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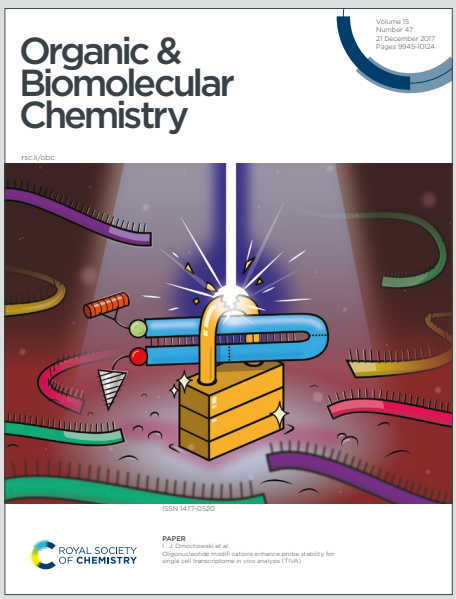

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ARTICLE

Organocatalytic Asymmetric Synthesis of Oxazolidino Spiropyrazolinones via *N,O*-acetalization/aza Michael addition domino reaction between *N*-Boc pyrazolinone ketimines and γ-hydroxyenones

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A squaramide-catalyzed asymmetric *N,O*-acetalization/aza Michael addition domino reaction between *N*-Boc ketimines derived from pyrazolin-5-ones and γ-hydroxyenones has been developed for the construction of pyrazolinone embedded spirooxazolidines. A hydroquinine derived bifunctional squaramide catalyst was found the most effective for this cascade spiroannulation. This new protocol allows the generation of two stereocenters and the desired products are obtained in good yields, moderate to good diastereoselectivity (up to 3.3:1 dr) and high enantioselectivity (up to >99% ee) from a range of substituted *N*-Boc pyrazolinone ketimines and γ-hydroxyenones. The developed protocol is amenable for a scale-up reaction.

Introduction

Chiral spiropyrazolone motifs, with a spiro-ring at the 4-position of the pyrazolone core, are present in many medicinally relevant compounds with potent biological activities as antitumor, analgesic, antibacterial, or anti-inflammatory agents.[1] For this reason, substantial research efforts have been invested toward the enantioselective synthesis of spirocyclic pyrazolone frameworks over the past years.[2]

Asymmetric approaches to access spiro[pyrrole-pyrazolone] derivatives through a catalytic cascade reaction, have been underdeveloped. In 1994 Grigg reported the synthesis of spiro[pyrrolidine–pyrazolones] via a [3+2] annulation of maleimide with an azomethine ylide.[3] More recently, Wang et al. developed a new strategy via organocatalytic asymmetric Michael/annulation of 4-isothiocyanato pyrazolones and alkynyl or allenyl ketones in the presence of quinine-derived bifunctional squaramide.[4] Stereoselective syntheses of chiral spiropyrazolones containing an O-heterocyclic ring have also been described in the literature. In 2018, Xu et al. reported a highly diastereo- and enantioselective synthesis of spirodihydrobenzofuran-pyrazolones by one-pot Michael/iodization/S_N2 nucleophilic substitution sequential catalytic reaction of pyrazolones and 2-hydroxy-β-nitrostyrene.[5] In a similar way, Xu and co-workers described a one-pot asymmetric synthesis of spiropyrazolone-linked benzofurans through a Michael addition/chlorination/nucleophilic substitution sequence.[6] Likewise, the bifunctional squaramide-catalysed reaction of in situ generated *o*-quinone methides with pyrazolin-5-ones and 4-halo pyrazolones provided easy access to chiral spiro-benzofuran pyrazolones.[7] Bhat and co-workers developed the enantioselective synthesis of spirooxindole dihydrofuran fused pyrazolones through a tertiary amine catalysed [3+2] annulation between isatin-derived Morita–Baylis–Hillman (MBH) carbonates and pyrazolone 4,5-diones.[8] Our group have recently described the first asymmetric synthesis of spirocyclic pyrazolone γ-butyrolactones by an NHC-catalysed [3+2] annulation reaction between pyrazolin-4,5-diones and enals.[9]

Chiral oxazolidines constitute an important structural motif present in many biologically active natural products and pharmaceuticals.[10] Despite their interest, the organocatalytic asymmetric synthesis of oxazolidines has been little studied. The group of Matsubara first developed an organocatalytic asymmetric route for the synthesis of 2,4-disubstituted chiral oxazolidines via formal [3+2] cycloaddition of γ-hydroxyenones with *N*-tosylaldimines, but the enantioselectivity was moderate (Scheme 1a).[11] Later, Terada described the [3+2] cycloaddition of β,γ-epoxysulfones with *N*-Boc-aldimines promoted by a chiral organosuperbase catalyst, to provide enantioenriched 1,3-oxazolidines with two stereogenic centers in a highly diastereo- and enantioselective manner (Scheme 1b).[12] Recently, Pan reported the asymmetric synthesis of 2,5-disubstituted oxazolidines via hemiaminal formation/Michael reaction between simple alkyl aldehydes and *N*-tosyl aminomethyl enones with excellent diastero- and enantioselectivities (Scheme 1c).[13] In 2021, the same group has also described the asymmetric synthesis of spirooxindole embedded oxazolidines via a domino reaction involving hemiaminal formation, followed by an aza-Michael reaction between isatin derived *N*-Boc ketimines and γ-hydroxyenones, promoted by a quinine derived bifunctional squaramide catalyst.[14] However, there is no report on the asymmetric synthesis of oxazolidino spiropyrazolinones, despite their potential to show bioactivities and other utilities.[15] Herein we develop the first organocatalytic asymmetric synthesis of these compounds via a cascade strategy involving hemiaminal formation,

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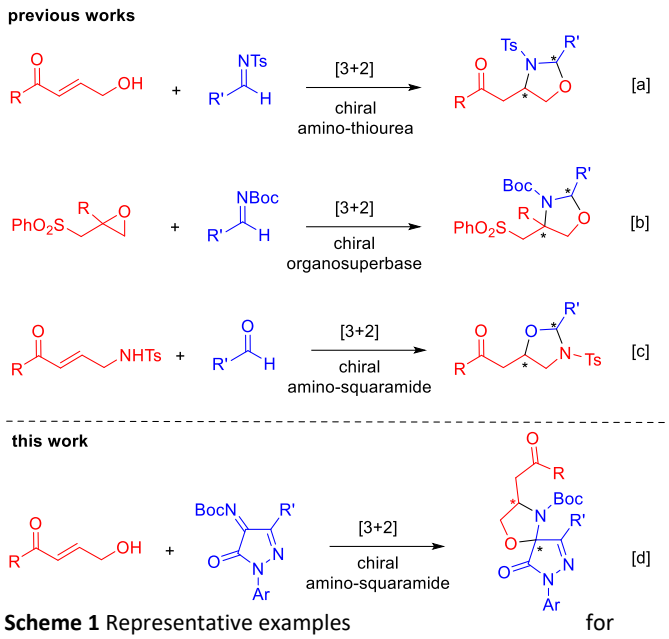
followed by an aza-Michael addition of *N*-Boc pyrazolinone ketimines[16] and γ-hydroxyenones (Scheme 1d).

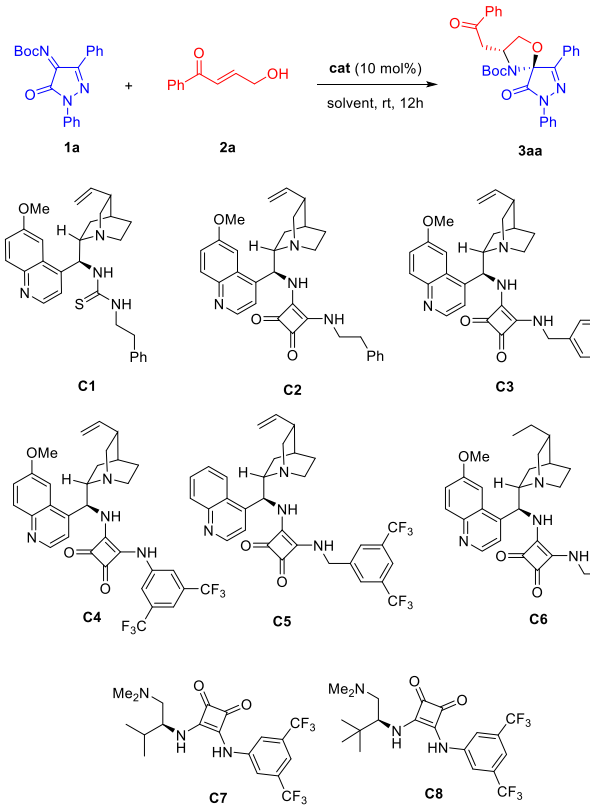


Scheme 1 Representative examples for organocatalytic asymmetric synthesis of oxazolidines.

Results and discussion

First, we investigated the reaction of *N*-Boc ketimine **1a** with 3-benzoyl-prop-2-en-1-ol (**2a**) as the model reaction in the presence of 10 mol% of bifunctional thiourea **C1**, derived from quinine, in toluene at room temperature (Table 1, entry 1). Satisfyingly, after stirring for 12 h, the desired spiro oxazolidine-pyrazolinone **3aa** was isolated in 89% yield as a mixture of diastereomers (1:1.2 dr). The enantiomeric excess of the major diastereomer was determined to be 62% ee and that of the minor 94% ee. When the quinine-derived bifunctional squaramide **C2** was used as catalyst, the diastereomeric ratio increased to 2.7:1. The enantiomeric excess of the major diastereomer was also improved to >99% ee, although the minor one was isolated with only 46% ee (Table 1, entry 2). Then, we analyzed the influence of the H-bonding donor group by comparing squaramide **C2** (bearing a phenethyl group) with **C3** (bis(trifluoromethyl)benzyl derivative) and **C4** (bis(trifluoromethyl)phenyl derivative) (Table 1, entries 2 and 3-4). Although with catalyst **C4** both diastereomers were achieved with high enantioselectivities, the diastereomeric ratio was worse (1.2:1 dr), so the best results so far were obtained with catalyst **C3**. To improve the diastereo- and enantioselectivity, additional attempts with the bifunctional squaramides **C5** and **C6** having bis(trifluoromethyl)benzyl groups were performed (Table 1, entries 5 and 6). Cinchonidine derived squaramide catalyst **C5** also failed to enhance the diastereoselectivity (1:1.5 dr) and a low conversion was achieved after 12 h of reaction, probably due to its lower solubility in toluene. Delightfully, hydroquinine-derived squaramide **C6** afforded adduct **3aa** in high yield (97%), the diastereomeric ratio was improved to 2.8:1 and enantiomeric excesses for two diastereomers were, respectively, 98% and 90% ee. Finally, valine and *tert*-leucine derived bifunctional catalysts **C7** and **C8** afforded the desired product with moderate diastereoselectivity (1:1.6) but high enantioselectivities in both diastereomers (Table 1, entries 7 and 8).

Table 1 Screening of catalysts and optimization of reaction conditions.[a]



Entry	Cat.	Solvent	Yield (%)[b]	dr (**3aa**:*epi*-**3aa**)[c]	ee (**3aa**)[c]	ee (*epi*-**3aa**)[c]
1	**C1**	PhMe	89	1:1.2	94	62
2	**C2**	PhMe	83	2.7:1	>99	46
3	**C3**	PhMe	78	2.7:1	98	80
4	**C4**	PhMe	79	1:1.2	>99	94
5	**C5**	PhMe	19	1:1.5	>99	54
6	**C6**	PhMe	**97**	**2.8:1**	**98**	**90**
7	**C7**	PhMe	88	1:1.6	92	78
8	**C8**	PhMe	87	1:1.6	98	88
9	**C6**	THF	72	1.1:1	>99	36
10	**C6**	Et_2O	92	2.8:1	>99	78
11	**C6**	CH_2Cl_2	90	1.6:1	>99	56
12	**C6**	MeCN	99	1:1.9	>99	-20
13[d]	**C6**	PhMe	92	2.8:1	98	88
14[e]	**C6**	PhMe	80	2.7:1	98	90

[a] Reaction conditions: 0.1 mmol of **1a** and 0.15 mmol **2a** in 1 mL of solvent using 10 mol% catalyst for 12 h. [b] Isolated yield after purification. [c] Determined by chiral HPLC analysis of the mixture of two diastereomers. [d] Reaction performed with 5 mol% catalyst for 48 h. [e] Reaction performed at 0 °C.

Then, a survey of different solvents such as THF, Et_2O, CH_2Cl_2 and MeCN (Table 1, entries 9-12) was also explored in reactions promoted by catalyst **C6**, but a better result was not found. In all cases, the enantioselectivity obtained for **3aa** was better, but the diastereocontrol was inferior, with the exception of diethyl ether,

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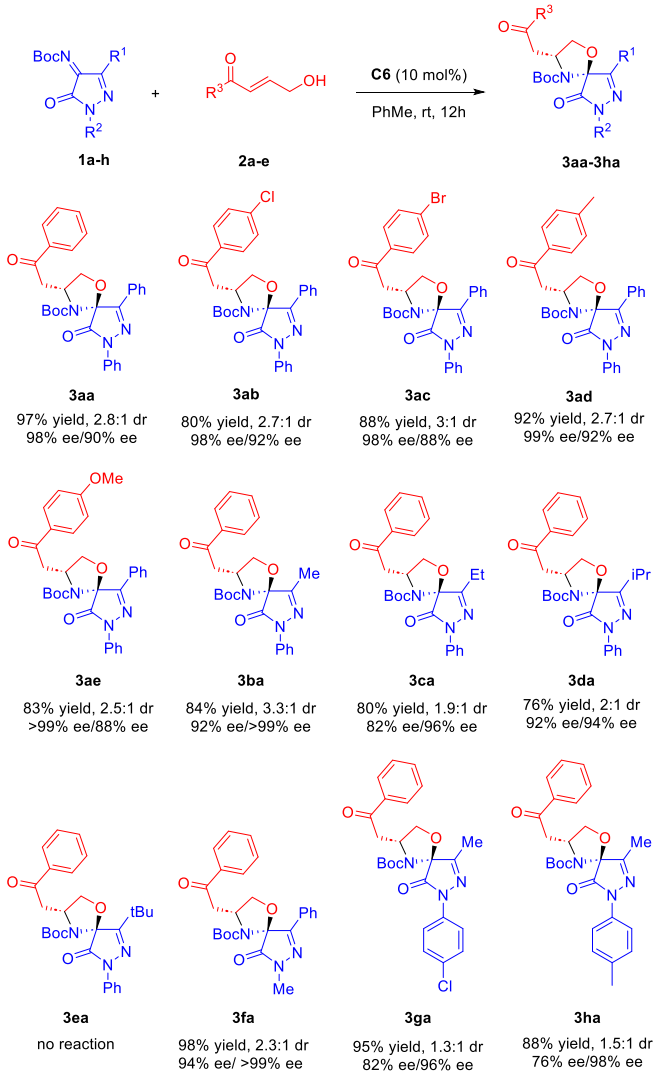
which provided similar results than toluene. Interestingly, the enantioselectivities obtained for *epi*-**3aa** depended strongly on the solvent, and another case of solvent-induced reversal of enantioselectivity was found with acetonitrile.[17] The catalyst loading of **C6** could be reduced to 5 mol% with similar chemical yield and stereoselectivity, but a considerable increase in reaction time was required (48 h, entry 13). The best result obtained at room temperature employing catalyst **C6** in toluene could not be ameliorated by lowering the reaction temperature to 0 °C (entry 14). With the optimised conditions in hand (Table 1, entry 6), the generality and the scope of the reaction was studied. Initially, different *para*-substituted phenyl γ-hydroxyenones (**2a-e**) were screened (Scheme 2), and gratifyingly, good results were achieved for the products **3aa-3ae** after a 12 h reaction time.[18] For example, 4-halo-substituted γ-hydroxyenones were tolerated in the reaction, providing adducts **3ab** and **3ac** with moderate diastereoselectivity (up to 3:1 dr) and high enantioselectivities. The reaction also worked with similar diastereo- and enantioselectivity with γ-hydroxyenones having a *p*-tolyl or anisole motif to deliver products **3ad** and **3ae**.

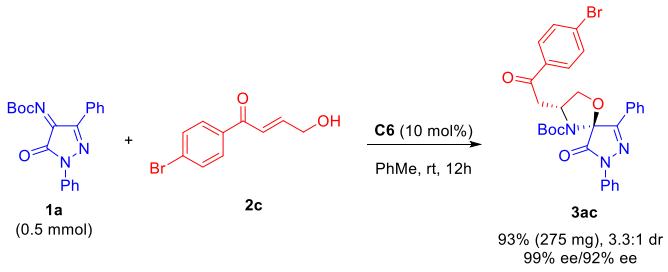


[a] Reaction conditions: 0.1 mmol of **1a-h** and 0.15 mmol **2a** in 1 mL of toluene using 10 mol% catalyst. [b] Isolated yield after purification. [c] Determined by chiral HPLC analysis of the mixture of two diastereomers.

Scheme 2 Scope of the reaction with different γ-hydroxyenones and *N*-Boc pyrazolinone ketimines.

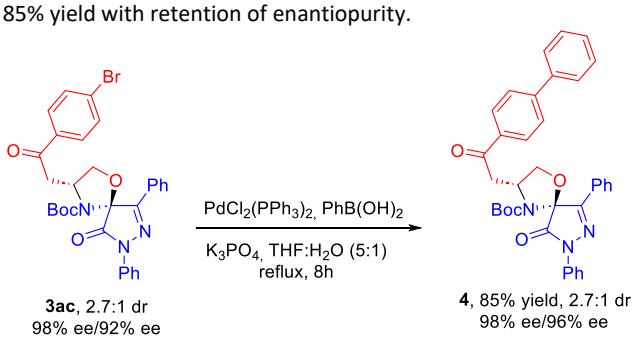
Next, the scope of *N*-Boc pyrazolinone ketimine **1** was investigated. Ketimines **1b-d**, with different alkyl substituents at the C-3 position (R^1, Scheme 2) were reacted with γ-hydroxyenone **2a** to produce the corresponding adducts **3ba**-**3da** in good yields. In particular, methyl-substituted imine **1b** afforded the desired product **3ba** with good diastereo- and enantioselectivity (3.3:1 dr, 92% ee). The imines **1c** and **1d** bearing ethyl and isopropyl substituent at C-3 position also worked well in the reaction albeit in somewhat diminished diastereoselectivity (1.9:1 and 2:1 dr). However, in the reaction of *N*-Boc ketimine **1e** bearing a *tert*-butyl group at the same position, no product was observed, presumably due to increased steric hindrance. Moreover, our methodology is also suitable for *N*-Boc ketimines with methyl (**1f**) or different aryl groups at the N-1 position (R^2, Scheme 2), whether it be electron-withdrawing (**1g**) or electrondonating (**1h**), and moderate diastereo- and acceptable enantioselectivity was detected for the corresponding products **3ga**-**3ha**.

Then, the performance of the method was examined at a larger scale, and the reaction of the *N*-Boc ketimine **1a** (0.5 mmol) with γ-hydroxyenone **2c** under the standard conditions afforded the desired product **3ac** in 93% yield without any loss of stereoselectivity (Scheme 3).



Scheme 3 Scale-up reaction of **1a** with **2c**.

To demonstrate the synthetic utility of our method, the preparation of biphenyl derivative **4** was achieved via a Pd-catalysed Suzuki coupling of the bromo derivative **3ac** with phenyl boronic acid (Scheme 4). The reaction progressed to deliver the desired product in 85% yield with retention of enantiopurity.



Scheme 4 Synthetic transformation of **3ac**.

The stereochemistry of the major diastereomer of compound **3ab** was determined to be (3*R*,5*S*) by a single crystal X-ray diffraction study (Figure 1).[19] The absolute configuration of the other products is expected to be the same by analogy.

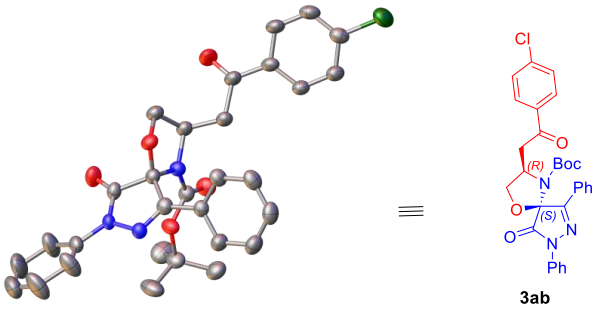
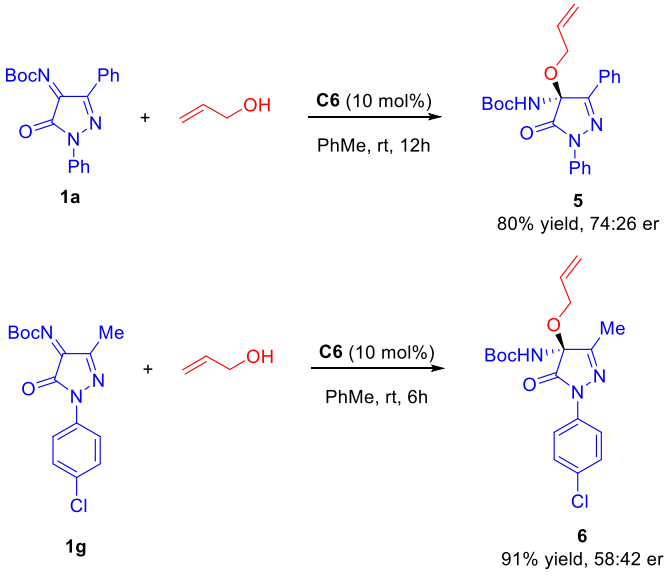


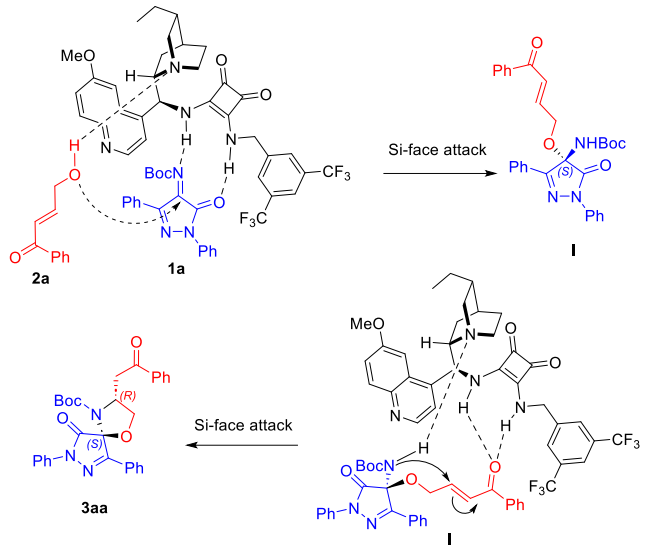
Figure 1 X-ray crystal structure of **3ab.**

Control experiments were performed in order to investigate the stereochemical outcome of this cascade reaction (Scheme 5). The reaction of ketimine **1a** with allyl alcohol mediated by **C6** in the optimised reaction conditions afforded the pyrazolone-derived *N,O*-aminal **5** in 80% yield and 74:26 er (Scheme 5). Similarly, reaction of ketimine **1g** with allyl alcohol under the same reaction conditions gave adduct **6** in 91% yield and 58:42 er. The enantiomeric ratio observed for products **5** and **6** matches with the diastereomeric ratio of products **3ac** and **3ga**. These results indicated that since the hemiaminal center is stable, the diastereoselectivity of this reaction might be due to the *N,O*-acetalization step.



Scheme 5. Enantioselective addition of allyl alcohol to N-Boc pyrazolinone ketimines **1a** and **1g**.

On the basis of the absolute configuration of the products, the results of control experiments and previous works,[14] a probable mechanism is proposed (Scheme 6), in which a bifunctional mode of activation operates. It is expected that the keto and imine groups of **1a** are activated by the squaramide moiety of the catalyst **C6**, whereas the OH group of **2a** is deprotonated by the quinuclidine motif of **C6**. The addition of the hydroxyenone **2a** takes place from the *Si*-face to provide hemiaminal **I**. The enone part of hemiaminal **I** is again activated by the squaramide moiety of **C6** and an intramolecular aza-Michael reaction, with Boc-carbamate as the nucleophile, proceeds from the *Si*-face of the enone to generate product **3aa**.



Scheme 6. Proposed mechanism.

Conclusions

In conclusion, we have developed the first organocatalytic asymmetric synthesis of pyrazolinone embedded oxazolidines via a domino reaction involving hemiaminal formation, followed by an aza-Michael reaction between pyrazolinone ketimines and γ-hydroxyenones. With 10 mol% of hydroquinine derived bifunctional squaramide, the oxazolidine products were synthesised in good to excellent yields, moderate to good diastereoselectivity and high enantioselectivity for a wide range of substrates. Due to the high pharmaceutical importance of pyrazolones, the developed protocol may prove useful for the development of new bioactive molecules.

Experimental

General Information

^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$ as solvent. Chemical shifts for protons are reported in ppm from TMS with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbons are reported in ppm from TMS and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad), coupling constants in Hertz, and integration. Specific rotations were measured on a Perkin-Elmer 341 digital polarimeter using a 1 mL cell with a 1-dm path length, and a sodium

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lamp, and concentration is given in g per 100 mL. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer and are reported in frequency of absorption (only the structurally most important peaks are given).

Flash chromatography was carried out using silica gel (230–240 mesh). TLC analysis was performed on glass-backed plates coated with silica gel 60 and F254 indicator and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Chiral HPLC analysis was performed on a JASCO HPLC system (JASCO PU-2089 and UV-2075 UV/Vis detector) with a quaternary pump, and on Hewett-Packard 1090 Series II instrument equipped with a quaternary pump, using Phenomenex Lux-cellulose-1 and Lux-i-cellulose-5; and Chiralpak IA and AD-H analytical columns (250 × 4.6 mm). Detection was monitored at 210, 220 and 254 nm. ESI mass spectra were obtained on an Agilent 5973 inert GC/MS system.

Commercially available organic and inorganic compounds were used without further purification. Solvents were dried and stored over microwave-activated 4Å molecular sieves.

Pyrazolinone ketimines **1a-h**,[16] hydroxyenones **2a-e**,[20] thiourea **C1**[21] and squaramides **C2-C8**[22] were prepared according to literature procedures. The racemic samples of spirocyclic pyrazolones were prepared by using an aquiral bifunctional thiourea derived from *N*[1], *N*[1]- dimethylethane-1,2-diamine[23] as catalyst.

General Procedure for Oxazolidino Spiropyrazolinones.

In a Wheaton vial equipped with a magnetic stirring bar the catalyst **C6** (0.01 mmol, 0.1 equiv) and the *N*-Boc ketimine **1a-h** (0.1 mmol) were weighed. Then toluene (1 mL) was added before the mixture was stirred. Several minutes later, hydroxyenone **2a-e** (0.15 mmol, 1.5 equiv) was introduced to the flask. After 16 h, the solvent was straight removed under reduced pressure and the residue was purified by column chromatography (hexane/ethyl acetate 10:1) to give the desired compound.

***tert*-Butyl (3*R*,5*S*)-9-oxo-3-(2-oxo-2-phenylethyl)-6,8-diphenyl-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3aa).** 49.6 mg (97% combined yield). Mixture of diastereomers, 2.8:1 dr. Major diastereomer (3*R*,5*S*). White solid. Mp 138-140 °C (from hexane). $[\alpha]^{25}_{D}$= -93.2 (c= 0.3, $CHCl_3$, 98% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9H), 3.17 (dd, *J*= 16.9, 10.9 Hz, 1H), 3.92 (d, *J*= 18.6 Hz, 1H), 4.22 (dd, *J*= 9.1, 2.0 Hz, 1H), 4.91 (t, *J*= 8.5 Hz, 1H), 5.03 (t, *J*= 8.2 Hz, 1H), 7.23 (t, *J*= 15.5, 1H), 7.43-7.56 (m, 7H), 7.59 (t, *J*= 7.4 Hz, 1H), 7.89-7.91 (m, 2H), 7.96 (dd, *J*= 10.9, 8.0 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.9, 42.6, 54.0, 71.2, 83.2, 91.1, 118.2, 125.3, 127.2, 128.1, 128.7, 129.0, 129.8, 130.9, 133.6, 136.2, 137.8, 151.3, 154.1, 168.8, 197.9. IR ν_{max}/cm^{-1} 512, 687, 760, 986, 1151, 1300, 1369, 1497, 1599, 1679, 1705, 1723, 2847, 2927, 2975. HRMS (ESI-TOF) m/z: calcd for $C_{30}H_{29}N_3NaO_5$ $[M+Na]^+$ 534.1999. Found 534.2008. HPLC (Lux i-Cellulose-5, n-hexane/2-propanol 90:10, λ= 210 nm, 0.8 mL/min): t_R (minor)= 33.3 min, t_R (major)= 40.4 min, (98% ee).

Minor diastereomer: Pale yellow oil. $[\alpha]^{25}_{D}$= +0.3 (c= 0.1, $CHCl_3$, 90% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 9H), 3.59 (dd, *J*= 19.6, 10.5 Hz, 1H), 4.31-4.37 (m, 2H), 4.82-4.86 (m, 2H), 7.24 (t, *J*= 6.5, 1H), 7.44-7.50 (m, 7H), 7.59 (t, *J*= 8.1 Hz, 1H), 7.87 (d, *J*= 10.8 Hz, 2H), 7.98 (d, *J*= 7.8 Hz, 2H), 8.03 (d, *J*= 7.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.7, 41.8, 53.6, 73.1, 83.2, 90.6, 113.8, 118.5, 125.4, 126.4, 128.2, 128.7, 128.9, 129.0, 130.5, 131.1, 133.5, 136.3, 137.8, 150.2, 154.4, 168.7, 198.5. **HPLC** (Lux i-Cellulose-5, n-hexane/2-propanol 90:10, λ= 210 nm, 0.8 mL/min): t_R (minor)= 9.9 min, t_R (major)= 11.3 min, (90% ee).

***tert*-Butyl (3*R*,5*S*)-3-(2-(4-chlorophenyl)-2-oxoethyl)-9-oxo-6,8-diphenyl-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3ab).** 43.2 mg (80% combined yield). Mixture of diastereomers, 2.7:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 2.7H, minor), 1.24 (s, 6.3H, major), 3.11 (dd, *J*= 16.8, 10.9 Hz, 0.7H, major), 3.54 (dd, *J*= 18.1, 9.7 Hz, 0.3H, minor), 3.88 (dd, *J*= 16.7, 1.8 Hz, 0.7H, major), 4.21 (dd, *J*= 9.1, 2.0 Hz, 0.7H, major), 4.28-4.33 (m, 0.6H, minor), 4.83-4.86 (m, 0.6H, minor), 4.86-4.89 (m, 0.7H, major), 5.02 (t, *J*= 8.1 Hz, 0.7H, major), 7.21-7.24 (1H), 7.43-7.57 (m, 7.2H), 7.85-7.90 (m, 3.3H), 7.96-7.98 (2.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.7, 27.9, 41.2, 42.6, 53.5, 53.9, 71.1, 73.0, 81.9, 83.3, 90.9, 91.1, 118.2, 118.5, 125.3, 126.4, 127.2, 128.7, 128.9, 129.0, 129.5, 129.6, 130.9, 131.1, 134.5, 134.6, 137.7, 140.0, 140.1, 150.2, 154.4, 168.7, 196.8, 197.3. IR ν_{max}/cm^{-1} 986, 1085, 1143, 1300, 1366, 1490, 1588, 1682, 1705, 1729, 2898, 2971. HRMS (ESI-TOF) m/z: calcd for $C_{30}H_{28}ClN_3NaO_5$ $[M+Na]^+$ 568.1610. Found 568.1618. HPLC (Lux i-cellulose 5, n-hexane/2-propanol 92:8, λ= 220 nm, 0.5 mL/min): major diastereomer: t_R (minor)= 51.4 min, t_R (major)= 59.1 min (98% ee); minor diastereomer: t_R (minor)= 14.7 min, t_R (major)= 17.9 min (92% ee).

***tert*-Butyl (3*R*,5*S*)-3-(2-(4-bromophenyl)-2-oxoethyl)-9-oxo-6,8-diphenyl-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3ac).** 51.8 mg (88% combined yield). Mixture of diastereomers, 3:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 2.7H, minor), 1.24 (s, 6.3H, major), 3.11 (dd, *J*= 16.8, 10.8 Hz, 0.7H, major), 3.54 (dd, *J*= 18.1, 9.7 Hz, 0.3H, minor), 3.88 (dd, *J*= 16.9, 2.0 Hz, 0.7H, major), 4.21 (dd, *J*= 9.1, 1.9 Hz, 0.7H, major), 4.27-4.33 (m, 0.6H, minor), 4.75-4.86 (m, 0.6H, minor), 4.84-4.90 (m, 0.7H, major), 5.02 (t, *J*= 8.1 Hz, 0.7H, major), 7.21-7.24 (0.9H), 7.43-7.57 (m, 7.2H), 7.85-7.90 (m, 3.9H), 7.96-7.98 (2.0H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.7, 27.9, 41.8, 42.5, 53.5, 53.9, 71.1, 73.0, 83.3, 90.9, 91.1, 1128.2, 118.5, 125.3, 125.5, 126.4, 127.2, 128.7, 128.9, 129.0, 129.6, 129.7, 129.8, 130.9, 131.1, 131.9, 132.1, 134.9, 135.0, 137.7, 150.2, 151.3, 153.9, 154.4, 168.7, 168.8, 196.9, 197.5. IR ν_{max}/cm^{-1} 512, 694, 753, 822, 983, 1067, 1140, 1297, 1366, 1486, 1585, 1680, 1709, 1727, 2847, 2920, 2975. HRMS (ESI-TOF) m/z: calcd for $C_{30}H_{28}BrN_3NaO_5$ $[M+Na]^+$ 612.1105. Found 612.1116. HPLC (Lux i-cellulose 5, n-hexane/2-propanol 92:8, λ= 220 nm, 0.5 mL/min): major diastereomer: t_R (minor)= 55.0 min, t_R (major)= 62.1 min (98% ee); minor diastereomer: t_R (minor)= 15.4 min, t_R (major)= 19.0 min (88% ee).

***tert*-Butyl (3*R*,5*S*)-9-oxo-3-(2-oxo-2-(p-tolyl)ethyl)-6,8-diphenyl-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3ad).** 46.2 mg (88% combined yield). Mixture of diastereomers, 2.7:1 dr. Major diastereomer (3*R*,5*S*). White solid. Mp 167-169 °C (from hexane). $[\alpha]^{25}_{D}$= -50 (c= 0.2, $CHCl_3$, 99% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9H), 2.43 (s, 3H), 3.15 (dd, *J*= 16.8, 11.0 Hz, 1H), 3.89 (d, *J*= 16.8 Hz, 1H), 4.22 (dd, *J*= 9.1, 2.0 Hz, 1H), 4.89 (t, *J*= 10.5 Hz, 1H), 5.02 (t, *J*= 8.2 Hz, 1H), 7.23 (t, *J*= 7.4, 1H), 7.27 (d, *J*= 7.9 Hz, 2H), 7.44 (t, *J*= 8.3 Hz, 2H), 7.49-7.56 (m, 3H), 7.85 (d, *J*= 8.2 Hz, 1H), 7.88-7.90 (m, 2H), 7.97 (d, *J*= 8.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.9, 42.4, 54.1, 71.2, 83.2, 91.1, 118.2, 125.3, 127.2, 128.2, 128.7, 129.0, 129.4, 129.8, 130.9, 133.8, 136.2, 137.8, 144.5, 151.3, 154.1, 168.9, 197.6. IR ν_{max}/cm^{-1} 754, 974, 1164, 1300, 1365, 1384, 1487, 1604, 1674, 1710, 2861, 2930, 2978, 3070, 3348. HRMS (ESI-TOF) m/z: calcd for

$C_{31}H_{31}N_3NaO_5$ [M+Na]$^+$ 548.2156. Found 548.2161. HPLC (Lux i-Cellulose-5, n-hexane/2-propanol 92:8, λ= 220 nm, 0.5 mL/min): t_R (minor)= 79.5 min, t_R (major)= 98.1 min, (99% ee).

***tert*-Butyl (3*R*,5*S*)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-9-oxo-6,8-diphenyl-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3ae).** 45.0 mg (83% combined yield). Mixture of diastereomers, 2.5:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 2.7H, minor), 1.24 (s, 6.3H, major), 3.10 (dd, *J*= 16.5, 11.1 Hz, 0.7H, major), 3.52 (dd, *J*= 17.9, 9.7 Hz, 0.3H, minor), 3.86-3.87 (m, 0.7H, major), 3.88 (s, 3H, minor and major), 4.23 (dd, *J*= 9.1, 2.0 Hz, 0.7H, major), 4.31-4.35 (m, 0.6H, minor), 4.81-4.84 (m, 0.6H, minor), 4.86-4.90 (m, 0.7H, major), 5.01 (t, *J*= 8.2 Hz, 0.7H, major), 6.95 (2H), 7.21-7.24 (m, 0.9H), 7.42-7.54 (m, 5.1H), 7.86- 8.00 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.7, 27.9, 41.4, 42.3, 53.7, 54.2, 55.5, 71.2, 73.2, 83.1, 83.2, 90.9, 91.1, 113.8, 113.9, 118.2, 118.5, 118.8, 125.3, 125.4, 126.4, 126.5, 127.2, 128.7, 128.9, 129.0, 129.1, 129.4, 129.5, 129.8, 130.5, 130.9, 131.0, 137.8, 150.2, 151.3, 154.1, 154.5, 163.8, 163.9, 168.8, 168.9, 196.5, 197.0. IR ν_{max}/cm^{-1} 761, 835, 1029, 1069, 1142, 1164, 1219, 1296, 1395, 1461, 1505, 1574, 1670, 1714, 1725, 2853, 2923, 2960, 3062. HRMS (ESI-TOF) m/z: calcd for $C_{31}H_{31}N_3NaO_6$ [M+Na]$^+$ 564.2105. Found 564.2113. HPLC (Lux i-cellulose 5, n-hexane/2-propanol 92:8, λ= 254 nm, 0.5 mL/min): major diastereomer: t_R (minor)= 145.6 min, t_R (major)= 161.5 min (>99% ee); minor diastereomer: t_R (minor)= 35.0 min, t_R (major)= 42.3 min (88% ee).

***tert*-Butyl (3*R*,5*S*)-6-methyl-9-oxo-3-(2-oxo-2-phenylethyl)-8-phenyl-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3ba).** 37.8 mg (84% combined yield). Mixture of diastereomers, 3.3:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 2.7H, minor), 1.30 (s, 6.3H, major), 2.15 (s, 0.9H, minor), 2.16 (s, 2.1H, major), 3.13 (dd, *J*= 16.6, 10.2 Hz, 0.7H, minor), 3.63 (dd, *J*= 18.2, 10.5 Hz, 0.3H, minor), 3.85 (dd, *J*= 16.2, 2.2 Hz, 0.7H, major), 4.06 (dd, *J*= 18.2, 2.9 Hz, 0.3H, minor), 4.13 (d, *J*= 7.6 Hz, 0.3H, minor), 4.26 (t, *J*= 9.1, 3.2 Hz, 0.7H, major), 4.54 (t, *J*= 8.9 Hz, 0.7H, major), 4.72-4.77 (m, 1H, minor and major), 4.82-4.85 (m, 0.3H, minor), 7.16-7.21 (1H), 7.38-7.42 (m, 2.1H), 7.46-7.52 (m, 2.1H), 7.57-7.61 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.3, 12.8, 27.9, 40.8, 42.0, 53.8, 71.1, 73.3, 83.1, 83.2, 90.0, 90.5, 117.9, 118.1, 124.9, 125.1, 128.2, 128.6, 128.8, 128.9, 133.5, 133.6, 136.1, 136.3, 137.7, 137.8, 150.1, 150.8, 156.3, 157.6, 167.9, 168.6, 197.8, 198.7. IR ν_{max}/cm^{-1} 688, 750, 1142, 1370, 1490, 1583, 1676, 1714, 1725, 2916, 2961. HRMS (ESI-TOF) m/z: calcd for $C_{25}H_{27}N_3NaO_5$ [M+Na]$^+$ 472.1843. Found 472.1855. HPLC (Lux i-cellulose 5, n-hexane/2-propanol 95:5, λ= 210 nm, 1 mL/min): minor diastereomer: t_R (minor)= 32.3 min, t_R (major)= 43.2 min (>99% ee); major diastereomer: t_R (major)= 17.3 min, t_R (minor)= 19.2 min (92% ee).

***tert*-Butyl (3*R*,5*S*)-6-ethyl-9-oxo-3-(2-oxo-2-phenylethyl)-8-phenyl-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3ca).** 37.1 mg (80% combined yield). Mixture of diastereomers, 1.9:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 3.6H, minor), 1.29 (s, 5.4H, major), 1.35-1.39 (m, 3H, minor and major), 2.41-2.58 (m, 2H, minor and major), 3.12 (dd, *J*= 16.7, 10.4 Hz, 0.6H, major), 3.63 (dd, *J*= 18.2, 10.5 Hz, 0.4H, minor), 3.85 (d, *J*= 16.9 Hz, 0.6H, major), 4.05 (d, *J*= 18.2 Hz, 0.4H, minor), 4.11 (d, *J*= 7.3 Hz, 0.6H, major), 4.26 (dd, *J*= 9.0, 3.0 Hz, 0.6H, major), 4.53 (t, *J*= 8.0 Hz, 0.4H, minor), 4.71-4.76 (m, 0.4H, minor), 4.83-4.86 (m, 1H, minor and major), 7.16-7.20 (m, 1H), 7.38-7.42 (m, 2H), 7.46-7.51 (m, 2H), 7.57-7.61 (m, 1H), 7.89-7.93 (m, 2H), 8.00-8.05 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.2, 9.5, 20.1, 20.6, 27.9, 28.0, 28.2, 29.7, 40.8, 42.0, 53.9, 71.0, 73.3, 82.9, 83.0, 90.2, 90.6, 117.9, 118.1, 118.6, 118.7, 124.9, 125.0, 128.1, 128.2, 128.6, 128.7, 128.9, 133.5, 133.6, 136.2, 136.3, 137.7, 138.0, 150.1, 150.9, 159.9, 161.3, 168.2, 168.8, 197.8, 198.7. IR ν_{max}/cm^{-1} 985, 1051, 1164, 1216, 1278, 1373, 1454, 1498, 1600, 1718, 2916, 2934, 2978, 3066. HRMS (ESI-TOF) m/z: calcd for $C_{26}H_{29}N_3NaO_5$ [M+Na]$^+$ 486.1999. Found 486.1999. HPLC (Chiralpak AD-H, n-hexane/2-propanol 98:2, λ= 254 nm, 0.7 mL/min): major diastereomer: t_R (major)= 44.2 min, t_R (minor)= 51.7 min (82% ee); minor diastereomer: t_R (minor)= 27.2 min, t_R (major)= 59.6 min (96% ee).

***tert*-Butyl (3*R*,5*S*)-6-isopropyl-9-oxo-3-(2-oxo-2-phenylethyl)-8-phenyl-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3da).** 36.3 mg (76% combined yield). Mixture of diastereomers, 2:1 dr. Major diastereomer (3*R*,5*S*). Pale yellow oil. $[\alpha]^{25}_D$= -7.0 (c= 0.1, $CHCl_3$, 92% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.34 (dd, *J*= 6.7, 4.2 Hz, 6H), 2.75-2.81 (m, 1H), 3.64 (dd, *J*= 18.1, 10.5 Hz, 1H), 4.10 (dd, *J*= 18.1, 2.8 Hz, 1H), 4.26 (dd, *J*= 9.0, 3.0 Hz, 1H), 4.57 (dd, *J*= 8.5, 5.8 Hz, 1H), 4.72-4.76 (m, 1H), 7.19 (t, *J*= 8.2 Hz, 1H), 7.41 (t, *J*= 7.8 Hz, 2H), 7.48 (t, *J*= 7.7 Hz, 2H), 7.58 (t, *J*= 7.7 Hz, 1H), 7.92 (d, *J*= 8.7 Hz, 2H), 8.03 (d, *J*= 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 9.2, 9.5, 20.1, 20.6, 27.9, 28.0, 28.2, 29.7, 40.8, 42.0, 53.9, 71.0, 73.3, 82.9, 83.0, 90.2, 90.6, 117.9, 118.1, 118.6, 118.7, 124.9, 125.0, 128.1, 128.2, 128.6, 128.7, 128.9, 133.5, 133.6, 136.2, 136.3, 137.7, 138.0, 150.1, 150.9, 159.9, 161.3, 168.2, 168.8, 197.8, 198.7. IR ν_{max}/cm^{-1} 992, 1047, 1146, 1366. 1392, 1498, 1600, 1677, 1714, 1725, 2934, 2978. HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{31}N_3NaO_5$ [M+Na]$^+$ 500.2156. Found 500.2164. HPLC (Chiralpak AD-H, n-hexane/2-propanol 95:5, λ= 210 nm, 0.8 mL/min): t_R (minor)= 10.1 min, t_R (major)= 22.4 min (92% ee).

***tert*-Butyl (3*R*,5*S*)-8-methyl-9-oxo-3-(2-oxo-2-phenylethyl)-6-phenyl-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3fa).** 44.2 mg (98% combined yield). Mixture of diastereomers, 2.3:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 2.7H, minor), 1.33 (s, 6.3H, major), 3.14 (dd, *J*= 17.0, 11.1 Hz, 0.7H, major), 3.40 (s, 2.1H, major), 3.41 (s, 0.9H, minor), 3.53 (dd, *J*= 15.1, 4.4 Hz, 0.3H, minor), 3.90 (d, *J*= 18.3 Hz, 0.7H, major), 4.16 (d, *J*= 10.7 Hz, 0.7H, major), 4.25-4.32 (m, 0.6H, minor), 4.73-4.80 (m, 0.6H, minor), 4.83 (t, *J*= 10.6 Hz, 0.7H, major), 4.96 (t, *J*= 7.9 Hz, 0.7H, major), 7.43-7.52 (m, 5.2H), 7.59 (1H), 7.75 (0.6H), 7.79 (1.4H), 7.94 (1.1H), 8.01 (0.7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.7, 28.0, 28.2, 29.7, 31.7, 31.8, 41.9, 42.4, 53.5, 53.9, 70.8, 72.8, 82.9, 89.7, 90.0, 126.0, 126.1, 126.8, 127.2, 128.1, 128.2, 128.6, 128.7, 128.8, 128.9, 129.2, 129.9, 130.6, 130.7, 133.5, 133.6, 136.2, 136.3, 150.2, 151.2, 153.3, 153.7, 169.8, 170.1, 198.0, 198.5. IR ν_{max}/cm^{-1} 681, 769, 860, 981, 1044, 1142, 1212, 1366, 1388, 1447, 1578, 1681, 1703, 1721, 2908, 2934, 2982. HRMS (ESI-TOF) m/z: calcd for $C_{25}H_{27}N_3NaO_5$ [M+Na]$^+$ 472.1843. Found 472.1852. HPLC (Chiralpak OD, n-hexane/2-propanol 93:7, λ= 210 nm, 0.5 mL/min): major diastereomer: t_R (minor)= 21.7 min, t_R (major)= 25.3 min (94% ee); minor diastereomer: t_R (minor)= 15.8 min, t_R (minor)= 17.5 min (>99% ee).

***tert*-Butyl (3*R*,5*S*)-8-(4-chlorophenyl)-6-methyl-9-oxo-3-(2-oxo-2-phenylethyl)-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3ga).** 37.8 mg (78% combined yield). Mixture of diastereomers, 1.3:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 3.6H, minor), 1.28 (s, 5.4H, major), 2.14 (s, 1.2H, minor), 2.15 (s, 1.8H, major), 3.12 (dd, *J*=

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16.5, 10.4 Hz, 0.6H, major), 3.59 (dd, *J*= 18.1, 1.9 Hz, 0.4H, minor), 3.83 (d, *J*= 16.5 Hz, 0.6H, minor), 4.05 (dd, *J*= 18.1, 10.6 Hz, 0.4H, minor), 4.13 (d, *J*= 7.6 Hz, 0.4H, minor), 4.25 (dd, *J*= 12.0, 9.0 Hz, 0.6H, major), 4.54 (td, *J*= 9.0, 1.7 Hz, 0.6H, major), 4.72-4.76 (m, 1H, minor and major), 4.82-4.85 (m, 0.4H, minor), 7.35-7.38 (m, 1.8H), 7.46-7.51 (2.1H), 7.57-7.61 (m, 1H), 7.84-7.89 (m, 2H), 7.99-8.02 (m, 2.1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.3, 12.8, 27.9, 40.8, 42.0, 53.8, 53.9, 71.2, 73.4, 83.1, 83.2, 89.9, 90.4, 118.9, 119.1, 1196.6, 119.7, 128.2, 128.7, 128.8, 129.0, 130.0, 130.2, 133.6, 133.7, 136.3, 136.4, 150.0, 150.7, 156.6, 157.9, 167.9, 168.5, 197.7, 198.6. IR v_{max}/cm^{-1} 512, 597, 765, 832, 979, 1113, 1294, 1360, 1494, 1591, 1676, 1720, 1738, 2915, 2978. HRMS (ESI-TOF) m/z: calcd for $C_{25}H_{26}ClN_3NaO_5$ $[M+Na]^+$ 506.1453. Found 506.1462. HPLC (Chiralpak IA, n-hexane/2-propanol 98:2, λ= 254 nm, 0.5 mL/min): major diastereomer: t_R (minor)= 51.9 min, t_R (major)= 72.9 min (82% ee); minor diastereomer: t_R (major)= 36.0 min, t_R (minor)= 61.3 min (96% ee).

***tert*-Butyl (3*R*,5*S*)-6-methyl-9-oxo-3-(2-oxo-2-phenylethyl)-8-(p-tolyl)-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (3ha).** 40.7 mg (88% combined yield). Mixture of diastereomers, 1.5:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 3.6H, minor), 1.30 (s, 5.4H, major), 2.14 (s, 1.2H, minor), 2.15 (s, 1.8H, major), 2.35 (s, 1.2H, minor), 2.36 (s, 1.8H, major), 3.12 (dd, *J*= 16.7, 10.4 Hz, 0.6H, major), 3.63 (dd, *J*= 18.2, 10.5 Hz, 0.4H, minor), 3.83 (dd, *J*= 17.0, 2.1 Hz, 0.6H, major), 4.05 (dd, *J*= 17.3, 3.0 Hz, 0.4H, minor), 4.12 (dd, *J*= 14.2, 6.9 Hz, 0.4H, minor), 4.25 (dd, *J*= 9.0, 3.1 Hz, 0.6H, major), 4.52-4.55 (m, 0.6H, major), 4.71-4.77 (m, 1H, minor and major), 4.82-4.84 (m, 0.4H, minor), 7.18-7.21 (m, 2H), 7.45-7.51 (2.2H), 7.56-7.62 (m, 1H), 7.72-7.78 (m, 1.9H), 7.99-8.05 (m, 1.9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.3, 12.8, 20.9, 27.8, 28.2, 40.8, 42.0, 53.8, 71.0, 73.3, 83.0, 83.1, 90.5, 118.0, 118.2, 128.2, 128.6, 128.8, 129.4, 133.5, 133.6, 134.6, 134.8, 135.4, 136.2, 136.3, 150.2, 150.9, 156.1, 157.4, 167.7, 168.3, 197.8, 198.7. IR v_{max}/cm^{-1} 508, 690, 814, 979, 1143, 1294, 1365, 1512, 1685, 1716, 2925, 2978. HRMS (ESI-TOF) m/z: calcd for $C_{26}H_{29}N_3NaO_5$ $[M+Na]^+$ 486.1999. Found 486.1990. HPLC (Lux Cellulose 1, n-hexane/2-propanol 70:30, λ= 254 nm, 0.2 mL/min): major diastereomer: t_R (major)= 24.5 min, t_R (minor)= 29.3 min (76% ee); minor diastereomer: t_R (major)= 22.2 min, t_R (minor)= 26.2 min (98% ee).

Transformation of spyrocyclic product 3ac.

To a solution of spyrocycle **3ac** (dr 2.7:1) (50 mg, 0.084 mmol), phenylboronic acid (15.5 mg, 0.127 mmol) and K_3PO_4 (35.7 mg, 0.168 mmol) in THF/H_2O 5:1 (1.5 mL) under a N_2 atmosphere, $PdCl_2(PPh_3)_2$ (0.008 mmol) was added. After refluxing for 8 h, the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (hexane/ethyl acetate 10:1) affording **4** as a pale yellow oil (41.8 mg, 85% yield).

***tert*-Butyl (3*R*,5*S*)-3-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)-9-oxo-6,8-diphenyl-1-oxa-4,7,8-triazaspiro[4.4]non-6-ene-4-carboxylate (4).** Mixture of diastereomers, 2.7:1 dr. Major diastereomer (3*R*,5*S*). Pale yellow oil. $[\alpha]^{25}_D$= -66.0 (c= 0.1, $CHCl_3$, 98% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 9H), 3.19 (dd, *J*= 16.8, 11.0 Hz, 1H), 3.95 (d, *J*= 18.9 Hz, 1H), 4.24 (dd, *J*= 9.1 Hz, 1H), 4.92 (t, *J*= 8.4 Hz, 1H), 5.04 (t, *J*= 7.4 Hz, 1H), 7.23 (t, *J*= 8.5 Hz, 1H), 7.42-7.50 (m, 5H), 7.51-7.58 (m, 3H), 7.63 (d, *J*= 6.1 Hz, 2H), 7.70 (d, *J*= 9.2 Hz, 2H), 7.90 (d, *J*= 8.2 Hz, 2H), 7.98 (d, *J*= 8.1 Hz, 2H), 8.02 (d, *J*= 8.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.9, 29.5, 42.6, 54.1, 71.2, 83.3, 91.1, 115.3, 118.2, 125.3, 127.2, 127.3, 127.4, 128.3, 128.7, 128.9, 129.0, 129.6, 129.8, 130.9, 134.9, 137.8, 139.7, 146.3, 151.3, 154.1, 168.8, 197.6. IR v_{max}/cm^{-1} 989, 1073, 1139, 1216, 1300, 1362, 1391, 1450, 1494, 1674, 1714, 2857, 2919, 2960. HRMS (ESI-TOF) m/z: calcd for $C_{36}H_{33}N_3NaO_5$ $[M+Na]^+$ 610.2312. Found 610.2318. HPLC (Lux i-cellulose 5, n-hexane/2-propanol 90:10, λ= 210 nm, 0.8 mL/min): t_R (minor)= 57.0 min, t_R (major)= 63.2 min (98% ee).

General Procedure for the enantioselective addition of allyl alcohol to N-Boc pyrazolinone ketimines 1a and 1g.

In a Wheaton vial equipped with a magnetic stirring bar the catalyst **C6** (0.1 equiv) and the *N*-Boc ketimine (0.17 mmol) were weighed. Then toluene (2.5 mL) was added before the mixture was stirred at rt. Several minutes later, allylic alcohol (0.25 mmol, 1.5 equiv) was introduced to the flask and the resulting mixture was stirred until the reaction completed (monitored by TLC). The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/ethyl acetate 10:1) to give the desired compound.

***tert*-Butyl (S)-(4-(allyloxy)-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)carbamate (5).** Pale yellow oil (53.2 mg, 74% yield). $[\alpha]^{25}_D$= -19.8 (c= 1.1, $CHCl_3$, 74:26 er). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9H), 4.05-4.15 (m, 2H), 5.15 (dd, *J*= 10.4, 1.3 Hz, 1H), 5.24 (dd, *J*= 17.2, 1.5 Hz, 1H), 5.77 (br, 1H), 5.78-5.87 (m, 1H), 7.24 (tt, *J*= 7.4, 1.1 Hz, 1H), 7.42-7.47 (m, 5H), 8.03-8.06 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.9, 66.0, 86.3, 125.4, 126.6, 128.8, 129.0, 131.0, 132.4, 137.8, 152.3, 153.5, 167.7. IR v_{max}/cm^{-1} 1154, 1260, 1366, 2395, 1464, 1597, 1703, 1729, 2857, 2923, 2971, 3300. HRMS (ESI-TOF) m/z: calcd for $C_{23}H_{25}N_3NaO_4$ $[M+Na]^+$ 430.1737. Found 430.1727. HPLC (Chiralpak AD-H, n-hexane/2-propanol 90:10, λ= 254 nm, 1 mL/min): t_R (major)= 10.1 min, t_R (minor)= 62.2 min (48% ee).

***tert*-Butyl (4-(allyloxy)-1-(4-chlorophenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (6).** Pale yellow oil (58.8 mg, 91% yield). $[\alpha]^{25}_D$ = -0.2 (c= 0.6, $CHCl_3$, 58:42 er). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.16 (s, 3H), 4.05-4.16 (m, 2H), 5.18 (dd, J= 10.4, 0.8 Hz, 1H), 5.26 (dd, J= 16.8, 1.5 Hz, 1H), 5.35 (br, 1H), 5.80-5.88 (m, 1H), 7.35 (d, J= 8.7 Hz, 1H), 7.88 (d, J= 8.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.9, 28.0, 65.3, 85.3, 118.2, 119.5, 128.9, 130.3, 132.7, 136.2, 152.4, 157.5, 167.1. IR v_{max}/cm^{-1} 1150, 1234, 1359, 1494, 1593, 1703, 1729, 2985, 3128, 3231. HRMS (ESI-TOF) m/z: calcd for $C_{18}H_{22}ClN_3NaO_4$ $[M+Na]^+$ 402.1191. Found 402.1196. HPLC (Chiralpak AD-H, n-hexane/2-propanol 95:5, λ= 254 nm, 1 mL/min): t_R (minor)= 8.4 min, t_R (major)= 25.3 min (16% ee).

Conflicts of interest

There are no conflicts to declare.

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