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Synthesis of 2,3-Dihydro-10b*H*-oxazolo[2,3-*a*]isoquinolines from *ortho*-Lithiated Phenyloxazolinyloxiranes†

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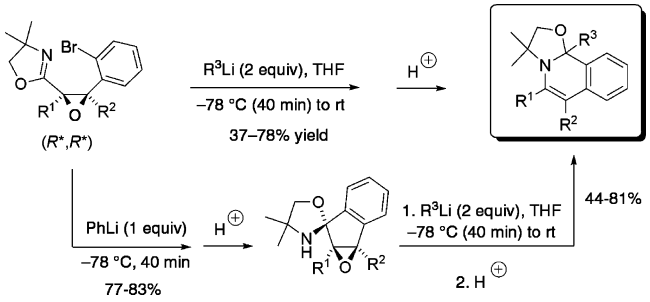
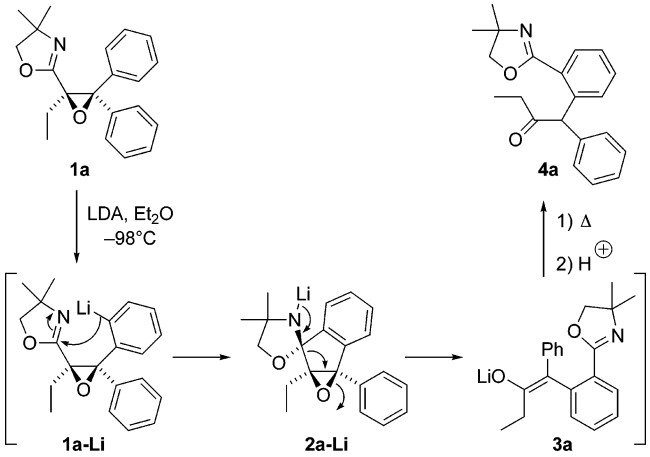


A general method for the synthesis of 2,3-dihydro-10b*H*-oxazolo[2,3-*a*]isoquinolines from the reaction of (*R**,*R**)-configured *ortho*-bromophenyloxazolinyloxiranes and organolithiums is described.

Lithiation *ortho* to functional groups of arenes followed by trapping with electrophiles is an appealing synthetic methodology. An added value follows when the *ortho*-positioned functional group can be elaborated into carbo- or hetero-ring annelations. Countless substances, natural products, and biologically active compounds have been made available by this methodology.

Aziridine[1] and oxirane[2] groups look like very good candidates for the *ortho*-lithiation−trapping−cyclization sequence for benzo-fused carbocycles or heterocycles in view of the stabilizing effect for the *ortho*-lithiated intermediate and their high ring strain, which is expected to facilitate the oxirane or aziridine ring-opening and the carbocycle or heterocycle ring-closing processes. Indeed, *ortho*-lithiated aryloxiranes that can be generated upon *ortho*-deprotonation or lithium−halogen exchange proved to be useful reactive intermediates for the preparation of phthalans,[3] tetrahydronaphthols,[4] benzocyclobutenols,[5] benzofurans,[6] and 2,3-dihydroindole derivatives.[7]

SCHEME 1. Synthesis of the Oxazolinylaryl Alkanone 4a



Few years ago, we reported that, when treated with LDA, a β-aryloxazolinyloxirane, such as **1a**, undergoes isomerization (presumably through **3a**) resulting in the formation of *ortho*-oxazolinylaryl alkanone **4a**.[8] Attempts, however, to trap under these conditions the putative *ortho*-lithiated intermediate **1a-Li**, presumed to be the first event of the above isomerization, as well as the spirocyclic intermediate **2a-Li**, which would originate upon its addition to the C−N double bond of the oxazoline moiety, failed (Scheme 1).

Herein, we wish to report that *ortho*-lithiated intermediates of the kind above can be easily generated by halogen−lithium exchange from β-*ortho*-bromoaryloxazolinyloxiranes. However, the fate of such intermediates proved to be quite different, opening a useful route to 2,3-dihydro-10b*H*-oxazolo[2,3-*a*]-isoquinolines, as described in this paper.

The starting β-*ortho*-bromophenyloxazolinyloxiranes were prepared by the Darzens reaction of α-lithiated 2-(chloroalkyl)-2-oxazolines and *ortho*-bromophenyl carbonyl compounds according to the reported procedure.[9] The obtained diastereoisomers were separated by flash chromatography on silica gel.[10]

Treatment of (*R**,*R**)-*ortho*-bromophenyloxazolinyloxirane **1b** with 2 equiv of PhLi (THF at −78 °C), followed by quenching with saturated aq NH_4Cl at rt, resulted in the formation of a new compound, in good yield, which was assigned the structure of **7a** on the basis of spectroscopic data, including ^1H and ^{13}C NMR, DEPT, $^1H-^{13}C$ HSQC, FT-IR, GC−MS, and elemental analysis (Scheme 2); this structure was confirmed by an X-ray analysis.[11]

† Dedicated to Prof. M. Tisler of the University of Ljubljana, Slovenia, on the occasion of his 80th birthday.

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(10) The relative configuration to **1b**−**e** was assigned by analogy to similar arylmethyloxazolinyloxiranes, as reported: (a) Abbotto, A.; Capriati, V.; Degennaro, L.; Luisi, R.; Pierrot, M.; Salomone, A. *J. Org. Chem.* **2001**, *66*, 3049−3058. (b) Perna, F. M.; Capriati, V.; Florio, S.; Luisi, R. *J. Org. Chem.* **2002**, *67*, 8351−8359.

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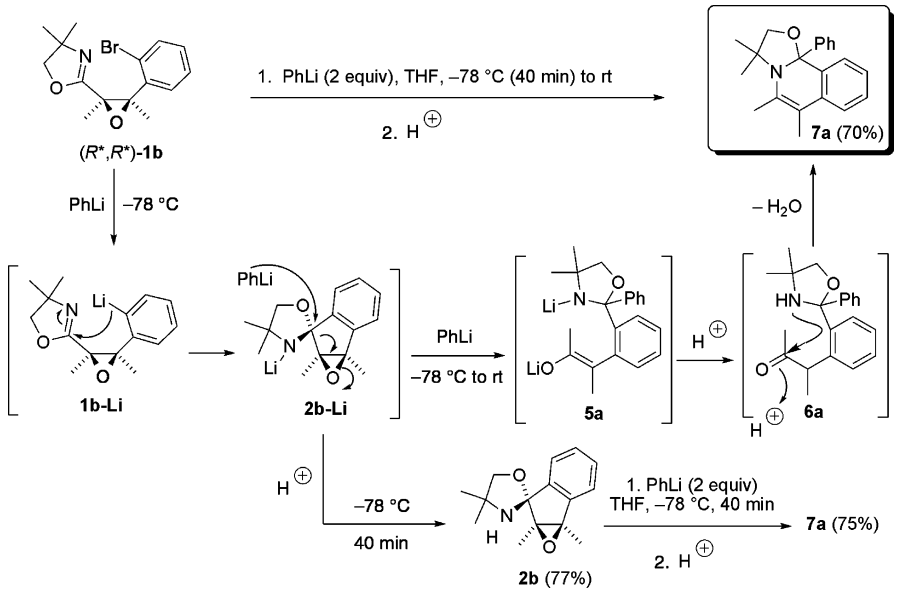
SCHEME 2. Synthesis of the Oxazoloisoquinoline Derivative 7a

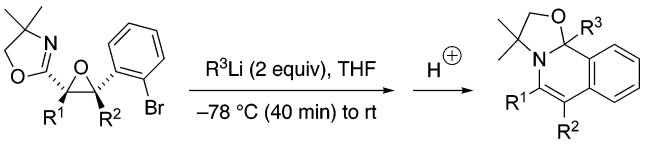


A plausible explanation for the formation of the oxazoloisoquinoline derivative **7a** is a domino reaction which is initiated with the generation of the *ortho*-lithiated phenyloxazolinyloxirane **1b-Li**, which then adds to the C−N double bond of the oxazoline, leading to the spirotetracyclic compound **2b-Li**. A second equiv of PhLi would then cause another domino reaction involving addition to the spirocyclic carbon followed by oxirane ring opening to give the enolate **5a**, which would isomerize to the ketone **6a** (not isolated). After acid quenching at rt, a condensation reaction would lead to the final compound **7a** (Scheme 2). The intermediacy of lithiated spirocyclic compound **2b-Li**, in the transformation of (*R**,*R**)-**1b** to **7a**, was proved by its trapping as **2b**[12] (77%, Table 2) after quenching with NH_4Cl at low temperature in the above reaction mixture; the following reaction of **2b** with 2 equiv of PhLi gave, similarly, the product **7a** (75%, Table 2, entry 1). The oxazolinylaryl alkanone **4b** could be, instead, obtained by the reaction of the oxirane (*R**,*R**)-**1b** (or the spirocyclic compound **2b**) with 1 equiv of PhLi and warming to rt followed by acid quenching after 20 h (Scheme 3). A base such as LDA proved to be ineffective in promoting the formation of **7a** starting from (*R**,*R**)-**1b**, probably because no bromo−lithium exchange occurs under that condition.[13] However, when isolated spirocyclic compound **2b** was treated with 1 equiv of LDA at −78 °C for 40 min (then warming the reaction mixture to rt), it was smoothly converted to **4b** (56%, Scheme 3), confirming that **2b** is a key intermediate either in the synthesis of oxazolinylaryl alkanones or on the route to oxazoloisoquinolines.

Comparable results were obtained when MeLi was used instead of PhLi to give compound **7b** (Table 1). Similarly, (*R**,*R**)-*ortho*-bromophenyloxazolinyloxiranes **1c**−**e** reacted with PhLi, *n*-BuLi, MeLi, and 2-thienylLi to furnish oxazoloisoquinolines **7c**−**f**,**j**,**k** (entries 3−6, 10, and 11). Instead, the reaction with *s*-BuLi and *i*-PrLi gave products **7g**,**h**, only detected in traces in the crude reaction mixture (entries 7 and 8), and the reaction with *t*-BuLi did not give the expected product **7i** (entry 9), probably because of steric interactions.

Similarly, oxazolinyloxiranes **1c**,**d**, after treating with 1 equiv of PhLi followed by acid quenching of the reaction mixture at low temperature, could be transformed into spirocyclic derivatives **2c**,**d** (Table 2). The latter could then be converted into the isoquinoline derivatives **7c**−**h**,**j** in good yields upon treat-

TABLE 1. Synthesis of Oxazoloisoquinolines 7 from the Reaction of (*R,*R**)-*ortho*-Bromophenyloxazolinyloxiranes 1 and Organolithiums**



(*R**,*R**)-**1b-e** **7a-h, j,k**

entry	oxirane **1**	R^1	R^2	R^3	isoquinoline **7** (yield %)[a]
1	**1b**	Me	Me	Ph	**7a** (70)
2	**1b**	Me	Me	Me	**7b** (67)
3	**1c**	Me	H	Ph	**7c** (78)
4	**1c**	Me	H	*n*-Bu	**7d** (50)
5	**1c**	Me	H	Me	**7e** (65)
6	**1c**	Me	H	2-thienyl	**7f** (45)
7	**1c**	Me	H	*i*-Pr	**7g** (<5)[b]
8	**1c**	Me	H	*s*-Bu	**7h** (<5)[b]
9	**1c**	Me	H	*t*-Bu	**7i**[c]
10	**1d**	Et	H	Ph	**7j** (76)
11	**1e**	Me	2-thienyl	Ph	**7k** (37)

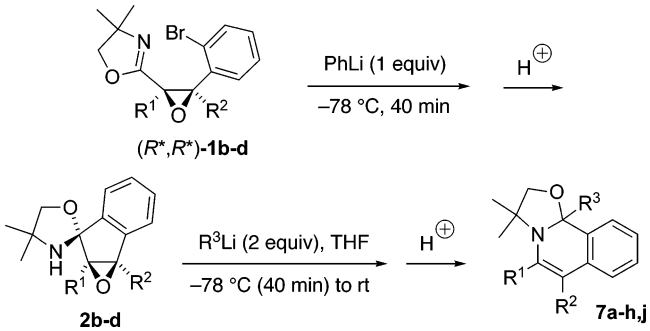
[a] Isolated yields after column chromatography on silica gel. [b] Products **7g**,**h** could only be detected in traces in the crude reaction mixture by ^1H NMR and GC−MS analysis. [c] Not formed.

(11) Crystallographic data for compound **7a** have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC-641274). Copies of data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax (int.): (44) 01223 336033; e-mail: deposit@ccdc.cam.ac.uk].

(12) Crystallographic data for compound **2b** have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC-641275). Copies of data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax (int.): (44) 01223 336033; e-mail: deposit@ccdc.cam.ac.uk].

(13) The use of LDA as the base is, instead, crucial for the **1a** to **4a** transformation, whereas no such rearrangement occurs with organolithiums such as *s*-BuLi; see ref 8.

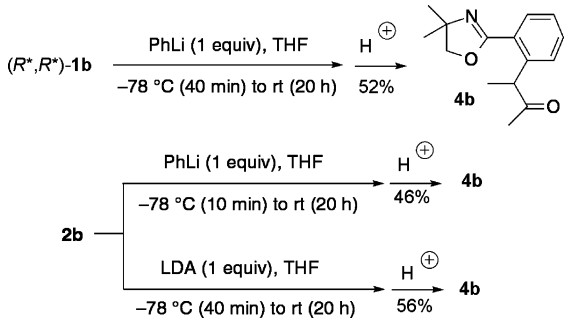
TABLE 2. Synthesis of Spirocyclic Compounds 2 and of Oxazoloisoquinolines 7 from the Reaction of Oxazolinyloxiranes 1 and Organolithiums



entry	spirocyclic compound **2** (yield %)[a]	R^1	R^2	R^3	isoquinoline **7** (yield %)[a]
1	**2b** (77)	Me	Me	Ph	**7a** (75)
2	**2c** (83)	Me	H	Ph	**7c** (78)
3	**2c** (83)	Me	H	*n*-Bu	**7d** (70)
4	**2c** (83)	Me	H	Me	**7e** (71)
5	**2c** (83)	Me	H	2-thienyl	**7f** (65)
6	**2c** (83)	Me	H	*i*-Pr	**7g** (44)
7	**2c** (83)	Me	H	*s*-Bu	**7h** (42)[b]
8	**2c** (83)	Me	H	*t*-Bu	**7i**[c]
9	**2d** (78)	Et	H	Ph	**7j** (81)

[a] Isolated yields after column chromatography on silica gel. [b] Inseparable mixture of diastereoisomers; diastereomeric ratio 1/1, calculated by ^{1}H NMR analysis on the crude reaction mixture. [c] Not formed.

SCHEME 3. Synthesis of the Oxazolinylaryl Alkanone 4b

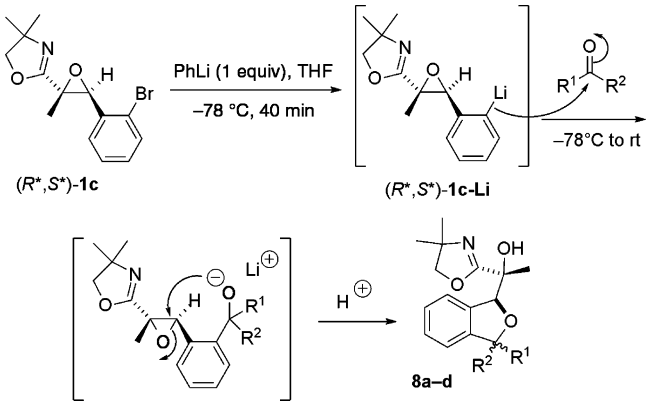


ment with 2 equiv of R^3Li in THF followed by warming up to rt (entries 2−7 and 9, Table 2).

Compounds **7a**−**h**,**j** are interesting because the oxazolo[2,3-*a*]isoquinoline core is present in the structure of natural products such as the Jadomicine B (I), an antifungal antibiotic produced by the bacterium *Streptomyces venezuelae*,[14] and routes to oxazoloisoquinolines are rather rare.[15]

As expected, the *ortho*-lithiated (*R**,*S**)-**1c-Li**, generated by bromo−lithium exchange from (*R**,*S**)-**1c**, because of the *trans* arrangement of the aryl and oxazolinyl groups, behaved differently from the corresponding (*R**,*R**)-isomers, and the trapping reaction with carbonyl compounds resulted in the formation of oxazolinyl-substituted hydroxyalkyl 1,3-dihydrobenzo[*c*]furans, as reported for other *ortho*-lithiated aryloxiranes.[3] Indeed, organolithium (*R**,*S**)-**1c-Li** reacted with acetone and diethyl ketone to give, after acidic quenching, the 1,3-dihydrobenzo-[*c*]furans **8a** (70%) and **8b** (64%) as the sole diastereoisomers, respectively (entries 1 and 2, Table 3). Unfortunately, the reaction with nonsymmetrical carbonyl compounds, such as butyrophenone and 4-chlorobenzaldehyde, proceeded with poor diastereoselectivity at the newly created stereogenic center, giving **8c**,**d** as an equimolar mixture of diastereoisomers (entries 3 and 4, Table 3).

TABLE 3. Synthesis of Hydroxyalkyl 1,3-Dihydrobenzo[*c*]furans 8 from *ortho*-Lithiated Oxazolinyloxiranes (*R,*S**)-1c-Li and Carbonyl Compounds**



entry	R^1	R^2	phthalan **8** (yield %)[a]	dr[b]
1	Me	Me	**8a** (70)	98/2
2	Et	Et	**8b** (64)	98/2
3	Ph	*n*-Pr	**8c** (86)	1/1[c]
4	4-ClC_6H_4	H	**8d** (80)	1/1[c]

[a] Isolated yields after column chromatography on silica gel. [b] Diastereomeric ratio calculated by ^{1}H NMR analysis on the crude reaction mixture. [c] Inseparable mixture of diastereoisomers.

In conclusion, a simple and useful synthetic method for the preparation of functionalized dihydroisoquinoline derivatives, based on the reaction between *β*-*ortho*-bromophenyloxazolinyloxiranes and organolithiums, has been developed. The key reaction step is the formation of the spirocyclic intermediate of the kind of **2** that is possible when the *ortho*-bromophenyl and oxazolinyl groups (in the starting oxirane) have a *cis* arrangement. Moreover, the bromo−lithium exchange in *trans*-configured (*R**,*S**)-*ortho*-bromophenyloxazolinyloxiranes, followed by the reaction with carbonyl compounds, is also a good way of making oxazolinyl-substituted 1,3-dihydrobenzo[*c*]furans.

Experimental Section

Preparation of Spirocyclic Compounds (2b−d). General Procedure. A solution of PhLi (1.0 mmol, 0.55 mL of a 1.8 M solution in *n*-dibutyl ether) was added to a precooled (−78 °C, dry ice/acetone bath) solution of the oxirane (**1b**−**d**) (1.0 mmol) in THF (6 mL) under N_2 and stirring. After 40 min at this temperature, the resulting mixture was quenched with saturated aq NH_4Cl and extracted with Et_2O (3 × 20 mL). The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (silica gel; petroleum ether/AcOEt 8/2) to give compounds **2b**−**d**.

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(1*R,2*R**,3*R**)-2,3,4′,4′-Tetramethyl-2,3-dihydrospiro(2,3-epoxyindene-1,2′-[1,3]oxazolidine) (2b):** white solid, mp 108−109 °C (hexane/Et_2O), 77%; ^1H NMR (500 MHz) δ 1.43 (s, 3H), 1.51 (s, 3H), 1.60 (s, 3H), 1.74 (s, 3H), 2.25 (br s, exchanges with D_2O, 1H), 3.86 and 3.93 (2 × d, AB system, J = 8.1 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.37 (d, J = 7.4 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz) δ 16.9, 22.8, 28.3, 28.4, 58.6, 68.2, 70.9, 78.4, 103.1, 126.7, 128.0, 130.2, 130.9, 141.0, 142.3; GC−MS (70 eV) *m*/*z* (%) 245 (M^+, 1), 230 (73), 228 (100), 203 (18), 148 (54), 130 (37), 103 (15), 77 (17); FT-IR (film, cm^{-1}) 3328, 2930, 2874, 1606, 1465, 1059, 855, 750, 701. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.79; H, 7.62; N, 5.55.

Preparation of Compounds 7a−h,j,k Starting from Oxiranes 1b−e. General Procedure. A solution of organolithium (2.1 mmol) was added to a precooled (−78 °C, dry ice/acetone bath) solution of the oxirane (**1b−e**) (1.0 mmol) in THF (6 mL) under N_2 and stirring. After 40 min at this temperature, the resulting mixture was allowed to warm to rt, quenched with saturated aq NH_4Cl, and extracted with Et_2O (3 × 20 mL). The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (silica gel; petroleum ether/AcOEt 90/10−95/5) to give compounds **7a−h**,**j**,**k**.

Preparation of Compounds 7a−h,j,k Starting from Spirocyclic Compounds 2b−d. General Procedure. A solution of organolithium (2.1 mmol) was added to a precooled (−78 °C, dry ice/acetone bath) solution of the spirocyclic compound (**2b−d**) (1.0 mmol) in THF (6 mL) under N_2 and stirring. After 10 min at this temperature, the resulting mixture was allowed to warm to rt, quenched with saturated aq NH_4Cl, and extracted with Et_2O (3 × 20 mL). The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (silica gel; petroleum ether/AcOEt 90/10−95/5) to give compounds **7a−h**,**j**,**k**.

3,3,5,6-Tetramethyl-10b-phenyl-2,3-dihydro-10b*H*-[1,3]oxazolo-[2,3-*a*]isoquinoline (7a): red solid, mp 55−56 °C (hexane), 75%; ^1H NMR (500 MHz) δ 1.05 (s, 3H), 1.58 (s, 3H), 1.95 (s, 3H), 2.07 (s, 3H), 3.57 (d, J = 8.4 Hz, 1H), 3.94 (d, J = 8.4 Hz, 1H), 7.11−7.34 (m, 6H), 7.43−7.47 (m, 1H), 7.61−7.63 (m, 2H); ^{13}C NMR (125 MHz) δ 13.3, 18.4, 24.1, 29.9, 61.6, 79.8, 95.9, 112.1, 120.8, 122.8, 125.3, 126.3, 127.1, 127.3, 127.6, 128.7, 133.9, 135.2, 143.6; GC−MS (70 eV) *m*/*z* 305 (M^+, 12), 232 (73), 228 (100), 189 (12), 173 (26); FT-IR (film, cm^{-1}) 3063, 2969, 2866, 1624, 1597, 1480, 1250, 1067, 750, 696. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.77; H, 7.34; N, 4.34.

Preparation of Compounds 8a−d. General Procedure. A solution of PhLi (1.1 mmol, 0.61 mL of a 1.8 M solution in *n*-dibutyl ether) was added to a precooled (−78 °C, dry ice/acetone bath) solution of the oxirane **1c** (1.0 mmol) in THF (5 mL) under N_2 and stirring. After 40 min at this temperature, a solution of the carbonyl compound (1.5 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred for 20 min at −78 °C, and then it was allowed to warm to rt, quenched with saturated aq NH_4Cl, and extracted with Et_2O (3 × 20 mL). The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (silica gel; petroleum ether/AcOEt 90/10−95/5) to give compounds **8a−d**.

(1*R,1′*R**)-1-(3,3-Diethyl-1,3-dihydroisobenzofuran-1-yl)-1-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)ethanol (8b):** white solid, mp 122−124 °C (hexane/Et_2O), 64%; H NMR (500 MHz) δ 0.66 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H), 1.26 (s, 3H), 1.35 (s, 3H), 1.55 (s, 3H), 1.85−1.93 (m, 4H), 4.03 and 4.06 (2 × d, AB system, J = 8.0 Hz, 2H), 5.34 (s, 1H), 6.52 (br s, exchanges with D_2O, 1H), 7.04 (d, J = 7.5 Hz, 1H), 7.18−7.38 (m, 2H), 7.56 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz) δ 8.3, 12.3, 24.8, 28.0, 28.5, 32.1, 33.0, 67.1, 70.3, 80.2, 86.8, 90.7, 121.1, 122.5, 127.8, 129.8, 132.4, 137.9, 168.3; GC−MS (70 eV) *m*/*z* (%) 300 (M^+ − OH, 17), 270 (4), 175 (100), 142 (18), 91 (7); FT-IR (film, cm^{-1}) 3387, 2915, 1668 (C═N), 1361, 1045, 801. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.15; H, 8.61; N, 4.29.

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Supporting Information Available: General experimental methods (S2); spectroscopic data for compounds **2c**,**d**, **4b**, **7b−k**, and **8a−d** (S3−S10); copies of ^1H or ^{13}C NMR spectra for compounds **2b−d**, **4b**, **7a−k**, and **8a−d** (S13−S41). Ortep view (S11, S12) and CIF files for compounds **2b** and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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