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Diastereoselective Synthesis of Nonplanar 3-Amino-1,2,4-oxadiazine Scaffold: Structure Revision of Alchornedine

Shuang-Qi Tang, Maeva Leloire, Séverine Schneider, Julie Mohr, Jacques Bricard, Patrick Gizzi, Delphine Garnier, Martine Schmitt, and Frédéric Bihel*

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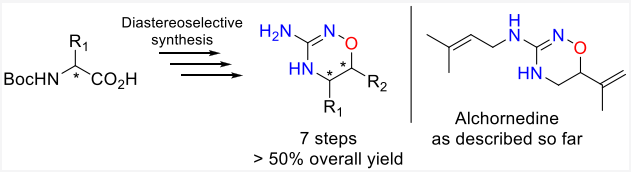
ABSTRACT: Herein, we report the diastereoselective synthesis of a 3-amino-1,2,4-oxadiazine (AOXD) scaffold. The presence of a N−O bond in the ring prevents the planar geometry of the aromatic system and induces a strong decrease in the basicity of the guanidine moiety. While DIBAL-H appeared to be the most efficient reducing agent because it exhibited high diastereoselectivity, we observed various behaviors of the Mitsunobu reaction on the resulting β-aminoalcohol, leading to either inversion or retention of the configuration depending on the steric hindrance in the vicinity of the hydroxy group. The physicochemical properties (pK_a and log D) and hepatic stability of several AOXD derivatives were experimentally determined and found that the AOXD scaffold possesses promising properties for drug development. Moreover, we synthesized alchornedine, the only natural product with the AOXD scaffold. Based on a comparison of the analytical data, we found that the reported structure of alchornedine was incorrect and hypothesized a new one.



INTRODUCTION

Limitations in solubility, pharmacokinetics, and bioavailability of highly aromatic molecules have been well recognized;[1] the medicinal chemistry community has become increasingly aware of the requirement to create drug-like compounds containing saturated building blocks.[2−4] Among them, the six-membered heterocycle oxadiazines containing one oxygen and two nitrogen atoms have been considered as important skeletons because of their interesting potential in organic and medicinal chemistry.[5−10] Unlike their aromatic triazine counterparts, the bivalent character of the oxygen atom endows oxadiazines with an interesting nonaromatic and nonplanar geometry which has recently been highlighted and utilized in drug discovery through the concept of "escape from flatland" developed by F. Lovering et al.[11,12]

Among the different types of oxadiazines classified on the basis of the positions of their heteroatoms, we focused our work on the 3- amino-1,2,4-oxadiazine (AOXD) scaffold (Figure 1). This scaffold is particularly interesting because it presents two stereogenic sp^3 centers; the presence of the bivalent oxygen atom in the α-position of the guanidine moiety affects pK_a, strongly decreasing the basicity of the guanidine moiety. This alkoxy-guanidine moiety is well known in its acyclic form in the natural amino acid L-canavanine, which possesses the arginine antimetabolite property and is synthesized by leguminous plants.[13] However, to date, only one natural product has been reported that consists of the cyclic form of AOXD. This natural guanidine-based alkaloid, alchornedine (Figure 1), was isolated from the leaves of *Alchornea glandulosa* and structurally identified by Barrosa et al. in 2014.[14] The authors also showed that alchornedine displayed antiprotozoal activity against *Trypanosoma cruzi* (Y strain). However, the total synthesis of this compound has not been reported yet, limiting the optimization of its activity against American trypanosomiasis.

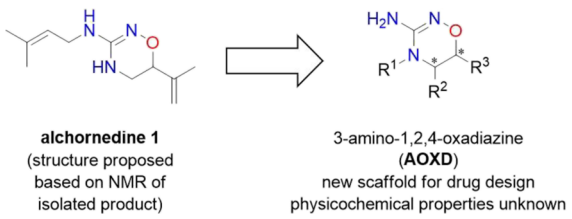


Figure 1. Alchornedine, the only natural product reported with a AOXD scaffold.

Because of its distinctive structure and properties, general synthetic methods for chiral AOXD using readily available reagents are desirable. Although several preparative methods have been described for 3-alkyl/aryl-1,2,4-oxadiazines,[15−17] the synthesis of chiral AOXD, to the best of our knowledge, has not been reported.

In this study, we established a general synthetic method to access chiral AOXD by using readily available *N*-Boc-amino

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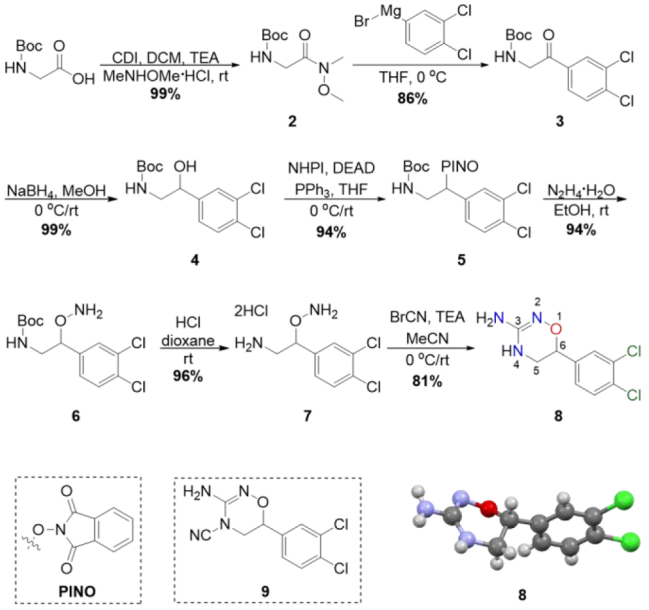
acids as starting materials. The first objective of this study was the synthesis of racemic AOXD, and its geometry has been confirmed by X-ray crystallography. Then, several conditions were screened for the diastereoselective synthesis of chiral AOXDs and the relationship between chirality and NMR characteristics was highlighted. As a novel scaffold, the physicochemical properties of AOXD were also investigated. Finally, alchornedine was synthesized, and its spectra and analytical data were compared with those of the isolated compound previously reported.[14]

RESULTS AND DISCUSSION

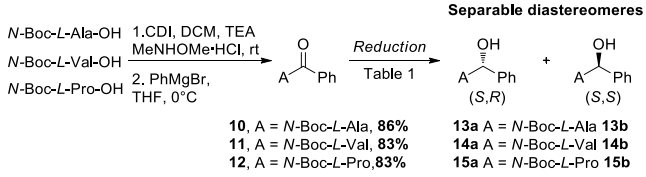
As an initial experiment, achiral *N*-Boc-glycine was used as the starting material for exploring the synthesis of racemic AOXD (Scheme 1). *N*-Boc-glycine reacted with *N*,*N*′-carbonyl diimidazole (CDI) and *N*,*O*-dimethylhydroxylamine to form the corresponding Weinreb amide **2** in 99% yield.[18] The nucleophilic addition between **2** and 3,4-dichloro-phenyl magnesium bromide furnished ketone **3** in 86% yield, which was directly reduced by $NaBH_4$ to yield alcohol **4** in 99% yield. As a key step in AOXD synthesis, the Mitsunobu reaction between alcohol **4** and *N*-hydroxyphthalimide (NHPI) was conducted to form the C−ON bond, affording the key intermediate, **5**, in 94% yield. Then, phthaloyl and Boc protections were successively removed by hydrazine hydrate and HCl treatments, affording **6** and **7** in 94 and 96% yields, respectively. Finally, the cyclization reaction of **7** was carried out with BrCN to afford racemic AOXD **8** and its 4-cyanated side product **9** in 81 and 17% yields, respectively (see Section SI). The presence of such a side product indicated that the nitrogen atom at position 4 (−HN−CH_2−) in **8** is more nucleophilic toward BrCN than those at positions 3 and 2, respectively. X-ray crystallography confirmed the AOXD structure of **8** (Scheme 1), with a C=N double bond located between N^2 and C^3, rather than C^3 and N^4, likely because of the stabilization of p−π conjugation between the oxygen atom and the C=N double bond. Meanwhile, the bivalent character of the oxygen atom induced the expected nonplanar geometry of AOXD, in which C^6 is located far out-of-plane constituted by the N^2=C^3−N^4 moiety. Moreover, the N^2−O^1 and N^4−C^5 bonds are unparallel because of the different bond angles between N^2−O^1−C^6 and N^4−C^5−C^6. Despite the absence of any functional groups at C^5 of AOXD, or on ortho position of the phenyl ring, the oxadiazine ring in **8** is perpendicular to the phenyl ring, which allows the hydrogen atom C^6H to be in the same axis as the aromatic ring (for more details of crystallographic data and structure refinement parameters, see Supporting Information).

Scheme 1. Synthesis of Racemic AOXD 8; X-ray Crystallographic Structure; Thermal Ellipsoids Are Shown at the 50% Probability Level



After determining the synthesis method of racemic AOXD, we selected *N*-Boc-L-alanine, *N*-Boc-L-valine, and *N*-Boc-L-proline as starting materials for the synthesis of chiral AOXDs exhibiting two stereogenic centers (Table 1). Using the synthetic approach described in Scheme 1, the *N*-Boc-L-amino acids were transformed into their corresponding ketones through the reactions of their corresponding Weinreb amides with PhMgBr, affording **10**, **11**, and **12** in 86, 83, and 83% overall yield, respectively. To reduce ketones **10**−**12** to their corresponding alcohols, several reductants were evaluated to determine optimal stereoselective conditions allowing one diastereomer to be favored over another (Table 1). Several reduction methods of α-amino ketones have been published recently;[19−23] however, none of them showed a systematic comparison of the reduction of α-aminoketones by borane- or aluminum-based reducing agents exhibiting more or less bulkiness.

Table 1. Reduction of Ketones 10−12[a]



		isolated yield (%)[b]					
		Ala		Val		Pro	
entry	reducing agents	13a	13b	14a	14b	15a	15b
1[c]	$NaBH_4$	77	22	82	18	24	72
2	L-selectride	57	41	64	33	57	43
3[d]	(*S*)-Me-CBS, BH_3	97	0	99	0	70	29
4[d]	(*R*)-Me-CBS, BH_3	28	71	59	41	64	36
5	$LiAlH_4$	74	25	52	47	45	55
6	DIBAL-H	99	0	97	0	99	0

[a]All reactions were carried out with ketones **10**, **11**, or **12** (0.1 mmol) and the reducing agent (0.2 mmol) in THF (1 mL) under Ar at 0 °C for 1 h and then at rt for 3 h. Yield of **10**, **11**, and **12** corresponds to the 2-step overall yield. [b]Isolated yield for each diastereomer identified by comparison with the literature.[38−41] [c]THF was replaced with MeOH (1 mL). [d](*S*)- or (*R*)-(−)-2-methyl-CBS-oxazaborolidine (0.01 mmol) and BH_3−Me_2S complex (0.2 mmol) were used.

Partial diastereoselectivity was observed when $NaBH_4$ was used (Table 1, entry 1), privileging formation of the (*S*,*R*) diastereomer for Ala- and Val-type ketones (77% (*S*,*R*) **13a** vs 22% (*S*,*S*) **13b** and 82% (*S*,*R*) **14a** vs 18% (*S*,*S*) **14b**, respectively), while the (*S*,*S*) diastereomer was favored for the Pro-type ketone [24% (*S*,*R*) **14a** and 72% (*S*,*S*) **14b**]. The bulky organoborane L-selectride led to a weak diastereoselective reduction of ketones **10**−**12** (Table 1, entry 2). As a well-known chiral reaction, Corey−Bakshi−Shibata (CBS) reduction was also attempted.[24] (*S*)-2-Me-CBS yielded only the (*S*,*R*)

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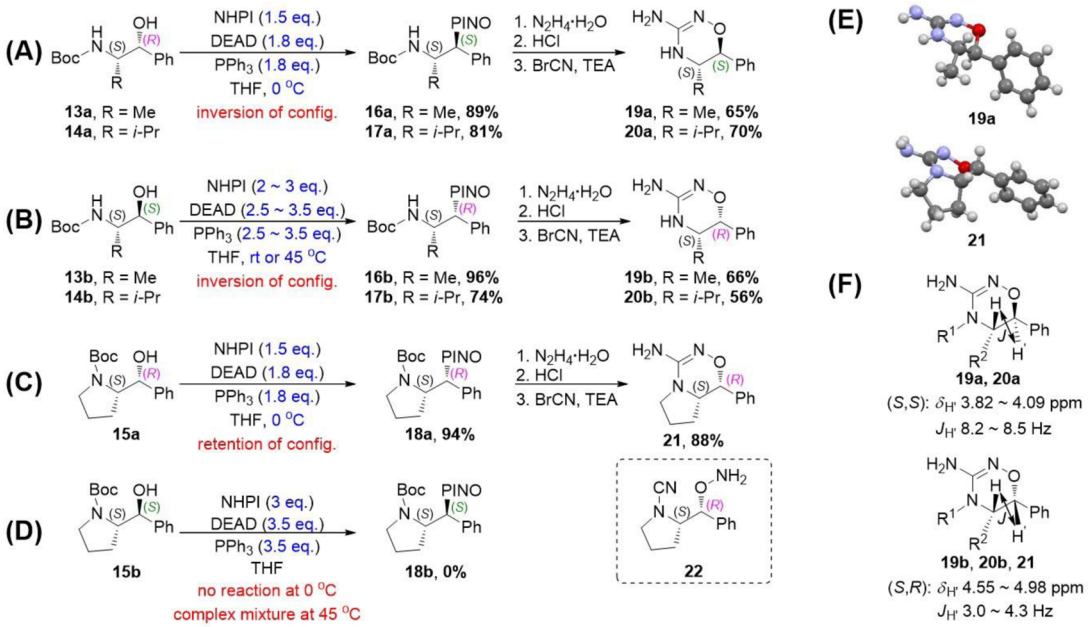

Figure 2. (A–D) Mitsunobu reaction and cyclization to afford AOXDs **19**–**21**. Yields for **19**-**21** correspond to the three-step overall yield. (E) X-ray crystallographic structures of **19a** and **21**. Thermal ellipsoids are shown at the 50% probability level. (F) Ranges of the ^{1}H chemical shift and coupling constant of diastereomeric AOXDs **19**–**21** in DMSO-d_6.

diastereomer in a nearly quantitative yield for Ala- and Val-type ketones (97% **13a** and 99% **14a**) (Table 1, entry 3) but appeared less efficient for the Pro-type ketone, leading to diastereomers (*S*,*R*) **15a** and (*S*,*S*) **15b** in 70% and 29% yields, respectively (Table 1, entry 3). In contrast, (*R*)-2-Me-CBS led to low diastereoselectivity regardless of the bulkiness of the ketone (Table 1, entry 4). Further, lithium aluminum hydride ($LiAlH_4$) exhibited low diastereoselectivity toward bulky ketones **11** and **12**, favoring the formation of (*S*,*R*) **13a** (74% yield) starting from Ala-type ketone **10** (Table 1, entry 5). In contrast to the bulky organoborane L-selectride, the bulky aluminum hydride DIBAL-H diastereoselectively reduced ketones **10**–**12**, yielding only the single (*S*,*R*) diastereomers **13a**–**15a** in a nearly quantitative yield (Table 1, entry 6). This excellent diastereoselectivity of DIBAL-H could be explained by the good complexation between the aluminum atom and the carbonyl oxygen atom as well as the steric hindrance between the isobutyl moieties of DIBAL-H and the Boc group following the Felkin–Anh model (see Section SII).

Next, the Mitsunobu reaction with NHPI was conducted to introduce the C–ON bond on the chiral alcohols **13**–**15** (Figure 2A–D). As expected, key intermediates **16** and **17** were obtained with the inversion of the configuration in 74–96% yields from the corresponding Ala- and Val-type alcohols (Figures 2A, B). However, with Pro-type (*S*,*R*) alcohol **15a**, the Mitsunobu reaction led to the unexpected retention of the configuration, affording key intermediate **18a** (*S*,*R*) in 94% yield (Figure 2C).

Intermediate **18a** was first characterized by NMR, and the retention of the configuration was confirmed by the X-ray crystallography of AOXD **21**, which was obtained from the cyclization of deprotected **18a** with BrCN (Figure 2E). Although it is not a frequent case, such configuration retention has been reported wherein the Mitsunobu reaction was performed on sterically hindered alcohols (see Section SIII).[25] Different reactivities were also observed between (*S*,*R*) and (*S*,*S*) diastereomers **13**–**15**. Moreover, (*S*,*R*) alcohols **13a**–**15a** underwent the Mitsunobu reaction at 0 °C (Figure 2A,C), while a higher temperature (rt or 45 °C) and an additional equivalent of reagents were required for the reactions involving (*S*,*S*) Ala- and Val-type alcohols **13b** and **14b** (Figure 2B). The Mitsunobu reaction of the (*S*,*S*) Pro-type alcohol **15b** yielded a complex mixture at 45 °C, possibly because of the hindrance of the Boc group under the configuration-retained mechanism (Figure 2D, also see Section SIV).

Finally, after the deprotection of the phthaloyl and Boc moieties, key intermediates **16**–**18** were cyclized in the presence of BrCN to obtain the corresponding diastereomeric AOXDs **19**–**21** after three steps in 56–88% overall yield (Figure 2A–C). Interestingly, cyanamide **22** could be isolated as an intermediate of the cyclization reaction of **18a** with BrCN (Figure 2D, dotted box), indicating that the secondary amine of the pyrroline moiety is more nucleophilic than alkoxyamine toward BrCN (see Section SV). The X-ray crystallographic structures of **19a** and **21** were obtained as representatives of (*S*,*S*) and (*S*,*R*) AOXDs (Figure 2E). To facilitate the identification of diastereomeric AOXDs, the ^{1}H chemical shifts (δ) and coupling constants (J) of **19**–**21** in DMSO-d_6 were determined and significant differences were observed. In particular, the proton of the >CH′–O– moiety in (*S*,*S*) **19a** and **20a** was detected at 3.82–4.09 ppm, with a coupling constant ($J_{H'}$) of 8.2–8.5 Hz (Figure 2F). In contrast, the corresponding proton in (*S*,*R*) **19b**, **20b**, and **21** was observed at 4.55–4.98 ppm, with a $J_{H'}$ of about 3–4.3 Hz.

The AOXDs described herein have not been previously characterized in terms of physicochemical properties. The presence of an oxygen atom in the α-position of the guanidine moiety would likely affect pK_a as well as the distribution coefficient log *D*. These parameters were experimentally measured and compared with those of the cyclic guanidine analogues **23**–**25** (Figure 3). Because of the strong basicity of guanidine, the pK_a of **23** was too high to be measured under the titration condition and was estimated to be >13. A negative value of log *D* ($D_{7.4}$ = −0.64 ± 0.06) indicates that **23** is hydrophilic

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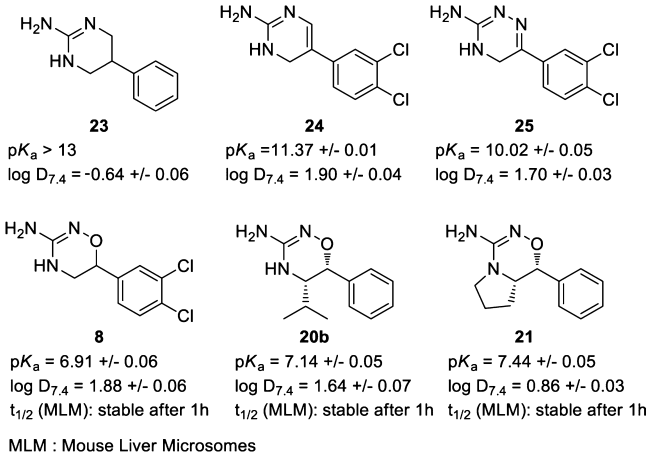
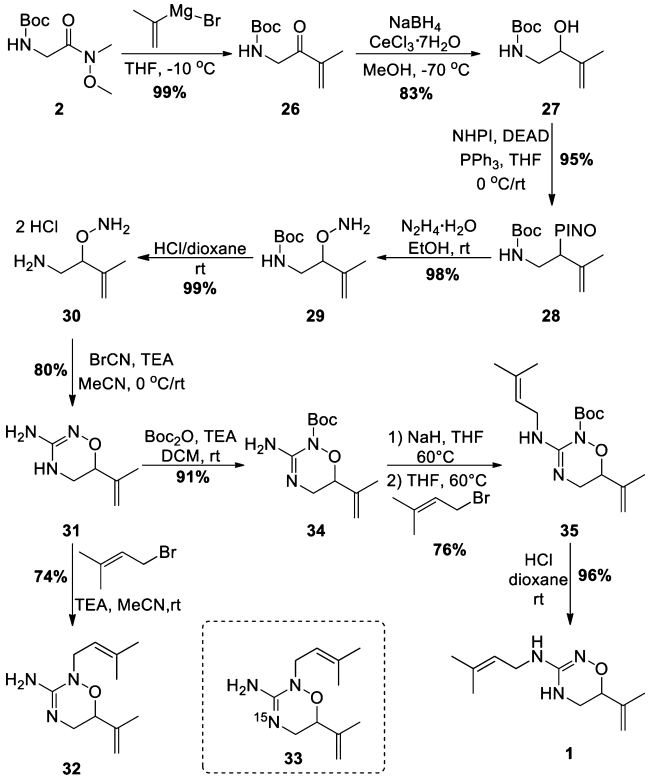


Figure 3. pK_a, log $D_{7.4}$, and hepatic stability in MLMs of AOXDs and its bioisosteres.

and unfavorable for membrane permeability by passive diffusion. Furthermore, the introduction of one double bond in **23** resulted in the formation of unsaturated cyclic guanidine **24**. As expected from the conjugation between the benzene ring and the guanidine moiety, pK_a decreased to 11.37 and log $D_{7.4}$ increased to 1.90 ± 0.04. Such a strong increase in log D is because of the decrease in pK_a and the presence of both chlorine atoms on the aromatic ring. Next, the unsaturated carbon atom adjacent to the guanidine moiety in **24** was replaced by a nitrogen atom, leading to the formation of cyclic iminoguanidine **25**. The resulting pK_a dropped to 10.02 and log $D_{7.4}$ slightly decreased to 1.70 ± 0.03, indicating sufficient hydrophobicity that can be attributed to the transposition of the α-nitrogen atom in **25** by an oxygen atom, dramatically decreasing pK_a to 6.91 with a suitable log $D_{7.4}$ at 1.88 ± 0.06. Diastereomers **20b** and **21** were slightly more basic and showed pK_a values of 7.14 and 7.44, respectively. Distribution coefficient log $D_{7.4}$ of **8**, **20b**, and **21** was <**2** despite the presence of the substituents. This is a promising phenomenon as it allows a comfortable margin of maneuver compared to the Lipinski recommendations.[26] Compared to nonconjugated cyclic guanidine **23**, AOXD **8**, **20b**, and **21** are more than six orders of magnitude less basic. Interestingly, at the physiological pH 7.4, a significant proportion of AOXDs are not protonated, improving their ability to cross biological barriers, unlike compounds **23**−**25** that only exist in their protonated forms at physiological pH. Finally, we determined the metabolic stability of AOXDs **8**, **20b**, and **21** in the presence of mouse liver microsomes (MLMs), and all of them exhibited complete stability after 1 h. For comparison, testorenone and dextrometorphan, FDA-approved drugs used as positive controls in this assay, showed half-lives of 5 and 19 min, respectively. These distinctive physicochemical properties and its stability in aqueous biological media make AOXD a promising scaffold for drug development.

Furthermore, the proposed synthetic approach for AOXD was utilized toward the total synthesis of alchornedine, the only natural product exhibiting a 3-amino-1,2,4-oxadiazine (AOXD) scaffold. Starting from *N*-Boc-glycine, AOXD **31** was synthesized as described previously (Scheme 2), except for the reduction of α,β-unsaturated ketone **26**, which was performed with $NaBH_4$ in the presence of $CeCl_3$. AOXD **31** was obtained from **2** after six steps and 61% overall yield. Direct alkylation of **31** using prenyl bromide in the presence of TEA afforded **32** in 74% yield (Scheme 2). To confirm the position of the prenyl

Scheme 2. Synthesis of Alchornedine 1



moiety, we synthesized its ^{15}N-labeled analogue (**33**) based on the principle that NMR signals of hydrogen or carbon atoms directly linked to ^{15}N will split. Following the synthetic method, as shown in Scheme 2, **33** was obtained after eight steps and 40% overall yield starting from ^{15}N-Boc-glycine (see Section SVI). The position of the prenyl moiety in **33** could be easily identified in the ^1H NMR spectra based on the presence of the $-NH_2$ signal as well as the split of ^{13}C signals of $>C{=}{}^{15}N-$ and $={}^{15}N-CH_2-$, while no split was observed for $>N-CH_2-$ from the prenyl moiety (see Section SVII). To modify the reactivity of **31** toward electrophiles, the nitrogen atom at position 2 was protected in the presence of $(Boc)_2O$, affording **34** in 91% yield (Scheme 2). The position of the Boc group was characterized unambiguously in 2D NMR (see Section SVIII). The amino group in **34** was then deprotonated by NaH and alkylated by prenyl bromide in tetrahydrofuran (THF), producing **35** in 76% yield. After Boc deprotection by HCl in dioxane, the structure of alchornedine **1**, as proposed by Barrosa et al.,[14] was obtained in 96% yield. The full structural characterization of **1** is shown in Section SIX, including ^1H and ^{13}C NMR, 2D-NMRs, and HRMS.

To confirm the structure of alchornedine, NMR spectra of **1** were compared with those reported for alchornedine (Figure 4A, Section SX).[14] Significant differences were found in both chemical shifts and coupling constants suggesting that Barrosa's proposed structure for alchornedine was incorrect. Such an error could be explained by the fact that all NMR analyses by Barrosa et al. were performed in MeOD, which prevented the observation of all signals corresponding to NH, which are the only protons between the prenyl group and CH_2 at position 5 of the 1,2,4-oxadiazine scaffold.

The reported mass spectrum of alchornedine shows a molecular peak at 210.16 (M + H), as well as a peak of fragmentation at 194.16, corresponding to the loss of a hydroxyl

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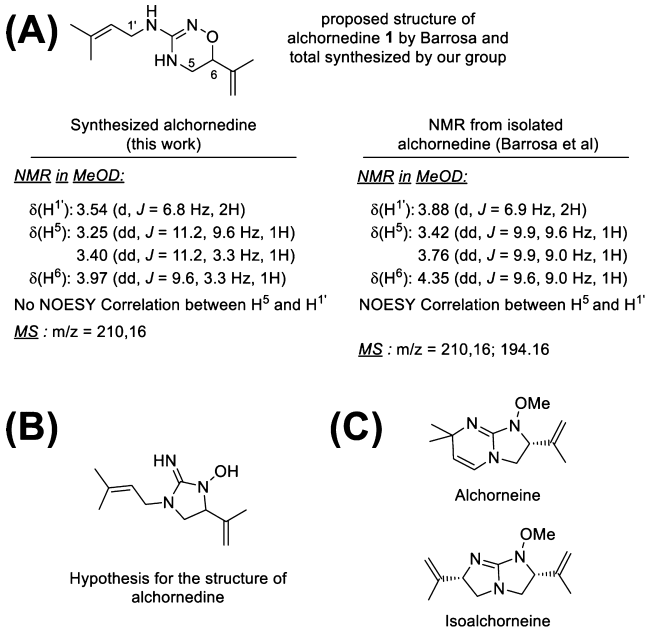

Figure 4. (A) Analytical comparison between synthesized and isolated alchornedine. (B) Alternative structure for alchornedine. (C) Structures of natural products alchorneine and isoalchorneine.

moiety. This result is not consistent with the AOXD scaffold but rather with that of the imidazolidine-1-ol scaffold, as shown in Figure 4B. Moreover, the NOESY signal reported for alchornedine between CH_2 in the ring and CH_2 of the prenyl moiety is attributed to the presence of the imidazolidine-1-ol scaffold. Furthermore, this imidazolidin-1-ol scaffold is identical to the reported structures of natural products, as it is found in alkaloids such as alchorneine and isoalchorneine.[42] Finally, it can be noticed that both the alkaloids correspond to a cyclized form of the structure we propose for alchornedine. However, the synthesis of this structure (Figure 4B) is not trivial and is under progress in our laboratory to confirm our hypothesis.

CONCLUSIONS

A general method for the synthesis of the AOXD scaffold was developed by using commercially available *N*-Boc amino acids as starting materials. We developed diastereoselective reactions to synthesize chiral compounds exhibiting nonplanar geometries and promising physicochemical properties because of which the compounds could be applicable in medicinal chemistry approaches. Based on the established method, alchornedine was synthesized and its structure was determined; however, spectral inconsistencies between the synthesized alchornedine and the one isolated from the leaves of *A. glandulosa* indicated that the proposed structure of alchornedine is incorrect. The total synthesis of alternative structures of alchornedine is currently underway. The determination of the correct structure of alchornedine will benefit medicinal chemistry because alchornedine exhibits promising antiprotozoal activity against American trypanosomiasis.[14]

EXPERIMENTAL SECTION

General Information and Typical Procedures. All commercial reagents were used without additional purification. Analytical TLC was performed using silica gel plates Merck 60 F_{254}, and the plates were visualized by exposure to ultraviolet light (254 nm). Compounds were purified on silica gel Merck 60 (particle size 0.040−0.063 nm). ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded on a Bruker AVANCE spectrometer operating at 400, 101, and 51 MHz, respectively. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. All chemical shift values δ and coupling constants J are quoted in ppm and in Hz, respectively, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, m = multiplet, and br = broad). Analytical RP-HPLC-MS was performed using a LC 1200 Agilent with quadrupole-time-of-flight (QTOF) (Agilent Accurate Mass QToF 6520) with a ZORBAX Agilent C18-column (C18, 50 mm × 2.1 mm; 1.8 μm) using the following parameters: (1) the solvent system: A (0.05% of formic acid in acetonitrile) and B (0.05% of formic acid in H_2O); (2) a linear gradient: t = 0 min, 98% B; t = 8 min, 0% B; t = 12.5 min, 0% B; t = 12.6 min, 98% B; t = 13 min, 98% B; (3) flow rate of 0.5 mL/min; (4) column temperature: 35 °C; (5) DAD scan from 190 to 700 nm; and (6) ionization mode: ESI^+ or ESI^-. HPLC were performed using a Dionex UltiMate 3000 using the following parameters: flow rate of 0.5 mL/min, column temperature: 30 °C, solvent system: A (MeOH) and B (0.05% of TFA in H_2O), t = 0 to 1 min: 50 to 60% of B, then t = 1 min to t = 10 min: 60 to 100% of B, and t = 10 min to t = 15 min: 100% of B. The single-crystal structure analysis was performed using X-ray diffraction with a Thermo Fisher ESCALAB 250 diffractometer.

Compound **23**−**25** were prepared according to the previous reported literatures.[27−30]

*Typical Procedure 1 (**TP1**) for the Preparation of Weinreb Amides **2**, **36**−**38**, and **45**.* CDI (1.5 equiv) was added slowly to a solution of *N*-Boc-amino acid (1 equiv) in dichloromethane (DCM) and stirred at rt for 30 min until CO_2 evolution ceased. Then, TEA (1.5 equiv) was added dropwise to the reaction mixture followed by the addition of *N*,*O*-dimethylhydroxylamine hydrochloride (1.5 equiv). After the addition was complete, the resulting mixture was stirred at rt for an additional 16 h. The reaction was then quenched by the addition of water and the resulting solution was extracted with DCM thrice. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* without further purification to afford the desired Weinreb amide.

*Typical Procedure 2 (**TP2**) for the Preparation of Ketones **3**, **10**−**12**, **26**, and **46**.* Grignard reagent (1.5−3.5 equiv) in THF was added dropwise to a solution of Weinreb amide (1 equiv) in THF at 0 °C under Ar. After the addition was complete, the reaction mixture was stirred at 0 °C overnight. The reaction mixture was then poured slowly into saturated NH_4Cl aqueous solution at 0 °C. After stirring for an additional 10 min, the resulting mixture was extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography to afford the desired ketone.

*Typical Procedure 3 (**TP3**) for the Preparation of Alcohols **4**, **13**−**15**, **27**, and **47**. Method 1 Associate with the Use of $NaBH_4$.* $NaBH_4$ (4 equiv) was added portionwise to a solution of ketone (1 equiv) in MeOH at 0 °C, and the resulting mixture was stirred at rt for an additional 6 h. The mixture was then poured slowly into a chilled saturated NH_4Cl aqueous solution and stirred for an additional 10 min. The resulting mixture was concentrated *in vacuo* to remove MeOH and then extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography or reverse phase C18 column chromatography to afford the desired alcohol.

Method 2 Associate with the Use of DIBAL-H. DIBAL-H (1 M in THF, 2 equiv) was added dropwise to a solution of ketone (1 equiv) in dry THF maintained at 0 °C under Ar, and the reaction mixture was stirred at rt for 6 h. The reaction mixture was then poured slowly into a chilled saturated NH_4Cl aqueous solution, stirred for an additional 10 min, and then extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* without further purification to afford the desired alcohol.

Method 3 Associate with the Use of (R)-2-Me-CBS and Borane Dimethylsulfide Complex. Borane dimethylsulfide complex (2 equiv)

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was added dropwise to a solution of (*R*)-2-Me-CBS-oxazaborolidine (0.4 M in THF, 0.1 equiv) in THF at 0 °C under Ar and the resulting solution was stirred for 20 min. The ketone solution (1 equiv) in THF was added slowly at 0 °C to the borane solution over a period of 15 min, the ice bath was removed, and the resulting mixture was stirred at rt for 16 h. The reaction solution was poured slowly into a chilled saturated citric acid aqueous solution (30 mL). After stirring for an additional 10 min, the resulting mixture was extracted with EtOAc thrice. The combined organic phases were concentrated *in vacuo* and purified by reverse phase C18 column chromatography to afford the desired alcohol.

Method 4 Associate with the Use of $LiAlH_4$. A solution of ketone (1 equiv) in dry THF was added dropwise to a suspension of $LiAlH_4$ (2 equiv) in THF at 0 °C under Ar and then stirred at rt for 6 h. The reaction mixture was poured slowly into a chilled saturated NH_4Cl aqueous solution and stirred for an additional 10 min while the temperature was kept at 0 °C. The resulting mixture was then extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography to afford the desired alcohol.

Method 5 Associate with the Use of $NaBH_4$ and $CeCl_3$. Trichlorocerium heptahydrate (1.6 equiv) was added to a solution of ketone (1 equiv) in MeOH and sonicated until the suspension became clear. Then, the mixture was cooled to −70 °C, $NaBH_4$ (1.5 equiv) was added portionwise and the reaction mixture was stirred at −70 °C for an additional 1 h. The reaction mixture was allowed to be warmed up to −20 °C and then quenched carefully by the addition of chilled H_2O. The crude was concentrated *in vacuo* to remove MeOH and the aqueous suspension was extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography to afford the desired alcohol.

*Typical Procedure 4 (**TP4**) for the Preparation of the PINO Derivatives **5**, **16**−**18**, **28**, and **48**.* The solution of corresponding alcohol **4**, **13**−**15** or **27** (1 equiv), NHPI (1.5−3 equiv), and PPh_3 (1.8−3.5 equiv) in dry THF was cooled 0 °C, degassed, and backfilled with Ar thrice. Then, DEAD (1.8−3.5 equiv) was added dropwise at 0 °C under Ar and allowed to stir at the given temperature for 16 h. The reaction mixture was quenched by the addition of water and extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography to afford the desired product.

*Typical Procedure 5 (**TP5**) for the Preparation of Compounds **6**, **29**, **39**, **41**, **43**, and **49**.* Hydrazine hydrate (15 equiv) was added dropwise to a solution of *N*-alkoxyl phthalimide (1 equiv) in EtOH and stirred at rt for 5 h. The reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography to afford the desired product.

*Typical Procedure 6 (**TP6**) for the Preparation of Compounds **7**, **30**, **40**, **42**, **44**, and **50**.* Boc amino alkoxyamine (1 equiv) was added to a hydrogen chloride solution in dioxane (4 M) and stirred at rt for 16 h. The reaction was concentrated *in vacuo* and dried under reduced pressure overnight to afford the alkoxyamines as a dihydrochloride salt.

*Typical Procedure 7 (**TP7**) for the Preparation of AOXDs **8**, **19**−**21**, **31**, and **51**.* TEA (4 equiv) was added dropwise to a solution of amino alkoxyamine dihydrochloride (1 equiv) in dry MeCN at 0 °C, under argon, and the mixture was stirred for 5 min. Then, a solution of BrCN (1.1 equiv) in MeCN was added dropwise, and stirring was maintained for 30 min at 0 °C. The ice bath was removed and the reaction stirred for 16 h while warming to ambient temperatures. The crude was concentrated *in vacuo* and purified by reverse phase C18 column chromatography ($MeCN/H_2O$) to afford the desired AOXD.

***N*-(3-Methylbut-2-en-1-yl)-6-(prop-1-en-2-yl)-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (1).** *tert*-Butyl 3-((3-methylbut-2-en-1-yl)amino)-6-(prop-1-en-2-yl)-5,6-dihydro-2*H*-1,2,4-oxadiazine-2-carboxylate **35** (1 equiv, 6.5 mg, 0.021 mmol) was added to a solution of HCl in dioxane (4 M, 1 mL) and stirred at rt for 16 h. The reaction mixture was concentrated *in vacuo* and basified with saturated aqueous solution of $NaHCO_3$ until pH reached 8. The crude was concentrated *in vacuo* and directly purified by reverse phase C18 column chromatography ($MeCN/H_2O$) to afford compound **1** as a white solid (4.2 mg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.76 (s, 1H), 5.20 (t, J = 6.9 Hz, 1H), 4.95 (s, 1H), 4.89 (s, 1H), 4.63−4.57 (m, 1H), 3.72 (dd, J = 9.5, 3.1 Hz, 1H), 3.43−3.36 (m, 2H), 3.28−3.24 (m, 1H), 3.01 (t, J = 10.3 Hz, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 153.8, 142.5, 132.6, 122.8, 111.9, 74.5, 43.7, 38.8, 25.4, 19.0, 17.7. ^{1}H NMR (400 MHz, MeOD-d_4): δ 5.29−5.20 (m, 1H), 5.02 (q, J = 1.2 Hz, 1H), 5.01−4.95 (m, 1H), 3.97 (dd, J = 9.6, 3.3 Hz, 1H), 3.54 (d, J = 6.8 Hz, 2H), 3.40 (dd, J = 11.2, 3.3 Hz, 1H), 3.25 (dd, J = 11.2, 9.6 Hz, 2H), 1.79 (t, J = 1.1 Hz, 3H), 1.73 (d, J = 1.4 Hz, 3H), 1.67 (d, J = 1.3 Hz, 3H). HRMS (ESI) m/z: calcd for $C_{11}H_{20}N_3O$ $[M + H]^+$, 210.1606; found, 210.1610.

***tert*-Butyl(2-(methoxy(methyl)amino)-2-oxoethyl)-carbamate (2).** Following general procedure **TP1** and starting from *N*-Boc glycine (1 equiv, 4 g, 22.8 mmol), CDI (1.5 equiv, 5.55 g, 34.2 mmol), TEA (1.5 equiv, 4.76 mL, 34.2 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (1.5 equiv, 3.34 g, 34.2 mmol) in DCM (50 mL), title compound **2** was obtained as a white solid (4.94 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.26 (s, 1H), 4.07 (d, J = 3.8 Hz, 2H), 3.70 (s, 3H), 3.19 (s, 3H), 1.45 (s, 9H). The analytical data are consistent with the previously reported characterization.[31]

***tert*-Butyl(2-(3,4-dichlorophenyl)-2-oxoethyl)carbamate (3).** According to general procedure **TP2**, 3,4-dichloro-phenyl magnesium bromide (1.5 equiv, 0.5 M, 27.5 mL, 13.7 mmol) was reacted with **2** (1 equiv, 2 g, 9.2 mmol) in THF (10 mL). After the work-up, the crude was purified by silica gel column chromatography (heptane/EtOAc = 5:1) to afford **3** as a white solid (2.4 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 2.1 Hz, 1H), 7.76 (dd, J = 8.4, 2.1 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 5.45 (s, 1H), 4.60 (d, J = 4.7 Hz, 2H), 1.47 (s, 9H). The analytical data are consistent with the previously reported characterization.[32]

***tert*-Butyl(2-(3,4-dichlorophenyl)-2-hydroxyethyl)-carbamate (4).** According to general procedure **TP3** (method 1), **3** (1 equiv, 1 g, 3.3 mmol) was treated with $NaBH_4$ (4 equiv, 0.5 g, 13.2 mmol) in MeOH (30 mL) to afford **4** as colorless oil (1 g, 99%) without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.19−7.15 (m, 1H), 4.98 (t, J = 6.2 Hz, 1H), 4.79 (dd, J = 7.7, 3.2 Hz, 1H), 3.78 (s, br, 1H), 3.49−3.38 (m, 1H), 3.26−3.13 (m, 1H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.4, 142.3, 132.8, 131.7, 130.5, 128.1, 125.4, 80.5, 73.2, 48.5, 28.5. HRMS (ESI) m/z: calcd for $C_{13}H_{17}Cl_2NO_3$ $[M + Na]^+$, 328.0483; found, 328.0492.

***tert*-Butyl(2-(3,4-dichlorophenyl)-2-((1,3-dioxoisoindolin-2-yl)oxy)ethyl)carbamate (5).** According to general procedure **TP4**, **4** (1 equiv, 500 mg, 1.6 mmol) was reacted with NHPI (1.5 equiv, 400 mg, 2.5 mmol), PPh_3 (1.8 equiv, 771 mg, 2.9 mmol), and DEAD (1.8 equiv, 0.46 mL, 2.9 mmol) in THF (15 mL) at rt. The crude was purified by silica gel column chromatography (heptane/EtOAc = 5:1) to afford **5** as a white solid (693 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84−7.78 (m, 2H), 7.77−7.73 (m, 2H), 7.63 (s, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.38 (dd, J = 8.3, 2.1 Hz, 1H), 5.50 (t, J = 6.2 Hz, 1H), 5.29 (t, J = 5.3 Hz, 1H), 3.61 (dd, J = 7.3, 5.0 Hz, 2H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.9, 151.8, 134.9, 133.4, 132.8, 130.6, 129.7, 128.9, 126.9, 124.4, 123.9, 87.2, 84.5, 44.3, 28.5. HRMS (ESI) m/z: calcd for $C_{21}H_{20}Cl_2N_2O_5$ $[M + Na]^+$, 473.0647; found, 473.0654.

***tert*-Butyl(2-(aminooxy)-2-(3,4-dichlorophenyl)ethyl)-carbamate (6).** According to general procedure **TP5**, **5** (1 equiv, 400 mg, 0.9 mmol) was reacted with hydrazine hydrate (15 equiv, 0.64 mL, 13.3 mmol) in EtOH (15 mL). The crude was purified by silica gel column chromatography (heptane/EtOAc = 2:1) to afford **6** as a white solid (268 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.41 (m, 2H), 7.16 (dd, J = 8.2, 1.8 Hz, 1H), 5.44 (s, 2H), 4.86 (s, 1H), 4.60 (dd, J = 7.9, 3.8 Hz, 1H), 3.56−3.44 (m, 1H), 3.19 (ddd, J = 14.4, 7.9, 4.8 Hz, 1H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.9, 139.9, 133.0, 132.2, 130.7, 128.8, 126.2, 84.7, 79.8, 44.9, 28.5.

2-(Aminooxy)-2-(3,4-dichlorophenyl)ethanamine Dihydrochloride (7). According to general procedure **TP6**, **6** (1 equiv, 100

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mg, 0.31 mmol) was treated with a solution of HCl in dioxane (4 M, 5 mL) to afford **7** as a white solid (88 mg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, br, 3H), 8.42 (s, br, 3H), 7.76−7.72 (m, 2H), 7.46 (dd, J = 8.3, 2.0 Hz, 1H), 5.43 (dd, J = 8.6, 4.0 Hz, 1H), 3.34−3.17 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 136.0, 132.1, 131.4, 131.0, 129.8, 128.1, 80.8, 41.7.

6-(3,4-Dichlorophenyl)-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (8) and 3-Amino-6-(3,4-dichlorophenyl)-5,6-dihydro-4*H*-1,2,4-oxadiazine-4-carbonitrile (9). According to general procedure **TP7**, **7** (1 equiv, 50 mg, 0.17 mmol) was dissolved in MeCN (10 mL) and treated successively with TEA (4 equiv 94.6 μL, 0.68 mmol) and a solution of BrCN (1.1 equiv, 19.8 mg, 0.19 mmol) in MeCN (0.5 mL) to afford **8** (33.9 mg, 81%) and **9** (7.8 mg, 17%) as white solids after purification by reverse phase C18 column chromatography (MeCN/H_2O). Compound **8** was recrystallized in MeCN at 4 °C. Analytical data for compound **8** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.64−7.60 (m, 2H), 7.35 (dd, J = 8.3, 2.0 Hz, 1H), 6.16 (s, 1H), 4.46 (s, 2H), 4.42 (dd, J = 9.0, 3.2 Hz, 1H), 3.45 (dd, J = 11.4, 3.2 Hz, 1H), 3.15 (dd, J = 11.4, 9.0 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 154.1, 140.4, 130.9, 130.4, 130.3, 128.7, 127.0, 72.0, 45.3. HRMS (ESI) m/z: calcd for $C_9H_{10}Cl_2N_3O$ [M + H]$^+$, 246.0201; found, 246.0208. Analytical data for compound **9** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72−7.65 (m, 2H), 7.44−7.40 (m, 1H), 5.78 (s, 2H), 4.82 (dd, J = 9.5, 3.2 Hz, 1H), 4.10 (dd, J = 11.0, 3.2 Hz, 1H), 3.97 (dd, J = 11.0, 9.5 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 147.2, 137.2, 131.3, 131.2, 130.7, 129.1, 127.3, 109.7, 72.1, 50.7. HRMS (ESI) m/z: calcd for $C_{10}H_9Cl_2N_4O$ [M + H]$^+$, 271.0153; found, 271.0156.

(*S*)-*tert*-Butyl(1-oxo-1-phenylpropan-2-yl)carbamate (10). Step 1: (*S*)-*tert*-butyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (**36**). Following general procedure **TP1** and starting from *N*-Boc-L-alanine (1 equiv, 4 g, 21.1 mmol), CDI (1.5 equiv, 5.14 g, 31.7 mmol), TEA (1.5 equiv, 4.41 mL, 31.7 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (1.5 equiv, 3.1 g, 31.7 mmol) in DCM (50 mL), the Weinreb amide of *N*-Boc-L-alanine **36** was obtained as a white solid (4.67 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.25 (d, J = 7.1 Hz, 1H), 4.73−4.57 (m, 1H), 3.74 (s, 3H), 3.18 (s, 3H), 1.41 (s, 9H), 1.28 (d, J = 6.9 Hz, 3H). The analytical data are consistent with the previously reported characterization.[33]

Step 2: (*S*)-*tert*-butyl (1-oxo-1-phenylpropan-2-yl)carbamate (**10**). According to general procedure **TP2**, phenyl magnesium bromide (1.5 equiv, 1 M, 12.9 mL, 12.9 mmol) was reacted with the above-described Weinreb amide of *N*-Boc-L-alanine **36** (1 equiv, 2 g, 8.6 mmol) in THF (25 mL). After a work-up, the crude was purified by silica gel column chromatography (heptane/EtOAc = 10:1) to afford **10** as colorless oil (1.93 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99−7.94 (m, 2H), 7.61−7.55 (m, 1H), 7.51−7.44 (m, 2H), 5.57 (d, J = 7.7 Hz, 1H), 5.35−5.21 (m, 1H), 1.45 (s, 9H), 1.39 (d, J = 7.1 Hz, 3H). The analytical data are consistent with the previously reported characterization.[34]

(*S*)-*tert*-Butyl(3-methyl-1-oxo-1-phenylbutan-2-yl)carbamate (11). Step 1: (*S*)-*tert*-butyl(1-(methoxy(methyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**37**). Following general procedure **TP1** and starting from *N*-Boc-L-valine (1 equiv, 4 g, 18.4 mmol), CDI (1.5 equiv, 4.48 g, 27.6 mmol), TEA (1.5 equiv, 3.84 mL, 27.6 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (1.5 equiv, 2.69 g, 27.6 mmol) in DCM (50 mL), the Weinreb amide of *N*-Boc-L-valine **37** was obtained as a white solid (4.51 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.12 (d, J = 9.4 Hz, 1H), 4.55 (t, J = 8.0 Hz, 1H), 3.74 (s, 3H), 3.19 (s, 3H), 1.96 (dq, J = 13.4, 6.7 Hz, 1H), 1.41 (s, 9H), 0.93 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H). The analytical data are consistent with the previously reported characterization.[35]

Step 2: (*S*)-*tert*-butyl(3-methyl-1-oxo-1-phenylbutan-2-yl)-carbamate (**11**). According to general procedure **TP2**, phenyl magnesium bromide (1.5 equiv, 1 M, 11.5 mL, 11.5 mmol) was reacted with the above-described Weinreb amide of *N*-Boc-L-valine **37** (1 equiv, 2 g, 7.7 mmol) in THF (25 mL). After a work-up, the crude was purified by silica gel column chromatography (heptane/EtOAc = 10:1) to afford **11** as colorless oil (1.88 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.87 (m, 2H), 7.63−7.54 (m, 1H), 7.48 (td, J = 7.5, 1.4 Hz, 2H), 5.43 (d, J = 8.6 Hz, 1H), 5.23 (dd, J = 9.1, 4.1 Hz, 1H), 2.24−2.03 (m, 1H), 1.45 (s, 9H), 1.03 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H). The analytical data are consistent with the previously reported characterization.[36]

(*S*)-*tert*-Butyl 2-Benzoylpyrrolidine-1-carboxylate (12). Step 1: (*S*)-*tert*-butyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (**38**). Following general procedure **TP1** and starting from *N*-Boc-L-proline (1 equiv, 4 g, 18.6 mmol), CDI (1.5 equiv, 4.52 g, 27.9 mmol), TEA (1.5 equiv, 3.88 mL, 27.9 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (1.5 equiv, 2.72 g, 27.9 mmol) in DCM (50 mL), the Weinreb amide of *N*-Boc-L-proline **38** was obtained as a white solid (4.51 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (ddd, J = 41.1, 8.6, 3.4 Hz, 1H), 3.76 (s, 1.5H), 3.69 (s, 1.5H), 3.61−3.32 (m, 2H), 3.17 (s, 3H), 2.25−2.08 (m, 1H), 1.99−1.77 (m, 3H), 1.43 (s, 4.5H), 1.39 (s, 4.5H). The analytical data are consistent with the previously reported characterization.[37]

Step 2: (*S*)-*tert*-butyl 2-benzoylpyrrolidine-1-carboxylate (**12**). According to general procedure **TP2**, phenyl magnesium bromide (1.5 equiv, 1 M, 11.6 mL, 11.6 mmol) was reacted with the above-described Weinreb amide of *N*-Boc-L-proline **38** (1 equiv, 2 g, 7.7 mmol) in THF (25 mL). After a work-up, the crude was purified by silica gel column chromatography (heptane/EtOAc = 10:1) to afford **12** as colorless oil (1.87 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04−7.87 (m, 2H), 7.61−7.50 (m, 1H), 7.50−7.40 (m, 2H), 5.39−5.27 (m, 0.4H), 5.24−5.14 (m, 0.6H), 3.74−3.41 (m, 2H), 2.40−2.18 (m, 1H), 2.01−1.84 (m, 3H), 1.45 (s, 3.5H), 1.25 (s, 5.5H). The analytical data are consistent with the previously reported characterization.[37]

***tert*-Butyl((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-carbamate (13a).** According to general procedure **TP3** (method 2), **10** (1 equiv, 1 g, 4 mmol) dissolved in THF (10 mL) was treated with DIBAL-H (2 equiv, 1 M, 8 mL, 8 mmol) without further purification to afford **13a** as colorless oil (1 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.26 (m, 5H), 4.85 (d, J = 3.0 Hz, 1H), 4.64 (s, 1H), 4.01 (s, 1H), 3.26 (s, br, 1H), 1.46 (s, 9H), 0.98 (d, J = 7.0 Hz, 3H). The analytical data are consistent with the previously reported characterization.[38]

***tert*-Butyl((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-carbamate (13b).** According to general procedure **TP3** (method 3), **10** (1 equiv, 1 g, 4 mmol) was dissolved in THF (10 mL) and treated with a borane dimethylsulfide complex (2 equiv, 0.76 mL, 8 mmol) and a solution of (*R*)-2-Me-CBS-oxazaborolidine (0.1 equiv 0.11 g, 4 mmol) in THF (10 mL) to afford **13b** as colorless oil (0.728 g, 71%) after purification by silica gel column chromatography (heptane/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.26 (m, 5H), 4.70 (s, 1H), 4.54 (d, J = 6.0 Hz, 1H), 3.93−3.79 (m, 1H), 3.27 (s, br, 1H), 1.40 (s, 9H), 1.07 (d, J = 6.8 Hz, 3H). The analytical data are consistent with the previously reported characterization.[39]

***tert*-Butyl((1*R*,2*S*)-1-hydroxy-3-methyl-1-phenylbutan-2-yl)-carbamate (14a).** According to general procedure **TP3** (method 2), **11** (1 equiv, 1 g, 3.6 mmol) dissolved in THF (10 mL) was treated with DIBAL-H (2 equiv, 1 M, 7.2 mL, 7.2 mmol) without further purification to afford **14a** as colorless oil (0.98 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.27 (m, 5H), 4.87 (t, J = 4.6 Hz, 1H), 4.35 (d, J = 9.8 Hz, 1H), 3.83−3.74 (m, 1H), 3.05 (d, J = 4.5 Hz, 1H), 1.78−1.66 (m, 1H), 1.39 (s, 9H), 1.04 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H). These data are consistent with the previously reported characterization.[20]

***tert*-Butyl((1*S*,2*S*)-1-hydroxy-3-methyl-1-phenylbutan-2-yl)-carbamate (14b).** According to general procedure **TP3** (method 4), **11** (1 equiv, 1 g, 3.6 mmol) in THF (10 mL) was added to a suspension of $LiAlH_4$ (2 equiv, 1 M, 7.2 mL, 7.2 mmol) to afford **14b** as colorless oil (0.47 g, 47%) after purification by silica gel column chromatography (heptane/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.31 (m, 5H), 4.83−4.76 (m, 2H), 3.52−3.40 (m, 1H), 2.96 (d, J = 4.4 Hz, 1H), 1.90−1.79 (m, 1H), 1.36 (s, 9H), 1.01 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H). The analytical data are consistent with the previously reported characterization.[40]

(*S*)-*tert*-Butyl 2-((*R*)-Hydroxy(phenyl)methyl)pyrrolidine-1-carboxylate (15a). According to general procedure **TP3** (method 2), **12** (1 equiv, 1 g, 3.6 mmol) in THF (10 mL) was treated with DIBAL-H (2 equiv, 1 M, 7.3 mL, 7.3 mmol) without further purification to afford **15a** as colorless oil (1 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ

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7.37−7.25 (m, 5H), 5.47 (s, 0.7H), 5.18 (s, 0.3H), 4.89 (s, 0.7H), 4.33 (s, 0.7H), 4.02 (s, 0.3H), 3.58 (s, 0.3H), 3.31 (s, 1H), 2.84 (s, 0.7H), 2.36−2.14 (m, 0.3H), 1.98−1.88 (m, 1H), 1.79 (s, 1H), 1.54 (s, 9H), 1.26−1.16 (m, 1H), 0.95−0.8 (m, 1H). The analytical data are consistent with the previously reported characterization.[41]

(*S*)-*tert*-Butyl 2-((*S*)-Hydroxy(phenyl)methyl)pyrrolidine-1-carboxylate (15b). According to general procedure **TP3** (Method 1), **12** (1 equiv, 1 g, 3.6 mmol) was dissolved in MeOH (30 mL) and treated with $NaBH_4$ (4 equiv, 0.55 g, 14.5 mmol) to afford **15b** as colorless oil (0.73 g, 72%). After purification by reverse phase C18 column chromatography ($MeOH/H_2O$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.24 (m, 5H), 5.81 (s, 0.7H), 5.41 (s, 0.3H), 5.16−4.60 (m, 1H), 4.56−4.21 (m, 1H), 4.12−4.00 (m, 0.8H), 3.53−3.16 (m, 2H), 2.79 (s, 0.2H), 1.75−1.58 (m, 3H), 1.48 (s, 9H). The analytical data are consistent with the previously reported characterization.[41]

***tert*-Butyl((1*S*,2*S*)-1-((1,3-dioxoisoindolin-2-yl)oxy)-1-phenylpropan-2-yl)carbamate (16a).** According to general procedure **TP4**, **13a** (1 equiv, 500 mg, 2 mmol) was reacted with NHPI (1.5 equiv, 487 mg, 3 mmol), PPh_3 (1.8 equiv, 939 mg, 3.6 mmol), and DEAD (1.8 equiv, 0.56 mL, 3.6 mmol) in THF (15 mL) at 0 °C. The crude was purified by silica gel column chromatography (heptane/EtOAc = 5:1) to afford **16a** as a white solid (702 mg, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.76−7.71 (m, 2H), 7.70−7.65 (m, 2H), 7.49−7.43 (m, 2H), 7.37−7.30 (m, 3H), 5.22 (d, J = 6.5 Hz, 1H), 5.13 (s, 1H), 4.18 (q, J = 7.0 Hz, 1H), 1.42 (s, 9H), 1.20 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.7, 155.4, 135.6, 134.5, 129.2, 129.0, 128.4, 128.4, 123.6, 90.9, 79.5, 50.1, 28.5, 17.9. HRMS (ESI) m/z: calcd for $C_{22}H_{24}N_2O_5$ $[M + Na]^+$, 419.1590; found, 419.1583.

***tert*-Butyl((1*R*,2*S*)-1-((1,3-dioxoisoindolin-2-yl)oxy)-1-phenylpropan-2-yl)carbamate (16b).** According to general procedure **TP4**, **13b** (1 equiv, 500 mg, 2 mmol) was reacted with NHPI (2 equiv, 649 mg, 4 mmol), PPh_3 (2.5 equiv, 1.3 g, 5 mmol), and DEAD (2.5 equiv, 0.78 mL, 5 mmol) in THF (20 mL) at rt. The crude was purified by silica gel column chromatography (heptane/EtOAc = 5:1) to afford **16b** as colorless oil (757 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.77−7.72 (m, 2H), 7.71−7.67 (m, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.39−7.27 (m, 3H), 5.43 (s, 1H), 5.40 (s, 1H), 4.06 (s, 1H), 1.43 (s, 9H), 1.24 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.8, 155.4, 136.3, 134.6, 129.0, 128.6, 128.2, 127.6, 123.6, 91.5, 79.5, 51.1, 28.5, 14.2. HRMS (ESI) m/z: calcd for $C_{22}H_{24}N_2O_5$ $[M + Na]^+$, 419.1583; found, 419.1590.

***tert*-Butyl((1*S*,2*S*)-1-((1,3-dioxoisoindolin-2-yl)oxy)-3-methyl-1-phenylbutan-2-yl)carbamate (17a).** According to general procedure **TP4**, **14a** (1 equiv, 500 mg, 1.8 mmol) was treated with NHPI (1.5 equiv, 438 mg, 2.7 mmol), PPh_3 (1.8 equiv, 845 mg, 3.2 mmol), and DEAD (1.8 equiv, 0.51 mL, 3.2 mmol) in THF (15 mL) at 0 °C. The crude was purified by silica gel column chromatography (heptane/EtOAc = 4:1), to afford **17a** as a white solid (615 mg, 81%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.72−7.64 (m, 4H), 7.51−7.47 (m, 2H), 7.33−7.27 (m, 3H), 5.52 (d, J = 4.8 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 3.81 (ddd, J = 10.1, 6.8, 4.7 Hz, 1H), 1.98−1.86 (m, 1H), 1.39 (s, 9H), 1.15 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.7, 156.1, 136.5, 134.5, 129.0, 128.9, 128.3, 128.1, 123.5, 88.2, 79.2, 60.0, 30.6, 28.5, 20.3, 18.5. HRMS (ESI) m/z: calcd for $C_{24}H_{28}N_2O_5$ $[M + Na]^+$, 447.1896; found, 447.1902.

***tert*-Butyl((1*S*,2*S*)-1-((1,3-dioxoisoindolin-2-yl)oxy)-3-methyl-1-phenylbutan-2-yl)carbamate (17b).** According to general procedure **TP4**, **14b** (1 equiv, 400 mg, 1.4 mmol) was treated NHPI (3 equiv, 700 mg, 4.3 mmol), PPh_3 (3.5 equiv, 1.3 g, 5 mmol), and DEAD (1.8 equiv, 0.79 mL, 5 mmol) in THF (15 mL) at 45 °C in an oil bath. The crude was purified by silica gel column chromatography (heptane/EtOAc = 5:1) to afford **17b** as a white solid (450 mg, 74%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.72−7.67 (m, 2H), 7.67−7.64 (m, 2H), 7.53−7.46 (m, 2H), 7.33−7.26 (m, 3H), 5.36 (d, J = 7.6 Hz, 1H), 4.50 (d, J = 10.7 Hz, 1H), 4.24−4.15 (m, 1H), 2.32−2.19 (m, 1H), 1.28 (s, 7H), 1.26 (s, 2H), 1.08 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.6, 155.6, 135.8, 134.4, 129.1, 128.9, 128.8, 128.1, 123.5, 89.3, 79.3, 57.7, 28.3, 28.1, 20.6, 16.4. HRMS (ESI) m/z: calcd for $C_{24}H_{28}N_2O_5$ $[M + Na]^+$, 447.1896; found, 447.1902.

(*S*)-*tert*-Butyl 2-((*R*)-((1,3-Dioxoisoindolin-2-yl)oxy)(phenyl)-methyl)pyrrolidine-1-carboxylate (18a). According to general procedure **TP4**, **15a** (1 equiv, 500 mg, 1.8 mmol) was treated with NHPI (1.5 equiv, 441 mg, 2.7 mmol), PPh_3 (1.8 equiv, 851 mg, 3.2 mmol), and DEAD (1.8 equiv, 0.51 mL, 3.2 mmol) in THF (15 mL) at 0 °C. The crude was purified by silica gel column chromatography (heptane/EtOAc = 4:1) to afford **18a** as a white solid (716 mg, 94%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.72−7.38 (m, 6H), 7.30−7.19 (m, 3H), 5.88 (s, 0.4H), 5.68 (s, 0.6H), 4.03 (m, 1H), 3.59−3.32 (m, 2H), 2.50−2.19 (m, 1H), 2.05 (m, 1H), 1.75 (m, 2H), 1.40 (s, 4H), 1.36 (s, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.6, 154.8, 134.4, 129.2, 128.6, 128.2, 127.8, 127.5, 123.5, 88.9, 77.4, 61.8, 46.8, 29.9, 22.8, 14.3. HRMS (ESI) m/z: calcd for $C_{24}H_{26}N_2O_5$ $[M + Na]^+$, 445.1740; found, 445.1746.

(5*S*,6*S*)-5-Methyl-6-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (19a). Step 1: *tert*-butyl((1*S*,2*S*)-1-(aminooxy)-1-phenylpropan-2-yl)carbamate (**39a**). According to general procedure **TP5**, **16a** (1 equiv, 400 mg, 1 mmol) in EtOH (15 mL) was treated with hydrazine hydrate (15 equiv, 0.73 mL, 15.1 mmol). The crude was purified by silica gel column chromatography (heptane/EtOAc = 2:1) to afford *tert*-butyl((1*S*,2*S*)-1-(aminooxy)-1-phenylpropan-2-yl)-carbamate **39a** as colorless oil (245 mg, 91%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.33 (m, 2H), 7.33−7.26 (m, 3H), 5.32 (s, 2H), 4.64−4.53 (m, 1H), 4.49 (d, J = 5.6 Hz, 1H), 3.99 (s, 1H), 1.40 (s, 9H), 1.05 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 155.5, 138.6, 128.6, 128.1, 127.5, 89.1, 79.4, 49.9, 28.5, 17.6.

Step 2: (1*S*,2*S*)-1-(aminooxy)-1-phenylpropan-2-amine dihydrochloride (**40a**). According to general procedure **TP6**, *tert*-butyl-((1*S*,2*S*)-1-(aminooxy)-1-phenylpropan-2-yl)carbamate **39a** (1 equiv, 100 mg, 0.38 mmol) was treated with a hydrogen chloride solution in dioxane (4 M, 5 mL) to afford (1*S*,2*S*)-1-(aminooxy)-1-phenylpropan-2-amine dihydrochloride **40a** as a white solid (89.8 mg, 100%). ^1H NMR (400 MHz, DMSO-d_6): δ 10.79 (s, br, 3H), 8.56 (s, br, 3H), 7.57−7.34 (m, 5H), 5.17 (d, J = 9.1 Hz, 1H), 3.58 (dt, J = 13.6, 6.8 Hz, 1H), 0.93 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 134.1, 129.7, 128.9, 128.3, 86.4, 49.3, 15.1.

Step 3: (5*S*,6*S*)-5-methyl-6-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (**19a**). According to general procedure **TP7**, the above (1*S*,2*S*)-1-(aminooxy)-1-phenylpropan-2-amine dihydrochloride **40a** (1 equiv, 50 mg, 0.21 mmol) was dissolved in MeCN (10 mL) and treated successively with TEA (4 equiv 116.2 μL, 0.84 mmol) and a solution of BrCN (1.1 equiv, 24.4 mg, 0.23 mmol) in MeCN (0.5 mL) to afford the title compound **19a** (28.4 mg, 71%) as a white solid after purification by reverse phase C18 column chromatography (MeCN/H_2O). Compound **19a** was recrystallized in MeCN at 4 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.39−7.27 (m, 5H), 6.10 (s, 1H), 4.39 (s, 2H), 3.82 (d, J = 8.5 Hz, 1H), 3.40−3.34 (m, 1H), 0.84 (d, J = 6.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 153.9, 138.4, 128.2, 128.1, 127.7, 80.9, 50.7, 17.6. HRMS (ESI) m/z: calcd for $C_{10}H_{14}N_3O$ $[M + H]^+$, 192.1137; found, 192.1139.

(5*S*,6*R*)-5-Methyl-6-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (19b). Step 1: *tert*-butyl((1*R*,2*S*)-1-(aminooxy)-1-phenylpropan-2-yl)carbamate (**39b**). According to general procedure **TP5**, **16b** (1 equiv, 400 mg, 1 mmol) in EtOH (15 mL) was treated with hydrazine hydrate (15 equiv, 0.73 mL, 15.1 mmol). The crude was purified by silica gel column chromatography (heptane/EtOAc = 2:1) to afford *tert*-butyl((1*R*,2*S*)-1-(aminooxy)-1-phenylpropan-2-yl)-carbamate **39b** as colorless oil (258 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.32 (m, 2H), 7.31−7.26 (m, 3H), 5.50 (s, br, 2H), 4.78−4.65 (m, 1H), 4.61 (d, J = 3.4 Hz, 1H), 4.15−4.00 (m, 1H), 1.45 (s, 9H), 0.98 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 155.6, 138.2, 128.5, 127.9, 127.1, 89.1, 79.3, 49.2, 28.6, 15.5.

Step 2: (1*R*,2*S*)-1-(aminooxy)-1-phenylpropan-2-amine dihydrochloride (**40b**). According to general procedure **TP6**, *tert*-butyl-((1*R*,2*S*)-1-(aminooxy)-1-phenylpropan-2-yl)carbamate **39b** (1 equiv, 100 mg, 0.38 mmol) was treated with a hydrogen chloride solution in dioxane (4 M, 5 mL) to afford (1*R*,2*S*)-1-(aminooxy)-1-phenylpropan-2-amine dihydrochloride **40b** as a white solid (88.9 mg, 99%). ^1H NMR (400 MHz, DMSO-d_6): δ 10.99 (s, br, 3H), 8.46 (s, br, 3H), 7.51−7.38 (m, 5H), 5.47 (d, J = 3.8 Hz, 1H), 3.59 (dt, J = 7.0, 3.1 Hz, 1H), 1.08 (d,

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J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 134.4, 129.0, 128.7, 126.9, 84.6, 50.0, 12.4.

Step 3: (5*S*,6*R*)-5-methyl-6-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (**19b**). According to general procedure **TP7**, the above (1*R*,2*S*)-1-(aminooxy)-1-phenylpropan-2-amine dihydrochloride **40b** (1 equiv, 50 mg, 0.21 mmol) was dissolved in MeCN (10 mL) and treated successively with TEA (4 equiv 116.2 μL, 0.84 mmol) and a solution of BrCN (1.1 equiv, 24.4 mg, 0.23 mmol) in MeCN (0.5 mL) to afford **19b** (27.6 mg, 69%) as a white solid after purification by reverse phase C18 column chromatography (MeCN/H_2O). ^1H NMR (400 MHz, DMSO-d_6): δ 7.36−7.22 (m, 5H), 6.25 (s, 1H), 4.55 (d, J = 3.0 Hz, 1H), 4.39 (s, 2H), 3.73−3.63 (m, 1H), 0.74 (d, J = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 154.0, 138.7, 127.9, 126.9, 125.8, 76.3, 48.4, 16.7. HRMS (ESI) m/z: calcd for $C_{10}H_{14}N_3O$ $[M + H]^+$, 192.1137; found, 191.1134.

(5*S*,6*S*)-5-Isopropyl-6-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (20a). Step 1: *tert*-butyl((1*S*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-yl)carbamate (**41a**). According to general procedure **TP5**, **17a** (1 equiv, 400 mg, 0.94 mmol) in EtOH (15 mL) was treated with hydrazine hydrate (15 equiv, 0.69 mL, 14.1 mmol). The crude was purified by silica gel column chromatography (heptane/EtOAc = 2:1) to afford *tert*-butyl((1*S*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-yl)carbamate **41a** as a white solid (266 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.29 (m, 5H), 5.29 (s, 2H), 4.72 (d, J = 10.4 Hz, 1H), 4.63 (d, J = 4.9 Hz, 1H), 3.63−3.53 (m, 1H), 1.79−1.69 (m, 1H), 1.34 (s, 9H), 1.00 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 156.1, 139.7, 128.6, 127.9, 127.0, 86.8, 79.0, 60.0, 30.1, 28.5, 20.3, 18.3.

Step 2: (1*S*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-amine dihydrochloride (**42a**). According to general procedure **TP6**, *tert*-butyl ((1*S*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-yl)carbamate **41a** (1 equiv, 100 mg, 0.34 mmol) was treated with a hydrogen chloride solution in dioxane (4 M, 5 mL) to afford (1*S*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-amine dihydrochloride **42a** as a white solid (85.3 mg, 94%). ^1H NMR (400 MHz, DMSO-d_6): δ 9.02 (s, br, 6H), 7.50−7.46 (m, 5H), 5.25 (d, J = 9.9 Hz, 1H), 3.44 (dd, J = 9.9, 2.5 Hz, 1H), 1.48−1.36 (m, 1H), 0.93 (d, J = 7.1 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 129.8, 129.8, 128.9, 128.4, 84.7, 58.1, 27.1, 19.1, 15.1.

Step 3: (5*S*,6*S*)-5-isopropyl-6-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (**20a**). According to general procedure **TP7**, the above (1*S*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-amine dihydrochloride **42a** (1 equiv, 50 mg, 0.19 mmol) was dissolved in MeCN (10 mL) and treated successively with TEA (4 equiv 104 μL, 0.75 mmol) and a solution of BrCN (1.1 equiv, 21.8 mg, 0.21 mmol) in MeCN (0.5 mL) to afford **20a** (30 mg, 73%) as a white solid after purification by reverse phase C18 column chromatography (MeCN/H_2O). ^1H NMR (400 MHz, DMSO-d_6): δ 7.43−7.28 (m, 5H), 5.86 (s, 1H), 4.44 (s, 2H), 4.09 (d, J = 8.2 Hz, 1H), 3.34−3.31 (m, 1H), 1.47−1.36 (m, 1H), 0.86 (d, J = 7.1 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 155.0, 138.8, 128.2, 128.0, 127.8, 77.0, 59.6, 28.2, 19.3, 15.1 HRMS (ESI) m/z: calcd for $C_{12}H_{18}N_3O$ $[M + H]^+$, 220.1450; found, 220.1454.

(5*S*,6*R*)-5-Isopropyl-6-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (20b). Step 1: *tert*-butyl ((1*R*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-yl)carbamate (**41b**). According to general procedure **TP5**, **17b** (1 equiv, 400 mg, 0.94 mmol) in EtOH (15 mL) was treated with hydrazine hydrate (15 equiv, 0.69 mL, 14.1 mmol). The crude was purified by silica gel column chromatography (heptane/EtOAc = 2:1) to afford *tert*-butyl((1*R*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-yl)carbamate **41b** as colorless oil (236 mg, 85%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.29 (m, 5H), 5.50 (s, 2H), 4.63 (d, J = 5.5 Hz, 1H), 4.31 (d, J = 10.8 Hz, 1H), 3.96−3.86 (m, 1H), 1.75−1.64 (m, 1H), 1.36 (s, 9H), 1.00 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 156.1, 138.5, 128.5, 128.0, 127.6, 87.4, 79.1, 57.7, 28.5, 28.4, 20.8, 17.9.

Step 2: (1*R*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-amine dihydrochloride (**42b**). According to general procedure **TP6**, *tert*-butyl((1*R*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-yl)carbamate **41b** (1 equiv, 100 mg, 0.34 mmol) was treated with a hydrogen chloride solution in dioxane (4 M, 5 mL) to afford (1*R*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-amine dihydrochloride **42b** as a white solid (90.8 mg, 94%). ^1H NMR (400 MHz, DMSO-d_6): δ 10.74 (s, br, 3H), 8.15 (s, br, 3H), 7.51−7.43 (m, 5H), 5.48 (d, J = 5.1 Hz, 1H), 3.51−3.48 (m, 1H), 1.82−1.75 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 129.2, 129.2, 128.8, 127.7, 83.5, 58.2, 26.8, 19.7, 17.7.

Step 3: (5*S*,6*R*)-5-isopropyl-6-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (**20b**). According to general procedure **TP7**, the above (1*R*,2*S*)-1-(aminooxy)-3-methyl-1-phenylbutan-2-amine dihydrochloride **42b** (1 equiv, 50 mg, 0.19 mmol) was dissolved in MeCN (10 mL) and treated successively with TEA (4 equiv 104 μL, 0.75 mmol) and a solution of BrCN (1.1 equiv, 21.8 mg, 0.21 mmol) in MeCN (0.5 mL) to afford **20b** (27.1 mg, 66%) as a white solid after purification by reverse phase C18 column chromatography (MeCN/H_2O). ^1H NMR (400 MHz, DMSO-d_6): δ 7.37−7.22 (m, 5H), 6.21 (d, J = 5.0 Hz, 1H), 4.61 (d, J = 3.6 Hz, 1H), 4.37 (s, 2H), 3.42 (dt, J = 5.1, 3.5 Hz, 1H), 1.35−1.26 (m, 1H), 0.78 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 154.3, 138.6, 127.9, 126.9, 125.9, 76.4, 57.3, 28.0, 21.1, 17.1. HRMS (ESI) m/z: calcd for $C_{12}H_{18}N_3O$ $[M + H]^+$, 220.1450; found, 220.1453.

(1*R*,8a*S*)-1-Phenyl-6,7,8,8a-tetrahydro-1*H*-pyrrolo[1,2-*d*][1,2,4]oxadiazin-4-amine (21). Step 1: (*S*)-*tert*-butyl 2-((*R*)-(aminooxy)(phenyl)methyl)pyrrolidine-1-carboxylate (**43**). According to general procedure **TP5**, **18a** (1 equiv, 400 mg, 0.95 mmol) in EtOH (15 mL) was treated with hydrazine hydrate (15 equiv, 0.69 mL, 14.2 mmol). The crude was purified by silica gel column chromatography (heptane/EtOAc = 2:1) to afford (*S*)-*tert*-butyl 2-((*R*)-(aminooxy)(phenyl)methyl)pyrrolidine-1-carboxylate **43** as colorless oil (269 mg, 97%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.27 (m, 5H), 5.43 (s, 2H), 5.01 (d, J = 44.7 Hz, 1H), 4.00 (d, J = 96.9 Hz, 1H), 3.61−3.26 (m, 2H), 2.13−1.70 (m, 3H), 1.63 (m, 1H), 1.52−1.46 (m, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.6, 140.0, 128.6, 127.6, 126.4, 88.1, 79.7, 62.0, 47.0, 28.7, 25.8, 23.7.

Step 2: *O*-((*R*)-phenyl((*S*)-pyrrolidin-2-yl)methyl)hydroxylamine dihydrochloride (**44**). According to general procedure **TP6**, (*S*)-*tert*-butyl 2-((*R*)-(aminooxy)(phenyl)methyl)pyrrolidine-1-carboxylate **43** (1 equiv, 100 mg, 0.34 mmol) was treated with a hydrogen chloride solution in dioxane (4 M, 5 mL) to afford *O*-((*R*)-phenyl((*S*)-pyrrolidin-2-yl)methyl)hydroxylamine dihydrochloride **44** as a white solid (97.1 mg, 96%). ^1H NMR (400 MHz, DMSO-d_6): δ 10.53 (s, br, 3H), 9.79 (s, br, 2H), 7.62−7.31 (m, 5H), 5.59 (d, J = 5.0 Hz, 1H), 3.95−3.76 (m, 1H), 3.24−3.06 (m, 2H), 2.04−1.71 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 135.1, 129.1, 128.8, 127.0, 83.2, 61.7, 45.4, 24.6, 23.5.

Step 3: (1*R*,8a*S*)-1-phenyl-6,7,8,8a-tetrahydro-1*H*-pyrrolo[1,2-*d*][1,2,4]oxadiazin-4-amine (**21**). According to general procedure **TP7**, the above *O*-((*R*)-phenyl((*S*)-pyrrolidin-2-yl)methyl) hydroxylamine dihydrochloride **44** (1 equiv, 50 mg, 0.19 mmol) in MeCN (10 mL) was treated successively with TEA (4 equiv 105 μL, 0.75 mmol) and a solution of BrCN (1.1 equiv, 22 mg, 0.21 mmol) in MeCN (0.5 mL) to afford **21** (38.5 mg, 94%) as a white solid after purification by reverse phase C18 column chromatography (MeCN/H_2O). Compound **21** was recrystallized in MeCN at 4 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.41−7.16 (m, 5H), 4.98 (d, J = 4.3 Hz, 1H), 4.79 (s, 2H), 3.67 (ddd, J = 9.5, 5.5, 4.4 Hz, 1H), 3.32−3.24 (m, 2H), 1.68−1.47 (m, 3H), 1.31−1.08 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 155.3, 138.7, 127.9, 127.2, 127.1, 75.4, 58.0, 47.4, 27.0, 22.5. HRMS (ESI) m/z: calcd for $C_{12}H_{16}N_3O$ $[M + H]^+$, 218.1293; found, 218.1288.

(*S*)-2-((*R*)-(Aminooxy)(phenyl)methyl)pyrrolidine-1-carbonitrile (22). To a solution of *O*-((*R*)-phenyl((*S*)-pyrrolidin-2-yl)-methyl)hydroxylamine dihydrochloride (1 equiv, 15 mg, 0.057 mmol) in MeCN (3 mL) at 0 °C, TEA (4 equiv, 31.4 μL, 0.23 mmol) was added dropwise and stirred for 5 min. Then, a solution of BrCN (1.1 equiv, 6.6 mg, 0.062 mmol) in MeCN (0.2 mL) was added dropwise, and stirring was maintained for an additional 30 min while the temperature was kept at 0 °C. The mixture was concentrated *in vacuo* and the crude was purified by reverse phase C18 column chromatography (MeOH/H_2O) to afford **22** (8.4 mg, 68%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 7.39−7.30 (m, 5H), 6.05 (s,

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2H), 4.54 (d, J = 4.0 Hz, 1H), 3.92 (ddd, J = 7.7, 5.2, 4.1 Hz, 1H), 3.28−3.12 (m, 2H), 1.81−1.63 (m, 3H), 1.42−1.32 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 138.7, 128.1, 127.6, 127.4, 117.0, 86.1, 64.2, 51.2, 26.2, 23.9. HRMS (ESI) m/z: calcd for $C_{12}H_{16}N_3O$ $[M + H]^+$, 218.1293; found, 218.1289.

***tert*-Butyl(3-methyl-2-oxobut-3-en-1-yl)carbamate (26).** According to general procedure **TP2**, **2** (1 equiv, 2 g, 9.2 mmol) in THF (10 mL) was treated with isopropenyl magnesium bromide (3.5 equiv, 0.5 M, 64.2 mL, 32.1 mmol) to afford **26** as colorless oil without further purification (1.81 g, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ 5.99 (s, 1H), 5.83 (q, J = 1.4 Hz, 1H), 5.36 (s, 1H), 4.35 (d, J = 4.7 Hz, 2H), 1.90 (t, J = 1.2 Hz, 3H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 196.1, 155.9, 142.5, 125.5, 79.9, 46.7, 28.5, 17.5.

***tert*-Butyl(2-hydroxy-3-methylbut-3-en-1-yl)carbamate (27).** According to general procedure **TP3** (method 5), **26** (1 equiv, 1 g, 5 mmol) was dissolved in MeOH (30 mL) and treated with trichlorocerium heptahydrate (1.6 equiv, 3 g, 8 mmol) and $NaBH_4$ (1.5 equiv, 0.28 g, 7.5 mmol). The crude was purified by silica gel column chromatography (heptane/EtOAc = 2:1) to afford **27** as colorless oil (0.84 g, 83%). ^1H NMR (400 MHz, $CDCl_3$): δ 5.04 (dt, J = 1.9, 1.0 Hz, 1H), 4.96−4.83 (m, 2H), 4.14 (dt, J = 7.3, 3.4 Hz, 1H), 3.44−3.31 (m, 1H), 3.11 (ddd, J = 13.5, 7.5, 5.3 Hz, 1H), 2.64 (s, br, 1H), 1.74 (t, J = 1.2 Hz, 3H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 157.0, 145.2, 111.8, 79.8, 75.1, 45.2, 28.5, 18.7. HRMS (ESI) m/z: calcd for $C_{10}H_{19}NNaO_3$ $[M + Na]^+$, 224.1263; found, 224.1259.

***tert*-Butyl(2-((1,3-dioxoisoindolin-2-yl)oxy)-3-methylbut-3-en-1-yl)carbamate (28).** According to general procedure **TP4**, **27** (1 equiv, 500 mg, 2.5 mmol) was dissolved in THF (15 mL) and treated with NHPI (1.5 equiv, 608 mg, 3.7 mmol), PPh_3 (1.8 equiv, 1.2 g, 4.5 mmol), and DEAD (1.8 equiv, 0.7 mL, 4.5 mmol) at rt. The crude was purified by silica gel column chromatography (heptane/EtOAc = 4:1) to afford **28** as colorless oil (818 mg, 95%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.86−7.66 (m, 4H), 5.42 (s, 1H), 5.09−4.97 (m, 2H), 4.70−4.55 (m, 1H), 3.55−3.38 (m, 2H), 1.92 (s, 3H), 1.46 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.9, 156.2, 140.3, 134.7, 128.9, 123.7, 117.7, 90.7, 79.6, 42.0, 28.5, 17.9. HRMS (ESI) m/z: calcd for $C_{18}H_{22}N_2O_5$ $[M + Na]^+$, 369.1427; found, 369.1436.

***tert*-Butyl(2-(aminooxy)-3-methylbut-3-en-1-yl)carbamate (29).** According to general procedure **TP5**, **28** (1 equiv, 400 mg, 1.16 mmol) was dissolved in EtOH (15 mL) and treated with hydrazine hydrate (15 equiv, 0.84 mL, 17.32 mmol). The crude was purified by silica gel column chromatography (heptane/EtOAc = 1:1) to afford **29** as colorless oil (245 mg, 98%). ^1H NMR (400 MHz, $CDCl_3$): 5.31 (s, br, 2H), 5.04−4.99 (m, 2H), 4.85 (s, 1H), 3.96 (dd, J = 7.7, 3.9 Hz, 1H), 3.46−3.34 (m, 1H), 3.14−3.01 (m, 1H), 1.71 (s, 3H), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 156.1, 142.3, 113.9, 87.2, 79.4, 42.3, 28.5, 18.6.

2-(Aminooxy)-3-methylbut-3-en-1-amine Dihydrochloride (30). According to general procedure **TP6**, **29** (1 equiv, 100 mg, 0.46 mmol) was treated with a hydrogen chloride solution in dioxane (4 M, 5 mL) to afford **30** as a white solid (86.6 mg, 99%). ^1H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, br, 3H), 8.35 (s, br, 3H), 5.24 (s, 1H), 5.22−5.19 (m, 1H), 4.79 (dd, J = 8.2, 4.0 Hz, 1H), 3.09−2.98 (m, 2H), 1.72 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 138.2, 118.0, 83.5, 17.4. ($-CH_2-NH_2-$ signal covered by DMSO-d_6).

6-(Prop-1-en-2-yl)-5,6-dihydro-4*H*-1,2,4-oxadiazin-3-amine (31). According to general procedure **TP7**, **30** (1 equiv, 50 mg, 0.26 mmol) in MeCN (10 mL) was treated successively with TEA (4 equiv 147 μL, 1.1 mmol) and a solution of BrCN (1.1 equiv, 30.8 mg, 0.29 mmol) in MeCN (0.5 mL) to afford **31** (29.9 mg, 80%) as a white solid after purification by reverse phase C18 column chromatography (MeCN/H_2O). ^1H NMR (400 MHz, DMSO-d_6): δ 6.08 (s, 1H), 4.94 (dt, J = 2.2, 1.0 Hz, 1H), 4.89 (t, J = 1.9 Hz, 1H), 4.48 (s, 2H), 3.74 (dd, J = 9.5, 3.1 Hz, 1H), 3.28 (dd, J = 11.2, 3.2 Hz, 1H), 3.02 (dd, J = 11.2, 9.5 Hz, 1H), 1.70 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 154.1, 142.4, 112.0, 74.3, 43.5, 19.0. HRMS (ESI) m/z: calcd for $C_6H_{12}N_3O$ $[M + H]^+$, 142.0980; found, 142.0979.

2-(3-Methylbut-2-en-1-yl)-6-(prop-1-en-2-yl)-5,6-dihydro-2*H*-1,2,4-oxadiazin-3-amine (32). **31** (1 equiv, 10 mg, 0.071 mmol) and TEA (2 equiv, 19.7 μL, 0.142 mmol) were dissolved in MeCN (0.6 mL), followed by the addition of prenyl bromide (1 equiv, 8.3 μL, 0.071 mmol). The resulting mixture was stirred at rt for 16 h and then concentrated *in vacuo*. The crude was purified by reverse phase C18 column chromatography (MeCN/H_2O) to afford **32** as a white solid (11 mg, 74%). ^1H NMR (400 MHz, DMSO-d_6): δ 7.65 (s, 2H), 5.32−5.19 (m, 1H), 5.10 (t, J = 1.7 Hz, 1H), 5.05 (q, J = 1.2 Hz, 1H), 4.46 (dd, J = 10.1, 3.3 Hz, 1H), 4.35 (dd, J = 15.9, 7.2 Hz, 1H), 4.17 (dd, J = 15.9, 7.1 Hz, 1H), 3.52 (dt, J = 12.5, 3.6 Hz, 1H), 3.36−3.29 (m, 1H), 1.77−1.71 (m, 6H), 1.68 (d, J = 1.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 153.3, 138.8, 138.5, 116.1, 115.1, 77.8, 48.9, 42.6, 25.4, 18.8, 17.9. ^1H NMR (400 MHz, MeOD-d_4): δ 5.36−5.29 (m, 1H), 5.16−5.11 (m, 1H), 5.09 (q, J = 1.1 Hz, 1H), 4.48 (dd, J = 10.0, 3.4 Hz, 1H), 4.34 (dd, J = 15.9, 7.0 Hz, 1H), 4.21 (dd, J = 15.9, 7.5 Hz, 1H), 3.54 (dd, J = 12.4, 3.5 Hz, 1H), 3.42 (dd, J = 12.4, 10.1 Hz, 1H), 1.81 (t, J = 1.2 Hz, 3H), 1.80 (d, J = 1.3 Hz, 3H), 1.76 (d, J = 1.3 Hz, 3H). HRMS (ESI) m/z: calcd for $C_{11}H_{20}N_3O$ $[M + H]^+$, 210.1606; found, 210.1606.

2-(3-Methylbut-2-en-1-yl)-6-(prop-1-en-2-yl)-5,6-dihydro-2*H*-1,2,(^15*N*)4-oxadiazin-3-amine (33). Step 1: *tert*-butyl (2-(methoxy(methyl)amino)-2-oxoethyl)(^{15}N)carbamate (**45**). According to general procedure **TP1**, ^{15}N-Boc glycine (1 equiv, 500 mg, 2.84 mmol) in DCM (15 mL) was treated with CDI (1.5 equiv, 690.3 mg, 4.26 mmol), TEA (1.5 equiv, 0.59 mL, 4.26 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (1.5 equiv, 415.3 g, 4.26 mmol) to afford Weinreb amide of ^{15}N-Boc glycine **45** as a white solid (543 mg, 87%) without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (t, J = 5.0 Hz, 0.5H), 5.14 (t, J = 4.9 Hz, 0.5H), 4.08 (d, J = 4.8 Hz, 2H), 3.71 (s, 3H), 3.20 (s, 3H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 170.4, 156.1, 155.9, 79.8, 61.6, 41.9, 41.8, 32.5, 28.5. ^{15}N NMR (51 MHz, $CDCl_3$): δ 73.3.

Step 2: *tert*-butyl(3-methyl-2-oxobut-3-en-1-yl)(^{15}N)carbamate (**46**). According to general procedure **TP2**, the above Weinreb amide of ^{15}N-Boc glycine **45** (1 equiv, 543 mg, 2.48 mmol) in THF (5 mL) was treated with isopropenyl magnesium bromide (3.5 equiv, 0.5 M, 17.3 mL, 8.67 mmol). The crude was purified by silica gel column chromatography (heptane/EtOAc = 5:1) to afford *tert*-butyl(3-methyl-2-oxobut-3-en-1-yl)(^{15}N)carbamate (**46**) as colorless oil (466 mg, 94%). ^1H NMR (400 MHz, $CDCl_3$): δ 5.98 (s, 1H), 5.82 (q, J = 1.6 Hz, 1H), 5.47 (t, J = 4.7 Hz, 0.5H), 5.24 (t, J = 4.7 Hz, 0.5H), 4.35 (d, J = 4.6 Hz, 2H), 1.91−1.87 (m, 3H), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 196.1, 156.0, 155.7, 142.4, 125.5, 79.8, 46.8, 46.6, 28.5, 17.5. ^{15}N NMR (51 MHz, $CDCl_3$): δ 72.4.

Step 3: *tert*-butyl(2-hydroxy-3-methylbut-3-en-1-yl)(^{15}N)carbamate (**47**). According to general procedure **TP3** (method 5), the above-described *tert*-butyl(3-methyl-2-oxobut-3-en-1-yl)(^{15}N)carbamate **46** (1 equiv, 590 mg, 2.95 mmol) in MeOH (15 mL) was treated with trichlorocerium heptahydrate (1.6 equiv, 1.76 g, 4.71 mmol) and $NaBH_4$ (1.5 equiv, 167.2 mg, 4.42 mmol). The crude was purified by silica gel column chromatography (heptane/EtOAc = 2:1) to afford *tert*-butyl(2-hydroxy-3-methylbut-3-en-1-yl)(^{15}N)carbamate **47** as colorless oil (587 mg, 98%). ^1H NMR (400 MHz, $CDCl_3$): δ 5.11−4.98 (m, 1.5H), 4.91 (dd, J = 2.5, 1.4 Hz, 1H), 4.84−4.77 (m, 0.5H), 4.18−4.08 (m, 1H), 3.45−3.29 (m, 1H), 3.19−3.03 (m, 1H), 2.70 (s, 1H), 1.74 (t, J = 1.2 Hz, 3H), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 157.1, 156.8, 145.2, 111.8, 79.8, 75.0, 45.2, 45.1, 28.5, 18.7. ^{15}N NMR (51 MHz, $CDCl_3$): δ 78.4.

Step 4: *tert*-butyl(2-((1,3-dioxoisoindolin-2-yl)oxy)-3-methylbut-3-en-1-yl)(^{15}N)carbamate (**48**). According to general procedure **TP4**, the above-described *tert*-butyl(2-hydroxy-3-methylbut-3-en-1-yl)-(^{15}N)carbamate **47** (1 equiv, 500 mg, 2.47 mmol) was dissolved in THF (15 mL) and treated with NHPI (1.5 equiv, 604.9 mg, 3.71 mmol), PPh_3 (1.8 equiv, 1.17 g, 4.45 mmol), and DEAD (1.8 equiv, 0.7 mL, 4.45 mmol) at rt. The crude was purified by silica gel column chromatography (heptane/EtOAc = 4:1) to afford *tert*-butyl(2-((1,3-dioxoisoindolin-2-yl)oxy)-3-methylbut-3-en-1-yl)(^{15}N)carbamate **48** as colorless oil (747 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.82−7.78 (m, 2H), 7.76−7.72 (m, 2H), 5.54 (t, J = 5.8 Hz, 0.5H), 5.31 (t, J = 5.8 Hz, 0.5H), 5.04 (dt, J = 1.6, 0.9 Hz, 1H), 5.02 (q, J = 1.6 Hz, 1H), 4.68−4.57 (m, 1H), 3.54−3.42 (m, 2H), 1.91 (dd, J = 1.5, 0.9 Hz, 3H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.9, 156.3,

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156.0, 140.3, 134.6, 129.0, 123.7, 117.7, 90.6, 79.6, 42.1, 41.9, 28.5, 17.9. ^{15}N NMR (51 MHz, $CDCl_3$): δ 77.1.

Step 5: *tert*-butyl(2-(aminooxy)-3-methylbut-3-en-1-yl)(^{15}N)-carbamate (**49**). According to general procedure **TP5**, the above-described *tert*-butyl(2-((1,3-dioxoisoindolin-2-yl)oxy)-3-methylbut-3-en-1-yl)(^{15}N)carbamate **48** (1 equiv, 400 mg, 1.15 mmol) in EtOH (15 mL) was treated with hydrazine hydrate (15 equiv, 0.84 mL, 17.27 mmol). The crude was purified by silica gel column chromatography (heptane/EtOAc = 2:1) to afford *tert*-butyl(2-(aminooxy)-3-methylbut-3-en-1-yl)(^{15}N)carbamate **49** as colorless oil (210 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (s, 2H), 5.06−4.99 (m, 2H), 4.95 (dd, J = 7.6, 4.6 Hz, 0.5H), 4.72 (dd, J = 7.6, 4.5 Hz, 0.5H), 4.00−3.94 (m, 1H), 3.48−3.36 (m, 1H), 3.12−3.03 (m, 1H), 1.72 (t, J = 1.2 Hz, 3H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.2, 155.9, 142.3, 114.0, 87.2, 79.5, 42.3, 42.2, 28.5, 18.6. ^{15}N NMR (51 MHz, $CDCl_3$): δ 77.9.

Step 6: 2-(aminooxy)-3-methylbut-3-en-1-(^{15}N)amine dihydrochloride (**50**). According to general procedure **TP6**, the above-described *tert*-butyl(2-(aminooxy)-3-methylbut-3-en-1-yl)(^{15}N)-carbamate **49** (1 equiv, 100 mg, 0.46 mmol) was treated with a solution of hydrochloride in dioxane (4 M, 5 mL) to afford 2-(aminooxy)-3-methylbut-3-en-1-(^{15}N)amine dihydrochloride **50** as a white solid (86.2 mg, 99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (s, br, 3H), 8.38 (s, br, 3H), 5.25−5.23 (m, 1H), 5.22−5.19 (m, 1H), 4.83−4.75 (m, 1H), 3.11−2.95 (m, 2H), 1.72 (t, J = 1.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 138.2, 118.1, 83.5, 17.4. (−CH_2−NH_2− signal covered by DMSO-d_6) ^{15}N NMR (51 MHz, DMSO-d_6): δ 31.9.

Step 7: 6-(prop-1-en-2-yl)-5,6-dihydro-4*H*-1,2,(^{15}N)4-oxadiazin-3-amine (**51**). According to general procedure **TP7**, the above-described 2-(aminooxy)-3-methylbut-3-en-1-(^{15}N)amine dihydrochloride **50** (1 equiv, 50 mg, 0.26 mmol) in MeCN (10 mL) was treated successively with TEA (4 equiv 146 μL, 1.05 mmol) and a solution of BrCN (1.1 equiv, 30.65 mg, 0.29 mmol) in MeCN (0.5 mL) to afford 6-(prop-1-en-2-yl)-5,6-dihydro-4*H*-1,2,(^{15}N)4-oxadiazin-3-amine **51** (31.8 mg, 85%) as a white solid after purification by reverse phase C18 column chromatography (MeCN/H_2O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.11 (s, 0.5H), 5.88 (s, 0.5H), 4.94 (s, 1H), 4.89 (d, J = 1.9 Hz, 1H), 4.40 (s, 2H), 3.72 (dd, J = 9.6, 3.0 Hz, 1H), 3.28 (dd, J = 11.5, 3.2 Hz, 1H), 3.01 (t, J = 10.3 Hz, 1H), 1.69 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 154.2, 154.0, 142.5, 111.9, 74.2, 43.6, 43.5, 19.0. ^{15}N NMR (51 MHz, DMSO-d_6): δ 60.8.

Step 8: 2-(3-methylbut-2-en-1-yl)-6-(prop-1-en-2-yl)-5,6-dihydro-2*H*-1,2,(^{15}N)4-oxadiazin-3-amine (**33**). 6-(Prop-1-en-2-yl)-5,6-dihydro-4*H*-1,2,(^{15}N)4-oxadiazin-3-amine **51** (1 equiv, 10 mg, 0.07 mmol) and TEA (2 equiv, 19.6 μL, 0.141 mmol) were dissolved in MeCN (0.6 mL) followed by the addition of prenyl bromide (1 equiv, 8.3 μL, 0.07 mmol). The resulting mixture was stirred at rt for 16 h and concentrated *in vacuo*. The crude was purified by reverse phase C18 column chromatography (MeCN/H_2O) to afford **33** as a white solid (12 mg, 81%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 2H), 5.30−5.22 (m, 1H), 5.09 (t, J = 1.7 Hz, 1H), 5.04 (q, J = 1.2 Hz, 1H), 4.44 (dd, J = 10.1, 3.3 Hz, 1H), 4.34 (dd, J = 15.9, 7.2 Hz, 1H), 4.16 (dd, J = 15.9, 7.1 Hz, 1H), 3.54−3.47 (m, 1H), 3.36−3.28 (m, 1H), 1.76−1.71 (m, 6H), 1.68 (d, J = 1.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 153.4, 153.2, 138.7, 138.6, 116.2, 115.0, 77.7, 48.9, 42.7, 42.7, 25.4, 18.8, 17.9. ^{15}N NMR (51 MHz, DMSO-d_6): δ 83.6 ^{1}H NMR (400 MHz, MeOD-d_4): δ 5.37−5.29 (m, 1H), 5.14 (dd, J = 1.7, 0.9 Hz, 1H), 5.09 (q, J = 1.1 Hz, 1H), 4.48 (dd, J = 10.1, 3.5 Hz, 1H), 4.34 (dd, J = 15.9, 7.0 Hz, 1H), 4.22 (dd, J = 15.9, 7.5 Hz, 1H), 3.55 (ddd, J = 12.4, 3.5, 1.2 Hz, 1H), 3.42 (dd, J = 12.4, 10.1 Hz, 1H), 1.81 (t, J = 1.3 Hz, 3H), 1.80 (d, J = 1.3 Hz, 3H), 1.76 (d, J = 1.3 Hz, 3H). HRMS (ESI) m/z: calcd for $C_{11}H_{20}N_2{}^{15}NO$ [M + H]$^+$, 211.1577; found, 211.1578.

***tert*-Butyl 3-Amino-6-(prop-1-en-2-yl)-5,6-dihydro-2*H*-1,2,4-oxadiazine-2-carboxylate (34).** TEA (2 equiv, 39.4 μL, 0.283 mmol) was added to a solution of **31** (1 equiv, 20 mg, 0.142 mmol) and Boc_2O (1.1 equiv, 34 mg, 0.156 mmol) in DCM (1 mL). The mixture was stirred at rt for 16 h and concentrated in vacuo. The crude was purified by reverse phase C18 column chromatography (MeOH/H_2O) to afford **34** as a white solid (31 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (s, 2H), 5.03 (q, J = 1.1 Hz, 1H), 5.01−4.99 (m, 1H), 4.11 (dd, J = 10.3, 3.0 Hz, 1H), 3.81 (dd, J = 12.0, 3.1 Hz, 1H), 3.51 (dd, J = 12.0, 10.3 Hz, 1H), 1.79 (t, J = 1.3 Hz, 3H), 1.50 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 151.8, 150.7, 140.6, 114.2, 84.0, 76.6, 48.4, 28.2, 19.2. HRMS (ESI) m/z: calcd for $C_{11}H_{19}N_3O_3$ [M − Boc + H]$^+$, 142.0980; found, 142.0980.

***tert*-Butyl 3-((3-Methylbut-2-en-1-yl)amino)-6-(prop-1-en-2-yl)-5,6-dihydro-2*H*-1,2,4-oxadiazine-2-carboxylate (35).** A solution of NaH (4 equiv, 4.61 mg, 0.182 mmol) in THF (0.4 mL) was slowly added to a solution of **34** (1 equiv, 11 mg, 0.046 mmol) in THF (0.7 mL) under Ar at rt. The mixture was stirred at 60 °C in an oil bath for 1 h, and then a solution of prenyl bromide (4 equiv, 21.4 μL, 0.182 mmol) in THF (0.1 mL) was added dropwise and stirred at 60 °C in an oil bath for an additional 4 h. The reaction mixture was concentrated *in vacuo* and purified by reverse phase C18 column chromatography (MeCN/H_2O) to afford **35** as a white solid (10.7 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 1H), 5.34−5.24 (m, 1H), 5.07−4.93 (m, 2H), 4.11 (d, J = 10.6 Hz, 1H), 3.81 (dd, J = 11.9, 3.1 Hz, 1H), 3.70−3.60 (m, 2H), 3.57−3.48 (m, 1H), 1.81 (s, 3H), 1.72 (s, 3H), 1.66 (s, 3H), 1.51 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.3, 150.5, 141.0, 138.9, 120.9, 113.7, 83.7, 76.5, 48.8, 39.9, 29.9, 28.3, 25.8, 19.2. HRMS (ESI) m/z: calcd for $C_{16}H_{27}N_3O_3$ [M − Boc + H]$^+$, 210.1606; found, 210.1615.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01764.

NMR studies about BrCN-mediated cyclization, diastereoselective reduction of ketone by DIBAL-H ^{1}H, ^{13}C NMR spectra, Mitsunobu reaction with the inversion of configuration, synthetic pathways and NMR characterization of cpd **22**, **33**, NMR and HRMS comparison between **1** and data from Barrosa et al.,[14] experimental procedures for log *D* determination and metabolic stabilities and ^{1}H and ^{13}C NMR for all new compounds (PDF)

FAIR Data includes the primary NMR FID files for compounds [**1**, **8**, **19a**, **19b**, **20a**, **20b**, and **21**] (ZIP)

Accession Codes

CCDC 2007599−2007601 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Frédéric Bihel − *Laboratoire d'Innovation Thérapeutique, Labex Médalis, UMR7200, CNRS, Université de Strasbourg, Faculty of Pharmacy, 67401 Illkirch-Graffenstaden, France;* orcid.org/0000-0002-4122-0929; Phone: +33 (0) 368854130; Email: fbihel@unistra.fr

Authors

Shuang-Qi Tang − *Laboratoire d'Innovation Thérapeutique, Labex Médalis, UMR7200, CNRS, Université de Strasbourg, Faculty of Pharmacy, 67401 Illkirch-Graffenstaden, France*

Maeva Leloire − *Laboratoire d'Innovation Thérapeutique, Labex Médalis, UMR7200, CNRS, Université de Strasbourg, Faculty of Pharmacy, 67401 Illkirch-Graffenstaden, France*

Séverine Schneider − *Laboratoire d'Innovation Thérapeutique, Labex Médalis, UMR7200, CNRS, Université de Strasbourg, Faculty of Pharmacy, 67401 Illkirch-Graffenstaden, France*

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Julie Mohr − *Laboratoire d'Innovation Thérapeutique, Labex Médalis, UMR7200, CNRS, Université de Strasbourg, Faculty of Pharmacy, 67401 Illkirch-Graffenstaden, France*
Jacques Bricard − *Laboratoire d'Innovation Thérapeutique, Labex Médalis, UMR7200, CNRS, Université de Strasbourg, Faculty of Pharmacy, 67401 Illkirch-Graffenstaden, France*
Patrick Gizzi − *CBIS, UMS3286, CNRS, Université de Strasbourg, ESBS, Pôle API, 67400 Illkirch-Graffenstaden, France*
Delphine Garnier − *Plateforme d'Analyse Chimique de Strasbourg-Illkirch, Faculty of Pharmacy, Université de Strasbourg, 67401 Illkirch-Graffenstaden, France*
Martine Schmitt − *Laboratoire d'Innovation Thérapeutique, Labex Médalis, UMR7200, CNRS, Université de Strasbourg, Faculty of Pharmacy, 67401 Illkirch-Graffenstaden, France;* orcid.org/0000-0002-8723-9502

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c01764

Notes

The authors declare no competing financial interest.

Deposition Numbers CCDC 2007599−2007601 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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