2H), 1.33 (bs, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 141.1, 140.4, 136.5, 132.6, 128.5, 115.9, 115.3, 64.4, 49.7; HRMS: m/z (ESI) calc for C$_{13}$H$_{15}$N$_3$FCl (M+H$^+$) 210.08580, found 210.08553; IR(film): $\nu$ [cm$^{-1}$] = 3080 (m), 2968 (m), 2817 (m), 1897 (w), 1838 (w), 1635 (s), 1477 (vs), 1457 (s), 1405 (m), 1286 (w), 1095 (vs).

$N$-allyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine, (137e), (Table 13, Entry 5). The general procedure for allylic aminations was followed with [Ir(cod)Cl$_2$] (27 mg, 0.04 mmol) ligand L$_3$ (44 mg, 0.08 mmol), DABCO (46 mg, 0.4 mmol), (E)-4-trifluoromethyl cynnamyl methyl carbonate (1.04 g, 4.0 mmol) and allylamine (342 mg, 450 µl, 6.0 mmol). The reaction was conducted at 50 °C for 24 h. $^1$H NMR analysis of the crude
reaction mixture indicated the ratio of regioisomers (b/l) to be 92/8. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 7/1) to give the title compound (723 mg, 75%) as colourless oil. $[\alpha]_D^{20} = -18.4$ (c = 1.10, CHCl$_3$); Enantiomeric excess not determined. $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.57 (d, 2H, J=8.1Hz), 7.46 (d, 2H, J=8.1Hz), 5.94-5.81 (m, 2H), 5.25-5.05 (m, 4H), 4.28 (d, 1H, J=7.2Hz), 3.22-3.10 (m, 2H), 1.44 (bs, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 146.8, 140.1, 136.4, 129.5, 127.6, 125.4, 122.8, 116.1, 115.8, 64.8, 49.8; HRMS: m/z (ESI) calc for C$_{13}$H$_{15}$NF$_3$ (M+H$^+$) 242.11511, found 242.11499; IR(film): $\nu$ [cm$^{-1}$] = 3420 (w), 3073 (m), 2975 (m), 2824 (m), 1640 (s), 1615 (vs), 1444 (s), 1411 (s), 1326 (vs), 1168 (vs), 1122 (vs), 1050 (s), 918 (vs), 846 (vs).

General Procedure for Protection of Secondary Amines:

To a stirred solution of amine (1 mmol) in 10 ml of dry DCM was added dry triethylamine (1.5 mmol) under the argon atmosphere. Reaction mixture was cooled down to 0 °C and stirred next 30 min at this temperature, then TsCl, or ClCO$_2$Et (1.5 mmol) was added in one portion. The mixture was allowed to stir at room temperature until the amine was fully converted as determined by TLC. After completion of the reaction, volatiles were removed in vacuo and the crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate) to give the desired product.

Ethyl allyl-phenylallylcarbamate, (139a), (Table 13, Entry 1)

To a stirred solution of N-allyl-1-phenylprop-2-en-1-amine (346 mg, 2.0 mmol) in 10 ml of dry THF was added dry triethylamine (303 mg, 0.40 ml, 3.0 mmol) under the argon atmosphere. Reaction mixture was cooled down to 0 °C and stirred next 30 min at this temperature, then chloroethyl formiate (325 mg, 0.3 ml, 3.0 mmol) was added dropwise via syringe. The mixture was allowed to stir at room temperature over night. After completion of the reaction, mixture was filtered through sintered glass filter, and the volatiles removed in vacuo. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (426 mg, 87 %) as yellowish oil. $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.27 (m, 5H), 6.12 (ddd, 1H, J = 6.6 Hz, J = 10.2 Hz, J = 17.0 Hz), 5.66 (m, 2H), 5.31 (d, 1H, J =
10.2 Hz), 5.21 (d, 1H, J = 17.2 Hz), 4.94 (d, 2H, J = 11.1 Hz), 4.14 (q, 2H, J = 7.1 Hz), 3.75 (m, 2H), 1.21 (t, 3H, J = 6.7 Hz); 13C-NMR (CDCl₃, 100 MHz) δ ppm 139.6, 135.5, 135.0, 128.5, 128.0, 127.5, 118.1, 116.3, 62.1, 61.5, 14.7; HRMS: m/z (ESI) calc for C₁₅H₂₀NO₂ (M+H⁺) 246.14886, found 246.14877; IR(film): ν [cm⁻¹] = 3067 (w), 2981 (m), 1694 (vs), 1451 (s), 1411 (s), 1247 (s), 1142 (m);

(R)-N- Allyl-4-methyl-N-(1-phenyl-allyl)-benzenesulfonamide, (139b), (Table 13, Entry 1)

The general procedure for tosylation was followed with allyl-(1-phenyl-allyl)-amine (420 mg, 2.4 mmol), Et₃N (0.48 ml, 3.6 mmol) and TsCl (694 mg, 3.6 mmol) in 25 ml of DCM. The reaction was conducted at room temperature for 30 h. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (676 mg, 86 %) as white solid. ¹H-NMR (CDCl₃, 400 MHz) δ ppm 7.69 (d, 2H, J = 8.1 Hz), 7.28-7.20 (m, 7H), 6.01 (ddd, 1H, J = 7.1 Hz, J = 10.3 Hz, J = 17.3 Hz), 5.65 (d, 1H, J = 6.9 Hz), 5.46 (tdd, 1H, J = 6.3 Hz, J = 10.2 Hz, J = 16.6 Hz), 5.24 (d, 1H, J = 10.3 Hz), 5.11 (d, 1H, J = 17.1 Hz), 4.93-4.82 (m, 2H), 3.75 (ddd, 2H, J = 6.3 Hz, J = 16.2 Hz, J = 38.2 Hz), 2.38 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 142.9, 138.2, 137.8, 134.8, 134.2, 129.2, 128.2, 128.0, 127.5, 127.2, 118.9, 116.9, 63.2, 47.6, 21.3; Analytical data fits with literature.¹¹²

N- allyl-1-(2-methoxyphenyl)-N-tosylprop-2-en-1-amine, (139c), (Table 13, Entry 3)

The general procedure for tosylation was followed with N-allyl-1-(2-methoxyphenyl)prop-2-en-1-amine (385 mg, 1.9 mmol), Et₃N (0.37 ml, 2.8 mmol) and TsCl (542 mg, 2.8 mmol) in 20 ml of DCM. The reaction was conducted at room temperature for 30 h. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 7/1) to give the title compound (550 mg, 81 %) as white solid. ¹H-NMR (CDCl₃, 400 MHz) δ ppm 7.51 (d, 2H, J = 8.2 Hz), 7.25-7.17 (m, 2H), 7.12 (d, 2H, J = 8.0 Hz), 6.86 (t, 1H, J = 7.4 Hz), 6.67 (d, 1H, J = 8.1 Hz), 6.13 (ddd, 1H, J = 6.2 Hz, J = 10.6 Hz, J = 16.9 Hz), 5.81 (d, 1H, J = 5.7 Hz), 5.44 (tdd, 1H, J = 6.2 Hz, J = 10.2 Hz, J = 16.6 Hz), 5.26 (d, 1H, J = 10.4 Hz), 5.21 (d, 1H, J = 17.2 Hz), 4.86 (d, 1H, J = 11.1 Hz), 4.82 (d, 1H, J = 3.8 Hz), 3.81 (qd, 1H, J = 6.2 Hz, J = 16.2 Hz, J = 39.9 Hz), 3.58 (s, 3H), 2.35 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 157.3,

142.3, 138.5, 136.2, 135.0, 129.2, 128.8, 127.4, 125.9, 120.0, 117.3, 116.7, 110.1, 58.4, 54.8, 49.0, 21.4; HRMS: m/z (ESI) calc for $\text{C}_{20}\text{H}_{24}\text{NO}_3\text{S} (\text{M}+\text{H}^+)$ 358.1477, found 358.1473; IR(film): ν [cm$^{-1}$] = 3040 (w), 2916 (w), 1589 (s), 1490 (vs), 1450 (s), 1340 (vs), 1240 (vs), 1155 (vs), 1089 (s), 1050 (s), 925 (s).

$N$-allyl-$1$-(4-methoxyphenyl)-$N$-tosylprop-$2$-en-$1$-amine, (139d), (Table 13, Entry 4)

The general procedure for tosylation was followed with $N$-allyl-$1$-(4-methoxyphenyl)prop-$2$-en-$1$-amine (460 mg, 2.3 mmol), Et$_3$N (0.48 ml, 3.6 mmol) and TsCl (694 mg, 3.6 mmol) in 25 ml of DCM. The reaction was conducted at room temperature for 24 h. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 6/1) to give the title compound (737 mg, 91%) as white solid. $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.68 (d, 2H, $J = 8.2$ Hz), 7.23 (d, 2H, $J = 8.0$ Hz), 7.12 (d, 2H, $J = 8.6$ Hz), 6.78 (d, 2H, $J = 8.7$ Hz), 5.99 (ddd, 1H, $J = 6.8$ Hz, $J = 10.3$ Hz, $J = 17.1$ Hz), 5.59 (d, 1H, $J = 6.7$ Hz), 5.43 (ddd, 1H, $J = 6.4$ Hz, $J = 10.1$ Hz, $J = 16.7$ Hz), 5.22 (d, 1H, $J = 10.3$ Hz), 5.10 (d, 1H, $J = 17.1$ Hz), 4.93-4.83 (m, 2H, $J = 12.8$ Hz), 3.78 (s, 3H), 3.74 (qd, 2H, $J = 6.8$ Hz, $J = 15$ Hz, $J = 39$ Hz), 3.67 (dd, 1H, $J = 6.7$ Hz, $J = 16.2$ Hz), 2.40 (s, 3H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 159.1, 142.9, 138.1, 135.1, 134.7, 130.4, 129.5, 129.3, 127.4, 118.7, 117.1, 113.7, 62.8, 55.2, 47.6, 21.5; HRMS: m/z (ESI) calc for $\text{C}_{20}\text{H}_{24}\text{NO}_3\text{S} (\text{M}+\text{H}^+)$ 358.1477, found 358.1473; IR(film): ν [cm$^{-1}$] = 3080 (m), 2929 (m), 2820 (w), 1615 (vs), 1525 (vs), 1340 (vs), 1240 (vs), 1162 (vs), 1030 (s), 932 (s), 813 (s).

$N$-allyl-$1$-(4-chlorophenyl)-$N$-tosylprop-$2$-en-$1$-amine, (139e), (Table 13, Entry 4)

The general procedure for tosylation was followed with $N$-allyl-$1$-(4-chlorophenyl)prop-$2$-en-$1$-amine (745 mg, 3.6 mmol), Et$_3$N (0.72 ml, 5.4 mmol) and TsCl (1.04 g, 5.4 mmol) in 25 ml of DCM. The reaction was conducted at room temperature for 30 h. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (1.2 g, 92%) as white solid. $^1$H-NMR (CDCl$_3$, 500 MHz) δ ppm 7.66 (d, 2H, $J = 8.3$ Hz), 7.25-7.16 (m, 6H), 5.97 (ddd, 1H, $J = 7.2$ Hz, $J = 10.3$ Hz, $J = 17.3$ Hz), 5.57 (d, 1H, $J = 7.2$ Hz), 5.48 (tdd, 1H, $J = 6.3$ Hz, $J = 10.2$ Hz, $J = 16.6$ Hz), 5.24 (d, 1H, $J = 10.4$ Hz), 5.08 (d, 1H, $J = 17.1$ Hz), 4.94-4.86 (m, 2H), 3.75 (qd, 2H, $J = 6.3$ Hz, $J = 16.2$ Hz), 2.38 (s, 3H); $^{13}$C-NMR (CDCl$_3$, 125 MHz) δ
ppm 143.0, 137.6, 137.1, 134.6, 133.7, 129.4, 129.2, 128.2, 127.2, 119.6, 117.3, 62.6, 47.8, 21.3; HRMS: m/z (ESI) calc for C_{19}H_{21}NO_2^{35}ClS (M+H^+) 362.09761, found 362.09768; IR(film): ν [cm^{-1}] = 3080 (w), 2915 (w), 1635 (w), 1602 (m), 1480 (s), 1352 (vs), 1162 (vs), 1096 (s), 925 (s).

N-allyl-1-(4-(trifluoromethyl)phenyl)-N-tosylprop-2-en-1-amine, (139f), (Table 13, Entry 5)

The general procedure for tosylation was followed with N-allyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine (550 mg, 1.4 mmol), Et_3N (0.28 ml, 2.1 mmol) and TsCl (405 mg, 2.1 mmol) in 25 ml of DCM. The reaction was conducted at room temperature for 30 h. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 12/1) to give the title compound (487 mg, 88 %) as white solid. 

^1^H-NMR (CDCl_3, 400 MHz) δ ppm 7.67 (d, 2H, J = 8.3 Hz), 7.53 (d, 2H, J = 8.2 Hz), 7.40 (d, 2H, J = 8.1 Hz), 6.03 (ddd, 1H, J = 7.4 Hz, J = 10.3 Hz, J = 17.4 Hz), 5.65 (d, 1H, J = 7.4 Hz), 5.54 (tdd, 1H, J = 6.4 Hz, J = 10.2 Hz, J = 16.6 Hz), 5.31 (d, 1H, J = 10.3 Hz), 5.12 (d, 1H, J = 17.1 Hz), 4.94-4.89 (m, 2H), 3.80 (qd, 2H, J = 6.4 Hz, J = 16.1 Hz, J = 37.9 Hz), 2.40 (s, 3H); ^13^C-NMR (CDCl_3, 100 MHz) δ ppm 143.3, 142.8, 134.6, 133.6, 129.9, 129.7, 129.4, 128.4, 127.3, 125.2, 120.3, 117.6, 63.1, 48.2, 21.4; HRMS: m/z (ESI) calc for C_{20}H_{21}NO_2SF_3 (M+H^+) 396.12396, found 396.12359; IR(film): ν [cm^{-1}] = 3080 (w), 2929 (w), 1621 (m), 1602 (w), 1484 (m), 1340 (vs), 1162 (vs), 1024 (s), 932 (s).

N-allyl-N-tosylpent-1-en-3-amine, (139g), (Table 13, Entry 6)

The general procedure for allylic aminations was followed with [Ir(cod)Cl]_2 (13.5 mg, 0.02 mmol) ligand L3 (22 mg, 0.040 mmol), DABCO (23 mg, 0.2 mmol), methyl carbonate derived from (E)-pent-2-en-1-ol (289 mg, 2.0 mmol) and allylamine (171 mg, 225µl, 3.0 mmol). The reaction was conducted at 50 °C for 24 h. Reaction mixture was cooled down to 0 ° and triethyl amine (305 mg, 0.4 ml, 3 mmol), and tosyl chloride (420 mg, 2.2 mmol) were added. The mixture was allowed to stir at room temperature over night. After completion of the reaction, mixture was filtered through sintered glass filter, and the volatiles removed in vacuo The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (391 mg, 68 %) as colourless oil. HPLC analysis indicated that the enantiomeric excess of the product was 98 % [Diachel Chiralcel OJ (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 182
99.5/0.5; flow rate = 1 ml/min; detection wavelength = 254 nm; TR = 29.7 (-), 34.1 (+) min. 
\[ \alpha \]_D^{20} = -45.4 (c = 0.54, CHCl_3); \(^1\)H-NMR (CDCl_3, 400 MHz) \( \delta \) ppm 7.68 (d, 2H, \( J = 8.2 \) Hz), 7.24 (d, 2H, \( J = 8.1 \) Hz), 5.86-5.75 (m, 1H), 5.54 (ddd, 1H, \( J = 6.3 \) Hz, \( J = 10.6 \) Hz, \( J = 17.1 \) Hz), 5.16-4.96 (m, 4H), 4.21 (q, 1H, \( J = 7.1 \) Hz), 3.78 (ddd, 2H, \( J = 6.2 \) Hz, \( J = 10.6 \) Hz, \( J = 16.1 \) Hz), 3.62 (dd, 1H, \( J = 6.9 \) Hz, \( J = 16.2 \) Hz), 2.39 (s, 3H), 1.58 (qd, 2H, \( J = 7.0 \) Hz, \( J = 14.3 \) Hz), 0.86 (t, 3H, \( J = 7.3 \) Hz); \(^{13}\)C-NMR (CDCl_3, 100 MHz) \( \delta \) ppm 142.9, 138.2, 136.2, 136.1, 129.4, 127.2, 117.7, 116.9, 61.8, 46.8, 25.2, 21.5, 11.0. HRMS: m/z (ESI) calc for C_{15}H_{22}NO_2S (M+H\(^{+}\)) 280.13658, found 280.13673; IR(film): \( \nu \) [cm\(^{-1}\)] = 3073 (w), 2962 (s), 1917 (w), 1595 (w), 1457 (w), 1339 (vs), 1162 (vs). N-allyl-N-tosylhex-1-en-3-amine, (139h), (Table 13, Entry 7)

The general procedure for allylic aminations was followed with [Ir(cod)Cl]_2 (13.5 mg, 0.02 mmol), ligand L3 (22 mg, 0.040 mmol), DABCO (23 mg, 0.2 mmol), methyl carbonate derived from (\( E \))-hex-2-en-1-ol (316 mg, 2.0 mmol) and allylamine (171 mg, 225µl, 3.0 mmol). The reaction was conducted at 50 °C for 20 h. Reaction mixture was cooled down to 0 °C and triethyl amine (305 mg, 3 mmol), and tosyl chloride ( 420 mg, 2.2 mmol) were added. The mixture was allowed to stir at room temperature over night. After completion of the reaction, mixture was filtered through sintered glass filter, and the volatiles removed in vacuo The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (411 mg, 70 %) as colourless oil. HPLC analysis indicated that the enantiomeric excess of the product was 98 % [Diachel Chiralcel OJ (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99/1; flow rate = 1 ml/min; detection wavelength = 254 nm; TR = 23.3 (-), 28.0 (+) min. [\( \alpha \]_D^{20} = -28.5 (c = 0.89, CHCl_3); \(^1\)H-NMR (CDCl_3, 400 MHz) \( \delta \) ppm 7.67 (d, 2H, \( J=8.2Hz \)), 7.24 (d, 2H, \( J = 8.1 \) Hz), 5.80 (m, 1H), 5.53 (ddd, 1H, \( J = 6.2 \) Hz, \( J = 10.5 \) Hz, \( J = 17.0 \) Hz), 5.08 (m, 4H), 4.31 (q, 1H, \( J = 7.1 \) Hz), 3.77 (m, 1H), 3.60 (dd, 1H, \( J = 7.0 \) Hz, \( J = 16.3 \) Hz), 2.38 (s, 3H), 1.51 (dd, 1H, \( J = 7.6 \) Hz, \( J = 15.2 \) Hz), 1.29 (tt, 1H, \( J = 6.9 \) Hz, \( J = 14.0 \) Hz), 0.85 (t, 1H, \( J = 7.4 \) Hz); \(^{13}\)C-NMR (CDCl_3, 100 MHz) \( \delta \) ppm 143.1, 138.3, 136.5, 136.3, 129.6, 127.4, 117.8, 116.8, 61.8, 46.9, 34.4, 21.6, 19.5, 13.8; HRMS: m/z (FAB) calc for C_{16}H_{24}NO_2S (M+H\(^{+}\)) 294.1522, found 294.1506; IR(film): \( \nu \) [cm\(^{-1}\)] = 2955 (vs), 2922 (vs), 2351 (w), 1740 (vs), 1451 (s), 1339 (m), 1260 (s), 1162 (vs), 1089 (m).
General procedure for the ring closing metathesis reaction

To a stirred solution of tertiary amine (1 mmol.) in dry DCM (15 ml) under argon atmosphere was added Grubbs I catalyst (0.05 mmol.) and the reaction was stirred at reflux until the amine was fully converted, as determined by TLC. After the reaction was complete, mixture was cooled down, diluted with saturated NaHCO₃ solution and organic phase was washed with water and brine, dried over MgSO₄, filtered and volatiles evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate) to give desired product.

Ethyl 2-phenyl-2H-pyrrole-1(5H)-carboxylate, (128a), (Table 13, Entry 1)

The general procedure for ring closing metathesis was followed with N-allyl-1-phenyl-N-tosylprop-2-en-1-amine (300 mg, 1.22 mmol) and Grubbs I catalyst (50 mg, 0.061 mmol) in 20 ml of CH₂Cl₂. The reaction was conducted at reflux for 24 h. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (243 mg, 92 %) as colourless oil. \([\alpha]_D^{20} = +174.4 \ (c = 0.45, \text{CHCl}_3)\); \(^1\)H-NMR (CDCl₃, 400 MHz) \(\delta\) ppm 7.25 (m, 5H, \(J = 7.2\) Hz, \(J = 14.0\) Hz), 5.87 (m, 1H), 5.74 (ddd, 1H, \(J = 1.9\) Hz, \(J = 6.2\) Hz, \(J = 15.1\) Hz), 5.49 (dd, 1H, \(J = 2.2\) Hz, \(J = 39.6\) Hz), 4.33 (m, 1H), 4.08 (m, 1H), 3.97 (q, 1H, \(J = 7.1\) Hz), 1.10 (dt, 1H, \(J = 7.1\)Hz, \(J = 93.4\) Hz); \(^13\)C-NMR (CDCl₃, 100 MHz) \(\delta\) ppm 155.1, 154.8; 141.9, 141.3; 131.2, 131.1; 128.6, 128.4; 127.6, 127.5; 127.0, 126.9; 124.9, 124.8; 68.3, 67.9; 61.1; 54.2, 53.8, 14.9, 14.5; HRMS: m/z (ESI) calc for C₁₃H₁₆NO₂ (M+H⁺) 218.11756, found 218.11756; IR(film): \(\nu\) [cm\(^{-1}\)] = 3060 (w), 2929 (w), 2981 (m), 1705 (vs), 1511 (m), 1451 (s), 1411 (s), 1242 (s), 1140 (m), 925 (s);

(R)-2,5-dihydro-2-phenyl-1-tosyl-1H-pyrrole, (128b), (Table 13, Entry 1)

The general procedure for ring closing metathesis was followed with N-allyl-1-phenyl-N-tosylprop-2-en-1-amine (420 mg, 1.28 mmol) and Grubbs I catalyst (53 mg, 0.064 mmol) in 20 ml of CH₂Cl₂. The reaction was conducted at reflux for 18 h. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 6/1) to give the title compound (364 mg, 95 %) as white crystals. \([\alpha]_D^{20} = +277.1 \ (c = 2.05, \text{CHCl}_3)\); \(^1\)H-NMR (CDCl₃, 500 MHz) \(\delta\) ppm 7.52 (d, 2H, \(J = 8.3\) Hz), 7.26 (m, 5H), 7.19 (d, 2H, \(J = 8.0\) Hz), 5.78 (dq, 1H, \(J = 1.9\) Hz, \(J = 6.1\) Hz), 5.65
(dq, 1H, J = 2.2 Hz, J = 6.3 Hz), 5.52 (dt, 1H, J = 2.1 Hz, J = 4.4 Hz), 4.35 (dq, 1H, J = 2.3 Hz, J = 14.6 Hz), 4.26 (ddt, 1H, J = 2.0 Hz, J = 5.6 Hz, J = 14.6 Hz), 2.38 (s, 3H); \(^{13}\)C-NMR (CDCl\(_3\), 125 MHz) \(\delta\) ppm 144.6, 141.9, 137.0, 130.9, 129.9, 129.3, 128.7, 125.9, 71.7, 56.9, 22.9; Analytical data fits with literature.\(^{112}\)

2,5-dihydro-2-(4-methoxyphenyl)-1-tosyl-1H-pyrrole, (128c), (Table 13, Entry 2)

![Structure](image)

The general procedure for ring closing metathesis was followed with N-allyl-1-(2-methoxyphenyl)-N-tosylprop-2-en-1-amine (736 mg, 2.06 mmol) and Grubbs I catalyst (85 mg, 0.103 mmol) in 20 ml of CH\(_2\)Cl\(_2\). The reaction was conducted at reflux for 24 h. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 6/1) to give the title compound (603 mg, 89 %) as white crystals. \([\alpha\]\(^{20}\) = +330.2 (c = 0.927, CHCl\(_3\)); \(^{1}\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) ppm 7.64 (d, 2H, J = 8.1 Hz), 7.39 (d, 1H, J = 7.5 Hz), 7.26-7.17 (m, 3H), 6.92 (t, 1H, J = 7.5 Hz), 6.79 (d, 1H, J = 8.2 Hz), 5.84 (s, 1H), 5.66 (dd, 1H, J = 2.1 Hz, J = 6.1 Hz), 5.60 (dd, 1H, J = 1.6 Hz, J = 6.1 Hz), 4.35-4.23 (m, 2H), 3.77 (s, 3H), 2.39 (s, 3H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 155.9, 143.1, 134.9, 130.2, 129.5, 129.2, 128.5, 127.6, 127.4, 123.4, 123.8, 120.8, 110.2, 65.3, 55.6, 55.3, 21.5; HRMS: m/z (ESI) calc for C\(_{18}\)H\(_{20}\)NO\(_3\)S (M+H\(^{+}\)) 330.1166, found 330.1156; IR(film): \(\nu\) [cm\(^{-1}\)] = 3415 (m), 2968 (w), 2942 (w), 2863 (w), 1602 (m), 1490 (s), 1457 (m), 1345 (vs), 1240 (s), 1162 (vs), 1090 (s), 1050 (s), 820 (w), 761 (s).

2,5-dihydro-2-(4-methoxyphenyl)-1-tosyl-1H-pyrrole, (128d), (Table 13, Entry 3)

![Structure](image)

The general procedure for ring closing metathesis was followed with N-allyl-1-(4-methoxyphenyl)-N-tosylprop-2-en-1-amine (845 mg, 2.36 mmol) and Grubbs I catalyst (97 mg, 0.12 mmol) in 20 ml of CH\(_2\)Cl\(_2\). The reaction was conducted at reflux for 24 h. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 6/1) to give the title compound (723 mg, 93 %) as white crystals. \([\alpha\]\(^{20}\) = +260.4 (c = 1.24, CHCl\(_3\)); \(^{1}\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) ppm 7.48 (d, 2H, J = 8.1 Hz), 7.15 (t, 4H, J = 8.6 Hz), 6.78 (d, 2H, J = 8.6 Hz), 5.75 (dd, 1H, J = 1.7 Hz, J = 6.1 Hz), 5.60 (dd, 1H, J = 2.1 Hz, J = 6.1 Hz), 5.46 (dd, 1H, J = 2.1 Hz, J = 4.8 Hz), 4.25 (ddd, 2H, J = 3.8 Hz, J = 14.5 Hz, J = 20.0 Hz), 3.77 (s, 3H), 2.36 (s, 3H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 159.2, 142.9, 135.5, 132.5, 130.6, 129.3, 128.5, 127.1, 124.3, 113.7, 69.6, 55.2, 55.1, 21.4; HRMS: m/z (ESI) calc for C\(_{18}\)H\(_{20}\)NO\(_3\)S (M+H\(^{+}\))
330.1166, found 330.1155; IR(film): v [cm⁻¹] = 3432 (w), 2955 (w), 2909 (w), 2850 (w), 1615 (m), 1510 (s), 1340 (vs), 1286 (m), 1254 (vs), 1155 (s) 1083 (s), 1055 (m), 833 (m), 807 (m);

2-(4-chlorophenyl)-2,5-dihydro-1-tosyl-1H-pyrrole, (128e), (Table 13, Entry 4)

The general procedure for ring closing metathesis was followed with N-allyl-1-(4-chlorophenyl)-N-tosylprop-2-en-1-amine (650 mg, 1.8 mmol) and Grubbs I catalyst (74 mg, 0.09 mmol) in 20 ml of CH₂Cl₂. The reaction was conducted at reflux for 18 h. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 10/1) to give the title compound (540 mg, 90 %) as white crystals. [α]D²⁰ = +215.2 (c = 0.955, CHCl₃); ¹H-NMR (CDCl₃, 500 MHz) δ ppm 7.51 (d, 2H, J = 8.1 Hz), 7.19 (q, 6H, J = 8.6 Hz), 5.76 (dd, 1H, J = 1.6 Hz, J = 6.0 Hz), 5.57 (dd, 1H, J = 2.0 Hz, J = 6.0 Hz), 5.44 (d, 1H, J = 2.3 Hz), 4.32-4.19 (m, 2H), 2.36 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 143.3, 139.0, 135.0, 128.5, 128.4, 127.1, 124.9, 69.4, 55.3, 21.4; HRMS: m/z (ESI) calc for C₁₇H₁₇NO₂S (M+H⁺) 334.06631, found 334.06649; IR(film): v [cm⁻¹] = 3248 (w), 3047 (w), 2922 (w), 1595 (m), 1490 (s), 1340 (vs), 1155 (vs), 1090 (s), 1055 (s), 820 (s).

2-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1-tosyl-1H-pyrrole, (128f), (Table 13, Entry 5)

The general procedure for ring closing metathesis was followed with N-allyl-1-phenyl-N-tosylprop-2-en-1-amine (397 mg, 1 mmol) and Grubbs I catalyst (41 mg, 0.05 mmol) in 20 ml of CH₂Cl₂. The reaction was conducted at reflux for 24 h. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 10/1) to give the title compound (334 mg, 91 %) as white crystals. [α]D²⁰ = +117.4 (c = 0.910, CHCl₃); ¹H-NMR (CDCl₃, 500 MHz) δ ppm 7.50 (t, 4H, J=7.4Hz), 7.34 (d, 2H, J=8.0Hz), 7.17 (d, 2H, J=8.0Hz), 5.80 (dd, 1H, J=1.7Hz, J=6.1Hz), 5.60 (dd, 1H, J=2.0Hz, J=6.1Hz), 5.51 (d, 1H, J=2.3Hz), 4.37-4.24 (m, 1H), 2.35 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 144.4, 143.5, 135.0, 129.9, 129.8, 129.5, 127.5, 127.1, 125.3, 125.3, 122.6, 69.6, 55.5, 21.3; HRMS: m/z (ESI) calc for C₁₈H₁₇NO₂F₃S (M+H⁺) 368.09266, found 368.09266; IR(film): v [cm⁻¹] = 3448 (w), 3021
(w), 2922 (m), 2863 (m), 1910 (m), 1589 (s), 1411 (s), 132 (vs), 1162 (s), 1110 (s), 1063 (s), 833 (vs).

2-ethyl-2,5-dihydro-1-tosyl-1H-pyrrole, (128g), (Table 13, Entry 6)

The general procedure for ring closing metathesis was followed with N-allyl-N-tosylpent-1-en-3-amine (334 mg, 1.20 mmol) and Grubbs I catalyst (49 mg, 0.060 mmol) in 20 ml of CH$_2$Cl$_2$. The reaction was conducted at reflux for 24 h. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 6/1) to give the title compound (256 mg, 85 %) as colourless oil. [$\alpha$]$^20_D$ = +117.5 (c = 0.876, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.64 (d, 2H, $J = 8.2$ Hz), 7.23 (d, 2H, $J = 8.0$ Hz), 5.58-5.46 (m, 2H), 4.42-4.36 (m, 1H), 4.06-4.01 (m, 1H), 2.34 (s, 3H), 1.78-1.70 (m, 2H), 0.82 (t, 3H, $J = 7.4$ Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 143.1, 134.5, 129.5, 129.1, 127.1, 124.7, 68.0, 55.6, 28.6, 21.3, 8.3; HRMS: m/z (ESI) calc for C$_{13}$H$_{18}$NO$_2$S (M+H$^+$) 252.10528, found 252.10528; IR(film): $\nu$ [cm$^{-1}$] = 3067 (w), 2968 (vs), 2922 (vs), 2856 (vs), 1602 (s), 1451 (s), 1345 (vs), 1168 (vs), 1085 (s), 827 (vs).

2,5-dihydro-2-propyl-1-tosyl-1H-pyrrole, (128h), (Table 13, Entry 7)

The general procedure for ring closing metathesis was followed with N-allyl-N-tosylhex-1-en-3-amine (305 mg, 1.04 mmol) and Grubbs I catalyst (42 mg, 0.052 mmol) in 20 ml of CH$_2$Cl$_2$. The reaction was conducted at reflux for 20 h. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 6/1) to give the title compound (262 mg, 94 %) as colourless oil. [$\alpha$]$^20_D$ = +166.7 (c = 1.1004, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.64 (d, 2H, $J = 8.2$ Hz), 7.24 (d, 2H, $J = 8.0$ Hz), 5.55-5.50 (m, 2H), 4.44-4.38 (m, 1H), 4.06-4.02 (m, 2H), 2.35 (s, 3H), 1.77-1.60 (m, 2H), 1.39-1.19 (m, 2H), 0.87 (t, 3H, $J = 7.4$ Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 143.2, 134.6, 129.6, 129.5, 127.2, 124.4, 67.1, 55.5, 38.2, 21.3, 17.7, 13.9; HRMS: m/z (ESI) calc for C$_{14}$H$_{20}$NO$_2$S(M+H$^+$) 266.12093, found 266.12098; IR(KBr): $\nu$ [cm$^{-1}$] = 2962 (s), 2922 (s), 2870 (s), 1602 (s), 1490 (s), 1463 (s), 1352 (s), 1168 (s), 1096 (s), 1043 (s), 820 (vs), 655 (vs).
**N-(1-phenylallyl)but-3-en-1-amine, (Table 14, Entry 1), (140a)**

The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (13.5 mg, 0.02 mmol), ligand L$_3$ (22 mg, 0.040 mmol), cinnamyl methyl carbonate (385 mg, 2.0 mmol) and homoallylamine (215 mg, 3.0 mmol). The reaction was conducted at room temperature for 48 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 96/4. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (277 mg, 74 %) as colourless oil. HPLC analysis indicated that the enantiomeric excess of the product was 96% [Diacet Chiralcel OJ (0.46 cm x 25 cm, 5 μm); heptane/2-propanol =99.9/0.1; flow rate = 1.4 mL/min; detection wavelength = 254 nm; TR = 5.6 (+), 6.2 (-) min]. $\alpha_{D}^{20} = - 8.7$ (c = 0.995, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm δ 7.31 (d, 4H, $J$ = 4.3 Hz), 7.23 (m, 1H), 7.23 (m, 1H), 5.90 (ddd, 1H, $J$ = 7.2 Hz, $J$ = 10.1 Hz, $J$=17.2Hz), 5.75 (tdd, 1H, $J$ = 6.9 Hz, $J$ = 10.2 Hz, $J$ = 17.0 Hz), 5.18 (d, 1H, $J$ = 17.1 Hz), 5.08 (s, 1H), 5.03 (dd, 2H, $J$ = 8.8 Hz, $J$ = 17.0 Hz), 4.16 (d, 1H, $J$ = 7.2 Hz), 2.60 (dtd, 1H, $J$ = 6.8 Hz, $J$ = 11.5 Hz, $J$ = 18.3 Hz), 2.24 (q, 2H, $J$ = 6.8 Hz), 1.45 (bs, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 141.2, 136.6, 128.6, 127.3, 127.3, 116.5, 115.0, 66.2, 46.6, 34.4; HRMS: m/z (FAB) calc for C$_{13}$H$_{18}$N (M+H$^+$) 188.1434, found 188.1454. IR(film): ν [cm$^{-1}$] =3448 (w), 2929(m), 2824(s),1832 (w),1641(s), 1541(s), 1116(s), 925(s), 702(s).

**N-(1-(4-methoxyphenyl)allyl)but-3-en-1-amine, (Table 14, Entry 2), (140b)**

The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (20 mg, 0.03 mmol), ligand L$_3$ (33 mg, 0.060 mmol), methyl carbonate derived from (E)-4-methoxycynnamyl alcohol (665 mg, 3.0 mmol) and homoallylamine (337 mg, 4.5 mmol). The reaction was conducted at room temperature for 48 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 95/5. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 3/1) to give the title compound (508 mg, 78 %) as yellowish oil. $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm δ 7.22 (d, 2H, $J$ = 8.6 Hz), 6.84 (d, 2H, $J$ = 8.6 Hz), 5.88 (ddd, 1H, $J$ = 7.2 Hz, $J$ = 10.2 Hz, $J$ = 17.2 Hz), 5.74 (tdd, 1H, $J$ = 6.8 Hz, $J$ = 10.1 Hz, $J$=17.0 Hz), 5.15 (d, 1H, $J$ = 17.1 Hz), 5.03 (m, 3H), 4.11 (d, 1H, $J$ = 7.1 Hz), 3.77 (s, 3H), 2.58 (dtd, 2H, $J$ = 6.9 Hz, $J$ = 11.5 Hz, $J$ = 18.3 Hz), 2.23 (q, 2H, $J$ = 6.8 Hz), 1.42 (s, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 158.8, 141.4, 136.6, 135.2, 128.4, 116.5, 114.7, 113.9, 65.5, 55.4, 46.6, 34.4; HRMS: m/z (FAB) calc for C$_{14}$H$_{19}$NO (M$^+$) 217.1467, found
217.1452; IR(film): ν [cm$^{-1}$] = 3310 (w), 2931(s), 2831(s), 1622(vs), 1515(vs), 1440(s), 1214(s), 1030(s), 919(s).

$N$-(1-(furan-2-yl)allyl)but-3-en-1-amine, (Table 14, Entry 3), (140c)

The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (13.5 mg, 0.02 mmol), ligand L3 (22 mg, 0.040 mmol), methyl carbonate derived from (E)-3-(2-furanyl)-2-propen-1-ol (365 mg, 2.0 mmol) and allylamine (171 mg, 225µl, 3.0 mmol). The reaction was conducted at room temperature for 4 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 94/6. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 9/1) to give the title compound (248 mg, 70 %) as yellowish oil. HPLC analysis indicated that the enantiomeric excess of the product was 94 % [Diacel Chiralcel OJ (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 99/1; flow rate = 1 ml/min; detection wavelength = 254 nm; TR = 7.5 (minor), 8.1 (major) min]. $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.34 (s, 1H), 6.29 (m, 1H), 6.15 (d, 1H, $J = 3.1$ Hz), 5.92 (ddd, 1H, $J = 7.3$ Hz, $J = 10.1$ Hz, $J = 17.3$ Hz), 5.75 (tdd, 1H, $J = 6.8$ Hz, $J = 10.1$ Hz, $J = 17.0$ Hz), 5.20 (dd, 2H, $J = 13.8$ Hz, $J = 16.9$ Hz), 5.04 (dd, 2H, $J = 13.6$ Hz, $J = 19.7$ Hz), 4.26 (d, 1H, $J = 7.2$ Hz), 2.62 (ddt, 2H, $J = 6.9$ Hz, $J = 11.4$ Hz, $J = 18.2$ Hz), 2.24 (q, 2H, $J = 6.8$ Hz), 1.52 (s, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 155.5, 141.9, 137.7, 136.4, 116.8, 116.6, 110.2, 106.3, 59.4, 46.3, 34.3; HRMS: m/z (FAB) calc for C$_{11}$H$_{15}$NO (M$^+$) 177.1153, found 177.1172; IR(film): ν [cm$^{-1}$] = 3322 (w), 3070 (s), 2975 (s), 2824 (s), 1840 (w), 1645 (vs), 1500 (s), 1449 (s), 1298 (m), 1153 (s), 1001 (s), 919 (s).

$N$-(1-(pyridin-3-yl)allyl)but-3-en-1-amine, (Table 14, Entry 4), (140d)

The general procedure for allylic aminations was followed with [Ir(cod)Cl]$_2$ (13.5 mg, 0.02 mmol), ligand L3 (22 mg, 0.040 mmol), methyl carbonate derived from (E)-3-(pyridin-3-yl)prop-2-en-1-ol (386 mg, 2.0 mmol) and homoallylamine (215 mg, 3.0 mmol). The reaction was conducted at room temperature for 24 h. $^1$H NMR analysis of the crude reaction mixture indicated the ratio of regioisomers (b/l) to be 97/3. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 1/1) to give the title compound (305 mg, 81 %) as colourless oil. HPLC analysis indicated that the enantiomeric excess of
the product was 97 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 98/2; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 16.5 (-), 28.2 (major+) min]. \([\alpha]_D^{20} = + 2.4 \) (c = 1.30, CHCl\(_3\)); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) ppm 8.54 (s, 1H), 8.48 (d, 1H, \(J = 4.6\) Hz), 7.65 (d, 1H, \(J = 7.8\) Hz), 7.23 (dd, 1H, \(J = 4.8\) Hz, \(J = 7.8\) Hz), 5.86 (ddd, 1H, \(J = 7.2\) Hz, \(J = 10.1\) Hz, \(J = 17.3\) Hz), 5.75 (m, 1H), 5.12 (tt, 4H, \(J = 14.5\) Hz, \(J = 13.8\) Hz), 4.20 (d, 1H, \(J = 7.2\) Hz), 2.58 (dtd, 2H, \(J = 6.8\) Hz, \(J = 11.6\) Hz, \(J = 18.2\) Hz), 2.23 (q, 2H, \(J = 6.7\) Hz), 1.52 (bs,1H); \(^1^3\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 149.4, 148.8, 140.2, 138.3, 134.9, 123.6, 116.7, 116.0, 63.8, 46.6, 34.3; Analytical data fits with literature\(^{113}\)

**ethyl but-3-enyl-(4-methoxyphenyl)allylcarbamate, (142)**

The general procedure for protection was followed with \(N\)-(1-(4-methoxyphenyl)allyl)but-3-en-1-amine (294 mg, 1.35 mmol), triethylamine (205 mg, 0.27 ml, 2.03 mmol) and chloroethyl formiate (220 mg, 0.2 ml, 2.03 mmol) in 15 ml of THF. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 4/1) to give the title compound (308 mg, 79 %) as yellowish oil. \([\alpha]_D^{20} = +26.4 \) (c = 0.92, CHCl\(_3\)); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.19 (d, 2H, \(J = 8.4\) Hz), 6.84 (d, 2H, \(J = 8.6\) Hz), 6.12-6.01 (m, 1H), 5.80-5.48 (m, 2H), 5.30 (d, 1H, \(J = 10.3\) Hz), 5.18 (d, 1H, \(J = 17.2\) Hz), 4.90-4.80 (m, 2H), 4.15 (q, 2H, \(J = 7.0\) Hz), 3.78 (s, 3H), 3.25-2.98 (m, 2H), 2.10 (bs, 1H), 1.78 (bs, 1H), 1.26-1.20 (m, 3H); \(^1^3\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 159.1, 135.8, 135.6, 131.6, 131.6, 129.5, 129.3, 117.4, 116.2, 113.9, 113.9, 113.8, 61.4, 61.3, 61.3, 55.4, 33.9, 30.4, 14.8; HRMS: m/z (FAB) calc for \(C_{17}H_{23}NO_3\) (M\(^{+}\)) 289.1678, found 289.1672; IR(film): \(\nu\) [cm\(^{-1}\)] = 3045 (w), 2985 (m), 1710 (vs), 1444 (s), 1411 (s), 1245 (s), 1110 (m);

**Ethyl 5,6-dihydro-2-(4-methoxyphenyl)pyridine-1(2H)-carboxylate, (143)**

The general procedure for ring closing metathesis was followed with ethyl allyl-1-(2-methoxyphenyl)allylcarbamate (365 mg, 1.32 mmol) and Grubbs I catalyst (54 mg, 0.066 mmol) in 20 ml of CH\(_2\)Cl\(_2\). The reaction was conducted at reflux for 18 h. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 5/1) to give the title compound

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(284 mg, 87 %) as yellowish oil. $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.31 (bs, 2H), 6.83 (d, 2H, $J$ = 8.6 Hz), 6.03-5.96 (m, 1H), 5.78 (d, 1H, $J$ = 7.8 Hz), 5.55 (d, 1H, $J$ = 41.4 Hz), 4.21-3.90 (m, 3H), 3.76 (s, 3H), 2.89 (td, 1H, $J$ = 3.8 Hz, $J$ = 12.9 Hz), 2.29 (bs, 1H), 2.06-1.96 (m, 1H), 1.30-1.18 (m, 1H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 159.06, 155.48, 133.07, 129.37, 127.33, 126.38, 113.74, 61.39, 55.38, 54.28, 36.78, 36.73, 25.15, 14.87; HRMS: m/z (FAB) calc for C$_{15}$H$_{19}$NO$_3$ (M$^+$) 261.1365, found 261.1325; IR(film): ν [cm$^{-1}$] = 3045 (w), 2916 (w), 1712 (vs), 1490 (vs), 1340 (s), 1240 (vs), 1155 (vs), 1089 (s), 1050 (s), 925 (s).

**General procedure for tandem hydroformylation / Fischer indolization reactions with subsequent addition of bromsted acid, General method A**

In a thick walled sample vial containing PTFE septum Rh(acac)(CO)$_2$ (0.01 equiv.), ligand (0.05 equiv.), phenylhydrazine (1 equiv.) and ligand (0.05 equiv.) were dissolved in dry THF (5 mL). The vial was placed in a pressure vessel, flushed with argon and pressurized with 10 bar H$_2$ and 50 bar CO. The reaction mixture was stirred for 5 days at 80 °C. A 4 wt. % solution of H$_2$SO$_4$ in THF (5 mL) was slowly added and the resulting mixture was refluxed for 3 hours. Reaction was quenched with ammonia solution (30% in water) and the aqueous phase was extracted with 4x10 mL DCM. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and volatiles were removed *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate) to give the desired product.

**General procedure for tandem hydroformylation / Fischer indolization reactions with subsequent addition of Lewis acid, General method B**

In a thick walled sample vial containing PTFE septum olefin (1 equiv.), phenylhydrazine (1 equiv.), Rh(acac)(CO)$_2$ (0.01 equiv.) and ligand (0.05 equiv.) were dissolved in dry THF (5 mL). The vial was placed in a pressure vessel, flushed with argon and pressurized with 10 bar H$_2$ and 50 bar CO. The reaction mixture was stirred for 5 days at 80 °C. After completion of the reaction volatiles were removed in vacuo, residue was dissolved in toluol (10 mL) and ZnCl$_2$ (4 equiv.) was added and the resulting mixture was refluxed for 12 hours. Reaction mixture was diluted with water and the aqueous phase was extracted with 4x10 mL DCM. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and
volatiles were removed *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate) to give the desired products.

**General procedure for tandem hydroformylation / Fischer indolization reactions in presence of Bronsted acid, General method C**

In a thick walled sample vial containing PTFE septum Rh(acac)(CO)$_2$ (0.01 equiv.), ligand (0.05 equiv.), benzophenone protected phenylhydrazine (1 equiv.), olefin (1 equiv.) and PTSA (1 equiv.) were dissolved in dry THF (5 mL). The vial was placed in a pressure vessel, flushed with argon and pressurized with 10 bar H$_2$ and 50 bar CO. The reaction mixture was stirred for 5 days at 80 °C. Reaction was quenched with ammonia solution (30% in water) and the aqueous phase was extracted with 4x10 mL DCM. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and volatiles were removed *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate) to give the desired products.

**General procedure for tandem hydroformylation / Fischer indolization reactions with subsequent addition of Lewis acid (general method D)**

In a thick walled sample vial containing PTFE septum olefin (1 equiv.), phenylhydrazine (1 equiv.), Rh(CO)$_2$ (0.01 equiv.) and ligand (0.05 equiv.) were dissolved in dry THF (5 mL). The vial was placed in a pressure vessel, flushed with argon and pressurized with 10 bar H$_2$ and 50 bar CO. The reaction mixture was stirred for 5 days at 80 °C. After completion of the reaction volatiles were removed in vacuo, residue was dissolved in ethyleneglycol (10 mL) and resulting mixture was refluxed for 24 h at 180 °C. Reaction mixture was extracted with 4x10 mL DCM. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and volatiles were removed *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate) to give the desired products.


The general procedure A was followed with 2,5-dihydro-2-phenyl-1-tosyl-1H-pyrrole (200 mg, 0.67 mmol), phenylhydrazine (72 mg, 1 mmol), Rh(acac)(CO)$_2$ (1.8 mg, 0.007 mmol)
and PPh₃ (9 mg, 0.033 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 6/1) to give (62 mg, 23 % yield) of the 133a and (167 mg, 62 % yield) of the 135a.

133a: HPLC analysis indicated that the enantiomeric excess of the product was 0 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 24.0, 27.3 min]. \([\alpha]_{D}^{20} = 0 \, (c = 0.98, \text{CHCl}_3)\); ¹H-NMR (CDCl₃, 400 MHz) δ ppm 7.70 (s, 1H), 7.59 (d, 2H, \(J = 8.2 \, \text{Hz})\), 7.41 (d, 1H, \(J = 7.8 \, \text{Hz})\),7.31-7.28 (m, 6H), 7.17 (t, 1H, \(J = 7.1 \, \text{Hz})\), 7.11-7.07 (m, 3H), 6.32 (s, 1H), 4.00 (dd, 1H, \(J = 5.3 \, \text{Hz}, J = 14.4 \, \text{Hz})\), 3.30 (ddd, 1H, \(J = 4.8 \, \text{Hz}, J = 11.7 \, \text{Hz}, J = 14.5 \, \text{Hz})\), 2.60 (ddt, 2H, \(J = 4.7 \, \text{Hz}, J = 13.6 \, \text{Hz}, J = 15.8 \, \text{Hz})\), 2.28 (s, 3H); 1³C-NMR (CDCl₃, 100 MHz) δ ppm 143.4, 139.5, 138.2, 130.6, 129.6, 128.9, 128.7, 127.1, 122.6, 119.9, 118.6, 111.2, 56.1, 39.7, 21.6, 20.4; Analytical data fits with literature.¹¹⁴

135a: HPLC analysis indicated that the enantiomeric excess of the product was 97 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 25.7 (-), 29.2 (+) min]. \([\alpha]_{D}^{20} = -185.1 \, (c = 0.560, \text{CHCl}_3)\); ¹H-NMR (CDCl₃, 400 MHz) δ ppm 7.82 (s, 1H), 7.64 (d, 2H, \(J = 8.2 \, \text{Hz})\), 7.42 (d, 1H, \(J = 7.7 \, \text{Hz})\), 7.27-7.23 (m, 3H), 7.15-7.06 (m, 7H), 5.55 (d, 1H, \(J = 6.3 \, \text{Hz})\), 4.81 (d, 1H, \(J = 17.0 \, \text{Hz})\), 3.96 (d, 1H, \(J = 17.0 \, \text{Hz})\), 3.17 (d, 1H, \(J = 16.2 \, \text{Hz})\), 2.88 (dd, 1H, \(J = 6.3 \, \text{Hz}, J = 16.2 \, \text{Hz})\), 2.28 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 143.5, 138.6, 137.7, 136.2, 129.7, 128.8, 128.5, 127.8, 127.7, 126.9, 122.2, 119.7, 118.1, 111.1, 107.3, 54.1, 39.5, 22.5, 21.6; HRMS: m/z (ESI) calc for C₂₄H₂₃N₂O₂S (M+H¹) 403.14748, found 403.14711; IR(film): ν [cm⁻¹] = 3395 (m), 2929 (w), 1602 (w), 1464 (s), 1326 (s), 1155 (vs), 1096 (s);


(Table 15, Entry 1) By a procedure similar to that of method A, pyrrole 128b (150 mg, 0.5 mmol) was converted into (46 mg, 23 % yield) of the 133a and (125 mg, 62 %) of 135a in

the presence of PPh$_3$ (6.5 mg, 0.025 mmol). (Table 15, Entry 2) By a procedure similar to that of method A, pyrrole 128b (150 mg, 0.5 mmol) in the presence of dppf (14 mg, 0.025 mmol) gave no products. (Table 15, Entry 3) By a procedure similar to that of method A, pyrrole 128b (150 mg, 0.5 mmol) was converted into (20 mg, 10 % yield) of the 133a and (24 mg, 12 %) of 135a in the presence of dppb (10.7 mg, 0.025 mmol). (Table 15, Entry 4) By a procedure similar to that of method A, pyrrole 128b (150 mg, 0.5 mmol) in the presence of BINAP (16 mg, 0.025 mmol) gave no products. (Table 15, Entry 5) By a procedure similar to that of Method A, pyrrole 128b (150 mg, 0.5 mmol) was converted into (12 mg, 6 % yield) of the 133a and (64 mg, 31 %) of 135a in the presence of of XANTPHOS (14.5 mg, 0.025 mmol). (Table 15, Entry 6) By a procedure similar to that of Method A, pyrrole 128b (150 mg, 0.5 mmol) was converted into (56 mg, 28 % yield) of the 133a and (89 mg, 44 %) of 135a in the presence of POPh$_3$ (7.8 mg, 0.025 mmol). (Table 15, Entry 7) By a procedure similar to that of Method A, pyrrole 128b (150 mg, 0.5 mmol) was converted into (68 mg, 34 % yield) of the 133a and (94 mg, 47 %) of 135a in the presence of BIPHEPHOS (20 mg, 0.025 mmol).

(Table 16, Entry 2) General procedure B was followed with 2,5-dihydro-2-phenyl-1-tosyl-1H-pyrrole (150 mg, 0.5 mmol), phenylhydrazine (54 mg, 0.5 mmol) and Rh(acac)(CO)$_2$ (1.3 mg, 0.005 mmol) in 8 ml of THF to yield (30 mg, 15 % yield) of the 133a and (40 mg, 20 %) of 135a. (Table 16, Entry 3) General procedure C was followed with 2,5-dihydro-2-phenyl-1-tosyl-1H-pyrrole (150 mg, 0.5 mmol), phenylhydrazine (54 mg, 0.5 mmol) and Rh(acac)(CO)$_2$ (1.3 mg, 0.005 mmol) in 8 ml of THF to yield (22 mg, 11 % yield) of the 133a and (42 mg, 21 %) of 135a. (Table 16, Entry 4) General procedure C was followed with 2,5-dihydro-2-phenyl-1-tosyl-1H-pyrrole (150 mg, 0.5 mmol), phenylhydrazine (54 mg, 0.5 mmol) and Rh(acac)(CO)$_2$ (1.3 mg, 0.005 mmol) in 8 ml of THF to yield no product.

**Crossover experiment**

The general procedure A was followed with 1 (346 mg, 1 mmol), and 2 (200 mg, 1 mmol), phenylhydrazine (220mg , 2 mmol), Rh(acac)(CO)$_2$ (5 mg, 0.02 mmol) and PPh$_3$ (25 mg, 0.1 mmol). NMR of crude mixture and LCMS analysis indicated only two depicted products are formed in the ratio 1:1. No crossover product could be observed.
Ethyl 3,4-dihydro-1-phenyl-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (133b). Ethyl 3,4-dihydro-3-phenyl-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (135b) (Table 17, Entry 2).

The general procedure A was followed with ethyl 2-phenyl-2H-pyrrole-1(5H)-carboxylate (350 mg, 1.6 mmol), phenylhydrazine (173 mg, 1.6 mmol), Rh(acac)(CO)₂ (4.1 mg, 0.016 mmol) and PPh₃ (21 mg, 0.08 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 6/1) to give (102 mg, 20% yield) of the 133b and (220 mg, 43 % yield) of 135b.

133b: HPLC analysis indicated that the enantiomeric excess of the product was 0 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 17.5, 36.2 min]. ¹H-NMR (CDCl₃, 500 MHz) δ ppm 7.91 (s, 1H), 7.57 (d, 1H, J = 7.6 Hz), 7.31-7.27 (m, 6H), 7.17 (dtd, 2H, J = 4.1 Hz, J = 10.4 Hz, J = 14.9 Hz), 6.51-6.33 (m, 1H), 4.43-4.20 (m, 3H), 3.19 (ddd, 1H, J = 4.2 Hz, J = 12.0 Hz, J = 13.4 Hz), 2.99-2.91 (m, 1H), 2.83 (dd, 1H, J = 3.2 Hz, J = 15.3 Hz),1.35-1.26 (m, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 140.1, 136.3, 131.5, 128.9, 128.5, 128.1, 126.7, 124.7, 122.1, 119.6, 118.2, 110.9, 61.6, 54.3, 38.2, 14.7; HRMS: m/z (FAB) calc for C₂₀H₂₀N₂O₂ (M⁺) 320.1525, found 320.1506; IR(film): ν [cm⁻¹] = 3395 (m), 3310 (s), 3060 (m), 2922 (s), 1681 (vs), 1464 (s), 1109 (s), 1010 (m), 735 (vs).
135b: HPLC analysis indicated that the enantiomeric excess of the product was 98% [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 19.9 (+), 22.1 (-) min]. \([\alpha]_D^{20} = -135.2\) (c = 0.722, CHCl3); \(^1\)H-NMR (CDCl3, 500 MHz) \(\delta\) ppm 8.01 (bs, 1H), 7.59 (d, 1H, \(J = 7.4\) Hz), 7.31 (dd, 1H, \(J = 1.1\) Hz, \(J = 7.0\) Hz), 7.25-7.13 (m, 7H), 5.93 (bs, 1H), 5.05 (bs, 1H), 4.30 (d, 2H, \(J = 5.6\) Hz), 3.89 (d, 1H, \(J = 16.5\) Hz), 3.40-3.27 (m, 2H), 1.36 (bs, 3H); \(^1^3\)C-NMR (CDCl3, 125 MHz) \(\delta\) ppm 156.1, 139.8, 136.3, 129.8, 128.3, 127.2, 126.9, 121.7, 119.4, 117.9, 110.9, 61.9, 52.1, 38.6, 23.4, 14.7; HRMS: m/z (FAB) calc for C20H20N2O2 (M⁺) 320.1525, found 320.1505; IR(film): \(\nu\) [cm\(^{-1}\)] = 3402 (m), 3323 (s), 2922 (s), 2850 (m), 1707 (vs), 1451 (s), 1418 (s), 1313 (m), 1234 (m), 1102 (s), 997 (s), 741 (s).

2,3,4,9-tetrahydro-1-(2-methoxyphenyl)-2-tosyl-1H-pyrido[3,4-b]indole (133c). 2,3,4,9-tetrahydro-3-(2-methoxyphenyl)-2-tosyl-1H-pyrido[3,4-b]indole (135c) (Table 17, Entry 3).

The general procedure A was followed with 2,5-dihydro-2-(2-methoxyphenyl)-1-tosyl-1H-pyrrole (30.009 mmol) and phenylhydrazine (98 mg, 0.9 mmol), Rh(acac)(CO)₂ (2.4 mg, 0.009 mmol) and PPh₃ (12 mg, 0.045 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 5/1) to give (43 mg, 11% yield) of the 133c and (236 mg, 60% yield) of the 135c.

133c: HPLC analysis indicated that the enantiomeric excess of the product was 0% [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 31.1, 54.6 min]. \(^1\)H-NMR (CDCl3, 500 MHz) \(\delta\) ppm 8.29 (s, 1H), 7.61 (d, 2H, \(J = 8.1\) Hz), 7.38 (d, 1H, \(J = 7.7\) Hz), 7.23 (d, 2H, \(J = 8.3\) Hz), 7.14-7.08 (m, 4H), 7.04 (t, 1H, \(J = 7.4\) Hz), 6.93 (d, 1H, \(J = 8.2\) Hz), 6.84 (t, 1H, \(J = 7.5\) Hz), 6.63 (s, 1H), 4.21 (dd, 1H, \(J = 3.1\) Hz, \(J = 14.1\) Hz), 3.92 (s, 3H), 3.59 (ddd, 1H, \(J = 5.0\) Hz, \(J = 9.6\) Hz, \(J = 14\) Hz), 2.72-2.60 (m, 2H), 2.31 (s, 3H); \(^1^3\)C-NMR (CDCl3, 100 MHz) \(\delta\) ppm 156.0, 143.0, 138.1, 135.7, 132.0, 129.3, 129.1, 128.7, 128.0, 126.8, 126.4, 121.9, 121.1, 119.3, 118.1, 111.4, 110.9, 108.3, 55.9, 50.8, 41.7, 21.4, 20.6; HRMS: m/z (ESI) calc for C25H25N2O3S (M+H⁺) 433.1586, found 433.1578; IR(film): \(\nu\) [cm\(^{-1}\)] = 3415 (m), 2909 (w), 2830 (w), 2364 (m), 2324 (m), 1602 (w), 1490 (m), 1339 (s), 1247 (m), 1162 (vs).
**135c**: HPLC analysis indicated that the enantiomeric excess of the product was 95% [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 17.5 (-), 19.9 (+) min]. \( \alpha_{20}^{20} = -37.5 \) (c = 0.431, CHCl₃); \(^1\)H-NMR (CDCl₃, 400 MHz) \( \delta \) ppm 7.92 (s, 1H), 7.38 (d, 1H, \( J = 7.7 \) Hz), 7.27 (d, 1H, \( J = 8.0 \) Hz), 7.14 (dd, 1H, \( J = 7.4 \) Hz, \( J = 14.9 \) Hz), 7.08-7.01 (m, 3H), 6.89 (d, 1H, \( J = 7.6 \) Hz), 6.81 (d, 1H, \( J = 8.2 \) Hz), 6.57 (t, 1H, \( J = 7.5 \) Hz), 5.98 (d, 1H, \( J = 6.8 \) Hz), 4.78 (d, 1H, \( J = 16.9 \) Hz), 4.08 (d, 1H, \( J = 16.9 \) Hz), 3.77 (s, 3H), 3.17 (dd, 1H, \( J = 6.9 \) Hz, \( J = 16.2 \) Hz), 2.99 (d, 1H, \( J = 16.2 \) Hz), 2.25 (s, 3H); \(^1\)C-NMR (CDCl₃, 100 MHz) \( \delta \) ppm 157.1, 142.9, 137.5, 136.0, 129.1, 128.9, 128.9, 127.7, 127.3, 127.0, 126.9, 121.9, 119.9, 119.4, 118.0, 110.9, 110.5, 107.7, 55.3, 48.5, 39.9, 24.4, 21.3; HRMS: m/z (ESI) calc for C\(_{22}\)H\(_{22}\)N\(_2\)O\(_3\)S (M+H\(^+\)) 433.1586, found 433.1578; IR(film): \( \nu \) [cm\(^{-1}\)] = 3395 (s), 3060 (w), 2922 (m), 2843 (m), 1910 (w), 1595 (s), 1478 (vs), 1470 (s), 1321 (m), 1148 (vs), 892 (s).

2,3,4,9-tetrahydro-1-(4-methoxyphenyl)-2-tosyl-1H-pyrido[3,4-b]indole (133d), 2,3,4,9-tetrahydro-3-(4-methoxyphenyl)-2-tosyl-1H-pyrido[3,4-b]indole (135d) (Table 17, Entry 4).

The general procedure A was followed with 2,5-dihydro-2-(4-methoxyphenyl)-1-tosyl-1H-pyrrole (30.009 mmol) and PPh\(_3\) (12 mg, 0.045 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 5/1) to give (47 mg, 12% yield) of the 133d and (252 mg, 64% yield) of the 135d.

**133d**: \( \alpha_{20}^{20} = 0 \) (c = 1.124, CHCl₃); \(^1\)H-NMR (CDCl₃, 500 MHz) \( \delta \) ppm 7.79 (s, 1H), 7.57 (d, 2H, \( J = 8.2 \) Hz), 7.40 (d, 1H, \( J = 7.8 \) Hz), 7.25 (d, 1H, \( J = 6.7 \) Hz), 7.19 (d, 2H, \( J = 8.6 \) Hz), 7.13 (dt, 2H, \( J = 8.0 \) Hz, \( J = 22.9 \) Hz), 7.07 (d, 2H, \( J = 7.9 \) Hz), 6.80 (d, 2H, \( J = 8.7 \) Hz), 6.27 (s, 1H), 3.98 (dd, 1H, \( J = 5.4 \) Hz, \( J = 14.4 \) Hz), 3.78 (s, 3H), 3.29 (ddd, 1H, \( J = 4.7 \) Hz, \( J = 11.9 \) Hz, \( J = 14.6 \) Hz), 2.66-2.51 (m, 2H), 2.28 (s, 3H); \(^1\)C-NMR (CDCl₃, 125 MHz) \( \delta \) ppm 159.5, 143.1, 137.9, 136.0, 131.4, 130.6, 129.9, 129.4, 126.7, 126.5, 122.2, 119.5, 118.2, 113.8, 110.9, 109.7, 55.3 (1xCH, 1xCH\(_2\)), 39.2, 21.4, 20.1; HRMS: m/z (ESI) calc for C\(_{22}\)H\(_{22}\)N\(_2\)O\(_3\)S (M+H\(^+\)) 433.1586, found 433.1577; IR(film): \( \nu \) [cm\(^{-1}\)] = 3395 (m), 3060 (w), 2922 (m), 2843 (m), 1910 (w), 1595 (s), 1478 (vs), 1470 (s), 1254 (s), 1148 (vs), 892 (s)
135d: HPLC analysis indicated that the enantiomeric excess of the product was 96% [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 37.0 (-), 51.7 (+) min].

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\alpha_{D}^{20} = +19.4 \quad (c = 0.642, \text{CHCl}_3); \quad \text{H-NMR (CDCl}_3, 400 MHz) \quad \delta \quad \text{ppm} \\
8.01 (s, 1H), 7.64 (d, 2H, \text{J} = 8.1 \text{ Hz}), 7.43 (d, 1H, \text{J} = 7.6 \text{ Hz}), 7.27 (d, 1H, \text{J} = 7.9 \text{ Hz}), 7.18-7.05 (m, 6H), 6.64 (d, 2H, \text{J} = 8.7 \text{ Hz}), 5.51 (d, 1H, \text{J} = 6.2 \text{ Hz}), 4.82 (d, 1H, \text{J} = 17.0 \text{ Hz}), 3.94 (d, 1H, \text{J} = 17.0 \text{ Hz}), 3.67 (s, 3H), 3.13 (d, 1H, \text{J} = 16.2 \text{ Hz}), 2.87 (dd, 1H, \text{J} = 6.3 \text{ Hz}, \text{J} = 15.9 \text{ Hz}), 2.28 (s, 3H); \quad \text{C-NMR (CDCl}_3, 100 MHz) \quad \delta \quad \text{ppm} \\
158.7, 143.3, 137.5, 136.0, 130.4, 129.5, 128.9, 128.8, 126.7, 126.6, 121.9, 119.4, 117.9, 113.6, 111.0, 106.9, 55.1, 53.4, 39.2, 22.5, 21.4; \quad \text{HRMS: m/z (ESI) calc for C}_{25}H_{25}N_2O_2S (M+H^+) 433.1586, found 433.1579; \quad \text{IR(film): } \nu \quad \text{[cm}^{-1}\text{]} = 3389 (m), 2922 (m), 2850 (m), 2922 (m), 2850 (m), 2108 (s), 1516 (vs), 1457 (s), 1332 (s), 1245 (s), 1162 (s), 918 (s);
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1-(4-chlorophenyl)-2,3,4,9-tetrahydro-2-tosyl-1H-pyrido[3,4-b]indole (133e). 3-(4-chlorophenyl)-2,3,4,9-tetrahydro-2-tosyl-1H-pyrido[3,4-b]indole (135e). (Table 17, Entry 5)

The general procedure A was followed with 2-(4-chlorophenyl)-2,5-dihydro-1-tosyl-1H-pyrrole (345 mg, 1.03 mmol), phenylhydrazine (113 mg, 1.03 mmol), Rh(acac)(CO)\textsubscript{2} (2.6 mg, 0.01 mmol) and PPh\textsubscript{3} (14 mg, 0.052 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 5/1) to give (98 mg, 22% yield) of the 133e and (234 mg, 52% yield) of the 135e.

133e: \text{H-NMR (CDCl}_3, 400 MHz) \quad \delta \quad \text{ppm} \\
7.96 (s, 1H), 7.54 (d, 2H, \text{J} = 8.1 \text{ Hz}), 7.37 (d, 1H, \text{J} = 7.8 \text{ Hz}), 7.26-7.12 (m, 6H), 7.08 (d, 1H, \text{J} = 7.5 \text{ Hz}), 7.04 (d, 2H, \text{J} = 8.0 \text{ Hz}), 6.27 (s, 1H), 3.97 (dd, 1H, \text{J} = 5.4 \text{ Hz}, \text{J} = 14.5 \text{ Hz}), 3.26-3.15 (m, 1H), 2.63-2.46 (m, 2H), 2.28 (d, 1H, \text{J} = 6.9 \text{ Hz}), 2.25 (s, 3H); \quad \text{C-NMR (CDCl}_3, 100 MHz) \quad \delta \quad \text{ppm} \\
143.4, 137.8, 137.6, 136.1, 134.2, 129.9, 129.7, 129.4, 128.6, 126.7, 126.4, 122.4, 119.6, 118.3, 111.0, 109.9, 55.1, 39.3, 21.4, 19.9; \quad \text{HRMS: m/z (ESI) calc for C}_{24}H_{22}N_2O_2SCl (M+H^+) 437.10850, found 437.10826; \quad \text{IR(film): v [cm}^{-1}\text{]} =3382 (s), 3054 (m), 2916 (s), 2850 (m), 2005 (m), 1516 (vs), 1451 (s), 1326 (s), 1240 (vs), 1155 (vs), 1089 (s);
2239 (w), 1930 (w), 1590 (s), 1483 (vs), 1444 (s), 1340 (vs), 1300 (s), 1162 (vs), 1096 (vs), 754 (vs).

**135e:** Enantiomeric excess could not be determined. $[\alpha]_{D}^{20} = +45.6$ (c = 1.24, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 8.07 (s, 1H), 7.65 (d, 2H, J = 8.2 Hz), 7.44 (d, 1H, J = 7.6 Hz), 7.28 (d, 1H, J = 7.8 Hz), 7.20-7.06 (m, 8H), 5.53 (d, 1H, J = 6.1 Hz), 4.87 (d, 1H, J = 17.1 Hz), 3.95 (d, 1H, J = 17.1 Hz), 3.13 (d, 1H, J = 16.2 Hz), 2.88 (dd, 1H, J = 6.2 Hz, J = 16.1 Hz), 2.28 (s, 3H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 143.5, 137.2, 136.9, 136.1, 133.3, 129.6, 129.1, 128.5, 128.4, 126.6, 126.5, 122.0, 119.5, 117.8, 111.0, 106.4, 53.4, 39.3, 22.3, 21.4; HRMS: m/z (ESI) calc for C$_{24}$H$_{22}$N$_2$OSCl (M+H$^+$) 437.10850, found 437.10824; IR(film): $\nu$ [cm$^{-1}$] = 3389 (vs), 3060 (m), 2909 (s), 2581 (w), 2305 (w), 1924 (w), 1707 (m), 1602 (s), 1490 (vs), 1332 (s), 1247 (s), 1175 (vs), 1024 (s), 932 (s), 761 (vs).

1-(4-(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-2-tosyl-1H-pyrido[3,4-b]indole (133f).
3-(4-(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-2-tosyl-1H-pyrido[3,4-b]indole (135f) (Table 17, Entry 6)
The general procedure A was followed with 2-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1-tosyl-1H-pyrrole (300 mg, 0.82 mmol), phenylhydrazine (89 mg, 0.82 mmol), Rh(acac)(CO)$_2$ (2.2 mg, 0.008 mmol) and PPh$_3$ (11 mg, 0.041 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 5/1) to give (92 mg, 24 % yield) of the 133f and (131 mg, 34 % yield) of the 135f.

**133f:** $^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.99 (bs, 1H), 7.53 (d, 2H, J = 8.1 Hz), 7.50 (d, 2H, J = 8.1 Hz), 7.38 (d, 3H, J = 7.9 Hz), 7.25 (d, 1H, J = 8.2 Hz), 7.16 (t, 1H, J = 7.5 Hz), 7.08 (t, 1H, J = 7.4 Hz), 7.03 (d, 2H, J = 8.0 Hz), 6.34 (s, 1H), 4.00 (dd, 1H, J = 5.0 Hz, J = 14.5 Hz), 3.27-3.17 (m, 1H), 2.66-2.47 (m, 2H), 2.25 (s, 3H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 143.5, 143.1, 137.4, 136.2, 130.6, 130.3, 129.4, 129.3, 128.9, 126.6, 126.4, 125.4, 122.5, 119.7, 118.3, 111.1, 109.9, 55.3, 39.6, 21.3, 19.9; HRMS: m/z (ESI) calc for C$_{25}$H$_{22}$N$_2$F$_3$S (M+H$^+$) 471.13486, found 471.13430; IR(film): $\nu$ [cm$^{-1}$] = 3382 (s), 3054 (m), 2929 (s), 2850 (m), 252 (w), 1917 (w), 1615 (s), 1602 (s), 1451(s), 1326 (vs), 1162 (vs), 1129 (vs), 1063 (s), 905 (vs).
**135f**: Enantiomeric excess could not be determined. $[\alpha]_D^{20} = +36.1$

c = 0.750, CHCl$_3$; $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 8.00 (s, 1H), 7.65 (d, 2H, $J = 8.2$ Hz), 7.44 (d, 1H, $J = 7.6$ Hz), 7.41-7.34 (m, 4H), 7.28 (d, 1H, $J = 7.9$ Hz), 7.18-7.07 (m, 4H), 5.60 (d, 1H, $J = 6.0$ Hz), 4.88 (d, 1H, $J = 17.1$ Hz), 3.96 (d, 1H, $J = 17.1$ Hz), 3.18 (d, 1H, $J = 16.3$ Hz), 2.93 (dd, 1H, $J = 5.9$ Hz, $J = 16.4$ Hz), 2.29 (s, 3H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 143.7, 143.3, 142.5, 137.2, 136.1, 129.9, 129.7, 129.5, 128.4, 128.0, 126.7, 126.5, 125.3, 122.2, 119.6, 117.9, 111.1, 106.4, 53.6, 39.5, 22.4, 21.4; HRMS: m/z (ESI) calc for C$_{25}$H$_{22}$N$_2$F$_3$S (M+H$^+$) 471.13486, found 471.13429; IR(film): $\nu$ [cm$^{-1}$] = 3389 (s), 3054 (w), 2916 (m), 2843 (m), 1937 (w), 1713 (m), 1621 (m), 1451 (s), 1313 (vs), 1175 (vs), 932 (s).

**1-ethyl-2,3,4,9-tetrahydro-2-tosyl-1H-pyrido[3,4-b]indole (133g)**. **1-ethyl-2,3,4,9-tetrahydro-2-tosyl-1H-pyrido[3,4-bj]indole (135g)** (Table 17, Entry 7).

The general procedure A was followed with 2-ethyl-2,5-dihydro-1-tosyl-1H-pyrrole (200 mg, 0.8 mmol), phenylhydrazine (87 mg, 0.8 mmol), Rh(acac)(CO)$_2$ (2.1 mg, 0.008 mmol) and PPh$_3$ (10 mg, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 8/1) to give (42 mg, 15 % yield) of the 133g and (142 mg, 50 % yield) of the 135g.

**133g**: HPLC analysis indicated that the enantiomeric excess of the product was 0 % [Diacle Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 17.0, 20.6 min]. $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 7.87 (bs, 1H), 7.61 (d, 2H, $J = 8.1$ Hz), 7.28 (dd, 2H, $J = 5.1$ Hz, $J = 7.5$ Hz), 7.12 (t, 1H, $J = 7.6$ Hz), 7.07 (d, 2H, $J = 8.1$ Hz), 7.02 (t, 1H, $J = 7.4$ Hz), 5.05 (dd, 1H, $J = 5.2$ Hz, $J = 8.3$ Hz), 4.11 (dd, 1H, $J = 5.6$ Hz, $J = 14.7$ Hz), 3.39 (ddd, 1H, $J = 4.5$, $J = 12.0$, $J = 14.6$), 2.47 (dd, 1H, $J = 4.3$ Hz, $J = 15.7$ Hz), 2.41-2.30 (m, 1H), 2.26 (s, 1H), 1.87 (td, 1H, $J = 7.3$ Hz, $J = 14.9$ Hz, $J = 37.5$ Hz), 1.10 (t, 1H, $J = 7.4$ Hz); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 143.1, 138.1, 135.7, 133.0, 129.4, 126.7, 126.6, 121.9, 119.4, 118.1, 110.8, 107.7, 54.5, 39.7, 28.9, 21.4, 19.7, 10.9; Analytical data fits with literature.

**135g**: HPLC analysis indicated that the enantiomeric excess of the product was 94 % [Diacle Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection
wavelength = 254 nm; TR = 18.2 (-), 22.5 (+) min. \([\alpha]_{D}^{20} = -6.8 (c = 0.852, \text{CHCl}_3)\); \(^1\)H-NMR (CDCl\(_3\), 500 MHz) \(\delta\) ppm 8.05 (bs, 1H), 7.65 (d, 2H, \(J = 8.1\) Hz), 7.35 (d, 1H, \(J = 7.8\) Hz), 7.27 (d, 1H, \(J = 8.0\) Hz), 7.13 (d, 2H, \(J = 8.4\) Hz), 7.05 (t, 1H, \(J = 7.4\) Hz), 4.91 (d, 1H, \(J = 16.8\) Hz), 4.32-4.24 (m, 2H), 2.67 (dd, 1H, \(J = 5.8\) Hz, \(J = 15.7\) Hz), 2.57 (d, 1H, \(J = 15.6\) Hz), 2.30 (s, 3H), 1.56-1.38 (m, 1H), 0.93 (t, 3H, \(J = 7.4\) Hz); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 143.2, 137.6, 136.1, 129.6, 127.8, 127.3, 126.6, 121.7, 119.3, 117.8, 110.9, 106.5, 53.9, 38.9, 24.2, 24.0, 21.4, 11.2, HRMS: m/z (ESI) calc for C\(_{20}\)H\(_{18}\)N\(_2\)O\(_2\)S (M+H\(^{+}\)) 355.14748, found 355.14755; IR(film): \(\nu [\text{cm}^{-1}] = 3375 (\text{m}), 3224 (\text{m}), 2962 (\text{m}), 2108 (\text{w}), 1654 (\text{m}), 1451 (\text{m}), 1326 (\text{s}), 1155 (\text{vs}), 1096 (\text{m}); \)

2,3,4,9-tetrahydro-1-propyl-2-tosyl-1H-pyrrole[3,4-b]indole (133h). \(\) 2,3,4,9-tetrahydro-3-propyl-2-tosyl-1H-pyrrole[3,4-b]indole (135h) (Table 17, Entry 8).

The general procedure A was followed with 2-ethyl-2,5-dihydro-1-tosyl-1H-pyrrole (200 mg, 0.75 mmol), phenylhydrazine (82 mg, 0.75 mmol), Rh(acac)(CO)\(_2\) (2.0 mg, 0.0075 mmol) and PPh\(_3\) (10 mg, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 8/1) to give (41 mg, 15 % yield) of the 133g and (149 mg, 54 % yield) of the 135g.

133h: HPLC analysis indicated that the enantiomeric excess of the product was 0 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 \(\mu\)m); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 18.0, 21.8 min].

\(^1\)H-NMR (CDCl\(_3\), 500 MHz) \(\delta\) ppm 7.85 (s, 1H), 7.60 (d, 2H, \(J = 8.2\) Hz), 7.27 (dd, 2H, \(J = 3.3\) Hz, \(J = 7.8\) Hz), 7.12 (t, 1H, \(J = 7.5\) Hz), 7.06 (d, 2H, \(J = 8.1\) Hz), 7.02 (t, 1H, \(J = 7.6\) Hz), 5.12 (t, 1H, \(J = 6.7\) Hz), 4.10 (dd, 1H, \(J = 5.7\) Hz, \(J = 14.7\) Hz), 3.39 (ddd, 1H, \(J = 4.6\) Hz, \(J = 12.1\) Hz, \(J = 14.8\) Hz), 2.46 (dd, 1H, \(J = 4.3\) Hz, \(J = 15.7\) Hz), 2.33 (dd, 1H, \(J = 5.5\) Hz, \(J = 11.4\) Hz), 2.25 (s, 3H), 1.81 (dd, 2H, \(J = 7.5\) Hz, \(J = 14.9\) Hz), 1.64-1.50 (m, 1H), 0.96 (t, 3H, \(J = 7.3\) Hz); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 143.1, 138.1, 135.7, 133.2, 129.4, 126.7, 126.6, 121.9, 119.4, 118.1, 110.8, 107.6, 53.0, 39.5, 38.1, 21.4, 19.7, 19.5, 13.9; HRMS: m/z (ESI) calc for C\(_{21}\)H\(_{23}\)N\(_2\)O\(_2\)S (M+H\(^{+}\)) 369.16313, found 369.16312; IR(film): \(\nu [\text{cm}^{-1}] = 3369 (\text{m}), 2948 (\text{m}), 2922 (\text{m}), 1924 (\text{w}), 1595 (\text{m}), 1444 (\text{m}), 1326 (s), 1162 (\text{vs}), 1089 (\text{m}); \)

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135h: HPLC analysis indicated that the enantiomeric excess of the product was 93 % [Diacel Chiralcel AD (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 16.5 (-), 20.9 (+) min]. \( [\alpha]_D^{20} = -14.2 \) (c = 0.608, CHCl3); \(^1\)H-NMR (CDCl3, 500 MHz) \( \delta \) ppm 8.03 (s, 1H), 7.65 (d, 2H, \( J = 8.2 \) Hz), 7.34 (d, 1H, \( J = 7.8 \) Hz), 7.28 (d, 1H, \( J = 7.9 \) Hz), 7.13 (d, 2H, \( J = 8.0 \) Hz), 7.08 (dt, 2H, \( J = 7.3 \) Hz, \( J = 15.0 \) Hz), 4.91 (d, 1H, \( J = 16.8 \) Hz), 4.39 (d, 1H, \( J = 6.4 \) Hz), 4.29 (d, 1H, \( J = 16.9 \) Hz), 2.67 (dd, 1H, \( J = 5.8 \) Hz, \( J = 15.6 \) Hz), 2.54 (d, 1H, \( J = 15.6 \) Hz), 2.30 (s, 3H), 1.50-1.30 (m, 4H), 0.85 (t, 3H, \( J = 6.9 \) Hz); \(^{13}\)C-NMR (CDCl3, 100 MHz) \( \delta \) ppm 143.1, 137.6, 136.1, 129.5, 127.8, 127.3, 126.7, 121.8, 119.3, 117.8, 110.9, 106.6, 52.0, 39.0, 33.3, 24.3, 21.4, 19.7; HRMS: m/z (ESI) calc for C\(_{21}\)H\(_{25}\)N\(_2\)O\(_2\)S (M+H\(^+\)) 369.16313, found 369.16318; IR(film): \( \nu \) [cm\(^{-1}\)] = 3382 (m), 2955 (m), 2929 (m), 1468 (m), 1457 (s), 1339 (s), 1148 (vs), 1096 (s).

2,3,4,9-tetrahydro-8-methyl-3-phenyl-2-tosyl-1H-pyrido[3,4-b]indole, (135i), (Table 18, Entry 1)

The general procedure C was followed with 2,5-dihydro-2-phenyl-1-tosyl-1H-pyrrole (300 mg, 1 mmol), 2-(diphenylmethylene)-1-otolyldrazine (286 mg, 1 mmol), PTSA (190 mg, 1 mmol), Rh(acac)(CO)\(_2\) (2.6 mg, 0.01 mmol) and PPh\(_3\) (13 mg, 0.05 mmol).

The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 6/1) to give (187 mg, 45 % yield) of the title compound. HPLC analysis indicated that the enantiomeric excess of the product was 95 % [Diacel Chiralcel OD-H (0.46 cm x 25 cm, 5 µm); heptane/2-propanol = 90/10; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 13.4 (-), 21.9 (+) min]. \( [\alpha]_D^{20} = -121.1 \) (c = 0.339, CHCl3); \(^1\)H-NMR (CDCl3, 500 MHz) \( \delta \) ppm 7.82 (s, 1H), 7.66 (d, 2H, \( J = 8.2 \) Hz), 7.32-7.24 (m, 3H), 7.18-7.14 (m, 3H), 7.12 (d, 2H, \( J = 8.1 \) Hz), 7.02 (t, 1H, \( J = 7.4 \) Hz), 6.96 (d, 1H, \( J = 7.1 \) Hz), 5.57 (d, 1H, \( J = 6.2 \) Hz), 4.86 (d, 1H, \( J = 17.0 \) Hz), 3.99 (d, 1H, \( J = 17.0 \) Hz), 3.18 (d, 1H, \( J = 16.2 \) Hz), 2.89 (dd, 1H, \( J = 6.2 \) Hz, \( J = 16.1 \) Hz), 2.41 (s, 3H), 2.29 (s, 3H); \(^{13}\)C-NMR (CDCl3, 100 MHz) \( \delta \) ppm 143.3, 138.4, 137.6, 135.6, 129.6, 128.4, 128.3, 127.7, 127.5, 1.7, 126.2, 122.6, 120.2, 119.7, 115.7, 107.5, 53.9, 39.4, 22.5, 21.4, 16.6; HRMS: m/z (ESI) calc for C\(_{25}\)H\(_{25}\)N\(_2\)O\(_2\)S (M+H\(^+\)) 417.1637, found 417.1628;
6-chloro-2,3,4,9-tetrahydro-1-phenyl-2-tosyl-1H-pyrido[3,4-b]indole (133j).

The general procedure C was followed with 2,5-dihydro-2-phenyl-1-tosyl-1H-pyrrole (300 mg, 1 mmol), 1-(4-chlorophenyl)-2-(diphenylmethylene)hydrazine (307 mg, 1 mmol), PTSA (190 mg, 1 mmol), Rh(acac)(CO)\(_2\) (2.6 mg, 0.01 mmol) and PPh\(_3\) (13 mg, 0.05 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate = 6/1) to give (35 mg, 8% yield) of the 133j and (144 mg, 33% yield) of the 135j.

**133j:** \([\alpha]_D^{20} = 0\) (c = 1.12, CHCl\(_3\)), \(^1\)H-NMR (CDCl\(_3\), 500 MHz) \(\delta\) ppm 7.81 (d, 1H, J = 11.0 Hz), 7.54 (d, 2H, J = 8.0 Hz), 7.34-7.20 (m, 6H), 7.15 (d, 1H, J = 8.6 Hz), 7.09 (d, 1H, J = 8.6 Hz), 7.05 (d, 2H, J = 7.9 Hz), 6.29 (s, 1H), 3.96 (dd, 1H, J = 4.9 Hz, J = 11.3 Hz, J = 14.6 Hz), 2.60-2.45 (m, 2H), 2.27 (s, 3H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 143.3, 138.9, 134.4, 131.9, 129.4, 128.7, 128.5, 127.6, 126.8, 125.3, 122.5, 117.9, 111.9, 109.7, 108.2, 55.7, 39.2, 21.4, 19.9; HRMS: m/z (ESI) calc for C\(_{24}\)H\(_{22}\)N\(_2\)O\(_2\)SCl (M+H\(^+\)) 437.1090, found 437.1083; IR(film): \(\nu\) [cm\(^{-1}\)] = 3054 (w), 2909 (w), 2843 (w), 1628 (m), 1589 (m), 1444 (s), 1326 (s), 1300 (s), 1155 (vs), 1090 (m), 938 (m).

**135j:** HPLC analysis indicated that the enantiomeric excess of the product was 95% [Diacel Chiralcel OJ-H (0.46 cm x 25 cm, 5 \(\mu\)m); heptane/2-propanol = 95/5; flow rate = 1 mL/min; detection wavelength = 254 nm; TR = 11.4 (-), 14.2 (+) min]. \([\alpha]_D^{20} = -114.2\) (c = 0.895, CHCl\(_3\)); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) ppm 7.84 (s, 1H), 7.65 (d, 2H, J = 8.1 Hz), 7.36 (d, 2H, J = 11.2 Hz), 7.24-7.06 (m, 8H), 5.54 (d, 1H, J = 6.2 Hz), 4.82 (d, 1H, J = 17.2 Hz), 3.94 (d, 1H, J = 17.2 Hz), 3.12 (d, 1H, J = 16.2 Hz), 2.83 (dd, 1H, J = 6.3 Hz, J = 16.3 Hz), 2.30 (s, 3H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 143.5, 138.1, 137.4, 134.3, 130.3, 129.6, 128.4, 127.8, 127.6, 126.8, 125.3, 122.2, 117.6, 111.9, 106.9, 53.8, 39.3, 22.1, 21.5; HRMS: m/z (ESI) calc for C\(_{24}\)H\(_{22}\)N\(_2\)O\(_2\)SCl (M+H\(^+\))
437.1090, found 437.1083; IR(film): ν [cm⁻¹] = 3054 (w), 3034 (w), 2902 (w), 2850 (w), 1595 (m), 1497 (m), 1437 (s), 1326 (vs), 1286 (s), 1155 (vs), 1090 (m), 920 (m), 754 (s).

2,3,4,9-tetrahydro-6-methoxy-3-phenyl-2-tosyl-1H-pyrido[3,4-b]indole (135k). (Table 18, Entry 3)

The general procedure C was followed with 2,5-dihydro-2-phenyl-1-tosyl-1H-pyrrrole (300 mg, 1 mmol), 1-(4-methoxyphenyl)-2-(diphenylmethylene)hydrazine (302 mg, 1 mmol), PTSA (190 mg, 1 mmol), Rh(acac)(CO)₂ (2.6 mg, 0.01 mmol) and PPh₃ (13 mg, 0.05 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/ethylacetate = 6/1) to give (198 mg, 46 % yield) of the title compound.

1H-NMR (CDCl₃, 400 MHz) δ ppm 8.12 (s, 1H), 7.75 (d, 2H, J = 7.9 Hz), 7.59 (d, 2H, J = 11.2 Hz), 7.44-7.16 (m, 8H), 5.61 (d, 1H, J = 6.9 Hz), 4.93 (d, 1H, J = 16.2 Hz), 3.96 (d, 1H, J = 17.2 Hz), 3.80 (s, 3H), 3.06 (d, 1H, J = 16.8 Hz), 2.90 (dd, 1H, J = 6.6 Hz, J = 16.2 Hz), 2.35 (s, 3H); HRMS: m/z (ESI) calc for C₂₅H₂₅N₂O₃S (M+H⁺) 432.15076, found 432.15070;

2,3,4,9-tetrahydro-3-phenyl-2-tosyl-6-(4H-1,2,4-triazol-4-yl)-1H-pyrido[3,4-b]indole, (157)

The general procedure C was followed with 2,5-dihydro-2-phenyl-1-tosyl-1H-pyrrrole (x) (250 mg, 0.8 mmol), α-Boc-1-(4-(4H-1,2,4-triazol-4-yl)phenyl)hydrazine (220 mg, 0.8 mmol), Rh(acac)(CO)₂ (2.79 mg, 0.008 mmol) and PPh₃ (12 mg, 0.04 mmol) The crude reaction mixture was purified by flash column chromatography on silica gel (DCM/MeOH = 15/1) to give (150 mg, 45 %) of the title compound. ¹H-NMR (CDCl₃, 400 MHz) δ ppm 8.56 (s, 1H), 8.46 (m, 2H), 7.70 (d, 2H, J = 8.3 Hz), 7.43 (d, 1H, J = 8.5 Hz), 7.41 (d, 1H, J = 1.8 Hz), 7.22 (m, 5H), 7.18 (d, 2H, J = 8.3 Hz), 7.13 (dd, 1H, J = 2.0 Hz, J = 8.5 Hz), 5.59 (d, 1H, J = 6.2 Hz), 4.93 (d, 1H, J = 17.1 Hz), 4.02 (d, 1H, J = 17.2 Hz), 3.21 (d, 1H, J = 16.1 Hz), 2.97 (dd, 1H, J = 6.4 Hz, J = 16.2 Hz), 2.33 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 143.5, 138.0, 137.4, 135.7, 131.9, 129.6, 128.5, 127.7, 127.5, 127.2, 126.8, 126.5, 116.8, 112.4, 112.3, 107.6, 55.6, 39.2, 35.7, 22.4, 21.5; HRMS: m/z (ESI) calc for C₂₆H₂₃N₂O₂S (M+H⁺) 470.1651, found 470.1639; IR(film): ν [cm⁻¹] = 3040 (w), 3029 (w), 2906 (w), 2850 (m), 1599 (s), 1488 (m), 1437 (s), 1321 (vs), 1240 (s), 1151 (vs), 1090 (m), 754 (s).
(R)-1-phenylprop-2-en-1-amine, (161)

To a solution of 2-((R)-1-phenylallyl)isoindoline-1,3-dione (3.45g, 13.1 mmol) in 50 ml of ethanol was added 1,2 ethanoldiamine (1.5g, 20 mmol) and resulting solution was stirred under reflux over night. After completion of reaction, formed solids were filtered of, filtrate was concentrated under reduced pressure and submitted to column chromatography on silica gel (cyclohexane/ethylacetate=1/1.5) to give the title compound (1.55 g , 89 %) as colourless oil. \([\alpha]_D^{20}=+10.0\) (c = 1.25, CHCl₃); \(^1\)H-NMR (CDCl₃, 500 MHz) δ ppm 7.36-7.29 (m, 4H), 7.26-7.20 (m, 1H), 6.01 (ddd, 1H, J = 6.1 Hz, J = 10.2 Hz, J = 16.6 Hz), 5.23 (d, 1H, J = 17.1 Hz), 5.09 (d, 1H, J = 10.3 Hz), 4.51 (d, 1H, J = 6.1 Hz), 1.53 (bs, 2H); \(^1\)C-NMR (CDCl₃, 100 MHz) δ ppm 144.4, 142.2, 128.5, 127.1, 126.6, 113.6, 58.4, 35.7; Analytical data fits with literature.\(^\text{115}\)

(R)-1-phenyl-N-tosylprop-2-en-1-amine, (162)

The general procedure for tosylation was followed with (R)-1-phenylprop-2-en-1-amine (1.4 g, 10.5 mmol), Et₃N (2 ml, 15 mmol) and TsCl (2.86 g, 15 mmol) in 25 ml of DCM. The reaction was conducted at r.t. for 22 h. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 10/1) to give the title compound (3.92 g, 91 %) as white solid. \([\alpha]_D^{20}=+52.8\) (c = 1.15, CHCl₃); \(^1\)H-NMR (CDCl₃, 400 MHz) δ ppm 7.61 (d, 2H, J = 8.2 Hz), 7.24-7.14 (m, 5H), 7.10-7.04 (m, 2H), 5.84 (ddd, 1H, J = 5.5 Hz, J = 10.5 Hz, J = 16.4 Hz), 5.12 (s, 1H), 5.09 (d, 1H, J = 7.7 Hz), 4.95-4.83 (m, 2H), 2.37 (s, 3H); \(^1\)C-NMR (CDCl₃, 100 MHz) δ ppm 143.2, 139.3, 137.6, 137.0, 129.4, 128.6, 127.8, 127.2, 127.0, 116.8, 59.8, 35.7, 21.5; Analytical data fits with literature.\(^\text{116}\)

(R)-1-phenyl-N-((R)-1-phenylallyl)-N-tosylprop-2-en-1-amine, (163)

To a solution of (R)-1-phenyl-N-tosylprop-2-en-1-amine (290 mg, 1 mmol) in 1 ml of dry THF at -78 °C under argon atmosphere was added LiHMDS (1 ml, 1M solution in THF), solution was stirred at this temperature for 30 min. After this time anion solution was added to a stirred solution of [Ir(COD)Cl]₂ (13.5 mg, 0.02


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mmol), ligand 5 (23 mg, 0.04 mmol) and cinnamyl methylcarbonate (190 mg, 1 mmol) at -40 °C under argon atmosphere and stirred at this temperature for next 2h and then allowed to warm to r.t. and stirred for next 48h. After completion reaction was diluted with 10 ml of CH₂Cl₂, quenched with saturated NH₄Cl solution, and extracted with 3x20 ml CH₂Cl₂. Collected organic extracts were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. ¹H NMR analysis of the crude reaction mixture indicated the ratio of diastereoisomers to be 90/10. Crude product was purified by column chromatography on silica gel (cyclohexane/ethylacetate= 15/1) to give title compound (190 mg, 47 % yield) as yellow oil. [α]₂⁰ = +41.5 (c = 0.787, CHCl₃); ¹H-NMR (CDCl₃, 500 MHz) δ ppm 7.38 (d, 2H, J = 8.1 Hz), 7.30-7.06 (m, 8H), 7.00 (d, 4H, J = 6.2 Hz), 6.46 (ddd, 2H, J = 7.6 Hz, J = 10.2 Hz, J = 17.5 Hz), 5.33-5.25 (m, 4H), 5.18 (d, 2H, J = 17.3 Hz), 2.38 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 142.7, 139.0, 138.9, 136.3, 129.0, 128.7, 127.9, 127.5, 127.4, 118.6, 64.1, 21.5; HRMS: m/z (ESI) calc for C₂₅H₂₆NO₂S (M+H⁺) 404.16788, found 404.167564; IR(film): ν [cm⁻¹] = 3068 (m), 3027 (m), 2981 (m), 2909 (m), 1963 (w), 1884 (w), 1799 (w), 1595 (vs), 1497 (vs), 1457 (vs), 1424 (s), 1326 (vs), 1162 (s), 918 (vs).

2,5-Diphenyl-1-(toluene-4-sulfonyl)-2,5-dihydro-1H-pyrrole, (164)

General procedure for Grubbs metathesis was followed with 1-phenyl-N-((R)-1-phenylallyl)-N-tosylprop-2-en-1-amine (180 mg, 0.45 mmol) and Grubbs I catalyst (20 mg, 0.023 mmol) in 20 ml of CH₂Cl₂. The reaction was conducted at reflux for 24 h. The mixture was purified by column chromatography on silica gel (cyclohexane/ethylacetate = 10/1) to give the title compound (154 mg, 90 %) as white crystals. [α]₂⁰ = +361.2 (c = 0.985, CHCl₃); ¹H-NMR (CDCl₃, 400 MHz) δ ppm 7.25 (bs, 10H), 6.91 (q, 4H, J=8.3Hz), 5.77 (bs, 2H), 5.71 (bs, 2H), 2.29 (s, 3H); ¹³C-NMR (CDCl₃, 100 MHz) δ ppm 141.9, 139.3, 137.6, 129.8, 128.6, 128.2, 127.9, 127.9, 126.6, 71.1, 21.3; HRMS: m/z (ESI) calc for C₂₃H₂₂N₂OS (M+H⁺) 376.13658, found 376.13652; IR(film): ν [cm⁻¹] = 3415 (w), 3021 (w), 2916 (w), 1608 (w), 1497 (m), 1451 (m), 1345 (vs), 1168 (vs), 1096 (vs), 1070 (m), 820 (m), 708 (s).
1,3-Diphenyl-2-(toluene-4-sulfonyl)-2,3,4,9-tetrahydro-1H-b-carboline, (165)

The general procedure A was followed with 2,5-diphenyl-1-(toluene-4-sulfonyl)-2,5-dihydro-1H-pyrrolle (50 mg, 0.13 mmol), phenylhydrazine (15 mg, 0.13 mmol), Rh(acac)(CO)$_2$ (1.0 mg, 0.0013 mmol) and PPh$_3$ (3 mg, 0.005 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane/Ethylacetate = 15/1) to give (44 mg, 71 % yield) of title compound as white solid. $[\alpha]_{D}^{20} = +13.4$ (c = 0.850, CHCl$_3$);

$^1$H-NMR (CDCl$_3$, 400 MHz) δ ppm 7.77 (s, 1H), 7.53 (d, 1H, $J$ = 7.6 Hz), 7.30-7.05 (m, 14H), 6.90 (d, 2H, $J$ = 8.0 Hz), 6.67 (d, 1H, $J$ = 8.1 Hz), 6.42 (s, 1H), 5.06 (dd, 1H, $J$ = 4.1 Hz, $J$ = 9.5 Hz), 3.68 (dd, 1H, $J$ = 9.7 Hz, $J$ = 15.4 Hz), 3.16 (dd, 1H, $J$ = 4.2 Hz, $J$ = 15.4 Hz), 2.25 (s, 3H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ ppm 142.3, 139.4, 139.2, 137.9, 136.4, 131.6, 129.0, 128.7, 128.5, 128.3, 127.8, 127.4, 126.9, 126.7, 122.3, 119.7, 118.4, 111.0, 110.5, 58.2, 56.4, 24.7, 21.3; HRMS: m/z (ESI) calc for C$_{30}$H$_{27}$N$_2$O$_2$S (M+H$^+$) 479.17878, found 479.17831; IR(film): ν [cm$^{-1}$] = 3345 (m), 2929 (w), 1612 (w), 1565 (w), 1468 (s), 1320 (s), 1150 (vs), 1096 (vs), 1010 (s), 795 (s).
7 Zusammenfassung


**Scheme 85. Zugang zu chiralen Tryptaminen und Tryptamiden**

Wenn $N$-Benzhydrylidenglycinate als Substrate für die enantioselektive Ir-katalysierte allylsische Substitution mit Allylcarbonaten verwendet werden, werden Allylglycinderivate erhalten. Diese sind geeignete Substrate für die Synthese von Molekülen, die das Homotryptophangerüst enthalten. Durch die Verwendung von Phosphoramiditliganden.
Mit diesem Nukleophil wurden die Endprodukte zum ersten Mal mit hoher Ausbeute und Enantioselektivität erhalten (s. Schema 86). Niedrige Katalysator- und Ligandenbeladungen und milde Reaktionsbedingungen werden von annehmbaren Reaktionszeiten, guten Ausbeuten und exzellenten Enantioselektivitäten in allen Fällen begleitet. All dies macht die Phosphoramiditliganden zu Liganden der Wahl für diese Reaktion.

**Scheme 86.** Enantioselektive Synthese von Allylglycinaten


**Scheme 87.** Synthese von primären Homotryptophanderivaten


Zusammenfassend konnte gezeigt werden, dass die Tandem Hydroformylierung / Fischer-Indol Synthese ein sehr effizientes Werkzeug für die Synthese verschiedener Arten von funktionalisierten Indolen, beginnend mit einfachen Tryptaminen bis komplexen Tryptophanhomologa die mehrere Stereozentren tragen, ist. Der Anwendungsbereich des Tandemprozesses der unter Hydroformylierungsbedingungen ausgeführt werden kann, wurde um die Tandem Hydroformylierung / Pictet-Spengler-Reaktion erweitert. Die Bedeutung dieses Ansatz liegt in der Tatsache das es den schnellen und bequemen Zugang zu pharmakologisch wichtigen annuierten Indolsystemen, die als Tetrahydro-β-carboline bekannt sind, gestattet. Die Tandem Hydroformylierung / Pictet-Spengler Reaktion wurde zum ersten Mal in Lösung durchgeführt. Reaktionen die unter aprotischen Bedingungen laufen und Tryptophanmethylster als nukleophile Komponente und carbocyclische Olefine als Aldehydprecursor verwenden, gestatten den Zugang zu cis und trans Tetrahydro-β-carbolinen in guten Ausbeuten und annähernd im 1:1 Verhältnis in allen Fällen (s. Schema 90).
Diese Reaktion verläuft unter protischen Bedingungen d. h. in Gegenwart von Brønstedäure und Tryptamin als nukleophile Komponente und verschiedenen carbozyklischen, methallylischen Aminen und methallylischen Alkoholen als Precursor der elektrophilen Komponente unter optimierten Bedingungen in guten Ausbeuten, obgleich mit nachweisbarer Bildung von Nebenprodukten die die Ausbeute der Reaktion senken und die auch nicht ganz unterdrückt werden kann (s. Schema 91).

Die Tandem Hydroformylierung / Pictet-Spengler Reaktion gestattet die Synthese von Tetrahydro-β-carbolinen ausgehend von 1,1′ disubstituierten terminalen Olefinen; sie zeigte sich aber ungeeignet wenn empfindlichere Substrate wie terminale Olefine die ein Stereozentrum tragen verwendet wurden, so dass die Herstellung von komplexeren Carbolinstrukturen verhindert wurde. Wegen dieses Nachteils, wurde eine alternative Methode für die Synthese von Tetrahydro-β-carbolinen die, die Tandem Hydroformylierung/ Fischer-Indol Synthese einbeziehen, untersucht. Diese leistungsfähige Methode wurde für die Synthese von Tetrahydro-β-carbolinen die Substituenten enthalten, die nicht durch die Tandem Hydroformylierung / Pictet-Spengler Reaktion zugänglich sind, angewandt. Diese Substituenten wurden ziemlich generell in Positionen eingeführt, die durch klassische
Methoden unzugänglich sind. Die Verwendung von enantiomerereinem 2-substituierten 2,5-Dihydropyrrollen (zuvor hergestellt durch die allylische Aminierung / Ringschluss Metathese Methode) in der sequentiellen Hydroformylierung/ Fischer-Indol Synthese lieferte die Tetrahydro-β-carbolinstrukturen in guten Ausbeuten und mittleren Selektivitäten (s. Schema 92).

**Scheme 92.** Synthese von Tetrahydro-β-carbolinen via Tandem Hydroformylierung / Fischer-Indole Synthese


Die Gegenwart der *p*-MeO Gruppe in 5 Position des Indolkerns hat wichtige medizinische Auswirkungen, wobei die Gegenwart von Halogeniden in dieser Position weitere Derivatisierung dieser Moleküle durch Kreuzkupplungstechniken erlaubt.

Die Verwendung von 2,5-disubstituierten Pyrrolen als Substrate für die Tandem Hydroformylierung / Fischer Indolisierung gestattet die Herstellung von 1,3-disubstituierten Tetrahydro-β-carbolinen in hohen Enantioselektivitäten (s. Scheme 95).