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Convenient Synthesis of Oxazolidinones and Oxazinones from Allyl and Homoallyl Amines under Mild Conditions

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Abstract: An efficient one-pot general method for the high-yield synthesis in solution of oxazolidinones and oxazinones from allyl- and homoallylamines, respectively, has been developed. The reaction is carried out at an atmospheric pressure between 0°C and room temperature using a solution of carbon dioxide in acetonitrile and hindered guanidine as the base.

Keywords: Carbon dioxide, iodine, oxazinones, oxazolidinones

Oxazolidin-2-ones and oxazin-2-ones are important classes of heterocyclic compounds containing five- and six-membered rings, respectively. The use of enantiomerically pure oxazolidinones as chiral auxiliaries was first introduced by Evans in 1981 (available from amino alcohols, which in turn are readily obtained from amino acids or norephedrine).[1] Several modifications were subsequently introduced by the groups of Hinterman and Bull.[2] As a result, these systems have been widely used in asymmetric synthesis for the preparation of enantiopure molecules. Thus, remarkable diastereoselectivity in alkylation, acylation, aldol condensation, conjugate addition, and Diels–Alder reactions could be obtained using such oxazolidinones in solution.[3] Nowadays, the emergence of solid-phase synthesis and combinatorial chemistry has led to these systems being used as supported chiral auxiliaries.[4]

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In addition, the oxazolidin-2-one ring is present in numerous natural and synthetic molecules with significant biological activity. This ring is also a component of a novel class of synthetic antimicrobial agents with activity against multidrug-resistant Gram-positive bacteria. Although these compounds were initially discovered by researchers at DuPont in the late 1980s (DuP 721), researchers at Pharmacia Corporation finally identified two clinical candidates, eperezolid and linezolid, with the latter being approved by the US Food and Drug Administration (FDA) in 2000 (Zivox®).[5]

Although a few methods have been published in the literature for the synthesis of oxazolidinones, only two papers have been published studying the synthesis of 5-substituted oxazolidin-2-ones using carbon dioxide (CO_2)—a reagent in which we are especially interested—and unsaturated amines. The first example involved the synthesis of iodooxazolidinones and iodooxazinones from allylamines and homoallylamines, respectively. The reaction was carried out in solution with dissolved CO_2, using either a large excess of the amine or caesium carbonate to generate the carbamate anion in the basic medium. Iodine was subsequently added to the reaction mixture. However, this method has important drawbacks because the yields are low and the reaction times are very long.[6]

The second article deals with a mechanistically similar one-step solid-phase procedure leading to 5-(iodomethyl)oxazolidin-2-ones from allylic amine hydrochlorides or free amines by reacting the allyl amine with the reagent obtained by adsorbing iodine onto the resin Amberlyst A 26 in the CO_3^{2-} form.[7]

In recent times, the nucleophilic reactivity of carbamate anions has been studied.[8] These carbamate anions were prepared from an amine using carbon dioxide and different bases. Among these bases, several hindered guanidines proved to be very efficient reagents. On the basis of our experience in the use of carbon dioxide as a reagent and the existing precedents in the literature, we developed efficient reaction conditions for the nucleophilic opening of iodonium ions by carbamate anions in solution.

Although weak bases such as amines or alkaline carbonates have been used previously, giving poor yields, the use of strong bases is recommended to shift the equilibrium between carbon dioxide and an amine to the carbamate anion. Guanidines have proved to be among the best choices, not only because of their basicity[9] but also because of the ability of the guanidinium ion to stabilize bidentate anions such as carbamates.[10] Dry acetonitrile was used as the solvent because guanidines behave as strong bases in acetonitrile.[11] In addition, the solubility of carbon dioxide in acetonitrile is rather high, thus ensuring a sufficiently high concentration of carbon dioxide in the reaction medium at atmospheric pressure.

The nonnucleophilic guanidines 2-phenyl-1,1,3,3-tetramethylguanidine (PhTMG **1**) and 2-cyclohexyl-1,1,3,3-tetramethylguanidine (CyTMG **2**) have previously been used as bases in the alkylation of carbamate anions with electrophiles.[8] Because both guanidines—PhTMG (**1**) and CyTMG

(**2**)—are noncommercial reagents, we prepared them by a slight modification of Bredereck's procedure, replacing benzene with toluene as the solvent.[12] Thus, preparation of the Vilsmeier salt of tetramethylurea and subsequent reaction with aniline and cyclohexylamine gave PhTMG and CyTMG in 87–98% and 46% yield, respectively. In our hands, PhTMG was obtained in a much higher yield than reported in the literature (52%), whereas CyTMG was obtained in moderate yield. An additional advantage of these bases is that at pH < 10 they are present in solution as guanidinium cations and are water soluble, whereas at pH 14 they are in the neutral form and can be recovered from an organic solution.

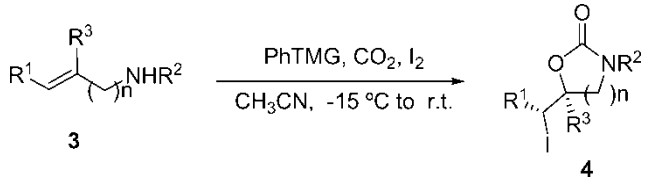
The reaction conditions were adjusted using commercial allylamine (**3a**) and diallylamine (**3b**) as substrates (Scheme 1, Table 1). To maintain the maximum concentration of carbon dioxide in solution, several attempts were made to prepare the initial solution by bubbling in carbon dioxide between -20 and 0°C. It was found that the optimal conditions were initial saturation of the solution with carbon dioxide at 0°C followed by stirring under a carbon dioxide atmosphere.

The reaction was carried out using Na_2CO_3, PhTMG, and CyTMG as the bases. Once the mixture of amine, base, and carbon dioxide in acetonitrile had been prepared, a solution of iodine in acetonitrile was added. Sodium carbonate proved to be very inefficient. Even after several days, the yields were very low (ca. 17%). In contrast, both guanidines behaved similarly, yielding the products in good to excellent yields in a few hours. Finally, PhTMG was selected as the base because it was obtained in higher yield.

The time and scope of the reaction was studied with a set of different allyl- and homoallylamines **3**. Several of these compounds were commercially available, and those that were not available were easily prepared by monoalkylation of primary amines with alkyl halides. The results of the reactions carried out with amines **3** according to Scheme 1 for different times are shown in Table 1.

The reaction seems to be rather fast, although it takes some time to reach completion. Within a few hours most of the product is formed, but the isolated yields increase until they are nearly quantitative when the reaction time approaches 1 day (entries 7, 8, and 9).

In general, reaction yields are very good with both primary and secondary amines. In addition, oxazolidinones, and oxazinones **4** are stable solids, and



Scheme 1.

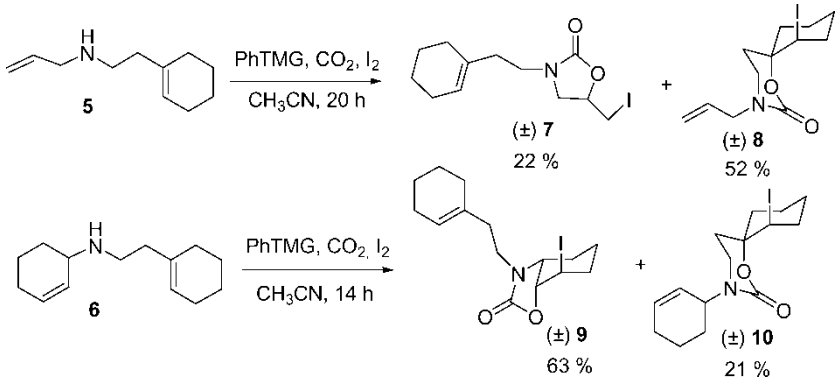
Table 1. Outcome for Scheme 1 reaction

Entry	Amine	n	Time (h)	Yield (%)	Product
1	**3a** $R^1 = R^2 = R^3 = H$	1	18	67	**4a**
2	**3b** $R^1 = R^3 = H$, $R^2 = CH_2CH{:}CH_2$	1	3	87	**4b**
3	**3b** $R^1 = R^3 = H$, $R^2 = CH_2CH{:}CH_2$	1	20	90	**4b**
4	**3c** $R^1 = R^3 = H$, $R^2 = Ph$	1	216	0	**4c**
5	**3d** $R^1 = R^3 = H$, $R^2 = Bn$	1	5	89	**4d**
6	**3d** $R^1 = R^3 = H$, $R^2 = Bn$	1	18	92	**4d**
7	**3e** $R^1 = H$, $R^3 = CH_3$, $R^2 = Et$	1	2	90	**4e**
8	**3e** $R^1 = H$, $R^3 = CH_3$, $R^2 = Et$	1	5	93	**4e**
9	**3e** $R^1 = H$, $R^3 = CH_3$, $R^2 = Et$	1	20	98	**4e**
10	**3f** R^1, $R^3 = -(CH_2)_4-$, $R^2 = Bn$	1	0.3	91	**4f**
11	**3f** R^1, $R^3 = -(CH_2)_4-$, $R^2 = Bn$	1	16	97	**4f**
12	**3g** $R^3 = H$, $R^1 = CH_3$, $R^2 = Bn$	1	2	76	**4g**
13	**3g** $R^3 = H$, $R^1 = CH_3$, $R^2 = Bn$	1	5	84	**4g**
14	**3g** $R^3 = H$, $R^1 = CH_3$, $R^2 = Bn$	1	20	93	**4g**
15	**3h** $R^3 = H$, $R^1 = Ph$, $R^2 = Bn$	1	20	86	**4h**
16	**3i** R^1, $R^2 = -(CH_2)_2-$, $R^3 = H$	1	24	0	**4i**
17	**3j** R^1, $R^3 = -(CH_2)_4-$, $R^2 = H$	2	2	51	**4j**
18	**3j** R^1, $R^3 = -(CH_2)_4-$, $R^2 = H$	2	5	70	**4j**
19	**3j** R^1, $R^3 = -(CH_2)_4-$, $R^2 = H$	2	21	94	**4j**

by-products are not generally found in the reaction mixture—although one exception was found. Initially, the reaction with allylamine (**3a**) gave rather poor yields (ca. 65%) due to losses in the workup resulting from the high solubility of the oxazolidinone (**4a**) in water. The yield could be increased to nearly 80% with a careful extraction in the workup. Nevertheless, two substrates did not give any product. Allylaniline (**3c**) was recovered unreacted after more than 1 week. This result clearly indicates that the low nucleophilicity of anilines in comparison with amines precludes the formation of the carbamate anion. It is more difficult to explain the low reactivity of 1,2,3,6-tetrahydropyridine (**3i**). In this case, the high energy needed to overcome the ring tension probably disfavors formation of the bicycle.

The reaction was found to be regioselective in all cases. Thus, with allylamines and homoallylamines, only five- and six-membered rings were obtained, respectively. Although the formation of the smaller possible ring can be easily rationalized in entropic terms, the factors affecting the reaction seem to be a bit more complex. When the reaction was carried out with allylhomoallylamines, a more detailed picture of the reaction was obtained. For example, substrate **5** gave an oxazolidinone–oxazinone ratio of 1:2.4, whereas compound **6** reversed the ratio to 3:1 (Scheme 2). This result clearly shows that ring size is not the only driving force in the reaction.

Further experiments are clearly needed in this area, but a possible explanation for this behavior can be given by considering the reaction mechanism

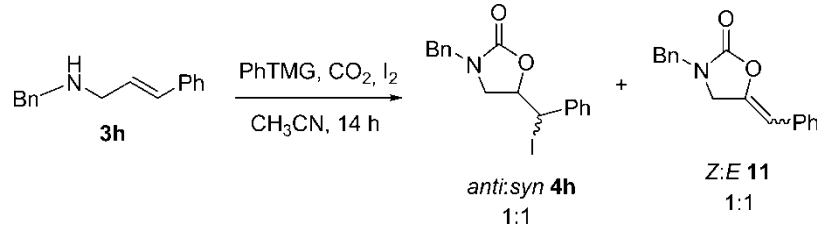


Scheme 2.

in more detail. In this type of reaction, as in other additions of halogens to alkenes, a halonium ion is postulated as an intermediate. It has been shown that reactivity increases with additional substitution of electron-releasing alkyl groups at the double bond. Thus, the outcome of the reaction can be predicted in that the most substituted alkene will react to form the smaller urethane ring.

Further evidence for the existence of an iodinium ion as an intermediate is provided by the stereochemistry of the resulting oxazolidinones and oxazinones. Only one diastereoisomer was obtained in all but one case. Entry 15 shows that reaction of *N*-benzyl-*N*-*trans*-cinnamylamine (**3h**) initially gave a 1:1 mixture of epimeric oxazolidinones *anti* and *syn* **4h** together with small amounts of elimination products **11** (Scheme 3).

Because the epimerization of alkyl iodides in the benzylic position in the presence of iodide ions is known, the reaction was repeated with the addition of silver oxide to remove iodide ions from the reaction medium. Under such conditions, only one diastereoisomer (*anti*-**4h**) was obtained along with a small amount of elimination product *E*-**11**, with the amount of the latter proportional to the reaction time. Once it had been demonstrated that in all cases only a single diastereomer is the initial result of the reaction, the stereochemistry had to be assigned.



Scheme 3.

In monocyclic oxazolidinones, the stereochemistry could be deduced indirectly from the elimination product. This elimination reaction can be assumed to be *anti* because only a single elimination product is obtained. Thus, the stereochemistry of olefin **11**, obtained as a single elimination product when silver oxide was used, can readily be derived from nuclear Overhauser effect (NOE) experiments. The existence of a homonuclear NOE between the H-4 methylenic protons of the oxazolidinone ring and the *ortho* protons of the benzene ring identifies the double bond of compound **11** as *E*. This alkene can only be obtained from the oxazolidinone resulting from *anti* addition to the allylamine. This result is in complete agreement with the stereochemistry of the electrophilic addition of halogens to double bonds.

Bicyclic oxazolidinones also provided evidence for the *anti* addition to the double bond. A full structural and conformational analysis of compound **4f** was performed in several solvents. Both homonuclear NOE correlations and ^{1}H NMR coupling constant analysis unambiguously indicated the *anti* relative stereochemistry between iodine and oxygen.[13]

The oxazinones obtained were also shown to be *anti*. ^{1}H NMR data were only compatible with the proposed stereochemistry. In addition, single-crystal X-ray analysis of compound **4j** confirmed the relative stereochemistry.[14]

EXPERIMENTAL

IR spectra were obtained on a Bruker Vector 22 FTIR spectrophotometer. Mass spectra were obtained on a Fisons VG Autospec M system. NMR spectra were obtained on either a Bruker ARX400 or a Bruker Avance DPX400 spectrometer. NMR spectra were recorded in deuterochloroform, and the chemical shifts are expessed in parts per million (ppm) (δ) relative to the residual solvent signal ($CDCl_3$ 7.27 for ^{1}H and $CDCl_3$ 77.00 for ^{13}C).

2-Phenyl-1,1,3,3-tetramethylguanidine (PhTMG) (1)[15]

A solution of phosphorus oxychloride (11.5 g, 7 mL, 0.075 mmol, 150 mol%) in dry toluene (10 mL) was slowly added to a solution of 1,1,3,3-tetramethylurea (5.81 g, 6 mL, 0.05 mmol, 100 mol%) in dry toluene (50 mL) under an Ar atmosphere at 0°C. The mixture was allowed to warm up to room temperature and stirred for 8 h. A solution of aniline (6.83 mL, 6.99 g, 75 mmol, 150 mol%) in dry toluene (20 mL) was slowly added at r.t. The mixture was stirred at r.t. for 30 min and heated under reflux for 8 h. The phases were separated. The oily phase (lower) was washed with toluene (3 × 10 mL) and cooled to 0°C. The pH was adjusted to 7–9 with 2 M NaOH, and the phase was washed with EtOAc/hexane (1:1, 2 × 25 mL). At 0°C, the aqueous phase was basified with 4 M NaOH until pH > 14, and the white precipitate

was filtered off and discarded. The aqueous phase was extracted with EtOAc/hexane (1:1, 4 × 40 mL), and the combined organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give PhTMG (**1**) as a pale pink oil (8.250–9.270 g, 87–98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (td, $J = 7.2$ and 1.7 Hz, 2 H), 6.77 (tt, $J = 7.3$ and 1.1 Hz, 1 H), 6.65 (dd, $J = 8.3$ and 1.1 Hz, 2 H), 2.64 (br s, 12 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.80 (s), 151.68 (s), 128.52 (d), 121.48 (d), 119.53 (d), 39.60 (q), 39.42 (q) ppm; FTIR (neat): ν_{max} 3071, 3056, 3006, 2924, 2885, 1604, 1576, 1506, 1377, 1139, 1108 cm^{-1}; MS (EI): m/e (relative intensity) 191 (M^+, 51), 176 (17), 147 (100), 132 (39), 120 (24), 77 (14), 72 (18); HRMS (EI): calcd. for $C_{11}H_{17}N_3$ 191.1422 (M^+), found 191.1432.

2-Cyclohexyl-1,1,3,3-tetramethylguanidine (2)

CyTMG was synthesized in a similar way to PhTMG (**1**) using 1,1,3,3-tetramethylurea (5.81 g, 6 mL, 0.05 mmol, 100 mol%), phosphorus oxychloride (11.5 g, 7 mL, 0.075 mmol, 150 mol%), and cyclohexylamine (8.6 mL, 7.44 g, 75 mmol, 150 mol%) in dry toluene (80 mL). CyTMG was obtained as a pale yellow oil (4.478 g, 46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (m, 1 H), 2.70 (s, 6 H), 2.64 (s, 6 H), 1.71 (m, 2 H), 1.57–1.55 (m, 3 H), 1.28–1.24 (m, 5 H).

General Procedure for the Preparation of Oxazolidinones and Oxazinones

CO_2 was bubbled through an ice-cooled solution of the amine and PhTMG (100–150 mol%) in acetonitrile for 10 min. Solid iodine (100–120 mol%) was added in one portion to the solution, and CO_2 was bubbled for an additional period of 10 min. The temperature was allowed to rise to room temperature, and the mixture was stirred for the given time, in the dark, under a CO_2 atmosphere. The solvent was removed under reduced pressure, and the crude product was dissolved in EtOAc. The organic phase was washed with 5% HCl and then with 10% $NaHSO_3$, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. PhTMG can be recovered from the aqueous phase.

5-Iodomethyl-oxazolidin-2-one (4a)

According to the general procedure, to a solution of allylamine (0.150 mL, 2.0 mmol) and PhTMG (**1**) (0.479 g, 2.5 mmol) in acetonitrile (30 mL), I_2 (0.508 g, 2.0 mmol) was added. After 18 h, the appropriate workup, and

chromatography (EtOAc/hexane 1:4 to 2:1), compound **4a** was obtained as a white crystalline solid (0.303 g, 67%).

Rf = 0.5 (EtOAc); mp = 117–118°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (br s, 1 H), 4.73 (m, 1 H), 3.78 (t, $J = 8.8$ Hz, 1 H), 3.43–3.38 (m, 2 H), 3.31 (dd, $J = 10.3$ and 8.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.18 (s), 75.13 (d), 46.36 (t), 5.83 (t); FTIR (KBr): ν_{max} 1782, 1734, 1244, 1097, 959 cm^{-1}; MS (EI): m/e (relative intensity), 227 (M^+, 64), 127 (7), 100 (100), 86 (38); HRMS (EI): calcd. for $C_4H_6INO_2$ 226.9443 (M^+), found 226.9444; Anal. calcd. for $C_4H_6INO_2$: C, 21.16; H, 2.66; N, 6.17; O, 14.10; found C, 20.90; H, 2.34; N, 6.55.

3-Allyl-5-iodomethyl-oxazolidin-2-one (4b)

According to the general procedure, to a solution of diallylamine (0.248 mL, 2.0 mmol) and PhTMG (**1**) (0.536 g, 2.8 mmol) in acetonitrile (30 mL), I_2 (0.508 g, 2.0 mmol) was added. After 20 h, the appropriate workup, and chromatography (EtOAc/hexane 1:9 to 1:4), compound **4b** was obtained as a yellow oil (0.477 g, 90%).

Rf = 0.38 (EtOAc/hexane 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (m, 1 H), 5.29–5.24 (m, 2 H), 4.57 (m, 1 H), 3.86–3.84 (m, 2 H), 3.66 (t, $J = 8.9$ Hz, 1 H), 3.33 (dd, $J = 10.4$ and 7.6 Hz, 1 H), 3.25 (dd, $J = 10.4$ and 4.1 Hz, 1 H), 3.20 (dd, $J = 9.2$ and 6.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.64 (s), 131.41 (d), 118.78 (t), 71.43 (d), 49.65 (t), 46.55 (t), 6.75 (t); FTIR (KBr): ν_{max} 1751, 1445, 1255 cm^{-1}; MS (EI): m/e (relative intensity), 267 (M^+, 82), 140 (100), 127 (12), 96 (90), 82 (11), 68 (49); HRMS (EI): calcd. for $C_7H_{10}INO_2$ 266.9756 (M^+), found 266.9743.

3-Benzyl-5-iodomethyl-oxazolidin-2-one (4d)

According to the general procedure, to a solution of *N*-allyl-*N*-benzylamine (**3d**) (0.300 g, 2.04 mmol) and PhTMG (**1**) (0.512 g, 2.68 mmol) in acetonitrile (30 mL), I_2 (0.568 g, 2.24 mmol) was added. After 18 h, the appropriate workup, and chromatography (EtOAc/hexane 1:9 to 1:4), compound **4d** was obtained as a brown oil (0.592 g, 92%).

Rf = 0.40 (EtOAc/hexane 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.27 (m, 5 H), 4.53 (m, 1 H), 4.46 (d, $J = 14.9$ Hz, 1 H), 4.36 (d, $J = 14.9$ Hz, 1 H), 3.54 (t, $J = 8.9$ Hz, 1 H), 3.33 (dd, $J = 10.3$ and 4.1 Hz, 1 H), 3.23 (dd, $J = 10.3$ and 7.9 Hz, 1 H), 3.14 (dd, $J = 8.9$ and 6.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.04 (s), 135.18 (s), 128.73 (d), 128.05 (d), 127.95 (d), 70.59 (d), 49.58 (t), 48.11 (t), 6.50 (t); FTIR (neat): ν_{max} 1754, 1445, 1253, 1089, 699 cm^{-1}; MS (EI): m/e (relative intensity) 317 (M^+, 13), 190 (94), 146 (25), 132 (14), 91 (100), 77 (5), 65 (18); HRMS (EI): calcd. for $C_{11}H_{12}INO_2$ 316.9913 (M^+), found 316.9906.

3-Ethyl-5-methyl-5-iodomethyl-oxazolidin-2-one (4e)

According to the general procedure, to a solution of *N*-ethyl-2-methylallylamine (0.264 mL, 2.00 mmol) and PhTMG (**1**) (0.505 g, 2.64 mmol) in acetonitrile (30 mL), I_2 (0.530 g, 2.08 mmol) was added. After 20 h, the appropriate workup, and chromatography (EtOAc/hexane 1:5 to 1:1), compound **4e** was obtained as a white crystalline solid (0.515 g, 98%).

Rf = 0.10 (EtOAc/hexane 1:4); mp = 39–40°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.44 (d, $J = 8.9$ Hz, 1 H), 3.33 (d, $J = 10.6$ Hz, 1 H), 3.28–3.20 (m, 4 H), 1.56 (s, 3 H), 1.08 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.01 (s), 76.39 (s), 54.25 (t), 38.39 (t), 25.08 (q), 13.25 (t), 12.21 (q); FTIR (KBr): ν_{max} 1748, 1300, 1054 cm^{-1}; MS (EI): *m/e* (relative intensity), 269 (M^+, 92), 254 (28), 210 (16), 142 (12), 128 (100), 98 (11), 84 (23), 69 (41); HRMS (EI): calcd. for $C_7H_{12}INO_2$ 268.9913 (M^+), found 268.9900; Anal. calcd. for $C_7H_{12}INO_2$: C, 31.25; H, 4.50; N, 5.21; O, 11.89; found C, 30.87; H, 4.33; N, 5.65.

(3*aR**, 7*R**, 7*aR**)-3-Benzyl-7-iodo-hexahydrobenzoxazolidin-2-one (4f)

According to the general procedure, to a solution of (±)-*N*-(3-cyclohexenyl)-*N*-benzylamine (**3f**) (0.379 g, 2.02 mmol) and PhTMG (**1**) (0.490 g, 2.56 mmol) in acetonitrile (30 mL), I_2 (0.526 g, 2.07 mmol) was added. After 16 h, the appropriate workup, and chromatography (EtOAc/hexane 1:9 to 1:1), compound **4f** was obtained as a white crystalline solid (0.698 g, 97%).

Rf = 0.28 (EtOAc/hexane 1:1); mp = 114–115°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5 H), 4.70 (d, $J = 15.4$ Hz, 1 H), 4.67 (t, $J = 6.3$ Hz, 1 H), 4.32 (m, 1 H), 4.10 (d, $J = 15.4$ Hz, 1 H), 3.68 (q, $J = 5.6$ Hz, 1H), 2.11 (m, 1 H), 1.92 (m, 1 H), 1.84–1.72 (m, 2 H), 1.54–1.39 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.12 (s), 135.53 (s), 128.81 (d), 128.12 (d), 127.97 (d), 79.41 (d), 53.57 (d), 45.92 (t), 32.92 (t), 26.46 (d), 24.71 (t), 20.09 (t); FTIR (KBr): ν_{max} 1748, 1396, 1042, 701 cm^{-1}; MS (EI): *m/e* (relative intensity), 357 (M^+, 5), 230 (9), 150 (61), 91 (100), 81 (40), 65 (7); HRMS (EI): calcd. for $C_{14}H_{16}INO_2$ 357.0226 (M^+), found 357.0224; anal. calcd. for $C_{14}H_{16}INO_2$: C, 47.08; H, 4.52; N, 3.92; O, 8.96; found C, 47.45; H, 4.12; N, 3.64.

(5*R**,1′*S**)-3-Benzyl-5-(1-iodoethyl)-oxazolidin-2-one (4g)

According to the general procedure, to a solution of *N*-benzyl-*N*-crotylamine (87:13 mixture of *trans* and *cis*) (**3g**) (0.161 g, 1.00 mmol) and PhTMG (**1**) (0.250 g, 1.31 mmol) in acetonitrile (25 mL), I_2 (0.277 g, 1.09 mmol) was

added. After 20 h, the appropriate workup, and chromatography (EtOAc/hexane 1:9 to 1:4), compound **4g** was obtained as a yellow solid (0.307 g, 93%).

Rf = 0.33 (EtOAc/hexane 1:4); mp = 42–43°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of epimers 87:13) δ 7.40–7.27 (m, 5 H), 4.52–4.34 (m, 3 H), 4.16–4.02 (m, 1 H), 3.59–3.49 (m, 1 H), 3.26–3.16 (m, 1 H), 1.96 (d, $J = 6.8$ Hz, 2.6 H), 1.82 (d, $J = 7.0$ Hz, 0.4 H); ^{13}C NMR (100 MHz, $CDCl_3$): (major epimer) δ 157.07, 135.17, 128.67, 127.97, 127.87, 76.72, 49.92, 48.01, 27.70, 23.47; FTIR (KBr): ν_{max} 1756 (br), 1441, 1257, 702 cm^{-1}; MS (EI): m/e (relative intensity), 331 (M^+, 6), 204 (62), 150 (50), 106 (12), 91 (100), 69 (41); HRMS (EI): calcd. for $C_{12}H_{14}INO_2$ 331.0069 (M^+), found 331.0084; anal. calcd. for $C_{12}H_{14}INO_2$: C, 43.52; H, 4.26; N, 4.23; O, 9.62; found C, 43.08; H, 3.87; N, 4.64.

(5*R**, 1′*S**)-3-Benzyl-5-(1-iodobenzyl)-oxazolidin-2-one (*anti*-4h) and (*E*)-3-Benzyl-5-(phenylmethylene)-2-oxazolidin-2-one ((*E*)-11)

According to the general procedure, to a solution of *N*-benzyl-*N*-*trans*-cinnamylamine (**3h**) (0.223 g, 1.00 mmol) and PhTMG (**1**) (0.205 g, 1.07 mmol) in acetonitrile (25 mL), I_2 (0.268 g, 1.06 mmol) and Ag_2O (0.237 g, 1.02 mmol) were added. After 30 min, the crude product was filtered off (Celite), and the appropriate workup and chromatography (EtOAc/hexane 1:9 to 1:3) gave compound *anti*-**4h** as a white solid (0.237 g, 64%) and compound (*E*)-**11** as a white solid (0.003 g, 1%).

anti-**4h**: Rf = 0.20 (EtOAc/hexane 1:3); mp = 125–126°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.28 (m, 10 H), 5.08 (d, $J = 7.7$ Hz, 1 H), 4.98 (td, $J = 8.5$ and 7.2 Hz, 1 H), 4.48 (d, $J = 14.9$ Hz, 1 H), 4.37 (d, $J = 14.9$ Hz, 1 H), 3.68 (t, $J = 8.8$ Hz, 1 H), 3.35 (dd, $J = 9.2$ and 7.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.12 (s), 138.46 (s), 135.26 (s), 129.02 (d), 128.93 (d), 128.89 (d), 128.80 (d), 128.24 (d), 128.13 (d), 128.11 (d), 128.07 (d), 75.81 (d), 50.33 (t), 48.25 (t), 33.38 (d); FTIR (KBr): ν_{max} 1752, 1250, 712, 697 cm^{-1}; MS (EI): m/e (relative intensity), 393 (M^+), 266 (80), 130 (5), 117 (7), 91 (100); HRMS (EI): calcd. for $C_{17}H_{16}INO_2$ 393.0226 (M^+), found 393.0253; anal. calcd. for $C_{17}H_{16}INO_2$: C, 51.93; H, 4.10; N, 3.56; O, 8.14; found C, 51.56; H, 4.57; N, 3.09.

(*E*)-11: Rf = 0.45 (EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.18 (m, 7 H), 7.20 (t, $J = 7.4$ Hz, 1 H), 7.04 (d, $J = 7.5$ Hz, 2 H), 6.30 (t, $J = 2.6$ Hz, 1 H), 4.55 (s, 2 H), 4.33 (d, $J = 2.6$ Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.15, 144.12, 134.90, 133.72, 129.05, 128.77, 128.31, 128.09, 127.24, 126.69, 105.32, 48.00, 47.76; FTIR (KBr): ν_{max} 1770, 1684, 1243, 1061 cm^{-1}; MS (EI): m/e (relative intensity), 265 (M^+, 47), 181 (16), 91 (100); HRMS (EI): calcd. for $C_{17}H_{15}NO_2$ 265.1103 (M^+), found 265.1109.

(6*R**, 7*S**)-7-Iodo-1,3-oxazinespiro[5.5]undecane-2-one (4j)

According to the general procedure, to a solution of 2-(1-cyclohexenyl)-ethylamine (0.280 mL, 2.00 mmol) and PhTMG (**1**) (0.511 g, 2.67 mmol) in acetonitrile (30 mL), I_2 (0.511 g, 2.01 mmol) was added. After 21 h, the appropriate workup, and chromatography (EtOAc/hexane 1:1 to EtOAc), compound **4j** was obtained as a white crystalline solid (0.540 g, 94%).

Rf = 0.28 (EtOAc); mp = 147–149°C (lit. 150–152°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (br s, 1 H), 4.51 (t, $J = 4.3$ Hz, 1 H), 3.38–3.25 (m, 2 H), 2.30 (m, 1 H), 2.24–2.10 (m, 2 H), 2.05–1.92 (m, 2 H), 1.88–1.66 (m, 3 H), 1.60–1.50 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.92 (s), 80.14 (s), 37.08 (d), 35.47 (t), 32.86 (t), 31.49 (t), 30.55 (t), 23.18 (t), 20.59 (t); FTIR (KBr): ν_{max} 3237, 3125, 2935, 1698, 1371, 1248, 1112, 1002 cm^{-1}; MS (EI): m/e (relative intensity) 295 (M^+), 168 (100), 150 (45), 125 (48),125 (49), 107 (20), 95 (33), 79 (16), 69 (19); HRMS (EI): calcd. for $C_9H_{14}INO_2$ 295.0069 (M^+), found 295.0059; anal. calcd. for $C_9H_{14}INO_2$: C, 36.63; H, 4.78; N, 4.75; O, 10.84; found C, 36.45; H, 4.63; N, 4.46.

3-[2-(1-Cyclohexenyl)-ethyl]-5-iodomethyl-2-oxazolidinone (7) and (6*R**, 7*S**)-3-Allyl-7-iodo-1,3-oxazinespiro[5.5]undecane-2-one (8)

According to the general procedure, to a solution of *N*-allyl-*N*-2-(1-cyclohexenyl)-ethylamine (**5**) (0.333 g, 2.02 mmol) and PhTMG (**1**) (0.430 g, 2.25 mmol) in acetonitrile (30 mL), I_2 (0.536 g, 2.11 mmol) was added. After 20 h, the appropriate workup, and chromatography (EtOAc/hexane 1:4 to 1:1), compound **7** was obtained as a yellow solid (0.149 g, 22%) and compound **8** was obtained as a white solid (0.353 g, 52%).

7: Rf = 0.37 (EtOAc/hexane 1:2); mp = 39–40°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47 (s, 1 H), 4.54 (m, 1 H), 3.65 (t, $J = 8.8$ Hz, 1 H), 3.42–3.19 (m, 5 H), 2.18 (t, $J = 6.9$ Hz, 2 H), 1.97–1.95 (m, 4 H), 1.64–1.51 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.86 (s), 134.09 (s), 123.78 (d), 71.69 (d), 49.88 (t), 41.83 (t), 35.75 (t), 27.67 (t), 25.22 (t), 22.70 (t), 22.20 (t), 6.35 (t); FTIR (KBr): ν_{max} 2925, 1752 (br), 1439, 1261, 1018 cm^{-1}; MS (EI): m/e (relative intensity), 335 (M^+, 37), 240 (12), 228 (56), 196 (27), 108 (100), 93 (18), 79 (25); HRMS (EI): calcd. for $C_{12}H_{18}INO_2$ 335.0382 (M^+), found 335.0382; anal. calcd. for $C_{12}H_{18}INO_2$: C, 43.00; H, 5.41; N, 4.18; O, 9.55; found C, 42.91; H, 5.23; N, 4.09.

8: Rf = 0.29 (EtOAc/hexane 1:2); mp = 66–70°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (m, 1 H), 5.18–5.13 (m, 2 H), 4.41 (t, $J = 4.4$ Hz, 1 H), 3.97–3.85 (m, 2 H), 3.22–3.14 (m, 2 H), 2.30–2.17 (m, 2 H), 2.13–1.42 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.02, 132.00, 117.92, 79.69, 51.27, 40.15, 37.29, 32.86, 31.45, 31.36, 23.21, 20.59; FTIR (KBr): ν_{max} 2938, 1696, 1493, 1448, 1278, 1099 cm^{-1}; MS (EI): m/e (relative intensity) 335 (M^+, 66), 228

(20), 208 (62), 164 (42), 114 (77), 108 (81), 95 (64), 70 (100); HRMS (EI): calcd. for $C_{12}H_{18}INO_2$ 335.0382 (M^+), found 335.0396; anal. calcd. for $C_{12}H_{18}INO_2$: C, 43.00; H, 5.41; N, 4.18; O, 9.55; found C, 42.87; H, 5.07; N, 4.45.

(3*aR**, 7*R**, 7*aR**)-3-[2-(1-Cyclohexenyl)-ethyl]-7-iodo-hexahydro-benzoxazolidin-2-one (9) and (6*R**, 7*S**)-3-(1-Cyclohexenyl)-7-iodo-1,3-oxazinespiro[5.5]undecane-2-one (10)

According to the general procedure, to a solution of (±) *N*-(3-cyclohexenyl)-*N*-2-(1-cyclohexenyl)-ethylamine (**6**) (0.415 g, 2.01 mmol) and PhTMG (**1**) (0.410 g, 2.14 mmol) in acetonitrile (30 mL), I_2 (0.525 g, 2.07 mmol) was added. After 14 h, the appropriate workup and chromatography (EtOAc/hexane 1:9 to 1:2), compound **9** was obtained as a white crystalline solid (0.475 g, 63%) and compound **10** was obtained as a brown oil (0.158 g, 21%).

9: Rf = 0.32 (EtOAc/hexane 1:4); mp = 112–113°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.45 (s, 1 H), 4.65 (t, J = 6.1 Hz, 1 H), 4.34 (m, 1 H), 3.86 (q, J = 5.9 Hz, 1 H), 3.54 (m, 1 H), 3.01 (m, 1 H), 2.16–1.89 (m, 9 H), 1.75–1.49 (m, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.55 (s), 134.19 (s), 123.66 (d), 79.19 (d), 53.61 (d), 40.11 (t), 35.84 (t), 32.59 (t), 28.02 (t), 26.58 (d), 25.21 (t), 25.03 (t), 22.76 (t), 22.19 (t), 20.19 (t); FTIR (KBr) ν_{max} 2929, 1749, 1396, 1015 cm^{-1}; MS (EI): m/e (relative intensity), 375 (M^+, 78), 280 (21), 268 (58), 248 (21), 236 (18), 207 (54), 168 (22), 154 (58), 140 (17), 108 (97), 93 (24), 81 (97), 79 (100); HRMS (EI): calcd. for $C_{15}H_{22}INO_2$ 375.0695 (M^+), found 375.0701; anal. calcd. for $C_{15}H_{22}INO_2$: C, 48.01; H, 5.91; N, 3.73; O, 8.53; found C, 47.64; H, 5.67; N, 3.24.

10: Rf = 0.16 (EtOAc/hexane 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of rotamers) δ 5.94 (m, 1 H), 5.47 (m, 1 H), 4.97 (m, 1 H), 4.47 (q, J = 4.8 Hz, 1 H), 3.34–3.09 (m, 2 H), 2.36–1.48 (m, 16 H); ^{13}C NMR (100 MHz, $CDCl_3$): (mixture of rotamers) δ 152.46 (s), 132.40 (d), 132.34 (d), 127.21 (d), 127.19 (d), 79.50 (s), 79.34 (s), 52.74 (d), 38.35 (d), 37.70 (d), 35.88 (t), 35.85 (t), 33.26 (t), 32.99 (t), 32.32 (t), 31.99 (t), 31.92 (t), 26.02 (t), 25.92 (t), 24.53 (t), 23.55 (t), 23.23 (t), 21.19 (t), 21.16 (t), 21.02 (t), 20.73 (t); FTIR (neat) ν_{max} 2937, 1689 (br), 1428, 1293, 1180, 1102, 753 cm^{-1}; MS (EI): m/e (relative intensity), 375 (M^+, 8), 248 (100), 204 (54), 176 (12), 168 (28), 140 (22), 109 (41), 96 (13), 81 (94), 67 (23); HRMS (EI): calcd. for $C_{15}H_{22}INO_2$ 375.0695 (M^+), found 375.0699.

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