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Authors: Pablo Martinez Pardo, Adrián Laviós, Amparo Sanz-Marco, Carlos Vila, José Pedro, and Gonzalo Blay

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Enantioselective Synthesis of Functionalized Diazaspirocycles from 4-Benzylideneisoxazol-5(4*H*)-one derivatives and Isocyanoacetate Esters

Pablo Martínez-Pardo,[+] Adrián Laviós,[+] Amparo Sanz-Marco, Carlos Vila, José R. Pedro,* and Gonzalo Blay*

Departament de Química Orgànica, Universitat de València, C/ Dr. Moliner 50, E-46100-Burjassot (València), Spain. E-mail: jose.r.pedro@uv.es; gonzalo.blay@uv.es

[+]These authors contributed equally. Received: ((will be filled in by the editorial staff))

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Abstract. Enantioenriched spirocyclic compounds bearing three contiguous stereocenters and high functionalization were obtained through a formal [3+2] cycloaddition reaction catalyzed by a cooperative system. The spiro compounds were synthesized from 4-arylideneisoxazol-5-ones and isocyanoacetate esters using a bifunctional squaramide/Brønsted base organocatalyst derived from a Cinchona alkaloid and silver oxide as Lewis acid. This method afforded two out of the four possible diastereomers with good yields and high enantiomeric excess for both diastereomers.

Keywords: Asymmetric catalysis; Enantioselectivity; Heterocycles; Cycloaddition; Spiro compounds

Organic spirocycles are unique compounds that feature two rings connected through just one shared carbon (the spiroatom). This structural feature is often present in natural products isolated from different sources, from plants to marine organisms.[1] Examples of spirocompounds of natural origin include horsfiline, a natural product isolated from *Horsfielda superba*,[1d] β-vetivone, extracted from vetiver oil,[1e] or (–)-gleenol isolated from the brown alga *Taonia atomaria* (Figure 1).[1f] Spirocyclic compounds have also found some interesting applications as privileged ligands for asymmetric catalysis such as spinol,[2] or in the production of circularly polarized photoluminescence.[3] Furthermore, the spirocyclic motif is becoming a prevalent template in drug discovery,[4] since this structural feature conveys both increased three-dimensionality for potential improved activity, and novelty for patenting purposes. An example of spirocyclic drugs is the marketed fenspiride,[5] used for the treatment of some respiratory diseases (Figure 1).

For these reasons, the synthesis of spirocyclic compounds has received a growing interest in the last decade.[6] In this context, the catalytic enantioselective construction of a chiral spiro quaternary carbon results especially challenging. The synthesis of quaternary stereocenters, in general, is hampered by the huge steric hindrance and low steric dissimilarity of the two carbon substituents on the prochiral center. Furthermore, the generation of a spiro quaternary stereocenter often requires overcoming ring strain to install useful functionalities, and the diastereoselectivity needs to be controlled because the construction of spiro systems is often accompanied by the formation of additional stereocenters.

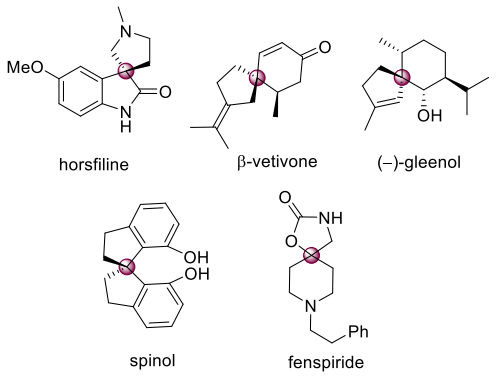

Figure 1. Selected examples of natural products and drugs with spirocyclic structure.

Among the different methodologies designed to achieve this goal, [7] cycloaddition reactions with cyclic compounds bearing an exocyclic double bond result especially appealing because of its simplicity and the vast variety of reaction partners that can participate in this kind of reactions. Five-membered nitrogen-containing heterocycles are privileged structures in medicinal chemistry. Among these, the spiropyrroline, [8] as well as the spiroisoxazol-5-one[9] scaffolds are featured in a great number of natural products, biologically active compounds and pharmaceuticals.

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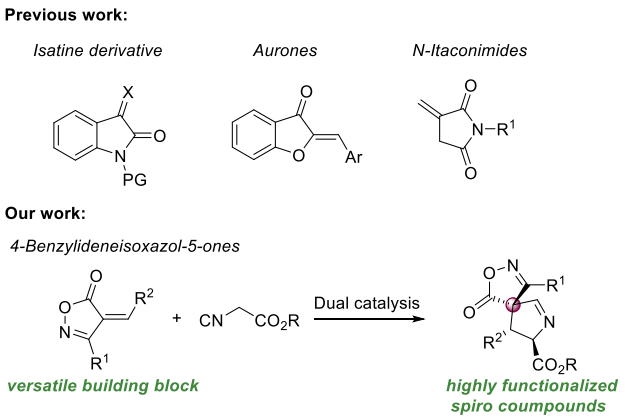
Isocyanoacetate esters are versatile scaffolds in organic synthesis and can participate as formal 1,3-dipoles in cycloaddition reactions leading to five-membered nitrogen-containing heterocycles. [10] In the last years, this approach has been used in the enantioselective synthesis of several spirocyclic compounds (Scheme 1). Thus, the groups of Zhong, Wang, Yan, Shi and He have reported the addition of isocyanoacetate esters to different isatin derivatives for the preparation of spirooxindoles. [11] Also recently, the groups of Shao/He and Zhao have reported the synthesis of spirocycles by the reaction of isocyanoacetate esters with aurones or *N*-itaconimides, respectively. [12]

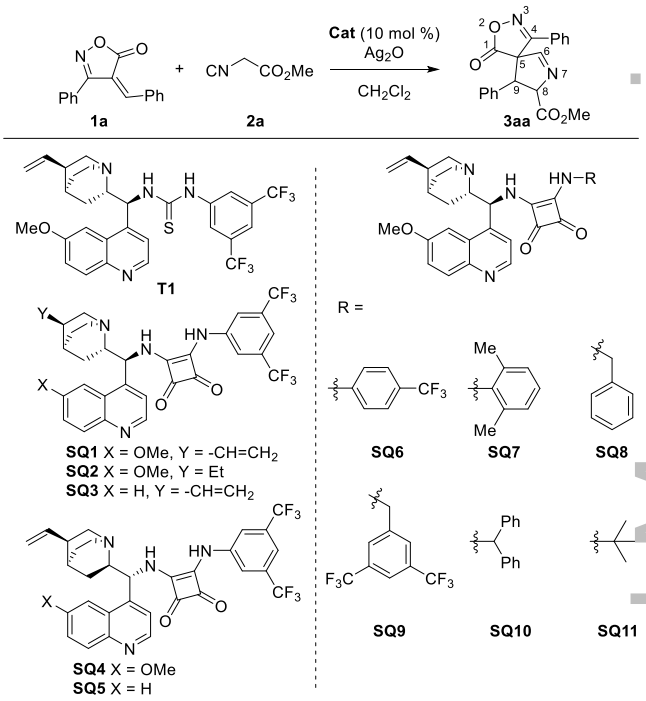
On the other hand, 4-arylideneisoxazol-5-ones, featuring an isoxazole-5-one ring with an exocyclic double bond, are structures present in natural products and other biologically active compounds, and have raised increased interest as electrophiles in Michael-type reactions, including organocatalyzed reactions. Moreover, the isoxazole-5-one ring is a versatile building block being used as synthetic equivalent of alkynes or ketones among others. [13] Following our research on enantioselective cycloaddition reactions with isocyanoacetate esters, [14] we report here the synthesis of chiral hybrid diazaspirocyclic compounds[15] combining a pyrroline and an isoxazol-5-one ring, via the formal [3+2] cycloaddition reaction of 4-benzylideneisoxazol-5-ones and isocyanoacetate esters (Scheme 1).



Scheme 1. Synthesis of spiro compounds employing isocyanoacetates as pronucleophiles.

In the onset of our research, the reaction between methyl isocyanoacetate (**2a**) and benzylidene-3-phenylisoxazol-5-one (**1a**) in dichloromethane was chosen to optimize the reaction conditions (Table 1). We started by checking bifunctional thiourea **T1** and squaramide **SQ1** catalysts in the presence of silver oxide following conditions previously established in our group, [14] which performed in a similar way providing the expected product **3aa** with good diastereoselectivity but low enantioselectivity (Table 1, entries 1 and 2). We also observed that silver oxide alone was able to catalyze the diastereoselective reaction in a non-enantioselective manner (Table 1, entry 3). To avoid this undesired background reaction, we performed the reaction with **T1** or **SQ1** in the absence of silver oxide (Table 1, entries 4 and 5). However, although in both cases the enantiomeric excess of the reaction product was improved under these conditions, the reaction required longer times and product **3aa** was obtained in low yield despite total consumption of the starting material. Also we observed that **SQ1** provided better enantioselectivity than **T1**.

Table 1. Reaction of methyl isocyanoacetate (**2a**) and benzylidene-3-phenylisoxazol-5-one (**1a**). Conditions and



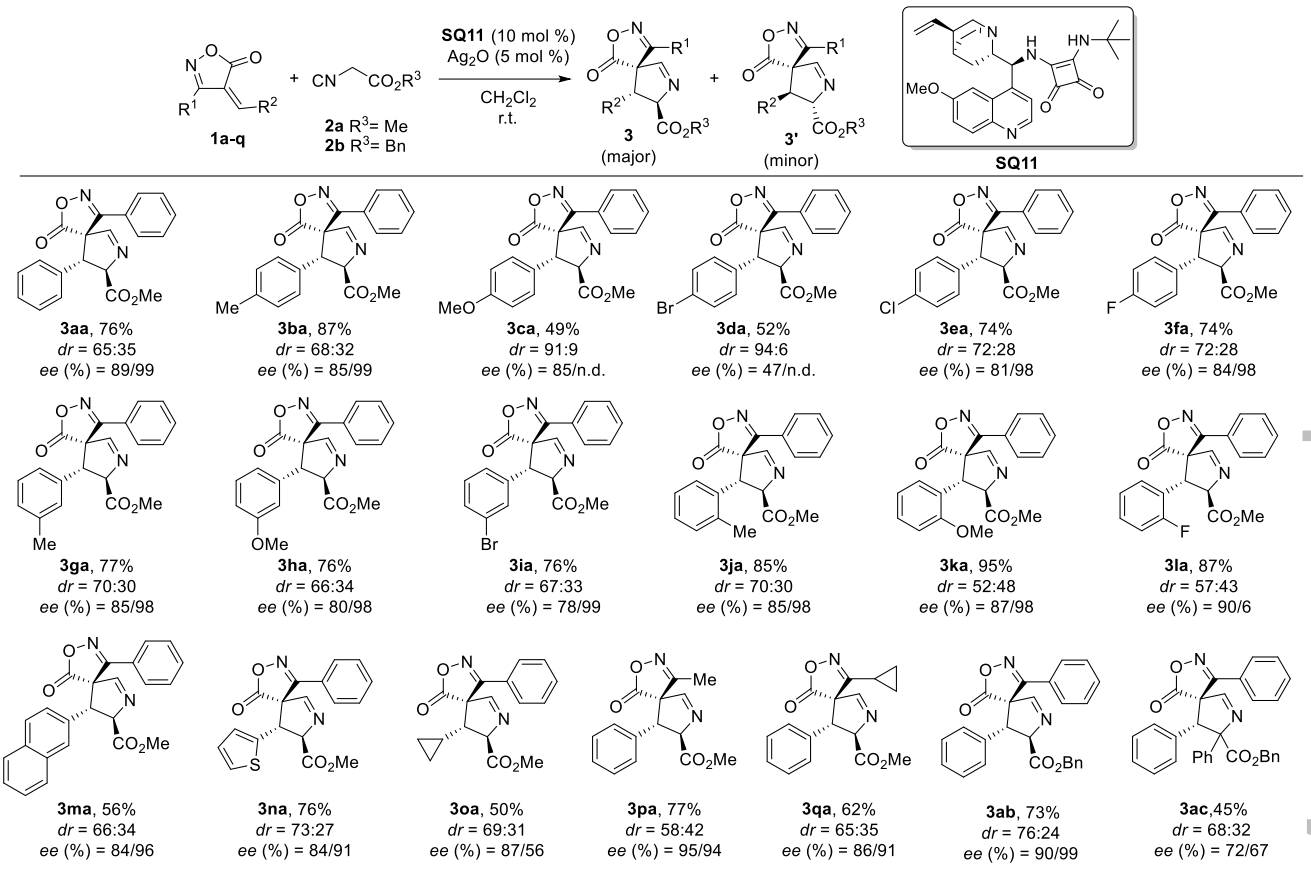
catalyst screening.[a]

Entry	cat	Ag_2O	yield (%)	dr[b]	*ee* (%)[c]
1[d]	**T1**	5 mol %	54	91:9	38/60
2[d]	**SQ1**	5 mol %	44	89:11	39/44
3[d]	-	5 mol %	70	95:5	-
4[d]	**T1**	-	18	81:19	57/76
5[d]	**SQ1**	-	12	95:5	85/n.d.
6	**SQ1**	-	traces	n.d	89/n.d.
7	**SQ1**	5 mol %	55	75:25	80/98
8	**T1**	5 mol %	72	95:5	58/n.d.
9	**SQ2**	5 mol %	55	92:8	30/n.d.
10	**SQ3**	5 mol %	48	74:26	75/98
11	**SQ4**	5 mol %	47	79:21	-54/-93
12	**SQ5**	5 mol %	51	74:26	-71-94
13	**SQ6**	5 mol %	47	84:16	52/93
14	**SQ7**	5 mol %	67	84:16	30/95
15	**SQ8**	5 mol %	67	76:24	80/99
16	**SQ9**	5 mol %	71	79:21	80/96
17	**SQ10**	5 mol %	66	81:19	65/95
18[e]	**SQ9**	5 mol %	75	74:26	84/96
19	**SQ11**	5 mol %	76	65:35	89/99

[a] Conditions: **1a** (0.1 mmol), **2a** (0.13 mmol), **cat** (0.01 mmol), Ag_2O, CH_2Cl_2 (5 mL). [b] Determined by ^1H NMR.

[c] Determined by HPLC over chiral stationary phases. [d] Reaction carried out in 1 mL of CH_2Cl_2. [e] Reaction carried out in 7.5 mL of CH_2Cl_2.

Table 2. Reaction of arylidene-3-phenylisoxazol-5-ones **1** and isocyanoacetate esters **2**. Reaction scope.[a]



[a] Conditions: **1** (0.25 mmol), **2** (0.33 mmol), **SQ11** (0.025 mmol), Ag_2O (0.0125 mmol), CH_2Cl_2 (19 mL); dr determined by ^1H NMR; *ee* determined by HPLC over chiral stationary phases.

Further investigation revealed that **1a** decomposed in great extent by standing in solution at the reaction concentration, bringing about the low yields observed. We also found out that decomposition rate of **1a** decreased in more diluted solution, unfortunately, the reaction of **1a** with the isocyano ester **2a** also slowed down and led to a small yield of **3aa**, although with high *ee* (Table 1, entry 6). At this point, addition of silver oxide to the diluted reaction accelerated the reaction and allowed to obtain the spirocyclic compound in 55%, with fair diastereoselectivity (75:25), and high enantiomeric excess for both diastereomers, 80% *ee* for the major diastereomer and 98% *ee* for the minor one (Table 1, entry 7). However, performing the reaction under these conditions with thiourea **T1** notably decreased the enantioselectivity (Table 1, entry 8).

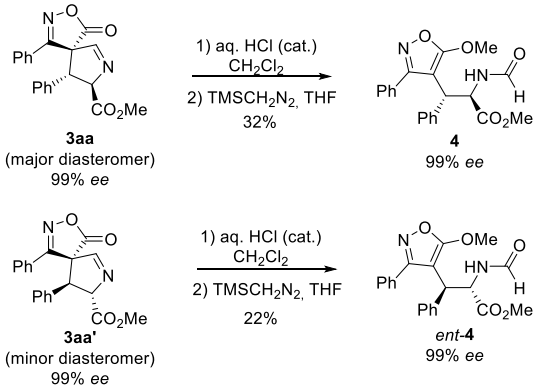
Other solvents and temperatures were tested, but none of these changes improved the results (see SI). Next, we carried out a screening of squaramide catalysts (Table 1, entries 9-17, see also SI). Catalyst **SQ2** derived from dihydroquinine improved the diastereoselectivity, but the enantiomeric excess suffered a dramatic decrease (Table 1, entry 9). Squaramide **SQ3**, derived from cinchonidine, performed with similar diastereoselectivity as **SQ1** but with silightly lower enantioselectivity (Table 1, entry 10). Squaramides **SQ3** and **SQ4**, derived from quinidine and cinchonine, respectively, delivered the opposite enantiomer but with lower enantioselectivity (Table 1, entries 11 and 12). Therefore, we decided to test other squaramides derived from quinine bearing an aniline or benzylamine derivative at the second amide moiety (Table 1, entries 13-17). Squaramides **SQ8**, **SQ9** lead to similar results as **SQ1**, with slightly better diastereoselectivity for **SQ9** (Table 1, entries 7, 15 and 16). At this point, further dilution of the reaction mixture allowed to improve the enantiomeric excess of **3aa** (Table 1, entry 18), despite some decrease of diastereoselectivity. Eventually, squaramide **SQ11** derived from *tert*-butylamine offered the best yield (76%), a slightly decreased diastereoselecivity (65:35), but the highest enantiomeric excess for both diastereomers (89% and 99%, respectively), under diluted conditions (Table 1, entry 19). Further attempts to improve the results by modifying the silver source, catalyst loading or **SQ**/Ag molar ratios were not successful (see SI).

Under the reaction conditions recorded in Table 1, entry 19, we studied the scope of the reaction (Table

2). Methyl isocyanoacetate (**2a**) was reacted with a number of 4-benzylidene-3-phenylisoxazol-5-one derivatives **1a-l** (R^1 = Ph, R^2 = aryl) bearing differently substituted aromatic rings attached to the exocyclic double bond. In general, the spirocyclic products were obtained in moderate to excellent yields, moderate diastereoselectivities and high enantiomeric excesses in both diastereomers, somehow depending on the position and electronic nature of the substituent. Groups of either electron-donating or electron-withdrawing character at the para position of the phenyl group were tolerated. However, in the case of *p*-halophenyl groups the size and electronegativity of the halide was determinant, the enantioselectivity of the reaction increasing through the series Br<Cl<F (products **3da**, **3ea**, **3fa**).

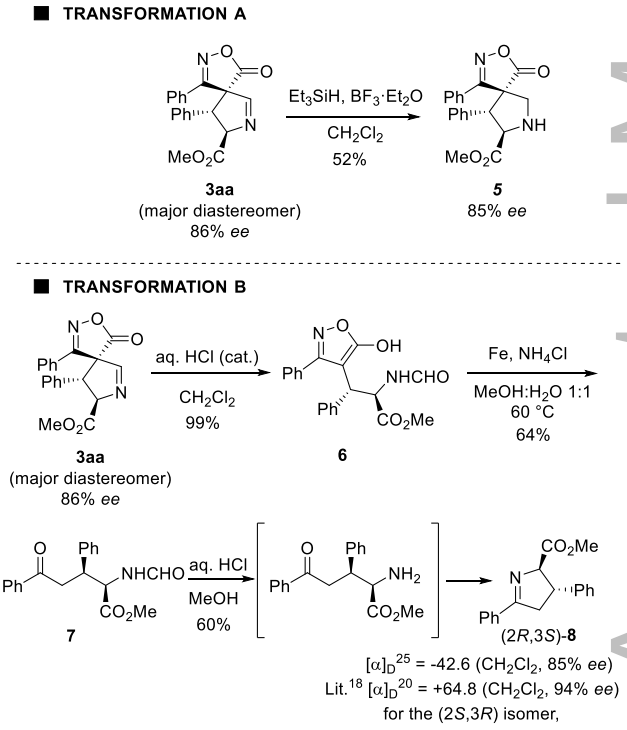
Electron-donating or electron-withdrawing groups at the *meta* (**1g-i**) or *ortho* (**1j-l**) positions were also compatible with the reaction. From these, compounds **1** having an *ortho*-substituted phenyl ring gave better yields although lower diastereomeric ratios, keeping the high enantiomeric excess in all the cases (products **3ja**, **3ka** and **3la**). Furthermore, the isoxazolone derivative can have a bulky naphthyl group (**1m**) providing spirocycle **3ma** with similar results to those obtained with phenyl derivatives.

Finally, compounds **1n** and **1o** bearing a heterocyclic 2-thienyl or a cyclopropyl group also reacted with methyl isocyanoacetate to give the expected products with good enantioselectivity. The substituent at the 3 position of the 4-benzilideneisoxazol-5-one can also be a methyl group, thus compound **1p** (R^1 = Ph, R^2 = Me) reacted with methyl isocyanoacetate providing **3pa** in good yield, fair diastereoselectivity and excellent enantioselectivity for both diastereomers. On the other hand, compound **1q** bearing a cyclopropyl group at this position yielded **3qa** with good results. Finally, benzyl isocyanoacetate (**2b**) could be used instead of methyl isocyanoacetate to give **3ab** upon reaction with **1a** with good results in terms of both diastereo- and enantioselectivity. The reaction can also be performed with α-substituted isocyanides such as methyl 2-isocyano-2-phenylacetate, although in this case the reaction product **3ac** was obtained with low yield (45%) and moderate diastereoselectivity and enantiomeric excess. Compound **3ac** was not stable and decomposed on standing in the NMR tube for a few days.



Scheme 2. Hydrolysis and *O*-methylation of product **3aa**.

It should be remarked that the cycloaddition reaction between the arylidene-3-phenylisoxazol-5-ones **1** and the isocyanoacetate esters **2** only gives two out of the four possible diastereomers. The relative stereochemistry of the two diastereomers produced in the reactions was determined by a combination of NMR experiments and synthetic transformations. Multiple $^1H–^1H$ nuclear Overhauser effect (NOE) spectroscopy experiments carried on **3ha** showed a *trans* disposition between the methyl ester group and the *m*-methoxyphenyl substituent, as well as a *trans* disposition between the phenyl group bonded to the isoxazol-5-one moiety and the *m*-methoxymethyl group, in the major diastereomer (see SI, Figure S1). A similar relative stereochemistry was assumed for the major diastereomer in all the cycloaddition reactions studied. Furthermore, when both diastereomers of compound **3aa** (**3aa'**) were separated[16] and subjected to hydrolysis and *O*-methylation, they afforded enantiomer products **4** and *ent*-**4**, respectively, without loss of enantiomeric excess (Scheme 2 and also SI). This fact, indicated that both diastereomers **3aa** and **3aa'** had identical configuration at the spiro carbon and opposite configurations at the two other stereogenic centers.



Scheme 3. Synthetic modifications and determination of the absolute stereochemical configuration of **3aa**.

Scheme 3 outlines some synthetic transformations of compound **3aa**. Transformation A shows the selective reduction of the imine group in the pyrrolinic moiety to give the pyrrolidine spirocycle **5** with moderate yield (52%) and preservation of the

enantiomeric excess, using triethylsilane and trifluoroborane as a Lewis acid catalyst. Transformation B exploits the transformation potential of the isoxazol-5-one structure and was used to determine the absolute stereochemistry of compound **3aa** by chemical correlation with a compound of known stereochemistry **8**. Acidic hydrolysis of the major diastereomer **3aa** gave quantitatively formamide **6**, which was transformed into the amidoketone **7** by reductive cleavage of the isoxazol-5-one ring with iron. [17] Further acidic hydrolysis of the formamide and concomitant cyclization of the intermediate aminoketone afforded pyrroline **8** without loss of enantiomeric excess and in 54% yield over the three steps. Compound **8** obtained in this way was assigned the (2*R*,3*S*) configuration as it showed identical spectroscopical features and opposite optical rotation sign compared with the known compound (2*S*,3*R*)-**8**.[18] Accordingly, the absolute stereochemistry for compound **3aa** (major diastereomer) should be (5*S*,8*R*,9*R*) and for compound **3aa'** (minor diastereomer) it should be (5*S*,8*S*,9*S*). For the remaining compounds **3**, the stereochemistry of both diastereomers was assigned upon the assumption of a uniform stereochemical pathway.[19]

In conclusion, we have developed an efficient, diastereo- and enantioselective synthesis of novel, highly functionalized spirocyclic compounds bearing a spiro quaternary and two tertiary stereocenters. The new spirocycles feature pyrroline and isoxazol-5-one rings, which are privileged structures in medicinal chemistry. The synthesis involved a formal [3+2] cycloaddition reaction between 4-arylideneisoxazol-5-ones and isocyanoacetate esters using a cooperative catalytic system that englobes a bifunctional squaramide/Brønsted base organocatalyst derived from a *Cinchona* alkaloid and silver oxide as Lewis acid. The transformation featured broad scope and simple operation, and delivered the resulting products in good yields, good diastereoselectivity (only two out of four possible diastereomers) and high enantiomeric excess. The potential applicability of the method has been shown by several transformations.

Experimental Section

Experimental procedure for the enantioselective reaction. Methyl isocyanoacetate (**2a**, 30 µL, 0.33 mmol) was added to a solution of 4-arylideneisoxazol-5-one (**1**, 0.25 mmol), organocatalyst **SQ11** (11.9 mg, 0.025 mmol) and silver oxide (2.9 mg, 0.0125 mmol) in dichloromethane (19 mL) protected from light. The reaction was stirred until complete consumption of compound **1** (TLC, *ca.* 12 h). The product **3** was obtained as a two diastereomer mixture after purification by flash chromatography eluting with hexane:EtOAc mixtures.

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[19] For a mechanistic proposal and stereochemical model see SI.

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