ENANTIOSELECTIVE SYNTHESIS OF UNSATURATED γ-LACTAMS

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Abstract. *As a part of several natural products and bioactive molecules, the development of new synthetic methods to obtain γ-lactams has drawn attention during the last years. Dihydropyrrolidin-2-ones represent a particular case of unsaturated γ-lactams which can be used in both, organic and medicinal chemistry and thus, the development of efficient methodologies for their preparation has an additional value. Considering the relevance of optically active molecules in medicinal chemistry, in this review, the existing catalytic asymmetric methods to obtain enantioenriched pyrrolidin-2-ones are summarized.*

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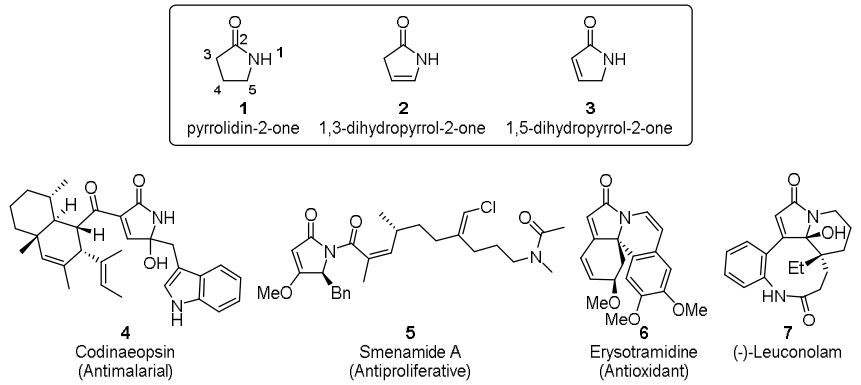
1. Introduction

Pyrrolidin-2-ones **1** or γ-lactam heterocycle ring is present in many biologically active molecules.[1] In particular, dihydropyrrol-2-ones contain an unsaturation in the γ-lactam structure and can be classified in 1,3-dihydropyrrol-2-ones **2** if this unsaturation takes place between positions 4 and 5 and 1,5-dihydropyrrol-2-ones **3**, if it takes place between carbons 3 and 4. Due to the conjugation of the unsaturation with the carbonyl group, 1,5-dihydropyrrol-2-one **3** is the most favored structure,[2] which is reflected in a higher number of biorelevant organic molecules containing scaffold **3** in their structure, while the most common examples of structures like **2** are related to 2-oxindoles,[3] which structure is stabilized by means of the fusion of the lactam ring with an aromatic group. Some cases of biorelevant molecules containing dihydropyrrol-2-ones include codinaeopsin **4** (antimalarial),[4] smenamide A **5** and its derivatives (that show antiproliferative properties),[5] erysotramidine **6** (antioxidant),[6] or the natural product leuconolam **7**,[7] to cite some examples (Scheme 1).

Considering the presence of this unsaturated γ-lactam framework in natural and biologically active molecules and their synthetic applications for the synthesis of widely explored pyrrolidyn-2-ones **1** by simple reduction, the development of new methodologies leading to the formation of heterocycles **2** and **3** represents an important task in organic and medicinal chemistry. Besides, the use of enantiomerically pure molecules for biological applications is well known and, thus, the synthesis of dihydropyrrol-2-ones is often planned through asymmetric synthesis. Although resolution, chiral pool or stereoselective synthetic strategies can be useful for this propose, they require a high amount of starting materials, specific synthetic

routes or additional synthetic steps to obtain the desired products. In contrast, asymmetric catalysis allows the construction of nonracemic molecules new in an enantioselective fashion by using substoichiometric amounts of chiral molecules. Thus, in this review, we summarize the existing catalytic enantioselective methodologies for the synthesis of nonracemic unsaturated γ-lactams **2** and **3** (Scheme 1).



Scheme 1. Biorelevant products containing dihydropyrrol-2-one moieties in their structure.

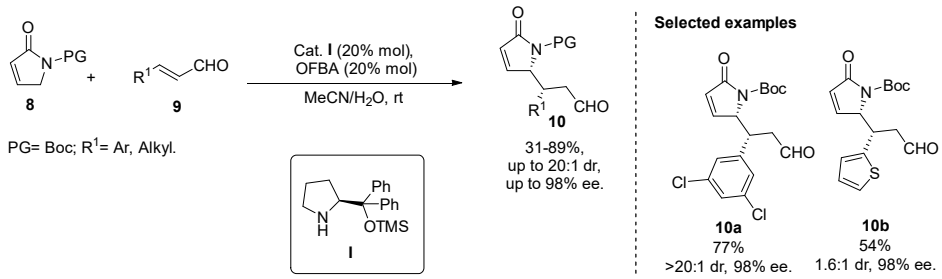
2. Enantioselective synthesis of 1,5-dihydropyrrol-2-ones

2.1. Vinylogous Michael reactions

Enantioselective synthesis of 1,5-dihydropyrrol-2-ones can be performed by vinylogous Michael reactions, through the addition of α,β-unsaturated γ-butyrolactams to α,β-unsaturated carbonyl compounds. Here, this approach is subdivided into various subcategories, considering the type of electrophile and the addition (1,4 or 1,6) involved.

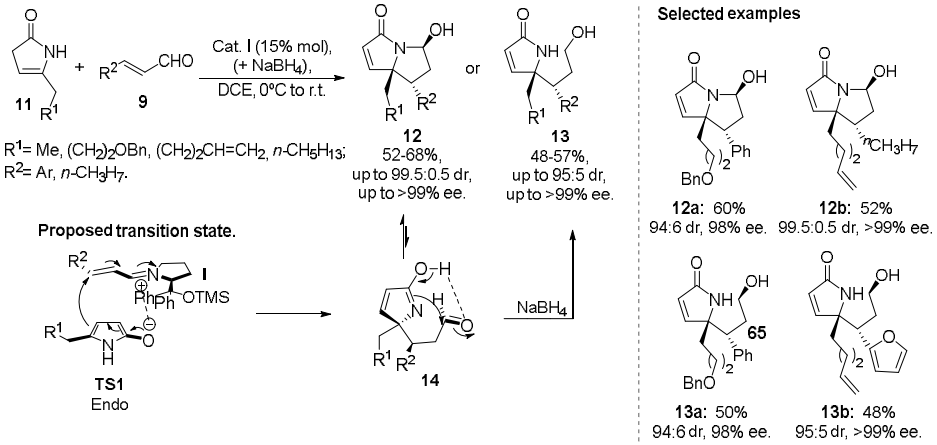
2.1.1. Conjugate addition to α,β-unsaturated aldehydes

Chen and co-workers described in 2010 the vinylogous Michael addition of *N*-Boc-substituted γ-lactams **8** to α,β-unsaturated aldehydes **9** (Scheme 2).[8] The reaction proceeds with high regio- and chemoselectivity, to give the major *syn* adduct **10** when *o*-formylbenzoic acid and catalyst **I** (20% mol) are used. Excellent diastereoselectivities (13:1->20:1) and enantioselectivities (91-98%) are also obtained using α,β-unsaturated aldehydes **9** substituted with aromatic groups bearing electron-withdrawing substituents. When electron-donating aryl substituents, heteroaryl substituents (R^1=2-thienyl, 2-furyl and 3-pyridinyl) and linear alkyl-substituted enals **9** (R^1=Me, Et) are used, although high enantiomeric excesses are still observed a decrease in the diastereoselectivity (5.7:1 dr) is noticed. Compounds **10a** and **10b** are some examples of this synthetic methodology.



Scheme 2. Vinylogous Michael reactions of α,β-unsaturated γ-butyrolactams **8** and α,β-unsaturated aldehydes **9**.

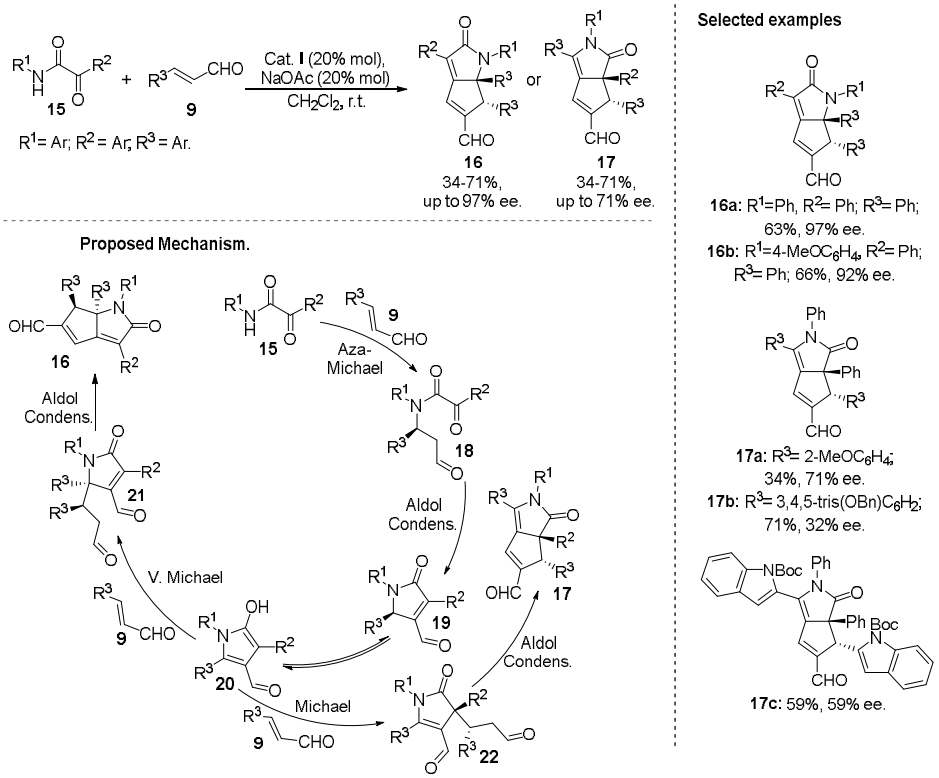
Another example of vinylogous Michael addition to α,β-unsaturated aldehydes **9** was described by Vassilikogiannakis and co-workers in 2018.[9] This versatile synthetic protocol enables the synthesis of bicyclic and non-bicyclic lactams **12** and **13** with formation of chiral quaternary carbons and high diastereo- and enantioselectivities (Scheme 3). The authors propose that the high stereoselectivity results from an ion-pair *endo* transition state (**TS1**), where the *Si* face of γ-lactam **11** attacks the *Si* face of the iminium ion. Then, the aldehydic group of intermediate **14** is trapped from the Si face to form bicyclic lactam **12** or alternatively, the aldehyde of intermediate **14** can be reduced by $NaBH_4$ to the corresponding alcohol, to yield products **13**. Different α,β-unsaturated aldehydes **9** (R^2=Ar or *n*-C_3H_7) and 2-pyrrolidinones **11** (R^1=H, $(CH_2)_2OBn$, $(CH_2)_2CH=CH_2$ or *n*-C_5H_{11}) were tested in dichloroethane in the presence of catalyst **I**. In most cases, bicyclic compounds **12** are obtained with excellent diastereo- and enantioselectivities (dr=94:6-99.5:0.5 and ee=97->99%) but with moderate yields (52-68%), except when 2-pyrrolidinone **11** (R^1=H) was used. Structures **12a** and **12b** are some examples of the substrates that may be obtained using this protocol. The reaction can be terminated at the final stage of the process by the addition of $NaBH_4$, leading to substrates **13**, with moderate yields (48-57%) but excellent diastereo- and enantioselectivities (dr=94:6-95:5 and ee=>99%).



Scheme 3. Vinylogous Michael reaction for the enantioselective synthesis of lactams **12** and **13**.

Another example of vinylogous Michael reactions, in which the construction of the lactam heterocycle is involved, was described by Enders in 2014.[10] This consists in a quadruple domino reaction of α-ketoamides **14** with two equiv. of α,β-unsaturated aldehydes **9** that is catalyzed by **I** and NaOAc (20% mol) in dichloromethane to afford 2-azabicyclo[3.3.0]octadienones **16** (Scheme 4). The quadruple cascade is initiated by an asymmetric aza-Michael addition of α-ketoamides **15** to different iminium-activated α,β-unsaturated aldehydes **9**. Intermediate **18** reacts in an intramolecular aldol condensation to form a γ-lactam cycle **19**. Under the reaction conditions, these new formed lactam **19** easily tautomerizes to aromatic 2-hydroxypyrrole **20**, which can react as nucleophile through the position 5 of the ring with a second molecule of α,β-unsaturated aldehyde **9** *via* iminium activation by catalyst **I**. This vinylogous 1,4-addition leads to intermediate **21**, which undergoes a second intra-molecular aldol condensation, yielding bicyclic products **16**. In addition, 2-hydroxypyrroles **20** can also act as nucleophiles at the position 3 with a second iminium-activated α,β-unsaturated aldehyde **9** and then, due to intramolecular aldol condensation, products **17** can be formed through intermediate **22**, although this second pathway remains minor. Diverse α,β-unsaturated aldehydes **9** (R^3=Ph, 4-$MeOC_6H_4$, 2,3-(OCH_2O) C_6H_3) were examined, and lactams **16** were always obtained as single diastereoisomers in moderate yields (34-56%) and very good enantioselectivities (ee=84-97%). However, the use of heteroaromatic or aliphatic α,β-unsaturated aldehydes **9** did not lead to satisfactory results. Regarding the scope of substituents on α-ketoamides **15** (R^1=Ph, 3-ClC_6H_4, 4-$NO_2C_6H_4$; R^2=Ph, 4-ClC_6H_4, 2-MeC_6H_4), the desired products were obtained in all cases as a single

diastereoisomers in good yields (58-71%) and excellent enantioselectivities (ee=88-95%). Compounds **16a** and **16b** are a couple of examples of this synthesis. Interestingly, if α,β-unsaturated aldehydes **9** bearing other strong electron-donor groups (R^3=2-$MeOC_6H_4$, 3,4,5-tris(OBn)C_6H_2, *N*-Boc-indol) are used in this reaction, only a single diastereoisomer of lactams **17** is obtained in moderate to good yields (34-71%) but lower enantioselectivities (ee=32-71%) compared to the main catalytic pathway. The authors only reported three examples of this type of lactams **17a**.



Scheme 4. Quadruple cascade reaction of α-ketoamides **15** with α,β-unsaturated aldehydes **9**.

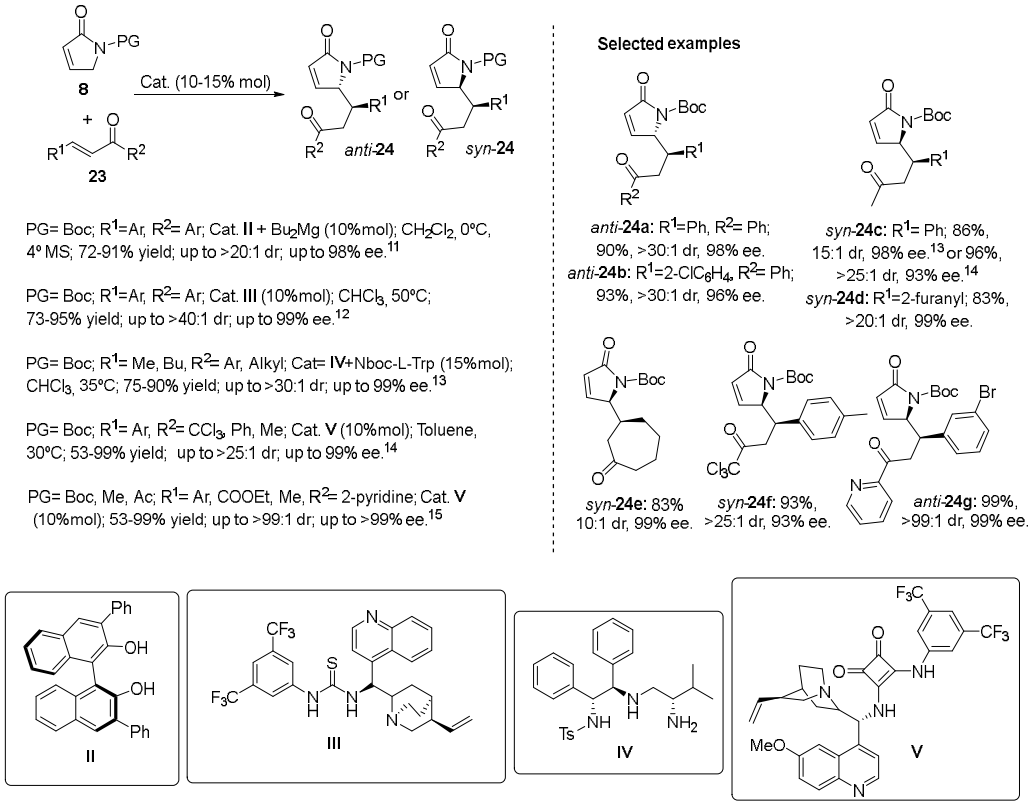
2.1.2. Conjugate addition to α,β-unsaturated ketones

α,β-Unsaturated ketones **23** are also good substrates for the enantioslective vinylogous Michael addition of butyrolactams **8**, leading to enantioenriched γ-lactam derivatives **18** (Scheme 5). In 2011, various research groups described for the first time different examples of this reaction using *N*-Boc-substituted γ-butyrolactams **8**. Wang and co-workers performed this reaction using aromatic α,β-unsaturated ketones **23** (R^1=Ar, R^2=Ar). The process is catalyzed by the complex Mg-**II** (10% mol) in dichloromethane at 0 ºC, to give the *anti* products **24** in good yields (80-91%) and excellent diastereo- and enantioselectivities (dr=10:1 to >20:1, ee=91-98%).[11] However, when the reaction is performed with 1- or 2-naphtyl-substituted ketones **23** (R^1=1-naphthyl, 2-naphtyl; R^2=Ph), the diastereoselectivity drops to 8:1 and 7:1, respectively. In addition, Wang's group described the same reaction, with similar results, using the chiral organocatalyst **III**, affording *anti* products **24** as the major diastereoisomers (10:1->30:1), with good yields (73-95%) and excellent enantiomeric excesses (ee=94-99%).[12]

In the same year, Ye described the vinylogous Michael reaction of α,β-unsaturated γ-butyrolactams **8** with alkyl α,β-unsaturated ketones **23** (R^1=Ar, Alkyl; R^2=Me, Bu) catalyzed by triamine **IV** and *N*-Boc-*L*-Trp (15% mol) in chloroform at 35 ºC (Scheme 5).[13] Various α,β-unsaturated methylketones **23**

(R^1=Ar; R^2=Me) with aromatic substituents bearing electron-donating or electron-withdrawing groups are employed, to give *syn*-**24** products in good yields (81-90%) and excellent enantio- and diastereoselectivities (ee=>98%, dr 13:1-25:1). This reaction can be extended to α,β-unsaturated methylketones **23** bearing aliphatic substituents (R^1=Me, *n*-Pr, *n*-Bu, pentyl, hexyl; R^2=Me, Bu) as well as to cyclic ketones, providing good dr values (10:1 to >20:1) and excellent enantioselectivities (ee=>98%). Some examples of Ye's work are products **24c, 24d** and **24e**.

Later on, in 2013, Wang and co-workers described the vinylogous Michael enantioselective reaction of α,β-unsaturated γ-butyrolactams **8** and α,β-unsaturated trichloromethyl ketones **23** (R^1=Ar; R^2=CCl_3) (Scheme 5).[14] This reaction proceeds smoothly in the presence of quinine-derived squaramide catalyst **V** (15%mol) in toluene at 30 ºC, affording the 1,4-addition products *syn*-**24** with good yields (73-91%) and high diastereo- and enantioselectivities (dr>25:1, ee=>90%) in all cases, except when 4-methoxyphenyl trichloromethyl ketone **23** (R^1=4-$MeOC_6H_4$; R^2=CCl_3) is used. The authors also synthesized compound **24a**, obtaining in this case the *syn* diastereoisomer (dr>25:1) in 99% ee and compound **24c**, and improving the diastereoselectivity compared to the previous works (dr>25:1), although a slight drop in the enantiomeric excess was found (ee=93%).



Scheme 5. Vinylogous Michael addition of α,β-unsaturated γ-butyrolactams **8** to α,β-unsaturated ketones **23**.

Using the squaramide catalyst **V**, the direct asymmetric addition reaction to 2-enoylpyridine type ketones **23** (R^1=Ar; R^2=2-pyridine) was described by Yuan and Xu in 2016.[15] Thus, ketones **23** containing electron-withdrawing, electron-donating and fused aromatic groups gave *anti* products like **24g** in 78-99% yields, with excellent enantiomeric excesses (ee=90-99%) and diastereoisomeric ratios (dr>99:1) in all cases. It is interesting to note that in this case the *syn* product, previously reported by Wang,[14] is not obtained,

probably due to double hydrogen bonding between the squaramide catalyst **V** and the 2-pyridine-substituted ketone **23** (Figure 1).

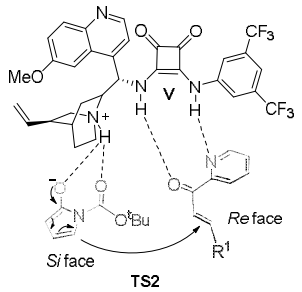
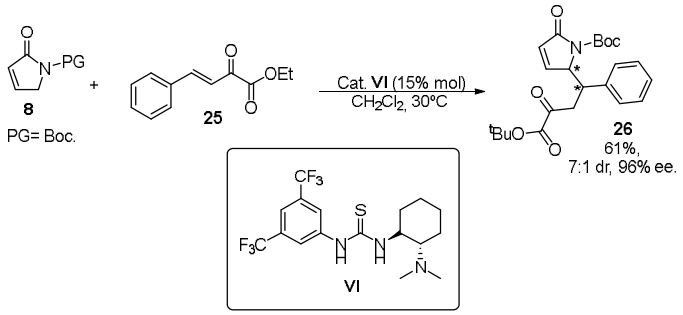


Figure 1. Plausible transition sate model of vinylogous Michael reaction with 2-enoylpyridyl ketones.[15]

Ketoesters and diketones are also appropriate substrates for the conjugate addition of pyrrolidine-2-ones. For example, product **26** can be obtained by the vinylogous Michael addition of α,β-unsaturated γ-butyrolactam **8** to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **25** in presence of thiourea catalyst **VI** (Scheme 6).[16]

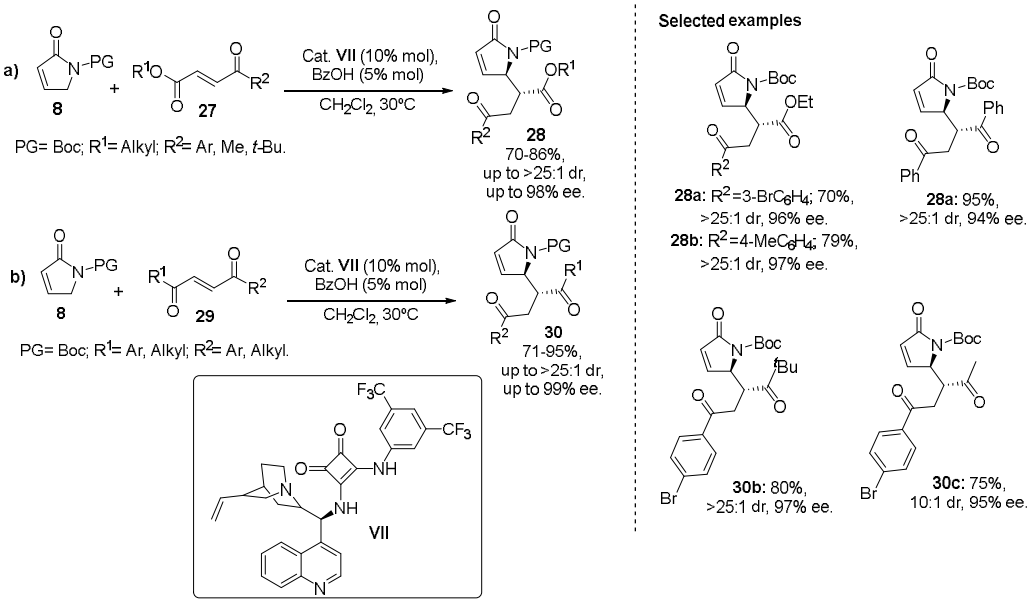


Scheme 6. Vinylogous Michael reactions of α,β-unsaturated γ-butyrolactam **8** to ethyl (E)-2-oxo-4-phenylbut-3-enoate **25**.

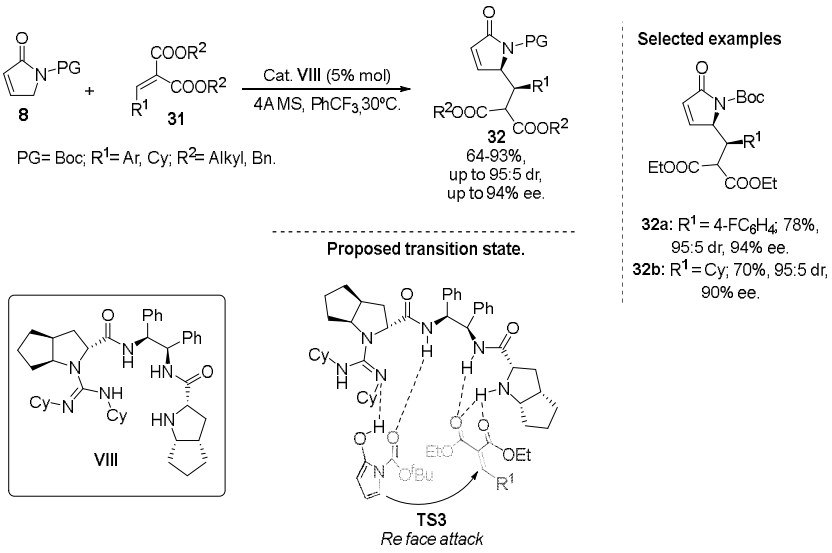
In 2015 Lin and co-workers described the vinylogous Michael reaction of α,β-unsaturated γ-butyrolactams **8** with 3-aroyl acrylates **27** (Scheme 7a) and enediones **29** (Scheme 7b), using squaramide catalyst **VII**.[17] The use of 3-acyl acrylates **27** (R^1=Et, Me, *i*-Pr; R^2=Ar, Me, *t*-Bu) yielded lactams **28** with *anti* configuration and excellent enantio- and diastereoselectivities (ee=87-98%, dr=12:1->25:1). The reaction tolerates electron-withdrawing (4-$NO_2C_6H_4$), electron-donating (4-MeC_6H_4, 4-$MeOC_6H_4$), fused-ring (2-naphtyl), halogen-substituted aromatic, heteroaromatic (2-thienyl) and aliphatic (Me, *t*-Bu) substituents in the ester functionality. In a similar manner, the use of symmetric enediones **29** (R^1=R^2) gave lactams **30** with high yields (56-95%) and excellent enantio- and diastereoselectivities (ee=83-99%, dr=>25:1). Good regioselectivities are also observed when unsymmetrical enodiones **29** (R^1≠R^2) with aliphatic and aromatic functional groups are used, obtaining substrates **30a** and **30b** with excellent enantiomeric excesses (ee=97% and 95%).

In addition to aldehydes and ketones, also α,β-unsaturated esters are good substrates for the preparation of enantiopure γ-lactam derivatives. Thus, Liu and Feng performed the asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam **8** to alkylidene malonates **31** in the presence of catalyst **VIII** (5% mol) in trifluorotoluene at 30 ºC with 4Å MS, affording *syn* lactams **32** with good yields (64-93%) (Scheme 8).[18] The use of different ester groups in the alkylidene malonates **31** (R^2=Me, Et or Bn) did not affect the diastereo- and enantioselectivities of the process (dr=95:5, ee=91-93%). The use of aromatic electron-withdrawing (R^1=HalogenC_6H_4) or electron-donating (R^1=4- or 3-MeC_6H_4, 4- or 3-$MeOC_6H_4$)

substituents on alkylidene malonates **31** gave the corresponding 5-substituted 3-pyrrolidin-2-ones **32** with excellent ee (89-94%) and diastereoselectivities values (94:6-95:5). Furthermore, this reaction is also described with hetero-aromatic (R^1=2 or 3-thienyl), aliphatic (R^1=Cy) and fused malonate substrates **31**, providing also excellent results in terms of diastereo- and enantioselectivity. The possible model of activation of the reaction **TS3** is shown in Scheme 8.



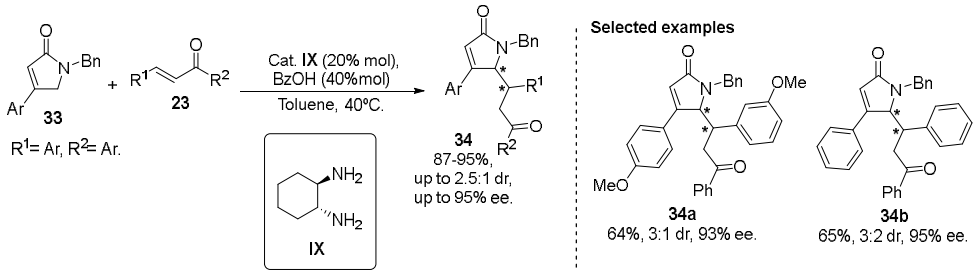
Scheme 7. Vinylogous Michael reactions of α,β-unsaturated γ-butyrolactam **8** with 3-aroyl acrylates **27** and enediones **29**.



Scheme 8. Vinylogous Michael reactions of α,β-unsaturated γ-butyrolactam **8** to alkylidene malonates **31**.

The basic guanidine in catalyst **VIII** could accelerate the deprotonation of γ-butyrolactam **8** to generate the dienolate. The *N*-Boc protection of **8** reinforces the dual hydrogen bonding with the guanidine and the amide moieties on the same part of catalyst **VIII**. The alkylidene malonate **31** is then activated through a network of hydrogen bonds from catalyst **VIII**. In view of the model proposed, the product could be obtained by a *Re*-face attack.

So far, we have shown 1,4-vinylogous Michael addition to ketones where the starting γ-lactam is unsubstituted, but there are some examples of such reaction with different substitution patterns. Thus, in 2017, Wang and Li described the enantioselective Michael addition of 4-aryl-substituted α,β-unsaturated γ-butyrolactam **33** (Ar=Ph, 4-BrC_6H_4, 4-$OMeC_6H_4$) to α,β-unsaturated ketones **23** in toluene at 40 ºC using diamine catalyst **IX** (20% mol) and benzoic acid as an additive (40% mol) (Scheme 9).[19] Substrates **34** are obtained in moderate to good yields (55-90%) and high enantioselectivities (ee=84-95%). The reaction proceeds efficiently in terms of yields and enantioselectivities with different substituents present at the position 4 of lactam **33** and at the α,β-unsaturated ketones **23**. In all cases case, *syn* products are obtained as the major products but with low diastereoselectivities (dr=1:1-3:1).



Scheme 9. Vinylogous Michael reactions of 4-substituted α,β-unsaturated γ-butyrolactam **33** and α,β-unsaturated ketones **23**.

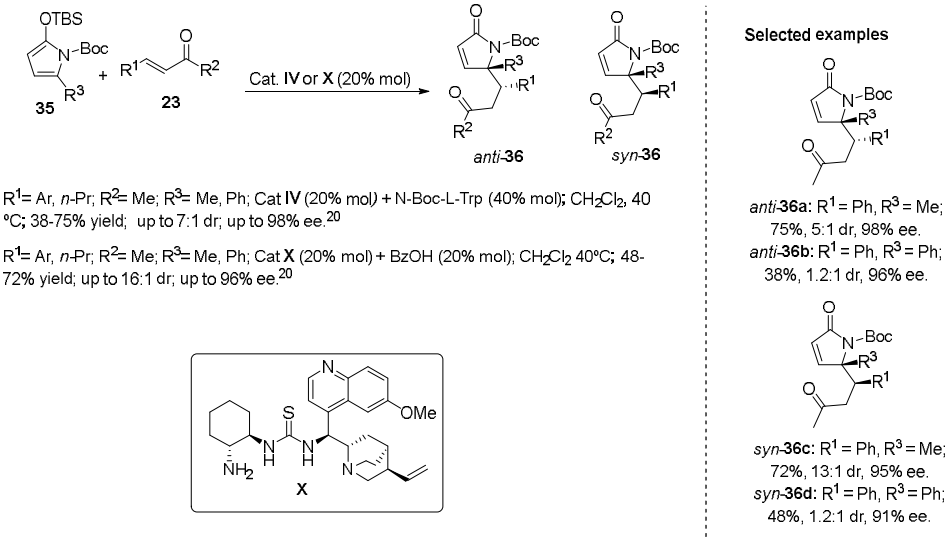
In 2014, Ye and Dixon described for the first time the 1,4-vinylogous Michael reaction for the synthesis of 1,5-dihydropyrrol-2-ones containing a chiral quaternary carbon.[20] This reaction consists on the addition of 5-substituted TBS-pyrroles **35** (R^3=Me, Ph) to α,β-unsaturated methyl ketones **23** (R^1=Ar, *n*-Pr; R^2=Me) (Scheme 10). If the reaction is carried out in dichloromethane at 40 ºC using triamine catalyst **IV** (20% mol) and *N*-Boc-*L*-Trp (40% mol), *anti*-**36** adducts are obtained in moderate to good yields (38-75%) and excellent enantiomeric excesses (ee=94-98%). The diastereoselectivity for alkyl-substituted TBS-pyrroles **35** (R^3=Me) range from 5:1 to 7:1, but there is a drop to 1.2:1 when the reaction is performed with phenyl-substituted TBS-pyrrole **35** (R^3=Ph). However, if the reaction is carried out using the thiourea catalyst **X** (20% mol) and benzoic acid (20% mol), *syn*-**36** adducts are obtained, also in good yields (48-72%) and excellent enantioselectivities (ee=91-96%). In this case, slightly better diastereoselectivities (11:1 to 16:1) are observed for methyl-substituted TBS-pyrrole **35** (R^3=Me), while in phenyl-substituted TBS-pyrrole **35** (R^3=Ph) it remains low.

A few years later, Maruoka reported the 1,4 Michael addition of 5-substituted α,β-unsaturated γ-butyrolactam **37** to methyl vinyl ketone **38** (R^1=Me) in MTBE at -10 ºC in presence of catalyst **XI** (2% mol) and K_2CO_3, affording γ-lactams **39** with good yields (60-88%) (Scheme 11).[21]

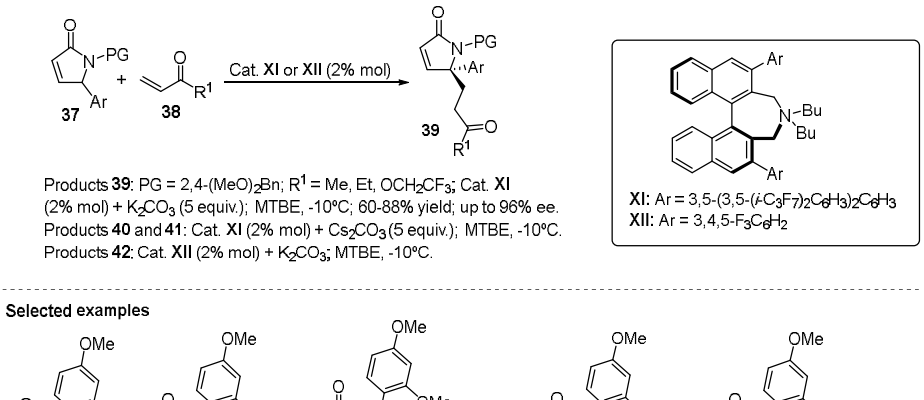
This methodology is applicable to lactam substrates with aromatic substituents bearing electron-donor (Ar=3-MeC_6H_4, 4-$MeOC_6H_4$) or halogen-substituted aromatic, hetero aromatic (Ar=3-pyridin, 2-furyl, 2-thienyl) and benzofused (Ar=2-Naphthyl) substituents in **37**, landing to lactams **39** with an enantiomeric excesses above 92%.

Other vinyl ketone derivatives **38** (R^1=Et, OCH_2CF_3) can be also used, affording lactams **39c** and **39d** in good yields (82-62%) and 86% ee in both cases. This reaction also works for 3- and 4-substituted butyrolactams **37**, affording substrates **40a**, **40b** and **41** using catalyst **XI** (2% mol) and Cs_2CO_3 (Scheme 11).

In addition, the same reaction has been reported using γ-butyrolactam **37** bearing an aromatic substituent in the position 3 of the ring and methyl vinyl ketone **38** (R^1=Me). In this case, catalyst **XII** (2% mol) needs to be used to afford substrates **42a-c** in 77% to 91% enantiomeric excesses.



Scheme 10. Vinylogous Michael reactions of 5-substituted TBS-pyrroles **35** and α,β-unsaturated methyl ketones **23**.



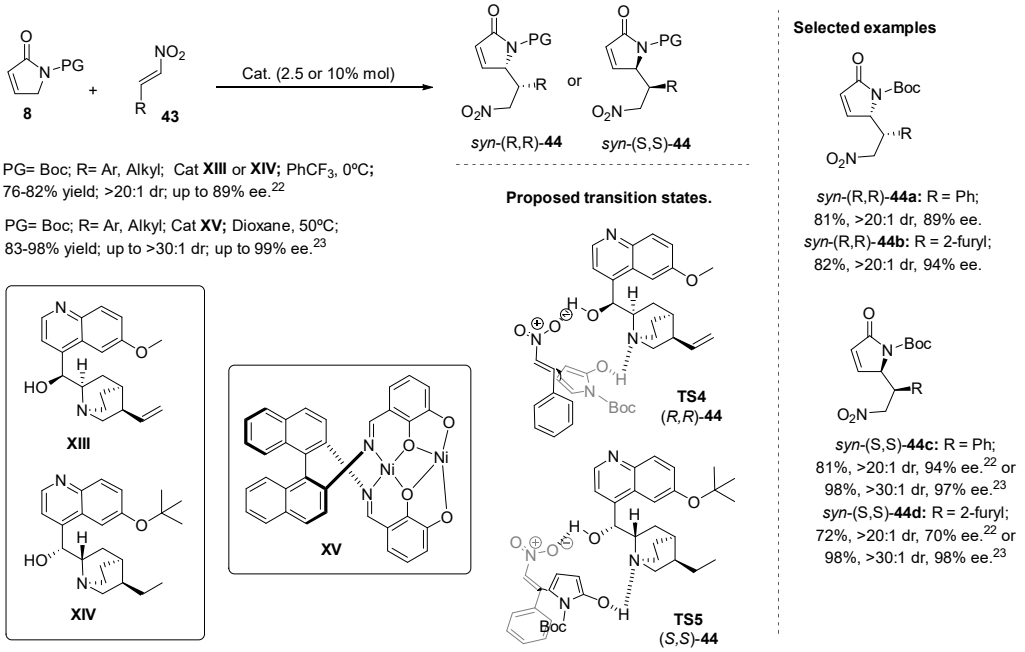
Scheme 11. Vinylogous Michael reactions of different 3-, 4-and 5-substituted α,β-unsaturated γ-butyrolactams **37** and vinyl ketones **38**.

2.1.3. Conjugate addition to nitroolefins

Besides addition reactions to conjugated aldehydes, ketones and esters, nitroolefins **43** are also good Michael acceptors for the functionalization of γ-lactams. For example, in 2012 Mukherjee and co-workers developed a synthetic protocol for the synthesis 1,5-dihydropyrrol-2-ones **44**, by allowing to react γ-butyrolactam **8** with nitroolefins **43** (Scheme 12).[22] The use of the cinchona derived catalyst **XIII** (10% mol) in trifluorotoluene at 0 ºC gave lactams *syn*-(*R,R*)-**44** in good yields (76-84%). However, if the reaction is performed at 25 ºC with catalyst **XIV** (10% mol), products *syn*-(*S,S*)-**44** are obtained (72-88% yield). In both cases nitroolefins **43** with aromatic groups bearing electron-withdrawing (R=HalogenC_6H_4) and electron-donating substituents (R=4-MeOC_6H_4) as well as with heteroaromatic (R=2-furyl, 2-thienyl) and aliphatic (*c*-Hex, *i*-Bu and *i*-Pr) groups are used. Lactams **44** are obtained with excellent diastereoselectivities (dr>20:1) and moderate to acceptable enantioselectivities for all tested nitroolefins **43**. Using catalyst **XIV**, in general, adducts *syn*-(*S,S*)-**44** are obtained with lower enantioselectivities (ee=54-84%) if compared to catalyst **XIII**, by which *syn*-(*R,R*)-**44** adducts are obtained in 60-89% ee.

The transition state proposed by the authors is based on the bifunctional coordination properties of cinchona alkaloids **XIII** and **XIV**. The nitroolefin **43** is activated *via* hydrogen bonding from the Brønsted acidic hydroxyl group whereas the Brønsted basic tertiary amine provides nucleophilic activation to γ-butyrolactam **8**. The stereochemistry of the Michael adducts is dictated by the orientation of the vicinal tertiary amine and hydroxyl groups in the catalyst. In the case of **XIII**, the *Si*-face of nitroolefin **43** is attacked by the *Si*-face of enolated γ-butyrolactam **8**, resulting in the formation of *syn*-(*R,R*)-**44** enantiomer as the major product **TS4**. As expected, the adduct *syn*-(*S,S*)-**44** is formed due to the Re-Re-face interaction between the two reactants and quinine derivative **XIV** (**TS5**).

Also in 2012, Matsunaga and Shibasaki, reported a similar reaction using Nikel catalyst **XV** (2.5% mol) in dioxane at 50 ºC, affording *syn-(S,S)*-**44** products in excellent yields (83-98%) and diastereoselectivities (16:1->30:1) (Scheme 12).[23] All the substrates were obtained in higher enantiomeric excesses (>97%) when compared to the use of cinchona derived catalyst **XIII**,[22] as can be seen for compounds **44c** and **44d** (ee=97% and 98%, respectively).

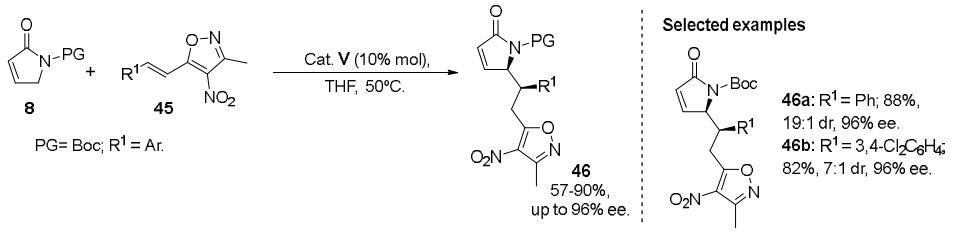


Scheme 12. Vinylogous Michael reactions of α,β-unsaturated γ-butyrolactam **8** and nitroolefins **43.**

2.1.4. Vinylogous Michael 1,6-additions

So far, in this report we have described a variety of 1,4-vinylogous Michael additions. Next, the corresponding 1,6-additions, always leading to the asymmetric synthesis of substituted γ-lactams will be outlined.

In 2013, Wang and co-workers reported the asymmetric vinylogous reactions of α,β-unsaturated γ-butyrolactam **8** with 3-methyl-4-nitro-5-alkenyl-isoxazoles **45** as 1,6-Michael acceptors.[14] The reaction proceeds successfully in THF at 50 ºC in the presence of squaramide catalyst **V** (10% mol), affording lactams **46** in good yields (57-90%) (Scheme 13). Isoxazol compounds **45** containing aromatic substituents bearing some halogen-substituted aromatic and electron-donating groups (R^1=4-MeC_6H_4, 4-$MeOC_6H_4$) as well as heteroaromatic (R^1=2-furanyl, 2-thiophenyl) groups were equally good substrates for this reaction, affording *syn* diastereoisomer as the major product (13:1-19:1) with excellent enantiomeric excesses (ee=92-96%). However, if substrates **45** with stronger electron-withdrawing groups (4-$CF_3C_6H_4$, 4-CNC_6H_4, 4-$NO_2C_6H_4$ and 3,4-ClC_6H_4) are used, the corresponding lactams **46** are obtained in good yields (77-85%) with excellent enantioselectivities (ee=91-96%) but with lower diastereoselectivities (4:1-7:1). Finally, when further conjugated isoxazole **45** (R^1=CH=CH-C_6H_5) was used as the Michael acceptor, a significant drop was observed in the enantio- and diastereoselectivity (dr=1.3:1, ee=84%).



Scheme 13. 1,6-Vinylogous Michael addition of α,β-unsaturated γ-butyrolactam **8** to 3-methyl-4-nitro-5-alkenyl-isoxazoles **45**.

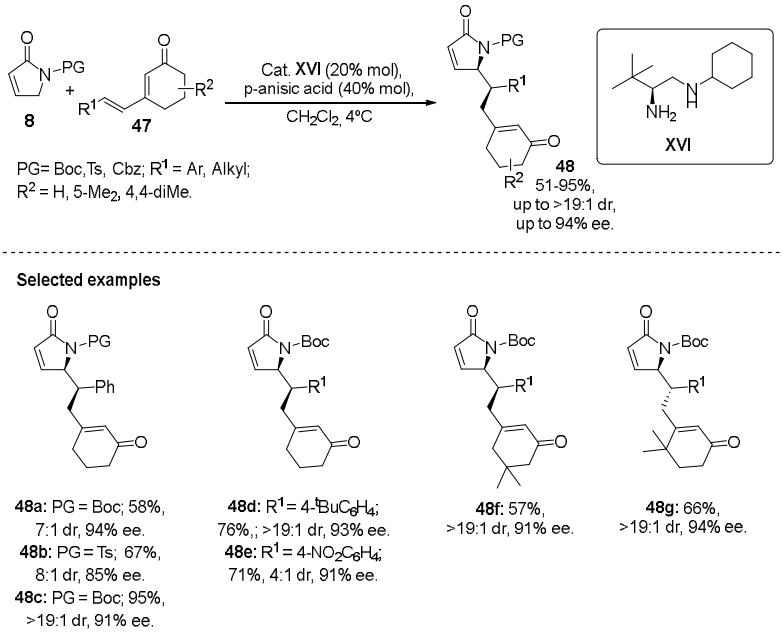
Another example of 1,6-vinylogous Michael enantioselective reaction is the nucleophilic addition of γ-butyrolactam **8** to cyclic dienones **47** in dichloromethane at 4 ºC in the presence of diamine catalyst **XVI** (20% mol) and *p*-anisic acid (40% mol) that leads to the formation of lactams **48** (Scheme 14).[24] Regarding the protecting group of the γ-butyrolactams **8**, the reaction proceeds successfully with Ts, Boc and Cbz groups. Although the enantioselectivities remain good in all cases (ee=85-91%), diastereoselectivities droped when Ts and Cbz groups were used, if compared to the dr observed (>19:1) for Boc group.

A wide range of 3-alkenyl cyclohex-2-enones **47** can be used in the reaction and products **48** are obtained in good yields (51-95%) in their *syn* configuration. Aryl-substituted dienones **47** with electron-donating substituents in the *para* and *meta* positions (R^1=4-MeC_6H_4, 4-*t*-BuC_6H_4, 3,4-$MeOC_6H_4$; R^2=H) gave excellent enantioselectivities (>90%) and diastereoselectivities (14:1->19:1), whilst the presence of various groups in the *ortho* position (R^1=2-MeC_6H_4, 2-$BocOC_6H_4$; R^2=H) produced worst ee values (ee=83 and 88%). The presence of electron-withdrawing and halogen (R^1=4-$NO_2C_6H_4$, HalogenC_6H_4; R^2=H), heteroaromatic (R^1=2-thienyl; R^2=H) and fused aromatic (R^1=2-naphtyl; R^2=H) substituents in **47** did not affect to the excellent results in diastereo- and enantioselectivity (dr=>13:1; ee=90-93%), except when nitro group was present, the dr decresases to 4:1. Furthermore, aliphatic-substituted dienones **47** (R^1=Me, *n*-Pr; R^2=H) were well tolerated (dr=9:1 and 11:1, ee=92% and 89%), as well as substituted cyclohexenones **41** (R^2≠H). Indeed, if the reaction is carried out with 5-substituted cyclohexanone **47** (R^1=Ph; R^2=5,5-dimethyl) *syn* product **48f** is obtained with >19:1 dr and 91% ee, while if 4-substituted cyclohexanone **47** (R^1=Ph; R^2=4,4-dimethyl) is used, *anti* product **48g** is formed, also with excellent dr (>19:1) and enantiomeric excess (94%).

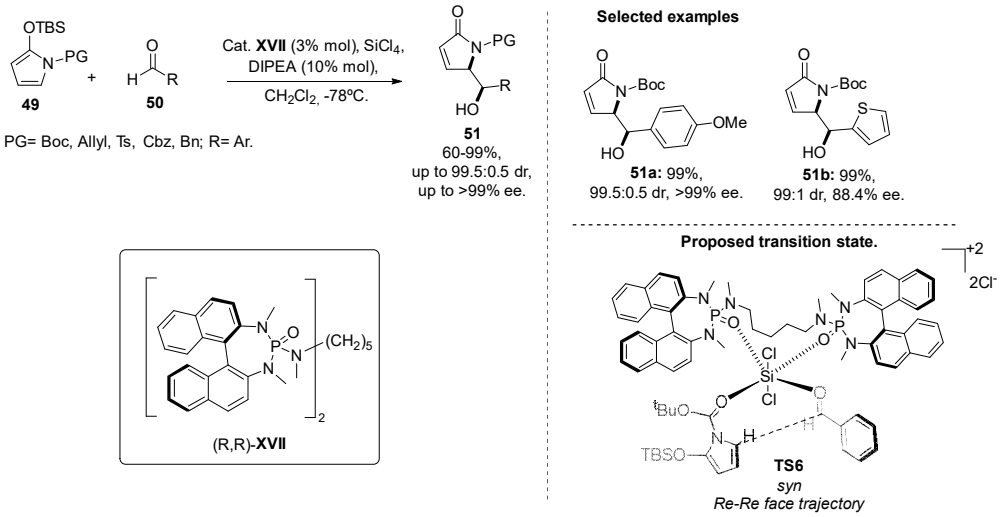
2.2. Vinylogous Mukaiyama reactions

Vinylogous Mukaiyama aldol reactions is also an excellent method for the production of enantioenriched unsaturated γ-lactam derivatives. Thus, using heterocyclic dienoxisilylates **49** with aromatic

and heteroaromatic aldehydes **50**, the synthesis of lactam derivatives **51** was reported by Casiraghi and Zanardi with a complete γ-addition and high diastereo- and enantioselectivity (Scheme 15).[25,26]



Scheme 14. 1,6-Vinylogous Michael addition of of α,β-unsaturated γ-butyrolactam **8** to 3-alkenyl cyclohex-2-enones **48.**



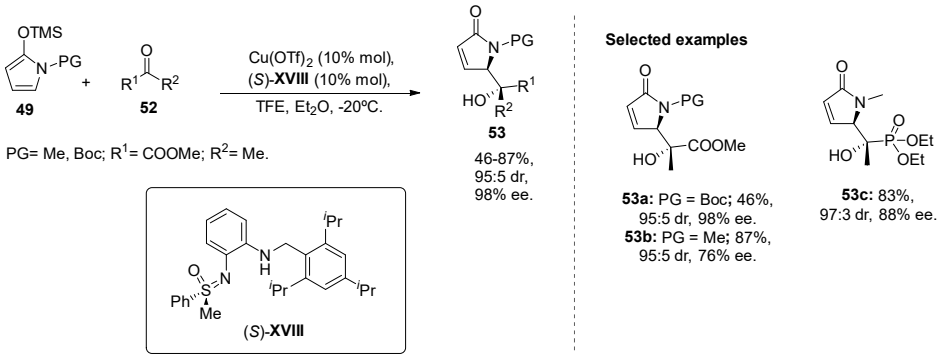
Scheme 15. Vinilogous Mukaiyama aldol reaction with aldehydes **50**.

The enantioselective vinylogous coupling of TBS-pyrroles **49** to aldehyde **50** is performed in presence of $SiCl_4$ (1.1 mol eq.) and chiral bisphosphoramide ligand **XVII** (3% mol) in dichloromethane at -78 ºC. In this case, the use of electron withdrawing nitrogen protecting groups on TBS-pyrroles **49** (PG=Boc, Ts and

Cbz) leads to a high diastereo- and enantioselectivity, obtaining *syn* products with 99.5:0.5 diastereoselectivity and enantiomeric excesses ranging from 93.7 to >99%. However, the use of electron donating protecting groups (PG=Bn, 4-$MeOC_6H_4$ and Allyl) caused a dramatic reversal of diastereoselectivity (dr=22:78-9:91) and losing of anantioselectivity (ee=0-23%). The reaction proceeded well with the use of different aromatic and heteroaromatic aldehydes, producing the expected *syn* configuration with outstanding results in diastereo- and enantioselectivity. Some examples are compounds **51a** and **51b** (Scheme 15).

Based on these experimental findings, the authors propose the transition state structure **TS6** (Scheme 15). In this case, when an extra-binding around the hypervalent silicon center occurs, as in the case of Boc-pyrrole nitrogen protecting group, an antiperiplanar bonding trajectory could be operative (*Re-Re* attack) leading to (5S,1'S)-adducts **51**.

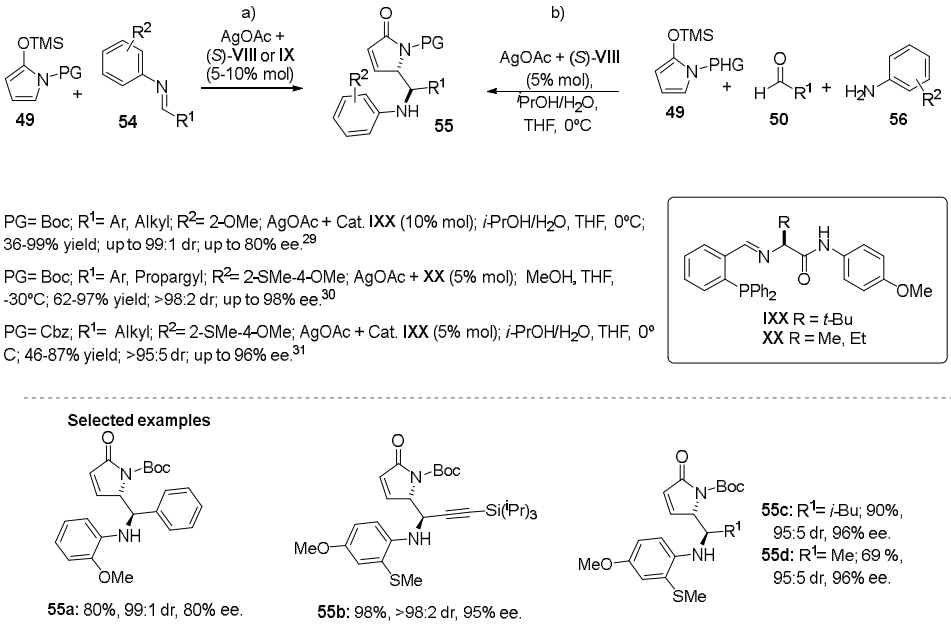
By the same time, Bolm and co-workers extended the enantioselective vinylogous coupling of TMS-pyrroles **49** to ketones **52,** although only two examples were described (Scheme 16).[27] Indeed, pyrroles **49** (PG=Me or Boc) react with keto ester electrophiles **52** (R^1=CO_2Me; R^2=Me) in the presence of $Cu(OTf)_2$ and chiral ligand **XVIII** (10% mol) in diethyl ether at -20 ºC. The *anti* product is obtained as the major diastereoisomer (dr=95:5) in 98% ee for **53a** (PG=Boc) and 76% ee for **53b** (PG=Me). A few years later, the same authors performed the reaction in the same conditions using phosphorylated ketone **52** (R^1 =P(O)OEt_2; R^2=Me) obtaining phosphorated substrate **53c** with good yield, 97:3 dr and 88% ee.[28]



Scheme 16. Vinylogous Mukaiyama aldol reaction with ketones **52**.

In addition to aldehydes and ketones, imines **54** can be also used in this vinylogous Mukaiyama reaction, as described by Casiraghi and Zanardi in 2011 (Scheme 17).[29] This reaction consists on the vinylogous addition of TMS-pyrroles **49** to aromatic imines **54** (R^1=Ar; R^2=2-OMe) catalyzed by AgOAc and ligand **IXX** (10% mol). The *anti* product is obtained as the major diastereoisomer (dr=>98:2) with excellent yields and an acceptable levels of enantioselectivity ranging from 42% to 80%. The best result is obtained for compound **55a**. However, the use of aliphatic-substituted imines **54** (R^1=*i*-Pr, *i*-Bu; R^2=2-OMe) results in a drastic decrease on the obtained yields (52% and 36%), although the enantiomeric excesses maintain moderate in both cases (ee=64%). Later, in 2015, Hoveyda and co-workers performed the reaction using aromatic imines **54** (R^1=Ar; R^2=2-SMe-4-OMe) in presence of AgOAc and ligand **XX** (5% mol). The major achievement of their work was the use arylpropagyl imines **54** (R^1=Propargyl; R^2 =2-SMe-4-OMe) as electrophiles for this reaction, obtaining the *anti* product as the mayor diastereoisomer (dr=>98:2) with excellent yields and enantioselectivities (ee=>86%) as in product **55b**.[30]

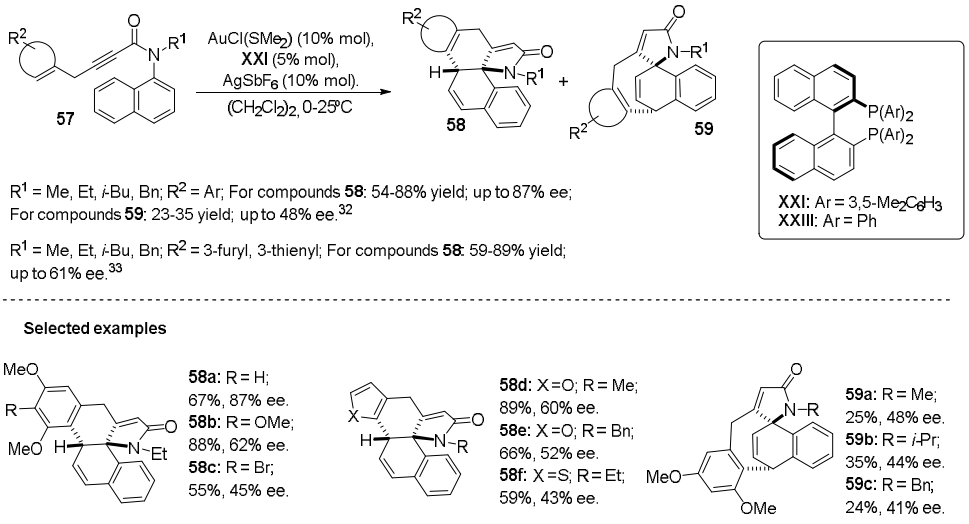
In 2011, Casiraghi and Zanardi described the three component version of this reaction using TMS-pyrroles **49**, aldehydes **50** and amines **56**, therefore avoiding the preformation of the imine (Scheme 17).[31] The reaction proceeds under the same conditions but with a lower loading of AgOAc and ligand **IXX** (5% mol). In this case, Cbz protecting group and aromatic amine **56** (R^2=2-SMe-4-OMe) were used with aliphatic aldehydes **50**, obtaining the *anti* diastereoisomers (dr=>95:5) with good yields (51-92%) and excellent enantiomeric excesses (ee=82-96%). Products **55c** and **55d** are some representative examples of this reaction.



Scheme 17. a)Vinylogous Mukaiyama aldol reaction with imines **54** (a). Three component vinylogous Mukaiyama aldol reaction (b).

2.3. Dearomatization and desymmetrization reactions

Some examples of catalytic asymmetric dearomatizations have been reported leading to the formation of 1,5-dihydropyrrol-2-ones. For example, the Tanaka's group described the catalytic asymmetric dearomatization of arenes through double C=C bond formation, using 3-benzyl-substituted propiolic acid 1-naphthylamides **57** (R^1=Me, Et, *i*-Bu, Bn; R^2=Aryl, 3-furyl, 3-thienyl) as substrates, and chiral cationic Au(I) complexes as a catalysts (Scheme 18).[32]

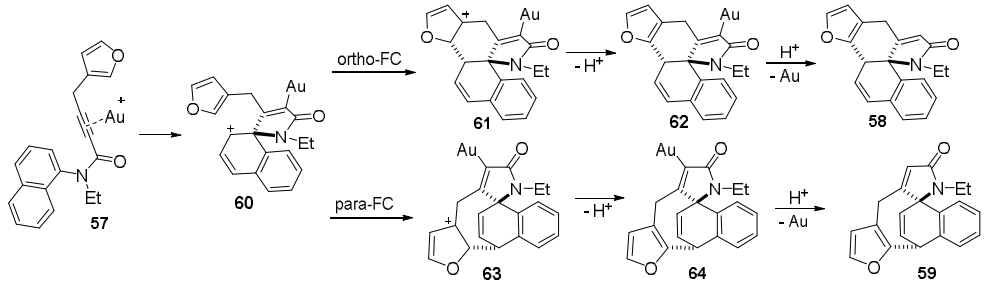


Scheme 18. Asymmetric dearomatization of naphthylamides **57**.

The use of naphthylamides **57** possessing a 3,5-$(MeO)_2C_6H_3$ group, gave both polycyclic substrates **58** and **59** in the presence of Au(I)/**XXI** complex (Scheme 18). The existence of sterically more demanding groups (R^1=*i*-Bu, Bn) gave lower ee values (ee=66% and 52% for **58**; ee=44% and 41% for **59**) than the use of *N*-methyl and *N*-ethyl substituents (ee=87% and 87% for **58**; ee=48% and 44% for **59**). Likewise, the reactions can be performed with naphthylamides **57** bearing various electron-rich aromatic groups (R^2=3,4,5-$(MeO)_3C_6H_2$, 3,4-dioxoleC_6H_3), affording the corresponding dearomatizated substrates **58** in good yields (55-88%) and with moderate ee values (ee=40-62%). In these cases, the corresponding eight-membered products **59** were not observed.

Later, the same group extended this methodology to substrates with 5-membered ring structures such as 3-furyl and 3-thienyl derivatives (Scheme 19).[33] Therefore, the use of 3-furyl substituents in **57** gave the desired products **58d-e**, in moderate yields and enantioselectivities (59-89% yield, ee=43-61%). In addition, thiophene-substituted substrate **57** (R^1=Et; R^2=3-thienyl) can also be used as starting material, providing product **58f** in 59% yield and 43% ee. In addition, the use of 3-furyl derivatives gave eight-membered ring containing byproducts **59** (ratio **58**:**59** 83:17 to 88:12), although they could not be isolated due to their instability.

A mechanistic proposal for the reaction is shown in Scheme 19. According to the authors, the reaction may start by the coordination of the cationic Au(I) complex to the triple bond of alkyne **57**, which induces the *ipso*-cyclization to generate a cationic intermediate **60**. Then, the reaction can evolve by two different paths. In the first of the proposed route, an *ortho*-Friedel-Crafts reaction would yield intermediate **61**, followed by a deprotonation to produce species **62**. Finally, a protonation regenerates the cationic Au(I) catalyst obtaining product **58**. The second path consist on a *para*-Friedel-Crafts reaction leading to intermediate **63**. Then, species **64** is formed, *via* deprotonation, and the reaction ends by a protonation that regenerates the Au(I) catalyst, obtaining products **59**.

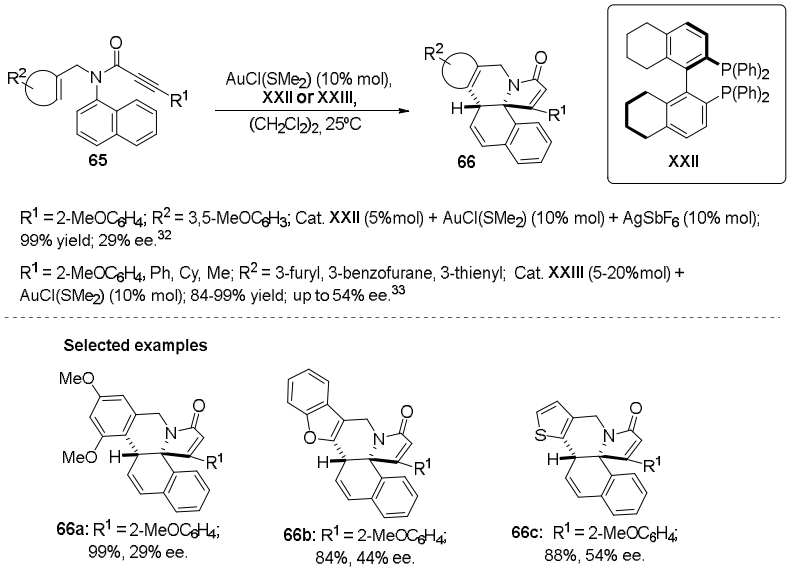


Scheme 19. Proposed mechanism for the Au(I)-catalyzed asymmetric dearomatization of naphthylamides **57**.

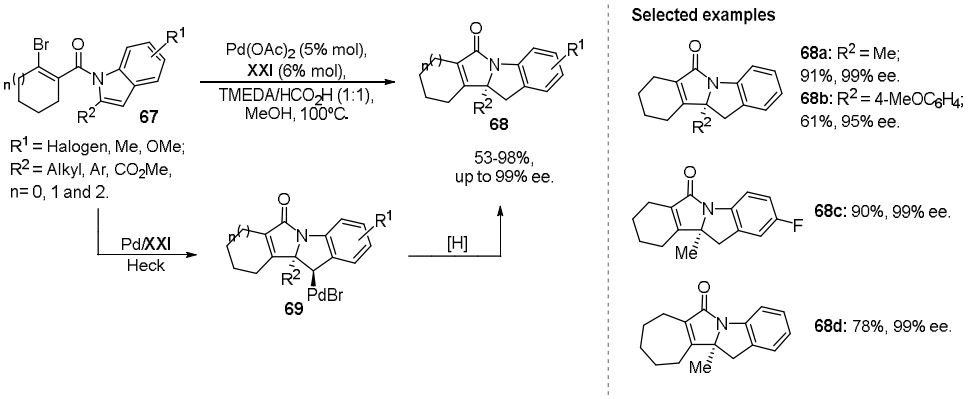
Next, the same research group located the benzyl or heteroarylmethyl groups directly in the amide nitrogen of 1-naphthylamides, instead of anchoring it to the alkyne chain terminus. Therefore, they applied this methodology to the asymmetric dearomatization of *N*-benzyl-substituted propiolic acid 1-naphthylamide **65** (R^2=3,5-$MeOC_6H_3$), using cationic Au(I)/**XXII** bisphosphine as catalyst (Scheme 20). In this way, product **66a**, where the nitrogen is shared by a six- and a five-membered ring is obtained with high yields but low enantiomeric excess (ee=29%).[32] The reaction can be also carried out with heteroarylmethylene-substituted 1-naphthylamides **65** (R^1=2-$MeOC_6H_4$; R^2=3-furyl, 3-benzofuran, 3-thienyl) using Au(I)/**XXIII** complex. In these cases, dearomatization products **66** are obtained in high yields (84-99%) with moderate ee values (ee=47-54%). However, the use of phenyl, cyclohexyl and methyl substituents on the alkyne (R^1), gave substrates **66** with low enantiomeric excesses (ee=12-14%).[33] In some of these cases, higher catalyst loading (up to 20% mol) had to be used.

If acrylamides derived from indoles **67** are used in the reaction instead of propiolic amide containing substrates, dearomatization-Heck reaction affords polycyclic indolines **68** bearing a γ-lactam core inside, through the formation of intermediate **69** (Scheme 21).[34] This transition-metal-catalyzed Pd/**XXI** reaction can be carried out using *N*-substituted indoles **67** with alkyl (R^2=Me, Et, cyclopropyl), ester (R^2=CO_2Me),

and diverse aromatic (R^2=Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 4-$CF_3C_6H_4$, HalogenC_6H_4), heteroaromatic (R^2=2-thienyl) and fused aromatic (R^2=2-naphtyl) groups. Moreover, C5- and C6-substituents (Cl, F, Me, MeO) in the indole ring were well tolerated, obtaining products **68** with 59-98% yield and 97-99% ee, although lower yields are observed when C6 position is substituted. Finally, the reaction can be extended to 5-, 7-, and 8-membered bromocycloalkene containing indoles **67**, providing good yields and excellent enantiomeric excesses.

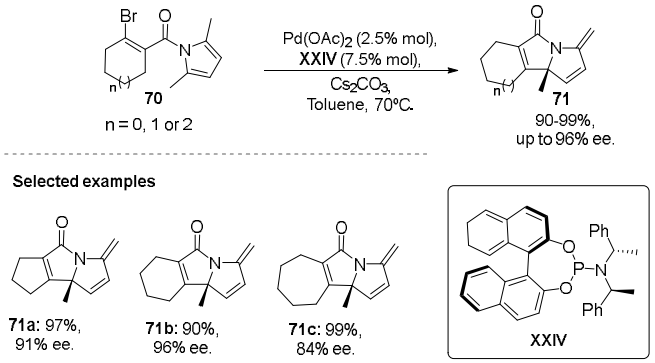


Scheme 20. Asymmetric dearomatization of naphthylamides **65**.



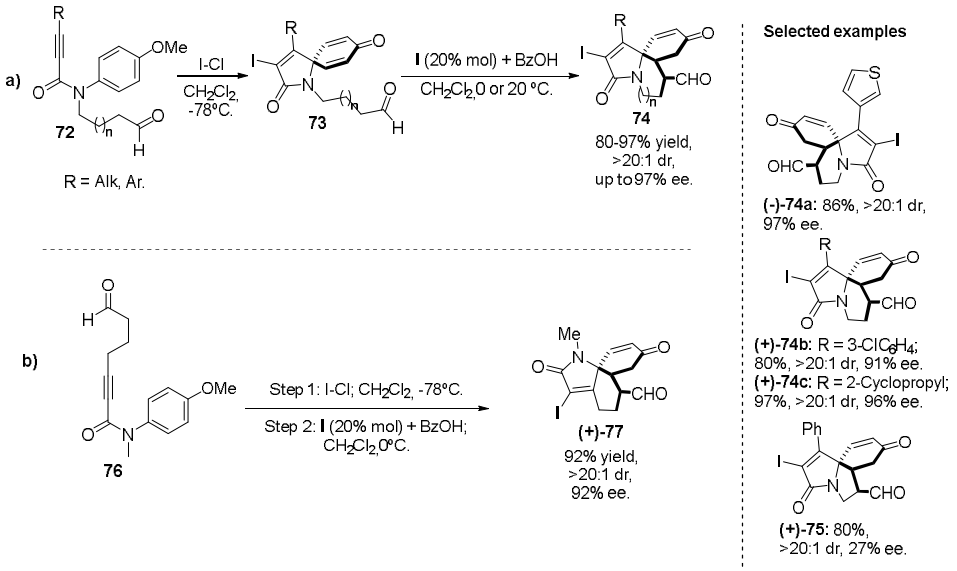
Scheme 21. Pd(II)-catalyzed asymmetric dearomatization of indoles **67**.

In 2018, You extended the reaction to the use of pyrrole derivatives instead of indole, and performed the asymmetric dearomatizing Heck reaction of cycloalkenyl *N*-acylpyrroles **70** to afford 1,5-dihydropyrrol-2-ones **71** (Scheme 22).[35] The reaction proceeds successfully in toluene at 70 ºC with $Pd(OAc)_2$ (2.5% mol) and ligand **XXIV** (7.5% mol) using cycloalkenyl -*N*-acylpyrroles **70** with different sized rings (n=0, 1 and 2) and affording tricyclic γ-lactams **71** in excellent yields and enantioselectivities.



Scheme 22. Pd(II)-catalyzed asymmetric dearomatization of pyrroles **70**.

On the other hand, Gaunt and co-workers in 2011 described for the first time an enantioselective cyclohexadienone desymmetrization for the preparation of tricyclic lactams **74** (Scheme 23a).[36] The reaction can be performed using aryl-substituted alkynes **72** (R=3-ClC_6H_4, 3-thiophene, Ph). More specifically, the use of electron rich thiophene group gave product **(–)-74a** in good yield and excellent enantioselectivity (86% yield, 97% ee). When 3-ClC_6H_4 substituent is used also excellent ee is observed (ee=91%) but in this case **(+)-74b** product, with opposite configuration is obtained. However, the presence of a phenyl substituent in alkyne **72**, combined with shorter linking chain between the aldehyde and amide function, led to the formation of the five-membered ring derivative **(+)-75**, with a remarkable drop in the enantiomeric excess (80% yield, ee=21%).



Scheme 23. Enantioselective cyclohexadienone desymmetrization for the preparation of tricyclic lactams **74**, **75** and **77**.

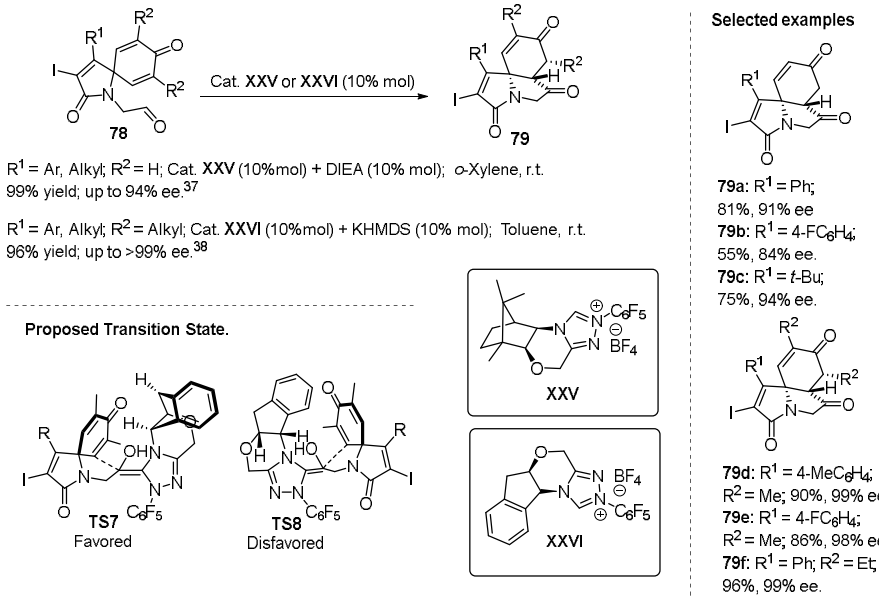
Moreover, alkynes **72** (R=*n*-Bu, cyclopropyl, $(CH_2)_3OTIPS$) with aliphatic substituents where used, affording in all cases tricyclic substrates **(+)-74** in 89-96% ee and 80-97% yield. In this case, the mechanism of the reaction would comprise an electrophilic I-Cl activation of alkyne **72** towards a 5-*endo-dig ipso*-iodocyclization, causing an intramolecular dearomatization that is followed by the loss of

the phenolic methyl ether group, forming spiro-substituted clohexadienone **73**. Then, without further purification, the desymmetrization step happens, starting with a condensation of prolinol derivative **I** with aldehyde **73** and then followed by an intramolecular Michael addition, obtaining products **74**.

The authors also extended the scope of the reaction, and found that the aldehyde motif and electrophilic alkyne can be incorporated into the same chain as in substrate **76**, to give the tricyclic compound **(+)-77** in excellent yield diastereo- and enantioselectivity (92% yield, dr=>20:1, ee=92%) (Scheme 23b).

In a similar way, You and co-workers performed a desymmetrization of cyclohexadienone aldehyde **78** *via N*-heterocyclic carbene (NHC)-catalyzed intramolecular Stetter reaction, obtaining tricyclic compounds **79** (Scheme 24).[37] The difference with the previous work, Gaunt's work, relays on the length of the linking unit between the aldehyde and amide in the starting materials **73** and **78** and the catalysis employed. The intramolecular reaction of lactams derivatives **78** (R^2=H) in the presence of catalyst **XXV** (10% mol) and DIEA (10% mol) in *o*-xylene at room temperature gave tricyclic lactams **79** (R^2=H) as single diastereoisomers. The position of the methyl group in the tolyl substituent at carbon 4 has a significant influence on the enantioselectivity of the reaction, with values ranging from 58% ee for 4-methylphenyl moiety to 89% ee for 2-methyl derivative. The use of halogen-substituted aryl groups in that position such as 4-FC_6H_4 and 4-ClC_6H_4 (in this case using Cs_2CO_3) provided the corresponding compounds **79** (R^2=H) in 54-55% yield and 84-86% ee. Moreover, a heteroaromatic 2-thienyl substituent was also well tolerated, yielding the desired tricyclic product with 75% ee. Finally, various alkyl-substituted lactams **78** (R^1=Me, *n*-Pr, *t*-Bu, cyclopropyl; R^2=H) were evaluated, obtaining tricyclic compounds **79** in 58-85% yield and 85-94% ee.

The same authors also described this reaction starting from dimethyl-substituted cyclohexadienones **78** (R^2=Me), using catalyst **XXVI** (10% mol) and KHMDS (10% mol) in toluene at room temperature (Scheme 24),[38] obtaining single diastereoisomers with excellent yields and enantiomeric excesses (80-96% yield, ee=98->99%). However, when double-substituted substrates **78** (R^1=Me; R^2=Me, 2-MeC_6H_4**)** are used, dr and ee values drop considerably. It is also possible to perform the reaction using substrates **78** bearing alky groups at the α position of the ketone. In this case the reaction proceeds with excellent yields and enantiomeric excesses (ee=99->99%). A postulated model for the transition state is depicted in Scheme 24.



Scheme 24. Enantioselective cyclohexadienone desymmetrization for the preparation of tricyclic lactams **79**.

The authors theorize that the high degree of enantioselectivity is obtained by avoiding the steric collision with aminoindanol backbone in the favored transition state **TS7** compared to disfavored **TS8**.

2.4. Mannich reactions

The Mannich reaction has also been successfully used as a tool for the synthesis of enantioenriched unsaturated γ-lactams. The acid-catalyzed three component reaction of aldehydes **50**, amines **56**, and ethyl pyruvate derivatives **80** to afford 3-amino-1,5-dihydropyrrol-2-ones **81** was described for the first time by our research group in 2006 (Scheme 25).[39] This reaction starts with the formation of enamines **82** and aldimines **54** through a simultaneous condensation of amines **56** with aldehydes **50** and pyruvate **80**. Then, the catalyst promotes the Mannich reaction between species **82** and **54** to give intermediate **83**, and finally the amide bond is formed after the intramolecular addition of the amine to the carboxylic group, leading to the formation of γ-lactam core.

A few years later, Cheng and Luo reported an enantioselective three-component reaction of benzaldehyde **50** (R^1=Ph), 4-anisidine **56** (R^2=4-$MeOC_6H_4$) and ethyl pyruvate **80** (R^3=H; R^4=Et) in a 1:2:3 ratio. Using 10% of chiral Brönsted catalyst **XXVII** in toluene at room temperature and in the presence of sodium sulfate, γ-lactam derivative **81a** is obtained in 77% yield but with modest enantiomeric excess (44%).[40] Then, in 2013 Huang reported a single example of this reaction, using *ter*t-butyl glyoxalate **50** (R^1=$CO_2{}^t$Bu), 4-anisidine **56** (R^2=4-$MeOC_6H_4$) and methyl pyruvate **80** (R^3=H, R^4=Me) to yield γ-lactam derivative **81b** in 72% ee, using 5% of catalyst **XXVIII** in toluene at 25 ºC.[41]

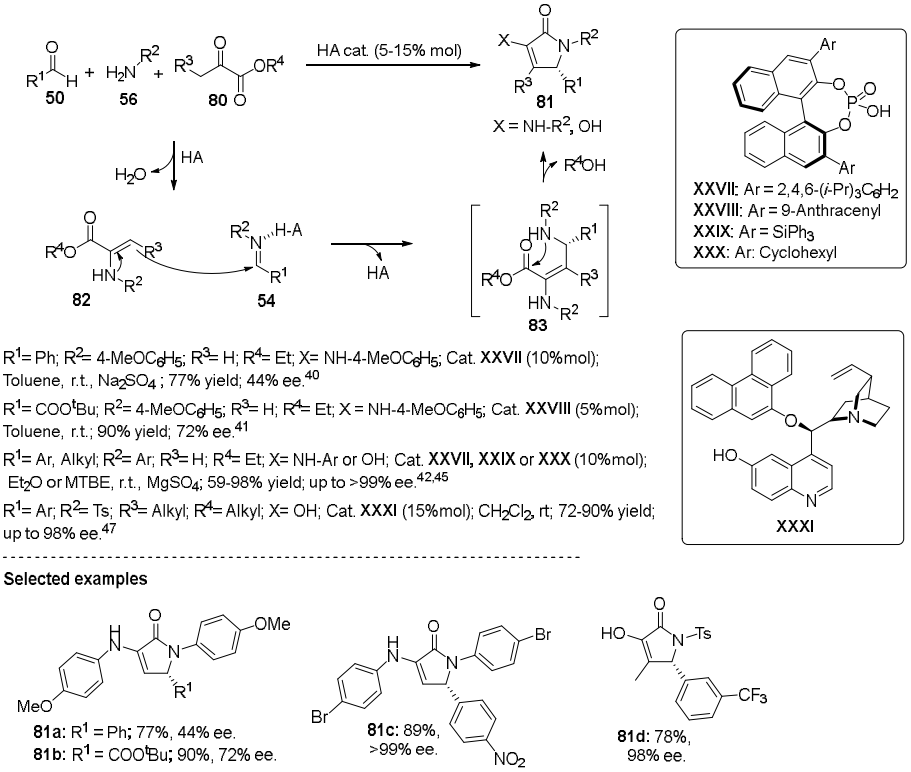
More recently, our research group has achieved a general enantioselective synthetic methodology for the preparation a large variety of this class of compounds.[42] In this case, diverse aldehydes **50**, amines **56** and pyruvate derivatives **80** react in diethyl ether at room temperature or MTBE at 55 ºC, in the presence of magnesium sulfate and 10% of phosphoric acid catalyst **XXVII**, **XXIX** or **XXX** (Scheme 25). While very good enantiomeric excesses are obtained with activated aromatic amines (ee=96->99%), aromatic amines with strong electron-withdrawing groups such as 3-trifluoromethylaniline afford the lactam derivatives with modest enantioselectivity (ee=62%). Benzaldehyde, electron-rich (R^1=4-$NO_2C_6H_4$), electron-poor (R^1=4-$CF_3C_6H_4$) and heteroaromatic aldehydes (R^1=2-thienyl) can be used in combination with various amines, obtaining excellent enantiomeric excesses (ee=62->99%). The reaction can be also performed with non-aromatic aldehydes **50**, such as cinnamaldehyde (R^1=CH=CHPh), 59 % yield, ee=>99%) and ethyl glyoxalate (R^1=CO_2Et, 95% yield, ee=97%), as well as aliphatic enolizable aldehydes such as iso-butyraldehyde (R^1=*i*-Bu, 77% yield, ee=82% ee) and cyclohexanecarboxaldehyde (R^1=Cy, 95 % yield, ee=79%). Besides, the use of substituted pyruvates **80** (R^3=Me, Bn) is feasible in this reaction, although in this case the reaction needs to be performed in refluxing MTBE in order to obtain tetrasubstituted γ-lactam derivatives **81** (X=NHR^2)with good yields (70% and 71%) but moderate enantiomeric excesses (ee=54% and 68%).

We have demonstrated that the introduction of fluorine and phosphorus substituents into heterocyclic structures leads to highly biologically active substrates.[43,44] For this reason, the same reaction was next extended to the use of phosphorated and fluorinated aldehydes **50** (R^1=$CH_2P(O)(OEt)_2$, $CH_2P(O)Ph_2$, C_6F_5, CF_3).[45] In the case of phosphorylated aldehydes, the reaction proceeds successfully in diethyl ether at room temperature obtaining phosphorus containing lactams **81** (X=NHR^2, R^1=CH_2-$P(O)(OEt)_2$, CH_2-$P(O)Ph_2$) in 90-91% ee. Likewise, the reaction needs heating when perfluorinated aldehydes **50** (R^1=C_6F_5, CF_3) are used and, for this reason the enantioselectivity drops to 60% ee with perfluorobenzaldehyde (R^1=C_6F_5) and 5% ee for trifluoroacetaldehyde (R^1=CF_3).

In addition, a similar multicomponent reaction for the synthesis of lactam derivatives can be performed using acetylene carboxylates instead of pyruvate derivatives.[46] Indeed, the three-component reaction of benzaldehyde with aliphatic and aromatic amines and diethyl acetylenedicarboxylate has been proved to proceed in the presence of a Brönsted acid catalyst in refluxing toluene. However, due to the high temperature needed for the reaction, very poor enantiomeric excesses (ee=5%) were obtained using chiral phosphoric acid catalysts.

Other kind of Mannich methodology, specifically the one used to obtain 3-hydroxy-1,5-dihydropyrrol-2-ones **81** (X=OH, Scheme 25), is the reaction of aldimines **54** (R^1=Ar; R^2=Ts) and pyruvate derivatives **80** (R^3=Me, Et; R^4=Me, Et, *n*-Pr) in a 1:2 ratio, in dichloromethane at room temperature in the presence of catalyst **XXXI** (15% mol).[47] The mechanism of this reaction is slightly

different in this case; the base catalyst activates pyruvate **80** through the formation of an enol intermediate (instead of the enamine described in the previous works), and this reacts with aldimine **54**, leading to the formation of γ-lactam ring. The substituents present in pyruvate derivatives **80** (R^3=Me, Et; R^4=Me, Et, *n*-Pr) and the aromatic substituent of aldimine **54** (R^1=Ar; R^2=Ts) did not make any remarkable difference in the synthesis of the enantioenriched products, obtaining excellent results in all cases, ranging from 87% to 98% ee (76-90% yield).



R^1= Ph; R^2= 4-MeOC$_6$H$_5$; R^3= H; R^4= Et; X= NH-4-MeOC$_6$H$_5$; Cat. **XXVII** (10%mol); Toluene, r.t., Na_2SO_4 ; 77% yield; 44% ee.[40]

R^1= COO^{t}Bu; R^2= 4-MeOC$_6$H$_5$; R^3= H; R^4= Et; X = NH-4-MeOC$_6$H$_5$; Cat. **XXVIII** (5%mol); Toluene, r.t.; 90% yield; 72% ee.[41]

R^1= Ar, Alkyl; R^2= Ar; R^3= H; R^4= Et; X= NH-Ar or OH; Cat. **XXVII, XXIX** or **XXX** (10%mol); Et_2O or MTBE, r.t., $MgSO_4$; 59-98% yield; up to >99% ee.[42,45]

R^1= Ar; R^2= Ts; R^3= Alkyl; R^4= Alkyl; X= OH; Cat. **XXXI** (15%mol); CH_2Cl_2, rt; 72-90% yield; up to 98% ee.[47]

Selected examples

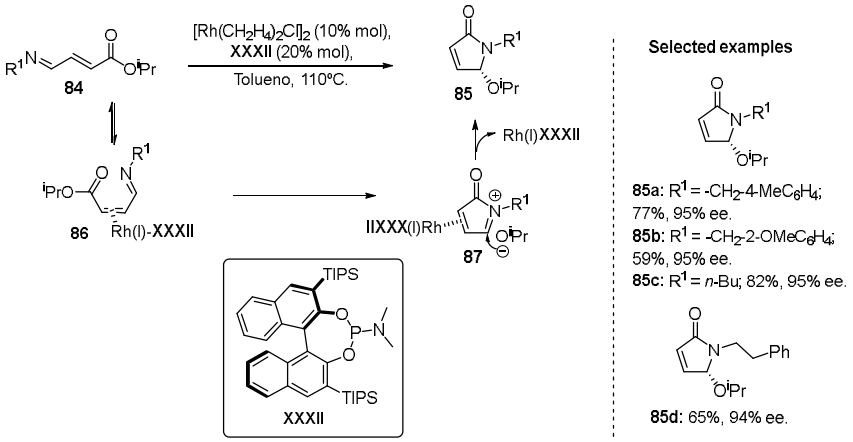
Scheme 25. Mannich reactions for the enantioselective synthesis of 1,5-dihydropyrrol-2-ones **81**.

2.5. Other methodologies

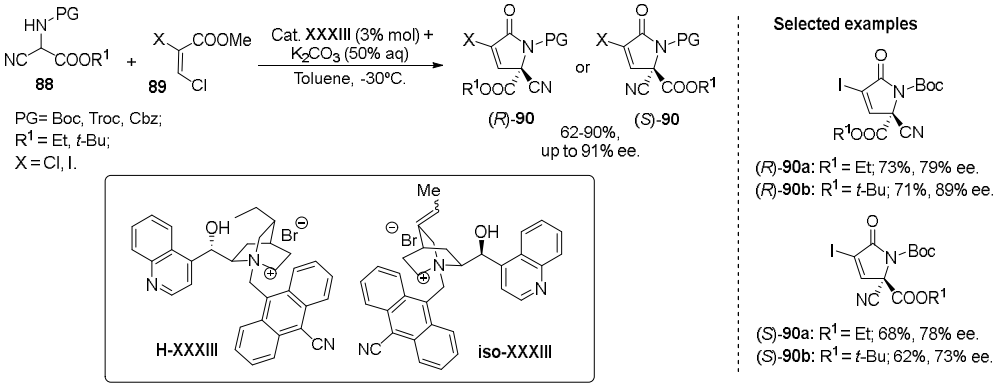
In 2016, Rovis's group disclosed the rhodium(I)/phosphoramidite **XXXII**-catalyzed intramolecular cyclization of 4-iminocrotonates **84** to give 5-isopropoxy-3-pyrrolin-2-ones **85** in good yields (51-77%) (Sheme 26).[48] The mechanism of this reaction consists on the initial coordination of 4-iminocrotonate **84** to the catalyst complex, so that it isomerizes from *E* to intermediate **86** with *Z* configuration. Then, the nitrogen of the imine attacks the carbonyl group, affording *N*-acyliminium intermediate **87**, which is trapped by alkoxide, thus delivering 5-alkoxy-3-pyrrolin-2-ones **85**. 4-Iminocrotonates **84** (R^1=CH_2-Ar) with *N*-benzyl substituents bearing electron-donating alkyl and alkoxy groups and electron-withdrawing trifluoromethyl and methoxycarbonyl substituents afford products **85** with high enantioselectivities (ee=>94) in all cases. The use of imine substrates **84** containing *N*-heteroaromatic or *N*-alkyl substituents also gave high enantioselectivities (ee=91-95%).

Jørgensen and co-workers described in 2008 the organocatalytic enantioselective vinylic substitution reaction of α-amino acid derivatives **88** with α,β-dihalogenated acrylate esters **89** for the synthesis of 3-halo-3-pyrrolin-2-ones **90** (Scheme 27).[49] In this substitution process, chiral phase-transfer catalysts **XXXIII** are used to form a C-C bond by the stereospecific substitution of the chlorine atom with 1,2-dinucleophiles **88**. Then a ring closure happens and products **90** are selectively formed. The reaction is

carried out in toluene at -30 ºC with catalyst **H-XXXIII** and K_2CO_3 and, even using different substituents in the starting molecules (PG=Boc, Troc, Cbz; R^1=Et, *t*-Bu; X=Cl, I), the final products are formed in good yields (63-73%) and *R* enantiomers are obtained with very good enantiomeric excesses (ee=78-91%). In addition, the authors describe a couple of examples in which catalyst ***iso*-XXXIII** is used, to generate *S* enantiomers in good yields and enantiomeric excesses (ee=73-78%).



Scheme 26. Enantioselective synthesis of 5-alkoxy-3-pyrrolin-2-ones **85**.

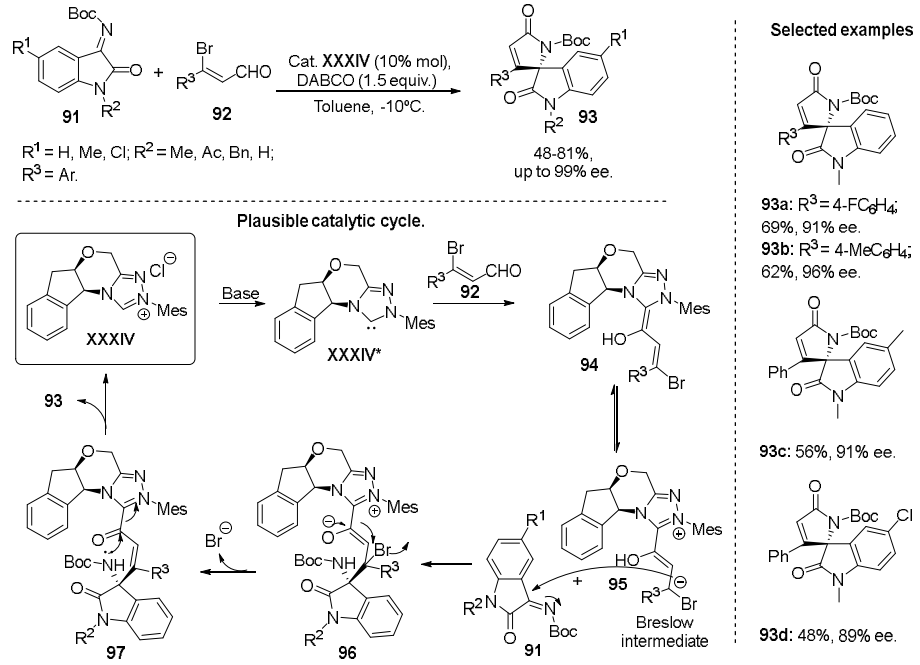


Scheme 27. Enantioselective synthesis of 3-halo-3-pyrrolin-2-ones **90**.

Hui and co-workers performed the triazolium carbene **XXXIV**-catalyzed-annulation reaction of isatin *N*-Boc ketimines **91** with 3-bromo-3-acrylaldehydes **92** in toluene at -10 ºC to afford spiro[indoline-3,2′-pyrrole] derivatives **93**.[50] As summarized in Scheme 28, the plausible catalytic cycle consists on the formation of the carbene **XXXIV*** through combination of catalyst **XXXIV** and DABCO followed by the 1,2-addition to 3-bromoenal **92**, forming species **94**, which is in equilibrium with Breslow intermediate **95**. This intermediate promotes an intermolecular nucleophilic addition reaction with isatin *N*-Boc ketimine **91**, thus forming intermediate **96** after proton transfer. Then, a proton transfer and a debromination generates intermediate **97**, which finally undergoes an intramolecular lactamization, to give products **93** in moderate to good yields (48-81%).

The use of different R^2 substituents on isatin **91** affects on the reaction yields and enantioselectivity. Thus, with electron-donating groups (R^2=Me, Bn), good yields (69% and 64%) and enantioselectivites (ee=93% and 95%) are observed, but when unsubstituted or acylated isatins **91** (R^2=H, Ac) are used, while

the enantioselectivities remains high, yields are very low (39% and 13%). The use of isatins **91** bearing substituents on the aromatic ring (R^1=Me, Cl) also give products **93** with good yields and enantioselectivities. On the other hand, various 3-aryl-3-bromoenals **92** were tested holding aromatic substituents with electron-withdrawing groups (R^3=HalogenC_6H_4, 4-$NO_2C_6H_4$) and electron-donating groups (R^3=4-MeC_6H_4, 4-$MeOC_6H_4$) as well as heteroaromatic (R^3=2-thienyl and 2-furyl) and fused aromatic (R^3=2-naphthyl) groups. In all cases the reaction occurred smoothly to form products **93** in 61-77% yield with 89-99% ee (Scheme 28).

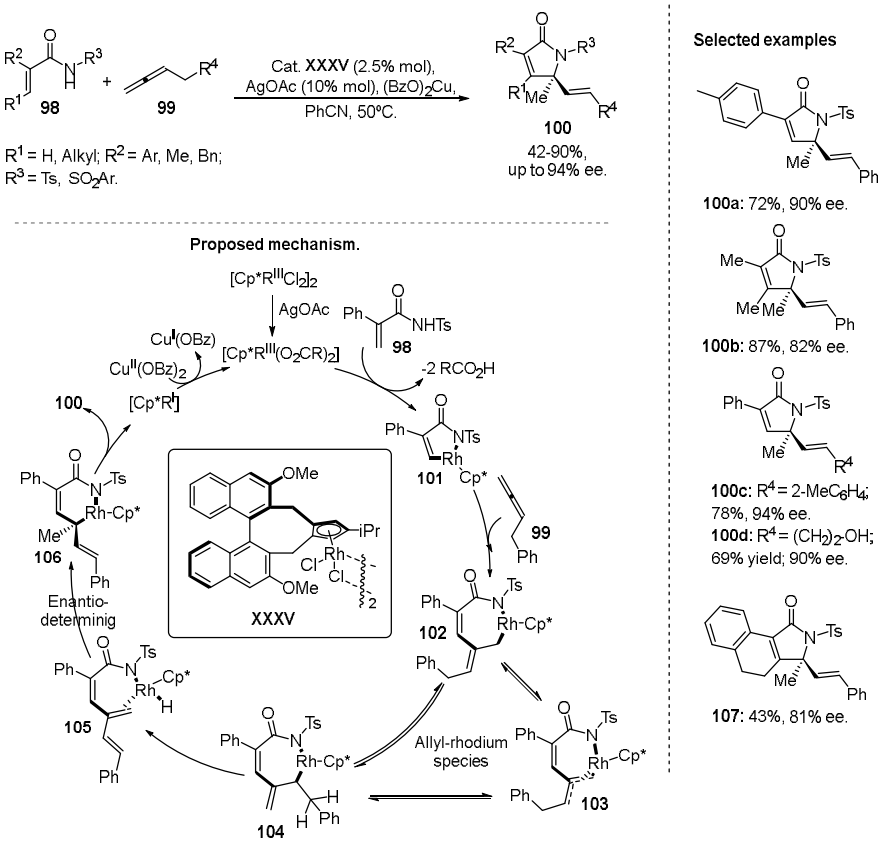


Scheme 28. Enantioselective synthesis of spiro[indoline-3,2′-pyrrole] derivatives **93**.

Cyclization involving acrylamides **98** and allenes **99** for the construction of enantio-enriched α,β-unsaturated γ-lactams has been described by Cramer.[51] The suggested mechanism (Scheme 29) starts when the N-H group of **98** binds to complex **XXXV** [Cp*Rh(III)], leading to the five-membered rhodacycle **101**. Then, the insertion of allene **99** provides a series of interconverting allyl-rhodium species **102**, **103** and **104**. In this case, instead of reductive elimination that would lead to [4+2]-products, β-H elimination happens, generating a diene product **105**. Then, the rhodium hydride adds to the double bond to give a six-membered rhodacycle intermediate **107** intermediate in the enantiodetermining step. Finally, reductive elimination delivers lactam **100** and Cp*Rh(I) species, that is regenerated by oxidation with the Cu(II) salt, thus closing the catalytic cycle.

The use of diverse aromatic substituents bearing electron-donating (R^2=2-, 3- or 4-MeC_6H_4, 3-$MeOC_6H_4$) or electron-withdrawing groups (R^2=HalogenC_6H_4) as well as fused aromatic (R^2=2-naphthyl) substituents in the α-position of acryl amides **98** gave lactams **100** in moderate to good yields and high levels of enantioselectivity (51-79% yield, ee=86-93%). In addition, the use of alkyl or benzyl groups in α- or β-positions of acryl amides **98** (R^1=Me; R^2=Me, Bn) gave products **100** in very good yields although with slightly reduced enantioselectivity (ee=58-82%). Finally, the use of various *N*-protecting groups on acryl amides **98** (R^3=Ts, SO_2Ph, $SO_2$4-FC_6H_4) gave lactams **100** with excellent enantioselectivities (>93% ee) and good yields (64-74%). In addition, these authors were able to synthesize a single example of a bicyclic γ-lactam **107**, which was prepared using cyclic acrylamide **98** (Scheme 29).

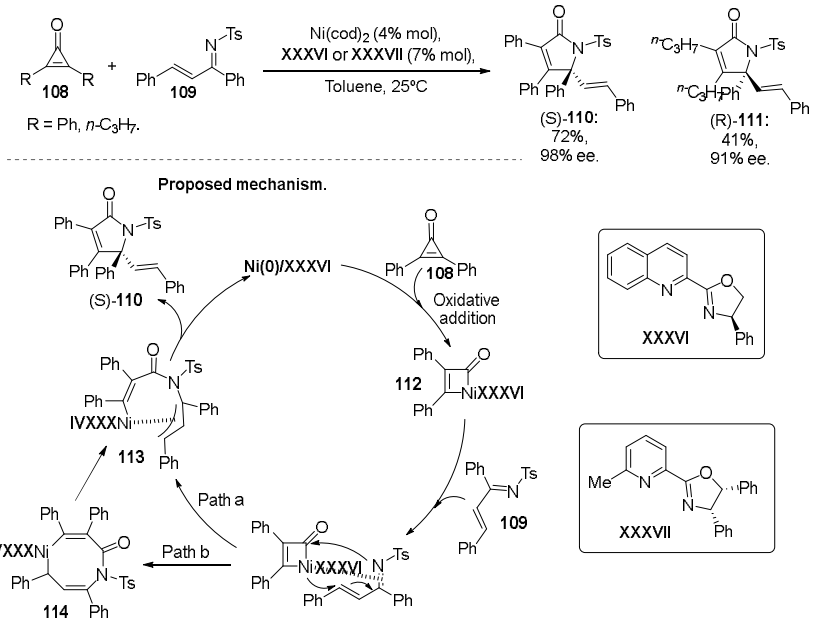
Regarding allenes **99**, a large variety of them can be used in this synthesis. For instance, those containing substituents that stabilize the product by conjugation (R^4=Ar, Carboxylate) gave lactams **100** in moderate to good yields (42-78%) and excellent selectivity (ee=90-94%). On the other hand, non-conjugated allenes **99** (R^4=$(CH_2)_n$CN, OH, OBn), perform equally well, providing lactams **100** with a similar range of yields (64-90%) and enantioselectivities (ee=87-91%).



Scheme 29. Rh(III)-catalyzed enantioselective synthesis of α,β-unsaturated γ-lactams **100**.

Finally, a $Ni(cod)_2$-catalyzed enantioselective formal [3+2]-annulation between cyclopropenones **108** and α,β-unsaturated imines **109** to afford γ-lactams **110** and **111** has been recently reported (Scheme 30).[52] When cyclopropenone **108** (R=Ph) and chiral ligand **XXXVI** is used, (*S*)-**110** product is obtained in 72% yield and 98% ee. However, if the reaction is performed with chiral ligand **XXXVII** and aliphatic-substituted cyclopropenone **108** (R=*n*-C_3H_7), (*R*)-**111** product is obtained, although with lower yield and enantiomeric excess (41% yield, ee=91%).

The proposed mechanism pathway may consist on an oxidative addition of cyclopropenone **108** to Ni(0), affording a 4 membered cyclic intermediate **112**, which is proposed to undergo enantioselective Ni-C(acyl) migratory insertion into the C=O bond (path a), obtaining intermediate **113**. Alternatively, the 4-membered cyclic intermediate may undergo concerted 4,1-insertion of the Ni-acyl into the imine **109** to give 8-membered intermediate **114** (path b). Both paths converge in the formation of a Ni(II)-allyl intermediate **113** that reductively eliminates the final product **110**, regenerating the catalyst.



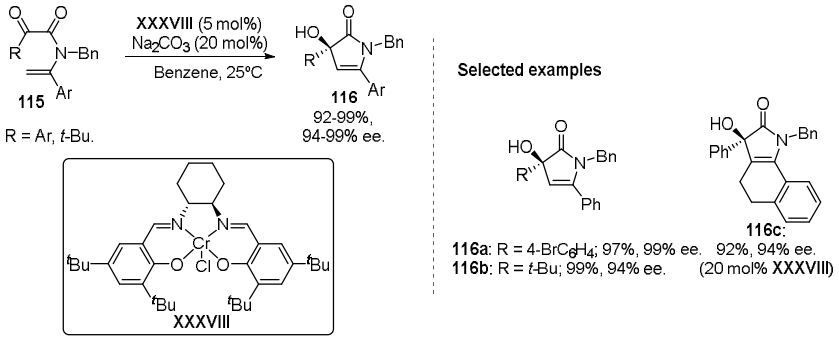
Scheme 30. Ni(cod)$_2$-catalyzed enantioselective formal [3+2]-annulation of cyclopropenones **108** and α,β-unsaturated imines **109**.

3. Enantioselective synthesis of 1,3-dihydropyrrol-2-ones

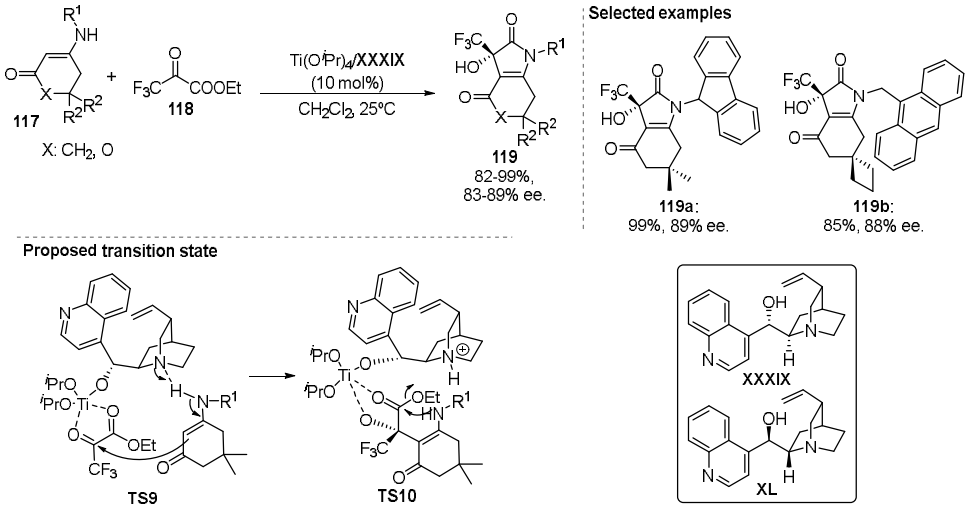
As mentioned above, 1,3-dihydropyrrol-2-ones **2** are almost unexplored products due to the isomerization of the double bond which easily leads to the formation of more stable α,β-unsaturated γ-lactams **3**. In fact, as will be seen below, most of the examples summarized in this review elude the isomerization by creating tetrasubstituted stereocentres at carbon 3, which, on the other hand, is known to be a very challenging task in asymmetric catalysis. In this context, the first example in the literature for the synthesis of a non-conjugated unsaturated γ-lactam was reported in 2009 by Wang´s group.[53] The synthesis of nonracemic lactams **116** (Scheme 31) was successfully achieved through an intramolecular addition of tertiary enamides to aromatic keto-amides **115** by using catalytic amounts of Cr(III)(salen)Cl complex **XXXVIII** and Na_2CO_3. Using this methodology, they were able to obtain a modest scope of γ-lactams in yields and enantioselectivities above 92%, including the lactam **116b** (by using a non-enolizable alkyl keto-amide instead of an aryl group), and the polycyclic lactam **116c**. Although they used 4-Me- or 4-halogen-substituted aromatic rings in both, the ketone and the enamide moieties, they did not report any example with aromatic groups bearing strong activating or deactivating substituents. In addition, they also evaluated the effect of the protecting group of the enamide, showing that 4-OMe-Bn provides similar enantiomeric excess (ee=98%), while other protecting groups resulted in a slight decrease of the enantiocontrol (Allyl, ee=94%; ee=89%; Ph, ee=88%) if compared with Bn (ee=96%).

Later on, the Shibata group reported the addition of enamines **117** derived from cyclic ketones to trifluoropyruvate **118** in the presence of 10% mol of Ti/cinchona alkaloid complexes,[54] obtaining excellent results when cinchonine **XXXIX** was used as a ligand (Scheme 32). A subsequent intramolecular cyclization affords bicyclic lactams **119** with yields above 82% and enantiomeric excesses up to 89%. The scope of the substrates includes the presence of four to six-membered alkyl spirocycles (R^2) and several protecting groups for the enamines (benzyl, CH_2-10-anthracenyl, 9-fluorenyl, $CHPh_2$) with no clear influence in the final yield or enantioselectivities. In contrast, the use of a cyclic ester (X=O) instead of a ketone, resulted in a drop in the yield to 58%, but only slight decrease in the enantiomeric excess (ee=83%). It is interesting to note that both enantiomers of some of the bicyclic products were obtained in similar enantiomeric excesses by using different commercially available and inexpensive cinchona derived alkaloids as chiral ligands (*e.g.*

the opposite enantiomer of **119a** was obtained in 96% yield and 93% ee using cinchonidine **XL**). According to the authors, the Ti/alkaloid complex acts as a Lewis acid by double coordination to the ketoester **TS9**, making it more electrophilic in the chiral environment provided by the alkaloid. After the addition of the enamine, the lactam ring is formed through an intramolecular addition of the amine moiety to the ester and the subsequent elimination of ethanol **TS10**.



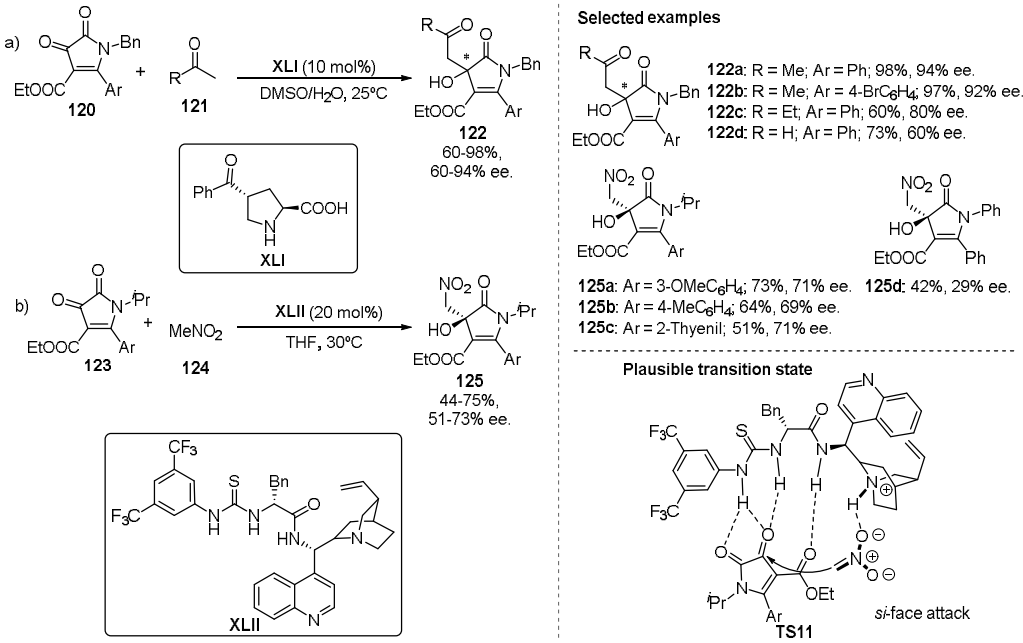
Scheme 31. Enantioselective synthesis of lactams **116**.



Scheme 32. Ti(O^{i}Pr)$_4$/**XXXIX**-catalyzed enantioselective addition of enamines **117** to trifluoropyruvate **118**.

In 2012, Zhao´s group reported the first example of an organocatalyzed synthesis of 1,3-dihydropyrrol-2-ones **122** by means of the addition of acetone **121** to 1*H*-pyrrole-2,3-diones **120** catalyzed by proline derivative **XLI** (Scheme 33a).[55] The methodology allows the preparation of highly functionalized and optically active γ-lactams **122** containing tertiary alcohol in C3 as in the above methods, although in this case, the lactam ring is already present in the starting material. The scope includes a few 4-substituted aromatic rings and a single example of a fused aromatic ring (2-naphthyl), observing a decrease on the product yield from 90% to 98% (Ph, 2-naphthyl, 4-MeC_6H_4, 4-BrC_6H_4 and 4-$NO_2C_6H_4$) to 83% when strong electron donor group (4-OMeC_6H_4) is used. In contrast, the enantioselectivities remain constant for all aromatic rings tested (ee=91-94%). It should be noted that even though the use of non-symmetrical butanone (R=Et) or acetaldehyde (R=H) as nucleophiles successfully afforded the corresponding addition products **122c** and **122d**, this resulted in a drastic increase of the reaction times and a decrease of the obtained yields (60-73%) and the enantioselectivities (ee=60-80%).

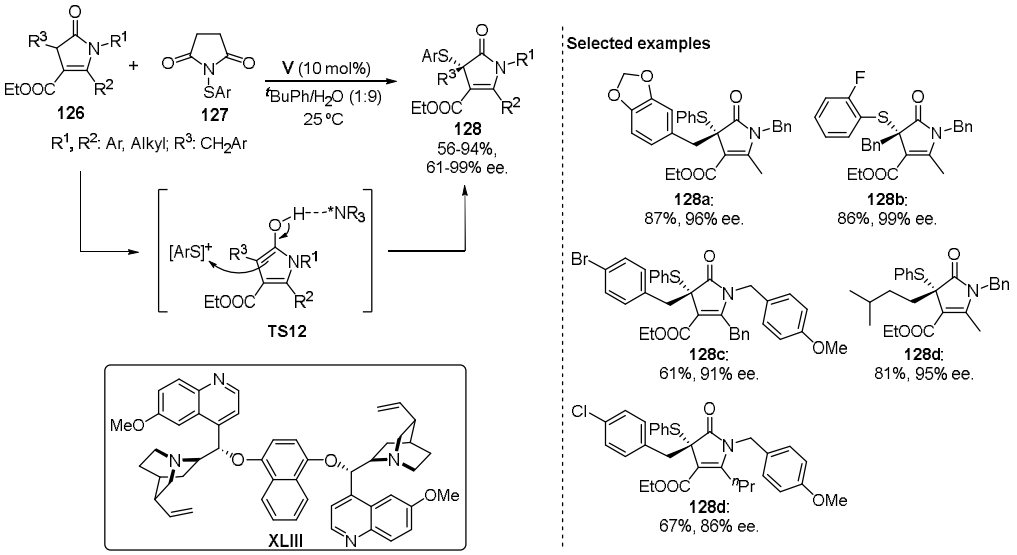
Using similar 1*H*-pyrrole-2,3-diones **123**, Yuan and co-workers published in 2016 the synthesis of lactams **125** in moderate yields and enantioselectivities through a thiourea **XLII**-organocatalyzed Henry reaction (Scheme 33b).[56] The bifunctional catalysts activates the substrate with several hydrogen-bonding to the carbonyl groups in order to improve the electrophilicity, while the tertiary amine of the alkaloid moiety increases the nucleophilicity of the nitromethane **124**. With respect to the scope, the lowest yields were obtained when Cl- and Br-substituted aromatic rings were used (44-53% yield). In contrast, Me-, OMe- or F-substituted aromatic substituents afforded yields from 64% to 73%. Nevertheless, only slight differences on the enantiocontrol can be observed for 2-, 3- or 4-substituted aromatic rings bearing electron donor and electron withdrawing groups (MeO, Me, Br, Cl, F), obtaining in all cases enantiomeric excesses ranging from 69% to 73%. Moreover, heteroaromatic and fused aromatic rings were also tested in the reaction, providing similar enantiocontrol for 2-thienyl (ee=71%) but a remarkable drop when 1-naphthyl was used (ee=51%). Even if the authors also tested several protecting groups on the nitrogen atom, these trials resulted in a drastic loss of both, yield and enantiocontrol **125d**.



Scheme 33. First organocatalyzed enantioselective synthesis of optically active 1,3-dihydopyrrol-2-ones.

More recently, Mukherjee´s group described another functionalization of a preexisting lactam ring, in this case by an "on water" enantioselective sulfenylation of 1,3-dihydopyrrol-2-ones **126** with succinimides **127** (Scheme 34).[57] The use of Brønsted basic catalyst **XLIII** derived from cinchona alkaloids allowed obtaining the corresponding lactams **128**, that contain a tetrasubstituted chiral carbon in their structure. According to the author's proposal, the enol form of the amide could be favoured by the basic alkaloid **XLIII**, making it possible to catalyze the addition of the intermediate **TS12** to the sulphur electrophile. The presence of a benzyl derived protecting group (Bn, 4-OMeBn, ee=96%) in the amide was found to be crucial in order to obtain high enantioselectivity, since the absence of any protecting group resulted in a drop in the enantiocontrol to 60% ee. Since the use of alkyl substituents in sulphur atom resulted in conversions below 5%, the reaction is limited to aryl groups in succinimides **127**, that tolerate electron donor and electron withdrawing substituents (OMe, Br, F, NO_2, 2-naphthyl) with enantioselectivities ranging from 93% to 99%. Although several benzyl and alkyl substituents are available in R^2, the increase of the bulkiness in that position resulted in a decrease on both, the yield and the enantiocontrol (Me, 88%, ee=96%; *n*-Pr, 67%,

ee=87%; Ph, 70%, ee=47%). Regarding the R^3 substituent, several Bn derivatives and some alkyl groups such as *n*-pentyl or *i*-pentyl are compatible with no relevant effect on the yield or the enantioselectivity, but the presence of bulkier substituent such as *i*-Bu completely blocks the reactivity. The authors also reported the analogous reaction by using Se-succinimide in similar yields and enantioselectivities.



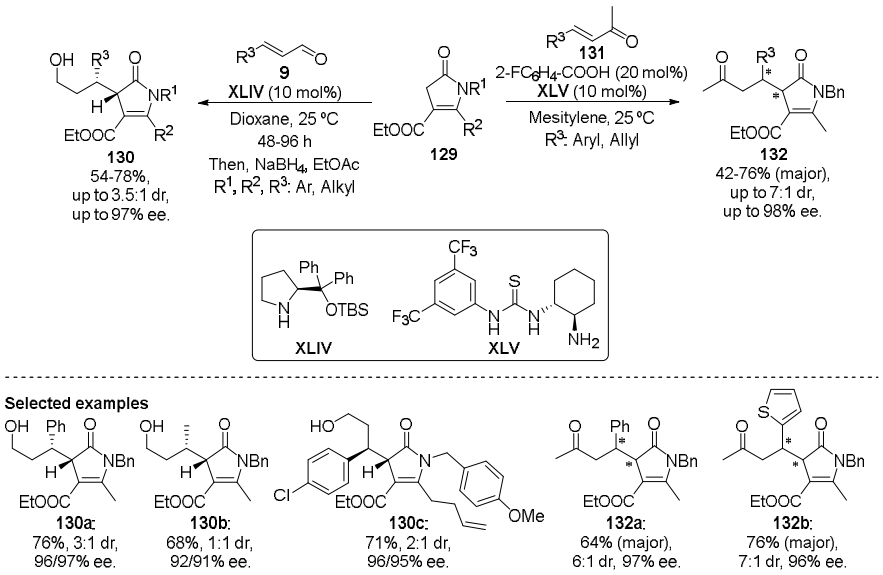
Scheme 34. "On water" enantioselective sulfenylation of 1,3-dihydopyrrol-2-ones **126**.

After that, and continuing with functionalization reactions of 1,3-dihydropyrrol-2-ones, the same authors reported an organocatalyzed Michael addition of lactams **129** to α,β-unsaturated aldehydes **9** and ketones **131** (Scheme 35).[58] For the 1,4-addition to aldehydes **9**, they used prolinol derived catalysts **XLIV** followed by a one-pot reduction of the aldehyde to afford optically active products **130** in high yields and enantioselectivities, but with moderate diastereocontrol. As an example, the use of cinnamaldehyde derivatives results in diastereoselectivities from 2:1 to 3.5:1 for **130a** and **130c**, while the use of crotonaldehyde results in a complete lack of diastereocontrol **130b**. Nevertheless, both diastereoisomers were obtained with high enantioselectivity levels in all cases. Thus, strongly activated and deactivated cinnamaldehyde derivatives were tested in the reaction with minor effect on the reaction (R^3=4-OMeC_6H_4, 70%, dr=3.5:1, ee=91%; R^3=4-$NO_2C_6H_4$, 78%, dr=3.3:1, ee=96%). In contrast, the use of 2-substituted cinnamaldehyde afforded the desired product in lower yield but no decrease on diastereo- and enantiocontrol (R^3=2-BrC_6H_4, 54%, dr=3.5:1, ee=92%). In the position 5 alkyl and aryl groups are well tolerated (R^2=Me, *n*-Pr, CH_2CH_2Ph, Ph were tested) with no relevant effect on the yield (67-74%) diastereo- and enantiocontrol (dr=2:1-3:1, ee=92-96%).

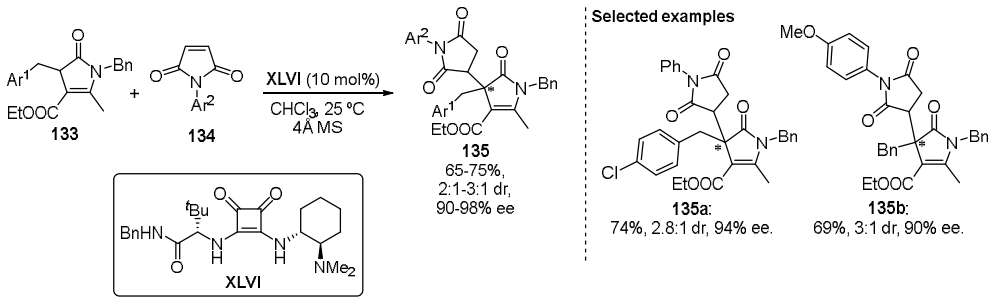
With respect to the corresponding conjugated ketones **131**, amine-thiourea catalyst **XLV** was found to be the optimal one. Due to the lower reactivity of ketones, compared with aldehydes, the reaction times were slightly higher, and the presence of a 2-fluorobenzoic acid became necessary in order to obtain good yields of chiral lactams **132**. In this case, the scope was limited to aromatic substituents in conjugated ketones **131** and to a single 1-benzyl-5-methyl-substituted lactam **129**. The reaction tolerates 2-, 3- or 4-substituted aromatic rings bearing electron donor and electron withdrawing substituents (OMe, Me, CF_3, Halogens), as well as heteroaryl substituents (2-thienyl, 2-furyl) and fused cycle, like 3,4-methylenedioxyphenyl or even (*E*)-styryl conjugated group, obtaining diastereomeric ratios from 3:1 to 7:1 and enantioselectivities ranging from 95% to 98%.

Similarly, the 1,4-addition of butyrolactams **133** to maleimides **134** was reported in 2019 (Scheme 36).[59] Squaramide organocatalysts **XLVI** allowed to obtain highly functionalized chiral lactams **135** in moderate yields and diastereoselectivities, but with enantiomeric excesses above 90%. The scope of the final

products is limited to OMe-, Me-, Br- and Cl-substituted aromatic rings in both, the butyrolactam and maleimide moieties, observing small differences on the reported results. Surprisingly, the authors did not report any example using strong deactivating aromatic substituents containing groups such as NO_2 or CF_3, or even less electron withdrawing group such as F.



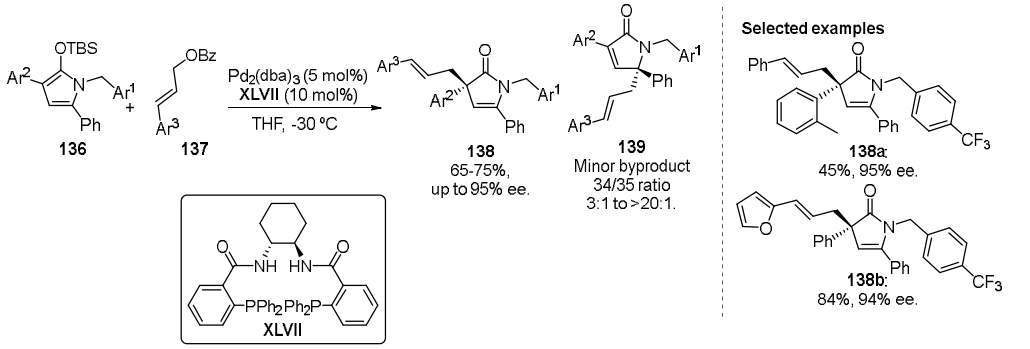
Scheme 35. Organocatalized Michael additions of lactams **129** to aldehydes **9** and ketones **131**.



Scheme 36. 1,4 addition of deconjugated butyrolactams **133** to maleimides **134**.

In the same year, a palladium-**XLVII**-catalyzed asymmetric allylic alkylation of 2-silyloxypyrroles **136** to obtain lactams **138** was reported by Cossy and co-workers (Scheme 37).[60] The reaction also afforded the allylated 1,5-dihydropyrrol-2-ones **139** as a minor byproduct with variable regioselectivities. Thus, even though the enantioselectivities of **138** were high, the yields remain moderate. The scope includes a few benzyl derivatives bearing electron donor and electron withdrawing aromatic rings as protecting group of the nitrogen atom (Ar^1=Ph, 4-$CF_3C_6H_4$, 4-$OMeC_6H_4$, 2-$OMeC_6H_4$), showing higher yields and enantioselectivities when strong deactivating CF_3-substituted benzyl was used. The scope of aromatic substituents in the starting silyloxypyrroles **136** (Ar^2), includes 2-, 3- and 4-substituted tolyl groups as well as strong deactivating 4-$CF_3C_6H_4$ and other aromatic groups like 2-naphthyl or 4-biphenyl. Although 2-tolyl group afforded higher enantiocontrol, the yield was found to be lower (45%, ee=95%) if compared with Ph (93%, ee=89%) or biphenyl (85%, ee=80%). Moreover, a wide scope of allylic nucleophiles **137** was evaluated, including weak and strong electron donor-groups (e.g. 4-$OMeC_6H_4$, 4-MeC_6H_4), polycyclic

(2-naphthyl), or heteroaryl substituents (2-thienyl, 2-furyl). Surprisingly, the presence of 4-tolyl group resulted in a drastic drop on both, yield and enantiocontrol (54%, ee=62%) when comparing with less activated Ph (93%, ee=89%) or strongly activated 4-$OMeC_6H_4$ (76%, ee=88%). The best enantiomeric excesses were obtained when 2-furyl was used as Ar^3 (84%, ee=94%), making it even more interesting considering that the reaction could be scaled up to 1 mmol without losing enantiocontrol.



Scheme 37. Asymmetric allylic alkylation of pyrroles **138**.

4. Conclusion

In summary, several catalytic asymmetric methodologies for the synthesis of optically active 1,5-dihydropyrrol-2-ones have been reported during the last decade. In contrast, the synthesis of the corresponding 1,3-dihydropyrrol-2-ones still requires further development, with only a few reported examples to date. Although most authors based their strategies on the functionalization of previously formed racemic γ-lactams, the enantioselective assembly of 5-membered lactam ring has also been reported. Remarkably, a relevant amount of examples regarding the generation of enantioenriched tetrasubstituted chiral centres, which always represent a challenge, have also been published. Considering the presence of pyrrolidin-2-one derivatives in many known bioactive molecules, these methodologies may be relevant in medicinal chemistry and drug discovery in the coming years.

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References

1. Caruano, J.; Muccioli, G. G.; Robiette, R. *Org. Biomol. Chem.* **2016**, *14*, 10134-10156.
2. Martínez de Marigorta, E.; de los Santos, J. M.; Ochoa de Retana, A. M.; Vicario, J.; Palacios, F. *Synthesis* **2018**, *50*, 4539-4554.
3. Martínez de Marigorta, E.; de Los Santos, J. M.; Ochoa de Retana, A. M.; Vicario, J.; Palacios, F. *Beilstein J. Org. Chem.* **2019**, *15*, 1065-1085.
4. Kontnik, R.; Clardy, J. *Org. Lett.* **2008**, *10*, 4149-4151.
5. Caso, A.; Laurenzana, I.; Lamorte, D.; Trino, S.; Esposito, G.; Piccialli, V.; Costantino, V. *Mar. Drugs* **2018**, *16*, 1-14.
6. Tanaka, H.; Hattori, H.; Tanaka, T.; Sakai, E.; Tanaka, N.; Kulkarni, A.; Etoh, H. *J. Nat. Med.* **2008**, *62*, 228-231.
7. Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127-19130.
8. Feng, X.; Cui, H. L.; Xu, S.; Wu, L.; Chen, Y. C. *Chem. Eur. J.* **2010**, *16*, 10309-10312.
9. Kalaitzakis, D.; Sofiadis, M.; Triantafyllakis, M.; Daskalakis, K.; Vassilikogiannakis, G. *Org. Lett.* **2018**, *20*, 1146-1149.
10. Joie, C.; Deckers, K.; Raabe, G.; Enders, D. *Synthesis* **2014**, *46*, 1539-1546.
11. Lin, L.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.* **2011**, *13*, 6410-6413.

12. Zhang, Y.; Shao, Y. L.; Xu, H. Sen; Wang, W. *J. Org. Chem.* **2011**, *76*, 1472-1474.
13. Huang, H.; Jin, Z.; Zhu, K.; Liang, X.; Ye, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3232-3235.
14. Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 9329-9331.
15. Wang, Z. H.; Wu, Z. J.; Yue, D. F.; You, Y.; Xu, X. Y.; Zhang, X. M.; Yuan, W. C. *Org. Biomol. Chem.* **2016**, *14*, 6568-6576.
16. Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 3300-3302.
17. Chen, Y. R.; Das, U.; Liu, M. H.; Lin, W. *J. Org. Chem.* **2015**, *80*, 1985-1992.
18. Yang, Y.; Dong, S.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2012**, *48*, 5040-5042.
19. Du, X.; Yin, D.; Ge, Z.; Wang, X.; Li, R. *RSC Adv.* **2017**, *7*, 24547-24550.
20. Li, X.; Lu, M.; Dong, Y.; Wu, W.; Qian, Q.; Ye, J.; Dixon, D. J. *Nat. Commun.* **2014**, *5*, 4479-4487.
21. Arlt, A.; Toyama, H.; Takada, K.; Hashimoto, T.; Maruoka, K. *Chem. Commun.* **2017**, *53*, 4779-4782.
22. Choudhury, A. R.; Mukherjee, S. *Org. Biomol. Chem.* **2012**, *10*, 7313-7320.
23. Tanabe, H.; Xu, Y.; Sun, B.; Matsunaga, S.; Shibasaki, M. *Heterocycles* **2012**, *86*, 611-622.
24. Gu, X.; Guo, T.; Dai, Y.; Franchino, A.; Fei, J.; Zou, C.; Dixon, D. J.; Ye, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 10249-10253.
25. Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Zanardi, F.; Casiraghi, G. *Tetrahedron Lett.* **2009**, *50*, 3428-3431.
26. Curti, C.; Ranieri, B.; Battistini, L.; Rassu, G.; Zambrano, V.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2010**, *352*, 2011-2022.
27. Frings, M.; Atodiresei, I.; Wang, Y.; Runsink, J.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2010**, *16*, 4577-4587.
28. Frings, M.; Thomé, I.; Schiffers, I.; Pan, F.; Bolm, C. *Chem. Eur. J.* **2014**, *20*, 1691-1700.
29. Curti, C.; Battistini, L.; Ranieri, B.; Pelosi, G.; Rassu, G.; Casiraghi, G.; Zanardi, F. *J. Org. Chem.* **2011**, *76*, 2248-2252.
30. Silverio, D. L.; Fu, P.; Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Tetrahedron Lett.* **2015**, *56*, 3489-3493.
31. Ranieri, B.; Curti, C.; Battistini, L.; Sartori, A.; Pinna, L.; Casiraghi, G.; Zanardi, F. *J. Org. Chem.* **2011**, *76*, 10291-10298.
32. Oka, J.; Okamoto, R.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2015**, *17*, 676-679.
33. Baba, T.; Oka, J.; Noguchi, K.; Tanaka, K. *Eur. J. Org. Chem.* **2015**, *2015*, 4374-4382.
34. R.X Liang, R.Z Yang, R.R Liu, and Y. . J. *Org. Chem. Front.* **2018**, *5*, 1840-1843.
35. Yang, P.; You, S. L. *Org. Lett.* **2018**, *20*, 7684-7688.
36. Leon, R.; Jawalekar, A.; Redert, T.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 1487-1490.
37. Jia, M. Q.; You, S. L. *Chem. Commun.* **2012**, *48*, 6363-6365.
38. Jia, M. Q.; Liu, C.; You, S. L. *J. Org. Chem.* **2012**, *77*, 10996-11001.
39. Palacios, F.; Vicario, J.; Aparicio, D. *Eur. J. Org. Chem.* **2006**, No. 12, 2843-2850.
40. Li, X.; Deng, H.; Luo, S.; Cheng, J. P. *Eur. J. Org. Chem.* **2008**, No. 25, 4350-4356.
41. Luo, C.; Huang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8193-8196.
42. del Corte, X.; Maestro, A.; Vicario, J.; Martinez de Marigorta, E.; Palacios, F. *Org. Lett.* **2018**, *20*, 317-320.
43. Carramiñana, V.; Ochoa de Retana, A. M.; Vélez del Burgo, A.; de los Santos, J. M.; Palacios, F. *Eur. J. Med. Chem.* **2019**, *163*, 736-746.
44. Carramiñana, V.; Ochoa de Retana, A. M.; de los Santos, J. M.; Palacios, F. *Eur. J. Med. Chem.* **2020**, *185*, 1-10.
45. del Corte, X.; López-Francés, A.; Maestro, A.; Martinez de Marigorta, E.; Palacios, F.; Vicario, J. *J. Org. Chem.* **2020**, *85*, 14369-14383.
46. del Corte, X.; Martinez de Marigorta, E.; Palacios, F.; Vicario, J. *Molecules* **2019**, *24*, 2951-2962.
47. Guo, W.; Wang, X.; Zhang, B.; Shen, S.; Zhou, X.; Wang, P.; Liu, Y.; Li, C. *Chem. Eur. J.* **2014**, *20*, 8545-8550.
48. Zhang, W. Z.; Chu, J. C. K.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2015**, *137*, 553-555.
49. Poulsen, T. B.; Dickmeiss, G.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem.* **2008**, *120*, 4765-4768.
50. Wang, C.; Zhu, S.; Wang, G.; Li, Z.; Hui, X. P. *Eur. J. Org. Chem.* **2016**, *2016*, 5653-5658.
51. Wang, S. G.; Liu, Y.; Cramer, N. *Angew. Chem. Int. Ed.* **2019**, *58*, 18136-18140.

52. Bai, D.; Yu, Y.; Guo, H.; Chang, J.; Li, X. *Angew. Chem. Int. Ed.* **2020**, *59*, 2740-2744.
53. Yang, L.; Wang, D. X.; Huang, Z. T.; Wang, M. X. *J. Am. Chem. Soc.* **2009**, *131*, 10390-10391.
54. Ogawa, S.; Iida, N.; Tokunaga, E.; Shiro, M.; Shibata, N. *Chem. Eur. J.* **2010**, *16*, 7090-7095.
55. Bhanushali, M.; Zhao, C. G. *Tetrahedron Lett.* **2012**, *53*, 359-362.
56. Zhang, M. L.; Yue, D. F.; Wang, Z. H.; Luo, Y.; Xu, X. Y.; Zhang, X. M.; Yuan, W. C. *Beilstein J. Org. Chem.* **2016**, *12*, 295-300.
57. Singha Roy, S. J.; Mukherjee, S. *Org. Biomol. Chem.* **2017**, *15*, 6921-6925.
58. Singha Roy, S. J.; Mukherjee, S. *J. Org. Chem.* **2018**, *83*, 12071-12085.
59. Ray, B.; Mukherjee, S. *Tetrahedron* **2019**, *75*, 3292-3298.
60. Song, T.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2019**, *21*, 603-607.