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XXX CICLO

Exploiting Alcohols as Alkylating Agents of Heterocyclic Nucleophiles through the "Borrowing Hydrogen" Process

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Contents

Abbreviations

Ac	acetyl
acac	acetylacetonate
BHT	butylated hydroxytoluene
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
BIPHEP	2,2'-Bis(diphenylphosphino)biphenyl
Bn	benzyl
cod	1,5-cyclooctadiene
cot	1,3,5- cyclooctatriene
Cp*	1,2,3,4,5-Pentamethylcyclopentadiene
DCM	dichloromethane
dppf	1,1′-Ferrocenediyl-bis(diphenylphosphine)
dppp	1,3-Bis(diphenylphosphino)propane
Ms	mesylate
MS	molecular sieves
MW	micro wave
NMR	nuclear magnetic resonance
Nu	nucleophile
Pc	phthalocyanine
Py	pyridine
THF	tetrahydrofuran
Ts	tosylate

1. Introduction

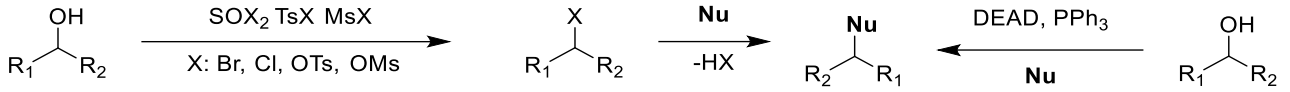
1.1 Introduction.

The extreme growth of global economy has led to a massive exploitation of fossil reserves both for energy need end for the production of chemicals. Nowadays these requests are partially provided from renewable sources. The passage form fossil-based economy to a more sustainable economy has become a top priority. This transition from fossil economy to a sustainable economy is necessary to meet the urgent environmental concerns in favour to a sustainable development, preserving the integrity, stability and beauty of natural biotic system. The use of renewable alternatives and sustainable sources has a number of advantages in comparison with the use of fossil sources, for example, reduction of air pollution, global warming, and dependence from petroleum.[1] Chemists, scientists, and engineers have a key role in the developing processes that exploit renewable sources. In recent years, there is an enormous interest in the usage of alcohols as starting materials, as they are readily available by a variety of industrial processes, inexpensive because they can be obtained renewably via fermentation or catalytic conversion of lignocellulosic biomass, relatively nontoxic, and easy to use.[2] The work presented in this thesis is focused on the use of alcohols as alkylating agents to develop new synthetic methodology exploiting the borrowing hydrogen process, as activation strategy that allow the preparation of valuable classes of molecules of industrial and pharmaceutical interest according to the guide lines of green chemistry.

1.2 Alcohols in alkylation reactions.

Alcohols are versatile, organic compounds since they undergo a wide variety of transformations. Considering the use of alcohols in alkylation reactions, they are able to react only prior activation. Conventionally the activation consists in the conversion of OH group into a good leaving group. To increase the electrophilicity at C1 of the alcohol and generate a good leaving group allowing the reactivity toward the nucleophilic attack the simplest method would be the protonation. Despite the protonation looks attractive as it produces only water as byproduct, this method can deactivate the nucleophile as occur in acid conditions, reducing drastically the scope and efficiencies of the reaction. Therefore, alcohol activation as alkylating agent is afforded by the interconversion of OH into alkyl halide, tosylate or mesylate. These kind of activations from a green metrics point of view does not respect the sustainability and the efficiency of the reaction. Not only an extra step is required but also both for the activation and the subsequent reaction a stoichiometric amount of

chemical waste is produced, reducing the safety due to the intrinsic mutagenicity and toxicity of the halide. Alternatively, also the in situ nucleophilic substitution of alcohols operated through a Mitsunobu reaction, has the problem of the stoichiometric use of the derivatizing reagents. Dialkyl azodicarboxylate (e. g. diethyl azodicarboxylate, DEAD) and triphenylphosphine, are also unsafe and toxic (Scheme 1).



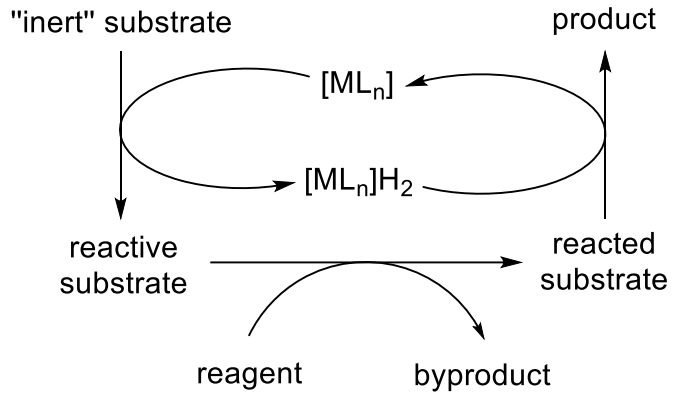
Scheme 1 Traditional activation of alcohols.

Despite these facts, the direct substitution/alkylation of alcohols has been developed. Through the use of Lewis acids and Bronsted acids, π-activated alcohol such as allylic and benzylic can undergo the direct substitution of the hydroxyl group, via formation of a carbocation.[3] However, many of these methods have some drawbacks, even if the problem of the stoichiometric use of Lewis acids or Bronsted acids is bypassed by the catalytic variation/form. Low yields of the products, long reaction times, harsh reaction conditions, tedious work-ups and relatively expensive reagents, the requirement for an inert atmosphere, and formation of a significant amount of side products, are still present. Only one example of the use of less-activated alcohols was reported, nevertheless the scope continues to be mainly restricted to π-activated alcohol.[4] For all these reasons aforementioned, the development of efficient and sustainable methodologies for the activation of alcohols is needed. Among the strategy developed for the direct use of alcohols as alkylating agents, the catalytic activation of alcohols by hydrogen borrowing has attracted significant attention in recent years as a powerful and sustainable solution for addressing some of the contemporary goals of pharmaceutical and chemical industries. As highlighted during the ACS GCI Pharmaceutical Roundtable the direct nucleophilic substitution of alcohols is one of the most important and challenging priorities both for academia and industry.[5]

1.3 The Borrowing Hydrogen Strategy

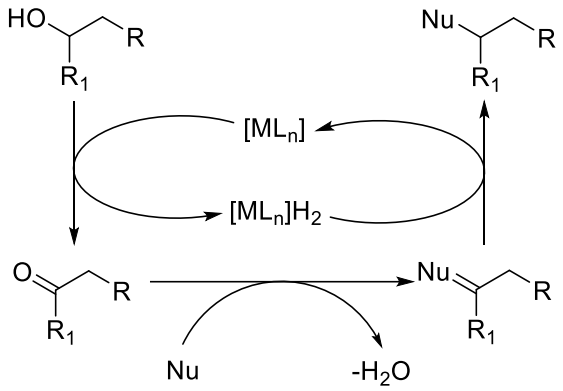
The increasing demand to have more green processes in chemistry has focused the attention to bond construction strategies that promote atom economy and avoid mutagenic reagents.[6] The borrowing hydrogen or hydrogen autotransfer is a catalytic fashion way to exploit the potential of alcohols to be ideal green substitute of halides or (pseudo)halides. Alcohols are ideal candidates for green chemistry because they have low-molecular-weight leaving group (HO, 17 u.m.a.), low environmental impact factor of the leaving group (H_2O), they are inexpensive and sustainable (most of them

come from biomasses and renewable sources[1]) and they are easy to handle and store (safely).[7] The more general description of the borrowing hydrogen process can be given as follow: an inert substrate after the dehydrogenation operated by a metal catalyst become reactive (oxidized species), this new reactive oxidized substrate will form the reacted substrate, and finally the metal catalyst makes the hydrogenation to form the final product. In this cycle, the catalyst act both as oxidant (dehydrogenation) and as reductant (hydrogenation) – Globally no net oxidation or reduction takes place in the catalytic cycle itself (Scheme 2).



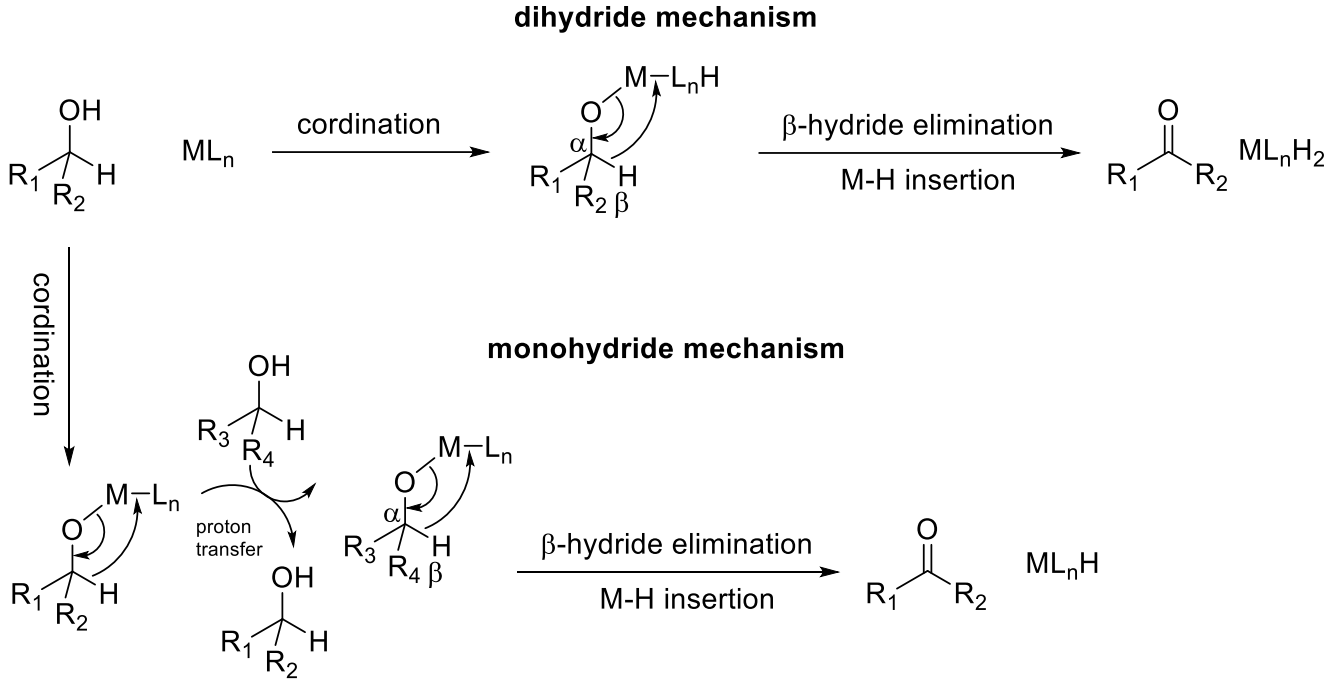
Scheme 2 General scheme of Borrowing Hydrogen Process.

The substrates involved in the borrowing hydrogen activation are alkanes,[8] alcohols,[9] and amines.[10] Regarding the catalytic cycle of borrowing hydrogen for alcohol activation mainly consists of two or three steps: The first step is the alcohol dehydrogenation run by the catalyst, then the correspondent carbonyl compounds derived from the dehydrogenation of alcohol can carry out its typical reactivity, and lastly in the third step the abstracted hydrogen is usually returned back to the intermediate. It is also possible to intercept the intermediate for a further functionalization or block the reaction and have the hydrogenation of the sacrificial intermediate or that the intermediate can react again with additional reagents or the abstracted hydrogen is further returned and incorporated to the final product, hence the reaction name (Scheme 3). In other words in some specific cases, the borrowing process can be truncated to the reactive intermediate using a hydrogen acceptor or H_2 gas removal. The result in these cases is a reactive final compound that might be ready for further functionalization/ additional cascade transformation.



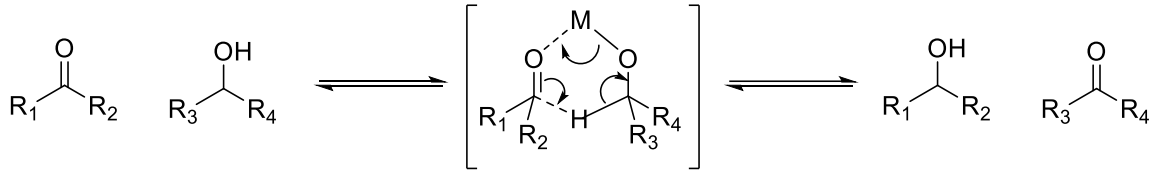
Scheme 3 General Borrowing Hydrogen Process for Alcohols Activation.

From a mechanistic point of view the borrowing hydrogen process (activation via dehydrogenation) operated by homogenous catalyst depends from the type of the complex, the substrates as well as the conditions of reaction. Considering that the catalytic cycle is based on three steps. (i) Dehydrogenation (ii) functionalization and (iii) hydrogenation and since functionalization in step (ii) is usually a classical organic transformation such us a nucleophilic addition and there is no catalyst needed as it can act probably coordinating the carbonyl compound enhancing the electrophilicit, it is possible to assume no participation of the catalyst in this step. The more significant and central steps are the first (i) and the third (iii), assuming reversibility between they are possible to discuss only the first (i). The mechanistic possibilities for the step (i) of transfer hydrogenation are mainly classified as: Inner sphere, intermediate sphere, outer sphere.[11] In the inner sphere, after the alcohol coordination to the metal centre trough an insertion, the correspondent carbonyl compound is formed via β-hydride elimination both for dihydride and monohydride mechanisms (Scheme 4).



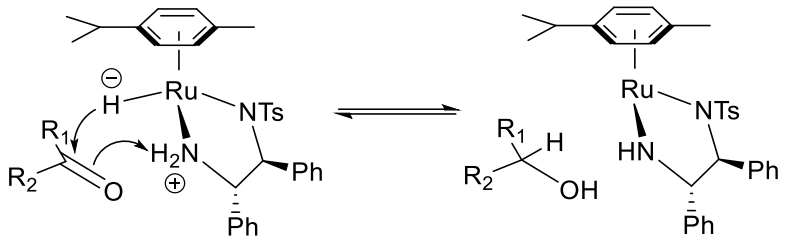
Scheme 4 Inner Sphere Transfer Hydrogenation Mechanisms.

The intermediate sphere mechanism consists in a transfer of the hydride from the donor to the acceptor where the metal hold together the two species like in the Meerwein-Ponndorf-Verley (Scheme 5).



Scheme 5 Intermediate Sphere - Mechanism of the Meerwein-Pondorf-Verley Reduction and Oppenauer Oxidation.

The outer sphere mechanism is plausible when the metal complex have no open site for binding the substrate. This kind of mechanism is for all the catalysts that have a hydride in position cis respect to the protonic hydrogen, typically in a form coordinating R_2NH ligand, like in the Noyori's Catalyst (Scheme 6).



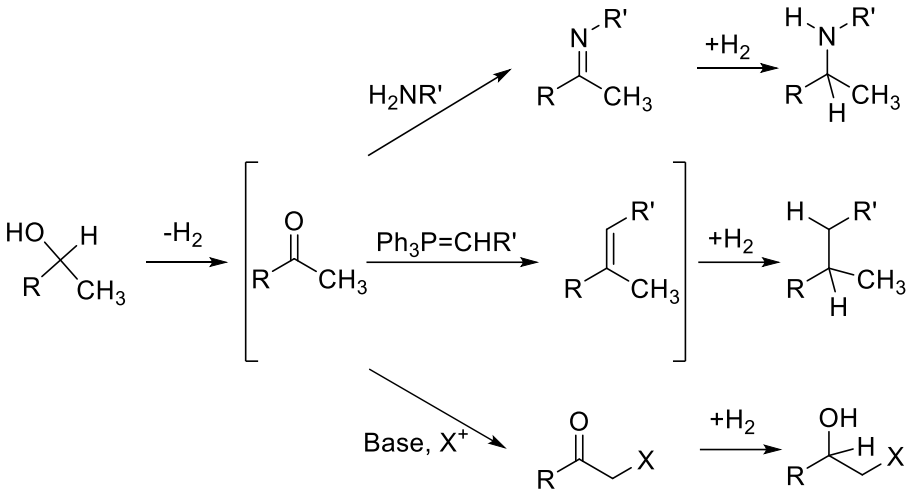
Scheme 6 Outer sphere transfer Hydrogenation of Noyori's Catalyst.

The mechanism of dehydrogenative activation via homogeneous transition-metal complexes varies greatly, depending on the substrate and catalyst employed as well as the conditions chosen. The two H atoms extruded can be delivered to the metal complex or directly to a hydrogen acceptor. The pathways for stepwise mechanisms generally consist of two separate components: association of the substrate with the catalyst followed by cleavage of a C-H bond. A saturated molecule must first coordinate in some manner to a transition-metal complex. This step often requires direct activation of a C-H bond for alkanes, or an O-H bond for alcohols, or an N-H bond for amines. Alcohol or amine binding to the metal catalyst is typically followed by a deprotonation event. The resulting metal alkoxide or amine complex then undergoes to a C-H bond cleavage, resulting in a metal hydride and a dehydrogenated organic species. Following the dehydrogenative step, a functionalization occurs. This process can be catalyzed by the same catalyst employed for dehydrogenation, catalyzed by a different species added to the reaction mixture for this purpose, or simply occurs without the need for a catalyst. Once generated, the resulting intermediate can react with additional reagents and be oxidized or reduced depending on the specific reaction sequence.

1.4 General Activation pathway via Borrowing Hydrogen.

The general reactivity of alcohols both as nucleophiles and as electrophiles is very limited and some kind of activation results necessary. As describe before, OH group is transformed to alkoxide to enhance the nucleophilicity, on the other end, electrophilicity is ideally enhanced adding an acid. This description involves the classical activation of alcohols. Another possibility is to convert alcohols transiently in to the correspondent carbonyl compound. In this way is possible to exploit the reactivity of carbonyls that in comparison to the alcohol, as functional groups, allow more transformation, and lastly, after the reaction, the intermediate product is reduced to the original oxidation state of the alcohol. This process become catalytic, when, after the oxidation of the alcohol (activation), the formation and the reaction of the carbonyl compound, the intermediate is reduced under the reaction conditions. Now a detailed discussion on the reactivity of the carbonyl compound follows. After

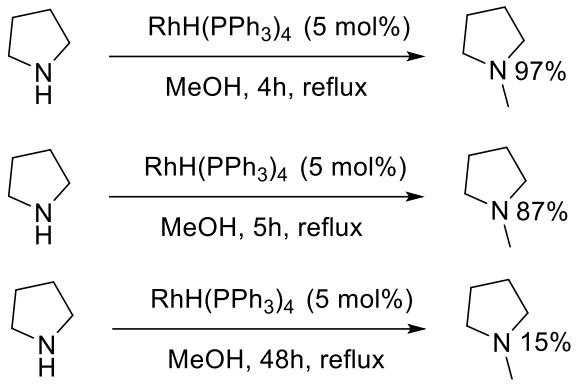
the oxidation, we can have aldehyde or ketone respectively from primary and secondary alcohol, that in term of reactivity they show almost the same reactivity. As shown in (Scheme 7) carbonyl compound reacts at C1 in nucleophilic addition reactions, and in C2 with electrophile exploiting the possible enol-enolate chemistry, and alkene formation in Wittig type reaction (ylide addition to C1).



Scheme 7 Alcohol Activation Pathways via Borrowing Hydrogen.

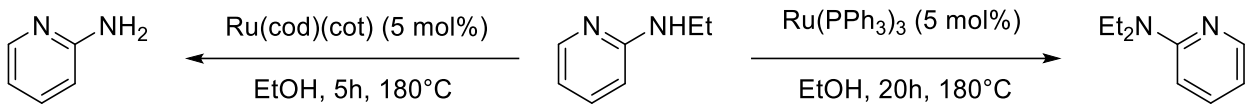
1.4.1 C-N Bond Formation-Amination of Alcohol: alcohol amination is traditionally achieved using alkyl halide agents. The alkyl halide strategy for the formation of amine by alkylation may have control limitation like the over alkylation. For example, the alkylation of a primary amine could results in the formation of a mixture of mono, di-alkylated amine and also the quaternary ammonium salt. This over alkylation simply happens because the more the amine is substituted, the more it becomes nucleophilic and reactive in the substitution reaction with alkyl halides. Methods for the controlled alkylation of primary amine have been reported, and in some instances, is possible to have mono alkylation under appropriate conditions. At the beginning Gabriel synthesis was introduced for the synthesis of primary amines[12] and many other methods was developed. For examples, more recently a potassium iodide catalyzed method for the selective N-monoalkylation of amines with alkyl halides and alkyl tosylate under microwave irradiation has been described. A simple method for the N-alkylation of primary amines was developed using ionic liquids as solvent in order to prepare secondary amines selectively. However, these approaches have some drawbacks even if they are selective they continue to employ mutagenic and toxic reagents. The direct amination via borrowing hydrogen resolve both the problems, over alkylation and the use of mutagenic and toxic reagents. The sequence of alcohol amination consists in: alcohol dehydrogenation operated by the metal catalyst, the resulting carbonyl compound react in an addition reaction with the

ammine generating an imine fially is reduced to amine by the catalyst, with the hydrogen borrowed from the alcohol in the dehydrogenation step. In this alcohol activation process the over alkylation is controlled, due to the initial secondary amine formed by alkylation of primary amine, the intermediate doesn't tend to react further because this would require the unfavorable formation of an iminium cation. The borrowing hydrogen activation process is a good alternative to the reductive amination. In other words, it could be considered the catalytic version of reductive amination employing alcohols rather than aldehydes that in some case result instable like α-amino aldehyde[13] that can react itself or lose the optical purity/stability. These problems are overcome with the borrowing hydrogen because the aldehyde is transiently formed and consumed soon after. Several examples of C-N bond formation via borrowing hydrogen have been reported, and among them, a selection of examples follows. The first alkylation of amine using alcohols via the borrowing hydrogen route date back to 1932 with a work where a heterogeneous nickel catalyst was employed.[14] The first report of N-alkylation with alcohols of primary and secondary amine via homogeneous catalysis was by Grigg and co-workers in 1981.[15] A screening with different catalysts based on rhodium, iridium and ruthenium was presented (Scheme 8).



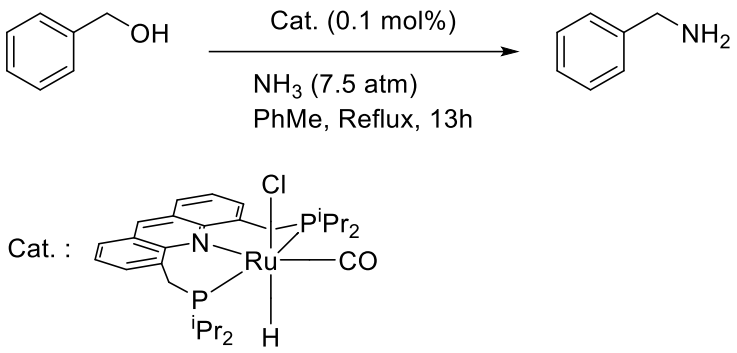
Scheme 8 N-alkylation via Borrowing Hydrogen with Rh Ir Ru Catalyst.

Watanabe has reported a study about the selectivity for N-alkylation of primary amine demonstrating that different ruthenium catalysts and adopted conditions show different selectivity between mono and di-alkylation for the same substrates (Scheme 9). [16]



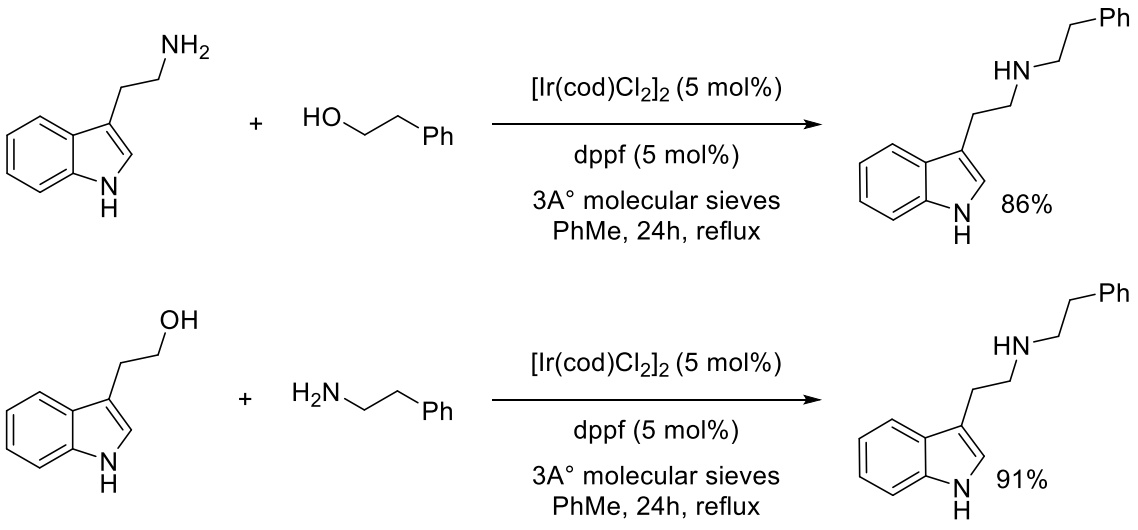
Scheme 9 Selectivity: Mono-Alkylation vs Di-Alkylation of Amines.

A method for converting primary alcohols in primary amines using a PNP pincer complex of ruthenium and reasonable pressure of ammonia has been reported by Milstein and co-workers (Scheme 10).[17]



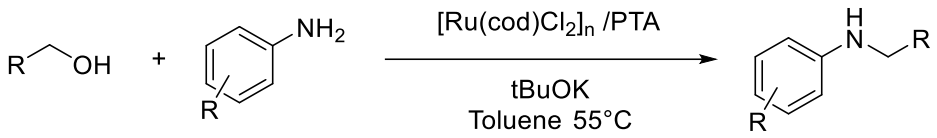
Scheme 10 Direct Formation of Primary Amine from Ammonia and Alcohol via Borrowing Hydrogen.

Alkylation of primary amines with primary alcohols has been accomplished by Williams and co-workers, an alternative combination of phenylethanol and tryptamine or tryptophol and phenylethanamine give the secondary amine product in good yields (Scheme 11).[18]



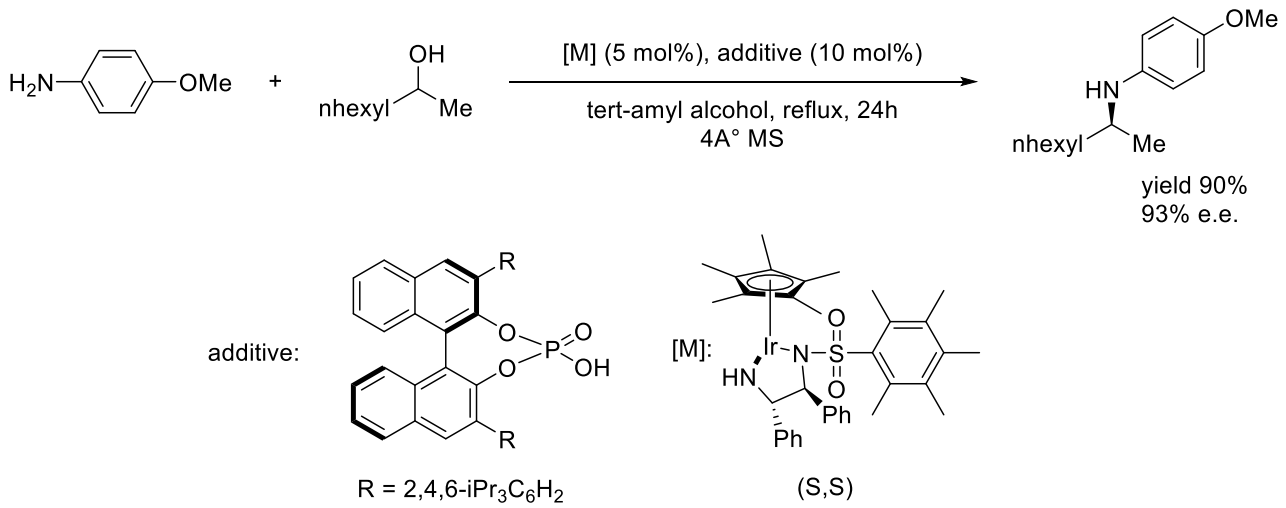
Scheme 11 Formation of Alkylated Tryptamine.

Taddei and co-workers reported an interesting example of C-N bond formation at low temperature, via borrowing hydrogen. The alkylation of arylamines has been achived using stoichiometric amounts of aliphatic and benzylic alcohols in the presence of *t*BuOK, the reaction was carried out at 55 °C using ruthenium with low catalyst loading. (Scheme 12).[19]



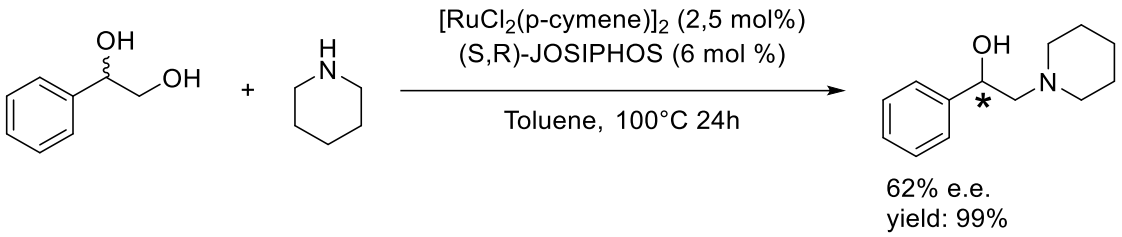
Scheme 12 Alkylation of different aniline under mild condition.

The catalytic enantioselective synthesis of chiral amines via borrowing hydrogen is possible and represents a highly efficient way to prepare chiral amines from simple alcohols. Zhao reported the cooperative catalysis by iridium and a chiral phosphoric acid where different amines and alcohols have been employed for the enatioselective synthesis of chiral amines (Scheme 13).[20]



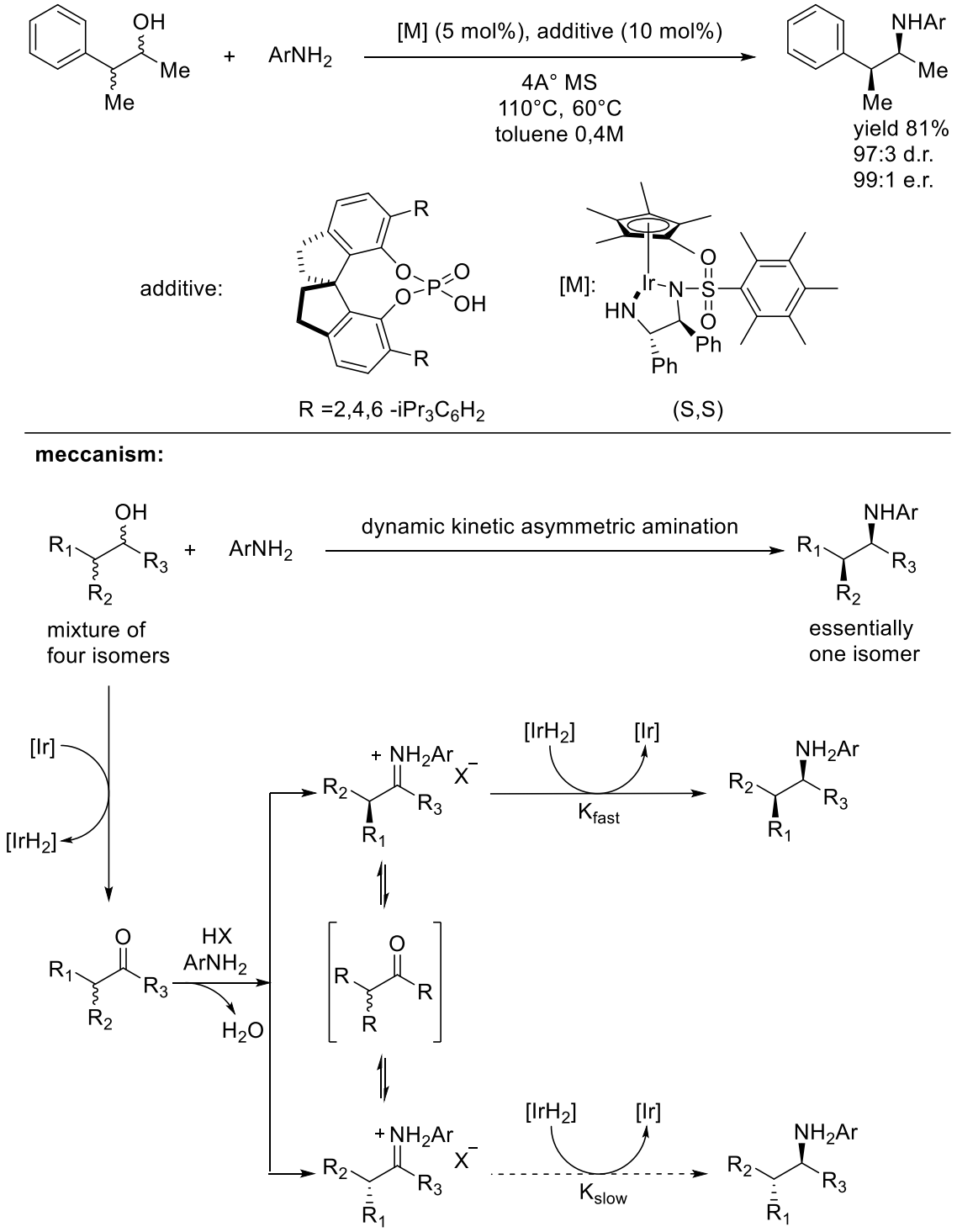
Scheme 13 Catalytic Enantioselective Synthesis of Chiral Amine.

Enantioselective version of C-N formation has been used for the formation of β-amino-alcohols from different diols and secondary amines. The reaction is catalyzed by ruthenium complex/JOSHIPHOS and proceeds mainly through amino ketone intermediates that are converted into the corresponding optically active β-amino alcohols (Scheme 14). [21]



Scheme 14 Enantioselective Synthesis of β-Amino Alcohols.

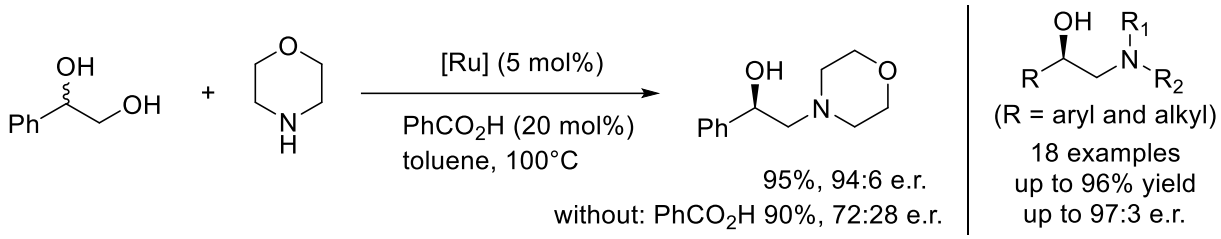
Dynamic kinetic resolution (DKR) for the amination of alcohols was recently presented by Zhao.[22] Applying the borrowing hydrogen concept, a cooperative catalysis by an iridium complex end chiral phosphoric acid, α-substituted alcohol that exist as a mixture of four isomers was converted in disastero- and enantio-pure amine. More precisely as shown in (Scheme 15) the initial racemic alcohol is converted in to the enantioenriched amine through a borrowing hydrogen pathway where a DKR take place. Dehydrogenation of the alcohol to ketone, condensation of ketone to form imine followed by transfer hydrogenation of amine and tautomerization /racemization of the two imines allow the formation into the amine that come from the fastest asymmetric hydrogenation.



Scheme 15 Dynamic Kinetic Asymmetric Amination of Alcohols and Mechanism.

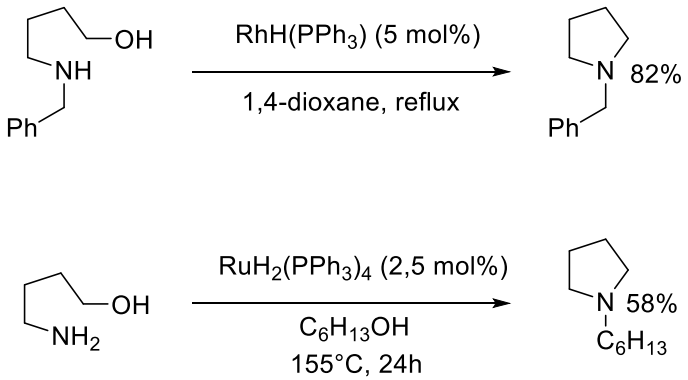
A recent related work has been presented by the same group, an acid-assisted Ru-catalyzed enantioselective amination of 1,2-diols through borrowing hydrogen. In this reaction, the involved mechanism is borrowing hydrogen combined with dynamic kinetic resolution, and from a preliminary mechanistic study the beneficial effect of

achiral Brønsted acids on the enantioselectivity of the reaction may come from an accelerated tautomerization/racemization. Several β-amino alcohols have been prepared through monoamination of readily available racemic diols (Scheme 16).



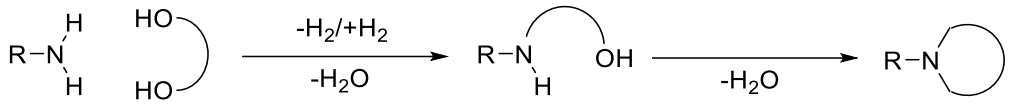
Scheme 16 Enantioselective Amination of Alcohols with Secondary Amine.

Nitrogen containing heterocycles are target of great interest in organic synthesis due to the common occurrence in natural products and pharmaceutical active compounds. The amination via borrowing hydrogen has been extended with success to the formation of nitrogen containing heterocycles. As strategy, amino alcohol cyclisation has been employed as shown in (Scheme 17), ruthenium and rhodium complexes are able to provide the reaction in good yield. [23]



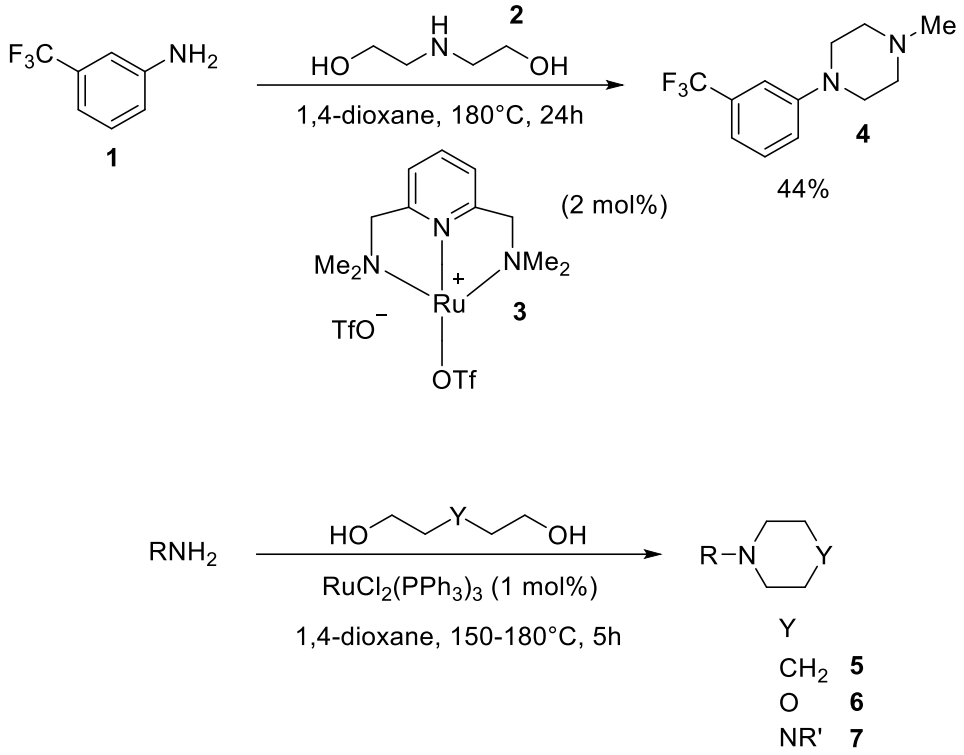
Scheme 17 Cyclization Reaction of Aminalcohols.

Annulation reaction employing diols and primary ammines is another disconnection affordable via borrowing hydrogen strategy for the preparation of nitrogen containing heterocycles. With a suitable catalyst is possible to promote a double alkylation of the primary amine, with the second step being an intramolecular alkylation (Scheme 18).



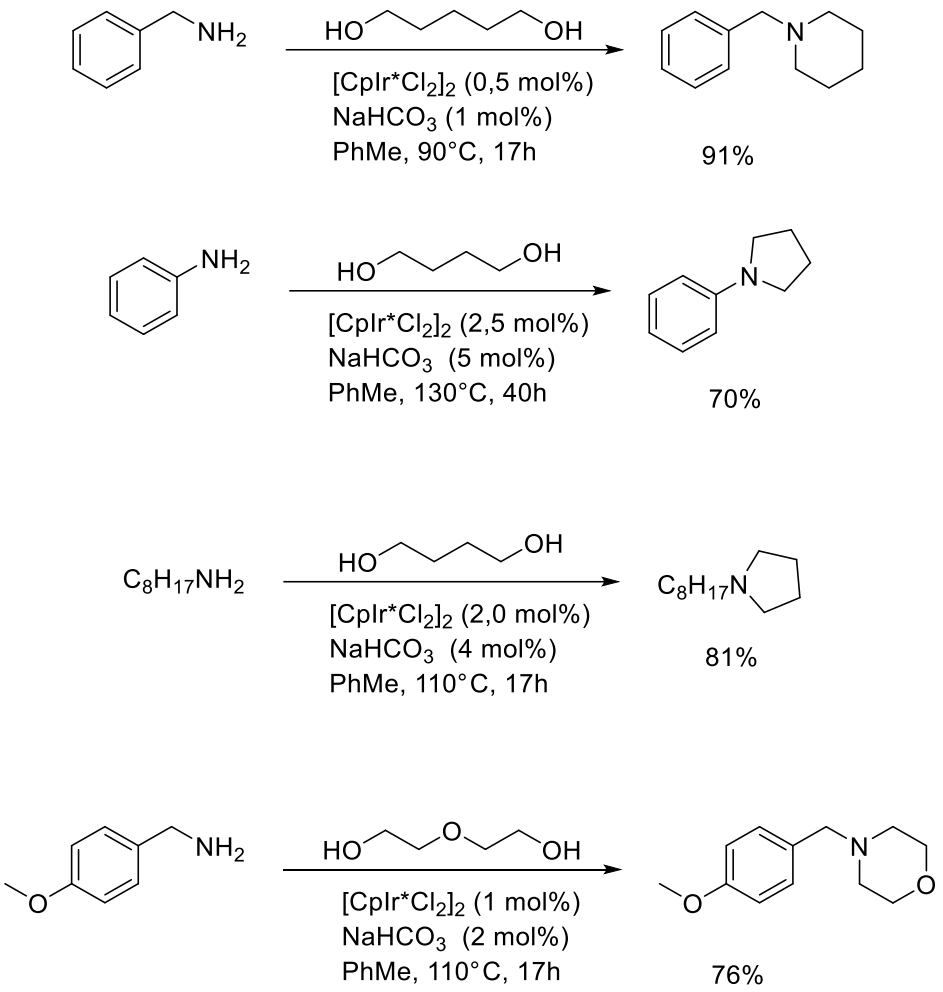
Scheme 18 Annulation Disconnection for the Formation of N-heterocycles from Primary Amine.

With this strategy Koten and co-workers have prepared piperazine **(4)** which is a potent serotonin agonist from aniline **(1)** and diol **(2)** using a ruthenium pincer complex (**3**).[24] Watanabe and co-workers have converted primary amine into piperidines **(5)** morpholines **(6)** and piperazines **(7)** by condensation with suitable diols in presence of ruthenium phosphine complex (Scheme 19).[25]



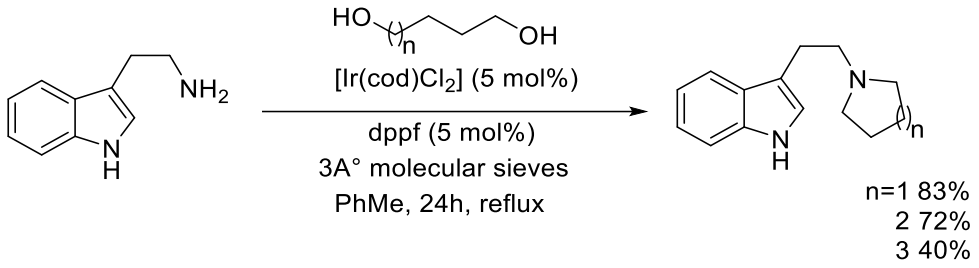
Scheme 19 N-Heterocyclization from Primary Amine via Borrowing Hydrogen.

Iridium complex $[IrCp^*Cl_2]_2$ has been used for this heterocyclization process. Representative examples include as primary amine the use of aliphatic amine, benzylamine, and aniline with different diols in good yields (Scheme 20).[26]



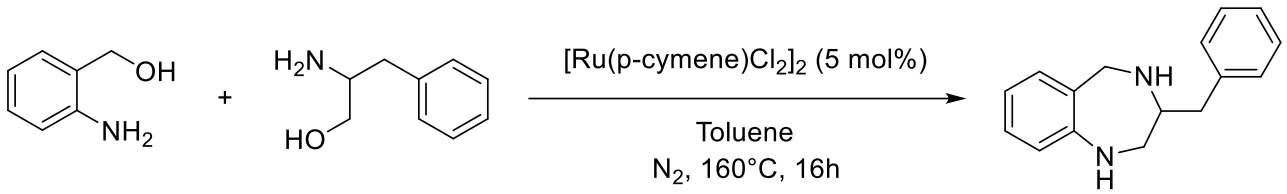
Scheme 20 Nitrogen Heterocycles Formation Catalyzed by $[IrCp^*Cl_2]_2$.

Moreover, an efficient method for the formation of 5-, 6-, and 7-membered cyclic amines from tryptamine and suitable diols has been presented employing an iridium complexes show in (Scheme 21).[27]



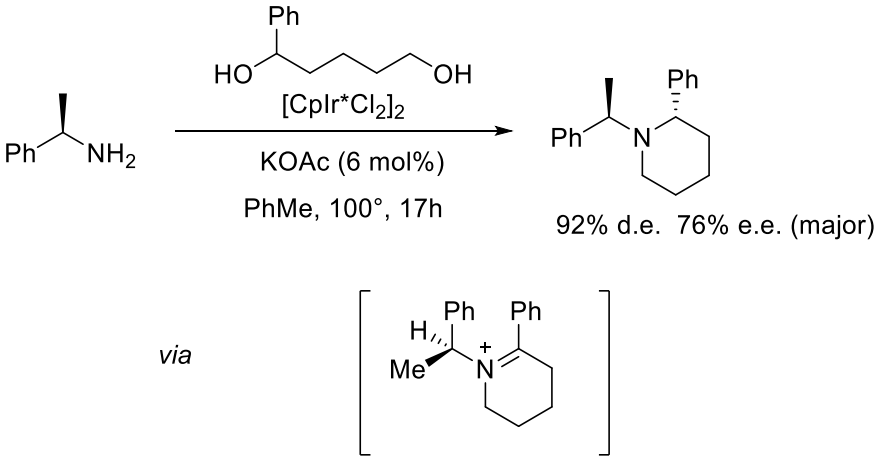
Scheme 21 Cyclic Amines from Tryptamine.

Another interesting N-heterocycles construction has been reported by Taddei and co-workers. In particular starting from 2-aminobenzyl alcohols and 1,2-aminoalcohols, 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines (THBDZ) can be prepared through a one-pot ruthenium-catalyzed reaction encompassing two consecutive borrowing hydrogen cycles (Scheme 22).[28]



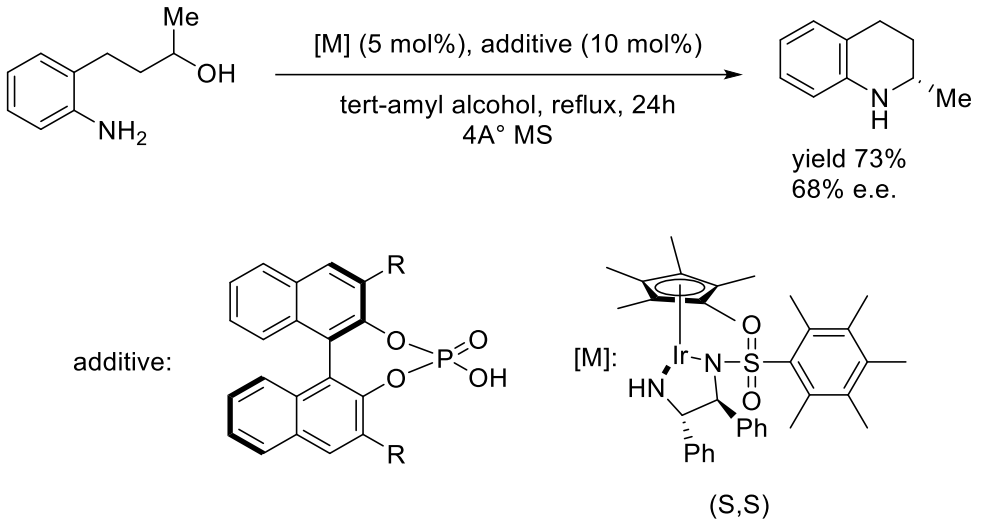
Scheme 22 Ru Catalyzed Benzodiazepine Derivatives Synthesis Reported by Taddei.

Stereoselective version of N-heterocycle construction has been reported by Fujita and Yamaguchi for the preparation of 2-substituted piperidines. Starting from racemic diols and enantioenriched amine the major diastereoisomer was formed in 92 % *de.* via reduction of the iminium intermediate, and 86% *ee.* The slight loss of enantiopurity is explained by the isomerization of intermediate (Scheme 23).[29]



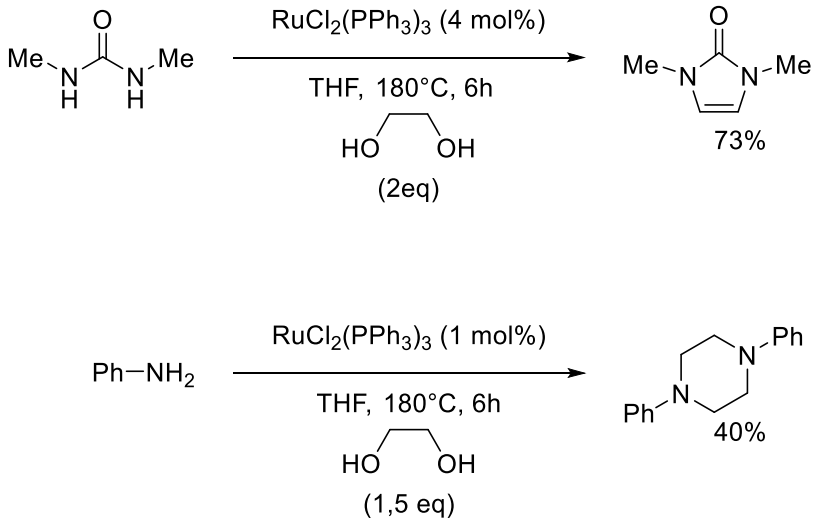
Scheme 23 Stereoselective Formation of a Cyclic Amine.

Zhao reported the stereoselective construction of 2-methyl-tetrahydroquinolin, using iridium complex as catalyst and chiral phosphoric acid as additive (Scheme 24).[19]



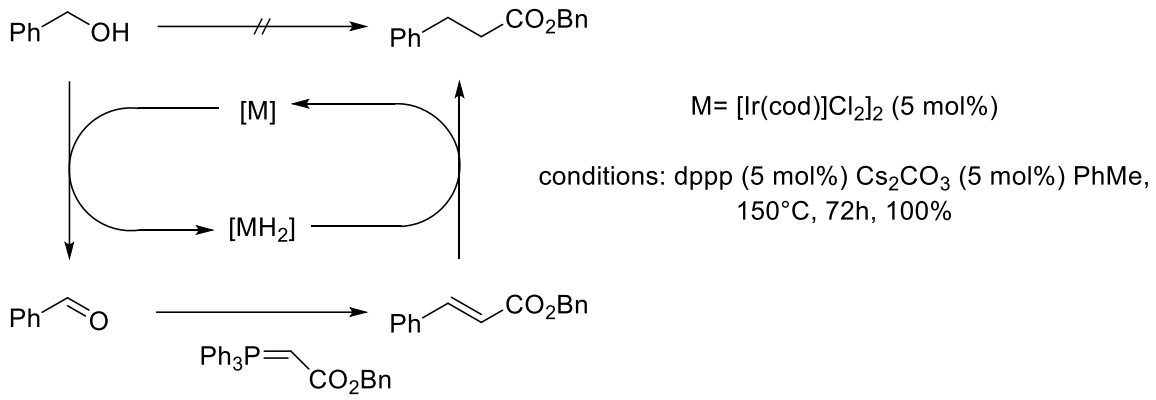
Scheme 24 Stereoselective Intramolecular Amination of Alcohols.

Urea motifs with glycol as diol can form the correspondent cyclic product dihydroimidazolone,[30] whereas employing the same catalytic system based on ruthenium and still using ethylene glycol with a primary amine, symmetric formation of piperazine has been reported (Scheme 25).[31]



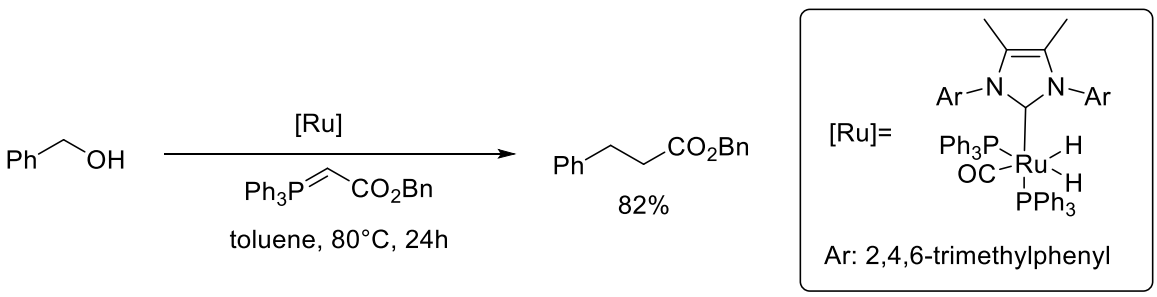
Scheme 25 Cyclisation of 1,2 Diols to Form Dihydroimidazolone and Piperazine.

1.4.2 C-C Bond Formation: In general, the carbon-carbon bond formation via borrowing hydrogen is affordable in two different manners. After the dehydrogenation of alcohol and formation of correspondent carbonyl compound, one is the attack of C1 of the carbonyl with a carbon nucleophile, usually methylene active compounds, electron rich aromatic compounds, and stabilized or non-stabilized phosphorus ylides. The other possibility is the β-functionalization with an electrophile, or a mixed case where the alcohol act as electrophile and nucleophile in the same reaction. Indirect Wittig reaction of alcohols via borrowing hydrogen has been described by Williams employing $[Ir(cod)Cl]_2$. After the dehydrogenation step of the benzylic alcohol the correspondent carbonyl compound readily undergo olefination with the ylide and then alkane is formed by hydrogenation completing the catalytic cycle (Scheme 26).



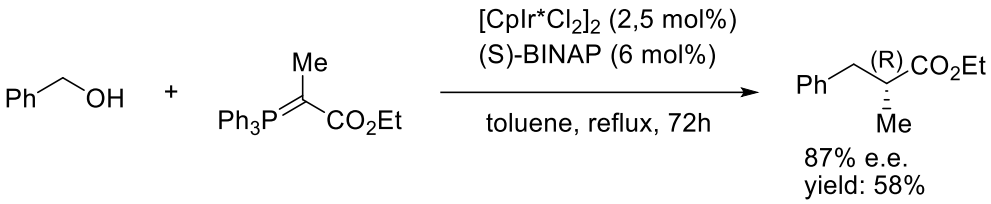
Scheme 26 Indirect Wittig Reaction of Alcohols by Borrowing Hydrogen Activation.

Moreover, Williams and co-worker uses a Ru-NHC complex with great result in term of yields and more mild conditions in the Wittig Type process with alcohols activation (Scheme 27).[32]



Scheme 27 Improved Indirect Wittig Reaction via Borrowing Hydrogen.

Stereoselective version of indirect Wittig has been developed by Williams using $[IrCp^*Cl_2]_2$ and a chiral phosphine BINAP, in the overall process the stereo-selection is introduced during the hydrogenation step (Scheme 28).[33]



Scheme 28 Stereoselective Wittig Reaction Via Borrowing Hydrogen.

In the realm of C-C bond formation through borrowing hydrogen several nucleophiles has been employed, an overview follows in (Table 1).

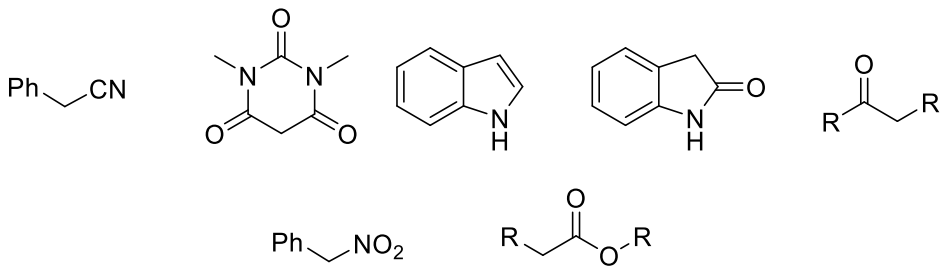
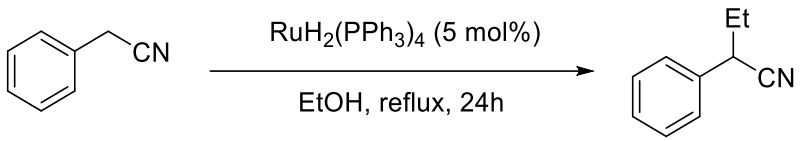


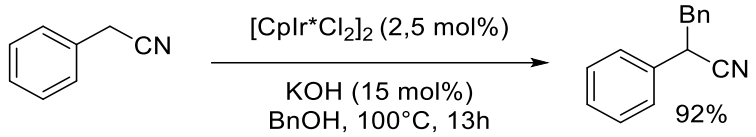
Table 1 Representative Nucleophile used in Browning Hydrogen.

Grigg published seminal work on C-C bond formation via hydrogen borrowing with the monoalkylation of arylacetonitriles by alcohols, where the catalyst was prepared in situ from rhodium trichloride triphenylphosphine and sodium carbonate (Scheme 29).[34]



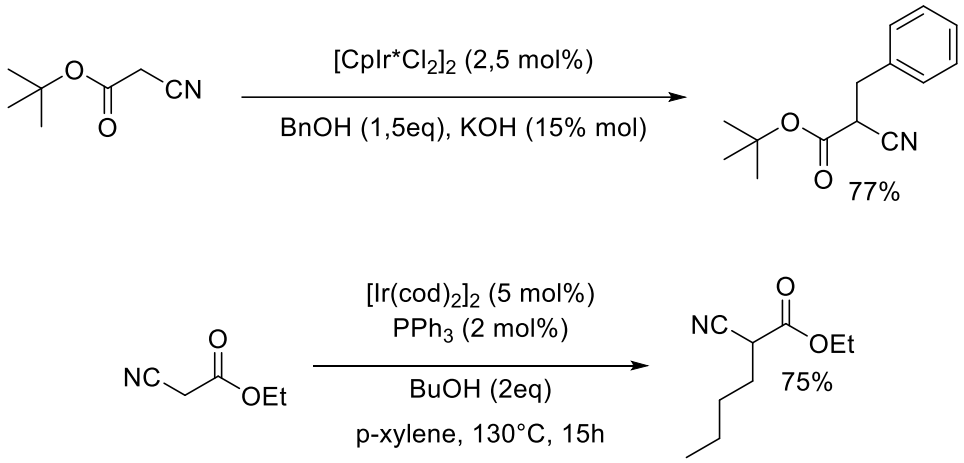
Scheme 29 First Example of Homogeneous Transition Metal Catalysed C-C Bond Formation via Borrowing Hydrogen.

More recently Grigg reported this transformation using $[IrCp^*Cl_2]_2$ as catalyst and catalytic amount of KOH as base. With this convenient and highly effective catalytic system has been achieved selective monoalkylation of arylacetonitriles with a wide range of aromatic, heteroaromatic, and aliphatic alcohols (Scheme 30).[35]



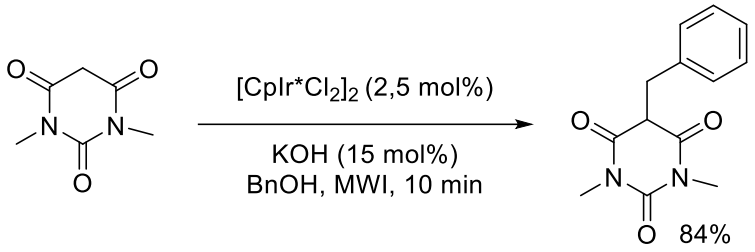
Scheme 30 Monoalkylation of Arylacetonitriles with Primary Alcohols.

Another methylene active compound studied, cyanoacetate, was reported by Grigg and Hisii in two distinct work. Grigg reported in his work the alkylation of T-butyl cyanoacetate with a variety of substituted benzyl and heteroaryl alcohols affording the corresponding α-alkylated products from moderate to high yield.[36] While Hisii with different cyanoacetate as methylene active compound reported the iridium catalyzed alkylation with different primary aliphatic alcohols (Scheme 31).[37]



Scheme 31 Monoalkylation of Cyanoacetates Via Borrowing Hydrogen.

Catalytic alkylation of 1,3-dimethylbarbituric acid as methylene active compound with various alcohols under solvent-free microwave irradiation (MWI) conditions and $[IrCp^*Cl_2]_2$ has been reported by Grigg (Scheme 32).[38]



Scheme 32 Alklyaltion of 1,3-dimethylbarbituric acid.

Indole is not a proper methylene active compound but can be considered an activated nucleophile. In particular, its electron rich system has been employed as nucleophile in C3, his behaviour is quite similar to enamine, and the resulting C3-nucleophilicity can be easily justified by resonance forms as shown in (Figure1).

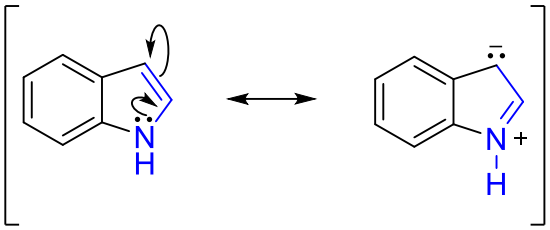
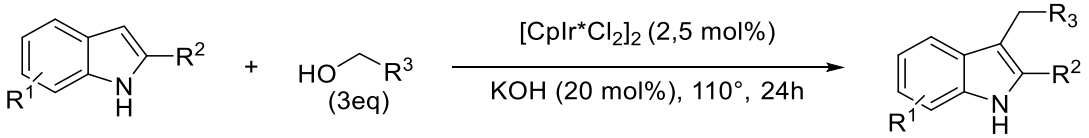


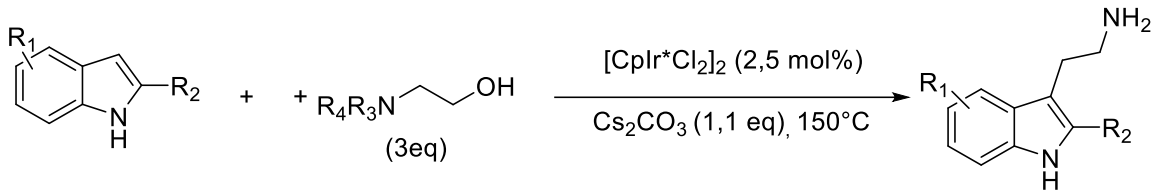
Figure 1

Grigg reported the formation of substituted indoles with benzylic alcohol catalyzed by $[IrCp^*Cl_2]_2$ (Scheme 33).



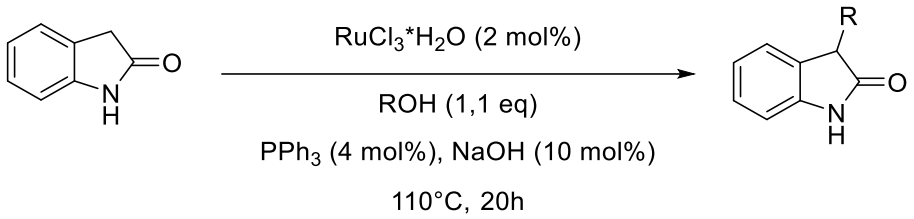
Scheme 33 Synthesis of Substituted Indoles Via Borrowing Hydrogen.

Inspired by the work of Grigg, Piersanti and co-workers reported the first iridium-catalyzed direct synthesis of tryptamines. Different substituted indoles (position 2, 4, 5, 6 and 7) were alkylated with different N-protected aminoles (Bn, dimethyl) using $[IrCp^*Cl_2]_2$ as catalyst end Cs_2CO_3 as base (Scheme 34). [39]



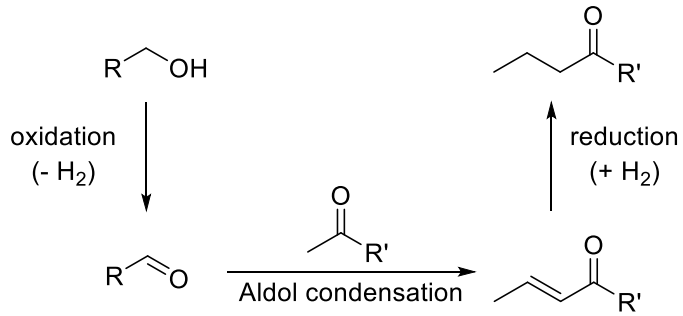
Scheme 34 Selective C3-Alkylation of Indoles with N-Protected Ethanolamines Involving the "Borrowing Hydrogen"

Since oxindole showns a pKa value of 18.2, and it is an interesting methylene active compound, has been exploited as nucleophile by Madsen. The use of $RuCl_3 \cdot H_2O$, PPh_3, and NaOH has been proved as a very effective catalytic system for the site selective mono 3-alkylation of unprotected and protected oxindoles with a range of aromatic, heteroaromatic, and aliphatic alcohols (Scheme 35).[40]



Scheme 35 Selective C3 alkylation o oxindoles with different alcohols.

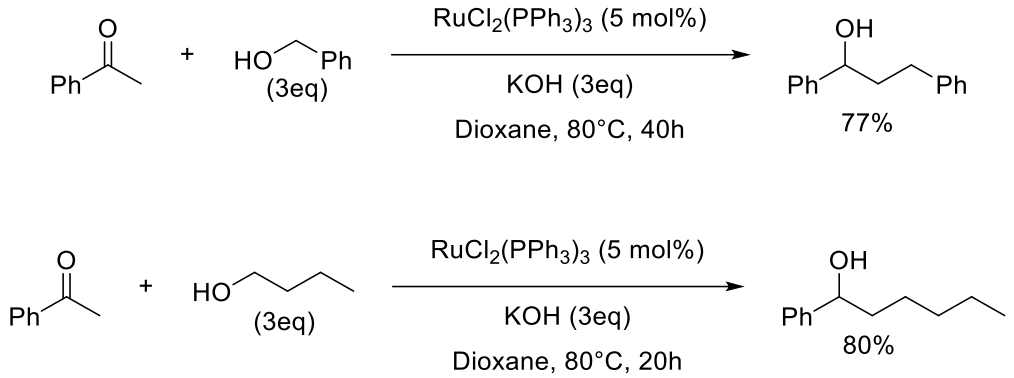
Other interesting nucleophiles are ketones, as they are nucleophile in C2 and they undergo to indirect α-alkylation with alcohols via borrowing hydrogen following the aldol reaction pathway as depicted in (Scheme 36).



Scheme 36 Oxidation/ Aldol Condensation/ Reduction Pathway.

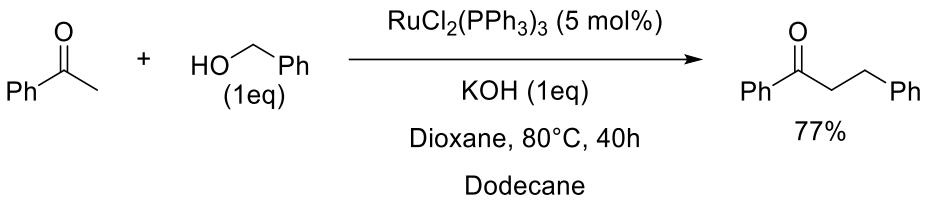
In this reaction, the intermediate is the α,β-unsaturated ketone, that can be transformed either in statured ketone or in the complete reduced form (alcohol) using an additional source of hydrogen or a high amount of alcohol (hydrogen source). For

example, ruthenium-catalyzed borrowing hydrogen of ketones and primary alcohols involving carbon-carbon bond formation has been developed by Cho and co-workers, acetophenone was alkylated with benzyl alcohol and butanol to obtain the correspondent alcohol, this when 3 equivalents of alcohol are used (Scheme 37).[41]



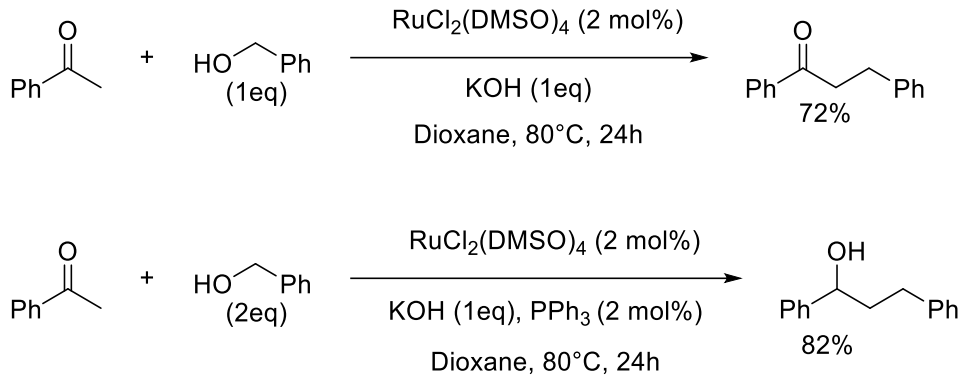
Scheme 37 α–Alkylation of Acetophenone with Benzylic Alcohol and Butanol.

The same ruthenium catalyst allows the formation of the correspondent carbonyl compound when only one equivalent of alcohol is used in a presence of dodecane as hydrogen acceptor (Scheme 38).[42]



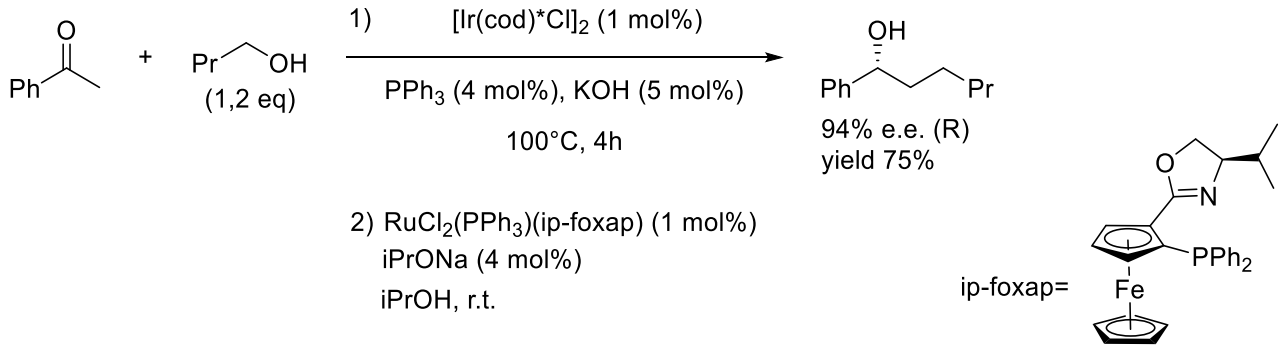
Scheme 38 α–Alkylation of Acetophenone with Benzylic Alcohol.

Yus and co-workers used a related approach employing a catalyst system based on ruthenium, employing 1 equivalent of alcohol is possible to obtain the final product as alcohol while exploiting the same catalyst system in presence of 2 equivalents of alcohol and a triphenylphosphine the ketone was obtained (Scheme 39).[43]



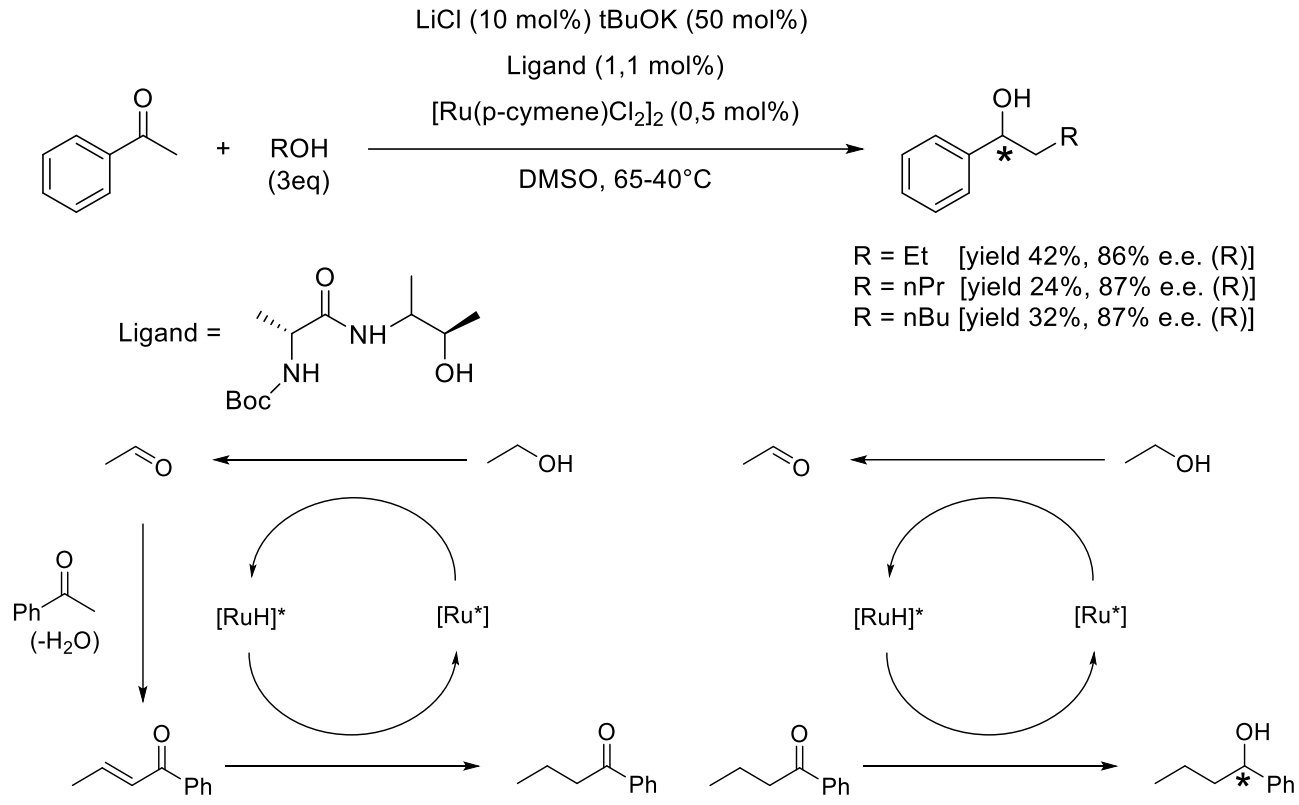
Scheme 39 α-Alkylation and Formation of Relative Ketone and Alcohol.

A one pot procedure was used by Nishibayashi to perform the condensation of an alcohol and a ketone in asymmetric way, where after the activation of alcohol operated by $[Ir(COD)Cl]_2$ and subsequent aldol reaction the reduction of α,β-unsaturated intermediate is operated by an asymmetric complex of ruthenium (Scheme 40).[44]



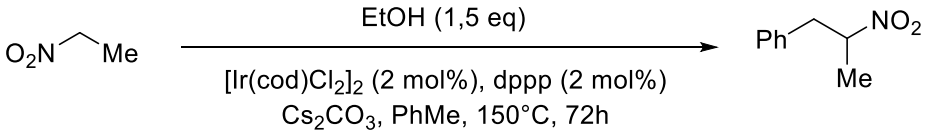
Scheme 40 Asymmetric α–Alkylation of Ketone with Alcohols.

More recently asymmetric tandem α-alkylation via borrowing hydrogen of acetophenone with primary alcohols was demonstrated using ruthenium and enantioenriched amino acid as chiral ligand (Scheme 41).[45]



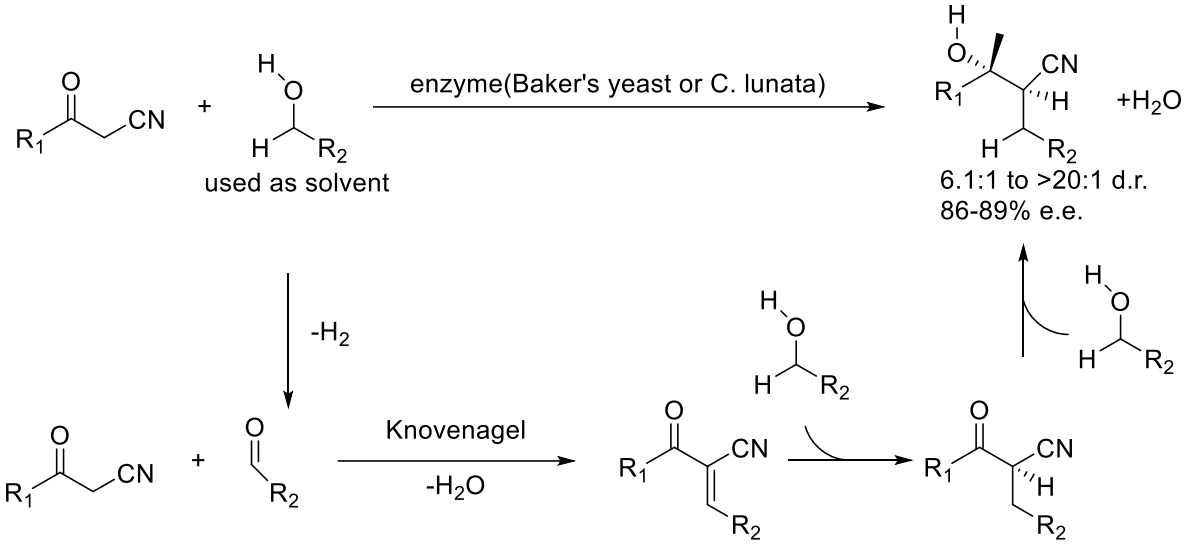
Scheme 41 Tandem α-Alkylation of Acetophenone with Primary Alcohols, and Relative Schematic Mechanism.

Finally, as methylene active nucleophile nitro alkane has been employed by Williams in nitro aldol reaction in the context of hydrogen borrowing with alcohols as electrophiles (Scheme 42).



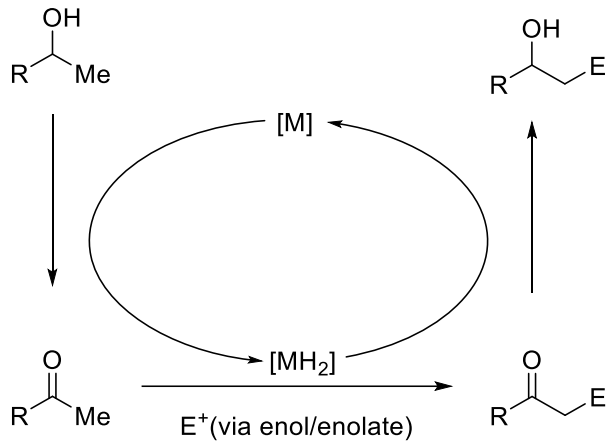
Scheme 42 Indirect Nitro Aldol Reaction via Borrowing Hydrogen.

Still in the realm of enantioselective formation of C-C bond with the borrowing hydrogen strategy, enzymes were used as catalyst. α-cyano-ketones were alkylated with different alcohols in the presence of Baker's Yeast or C. Lunata as enzyme. In this biocatalysis example, the followed pathway is the borrowing hydrogen process (Scheme 43).



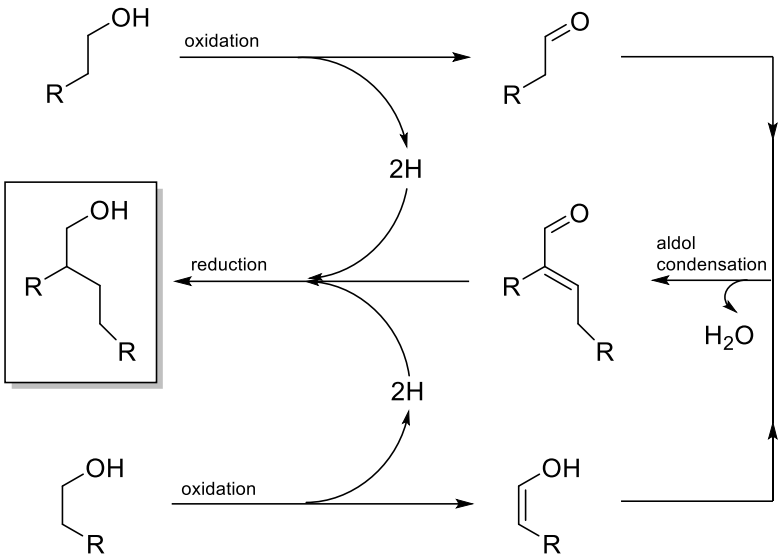
Scheme 43 Biocatalysis example of Borrowing Hydrogen.

β-alkylation of Alcohols: When carbonyls compounds are formed transiently form alcohols they can undergo to enol-enolate chemistry as shown in (Scheme 44).



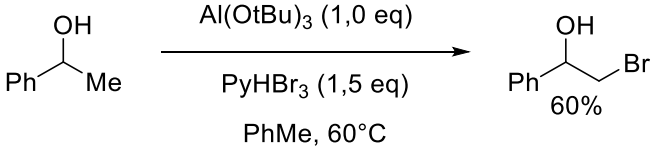
Scheme 44 β- Functionalization of Alcohol via Borrowing Hydrogen.

In this reaction, different electrophiles can be employed, if the electrophile is a carbonyl compound, it can be directly added as regent in the reaction or can be formed in situ from another alcohol. Another possibility is that the initial alcohol can react with itself according to a Geurbet aldol pathway (Scheme 45).



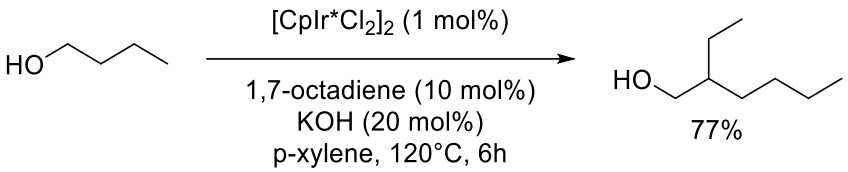
Scheme 45 Guerbet Product Formation

Considering the reaction stoichiometry during an alcohol-alcohol coupling the product is an alcohol, except when the hydrogen is transferred to another spices or is liberated in atmosphere, otherwise results in α,β-unsaturated carbonyl. While carbonyl and alcohol react together is possible to obtain an alcohol or a carbonyl, based on the amount of alcohol (hydrogen donor). In particular in the presence of an excess of alcohol (hydrogen donor) is possible to reduce the intermediate α,β-unsaturated carbonyl all the way down to alcohol. Examples of the aforementioned chemistry follow. Indirect β-bromination of alcohol has been presented by Williams, using aluminium alkoxide as catalyst and pyridinium tribromide as brominating agent. The reaction via temporary oxidation of the alcohol to a ketone, giving the β-brominated product in good yield (Scheme 46).[46]



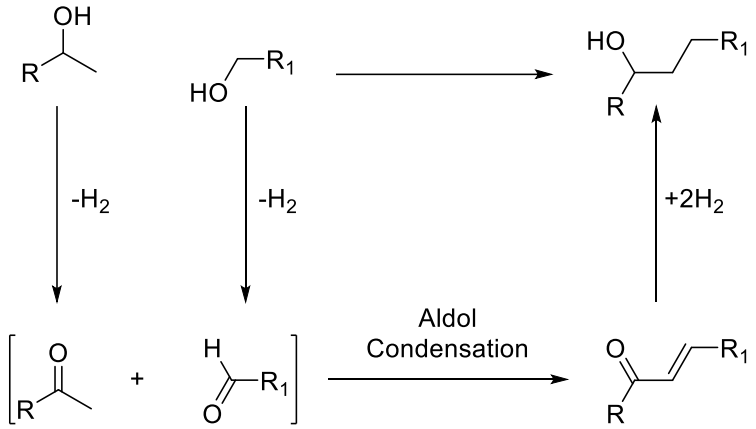
Scheme 46 Indirect Bromination of Alcohol via Borrowing Hydrogen Activation.

Self-condensation of alcohol (Guerbet Reaction) of primary alcohols leading to β-alkylated dimer alcohols catalyzed by iridium complexes has been reported by Ishii in good yields (Scheme 47).[47]



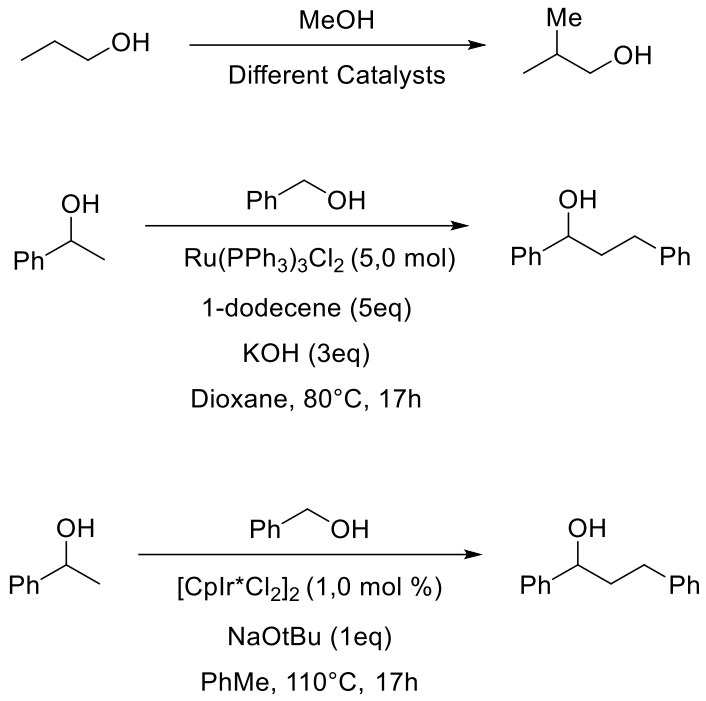
Scheme 47 Guerbet Reaction of Primary Alcohols.

Two alcohols can react together forming a new C-C bond, usually a primary alcohol and a secondary alcohol are coupled. From a mechanistic point of view, both alcohols are oxidized to the correspondent carbonyl compounds (ketone, and aldehyde). These react together in aldol condensation giving an α,β-unsaturated ketone, which undergoes reduction to give the saturated corresponding alcohol (Scheme 48).



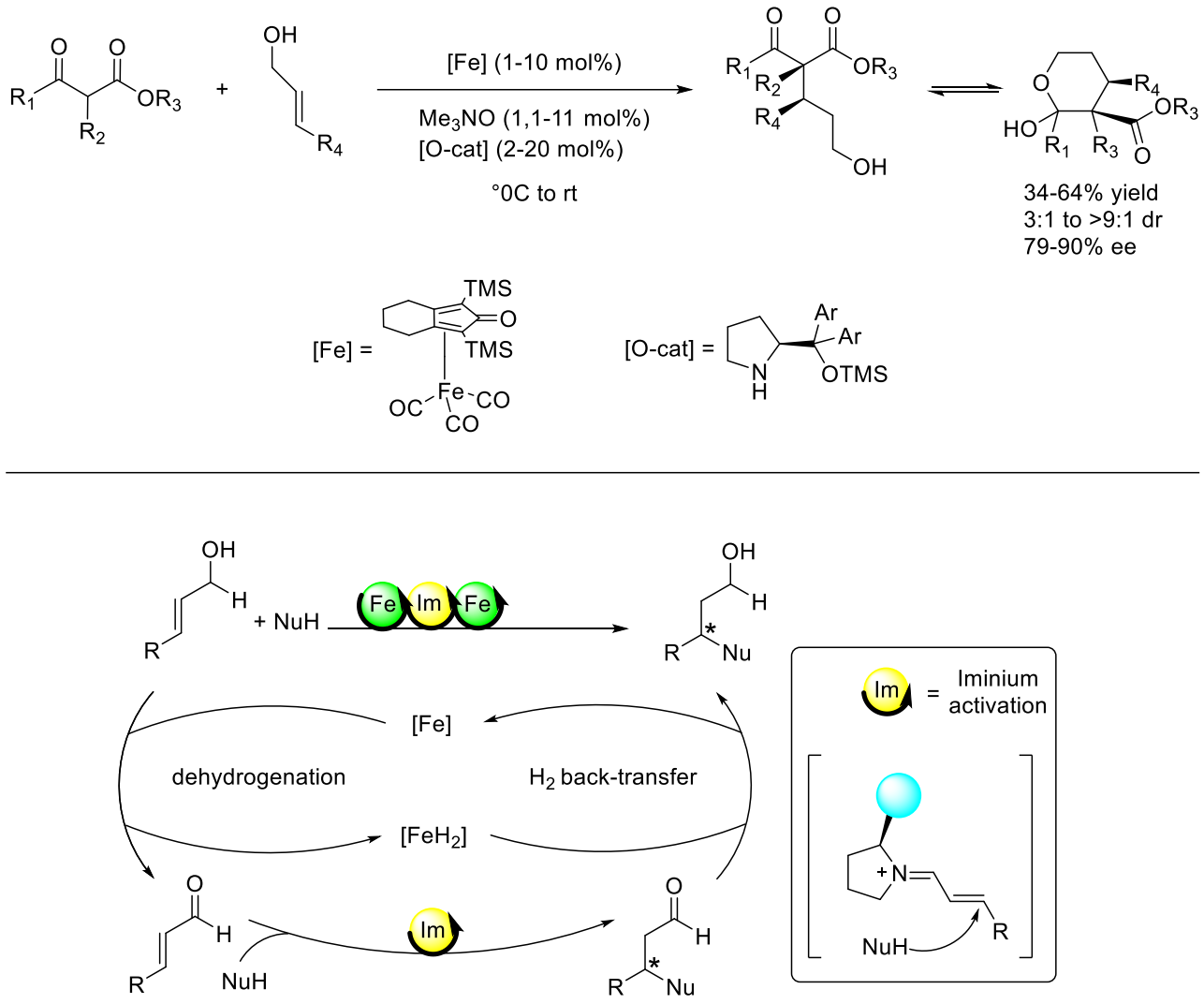
Scheme 48 General Mechanism for Alcohol Indirect Aldol Condensation.

For example, butanol and methanol has been proved to react together employing different catalyst systems producing isobutyl alcohol. $Ru(PPh_3)_3Cl_2$ has been used for the coupling of a secondary alcohol with primary alcohols, using1-dodecene as hydrogen source. Yamguchi for the same reaction has reported a different catalyst system, based on iridium, enhancing the yield (Scheme 49).



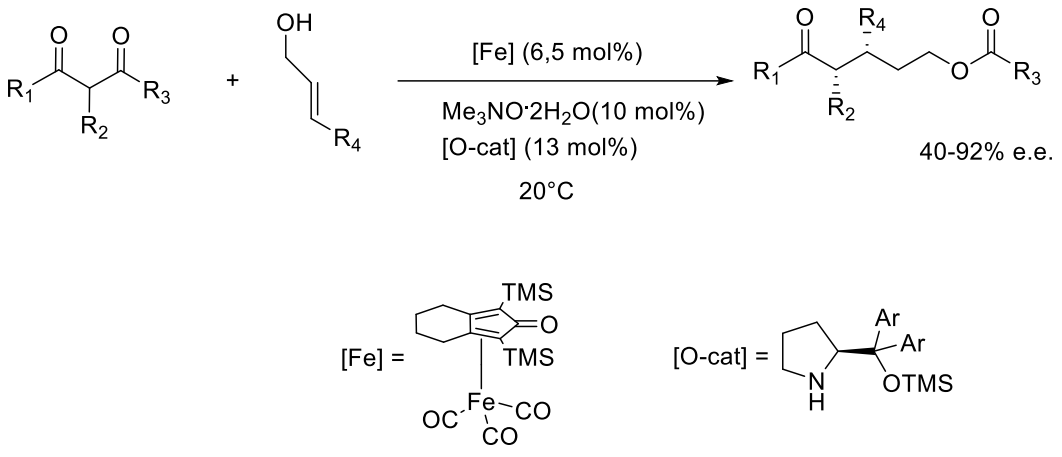
Scheme 49 Examples of Alcohol-Alcohol Coupling.

As extension in the C-C bond formation, we can consider the functionalization of allylic alcohol, as they can be considered as homo version γ-functionalization of alcohols. Quintard and Rodriguez reported a dual catalyst system based on iron catalyst and an organocatalysts, for the enantioselective functionalization of allylic alcohol with Keto-ester as nucleophile (Scheme 50). [48]

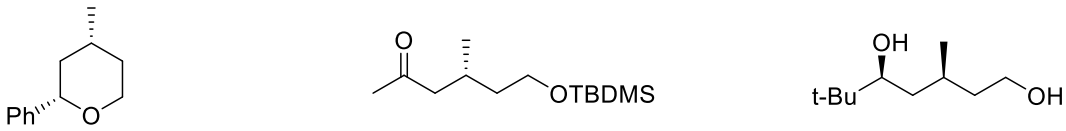


Scheme 50 Enantioselective Addition of Ketoester to Allylic Alcohols, and Relative Concept of Dual Catalysis.

Interestingly, the chiral linear alcohols obtained in this transformation are in equilibrium with the closed lactol form. Building on this initial report, the same team reported the use of the same catalytic system for diketones instead of ketoesters leading directly to a linear 3-alkyl-pentanol scaffolds.[49] This dual catalyst system allows the preparation of important synthetic intermediates that otherwise require long and tedious synthesis (Scheme 51).[50]



Examples of molecules of interesr prepared



3 steps
80% e.e.

Most odorant isomers of Doremox®

3 steps
80% e.e.

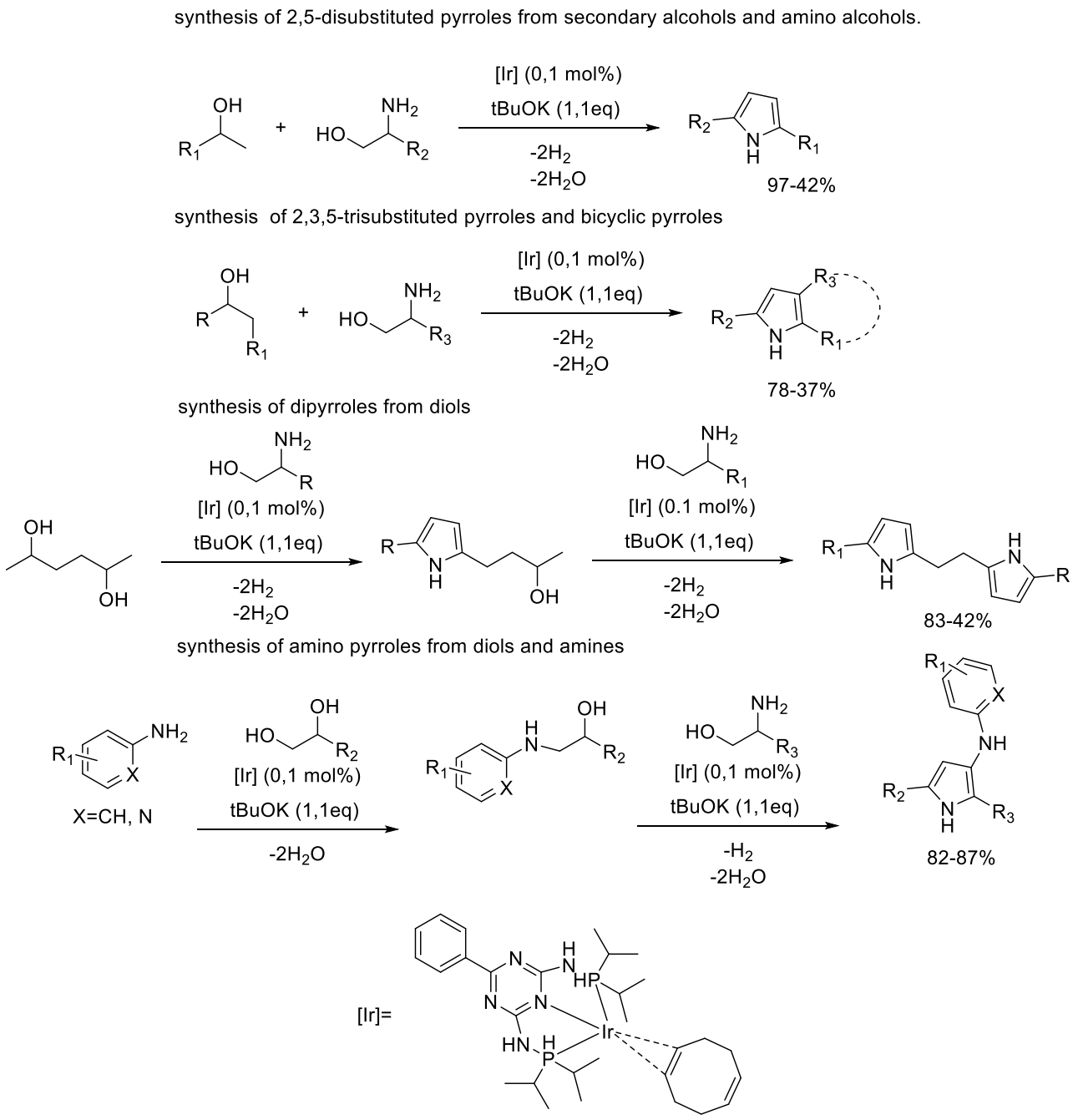
Iyconadin A fragment

3 steps
99% e.e.
apratoxin A fragment

Scheme 51 Dual Catalysis: Enantioselective Addition of Diketones to Allylic Alcohols.

1.4.3 Consecutive C-C, C-N bond formation.

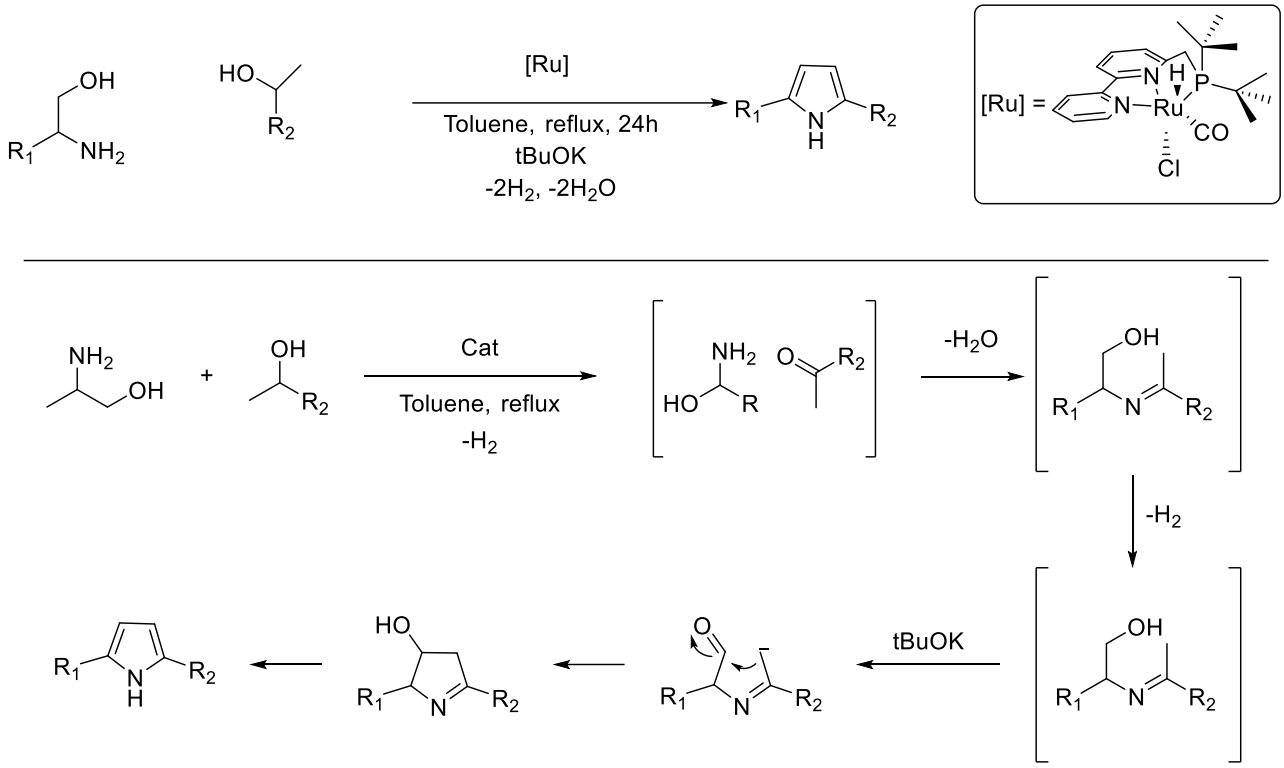
In the field of borrowing hydrogen, the last past year's investigations have focused on the development of new catalytic systems more and more efficient with the goal to reach mild condition and low catalyst loading for the formation of C-C and C-N bonds. More recently considering the raising interest in the construction of complex structure motif in the most efficient possible way, and the interest in the formation of N-containing heterocycle due to their relevance from a medicinal point of view, the focus of borrowing hydrogen is addressed to the synthesis of sustainable consecutive formation of C-C and C-N bond for the preparation of N-heterocycles and more general to the combination of C-C and C-N bond formation in one pot process[51]. Kempe and Co Worker reported the use of a PNP-type iridium-based catalyst for an efficient synthesis of pyrroles. They presented the formation of several substituted pyrroles, in particular: the formation of 2,5 and 2,3,5 di-and tri-substituted pyrroles, bicyclic pyrroles from cyclic secondary alcohols, dipyrroles from diols, and substituted pyrroles form amines and diols (Scheme 52).[52]



Scheme 52 Synthesis of Pyrroles via Borrowing Hydrogen.

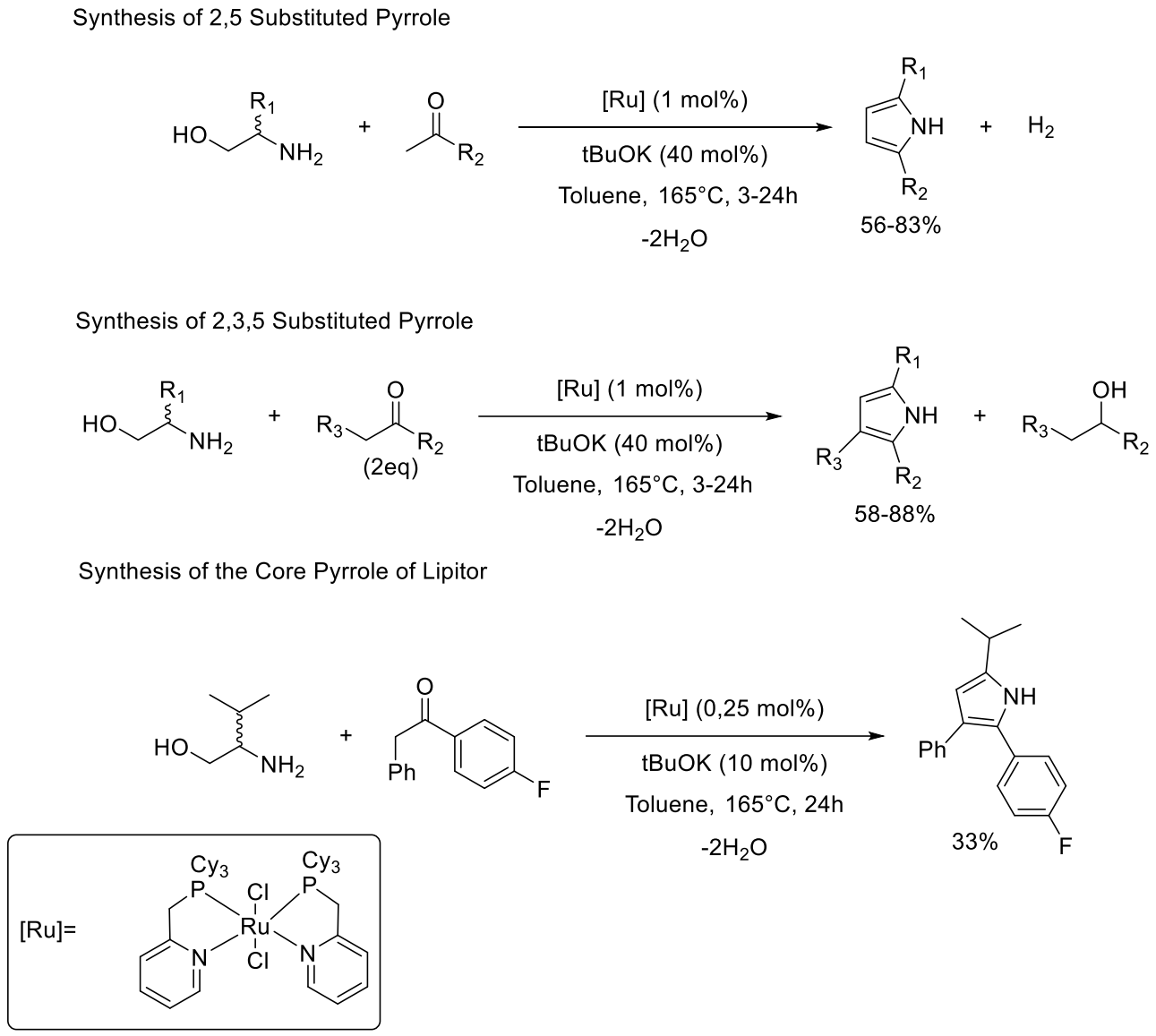
Soon after Milstein presented another efficient, atom-economical, one-step synthesis of pyrroles, based on dehydrogenative coupling of β-aminoalcohols with secondary alcohols, catalyzed by a ruthenium pincer catalyst. Alfa amino aldehyde is generated from the corresponding β-aminoalcohols, and the ketone is generated from the secondary alcohol, these two activated species can undergo to coupling to form the correspondent pyrroles in the presence of base. Therefore, formation of pyrroles

through selective and consecutive C-C and C-N bond formations take place (Scheme 53).[53]



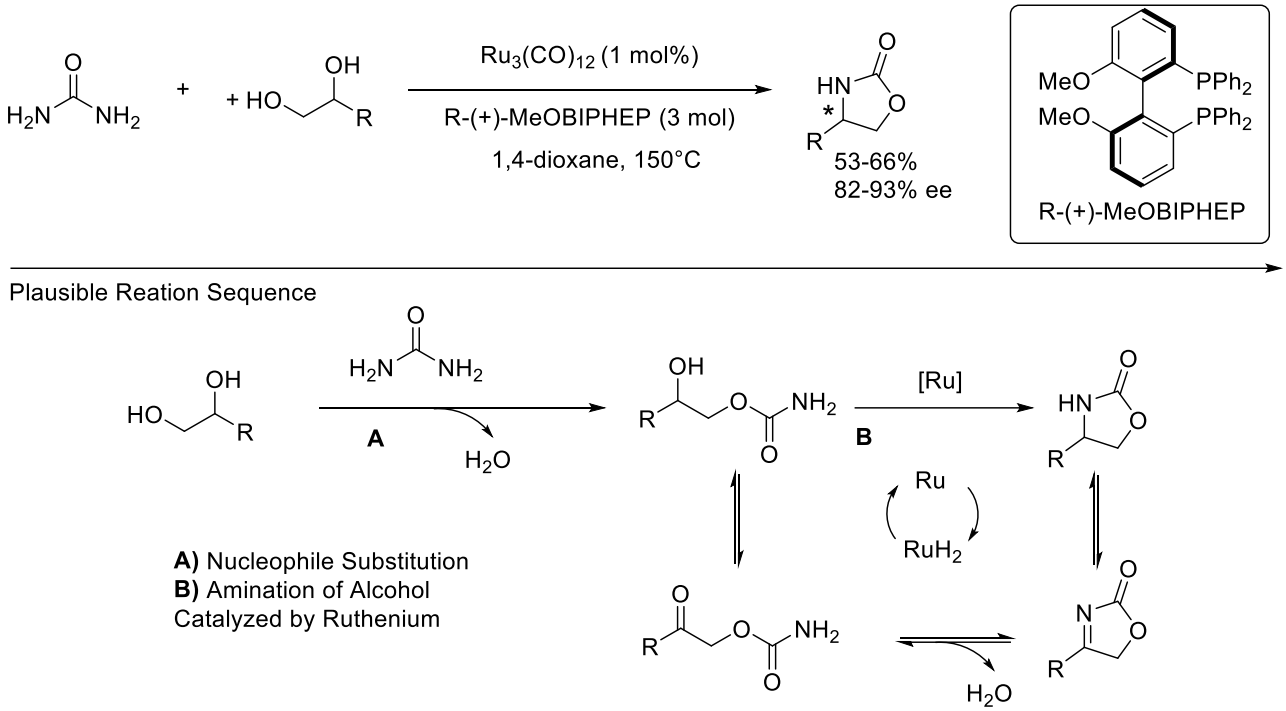
Scheme 53 Ruthenium Catalyzed Pyrroles Synthesis via Browning Hydrogen.

Saito reported the direct formation of pyrroles form 1, 2 amino alcohols and ketones instead useing the secondary alcohols as above described by Milstein, employing a ruthenium catalyst. In his work Saito demonstrated the preparation of 2, 5 and 2, 3, 5 di-and tri-substituted pyrroles and the synthesis of the core pyrrole of Lipitor (Scheme 54).[54]



Scheme 54 Saito Strategy for the Synthesis of Diverse Substituted Pyrroles via Borrowing Hydrogen.

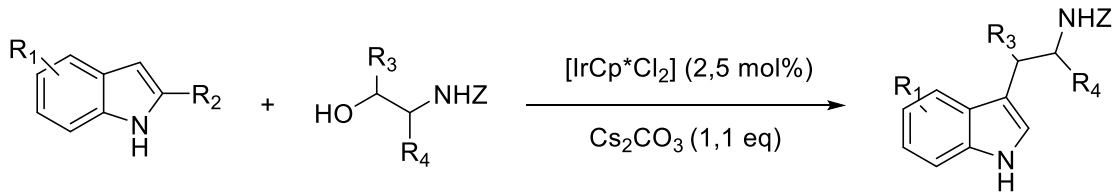
In the panorama of one pot multiple formation, an extra example outside the C-C and C-N bond follows. Beller reported the enantioselective synthesis of oxazolidin-2-ones from urea and diols. The synthesis of this heterocycle experiences the sequential formation of two different C-O and C-N bonds, in a domino process consisting of nucleophilic substitution and alcohol amination (Scheme 55).[55]



Scheme 55 Ruthenium-Catalyzed Synthesis of Oxazolidin-2-ones from Urea and Vicinal Diols.

2. Aim of the Thesis

The work presented in this thesis is focused on the use of alcohol as green alkylating agents to develop novel synthetic routes using borrowing hydrogen methodology to synthesize small molecules and biologically active natural products. Initially, based on the recently reported protocol for the direct Ir-catalyzed alkylation of indoles with N-substituted ethanolamines (Scheme 1),[37] the synthesis of substituted tryptamine derivatives starting from indoles and amino alcohols via the borrowing hydrogen process were considered. / Initially was considered the synthesis of substituted tryptamine derivatives starting from indoles and amino alcohols via the borrowing hydrogen process based on the recently reported protocol for the direct Ir-catalyzed alkylation of indoles with N-substituted ethanolamines (Scheme 1).[37]



Scheme 1 C3-Alkylation of Indoles with N-substituted Tryptamine.

Tryptamine is commercially available through a variety of suppliers; however, when the indole ring of tryptamine is functionally substituted, the commercial availability of the resulting derivatives decreases while their cost increases, especially with 4 or 6-substituted tryptamine derivatives. Tryptamine motif occurs in a wide range of biologically active molecules, pharmaceuticals and naturally occurring compounds, such as those outlined in (Figure 1).

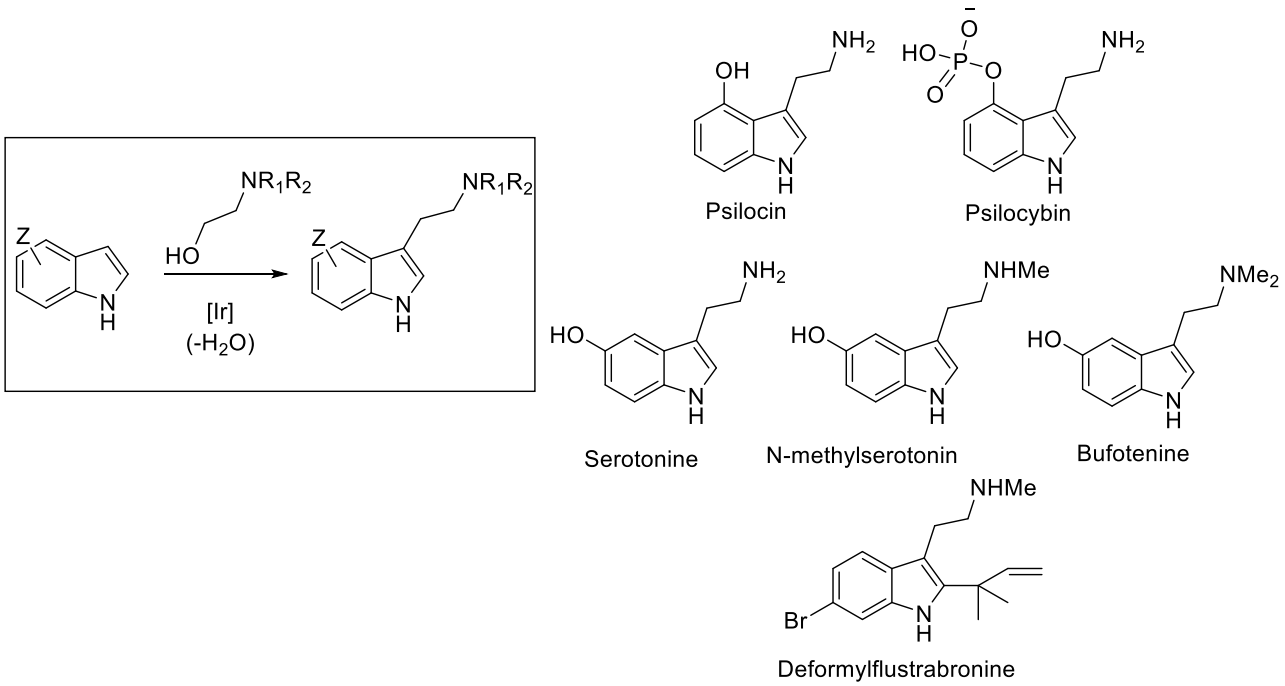
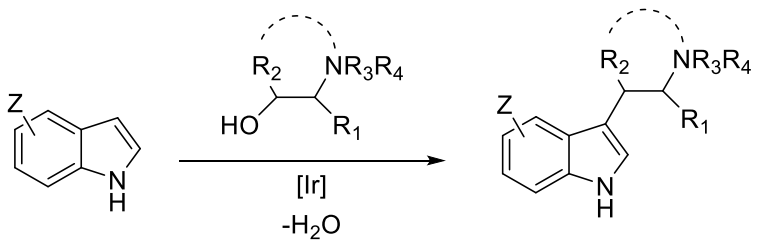


Figure 1 Synthesis of Biologically Interesting Tryptamine.

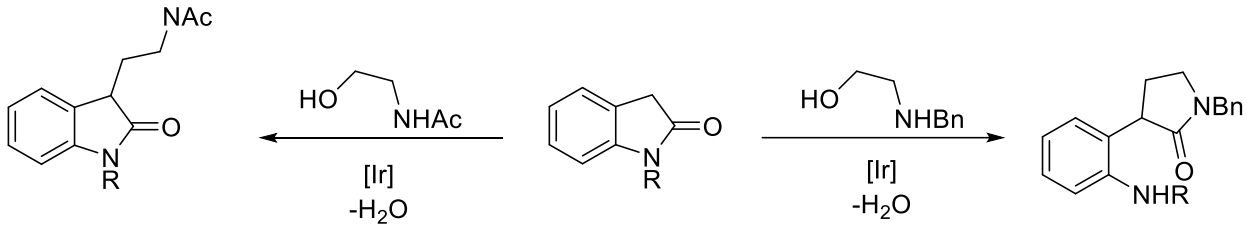
Tryptamine derivatives have attracted comprehensive and continuous interest from the chemical community.[56] Moreover, tryptamine represent the basis for some condensed ring alkaloids, and it is a key starting building block for many intents and purposes, such as the total synthesis of polycyclic tryptamine-derived indole alkaloids.[57] Simple synthetic approaches tryptamine derivatives are highly desirable considering their practical importance and because they avoid the lees sustainable approach.[58] For this purpose efficient formation via borrowing hydrogen of N-acetyl-protected branched tryptamines and homotryptamine derivatives, as well as N-methylated tryptamine cores of biological importance such as psilocin, bufotenin and serotonin, were taken in consideration.



Scheme 2 Synthesis of Tryptamine Derivatives by the Use of Borrowing Hydrogen Method.

Further oxindole, another scaffold that characterizes a large number of natural[59] and synthetic compounds with important biological activities,[60] will be explored in order

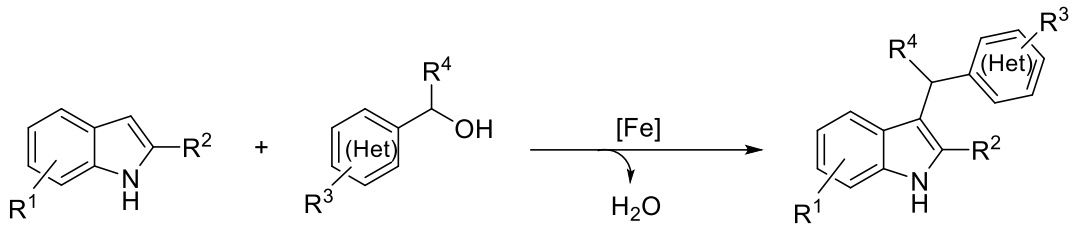
to show the importance and versatility of ethanolamines as alkylating agents in a different context and the power of iridium catalyst system already developed. Oxindoles have a wide range of applications and they show an extensive range of biological effects. Moreover, the biological activity of the oxindoles and their derivatives has made them very important in synthetic organic and medicinal chemistry. These characteristics of oxindoles prompt chemist to provide various applications of oxindoles and their derivatives. In particular using the already developed iridium catalyst[37] it has been planned to present a divergent synthesis employing diversely substituted oxindoles: when N-acetyl-ethanolamine is used the C3-alkylation via borrowing hydrogen methodology has been expected, alternatively when N-benzyl ethanolamine is used a sequential/domino process, consisting of alkylation and transamidation processes, should took place providing α-substituted γ-lactams. When N-aryl oxindoles will be employed with N-benzyl ethanolamine, substituted diarylamines could be obtained, which represent an important class of compounds due to their wide applications and special pharmacological activities (Scheme 3).[61]



Scheme 3 Divergent Borrowing Hydrogen Approach from Oxindoles end Ethanolamines: Synthesis of C3-Substituted Oxindoles and Substituted Diarylamines.

Though, in terms of sustainability, the use of precious transition metals should be substituted by more eco-friendly, inexpensive and earth-abundant metals. Among these metals, iron attracts significant attention and is considered as a valuable alternative.[62] In the last decades, iron catalysts have increasingly been used in organic synthesis in a number of reactions.[63] Feringa and Barta, Wills and Zhao have reported the alkylation of primary amines with alcohols to give secondary and tertiary amines by utilizing iron catalysts featuring functionalized cyclopentadienone or hydroxy cyclopentadienyl ligands based on Knölker's complex or derivatives thereof.[64] However, the borrowing hydrogen methodology using iron with alcohol in C-C- bond formation has been reported in few publications.[65] Therefore, the focus was placed on the search for an iron catalyst able to afford the selective iron C3-alkylation of indoles with different substituted benzylic alcohol. After a search for a suitable

catalyst system based on a commercial available iron complex, the reaction scope will be tested with different substituted primary and secondary benzyl alcohol and eterobenzylic alchol (Scheme 4).



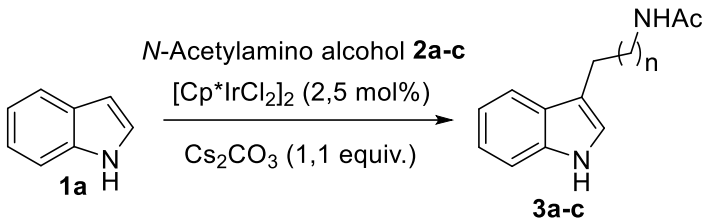
Scheme 4 Iron Catalyzed Direct C3-Benzylation of Indoles with Benzyl Alcohols.

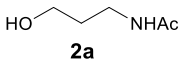
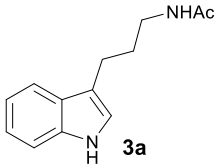
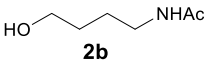
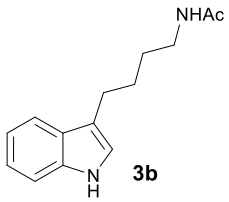
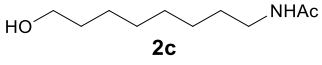
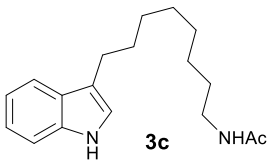
Mechanistic studies were expected to ensure that the catalytic process involves the borrowing hydrogen mechanism.

3. Results and Discussion

3.1 Observations concerning the synthesis of tryptamine homologues and branched tryptamine derivatives via the borrowing hydrogen process: synthesis of psilocin, bufotenin, and serotonin.

Initial studies were carried out using N-acetyl-protected propanolamine **(2a)** and butanolamine **(2b)** as representative suitable three-carbon and four-carbon nitrogen-containing electrophiles. Pleasingly, complete indole consumption and good yields of homotryptamine **(3a)** and dihomotryptamine **(3b)** were observed after 48 h at 150°C when powdered Cs_2CO_3 was used as the base and $[Cp^*IrCl_2]_2$ was used as the catalyst (Table 1, entries 1 and 2). We succeeded in carrying out the alkylation reaction even with longer carbon chain N-acetylated primary amino alcohols; for example, using **(2c)**, **(3c)** has isolated in modest yield (Table 1, entry 3).



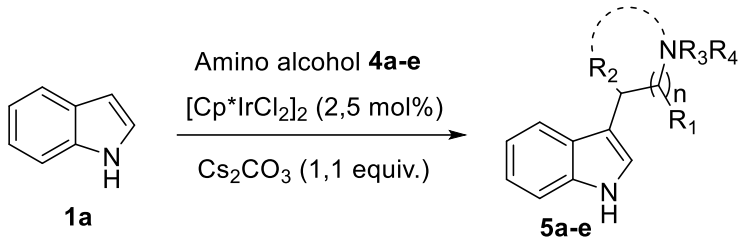
Entry	N-Acetylamino Alcohol	Product	Yield (%)[b]
1			54
2			76
3			57

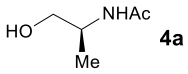
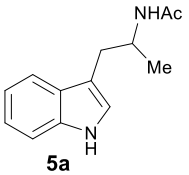
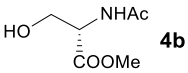
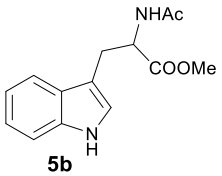
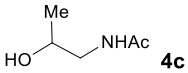
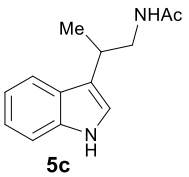
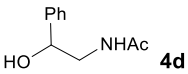
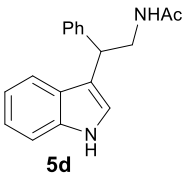
[a]Reactions were carried out in a sealed vial at 150 °C for 48 h with indole (1 equiv.), N-acetylamino alcohol (3 equiv.), $[Cp^*IrCl_2]_2$ (2.5 mol%), and Cs_2CO_3 (1.1 equiv.). [b]Isolated yield.

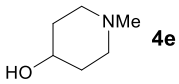
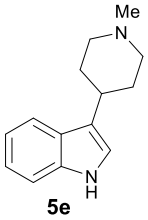
Table 1 Synthesis of N-Actyltryptamine Homologues[a].

Lower conversions and increased byproduct formation were generally observed when solvents such as toulene, tert-amylalcohol, and trifluoroethanol were employed. Apart from tryptamine analogues and homologues with linear side chains, derivatives with branched side chains, both in the α- and β-positions, are becoming increasingly studied in medicinal chemistry due to their ability to discriminate between the serotonin/melatonin receptor family subtypes. Recently, the first examples of branched tryptamines possessing pharmacologically interesting properties have been developed.[66] Thus, we then turned our attention to more sophisticated substituted N-acetylethanol-amines, such as the homochiral primary N-acetyl-L-alaninol **(4a)** and N-acetyl-L-serine **(4b)**, knowing their sensitivity toward racemization, once oxidised to the transient aldehyde. Interestingly, the methyl-substituted amino alcohol derivative **(4a)** performed poorly in this reaction, possibly due to the increased steric hindrance around the nitrogen atom that precludes effective ligand dissociation from the iridium centre. Notably, we did not observe any products that could arise from the potentially competitive four- membered ring cycloiridation pathway. Strong electron-withdrawing groups adjacent to the amine motif also failed to produce the desired product tryptophans in acceptable yields. In addition, the small amounts of products **(5a)** and **(5b)** obtained were racemic, as expected (Table 2, entries 1 and 2). A different outcome was obtained when we examined the applicability of the borrowing hydrogen reaction of indoles with racemic secondary N-acetyl ethanolamines, which proceeds via generally less electrophilic ketones (Table 2, entries 3 and 4). Therefore, we elected to examine the behaviour of indole in a borrowing hydrogen alkylation with N-acetyl-2-propanolamine **(4c)** and 2-acetamido-1-phenylethanol **(4d)**. We found that iridium- catalyzed indole alkylation with branched alcohol **(4c)** afforded a superior yield to the parent linear congeners, and we ascribe this reactivity to the relatively lower energetic demand of secondary alcohol dehydrogenation compared to primary alcohols, as well as the faster elimination of water from the adduct-formed alcohol- containing products of ketone addition. Unsatisfactory results were obtained when chiral Ir complexes and/or chiral ligands were employed to attempt an enantioselective version of this approach, although good yields were confirmed.[67] On the contrary, the secondary alcohol **(4d)** gave a complex mixture of unidentified compounds, containing only trace quantities of a compound identified as the desired protected tryptamine by LC/MS. This latter result was quite surprising because secondary benzyl alcohols are known to be good substrates in redox-neutral alkylations, reflecting their more favourable oxidation relative to higher alcohols[68]. Therefore, we suspected that the initial alcohol oxidation step had occurred but that alternative pathways (aldol-type reactions) prevented condensation (the resulting

conjugated ketone is notably less electrophilic) and the return of the hydrogen back to the desired indolenium intermediate, thus stalling the reaction.



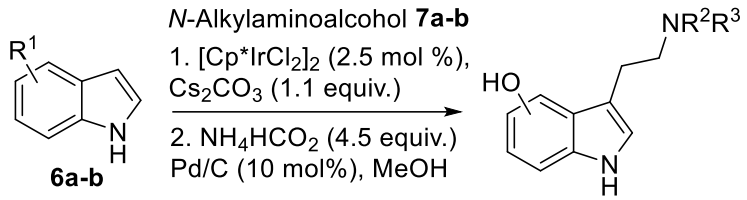
Entry	Amino alcohol	Product	Yield (%)[b]
1	 4a	 5a	37
2	 4b	 5b	15
3	 4c	 5c	78
4	 4d	 5d	Traces

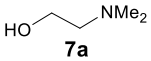
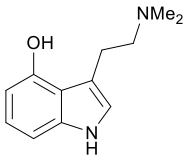
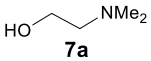
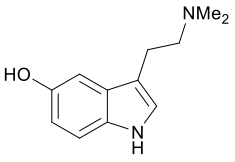
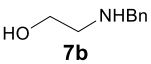
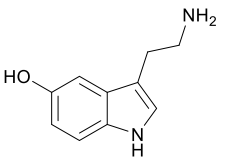
5	 **4e**	 **5e**	72

[a]Reactions were carried out in a sealed vial at 150 °C for 48 h with indole (1 equiv.), amino alcohol (3 equiv.), $[Cp^*IrCl_2]_2$ (2.5 mol%), and Cs_2CO_3 (1.1 equiv.). [b]Isolated yield.

Table 2 Synthesis of α- and β-branched tryptamines and branched homotryptamines from indole and amino alcohols.[a]

To confirm this hypothesis, we tested the viability of N-methyl-4-piperidinol **(4e)** as a secondary alcoholic substrate for hydrogen borrowing alkylation with indole, which allowed us to extend the methodology to branched homotryptamines (Table 2, entry 5). The reaction of indole with piperidine alcohol **(4)** under the same reaction conditions gave a good yield of 3-(N-methylpiperidyl) indole **(5e)**, which is an important structural element of clinical candidates such as the antimigraine compound LY334370 and naratriptan (Fig. 1).[69] Since most indole-based central nervous system drugs used in the treatment of migraines and cluster headaches, as well as some psychoactive natural product tryptamines, are tryptamine-based dimethylated amines,[70] we used the commercially available and highly interesting amino alcohol N,N-dimethylethanolamine **(7a)** to further demonstrate the application of this methodology. We adopted this chemistry for the total syntheses of psilocin and bufotenin in a straightforward manner (Table 3). Thus, the reaction of known 4-benzyloxyindole **(6a)** and 5-benzyloxyindole **(6b)** with N,N-dimethylethanolamine **(7a)** provided the desired products, which were debenzylated under hydrogenolysis conditions to afford psilocin and bufotenin in 61% and 67% overall yields, respectively. The salient features of this method include the single step preparation of the tryptamine core through displacement of the alcohol without the need for prior activation and without resorting to a high dilution or the use of a protected amine or final reductive alkylation for the tertiary amine. Among the biologically important hydroxytryptamines, serotonin is perhaps the most important and best known as a neurotransmitter that modulates neural activity and a wide range of neuropsychological processes.[71] Despite the fact that several syntheses and biosynthesis of serotonin have been described,[72] none seem practical or economical; thus, serotonin is still quite expensive on the market. Using our procedure of treating 5-benzyloxyindole with N-benzylethanolamine under Ir-catalyzed borrowing hydrogen conditions, followed by double debenzylation by catalytic reduction with palladium on carbon as the catalyst, serotonin was obtained in good overall yield.



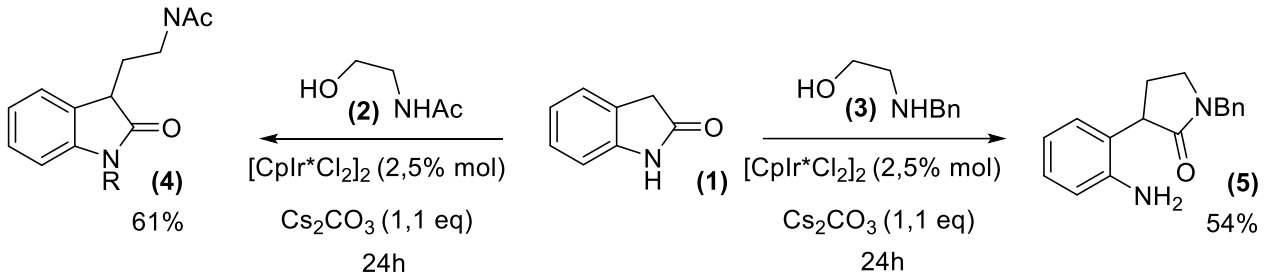
Entry	R^1	N-Akylamino alcohol	Product	Yield (%)[b]
1	4-OBn	 **7a**	 Psilocin	61
2	5-OBn	 **7a**	 Bufotenin	67
3	5-OBn	 **7b**	 Serotonin	62

[a]Reactions were carried out in a sealed vial at 150 °C for 48 h with indole (1 equiv.), *N*-alkylamino alcohol (3 equiv.), $[Cp^*IrCl_2]_2$ (2.5 mol%), and Cs_2CO_3 (1.1 equiv.), followed by hydrogenolysis with NH_4HCO_2 (4.5 equiv.) and Pd/C (10%) in MeOH at 70 °C for 45 min. [b]Isolated overall yield.

Table 3 Syntheses of psilocin, bufotenin, and serotonin from *N*-alkylated ethanolamines[a]

3.2 Divergent Borrowing Hydrogen Approach from Oxindoles and Ethanolamine: Synthesis of C3-Substituted Oxindoles and γ-Lactams.

Herein, we describe a convenient iridium-catalyzed process for the alkylation of 2-oxindoles with ethanolamines. The studies began with the investigation of the direct C3 catalytic alkylation of oxindole **(1)** with two aminoles **(2)** and **(3)**. As catalytic system we used the commercially available trivalent iridium complex $[Cp^*IrCl_2]_2$ in the conditions previously developed in our laboratories.[37] Essentially, we found that when the N-acetyl ethanolamine **(2)** reacts with oxindole **(1)** a direct alkylation of C-3 occurs giving the oxindole ethyl acetamide **(4)** in 61% yield. Unexpected result was obtained with aminol **(3)**. Instead, to obtain the simply alkylated oxindoles in C-3, α-substituted γ-lactam **(5)** was formed in 54% yield (Scheme 1).



Scheme 1 Divergent Reaction of Oxindoles with Ethanolamines Via Borrowing Hydrogen.

Therefore, we speculate on a possible pathway for the formation of α-substituted γ-lactam. Sequential/domino process consisting of alkylation and intramolecular secondary amide transamidation process could take place as shown in (Figure 1).

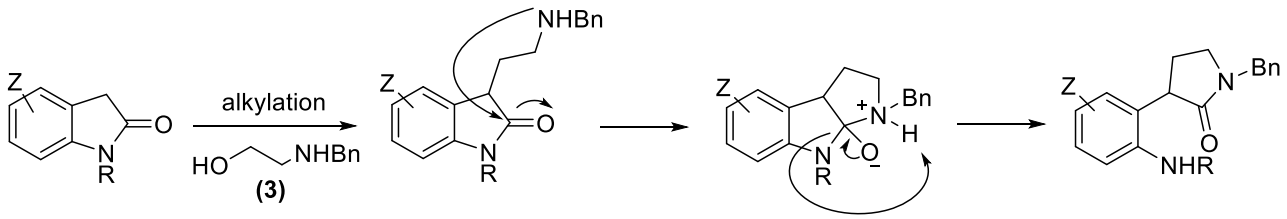
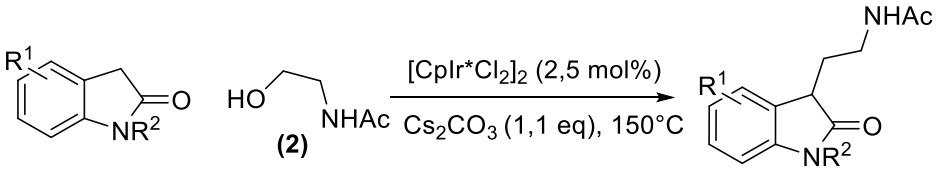


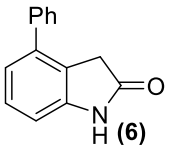
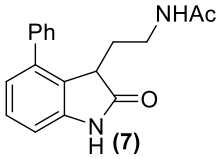
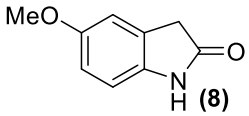
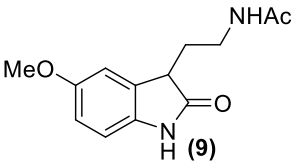
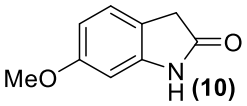
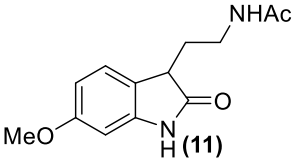
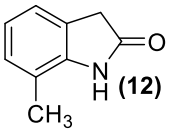
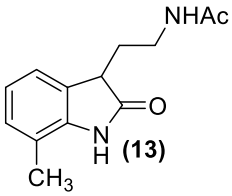
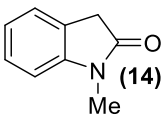
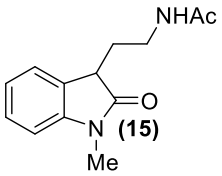
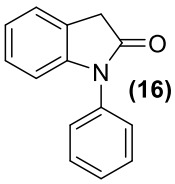
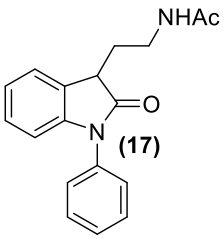
Figure 1 Proposed Opening Ring Mechanism.

We can justify the different behaviour of ethanolamines considering the different availability of the lone pair on the ethanolamines nitrogen atom. In the case of the ethanolamine **(2)**, the lone pair is delocalized due to the resonance with the acetyl

group resulting not enough nucleophilic to give the intermolecular addition/elimination. Instead, ethanolamine **(3)** have a strong nucleophilic nitrogen and could give the intramolecular addition/elimination on the carbonyl of oxindole **(1)**. After this finding, we have extended the scope of this divergent reaction studying different substituted oxindoles. First, we investigated the reactivity of N-acetyl ethanolamine **(2)**, with different substituted 2-oxindoles (Table 1). Through the treatment of 2-oxindoles (**6**), (**8**), (**10**) end (**12**) with N-acetylethanolamine (**2**) under the above-mentioned conditions, C3-amidoethyl oxindoles (**7**), (**9**), (**11**) and (**13**) were selectively achieved in 54–88% yield (Table 1, entries 1–4).[73] High yields were also achieved using N-methyl and N-phenyloxindoles (**14**) and (**16**) (Table 1, entries 5–6). Given the enormous effort that has already been dedicated to the catalytic asymmetric construction of oxindoles bearing a C3-quaternary stereocenter from simple C3-monoalkylated oxindoles,[74] which are then often converted into 2-oxindole containing a 2-aminoethyl side chain (and subsequently cyclized under reductive conditions to generate the tricyclic pyrrolidinoindoline ring system), the C3-amidoethylated 2-oxindoles (**7**), **(9**), (**11**), (**13**), (**15**), and (**17**) can be considered as advanced starting materials for the more direct asymmetric synthesis of enantio-enriched 3,3-disubstituted oxindoles and some related natural products/drug candidates. Furthermore in this series, compound (**4**) can be readily converted to the natural product (±)-*N*-[2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)ethyl]acetamide, which is an antiproliferative compound from *Selaginella pulvinata*, using a previously developed cobalt-catalyzed peroxidation reaction with hydroperoxide and a hydrogenation reaction,[75] whereas 2-oxo-2,3-dihydromelatonin (**9**), an oxidized analog of the neurohormone melatonin, is a valuable precursor for 2-substituted melatonin.[76]



Entry	Substrate	Product	Yield (%)[b]

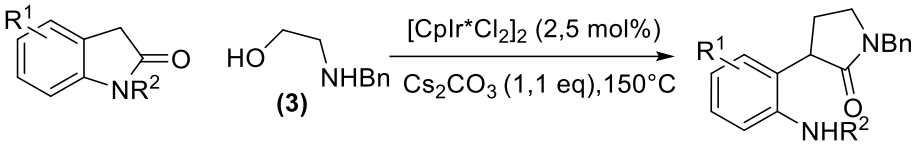
1			57
2			54
3			70
4			88
5			99
6			54

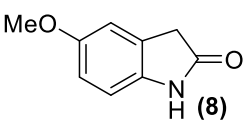
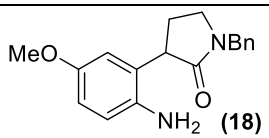
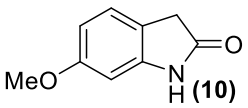
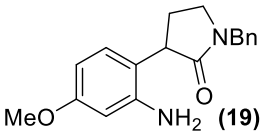
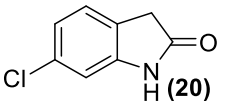
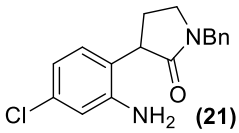
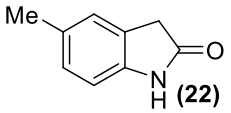
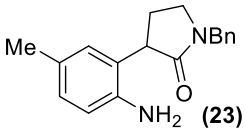
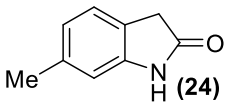
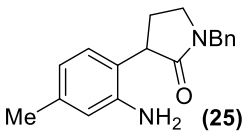
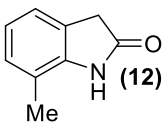
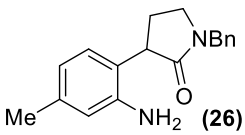
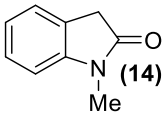
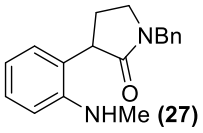
[a]Reactions were carried out in a sealed vial at 150 °C for 24 h with oxindole (1 equiv.), *N*-Ac ethanolamine (3 equiv.), $[Cp^*IrCl_2]_2$ (2.5 mol%), and Cs_2CO_3 (1.1) equivalent
[b]Isolated yield.

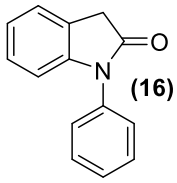
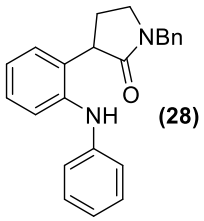
Table 1 Scope for the Direct C3-Alkylation of Substituted Oxindoles respect to Acetyl ethanolamine[a]**.**

Then we investigated the reactivity of N-benzylethanolamine **(3)** with different substituted oxindoles (Table 2). In particular, this method was compatible with modification of the benzyl moiety of the 2-oxindole core, and substitution (e.g., Cl, OMe, and Me) was readily tolerated on the aromatic ring (Table 2, entries 1–6). Finally, we studied the domino alkylation/annulation of *N*-substituted 2-oxindoles such as *N*-methyl and *N*-phenyl oxindole (**14, 16**) with *N*-benzylethanolamine (**3**), and a decent yield was achieved with substrate **16** to afford *ortho*-substituted

diarylaniline **28** (Table 2, entry 8). Importantly, the diarylamine products of the type generated from the reactions described herein are highly valued motifs with important structural, electronic, and mechanical properties suitable for therapeutic applications. In addition, the amide of the γ-lactams can be cleaved to provide access to a variety of 2-(2-phenylamino)phenyl)ethanoic acid nonsteroidal anti-inflammatory agent derivatives, such as Lumiracoxib and Diclofenac.[59]



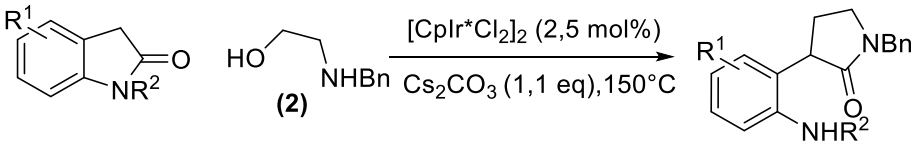
Entry	Substrate	Product	Yield (%)[b]
1			37
2			42
3			35
4			48
5			46
6			72
7			35

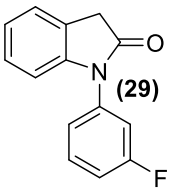
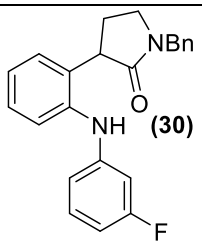
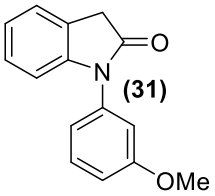
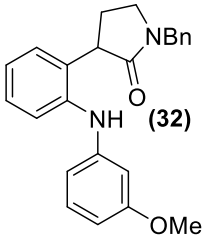
8	 (16)	 (28)	68

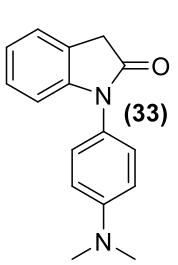
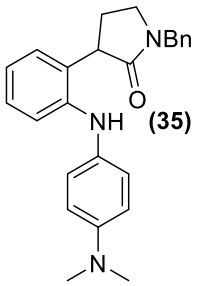
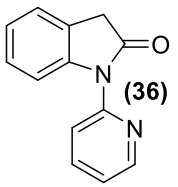
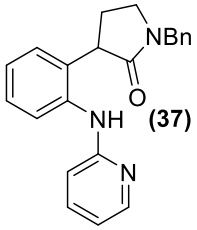
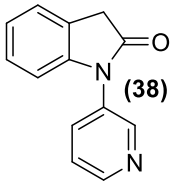
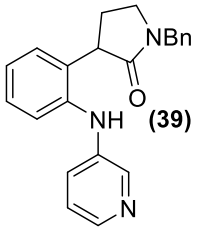
[a]Reactions were carried out in a sealed vial at 150 °C for 24 h with indole (1 equiv.), *N*-Benzyl ethanolamine (3 equiv.), $[Cp^*IrCl_2]_2$ (2.5 mol%), and Cs_2CO_3 (1.1) equivalent
[b]Isolated yield.

Table 2 Scope for the Direct C3-Alkylation of Substituted Oxindoles respect to Benzyl ethanolamine[a]**.**

Since the importance of pharmaceutical and biological activity of the diaryl amines, obtained with the strategy described above, where oxindoles are N-substituted with aril group, we extended and explore more structure with different substitution on aryl and heteroaryl group (Table 3).



Entry	Substrate	Product	Yield (%)[b]
1	 (29)	 (30)	69
2	 (31)	 (32)	64

3	 (33)	 (35)	60
4	 (36)	 (37)	49
5	 (38)	 (39)	70

[a]Reactions were carried out in a sealed vial at 150 °C for 24 h with indole (1 equiv.), *N*-Acetyl ethanolamine (3 equiv.), $[Cp^*IrCl_2]_2$ (2.5 mol%), and Cs_2CO_3 (1.1) equivalent
[b]Isolated yield.

Table 3 Scope for the Direct C3-Alkylation of N-Aryl Substituted Oxindoles respect to Benzyl ethanolamine[a]**.**

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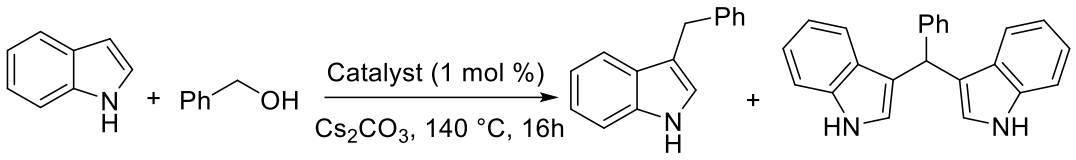
Transformations of *N*-aryloxindoles bearing a halogen atom, such as fluorine (**29**), afforded the corresponding product **30** in 69% yield (Table 3, entry 1). For *N*-aryloxindoles bearing an even stronger electron-withdrawing substituent, such as pyridil (**36, 38**), the reaction proceeded smoothly to afford the desired products **37, 39** in 49% and 70% yield, respectively (Table 3, entries 4, 5). Furthermore, when the alkylation/annulation was applied to *N*-aryloxindoles bearing an electron-donating substituent, such as a methoxy or dimethylamine group (**31, 33**), the corresponding products **32, 35** were afforded in 64% and 60% yield, respectively (Table 3, entries 2, 3).

3.3 Iron-Catalyzed Direct C3-Benzylaion of Indoles with Benzyl Alcohols through Borrowing Hydrogen

Inspired by the recent studies to use the metals of first row as catalysts, we report herein a green, economical, and efficient iron-catalyzed C3-selective alkylation of indole. This reaction employs iron(II) phthalocyanine (Fe(II)Pc), an inexpensive commercially available compound that is typically used as an industrial additive for ink as well as photonic and optical material manufacturing. Of note, to date, Fe(II)Pc complexes have not been applied as catalysts for the formation of new carbon−carbon bonds via the borrowing hydrogen process.[77] The reaction of unsubstituted indole **(1a)** with benzyl alcohol **(2a)** was selected as the model reaction to establish the best reaction conditions. Initially, the effect of various iron based catalysts was investigated (Table 1).



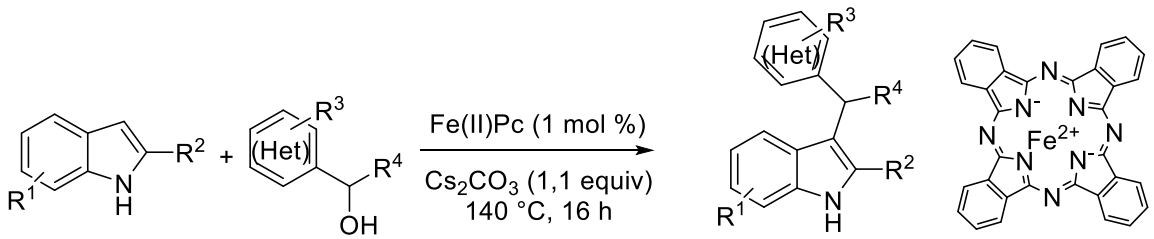
1a **2a** **3a** **4**

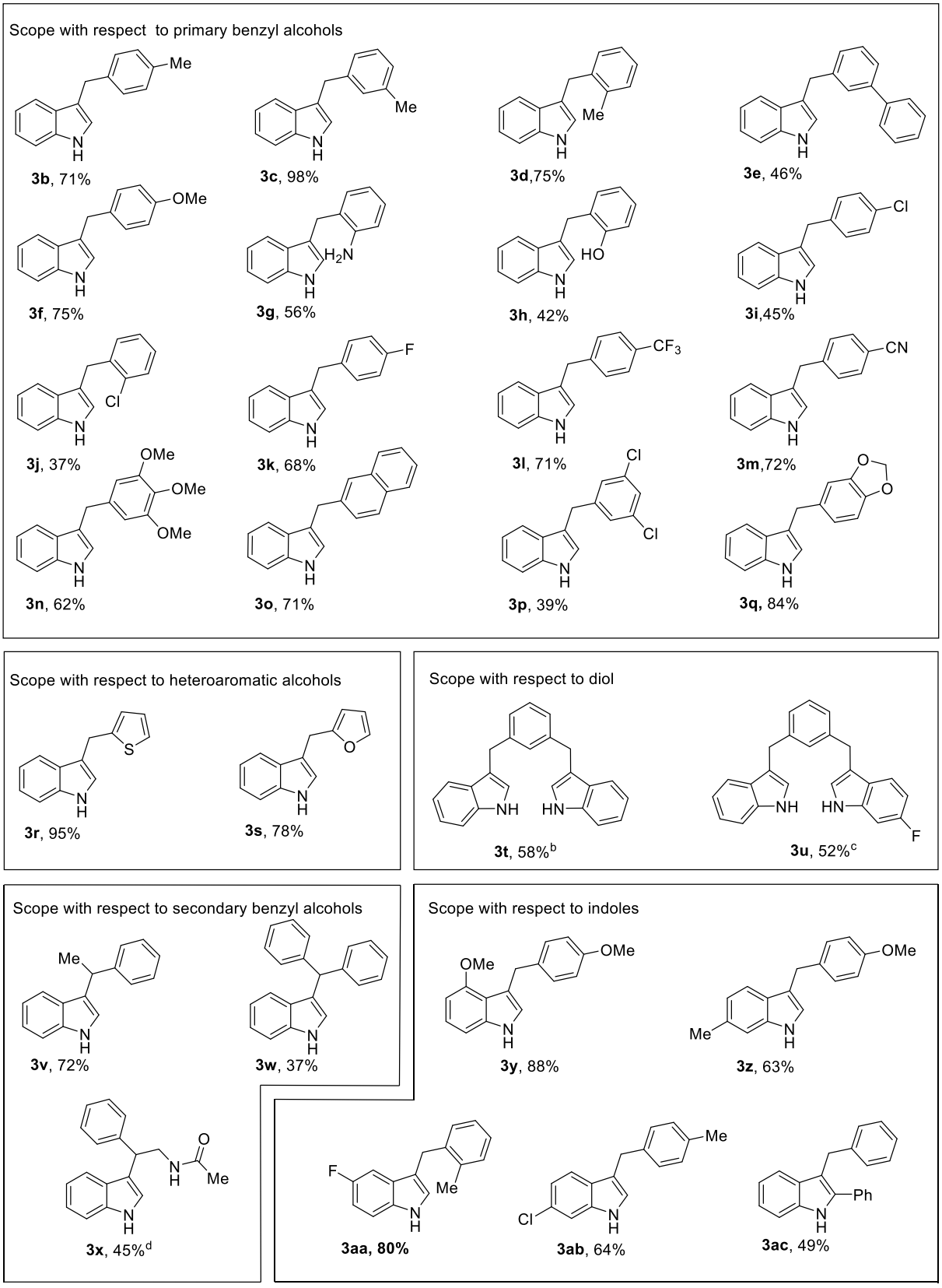
Entry[a]	Catalyst	Yield of 3[b] (%)
1	-	-
2	$FeSO_4$ [c]	-
3	$FeCl_2$[d]	-
4	$Fe(acac)_3$	-
5	Fe(II)Pc	99
6	Fe(II)Pc [e]	8
7	Fe(II)Pc [f]	Trace
8	Fe-Knölker	-
9	Fe-Knölker with PPh_3	-
10	Fe-Knölker with Me_3NO	-
11	Fe(II)Pc in the dark	97
12	Fe(II)Pc with BHT	98

[a]Reaction conditions: indole (0.5 mmol), benzyl alcohol (1 mmol), Cs_2CO_3 (0.55 mmol), catalyst (1 mol%) at 140 °C for 16 h. [b]Isolated yield. [c]Only **4** was isolated in 13% yield. [d]Only **4** was isolated in 21% yield [e]Cs_2CO_3 (0.05 mmol). [f]Without base.

Table 1 Optimization of the Reaction Conditions for C3-Alkylation of Indole with Benzyl Alcohol.

The reaction did not proceed without catalyst in the presence of Cs_2CO_3, which excluded the contribution of the base itself as a catalyst (Table 1, entry 1).[78] The highest activity was observed with Fe(II)Pc and a stoichiometric amount of Cs_2CO_3 (Table 1, entries 5−7). Other iron salts were found to be ineffective and, not surprisingly, led to the formation of bis(indolyl)methane **(4)** in poor yields (Table 1, entries 2−4).[79] Due to its inherent redox properties, the iron(0)tricarbonyl complex such as the Knölker-type catalyst is widely known to activate inert substrates via dehydrogenation/hydrogenation reactions and has been reported previously for C−C bond formation.[80] Neither alone (Table 1, entry 8) nor in the presence of 10 mol % Me_3NO oxidant (to form active catalyst) and PPh_3 ligand did the alkylated product form (Table 1, entries 9 and 10). This solvent-free reaction with Fe(II)Pc as the catalyst was excellent in terms of both yield and selectivity as compared with the corresponding reaction in toluene (1.0 M, 54% yield; 0.5 M, 10% yield) or tert-amyl alcohol (at reflux under air atmosphere for 16 h afforded the desired alkylated product **3a** in 31% yield). The desired coupling product was also obtained in the absence of light as well as in the presence of radical scavengers such butylated hydroxytoluene (BHT), thus discarding the involvement of radical species in the reaction pathway, more precisely using TEMPO as a radical scavenger, only oxidative degradation of indole was observed. (Table 1, entries 11 and 12). Once the optimal reaction conditions were achieved, we examined the scope of the alkylation with respect to alcohols catalyzed by Fe(II)Pc, and these results are outlined in (Table2).



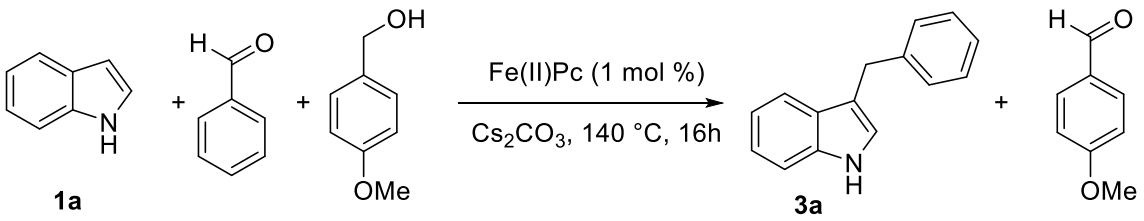


[a] Reaction conditions: indole (0.5 mmol), alcohol (1 mmol), Cs_2CO_3 (0.55 mmol), Fe(II)Pc (0.055 mmol) at 140 °C for 16 h. [b]Indole (1mmol), alcohol (0.5 mmol). [c]1H-indole (0.5 mmol), 6-fluoro-1H-indole (0.5 mm0l), 2-(hydroxymethyl)phenol (0.5 mmol). [d] 140 °C for 36h.

Table 2 Scope of C3-Alkylation of Indole with Benzyl Alcohol[a]

The C3-alkylation of indole with primary benzylic alcohols bearing an electron-donating substituent such as methyl, phenyl, and methoxy groups afforded the corresponding products **(3b−f)** in 46−98% yields. Also, (2-aminophenyl)- methanol and 2-(hydroxymethyl)phenol provided the products **(3g−h)** in good yield, 56% and 42%, respectively. Similarly, electronically deactivated benzylic alcohols, which are very poor substrates in Lewis- or Brønsted acid-catalyzed Friedel−Crafts reactions[81], bearing an electron-withdrawing group such as chloro, fluoro, cyano and trifluoromethyl groups were converted to the desired products **(3i−m)** in 37−71% yields. A trisubstituted benzyl alcohol, such as 3,4,5-trimethoxybenzyl alcohol, was successfully transformed to 3-(3,4,5-trimethox- ybenzyl)-1H-indole in 62% yield. A naphthyl alcohol (naphthalen-2-ylmethanol), (3,5-dichlorophenyl)methanol, and benzo[1,3]dioxonyl were converted to give the corresponding alkylated indole products (**3o−q)** in good yields. Heteroaromatic alcohols with furanyl and thienyl groups were also tolerated, and the corresponding indoles **(3r−s)** were obtained in 95% and 78% yields, respectively. This reaction sequence was demonstrated for the preparation of symmetrical bisindole compound **(3t)**, whereby indole, used in excess, was double alkylated with 1,3-phenylenedimethanol through a one-pot process in satisfactory yield. Moreover, sequential functionalization of diols is undoubtedly a valuable synthetic tool to obtain compounds with great diversity. We explored a selective iron-catalyzed method that allows for the preparation of nonsymmetrical, functionalized bisindoles. This reaction sequence was demonstrated for the preparation of compound **(3u)**, whereby 1,3-phenylenedimethanol was selectively monoalkylated with indole to form (3-((1H-indol-3-yl)methyl)phenyl)methanol and subsequently treated with 6-fluoroindole to provide **(3u)**. Next, secondary benzylic alcohols, which are less prone to the condensation and hydrogenation step in comparison to primary ones, were used as the substrate. 1-Phenylethanol, diphenylmethanol, and 2-acetamido-1-phenylethanol reacted smoothly with indole, and the corresponding products **(3v−x)** were obtained in moderate to good yields. When cinnamyl alcohol was utilized, the desired product was obtained in poor yield due to large contamination of saturated derivatives; whereas with aliphatic alcohols such as cyclo- hexanol, cyclopropyl methanol, and 1-octanol, the reaction failed. Next, we examined some representative substituted indoles to explore the generality of this novel reaction. For example, the electron-rich and sterically hindered 4-methoxyindole was converted to the desired product **(3x)** in a very good yield and selectivity. The 6-methyl-, 5-fluoro-, and 6-chloroindole- benzylated derivatives **(3z)** and **(3aa−3ab)** were also obtained in decent yields, although the yields were lower than those of the 4-OMe analogue. Pleasingly, the presence of a substituent at C2 did not influence the reaction, despite the potential steric crowding around the reaction

site. Thus, 2-phenylindole reacted efficiently with benzyl alcohol to give the corresponding product **(3ac)**. Not surprisingly, N-methylindole proved to be inert, suggesting the involvement of the indole N−H in a key interaction with the base during the rate-determining step. However, nearly complete recovery of the starting material was observed when C3-substituted indole, such as 3-methyl or 3-benzylindole, was allowed to react with benzyl alcohol under the reaction conditions reported above. Neither dearomatization of the indole nucleus to 3-benzylindolenine products nor C3- to C2-benzyl migration and rearomatization to afford 2,3-disubstituted indoles were detected, in spite of recent reports.[82] To highlight the synthetic utility of the present protocol, a gram-scale reaction with indole (**1a**) and benzylic alcohol **(2a)** was performed, and the efficiency of the small-scale reaction was retained upon scale-up, delivering **3a** in 92% yield. To obtain insight into the reaction mechanism of the catalytic process, other experiments were carried out, thus providing significant evidence for a plausible borrowing hydrogen mechanism rather than a general acidic strategy involving the formation of a stabilized benzylic cation. The reaction of indole with benzyl bromide (2 equiv.) under the optimized reaction conditions gave a mixture of 1-benzyl-1H- indole (45%) and 1,3-dibenzyl-1H-indole (28%). Then, we repeated the reaction using triphenylmethanol, and the starting unchanged indole was recovered, which is another indirect proof that the cationic benzyl intermediate is not involved. When benzylic alcohol was heated in the presence of Fe(II)Pc and cesium carbonate at 140 °C in a sealed tube for 16 h, formation of a small amount of benzaldehyde (11% according to GC-analysis of the crude mixture) was observed. Finally, the competitive reaction of indole with benzaldehyde and (4-methoxyphenyl)methanol (Scheme 2) gave a mixture 6:1 of 3-benzylated compounds (based on 1H NMR spectra), in which the main product was that arising from the condensation with benzaldehyde followed by reduction of benzylideneindolenine (obviously, large formation of p-methoxybenzaldehyde was also observed).



Scheme 2 Competitive Experiment between an Aldehyde and an Alcohol.

All of these data together with the presence of bisindole side product **4**, obtainable only in the presence of aldehyde in the reaction mixture, and the good yields obtained with electron poor benzylic alcohols (compounds **3l**, **3m**) are confirming our initial borrowing hydrogen mechanistic hypothesis.

4. Conclusions

In summary during my research project, I extended the selective indole alkylation reaction using $[Cp^*IrCl_2]_2$ catalyzed-borrowing hydrogen methodology[37] for the synthesis of novel branched and nonbranched tryptamines and tryptamine homologues using amino alcohols as suitable nitrogen-containing electrophiles. In addition, the short alternative and expedient syntheses of psilocin, bufotenin and serotonin were achieved by employing this chemistry. The subtle factors influencing the competing pathways in the critical borrowing hydrogen reaction of indoles with complex amino alcohols,[83] as well as some limitations on the broad applicability of the chemistry, were discussed. Nevertheless, encouraged by some key examples of this methodology, I believe that it has the potential to deliver improved processes for pharmaceutical manufacturing. This catalytic and modular approach tolerates the presence of substituents at C3 of the indole core, variations in the amine moiety, and the distance of the amine moiety to the indole core to the final synthetic step to be easily defined for a quick access to tryptamine derivatives. Then, the same catalyst system $[Cp^*IrCl_2]_2$ was explored in the alkylation of oxindole with N-protected ethanolamines to provides a potential 'green' route to the formation C-3-substituted oxindole derivatives and more complex derivatives. In particular, a divergent synthesis has been presented: when N-acetyl-ethanol amine was used simply C3-alkylation via borrowing hydrogen methodology occurs, alternatively employing N-benzyl-ethanolamine diversely functionalized α-substituited γ-lactams from oxindoles via the modern borrowing hydrogen methodology were obtained. A sequential/domino process was proposed to elucidate the formation of these products. In both cases were also tested N-methyl and N-phenyl group as substituent on oxindoles, demonstrating that the reaction does not suffer the presence of a substituent on oxindole N-H. With N-benzyl-ethanolamine and different N-aryl and N-heteroaryl substituted oxindoles different diaryl amines, representing important class of compound due to their wide application and special pharmacological activates, were obtained with this synthetic challenging route. Finally, considering the recent and high interest on first- row, heart-abundant metals, to enable the state of the art, the use of iron as catalyst in the borrowing hydrogen process has been take in consideration. So, for the first time, a general methodology for the catalytic formation of value-added 3-benzylindoles has been established through the use of indole and primary, secondary and heteroaromatic benzyl alcohols using an easily handled, air- and moisture-stable earth-abundant iron complex catalyst (iron phthalocyanine). This operates through a hydrogen-borrowing mechanism, demonstrated by experimental evidence and competitive studies. Many synthetically challenging routes were systematically explored, starting from readily accessible substrates that do not require

prior alcohol activation by stoichiometric methods. This included the one-pot synthesis of symmetrical bisindoles, the sequential functionalization of diols and the use of a secondary alcohol coupling partner under the catalytic conditions, which then enabled the formation of the desired branched alkylated indole.

5. Experimental Data

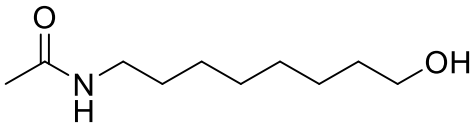
5.1 Materials and Methods

All reactions were run in air unless otherwise noted. Column chromatography purifications were performed in flash chromatography conditions using 230−400 mesh silica gel. Analytical thin-layer chromatography (TLC) was carried out on silica gel plates (Silica Gel 60 F254) that were visualized by exposure to ultraviolet light and an aqueous solution of $KMnO_4$, cerium ammonium molybdate (CAM), p-anisaldehyde, or ninhydrin. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 spectrometer, using $CDCl_3$ or CD_3OD, [D6]-acetone or [D6]-DMSO. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in hertz (Hz). ESI-MS spectra were taken on a Waters Micromass ZQ instrument, only molecular ions (M + 1 or M − 1) are given. IR spectra were obtained on Nicolet Avatar 360 FT-IR spectrometer, and absorbance is reported in cm^{-1}. Melting points were determined on a capillary melting point a Buchi SMP-510 apparatus and are uncorrected. HRMS analysis was performed using a Q-TOF microTM mass spectrometer. Elemental analyses were performed on a Carlo Erba analyzer and the results are within ±0.4 of the theoretical values (C, H, N). 4-(Benzyloxy)-1H-indole **(6a)** was synthesized according to the literature procedure[84]. 5-(Benzyloxy)-1H-indole (**6b)** was purchased from Apollo Scientific and was used without further purification. The aminoalcohols **(2a-b)** and **(4c-d)** were synthesized according to the literature procedure[85]. The aminoalcohol **(2c)** and **(4a-b)** were synthesized as described below. The aminoalcohol **(7a)** and **(4e)** were purchased from SigmaeAldrich, **(7b)** from Alfa Aesar and were all used without further purification. Ethanolamines **(2)**, **(3)** and Oxindoles **(8)**, **(10)**, **(12)**, **(14)**, **(16)**, **(20), (22), (24),** are commercial available. 1H-indole, 6-fluoro-1H-indole, 4-methoxy-1H- indole, 6-methyl-1H-indole, 5-fluoro 1H-indole, 6-chloro-1H-indole, 2-phenyl-1H-indole, benzyl alcohol, p-tolylmethanol, m-tolylmethanol, o-tolylmethanol, biphenyl-3-ylmethanol, (N-(2-hydroxy-2-phenylethyl)acetamide, 4-methoxyphenyl)methanol, (2-aminophenyl)methanol, 2 (hydroxymethyl)phenol, (4-chlorophenyl)- methanol, (2-chlorophenyl)methanol, (4 fluorophenyl)methanol, (4-(trifluoromethyl)phenyl)methanol, 4-(hydroxymethyl)benzonitrile, (3,4,5-trimethoxyphenyl)methanol, naphthalen-2-ylmethanol, (3,5-dichlorophenyl)methanol, furan-2-ylmethanol, thiophen-2ylmethanol, benzo[d][1,3]dioxol-5-ylmethanol, 1-phenylethanol, and diphenylmethanol are commercially available.

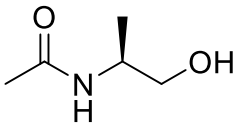
5.2 Compound Characterization and Synthetic Methods

5.2.1 Observations concerning the synthesis of tryptamine homologues and branched tryptamine derivatives via the borrowing hydrogen process: synthesis of psilocin, bufotenin, and serotonin.

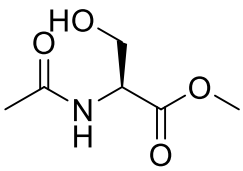
General procedure for the synthesis of N-Acetylaminols (2c) and (4a-b). To a solution of aminol (2 mmol) and TEA (585 mL, 4.2 mmol) in CH_2Cl_2 dry (6 mL) was added acetyl chloride (149 mL, 2.1 mmol) at 0°C. The reaction mixture was stirred vigorously at 0°C under N_2 until TLC analysis shows complete conversion of the starting materials. The solvent was removed under reduce pressure and the residue was purified by flash column chromatography on silica gel to afford the desired product**.**



N-(8-Hydroxyoctyl)acetamide (2c). (224 mg, 60%), white solid. MS(ESI): 188 $[M+H]^+$. ^1H NMR(400 MHz, $CDCl_3$): δ 1.25-1.29 (m, 8H), 1.43-1.51 (m, 4H), 1.53 (s, 3H), 3.15-3.20 (m, 2H), 3.56-3.60 (m, 2H), 6.14 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 25.6, 26.7, 29.1, 29.2, 29.5, 32.6, 39.6, 62.6, 76.7, 77.1, 77.4, 170.4. FTIR (film, $cm^{-}1$): 1640, 3385; Anal. Calcd. For $C_{10}H_{21}NO_2$ (187.16): C, 64.13; H, 11.30; N, 7.48; Found: C 64.21; H, 11.41; N, 7.45.



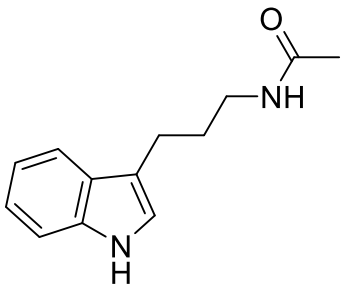
(S)-N-(1-Hydroxypropan-2-yl)acetamide (4a). (201 mg, 86%), colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (d, 3H, J=6.5 Hz), 1.90 (s, 3H), 3.37-3.58 (m, 2H), 3.86-3.98 (m, 1H), 4.39 (brs, 1H), 6.87 (brs, 1H, J=7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 23.1, 47.5, 65.9, 171.1. FTIR (film, $cm^{-}1$): 1653; Anal. Calcd. For $C_5H_{11}NO_2$ (117.08): C 51.26; H, 9.46; N, 11.96; Found: C, 51.20; H, 11.52; N, 11.92.



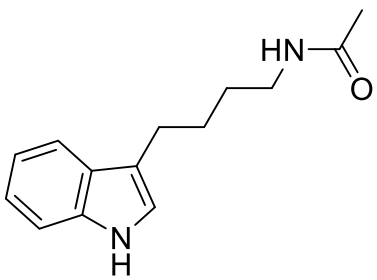
(S)-Methyl 2-acetamido-3-hydroxypropanoate (4b). (251 mg, 78%), colorless oil. ^1H NMR (400 MHz, $CDCl_3$): d 2.09 (s, 3H), 3.81 (s, 3H), 3.95-3.99 (m, 2H), 4.66-4.73 (m,1H), 6.46 (brs, 1H). The chemical-physical data are according to those published the literature[86].

General procedure for the synthesis of N-Substituted tryptamines. A mixture of the suitable indole (1a) or (6a-b) (0.25 mmol), Cs_2CO_3 (90 mg, 0.275 mmol), $[Cp^*IrCl_2]_2$ (5 mg, 0.00625 mmol) and the appropriate N-protected ethanolamine 2a-c, (4a-e) or (7a-b) (0.75 mmol) was stirred under N_2 atmosphere at 150 °C for 48 h in

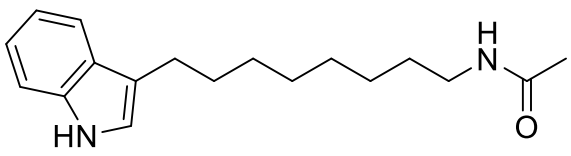
a sealed vial. After cooling to room temperature, the reaction mixture was dissolved in EtOAc/MeOH 9:1 (1 mL) and filtered through a silica gel pad. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel.



N-(3-(1H-Indol-3-yl)propyl)acetamide (3a). Prepared according to the general procedure from 1H-indole and N-(3-hydroxypropyl)acetamide (2a). Flash chromatography (EtOAc) gave (3a) (29 mg, 54%) as a light oil. MS (ESI): 217 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88-1.98 (m, 2H), 1.92 (s, 3H), 2.80 (t, 2H, J=7.5 Hz), 3.31 (dt, 2H, $J_1 \approx J_2$=7.5 Hz), 5.62 (brs, 1H), 6.70 (d, 1H, J01.5 Hz), 7.12 (ddd, 1H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.20 (ddd, 1H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.36 (dd, 1H, J=8.0 Hz), 7.59 (dd, 1H, J=8.0 Hz), 8.26 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 23.3, 29.7, 39.5, 111.2, 115.3, 118.7, 119.1, 121.6, 121.9, 127.3, 136.4, 170.3. The chemical-physical data are according to those published the literature[87].

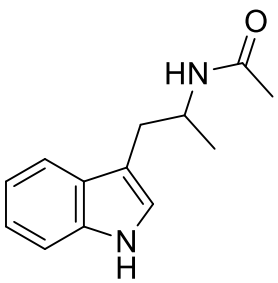


N-(4-(1H-Indol-3-yl)butyl)acetamide (3b). Prepared according to the general procedure from 1H-indole and N-(4-hydroxybutyl)acetamide (2b). Flash chromatography (EtOAc) gave (3b) (44 mg, 76%) as a light oil. MS (ESI): 231 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53-1.61 (m, 2H), 1.70-1.77 (m, 2H), 1.93 (s, 3H), 2.78 (t, 2H, J=7.0 Hz), 3.23-3.28 (m, 2H), 5.57 (brs, 1H), 6.96 (d, 1H, J=1.5 Hz), 7.12 (ddd, 1H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.19 (ddd, 1H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.35 (ddd, 1H, $J_1 \approx J_2$=1.0 and J_3=8.0 Hz), 7.59 (d, 1H, J=8.0 Hz), 8.20 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 24.7, 27.4, 29.3, 39.6, 111.2, 116.1, 118.8, 119.1, 121.4, 121.8, 127.4, 136.4, 170.2; FTIR (Nujol, cm^{-1}): 1626, 3285; Anal. Calcd. For $C_{14}H_{18}N_2O$ (230.14): C, 73.01; H, 7.88; N, 12.16; Found: C, 73.12; H, 7.85; N, 12.19.

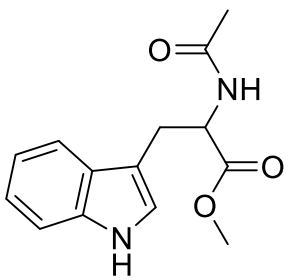


N-(8-(1H-Indol-3-yl)octyl)acetamide (3c). Prepared according to the general procedure from 1H-indole and N-(8-hydroxyoctyl)acetamide (2c). Flash chromatography (EtOAc) gave (3c) (41 mg, 57%) as a light oil. MS (ESI): 287 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27-1.39 (m, 8H), 1.43-1.49 (m, 2H), 1.68-1.74 (m, 2H), 1.97 (s, 3H), 2.76 (t, 2H, J=7.5 Hz), 3.19-3.24 (m, 2H), 5.74 (brs, 1H), 6.96 (s, 1H, J¼2.0 Hz), 7.12 (ddd, 1H, J1¼1.0, J2¼7.0, J3¼8.0 Hz), 7.19 (ddd, 1H, J1¼1.0, J2¼7.0, J3¼8.0 Hz), 7.35 (ddd, 1H, J1¼J2¼1.0 and J3¼8.0 Hz), 7.63 (d, 1H,

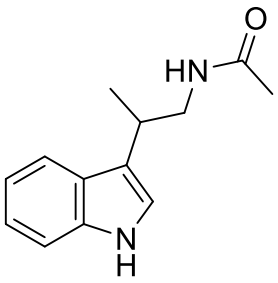
J¼8.0 Hz), 8.31 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): d 23.3, 25.1, 26.9, 29.3, 29.4, 29.5, 29.6, 30.1, 39.8, 111.2, 116.8, 118.9, 119.0, 121.3, 121.7, 127.6, 136.4, 170.3; FTIR (film, cm^{-}1): 1642, 3391; Anal. Calcd. For $C_{18}H_{26}N_2O$ (286.20): C, 75.48; H, 9.15; N, 9.78; Found: C, 75.66; H, 9.24; N, 9.91.



N-(1-(1H-Indol-3-yl)propan-2-yl)acetamide (5a). Prepared according to the general procedure from 1H-indole and (S)-N-(1-hydroxypropan-2-yl)acetamide (4a). Flash chromatography (EtOAc) gave (5a) (20 mg, 37%) as a light oil. MS (ESI): 217 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, 3H, J¼6.5 Hz),1.92 (s, 3H), 2.95 (d, 2H, J=6.0 Hz), 4.35-4.42 (m,1H), 5.39 (brs,1H), 7.04 (d, 1H, J=2.0 Hz), 7.14 (ddd, ^{1}H, J^1=1.0, J_2=7.0, J_3=8.0 Hz), 7.21 (ddd,^{1}H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.38 (d, 1H, J=8.0 Hz), 7.64 (d, 1H, J=8.0 Hz), 8.20 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 23.5, 31.7, 45.6, 111.1, 111.9, 119.0, 119.6, 122.1, 122.7, 128.0, 136.2, 169.5; FTIR (Nujol, cm^{-}1): 1740, 3398; Anal. Calcd. For $C_{13}H_{16}N_2O$ (216.13): C, 72.19; H, 7.46; N, 12.95; Found: C, 72.28; H, 7.52; N, 12.90.

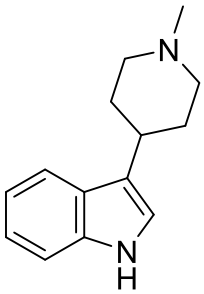


Methyl 2-acetamido-3-(1H-indol-3-yl)propanoate (5b). Prepared according to the general procedure from 1H-indole and methyl 2-acetamido-3-hydroxypropanoate (4b). Flash chromatography (cyclohexane:EtOAc 4:6 to EtOAc) gave 5b (20 mg,15%) as a white solid. MS (ESI): 261 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, 3H), 3.31 (dd, 1H, J_1=5.5, J_2=15.0 Hz), 3.36 (dd, 1H, J_1=5.5, J_2=15.0 Hz), 3.71 (s, 3H), 4.97 (ddd, 1H, $J_1 \approx J_2$=5.5, J_3=8.0 Hz), 6.03 (brs, 1H), 6.98 (s, 1H), 7.13 (ddd, 1H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.20 (ddd,1H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.37 (d, 1H, J=8.0 Hz), 7.54 (d, 1H, J=8.0 Hz), 8.29 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 27.6, 52.3, 53.1, 110.0, 111.3, 118.5, 119.7, 122.3, 122.7, 127.7, 136.1, 169.8, 172.4. The chemicalephysical data are according to those published the literature[88].

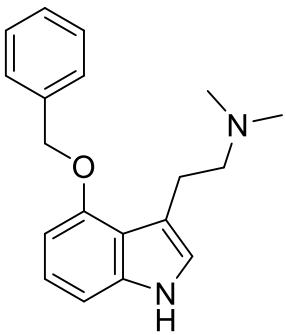


N-(2-(1H-Indol-3-yl)propyl)acetamide (5c). Prepared according to the general procedure from 1H-indole and N-(2-hydroxypropyl)acetamide (4c). Flash chromatography (EtOAc) gave (5c) (42 mg, 78%) as a light oil. MS (ESI): 217 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (d, 3H, J=7.0 Hz), 1.89 (s, 3H), 3.25-3.34 (m, 1H), 3.42-3.49 (m, 1H), 3.64-3.71 (m, 1H), 5.57 (brs, 1H), 7.03 (d, 1H, J=2.0 Hz), 7.13 (ddd, 1H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.22 (ddd, 1H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.39 (d, 1H, J=8.0 Hz), 7.66 (d, 1H, J=8.0 Hz), 8.50 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 23.4, 31.2, 45.7, 111.4, 118.7, 119.1, 119.4, 120.8, 122.2, 126.7, 136.6, 170.2; FTIR (Nujol, cm^{-}1):

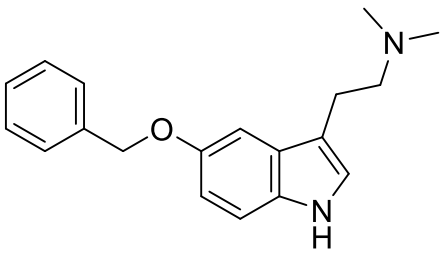
1650, 3407; Anal. Calcd. For $C_{13}H_{16}N_2O$ (216.13): C, 72.19; H, 7.46; N, 12.95; Found: C, 72.25; H, 7.41; N, 12.98.



3-(1-Methylpiperidin-4-yl)-1H-indole (5e). Prepared according to the general procedure from 1H-indole and 1-methylpiperidin-4-ol (4e). Flash chromatography (DCM:MeOH 9:1 and 1% of TEA) gave 5e (39 mg, 72%) as a light oil. MS (ESI): 215 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87 (ddd, 2H, J_1=3.5, J_2=12.0, J_3=25.0 Hz), 2.07-2.10 (m, 2H), 2.17 (ddd, 2H, J_1=2.5, J_2=$J_3$12.0 Hz), 2.38 (s, 3H), 2.84 (dddd, 1H, J_1=J_2=3.5, J_3=J_4=12.0 Hz), 3.00-3.03 (m, 2H), 6.97 (d, 1H, J=2.0 Hz), 7.12 (ddd, 1H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.20 (ddd, 1H, J_1=1.0, J_2=7.0, J_3=8.0 Hz), 7.36 (ddd, 1H, J_1=J_2=1.0, J_3=8.0 Hz), 7.67 (d, 1H, J=8.0 Hz), 8.35 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.9, 33.1, 46.6, 56.5, 111.2, 119.0, 119.1, 119.7, 121.3, 121.9, 126.7, 136.6. The chemical-physical data are according to the literature[89].

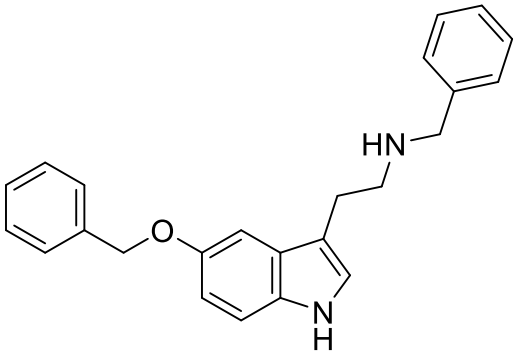


2-(4-(Benzyloxy)-1H-indol-3-yl)-N,N-dimethylethan-1-amine. Prepared according to the general procedure from 4-(benzyloxy)-1H-indole (6a) and 2-(dimethylamino)ethan-1-ol (7a).Flash chromatography (DCM:MeOH 9:1 and 1% of TEA) gave the product (45mg, 61%) as a light yellowsolid. MS (ESI): 295 $[M+H]^+$. ^{1}HNMR (400 MHz, CDCl3): d 2.18 (s, 6H), 2.67 (t, 2H, J 8.0 Hz), 3.09 (t, 2H, J 8.0Hz), 5.19 (s, 2H), 6.56 (d,1H, J 8.0Hz), 6.83 (s,1H), 6.95 (d,1H, J 8.0Hz), 7.06 (dd,1H, J1 J2 8.0 Hz), 7.32e7.42 (m, 3H), 7.52 (d,1H, J 7.5Hz),8.78(br s,1H).^{13}CNMR(100MHz,CDCl3): d22.8,42.5,59.6, 70.3, 100.0, 105.6, 110.1, 116.7, 122.3, 122.7, 128.6, 128.8, 129.0, 137.1, 138.3, 153.2. FTIR (film, cm^{-}1): 3108. Anal. Calcd. For $C_{19}H_{22}N_2O$ (294.17): C, 77.52; H, 7.53; N, 9.52; Found: C, 77.71; H, 7.45; N, 9.31.



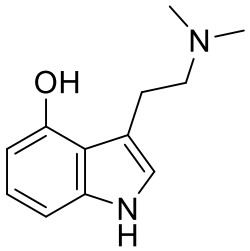
2-(5-(Benzyloxy)-1H-indol-3-yl)-N,N-dimethylethan-1-amine. Prepared according to the general procedure from 5-(ben- zyloxy)-1H-indole **(6b)** and 2-(dimethylamino)ethan-1-ol **(7a)**. Flash chromatography (DCM:MeOH 9:1 and 1% of TEA) gave the product (49 mg, 67%) as a light red solid. MS (ESI): 295 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 6H), 2.68 (t, 2H, J=8.0 Hz), 2.95 (t, 2H, J=8.0 Hz), 5.13 (s, 2H), 6.94 (dd, 1H, J_1=2.5, J_2=8.5 Hz), 7.02 (s, 1H), 7.14 (d, 1H, J=2.5 Hz), 7.26 (d, 1H, J=8.5 Hz), 7.31-7.36 (m, 1H), 7.38-7.42 (m, 2H), 7.49 (d, 2H, J=7.5 Hz), 7.96 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 45.2, 59.9, 71.0, 102.5, 111.8, 112.9, 113.6, 122.4,

127.6, 127.7, 127.8, 128.5, 131.6, 137.7, 153.1. FTIR (film, cm^{-1}): 3235. Anal. Calcd. For $C_{19}H_{22}N_2O$ (294.17): C, 77.52; H, 7.53; N, 9.52; Found: C, 77.63; H, 7.48; N, 9.39.

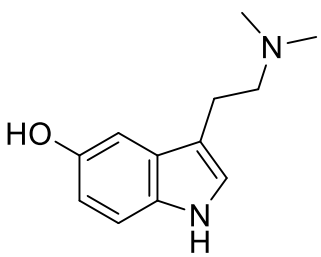


N-Benzyl-2-(5-(benzyloxy)-1H-indol-3-yl)ethan-1-amine. Prepared according to the general procedure from 5-(ben-zyloxy)-1H-indole (6b) and 2-(benzylamino)ethan-1-ol (7b). Flash chromatography (DCM:MeOH 9:1 and 1% of TEA) gave the product (55 mg, 62%) as a yellow oil. MS (ESI): 357 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): d 1.94 (brs, 1H), 2.95 (s, 4H), 3.79 (s, 2H), 5.04 (s,2H), 6.90 (dd, 1H, J_1=2.5, J_2=9.0 Hz), 6.93 (d, 1H, J=1.5 Hz), 7.10 (d, 1H, J=2.5 Hz), 7.18-7.23 (m, 2H), 7.26-7.31 (m, 5H), 7.34-7.38 (m, 2H), 7.44-7.46 (m, 2H), 8.05 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 48.8, 53.4, 71.0, 102.4, 111.9, 112.9, 113.1, 123.0, 127.3, 127.6, 127.7, 127.8, 128.4, 128.5, 128.6, 131.7, 137.7, 138.8, 153.1. The chemical-physical data are according to those published the literature[90].

General procedure for the hydrogenolysis for the synthesis of the natural products. Psilocin, Bufotenin and Serotonin. To a stirred suspension of the suitable tryptamine (0.25 mmol) and an equal weight of 10% Pd-C in dry methanol (7 mL), anhydrous ammonium formate (71 mg, 1.125 mmol) was added in a single portion under N_2. The resulting reaction mixture was stirred at 70 °C for 45 min. The solution was filtered through a pad of Celite, the solvent was removed under reduce pressure and the residue was purified by flash column chromatography on silica gel (DCM:MeOH 9:1 and 1% of TEA) to give the corresponding natural product in quantitative yield.

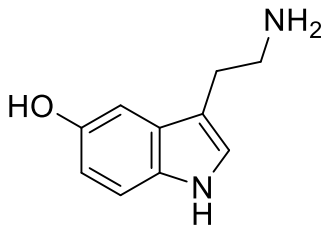


Psilocin. Prepared according to the general procedurefrom2-(4-(benzyloxy)-1H-indol-3-yl)-N,N-dimethylethan-1-amine. Yellowish solid (51 mg, 100%). MS (ESI): 205 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 6H), 2.71-2.73 (m, 2H), 2.95-2.97 (m, 2H), 6.58 (dd, 1H, J_1=0.5, J_2=7.5 Hz), 6.84 (d, 1H, J=2.0 Hz), 6.87 (dd, 1H, J_1=0.5, J_2=8.0 Hz), 7.04-7.08 (m, 1H), 8.03 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 45.3, 61.6, 102.5, 106.4, 114.4, 117.5, 120.9, 123.5, 139.1, 152.1. The chemical-physical data are according to those published the literature[91].



Bufotenin. Prepared according to the general procedure from 2-(5-(benzyloxy)-1H-indol-3-yl)-N,N-

dimethylethan-1-amine. White solid (51 mg, 100%). MS (ESI): 205 $[M+H]^+$. ^1H NMR (400 MHz, MeOD): δ 2.38 (s, 6H), 2.65-2.70 (m, 2H), 2.86-2.90 (m, 2H), 6.65 (dd, 1H, J_1=2.5, J_2=8.5 Hz) 6.90 (dd, 1H, J_1=0.5, J_2=2.5 Hz), 7.00 (s, 1H), 7.15 (dd, 1H, J_1=0.5, J_2=8.5 Hz). ^{13}C NMR (100 MHz, MeOD): δ 23.5, 44.7, 60.6, 103.3, 111.4, 112.5, 112.8, 124.3, 129.1, 133.1, 151.3. The chemical-physical data are according to those published the literature[70d].

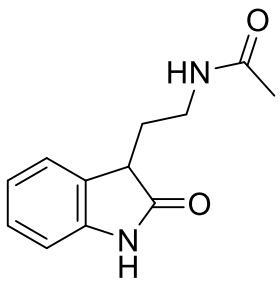


Serotonin. Prepared according to the general procedure from N-benzyl-2-(5-(benzyloxy)-1H-indol-3-yl)ethan-1-amine. White solid (44 mg, 100%). MS (ESI): 177 $[M+H]^+$; ^1H NMR (400 MHz, MeOD): δ 2.90 (t, 2H, J=6.5 Hz), 3.00 (t, 2H, J=6.5 Hz), 6.69 (dd, 1H, J_1=1.5, J_2=8.5 Hz), 6.95 (d, 1H, J=1.5 Hz), 7.04 (s, 1H), 7.18 (d, 1H, J=8.5 Hz). ^{13}C NMR (100 MHz, MeOD): δ 27.0, 41.1, 102.0 110.4, 111.1, 111.4, 123.1, 127.9, 131.8, 149.8. The chemical-physical data are according to those published the literature[92].

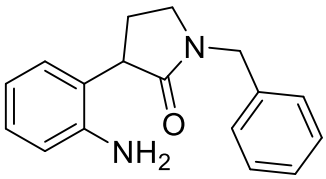
5.2.2 Divergent Borrowing Hydrogen Approach from Oxindoles and Ethanolamine: Synthesis of C3-Substituted Oxindoles and Diarylamine.

General procedure for the synthesis of C3-Substituted Oxindoles and α-substituted γ-lactams. A mixture of the suitable oxindole, (0.5 mmol), Cs_2CO_3 (180 mg, 0.55 mmol), $[Cp^*IrCl_2]_2$ (10 mg, 0.00125 mmol) and N-acetyl-ethanolamine (2) or N-benzyl-ethanolamine (3), (1,5 mmol) was stirred under N_2 atmosphere at 150 °C for 24 h in a sealed vial. After cooling to room temperature, the reaction mixture was dissolved in EtOAc/MeOH 9:1 (1 mL) and filtered through a silica gel pad. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to afford the desired product.

General procedure (2): preparation of N-aryl oxindoles: A dried vial was charged with CuI (0.10 mmol), oxindole (1.00 mmol), aryl halide (1.20 mmol, if solid), K_2CO_3 (2.0 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The test tube was evacuated and back-filled with dry argon. Aryl halide (1.20 mmol, if liquid), rac-trans-N,N'-dimethylcyclohexane-1,2-diamine (0.20 mmol) and 1,4-dioxane (1.0 mL) were then added successively. The rubber septum was removed and the reaction tube was quickly sealed with a Teflon-lined septum. The vessel was immersed in a pre-heated oil bath and stirred vigorously until TLC analysis of the crude reaction mixture indicated that the limiting reagent had been completely consumed. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (15 mL), and filtered through a plug of silica, eluting with additional ethyl acetate (50mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (hexanes/ethyl acetate) to provide the desired product.

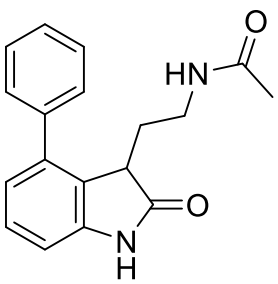


N-(2-(2-oxoindolin-3-yl)ethyl)acetamide (4) The titled compound was prepared according to the general procedure using indolin-2-one (1) and N-acetylethanolamine (2). The product was purified by flash chromatography (gradient from EtOAc to EtOAc/MeOH 95:5) to give 4 (67 mg, 61%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.39 (br s, 1H), 3.53 – 3.45 (m, 3H), 2.28 – 2.20 (m, 1H), 2.10 – 2.02 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 170.4, 141.1, 129.2, 128.2, 124.2, 122.7, 109.8, 44.4, 37.2, 30.0, 23.2; mp: 138−140 °C; IR (film): 3280, 1740 cm−1; HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2O_2$ [M+H]+ 219.1128; found 219.1113. The chemical-physical data are in accordance whit the literature[93].



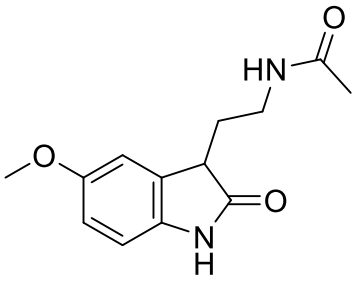
3-(2-aminophenyl)-1-benzylpyrrolidin-2-one (5) The titled compound was prepared according to the general procedure using indolin-2-one (1) and N-benzylethanolamine (2). The product was purified by flash chromatography (cyclohexane/EtOAc 1:1) to give 5 (72 mg, 54%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.37 – 7.29 (m, 4H), 7.22 – 7.20 (m, 1H), 7.17 – 7.12 (m, 1H), 6.78 – 6.73 (m, 1H), 4.49 (d, J = 15.0 Hz, 1H), 4.42 (d, J = 15.0 Hz, 1H), 4.40 (br s, 2H), 4.04 (dd, J = 9.0 and 6.0 Hz, 1H), 3.52 – 3.43 (m, 1H), 3.38 – 3.32(m, 1H), 2.49 – 2.36 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.4, 145.9, 136.2, 128.7, 128.0, 127.9, 127.6, 126.1, 124.6, 119.0, 117.4, 46.8, 45.4, 43.4, 24.1; IR (film) 1755 cm−1; HRMS (ESI) m/z calcd for $C_{17}H_{19}N_2O$ [M+H]+ 267.1492; found 267.1495.

One-pot C-H Activation/Borylation/Oxidation Sequence for the synthesis 4-phenylindolin-2-one (6): A flame dried vial was charged with (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (10.5 mg, 15.5 µmol), 4,4'-di-tert-butyl-2,2'-dipyridyl (8.33 mg, 31.1 µmol), bis(pinacolato)diboron (409 mg, 2.07 mmol), 4-phenyl-1H-indole (prepared as reported in literature[94]) (200 mg, 1.03 mmol), and a stirring bar and sealed with a septum under an atmosphere of argon. Anhydrous dichloromethane (3.0 mL) was added via syringe to give a colorless suspension. The septum was replaced with the stopper vial's and sealed with Teflon. The entire mixture was heated in an oil bath set to 65 °C. The reaction mixture gradually turned into a clear dark amber solution. After 3 h, the mixture was allowed to cool to 23 °C and the volatiles were removed under reduced pressure. The reaction mixtrure was dissolved in THF (17 ml) and cooled to 0 °C. H_2O_2 (1 mL, 30% in H_2O) and NaOH (0.5 mL, 1M) were added and the mixture stirred at 0 °C for 1.5 h. EtOAc (30 mL) was added and the organic layer was washed with H_2O (20 mL) and brine (20 mL). The solvent was removed under vacuum and the resulting mixture was purified by flash chromatography (cyclohexane/ EtOAc 1:1) to give (6) (120 mg, 55%) as off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ 8.90 (s, 4H), 7.50 – 7.44 (m, 1H), 7.42 – 7.36 (m, 1H), 7.32 (tt, J = 7.8, 0.8 Hz, 1H), 7.10 (dd, J = 7.9, 1.0 Hz, 1H), 6.91 (dt, J = 7.8, 0.9 Hz, 1H), 3.64 (s, 2H). ^{13}C (101 MHz, $CDCl_3$): 177.5, 142.8, 139.6, 138.7, 128.9, 128.7, 128.4, 128.3, 128.0, 127.7, 122.9, 122.9, 108.7, 36.3. Mp:192-194°C IR (film): 1745 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{14}H_{12}NO$ $(M+H)^+$ 210.0913; found 210.0909.

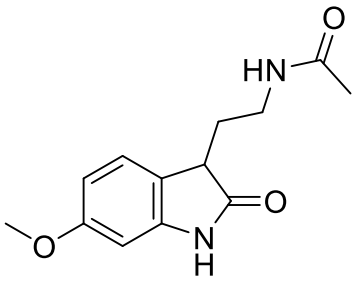


N-(2-(2-oxo-4-phenylindolin-3-yl)ethyl)acetamide (7) The titled compound was prepared according to the general procedure using 4-phenylindolin-2-one (6) and N-acetylethanolamine (2). The product was purified by flash chromatography (gradient from EtOAc to EtOAc/ MeOH 99:1) to give 7 (84 mg, 57%) as

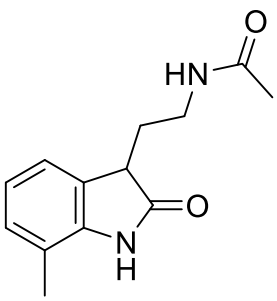
off-white solid. ^{1}H NMR (400 MHz, CD3OD) δ 7.63 (br s, 1H), 7.49 – 7.35 (m, 5H), 7.29 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 3.96 (dd, J = 7.0 and 3.5 Hz, 1H), 2.88 – 2.83 (m, 2H), 1.91 – 1.82 (m, 1H), 1.77 (s, 3H), 1.54 – 1.47 (m, 1H); ^{13}C NMR (101 MHz, CD3OD) δ 182.2, 173.1, 144.5, 141.4, 140.7, 130.1, 129.9, 129.4, 129.1, 127.5, 124.6, 110.3, 45.5, 37.1, 28.8, 22.7; mp: 145−148 °C; IR (film): 1743, 1758 cm−1; HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O_2$ [M+H]+ 295.1441; found 295.1451.



N-(2-(5-methoxy-2-oxoindolin-3-yl)ethyl)acetamide (9) The titled compound was prepared according to the general procedure using 5-methoxyindolin-2-one (8) and N-acetylethanolamine (2). The product was purified by flash chromatography (gradient from EtOAc to EtOAc/MeOH 99:1) to give 9 (67 mg, 54%) as white solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 6.90 (s, 1H), 6.77 – 6.76 (m, 2H), 6.38 (br s, 1H), 3.78 (s, 3H), 3.50 – 3.47 (m, 3H), 2.27 – 2.22 (m, 1H), 2.08 – 2.01 (m, 1H), 1.97 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 180.0, 170.5, 156.0, 134.4, 130.5, 112.9, 111.2, 110.2, 55.8, 44.8, 37.2, 30.0, 23.2; mp: 127−130 °C; IR (film): 1760, 1748 cm−1; HRMS (ESI) m/z calcd for $C_{13}H_{17}N_2O_3$ [M+H]+ 249.1234; found 249.1242. The chemical-physical data are in accordance whit the literature.[95]

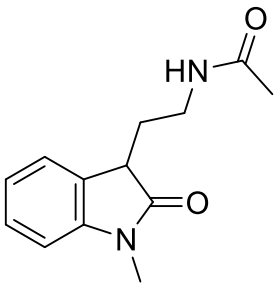


N-(2-(6-methoxy-2-oxoindolin-3-yl)ethyl)acetamide (11) The titled compound was prepared according to the general procedure using 6-methoxyindolin-2-one (10) and N-acetylethanolamine (2). The product was purified by flash chromatography (gradient from EtOAc to EtOAc/MeOH 99:1) to give 11 (87 mg, 70%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.56 (dd, J = 8.0 and 2.5 Hz, 1H), 6.48 (d, J = 2.5 Hz, 1H), 6.40 (br s, 1H), 3.80 (s, 3H), 3.51 – 3.44 (m, 3H), 2.23 – 2.18 (m, 1H), 2.06 – 1.99 (m, 1H), 1.98 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 180.6, 170.4, 160.1, 142.1, 124.8, 121.0, 107.2, 97.3, 55.5, 43.8, 37.2, 30.2, 23.2; mp: 145−148 °C; IR (film): 1770, 1758 cm−1; HRMS (ESI) m/z calcd. for $C_{13}H_{17}N_2O_3$ [M+H]+ 249.1234; found 249.1211.

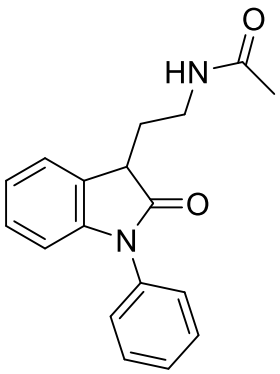


N-(2-(7-methyl-2-oxoindolin-3-yl)ethyl)acetamide (13) The titled compound was prepared according to the general procedure using 7-methylindolin-2-onee (12) and N-acetylethanolamine (2). The product was purified by flash chromatography (gradient from EtOAc to EtOAc/MeOH 99:1) to give 13 (102 mg, 88%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.34 (br s, 1H), 3.53 – 3.46 (m, 3H), 2.28 (s, 3H), 2.27 –

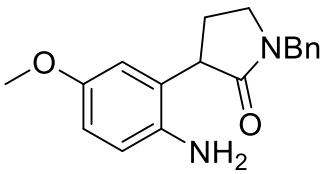
2.23 (m, 1H), 2.22 – 2.00 (m, 1H), 1.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.4, 170.2, 139.7, 129.5, 128.8, 122.7, 121.5, 119.0, 44.9, 37.4, 30.1, 23.2, 16.4; mp: 132−136 °C; IR (film): 1777, 1788 cm−1; HRMS (ESI) m/z calcd. for $C_{13}H_{17}N_2O_2$ [M+H]+ 233.1285; found 233.1294.



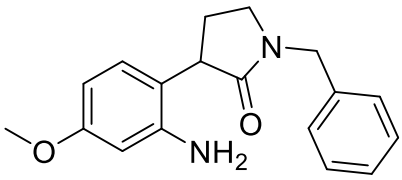
N-(2-(1-methyl-2-oxoindolin-3-yl)ethyl)acetamide (15) The titled compound was prepared according to the general procedure using 1-methylindolin-2-one (14) and N-acetylethanolamine (2). The product was purified by flash chromatography (gradient from EtOAc to EtOAc/MeOH 99:1) to give 15 (116 mg, 99%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 7.06 – 7.02 (m, 1H), 6.81 – 6.79 (m, 2H), 3.46 – 3.40 (m, 3.H), 3.17 (s, 3H), 2.18 – 2.13 (m, 1H), 2.03 – 1.89 (m, 1H), 1.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 170.4, 143.8, 128.5, 128.2, 123.9, 122.8, 108.2, 44.0, 37.3, 30.1, 26.2, 23.2; mp: 142−146 °C; IR (film): 1767 cm−1; HRMS (ESI) m/z calcd. for $C_{13}H_{17}N_2O_2$ [M+H]+ 233.1285; found 233.1273.



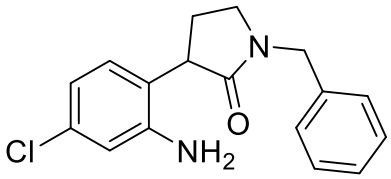
N-(2-(2-oxo-1-phenylindolin-3-yl)ethyl)acetamide (17) The titled compound was prepared according to the general procedure using 1-phenylindolin-2-one (16) and N-acetylethanolamine (2). The product was purified by flash chromatography (cyclohexane/EtOAc 6:4) to give 17 (79 mg, 54%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (t, J = 8.0 Hz, 2H), 7.44 – 7.37 (m, 4H), 7.22 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.53 (br s, 1H), 3.69 – 3.65 (m, 1H), 3.61 – 3.42 (m, 2H), 2.38 – 2.30 (m, 1H), 2.17 – 2.08 (m, 1H), 1.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 170.4, 143.9, 134.3, 129.7, 128.4, 128.3, 128.1, 126.6, 124.2, 123.3, 109.5, 44.2, 37.4, 30.3, 23.2; mp: 135−138 °C; IR (film): 1757 cm−1; HRMS (ESI) m/z calcd. for $C_{18}H_{19}N_2O_2$ [M+H]+ 295.1441; found 295.1431.



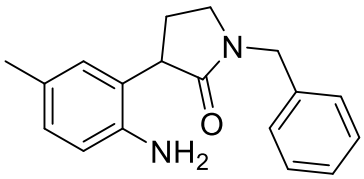
3-(2-amino-5-methoxyphenyl)-1-benzylpyrrolidin-2-one (18). The titled compound was prepared according to the general procedure using 5-methoxyindolin-2-one (8) and N-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give 18 (55 mg, 37%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 8H), 6.74 – 6.68 (m, 2H), 4.48 (s, 2H), 3.99 – 3.96 (m, 1H), 3.74 (s, 3H), 3.49 – 3.43 (m, 1H), 3.38 – 3.32 (m, 1H), 2.44 – 2.31 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 153.2, 139.5, 136.3, 128.7, 128.1, 127.7, 126.5, 118.4, 113.2, 112.6, 55.8, 46.9, 45.4, 43.6, 24.1;. IR (film): 3459, 3390, 1760 cm−1; HRMS (ESI) m/z calcd for $C_{18}H_{21}N_2O_2$ [M+H]+ 297.1598; found 297.1571.



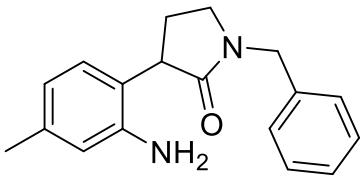
3-(2-amino-4-methoxyphenyl)-1-benzylpyrrolidin-2-one (19). The titled compound was prepared according to the general procedure using oxindole (10) and N-benzylethanolamine (3). The product was purified by flash chromatography (AcOEt:MeOH 98:2) to give 19 (62mg, 42%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.06 (m, 5H), 6.90 (d, J = 9.2 Hz, 1H), 6.33 – 6.20 (m, 2H), 4.39 (s, 2H), 3.92 – 3.77 (m, 1H), 3.68 (s, 3H), 3.41 – 3.33 (m, 1H), 3.31 – 3.21 (m, 1H), 2.39 – 2.19 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) 172.6, 158.7, 146.5, 136.3, 129.7, 128.1, 127.7, 126.5, 122.4, 104.2, 103.6, 55.8, 48.9, 45.4, 43.5, 24.2. IR (film): 3447, 3395, 1780cm^{-1}; HRMS (ESI) m/z calcd. for $C_{18}H_{21}N_2O_2$ $(M+H)^+$ 297.3775; found 297.3772.



3-(2-amino-4-chlorophenyl)-1-benzylpyrrolidin-2-one (21). The titled compound was prepared according to the general procedure using 6-chloroindolin-2-one (20) and N-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 1:1) to give 21 (52 mg, 35%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 3H), 7.23 – 7.21 (m, 2H), 6.98 (d, J = 8.0 Hz, 1H), 6.75 – 6.72 (m, 2H), 4.51 (br s, 2H), 4.47 (s, 2H), 3.89 (dd, J = 9.0 and 6.5 Hz, 1H), 3.48 – 3.32 (m, 2H), 2.46 – 2.28 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) 175.0, 147.4, 136.1, 133.3, 128.8, 128.0, 127.7, 127.3, 122.9, 118.7, 116.9, 46.9, 45.4, 43.0, 24.1; IR (film): 3457, 3385, 1769 cm−1; HRMS (ESI) m/z calcd. for $C_{17}H_{18}ClN_2O$ [M+H]+ 301.1102; found 301.1107.

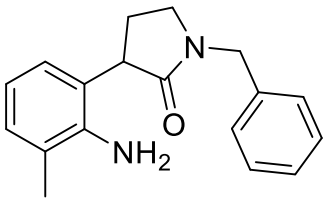


3-(2-amino-5-methylphenyl)-1-benzylpyrrolidin-2-one (23). The titled compound was prepared according to the general procedure using 5-methylindolin-2-one (22) and N-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 6:4) to give 23 (67 mg, 48%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.15 (m, 5H), 6.82 (d, J = 8.0 Hz, 1H), 6.79 (s, 1H), 6.60 (d, J = 8.0 Hz, 1H), 4.41 (d, J = 15.0 Hz, 1H), 4.36 (d, J = 15.0 Hz, 1H), 3.86 (dd, J = 15.0 and 7.0 Hz, 1H) 3.44 – 3.32 (m, 1H), 3.31 – 3.20 (m, 1H), 2.47 – 2.18 (m, 2H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 175.4, 143.3, 136.4, 128.7, 128.5, 128.2, 128.1, 127.6, 127.0, 124.8, 117.5, 46.9, 45.4, 43.5, 24.2, 20.7; IR (film): 3497, 3385, 1743 cm−1; HRMS (ESI) m/z calcd. for $C_{18}H_{21}N_2O$ [M+H]+ 281.1648; found 281.1654.

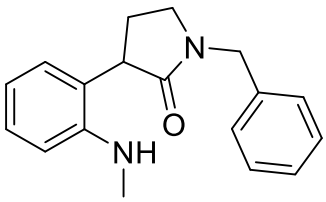


3-(2-amino-4-methylphenyl)-1-benzylpyrrolidin-2-one (25). The titled compound was prepared according to the general procedure using 6-methylindolin-2-one (24) and N-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 6:4) to give 25 (64

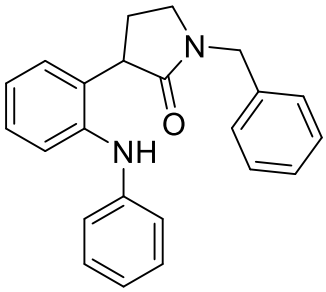
mg, 46%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 7.24 – 7.22 (m, 2H), 6.96 (d, J = 8.0 Hz, 1H), 6.61 – 7.60 (m, 1H), 4.50 (d, J = 14.5 Hz, 1H), 4.44 (d, J = 14.5 Hz, 1H), 3.92 (dd, J = 9.5 and 5.5 Hz, 1H), 3.49 – 3.43 (m, 1H), 3.37 – 3.31 (m, 1H), 2.42 – 2.33 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 145.9, 137.8, 136.3, 128.7, 128.1, 127.6, 126.1, 121.7, 119.8, 118.1, 46.8, 45.4, 43.1, 24.2, 21.0; IR (film): 3490, 3380, 1753 cm−1; HRMS (ESI) m/z calcd for $C_{18}H_{21}N_2O$ [M+H]+ 281.1648; found 281.1654.



3-(2-amino-3-methylphenyl)-1-benzylpyrrolidin-2-one (26). The titled compound was prepared according to the general procedure using 7-methylindolin-2-one (12) and N-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 7:3) to give 3e (100 mg, 72%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 5H), 7.25 – 7.23 (m, 2H), 7.01 (d, J = 7.5 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.72 (t, J = 7.5 Hz, 1H), 4.52 (d, J = 14.5 Hz, 1H), 4.35 (d, J = 14.5 Hz, 1H), 3.97 (dd, J = 9.0 and 6.0 Hz, 1H), 3.53 – 3.47 (m, 1H), 3.39 – 3.33 (m, 1H), 2.46 – 2.38 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 144.3, 136.3, 129.3, 128.7, 128.0, 127.6, 124.0, 123.9, 123.5, 118.2, 46.8, 45.5, 43.4, 24.4, 17.9; IR (film): 3475, 3362, 1763 cm−1; HRMS (ESI) m/z calcd for $C_{18}H_{21}N_2O$ [M+H]+ 281.1648; found 281.1647.

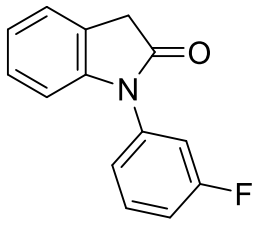


1-benzyl-3-(2-(methylamino)phenyl)pyrrolidin-2-one (27). The titled compound was prepared according to the general procedure using 1-methylindolin-2-one (14) and N-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give 27 (60 mg, 35%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 3H), 7.25 – 7.20 (m, 3H), 7.10 (dd, J = 8.0 and 1.5 Hz, 1H), 6.77 – 6.74 (m, 2H), 4.49 (d, J = 14.5 Hz, 1H), 4.43 (d, J = 14.5 Hz, 1H), 3.95 (dd, J = 9.0 and 6.0 Hz, 1H), 3.53 – 3.45 (m, 1H), 3.39 – 3.33 (m, 1H), 2.87 (s, 3H), 2.44 – 2.28 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 148.6, 136.3, 128.8, 128.2, 128.0, 127.6, 125.6, 124.5, 117.4, 111.3, 46.8, 45.6, 43.1, 30.8, 24.4; IR (film): 3465, 1753 cm−1; HRMS (ESI) m/z calcd for $C_{18}H_{21}N_2O$ [M+H]+ 281.1648; found 281.1635.

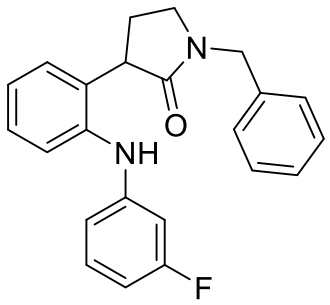


1-benzyl-3-(2-(phenylamino)phenyl)pyrrolidin-2-one (28). The titled compound was prepared according to the general procedure using 1-phenylindolin-2-one (16) and *N*-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give 28 (116 mg, 68%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.32 (m, 3H), 7.29 – 7.22 (m, 6H), 7.06 – 7.02 (m, 3H), 6.88 (t, *J* = 7.5 Hz, 1H), 4.53 (d, *J* = 15.0

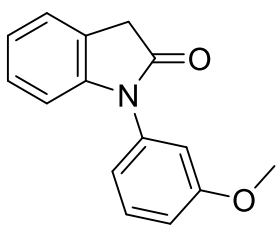
Hz, 1H), 4.49 (d, *J* = 15.0 Hz, 1H), 4.17 (t, *J* = 8.0 Hz, 1H), 3.51 – 3.48 (m, 1H), 3.39 – 3.37 (m, 1H), 2.47 – 2.41 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 144.6, 142.9, 136.2, 130.3, 129.3, 128.8, 128.0, 127.9, 127.7, 126.6, 122.3, 120.9, 119.6, 116.9, 46.9, 45.5, 43.8, 24.3; IR (film): 3455, 1784 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{23}N_2O$ $[M+H]^+$ 343.1805; found 343.1826.



1-(3-fluorophenyl)indolin-2-one (29). The titled compound was prepared according to the general procedure 2, using indolin-2-one (1) and 1-bromo-3-fluorobenzene to give 29 (177 mg, 78%) as pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.48 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.08 (m, 5H), 6.86 (d, *J* = 8.0 Hz, 1H), 3.73 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 163.1 (d, J = 246 Hz), 144.6, 136.0 (d, *J* = 10 Hz), 130.8 (d, *J* = 10 Hz), 127.9, 124.9, 124.2, 123.1, 122.2 (d, *J* = 3 Hz), 115.2 (d, *J* = 22 Hz), 114.1 (d, J = 22 Hz), 109.4, 36.0; mp: 89 – 100 °C; IR (film): 3326, 1691 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{14}H_{11}FNO$ $[M+H]^+$ 228.0819; found 228.0831.

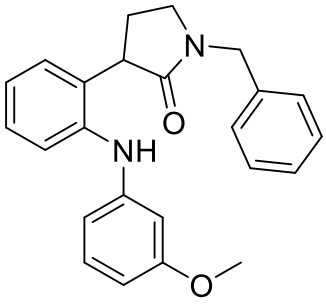


1-benzyl-3-(2-((3-fluorophenyl)amino)phenyl)pyrrolidin-2-one (30). The titled compound was prepared according to the general procedure using 1-(3-fluorophenyl)indolin-2-one (29) and *N*-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 7:3) to give 30 (124 mg, 69%) as pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.49 (dd, *J* = 8.5 and 1.5 Hz, 1H), 7.35 – 7.31 (m, 3H), 7.27 – 7.22 (m, 4H), 7.20 – 7.24 (m, 1H), 7.10 – 7.05 (m, 1H), 6.75 – 6.72 (m, 1H), 6.69 (dt, *J* = 11.5 and 2.5 Hz, 1H), 6.53 (td, *J* = 8.5 and 2.5 Hz, 1H), 4.53 (d, *J* = 15.0 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 4.13 (t, *J* = 8.0 Hz, 1H), 3.51 – 3.45 (m, 1H), 3.41 – 3.35 (m, 1H), 2.46 – 2.40 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 163.9 (d, *J* = 242 Hz), 146.7 (d, *J* = 10 Hz), 141.8, 136.1, 130.3 (d, *J* = 10 Hz), 128.8, 128.0, 127.9 (d, *J* = 22 Hz), 126.6, 123.2, 122.1, 111.9 (d, *J* = 2 Hz), 105.7 (d, *J* = 22 Hz), 102.7 (d, *J* = 25 Hz), 46.9, 45.5, 43.8, 24.2; mp: 96-98 °C; IR (film): 3330, 1668, cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{22}FN_2O$ $[M+H]^+$ 361.1711; found 361.1736.

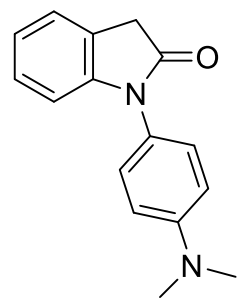


1-(3-methoxyphenyl)indolin-2-one (31). The titled compound was prepared according to the general procedure 2, using indolin-2-one (1) and 1-bromo-3-methoxybenzene to give 31 (149 mg, 62%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.03 – 6.95 (m, 3H), 6.83 (d, *J* = 8.0 Hz,

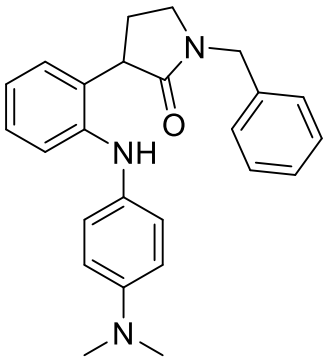
1H), 3.84 (s, 3H), 3.72 (s, 2H); HRMS (ESI) m/z calcd. for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1092; found 240.1085. The chemical-physical data are in accordance whit the literature.[96]



1-benzyl-3-(2-((3-methoxyphenyl)amino)phenyl)pyrrolidin-2-one (32). The titled compound was prepared according to the general procedure using 1-(3-methoxyphenyl)indolin-2-one (31) and *N*-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 7:3) to give 32 (119 mg, 64%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.53 – 7.49 (m, 1H), 7.38 – 7.30 (m, 3H), 7.29 – 7.22 (m, 4H), 7.20 – 7.13 (m, 1H), 7.07 – 7.01 (m, 1H), 6.63 – 6.56 (m, 2H), 6.46 – 6.42 (m, 1H), 4.52 (d, *J* = 15.0 Hz, 1H), 4.49 (d, *J* = 15.0 Hz, 1H), 4.18-4.12 (m, 1H), 3.79 (s, 3H), 3.51 – 3.45 (m, 1H), 3.40 – 3.34 (m, 1H), 2.46 – 2.41 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 160.8, 146.1, 142.5, 136.1, 130.5, 130.0, 128.8, 128.0, 127.9, 127.7, 126.5, 122.6, 121.7, 109.4, 105.2, 102.2, 55.2, 46.9, 45.5, 43.7, 24.0; IR (film): 3333, 1683 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{25}N_2O_2$ $[M+H]^+$ 373.1911; found 373.1932.

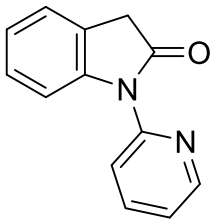


1-(3-(dimethylamino)phenyl)indolin-2-one (33). The titled compound was prepared according to the general procedure 2, using indolin-2-one (1) and 4-bromo-N,N-dimethylaniline to give 33 (155 mg, 62%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.0 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.91 – 6.83 (m, 2H), 6.79 (d, *J* = 7.5 Hz, 1H), 3.74 (s, 2H), 3.06 (s, 6H); HRMS (ESI) m/z calcd. for $C_{16}H_{17}N_2O$ $[M+H]^+$ 253.1335; found 253.1341. The chemical-physical data are in accordance whit the literature.[87]

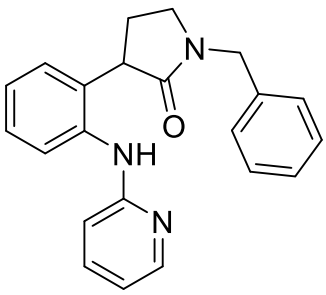


1-benzyl-3-(2-((4-(dimethylamino)phenyl)amino)phenyl)pyrrolidin-2-one (35). The titled compound was prepared according to the general procedure using 1-(4-(dimethylamino)phenyl)indolin-2-one (33) and *N*-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 7:3) to give 35 (115 mg, 60%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (br s, 1H), 7.23 – 7.00 (m, 7H), 6.99 – 6.89 (m, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.68-6.59 (m, 1H), 6.60 (d, *J* = 9.0 Hz, 2H), 4.41 – 4.25 (m, 2H), 3.93 (dd, *J* = 9.0 and 6.5 Hz, 1H), 3.39 – 3.28 (m, 1H), 3.25 – 3.16 (m, 1H), 2.71 (s, 6H), 2.30 – 2.22 (m, 2H);

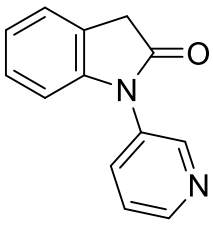
^{13}C NMR (101 MHz, Acetone-d_6) δ 175.3, 146.4, 145.5, 137.0, 134.3, 128.6, 128.2, 127.8, 127.3, 126.5, 121.0, 119.8, 116.5, 114.2, 46.2, 45.2, 43.1, 40.6, 24.4; IR (film): 3328, 1721 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{28}N_3O$ $[M+H]^+$ 386.2227; found 386.2231.



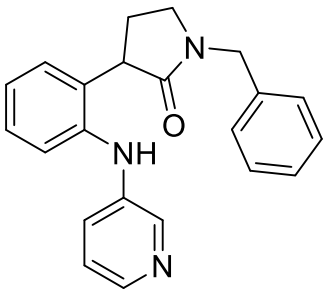
1-(pyridin-2-yl)indolin-2-one (36). The titled compound was prepared according to the general procedure, using indolin-2-one (1) and 2-bromopyridine to give 36 (108 mg, 51%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.0 Hz, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.25 (m, 3H), 7.12 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 2H); mp: 145-147 °C. HRMS (ESI) m/z calcd. for $C_{13}H_{11}N_2O$ $[M+H]^+$ 211.0866; found 211.0857. The chemical-physical data are in accordance whit the literature[97].



1-benzyl-3-(2-(pyridin-2-ylamino)phenyl)pyrrolidin-2-one (37). The titled compound was prepared according to the general procedure using 1-(pyridin-2-yl)indolin-2-one (36) and *N*-benzylethanolamine (3). The product was purified by flash chromatography (cyclohexane/EtOAc 1:9) to give 37 (83 mg, 49%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 3.0 Hz, 1H), 8.10 (dd, *J* = 5.0 and 1.0 Hz, 1H), 7.98 (s, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.33 – 7.20 (m, 8H), 7.15 – 7.12 (m, 1H), 7.07 – 7.03 (m, 1H), 4.53 – 4.44 (m, 2H), 4.17 – 4.13 (m, 1H), 3.52 – 3.48 (m, 1H), 3.41– 3.36 (m, 1H), 2.48 – 2.43 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 141.9, 141.0, 140.7, 139.5, 135.9, 128.8, 128.6, 128.4, 128.0, 127.9, 127.8, 126.5, 123.7, 123.0, 122.7, 120.7, 47.0, 45.6, 43.7, 24.0; IR (film): 3308, 1758 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{22}N_3O$ $[M+H]^+$ 344.1757; found 344.1786.



1-(pyridin-3-yl)indolin-2-one (38). The titled compound was prepared according to the general procedure 2, using indolin-2-one (1) and 3-bromopyridine to give 38 (103 mg, 49%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (br d, *J* = 2.5 Hz, 1H), 8.66 – 8.65 (m, 1H), 7.82 – 7.79 (m, 1H), 7.49 (dd, *J* = 8.0 and 5.0 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.75 (s, 2H); mp: 165-167 °C; HRMS (ESI) m/z calcd. for $C_{13}H_{11}N_2O$ $[M+H]^+$ 211.0866; found 211.0859. The chemical-physical data are in accordance whit the literature[98].

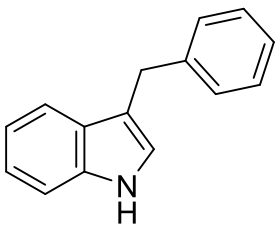


1-benzyl-3-(2-(pyridin-3-ylamino)phenyl)pyrrolidin-2-one (39). The titled compound was prepared according to the general procedure using 1-(pyridin-3-yl)indolin-2-one (38) and *N*-benzylethanolamine (3). The product was purified by

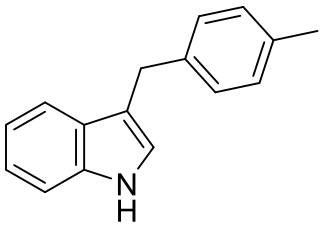
flash chromatography (cyclohexane/EtOAc 1:9) to give 39 (119 mg, 70%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 8.19 (d, *J* = 4.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.34 – 7.10 (m, 7H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.73 – 6.67 (m, 2H), 4.53 (d, *J* = 14.5 Hz, 1H), 4.45 (d, *J* = 14.5 Hz, 1H), 4.14 (t, *J* = 8.0 Hz, 1H), 3.46 – 3.40 (m, 1H), 3.36 – 3.30 (m, 1H), 2.41 – 2.32 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 156.9, 148.3, 139.9, 137.5, 136.2, 132.0, 128.8, 128.1, 127.9, 127.7, 126.7, 124.2, 114.4, 109.0, 47.0, 45.3, 43.9, 24.7; IR (film): 3318, 1778 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{22}N_3O$ $[M+H]^+$ 344.1757; found 344.1758.

5.3.3 Iron-Catalyzed Direct C3-Benzylaion of Indoles with Benzyl Alcohols through Borrowing Hydrogen

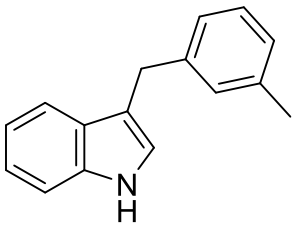
General Procedure for C3-Alkylation of Indole with Benzyl Alcohol. A vial was charged with the appropriate indole (0.5 mmol), the appropriate alcohol (1 mmol), iron(II) phthalocyanine ($Fe^{(II)}Pc$) (3 mg, 0.005 mmol), and Cs_2CO_3 (179 mg, 0.55 mmol). The vial was immersed in a preheated (140 °C) oil bath and stirred at this temperature for 16 h. The reaction mixture was diluted with ethyl acetate and filtered over a plug of Celite. The solvent was evaporated under reduced pressure, and the residue obtained was purified by flash chromatography.



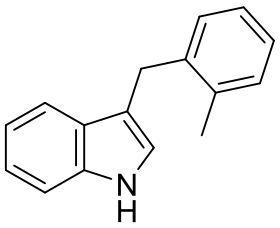
3-Benzyl-1H-indole (3a). The title compound was prepared according to the general procedure using 1H-indole and benzyl alcohol. The product was purified by flash chromatography (cyclo- hexane/EtOAc 8:2) to give (3a) (102 mg, 99%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (br s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.33−7.30 (m, 4H), 7.24−7.14 (m, 2H), 7.12 (t, J = 7.0 Hz, 1H), 6.93 (s, 1H), 4.16 (s, 2H); HRMS (ESI) m/z calcd for $C_{15}H_{13}NNa$ $(M+Na)^+$ 230.0940; found 230.0946. The chemical-physical data are in accordance with literature[99].



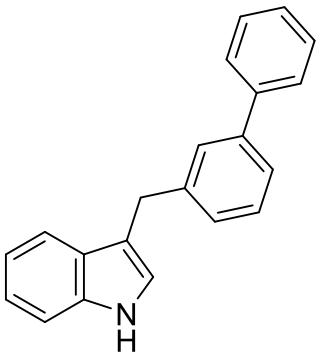
3-(4-Methylbenzyl)-1H-indole (3b). The title compound was prepared according to the general procedure using 1H-indole and p-tolylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give (3b) (78 mg, 71%) as pinkish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.26−7.22 (m, 3H), 7.16−7.12 (m, 3H), 6.92−6.91 (m, 1H), 4.14 (s, 2H), 2.38 (s, 3H); HRMS (ESI) m/ z calcd for $C_{16}H_{16}N$ $(M+H)^+$ 222.1277; found 222.1286. The chemical-physical data are in accordance with literature[100].



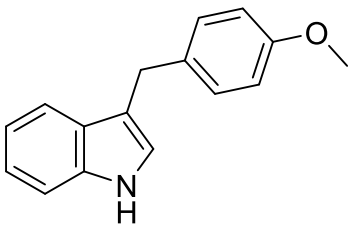
3-(3-Methylbenzyl)-1H-indole (3c). The title compound was prepared according to the general procedure using 1H-indole and m-tolylmethanol. The product was purified by flash chromatography(cyclohexane/EtOAc 8:2) to give (3c) (108 mg, 98%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (br s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 8.0 Hz, 2H), 7.27−7.23 (m, 3H), 7.17 (d, J = 7.0 Hz, 1H), 6.92 (s, 1H), 4.22 (s, 2H), 2.46 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{16}N$ $(M+H)^+$ 222.1277; found 222.1283. The chemical-physical data are in accordance with literature[86].



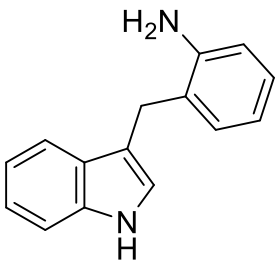
3-(2-Methylbenzyl)-1H-indole (3d). The title compound was prepared according to the general procedure using 1H-indole and o-tolylmethanol. The product was purified by flash chromatography (gradient from cyclohexane/EtOAc 8:2 to cyclohexane/EtOAc 7:3) to give (3d) (83 mg, 75%) as pinkish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.30−7.15 (m, 6H), 6.74 (s, 1H), 4.15 (s, 2H), 2.41 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{16}N$ $(M+H)^+$ 222.1277; found 222.1274. The chemical-physical data are in accordance with literature[86].



3-(Biphenyl-3-ylmethyl)-1H-indole (3e). The title compound was prepared according to the general procedure using 1H-indole and biphenyl-3-ylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give (3e) (65 mg, 46%) as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.61−7.57 (m, 3H), 7.53 (d, J = 8.0 Hz, 3H), 7.44 (t, J = 8.0 Hz, 2H), 7.40−7.32 (m, 3H), 7.24−7.20 (m, 1H), 7.14−7.10 (m, 1H), 6.98 (br s, 1H), 4.18 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 140.4, 138.8, 136.4, 129.1, 128.7, 127.5, 127.1, 127.0, 122.4, 122.1, 119.4, 119.2, 115.7, 111.1, 31.2; mp 194−196 °C; IR (film): 3412, 3056 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{18}N$ $(M+H)^+$ 284.1434; found 284.1439.

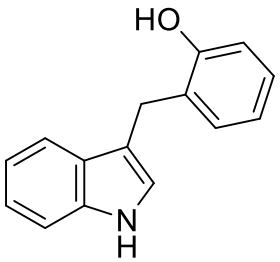


3-(4-Methoxybenzyl)-1H-indole (3f). The title compound was prepared according to the general procedure using 1H-indole and (4-methoxyphenyl)methanol. The product was purified by flash chromatography (gradient from cyclohexane/EtOAc 95:5 to cyclo- hexane/EtOAc 90:10) to give (3f) (89 mg, 75%) as brown solid. 1H NMR (400 MHz, CDCl3) δ 7.96 (br s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.29−7.22 (m, 3H), 7.14 (t, J = 8.0 Hz, 1H), 6.93 (s, 1H), 6.88 (d, J = 8.0 Hz, 2H), 4.11 (s, 2H), 3.83 (s, 3H); HRMS (ESI) m/z calcd for C16H16NO (M + H)+ 238.1226; found 238.1221. The chemical-physical data are in accordance with literature[101].

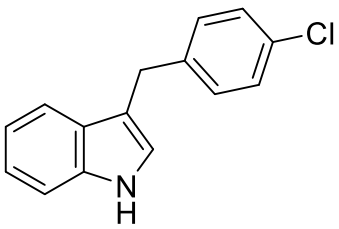


2-((1H-Indol-3-yl)methyl)aniline (3g). The title compound was prepared according to the general procedure using 1H-indole and (2- aminophenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give (3g) (62 mg, 56%) as off-white solid. ^{1}H NMR (400 MHz, acetone-d6) δ 10.05 (br s, 1H), 7.53−7.51 (m, 1H), 7.40 (dt, J = 8.0, 1.0 Hz,

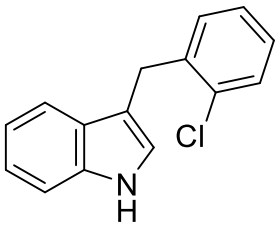
1H), 7.13−7.05 (m, 3H), 7.01−6.95 (m, 2H), 6.72 (dd, J = 8.0, 1.5 Hz, 1H), 6.59 (dt, J = 7.5, 1.5 Hz, 1H), 4.40 (br s, 2H), 3.99 (s, 2H). ^{13}C NMR (101 MHz, Acetone-d6) δ 146.0, 137.1, 129.7, 127.7, 126.8, 125.0, 122.9, 121.3, 118.8, 118.5, 117.1, 115.1, 113.0, 111.3, 27.4; HRMS (ESI) m/z calcd for C15H15N2 $(M+H)^+$ 223.1230; found 223.1241. The chemical-physical data are in accordance with literature[102].



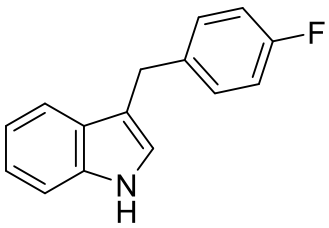
2-((1H-Indol-3-yl)-methyl)phenol (3h). The title compound was prepared according to the general procedure using 1H-indole and 2- (hydroxymethyl)phenol. The product was purified by flash chromatography (cyclohexane/EtOAc 1:1) to give (3h) (47 mg, 42%) as pale yellow solid. ^{1}H NMR (400 MHz, acetone-d6) δ 9.99 (br s, 1H), 8.28 (s, 1H), 7.57−7.54 (m, 1H), 7.38 (dt, J = 8.0, 1.0 Hz, 1H), 7.12−7.06 (m, 3H), 7.04−6.96 (m, 2H), 6.88 (dd, J = 8.0, 1.0 Hz, 1H), 6.71 (dt, J = 7.5, 1.0 Hz, 1H), 4.10 (s, 2H); HRMS (ESI) m/z calcd for $C_{15}H_{14}NO$ $(M+H)^+$ 224.1070; found 224.1079. The chemical-physical data are in accordance with literature[103].



3-(4-Chlorobenzyl)-1H-indole (3i). The title compound was prepared according to the general procedure using 1H-indole and (4-chlorophenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give (3i) (54 mg, 45%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.33−7.22 (m, 5H), 7.12 (t, J = 7.0 Hz, 1H), 6.93 (s, 1H), 4.12 (s, 2H); HRMS (ESI) m/z calcd for $C_{15}H_{13}ClN$ $(M+H)^+$ 242.0731; found 242.0726. The chemical- physical data are in accordance with literature[89].

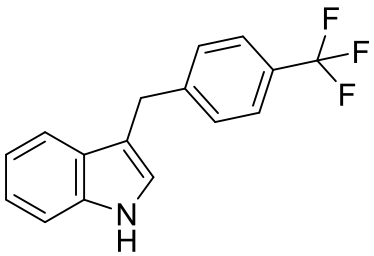


3-(2-Chlorobenzyl)-1H-indole (3j). The title compound was prepared in according to the general procedure using 1H-indole and (2-chlorophenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give (3j) (44 mg, 37%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (br s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.43−7.38 (m, 2H), 7.25−7.11 (m, 5H), 6.96 (s,1H), 4.25 (s, 2H); 13C NMR (100 MHz, $CDCl_3$): δ 138.7, 136.4, 134.0, 130.6, 129.4, 127.4, 127.3, 126.7, 122.7, 122.1, 119.5, 119.1, 114.0, 111.1, 29.1; HRMS (ESI) m/z calcd for $C_{15}H_{13}ClN$ $(M+ H)^+$ 242.0731; found 242.0742.

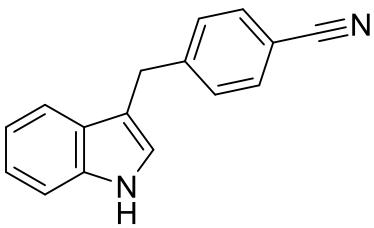


3-(4-Fluorobenzyl)-1H-indole (3k). The title compound was prepared according to the general procedure using 1H-indole and (4-fluorophenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2)

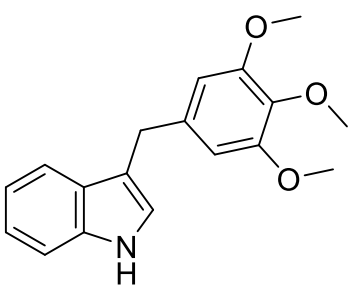
to give (3k) (76 mg, 68%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.23−7.14 (m, 3H), 7.13− 6.99 (m, 4H), 4.15 (s, 2H); HRMS (ESI) m/z calcd for $C_{15}H_{13}FN$ $(M+H)^+$ 226.1027; found 226.1036. The chemical-physical data are in accordance with literature[86].



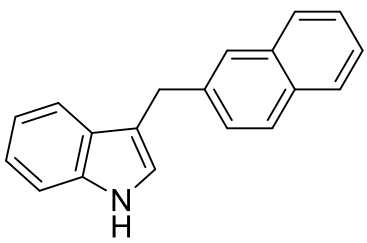
3-(4-(Trifluoromethyl)benzyl)-1H-indole (3l). The title compound was prepared according to the general procedure using 1H-indole and(4 (trifluoromethyl)phenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give (3l) (97 mg, 71%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.41−7.39 (m, 3H), 7.23 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.02−6.93 (m, 1H), 4.19 (s, 2H); HRMS (ESI) m/z calcd for $C_{16}H_{13}F_3N$ $(M+H)^+$ 276.0995; found 275.0988. The chemical-physical data are in accordance with literature[86].



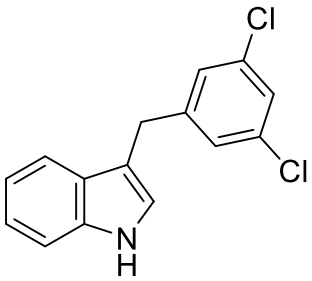
4-((1H-Indol-3-yl)methyl)benzonitrile (3m). The title compound was prepared according to the general procedure using 1H-indole and 4-(hydroxymethyl)benzonitrile. The product was purified by flash chromatography (from cyclohexane/EtOAc 1:1 to cyclohexane/ EtOAc 1:9) to give (3m) (83 mg, 72%) as off-white solid. ^{1}H NMR (400 MHz, acetone-d6) δ 10.11 (br s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.19−7.18 (m,1H), 7.11−7.07 (m,1H), 6.99−6.95 (m,1H), 4.18 (s, 2H); HRMS (ESI) m/ z calcd for $C_{16}H_{13}N_2$ $(M+H)^+$ 233.1073; found 233.1068. The chemical-physical data are in accordance with literature[104].



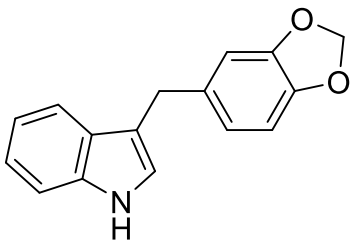
3-(3,4,5-Trimethoxybenzyl)-1H-indole (3n). The title compound was prepared according to the general procedure using 1H-indole and (3,4,5-trimethoxyphenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give (3n) (92 mg, 62%) as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 6.95 (s, 1H), 6.54 (s, 2H), 4.07 (s, 2H), 3.84 (s, 3H), 3.81 (s, 6H); HRMS (ESI) m/z calcd for $C_{18}H_{20}NO_3$ $(M+H)^+$ 298.1438; found 298.1435. The chemical-physical data are in accordance with literature[85].



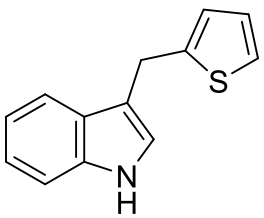
3-(Naphthalen-2-ylmethyl)-1H-indole (3o). The title compound was prepared according to the general procedure using 1H-indole and naphthalen-2-ylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give (3o) (91 mg, 71%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.83−7.74 (m, 4H), 7.56 (dd, J = 8.0, 1.0 Hz, 1H), 7.46−7.41 (m, 3H), 7.39 (dt, J = 8.0, 1.0 Hz, 1H), 7.21 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.09 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.96−6.95 (m, 1H), 4.30 (s, 2H); HRMS (ESI) m/z calcd for $C_{19}H_{16}N$ $(M+H)^+$ 258.1277; found 258.1271. The chemical-physical data are in accordance with literature[105].



3-(3,5-Dichlorobenzyl)-1H-indole (3p). The title compound was prepared according to the general procedure using 1H-indole and (3,5- dichlorophenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 98:2) to give (3p) (53 mg, 39%) as brown oil. ^{1}H NMR (400 MHz, CDCl3) δ 8.02 (br s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.29−7.12 (m, 5H), 6.98 (s, 1H), 4.08 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 136.4, 134.7, 127.14, 127.08, 126.2, 122.6, 122.4, 119.7, 118.9, 114.0, 111.2, 31.1; IR (film): 3170, 2949, 2824, 1555 cm−1; HRMS (ESI) m/ z calcd for $C_{15}H_{12}C_{l2}N$ $(M+H)^+$ 276.0341; found 276.0334.

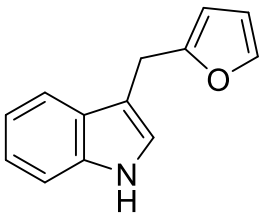


3-(Benzo[d][1,3]dioxol-5-ylmethyl)-1H-indole (3q). The title comound was prepared according to the general procedure using 1H- indole and benzo[d][1,3]dioxol-5-ylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give (3q) (105 mg, 84%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 6.94 (s, 1H), 6.82−6.76 (m, 3H), 5.93 (s, 2H), 4.07 (s, 2H); HRMS (ESI) m/z calcd for $C_{16}H_{14}NO_2$ $(M+H)^+$ 252.1019; found 252.1013. The chemical- physical data are in accordance with literature[87].

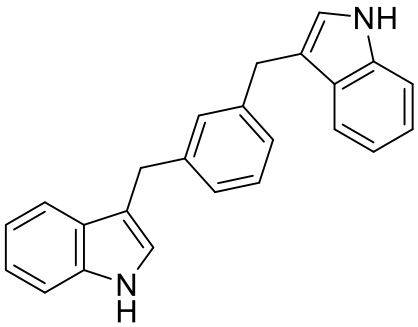


3-(Thiophen-2-ylmethyl)-1H-indole (3r). The title compound was prepared according to the general procedure using 1H-indole and thiophen-2-ylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give (3r) (101 mg, 95%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.25−7.21 (m, 1H), 7.16−7.11 (m, 2H), 7.06−7.05 (m, 1H), 6.95 (dd, J = 5.0, 4.0 Hz, 1H), 6.91−6.90 (m, 1H), 4.35 (s,

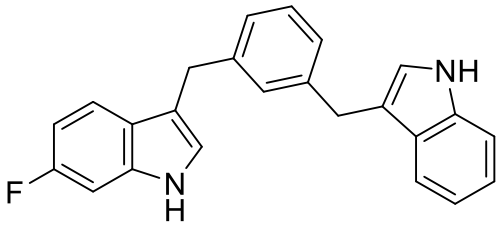
2H); HRMS (ESI) m/z calcd for: $C_{13}H_{12}NS$ $(M+H)^+$ 214.0685; found 214.0677. The chemical-physical data are in accordance with literature[87].



3-(Furan-2-ylmethyl)-1H-indole (3s). The title compound was prepared according to the general procedure using 1H-indole and furan-2-ylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 95:5) to give (3s) (76 mg, 78%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.34 (dt, J = 8.0, 7.6 Hz, 2H), 7.27−7.21 (m, 1H), 7.02 (s, 1H), 6.41 (dd, J = 3.0, 2.0 Hz, 1H), 6.16 (d, J = 3.0 Hz, 1H), 4.24 (s, 2H); HRMS (ESI) m/z calcd for $C_{13}H_{11}NONa$ $(M+Na)^+$ 220.0733; found 220.0737. The chemical-physical data are in accordance with literature[87].

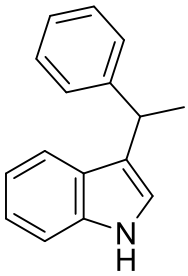


1,3-Bis((1H-indol-3-yl)methyl)benzene (3t). The title compound was prepared according to the general procedure using 1H-indole (234 mg, 2 mmol) and 1,3-phenylenedimethanol (138 mg, 1 mmol). The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give (3t) (97 mg, 58%) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (br s, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.28 (br s, 1H), 7.23−7.19 (m, 3H), 7.15−7.04 (m, 4H), 6.87 (s, 2H), 4.09 (s, 4H); ^{13}C NMR (101 MHz, CDCl3): δ 141.2, 136.4, 129.2, 128.3, 127.5, 126.3, 122.3, 122.0, 119.3, 119.2, 116.0, 111.1, 31.6; IR (film): 3165, 2929, 2820, 1556 cm−1; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2$ $(M+H)^+$ 337.1699; found 337.1691.

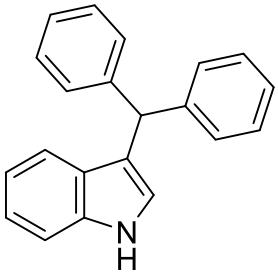


3-(3-((1H-Indol-3-yl)methyl)benzyl)-6-fluoro-1H-indole (3u). A vial was charged with 1H-indole (59 mg, 0.5 mmol), 1,4-phenyl-enedimethanol (69 mg, 1 mmol), iron(II) phthalocyanine (2.5 mg, 0.005 mmol), and Cs_2CO_3 (179 mg, 0.55 mmol). The vial was immersed in a preheated (140 °C) oil bath and stirred at this temperature for 16 h. Than the vial was removed from oil bath, and 6-fluoro-1H-indole (67 mg, 0.5 mmol) was added to the reaction mixture and stirred again for 16 h at 140 °C. The reaction mixture was diluted with ethyl acetate and filtered over a plug of silica gel. The solvent was evaporated under reduced pressure, and the residue obtained was purified by flash chromatography (cyclohexane/EtOAc 7:3) to give (3u) (93 mg, 52%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (br s, 1H), 7.94 (br s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.23−7.18 (m, 3H), 7.14−7.01 (m, 5H), 6.88−6.78 (m, 3H), 4.08 (s, 2H), 4.04 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.9 (d, J = 236 Hz), 141.0 (d, J =

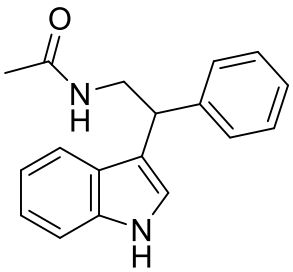
39 Hz), 136.43, 136.39, 136.3, 129.1, 128.3, 127.4, 126.4, 126.3, 126.2, 124.1, 122.5 (d, J = 3 Hz), 122.2, 122.0, 120.0, 119.9 (d, J = 10 Hz), 119.2 (d, J = 10 Hz), 116.0 (d, J = 12 Hz), 111.0, 108.0 (d, J = 25 Hz), 97.3 (d, J = 25 Hz), 31.59, 31.57; mp 166−168 °C; IR (film): 3161, 2932, 2816, 1549 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_20FN_2$ $(M+H)^+$ 355.1605; found 355.1611.



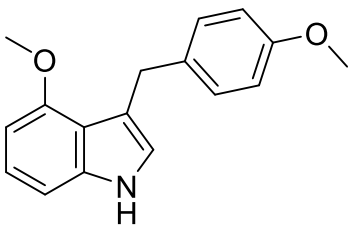
3-(1-Phenylethyl)-1H-indole (3v). The title compound was prepared according to the general procedure using 1H-indole and 1-phenylethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give (3v) (79 mg, 72%) as yellowish solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.45 (dd, J = 8.0, 2.5 Hz, 1H), 7.38−7.35 (m, 4H), 7.26−7.21 (m, 2H), 7.11−7.07 (m, 1H), 7.02 (s, 1H), 4.45 (q, J = 7.0 Hz, 1H), 1.78 (d, J = 7.0 Hz, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{16}N$ $(M+H)^+$ 222.1277; found 222.1269. The chemical-physical data are in accordance with literature[86].



3-Benzhydryl-1H-indole (3w). The title compound was prepared according to the general procedure using 1H-indole and diphenylmethanol. The product was purified by flash chromatography (cyclo- hexane/EtOAc 9:1) to give (3w) (52 mg, 37%) as yellowish solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.38−7.19 (m, 13H), 7.04 (dt, J = 7.5, 1.0 Hz, 1H), 6.57 (t, J = 2.0, 1.0 Hz, 1H), 5.73 (s, 1H); HRMS (ESI) m/z calcd for $C_{21}H_{18}N$ $(M+H)^+$ 284.1434; found 284.1439. The chemical-physical data are in accordance with literature[86].

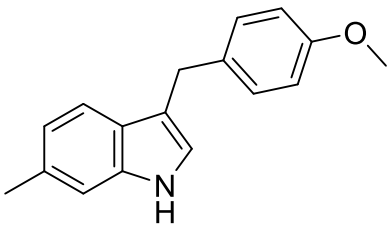


N-(2-(1H-indol-3-yl)-2-phenylethyl)acetamide (3x). The title compound was prepared according to the general procedure using 1H-indole and N-(2-hydroxy-2-phenylethyl)acetamide. The product was purified by flash chromatography (EtOAc) to give (3x) (62 mg, 45%) as yellowish solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.32−7.31 (m, 4H), 7.24 (dd, J = 5.0, 4.0 Hz, 1H), 7.21−7.16 (m, 1H), 7.09 (br s, 1H), 7.07−7.03 (m, 1H), 5.51 (br s, 1H), 4.44 (t, J = 8.0 Hz, 1H), 4.11−4.04 (m, 1H), 3.86−3.79 (m, 1H), 1.91 (s, 3H); HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O$ $(M+H)^+$ 279.1492; found 279.1486. The chemical-physical data are in accordance with literature[106].

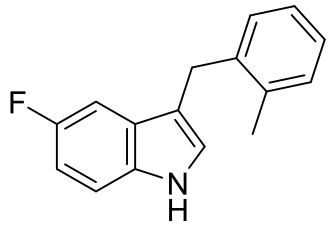


4-Methoxy-3-(4-methoxybenzyl)-1H-indole (3y). The title compound was prepared according to the general procedure using 4- methoxy-1H-indole and (3-((1H-indol-3-

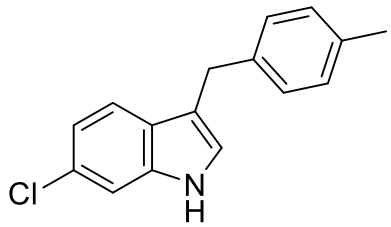
yl)methyl)phenyl)methanol. The product was purified by flash chromatography (gradient from cyclohexane/EtOAc 8:2 to cyclohexane/EtOAc 6:4) to give (3y) (117 mg, 88%) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (br s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.11 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0, 1H), 6.87−6.85 (m, 2H), 6.64 (br s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 4.26 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H); 13C NMR (101 MHz, $CDCl_3$): δ 157.6, 155.1, 138.1, 134.7, 129.8, 122.8, 120.9, 117.4, 117.2, 113.6, 104.4, 99.5, 55.3, 55.1, 32.2; IR (film): 3397, 2848,1387 cm^{-1}; HRMS (ESI) m/z calcd for: C17H18NO2 $(M+H)^+$ 268.1332; found 268.1338.



3-(4-Methoxybenzyl)-6-methyl-1H-indole (3z). The title compound was prepared according to the general procedure using 6-methyl-1H-indole and (3-((1H-indol-3-yl)methyl)phenyl)methanol. The product was purified by flash chromatography (cyclohexane/ EtOAc 8:2) to give (3z) (79 mg, 63%) as pinkish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.29−7.23 (m, 2H), 7.16 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.88 (m, 2H), 6.84 (s, 1H), 4.09 (s, 2H), 3.83 (s, 3H), 2.51 (s, 3H); HRMS (ESI) m/z calcd for $C_{17}H_{18}NO$ $(M+H)^+$ 252.1383; found 252.1379. The chemical- physical data are in accordance with literature[107].

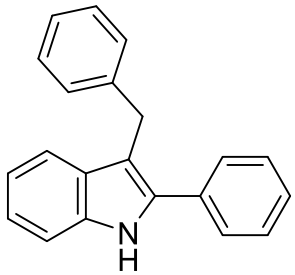


5-Fluoro-3-(2-methylbenzyl)-1H-indole (3aa). The title compound was prepared according to the general procedure using 5-fluoro-1H- indole and (3-((1H-indol-3-yl)methyl)phenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give (3aa) (95 mg, 80%) as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.30−7.26 (m, 2H), 7.23−7.14 (m, 4H), 6.95 (td, J = 9.0, 2.5 Hz, 1H), 6.80 (s, 1H), 4.03 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (d, J = 234 Hz), 138.8, 136.5, 133.0, 130.3, 129.4, 128.0 (d, J = 10 Hz), 126.4, 126.1, 124.4, 115.3 (d, J = 5 Hz), 111.8 (d, J = 10 Hz), 110.4 (d, J = 26 Hz), 104.0 (d, J = 23 Hz), 29.3, 19.6; mp 65−66 °C; IR (film): 3310, 2901,1354 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{15}FN$ $(M+H)^+$ 240.1183; found 240.1180.

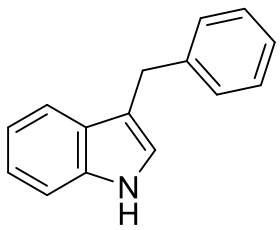


6-Chloro-3-(4-methylbenzyl)-1H-indole (3ab). The title compound was prepared according to the general procedure using 6-chloro-1H-indole and (3-((1H-indol-3-yl)methyl)phenyl)methanol. The product was purified by flash chromatography (cyclohexane/ EtOAc 8:2) to give (3ab) (82 mg, 64%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br s, 1H),

7.41 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.05 (dd, J = 8.0, 2.0 Hz, 1H), 6.92 (d, J = 1.0 Hz, 1H), 4.06 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 136.8, 135.5, 129.1, 128.5, 128.0, 126.1, 122.8, 120.1, 116.3, 110.9, 31.0, 21.0; mp 98−99 °C; IR (film): 3220, 2965, 2837, 1601 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{15}ClN$ $(M+H)^+$ 256.0888; found 256.0895.



3-Benzyl-2-phenyl-1H-indole (3ac). The title compound was prepared according to the general procedure using 2-phenyl-1H-indole and benzyl alcohol. The product was purified by flash chromatography (cyclohexane/DCM 1:9) to give (3ac) (69 mg, 49%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.55−7.52 (m, 2H), 7.46−7.44 (m, 4H), 7.38−7.31 (m, 2H), 7.26− 7.16 (m, 5H), 7.10−7.06 (m, 1H), 4.29 (s, 2H); HRMS (ESI) m/z calcd for $C_{21}H_{18}N$ $(M+H)^+$ 284.1434; found 284.1438. The chemical-physical data are in accordance with literature[108].



Procedure for Large-Scale Synthesis of Compound (3a). A 50 mL Schlenk flask equipped with a magnetic stir bar was charged with indole (1 g, 8.5 mmol), benzyl alcohol (1.8 g, 17 mmol), iron(II) phthalocyanine (48 mg, 0.085 mmol), and Cs_2CO_3 (3 g, 9.35 mmol). The reaction mixture was immersed in a preheated (140 °C) oil bath and stirred at this temperature for 16 h. The reaction mixture was diluted with ethyl acetate and filtered over a plug of Celite. The solvent was evaporated under reduced pressure, and the residue obtained was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give (3a) (1.6 g, 92%) as white solid. The chemical-physical data are in accordance as reported above.

6. Notes and References

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The following work has been done during my period of visiting spent abroad at Lund University under the guidance of Professor **Peter Somfai**.

Asymmetric Lewis Acid Mediated [1,2]-Rearrangement Approach Towards the Formal Synthesis of Cephalotaxine

Department of Chemistry

LUND UNIVERSITY

Centre for Analysis and Synthesis

KEMICENTRUM

Contents

Abbreviations

Boc	di-tert-butyl dicarbonate
DBU	1,5-diazabiciclo(5.4.0)undec-5-ene
DCM	dichloromethane
DMF	dimethylformamide
HBTU	(2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)
HFIP	hexafluoro-2-propanol
LDA	Lithium diisopropylamide
NMR	nuclear magnetic resonance
OHBt	2-Hydroxybenzothiazole
TFA	trifluoro acetic acid
TFE	trifluoro ethanol
THF	tetrahydrofuran

1. Introduction

1.1 Introduction

Cephalotaxine is the most abundant alkaloid isolated form *cephalotaxus harringtonii*, an evergreens conifer species native to Japan, India and China. Cephalotaxine was isolated by Paudlar and co-workers[1] and was later described and characterized by Powell and co-workers.[2] The structure has an unique skeleton with an unusual 1-azaspiro[4,4] moiety fused to a benzazepine system. Cephalotaxine itself does not display any biological activity but various esters of cephalotaxine were isolated and named harringtonine, homoringtonine, isoharringtonine and deoxyharringtonine. These derivatives show significant inhibitor activity against lymphoid leukemia in mice[3] and clinical trials have reached phase II-III[4] and, more recently, homoharringtonine has been investigated in the treatment of chloroquine resistant malaria (Figure1).[5]

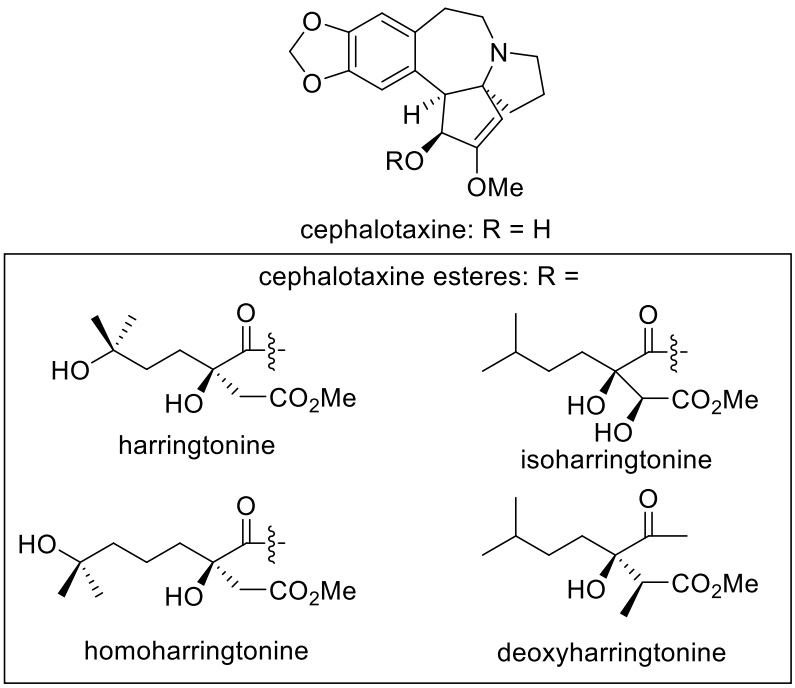


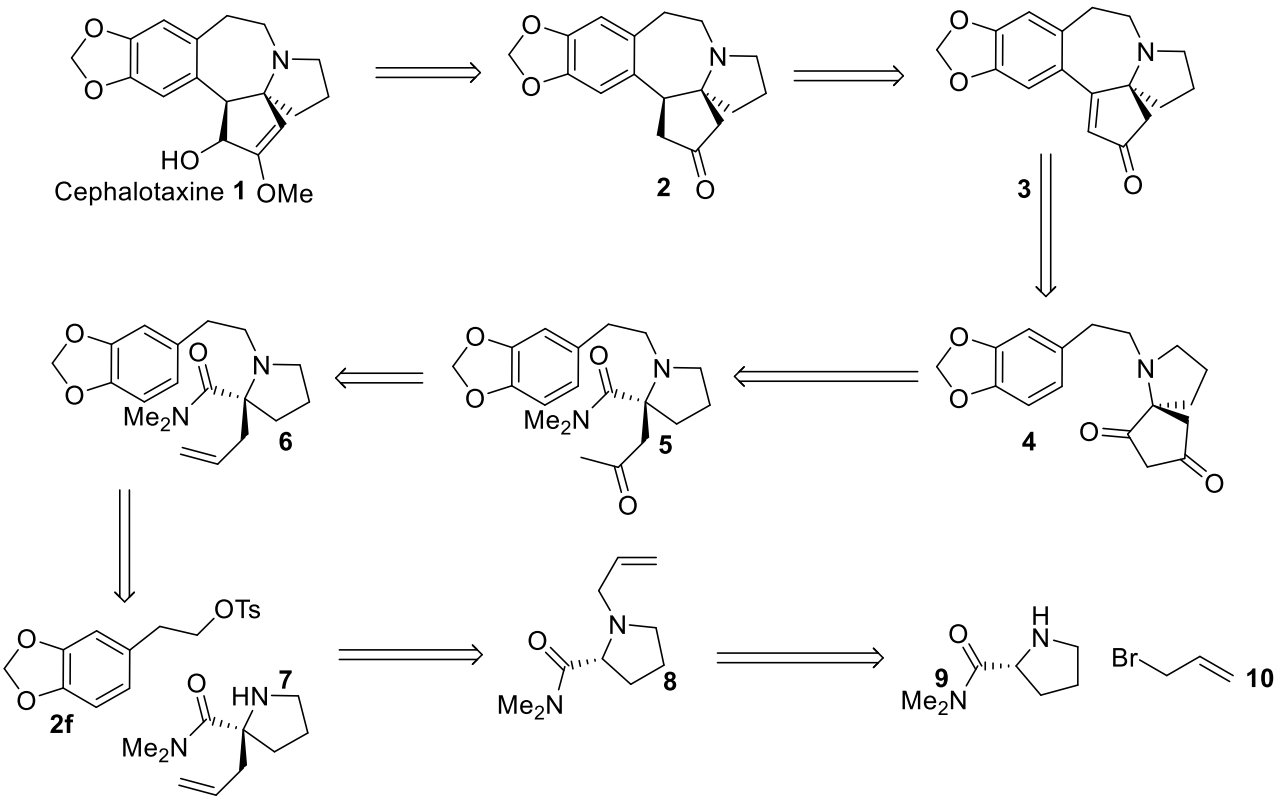
Figure 1 Cephalotaxine alkaloids.

Cephalotaxine has become an interesting synthetic target, not only because of its unique ring skeleton but also for the biological activity shown from the ester

derivatives aforementioned. Several elegant total syntheses both racemic and enantiopure of cephalotaxine have been reported.[6]

2. Aim of the thesis

The goal of the present work is to achieve a short, efficient and novel route to cephalotaxine using as a key step an highly selective 1,2-Stevens rearrangement to establish the correct stereochemistry of the quaternary stereocenter transforming (S)-1-allyl-N,N-dimethylpyrrolidine-2-carboxamide **(8)** in to (R)-2-allyl-N,N-dimethylpyrrolidine-2-carboxamide **(7)**. A recent work on 1,2-Stevens rearrangement was previously developed by P. Somfai and co-workers.[7]



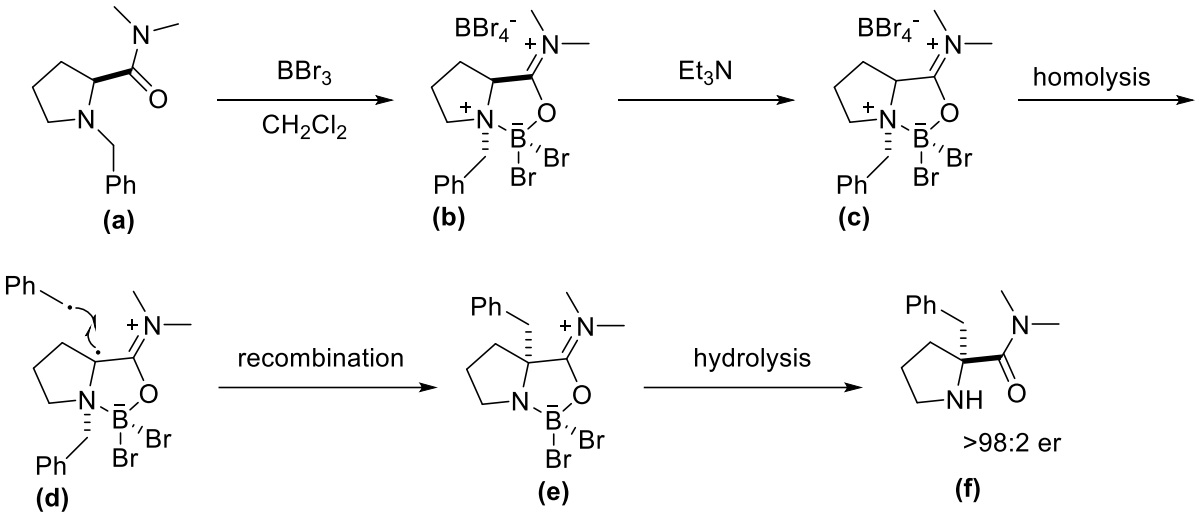
Scheme 1 Retrosynthetic analysis of cephalotaxine (1).

Retrosynthesis of **(1)** lead to compound **(2)** that was recently reported by Li and co-worker[8] and previously reported by Weinreb[9], Dolby[10] and Weinstein[11] so the sequence from **(1)** to **(2)** has been already demonstrated. We want to highlight that not only it should be possible to prepare the pentacyclic intermediate **(2)** in seven steps against nine steps already reported by Li but also in a stereoselective way. Compound **(2)** come from the hydrogenation of the double bond present in molecule **(3)**. The stereocontrol should be guided from the substrate. The molecular model

shows us that the hydrogen should approach the double bond form the less hindered face to give the desired stereochemistry (substrate control). The seven-carbon ring in molecule **(3)** should be formed starting from bis-ketone **(4)** under acidic condition. Reasonably a kind of Friedel-Crafts acylation should take place with a thermodynamic regiocontrol guided from the possible formation ring size and the geometry of the starting molecule, that favour the closest carbonyl due to the spatial proximity. Molecule **(4)** should be formed in basic condition promoting the enolate formation of ketone **(5)** and the subsequent addition-elimination steps to the amide to from the ring containing the double ketone in molecule **(4)**.[12] Ketone **(5)** should be formed form the double bond using the well establish Wacker oxidation process. Compound **(6)** should be made by N-alkylation of the proline amide **(7)** with the homopiperonyl tosylate **(2f)**. The key step involving the asymmetric transformation of **(8)** in **(7)** among the [1,2]-Stevens rearrangement should be achieved using an optimization of the previous reported condition by P. Somfai and co-workers.[7] Finally **(8)** should be prepared by N- allylation of the commercial available L-proline amide.

3. Results and Discussion

As shown in the retrosynthesis (Scheme 1) the synthesis commenced from the commercial available L-proline amide to form the N-allylated proline amide **(8)**. The nucleophilic substitution was carried out as microwaved assisted reaction in acetonitrile using allyl bromide as alkylating agent. This reaction proceeds in 30 min and in 98% yield. Based on the previously reported work of asymmetric Lewis acid mediated [1,2]-rearrangement of *N*-benzylic proline amides to form quaternary proline derivatives with high C-N-C chirality transfer prompt us to try this procedure on our compound **(8)**. We have thought to apply that procedure to compound **(8)** where instead to have a transfer of a benzyl group we could have the transfer of allyl group. In this transformation the high level of C-N-C chirality transfer can be explained by in situ formation of the rigid bicyclic complex **(b)** (Scheme 2). Treatment of amide with BBr_3 results in coordination of the Lewis acid cis to the amide moiety which is followed by formation of structure **(b)** (Scheme 2) resulting in an efficient transfer of chirality from the α-carbon to the nitrogen nucleus. Subsequent deprotonation with Et_3N provides **(c)** (Scheme 2), which suffers a homolytic cleavage of the C-N bond (see structure **(d)** in Scheme 2) and then a radical recombination occurs to form complex **(e)** (Scheme 2). Bicyclic structure **(d)** (Scheme 2) is chiral because of is non-planar so, efficient N-C chirality transfer is secured by selective migration of the benzyl radical on the α-face. Finally, hydrolysis of **(e)** (Scheme 2) gives **(f)** (Scheme 2), the absolute stereochemistry of which is identical to the starting material **(a)** (Scheme 2).



Scheme 2 Proposed Mechanism for the Stevens Rearrangement.

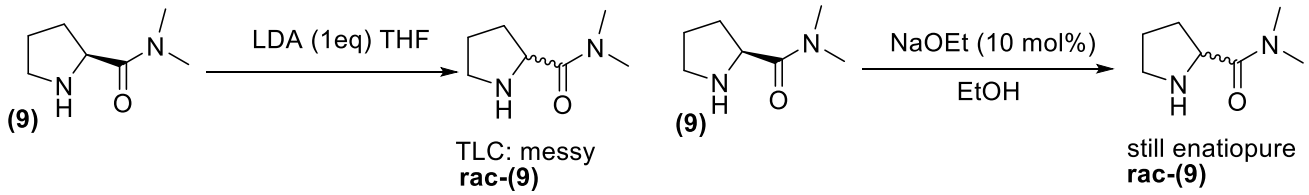
The goal of the aforementioned publication was to study the transfer of different substituted aryl groups. Herein we have studied if it was possible to maintain the efficiencies in term of yield and the sterocontrol transferring the N-allyl group. First of all was tried the previous reported condition used for the benzyl group (Table 1, entry 1), isolating only traces of the desired product. We believed that the product was formed but not completely recovered from the aqueous phase. For this reason the reaction was repeated changing the work up using NaOH instead $NaHCO_3$ to have an higher pH that should ensure the neutral form of the secondary amine. Nevertheless in this case we had the consume of the starting material without any formation of the desired product. We also increased the temperature considering the possible higher energy barrier for the formation of complex **(b)** (Scheme 1) in the case of allyl compared to the benzyl. As shown in (Table 1, entry 3 and 4) temperature was increased, respectively refluxing in dichloromethane at 50°C and toluene at 110°C but we obtained the consume of the starting material without formation of the product. Finally, we change the base believing that the problem was the passages from **(b)** to **(c)** (Scheme 2) that was blocked due to the base that was not able to deprotonate the complex **(b)** (Scheme 2). LDA was used without success causing a mess reaction, probably it is too strong as base (Table 1, entry 5). Instead using 1,5-diazabiciclo(5.4.0)undec-5-ene (DBU) (Table 1, entry 6) right condition was found allowing the rearrangement to give product **(7)** in 73 % yield.

Entry	T (°C)	Solvent	Base	Work Up	Comments
1	r.t.	DCM	TEA	$NaHCO_3$	traces
2	rt	DCM	TEA	NaOH	-
3	50	DCM	TEA	$NaHCO_3$	-
4	110	toluene	TEA	$NaHCO_3$	-
5	r.t.	DCM	LDA	$NaHCO_3$	messy
6	r.t.	DCM	DBU	$NaHCO_3$	Yield 73%

Table 1 Reaction Conditions: BBr_3 2eq (1.98 M in DCM), 5eq of Base, 2,5h.

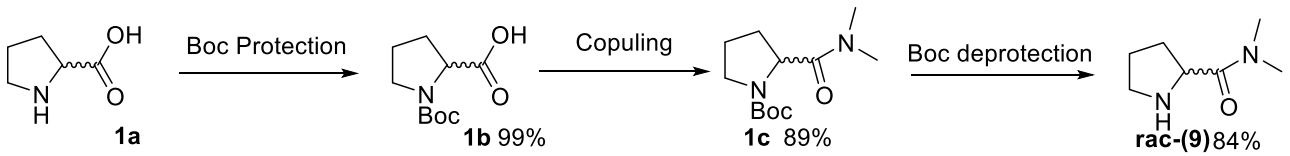
With the rearrangement conditions in hand, it was consequently possible to evaluate the enantiomeric ratio. The sequence was repeated for the formation of **(7)**, starting

from the commercially available DL-proline amide. Dissolving 5mg in 1 mL of isopropanol of the racemic form of **(7)** were run different chiral-hplc using a variety of chiral stationary phases (AI, AB, AC, ODH, ABH, ADH, OJ) and a variable elution system made of hexane: isopropanol with a ratio variable in the range of 90:10 to 99:1 and a flow in the range of 1ml/min to 0.5ml/min. It was not possible to find the HPLC condition for the separation of the racemate **(7)**. As alternative, a derivatization of the secondary amine was done, making the protection of the secondary ammine (**7**) as Boc, and all the condition aforementioned were tried again without any result. The doubtful results convinced us to check if the initial commercial reagent was actually racemic. Using a polarimeter to evaluate the angle of rotation caused by passing polarized light through an optically active substance were compared the two commercial available racemic and enantiopure prolineamides **(9)** and was found that the racemic form of **(9)** actually was enantiopure measuring an $[\alpha]_D^{20}$ of -44° (c 1.00, $CHCl_3$). Conscious of this inconvenient we decided to prepare the racemate by ourselves. First, we tried to racemize the enantiopure proline amide using a different base that should promote the enolization of the amide and the consequence racemization, but without satisfactory results. LDA (1 eq) was tired but the proline amide was degraded, while NaOEt (10%) was used the enantiopure form was recoverd (Scheme 3), so it was decided to prepare the raceme proline amide starting from the DL-proline.



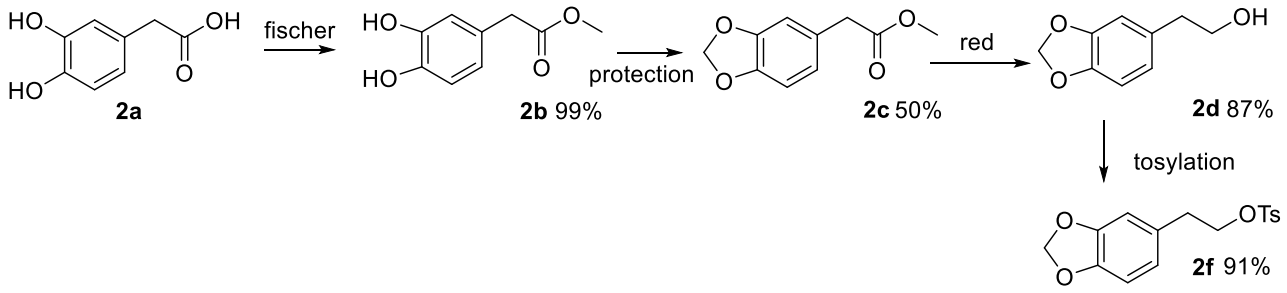
Scheme 3 Racemization Attempts.

After many efforts, a practical route to produce DL-proline was found (Scheme 3).



Scheme 3 Racemic Proline Amide Synthetic Route.

DL-proline **(1a)** was converted in N-Boc-DL-proline **(1b)** in quantitative yield using the classical Shotten-Baumann conditions.[13] Then the coupling with the dimethylamine was realized through the activation of acid employing HBTU, OHBt, running the reaction in DCM and diisopropylamine as base at room temperature for 24h, giving **(1c)** in 89% yield. Due to the water solubility of **(1d)** the Boc deprotection cannot be performed using TFA because of the basic/water extraction needed to remove the excess of acid (TFA) and also to restore the neutral form of the proline amide **(1d)**. So, to this end the extraction with basic aqueous solution was avoided by using hexafluoroisopropanol (HFIP) as deprotecting reagent. The reaction was performed in a microwave at 150°C for 1h using only HFIP both as reagent and solvent. In this case, there is no need to extract with water solutions because the work up is simply the removal of the solvent under reduced pressure to afford the racemic proline amide **rac-(9)** in 84% yield. Finally, **rac-(9)** was used in the aforementioned discussed sequence for the formation of racemic compound **(7)**. Once more, all the analysis aforementioned for the chiral-hplc were repeated without obtaing a separation of the two enantiomers of **(7)**. Moreover, 1% of dimethylamine was added as additive in the HPLC elution systems describe before and both the racemates **(7)** and **(7)**-boc-protected, were not separated with these conditions, highlighting the difficulty to separate the two enantiomers via chiral-HPLC. As last resorts to evaluate the enantiomeric ratio diastereoisomer of **(7)** with the (*R*)-Mosher acid chloride were made and finally the diasteromeric ratio was evaluated, as 4(RR):6(RS). Considering that the rearrangement reaction of **(8)** is performed only starting from the S form (99,9% purity) and for the racemate there is no preferential reaction on of the two enantiomers with the R-Mosher acid chloride is possible to transfer the d.r. to e.r. so e. r. = 94(R):6(S). An assumption was done: the retention of chirality is maintained as reported in the precedent work for the transfer of benzyl group. Finally, to assign the stereochemistry of **(7)** should be transformed in a known compound, for example **(1)** and check the alfa rotation to assign the stereo descriptor. Afterwards moving on in the synthesis the preparation of homopiperonyl tosylate was considered (Scheme 4).



Scheme 4 Homopiperonyl Tosylate Synthetic Route.

The acid (2a) was quantitatively transformed in the corresponding ester **(2b)** using the Fischer esterification, then the protection of catechol **(2b)** was achieved in 50% yield refluxing in DMF/ dichloromethane, which undergo a double substitution reaction. **(2c)** was reduced to the correspondent alcohol **(2d)** with $LiALH_4$, refluxing in THF for 2h. The 1,3-dioxolane moiety is unstable to acid condition, so the chosen work up for this reaction was Fieser work up, consisting in a basic washing with and aqueous solution of NaOH at 15%. **(2d)** was obtained in 87% yield. Finally, the homopiperonyl tosylate **(2f)** was simply obtained from tosyl chloride in 91% yield. Compound **(2f)** and **(7)** were allowed to react together in a nucleophilic substitution, using acetonitrile as solvent, potassium carbonate as base and KI as catalyst, producing **(6)** in 98% yield. Working on compound **(6)** different variants of Wacker process to achieve the ketone were tried **(5)**.

entry	T (°C)	solvent	catalyst	equivalents	comments
1	r.t.	DMF/H_2O	$PdCl_2$/CuI	0.25/1.50	SM recover
2	60°C	DMF/H_2O	$PdCl_2$/CuI	0.25/1.50	SM recover
3	60°C	DMF/H_2O	$PdCl_2$/CuI	3/1.5	SM recover
5	60°C	DMF/H_2O/H^+	$PdCl_2$/CuI	3/1.5	Traces of TM

Table 2 Wacker Process, Screening Conditions. O_2 (1atm) ,24h for all the reaction runs.

The first condition tested (Table 2, entry 1) was the classical Wacker reaction with $PdCl_2$/CuCl where $PdCl_2$ is used in catalytic amount. In this case, we recovered only

the starting material, then we repeated the same reaction conditions heating at 60°C for 24h (Table 2, entry 2), nevertheless continuing to recover starting material. In literature, it was found that the nitrogen bond can influence the course of the Wacker oxidation due to the affinity to coordinate palladium.[14] To avoid this inconvenient and to allow the reaction to continue to work, two possibilities were taken in consideration: 1) overloading of catalysts using an excess of it; 2) protonation of amine. In (Table 2, entry 3) it was tried the super-stochiometric conditions without good results. In the conditions of (Table 2, entry 4) the amine **(6)** was protonated with one equivalent of hydrochloric acid and it was used also a super-stochiometric condition of catalyst load and traces of product were obtained. Another issue is that compound **(6)** contain the methylenedioxy moiety that is not stable in acid conditions, influencing the yield of the process.

4. Conclusion

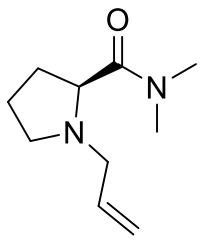
The formal synthesis of Cephalotaxine was taken in consideration. The condition of 1,2-stevens rearrangement for the allyl group transfer was found and I supposed to have the correct stereochemistry of the quaternary stereocenter. Indeed, based on the previous reported work of Somfai and co-workers[7] , there was a retention of chirality. In the present case we transfor (S)-1-allyl-N,N-dimethylpyrrolidine-2-carboxamide in to (R)-2-allyl-N,N-dimethylpyrrolidine-2-carboxamide in the presence of BBr_3 as Lewis acid DBU as base and DCM as solvent at room temperature in 3h with 89 % yields and almost complete transfer of chirality. Starting from 99,9 % (S) proline amide (9) we obtain (7) e.r. = 94(R):6(S). Finally, I worked on the transformation of double bond on compound **(6)** to ketone **(5)** furnishing for now only traces of product, that means the reaction works, but remain to be optimized. The planned synthesis is almost of half of the way.

5. Experimental Section

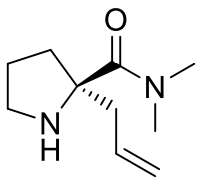
5.1 Materials and Methods

Unless stated specifically, all reactions were performed under argon atmosphere. Analytical thin-layer chromatography was performed with Merck Silica gel 60. Flash silica gel column chromatography was performed with Acros silica gel 40- 60. ^{1} H NMR spectra were recorded on a Bruker Avance II at 400 MHz and Bruker Avance III HD at 500 MHz. Chemical shifts are reported relative to Me_4Si. ^{13}C NMR spectra were recorded on a Bruker Avance II at 100 MHz and Bruker Avance III HD at 125 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0). Infrared spectra were recorded on a Bruker Alpha-P FT/IR instrument with a Diamond ATR sensor for detection in the range from ῡ = 4500 cm–1 to ῡ = 500 cm–1. Samples were prepared as a film for liquid or neat for solid substances. High resolution mass spectra (HRMS) were recorded on Waters XEVO-G2 QTOF with electrospray ionization (ESI). Melting points were measured on a BÜCHI B-540 melting point apparatus and are uncorrected.

5.2 Compound Characterization and Synthetic Methods

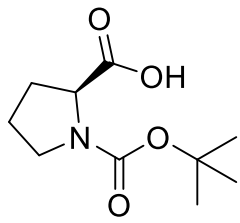


(S)-1-allyl-N,N-dimethylpyrrolidine-2-carboxamide (8) To the cold (0°) solution of proline amide (9) (90mg, 0.632 mmol) in CH_3CN (330 µl) was added allyl bromide (10) (82µL, 0.949 mmol) and resulting mixture was heated in micro-wave reactor at 120 °C (100W) for 30 min. The resulting mixture was poured into the aqueous saturated $NaHCO_3$ (2.5 mL) and extracted with CH_2Cl_2 (3x5 mL). The combined organic phases were washed with brine, dried over K_2CO_3 and concentrated. The residue was purified by column flash chromatography (SiOx, 20% of EtOAc in Heptane containing 1% iPrNH2) to afford (5) (114 mg, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.98-5.89 (m, 1H), 5.12 (dd, *J* = 17.0, 1.0 Hz, 2H), 5.03 (dd, *J* = 10.0, 1.0 Hz, 2H), 3.36 - 3.26 (m, 2H), 3.18 (t, *J* = 8.5 Hz, 1H), 3.03 (s, 3H), 3.01 - 2.95 (m, 1H), 2.92 (s, 3H), 2.35- 2.27 (m, 1H), 2.13 – 2.02 (m, 1H), 1.96 – 1.88 (m, 1H), 1.84 – 1.73 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.0, 135.9 , 116.6 , 63.7, 57.4 , 53.1 , 36.7 , 35.9 , 28.7 , 22.8 . IR (film): 1671 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{10}H_{19}N_2O$ $(M+H)^+$ 183.1492; found 2183.1489. Rf:0,20 using heptane: ethyl acetate (80:20 + 1% $iPrNH_2$). Yellow spot is obtained staining with permanganate solution

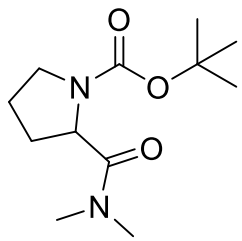


(R)-2-allyl-N,N-dimethylpyrrolidine-2-carboxamide (7) A solution of 5 (160 mg, 0.877 mmol, 1.0 equiv.) in dry CH_2Cl_2 (4 mL) under a nitrogen atmosphere was cooled to -78 °C and BBr3 (880 µL, 1.76 mmol, 2 M solution in CH_2Cl_2, 2.0 equiv) was added dropwise. Cooling bath was removed and resulting solution was stirred for 1 h (-78 °C → rt). To the resultant mixture DBU (655 µL, 4.39 mmol, 5.0 equiv) was added drop wise at 0°C and the reaction mixture was stirred for 1h at room temperature. Reaction was then quenched at 0°C by addition of 1 M HCl (1.0 mL) and stirred for 1h then poured into the saturated $NaHCO_3$ (5 mL) until basic pH solution and extracted with CH_2Cl_2 (3x5 mL). Organic phases were combined and washed with brine (1x10 mL) and dried over K_2CO_3, then evaporated. Purification of the residue by column chromatography, silica gel heptane:acetone (50:50 + 1% $iPrNH_2$) afforded amide 6 (90mg, 56%) as colourless oil. ^{1}H NMR (CDCl3, 400 MHz) δ 5.81-5.71 (m, 1H), 5.05-5.03 (m, 1H), 5.02-4.99 (m, 1H), 3.09-2.88 (m, 1H), 2.78-2.72 (m, 1H), 1.87-1.81 (m, 1H), 1.80-1.65 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 175.5, 134.2, 117.5, 68.4, 46.5, 44.7, 35.2, 26.5. IR (film): 1697 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{10}H_{19}N_2O$ $(M+H)^+$ 183.1492; found 183.1499 Rf:0,52 using heptane:acetone (50:50 + 1% iPrNH2). Brown spot is obtained staining with ninhydrin solution.

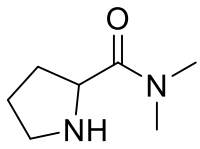
Preparation sequence of racemic prolineamide rac-(9):



(tert-butoxycarbonyl)-proline (1b) A solution of 729 mg (6.33 mmol) of DL-proline (1a) in 9 mL of saturated $NaHCO_3$ solution (= 0.7 mol/l) was cooled in an ice bath, treated dropwise with a solution of Boc_2O in THF (2 mol/l) and stirred for 19 h at room temp. In the following THF was removed under reduced pressure, the residue cooled to 0 °C, then acidified by the addition of 2 mL of 3 M HCl solution and other 10 mL of 3 N HCl solution from pH = 8 to 2 and extracted three times with 20 mL of EtOAc. After drying of the combined organic phases over $MgSO_4$, concentration under reduced pressure and drying in oil pump vacuum 805 mg of the acid 7 were obtained as a colorless solid. Purification of the residue by column chromatography is also possible when necessary using, silica gel ethyl acetate:methanol (90:10) afforded amide 6 (90mg, 56%) as colourless oil. ^{1}H NMR (CDCl3, 400 MHz, mixture of rotamers) δ 8.16 (bs, 1H), 4.15 (bs, 1H), 3.51-3.30 (m, 2H), 2.08-1.92 (m, 3H), 1.83-1.79 (m, 1H), 1.42 (s, 1H). Rf:0,25 using ethyl acetate:methanol (90:10 + 1% $iPrNH_2$). Yellow elongated spot is obtained staining with permanganate solution. The chemical-physical data are in accordance with literature[15].

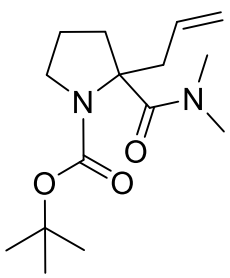


Tert-butyl-2-(dimethylcarbamoyl)pyrrolidine-1-carboxylate (1c) To a solution of (1b) (650 mg, 3.02 mmol), 1-hydroxybenzotriazole (448.8 mg, 3.32 mmol) and N,N-diisopropylethylamine (1.05 mL, 7.55 mmol) in CH_2Cl_2 (6 mL) was added HBTU (1.15 g, 3.02 mmol), and the reaction mixture was then stirred for 30 min. Dimethylamine solution in THF (1.05 mL, 2M) was then added portionwise over 15 min. After stirring at room temperature for 24 h, the solvent was removed under vacuum and then the residue was diluted with CH_2Cl_2 (10 mL), washed with saturated sodium hydrogen carbonate solution (8 mL), saturated aqueous ammonium chloride solution (8 mL) and brine (8 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue obtained was purified by flash chromatography (ethyl acetate:methanol 90:10) to give 719 mg (89%) of coupled product 8 as yellow oil.^{1}H NMR (CDCl3, 400 MHz, mixture of rotamers) δ 7.00 (s, 1H), 4.63 (dd, 8.5, 3.0 Hz 1H), 4.53 (dd, *J* = 8.5, 4.5 Hz, 1H), 3.55 – 3.37 (m, 3H), 3.06 (d, *J* = 8.0 Hz, 3H), 2.94 (d, *J* = 7.0 Hz, 3H), 2.20-2.11 (m, 1H), 2.04-2.98 (m, 1H), 1.88-1.79 (m, 2H). 1.38-1.36 (m, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz, mixture of rotamers) δ 173.0 , 172.4 , 154.59 , 154.1 , 79.8 , 79.6 , 56.6, 56.5, 46.8, 46.6, 45.5, 36.9, 36.0, 30.2, 29.5, 28.5, 28.3, 24.2, 23.7. Note: 1,1,3,3-tetramethylurea signals are detected as impurity. At the moment no way found to remove it. Rf:0,70 using ethyl acetate:methanol (90:10 + 1% $iPrNH_2$). Yellow spot is obtained staining with permanganate solution. The chemical-physical data are in accordance with literature[16].



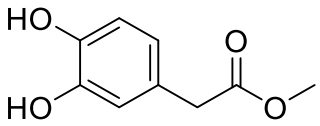
N,N-dimethylpyrrolidine-2-carboxamide (1d) A solution of the N-Boc protected prolineamine (1c) (350mg, 1.44mmol) in hexafluoroisopropanol (15 mL) was placed in a sealed microwave vial. The reaction mixture was heated (150°C) in a Biotage–microwave instrument stirring for 1h.. After cooling to room temperature, the mixture was evaporated to dryness under reduced pressure. The crude product was purified by flash-column chromatography using (ethyl acetate:methanol 90:1 + 1% $iPrNH_2$) to give 174mg (84%) of deprotected product 9 as transparent oil. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.11 (dd, *J* = 8., 6.0 Hz, 1H), 3.70 (bs, 2H), 3.24 – 3.18 (m, 1H), 3.03 (s, 3H), 2.97 (s, 3H), 2.24 – 2.14 (m, 1H), 1.91 – 1.84 (m, 1H), 1.80 – 1.64 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.8 , 58.1, 47.4, 36.6, 35.9, 30.4, 26.1. IR (film): 1850 cm^{-1}; HRMS (ESI) m/z calcd. for $C_7H_{15}N_2O$ $(M+H)^+$ 143.1179; found 143.1188. Rf:0,25 using ethyl acetate:methanol (90:10 + 1% $iPrNH_2$). Yellow spot is obtained staining with permanganate solution or brown spot staining with ninhydrin.

Procedure for the Boc protection of (7) and rac-(7)

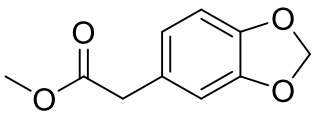


Tert-butyl 2-allyl-2-(dimethylcarbamoyl)pyrrolidine-1-carboxylate. Et_3N (43 µl, 0,30 mmol) and Boc_2O (67 mg, 0,30 mmol) were added sequentially to a solution of compound 7 or rac-(7) (40 mg, 0.22 mmol) in CH_2Cl_2 (450 µL) at room temperature. The reaction mixture was stirred overnight and then saturated aqueous $NaHCO_3$ (2.5 mL) was carefully added. The mixture was extracted with CH_2Cl_2 (3×5 mL). The combined extracts were dried on $MgSO_4$ and concentrated under vacuo. The crude was purified by flash-column chromatography using (ethyl acetate 100%) to give 80 mg (100%) of protected product 10 as yellow-transparent oil.^{1}H NMR ($CDCl_3$ 400 MHz) δ 5-94-5.84 (m, 1H), 5.11-5-04 (m, 2H), 3.64-3.58 (1H, m), 3.50-3.45 (m, 1H), 2.96 (s, 6H), 2.79 (dd, J = 7.0, 1.0 Hz, 1H), 3.22 – 3.08 (m, 2H), 2.05-1.90 (m, 2H), 1.44 (s, 3H), 1.41 (s, 6H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.86, 153.24, 146.71, 135.11, 118.18, 85.13, 80.09, 68.16, 47.16, 42.60, 35.63, 28.27, 27.38, 21.80. IR (film): 1787 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{12}H_{23}N_2O_3$ $(M+H)^+$ 243.1703; found 243.1714. Rf:0,85 using ethyl acetate (100%).Yellow spot is obtained staining with permanganate solution or brown spot staining with ninhydrin.

Sequence for the preparation of the homopiperonyl moiety:

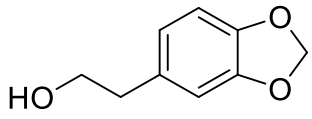


methyl 2-(3,4-dihydroxyphenyl)acetate (2b) Dihydroxyphenylacetic acid (2a) (100 mg, 0.60 mmol) was treated by MeOH (2 mL) in acid medium with concentrated H_2SO_4 (25 µL), stirred and refluxed for 3 h. Then, the MeOH was evaporated off under reduced pressure to afford a residue of 3,4-dihydroxyphenylacetyl methyl ester. The crude was purified by flash-column chromatography using (heptane:ethyl acetate 50:50) to give 100 mg (98%) of 11 as oil.^{1}H NMR ($CDCl_3$ 400 MHz) δ 6.74 (s, 0H), 6.73 (d, *J* = 8.9 Hz, 1H), 6.62 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.42 (s, 1H), 6.21 (s, 1H), 3.71 (s, 2H), 3.51 (s, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.9, 143.9, 143.2, 125.9, 121.7, 116.4, 115.5, 52.5, 40.5. Rf:0,55 using (heptane:ethyl acetate 50:50).Yellow spot is obtained staining with permanganate solution. The chemical-physical data are in accordance with literature[17].

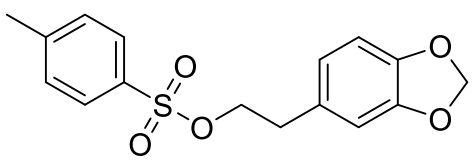


methyl 2-(benzo[d][1,3]dioxol-5-yl)acetate (2c) Dichloromethane (140 µL, 2.2 mmol) and CsF (400 mg, 2.64 mmol) were added to a solution of (2b) (100mg, 0.55 mmol) in anhydrous DMF (2 mL), and the mixture was refluxed for 3 h with stirring. After cooling, the reaction mixture was extracted with CH_2Cl_2 and the organic layer was

washed with 5% aq $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated in vacuo to dryness. The residue was purified by flash chromatography using as eluent CH_2Cl_2:hexane (60:40) furnishing 30 mg (43%) of 3,4-methylenedioxyphenylacetyl methyl ester 12 as a pale yellow oil. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 6.76 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 2.0 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.66 (d, *J* = 2.0 Hz, 0H), 3.81 (t, *J* = 6.5 Hz, 2H), 2.78 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 147.8, 146.2, 132.2, 121.9, 109.3, 108.4, 100.9, 63.8, 38.9. Rf:0,35 using (CH_2Cl_2:hexane 60:40). Yellow spot is obtained staining with permanganate solution. The chemical-physical data are in accordance with literature[17].

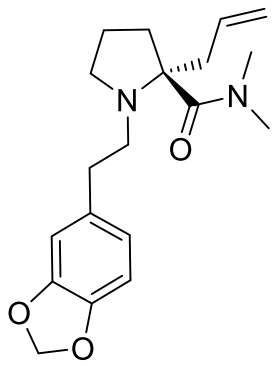


2-(benzo[d][1,3]dioxol-5-yl)ethan-1-ol (2d) A 0.2 M solution of 3,4-dihydroxyphenylacetic acid (2c) (10mg, 0.05 mmol) in dry tetrahydrofuran was added to a suspension (1.95 mg, 0.05 mmol) of $LiAlH_4$ in the same solvent (1 mL) dropwise, under magnetic stirring and at 0°C. Soon after, the mixture was heated until reflux and left under reflux for 2 h. Afterward, the reaction mixture was cooled (0°C) and treated with ethyl acetate (2 mL), water (2ml), 15 % of aqueous sodium hydroxide (2 mL), and was stirred for 15 min, and then was add anhydrous magnesium sulphate and stirred other 15 min, finally the mixture was filtered and then concentrated under reduced pressure. The residue was purified by flash chromatography using as eluent ethyl heptane:ethyl acetate (20:80) furnishing 7.7 mg (87%) of 13 as a pale yellow oil. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 6.76 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 1.7 Hz, 1H), 6.68 (dd, *J* = 7.8, 1.7 Hz, 1H), 3.81 (t, *J* = 6.5 Hz, 2H), 2.79 (t, *J* = 6.5 Hz, 2H), 1.48 (s, 2H).^{13}C NMR ($CDCl_3$, 101 MHz) δ 147.8, 146.2, 132.2, 121.9, 109.3, 108.4, 100.9, 63.8, 38.9. Rf:0,45 using (heptane:ethyl acetate 20:80). Yellow spot is obtained staining with permanganate solution. The chemical-physical data are in accordance with literature[18].



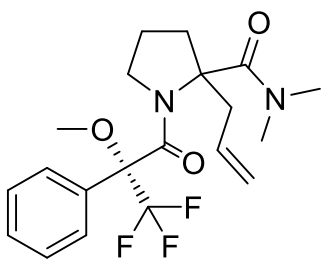
2-(benzo[d][1,3]dioxol-5-yl)ethyl 4-methylbenzenesulfonate (2f) To a dry round-bottom flask equipped with a stirbar under N_2 were added of TsCl (9.5 mg 0.50 mmol), DMAP (0.55 mg, 0,05 mmol), NEt_3 (12 μL, 0.90 mmol), and 0.5 mL of DCM. The resulting mixture was cooled to 0° C, and a solution of (2d) (7.50 mg, 0.45 mmol) in 0.5 mL of DCM was added dropwise. The mixture was allowed to warm to room temperature and was stirred overnight. The solution was then washed with sat. aq. $NaHCO_3$ (1 × 1 mL) and H_2O (1 × 1 mL). The combined aqueous layers were extracted with DCM (1 × 5 mL) and the combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The residue was purified by flash chromatography using as

eluent ethyl heptane:ethyl acetate (20:80) furnishing 15 mg (48%) of 14 as a white solid. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.70 (d, *J* = 8.5 Hz, 1H), 7.31 – 7.28 (m, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.58 – 6.54 (m, 1H), 5.92 (s, 1H), 4.15 (t, *J* = 7.0 Hz, 1H), 2.86 (t, *J* = 7.0 Hz, 1H), 2.44 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 147.7, 146.5, 144.7, 132.9, 129.9, 129.8, 127.9, 127.0, 121.9, 109.2, 108.3, 100.9, 70.8, 35.1, 21.7. IR (film): 1507 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{16}H_{17}O5_S$ $(M+H)^+$ 321.0791; found 321.0798. Rf:0,85 using (heptane:ethyl acetate 20:80). Yellow spot is obtained staining with permanganate solution.



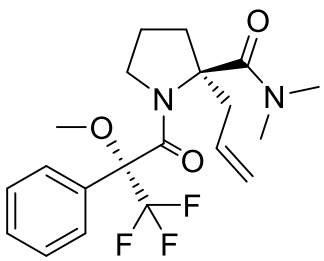
(R)-2-allyl-1-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-N,N-dimethylpyrrolidine-2-carboxamide (6) Tosylate 14 (130mg, 0,71mmol) was added to a mixture of a secondary amine, NaI (106mg, 0.71mmol), and K_2CO_3 (295mg, 2.14mmol) in CH_3CN (0.5 M). The reaction was heated to reflux for 16 h and then cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL), and the solid was filtered off. The filtrate was concentrated under vacuum, and the residue was dissolved in CH_2Cl_2. The resulting solution was washed with 5 % of aqueous NaOH, brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified through silica gel flash chromatography using as eluent ethyl heptane:ethyl acetate (50:50) furnishing 146 mg (62%) of 15 as a yellowish-transparent oil. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 6.68 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 6.57 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.99 – 5.90 (m, 1H), 5.87 (dd, *J* = 2.0, 1.5 Hz, 2H), 5.01 – 4.99 (m, 1H), 4.98 – 4.96 (m, 1H), 3.20 (ddd, *J* = 9.0, 8.0, 4.0 Hz, 1H), 2.86 (s, 6H), 2.82 – 2.74 (m, 1H), 2.75 – 2.60 (m, 3H), 2.57 – 2.49 (m, 2H), 2.08 – 1.94 (m, 3H), 1.88 – 1.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.1, 147.4, 145.6, 137.4, 134.7, 121.4, 116.9, 109.0, 107.9, 100.7, 71.6, 50.5, 49.9, 37.7, 36.4, 35.1, 31.2, 22.0. IR (film): 1787 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{19}H_{26}N_2O_3$ $(M+H)^+$ 330.1938; found 330.1944. Rf:0,50 using (heptane:ethyl acetate 50:50). Yellow spot is obtained staining with permanganate solution.

Evaluation of enantiomeric ratio by means NMR study of the diasteromeric mosher amide derivatives.



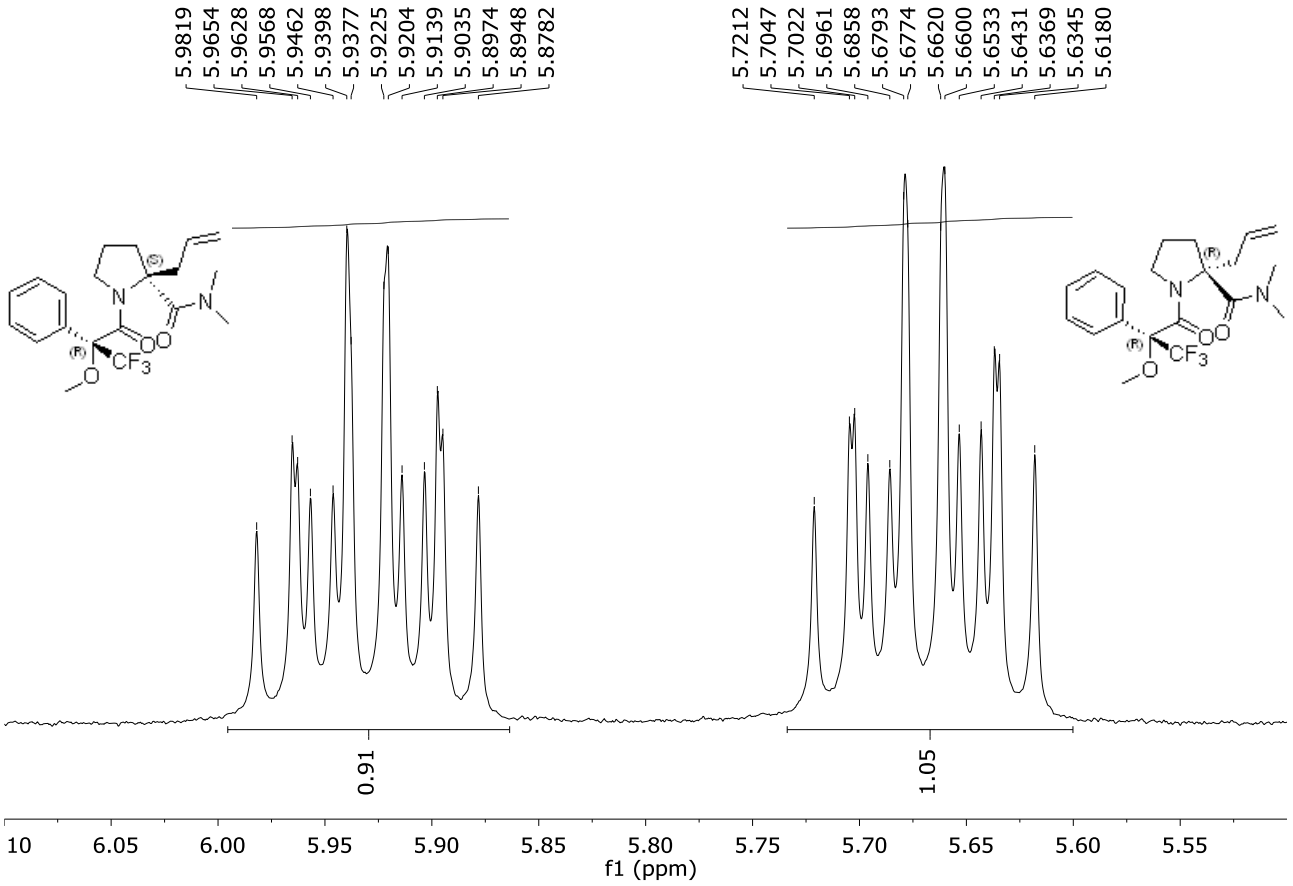
2-allyl-N,N-dimethyl-1-((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)pyrrolidine-2-carboxamide rac-(7) In a vial under argon were added the prolineamide 9 (30 mg, 0,21mmol, racemate) 0,5 ml of anhydrous DCM, (45 μL,

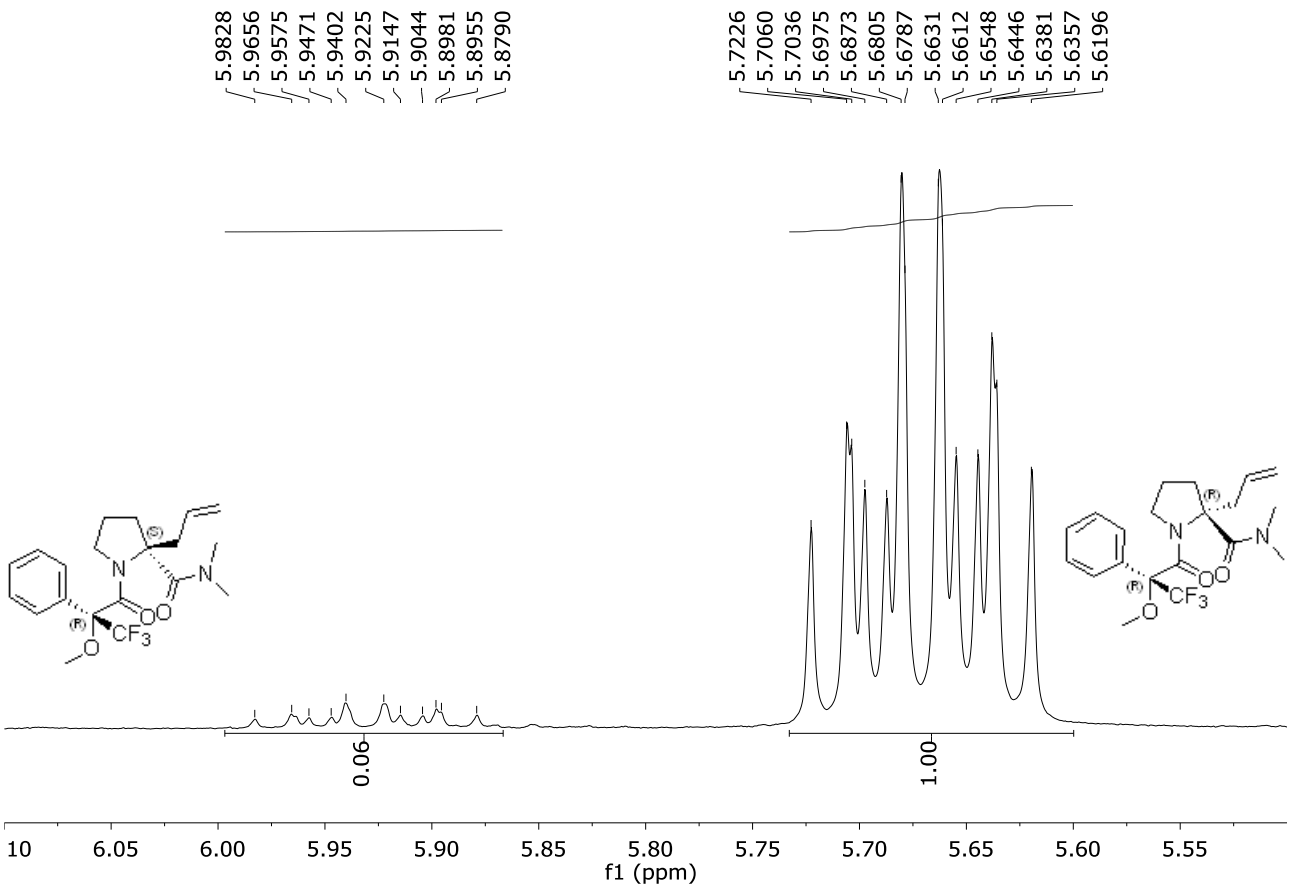
0.26mmol) of DIPEA and finally (R)-Mosher's acid chloride (40, μL, 0.21mmol). The reaction was heated at 40°C over night and after the complete consuming of starting material, $NaHCO_3$ (1ml) was added and extracted with DCM (3 x 1mL), the combined organic phases was dried on Na_2SO_4, and reduced under high vacuum, furnishing 65 mg (100%) of (7) as a light yellow transparent oil. ^{1}H NMR ^{1}H NMR ($CDCl_3$ 400 MHz, racemate) δ 7.75 – 7.72 (m, 1H), 7.64 – 7.66 (m, 2H), 7.40 – 7.36 (m, 6H), 5.97 – 5.90 (m, 1H), 5.70 – 5.61 (m, 1H), 5.16 – 5.02 (m, 4H), 3.94 (q, *J* = 2.0 Hz, 3H), 3.73 (q, *J* = 2.0 Hz, 3H), 3.63 (ddd, *J* = 11.5, 8.0, 5.5 Hz, 1H), 3.50 (ddd, *J* = 11.5, 8.5, 7.0 Hz, 1H), 3.38 (ddt, *J* = 14.0, 6.5, 1.5 Hz, 1H), 3.09 ddt, *J* = 14.0, 7.5, 1.0 Hz, 1H)), 3.03 (s, 3H), 3.02 – 2.96 (m, 1H), 2.94 (s, 3H), 2.93 – 2.82 (m, 2H), 2.78 (dt, *J* = 11.5, 7.5 Hz, 1H), 2.07-1.93 (m, 2H), 1.96-1.98 (m, 2H), 1.86 – 1.77 (m, 1H), 1.73 – 1.64 (m, 3H), 1.57 – 1.50 (m, 1H), 1.29 – 1.22 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, racemate) δ 171.4, 170.9, 165.2, 164.2, 134.6, 134.2, 133.6, 132.8, 129.3, 129.2, 127.9, 127.9, 127.6, 127.2, 125.2, 122.3, 118.8, 118.5, 77.4, 77.3, 77.1, 76.7, 72.3, 72.1, 56.0, 55.6, 47.4, 47.3, 39.9, 39.1, 38.4, 38.3, 33.5, 32.4, 31.9, 29.0, 24.1, 23.8, 22.7, 14.1. IR (film): 1757 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{20}H_{26}F_3N_2O_3$ $(M+H)^+$ 399.1890; found 399.1878. Rf:0,60 using (heptane:actone (50:50) + 1% $iPNH_2$). Yellow spot is obtained staining with permanganate solution.



(R)-2-allyl-N,N-dimethyl-1-((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)pyrrolidine-2-carboxamide (7) In a vial under argon were added the prolineamide 6 (30 mg, 0,21mmol, enatipure) 0,5 ml of anhydrous DCM, (45 μL, 0.26mmol) of DIPEA and finally (R)-Mosher's acid chloride (40, μL, 0.21mmol). The reaction was heated at 40°C over night and after the complete consuming of starting material, $NaHCO_3$ (1ml) was added and extracted with DCM (3 x 1mL), the combined organic phases was dried on Na_2SO_4, and reduced under high vacuum, furnishing 65 mg (100%) of (7) as a light yellow transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$, enantiopure) δ 7.63 – 7.60 (m, 2H), 7.39 – 7.37 (m, 3H), 5.71 – 5.62 (m, 1H), 5.12 – 5.03 (m, 2H), 3.94 (q, *J* = 2.0 Hz, 3H), 3.50 (ddd, *J* = 11.5, 8.5, 7.0 Hz, 1H), 3.38 (ddt, *J* = 14.0, 6.5, 1.5 Hz, 1H), 3.03 (s, 6H), 2.93 – 2.83 (m, 3H), 2.04 – 1.98 (m, 1H), 1.96 – 1.91 (m, 1H), 1.72 – 1.66 (m, 1H), 1.55 – 1.48 (m, 1H), 1.28 – 1.22 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, enantiopure) δ 171.35, 165.22, 134.17, 133.55, 129.27, 129.17, 128.02, 127.96,

127.93, 127.21, 125.13, 122.25, 118.47, 72.31, 56.02, 47.35, 39.10, 38.41, 33.49, 31.89, 29.03, 24.10, 22.70, 14.13.): 1758 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{20}H_{26}F_3N_2O_3$ $(M+H)^+$ 399.1890; found 399.1876. Rf:0,60 using (heptane:actone (50:50) + 1% $iPNH_2$). Yellow spot is obtained staining with permanganate solution.





$d.r. = \frac{RR}{RS+RR} = \frac{1.00}{1.00+0.06} = d.r.$ = 94(RR):6(RS) Considering the rearrangement reaction of (8) is performed only starting from the S form (99,9% purity), and for the racemate there is no preferential reaction on of the two enantiomers with the R-Mosher chloride is possible to transfer the d.r. to e.r. => $e.r.$ = 94(R):6(S).

6. Notes and References

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