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COMMUNICATION

Organocatalytic enantioselective 1,6-*aza*-Michael addition of isoxazolin-5-ones to *p*-quinone methides

Ricardo Torán,[a] Carlos Vila,[a] Amparo Sanz-Marco,[a] M.Carmen Muñoz,[b] José R. Pedro,*[a] and Gonzalo Blay*[a]

Abstract: A thiourea-Brønsted base bifunctional catalyst allowed the enantioselective 1,6-*aza*-Michael addition of isoxazolin-5-ones to *p*-quinone methides to give isoxazolin-5-ones having a chiral diarylmethyl moiety attached to the N atom with fair to good yields and enantiomeric excesses. To the best of our knowledge this reaction represents the first example of enantioselective *N*-alkylation of isoxazolin-5-ones as well as the first example of enantioselective 1,6-*aza*-Michael reaction involving *p*-quinone methides.

Asymmetric conjugate addition reactions constitute one of the most powerful and efficient methods for the enantioselective construction of C-C and C-X bonds. Excellent levels of regio- (1,4-*vs* 1,2- addition) and stereoselectivity have been achieved for 1,4-conjugate additions of a range of nucleophiles and Michael acceptors.[1] Compared with the 1,4-addition reaction, the enantioselective 1,6-conjugate addition is more challenging because of the longer distance between the carbonyl and the reaction site (reduced reactivity and stereogenic control) as well as for the presence of an additional electrophilic atom (regioselectivity).[2] Nevertheless excellent results in terms of regio- and enantioselectivity have been obtained by using metal-catalysis[3] or organocatalysis.[4] In this context, *p*-quinone methides (*p*-QMs), characterized by a six-membered cyclic bis-vinylogous enone framework prone to aromatize, have emerged as reactive electrophiles in enantioselective 1,6-conjugate additions to give compounds possessing a chiral diarylmethyl unit.[5] Most examples involve carbon nucleophiles,[5,6] although the addition of $B_2(pin)_2$ and thioacetic acid have been also reported.[7] However, there are no examples on enantioselective 1,6-conjugate addition of nitrogen nucleophiles to *p*-QMs, to the best of our knowledge,[8] although the enantioselective *N*-akylation of 2,3-disubstituted indoles with the related *aza*-*p*-QMs has been reported.[9]

On the other hand, the isoxazolin-5-one heterocyclic moiety is found in a variety of natural products isolated from different plant families[10] and insects.[11] Many of these compounds show biological activity and, therefore, the isoxazol-5-one group has become a platform for the development of new drug candidates. Examples include compounds with antibacterial[12] and cytostatic[13] activities as well as enzyme inhibitors for hormone-sensitive lipase,[14] human neutrophil elastase,[15] p38 MAP*a* kinase[16] and NAD^+-dependent protein deacetylases (Figure 1).[17] Isoxazol-5-ones are also being studied for the development of new materials for photonic applications.[18] Furthermore, isoxazol-5-ones are highly functionalized and show a rich panorama of chemical reactivity, being used in organic synthesis as versatile building blocks.[19]

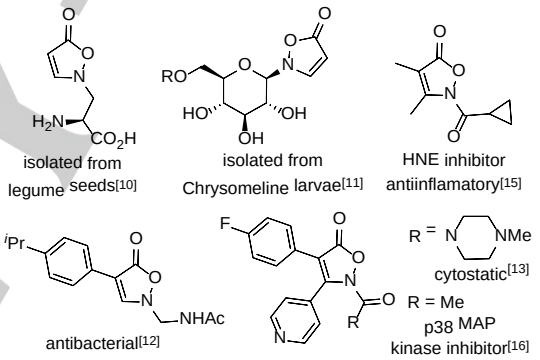

Figure 1. Examples of natural and bioactive *N*-substituted isoxazolin-5-ones

Accordingly, the development of new procedures for the synthesis of this particular heterocyclic and its decoration constitutes an important goal for organic chemists. Despite this, the use of isoxazolin-5-ones as nucleophiles in enantioselective reactions is still underdeveloped. Ma reported the first example consisting of a sequential conjugate addition/dearomative fluorination with nitroolefins catalyzed by a bifunctional chiral tertiary amino-thiourea catalyst.[20] Later, Wang described the organocatalytic asymmetric fluorination of 4-substituted isoxazolinones.[21] Peters reported the regioselective *C*-alkylation of 4-substituted isoxazolinones forming quaternary stereocenters by a palladium-catalyzed 1,4-addition to vinyl ketones.[22] The same group reported later a regioselective asymmetric *C*-allylation of isoxazolinones via a iridium-catalyzed *N*-allylation followed by a spontaneous *aza*-Cope rearrangement. In this study, *N*-allylated products were obtained when allyl carbonates substituted with alkyl chains were used.[23] Finally, an organocatalytic asymmetric four-component [5+1+1+1] cycloaddition via a cascade process that involves a double alkylation at C4 in isoxazolinones has been developed by Du and Chen, recently.[24]

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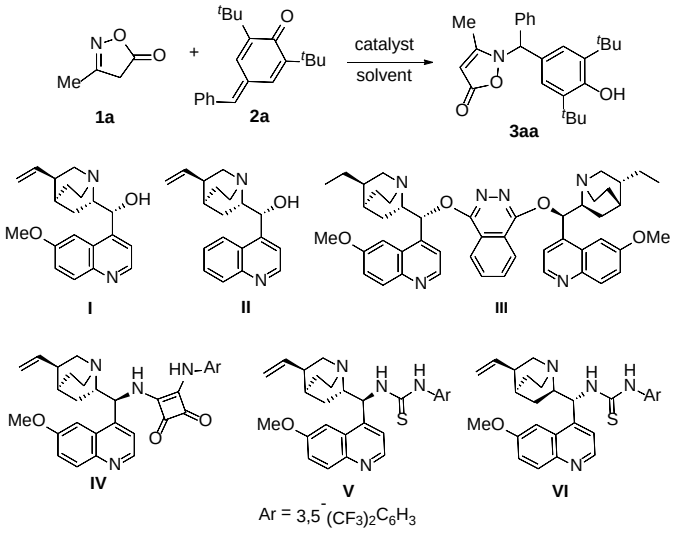
COMMUNICATION

In this communication, we report our results on the asymmetric *N*-alkylation of isoxazolinones via a 1,6-*aza*-Michael addition to *p*-QMs to give isoxazolinones bearing a chiral diarylmethyl motif attached to the N atom (Scheme 1). To the best of our knowledge, this is the first example of asymmetric 1,6-nucleophilic addition of *N*-nucleophiles to *p*-QMs.



Scheme 1. Reaction between 3-methyl-4(*H*)-isoxazol-5-one (**1a**) and *p*-QM **2a**, and organocatalysts used in this study.

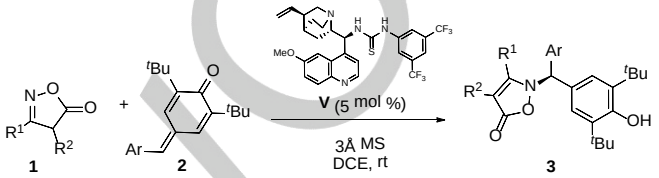
Table 1. *Enantioselective addition of* 3-methyl-4(*H*)-isoxazol-5-one (**1a**) *to* p-QM **2a**. Optimization of the reaction conditions. [a]

entry	catalyst	solvent	yield [%][b]	*ee* [%][c]
1	**I**	toluene	30	56
2	**II**	toluene	36	52
3	**III**	toluene	30	25
4	**IV**	toluene	31	9
5	**V**	toluene	48	66
6	**VI**	toluene	23	37
7	**V**	DCE	42	85
8[d]	**V**	DCE	48	86
9[d,e]	**V**	DCE	65	87

[a] **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (0.005 mmol), solvent (1 mL), room temperature, 6 days. [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases. [d] Reaction carried out with **1a** (0.1 mmol) and **2a** (0.15 mmol). [e] Reaction carried out in the presence of 3 Å MS (32 mg).

The reaction between 3-methy-4(*H*)-isoxazol-5-one (**1a**) and *p*-QM **2a** in toluene at room temperature was used for the optimization of the reaction conditions (see also SI). Several organocatalyst (5 mol %) including *Cinchona* alkaloid bases as well as bifunctional squaramides and thioureas were screened. In all the cases the main reaction product obtained was the *N*-alkylated isoxazolinone **3aa** (Scheme 1). The best result in terms of enantioselectivity (66% *ee*) was obtained with quinine-derived thiourea **V** (Table 1, entry 5). Changing the solvent to dichloroethane (DCE) allowed to increase the enantiomeric excess of the reaction product to 85% (Table 1, entry 7). The yield of the reaction could be improved by adding an excess of *p*-QM (Table 1, entry 8). Finally, using 3 Å MS as an additive permitted further increase of the enantioselectivity, compound **3aa** being obtained in 65% yield and 87% *ee* (Table 1, entry 9).

Table 2. Enantioselective 1,6-*aza*-Michael addition of 4(*H*)-isoxazol-5-ones **1** to *p*-quinone methides **2** catalyzed by thiourea **V**. Reaction scope.[a]



entry	**1**	R^1	R^2	**2**	Ar	t [d]	**3**	yield [%][b]	*ee* [%][c]
1	**1a**	Me	H	**2a**	Ph	6	**3aa**	65	87
2	**1b**	Et	H	**2a**	Ph	6	**3ba**	51	81
3	**1c**	Pr	H	**2a**	Ph	6	**3ca**	50	81
4	**1d**	Ph	H	**2a**	Ph	6	**3da**	77	54
5	**1e**	^{c}Pr	H	**2a**	Ph	1	**3ea**	78	89
6	**1f**	Me	Me	**2a**	Ph	1	**3fa**	62	47
7	**1a**	Me	H	**2b**	*p*-MeC_6H_4	6	**3ab**	23	72
8	**1a**	Me	H	**2c**	*p*-$MeOC_6H_4$	6	**3ac**	66	62
9	**1a**	Me	H	**2d**	*p*-ClC_6H_4	6	**3ad**	62	88
10	**1a**	Me	H	**2e**	*p*-$O_2NC_6H_4$	6	**3ae**	74	84
11	**1a**	Me	H	**2f**	*o*-$MeOC_6H_4$	6	**3af**	43	48
12	**1a**	Me	H	**2g**	*o*-ClC_6H_4	6	**3ag**	47	89
13	**1a**	Me	H	**2h**	*o*-BrC_6H_4	6	**3ah**	43	90
14	**1a**	Me	H	**2i**	*m*-$MeOC_6H_4$	6	**3ai**	20	25
15	**1a**	Me	H	**2j**	*m*-ClC_6H_4	6	**3aj**	36	81
16	**1a**	Me	H	**2k**	*m*-$O_2NC_6H_4$	6	**3ak**	56	77
17	**1e**	^{c}Pr	H	**2c**	*p*-$MeOC_6H_4$	1	**3ec**	75	79
18	**1e**	^{c}Pr	H	**2d**	*p*-ClC_6H_4	1	**3ed**	78	88
19	**1e**	^{c}Pr	H	**2e**	*p*-$O_2NC_6H_4$	1	**3ee**	80	86
20	**1e**	^{c}Pr	H	**2g**	*o*-ClC_6H_3	1	**3eg**	76	92
21	**1e**	^{c}Pr	H	**2i**	*m*-$MeOC_6H_4$	2	**3ei**	82	82
22	**1e**	^{c}Pr	H	**2j**	*m*-ClC_6H_4	1	**3ej**	80	88
23[d]	**1e**	^{c}Pr	H	**2a**	Ph	1	**3ea**	71	86

[a] **1a** (0.1 mmol), **2a** (0.15 mmol), **V** (0.005 mmol), DCE (1 mL), 3 Å MS (32 mg), room temperature. [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases. [d] Reaction carried out with 1 mmol of **1e**.

Under these conditions, we examined next the scope of the reaction (Table 2).The effect of the substitution on the isoxazolinone ring was first tested with *p*-QM **2** (Table 2, entries 1-6). Increasing the bulk of the substituent at C3 in the oxazolinone from methyl to propyl caused a decrease of yield and enantioselectivity (Table 2, entires 1-3). Isoxazolinone **1d** bearing a phenyl ring at this position also reacted with good yield but moderate enantioselectivity (Table 2, entry 4). On the other hand, the presence of a cyclopropyl group attached at C3 increased the reactivity of the oxazolinone and allowed to obtain the corresponding product **3ea** with good yield (78%) and 89% *ee* (Table 2, entry 5). The disubstituted 3,4-dimethy-4(*H*)-isoxazol-5-onone (**1f**) also reacted quick but the expected product **3fa** was obtained with only 47% *ee* (Table 2, entry 6).

Next we examined the scope regarding the *p*-quinone methide partner. In general, *p*-QMs having aryl groups substituted with electron-donating substituents at either position reacted with isoxazolinone **1a** with lower yields and enantioselectivities than their analogues having aryl groups substituted with electron-withdrawing groups (Table 2, entries 7, 8 and 11 *vs* entries 9, 10, 12, 15 and 16). Furthermore, it was found that, for a same substituent, *ortho*- or *para*- substituted rings performed better than *meta*-substituted ones (Table 2, entries 7-10 vs entries 14-16).

We also examined the reaction of cyclopropyl-substituted isoxazolinone **1e** with a number of *p*-QMs (Table 2, entries 17-22). Again, we found better results in terms of yield and enantioselectivity compared with the reactions with methyl-substituted isoxazolinone **1a**. In this case, good results were obtained even for *p*-QMs having *ortho*-, *meta*- or *para*-substituted phenyl rings. Finally, it should be noted that the reaction between isoxazolinone **1e** and *p*-QM **2a** was scaled up to 1 mmol scale with just a minor erosion on the yield and enantioselectivity (Table 2, entry 23).

The configuration of the stereogenic center in compound **3ad** was determined to be (*S*) on the basis of X-ray crystallographic analysis (Figure 2);[25] the stereochemistry of the remaining compounds **3** was assigned on the assumption of a uniform stereochemical pathway.

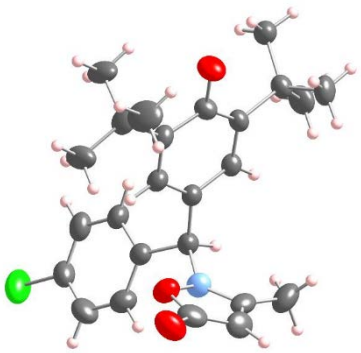


Figure 2. Ortep plot for the X-ray structure of compound **3ad**. The thermal ellipsoids are drawn at the 50% probability level. Flack parameter -0.07(9).

In summary, a bifunctional thiourea-Brønsted base catalyst allowed the first asymmetric 1,6-*aza*-Michael addition to *p*-quinone methides. Isoxazolinones were used as *N*-nucleophiles to give isoxazolinones having a chiral diarylmethyl moiety attached to the N atom. The reaction is broad in scope and provided the expected products with fair to good yields and high enantiomeric excesses. Further research to extend this enantioselective reaction to other nitrogen-containing compounds is underway in our laboratory.

Experimental Section

General procedure for the 1,6-*aza*-Michael addition. A round bottom flask was charged with the *para*-quinone methide **2** (0.15 mmol), isoxazolin-5-one **1** (0.1 mmol), 3Å MS (32 mg) and thiourea **V** (3.7 mg, 0.005 mmol). 1,2-Dichloroethane (1 mL) was added and the mixture was stirred at room temperature until completion (TLC). The MS was removed by filtration and the resulting solution was chromatographed on silica gel eluting with hexane:EtOAc mixtures to give compound **3**.

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Keywords: Asymmetric catalysis • enantioselectivity • conjugate addition • heterocycles • alkylation

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[25] CCDC 1961393 contain the supplementary crystallographic data for compound **3ad**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Asymmetric organocatalysis

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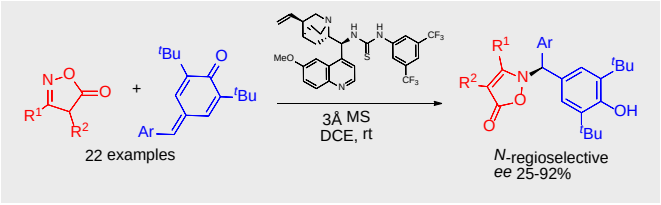

A bifunctional organocatalyst allowed the enantioselective 1,6-*aza*-Michael addition of isoxazolin-5-ones to *p*-quinone methides to give isoxazolin-5-ones having a chiral diarylmethyl moiety attached to the N atom with fair to good yields and enantiomeric excesses.

Ricardo Torán, Carlos Vila, Amparo Sanz-Marco, M.Carmen Muñoz, José R. Pedro, and Gonzalo Blay**

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Organocatalytic enantioselective 1,6-*aza*-Michael addition of isoxazolin-5-ones to *p*-quinone methides