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Organocatalytic enantioselective Mannich reaction of isoxazol-5(4*H*)-ones to isatin-derived ketimines†‡

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An efficient organocatalytic asymmetric Mannich reaction between isoxazol-5(4*H*)-ones and isatin-derived ketimines has been developed. A bifunctional squaramide/Brønsted base organocatalyst catalyzed the enantioselective Mannich addition to afford chiral 3-aminoxindoles bearing a tetrasubstituted stereocenter at C3 decorated with an isoxazole moiety in good yields and with excellent enantioselectivities. Additionally, several synthetic transformations were described showing the versatility of the prepared compounds.

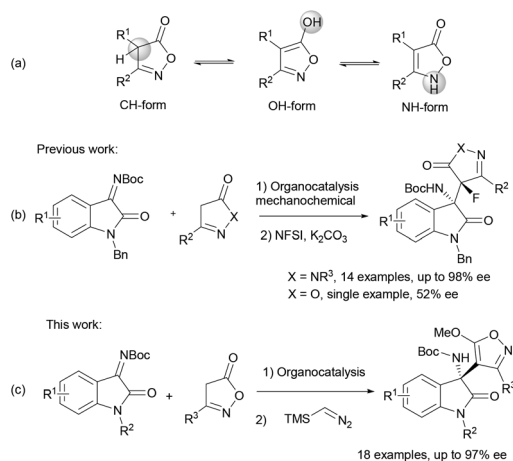
The isoxazol-5(4*H*)-one is a privileged heterocycle which is found in a wide range of drugs, natural products and biological active compounds.¹ Moreover, this heterocycle is a versatile building block for the synthesis of β -amino acids or alkynes, among others.² Additionally, isoxazol-5-ones have found applications in materials science due to their photonic properties.³ Based on the presence of the isoxazol-5(4*H*)-one moiety in bioactive compounds and on the potential applications of their derivatives, the interest in developing new procedures for the synthesis and functionalization of this kind of heterocycles is understandable, particularly in an enantioselective fashion.

Isoxazol-5(4*H*)-ones are methylene active compounds on account of the relatively acidic character of the C4-H;⁴ with three potential nucleophilic sites in the ring: the N2, the C4, and the exocyclic carbonyl O atom although they normally react at the N2 and C4 positions (Scheme 1a). Despite recent advances, asymmetric methods for the electrophilic functionalization of isoxazol-5(4*H*)-ones at either N2⁵ or C4⁶ are still scarce, compared with other related five-membered heterocycles. Focusing on organocatalytic procedures,⁷ nitroolefins,⁸ *N*-fluorobenzenesulfonimide,⁹ α' -alkylidene-2-cyclopentenones¹⁰ and β,γ -alkynyl- α -imino esters¹¹ have been efficiently

used as electrophiles in the asymmetric C4-regioselective functionalization of isoxazol-5-ones. Despite these examples, a successful aminalkylation (Mannich) reaction of isoxazol-5(4*H*)-ones is still missing in the literature.

The asymmetric Mannich addition is an extremely useful strategy to obtain chiral molecules bearing amino substituents in the stereogenic center.¹² Among the variety of imines that have been employed in this reaction, the isatin-derived ketimines are one of the most interesting substrates.¹³ These compounds are very popular in Mannich reactions as they allow obtaining 3-aminoxindoles with a fully substituted C3. This structure has an enormous interest in medicinal and organic chemistry and can be found in numerous bioactive and natural products.¹⁴

The addition of pyrazolones to isatin-derived ketimines has been previously reported by several groups,¹⁵ including ours.^{15b} However, to the best of our knowledge, there is only a single example of Mannich reaction involving an isoxazol-5(4*H*)-one as nucleophile that has been reported as an extension of one of these previous studies carried out with pyrazolones



Scheme 1 Tautomeric forms of isoxazol-5-(4*H*)-ones and asymmetric Mannich reaction with isatin-derived ketimines.

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(Scheme 1b).^{15c} This reaction consisted of an asymmetric organocatalytic domino Mannich reaction-fluorination with isatin-derived ketimines with mechanochemical activation. Although high yields and enantioselectivities were afforded for the products obtained from pyrazolones, the product obtained from isoxazol-5(4*H*)-one (single example) was achieved in low yield and moderate enantioselectivity. Following our interest on the use of ketimines¹⁶ and isoxazol-5(4*H*)-ones^{5a,17} in asymmetric reactions, herein we describe an efficient asymmetric Mannich reaction between isatin-derived ketimines and isoxazol-5(4*H*)-ones catalyzed by bifunctional squaramide/Brønsted base organocatalyst (Scheme 1c).

To develop this methodology, we began our study to examine the model reaction of 3-phenyl-4(*H*)-isoxazol-5-one (**2a**) and isatin-derived *N*-Boc ketimine **1a** in the presence of 10 mol% organocatalyst **I** in dichloromethane at room temperature (Table 1, entry 1).

To our delight, in the presence of catalyst **I** the reaction proceeded cleanly to give the expected addition product as a tautomer. To determine the enantioselectivity of the reaction, the diastereomer mixture was subjected to *O*-alkylation by treatment with trimethylsilyldiazomethane to give compound **3aa** in 70% yield and 76% ee (Table 1, entry 1). Next, different bifunctional squaramide and thiourea organocatalysts were tested (Table 1, entries 2–6). Remarkably, using the bifunctional squaramide **IV** the desired aminooxindole **3aa** was obtained in 70% yield and with higher 93% ee (Table 1, entry

4). Moreover, other solvents were studied (Table 1, entries 7 and 8) but none of them improved the results obtained in dichloromethane. Lowering the reaction temperature (Table 1, entry 9) or reducing the catalyst load (Table 1, entry 10) compromised the yield, although the enantioselectivity was not seriously affected.

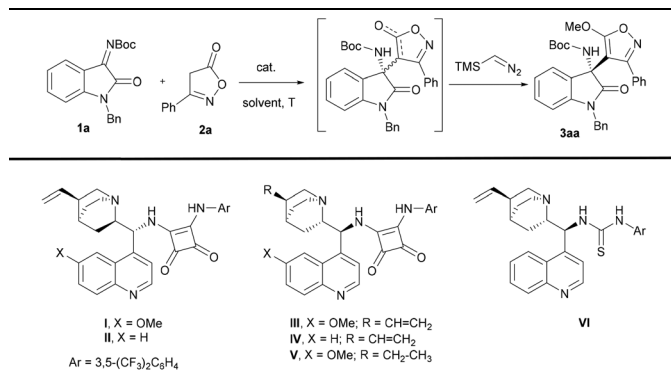
Having established the optimal reaction conditions (Table 1, entry 4),§ the generality of the developed methodology was evaluated (Table 2). A range of isatin-derived *N*-Boc ketimines **1b–1l** bearing a variety of substituents with different electronic properties or different *N1*-protecting groups were successfully tested with isoxazolone **2a**, showing the robustness and efficiency of our protocol. The desired products **3ba–3la** were obtained with excellent enantioselectivities (>90% ee), and in fair to good yields for the overall Mannich addition/methylation process. Electron-withdrawing (NO₂, Cl) or electron-donating groups (OMe, Me) at the 5 position of the isatin derived ketimines (**1b–1f**) were tolerated and the corresponding aminooxindole products **3ba–3fa** were obtained with good results (95–99% ee). Additionally, isatin-derived ketimines bearing substituents at the positions 6 or 7 of the homoaromatic ring **1g–1i** as well as disubstituted substrate **1j** were evaluated affording the products **3ga–3ja** in moderate yields and high enantioselectivities (92–94%). Moreover, other isatin ketimines derivatives bearing different substituents at the *N1*-atom were studied (**1k–1l**). Methyl and methoxymethyl were appropriate groups affording the desired product with high enantioselectivities.

A variety of isoxazol-5(4*H*)-ones **2** was then explored. The reaction with isoxazolinones bearing *para*-substituted phenyl rings at C3 (**2b–2c**) afforded the desired products **3ab**, **3ac** and **3fb** with high enantioselectivities. However, when aliphatic substituents at C3 of compound **2** were used (**2d–2e**), the corresponding products were obtained with somehow lower enantioselectivity.

Finally, we faced the reaction with isoxazolinones substituted at C4 to obtain oxindoles featuring two consecutive tetra-substituted stereogenic centers, a challenging goal due to steric congestion.¹⁸ Under the reaction conditions, isoxazolone **2f** reacted with ketimine **2a** to give oxindole **3af** in 85% yield, 41:59 dr favoring the anti diastereomer and high enantioselectivity (99% and 72% ee, respectively). Similarly, isoxazolinone **2g**, bearing a Ph group at C3 and a Me group at C4, reacted with **1a** to give compound **3ag** with excellent yield, similar dr and higher enantiomeric excess for the major anti diastereomer. On the other hand, isoxazolinone **2h** featuring a C3 methyl group reacted with lower stereoselectivity, in a similar way as the related 3-methyl isoxazolinone **2d**, although still with good yield.

Next, we achieved some modifications to show the synthetic potential of the developed Mannich reaction. First, we demonstrated the scalability and applicability of this methodology by performing the asymmetric Mannich reaction of **1a** and **2a** at one mmol scale (Scheme 2A). The reaction afforded oxindole **3aa** in acceptable yield without alteration of the enantioselectivity. On the other hand, a modification of the work up

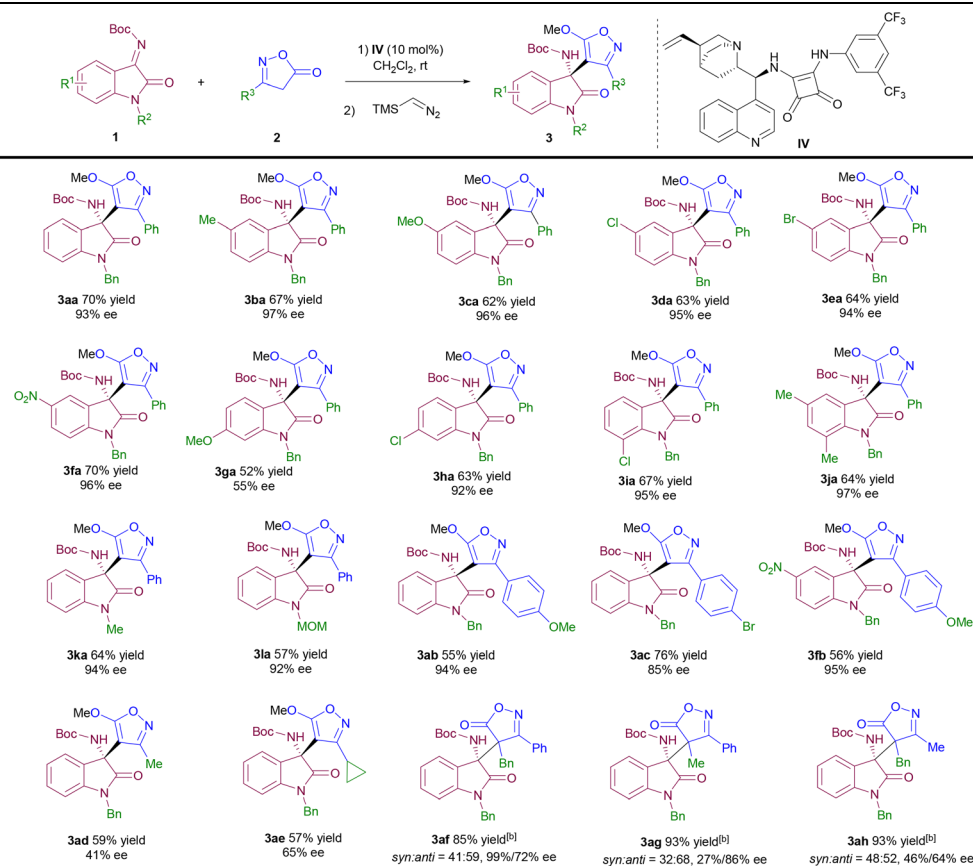
Table 1 Enantioselective Mannich reaction of isoxazolone **2a** and ketimine **1a**. Effect of organocatalyst and solvent^a



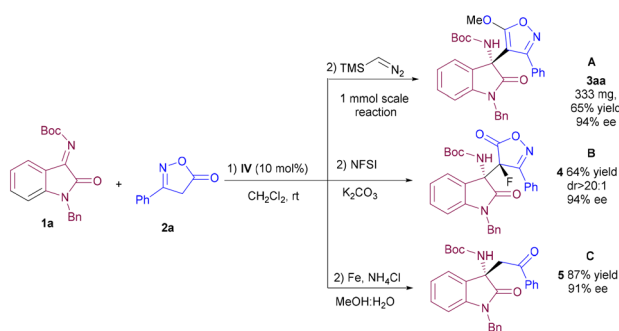
Entry	Cat.	Solvent	Yield ^b (%)	ee ^c (%)
1	I	CH ₂ Cl ₂	72	76
2	II	CH ₂ Cl ₂	67	83
3	III	CH ₂ Cl ₂	67	91
4	IV	CH ₂ Cl ₂	70	93
5	V	CH ₂ Cl ₂	62	89
6	VI	CH ₂ Cl ₂	63	83
7	IV	Toluene	6	87
8	IV	CHCl ₃	55	85
9 ^d	IV	CH ₂ Cl ₂	57	92
10 ^e	IV	CH ₂ Cl ₂	60	90

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), Cat. (0.02 mmol), solvent (2 mL), rt, 20 h. ^b Isolated yield of **3aa**. ^c Determined by chiral HPLC analysis. ^d Reaction performed at 0 °C. ^e Reaction performed with 0.005 mmol of **IV**.



Table 2 Organocatalytic asymmetric Mannich reaction between isatin-derived ketimines **1** and isoxazol-5(4*H*)-ones **2**. Reaction scope^a

^a Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), **IV** (0.02 mmol), solvent (2 mL), room temperature, 20 h. Overall isolated yields. Enantiomeric excesses determined by chiral HPLC analysis. ^b Treatment with TMSCHN₂ omitted.



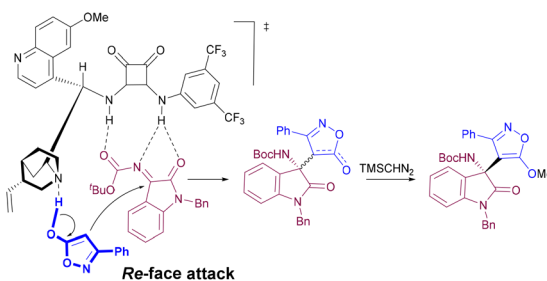
Scheme 2 One mmol scale reaction and synthetic transformations. Overall isolated yields.

treating the Mannich reaction mixture with NFSI in basic medium provided oxazolinone **4** bearing a fluorinated tetra-substituted stereocenter in good yield as a single diastereomer in 94% ee (Scheme 2B). Finally, a decarboxylative protocol of the isoxazol-5-one moiety provided the known β -chiral branched carbonyl compound **5** in high yield and enantioselectivity for the overall two-step procedure (Scheme 2C). This strategy shows that isoxazol-5(4*H*)-ones can act as suitable sur-

rogates for aryl methyl ketones in the asymmetric catalytic Mannich reaction with *N*-alkoxycarbonyl isatin imines.

A comparison of the optical rotation of compound **5** obtained in this way with that reported in the literature¹⁹ allowed us to assign the configuration of C3 in the aminooxindole skeleton as *S*. Accordingly, the absolute stereochemistry of compounds **3** and **4** was assigned by chemical correlation.

To explain the observed stereochemistry, we propose the transition-state model outlined in Scheme 3, where the bifunc-



Scheme 3 Plausible transition-state model for the reaction of isoxazol-5(4*H*)-ones **2** and isatin-derived ketimines **3** catalyzed by bifunctional catalyst **IV**.



tional catalyst is responsible for the activation and pre-orientation of the reacting partners.^{15b} Thus, the isoxazolinone is deprotonated by the tertiary amine of the catalyst while the ketimine is activated upon formation of hydrogen bonds between the *N*-Boc group and the squaramide moiety. The isoxazolinone will approach the *Re* face of the ketimine double bond, thus accounting for the observed stereochemistry.

Conclusions

In conclusion, we have developed an enantioselective organocatalytic asymmetric Mannich reaction between isatin-derived ketimines **1** and isoxazol-5(4*H*)-ones **2**. The reaction is catalyzed by a bifunctional squaramide derived from quinine and provides 3-aminooxindoles with an isoxazolinone ring in their structure which make them interesting compounds for medicinal and organic chemistry. Moreover, this methodology has been extended to synthesized 3-aminooxindoles featuring two consecutive tetrasubstituted stereogenic centers. Finally, several synthetic transformations have been carried out in order to prove the versatility and synthetic potential of this methodology.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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§ General procedure for the enantioselective Mannich reaction/*O*-alkylation: an oven dried test tube was charged with isatin-derived ketimine **1** (0.2 mmol), isoxazol-5-one **2** (0.2 mmol) and squaramide **IV** (12.0 mg, 0.02 mmol). The test tube was purged with N₂ 10 minutes. Dichloromethane (2 mL) was added and the mixture was stirred at room temperature until completion (TLC). A 1 M solution of TMS-diazomethane in diethyl ether (0.4 mL, 0.4 mmol) was added *via* a syringe and the reaction was stirred 2 hours at room temperature. The reaction mixture was chromatographed on silica gel eluting with hexane : EtOAc mixtures to give compound **3**.

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