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Organocatalytic Multicomponent Reactions of 1,3-Dicarbonyls for the Synthesis of Enantioenriched Heterocycles

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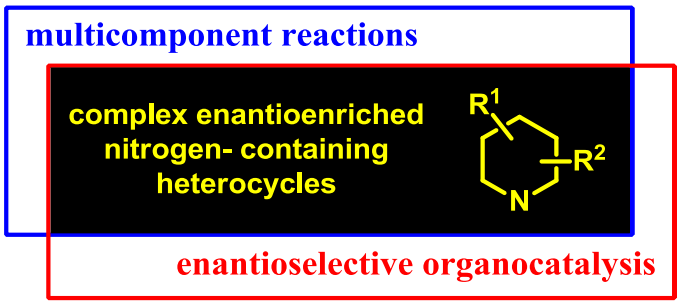


Abstract In this feature article, we present a general perspective of our research program aimed towards the preparation of polycyclic heterocycles by the means of enantioselective organocatalytic multicomponent reactions. Guidelines for reaction design, including the selection of substrates and organocatalysts are discussed. For all transformations, scope and limitations will be presented, along with post-functionalization to afford diversified heterocyclic scaffolds.

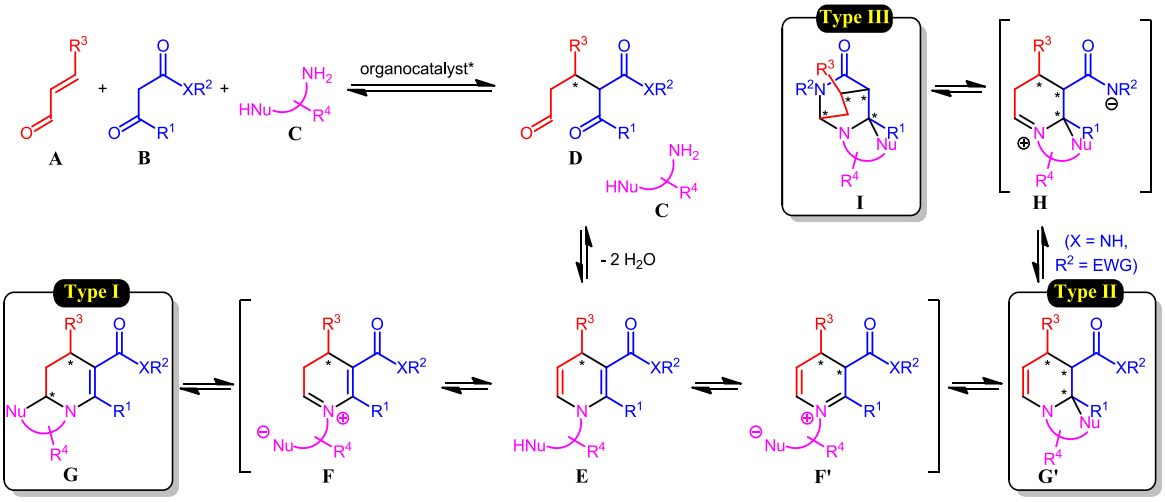
1 Introduction
2 Type I Products: 1,4,5,6-Tetrahydropyridines
3 Type II Products: 1,2,3,4-Tetrahydropyridines
4 Type III Products: Bridged Perhydropyridines
5 Conclusion and Perspective

Key words 1,3-Dicarbonyls - Enantioselectivity - Heterocycles - Michael Addition - Multicomponent Reactions - Organocatalysis

1 Introduction

Heterocycles are key synthetic targets in view of their ubiquitous presence in bioactive molecules.[1] When these molecules bear stereogenic elements, it is of utter importance to control their configuration as the stereochemical information may have a deep influence on their interaction with the biological target. In that prospect, organocatalysis[2] has emerged as a very powerful tool since it allows the stereoselective synthesis of a large variety of heterocyclic compounds with high enantiomeric excesses.[3] Among these heterocycles, polyhydropyridines are both interesting synthetic targets and an inspiration for the development of new patterns of reactivity. Thus, many new strategies were designed following the seminal contributions of Renaud's and Gong's research groups using Brønsted acid catalysis[4] and Hayashi's and Jørgensen's teams by applying iminium activation.[5] When we became interested in this area of research, we hypothesized that multicomponent reactions,[6] that is to say the initial simultaneous introduction of at least three reaction partners that will be integrated in the target product, would be an interesting tool to efficiently prepare new enantioenriched polyhydropyridine motifs. β-Dicarbonyl compounds are generally used as pronucleophiles in the synthesis of these heterocycles and their polyfunctional nature makes them ideal substrates for multiple bond-forming transformations (MBFT's) including domino processes and multicomponent reactions.[7]

Our starting point was the combination of an α,β-unsaturated aldehyde **A**, a β-dicarbonyl **B** and a functionalized amine **C** in the presence of a chiral non-racemic organocatalyst (Scheme 1). After the initial catalyst-controlled enantioselective Michael addition that forges the first stereogenic center,[8] the amine functionality combines with the aldehyde and the ketone of the Michael adduct **D** affording 1,4-dihydropyridine **E** with loss of two molecules of water. In 1,4-dihydropyridine **E**, each side of the dienamine motif can tautomerize to the corresponding iminium ion to deliver reactive intermediates **F** and **F'**, whose trapping by the pendant nucleophile delivers fused 1,4,5,6-tetrahydropyridines **G** (**Type I**)[9] and 1,2,3,4-tetrahydropyridines **G'** (**Type II**), bearing two or three stereogenic centers, respectively.[10] When a secondary amide group is present on the substrate, a zwitterionic intermediate **H** can then be envisaged, whose cyclization leads to the formation of bridged perhydropyridines **I** (**Type III**) incorporating up to four stereogenic carbon atoms.[11] Of course, for this last family of products, the order of the cyclization events can also be interchanged. In principle, all the elemental steps of the different reaction pathways (acido-basic exchanges, Michael additions, dehydrations, tautomerizations and iminium ion trappings) can be reversible. In addition to their inherent step-economic nature and high synthetic efficiency for the fast elaboration of highly complex architectures, multicomponent reactions also offer interesting opportunities in terms of efficiency and stereoselectivity. Indeed, if one or several of the bond-forming events are kinetically and/or thermodynamically favored, this could help driving the whole sequence towards the efficient



Scheme 1. General reactivity pattern for the organocatalytic multicomponent synthesis of enantioenriched heterocycles.

formation of the desired product. Moreover, for enantioselective transformations, the steps that follow the enantiodiscriminating one can prevent its reversibility, thereby avoiding the racemization of the product, which was for example already noticed in a related stepwise synthesis of 1,4-dihydropyridines.[5b] However, two important conditions have to be respected for the design of multicomponent enantioselective transformations: (i) the third reaction partner should not interact in a deleterious way with the organocatalyst; (ii) all the steps of the sequence should occur fast enough in similar reaction conditions, which might become problematic, especially when low temperature is required to ensure good enantioselection during the Michael addition.

Complementary to scarce reports by other groups for the inclusion of β-dicarbonyls in organocatalytic enantioselective multicomponent transformations,[7h,12] we have recently disclosed independent synthetic routes towards three families of enantioenriched heterocycles (Figure 1): pyrrolopiperazine derivatives with a 1,4,5,6-tetrahydropyridine motif (**Type I**),[9] 1,2,3,4-tetrahydropyridines (**Type II**)[10] and 2,6-diazabicyclo[2.2.2]octan-3-ones (2,6-DABCOs, **Type III**).[11,13,14] In this Feature Article, we wish to provide the readers, with a general overview of our reaction design to help trigger new development in this area. The structure of the different reaction

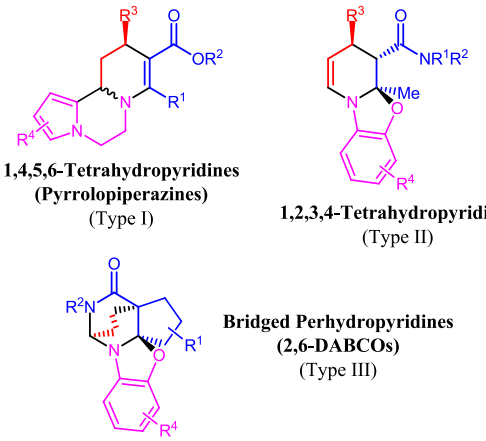


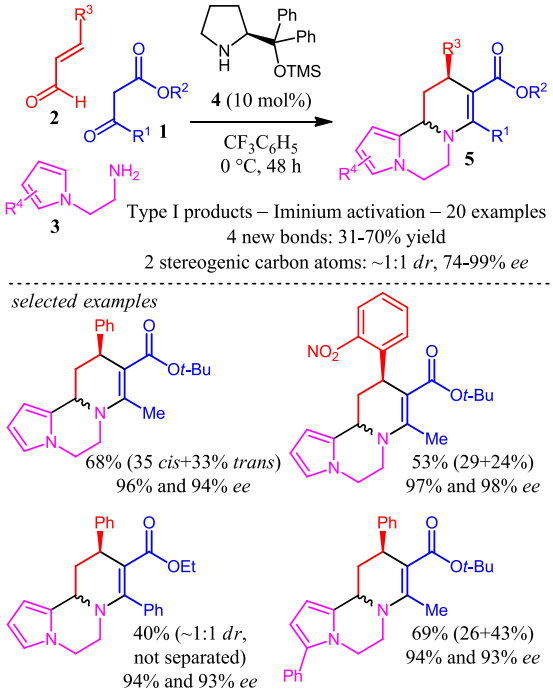
Figure 1. Families of polyheterocycles discussed in this article.

partners, especially the β-dicarbonyl and the pendant nucleophile on the amine, the mode of action of the organocatalyst and the reaction conditions are among the key factors that control the chemo- and enantioselective formation of one defined product. Scope, limitations and bridging between the different patterns of reactivity will be discussed. Moreover, post-functionalizations of the products to afford structurally diverse heterocyclic scaffolds will also be presented.

2 Type I Products: 1,4,5,6-Tetrahydropyridines (Pyrrolopiperazines)

With the general reactivity pattern presented in Scheme 1 in mind, **Type I** products first appeared as the easiest synthetic targets. Indeed, tautomerization of the common intermediate **E** should favor the formation of iminium ion **F**, which exhibits higher conjugation and whose electrophilic reactive center is less hindered than in its congener **F'**. A number of similar organocatalytic sequences involving a secondary amine-catalyzed Michael addition followed by the cyclization of a pendant nucleophile, either an electron-rich aromatic ring[15] or an heteroatom,[16] had already been described before but in a stepwise fashion, with the requirement of a strong and/or stoichiometric acid. As the presence of this additive was likely to damage the activity of the secondary amine catalyst, we set out to find a nucleophilic moiety that could react even in the absence of an acid. Since the pyrrole ring is known to exhibit strong nucleophilicity, which is further increased when it is alkylated,[17] it was selected as the third reaction partner, with the aim to trap the iminium intermediate through a Pictet-Spengler-type cyclization. Pleasingly, mixing equimolar ratios of an α-methylene β-ketoester **1** and *N*-(2-aminoethyl)pyrrole (**3**) with a 1.5-fold excess of an enal **2** in the presence of Hayashi-Jørgensen catalyst **4** delivered the expected polycyclic structure **5** (Scheme 2).[9a] It should be noted that other classical secondary amine organocatalysts performed very poorly in this transformation and that trifluorotoluene as the solvent had an appreciable positive impact on the enantioselectivity of the reaction. The overall transformation allowed the formation of four new bonds, a tricyclic pyrrolopiperazine core and two stereogenic carbon atoms. Twenty different products with possibilities of variation

on all three reaction partners were prepared in moderate yields because of the fragility of the pyrrole unit.



Scheme 2. Pyrrolopiperazines incorporating a 1,4,5,6-tetrahydropyridine core: previous results.[9a]

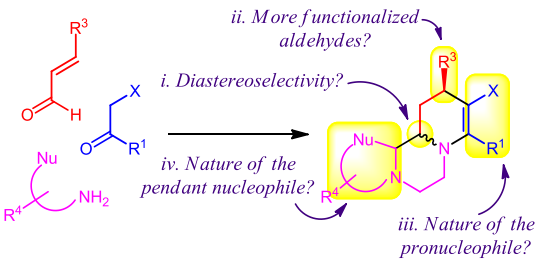
If enantioselectivities were generally good to excellent (74-99% *ee*), there was no diastereoselectivity during the Pictet-Spengler cyclization, but this drawback was counterbalanced by the fact that the two diastereomers could generally be separated by flash chromatography. To widen the application range of this transformation, we then wished to pursue the four following directions (Scheme 3):

(i) Why is there no diastereoselectivity and is there a way to solve this issue?

(ii) Is it possible to replace the alkyl or aryl group at R^3 by a more functionalized one?

(iii) Could the β-ketoester be replaced by other pronucleophiles?

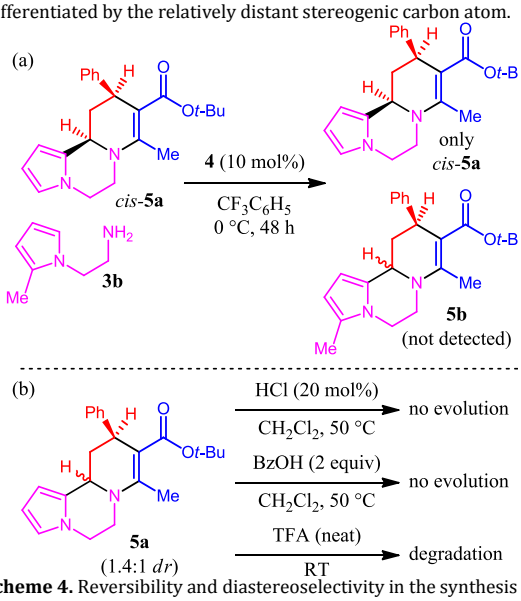
(iv) Could other bis-nucleophilic units than *N*-(2-aminoethyl)pyrroles participate in the reaction?



Scheme 3. 1,4,5,6-Tetrahydropyridines: open questions.

2.1 Diastereoselectivity of the reaction

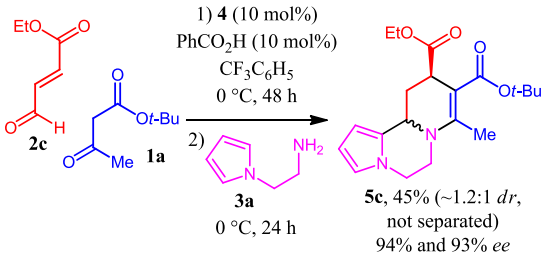
Before studying the diastereoselectivity of the process, it was necessary to determine whether the second stereogenic carbon atom was forged under kinetic or thermodynamic control. When diastereomerically pure *cis*-**5a** was placed back in the reaction conditions in the presence of a substituted *N*-(2-aminoethyl)pyrrole **3b** (Scheme 4a), it was recovered unchanged (neither epimerization, nor cross-over product **5b**), pointing towards an irreversibility of the cyclization process. In related enantioselective Michael addition-Pictet-Spengler domino processes, an improvement of the diastereoselectivity was observed by the addition of a strong acid at the end of the reaction.[15a,18] In the present case, treatment of **5a** as a 1.4:1 mixture of diastereomers with an acid resulted either in no evolution or in its complete degradation (Scheme 4b). Thus, diastereoselectivity in this system seems difficult to control since both faces of iminium ion intermediate are not enough differentiated by the relatively distant stereogenic carbon atom.



Scheme 4. Reversibility and diastereoselectivity in the synthesis of pyrrolopiperazines.

2.2 Reaction with ethyl 4-oxobut-2-enoate

In our initial studies, we had used aldehydes bearing alkyl, vinyl and (hetero)aryl substituents at their β position. To broaden the synthetic usefulness of the present transformation, we became interested in the use of ethyl 4-oxobut-2-enoate **2c** (Scheme 5). Directly applying the standard multicomponent conditions or trying to alter them (use of various solvents: CH_2Cl_2, CH_3CN; reaction at room temperature; addition of benzoic acid as co-catalyst) failed to provide the expected product. We surmised that the high electrophilicity of this enal might result in side reactions with the other reaction partners. To solve this issue, we came back to a one-pot two-step process: pleasingly, if *N*-(2-aminoethyl)pyrrole (**3a**) was added after two days and the reaction mixture kept at 0 °C for an additional day, pyrrolopiperazine **5c** was isolated in 45% yield as a ~1.2:1 diastereomeric mixture with high enantioselectivities (94% and 93% *ee* for each diastereomer, respectively).

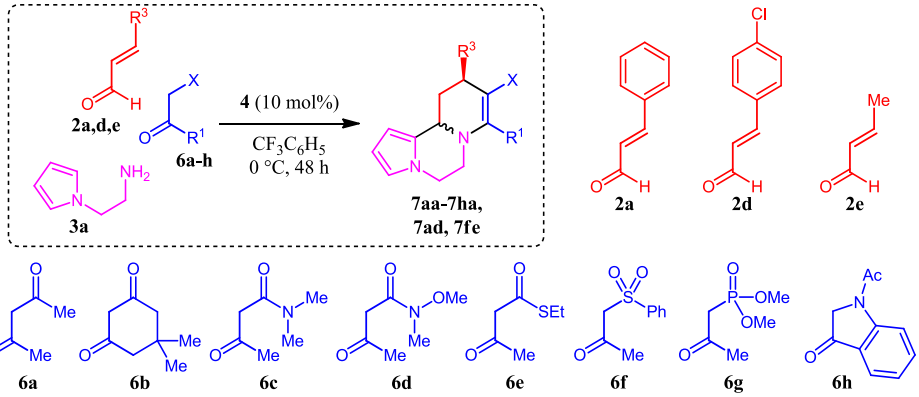


Scheme 5. Enantioselective synthesis of pyrrolopiperazine **5c** from ethyl 4-oxobut-2-enoate **2c**.

2.3 More diversified Michael pronucleophiles

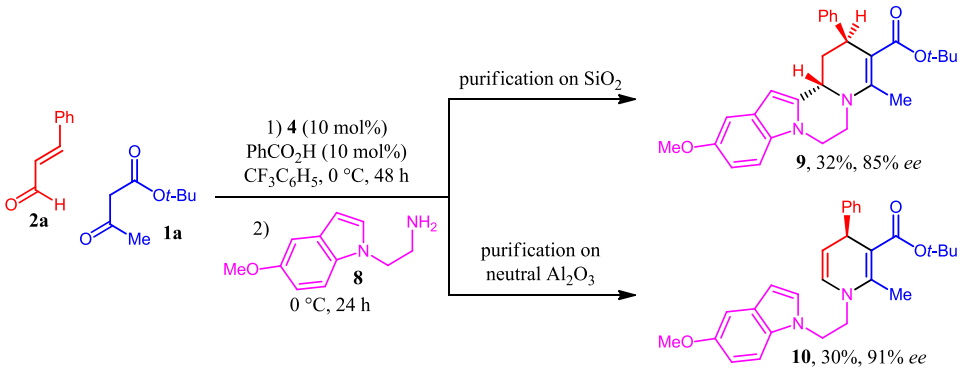
Our initial studies were limited to the use of β-ketoesters as pronucleophiles. However, a large variety of Michael donors have demonstrated the ability to add enantioselectively to enals activated as the corresponding iminium ions by a secondary amine catalyst.[19] A certain number of these compounds of type **6a-h** were evaluated and many of them proved to be able to deliver the corresponding pyrrolopiperazine products **7aa-ha**, **7ad** and **7fe** at the cost of slight modifications of the standard reaction conditions (Table 1). With acetylacetone (**6a**) as the pronucleophile, a low yield of product **7aa** and only moderate enantioselectivity were obtained in the standard reaction

Table 1. Scope of various Michael donors for the enantioselective multicomponent synthesis of pyrrolopiperazines.[a]



Entry	Michael donor	Enal	Changes from the standard reaction conditions	Product	Yield (*cis*+*trans*)[b]	*ee*[c]
1	**6a**	**2a**	none	**7aa**	<30%	72% and n.d.[d]
2	**6a**	**2a**	$PhCO_2H$ (10 mol%)	**7aa**	60%	82% and n.d.[d]
3	**6a**	**2a**	$PhCO_2H$ (20 mol%), CH_2Cl_2 as solvent, −10 °C	**7aa**	68% (45+23%)	94% and 91%
4	**6a**	**2d**	$PhCO_2H$ (20 mol%), CH_2Cl_2 as solvent, −10 °C	**7ad**	67% (38+29%)	91% and 91%
5	**6b**	**2a**	none	**7ba**	~50%[e]	64% and n.d.[d]
6	**6b**	**2a**	$PhCO_2H$ (20 mol%)	**7ba**	~40%[e]	36% and n.d.[d]
7	**6c**	**2a**	none	**7ca**	25% (only *trans*)	92%
8	**6d**	**2a**	none	**7da**	28% (only *trans*)	88%
9	**6e**	**2a**	none	**7ea**	50% (21+29%)	49% and 54%
10	**6f**	**2a**	none	**7fa**	no product	-
11	**6f**	**2e**	none	**7fe**	~45%[e]	77% and 76%
12	**6f**	**2e**	$PhCO_2H$ (20 mol%), THF as solvent	**7fe**	~55%[e]	60% and 61%
13	**6f**	**2e**	reaction time: 96 h	**7fe**	~50% (31+22%)[e]	89% and 85%
14	**6g**	**2a**	none	**7ga**	no product	-
15	**6h**	**2a**	none	**7ha**	~65% (1.6:1 *dr*)[e,f]	80% and 80%
16	**6h**	**2a**	CH_2Cl_2 as solvent	**7ha**	68% (1.5:1 *dr*)[f]	88% and 87%

[a]All reactions were run using **6a-h** (0.200 mmol, 1 equiv), **2a,d,e** (0.300 mmol, 1.5 equiv), **3a** (0.200 mmol, 1 equiv) and catalyst **4** (0.020 mmol, 0.1 equiv) in $CF_3C_6H_5$ (2.5 mL) for 48 h at 0 °C. Changes from these standard reaction conditions are notified in the table. [b]Yields of analytically pure isolated products (yields between brackets are those of the *cis* and *trans* diastereomers, respectively, when they could be separated). [c]Enantiomeric excesses (*ee*) were determined by HPLC analysis on a chiral stationary phase. [d]During optimization studies, only the *ee* of the *cis* diastereomer was determined, as both of them usually have similar values. [e]Product purities ~90%. [f]The diastereomers could not be separated and the diastereomeric ratios (*dr*) were determined by ^1H NMR spectroscopy analysis after purification.



Scheme 6. Use of *N*-(2-aminoethyl)indole derivative **8**.

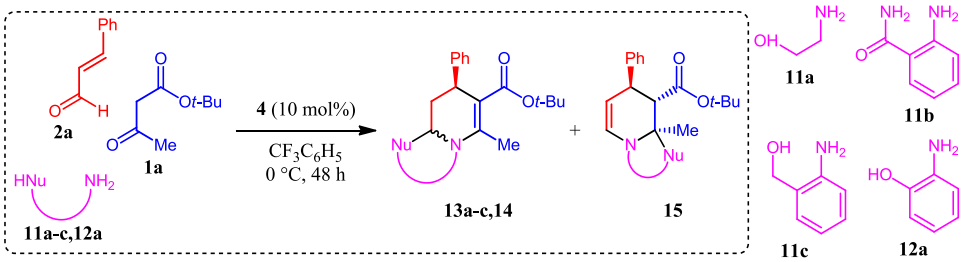
conditions (Entry 1). However, the addition of benzoic acid as a co-catalyst proved beneficial for the product formation (Entry 2). Ultimately, replacing $CF_3C_6H_5$ by CH_2Cl_2 as the solvent and decreasing the reaction temperature to −10 °C delivered **7aa** with yields and enantioselectivities similar to those obtained with the β-ketoesters (Entry 3). Those optimized reaction conditions transposed efficiently to prepare **7ad** from 4-chlorocinnamaldehyde (**2d**) (Entry 4). On the contrary, cyclic diketones such as dimedone (**6b**) proved to be more challenging substrates: only moderate yields and enantioselectivities were obtained for **7ba**, and the addition of an acidic co-catalyst was deleterious (Entries 5 and 6). We have recently reported that tertiary β-ketoamides can be potent Michael donors that can add to nitroolefins under hydrogen-bonding organocatalysis with high enantio- and diastereoselectivities.[20] We were intrigued whether they could also participate in the multicomponent organocatalytic synthesis of pyrrolopiperazines. Both *N*,*N*-dimethyl and Weinreb β-ketoamides **6c** and **6d** reacted in the standard reaction conditions (Entries 7 and 8): even though both diastereomers are present in the crude reaction mixture, only the *trans* diastereomers of products **7ca** and **7da** could be obtained pure, and their enantiomeric excesses were satisfying. β-Ketothioester **6e** was also a potent pronucleophile in this transformation, but product **7ea** was formed only with a moderate enantioselectivity. The next step was to substitute the ester moiety by a sulfone or a phosphonate. Both substrates **6f** and **6g** failed to react when cinnamaldehyde (**2a**) was used as the electrophile (Entries 10 and 14). However, based on literature precedents showing that **6f** reacts preferentially with enals bearing an aliphatic group at the β position,[21] crotonaldehyde (**2e**) was combined with **6f** and **3a** in the standard reaction conditions (Entry 11): this time, product **7fe** was obtained, but in mixture with inseparable impurities. Once again, an acidic co-catalyst was inefficient (Entry 12), but extending the reaction time somewhat improved the results (Entry 13). To finish with, 1-acetylindolin-3-ones are also known to add to enals under secondary amine catalysis.[22] Our standard reaction conditions applied to substrate **6h** delivered the expected fused pentacyclic product **7ha** as an inseparable mixture of diastereomers in good yield and enantioselectivities, which could even be improved by using CH_2Cl_2 as solvent (Entries 15 and 16).

2.4 Alternative bis-nucleophilic units

The last direction we wanted to explore for the **Type I** products was the possibility to replace the pyrrole ring by other nucleophilic units. Disappointingly, our initial attempts with indole derivatives failed to provide the expected products.[9a] We wanted to re-investigate their use and turned our attention towards more electron-rich *N*-(2-aminoethyl)indole derivative **8** (Scheme 6). When it was added to the reaction mixture after an initial organocatalytic Michael addition between **1a** and **2a**, the expected indolopiperazine **9** was obtained as its pure *trans* diastereomer in 32% yield and 85% *ee* after purification by flash chromatography on silica gel. Alternatively, a purification of the crude reaction mixture on neutral alumina delivered the corresponding 1,4-dihydropyridine **10** in 30% yield and 91% *ee*. This last result demonstrates that the Pictet-Spengler cyclization with the indole derivative is not spontaneous in the reaction conditions and requires an acidic environment, thus highlighting the unique behavior of the pyrrole ring in its ability to cyclize in acid-free conditions.

In a complementary fashion, we were interested in using heteroatom-based pendant nucleophiles instead of an electron-rich heteroaromatic ring.[23] *tert*-Butyl acetoacetate (**1a**) and cinnamaldehyde (**2a**) were combined with five different bis-nucleophiles **11a-c,12a**in the presence of Hayashi-Jørgensen catalyst **4** (Table 2). No product formation was observed with 2-aminoethanol (**11a**) and anthranilamide (**11b**) (Entries 1 and 2).[24] Conversely, the use of 2-aminobenzyl alcohol (**11c**) delivered the moderately pure expected product **13c** in modest amount but with a fair enantioselectivity (Entry 3). At last, using 2-aminophenol (**12a**) resulted in a mixture of a small amount of expected **14** together with its regioisomer **15** (Entry 5).[25] This result was all the more interesting since, contrary to products **13c** and **14**, the new 1,2,3,4-tetrahydropyridine **15 Type II** product bearing three contiguous stereogenic centers was formed virtually as a single diastereomer and also with excellent enantioselectivity. This discovery paved the way for further developments towards the enantioselective synthesis of this uncommon heterocyclic motif, which will be discussed in details in the following section.

Table 2. Screening of heteroatomic bis-nucleophiles for the enantioselective multicomponent synthesis of tetrahydropyridines.[a]

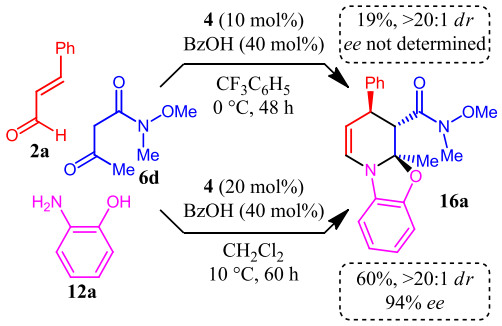


Entry	Bis-nucleophile	Product **13a-c,14**		Product **15**	
		Yield (*dr*)[b]	*ee*[c]	Yield (*dr*)[b]	*ee*[c]
1	**11a**	**13a**: no product	-	-	-
2	**11b**	**13b**: no product	-	-	-
3	**11c**	**13c**: ~25% (1.3:1 *dr*)	88% and 90%	-	-
4	**12a**	**14**: <10% (1.5:1 *dr*)[d]	n.d.	**15**: 25% (>20:1 *dr*)	94%

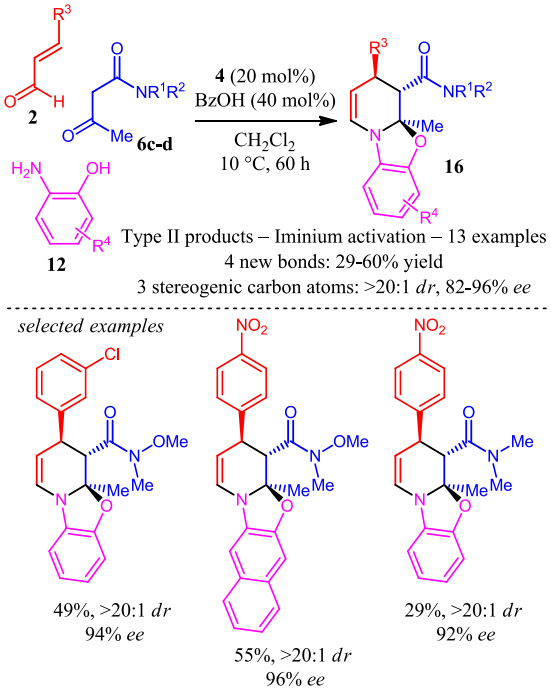
[a]All reactions were run using **1a** (0.200 mmol, 1 equiv), **2a** (0.300 mmol, 1.5 equiv), **11a-c,12a** (0.200 mmol, 1 equiv) and catalyst **4** (0.020 mmol, 0.1 equiv) in $CF_3C_6H_5$ (2.5 mL) for 48 h at 0 °C. [b]Yields of analytically pure isolated products and diastereomeric ratios (*dr*) determined by ^{1}H NMR spectroscopy analysis after purification. [c]Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [d]The product could not be obtained pure.

3 Type II Products: 1,2,3,4-Tetrahydropyridines

Having observed the formation of **Type II** product **15** (Table 2), we became interested in trying to fully counterbalance the regioselectivity of the multicomponent reaction to obtain this previously unknown family of 1,2,3,4-tetrahydropyridines, exclusively. We hypothesized that the equilibrium between iminium ions **F** and **F'** and the relative stabilities of products **G** and **G'** (Scheme 1) would be key factors to reach this goal. The usual higher stability of **F** and **G** over **F'** and **G'**, respectively, can be explained by the higher delocalization of π electrons through the enaminoester. We hypothesized that replacing the ester group by a bulkier tertiary amide would create strong 1,3-allylic strain, which could outcompete the stabilization energy brought about by the conjugation, thereby forcing the amide group to turn outside of the plane.[20,26] Pleasingly, when *tert*-butyl acetoacetate (**1a**) was replaced by the corresponding Weinreb β-ketoamide **6d**, only 1,2,3,4-tetrahydropyridine **16a** was obtained in modest yield, as a single diastereomer (Scheme 7). Thereafter, a thorough optimization of the reaction conditions was conducted pointing towards: (i) an increase of the catalyst loading to 20 mol%; (ii) the use of benzoic acid as co-catalyst; (iii) the replacement of trifluorotoluene by CH_2Cl_2; (iv) the increase of the temperature to 10 °C and of the reaction time to 60 h.[10] This new reaction was then exemplified on a variety of cinnamaldehyde derivatives **2** and functionalized 2-aminophenols **12** (Scheme 8). Products **16**, in which four new bonds and three stereogenic centers are installed in a single synthetic operation were obtained with moderate yields, but high stereoselectivities. Variations on the β-ketoamide were less straightforward since



Scheme 7. 1,2,3,4-Tetrahydropyridines: control of regio- and stereoselectivity with Weinreb β-ketoamide **6d**.[10]

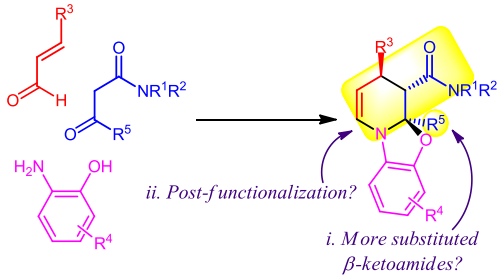


Scheme 8. 1,2,3,4-Tetrahydropyridines: previous results.[10]

the replacement of Weinreb amide **6d** by the less activated *N*,*N*-dimethyl analogue **6c** delivered the expected product with lower yield but preserved stereoselectivities. After our initial studies, we foresaw two different directions to increase the synthetic usefulness of this transformation (Scheme 9):

(i) Is it possible to replace the methyl group on the ketone by other substituents?

(ii) Are the different functionalities of the product (enamine, aminal and amide) amenable to post-functionalization to reach more diversified scaffolds?



Scheme 9. 1,2,3,4-Tetrahydropyridines: open questions.

3.1 Use of more diverse β-ketoamides

At first, we screened γ-alkyl- and γ-aryl-β-ketoamides **17a-d**, which we had used in our organocatalytic Michael addition to nitroolefins,[20a] in the standard reaction conditions to prepare the corresponding 1,2,3,4-tetrahydropyridines (Figure 2). Unfortunately, all of them proved to be not reactive enough and the expected products where obtained with less than 15% yields. To try to overcome this issue, γ-bromo-ketoamide **17d** was prepared[27] with the hope that the inductive withdrawing effect of the bromine atom would render the activation of the β-ketoamide easier. Moreover, it could also serve as a handle for post-functionalization. However, once again, only low conversion into the 1,2,3,4-tetrahydropyridine was observed.

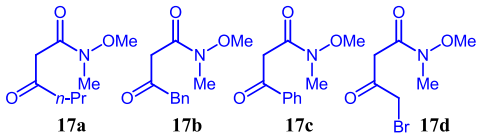
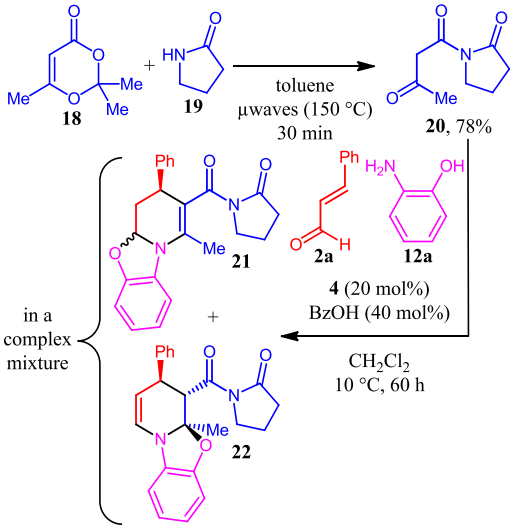


Figure 2. Unsuitable β-ketoamide substrates **17a-d**.

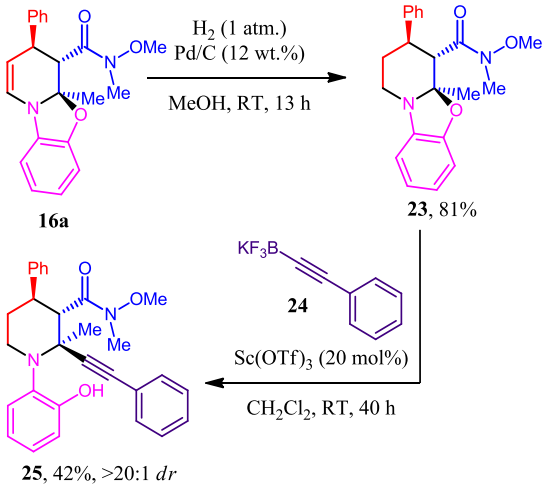
The only other option left was to modify the amide moiety, by replacing the *N*-methoxy-*N*-methyl unit by a group with stronger electron-withdrawing ability and/or that could provide a better interaction with the catalyst. Following the work of Jørgensen and co-workers on the Michael addition of 1,3-dicarbonyls bearing an oxazolidinone to nitroolefins,[28] we turned our attention towards the use of the pyrrolidinone derivative **20**. It was easily prepared by the thermal decomposition of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **18**, followed by the trapping of the intermediate α-oxoketene by pyrrolidinone **19**.[29] This new substrate was then exposed to the standard conditions for the multicomponent synthesis of 1,2,3,4-tetrahydropyridines, resulting in a complex mixture including regioisomeric products **21** and **22**. From this result, we can see that it seems to be a balance between reactivity and regioselectivity as β-dicarbonyl compounds with a more acidic α position are more easily activated in the catalytic conditions but also tend to provide the 1,4,5,6-tetrahydropyridine regioisomer.



Scheme 10. Pyrrolidinone-derived β-ketoamide **20**: synthesis and use in the multicomponent reaction.

3.2 Post-functionalization on the products

The major structural originality of 1,2,3,4-tetrahydropyridines compared to the products obtained in other methodologies targeting enantioenriched polyhydropyridines, is the presence of the enamine function. In our previous studies, we showed that both its reduction with dihydrogen in the presence of a catalytic amount of Pd/C and its isomerization into the corresponding iminium ion under $Sc(OTf)_3$-catalysis and the subsequent trapping with a potassium alcynyltrifluoroborate proceeded with good yields and good preservation of the enantiomeric excesses.[10]. To study the reactivity on other positions of the product, the reduction was repeated on enamine **16a** to furnish **23**(Scheme 11). In the presence of scandium (III) triflate as a



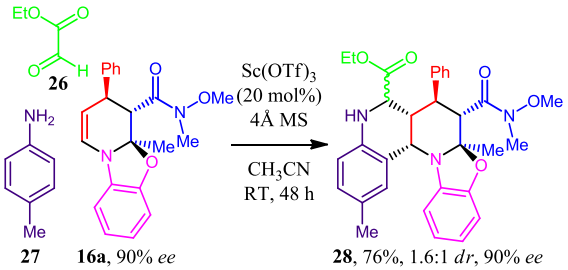
Scheme 11. Sequential post-functionalization of 1,2,3,4-tetrahydropyridines **16a**

catalytic Lewis acid, potassium phenylethynyltrifluoroborate (**24**) could then add to the transient iminium ion obtained by the opening of aminal **23** to furnish compound **25** in moderate yield but as a single diastereomer.[30] Unfortunately, all attempts to have the Weinreb amide functionalities of **16a**, **23** or **25** being reduced by treatment with metal hydrides did not meet with success, since either no conversion or extensive degradation was observed.

Another possibility to valorize the 1,2,3,4-tetrahydropyridines is to combine two multicomponent reactions sequentially to attain extremely high molecular complexity in a very short synthetic sequence.[31] The three-component reaction of enamines with in-situ generated 2-azadienes has been known as the Povarov reaction.[32] Combining enamine **16a** with ethyl glyoxylate (**26**) and *p*-toluidine (**27**) in the presence of a catalytic amount of $Sc(OTf)_3$ triggered the cycloaddition process to afford the expected product **28** in good yield (Scheme 12). Pleasingly, the two new stereogenic centers at the ring junction were installed in a *cis* relationship with complete diastereoselectivity. On the opposite, there was no control of the stereogenic center α to the ester functionality, presumably because the intermediate imine was formed as a mixture of (*E*) and (*Z*) diastereomers. All in all, the enantioenriched fused pentacyclic scaffold **28** has been elaborated in only two steps from five very simple starting materials.

3.3 Attempts of four-component reaction

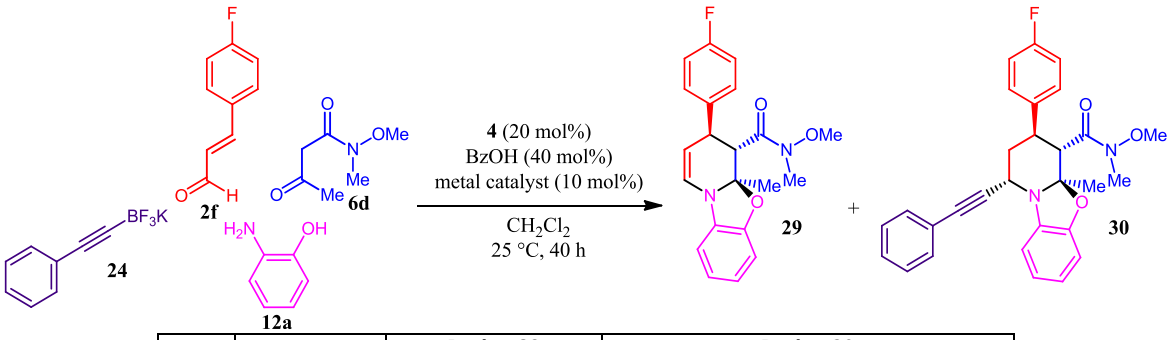
Having post-functionalized the enamine moiety of 1,2,3,4-tetrahydropyridines with potassium organotrifluoroborate **24**, we also became intrigued by the possibility to integrate it directly in the multicomponent reaction (Table 3).



Scheme 12. Post-functionalization of 1,2,3,4-tetrahydropyridine **16a** by a Povarov reaction.

4-Fluorocinnamaldehyde **2f** was selected as Michael acceptor to allow an easy identification of three- and four-component products **29** and **30** by ^{19}F NMR in the potentially complex crude reaction mixture.[33] At first, we could show that potassium phenylethynyltrifluoroborate **24** does not interfere with the initial organocatalytic process since three-component product **29** was formed in 82% NMR yield but four-component product **30** could not be observed in the crude reaction mixture (Entry 1).[34] Lewis acids were then evaluated as co-catalysts to help in the tautomerization process required to generate and trap the iminium ion. The development of such a transformation would represent a unique dually-catalyzed four-component reaction.[35] $Sc(OTf)_3$ had only a limited influence since it decreased the yield of **29** but did not trigger the formation of **30** (Entry 2). On the contrary, with $ZrCl_4$ and $NbCl_5$, small amounts (~20% yields) of four-component product **30** could be observed, unfortunately as racemic mixtures (Entries 3 and 4). The replacement of the Lewis acid with a Rh complex was also inefficient (Entry 5).

Table 3. Attempts of synthesis of tetrasubstituted piperidines by a dually-catalyzed four-component reaction.[a]

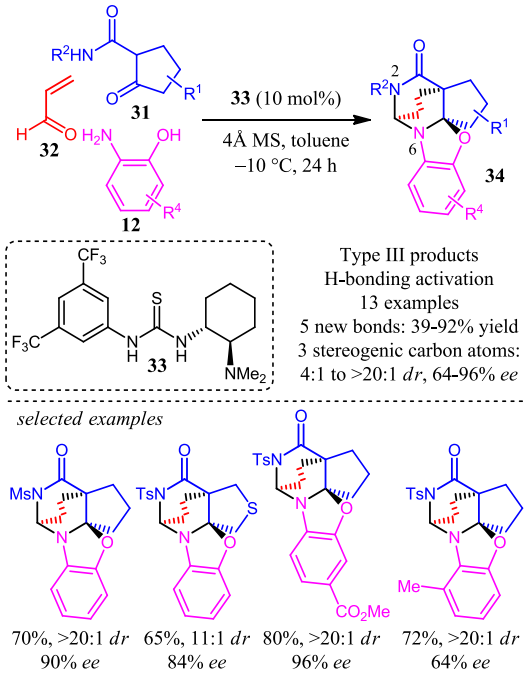


Entry	Metal catalyst	Product **29**	Product **30**	
		NMR Yield[b]	NMR Yield[b]	*ee*[c]
1	none	82%	no product	-
2	$Sc(OTf)_3$	54%	no product	-
3	$ZrCl_4$	4%	21%	0%
4	$NbCl_5$	no product	20%	0%
5	$[Rh(cod)Cl]_2$[d]	47%	no product	-

[a]All reactions were run using **6d** (0.200 mmol, 1 equiv), **2f** (0.300 mmol, 1.5 equiv), **12a** (0.200 mmol, 1 equiv), **23** (0.300 mmol, 1.5 equiv), catalyst **4** (0.020 mmol, 0.1 equiv) $PhCO_2H$ (0.040 mmol, 0.2 equiv) and the metal catalyst (0.010 mmol, 10 mol%) in CH_2Cl_2 (2.5 mL) for 40 h at 25 °C. [b]NMR yields of products **29** and **30** were determined by ^{19}F NMR spectroscopy analysis of the crude reaction mixture. [c]Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [d]5 mol% of metal catalyst were used.

4 Type III Products: Bridged Perhydropyridines (2,6-DABCOs)

A careful study of the structure of 1,2,3,4-tetrahydropyridines presented in the previous section highlights the presence of the enamine moiety that could interconvert with the corresponding iminium ion and of an inert tertiary amide. Replacing the latter one by a secondary amide would add another nucleophilic position and a cyclization onto the electrophilic iminium ion could be envisioned, delivering bridged perhydropyridines as **Type III** products (Scheme 1). Relying on our studies on the addition of cyclic secondary β-ketoamides to α,β-unsaturated ketones and aldehydes under bifunctional hydrogen-bonding organocatalysis,[36,37] we studied the possibility to add a bis-nucleophilic species to these reaction conditions. Pleasingly, mixing cyclic secondary β-ketoamides **31** with acrolein (**32**) and aminophenols **12** in the presence of bifunctional thiourea catalyst **33**[38] delivered chemoselectively bridged perhydropyridines **34** (Scheme 13).[11a] Because of their resemblance with DABCO, but with the nitrogen atoms not located on the bridgehead positions, we decided to call these compounds 2,6-DABCOs.



Scheme 13. Bridged perhydropyridines (2,6-DABCOs): previous results.[11a]

During the development of this transformation, we also uncovered the following important parameters for its success:

(i) A strongly electron-withdrawing group is required on the β-ketoamide's nitrogen atom, such as a sulfonyl group, to ensure both productivity and enantioselectivity. In addition to this, the reaction with acyclic pronucleophiles is poorly enantioselective.

(ii) The structure of the aminophenols has a strong influence on the enantioselectivity of the reaction. Moreover, they are the only suitable bis-nucleophiles as free or mono-protected phenylene diamine resulted in complete degradation, whereas 2-aminobenzyl alcohol (**11c**) or salicylic acid yielded to trace amounts of the desired products.

(iii) Other enals than acrolein (**32**) perform very poorly in the multicomponent reaction: low yield of product was obtained with methacrolein, while crotonaldehyde delivered virtually racemic product.

(iv) 4Å molecular sieves are required to attain high levels of enantioselectivity, presumably by trapping the water produced during the course of the reaction.

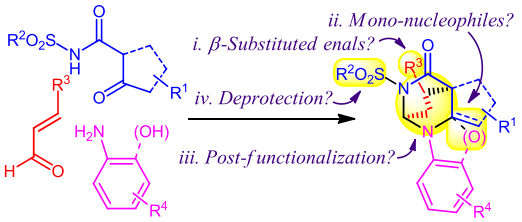
In view of the intriguing structure of these products, but also the limitations is terms of substrate diversity revealed by the scope study, we deemed it interesting to proceed to more detailed studies in the following directions (Scheme 14):

(i) Could β-substituted enals participate in this transformations, possibility by modifying the other substrates and the mode of activation of the organocatalyst?

(ii) Can we envisage to get rid of the phenol moiety on the aniline, to replace the final iminium ion trapping by a tautomerization into the corresponding enamine?

(iii) Could the synthetic potential of the reaction be increased by taking advantage of the reactivities of the aminal functionalities?

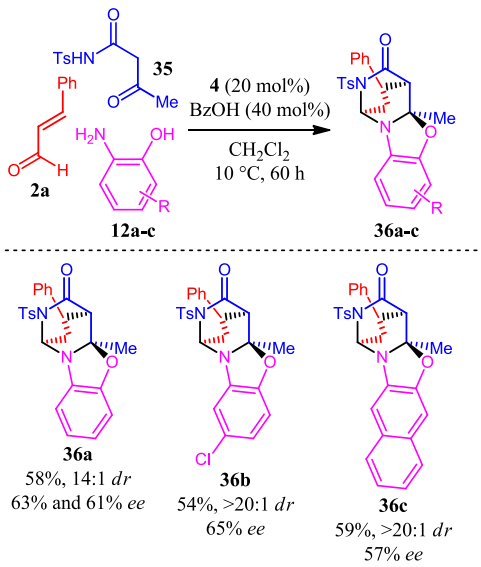
(iv) Is it possible to cleave the sulfonyl group on the product, whose presence on the β-ketoamide substrate is essential for the success of the transformation?



Scheme 14. Bridged perhydropyridines (2,6-DABCOs): open questions.

4.1 Introduction of β-substituted enals

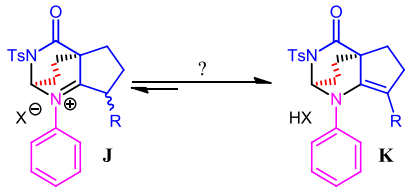
Given the results obtained for the preparation of **Type II** products from α-methylene tertiary β-ketoamides and cinnamaldehyde derivatives with a secondary amine as catalyst (Scheme 8), we hypothesized that applying the very same reaction conditions to the corresponding secondary amides might be an interesting entry to expand the substrate scope of 2,6-DABCO synthesis (Scheme 15). More specifically, acyclic *N*-tosyl secondary β-ketoamide **35** could be introduced directly in the reaction conditions used to prepare the **Type II** products, resulting in the production of the expected 2,6-DABCOs **36a-c** with high diastereoselectivities but only moderate enantiomeric excesses.[39]



Scheme 15. Synthesis of 2,6-DABCOs under iminium ion activation.

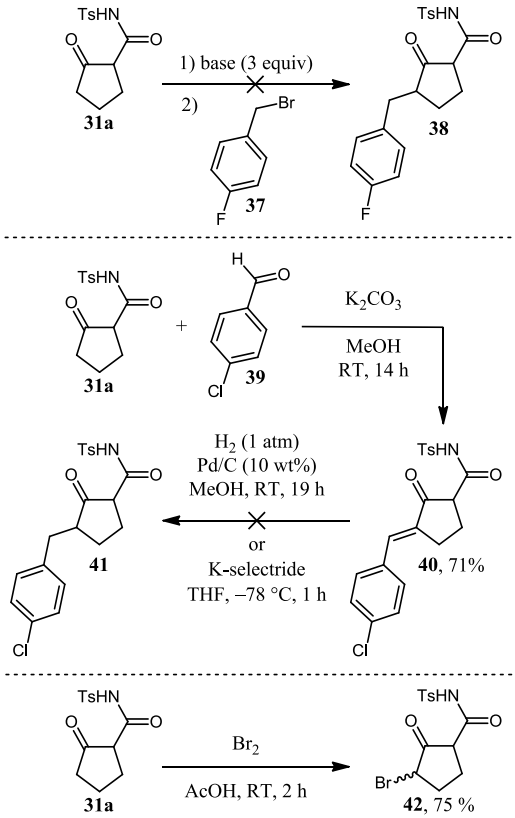
4.2 Tautomerization into the enamine

Initially, the aromatic hydroxyl functionality appeared as an essential structural feature to observe the formation of the 2,6-DABCO products. In subsequent studies, we wanted to investigate what is happening in its absence, especially whether the iminium ion **J** could tautomerize into a stable tetrasubstituted enamine **K**, when no nucleophile is present to trap it (Scheme 16). The presence of an additional substituent (R) on the enamine might be useful to increase its stability.



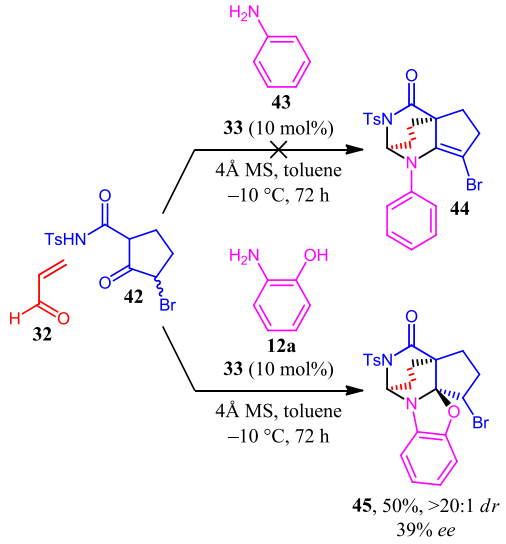
Scheme 16. Working hypothesis for the tautomerization of the iminium ion **J** into the enamine **K**.

To test this hypothesis, we needed at first to be able to prepare the corresponding γ-substituted β-ketoamides, which had never been described in the literature before and represent a real synthetic challenge because of their sensibility to a variety of acidic or basic reaction conditions. The γ-alkylation of substrate **31a** would require the intermediate preparation of a tris-anion before adding an alkylating agent, 4-fluorobenzyl bromide (**37**), which would react with the least stabilized anion (Scheme 17). Unfortunately, all our attempts to obtain product **38** failed because of competing α-alkylation and degradation processes. An alternative pathway would go through a γ-aldolization-crotonization sequence followed by the reduction of the carbon-carbon double bond.[40] Alkenylation of **31a** with 4-chlorobenzaldehyde (**39**) proceeded efficiently and stereoselectively but attempts to reduce enone **40** into **41** either by catalytic hydrogenation or conjugate hydride addition resulted into complex reaction mixtures. Fortunately, γ-functionalization could eventually be attained by the bromination of **31a** in classical conditions, with compound **42** being obtained as a 1:1 mixture of diastereomers.



Scheme 17. Preparation of γ-substituted β-ketoamides.

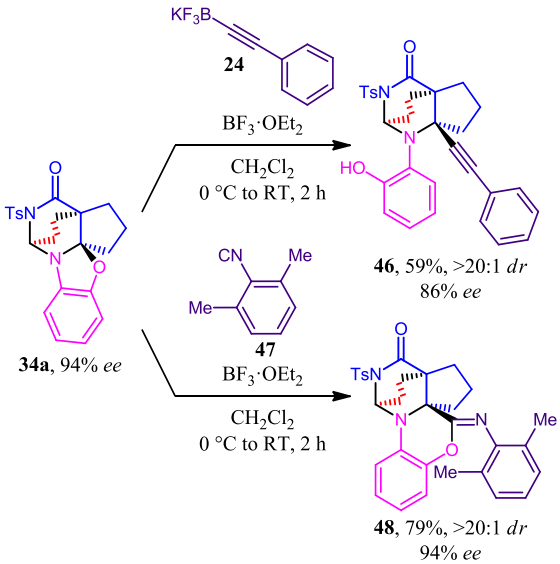
Substrate **42** was then evaluated in the multicomponent enantioselective synthesis of 2,6-DABCOs (Scheme 18). At first, aniline (**43**) was tested as the third reaction partner in the reaction with **42** to try to obtain enamine product **44**. Unfortunately the bromine atom did not seem to bring enough stability to the enamine and a complete degradation of the reaction mixture was observed. On the opposite, γ-bromo-β-ketoamide revealed itself as a potent pronucleophile in the traditional 2,6-DABCO synthesis with 2-aminophenol (**12a**). In this case, product **45** was obtained in 50% yield as a single diastereomer and with 39% *ee*.[41] Even though, this level of enantioselectivity is not high enough in a synthetic context, it indicates that kinetic resolution can occur to some extent during the multicomponent organocatalytic process. In addition to this, when γ,δ-unsaturated β-ketoamide **40** was placed in the reaction conditions, no 2,6-DABCO product could be observed (not depicted).



Scheme 18. Synthesis of 2,6-DABCO from γ-bromo-β-ketoamide **42**.

4.3 Post-functionalization of the products

In our seminal publication,[11a] we had shown that the *N*,*O*-aminal functionality of the 2,6-DABCO could be re-opened in the presence of a Lewis acid such as boron trifluoride etherate and the resulting iminium ion could be trapped with a potassium alkynyltrifluoroborate. We repeated those reaction conditions by combining **34a** and **24** to verify that the enantiopurity of the product is maintained during this post-functionalization (Scheme 19). Pleasingly, the addition product **46** was isolated in 59% yield with only a minor erosion of the enantiomeric excess from 94% to 86%.

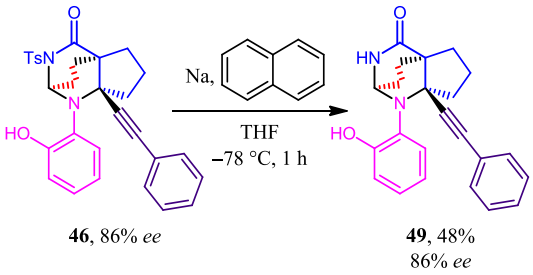


Scheme 19. Post-functionalization of 2,6-DABCO **34a**.

Other nucleophiles were also evaluated to intercept the transient iminium ion. Neither allyltrimethylsilane nor hydride sources such as triethylsilane, sodium borohydride or Hantzsch ester showed reactivity. On the contrary, complete degradation of the starting material was observed with trimethylsilyl cyanide. We also hypothesized that it would be possible to perform an insertion reaction in the C-O bond of the *N*,*O*-aminal. Indeed, the reaction of **34a** with (2,6-dimethylphenyl)isocyanide (**47**) afforded imidate **48** with good yield and complete retention of the stereochemical information. Because isocyanides are among the most popular partners in multicomponent reactions,[42] an attempt was made to introduce **47** directly in the reaction conditions used to produce the 2,6-DABCOs. Unfortunately, it behaved only as a spectator since no four-component coupling could be found but instead the reaction proceeded as usual to furnish the three-component product.

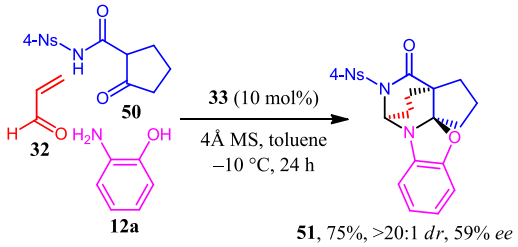
4.4 Cleavage of the sulfonyl group

To finish our study, we wanted to explore the possibility to cleave the sulfonyl group on the 2,6-DABCO products. Indeed, this group is absolutely required to obtain high yields and stereoselectivities and being able to remove it would significantly expand the synthetic potential of the method. Unfortunately, applying classical deprotection conditions for a tosyl group on the nitrogen atom of an amide (either sodium naphthalenide or TBAF) to **34a** resulted in the complete degradation of the starting material. Surmising that the labile *N*,*O*-aminal was responsible for this failure, the first deprotection conditions were attempted again on compound **46** (Scheme 20). This time, the cleavage occurred smoothly and deprotected 2,6-DABCO **49** could be isolated in 48% yield without any change in the enantiomeric excess. A solution to circumvent the problems encountered during the deprotection could be to replace the tosyl group by a 4-nosyl unit, which could be cleaved in milder reaction conditions.



Scheme 20. Deprotection of the tosyl group.

Moreover, the corresponding *N*-nosyl-β-ketoamides such as **50** had already been used in an independent study to access enantioenriched glutarimides by coupling them with α,β-unsaturated acyl cyanides.[36e] Notably, the stronger electron-withdrawing effect of the 4-nosyl group also had a positive influence on the stereoselectivity of the reaction. When **50** was placed in the standard reaction conditions, the expected 2,6-DABCO **51** was formed in good yield and very high diastereoselectivity but with only 59% *ee* (Scheme 23). This low enantioselectivity combined with issues of solubility and stability of the product led us to abandon this direction.

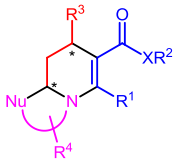
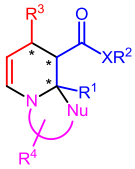
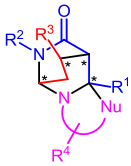


Scheme 21. Synthesis of *N*-(4-nosyl)-2,6-DABCO **51**.

5 Conclusion and Perspective

As a conclusion, in this Feature Article, we have thoroughly discussed all our recent work on the enantioselective preparation of nitrogen-containing six-membered heterocycles from very simple starting materials by the introduction of organocatalysts in multicomponent reactions. The general reaction scheme proceeds from a Michael donor, a Michael acceptor and a third component containing a primary amine, which will be able to cross-link the diverse carbonyl functionalities present on the two other partners after the initial

Table 4. General summary of reactions parameters for the three families of organocatalytic enantioselective multicomponent reactions (✓ = suitable and efficient; – = moderately efficient and/or selective; ✗ = not suitable).

	1,4,5,6-Tetrahydropyridines	1,2,3,4-Tetrahydropyridines	Bridged Perhydropyridines
Family of products	Type I 	Type II 	Type III 
Michael donor	✓ open-chain α-methylene β-ketoesters and diketones ✗ cyclic diketones – α-methylene β-ketoamides (reduced yields) – α-methylene β-keto-thioesters (reduced *ee*) ✓ 1-acetylindolin-3-ones	– open-chain α-methylene β-ketoesters (mixture) ✓ open-chain α-methylene Weinreb β-ketoamides – open-chain α-methylene β-ketoamides (reduced yields)	✓ cyclic β-ketoamides with a strongly electron withdrawing group – open-chain α-methylene Weinreb β-ketoamides (reduced *ee*)
Michael acceptor	✓ β-arylenals – β-alkylenals (reduced yields) – ethyl 4-oxobut-2-enoate (reduced yields)	✓ β-arylenals – β-alkylenals (reduced yields)	✓ acrolein – methacrolein (reduced yield) ✗ crotonaldehyde (racemic) – β-alkylenals (reduced *ee*)
Third component	✓ *N*-(2-aminoethyl)pyrroles – *N*-(2-aminoethyl)indoles (acid required) ✗ 2-aminoethanol ✗ anthranilamide – 2-aminobenzyl alcohol (reduced yield) ✓ 2-aminoethylphenol – 2-aminophenol (mixture)	✓ 2-aminophenols	✓ 2-aminophenols ✗ phenylene diamine ✗ anthranilic acid
Organocatalyst	Iminium activation (catalyst **4**). Addition of BzOH is sometimes useful.	Iminium activation (catalyst **4**), in the presence of BzOH as co-catalyst.	Bifunctional hydrogen-bonding (catalyst **34**) for acrolein. Iminium activation (catalyst **4**) for aromatic enals.
Results	✓ good yields ✗ no diastereoselectivities ✓ good enantioselectivities	– moderate yields ✓ high diastereoselectivity ✓ good enantioselectivities	✓ good yields ✓ good diastereoselectivities – moderate to good enantioselectivities

enantioselective Michael addition. Three main families of product were obtained: 1,4,5,6-tetrahydropyridines, 1,2,3,4-tetrahydropyridines and bridged perhydropyridines. The main required features of the substrates for each family of products, along with the subsequent choice of the suitable organocatalyst, are summarized in Table 4.

Beyond the potential interest of the present methods to prepare previously unknown polyheterocyclic scaffolds, we believe that the main input of our work is to provide pieces of evidence that organocatalysis, because of its high functional compatibility, can develop as a general and efficient tool to effect organic transformations in complex reaction media with excellent chemo- and stereoselectivities.

Starting Materials

- Unless specified, commercial reagents and solvents were used as received.
- Except the new substrates, which are described below, all β-ketoamides were prepared according to known literature procedures.[11a,20a,29b]
- Acrolein and (*E*)-cinnamaldehyde were distilled just prior to use.
- Catalyst **4** was purchased from Sigma-Aldrich and catalyst **33** from Strem.
- Crushed 4Å molecular sieves was stored in an oven at 110 °C.
- $BF_3{\cdot}OEt_2$ was refluxed on CaH_2 and distilled prior to use.
- Potassium phenylethynyltrifluoroborate **24** was prepared according to known literature procedure.[43]
- CH_2Cl_2, THF and toluene were dried using a M-Braun SPS-800 system. Other solvents (α,α,α-trifluorotoluene, CH_3CN, $CHCl_3$, MeOH and AcOH) were purchased in anhydrous quality and used without further drying.

Instrumentation and Analyses

- Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 aluminum plates (Macherey-Nagel) containing a 254 nm fluorescent indicator. TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and to anisaldehyde (2.5 mL of *p*-anisaldehyde, 3 mL of concentrated H_2SO_4 and 1.5 mL of AcOH in 100 mL of EtOH) or vanillin (2 g of vanillin and 4 mL of concentrated H_2SO_4 in 100 mL of EtOH) followed by heating.
- Flash column chromatography was performed using silica gel (35–70 µm, Acros or 35–70 µm, Macherey-Nagel) and basic Al_2O_3 (Macherey-Nagel)
- Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Bruker AV 400 spectrometer. Proton chemical shifts are reported in parts per million (δ scale), and are referenced using residual protium in the NMR solvent ($CDCl_3$: δ 7.26 ($CHCl_3$) or d^6-DMSO: δ 2.50 (d^5-DMSO)). Data are reported as follows: chemical shift (multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sept = septuplet, m = multiplet), coupling constant(s) (Hz), integration).
- Carbon-13 nuclear magnetic resonance (^{13}C NMR: CPD and DEPT-135) spectra were recorded with Bruker AV 300 or AV 400 spectrometers. Carbon chemical shifts are reported in parts per million (δ scale), and are referenced using the carbon resonances of the solvent (δ 77.16 ($CHCl_3$) or d^6-DMSO: δ 39.53 (d^6-DMSO)). Data are reported as follows: chemical shift (CH_n where n is the number of hydrogen atoms linked to the carbon atom).
- Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with Bruker an AV 400 spectrometer. Fluorine chemical shifts are reported in parts per million (δ scale), and are referenced using 4-fluorobenzene as an added internal standard (δ −113.15).
- High resolution mass spectra (HRMS) were recorded on a Waters Synapt G2 HDMS apparatus using a positive electrospray (ESI) ionization source.
- HPLC analyses for the determination of enantiomeric excesses were performed on a Merck-Hitachi system equipped with Chiralcel OD-3, Chiralpak AD-H, Chiralpak AZ-H, Chiralpak IA, Chiralpak IB, Chiralpak IC, Chiralpak ID, Chiralpak IE, Chiralpak IF, Lux-Amylose-2 and Lux-Cellulose-4 columns.
- Optical Rotations were recorded on a Perkin Elmer 241 Polarimeter or an Anton Paar MCP 200 Polarimeter at 589 nm and 25 °C. Specific rotations are reported as follows: specific rotation (concentration in grams/100 mL of solution, solvent).

Procedures

General procedure A for the three-component synthesis of pyrrolopiperazines 5 and 7aa-ha,7ad,7fe, and tetrahydropyridines 13c and 15: A reaction tube was charged with (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (**4**) (6.6 mg, 0.020 mmol, 0.1 equiv), dry α,α,α-trifluorotoluene (2.5 mL), flushed with argon and placed at 0 °C. β-ketoester **1** (0.200 mmol, 1 equiv) was then added followed by freshly distilled (*E*)-α,β-unsaturated aldehyde **2** (0.300 mmol, 1.5 equiv) and *N*-(2-aminoethyl)pyrrole **3** or substituted aniline **11c,12** (0.200 mmol, 1 equiv). After 2 days, the solution was directly purified by flash column chromatography on silica gel to provide the pyrrolopiperazines **5**, generally as two separable diastereomers or the tetrahydropyridines **13c** or **15**. For the description of products **5** (Scheme 2), see reference 9a.

General procedure B for the three-component synthesis of 1,2,3,4-tetrahydropyridines 16 and 2,6-DABCOs 36a-c: In a reaction tube, β-ketoamide **6c-d,35** (0.2 mmol, 1 equiv), (*E*)-cinnamaldehyde derivative **2** (0.3 mmol, 1.5 equiv), functionalized 2-aminophenol **16** (0.2 mmol, 1equiv) and benzoic acid (0.08 mmol, 0.4 equiv) were dissolved in dry CH_2Cl_2 (2 mL) under argon and placed at 10 °C. Then, (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (**4**) (0.04 mmol, 0.2 equiv) was added to the mixture. After 60 h, around ten drops of NH_4Cl were added to the reaction mixture to deactivate the catalyst. The organic layer was then separated and concentrated under vacuum. The diastereomeric ratio of the crude product was determined by ^{1}H NMR. Purification by flash chromatography over silica gel yielded the corresponding three-component product. For the description of products **16** (Schemes 7 and 8), see reference 10.

General procedure C for the three-component synthesis of 2,6-DABCOs 34, 45 and 51: Crushed 4Å molecular sieves (200 mg) was placed in a 25-mL reaction tube equipped with a septum. Air was evacuated under high vacuum and the reaction flask heated by means of a heat gun. After coming back to room temperature, the reaction flask was filled with argon. This operation was repeated a second time. (*R*,*R*)-Takemoto catalyst **33** (8.3 mg, 0.020 mmol, 0.1 equiv), β-ketoamide **31** (0.200 mmol, 1 equiv) and functionalized aminophenol **12** (0.300 mmol, 1.5 equiv) were introduced in the reaction flask, which was once again flushed with argon. Dry toluene (6 mL) was added and the reaction flask was cooled to −10 °C. After 10 minutes, acrolein (**32**) (0.400 mmol, 2 equiv) was added via syringe and the reaction mixture was stirred at −10 °C for 24 h. It was then filtered over a short pad of silica gel (2 cm) that was washed with EtOAc (50 mL). Concentration under reduced pressure afforded a solid that was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc) to provide the pure 2,6-DABCO **34**. For the description of products **34** (Scheme 13), see reference 11a.

(10*R*)-9-*tert*-butyl 10-ethyl 8-methyl-6,10,11,11a-tetrahydro-5*H*-pyrido[1,2-*a*]pyrrolo [2,1-*c*]pyrazine-9,10-dicarboxylate (5c). A reaction tube was charged with (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (**4**) (6.6 mg, 0.020 mmol, 0.1 equiv), benzoic acid (4.9 mg, 0.040 mmol, 0.2 equiv), dry α,α,α-trifluorotoluene (2.5 mL), flushed with argon and placed at 0 °C. *tert*-Butyl acetoacetate (**1a**) (31.6 mg, 32.9 µL, 0.200 mmol, 1 equiv) and (*E*)-ethyl 4-oxobut-2-enoate (**2c**) (30.8 mg, 28.9 µL, 0.240 mmol, 1.2 equiv) were then added. After full conversion of *tert*-butyl acetoacetate (**1a**) as monitored by TLC, followed by the addition of *N*-(2-aminoethyl)pyrrole (**3a**) (22.0

mg, 21.6 μL, 0.200 mmol, 1 equiv), the mixture was stirred at 0 °C for another 24 h. After reaction, direct purification by flash chromatography (PE/EtOAc 80:20) afforded **5c** as a mixture of diastereomers as a yellow oil (32.4 mg, 0.090 mmol, 45% yield, ~1.2:1 *dr*, 94% and 93% *ee*).

TLC (PE/EtOAc 4:1) R*f* 0.18 (UV, vanillin).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *cis-(10R,11aR)-diastereomer (minor)*: 6.55 – 6.53 (m, 1H), 6.17 (t, *J* = 3.2 Hz, 1H), 5.92 – 5.89 (m, 1H), 4.41 (dd, *J* = 8.9, 3.2 Hz, 1H), 4.23 – 4.09 (m, 3H), 4.09 – 3.93 (m, 2H), 3.67 – 3.62 (m, 1H), 3.40 – 3.31 (m, 1H), 2.54 – 2.49 (m, 1H), 2.49 (s, 3H), 2.20 – 2.11 (m, 1H), 1.42 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H); *trans-(10R,11aS)-diastereomer (major):* 6.58 – 6.56 (m, 1H), 6.13 (t, *J* = 3.2 Hz, 1H), 5.96 – 5.93 (m, 1H), 4.36 (dd, *J* = 11.5, 3.2 Hz, 1H), 4.09 – 3.93 (m, 5H), 3.71 – 3.67 (m, 1H), 3.40 – 3.31 (m, 1H), 2.54 – 2.49 (m, 1H), 2.46 (s, 3H), 1.99 – 1.90 (m, 1H), 1.44 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) *cis-(10R,11aR)-diastereomer (minor)*: 175.3 (C), 167.6 (C), 153.7 (C), 128.8 (C), 119.0 (CH), 108.5 (CH), 103.5 (CH), 99.8 (C), 79.3 (C), 60.5 (CH_2), 52.9 (CH), 44.9 (CH_2), 44.2 (CH_2), 41.2 (CH), 32.4 (CH_2), 28.4 (3 CH_3), 17.0 (CH_3), 14.2 (CH_3); *trans-(10R,11aS)-diastereomer (major):* 175.8 (C), 168.1 (C), 153.3 (C), 129.3 (C), 118.9 (CH), 108.6 (CH), 103.1 (CH), 97.6 (C), 79.1 (C), 60.8 (CH_2), 50.8 (CH), 45.1 (CH_2), 44.2 (CH_2), 39.6 (CH), 30.7 (CH_2), 28.5 (3 CH_3), 17.2 (CH_3), 14.5 (CH_3).

HRMS (ESI) calc´d for $[C_{20}H_{28}N_2O_4+H]^+$: 361.2122, found: 361.2119.

HPLC *cis-(10R,11aR)-diastereomer (minor)*: Chiralcel OD-3, Heptane/ethanol 90:10, 25°C, 1 ml/min, λ = 254 nm, τ_{major} = 17.66 min, τ_{minor} = 10.93 min; *trans-(10R,11aS)-diastereomer (major):* Chiralpak AD-H, Heptane/ethanol 90/10, 25°C, 1 ml/min, λ = 254 nm, τ_{major} = 6.90 min, τminor = 10.82 min.

1-(8-methyl-10-phenyl-6,10,11,11*a*-tetrahydro-5*H*-pyrido[1,2-*a*] pyrrolo[2,1-*c*]pyrazin-9-yl)ethanone (7aa). Prepared according to the general procedure A using acetylacetone (**6a**) (20.0 mg, 20.5 μL, 0.200 mmol, 1 equiv), (*E*)-cinnamaldehyde (**2a**) (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv) and *N*-(2-aminoethyl)pyrrole (**3a**) (22.0 mg, 21.6 μL, 0.200 mmol, 1 equiv.), with the following modifications: dry CH_2Cl_2 (2.5 mL) instead of α,α,α-trifluorotoluene as solvent, benzoic acid (4.9 mg, 0.040 mmol, 0.2 equiv) as co-catalyst and reaction run at –10 °C instead of 0 °C. Purification by flash chromatography (PE/Et_2O 33:67) afforded *cis*-(10*S*,11a*R*)-**7aa** as a pale solid (27.5 mg, 0.090 mmol, 45% yield, 94% *ee*) and *trans*-(10*S*,11a*S*)-**7aa** as a pale yellow oil (14.0 mg, 0.046 mmol, 23% yield, 90% *ee*).

cis-(10S,11aR) diastereomer:

TLC (PE/Et_2O 1:2) R*f* 0.36(UV, vanillin).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24 – 7.08 (m, 5H), 6.51 (d, *J* = 1.8 Hz, 1H), 6.05 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.73 (dt, *J* = 3.4, 1.4 Hz, 1H), 4.54 (dd, *J* = 9.7, 3.0 Hz, 1H), 4.12 – 3.99 (m, 4H), 3.37 (ddd, *J* = 10.3, 7.8, 4.3 Hz, 1H), 2.62 (ddd, *J* = 13.6, 6.4, 3.3 Hz, 1H), 2.45 (d, *J* = 1.0 Hz, 3H), 2.10 – 2.05 (m, 1H), 1.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 200.2 (C), 151.0 (C), 146.2 (C), 129.1 (C), 128.7 (2 CH), 127.2 (2 CH), 126.2 (CH), 118.6 (CH), 112.9 (C), 108.7 (CH), 103.4 (CH), 53.6 (CH), 45.2 (CH_2), 44.0 (CH_2), 41.8 (CH), 40.7 (CH_2), 30.6 (CH_3), 17.1 (CH_3).

HRMS (ESI) calc´d for $[C_{20}H_{22}N_2O +H]^+$: 307.1805, found: 307.1802.

HPLC Lux-Amylose-2, Hexane/ethanol 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 11.43 min, τ_{minor} = 9.02 min.

$[\alpha]_D^{20}$ = –4.7 (c 0.5, $CHCl_3$).

trans-(10S,11aS) diastereomer:

TLC (PE/Et_2O 1:2**)** R*f* 0.33(UV, vanillin).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 6.55 (d, *J* = 1.8 Hz, 1H), 6.11 (t, *J* = 3.0 Hz, 1H), 5.80 (dt, *J* = 3.5, 1.2 Hz, 1H), 4.19 – 4.07 (m, 3H), 4.08 – 3.95 (m, 2H), 3.42 (ddd, *J* = 13.7, 9.5, 4.4 Hz, 1H), 2.61 (s, 3H), 2.43 (ddd, *J* = 13.0, 3.5, 2.8 Hz, 1H), 2.18 (dd, *J* = 12.1, 5.0 Hz, 1H), 2.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 198.1 (C), 154.3 (C), 146.0 (C), 129.5 (C), 128.7 (2 CH), 128.1 (2 CH), 126.6 (CH), 118.9 (CH), 108.6 (CH), 107.8 (C), 103.0 (CH), 49.5 (CH), 45.0 (CH_2), 44.5 (CH_2), 39.8 (CH), 36.3 (CH_2), 29.6 (CH_3), 18.0 (CH_3).

HRMS (ESI) calc´d for $[C_{20}H_{22}N_2O+H]^+$: 307.1805, found: 307.1801.

HPLC Lux-Amylose-2, Hexane/ethanol 90:10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 22,68 min, τ_{minor} = 18,58 min.

$[\alpha]_D^{20}$ = –9.9 (c 0.3, $CHCl_3$).

1-(10-(4-chlorophenyl)-8-methyl-6,10,11,11*a*-tetrahydro-5*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-9-*yl*)ethanone (7ad). Prepared according to the general procedure A using acetylacetone (**6a**) (20.0 mg, 20.5 μL, 0.200 mmol, 1 equiv), (*E*)-4-chlorocinnamaldehyde (**2d**) (50.0 mg, 0.300 mmol, 1.5 equiv) and *N*-(2-aminoethyl)pyrrole (**3a**) (22.0 mg, 21.6 μL, 0.200 mmol, 1 equiv.), with the following modifications: dry CH_2Cl_2 (2.5 mL) instead of α,α,α-trifluorotoluene as solvent, benzoic acid (4.9 mg, 0.040 mmol, 0.2 equiv) as co-catalyst and reaction run at –10 °C instead of 0 °C. Purification by flash chromatography (PE/Et_2O 33:67) afforded *cis*-(10*S*,11a*R*)-**7ad** as a pale solid (25.8 mg, 0.076 mmol, 38% yield, 91% *ee*) and *trans*-(10*S*,11a*S*)-**7ad** as a pale yellow oil (19.8 mg, 0.058 mmol, 29% yield, 91% *ee*).

cis-(10S,11aR) diastereomer:

TLC (PE/EtOAc 1:2**)** R*f* 0.36(UV, vanillin).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.16 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.53 – 6.46 (m, 1H), 6.03 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.65 (dt, *J* = 3.4, 1.3 Hz, 1H), 4.55 (dd, *J* = 9.0, 3.3 Hz, 1H), 4.13 – 4.06 (m, 2H), 4.03 – 3.95 (m, 2H), 3.43 – 3.31 (m, 1H), 2.58 (ddd, *J* = 13.6, 6.4, 3.6 Hz, 1H), 2.46 (d, *J* = 0.9 Hz, 3H), 2.13 – 2.03 (m, 1H), 1.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 199.6 (C), 151.6 (C), 144.7 (C), 131.8 (C), 128.76 (2 CH), 128.72 (2 C), 128.5 (2 CH), 118.6 (CH), 112.1 (C), 108.7 (CH), 103.4 (CH), 53.4 (CH), 45.1 (CH_2), 44.2 (CH_2), 41.0 (CH), 39.9 (CH_2), 30.5 (CH_3), 17.2 (CH_3).

HRMS (ESI) calc´d for $[C_{20}H_{21}N_2OCl+H]^+$: 341.1415, found: 341.1414.

HPLC Chiralpak AD-H, Hexane/ethanol 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 8.34 min, τ_{minor} = 9.90 min.

$[\alpha]_D^{20}$ = –3.3 (c 0.9, $CHCl_3$).

trans-(10S,11aS) diastereomer:

TLC (PE/EtOAc 1:2**)** R*f* 0.33(UV, vanillin).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 – 7.24 (m, 2H), 7.17 – 7.13 (m, 2H), 6.61 – 6.55 (m, 1H), 6.14 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.85 – 5.79 (dt, *J* = 3.4, 1.4 Hz,, 1H), 4.18 (dt, *J* = 13.5, 3.8 Hz, 1H), 4.14 – 3.98 (m, 4H), 3.44 (ddd, *J* = 13.7, 9.1, 4.7 Hz, 1H), 2.61 (s, 3H), 2.44 – 2.38 (m, 1H), 2.18 (ddd, *J* = 13.1, 12.0, 5.0 Hz, 1H), 2.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 197.7 (C), 154.5 (C), 144.5 (C), 132.4 (C), 129.5 (2 CH), 129.2 (C), 128.9 (2 CH), 119.0 (CH), 108.6 (CH), 107.5 (C), 103.1 (CH), 49.4 (CH), 44.9 (CH_2), 44.5 (CH_2), 39.3 (CH), 36.2 (CH_2), 29.6 (CH_3), 18.0 (CH_3).

HRMS (ESI) calc´d for $[C_{20}H_{21}N_2OCl+H]^+$: 341.1415, found: 341.1411.

HPLC Lux-Amylose-2, Hexane/ethanol 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 13.32 min, τ_{minor} = 10.93 min.

$[\alpha]_D^{20}$ = +2.5 (c 0.7, $CHCl_3$).

(10*S*,11aS)-*N*,*N*,8-trimethyl-10-phenyl-6,10,11,11a-tetrahydro-5*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazine-9-carboxamide (7ca). Prepared according to the general procedure A using *N*, *N*-dimethyl-3-oxobutanamide (**6c**) (25.8 mg, 0.200 mmol, 1 equiv), (*E*)-cinnamaldehyde (**2a**) (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole (**3a**) (22.0 mg, 21.6 μL, 0.200 mmol, 1 equiv). Purification by flash chromatography (CH_2Cl_2/MeOH 98:2 then CH_2Cl_2/MeOH/AcOH 98:2:0.5) afforded *trans*-(10*S*,11a*S*)-**7ca** as a yellow oil (16.8 mg, 0.050 mmol, 25% yield, 92% *ee*).

TLC (CH_2Cl_2/MeOH 50:1**)** R*f* 0.5 (UV, vanillin).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.29 – 7.16 (m, 4H), 7.12 – 7.08 (m, 1H), 6.49 – 6.44 (m, 1H), 6.05 (t, *J* = 3.0 Hz, 1H), 5.74 (d, J = 2.7 Hz, 1H),

4.16 (d, *J* = 7.3 Hz, 1H), 3.92 (dtt, *J* = 11.4, 8.2, 3.5 Hz, 2H), 3.83 – 3.68 (m, 2H), 3.26 – 3.14 (m, 1H), 2.78 (s, 6H), 2.27 – 2.12 (m, 2H), 1.87 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 172.7 (C), 145.1 (C), 139.3 (C), 130.3 (C), 128.5 (2 CH), 128.2 (2 CH), 126.4 (CH), 118.9 (CH), 108.4 (CH), 107.2 (C), 102.4 (CH), 50.5 (CH), 45.2 (CH_2), 44.5 (CH_2), 39.5 (CH), 39.5 (2 CH_3), 35.3 (CH_2), 17.2 (CH_3).

HRMS (ESI) calc´d for [$C_{21}H_{25}N_3O$ +H]$^+$: 336.2070, found: 336.2071.

HPLC Lux-Cellulose-4, Hexane/ethanol 90:10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 26.36 min, τ_{minor} = 24.29 min.

[α]$_D^{20}$ = – 24.6 (c 0.3, CHCl$_3$).

(10*S*,11a*S*)-*N*-methoxy-*N*,8-dimethyl-10-phenyl-6,10,11,11a-tetra hydro-5*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazine-9-carboxamide (7da). Prepared according to the general procedure A using *N*-methoxy-*N*-methyl-3-oxobutanamide (**6d**) (29.0 mg, 0.200 mmol, 1 equiv), (*E*)-cinnamaldehyde (**2a**) (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole (**3a**) (22.0 mg, 21.6 μL, 0.200 mmol, 1 equiv). Purification by flash chromatography (CH_2Cl_2/MeOH 98:2 then CH_2Cl_2/MeOH/AcOH 98:2:0.5) afforded *trans*-(10*S*,11a*S*)-**7da** as a yellow oil (19.7 mg, 0.056 mmol, 28% yield, 88% *ee*).

TLC (CH_2Cl_2/MeOH 50:1**)** R*f* 0.36 (UV, vanillin).

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.24 – 7.09 (m, 5H), 6.46 – 6.42 (m, 1H), 6.02 (t, *J* = 3.0 Hz, 1H), 5.72 (d, *J* = 2.9 Hz, 1H), 4.12 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.93 – 3.79 (m, 4H), 3.29 (s, 3H), 3.25 – 3.14 (m, 1H), 2.95 (s, 3H), 2.17 (dtt, *J* = 18.7, 9.1, 5.0 Hz, 2H), 1.95 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 171.3 (C), 145.1 (C), 141.7 (C), 130.3 (C), 128.5 (2 CH), 128.3 (2 CH), 126.4 (CH), 118.9 (CH), 108.4 (CH), 106.4 (C), 102.4 (CH), 60.8 (CH_3), 50.7 (CH), 44.9 (CH_2), 44.7 (CH_2), 38.6 (CH), 35.2 (CH_2), 34.0 (CH_3), 17.3 (CH_3).

HRMS (ESI) calc´d for [$C_{21}H_{25}N_3O_2$+H]$^+$: 352.2020, found: 352.2021.

HPLC Chiralpak AD-H, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 10.21 min, τ_{minor} = 7.59 min.

[α]$_D^{20}$ = – 31.2 (c 0.2, CHCl$_3$).

Ethyl 8-methyl-10-phenyl-6,10,11,11a-tetrahydro-5*H*-pyrido[1,2-*a*] pyrrolo [2,1-*c*] pyrazine-9-carbothioate (7ea). Prepared according to the general procedure A using *S*-ethyl acetothioacetate (**6e**) (29.2 mg, 26.8μL 0.200 mmol, 1 equiv), (*E*)-cinnamaldehyde (**2a**) (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole (**3a**) (22.0 mg, 21.6 μL, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et_2O 80:20 then PE/Et_2O/AcOH 80:20: 0.5) afforded *cis*-(10*S*,11a*R*)-**7ea** as a yellow oil (15.0 mg, 0.042 mmol, 21% yield, 49% *ee*) and *trans*-(10*S*,11a*S*)-**7ea** as a yellow oil (23.2 mg, 0.058 mmol, 29% yield, 54% *ee*).

cis-(10S,11aR) diastereomer:

TLC (PE/EtOAc 4:1) R*f* 0.29 (UV, vanillin).

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.19 – 7.13 (m, 2H), 7.13 – 7.04 (m, 3H), 6.51 – 6.42 (m, 1H), 5.99 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.63 (dt, *J* = 3.5, 1.4 Hz, 1H), 4.55 (dd, *J* = 8.6, 3.6 Hz, 1H), 4.26 – 4.18 (m, 1H), 4.07 (dt, *J* = 13.0, 3.4 Hz, 1H), 4.03 – 3.97 (m, 2H), 3.39 (ddd, *J* = 13.5, 8.9, 5.2 Hz, 1H), 2.74 – 2.57 (m, 3H), 2.42 (d, *J* = 1.1 Hz, 3H), 2.19 (dt, *J* = 13.6, 8.8 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm) 192.4 (C), 149.4 (C), 145.5 (C), 128.9 (C), 128.2 (2 CH), 127.5 (2 CH), 125.9 (CH), 118.5 (CH), 111.4 (C), 108.7 (CH), 103.4 (CH), 53.5 (CH), 45.2 (CH_2), 44.4 (CH_2), 40.9 (CH), 39.5 (CH_2), 23.5 (CH_2), 17.4 (CH_3), 15.0 (CH_3).

HRMS (ESI) calc´d for [$C_{21}H_{24}N_2OS$+H]$^+$: 353.1682, found: 353.1681.

HPLC Lux-Amylose-2, Hexane/ethanol 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 7.15 min, τ_{minor} = 6.20 min.

[α]$_D^{20}$ = – 11.6 (c 0.2, CHCl$_3$).

trans-(10S,11aS) diastereomer:

TLC (PE/EtOAc 4:1) R*f* 0.2 (UV, vanillin).

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.34 – 7.29 (m, 2H), 7.24 – 7.19 (m, 3H), 6.55 (tt, *J* = 1.7, 0.6 Hz, 1H), 6.12 (dd, *J* = 3.6, 2.7 Hz, 1H), 5.80 (dt, *J* = 3.6, 1.4 Hz, 1H), 4.37 (dd, *J* = 4.9, 2.7 Hz, 1H), 4.21 – 4.10 (m, 2H), 4.07 – 3.99 (m, 2H), 3.43 (ddd, *J* = 13.8, 9.6, 4.4 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.67 (dt, *J* = 13.3, 7.4 Hz, 1H), 2.60 (s, 3H), 2.46 (ddd, *J* = 13.1, 4.0, 2.7 Hz, 1H), 2.17 (ddd, *J* = 13.1, 12.0, 4.8 Hz, 1H), 1.15 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm) 190.2 (C), 152.5 (C), 145.6 (C), 129.4 (C), 128.5 (2 CH), 127.9 (2 CH), 126.4 (CH), 118.9 (CH), 108.6 (CH), 106.2 (C), 103.0 (CH), 49.6 (CH), 44.9 (CH_2), 44.7 (CH_2), 38.6 (CH), 36.1 (CH_2), 23.5 (CH_2), 17.9 (CH_3), 15.1 (CH_3).

HRMS (ESI) calc´d for [$C_{21}H_{24}N_2OS$+H]$^+$: 353.1682, found: 353.1685.

HPLC Chiralpak AD-H, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 12.07 min, τ_{minor} = 8.08 min.

[α]$_D^{20}$ = – 28.9 (c 0.2, CHCl$_3$).

1-((5*S*)-5-phenyl-4,5,12,13-tetrahydropyrrolo[2'',1'':3',4']pyrazino[1',2':1,6]pyrido[3,2-b] indol-6(3b*H*)-yl)ethanone (7ha). Prepared according to the general procedure A at 0 °C using 1-acetylindolin-3-one (**6h**) (35.0 mg, 0.200 mmol, 1 equiv), (*E*)-cinnamaldehyde (**2a**) (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv.), *N*-(2-aminoethyl)pyrrole (**3a**) (22.0 mg, 21.6 μL, 0.200 mmol, 1 equiv), with CH_2Cl_2 (2.5 mL) instead of α,α,α-trifluorotoluene as solvent. Purification by flash chromatography (PE/Et_2O 4:1) afforded **7ha** as a white solid (52.8 mg, 0.136 mmol, 68% yield, ~1.5:1 *dr*, 88% *ee* and 87% *ee*).

TLC (PE/Et_2O 4:1) R*f* 0.15 (UV, vanillin).

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) *cis-(10S,11aR)-diastereomer (major):* 8.04 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.41 – 7.27 (m, 3H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.62 – 6.57 (m, 1H), 6.17 (t, *J* = 3.1 Hz, 1H), 5.98 (d, *J* = 3.2 Hz, 1H), 4.70 (dd, *J* = 10.4, 7.5 Hz, 1H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.38 (d, *J* = 10.2 Hz, 1H), 4.19 – 4.07 (m, 1H), 3.79 (dt, *J* = 12.7, 3.9 Hz, 1H), 3.57 (ddd, *J* = 12.9, 9.7, 3.5 Hz, 1H), 2.50 – 2.42 (m, 1H), 2.36 (s, 3H), 2.04 – 1.91 (m, 1H); *trans-(10S,11aS)-diastereomer (minor):* 8.12 (d, *J* = 8.2 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.40 – 7.27 (m, 3H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.11 (d, *J* = 7.3 Hz, 2H), 6.62 – 6.57 (m, 1H), 6.14 (t, *J* = 3.1 Hz, 1H), 5.77 (d, *J* = 3.3 Hz, 1H), 4.79 (d, *J* = 3.9 Hz, 1H), 4.35 – 4.26 (m, 2H), 4.19 – 4.07 (m, 1H), 3.71 (dt, *J* = 12.6, 4.2 Hz, 1H), 3.65 (dt, *J* = 7.6, 3.8 Hz, 1H), 2.56 (td, *J* = 13.4, 5.6 Hz, 1H), 2.48 (s, 3H), 2.12 (dt, *J* = 13.6, 2.0 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm) *cis-(10S,11aR)-diastereomer (major):* 169.6 (C), 144.7 (C), 136.1 (C), 134.1 (C), 129.3 (C), 128.9 (2 CH), 127.9 (2 CH), 127.0 (2 CH), 125.1 (CH), 124.6 (C), 123.0 (CH), 118.7 (CH), 118.4 (CH), 115.4 (CH), 108.4 (CH), 103.9 (CH), 54.6 (CH), 46.2 (CH_2), 45.7 (CH_2), 42.3(CH), 39.0 (CH_2), 26.8 (CH_3); *trans-(10S,11aS)-diastereomer (minor):* 169.1 (C), 145.2 (C), 135.9 (C), 131.8 (C), 129.5 (C), 128.8 (2 CH), 126.7 (2 CH), 126.6 (2 CH), 125.0 (CH), 124.2 (C), 123.1 (CH), 118.8 (CH), 118.5 (CH), 116.3 (CH), 108.3 (CH), 103.6 (CH), 50.0 (CH), 46.9 (CH_2), 45.6 (CH_2), 40.1 (CH), 35.2 (CH_2), 27.2 (CH_3).

HRMS (ESI) calc´d for [$C_{25}H_{23}N_3O$+H]$^+$: 382.1914, found: 382.1913.

HPLC *cis-(10S,11aR)-diastereomer (major):* Chiralpak AZ-H, Hexane/ethanol 50:50, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 14.25 min, τ_{minor} = 10.45 min; *trans-(10S,11aS)-diastereomer (minor):* Chiralpak AZ-H, Hexane/ethanol 50:50, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 11.58 min, τ_{minor} = 7.09 min.

(2*S*,13b*S*)-*tert*-butyl 11-methoxy-4-methyl-2-phenyl-2,6,7,13b-tetrahydro-1*H*-pyrido[2',1':3,4] pyrazino [1,2-*a*]indole-3-carboxylate (9). A reaction tube was charged with (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**4**) (12.0 mg, 0.020 mmol, 0.1 equiv), dry α,α,α-trifluorotoluene (2.5 mL), flushed with argon and placed at 0 °C. *tert*-butyl acetoacetate (**1a**) (31.6 mg, 32.9 μL, 0.200 mmol, 1 equiv) and (*E*)-cinnamaldehyde (**2a**) (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv) were then added. After full conversion of *tert*-butyl acetoacetate (**1a**) as monitored by TLC (48 h), followed by the addition of 2-(5-methoxy-1*H*-indol-1-yl)ethanamine (**8**) (38.0 mg, 0.200 mmol, 1 equiv), the mixture was stirred at 0 °C for another 24 h. After reaction, the solution was filtered through a short pad of silica gel, which was thoroughly washed with EtOAc. The solvent was evaporated by reduced pressure to obtain the crude compound, which was analyzed by ^{1}H NMR, which was identified as the dihydropyridine **10**. Purification by

flash column chromatography (PE/EtOAc 80:20 and then PE/EtOAc/AcOH 80:20:0.5) on silica gel provided the pure *trans*-(2*S*,13b*S*)-indolopiperazine **9** as pale yellow solid (28.4 mg, 0.064 mmol, 32% yield, 85% *ee*).

TLC (PE/EtOAc 4:1) R*f* 0.53 (UV, vanillin).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 – 7.27 (m, 2H), 7.27 – 7.17 (m, 3H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.09 (s, 1H), 4.38 – 4.23 (m, 2H), 4.21 – 4.08 (m, 2H), 4.02 (td, *J* = 11.3, 4.2 Hz, 1H), 3.83 (s, 3H), 3.41 (ddd, *J* = 13.9, 11.5, 3.7 Hz, 1H), 2.55 (s, 3H), 2.40 (dt, *J* = 13.3, 3.3 Hz, 1H), 2.25 (ddd, *J* = 13.2, 11.3, 5.7 Hz, 1H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 168.5 (C), 154.6 (C), 152.5 (C), 147.5 (C), 137.9 (C), 131.3 (C), 128.7 (C), 128.3 (C), 128.3 (2 CH), 128.1 (2 CH), 126.0 (CH), 111.2 (CH), 109.3 (CH), 102.5 (CH), 96.1 (CH), 78.8 (C), 56.1 (CH_3), 50.2 (CH), 44.3 (CH_2), 42.6 (CH_2), 38.9 (CH), 36.1 (CH_2), 28.2 (3 CH_3), 17.5 (CH_3).

HRMS (ESI) calc´d for $[C_{28}H_{32}N_2O_3+H]^+$: 445.2486, found: 445.2485.

HPLC Chiralpak AZ-H, Heptane/ethanol 90:10, 25°C, 1.0 mL/min, λ = 254 nm, τ_{major} = 11.47 min, τ_{minor} = 9.83 min.

(*S*)-*tert*-butyl 1-(2-(5-methoxy-1*H*-indol-1-yl)ethyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (10). A reaction tube was charged with (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**4**) (12.0 mg, 0.020 mmol, 0.1 equiv), dry α,α,α-trifluorotoluene (2.5 mL), flushed with argon and placed at 0 °C. *tert*-butyl acetoacetate (**1a**) (31.6 mg, 32.9 μL, 0.200 mmol, 1 equiv) and (*E*)-cinnamaldehyde (**2a**) (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv) were then added. After full conversion of *tert*-butyl acetoacetate (**1a**) as monitored by TLC (48 h), followed by the addition of 2-(5-methoxy-1*H*-indol-1-yl)ethanamine **8** (38.0 mg, 0.200 mmol, 1 equiv), the mixture was stirred at 0 °C for another 24 h. After reaction, the solution was filtered through a short pad of silica gel, which was thoroughly washed with EtOAc. The solvent was evaporated by reduced pressure to obtain the crude compound, which was analyzed by ^{1}H NMR, which was identified as the dihydropyridine **10**. Purification by flash column chromatography over aluminium oxide 90 neutral (PE/EtOAc 85:15) provided the pure (*S*)-dihydropyridine **10** as pale yellow solid (26.3 mg, 0.060 mmol, 30% yield, 91% *ee*).

TLC (PE/EtOAc 6:1) R*f* 0.42 (UV, vanillin).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 – 7.26 (m, 1H), 7.23 – 7.19 (m, 3H), 7.18 – 7.18 – 7.12 (m, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 6.98 (d, *J* = 3.1 Hz, 1H), 6.89 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.43 (d, *J* = 2.6 Hz, 1H), 5.61 (d, *J* = 7.8 Hz, 1H), 4.83 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.55 (d, *J* = 5.0 Hz, 1H), 4.35 – 4.14 (m, 2H), 3.85 (s, 3H), 3.84 – 3.73 (m, 2H), 3.60 (dt, *J* = 15.0, 6.2 Hz, 1H), 2.19 (s, 3H), 1.21 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 168.5 (C), 154.3 (C), 149.1 (C), 146.4 (C), 131.1 (C), 129.4 (C), 128.7 (CH), 128.3 (2 CH), 127.8 (CH), 127.6 (2 CH), 126.1 (CH), 112.4 (CH), 109.6 (CH), 108.5 (CH), 103.0 (CH), 102.7 (C), 101.8 (CH), 79.2 (C), 56.0 (CH_3), 49.7 (CH_2), 46.6 (CH_2), 41.1 (CH), 28.2 (3 CH_3), 15.5 (CH_3).

HRMS (ESI) calc´d for $[C_{28}H_{32}N_2O_3+H]^+$: 445.2486, found: 445.2487.

HPLC Chiralpak AZ-H, Heptane/ethanol 90:10, 25°C, 1.0 mL/min, λ = 254 nm, τ_{major} = 12.11 min, τ_{minor} = 14.10 min.

(3*S*)-*tert*-butyl 1-methyl-3-phenyl-3,4,4a,6-tetrahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (13c). Prepared according to the general procedure A using *tert*-butyl acetoacetate (**1a**) (31.6 mg, 32.9 μL, 0.200 mmol, 1 equiv), (*E*)-cinnamaldehyde (**2a**) (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv), 2-aminobenzyl alcohol (**11c**) (24.6 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography over silica gel (PE/Et_2O 80:20) afforded **12c** as a pale yellow solid (~20 mg, ~0.050 mmol, ~2% yield, 1.3:1 *dr*, 88% *ee*).

TLC (PE/Et_2O 80:10) R*f* 0.36 and 0.40 (UV, vanillin).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *major diastereomer*: 7.35 – 7.17 (m, 5H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 4.79 (d, *J* = 14.3 Hz, 1H), 4.68 (d, *J* = 14.3 Hz, 1H), 4.19 – 4.09 (m, 1H), 3.80 – 3.75 (m, 1H), 2.33 (s, 3H), 2.15 – 1.78 (m, 2H), 1.10 (s, 9H); *minor diastereomer*: 7.35 – 7.17 (m, 5H), 7.07 (t, *J* = 6.9 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.80 – 6.72 (m, 2H), 4.74 (app s, 2H), 4.27 – 4.19 (m, 1H), 3.80 – 3.73 (m, 1H), 2.31 (s, 3H), 2.10 – 1.82 (m, 2H), 1.10 (s, 9H).

HPLC Chiralpak AD-H, Hexane/ethanol 90:10, 25 °C, 1.0 mL/min, λ = 254 nm, *major diastereromer:* τ_{minor} = 15.72 min, τ_{major} = 22.33 min; *minor diastereromer:* τ_{minor} = 17.95 min, τ_{major} = 19.12 min

(3*R*,4*S*,4a*R*)-*tert*-butyl 4a-methyl-3-phenyl-4,4a-dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxylate (15). Prepared according to the general procedure A using *tert*-butyl acetoacetate (**1a**) (31.6 mg, 32.9 μL, 0.200 mmol, 1 equiv), (*E*)-cinnamaldehyde (**2a**) (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv), 2-aminophenol (**12a**) (21.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography over silica gel (PE/Et_2O 90:10) afforded **15** as a pale yellow oil (18.2 mg, 0.050 mmol, 25% yield, >20:1 *dr*, 92% *ee*). More polar regioisomer **14** could not be obtained pure.

TLC (PE/Et_2O 80:20) R*f* 0.45 (UV, vanillin).

HRMS (ESI) calc´d for $[C_{23}H_{25}NO_3+H]^+$: 364.1907, found: 364.1909.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26 – 7.16 (m, 5H), 6.82 – 6.77 (m, 1H), 6.73 – 6.66 (m, 2H), 6.63 – 6.59 (m, 1H), 6.54 (dd, *J* = 7.6, 2.1 Hz, 1H), 4.82 (dd, *J* = 7.6, 2.0 Hz, 1H), 3.81 (dt, *J* = 11.9, 2.0 Hz, 1H), 2.92 (d, *J* = 11.9 Hz, 1H), 1.70 (s, 3H), 1.21 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.3 (C), 149.8 (C), 141.7 (C), 134.6 (C), 128.5 (2 CH), 128.3 (2 CH), 127.3 (CH), 124.0 (CH), 121.4 (CH), 120.2 (CH), 108.9 (CH), 107.0 (CH), 106.9 (CH), 100.0 (C), 81.2 (C), 54.9 (CH), 43.4 (CH), 28.0 (3 CH_3), 20.8 (CH_3).

HPLC Chiralpak IA, Hexane/isopropanol 95:5, 25°C, 1.0 mL/min, λ = 254 nm, τ_{major} = 4.99 min, τ_{minor} = 5.99 min.

$[\alpha]_D^{20}$ = – 11.3 (c 0.3, $CHCl_3$).

4-bromo-*N*-methoxy-*N*-methyl-3-oxobutanamide (17d). To a solution of *N*-methoxy-*N*-methyl-3-oxobutanamide (**6d**) (1.02 g, 7 mmol, 1 equiv) in dry chloroform (10 mL) at 0 °C was added bromine (360 μL, 7 mmol, 1 equiv) dropwise over 45 min with vigorous stirring. After the mixture was stirred at room temperature for 24 h, cold water was added (20 mL), and the organic layer washed with a sodium thiosulfate aqueous solution (3 x 20 mL). The organic layer was dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography over silica gel (PE/EtOAc 70:30 to 50:50) yielded product **17d** as an orange oil (710 mg, 3.17 mmol, 45% yield, ~1.3:1 ketone vs enol forms).

TLC (PE/EtOAc 50:50) R*f* 0.23 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_6H_{10}BrNO_3+H]^+$: 223.9917, found: 223.9915.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) *ketone form:* 4.04 (s, 2H), 3.79 (s, 2H), 3.68 (s, 3H), 3.19 (s, 3H); enol form: 13.68 (s, 1H), 5.67 (s, 1H), 3.85 (s, 2H), 3.68 (s, 3H), 3.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) *ketone form:* 195.7 (C), 170.5 (C), 61.6 (CH_3), 44.6 (CH_2), 32.2 (CH_3), 34.4 (CH_2); *enol form:* 171.6 (C), 167.4 (C), 88.6 (CH), 61.7 (CH_3), 31.8 (br, CH_3), 29.9 (CH_2).

1-(2-oxopyrrolidin-1-yl)butane-1,3-dione (20). 2-Pyrrolidinone (**19**) (1.70 g, 20 mmol, 1 equiv) was dissolved in dry toluene (10 mL) under argon atmosphere. Then, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**18**) (2.63 mL, 20 mmol, 1 equiv) was added and the reactor was irradiated under microwave at 150 °C during 30 min. Solvent was removed under reduced pressure. Purification by flash column chromatography over silica gel (PE/EtOAc 70:30 to 50:50) yielded product **20** as an orange oil (2.65 g, 15.7 mmol, 78% yield, ~9:1 ketone vs enol forms).

TLC (PE/EtOAc 50:50) R*f* 0.20 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_8H_{11}NO_3+H]^+$:170.0812, found: 170.0814.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *ketone form:* 3.92 (s, 2H), 3.79 (t, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 8.1 Hz, 2H), 2.20 (s, 3H), 2.06 – 1.95 (m, 2H). NMR signals are in accordance with literature.[44]

(3*R*,4*S*,4a*R*)-*N*-methoxy-*N*,4a-dimethyl-3-phenyl-2,3,4,4a-tetrahydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide (23). The three-component product **16a** (144 mg, 0.411 mmol, 1 equiv) was dissolved in methanol (15 mL) under argon atmosphere. Then, Pd/C (18 mg, 0.164 mmol, 12 wt.%) was added to the solution before flushing the reaction mixture with hydrogen. The reaction was stirred at room temperature during 13 h. After filtration on celite and washing with CH_2Cl_2, solvents were removed under vacuum. Purification by flash column chromatography over silica gel (PE/EtOAc 80:20 to 50:50) yielded the hydrogenated product **23** as a yellowish oil (117 mg, 0.332 mmol, 81 % yield, >20:1 *dr*).

TLC (PE/EtOAc 70:30) R*f* 0.65 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{21}H_{22}N_2O_3+H]^+$: 353.1860, found: 353.1862.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24 – 7.11 (m, 5H), 6.88 – 6.80 (m, 1H), 6.69 – 6.61 (m, 2H), 6.45 (d, *J* = 7.4 Hz, 1H), 3.95 (d, *J* = 10.4 Hz, 1H), 3.75 (ddd, *J* = 14.7, 4.2, 1.6 Hz, 1H), 3.62 (s, 3H), 3.40 – 3.17 (m, 2H), 2.86 (s, 3H), 1.91 (s, 3H), 1.87 – 1.75 (td, *J* = 12.7, 4.2 Hz, 1H), 1.71 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (C), 148.7 (C), 142.5 (C), 138.8 (C), 128.3 (2 CH), 127.7 (2 CH), 126.7 (CH), 121.7 (CH), 118.4 (CH), 108.5 (CH), 105.6 (CH), 102.2 (C), 61.2 (CH_3), 47.8 (CH), 43.6 (CH_3), 41.7 (CH_2), 32.0 (CH), 30.5 (CH_2), 20.4 (CH_3).

$[\alpha]_D^{20}$ = +162 (c 1.0, $CHCl_3$).

(2*S*,3*S*,4*R*)-1-(2-hydroxyphenyl)-*N*-methoxy-*N*,2-dimethyl-4-phenyl-2-(phenylethynyl) piperidine -3-carboxamide (25). A mixture of product **23** (64 mg, 0.182 mmol, 1 equiv), potassium phenylethynyltrifluoroborate (**24**) (99 mg, 0.436 mmol, 2.4 equiv) and scandium (III) triflate (17.9 mg, 0.036 mmol, 0.2 equiv) was dissolved in dry CH_2Cl_2 (2 mL) under argon atmosphere. The reaction mixture was stirred at room temperature during 40 h. After filtration on celite, the CH_2Cl_2 was removed under vacuum. Purification by flash column chromatography over silica gel (cyclohexane/EtOAc 75:25) yielded product **25** as a colorless oil (35 mg, 0.077 mmol, 42% yield, >20:1 *dr*).

TLC (Cyclohexane/EtOAc 75:25) R*f* 0.47 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{29}H_{30}N_2O_3+H]^+$: 455.2329, found: 455.2328.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.00 (s, 1H), 7.62 - 7.57 (m, 2H), 7.55 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.43 - 7.37 (m, 3H), 7.35 - 7.17 (m, 5H), 7.11 (td, *J* = 7.9, 1.4 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.79 (td, *J* = 7.6, 1.3 Hz, 1H), 3.77 - 3.62 (m, 2H), 3.56 (d, *J* = 4.4 Hz, 1H), 3.08 - 2.95 (m, 2H), 3.01 (s, 3H), 2.94 (s, 3H), 1.74 – 1.64 (m, 1H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 172.9 (C), 155.8 (C), 143.3 (C), 135.5 (C), 131.9 (2 CH), 128.6 (2 CH), 128.52 (CH), 128.50 (2 CH), 128.3 (2 CH), 127.7 (CH), 127.1 (CH), 126.1 (CH), 123.2 (C), 119.2 (CH), 114.4 (CH), 90.7 (C), 86.5 (C), 60.7 (CH_3), 57.9 (C), 50.8 (CH), 50.5 (CH_2), 43.4 (CH_3), 31.9 (CH), 27.5 (CH_2), 24.8 (CH_3).

$[\alpha]_D^{20}$ = +162 (c 1.0, $CHCl_3$).

Ethyl (6a*S*,7*R*,8*S*,8a*R*,14a*S*)-8-(methoxy(methyl)carbamoyl)-2,8a-dimethyl-7-phenyl-5,6a,7,8,8a,14a-hexahydro-6*H*-benzo[*h*]benzo[4,5]oxazolo[3,2-*a*][1,6]naphthyridine-6-carboxylate (28). 4Å molecular sieves (ca. 600mg) and $Sc(OTf)_3$ (9.8 mg, 0.020 mmol, 0.2 equiv) were added to a solution of ethyl glyoxalate (**26**) (50% in toluene, 13 µL, 0.100 mmol, 1 equiv) and *p*-toluidine (**27**) (10.7 mg, 0.100 mmol, 1 equiv) in dry CH_3CN (2 mL), and the mixture as stirred at room temperature. After 5 min, the three-component product **16a** (35 mg, 0.100 mmol, 1 equiv) was added, and the resulting suspension was stirred under argon atmosphere at the same temperature for 48 h. An aqueous saturated $NaHCO_3$ solution (5 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (PE/EtOAc 70:30) to afford the desired piperidine **28** as a colorless oil (41 mg, 0.076 mmol, 76% yield, 1.6:1 *dr*).

TLC (PE/EtOAc 70:30) R*f* 0.47 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{32}H_{35}N_3O_5+H]^+$: 542.2649, found: 542.2650.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) Most aromatic protons and NH could not be attributed unambiguously to one diastereomer or the other: *major diastereomer* 7.34 – 7.27 (m, 2H), 7.23 - 7.08 (m, 2 or 3H), 7.00 - 6.85 (m, 3 or 4H), 6.74 - 6.66 (m, 2H), 6.65 – 6.52 (m, 2H), 5.33 (d, *J* = 5.8 Hz, 1H), 4.32 or 3.98 (s, 1H, NH), 4.29 - 4.00 (m, 1H), 3.68 (s, 3H), 3.63 - 3.50 (m, 3H), 3.14 - 3.04 (m, 1H), 2.99 (dd, *J* = 11.3, 5.7 Hz, 1H), 2.68 (s, 3H), 2.24 (s, 3H), 1.46 (s, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); *minor diastereomer* 7.34 – 7.27 (m, 2H), 7.23 - 7.08 (m, 2 or 3H), 7.00 - 6.85 (m, 3 or 4H), 6.74 - 6.66 (m, 2H), 6.65 – 6.52 (m, 2H), 5.06 (d, *J* = 5.7 Hz, 1H), 4.32 or 3.98 (s, 1H, NH), 4.29 - 4.00 (m, 3H), 3.66 (s, 3H), 3.44 (t, *J* = 11.9 Hz, 1H), 3.36 (d, *J* = 2.6 Hz, 1H), 2.84 (ddd, *J* = 11.9, 5.9, 2.7 Hz, 1H), 2.76 (s, 3H), 2.22 (s, 3H), 1.54 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): The complexity of the structure, its existence as two diastereomers, which causes overlaps between some signals, and its moderate stability made it difficult to obtain a complete ^{13}C NMR description. For each diastereomer, 30 signals are expected: 2 carbonyls, 6 aromatic C, 10 aromatic CH (including two accounting for two carbon atoms), 1 aliphatic C (aminal), 5 aliphatic CH, 1 aliphatic CH_2 and 5 aliphatic CH_3. δ (ppm): 173.6, 173.4, 171.5, 170.1 (carbonyl C); 148.4, 143.9, 141.5, 140.7, 140.1, 140.0, 139.7, 138.5, 137.4, 131.8, 131.3, 120.1, (aromatic C); 133.1, 129.9, 129.9, 129.5, 129.4, 129.4, 128.6, 127.9, 127.8, 127.2, 127.0, 121.7, 121.6, 118.7, 118.6, 115.4, 115.3, 115.2, 108.4, 105.1 (aromatic CH); 102.3, 102.1 (aminal C); 61.5, 61.0 (aliphatic CH_2); 77,4, 61.3, 57.7, 55.6, 55.3, 50.3, 48.5, 42.3, 40.2, 38.6, 32.1, 30.5, 23.7, 20.8, 20.7, 14.4, 14.3, 14.2, 13.8 (aliphatic CH and CH_3).

HPLC Chiralpak IE, Heptane/Ethanol 80:20, 1 mL/min, λ = 254 nm, major diastereomer: τ_{minor} = 7.35 min, τ_{major} = 9.19 min, minor diastereomer: τ_{minor} = 12.43 min, τ_{major} = 13.98 min.

$[\alpha]_D^{20}$ = +146 (c 1.0, $CHCl_3$).

(3*R*,4*S*,4a*R*)-3-(4-fluorophenyl)-*N*-methoxy-*N*,4a-dimethyl-4,4a-dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide (29). Prepared according to the general procedure B using Weinreb β-ketoamide (**6d**) (29.0 mg, 0.200 mmol, 1 equiv), (*E*)-4-fluorocinnamaldehyde (**2f**) (45.0 mg, 39.3 µL, 0.300 mmol, 1.5 equiv) and 2-aminophenol (**12a**) (21.8 mg, 0.200 mmol, 1 equiv), at 25 °C instead of 10 °C Purification by flash chromatography over silica gel (PE/EtOAc 80:20) afforded **29** as a yellow solid (33.8 mg, 0.092 mmol, 46% yield, >20:1 *dr*, 91% *ee*).

TLC (PE/EtOAc 80:20) R*f* 0.50 (UV, vanillin).

HRMS (ESI) calc´d for $[C_{21}H_{21}FN_2O_3+H]^+$: 369.1609, found: 369.1606.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.22 (dd, *J* = 8.3, 5.6 Hz, 2H), 6.93 (t, *J* = 8.7 Hz, 2H), 6.83 (td, *J* = 7.4, 1.6 Hz, 1H), 6.75 – 6.57 (m, 4H), 4.89 (dd, *J* = 7.6, 1.7 Hz, 1H), 3.99 (d, *J* = 11.6 Hz, 1H), 3.60 (d, *J* = 11.6 Hz, 1H), 3.32 (s, 3H), 3.01 (s, 3H), 1.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 171.2 (C), 162.0 (C, d, $J_{C\text{-}F}$ = 245 Hz), 149.5 (C), 137.7 (C, d, $J_{C\text{-}F}$ = 3.0 Hz), 134.5 (C), 129.7 (2 CH, d, $J_{C\text{-}F}$ = 7.8 Hz), 124.0 (CH), 121.5 (CH), 120.1 (CH), 115.4 (CH), 115.2 (CH), 108.6 (CH), 106.8 (2 CH, d, $J_{C\text{-}F}$ = 12.3 Hz), 100.6 (C), 61.2 (CH_3), 48.9 (CH), 42.5 (CH_3), 32.1 (CH), 21.0 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –115.75.

HPLC Chiralpak IF, Heptane/Isopropanol 95:5, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 7.65 min, τ_{minor} = 6.79 min.

(1*S*,3*R*,4*S*,4a*R*)-3-(4-fluorophenyl)-*N*-methoxy-*N*,4a-dimethyl-1-(phenylethynyl)-2,3,4,4a-tetrahydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide (30). The three-component product **29** (73.6 mg, 0.200 mmol, 1 equiv, 91% *ee*), potassium phenylethynyltrifluoroborate (**24**) (49.9 mg, 0.240 mmol, 1.2 equiv), scandium (III) triflate (9.8 mg, 0.020 mmol, 10 mol%) were stirred in CH_2Cl_2 (1 mL) at 25 °C. After 4 h, the crude solution was filtrated through a short pad of Celite and the solvent concentrated under vacuum. Purification by flash chromatography over silica gel (PE/EtOAc 90:10) afforded **30** as a yellow solid (quantitative yield, 91% *ee*).

TLC (PE/EtOAc 80:20) R*f* 0.18 (UV, vanillin).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.54 – 7.43 (m, 2H), 7.39 – 7.31 (m, 3H), 7.20 – 7.10 (m, 2H), 6.98 – 6.81 (m, 3H), 6.76 – 6.59 (m, 2H), 6.53 (d, *J* = 7.5 Hz, 1H), 5.00 (dd, *J* = 4.8, 2.1 Hz, 1H), 3.94 (d, *J* = 12.1 Hz, 1H), 3.76 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.68 (s, 3H), 2.89 (s, 3H), 2.13 (s, 3H), 2.11 – 2.03 (m, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –116.13.

HPLC Chiralpak IA, Heptane/ethanol 80/20, 25°C, 1.0 mL/min, DAD + polarimeter, τ_{major} = 4.76 min, τ_{minor} = 6.95 min.

(4a*R*)-4a-methyl-3-phenyl-12-tosyl-2,3,4,4a-tetrahydro-1*H*-1,4-(epiminomethano)benzo[4,5]oxazolo[3,2-a]pyridin-11-one (36a). Prepared according to the general procedure B using 3-oxo-*N*-tosylbutanamide (**35**) (48.3 mg, 0.200 mmol, 1 equiv), (*E*)-cinnamaldehyde (**2a**) (38 µL, 0.300 mmol, 1.5 equiv) and 2-aminophenol (**12a**) (21.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography over silica gel (CH_2Cl_2/EtOAc 99.5:0.5) afforded product **36a** as a yellowish solid (52 mg, 0.117 mmol, 58% yield, 14:1 *dr*, 65% *ee* (*major diastereomer*), 61% *ee* (*minor diastereomer*)).

TLC (CH_2Cl_2/EtOAc 99.5:0.5) R*f* 0.59 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{26}H_{24}N_2O_4S+H]^+$: 461.1530, found: 461.1531.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 - 7.19 (m, 8H), 7.09 - 7.00 (m, 4H), 6.54 - 6.51 (m, 1H), 5.95 (t, *J* = 2.5 Hz, 1H), 3.59 - 3.52 (m, 1H), 3.10 (d, *J* = 2.2 Hz, 1H), 2.91 - 2.82 (m, 1H), 2.38 (s, 3H), 2.38 - 2.34 (m, 1H), 1.67 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 166.1 (C), 151.6 (C), 144.6 (C), 141.1 (C), 136.2 (C), 135.1 (C), 129.3 (2 CH), 129.2 (2 CH), 128.6 (2 CH), 127.7 (CH), 127.6 (2 CH), 125.8 (CH), 121.9 (CH), 117.5 (CH), 110.2 (CH), 102.1 (C), 74.2 (CH), 56.2 (CH), 36.5 (CH and CH_2), 23.3 (CH_3), 21.8 (CH_3).

HPLC Chiralpak IA, Heptane/Ethanol 50:50, 1 mL/min, λ = 254 nm, *major diastereomer:* τ_{minor} = 12.65 min, τ_{major} = 23.70 min, *minor diastereomer:* τ_{minor} = 21.32 min, τ_{major} = 10.69 min.

$[\alpha]_D^{20}$ = +158 (c 1.0, $CHCl_3$).

m.p. = 76-78 °C.

(4a*R*)-7-chloro-4a-methyl-3-phenyl-12-tosyl-2,3,4,4a-tetrahydro-1*H*-1,4-(epiminomethano)benzo[4,5]oxazolo[3,2-*a*]pyridin-11-one (36b). Prepared according to the general procedure B using 3-oxo-*N*-tosylbutanamide (**35**) (48.3 mg, 0.200 mmol, 1 equiv), (*E*)-cinnamaldehyde (**2a**) (38 µL, 0.300 mmol, 1.5 equiv) and 2-amino-5-chlorophenol (**16b**) (21.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography over silica gel (PE/EtOAc 70:30) afforded product **36b** as a yellowish solid (58 mg, 0.117 mmol, 59% yield, >20:1 *dr*, 59% *ee*).

TLC (PE/EtOAc 70:30) R*f* 0.45 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{26}H_{23}ClN_2O_4S+H]^+$: 495.1140, found: 495.1136.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41 – 7.25 (m, 6H), 7.22 (d, J = 8.2 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.2, 1H), 6.95 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 5.85 (d, *J* = 2.6 Hz, 1H), 3.51 (ddd, *J* = 10.4, 5.1, 2.1 Hz, 1H), 3.10 (d, *J* = 2.2 Hz, 1H), 2.82 (ddd, *J* = 13.5, 10.6, 2.3 Hz, 1H), 2.41 (s, 3H), 2.36 (ddd, *J* = 13.5 Hz, 5.2, 3.2 Hz, 1H), 1.62 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$ δ (ppm) 165.8 (C), 152.4 (C), 145.0 (C), 140.9 (C), 135.1 (C), 134.8 (C), 131.2 (C), 129.4 (2 CH), 129.3 (2 CH), 128.4 (2 CH), 127.8 (CH), 127.6 (2 CH), 121.7 (CH), 117.9 (CH), 110.9 (CH), 103.7 (C), 74.3 (CH), 56.1 (CH), 36.5 (CH_2), 36.4 (CH), 23.2 (CH_3), 21.8 (CH_3).

HPLC Chiralpak IE, Heptane/Ethanol 50:50, 1 mL/min, λ = 254 nm, τ_{minor} = 8.19 min, τ_{major} = 11.71 min.

$[\alpha]_D^{20}$ = +172 (c 1.0, $CHCl_3$).

m.p. = 80-82 °C.

(4a*R*)-4a-methyl-3-phenyl-14-tosyl-2,3,4,4a-tetrahydro-1*H*-1,4-(epiminomethano)naphtha[2',3':4,5]oxazolo[3,2-*a*]pyridin-13-one (36c). Prepared according to the general procedure B using 3-oxo-*N*-tosylbutanamide (**35**) (48.3 mg, 0.200 mmol, 1 equiv), (*E*)-cinnamaldehyde (**2a**) (38 µL, 0.300 mmol, 1.5 equiv) and 3-aminonaphthalen-2-ol (**16c**) (31.8 mg, 0.2 mmol, 1 equiv). Purification by flash chromatography over silica gel (CH_2Cl_2/EtOAc 99.5:0.5) afforded product **36c** as a yellowish solid (54 mg, 0.109 mmol, 54% yield, >20:1 *dr*, 65% *ee*).

TLC (CH_2Cl_2/EtOAc 99.5:0.5) R*f* 0.59 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{30}H_{26}N_2O_4S+H]^+$: 511.1686, found: 511.1686.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.84 - 7.75 (m, 1H), 7.57 - 7.51 (m, 1H), 7.48 (s, 1H), 7.45 - 7.33 (m, 4H), 7.33 - 7.27 (m, 3H), 7. (d, *J* = 8.2 Hz, 2H), 6.62 (s, 1H), 6.43 (d, *J* = 8.2 Hz, 2H), 6.06 (t, *J* = 2.4 Hz, 1H), 3.58 (ddd, *J* = 10.3, 4.6, 2.0 Hz, 1H), 3.19 (d, *J* = 2.0 Hz, 1H), 2.90 (ddd, *J* = 13.0, 10.5 Hz, 1.9 Hz, 1H), 2.46 (ddd, *J* = 13.5, 4.4 Hz, 2.4 Hz, 1H), 2.15 (s, 3H), 1.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 165.9 (C), 150.5 (C), 144.3 (C), 141.1 (C), 137.7 (C), 134.5 (C), 133.2 (C), 130.3 (C), 129.4 (2 CH), 128.8 (2 CH), 128.0 (2 CH), 127.8 (CH), 127.6 (3 CH), 126.9 (CH), 125.6 (CH), 124.4 (CH), 114.3 (CH), 104.8 (CH), 102.5 (C), 75.1 (CH), 56.6 (CH), 36.5 (CH_2), 36.4 (CH), 23.8 (CH_3), 21.6 (CH_3).

HPLC Chiralpak IC, Heptane/Ethanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 13.50 min, τ_{major} = 15.73 min.

$[\alpha]_D^{20}$ = +145 (c 1.0, $CHCl_3$).

m.p. = 88-90 °C.

(*E*)-3-(4-chlorobenzylidene)-2-oxo-*N*-tosylcyclopentane carboxamide (40). In a 50-mL flask under argon atmosphere, β-ketoamide **31a** (563 mg, 2.00 mmol, 1 equiv), 4-chlorobenzaldehyde (**39**) (281 mg, 2.00 mmol, 1 equiv) and K_2CO_3 (553 mg, 4.00 mmol, 2 equiv) were stirred in dry MeOH (8 mL) at room temperature for 14 h. A 1M aqueous solution of HCl (30 mL) was added and the reaction mixture extracted with EtOAc (3 x 30 mL). Combined organic layers were washed with 1M HCl (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The pale yellow solid was suspended in Et_2O (10 mL), filtered, washed with Et_2O (10 mL) and dried under vacuum to afford product **40** as a white solid (570 mg, 1.41 mmol, 71% yield, ~2:1 mixture of ketone and enol tautomers, with still some inseparable *p*-tosylamide inside).

TLC (Tol/EtOAC/AcOH 70:30:1) R*f* 0.41 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{20}H_{18}ClNO_4S+H]^+$: 404.0718, found: 404.0717.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) *ketone tautomer:* 9.88 (br s, 1H), 8.05 - 7.84 (m, 2H), 7.49 - 7.22 (m, 5H), 7.17 (d, *J* = 7.2 Hz, 2H), 3.29 (app t, *J* = 9.8 Hz, 1H), 2.99 (ddt, *J* = 17.6, 9.1, 2.7 Hz, 1H), 2.78 (ddd, *J* = 17.6, 8.6, 3.1 Hz, 1H), 2.42 (s, 3H), 2.39-2.21 (m, 2H); *enol tautomer:* 10.92 (br s, 1H), 8.05 - 7.84 (m, 2H), 7.78 (br s, 1H), 7.49 - 7.22 (m, 6H), 6.89 (s, 1H), 2.88 (br s, 2H), 2.61 (br s, 2H), 2.46 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) *ketone tautomer:* 202.2 (C), 165.2 (C), 145.2 (C), 138.0 (C), 137.7 (C), 135.4 (CH), 134.8 (C), 133.1 (C), 132.2 (2 CH), 129.7 (2 CH), 129.4 (2 CH), 128.7 (2 CH), 53.9 (CH), 26.6 (CH_2), 21.8 (CH_2), 21.6 (CH_3); *enol tautomer:* 172.5 (C), 166.8 (C), 145.4 (C), 137.7 (C), 135.8 (C), 134.8 (C), 133.9 (C), 130.6 (2 CH), 129.8 (2 CH), 129.0 (2 CH), 125.4 (2 CH) 124.8 (CH), 105.1 (C), 29.8 (CH_2), 26.2 (CH_2), 21.9 (CH_3).

m.p. = 174-176 °C.

3-bromo-2-oxo-*N*-tosylcyclopentanecarboxamide (42). In a 100-mL flask equipped with a dropping funnel under argon atmosphere, β-ketoamide **31a** (1.41 g, 5.00 mmol, 1 equiv), was dissolved in glacial AcOH (15 mL) at room temperature. A solution of Br_2 (283 µL, 5.50 mmol, 1.1 equiv) in glacial AcOH (10 mL) was placed in the dropping funnel and added dropwise. After 2 h of stirring at room temperature, acetone (1 mL) was added to quench the excess of Br_2. After an additional hour at room temperature, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). Combined organic layers were washed with saturated $Na_2S_2O_3$ aqueous solution (50 mL), water (50 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The pale yellow solid was suspended in Et_2O (10 mL), filtered, washed with Et_2O (10 mL) and dried under vacuum to afford product **42** as a white solid (1.35 g, 3.75 mmol, 75% yield).

TLC (Tol/EtOAC/AcOH 80:20:1) R*f* 0.36 (UV, vanillin).

HRMS (ESI) calc´d for $[C_{13}H_{14}BrNO_4S+H]^+$: 359.9900, found: 359.9901.

^{1}H NMR (400 MHz, d^6-DMSO): δ (ppm) 12.37 (br s, 1H, 1 diastereomer), 10.76 (br s, 1 diastereomer), 7.86 (d, *J* = 8.4 Hz, 2H, 1 diastereomer), 7.47 - 7.39 (m, 2H, 2 diastereromers), 5.08 – 5.02 (m, 1H, 1 diastereromer), 4.75 – 4.63 (m, 1H, 1 diastereromer), 3.45 (d, *J* = 8.5 Hz, 1H, 1 diastereomer), 3.34 (d, *J* = 8.5 Hz, 1H, 1 diastereomer), 2.48 – 1.94 (m, 4H, 2 diastereromers), 2.39 (s, 3H, 2 diastereomers).

Because of solubility and stability issues, conjugated with the presence of diastereomers and ketone-enol tautomerism, no clear **^{13}C NMR** description could be obtained.

m.p. = 143-145 °C.

(1*R*,3a*S*,6*S*,12a*S*)-1-bromo-13-tosyl-1,2,3,4,5,6-hexahydro-6,3a-(epiminomethano)benzo[4,5]oxazolo[3,2-*a*]cyclopenta[*b*]pyridin-14-one (45). Prepared according to the general procedure C using 3-bromo-2-oxo-*N*-tosylcyclopentanecarboxamide (**32**) (72.0 mg, 0.200 mmol, 1 equiv), acrolein (**32**) (27 µL, 0.400 mmol, 2 equiv) and 2-aminophenol (**12a**) (32.7 mg, 0.3 mmol, 1.5 equiv) with a reaction time of 72 h. Purification by flash chromatography over silica gel (pure CH_2Cl_2 then CH_2Cl_2/EtOAc 98:2) afforded product **45** as a yellowish solid (49.2 mg, 0.101 mmol, 50% yield, >20:1 *dr*, 39% *ee*).

TLC (CH_2Cl_2/EtOAc 95:5) R*f* 0.93 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{22}H_{21}BrN_2O_4S+H]^+$: 489.0478, found: 489.0480.

^{1}H NMR (300 MHz, d^6-DMSO): δ (ppm) 7.42 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.15 – 6.98 (m, 4H), 6.60 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.01 (d, *J* = 1.6 Hz, 1H), 4.44 (dd, *J* = 8.6, 3.3 Hz, 1H), 2.88 (dt, *J* = 14.3, 9.3 Hz, 1H), 2.46 – 2.28 (m, 3H), 2.34 (s, 3H), 2.24 – 2.00 (m, 2H), 1.91 – 1.77 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 168.4 (C), 149.9 (C), 144.5 (C), 137.0 (C), 135.3 (C), 129.4 (2 CH), 128.4 (2 CH), 126.2 (CH), 122.5 (CH), 117.8 (CH), 111.2 (C), 110.0 (CH), 77.2 (CH), 53.3 (C), 48.9 (CH), 33.7 (CH_2), 28.4 (CH_2), 25.3 (CH_2), 23.3 (CH_2), 21.8 (CH_3).

HPLC Chiralpak ID, Heptane/Ethanol 80:20, 1 mL/min, λ = 205 nm, τ_{minor} = 12.83 min, τ_{major} = 14.54 min.

$[\alpha]_D^{20}$ = +4.8 (c 0.5, $CHCl_3$).

m.p. = 150-152 °C (decomposition).

(2*S*,4a*R*,7a*R*)-1-(2-hydroxyphenyl)-7a-(phenylethynyl)-9-tosyl octahydro-2,4a-(epiminomethano)cyclopenta[*b*]pyridin-8-one (46). A mixture of product **34a** (205 mg, 0.500 mmol, 1 equiv) and potassium phenylethynyltrifluoroborate (**24**) (312 mg, 1.50 mmol, 3 equiv) were suspended in dry CH_2Cl_2 (5 mL) and cooled at 0 °C. Boron trifluoride etherate (126 µL, 1.00 mmol, 2 equiv) was added dropwise and the reaction mixture allowed to reach room temperature, where it was stirred for 2 h. The reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). Combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography over silica gel (CH_2Cl_2/EtOAc 99.5:0.5 to 99:1) afforded product **46** as a brown foamy solid (151 mg, 0.295 mmol, 59% yield, >20:1 *dr*, 86% *ee*).

TLC (CH_2Cl_2/EtOAc 98:2) R*f* 0.84 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{30}H_{28}N_2O_4S+H]^+$: 513.1843, found: 513.1840.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.97 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.29 (m, 8H), 7.16 (td, *J* = 8.0, 1.4 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.81 (td, *J* = 8.0, 1.5 Hz, 1H), 6.64 (s, 1H), 5.57 (dd, *J* = 3.9, 1.4 Hz, 1H), 2.74 – 2.33 (m, 3H), 2.47 (s; 3H), 2.26 – 2.09 (m, 1H), 1.94 – 1.49 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 172.3 (C), 153.5 (C), 145.4 (C), 135.8 (C), 131.9 (C), 131.7 (2 CH), 129.8 (2 CH), 129.0 (CH), 128.60 (2 CH), 128.56 (2 CH), 128.5 (CH), 126.9 (CH), 121.9 (C), 120.2 (CH), 115.4 (CH), 89.5 (C), 86.3 (C), 74.3 (CH), 67.8 (C), 59.1 (C), 37.6 (CH_2), 30.0 (CH_2), 26.0 (CH_2), 23.6 (CH_2), 21.9 (CH_3), 20.1 (CH_2).

HPLC Chiralpak IA, Heptane/Ethanol 80:20, 1 mL/min, λ = 254 nm, τ_{major} = 6.78 min, τ_{minor} = 8.24 min.

$[\alpha]_D^{20}$ = +12.3 (c 0.66, $CHCl_3$).

m.p. = 181-183 °C.

(6*S*,8a*R*,11a*S*)-12-((2,6-dimethylphenyl)imino)-15-tosyl-7,8,9,10, 11,12-hexahydro-6*H*-6,8a-(epiminomethano)benzo[*b*]cyclopenta [2,3]pyrido[1,2-*d*][1,4]oxazin-14-one (48). A mixture of product **34a** (41.1 mg, 0.100 mmol, 1 equiv) and 2,6-dimethylphenylisocyanide (**47**) (26.4 mg, 0.200 mmol, 2 equiv) were dissolved in dry CH_2Cl_2 (1 mL) and cooled at 0 °C. Boron trifluoride etherate (25 µL, 0.200 mmol, 2 equiv) was added dropwise and the reaction mixture allowed to reach room temperature, where it was stirred for 2 h. The reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). Combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography over silica gel (pure CH_2Cl_2) afforded product **48** as a brown foamy solid (42.7 mg, 0.079 mmol, 79% yield, >20:1 *dr*, 94% *ee*).

TLC (CH_2Cl_2/EtOAc 98:2) R*f* 0.92 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{31}H_{31}N_3O_4S+H]^+$: 542.2108, found: 542.2106.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.99 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.27 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.10 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H), 7.04 (br d, *J* = 7.5 Hz, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.87 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 6.81 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.17 (dd, *J* = 3.7, 1.8 Hz, 1H), 3.14 (ddd, *J* = 13.6, 9.9, 2.3 Hz, 1H), 2.55 – 2.45 (m, 2H), 2.43 (s, 3H), 2.33 – 1.76 (m, 12H), 1.04 – 0.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 172.3 (C), 146.0 (C), 145.3 (C), 143.9 (C), 142.5 (C), 135.7 (C), 129.7 (2 CH), 128.6 (C), 128.5 (2 CH), 128.0 (2 CH), ~127.0 (br, 2 C), 124.3 (CH), 123.4 (CH), 121.9 (CH), 118.0 (CH), 116.8 (CH), 71.7 (CH), 63.33 (C), 57.1 (C), 37.1 (CH_2), 28.1 (CH_2), 25.7 (CH_2), 21.8 (CH_3), 20.6 (CH_2), 20.4 (CH_2), 18.7 (br, 2 CH_3).

HPLC Chiralpak IF, Heptane/Ethanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 10.09 min, τ_{major} = 11.65 min.

$[\alpha]_D^{20}$ = +37.5 (c 1.0, $CHCl_3$).

m.p. = 198-200°C.

(2*R*,4a*R*,7a*R*)-1-(2-hydroxyphenyl)-7a-(phenylethynyl)octahydro-2,4a-(epiminomethano)cyclopenta[*b*]pyridin-8-one (49). Product **34a** (35.9 mg, 0.070 mmol, 1 equiv) was dissolved in dry THF (0.6 mL) and cooled at −78 °C. A solution of sodium naphthalenide (0.5 M, 1.4 mL, 0.700 mmol, 10 equiv) was added dropwise and the reaction mixture stirred at −78 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3 x 5 mL). Combined organic layers were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography over silica gel (CH_2Cl_2/EtOAc 80:20 to 70:30) afforded product **49** as a yellowish solid (12.0 mg, 0.034 mmol, 48% yield, >20:1 *dr*, 86% *ee*).

TLC (CH_2Cl_2/EtOAc 70:30) R*f* 0.43 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{23}H_{22}N_2O_2+H]^+$: 359.1754, found: 359.1754.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (br s, 1H), 7.51 – 7.43 (m, 2H), 7.38 – 7.29 (m, 4H), 7.07 (td, *J* = 7.7, 1.5 Hz, 1H), 7.02 (s, 1H), 6.95 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.72 (td, *J* = 7.7, 1.6 Hz, 1H), 4.61 (dd, *J* = 4.7, 3.3 Hz, 1H), 2.64 (ddd, *J* = 12.8, 9.1, 3.6 Hz, 1H), 2.58 – 2.47 (m, 2H), 2.11 – 2.01 (m, 1H), 1.95 – 1.84 (m, 3H), 1.78 – 1.70 (m, 2H), 1.68 – 1.58 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 175.7 (C), 153.2 (C), 133.7 (C), 131.8 (2 CH), 128.8 (CH), 128.6 (2 CH), 127.4 (CH), 125.4 (CH), 122.4 (C), 119.9 (CH), 115.3 (CH), 91.0 (C), 85.5 (C), 68.7 (CH), 68.2 (C), 57.0 (C), 36.7 (CH_2), 30.3 (CH_2), 26.1 (CH_2), 24.5 (CH_2), 20.5 (CH_2).

HPLC Chiralpak IE, Heptane/Ethanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 6.04 min, τ_{major} = 6.87 min.

$[\alpha]_D^{20}$ = +18.9 (c 0.5, $CHCl_3$).

(3a*R*,6*S*,12a*R*)-13-((4-nitrophenyl)sulfonyl)-1,2,3,4,5,6-hexahydro-6,3a-(epiminomethano)benzo[4,5]oxazolo[3,2-*a*]cyclopenta[*b*] pyridin-14-one (51). Prepared according to the general procedure C using *N*-(4-nitrobenzenesulfonyl)-3-oxobutanamide (**50**) (62.5 mg, 0.200 mmol, 1 equiv), acrolein (**32**) (27 µL, 0.400 mmol, 2 equiv) and 2-aminophenol (**12a**) (32.7 mg, 0.3 mmol, 1.5 equiv). Purification by flash chromatography over silica gel (CH_2Cl_2/EtOAc 99:1) afforded product **51** as a white solid (66.3 mg, 0.150 mmol, 75% yield, >20:1 *dr*, 59% *ee*).

TLC (PE/EtOAc 60:40) R*f* 0.46 (UV, *p*-anisaldehyde).

HRMS (ESI) calc´d for $[C_{21}H_{19}N_3O_6S+H]^+$: 442.1067, found: 442.1070.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.03 (d, *J* = 8.9 Hz, 2H), 7.42 (d, *J* = 8.9 Hz, 2H), 7.18 – 7.13 (m, 1H), 7.04 – 6.94 (m, 2H), 6.39 – 6.29 (m, 1H), 5.81 (t, *J* = 2.6 Hz, 1H), 2.44 – 2.31 (m, 2H), 2.26 – 2.16 (m, 1H), 2.15 – 2.06 (m, 1H), 2.03 – 1.87 (m, 5H), 1.74 – 1.66 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.5 (C), 151.0 (C), 143.7 (C), 137.5 (C), 129.8 (2 CH), 126.2 (CH), 123.8 (2 CH), 121.9 (CH), 117.5 (CH), 112.6 (C), 109.9 (CH), 77.5 (CH), 68.7 (C), 54.1 (C), 33.4 (CH_2), 28.8 (CH_2), 25.2 (CH_2), 23.9 (CH_2), 19.3 (CH_2). Partial degradation of the product occured during the recording of the ^{13}C NMR spectra.

HPLC Chiralpak IB, Hexane/Ethanol 50:50, 10 °C, 1 mL/min, λ = 254 nm, τ_{major} = 6.15 min, τ_{minor} = 7.93 min.

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