

RESEARCH ARTICLE

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

derivatives have been employed as electrophilic arylating agents to construct various chiral functionalized compounds under a variety of organocatalytic conditions.⁸ Despite these remarkable achievements, the asymmetric catalytic arylation of α,α -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.

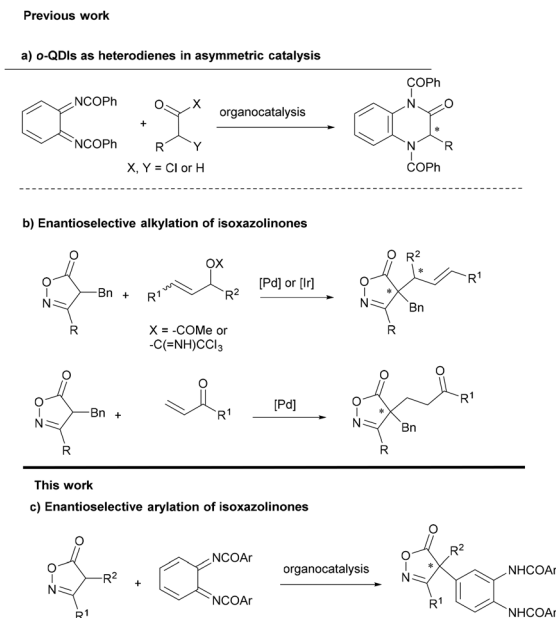
o-Quinone diimides (*o*-QDIs) are the diaza analogues of *o*-quinones, featuring a unique 1,2-diiminocyclohexa-3,5-diene structure. They are synthesized *via* the oxidation of 1,2-diaminobenzamides. *o*-QDIs have gained significant attention for their utility as heterodienes in asymmetric formal [4 + 2] cycloaddition reactions⁹ 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.¹⁰

Isoxazolinones are structural constituents of a wide range of drugs and natural products.¹¹ They are synthetically versatile building blocks for the synthesis of β -amino acids and other heterocycles.¹² Despite this, asymmetric methods for the alkylation of isoxazolin-5-ones are scarce, compared with other related five-membered heterocycles.¹³ This holds particularly true for reactions that produce quaternary stereocenters. Peters described in 2015 the enantioselective alkylation of isoxazolin-5-ones with vinyl ketones¹⁴ and later two methods of C4-allylation using iridium or palladium catalysis (Scheme 1b).¹⁵

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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 α -amino allenates.¹⁶

Herein we report the asymmetric organocatalytic arylation of isoxazolin-5-ones with *o*-QDIs to provide isoxazol-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 reagents¹⁷ 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^a

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

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

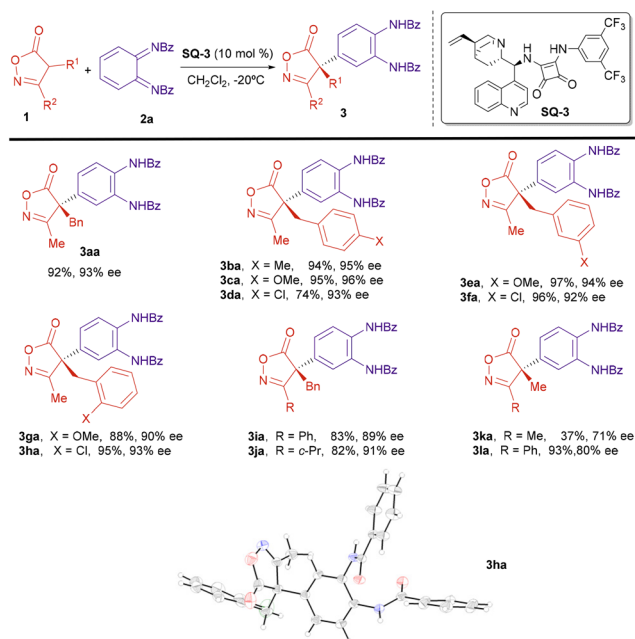
^c Determined by HPLC; different sign indicates opposite enantiomer.

^d 5 mL of dichloromethane were used.

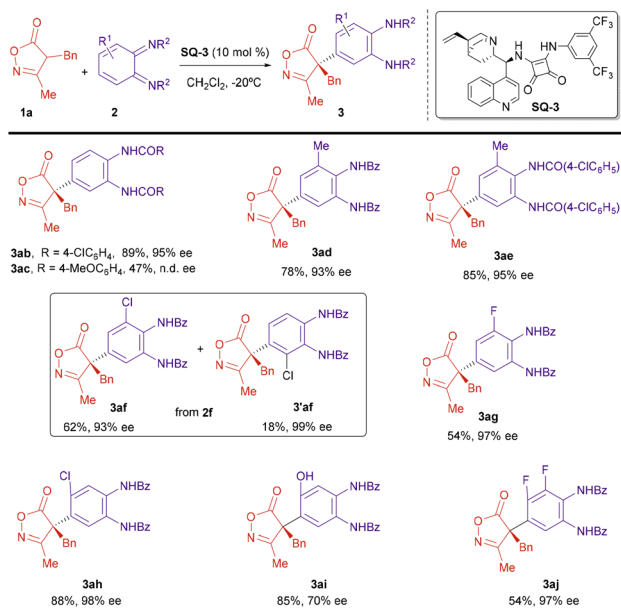
isoxazolinones bearing benzyl derivatives attached to C4 reacted with diimide **2a** to give the corresponding arylated compounds with high yields and excellent enantiomeric excesses, above 90% (**3aa–3ha**). Electron-donating (MeO) or electron-withdrawing (Cl) were groups at different positions of the 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** (R¹ = Bn, R² = Ph) and **1j** (R¹ = Bn, R² = 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_2Cl_2 (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)].[†]

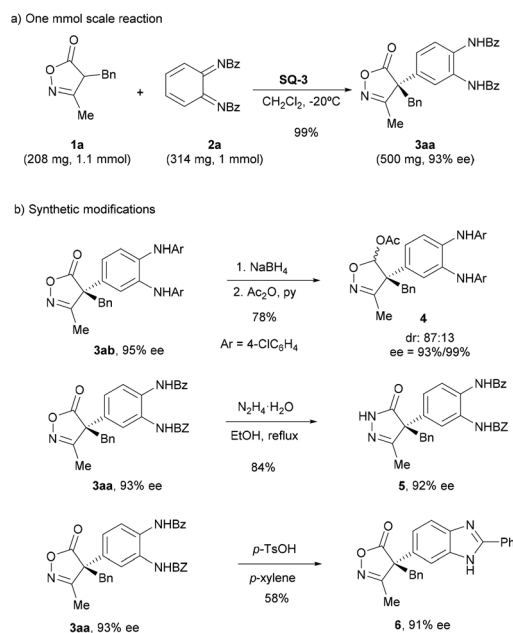


Scheme 4 Enantioselective arylation; *o*-QDI scope: **1a** (0.11 mmol), **2** (0.10 mmol), **SQ-3** (0.01 mmol), CH_2Cl_2 (10 mL), -20°C , 3 h. Yields of compounds **3** after column chromatography. ee determined by HPLC.

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[†]). 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-difluoro 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,¹⁶ 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.¹⁸ 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.¹⁹

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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References

- (a) A. B. Richon, M. E. Maragoudakis and J. S. Wasvary, Isoxazolidine-3,5-diones as lens aldose reductase inhibitors, *J. Med. Chem.*, 1982, **25**, 745; (b) H. Koga, H. Sato, T. Dan and B. Aoki, Studies on uricosuric diuretics. 4. Three-dimensional structure-activity relationships and receptor mapping of (aryloxy)acetic acid diuretics, *J. Med. Chem.*, 1991, **34**, 2702; (c) M. A. Mroue, K. L. Euler, M. A. Ghuman and M. Alam, Indole alkaloids of Haplophyton crooksii, *J. Nat. Prod.*, 1996, **59**, 890; (d) D. Katayev and E. P. Kündig, Catalytic Enantioselective Synthesis of a 3-Aryl-3-benzoyloxindole (= 3-Aryl-3-benzyl-1,3-dihydro-2*H*-indol-2-one) Exhibiting Antitumor Activity, *Helv. Chim. Acta*, 2012, **95**, 2287.
- Reviews: (a) L. Susse and B. M. Stoltz, Enantioselective Formation of Quaternary Centers by Allylic Alkylation with First Row Transition Metal Catalysts, *Chem. Rev.*, 2021, **121**, 4084; (b) Z. Wang, Construction of all-carbon quaternary stereocenters by catalytic asymmetric conjugate addition to cyclic enones in natural product synthesis, *Org. Chem. Front.*, 2020, **7**, 3815; (c) E. V. Prusov, Construction of Quaternary Stereogenic Centers in the Total Synthesis of Natural Products, *Angew. Chem., Int. Ed.*, 2017, **56**, 14356; (d) Y. Liu, S.-J. Han, W.-B. Liu and B. M. Stoltz, Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of Key Building Blocks for the Synthesis of Biologically Active Molecules, *Acc. Chem. Res.*, 2015, **48**, 740; (e) Y. Minko and I. Marek, Stereodefined acyclic trisubstituted metal enolates towards the asymmetric formation of quaternary carbon stereocentres, *Chem. Commun.*, 2014, **50**, 12597; (f) M. Bella and T. Gasperi, Organocatalytic formation of quaternary stereocenters, *Synthesis*, 2009, 1583; (g) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, ed. J. Christoffers and A. Baro, Wiley-VCH, Weinheim, Germany, 2006.
- For an excellent review see: Y.-J. Hao, X.-S. Hu, Y. Zhou, J. Zhou and J.-S. Yu, Catalytic Enantioselective α -Arylation of Carbonyl Enolates and Related Compounds, *ACS Catal.*, 2020, **10**, 955.
- (a) Friedel–Crafts reaction: J. Zhou, Z.-H. Li, L. Wang, J.-C. Kang, X.-H. Wang and S.-Y. Zhang, Base-Promoted Cobalt-Catalyzed Regio- and Enantioselective para-Friedel–Crafts Alkylation of Aniline Derivatives, *Org. Lett.*, 2021, **23**, 9353; (b) Boronic esters: F.-L. Wang, L. Liu, C.-J. Yang, C. Luan, J. Yang, J.-J. Chen, Q.-S. Gu, Z.-L. Li and X.-Y. Liu, Synthesis of α -Quaternary β -Lactams via Copper-Catalyzed Enantioconvergent Radical C(sp³)-C(sp²) Cross-Coupling



- with Organoboronate Esters, *Angew. Chem., Int. Ed.*, 2023, **62**, e202214709; (c) Aryl tin reagents: Y. Liang and G. C. Fu, Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides: Negishi Cross-Couplings of Racemic α,α -Dihaloketones, *J. Am. Chem. Soc.*, 2014, **136**, 5520; (d) Grignard reagents: H. Yin and G. C. Fu, Mechanistic Investigation of Enantioconvergent Kumada Reactions of Racemic α -Bromoketones Catalyzed by a Nickel/Bis(oxazoline) Complex, *J. Am. Chem. Soc.*, 2019, **141**, 15433; (e) For an α -arylation of α -diazoesters see: X.-S. Liu, Z. Tang, Z.-Y. Si, Z. Zhang, L. Zhao and L. Liu, Enantioselective para-C(sp²)-H Functionalization of Alkyl Benzene Derivatives via Cooperative Catalysis of Gold/Chiral Bronsted Acid, *Angew. Chem., Int. Ed.*, 2022, **61**, e202208874.
- 5 Pioneering and selected examples: (a) T. Hamada, A. Chieffi, J. Åhman and S. L. Buchwald, An Improved Catalyst for the Asymmetric Arylation of Ketone Enolates, *J. Am. Chem. Soc.*, 2002, **124**, 1261; (b) G. Chen, F. Y. Kwong, H. O. Chan, W.-Y. Yu and A. S. C. Chan, Nickel-catalyzed asymmetric α -arylation of ketone enolates, *Chem. Commun.*, 2006, 1413; (c) X. Liao, Z. Weng and J. F. Hartwig, Enantioselective α -Arylation of Ketones with Aryl Triflates Catalyzed by Difluorophos Complexes of Palladium and Nickel, *J. Am. Chem. Soc.*, 2008, **130**, 195; (d) J. Cornella, E. P. Jackson and R. Martin, Nickel-Catalyzed Enantioselective C-C Bond Formation through CSP₂-O Cleavage in Aryl Esters, *Angew. Chem., Int. Ed.*, 2015, **54**, 4075; (e) A. Ghosh, J. A. Walker Jr., A. Ellern and L. M. Stanley, Coupling Catalytic Alkene Hydroacylation and α -Arylation: Enantioselective Synthesis of Heterocyclic Ketones with α -Chiral Quaternary Stereocenters, *ACS Catal.*, 2016, **6**, 2673; (f) X. Rao, N. Li, H. Bai, C. Dai, Z. Wang and W. Tang, Efficient Synthesis of (–)-Corynoline by Enantioselective Palladium-Catalyzed α -Arylation with Sterically Hindered Substrates, *Angew. Chem., Int. Ed.*, 2018, **57**, 12328; (g) X. Xie, Y. Chen and D. Ma, Enantioselective Arylation of 2-Methylacetoacetates Catalyzed by CuI/trans-4-Hydroxy-L-proline at Low Reaction Temperatures, *J. Am. Chem. Soc.*, 2006, **128**, 16050; (h) E. P. Kündig, T. M. Seidel, Y. X. Jia and G. Bernardinelli, Bulky chiral carbene ligands and their application in the palladium-catalyzed asymmetric intramolecular α -arylation of amides, *Angew. Chem., Int. Ed.*, 2007, **46**, 8484; (i) C. I. Jette, I. Geibel, S. Bachman, M. Hayashi, S. Sakurai, H. Shimizu, J. B. Morgan and B. M. Stoltz, Palladium-Catalyzed Construction of Quaternary Stereocenters by Enantioselective Arylation of γ -Lactams with Aryl Chlorides and Bromides, *Angew. Chem., Int. Ed.*, 2019, **58**, 4297.
- 6 (a) M. Bella, S. Kobbelgaard and K. A. Jørgensen, Organocatalytic Regio- and Asymmetric C-Selective SNAr Reactions-Stereoselective Synthesis of Optically Active Spiro-pyrrolidone-3,3'-oxoindoles, *J. Am. Chem. Soc.*, 2005, **127**, 3670; (b) S. Shirakawa, K. Koga, T. Tokuda, K. Yamamoto and K. Maruoka, Catalytic asymmetric synthesis of 3,3'-diaryloxindoles as triarylmethanes with a chiral all-carbon quaternary center: Phase-transfer-catalyzed SNAr reaction, *Angew. Chem., Int. Ed.*, 2014, **53**, 6220; (c) S. Shirakawa, K. Yamamoto and K. Maruoka, Phase-Transfer-Catalyzed Asymmetric SNAr Reaction of α -Amino Acid Derivatives with Arene Chromium Complexes, *Angew. Chem., Int. Ed.*, 2015, **54**, 838.
- 7 J. Guo, S. Dong, Y. Zhang, Y. Kuang, X. Liu, L. Lin and X. Feng, Chiral Scandium(III)-Catalyzed Enantioselective α -Arylation of N-Unprotected 3-Substituted Oxindoles with Diaryliodonium Salts, *Angew. Chem., Int. Ed.*, 2013, **52**, 10245.
- 8 (a) J. Alemán, B. Richter and K. A. Jørgensen, Organocatalytic highly enantioselective α -arylation of β -ketoesters, *Angew. Chem., Int. Ed.*, 2007, **46**, 5515; (b) W.-Y. Siau, W. Li, F. Xue, Q. Ren, M. Wu, S. Sun and H. Guo, Catalytic and Enantioselective α -Functionalization of Oxindoles Through Oxidative Reactions with Naphthoquinones, *Chem. – Eur. J.*, 2012, **18**, 9491; (c) J.-S. Yu, F. Zhou, Y.-L. Liu and J. Zhou, Organocatalytic asymmetric Michael addition of unprotected 3-substituted oxindoles to 1,4-naphthoquinone, *Beilstein J. Org. Chem.*, 2012, **8**, 1360; (d) G. Li, W. Sun, J. Li, F. Jia, L. Hong and R. Wang, Organocatalytic enantioselective formal arylation of azlactones using quinones as the aromatic partner, *Chem. Commun.*, 2015, **51**, 11280; (e) Y. Liu, J. Li, X. Ye, X. Zhao and Z. Jiang, Organocatalytic asymmetric formal arylation of benzofuran-2(3H)-ones with cooperative visible light photocatalysis, *Chem. Commun.*, 2016, **52**, 13955; (f) G. Zhu, G. Bao, Y. Li, J. Yang, W. Sun, J. Li and R. Hong, Chiral Phosphoric Acid Catalyzed Asymmetric Oxidative Dearomatization of Naphthols with Quinones, *Org. Lett.*, 2016, **18**, 5288.
- 9 (a) C. J. Abraham, D. H. Paull, M. T. Scerba, J. W. Grebinski and T. Lectka, Catalytic, Enantioselective Bifunctional Inverse Electron Demand Hetero-Diels-Alder Reactions of Ketene Enolates and *o*-Benzoquinone Diimides, *J. Am. Chem. Soc.*, 2006, **128**, 13370; (b) R. Huang, X. Chen, C. Mou, G. Luo, Y. Li, X. Li, W. Xue, Z. Jin and Y. R. Chi, Carbene-Catalyzed α -Carbon Amination of Chloroaldehydes for Enantioselective Access to Dihydroquinoxaline Derivatives, *Org. Lett.*, 2019, **21**, 4340; (c) S.-L. Zhou, J.-L. Li, L. Dong and Y.-C. Chen, Organocatalytic Sequential Hetero-Diels-Alder and Friedel-Crafts Reaction: Constructions of Fused Heterocycles with Scaffold Diversity, *Org. Lett.*, 2011, **13**, 5874.
- 10 Two examples of allylation reactions of *o*-QDIs using allyltri-*n*-butylstannane or allyltri-*n*-butylstannanes have been reported under achiral Lewis acid catalysis: (a) V. Nair, R. Dhanya, N. Vidya and S. Devipriya, Lewis acid catalyzed addition of allylsilane to *o*-quinonediimides: formal Diels-Alder reaction versus allylation, *Synthesis*, 2006, 107; (b) V. Nair, R. Dhanya, C. Rajesh, M. M. Bhadbhade and M. Manoj, Lewis Acid-Promoted Annulation of *o*-Quinonediimines by Allylstannane: A Facile Synthesis of Quinoxaline Derivatives, *Org. Lett.*, 2004, **6**, 4743.
- 11 (a) P. Rozan, Y.-H. Kuo and F. Lambein, Amino acids in seeds and seedlings of the genus *Lens*, *Phytochemistry*,



- 2001, **58**, 281; (b) E. Hedner, M. Sjögren, S. Hodzic, R. Andersson, U. Göransson, P. R. Jonsson and L. Bohlin, Antifouling Activity of a Dibrominated Cyclopeptide from the Marine Sponge *Geodia barretti*, *J. Nat. Prod.*, 2008, **71**, 330; (c) S. S. Mahajan, M. Scian, S. Sripathy, J. Posakony, U. Lao, T. K. Loe, V. Leko, A. Thalhofer, A. D. Schuler, A. Bedalov and J. A. Simon, Development of Pyrazolone and Isoxazol-5-one Cambinol Analogues as Sirtuin Inhibitors, *J. Med. Chem.*, 2014, **57**, 3283; (d) B. Kafle, N. G. Aher, D. Khadka, H. Park and H. Cho, Isoxazol-5(4H)one Derivatives as PTP1B Inhibitors Showing an Anti-Obesity Effect, *Chem. – Asian J.*, 2011, **6**, 2073; (e) C. Vergelli, I. A. Schepetkin, L. Crocetti, A. Iacovone, M. P. Giovannoni, G. Guerrini, A. I. Khlebnikov, S. Ciattini, G. Ciciani and M. T. Quinn, Isoxazol-5(2H)-one: a new scaffold for potent human neutrophil elastase (HNE) inhibitors, *J. Enzyme Inhib. Med. Chem.*, 2017, **32**, 821.
- 12 (a) A review: A. F. da Silva, A. A. G. Fernandes, S. Thurow, M. L. Stivanin and I. D. Jurberg, Isoxazol-5-ones as Strategic Building Blocks in Organic Synthesis, *Synthesis*, 2018, 2473; (b) M. L. Stivanin, M. Duarte, C. Sartori, N. M. R. Capreti, C. F. F. Angolini and I. D. Jurberg, An Aminocatalyzed Michael Addition/Iron-Mediated Decarboxylative Cyclization Sequence for the Preparation of 2,3,4,6-Tetrasubstituted Pyridines: Scope and Mechanistic Insights, *J. Org. Chem.*, 2017, **82**, 10319; (c) N. Wannenmacher, C. Pfeffer, W. Frey and R. Peters, Enantioenriched γ -Aminoalcohols, β -Amino Acids, β -Lactams and Azetidines Featuring Tetrasubstituted Fluorinated Stereocenters via Palladacycle-Catalyzed Asymmetric Fluorination of Isoxazolinones, *J. Org. Chem.*, 2022, **87**, 670.
- 13 Enantioselective *N*-alkylation: (a) R. Torán, C. Vila, A. Sanz-Marco, M. C. Muñoz, J. R. Pedro and G. Blay, Organocatalytic Enantioselective 1,6-aza-Michael Addition of Isoxazolin-5-ones to *p*-Quinone Methides, *Eur. J. Org. Chem.*, 2020, 627; (b) S.-S. Qi, Z.-H. Jiang, M.-M. Chu, Y.-F. Wang, X.-Y. Chen, W.-Z. Ju and D.-Q. Xu, Regioselective catalytic asymmetric *N*-alkylation of isoxazol-5-ones with *para*-quinone methides, *Org. Biomol. Chem.*, 2020, **18**, 2398; (c) F. Li, S. Liang, Y. Luan, X. Chen, H. Zhao, A. Huang, P. Li and W. Li, Organocatalytic regio-, diastereo- and enantioselective γ -additions of isoxazol-5(4H)-ones to β,γ -alkynyl- α -imino esters for the synthesis of axially chiral tetrasubstituted α -amino allenoates, *Org. Chem. Front.*, 2021, **8**, 1243. Enantioselective *C*-alkylation: (d) R. Torán, D. Puchan, A. Sanz-Marco, C. Vila, J. R. Pedro and G. Blay, Organocatalytic enantioselective Mannich reaction of isoxazol-5(4H)-ones to isatin-derived ketimines, *Org. Biomol. Chem.*, 2022, **20**, 8395; (e) W.-T. Meng, Y. Zheng, J. Nie, H.-Y. Xiong and J.-A. Ma, Organocatalytic asymmetric one-pot sequential conjugate addition/dearomatic fluorination: synthesis of chiral fluorinated isoxazol-5(4H)-ones, *J. Org. Chem.*, 2013, **78**, 559.
- 14 T. Hellmuth, W. Frey and R. Peters, Regioselective Catalytic Asymmetric *C*-Alkylation of Isoxazolinones by a Base-Free Palladacycle-Catalyzed Direct 1,4-Addition, *Angew. Chem., Int. Ed.*, 2015, **54**, 2788.
- 15 (a) S. Rieckhoff, J. Meisner, J. Kästner, W. Frey and R. Peters, Double Regioselective Asymmetric *C*-Allylation of Isoxazolinones: Iridium-Catalyzed *N*-Allylation Followed by an Aza-Cope Rearrangement, *Angew. Chem., Int. Ed.*, 2018, **57**, 1404; (b) X. Yu, L. Hu, W. Frey, G. Lu and R. Peters, Stereoretentive Regio- and Enantioselective Allylation of Isoxazolinones by a Planar Chiral Palladacycle Catalyst, *Angew. Chem., Int. Ed.*, 2022, **61**, e202210145.
- 16 F. Li, S. Liang, Y. Luan, X. Chen, H. Zhao, A. Huang, P. Li and W. Li, Organocatalytic regio-, diastereo- and enantioselective γ -additions of isoxazol-5(4H)-ones to β,γ -alkynyl- α -imino esters for the synthesis of axially chiral tetrasubstituted α -amino allenoates, *Org. Chem. Front.*, 2021, **8**, 1243.
- 17 Recently, we have reported the non enantioselective arylation of isocyanacetate esters with *o*-QDIs: A. Laviós, P. Martínez-Pardo, A. Sanz-Marco, C. Vila, J. R. Pedro and G. Blay, Synthesis of α,α -Diaryl- α -amino Acid Precursors by Reaction of Isocyanacetate Esters with *o*-Quinone Diimides, *Org. Lett.*, 2023, **25**, 5608.
- 18 T. Zhao, H. Zhang, L. Cui, C. Wang, J. Qu and B. Wang, A ZnCl₂-Catalyzed Knoevenagel Condensation/1,5-Hydride Shift/Cyclization Sequence: Synthesis of Novel Spiroisoxazol-5-one Tetrahydroquinolines, *ChemistrySelect*, 2016, **1**, 3713.
- 19 M. R. DeLuca and S. M. Kerwin, The *para*-toluenesulfonic acid-promoted synthesis of 2-substituted benzoxazoles and benzimidazoles from diacylated precursors, *Tetrahedron*, 1997, **53**, 457.

