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Enantioselective synthesis of chiral oxazolines from unactivated ketones and isocyanoacetate esters by synergistic silver/organocatalysis†

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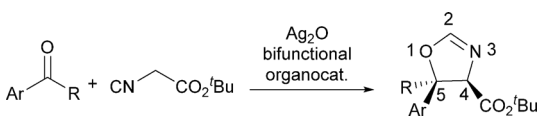
A multicatalytic approach that combines a bifunctional Brønsted base–squaramide organocatalyst and Ag^+ as Lewis acid has been applied in the reaction of unactivated ketones with *tert*-butyl isocyanoacetate to give chiral oxazolines bearing a quaternary stereocenter. The formal [3+2] cycloaddition provided high yields of the corresponding *cis*-oxazolines with good diastereoselectivity and excellent enantioselectivity, being applied to aryl–alkyl and alkyl–alkyl ketones.

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,[1] and they have found wide application as privileged chiral ligands in asymmetric catalysis.[2] In particular, the chiral 2-oxazoline-4-carboxyl framework is present in a large number of natural products with antibacterial, antiviral or antitumor activities.[3] These compounds are also intermediates in the synthesis of b-hydroxy-a-amino acids *via* hydrolysis or reduction of the oxazoline ring.[4] Accordingly, the development of procedures for the efficient enantioselective synthesis of such compounds is of great interest to synthetic and medicinal chemists. In 1970 Schöllkopf described a straightforward procedure for the synthesis of 2-oxazoline-4-carboxylate esters *via* a formal [3+2] cycloaddition reaction between ethyl isocyanoacetate and carbonyl compounds catalyzed by sodium cyanide.[5] Since then, different experimental conditions have been implemented[6] to achieve this reaction even in an enantioselective fashion. Thus, the catalytic asymmetric version has been widely studied with aldehydes under metal,[7] organo,[8] or mixed metal-organo catalysis.[9] In contrast, the asymmetric reaction of isocyanoacetates with ketones, which provides oxazolines having a quaternary stereocenter, has been scarcely studied. Two examples involving 1,2-dicarbonyl compounds have been reported. Zhao and Shi achieved the addition of 2-phenylisocyanoacetates to isatins using an amine-thiourea organocatalyst obtaining spirooxindole oxazolines with good diastereo- and enantioselectivity,[10] while Chen and Huang have also used a thiourea organocatalyst to carry out the reaction between isocyanoacetates and a-keto esters with good enantioselectivity and moderate diastereoselectivity.[11] Furthermore, Dixon has reported the, so far, only example of this kind of reaction with unactivated aryl–alkyl ketones giving rise to *trans*-4-carboxyl-2-oxazolines with good diastereo- and enantioselectivity.[12] Despite these advances, limitations regarding stereoselectivity and the substrate scope still remain strong. Therefore, the development of new procedures for this formal [3+2] cycloaddition that allow modifying the diastereoselectivity and/or expanding the application to other unactivated ketones is highly desirable.

In this communication we report a new catalytic procedure for the reaction of *tert*-butyl isocyanoacetate with unactivated ketones which provides *cis*-4-carboxyl-2-oxazolines in a complementary mode to the reaction described by Dixon (Scheme 1).

Our strategy is based on a multicatalytic approach that combines a bifunctional Brønsted base–squaramide organocatalyst and Ag^+ as Lewis acid (Fig. 1). In this catalytic system, the squaramide moiety would provide electrophilic activation of the ketone through hydrogen bonding at the same time as the coordination of Ag^+ to the isocyano group would facilitate the deprotonation of the isocyanoacetate by the Brønsted base



Scheme 1 Formal [3+2] cycloaddition of ketones and isocyanoacetate ester.

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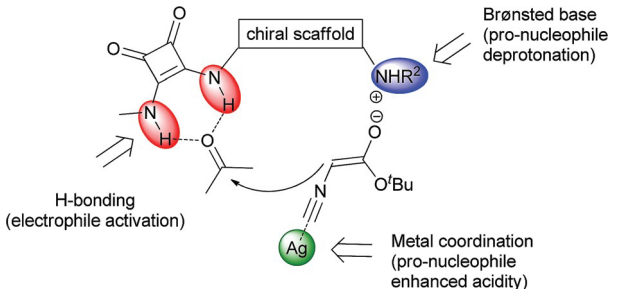


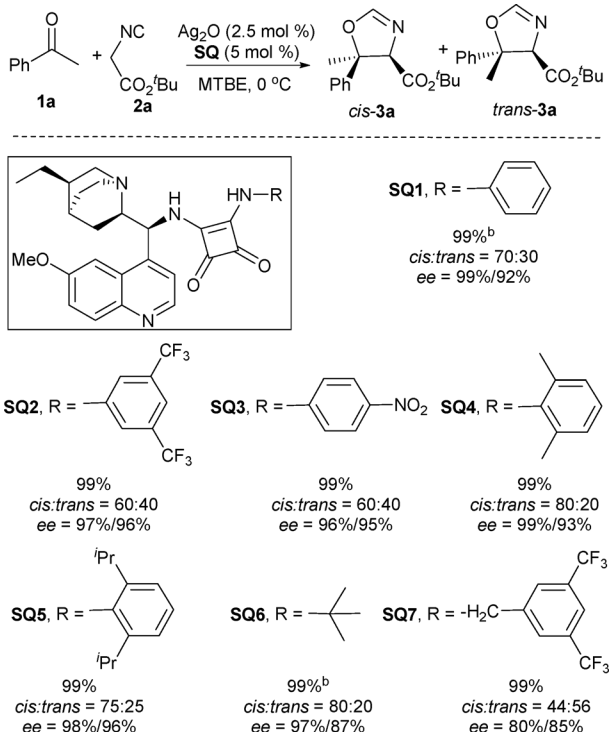
Fig. 1 Multicatalytic approach.

organocatalyst, enhancing the reaction rate *via* this double activation of the pronucleophile.[13]

The reaction of acetophenone (1a) with *tert*-butyl isocyanoacetate (2) in methyl *tert*-butyl ether (MTBE) was selected as a model system to assess the performance of several Ag_2O/dihydroquinine–squaramide catalytic systems, which were employed in a 1 : 2 ratio of metal oxide and organocatalysts (Table 1).‡

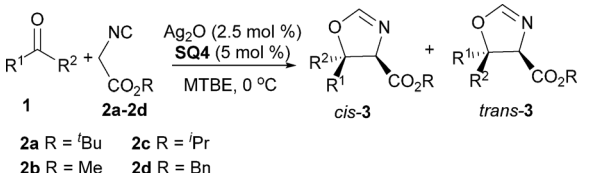
All the organocatalysts (5 mol%) tested in combination with silver oxide (2.5 mol%) provided oxazoline 3a in quantitative yield after 24 hours of reaction. In all the cases, except with SQ7 derived from a benzylic amine, the *cis* oxazoline was obtained as the major diastereomer. This result contrasts with that reported by Dixon, who obtained the *trans* isomer as the major product with his catalyst. Most of the squaramides tested gave the expected oxazolines with excellent enantiomeric excesses.

Table 1 Organocatalyst screening[a]



[a] 1a (0.25 mmol), 2 (0.32 mmol) Ag_2O (0.0063 mmol), SQ (0.0125 mmol), MTBE (8 mL), 0 °C. [b] Reaction carried out at r.t.

Table 2 Substrate scope of the formal [3+2] cycloaddition[a]



Entry	1	2	R^1	R^2	*t* (h)	3	Yield[b] (%)	*cis* : *trans*[c]	ee[d] (%)
1	1a	2a	Ph	Me	26	3a	99	80 : 20	99/93
2	1b	2a	4-MeC_6H_4	Me	20	3b	79	77 : 23	99/90
3	1c	2a	4-$MeOC_6H_4$	Me	72	3c	70	78 : 22	98/99
4	1d	2a	4-BrC_6H_4	Me	48	3d	99	75 : 25	98/93
5	1e	2a	4-$NO_2C_6H_4$	Me	20	3e	95	56 : 44	96/95
6	1f	2a	3-MeC_6H_4	Me	13	3f	88	62 : 38	99/97
7	1g	2a	3-$MeOC_6H_4$	Me	14	3g	60	70 : 30	98/93
8	1h	2a	3-ClC_6H_4	Me	14	3h	75	74 : 26	99/91
9	1i	2a	3-$NO_2C_6H_4$	Me	13	3i	97	63 : 37	95/90
10	1j	2a	2-MeC_6H_4	Me	24	3j	91	91 : 9	99/89
11	1k	2a	2-$MeOC_6H_4$	Me	16	3k	99	95 : 5	99/—
12	1l	2a	2-ClC_6H_4	Me	12	3l	99	92 : 8	98/92
13	1m	2a	2-$NO_2C_6H_4$	Me	12	3m	99	73 : 30	95/30
14	1n	2a	2-Thienyl	Me	20	3n	81	45 : 55	92/98
15	1o	2a	Ph	iPr	12	3o	63	98 : 2	97/—
16	1p	2a	Ph	$PhCH_2$	48	3p	99	61 : 39	97/95
17	1q	2a	Me	Me	20	3q	85	—	96
18	1r	2a	$-(CH_2)_5-$		20	3r	96	—	95
19	1s	2a	iPr-CH_2	Me	48	3s	71	70 : 30	98/56
20	1t	2a	Cyclopropyl	Me	48	3t	81	56 : 44	97/87
21	1a	2b	Ph	Me	72	3u	82	80 : 20	96/84
22	1a	2c	Ph	Me	48	3v	76	70 : 30	97/90
23	1a	2d	Ph	Me	48	3w	78	80 : 20	96/82

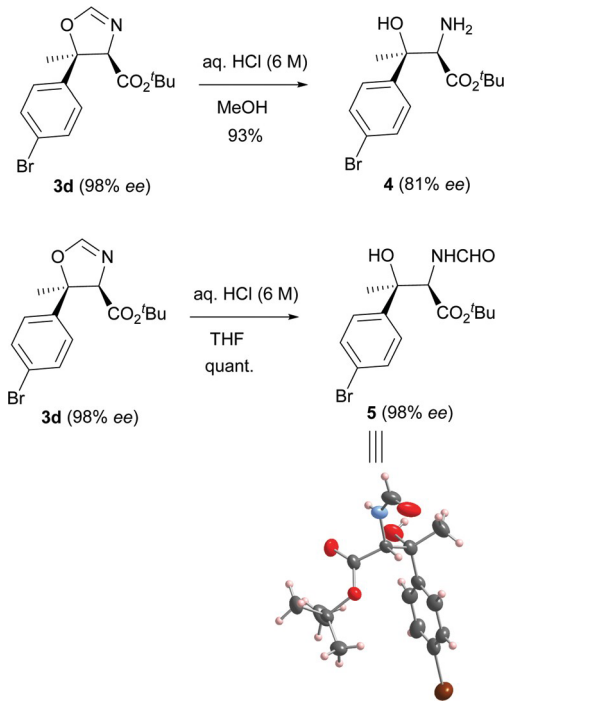
[a] 1 (0.25 mmol), 2 (0.32 mmol) Ag_2O (0.0063 mmol), SQ4 (0.0125 mmol), MTBE (8 mL), 0 °C. [b] Yield of isolated products. [c] Determined by ^1H NMR. [d] Determined by HPLC over chiral chromatography phases.

Squaramides SQ4 and SQ6, derived from 1,6-dimethylaniline and *tert*-butyl amine, respectively, also provided the best diastereoselectivity, keeping high enantiomeric excesses.

Using SQ4/Ag_2O as the best combination, we proceeded to study the scope of the reaction of *tert*-butyl isocyanoacetate with different ketones (Table 2).§ Several acetophenone derivatives substituted with either electron-withdrawing or electron-donating groups at different positions of the aromatic ring afforded the *cis*-configured oxazolines 3a–3m with good yields and fair to good (62 : 38 to 95 : 5) diastereoselectivities (Table 2, entries 1–13) except for nitroacetophenones (Table 2, entries 5, 9 and 13). Diastereoselectivities were especially high with *ortho*-substituted acetophenones (Table 2, entries 10–13).

In all the cases, both diastereomers were obtained with excellent enantiomeric excesses, higher than 95% for the major *cis*-diastereomer. In general, the reaction with substituted acetophenones took place with slightly lower diastereoselectivity but higher enantiomeric excesses than those obtained with Dixon's catalyst for similar substrates.

The reaction also proceeded with heterocyclic 2-acetylthiophene (1n) to give the corresponding oxazoline 3n with low diastereoselectivity, slightly favoring the *trans* isomer, but still with excellent enantiomeric excesses for both diastereomers (Table 2, entry 14). Isopropyl ketone 1o afforded the *cis* oxazoline



Scheme 2 Hydrolysis of compound *cis*-3d. ORTEP plot for the X-ray structure of compound 5. Flack parameter = 0.019(10), Hooft parameter = 0.037(10).

3o as almost only one diastereomer with 97% ee (Table 2, entry 15), while deoxybenzoin (1p) yielded a 61 : 39 diastereomer mixture of oxazolines 3p with excellent enantioselectivity for both isomers (Table 2, entry 16). Finally, we studied the reaction with several aliphatic ketones, which are challenging substrates for this reaction. Remarkably, acetone (1q), which provided the corresponding oxazoline almost in the racemic form under Dixon's conditions, gave oxazoline 3q in excellent yield and enantiomeric excess (Table 2, entry 17). Similarly, cyclohexanone (1r) gave spirocyclic oxazoline 3r in 96% yield and 95% ee (Table 2, entry 18). Unsymmetrical ketones such as 4-methyl-2-pentanone (1s) and acetylcyclopropane (1t) lead to the corresponding oxazolines 3s and 3t with moderate diastereoselectivity but excellent enantioselectivity for the major diastereomers (Table 2, entries 19 and 20), demonstrating the broad scope of the reaction with respect to unactivated ketones.

Other isocyanoacetate esters were tested (Table 2, entries 21–23). Methyl- (2b), isopropyl- (2c) and benzyl- (2d) isocyanoacetates reacted with acetophenone (1a) to give the expected oxazolines 3u–3w with good yields, diastereoselectivities and excellent enantioselectivities for the major diastereomer. Methyl- and benzyl-isocyanoacetates gave similar diastereomeric ratios to those of the *tert*-butyl ester, while isopropyl isocyanoacetate gave lower diastereoselectivity.

Oxazolines are synthetic precursors of amino alcohols. Thus, treatment of oxazoline 3d with aqueous hydrochloric acid in MeOH for 24 hours provided amino alcohol 4 in 93% yield, although with a noticeable loss of enantiomeric excess (Scheme 2). Similarly, partial hydrolysis of compound 3d upon treatment with aqueous hydrochloric acid in THF gave a quantitative yield of hydroxyformamide 5 without any noticeable loss of ee, which could be crystallized and subjected to X-ray analysis.¶ In this way, the absolute stereochemistry of compound 5 could be determined, and hence compound *cis*-3d was assigned the 4*R*,5*R* configuration. The stereochemistry of the remaining oxazolines *cis*-3a–3r was assigned on the assumption of a uniform stereochemical pathway. On the other hand, the absolute stereochemistry of the minor *trans*-diastereomers 3a–3r was assigned as 4*R*,5*S* by comparing with the data reported by Dixon for these compounds in his pioneering work.[12]

In summary, we have developed a new catalytic enantioselective procedure for the reaction between unactivated ketones and isocyanoacetates to give chiral oxazolines bearing a quaternary stereocenter. Our strategy is based on a multicatalytic approach that combines a bifunctional Brønsted base–squaramide organocatalyst and Ag^+ as a Lewis acid. The reaction provides the corresponding *cis*-oxazolines with good diastereoselectivity and excellent enantioselectivity. In this way, our method may be considered complementary to that of Dixon since we obtain *cis*- instead of *trans*-oxazolines. Furthermore, our reaction shows a broader substrate scope and can be applied not only to aryl–alkyl but also to alkyl–alkyl ketones. Further research addressed to develop new applications of this reaction is underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ In the absence of either Ag_2O or squaramide, no progress of the reaction between 1a and 2a was observed after 48 h at 0 ºC. These control experiments indicate that catalysis requires the synergistic action of both metal and the organocatalyst.

§ Squaramide SQ4 (6.6 mg, 0.0125 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a 25 mL round bottom flask followed by MTBE (8 mL) and ketone 1 (0.25 mmol). The flask was closed with a stopper and placed in an ice bath. After 5 min, *tert*-butyl isocyanoacetate 2 (48 mL, 0.330 mmol) was added and the mixture was stirred at 0 ºC until consumption of the ketone 1 (TLC). After this, the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure. A small aliquot was analyzed by ^{1}H NMR to determine the diastereomer ratio and by HPLC to determine the enantiomeric excess of products 3. The remaining crude was chromatographed on silica gel eluting with hexane:EtOAc mixtures (9 : 1 to 8 : 2) to obtain the separated diastereomers *cis*-3 and *trans*-3.

¶ CCDC 1818227 contains the supplementary crystallographic data for compound 5.

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