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Beyond simple proton transfer processes: domino reaction between 4-substituted indoles and nitroethene as a new gateway to ergot alkaloid

Tesi di laurea sperimentale

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Summary

Abstract

The multimodal biology activity of ergot alkaloids is known by humankind since middle ages. Synthetically modified ergot alkaloids are used for the treatment of various medical conditions. Despite the great progress in organic syntheses, the total synthesis of ergot alkaloids remains a great challenge due to the complexity of their polycyclic structure with multiple stereogenic centres. This project has developed a new domino reaction between indoles bearing a Michael acceptor at the 4 position and nitroethene, leading to potential ergot alkaloid precursors in highly enantioenriched form. The reaction was optimised and applied to a large variety of substrate with good results. Even if unfortunately all attempts to further modify the obtained polycyclic structure failed, it was found a reaction able to produce the diastereoisomer of the polycyclic product in excellent yields. The compounds synthetized were characterized by NMR and ESIMS analysis confirming the structure and their enantiomeric excess was determined by chiral stationary phase HPLC. The mechanism of the reaction was evaluated by DFT calculations, showing the formation of a key bicoordinated nitronate intermediate, and fully accounting for the results observed with all substrates. The relative and absolute configuration of the adducts were determined by a combination of NMR, ECD and computational methods.

L'attività biologia multimodale degli alcaloidi della segale cornuta è conosciuta dal genere umano sin dal Medioevo. Alcaloidi dell'ergot sinteticamente modificati vengono utilizzati per il trattamento di varie condizioni mediche. Nonostante il grande progresso nella sintesi organica, la sintesi totale di alcaloidi dell'ergot rimane una grande sfida a causa della complessità della loro struttura policiclica con più centri stereogenici. Questo progetto ha sviluppato una nuova reazione domino tra indoli recanti un accettore di Michael nella posizione 4 e nitroetene, portando a potenziali precursori di alcaloidi dell'ergot in forma altamente enantioarricchita. La reazione è stata ottimizzata e applicata ad una grande varietà di substrati con buoni risultati. Anche se purtroppo tutti i tentativi di modificare ulteriormente la struttura policiclica ottenuto sono falliti, è stata trovata una reazione in grado di produrre il diastereoisomero del prodotto policiclico in ottime rese. I composti sintetizzati sono stati caratterizzati mediante analisi NMR e ESIMS confermando la struttura e il loro eccesso enantiomerico è stata determinata mediante HPLC fase stazionaria chirale. Il meccanismo della reazione è stato valutata mediante calcoli DFT, che mostrano la formazione di un intermedio nitronato bicoordinato chiave. La configurazione relativa e assoluta degli addotti è stata determinata dalla combinazione di analisi NMR, ECD e metodi computazionali.

1 - Introduction

1.1 Ergot alkaloids[1]

Ergot alkaloids are one of the most attractive alkaloid classes due to their multimodal biology activities and the possibility of development of new medicinal drugs. Some of them have been used in medical field as vasoconstrictors or for the treatment of nervous system disorders (Parkinson's disease), some others have been illegally used as psychedelic substances, such as the well-known LSD. The biological properties of these molecules are not yet totally understood and are still object of intense research activities, due to the complexity of the nervous system and the complex way the ergot alkaloids might interact with it: multiple neuroreceptors might be interacting simultaneously and the effect might change according to the alkaloid structure.

Natural ergot alkaloids are mainly produced by two orders of fungi and three families of plants. Fungi producing ergot alkaloids belong to the order of *Eurotiales* and *Hypocreales*, the most relevant fungus being *Claviceps purpurea*, an ergot fungus that grows mainly on the ears of rye and also on related cereal and forage plants. It grows a kernel called *Sclerotium clavus* which is a compact mass of hardened fungal mycelium containing the food reserve of the fungus. Consumption of cereal contaminated by this fungus can lead to ergotism, a disease that can cause convulsion and even dry gangrene.

The ergot alkaloids are characterized by the tetracyclic ergoline ring system, or by the related tricyclic alkaloids open among the N(6) and the C(7) (ergoline numbering). They are categorized as clavines, lysergic acid and its simple amides, and ergopeptines (*Figure* 1).

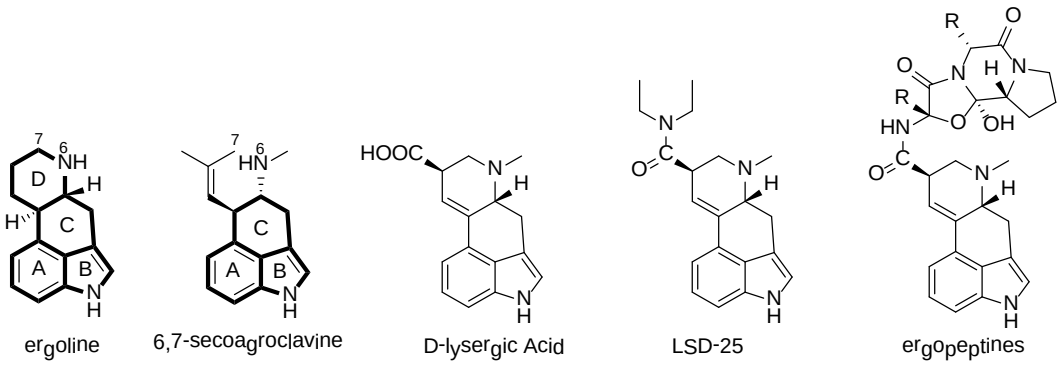


Figure 1

[1] C. L. Schardl, D. G. Panaccione, P. Tudzynki "Ergot Alkaloids – Biology and Molecular Biology" In *The Alkaloids*, Ed. G. A. Cordell, Elsevier **2006**, *63*, 45.

1.1.1 Biosynthesis of ergot alkaloids

Nearly half a century of intensive investigations on the biosynthetic precursors, enzymes and pathways have been additionally informed by the recent identification of gene clusters that are likely to encode all or most of the enzymes for ergot alkaloids biosynthesis.

Although it was already broadly used to produce ergot alkaloids through fermentation culture, the mechanism to obtain this molecule was still unknown until 1959. In that year researchers used radioactive carbon labelled tryptophan to feed the fungus by injecting the marked compound in its sclerotium. In this way, it was possible to follow step by step the synthesis of ergoline inside the cells.

The first step in the biosynthesis of ergoline (*Figure 2*) consists in the prenylation of the aromatic ring. This step was further supported by the identification and isolation of tryptophan dimetylallytransferase from the fungi culture. This enzyme transfers the dimethylallyl moiety from dimethylallyl-diphosphate (DMAPP) to the 4-position of the indole ring of L-tryptophan.

The second step consists in the methylation of the α-amine by an N-methyltransferase. This step is confirmed to be subsequent to the prenylation and preceding the cyclisation because neither the N-methylated-tryptophan is able to receive the prenylation, nor the prenylated NH_2 tryptophan is able to cyclise to obtain the desired alkaloid.

The following steps consist mainly in oxidations and reductions to give the final ergoline scaffold.

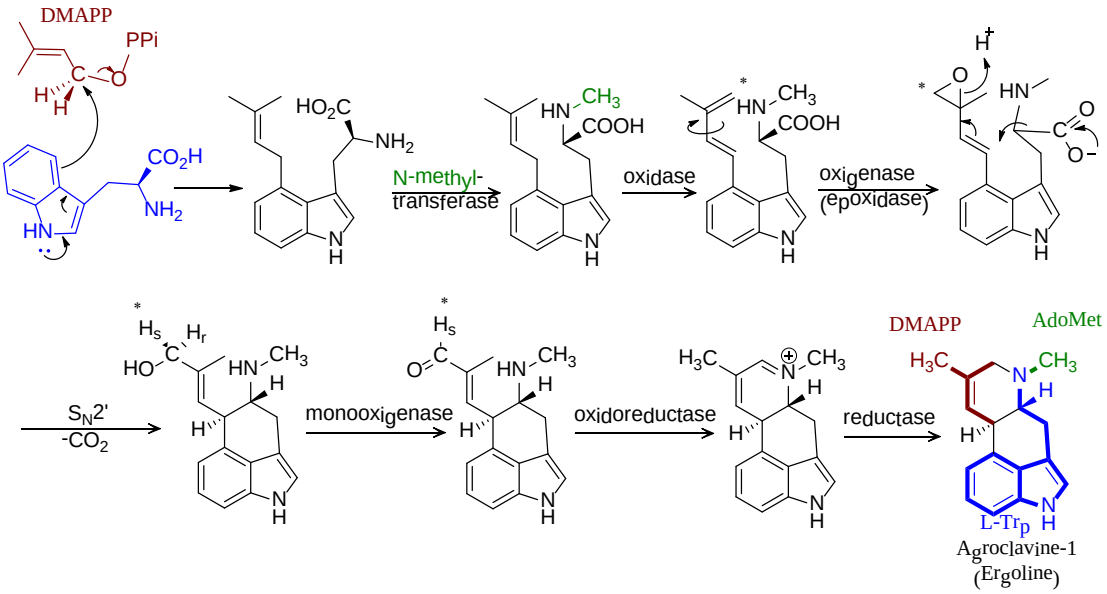


Figure 2

1.1.2 A synthetic entry to the ergot alkaloids

Many synthetic studies directed toward ergot alkaloids (secoagroclavine, chanoclavine, agroclavine, lysergic acid etc.) have been reported due to their interesting medical properties and challenging production from nature.

In *Figure 3* is shown an interesting example of a synthetic route to obtain 6,7-secoagroclavine, in nine steps starting from a commercial available compound.[2]

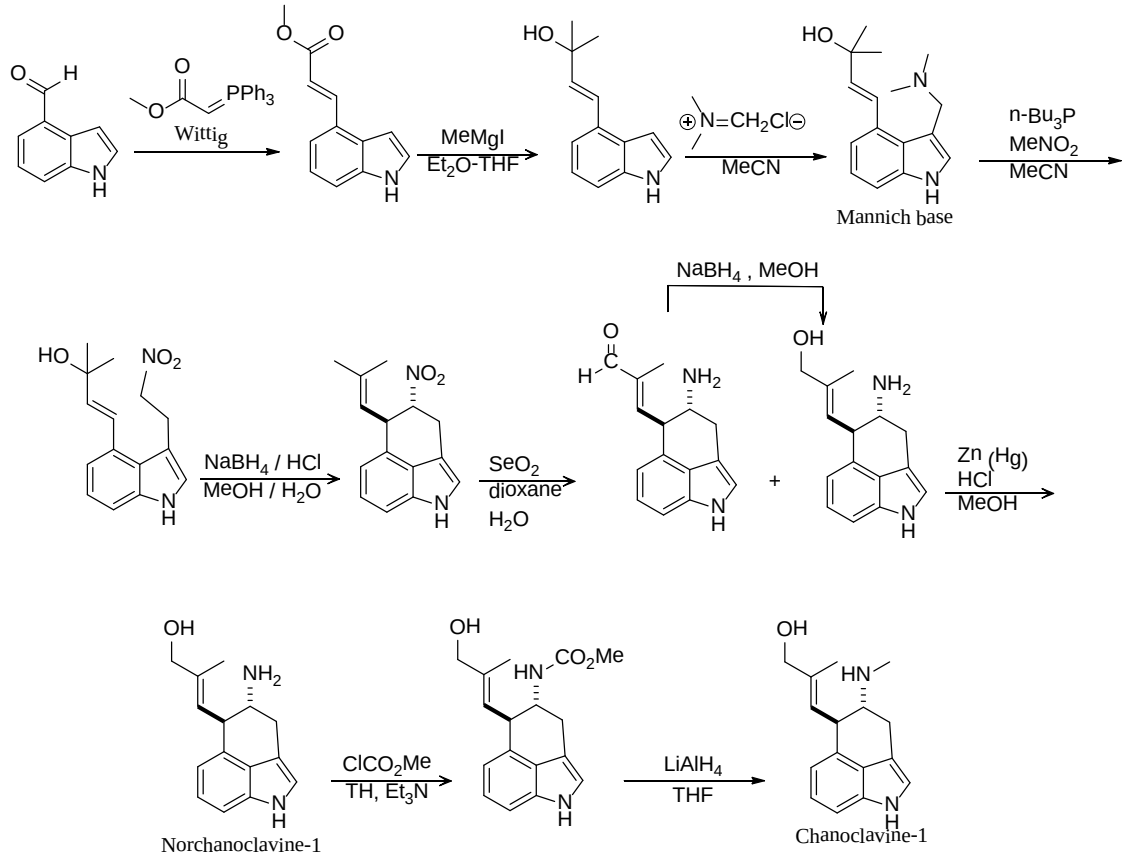


Figure 3

The first step consists in a Wittig reaction, which transforms the carbonyl group of indole-4-carbaldehyde in the corresponding vinyl compound in *trans* configuration.

The obtained product is then treated with a large excess of methyl magnesium iodide in diethyl ether and THF, in order to obtain the allylic tertiary alcohol, which is transformed to the corresponding Mannich base through a reaction with N,N-dimethyl-methylene iminium chloride in acetonitrile. Afterwards, the dimethylamino moiety of this compound is substituted with nitromethane, in the presence of tributylphosphine as catalyst in order to obtain the analogous nitro compound.

[2] F. Yamada, Y. Makita, M. Somei, *Heterocycles*, **2007**, *72*, 599.

The subsequent step involves the cyclisation of this compound in order to form the characteristic three-fused ring of 6,7-secoagroclavine. This reaction (*Figure 4*) exploits the concept of the formation of the nitronate ion through a base, and the contemporaneous formation of a stabilized carbocation thanks to a Lewis or Brønsted acid. In these conditions, the nitronate ion is able to perform a nucleophilic attack to the double bond causing the ring closure only if the nitronate is not quenched by protonation. A combination between $NaBH_4$ and HCl in a solution of MeOH and water, proved to be optimal for obtaining the desired tricyclic compound, which revealed to be a mixture of two diasteroisomers enriched in the *trans*-isomer.

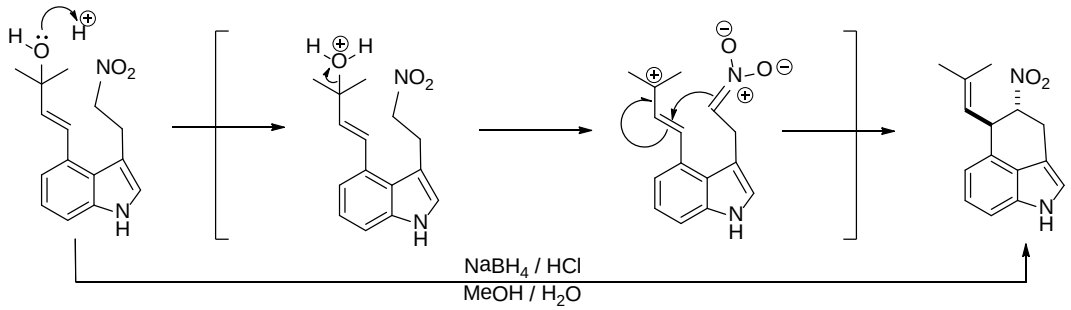


Figure 4

Afterwards, one of the allylic methyl group is oxidised with selenium dioxide (*Figure 3*). Subsequent reduction of the aldehyde with $NaBH_4$ in MeOH gives the corresponding primary allylic alcohol. Reduction of the nitro group with zinc in refluxing methanolic HCl provides (±)-norchanoclavine as a single product.

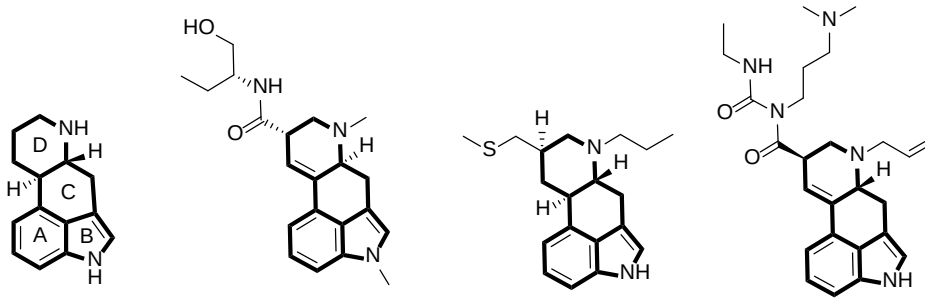
The last two steps give the methylation of the amine group, first treating the (±)-norchanoclavine with methyl chloroformate and triethylamine in THF to form the corresponding carbamate, which is reduced with $LiAlH_4$ in THF forming the natural compound chanoclavine-I in racemic form.

Further transformations on the chanoclavine structure may provide synthetic access to other ergot alkaloids.

1.1.3 Synthetic derivatives of ergot alkaloids in medicine

The double nature of ergot alkaloids as drugs and as lethal poisoning agents is documented since the ancient time: in Mesopotamia, (modern day Iraq) doctors used ergot alkaloids to treat uterine atonia and as post-partum bleeding inhibitor. In Europe, poisoning caused by ergot-infected rye bread is known since middle ages, where there have been large epidemics of ergotism in many regions. Even in the 20th century, outbreaks of ergot poisoning were reported in Ethiopia and India. In the late 18th century begun the investigation on this alkaloids and on their dual behaviour, after isolation and determination of their structure. The way to the synthetic modification to ergot alkaloid was opened.[3]

Nowadays different pathologies are treated by using as drugs synthetically modified ergot alkaloids, such as methysergide (*Figure 5*), used for the prophylaxis of cluster headache and migraine headache. Pergolide was instead used for the treatment of Parkinson disease but was soon withdrawn by the producers due to the non-negligible side effect (hearth valve damage and cardiac fibrosis). This drug was replaced with another ergot alkaloid derivative, cabergoline.



ergoline Methysergide Pergolide Cabergoline

Figure 5

[3] C. Chirivì, G. Fontana, D. Monti, G. Ottolina, S. Riva, B. Danieli, *Chem. Eur. J.*, **2012**, *18*, 10355.

1.2 Brønsted–Lowry acids and Lewis acids

The IUPAC definition of a Brønsted acid is *"a molecular entity capable of donating a hydron (proton) to a base or the corresponding chemical species"*. This model of proton donors and proton acceptors in acid–base reactions is an improvement of the Arrhenius theory, which was more limited, stating that bases had to contain the hydroxyl group.

The IUPAC definition of a Lewis acid is "a molecular entity (and the corresponding chemical species) that is an electron-pair acceptor and therefore able to react with a Lewis base to form a Lewis adduct, by sharing the electron pair furnished by the Lewis base". This definition allows to extend the concept of acid species to molecules and atoms without hydrogens, such as metal cations, and trigonal planar species (*Figure 6*).

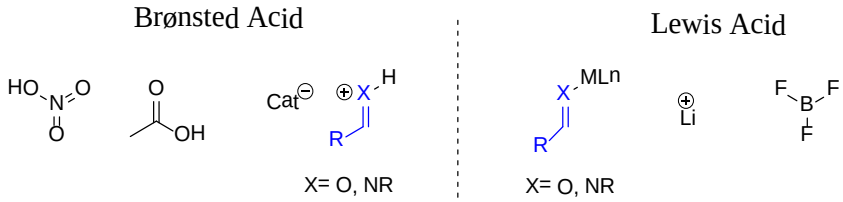


Figure 6

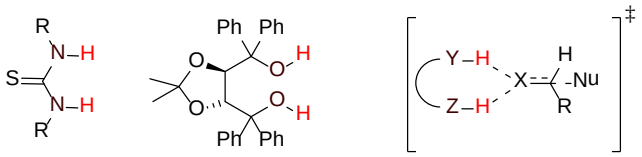
The most important role of a Lewis acid as catalyst consists in the activation of C=X bonds (X = O, NR) by the coordination to a non-ligand lone pair, with the consequent increase of electrophilicity of the system resulting in the promotion of a nucleophilic addition. The combination of a Lewis acid with a chiral ligand brings to the formation of catalysts suitable for asymmetric synthesis. These kinds of catalysts have been widely studied and have led to the development of astonishing levels of enantioselectivity in several reactions.

While Lewis acids have been broadly used for the formation of C-C bonds, Brønsted acids has been used mainly for the hydrolysis and formation of esters, acetals, etc., even if it is possible to imagine an activation of a carbonylic group by a Brønsted acid similar to the Lewis acid one (*Figure 6*). Indeed, the synthetic usefulness of Brønsted acids as catalysts for the formation of C-C bonds has recently emerged as a powerful tool for the development of new enantioselective reactions, in which chiral Brønsted acid systems are used as a new class of catalysts.

Chiral Brønsted acids are mainly dived into two categories:

Neutral Brønsted acids, such as thioureas and diols. This class of catalyst develops a generic acid catalysis, namely the reaction is promoted by hydrogen bond stabilization of

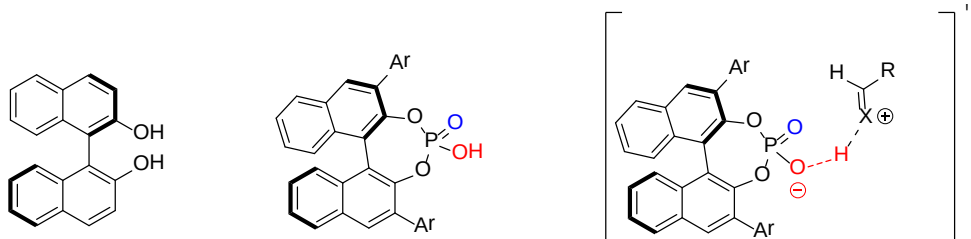
the transition state resulting from a nucleophilic addition to the carbonyl group (*Figure 7*).



Modified Thiourea | TADDOL | X = O, NR; Y/Z = O, N

Figure 7

Strong Brønsted acids, such as BINOL derivatives and their phosphoric acids. This class of catalyst transfers partially or completely an acidic proton to the substrate, activating it for a subsequent nucleophilic attack (*Figure 8*).



($^{(R)}$-BINOL) | Ar=Phenyl; Ar=3,5-bis(trifluoromethyl)phenyl; Ar=2,4,6-triisopropylhenil (TRIP); Ar=9-Antracenyl | X= O, NR; Specific Acid Catalysis

Figure 8

In particular, BINOL derived phosphoric acids have been found to be extremely useful in the promotion of asymmetric transformations. These catalysts have been developed and synthetized first by Terada and Akiyama.[4] The hindered rotation of the bi-arylic bond allows the creation of dissymmetry in the structure. To enhance the enantioselectivity induced by the catalyst, aromatic substituents are generally installed at the 3 and 3'-positions of the BINOL core.

However, as it will be shown in the next section, the type of catalysis does not only depend on the strength of the acidic catalyst but also on the basic properties of the substrate. On the other hand, most of the best performing Brønsted acid catalysts do not

[4] D. Uraguchi, M. Terada, *J. Am. Chem. Soc*., **2004**, *126*, 5356; T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed*., **2004**, *43*, 1566.

exert their activity simply by coordinating the electrophilic component, but rather through a bifunctional mode of action (bifunctional catalysts).

1.3 Friedel-Crafts reactions of indoles to nitroalkenes catalysed by Brønsted acids[5]

Friedel-Crafts additions are a set of reactions in which different kind of electrophiles, such as alkyl or acyl halides, are attacked by a nucleophilic aromatic ring, using a strong Lewis acid as catalyst for their activation. The well-known mechanism of the reaction manly consists of three steps: formation of a carbocation mediated by the catalyst, nucleophilic attach of the aromatic ring to the carbocation and fast rearomatization with loss of a proton (*Figure 9*).

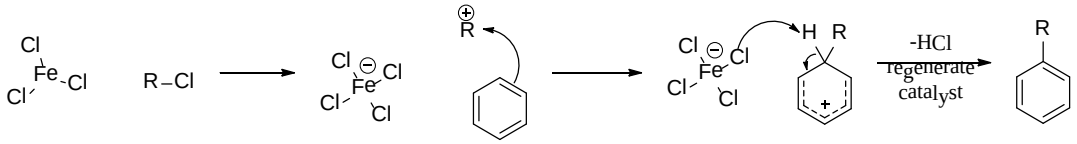


Figure 9

Friedel-Crafts reactions occur not only with halogen derivatives, but also with compounds bearing a double bond conjugated with strong electron-withdrawing groups as nitroalkenes. The synthesis of compounds such as tryptamine derivatives can indeed be realised via the Friedel-Crafts reaction between indoles and nitroalkenes (*Figure 10*).

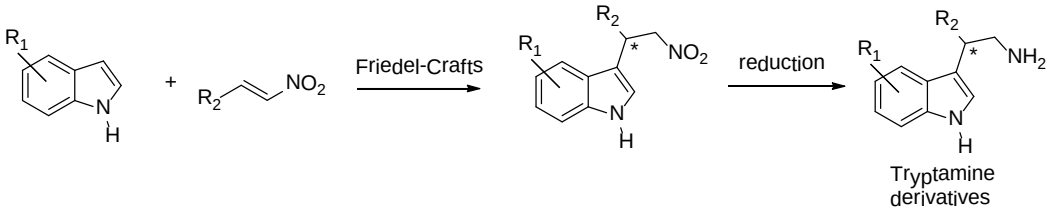


Figure 10

These reactions, including asymmetric versions, can be efficiently promoted by Brønsted acids. In particular, the already mentioned BINOL-derived phosphoric acids have proven

[5] L. Bernardi, A. Ricci, chapter 2.3, In "*Catalytic Asymmetric Friedel-Crafts Alkylation*", Eds. M. Bandini, A. Umani-Ronchi, Wiley-VCH, Weinheim, **2009**, 67.

to be very efficient chiral catalysts for these transformations.[6] The mechanism of these reactions, shown in

Figure 11, was later investigated by computational studies,[7] which showed that the BINOL derived phosphoric acids act as bi-functional catalysts, in line with the generally accepted model of phosphoric acid catalysed reactions.[8] In particular, in the transition state of the reaction, whereas the acidic moiety (OH) of the catalyst coordinates the nitro group, bearing a negative charge, the phosphoryl group (P=O) coordinates the hydrogen of the indole core. This double coordination results in a highly ordered transition state, thus favouring the formation of the product with high enantioselectivity, and can assist subsequent proton transfer processes from nucleophile to electrophile. Finally, it can be noted that even if these catalysts were introduced in one of the previous paragraphs as promoters for specific acid catalysis, in this case due to the low basicity of the nitroalkene (the electrophile), protonation in the ground state of the reaction can be considered as negligible, thus the reaction should be rather considered to proceed through a general acid catalysed pathway.

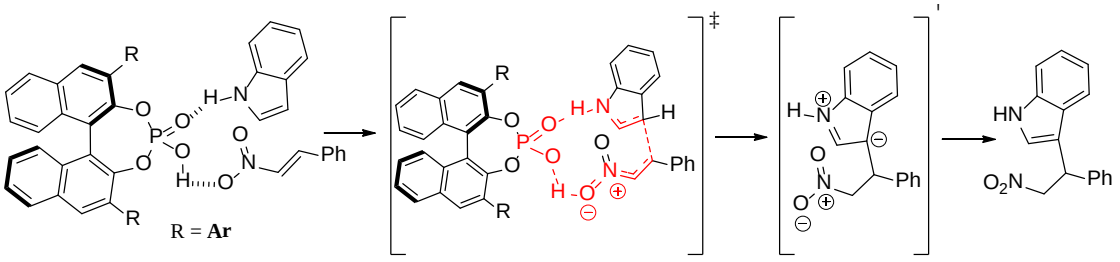


Figure 11

1.4 A new approach to natural compound synthesis: domino reactions[9]

The complexity and structural diversity of natural products have fascinated organic chemists for a very long time. Millions of years of evolution have allowed Nature to develop ingenious synthetic strategies and reaction pathways for the construction of architectural complexity. The blueprints of biosynthesis are based on some key elements, namely cascade reaction sequences and the avoidance of protecting-group strategies; the field of chemical synthesis is young, with its beginnings dating back to the early 1800's.

[6] J. Itoh, K. Fichibe, T. Akiyama, *Angew. Chem. Int. Ed.*, **2008**, *47*, 4016.
[7] C. Zheng, Y.-F. Sheng, Y.-X. Li, S.-L. You, *Tetrahedron*, **2010**, *66*, 2875; T. Hirata, M. Yamanaka, *Chem. Asian J.*, **2011**, *6*, 510.
[8] L. Simón, J. M. Goodman, *J. Org. Chem.*, **2011**, *76*, 1775.
[9] C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.*, **2010**, *2*, 167; A. M. Walji, D.W. C. MacMillan, *Synlett*, **2007**, 1477.

Curiously, chemical synthesis appears capable of building almost any known natural product, isolated in small quantities, yet it seems to be many decades away from operational strategies or technologies that will allow access to complexity on a scale suitable for society's consumption. The synthesis of complex natural compounds actually can be performed only in small scale; in fact, traditional approach adopted in multistep synthesis is not applicable on industrial scale. The main disadvantage of multistep synthesis is the purification and isolation of the key compound before and after each step, causing the inevitable loss of product.

This stands in contrast with the biosynthesis of complex structures, such as taxol (commercialized under the name of paclitaxel) which is a classic example. The shortest multistep synthesis of this compound consists in 37 steps with an overall yield of 0.4%. The superefficient biosynthesis, instead, consists in only 4 consecutive step and is shown in *Figure 12*. The geranylgeranyl-pyrophosphate (GGPP) is turned into the polycyclic compound by the *Taxadiene Synthase*, taxadiene is then chemoselectivel oxidised, acylated and coupled with a side chain, all these step are consecutive and, obviously, done in the same flask called plant cell.

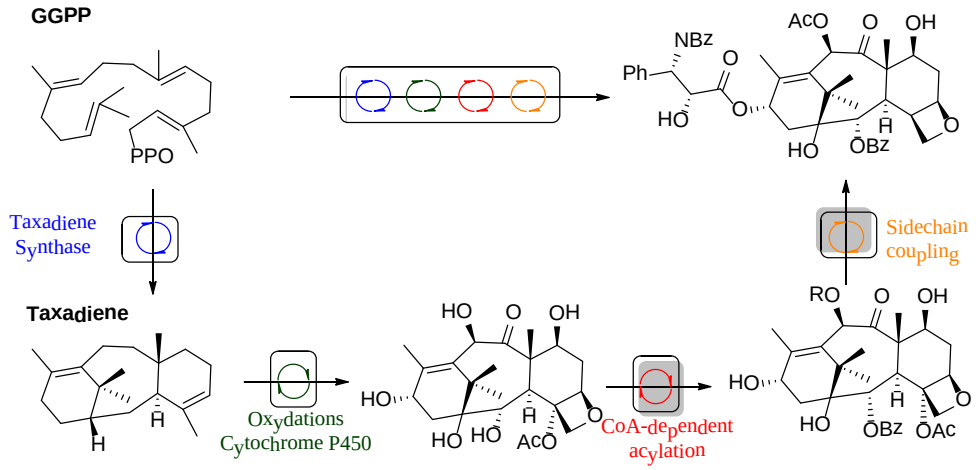


Figure 12

Following the footsteps of nature, in the last years a great amount of new "cascade" or "domino" reactions have been developed, especially by using organic molecules as catalysts. Whereas the majority of these transformations employs chiral secondary amines and/or chiral Brønsted bases as catalysts, very few of them are based on Brønsted acids, for reasons clearly outlined later in this thesis. A relevant example is the domino Friedel-

Crafts-Henry addition of indole to a functionalised nitroalkene,[10] which proceeds in the presence of a positively charged acidic catalyst, and leads to *cis*-amino-indanol precursors (*Figure 13*). This structure is a very important building block in asymmetric syntheses as it is included in a large number of chiral catalysts, including the one used for the reaction itself.

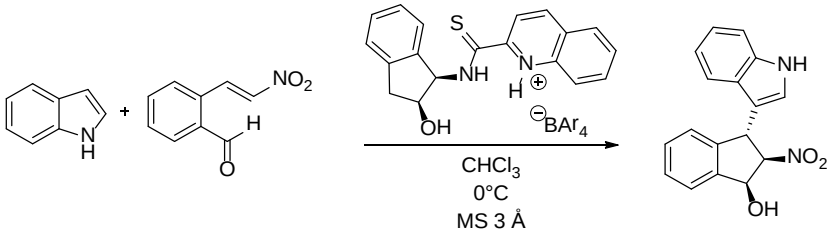


Figure 13

The main problem of this reaction consists in the presence of two possible acceptors such as the nitroalkene and the aldehydic groups. Thanks to the catalyst, it was possible to differentiate between these acceptors and perform a domino organocatalytic asymmetric Friedel-Crafts-Henry reaction, with the catalyst acting as a Brønsted acid by coordinating the substrates with hydrogen bonds (*Figure 14*).

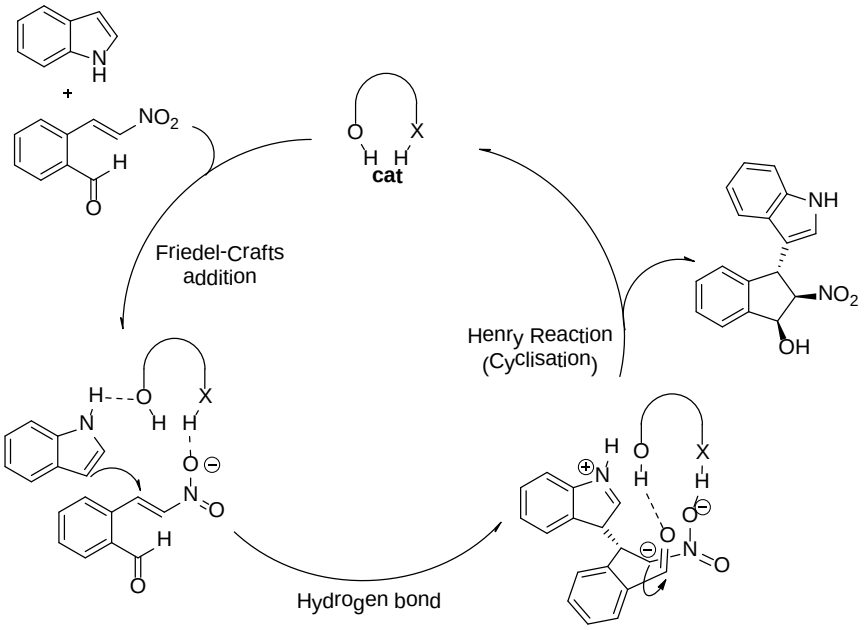


Figure 14

[10] C. C. J. Loh, I. Atodiresei, D. Enders, *Chem. Eur. J.*, **2013**, *19*, 10822.

2 - Objectives

Based on these considerations, we have planned in this project the development of a new domino reaction between 4-substituted indoles **1** and nitroethene **2** (*Figure 15*). The resulting products **4** feature the same atom connectivity of ergot alkaloids. Indeed, a product of type **4** featuring an ester group (R_2 = MeO) has been used to prepare 6,7-secoagroclavine in racemic form. These adducts present two stereocenters on the newly formed ring; in order to obtain compounds useful for the synthesis of ergot alkaloids in enantioenriched form, the stereochemistry of these centres must be controlled. To this purpose, we planned to use a chiral Brønsted acid **3**, such as the ones described in the introduction, which should activate nitroethene **2** for the Friedel-Crafts reaction, triggering a subsequent cyclization through an intramolecular nitro-Michael addition, affording the desired polycyclic compounds **4**, potential synthetic precursors of ergot alkaloids.

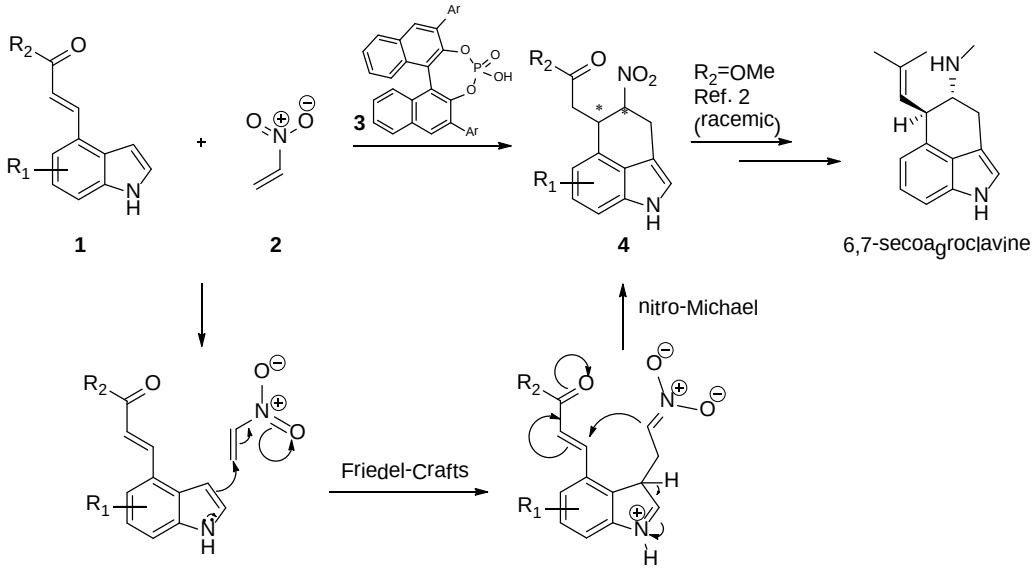


Figure 15

Despite the simplicity of the sequence shown, consisting in a nucleophilic attack followed by a ring-closure, a series of aspects makes this reaction particularly challenging (*Figure 16*).

*Avoidance of a simple proton transfer reaction leading to un-cyclised product **4'***. As shown in the introduction, Brønsted acid catalysts are very effective in promoting, through a bifunctional mechanism, reactions proceeding through the transfer of a proton from a nucleophile to an electrophile. However, in our case it is necessary for the

cyclisation to occur that the nitronate intermediate does not get protonated, to react instead with the Michael acceptor present at the 4-position of the indole core. To favour this latter process, it could be envisioned the use of a strongly electron withdrawing group in the indole Michael acceptor. However, this strategy is unfeasible, as it would suppress the Friedel-Crafts step.

*Low nucleophilic reactivity of the C3 carbon in indoles **1**:* the nucleophilic site at C3 of the indole is conjugated with the Michael acceptor at C4 (electron withdrawing group); as a result the C3 is considerably less electron rich than in a non-substituted indole. Therefore, it can be expected that the first Friedel-Crafts process requires much more substrate activation than usual additions of unsubstituted indoles to electrophiles, as already observed in iminium ion catalysed Friedel-Crafts reactions of substrates **1** with enals.[11] Furthermore, on these premises, the employment of a highly electron poor Michael acceptor, which could solve the issues described in the previous point, results impracticable.

Control of the absolute and relative stereoselectivity of the reaction: all the previously described Friedel-Crafts additions involved in domino reaction sequences present the generation of the chirality of the product during the Friedel-Crafts step, in which the indole adds to a prochiral substrate; in our case, the chirality is formed during the nitro-Michael step. Consequently, the catalyst must maintain the coordination with the nitro group not only during the Friedel-Craft step, but also in the cyclisation.

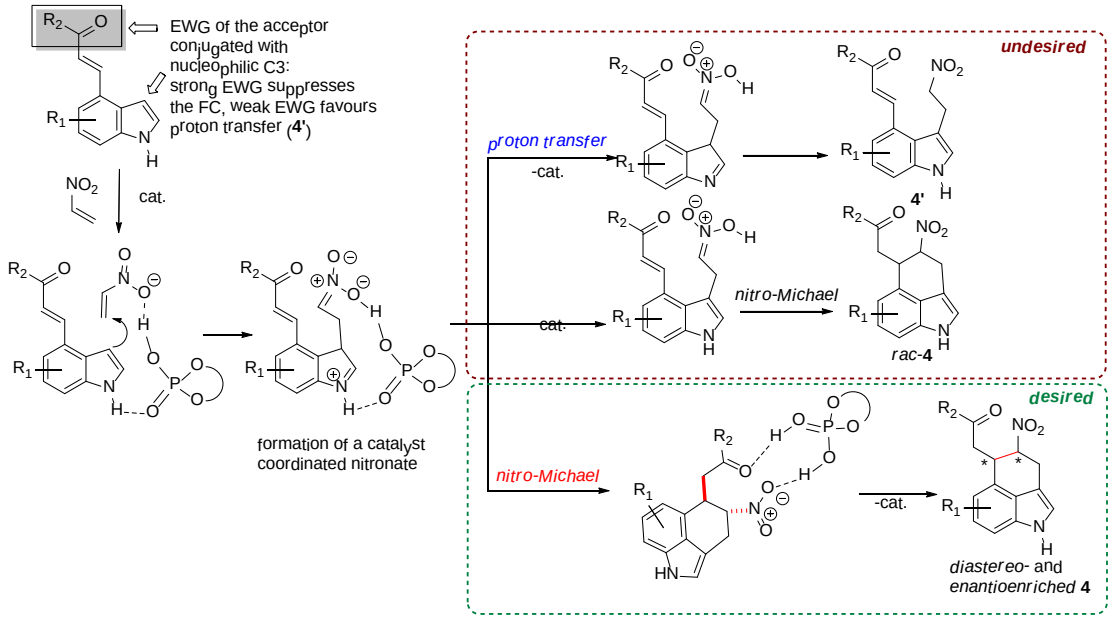


Figure 16

[11] L. Caruana, M. Fochi, M. Comes Franchini, S. Ranieri, A. Mazzanti, L. Bernardi, *Chem. Commun.*, **2014**, *50*, 445.

*Poor stability of nitroethene **2** under acidic conditions:* use of this particular olefin is mandatory as the general structure of ergot alkaloids features a methylene group at the indol-3-yl benzylic position, accessible only with nitroethene **2**. However, nitroethene **2** is a highly reactive olefin, and can undergo various side reactions, from oligomerisation to additions of other nucleophiles, which can be promoted by the acidic catalyst. On the other hand, the high reactivity of this Michael acceptor should somehow compensate the low nucleophilicity of indoles **1**.

Before the commencement of this thesis work, some preliminary studies carried out in the same laboratory showed the feasibility of the planned project. In particular, very promising results were obtained in the reaction between the phenyl α,β-unsaturated ketone **1a** and nitroethene **2**, catalysed by the phosphoric acid derivative **3** (also known as (*R*)-TRIP) at rather high loadings, in toluene as solvent (*Figure 17*). The reaction gave the exclusive formation of the desired product **4a** as a single *trans*-diastereoisomer with good conversion and high enantioselectivity. Importantly, the undesired uncyclised product **4'a** was detected only in trace amount.

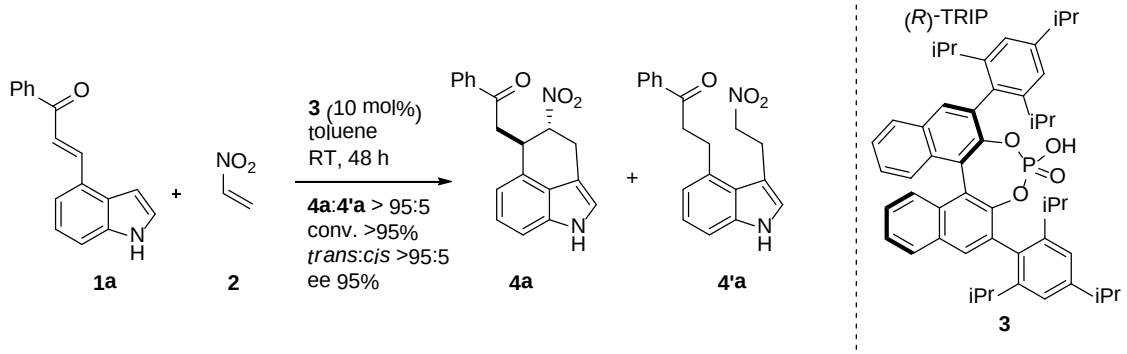


Figure 17

On these promising bases, the specific objectives of the work described in this thesis consist in:

- *optimisation of the reaction conditions*: study of the influence of the solvent (type and amount), reaction temperature and additives on the reaction outcome, in order to lower the catalyst loading while developing a robust and general protocol for the reaction.
- *study of the generality of the reaction*: by varying the indole substrate **1**, both at the Michael acceptor and at the indole portion, to indicate the possible variations tolerated by the optimised protocol and its limitations.

- *product elaborations*: study of possible transformations on the catalytic products **4**, with the ultimate goal of obtaining ergot alkaloids or synthetic precursors in enantioenriched form.
- *mechanistic proposal*: study of the mechanism of the reaction through a computational approach, in collaboration with Dr Stefano Santoro and Prof. Fahmi Himo of the University of Stockholm (SE). The exclusive obtainment of compound **4a** in the presence of a phosphoric acid catalyst is very intriguing, since it could be expected that such an acidic catalyst would be able to promote the proton transfer to the intermediate nitronate leading to the undesired, uncyclised product **4'a**, thus calling for a mechanistic investigation.
- *determination of the relative and absolute configuration of the adducts*: by exploiting computational methods combined with NMR and ECD experiments, in collaboration with Prof. Andrea Mazzanti.

3.-.Results and discussion

3.1 Preparation of the initial substrates

We started the project by preparing some indole substrates **1a-k**, bearing a Michael acceptor at the 4-position, through the Wittig olefination of the corresponding 4-formyl indoles (*Figure 18*). Phosphorous ylides for these olefinations were prepared through an easy basic washing (NaOH 2 M) of the corresponding phosponium salt suspension in dichloromethane. In some cases, the phosponium salt was not commercially available, it was therefore necessary to prepare it, with an alkylation of triphenylphosphine with the corresponding halide derivative. The 4-formyl indole derivative and the Wittig reagent were mixed in a solution of toluene or toluene/dioxane and heated to reflux. The obtained alkene products **1** were found to be only in the *trans*-isomer form, as verified through ^{1}H NMR spectroscopic analysis after purification with silica gel chromatography. All the Wittig reagents were stabilized ylides, i.e. ylides with electron withdrawing groups (in our case a ketone or an ester) able to stabilize the negative charge. This type of ylides is known to promote the formation of the *trans*-olefin selectively.[12]

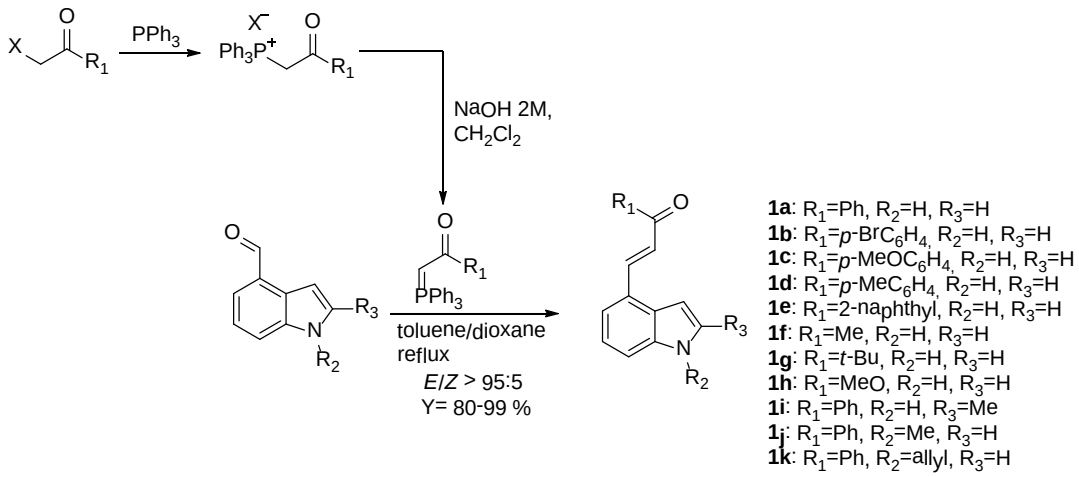


Figure 18

Whereas the unsubstituted 4-formyl (R_2=H, R_3=H) indole is commercially available, its corresponding N-alkyl counterparts are not. They were prepared through a simple alkylation of the indole nitrogen of 4-formyl indole. Using methyliodide and allylbromide

[12] J. March, chapter 16, In "Advanced Organic Chemistry", 4th Edition, Wiley-VCH, **1992**.

as alkylating agents under basic conditions, it was possible to obtain the corresponding N-alkyl-4-formyl indoles (*Figure 19*), ready for the olefination step, after purification by silica gel chromatography.

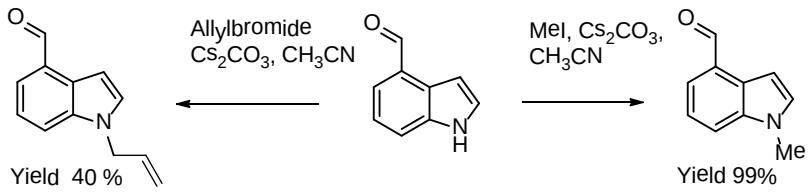


Figure 19

In addition, the 2-methyl indole aldehyde is not commercial. Its synthesis consisted in a multi-step sequence applied to 3-methylisoquinioline,[13] a commercial product, as shown in *Figure 20*:

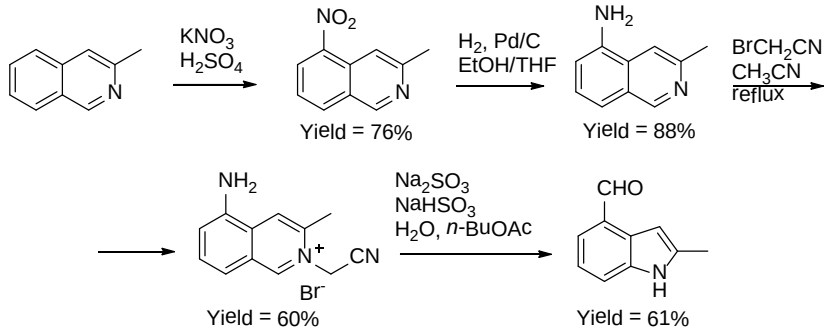


Figure 20

Nitration of the isoquinoline followed the classic procedure, employing a sulphonitric mixture at 0 °C; the reaction showed to be regioselective as expected with the predominant formation of the compound substituted with the nitro group at the 5-position, with trace of the 8-substituded compound. Thus, the product had to be purified by crystallization and subsequent purification of the mother liquor through silica chromatography, with an overall yield even superior than the one reported in literature. The following reduction of the nitro group to an amine was performed by keeping the nitro derivative under a hydrogen atmosphere and using carbon supported palladium (Pd/C 10% $^{w}/_{w}$) as catalyst. After filtration with celite in order to remove the catalyst, the crude mixture was purified through crystallization. The preparation of the corresponding N-alkyl-5-aminoisoquinilic salt consisted in the alkylation of the nitrogen of the isoquinoline core, with bromoacetonitrile, performed in acetonitrile under reflux. The

[13] J. M. Muchowaski, *J. Heterocyclic Chem*., **2000**, *37*, 1293.

product suspended in the solvent was recovered from the reaction mixture through filtration. The N-alkyl-5-aminoisoquinolinium salt was then converted in the target formyl indole by heating it for prolonged reaction times in a biphasic water/*n*-BuOAc mixture containing sodium bisulphite and sodium sulphite. The mechanism, shown in *Figure 21*, consists in a basic hydrolysis of the isoquiniolinium with ensuing ring opening, tautomerization of the newly formed enamine to imine and subsequent hydrolysis to ketone. Then, the nucleophilic attack of the amino group to this ketone group occurs, forming a hemiaminal, which dehydrates and then re-aromatize forming the desired 2-methyl-4-formyl indole.

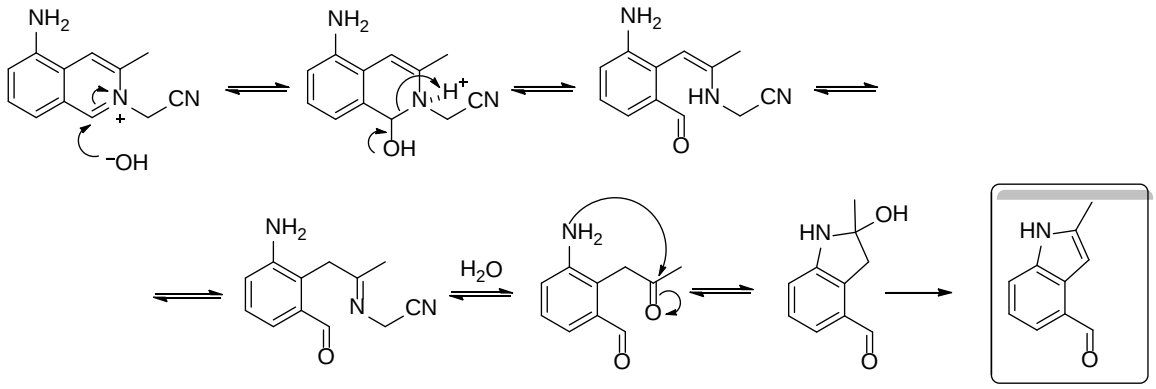


Figure 21

Nitroethene **2** was instead obtained by dehydration of 2-nitroetanol with phthalic anhydride as shown in *Figure 22*.[14] The reaction is performed in a Claisen apparatus under controlled low pressure: nitroethene is distilled as it is formed and condensed in a liquid nitrogen cooled trap. This reactive olefin, obtained in variable yields (25-80%) can be stored for months after a dilution with toluene and keeping the solution at about -20 °C (~1 M solution in toluene, concentration determined by ^{1}H NMR spectroscopic analysis).

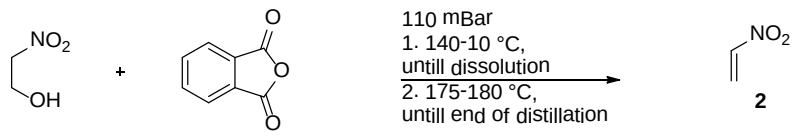


Figure 22

[14] D. Ranganathan, C. B. Rao, S. Ranganathan, A. K. Mehrotra, R. Iyengar, *J. Org. Chem*., **1980**, *45*, 1185.

3.2 Optimisation of the reaction

The first objective of this thesis concerned the optimization of the reaction conditions between indole **1a** and nitroethene **2** catalysed by **3**. Catalyst **3** was previously prepared in the laboratory where I worked on this thesis. Table 1, entry 1 recalls the preliminary results obtained before the start of this thesis and already reported in *Figure 17*, regarding the reaction between the polyfunctionalised indole **1a** and nitroethene **2**. Under those conditions, the desired compound **4a** was obtained as single *trans*-diasteroisomer, without the formation of the proton transfer product **4'a**. The optimal catalyst (*R*)-TRIP **3**, a phosphoric acid derived from (*R*)-BINOL with very large hindering groups placed at the 3 and 3' positions of the binaphthyl scaffold, was identified after a very large catalyst screening, including BINOL and VAPOL derived phosphoric acid, and less acidic thiourea and ureic derivatives. A rational explanation for the very promising enantioselectivity obtained is that the steric hindrance of the 2,4,6-tris-*iso*-propyl phenyl groups allows the acid to create an efficient chiral pocket in which the reaction occurs.

The objective of the optimisation was to find a robust reaction protocol applicable to different substrates, maintaining or even increasing the conversion and the enantiomeric excess and lowering the catalyst loading if possible. The first tests on the reaction consisted in using indoles featuring different phenyl substituents, in order to check if those preliminary conditions were applicable also to compounds slightly different from the simple phenyl derivative **1a**. However, it was immediately discovered that differently substituted phenyl indole, showed a much reduced conversion, presumably due to their lower solubility in toluene (data not shown). Thus, we switched to dichloromethane as solvent, for the much better solubility of all compounds **1** in this chlorinated medium. Fortunately, in this solvent not only the un-substituted compound **1a** gave results comparable to toluene (entry 2), but the other substrates, such as the 4-bromo derivative **1b**, behaved similarly (entry 3).

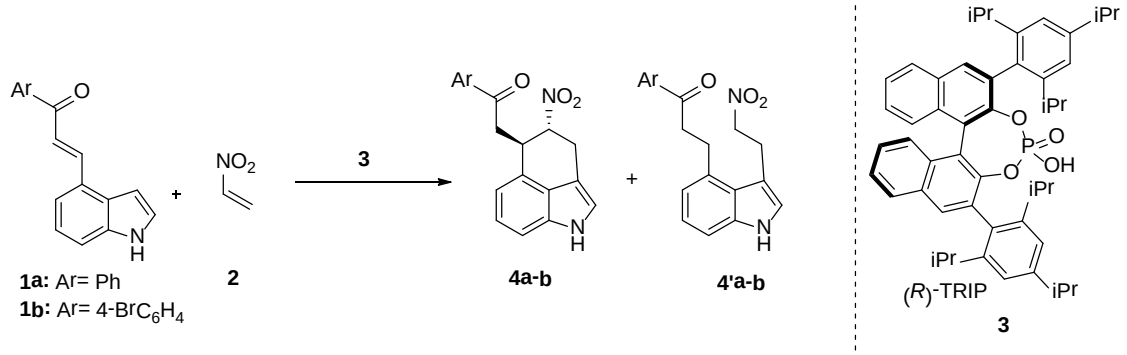


Figure 23

Table 1 Optimisation of the reaction conditions: selected results

Entry[a]	**1**	Solvent	**3** (mol%)	Additives	**T** (°C)	**t** (h)	**Conv.** (%)[b]	**4a** : **4'a**[b]	**ee** (%)[c]
1	**1a**	Toluene	10	-	rt	60	87	>95:5	96
2	**1a**	CH_2Cl_2	10	-	rt	18	80	>95:5	95
3	**1b**	CH_2Cl_2	10	-	rt	24	99	>95:5	95
4	**1a**	CH_2Cl_2	5	-	rt	18	83	>95:5	95
5	**1a**	CH_2Cl_2	5	-	0	60	59	>95:5	96
6	**1a**	CH_2Cl_2	5	MS 4Å [powder]	0	60	89	90:10	97
7	**1a**	CH_2Cl_2	5	MS 4Å [powder]	0	60	19	90:10	-
8	**1a**	CH_2Cl_2	5	MS 4Å [powder]	0	60	<5	-	-
9	**1a**	CH_2Cl_2	5	MS 5Å [powder]	0	60	98	>95:5	84
10	**1a**	CH_2Cl_2	5	MS 5Å [powder]	0	60	<5	29:35	-
11	**1a**	CH_2Cl_2	5	MS 4Å [pellets]	0	60	99	72:27	30
12[d]	**1a**	CH_2Cl_2	5	MS 4Å [powder]	0	60	95	76:19	97
13	**1a**	Dry CH_2Cl_2 (Al_2O_3)	5	-	0	60	69	>95:5	95
14	**1a**	Dry CH_2Cl_2 (dist.)	5	-	0	60	76	>95:5	97
15	**1a**	Dry CH_2Cl_2 (dist.)	5	$MgSO_4$	0	60	>99	>95:5	97
16	**1a**	Dry CH_2Cl_2 (dist.)	2.5	$MgSO_4$	0	60	70	>95:5	97

a Reaction conditions: indole **1a** (0.05 mmol), nitroethene **2** (0.075 mmol, 1.5 equiv., toluene solution), solvent (conc. 0.2 M referred to indole); b Determined by ^{1}H NMR spectroscopy on the crude mixture after filtration through a silica gel plug and evaporation of the solvents. A single *trans*-diasteroisomer was observed in all reactions; c Determined by chiral stationary phase HPLC; d Nitroethene **2** added in two portions (0.06 mmol + 0.06 mmol after 24 h).

The next objective in the optimization was to lower the catalyst loading, and to improve the robustness of the reaction in order to guarantee uniform enantioselectivity with different substrates, by cooling the mixture. Employing 5 mol% catalyst loading, which was attainable at room temperature (entry 4), and performing the reaction at 0 °C the conversion was drastically reduced, but the enantiomeric excess was slightly improved, as expected (entry 5). This behaviour of the reaction might be provoked by different reasons: taking into account the low reactivity of the indole **1a**, the reaction might be considerably slower at 0 °C than the one at room temperature. If this were the case, it would be very difficult to avoid this behaviour. However, considering the phosphoric catalyst, traces of water might decrease its activity, lowering the rate of the reaction. A common practice in order to remove traces of water is the addition of 4-5 Å molecular sieves (MS) to the reaction medium. Accordingly, several tests with different kinds of MS with different

pore diameters and shapes were carried out. The reactions turned out to be irreproducible, showing drastically different conversions under identical conditions, and in some cases even showing the formation of the undesired proton transfer product **4'a** (entries 6-12). These failures suggested us to circumvent the use of molecular sieves. In order to avoid the presence of water in the reaction solvent we tried to use anhydrous dichloromethane (entries 13, 14), obtained either by filtration on basic alumina or, more rigorously, by distillation from CaH_2. The reactions turned again to be reproducible and with the usually good enantiomeric excess, but even if the results in terms of conversions were slightly improved compared to the reaction with reagent grade dichloromethane (entry 5), they were still not fully satisfactory.

It was speculated that another possible reason for the suboptimal conversion might have been the behaviour of nitroethene **2** for the prolonged reaction times employed. First of all, it is a rather volatile compound, which can thus evaporate out from the reaction mixture; furthermore, as mentioned, it is a highly reactive olefin, and can undergo various side reactions, from oligomerization to additions of other nucleophiles, which can be promoted by the acidic catalyst and/or by the additives.
In order to better understand the reaction behaviour, two kinetic studies, one without additives and one with 4Å MS (powder), were carried with the same catalyst loading (5 mol%), 1.2 equivalents of nitroethene **2**, in $CDCl_3$ as solvent at 0 °C. The deuterated solvent was employed in order to follow the reaction with ^1H NMR spectroscopy by simply sampling the mixture and diluting it with further $CDCl_3$. The results in terms of conversion are shown in *Figure 24*: squares refer to **1a** and triangles to nitroethene **2** detected in the reaction mixture.

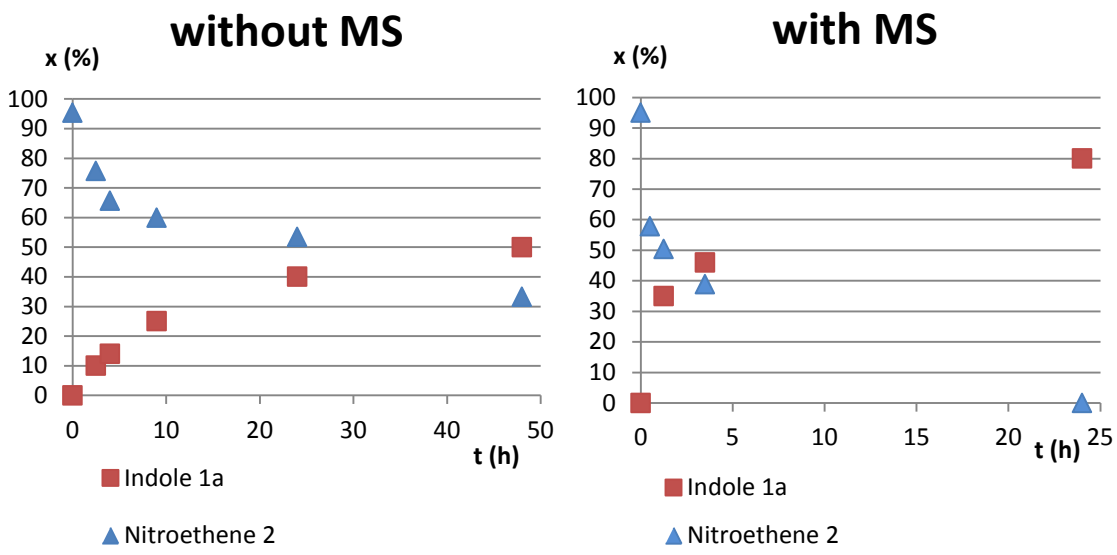


Figure 24

Reactions in $CDCl_3$ without MS revealed nitroethene **2** to be stable during all the reaction time, disproving the hypothesis that the low conversion was caused by oligomerization of this compound. On the contrary, the reaction with the MS revealed the absence of nitroethene already after 24 hours, confirming the incompatibility of the use of molecular sieves in this procedure. It can also be observed that in the reaction in $CDCl_3$ without molecular sieves the rate resulted to be very low, after almost 50 hour only 50% conversion being reached, whereas the same conversion was attained in less than 5 hours with the use of MS, thus substantiating our assumption on the negative influence of the presence of water on catalyst activity ($CDCl_3$ was used without treatment and thus contained considerable amounts of water).

Thus, the absence of water could be considered as a key point for the optimisation of the reaction. As unfortunately MS, the usual drying agents, could not be employed and distillation was not sufficient, this issue was tackled by testing freshly distilled dichloromethane and flame dried $MgSO_4$ powder as alternative drying agent. Finally, as shown in entry 15, it was possible for the first time to reach full conversion in the product **4a** even by employing 5 mol% catalyst loading at 0 °C, still keeping the excellent enantioselectivity attained at this temperature. Importantly, these conditions proved to be fully reproducible, and were thus elected as optimal for the reaction (*Figure 25*), also considering that further reduction in catalyst loading was not applicable (entry 16).

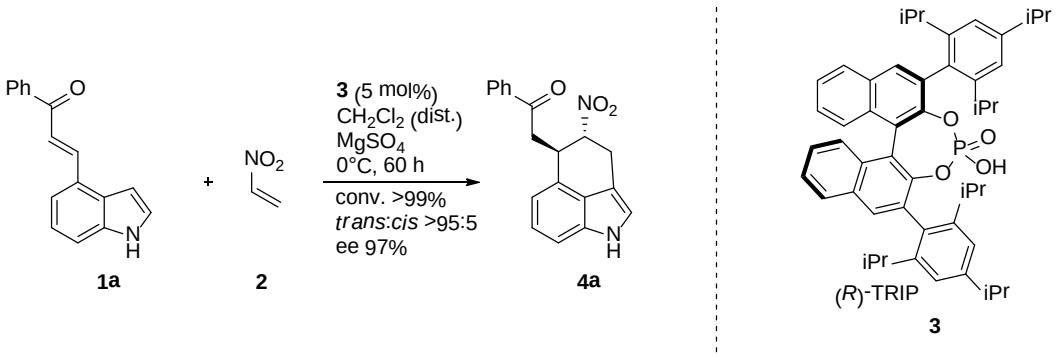

Ph
O
N
H
1a
+
NO2
2
3 (5 mol%)
CH2Cl2 (dist.)
MgSO4
0°C, 60 h
conv. >99%
trans:cis >95:5
ee 97%
Ph
O
NO2
N
H
4a
iPr
iPr
iPr
O
P
O
OH
O
iPr
iPr
iPr
(R)-TRIP
3

Figure 25

3.3 Study of the generality and the limitations of the reaction

Having in our hands a robust reaction protocol, (*Figure 25*), the study of the generality of the reaction was undertaken (*Figure 26* and
Table 2), by varying the structure of the indole substrate **1**, both at the Michael acceptor and at the indole portions.

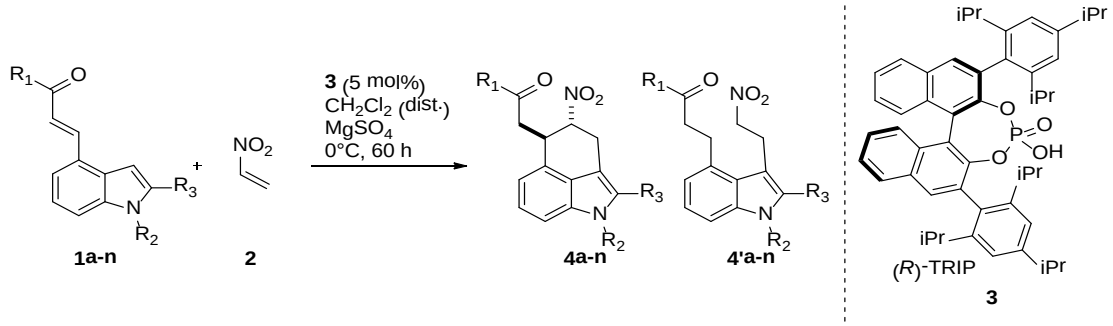


Figure 26

Table 2

Entry[a]	**1**	R_1	R_2	R_3	**4**-Yield[b] (%)	ee[c] (%)
1	**1a**	Ph	H	H	**4a**-95	97
2	**1b**	*p*-BrC_6H_4	H	H	**4b**-99	97
3	**1c**	*p*-$MeOC_6H_4$	H	H	**4c**-91	97
4	**1d**	*p*-MeC_6H_4	H	H	**4d**-99	99
5	**1e**	2-naphthyl	H	H	**4e**-98	97
6	**1f**	Me	H	H	**4f**-99	56
7	**1g**	*t*-Bu	H	H	**4g**-90	94
8[d]	**1h**	MeO	H	H	**4'h**-62	-
9	**1i**	Ph	H	Me	**4i**-90	95
10	**1j**	Ph	Me	H	**4j**-60[e]	nd
11[f]	**1j**	Ph	Me	H	**4j**-75	96
12	**1k**	Ph	Allyl	H	**4k**-48[e]	nd
13[g]	**1k**	Ph	Allyl	H	**4k**-70	94
14	**1l**	$(CF_3)_2CHO$	H	H	**4'l**-58[e]	-
15[d]	**1m**	pyrrol-1-yl	H	H	**4'm**-94	-

a Conditions: indole **1** (0.10 mmol), catalyst **3** (0.005 mmol, 5 mol%), freshly distilled CH_2Cl_2 (300 µL), nitroethene **2** (0.075 mmol, 1.5 equiv., toluene solution), 0 °C, 60 h. b Isolated yield after silica gel chromatography. A single *trans*-diasteroisomer was observed by ^{1}H NMR spectroscopy in the crude of all reactions. c Determined by chiral stationary phase HPLC. d Reaction performed at RT in the presence of activated 4 Å MS for 24 h. e Conversion, determined by ^{1}H NMR spectroscopy. f Reaction performed with 2.25 equiv. of **2**. g Reaction performed at RT with 7.5 mol% catalyst **3**.

The results reported in Table 2 show that with three exceptions commented below, the prepared substrates **1a-m** furnished the expected products **4a-m** as single *trans*-diasteroisomers with excellent results. In particular, considering the ketone group in the

Michael acceptor portion, the reactions with aromatics other than the simple phenyl (substrates **1a**-**e**, entries 1-5) presented outstanding results, furnishing the corresponding products **4a**-**e** in nearly quantitative yields and enantiopure form. With a non-aromatic group such as methyl at the ketone in **1f** the situation drastically changed. A considerable lowering in the enantioselectivity was observed, the corresponding product **4f** being obtained with only 56% ee (entry 6). At first, the low enantioselectivity given by this substrate **1f** was thought to be caused by the absence of a π-stacking interaction between the tris-*iso*-propylphenyl groups of the catalyst **3** and the substituent of the ketone. However, this hypothesis was rejected after the result displayed by the *tert*-butyl derivative **1g**, which furnished adduct **4g** with very good enantiomeric excess (entry 7). Thus, the enantioselectivity of this transformation is mostly influenced by the steric hindrance offered by the substituent present at the ketone of the Michael acceptor, and not by π-stacking interactions between this group and the catalyst **3**. A weaker Michael acceptor (an ester group) could not be employed in the domino reaction, as substrate **1h** gave exclusively the open chain adduct **4'h** (entry 8). Apparently, with this less reactive acceptor the direct proton transfer from indole to nitronate, which gave initial concern about the feasibility of the domino process, prevailed over the desired intramolecular nitro-Michael addition. Interestingly, this substrate **1h** gave a much better yield in the product **4'h** when MS were employed as drying agents, instead of $MgSO_4$, optimal for the other substrates.

Substitution in the indole portion was then briefly inspected with substrates **1i**-**k**. Whereas a methyl substituent at the 2-position of the indole core in **1i** was very well tolerated, as its corresponding adduct **4i** was afforded with very good results (entry 9), alkyl substitution at the indole nitrogen in **1j** and **1k** caused a considerable decrease in reactivity (entries 10,12), the products **4j** and **4k** being produced only in moderate yields under the standard reaction conditions. Nevertheless, slight modifications to the optimised protocol allowed the obtainment of the desired adducts **4j** and **4k** in better yields and very good enantioselectivity (entries 11, 13). The decreased reactivity of these latter substrates was attributed to the unattainable coordination of the indole NH to the Lewis basic moiety (P=O) of catalyst **3**, which provides additional activation in the Friedel-Crafts step through the bifunctional mechanism described in *Figure 11*. The high enantioselectivity observed with these substrates proved instead that this coordination is not present or is not relevant during the step which establishes the chirality of the product in the domino

process, that is the intramolecular nitro-Michael reaction, as discussed thoroughly in the next section.

From a wider point of view, as pointed out in the objectives section, the presence of an ester group on the final polycyclic products **4** would be of great synthetic interest in order to obtain ergot alkaloid precursors. As a simple ester in substrate **1h** did not give the expected polycyclic compound **4h**, promoting instead a direct proton transfer process giving the uncyclised product **4'h**, it was decided to try to synthesise and test indoles bearing at the 4-positions carboxylic Michael acceptors, more reactive than the methyl ester, such as a 1,1,1,3,3,3-hexafluoro-*i*-propyl ester, or a pyrrol-1-yl derivative, that can be easily turned into an ester functionality after the reaction has taken place.

(*E*)-1,1,1,3,3,3-hexafluoropropan-2-yl 3-(1H-indol-4-yl)acrylate (**1l**) was obtained through the esterification of the corresponding acid.[15] To a solution of (*E*)-3-(1*H*-indol-4-yl)acrylic acid at 0 °C, was added 1-ethyl-3-(3-dimethylaminpropyl)carbodiimide, dimethylaminopyridine and the exafluoro-*iso*-propyl alcohol, the reaction was left a 0 °C for two hours, and then warmed to room temperature, obtaining the desired product after chromatographic purification (*Figure 27*).

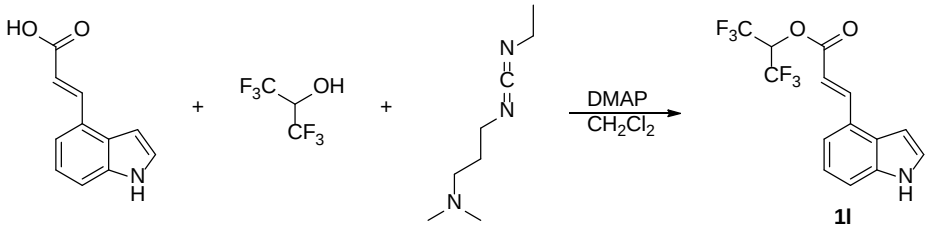


Figure 27

The 1-pyrrolyl derivative **1m** was instead obtained through a three-step synthesis starting from carbonyl diimidazole,[16] which was first treated with pyrrole, leading to di(1*H*-pyrrol-1-yl)methanone (*Figure 28*). Then, the desired ylide was formed through a deprotonation of (methyl)triphenylphosphonium bromide with *n*-BuLi, and subsequent slow addition of the carbonyl dipyrrole at -78 °C. **1m** was finally obtained through the usual Wittig olefination reaction with indole-4-carboxaldehyde.

[15] C. L. Rigby, D. J. Dixon, *Chem. Comm.*, **2008**, *32*, 3798;
[16] B. Vakulya, S. Varga, T. Soòs, *J. Org. Chem.*, **2008**, *73*, 3475.

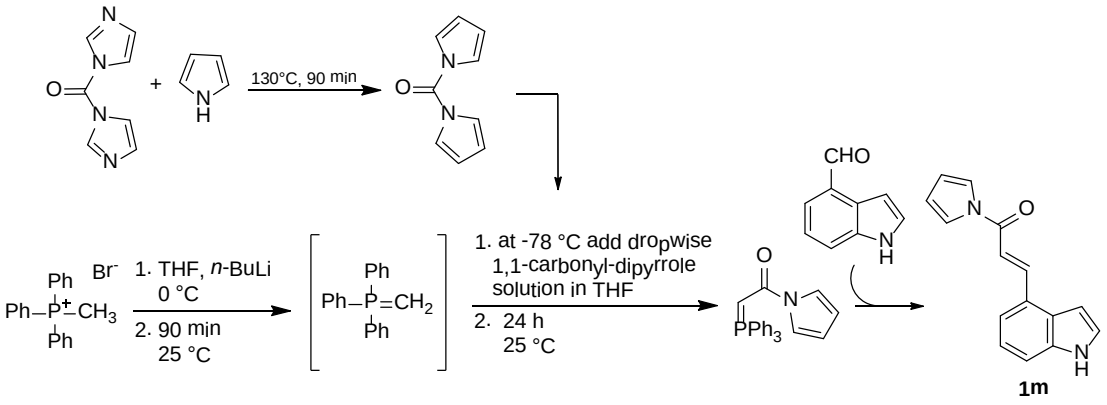


Figure 28

Unfortunately, the results with **1l** and **1m** were the same as the one obtained with the ordinary methyl ester **1h**, only the proton transfer products **1'l** and **1'm** being observed in the crude mixture (entries 14,15).

In order to succeed in achieving a catalytic asymmetric reaction delivering a desired ester substituted adduct, since the Baeyer-Villiger reaction on product **4c** failed (see one of the next sections), a number of different ester surrogates could have been considered at this point. However, to avoid the not-easy preparation of several new substrates, without guaranteed efficiency in the reaction, it was decided to try to rationalise the results obtained so far with a simple computational approach, to have useful hints in the prediction of the behaviour of new substrates bearing ester surrogates, thus avoiding their preparation if not promising.

To better understand the behaviour of the different indole derivatives used so far, a parallel study on their frontier molecular orbital energy was carried out with ChemBio3D ultra 12.0™ . It was speculated that the tendency of the substrates to cyclise giving products **4** instead of the H-transfer adducts **4'** depended on the energy of the LUMO orbital of the Michael acceptor, whereas the enantioselectivity was strongly governed by the sterics of the ketone group. To be reliably predicting, this approach should first be consistent with the experimental results already obtained with the substrates **1a**-**m**.

Regarding the sterics of the ketone group it was observed that aromatic group or large hindering group at the keto group gave the best result in terms of enantioselectivity, while the small methyl group gave a poor enantiomeric excess (*Figure 29*).

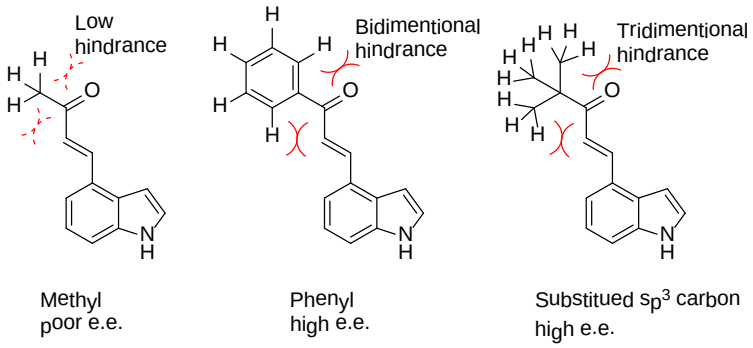


Figure 29

To determine a predicted correlation between the tendency of a substrate to undergo the cyclisation giving the desired product **4** instead of the proton-transfer adduct **4'** it was investigated the energy of the LUMO orbitals relative to the most stable conformer of the different substrates used. Calculated values are shown in Table 3.

Table 3 LUMO Energy of the substrates 1a-m

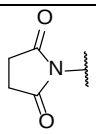
Entry	**1**	R_1	LUMO (eV)	Product
1	**1a**	Ph	-6.548	4a
2	**1b**	*p*-BrC_6H_4	-6.307	4b
3	**1c**	*p*-$MeOC_6H_4$	-6.317	4c
4	**1d**	*p*-MeC_6H_4	-6.464	4d
5	**1e**	2-naphthyl	-6.587	4e
6	**1f**	Me	-6.060	4f
7	**1g**	*t*-Bu	-6.031	4g
8	**1h**	MeO	-5.563	4'h
9	**1l**	$(CF_3)_2CHO$	-5.497	4'l
10	**1m**	Pyrrol-1-yl	-5.765	4'm

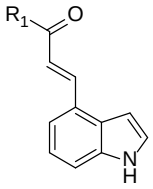
Comparing this *in silico* evaluation with the experimental results, we could find a correlation between the LUMO energy and the capability of the substrates **1** to cyclize: if the LUMO energy of a substrate **1** is higher than ~ -6.0 eV, such as the esters or pyrrol-1-yl substrates **1h-m** (entries 8-10), the proton transfer product **4'** prevails over the cyclised product **4**, which is favoured at the lower LUMO energies featured by ketone substrates **1a-g** (entries 1-7).

Having in hand two simple rules to follow to predict the results of new substrates, that are 1) only substrates featuring a highly hindered ketone substituent give high enantioselectivity, and 2) only substrates with a LUMO energy lower than ~ -6.0 eV give the desired cyclised product **4**, it was possible to screen a large amount of potential substrates for our reaction without losing time in their synthesis.

Part of this screening is reported in Table 4 Summary of substrate screening showing different interesting candidates for the reaction. A tick (✓) corresponds to a presumably highly hindered Michael acceptor, predicting high enantioselectivity, otherwise a cross (✗) when steric hindrance was supposed to be insufficient. This evaluation is a result of a qualitative observation on the optimised Chem3D structures. The same holds for the LUMO energy, a tick corresponds to an energy lower than -6.0 eV, predicting cyclisation, a cross to higher energy and thus proton transfer process.

Table 4 Summary of substrate screening

	R_1	Hindrance	E LUMO		R_1	Hindrance	E LUMO
1)		✗	✗	2)		✗	✗
3)		✓	?	4)		✓	?
5)		✓	✓	**6)**		?	✓
7)		?	✓	8)		?	✓
9)		✓	✓	10)		✓	✓



The failed reaction attempt with the methyl ester substrate **1h** drove the attention towards aromatic, thus more reactive, esters (entry 1); unfortunately, also in these compound the LUMO energy is too high, making esters non-exploitable for this reaction. It was then checked if the corresponding thioester would satisfy our request, but their properties appeared to be the same as the esters (entries 2). Switching to different carbonyls, such as imides, these revealed ambiguous properties. Succinimmide and oxazolidin-2-one featured in fact a borderline LUMO (entries 3,4) even if their hindrance was thought to be sufficient. Moving to ketones, N-methylimidazole showed a promising LUMO energy and was expected to feature a steric hindrance similar to an aromatic group (entry 5). It was also decided to move towards heavier atoms, such as dimethyl phosphonate (entry 6),

an easy removable group convertible into the corresponding ester after the reaction. The phosphonate derivative resulted to be bulky enough to suggest good enantioselectivity and with a good LUMO energy. A literature search showed that the synthesis of acylphosphonate Michael acceptors is usually achieved through the aldehyde intermediate (hydrophosphonylation followed by oxidation). However, the synthesis of the required indol-4-yl-acrylaldehyde was already attempted without success in our laboratory, thus preventing the preparation of this otherwise promising substrate. Large hindering groups such as triphenyl silane (entry 7) and trimethyl silane (entry 8) showed also a good LUMO energy, but the large dimension of the silicon atom raised doubts about the effective hindrance of the group: the large radius of the atom might move his substituent too far from the ketone group lowering their steric effect. Furthermore, the most popular method for the preparation of acylsilane Michael acceptors proceeds through the intermediate aldehyde, similarly to the acyl phosphonate. Therefore, also these substrates were not considered further.

As the *t*-butyl ketone substrate **1g** worked well it was then decided to investigate similar hindering groups: dimethoxy acetal was an interesting group (entry 9), almost as bulky as the *t*-butyl and potentially convertible into an ester or amenable to other useful elaborations, and the 2-hydroxy-*iso*-propyl ketone group[17] (entry 10), widely employed as an ester surrogate in the past, and which bearing two methyl and an hydroxyl groups might be as hindering as the *t*-butyl; both compounds, being ketones, showed a good LUMO energy suitable for the cyclization.

Based on this study, we undertook the preparation of the three potentially useful and synthetically accessible substrates.

(*E*)-4-(1*H*-indol-4-yl)-1,1-dimethoxybut-3-en-2-one (**1n**) was not obtainable through a Wittig reaction. Therefore, we used a Knoevenagel condensation between the carbonyl group of 4-formyl-indole and 1,2-dimethoxypropan-2-one, performed in methanol-water as the solvent in the presence of K_2CO_3 and piperidine at reflux temperature (*Figure 30*).[18]

[17] C. Palomo, M. Oiarbide, J. M. Garcia, A. Gonzalez, E. Arceo, *J. Am. Chem. Soc*., **2003**, *125*, 13942.
[18] S. Tian, R. Hong, L. Deng, *J. Am. Chem. Soc*., **2003**, *125*, 9900; M. Somei, F. Yamada, H. Ohnishi, Y. Makita, M. Kuriki, *Heterocycles*, **1987**, *26*, 2825.

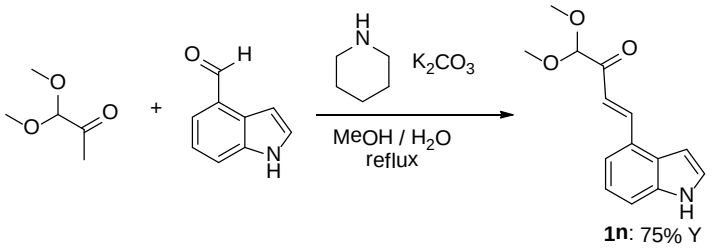


Figure 30

(*E*)-3-(1*H*-Indol-4-yl)-1-(1-methyl-1*H*-imidazol-2-yl)prop-2-en-1-one **1o** could be instead obtained through a Wittig reaction: first, the necessary ylide was synthetized from the corresponding imidazole derivative and triphenylphosphine, and then reacted with the 4-formyl-indole to obtain the desired compound **1o** (*Figure 31*).[19]

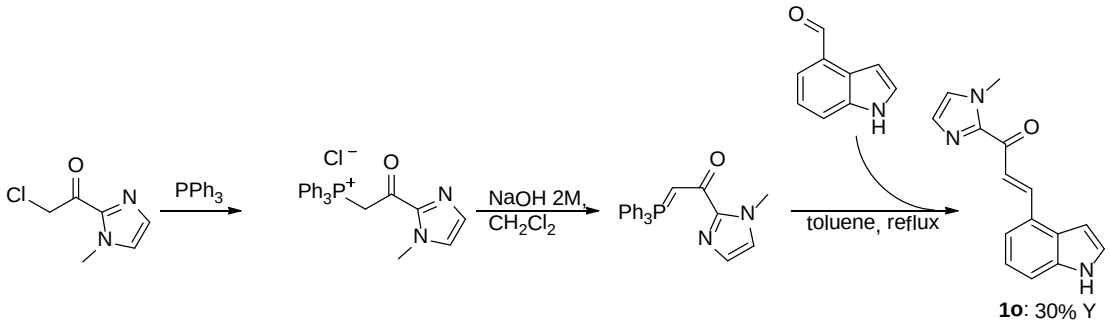


Figure 31

The synthesis of (*E*)-4-hydroxy-1-(1*H*-indol-4-yl)-4-methylpent-1-en-3-one **1p** was initially attempted following two different synthetic routes (*Figure 32*): one taken from the literature for the synthesis of similar ketones (reaction 1), and the other according to the more classic Knoevenagel conditions already used for compound **1n** (reaction 2).

[19] D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Am. Chem. Soc.*, **2005**, *127*, 8942.

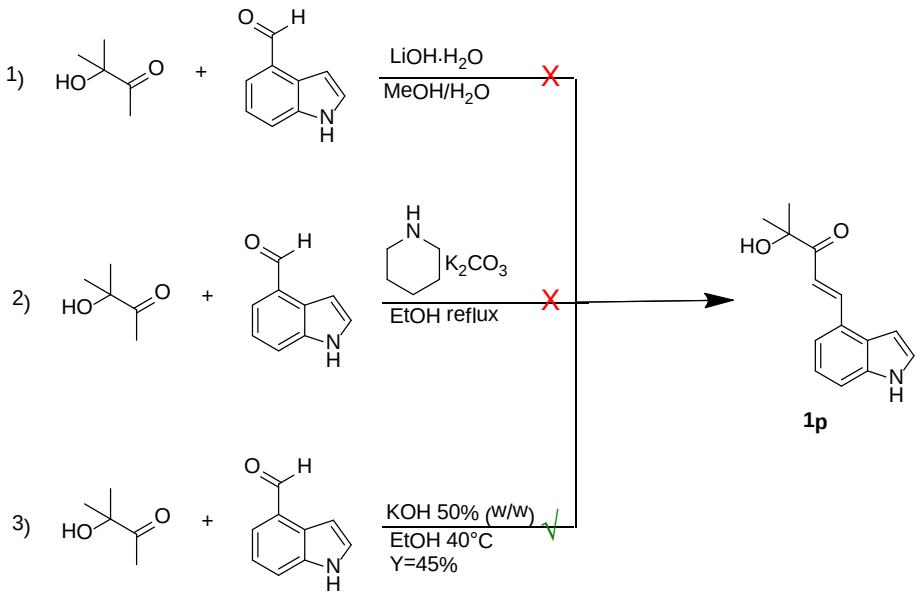


Figure 32

Unfortunately, these two reactions did not give the desired product **1p**, as the ^{1}H NMR analysis of the crude mixtures showed the presence of different by-products. Thus, we tested a third procedure (Reaction 3, *Figure 32*), which was recently developed for very electron rich benzaldehydes.[20] Fortunately, thanks to its drastically basic conditions, this third reaction afforded the desired compound with moderate yield.

Next to these ester surrogates wherein a single carbonyl group is activating the olefin, we considered a structurally distinct compound **1q** derived from Meldrum acid (*Figure 33*). This compound has a promising LUMO energy -6.059 eV. It was obtained through a simple Knoevenagel condensation: to a 0 °C solution of 4-formyl indole in ethanol was added the Meldrum acid and warmed at room temperature.[21]

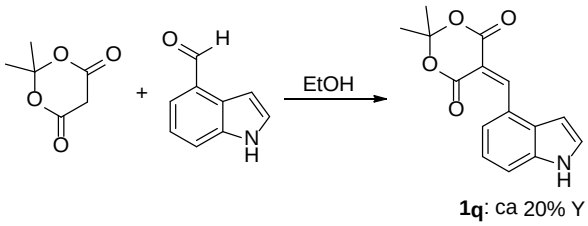


Figure 33

[20] M. V. Mavrov, S. I. Firgang, *Russ. Chem. Bull.*, **2012**, *61*, 606.
[21] O. Kaumanns, H. Mayr, *J. Org. Chem.*, **2008**, *73*, 2738.

Having at hand the four new substrates **1n-q,** various tests on their reactivity were done. When the standard optimised conditions did not give satisfactory results, as it will be the case for most of these substrates, different catalyst loadings, temperatures and drying agents were also tested.

The dimethoxymethyl derivative **1n** revealed to be a good substrate. Even if the reaction at 0 °C under the optimised conditions was not fully satisfactory in terms of yield, a second experiment performed at RT and with shorter times gave an improvement in the yield, and, more importantly, a very good enantiomeric excess (96%) even at this higher temperature (*Figure 34*). This result confirmed our assumptions of the requirement of a hindered group on the ketone Michael acceptor.

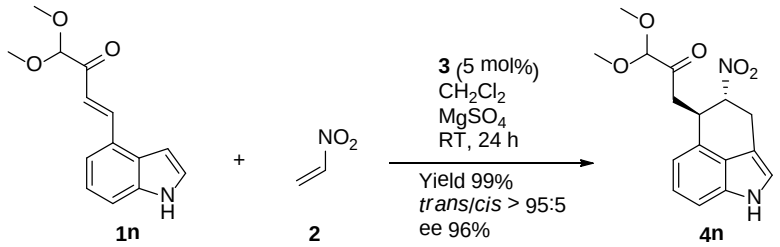


Figure 34

The imidazole derivative **1o** gave instead unsatisfactory results. This substrate seemed to magnify the necessity of anhydrous reaction conditions, as without drying agents the analysis on the crude mixture showed a low conversion in terms of product **4o** (~6%) and in terms of sideproduct **4'o** (~7%). These conversions greatly increased if the reaction was performed with drying agents, but still without reaching sufficient conversion nor full selectivity towards the cyclic product **4o** (*Figure 35*). To better understand if this low conversion was caused by the basicity or the low reactivity of this substrate, it was performed a reaction with the standard indole **1a** with an equimolar amount of 1-methyl-1*H*-imidazole. The reaction did not occur at all. Thus, the low conversion observed with **1o** is caused by the imidazole portion of the substrate, which quenches the acidity of the catalyst **3**, and not by the low reactivity of the indole C3 of the substrate towards the Friedel-Crafts reaction. The non-methylated nitrogen in the imidazole core bears a lone pair that can in fact act as a Brønsted base, and deprotonate the acid catalyst **3**, quenching it.

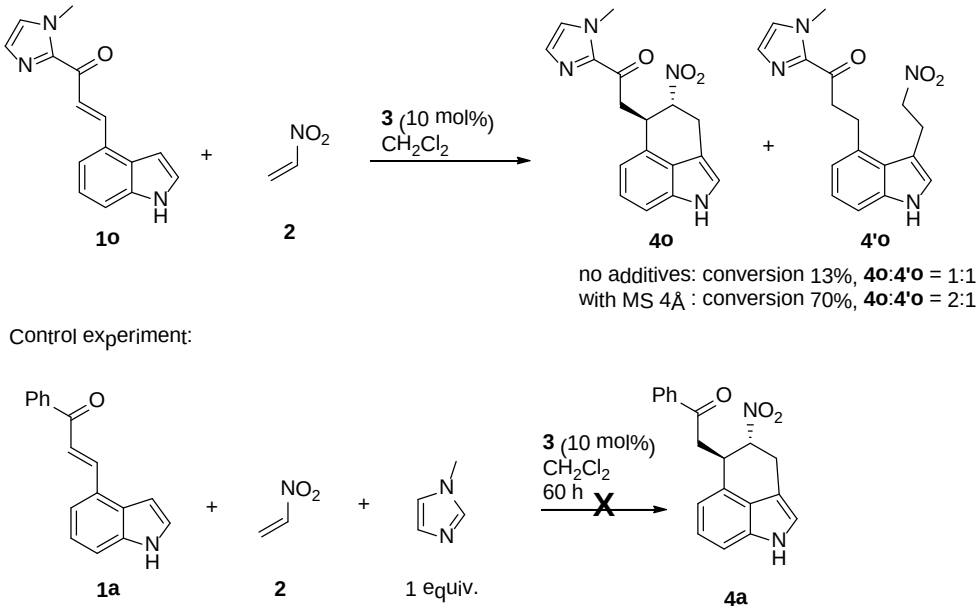


Figure 35

The 2-hydroxy-*iso*-propyl derivative **1p** revealed to be very reactive with good conversion but presented a poor enantiomeric excess (58%). It was supposed that the hydrogen of the hydroxyl group might coordinate with the catalyst lowering its ability to induce enantioselectivity (*Figure 36*).

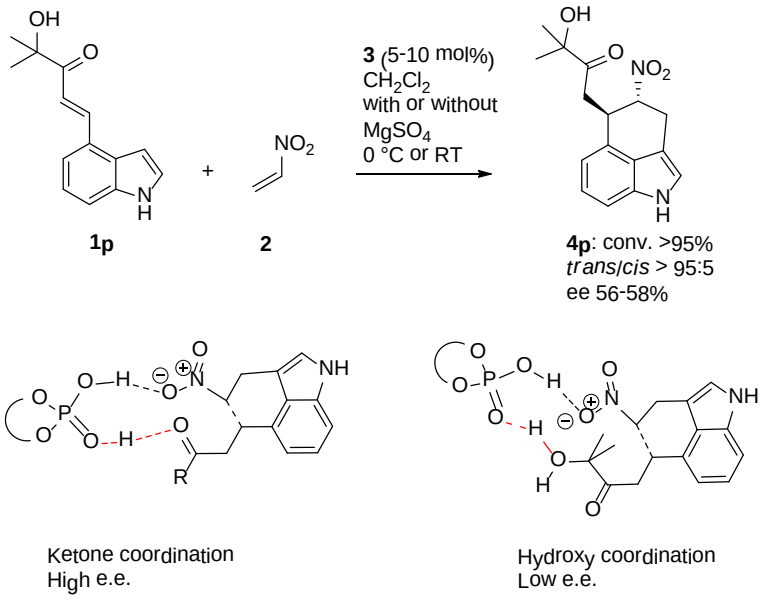


Figure 36

The Meldrum acid derivative **1q** revealed instead to be poorly reactive, the analysis on the crude mixtures showed invariably the presence of the unreacted starting material as the

major component (*Figure 37*). Plausibly, the strong electron withdrawing properties of the Meldrum acid portion decreased the nucleophilicity of the indole moiety, thus preventing the Friedel-Crafts step of the domino reaction.

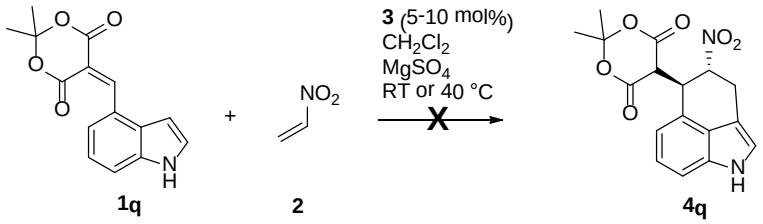


Figure 37

In conclusion, with the exception of the dimetoxy methyl derivative **1n**, the newly synthetized substrates did not fulfil our expectations. The substrate **1n** proved in fact to be suitable, affording the corresponding product **4n** in good yield and with a satisfactory enantiomeric excess of 96%, even at RT. The N-methylimidazole substrate **1o** showed instead a low conversion due to the interfering basicity of the lone pair present on the non-methylated nitrogen. The substrate **1p** proved to be reactive in terms of conversion, but gave unsatisfactory enantioselectivity; in this case, the hydroxyl group does not inhibit the catalyst activation, but has a negative influence on the stereodetermining step of the reaction. The Meldrum acid substrate **1q** showed no reactivity due to the strong electron withdrawing properties of the Meldrum acid moiety, which suppressed the Friedel-Crafts step of the reaction.

3.4 Product elaborations

After the preliminary study of the generality of the reaction (Table 2), showing that several aromatic derivatives can be employed, it was then decided to take a next step towards the realization of a formal synthesis of 6,7-secoagroclavine. In particular, Somei and co-workers showed that compound **4h**, bearing an ester group, can be converted into 6,7-secoagroclavine in a few steps. Unfortunately, our reaction was not able to furnish compound **4h**, as substrate **1h** was giving exclusively the open chain adduct **4'h**. Thus, we decided to obtain this compound by selective oxidation of the ketone group in one of the other compounds **4** (*Figure 38*).

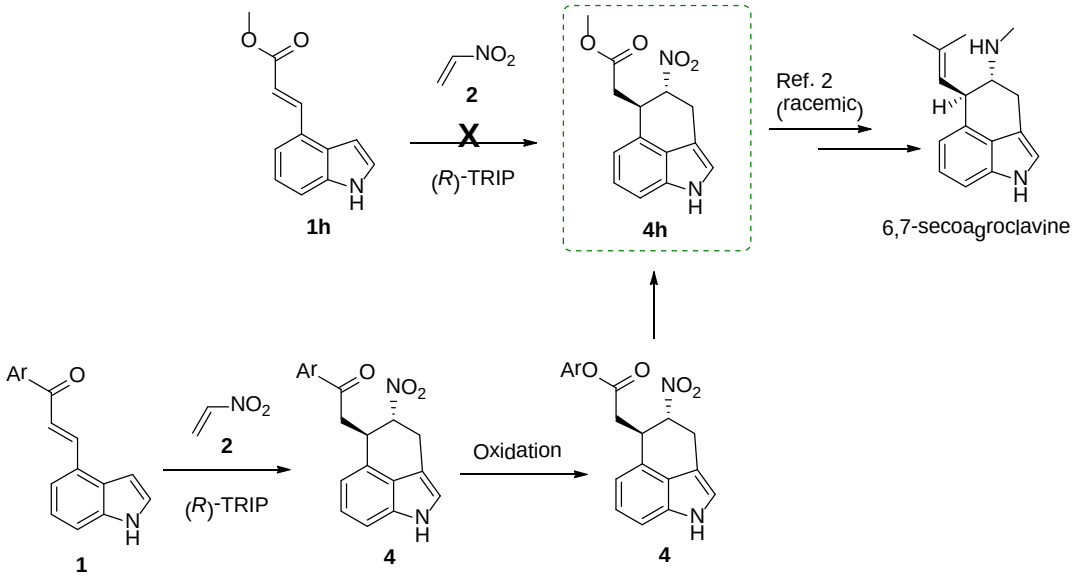


Figure 38

Bayer-Villiger oxidation is a well-known reaction in literature able to convert ketone moieties into esters using *meta*-chloroperoxybenzoic acid (mCPBA) in the presence of a weak base. For asymmetric ketones, the oxidation results to be regioselective, with the oxygen placed between the ketone carbon and the substituent which is most able to stabilize a positive charge.

A literature search provided a potentially useful procedure, applied to a compound similar to our tricyclic derivative **4c**[22] and able to afford the desired compound under relatively mild conditions (*Figure 39*).

[22] Q. Dai, A. Harman, J. C.-G. Zhao, *Chem. Eur. J.*, **2013**, *19*, 1666.

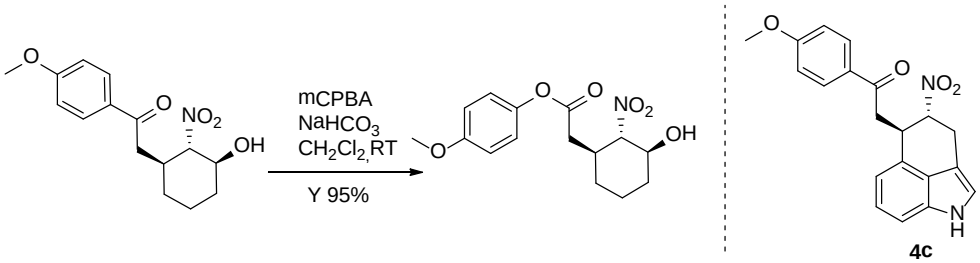


Figure 39

The result shown in Table 5 show the preliminary tests done on the oxidation of **4c**, based on the mentioned literature, under different reaction conditions (amount of oxidant, inorganic base). Unfortunately none of these conditions afforded the desired ester, leading to decomposition of the starting material, possibly due to the susceptibility of the indole ring to oxidative conditions.

Table 5

Entry	mCPBA (eq)	Base (eq)
1	1	$NaHCO_3$ (2)
2	1.5	Na_2CO_3 (2)
3	1	Na_2CO_3 (2)
4	3	Na_2CO_3 (2)
5	3	$NaHCO_3$ (2)

It was thus decided to move towards different mild oxidation of keto moieties, in order to avoid the oxidation of the indole core. Another interesting procedure able to turn electron rich aromatic aldehydes into aromatic alcohols is the Dakin oxidation. The reaction is performed by oxidising the substrate with the urea-hydrogen peroxide complex (UHP) under strongly basic conditions (hydroxides). Different tests were done on this reaction with substrate **4c** with different amounts of UHP and base loadings. However, even if in this case indole decomposition was avoided, no results in terms of ketone oxidation were observed: the ^{1}H NMR analysis of the crude showed the presence of the starting material **4c** accompanied by a similar compound, that after a careful analysis revealed to be its *cis*-diasteroisomer *epi*-**4c**. This result prompted us to study the epimerization of adducts **4**, which will be described later.

As the direct oxidation of the cyclic compound **4c** was not a viable pathway, it was decided to protect its indole core using di-*tert*-butyl-carbonate (Boc_2O). It was expected that protection of the indole with an electron withdrawing group would render it much

less reactive towards electrophilic oxidising agents, thus allowing the application of the strong oxidant mCPBA for a Baeyer-Villiger reaction. Protection of the indole in **4c** with a Boc group proved to be much more challenging than expected. The reactions were performed at 0 °C in acetonitrile by mixing Boc_2O with our cyclic substrate **4c** and then adding slowly 4-dimethylamino pyridine (DMAP). The analysis on the crudes showed the presence of some decomposition products and three main compounds: the starting material, and the two N-Boc protected diasteroisomers. Different amounts of acylating agent and DMAP were tested to maximise the formation of the desired protected compound. A brief summary of the tested conditions are shown in Table 6. By applying the conditions reported in entry 6 it was possible to obtain the desired N-Boc protected product, with partial epimerisation at the α-nitro chiral centre, in moderate yield.

Table 6

Entry	**4**	Boc_2O (eq)	DMAP (eq)	Solvent
1	**4c**	1.2	0.01	Acetonitrile
2	**4c**	1.2	0.1	Acetonitrile
3	**4c**	1.5	0.5 x2	Acetonitrile
4	**4c**	1.2	1	Acetonitrile
5	**4c**	2	0.2	Acetonitrile
6	**4c**	1	0.2	Acetonitrile

Having at hand the mixture of the two protected diasteroisomers, it was performed the Bayer-Villiger reaction, which unfortunately gave poor result; the ^1H NMR analysis on the crude showed a large number of by-products, which were not isolable via silica gel chromatography.

It was then decided to move towards a different protecting group such as the *p*-toluenesulphonyl (Ts), able to protect the nitrogen in the indole core under basic conditions and possibly even more electron-withdrawing than the Boc. However, also in this case installing the tosyl group on the NH of substrate **4c** proved to be very difficult. A brief summary of the conditions which were tested are shown in Table 7.

Table 7

Entry	**4**	TsCl (eq)	Base (eq)	Additive (eq)	Solvent	T
1	**4c**	1	Triethylamine (1.25)	-	CH_2Cl_2	RT
2	**4c**	1.2	DMAP (1)	Triethylamine (0.5)	CH_2Cl_2	RT
3	**4c**	1.2	DMAP (1)	-	CH_2Cl_2	RT
4	**4c**	1.2 x2	NaOH (1.8)	TEBA (0.1)	CH_2Cl_2	RT
5	**4c**	1.4	NaOH (1.4)	TEBA (0.1)	CH_2Cl_2	RT
6	**4c**	2.4 x2	NaOH (large excess)	-	CH_2Cl_2	RT

A preliminary test was done with a weak base in order to avoid the formation of the diasteroisomer (entry 1). No reaction occurred. Further tests were done with NaOH, a strong base poorly soluble in organic solvents, with benzyl(triethyl)ammonium chloride (TEBA) as a phase-transfer catalyst. The reaction occurred in half an hour but with the formation of a large amount of by-products. It was then decided to try the reaction without phase-transfer catalyst but with a large amount of base (entry 6). With this procedure, it was possible to isolate a small amount of the desired N-tosyl protected product, thus allowing us to perform the oxidation. However, also in this case the Baeyer-Villiger oxidation led to a mixture of unidentified by-products.

After these unsuccessful results, the pathway with the oxidation of the aromatic keto compound with or without protecting the indole core was abandoned.

From a synthetic point of view, another promising product obtained through the domino reaction was the dimetoxy derivative **4n**. It can be envisioned that few synthetic steps lead to a diol, possibly cleavable under oxidative conditions drastically different from the Baeyer-Villiger reaction and leading to the obtainment of the target product **4h** (*Figure 40*).

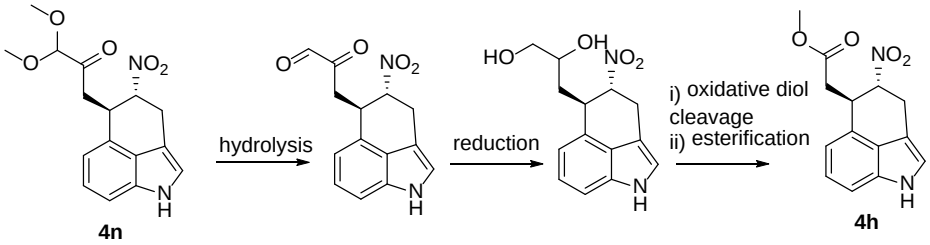


Figure 40

First tests consisted in the removal of the acetal moiety in acidic environment. Despite the simplicity of this reaction, after a screening of different acids (Table 8), none of our attempts afforded the desired α-keto aldehyde.

Table 8

°Entry	Acid (eq)	Solvent
1	CF_3COOH (10)	H_2O
2	H_2SO_4 (10)	H_2O
3	HCl (5)	H_2O

It was then decided to move towards the direct oxidative cleavage of the α-keto acetal group through different reactions. It was speculated that if a small amount of hemiacetal

was formed, this might participate in an oxidative cleavage reaction with the enol of the ketone. Unfortunately, none of the tested conditions (Table 9) gave the desired carboxylic compound, but lead to recovery of the starting material or indole decomposition.

Table 9

Entry	Oxidant	Equivalent	Solvent	T (°C)
1	UHP + NaOH	8	MeOH	RT
2	MnO_2	1	DCM	RT
3	$(NH_4)_2Ce(NO_3)_6$	3	CH_3CN/H_2O (3:1)	RT
4	H_2O_2	1	H_2O	RT
5	HIO_4	1.2	Et_2O	0
6	$NaIO_4$	1.2	$MeOH/H_2O$ (3:1)	RT

Thus, it was decided to first reduce the keto moiety, with subsequent (one pot) acidic acetal removal. After a successful reduction via $NaBH_4$ we obtained compound **5n**. It was then repeated the procedure, and to the crude mixture were added few drops of HCl (1 M), and left it stirred at RT for several hours. After an aqueous work up, the ^1H NMR analysis of the crude did not show the presence of the hydroxy-aldehyde **6n**, but mostly starting material accompanied by another product which structure was tentatively assigned as the tetracyclic product **6'n**. A summary of all attempts and failures with adduct **4n** is reported in *Figure 41*, showing that the preparation of the desired compound **4h** was found to be an unsurmountable task even by using **4n** as starting material. This objective was thus abandoned.

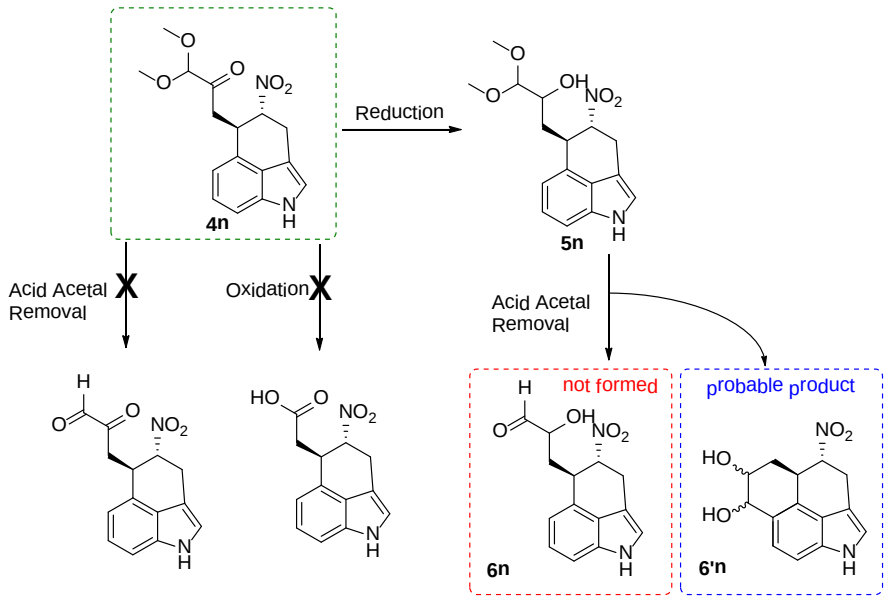


Figure 41

As previously described, during the attempted Dakin oxidation of the cyclic compound **4c**, it was found that the presence of a strong base brought to the formation of its diasteroisomer. As this transformation is synthetically very important, as it demonstrates access to both diasteroisomers of the product using the same catalytic asymmetric methodology (*Figure 42*), it was decided to optimise the conditions by performing multiple tests with different bases in different amounts, as reported in Table 10. The first two lines do not represent reactions; instead they show the diastereomeric ratios and enantiomeric excesses of the starting materials **4a** and **4c** used in the reaction.

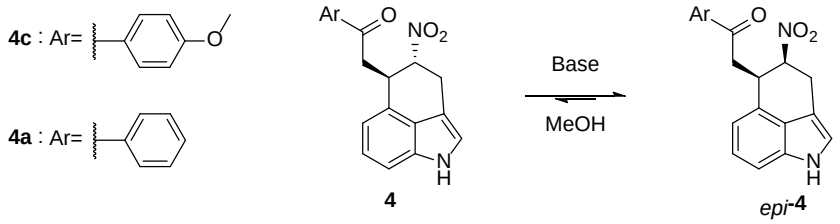


Figure 42

Table 10

Entry	Substrate	R=	Base (eq)	Solvent (conc **4**)	cis : trans[a]	ee[b] (%)
	4c	*p*-$MeOC_6H_4$	-	-	< 5:95	97
	4a	Ph	-	-	< 5:95	97
1	**4c**	*p*-$MeOC_6H_4$	NaOMe (1.5)	MeOH (0.28 M)	28:72	nd
2	**4c**	*p*-$MeOC_6H_4$	NaOH (1.5)	MeOH (0.14 M)	36:64	nd
3	**4c**	*p*-$MeOC_6H_4$	NaOH (6)	MeOH (0.36 M)	65:35	nd
4	**4c**	*p*-$MeOC_6H_4$	NaOH (12)	MeOH (0.36 M)	88:12	97
5	**4a**	Ph	NaOH (6)	MeOH (0.36 M)	92:8	96

a: diastereoisomeric ratio determined through ^{1}H NMR spectroscopy on the crude of the reactions; b: determined by chiral stationary phase HPLC.

As the *p*-$MeOC_6H_4$ derivative **1c** was the chosen substrate for the oxidation reaction, the first tests for the epimerization were done on this compound. Preliminary tests were done with a low amount of base in order to maintain the reaction environment as similar as possible to the oxidation and to avoid racemisation through a retro-Michael reaction. Sodium hydroxide resulted to be the most active base; however, a small amount of it gave only a ca 7:3 diasteromeric ratio in favour of starting *trans*-**4c** (entries 1,2). Based on the ratios observed during the Dakin oxidation, it was speculated that these reaction did not reach the thermodynamic ratios. It was thus decided to increase the amount of base to further promote the epimerization. Larger amount of base and higher concentration of the substrate (entries 3,4) revealed to increase the diasteromeric ratio after the reaction, leading to an optimal 88:12 value favouring the *cis* isomer. Importantly, it was demonstrated that no racemisation occurred during this epimerisation step. This epimerisation protocol was then extended to the benchmark compound **4a** (entry 5): the

result was even better than the one obtained with **4c**. Using only 6 equiv. of NaOH it was possible to obtain the *cis* diastereoisomer with good diastereoselectivity (92:8). Importantly, also in this case HPLC analysis showed that the product simply epimerised, keeping the same enantiomeric excess of the starting *trans*-adduct **4a**. As shown in the relative chapter, it was confirmed by ECD that the chiral centre which underwent epimerisation was the one α to the nitro functionality, as expected considering its higher acidity.

3.5 Mechanistic proposal

As highlighted in the objective section, the formation of the cyclic products **4** with the rather acidic catalyst **3** is quite intriguing. In fact, mainly two possible mechanisms can be proposed.

A first hypothesis is shown in Figure 43.

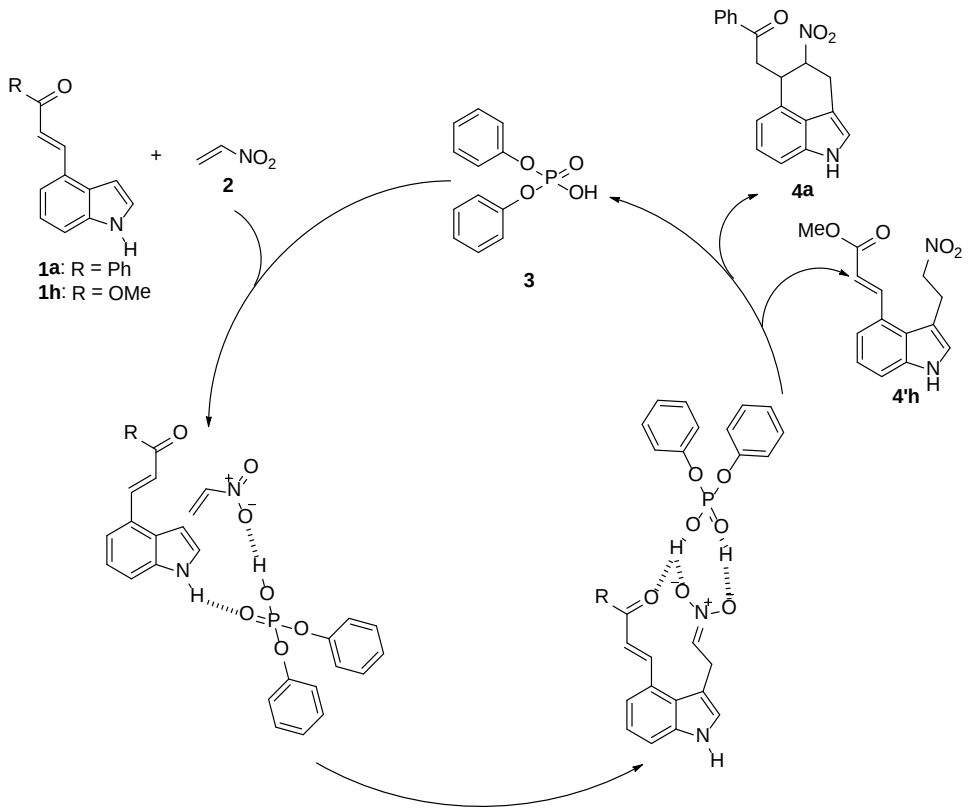


Figure 43

Catalyst **3** (represented in a simplified form) is supposed to activate both substrates, nitroethene **2** through its acidic proton and coordinate the indole N-H through the phosphoryl oxygen, acting as a Lewis base. This coordination stabilizes the positive charge formed during the Friedel-Crafts step of the reaction on the nitrogen of the indole. Through this bifunctional mechanism the catalyst is able to promote the rearomatization of the indole core by simply abstracting the C3-proton. This hypothesis is based on previous study on the mechanism of Friedel Crafts reaction between indoles and nitroalkenes catalysed b phosphoric acids.[6,7] With non-substituted indoles the proton is transferred from the catalyst to the basic nitronate formed by the Friedel-Crafts reaction.

This transfer indeed occurred in the case of substrate **1h**, preventing the formation of the polycyclic adduct. Most likely, the non-cyclization is caused by the low reactivity of the Michael acceptor moiety (an ester in the case of **1h**), which lead to the proton transfer product. With stronger Michael acceptors as in **1a** the nitronate coordinated by the catalyst is able to undergo a conjugated addition to the vinyl β-keto carbon, leading to the desired **4a**. However, it can be considered rather surprising that the basic nitronate is not quenched by the protonated phosphoric acid, which is an extremely acidic compound, and prefers to perform the conjugated addition.

It can also be hypothesised a second mechanism, shown in Figure 44, wherein the rearomatization occurs subsequent to the nitro-Michael reaction.

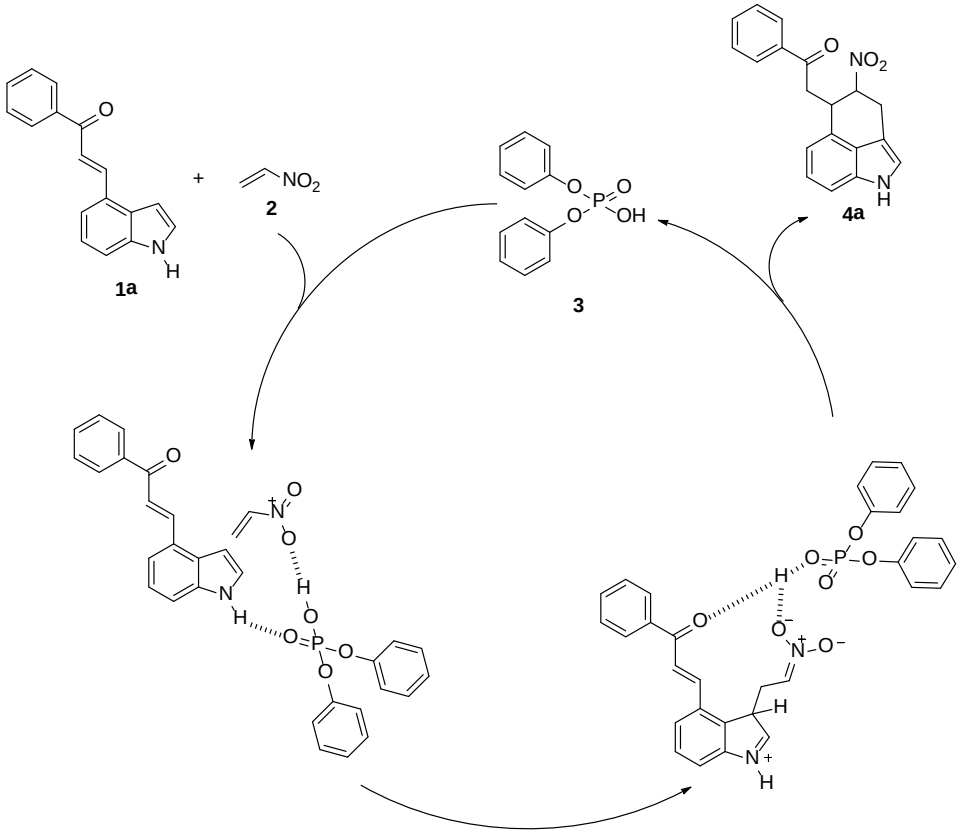


Figure 44

Another hypothesis was that after the Friedel-Crafts step the catalyst could detach from the simple Friedel-Crafts adduct, and subsequently re-coordinate the un-cyclized molecule and promote the nitro-Michael step. This hypothesis was soon rejected as treating the un-cyclic adduct **4'a** (obtained from one of the reactions performed in the presence of molecular sieves) with catalyst **3** no cyclization occurred (*Figure 45*).

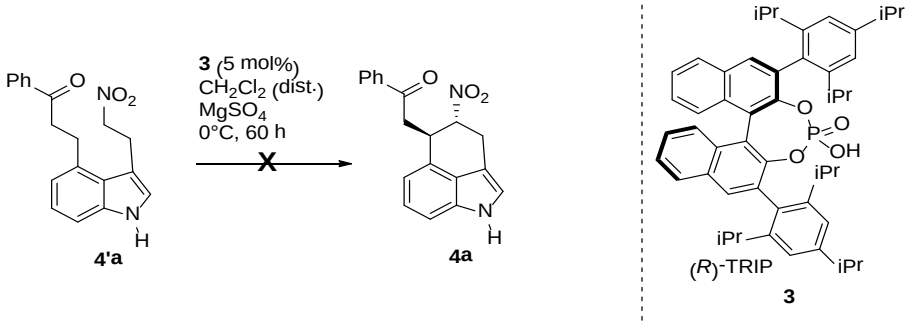


Figure 45

To get insight about the actual reaction pathway followed by the reaction, we turned to a computational approach, carried out by Dr Stefano Santoro and Prof. Fahmi Himo of the University of Stockholm. These DFT calculations using the B3LYP-D functional were carried out by studying the possible intermediates and transition states in order to achieve the formation of the cyclic compound. To shorten the computational study, a simplified catalyst structure was used, and, as starting material, substrate **1f**.

The results of the elaboration are shown in Figure 46 and Figure 47.

The first low energy transition state (TS1) involves the double coordination of the catalyst with the N-H of the indole moiety through the Lewis base site of the catalyst, and with the nitroethene through the acidic hydrogen. Another low energy TS (TS5) consists in the coordination of the catalyst with the nitroethene as before, but with simultaneous coordination of the indole through the C3 carbon. Interestingly, this TS5 results to be at available energy, thus justifying the observed reactions of N-substitued indoles **1j** and **1k**, which indeed required slightly more forcing conditions to react. Both TS imply the Friedel-Crafts attack from the C3 electron rich position in the indole to the electron poor position in the nitroethene, leading to the formation of the same intermediate INT1, wherein the catalyst coordinates the nitronate and the C3H. Direct nitro-Michael addition from this intermediate was found to be energetically unviable. This intermediate INT1 is instead ready to re-aromatize the indole through TS2, leading to a doubly coordinated nitronate (INT2). A proton-relay mechanism featuring a simultaneous rearomatization and nitronate protonation with catalyst release was found to be unviable.

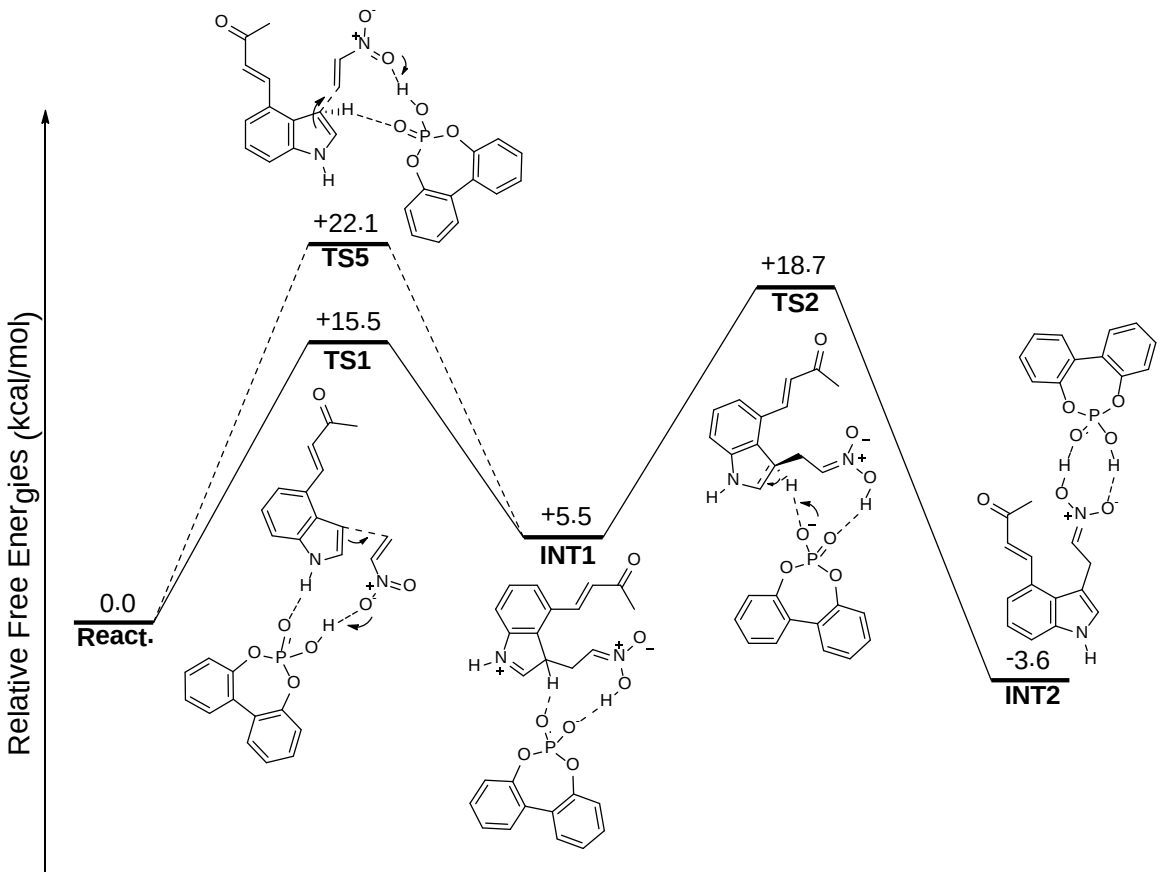


Figure 46

The nitronate INT2 is a crucial point for the reaction. Surprisingly, this INT2 presents a rather low energy. From this intermediate, coordination of the catalyst to the keto group of the molecule leads to the reaction pathway giving the desired cyclic compound **4** with an energy barrier of 13.8 kcal/mol. However, from this same intermediate INT2 a proton shift can occur through TS7, leading to the undesired non-cyclic compound **4'**.

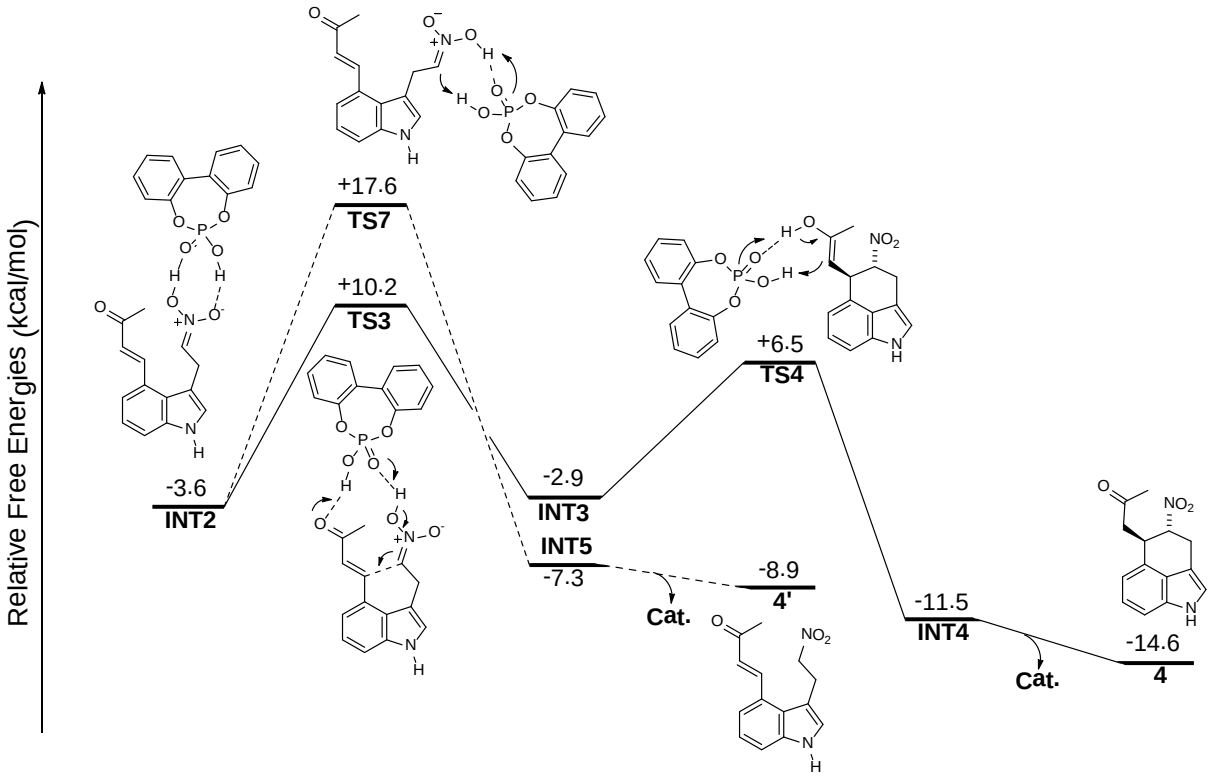


Figure 47

In conclusion, these computational studies showed that rearomatization of the indole core occurs before the nitro-Michael step, and that the reaction likely proceeds through a nitronate type intermediate, in line with the first hypothesised mechanism. With a highly reactive Michael acceptor, the cyclisation is energetically favoured over the proton-transfer step, even if it is known that this type of calculations cannot be considered accurate for evaluating the energy of proton transfer steps, and thus the energy value of TS7 must be considered only as an estimate.

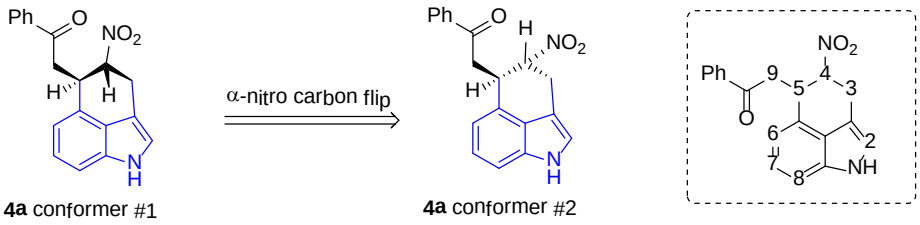
It can also be observed that the rate determining step of the reaction is the first Friedel-Crafts step, and that coordination to the indole NH is not present during the stereodetermining nitro-Michael cyclisation, thus fully accounting for the results obtained with the N-alkyl substituted indoles **1j** and **1k**.

3.6 Determination of the relative and absolute configuration of the adducts

As all the attempts to obtain crystals suitable for X-ray crystallography on the prepared compounds **4** were not successful, the relative and absolute configuration of these adducts were determined by a combination of conformational analysis and theoretical simulation of chiro-optical spectra, performed by Prof. A. Mazzanti.

Having in our hands the procedures to obtain both diasteroisomers of the polycyclic compound (**4a** and *epi*-**4a**), one directly by the Friedel-Craft-nitro-Michael reaction, one by selective epimerization of the α-nitro carbon, it was decided to start the determination of the configuration by carrying out computationally a conformational analysis on compound **4a**.

Despite the rigidity of the heterocyclic indole core of compound **4a**, where almost all carbons of the polycyclic system lye on the same plane (drawn in blue in Figure 48) it was identified that these products could appear under various possible conformers. The main ones are depicted in *Figure 48*. Considering the plane where the indole lies, the α-nitro carbon can be found either on the same side of the ketone (conformer #1), or on the opposite side (conformer #2).



4a conformer #1 **4a** conformer #2

Figure 48

The relative stereochemistry of the two stereogenic centres at C-4 and C-5 of compound **4a** were determined by means of NMR spectroscopy, full assignment of the ^{1}H and ^{13}C spectra was preliminarily achieved by bi-dimensional experiment. Further DPFGSE-NOE experiments[23] were acquired in order to assign the relative stereochemistry at C-4 and C-5. The observed NOEs suggested that the H5 hydrogen occupies a pseudo-equatorial position (conformer #2 in Figure 48), otherwise a strong NOE should be observed on H3. Further NOE experiment were done confirming the previous result, confirming the *4R*,5R** relative configuration, with the substituents in *trans* position (Figure 49).

[23] K. Stott, J. Stonehouse, J. Keeler, T.-L. Hwang, A. J. Shaka, *J. Am. Chem. Soc.*, **1995**, *117*, 4199.

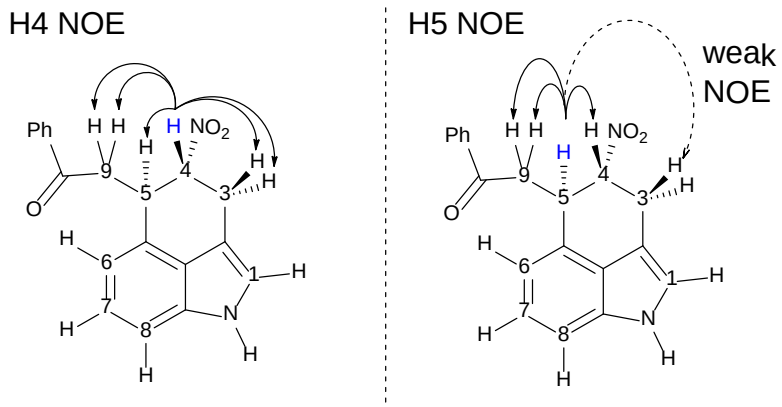


Figure 49

The determination of the absolute configuration of **4a** was instead obtained by comparing the experimental electronic circular dichroism (ECD) spectrum with the computed one. Preliminary tests were done in order to determine the proper distribution ratio of the different conformers of the compound. After DFT minimization, four conformations were found to be the most stable, all of them showing the same shape of the six membered ring corresponding to a pseudo boat conformation with the nitro group out of the plane. Within each pair, the conformations are different in the disposition of the CH_2COPh moiety.

Having in hand the relative configuration and suitable experiment data supporting the preferred conformations, the assignment of the absolute configuration was pursued. Various simulations of the experimental ECD spectrum were done, by using 4 different calculation methods, and different conformer ratios. The optimized ratio resulted to fit well with the empiric spectrum as shown in Figure 50, and thus the absolute configuration of compound **4a** could be assigned as 4*R*,5*R*.

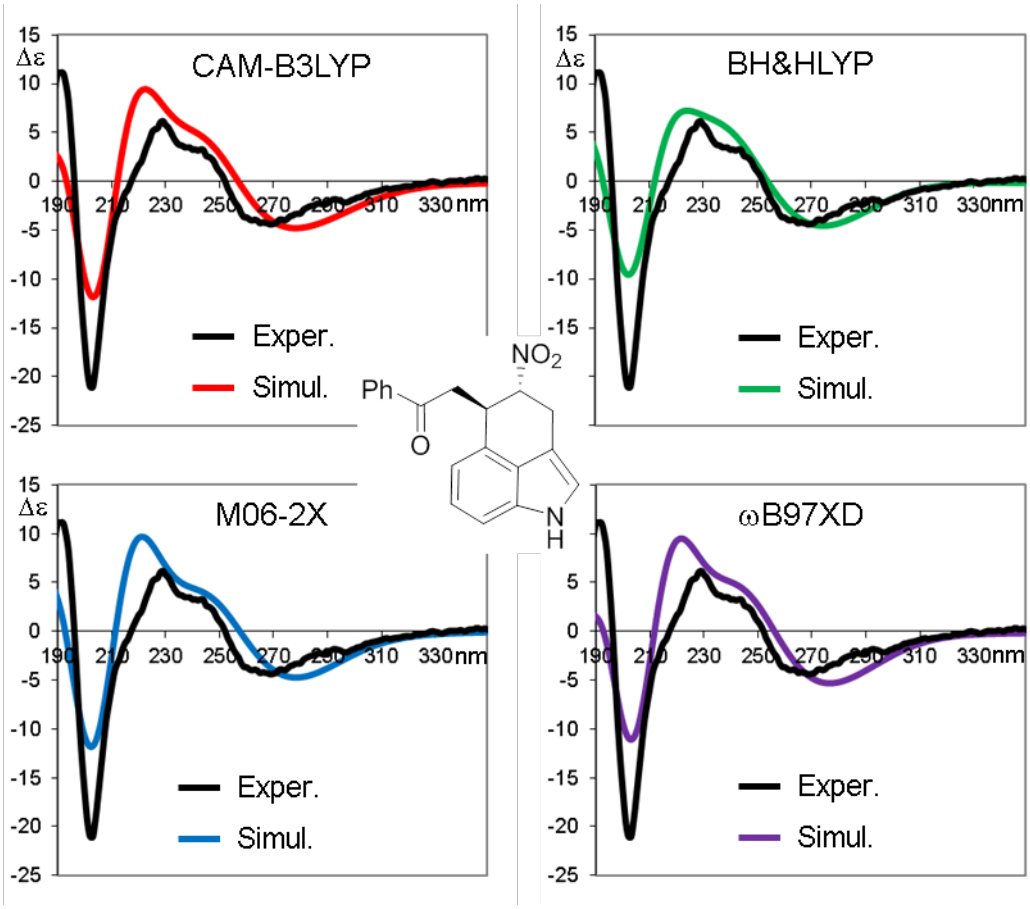


Figure 50

As a cross check, NOE spectra and ECD analysis were done also for the *cis*-diasteroisomer *epi*-**4a**, confirming the epimerization of compound **4a** occurred with inversion of chirality at the nitro bearing carbon.

We assume, that all other compound **4** present the same relative and absolute configuration, being produced with the same reaction pathway.

4 - Conclusion

In conclusion, most of the objectives we set for this work were achieved.

Optimisation of the reaction condition: The reaction with the standard substrate **1a** was optimized reaching very satisfactory results, with a substantial improvement in terms of decrease of catalyst loading, and improvement of enantiomeric excess, robustness and reproducibility (*Figure 51).*

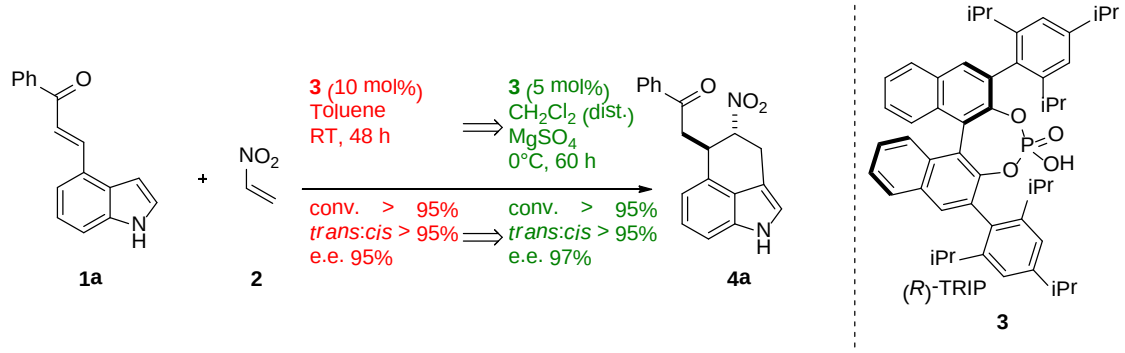


Figure 51

Study of the generality of the reaction: With the well-optimized reaction conditions different tests were done, generally obtaining very good results (Figure 52). Indole derivatives bearing aryl substituents at the keto group of the Michael acceptor gave excellent result in terms of yields, diasteroisomeric ratios and enantiomeric excesses, confirming the suitability of this compounds in our reaction. The derivatization of these compounds on the N-indole position did not prevent the successful occurrence of the reaction. Increasing temperature, nitroethene and catalyst loading, N-alkyl indole substrates furnished the corresponding products **4** with very good results. Moving to non-aromatic keto substrates provided satisfactory results only when a highly hindered *t*-butyl ketone was employed, the less bulky methyl derivative affording good yield but poor enantioselectivity. Ester derivatives and some of their surrogates were also tested, however these substrates were not found to be suitable for the domino cyclisation, as the only products detected were the linear adducts **4'**.

A Chem3D analysis of these first experimental results showed that only substrates featuring a LUMO energy at the Michael acceptor lower than ca -6.0 eV were able to give the desired domino product, and that a highly hindered substituent was required on the ketone to give good enantiomeric excess in the reaction. These observations allowed us to select three promising candidates with different groups at the ketone (a dimethoxyacetal,

a 1-Me-1*H*-imidazole and a 2-propanol) for the extension of the reaction scope, thus avoiding the synthesis of a series of potentially useless substrates. However, only the substrate featuring a dimethoxyacetal at the ketone gave excellent results, whereas the other two substrates prepared behaved poorly for different reasons (interference with the catalyst coordination giving poor enantioselectivity in the case of the alcoholic substrate, and catalyst quench by the basic moiety of the substrate in the case of the imidazole). A Meldrum acid derivative was also prepared but resulted too poorly reactive.

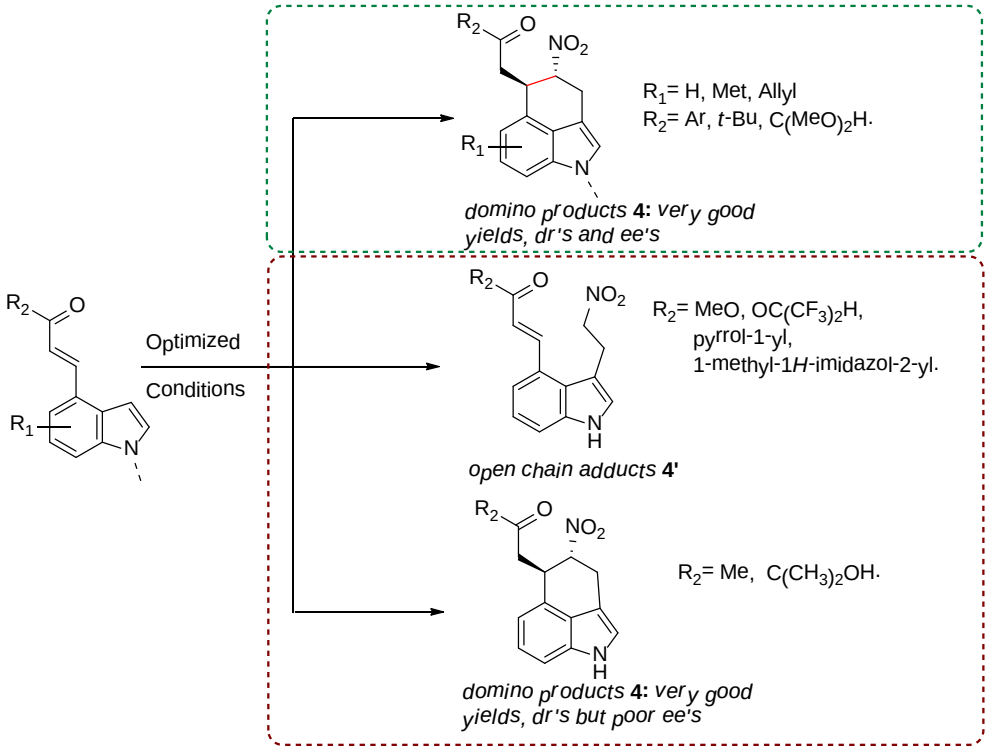


Figure 52

Product elaborations: Various tests were done in order to demonstrate that the products could be employed for a formal synthesis of 6,7-secoagroclavine synthesis (*Figure 53*). It was first tried to convert an aryl ketone product in an ester by an oxidative procedure. Unfortunately no result was obtained, even after the protection of the indole NH. A number of attempts were also done with another substrate, which however were also met with failures. This objective was thus not reached.

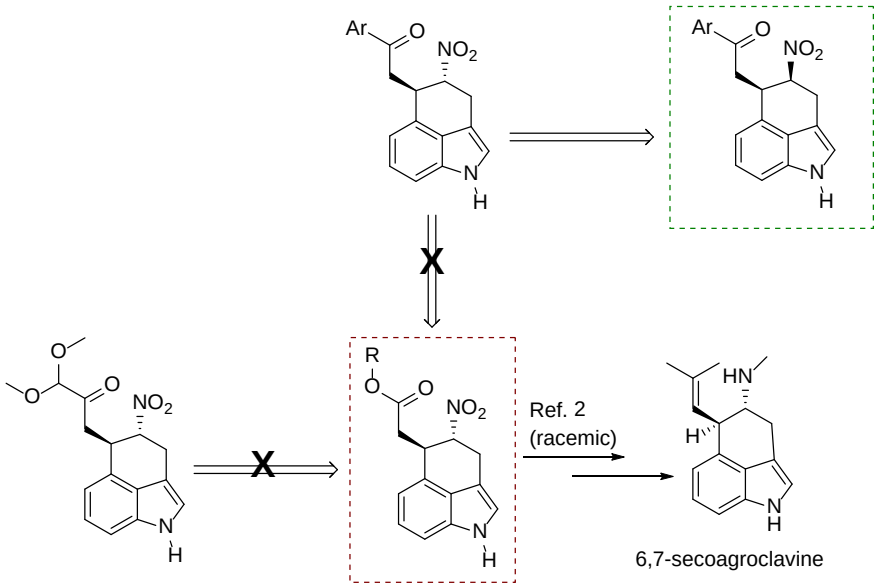


Figure 53

However, during the umpteenth effort to protect the indole it was found that a clean epimerization reaction occurred under strongly basic conditions. The individuation of this reaction was a silver lightning between black clouds, allowing to change selectively the stereochemistry of the carbon bearing the nitro group, thus giving access to both diastereomers of the product with the same catalytic enantioselective procedure.

Mechanistic proposal: The exclusive obtainment of compound **4** in the presence of phosphoric acid catalyst was very intriguing. Computational investigations of the acid catalysed domino reaction, performed at the University of Stockholm (SE), showed that rearomatisation of the indole core precedes the nitro-Michael step, and that a key bicoordinated nitronate intermediate is formed, from which the reaction can proceed through the stereoselective nitro-Michael pathway, or simply lead to nitronate protonation. Importantly, this mechanistic proposal fully accounts for the results observed with the N-alkyl substituted indole substrates.

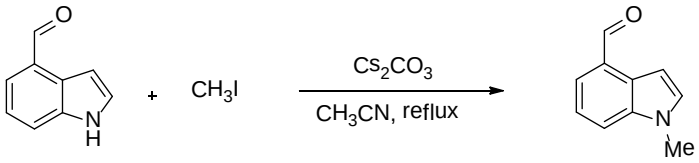
Determination of the relative and absolute configuration of the adducts: due to the failure to obtain crystals of the products suitable for X-ray crystallographic analysis, the absolute and relative configuration were assigned on compound **4a** by combining spectroscopic NMR analysis, ECD spectra and computational methods. It was also demonstrated that its diastereoisomer *epi*-**4a** is epimeric at the α-nitro chiral centre, as expected.

5 - Experimental part

General Methods. ^{1}H, ^{13}C NMR spectra were recorded on a Varian AS 300, 400 or 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H and ^{13}C NMR.[24] ^{13}C NMR spectra were acquired with ^{1}H broad band decoupled mode. Chromatographic purifications were performed using 70-230 mesh silica. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES) ionisation techniques or using electron impact (EI) ionisation techniques. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC, using a UV detector operating at a fixed wavelength (254 nm). Dichloromethane used in the catalytic reaction was filtered on basic alumina and then distilled from CaH_2 prior to use. THF was treated with KOH pellets, filtered through basic alumina and distilled from Na/benzophenone prior to use. Catalyst **3** was previously prepared according to the literature.[25]

5.1 Substrate preparation

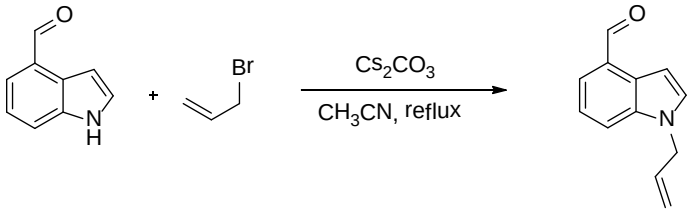
5.1.1 Synthesis of 1- and 2-alkyl-4-formyl indoles[26]



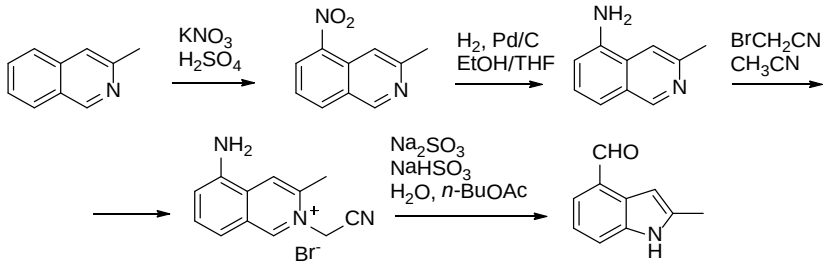
To a solution 4-formyl-indole (500 mg; 3.5 mmol) in 3 mL of acetonitrile were added 2.28 g of caesium carbonate (7.00 mmol), and the mixture was heated at 80 °C for 60 min. Then, the mixture was cooled to RT, and 467 µL of methyl iodide (7.00 mmol) were added. The resulting mixture was heated again at 80 °C for 2 h, then cooled to RT, filtered through celite, evaporated and purified by silica gel chromatography (CH_2Cl_2 as eluent). The product was obtained as a yellow powder in 88% yield. ^{1}H NMR (300 MHz,

[24] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.*, **1997**, *62*, 7512.
[25] M. Klussmann, L. Ratjen, S. Hoffmann, V. Wackhaure, R. Goddard, B. List, *Synlett*, **2010**, 2189.
L. He, M. Bekkaye, P. Retailleau, G. Masson, *Org. Lett.*, **2012**, *14*, 3158.
[26] M. Antoine, P. Marchand, G. Le Baut, M. Czech, S. Baasner, E. Gunther, *J. Enzyme Inhib. Med.*, **2008**, *23*, 686.
R. J. Perner et al, *J. Med. Chem.*, **2007**, *50*, 3651.
J. M. Muchowski, *J. Heterocyclic Chem.*, **2000**, *37*, 1293.

$CDCl_3$): 10.25 (s, 1H); 7.65-7.58 (m, 2H); 7.38-7.32 (m, 1H); 7.28-7.24 (m, 2H); 3.86 (s, 3H).



Following the procedure outlined above, and 343 µL of allyl bromide as alkylating agent, the product was obtained as a yellow powder in moderate yield. **^{1}H NMR** (300 MHz, $CDCl_3$): 10.20 (s, 1H); 7.62-7.53 (m, 2H); 7.33-7.19 (m, 2H); 6.03-5.76 (m, 1H); 5.22-5.15 (m, 1H); 5.07-4.97 (m, 1H); 4.79-4.72 (m, 2H).



To a solution of commercial 3-methyl isoquinioline (1.92 g, 13.4 mmol) in 22 mL of sulphuric acid at 0 °C, 1.49 g (14.7 mmol) of potassium nitrate was added in 4 subsequent aliquots. After 2 hours of stirring, ice was slowly added to the strongly acid reaction mixture, provoking a great increase in the temperature. The reaction mixture was then basified with 25% (w/w) NaOH, diluted with water, and extracted twice with CH_2Cl_2. The organic phase were collected and washed with brine, dried with magnesium sulphate, filtered and concentrated. The ^{1}H NMR analysis on crude mixture showed the presence of a small amount of an undesired regioisomer. The product was crystallized with a hexane - ethyl acetate (2:1) mixture. The ^{1}H NMR analysis on the dried filtered precipitate showed the presence of the desired product, but in moderate yield. In order to recover the highest quantity possible of product, the mother liquor were crystallized with the same previously used mixture; the ^{1}H NMR analysis of the crystallised product showed however the presence of the undesired regioisomer, therefore it was purified by silica gel chromatography (eluent: CH_2Cl_2 / Et_2O = 2 : 1). The purified fraction was combined with

the previous crystallized product giving an overall yield of 76% in 3-methyl-5-nitroisoquinioline (1.93 g).

The next step consisted in the catalytic hydrogenation of the nitro group with molecular hydrogen. In a glass hydrogenation reactor, to a solution of the previously obtained 3-methyl-5-nitrisoquinioline (10.2 mmol) in EtOH and THF (1:1, 72 mL) 122 mg of Pd/C 10% (w/w) were added. After 18 h of vigorous stirring under hydrogen atmosphere (1.5 atm), the catalyst was filtered through celite and the solution was dried under reduced pressure. The crude compound was then crystallized with a CH_2Cl_2:hexane:MeOH 35:35:30 mixture. After 2 days in the freezer, the precipitate was filtered, and the mother liquor were crystallized and filtered again. The ^{1}H NMR analysis of the 2 precipitates showed the only presence of the desired product, the fraction were combined obtaining the 3-methyl-isoquiniolin-5-amine in 88% yield.

The third step of the synthesis consisted in the preparation of the 5-amino-2-(cyanomethyl)-3-methylisoquinolin-2-ium salt through the alkylation of the previously prepared isoquinioline.

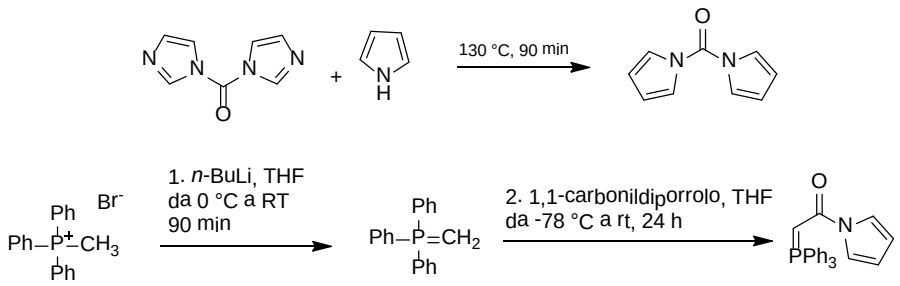
A solution of 2-bromoacetonitrile (0.27 mL, 3.82 mmol) and 3-methylisoquinolin-5-amine (582 mg, 3.8 mmol) in acetonitrile was heated under reflux. After just one hour the product was visible as a suspension. After 18 hours the product was filtered, and the mother liquors were heated again under reflux with a further 0.15 mL of 2-bromoacetonitrile for 24 h, then filtered in order to obtain more product. The ^{1}H NMR analysis of the two precipitates showed the presence of the pure compound so they were used in the next step without further purification. The two precipitates were combined obtaining 600 mg (2.28 mmol) of the desired product 5-amino-2-(cyanomethyl)-3-methylisoquinolin-2-ium bromide salt, with a yield of 60%.

The last step consisted in the hydrolysis, ring-opening and rearrangement to obtain the corresponding 4-formyl indole.

To a solution of 5-amino-2-(cyanomethyl)-3-methylisoquinolin-2-ium bromide salt (600 mg, 2.28 mmol) in water (45 mL), were added 4.88 g (46 mmol) of sodium bisulphite and 2.90 g (23 mmol) of sodium sulphite. The following addition of n-butyl acetate brought to the formation of a biphasic system. After 90 hours of reflux and vigorous stirring, the organic phase was first washed with a 10% HCl solution, then with a 10% sodium carbonate solution, and in the end with brine. After anhydrification with magnesium sulphate, the solution was filtered and evaporated. ^{1}H NMR analysis showed the only presence of the desired product, which was not purified further. 223 mg (1.40 mmol) of 1-

H-2-methyl-4-formyl indole were obtained (61% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$): 10,22 (s, 1H); 8.19 (br s, 1H); 7.60-7.52 (m, 2H); 7.27-7.22 (m, 1H); 7.06 (s, 1H); 2.52 (s, 3H).

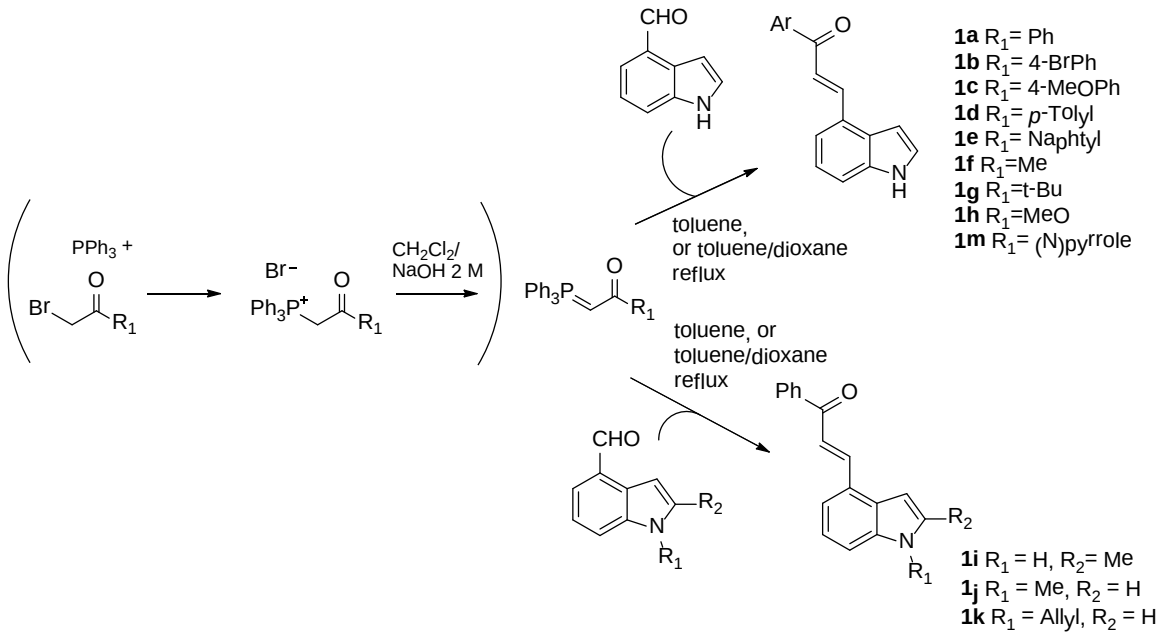
5.1.2 Synthesis of 4-vinylindoles by Wittig reactions[27]



In a flask equipped with magnetic stirring bar and condenser, di(1*H*-imidazol-1-yl)methanone (3.2 g, 20 mmol) and pyrrole (4.0 g, 4.2 mL, 60 mmol) were added, and heated at 130 °C for 90 min. After the removal of volatiles, the crude mixture was dissolved in CH_2Cl_2 and filtered with celite. The organic phase was then washed twice with 1 M HCl and brine to avoid the formation of emulsions. The organic phase was then dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure.

In the next step, in a three neck round bottom flask equipped with a magnetic stirring bar, methyltriphenylphosphonium bromide (14.8 g, 41.5 mmol) was added and suspended in anhydrous THF (104 mL). To the suspension, stirred and cooled to 0 °C, *n*-butyl lithium (1.6 M in hexane, 37.3 mmol, 23.3 mL) was slowly added, and the mixture left stirring for 1 h at RT. The reaction mixture was then cooled to -78 °C, and then a solution of di(1*H*-pyrrol-1-yl)methanone (2.2 g, 13.6 mmol) in anhydrous THF (21 mL) was added dropwise. After the addition, the reaction mixture was left warming at RT and left stirring for 24 h. The solvent was removed, the residue was then treated with water and extracted three times with an EtOAc / CH_2Cl_2 5:1 mixture. The organic phase were washed with brine, dried with $MgSO_4$, filtered and after the removal of the solvent the crude mixture was purified with silica gel chromatography ($CHCl_3$ / EtOAc 4:1). The obtained ylide was obtained as a white solid in 80% yield.

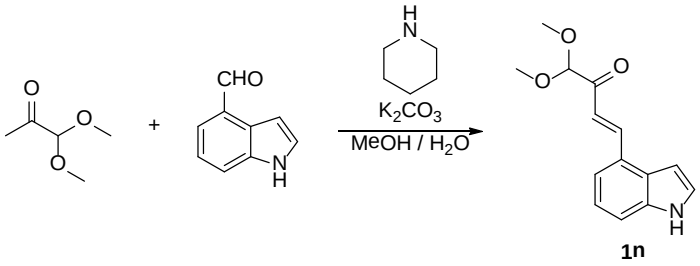
[27] B. Vakulya, S. Varga, T. Soós, *J. Org. Chem.*, **2008**, *73*, 3475.



Most of phosphonium salts are commercial. Otherwise, the preparation of the 4-bromophenyl derivative is typical. 2-Bromo-1-(4-bromophenyl)ethanone (1.4 g; 5 mmol) and triphenylphosphine (1.3 g; 5 mmol) were dissolved in 10 mL of acetone. The reaction was followed by TLC, when the conversion resulted almost complete the reaction was filtered obtaining 1.04 g (1.92 mmol) of the corresponding phosphonium salt as a white powder (yield 38%). This phosphonium salt was suspended in CH_2Cl_2 in a separatory funnel and treated with an aqueous solution of NaOH (2 M), under vigorous shacking. The organic phase was collected, dried with magnesium sulphate, filtered and the solvent was removed, obtaining 680 mg (1.48 mmol) of the stabilized phosphonium ylide as a white powder. A solution of the obtained ylide and 4-fomyl-indole (680 mg; 1 mmol) in toluene, or toluene/dioxane 5:2 mixture, (3 mL) was heated under reflux for 22 h. The ylide was used in excess in order to have full conversion of the 4-formyl-indole, difficult to separate by chromatography from the product. After the olefination, the mixture was dried under vacuum and purified by silica gel chromatography (petroleum ether / ethyl acetate 1.3/1 or CH_2Cl_2), the product (**1b**) was obtained as a yellow solid in 85% yield, as a single *trans*-diasteroisomer. The identity and the purity of the product were verified by ^{1}H NMR spectroscopy.

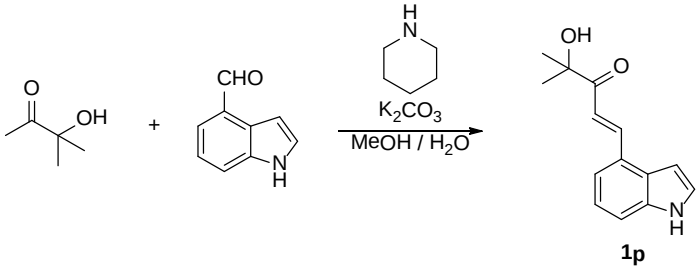
The rest of substrates **1** were obtained in an analogous way, even if in some instances (especially with the alkyl substituted indoles) additional time was necessary to achieve a satisfactory conversion (as checked by TLC), or the crude product showed a reduced conversion and was thus again treated a second time under the above olefination conditions.

5.1.3 Synthesis of 4-vinyl indoles by Knoevenagel reactions



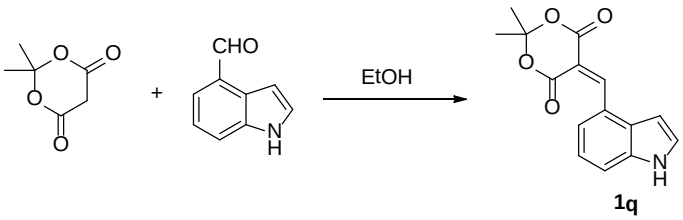
1n

To a solution of α,α-dimethoxyacetone (0.164 mL 1.37 mmol), 4-formyl-1H-indole (250 mg, 1.72 mmol) and potassium carbonate (3.4 mg) in methanol (1.0 mL) and water (300 µL), piperidine (0.137 mL, 1.37 mmol) was slowly added. The mixture was heated at 95 °C until total consumption of α,α-dimethoxyacetone (monitored by TLC). Once complete, the mixture was cooled to RT, diluted with EtOAc and washed with sat. $NaHCO_3$. The organic phase was then dried with $MgSO_4$, filtered and evaporated. The residue was purified by silica gel chromatography (eluent: dichloromethane) to give the desired ketone **1n**.



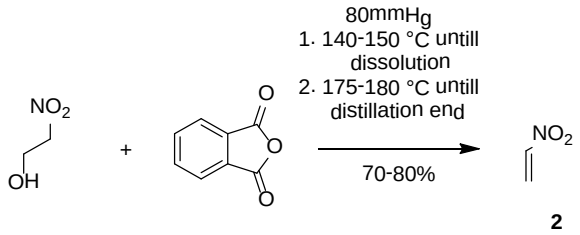
1p

To a solution of 3-hydroxy-3-methylbutan-2-one (0.132mL 1.0 mmol) and 4-formyl-1H-indole (145.2 mg 1.0 mmol) in ethanol was added dropwise a solution of aqueous KOH 50% (w/w). The mixture was heated at 40 °C until total consumption of 4-formyl-1H-indole (monitored by TLC). Once complete, the mixture was cooled to RT, diluted with distilled water, and neutralized with HCl. The mixture was extracted with toluene and twice with dichloromethane. The organic phase was then dried with $MgSO_4$, filtered and evaporated. The residue was purified by silica gel chromatography (eluent: dichloromethane + 3% diethyl ether) to give the desired ketone **1p**.



To a solution of 4-formyl 1H-indole (145 mg, 1 mmol) in ethanol (1 mL), was added 2,2-dimethyl-1,3-dioxane-4,6-dione. After three hours the solvent is removed, and the crude mixture purified by silica gel chromatography (eluent: diethyl ether/hexane 4/1).

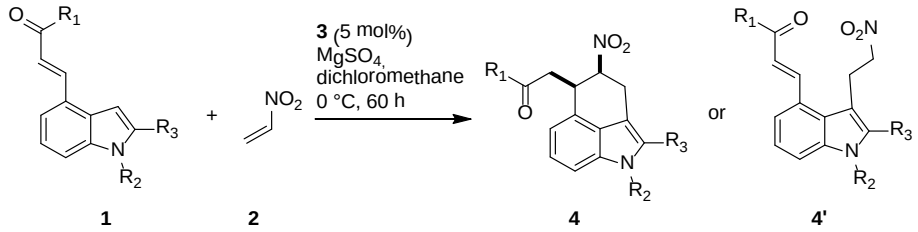
5.1.4 Sintesi nitroetene[14]



In a Claisen apparatus equipped for vacuum distillation and liquid nitrogen cooled trap, 2-nitroethanol (0.97 mL, 12.6 mmol) and phthalic anhydride (2.8 g, 18.8 mmol) were added. The pressure is set to 110 mbar and the temperature of the mixture was raised to 150 °C and left at that temperature until the distillation ceased. Nitroethene **2**, a yellow liquid, was collected from the cold trap by diluting with toluene. The liquid was dried with $CaCl_2$, filtered and further diluted, in order to obtain a nitroethene ~ 1 M solution in toluene, as determined by ^{1}H NMR spectroscopy.

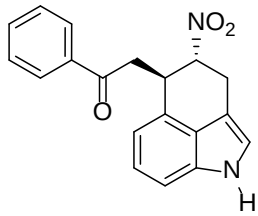
5.2 Friedel-Crafts – Michael Domino reaction between 4-vinyl indole and nitroethene catalysed by (*R*)-TRIP

General procedure for the catalytic reaction



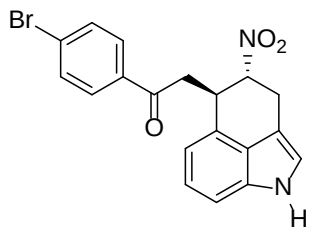
To a Schlenk tube equipped with a magnetic stirring bar, $MgSO_4$ (30 g) was added and flame dried. The Schlenk was evacuated and flame dried again under vacuum. Once cooled to room temperature, the Schlenk was filled with nitrogen. The indole derivative **1** (0.1 mmol), catalyst **3** (3.8 mg, 0.005 mmol) and freshly distilled dichloromethane (0.30 mL) were sequentially added, the resulting mixture cooled at 0 °C and stirred for five minutes, then nitroethene **2** (1.00 M in toluene, 0.15 mmol, 150 mol%) was added in one portion. After 60 h at 0 °C, the reaction mixture was filtered through a plug of silica gel, and the plug was washed with dichloromethane and Et_2O. After removal of the solvents, the reaction crude was analysed by ^1H NMR spectroscopy to determine the diasteromeric ratio of the cycloadducts. Finally, the residue was purified by chromatography on silica gel.

1-((4*R*,5*R*)-4-Nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)-1-phenylethanone (3a)



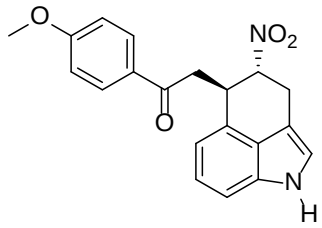
Following the general procedure, the title compound was obtained as a white solid in 95% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 33.6 min, t_{min} = 28.6 min, 97% ee).^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.06 (br s, 1H), 7.96-7.93 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.44 (m, 2H), 7.21 (br d, J = 8.0 Hz, 1H), 7.14 (br t, J = 8.0 Hz, 1H), 6.96-6.93 (m, 1H), 6.83 (d, J = 7.1 Hz, 1H), 5.24 (dt, J_t = 5.8 Hz, J_d = 4.4 Hz, 1H), 4.65 (q, J = 6.2 Hz, 1H), 3.79 (dd, J = 16.0, 5.7 Hz, 1H), 3.43 (dd, J = 18.1, 6.0 Hz, 1H), 3.40 (ddd, J = 16.2, 4.3, 1.1 Hz, 1H), 3.33 (dd, J = 18.1, 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 197.2, 136.5, 133.7, 133.5, 129.6, 128.8, 128.1, 124.8, 123.6, 118.9, 116.0, 109.5, 107.3, 85.4, 41.9, 36.9, 25.1; $[\alpha]_D^{25}$ = -107 (c = 0.586 in CH_2Cl_2); ESIMS = 343 ($M + Na^+$).

1-(4-Bromophenyl)-2-((4*R*,5*R*)-4-nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)ethanone (3b)



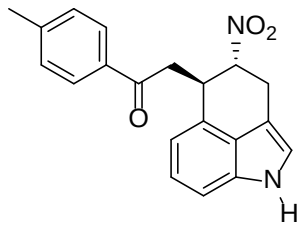
Following the general procedure, the title compound was obtained as white solid in 99% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 37.3 min, t_{min} = 33.7 min, 97% ee).^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.01 (br s, 1H), 7.74-7.70 (m, 2H), 7.54-7.49 (m, 2H), 7.15-7.02 (m, 2H), 6.89 (br s, 1H), 6.79-6.74 (m, 1H), 5.13 (dt, J_t = 5.7 Hz, J_d = 4.4 Hz, 1H), 4.53 (q, J = 6.1 Hz, 1H), 3.70 (dd, J = 16.8, 6.3 Hz, 1H), 3.39-3.29 (m, 2H), 3.20 (dd, J = 18.2, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 196.1, 135.2, 133.7, 132.0, 129.6, 129.3, 128.8, 124.7, 123.5, 119.0, 115.9, 109.6, 107.2, 85.4, 41.6, 36.9, 25.2; $[\alpha]_D^{25}$ = -85 (c = 0.580 in CH_2Cl_2); ESIMS = 421-423 ($M + Na^+$).

1-(4-Methoxyphenyl)-2-((4*R*,5*R*)-4-nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)ethanone (3c)



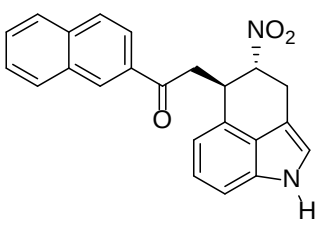
Following the general procedure, the title compound was obtained as a white solid in 91% yield, after chromatography on silica gel (CH_2Cl_2 + 1% Et_2O). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 59.4 min, t_{min} = 50.1 min, 97% ee).^{1}H NMR ($CDCl_3$, 600 MHz) δ = 8.12 (br s, 1H), 7.95-7.90 (m, 2H), 7.19-7.10 (m, 2H), 6.94-6.90 (m, 3H), 6.88 (d, J = 7.2 Hz, 1H), 5.23 (br q, J = 5.6 Hz, 1H), 4.63 (br q, J = 6.2 Hz, 1H), 3.86 (s, 3H), 3.77 (dd, J = 16.8, 6.8 Hz, 1H), 3.47-3.36 (m, 2H), 3.24 (dd, J = 17.8, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 195.7, 163.8, 133.6, 130.4, 129.6, 129.5, 124.7, 123.4, 118.9, 115.9, 113.8, 109.5, 107.2, 85.4, 55.5, 41.6, 37.0, 24.9; $[\alpha]_D^{25}$ = -140 (c = 0.472 in CH_2Cl_2); ESIMS = 373 ($M + Na^+$).

2-((4*R*,5*R*)-4-Nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)-1-(*p*-tolyl)ethanone (3d)



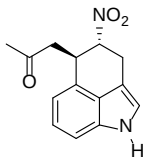
Following the general procedure, the title compound was obtained as a white solid in 99% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 35.8 min, t_{min} = 30.5 min, 99% ee). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.06 (br s, 1H), 7.88-7.81 (m, 2H), 7.29-7.08 (m, 4H), 6.94 (br s,1H), 6.90-6.84 (m, 1H), 5.22 (q, J = 5.6 Hz, 1H), 4.62 (q, J = 6.2 Hz, 1H), 3.77 (dd, J = 16.7, 5.8 Hz, 1H), 3.53-3.35 (m, 2H), 3.27 (dd, J = 18.0, 7.2 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ =196.8, 144.5, 134.1, 133.7, 130.0, 129.4, 128.2, 124.8, 123.5, 119.0, 116.0, 109.5, 107.3, 85.4, 41.8, 37.0, 25.1, 21.7; $[\alpha]_D^{25}$ = -186 (c = 0.560 in CH_2Cl_2); ESIMS = 357 ($M + Na^+$).

1-(Naphthalen-2-yl)-2-((4*R*,5*R*)-4-nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)ethanone (3e)



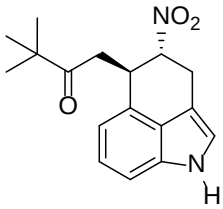
Following the general procedure, the title compound was obtained as a white solid in 98% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 49.4 min, t_{min} = 34.6 min, 97% ee). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.44 (br s, 1H), 8.12-8.01 (m, 2H), 7.95-7.85 (m, 3H), 7.65-7.51 (m, 2H), 7.23-7.11 (m, 2H), 7.02-6.90 (m, 2H), 5.27 (br q, J = 5.3 Hz, 1H), 4.70 (q, J = 5.9 Hz, 1H), 3.79 (dd, J = 16.8, 6.0 Hz, 1H), 3.61 (dd, J = 17.9, 5.7 Hz, 1H), 3.50-3.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 197.1, 135.8, 133.8, 133.7, 132.4, 130.0, 129.6, 128.8, 128.7, 127.8, 127.0, 124.8, 123.7, 123.6, 119.0, 116.1, 110.0, 107.3, 85.4, 42.0, 37.0, 25.1; $[\alpha]_D^{25}$ = -110 (c = 0.793 in CH_2Cl_2); ESIMS = 393 ($M + Na^+$).

1-((4*R*,5*R*)-4-Nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)propan-2-one (3f)



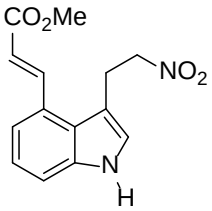
Following the general procedure, the title compound was obtained as a pale yellow solid in 99% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 30.1 min, t_{min} = 24.6 min, 56% ee).^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.05 (br s, 1H), 7.21-7.11 (m, 2H), 6.93 (br s, 1H), 6.83 (br d, J = 7.1 Hz, 1H), 5.07 (dt, J_t = 6.2 Hz, J_d = 4.8 Hz, 1H), 4.39 (br q, J = 5.9 Hz, 1H), 3.71 (dd, J = 16.1, 6.3 Hz, 1H), 3.35 (dd, J = 17.0, 4.5 Hz, 1H), 2.90 (dd, J = 17.6, 6.0 Hz, 1H), 2.80 (dd, J = 18.2, 6.0 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 205.7, 133.6, 129.2, 124.7, 123.5, 118.8, 115.7, 109.5, 107.2, 85.5, 46.2, 36.8, 30.4, 25.3; $[\alpha]_D^{25}$ = -47 (c = 0.436 in CH_2Cl_2); ESIMS = 281 ($M + Na^+$).

3,3-Dimethyl-1-((4*R*,5*R*)-4-nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)butan-2-one (3g)



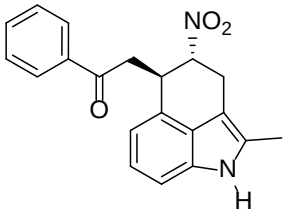
Following the general procedure, the title compound was obtained as a white solid in 90% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 13.9 min, t_{min} = 11.7 min, 94% ee).^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.03 (br s, 1H), 7.23-7.12 (m, 2H), 6.97 (br s, 1H), 6.81 (br d, J = 6.9 Hz, 1H), 5.10 (q, J = 6.9 Hz, 1H), 4.43 (q, J = 6.2 Hz, 1H), 3.77 (dd, J = 16.6, 5.9 Hz, 1H), 3.32 (br dd, J = 16.4, 4.5 Hz, 1H), 2.96 (dd, J = 18.2, 5.9 Hz, 1H), 2.83 (dd, 18.3, 7.0 Hz, 1H), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 213.0, 133.7, 129.7, 124.7, 123.5, 118.8, 116.0, 109.4, 107.3, 85.2, 44.3, 40.1, 36.6, 26.4, 24.9; $[\alpha]_D^{25}$ = -93 (c = 0.500 in CH_2Cl_2); ESIMS = 323 ($M + Na^+$).

Methyl 3-(3-(2-nitroethyl)-1*H*-indol-4-yl)acrylate (**3'h**)



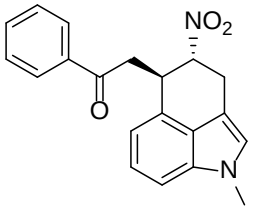
Following the general procedure but performing the reaction at RT for 24 h in the presence of 4 Å MS (45 mg) instead of $MgSO_4$, the title compound was obtained as a pale yellow solid in 62% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed a 96:4 *E*/*Z* ratio, corresponding to the *E*/*Z* ratio of the starting substrate **1b**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = [signals of the *E*-isomer] 8.36 (d, J = 16.1 Hz, 1H), 8.29 (br s, 1H), 7.44-7.37 (m, 2H), 7.27-7.18 (m, 1H), 7.13 (br s, 1H), 6.48 (d, J = 15.7 Hz, 1H), 4.70 (t, J = 6.8 Hz, 2H), 3.84 (s, 3H), 3.65 (t, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = [signals of the *E*-isomer] 167.4, 142.6, 137.2, 127.6, 124.9, 124.7, 122.6, 119.3, 118.8, 113.4, 110.3, 75.8, 51.8, 25.7; ESIMS = 297 ($M + Na^+$).

2-((4*R*,5*R*)-2-Methyl-4-nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)-1-phenylethanone (3i)



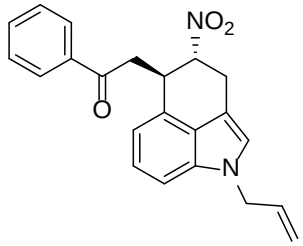
Following the general procedure, the title compound was obtained as a white solid in 90% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 33.4 min, t_{min} = 26.1 min, 95% ee).^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.00-7.92 (m, 2H), 7.80 (br s, 1H), 7.62-7.56 (m, 1H), 7.50-7.43 (m, 2H), 7.12-7.01 (m, 2H), 6.83 (br d, J = 6.3 Hz, 1H), 5.19 (br q, J = 6.0 Hz, 1H), 4.58 (br q, J = 5.9 Hz, 1H), 3.65 (dd, J = 16.2, 6.2 Hz 1H), 3.45 (dd, J = 17.9, 5.8 Hz, 1H), 3.35-3.22 (m, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 197.3, 136.6, 133.5, 133.3, 129.2, 128.7, 128.5, 128.1, 125.8, 122.4, 115.8, 108.7, 103.4, 85.5, 41.8, 36.9, 24.7, 11.6; $[\alpha]_D^{25}$ = -184 (c = 0.524 in CH_2Cl_2); ESIMS = 357 ($M + Na^+$).

2-((4*R*,5*R*)-1-Methyl-4-nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)-1-phenylethanone (3j)



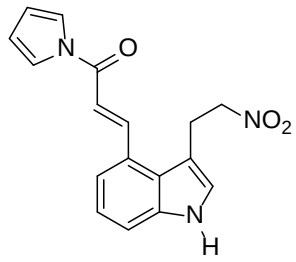
Following the general procedure but using 2.25 equiv. of nitroethene **2**, the title compound was obtained as a white solid in 75% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 36.0 min, t_{min} = 46.9 min, 96% ee).^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.97-7.92 (m, 2H), 7.61-7.54 (m, 1H), 7.49-7.42 (m, 2H), 7.19-7.12 (m, 2H), 6.88-6.80 (m, 2H), 5.22 (br q, J = 5.6 Hz, 1H), 4.63 (br q, J = 6.1 Hz, 1H), 3.78 (dd, J = 16.5, 5.8 Hz, 1H), 3.75 (s, 3H), 3.47 (dd, J = 18.1, 5.8 Hz, 1H), 3.40 (dd, J = 16.2, 4.1 Hz, 1H), 3.30 (dd, J = 18.1, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 197.1, 136.5, 134.8, 133.5, 129.7, 128.7, 128.1, 125.1, 123.6, 123.1, 115.4, 107.8, 105.9, 85.4, 41.9, 36.9, 32.9, 25.0; $[\alpha]_D^{25}$ = -102 (c = 0.332 in CH_2Cl_2); ESIMS = 357 ($M + Na^+$).

2-((4*R*,5*R*)-1-Allyl-4-nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)-1-phenylethanone (**3k**)



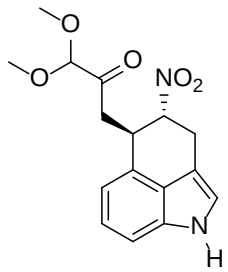
Following the general procedure but using 7.5 mol% (*R*)-TRIP catalyst, 2 equiv. of nitroethene **2** and at RT, the title compound was obtained as a white solid in 70% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 31.8 min, t_{min} = 26.1 min, 94% ee). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.96 (bd, J = 8.1 Hz, 2H), 7.58 (bt, J = 7.0 Hz, 1H), 7.46 (bt, J = 7.3 Hz, 2H), 7.15-7.12 (m, 2H), 6.89-6.84 (m, 2H), 6.03-5.95 (m, 1H), 5.28-5.10 (m, 3H), 4.72-4.65 (m, 2H), 4.63 (bq, J = 6.1 Hz, 1H), 3.78 (dd, J = 16.1, 6.1 Hz, 1H), 3.48 (dd, J = 17.9, 5.8 Hz, 1H), 3.41 (dd, J = 15.8, 4.2 Hz, 1H), 3.32 (dd, J = 17.6, 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 197.1, 136.5, 134.2, 133.5, 133.5, 129.8, 128.7, 128.0, 125.3, 123.1, 122.5, 117.5, 115.5, 108.2, 106.3, 85.4, 49.1, 41.9, 36.9, 25.1; $[\alpha]_D^{25}$ = -75 (c = 0.334 in CH_2Cl_2); ESIMS = 360 ($M + Na^+$).

(*E*)-3-(3-(2-Nitroethyl)-1*H*-indol-4-yl)-1-(1*H*-pyrrol-1-yl)prop-2-en-1-one (**3'm**)



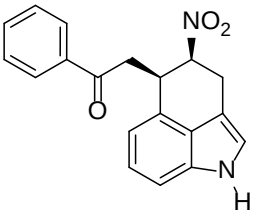
Following the general procedure but performing the reaction at RT for 20 h in the presence of 4 Å MS (45 mg) instead of $MgSO_4$, the title compound was obtained as a yellow solid in 94% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed a single *E* stereoisomer. ^{1}H NMR (acetone-d_6, 400 MHz) δ = 10.55 (br s, 1H), 8.77 (d, J = 15.2 Hz, 1H), 7.78-7.72 (m, 3H), 7.62-7.58 (m, 2H), 7.43 (br s, 1H), 7.25 (t, J = 8.1 Hz, 1H), 6.42-6.40 (m, 2H), 4.97 (t, J = 7.5 Hz, 2H), 3.77 (t, J = 7.45 Hz, 2H); ^{13}C NMR (acetone-d_6, 100 MHz) δ = 163.6, 146.2, 138.7, 128.2, 126.8, 126.4, 122.6, 120.9, 119.7, 117.5, 115.3, 115.2, 113.7, 110.8, 76.4, 26.4; ESIMS = 332 ($M + Na^+$).

1,1-Dimethoxy-3-((4*R*,5*R*)-4-nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)propan-2-one (3n)



Following the general procedure, but performing the reaction at RT for 24 h, the title compound was obtained as a white solid in 99% yield, after chromatography on silica gel (CH_2Cl_2). ^{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 30.0 min, t_{min} = 19.5 min, 98% ee). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.03 (br s, 1H), 7.25-7.10 (m, 2H), 6.96 (br s, 1H), 6.86 (br d, J = 7.0 Hz, 1H), 5.09 (dt, J_t = 6.1 Hz, J_d = 4.5 Hz, 1H), 4.43 (s, 1H), 4.42 (q, J = 6.1 Hz, 1H), 3.73 (br dd, J = 16.1, 5.9 Hz, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.44-3.35 (m, 1H), 3.05 (dd, J = 19.3, 6.5 Hz, 1H), 3.00 (dd, J = 19.7, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 203.0, 133.7, 129.2, 124.7, 123.5, 118.8, 115.9, 109.5, 107.4, 104.5, 85.4, 55.2, 55.1, 40.0, 36.1, 25.3; $[\alpha]_D^{25}$ = -36 (c = 0.39 in CH_2Cl_2); ESIMS = 341 ($M + Na^+$).

Preparation of *epi*-3a (1-((4*S*,5*R*)-4-nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)-1-phenylethanone) via base promoted epimerisation. In a vial equipped with a magnetic stirring bar, compound **3a** (0.072 mmol, 97% ee) was dissolved in MeOH (200 μL), and the resulting solution cooled to 0 °C with stirring. A NaOH solution in MeOH (268 μL of a solution prepared dissolving 96 mg NaOH in 1.5 mL of MeOH, 0.43 mmol, 6 equiv.) was added, the reaction allowed to warm to RT. After 2 h stirring, it was judged by TLC (*n*-hexane/Et_2O 3/7) that the diastereomeric mixture had reached the equilibrium composition. The mixture was diluted with Et_2O, sat. aq. NH_4Cl was added, the phases separated, and the aqueous phase extracted with EtOAc (3 x). The combined organic extracts were dried by filtration on a Celite® plug, evaporated and analysed by ^{1}H NMR spectroscopy, which showed a 91:9 diastereomeric ratio favouring the *cis*-isomer. The product was purified by chromatography on silica gel (*n*-hexane/EtOAc 35:65), affording an analytically pure sample of the title compound as a white solid accompanied by its diasteremoeric mixture with the starting **3a** (overall 92% yield). The enantiomeric excess of the product was determined by chiral stationary phase



HPLC (Chiralpak ADH column, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 23.2 min, t_{min} = 20.4 min, 96% ee), showing that epimerisation occurred without racemisation, under these conditions. Optical rotation was not measured due to the very small amount of pure compound available. ^{1}H NMR (acetone-d_6, 600 MHz) δ = 10.07 (br s, 1H), 8.01 (br d, J = 8.3 Hz, 1H), 7.60 (br t, J = 8.3 Hz, 1H), 7.49 (br t, J = 8.4 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.16 (br s, 1H), 7.02 (br t, J = 8.3 Hz, 1H), 6.86 (br d, J = 8.3 Hz, 1H), 5.32 (br quint, J = 4.0 Hz, 1H), 4.60 (br quint, J = 4.0 Hz, 1H), 3.67 (ddd, J = 15.9, 9.2, 1.7 Hz, 1H), 3.62 (br dd, J = 15.5, 7.4 Hz, 1H), 3.59 (dd, J = 15.9, 4.9 Hz, 1H), 3.36 (br dd, J = 17.6, 3.9 Hz, 1H); ^{13}C NMR (acetone-d_6, 150 MHz) δ = 198.7, 138.7, 135.6, 134.6, 131.9, 130.2, 129.6, 126.9, 124.0, 121.1, 117.0, 111.2, 108.9, 87.0, 41.0, 38.5, 31.1, 26.1; ESIMS = 343 ($M + Na^+$).