ENANTIOSELECTIVE SYNTHESIS OF FIVE-MEMBERED HETEROCYCLES THROUGH [3+2]-CYCLOADDITIONS WITH ISOCYANO ESTERS

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Abstract. *The formal [3+2]-cycloaddition reaction of α-isocyano esters (isocyanoacetates) and electrophilic double bonds provides a straightforward and atom economical access to five-membered, chiral nitrogen-containing heterocycles. Reaction of α-isocyano esters with carbonyl compounds or imines yields oxazolines or imidazolines, respectively, bearing cyclic structures containing two heteroatoms in the ring. On the other hand, cycloaddition reaction with alkenes conjugated with electron-withdrawing groups gives pyrrolines and related pyrrole derivatives, while 1,2,4-triazolines can be prepared form azodicarboxylates. Herein, we describe the efforts carried out to develop enantioselective versions of these reactions by using catalytic methodologies.*

Contents

1. Introduction

Five-membered, chiral *aza*-heterocycles are prevalent structural units found in natural products and other compounds that show a wide range of biological and pharmaceutical activities.[1] Representative examples include the insecticide ethoxazole,[2] the marine metabolite Westiellamide,[3] the cytotoxic sponge alkaloid 4,5-dihydro-6'-deoxybromotopsentin,[4] the anticancer imidazoline SP-4-84,[5] the proteasome inhibitor lactacystin[6] or the vasopressin V1b receptor antagonist nelivaptan,[7] among many others (Figure 1).

These heterocycles also constitute key intermediates with widespread application in organic synthesis. Thus, the development of new synthetic methods to readily access these targets in both highly structural diversity and stereoselectivity is of great interest in organic and medicinal chemistry.[8] Among the many stereoselective synthetic routes available for these compounds, the 1,3-dipolar cycloaddition reaction constitutes one of the most appealing approaches, given the variety of dipoles and dipolarophiles that can be employed permitting the access to a wide range of heterocycles containing one or more heteroatoms.[9]

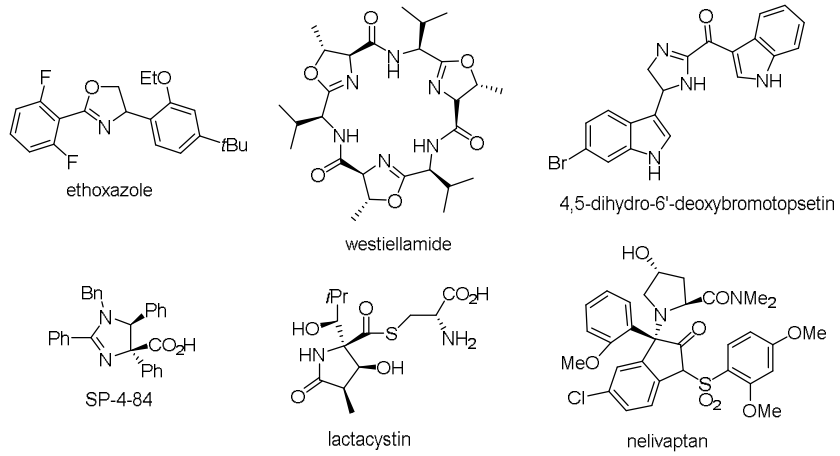
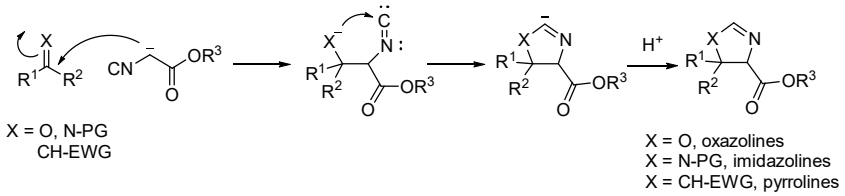


Figure 1. Examples of natural and bioactive five-membered, chiral *aza*-heterocycles.

Isocyanides are useful synthons in organic synthesis owing to their unusual valence state and reactivity. The synthetically most important property of isocyanides is their ability to react both with nucleophiles and electrophiles at the isocyanide carbon, a feature that has been thoroughly exploited in the development of useful multicomponent reactions.[10] Another important feature of isocyanides is their α-acidity, which can be further increased by the presence of electron-withdrawing substituents, such as carboxylic esters, nitriles, phosphoric esters, or sulfonyl groups. Among these, isocyanoacetate derivatives occupy an important place in the field of synthetic application,[11] in particular for the synthesis of *aza*-heterocycles. The carbanion of an isocyano ester can undergo nucleophilic addition to an electrophilic double bond, such as carbonyl, imine or C-C double bond conjugated with an electron withdrawing group. The resulting anions have a strong tendency to cyclize by addition of the electron pair to the empty orbital of the isocyanide forming a five-membered heterocycle in a reaction that can be formally considered as a [3+2]-cycloaddition (Scheme 1). During these reactions one or more stereogenic centers are formed, what has encouraged the development of enantioselective versions. In this chapter we review the most relevant literature involving the synthesis of five-membered, chiral nitrogen-containing heterocycles through the catalytic asymmetric [3+2]-cycloaddition of isocyanoacetate derivatives.

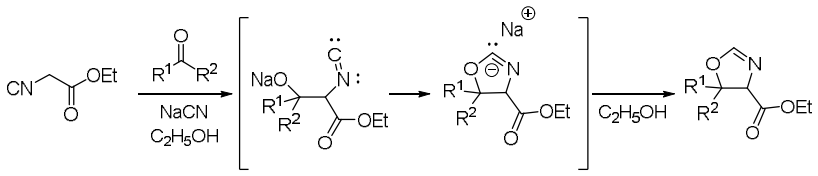


Scheme 1. Formal [3+2]-cycloaddition of isocyanoacetate esters.

2. Enantioselective synthesis of 2-oxazolines from carbonyl compounds

2-Oxazolines are five-membered heterocycles bearing an O atom and a N atom in 1,3-positions, and a double bond that can be located in one of three different positions. The most common 2-oxazolines have a great relevance in natural product, pharmaceutical and agricultural chemistry,[12] and they have found wide application as privileged chiral ligands in asymmetric catalysis[13] as well as synthetic intermediates for 1,2-aminoalcohols and other relevant compounds.[14]

In 1968, Schöllkpof reported the addition of a α-lithiated isocyanides to carbonyl compounds providing 2-oxazolines.[15] The procedure required strongly basic conditions (organolithium reagent) to deprotonate the isocyanide reagent. Later in 1970,[16] the same author reported a similar reaction using ethyl isocyanoacetate as the nucleophile. In this case, the ester moiety expedite the deprotonation at the α-position of the isocyanide allowing to perform the reaction with aldehydes, cyclohexanone and acetone in the presence of a catalytic amount of sodium cyanide as the base in ethanol, yielding the *trans* oxazolines as the major products. This formal [3+2]-cycloaddition most probably involves the aldol addition of the ester enolate to the carbonyl group followed by addition of the resulting alkoxide to the isocyanide carbon (Scheme 2).



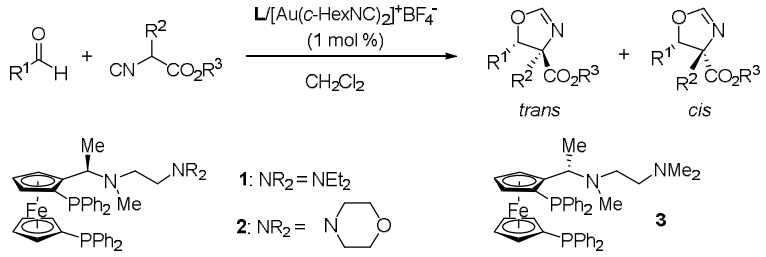
Scheme 2. First synthesis of oxazolines from ethyl isocyanoacetate and carbonyl compounds.

Since these first reports, many different experimental protocols, involving different catalysts and conditions have been developed to achieve this reaction in an enantioselective manner, first with aldehydes, and more recently with ketones.

2.1. Enantioselective reactions of α-isocyano esters with aldehydes

2.1.1. Gold and silver catalysis

The first enantioselective example of such reaction was developed by Ito and Hayashi in 1986,[17] using the gold complex generated *in situ* by mixing bis(cyclohexylisocyanide)gold(I) tetrafluoroborate and (*R*)-*N*-methyl-*N*-[2-(dialkylamino)ethyl]-l-[(*S*)-l,2-bis(diphenylphosphino)ferrocenyl]ethylamine ligands **1-3** (Scheme 3).



Scheme 3. First synthesis of oxazolines from ethyl isocyanoacetate and carbonyl compounds.

The authors found that the ferrocenylphosphine ligand **2** bearing a morpholino group at the end of the ferrocene side chain improved the stereoselectivity with respect to that bearing a dimethylamino group **1** (Table 1, entries 1,3,5,7 *vs* 2,4,6,8).[18] Furthermore, the reaction could also be carried out with α-alkyl-α-isocyanocarboxylates, which reacted slower than unsubstituted isocyanoacetates but provided the expected 4-(methoxycarbonyl)-4,5-dialkyl-2-oxazolines with high stereoselectivity, which decreased with

the size of the α-alkyl group (Table 1, entries 9-13).[19] Some representative examples of this reactions are gathered in Table 1.

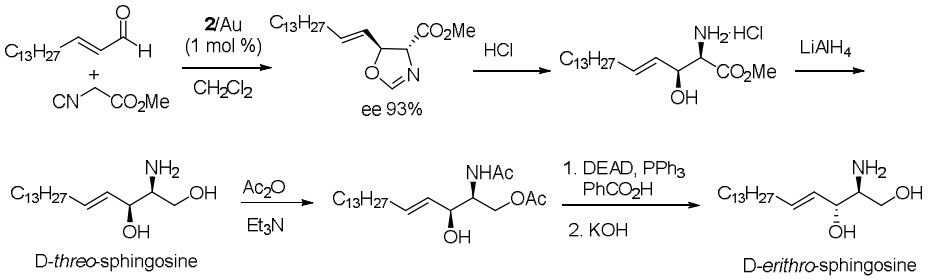
In general, the gold-catalyzed reaction of α-isocyanoacetates was highly stereoselective with aromatic aldehydes and secondary alkyl aldehydes such as isobutyraldehyde, but the stereoselectivity was not so high with primary alkyl aldehydes. In these cases, the authors found that the use of *N.N*-dialkyl-α-isocyanoacetamides instead of the corresponding esters improved both the enantio- and *trans*-diastereoselectivity.[20] An extension of this reaction to fluorinated benzaldehydes has been also described in the literature.[21]

Parallel to this work by Ito and Hayashi, Pastor and Togni performed mechanistic studies on this reaction. These studies indicated that both, the planar chirality of the ferrocene moiety as well as the central chirality of the stereogenic center in the side chain played a role in the stereoselectivity of the reaction. Thus, a change of configuration of the stereogenic carbon atom from *R* to *S* (from **2** to **3**) resulted in both a reduction of the *trans/cis* diastereomeric ratio (dr) and the ee of the *trans* isomer but also the opposite enantiomer of the *trans*-oxazoline was formed. Furthermore, the ee of the *cis* isomer increased (Table 1, entry 7 *vs* 14). The optimal stereoselectivity for the *trans* oxazoline was obtained when the ferrocenylamine ligand employed had opposite planar and central chiralities, indicating that, in this case, both chirality elements act cooperatively.[22] The studies also showed the importance of steric and electronic factors in both the aldehyde and the isocyanide ester.[23]

Table 1. Asymmetric aldol reaction of aldehydes with methyl isocyanocarboxylates catalyzed by ferrocenylphosphine-gold(I) complexes.

Entry	R^1	R^2	R^3	L	yield	*trans/cis*	ee_{trans}	ee_{cis}
1	Me	H	Me	**1**	100	84/16	72 (4*S*,5*R*)	44 (4*R*,5*R*)
2	Me	H	Me	**2**	99	89/11	89(4*S*,5*R*)	10 (4*S*,5*S*)
3	^{i}Pr	H	Me	**1**	99	98/2	90 (4*S*,5*R*)	-
4	^{i}Pr	H	Me	**2**	100	99/1	92 (4*S*,5*R*)	1
5	^{n}PrCH=CH	H	Me	**1**	83	81/19	84 (4*S*,5*R*)	52 (4*R*,5*R*)
6	^{n}PrCH=CH	H	Me	**2**	85	87/13	92 (4*S*,5*R*)	47 (4*R*,5*R*)
7	Ph	H	Me	**1**	98	89/11	93 (4*S*,5*R*)	49 (4*R*,5*R*)
8	Ph	H	Me	**2**	93	95/5	95 (4*S*,5*R*)	49 (4*S*,5*S*)
9	Me	Me	Me	**2**	86	56/44	86 (4*S*,5*R*)	54 (4*S*,5*S*)
10	Me	Et	Me	**2**	92	54/46	87 (4*S*,5*R*)	66 (4*S*,5*S*)
11	Me	^{i}Pr	Me	**2**	100	24/76	26 (4*S*,5*R*)	51 (4*S*,5*S*)
12	Ph	Me	Me	**2**	97	93/7	94 (4*S*,5*R*)	53 (4*S*,5*S*)
13	Ph	^{i}Pr	Me	**2**	86	62/38	88 (4*S*,5*R*)	17 (4*S*,5*S*)
14	Ph	H	Me	**3**	90	84/16	41 (4R,5S)	20 (4S,5S)

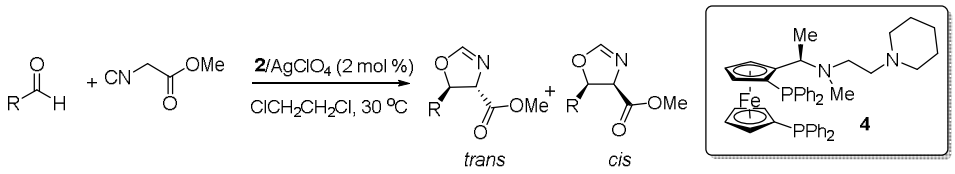
The synthetic potential of the gold-catalyzed reaction has been demonstrated in the synthesis of several natural or bioactive compounds. For instance, Hayashi performed the asymmetric synthesis of sphingosines starting from (*E*)-2-hexadecenal (Scheme 4).[24]



Scheme 4. Enantioselective synthesis of sphingosines.

Reaction of this aldehyde with methyl isocyanoacetate in the presence of the **2**/Au complex gave the expected *trans*-oxazoline with 93% ee. Hydrolysis of the oxazoline followed by reduction with $LiAlH_4$ gave D-*threo*-sphingosine. After diacetylation of this product, Mitsonobu inversion of the secondary alcohol and deprotection of the primary alcohol yielded D-*erythro*-sphingosine (Scheme 4).

Hayashi has also studied the aldol reaction of methyl isocyanoacetate with several aldehydes using the silver complex prepared by mixing silver perchlorate and ligand **4** (which is related to **2**), followed by slow addition of methyl isocyanoacetate to the solution of the catalyst and the aldehyde in 1,2-dichloroethane at 30 °C.[25] The reaction shows an unusual dependence of the stereoselectivity on the reaction temperature, both diastereo- and enantioselectivity being higher at higher reaction temperature. The few examples reported provided the *trans*-oxazoline with almost full diastereoselectivity and enantiomeric excesses up to 90% (Scheme 5, Table 2).



Scheme 5. Silver catalyzed synthesis of oxazolines.

Table 2. Asymmetric aldol reaction of aldehydes with methyl isocyanocarboxylates catalyzed by the **4**-silver(I) complex.

Entry	R	yield	*trans/cis*	ee_{trans}
1	Ph	90	96/4	80 (4*S*,5*R*)
2	^{i}Pr	90	99/1	90 (4*S*,5*R*)
3	^{t}Bu	91	99/1	88 (4*S*,5*R*)
4	CH_2=C(Me)	90	97/3	87 (4*S*,5*R*)

2.1.2. Platinum and palladium catalysis

A number of palladium and platinum complexes with chiral tridentated PCP or NCN ligands have been prepared and tested in the aldol reaction between aldehydes and methyl isocyanoacetate (Figure 2).

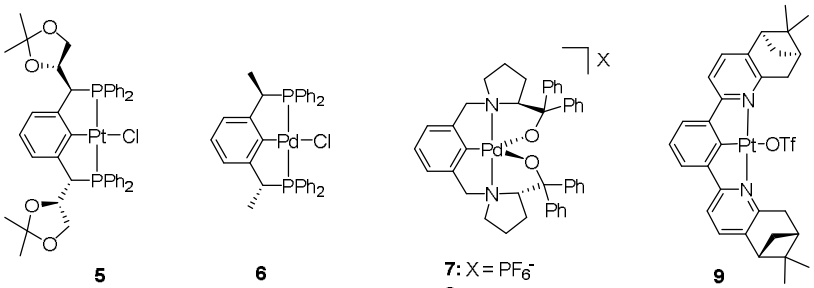


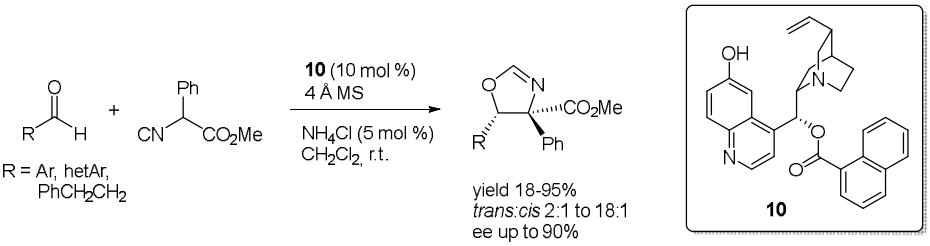
Figure 2. Palladium and platinum complexes essayed in the enantioselective reaction of aldehydes and methyl isocyanoacetate.

Venanzi synthesized an optically active platinum(II) complex **5** containing a terdentate PCP ligand and tested its catalytic activity in the asymmetric reaction of methyl isocyanoacetate and several aldehydes. The catalyst was obtained after treatment of **5** with silver triflate and a base was required. The reaction could be applied to aromatic and aliphatic aldehydes providing the expected oxazolines with good yields, moderate *trans/cis* diastereoselectivity (from 56/44 to 93/7), and enantiomeric excesses between 14-64% for the *trans* isomer and 6-32% for the *cis* isomer.[26] In a similar way, the palladium(II) complex **6** catalyzed the reaction

in the presence of silver triflate and diisopropylamine.[27] The chiral oxazolines were obtained with *trans/cis* diastereoselectivities from 45/5 to 91/9. However, better enantiomeric excesses were obtained for the minor *cis* oxazolines (42-77%) than for the *trans* oxazolines (1-31%). Gebbink has prepared five-coordinated NCN-pincer palladium complexes bearing proline substituents **7** and **8** that performed with low diastereo- and enantioselectivity in the addition of methyl isocyanoacetate to several aromatic aldehydes.[28] Similarly the platinum complex **9** and other NCN platinum complexes reported by Ahn showed poor performance in the reaction providing the expected oxazolines with enantiomeric excesses below 10%.[29]

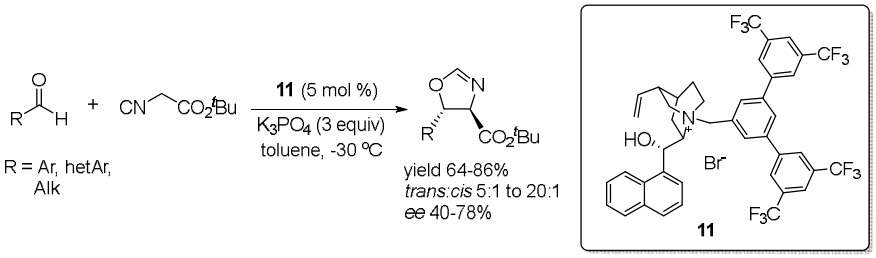
2.1.3. Organocatalytic reactions

The first enantioselective organocatalytic method for this kind of reactions was reported by Guo in 2009 (Scheme 6).[30] These authors used a cupreine ester **10** to perform the addition of methyl phenylisocyanoacetate to aldehydes obtaining the highly substituted *trans* 2-oxazolines with good diastereoselectivity (up to 18:1 dr) and enantiomeric excesses (up to 90% ee). The use of 4Å molecular sieves and a catalytic amount of ammonium chloride speeded up the reaction. The reaction tolerated both electron poor and neutral aromatic and aliphatic aldehydes. Highly electron-poor benzaldehydes underwent clean cycloaddition reactions, affording fairly good enantioselectivities ranging from 70-88% ee, while halogenated benzaldehydes gave enantioselectivities ranging 72-85% ee. No examples with electron-rich aromatic aldehydes were reported.



Scheme 6. Asymmetric [3+2]-cycloaddition reaction with aldehydes using a cupreine ester catalyst.

Recently, the formal [3+2]-cycloaddition of *tert*-butyl isocyanoacetate with aldehydes under phase-transfer catalysis (PTC) has been reported.[31] The reaction was carried out in toluene at -30 °C with K_3PO_4 as the base and a bulky cinchonine-derived quaternary ammonium salt **11** as the catalyst. The process allowed both aromatic, heteroaromatic and aliphatic aldehydes, affording a broad range of chiral *trans* oxazolines in diastereoselectivities up to 20:1 and enantioselectivities up to 78% ee (Scheme 7).

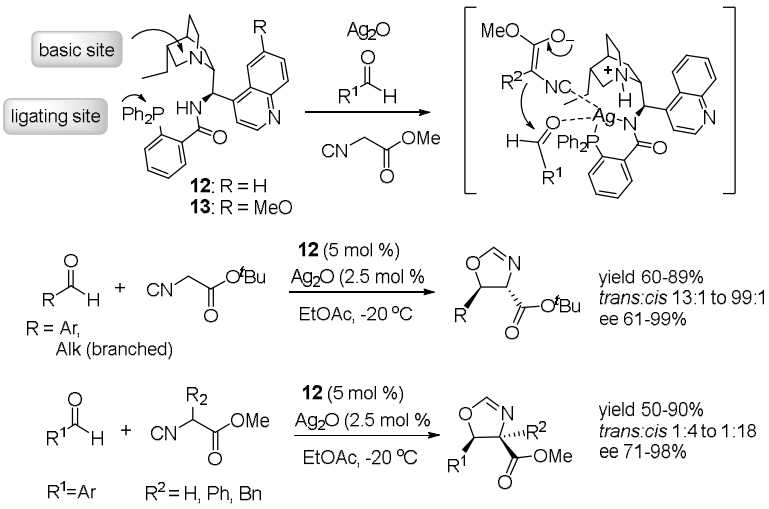


Scheme 7. PTC-catalyzed reaction between *tert*-butyl isocyanoacetate and aldehydes.

2.1.4. Cooperative metal/organocatalysis

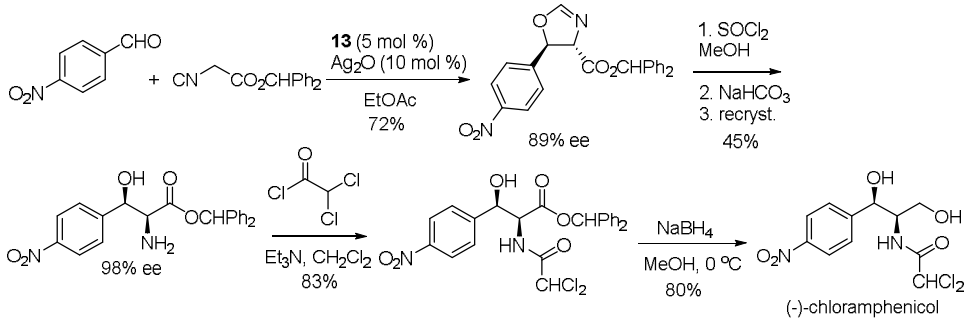
In 2011, Dixon reported a cooperative catalytic system for the formal [3+2]-cycloaddition with aldehydes. The catalyst involved an amidophosphine with the 9-amino(9-deoxy)epicinchone alkaloid scaffold pre-catalyst **12** and silver oxide. The authors envisaged that the differential in hard/soft character of the two Lewis bases would allow a selective binding of the phosphine to the silver ion, leaving the amine

partially free from complexation and therefore able to act as an organic base in the reaction of interest (Scheme 8). Oxazolines from *tert*-butyl isocyanate and aromatic or alkyl branched aldehydes were obtained with excellent diastereo- and enantioselectivity. However, linear aliphatic aldehydes reacted under the reported conditions but gave rise to low enantiocontrol, and acetaldehyde failed as a reaction partner affording homoaldol side products. α-Substituted isocyanoacetates also reacted with aromatic aldehydes to give in this case the *cis*-oxazolines with excellent stereoselectivity.[32]



Scheme 8. Enantioselective synthesis of oxazolines under cooperative catalysis by Dixon. Catalytic model and results.

This reaction, after further adjustments, was applied in the enantioselective synthesis of the antibiotic chloramphenicol (Scheme 9).[33] Reaction of *p*-nitrobenzaldehyde with diphenylmethyl isocyanoacetate under asymmetric conditions gave the corresponding oxazoline with 72% yield and 89% enantiomeric excess. Ring opening using thionyl chloride in methanol afforded an amino alcohol in 75% yield whose enantiomeric purity could be improved to 98% ee by a single recrystallization from toluene. The amino alcohol was then acylated with dichloroacetyl chloride and the ester group chemoselectively reduced with sodium borohydride to deliver enantiomerically pure (-)-chloramphenicol (Scheme 9).[33]



Scheme 9. Enantioselective synthesis of (-)-chloramphenicol.

Simultaneously to Dixon's work, the group of Oh reported another cooperative system combining a cobalt complex formed from CoI_2 and a chiral amino alcohol **14** (10 mol %) and an achiral thiourea **15** (20

mol %) (Figure 3).[34] The reaction of methyl isocyanoacetate and several aryl and alkyl aldehydes was performed in the presence of DBU as a base (20 mol %) in THF to give the *trans* oxazolines as the major products with excellent diastereo- (dr >20:1) and enantioselectivities (90-98% ee). Less satisfactory enantioselectivities were found in the reactions of 2-thiophenecarboxaldehyde (84% ee) and pivalaldehyde (74% ee). However, *ortho*- and *meta*-substituted benzaldehydes constitute a limitation for the method, the corresponding products being obtained in low enantioselectivity (20-50% ee).

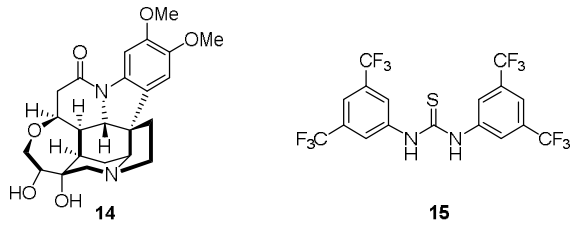


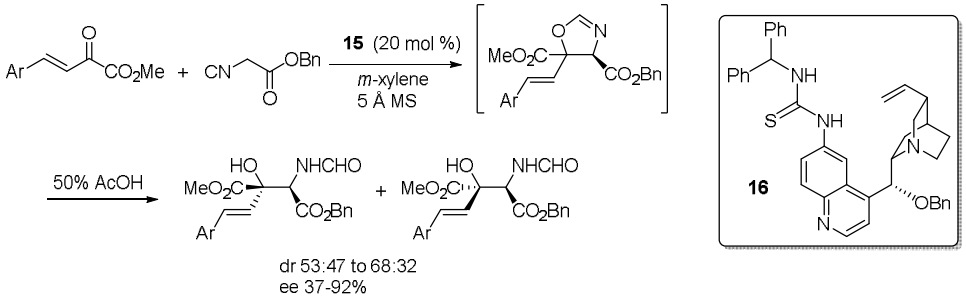
Figure 3. Chiral amino alcohol ligand and achiral thiourea employed by Oh.

2.2. Enantioselective reactions of α-isocyano esters with ketones

2.2.1. Enantioselective reactions with 1,2-dicarbonyl compounds

Ito and Hayashi reported the first cycloaddition of α-isocyano carboxyl derivatives with ketones. The asymmetric reaction of α-ketoesters with methyl isocyanoacetate or *N,N*-dimethyl isocyanoacetamide was carried out under essentially the same conditions as the reaction with aldehydes using the **2**/Au(I). The oxazolines were obtained as *trans/cis* diastereomeric mixtures favoring the *cis* isomer with moderate diastereo- and enantioselectivities, which were better for the isocyano amides than for the isocyano esters.[35]

The first organocatalytic asymmetric aldol reaction of isocyano esters with β,γ-unsaturated α-ketoesters was reported by Lu in 2014, using a cinchona alkaloid-derived bifunctional thiourea **16** as the catalyst. The oxazolines were not isolated and, after acidic hydrolysis, β-hydroxy-α-amino acid derivatives were obtained in low diastereo- and moderate enantioselectivity (Scheme 10).[36]

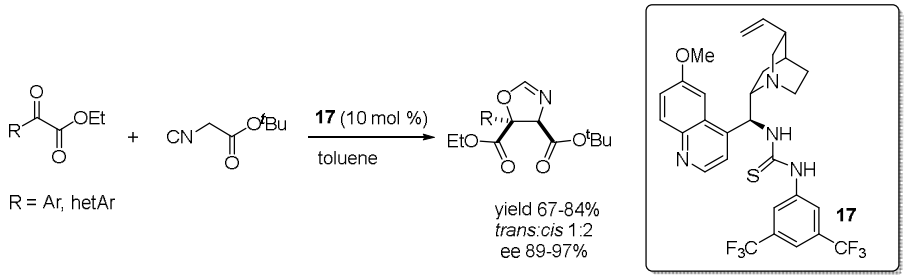


Scheme 10. Organocatalytic asymmetric reaction of benzyl isocyanoacetate with β,γ-unsaturated α-ketoesters

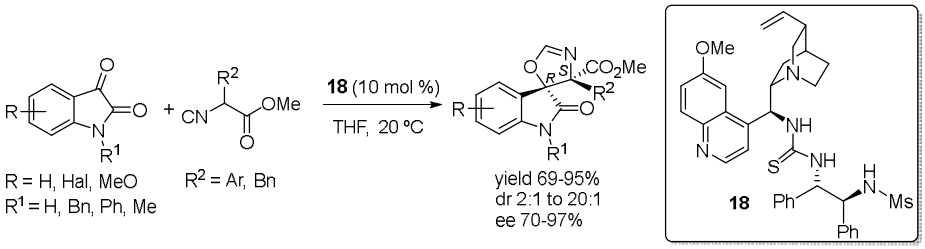
In 2017, Wang described another example of enantioselective addition of isocyanoacetates to α-ketoesters employing a bifunctional thiourea **17** derived from quinine and 3,5-bis(trifluoromethyl)aniline. The *cis* oxazolines were obtained with good yields and enantiomeric excesses, although with low diastereoselectivity (Scheme 11).[37] The reaction allowed ketoesters having *meta*- or *para*-substituted aromatic as well as heteroaromatic rings attached to the carbonyl group, and the *cis* oxazolines were obtained as the major products with constant 2:1 diastereomeric ratios and enantiomeric excesses from 89-97%.

Hydrogen bonding catalysis by a chiral thiourea **18** derived from quinine was used in 2013 by Zhao and Shi in the reaction of α-substituted-α-isocyano esters with isatins to give the corresponding

spirooxindole oxazolines (Scheme 12). In general, all of the isatin derivatives afforded the desired products in moderate to high yields (69-95%) along with good to excellent stereoselectivities (up to >20:1 dr, 70–97% ee). *N*-Unprotected or *N*-benzyl isatins gave the best stereoselectivities. The reaction tolerated electron-withdrawing or electron-donating groups on the aromatic ring, with the first ones giving much better results. 4-Substituted isatins gave the best enantioselectivities (above 90% ee) although with low diastereoselectivity. Regarding the isocyano ester, these allowed α-aryl or α-benzyl substituents, however, unsubstituted ethyl isocyanoacetate reacted with poor diastereo- and enantioselectivity.[38]

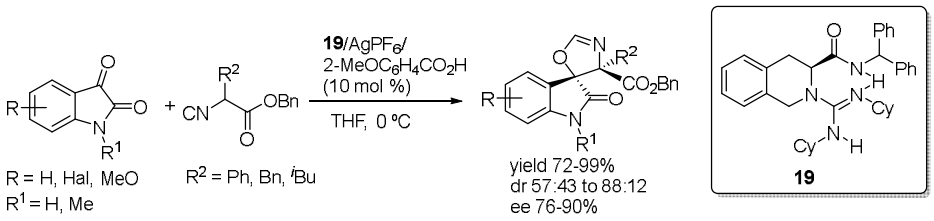


Scheme 11. Bifunctional thiourea-catalyzed addition of isocyanoacetates to α-ketoesters.



Scheme 12. Thiourea-catalyzed reaction of α-substituted-α-isocyano esters with isatins.

A similar reaction was described later in 2017 by Feng using a cooperative chiral guanidine **19**/Ag(I) catalytic system, which gave the corresponding chiral spirooxindole oxazolines in good yields (up to 99%), moderate diastereoselectivities (up to 88:12 dr) and good enantioselectivities (up to 90% ee) (Scheme 13). In general, α-isocyano esters having alkyl substituents at the α position worked better than the aryl-substituted. A variety of isatins were tested for the reaction with the α-isobutyl-α-isocyanide benzyl ester providing the expected products with moderate diastereoselectivity and enantiomeric excesses (76-90%).[39] The *N*-protecting group of isatins had just a small effect on the diastereoselectivity and yield.

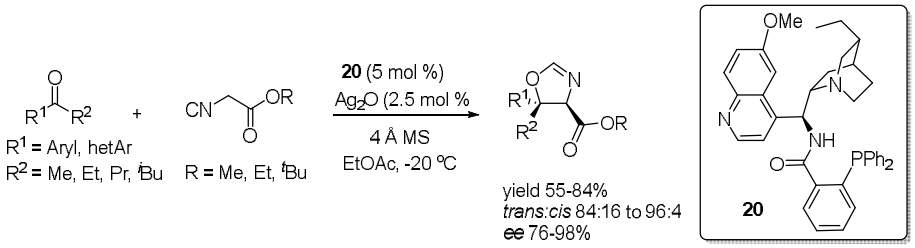


Scheme 13. Cooperative chiral guanidine/Ag catalysis in the synthesis of spirooxindole oxazolines.

2.2.2. Enantioselective reactions with unactivated ketones

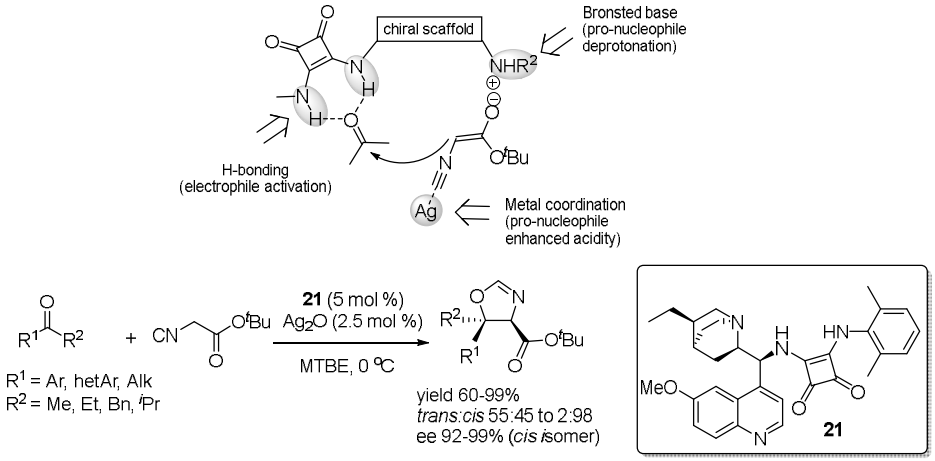
The first enantioselective reaction of isocyanoacetate esters and unactivated ketones was reported by Dixon. This group used practically the same catalytic conditions previously reported for the reaction with

aldehydes but with a different amidophosphine ligand **20**. The reaction with ketones provided the *trans* oxazolines bearing a quaternary stereocenter attached to oxygen (Scheme 14). Although the reaction was restricted to aryl alkyl ketones, the final products were obtained in good yields with high diastereomeric ratios (up to 9:1) and enantiomeric excesses (up to 98%). The alkoxy group in the ester moiety of the isocyanoacetate had not an important effect on the stereoselectivity of the reaction. No examples with α-substituted isocyanoacetates were reported.[40]



Scheme 14. Reaction of isocyanoacetates with unactivated ketones under cooperative catalysis.

Recently, our group has described a new catalytic procedure for the reaction of *tert*-butyl isocyanoacetate and unactivated ketones based in a multicatalytic approach that combines a bifunctional Brønsted base-squaramide organocatalyst **21** and Ag^{+} as Lewis acid (Scheme 15). In this catalytic system, the squaramide moiety would provide electrophilic activation of the ketone through hydrogen bonding at the same time that coordination of Ag+ to the isocyano group would facilitate the deprotonation of the isocyanoacetate by the Brønsted base of the organocatalyst, enhancing the reaction rate via this double activation of the pro-nucleophile. *tert*-Butyl isocyanoacetate provided better results than other isocyanoacetates esters. In contrast with Dixon's catalyst, this new cooperative system provided the *cis* oxazolines as the major diastereomers. The reaction with different aryl or heteroaryl alkyl ketones gave the oxazolines in good yields with fair to good diastereoselectivities (62:38 to 95:5), which were especially good for o*rtho*-substituted acetophenones, and excellent enantiomeric excesses above 95% for the major *cis*-diastereomer. Furthermore, unlike Dixon's catalyst, symmetrical and unsymmetrical dialkyl ketones were suitable substrates in this reaction providing the *cis* oxazolines with moderate diastereoselectivity but excellent enantioselectivity.[41]



Scheme 15. Enantioselective synthesis of oxazolines from ketones under Ag/squaramide cooperative catalysis. Catalytic model and results.

3. Enantioselective synthesis of 2-imidazolines from imines

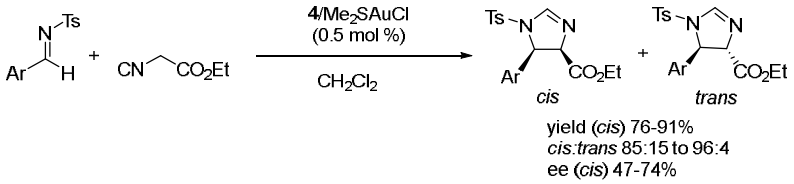
2-Imidazolines are five-membered heterocycles bearing two nitrogen atoms in 1,3-position, and a double bond located at the carbon between both nitrogen atoms.[42] Optically active 2-imidazolines have emerged as attractive synthetic targets due to their wide applications in the synthesis of natural products,[43] as chiral auxiliaries[44] or as chiral ligands.[45] Moreover, chiral 2-imidazolines are versatile building blocks for the synthesis of biologically active molecules[46] such as α,β-diamino acids and their derivatives.[47]

From the different methodologies developed for the synthesis of chiral 2-imidazolines, the asymmetric nucleophilic addition/cyclization of α-isocyano esters with imines is one of the most straightforward. Recently, several asymmetric approaches involving different catalytic systems have been developed to achieve this reaction with aldimines as well as with the more challenging ketimines.

3.1. Enantioselective reactions of α-isocyano esters with aldimines

3.1.1.Metal catalysis

The first enantioselective example of the synthesis of chiral 2-imidazolines via enantioselective addition of isocyanoacetates to imines was reported by Lin in 1999,[48] using the gold complex generated *in situ* by mixing (dimethylsulfide)gold(I) chloride and the chiral ferrocenylphosphine ligand **4** (Scheme 16) to generate the *cis* 2-imidazoline derivatives as the major isomers with good diastereomeric rations and moderate enantioselectivities. The authors found that the ferrocenyl phosphine ligand **4** bearing a piperidino group at the end of the ferrocene side chain gave the best enantioselectivity. The reaction was performed with several aromatic aldimines. The enantioselectivity was not affected by the electronic character of the substituent on the phenyl ring of the imine. However, bulkier substituents at the phenyl ring gave higher enantioselectivities. For example, *p*-iodobenzaldimine gave the best enantioselectivity (88% ee). The enantiomeric excesses of the products could be improved up to 99% ee by simple recrystallization from THF/*n*-hexane.[48b]



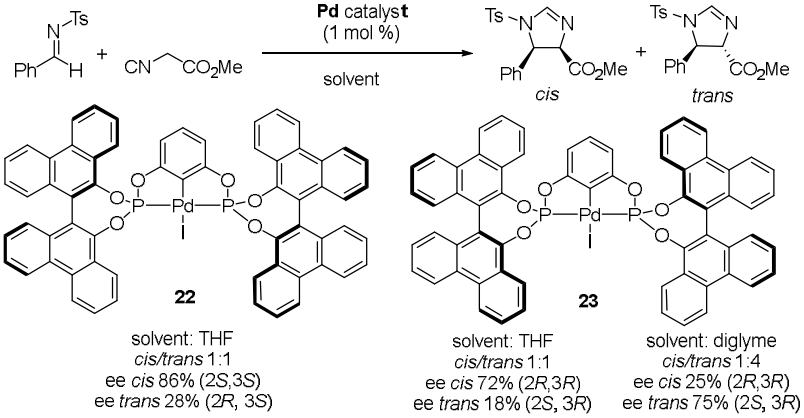
Scheme 16. First reported synthesis of 2-imidazolines from ethyl isocyanoacetate and imines.

Szabó described the use of chiral palladium-pincer complexes **22** and **23** as catalysts for the asymmetric addition of methyl isocyanoacetate to *N*-tosyl benzaldimine (Scheme 17).[49] When THF was used as the solvent, catalyst **22** provided the best enantioselectivity for the *cis* 2-imidazoline (86% ee), however the diastereomeric ratio was very poor (1:1). In the same solvent, catalyst **23** provided the *cis* 2-imidazoline with identical dr but lower ee (72%). Interestingly, the authors observed an improvement of the diastereoselectivity favoring the *trans* isomer (4:1) with similar ee (75%) when catalyst **23** was used in diglyme as solvent.

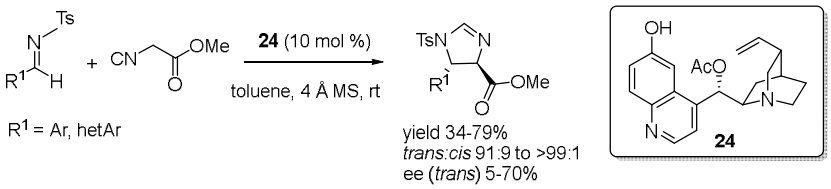
3.1.2.Organocatalytic reactions

The first enantioselective organocatalytic addition of α-isocyano esters to aromatic aldimines was described by Lu in 2010.[50] These authors used a cupreidine ester **24** to perform the addition of methyl isocyanoacetate to *N*-sulfonyl imines obtaining *trans* 2-imidazolines with good yields (up to 79%), excellent diastereoselectivities (up to 99:1 dr), but with just moderate enantioselectivities (up to 70% ee). The addition of 4Å molecular sieves led to shorter reaction times and significantly higher enantioselectivies. The reaction tolerated electron-withdrawing groups (Cl, Br) and electron-donating groups on the aromatic ring of the imine. However, the presence of a strong electron-withdrawing group (NO_2) afforded the corresponding product with high diastereomeric ratio (94:6) but poor enantiomeric excess (5%). Heteroaromatic *N*-tosyl aldimines gave disparate results, while 2-thienyl *N*-tosyl imine gave good yield (79%), high dr (95:5) and

moderate enantiomeric excess (52%), the 2-furyl *N*-tosyl imine gave lower yield (62%) and enantioselectivity (18% ee). No examples with aliphatic aldimines were reported (Scheme 18).

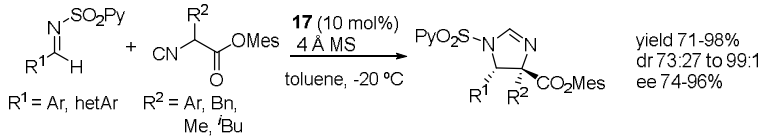


Scheme 17. Pd-Catalyzed asymmetric synthesis of 2-imidazolines from methyl isocyanoacetate and *N*-tosyl benzaldimine.



Scheme 18. First enantioselective organocatalytic addition of isocyanoacetates to aldimines.

Nakamura and Shibata, in 2012,[51] reported the first enantioselective addition of α-substituted isocyanoacetates to *N*-sulfonyl imines using the bifunctional thiourea organocatalyst **17** derived from quinine (Scheme 19), affording the corresponding 2-imidazolines having a quaternary stereocenter.



Scheme 19. Organocatalytic reaction of *N*-(2-pyridinesulfonyl)imines and α-substituted-α-isocyano esters catalyzed by a quinine-derived thiourea.

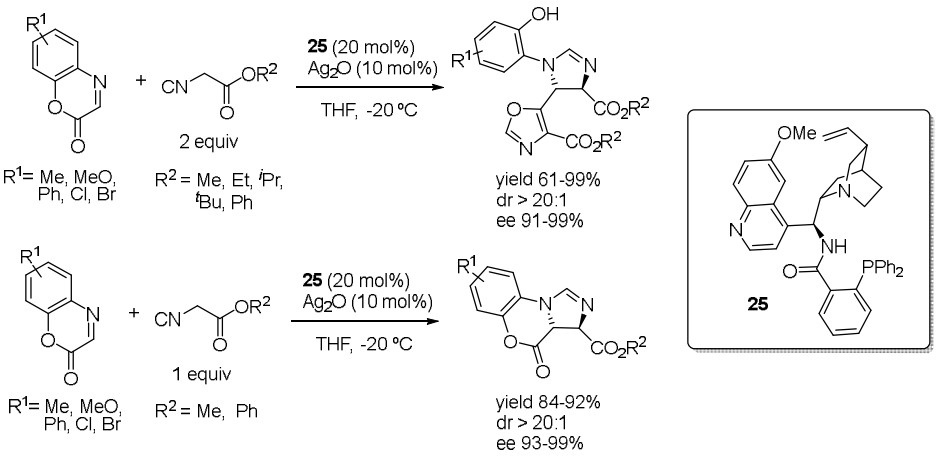
The protecting group on the *N*-sulfonyl imine proved very important, the best enantioselectivity was obtained when the 2-pyridinesulfonyl group was used as the protecting group. The ester group in the isocyano acetate also played a crucial role on the stereoselectivity of the reaction, the best results being obtained with the 2,4,6-trimethylphenyl (Mes) ester. The addition of 4Å molecular sieves improved the diastereoselectivity of the reaction without loss of enantioselectivity. The reaction worked efficiently with both electron-withdrawing and electron-donating imines, giving the corresponding chiral 2-imidazolines in high yields (83-98%) and high stereoselectivity (up to 99:1 dr, and up to 96% ee). Curiously, the best enantioselectivity was obtained with the imine derived from *p*-nitrobenzaldehyde. The reaction of imines having naphthyl or heteroaromatic groups, also resulted in good outcomes. Moreover, several α-substituted isocyanoacetates afforded the corresponding products with high diastereo- and enantioselectivity. The

authors could remove the pyridinosulfonyl group by treatment with magnesium in MeOH, to give the unprotected 2-imidazolines without erosion of diastereo- and enantiopurity.

3.1.3. Cooperative metal/organocatalysis

Zhao and Cao, in 2017, described the asymmetric Mannich reaction of α-substituted isocyanoacetates with *N*-Boc-aldimines, catalyzed by a combination of an aminoacid-derived chiral phosphine catalyst and methyl acrylate with good yields and enantioselectivities but low diastereomeric ratios.[52] However, to obtain the cyclized product the addition of silver acetate and methyldiphenylphosphine was required and the chiral 2-imidazolines were produced with low diastereo- and enantioselectivity.

In 2014, Zhao and coworkers presented an interesting methodology for the highly diastero- and enantioselective silver-catalyzed double [3+2] cyclization of cyclic aldimines and isocyano esters, providing directly linked oxazole-imidazolines with excellent results (Scheme 20).[53] Dixon's cooperative catalytic system composed by silver oxide and amidophosphine **25** was employed in this reaction. Different ester groups (Me, Et, ^{i}Pr, ^{t}Bu or Ph) on the isocyanoacetate and different substitution patterns on the aryl ring of the cyclic imines were tolerated. However, when a cyclic ketimine was used as the substrate, the corresponding *cis* product was obtained but in moderate yield and low enantioselectivity (37% ee), although with good diastereoselectivity. The authors identified that the mechanism of the double cyclization reaction took place in a stepwise manner. Taking into account the stepwise nature of the reaction, the authors also developed conditions to obtain the product of mono [3+2] cyclization using only one equivalent of the isocyanoacetate. The corresponding fused 2-imidazolines were obtained with excellent yield, diastero- and enantioselectivity.



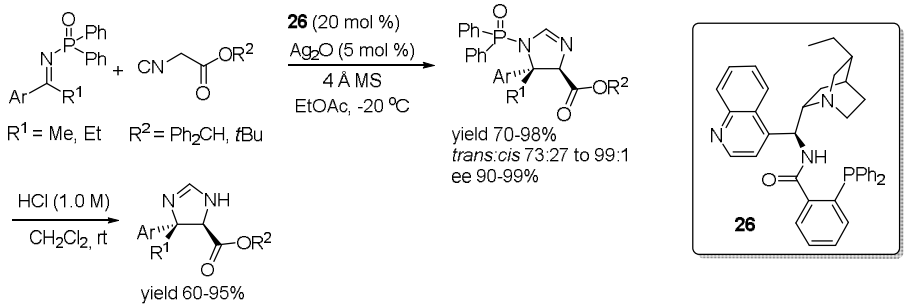
Scheme 20. Diastero- and enantioselective double [3+2] cyclization of α-imino esters and isocyanoacetates catalyzed by a quinine-derived catalyst and Ag_2O.

3.2. Enantioselective reactions of α-isocyano esters with ketimines

3.2.1. Reaction with acyclic ketimines

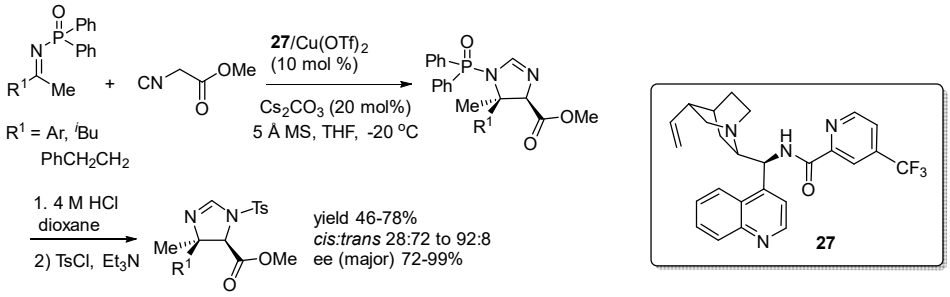
Ketimines are more challenging electrophiles than aldimines, because ketimines have a significantly lower reactivity. In 2014,[54] Dixon reported the first asymmetric addition/cyclization reaction of isocyanoacetates to ketimines using a similar cooperative catalytic system as the previously used by this group with aldehydes, which involved the amidophosphine **26** and Ag_2O (Scheme 21). The reaction of diphenylmethyl- or *tert*-butyl- isocyanoacetates with *N*-diphenylphosphinoyl ketimines derived from substituted acetophenones gave the highly substituted chiral 2-imidazolines with excellent yields, high diastereoselectivity (up to 99:1) and excellent enantioselectivities (up to 99% ee). The *trans* isomer was obtained majorly and the enantioselectivity was independent of the electronic character and the position of the substituents on the aromatic ring of the ketimine. Moreover, the phosphinoyl protecting group could be

removed using HCl 0.1 M, without compromising the diastero- and enantiopurity of the compounds. Furthermore, the treatment of the unprotected 2-imidazolines with KOH gave the corresponding chiral α,β-diaminoacids.



Scheme 21. Enantioselective synthesis of 2-imidazolines under cooperative catalysis by Dixon.

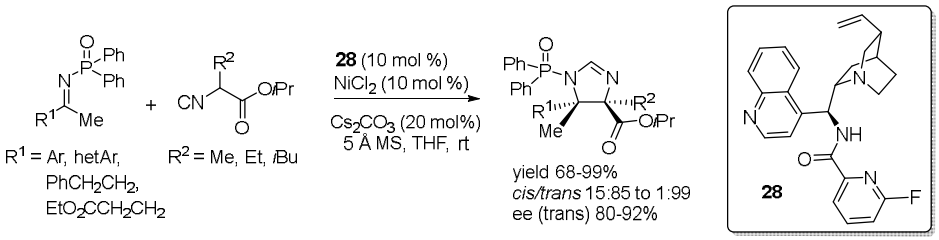
The same year, Nakamura and coworkers described a cooperative catalytic system for the formal [3+2]-cycloaddition of ketimines and methyl isocyanoacetate affording chiral *cis* 2-imidazolines.[55] This catalytic system involved *N*-picolynoyl-9-amino-9-deoxy-*epi*-cinchonine ligand **27** and $Cu(OTf)_2$ (Scheme 22). This catalytic system is complementary to that reported by Dixon, as it yields the *cis* isomer as the major diastereomer. Due to the low thermal stability of the resulting diphenylphosphinoyl imidazolines, the products were converted into the corresponding tosyl imidazolines in two steps. The reaction tolerated aryl ketimines substituted with either electron-withdrawing or electron-donating groups at the benzene ring. Ketimines bearing naphthyl or heteroaryl groups were also competent substrates, obtaining the corresponding *cis* 2-imidazolines with good yields (46-68%), high diastereomeric ratios (*cis:trans* up to 92:8) and excellent enantiomeric excesses (95-99%). Imines derived from dialkyl ketones could be used, although the diastereoselectivity decreased, and the *trans* imidazolines were produced as the major diastereomers, which were obtained with lower enantioselectivities (72-89% ee).



Scheme 22. Enantioselective synthesis of 2-imidazolines under cooperative Cu/organocatalysis.

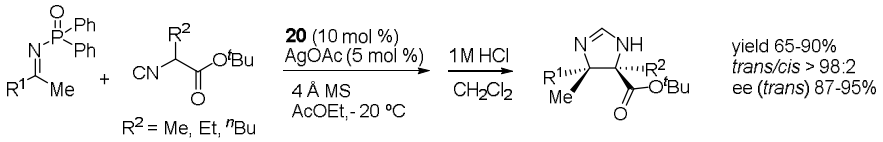
In 2016, Nakamura and Dixon reported the extension of their respective works to the reaction of α-substituted isocyanoacetates and *N*-diphenylphosphinoyl ketimines producing 2-imidazolines containing two congested vicinal tetrasubstituted stereocenters.[56] Nakamura performed the formal [3+2]-cycloaddition reaction using a catalytic system related to that employed for the addition of methyl isocyanoacetate but with a different amide derived from 9-amino-9-deoxy-*epi*-cinchonidine **28** and $NiCl_2$ (instead of copper triflate), Cs_2CO_3 (20 mol%) and 5 Å MS in THF at room temperature (Scheme 23). Under the reaction conditions, ketimines derived from substituted acetophenones bearing either electron-donating or electron-withdrawing substituents on the aryl group, as well as 2-acetylnaphthalene and heteroaryl methyl ketimines, reacted smoothly with isopropyl 2-isocyanopropanoate (R^2=Me) to give the corresponding 2-imidazolines with

excellent yields, high diastereo- and good enantioselectivity. Moreover, ketimines derived from dialkyl ketones, could be used in the reaction with similar results. Other α-alkyl isocyanoacetates (R^2=Et, ^{i}Bu) were proper substrates in the reaction, however, no α-aryl isocyanoacetates were reported.



Scheme 23. Nickel-catalyzed enantioselective addition of α-substituted isocyanoacetates to unactivated ketimines.

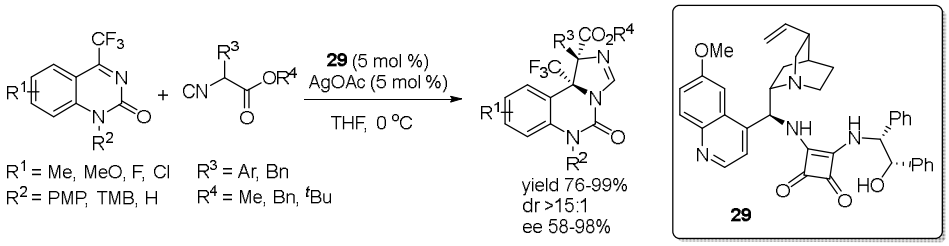
On the other hand, Dixon applied his cooperative catalytic system but using the amidophosphine derived from cinchonidine **20** and AgOAc as the silver source (Scheme 24).[57] Previous to characterization of the resulting products and determination of the enantiomeric excess *via* HPLC, the diphenylphosphinoyl protecting group was removed using 1M HCl in CH_2Cl_2. The corresponding *trans* 2-imidazolines bearing two quaternary stereogenic centers were obtained with good yields, as only one diastereomer with high enantioselectivity for a number of aryl and heteroaryl ketimines. The reaction worked with isocyanoacetates bearing alkyl groups at the α-position. The bulky *tert*-butyl ester was preferred as the methyl ester reacted with good stereoselectivity but very low yield.



Scheme 24. Enantioselective synthesis of 2-imidazolines under cooperative Ag/organocatalysis.

3.2.2. Reaction with cyclic and isatin ketimines

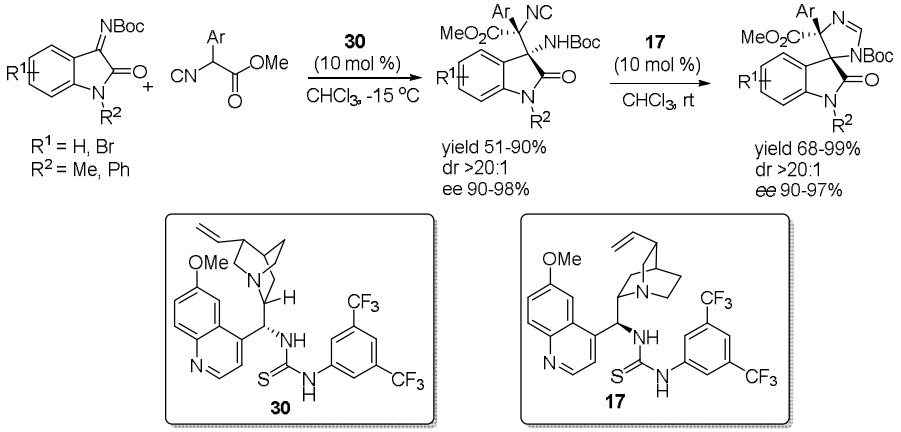
In 2014, the group of Shi reported the diastereo- and enantioselective Mannich/cyclization cascade reaction of α-substituted isocyanoacetates to trifluoromethylated cyclic ketimines, affording the corresponding optically active trifluoromethyl-substituted tetrahydroimidazo[1,5-c]quinozaline derivatives in excellent yields along with outstanding stereoselectivities (Scheme 25).[58]



Scheme 25. Diastereo- and enantioselective formal [3+2]-cycloadditionof isocyanoacetates and cyclic trifluoromethyl ketimines catalyzed by quinine-derived squaramide/AgOAc.

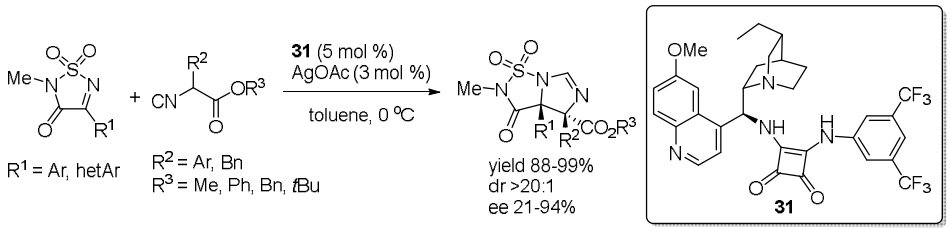
The same authors, in 2015, described the asymmetric Mannich reaction of α-substituted isocyanides with isatin-derived ketimines and the subsequent cyclization to spirooxindole imidazolines (Scheme 26).[59] In

order to obtain good stereoselectivities, the reaction needed to be performed at low temperature (-15 ºC), which prevented the cyclization step affording the corresponding Mannich type products with excellent diastereoselectivity and enantioselectivity when the quinidine-derived thiourea **30** was used as the catalyst. Afterwards, the authors studied the cyclization step that was better performed in the presence of the quinine-derived thiourea **17** at room temperature, which presented a better chirality match between the substrate and the organocatalyst. In this way the corresponding spirooxindole imidazolines were obtained with good yields and without erosion of dr and ee with respect to the Mannich products.



Scheme 26. Diastereo- and enantioselective synthesis of spirooxindole imidazolines developed by Shi.

The most recent example of Mannich/cyclization cascade reaction using isocyanoacetates and ketimines was described by Zhao and Shi in 2018.[60] They developed an efficient diastereo- and enantioselective formal [3+2] cyclization of α-substituted isocyanoacetates and cyclic sulfamide ketimines, obtaining highly functionalized fused sulfamidate-imidazoline products with excellent yields and diastereoselectivity and high enantiomeric excesses (Scheme 27). This reaction uses a cooperative catalysis involving the combination of a dihydroquinine-derived squaramide **31** and AgOAc. A wide variety of isocyanoacetates and ketimines were tolerated in this methodology, affording a library of interesting enantioenriched 2,3,3*a*,4-tetrahydroimidazo[1,5-*b*][1,2,5]thiadiazole-1,1-dioxide derivatives.



Scheme 27. Formal [3+2]-cycloaddition reaction of isocyanoacetates and cyclic sulfamide ketimines catalyzed by squaramide/AgOAc.

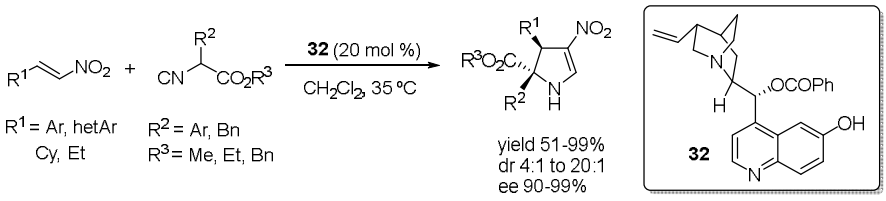
4. Enantioselective synthesis of dihydropyrroles and related compounds

Chiral pyrrolidine constitutes a structural motif present in a number of biologically active compounds.[61] Beside, compounds having this moiety have been used as building blocks in the synthesis of natural products and other complex molecules.[62] However, approaches to access these molecules in an enantioselective manner are limited. In recent years, the catalytic asymmetric [3+2]-cycloaddition of

α-isocyano esters with electron-deficient alkenes has emerged as a powerful strategy for the construction of chiral 2,3-dihydropyrroles. These methods are reviewed next in this chapter section.

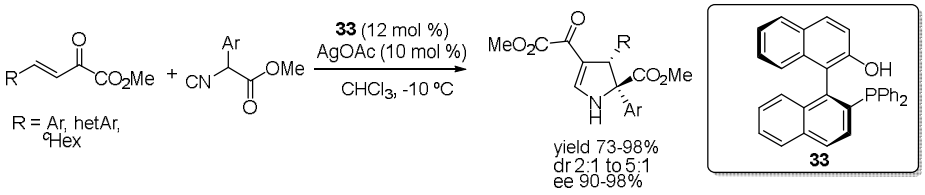
4.1. Enantioselective reactions of α-isocyano esters with acyclic electrophilic alkenes

Specifically, the formal cycloaddition reaction of metalated isocyanides to electrophilic alkenes offer a very straightforward method to produce functionalized 2,3-dihydropyrroles.[63] However, the first enantioselective version of this reaction was not available until 2008 Gong's report on the cycloaddition of α-isocyano esters and nitroolefins catalyzed by a *Cinchona* alkaloid ester **32** (Scheme 28).[64] Useful nitroolefins included β-aryl nitroalkenes bearing electron-withdrawing or electron-donating substituents on the aryl ring as well as β-alkyl nitroalkenes. Electron-deficient aryl substituents facilitated the cycloaddition with excellent stereoselectivity. Electron-rich aryl nitroolefins, heteroaryl-substituted nitroolefins and bulky nitroolefins also underwent smooth cycloaddition with slightly lower stereoselectivity. Alkyl substituted nitroalkenes also furnished the expected products with high diastereo- and enantioselectivities, although they required longer reaction times and gave lower yields. A variety of α-substituted isocyanoacetates bearing aromatic or benzyl substituents at this position were suitable reactants and gave the pyrrolidines with good diastero- and enantioselectivity. However, α-unsubstituted alkyl isocyanoacetates failed to undergo the cycloaddition, indicating that the substituent is crucial for the success of the reaction.



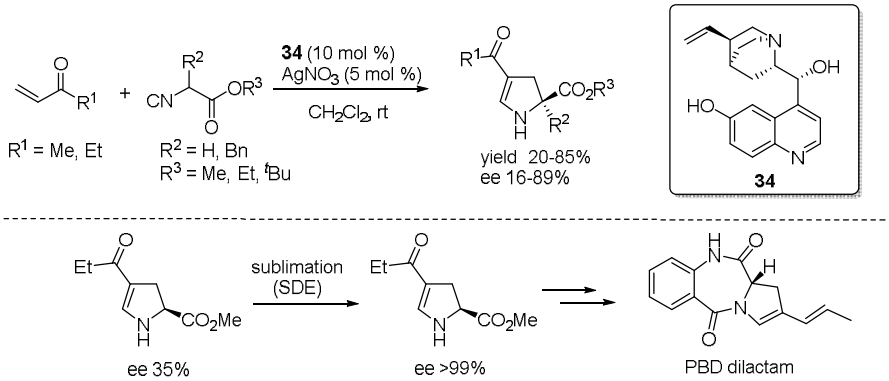
Scheme 28. First enantioselective cycloaddition of α-isocyano esters and nitroolefins.

However, extension of this organocatalytic protocol to unsaturated carbonyl compounds, *i.e.* β,γ-unsaturated-α-keto esters was unsuccessful and provided the expected pyrrolidines with moderated yield and low levels of stereoselectivity. To address this challenge, the same group developed in 2011 a silver-catalyzed reaction using a chiral binaphthyl hydroxy phosphine ligand **33** (Scheme 29).[65] Conjugated keto esters bearing either electronically rich or electronically poor phenyl groups attached to the double bond underwent smooth cyclization reactions to give the 4,5-dihydropyrroles bearing two consecutive stereogenic centers with good yields, good diastereomeric ratios and enantiomeric excesses above 90% for all the examples studied. A 2-furyl as well as a bulky 2-naphthyl substituent were also tolerated with excellent enantioselectivity, although with lowest dr (2:1). Methyl 4-cyclohexyl 2-oxobutenoate reacted also well in a high yield and with a higher dr (5:1) and 93% ee for the major diastereomer. The reaction could also be performed with a variety of α-aryl isocyano acetates. Either electronically rich or electronically poor α-aryl isocyanoacetates participated in the cyclization reaction in high yields and with excellent levels of enantioselectivity.



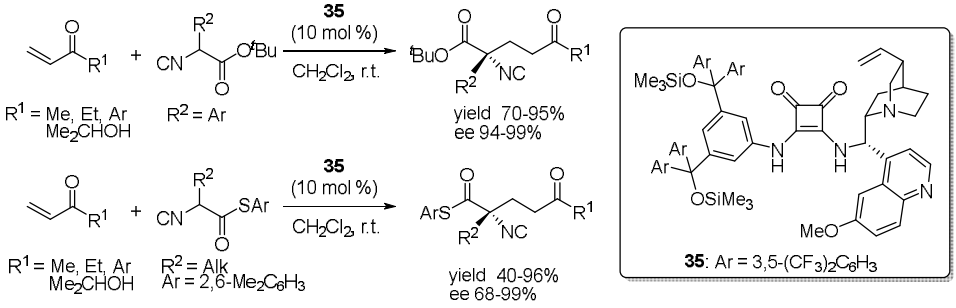
Scheme 29. Silver-catalyzed enantioselective reaction of α-isocyano esters and β,γ-unsaturated-α-keto esters.

Almost simultaneously to this report by Gong, the group of Escolano described the first asymmetric cycloaddition of α-isocyano esters with vinyl ketones using a cooperative catalytic system composed by a combination of silver nitrate and cupreine (**34**) as a bifunctional organocatalyst (Scheme 30).[66] According to the authors, complexation to the isocyanide carbon in the initial step increased the acidity of the α-proton facilitating deprotonation by the quinuclidine nitrogen of cupreine. The resulting chiral ion pair would experiment a 1,4-addition to the vinyl ketone assisted by the formation of a hydrogen bonding between the C6-hydroxyl group of cupreine and the enone carbonyl group. Finally, nucleophilic attack of the resulting enol to the isocyanide carbon would be promoted by silver activation to give the corresponding pyrrolidine. Cupreine acts, therefore, as a Brønsted base/hydrogen bonding bifunctional catalyst, while silver plays a dual role increasing the acidity of the α-hydrogen of the isocyanide and promoting cyclization to the pyrrolidine. Despite this multicatalytic approach, the expected pyrrolidines were obtained with low yields and low (R^2=Bn) to moderated (R^2=H) enantiomeric excesses in most of the cases. In a later work, the same group described the enantiomeric enrichment of the oxazoline resulting from the reaction of methyl isocyanoacetate and ethyl vinyl ketone via the self-disproportionation of enantiomers (SDE) phenomenon upon repeated sublimation. The enantioenriched oxazoline was used in the synthesis of a pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dilactam.[67]



Scheme 30. Asymmetric cycloaddition of α-isocyano esters with vinyl ketones under cooperative Ag/organocatalysis

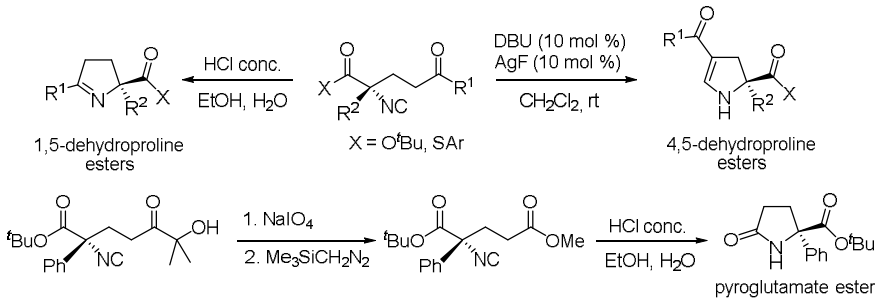
In 2017, the group of Palomo described a pure organocatalytic approach for the related reaction of α-substituted isocyanoacetates with vinyl ketones. These authors found that, in the absence of metal catalyst, the intramolecular cyclization step was prevented leading to the 1,4-addition adducts (Scheme 31).[68]



Scheme 31. Asymmetric organocatalytic 1,4-addition of α-isocyano esters to vinyl ketones.

The 1,4-addition was catalyzed by a bifunctional tertiary amine/squaramide catalyst **35**, featuring a bulky poliaryl sidearm. Both alkyl and aryl vinyl ketones reacted with a variety of α-aryl isocyanoacetates to give the adducts with good isolated yields and enantiomeric excesses above 96%. Nonetheless, *o*-substituted aryl isocyanoacetates as well as α-alkyl isocyanoacetates were not suitable reaction partners. To address the inability of alkyl isocyanoacetates to react under the developed conditions the authors used the corresponding thioesters instead. The authors found that α-alkyl isocyanoacetate thioesters with a di-*ortho*-substituted phenyl group reacted cleanly to produce the expected adducts avoiding the formation of other by-products observed with other thioesters. The reactivity partner was quite general for isocyanoacetates bearing short, medium and long alkyl linear or branched chains.

The obtained adducts could be subjected to cyclization under different conditions providing divergent access to optically active quaternary 1,5- and 4,5-dehydroprolines. Thus, mild acid hydrolysis followed by spontaneous cyclization provided 1,5-dehydroproline esters, while basic treatment with DBU and AgF led to 4,5-dehydroprolines in good yields. On the other hand, the adduct resulting from the reaction with the hydroxyketone (R^1=Me_2CHOH), a surrogate of methyl acrylate, was transformed into a pyroglutamate ester after oxidative cleavage, methylation and hydrolysis (Scheme 32).

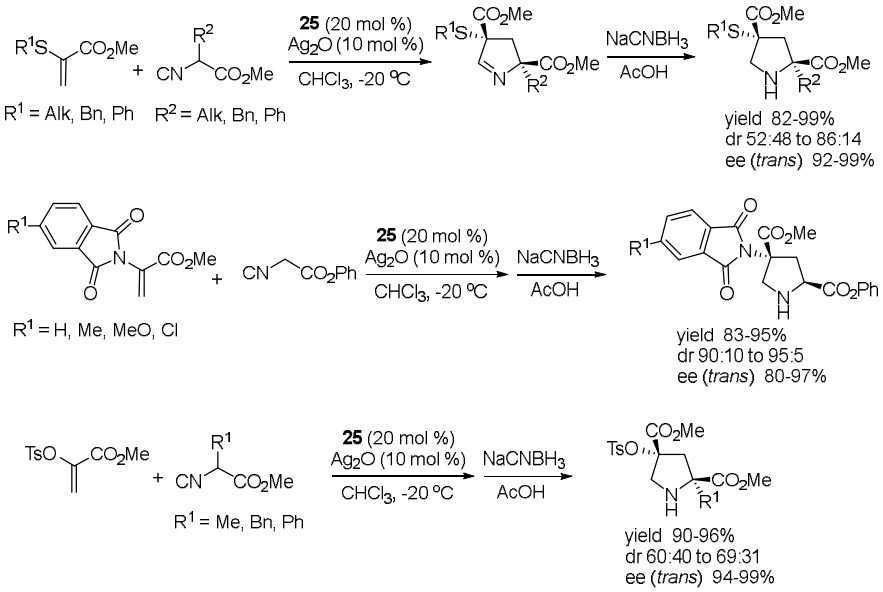


Scheme 32. Divergent cyclization of 1,4-addition products.

Shao and He have reported the formal [3+2]-cycloaddition of isocyanoacetate esters with alkenes bearing captodative substitution, such as acrylates featuring a heteroatom substituent at the α-position, to obtain 1-pyrrolines bearing a heteroatom substituted quaternary stereocenter, which were transformed into the corresponding pyrrolidines after reduction (Scheme 33).[69] The reaction of α-thioacrylates with methyl isocyanoacetate was carried out using the catalytic system developed by Dixon, which combines the chiral organocatalyst **25** and Ag_2O in either $CHCl_3$ or toluene as the solvent. In both cases excellent enantioselectivities were obtained, although toluene provided better diastereoselectivities (*trans/cis* from 58:42 to 86:14 in $CHCl_3$ *vs* 70:30 to 95:5 in toluene) but lower yields than chloroform due to elimination of thioether moieties of the cycloadducts to form pyrroles in the reaction conditions. The resulting 1-pyrrolines showed low stability during purification by column chromatography and, therefore, the crude mixture was subjected to reduction with $NaBH_3CN$/AcOH to give the corresponding pyrrolidines. α-Substituted phenyl isocyanoacetates were also competent substrates in this reaction and, after reduction, pyrrolidines bearing two quaternary stereocenters were obtained in good yields and high enantioselectivites (ee>90%), although with low diastereoselectivity (*trans/cis* from 52:48 to 75:25).

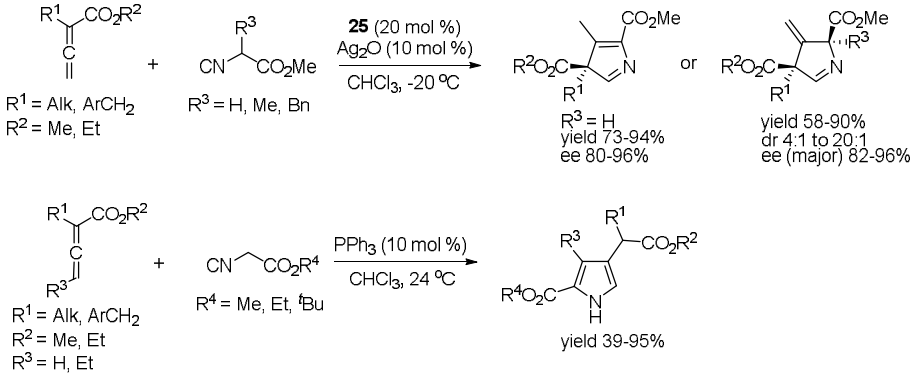
The same set of conditions could also be applicable to phthalimide-substituted acrylates and methyl isocyanoacetate furnishing 4-aminopyrrolidine-2,4-dicarboxylic acids containing quaternary α-amino acid units in good to excellent yields (83-95%), diastereoselectivities (*trans/cis* from 90:10 to 95:5), and enantioselectivities (80-97% ee). In this reaction the presence of an electron-withdrawing group (Cl) on the phtalimide resulted deleterious for the outcome of the reaction.

Finally, the authors reported a few examples of asymmetric [3+2]-cycloaddition/reduction of α-tosyloxyacrylate with α-substituted isocyanoacetates to produce pyrrolidine derivatives, which bear tetrasubstituted α-hydroxy acid moieties. Pyrrolidine derivatives with 2-methyl, benzyl, and phenyl groups were all produced in excellent yields (90-96%) and enantioselectivities (94-99%).



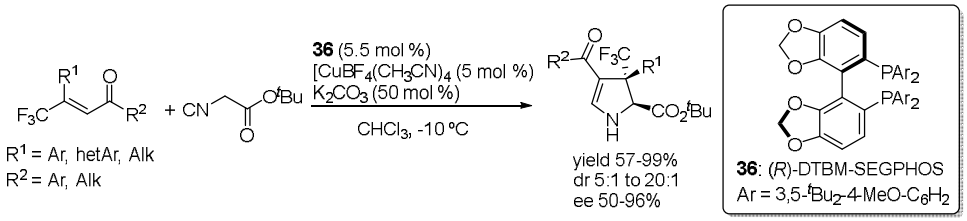
Scheme 33. Asymmetric [3+2]-cycloaddition of α-heteroatom-substituted acrylates with α-isocyano esters.

Dixon's catalyst has been used by Zhao in the reaction of allenoates with isocyanoacetate esters (Scheme 34).[70] The reaction of methyl isocyanoacetate with different allenoates provided 3*H*-pyrroles bearing a quaternary stereocenter through a [3+2] cyclization followed by a 1,3-H shift. The scope of this procedure proved to be broad and allowed to obtain 3*H*-pyrroles with different 3-substituents including benzyl, allyl and alkyl groups in high yield (73-94%) with good to excellent ee (80-96%). The authors extended the study of this reaction to substituted isocyanoacetates (methyl 2-isocyano-3-phenyl propanoate and methyl 2-isocyanopropanoate), which provided the [3+2]-cyclization products with an exocyclic double bond and two quaternary stereocenters. An ethyl instead of methyl ester in the allenoate improved the diasteresoselectivity. Also, various substituted benzyl groups as well as an allyl substituent on the allenoate structure could be tolerated to deliver the products in high yield and selectivity (82-96% ee; dr up >20:1). Interestingly, in the absence of metal catalyst, using triphenylphosphine as the catalyst the same set of reagents reacted to give di- and trisubstituted pyrroles in good yields.



Scheme 34. Divergent reaction pathways for allenoate esters and α-isocyano esters.

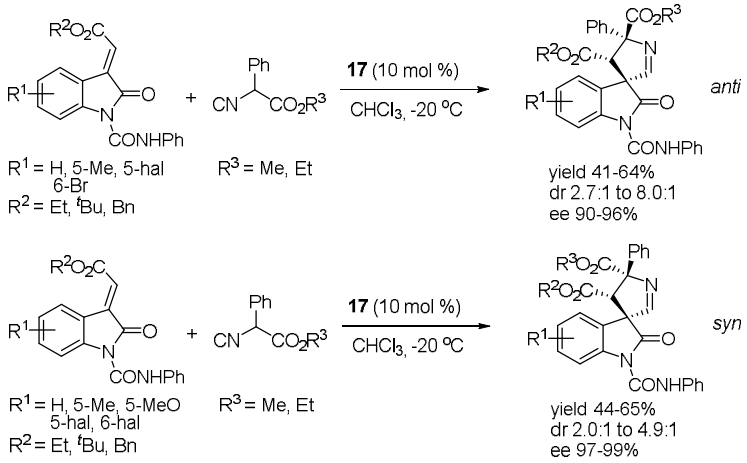
Recently, the group of Zhang has described the direct asymmetric formal [3+2]-cycloaddition reaction of isocyano esters with β-trifluoromethyl β,β-disubstituted enones leading to optically active dihydropyrroles bearing a trifluoromethylated quaternary sterocenter.[71] The reaction was catalyzed by a complex generated *in situ* from $[Cu(BF_4)(CH_3CN)_4]$ and the (*R*)-DTBM-SEGPHOS complex **36** in the presence of K_2CO_3 (Scheme 35). *tert*-Butyl isocyanoacetate performed better than the analogues methyl or ethyl esters. A number of β-methyl-β-triflurometyl enones bearing aromatic or heteroaromatic groups attached to the carbonyl moiety provided the expected products with enantiomeric excesses above 90% in most of the studied examples. However, ketones having alkyl groups attached to the carbonyl reacted with lower enantioselectivity. Notably, the variation of the second β-substituent affected the diastereoselectivity rather than the enantioselectivity. Thus, while β-methyl-β-trifluoromethyl enones provided just one diastereomer (dr >20:1), substitution of the methyl group to ethyl, butyl or aryl decreased the diasteromeric ratio to 6:1. Finally, it should be noted that the presence of the β-trifluoromethyl group was required for the success of the reaction. Lower yield, diastereo- and enantioselectivity were observed when moving from CF_3 to CF_2H and to CFH_2, while no reaction was observed with a β,β-dimethyl enone.



Scheme 35. Copper-catalyzed asymmetric formal [3+2]-cycloaddition reaction of isocyano esters with β-trifluoromethyl β,β-disubstituted enones.

4.2. Enantioselective synthesis of 3,3'-pyrrolidinyl spirooxindoles

The 3,3'-pyrrolidinyl spirooxindole scaffold is found in natural alkaloids and bioactive molecules and can serve as the core structure for new pharmaceuticals.[72] Recently these kind of structures have been accessed via [3+2]-cycloadditions of isocyano esters and methyleneindolinones. The first example of such a reaction was reported by Xu and Wang in 2012 using a chiral bifunctional thiourea derived from quinine **17** as catalyst (Scheme 36).[73]

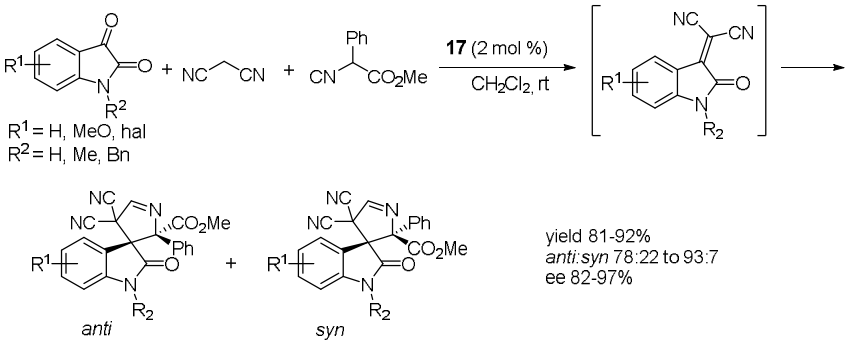


Scheme 36. Asymmetric synthesis of 3,3'-pyrrolidinyl spirooxindoles.

The authors also found that the diastereoselection of the reaction could be inverted by modifying the protecting group on the nitrogen atom of the indolinone. Thus, *N*-phenylamide protected indolinones provided the *anti* diastereomer as the major product. Substituents of different electronic nature in different positions of the aromatic ring of the indolinone were tolerated, the resulting products being obtained with moderate to good yields and diastereoselectivities, and excellent enantiocontrol. However, the reactivity and diasterocontrol slightly decreased with the increase of the bulkiness of the ester group on the methyleneindolinone side arm. On the other hand, *N*-Boc protected methyleneindolinones reacted under the same conditions with a shift of diastereoselectivity to give the corresponding *syn* products. Again, different substitution on the aromatic ring of the indolinone was allowed and the spirooxindoles were obtained with excellent enantiomeric excesses. Unfortunately, α-methyl and α-benzyl isocyanoacetates were not appropriate substrates for these reactions due to the low basicity of the α-hydrogen.

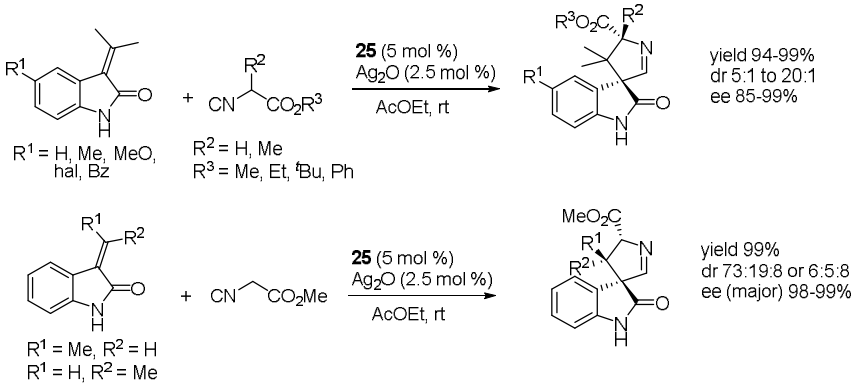
A similar reaction using a related thiourea catalyst has been reported also by Zhong. These authors found that the swift in diastereoselection was also observed when changing from *N*-Boc to *N*-benzyl protected indolinones.[74]

Almost simultaneously to the work by Xu and Wang, the group of Yan developed an enantioselective synthesis of 3,3'-pyrrolidinyl oxindoles via an organocatalytic three-component reaction of isatins, malononitrile and methyl α-phenylisocyanoacetate (Scheme 37).[75] The reaction was catalyzed by the quinine-derived bifunctional thiourea **17** and takes place through formal cycloaddition of the isocyano ester with the dicyanomethylene indolinone generated *in situ*. Remarkably, the initial nucleophilic attack of the isocyano ester takes place on the olefinic carbon in α to the amide carbonyl. Isatins having different substitution on the aromatic ring, unprotected or protected with Me or Bn groups at the nitrogen atom could be used and the resulting spirooxindoles were obtained in good yields and diastereoselectivity, and excellent enantioselectivity. *N*-acyl protected isatins, however, were not reactive substrates. The reaction could be performed with other α-(*p*-substituted aryl)-isocyanoacetate esters with good results, but the reaction with α-unsubstituted methyl isocyanoacetate provided the expected product with low enantioselectivity.



Scheme 37. Three component asymmetric synthesis of 3,3'-pyrrolidinyl spirooxindoles.

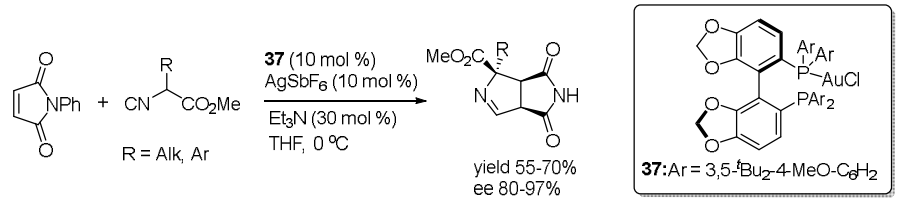
While the previous thiourea-catalyzed reactions provided good stereoselectivity with α-aryl substituted isocyano esters, they lead to poor results with α-unsubstituted or α-alkyl substituted isocyanoacetates. Shao, Zhao and He found that Dixon's catalytic system allowed the reaction of these isocyano esters with alkylidene oxazolinones to give the corresponding spirooxindoles (Scheme 38).[76] A number of 3-isopropylidene oxazolinones substituted at the 5-position with either electron-donating or electron-withdrawing groups reacted with methyl, ethyl, *tert*-butyl or phenyl isocyanoacetates to give the corresponding pyrrolidinyl oxindoles in quantitative yields, high diastereoselectivities and excellent enantioselectivities. Similar results were obtained with methyl α-isocyanopropanoate. On the other hand, mono-substituted 3-methyleneindolinones were suitable substrates and provided the corresponding cycloadducts in excellent yields, good diastereoselectivity (3 diastereomers were observed) and excellent enantioselectivity.



Scheme 38. Asymmetric synthesis of 3,3'-pyrrolidinyl spirooxindoles under cooperative Ag/organocatalysis.

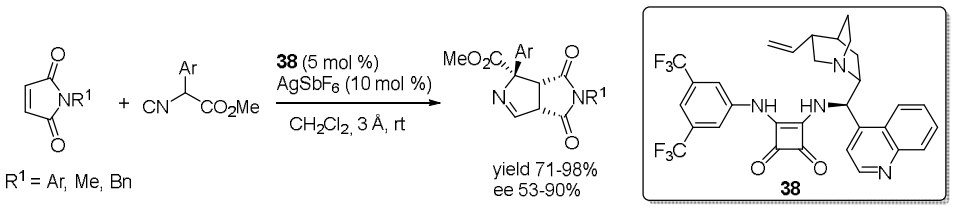
4.3. Desymmetrization of cyclic olefins

The group of Carretero reported in 2012 the reaction of several α-substituted α-isocyano esters with *N*-phenylmaleimide to give bicyclic 1-pyrrolines bearing a quaternary stereocenter at C5. The reaction was catalyzed by a gold complex **37** and $AgSbF_6$ in dichloromethane as the solvent and triethylamine as base (Scheme 39). The silver salt was required to form a cationic gold complex which was the real catalyst, no reaction being observed in the absence of silver salt or base. The reaction of α-aryl-substituted isocyanoacetates provided the 1-pyrroline adduct as a single diastereomer and with high enantiocontrol (80-92% ee). The catalyst could be also employed with α-alkyl-substituted isocyanoacetates. Highly enantioselectivities were obtained particularly with substrates having a sterically demanding substituent (^{i}Pr, ^{s}Bu and ^{t}Bu). In all the cases tested, α-substituted isocyano esters gave improved results with respect to methyl isocyanoacetate, which reacted with the maleimide to give the corresponding product with only 78% ee.[77]



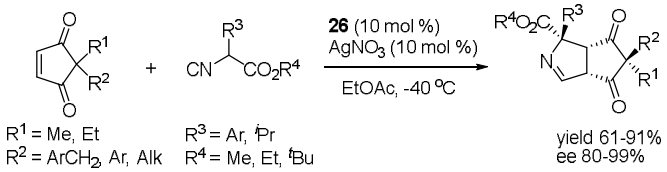
Scheme 39. Gold-catalyzed reaction of α-substituted α-isocyano esters with *N*-phenylmaleimide.

The same year, Zhao and Shi reported another catalytic procedure for this reaction. The authors employed a cooperative catalysis that combined a bifunctional cinchonine-derived squaramide **38** and $AgSbF_6$ (Scheme 40).[78] Generally, *N*-aryl substituted maleimides underwent the [3+2]-cycloaddition reaction with methyl α-phenylisocyanoacetate to give the desired adducts in high yield (90-96%), excellent diastereoselectivity (20:1), and good enantioselectivity (74-89%), the best result being obtained with *N*-phenyl maleimide. *N*-methyl- and *N*-benzyl- maleimides were suitable substrates but afforded the corresponding cycloadducts with lower enantioselectivity (53% and 65% ee, respectively). Regarding the isocyano ester partner, α-aryl-substituted isocyanoacetates bearing an electron-withdrawing group on the aromatic ring led to a better enantioselectivity than those bearing an electron-donating group. Either *ortho*-, *meta*- or *para*- substituted aromatic rings were tolerated. However, α-alkyl- or unsubstituted isocyanoacetates were not appropriate substrates and provided the adducts with low enantioselectivity (only ca. 10% ee).



Scheme 40. [3+2]-Cycloaddition of α-substituted-α-isocyano esters with maleimides under cooperative Ag/organocatalysis.

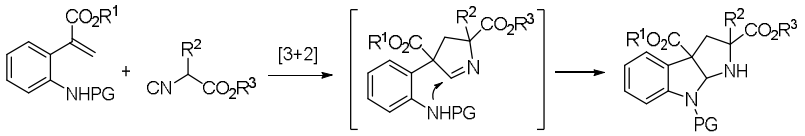
Dixon's catalyst has been employed by Oh to carry out the desymmetrization of cyclopentenediones upon [3+2]-cycloaddition with α-substituted-α-isocyano esters (Scheme 41).[79] The reaction, that tolerates moisture and air, and readily utilizes class III solvents such as EtOAc and acetone, gives bicyclic pyrrolines with four stereogenic centers, including two quaternary centers. The catalytic system was applicable to an extensive array of cyclopentenediones with different electronic and steric characters. Thus, 2-alkyl cyclopentenediones with different benzyl substituents at C2 provided the expected products as a single diastereomer with excellent enantioselectivities. 2-Methylcyclopentenediones with phenyl derivatives at C2 were also successful substrates. Cyclopentenediones with two alkyl substituents at C2 led to mixtures of diastereomers that could be purified by recrystallization to give single diastereomeric products with 99% ee. A variety of α-aryl and α-alkyl isocyanoacetates with different alkyl ester moieties were competent substrates in the reaction. However, methyl isocyanoacetate without α-substitution, provided the distereomerically pure product in racemic form.



Scheme 41. Desymmetrization of cyclopentenediones upon [3+2]-cycloaddition with α-substituted-α-isocyano esters.

4.4. Enantioselective synthesis of pyrroloindolines via cascade reactions

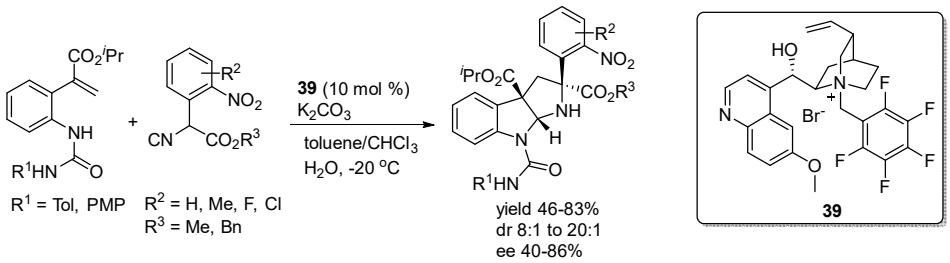
Pyrroloindolines are core scaffolds embedded in a large array of biologically active natural products. Recently, a cascade approach from isocyanoacetates and 2-(2'-aminophenyl)acrylates involving initial [3+2]-cycloaddition followed by intramolecular nitrogen addition to the resulting imine has been devised for the synthesis of this kind of compounds (Scheme 42).



Scheme 42. Cascade approach to pyrroloindolines from isocyanoacetates and 2-(2'-aminophenyl)acrylates.

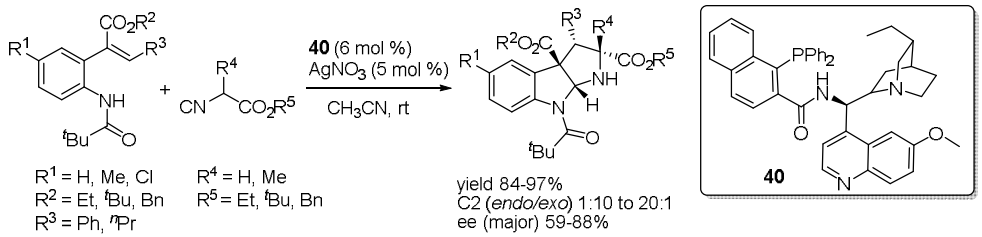
Two enantioselective versions for this approach have been developed. Phase transfer catalysis (PTC) using a chiral quinidinium salt **39** was applied by Smith (Scheme 43).[80] The scope of the enantioselective reaction was explored using a range of α-aryl-substituted isocyanides. In general the reaction furnished pyrroloindolines with up to three stereocenters, some of them being all-carbon quaternary, in good yield and good to excellent diastereoselectivity as well as good enantioselectivity. The reaction allowed different ester

groups on the isocyanide. A limitation is that an *ortho*-nitro group in the α-aryl substituent of the isocyanide, to provide sufficient acidity, is required for satisfactory results.



Scheme 43. Enantioselective synthesis of pyrroloindolines under PTC conditions.

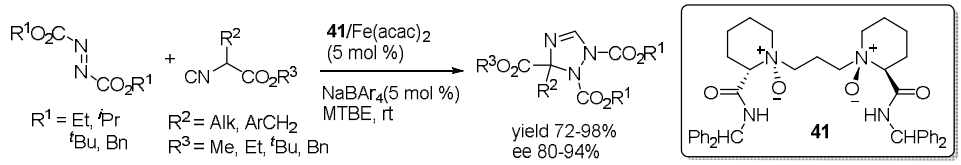
On the other hand, Gong performed a similar cascade reaction using a silver catalyst formed by silver nitrate and a *Cinchona* alkaloid-derived amidophosphine ligand **40** related to that developed by Dixon (Scheme 44).[81] 2-[2'-(Pivalamido)phenyl]-acrylates either unsubstituted or bearing a methyl group or a Cl atom at the 5-position of the phenyl group reacted with ethyl isocyanoacetate to give the expected cascade products having the C2 *endo* substitution in good yields, with low diastereoselectivity and good enantioselectivity (up to 85 % ee). Acrylates having aryl or alkyl groups on their β-position (R^3=Ph, ^{n}Pr) reacted with the same isocyanoacetate furnishing the tricyclic product as only one diastereomer with moderate to good enantiomeric excesses (80%, 76% ee, respectively). Benzyl α-isocyanpropanoate (R^4=Me, R^5=Bn) reacted with reversal of diastereoselectivity to provide the product with C2 *exo* substitution. Finally, 2-[2'-(amino)phenyl]-acrylates having other *N*-protecting groups (Ts, Ac, Boc) led to racemic products under the reaction conditions.



Scheme 44. Enantioselective synthesis of pyrroloindolines under Ag/organocatalysis.

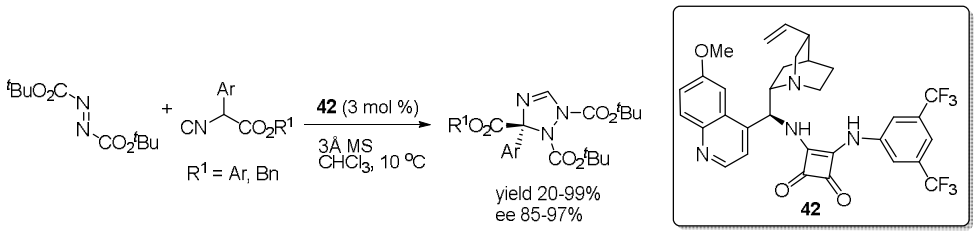
5. Enantioselective synthesis of 1,2,4-triazolines

In 2011, Jørgensen described the first straightforward synthesis of 1,2,4-triazolines through the formal [3+2]-cycloaddition of α-isocyano esters and azodicarboxylates under basic catalysis. Although the authors made some attempts to carry out the reaction enantioselectively under phase-transfer conditions with catalyst **39**, the expected products could be obtained only with moderate enantioselectivity (up to 60% ee).[82] Later in 2013, Liu and Feng reported the reaction of α-substituted isocyanoacetate esters with azodicarboxylates catalyzed by an iron complex generated from $Fe(acac)_2$ and the *N*,*N*'-dioxide ligand **41** (Scheme 45).[83] The reaction was carried out in MTBE as the solvent in the presence of $NaBAr_4$ (Ar=3,5-$(CF_3)_2C_6H_3$), which favored higher enantioselectivities. The reaction was carried out with several isocyanoacetates having alkyl or benzyl groups at the α-position. Regarding the ester group, benzyl, methyl and *tert*-butyl isocyano esters were allowed, *tert*-butyl esters giving the highest enantioselectivity. On the other hand, the alkoxy group in the diazocarboxylate showed little effect on the reaction outcome. The chiral 1,2,4-triazolines were obtained with good yields (72-98%) and moderated to good enantioselectivity (80-94% ee).



Scheme 45. Iron-catalyzed enantioselective synthesis of 1,2,4-triazolines.

The same year, Zhao and Shi reported a similar reaction catalyzed by the *Cinchona* alkaloid-derived squaramide **42** (Scheme 46).[83] α-Aryl isocyanoacetates reacted efficiently with azodicarboxylates to give the corresponding triazolines with good yields and high to excellent enantiomeric excesses. Isocyanoacetates without a substituent or bearing an electron-donating group on the benzene ring afforded the expected products in slightly higher yields along with better enantioselectivities than similar substrates with electron-withdrawing groups. The presence of a substituent at the *ortho* position decreased the reaction rate but the triazolines were still obtained with good enantiomeric excesses. Unfortunately α-alkyl- or α-benzyl-substituted isocyanoacetates did not react or gave very low yield (20%), respectively, while unsubstituted ethyl isocyanoacetate gave the expected product with low yield (45%) and ee (54%). On the other hand, the alkoxy group in the diazocarboxylate was amenable to variation, although the best results were obtained with di-*tert*-butyl azodicarboxylate. However, 1,2-diphenyldiazene did not react under the reaction conditions.



Scheme 46. Organocatalytic enantioselective synthesis of 1,2,4-triazolines.

Conclusion

α-Isocyano esters (isocyanoacetates) occupy an important place in the field of organic synthesis. Two special features of these compounds, the high α-acidity due to the presence of the isocyano and ester groups, as well as the electrophilic ability of the isocyano group, allow isocyano esters to undergo tandem/cascade reactions with unsaturated systems involving nucleophilic addition followed by intramolecular attack of the resulting anion to the empty orbital of the isocyano group. These reactions, which may be considered as formal [3+2]-cycloadditions, are useful for the synthesis of five-membered *aza*-heterocycles. In the last years a number of procedures to achieve these reactions in catalytic enantioselective fashion using either metal catalysis, organocatalysis or cooperative catalysis have been developed. Oxazolines and imidazolines have been prepared through the reaction of α-isocyano esters and carbonyl compounds or their imines. Structurally diversed pyrrolines and related compounds have been obtained from electrophilic C-C double bonds conjugated with electron-withdrawing groups, while reaction of α-isocyano esters and azodicarboxylates has open a new route to 1,2,4-triazolines. Despite these advances, there are still limitations in terms of substrate applicability and selectivity, which will require further work. Furthermore, the extraordinary and unusual reactivity of α-isocyano esters open exciting research expectatives for new enantioselective applications.

Acknowledgements

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