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


Abstract: A thiourea-Bronsted 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 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 thiaocetic 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-alkylation 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 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]

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 isoxazolrones.[21] Peters reported the regioselective C-alkylation of 4-substituted isoxazolonones forming quaternary stereocenters by a palladium-catalyzed 1,4-addition to vinyl ketones.[22] The same group reported later a regioselective asymmetric C-alkylation of isoxazolinones via a iridium-catalyzed N-alkylation followed by a spontaneous aza-Cope rearrangement. In this study, N-alkylated 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]
In this communication, we report our results on the asymmetric N-alkylation of isoxazolines via a 1,6-aza-Michael addition to p-QMs to give isoxazolines 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(3H)-isoxazol-5-one (1a) and p-QM 2a. and organocatalysts used in this study.](image)

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

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[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-methyl-4(3H)-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 isoxazolines 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(3H)-isoxazol-5-ones 1 to p-quinone methides 2 catalyzed by thiourea V. Reaction scope. 

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[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, entries 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-dimethyl-4(H)-isoxazol-5-one (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-quinoine 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.


Asymmetric organocatalysis

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.

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Materials and methods.

All reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for $^1$H and at 75 MHz for $^{13}$C NMR using residual nondeuterated solvent (CHCl$_3$) as internal standard ($\delta$ 7.26 and 77.0 ppm, respectively). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI). Specific optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary phase columns from Daicel or Phenomenex.

General procedure for the synthesis of isoxazole-5-ones (1a-1d).$^{[1,2]}$

To a round bottom flask charged with HONH$_2$$\cdot$HCl (1.5 eq) in EtOH (0.5 M respect to the $\beta$-ketoester), is added NaOAc (1.5 eq). The mixture is allowed to stir at room temperature for 5 min. Then, the $\beta$-ketoester (1 eq) is added. The reaction is heated to reflux until no more starting material is detected on TLC (one typically observes the presence of both the final product and the oxime intermediate). At this point, the solution is allowed to cool to room temperature, HCl$_{37\%}$ (5 $\mu$L/ mmol $\beta$-ketoester) is added, and the solution is heated back to reflux until no more oxime can be observed on TLC (4-6h). Next, the solution is filtered and concentrated under reduced pressure. If necessary, the crude material can be purified by recrystallization or flash column chromatography.

3-Methylisoxazol-5(4H)-one (1a)$^{[1]}$

From ethyl acetoacetate (2.0 g, 15.4 mmol), 1.45 g (95%) of compound 1a were obtained after column chromatograph.; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.39 (2H, q, $J = 0.9$ Hz, CH$_2$), 2.16 (3H, t, $J = 0.9$ Hz, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.3 (C, C=O), 163.6 (C=N), 36.9 (CH$_3$), 14.7 (CH$_3$).
3-Ethylisoxazol-5(4H)-one (2b)\cite{1}

From ethyl 3-oxopentanoate (1.0 g, 6.93 mmol), 768.9 mg (98%) of compound 1b were obtained after column chromatography. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.38 (2H, s, CH$_2$-C=O), 2.50 (2H, q, $J$ = 7.5 Hz, CH$_2$-CH$_3$), 1.23 (3H, t, $J$ = 7.5 Hz, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.2 (C, C=O), 167.7 (C, C=N), 35.6 (CH$_2$, CH$_2$-C=O), 22.8 (CH$_2$, Et), 10.1 (CH$_3$, Et).

3-Propylisoxazol-5(4H)-one (1c)\cite{2}

From ethyl 3-oxohexanoate (1.0 g, 6.33 mmol), 739.8 mg (92%) of compound 1c were obtained after column chromatography. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.37 (2H, s, CH$_2$-CO), 2.44 (2H, t, $J$ = 7.5 Hz, CH$_2$-CH$_2$-CH$_3$), 1.64 (2H, sextuplet, $J$ = 7.5 Hz, CH$_2$-CH$_2$-CH$_3$), 1.00 (3H, t, $J$ = 7.5 Hz, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.3 (C, C=O), 166.8 (C, C=N), 35.7 (CH$_2$, CH$_2$-C=O), 30.9 (CH$_2$, CH$_2$-CH$_2$-CH$_3$), 19.3 (CH$_2$, CH$_2$-CH$_2$-CH$_3$), 13.6 (CH$_3$, CH$_2$-CH$_2$-CH$_3$).

3-Phenylisoxazol-5(4H)-one (1d)\cite{1}

From ethyl 3-oxo-3-phenylpropanoate (1.0 g, 5.20 mmol), 721.1 mg (86%) of compound 1d were obtained after column chromatography. $^1$H NMR (300 MHz, CDCl$_3$), $\delta$ 7.68 (2H, dt, $J_1$ = 5.7 Hz, $J_2$ = 1.5 Hz, Ar), 7.67-7.47 (3H, m, Ar), 3.81 (2H, t, $J$=2.7 Hz, CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ 174.7 (C, C=O), 163.1 (C, C=N), 132.1 (CH, Ar), 129.2 (CH, Ar), 127.5 (C, Ar), 126.6 (CH, Ar), 33.9 (CH$_2$, CH$_2$-CO).

Synthesis of 3-cyclopropylisoxazol-5(4H)-one (1e)\cite{3}

Et$_3$N (2.19 mL, 15.8 mmol) is added to a solution of HONH$_2$·HCl (1.09 g, 15.8 mmol) in MeOH (37 mL). The mixture is stirred at room temperature for 5 min and methyl 3-cyclopropyl-3-oxopropanoate (2.00 g, 14.1 mmol) is added. The reaction is heated to reflux for 3 hours, then allowed to cool to room temperature, filtered and washed with EtOAc (30 mL). The filtrate was concentrated under reduced pressure and chromatographed eluting with EtOC to give 1.47 g (83%) of compound 1e. $^1$H NMR
(300 MHz, CDCl3) δ 3.25 (2H, t, J = 0.5 Hz, CH₂), 1.85-1.78 (1H, m, c-Pr), 1.09-1.06 (2H, m, c-Pr), 0.91-0.86 (2H, m, c-Pr); ¹³C NMR (75 MHz, CDCl3) δ 175.0 (C, C=O), 168.9 (C, C=N), 34.2 (CH₂, CH₂-CO), 10.1 (CH, c-Pr), 7.39 (CH₂, c-Pr).

Procedure for the synthesis of 3,4-dimethylisoxazol-5(4H)-one (1f).[4]

Pyridine (3.35 mL, 41.6 mmol) is added to a solution of HONH₂·HCl (1.92 g, 27.7 mmol) in EtOH (14 mL). The mixture is stirred at room temperature for 5 min and ethyl 2-methyl-3-oxobutanoate (2.00 g, 13.9 mmol) is added. The reaction mixture is heated to 60 ºC for x hours until no starting material is detected (TLC) and allowed to cool to rt. H₂O (40 mL) is added and the mixture is extracted with EtOAc (3 × 40 mL), the organic layer is washed with 1M HCl (20 mL) and brine (2 × 20 mL). The combined organic layer is dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Column chromatography gave 0.988 mg (63%) of compound 1f. ¹H NMR (300 MHz, CDCl₃), δ 3.30 (1H, q, J = 7.8 Hz, CHimine), 2.14 (1.50H, s, CH₃, enamine), 2.10 (3H, s, CH₃, imine), 1.77 (1.50H, s, CH₃, enamine), 1.45 (3H, s, CH₃, imine).

General procedure for the synthesis of p-quinone methides (2a-2n).[5-6]

A mixture of aldehyde (4.85 mmol) and 2,6-di-tert-butylphenol (1.0 g, 4.85 mmol) in toluene (20 mL) was placed in a round bottom flask provided with a Dean-Stark system. The mixture was brought to reflux and piperidine (0.96 mL, 4.85 mmol) was dropwise added within an hour and the resultant mixture was stirred at reflux temperature for further 12 hours. The reaction mixture was cooled to 100 ºC and acetic anhydride (0.92 mL, 9.7 mmol) was added and the resulting solution was stirred for 30 minutes at the same temperature. The reaction mixture was then cooled to room temperature and poured into ice cold water (50 mL) and extracted with dichloromethane (2 × 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and
concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain a pure $p$-quinone methide.

4-Benzylidene-2,6-di-tert-butylcyclohexa-2,5-dien-1-one (2a)\textsuperscript{[5]}

From 2,6-di-tert-butylphenol (2.0 g, 9.69 mmol) and benzaldehyde (0.98 mL, 9.69 mmol), 1.49 g (52\%) of compound 2a were obtained after column chromatography. $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.36 (1H, d, $J$ = 2.4 Hz), 7.27-7.17 (5H, m), 6.98 (1H, s), 6.84 (1H, d, $J$ = 2.4 Hz), 1.17 (9H, s), 1.13 (9H, s); $^{13}$C NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ 186.6 (C), 147.8 (C), 145.9 (C), 142.5 (CH), 135.1 (CH), 131.9 (C), 130.3 (CH), 129.0 (C), 128.7 (CH), 127.8 (CH), 35.4 (C), 34.9 (C), 29.5 (CH\textsubscript{3}), 29.4 (CH\textsubscript{3}).

2,6-Di-tert-butyl-4-(4-methylbenzylidene)cyclohexa-2,5-dien-1-one (2b)\textsuperscript{[5]}

From 2,6-di-tert-butylphenol (1.0 g, 4.85 mmol), and 4-methylbenzaldehyde (0.57 mL, 4.85 mmol), 598.4 mg (40\%) of compound 2b were obtained after column chromatography. $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.55 (1H, d, $J$ = 2.3 Hz), 7.38 (1H, s), 7.36 (1H, s), 7.27 (1H, s), 7.25 (1H, s), 7.16 (1H, s), 7.01 (1H, d, $J$ = 2.3 Hz), 2.41 (3H, s), 1.34 (9H, s), 1.31 (9H, s); $^{13}$C NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ 186.5 (C), 149.7 (C), 148.1 (C), 140.6 (CH), 135.1 (C) 134.9 (CH), 134.4 (C), 132.4 (C), 131.5 (CH), 129.1 (CH), 127.3 (CH), 35.5 (C), 35.0 (C), 29.5 (CH\textsubscript{3}), 29.4 (CH\textsubscript{3}).

2,6-Di-tert-butyl-4-(4-methoxybenzylidene)cyclohexa-2,5-dien-1-one (2c)\textsuperscript{[5]}

From 2,6-di-tert-butylphenol (1.0 g, 4.85 mmol) and 4-methoxybenzaldehyde (0.59 mL, 4.85 mmol), 849.8 mg (54\%) of compound 2c were obtained after column chromatography. $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.56-7.60 (1H, m), 7.45-7.43 (2H, m), 7.13 (1H, s), 7.00-7.09 (2H, m), 6.97 (1H, m), 3.87 (3H, s), 1.33 (9H, s), 1.32 (9H, s); $^{13}$C NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ 186.5 (C), 160.6 (C), 148.9 (C), 147.2 (C), 142.7 (CH), 135.4 (CH), 132.2 (CH), 130.5 (C), 128.6 (C), 127.8 (CH), 114.4 (CH), 55.8 (CH\textsubscript{3}O), 35.4 (C), 34.9 (C), 29.6 (CH\textsubscript{3}), 29.5 (CH\textsubscript{3}).
**2,6-Di-**-**tert**-butyl-4-(4-chlorobenzylidene)cyclohexa-2,5-dien-1-one (2d)**[5]**

From 2,6-di-**tert**-butylphenol (1.0 g, 4.85 mmol), and 4-chlorobenzaldehyde (0.68 g, 4.85 mmol), 733.7 mg (46%) of compound 2d were obtained after column chromatography.  

**\( ^1H \) NMR** (300 MHz, CDCl3) \( \delta \) 7.44-7.36 (5H, m), 7.11 (1H, s), 6.98 (1H, d, \( J = 2.4 \) Hz), 1.33 (9H, s), 1.29 (9H, s);  

**\( ^13C \) NMR** (75 MHz, CDCl3) \( \delta \) 186.6 (C), 149.1 (C), 147.5 (C), 142.8 (CH), 139.5 (C), 135.3 (CH), 133.2 (C), 131.4 (C), 130.5 (CH), 129.6 (CH), 127.9 (CH), 35.4 (C), 34.9 (C), 29.5 (CH3), 29.4 (CH3).

**2,6-Di-**-**tert**-butyl-4-(4-nitrobenzylidene)cyclohexa-2,5-dien-1-one (2e)**[5]**

From 2,6-di-**tert**-butylphenol (1.0 g, 4.85 mmol), and 4-nitrobenzaldehyde (0.73 g, 4.85 mmol), 856.1 mg (52%) of compound 2e were obtained after column chromatography.  

**\( ^1H \) NMR** (300 MHz, CDCl3) \( \delta \) 7.60-7.63 (2H, m), 7.55-7.57 (2H, m), 7.37 (1H, d, \( J = 2.4 \) Hz), 7.15 (1H, s), 7.01 (1H, d, \( J = 2.4 \) Hz), 1.33 (9H, s), 1.29 (9H, s);  

**\( ^13C \) NMR** (75 MHz, CDCl3) \( \delta \) 186.4 (C), 150.7 (C), 149.1 (C), 147.4 (C), 142.3 (C), 138.3 (CH), 134.4 (C), 134.3 (CH), 130.7 (CH), 126.6 (CH), 123.9 (CH), 35.5 (C), 35.1 (C), 29.5 (CH3), 29.4 (CH3).

**2,6-Di-**-**tert**-butyl-4-(2-methoxybenzylidene)cyclohexa-2,5-dien-1-one (2f)**[5]**

From 2,6-di-**tert**-butylphenol (1.0 g, 4.85 mmol), and 2-methoxybenzaldehyde (0.59 mL, 4.85 mmol), 676.7 mg (43%) of compound 2f were obtained after column chromatography.  

**\( ^1H \) NMR** (300 MHz, CDCl3) \( \delta \) 7.46 (1H, d, \( J = 2.3 \) Hz), 7.42 (2H, m), 7.36 (1H, s), 7.07 (1H, d, \( J = 2.3 \) Hz), 6.94-7.04 (2H, m), 3.89 (3H, s), 1.34 (9H, s), 1.29 (9H, s);  

**\( ^13C \) NMR** (75 MHz, CDCl3) \( \delta \) 186.7 (C), 158.3 (C), 148.9 (C), 147.4 (C), 138.7 (CH), 135.3 (CH), 131.8 (CH), 131.1 (C), 130.8 (CH), 128.3 (CH), 124.9 (C), 120.5 (CH), 110.8 (CH), 55.5 (CH3), 35.4 (C), 34.9 (C), 29.5 (CH3), 29.4 (CH3).
2,6-Di-tert-butyl-4-(2-chlorobenzylidene)cyclohexa-2,5-dien-1-one (2g)\[^5\]

![Image of 2,6-Di-tert-butyl-4-(2-chlorobenzylidene)cyclohexa-2,5-dien-1-one (2g)](image)

From 2,6-di-tert-butylphenol (1.0 g, 4.85 mmol), and 2-chlorobenzaldehyde (0.54 mL, 4.85 mmol), 845.4 mg (53%) of compound 2g were obtained after column chromatography. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.50-7.30 (6H, m), 7.07 (1H, d, \(J = 2.3\) Hz), 1.34 (9H, s), 1.27 (9H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 186.6 (C), 149.7 (C), 148.3 (C), 148.6 (CH), 134.6 (CH), 134.1 (C), 132.8 (C), 132.1 (CH), 130.1 (CH), 130.0 (CH), 127.6 (CH), 126.6 (CH), 35.4 (C), 35.1 (C), 29.5 (CH\(_3\)), 29.4 (CH\(_3\)).

4-(2-Bromobenzylidene)-2,6-di-tert-butylcyclohexa-2,5-dien-1-one (2h)\[^6\]

From 2,6-di-tert-butylphenol (1.0 g, 4.85 mmol), and 2-bromobenzaldehyde (0.57 mL, 4.85 mmol), 1.01 g (56%) of compound 2h were obtained after column chromatography. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.68 (1H, d, \(J = 2.3\) Hz), 7.40 (1H, s), 7.28-7.25 (1H, m), 7.23 (1H, s), 7.07 (1H, d, \(J = 2.3\) Hz), 1.34 (9H, s), 1.27 (9H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 186.6 (C), 149.7 (C), 148.3 (C), 140.8 (CH), 135.8 (C), 134.6 (CH), 133.2 (CH), 132.6 (C), 132.2 (CH), 127.6 (CH), 127.2 (CH), 125.1 (C), 35.4 (C), 35.1 (C), 29.5 (CH\(_3\)), 29.4 (CH\(_3\)).

2,6-Di-tert-butyl-4-(3-methoxybenzylidene)cyclohexa-2,5-dien-1-one (2i)\[^5\]

From 2,6-di-tert-butylphenol (1.0 g, 4.85 mmol), and 3-methoxybenzaldehyde (0.59 mL, 4.85 mmol), 660.9 mg (42%) of compound 2i were obtained after column chromatography. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.56 (1H, d, \(J = 2.3\) Hz), 7.36 (1H, t, \(J = 7.9\) Hz), 7.16 (1H, s), 7.00 (4H, m), 3.85 (3H, s), 1.36 (9H, s), 1.30 (9H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 186.5 (C), 159.7 (C), 149.3 (C), 147.8 (C), 142.4 (CH), 137.2 (C), 135.1 (CH), 129.8 (CH), 127.8 (CH), 127.9 (CH), 122.9 (C), 115.2 (CH), 55.3 (CH\(_3\)), 35.4 (C), 34.9 (C), 29.5 (CH\(_3\)), 29.4 (CH\(_3\)).
2,6-Di-tert-butyl-4-(3-chlorobenzylidene)cyclohexa-2,5-dien-1-one (2j)[5]

From 2,6-di-tert-butylphenol (1.0 g, 4.85 mmol), and 3-chlorobenzaldehyde (0.55 mL, 4.85 mmol), 909.2 mg (57%) of compound 2j were obtained after column chromatography. \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.44-7.30 (5H, m), 7.10 (1H, s), 6.99 (1H, d, \( J = 2.3 \) Hz), 1.32 (9H, s), 1.29 (9H, s); \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 186.5 (C), 149.8 (C), 148.3 (C), 140.0 (CH), 137.6 (C), 134.7 (C), 134.6 (CH), 132.8 (C), 130.0 (CH), 129.9 (CH), 128.8 (CH), 128.2 (CH), 127.2 (CH), 35.5 (C), 35.0 (C), 29.5 (CH\(_3\)), 29.4 (CH\(_3\)).

2,6-Di-tert-butyl-4-(3-nitrobenzylidene)cyclohexa-2,5-dien-1-one (2k)[6]

From 2,6-di-tert-butylphenol (1.0 g, 4.85 mmol) and 3-nitrobenzaldehyde (0.73 g, 4.85 mmol), 806.7 mg (49%) of compound 2k were obtained after column chromatography \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.33 (1H, m), 8.25 (1H, m), 7.75 (1H, d, \( J = 7.9 \) Hz), 7.64 (1H, t, \( J = 7.9 \) Hz), 7.40 (1H, d, \( J = 2.3 \) Hz), 7.15 (1H, s), 7.02 (1H, d, \( J = 2.3 \) Hz), 1.33 (9H, s), 1.29 (9H, s); \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 186.4 (C), 150.6 (C), 148.9 (C), 147.4 (C), 138.1 (CH), 135.6 (C), 133.8 (C), 129.8 (CH), 126.5 (CH), 124.8 (CH), 123.3 (CH), 35.5 (C), 35.1 (C), 29.5 (CH\(_3\)), 29.4 (CH\(_3\)).
General procedure for the enantioselective synthesis of N-alkylated isoxazolin-5-ones (3).

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.

(S)-2-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-methylisoxazol-5(2H)-one (3aa).

From 9.9 mg of 1a and 44.2 mg of 2a, were obtained 25.6 mg (65%) of 3aa. Enantiomeric excess (87%) was determined using chiral HPLC (Chiralcel OD-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer \( t_r = 12.2 \) min, major enantiomer \( t_r = 13.7 \) min.

Yellow solid; \( \text{m.p.} = 167.9-169.8 \) °C; \( [\alpha]_D^{25} = +12.9 \) (\( c = 0.85, \) CHCl3, 87% ee); \( ^1H \text{ NMR} \) (300 MHz, CDCl3), \( \delta \) 7.36-7.26 (5H, m, Ar), 7.03 (2H, s, Ar), 6.04 (1H, s, CH-N), 5.27 (1H, s, OH), 5.02 (1H, q, \( J = 0.9 \) Hz, CH-COO), 2.20 (3H, d, \( J = 0.9 \) Hz, CH3), 1.38 (18H, s, t-Bu); \( ^13C \text{ NMR} \) (75 MHz, CDCl3), \( \delta \) 170.9 (C, C=O), 163.6 (C, C=C-N), 153.7 (C, Ar), 137.0 (C, Ar), 135.9 (C, Ar), 128.5 (CH, Ar), 128.2 (CH, Ar), 128.2 (C, Ar), 126.8 (C, Ar), 125.1 (CH, Ar), 91.0 (CH, C=C-C=O), 68.3 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH3, t-Bu), 13.9 (CH3); IR 3400, 2951, 1702 (C=O), 1565, 758, 703 cm\(^{-1}\); HRMS (ESI) m/z: 416.2191 [M+Na]+, C\(_{25}\)H\(_{31}\)NNaO\(_{3}\) requires 416.2196.

(3)-2-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-ethylisoxazol-5(2H)-one (3ba).

From 11.3 mg of 1b and 44.2 mg of 2a, were obtained 20.8 mg (51%) of 3ba. Enantiomeric excess (81%) was determined using chiral HPLC (Chiralcel OD-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer \( t_r = 8.2 \) min, major enantiomer \( t_r = 11.9 \) min

Yellow solid; \( \text{m.p.} = 154.8-157.1 \) °C; \( [\alpha]_D^{25} = +10.3 \) (\( c = 0.72, \) CHCl3, 81% ee); \( ^1H \text{ NMR} \) (300 MHz, CDCl3), \( \delta \) 7.36-7.28 (5H, m, Ar), 7.01 (2H, s, Ar), 6.04 (1H, s, CH-N), 5.26 (1H, s, OH), 5.04 (1H, s, CH-COO), 2.53 (2H, q, \( J = 7.5 \) Hz, CH2), 1.38 (18H, s, t-Bu), 1.25 (3H, t, \( J = 7.5 \) Hz, CH3); \( ^13C \text{ NMR} \) (75 MHz, CDCl3), \( \delta \) 171.0 (C, C=O), 169.3 (C, C=C-N), 153.7 (C, Ar), 137.1 (C, Ar), 135.9 (C, Ar), 128.5
(S)-2-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-propylisoxazol-5(2H)-one (3ca).

From 12.7 mg of 1c and 44.2 mg of 2a, were obtained 24.9 mg (59%) of 3ca. Enantiomeric excess (81%) was determined using chiral HPLC (Chiralcel OD-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 7.9 min, major enantiomer t_r = 9.8 min

Yellow solid; m.p. = 117.5-121.8 °C; [α]_D^{25} = + 19.4 (c = 0.91, CHCl_3, 81% ee); _1^H NMR (300 MHz, CDCl_3), δ 7.36-7.27 (5H, m, Ar), 7.01 (2H, s, Ar), 6.06 (1H, s, CH-N), 5.27 (1H, s, OH), 5.03 (1H, s, CH-COO), 2.50 (2H, t, J = 7.5 Hz, CH_2) 1.69 (2H, sextuplet, J = 7.5 Hz, CH_2), 1.38 (18H, s, t-Bu), 1.00 (3H, t, J = 7.5 Hz, CH_3); _13^C NMR (75 MHz, CDCl_3), δ 171.1 (C, C=O), 167.9 (C, C=O), 157.1 (C, Ar), 137.1 (C, Ar), 135.9 (C, Ar), 128.5 (CH, Ar), 128.2 (CH, Ar), 128.1 (CH, Ar), 125.0 (CH, Ar), 89.6 (CH, C=C=O), 68.1 (CH, C-N), 34.3 (C, t-Bu), 28.8 (CH_2), 20.7 (CH_2), 13.7 (CH_3); IR ν 3367, 2950, 1699 (C=O), 1435, 1118, 885, 763, 705 cm⁻¹; HRMS (ESI) m/z: 444.2497 [M+Na]^+, C_{27}H_{35}NNaO_3^+ requires 444.2509.

(S)-2-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-phenylisoxazol-5(2H)-one (3da).

From 16.2 mg of 1d 44.2 mg of 2a, were obtained 34.6 mg (77%) of 3da. Enantiomeric excess (65%) was determined using chiral HPLC (Chiralpak IC), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 26.8 min, major enantiomer t_r = 21.1 min

Yellow solid; m.p. = 160.9-165.5 °C; [α]_D^{25} = + 19.8 (c = 1.10, CHCl_3, 77% ee) _1^H NMR (300 MHz, CDCl_3), δ 7.59-7.46 (5H, m, Ar), 7.33-7.32 (5H, m, Ar), 6.85 (2H, s, Ar), 6.00 (1H, s, CH-N), 5.38 (1H, s, OH), 5.25 (1H, s, CH-COO), 1.35 (18H, s, t-Bu); _13^C NMR (75 MHz, CDCl_3), δ 171.1 (C, C=O), 169.5 (C, C=C=O), 153.7 (C, Ar), 136.9 (C, Ar), 135.5 (CH, Ar), 131.5 (C, Ar), 129.4 (C, Ar), 128.4 (CH,
Ar), 128.3 (C, Ar), 128.2 (CH, Ar), 127.9 (CH, Ar), 127.8 (CH, Ar), 126.1 (CH, Ar), 125.6 (CH, Ar) 93.9 (CH, C=O), 70.9 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH3, t-Bu); IR ν 2959, 1718 (C=O), 1435, 1099, 763, 735, 691 cm⁻¹; HRMS (ESI) m/z: 456.2527 [M+H]+, C30H34NO3 requires 456.2533.

(S)-3-Cyclopropyl-2-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)isoxazol-5(2H)-one (3ea).

From 12.5 mg of 1e and 44.2 mg of 2a, were obtained 32.7 mg (78%) of 3ea. Enantiomeric excess (89%) was determined using chiral HPLC (Chiralpak AD-H), hexane/i-PrOH 85:15, 1 mL/min.

Minor enantiomer tᵣ = 6.7 min, major enantiomer tᵣ = 8.4 min.

Yellow solid; m.p. = 146.1-147.5 °C; [α]D 25 = + 9.2 (c = 1.09, CHCl₃, 89% ee); ¹H NMR (300 MHz, CDCl₃) 7.37-7.31 (5H, m, Ar), 7.07 (2H, Ar), 5.26 (1H, s, CH-N), 4.68 (1H, d, J = 0.6 Hz, CHCOO), 1.74-1.65 (1H, m, c-Pr), 1.38 (18H, s, t-Bu), 0.79-0.71 (2H, m, c-Pr); ¹³C NMR (75 MHz, CDCl₃), δ 171.3 (C, C=O), 171.1 (C, C=C-N), 153.7 (C, Ar), 137.2 (C, Ar), 135.7 (C, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 128.0 (CH, Ar), 126.9 (C, Ar), 125.4 (CH, Ar), 85.7 (CH, C=C=O), 68.7 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH₃, t-Bu), 9.5 (CH₂, c-Pr), 9.2 (CH₂, c-Pr), 7.9 (CH, c-Pr); IR ν 3419, 2952, 1697 (C=O), 1552, 1433, 1138, 1118, 916, 760 cm⁻¹; HRMS (ESI) m/z: 442.2359 [M+Na]⁺, C₂₇H₃₃NNaO₃ requires 442.2353.

(S)-2-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-3,4-dimethylisoxazol-5(2H)-one (3fa).

From 11.3 mg of 1f and 44.2 mg of 2a, were obtained 25.3 mg (62%) of 3fa. Enantiomeric excess (47%) was determined using chiral HPLC (Chiralpak AY-H), hexane/i-PrOH 90:10, 1 mL/min.

Minor enantiomer tᵣ = 9.9 min, major enantiomer tᵣ = 12.9 min.

Yellow solid; m.p. = 142.6-143.9 °C; [α]D 25 = + 4.2 (c = 1.27, CHCl₃, 47% ee); ¹H NMR (300 MHz, CDCl₃) 7.32-7.30 (5H, m, Ar), 7.04 (2H, s, Ar), 5.95 (1H, s, CH-N), 5.25 (1H, s, OH), 2.14 (3H, s, CH₃), 1.71 (3H, s, CH₃), 1.38 (18H, s, t-Bu); ¹³C NMR (75 MHz, CDCl₃), δ 171.9 (C, C=O), 160.3 (C, C=C-N), 153.7 (C, Ar), 137.0 (C, Ar), 135.8 (C, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 127.0 (C,
Ar), 125.1 (CH, Ar), 113.6 (CH, Ar), 100.7 (CH, C=C-C=O), 68.8 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH₃, t-Bu), 11.7 (CH₃), 6.74 (CH₃); **IR** ν 3559, 2955, 1701 (C=O), 1623, 1433, 1114, 1030, 747, 702 cm⁻¹; **HRMS** (ESI) m/z: 430.2357 [M+Na]⁺, C₂₆H₃₃NNaO₃⁺ requires 430.2353.

(S)-2-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(p-tolyl)methyl)-3-methylisoxazol-5(2H)-one (3ab).

From 9.9 mg of 1a and 46.2 mg of 2b, were obtained 9.3 mg (23%) of 3ab. Enantiomeric excess (72%) was determined using chiral HPLC (Chiralcel OD-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer tᵣ = 10.2 min, major enantiomer tᵣ = 15.2 min.

Yellow solid; m.p. = 52.3-53.5 °C; [α]D²⁵ = + 1.2 (c = 0.72, CHCl₃, 72% ee); **¹H NMR** (300 MHz, CDCl₃), δ: 7.15 (4H, m, Ar), 7.03 (2H, s, Ar), 6.00 (1H, s, CH=N), 5.26 (1H, s, OH), 5.01 (1H, q, J = 0.9 Hz, CHCOO), 2.35 (3H, s, CH₃), 2.19 (3H, d, J = 0.9 Hz, CH₃), 1.38 (18H, s, t-Bu); **¹³C NMR** (75 MHz, CDCl₃), δ: 170.9 (C, C=O), 163.6 (C, C=C-N), 153.7 (C, Ar), 137.9 (C, Ar), 135.9 (C, Ar), 133.9 (C, Ar), 129.2 (CH, Ar), 128.2 (CH, Ar), 127.1 (C, Ar), 124.9 (CH, Ar), 90.9 (CH, C=C=C=O), 68.1 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH₃, t-Bu), 21.1 (CH₃), 12.9 (CH₃); **IR** ν 3322, 2953, 1695 (C=O), 1574, 1433, 1120, 926, 780 cm⁻¹; **HRMS** (ESI) m/z: 430.2354 [M+Na]⁺, C₂₆H₃₃NNaO₃⁺ requires 430.2538.

(S)-2-(((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)-3-methylisoxazol-5(2H)-one (3ac).

From 9.9 mg of 1a and 48.7 mg of 2c, were obtained 28.0 mg (66%) of 3ac. Enantiomeric excess (62%) was determined using chiral HPLC (Chiralpak AY-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer tᵣ = 19.9 min, major enantiomer tᵣ = 25.3 min.

Yellow solid; m.p. = 138.9-146.1 °C; [α]D²⁵ = + 1.1 (c = 0.93, CHCl₃, 62% ee); **¹H NMR** (300 MHz, CDCl₃), δ: 7.22-7.18 (2H, m, Ar), 7.03 (2H, s, Ar), 6.88-6.85 (2H, m, Ar), 6.00 (1H, s, CH=N), 5.25 (1H, s, OH), 5.01 (1H, q, J = 0.9 Hz, CHCOO), 3.81 (3H, s, MeO), 2.20 (3H, d, J = 0.9 Hz, CH₃), 1.39 (18H, s, t-Bu); **¹³C NMR** (75 MHz, CDCl₃), δ: 170.9 (C, C=O), 163.6 (C, C=C-N), 159.4 (C, Ar), 153.6 (C, Ar), 139.5 (C, Ar), 129.6 (CH,
Ar), 128.9 (C, Ar), 127.3 (C, Ar), 124.8 (CH, Ar), 113.9 (CH, Ar), 91.1 (CH, C=C-C=O), 67.9 (CH, C-N), 55.3 (CH₃, OMe), 34.3 (C, t-Bu), 30.2 (CH₃, t-Bu), 12.9 (CH₃); IR v 3625, 2956, 1716 (C=O), 1511, 1434, 1237, 1176, 752 cm⁻¹; **HRMS** (ESI) m/z: 446.2297 [M+Na]⁺, \( C_{26}H_{33}NNaO_{4} \) requires 446.2302.

**S**)-2-((4-Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-3-methylisoxazol-5(2H)-one (3ad).

From 9.9 mg of 1a and 49.5 mg of 2d, were obtained 26.5 mg (62%) of 3ad. Enantiomeric excess (88%) was determined using chiral HPLC (Chiralpak AY-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer \( t_r = 12.5 \) min, major enantiomer \( t_r = 13.5 \) min

Yellow solid; \( m.p. = 154.8-157.1 \) °C; \( [\alpha]_D^{25} = + 11.2 \) (c = 0.88, CHCl₃, 88% ee); \( ^1H \text{ NMR} \) (300 MHz, CDCl₃), \( \delta 7.35-7.31 \) (2H, m, Ar), 7.26-7.21 (2H, m, Ar), 7.00 (2H, s, Ar), 5.99 (1H, s, CH-N), 5.30 (1H, s, OH), 5.04 (1H, q, \( J = 0.9 \) Hz, CH-COO), 2.21 (3H, d, \( J = 0.9 \) Hz, CH₃), 1.39 (18H, s, t-Bu); \( ^{13}C \text{ NMR} \) (75 MHz, CDCl₃), \( \delta 170.7 \) (C, C=O), 163.9 (C, C=C-N), 153.9 (C, Ar), 126.1 (C, Ar), 135.6 (C, Ar), 134.1 (C, Ar), 129.6 (CH, Ar), 128.7 (CH, Ar), 126.4 (C, Ar), 124.9 (CH, Ar), 91.7 (CH, C=C-C=O), 67.7 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH₃, t-Bu), 12.9 (CH₃); IR v 3411, 2967, 1721 (C=O), 1489, 1435, 1235, 1136, 859, 762 cm⁻¹; **HRMS** (ESI) m/z: 450.1795 [M+Na]⁺, \( C_{25}H_{30}ClNNaO_{3} \) requires 450.1806.

**S**)-2-((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-nitrophenyl)methyl)-3-methylisoxazol-5(2H)-one (3ae).

From 9.9 mg of 1a and 51.0 mg of 2e, were obtained 32.5 mg (74%) of 3ae. Enantiomeric excess (84%) was determined using chiral HPLC (Chiralcel OD-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer \( t_r = 25.1 \) min, major enantiomer \( t_r = 38.2 \) min

Orange solid; \( m.p. = 158.6-159.8 \) °C; \( [\alpha]_D^{25} = + 7.7 \) (c = 1.08, CHCl₃, 84% ee); \( ^1H \text{ NMR} \) (300 MHz, CDCl₃), \( \delta 8.23-8.18 \) (2H, m, Ar), 7.51-7.48 (2H, m, Ar), 7.00 (2H, s, Ar), 6.05 (1H, s, CH-N), 5.35 (1H, s, OH), 5.09 (1H, q, \( J = 0.6 \) Hz, CH-COO), 2.24 (3H, d, \( J = 0.6 \) Hz, CH₃), 1.39 (18H, s, t-Bu); \( ^{13}C \text{ NMR} \) (75 MHz, CDCl₃), \( \delta 170.4 \) (C, C=O), 164.5 (C,
(R)-2-((3,5-Di-tert-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)-3-methylisoxazol-5(2H)-one (3af).

From 9.9 mg of 1a and 48.7 mg of 2f, were obtained 18.2 mg (43%) of 3af. Enantiomeric excess (48%) was determined using chiral HPLC (Chiralpak AY-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer $t_r = 16.5$ min, major enantiomer $t_r = 19.7$ min.

Yellow oil; $[\alpha]_D^{25} = +12.1$ (c = 1.12, CHCl$_3$, 48% ee); $^1$H NMR (300 MHz, CDCl$_3$), $\delta$ 7.28-7.20 (4H, m, Ar), 6.99 (2H, d, Ar), 6.58 (1H, s, CH-N), 5.22 (1H, s, OH), 4.90 (1H, q, $J = 0.9$ Hz, CHCOO), 3.80 (3H, s, OMe), 2.20 (3H, d, $J = 0.9$ Hz, CH$_3$), 1.35 (18H, s, t-Bu); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ 170.9 (C, C=O), 167.8 (C, C=C-N), 156.4 (C, Ar), 135.8 (C, Ar), 130.5 (C, Ar), 129.6 (CH, Ar), 127.6 (CH, Ar), 124.5 (CH, Ar), 120.9 (CH, Ar), 110.4 (CH, Ar), 88.4 (CH, C=C-C=O), 60.2 (CH, C-N), 55.5 (CH$_3$, MeO), 34.3 (C, t-Bu), 30.2 (CH$_3$, t-Bu), 12.5 (CH$_3$); IR $\nu$ 3630, 2955, 1718 (C=O), 1599, 1433, 1239, 1105, 753 cm$^{-1}$; HRMS (ESI) m/z: 446.2297 [M+Na]$^+$, C$_{25}$H$_{29}$NNaO$_4^+$ requires 446.2302.

(R)-2-((2-Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-3-methylisoxazol-5(2H)-one (3ag).

From 9.9 mg of 1a and 49.5 mg of 2g, were obtained 20.2 mg (47%) of 3ag. Enantiomeric excess (89%) was determined using chiral HPLC (Chiralpak IC), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer $t_r = 53.7$ min, major enantiomer $t_r = 60.5$ min.

Yellow solid; m.p. = 123.5-129.2 °C; $[\alpha]_D^{25} = +25.2$ (c = 1.01, CHCl$_3$, 89%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.46-7.40 (2H, m, Ar), 7.33-7.35 (2H, m, Ar), 6.94 (2H, s, Ar), 6.56 (1H, s, CH-N), 5.26 (1H, s, OH), 5.01 (1H, q, $J = 0.9$ Hz, CHCOO), 2.24 (3H, d, $J = 0.9$ Hz, CH$_3$), 1.38 (18H, s, t-Bu); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.7 (C, C=O), 167.8 (C, C=C-N), 153.7 (C, Ar), 136.1 (C, Ar), 134.8 (C, Ar), 133.3...
(C, Ar), 130.8 (CH, Ar), 129.7 (CH, Ar), 126.3 (C, Ar), 124.4 (CH, Ar), 89.3 (CH, C=C-C=O), 63.6 (CH, C-N), 34.3 (C, t-Bu), 30.1 (CH₃, t-Bu), 12.6 (CH₃); IR ν 2955, 1725 (C=O), 1559, 1433, 1115, 885, 754 cm⁻¹; HRMS (ESI) m/z: 450.1802 [M+Na]⁺, C₂₅H₃₀NNaO₃⁺ requires 450.1806.

\((R)-2-((2-Bromophenyl)(3,5-di-tert-buty 4-hydroxyphenyl)methyl)-3-methylisoxazol-5(2H)-one\) (3ah).

From 9.9 mg of 1a and 55.9 mg of 2h, were obtained 20.2 mg (43%) of 3ah. Enantiomeric excess (90%) was determined using chiral HPLC (Chiralpak AY-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer \(t_r\) = 19.2 min, major enantiomer \(t_r\) = 20.9 min.

Yellow solid; m.p. = 132.1-133.4 °C; \([\alpha]_D^{25} = +7.5\ (c = 1.01, \text{CHCl}_3, 90\% \text{ ee});\)^{1H NMR (300 MHz, CDCl₃)} \(\delta\) 7.61 (1H, dd, \(J₁ = 7.9, J₂ = 1.3\ \text{Hz, Ar}), 7.44 (1H, dd, \(J₁ = 7.8, J₂ = 1.8\ \text{Hz, Ar}), 7.32 (1H, td, \(J₁ = 7.6, J₂ = 1.4\ \text{Hz, Ar}, 7.23-7.18 (2H, m, Ar), 6.92 (2H, s, Ar), 6.53 (1H, s, CH-N), 5.26 (1H, s, OH), 5.02 (1H, q, \(J = 0.8\ \text{Hz, CHCOO}), 2.25 (3H, d, \(J = 0.8\ \text{Hz, CH₃}), 1.38 (18H, s, t-Bu);\)^{13C NMR (75 MHz, CDCl₃)} \(\delta\) 170.7 (C, C=O), 162.7 (C, C=C-N), 153.7 (C, Ar), 136.5 (C, Ar), 136.1 (C, Ar), 132.9 (CH, Ar), 130.9 (CH, Ar), 129.9 (CH, Ar), 127.9 (CH, Ar), 126.4 (C, Ar), 124.4 (CH, Ar), 123.9 (C, Ar), 89.2 (CH, C=C-C=O), 66.2 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH₃, t-Bu), 12.7 (CH₃); IR ν 3423, 2957, 1705 (C=O), 1571, 1161, 1120, 911, 751 cm⁻¹, HRMS (ESI) m/z: 494.1303 [M+Na]⁺, C₂₆H₃₀BrNaO₃⁺ requires 494.1301.

\((R)-2-((3,5-Di-tert-buty 4-hydroxyphenyl)(3-methoxyphenyl)methyl)-3-methylisoxazol-5(2H)-one\) (3ai).

From 9.9 mg of 1a and 48.7 mg of 2i, were obtained 8.8 mg (20%) of 3ai. Enantiomeric excess (25%) was determined using chiral HPLC (Chiralcel OD-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer \(t_r\) = 14.9 min, major enantiomer \(t_r\) = 21.0 min.

Yellow oil; \([\alpha]_D^{25} = +1.7\ (c = 0.63, \text{CHCl}_3, 25\% \text{ ee});\)^{1H NMR (300 MHz, CDCl₃)} 7.29-7.24 (1H, m, Ar), 7.04 (2H, s, Ar), 6.88-6.82 (3H, m, Ar), 5.99 (1H, s, CH-N), 5.27 (1H, s, OH), 5.02 (1H, q, \(J = 0.9\ \text{Hz, CHCOO}), 3.78 (3H, s, MeO), 2.20 (3H, d, \(J = 0.9\ \text{Hz, CH₃}), 1.38 (18H, s, t-Bu);\)^{13C NMR (75 MHz, CDCl₃)} \(\delta\) 170.9 (C, C=O), 163.7 (C,
C=C-N), 159.7 (C, Ar), 153.7 (C, Ar), 138.6 (C, Ar), 135.9 (C, Ar), 129.6 (CH, Ar), 126.6 (C, Ar), 125.1 (CH, Ar), 120.5 (CH, Ar), 113.9 (CH, Ar), 113.6 (CH, Ar), 91.2 (CH, C=C-C=O), 68.2 (CH, C-N), 34.3 (C, t-Bu), 30.1 (CH3, t-Bu), 12.9 (CH3); IR \( \nu \) 3375, 2950, 1690 (C=O), 1431, 1263, 1159, 911, 760 cm\(^{-1}\); HRMS (ESI) m/z: 446.2297 [M+Na]\(^+\), \( C_{26}H_{33}NNaO_{4}^+ \) requires 446.2302.

(\(R\))-2-((3-Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-3-methylisoxazol-5(2\(H\))-one (3aj).

From 9.9 mg of 1a and 49.5 mg of 2j, were obtained 15.5 mg (36\%) of 3aj. Enantiomeric excess (81\%) was determined using chiral HPLC (Chiralpak AY-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer \( t_r = 11.8 \) min, major enantiomer \( t_r = 13.1 \) min.

Brown solid; m.p. = 145.7-148.8 °C; [\( \alpha \]d\(^{25} \) = +10.2 (c = 1.10, CHCl3, 81\% ee); \(^1\)H NMR (300 MHz, CDCl3) \( \delta \) 7.33-7.29 (3H, m, Ar), 7.19-7.17 (1H, m, Ar), 6.94 (2H, s, Ar), 5.97 (1H, s, C-H-N), 5.30 (1H, s, OH), 5.05 (1H, q, \( J = 0.9 \) Hz, \( CH\text{COO} \)), 2.21 (3H, d, \( J = 0.6 \) Hz, CH3), 1.39 (18H, s, t-Bu); \(^13\)C NMR (75 MHz, CDCl3) \( \delta \) 170.6 (C, C=O), 163.9 (C, C=C-N), 154.0 (C, Ar), 139.3 (C, Ar), 136.2 (C, Ar), 134.5 (C, Ar), 129.8 (CH, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 126.4 (CH, Ar), 126.0 (C, Ar), 125.1 (CH, Ar), 91.8 (CH, C=C-C=O), 67.7 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH3, t-Bu), 12.9 (CH3); IR \( \nu \) 2955, 1703 (C=O), 1571, 1433, 1121, 882, 769 cm\(^{-1}\); HRMS (ESI) m/z: 450.1801 [M+Na]\(^+\), \( C_{25}H_{30}ClNNaO_{3}^+ \) requires 450.1806.

(\(R\))-2-((3,5-di-tert-butyl-4-hydroxyphenyl)(3-nitrophenyl)methyl)-3-methylisoxazol-5(2\(H\))-one (3ak).

From 9.9 mg of 1a and 50.8 mg of 2k, were obtained 24.4 mg (56\%) of 3ak. Enantiomeric excess (77\%) was determined using chiral HPLC (Chiralcel OD-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer \( t_r = 27.7 \) min, major enantiomer \( t_r = 18.7 \) min.

Brown solid; m.p. = 131.3-133.4 °C; [\( \alpha \]d\(^{25} \) = +8.1 (c = 1.22, CHCl3, 77\% ee); \(^1\)H NMR (300 MHz, CDCl3) \( \delta \) 8.21-8.18 (2H, m, Ar), 7.68 (1H, d, \( J =7.8 \) Hz, Ar), 7.55 (1H, m, Ar), 7.02 (2H, s, Ar), 6.05 (1H, s, CH-N), 5.35 (1H, s, OH), 5.10 (1H, q, \( J = 0.9 \) Hz,
CHCOO), 2.25 (3H, d, J = 0.9 Hz, CH₃), 1.39 (18H, t-Bu); ¹³C NMR (75 MHz, CDCl₃) δ 170.4 (C, C=O), 164.6 (C, C=C-N), 154.3 (C, Ar), 148.3 (C, Ar), 139.6 (C, Ar), 136.4 (C, Ar), 134.3 (CH, Ar), 129.5 (CH, Ar), 125.2 (C, Ar), 125.1 (CH, Ar), 123.2 (CH, Ar), 123.1 (CH, Ar), 93.0 (CH, C=C-C=O), 67.7 (CH, C-N), 34.4 (C, t-Bu), 30.1 (CH₃, t-Bu), 13.6 (CH₃); IR ν 3580, 2957, 1729 (C=O), 1522, 1435, 1341, 909, 738 cm⁻¹; HRMS (ESI) m/z: 461.2044 [M+Na]+, C₂₆H₃₃NNaO₄ requires 461.2047.

(S)-3-Cyclopropyl-2-((3,5-di-tert-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)isoxazol-5(2H)-one (3ec).

From 12.5 mg of 1e and 48.7 mg of 2c, were obtained 33.6 mg (75%) of 3ec. Enantiomeric excess (79%) was determined using chiral HPLC (Chiralpak AD-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer tᵣ = 13.4 min, major enantiomer tᵣ = 21.5 min.

Yellow solid; m.p. = 141.9-144.2 °C; [α]D25 = +0.6 (c = 1.12, CHCl₃, 79% ee); ¹H NMR (300 MHz, CDCl₃) 7.28-7.23 (2H, m, Ar), 7.02 (2H, s, Ar), 6.88 (2H, m, Ar) 6.24 (1H, s, CH-N), 5.25 (1H, s, OH), 4.67 (1H, d, J = 0.6 Hz, CHCOO), 1.74-1.65 (1H, m, c-Pr), 1.39 (18H, s, t-Bu), 3.81 (3H, s, OMe), 1.14-1.08 (2H, m, c-Pr), 0.78-0.72 (2H, m, c-Pr); ¹³C NMR (75 MHz, CDCl₃) δ 171.3 (C, C=O), 171.1 (C, C=C-N), 159.3 (C, Ar), 153.5 (C, Ar), 135.7 (C, Ar), 129.8 (CH, Ar), 129.2 (C, Ar), 127.3 (CH, Ar), 125.1 (CH, Ar), 113.7 (C, Ar), 85.6 (CH, C=C-C=O), 68.4 (CH, C-N), 55.2 (CH₃, MeO), 34.3 (C, t-Bu), 30.2 (CH₃, t-Bu), 9.4 (CH₂, c-Pr), 9.3 (CH₂, c-Pr), 7.9 (CH, c-Pr); IR ν 3421, 2954, 1695 (C=O), 1511, 1435, 1235, 1112, 764 cm⁻¹; HRMS (ESI) m/z: 472.2459 [M+Na]+, C₂₈H₃₅NNaO₄ requires 472.2458.

(S)-2-((4-Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-3-cyclopropylisoxazol-5(2H)-one (3ed).

From 12.5 mg of 1e and 49.3 mg of 2d, were obtained 35.3 mg (78%) of 3ed. Enantiomeric excess (88%) was determined using chiral HPLC (Chiralpak AY-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer tᵣ = 15.5 min, major enantiomer tᵣ = 17.5 min.
Yellow solid; m.p. = 164.1-165.4 ºC; \([\alpha]_D^{25} = + 20.8 \ (c = 1.18,\ CHCl_3, 88\%\ ee)\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.34-7.27 (4H, m, Ar), 7.04 (2H, Ar), 6.23 (1H, s, CH-N), 5.29 (1H, s, OH), 4.68 (1H, d, J = 0.6 Hz, CHCOO), 1.73-1.64 (1H, m, c-Pr), 1.39 (18H, s, t-Bu), 1.16-1.11 (2H, m, c-Pr), 0.84-0.66 (2H, m, c-Pr); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.5 (C, C=O), 171.1 (C, C=C-N), 153.8 (C, Ar), 135.9 (C, Ar), 135.8 (C, Ar), 133.9 (C, Ar), 129.8 (CH, Ar), 128.6 (CH, Ar), 126.4 (C, Ar), 124.5 (CH, Ar), 124.4 (CH, Ar), 86.4 (CH, C=C-C=O), 68.2 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH\(_3\), t-Bu), 9.7 (CH\(_2\), c-Pr), 9.3 (CH\(_2\), c-Pr), 7.9 (CH, c-Pr); IR \(\nu\) 3384, 2957, 1697 (C=O), 1552, 1435, 1105, 877 cm\(^{-1}\); HRMS (ESI) m/z: 476.1965 [M+Na]\(^+\), C\(_{27}\)H\(_{32}\)ClNNaO\(_3\)+ requires 476.1963.

\((S)-3\)-Cyclopropyl-2-((3,5-di-tert-butyl-4-hydroxyphenyl)(4-nitrophenyl)methyl)isoxazol-5(2H)-one (3ee).

From 12.5 mg of 1e and 50.9 mg of 2e, were obtained 37.2 mg (80%) of 3ee. Enantiomeric excess (86%) was determined using chiral HPLC (Chiralcel OD-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer \(t_r = 25.9\) min, major enantiomer \(t_r = 22.1\) min.

Yellow solid; m.p. = 87.5-89.9 ºC; \([\alpha]_D^{25} = + 10.5 \ (c = 1.24,\ CHCl_3, 86\%\ ee)\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 8.23-3.20 (2H, m, Ar), 7.57-7.55 (2H, m, Ar), 7.04 (2H, s, Ar), 6.29 (1H, s, CH-N), 5.33 (1H, s, OH), 4.73 (1H, d, J = 0.6 Hz, CHCOO), 1.75-1.66 (1H, m, c-Pr), 1.39 (18H, s, t-Bu), 1.21-1.15 (2H, m, c-Pr), 0.87-0.80 (1H, m, c-Pr), 0.75-0.68 (1H, m, c-Pr); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 172.1 (C, C=O), 170.8 (C, C=C-N), 154.2 (C, Ar), 147.5 (C, Ar), 147.5 (C, Ar), 144.9 (C, Ar), 136.2 (C, Ar), 129.2 (CH, Ar), 125.6 (CH, Ar), 125.4 (C, Ar), 123.5 (CH, Ar), 87.4 (CH, C=C-C=O), 68.5 (CH, C-N), 34.4 (C, t-Bu), 30.2 (CH\(_3\), t-Bu), 10.2 (CH\(_2\), c-Pr), 9.3 (CH\(_2\), c-Pr), 8.0 (CH, c-Pr); IR \(\nu\) 3449, 2961, 1701 (C=O), 1517, 1343, 1234, 1108, 702 cm\(^{-1}\); HRMS (ESI) m/z: 487.2201 [M+Na]\(^+\), C\(_{27}\)H\(_{32}\)N\(_2\)NaO\(_5\)+ requires 487.2203.
(R)-2-((2-Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-3-cyclopropylisoxazol-5(2H)-one (3eg).

From 12.5 mg of 1e and 49.3 mg of 2g, were obtained 34.8 mg (76%) of 3eg. Enantiomeric excess (92%) was determined using chiral HPLC (Chiralpak AY-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer tR = 12.6 min, major enantiomer tR = 14.1 min.

Yellow solid; m.p. = 124.4-125.2 °C; [α]D25 = -5.6 (c = 1.16, CHCl3, 92% ee); 1H NMR (300 MHz, CDCl3) 7.55-7.49 (1H, m, Ar), 7.42-7.36 (1H, m, Ar), 7.28-7.23 (2H, m, Ar), 7.03 (2H, s, Ar), 6.77 (1H, s, CH-N), 5.22 (1H, s, OH), 4.67 (1H, d, J = 0.6 Hz, CHCOO), 1.74-1.66 (1H, m, c-Pr), 1.34 (18H, s, t-Bu), 1.11-1.02 (2H, m, c-Pr), 0.75-0.62 (2H, m, c-Pr); 13C NMR (75 MHz, CDCl3) δ 171.1 (C, C=O), 170.1 (C, C=C-N), 153.7 (C, Ar), 135.9 (C, Ar), 135.1 (C, Ar), 133.3 (C, Ar), 130.5 (CH, Ar), 129.6 (CH, Ar), 129.5 (CH, Ar), 127.2 (CH, Ar), 126.2 (CH, Ar), 124.7 (C, Ar), 84.5 (CH, C=C-C=O), 64.2 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH3, t-Bu), 9.1 (CH2, c-Pr), 8.8 (CH2, c-Pr), 7.6 (CH, c-Pr); IR ν 3632, 2955, 1733 (C=O), 1582, 1431, 1235, 1161, 911, 752 cm⁻¹; HRMS (ESI) m/z: 476.1965 [M+Na]+, C27H32ClNNaO3+ requires 476.1963.

(R)-3-cyclopropyl-2-((3,5-di-tert-butyl-4-hydroxyphenyl)(3-methoxyphenyl)methyl)isoxazol-5(2H)-one (3ei).

From 12.5 mg of 1e and 48.7 mg of 2i, were obtained 36.7 mg (82%) of 3ei. Enantiomeric excess (82%) was determined using chiral HPLC (Chiralpak AY-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer tR = 19.8 min, major enantiomer tR = 28.5 min.

White solid; m.p. = 56.1-57.1 °C; [α]D25 = + 5.8 (c = 1.22, CHCl3, 82% ee); 1H NMR (300 MHz, CDCl3) 7.30-7.23 (1H, m, Ar), 7.08 (2H, s, Ar), 6.93-6.84 (3H, m, Ar), 6.24 (1H, s, CH-N), 5.27 (1H, s, OH), 4.68 (1H, d, J = 0.6 Hz, CHCOO), 3.78 (3H, s, MeO), 1.73-1.64 (1H, m, c-Pr), 1.39 (18H, s, t-Bu), 1.14-1.08 (2H, m, c-Pr), 0.84-0.70 (2H, m, c-Pr); 13C NMR (75 MHz, CDCl3) δ 171.2 (C, C=O), 171.1 (C, C=C-N), 159.6 (C, Ar), 153.7 (C, Ar), 138.8 (C, Ar), 135.8 (C, Ar), 129.4 (CH, Ar), 126.7 (C, Ar), 125.4 (CH, Ar), 120.7 (CH, Ar), 114.1 (CH, Ar), 113.4 (CH, Ar), 85.8 (CH, C=C-C=O), 68.7 (CH, C-N), 34.3 (C, t-Bu), 30.2 (CH3, t-Bu), 9.5 (CH2, c-Pr), 9.2 (CH2, c-Pr), 7.9 (CH, c-Pr);
IR ν 3630, 2955, 1716 (C=O), 1578, 1433, 1049, 784, 771 cm⁻¹; HRMS (ESI) m/z: 472.2459 [M+Na]⁺, C₂₈H₃₅NNaO₄⁺ requires 472.2458.

(R)-2-((3-Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-3-cyclopropylisoxazol-5(2H)-one (3ej).

From 12.5 mg of 1e and 49.3 mg of 2j, were obtained 35.3 mg (78%) of 3ej. Enantiomeric excess (88%) was determined using chiral HPLC (Chiralpak AD-H), hexane/i-PrOH 90:10, 1 mL/min. Minor enantiomer tᵣ = 11.3 min, major enantiomer tᵣ = 13.3 min.

White solid; m.p. = 57.1-58.8 ºC; [α]D²⁵ = +22.4 (c = 1.18, CHCl₃, 88% ee); ¹H NMR (300 MHz, CDCl₃) 7.26-7.36 (1H, m, Ar), 7.30-7.24 (3H, m, Ar), 7.05 (2H, s, Ar), 6.22 (1H, s, CH-N), 5.30 (1H, s, OH), 4.69 (1H, d, J = 0.6 Hz, CHCOO), 1.74-1.64 (1H, m, c-Pr), 1.39 (18H, s, t-Bu), 1.19-1.10 (2H, m, c-Pr), 0.84-0.77 (1H, m, c-Pr), 0.74-0.68 (1H, m, c-Pr); ¹³C NMR (75 MHz, CDCl₃) δ 171.5 (C, C=O), 171.1 (C, C=O-C=N), 153.9 (C, Ar), 139.5 (C, Ar), 135.9 (C, Ar), 134.3 (C, Ar), 129.6 (CH, Ar), 128.4 (CH, Ar), 128.2 (CH, Ar), 126.5 (CH, Ar), 126.0 (C, Ar), 125.5 (CH, Ar), 86.5 (CH, C=C=O), 68.3 (CH, C=N), 34.3 (C, t-Bu), 30.2 (CH₃, t-Bu), 9.9 (CH₂, c-Pr), 9.2 (CH₂, c-Pr), 7.9 (CH, c-Pr); IR ν 3449, 2950, 1720 (C=O), 1597, 1414, 1116, 930, 777 cm⁻¹; HRMS (ESI) m/z: 476.1965 [M+Na]⁺, C₂₇H₃₂ClINaO₃⁺ requires 476.1963.

Synthesis of compound 3ea at 1 mmol scale.

In a round bottom flask charged with the para-quinone methide 2a (441.7 mg, 1.5 mmol) and the isoxazolin-5-one 1e (125.1 mg, 1 mmol) is added 3Å MS (320 mg) and the thiourea V (37 mg, 10 mol %). Then 1,2-dichloroethane (10 mL) is added and the mixture is allowed to stir at rt for 24 hours. Then, the reaction is purified by flash column chromatography obtaining 297.9 mg (71%) of 3ea (86% ee).
References


$\textbf{3aa}$

$^1\text{H NMR, CDCl}_3$, 300 MHz

$\textbf{3aa}$

$^{13}\text{C NMR, CDCl}_3$, 75 MHz
Compound 3aa

Retention Time | Area | Area Percent
--- | --- | ---
11.58 | 77414976 | 49.841
13.48 | 77907582 | 50.159

Retention Time | Area | Area Percent
--- | --- | ---
12.19 | 16368611 | 6.395
13.66 | 239602039 | 93.605

Wavenumbers [cm⁻¹]

1700-1800
1600-1700
1300-1400
900-1000
600-700
3ba

$^1$H NMR, CDCl$_3$, 300 MHz

3ba

$^{13}$C NMR, CDCl$_3$, 75 MHz
Compound 3ba
3ca
$^1$H NMR, CDCl$_3$,
300 MHz

3ca
$^{13}$C NMR, CDCl$_3$,
75 MHz
Compound 3ca
$$\text{3da}$$

$^1$H NMR, CDCl$_3$, 300 MHz

$$\text{3da}$$

$^{13}$C NMR, CDCl$_3$, 75 MHz
Compound 3da
$^1$H NMR, CDCl$_3$, 300 MHz

$^{13}$C NMR, CDCl$_3$, 75 MHz
Compound 3ea
**3fa**

$^1$H NMR, CDCl$_3$,
300 MHz

---

**3fa**

$^{13}$C NMR, CDCl$_3$,
75 MHz
Compound 3fa

Retention Time | Area | Area Percent
---|---|---
9.89 | 114302447 | 51,103
13.00 | 109368629 | 48,897

Retention Time | Area | Area Percent
---|---|---
9.90 | 30926669 | 26,268
12.88 | 86808559 | 73,732
$^{3}$H NMR, CDCl$_3$, 300 MHz

$^{13}$C NMR, CDCl$_3$, 75 MHz
Compund 3ab
3ac

$^1$H NMR, CDCl$_3$, 300 MHz

3ac

$^{13}$C NMR, CDCl$_3$, 75 MHz
Compound 3ac
$3\text{ad}$

$^1\text{H NMR, CDCl}_3$, 300 MHz

$^{13}\text{C NMR, CDCl}_3$, 75 MHz
Compound 3ad
$3ae$

$^1$H NMR, CDCl$_3$, 300 MHz

---

$3ae$

$^{13}$C NMR, CDCl$_3$, 75 MHz
Compound 3ae
3af
\(^1\)H NMR, CDCl\(_3\), 300 MHz

3af
\(^{13}\)C NMR, CDCl\(_3\), 75 MHz
Compound 3af

18: 270 nm, 4 nm
Results

<table>
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<tr>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.32</td>
<td>42339058</td>
<td>52,169</td>
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<td>19.70</td>
<td>39819171</td>
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18: 270 nm, 4 nm
Results

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<tr>
<td>16.51</td>
<td>24199330</td>
<td>26,862</td>
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<td>19.66</td>
<td>65889351</td>
<td>73,138</td>
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</table>

Long. de onda (cm⁻¹)
3ag

$^1$H NMR, CDCl$_3$,
300 MHz

3ag

$^{13}$C NMR, CDCl$_3$,
75 MHz
Compound 3ag
3ah

$^1$H NMR, CDCl$_3$, 300 MHz

3ah

$^{13}$C NMR, CDCl$_3$, 75 MHz
Compound 3ah
**3ai**

$^1$H NMR, CDCl$_3$, 300 MHz

$^{13}$C NMR, CDCl$_3$, 75 MHz
Compound 3ai
Compound 3aj
3ak
$^1$H NMR, CDCl$_3$
300 MHz

3ak
$^{13}$C NMR, CDCl$_3$
75 MHz
Compound 3ak
1H NMR, CDCl₃, 300 MHz

3ec

13C NMR, CDCl₃, 75 MHz

S54
Compound 3ee
**3ed**

$^1$H NMR, CDCl$_3$, 300 MHz

**3ed**

$^{13}$C NMR, CDCl$_3$, 75 MHz
Compound 3ed
3ee

$^1$H NMR, CDCl$_3$, 300 MHz

3ee

$^{13}$C NMR, CDCl$_3$, 75 MHz
Compound 3ee
$^{1}H$ NMR, CDCl$_3$, 300 MHz

$^{13}C$ NMR, CDCl$_3$, 75 MHz
Compound 3eg
$\textbf{3ei}$

$^1\text{H NMR, CDCl}_3$, 300 MHz

$\textbf{3ei}$

$^{13}\text{C NMR, CDCl}_3$, 75 MHz
Compound 3ei

Results

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<tr>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
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<td>21.41</td>
<td>47899978</td>
<td>49.491</td>
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<td>32.56</td>
<td>48886206</td>
<td>50.509</td>
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Results

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<th>Area Percent</th>
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<td>19.75</td>
<td>16971436</td>
<td>8.735</td>
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<td>28.45</td>
<td>177324020</td>
<td>91.265</td>
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</table>

Results
**3ej**

\[^{1}H\] NMR, CDCl\(_3\),

300 MHz

\[^{13}C\] NMR, CDCl\(_3\),

75 MHz
Compound 3ej

Retention Time | Area    | Area Percent |
---------------|---------|--------------|
12,61         | 21755299 |              |
13,92         | 21866388 |              |

Retention Time | Area    | Area Percent |
---------------|---------|--------------|
11,31         | 10839055 |              |
13,29         | 164853877 |             |

Transm. 80     | 90      | 95           |
3498.7, 950.584 | 2871.9, 83.237 | 2850.2, 78.967 |
1198.3, 64.589  | 433.2, 61.341  | 1116.3, 60.651 |
1414.5, 60.609  | 56.402, 61.727 |
777.1, 48.263   | 37.597      | 35.002       |

Long. de onda (cm⁻¹)

S65
Additional optimization experiments

Table S1. Enantioselective addition of 3-methyl-4(\(H\))-isoxazol-5-one (1a) to \(p\)-QM 2a. Screening of ligands.\[^a\]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>yield [%][^b]</th>
<th>ee [%][^c]</th>
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<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>II</td>
<td>36</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>IV</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>V</td>
<td>48</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>VI</td>
<td>23</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>VII</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>VIII</td>
<td>41</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>IX</td>
<td>49</td>
<td>58</td>
</tr>
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</table>

\[^a\] 1a (0.1 mmol), 2a (0.1 mmol), catalyst (0.005 mmol), toluene (1 mL), room temperature, 6 days. \[^b\] Yield after column chromatography. \[^c\] Determined by HPLC using chiral stationary phases.
Table S2. Enantioselective addition of 3-methyl-4(\(H\))-isoxazol-5-one (1a) to \(p\)-QM 2a. Screening of solvents.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>V</td>
<td>toluene</td>
<td>48</td>
<td>66</td>
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<tr>
<td>2</td>
<td>V</td>
<td>MTBE</td>
<td>34</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>V</td>
<td>Et(_2)O</td>
<td>33</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>V</td>
<td>EtOAc</td>
<td>38</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>V</td>
<td>Acetonitrile</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>V</td>
<td>DCM</td>
<td>61</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>V</td>
<td>CHCl(_3)</td>
<td>27</td>
<td>74</td>
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<tr>
<td>8</td>
<td>V</td>
<td>DCE</td>
<td>42</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>X</td>
<td>DCE</td>
<td>37</td>
<td>85</td>
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</table>

\(^a\)1a (0.1 mmol), 2a (0.1 mmol), catalyst VIII (0.005 mmol), solvent (1 mL), room temperature, 6 days. [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases.

Table S3. Enantioselective addition of 3-methyl-4(\(H\))-isoxazol-5-one (1a) to \(p\)-QM 2a. Effect of temperature, molar ratio and additives.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>catalyst [mol %]</th>
<th>1a/2a [molar ratio]</th>
<th>additive</th>
<th>(T) [(^\circ)C]</th>
<th>yield [%]</th>
<th>ee [%]</th>
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<tr>
<td>1</td>
<td>V</td>
<td>5</td>
<td>1:1</td>
<td>-</td>
<td>r.t.</td>
<td>42</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>V</td>
<td>5</td>
<td>1:1</td>
<td>-</td>
<td>0</td>
<td>26</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>V</td>
<td>5</td>
<td>1.5:1</td>
<td>-</td>
<td>r.t.</td>
<td>43</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>V</td>
<td>5</td>
<td>1:1.5</td>
<td>-</td>
<td>r.t.</td>
<td>48</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>V</td>
<td>2.5</td>
<td>1:1.5</td>
<td>-</td>
<td>r.t.</td>
<td>37</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>V</td>
<td>10</td>
<td>1:1.5</td>
<td>-</td>
<td>r.t.</td>
<td>85</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>XI</td>
<td>5</td>
<td>1:1.5</td>
<td>-</td>
<td>r.t.</td>
<td>44</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>XII</td>
<td>5</td>
<td>1:1.5</td>
<td>-</td>
<td>r.t.</td>
<td>nd</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>V</td>
<td>5</td>
<td>1:1.5</td>
<td>3 Å MS</td>
<td>r.t.</td>
<td>65</td>
<td>87</td>
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<tr>
<td>10</td>
<td>V</td>
<td>5</td>
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<td>4 Å MS</td>
<td>r.t.</td>
<td>57</td>
<td>87</td>
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<tr>
<td>11</td>
<td>V</td>
<td>5</td>
<td>1:1.5</td>
<td>5 Å MS</td>
<td>r.t.</td>
<td>59</td>
<td>85</td>
</tr>
</tbody>
</table>

\(^a\) 1a (0.1 mmol), 2a, catalyst (0.005 mmol), DCE (1 mL), additive (32 mg), room temperature, 6 days. [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases.