[3+2]-Cycloaddition Reaction between Chiral Oxaziridines and Nitriles: Enantioselective Synthesis of 2,3-Dihydro-1,2,4-oxadiazoles

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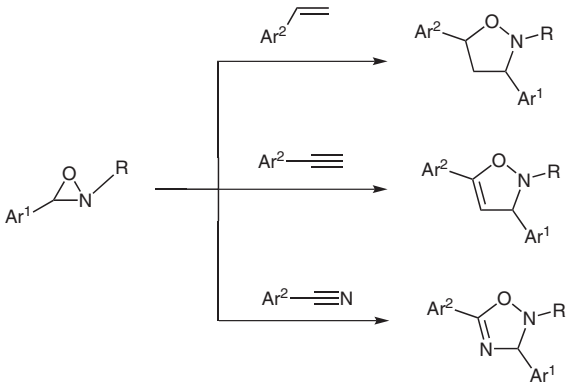
Abstract: Enantiomerically pure 2,3-dihydro-1,2,4-oxadiazoles were synthesized by a cycloaddition reaction between chiral oxaziridines and nitriles. Assignment of absolute configurations was made by X-ray diffraction analysis, NOESY spectra, and theoretical calculations.

Key words: oxaziridines, oxadiazolines, stereoselectivity, cycloaddition, nitriles

The oxaziridine ring has received considerable attention mainly due to the chirality of the nitrogen atom, which has an inversion barrier of 25–32 kcal/mol in *N*-alkyl-substituted oxaziridines.[1] Owing to the presence of an inherently weak N–O bond, due to the strained ring, oxaziridines can be used as oxygenating agents toward enolates,[2] alkenes,[3–8] thioethers,[9,10] enamines,[11] organometallic reagents,[12] and C–H[13,14] and Si–H[15] bonds. Moreover, oxaziridines can be used as aminating agents in the conversion of alcohols into *O*-alkyl oximes,[16] thioethers into sulfimides,[17] enolates into α-aminocarbonyl compounds and structures with C–H bonds into amines.[18,19]

Recently, we identified a novel reactivity of oxaziridines; a [3+2]-cycloaddition reaction performed with alkenes,[20,21] alkynes,[22] and nitriles[23] by selective cleavage of the C–O bond to afford stable isoxazolidines, isoxazolines, and 2,3-dihydro-1,2,4-oxadiazoles (or 1,2,4-oxadiazolines), respectively (Scheme 1).



Scheme 1 [3+2] Cycloaddition with alkenes, alkynes, and nitriles

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The valuable and diverse biological activity of molecules containing isoxazoline and/or isoxazolidine,[24] and 1,2,4-oxadiazoline[25] rings, in addition to the high level of asymmetric induction observed in the heteroatom transfer to alkenes[26] and sulfides[27,28] by N-protected oxaziridines, suggest that chiral oxaziridines could be employed in the [3+2]-cycloaddition reaction with alkenes, alkynes, and nitriles with a good level of stereocontrol.

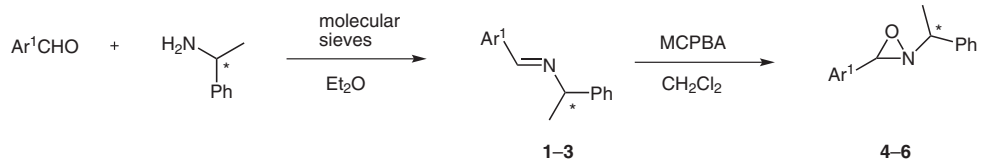
Herein we report the results on the [3+2]-cycloaddition reaction of chiral oxaziridines with nitriles in order to obtain chiral 2,3-dihydro-1,2,4-oxadiazoles.

The enantiomerically pure imines **1**–**3**[29–34] were prepared by reacting (*R*)- or (*S*)-1-phenylethylamine (1.0 mmol) with the corresponding arylaldehyde (1.0 mmol) in anhydrous diethyl ether in the presence of molecular sieves for 2–3 hours.[35] After completion of the reaction (yield >95%), the solvent was removed under reduced pressure to yield the pure imines. The oxidation of the obtained imines **1**–**3** was performed according to previously reported methodology (Scheme 2).[36]

The addition of *m*-chloroperoxybenzoic acid (1.1 mmol) to imines **1**–**3** (1.0 mmol) in dichloromethane at 0 °C afforded oxaziridines **4**–**6** in high overall yields (85–95%) (Table 1). All the reactions proceeded with fairly good stereoselectivity. From each imine, two diastereomeric oxaziridines were generated, both in a *trans* configuration, in which the nitrogen atoms have become stereocenters because of the high interconversion barrier.[1] The oxaziridines were isolated in enantiomerically pure form after column chromatography on silica gel.

The observed *trans* stereoselectivity (*trans*/*cis*, 100:0) may be due to synchronous oxygen transfer from the *m*-chloroperoxybenzoic acid to the imine, which in solution assumes the more stable *trans* structure, while the stereochemistry of the new stereogenic centers (C3 and N2) of the oxaziridine ring is the outcome of asymmetric induction exerted by the pre-existing closest stereocenter.[21]

Subsequently, these oxaziridines were used in their enantiomerically pure form for the [3+2]-cycloaddition reaction with nitriles. In detail, the oxaziridine (–)-(1′*S*,2*S*,3*S*)-**4** (1.0 mmol) was reacted in refluxing benzonitrile (5.0 mL) and the reaction was followed by TLC. After 15 hours, when the oxaziridine was completely consumed, the reaction mixture was cooled to room temperature and concentrated to remove the solvent under reduced pres-



Scheme 2 Synthesis of the chiral oxaziridines **4–6**

Table 1 Yield and Isomeric Distribution of Chiral Oxaziridines **4–6**

Entry	Ar^1	1-Phenylethylamine	Total yield (%)	Isomeric distribution (%)
1	Ph	(*S*)	95	(–)-(1′*S*,2*S*,3*S*)-**4** (23); (+)-(1′*S*,2*R*,3*R*)-**4** (77)
2	Ph	(*R*)	95	(+)-(1′*R*,2*R*,3*R*)-**4** (25); (–)-(1′*R*,2*S*,3*S*)-**4** (75)
3	4-ClC_6H_4	(*S*)	85	(–)-(1′*S*,2*S*,3*S*)-**5** (19); (+)-(1′*S*,2*R*,3*R*)-**5** (81)
4	4-ClC_6H_4	(*R*)	85	(+)-(1′*R*,2*R*,3*R*)-**5** (20); (–)-(1′*R*,2*S*,3*S*)-**5** (80)
5	4-MeC_6H_4	(*S*)	90	(–)-(1′*S*,2*S*,3*S*)-**6** (18); (+)-(1′*S*,2*R*,3*R*)-**6** (82)
6	4-MeC_6H_4	(*R*)	90	(–)-(1′*R*,2*R*,3*R*)-**6** (18); (+)-(1′*R*,2*S*,3*S*)-**6** (82)

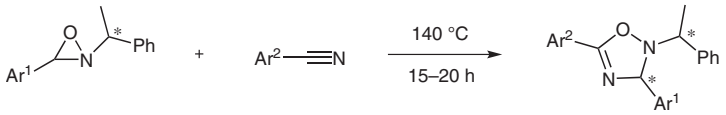
sure. The reaction time was considerably longer (96 h), when the oxaziridines (1.0 mmol) and the benzonitrile (2.0 mmol) were reacted in refluxing toluene. The crude mixture was purified by column chromatography on silica gel. The oxadiazolines (+)-(1′*S*,3*S*)-**7** and (–)-(1′*S*,3*R*)-**7** were isolated in a diastereomeric ratio of 81:19 (Table 2, entry 2).

The reaction was also monitored by ^{1}H NMR spectroscopy, which showed the progressive decrease of the oxaziridine and the formation of the two oxadiazolines **7**, with the same diastereomeric ratio of 81:19.

When the oxaziridine (+)-(1′*S*,2*R*,3*R*)-**4** was reacted under the usual conditions, the same diastereomers that were obtained in entry 2, (+)-(1′*S*,3*S*)-**7** and (–)-(1′*S*,3*R*)-**7**, were isolated in a similar ratio (Table 2, entry 1), as confirmed by ^{1}H and ^{13}C NMR analysis and by specific rotation measurements.

However, when the oxaziridines (+)-(1′*R*,2*R*,3*R*)-**4** and (–)-(1′*R*,2*S*,3*S*)-**4** were used in the [3+2]-cycloaddition reaction, the oxadiazolines (–)-(1′*R*,3*R*)-**7** and (+)-(1′*R*,3*S*)-**7** were formed in a ratio of ~82:18. In both cases (entries 3 and 4), ^{1}H and ^{13}C NMR spectra and specific rotation values confirmed that the oxadiazolines are enantiomers of the products formed from (+)-(1′*S*,2*R*,3*R*)-**4** and (–)-(1′*S*,2*S*,3*S*)-**4** (cf. entries 1 and 2 with entries 3 and 4).

Table 2 Synthesis of 2,3-Dihydro-1,2,4-oxadiazoles **7–10**



Entry	Oxaziridine	Ar^1	Ar^2	Total yield (%)	Isomeric distribution (%)[a] and specific rotation [α][b]
1	(+)-(1′*S*,2*R*,3*R*)-**4**	Ph	Ph	75	(1′*S*,3*S*)-**7** (80) [α] +59.2; (1′*S*,3*R*)-**7** (20) [α] –60.6
2	(–)-(1′*S*,2*S*,3*S*)-**4**	Ph	Ph	73	(1′*S*,3*S*)-**7** (81) [α] +58.5; (1′*S*,3*R*)-**7** (19) [α] –60.0
3	(–)-(1′*R*,2*S*,3*S*)-**4**	Ph	Ph	70	(1′*R*,3*R*)-**7** (82) [α] –61.4; (1′*R*,3*S*)-**7** (18) [α] +62.8
4	(+)-(1′*R*,2*R*,3*R*)-**4**	Ph	Ph	69	(1′*R*,3*R*)-**7** (80) [α] –60.8; (1′*R*,3*S*)-**7** (20) [α] +62.0
5	(+)-(1′*S*,2*R*,3*R*)-**5**	4-ClC_6H_4	4-ClC_6H_4	57	(1′*S*,3*S*)-**8** (71) [α] +77.5; (1′*S*,3*R*)-**8** (29) [α] –72.1
6	(+)-(1′*R*,2*R*,3*R*)-**5**	4-ClC_6H_4	4-ClC_6H_4	62	(1′*R*,3*R*)-**8** (76) [α] –78.0; (1′*R*,3*S*)-**8** (24) [α] +71.3
7	(–)-(1′*R*,2*R*,3*R*)-**6**	4-MeC_6H_4	4-MeC_6H_4	79	(1′*R*,3*R*)-**9** (74) [α] –38.5; (1′*R*,3*S*)-**9** (26) [α] +27.0
8	(–)-(1′*R*,2*R*,3*R*)-**4**	Ph	BTz[c]	81	(1′*R*,3*R*)-**10** (70) [α] –34.9; (1′*R*,3*S*)-**10** (30) [α] +38.7

[a] Isomeric distribution was calculated by ^{1}H NMR spectroscopy on the crude product.
[b] For specific details see the experimental section.
[c] BTz = benzothiazol-2-yl.

A similar pathway was observed with the oxaziridine **5**. In detail, from reaction of oxaziridine (+)-(1′*S*,2*R*,3*R*)-**5** with the benzonitrile gave the oxadiazolines (+)-(1′*S*,3*S*)-**8** (71%) and (–)-(1′*S*,3*R*)-**8** (29%), while the oxaziridine (+)-(1′*R*,2*R*,3*R*)-**5** gave the oxadiazolines (–)-(1′*R*,3*R*)-**8** (76%) and (+)-(1′*R*,3*S*)-**8** (24%). The results were confirmed again by ^{1}H and ^{13}C NMR spectra and specific rotation values.

The same pathway was observed in the cycloaddition reaction either between oxaziridine **6** and benzonitrile (entry 7) or between oxaziridine **4** and benzothiazole-2-carbonitrile (entry 8).

The structure of one of the less abundant diastereomers, specifically the compound (+)-(1′*R*,3*S*)-**10**, was obtained by X-ray diffraction analysis (Figure 1).[37]

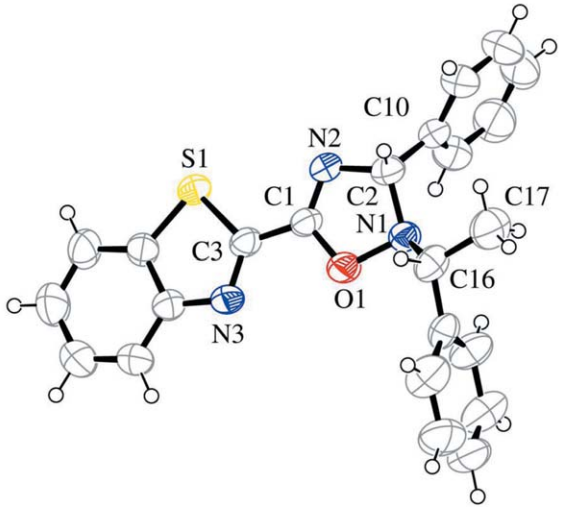
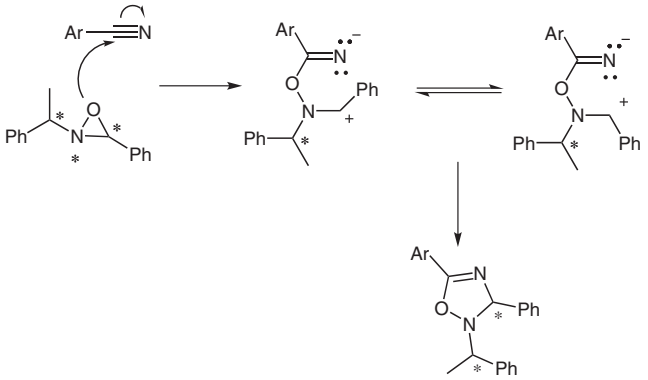


Figure 1 Plot of compound (+)-(1′*R*,3*S*)-**10** with partial numbering scheme; ellipsoids at 50% probability level, H atoms not to scale

The stereoselectivity in the formation of the 2,3-dihydro-1,2,4-oxadiazoles was attributed to the stereocontrol exerted by the stereocenter external to the oxaziridine ring bonded to the nitrogen. In fact, the analysis of the results reported in Table 2 indicates that diastereomeric oxadiazolines (1′*R*,3*R*) were predominantly formed from all oxaziridines that contained the (1′*R*)-stereocenter (entries 3, 4, and 6–8), while diastereomeric oxadiazolines (1′*S*,3*S*) were generated in a greater amount from oxaziridines that contained the (1′*S*)-stereocenter (entries 1, 2, and 5). Therefore, C3 in the 1,2,4-oxadiazolines did not necessarily retain the starting absolute configuration of the oxaziridine. This suggests that the [3+2] cycloaddition occur according to the mechanism reported in Scheme 3. In detail, initially the oxaziridine oxygen attacks the carbon on the nitrile and then the nitrogen of the nitrile attacks the oxaziridine C3, which, influenced by the pre-existing stereocenters, rotates giving the more stable diastereomer.

The configurational assignment was also based on computational methods of the relative energy of diastereomers (–)-(1′*R*,3*R*)-**7** and (+)-(1′*R*,3*S*)-**7**. The most stable conformations of these configurations are shown in Figure 2, structures **2A** and **2B**, respectively. The difference in the total energy (ΔE) of these diastereomers is 2.27 kcal/mol; the configuration (–)-(1′*R*,3*R*)-**7** is at lower relative energy (0 kcal/mol). In these cases the *trans* relationship between the substituent at C3 and the substituent at N2 was chosen. If we suppose, instead, that there is a *cis* relationship between these substituents in the (–)-(1′*R*,3*R*)-**7** and (+)-(1′*R*,3*S*)-**7** diastereomers, as shown in Figure 2, structures **2C** and **2D**, respectively, ΔE values obtained by calculation were 4.13 and 2.65 kcal/mol, respectively. Thus, the most probable configuration, justified also by the cycloaddition stereoselectivity, is the *trans* (1′*R*,3*R*) configuration.



Scheme 3 Mechanism for 2,3-dihydro-1,2,4-oxadiazoles synthesis

The conformational search for each diastereomer was performed by molecular mechanics calculation through an iterative process using the MM2 force field by the Chem-Bio 3D Ultra package and a molecular dynamic program with 10000 steps and a target temperature of 300 K was applied to obtain the minimum energy conformation for the configurations shown in Figure 2. The bond lengths and bond angles of the heterocyclic ring used were identical for all diastereomers.

Moreover, NOESY measurements on the diastereomer (+)-(1′*R*,3*S*)-**10** showed that the substituents on N2 and C3 adopt and strongly maintain a stable *trans* configuration at room temperature and also in deuterochloroform solution. As consequence, N2 of the oxadiazoline became a stable stereocenter with known configuration always opposite to that of C3, i.e. (*S*)-N2 vs (*R*)-C3 and vice versa.

In conclusion, the described methodology afforded chiral 2,3-dihydro-1,2,4-oxadiazoles with good yield, regio- and stereoselectivity. In detail: (a) the oxaziridine rings were opened along the C–O bond and the addition to –CN was regiocontrolled, specifically the oxygen attacks the nitrile carbon and the carbon bonds to the nitrile nitrogen; (b) only *trans*-oxadiazolines were isolated and the absolute configuration of the various chiral centers was assigned by X-ray diffraction analysis, NOESY measurements, and theoretical calculations.

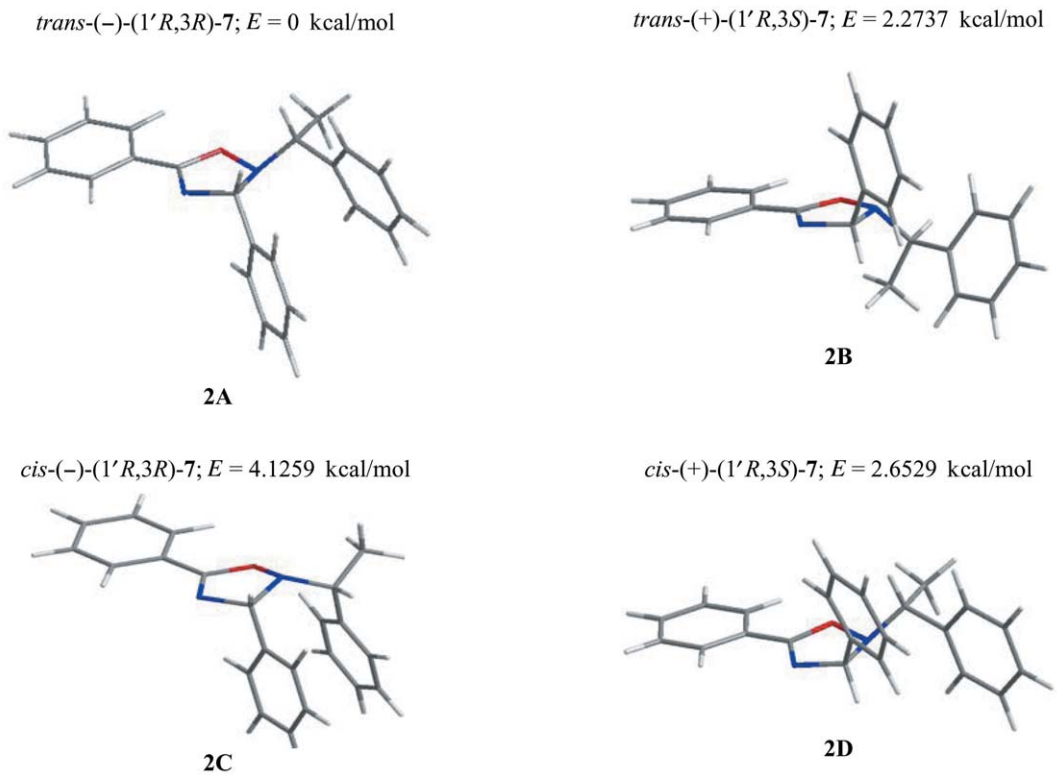


Figure 2 The most stable conformations of compound **7**

All reactions were performed under an atmosphere of N_2 in oven-dried glassware, using syringe/septum cap techniques. Reagents were generally the best quality commercial grade and used without further purification unless otherwise indicated. Et_2O and THF were purified by distillation from Na before use. CH_2Cl_2 was distilled from CaH_2 before use. Petroleum ether (PE) refers to the fraction with bp 40–60 °C. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 apparatus (400.13 and 100.62 MHz, for ^1H and ^{13}C, respectively) with $CDCl_3$ as solvent and TMS as internal standard [δ = 7.26 (^1H); δ = 77.0 (^{13}C)]. IR spectra were recorded with an FT-IR spectrophotometer Digilab Scimitar Series FTS 2000. Polarimetric measurements were performed by a Jasco P-120 polarimeter. GC-MS analyses were performed with an Agilent Technologies 6850 series II gas chromatograph (5% phenyl-polymethylsiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with a 5973 Network mass-selective detector operating at 70 eV. The electrospray ionization [HRMS (ESI)] experiments were carried out in a hybrid QqTOF mass spectrometer (PE SCIEX–QSTAR) equipped with a ion spray ionization source. MS (+) spectra were acquired by direct infusion (5 μL/min) of a soln containing the appropriate sample (10 pmol/μL), dissolved in 0.1% AcOH in MeOH–H_2O (50:50) soln at the optimum ion voltage of 4800 V. The N_2 gas flow was set at 2.07 bar and the potentials of the orifice, the focusing ring, and the skimmer were kept at 30 V, 50 V, and 25 V relative to ground, respectively. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatography was performed on silica gel (63–200 mm) using PE–Et_2O or PE–EtOAc mixtures.

Imines 1–3; General Procedure

The appropriate 1-phenylethylamine (1 mmol) and the corresponding aldehyde (1 mmol) were dissolved in anhyd Et_2O (20 mL) in the presence of molecular sieves (4 Å, 1.6 mm pellets, 7.0 g), according to Taguchi's protocol[35] (GC monitoring). After 1–3 h, the molecular sieves were filtered and the mixture was concentrated under vacuum to obtain the pure imine. The spectroscopic data observed were in agreement with those reported in the literature for the same imines.[29–34]

Oxaziridines 4–6; General Procedure

A small excess of *m*CPBA (1.1 mmol) in CH_2Cl_2 (3 mL) was added to a soln of imine (1.0 mmol) dissolved in CH_2Cl_2 (5 mL) that was stirred and cooled (0–5 °C). When the reaction was complete, the organic mixture was washed with 5% Na_2SO_3 soln (2 × 5 mL) and 5% Na_2CO_3 soln (5 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo; the crude product was purified by column chromatography [silica gel partly deactivated with Et_3N, PE–Et_2O, 95:5 (phenyloxaziridines) and PE–Et_2O, 8:2 (all other oxaziridines)]. The spectroscopic data observed were in agreement with those reported in the literature for the same imines.[21]

Oxadiazoles 7–9; General Procedure

A soln of oxaziridine **4**–**6** (1.0 mmol) in PhCN (3 mL) was heated at 140 °C under magnetic stirring. When TLC showed the reaction to be complete, the soln was cooled to r.t. and then the PhCN was distilled off under reduced pressure to give a yellow crude material. The products were isolated by flash chromatography (silica gel, PE–Et_2O, 95:5) and identified by spectroscopic analysis; GC-MS: all compounds were unstable on the chromatography column.

3,5-Diphenyl-2-(1-phenylethyl)-2,3-dihydro-1,2,4-oxadiazole (7)

(+)-(1′*S*,3*S*)-7

Yellow oil; $[\alpha]_D^{24.0}$ +59.2 (*c* 0.02, $CHCl_3$).

IR ($CHCl_3$): 3030, 2989, 2926, 1664, 1493, 1452, 1322, 1220 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.67 (d, *J* = 6.4 Hz, 3 H, CH_3), 4.11 (q, *J* = 6.4 Hz, 1 H, CH_3CHPh), 5.90 (s, 1 H, NC*H*N), 7.08–

7.10 (m, 2 H, H_{Ph}), 7.22–7.58 (m, 11 H, H_{Ph}), 8.05 (d, *J* = 7.5 Hz, 2 H, H_{Ph}).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.7, 67.2, 89.3, 125.6, 126.0, 126.4, 128.0, 128.1, 128.3, 128.6, 126.8, 129.1, 132.1, 139.9, 140.9, 161.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}N_2O$: 329.1576; found: 329.1578.

(–)-(1′*S*,3*R*)-7

Yellow oil; $[\alpha]_D^{24.0}$ –60.0 (*c* 0.02, $CHCl_3$).

IR ($CHCl_3$): 3030, 2988, 2927, 1655, 1495, 1452, 1322, 1220 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$), 4.22 (q, *J* = 6.6 Hz, 1 H, CH_3C*H*Ph), 6.13 (s, 1 H, NC*H*N), 7.22–7.52 (m, 13 H, H_{Ph}), 7.78(d, *J* = 7.0 Hz, 2 H, H_{Ph}).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 19.3, 66.2, 88.9, 125.5, 126.7, 127.1, 127.6, 127.9, 128.2, 128.4, 128.5, 129.1, 131.8, 140.6, 141.2, 161.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}N_2O$: 329.1576; found: 329.1577.

3-(4-Chlorophenyl)-5-phenyl-2-(1-phenylethyl)-2,3-dihydro-1,2,4-oxadiazole (8)

(+)-(1′*S*,3*S*)-8

Yellow solid; mp 61.5–63.0 °C; $[\alpha]_D^{24.0}$ +77.5 (*c* 0.02, $CHCl_3$).

IR ($CHCl_3$): 3030, 2987, 2927, 2855, 1654, 1492, 1452, 1322, 1090 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (d, *J* = 6.3 Hz, 3 H, C*H*$_3$), 4.10 (q, *J* = 6.3 Hz, 1 H, CH_3C*H*Ph), 5.85 (s, 1 H, NC*H*N), 7.02 (d, *J* = 8.3 Hz, 2 H, H_{Ph}), 7.19 (d, *J* = 8.3 Hz, 2 H, H_{Ph}), 7.31–7.36 (m, 5 H, H_{Ph}), 7.48 (t, *J* = 7.7 Hz, 2 H, H_{Ph}), 7.55 (d, *J* = 7.3 Hz, 1 H, H_{Ph}), 8.02 (d, *J* = 8.3 Hz, 2 H, H_{Ph}).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.7, 67.3, 88.8, 125.4, 127.9, 128.3, 128.4, 128.6, 128.8, 128.9, 132.2, 133.8, 138.6, 140.7, 161.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}ClN_2O$: 363.1186; found: 363.1187.

(–)-(1′*S*,3*R*)-8

Yellow oil; $[\alpha]_D^{24.0}$ –72.1 (*c* 0.02, $CHCl_3$).

IR ($CHCl_3$): 3030, 2926, 2855, 1656, 1490, 1457, 1375, 1091 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$), 4.23 (q, *J* = 6.6 Hz, 1 H, CH_3C*H*Ph), 6.08 (s, 1 H, NC*H*N), 7.30–7.42 (m, 10 H, H_{Ph}), 7.48 (t, *J* = 7.4 Hz, 2 H, H_{Ph}), 7.77 (d, *J* = 8.4 Hz, 2 H, H_{Ph}).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 22.7, 66.1, 88.1, 125.2, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 132.0, 134.0, 139.2, 140.8, 161.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}ClN_2O$: 363.1186; found: 363.1185.

5-Phenyl-2-(1-phenylethyl)-3-(4-tolyl)-2,3-dihydro-1,2,4-oxadiazole (9)

(–)-(1′*R*,3*R*)-9

Yellow oil; $[\alpha]_D^{24.0}$ –38.5 (*c* 0.02, $CHCl_3$).

IR ($CHCl_3$): 3020, 2927, 2858, 1657, 1453, 1375, 1090 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$CH), 2.27 (s, 3 H, PhC*H*$_3$), 4.09 (q, *J* = 6.4 Hz, 1 H, CH_3C*H*Ph), 5.86 (s, 1 H, NC*H*N), 6.97 (d, *J* = 8.1 Hz, 2 H, H_{Ph}), 7.04 (d, *J* = 8.1 Hz, 2 H, H_{Ph}), 7.28–7.38 (m, 5 H, H_{Ph}), 7.47 (t, *J* = 7.2 Hz, 2 H, H_{Ph}), 7.54 (d, *J* = 7.3 Hz, 1 H, H_{Ph}), 8.03 (d, *J* = 8.3 Hz, 2 H, H_{Ph}).

^{13}C NMR ($CDCl_3$): δ = 21.1, 22.8, 67.2, 89.3, 126.3, 128.1, 128.4, 128.6, 128.7, 128.8, 129.0, 129.1, 132.0, 137.1, 137.7, 141.1, 161.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{23}N_2O$: 343.1732; found: 343.1734.

(+)-(1′*R*,3*S*)-9

Yellow oil; $[\alpha]_D^{24.0}$ +27.0 (*c* 0.02, $CHCl_3$).

IR ($CHCl_3$): 3020, 2928, 2857, 1657, 1452, 1375, 1090 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$CH), 2.33 (s, 3 H, PhC*H*$_3$), 4.20 (q, *J* = 6.7 Hz, 1 H, CH_3C*H*Ph), 6.09 (s, 1 H, NC*H*N), 7.16 (d, *J* = 8.0 Hz, 2 H, H_{Ph}), 7.28–7.49 (m, 10 H, H_{Ph}), 7.77 (d, *J* = 8.0 Hz, 2 H, H_{Ph}).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 19.4, 21.2, 66.2, 88.9, 125.5, 126.6, 127.6, 127.9, 128.4, 128.5, 129.2, 130.9, 131.8, 137.7, 137.9, 141.3, 160.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{23}N_2O$: 343.1732; found: 343.1731.

5-(Benzothiazol-2-yl)-3-phenyl-2-(1-phenylethyl)-2,3-dihydro-1,2,4-oxadiazole (10)

A soln of benzothiazole-2-carbonitrile (BTCN, 1.5 mmol) and oxaziridine **4** (1.0 mmol) in toluene (10 mL) was refluxed under magnetic stirring (TLC monitoring). When the reaction was complete, the soln was cooled to r.t. and the solvent was evaporated under reduced pressure giving a yellow crude material. The products were isolated by flash chromatography (silica gel, PE–Et_2O, 9:1) and identified by spectroscopic analysis; GC-MS: both compounds were unstable on the chromatography column.

(–)-(1′*R*,3*R*)-10

Yellow solid; mp 90–92 °C; $[\alpha]_D^{24.0}$ –34.9 (*c* 0.02, $CHCl_3$).

IR ($CHCl_3$): 3030, 3007, 2927, 2854, 1655, 1495, 1454, 1376, 1310, 1080 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$CH), 4.23 (q, *J* = 6.4 Hz, 1 H, CH_3C*H*Ph), 6.00 (s, 1 H, NC*H*N), 7.18–7.40 (m, 10 H, H_{Ph}), 7.50–7.60 (m, 2 H, H_{BTz}), 7.97 (d, *J* = 7.8 Hz, 1 H, H_{BTz}), 8.24 (d, *J* = 8.2 Hz, 1 H, H_{BTz}).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.7, 67.6, 89.5, 121.8, 124.9, 125.0, 126.6, 127.0, 127.2, 127.9, 128.3, 128.8, 131.3, 136.0, 137.1, 140.3, 153.4, 156.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}N_3OS$: 386.1249; found: 386.1751.

(+)-(1′*R*,3*S*)-10

Colorless crystal; mp 78–80 °C; $[\alpha]_D^{24.0}$ +38.7 (*c* 0.02, $CHCl_3$).

IR ($CHCl_3$): 3030, 3008, 2927, 2856, 1661, 1496, 1455, 1377, 1311, 1080 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$CH), 4.33 (q, *J* = 6.7 Hz, 1 H, CH_3C*H*Ph), 6.16 (s, 1 H, NC*H*N), 7.27–7.63 (m, 12 H, H_{Ph}, H_{BTz}), 7.91 (d, *J* = 7.8 Hz, 1 H, H_{BTz}), 8.19 (d, *J* = 8.2 Hz, 1 H, H_{BTz}).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 18.5, 66.5, 88.8, 121.8, 124.9, 125.3, 126.8, 127.0, 127.7, 128.0, 128.5, 129.1, 131.8, 135.9, 139.3, 139.5, 153.1, 156.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}N_3OS$: 386.1249; found: 386.1750.

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(37) X-ray crystallographic data for **10**: $C_{23}H_{19}N_3OS$, *Mr* = 85.47, $0.10 \times 0.35 \times 0.37$ mm^3, pale orange, monoclinic, space group *P*21, *a* = 11.6205(12), *b* = 6.2907(5), *c* = 13.6858(15) Å, β = 96.168(10)°, *V* = 994.66(17) Å^3, *Z* = 2, D_c = 1.287 g cm^{-3}, λ(Mo-Kα) = 0.71073 Å, μ(Mo-Kα) = 0.181 mm^{-1}. Bruker SMART APEX2 diffractometer, data collection below 2θ = 55°, 4024 data collected, 3153 independent, 2804 observed [$I > 2\sigma(I)$]. The structure was solved by SIR2002[38a], and refined on F^2 by SHELX97[38b]. Final *R* = 0.0369, *wR* = 0.0944, on observed data, goodness-of-fit = 1.033; Flack parameters –0.03 (8); $-0.21 < \Delta\rho < 0.25$ eÅ^{-3}. Crystallographic data, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 767590. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk.
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