

## RESEARCH ARTICLE

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Cite this: *Org. Chem. Front.*, 2023, **10**, 6081Enantioselective construction of quaternary stereocenters *via* organocatalytic arylation of isoxazolin-5-ones with *o*-quinone diimides†Ricardo Torán,<sup>ID</sup> Eduardo Portillo, Amparo Sanz-Marco,<sup>ID</sup> Carlos Vila<sup>ID</sup> and Gonzalo Blay<sup>ID</sup>\*Received 28th September 2023,  
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A bifunctional squaramide derived from *Cinchona* alkaloid catalyzes the enantioselective arylation of isoxazolin-5-ones with *o*-quinone diimides (*o*-QDIs) to give isoxazolin-5-ones featuring an arylated quaternary stereocenter in high yields and excellent enantioselectivities. To the best of our knowledge, this is the first reported enantioselective arylation of isoxazolin-5-ones and the first application of *o*-QDIs as arylating reagents in asymmetric catalysis.

## Introduction

Carbonyl and related compounds featuring an arylated quaternary stereocenter at the  $\alpha$ -position represent important structural motifs often found in natural products, drugs and bioactive molecules.<sup>1</sup> The construction of these highly congested stereocenters in an enantioselective fashion constitutes a formidable challenge that has garnered increasing attention from synthetic organic chemists.<sup>2</sup> With this regard, catalytic enantioselective  $\alpha$ -arylation of carbonyl or related compounds appears as a convenient strategy to access optically active  $\alpha$ -aryl carbonyl compounds.<sup>3</sup> Two major approaches have been devised to reach this goal: (a) the catalytic asymmetric cross-coupling of electrophilic  $\alpha$ -halocarbonyl compounds with nucleophilic aryl species and (b) the catalytic enantioselective  $\alpha$ -arylation of nucleophilic  $\alpha$ -carbonyl enolates with arylating electrophiles. Approach (a) has found success in generating tertiary stereocenters, although its application in constructing quaternary stereocenters has been limited.<sup>4</sup> On the other hand, there exists a wide array of reactions enabling the arylation of  $\alpha,\alpha$ -disubstituted enolates (approach b). Aryl halides and aryl triflates have been extensively used as arylating reagents under metal catalysis by different authors.<sup>5</sup> Nucleophilic aromatic substitution with  $\alpha$ -substituted esters has been achieved using nitroaryl fluorides or fluoroarene chromium complexes under PTC conditions,<sup>6</sup> while oxindole has been arylated with diaryliodonium salts.<sup>7</sup> Finally, quinone

derivatives have been employed as electrophilic arylating agents to construct various chiral functionalized compounds under a variety of organocatalytic conditions.<sup>8</sup> Despite these remarkable achievements, the asymmetric catalytic arylation of  $\alpha,\alpha$ -disubstituted enolates is still to be developed and there are many limitations in terms of available arylating reagents and the scope of enolate precursors that limit the synthetic applicability. Moreover, many of the reported methods require the use of expensive chiral ligands and precious metals and need harsh conditions, evidencing a shortage of metal-free approaches. Therefore, the development of new reactions based on organocatalytic methods with new arylating agents and other weakly acidic carbon pro-nucleophiles is of great interest to synthetic chemists.

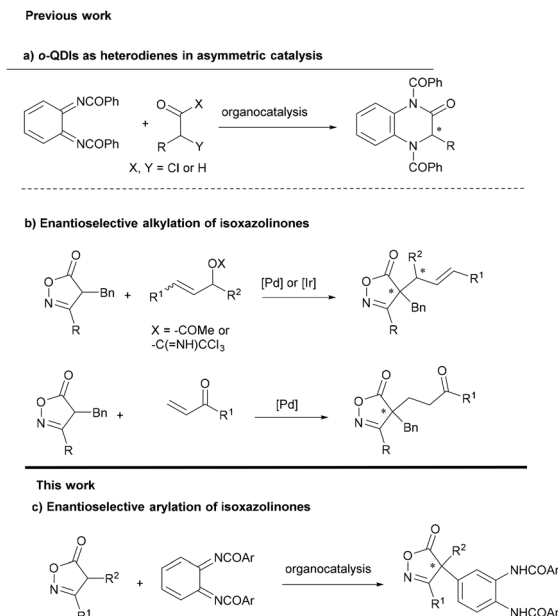
*o*-Quinone diimides (*o*-QDIs) are the diaza analogues of *o*-quinones, featuring a unique 1,2-diiminocyclohexa-3,5-diene structure. They are synthesized *via* the oxidation of 1,2-diaminobenzamides. *o*-QDIs have gained significant attention for their utility as heterodienes in asymmetric formal [4 + 2] cycloaddition reactions<sup>9</sup> that are triggered by aromatization (Scheme 1a). However, there are no antecedents in the literature involving the participation of quinone diimides as arylating reagents in asymmetric reactions.<sup>10</sup>

Isoxazolinones are structural constituents of a wide range of drugs and natural products.<sup>11</sup> They are synthetically versatile building blocks for the synthesis of  $\beta$ -amino acids and other heterocycles.<sup>12</sup> Despite this, asymmetric methods for the alkylation of isoxazolin-5-ones are scarce, compared with other related five-membered heterocycles.<sup>13</sup> This holds particularly true for reactions that produce quaternary stereocenters. Peters described in 2015 the enantioselective alkylation of isoxazolin-5-ones with vinyl ketones<sup>14</sup> and later two methods of C4-allylation using iridium or palladium catalysis (Scheme 1b).<sup>15</sup>

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**Scheme 1** Enantioselective reactions with *o*-QDIs and C–C bond formation at C4 in 4-substituted isoxazolinones.

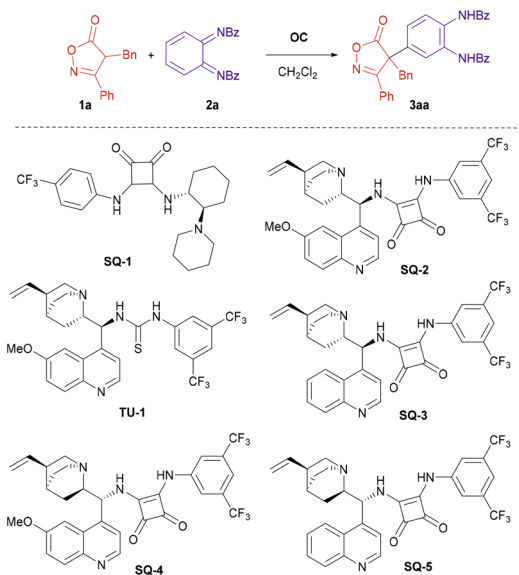
Recently, the group of Li and Li have achieved an organocatalytic addition of isoxazolinones to alkynyl iminoesters providing chiral tetrasubstituted  $\alpha$ -amino allenates.<sup>16</sup>

Herein we report the asymmetric organocatalytic arylation of isoxazolin-5-ones with *o*-QDIs to provide isoxazolin-5-ones bearing an arylated quaternary stereocenter with excellent enantioselectivity (Scheme 1c). To the best of our knowledge this is the first time that *o*-QDIs are used as arylating reagents<sup>17</sup> in enantioselective catalysis and the first enantioselective C4-arylation of isoxazolinones.

## Results and discussion

In the onset of our research we tested the reaction of isoxazolinone **1a** and diimide **2a** in the presence of different organocatalysts (Scheme 2 and Table 1). *Cinchona* alkaloid-derived organocatalyst **SQ-2** gave better results than cyclohexane diamine-derived analogue **SQ-1** (Table 1, entry 1 vs. entry 2), and squaramides gave better results than thioureas (Table 1, entry 2 vs. entry 3). Several *Cinchona* squaramides were tested at 0 °C, **SQ-3** derived from cinchonidine providing the best result (Table 1, entry 5). Replacing dichloromethane by toluene resulted in lower yield and enantioselectivity (Table 1, entry 8). On the other hand, lowering the reaction temperature to –20 °C permitted to further increase the ee of compound **3aa** to 93% keeping the high yield (Table 1, entry 9). Finally, increasing the concentration had a deleterious effect on the yield and enantioselectivity (Table 1, entry 10).

Next, we explored the applicability of the reaction under the optimized conditions. The scope of the isoxazolinone component was first studied (Scheme 3). A number of 3-methyl-



**Scheme 2** Arylation of isoxazolin-5-one **1a** with *o*-QDI **2a** and catalysts used in this study.

**Table 1** Optimization of the reaction conditions according to Scheme 2<sup>a</sup>

Entry	OC	Solvent	<i>T</i> (°C)	Yield <b>3aa</b> <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>SQ-1</b>	CH <sub>2</sub> Cl <sub>2</sub>	rt	55	–33
2	<b>SQ-2</b>	CH <sub>2</sub> Cl <sub>2</sub>	rt	98	78
3	<b>TU-1</b>	CH <sub>2</sub> Cl <sub>2</sub>	rt	83	54
4	<b>SQ-2</b>	CH <sub>2</sub> Cl <sub>2</sub>	0	84	83
5	<b>SQ-3</b>	CH <sub>2</sub> Cl <sub>2</sub>	0	93	90
6	<b>SQ-4</b>	CH <sub>2</sub> Cl <sub>2</sub>	0	79	–89
7	<b>SQ-5</b>	CH <sub>2</sub> Cl <sub>2</sub>	0	83	–80
8	<b>SQ-3</b>	Toluene	0	90	83
9	<b>SQ-3</b>	CH <sub>2</sub> Cl <sub>2</sub>	–20	92	93
10 <sup>d</sup>	<b>SQ-3</b>	CH <sub>2</sub> Cl <sub>2</sub>	–20	90	83

<sup>a</sup> Reaction conditions: **1a** (0.11 mmol), **2** (0.10 mmol), OC (0.01 mmol), solvent (10 mL), 3 h. <sup>b</sup> Yield of **3aa** after column chromatography.

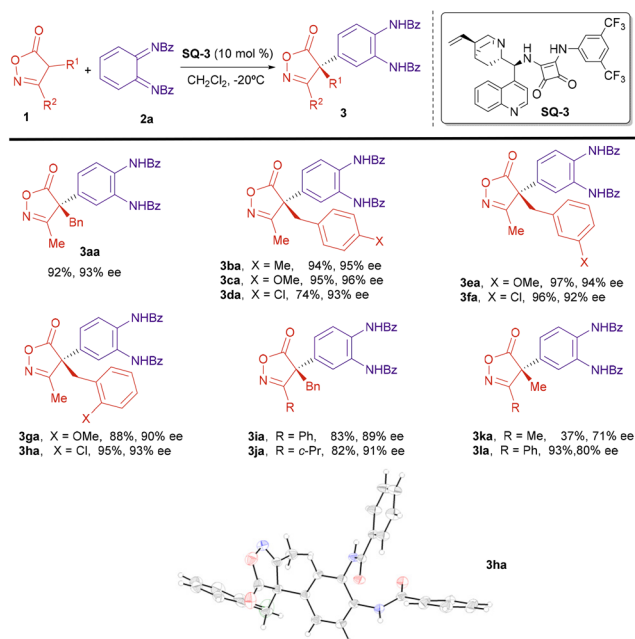
<sup>c</sup> Determined by HPLC; different sign indicates opposite enantiomer.

<sup>d</sup> 5 mL of dichloromethane were used.

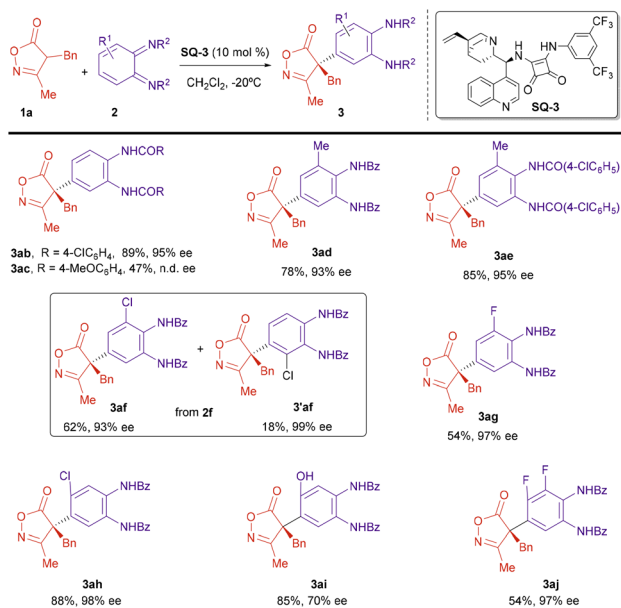
isoxazolinones bearing benzyl derivatives attached to C4 reacted with diimide **2a** to give the corresponding arylated compounds with high yields and excellent enantiomeric excesses, above 90% (**3aa–3ha**). Electron-donating (MeO) or electron-withdrawing (Cl) were groups at different positions of the aromatic ring in the benzyl substituents were allowed without a big effect on the enantioselectivity of the reaction. The substituent at C3 of the isoxazolinone was also amenable to variation. Isoxazolinones **1i** (R<sup>1</sup> = Bn, R<sup>2</sup> = Ph) and **1j** (R<sup>1</sup> = Bn, R<sup>2</sup> = cyclopropyl) reacted also with good yields and enantiomeric excesses near 90%. However, introduction of an alkyl (Me) group at C4 provided the reaction products **3ka** and **3la** with lower ee.

Next, we studied the scope of the diimide **2** (Scheme 4). The benzoic amide group can be substituted by a *p*-chlorobenzoic amide without affecting yield or enantioselectivity (**3ab**).





**Scheme 3** Enantioselective arylation; isoxazolinone scope. Reaction conditions: **1** (0.11 mmol), **2a** (0.10 mmol), **SQ-3** (0.01 mmol), CH<sub>2</sub>Cl<sub>2</sub> (10 mL), -20 °C, 3 h. Yields of compounds **3** after column chromatography. ee determined by HPLC. X-Ray structure of compound **3ha** [Flack parameter 0.042(10)].<sup>†</sup>

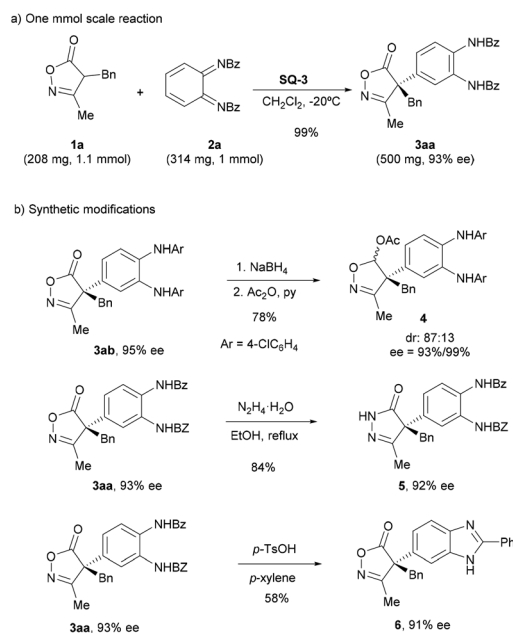


**Scheme 4** Enantioselective arylation; *o*-QDI scope: **1a** (0.11 mmol), **2** (0.10 mmol), **SQ-3** (0.01 mmol), CH<sub>2</sub>Cl<sub>2</sub> (10 mL), -20 °C, 3 h. Yields of compounds **3** after column chromatography. ee determined by HPLC.

A *p*-methoxybenzoic group is also possible, although in this case the reaction took place with lower yield and the ee could not be determined under any of the chromatographic conditions available (**3ac**). Next, we studied the effect of

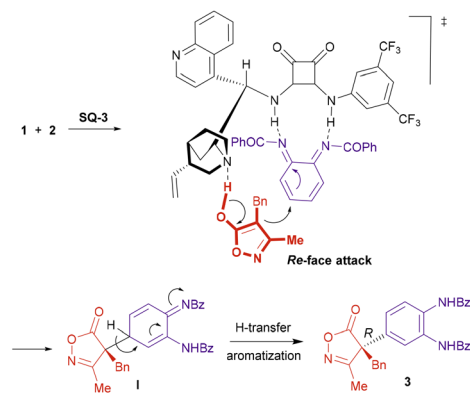
substitution on the cyclohexane ring of the diimide **2**. A methyl group at position 3 was tolerated and the reaction proceeded regioselectively, with excellent yield and enantioselectivity (**3ad** and **3ae**). However, when an electron-withdrawing Cl group was present at position 3, the reaction with oxazolinone **1a** provided a *ca.* 3 : 1 mixture of two regioisomers **3af** and **3'af** with good overall yield and excellent enantioselectivity for both regioisomers (for structure determination of compounds **3ad–3ag** and differentiation between regioisomers **3af** and **3'af**, see ESI<sup>†</sup>). On the other hand, the reaction with the related fluoro-substituted diimide **2g**, provided only one regioisomer **3ag**, in moderated yield and excellent enantioselectivity. Diimides substituted at position 4 were also proper reaction partners. Better enantioselectivities were obtained when this substituent was an electronegative halogen (**3ah**) while a hydroxyl group led to lower enantioselectivity (**3ai**). Finally, we performed the reaction with the 3,4-difluoride substituted imine **2j** that provided the reaction product **3aj** with excellent ee, although in moderated yield.

To show the robustness of the method, the reaction of **1a** with **2a** was performed at 1 mmol scale to provide the expected product **3aa** with excellent yield and identical ee to that obtained in the reaction at 0.1 mmol scale (Scheme 5a). Next, the synthetic potential of the resulting products was shown by performing some chemical transformations (Scheme 5b). Thus, the carbonyl group of the isoxazolinone moiety in **3ab** was selectively reduced upon treatment with sodium borohydride to give an 87 : 13 diastereomeric mixture of the corresponding lactol,<sup>16</sup> which was acetylated to give compound **4**. Transformation of the isoxazolinone ring into a pyrazolone ring **5** could be achieved by treatment with hydrazine in good yield.<sup>18</sup> Finally, the *N,N'*-bis(benzoyl)phenylene-1,2-diamine



**Scheme 5** Synthesis of compound **3aa** at 1 mmol scale and examples of synthetic transformations of compounds **3**.





**Scheme 6** Mechanistic and stereochemical proposal for the arylation reaction.

moiety was converted into benzoimidazole ring **6** upon cyclization in the presence of *p*-TsOH.<sup>19</sup>

Scheme 6 illustrates a plausible mechanism and a stereochemical model for the arylation reaction. The bifunctional catalyst would be responsible for both the activation of the reactants and their orientation in the space. The isoxazolinone would be deprotonated by the tertiary amine of the catalyst, while the quinone diimide would be electrophilically activated through the formation of hydrogen bonds with the squaramide moiety. This arrangement would promote the conjugate addition of the isoxazolinone enolate from its *Re*-face to one of the C–C double bonds in the quinone diimide, resulting in the formation of intermediate **I**. Subsequent proton transfer and concomitant rearomatization would provide compound **3** with the observed *R* configuration at the quaternary stereocenter.

## Conclusions

In conclusion, we have shown by the first time the application of *o*-QDIs as arylating reagents in asymmetric catalysis. A bifunctional squaramide catalyst derived from *Cinchona* alkaloid allowed the enantioselective arylation of isoxazolin-5-ones providing the corresponding products featuring an arylated quaternary stereocenter in high yields and excellent enantioselectivities for a broad range of substrates. To the best of our knowledge, this is the first reported enantioselective arylation of isoxazol-5-ones. The reaction can be scaled up and the synthetic potential has been shown by different synthetic transformations.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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