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XXXII Cycle

Department of Pharmaceutical Science

SYNTHESIS OF NITROGEN-CONTAINING HETEROCYCLIC SYSTEMS OF BIOLOGICAL INTEREST THROUGH DOMINO STRATEGIES

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If you want great things to happen,

you just need the courage to push the first domino.

To the ones, who give me this courage.

Acknowledgements

Let me express my warmest thanks to my supervisor, prof. Egle Maria Beccalli, because this achievement would not have been possible without her as guide. I thank her for having had a key role and for having motivated me in scientific research through curiosity and perseverance. I also thank her for being a master of strength in life, for the determination shown in many occasions.

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I thank all my dearest friends, because despite everything, they are still beside me, making everything around me so beautiful.

I deeply thank my parents, Anna Maria and Francescantonio, for having brought up to become the person I am, for having always been by my side and helped me in the most difficult choices, without forgetting my brother, Daniele and his girlfriend, Silvia.

Finally, I thank my beloved Martin for being an emotional support, for being my motivation and my strength and for having believed in me until the end.

I also want to thank these three years of PhD, because I did not only enrich my scientific knowledge, but I also conquered more energy, balance and

independence than before. I think that scientific research is similar to the pursuit of happiness, you never know exactly what will happen and what will make you really happy. You know that what seems the most promising and extraordinary it is obviously unreachable.

But it is by pursuing what you believe in that you find the strength to face the everyday challenge. Probably your initial idea will change, new paths and prospects will open up. That idea may never be reached, but you would have put passion for every choice. Would you be satisfied to fight for something that you already know it will work, abandoning any visionary idea with the regret of never having tried it? Or would you accept the risk of believing in something bigger, without knowing where it will take you?

I have accepted this risk for the future and so I would like to thank each of you because if you are here beside me, it means that you are part of my pursuit of happiness.

Contents

Abbreviations List

Ac	Acetyl
Ala	Alanine
Boc	*tert*-butyloxycarbonyl
BQ	Benzoquinone
COSY	Correlation Spectroscopy
DCE	Dichloroethane
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
DTBB	4,4′-di-*tert*-butylbiphenyl
ESI	Electrospray ionization
FDA	Food and Drug Administration
HSQC	Heteronuclear Single Quantum Coherence
LCQ	Liquid Chromatography Quadrupole

mcba	*m*-chlorobenzoate
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
ofba	*o*-fluorobenzoate
PIDA	Phenyliodine(III) diacetate - $PhI(OAc)_2$
PIFA	Phenyliodine(III) bis-trifluoroacetate - $PhI(OCOCF_3)_2$
PMP	*p*-methoxy-phenyl
Pyox	Pyridine–oxazoline
Qox	Quinoline–oxazoline
SM	Starting material
THF	Tetrahydrofuran
Ts	Tosyl
TS	Transition State

Introduction

Nitrogen heterocycles are among the most significant structural components of pharmaceuticals.[1] The analysis of FDA approved drugs reveals that 59% of unique small-molecule drugs contain a nitrogen heterocycle and if we consider unique drugs containing at least one nitrogen atom the percentage rises up to 84%. The relative prevalence of the various nitrogen heterocyclic classes in the approved drugs consists of 59% for six-membered rings,[2] followed by five-membered[3] (39%) and fused rings (14%).

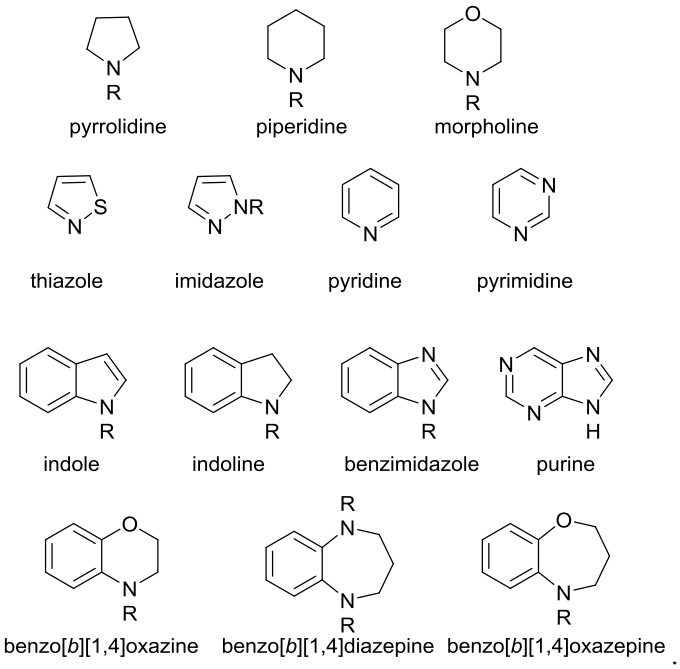


Figure 1. N-containing molecules as important core in pharmaceuticals.

The attractiveness and utility of *N*-containing heterocycles in medicinal chemistry rely on the heteroatom ability to interact with the biological

environment. Indeed, heterocycles are able to get involved in a variety of reactions; depending on the pH of the medium they can act as acids or bases, forming anions or cations. Some of them interact with electrophilic reagents, others with nucleophiles, yet others with both. Sometimes they show amphoteric behaviours against reduction or oxidation, too. Moreover, the ability of many *N*-based heterocycles to produce stable complex with metal ions has great biochemical significance. Among the various clinical applications, heterocyclic compounds have a considerable active role as anti-bacterial,[4] anti-viral,[5] anti-fungal,[6] anti-inflammatory,[7] and anti-tumor drugs.[8,1b]

For that reason, it is not a surprise that nature privileges heterocyclic molecules and mostly the *N*-based ones, thanks to their specific properties. Naturally, that is not the only characteristic related to their biological activity. Also the type and size of ring structures together with the substituent groups on the core scaffold play a key role in the physicochemical properties.[9] It is exactly on the latter properties that the medicinal chemistry is working in order to alter the possible mechanisms of action of pharmaceutical drugs in an attempt to obtain molecularly targeted agents. Indeed, thanks to bioisosteric replacements, lipophilicity, polarity, and aqueous solubility is possible to modulate potency and selectivity of a drug.

For that reason, to answer the growing request of new pharmaceutical compounds with more efficacy and selectivity, there is still need to develop easy procedure tolerating different functional groups for achieving complex heterocycles in few steps.

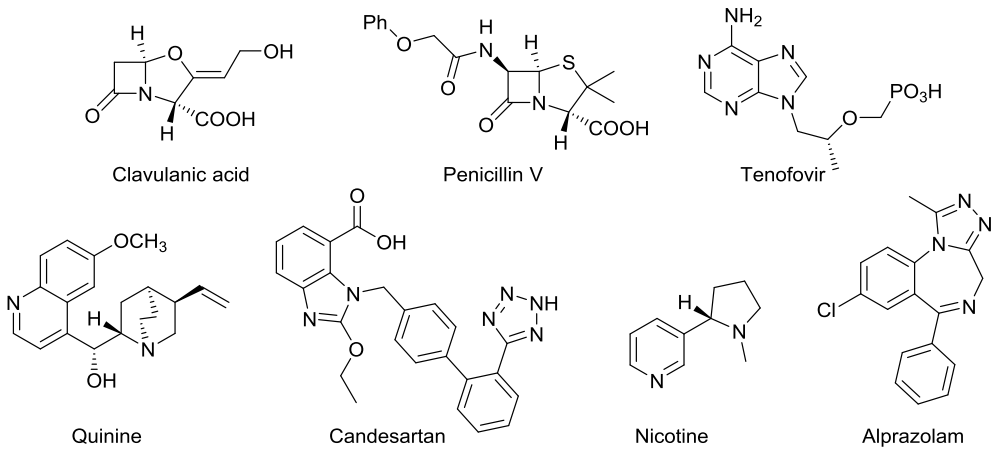


Figure 2. Most common pharmaceuticals containing N-heterocycles

Domino reactions

Achieving complex structure in an easy way, as nature usually does, it is not as straightforward as we could expect and mostly the synthesis needed are really demanding. On the other hand, nature presents its limitations, too. Thus, our goal as scientists is trying to develop strategies that could mimic nature behaviour and go beyond it, offering better pathways and molecules which otherwise could not be synthetized.

Over the past decades, organic chemistry was capable of overcoming the synthetic challenges. Several highly selective procedures have been developed, allowing the preparation of complex molecules with excellent regio-, chemo-, diastereo-, and enantioselectivity. One of the most remarkable examples is the synthesis of Palytoxin with 64 stereogenic centres.[10] Despite the significance of this accomplishment, the organic chemistry is not focused anymore on what it is possible to synthetize but how we can do it. Nowadays, the organic chemistry is influenced by the increasing importance of environmental problems. The chemical resources have a limit and some of them could negatively influence the ecological balance.

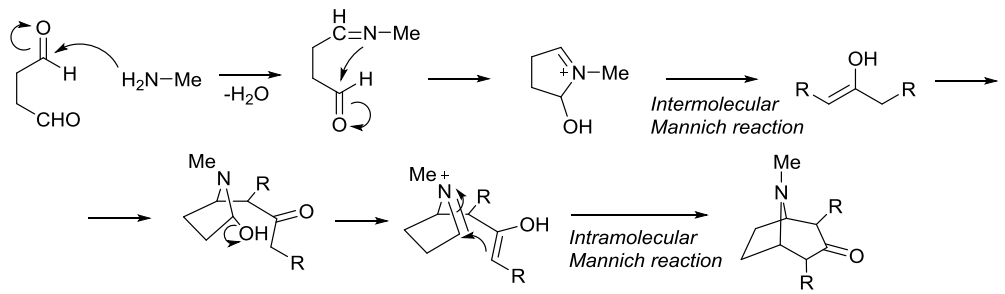
For that reason, the development of sustainable procedures that are able to reduce the waste, to preserve the resources and to increase efficiency is an emerging need. One of the possibility to do that is to replace the common stepwise reactions with domino reactions.[11] The formation of multiple bonds at the same time, not only will be favourable for the environment, but will also allow a reduction in production cost. In fact, the amount of solvents, reagents, energy and work would be dramatically decreased.

Thus, according to the definition of L. F. Tietze[11a], *a domino reaction is a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.*

Therefore, the three cardinals of domino reactions are:

- the bond-forming economy defined by the number of bonds formed in one sequence;
- the structure economy determined by the increase in structural complexity;
- the suitability for wider application.

The first domino reaction of a natural product was performed by Schöpf and Robinson[12] in 1917, where the bicyclic tropinone was formed through a double Mannich reaction starting form a simple mixture of succindialdehyde, methylamine, and acetonedicarboxylic acid (Scheme 1). The *one-step* synthesis of the tropinone ring, structure present in several alkaloids such as cocaine and atropine, enhances the synthetic advantage of this reaction.



Scheme 1. Tropinone synthesis by Robinson in 1917.

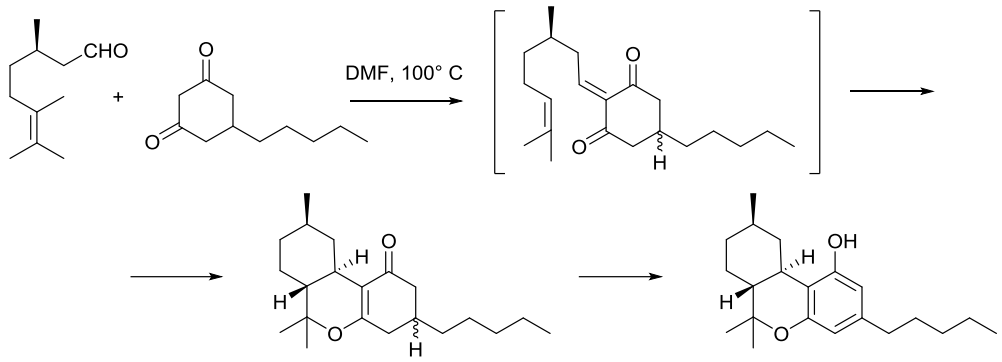
At this point, a classification of the different types of domino reactions will allow a better understanding of the domino reactions that will be discussed later. The classification is based on the intermediate generated in the first step. Therefore, we can distinguish six categories:

1. Cationic
2. Anionic
3. Radical
4. Pericyclic
5. Photochemical
6. Transition metal-catalysed
7. Oxidative/Reductive

A further distinction takes in consideration if the combinations of steps involved are of the same mechanism or if they are different. Indeed, if the subsequent steps are all of the same kind, we are talking about a homo-domino reaction, otherwise a hetero-domino reaction.

Considering that during the whole process the reaction conditions are not modified, it is understandable that the homo-domino reactions such as cationic-cationic, anionic-anionic, radical-radical, pericyclic-pericyclic, and transition metal-catalysed reactions are found in literature more frequently. However, with a deeply study of the starting material structure, it is possible to have also very powerful hetero-domino reactions[13] (

Scheme 2) such as the anionic-pericyclic sequence or even anionic-pericyclic-pericyclic one.

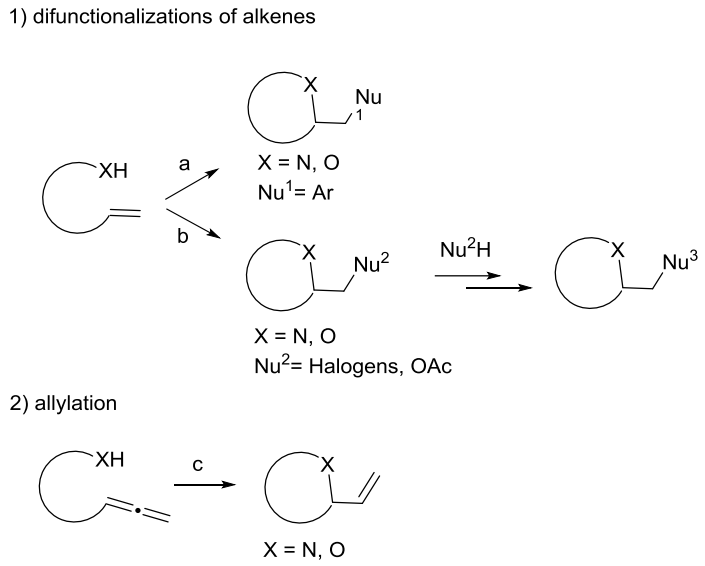


Scheme 2. Synthesis of Hexahydrocannabinol, a Domino Knoevenagel Hetero-Diels-Alder reaction.

Aim of the Thesis

The development of efficient synthesis of bioactive compounds such as natural products, drugs, diagnostics, and agrochemicals is a very important issue of modern chemistry. Indeed, the utility and the value of a molecule decrease in function of the increasing number of step necessary for its synthesis, due to a lack of economy and ecology which limits its widespread use. For that reason, taking in consideration the careful use of our resources and of our time, the decrease of the waste, and, finally, the abolishment of all toxic reagents and solvents, optimal synthesis need to be still developed in order to achieve different functionalized compounds in an automatized way.

Therefore, the aim of my research foresees the synthesis of a library of heteropolycycles, through domino reactions, in order to achieve the heterocyclic ring and, at the same time, its functionalization with an appropriate nucleophile. The nature of the nucleophile will depend on the functionality to pursuit. Thus, when it will be possible, the nucleophile of interest, such as aryls and other heterocycles, will be inserted directly during the *one-pot* process (Scheme 3, 1a). On the other hand, when the conditions required for the domino process will not be compatible with the nucleophile of interest or with the final product, the heterocyclic nuclei will be functionalized with halogens or acetoxy groups, which can be replaced or undergo further transformations (Scheme 3, 1b). Also an intramolecular addition of nucleophiles to allenes will be illustrated in the last chapter, as means of achieving enantioenriched vinyl-substituted heterocycles (Scheme 3, 2c).



Scheme 3. General scheme for the intramolecular addition of nucleophiles to alkenes and allenes.

So, starting from not-activated substrates such as alkenes and allenes bearing a nucleophile heteroatom at an appropriate position of the carbon chain, intramolecular reactions will be investigated as tools to achieve significant pharmaceuticals nuclei.[14,1a] An enantioselective version of the same will be discussed, focusing on strengths and limitations of this approach.

CHAPTER 1

Pd-catalysed Domino Reaction

Among the different types of domino reactions described above, the transition metal-catalysed ones play a key role.[15] Indeed, the choice of the transition metals catalysis is due to their well-known ability to construct complicated molecules from readily accessible starting materials, under mild reaction conditions,[16] obtaining heteropolycyclic systems in an efficient and powerful way.[17] Therefore, the use of this type of transformations as part of a domino reaction is of increasing interest. Moreover, the utility of a metal-catalysed transformation compare to classic organic synthesis is implemented by the possibility to perform reactions in a highly enantioselective fashion with the use of catalytic amount of chiral ligands.

Among transition metals, palladium has always played a great role, due to the wide range of reactions which is able to catalyse.[18] The range of functional groups tolerated, the different types of reaction catalysed together with the formation of C–C, C–O, and C–N bonds as well as other connections under mild reaction conditions distinguish palladium among the other metals.

However, a discrimination between Pd(0)- and Pd(II)-catalysed reactions has to be made. The most common Pd(0)-transformations are the Heck[19] and the cross-coupling transformations such as the Suzuki,[20] the Stille,[21]

and the Sonogashira[22] reaction, which allow the arylation or alkenylation of C–C double bonds, by using boronic acid derivatives, stannanes, and alkynes, respectively. Another important Pd(0)-transformation is the nucleophilic substitution of usually allyl acetates or carbonates known as the Tsuji–Trost reaction.[23]

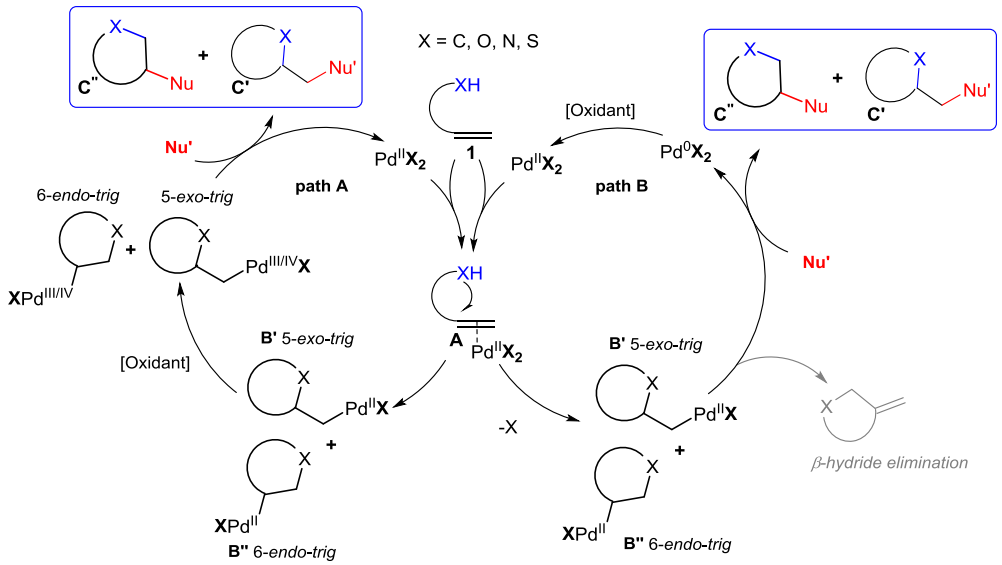
The most versatile Pd(II)-catalysed transformation is the industrially used synthesis of acetaldehyde from ethylene, known as Wacker oxidation.[24] Thus, palladium(II) complexes are extremely important in organopalladium chemistry in so far as they are typically electrophilic, soluble in most common organic solvents, and stable to air, avoiding problems of storage and handling. The most common organic substrates for Pd(II) are electronrich species, such as olefins, alkynes, and arenes, with reversible formation of Pd(II) complexes, which could undergo subsequent attack by nucleophiles.

So, by combining two or more Pd-catalysed transformations in a domino process we are able to offer not only a more efficient and elegant approach but also ecological and economical advantages.

After the pioneering work on difunctionalizations of alkenes[25] of Hegedus and Bäckvall[26] describing processes based on the use of palladium(II) salts mostly in a stoichiometric amount, the use of catalytic amounts of palladium(II) coupled with an appropriate reoxidant was conveniently and deeply investigated by Sorensen,[27] Muñiz,[28] Stahl,[29] Sanford,[30] and Michael.[31]

In the Scheme 4 are summed up the main oxidative pathways[32] which a Pd(II)-complex could undergo. These reactions generally rely on the strong interaction of palladium(II) salts with the π-orbitals of alkenes, alkynes or allenes, which opens up several different reaction pathways where new carbon–heteroatom bonds can be formed. Importantly, these pathways are often finely balanced, with similar substrates sometimes undergoing

oxidation *via* different mechanisms. The choice of catalyst and/or ligand can influence the reaction pathway, allowing different products to be accessed from the same substrate with high control.



Scheme 4. Pd(II) oxidative pathways strarting from alkenes.

Coordination of an alkene **1** (Scheme 4) to a palladium(II) salt makes a typically electronrich alkene considerably more electrophilic, allowing **A** to be attacked by a nucleophile. The attack of the nucleophile onto the activated alkene **A** through a concerted nucleopalladation gives the σ-alkylpalladium intermediate **B**, which could exist in the two regioisomers, **B'** and **B"**, in function that the cyclisations proceeds *via exo*- or *endo*-trig. A Pd(0)/Pd(II) (path B, Scheme 4) or Pd(II)/Pd(IV) (path A, Scheme 4) catalytic cycle is observed depending on the reaction conditions employed. The *β*-hydride elimination from the σ-alkylpalladium intermediate is the step accountable for the Pd(0)/Pd(II) cycle. After the step of nucleometallation, in the presence of a second nucleophile, the difunctionalization of the starting material, instead of the normal *β*-

hydride elimination, could be observed as a result of a domino process affording products **C**' and/or **C"**.

Thus, starting from alkenes bearing a nucleophile heteroatom at an appropriate position of the carbon chain is possible to achieve four-, five-, six- or seven-membered heterocycles.

1.1 Aminoarylation[a]

Among the transition metal-catalysed reactions, the double functionalization of unsaturated systems under palladium catalysis represents a rapid and economical method to obtain functionalized substrates. In particular, in this case the formation of an intramolecular C-N bond on alkenes combined to a new C-C bond formation results in the synthesis of functionalized heterocyclic systems.[33] In that case, the use of the palladium catalyst in oxidative conditions,[34] rather than the Pd(0)-catalysed reactions of aryl(alkyl) halides, offers the possibility of alternative regioselectivity in the bonds formation.

The interest in the difunctionalization reaction is motivated by the extensive work made by my group in the last years, using palladium-catalysed reactions in arylation/halogenation, arylation/esterification, aminohalogenation and diamination processes.[35] In a recent work on oxyarylation[36], oxazepanes ring were obtained through a selective 7-*endo*-cyclization process, starting from *N*-allyl-*N*-tosyl aminoethanol in the presence of a Pd(II) catalysis.

Aminoarylation reaction have received particular attention due to their ability to provide functionalized heterocyclic systems.[37] Indeed, the imidazolinone ring is present in natural products[38a] and in different pharmaceutical compounds including anti-inflammatory,[38b] anti-infective,[38c] antibacterial,[37d] antitumoral,[37e-h] and antipsychotic[37i].

[a] Adapted from the published paper. S. Giofrè, E. M. Beccalli, F. Foschi, C. La Rosa, L. Lo Presti, M. S. Christodoulou, *Synthesis* **2019**, 51(18), 3462-3470

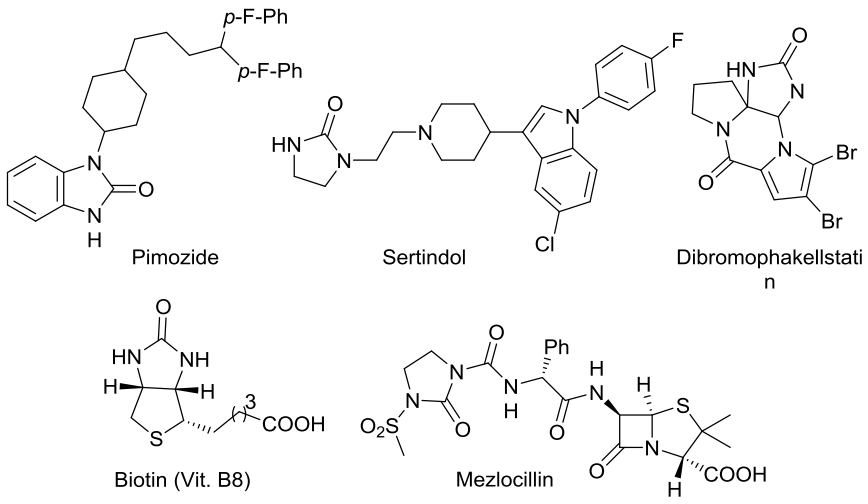


Figure 3. Pharmaceuticals and natural products containing urea moieties

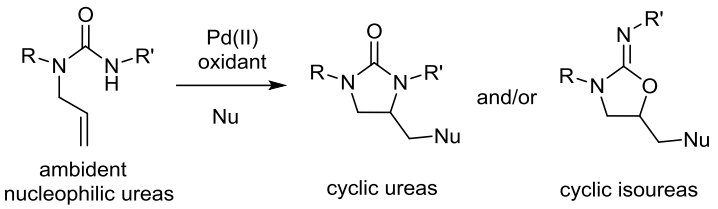
Regarding the aminoarylation process, the goals to pursuit are:

a) the search of new conditions for the difunctionalization of alkenes;

b) a depth study of the chemo- and regioselectivity of the process;

c) the use of mild reaction conditions.

In the introductory part "Pd-catalysed Domino Reaction", we have already discussed about the two possible regioselective 5-*exo*- and 6-*endo*-trig cyclisations in the intramolecular step. Thus, together with this double *exo*/*endo* regioselectivity, depending on the reaction conditions and on the substrates, *N*-allylureas, acting as ambident nucleophiles, compete between C-N and C-O bonds formation, too. The chemoselectivity showed in each case allows the construction of cyclic ureas or isoureas, respectively.[39]

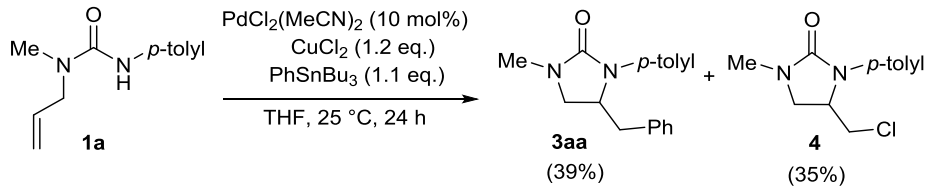


Scheme 5. Chemoselectivity of secondary N-allylureas.

The substrate **1a** arises in quantitative yield, from the simple *one-step* reaction between the *p*-tolylisocyanate and the *N*-allylmethylamine performed at rt in acetonitrile as solvent.

Initially, we tested the use of catalytic $PdCl_2(MeCN)_2$ 10 mol% in the presence of a slight excess of both $CuCl_2$ as oxidant, and phenyltributylstannane (**2a**) as nucleophile. Indeed to this purpose, the palladium(II)/copper(II) combination, as catalyst and oxidizing agent, respectively, has been demonstrated to be productive in developing new procedures for the synthesis of functionalized (poly)heterocyclic systems.[40] Despite many works have been published regarding the employment of organostannane as reactant in coupling reaction (Stille reaction)[21], their use in domino reactions coupled with Pd(II) catalyst for oxidative addition reactions is less studied and explored.

Therefore, the reaction afforded the aminoarylation product **3aa**, isolated in 39% yield, and also the 4-chloromethyl-imidazolidinone **4** (35% yield), arising from an aminohalogenation process, due to the double action of the copper salt as oxidant and as nucleophile (Scheme 6).

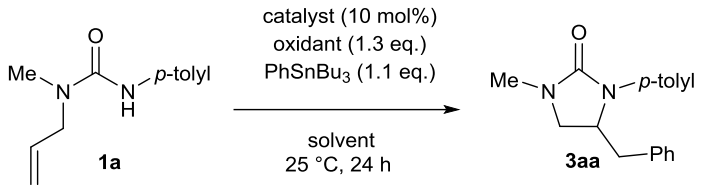


*Scheme 6. Aminoarylation reaction of the substrate **1a***

Beside the formation of the side product **4**, the observed cyclisation was totally chemoselective due to the addition of the nitrogen to the double bond with the obtainment of cyclic urea. Moreover, the reaction gave exclusive 5-*exo*-trig cyclisation, showing total regioselectivity with the formation of the 4-substituted imidazolidinones. About this latter, the result obtained is quite outstanding. Indeed, beside *exo*-cyclisations on protected aminoalkenes have been reported,[41] generally palladium-catalysed difunctionalization of 4-pentenyl-amides in oxidative conditions afforded hexatomic rings, a result which was never observed in our experiments (see Table 1-2).[42,40a-b] Moreover, palladium-catalysed oxidative oxyarylation reactions highlighted the preference for the *endo*-cyclizations.[43,36]

Thus, in order to exclude the formation of the side product **4** and to improve the yield of the reaction, different reaction conditions were investigated changing the oxidant reagent and the solvent (Table 1). The use of $Cu(OAc)_2$ as oxidant was unfruitful (entry 2), as well as the silver salt (entry 3) and 1,4-benzoquinone (entry 4). Only when the oxidant was replaced with the inexpensive H_2O_2, improvements were observed (entry 5). The palladium catalyst was essential for the outcome of the reaction (entry 6), whereas different solvents than THF didn't afford the formation of the product (entries 7, 8). This result is quite attractive, since the use of hydrogen peroxide as the sole oxidant in this context is quite rare.

*Table 1. Optimization of the conditions for the aminoarylation reaction of N-allyl-urea **1a***



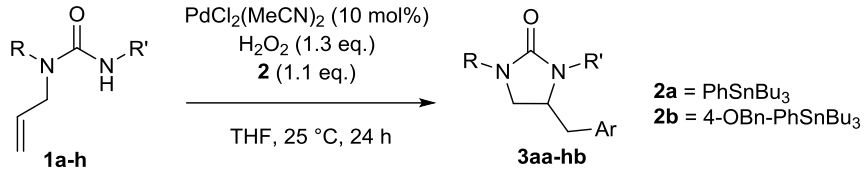
Entry	Catalyst	Oxidant	Solvent	3aa(%)[b]
1	$PdCl_2(MeCN)_2$	$CuCl_2$	THF	39[c]
2	$PdCl_2(MeCN)_2$	$Cu(OAc)_2$	THF	--
3	$PdCl_2(MeCN)_2$	$AgCO_3$	THF	traces
4	$PdCl_2(MeCN)_2$	BQ	THF	traces
5	**$PdCl_2(MeCN)_2$**	**H_2O_2**	**THF**	**59**
6	**-**	H_2O_2	THF	SM
7	$PdCl_2(MeCN)_2$	H_2O_2	MeCN	traces
8	$PdCl_2(MeCN)_2$	H_2O_2	DMF	traces

Reaction conditions: **1a** (0.25 mmol), catalyst (10 mol%), oxidant (1.3 equiv), arylating agent (1.1 equiv), solvent (5 mL). [b] Yield of isolated products. [c] Compound **4** was also isolated (35% yield).

The use of different aryl nucleophiles such as aryl boronic acids, Grignard reagents and arylzinc bromide didn't provide any C-C bond formation in the intermolecular step but instead a C-halogen bond. To exploit the central role of the arylstannane reagents, the 4-benzyloxyphenyltributylstannane (**2b**) was also tested with various *N*-allylureas. In the same reaction conditions (Table 1, entry 5), the *N*-allylureas (**1b-h**) provide the exclusive formation of the 4-substituted imidazolidinones **3**, through a selective 5-*exo* cyclization (Table 2).

However, in the case of substrates **1a** and **1g** with the arylstannanes **2b** and **2a**, the corresponding products were not isolated from the reaction mixture.

*Table 2. Aminoarylation process of N-allylureas **1a-h***



Substrate	R	R'	$ArSnBu_3$	Product	Yield (%)
1a	Me	*p*-tolyl	**2a**	**3aa**	73
1a	Me	p-tolyl	**2b**	**3ab**	--
1b	Me	Ts	**2a**	**3ba**	59
1b	Me	Ts	**2b**	**3bb**	48
1c	Me	4-Cl-Ph	**2a**	**3ca**	66
1c	Me	4-Cl-Ph	**2b**	**3cb**	51
1d	cyclohexyl	Ts	**2a**	**3da**	62
1d	cyclohexyl	Ts	**2b**	**3db**	71
1e	cyclohexyl	4-Cl-Ph	**2a**	**3ea**	58
1e	cyclohexyl	4-Cl-Ph	**2b**	**3eb**	50
1f	Ph	4-Cl-Ph	**2a**	**3fa**	38
1f	Ph	4-Cl-Ph	**2b**	**3fb**	56
1g	Ph	Ts	**2a**	**3ga**	--
1g	Ph	Ts	**2b**	**3gb**	55
1h	Ph	4-Me-Ph	**2a**	**3ha**	59
1h	Ph	4-Me-Ph	**2b**	**3hb**	54

The ring structure was confirmed by single crystal X-ray diffraction analysis of the product **3ea** (Figure 4).[12]

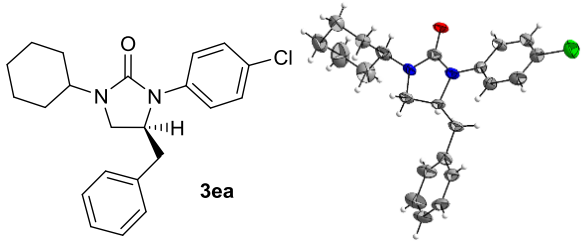
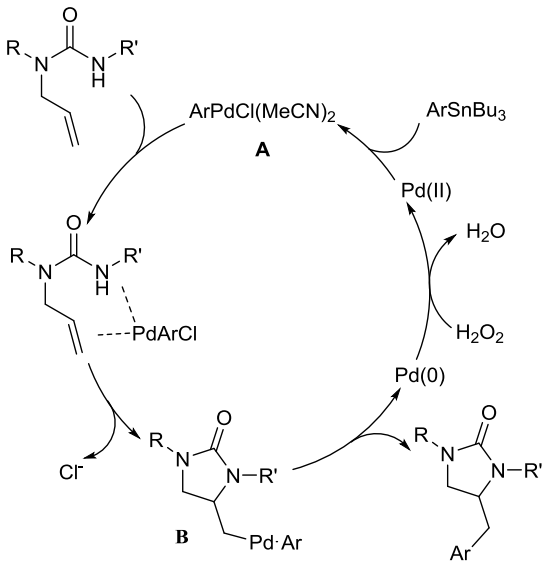


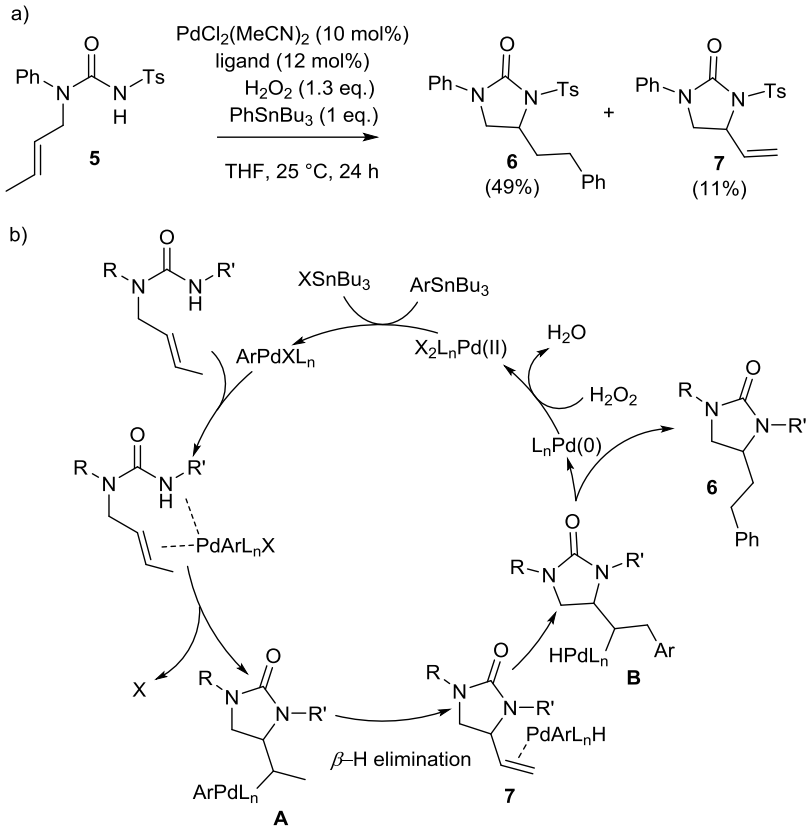
*Figure 4. Left: Molecular structure of the S-enantiomer of the compound **3ea**, as determined by single crystal X-ray diffraction. Right: ORTEP scheme showing the corresponding in-crystal molecular conformation of (S)-3ea at r.t. Thermal ellipsoids are drawn at the at the 25 % probability level. C: gray; H: white; O: red; N: blue; Cl: green.*

On the basis of the previously results reported on the aminoarylation of alkenes, under Pd(II) catalysis,[37e,i,r,s] a plausible mechanism is shown in Scheme 7. Arylpalladium(II) species (**A**) was first formed by transmetalation of arylstannane, followed by a concerted intramolecular nucleophilic attack and insertion of Pd(II) species to the less hindered carbon of the double bond, generating the σ-alkyl-Pd(II) intermediate (**B**). Consequently the reductive elimination of the metal and oxidation of Pd(0) to Pd(II) by H_2O_2 completed the catalytic cycle.



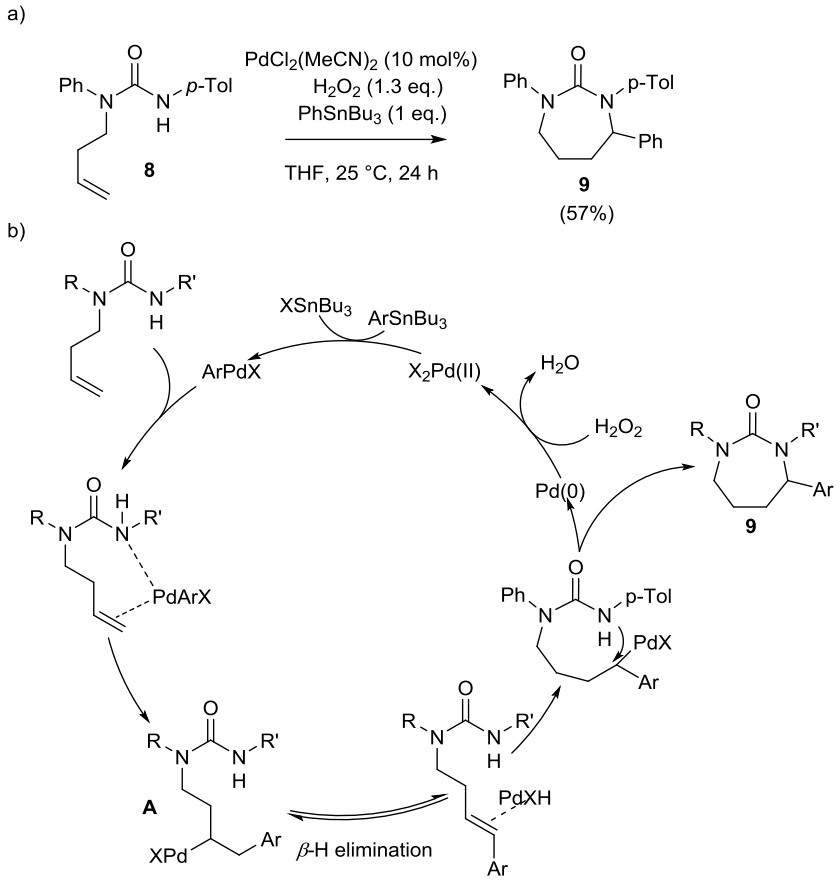
*Scheme 7. Proposed mechanism for the 5-exo-trig cyclization of the substrates **1**.*

The aminoarylation process was also investigated on substrates with modified chain. Starting from the methyl substituted alkene, *N*-2-butenyl-*N*-phenyl-*N'*-tosylurea **5,** the 4-(2-phenylethyl)-imidazolidinone **6** was isolated (Scheme 8). In this case, the process was enhanced by using the (*S*)-4-tert-butyl-2-(2-pyridyl)oxazoline ligand. The mechanism proposed for the compound **6** (Scheme 8) justified the mechanism discussed above. Indeed, in this case after the formation of σ-alkyl-Pd(II) complex (**A**), the faster *β*-hydride elimination leads to the formation of 4-vinylimidazolidin-2-one **7**. The further activation of the double bond made by palladium, affords the aminoarylation product **6** with reverse regiochemistry. Indeed, in the oxidative addition, the aryls attack occurs on the less hindered carbon.



*Scheme 8. a) Aminoarylation reaction of the substrate **5**; b) Mechanism for the formation of the compounds **6** and **7***

On the other hand, the reaction of the *N*-homoallylic substituted urea **8**, in the presence of phenyltributylstannane under the same reaction conditions, gave the 4-phenyl-1,3-diazepan-2-one **9**, as only product, through a 7-*endo*-trig cyclization (Scheme 9). In this case, instead, the first step is the arylation (through the insertion of PhPdCl arising from transmetalation) with the formation of the σ-alkyl-Pd(II) intermediate (**A**). *β*-Hydride elimination and subsequent amination step with reverse regiochemistry, involving the benzylic position provided the 4-phenyl-1,3-diazepane **9**.



Scheme 9. a) Aminoarylation reaction of the substrate 8; b) Mechanism for the formation of the compound 8.

In conclusion, an aminoarylation process of *N*-allylureas employing a Pd(II) catalyst, handy and not so moisture sensitive as Pd(0), in the presence of an organostannane and H_2O_2 as sole oxidant has been developed. The reaction shows a selective *5-exo* ring-closure and C-N selectivity, affording the imidazolidinones as exclusive ring at room temperature.

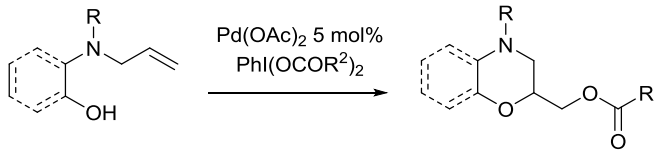
1.2 Alkoxyacylation

In the Chapter 1.1, we have already seen how it is possible to construct C-N and C-C bond from readily available starting materials, providing a variety of cyclic scaffolds, not easily obtained by conventional synthetic methods. The palladium(II)-catalysed addition of nitrogen nucleophiles to alkenes is a well-developed process for forming C-N bonds.[44] A wide variety of nitrogen nucleophiles are known to attack the palladium(II)-activated alkene to give an alkyl palladium(II) intermediate.

On the other hand, strategies which foresee an intramolecular C-O bond, starting from alcohols, phenols, or carboxylic acids as well as from secondary amides, ureas, and carbamates are known in literature, as approach to build oxygen-containing heterocycles.[45] The formation of an intramolecular C–O bond as one step of domino processes can be successfully combined with and intra/intermolecular C–C, C–N, or to another C–O bond-forming step in reactions with alkenes, alkynes, or allenes.[46]

Since the pioneering work of Sorensen in 2005,[41a] reporting a palladium-catalysed aminoacetoxylation of unactivated olefins in the presence of (diacetoxyiodo)benzene as oxidant, this new synthetic methodology has emerged as an interesting alternative to the classical osmium-based Sharpless dihydroxylation and aminohydroxylation.[47] While a wide range of palladium-catalysed methods have been reported for aminoacetoxylation[48] and diamination[49] of alkenes with hypervalent iodine [$PhI(O_2CR)_2$] as the stoichiometric oxidant, less explored are the intramolecular alkoxyacylation.[50]

Herein, we discuss the development of a regioselective 6-*exo*-trig Pd(II)-catalysed cyclisation of *N*-allyl aminophenol and *N*-allyl aminoethanol in the presence of a hypervalent iodine as oxidizing agent.



Scheme 10. Alkoxyacylation of unactiveted N-allyl aminophenols and N-allyl aminoethanols

Our interest in the formation of benzoxazine ring is motivated by the antitumoral activities[14] showed by these scaffolds when they are functionalized with purine derivatives (Figure 5). Their use as medicaments for the treatment and prevention of cancer, in particular for the treatment of breast, lung, colorectal, pancreas, myelo-proliferative neoplasms and syndromes, has been demonstrated.

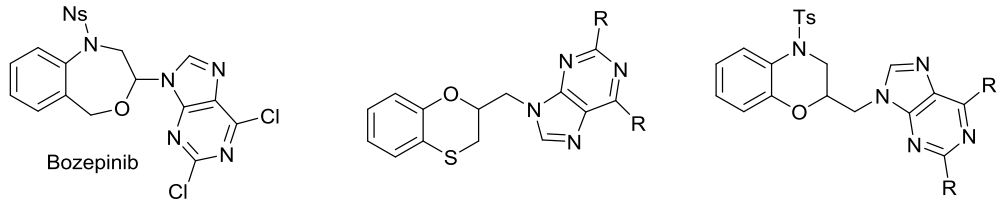
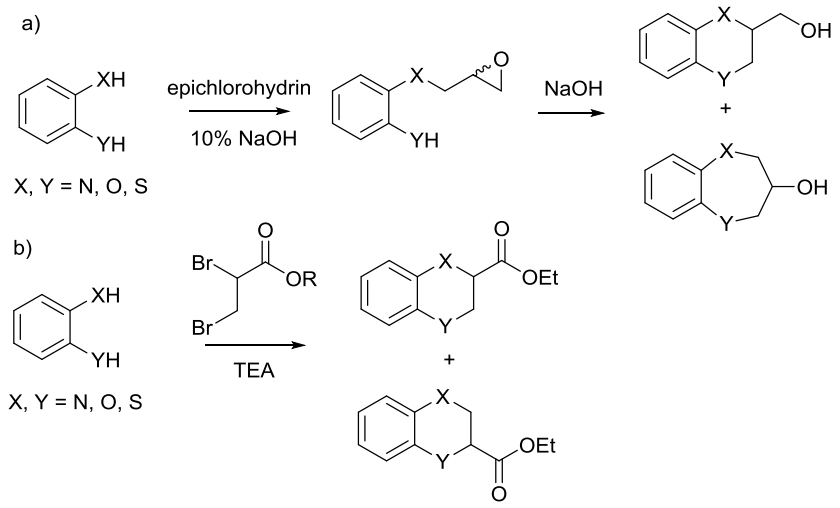


Figure 5. Bozepinib and benzo-fused analogous with antitumor activities.

However, together with the goal to achieve these structures, an efficient transition metal-catalysed domino process needs to be developed. Even though procedures for the synthesis of these nuclei are described in literature, a transition metal-catalysed alkoxyacylation has still not been

investigated, paving the ways for *one-pot* regioselective procedures (Scheme 11).



Scheme 11. Synthetic pathways described in literature for the achievement of benzo-condensed nuclei.

Thus, particular attention will be given to the regioselectivity showed during the cyclisation step and moreover, an enantioselective version of the same reaction will be investigated through the use of chiral ligands coordinating the catalyst.

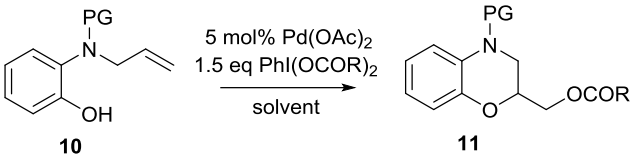
The key reagent for the alkoxyacylation together with the $Pd(OAc)_2$ will be the hypervalent iodine.[51] I(III) are well-known for being versatile reagents for a wide-type of reaction thanks to their mild oxidative properties, their good stability and low toxicity.

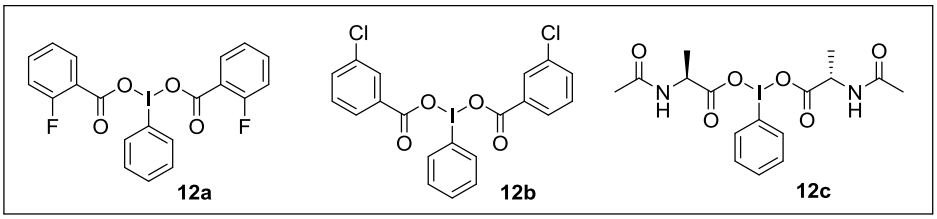
Thus, we investigated the cyclisation of *N*-tosyl aminophenol **10** in CH_3CN, using $Pd(OAc)_2$ as catalyst and (diacetoxyiodo)benzene as the oxidating reagent (Table 3, entry 1), offering a reaction which was neither air- nor moisture-sensitive.

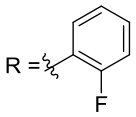
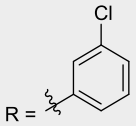
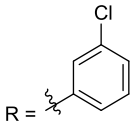
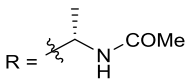
Even if the product **11** was obtained as the only product through a 6-*exo*-trig cyclization, the yields of the process were really low. The change of the solvent didn't affect the outcome of the reaction (entry 2-3).

With the purpose to increase yields, different functionalized hypervalent reagents **12** were synthetized, due to the more reactivity shown in literature in alkene addition reaction,[52a] or C-H functionalization reaction.[52b] Indeed, employing the oxidizing agent **12a** (entry 3) and **12b** (entry 4-5) instead of the commercially available PIDA, the alkoxyacylation reaction afforded compound **11b**, **11c**, respectively with a 96% and 94% yields, and the Boc-derivative **11d** with 85%. Afterwards, a hypervalent aminoacid-type **12c** was prepared and used in the same reaction. Also in this case the desired product **11e** was achieved in good yields (71%), even if as an inseparable mixture of the two diastereoisomers.

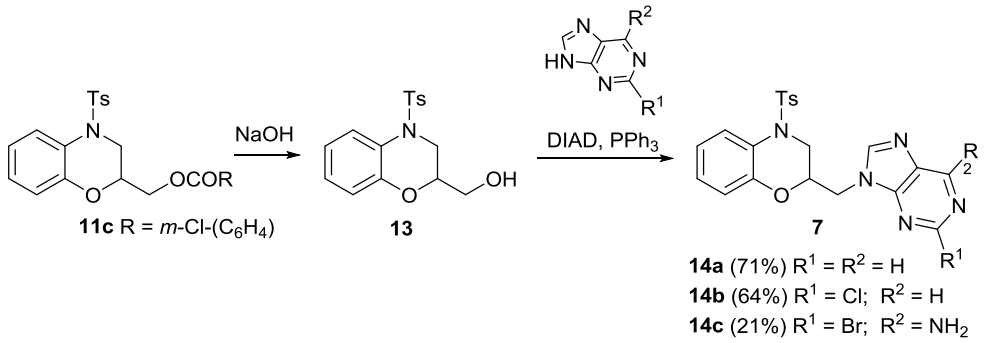
Table 3. Optimization of the conditions for the alkoxyacylation reaction.





Entry	PG	Oxidant	Solvent	T (°C)	Yields (%)
1	Ts	PIDA (2eq)	CH_3CN	rt	**11a** 30%
1	Ts	PIDA (2eq)	THF	rt	**11a** 26%
2	Ts	PIDA (2eq)	DCM	rt	**11a** 32%
3	Ts	**12a** (1 eq)	CH_3CN	rt	**11b** 96% 
4	Ts	**12b** (1 eq)	CH_3CN	rt	**11c** 95% 
5	Boc	**12b** (1 eq)	CH_3CN	rt	**11d** 85% 
8	Ts	**12c** (1.5 eq)	CH_3CN	50 °C	SM
7	Ts	**12c** (1.5 eq)	DCM	40 °C	**11e** 71% 

After achieving the product **11** with a complete 6-*exo*-regioselectivity and in optimal yields, the synthesis of the following purine derivatives **14** was performed (Scheme 12). The hydrolysis of the product **11c** was carried out in an aqueous solution of NaOH in methanol, affording the product **13** in 92% yield. Afterwards, the hydroxyl group obtained was functionalized with the purines, exploiting a Mitsunobu reaction.[53]



*Scheme 12. Synthesis of the purine derivatives **14**.*

1.2.1 Stereoselective alkoxyacylation: N-allyl aminophenol as substrate

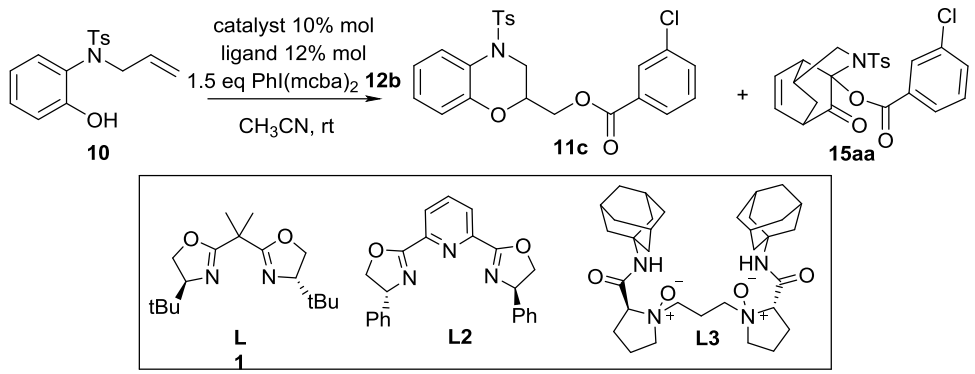
As I anticipated, more challenging but less studied are the domino reactions involving stereocontrol, with few examples mostly of palladium, ruthenium and gold-catalysed reactions.[54] The possibility to construct functionalized and complex molecules in *one-step* and in an enantio- or diastereoselective way, avoiding problems of separation and preinstallation of chiral functional groups, is surely an attractive goal.

Even if asymmetric palladium-catalysed intramolecular oxidative amination of alkenes has been more studied then asymmetric alkoxylation, both of them remain a big challenge in organic synthesis. So far, good enantioselectivity on difunctionalization of alkenes has been

obtained only on substituted aminoalkenes,[42a] where the presence of alkyl groups on the chain facilitates a good stereocontrol in the final product (Thorpe-Ingold effect).

Our initial investigations started with nitrogen-based and *N*-oxide chiral ligands, which, however, significantly inhibited the reaction (Table 4). Thus, not only the yields of the product **11c** decreased to zero but also the by-product **15aa** (which will be discussed in the next chapter) was obtained.

Table 4. . Optimization of the conditions for the enantioselective alkoxyacylation of N-allyl aminophenol.



Entry	Catalyst	Ligand	Solvent	time	Yield 11c (%)	Yield 15aa(%)
1	$Pd(OAc)_2$	**L1** 12%	CH_3CN	1d	15%	49%
2	$Pd(OAc)_2$	**L3** 12%	CH_3CN	1d	10%	43%
3	$Pd(OAc)_2$	**L2** 12%	CH_3CN	1d		51%
4	$Pd(CH_3CN)_2$	**L1** 12%	CH_3CN	1d	-	54%

Then, we turned our attention to explore some new chiral ligands that would be helpful to enhance both reactivity and enantioselectivity. In fact,

the ligand employed probably were not as good as the Pyox/Qox, known to be privileged ligand for the oxidative amination reaction.[55]

In particular, G. Liu group[42a] in 2018 reported an enantioselective 6-*endo* aminoacetoxylation, through the employment of Pyox ligands with a sterically bulky R group at the C-6 position of the pyridine. The rationale beyond the synthesis of these new ligands is the more electrophilicity showed by this type of ligated palladium catalyst. Actually, the presence of a bulky R group increases the Py(N)−Pd bond length,[56] leading to an enhance Pd-electrophilicity important for the olefins activation.[57]

For this reason, the ligands **L4-L7** have been prepared (Figure 6) and employed for the alkoxyacylation instead of the reported aminoacetoxylation, in order to investigate also their efficiency in C-O ring closing reaction.

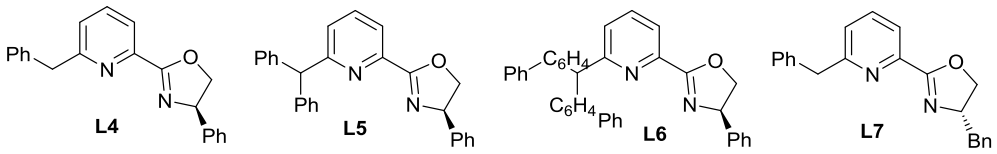
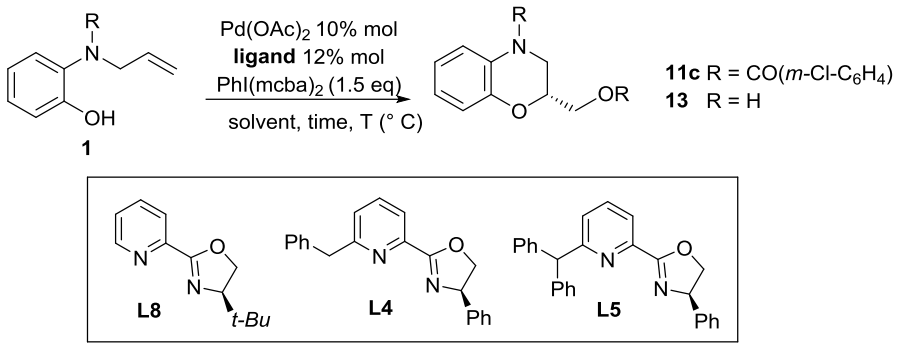


Figure 6. Pyox ligands modified at the pyridine C-6 positions.

Starting our investigations with the reported reaction conditions, 10 mol% $Pd(OAc)_2$, ligand **L4**, and $PhI(OAc)_2$ in DCM (0.6 M), the alkoxyacetoxylated product was not even achieved (entry 1, Table 5), probably due to the low yields already obtained in the absence of the ligand (entry 3, Table 3). For that reason, we move to the use of the hypervalent iodine **12b.** Even if in this case the by-product **15aa** was never obtained or there were only traces from the NMR, we observed the formation of

Table 5. Optimization of the conditions for the enantioselective alkoxyacylation of N-allyl aminophenol.



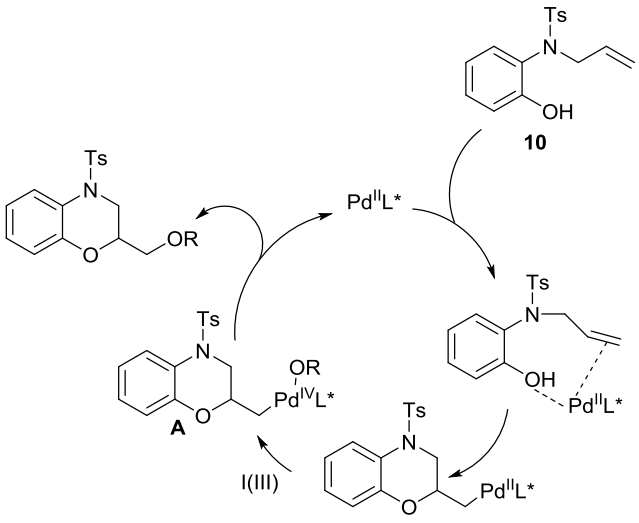
Entry	R	Lig	Oxidant	Solvent	time	T °C	11c	13
7	Ts	**L4**	$PhI(OAc)_2$	DCM	48h	rt	-	-
1	Ts	**L4**	$PhI(mcba)_2$	$PhCF_3$	24h	rt	-	54% 31%ee
2	Ts	**L5**	$PhI(mcba)_2$	DCM	30h	0°C	-	52% 49%ee
3	Ts	**L5**	$PhI(mcba)_2$	toluene	48h	0°C	-	45% 49%ee
4	Ts	**L5**	$PhI(mcba)_2$.	THF	48h	0°C	-	36% 46%ee
5	Ts	**L5**	$PhI(mcba)_2$	EtOAc	48h	0°C	-	34% 46%ee
6	Ts	**L5**	$PhI(mcba)_2$.	PhCl	48h	0°C	-	33% 42%ee
8	Ts	**L5**	$PhI(mcba)_2$ sieves 4°	DCM	30h	0°C		45% -
9	Ts	**L5**	$PhI(mcba)_2$ Selectfluor 1 eq	DCM	30h	0°C	-	35% -
10	Ts	**L5**	$PhI(mcba)_2$ BQ 0.3 eq.	DCM	48h	0°C	-	35% 40%*ee*
11	Ts	**L5**	$PhI(mcba)_2$	DMF	48h	0°C	-	28% -
12	Ts	**L8**	$PhI(mcba)_2$	DCM	48h	0°C	-	36% 14%*ee*
13	Ts	**L5**	$PhI(mcba)_2$	CH_3CN	6h	0°C	93% 10% ee	-
14	Ts	**L5**	$PhI(mcba)_2$	CH_3CN/ toluene 1:5	48h	0°C	78% 30%*ee*	6% 10%*ee*
15	Ts	**L5**	$PhI(mcba)_2$	CH_3CN	48h	-30 °C	25% 10%*ee*	
16	Ts	**L5**	$PhI(mcba)_2$	CH_3CN/ H_2O 1:3	48h	0°C	-	-
17	Boc	**L5**	$PhI(mcba)_2$	DCM	48h	0°C		-

another unexpected product, the compound **13**. Thus, performing the reaction at 0° C in DCM, we were able to achieve the hydroxylated heterocycle **13** with 52% yield and 49% *ee*. Any attempt made to increase the yields and the *ee,* from changing the solvent to adding some additives (entry 3-12, Table 5), didn't affect the outcome of the reaction. Only when we employed the acetonitrile as solvent (entry 13), the expected ester derivative **11c** was achieved in excellent yield but with a decrease of the enantiomeric excess. The explanation of this behavior may depend on the acetonitrile properties, where the interaction of nitrile with the palladium species could affect the formation of the complex Pd-ligand, resulting in a lower enatiomeric excess. Fort that reason, we evaluated the influence of temperature and co-solvents (entry 14-16). Despite the unsuccessful attempt made at -30° C, the use of a 1 to 3 mixture of CH_3CN and toluene allows us to isolate both products, **11c** and **13**. The ester was isolated with a greater *ee* (30%), while **13** was obtained with only 10% *ee*. These result was crucial to understand that the product **13** was not the result of the hydrolysis of the ester, but rather the product of another mechanism.

Therefore, a preliminary explanation for the formation of product **13** is here given. The first assumption is that the hydroxylated product is the result neither of the ester hydrolysis, nor of Pd-catalysed water addition on alkenes. For the former, the justification came from the entry 14, Table 5, while for the latter, we should expect the same behaviour on *N*-allyl aminoethanol, too (see Chapter 1.2.2). Moreover, also an anhydrous reaction under N_2 has been performed in order to exclude this possibility (entry 8).

As a consequence, the hypothesis formulated is based on a different oxidative pathway (Scheme 14) operated by the hypervalent iodine (III) on the Pd(II) complex. We cannot say with certainty at which stage the oxidation of the Pd(II) to the Pd(IV) occurs, in order to justify the

dissimilar enantioselectivity observed for both substrates, **11c** and **13**, but what we suggest it is a different coordination sphere (-OR) of the Pd(IV) species (**A**). Thus, the subsequent reductive elimination of the catalyst leads to the formation of the product functionalized with the corresponding hydroxyl- or acyl group, **13** and **11c** respectively.



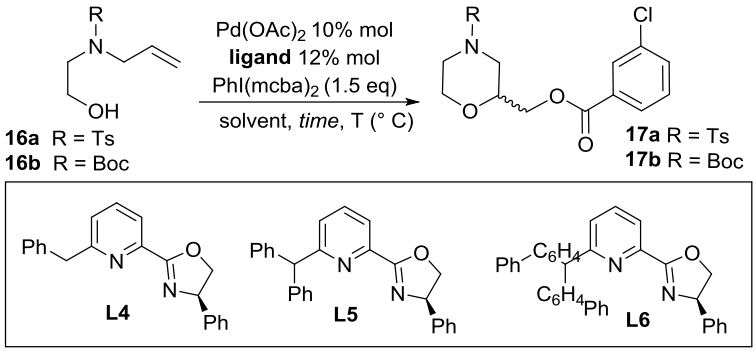
*Scheme 13. Mechanism proposed for the formation of compound **11c** and **13.***

Further studies on the mechanism are still ongoing, in order to confirm this hypothesis and to exclude the possible formation of an epoxide, promoted by the hypervalent iodine (III), and the subsequent Pd-catalysed oxirane-ring opening[58]. The deep understanding of this process will enable us to improve the results achieved so far.

1.2.2. Stereoselective alkoxyacylation: N-allyl aminoethanol as substrate

Better results have been achieved starting from the *N*-allyl aminoethanol **17**, where side reactions were not observed. In this case, the low temperatures influence the enantiomeric excess in a positive way, increasing it from 59% up to 77% when the temperature was changed from 0° C to -20° C (entry 5-6, Table 6).

Table 6. Optimization of the conditions for the enantioselective alkoxyacylation on N-allyl aminoethanol



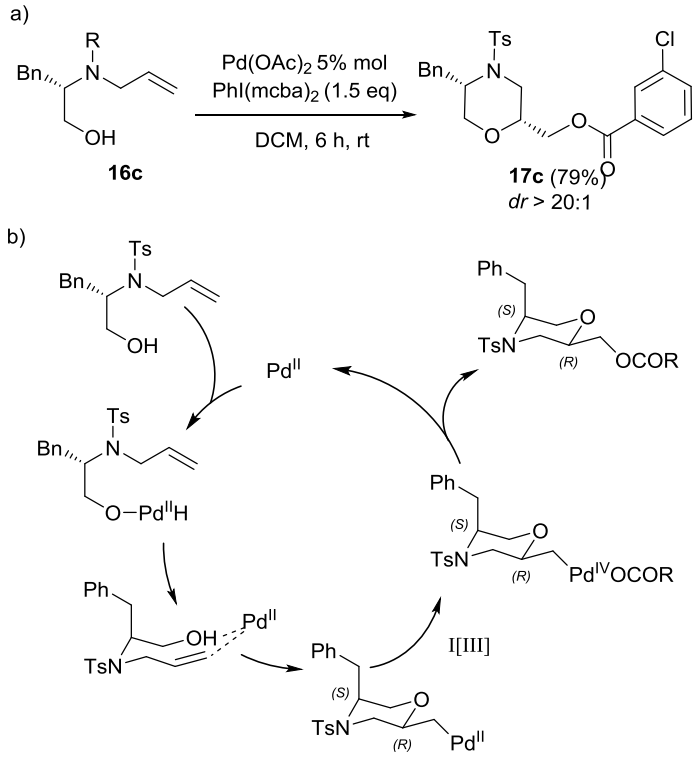
Entry	R	Ligand	Solvent	T°C	Yields% 17	ee%
1	Ts	-	$PhCF_3$ (0.6 M)	rt	63%	rac
2	Ts	**12**	$PhCF_3$ (0.6 M)	rt	81%	6%
3	Ts	**12**	$PhCF_3$ (0.6 M)	10 °C	75%	40%
4	Ts	**12**	DCM (0.6 M)	0 °C	72%	56%
5	Ts	**13**	DCM (0.6 M)	0 °C	73%	59%
6	Ts	**13**	DCM (0.6 M)	- 20 °C	72%	77%
7[a]	Ts	**13**	DCM (0.6 M)	- 20 °C	51%	34%
8	Ts	**14**	DCM (0.6 M)	- 20 °C	80%	69%
9	Boc	**12**	DCM (0.6 M)	- 20 °C	70%	75%

[a] $PhI(OAc)_2$ was used as oxidizing agent instead of $PhI(mcba)_2$

The best ligand, so far, is the **L5**. Indeed, the use of a ligand with more sterically congested bulky group at the C-6 position of the pyridine, **L6**, didn't improve the *ee*, even if a slight increase of the yields was observed,

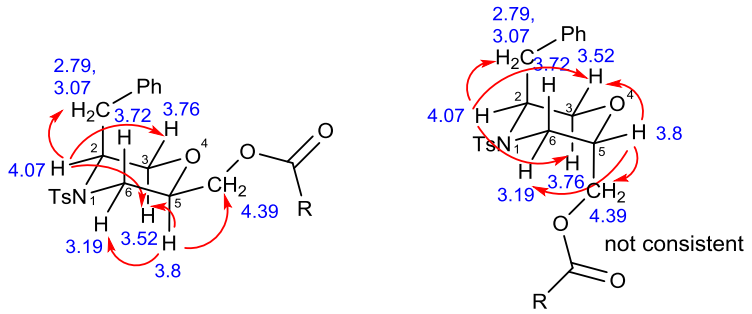
80% (entry 8). When we replaced the Ts-protecting group with the Boc-group, the Boc-derivative was still achieved with comparable results (entry 9).

Also in this case optimization of reaction conditions and extension of the scope are still ongoing. Anyway, what we achieved until now, it is that when the reaction was performed starting from chiral *N*-allyl aminoethanol obtained easily from the reduction of aminoacids to alcohols, the alkoxyacylated product was isolated as single diastereoisomer in absence of the chiral ligand. The formation of a six-membered ring intermediate, together with the Pd-coordination to both double bond and nucleophilic oxygen, may explain the 2,5-*cis*-diastereoselectivity observed in the case of the product **17c** (Scheme 16).[59]



Scheme 14. a) Diastereoselective alkoxyacylation; b) Proposed mechanism for the observed 2,5-cis-diastereoselectivity of compound ***17c****.*

The 2,5-*cis*-disubstitued morpholine structure has been confirmed by ^{1}H-NOESY NMR (Figure 7, for more details see Experimentals). Indeed, the noesy coupling between H(5) and only one proton of C(6) may be explained only through a *cis*-disubstitution (Figure 7a). Moreover, the coupling showed between H(5) and H(3), whose signals falls at 3.8 ppm and 3.52 ppm, respectively, and the lack of couplings between H(2) and H(6) are consistent only with the geometry of the *cis*-derivative.



a) 2,5-cis-disubstituted morpholine *b) 2,5-trans-disubstituted morpholine*

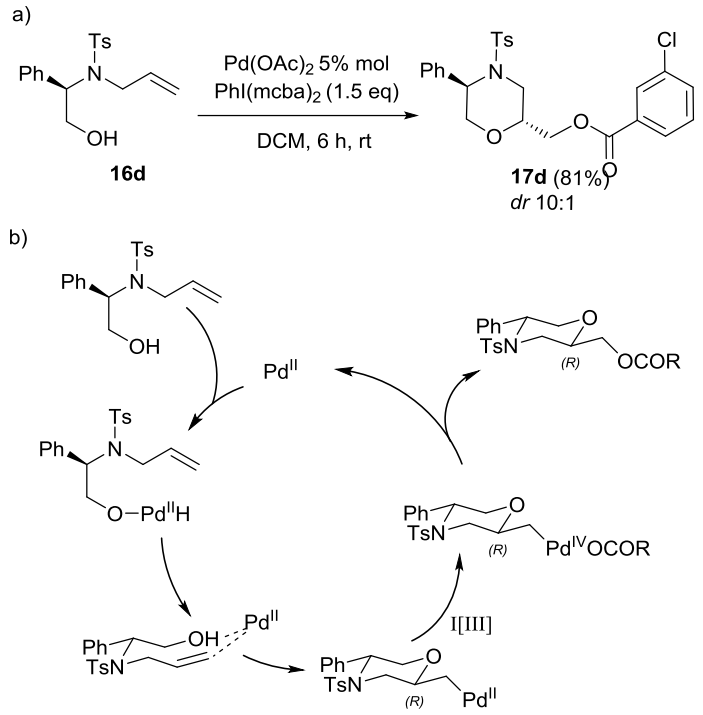
Figure 7. a) ^{1}H-NOESY couplings for the 2,5-cis-disubstituted morpholine structure, ***17c****; b) contradictory ^{1}H-NOESY couplings for the 2,5-trans-disubstituted morpholine structure,* ***17c****.*

Instead, performing the reaction, starting from the (*R*)-*N*-allyl 2-phenyl aminoethanol **16d** in racemic conditions**,** the 2,5-*trans*-disubstituted morpholine has been obtained, with a diastereoisomeric ratio 10 to 1 with the corresponding *cis*-derivative (Scheme 17). The explanation is given by the preferred equatorial attack by the Pd(II), affording *cis*- or *trans*-substituted morpholine in function of the geometry of the system.

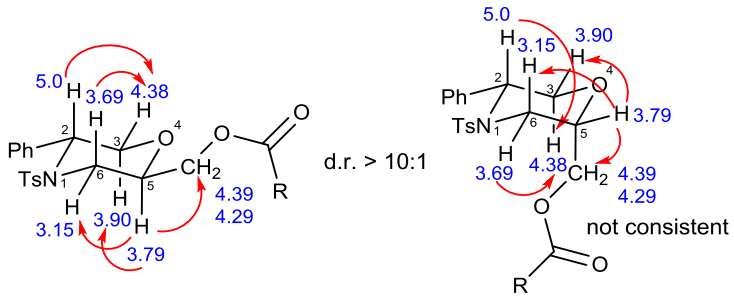
In particular, with this last substrate, we were able to offer a synthesis for the preparation of 2,5-*trans*-substituted morpholine, in opposition to the 2,5-*cis* reported one.[59]

Also in this case, confirmation of the structure was obtained by ^{1}H-NOESY analysis (Figure 8, for more details see Experimentals). The lack of

consistency in the noesy couplings between protons in the 2,5-*cis* structure corroborate the formation of the 2,5-*trans* product **17d** as major isomer (Figure 8).



*Scheme 15. a) Diastereoselective alkoxyacylation of **17d**; b) Proposed mechanism for the observed 2,5-cis-diastereoselectivity of compound **17c***



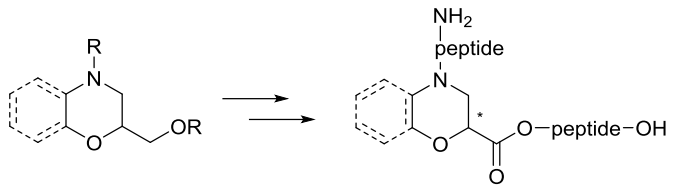
a) 2,5-trans-disubstituted morpholine *b) 2,5-cis-disubstituted morpholine*

Figure 8. a) ^{1}H-NOESY couplings for the 2,5-trans-disubstituted morpholine structure; b) contradictory ^{1}H-NOESY couplings for the 2,5-cis-disubstituted morpholine structure.

In conclusion, we were able to develop an efficient alkoxyacylation process to construct benzoxazine and morpholine nuclei. Further investigations starting from both chiral and achiral alcohol are still under studies.

1.2.3. Benzoxazine and morpholine ring as precursors of ß-aminoacid

Another synthetic utility of the benzoxazine and morpholine rings is the chance to use them as precursors of ß-amino acids and thus, as scaffold in peptide synthesis.



Scheme 16. Morpholine and benzoxazine nuclei as precursors of β-amino acids.

Indeed, their aminoacidic portion leads to the possibility to construct peptidic chains, able to mimic the role and the behavior of natural peptides, such as protein-protein interactions. On the other hand, the characteristic to be unnatural increases the stability towards the proteases.

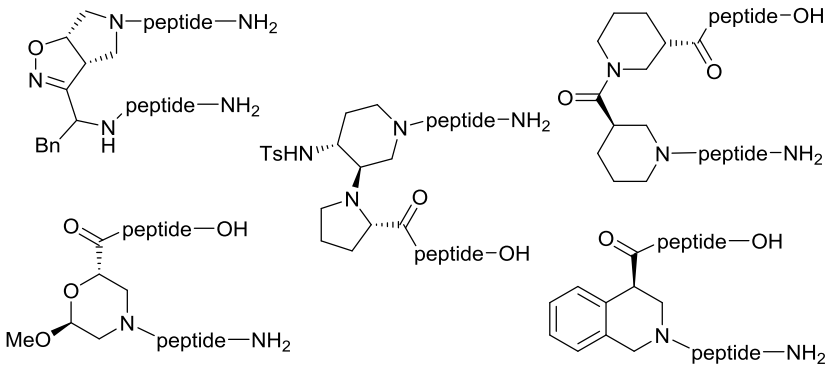
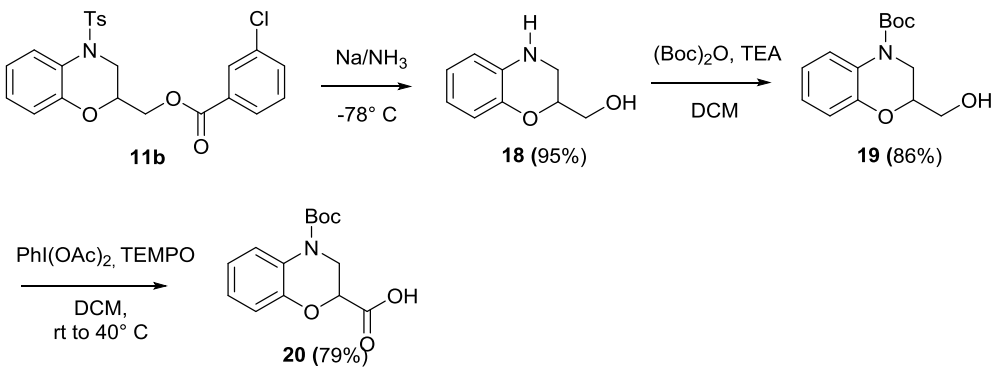


Figure 9. Examples of amino acid scaffolds employed as a tool to stabilize turn in peptides.

The development of an enantioselective reaction is also strengthened by the role of an enantiomer rather than the other to induce a proper and effective conformation in the peptidic chain.[60]

Thus, I show below, how it is possible to achieve *β*-amino acids in good yields, starting from the racemic compound **11c** through a three-steps synthesis (Scheme 19). The choice of the benzo-fused ring compare to the morpholine ring is motivated by the unexplored use of the former compare to the latter.[61] The interest is motivated by the presence of the aromatic portion, which could increase the biological interactions thanks to the π-π interactions, known for their active role in molecular recognition.[62]



*Scheme 17. Pathway for the synthesis of β-amino acids starting from **11c**.*

The steps of *N*-deprotection and *N*-protection are due to the impossibility to achieve the enantioenriched cyclised product starting from the *N*-Boc-protected *N*-allyl aminophenol (entry 17, Table 5). Step that it is not necessary, instead, starting from the *N*-allyl aminoethanol, where the Boc-group does not influence the outcome of the reaction (entry 9, Table 6).

CHAPTER 2

Metal-free Domino Reactions

Iodine as a powerful tool in green chemistry

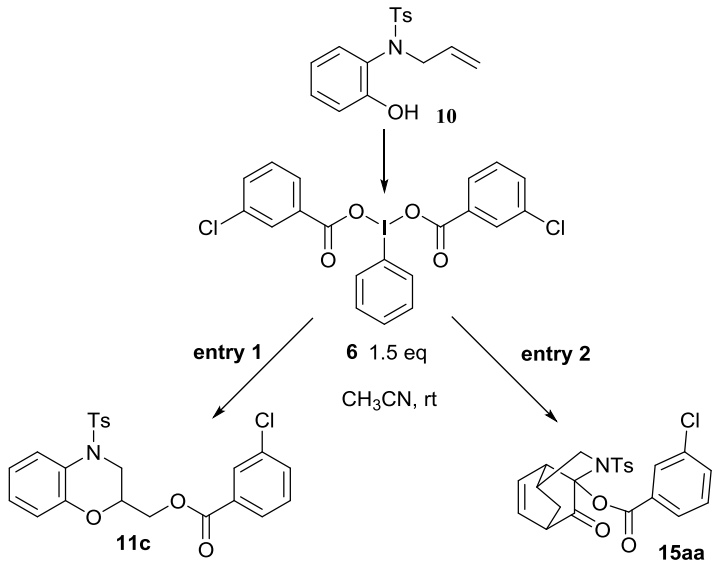
2.1 IMDA (Intramolecular Diels Alder reaction)

As we have already anticipated in the Chapter 1.2, herein the investigation and the development of an oxidative side reaction will be discussed.

Initially, for inducing chirality in the alkoxyacylation process, PyBox, Box and *N*-oxide ligands were employed in Pd(II)-catalysis. The ability to look for the perfect combination of metals and ligands becomes more challenging in those processes, where side reactions could occur easily. This is, indeed, our case. The use of a substrate easily oxidizable, such as a phenol, in oxidative conditions, represents a challenge, not without its risks. For that reason, the use of not suitable Pd(II)-ligands favoured a reaction promoted exclusively by the hypervalent iodine. Indeed, in the conditions of the Table 4, Chapter 1.2, beside the Pd-catalysed alkoxyacylated product **11c**, the compound **15aa** was achieved as major or only product. Thus, the explanation could rely on the inability of the ligands **L1-L3** to keep the electrophilicity of Pd(II), kidnapping the palladium and promoting a hypervalent iodine-based reaction.

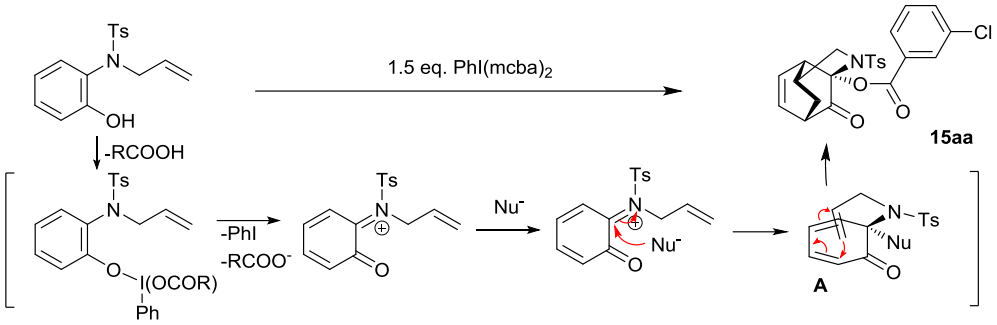
As a matter of fact, repeating the reaction in absence of palladium and in the presence of the only hypervalent iodine **12b**, the compound **15aa** was obtained as exclusive product with a 72% yields (Table 7).

Table 7. Divergent reactivity of N-allyl aminophenol in the presence/absence Pd(II)-catalyst.



Entry	Catalyst	Oxidant	Solvent	Time	T °C	Yield% 11c	Yield% 15aa
1	$Pd(OAc)_2$ 5 mol%	$PhI(mcba)_2$	CH_3CN	20h	rt	95%	-
2	-	$PhI(mcba)_2$	CH_3CN	48h	rt	-	72%

The mechanism behind the formation of this tricyclic system is herein described (Scheme 18). The first step is an oxidation/dearomatization of the aminophenol induced by the coordination of the iodine to the phenolic oxygen. The formation of the ketone group together with the attack of the nucleophile on the carbon in α-position to the nitrogen affords the intermediate **A**. At this point, the intramolecular Diels-Alder reaction is a consequence of the reaction between the just formed diene and the dienophile coming from the allyl group.



*Scheme 18. Mechanism suggested for the formation compound **15aa**.*

The process is fully diastereoselective with formation of only one diastereoisomer among the 8 possible combinations. Thus, the product **15aa** was obtained in good yield and in a diastereoselective fashion, and its structure has been confirmed by single crystal X-ray diffraction analysis (Figure 10).

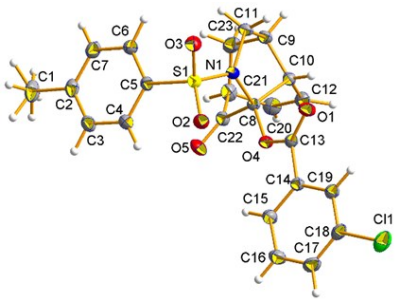


*Figure 10. Molecular unit of **15aa** at rt, with the atom-numbering scheme. Thermal ellipsoids of non-H atoms are drawn at the 30 % probability level. The usual colour code was employed for atoms (grey: C; white: H; yellow: S; blue: N; red: O; green: Cl). The terminal methyl group C1 is rotationally disordered across 2 positions with site occupation factors as large as 0.52(7) and 0.48(7).*

This kind of reactivity was already anticipated by the Tamura-Pelter oxidation,[63] as means of access to *p*-quinone dialkyl monoketals through oxidative dearomatization of phenols in methanol, and then, deeply studied by the pioneering work of Liao[64] through an intermolecular

entrapment of various allylic alcohols undergoing intramolecular Diels-Alder cyclization as a subsequent step. As a consequence, in the last years, the intramolecular Diels-Alder reactions in combination with other reactions, have been fully investigated in domino/tandem processes due to the achievement of densely functionalized intermediates that are generally useful in synthetic chemistry and valuable for the assembly of core units of structurally unique alkaloids, Himandrine,[65] natural products, O-Debenzoyltashironin,[66] Penicillones A and B, [67] Palhinine A,[68] Bilosespenes A,[69] (±)-Atropurpuran,[70] and morphine congeners, *ent*-Hydromorphone[71]

However, while all the cited works refers to phenols, aminophenols are less described. About them, there is only one paper published in 2012,[72] for the synthesis of aza-caged analogous of *Garcinia* xanthones, known for their antitumor activities (Figure 11).

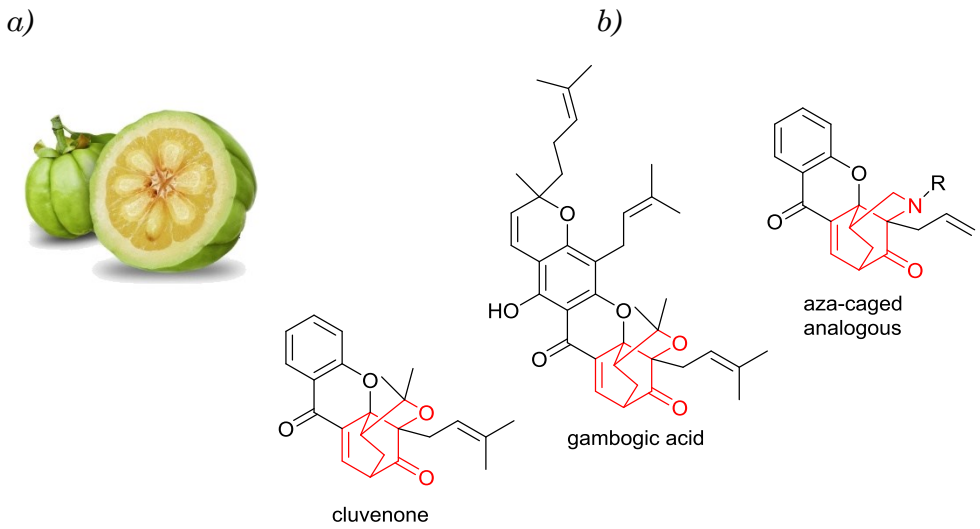
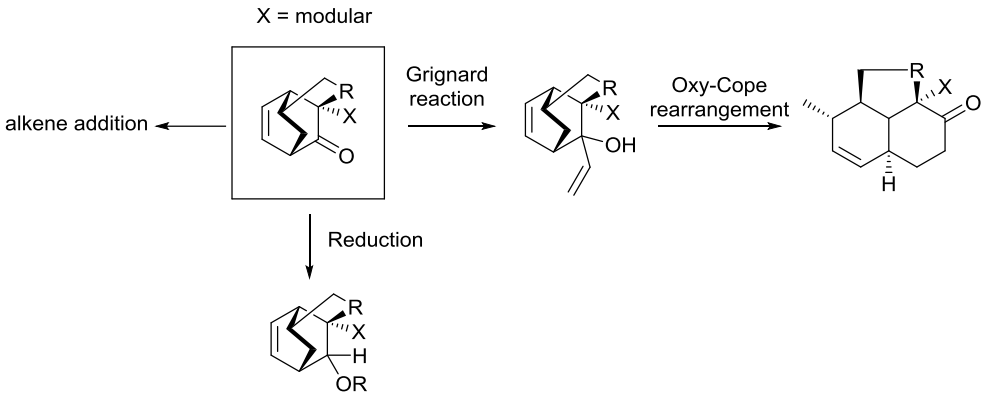


Figure 11. a) Garcinia cambogia; b) Garcinia xhantones and aza-caged analogous

Moreover, there is another detail which should not be overlooked. In literature for this type of reactions there are no records that the nucleophile can be donated by the hypervalent iodine, paving the ways for

further functionalizations (Scheme 19). Indeed, the nucleophilic species reported are mostly unsaturated alcohols with some rare case of sulphonamides.



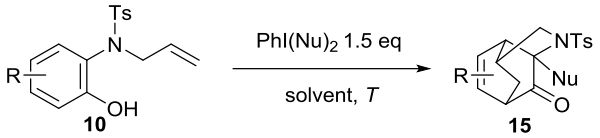
Scheme 19. Representative scheme of the transformations that the tricyclic nuclei could undergo.

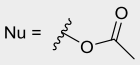
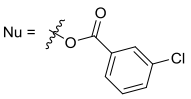
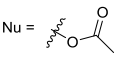
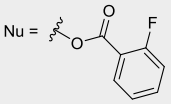
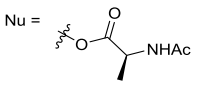
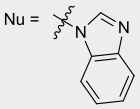
Thus, I described a mild procedure for the achievement of different functionalized tricyclic structures, simply varying the hypervalent iodine species.

Initially, we tested the behaviour of our substrate in the presence of the commercially available $PhI(OAc)_2$, and we observed the formation of the acetoxy derivative with lower yields and longer reaction time (entry 1, Table 8). In order to check the need to pre-functionalize the hypervalent iodine, a control reaction was carried out in the presence of $PhI(OAc)_2$ and *m*-chlorobenzoic acid as external nucleophile (entry 2). The achievement of a mixture of both tricyclic systems, functionalized with the *m*-chlorobenzoate and the acetoxy group, respectively, confirmed the need to pre-installed the nucleophile of interest into the iodine(III). Therefore, good results have been obtained employing both $PhI(ofba)_2$ **12a** (entry 3) and the aminoacid-type iodine (III), $PhI(N\text{-Ac-Ala})_2$ **12c** (entry 4). When a good nucleophile was employed, such as the benzimidazole, the reaction

could be carried out by using $PhI(OAc)_2$ and 1.2 eq of benzimidazole in CH_3CN at rt (entry 5). Unexpectedly, the reaction was not effective when the benzimidazole was employed together with $PhI(OCOCF_3)_2$ (entry 6).

Table 8. Substrate scope varying the hypervalent iodine

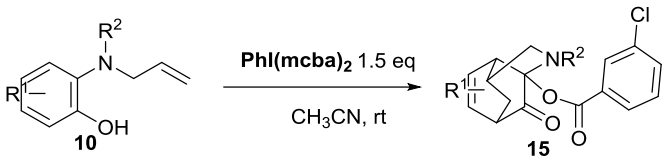


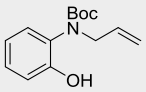
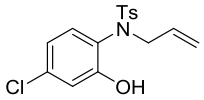
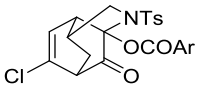
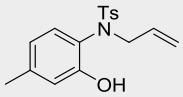
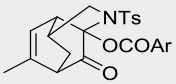
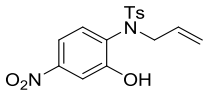
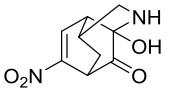
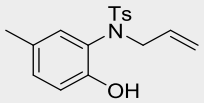
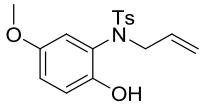
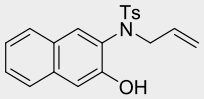
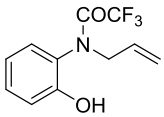
Entry	hypervalent iodine	Solvent	T ° C	time	Products
1	$PhI(OAc)_2$	CH_3CN	rt	30 h	**15ab** 23% 
2	$PhI(OAc)_2$, 1.2 eq *m*-chlorobenzoic acid	CH_3CN	rt	30 h	**15aa** 35%  **15ab** 19% 
3	$PhI(ofba)_2$ **12a**	CH_3CN	rt	30 h	**15ac** 67% 
4[a]	$PhI(N\text{-Ac-Ala})_2$ **12c**	DCM	40° C	30 h	**15ad** 61% 
5	$PhI(OAc)_2$, 1.2 eq benizimidazole	CH_3CN	rt	30 h	**15ae** 63% 
6	$PhI(OCOCF_3)_2$, 1.2 eq benizimidazole	CH_3CN	rt	30 h	-

[a] The product has been isolated as inseparable diastereoisomeric mixture.

Less satisfying are the results obtained varying the starting material, Table 9.

Table 9. Substrate scope varying the starting material

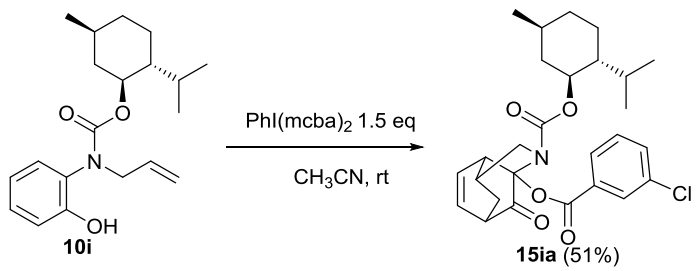


Entry	Substrate	Solvent	T ° C	time	Products
1	**10b** 	CH_3CN	rt	30 h	(complex mixture)
2	**10c** 	CH_3CN	rt	30 h	**15ca** 57%  Ar = *m*-Cl-(C_6H_4)
3	**10d** 	CH_3CN	rt	30 h	**15da** 52%  Ar = *m*-Cl-(C_6H_4)
4	**10e** 	CH_3CN	rt	30 h	**15ea** 63% 
5	**10f** 	CH_3CN	rt	30 h	-
6	**10g** 	CH_3CN	rt	30 h	-
7	**10h** 	CH_3CN	rt	30 h	-
8	**10k** 	CH_3CN	rt	30 h	SM

Indeed, both the trifluoroacetoxy- and the Boc- group were not compatible protecting groups (entry 1,8); the former allowed the complete recovery of the starting material also after 48 h, entry 8; the latter gave a complex crude mixture, entry 1. When the tosyl group was kept constant and the substituents on the aromatic ring were modified, we observed good results only if the substituent was present to the 5-position, affording compounds **15ca-ea** in 52-63% yields (Table 9, entry 2-4).

To investigate an asymmetric IMDA, a chiral precursor was synthetized, the (-)-menthyl-protected aminophenol **10i**. Indeed, among the IMDA, to the best of our knowledge, there are only few example of asymmetric process.[73] For example, in the work of Liao *et al.* it is reported a diastereoselectvity up to 1 to 3.3 between the two diastereoisomers, working on a per-*O*-benzylated *β*-D-glucopyranosyl catechol in the presence of $PhI(OAc)_2$ at -78° C.

In our case, the chiral portion, arising from the nucleophilic acyl substitution with (1*R*)-(-)-menthyl chloroformate, is located on the nitrogen atom. The first attempt has been made in acetonitrile as solvent and using $PhI(mcba)_2$. However, so far, the product was isolated in 51% yields and as an inseparable mixture of the two diastereoisomers (Scheme 20).



*Scheme 20. Oxidative dearomatization and IMDA on the derivative **10i**.*

In summary, an oxidative dearomatization with subsequent intramolecular Diels Alder reaction has been developed starting from different aminophenols and by using different hypervalent iodines. The mild conditions together with the possibility to broad the scope simply varying the hypervalent iodine opens the ways also to further functionalizations not yet explored, as aminoacids and heterocyclic nuclei.

2.2 Aminoiodination reaction[b]

In this chapter, we will discuss the development of greener reaction conditions for the aminoiodination of alkenes, affording *N*-containing heterocycles in an environmental friendly way.

The usefulness of heterocycles containing a vicinal iodoamine moiety as versatile synthetic intermediates[74] or as potential medicinal agents,[75] motivates our investigations. Indeed some iodomethyl substituted nitrogen-containing heterocycles have shown antitumor, anti-infective, and anti-inflammatory activities (Figure 12).[76,14i]

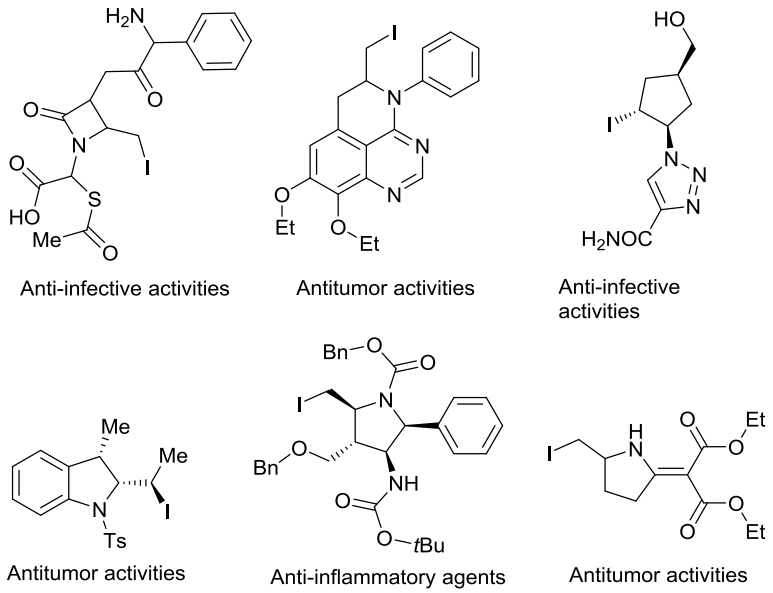
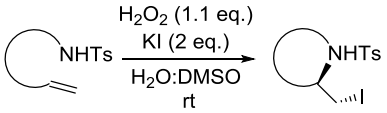


Figure 12. Selected bioactive vicinal iodoamine derivatives.

[b] Adapted from the published paper. S. Giofrè,_R. Sala, E.M. Beccalli, L. Lo Presti, G. Broggini. *Helv. Chim. Acta,* **2019,** 102, 7, e1900088

Haloamination of alkenes involving an intramolecular carbon-nitrogen bond formation received great attention as fruitful methodology for the synthesis of nitrogen-containing heterocycles.[77] Among the alkene halocyclizations, iodoamination reactions represent a powerful tool for the preparation of heterocycles suitable for further introduction of functionalities.[78] The formation of a carbon-iodine bond provides high added value to the process as demonstrated by the multi-faceted conversions which can undergo. While the most efficient procedures for the access to vicinal chloro- and bromoamines are based on transition metal-catalysed reactions, direct formation of vicinal iodoamines from aminoalkenes can be typically realized by initial activation of the carbon-carbon double bond with different sources of electrophile. Molecular iodine and *N*-iodosuccinimide (NIS) have been widely used with amide-type substrates[79] as well as with alkenyl imidates.[80] Alternatively, KI in the presence of a hypervalent iodine derivatives[81] or a transition metal-catalyst[82] were proven to be effective for this goal. Also NaI, combined with MnI_2 as catalyst, has been proven a useful source of iodine for iodoamination of unfunctionalized olefins.[83]

Inspired by sustainable synthesis and green synthetic approaches, a domino strategy mainly based on waste reduction and use of ecofriendly materials and solvents, has been investigated. Thus, a strategy relying on the use of KI as iodine source and H_2O_2 as oxidant agent which act in water at room temperature has been successful in providing iodomethyl-substituted heterocycles. Although it is known that H_2O_2 has been used combined to tetrabutylammonium iodide to promote an amination reaction,[84] to the best of our knowledge the possibility to perform iodoamination reactions by the use of KI/H_2O_2 is unknown in the literature.

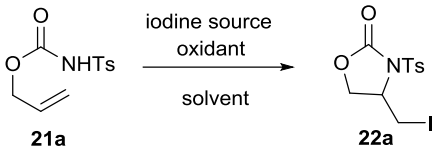


Scheme 21. Green iodoamination conditions on aminoalkenes.

Our study started from the *O*-allyl-*N*-tosylcarbamate **21a** with preliminary experiments aimed to explore new conditions for the feasibility of the iodoamination reaction. Various combinations of iodine sources and oxidant agents in different solvents are collected in Table 10. A stoichiometric amount of molecular iodine or NIS in acetonitrile at room temperature furnished the oxazolidinone product **22a** in unsatisfactory yields in a complex crude mixture, in the latter case also due to the formation of the *O*-(2,3-diiodopropyl)-*N*-tosyl-carbamate (entries 1-2, Table 10). The same acyclic diiodinated compound was obtained as by-product when the reaction was carried out in the presence of NIS and $CuCl_2$ as the oxidant in oxygen atmosphere (entry 3). An iodocyclizative process was observed when I_2 and NIS were combined with PIFA, although the product resulted in the 3-unsubstituted 4-iodomethyloxazolidinone, isolated in both cases in moderate yields (entries 4-5). Conversely, the use of PIFA was effective if used with KI as iodine source, providing **22a** in 81% yield (entry 6).

Other hypervalent iodine derivatives such as PIDA and $PhI(mcba)_2$ promoted the formation of **22a**, although with a slight decrease in yield (entries 7-8). Following these preliminary results, we focused on other conditions based on the presence of KI as iodine source. Using molecular iodine in O_2 atmosphere combined with benzoquinone as further oxidant in acetonitrile, no formation of **22a** was observed and carbamate **21a** was completely recovered (entry 9). Also MnO_2 was tested as additive in the reaction mixture under oxygen atmosphere but **22a** was achieved in low yield (entry 10).

Table 10. Optimization of the reaction conditions.



21a 22a

Entry	Iodine source	Oxidant	Solvent[a]	Time (h)	22a[b] (%)
1	I_2	-	CH_3CN	30	52
2	NIS	-	CH_3CN	18	29[c]
3[d]	NIS	$CuCl_2$ (5 mol%), O_2	CH_3CN	24	49[c]
4	I_2	PIFA	CH_3CN	4	-[e]
5	NIS	PIFA	CH_3CN	6	-[e]
6	KI	PIFA	CH_3CN	3	81
7	KI	PIDA	CH_3CN	8	68
8	KI	$PhI(mcba)_2$	CH_3CN	20	73
9	KI	BQ (20 mol%), O_2	CH_3CN	48	-
10	KI	MnO_2 (20 mol%), O_2	CH_3CN	48	31
11[f]	KI	H_2O_2	CH_3CN	24	79
12[f]	KI	H_2O_2	DMF	24	32
13[f]	KI	H_2O_2	Dioxane	24	54
14[f]	**KI**	**H_2O_2**	**H_2O/ DMSO**[g]	**24**	**78**
15[f]	KI	H_2O_2	H_2O/CH_3CN[h]	24	67

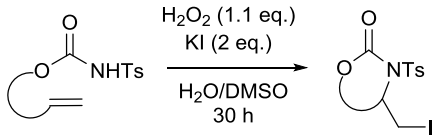
[a] The reactions were carried out at room temperature unless otherwise stated. [b] Yields of purified products. [c] *O*-(2,3-Diiodopropyl)-*N*-tosyl-carbamate has been isolated in 57% yield (entry 2) and 37% yield (entry 3). [d] The reaction was performed in CH_3CN at reflux under O_2 atmosphere. [e] 3-Unsubstituted 4-iodomethyl-oxazolidin-2-one has been isolated in 54% yield (entry 4) and 43% yield (entry 5). [f] The reaction was carried out at room temperature using a 30% solution of H_2O_2 in water. [g] In 3:1 ratio. [h] In 2:1 ratio.

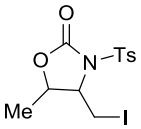
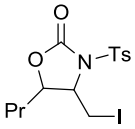
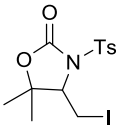
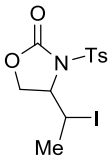
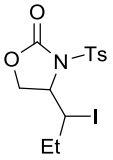
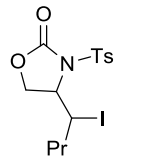
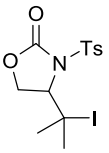
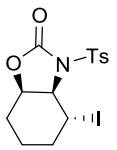
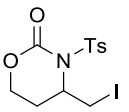
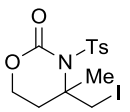
Surprisingly, a consistent improvement of the outcome of the reaction was detected when H_2O_2 was used as the sole oxidant in the presence of KI in CH_3CN. These conditions determined a neat conversion of **21a**, providing the desired iodoamination product in 79% yield (entry 11). Use of DMF or dioxane leads to a remarkable decrease of the yield (entries 12-13), while water associated to DMSO or CH_3CN as a co-solvent was proven to be a good medium for the complete conversion of the substrate in mild conditions (entries 14-15). Working in the discussed conditions of Table 10, entry 14, the crude mixture resulted cleaner than the corresponding reaction carried out with I_2 or NIS as iodine source. Moreover, the precipitation of the product from the reaction mixture, once the reaction ended, allowed us to achieve the purified product only through filtration.

With these reaction conditions in hand (entry 14, Table 10), the substrate scope was extended to different classes of molecules. Initially, variously substituted alkenyl carbamates were studied, as reported in Table 11. The presence of substituents on the allylic moiety is compatible with reaction conditions, as demonstrated by the formation of compounds **22b-h**, although a mild heating in some cases was required. Compounds **22b** and **22c** were obtained as a mixture of *cis/trans* diastereoisomers, easily separated and fully characterized.

The (*R**,*R**)-configuration of a representative iodo-derivative arising from *O*-allyl-carbamates mono-substituted at terminal position was confirmed by X-ray analysis of compound **22f** (Figure 13), achieved by iodocyclization of the *O*-pent-2-enyl carbamate in the (*Z*)-configuration. The *O*-2-cyclohexenyl-*N*-tosyl-carbamate furnished exclusively the bicyclic oxazolidinone **22i** in 66% yield. The reaction conditions are also suitable for the iodoamination of *O*-alk-3-enyl carbamates, which provided the 1,3-oxazin-2-one products **22j** and **22k**.

Table 11. Reaction of iodoamination of alkenyl carbamates.



				
22b	**22c**	**22d**	**22e**[a]	**22f**[b]
H_2O:DMSO 2.5:1, r.t.	H_2O:DMSO 1:1, 40 °C	H_2O:DMSO 2:1	H_2O:DMSO 2.5:1	H_2O:DMSO 2:1
cis/trans 2:1, 67%	*cis/trans* 2.5:1, 60%	r.t., 61%	r.t., 67%	r.t., 66%
				
22g[c]	**22h**	(+)-**22i**	**22j**	**22k**
H_2O:DMSO 1:1	H_2O:DMSO 1:2	H_2O:DMSO 1:1.5	H_2O:DMSO 3:1	H_2O:DMSO 1.5:1
40 °C, 64%	r.t., 55%	r.t., 66%	r.t., 74%	r.t., 68%

[a] Starting from a mixture of (*E*/*Z*)-**21e**. [b] Starting from (*Z*)-**21f**. [c] Starting from (*E*)-**21g**.

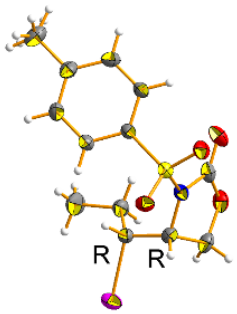
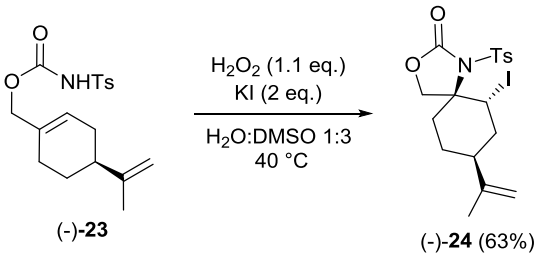


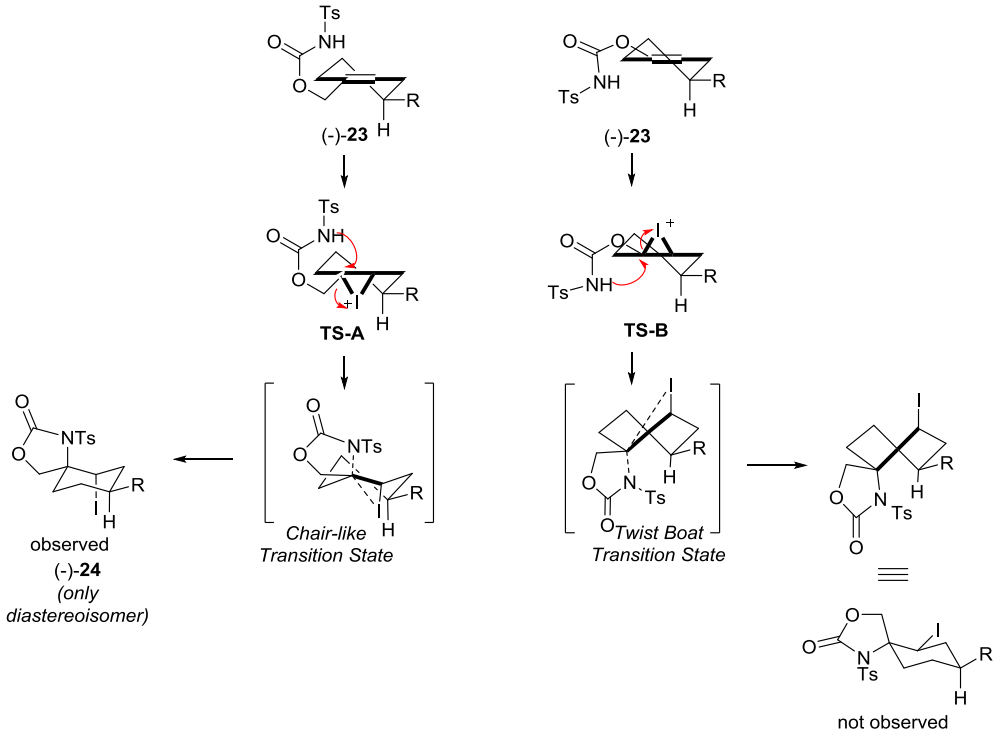
*Figure 13. Molecular structure of the (R,R) enantiomer of **22f** at room temperature, as derived from single crystal X-ray diffraction. The methyl of the tosyl group is rotationally disordered with site occupation factors of 0.64(7) and 0.36(7). Thermal ellipsoids are drawn at the 30% probability level. Configurational descriptors of the stereogenic centres are also shown.*

Interestingly, the treatment of the optically active carbamate **23** with H_2O_2 and KI in H_2O/DMSO 1:3 at 40 °C resulted selectively in an *exo*-

cyclization, providing the spiro-compound **24** as the sole product (Scheme 22).



*Scheme 22. Iodoamination of the optically active carbamate **23**.*



*Scheme 23. Selective formation of the sole diastereoisomer (-)-**24**.*

The stereoselective reaction path is due to the difference arisen from the torsional strain of the two plausible transition states having a substituent on the pseudo equatorial position.[85] The stability of the chair-like transition state (from **TS-A**) rather than the twist-boat state (from **TS-B**)

afforded only the *trans*-diaxial addition product (-)-**24** (Scheme 23). The configuration was assigned by X-ray diffraction analysis (Figure 14).

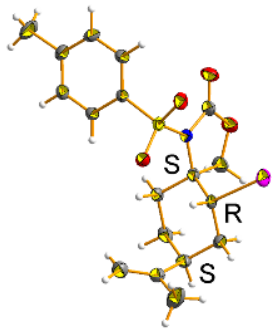
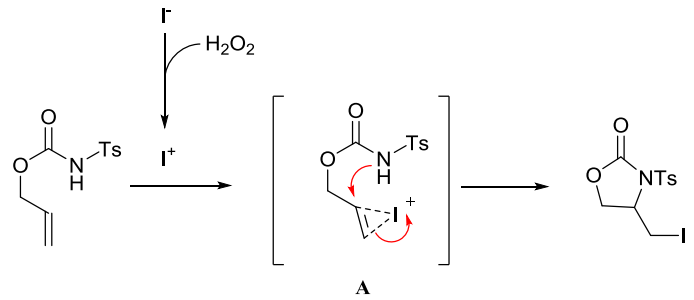


*Figure 14. Molecular structure of **24** at room temperature, as derived from single crystal X-ray diffraction. Thermal ellipsoids are drawn at the 30% probability level. Configurational descriptors of the stereogenic centres are also shown.*

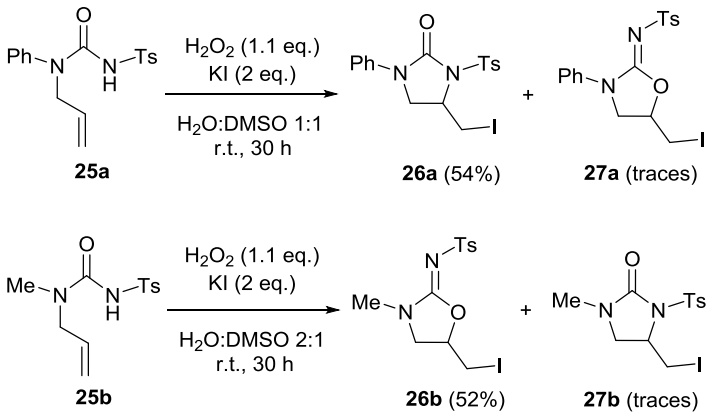
Based on the observed results and literature data, a plausible mechanism for the iodocyclization is shown in Scheme 24 taking carbamate **21a** as example. The I^+ species generated *in situ* from KI and H_2O_2 suggested the formation of the electrophilic iodinated intermediate **A**,[86] which through an *anti*-attack mediated by the nucleophilic tosylamino group afforded the 4-iodomethyl oxazolidinone product.



Scheme 24. Proposed iodoamination reaction mechanism

The use of H_2O_2 and KI for the iodocyclization of *N*-allyl-*N'*-tosylureas resulted in a different outcome of the reaction depending on the

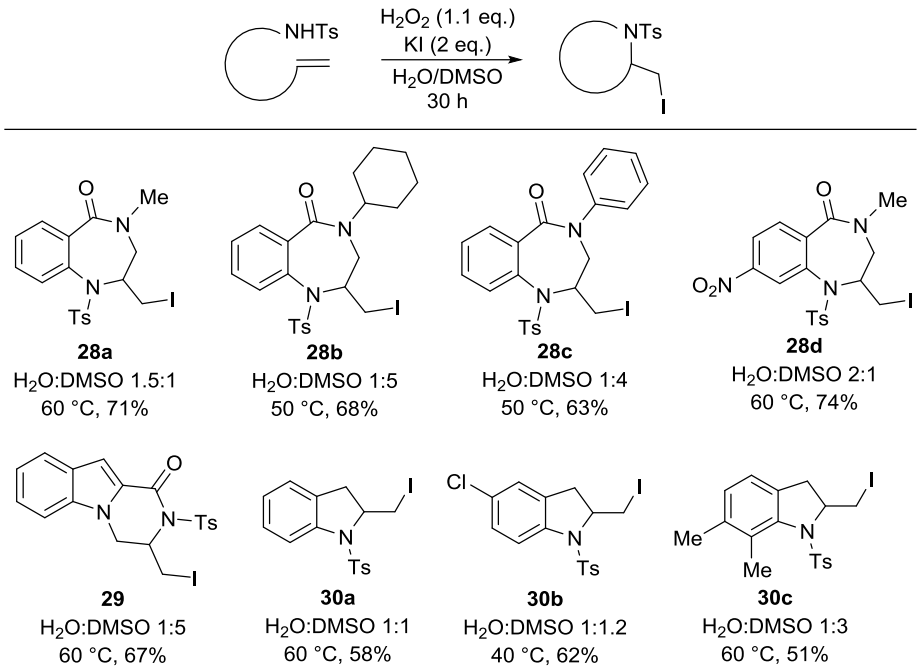
substituent on the nitrogen atom. If the phenyl-substituted urea **25a** provided the 4-iodomethyl-imidazolidinone **26a** as the major product, the *N*-allyl-*N*-methyl-urea **25b** followed mainly an iodoalkoxylation process giving the 2-imino-oxazolidine **26b** in 52% yield (Scheme 25). In both cases, minor products were detected in the crude mixtures, specifically arising from iodoalkoxylation (imino-oxazolidine **27a** from **25a**) and iodoamination (imidazolidinone **27b** from **25b**) reactions. The possibility of C-O vs C-N bond formation in intramolecular reactions of secondary ureas is well known in literature.[87] However, the low selectivity achieved in cyclization of compounds **25a**,**b** decreases our interest for the application of this procedure to different alkenyl ureas.



Scheme 25. Iodoamination reactions of allyl ureas.

Further extension of the reaction scope was attempted taking into account other alkenyl sulphonamides. The iodomethyl-substituted heterocyclic products, obtained by reaction with KI and H_2O_2 using H_2O/DMSO in a ratio depending on the solubility of the substrates, are collected in Table 12.

Table 12. Reaction of iodoamination of alkenyl tosylamines



N-Allyl 2-tosylamino-benzamides, already used for the synthesis of benzodiazepine scaffolds,[88] were proven compatible with the iodoamination process, giving the 2-iodomethyl-substituted 1,2,3,4-tetrahydro-benzodiazepin-5-one derivatives **28a-d** in 63-74% yield. Satisfyingly, this procedure also represents an alternative for the reported *N*-Allyl benzamides aminochlorination.[89] The iodocyclisation conditions were found effective also for the conversion of the 1-allyl-indole-2-*N*-tosylcarboxamide into the iodomethyl-substituted pyrazino[1,2-*a*]indole **29**. It is noteworthy the reluctance of these substrates to afford haloamination processes in palladium-catalysed reactions,[33c] as further proof of the fruitfulness of the KI/H_2O_2 system. Finally, we explored the behaviour of 2-allyl-*N*-tosylanilines, already employed for iodoamination investigations in palladium-catalysed conditions.[82b] Treatment of these substrates with the standard iodocyclization conditions provided the iodo-indolines **30a-c**, although in moderate yields.

In conclusion, we developed an ecofriendly iodoamination procedure on alkenes bearing a secondary sulphonamide group based on the use of KI/H_2O_2 system. The C-N and C-I bonds formations allows to achieve easily different kind of iodomethyl-substituted nitrogen containing heterocycles by totally selective *exo*-cyclisation.

This iodoamination reaction proceeds smoothly in water needing the minimum amount of DMSO as co-solvent to solubilize the substrates.

CHAPTER 3

Rhodium-Catalysed Allylation[c]

Among transition metal catalysis the reaction catalysed by palladium are just the tip of the iceberg and in the huge catalysis world, great attention deserves Rh-catalysis.[90]

Rhodium has proven to be an extremely useful metal due to its ability to catalyse a variety of synthetic transformations. Hydrogenation, C-H activation, allylic substitution, and numerous other reactions are catalysed by this metal with an often excellent selectivity, which presumably gives grounds for the dramatic increase in the number of articles that have recently emerged on this topic.[91] The versatility of rhodium catalysis comes from the high reactivity for both polar and non-polar chemical bonds; such as dihydrogen, Si-H, B-H, and even unreactive C-H bonds. Additionally, in situ generated organometallic rhodium species are highly susceptible to additional elementary reactions such as transmetalation, migratory insertion, and reductive elimination which restore their catalytic potential.

[c] Prof. B. Breit – Alberts Ludwig Universität Freiburg (abroad research)

The correct choice and the design of a specific ligand is of primary importance. A ligand can optimize both the steric and electronic properties of the rhodium center to enhance the overall catalytic performance in a specific reaction. Due to the high electron density of the rhodium species, generally π-acceptor ligands such as phosphines, alkenes, and carbonmonoxide are privileged. Among these, phosphine ligands[92] have been widely used due to their well-established syntheses as well as the ability to systematically tune and define their electronic and structural properties (Figure 15).

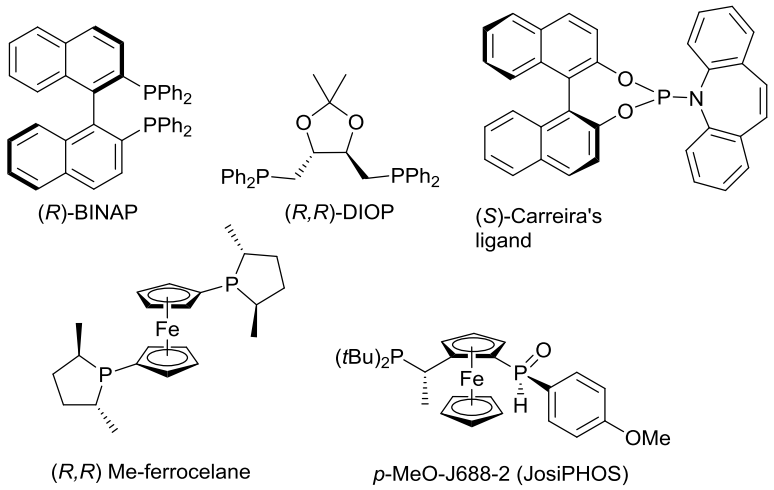
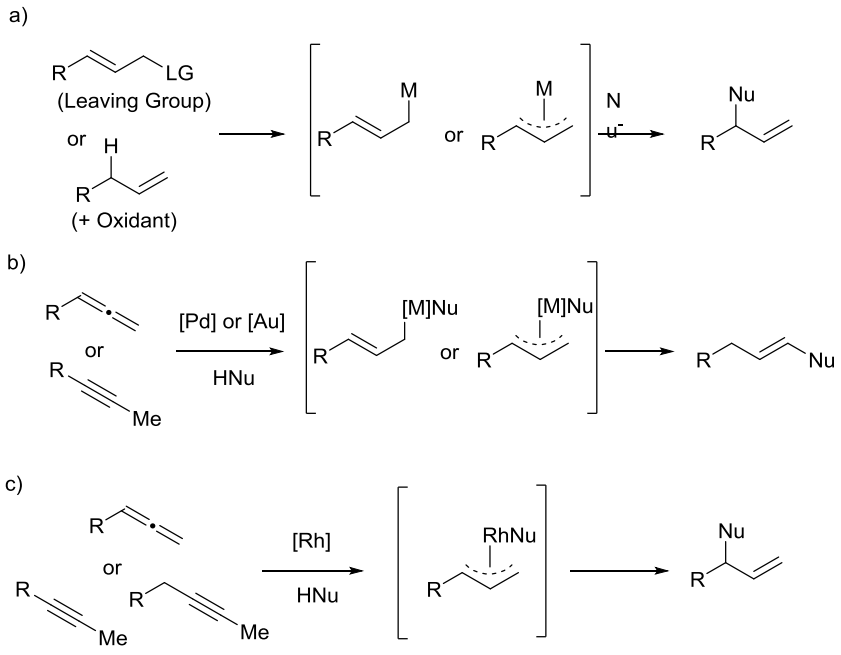


Figure 15. Selected phosphine ligands

There is practically no limit for the design of chiral backbones and ligands and there are several approaches to find new ones. But we know, the most successful developments are often due to serendipity and the Josiphos ligands are a very good example.[93] The possibility to chirally-functionalize the ferrocenyl chain by using a secondary phosphine paves the ways to a whole world of highly enantioselective transformations never explored.

Among the variety of reaction Rh-catalysed and focusing mostly on heterocyclic cyclization, the allylation of alkynes and allenes has shown to be a leading reaction in the natural products and pharmaceuticals' synthesis.[94] The Rh-catalysed allylation on alkynes and allenes developed by Breit's group[95] overcome some contraints that allylic substitution,[96] and allylic oxidation[97] had, such as the need to preinstall functional groups or the use of stoichiometric amounts of oxidant. (Scheme 28a) A more atom efficient pathway was proposed by Trost and Yamamoto[98] introducing sulfonyl amides as suitable pronucleophiles for the Pd-catalysed intramolecular addition to alkynes and allenes,[99] or more recently, the Brønstedt acids and Au(I)-asymmetric addition of amides and amines to internal allenes developed by Toste,[100] Widenhoefer[101] and Liu[102] (Scheme 28b). Unfortunately, also these reactions suffer of some drawbacks, with a limited range of substrates reactivity.



Scheme 26. Background of allylic substitution

Thus, Breit's group recently reported a complementary branch regioselectivity on rhodium-catalysed pronucleophile addition reactions to allenes and alkynes (Scheme 28c). Hydroamination,[103] hydroesterification,[104] hydroacylation[105] and hydrothiolation[106] have been studied as a tool to afford versatile enantioenriched branched allylic products.

Thus, this heading just introduces two subchapters, 3.1 and 3.2, which will show once again how Rh(I) was able to go beyond Pd(II), giving the opportunity to achieve the desired heterocyclic cores in an efficient, and enantioselective way.

3.1 Hydroamination

The hydroamination reaction provides a facile way to the C–N bond formation through the addition of an amine to an unsaturated C–C bond with high atom-economy. Allenes tethered to amino group have demonstrated to be the suitable substrates for intramolecular hydroamination,[103] providing branched allylic *N*-heterocycles.

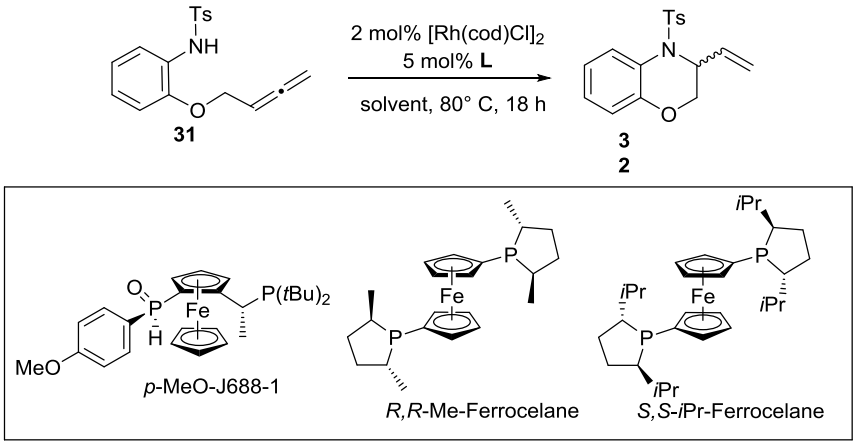
3.1.1 Intramolecular hydroamination of Ts-protected aminoallenes

Focusing on our aim to achieve benzoxazine nuclei (see Chapter 1.2.1), the hydroamination was investigated on allenes tethered to the oxygen of *N*-Ts-protected aminophenols. Thus, at first glance ligands belonging to the ferrocene-based family were used. In this case, not only the benzoxazine nuclei was obtained without side reactions, but we were able to isolate it with a good enantiomeric excess. Indeed, the first attempts made with $Pd(OAc)_2$, in oxidative conditions starting from the corresponding alkene resulted in the complete recovery of the starting material, when $PhI(mcba)_2$ was used as oxidating agent and in the formation of the racemic halogenated derivative when copper chloride or bromide was used in stechiometric amount as oxidant.

The successful outcomes obtained in the Table 13 and 14, show once again the ability of Rh(I) to catalyse a hydroamination process in a complete selective way, mostly modulating the type of ligand employed. Indeed, among the three ligands showed in Table 13, only the *p*-MeO-J688 Josiphos ligand was able to induce good yields and enantioselectivity mainly when associated with pyridinium paratoluensulfonate as additive

(entry 4, Table 13). This are the best conditions achieved so far (71%, 81% *ee).*

*Table 13. Optimization of the conditions of hydroamination of compound **31**.*



Entry	Ligand (5 mol%)	Additive	Solvent	32 (%) – *ee%*
1	p-MeO-J688-2	-	DCE (0.4 M)	33% -57% *ee*
2	p-MeO-J688 (rac)	-	DCE (0.4 M)	35% - rac
4	p-MeO-J688-1	PPTS (10 mol%)	DCE (0.2 M)	71% -81% *ee*
5	*R,R*-Me-Ferrocelane	-	DCE (0.2 M)	27% -71% *ee*
6	*R,R*-Me-Ferrocelane	$HOP(O)(OPh)_2$ (5 mol%)	DCE (0.2 M)	-
7	*S,S*-iPr-Ferrocelane	$HOP(O)(OPh)_2$ (5 mol%)	DCE (0.2 M)	-
8	*R,R*-Me-Ferrocelane	K_2CO_3 (0.5 eq)	DCE (0.2 M)	37% -59% *ee*
9	*R,R*-Me-Ferrocelane	K_2CO_3 (1 eq)	DCE (0.2 M)	65% -34% *ee*
10	*R,R*-Me-Ferrocelane	Cs pivalate (0.5 eq)	DCE (0.2 M)	67% -46% *ee*

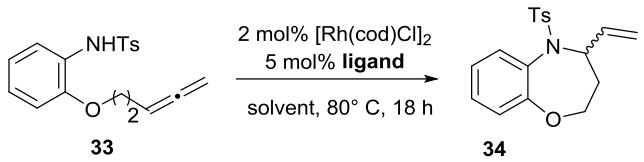
On the other hand, when we replaced the described ligand with the *R,R*-Me-Ferrocelane, the vinyl-substituted benzoxazine was still obtained with good enantiocontrol but with lower yields (entry 5). Moreover, using it in

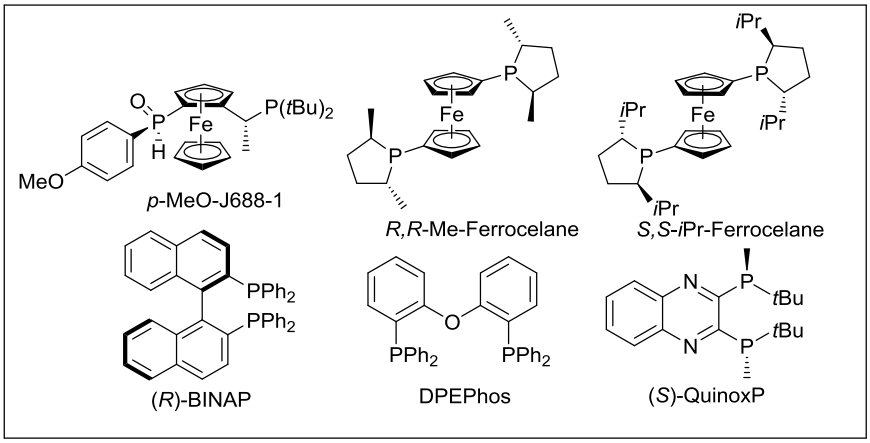
acid conditions (entry 6), in the presence of a phosphoric acid, the product **32** was not even achieved. Repeating the experiment in basic conditions (entry 8-10), the product was obtained in moderate yield and low *ee*%.

However, these results represent an impressive goal in Rh(I) chemistry due to the employment of substrates not so easy to manage (heteroatom located on the α-position to the allene).

Even more outstanding is the result obtained starting from the 4-methyl-*N*-(2-(penta-3,4-dien-1-yloxy)phenyl)benzenesulfonamide **33**. Indeed, not only we obtained a 7-membered ring, usually not so easy to achieve and important core in pharmaceuticals, but also an excellent enantiomeric excess was observed in the same conditions reported before (entry 6, Table 14). All the other ligands employed were not so successful (entry 3-4), except from the (*R,R*) Me-ferrocelane used in neutral conditions (entry 8), where the product **34** was isolated with 55% yields and 78% *ee*.

*Table 14. Optimization of the conditions of hydroamination of compound **33**.*

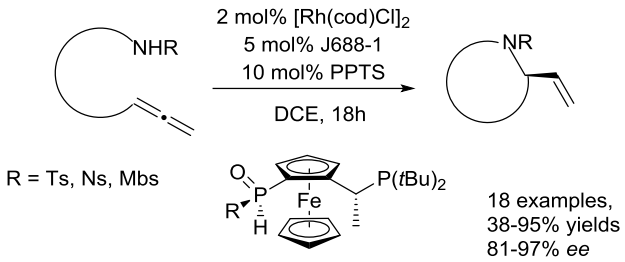




entry	Ligand (5 mol%)	additive	solvent	34 (%) – *ee%*
1	DPEPhos	-	DCE (0.4 M)	-
2	(*R*)-BINAP	-	DCE (0.4 M)	-
3	p-MeO-J688-1	-	DCE (0.4 M)	28% - 63% *ee*
4	(*S*)-QuinoxP	-	DCE (0.4 M)	-
5	p-MeO-J688 (rac)	-	DCE (0.4 M)	27%
6	p-MeO-J688-1	PPTS (10 mol%)	DCE (0.2 M)	38% - 84% *ee*
7	p-MeO-J688-1	.	MeCN (0.2 M)	24% - 69% *ee*
8	(*R,R*) Me-ferrocelane	.	DCE (0.2 M)	55% - 78% *ee*
9	(*R,R*) Me-ferrocelane	K_2CO_3 (1 eq)	DCE (0.2 M)	-

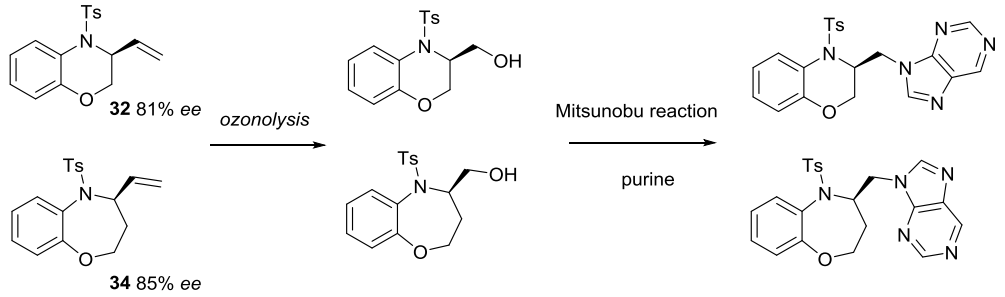
These two substrates come within a bigger scope, developed mainly on differently alkyl-substituted allenyl sulfonamide, but that includes carbamates, ureas and benzofused rings, too. The work, made by D.

Berthold, the PhD student working on this Rh(I)-methodology has shown his wide applicability on a variety of different substrates (Scheme 27).



Scheme 27. Rh(I)-catalysed hydroamination employing Josiphos ligand.

The synthetic utility of these intermediates (**32**, **34**) able to react in different reaction conditions, opens the ways to different functionalized benzoxazines and benzoxazepines, in particular, to enantio-enriched purine derivatives which have not been synthetized in an enantioselective way, yet.



3.1.2 Intramolecular hydroamination of PMP-protected aminoallenes

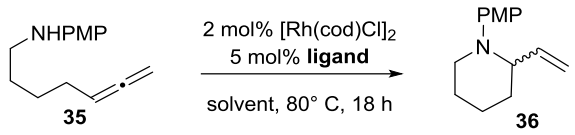
The role of *N*-protecting group in Rh(I)-catalysed hydroamination has been investigated, too. As we have already underlined at pag. 80, in the hydroamination field sulphonamides keep their fundamental function to activate the nitrogen towards unsaturated C-H functionalizations. The reactivity showed by tosyl group or other analogous towards C-H functionalizations has been significantly higher than other *N*-protecting groups.

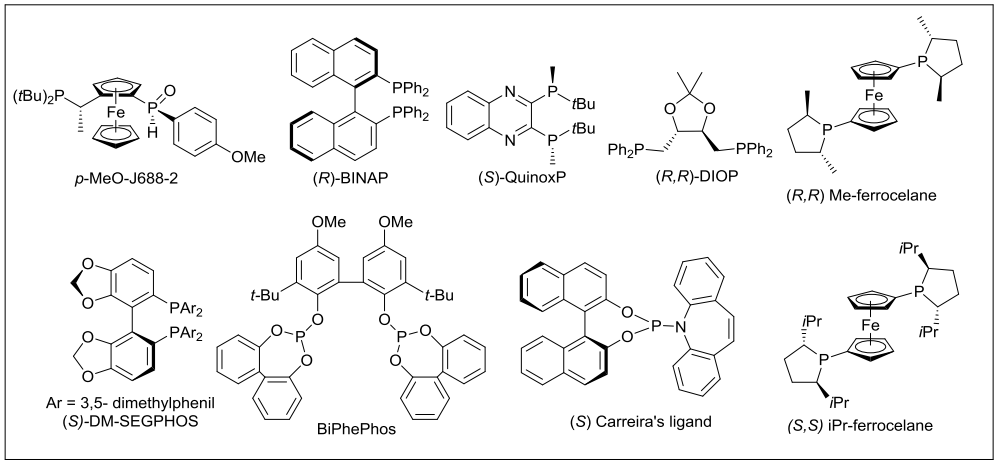
Therefore, the results arising from aminoallenes protected with a *p*-methoxy phenyl group were not so satisfying (Table 15). Indeed, even if a broader range of ligands have been employed, under no circumstances the enantiomeric excess was noteworthy, with values reaching 60% *ee* only by using (*R,R*) Me-ferrocelane as ligand and 10 mol% TFA as additive (entry 10).

Using the isopropyl derivative of the same ligand family, (*S,S*)-*i*Pr-ferrocelane, the *p*-methoxy phenyl-protected vinyl piperidine was obtained with 90% yields but with an enantiomeric excess still below 50% (entry 6).

The poor results achieved in this field and the lack of benefits discouraged us to further investigate this reactivity.

*Table 15. Optimization of the conditions for the hydroamination of compound **35**.*





Entry	Ligand (5 mol%)	Additive	Solvent	35 (%) – *ee%*
1	(*R*)-BINAP	-	DCE (0.4 M)	41% - 17% *ee*
2	(*R,R*)-DIOP	-	DCE (0.4 M)	48% - 4 % *ee*
3	p-MeO-J688-2	-	DCE (0.4 M)	62% - 3 % *ee*
4	(*S*)-QuinoxP	-	DCE (0.4 M)	56%- 17 % *ee*
5	(*R,R*)Me-ferrocelane	$HOP(O)(OPh)_2$ (5 mol%)	DCE (0.4 M)	69% - 52% *ee*
6	(*S,S*)*i*Pr-ferrocelane	$HOP(O)(OPh)_2$ (5 mol%)	DCE (0.4 M)	90% - 46% *ee*
7	(*S*)-DM-SEGPHOS	-	DCE (0.4 M)	52% - 3% *ee*
8	BiPhePhos	-	DCE (0.4 M)	SM
9	(*S*)-Carreira's ligand	-	DCE (0.4 M)	38% - 8% *ee*
10	(*R,R*)Me-ferrocelane	TFA (10 mol%)	DCE (0.2 M)	51% - 60% *ee*

3.2 Hydroalkoxylation

The Rh(I)-ring closing reaction has been studied also with *O*-pronucleophiles, where the furnished allylic ethers serves as versatile synthetic intermediates for further construction of numerous structures.[107] Moreover, cyclic ethers represent key components of natural products, such as Callipeltoside A,[108] (-)-Bruceol,[109] and of approved pharmaceuticals with antiobiotic, analgesic and antitumor activities.

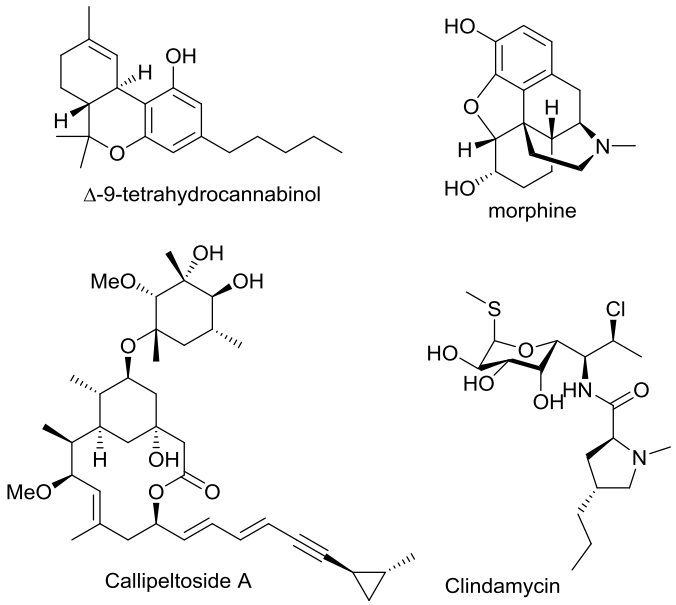


Figure 16. Cyclic ethers as key components in pharmaceuticals and natural products.

In the last decade, significant progresses have been made in order to achieve allyl ethers mainly based on transition metal catalysed allylic substitutions. Indeed, an extensive work has been developed by Evans *et al.*,[90b,96] through the use of allyl acetates and carbonates as electrophiles.

Otherwise this procedure lacks of the principle of atom-economy by formation of stoichiometric amount of side products.

In an another studies allylic alcohols were used as allyl precursors,[110] too, but only after premetalating the alkoxides along with metals to soften their hard nucleophilic character.[111]

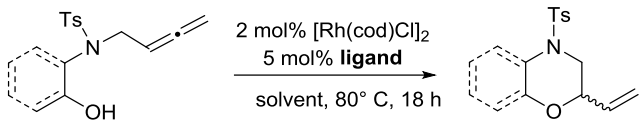
In the 1990s and 2000s Yamamoto[98] reported a Pd-catalysed addition of nucleophiles to alkynes, which could be regarded as atom-economic alternatives to allylic substitution. Even if in some case good enantioselectivity was obtained, drawbacks arise from the need to use defined substrates. Indeed, when the hydroalkoxylation reaction was investigated on phenyl susbstituted alkynes, the presence of electron-donating substituents attached at the para position of the aromatic ring gave lower yields and *ee*.[112]

Thus, since allenes are a readily accessible and remarkably stable substrate class, a Rh(I)-catalysed hydroalkoxylation has been studied aligned with Breit and co-workers' recent works.

Starting from the *N*-(buta-2,3-dien-1-yl)-*N*-Ts-2-aminophenol **37a**, *N*-substituted analogous of compound **31**, the reaction was performed in the same reaction conditions reported before, 2 mol% $[Rh(cod)Cl]_2$, 5 mol% *p*-MeO-J688-2 in DCE at 80° C (entry 1, Table 16). In this case the corresponding product was obtained only with 15% *ee*. With the purpose to increase significantly the enantiomeric excess, the Josiphos ligand was substituted with the Ferrocelane family (entry 2-8). In this case good results were achieved only when the methyl-substituted ligand was used. Indeed, the isopropyl derivative even if more hindered results in a decrease of the enatioselectivity (entry 4). In order to further enhance the outcomes, different acid additives were explored, due to their active role in the hydroalkoxylation of substrate **37a** (entry 3). Therefore, using 10 mol% of benzoic acid (entry 5) or TFA (entry 6) we were able to increase

the *ee* up to 81% or 84%, respectively, affording the benzoxazine nuclei surprisingly with optimal yield and good enantiomeric excess, in absence of any kind of side reactions (see Chapter 1.2.1).

*Table 16. Optimization of the conditions for the synthesis of compound **38a-b.***



37
a = *N*-(buta-2,3-dien-1-yl)-*N*-Ts-2-aminophenol
b = *N*-(buta-2,3-dien-1-yl)-*N*-Ts-2-aminoethanol

38a-b

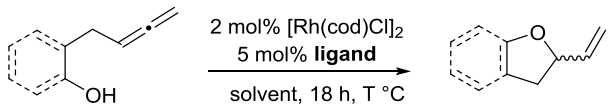
Entry	SM	Ligand	Additive	Solvent	38 (%) – *ee%*
1	**37a**	p-MeO-J688-2	-	DCE (0.4 M)	65% 15% *ee*
2	**37a**	*R,R*-Me-Ferrocelane	$HOP(O)(OPh)_2$ (5 mol%)	DCE (0.4 M)	46% 77% *ee*
3	**37a**	*R,R*-Me-Ferrocelane	-	DCE (0.4 M)	-
4[a]	**37a**	-	$HOP(O)(OPh)_2$ (5 mol%)	DCE (0.4 M)	-
5	**37a**	*S,S*-iPr-Ferrocelane	$HOP(O)(OPh)_2$ (5 mol%)	DCE (0.4 M)	28% 8% *ee*
6	**37a**	*R,R*-Me-Ferrocelane	Benzoic acid (10 mol%)	DCE (0.2 M)	86% 84% *ee*
7	**37a**	*R,R*-Me-Ferrocelane	TFA (10 mol%)	DCE (0.2 M)	74% 81% *ee*
8	**37b**	*R,R*-Me-Ferrocelane	$HOP(O)(OPh)_2$(10 mol%)	DCE (0.2 M)	72% 76% *ee*
9	**37b**	*R,R*-Me-Ferrocelane	TFA (20 mol%)	DCE (0.2 M)	79% 65% *ee*

[a] The catalyst $[Rh(cod)Cl]_2$ has not been used.

The same conditions were investigated on the corresponding aliphatic derivative **37b**, too (entry 8-9), even if in this case the morpholine nuclei was already achieved before with comparable results (see Chapter 1.2.2).

With these reactions conditions in hand, different classes of substrates **38c-f**, aromatic and aliphatic, were investigated (Table 17–18), giving particular attention to the type of the acid additive employed. In the Table 17, starting from hexa-4,5-dien-1-ol **38c** and working at 40° C, instead of 80° C, we were able to increase up to 87% the *ee* of the final product when TFA was used as additive (entry 2). In the case of to the corresponding allenyl phenol similar outcome has been obtained in the described reaction condition (entry 5, Table 17).

*Table 17. Optimization of the condtions for the synthesis of compound **38c-d**.*



37
c = hexa-4,5-dien-1-ol
d = 2-(buta-2,3-dien-1-yl)phenol

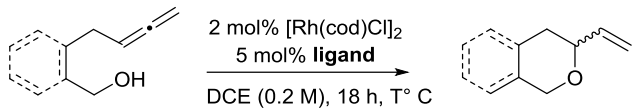
38c-d

Entry	SM	Additive	Solvent	T ° C	38 (%) – *ee*%
1[a]	**37c**	$HOP(O)(OPh)_2$ (10 mol%)	DCE (0.2 M)	40 °C	82%
2[a]	**37c**	TFA (10 mol%)	DCE (0.2 M)	40 °C	87%
3[a]	**37c**	(*R*)-Binol-phosphoric acid (10 mol%)	DCE (0.2 M)	40 °C	84%
4	**37d**	TFA (10 mol%)	DCE (0.2 M)	80 °C	82% - 81% *ee*
5	**37d**	TFA (10 mol%)	DCE (0.2 M)	60 °C	86%- 84% ee

[a] Only the enantiomeric excess has been determined by GC due to the volatile properties of the product; [b] *S,S*-Et-Ferrocelane was used as ligand

While for the substrate affording the vinyl tetrahydropyran **38e** the best additive is still the trifluoroacetic acid (89%*ee)*, entry 7, Table 18, different is the situation for the substrate **38f.**

Table 18. Optimization of the condtions for the synthesis of compound **38e-f**.



37
e = hepta-5,6-dien-1-ol
f = (2-(buta-2,3-dien-1-yl)phenyl)methanol

38e-f

Entry	SM	Additive	T ° C	38 (%) – *ee%*
1	**37e**	$HOP(O)(OPh)_2$(10 mol%)	40 °C	75%[a]
2	**37e**	$HOP(O)(OPh)_2$ (10 mol%)	40 °C	77%[a]
3	**37e**	-	40 °C	82%[a]
4 [b]	**37e**	$HOP(O)(OPh)_2$ (10 mol%)	40 °C	-%[a]
5	**37e**	(*L*)-tartaric acid (10 mol%)	40 °C	84%[a]
6	**37e**	Benzoic acid (10 mol%)	40 °C	84%[a]
7	**37e**	TFA (10 mol%)	40 °C	89%[a]
8	**37e**	2-Cl-benzoic acid (10 mol%	40 °C	84%[a]
9	**37e**	3-Cl-benzoic acid (10 mol%	40 °C	77%[a]
10	**37e**	$(Ph)_2CHCOOH$ (10 mol%)	40 °C	69%[a]
11	**37e**	TFA (30 mol%)	40 °C	88%[a]
12[b]	**37e**	TFA (30 mol%)	40 °C	84%[a]
13	**37e**	TFA (30 mol%) LiCl (30 mol%)	40 °C	64%[a]
14	**37e**	*L*-lactic acid (30 mol%)	40 °C	84%[s]
15	**37e**	TFA (30 mol%)	rt	64%[s]
16	**37f**	$HOP(O)(OPh)_2$ (10 mol%)	80 °C	61% - 55% *ee*
17	**37f**	TCA (10 mol%)	80 °C	35% - 35% *ee*
18	**37f**	TFA (10 mol%)	80 °C	81% - 48% *ee*
19	**37f**	PPTS (10 mol%)	80 °C	75% - 46% *ee*
20	**37f**	(*R*)-Binol-phosphoric acid 10 mol%	60 °C	84% - 79% *ee*
21	**37f**	Benzoic acid (10 mol%)	60 °C	88% - 76% *ee*

[a] only the enantiomeric excess has been determined by GC due to the volatile properties of the product; [b] The reaction was carried out in DCE/EtOH 4:1 (0.2 M)

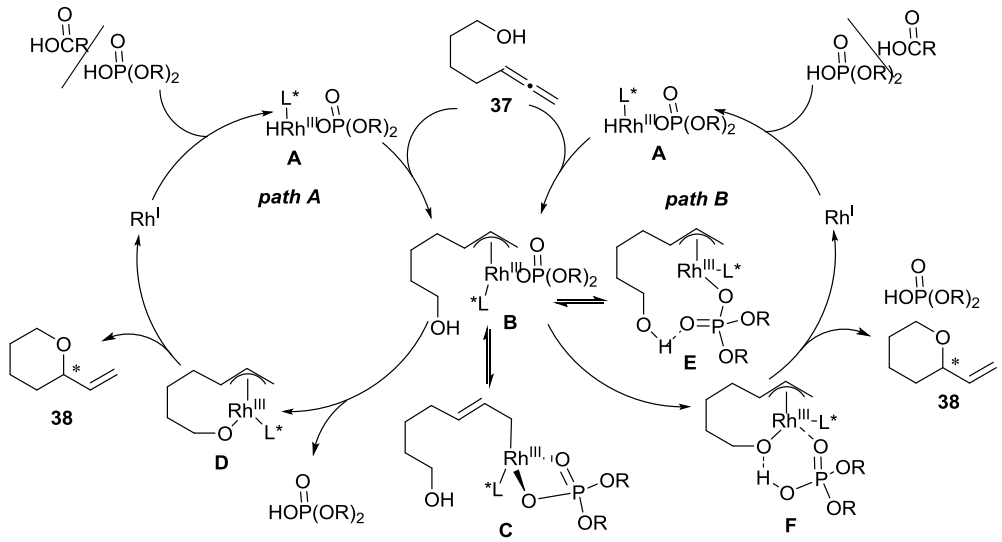
Indeed, in this case, using 10 mol% TFA the benzofused ring was isolated only with 48% *ee*. When we moved to chiral and not chiral aromatic

additive, such as (*R*)-Binol-phosphoric acid and benzoic acid, the enantioselectivty increases up to 79% and 76%, respectively.

The intrinsic difference of each substrate to the other ones may explain the need to investigate different additives. As a consequence, where the aromatic starting material gave poor results, better enantioselectivity was observed when aromatic acids were used (entry 5, Table 16, entry 20-21, Table 18), probably due to π-π interactions.

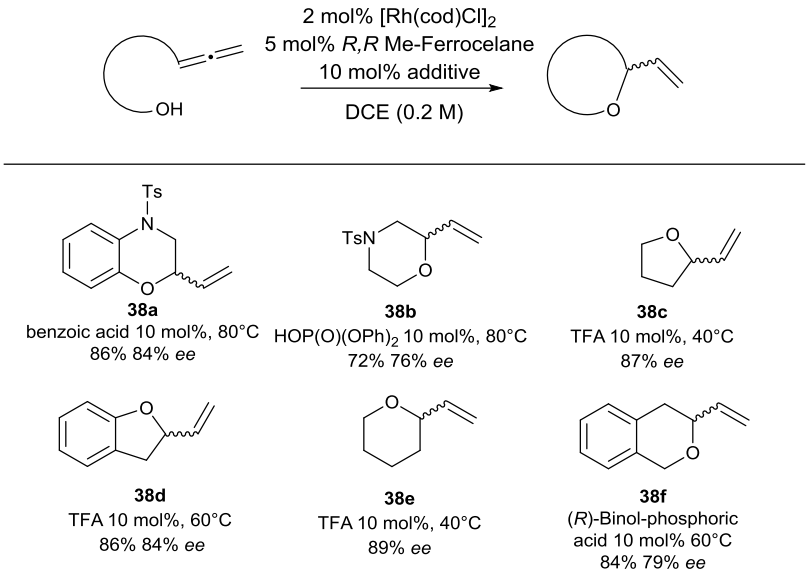
On the basis of some previous investigations,[113] a reaction mechanism to justifity the role of the additive is herein proposed in Scheme 28, path B. Indeed, having as a reference a previously proposed mechanism for addition of alcohols to allenes (path A),[114] an alternative mechanism is suggested, taking into account the role of the acid in the cyclisation step. Thus, we propose that the rhodium catalyst undergoes oxidative addition with the diphenyl phosphate (or other acids) to yield the rhodium(III) hydride (**A**). Hydrometalation of the allene furnishes the s- or p-rhodium-allyl species (**C** or **B**). At this point, instead of anion exchange with the alcohol followed by a reductive elimination of **D** to generate the vinyl-substituted cycle and restore the rhodium(I) catalyst, an alternative pathway is proposed. Indeed, in compliance with the improved enantioselectivity observed varying the acids and the recent enantioselective Brønsted-acid catalysis,[115] the presence of the intermediate **E** is hypothesized. The activation of the nucleophilic alcohol through hydrogen bond with the phosphoric/carboxylic oxygen may explain the results obtained so far. At this point, the oxygen of the alcohol is more susceptible to the attack of Rh(III). The subsequent proton exchange with the acid and the formation of the intermediate **F** with its six-membered cycle are at the base of our hypothesis. Afterwards, the reductive elimination generates the product **38**, restoring the rhodium(I)

catalyst as in path A. Detailed mechanistic studies of this rhodium-catalysed enantioselective OH-addition to allenes are currently underway.



Scheme 28. Proposed mechanism for the hydroalkoxylation, pointing out the role of the additive.

In conclusion, as simplification I report the best reaction conditions, achieved so far, for each substrate studied (Scheme 29).

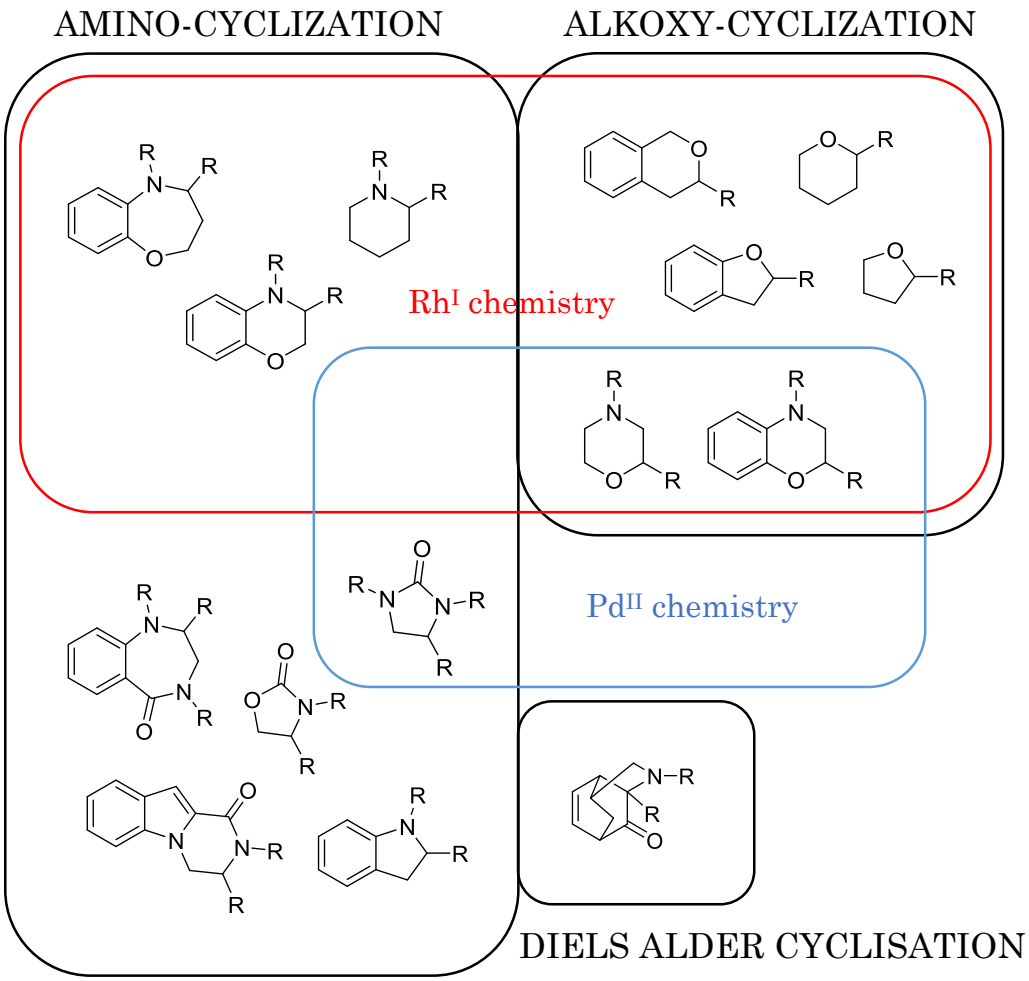


*Scheme 29. Optimized reaction conditions for compounds **38**.*

Further studies on the scope and deeply understanding of the mechanism are still ongoing in the group of Prof. B. Breit.

Conclusion

In conclusion, a library of benzoxazines, ureas and other heteropolycyclic nuclei, scaffolds present in different molecules with biological activity[1a,14,38,65-72,75,76,108,109] have been synthetized through different strategies.



Experimentals

General information

Melting points were determined by the capillary method with a Büchi B-540 apparatus and are uncorrected.

Chemicals were obtained from Sigma Aldrich and used without further purification.

Thin-layer chromatographic separations were performed on Merck silica-gel 60-F_{254} precoated. Preparative separations were performed by flash chromatography by using Merck silica gel 0.035-0.070 mm.

IR spectra were measured with a Jasco FT/IR 5300 spectrometer.

Nuclear Magnetic Resonance Spectroscopy (NMR)

^{1}H NMR and ^{13}C in open capillary tubes. NMR spectra were recorded with: AVANCE 400 Bruker spectrometer at 400 and 100 MHz, Varian Oxford 300 MHz spectrometer at 300 and 75 MHz and AVANCE 500 Bruker spectrometer at 500 and 125 MHz, respectively. Chemical shifts are given as δ values in ppm relative to residual solvent peaks ($CHCl_3$) as the internal reference, and the coupling constants *J* are reported in Hertz (Hz). ^{13}C NMR spectra are ^{1}H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence.

High Pressure Liquid Chromatography (HPLC)

In the analytic department of the Institute of Pharmaceutical Science at the University of Milan chiral HPLC analysis were carried out on a Kromasil 5-AmyCoat column (4.6 mm i.d. × 250 mm, 5 µm, AkzoNobel). ESI mass spectra were recorded on a LCQ Advantage spectrometer from Thermo Finningan and on a LCQ Fleet spectrometer from Thermo Scientific.

In the analytic department of the Institute of Organic Chemistry at the University of Freiburg Chiral HPLC measurements were performed on a

Merck Hitachi HPLC apparatus (pump: L-7100, UV detector: L-7400, auto sampler: L-7200, oven: L-7360), a Varian Pro Star (pump: 230, UV detector: 310, auto sampler: 410, oven: 510) and a Hitachi Primade (pump: 1100, DAD detector: 1430, auto sampler: 1210, oven: 1310).

Optical rotations were measured on a Perkin–Elmer 343 polarimeter at 20° C (concentration in g/100 mL).

Mass spectrometry

In the analytic department of the Institute of Pharmaceutical Science at the University of Milan mass spectra were determined with a LCQ Advantage Thermo Finningan.

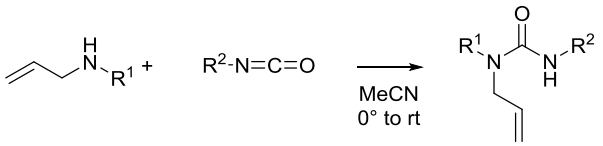
In the analytic department of the Institute of Organic Chemistry at the University of Freiburg high resolution mass spectrometry (HRMS) was performed on an Executive mass spectrometer (ESI or APCI) with orbitrap analyzer from Thermo Fisher Scientific Inc. The analyzer was externally calibrated and had a resolution of M/ΔM = 20 0000 - 100 000.

Gas Chromatogrpahy

In the analytic department of the Institute of Organic Chemistry at the University of Freiburg analytical gas chromatography was performed using a 6850 Agilent Technologies apparatus equipped with a Macherey-Nagel Hydrodex-ß-TBDAc (25 m × 0.25 mm ID) column and flame ionization detector (FID).

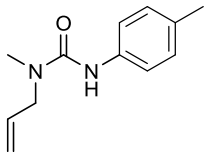
Aminoarylation

General procedure for the preparation of *N*-protected allyl ureas (GP1)



To a solution of allyl amine (1 mmol, 1 eq) in acetonitrile (10 mL), the isocyanate (1 mmol, 1 eq) was added dropwise at 0 °C under inert atmosphere. The reaction mixture was allowed to warm to room temperature and it was stirred for 24 h. The solvent was evaporated under reduced pressure and the crude product was used without any further purification

N-Allyl-*N*-methyl-*N*'-tolyl-urea (1a)

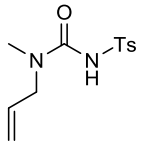


Compound **1a** was prepared according to the general procedure (GP1) and isolated as white solid (yield 76%).

The data are in good agreement with those reported in the literature.[d]

[d] D. Li, T. Mao, J. Huang, Q. Zhu, *Chem. Commun.,* **2017**, *53*, 3450

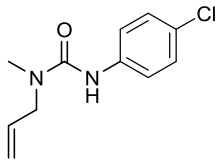
N-Allyl-*N*-methyl-*N*-tosyl-urea (1b)



Compound **1b** was prepared according to the general procedure (GP1) and isolated as colourless oil (yield 97%)

The data are in good agreement with those reported in the literature.[d]

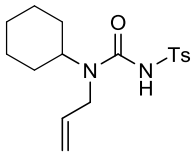
N-Allyl-*N*-methyl-*N*'-(4-chlorophenyl)urea (1c)



Compound **1c** was prepared according to the general procedure (GP1) and isolated as white solid (yield 94%).

The data are in good agreement with those reported in the literature.[e]

N-Allyl-*N*-cyclohexyl-*N*'-tosyl-urea (1d)



Compound **1d** was prepared according to the general procedure (GP1) and isolated as yellow oil (yield 98%).

IR: 1658 cm^{-1}

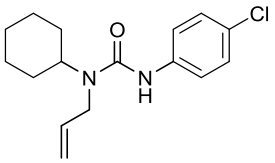
^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 5.99 – 5.84 (m, 1H), 5.35 – 5.18 (m, 2H), 3.52 (d, J = 6.7 Hz, 2H), 2.91 – 2.72 (m, 1H), 2.40 (s, 3H), 1.98 – 0.96 (m, 10H).

[e] S. T. W. Balko, R. S. Brinkmayer, N. H. Terando, *Tetrahedron Lett*. **1989,** 30, 2045.

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3 (s), 143.4 (s), 142.5 (s), 139.3 (s), 129.9 (d), 129.6 (d), 126.4 (d), 121.7 (t), 55.7 (d), 47.0 (t), 29.5 (t), 25.9 (t), 25.1 (t), 24.6 (t), 21.5 (q).

MS: *m/z* 337.26 $(M+H)^+$

N-Allyl-*N*-cyclohexyl-*N'*-(4-chlorophenyl)urea (1e)



Compound **1e** was prepared according to the general procedure (GP1) and isolated as white solid (yield 95%).

M.p. 122° C

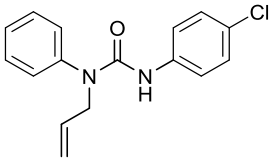
IR: 1663 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 7.23 – 7.15 (m, 2H), 6.52 (br s, 1H), 5.90 (ddt, *J* = 17.3, 10.1, 5.0 Hz, 1H), 5.54 – 5.14 (m, 2H), 4.23 (tt, *J* = 11.5, 3.4 Hz, 1H), 3.83 (dt, *J* = 4.8, 1.8 Hz, 2H), 1.95 – 0.90 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4 (s), 138.1 (s), 136.2 (d), 128.7 (d), 127.5 (s), 120.6 (d), 117.2 (s), 54.2 (d), 45.1 (t), 31.0 (t), 25.8 (t), 25.5 (t).

MS: *m/z* 293.75 $(M+H)^+$

N-Allyl-*N*-phenyl-*N*'-(4-chlorophenyl)urea (1f)



Compound **1f** was prepared according to the general procedure (GP1) and isolated as white solid (yield 96%).

M.p. 75-76° C

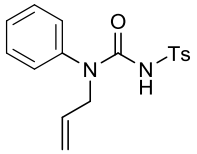
IR: 1670 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.07 (m, 9H), 6.19 (br s, 1H), 6.08 – 5.76 (m, 1H), 5.29 – 5.05 (m, 2H), 4.35 (d, J = 6.1 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8 (s), 141.1 (s), 137.4 (s), 133.9 (d), 130.3 (d), 128.7 (d), 128.5 (d), 128.3 (d), 127.8 (s), 120.4 (d), 117.6 (t), 52.3 (t).

MS: m/z 287.54 $(M+H)^+$

N-Allyl-*N*-phenyl-*N'*-tosyl-urea (1g)



Compound **1g** was prepared according to the general procedure (GP1) and isolated as orange solid (yield 98%).

M.p. 74-76° C

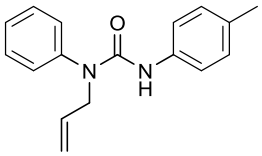
IR: 1696 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.53 – 7.38 (m, 3H), 7.38 – 7.26 (m, 2H), 7.19 (d, J = 7.2 Hz, 2H), 7.09 (br s, 1H), 5.79 (ddt, J = 16.7, 10.2, 6.4 Hz, 1H), 5.13 – 4.97 (m, 2H), 4.18 (d, J = 6.3 Hz, 2H), 2.46 (s, J = 5.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1 (s), 144.6 (s), 139.3 (s), 136.1 (s), 132.4 (d), 130.6 (d), 129.5 (d), 129.1 (d), 128.4 (d), 128.3 (d), 118.7 (t), 52.4 (t), 21.7 (q).

MS: (ESI) 353.67 *m/z* $(M+Na)^+$

_N_-Allyl-_N_-phenyl-_N'_-tolyl-urea (1h)



Compound **1h** was prepared according to the general procedure (GP1) and isolated as pale yellow solid (yield 94%).

M.p. 83-84° C

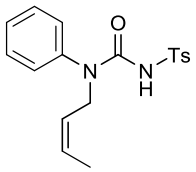
IR: 1660 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.24 (m, 5H), 7.24 – 7.16 (m, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.15 (br s, 1H), 5.97 (ddt, *J* = 17.4, 9.8, 6.1 Hz, 1H), 5.27 – 4.96 (m, 2H), 4.37 (dt, *J* = 6.1, 1.2 Hz, 2H), 2.29 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (s), 141.5 (s), 136.2 (s), 134.2 (d), 132.5 (s), 130.2 (d), 129.3 (d), 128.5 (d), 128.0 (d), 119.4 (d), 117.4 (t), 52.3 (t), 20.7 (q).

MS: *m/z* 267.27 $(M+H)^+$, 289.29 $(M+Na)^+$.

***(E)*-_N_-But-2-en-1-yl-_N_-phenyl-_N'_-tosyl-urea (5)**



Compound **5** was prepared according to the general procedure (GP1) and isolated as white solid (yield 79%).

M.p. 104-107° C (decomp.)

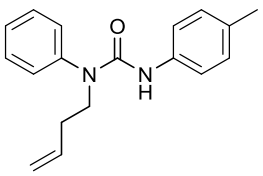
IR: 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.85 (m, 2H), 7.50 – 7.26 (m, 5H), 7.19 – 7.11 (m, 2H), 6.93 (br s, 1H), 5.46 – 5.36 (m, 2H), 4.12 – 4.01 (m, 2H), 2.44 (s, 3H), 1.58 (ddd, *J* = 4.0, 2.0, 1.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9 (s), 144.5 (s), 139.4 (s), 136.2 (s), 130.4 (d), 130.2 (d), 129.4 (d), 129.0 (d), 128.4 (d), 128.3 (d), 125.1 (d), 51.7 (t), 21.6 (q), 17.6 (q).

MS: *m/z* 345.62 $(M+H)^+$

1-(But-3-en-1-yl)-1-phenyl-3-(*p*-tolyl)urea (8)



Compound **8** was prepared according to the general procedure (GP1) and isolated as pale yellow oil (yield 89%).

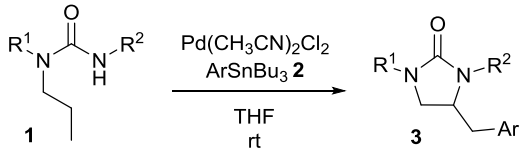
IR: 1678 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.4 Hz, 2H), 7.38 (dd, *J* = 15.1, 7.7 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.03 (s, 1H), 5.80 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.06 (dd, *J* = 21.0, 5.3 Hz, 2H), 3.92 – 3.73 (m, 2H), 2.39 – 2.28 (m, 2H), 2.26 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2 (s), 141.4 (s), 136.3 (s), 135.4 (d), 132.4 (s)l, 130.3 (d), 129.2 (d), 128.8 (d), 128.1 (d), 119.4 (d), 116.6 (t), 48.7 (t), 32.9 (t), 20.7 (q).

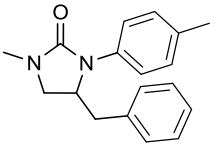
MS: *m/z* 190.24 $(M+H)^+$

General procedure for the aminoarylation of *N*-allyl ureas (GP2)



A mixture of *N*-allylurea **1** (0.25 mmol. 1 eq), $PdCl_2(CH_3CN)_2$ (0.025 mmol, 10 mol%), H_2O_2 (0.33 mmol, 1.3 eq), and $ArSnBu_3$ (0.25 mmol, 1 eq) in THF (1.25 mL, 0.2 M) was stirred at room temperature. In the case of the substrate **5**, also (*S*)-4-tert-butyl-2-(2-pyridyl)oxazoline ligand (12 mol%) was added to the reaction mixture. After 24 h the solvent was evaporated under reduced pressure and water (10 mL) was added. The aqueous layer was extracted with DCM (3 x 10 mL), then the organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding imidazolidinone **3.**

4-Benzyl-1-methyl-3-tolyl-imidazolidin-2-one (3aa)



Compound **3aa** was prepared according to the general procedure (GP2) and isolated as yellow oil (yield 73%) after a first flash chromatography in Hex/EtOAc 3:1 and a second one in DCM/MeOH 100:1.

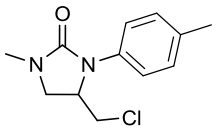
IR: 1680 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.03 (m, 7H), 4.40 – 4.29 (m, 1H), 3.27 (t, *J* = 8.7 Hz, 1H), 3.14 – 3.00 (m, 2H), 2.72 (s, 3H), 2.59 (dd, *J* = 13.6, 9.7 Hz, 1H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 (s), 136.2 (s), 133.4 (s), 129.6 (d), 129.2 (d), 128.7 (d), 126.8 (d), 121.4 (d), 54.8 (d), 49.4 (t), 38.1 (t), 31.1 (q), 20.8 (q).

MS: *m/z* 281.51 $(M+H)^+$

4-(chloromethyl)-1-methyl-3-(p-tolyl)imidazolidin-2-one (4)



Compound **4** was prepared according to the general procedure (GP2) and isolated as yellow oil (yield 35%) after a first flash chromatography in Hex/EtOAc 3:1 and a second one in DCM/MeOH 100:1.

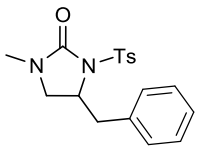
IR: 1696 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.60 – 4.27 (m, 1H), 3.70 – 3.59 (m, 2H), 3.56 – 3.38 (m, 2H), 2.90 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (s), 135.5 (s), 134.2 (s), 129.8 (d), 121.7 (d), 54.5 (d), 48.4 (t), 43.8 (t), 31.0 (q), 20.8 (q).

MS: *m/z* 239.34 $(M+H)^+$

4-Benzyl-1-methyl-3-tosyl-imidazolidin-2-one (3ba)



Compound **3ba** was prepared according to the general procedure (GP2) and isolated as yellow oil (yield 59%) after a first flash chromatography in Hex/EtOAc 3:1 and a second one in DCM/MeOH 100:1.

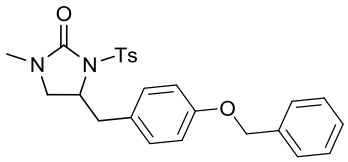
IR: 1690 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.07 (m, 7H), 4.54 – 4.34 (m, 1H), 3.43 (dd, *J* = 13.0, 3.6 Hz, 1H), 3.19 (t, *J* = 9.0 Hz, 1H), 2.98 (dd, *J* = 9.2, 3.4 Hz, 1H), 2.71 (dd, *J* = 13.2, 9.9 Hz, 1H), 2.58 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9 (s), 144.6 (s), 136.6 (s), 135.7 (s), 129.6 (d), 129.5 (d), 128.8 (d), 128.2 (d), 127.2 (d), 115.2 (d), 54.9 (d), 48.7 (t), 40.8 (t), 30.5 (q), 21.7 (q).

MS: *m/z* 345.32 $(M+H)^+$

4-(4-Benzyloxyphenyl)methyl-1-methyl-3-tosylimidazolidin-2-one (3bb)



Compound **3bb** was prepared according to the general procedure (GP2) and isolated as yellow oil (yield 48%) after a first flash chromatography in Hex/EtOAc 3:1 and a second one in DCM/MeOH 100:1.

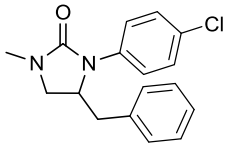
IR: 1696 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 18.8, 8.3 Hz, 2H), 7.43 – 7.20 (m, 7H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.97 (s, 2H), 4.46 – 4.26 (m, 1H), 3.34 (dd, *J* = 13.5, 3.3 Hz, 1H), 3.19 (t, *J* = 9.0 Hz, 1H), 2.97 (dd, *J* = 9.4, 3.2 Hz, 1H), 2.66 (dd, *J* = 13.4, 9.7 Hz, 1H), 2.57 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (s), 153.9 (s), 144.5 (s), 136.9 (s), 136.6 (s), 130.5 (d), 129.6 (d), 128.6 (d), 128.2 (d), 128.0 (d), 127.9 (s), 127.5 (d), 70.1 (t), 55.0 (d), 48.7 (t), 39.9 (t), 30.5 (q), 21.7 (q).

MS: *m/z* 451.39 $(M+H)^+$

4-Benzyl-1-methyl-3-(4-chlorophenyl)imidazolidin-2-one (3ca)



Compound **3ca** was prepared according to the general procedure (GP2) and isolated as white solid (yield 66%) after a first flash chromatography in Hex/EtOAc 3:1 and a second one in DCM/MeOH 100:1.

M.p. 90° C

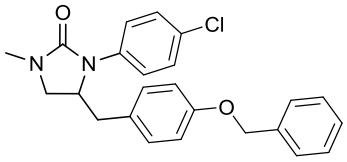
IR: 1651 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.42 – 7.21 (m, 5H), 7.16 (d, *J* = 7.2 Hz, 2H), 4.45 (ddd, *J* = 12.9, 8.6, 4.1 Hz, 1H), 3.40 (t, *J* = 8.8 Hz, 1H), 3.23 (dd, *J* = 8.9, 4.7 Hz, 1H), 3.12 (dd, *J* = 13.8, 3.1 Hz, 1H), 2.82 (s, 3H), 2.72 (dd, *J* = 13.7, 9.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5 (s), 136.2 (s), 131.3 (s), 129.2 (d), 129.0 (d), 128.8 (d), 128.5 (s), 127.0 (d), 121.7 (d), 54.3 (d), 49.1 (t), 37.9 (t), 31.0 (q).

MS: *m/z* 301.79 $(M+H)^+$

4-(4-Benzyloxyphenyl)methyl-1-methyl-3-(4-chlorophenyl)imidazolidin-2-one (3cb)



Compound **3cb** was prepared according to the general procedure (GP2) and isolated as yellow oil (yield 51%) after a first flash chromatography in Hex/EtOAc 3:1 and a second one in DCM/MeOH 100:1.

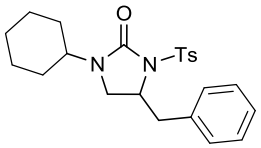
IR: 1646 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.28 (m, 10H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 5.04 (s, 2H), 4.43 – 4.28 (m, 1H), 3.37 (t, *J* = 8.7 Hz, 1H), 3.18 (dd, *J* = 8.5, 4.4 Hz, 1H), 3.00 (d, *J* = 13.9 Hz, 1H), 2.78 (s, 3H), 2.65 (dd, *J* = 13.7, 9.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (s), 157.9 (s), 137.5 (s), 136.9 (s), 130.2 (d), 129.1 (d), 129.0 (d), 128.6 (d), 128.4 (s), 128.0 (d), 127.5 (d), 121.8 (d), 115.2 (d), 70.1 (t), 54.4 (d), 49.1 (t), 37.00 (t), 31.0 (q).

MS: *m/z* 407.85 $(M+H)^+$

4-Benzyl-1-cyclohexyl-3-tosyl-imidazolidin-2-one (3da)



Compound **3da** was prepared according to the general procedure (GP2) and isolated as yellow oil (yield 62%) after a first flash chromatography in Hex/EtOAc 4:1 and a second one in DCM/MeOH 100:1.

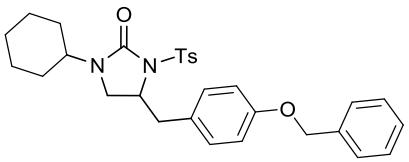
IR: 1658 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.16 (m, 5H), 7.10 (d, *J* = 7.2 Hz, 2H), 4.54 – 4.37 (m, 1H), 3.58 – 3.42 (m, 1H), 3.31 (dd, *J* = 13.4, 3.4 Hz, 1H), 3.17 (t, *J* = 9.0 Hz, 1H), 2.95 (dd, *J* = 9.3, 2.6 Hz, 1H), 2.70 (dd, *J* = 13.3, 9.4 Hz, 1H), 2.35 (s, 3H), 1.79 – 0.62 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (s), 144.5 (s), 136.7 (s), 135.7 (s), 129.6 (d), 129.5 (d), 128.8 (d), 128.2 (d), 127.1 (d), 55.0 (d), 51.4 (d), 42.1 (t), 40.4 (t), 30.0 (t), 29.7 (t), 25.3 (t), 25.2 (t), 21.7 (q).

MS: *m/z* 413.26 $(M+H)^+$

4-(4-Benzyloxyphenyl)methyl-1-cyclohexyl-3-tosylimidazolidin-2-one (3db)



Compound **3db** was prepared according to the general procedure (GP2) and isolated as yellow oil (yield 71%) after a first flash chromatography in Hex/EtOAc 4:1 and a second one in DCM/MeOH 100:1.

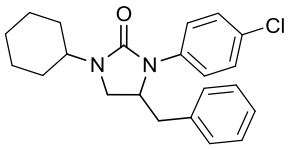
IR: 1692 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.47 – 7.28 (m, 7H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.06 (s, 2H), 4.61 – 4.44 (m, 1H), 3.69 – 3.52 (m, 1H), 3.46 – 3.23 (m, 2H), 3.04 (dd, *J* = 9.2, 2.6 Hz, 1H), 2.75 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.44 (s, 3H), 1.92 – 0.87 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (s), 152.9 (s), 144.4 (s), 137.0 (s), 136.8 (s), 130.6 (d), 129.5 (d), 128.6 (d), 128.3 (d), 128.1 (d), 128.0 (d), 127.9 (s), 127.4 (d), 115.2 (d), 70.1 (t), 55.1 (d), 51.4 (d), 42.2 (t), 39.5 (t), 30.1 (t), 29.7 (t), 25.3 (t), 25.2 (t), 21.7 (q).

MS: *m/z* 519.67 $(M+H)^+$

4-Benzyl-1-cyclohexyl-3-(4-chlorophenyl)imidazolidin-2-one (3ea)



Compound **3ea** was prepared according to the general procedure (GP2) and isolated as white solid (yield 58%) after a first flash chromatography in Hex/EtOAc 4:1 and a second one in DCM/MeOH 100:1.

M.p. 76° C

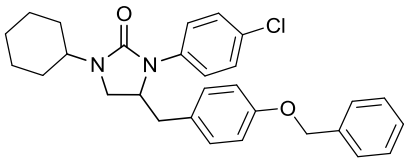
IR: 1698 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.7 Hz, 2H), 7.42 – 7.23 (m, 5H), 7.13 (d, *J* = 6.8 Hz, 2H), 4.51 – 4.32 (m, 1H), 3.81 – 3.62 (m, 1H), 3.38 (t, *J* = 8.7 Hz, 1H), 3.17 (dd, *J* = 8.8, 3.9 Hz, 1H), 3.04 (dd, *J* = 14.0, 2.7 Hz, 1H), 2.71 (dd, *J* = 13.8, 8.8 Hz, 1H), 1.88 – 0.98 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7 (s), 137.7 (s), 136.2 (s), 129.2 (d), 129.0 (d), 128.7 (d), 128.0 (s), 126.9 (d), 121.3 (d), 54.3 (d), 51.2 (d), 42.1 (t), 37.6 (t), 30.2 (t), 29.9 (t), 25.5 (t), 25.5 (t).

MS: *m/z* 369.45 (M+H)

4-(4-Benzyloxyphenyl)methyl-1-cyclohexyl-3-(4-chlorophenyl)imidazolidin-2-one (3eb)



Compound **3eb** was prepared according to the general procedure (GP2) and isolated as pale-yellow oil (yield 50%) after a first flash chromatography in Hex/EtOAc 3:1 and a second one in DCM/MeOH 100:1.

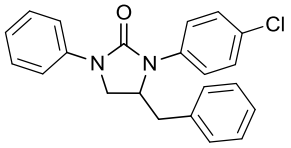
IR: 1698 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.51 (m, 2H), 7.49 – 7.30 (m, 7H), 7.10 – 7.00 (m, 2H), 6.98 – 6.89 (m, 2H), 5.07 (s, 2H), 4.40 (ddd, *J* = 12.5, 8.6, 3.9 Hz, 1H), 3.74 (tt, *J* = 12.1, 3.9 Hz, 1H), 3.39 (t, *J* = 8.8 Hz, 1H), 3.17 (dd, *J* = 8.9, 4.3 Hz, 1H), 2.98 (dd, *J* = 13.9, 3.3 Hz, 1H), 2.68 (dd, *J* = 13.9, 8.7 Hz, 1H), 1.93 – 0.95 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9 (s), 156.7 (s), 137.8 (s), 137.0 (s), 130.3 (d), 129.0 (d), 128.6 (d), 128.5 (s), 128.0 (d), 127.4 (d), 121.3 (d), 115.1 (d), 70.1 (t), 54.4 (d), 51.2 (d), 42.1 (t), 36.8 (t), 30.3 (t), 29.9 (t), 25.5 (t), 25.5 (t).

MS: *m/z* 475.56 $(M+H)^+$, 498.03 $(M+Na)^+$

4-benzyl-3-(4-chlorophenyl)-1-phenylimidazolidin-2-one (3fa)



Compound **3fa** was prepared according to the general procedure (GP2) and isolated as colourless oil (yield 38%) after a first flash chromatography in Hex/EtOAc 4:1 and a second one in DCM/MeOH 100:1.

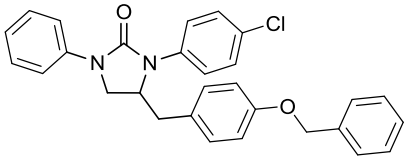
IR: 1690 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 2H), 7.51 – 7.44 (m, 2H), 7.43 – 7.13 (m, 8H), 7.11 – 7.02 (m, 2H), 4.67 – 4.51 (m, 1H), 3.90 (t, J = 9.0 Hz, 1H), 3.67 (dd, J = 9.3, 4.8 Hz, 1H), 3.18 (dd, J = 13.8, 3.4 Hz, 1H), 2.77 (dd, J = 13.8, 9.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8 (s), 139.7 (s), 136.8 (s), 135.7 (s), 129.4 (s), 129.1 (d), 128.9 (d), 128.8 (d), 127.2 (d), 123.2 (d), 122.7 (d), 118.2 (d), 53.9 (d), 47.0 (t), 38.3 (t).

MS: m/z 363.17 $(M+H)^+$

4-(4-Benzyloxyphenyl)methyl-1-phenyl-3-(4-chlorophenyl) imidazolidin-2-one (3fb)



Compound **3fb** was prepared according to the general procedure (GP2) and isolated as yellow oil (yield 56%) after a first flash chromatography in Hex/EtOAc 4:1 and a second one in DCM/MeOH 100:1.

IR: 1688 cm^{-1}

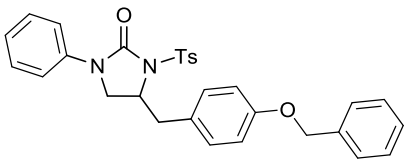
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.28 (m, 13H), 7.15 – 7.03 (m, 3H), 6.97 – 6.84 (m, 2H), 5.04 (s, 2H), 4.62 – 4.46 (m, 1H), 3.90 (t, J = 9.0 Hz, 1H),

3.66 (dd, *J* = 9.2, 4.9 Hz, 1H), 3.10 (dd, *J* = 13.9, 3.4 Hz, 1H), 2.73 (dd, *J* = 13.9, 9.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0 (s), 154.9 (s), 139.7 (s), 136.9 (s), 130.2 (d), 129.4 (s), 129.1 (d), 128.8 (d), 128.6 (d), 128.0 (d), 127.9 (s), 127.4 (d), 123.1 (d), 122.6 (d), 118.2 (d), 115.3 (d), 70.1 (t), 53.9 (d), 47.0 (t), 37.4 (t).

MS: *m/z* 469.57 $(M+H)^+$

4-(4-Benzyloxyphenyl)methyl-1-phenyl-3-tosylimidazolidin-2-one (3gb)



Compound **3gb** was prepared according to the general procedure (GP2) and isolated as yellow oil (yield 55%) after a first flash chromatography in Hex/EtOAc 3:1 and a second one in DCM/MeOH 100:1.

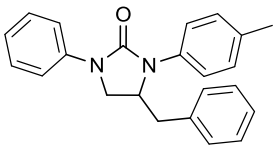
IR: 1695 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.15 (m, 11H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.00 (t, *J* = 7.1 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.97 (s, 2H), 4.65 – 4.41 (m, 1H), 3.72 (t, *J* = 9.1 Hz, 1H), 3.50 – 3.37 (m, 2H), 2.76 (dd, *J* = 13.4, 9.8 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (s), 151.4 (s), 144.9 (s), 138.4 (s), 136.9 (s), 136.3 (s), 130.6 (d), 129.6 (d), 128.9 (d), 128.6 (d), 128.4 (d), 128.0 (d), 127.7 (s), 127.5 (d), 124.3 (d), 118.8 (d), 115.3 (d), 70.1 (t), 54.5 (d), 47.2 (t), 40.0 (t), 21.7 (q).

MS: *m/z* 513.43 $(M+H)^+$

4-benzyl-1-phenyl-3-(p-tolyl)imidazolidin-2-one (3ha)



Compound **3ha** was prepared according to the general procedure (GP2) and isolated as colourless oil (yield 59%) after a first flash chromatography in Hex/EtOAc 4:1 and a second one in DCM/MeOH 100:1.

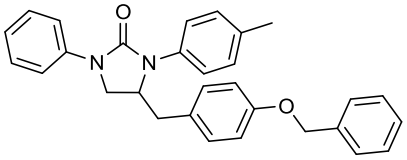
IR: 2921, 1705, 1404, 1292 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.44 (m, 4H), 7.37 – 7.13 (m, 9H), 7.10 – 7.01 (m, 1H), 4.64 – 4.51 (m, 1H), 3.85 (t, *J* = 9.0 Hz, 1H), 3.65 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.20 (dd, *J* = 13.7, 3.3 Hz, 1H), 2.74 (dd, *J* = 13.7, 9.6 Hz, 1H), 2.36 (d, *J* = 8.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3 (s), 140.1 (s), 136.1 (s), 135.5 (s), 134.3 (s), 129.7 (d), 129.4 (d), 129.2 (d), 128.8 (d), 128.8 (d), 127.0 (d), 122.8 (d), 122.3 (d), 118.0 (d), 54.3 (d), 47.1 (t), 38.5 (t), 20.9 (q).

MS: *m/z* 343.60$(M+H)^+$.

4-(4-Benzyloxyphenyl)methyl-1-phenyl-3-tolylimidazolidin-2-one (3hb)



Compound **3hb** was prepared according to the general procedure (GP2) and isolated as colourless oil (yield 54%) after a first flash chromatography in Hex/EtOAc 4:1 and a second one in DCM/MeOH 100:1.

IR: 1690 cm^{-1}

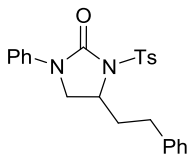
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.19 (m, 13H), 7.12 – 7.04 (m, 3H), 6.97 – 6.88 (m, 2H), 5.04 (s, *J* = 7.3 Hz, 2H), 4.59 – 4.45 (m, 1H), 3.86 (t, *J* = 8.9

Hz, 1H), 3.64 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.12 (dd, *J* = 13.8, 3.3 Hz, 1H), 2.69 (dd, *J* = 13.8, 9.5 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9 (s), 155.3 (s), 140.1 (s), 136.9 (s), 135.5 (s), 134.2 (s), 130.2 (d), 129.7 (d), 128.7 (d), 128. 6 (d), 128.3 (s), 128.0 (d), 127.4 (d), 122.7 (d), 122.2 (d), 118.0 (d), 115.2 (d), 70.1 (t), 54.3 (d), 47.1 (t), 37.5 (t), 20.9 (q).

MS: *m/z* 449.48 $(M+H)^+$, 471.52 $(M+Na)^+$

4-phenethyl-1-phenyl-3-tosylimidazolidin-2-one (6)



Compound **6** was prepared according to the general procedure (GP2) and isolated as colourless oil (yield 49%) after a first flash chromatography in Hex/EtOAc 4:1 and a second one in DCM/MeOH 100:1.

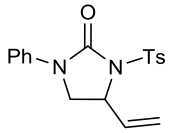
IR: 1695 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.50 – 7.08 (m, 12H), 4.57 – 4.46 (m, 1H), 4.03 (t, *J* = 9.1 Hz, 1H), 3.56 (dd, *J* = 9.2, 3.4 Hz, 1H), 2.77 – 2.64 (m, 2H), 2.50 – 2.37 (m, 4H), 2.28 – 2.15 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8 (s), 140.0 (s), 138.3 (s), 136.1 (s), 129.6 (d), 129.0 (d), 128.6 (d), 128.3 (d), 128.3 (d), 126.4 (d), 124.4 (d), 119.5 (s), 118.7 (d), 53.1 (d), 48.1 (t), 36.3 (t), 30.3 (t), 21.7 (q).

MS: *m/z* 420.90 $(M+H)^+$

4-vinyl-1-phenyl-3-tosylimidazolidin-2-one (7)



Compound **7** was prepared according to the general procedure (GP2) and isolated as colourless oil (yield 11%) after a first flash chromatography in Hex/EtOAc 4:1 and a second one in DCM/MeOH 100:1.

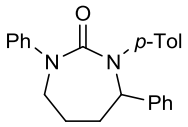
IR: 1689 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.97 (m, 2H), 7.48 – 7.43 (m, 2H), 7.38 – 7.31 (m, 4H), 7.14 (d, *J* = 7.4 Hz, 1H), 5.95 (ddd, *J* = 17.0, 10.1, 8.0 Hz, 1H), 5.53 (d, *J* = 17.0 Hz, 1H), 5.38 (d, *J* = 10.2 Hz, 1H), 4.94 (td, *J* = 8.8, 3.4 Hz, 1H), 4.15 (t, *J* = 9.1 Hz, 1H), 3.58 (dd, *J* = 9.3, 3.4 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR (126 MHz, CDCl3) δ 151.3 (s), 144.7 (s), 138.4 (s), 136.2 (s), 135.2 (d), 129.5 (d), 129.0 (d), 128.6 (d), 124.4 (d), 119.4 (t), 118.7 (d), 55.8 (d), 49.2 (t), 21.7 (q).

MS: *m/z* 365.22 $(M+Na)^+$

1,4-diphenyl-3-(*p*-tolyl)-1,3-diazepan-2-one (9)



Compound **9** was prepared according to the general procedure (GP2) and isolated as colourless oil (yield 57%) after a first flash chromatography in Hex/EtOAc 3:1 and a second one in DCM/MeOH 100:1.

IR: 1694 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.11 (m, 28H), 7.05 (d, J = 8.4 Hz, 5H), 4.93 (dd, J = 8.1, 6.2 Hz, 2H), 3.82 (td, J = 7.3, 2.0 Hz, 4H), 2.28 (s, 7H), 2.24 – 2.02 (m, 4H), 1.90 – 1.49 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 (s), 141.7 (s), 141.1 (s), 136.2 (s), 132.5 (s), 130.4 (d), 129.3 (d), 128.7 (d), 128.6 (d), 128.3 (d), 128.2 (d), 126.9 (d), 119.5 (d), 63.4 (d), 48.3 (t), 37.1 (t), 26.0 (t), 20.7 (q).

MS: m/z 379.81 $(M+Na)^+$

X-Ray Cristallography (Dr. Leonardo Lo Presti)

Single crystal X-ray diffraction analysis of the compound 3ea

The data collection was carried out on a Bruker AXS Smart APEX 3-circle diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at a nominal power of the source of 50 kV × 30 mA. A 100% complete full sphere of reflections was measured up to a resolution of $\sin\theta/\lambda = 0.45$ Å $^{-1}$ by means of 5 ω scans of the reciprocal lattice. The Saint+[f] and SADABS[g] programs were employed to account for systematic errors, including absorption and beam anisotropy corrections. The compound crystallizes in a P2 1/c centric lattice [a = 11.1136(19) Å, b = 12.867(2) Å, c = 29.058(5) Å, β = 94.558(11)°] as a 1:1 racemate, with two molecules with inverse handedness per asymmetric unit and a total of 8 molecules per cell. The molecular structure was solved through the charge flipping method[h] and least- squares refined within the Independent Atom Model approximation implemented in SHELX.[i] A total of 23311 individual structure factor amplitudes, corresponding to 3255 independent observations, entered the fitting, giving a final agreement factor R1(F) of 0.1064 for 1758 F σ > 4σ(F_o) in conjunction with a goodness-of-fit of 1.040 and largest Fourier residuals of +0.40/–0.31 e/Å 3 , both close to the chlorine heavy atom.

The compound is chiral and crystallizes in the centric space group $P2_1/c$ as a racemate, with two molecules with inverse handedness per asymmetric unit (ASU). An attempt to model the structure in the non-centrosymmetric

f Bruker AXS Inc., SAINT+, Madison, Wisconsin, USA, 2012.

g Bruker AXS Inc., SADABS, Madison, Wisconsin, USA, 2001.

h L. Palatinus, G. Chapuis, J. Appl. Crystallogr. 2007, 40, 786.

i M. Sheldrick, Acta Crystallogr. 2015, 71, 3–8.

$P2_1$ space group with 4 independent molecules in the ASU was unsuccessful, as the least-squares refinement invariably led to a 100% correlation between [x, y, z] and [–x, –y, –z] coordinates. Figures S1 and S2 show the absolute configuration of the chiral centres in the asymmetric unit. The configurational descriptor of the unique stereogenic centre is C9 (R) for the molecule A and C9 (S) for the molecule B (see Figure S1 for the atom numbering).

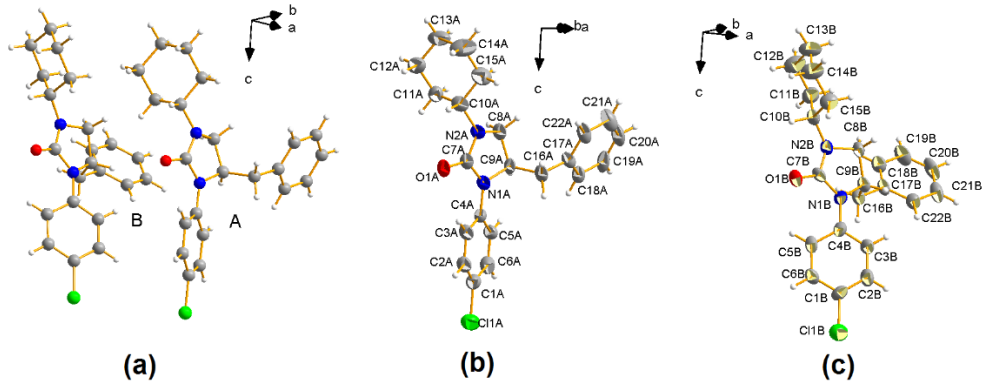


Figure S1. (a) Asymmetric unit of 3ea at RT. The crystallographic reference system is also shown. (b) Molecule A, with the atom-numbering scheme. Thermal ellipsoids of non-H atoms were drawn at the 25 % probability level. (c) As (b), for the molecule B. The usual colour code was employed for atoms (grey: C; white: H; blue: N; red: O; green: Cl).

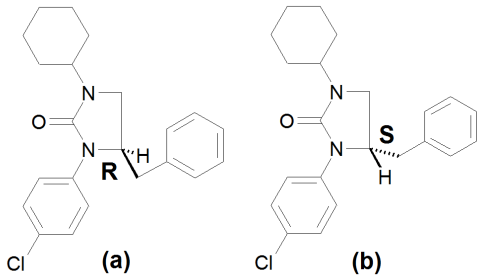


Figure S2. Molecular structure of **3ea**, with the CIP descriptors highlighted. Both symmetry-independent molecules in the asymmetric unit are shown. (a) Molecule A. (b) Molecule B.

This substance crystallizes in very thin needles, which also give very low diffraction intensities. After various attempts, we eventually managed to obtain X-ray quality crystals by slow evaporation (~ 1 month) from CH_3CN at room temperature. The crystalline material is highly elastic and has a fibrous appearance. We cut a sample with a needle habit, transparent, with dimensions 0.800 x 0.100 x 0.050 mm from a larger agglomerate using a blade (Figure S3). It showed pleochroism under polarized light (from colourless to green-light blue). After polishing by mechanical ablation in a drop of perfluorinated oil, we mounted it on the diffractometer to carry out the data collection.

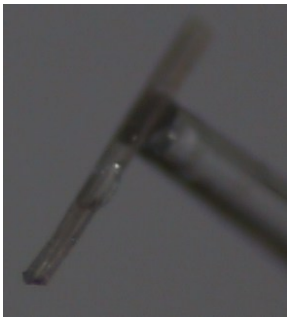


Figure S3. Sample used for the present structural determination.

The resolution of the overall data collection is quite low (~ 1 Å), as at higher Bragg angles the count statistics was too low to be meaningful. Consequently, the present structural analysis suffers of various drawbacks (poor data-to-parameter ratio, low resolution), which result in a general low precision of the geometrical parameters (bond lengths, angles) and high agreement factors. However, the purpose of the present work was to secure the molecular connectivity, and particularly to determine whether the 4-chlorobenzyl substituent is connected either to oxygen or nitrogen of the imidazolidin-2-one ring. In this respect, the experiment was successful, as the data are fully consistent with the model shown in Figures S1-S2.

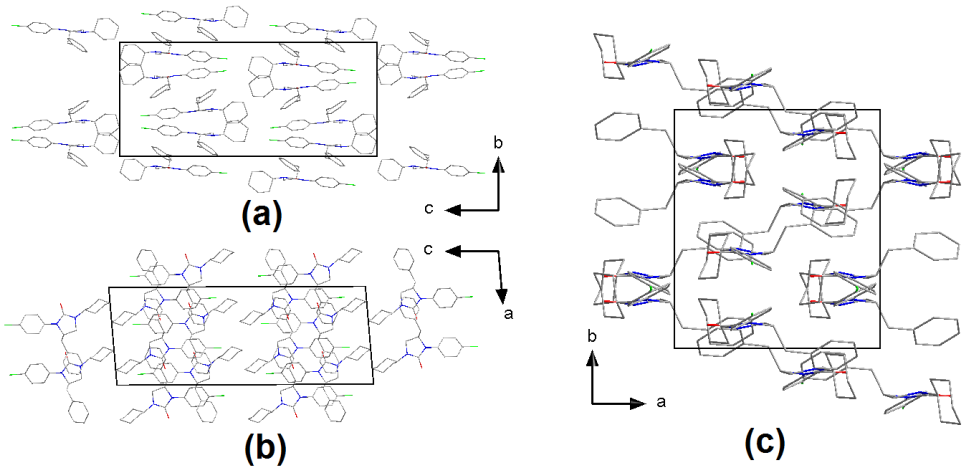


Figure S4. Crystal packing of **3ea** at RT, as seen as wires-stick molecular representations (a) along the *a* cell axis; (b) the *b* cell axis; (c) the *c* cell axis. Colour code as in Figure 1. H atoms are omitted for clarity. The crystallographic reference system is also shown.

Figure S4 shows the main packing motifs of **3ea**. No strong hydrogen bond donors are present: only C–H···O contacts with distance H···acceptor lower than the sum of the van der Waals radii and favourable geometries are set up (Table S1, Figure S5). "A" molecules exploit the phenyl C19A–H19A···O1A contact to form CH···O hydrogen-bonded infinite chains with translation-related images of themselves along the *a* axis. "B" molecules form an analogue, parallel chain-like arrangement, using the phenyl C21B–H21B···O1B contact. Parallel chains of "A" and "B" molecules are cross-linked through C9A–H9A···O1B and C9B–H9B···O1A contacts, C9 being the asymmetric ternary carbon (see above). No significant halogen-bonded contacts are set up.

Table 1. Short intermolecular C–H···O halogen bonded contacts with $d_{H\cdots O} < 3.0$ Å and $120^{o} \leq \alpha_{CHO} \leq 180^{o}$ in **3ea** at room temperature. Distances are expressed in Å and angles in degrees. Estimated standard deviations are given in parentheses.

C–H···O	$d_{C–H}$	$d_{H···O}$	$d_{C···O}$	α_{CHO}	symmetry
C19A–H19A···O1A	0.93	2.53	3.35(2)	147	1+x, y, z
C21B–H21B···O1B	0.93	2.57	3.36(2)	143	1+x, y, z
C9A–H9A···O1B	0.98	2.41	3.36(1)	162	1+x, y, z
C9B–H9B···O1A	0.98	2.42	3.35(1)	158	x, y, z

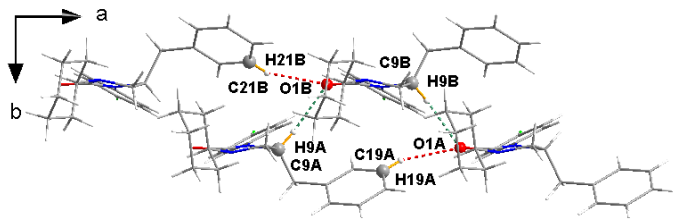


Figure S5. Short CH···O contacts in the parallel chains of A and B molecules of **3ea** at room temperature, as viewed down the c axis. See Table 1 for geometrical parameters.

Puckering analysis (D. Cremer & J.A. Pople, J.Amer.Chem.Soc., 97, (1975), 1354-1358), shows that the imidazolidin-2-one ring of both the enantiomers is not completely planar. The configurational descriptors (Molecule A: Q_2 = 0.214, φ_2 = 116.52 deg; Molecule B: Q_2 = 0.210 Å, φ_2 = 296.42 deg) are invariably compatible with a slight distortion toward a half-chair conformation. Both cyclohexyl rings, on the other hand, assume regular chair conformations, with puckering descriptors Q = 0.583 Å, θ = 2.24 deg, φ = 253.20 deg (Molecule A) and Q = 0.539 Å, θ = 0.59 deg, φ = 245.19 deg (Molecule B).

A ~ 124 Å^3 large void space is present in the unit cell. It might potentially allocate solvent molecules, and it has likely a strong hydrophobic nature,

as it is bounded by cyclohexyl substituents and chlorine atoms (Figure S6). Indeed, due to the poor diffracting ability of this substance, and consequently to poor intensity statistics, we cannot exclude the presence of partially or totally disordered solvent in this cavity. However, the highest Fourier residuals are smaller than +0.4/-0.3 e/A^3, and localized in close proximity of the chlorine atoms. Any attempt to locate meaningful solvent residual inside the cavity were unsuccessful.

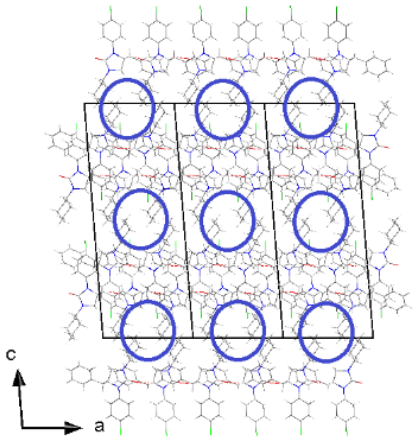
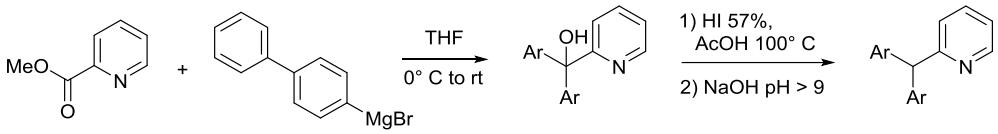


Figure S6. Crystal packing of **3ea** viewed down the *b* axis. The void space among cyclohexyl units, potentially able to allocate solvents, is highlighted as blue circles.

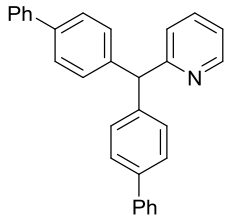
Acetoxylation

Synthesis of 2-(di([1,1'-biphenyl]-4-yl)methyl)pyridine



A 250 mL oven-dried flask was charged with magnesium turnings (691 mg, 28.8 mmol, 5 equiv) and THF (26 mL) under a nitrogen atmosphere, followed by adding a small amount of (1,1'-biphenyl)-4-yl bromide. After the observation of gas evolution, a solution of (1,1'-biphenyl)-4-yl bromide (Ar-Br, 3.99 g, 17 mmol, 3 equiv) in THF (16 mL) was added dropwise. The reaction mixture was heated at reflux for 5 h. The ArMgBr solution was then cooled with an ice-water bath, a solution of methyl picolinate (794 mg, 5.8 mmol, 1.00 equiv) in THF (15 mL) was added carefully. After stirring at room temperature for 1.5 hours, the reaction mixture was quenched with aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were dried over $NaSO_4$. After concentration, the residue was purified by column chromatography on silica gel (Hex/AcOEt 3:1), affording di([1,1'-biphenyl]-4-yl)(pyridin-2-yl)methanol as a white solid (2.04 g, 4.93 mmol, 85%). In a 50 mL round bottle flask, the obtained alcohol (2.04 g, 4.93 mmol) was dissolved in HOAc (14 mL), then HI (3.3 mL, 57 wt% aq) was added and the mixture was heated to 100 °C for 4 h. The mixture was cooled to 0 °C and basified to pH > 9 with NaOH (2 M aq), then diluted with ethyl acetate (45 mL), followed by washing with $NaHSO_3$ aq and brine. The combined organic layers were dried over $NaSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (Hex:AcOEt 1.5:1) giving the desired product 2-(di([1,1'-biphenyl]-4-yl)methyl)pyridine as a pale white solid (1.64 g, 83%).

2-(di([1,1'-biphenyl]-4-yl)methyl)pyridine



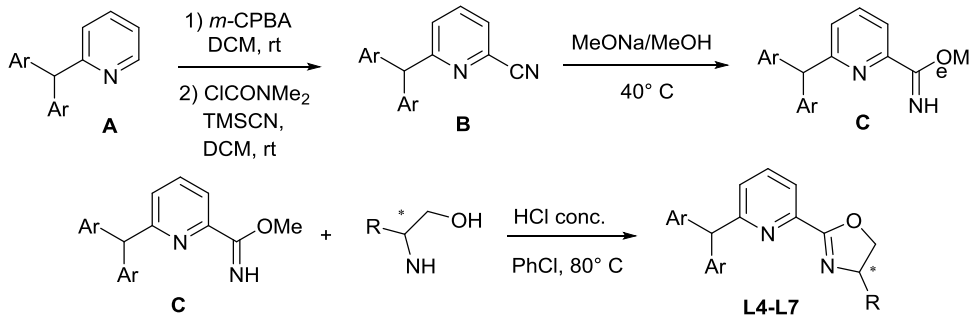
M.p. 179° C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 – 8.57 (m, 1H), 7.73 – 7.54 (m, 9H), 7.45 (t, *J* = 7.4 Hz, 4H), 7.40 – 7.29 (m, 6H), 7.26 – 7.13 (m, 2H), 5.81 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (s), 149.7 (d), 141.8 (s), 140.9 (s), 139.5 (s), 136.5 (d), 129.8 (d), 128.7 (d), 127.2 (d), 127.2 (d), 127.1 (d), 127.1 (d), 123.8 (d), 121.6 (d), 58.8 (d).

MS (ESI): m/z 398.26 $[M+H]^+$

Genereal procedure for the preparation of C-6 modified Pyox ligand (GP3)

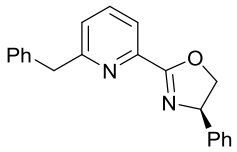


In a 250 mL round bottom flask, pyridine (1 eq) was dissolved in DCM (0.3 M). Then *m*-CPBA (meta-chloroperoxybenzoic acid, 1.7 eq) was added, and the mixture was stirred at room temperature. After the reaction was completed, K_2CO_3 (5 eq) was added. The mixture was stirred for 30 min at room temperature. After filtered through a celite pad, the filtrate was concentrated under vacuum to give the desired *N*-oxide, which was used without further purification. To a solution of the crude *N*-oxide in DCM

(0.7 M), dimethylcarbamic chloride (1.3 eq) was added at room temperature. The mixture was stirred for 10 min, then TMSCN (1.3 eq) was added. The mixture was stirred at room temperature. After the reaction was completed, the mixture was quenched with 10% aq K_2CO_3, and the mixture was extracted two times with DCM. The combined organic layers were washed with brine, dried over $NaSO_4$, and filtered. After concentration, the crude residue was purified by column chromatography on silica gel or crystallization to afford product **B**.

In a 50mL round bottom flask, **B** (1 eq) was dissolved in MeOH (1.5 M). Then NaOMe (0.3 eq) was added. The reaction mixture was stirred at 40° C overnight. After that, the solvent was removed under vacuum, and the residue was dissolved in EtOAc. The solution was washed with water and brine, then the organic phase was separated and dried over $NaSO_4$. After filtration, the filtrate was concentrated under vacuum to give the imine **C**, which was used without any further purification. The crude imine (1 eq) and (*R*)-2-amino-2-phenyl ethan-1-ol (1 eq) or (*S)*-phenilalanilol were weighted into a 100 mL round bottom flask, then dissolved in PhCl (0.5 M). Concentrated HCl (2 drops) was added to the solution and the mixture was heated to 80° C under nitrogen atmosphere. After the reaction was completed, the organic solvent was removed under vacuum. The residue was purified by column chromatography on silica gel or crystallography to afford ligand **L4-L7**.

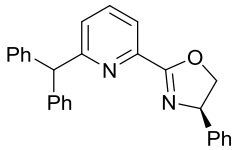
(*R*)-2-(6-benzylpyridin-2-yl)-4-phenyl-4,5-dihydrooxazole (L4)



Compound **L4** was prepared according to the general procedure (GP3) and isolated as white solid (overall yield 69%) after flash chromatography (Hex:AcOEt 6:1 → 4:1) for the first purification step and (Hex:AcOEt 3:1) for the second one.

The data are in good agreement with those reported in the literature.[j]

(*R*)-2-(6-benzhydrylpyridin-2-yl)-4-phenyl-4,5-dihydrooxazole (L5)

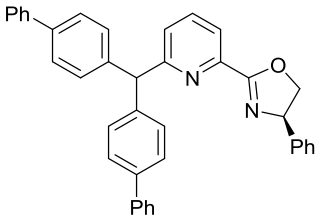


Compound **L5** was prepared according to the general procedure (GP3) and isolated as white solid (overall yield 63%) after flash chromatography (Hex:AcOEt 8:1) for the first purification step and (Hex:AcOEt 4:1) for the second one

The data are in good agreement with those reported in the literature.[j]

[j] X. Qi, C. Chen, C. Hou, L. Fu, P. Chen, G. Liu, *J. Am. Chem. Soc.*, **2018**, 140 (24), 7415-7419

(*R*)-2-(6-(di([1,1'-biphenyl]-4-yl)methyl)pyridin-2-yl)-4-phenyl-4,5-dihydrooxazole (L6)



Compound **L6** was prepared according to the general procedure (GP3) and isolated as white solid (overall yield 66%) after crystallization (n-Hex/AcOEt).

M.p. 228° C

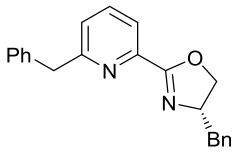
IR = 1637, 1486, 1110, 747, 732 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.8 Hz, 1H), 7.66 – 7.53 (m, 7H), 7.51 – 7.24 (m, 14H), 6.04 (s, 1H), 5.46 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.92 (dd, *J* = 10.3, 8.7 Hz, 1H), 4.41 (t, *J* = 8.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (s), 163.4 (s), 146.6 (s), 141.9 (s), 141.6 (s), 140.8 (s), 139.5 (s), 137.0 (d), 137.0 (d), 129.8 (d), 128.7 (d), 127.7 (d), 127.21 (d), 127.0 (d), 126.8 (d), 126.1 (d), 126.1 (d), 122.5 (d), 75.46 (t), 70.3 (d), 58.7 (d)

MS (ESI): m/z 543,31 $[M+H]^+$

(*S*)-4-benzyl-2-(6-benzylpyridin-2-yl)-4,5-dihydrooxazole (L7)



Compound **L7** was prepared according to the general procedure (GP3) and isolated as yellow oil (overall yield 58%) after flash chromatography (Hex:AcOEt 8:1) for the first purification step and (Hex:AcOEt 3:1) for the second one.

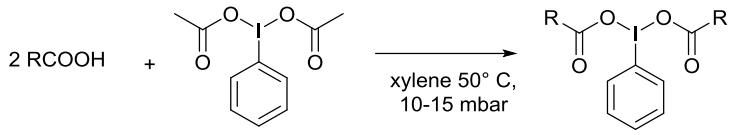
IR = 1645, 1491, 1449, 1107, 695 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.41 – 7.22 (m, 10H), 7.14 (d, *J* = 7.8 Hz, 1H), 4.82 – 4.59 (m, 1H), 4.48 (t, *J* = 9.0 Hz, 1H), 4.37 – 4.22 (m, 3H), 3.35 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.78 (dd, *J* = 13.7, 9.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (s), 161.6 (s), 146.2 (s), 139.0 (s), 137.9 (s), 137.0 (d), 129.4 (d), 129.2 (d), 128.7 (d), 128.6 (d), 126.6 (d), 126.6 (d), 125.2 (d), 121.7 (d), 72.6 (t), 68.1 (d), 44.7 (t), 41.7 (t).

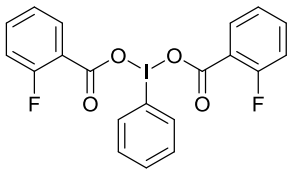
MS (ESI): m/z 329.20 $[M+H]^+$

General procedure for the preparation of differently substituted hypervalent iodine (III) (GP4)



Following the procedure,[k] to a round-bottom flask, $PhI(OAc)_2$ (10 mmol, 1.0 eq.) and the corresponding acid (20 mmol, 2 eq) were dissolved in xylene (0.2 M) and the flask was heated to 50° C under reduced pressure (about 10.15 mbar) using a diaphragm pump. When the xylene was removed, a mixture of n-hexane/AcOEt 3:1 was used to wash the solid. The white solid was then filtered and dried *in vacuo*. The corresponding hypervalent iodine (III) **12** was obtained and used directly in the following reaction without any further purification.

phenyl-λ3-iodanediyl bis(2-fluorobenzoate) (12a)



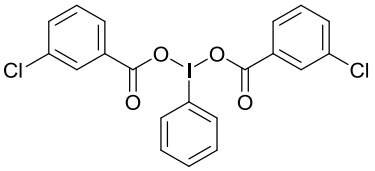
Compound **12a** was prepared according to the general procedure (GP4) and isolated as white solid (yield 95%).

The data are in good agreement with those reported in the literature.[l]

[k] Y.Wang, L. Zhang, Y. Yang, P. Zhang, Z. Du, C. Wang, *J. Am. Chem. Soc.* **2013**, 135 (48), 18048-18051

[l] K. Muñiz B. García C. Martínez, A. Piccinelli, *Chem Eur J,* **2017**, 23(7), 1539-1545

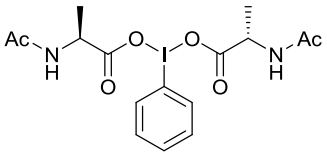
phenyl-λ3-iodanediyl bis(3-chlorobenzoate) (12b)



Compound **12b** was prepared according to the general procedure (GP4) and isolated as white solid (yield 97%).

The data are in good agreement with those reported in the literature.[l]

phenyl-λ3-iodanediyl (2*S*,2'*S*)-bis(2-acetamidopropanoate) (12c)

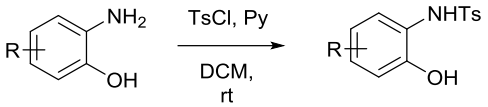


Compound **12c** was prepared according to the general procedure (GP4) and isolated as white solid (yield 83%).

The data are in good agreement with those reported in the literature.[m]

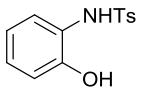
[m] *Zhurnal Organicheskoi Khimii,* **1975,** 11 (6), 1259-1263

General procedure for the Ts-protection (GP5)



To a solution of a different substituted aniline (1 eq) in DCM (0.2 M)), pyridine (3 eq) and tosyl chloride (1.3 eq.) were added at 0° C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. Then, the reaction mixture was cooled at 0° C and rinsed with DCM, washed with HCl 1 M and brine. The collected organic phases were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel or by crystallization.

N-(2-hydroxyphenyl)-4-methylbenzenesulfonamide

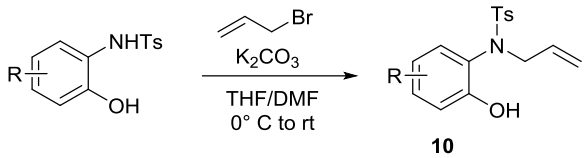


N-(2-hydroxyphenyl)-4-methylbenzenesulfonamide was prepared according to the general procedure (GP5) and isolated as yellow solid (yield 65%) after crystallization (Hex/EtOAc).

The data are in good agreement with those reported in the literature.[n]

[n] K. Wen, Z. Wu, B. Huang, Z. Ling, I. D. Gridnev, W. Zhang, *Org. Lett.,* **2018,** 206, 1608-1612

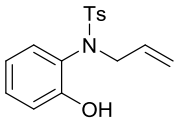
General procedure for the *N*-allylation of Ts-protected aminophenol (GP6)



10

In a two-neck round-bottom flask the corresponding Ts-protected aminophenol (1 eq.) was dissolved in a THF/DMF mixture (5:1, 0.2 M) and then K_2CO_3 (1.2 eq) was added. The reaction mixture was cooled to 0° C and afterwards, a solution of allyl bromide (1.2 eq) in THF (1 M) was added dropwise over 30 min. Then, the reaction was allowed to warm to room temperature and stirred for 24 h. Once the reaction has occurred as completely as possible, the mixture was filtered under vacuum, rinsed with AcOEt and washed with brine. The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel or by crystallization.

N-allyl-*N*-(2-hydroxyphenyl)-4-methylbenzenesulfonamide (10a)



Compound **10a** was prepared according to the general procedure (GP6) and isolated as white solid (yield 64%) after flash chromatography (Hex:AcOEt 6:1).

M.p. 110.0 - 112.5° C

IR: 3451, 2919, 1643, 1594, 1493 cm^{-1}

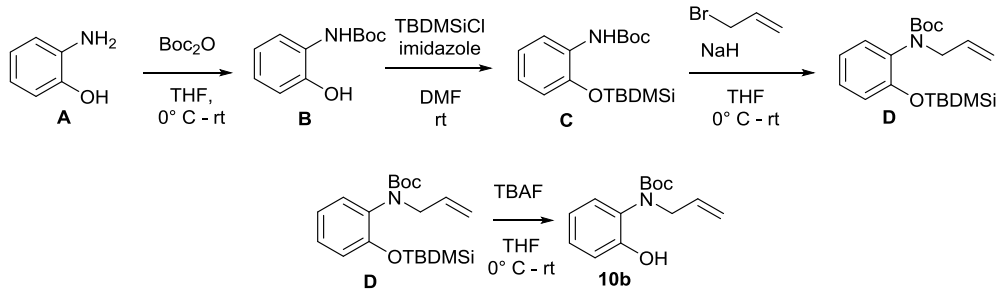
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.53 (2H, d, *J* = 8.4 Hz), 7.28 (2H, d, *J* = 8.4 Hz), 7.23 – 7.12 (1H, m), 7.03 (1H, dd, *J* = 8.2, 1.5 Hz), 6.69 (1H, td, *J* = 7.7, 1.5 Hz), 6.59 (1H, br s), 6.36 (1H, dd, *J* = 8.0, 1.6 Hz), 5.86 – 5.56 (1H,

m), 5.08 (1H, dd, *J* = 6.0, 1.1 Hz), 5.03 (1H, t, *J* = 1.1 Hz), 4.15 (2H, br s), 2.44 (3H, s).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 154.8 (s), 144.3 (s), 133.7 (s), 131.8 (d), 129.9 (d), 129.6 (d); 128.1 (d), 127.5 (d), 125.7 (s), 120.3 (d), 119.9 (t), 117.4 (d), 54.6 (t), 21.6 (q).

MS (ESI): m/z 326.37 $[M+Na]^+$

Synthesis of *tert*-butyl allyl(2-hydroxyphenyl)carbamate (10b)



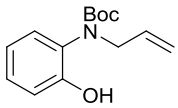
To a two-neck round-bottom flask 2-aminoethanol **A** (1500 mg, 13.76 mmol, 1 eq) was added and dissolved in THF (13 mL, 1 M). After cooling to 0° C, di-*tert*-butyl dicarbonate (3150 mg, 14.4 mmol, 1.05 eq) was added. The solution was allowed to warm to rt and stirred for 13 h. Afterwards, the solvent was evaporated under reduced pressure and the remaining solid was washed with CCl_4 to yield the *N*-Boc-protected aminophenol **B** (2007 mg, 12.93 mmol, 94%) as a white solid.

A solution of *N*-protected aminophenol **B** (14.4 mmol, 1 eq), tert-butyldimethylsilyl chloride (14.4 mmol, 1 eq) and imidazole (14.4 mmol, 1 eq) in DMF (0.2 M) was stirred at room temperature overnight. The reaction was taken up with brine (50 mL), extracted with Et_2O (3 x 50 mL), dried over Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography gel (n-Hex/EtOAc 5:1) to afford **C** (2402 mg, 7.17 mmol, 49%).

To a mixture of sodium hydride (10.8 mmol, 1.5 eq) in DMF (18 mL) at 0 °C under argon atmosphere, a solution of **C** (2402 mg, 7.17 mmol, 1 eq) in THF (3 mL) was dropped. The reaction mixture was stirred for 30 min at room temperature, then cooled at 0 °C. A solution of allyl bromide (7.52 mmol, 1.05 eq) in THF (7 mL) was dropped and the mixture was stirred at room temperature overnight. The mixture was quenched with water (10 mL) and concentrated at reduced pressure. Then, the crude mixture was rinsed with EtOAc (3 x 40 mL), washed with brine (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex:AcOEt 4:1) to afford **D** (1398 mg, 3.72 mmol, 52%).

A mixture of the corresponding **D** (1398 mg, 3.72 mmol, 1 eq) and tetrabutylammonium fluoride (4.46 mmol, 1.2 eq) in THF (0.2 M) was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure; water was added (10 mL). The reaction mixture was extracted with DCM (3 x 20 mL), then dried over Na_2SO_4, and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex:AcOEt 4:1) to afford **10b** (794 mg, 3.19 mmol, 86%) as a white solid.

***tert*-butyl allyl(2-hydroxyphenyl)carbamate (10b)**



M.p. 134-136° C

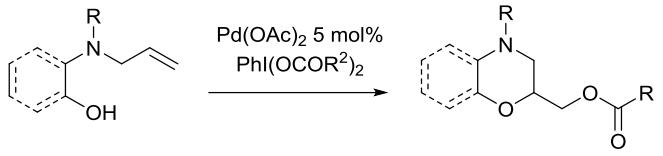
IR: 3249, 1649, 1396, 761 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, J = 7.0 Hz, 2H), 7.00 (d, J = 7.6 Hz, 1H), 6.95 – 6.83 (m, 1H), 5.92 (ddd, J = 15.9, 10.7, 5.6 Hz, 1H), 5.33 – 5.06 (m, 2H), 4.20 (d, J = 5.4 Hz, 2H), 1.48 (s, J = 13.8 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) ongoing

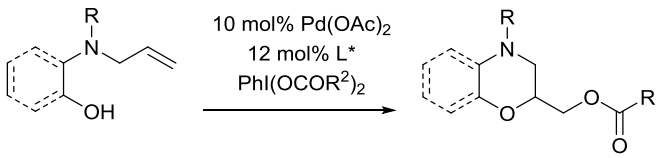
MS (ESI): m/z 273.35 $[M+Na]^+$

General procedure for the racemic intramolecular alkoxyacylation (GP7)



To a solution of the compound **10** (0.3 mmol, 1 eq) in the corresponding solvent (0.2 M), $Pd(OAc)_2$ (0.015 mmol, 0.05 eq) and $PhI(OCOR^2)_2$ (0.45 mmol, 1.5 eq) were added subsequently. The reaction mixture was stirred at rt for 16 h. Once the reaction had occurred as completely as possible, the solvent was evaporated under vacuum. The crude product was rinsed with AcOEt, washed with a saturated solution of Na_2CO_3 (until pH = 8/9) and with brine. The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

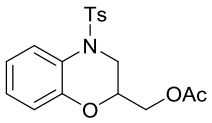
General procedure for the asymmetric intramolecular alkoxyacylation (GP8)



In a 5 mL glass vial $Pd(OAc)_2$ (0.025 mmol, 12 mol%) and the ligand **L1-L8** (0.03 mmol, 12 mol%) were added and dissolved in the corresponding solvent (0.6 M). The complex was preformed, stirring the mixture at rt for 15 min. Afterwards the reaction was cooled to 0° C or – 20° C and the compound **10** (0.3 mmol, 1 eq) and $PhI(mcba)_2$ (0.45 mmol, 1.5 eq) were added subsequently. The reaction mixture was stirred at 0° C or – 20° C for 48 h.

Once the reaction had occurred as completely as possible, the reaction mixture was immediately filtered through a plug of silica gel (3 cm) and washed with EtOAc. Then the collected fractions were evaporated under vacuum. The crude product was rinsed with AcOEt, washed with a saturated solution of Na_2CO_3 (until the pH = 8/9) and with brine. The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

(4-tosyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methyl acetate (11a)



Compound **11a** was prepared according to the general procedure (GP7) and isolated as white solid (yield 29%) after flash chromatography (Hex:AcOEt 3:1).

M.p. 96.0° C

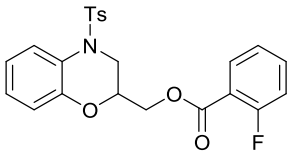
IR: 2913 1746, 1597, 1584, 1488 cm^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.83 (1H, dd, *J* = 8.3, 1.5 Hz), 7.51 (2H, d, *J* = 8.4 Hz,), 7.23 (2H, d, *J* = 8.4 Hz), 7.07 (1H, ddd, *J* = 8.1, 7.3, 1.6 Hz), 6.95 (1H, ddd, *J* = 8.2, 7.3, 1.6 Hz), 6.83 (1H, dd, *J* = 8.1, 1.6 Hz), 4.32 (1H, dd, *J* = 14.4, 2.5 Hz), 4.21 – 4.05 (2H, m), 3.55 (1H, tdd, *J* = 7.2, 4.7, 2.5 Hz), 3.26 (1H, dd, *J* = 14.4, 10.1 Hz), 2.39 (3H, s), 2.08 (3H, s).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 170.4 (s), 146.5 (s), 144.4 (s), 135.4 (s), 130.0 (d), 127.2 (d), 126.3 (d), 124.5 (d), 123.4 (s), 121.2 (d), 117.5 (d), 69.4 (d), 63.4 (t), 45.7 (t), 21.6 (q), 20.7 (q).

MS (ESI): m/z 362,33 $[M+H]^+$ 384,53 $[M+Na]^+$

(4-tosyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methyl 2-fluorobenzoate (11b)



Compound **11b** was prepared according to the general procedure (GP7) and isolated as solid (yield 95%) after flash chromatography (Hex/AcOEt 3:1).

M.p. 104° C

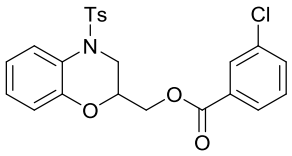
IR = 1721, 1478 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.82 (m, 2H), 7.63 – 7.48 (m, 3H), 7.28 – 7.12 (m, 4H), 7.12 – 7.03 (m, 1H), 7.00 – 6.91 (m, 1H), 6.85 (dd, *J* = 8.2, 1.6 Hz, 1H), 4.53 – 4.24 (m, 3H), 3.74 – 3.47 (m, 1H), 3.36 (dd, *J* = 14.5, 10.1 Hz, 1H), 2.37 (s, *J* = 6.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (s), 160.3 (s), 146.5 (s), 144.4 (s), 135.4 (s), [135.1, 135.0] (d), 132.2 (d), 130.0 (d), 127.2 (d), 126.3 (d), 124.7 (d), [124.1, 124.0] (d), 123.5 (s), 121.2 (d), 117.8 (s), 117.5 (d), [117.3, 117.0] (d), 69.2 (s), 64.0 (d), 46.0 (d), 21.5 (q).

MS (ESI): m/z 441.95 $[M+H]^+$

(4-tosyl -3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methyl 3-chlorobenzoate (11c)



Compound **11c** was prepared according to the general procedure (GP7 and GP8) and isolated as white solid (yield 95%) after flash chromatography (Hex:AcOEt 4:1).

M.p. 103° C

IR = 1714, 1487, 731 cm^{-1}

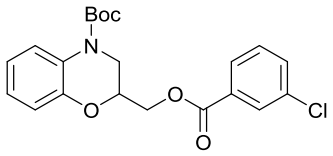
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (t, *J* = 1.7 Hz, 1H), 7.96 – 7.83 (m, 2H), 7.60 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.17 – 7.07 (m, 1H), 7.05 – 6.93 (m, 1H), 6.88 (dd, *J* = 8.1, 1.4 Hz, 1H), 4.56 – 4.28 (m, 3H), 3.63 (dtd, *J* = 9.6, 4.7, 2.4 Hz, 1H), 3.38 (dd, *J* = 14.4, 10.1 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (s), 155.7 (s), 146.9 (s), 144.9 (s), 135.7 (s), 135.1 (d), 133.9 (s), 131.5 (d), 130.5 (d), 130.3 (d), 130.1 (d), 128.2 (d), 127.6 (d), 126.8 (d), 125.1 (s), 123.8 (d), 121.7 (d), 118.0 (d), 69.7 (d), 64.5 (t), 46.3 (t), 22.0 (q).

MS (ESI): m/z 480.00, 481.98 $[M+Na]^+$

From GP8. *Reaction conditions*: $Pd(OAc)_2$ 10 mol%, **L5** 12 mol% in CH_3CN/toluene 1:5 (0.4 M) T = 0° C. 30%*ee* HPLC (Chiracel OD-H, l = 225 nm, n-Hex/iPrOH = 70:30, 0.5 mL/min): tR = 10.0 min (minor), 13.6 min (major).

tert-butyl 2-(((3-chlorobenzoyl)oxy)methyl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (11d)



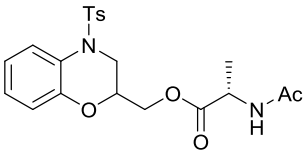
Compound **11d** was prepared according to the general procedure (GP7) and isolated as white solid (yield 85%) after flash chromatography (Hex:AcOEt 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (t, *J* = 1.7 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.82 – 7.66 (m, 1H), 7.59 – 7.49 (m, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.05 – 6.98 (m, 1H), 6.96 – 6.83 (m, 2H), 4.59 – 4.43 (m, 3H), 4.29- 4.13 (m, 1H), 3.69 – 3.51 (m, 1H), 1.52 (s, *J* = 8.6 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): ongoing.

MS (ESI): m/z 427.09 $[M+Na]^+$

(4-tosyl-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-2-yl)methyl acetyl-*L*-alaninate (11e)



Compound **11e** was prepared according to the general procedure (GP7) and isolated as a light yellow solid (yield 71%) after flash chromatography (Hex/AcOEt 3:1 → 1:1).

M.p. 220° C (decomp.)

IR = 1732, 1349, 1160 cm^{-1}

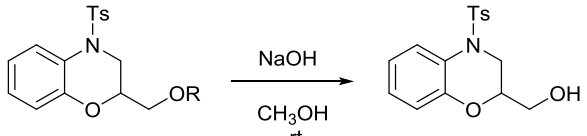
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (ddd, *J* = 8.2, 5.1, 1.5 Hz, 1H), 7.55 (dd, *J* = 8.3, 1.8 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.14 – 7.03 (m, 1H), 7.03 – 6.89 (m, 1H), 6.84 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.01 (d, *J* = 5.9 Hz, 1H), 4.82 –

4.48 (m, 1H), 4.35 – 3.99 (m, 3H), 3.83 – 3.51 (m, 1H), 3.32 (ddd, *J* = 14.3, 9.8, 7.8 Hz, 1H), 2.41 (s, *J* = 15.0 Hz, 3H), 2.04 (s, *J* = 7.2 Hz, 3H), 1.42 (dd, *J* = 7.2, 4.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [172.7, 172.6] (s), 169.6 (s), [146.4, 146.3] (s), [144.5, 144.5] (s), [135.6, 135.5] (s), 130.1 (d), 127.2 (d), 126.3 (d), 124.3 (d), 123.5 (s), [121.3, 121.3] (d), [117.5, 117.5] (d), [69.5, 69.4] (d), [64.1, 63.9] (t), 48.0 (d), [45.6, 45.6] (t), 23.1 (q), 21.6 (q), 18.41 (q).

MS (ESI): m/z 433.26 $[M+Na]^+$

Synthesis of (4-tosyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol (13)

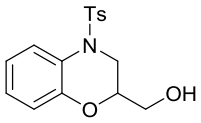


11a R = Ac
11c R = CO(*m*-ClC_6H_4)

12

To a solution of compound **11** (430 mg, 1,19 mmol, 1 eq) in CH_3OH (20 mL), an aqueous solution of NaOH 50% p/V (0,95 mL, 11,90 mmol, 10 eq) has been added. The reaction mixture was stirred at room temperature for 1 h. After the reaction was completed, the solvent has been removed under reduced pressure. The crude product was rinsed with AcOEt (25 mL) and washed with HCl 2 M (1 x 10 mL) and brine (1 x 10 mL). The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hex:AcOEt 1:1) affording **13** as a white solid (311 mg, 0.98 mmol, 82%).

(4-tosyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol (13)



M.p. 126.7° C

IR: 3401, 2919, 1600, 1582, 1486 cm^{-1}

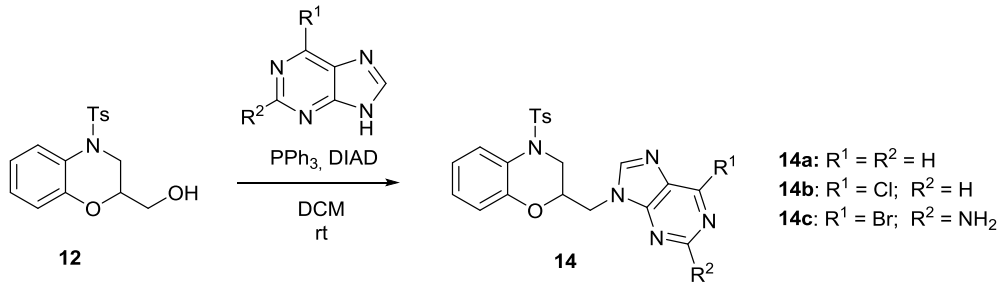
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.81 (1H, dd, *J* = 8.2, 1.5 Hz), 7.53 (2H, d, *J* = 8.2 Hz), 7.23 (2H, d, *J* = 8.2 Hz), 7.07 (1H, ddd, *J* = 8.1, 7.3, 1.6 Hz), 6.94 (1H, ddd, *J* = 8.3, 7.3, 1.6 Hz), 6.83 (1H, dd, *J* = 8.1, 1.5 Hz), 4.27 (1H, dd, *J* = 14.3, 2.3 Hz), 3.70 (2H, ddd, *J* = 31.0, 12.0, 4.3 Hz), 3.57 – 3.44 (1H, m), 3.37 (1H, dd, *J* = 14.3, 9.9 Hz), 2.38 (3H, s), 1.93 (1H, br s).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 146.7 (s), 144.3 (s), 135.6 (s), 129.9 (d), 127.2 (d), 126.2 (d), 124.4 (d), 123.6 (s), 121.1 (d), 117.4 (d), 72.0 (d), 62.6 (t), 45.4 (t), 21.6 (q).

MS (ESI): m/z 342,37 $[M+Na]^+$

From GP8. *Reaction conditions*: $Pd(OAc)_2$ 10 mol%, **L5** 12 mol% in DCM (0.4 M) T = 0° C. 49%*ee* HPLC (Chiracel OD-H, l = 225 nm, n-Hex/iPrOH = 70:30, 0.5 mL/min): tR = 7.9 min (minor), 8.9 min (major).

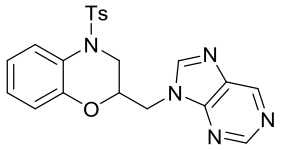
General procedure for the synthesis of compounds 14 (GP9)



In a two-neck round-bottom flask the compound **13** (1 eq) was suspendend in DCM (0.08 M). The different substituted purine (1.5 eq) was added under nitrogen atmosphere, followed by the addition of PPh_3 (1.6 eq). The

suspension was cooled to 0°C and a solution of DIAD (1.6 eq) was added dropwise (30 min). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Afterwards, the reaction mixture was rinsend with DCM and washed with brine. Then, the organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

2-((9H-purin-9-yl)methyl)-4-tosyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (14a)



Compound **14a** was prepared according to the general procedure (GP9) and isolated as white solid (yield 71%) after flash chromatography (Hex:AcOEt 1:5 → AcOEt → AcOEt:MeOH 20:1).

M.p. 188.8 – 194.1° C

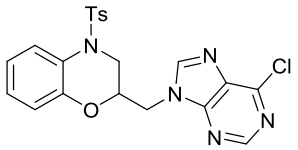
IR: 2920, 1593, 1582, 1492, 1355 cm^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.15 (1H, s), 9.01 (1H, s), 8.13 (1H, s), 7.75 (1H, dd, *J* = 8.2, 1.4 Hz), 7.47 (2H, d, *J* = 8.2 Hz), 7.16 (2H, d, *J* = 8.1 Hz), 7.13 – 7.00 (1H, m), 6.99 – 6.86 (1H, m), 6.81 (1H, dd, *J* = 8.1, 1.4 Hz), 4.64 – 4.26 (3H, m), 3.87 – 3.56 (1H, m), 3.13 (1H, dd, *J* = 14.4, 9.6 Hz), 2.32 (3H, s).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 152.5 (d), 151.5 (s), 148.5 (d), 146.0 (d), 145.7 (s), 144.6 (s), 135.3 (s), 133.7 (s), 130.1 (d), 127.1 (d), 126.5 (d), 124.4 (d), 123.4 (s) 121.7 (d), 117.4 (d), 69.7 (d), 45.8 (t), 44.8 (t), 21.5 (q).

MS (ESI): m/z 422.60 $[M+H]^+$

2-((6-chloro-9H-purin-9-yl)methyl)-4-tosyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (14b)



Compound **14b** was prepared according to the general procedure (GP9) and isolated as white solid (yield 64%) after flash chromatography (Hex:AcOEt 1:1 → Hex:AcOEt 1:4).

IR: 2923, 1735, 1596, 1569, 1490 cm^{-1}

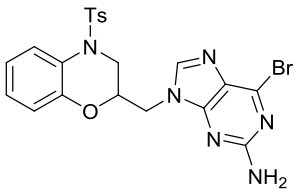
M.p. 189.0 ° C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.75 (1H, s), 8.15 (1H, br s), 7.73 (1H d, *J* = 8.1 Hz), 7.48 (2H, d, *J* = 7.9 Hz), 7.18 (2H, d, *J* = 7.8 Hz), 7.05 (1H, t, *J* = 7.2 Hz), 6.93 (1H, t, *J* = 7.7 Hz), 6.79 (1H, d, *J* = 7.7 Hz), 4.63 – 4.28 (3H, m), 3.82 (1H, dd, *J* = 4.0, 1.4 Hz), 3.13 (1H, dd, *J* = 13.8, 9.5 Hz), 2.33 (3H, s).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 152.1 (d), 151.8 (s), 151.3 (s), 146.0 (d), 145.6 (s), 144.6 (s), 135.3 (s), 131.4 (s), 130.1 (d), 127.1 (d), 126.5 (d), 124.3 (d), 123.3 (s), 121.8 (d), 117.4 (d), 69.6 (d), 45.8 (t), 45.4 (t), 21.6 (q).

MS (ESI): m/z 478.39 $[M+Na]^+$

6-bromo-9-((4-tosyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methyl)-9H-purin-2-amine (14c)



Compound **14c** was prepared according to the general procedure (GP9) and isolated as white solid (yield 21%) after flash chromatography (Hex:AcOEt 1:1 → Hex:AcOEt 2:3).

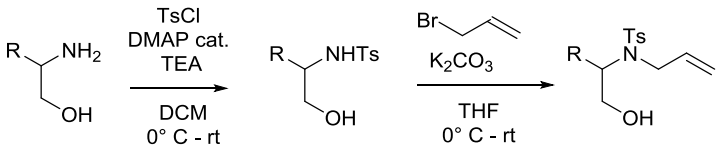
M.p. 134° C (decomp.)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.78 (1H, br s), 7.74 (1H, dd, *J* = 8.3, 1.5 Hz), 7.45 (2H, d, *J* = 8.2 Hz), 7.18 (2H, d, *J* = 8.1 Hz), 7.06 (1H, td, *J* = 8.2, 1.5 Hz), 6.99 – 6.86 (1H, m), 6.80 (1H, dd, *J* = 8.1, 1.3 Hz), 5.32 (2H, br s), 4.47 – 4.06 (3H, m), 3.79 – 3.57 (1H, m), 3.11 (1H, dd, *J* = 14.4, 9.8 Hz), 2.33 (3H, s).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 159.0 (s), 152.5 (s), 145.8 (s), 144.6 (s), 143.7 (s), 135.3 (s), 130.0 (d), 127.4 (s), 127.1 (d), 126.4 (d), 124.3 (d), 124.3 (d), 123.3 (s), 121.6 (d), 117.4 (d), 69.8 (d), 45.9 (t), 44.8 (t), 21.5 (q).

MS (ESI): m/z 537.81 $[M+Na]^+$

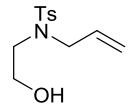
General procedure for the synthesis of *N*-allyl Ts-protected aminoethanols 16 (GP10)



To a solution of aminoalcohol (20 mmol, 1 eq), DMAP (2 mmol, 0.1 eq) and TEA (40 mmol, 2 eq) in DCM (2 M) at 0 °C, a solution of tosyl chloride was added dropwise (21 mmol, 1.05 eq) in DCM (0.8 M) and the resulting mixture was stirred at room temperature overnight. The mixture was washed with water (3 x 40 mL) and brine (1 x 40 mL), then dried over Na_2SO_4, and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding protected aminoalcohol.

In a two-neck round-bottom flask the corresponding Ts-protected aminophenol (1 eq) was dissolved in a THF/DMF mixture (5:1, 0.2 M) and then K_2CO_3 (1.2 eq) was added. The reaction mixture was cooled to 0° C and afterwards, a solution of allyl bromide (1.2 eq) in THF (1 M) was added dropwise over 30 min. Then, the reaction was allowed to warm to room temperature and stirred for 24 h. Once the reaction has occurred as completely as possible, the mixture was filtered under vacuum, rinsed with AcOEt and washed with brine. The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford **16a,c,d**.

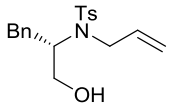
N-allyl-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (16a)



Compound **16a** was prepared according to the general procedure (GP10) and isolated as a colourless gum (overall yield 63%) after flash chromatography (Hex/AcOEt 2:1 → 1:1).

The data are in good agreement with those reported in the literature.[o]

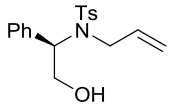
(*S*)-*N*-allyl-*N*-(1-hydroxy-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (16c)



Compound **16c** was prepared according to the general procedure (GP10) and isolated as a colourless gum (overall yield 59%) after flash chromatography (Hex:AcOEt 2:1).

The data are in good agreement with those reported in the literature.[p]

(*R*)-*N*-allyl-*N*-(2-hydroxy-1-phenylethyl)-4-methylbenzenesulfonamide (16d)



Compound **16d** was prepared according to the general procedure (GP10) and isolated as a colourless oil (overall yield 61%) after flash chromatography (Hex:AcOEt 3:1).

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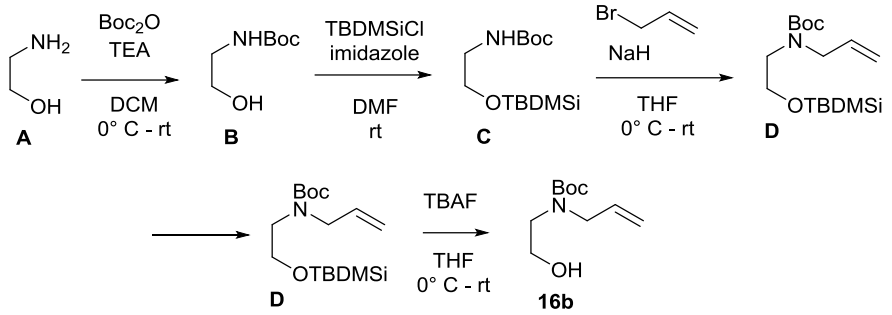
[o] M. Poornachandran, R. Raghunathan, *Tetrahedron* **2008**, 64 (27), 6461-6474

[p] M. Poornachandran, R. Raghunathan, *Tetrahedron: Asymmetry* **2008**, 19 (18), 2177-2183

The data are in good agreement with those reported in the literature.[q]

Synthesis of *tert*-butyl allyl(2-hydroxyethyl)carbamate (16b)



To a two-neck round-bottom flask 2-aminoethanol **A** (610 mg, 10 mmol, 1 eq) was added and dissolved in DCM (12 mL, 0.2 M). After cooling to 0° C, di-*tert*-butyl dicarbonate (2616 mg, 12 mmol, 1.2 eq) was added, followed by trimethylamine (1.6 mL, 12 mmol, 1.2 eq). The solution was allowed to warm to rt and stirred for 24 h. The reaction mixture was washed with saturated solution of NH_4Cl until pH~7 and with brine (20 mL). Then, the organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (n-Hex/EtOAc 1:1) affording the compound **B** (1384 mg, 8.6 mmol, 86%) as a colourless oil.

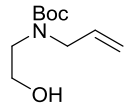
A solution of *N*-protected aminoalcohol **B** (8.6 mmol, 1 eq), tert-butyldimethylsilyl chloride (8.6 mmol, 1 eq) and imidazole (8.6 mmol, 1 eq) in DMF (0.2 M) was stirred at room temperature overnight. The reaction was taken up with brine (40 mL), extracted with Et_2O (3 x 40 mL), dried over Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography gel (n-Hex/EtOAc 4:1) to afford **C** (1521 mg, 5.3 mmol, 62%).

[q] F.C. Sequeira, S. R. Chemler, *Org. Lett.,* **2012**, 141 (7), 4482-4485

To a mixture of sodium hydride (7.95 mmol, 1.5 eq) in THF (16 mL) at 0° C under nitrogen atmosphere, a solution of **C** (1521 mg, 5.3 mmol, 1 eq) in THF (16 mL) was dropped. The reaction mixture was stirred for 30 min at room temperature, then cooled at 0 °C. A solution of allyl bromide (5.56 mmol, 1.05 eq) in THF (5 mL) was dropped and the mixture was stirred at room temperature overnight. The mixture was concentrated at reduced pressure, washed with water (20 mL), extracted with Et_2O (3 x 60 mL), dried on Na_2SO_4, and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex:AcOEt 6:1) to afford **D** (1003 mg, 3.07 mmol, 58%).

A mixture of the corresponding **D** (1003 mg, 3.07 mmol, 1 eq) and tetrabutylammonium fluoride (3.07 mmol, 1.2 eq) in THF (0.2 M) was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure, water was added (10 mL) and the reaction mixture was extracted with DCM (3 x 20 mL). Then the organi phase was dried over Na_2SO_4, and the solvent concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex:AcOEt 3:1 → 1.5:1) to afford **16b** (530 mg, 2.64 mmol, 85%) as a colourless gum.

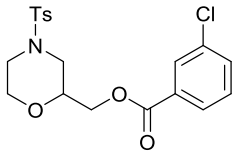
***tert*-butyl allyl(2-hydroxyethyl)carbamate (16b)**



The data are in good agreement with those reported in the literature.[r]

[r] M. Schuster, J. Pernerstorfer, S. Blechert, *Angew Chem, Int Ed,* **1996**, 35 (17) 1979-1980

(4-tosylmorpholin-2-yl)methyl 3-chlorobenzoate (17a)



Compound **17a** was prepared according to the general procedure (GP8) and isolated as colourless oil (yield 72%) after flash chromatography (Hex:AcOEt 2:1).

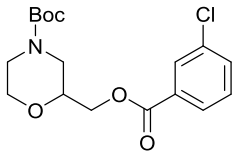
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (t, *J* = 1.9 Hz, 1H), 7.90 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.55 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.42 – 7.31 (m, 3H), 4.40 – 4.22 (m, 2H), 4.01 – 3.87 (m, 2H), 3.79 – 3.63 (m, 2H), 3.59 – 3.45 (m, 1H), 2.51 – 2.40 (m, 4H), 2.34 – 2.20 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 144.2, 134.7, 133.4, 132.2, 131.5, 129.9, 129.9, 128.0, 73.2, 66.0, 65.1, 47.6, 45.5, 21.6.

MS (ESI): m/z 410.21 $[M+H]^+$

From GP8. *Reaction conditions*: $Pd(OAc)_2$ 10 mol%, **L5** 12 mol% in DCM (0.4 M) T = -20° C. 77%*ee* HPLC (Amylose column 3µm, l = 230 nm, n-Hex/iPrOH = 70:30, 0.5 mL/min): tR = 13.6 min (major), 16.4 min (minor).

***tert*-butyl 2-(((3-chlorobenzoyl)oxy)methyl)morpholine-4-carboxylate (17b)**



Compound **17b** was prepared according to the general procedure (GP7-8) and isolated as colourless oil (yield 70%) after flash chromatography (Hex:AcOEt 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 – 8.00 (m, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H), 4.46 – 4.22 (m, 2H), 4.17

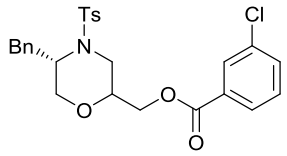
– 3.69 (m, 4H), 3.58 (td, J = 11.7, 2.6 Hz, 1H), 3.13 – 2.67 (m, 2H), 1.49 (s, J = 7.7 Hz, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5 (s), 155.1 (s), 135.0 (s), 133.8 (s), 133.6 (d), 131.9 (s), 130.2 (d), 128.3 (d), 80.8 (s), 73.6 (d), 66.9 (t), 65.63 (2 signals – (d) + (t)), 46.1 (t – overlapping), 43.5 (t – overlapping), 28.8 (q).

MS (ESI): m/z 378.19 $[M+Na]^+$

From GP8. *Reaction conditions*: $Pd(OAc)_2$ 10 mol%, **L5** 12 mol% in DCM (0.4 M) T = -20° C. 75%*ee* HPLC (Chiralcel OD-H short, l = 225 nm, n-Hex/iPrOH = 90:10, 0.5 mL/min): tR = 7.2 min (major), 8.3 min (minor).

((5*S*)-5-benzyl-4-tosylmorpholin-2-yl)methyl 3-chlorobenzoate (17c)



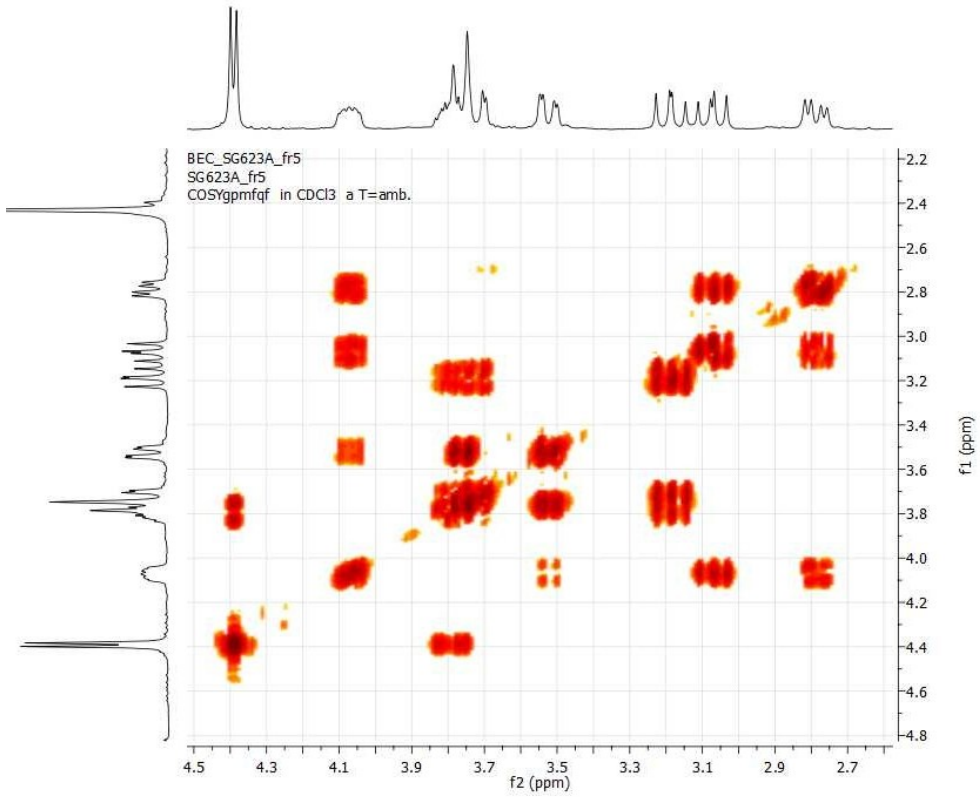
Compound **17c** was prepared according to the general procedure (GP7) and isolated as a colourless oil and only diastereoisomer (yield 79%) after flash chromatography (Hex:AcOEt 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 – 8.00 (m, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.71 – 7.51 (m, 3H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.35 – 7.16 (m, 7H), 4.39 (d, *J* = 4.8 Hz, 2H), 4.14 – 3.99 (m, 1H), 3.88 – 3.62 (m, 3H), 3.52 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.26 – 2.99 (m, 2H), 2.79 (dd, *J* = 13.2, 5.1 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0 (s), 143.6 (s), 137.6 (s), 137.3 (s), 134.7 (s), 133.3 (d), 131.4 (s), 129.9 (d), 129.8 (d), 129.8 (d), 129.4 (d), 128.7 (d), 127.8 (d), 127.2 (d), 126.7 (d), 73.1 (d), 67.4 (t), 65.1 (t), 54.1 (d), 42.2 (t), 34.2 (t), 21.5 (q).

MS (ESI): m/z 500.32 [M+H]

COSY NMR


BEC_SG623A_fr5
SG623A_fr5
COSYgpmfqf in CDCl3 a T=amb.
f1 (ppm)
f2 (ppm)
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
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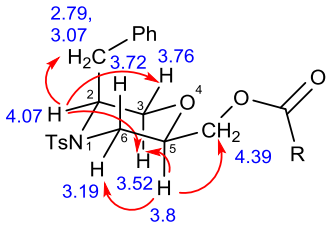
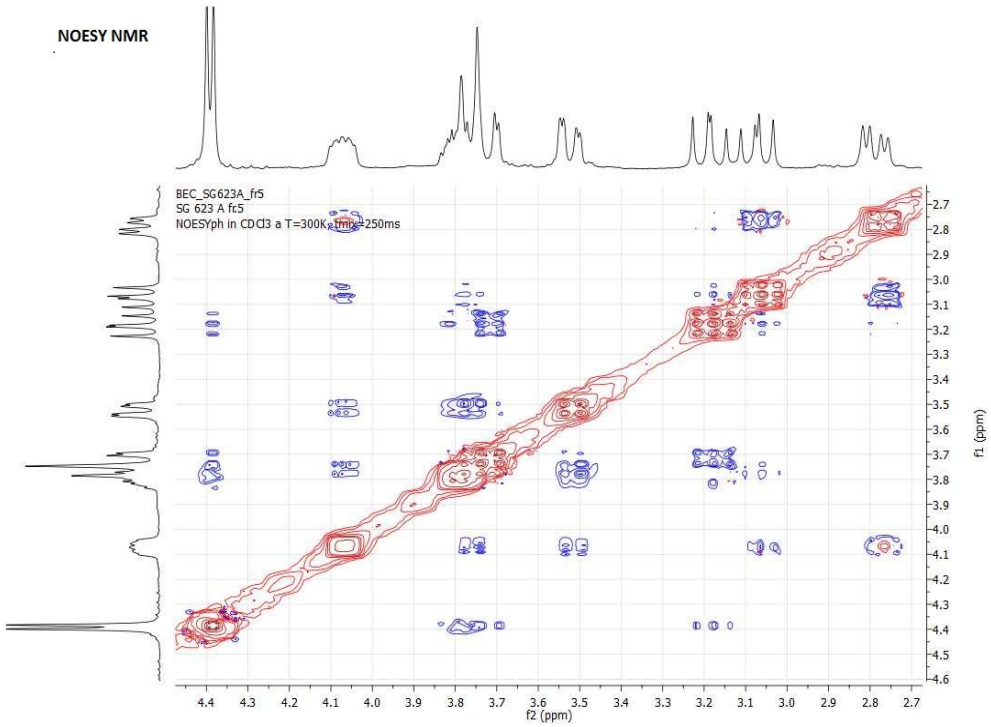
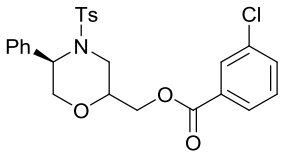
4.5
4.3
4.1
3.9
3.7
3.5
3.3
3.1
2.9
2.7





((5*S*)-5-benzyl-4-tosylmorpholin-2-yl)methyl 3-chlorobenzoate (17d)

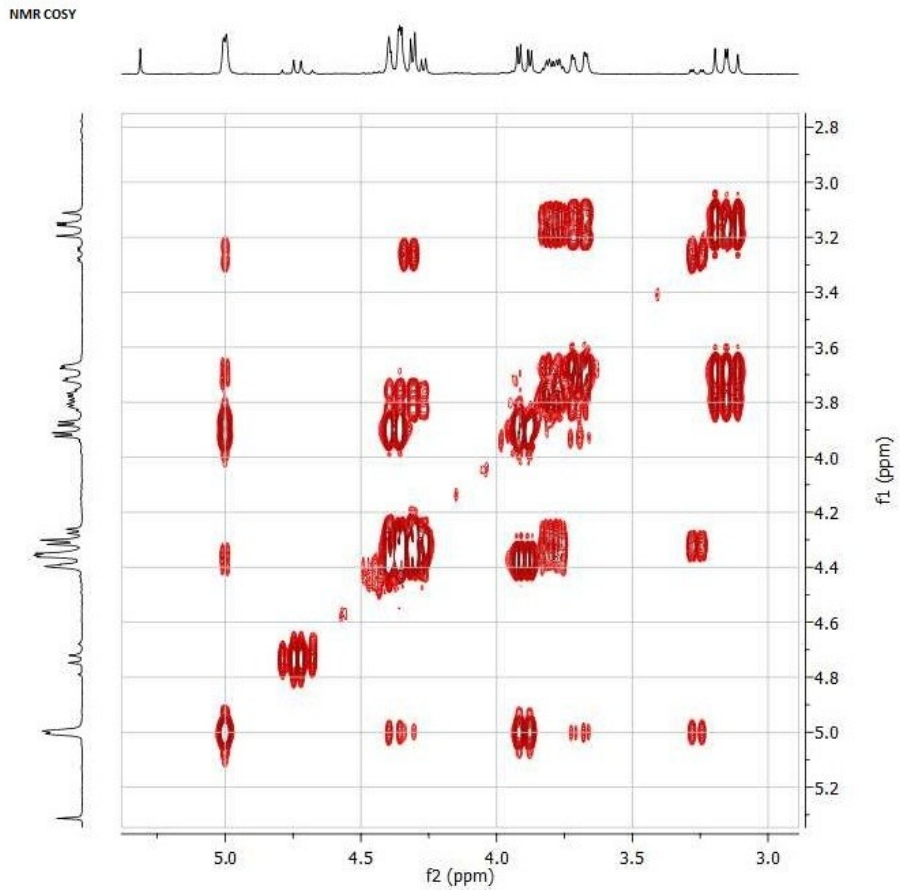


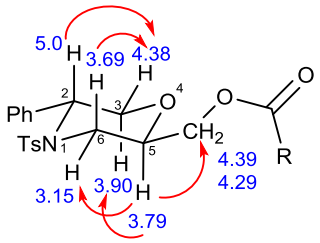
Compound **17d** was prepared according to the general procedure (GP7) and and isolated as a colourless oil and only diastereoisomer (yield 81%) after flash chromatography (Hex:AcOEt 4:1).

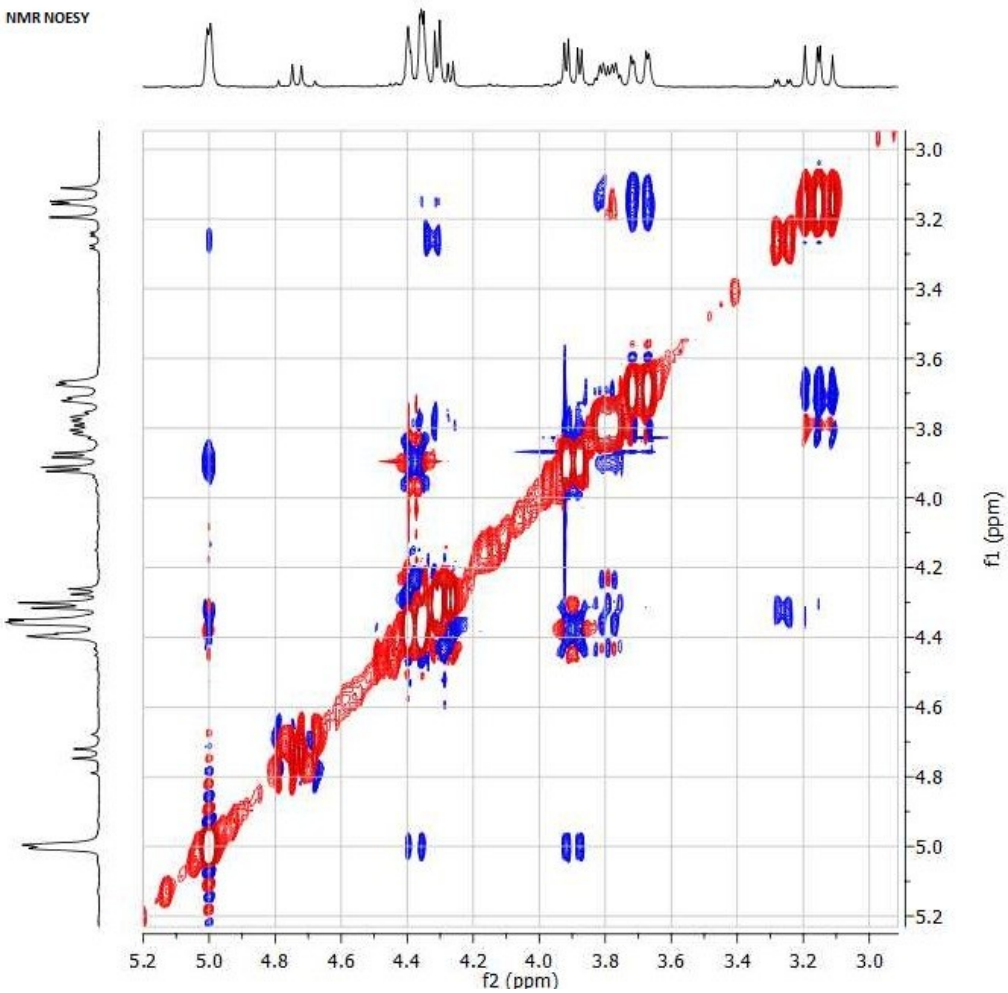
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.89 (m, 1H), 7.89 – 7.80 (m, 1H), 7.73 – 7.46 (m, 4H), 7.43 – 7.21 (m, 5H), 5.00 (d, J = 3.0 Hz, 1H), 4.46 – 4.27 (m, 3H), 3.95 – 3.61 (m, 3H), 3.15 (dd, J = 13.7, 11.4 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 (s), 144.0 (s), 137.8 (s), 137.6 (s), 135.0 (s), 133.7 (d), 131.7 (s), 130.2 (d), 130.1 (d), 128.9 (d), 128.8 (d), 128.3 (d), 128.2 (d), 127.6 (d), 72.9 (d), 69.2 (t), 65.4 (t), 54.8 (d), 42.7 (t), 21.9 (q).

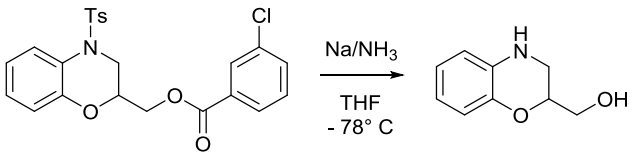
MS (ESI): m/z 485.92 $[M+H]^+$, 508.12 $[M+Na]^+$




5.0
H
3.69
4.38
H
H
2
3
4
O
O
O
Ph
TsN
1
6
5
CH2
R
H
H
4.39
4.29
3.15
3.90
H
3.79

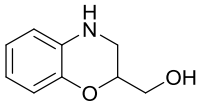

NMR NOESY
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
f2 (ppm)
f1 (ppm)

Synthesis of (3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol (18)



A two-neck round-bottom flask equipped with a magnetic stirring bar and a rubber septum was cooled to −78° C. Liq. NH_3 (50 mL) was collected into the flask by standard ammonia cooling device. A solution of the compound **11c** (1038 mg, 2.27 mmol) in THF (20 mL, 0.05 M) was added *via* syringe, followed by small pieces of freshly cut sodium until a permanent deep blue color persisted. The solution was stirred for 1.5 h and cautiously quenched by addition of a large excess of solid NH_4Cl (~100g). The ammonia was allowed to evaporate, the solid residue was washed with EtOAc (100 mL) and filtered. Then, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel (n-Hex/EtOAc 3:1 → 1:1) affording the compound **18** (360 mg, 2.18 mmol, 96%) as a colourless oil.

(3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol (18)

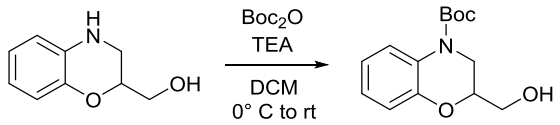


^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 – 6.48 (m, 4H), 4.39 – 4.15 (m, 1H), 3.99 – 3.72 (m, 2H), 3.49 – 3.21 (m, 2H), 3.04 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6 (s), 132.82 (s), 121.47 (d), 119.30 (d), 116.84 (d), 115.69 (d), 74.33 (d), 63.41 (t), 42.06 (t).

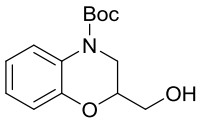
MS (ESI): m/z 188.12 $[M+Na]^+$

Synthesis of *tert-butyl* 2-(hydroxymethyl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (19)



To a two-neck round-bottom flask compound **18** (360 mg, 2.18 mmol, 1 eq) was added and dissolved in DCM (12 mL, 0.2 M). After cooling to 0° C, di-*tert*-butyl dicarbonate (570 mg, 2.6 mmol, 1.2 eq) was added, followed by TEA (0.36 mL, 2.6 mmol, 1.2 eq). The solution was allowed to warm to rt and stirred for 24 h. The reaction mixture was washed with saturated solution of NH_4Cl until pH~7 and with brine (15 mL). Then, the organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (*n*-Hex/EtOAc 3:1) affording the compound **19** (496 mg, 1.87 mmol, 86%) as a yellow solid.

***tert-butyl* 2-(hydroxymethyl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate (19)**



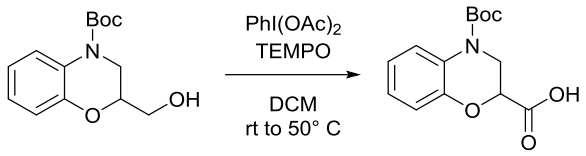
M.p. 97° C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.12 – 6.95 (m, 1H), 6.93 – 6.83 (m, 2H), 4.29 (dtd, *J* = 7.8, 5.1, 2.8 Hz, 1H), 4.03 (dd, *J* = 13.7, 2.7 Hz, 1H), 3.79 (t, *J* = 5.6 Hz, 2H), 3.63 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.09 (t, *J* = 5.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8 (s), 125.9 (s), 124.7 (d), 123.9 (d), 120.3 (d), 116.9 (d), 81.9 (t), 75.0 (d), 62.2 (t), 28.27 (q).

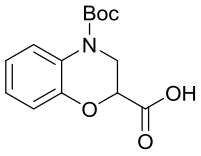
MS (ESI): m/z 288.11 $[M+Na]^+$

Synthesis of 4-(*tert*-butoxycarbonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid (20)



To a two-neck round-bottom flask the compound **19** (100 mg, 0.38 mmol, 1 eq) was added and dissolved in DCM (2 mL, 0.2 M). Then, $PhI(OAc)_2$ (244 mg, 0.76 mmol, 2 eq) was added, followed by TEMPO (11.9 mg, 0.076 mmol, 0.2 eq). The reaction was heated to 50° C and stirred for 24 h. Once the reaction had occurred as completely as possible, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (n-Hex/EtOAc 1:1) affording the compound **20** (83 mg, 0.3 mmol, 79%) as a white solid.

4-(*tert*-butoxycarbonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-2-carboxylic acid (20)



M.p. 76° C

IR = 3420, 2977, 1682, 1610 1494, 746 cm^{-1}

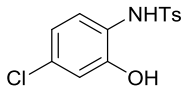
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (br s, 1H), 6.90 (br s, 1H), 6.77 (br d, J = 5.4 Hz, 2H), 4.44 (br s, 1H), 4.18 (br dd, J = 35.3, 9.7 Hz, 1H), 3.86 (br s, 1H [COOH]), 3.59 – 3.33 (m, 1H), 1.42 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): ongoing

MS (ESI): m/z 301.98 $[M+Na]^+$, 278.39 $[M-H]^-$

IMDA (Intramolecular Diels Alder reaction)

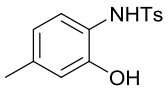
***N*-(4-chloro-2-hydroxyphenyl)-4-methylbenzenesulfonamide**



N-(4-chloro-2-hydroxyphenyl)-4-methylbenzenesulfonamide was prepared according to the general procedure (GP5) and isolated as brown solid (yield 71%) after flash column chromatography (Hex/EtOAc 3:1 → 2:1).

The data are in good agreement with those reported in the literature.[n]

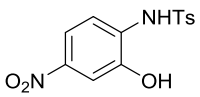
***N*-(2-hydroxy-4-methylphenyl)-4-methylbenzenesulfonamide**



N-(2-hydroxy-4-methylphenyl)-4-methylbenzenesulfonamide was prepared according to the general procedure (GP5) and isolated as white solid (yield 83%) after flash column chromatography (Hex/EtOAc 2:1).

The data are in good agreement with those reported in the literature.[n]

***N*-(2-hydroxy-4-nitrophenyl)-4-methylbenzenesulfonamide**

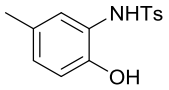


N-(2-hydroxy-4-nitrophenyl)-4-methylbenzenesulfonamide was prepared according to the general procedure (GP5) and isolated as yellow solid (yield 57%) after flash column chromatography (Hex/EtOAc 3:1).

The data are in good agreement with those reported in the literature.[s]

[s] W. Phetsang, S. Chaturongakul, C. Jiarpinitnun, *Monatsh Chem*, **2013**, 144 (4), 461-471

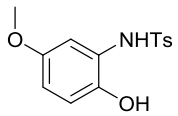
N-(2-hydroxy-5-methylphenyl)-4-methylbenzenesulfonamide



N-(2-hydroxy-5-methylphenyl)-4-methylbenzenesulfonamide was prepared according to the general procedure (GP5) and isolated as white solid (yield 85%) after flash column chromatography (Hex/EtOAc 3:1).

The data are in good agreement with those reported in the literature.[n]

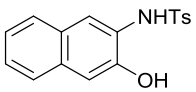
N-(2-hydroxy-5-methoxyphenyl)-4-methylbenzenesulfonamide



N-(2-hydroxy-5-methoxyphenyl)-4-methylbenzenesulfonamide was prepared according to the general procedure (GP5) and isolated as white solid (yield 69%) after flash column chromatography (Hex/EtOAc 3:1 → 2:1).

The data are in good agreement with those reported in the literature.[t]

N-(3-hydroxynaphthalen-2-yl)-4-methylbenzenesulfonamide



N-(3-hydroxynaphthalen-2-yl)-4-methylbenzenesulfonamide was prepared according to the general procedure (GP5) and isolated as brown solid (yield 51%) after flash column chromatography (Hex/EtOAc 3:1 → 1:1).

The data are in good agreement with those reported in the literature.[n]

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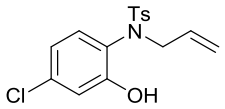
[t] H. Shen, Y.F. Wu, Y. Zhang, L.F. Fan, Z.Y. Han, L.Z. Gong, Angew. *Chem, Int Ed*, **2018**, 57(9), 2372-2376

N-allyl-*N*-(4-chloro-2-hydroxyphenyl)-4-methylbenzenesulfonamide (10c)



Compound **10c** was prepared according to the general procedure (GP6) and isolated as pale-yellow solid (yield 71%) after flash chromatography (Hex/AcOEt 4:1).

M.p. 91 – 92° C

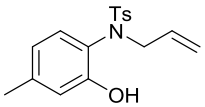
IR: 3311, 1623, 1541, 1343 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.15 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.61 (d, *J* = 5.5 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 5.70 (ddt, *J* = 17.2, 9.8, 6.5 Hz, 1H), 5.12 – 4.99 (m, 2H), 4.11 (br s, 2H), 2.46 (s, 3H).

^{13}C NMR (75 MHz, CDC_3) δ 153.7 (s), 144.7 (s), 133.3 (s), 131.4 (d), 129.9 (d), 129.7 (d), 128.1 (d), 127.5 (d), 126.7 (s), 124.5.5 (s), 120.2 (t), 118.5 (d), 54.6 (t), 21.6 (q).

MS (ESI): m/z 337.95 $[M+H]^+$

N-allyl-*N*-(2-hydroxy-4-methylphenyl)-4-methylbenzenesulfonamide (10d)



Compound **10d** was prepared according to the general procedure (GP6) and isolated as pale-yellow solid (yield 74%) after flash chromatography (Hex/AcOEt 4:1).

M.p. 119° C

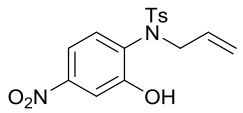
IR = 3422, 2978, 1534 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.20 (m, 2H), 6.87 – 6.80 (m, 1H), 6.52 – 6.42 (m, 2H), 6.23 (d, *J* = 8.1 Hz, 1H), 5.81 – 5.59 (m, 1H), 5.12 – 4.99 (m, 2H), 4.13 (br s, 2H), 2.44 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 (s), 144.1 (s), 140.3 (s), 134.0 (s), 132.0 (d), 129.5 (d), 128.1 (d), 127.1 (d), 123.0 (s), 121.2 (d), 119.6 (t), 117.8 (d), 54.6 (t), 21.6 (q), 21.3 (q).

MS (ESI): m/z 317.78 $[M+H]^+$

_N_-allyl-_N_-(2-hydroxy-4-nitrophenyl)-4-methylbenzenesulfonamide (10e)



Compound **10e** was prepared according to the general procedure (GP6) and isolated as yellow solid (yield 35%) after flash chromatography (Hex/AcOEt 3:1).

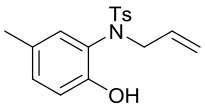
M.p. 128 – 129° C

IR = 3302, 1595, 1524, 1339 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.69 – 7.57 (m, 2H), 7.44 (br s, 1H), 7.35 – 7.18 (m, 3H), 5.97 (ddd, *J* = 22.6, 10.9, 5.6 Hz, 1H), 5.45 – 5.31 (m, 2H), 4.61 (dt, *J* = 5.5, 1.3 Hz, 2H), 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8 (s), 144.7 (s), 135.8 (s), 132.7 (s), 131.1 (d), 129.9 (d), 127.3 (d), 119.8 (t), 117.5 (d), 107.1 (d), 70.3 (t), 21.6 (q).

_N_-allyl-_N_-(2-hydroxy-5-methylphenyl)-4-methylbenzenesulfonamide (10f)



Compound **10f** was prepared according to the general procedure (GP6) and isolated as white solid (yield 82%) after flash chromatography (Hex/AcOEt 4:1).

M.p. 124° C

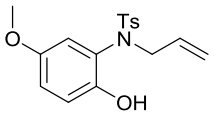
IR = 3439, 1594, 1505, 832, 817 cm-1

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.04 – 6.82 (m, 2H), 6.38 (s, 1H), 6.15 (d, *J* = 1.8 Hz, 1H), 5.72 (ddt, *J* = 16.6, 10.1, 6.5 Hz, 1H), 5.12 – 4.98 (m, 2H), 4.12 (br s, 2H), 2.44 (s, 3H), 2.06 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4 (s), 144.2 (s), 134.1 (s), 132.0 (d), 130.5 (d), 129.7 (s), 129.4 (d), 128.1 (d), 127.9 (d), 125.4 (s), 119.5 (t), 117.0 (d), 54.5 (t), 21.5 (q), 20.3 (q).

MS (ESI): m/z 318.45 $[M+H]^+$

N-allyl-*N*-(2-hydroxy-5-methoxyphenyl)-4-methylbenzenesulfonamide (10g)



Compound **10g** was prepared according to the general procedure (GP6) and isolated as white solid (yield 66%) after flash chromatography (Hex/AcOEt 4:1).

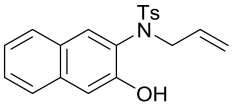
M.p. 118° C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 1H), 6.76 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.24 (s, 1H), 5.90 (d, *J* = 3.0 Hz, 1H), 5.73 (ddt, *J* = 16.6, 10.1, 6.5 Hz, 1H), 5.19 – 4.97 (m, 2H), 4.15 (br s, 2H), 3.52 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0 (s), 148.8 (s), 144.3 (s), 134.0 (s), 131.9 (d), 129.6 (d), 128.1 (d), 125.9 (s), 119.7 (t), 117.9 (d), 115.78 (d), 112.9 (d), 55.65 (q), 54.5 (t), 21.5 (q).

MS (ESI): m/z 357.23 $[M+Na]^+$

N-allyl-*N*-(3-hydroxynaphthalen-2-yl)-4-methylbenzenesulfonamide (10h)



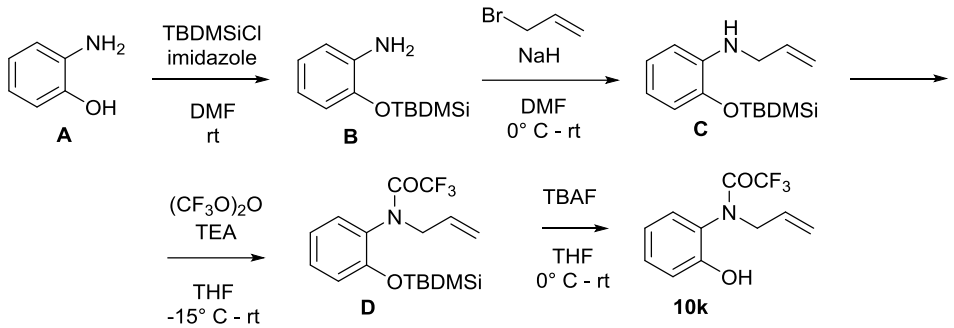
Compound **10h** was prepared according to the general procedure (GP6) and isolated as brown gum (yield 66%) after flash chromatography (Hex/AcOEt 5:1 → 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.63 (m, 1H), 7.60 – 7.48 (m, 2H), 7.48 – 7.37 (m, 3H), 7.33 – 7.25 (m, 3H), 6.87 (s, 1H), 6.58 (s, 1H), 5.75 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.13 – 4.99 (m, 2H), 4.26 (br s, *J* = 73.6 Hz, 2H), 2.46 (s, *J* = 9.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0 (s), 144.4 (s), 134.4 (s), 133.6 (s), 131.6 (d), 129.6 (d), 128.3 (d), 128.1 (s), 127.9 (s), 127.5 (d), 127.4 (d), 127.2 (d), 126.5 (d), 123.8 (d), 120.1 (t), 112.1 (d), 55.2 (t), 21. (q).

MS (ESI): m/z 376.13 $[M+Na]^+$

Synthesis of *N*-allyl-2,2,2-trifluoro-*N*-(2-hydroxyphenyl)acetamide (10k)



A solution of *2*-aminophenol **A** (2.0 gr, 18.5 mmol, 1 eq), *tert*-butyldimethylsilyl chloride (18.5 mmol, 1 eq) and imidazole (18.5 mmol, 1 eq) in DMF (0.3 M) was stirred at room temperature overnight. The reaction was taken up with brine (50 mL), extracted with Et_2O (3 x 50 mL), dried over Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography gel (n-Hex/EtOAc 10:1) to afford **B** (3.68 gr, 16.5 mmol, 89%).

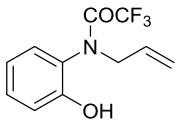
In a two-neck round-bottom flask **B** (1 gr, 4.48 mmol,1 eq.) was dissolved in a THF/DMF mixture (5:1, 0.2 M) and then K_2CO_3 (4.48 mmol, 1 eq) was added. The reaction mixture was cooled to 0° C and afterwards, a solution of allyl bromide (4.48 mmol, 1. eq) in THF (1 M) was added dropwise over 30 min. Then, the reaction was allowed to warm to room temperature and stirred for 24 h. Once the reaction has occurred as completely as possible, the mixture was filtered under vacuum, rinsed with AcOEt and washed with brine. The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by

flash chromatography on silica gel (n-Hex/EtOAc 15:1) to afford **C** (814 mg, 3.08 mmol, 69%).

To a two-neck round-bottom flask **C** (814 mg, 3.08 mmol, 1 eq) was added and dissolved in THF (13 mL, 1 M). After cooling to -15° C, TEA (0.43 mL, 3.08 mmol, 1.0 eq) and trifluoroacetic anyhydride (0.44 mL, 3.08 mmol, 1.0 eq) were added dropwise. The solution was allowed to warm to rt and stirred for 2 h. Afterwards, the solvent was evaporated under reduced pressure and the crude mixture was rinsed with Et_2O (20 mL) and washed with water (20 mL). The solvent was dried over Na_2SO_4, filtered and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel (n-Hex/EtOAc 10:1) to afford **D** (814 mg, 1.63 mmol, 53%).

A mixture of the corresponding **D** (590 mg, 1.63 mmol, 1 eq) and tetrabutylammonium fluoride (1.63 mmol, 1 eq) in THF (0.2 M) was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure, water was added (5 mL) and the reaction mixture was extracted with DCM (3 x 20 mL), then dried over Na_2SO_4, and the mixture concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex/AcOEt 5:1) to afford the **10k** (355 mg, 1.45 mmol, 89%) as a as brown oil.

_N_-allyl-2,2,2-trifluoro-_N_-(2-hydroxyphenyl)acetamide (10k)

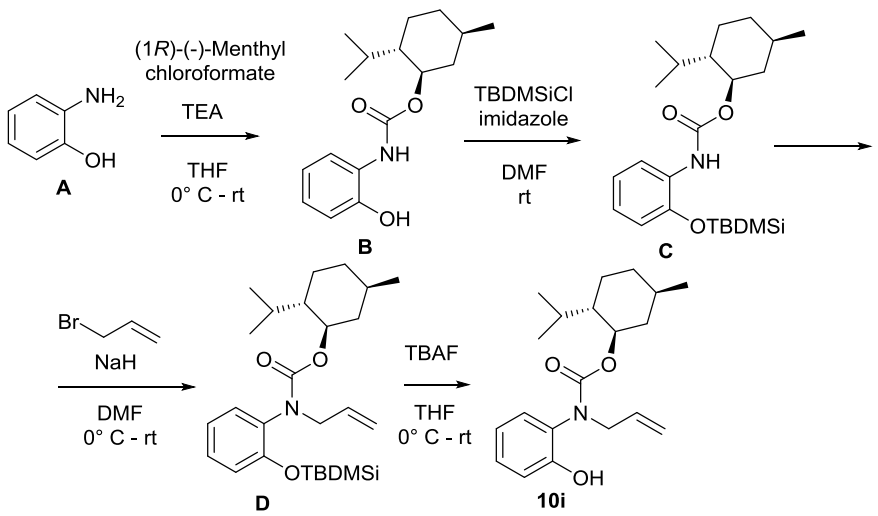


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.00 – 6.86 (m, 2H), 5.98 – 5.74 (m, 1H), 5.25 – 5.13 (m, 2H), 4.60 (dd, J = 14.3, 6.1 Hz, 1H), 3.97 (dd, J = 14.3, 7.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2 (s), 136.7 (s), 130.8 (d), 130.7 (d), 130.3 (d), 125.6 (s), 120.6 (d), 120.4 (t), 116.7 (d), 116.1 (s), 53.3 (t).

MS (ESI): m/z 245.98 $[M+H]^+$

Synthesis of *N*-allyl-2,2,2-trifluoro-*N*-(2-hydroxyphenyl)acetamide (10i)



To a two-neck round-bottom flask 2-aminophenol **A** (1 gr, 9.16 mmol, 1 eq) was added and dissolved in THF (30 mL, 0.3 M). After cooling to 0° C, TEA (2.55 mL, 18.33 mmol, 2.0 eq) was added, followed by (1*R*)-(−)-menthyl chloroformate (3.8 mL, 18.33 mmol, 2.0 eq) The solution was allowed to warm to rt and stirred for 16 h. Afterwards, the solvent was evaporated under reduced pressure, the crude mixture rinsed with AcOEt (30 mL) and washed with saturated solution of NH_4Cl (2 x 20 mL) and brine (20 mL). The organic phases were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (Hex/AcOEt 10:1) to afford **A** (19.19 gr, 6.6 mmol, 72%).

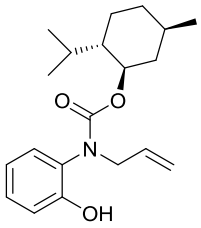
A solution of the *N*-protected aminophenol **B** (19.19 gr, 6.6 mmol, 1 eq), *tert*-butyldimethylsilyl chloride (6.6 mmol, 1 eq) and imidazole (6.6 mmol,

1 eq) in DMF (0.2 M) was stirred at room temperature overnight. The reaction was taken up with brine (50 mL), extracted with Et_2O (3 x 50 mL), dried over Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex/EtOAc 20:1) to afford **C** (2.93 gr, 5.02 mmol, 76%).

To a mixture of sodium hydride (7.53 mmol, 1.5 eq) in THF (15 mL) at 0° C under nitrogen atmosphere, a solution of **C** (2.93 gr, 5.02 mmol, 1 eq) in THF (3 mL) was dropped. The reaction mixture was stirred for 30 min at room temperature, then cooled at 0 °C. A solution of allyl bromide (5.2 mmol, 1.05 eq) in THF (3 mL) was dropped and the mixture was stirred at room temperature overnight. The mixture was quenched with water (10 mL) and concentrated at reduced pressure. Then, the crude mixture was rinsed with EtOAc (3 x 40 mL), washed with brine (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex/AcOEt 20:1) to afford **D** (1.47 gr, 3.21 mmol, 64%).

A mixture of the corresponding **D** (1.47 gr, 3.21 mmol, 1 eq) and tetrabutylammonium fluoride (3.21 mmol, 1 eq) in THF (0.2 M) was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure; water was added (10 mL). The reaction mixture was extracted with DCM (3 x 20 mL), then dried over Na_2SO_4, and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex/AcOEt 4:1) to afford **10i** (997 mg, 2.95 mmol, 92%) as a colourless oil.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl allyl(2-hydroxyphenyl)carbamate (10i)

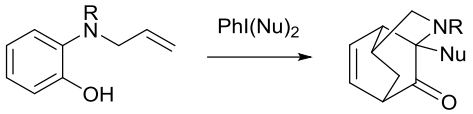


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.08 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 7.1 Hz, 1H), 6.03 – 5.72 (m, 1H), 5.25 – 5.09 (m, 2H), 4.68 (br s, 1H), 4.24 (br d, *J* = 4.8 Hz, 2H), 2.22 – 0.69 (m, 19H).

^{13}C NMR (75 MHz, $CDCl_3$) ongoing.

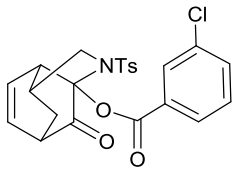
MS (ESI): m/z 332.10 $[M+H]^+$

General procedure for the intramolecular Diels Alder reaction (GP11)



The compound **15** (0.3 mmol, 1 eq.) was dissolved in CH_3CN (0.04 M) and then $PhI(Nu)_2$ (0.44 mmol, 1.5 eq) was added [when benzimidazole was used as nucleophile, $PhI(OAc)_2$ (0.44 mmol, 1.5 eq) was added toghether with the benzimidazole (0.44 mmol, 1.5 eq)]. The reaction mixture was stirred for 24 h. Once the reaction had occurred as completely as possible, the solvent was evaporated under vacuum. The crude product was rinsed with AcOEt and washed with brine. The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

7-oxo-1-tosyl-1,2,3,3a,6,7-hexahydro-7aH-3,6-methanoindol-7a-yl 3-chlorobenzoate (15aa)



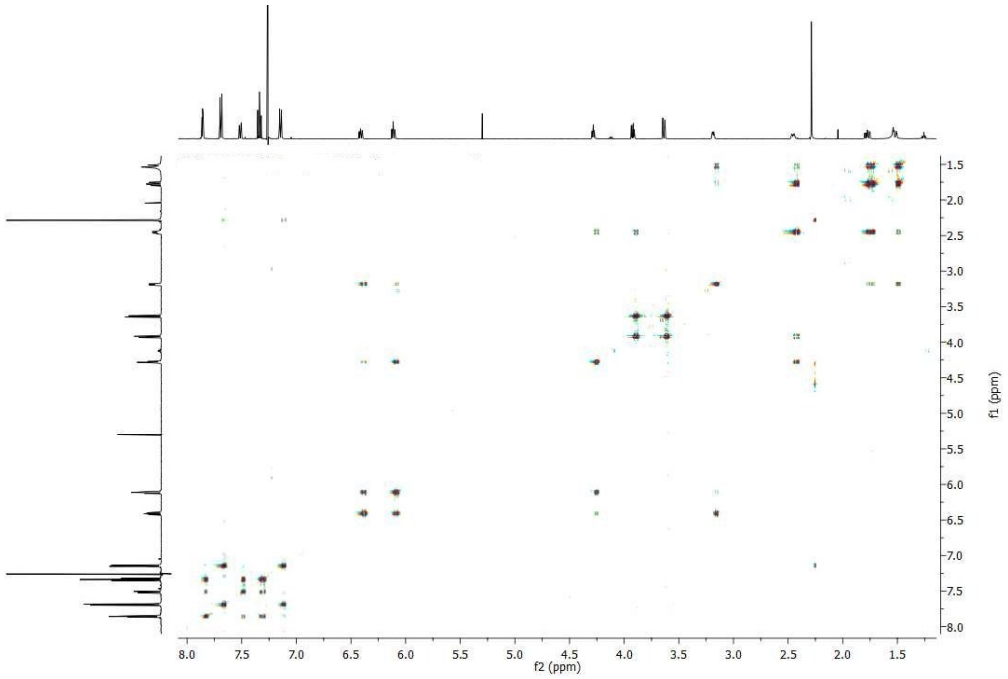
Compound **15aa** was prepared according to the general procedure (GP11) and isolated as white solid (yield 72%) after flash chromatography (Hex/AcOEt 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.78 (m, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.59 – 7.47 (m, 1H), 7.34 (t, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.41 (td, *J* = 7.6, 1.8 Hz, 1H), 6.21 – 6.02 (m, 1H), 4.28 (ddd, *J* = 6.2, 4.1, 1.9 Hz, 1H), 3.92 (dd, *J* = 9.5, 3.2 Hz, 1H), 3.64 (d, *J* = 9.5 Hz, 1H), 3.20 – 3.15 (m, 1H), 2.52 – 2.38 (m, 1H), 2.29 (s, 3H), 1.85 – 1.70 (m, 1H), 1.61 – 1.44 (m, 1H).

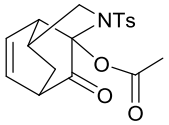
^{13}C NMR (126 MHz, $CDCl_3$) δ 195.7 (s), 163.3 (s), 143.9 (s), 136.3 (s), 134.5 (s), 133.5 (d), 132.7 (d), 131.6 (s), 130.1 (d), 129.6 (d), 129.4 (d), 129.4 (d), 128.4 (d), 128.2 (d), 89.2 (d), 54.7 (t), 46.3 (d), 45.7 (d), 33.2 (d), 28.5 (t), 21.6 (q).

HR-MS ($C_{23}H_{20}NO_5ClS$); $[M+H]^+$, pos. APCI: calcd: 458.0751, found: 458.0823

^{1}H COSY NMR



7-oxo-1-tosyl-1,2,3,3a,6,7-hexahydro-7aH-3,6-methanoindol-7a-yl acetate (15ab)



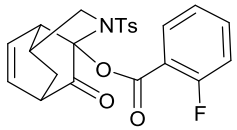
Compound **15ab** was prepared according to the general procedure (GP11) and isolated as colourless oil (yield 23%) after flash chromatography (Hex/AcOEt 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.48 – 6.28 (m, 1H), 6.12 (ddd, *J* = 7.7, 6.4, 1.1 Hz, 1H), 4.15 (ddd, *J* = 6.2, 4.2, 1.9 Hz, 1H), 3.85 (dd, *J* = 9.3, 3.2 Hz, 1H), 3.46 (d, *J* = 9.3 Hz, 1H), 3.11 – 3.06 (m, 1H), 2.50 – 2.24 (m, 4H), 2.26 – 1.88 (m, 4H), 1.83 – 1.59 (m, 1H).

^{13}C NMR (75 MHz, CDC_3) δ 195.2 (s), 169.2 (s), 143.7 (s), 132.1 (s), 129.3 (s), 129.3 (d), 127.8 (d), 88.5 (d), 54.55 (t), 45.7 (s), 45.4 (s), 32.6 (s), 28.5 (t), 22.6 (q), 21.5 (q).

MS: (ESI) *m/z* 361.84 $[M+H]^+$

7-oxo-1-tosyl-1,2,3,3a,6,7-hexahydro-7aH-3,6-methanoindol-7a-yl 2-fluorobenzoate (15ac)



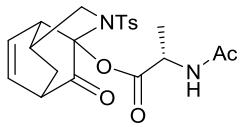
Compound **15ac** was prepared according to the general procedure (GP11) and isolated as white solid (yield 67%) after flash chromatography (Hex/AcOEt 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (td, *J* = 7.6, 1.8 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.61 – 7.47 (m, 1H), 7.15 (dddd, *J* = 10.9, 9.2, 6.6, 0.9 Hz, 4H), 6.53 – 6.36 (m, 1H), 6.23 – 6.09 (m, 1H), 4.33 (ddd, *J* = 6.1, 4.1, 1.9 Hz, 1H), 3.92 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.60 (d, *J* = 9.4 Hz, 1H), 3.21 – 3.13 (m, 1H), 2.52 – 2.25 (m, 4H), 1.92 – 1.67 (m, 1H), 1.57 – 1.42 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5 (s), 164.2 (s), 161.2 (s), 160.7 (s), 143.8 (s), 136.3 (s), [135.0, 134.9] (d), 132.9 (d), 132.5 (d), 129.4 (d), 129.3 (d), 128.0 (d), [124.0, 123.9] (d), [116.8, 116.6] (d), 54.6 (t), 46.1 (d), 45.6 (d), 33.0 (d), 28.43 (t), 21.5 (q).

MS: (ESI) *m/z* 441.95 $[M+H]^+$

7-oxo-1-tosyl-1,2,3,3a,6,7-hexahydro-7aH-3,6-methanoindol-7a-yl acetyl-*L*-alaninate (15ad)



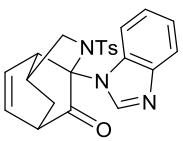
Compound **15ad** was prepared according to the general procedure (GP11) and isolated as a white solid (diastereosiomeric mixture) (yield 61%) after flash chromatography (Hex/AcOEt 2:1 → 1:1).

M.p. 84 – 86° C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.4, 2.6 Hz, 2H), 7.36 – 7.29 (m, 2H), 6.49 – 6.26 (m, 2H), 6.25 – 6.01 (m, 1H), 4.60 (pd, *J* = 7.2, 3.6 Hz, 1H), 3.94 (dddd, *J* = 10.6, 6.1, 4.2, 1.8 Hz, 1H), 3.79 (td, *J* = 9.2, 3.2 Hz, 1H), 3.38 (dd, *J* = 19.6, 9.4 Hz, 1H), 3.11 – 2.93 (m, 1H), 2.55 – 2.28 (m, 4H), 2.03 (s, *J* = 4.3 Hz, 3H), 1.78 – 1.59 (m, 1H), 1.50 (dd, *J* = 7.2, 3.7 Hz, 3H), 1.23 – 1.05 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ [195.18, 194.91] (s), [170.47, 170.41] (s), [170.16, 170.12] (s), [144.13, 144.05] (s), [136.18, 136.13] (s), [131.47, 131.39] (d), [129.65, 129.61] (d), [129.53, 129.50] (d), [127.80, 127.77] (d), [89.36, 89.33] (s), 54.49 (t), [49.03, 48.94] (d), [46.52, 46.21] (d), 45.38 (d), [32.84, 32.72] (d), [28.58, 28.46] (t), [23.03, 23.00] (q), 21.59 (q), [17.90, 17.76] (q).

7a-(1H-benzo[*d*]imidazol-1-yl)-1-tosyl-1,2,3,3a,6,7a-hexahydro-7H-3,6-methanoindol-7-one (15ae)



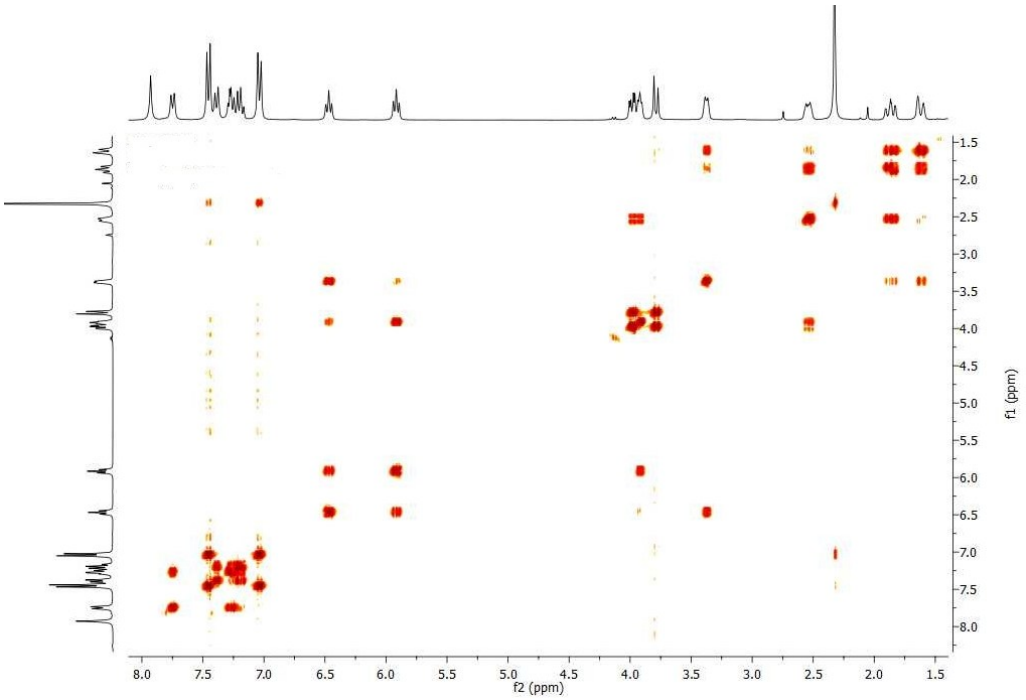
Compound **15ae** was prepared according to the general procedure (GP11) and isolated as white solid (yield 63%) after flash chromatography (Hex/AcOEt 2:1 → 1:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, *J* = 28.7 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.58 – 7.11 (m, 5H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.47 (t, *J* = 6.8 Hz, 1H), 5.92 (t, *J* = 6.9 Hz, 1H), 4.07 – 3.84 (m, 2H), 3.79 (d, *J* = 10.0 Hz, 1H), 3.51 – 3.23 (m, 1H), 2.62 – 2.45 (m, 1H), 2.32 (s, 3H), 1.94 – 1.73 (m, 1H), 1.62 (d, *J* = 13.6 Hz, 1H).

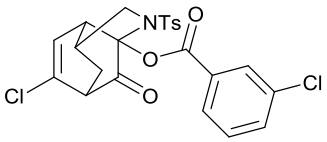
^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9 (s), 144.2 (s), 143.9 (s), 142.5 (d), 134.6 (s), 132.1 (d), 132.0 (s),129.5 (d), 128.9 (d), 127.9 (d), 123.1 (d), 122.6 (d), 120.6 (d), 112.6 (d), 55.1 (t), 48.8 (d), 46.3 (d), 32.0 (d), 29.0 (t), 21.5 (q).

MS (ESI): m/z 423.24$[M+H]^+$

^{1}H COSY NMR



5-chloro-7-oxo-1-tosyl-1,2,3,3a,6,7-hexahydro-7aH-3,6-methanoindol-7a-yl 3-chlorobenzoate (15ca)



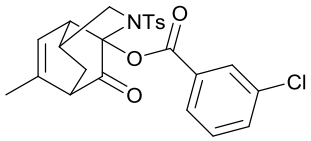
Compound **15ca** was prepared according to the general procedure (GP11) and isolated as orange solid (yield 57%) after flash chromatography (Hex/AcOEt 4:1 → 2:1).

M.p. 181° C (decomp.)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.81 (m, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 8H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.32 (dd, *J* = 7.6, 2.6 Hz, 1H), 4.25 (dd, *J* = 3.9, 2.8 Hz, 1H), 3.92 (dd, *J* = 9.6, 3.1 Hz, 6H), 3.67 (d, *J* = 9.5 Hz, 1H), 3.26 (dt, *J* = 7.6, 2.5 Hz, 1H), 2.82 – 2.67 (m, 1H), 2.52 – 2.21 (m, 4H), 1.99 – 1.79 (m, 1H), 1.58 (d, *J* = 13.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4 (s), 163.0 (s), 144.1 (s), 136.0 (s), 134.4 (s), 133.56 (d), 132.1 (s), 131.0 (s), 130.1 (d), 129.6 (d), 129.4 (d), 128.4 (d), 128.1 (d), 126.0 (d), 54.4 (d), 54.0 (t), 46.2 (d), 33.5 (d), 28.7 (t), 21.46 (q).

5-methyl-7-oxo-1-tosyl-1,2,3,3a,6,7-hexahydro-7aH-3,6-methanoindol-7a-yl 3-chlorobenzoate (15da)



Compound **15da** was prepared according to the general procedure (GP11) and isolated as white solid (yield 52%) after flash chromatography (Hex/AcOEt 3:1).

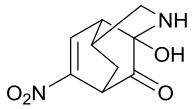
M.p. 95° C

IR = 2918, 1731, 1596 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.80 (m, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.45 (m, 1H), 7.35 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 2H), 5.85 – 5.62 (m, 1H), 4.24 (dd, *J* = 6.4, 4.2 Hz, 1H), 3.94 (dd, *J* = 9.5, 3.1 Hz, 1H), 3.65 (d, *J* = 9.5 Hz, 1H), 2.53 – 2.37 (m, 1H), 2.30 (s, *J* = 16.0 Hz, 3H), 1.87 (d, *J* = 1.5 Hz, 3H), 1.86 – 1.69 (m, 1H), 1.56 – 1.46 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2 (s), 163.2 (s), 143.8 (s), 142.35 (s), 136.21 (s), 134.32 (s), 133.32 (d), 131.65 (s), 130.0 (d), 129.5 (d), 129.3 (d), 128.3 (d), 128.1 (d), 121.3 (d), 54.67 (t), 51.0 (d), 45.7 (d), 33.9 (d), 28.1 (t), 21.45 (q), 19.92 (q).

5-nitro-1,2,3,3a,6,7a-hexahydro-7H-3,6-methanoindol-7-one (15ea)



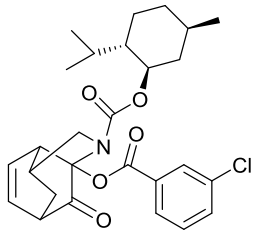
Compound **15ea** was prepared according to the general procedure (GP11) and isolated as white solid (yield 63%) after flash chromatography (Hex/AcOEt 2:1 → 1:1).

IR = 2920, 1743, 1344 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.6, 2.8 Hz, 1H), 4.37 (dd, *J* = 8.2, 3.2 Hz, 1H), 4.29 (dd, *J* = 4.2, 2.8 Hz, 1H), 4.00 (s, 1H), 3.84 (d, *J* = 8.2 Hz, 1H), 3.65 – 3.56 (m, 1H), 2.78 (dd, *J* = 8.4, 5.4 Hz, 1H), 2.15 – 1.89 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3 (s), 149.9 (s), 133.7 (s) 132.3 (d), 73.1 (t), 44.9 (d), 44.5 (d), 35.85 (d), 30.04 (t).

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 7a-((3-chlorobenzoyl)oxy)-7-oxo-2,3,3a,6,7,7a-hexahydro-1H-3,6-methanoindole-1-carboxylate (10i)



Compound **10i** was prepared according to the general procedure (GP11) and isolated as light orange solid (yield 51%) after flash chromatography (Hex/AcOEt 4:1).

M.p. 73° C

IR = 2953, 1753, 1731, 1694 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$) δ 8.15 – 7.93 (m, 2H), 7.66 – 7.48 (m, 1H), 7.45 – 7.35 (m, 1H), 6.58 – 6.35 (m, 1H), 6.30 – 6.08 (m, 1H), 4.72 – 4.32 (m, 1H), 4.30 – 3.99 (m, 1H), 3.87 (dt, *J* = 10.0, 3.3 Hz, 1H), 3.76 – 3.50 (m, 1H), 3.40 – 3.25 (m, 1H), 2.65 – 2.35 (m, 1H), 2.28 – 0.37 (m, 20H).

MS: (ESI) *m/z* 485.86 $[M+H]^+$

X-Ray Cristallography (Dr. Leonardo Lo Presti)

Single crystal X-ray diffraction analysis of the compound 15aa

The compound is chiral and crystallizes in the centric space group P 1 as a perfect 1:1 racemate, with 1 molecule per asymmetric unit. Figures S7 and S9 show the absolute configuration of the chiral centres at C8 (S), C9 (R), C10 (S) and C21 (S); every unit cell contains also the R, S, R, R enantiomer.

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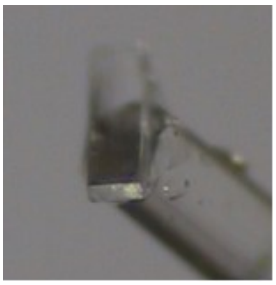
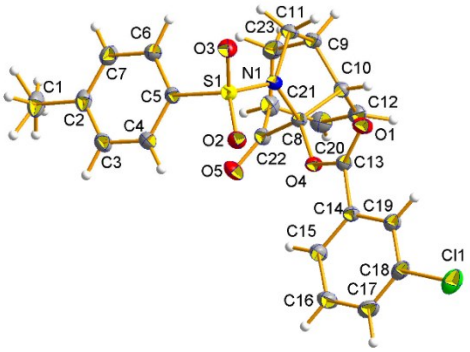


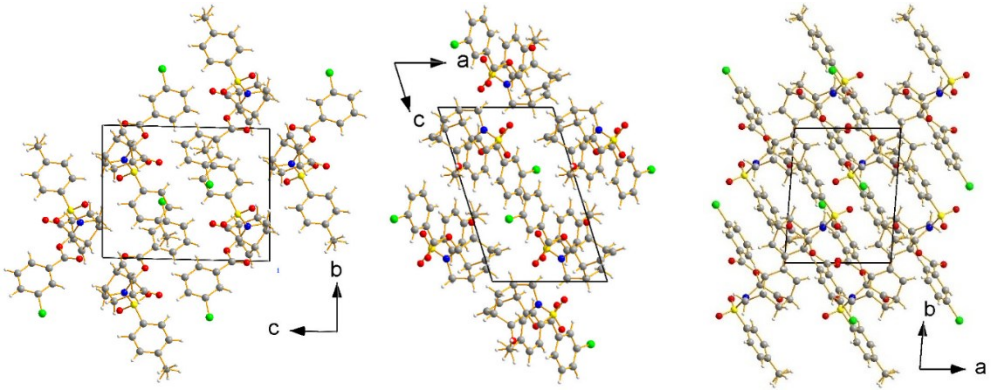


…… a) b)

Figure S7*. (a) Sample used for the present structural determination. (b) Molecular unit of* ***15aa*** *at rt, with the atom-numbering scheme. Thermal ellipsoids of non-H atoms are drawn at the 30 % probability level. The usual colour code was employed for atoms (grey: C; white: H; yellow: S; blue: N; red: O; green: Cl). The terminal methyl group C1 is rotationally disordered across 2 positions with site occupation factors as large as 0.52(7) and 0.48(7).*

The terminal C1 methyl group is rotationally disordered (Figure S7) into two positions with roughly 50% probability of being occupied (site occupation factors: 0.52(7) and 0.48(7)). Data collection at lower T are

required to improve the description of this group, as well as to gain insights into the nature of this disorder.



a) b) c)

Figure S8. Ball-and-stick representation of the crystal packing of SG53_F41 at RT, as seen (a) down the a cell axis; (b) the b cell axis; (c) the c cell axis. Colour code as in Figure 1. The crystallographic reference system is also highlighted.

Figure S8 shows the main packing motifs of **15aa**. The molecule consists of a rather globular aliphatic core, connected with a couple of aromatic rings that are arranged in a ladder-like motif (Figures S7 and S8a) forming stacks that run along the [110] direction (Figure S8c). According with the crystallographic inversion symmetry, C-Cl bonds are oriented antiparallel along the c direction (Figure S8b).

No significant hydrogen bond donors are present in this molecule, which exploits only weak CH···O contacts with both kinds of its symmetry-related images (Table S2). Despite the presence of chlorine, no halogen bonded contacts are found

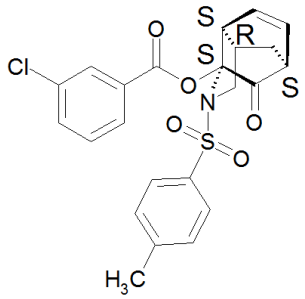


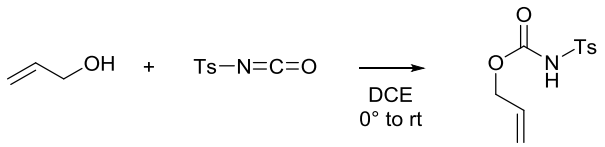
Figure S9. Molecular structure of one enantiomer of **15aa**, with the CIP descriptors highlighted.

Table S2. CH···O intermolecular hydrogen bonded contacts with dH···O < 3.0 Å and 120 < α_{CHO} < 180 deg in **15aa** at room temperature. The disordered C1 group is also likely involved in short contacts with O4 and O5 oxygen atoms (not included). Distances are expressed in Å and angles in degrees. Least–squares estimated standard deviations are given in parentheses

C–H···O	*d*C–H	*d*H···O	*d*C···O	αCHO	Symmetry (CH)
C(11)–H(11A)···O(3)	0.97(2)	2.58(2)	3.518(2)	162(2)	1–x, 1–y, –z
C(6)–H(6)···O(3)	0.99(2)	2.57(2)	3.560(2)	177(2)	1–x, 1–y, –z
C(21)–H(21)···O(2)	0.96(2)	2.96(2)	3.569(2)	123(1)	1+x, y, z
C(20)–H(20)···O(2)	0.95(2)	2.68(2)	3.369(2)	130(2)	1+x, y, z
C(20)–H(20)···O(1)	0.95(2)	2.90(3)	3.719(2)	145(2)	1+x, y, z
C(17)–H(17)···O(2)	0.97(2)	2.53(3)	3.321(3)	139(2)	1–x, –y, 1–z
C(10)–H(10)···O(1)	0.93(1)	2.73(1)	3.458(2)	135(1)	1–x, –y, –z
C(11)–H(11B)···O(1)	1.01(2)	2.62(2)	3.418(2)	137(1)	1–x, –y, –z
C(3)–H(3)···O(5)	0.98(2)	2.60(2) 3.518(2)		156(2)	–x, 1–y, –z

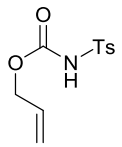
Aminoiodination reaction

General procedure for the preparation of *N*-protected alkenyl carbamates (GP12)



To a solution of the corresponding alkenyl alcohol (1 mmol, 1 eq) in DCE (10 mL), the tosyl isocyanate (1 mmol, 1 eq) was added dropwise at 0° C under inert atmosphere. The reaction mixture was allowed to warm to room temperature and it was stirred for 24 h. The solvent was evaporated under reduced pressure and the crude product was used without any further purification.

O-Allyl-*N*-tosylcarbamate (21a)

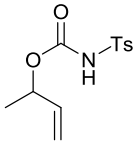


Compound **21a** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 96%).

The data are in good agreement with those reported in the literature.[u]

[u] D. Xing, D. Yang, *Org. Lett*. 2010, **12**, 1068-1071

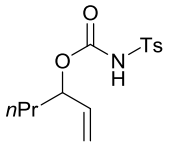
O-But-3-en-2-yl-*N*-tosylcarbamate (21b)



Compound **21b** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 95%).

The data are in good agreement with those reported in the literature.[v]

O-Hex-1-en-3-yl-N-tosylcarbamate (21c)



Compound **21c** was prepared according to the general procedure (GP12) and isolated as white solid (yield 98%).

M.p. 74−75 °C

IR: 3177, 3095, 2955, 1716, 1343, 1164, 1089, 925, 816, 663, 543 cm^{-1}

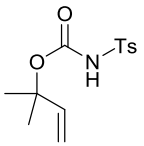
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.64 (ddd, *J* = 17.1, 10.4, 6.6 Hz, 1H), 5.23 – 5.04 (m, 2H), 2.43 (s, 3H), 1.68 – 1.33 (m, 2H), 1.26 – 1.10 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1 (s), 144.9 (s), 135.7 (s), 135.2 (d), 129.5 (d), 128.3 (d), 117.5 (t), 78.1 (d), 36.1 (t), 21.6 (q), 18.0 (t), 13.7 (q).

MS: (ESI) *m/z* 296.37 $[M-H]^-$, 320.26 $[M+Na]^+$

[v] S. Nicolai, C. Piemontesi, J. Waser, *Angew. Chem., Int. Ed.* 2011, **50**, 4680-4683

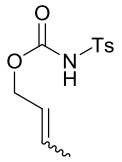
O-2-Methylbut-3-en-2-yl-*N*-tosylcarbamate (21d)



Compound **21d** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 96%).

The data are in good agreement with those reported in the literature.[u]

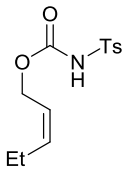
(*E/Z*)-*O*-But-2-en-1-yl-*N*-tosylcarbamate (21e)



Compound **21e** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 93%)

The data are in good agreement with those reported in the literature.[u]

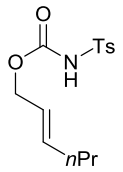
(*Z*)-*O*-Pent-2-en-1-yl-*N*-tosylcarbamate (21f)



Compound **21f** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 95%).

The data are in good agreement with those reported in the literature.[u]

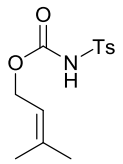
(*E*)-*O*-Hex-2-en-1-yl-*N*-tosylcarbamate (21g)



Compound **21g** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 94%).

The data are in good agreement with those reported in the literature.[w]

O-3-Methylbut-2-en-1-yl-*N*-tosylcarbamate (21h)



Compound **21h** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 94%).

IR: 3264, 2946, 1758, 1633, 1552, 1454, 1318, 1158, 849, 668 cm^{-1}.

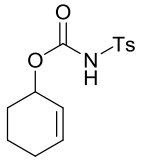
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 5.23 (t, J = 7.1 Hz, 1H), 4.56 (d, J = 7.3 Hz, 2H), 2.42 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9 (s), 144.9 (s), 140.5 (s), 135.7 (s), 129.5 (d), 128.4 (d), 117.4 (d), 63.7 (t), 25.7 (q), 21.6 (q), 18.0 (q).

MS: (ESI) m/z 306.04 $[M+Na]^+$

[w] J. M. Bauer, F. Frey, R. Peters, *Angew. Chem., Int. Ed.,* 2014, **53**, 7634-7638

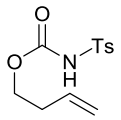
O-Cyclohex-2-en-1-yl-*N*-tosylcarbamate (21i)



Compound **21i** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 95%).

The data are in good agreement with those reported in the literature.[u]

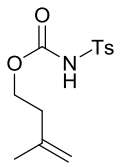
O-But-3-en-1-yl-*N*-tosylcarbamate (21j)



Compound 2**1j** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 96%).

These data are in good agreement with those reported in the literature.[v]

O-3-Methylbut-3-en-1-yl-*N*-tosylcarbamate (21k)

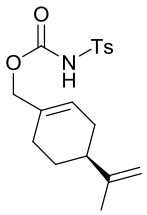


Compound **21k** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 98%).

These data are in good agreement with those reported in the literature.[x]

[x] G. Fan, M. Sun, G. Gao, J. Chen, L. Zhou, *Synlett,* 2014, **25**, 1921-1925

(*S*)-*O*-[4-(Prop-1-en-2-yl)cyclohex-1-en-1-yl]methyl-*N*-tosylcarbamate (-)-(23)



Compound (-)-**23** was prepared according to the general procedure (GP12) and isolated as colorless oil (yield 91%).

IR: 2923, 1749, 1644, 1597, 1447, 1348, 1160, 1090, 862, 814, 663 cm^{-1}

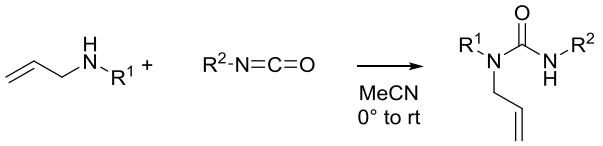
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.60 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 5.72 (d, *J* = 3.7 Hz, 1H), 4.74 (dd, *J* = 6.8, 5.4 Hz, 2H), 4.47 (s, 2H), 2.47 (s, 3H), 2.23 – 1.23 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4 (s), 149.2 (s), 145.0 (s), 135.6 (s), 131.5 (s), 129.6 (d), 128.4 (d), 127.4 (d), 108.9 (t), 70.9 (t), 40.6 (d), 30.4 (t), 27.1 (t), 26.1 (t), 21.7 (q), 20.7 (q).

MS: (ESI) *m/z* 372,18 $[M+Na]^+$

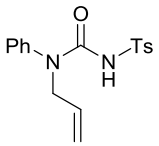
$[\alpha]^{D}_{20}$: -14° (c: 0.2 in $CHCl_3$)

General procedure for the preparation of *N*-protected allyl ureas (GP13)



To a solution of allyl amine (1 mmol, 1 eq) in acetonitrile (10 mL), the isocyanate (1 mmol, 1 eq) was added dropwise at 0 °C under inert atmosphere. The reaction mixture was allowed to warm to room temperature and it was stirred for 24 h. The solvent was evaporated under reduced pressure and the crude product was used without any further purification.

N-Allyl-*N*-phenyl-*N'*-tosyl-urea (25a)



Compound **25a** was prepared according to the general procedure (GP13) and isolated as orange solid (yield 98%).

M.p. 74-76 °C

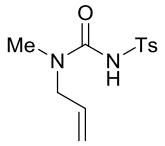
IR: 3392, 3261, 1696, 1438, 1365, 1164, 666, 546 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.53 – 7.38 (m, 3H), 7.38 – 7.26 (m, 2H), 7.19 (d, *J* = 7.2 Hz, 2H), 7.09 (br s, 1H), 5.79 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 1H), 5.13 – 4.97 (m, 2H), 4.18 (d, *J* = 6.3 Hz, 2H), 2.46 (s, *J* = 5.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1 (s), 144.6 (s), 139.3 (s), 136.1 (s), 132.4 (d), 130.6 (d), 129.5 (d), 129.1 (d), 128.4 (d), 128.3 (d), 118.7 (t), 52.4 (t), 21.7 (q).

MS: (ESI) 353,34 *m/z* [M+Na]$^+$

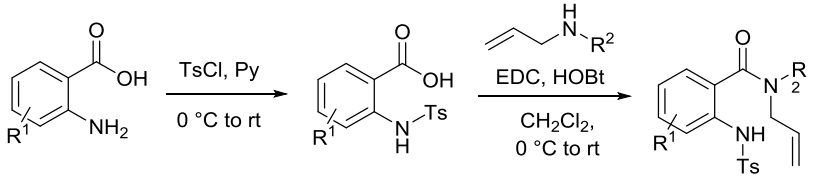
N-Allyl-*N*-methyl-*N*-tosyl-urea (25b)



Compound **25b** was prepared according to the general procedure (GP13) and isolated as colourless oil (yield 97%)

The data are in good agreement with those reported in the literature.[y]

General procedure for the preparation of *N*-protected *ortho*-allyl benzamides (GP14)



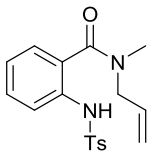
To a solution of the appropriate anthranilic acid (1 mmol, 1eq) in dry pyridine (3 mL), tosyl chloride (1.1 mmol, 1.1 eq) was added at 0 °C under nitrogen atmosphere. After 10 h, the reaction was quenched with ice/water (~10 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 20 mL). The organic layers were combined, washed with HCl 10% (~10 mL) and brine, then dried, filtered and concentrated under reduced pressure. The crude product was purified by crystallization (Hex/EtOAc) to afford the desired product (87-89% yields).

A solution of N-(*p*-tosyl)anthranilic acid (1 equiv.) in DCM was cooled to 0 °C, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.2 equiv) was added, followed by 1-hydroxybenzotriazole (1.2 equiv.). After 1 h, the

[y] D. Li, T. Mao, J. Huang, Q. Zhu, *Chem. Commun.,* 2017, **53**, 3450-3453

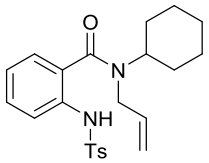
corresponding allyl amine (1 equiv) was dropped, followed by the addition of *N,N'*-diisopropylethylamine (1.5 equiv.) The reaction mixture was allowed to warm to room temperature and stirred for 30 h. Then the reaction mixture was washed with 5% $KHSO_4$ (~10 mL), s.s. $NaHCO_3$ (~10 mL) and brine (~10 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography afforded the desired product (82-85% yields).

_N_-Allyl-_N_-methyl-2-tosylamino-benzamide



N-Allyl-*N*-methyl-2-tosylamino-benzamide was prepared according to the general procedure (GP14) and isolated as orange oil (overall yield 74%). The data are in good agreement with those reported in the literature.[z]

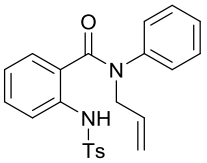
_N_-Allyl-_N_-cyclohexyl-2-tosylamino-benzamide



N-Allyl-*N*-cyclohexyl-2-tosylamino-benzamide was prepared according to the general procedure (GP14) and isolated as white solid (overall yield 75%). The data are in good agreement with those reported in the literature.[z]

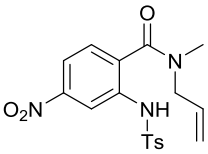
[z] E. M. Beccalli, G. Broggini, G. Paladino, A. Penoni, C. Zoni, *J. Org. Chem.,* 2004, **69**, 5627-5630

_N_-Allyl-_N_-methyl-2-tosylamino-benzamide



_N_-Allyl-_N_-methyl-2-tosylamino-benzamide was prepared according to the general procedure (GP14) and isolated as white solid (overall yield 78%). The data are in good agreement with those reported in the literature.[z]

_N_-Allyl-_N_-methyl-4-nitro-2-tosylamino-benzamide



_N_-Allyl-_N_-methyl-4-nitro-2-tosylamino-benzamide was prepared according to the general procedure (GP14) and isolated as yellow solid (overall yield 73%) after flash column chromatography (Hex/EtOAc 1:1).

M.p. 114-115 °C

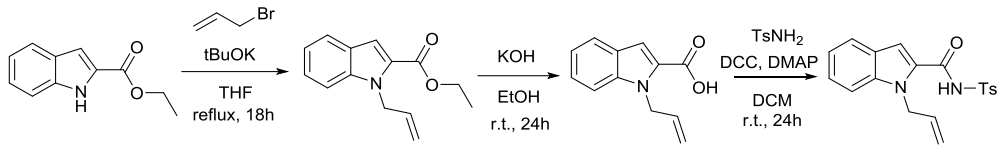
IR: 3202, 2925, 1625, 1601, 1524, 1350, 1163, 1089, 742, 724, 682, 567, 538 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (br s, 2H), 7.90 (br s, 1H), 7.75 (br s, 2H), 7.44 – 7.15 (overlapping 3H), 5.85 – 5.53 (m, 2H), 5.36 – 5.12 (overlapping, 2H), 4.06 (br s, 1H), 3.49 (br s, 1H), 3.00 (br s, 1.5H), 2.64 (br s, 1.5H), 2.39 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0 (s), 144.4 (s), 137.5 (s), 136.3 (s), 131.7 (d), 129.9 (d), 128.4 (d), 127.3 (d), 118.2 (d), 116.9 (d), 49.8 (q), 33.4 (t), 25.4 (t), 24.7 (t), 21.5 (q).

MS: (ESI) *m/z* 388.47 $[M-H]^-$, 412.41 $[M+Na]^+$

Procedure for the preparation of *N*-protected allyl-1*H*-indole-2-carboxamide



Following the procedure,[aa] to a solution of ethyl-1*H*-indole-2-carboxylate (1 equiv) in dry THF (10 mL), tBuOK (1.1 equiv) was added, followed by allyl bromide (1.1 equiv). The reaction mixture was refluxed overnight, then cooled to r.t. and filtered. The solvent was evaporated under reduced pressure. The crude product was purified using flash column chromatography (Hex/EtOAc 95:5) to afford the desired product (85% yield).

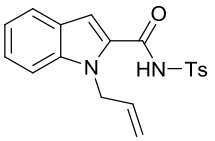
To a solution of ethyl 1-allyl-1*H*-indole-2-carboxylate (1 equiv.) in EtOH, a solution of KOH (2 equiv, 1M) in water was added. The reaction was stirred overnight at room temperature, then the solvent was removed under reduced pressure. The organic residues were dissolved into water and HCl 10% was added. Then the aqueous layer was extracted with DCM (2 x 15 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure to give the desired product (95% yield).

A solution of 1-allyl-1*H*-indole-2-carboxylic acid (1 equiv.) in DCM was cooled to 0 °C, and *N,N'*-dicyclohexylcarbodiimide (1.3 equiv) was added, followed by 4-dimethylaminopyridine (1.2 equiv.) and $TsNH_2$ (1.2 equiv.), The reaction mixture was allowed to warm to room temperature and stirred for 24 h. Then the solvent was evaporated under reduced pressure.

[aa] Padwa, D. L. Hertzog, W. R. Nadler, M. H. Osterhout, A. T. Price, *J. Org. Chem*., 1994, **59**, 1418–1427

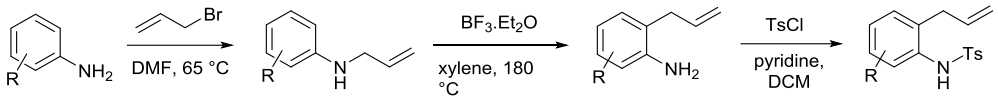
Purification of the crude product by flash chromatography (Hex/EtOAc 9:1) afforded the desired product (75% yield) as a white solid.

1-Allyl-*N*-tosyl-1*H*-indole-2-carboxamide



The data are in good agreement with those reported in the literature.[bb]

General procedure for the preparation of *N*-protected *ortho*-allyl anilines (GP15)



Following the procedure,[cc] to a solution of the appropriate aniline (5 mmol, 1 eq) in dry DMF (10 mL, 2M), K_2CO_3 (5 mmol, 1 eq) was added, followed by allyl bromide (5.5 mmol, 1.1 eq). The reaction mixture was refluxed overnight, then cooled to r.t. and filtered. The solvent was evaporated under reduced pressure. The crude product was purified using flash column chromatography (Hex/EtOAc 20:1) to afford the desired product (78-85% yields).

N-Allylaniline (1 equiv.) was injected into a large pressure tube equipped with a magnetic stirrer and sealed with a septum under a nitrogen atmosphere, followed by the addition of xylenes (1M) *via* syringe. The pressure tube was cooled to 0 °C. Then, $BF_3{\cdot}OEt_2$ (1 equiv.) was added dropwise via syringe and the mixture was stirred for 10 min at room

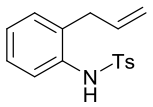
[bb] *Y. A. Cheng, W. Z. Yu, Y.Y. Yeung, J. Org. Chem.*, 2016, **81**, 545-552

[cc] K. Muniz, A. Lishchynskyi, J. Streuff, M. Nieger, E. C. Escudero-Adan, M. Belmonte, *Chem. Commun.*, 2011, **47**, 4911-4913

temperature. Subsequently, the pressure tube was sealed with a cap and warmed to 180 °C in an oil bath and stirred for 4 h. After cooled to ambient temperature, the reaction was quenched by the addition of NaOH (2N) (~5 mL). The organic residues were extracted with Et_2O (2 x 20 mL) and washed with brine (~20 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography (Hex/EtOAc 30:1 to 10:1) to afford the desired product (47-61% yields).

Substituted 2-allylaniline (1 equiv.) was dissolved in dry DCM (0.25 M) in a round bottom flask under a nitrogen atmosphere, and was cooled to 0 °C. The solution was stirred with a magnetic stirrer and pyridine (3 equiv.) was added dropwise *via* a syringe. The tosyl chloride (1.2 equiv.) was then added into the flask *via* a syringe and the reaction was stirred at 0 °C and gradually allowed to warm to room temperature. After 30 h, the reaction was quenched with ice/water (~10 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 20 mL). The organic layers were combined, and washed with HCl 10% (~5 mL) and brine. The organic layer was dried, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography (Hex/EtOAc 10:1) to afford the desired product (87-92% yields).

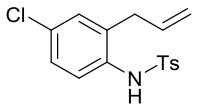
2-Allyl-*N*-tosylaniline



2-Allyl-*N*-tosylaniline was prepared according to the general procedure (GP15) and isolated as white solid (overall yield 33%).

The data are in good agreement with those reported in the literature.[dd]

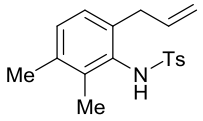
2-Allyl-4-chloro-*N*-tosylaniline



2-Allyl-4-chloro-*N*-tosylaniline was prepared according to the general procedure (GP15) and isolated as white solid (overall yield 36%).

The data are in good agreement with those reported in the literature.[dd]

6-Allyl-2,3-dimethyl-*N*-tosylaniline



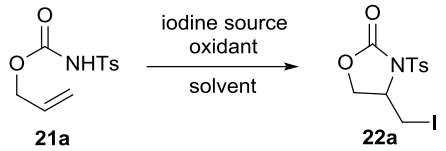
6-Allyl-2,3-dimethyl-*N*-tosylaniline was prepared according to the general procedure (GP15) and isolated as white solid (overall yield 46%). The data are in good agreement with those reported in the literature.[ee]

[dd] P. H. Fuller, J. W. Kim, S. Chemler, *J. Am. Chem. Soc.*, 2008, **130**, 17638-17639

[ee] L. Chen, X. Luo, Y. Li, *Monath. Chem.*, 2017, **148**, 957-961

Screening for optimized reaction conditions

Table S3. Screening of oxidizing agents and iodine source for the aminoiodination reaction of allyl carbamates.

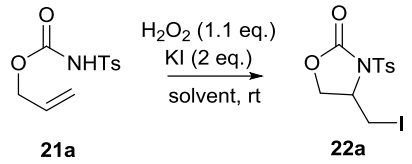


21a **22a**

Entry	Iodine source	Oxidant	Solvent	time (h)	**22a**[b] (% yield)
1	I_2	-	CH_3CN	30	52
2	NIS	-	CH_3CN	18	29[c]
3[d]	NIS	$CuCl_2$ (5 mol%), O_2	CH_3CN	24	49[c]
4	I_2	PIFA	CH_3CN	4	-[e]
5	NIS	PIFA	CH_3CN	6	-[e]
6	KI	PIFA	CH_3CN	3	81
7	KI	PIDA	CH_3CN	8	68
8	KI	$PhI(mcba)_2$	CH_3CN	20	73
9	KI	O_2	CH_3CN	30	-
10	KI	BQ (20 mol%), O_2	CH_3CN	48	-
11	KI	BQ (20 mol%), O_2	THF	48	-
12	KI	MnO_2 (20 mol%), O_2	CH_3CN	48	31
13[f]	KI	MnO_2 (20 mol%), O_2	CH_3CN	24	41
14	KI	MnO_2 (20 mol%), O_2	THF	24	12
15	KI	MnO_2 (20 mol%), O_2	DMF	48	34
16[g]	KI	H_2O_2	CH_3CN	24	79

[a] *The reactions were carried out at room temperature unless otherwise stated.* [b] *Yields of purified products.* [c] *O-(2,3-diiodopropyl)-N-tosyl-carbamate has been isolate in 57% yield (entry 2) and 37% yield (entry 3).* [d] *The reaction was performed in CH_3CN at reflux under O_2 atmosphere.* [e] *3-Unsubstituted 4-iodomethyl-oxazolidin-2-one has been isolate in 54% yield (entry 4) and 43% yield (entry 5).* [f] *The reaction was performed under O_2 atmosphere at 40 °C.* [g] *The reaction was carried out at room temperature using a 30% solution of H_2O_2 in water.*

Table S4. Screening of solvent for the aminoiodination reaction of allyl carbamates.

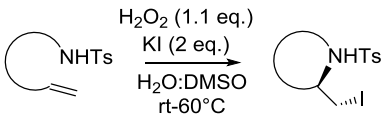


21a **22a**

Entry	**Iodine source**	**Oxidant**	**Solvent**[a]	**Time** (h)	**22a**[b] (% yield)
17[a]	KI	H_2O_2	DMF	24	32
18[a]	KI	H_2O_2	Dioxane	24	54
19[a]	KI	H_2O_2	H_2O/ DMSO[c]	24	78
20[g]	KI	H_2O_2	H_2O/CH_3CN[d]	24	67

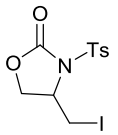
[a] *The reaction was carried out at room temperature using a 30% solution of H_2O_2 in water.* [b] *Yields of purified products.* [c] *In 3:1 ratio.* [d] *In 2:1 ratio.*

General procedure for the aminoiodination reaction (GP16)



To a solution of the appropriate olefins (1 equiv.) in a mixture of DMSO and water, potassium iodide (2 equiv.) was added at room temperature, followed by the addition of a solution of 30% H_2O_2 (1.1 equiv) in water. The reaction was monitored by TLC. Then, the reaction mixture was quenched with $Na_2S_2O_3$ (1M), and ethyl acetate was added. The organic layer was separated and washed with brine (6 x 15 mL). Afterwards, the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The purification by flash silica gel column chromatography afforded the corresponding products.

4-(Iodomethyl)-3-tosyloxazolidin-2-one (22a)

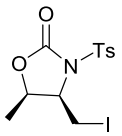


Compound **22a** was prepared according to the general procedure (GP16) (H_2O/DMSO 3:1, 30h, rt) and isolated as white solid (yield 78%) after flash column chromatography (Hex/EtOAc 3:1).

The data are in good agreement with those reported in the literature.[ff]

[ff] H. Liu, Y. Pan, C. Tan, *Tetrahedron Lett.,* 2008**, 49**, 4424-4426

(4*R,5*R**)-4-(iodomethyl)-5-methyl-3-tosyloxazolidin-2-one (*cis*-22b)**

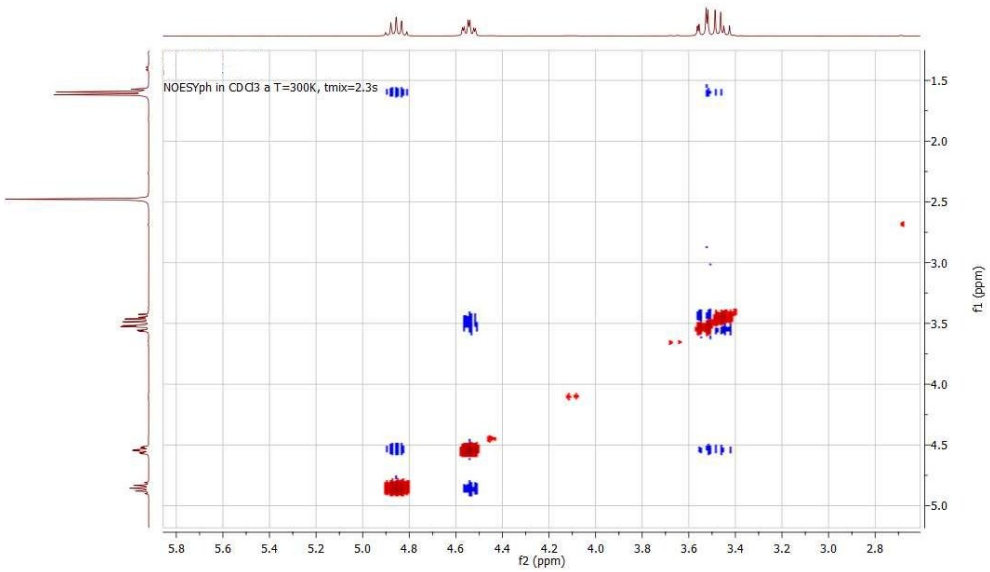


Compound ***cis*-22b** was prepared according to the general procedure (GP16) (H_2O/DMSO 2.5:1, 30h, rt) and isolated as white solid (yield 45%) after flash column chromatography (Hex/EtOAc 2:1).

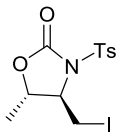
IR: 3428, 2975, 1778, 1359, 1163, 1135, 819, 666, 594, 572, 541 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 4.91 – 4.79 (m, 1H), 4.54 (td, J = 7.2, 2.2 Hz, 1H), 3.58 – 3.40 (m, 2H), 2.48 (s, 3H), 1.61 (d, J = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2 (s), 145.9 (s), 134.7 (s), 129.9 (d), 128.7 (d), 75.0 (d), 59.3 (d), 21.8 (q), 13.5 (q), -0.5 (t). MS: (ESI) m/z 418.05 [M+Na^+]



(4*R,5*S**)-4-(Iodomethyl)-5-methyl-3-tosyloxazolidin-2-one (*trans*-22b)**



Compound ***trans*-22b** was prepared according to the general procedure (GP16) (H_2O/DMSO 2.5:1, 30h, rt) and isolated as white solid (yield 22%) after flash column chromatography (Hex/EtOAc 2:1).

M.p. 146-147 °C

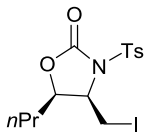
IR: 3435, 2984, 1785, 1595, 1359, 1166, 1131 1088, 816, 665, 596, 568, 539 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 4.36 (dd, J = 6.3, 3.0 Hz, 1H), 4.02 (dt, J = 8.9, 2.7 Hz, 1H), 3.57 (dd, J = 10.3, 2.6 Hz, 1H), 3.31 (t, J = 9.7 Hz, 1H), 2.39 (s, 3H), 1.31 (d, J = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0 (s), 146.0 (s), 134.6 (s), 129.9 (d), 128.5 (d), 77.3 (d), 62.8 (d), 21.8 (q), 21.1 (q), 6.5 (t).

MS: (ESI) m/z 418.12 [$M+Na^+$]

(4*R,5*R**)-4-(Iodomethyl)-5-propyl-3-tosyloxazolidin-2-one (*cis*-22c)**



Compound ***cis*-22c** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:1, 24h, 40 °C) and isolated as white solid (yield 28%) after flash column chromatography (Hex/EtOAc 5:1 to 2:1).

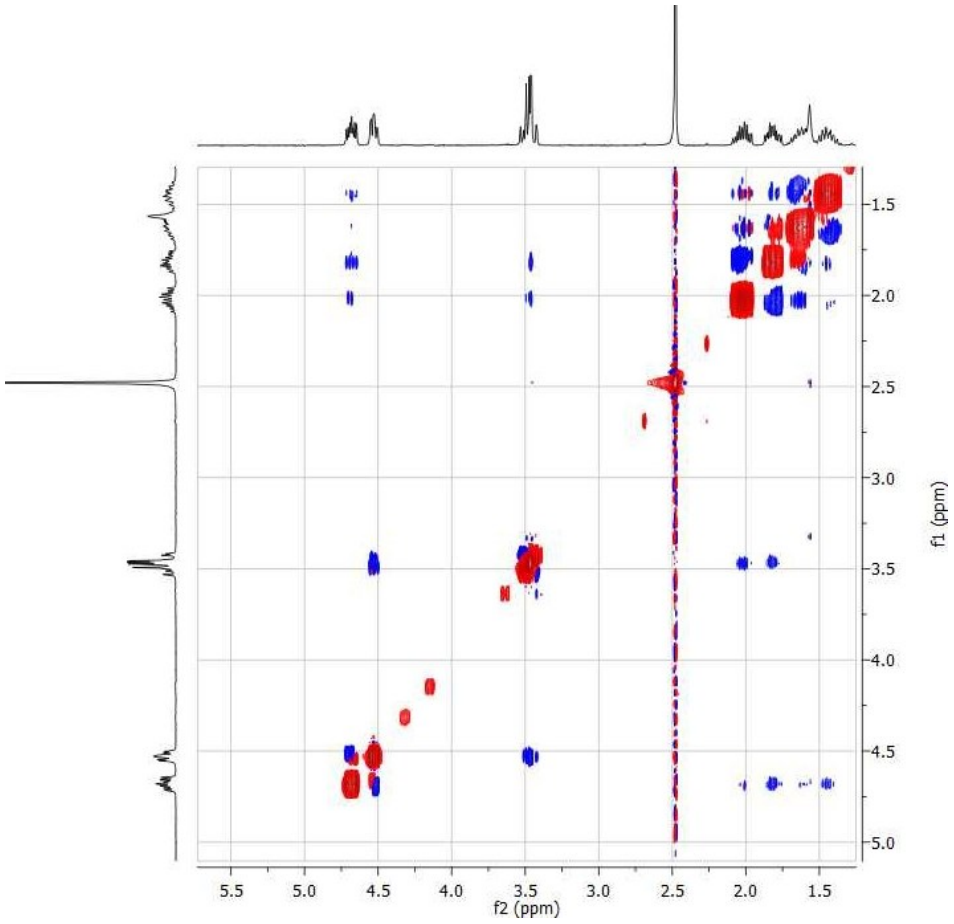
M.p. 130-131 °C

IR: 3435, 2973, 1788, 1366, 1160, 657, 560 cm^{-1}

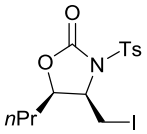
^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.70 – 4.54 (m, 1H), 4.55 – 4.39 (m, 1H), 3.51 – 3.40 (m, 2H), 2.39 (s, 3H), 2.04 – 1.98 (m, 1H), 1.85 – 1.79 (m, 1H), 1.80 – 1.46 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (s), 146.0 (s), 135.0 (s), 130.0 (d), 128.9 (d), 78.8 (d), 59.1 (d), 29.6 (t), 21.9 (q), 19.3 (t), 13.8 (q), -0.0 (t).

MS: (ESI) m/z 424.82 [M^+], 446.54 [$M+Na^+$]



(4*R,5*S**)-4-(Iodomethyl)-5-propyl-3-tosyloxazolidin-2-one (*trans*-22c)**



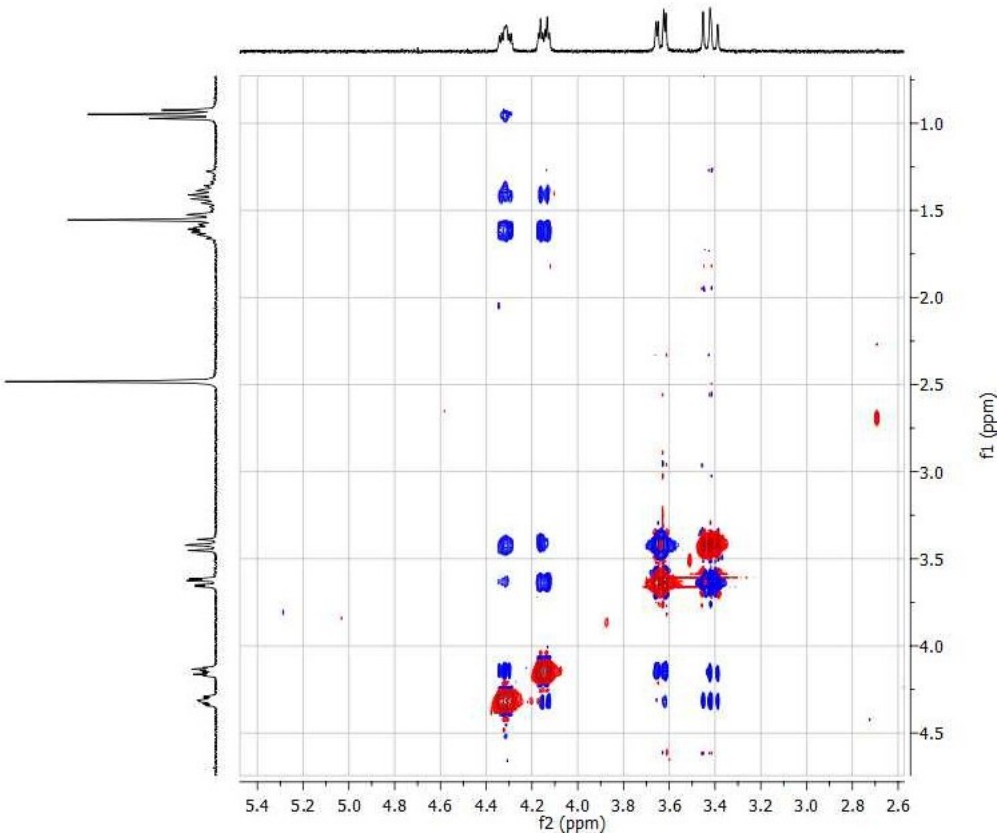
Compound ***trans*-22c** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:1, 24h, 40 °C) and isolated as white solid (yield 32%) after flash column chromatography (Hex/EtOAc 5:1 to 2:1).

M.p. 118-119 °C

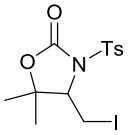
IR: 3437, 2969, 1786, 1361, 1158, 655, 563 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 4.39 – 4.24 (m, 1H), 4.15 (dt, *J* = 8.8, 2.8 Hz, 1H), 3.64 (dd, *J* = 10.3, 2.8 Hz, 1H), 3.42 (dd, *J* = 10.2, 8.8 Hz, 1H), 2.48 (s, 3H), 1.74 – 1.27 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9 (s), 134.6 (s), 129.9 (d), 128.5 (d), 80.4 (d), 61.2 (d), 37.0 (t), 21.7 (q), 17.3 (d), 13.5 (q), 7.0 (t).

MS: (ESI) *m/z* 424.82 [M^+], 446.54 [$M+Na^+$]



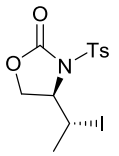
4-(Iodomethyl)-5,5-dimethyl-3-tosyloxazolidin-2-one (22d)



Compound **22d** was prepared according to the general procedure (GP16) (H_2O/DMSO 2:1, 30h, rt) and isolated as white solid (yield 61%) after flash chromatography (Hex/EtOAc 3:1).

The data are in good agreement with those reported in the literature.[ff]

(4*R,2'*R**)-4-(1-Iodopropyl)-3-tosyloxazolidin-2-one (22e)**



Compound **22e** was prepared according to the general procedure (GP16) (H_2O/DMSO 2.5:1, 30h, rt) and isolated as white solid (yield 67%) after flash column chromatography (Hex/EtOAc 2:1).

M.p. 164-165 °C

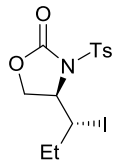
IR: 2998, 1781, 1602, 1346, 1174, 1126 1075, 810, 603, 575, 549 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.81 – 4.62 (m, 1H), 4.33 (t, *J* = 9.0 Hz, 1H), 4.14 (dd, *J* = 9.0, 3.7 Hz, 1H), 3.90 (dq, *J* = 6.6, 3.1 Hz, 1H), 2.39 (s, 3H), 1.77 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6 (s), 145.9 (s), 134.6 (s), 129.8 (d), 128.8 (d), 66.4 (t), 61.3 (d), 29.2 (d), 23.1 (q), 21.8 (q).

MS: (ESI) *m/z* 418.26 [M+Na^+]

(4*R,2'*R**)-4-(1-Iodopropyl)-3-tosyloxazolidin-2-one (22f)**



Compound **22f** was prepared according to the general procedure (GP16) (H_2O/DMSO 2:1, 30h, rt) and isolated as white solid (yield 66%) after flash column chromatography (Hex/EtOAc 1:1).

M.p. 146-147 °C

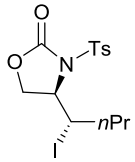
IR: 3435, 2971, 2873, 2850, 1784, 1369, 1356, 1175, 1164, 1116, 668, 596, 540 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 5.02 – 4.95 (m, 1H), 4.60 – 4.50 (m, 1H), 4.48 – 4.36 (m, 2H), 2.48 (s, 3H), 1.62 – 1.45 (m, 2H), 1.01 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7 (s), 146.5 (s), 134.9 (s), 130.3 (d), 128.8 (d), 66.9 (t), 62.0 (d), 37.5 (d), 24.1 (t), 22.2 (q), 14.7 (q).

MS: (ESI) *m/z* 432.38 [M+Na^+]

(4*R,2'*S**)-4-(1-Iodobutyl)-3-tosyloxazolidin-2-one (22g)**



Compound **22g** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:1, 24h, 40 °C) and isolated as white solid (yield 64%) after flash column chromatography (Hex/EtOAc 4:1).

M.p. 136-137 °C

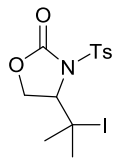
IR: 3439, 2965, 1784, 1352, 1121, 645, 565 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.73 – 4.56 (m, 1H), 4.32 (t, *J* = 9.0 Hz, 1H), 4.16 (dd, *J* = 9.0, 3.8 Hz, 1H), 4.09 – 3.98 (m, 1H), 2.39 (s, 3H), 1.73 – 1.28 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7 (s), 145.9 (s), 134.7 (s), 129.8 (d), 128.8 (d), 66.6 (t), 60.2 (d), 38.6 (d), 37.3 (t), 22.7 (t), 21.8 (q), 13.1 (q).

MS: (ESI) *m/z* 446.21 [M+Na^+]

4-(1-Iodo-1-methyl-ethyl)-3-tosyloxazolidin-2-one (22h)



Compound **22h** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:2, 30h, rt) and isolated as white solid (yield 55%) after flash column chromatography (Hex/EtOAc 2.5:1).

M.p. 156-160 °C (decomp.)

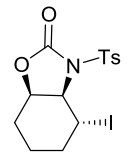
IR: 3396, 2921, 1783, 1165, 1160, 665, 554, 538 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 4.79 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.63 (dd, *J* = 9.9, 1.6 Hz, 1H), 4.38 (dd, *J* = 9.7, 7.9 Hz, 1H), 2.48 (s, 3H), 2.16 (s, 3H), 1.89 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 145.9, 134.7, 129.9, 128.6, 69.9, 67.1, 49.0, 35.4, 30.0, 21.7.

MS: (ESI) *m/z* 432,24 [M+Na^+]

(3a*R,4*R**,7a*R**)-4-Iodo-3-tosylhexahydrobenzo[*d*]oxazol-2(3*H*)-one (22i)**



Compound **22i** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:1.5, 30h, rt) and isolated as white solid (yield 66%) after flash column chromatography (Hex/EtOAc 3:1).

M.p. 171-172 °C

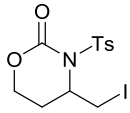
IR: 3294, 2940, 1787, 1175, 1163, 671, 558, 541 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 5.00 (dd, *J* = 8.0, 3.9 Hz, 1H), 4.77 (dd, *J* = 11.1, 6.2 Hz, 1H), 4.67 (dd, *J* = 6.5, 3.6 Hz, 1H), 2.48 (s, 3H), 2.28 – 1.58 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9 (s), 129.9 (d), 128.6 (d), 74.3 (d), 63.3 (d), 29.0 (t), 25.6 (d), 25.1 (t), 21.7 (q), 18.2 (t).

MS: (ESI) *m/z* 444.32 [$M+Na^+$]

4-(Iodomethyl)-3-tosyl-1,3-oxazinan-2-one (22j)



Compound **22j** was prepared according to the general procedure (GP16) (H_2O/DMSO 3:1, 30h, rt) and isolated as white solid (yield 74%) after flash chromatography (Hex/EtOAc 2:1).

M.p. 127-128 °C

IR: 3324, 1722, 1358, 1271, 1170, 1143, 669, 612, 542, 533 cm^{-1}

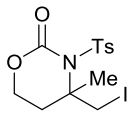
^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 4.75 – 4.57 (m, 1H), 4.33 – 4.14 (m, 2H), 3.69 (dd, *J* = 10.1, 3.0 Hz,

1H), 3.24 (t, *J* = 10.6 Hz, 1H), 2.53 – 2.42 (m, 1H), 2.36 (s, 3H), 2.22 – 2.06 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0 (s), 145.5 (s), 135.2 (s), 129.5 (d), 129.2 (d), 63.9 (t), 55.4 (d), 26.0 (t), 21.7 (q), 5.4 (t).

MS: (ESI) *m/z* 418.51 [M+Na$^+$]

4-(Iodomethyl)-4-methyl-3-tosyl-1,3-oxazinan-2-one (22k)



Compound **22k** was prepared according to the general procedure (GP16) (H_2O/DMSO 1.5:1, 30h, rt) and isolated as colorless oil (yield 68%) after flash chromatography (Hex/EtOAc 4:1).

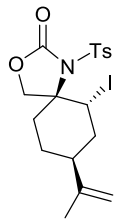
IR: 2936, 1755, 1342, 1176, 667, 562, 546 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.30 (d, *J* = 10.4 Hz, 1H), 4.23 – 4.15 (m, 2H), 3.89 (d, *J* = 10.4 Hz, 1H), 2.57 – 2.45 (m, 1H), 2.42 (s, 3H), 2.11 – 1.96 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 145.0, 136.7, 129.5, 129.2, 64.0, 62.7, 38.4, 25.9, 21.7, 14.0.

MS: (ESI) *m/z* 432.45 [M+Na$^+$]

(5*S*,6*R*,8*S*)-6-Iodo-8-(prop-1-en-2-yl)-1-tosyl-3-oxa-1-azaspiro[4.5]decan-2-one (-)-(24)



Compound (-)-**24** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:3, 24h, 40 °C) and isolated as white solid (yield 63%) after flash chromatography (Hex/EtOAc 3:1).

M.p. 160-164 °C (decomp.)

IR: 3358, 3261, 2959, 2922, 1785, 1188, 1168, 1084, 667, 562, 545 cm^{-1}

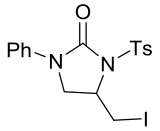
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 5.46 (dd, *J* = 13.6, 4.1 Hz, 1H), 5.17 (s, 1H), 5.01 (s, 1H), 4.48 (d, *J* = 8.3 Hz, 1H), 4.31 (d, *J* = 8.7 Hz, 1H), 3.03 (td, *J* = 13.8, 3.2 Hz, 1H), 2.93 – 2.82 (m, 1H), 2.46 (s, 3H), 2.33 – 1.99 (m, 4H), 1.83 (s, 3H), 1.71 – 1.56 (m, 1H). [1]

^{3}C NMR (300 MHz, $CDCl_3$) δ 152.0 (s), 145.6 (s), 143.1 (s), 135.1 (s), 129.7 (d), 129.2 (d), 112.7 (t), 71.5 (t), 70.0 (s), 40.5 (d), 39.3 (t), 34.22 (d), 30.5 (t), 24.6 (t), 22.5 (q), 21.7 (q).

MS: (ESI) *m/z* 498,23 $[M]^+$.

$[\alpha]^{D}_{20}$: -17° (c: 0.1 in $CHCl_3$)

4-(Iodomethyl)-1-phenyl-3-tosylimidazolidin-2-one (26a)



Compound **26a** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:1, 30h, rt) and isolated as pale yellow solid (yield 54%) after flash chromatography (Hex/EtOAc 2.5:1).

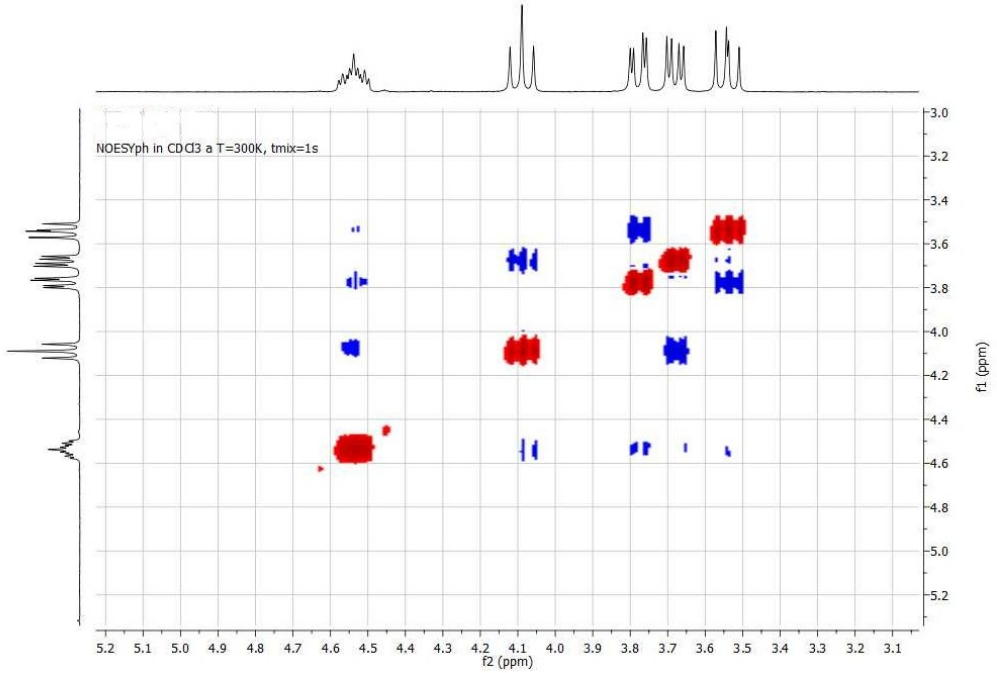
M.p. 148-149 °C

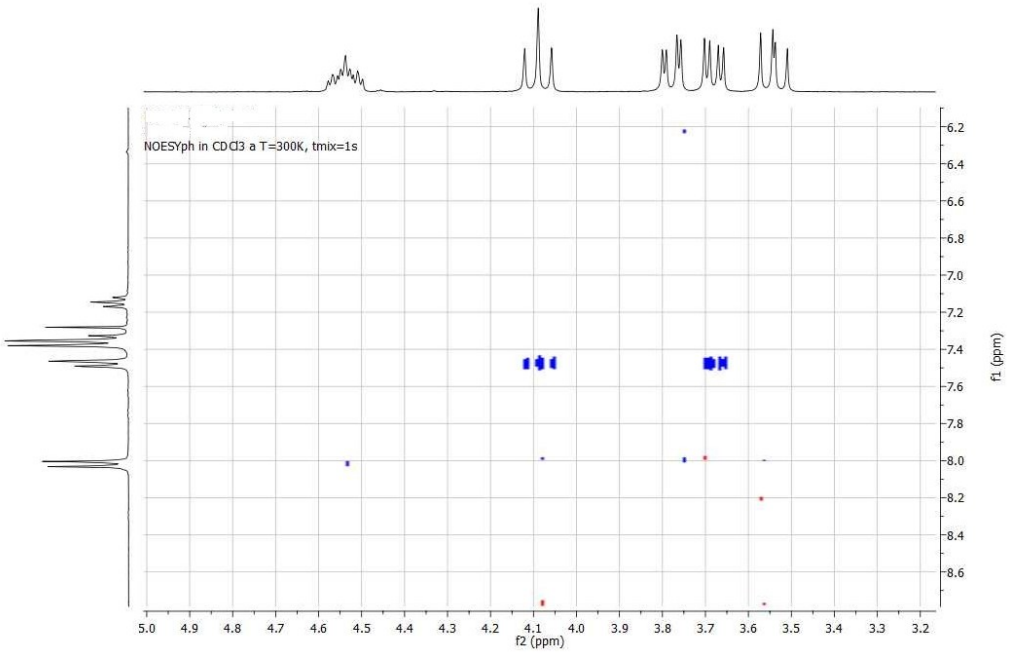
IR: 2958, 1716, 1599, 1504, 1359, 1170, 1131, 751, 666, 592, 554 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.43 (m, 2H), 7.35 (t, *J* = 8.0 Hz, 4H), 7.14 (t, *J* = 7.4 Hz, 1H), 4.54 (tt, *J* = 8.8, 3.2 Hz, 1H), 4.09 (t, *J* = 9.4 Hz, 1H), 3.78 (dd, *J* = 10.2, 2.7 Hz, 1H), 3.68 (dd, *J* = 9.6, 3.7 Hz, 1H), 3.54 (dd, *J* = 10.2, 8.4 Hz, 1H). 7.54 – 7.44 (m, 2H), 7.41 – 7.32 (m, 4H), 7.14 (t, *J* = 7.4 Hz, 1H), 4.72 – 4.41 (m, 1H), 4.09 (t, *J* = 9.4 Hz, 1H), 3.73 (ddd, *J* = 29.8, 9.9, 3.2 Hz, 1H), 3.54 (dd, *J* = 10.2, 8.4 Hz, 1H), 2.46 (s, 3H).

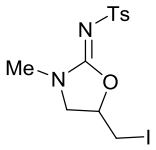
^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1 (s), 145.2 (s), 137.9 (s), 135.6 (s), 129.7 (d), 129.1 (d), 128.5 (d), 124.7 (d), 118.9 (d), 52.9 (d), 49.6 (t), 21.7 (q), 9.3 (t).

MS: (ESI) m/z 479.20 [$M+Na^+$]


NOESYph in CDCl3 a T=300K, tmix=1s
f2 (ppm)
f1 (ppm)


NOESYph in CDCl3 a T=300K, tmix=1s
f2 (ppm)
f1 (ppm)

5-(Iodomethyl)-3-methyl-2-tosylimino-oxazolidine (26b)



Compound **26b** was prepared according to the general procedure (GP16) (H_2O/DMSO 2:1, 30h, rt) and isolated as white solid (yield 52%) after flash chromatography (Hex/EtOAc 1:1).

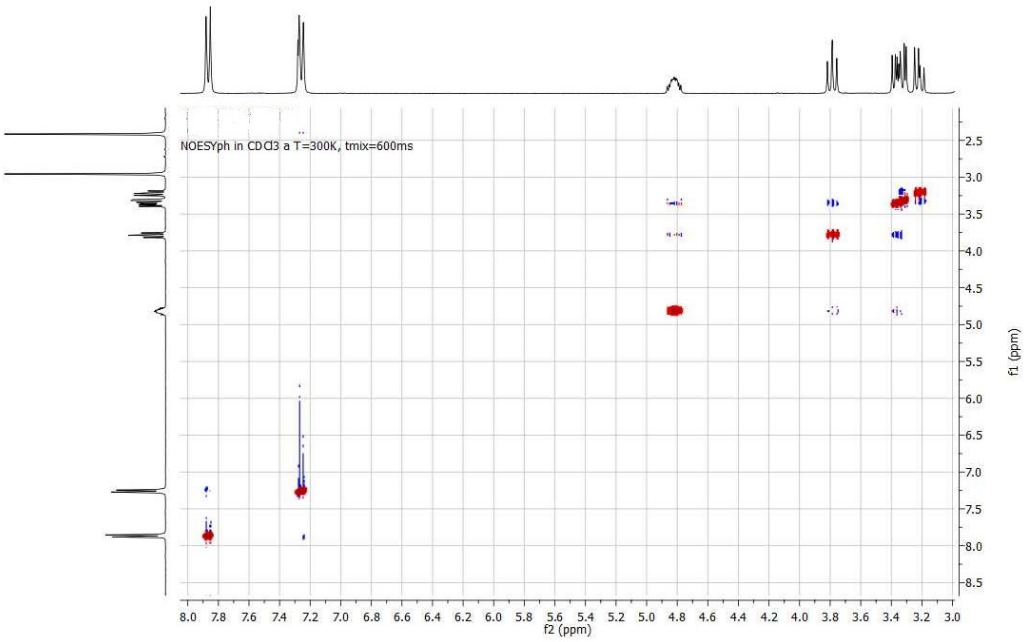
M.p. 120-121 °C

IR: 2920, 1728, 1358, 1172, 1140, 666, 590 cm^{-1}

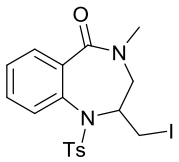
^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 5.00 – 4.55 (m, 1H), 3.79 (t, J = 9.2 Hz, 1H), 3.37 – 3.22 (m, 3H), 2.96 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (s), 142.8 (s), 140.3 (s), 129.4 (d), 127.6 (d), 77.1 (d), 53.5 (t), 32.1 (q), 21.9 (q), 5.2 (t).

MS: (ESI) m/z 417.22 [M+Na^+]



2-(Iodomethyl)-4-methyl-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (28a)



Compound **28a** was prepared according to the general procedure (GP16) (H_2O/DMSO 1.5:1, 20h, 60 °C) and isolated as white solid (yield 71%) after flash chromatography (Hex/EtOAc 1.5:1).

M.p. 156-157 °C

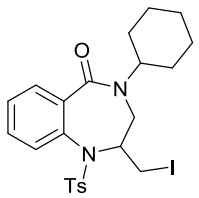
IR: 3074, 1670, 1382, 1157, 1145, 1049, 712, 667 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.2 Hz, 1H), 7.60 – 7.38 (m, 5H), 7.27 (d, *J* = 7.7 Hz, 2H), 4.72 – 4.33 (m, 1H), 3.75 – 3.45 (m, 2H), 3.28 – 2.93 (m, 2H), 2.62 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5 (s), 144.1 (s), 135.4 (s), 134.5 (s), 133.6 (d), 132.3 (s), 131.9 (d), 130.1 (d), 129.9 (d), 129.5 (d), 127.2 (d), 61.6 (d), 52.8 (t), 34.2 (q), 21.6 (q), 4.0 (t).

MS: (ESI) *m/z* 471,22 [M+Na^+]

4-Cyclohexyl-2-(iodomethyl)-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (28b)



Compound **28b** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:5, 30h, 50 °C) and isolated as white solid (yield 68%) after flash chromatography (Hex/EtOAc 7:3).

M.p. 158-159 °C

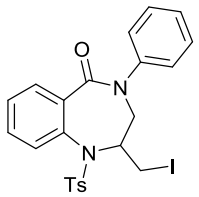
IR = 2924, 1640, 1347, 1157, 1139, 1055, 710, 662 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8 Hz, 1H), 7.47 – 7.38 (m, 5H), 7.17 (d, *J* = 8 Hz, 2H), 4.16 - 4.09 (m, 1H), 3.84 – 3.78 (m, 1H), 3.69 (dd, *J* = 15.5Hz, 4.5Hz, 1H), 3.53 (dd, *J* = 9.9 Hz, 3.7 Hz, 1H), 2.97 (t, *J* = 10.1 Hz, 1H), 2.73 (dd, *J* = 15.4, 11.9 Hz, 1H), 2.34 (s, 3H), 1.74 – 0.81 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5 (s), 144.2 (s), 135.7 (s), 135.2 (s), 132.9 (d), 132.4 (s), 131.6 (d), 130.5 (d), 129.7 (d), 129.3 (d), 127.8 (d), 64.1 (d), 53.0 (d), 45.6 (t), 30.5 (t), 30.2 (t), 25.7 (t), 25.4 (t), 25.3 (t), 21.6 (q), 4.1 (t).

MS: (ESI) *m/z* 561.45 [$M+Na^+$]

2-(Iodomethyl)-4-phenyl-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (28c)



Compound **28c** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:4, 30h, 50 °C) and isolated as white solid (yield 63%) after flash chromatography (Hex/EtOAc 4:1).

M.p. 87–88 °C

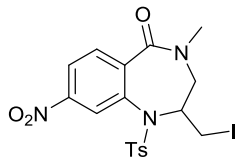
IR = 1653, 1398, 1350, 1170, 1087, 1050, 743, 717 cm^{-1}

^{1}H NMR (400MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.4 Hz, 1H), 7.55 – 7.42 (m, 5H), 7.21 –7.14 (m, 5H), 6.59 (d, *J* = 7.5Hz, 2H), 4.46 – 4.40 (m, 1H), 4.02 (dd, *J* = 15.1, 4.3Hz, 1H), 3.60 – 3.35 (m, 2H), 3.11 (t, *J* = 9.8Hz, 1H), 2.33 (s, 3H).

^{13}C NMR (101MHz, $CDCl_3$): δ 157.3 (s), 144.3 (s), 141.4 (s), 135.9 (s), 134.8 (s), 133.4 (d), 132.5 (s), 132.1 (d), 130.5 (d), 130.1 (d), 129.5 (d), 129.0 (d), 127.7 (d), 126.9 (d), 125.4 (d), 62.1 (d), 54.3 (t), 21.6 (q), 4.2 (t).

MS: (ESI) *m/z* 555.23 [$M+Na^+$]

2-(Iodomethyl)-4-methyl-8-nitro-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (28d)



Compound **28d** was prepared according to the general procedure (GP16) (H_2O/DMSO 2:1, 24h, 60 °C) and isolated as pale yellow solid (yield 74%) after flash chromatography (Hex/EtOAc 1:1).

M.p. 85-86 °C

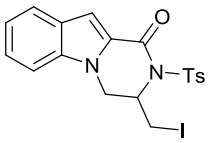
IR: 2921, 1654, 1334, 1155, 1111, 709, 666, 583, 571 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.1 Hz, 1H), 8.30 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.22 (m, 2H), 4.66 – 4.28 (m, 1H), 3.66 – 3.48 (m, 2H), 3.28 – 3.07 (m, 2H), 2.64 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8 (s), 140.1 (s), 134.7 (s), 133.8 (s), 131.3 (d), 130.2 (d), 129.0 (d), 127.2 (d), 124.0 (d), 61.3 (d), 52.8 (t), 34.4 (q), 21.6 (q), 4.1 (t).

MS: (ESI) *m/z* 538.43[M+Na^+]

3-(Iodomethyl)-2-tosyl-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one (29)



Compound **29** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:5, 6h, rt) and isolated as white solid (yield 67%) after flash chromatography (Hex/EtOAc 4:1).

M.p. 173-174 °C

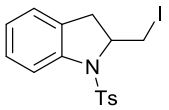
IR: 3435, 2922, 1690, 1536, 1346, 1163, 742, 715, 556 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.33 (m, 5H), 7.26 – 7.13 (m, 1H), 5.37 – 5.25 (m, 1H), 5.13 (d, *J* = 13.2 Hz, 1H), 4.33 (dd, *J* = 12.8, 3.0 Hz, 1H), 3.62 – 3.49 (m, 1H), 3.17 (dd, *J* = 11.6, 10.3 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3 (s), 145.6 (s), 137.3 (s), 135.8 (s), 129.6 (d), 129.1 (d), 127.4 (s), 126.5 (d), 126.1 (s), 123.2 (d), 121.6 (d), 110.1 (d), 56.9 (d), 42.9 (t), 21.7 (q), 2.8 (t).

MS: (ESI) *m/z* 481.25 [M^+], 503.38 [$M+Na^+$]

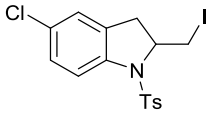
2-(Iodomethyl)-1-tosylindoline (30a)



Compound **10a** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:1, 24h, 60 °C) and isolated as pale yellow solid (yield 58%) after flash chromatography (Hex/EtOAc 10:1).

The data are in good agreement with those reported in the literature.[gg]

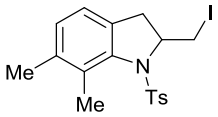
5-Chloro-2-(iodomethyl)-1-tosylindoline (30b)



Compound **10b** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:1.2, 20h, 40 °C) and isolated as white solid (yield 62%) after flash chromatography (Hex/EtOAc 10:1).

The data are in good agreement with those reported in the literature.[gg]

2-(Iodomethyl)-6,7-dimethyl-1-tosylindoline (30c)



Compound **30c** was prepared according to the general procedure (GP16) (H_2O/DMSO 1:3, 20h, 60 °C) and isolated as pale yellow solid (yield 51%) after flash chromatography (Hex/EtOAc 12:1).

The data are in good agreement with those reported in the literature.[ee]

[gg] G. Liu, Y. Li, *J. Org. Chem.,* 2014, **79**, 10094-10109

X-Ray Cristallography (Dr. Leonardo Lo Presti)

Single crystal X-ray diffraction analysis of the compound 22f and 24

Single-crystal X-ray diffraction experiments were carried out on a Bruker AXS three-circle diffractometer equipped with an Apex II CCD area detector. Data were collected using graphite-monochromated Mo Kα radiation (λ=0.71073 Å) at a nominal X-rays power of 50 kV x 30 mA. A 100% complete full sphere of reflections was recorded up to a maximum resolution of 0.77 Å, resulting in 3578 (compound **22f**) and 4460 (compound **24**) independent structure factor amplitudes. The latter were reduced with the SAINT+ software[hh] and corrected for absorption using the empirical procedure implemented in SADABS.[ii] The structures were solved by either iterative charge-flipping methods implemented in SUPERFLIP[jj] (compound **22f**) or by direct methods (SIR92).[kk] Structure refinements were carried out in the independent atom approximation with the least squares algorithm implemented in shelxl.[ll] Molecular drawings were plotted with Diamond 3.0k (©1997–2014 Crystal Impact GbR, Bonn, Germany).

X-ray-quality crystals of the compound **22f** (prismatic habit, colorless) were grown by slow evaporation (~ 10 hrs) from a 1:1 mixture of hexane and DCM at room temperature. The specimen used for the X-ray diffraction experiment was cut from a larger agglomerate and polished by

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[hh] Bruker AXS Inc., SAINT+, Madison, Wisconsin, USA, **2012**.

[ii] Bruker AXS Inc., SADABS, Madison, Wisconsin, USA, **2001**.

[jj] L. Palatinus, G. Chapuis, *J. Appl. Crystallogr*. **2007**, 40, 786.

[kk] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, *J. Appl. Crystallogr*. **1993**, 26, 343

[ll] G. M. Sheldrick, *Acta Crystallogr*. **2015**, 71, 3.

mechanical ablation in a drop of perfluorinated oil. It showed pleochroism under polarized light (from colourless to dark grey). **22f** is chiral and crystallizes in the monoclinic centric space group $P2_1/n$ as a racemate, with one molecule per asymmetric unit and absolute configurations (*S,S*) or (*R,R*). The oxazolidin-2-one ring is slightly distorted toward a half-chair conformation. Unit cell (Å, deg, Å^3), as estimated from 9987 intense reflections with $4.7 \leq 2\theta \leq 56.2$ deg: a = 7.8801(2), b = 17.1890(5), c = 11.5884(3), β = 96.156(1), V = 1560.6(1).

X-ray quality crystals (prismatic habit, colorless) were grown by slow evaporation (~ 6 hrs) from a 1:1 hexane:DCM mixture at room temperature. The sample chosen for the X-ray analysis was cut from a larger agglomerate and polished by mechanical ablation in a drop of perfluorinated oil. It showed pleochroism under polarized light (from colourless to dark grey). The compound is chiral and crystallizes in the orthorhombic acentric space group $P2_12_12_1$ as a pure enantiomer, with one molecule per asymmetric unit. The presence of sulphur and iodine anomalous scatterers allow to secure the absolute molecular configuration, with a Flack parameter[mm] as low as 0.02(2) by classical fit to all intensities. The saturated six-membred ring assumes an almost perfect chair conformation, while the oxazolidin-2-one ring, analogously to compound **22f**, adopts a slightly distorted half-chair conformation. Unit cell (Å, Å^3), as estimated from 8060 intense reflections with $5.3 \leq 2\theta \leq 47.2$ deg: a = 8.1577(2), b = 11.8874(2), c = 20.0540(4), V = 1944.7(1).

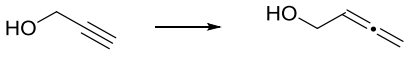
[mm] H. D. Flack., *Acta Crystallogr.* **1983**, A39, 876

Hydroamination

General procedure for the CRABBÉ Homologation[nn] (GP17)

Substrate (1.0 eq), CuBr (0.70 eq) and $(CH_2O)_n$ (2.0 eq) were suspended in 1,4-dioxane (0.1 M) at rt. The mixture was stirred for 30 min until Cy_2NH (2.0 eq) was added. After strring at rt for 1 h the reaction mixture was refluxed at 120 °C for 18 h. Then the reaction mixture was cooled to 0 °C and quenched by the addition of aq. HCl (8 mL/mmol, 2.0 M). The aqueous phase was extracted with AcOEt (3 × 10 mL/mmol) and the organic phases were combined. They were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

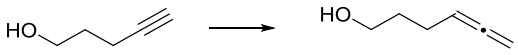
Synthesis of buta-2,3-dien-1-ol



Buta-2,3-dien-1-ol was prepared according to the general procedure (GP17).

The data are in good agreement with those reported in the literature.[oo]

Synthesis of hexa-4,5-dien-1-ol (37c)



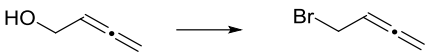
Hexa-4,5-dien-1-ol was prepared according to the general procedure (GP17).

[nn] (a) P. Crabbé, D. André, H. Fillion, *Tetrahedron Lett.* **1979**, 20, 893-896. (b) P. Crabbé, H. Fillion, D. André, J.L. Luche, *J. Chem. Soc., Chem. Commun.* **1979,** 859. (c) S. Searles, Y. Li, B. Nassim, M.T. R. Lopes, P.T. Tran, P. Crabbé, J. *Chem. Soc., Perkin Trans.* 1 **1984**, 747-751. (d) P. Crabbé, B. Nassim, M.T. Robert-Lopes, *Org. Synth.* **1985,** 63, 203-205.

[oo] W. J. Bailey, C. R. Pfeifer, *J. Org. Chem.* **1955**, 20, 1337-1341

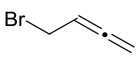
The data are in good agreement with those reported in the literature.[pp]

Synthesis of 4-bromobuta-1,2-diene



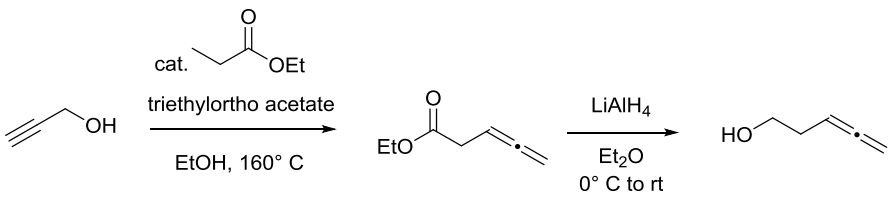
To a cooled solution of PBr_3 (1.9 mL, 20 mmol, 0.4 eq) in Et_2O (33 mL), a mixture of buta-2,3-dien-1-ol (3.51 g, 50 mmol, 1 eq) and pyridine (2.02 mL, 25 mmol, 0.5 eq) was added *via* dropping funnel. After the complete addition, the reaction mixture was stirred at room temperature and monitored by TLC. After consumption of the starting material, distilled water was added (20 mL). The organic layer was extracted with Et_2O (3 x 20 mL), and the extract was washed with brine, dried over $MgSO_4$ and filtered. The solvent was distilled off under atmospheric pressure. The residue was distilled under reduced pressure (60-62° C/ 110 mmHg) to afford 4-bromobuta-1,2-diene (2.96 g, 45%) as a light-brown oil.

4-bromobuta-1,2-diene



The data are in good agreement with those reported in the literature.[qq]

Synthesis of penta-3,4-dien-1-ol



A solution of propargylic alcohol (34 mL, 0.29 mol, 0.5 eq) in triethylortho acetate (111 mL, 0.61 mol, 1.05 eq) was heated to 100° C. Proprionic acid

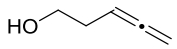
[pp] B. M. Trost, A. B. Pinkerton, M. Seidel, *J. Am. Chem. Soc.* **2001,** 123, 12466-12476.

[qq] M. Meguro, Y. Yamamoto, *J. Org. Chem*. **1999**, 64, 694-695.

(1.73 mL, 0.023 mol, 4 mol%) was added dropwise. The mixture was heated to 160° C and EtOH was distilled off. After 1 h another aliquot of proprionic acid was added. After the distillation ended another aliquot of propionic acid was added. Upon completion the mixture was quenched with aq. HCl (2M, 80 mL) and the aqueous phase was washed with Et_2O (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and volatiles were removed in vacuo. The product (32.76 g, 0.26 mol, 87%) was obtained as yellow oil and used without any further purification.

To a solution of $LiAlH_4$ (4.74 g, 0.13 mol, 1.05 eq) in Et_2O (100 mL), the compound ethyl penta-3,4-dienoate (15 g, 0.12 mol, 1 eq) dissolved in Et_2O (50 mL) was added dropwise at 0° C. The reaction was allowed to warm to room temperature and stirred for 2 h. After cooling to 0° C the mixture was quenched with H_2O (37 mL). An aqueous solution of NaOH (10% p/V, 37 mL) was added and the mixture was stirred at room temperature until discoloration. After addition of H_2O (37 mL), the mixture was dried over $MgSO_4$ and then filtered. Purification by fractioned distillation (25 mbar) gave the product (4.8 g, 0.06 mol, 47%, bp. 62° C) as a colorless liquid.

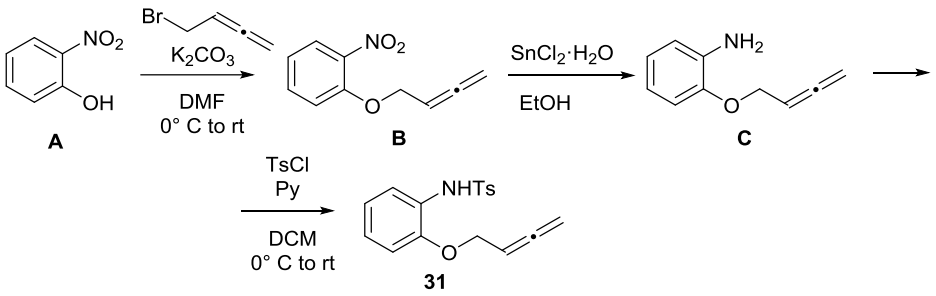
Penta-3,4-dien-1-ol



The data are in good agreement with those reported in the literature.[rr]

[rr] (a) P. M. Bertrand, J.P. Dulcere, G. Gil, J. Grimaldi, P. Sylvestre-Panthet, *Tetrahedron Lett.* **1976**, 37, 3305-3308; (b) B. M. Trost, A. B. Pinkerton, M. Seidel, *J. Am. Chem. Soc.* **2001**, 123, 12466-12476.

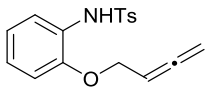
Synthesis of *N*-(2-(Buta-2,3-dien-1-yloxy)phenyl)-4-methylbenzenesulfonamide (31)



2-Nitrophenol **A** (1.39 g, 10.0 mmol, 1 eq) and K_2CO_3 (276 mg, 20.0 mmol, 2 eq) were suspended in DMF (0.1 M) and cooled to 0 °C. 4-Bromobuta-1,2-diene (1.46 g, 11.0 mmol, 1.1 eq) was added dropwise and the resulting mixture was stirred at 0 °C for 30 min. It was then stirred at rt for 12 h. The reaction mixture was cooled to 0° C and then filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography (Hex/AcOEt 10:1) to give the phenyl ether as a yellowish gum (1.57 g, 8.21 mmol, 82%). 1-(Buta-2,3-dien-1-yloxy)-2-nitrobenzene **B** (1.55 g, 8.11 mmol, 1 eq) and $SnCl_2 \cdot H_2O$ (9.16 g, 40.6 mmol, 5 eq) were dissolved in EtOH (40.6 mL, 0.2 M) at rt. The reaction mixture was then heated at 50 °C for 12 h. After cooling to rt it was concentrated under reduced pressure and the residue was rinsed with AcOEt (50 mL). It was treated with saturated solution of $NaHCO_3$ (40 mL), the resulting white slurry was filtered over celite pad and the residue rinsed with AcOEt (200 mL). After removal of the solvent and purification by flash column chromatography (Hex/AcOEt 10:1 - 5:1) the free aniline **C** (1.14 g, 7.06 mmol, 87%) was obtained as a yellowish gum. It was then dissolved together with pyridine (1.26 mL, 1.23 g, 15.5 mmol, 2.2 eq) in DCM (50 mL) and treated dropwise with a solution of TsCl (1.48 g, 7.77 mmol, 1.1 eq) in DCM (20.6 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 12 h. After that, it was quenched by the addition of H_2O (30 mL). After separation of the two phases, the aqueous

phase was extracted with DCM (3 × 20 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (Hex/AcOEt 5:1) to yield the product **31** (2.03 g, 6.43 mmol, 91%) as a pale-white solid.

N-(2-(buta-2,3-dien-1-yloxy)phenyl)-4-methylbenzenesulfonamide (31)



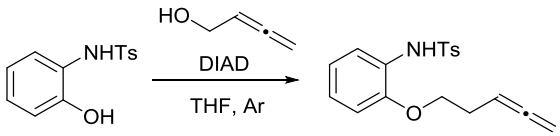
M.p. 105 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (t, *J* = 7.9 Hz, 2H), 7.57 – 7.50 (m, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.04 – 6.97 (m, 2H), 6.94 – 6.88 (m, 1H), 6.76 – 6.71 (m, 1H), 5.21 – 5.04 (m, 1H), 4.96 – 4.79 (m, 2H), 4.39 – 4.27 (m, 2H), 2.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.5 (s), 148.3 (s), 143.7 (s), 136.4 (s), 129.4 (d), 127.4 (d), 126.5 (s), 125.3 (d), 121.5 (d), 112.1 (d), 86.6 (t), 66.3 (t), 21.6 (q).

HR-MS ($C_{17}H_{17}NO_3S$); $[M+H]^+$, pos. APCI: calcd: 316.1007, found: 316.1008.

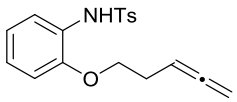
Synthesis of 4-methyl-N-(2-(penta-3,4-dien-1-yloxy)phenyl)benzenesulfonamide (33)



A solution of diisopropyl azodicarboxylate (1,12 mL, 5.7 mmol,1.5 eq) in THF (8 mL) was added dropwise to a solution of triphenyl phospine (1500 mg, 5.7 mmol, 1.5 eq), compound *N*-tosyl-aminophenol (1000 mg, 3.8 mmol, 1 eq) and buta-2,3-dien-1-ol (479 mg, 5.7 mmol, 1.5 eq) at 0° C and under

argon. The reaction mixture was allowed to warm slowly to room temperature and stirred overnight. Once the reaction was completed, it was concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hex/AcOEt 9:1) to yield the product **33** (637 mg, 1.94 mmol, 51 %) as a white solid.

4-methyl-N-(2-(penta-3,4-dien-1-yloxy)phenyl)benzenesulfonamide (33)

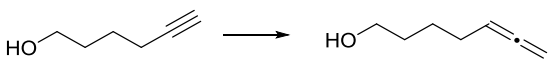


M.p. 76° C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.24 – 7.17 (m, 1H), 7.05 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.75 – 6.63 (m, 1H), 6.59 (s, 1H), 6.40 – 6.28 (m, 1H), 5.06 (p, *J* = 6.8 Hz, 1H), 4.70 (dt, *J* = 6.5, 3.1 Hz, 2H), 4.23 – 3.03 (overlapping, 2H), 2.44 (s, 3H), 2.19 – 2.05 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.1, 155.2, 144.3, 133.8, 130.1, 129.6, 128.2, 127.3, 125.8, 120.5, 117.6, 86.5, 75.8, 51.5, 27.5, 21.7.

Synthesis of hepta-5,6-dien-1-ol (37e)

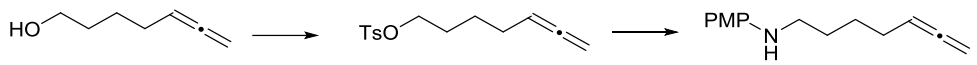


Hepta-5,6-dien-1-ol was prepared according to the general procedure GP17.

The data are in good agreement with those reported in the literature.[ss]

[ss] M. Tomoya, *Beilstein J Org Chemistry* **2011**, 7, 578-581.

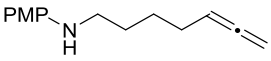
Synthesis of *N*-(hepta-5,6-dien-1-yl)-4-methoxyaniline (35)



TsCl (2.36 g, 12.4 mmol, 1.05 eq) was dissolved in DCM (25 mL, 0.5 M) and the resulting solution was cooled to 0° C. Hepta-5,6-dien-1-ol (1.33 g, 11.76 mmol, 1 eq) and TEA (3.28 Ml, 23.5 mmol, 2 eq) were added subsequently and the resulting mixture was allowed to warm to room temperature overnight. It was quenched by the addition of H_2O (10 mL), the layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $NaSO_4$ and the solvent was removed under reduced pressure. The crude product was used in the following step without any further purification.

Hepta-5,6-dien-1-yl 4-methylbenzenesulfonate was dissolved together with *p*-anisidine (2.03 mL, 17.64 mmol, 1.5 eq) and KI (196 mg, 1.18 mmol, 10 mol%) in DMF (24 mL, 0.5 M). K_2CO_3 (4.63 g, 33.53 mmol, 3 eq) was then added and the reaction mixture was stirred at 90° C for 2 h. After cooling to rt, the resulting mixture was quenched by the addition of saturated solution of NH_4Cl (10 mL). It was then extracted wit AcOEt (3 x 40 mL). The organic phases were washed with H_2O (50 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel (Hex/AcOEt 4:1) to yield the product **35** (1.19 g, 5.52 mmol, 47 %) as orange oil.

***N*-(hepta-5,6-dien-1-yl)-4-methoxyaniline (35)**



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (m, 2H), 6.59 (m, 2H), 5.02 (tt, J = 6.8, 6.8 Hz, 1H), 4.67 (tt, J = 6.5, 3.2 Hz, 2H), 3.75 (s, 3H), 6.59 (s, 1H), 3.49 (br

s, 1H), 3.08 (t, *J* = 7.0 Hz, 2H), 2.09 – 2.02 (m, 2H), 1.62 (m, 2H), 1.58 – 1.49 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 152.2, 142.8, 115.1, 114.2, 89.8, 75.0, 56.0, 45.0, 29.2, 28.1, 26.7.

HR-MS ($C_{17}H_{17}NO_3S$); $[M+H]^+$, pos. APCI: calcd: 218.15394, found: 218.15410.

General procedure for the racemic intramolecular hydroamination (GP18)

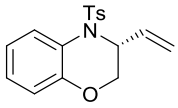
A 20 mL screw-cap SCHLENK tube was flame-dried under vacuum, cooled to rt and backfilled with argon using a standard SCHLENK line apparatus. Then, the tube was charged with $[\{Rh(cod)Cl\}_2]$ (2.96 mg, 0.006 mmol, 2.00 mol%) and *rac*-OMe-J688 (7.5 mg, 0.015 mmol, 5.00 mol%). It was put under vacuum and backfilled with argon. DCE (1.5 mL, 0.2 M) was added and the catalyst solution was preformed by stirring at rt for 10 min. Then, the substrate (0.3 mmol, 1 eq) was added under a flow of argon. The tube was sealed by a screw-cap and the containing reaction mixture was stirred at 80 °C for 12 h. After cooling to rt, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography.

General procedure for the asymmetric intramolecular hydroamination (GP19)

A 20 mL screw-cap SCHLENK tube was flame-dried under vacuum, cooled to rt and backfilled with argon using a standard SCHLENK line apparatus. Then, the tube was charged with $[\{Rh(cod)Cl\}_2]$ (2.96 mg, 0.006 mmol, 2.00 mol%) and *(S)*-OMe-J688 (7.5 mg, 0.015 mmol, 5.00 mol%) and PPTS (7.54 mg, 0.03 mmol, 10.0 mol%) was added. It was put under vacuum shortly and backfilled with argon. DCE (1.5 mL, 0.2 M) was added and the catalyst solution was preformed by stirring at rt for 10 min. Then,

the substrate (0.3 mmol, 1.00 eq) was added under a flow of argon. The tube was sealed by a screw-cap and the containing reaction mixture was stirred 80 °C for 12 h. After cooling to rt, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography.

(*R*)-4-Tosyl-3-vinyl-3,4-dihydro-2H[*b*][1,4]oxazine (33)

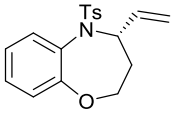


Compound **33** was prepared according to the general procedure (GP19) and isolated as a colourless gum (yield 76%, 81% ee) after flash column chromatography (Hex/AcOEt 10:1 → 2:1).

HPLC (Chiracel AD-3, l = 218 nm, *n*-Heptane/EtOH = 80:20, 0.5 mL/min): tR = 8.5 min (minor), 9.1 min (major).

The data are in good agreement with those reported in the literature.[tt]

(*S)*-5-tosyl-4-vinyl-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (34)



Compound **34** was prepared according to the general procedure (GP19) and isolated as a white solid (yield 38%, 84% ee) after flash column chromatography (Hex/AcOEt 10:1 → 2:1).

M.p. 86° C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.50 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.23 – 7.16 (m, 3H), 7.08 (td, *J* = 7.7, 1.6 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.86 – 5.66 (m, 1H), 5.16 – 5.01 (m, 2H), 4.20 (dd, *J* = 9.8,

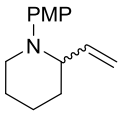
[tt] K. Wen, Z. Wu, B. Huang, Z. Ling, I. D. Gridnev, W. Zhang*, Org. Lett.,* **2018,** 206, 1608-1612

4.7 Hz, 1H), 4.06 (dd, *J* = 12.3, 6.0 Hz, 1H), 3.58 – 3.39 (m, 1H), 2.39 (d, *J* = 3.3 Hz, 3H), 1.92 – 1.79 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 137.9, 137.3, 130.7, 129.5, 128.9, 127.5, 124.1, 122.8, 115.8, 80.5, 47.5, 33.8, 21.6.

HPLC (Chiracel AD-3, l = 218 nm, *n*-Heptane/EtOH = 95:5, 0.5 mL/min): tR = 19.8 min (minor), 24.2 min (major).

1-(4-methoxyphenyl)-2-vinylpiperidine (36)



Compound **36** was prepared according to the general procedure (GP19, even if using 5 mol% (*R,R*)-Me-ferrocelane as ligand and 10 mol% TFA as additive) and isolated as a white solid (yield 51%, 60% ee) after flash column chromatography (Hex/AcOEt 20:1 → 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (m, 2H), 6.80 (m, 2H), 5.74 (m, 1H), 5.01 – 4.96 (m, 2H), 3.83 (m, 1H), 3.76 (s, 3H), 3.13 – 3.07 (m, 1H), 2.99 – 2.93 (m, 1H), 1.89 – 1.82 (m, 1H), 1.77 – 1.65 (m, 4H), 1.56 – 1.47 (m, 1H),

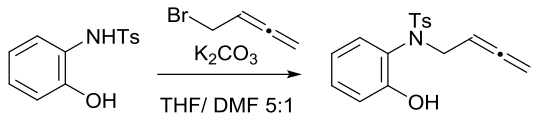
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 145.9, 139. 4, 121.9, 115.7, 114.2, 61.6, 55.6 50.8 32.3, 26.3 21.8.

HPLC (OD-3, l = 210 nm, *n*-Heptane/iPrOH = 500:1, 1 mL/min): tR = 7.4 min (minor), 9.9 min (major),

HR-MS ($C_{14}H_{19}NO$); $[M+H]^+$, pos. APCI: calcd: 218.1539, found: 218.1540.

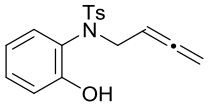
Hydroalkoxylation

Synthesis of *N*-(buta-2,3-dien-1-yl)-*N*-(2-hydroxyphenyl)-4-methylbenzenesulfonamide (37a)



In a two-neck round-bottom flask the compound **37a** (540 mg, 2.95 mmol, 1 eq.) was dissolved in a THF/DMF mixture (5:1, 0.2 M) and then K_2CO_3 (283 mg, 2.05 mmol, 1 eq) was added. The reaction mixture was cooled to 0° C and afterwards, a solution of 4-bromobuta-1,2-diene (300 mg, 2.25 mmol, 1.2 eq) in THF (1 M) was added dropwise over 30 min. Then, the reaction was allowed to warm to room temperature and stirred for 24 h. Once the reaction had occurred as completely as possible, the mixture was filtered under vacuum, rinsed with AcOEt and washed with brine. The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hex/EtOAc 5:1 → 2:1) to afford compound **37a** (530 mg, 1.68 mmol, 82%) as a pale-yellow solid.

N-(buta-2,3-dien-1-yl)-*N*-(2-hydroxyphenyl)-4-methylbenzenesulfonamide (37a)



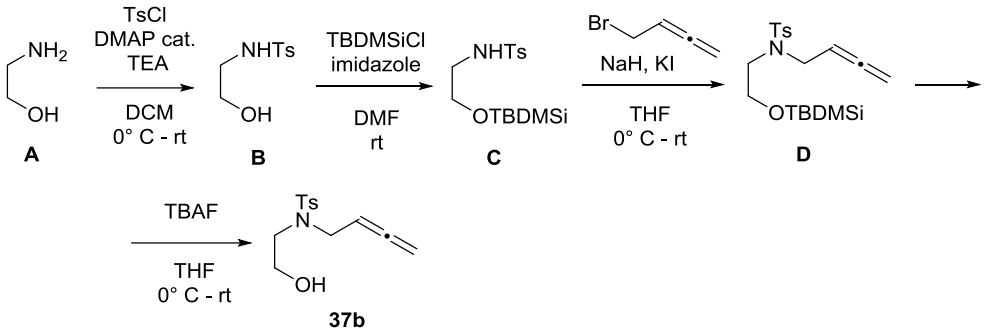
M.p. 97° C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.22 – 7.15 (m, 1H), 7.04 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.69 (td, *J* = 7.8, 1.4 Hz, 1H), 6.54 (s, 1H), 6.38 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.07 (p, *J* = 6.8 Hz, 1H), 4.68 – 4.60 (m, 2H), 4.47 – 3.76 (m, 2H), 2.44 (s, *J* = 10.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 210.0, 155.1, 144.4, 134.0, 130.1, 129.7, 128.3, 127.8, 125.7, 120.4,

HR-MS ($C_{13}H_{17}NO_3S$); $[M-H]^-$, neg. ESI: calcd: 314.0929, found: 314.0856

Synthesis of *N*-(buta-2,3-dien-1-yl)-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (37b)



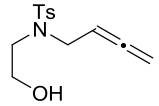
To a solution of aminoalcohol **A** (1.5 gr, 25 mmol, 1 eq), DMAP (305 mg, 2.5 mmol, 0.1 eq) and TEA (7 mL, 50 mmol, 2 eq) in DCM (2 M) at 0 °C, a solution of the tosyl chloride (5.0 gr, 26.2 mmol, 1.05 eq) was added dropwise in DCM (0.8 M) and the resulting mixture was stirred at room temperature overnight. The mixture was washed with water (3 x 50 mL) and brine (1 x 50 mL), then dried over Na_2SO_4, and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex/EtOAc 1:2 → 1:4) to afford the *N*-tosyl-protected aminoalcohol **B** (4.47 gr, 20 mmol, 80%).

A solution of *N*-protected aminoalcohol **B** (20 mmol, 1 eq), *tert*-butyldimethylsilyl chloride (2.29 gr, 20 mmol, 1 eq) and imidazole (1.35 gr, 20 mmol, 1 eq) in DMF (0.2 M) was stirred at room temperature overnight. The reaction was taken up with brine (40 mL), extracted with Et_2O (3 x 40 mL), dried over Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex/EtOAc 2:1) to afford the *O*-(tert-butyldimethylsilyl)-*N*-protected aminoalcohol **C** (5.56 gr, 17.2 mmol, 86%).

In a mixture of sodium hydride (77 mg, 3.21 mmol, 1.5 eq) in THF (11 mL) at 0° C under argon atmosphere, KI was added (374 mg, 2.25 mmol, 1.05 eq) and a solution of the protected aminoalcohol **C** (727 mg 2.14 mmol, 1 eq) in THF (11 mL) was dropped. The reaction mixture was stirred for 30 min. at room temperature, then cooled at 0 °C. A solution of 4-bromobuta-1,2-diene (300 mg, 2.25 mmol, 1.05 eq) in THF (5 mL) was dropped and the mixture was stirred at room temperature overnight. The mixture was concentrated at reduced pressure, washed with water (15 mL), extracted with Et_2O (3 x 60 mL), dried on Na_2SO_4, and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex/EtOAc 4:1) to afford **D** (530 mg, 1.25 mmol, 39%).

A mixture of the **D** (1.25 mmol, 1 eq) and tetrabutylammonium fluoride (1.25 mmol, 1.2 eq) in THF (0.2 M) was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure, water was added (10 mL) and the reaction mixture was extracted with DCM (3 x 20 mL), then dried over Na_2SO_4, and the mixture concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (Hex/EtOAc 4:1) to afford the product **37b** (310 mg, 1.16 mmol, 93%) as a colourless oil.

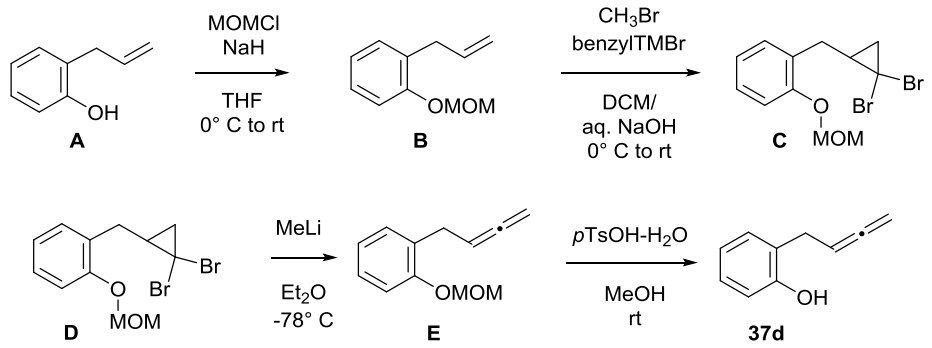
_N_-(buta-2,3-dien-1-yl)-_N_-(2-hydroxyethyl)-4-methylbenzenesulfonamide (37b)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.28 (m, 2H), 5.07 – 4.86 (m, 1H), 4.73 (dt, *J* = 6.6, 2.6 Hz, 2H), 3.90 (dt, *J* = 7.0, 2.6 Hz, 2H), 3.77 (t, *J* = 5.4 Hz, 2H), 3.31 (t, *J* = 5.4 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6 (s), 143.7 (s), 136.7 (s), 129.9 (d), 127.4 (d), 86.3 (d), 76.6 (t), 61.0 (t), 49.8 (t), 48.3 (t), 21.6 (q).

Synthesis of 2-(buta-2,3-dien-1-yl)phenol (37d)



In a two-neck round bottom flask to a solution of 60% NaH (1 g, 25 mmol, 1.5 eq) in DMF (10 ml), 2-allyl phenol **A** (2.14 g, 16 mmol, 1 eq) was added at 0° C and under argon atmosphere. Then methoxymethyl chloride (1.88 mL, 25 mmol, 1.5 eq.) was added dropwise and the reaction was stirred at 0° C for 30 min and then other 30 min at rt. The reaction was quenched with a saturated solution of $NaHCO_3$ (20 mL) and washed with EtOAc (2 x 40 mL). The collected organic phases were washed with brine (3 x 15 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hex/EtOAc 25:1) to afford compound **B** (2.8 g, 16 mmol, quant. %).

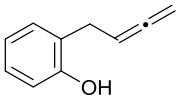
$CHBr_3$ (4.2 mL, 48 mmol, 3 eq) was added dropwise to a mixture of 1-allyl-2-(methoxymethoxy)benzene **C** (2.8 g, 16 mmol,1 eq) and benzyltrimethyl bromide (736 mg, 3.2 mmol, 0.2 eq) in DCM (88 mL) and 10 N NaOH (3 mL). The reaction mixture was stirred at rt for 2 days. The reaction was quenched with ice-cold H_2O (15 mL), afterwards the aqueous layer was extracted with DCM (2 x 15 mL). The combined organic phases were washed with brine (2 x 20 mL) and dried over $MgSO_4$. After removal of the solvent *in vacuo*, the crude product was flushed through a plug of silica gel (7 cm) and washed with EtOAc. The organic layer was washed with 6 N NaOH (10 mL) and concentrated *in vacuo*. The crude product was purified

by flash chromatography on silica gel (Hex/EtOAc 30:1) to afford compound **C** (2.05 g, 5.09 mmol, 37%).

MeLi (1.6 M in Et_2O, mL, 7.08 mmol, 1,2 eq) was added dropwise over 30 min to a solution of 1-((2,2-dibromocyclopropyl)methyl)-2-(methoxymethoxy)benzene (2.05 g, 5.9 mmol, 1 eq) in Et_2O (6 mL) at -78° C. The reaction mixture was stirred for 30 min at -78° C and then the reaction was allowed to warm to rt. The reaction was quenched with H_2O (5 mL) and the aqueous layer was extracted with Et_2O (2 x 20 mL). The collected organic phases were washed with brine until pH = 7, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure, affording the product **D** that was used in the next step without any further purification.

1-(buta-2,3-dien-1-yl)-2-(methoxymethoxy)benzene (1.13 g, 5.9 mmol, 1 eq) and *p*TsOH-H_2O (112 mg, 0.59 mmol, 0.1 eq) were dissolved in MeOH (30 mL). The reaction was stirred at rt for 20 h. The solvent was removed under reduced pressure and the crude product was rinsend wit Et_2O (40 mL), washed with a saturated solution of $NaHCO_3$ (10 mL) and brine (10 mL). The crude product was purified by flash chromatography on silica gel (Hex/EtOAc 30:1 → 10:1) to afford compound **37d** (810 mg, 5.54 mmol, 94%) as a colourless oil.

2-(buta-2,3-dien-1-yl)phenol (37d)

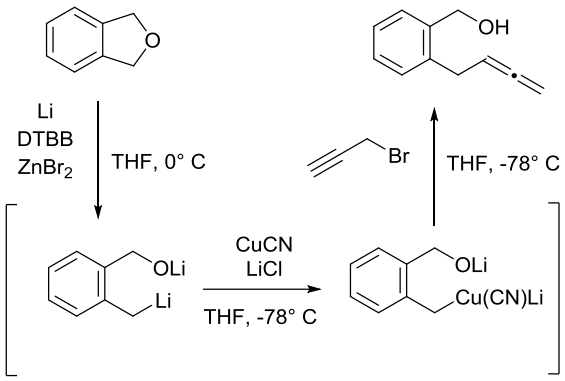


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.05 (m, 2H), 6.94 – 6.84 (m, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.31 (p, *J* = 6.9 Hz, 1H), 4.76 (dt, *J* = 6.4, 3.1 Hz, 2H), 3.40 – 3.30 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2 (s), 130.3(d), 128.1 (d), 125.7 (s), 121.0 (d), 115.8 (d), 88.6 (d), 75.9 (t), 30.3 (t).

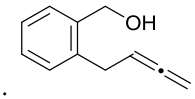
HR-MS ($C_{10}H_{10}O$); $[M-H]^-$, neg. ESI: calcd: 145.0732, found: 145.0658

Synthesis of (2-(buta-2,3-dien-1-yl)phenyl)methanol (37f)



The isochroman (2.4 g, 20 mmol, 1 eq) was added dropwise at 0° C under argon, to a stirred green suspension of lithium powder (350 mg, 100 mmol, 10 eq) and DTBB (530 mg, 2 mmol, 20 mol%) in THF (100 mL). The colour disappeared after the addition, and reappeared after 45 min stirring. The excess of lithium was then filtered off using inert conditions and the resulting solution was added to a solution of zinc bromide (4.5 g, 20 mmol, 1 eq) in THF (50 mL). A solution of CuCN·2LiCl [prepared by dissolving copper(I) cyanide (1.8 g, 20 mmol, 1 eq) and lithium chloride (850 mg, 40 mmol, 2 eq) in THF (10 mL)] was added to the resulting mixture, which was then cooled to −78° C. After 10 min stirring, the corresponding propargylic bromide (22 mmol, 1.05 eq) was added. After 1 h stirring at the same temperature the mixture was hydrolysed with water (100 mL), acidified with 3M HCl (60 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was washed with brine (2 × 80 mL) and dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex/EtOAc 20:1) to afford compound **37f**.

(2-(buta-2,3-dien-1-yl)phenyl)methanol (37f)



The data are in good agreement with those reported in the literature.[uu]

General procedure for the racemic intramolecular hydroalkoxylation (GP20)

A 20 mL screw-cap SCHLENK tube was flame-dried under vacuum, cooled to rt and backfilled with argon using a standard SCHLENK line apparatus. Then, the tube was charged with [{Rh(cod)Cl}$_2$] (2.96 mg, 0.006 mmol, 2.00 mol%) and dppf (8.31 mg, 0.015 mmol, 5.00 mol%). It was put under vacuum and backfilled with argon. DCE (1.5 mL, 0.2 M) was added and the catalyst solution was preformed by stirring at rt for 10 min. Then, the substrate (0.3 mmol, 1 eq) was added under a flow of argon. The tube was sealed by a screw-cap and the containing reaction mixture was stirred either at 40° C (for substrate **38c-38e**), 60°C (for substrate **38d-38f**), and 80 °C (for substrate **38a-38b**) for 12 h. After cooling to rt, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography.

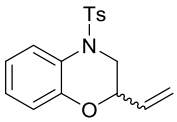
General procedure for the asymmetric intramolecular hydroalkoxylation (GP21)

A 20 mL screw-cap SCHLENK tube was flame-dried under vacuum, cooled to rt and backfilled with argon using a standard SCHLENK line apparatus. Then, the tube was charged with [{Rh(cod)Cl}$_2$] (2.96 mg, 0.006 mmol, 2.00 mol%) and *(S)*-OMe-J688 (7.5 mg, 0.015 mmol, 5.00 mol%) and the suitable additive (0.03 mmol, 10.0 mol%) was added. It was put under vacuum shortly and backfilled with argon. DCE (1.5 mL, 0.2 M) was added

[uu] M. Meguro, Y. Yamamoto, *J. Org. Chem.***1999**, 64 (3), 694-695

and the catalyst solution was preformed by stirring at rt for 10 min. Then, the substrate (0.3 mmol, 1.00 eq) was added under a flow of argon. The tube was sealed by a screw-cap and the containing reaction mixture was stirred either at 40° C (for substrate **38c-38e**), 60°C (for substrate **38d-38f**), and 80 °C (for substrate **38a-38b**) or 12 h. After cooling to rt, the solvent was removed underreduced pressure and the residue was purified by flash column chromatography.

4-tosyl-2-vinyl-3,4-dihydro-2H-benzo[*b*][1,4]oxazine (38a)

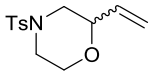


Compound **38a** was prepared according to the general procedure (GP21) in a 0.3 mmol scale, using benzoic acid (10 mol%) as additive. It has been isolated after flash column chromatography (Hex/AcOEt 10:1) as a white solid (yield 86%, 84% ee)

HPLC (LC-3, λ= 234 nm, *n*-Heptane/EtOH = 90:10, 0.5 mL/min, 22°C): tR = 9.9 min (major), 11.1 min (minor).

The data are in good agreement with those reported in the literature.[vv]

4-tosyl-2-vinylmorpholine (38b)



Compound **38b** was prepared according to the general procedure (GP21) in a 0.3 mmol scale, using $HOP(O)(OPh)_2$ (10 mol%) as additive. It has been isolated after flash column chromatography (Hex/AcOEt 1:1.5) as colourless oil (yield 72%,75% ee)

[vv] J. S. Cannon, A. C. Olson, L. E. Overman, N. S. Solomon, *J. Org. Chem*. **2012**, 77, 1961-1973

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.33 (m, 2H), 5.74 (ddd, *J* = 17.4, 10.7, 5.4 Hz, 1H), 5.44 – 5.15 (m, 2H), 4.11 – 4.03 (m, 1H), 3.97 (ddd, *J* = 11.6, 3.4, 1.6 Hz, 1H), 3.74 (td, *J* = 11.5, 2.7 Hz, 1H), 3.67 – 3.59 (m, 1H), 3.58 – 3.50 (m, 1H), 2.54 – 2.36 (m, 4H), 2.14 (dd, *J* = 11.4, 10.2 Hz, 1H).

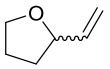
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 134.8, 132.4, 129.9, 128.0, 117.8, 75.8, 65.9, 50.1, 45.5, 21.7.

HPLC (LC-3, λ= 218 nm, Hep/EtOH = 90:10, 0.5 mL/min, 22°C): tR = 9.4 min (major), 10.3 min (minor)

HR-MS ($C_{13}H_{17}NO_3S$); $[M+H]^+$ pos. ESI: calcd: 268.0929, found: 268.1002; $[M+Na]^+$, pos. ESI: calcd: 290.0827, found: 218.0821.

The data are in good agreement with those reported in the literature.[ww]

2-vinyltetrahydrofuran (38c)



Compound **38c** was prepared according to the general procedure (GP21) in a 0.3 mmol scale, using TFA (10 mol%) as additive.

The *ee* has been determined by GC: carrier gas (N_2, 1.2kg /cm^2), column temperature (40 °C), injection temperature (150 °C), detection temperature (150 °C), tR = 19.4 min (minor), tR = 19.6 min (major).

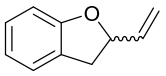
87% ee.

The data are in good agreement with those reported in the literature.[xx]

[ww] J. S. Cannon, A. C. Olson, L. E. Overman, N. S. Solomon, *J. Org. Chem*. **2012**, 77, 1961

[xx] S. Tanaka, T. Seki, M. Kitamura, *Angew Chem, Int Ed* **2009**, 48(47), 8948-8951

2-vinyl-2,3-dihydrobenzofuran (38d)

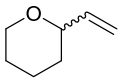


Compound **38d** was prepared according to the general procedure (GP21) in a 0.3 mmol scale, using TFA (10 mol%) as additive. It has been isolated after flash column chromatography (Hex/AcOEt 30:1) as a colourless oil (yield 86%, 84% ee)

HPLC (LC-3, λ = 212 nm, *n*-Heptane/EtOH = 99.5:0.5, 0.5 mL/min, 22°C): tR = 8.3 min (major), 9.3 min (minor).

The data are in good agreement with those reported in the literature.[yy]

2-vinyltetrahydro-2H-pyran (38e)



Compound **38e** was prepared according to the general procedure (GP21) in a 0.3 mmol scale, using TFA (10 mol%) as additive.

The *ee* has been determined by GC: carrier gas (N_2, 1.2kg /cm^2), column temperature (40 °C), injection temperature (150 °C), detection temperature (150 °C), tR = 19.7 min (major), tR = 20.1 min (minor).

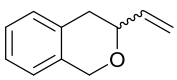
89% ee.

The data are in good agreement with those reported in the literature.[zz]

[yy] M. A. Schafroth, S.M. Rummelt, D. Sarlah, E. M. Carreira*, Org. Lett.,* **2017**, 19 (12), 3235-3238

[zz] (a) P.Audin, A. Doutheau, J. Gore, *Tetrahedron Lett.* **1982**, 23, 4337; (b) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.***2006**, 128 (28), 9066-9073

3-vinylisochromane (38f)



Compound **38f** was prepared according to the general procedure (GP21) in a 0.3 mmol scale, using (*R*)-Binol-phosphoric acid (10 mol%) as additive. It has been isolated after flash column chromatography (Hex/AcOEt 25:1) as colourless oil (yield 84%,79% ee)

HPLC (Chiracel AD-3, λ = 212 nm, *n*-Heptane/*i*Pr = 95:5, 0.5 mL/min, 22°C): tR = 5.3 min (major), 5.8 min (minor).

The data are in good agreement with those reported in the literature.[aaa]

[aaa] L. Chu, C. Ohta, Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.,* **2014** 136 (31), 10834-10837

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