Catalytic diastereo- and enantioselective synthesis of 2-imidazolinones

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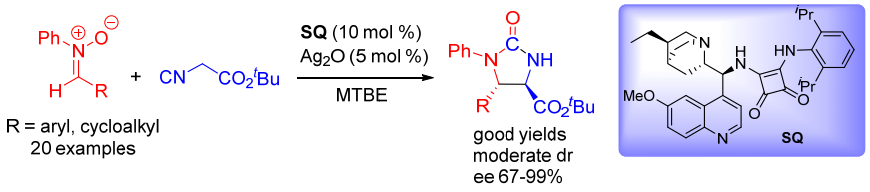
Supporting Information Placeholder

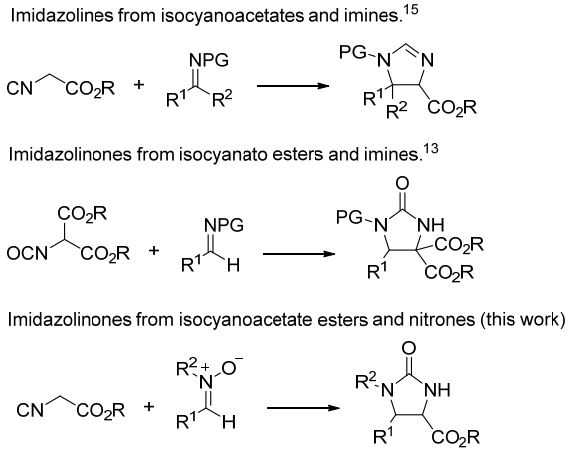


ABSTRACT: Chiral cyclic ureas (2-imidazolinones) were prepared by the reaction of nitrones and isocyanoacetate esters using a multicatalytic system that combines a bifunctional Brønsted base-squaramide organocatalyst and Ag^+ as Lewis acid. The reaction could be achieved with a range of nitrones derived from aryl- and cycloalkylaldehydes with moderate diastereo- and good enantioselectivity. A plausible mechanism involving an initial formal [3+3] cycloaddition of the nitrone and isocyanoacetate ester, followed by rearrangement to an aminoisocyanate and cyclization to the imidazolinone is proposed.

Cyclic ureas, in particular 2-imidazolinones, are structural units often found in natural products,[1] and biologically and pharmacologically interesting molecules, including HIV protease inhibitors,[2] 5-HT3 receptor and PX27 receptor antagonists,[3] NK1 antagonists,[4] and ACE inhibitor hypertensive drugs.[5] Chiral imidazolidin-2-ones have also been widely utilized as chiral auxiliaries,[6] chiral ligands,[7] and intermediates in organic synthesis.[8] For these reasons, many methodologies have been developed to generate these molecules. Examples include the carboxylation of 1,2-diamines,[9] intramolecular amidation reactions,[10] intermolecular diamidation reactions,[11] or reactions involving isocyanates.[12] However, only few procedures allow the enantioselective formation of the 2-imidazolinone ring and a C-C bond simultaneously.[13]

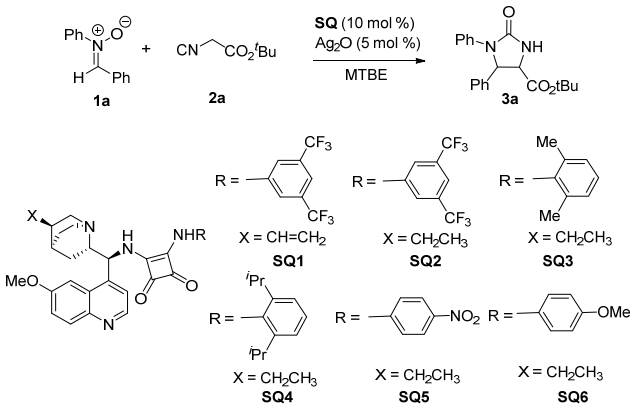
In recent years, isocyanoacetate esters have emerged as formal 1,3-dipoles that can react with different electrophilic unsaturated functional groups to give five-membered, nitrogen-containing heterocycles.[14] Thus, chiral imidazolines have been prepared by several authors from isocyano acetates and imines under different conditions.[15] Within this area, our group has contributed with the development of a highly enantioselective synthesis of 2-oxazolines from ketones and isocyanoacetate esters using a multicatalytic system that combines a bifunctional squaramide-Brønsted base and silver as Lewis acid.[16] Wishing to extend the structural diversity of compounds that can be prepared enantioselectively with this chemistry we became interested in studying other nitrogen-containing electrophiles. Herein we report the reaction of isocyanoacetates with nitrones, which are typical 1,3-dipoles used in cycloaddition reactions. The reaction provided chiral 2-imidazolinones instead of the expected [3+3] cycloaddition products.[17]

Scheme 1. Synthesis of imidazolines and imidazolinones from imine derivatives



The reaction of nitrone **1a** and *tert*-butyl isocyanoacetate (**2a**) was chosen to optimize the reaction conditions (Table 1). Following our methodology previously developed for the reaction with ketones, we tested different chiral squaramide organocatalysts in the presence of silver oxide in *tert*-butyl methyl ether as the solvent (Table 1). **SQ3** and **SQ4**, which are derivatives of dihydro 9-deoxy-9-*epi*-9-aminoquinine and 2,6-disubstituted anilines, provided the highest enantioselectivity for the major *trans* diastereomer (Table 1, entries 3 and 4).

Table 1. Screening of organocatalysts.[a]



entry	SQ	*t* (d)	yield (%)[b]	trans:cis[c]	ee$_{trans}$ (%)[d]
1	**SQ1**	1	83	46:54	70
2	**SQ2**	1	73	48:52	70
3	**SQ3**	1	75	71:29	84
4	**SQ4**	2	89	61:39	84
5	**SQ5**	2	70	55:45	58
6	**SQ6**	7	43	52:48	83

[a] Conditions: **1a** (0.13 mmol), **2a** (0,17 mmol), **SQ** (0.013 mmol), Ag_2O (0.0063 mmol), TBME (1 mL), room temperature. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR. [d] Determined by HPLC over chiral stationary phases.

Table 2. Effect of solvents and concentration.[a]

entry	SQ	solvent	[**1a**][b]	*t* (d)	yield (%)[c]	trans:cis[d]	ee$_{trans}$ (%)[e]
1	**SQ3**	MTBE	0.13	1	75	71:29	84/-6
2	**SQ4**	MTBE	0.13	1	83	61:39	84/-13
3	**SQ3**	dioxane	0.13	2	70	71:29	90/30
4	**SQ3**	toluene	0.13	2	71	70:30	87/3
5	**SQ3**	Et_2O	0.13	2	70	69:31	79/6
6	**SQ3**	EtOAc	0.13	2	60	65:35	79/6
7	**SQ3**	DCM	0.13	2	39	41:59	59:12
8	**SQ3**	dioxane	0.063	2	46	73:27	99/3
9	**SQ4**	dioxane	0.063	3	60	50:50	78/21
10	**SQ4**	MTBE	0.063	2	84	68:32	88/-9
11[f]	**SQ4**	MTBE	0.063	4	78	67:37	88/-3
12[g]	**SQ4**	MTBE	0.063	1	60	66:33	88/-2
13	**SQ4**	MTBE	0.042	4	78	71:29	90/-3

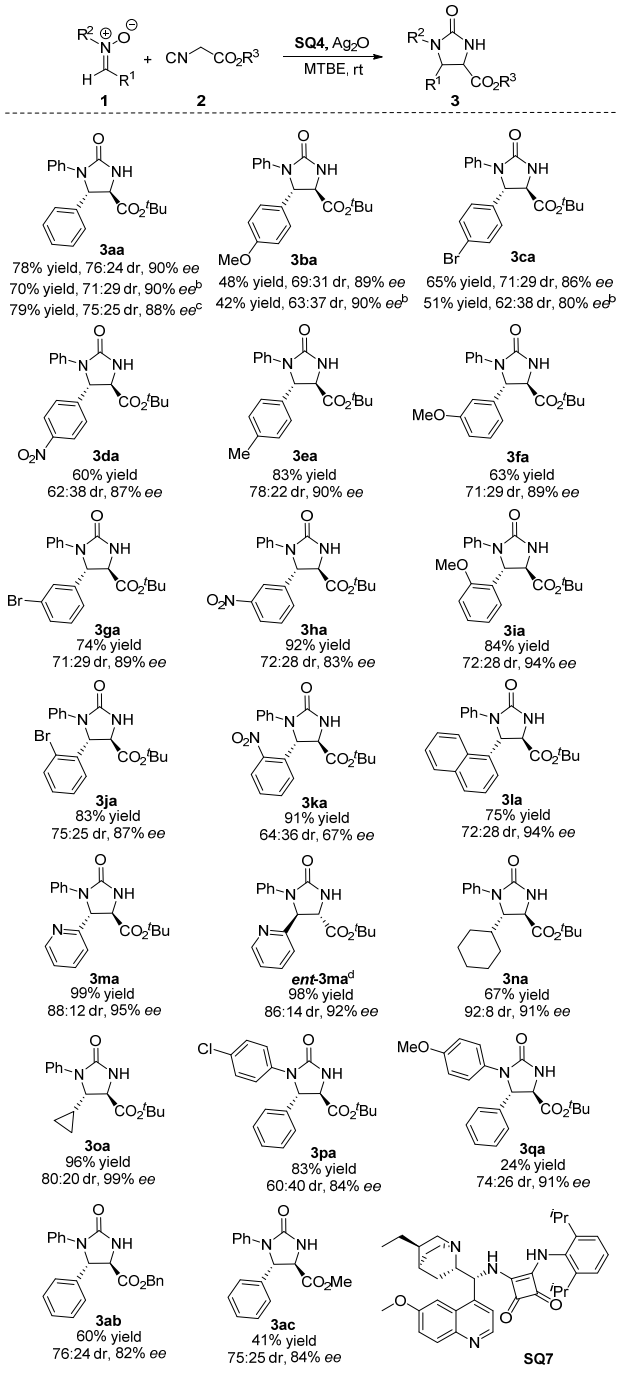
[a] Conditions: **1a** (0.13 mmol), **2a** (0.17 mmol), **SQ** (0.013 mmol), Ag_2O (0.0063 mmol), solvent, room temperature. [b] Molar concentration of **1a**. [c] Isolated yield after column chromatography. [d] Determined by ^{1}H NMR. [e] Determined by HPLC over chiral stationary phases. [f] Reaction carried out at 0 °C. [g] Reaction carried out at 35 °C

Further optimization was carried out first with organocatalyst **SQ3** (Table 2). From the different solvents tested (Table 2, entries 3-7), dioxane allowed to obtain the best diastereo- (*trans:cis* 71:29) and enantioselectivity (90%). By performing the reaction under more dilute conditions, the ee could be raised up to 99%, however with a huge detriment of yield (Table 2, entry 8). Other attempts to increase the yield and/or stereoselectivity with **SQ3** in dioxane were unsuccessful (see SI). Therefore, we turned our attention back to squaramide **SQ4**. This organocatalyst was tested in dioxane as the solvent under identical conditions as those previously used for **SQ3** providing compound **3aa** as a 1:1 mixture of diastereomers in 78% ee (Table 2, entry 9). Since dioxane seemed not to be a good solvent for this catalyst, the reaction was repeated in MTBE under dilute conditions yielding the expected urea **3aa** with fair diastereoselectivity (dr = 68:32) and high enantioselectivity (88% ee), without detriment in the yield (Table 1, entry 10). Attempts to improve the stereoselectivity by changing the reaction temperature were unsuccessful (Table 1, entries 11 and 12). Finally, a small increase of diastereo- and enantioselectivity could be obtained by further dilution of the reaction mixture (Table 1, entry 13).

Given the similar results obtained either with **SQ3** in dioxane (Table 2, entry 3) or with **SQ4** in MTBE (Table 2, entry 13), both reaction condition manifolds were tested with two nitrones **3b** and **3c** derived from *p*-substituted aldehydes (Scheme 2). The **SQ3**/dioxane system provided the expected ureas **3ba** and **3ca** with similar or lower stereoselectivities to those obtained with **SQ4**/MTBE, and in significant lower yields. Accordingly, the study of the reaction scope was continued under the optimized conditions for **SQ4** in MTBE. In general, the reaction conditions could be applied to the addition of *tert*-butyl isocyanoacetate (**2a**) with a large range of *N*-phenylnitrones derived from substituted benzaldehydes bearing substituents of different electronic nature in different positions of the aromatic ring. The chiral 2-imidazolinones **3aa**-**3ka** were obtained with fair to good diastereoselectivity (62:38 to 78:22) and high enantiomeric excesses (67-94%). The presence of electron-donating groups (Me, MeO) (**3ba**, **3ea**, **3fa**, **3ia**), favored higher enantioselectivities than electron-withdrawing groups (Br, NO_2) (**3ca**, **3da**, **3ga**, **3ha**, **3ja**, **3ka**) regardless of the position of these groups on the aromatic ring. The reaction also worked with the *N*-phenyl nitrone derived of the bulky 2-naphthylcarbaldehyde delivering urea **3la** with good yield, good dr and excellent ee. 2-Pyridine-derived nitrone **1m** reacted with *tert*-butyl isocyanoacetate to give compound **3ma** in quantitative yield, with good diastereoselectivity (dr = 88:12) and excellent enantioselectivity (95% ee). This result contrasts with those obtained with nitrones derived from nitrobenzaldehydes and it is quite surprising since both the pyridine and the nitrophenyl are electron-poor rings. Furthermore, the enantiomer of **3ma** could be also obtained with very good result by using squaramide **SQ7**, derived from dihydroquinidine, in place of **SQ4**. Cycloalkylcarbaldehyde-derived nitrones were also suitable substrates for the reaction. Compounds **3na** and **3oa**, bearing a cyclohexyl o cyclopropyl substituent, respectively, were obtained with very high enantiomeric excesses. The effect of the substituent on the N atom of the nitrone was also tested. *N*-(4-chlorophenyl) imine reacted with *tert*-butyl isocyanoacetate to give compound **3pa** with good yield but moderate diastereo- and enantioselectivity. On the other hand, the *N*-(4-methoxyphenyl) nitrone provided compound **3qa** with good enantioselectivity (91% ee) but in very low yield (24%), unfortunately. Finally, we tested the reaction with benzyl (**2b**) and methyl (**2c**) isocyanoacetates, none of them performing better than *tert*-butyl isocyanoacetate. The reaction could be carried out at 1 mmol

scale without noticeable effect on the results (Scheme 2, footnote c).

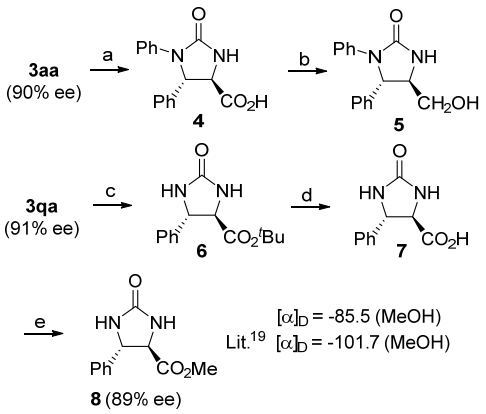
Scheme 2. Scope of the reaction of nitrones **1** and isocyanoacetates **2.**[a]



[a] Reaction conditions: **1** (0.25 mmol), **2** (0.33 mmol), **SQ4** (0.025 mmol), Ag_2O (0.013 mmol), MTBE (6 mL), rt. [b] Reaction conditions: **1** (0.13 mmol), **2** (0.17 mmol), **SQ3** (0.013 mmol), Ag_2O (0.0063 mmol), dioxane (1 mL), rt. [c] Reaction carried out with 1 mmol of **1a**. [d] Reaction carried out with squaramide **SQ7**. Yields after column chromatography, dr determined by ^{1}H NMR, *ee* determined by HPLC.

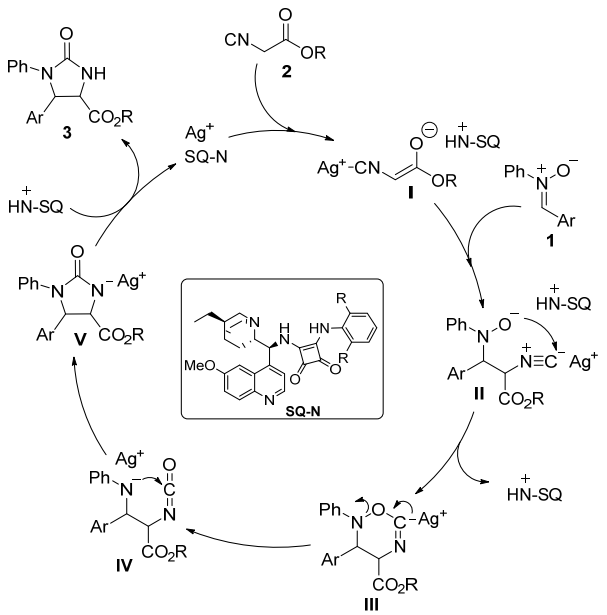
Scheme 3 outlines some synthetic modifications of compounds **3**. Deprotection of the *tert*-butyl ester can be achieved with trifluoroacetic acid to give acid **4** which can be converted into alcohol **5** after reduction with borane. On the other hand, the absolute stereochemistry of compounds **3** was determined by chemical correlation with a compound of known stereochemistry (Scheme 3). Thus, the N atom in compound **3qa** was deprotected with CAN to give compound **6**, which after hydrolysis of the *tert*-butyl ester with trifluoroacetic acid yielded acid **7**. Finally, Fisher esterification gave the ester **8**, which showed identical spectroscopic features and optical rotation sign as those described in the literature for (4*R*,5*S*)-**8,**[19] allowing to assign the stereochemistry of compound **3qa**. The absolute stereochemistry of the remaining compounds **3** was assigned upon the assumption of a uniform mechanistic pathway.

Scheme 3. Synthetic modifications and determination of the absolute stereochemistry of compounds **3**.[a]



[a] Reaction conditions: a) CF_3CO_2H/CH_2Cl_2, rt, 5h, 89%. b) $BH_3{\cdot}SMe_2$, THF, rt, 24 h, 76%. c) CAN (3.0 equiv), MeCN/H_2O, 0 °C to rt, 1 h, 75%. d) CF_3CO_2H/CH_2Cl_2, rt, 7 h, 87%. e) H_2SO_4 (cat), MeOH, reflux, 6 h, 89%

Scheme 4. Proposed catalytic cycle for the synthesis of 2-imidazolinones



Scheme 4 shows a plausible mechanism for the formation of cyclic ureas **3**. Thus, deprotonation of the isocyanoacetate **2** by

the basic bifunctional squaramide assisted by silver would give the corresponding enolate **I** that would undergo nucleophilic addition to the C-N double bond of nitrone **1** to give intermediate **II**, followed by intramolecular alkoxide addition to the isocyanide giving the formal [3+3] cycloaddition product **III**. This would rearrange to the amino isocyanate **IV**, which after amide addition would give the deprotonated imidazolinone **V**. Finally, protonation by the catalyst conjugate acid provides product **3** and releases the catalyst.

In summary, we have developed an unprecedented catalytic, connective, diastereo- and enantioselective synthesis of cyclic ureas (2-imidazolinones) by reaction of isocyanoacetate esters and nitrones. The reaction is catalyzed by a bifunctional Brønsted base-squaramide organocatalyst and Ag^+ as Lewis acid and provides the chiral *trans*-2-imidazolinones with good diastereoselectivity and high enantioselectivity in most of the examples tested, applicable to nitrones derived from aromatic and heteroaromatic aldehydes as well as nitrones derived from cycloalkylcarbaldehydes. The reaction most probably involves the initial formal [3+3] cycloaddition of the nitrone and isocyanoacetate ester, followed by rearrangement to an amino isocyanate and cyclization to the imidazolinone.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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