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Regio- and Stereodivergent Allylic Reductions of Bicyclic Piperidine Enecarbamate Derivatives

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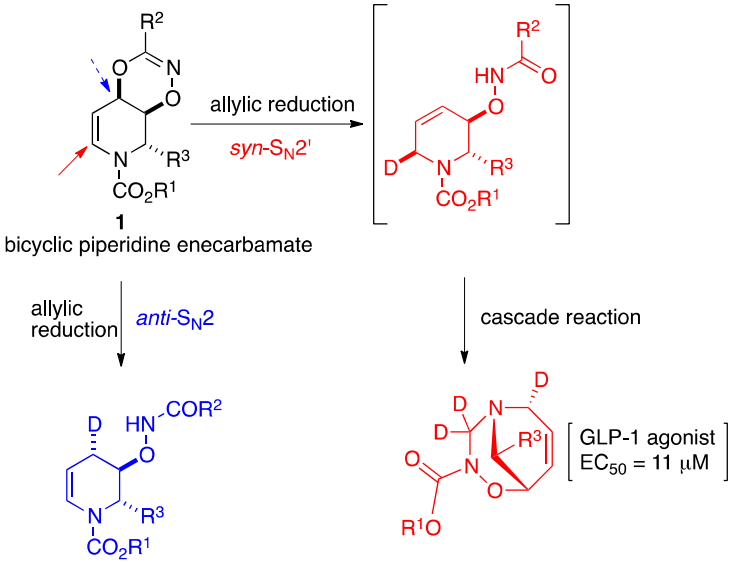
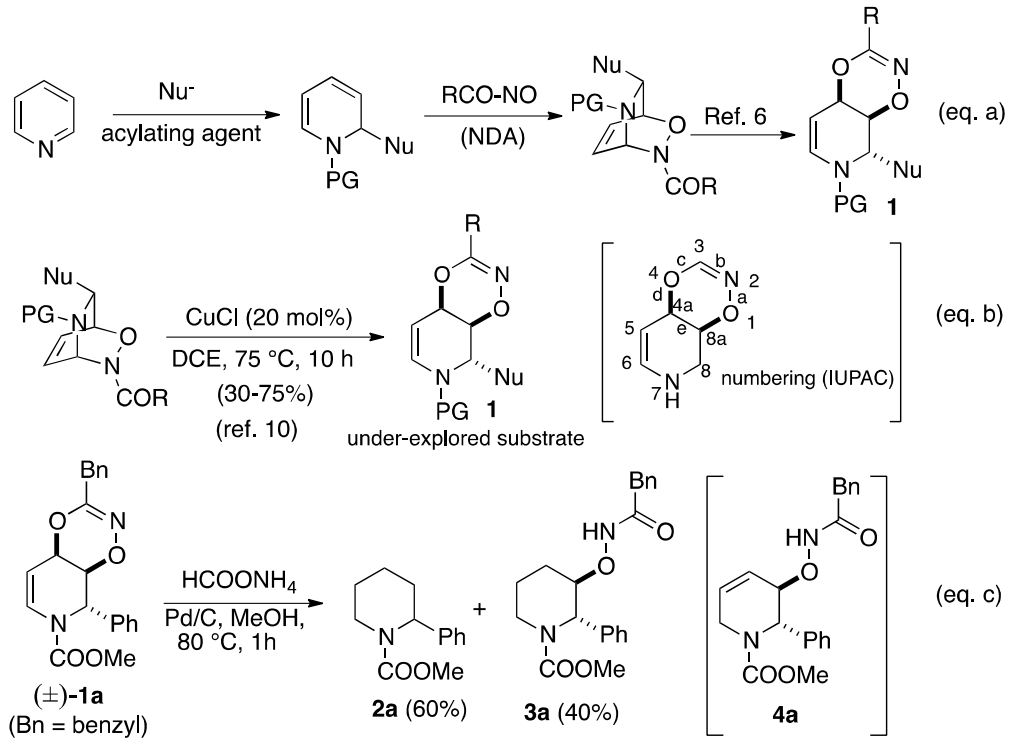


ABSTRACT: The particular nature of tetrahydropyrido[4,3-e]-1,4,2-dioxazines of type **1** allows the regio- and stereoselective obtainment of substituted N-carbamoyl tetrahydropyridines by common reducing agents. A completely novel, biologically active, bicyclic 1,3-diaza-4-oxa-[3.3.1]-nonene scaffold can be generated by the use of lithium triethylborohydride through an unprecedented cascade *syn*-S_N2' reduction/carbamate reduction/cyclization reactions. The remarkable regioselectivity switches of allylic reduction process have been rationalized with the aid of computational studies.

Tetrahydropyridines are important targets in synthetic organic chemistry due to their relevance as privilege structure in medicinal chemistry.[1] Therefore, considerable efforts have been devoted to the individuation of new methods for their regio- and stereoselective synthesis and functionalization.[2] However, a regio- and stereodivergent reduction of piperidine enecarbamates bearing an allylic leaving group has not yet been reported. The main reason for this shortcoming can be found in the relative instability of 1,2,3,4-tetrahydropyridine derivatives containing common leaving groups at the C_4-position. We recently became interested in the elaboration of nitroso cycloadducts derived from 2-substituted-1,2-dihydropyridines,[3] easily accessible by addition of nucleophiles to activated pyridinium salts (eq. a, Scheme 1).[4,5] The [3,3]-hetero Cope rearrangement of the obtained nitroso Diels-Alder (NDA) cycloadducts has been reported to give 4a,7,8,8a-tetrahydropyrido[4,3-e]-1,4,2-dioxazines of type **1** (eq. a, Scheme 1).[6] We noticed that the study of their reactivity is limited to the N-O reductive cleavage with Raney nickel to obtain racemic aminoarabinose and aminoaltrose derivatives.[6a] On the other hand, palladium-catalyzed allylic reduction have been used extensively in synthetic organic chemistry to

introduce hydride species into a variety of allylic substrates in a regio- and stereoselective fashion.[7-9] We herein report a new method to regio- and stereoselectively reduce piperidine enecarbamates, with the individuation of a fused 1,2,4-dioxazine framework as an unconventional allylic leaving group (see compound of type **1**, Scheme 1).

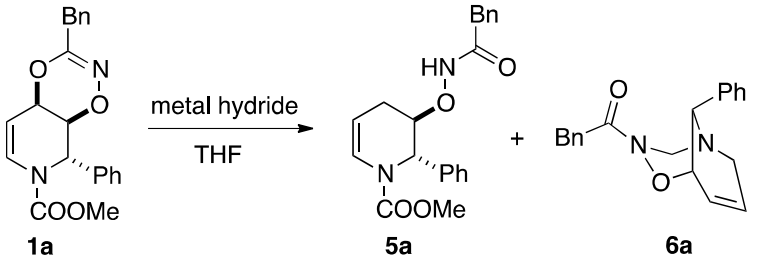
At the outset of this study, we identified optimal reaction conditions to obtain 1,2,4-dioxazine derivatives of type **1** reproducibly and in satisfactory yields (eq. b, Scheme 1).[10] While attempting to reduce the N-O bond of racemic 1,4,2-dioxazine **1a**, easily prepared in gram scale and taken as a model substrate, we serendipitously found that a heterogeneous hydrogenation carried out with ammonium formate at 80 °C in the presence of Pd/C (20 mol%) at 80 °C readily afforded a 60/40 mixture of saturated derivatives **2a** and **3a** (eq. c, Scheme 1).[11]



Scheme 1. State of the art, synthesis and preliminary reduction of tetrahydropyrido[4,3-e]-1,4,2-dioxazines (**1**).

A result of this kind can be reasonably explained by admitting the intervention of 4,5-dehydro-intermediate **4a** by initial hydride transfer at the position adjacent to the nitrogen, followed by an allylic deoxygenation of the C_3-O bond.

Stimulated by these preliminary results, we decided to carry out a deeper investigation of the reduction of enecarbamate **1a** with hydride species in order to develop selective allylic reduction processes.[8b,12] While sodium borohydride was totally ineffective, the use of the lithium analog ($LiBH_4$) afforded 2,3-dehydropiperidine **5a** with complete regioselectivity in attack of the hydride at the C_4 position (Scheme 2). It should be noted that 3-oxygenated-2-aryl-piperidines such as **5a** are compounds of considerable importance in medicinal chemistry.[13]



$NaBH_4$, 0 °C to rt, 18h	no reaction	
$LiBH_4$, 0 °C to rt, 18h	48% yield	<2%
$LiBEt_3H$, 0 °C, 1h	<2%	80% yield
$LiAlH_4$, 0 °C, 5h	complex mixture	
$NaBEt_3H$, 0 °C, 5h	<2%	55% yield

Scheme 2. Reduction of 1,2,4-dioxazine **1a** with metal hydride species.

Much to our surprise, the reaction of **1a** with an excess of highly reactive lithium triethylborohydride (Super-H®) afforded readily a good yield of compound **6a** possessing a novel 1,3-diaza-4-oxa-[3.3.1]-bicyclic scaffold, whose structure was unequivocally

determined by single crystal X-ray analysis (Figure 1).[14] This reaction to can be easily scaled-up to 1.0 mmol scale with only marginal deviations from the initial reaction conditions carried out on a 0.15 mmol scale. The use of analog sodium salt ($NaEt_3BH$) afforded the same compound with a lower yield and an increased reaction time. The use of $LiAlH_4$ afforded a complex mixture of products in which only **6a** could be detected.

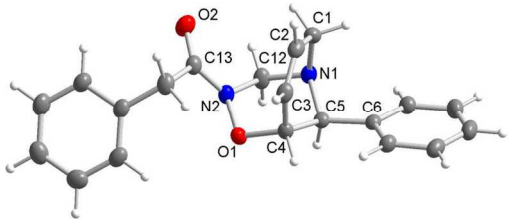


Figure 1. ORTEP diagram of **6a**. Thermal ellipsoids are at 30% probability. Relevant bond distances (Å): C1–N1 1.468(2), C1–C2 1.498(2), C2–C3 1.315(2), C3–C4 1.490(2), C4–O1 1.483(1), C4–C5 1.524(1), C5–N1 1.479(1), N1–C12 1.454(1), O1–N2 1.403(1), N2–C12 1.460(1).

In order to get more insight into the reaction mechanism we carried out the reaction using $LiEt_3BD$ as the reducing agent (Figure 2).

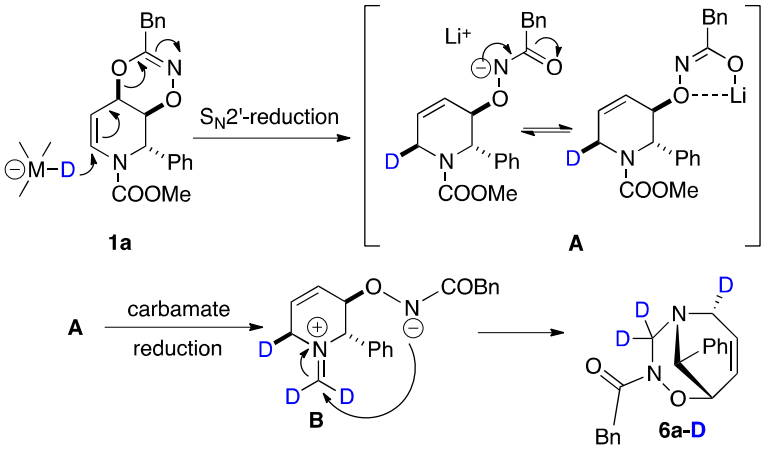
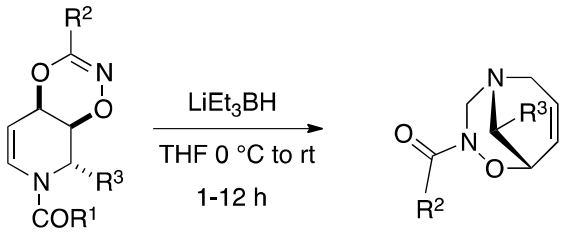


Figure 2. Plausible mechanism for the formation of the 1,3-diaza-4-oxa-[3.3.1]-nonene framework.

NMR analysis of deuterated bicyclic compound **6a-D** showed clearly the regio- and stereochemistry of deuterium incorporation.[15] The only way to obtain 1,3-diaza-4-oxa-[3.3.1]-bicyclic framework **6a** comes from a regioselective S_N2'-addition of the hydride to enecarbamate **1a**, which turned out to be *syn* to the dioxazine leaving group. The *syn*-stereoselectivity can be reasonably ascribed to simultaneous coordination of the cation to the oxygen of the leaving group and the hydride of the M-$HBEt_3$ on conformation **1a-B** (see Supporting Information).[16,17] The obtained anionic 3,4-unsaturated intermediate **A** does not undergo a further reduction of the oxyamido functionality arguably due to a intramolecular chelate stabilization. It is also likely that the concomitant reduction of the carbamate moiety of species **A** gives rise to zwitterionic iminium ion **B** that undergoes intramolecular trapping by N-alkylation to deliver the bicyclic framework **6a-D** (Figure 2). In accordance with the proposed mechanism, the formation of such a bicyclic framework necessarily requires the presence of a carbamate protecting group on the endocyclic piperidine nitrogen. As a matter of fact, the $LiEt_3BH$ reduction of enamides **1b-d** afforded a complex mixture of products not containing the corresponding oxadiazabicyclononene scaffold (Scheme 3). Hence, only using enecarbamates **1e-1k** it was possible to obtain the corresponding bicyclic structures **6b-g**, albeit with variable yields (Scheme 3).



1b, R^1 = Me, R^2 = Bn, R^3 = Ph	(not formed)
1c, R^1 = Me, R^2 = Ph, R^3 = Ph	(not formed)
1d, R^1 = Ph, R^2 = Bn , R^3 = PhCC	(not formed)
1e, R^1 = OMe, R^2 = Bn, R^3 = Et	**6b** (65% yield)
1f, R^1 = OPh, R^2 = Bn, R^3 = H	**6c** (35% yield)
1g, R^1 = OBn, R^2 = Bn, R^3 = H	**6c** (25% yield)
1h, R^1 = OMe, R^2 = Ph, R^3 = Ph	**6d** (55% yield)
1i, R^1 = OMe, R^2 = Bn, R^3 = vinyl	**6e** (40% yield)
1j, R^1 = OMe, R^2 = Bn, R^3 = Chx	**6f** (23% yield)
1k, R^1 = OMe, R^2 = Bn, R^3 = allyl	**6g**(72% yield)

Scheme 3. Scope of the formation of [3.3.1]-bicyclic scaffold.

The first step (S_N2'-reduction) of this sequential reaction is consistent with the known ability of highly nucleophilic and soft reagent lithium triethylborohydride to undergo addition to double bonds of different nature including the fast reduction of pyridine to tetrahydropyridine.[18] NBO calculations showed that $\pi^*_{C=C}$ (+0.0269 au) is less energetic than $\sigma^*_{C\text{-}O}$ (+0.2330 au) and therefore a softer reagent should have a preference for the C_2 position. On the other hand, by examination of an electrostatic map of the fused dioxazine **1a** it is clear that the C_4 is more electropositive than C_2 carbon (Figure 3). Evidently, the C_4 is the more reactive position when dealing with harder $LiBH_4$, a reagent that is known to favor 1,2-addition products in conjugated systems.[19]

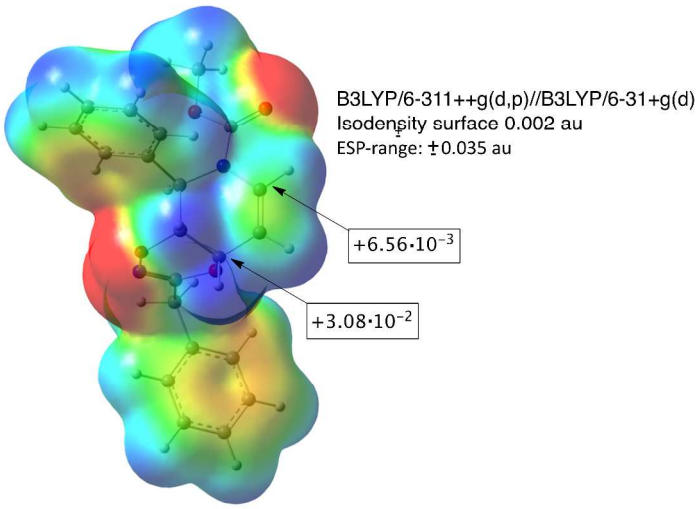
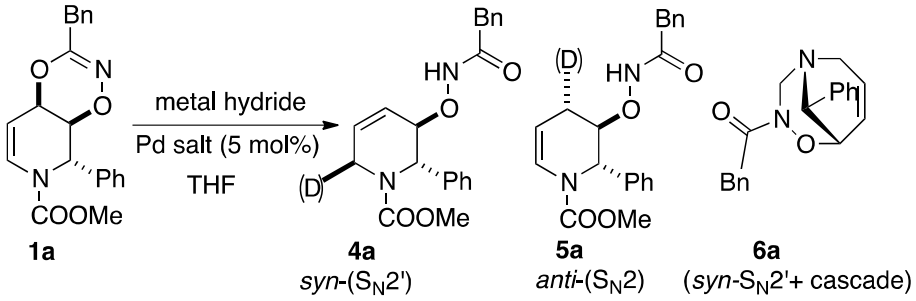


Figure 3. Molecular electrostatic potential of dioxazine **1a**.

Having established that the C_4-oxygen part of the 1,2,4-dioxazine framework can act as a leaving group in regioselective allylic displacement reactions with metal hydrides, we were intrigued how palladium catalysis could influence such reactivity on model compound **1a**. The electrophilic Pd(II)-center activates the allyl system for the nucleophilic attack at the allylic termini, which is usually the rate limiting step.[8] It also commonly accepted that hydride as nucleophile is initially transferred to palladium and from there to the allylic ligand by reductive elimination.[8,9] When **1a** was allowed to react with sodium borohydride in the presence of catalytic amounts of $(PPh_3)_2PdCl_2$ a sluggish reaction now occurred to afford an equimolar mixture of compounds **5a** (S_N2-reduction) and **4a** (S_N2'-reduction) (Table 1, entry 1). The same reaction carried out with $NaBD_4$ afforded compound **4a-D** with the deuterium atom incorporated in a *trans* fashion to the 2-phenyl group (entry 2).[15] This clearly indicated that the *syn*-S_N2'-reduction pathway is external to the coordination sphere of palladium. On the other hand, in this reaction compound **5a-D** was obtained with

inversion of configuration with respect to the leaving group (i.e. from the same side of palladium).[15] When the reaction of **1a** with sodium borohydride was carried out in the presence of catalytic amounts of $(CH_3CN)_2PdCl_2$, compound **5a** was obtained with a complete regiocontrol (entry 3).

Table 1. Reduction of **1a** with metal hydrides in the presence of palladium salts.



entry[a]	M-H	Pd	t[h]	**4a/5a/6a**[b]	Yield [%][c]
1	$NaBH_4$	$(PPh_3)_2PdCl_2$	24	60/40/0	45
2	$NaBD_4$	$(PPh_3)_2PdCl_2$	8	43/57/0	37
3	$NaBH_4$	$(CH_3CN)_2PdCl_2$	32	0/100/0	25
4	$LiBH_4$	$(PPh_3)_2PdCl_2$	1	28/72/0	50
5	$LiBH_4$	$(CH_3CN)_2PdCl_2$	1	0/100/0	58
6	$LiAlH_4$	$(PPh_3)_2PdCl_2$	1	complex mixture	
7	$LiEt_3BH$	$(PPh_3)_2PdCl_2$	0.5	0/10/90	65
8	$LiEt_3BH$	$[(PPh_3)]_4Pd$	0.5	0/3/97	75
9	$LiEt_3BH$	$Pd(dba)_2$	1	0/63/37	53
10	$LiEt_3BH$	$(CH_3CN)_2PdCl_2$	0.5	0/100/0	60
11	$NaEt_3BH$	$(CH_3CN)_2PdCl_2$	1	0/100/0	55

[a] Unless stated otherwise, all reactions were carried out at 0 °C using **1a** (0.15 mmol), Pd-salt (0.0075 mmol), THF (0.75 mL), metal hydride (0.9 mmol).[b] Determined by ^1H NMR of the crude mixture (value of 0 means not detected by NMR). [c] Isolated yields of products after chromatographic purification on SiO_2.

The examination of other hydrides *per se* able to reduce **1a** and therefore in competition with the palladium-catalyzed reduction was rather instructive. Palladium-catalysis gave a clear acceleration of the reduction process using lithium borohydride, but only $(PPh_3)_2PdCl_2$ modified the inherent regioselectivity of the reaction with lithium borohydride (entries 4 and 5). The inherent reactivity of Super-hydride® with **1a** was only marginally affected by the presence of $(PPh_3)_2PdCl_2$ and $Pd[(PPh_3)]_4$ (entries 7 and 8). The use of $Pd(dba)_2$ gave a mixture of regioisomers with a prevalence of S_N2-addition product **5a** (entry 9). Interestingly, a complete reversal of regioselectivity with the exclusive formation of 1,2,3,4-tetrahydropyridine **5a** was obtained using $LiEt_3BH$ or $NaEt_3BH$ in the presence of catalytic amount of $(CH_3CN)_2PdCl_2$ (entries 10 and 11). Hence, it is plausible that when only more coordinating ligands are used, the inherent reactivity of the hydride species can compete with the reductive elimination pathway from palladium. A computational study performed at the DFT level revealed the unsymmetrical structure of the corresponding PdL_2-allyl complex with a Pd-C_4 bond strongly shorter of the Pd-C_2 bond (Figure 4), regardless of the palladium ligand, with a consequent marked carbocationic character of C(2) atoms, as confirmed by NBO analysis (+0.188 au for L=CH_3CN and +0.184 au for L=Ph_3P).[17]

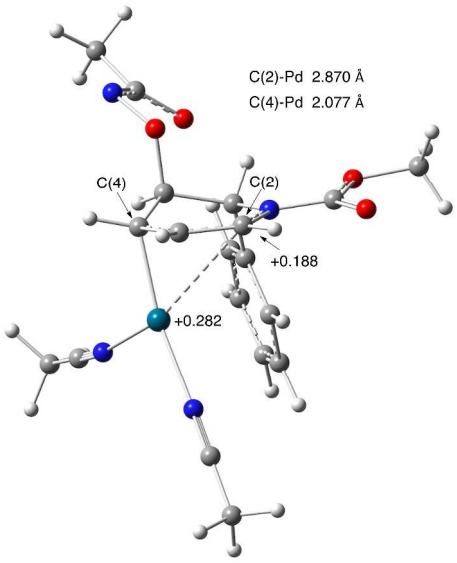


Figure 4. DFT optimized structure and NBO Charges (Pd and C(2) atoms) of Pd-allyl complex derived from $(CH_3CN)_2PdCl_2$

At the same time Pd atom is more electropositive in the Pd-allyl complex derived from $(CH_3CN)_2PdCl_2$ (NBO Charge +0.282 au) than in the one derived from $(Ph_3P)_2PdCl_2$ (NBO Charge +0.036 au). It is plausible that a more positive palladium (L=CH_3CN) undergoes more readily the reduction and the subsequent reductive elimination at the C_4-position, whereas in the case of a less positive palladium (L=Ph_3P) reduction at C(2) becomes competitive.

In summary, we have developed new regioselective reductions of piperidine enecarbamates bearing a stable allylic leaving group. By the use of common reducing agents, with or without palladium catalysts, it is possible to obtain selectively $\Delta^{2,3}$- or $\Delta^{3,4}$-piperidine derivatives with unconventional substitution patterns. By transient formation of the latter derivative, a new stable oxadiaza-[3.3.1]-bicyclic scaffold can be obtained by a robust cascade reaction. To our delight, compound **6a** selectively stimulated GLP-1 secretion in mouse enteroendocrine-like STC-1 cells with an EC_{50} = 11 ⍰M. Further studies

are ongoing to assess the biological activity of a library of compounds based on this original scaffold.

EXPERIMENTAL SECTION

General Information. All reactions dealing with air or moisture sensitive compounds were carried out under an argon atmosphere in oven dried 10 mL or 25 mL Schlenk tubes. Analytical TLC were performed on Merck TLC Silica gel 60 silica gel sheets with detection by exposure to ultraviolet light (254 nm) and/or by immersion in an acidic staining solution of *p*-anisaldehyde in EtOH. Silica gel 60 was used for flash chromatography (230-400 mesh). Automated column chromatography was performed using prepacked silica gel cartridges on a Biotage Isolera 1.5.2 (27-53 μm). ^{1}H NMR spectra were recorded on Bruker Avance II 250 MHz spectrometer or on Bruker Avance III 300 MHz spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.26, deuteroacetonitrile: δ 1.94). ^{13}C NMR spectra were recorded on a Bruker Avance II 250 spectrometer (62.5 MHz) with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 77.16, deuteroacetonitrile: δ 1.32). Melting points were determined on a Kofler apparatus and are uncorrected. Mass spectra ESIMS were measured on a Finnigan LC-Q Deca Termoquest spectrometer, equipped with a software Xcalibur. Solvents for extraction and chromatography were distilled before use. Compounds of type **1** were prepared in accordance to the indicated literature procedures.[10] $LiBDEt_3$ was prepared by procedure of Brown.[20]

General procedure for the synthesis of inverse cycloadducts A1-3 (Scheme S1, Supporting Information)*:* a round-bottomed flask was charged with the appropriate 1,2-dihydropyridine and *N*-hydroxy-2-phenylacetamide in a 3:1 solution of MeOH/H_2O (0.17 M) at 0 °C. $NaIO_4$ (1.1 eq, 99.5% purity) was slowly added and the resulting heterogeneous mixture was allowed to stir until no 1,2-dihydropyridine was detected by TLC analysis. The reaction crude was concentrated and diluted with CH_2Cl_2/H_2O to give a biphasic solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting residue was subjected to flash chromatography.

Methyl (1S*,4R*)-3-(2-phenylacetyl)-6-vinyl-2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**A1**)**.** According to the general procedure, methyl 2-vinylpyridine-1(2*H*)-carboxylate (300 mg, 1.8 mmol),[21] *N*-hydroxy-2-phenylacetamide (302 mg, 2.0 mmol), $NaIO_4$ (430 mg, 2.0 mmol), MeOH (7.2 mL) and H_2O (3.6 mL). Subsequent flash chromatography (petroleum ether/AcOEt 7:3 + 2% Et_3N, R_f = 0.33) afforded the title compound as a colorless oil (216 mg, 38%). ^{1}H NMR (250 MHz, CD_3CN, 60 °C) δ 7.37 – 7.17 (m, 5H), 6.80 – 6.65 (m, 2H), 6.44 – 6.34 (m, 1H), 5.61 – 5.43 (m, 1H), 5.22 (dt, *J* = 11.2, 1.4 Hz, 1H), 5.17 (dt, *J* = 4.2, 1.4 Hz, 1H), 4.93 – 4.88 (m, 1H), 4.57 – 4.50 (m, 1H), 3.69 (s, 3H), 3.66 – 3.55 (m, 2H). ^{13}C NMR (62.5 MHz, CD_3CN) δ 174.5, 156.7, 135.3, 134.8, 132.9, 130.6, 129.3, 129.2, 127.6, 118.6, 74.9, 60.0, 59.3, 53.5, 40.5. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{17}H_{18}N_2O_4Na$ 337,1164, found 337,1159.

Methyl (1S*,4R*)-6-cyclohexyl-3-(2-phenylacetyl)-2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**A2**). According to the general procedure, methyl 2-cyclohexylpyridine-1(2*H*)-carboxylate (1.4 g, 2.5 mmol, 40 % purity),[21] *N*-hydroxy-2-phenylacetamide (422 mg, 2.8 mmol), $NaIO_4$ (599 mg, 2.8 mmol), MeOH (10 mL) and H_2O (5 mL). Subsequent flash chromatography (petroleum ether/AcOEt 7:3 + 2% Et_3N, R_f = 0.18) afforded the title compound as a yellow oil (444 mg, 48%). ^{1}H NMR (250 MHz, CD_3CN) δ 7.37 – 7.16 (m, 5H), 6.74 – 6.65 (m, 1H), 6.65 – 6.57 (m, 1H), 6.51 – 6.41 (m, 1H), 5.03 – 4.95 (m, 1H), 3.90 (dd, *J* = 6.8, 3.6 Hz, 1H), 3.82 – 3.78 (m, 1H), 3.71 (s, 3H), 3.58 (ABq, *J* = 15.1 Hz, 2H), 1.73 (s, 2H), 1.68 – 1.43 (m, 4H), 1.28 – 1.01 (m, 5H). ^{13}C NMR (62.5 MHz, CD_3CN) δ 175.8, 158.5, 136.0, 133.0, 131.3, 130.9, 129.9, 128.2, 74.7, 64.0, 61.3, 54.3, 41.5, 41.3, 31.3, 31.2, 27.8, 27.7, 27.7. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{21}H_{26}N_2O_4Na$ 393,1790, found 393,1786.

Methyl (1S*,4R*)-6-allyl-3-(2-phenylacetyl)-2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**A3**). According to the general procedure, methyl 2-allylpyridine-1(2*H*)-carboxylate (716 mg, 4.0 mmol),[22] *N*-hydroxy-2-phenylacetamide (665 mg, 4.4 mmol), $NaIO_4$ (940 mg, 4.4 mmol), MeOH (16 mL) and H_2O (8 mL). Subsequent flash chromatography (petroleum ether/Et_2O 6:4 + 2% Et_3N, R_f = 0.18) afforded the title compound as a yellow oil (603 mg, 46%). ^{1}H NMR (250 MHz, CD_3CN, 60 °C) δ 7.38 – 7.15 (m, 5H), 6.79 – 6.69 (m, 1H), 6.67 – 6.58 (m, 1H), 6.50 – 6.39 (m, 1H), 5.90 – 5.69 (m, 1H), 5.13 (dd, *J* = 4.7, 3.4 Hz, 1H), 5.07 (bs, 1H), 4.96 – 4.86 (m, 1H), 4.07 – 3.95 (m, 1H), 3.60 (ABq, *J* = 15.3 Hz, 2H), 3.72 (s, 3H), 2.61 – 2.47 (m, 1H), 2.03 – 1.84 (m, 1H). ^{13}C NMR (62.5 MHz, CD_3CN), major rotamer δ 174.6, 156.5, 136.0, 135.3, 134.5, 132.9, 130.6, 129.2, 127.6,

118.4, 74.3, 59.6, 58.0, 53.6, 40.6, 36.8. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{18}H_{20}N_2O_4Na$ 351,1321, found 351.1317.

General procedure for the synthesis of the dioxazine derivatives 1i-k:[10] an oven-dried 10 mL pyrex vial was charged with the specified inverse cycloadduct of type **A**, copper(I) chloride (0.20 eq) and 1,2-dichloroethane (DCE) (0.15 M). The resulting mixture was allowed to react until no compound **A1-3** was detected by TLC analysis. The reaction was quenched with H_2O and the aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. Removal of the solvent gave a residue that was purified by flash chromatography.

(4aR*,8S*,8aS*)-Methyl 3-benzyl-8-vinyl-8,8a-dihydropyrido[4,3-e][1,4,2]dioxazine-7(4aH)-carboxylate (**1i**). According to the general procedure, **A1** (193 mg, 0.61 mmol), CuCl (12.2 mg, 0.123 mmol) in DCE (4.10 mL) reacted at 75 °C for 17 h. Subsequent flash chromatography (petroleum ether /AcOEt 7:3, R_f = 0.23) afforded the title compound as a colorless oil (140 mg, 72.5 %). ^{1}H NMR (250 MHz, CD_3CN, 65 °C) δ 7.39 – 7.18 (m, 5H), 6.91 (d, *J* = 8.5 Hz, 1H), 5.74 (ddd, *J* = 15.7, 10.6, 4.8 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 5.18 (d, *J* = 17.4 Hz, 1H), 4.94 (bs, 1H), 4.79 (bs, 1H), 4.66 (d, *J* = 8.3 Hz, 1H), 4.06 – 3.98 (m, 1H), 3.75 (s, 3H) 3.48 (s, 2H). ^{13}C NMR (62.5 MHz, CD_3CN) δ 156.5, 154.6, 136.9, 131.5, 129.6, 129.5, 127.9, 127.1, 117.9, 102.1, 67.1, 66.7, 57.3, 54.1, 38.6. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{17}H_{18}N_2O_4Na$ 337,1164, found 337.1159.

(4aR*,8S*,8aS*)-Methyl 3-benzyl-8-cyclohexyl-8,8a-dihydropyrido[4,3-e][1,4,2]dioxazine-7(4aH)-carboxylate (**1j**). According to the general procedure, **A2** (69 mg, 0.18 mmol), CuCl (3.7 mg, 0.037 mmol) in DCE (1.3 mL) reacted at 75 °C for 2 h. Subsequent flash chromatography (petroleum ether /AcOEt 8:2, R_f = 0.25) afforded the title compound as a white amorphous solid (40 mg, 58 %). ^{1}H NMR (250 MHz, CD_3CN, 65 °C) δ 7.39 – 7.20 (m, 5H), 6.83 (d, *J* = 7.7 Hz, 1H), 4.92 (bs, 1H), 4.70 (d, *J* = 7.5 Hz, 1H), 4.19 (d, *J* = 8.9 Hz, 1H), 4.07 (s, 1H), 3.73 (s, 1H), 3.47 (s, 2H), 1.82 – 1.40 (m, 6H), 1.32 – 0.98 (m, 5H).^{13}C NMR (62.5 MHz, CD_3CN) δ 156.6, 155.3 and 155.2*, 136.9, 129.6, 129.5, 127.8, 127.6 and 127.3*, 103.2* and102.7, 67.5, 65.5, 60.0, 54.0 and 53.7*, 38.6, 37.9, 30.3, 26.8, 26.6, 26.5. [* minor rotamer]. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{21}H_{26}N_2O_4Na$ 393,1790, found 3931784.

(4aR*,8S*,8aS*)-Methyl 3-benzyl-8-allyl-8,8a-dihydropyrido[4,3-e][1,4,2]dioxazine-7(4aH)-carboxylate (**1k**). According to the general procedure, **A3** (70 mg, 0.21 mmol), CuCl (4.2 mg, 0.043 mmol) in DCE (1.4 mL) reacted at 75 °C for 18h. Subsequent flash chromatography (hexanes /AcOEt 7:3, R_f = 0.25) afforded the title compound as a colorless oil (40 mg, 58 %). ^{1}H NMR (250 MHz, CD_3CN, 65 °C) δ 7.42 – 7.20 (m, 5H), 6.85 (d, *J* = 8.4 Hz, 1H), 5.96 – 5.69 (m, 1H), 5.21 – 5.02 (m, 2H), 4.97 – 4.92 (m, 1H), 4.74 – 4.65 (m, 1H), 4.46 (td, *J* = 7.4, 3.0 Hz, 1H), 3.96 (dd, *J* = 5.9, 3.0 Hz, 1H), 3.75 (s, 3H), 3.49 (s, 2H), 2.43 – 2.18 (m, 2H). ^{13}C NMR (62.5 MHz, CD_3CN) δ 156.4, 154.6* and 154.3, 136.8, 134.2, 129.6, 129.4, 127.8, 126.7, 118.8, 102.1* and 101.7, 67.0, 66.4, 54.7, 53.9, 38.6, 34.7* and 34.3. [* minor rotamer]. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{18}H_{20}N_2O_4Na$ 351,1321, found 351.1317.

***Methyl 2-phenylpiperidine-1-carboxylate* (2a).** A round-bottomed flask was charged with dioxazine derivative **1a** (55 mg, 0.15 mmol), Pd/C 10 % (11 mg), ammonium formate (56 mg, 0.90 mmol) and methanol (1.2 mL). The resulting mixture was allowed to stir 1 h at 80 °C. The mixture was taken up with CH_2Cl_2 and filtered over a short pad of Celite. Removal of solvent afforded a reaction crude that was purified by flash chromatography (hexanes /AcOEt 6:4 + 1% Et_3N, R_f = 0.66) to give the title compound (15 mg, 45%). The spectral data are consistent with prior reports.[23]

***(2S*,3R*)-Methyl 2-phenyl-3-((2-phenylacetamido)oxy)piperidine-1-carboxylate* (3a).** The second eluting fraction of the above flash chromatography (R_f = 0.15) afforded the title compound as a white amorphous solid (22 mg, 39 %). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.42 – 7.11 (m, 10H), 5.64 (s, 1H), 4.74 (s, 1H), 4.05 – 3.88 (m, 1H), 3.85 – 3.66 (m, 3H), 3.66 – 3.42 (m, 2H), 2.94 – 2.79 (m, 1H), 2.14 –2.00 (m, 1H), 1.96 – 1.57 (m, 2H), 1.34 – 1.17 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 168.8, 158.6, 136.8, 134.2, 129.2, 129.0, 127.4, 127.3, 126.5, 126.4, 79.0, 54.5, 53.3, 41.1, 40.4, 23.5, 19.6. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{21}H_{24}N_2O_4Na$ 391.1634; Found 391.1631.

General procedure for the addition of metal hydrides to 1a (Scheme 1)

An over-dried 5 mL Schlenk tube was charged with the dioxazine derivative and freshly distilled THF under argon protection. The resulting mixture was cooled at 0 °C and the hydride source was slowly added. Upon disappearance of the dioxazine derivative, the reaction was quenched with water and the aqueous phase was extracted with Et_2O. The

combined organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography.

(2S*,3R*)-Methyl 2-phenyl-3-((2-phenylacetamido)oxy)-3,4-dihydropyridine-1(2H)-carboxylate (**5a**). According to the general procedure, dioxazine **1a** (55 mg, 0.15 mmol), $LiBH_4$ (20 mg, 0.9 mmol) and THF (0.26 mL), 0 °C for 18 h. Subsequent flash chromatography (hexanes /AcOEt 6:4, R_f = 0.15) afforded the title compound as an amorphous solid (26 mg, 48 %). ^{1}H NMR (250 MHz, $CDCl_3$) 9.04 (bs, 1H) and 8.60* (bs, 1H) (exchangeable with D_2O), 7.39 – 7.21 (m, 8H), 7.18 – 7.08 (m, 2H), 7.02 (d, J = 7.4 Hz, 1H), 5.59 (s, 1H) and 5.44* (s, 1H), 4.77 (bs, 1H), 4.44 (bs, 1H), 3.74 (s, 3H) and 3.61* (s, 3H), 3.60 - 3.48 (m, 2H), 2.38 – 2.11 (m, 1H), 2.08-1.79 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.5, 154.7 and 154.4*, 138.4 and 138.2*, 134.2, 129.3, 129.0, 128.9, 127.8, 127.4, 125.7, 125.3, 124.7, 102.6 and 102.0*, 79.9 and 79.4*, 56.4 and 55.8*, 53.5, 40.9, 22.0 and 21.3*. [*Minor rotamer] HRMS (ESI) m/z [M + Na^+] Calcd for $C_{21}H_{22}N_2O_4Na$ 389.1477; Found 389.1472.

General procedure for the synthesis of [3.3.1]-bicyclic derivatives 6a-g (Scheme 2)

An over-dried 5 mL Schlenk tube was charged with the dioxazine derivative and freshly distilled THF under argon protection. The resulting mixture was cooled at 0 °C and a solution of $LiBHEt_3$ (1.0 M in THF, 6.0 eq.) was dropwise added (CAUTION PYROFORIC REAGENT). Upon disappearance of the dioxazine derivative, the reaction was quenched with water and the aqueous phase was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography.

2-Phenyl-1-((1R*,5S*,9R*)-9-phenyl-4-oxa-1,3-diazabicyclo[3.3.1]non-6-en-3-yl)ethanone (**6a**)**.** According to the general procedure, dioxazine **1a** (365 mg, 1.0 mmol), $LiBHEt_3$ (6.0 ml, 6.0 mmol) and THF (1.6 mL), 0°C for 1h. Subsequent flash chromatography (hexanes /AcOEt 8:2, R_f = 0.17) afforded the title compound as a white solid (321 mg, 76 %). M.p. = 156-159 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 10H), 6.07 – 5.95 (m, 2H), 5.61 (d, 1H, *J* = 13.2 Hz), 4.99 – 4.89 (m, 1H), 4.57 (d, 1H, *J* = 2.2 Hz), 4.48 (d, 1H, *J* = 13.2 Hz), 3.82 (d, 1H, J = 14.7 Hz), 3.55 (d, 1H, *J* = 14.7 Hz), 3.45 – 3.18 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.3, 137.0, 129.7, 128.7, 128.5, 128.4, 128.0, 127.7, 126.9, 126.8, 119.4, 72.3, 65.7, 59.6, 47.6, 39.8. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{20}H_{20}N_2O_2Na$ 343.1422; Found 343.1421.

2-Phenyl-1-((1R*,5S*,8R*,9R*)-9-phenyl-4-oxa-1,3-diazabicyclo[3.3.1]non-6-en-3-yl-2,2,8-D3)ethan-1-one (**6a-D**). According to the general procedure, dioxazine **1a** (59 mg, 0.16 mmol), $LiBDEt_3$ (0.97 ml, 0.97 mmol) and THF (0.28 mL), 0°C for 1 h. Subsequent crystallization (hexanes/AcOEt) afforded the title compound as a white solid (11 mg, 21.3%). M.p.=159 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 10H), 6.07 – 5.94 (m, 2H), 4.96 – 4.88 (m, 1H), 4.59 – 4.52 (m, 1H), 3.82 (d, *J* = 14.7 Hz, 1H), 3.54 (d, *J* = 14.7 Hz, 1H), 3.31 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.3, 137.1, 137.0, 135.1, 129.7, 128.5, 128.3, 127.6, 126.9, 126.7, 119.4, 72.3, 59.5, 47.25 (*J* = 21.1 Hz), 39.8. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{20}H_{17}D_3N_2O_2Na$ 346.1611; Found 346.1608.

1-((1R*,5S*,9R*)-9-Ethyl-4-oxa-1,3-diazabicyclo[3.3.1]non-6-en-3-yl)-2-phenylethanone (**6b**). According to the general procedure, dioxazine **1d** (50 mg, 0.15 mmol), $LiBHEt_3$ (0.90 ml, 0.90 mmol) and THF (0.26 mL), 0°C for 30 minutes. Subsequent flash chromatography (hexanes /AcOEt 5:5, R_f = 0.30) afforded the title compound as a white solid (27 mg, 65 %). M.p. = 68-70 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 – 7.10 (m, 5H), 6.20 – 6.13 (m, 1H), 5.91–5.77 (m, 1H), 5.48 (d, 1H, *J* = 13.1 Hz), 4.33 – 4.19 (m, 2H), 3.77 (d, 1H, *J* = 14.7 Hz), 3.61 - 3.46 (m, 2H), 3.45 – 3.31 (m, 1H), 3.25 (*app*-t, 1H, *J* = 7.4 Hz), 1.51-1.33 (m, 2H), 0.99 (t, 3H *J* = 7.4 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.2, 136.5, 135.1, 129.6, 128.5, 126.8, 119.0, 73.6, 65.9, 59.5, 47.5, 39.6, 22.7, 10.6. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{16}H_{20}N_2O_2Na$ 295.1422; Found 295.1421.

1-((1R*,5S*)-4-Oxa-1,3-diazabicyclo[3.3.1]non-6-en-3-yl)-2-phenylethanone (**6c**). According to the general procedure, dioxazine **1e** (53 mg, 0.15 mmol), $LiBHEt_3$ (0.90 mL, 0.90 mmol) and THF (0.26 mL), 0°C for 30 minutes. Subsequent flash chromatography (hexanes /AcOEt 5:5 + 5% Et_3N, R_f = 0.20) afforded the title compound as a white solid (13 mg, 35 %). M.p. = 95-98 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 5H), 6.22 (dt, 1H *J* =10.0, 5.4 Hz), 6.03 - 5.91 (m , 1H), 5.39 (d, *J* = 13.2 Hz, 1H), 4.36 (d, *J* = 6.1 Hz, 1H), 4.30 (d, *J* = 13.2 Hz, 1H), 3.83 – 3.42 (m, 5H), 3.0 (d, 1H, J= 13.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.1, 136.8, 135.0, 129.6, 128.5, 126.8, 121.1, 70.1, 64.3, 52.0, 50.0, 39.6. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{14}H_{16}N_2O_2Na$ 267.1109; Found 267.1110

Phenyl((1R*,5S*,9R*)-9-phenyl-4-oxa-1,3-diazabicyclo[3.3.1]non-6-en-3-yl)methanone (**6d**)**.** According to the general procedure, dioxazine **1h** (30 mg, 0,08 mmol), $LiBHEt_3$ (0.51

mL, 0.51 mmol) and THF (0.15 mL), 0 °C for 12 h. Subsequent flash chromatography (hexanes /AcOEt 5:5, R_f = 0.57) afforded the title compound as a white solid (15 mg, 55%). M.p. = 120-122 °C. ^{1}H NMR (250 MHz, CD_3CN, 55 °C) δ 7.64 – 7.54 (m, 2H), 7.51 – 7.38 (m, 3H), 7.36 – 7.21 (m, 5H), 5.96 (dt, *J* = 10.1, 2.7 Hz, 1H), 5.75 – 5.54 (m, 3H), 4.82 (d, *J* = 6.4 Hz, 1H), 4.69 (d, *J* = 13.0 Hz, 1H), 4.63 (s, 1H), 3.39 (d, *J* = 20.5 Hz, 1H), 3.23 (d, *J* = 19.6 Hz, 1H). ^{13}C NMR (62.5 MHz, CD_3CN) δ 172.3, 138.3, 137.1, 136.0, 131.2, 129.9, 129.0, 128.7, 128.2, 127.6, 121.3, 73.1, 66.9, 60.0, 48.4. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{19}H_{18}N_2O_2Na$ 329.1266; Found 329,1261.

2-Phenyl-1-((1R*,5S*,9R*)-9-vinyl-4-oxa-1,3-diazabicyclo[3.3.1]non-6-en-3-yl)ethanone (**6e**)**.** According to the general procedure, dioxazine **1i** (110 mg, 0.35 mmol), $LiBHEt_3$ (2.1 ml, 2.1 mmol) and THF (0.6 mL), 0 °C for 7 h. Subsequent flash chromatography (petroleum ether /AcOEt 5:5, R_f = 0.20) afforded the title compound as a colorless oil (38 mg, 40%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 – 7.17 (m, 5H), 6.18 – 6.08 (m, 1H), 5.94 – 5.83 (m, 1H), 5.69 (ddd, *J* = 17.4, 10.6, 5.4 Hz, 1H), 5.47 (d, *J* = 13.3 Hz, 1H), 5.36 – 5.21 (m, 2H), 4.37 – 4.32 (m, 1H), 4.29 (d, *J* = 13.1 Hz, 1H), 3.96 (dd, *J* = 3.4, 1.4 Hz, 1H), 3.75 (d, *J* = 14.8 Hz, 1H), 3.65 – 3.53 (m, 1H), 3.48 (d, *J* = 14.7 Hz, 1H), 3.44 – 3.31 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.2, 136.7, 135.0, 133.2, 129.6, 128.5, 126.8, 119.0, 118.7, 72.9, 65.2, 59.5, 47.9, 39.6. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{16}H_{18}N_2O_2Na$ 293.1266; Found 293.1261.

2-Phenyl-1-((1R*,5S*,9R*)-9-cyclohexyl-4-oxa-1,3-diazabicyclo[3.3.1]non-6-en-3-yl)ethanone (**6f**). According to the general procedure, dioxazine **1j** (155 mg, 0.42 mmol), $LiBHEt_3$ (2.5 ml, 2.5 mmol) and THF (0.72 mL), 0 °C for 6.5 h. Subsequent flash

chromatography (petroleum ether /AcOEt 7:3, R_f = 0.17) afforded the title compound as a withe solid (32 mg, 23%; m.p. = 139-142°C) and starting material **1j** (Conv: ca 50%, *Rf* = 0.23). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 5H), 6.20 – 6.10 (m, 1H), 5.90 – 5.78 (m, 1H), 5.45 (d, *J* = 13.0 Hz, 1H), 4.41 (d, *J* = 5.9 Hz, 1H), 4.19 (d, *J* = 13.1 Hz, 1H), 3.75 (d, *J* = 14.7 Hz, 1H), 3.55 – 3.26 (m, 3H), 2.95 (d, *J* = 10.3 Hz, 1H), 1.96 (d, *J* = 12.5 Hz, 1H), 1.80 – 1.56 (m, 4H), 1.38 – 1.09 (m, 4H), 1.06 – 0.78 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.1, 137.0, 135.2, 129.6, 128.4, 126.7, 118.9, 72.5, 66.2, 63.0, 47.6, 39.6, 36.3, 30.2, 29.1, 26.5, 25.9, 25.9. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{20}H_{26}N_2O_2Na$ 349.1892; Found 349.1887.

2-Phenyl-1-((1R*,5S*,9R*)-9-allyl-4-oxa-1,3-diazabicyclo[3.3.1]non-6-en-3-yl)ethanone (**6g**)**.** According to the general procedure, dioxazine **1k** (115 mg, 0.35 mmol), $LiBHEt_3$ (2.1 ml, 2.1 mmol) and THF (0.6 mL), 0 °C for 1.5 h. Subsequent flash chromatography (hexane/AcOEt 6:4, R_f = 0.13) afforded the title compound as a colorless oil (72 mg, 72 %). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 – 7.13 (m, 5H), 6.17 (dt, *J* = 10.0, 2.6 Hz, 1H), 5.91 – 5.72 (m, 2H), 5.45 (d, *J* = 13.1 Hz, 1H), 5.18 – 5.04 (m, 2H), 4.30 – 4.15 (m, 2H), 3.74 (d, *J* = 14.7 Hz, 1H), 3.59 – 3.32 (m, 4H), 2.27 – 2.02 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.1, 136.5, 135.0, 134.3, 129.6, 128.4, 126.7, 118.7, 117.6, 73.1, 65.8, 57.5, 47.5, 39.6, 34.4. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{17}H_{20}N_2O_2Na$ 307.1422; Found 307.1419.

General procedure for the addition of metal hydrides to 1a in the presence of palladium catalysts (Table 1)

An over-dried 5 mL Schlenk tube was charged with the dioxazine derivative, the palladium catalyst (0.05 eq) and freshly distilled THF under argon protection. The resulting mixture was cooled at 0 °C and the hydride source was slowly added. Upon disappearance of the dioxazine derivative, the reaction was quenched with water and the aqueous phase was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography.

(5R*,6S*)-Methyl 6-phenyl-5-((2-phenylacetamido)oxy)-5,6-dihydropyridine-1(2H)-carboxylate (**4a**)**.** According to the general procedure, dioxazine **1a** (54.7 mg, 0.15 mmol), $(PPh_3)_2PdCl_2$ (5.4 mg, 0.078 mmol), $NaBH_4$ (35 mg, 0.9 mmol) and THF (0.75 mL) for 24 h at rt. Subsequent flash chromatography (hexanes /AcOEt 6:4, R_f = 0.22) afforded the title compound as sticky oil (16 mg, 30%). The slower eluting fractions afforded compound **5a** (*vide supra*). ^{1}H NMR (250 MHz, CD_3CN, 65 °C) δ 9.21 (bs, 1H), 7.39 – 7.24 (m, 8H), 7.21 – 7.13 (m, 2H), 6.14* (dd, *J* = 3.5, 2.7 Hz, 1H) and 6.10 (dd, *J* = 3.5, 2.7 Hz, 1H), 6.03 – 5.93 (m, 1H), 5.67 (s, 1H), 4.63 (d, *J* = 5.7 Hz, 1H), 4.42 – 4.37* (m, 1H) and 4.34 – 4.30 (m, 1H), 3.71 (s, 3H), 3.66 (dd, *J* = 4.0, 1.9 Hz, 1H) and 3.59* (dd, *J* = 4.0, 2.0 Hz, 1H), 3.48 (s, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.0, 157.0, 136.7, 134.1, 132.2, 129.2, 128.9, 128.7, 127.9, 127.4, 127.2, 121.1, 53.5, 53.2, 41.25, 31.0, 29.8. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{21}H_{22}N_2O_4Na$ 389.1477; Found 389.1478.

Compound **4a-D**. According to the general procedure, dioxazine **1a** (57 mg, 0.15 mmol),

$(PPh_3)_2PdCl_2$ (5.4 mg, 0.078 mmol), $NaBD_4$ (60 mg, 1.4 mmol) and THF (0.75 mL), rt for 8 h. Subsequent flash chromatography (hexanes /AcOEt 6:4, R_f = 0.19) afforded the title compound as white amorphous solid (8 mg, 15%). ^{1}H NMR (250 MHz, CD_3CN, 65 °C) δ 9.22 (s, 1H), 7.38 – 7.24 (m, 8H), 7.21-7.13 (m, 2H), 6.11 (dd, *J* = 10.2, 2.2 Hz, 1H), 6.03 – 5.93 (m, 1H), 5.68 (s, 1H), 4.64 (dt, *J* = 5.5, 1.7 Hz, 1H), 3.71 (s, 3H), 3.64-3.56 (m, 1H), 3.48 (s, 2H). ^{13}C NMR (75 MHz, CD_3CN) δ 169.6, 157.5, 139.6, 136.4, 132.7, 130.1, 129.6, 129.5, 128.5, 127.8, 127.5, 121.2, 79.5, 57.5, 55.8, 53.4, 42.1 (*J* = 21.9 Hz), 40.8. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{21}H_{21}DN_2O_4Na$ 390.1540; Found 390.1538.

Compound **5a-D**. From the slower eluting fraction of the above flash chromatography (hexanes /AcOEt 6:4, R_f = 0.10) was recovered the title compound as white amorphous solid (12 mg, 22%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.92 (bs, 1H) and 8.50* (bs, 1H) (exchangeable with D_2O), 7.40 – 7.26 (m, 8H), 7.18 –7.02 (d, *J* = 8.4 Hz, 1H), 5.60 (s, 1H) and 5.45* (s, 1H), 4.93 – 4.71 (m, 1H), 4.45 (bs, 1H), 3.74 (s, 3H) and 3.61* (s, 3H), 3.52 (d, *J* = 18.3 Hz, 2H), 2.21 (d, *J* = 15.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 154.7* and 154.5, 138.4* and 138.1, 134.1, 129.3, 129.1, 128.9, 127.8, 127.6, 125.7, 125.4, 102.5* and 101.9, 79.8, 56.5* and 55.8, 53.5, 41.1, 22.1-21.1 (m). [* minor rotamer] HRMS (ESI) m/z [M + Na+] Calcd for $C_{21}H_{21}DN_2O_4Na$ 390.1540; Found 390.1538.

Supporting Information Available: The Supporting Information is available free of charge on the ACS Publications website at DOI: Computational and X-ray data, copies of ^{1}H and ^{13}C NMR spectra of all new compounds, and ^{1}H NMR spectrum of known compound **2a**.

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Notes

The authors declare no competing financial interest.

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14) CCDC 1587512 contains the supplementary crystallographic data for this paper. Crystal data for **6a**: $C_{20}H_{20}N_2O_2$, Mr = 320.38, monoclinic, space group $P2_1/c$ (no. 14), a = 10.9704(3) Å, b = 6.5342(2) Å, c = 23.6337(7) Å, β = 101.584(2), V = 1659.62(8) Å^3, Z = 4, $F(000)$ = 680, D_c = 1.282 g·cm^{-3}, μ(Mo-$K\alpha$) = 0.084 mm^{-1}, T = 296 K, 19785 reflections

collected, 5574 unique (R_{int} = 0.0197), 232 variables refined with 3963 reflections with $F_o > 4\sigma(F_o)$ to R_1 = 0.0451. CCDC 1587512 for more details.

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16) The hydrogen of B-H bond has an increased hydride character in Super-H® than in BH_4^-, and it is also more tightly coordinated to the cation. For example, see : Golub, I. E.; Filippov, O. A.; Gulyaeva, E.; Gutsul, E. I.; Belkova, N. V. The Interplay of Proton Accepting and Hydride Donor Abilities in the Mechanism of Step-wise Boron Hydrides Alcoholysis. *Inorganica Chimica Acta* **2017**, *456*, 113-119 and references therein.

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