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Carbamoyl Anion Addition to Nitrones

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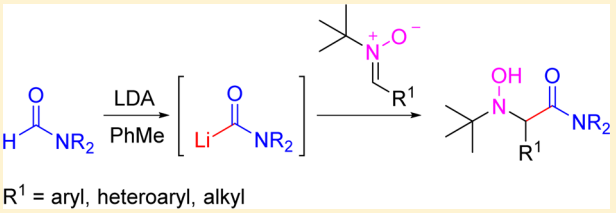
Supporting Information

ABSTRACT: The addition of carbamoyl anions derived from *N*,*N*-disubstituted formamides and LDA to *N*-*tert*-butyl nitrones is described. The reaction was demonstrated with a variety of formamides and nitrones and provided a direct route to α-(*N*-hydroxy)amino amides. The use of a *tert*-leucinol derived chiral auxiliary on the nitrone provided products in good diastereoselectivity. Derivatization of the products by *tert*-butyl deprotection or *N*-deoxygenation was demonstrated.



The α-(*N*-hydroxy)amino amide moiety is present in many pharmaceutically important synthetic and naturally occurring peptides (Figure 1).[1] The natural product azinothricin (**1**) and related cyclodepsipeptides have demonstrated powerful antibiotic and antitumor activities.[2] Callyspongidipeptide A (**2**) is a marine sponge derived diketopiperazine.[3] Synthetic *N*-hydroxylated peptides such as **3** have been developed as HIV protease inhibitors.[4]

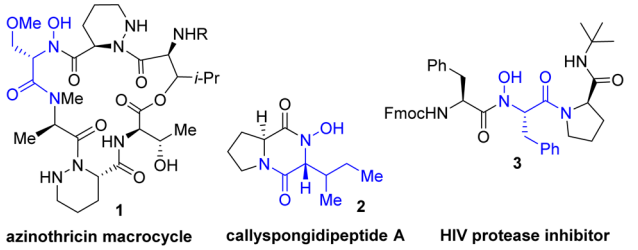
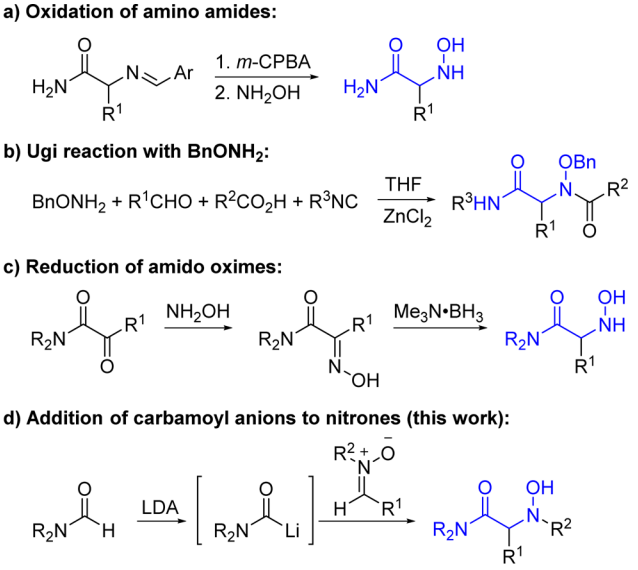


Figure 1. Selected bioactive natural and synthetic products containing α-(*N*-hydroxy)amino amides.

Several procedures have been employed for the synthesis of α-(*N*-hydroxy)amino amides (Scheme 1). These methods include the *N*-oxidation of amino amides (method a) via Schiff base intermediates,[5] the Ugi reaction employing O-protected hydroxylamine derivatives (method b),[6] and the reduction of α-ketoamide derived oximes (method c).[7] We recently reported the addition of carbamoyl anions to *N*-sulfinyl imines to provide *N*-sulfinyl α-aminoamide products in high diastereoselectivity.[8] Carbamoyl anions are readily generated by deprotonation of *N*,*N*-disubstituted formamides with strong bases such as LDA.[9] Their synthesis and utility in additions to a variety of electrophiles was described in the pioneering reports of Schöllkopf, Seebach, and Enders.[10] Herein we report that carbamoyl anions react with aldehyde derived nitrones to provide α-(*N*-hydroxy)amino amides (method d).

Scheme 1. Synthesis of α-(*N*-Hydroxy)amino Amides



Our initial work was focused on the addition of carbamoyl anions to *N*-alkyl aldimines, specifically derivatives of chiral α-arylethylamines. The addition of *N*,*N*-diisopropylformamide to imines **4a**–**c** proceeded to give the desired products **5a**–**c** in good yields and with diastereoselectivities as high as 90:10 for **5b** (Scheme 2).[11] Unfortunately, the use of less bulky formamides such as *N*,*N*-dimethylformamide, *N*,*N*-diethylformamide, *N*,*N*-dibutylformamide, 4-formylmorpholine, and 1-formylpyrrolidine gave little to no product. Inclusion of Lewis acid additives such as $ZnBr_2$, $Cu(OTf)_2$, or $BF_3{\cdot}OEt_2$ did not lead to any improvement. This lack of reactivity can be attributed to both the lesser stability of carbamoyl anions

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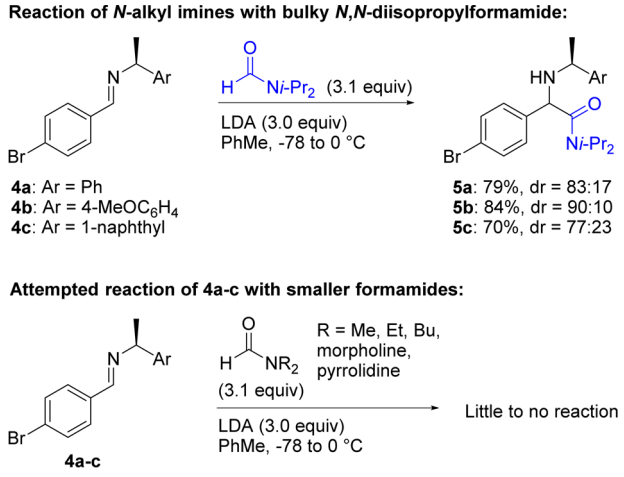
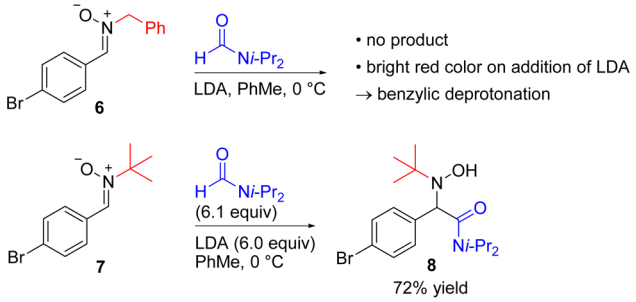
Scheme 2. Carbamoyl Anion Addition to *N*-Alkyl Imines



derived from smaller formamides, which undergo dimerization in the absence of a suitably reactive electrophile, and the relatively low electrophilicity of *N*-alkyl imines **4a**–**c**.[12] The bulky *N*,*N*-diisopropylcarbamoyllithium is comparatively stable and its addition to **4a**–**c** is competitive relative to dimerization.

It is known that nitrones have increased reactivity toward nucleophilic attack relative to the corresponding *N*-alkyl imines.[13] We hoped that this increased electrophilicity could facilitate the addition of a broad spectrum of formamides to nitrones. To test the reaction feasibility, *N*-benzyl nitrone **6** was reacted with *N*,*N*-diisopropylformamide and LDA in toluene at 0 °C (Scheme 3). No product formation was observed. On

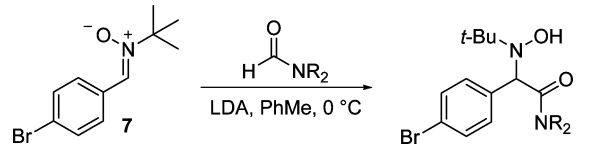
Scheme 3. Reactions with *N*-Benzyl and *N*-*tert*-Butyl Nitrones

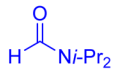
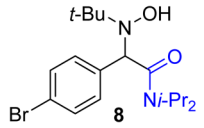
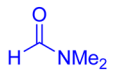
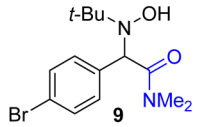
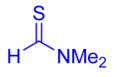
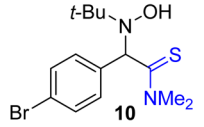
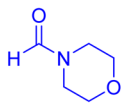
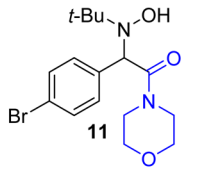
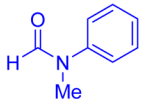
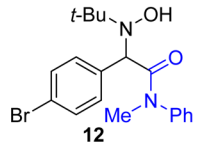


addition of LDA, the reaction mixture became bright red in color. Since carbamoyllithium formation is not accompanied by such color changes, we suspected that under the strongly basic reaction conditions benzylic deprotonation of the nitrone occurred. A similar competitive benzylic deprotonation of an *N*-benzyl nitrone with MeLi was observed by Coates and Chang.[13a] In order to prevent this side reaction, *N*-*tert*-butyl nitrone **7**, bearing no protons α to the nitrogen, was subjected to the same conditions.[14] In this case, the desired reaction proceeded smoothly to give amide **8** in 72% isolated yield. The use of 6 equiv of carbamoyl anion proved necessary to achieve complete conversion of the nitrone.

The reaction of nitrone **7** with a variety of formamides was explored (Table 1). In contrast to the *N*-alkyl imines **4a**–**c**, **7** reacted with both large and small formamides. The reaction with DMF (entry 2) gave the adduct **9** in 67% yield after purification by chromatography. Alternatively, **9** could be

Table 1. Scope of Carbamoyl Anion Addition to Nitrone 7[a]



entry	formamide	product	yield[b]
1		 **8**	72%
2[c]		 **9**	67% (79%)[d]
3		 **10**	59%
4		 **11**	70%
5		 **12**	76%

[a]Typical reaction conditions: 1 equiv nitrone, 6.1 equiv formamide, 6.0 equiv LDA, PhMe, 0 °C. [b]Isolated yield. [c]LiTMP used instead of LDA. [d]Isolated yield of oxalic acid salt.

isolated as its crystalline oxalate salt in 79% yield by treatment of the crude reaction mixture with oxalic acid. The reactions with DMF employed LiTMP as base instead of LDA to minimize transformylation. The addition of *N*,*N*-dimethylthioformamide (entry 3) gave access to the uncommon α-(*N*-hydroxy)amino thioamide moiety. The use of a cyclic formamide (entry 4) and an *N*-alkyl-*N*-aryl formamide (entry 5) were also possible.

The scope of the reaction was next explored with respect to variation in nitrone structure (Table 2). The *ortho*-substituted aryl nitrone **13** reacted with *N*,*N*-diethylformamide to give adduct **14** in 88% yield (entry 1). The electron rich aryl nitrone **15** reacted smoothly, giving adduct **16** in 72% yield (entry 2). Heterocyclic (entries 3 and 4) and aliphatic (entries 5 and 6) nitrones were amenable to carbamoyl anion addition. The hindered pivaldehyde derived nitrone **21** gave α-(*N*-hydroxy)-amino amide **22** in 56% yield (entry 5). Finally, the enolizable nitrone **23** could be converted to amide **24** (entry 6).

The use of a chiral nitrone was examined to see if the carbamoyl anion addition could occur in a diastereoselective manner. The synthesis of chiral nitrone **28** is outlined in Scheme 4. Thus, *O*-benzyl *R*-*tert*-leucinol **25**[15] was treated with benzoyl peroxide to give the *O*-benzoyl hydroxylamine **26**.[16] Subsequent exposure to NH_4OH caused debenzoylation to yield hydroxylamine **27**.[16] Condensation of **27** with 4-bromobenzaldehyde provided the chiral nitrone **28**.

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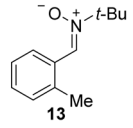
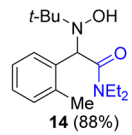
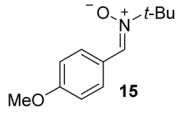
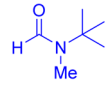
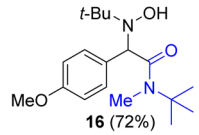
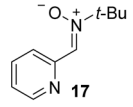
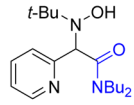
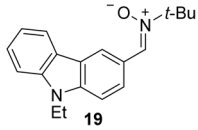
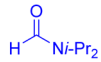
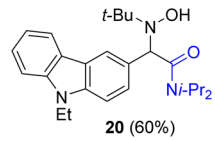
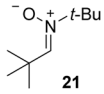
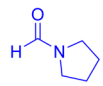
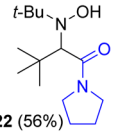
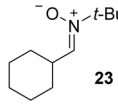
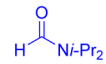
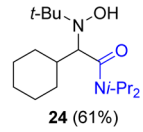
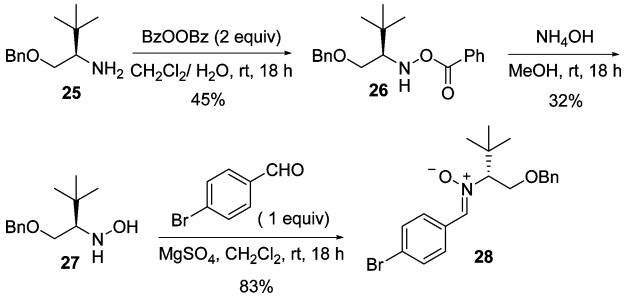
Table 2. Scope of Carbamoyl Anion Addition to Various Nitrones[a]

entry	nitrone	formamide	product (yield)[b]
1	 **13**		 **14** (88%)
2	 **15**		 **16** (72%)
3	 **17**		 **18** (53%)
4	 **19**		 **20** (60%)
5	 **21**		 **22** (56%)
6	 **23**		 **24** (61%)

[a]Typical reaction conditions: 1 equiv nitrone, 6.1 equiv formamide, 6.0 equiv LDA, PhMe, 0 °C. [b]Isolated yield.

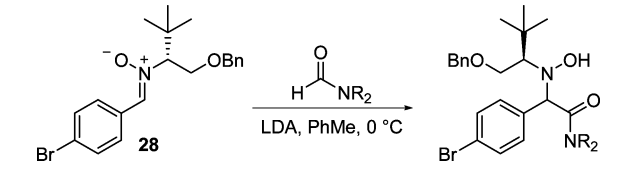
Scheme 4. Chiral Nitrone Synthesis

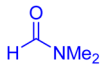
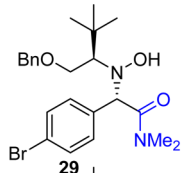
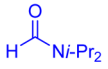
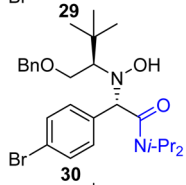
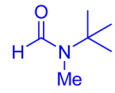
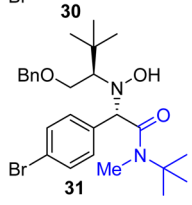


The results of the addition of carbamoyl anions to chiral formamide **28** are shown in Table 3. For the addition of DMF, LiTMP was employed as the base, and the product **29** was formed in a modest diastereomeric ratio of 80:20 (entry 1). The reactions of the more bulky formamides *N*,*N*-diisopropylformamide (entry 2) and *N*-methyl-*N*-*tert*-butylformamide (entry 3) proceeded with higher selectivity, yielding adducts **30** and **31** in diastereomeric ratios of 88:12 and 89:11, respectively.[17]

The stereochemistry of the newly formed chiral center in adduct **31** was assigned as (*S*) from single crystal X-ray structure determination (Scheme 5). By analogy, adducts **29** and **30** are assumed to have been formed with the same

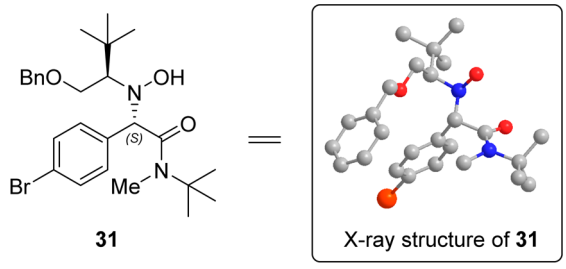
Table 3. Diastereoselective Carbamoyl Anion Additions[a]



entry	formamide	product	yield[b]	dr[c]
1[d]		 **29**	56%	80:20
2		 **30**	73%	88:12
3		 **31**	72%	89:11

[a]Typical reaction conditions: 1 equiv nitrone, 6.1 equiv formamide, 6.0 equiv LDA, PhMe, 0 °C. [b]Isolated yield. [c]Determined from ^{1}H NMR of crude product. [d]LiTMP used instead of LDA.

Scheme 5. Stereochemical Assignment of 31



stereochemistry and are drawn accordingly in Table 3. The stereochemistry of the reaction is consistent with that observed for the addition of MeLi to valinol *O*-alkyl ether derived aryl nitrones and can be rationalized by a chelation controlled transition state.[13a]

The α-(*N*-hydroxy)amino amide products could be further elaborated as shown in Scheme 6. The *tert*-butyl group was deprotected by heating **11** in MsOH at 60 °C, giving hydroxylamine **32** in 68% yield. Alternatively, the hydroxylamine moiety could be reduced under mild conditions by treatment of **11** with carbon disulfide at rt, providing amine **33** in 84% yield.[18]

In conclusion, the addition of carbamoyl anions to nitrones has been demonstrated. The use of *N*-*tert*-butyl nitrones allows for the addition of a variety of formamides to aldehyde derived nitrones. Aryl, heteroaryl, and aliphatic nitrones were amenable to the addition reaction. The extension of the reaction to a *tert*-leucinol derived chiral nitrone was shown to proceed with diastereoselectivity up to 89:11. Finally, the products could be derivatized by either *tert*-butyl deprotection under acidic conditions or deoxygenation with CS_2.

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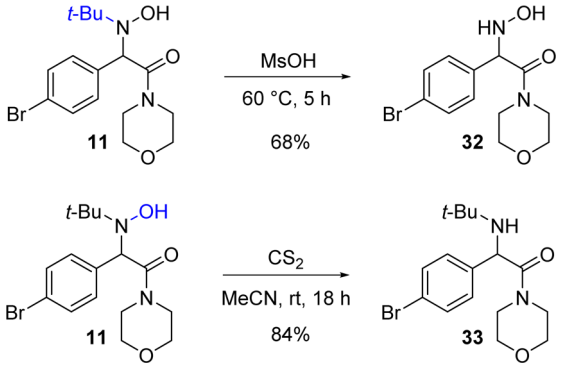
Scheme 6. Deprotection and Deoxygenation of Products



EXPERIMENTAL SECTION

General Information. All starting materials and reagents were purchased from commercial sources and used as received unless otherwise noted. Melting points are uncorrected. NMR spectra were recorded on 400 or 500 MHz instruments. All ^{1}H and ^{13}C NMR data were referenced to the internal deuterated solvent relative to TMS at 0 ppm. High resolution mass spectroscopy (HRMS) was performed on a TOF instrument with ESI in positive ionization mode. Flash chromatography was performed on an automated system with silica columns. The following nitrones have been described in the literature with either no characterization data or partial characterization data: **4a**,[19] **6**,[20] **7**,[21] **13**,[22] **15**,[23] **21**,[24] and **23**.[25] Melting point ranges, ^{1}H and ^{13}C NMR data and copies of spectra, and HRMS data are provided for these known compounds for completeness.

(*S*)-1-(4-Bromophenyl)-*N*-(1-phenylethyl)methanimine (4a). A flask was charged successively with 4-bromobenzaldehyde (10.0 g, 54.0 mmol), $MgSO_4$ (26.0 g, 0.216 mol), CH_2Cl_2 (100 mL), and (*S*)-α-methylbenzylamine (6.88 mL, 54.0 mmol). The resultant slurry was stirred at rt for 18 h and then filtered through a medium porosity stone frit filter. The solid was washed with CH_2Cl_2, and the filtrate was concentrated to a solid. The solid was dissolved in a minimal amount of warm CH_2Cl_2, and the product was crystallized out by the addition of heptane. The solid was filtered, rinsed with heptane, and dried under vacuum to afford **4a** (8.20 g, 53%) as a white solid. mp 86.5−88.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 7.62 (d, J = 8.4 Hz, 2 H), 7.50 (d, J = 8.4 Hz, 2 H), 7.41−7.39 (m, 2 H), 7.34−7.30 (m, 2 H), 7.24−7.20 (m, 1 H), 4.51 (q, J = 6.6 Hz, 1 H), 1.57 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 145.0, 135.4, 131.8, 129.8, 128.6, 127.0, 126.7, 125.0, 69.8, 24.9; HRMS: calcd for $C_{15}H_{15}BrN$ [M + H]: 288.0382. Found: 288.0379.

(*S*)-1-(4-Bromophenyl)-*N*-(1-(4-methoxyphenyl)ethyl)-methanimine (4b). A flask was charged successively with 4-bromobenzaldehyde (10.0 g, 54.0 mmol), $MgSO_4$ (26.0 g, 0.216 mol), CH_2Cl_2 (100 mL), and (*S*)-1-(4-methoxyphenyl)ethylamine (8.58 g, 56.8 mmol). The resultant slurry was stirred at rt for 18 h and then filtered through a medium porosity stone frit filter. The solid was washed with CH_2Cl_2, and the filtrate was concentrated to a solid. The solid was dissolved in the minimal amount of warm CH_2Cl_2, and the product was crystallized out by the addition of heptane. The solid was filtered, rinsed with heptane, and dried under vacuum to afford **4b** (11.1 g, 64%) as a white solid. mp 103−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1 H), 7.61 (d, J = 8.4 Hz, 2 H), 7.50 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 4.48 (q, J = 6.6 Hz, 1 H), 3.77 (s, 3 H), 1.55 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 157.9, 137.1, 135.4, 131.8, 129.7, 127.7, 124.9, 113.9, 69.2, 55.3, 24.8; HRMS: calcd for $C_{16}H_{17}BrNO$ [M + H]: 318.0488. Found: 318.0490.

(*S*)-1-(4-Bromophenyl)-*N*-(1-(naphthalen-1-yl)ethyl)-methanimine (4c). A flask was charged successively with 4-bromobenzaldehyde (10.0 g, 54.0 mmol), $MgSO_4$ (26.0 g, 0.216 mol), CH_2Cl_2 (100 mL), and (*S*)-1-(1-naphthyl)ethylamine (9.25 g, 54.0 mmol). The resultant slurry was stirred at rt for 18 h and then filtered through a medium porosity stone frit filter. The solid was washed with CH_2Cl_2, and the filtrate was concentrated to a solid. The solid was dissolved in a minimal amount of warm CH_2Cl_2, and the product was crystallized out by the addition of heptane. The solid was filtered, rinsed with heptane, and dried under vacuum to afford **4c** (15.9 g, 87%) as a white solid. mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 8.29 (d, J = 8.4 Hz, 1 H), 7.93−7.91 (m, 1 H), 7.86−7.84 (m, 1 H), 7.81 (d, J = 8.2 Hz, 1 H), 7.71−7.68 (m, 2 H), 7.61−7.51 (m, 5 H), 5.39 (q, J = 6.6 Hz, 1 H), 1.79 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 141.0, 135.4, 134.1, 131.8, 130.7, 129.8, 129.1, 127.5, 126.0, 125.8, 125.5, 125.0, 124.1, 123.6, 65.8, 24.6; HRMS: calcd for $C_{19}H_{17}BrN$ [M + H]: 338.0539. Found: 338.0536.

2-(4-Bromophenyl)-*N*,*N*-diisopropyl-2-(((*S*)-1-phenylethyl)-amino)acetamide (5a). A flask was charged with **4a** (0.500 g, 1.74 mmol), *N*,*N*-diisopropylformamide (0.780 mL, 5.38 mmol), and toluene (10 mL). The solution was cooled to −78 °C and treated dropwise with LDA (2.60 mL, 5.21 mmol, 2.0 M solution in THF/heptane/ethylbenzene). After the LDA addition, the reaction mixture was stirred at −78 °C for 10 min and then warmed to 0 °C, at which point the reaction was quenched with water. The mixture was extracted with EtOAc, and the organic phase dried (Na_2SO_4), filtered, and concentrated. ^{1}H NMR analysis of the crude product mixture showed a reaction diastereoselectivity of 83:17. The crude product was purified by chromatography on SiO_2 (hexanes/MTBE, 75:25) to afford the pure major diastereomer of **5a** (572 mg, 79%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.38 (m, 4 H), 7.36−7.32 (m, 2 H), 7.27−7.24 (m, 1 H), 7.07−7.06 (m, 2 H), 4.11 (s, 1 H), 3.76 (q, J = 6.5 Hz, 1 H), 3.56−3.48 (m, 1 H), 3.36−3.32 (m, 1 H), 2.79 (br, 1 H), 1.53 (d, J = 6.8 Hz, 3 H), 1.43 (d, J = 6.8 Hz, 3 H), 1.35 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.65 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 145.3, 139.1, 131.9, 129.4, 128.6, 127.3, 127.2, 121.5, 60.6, 57.3, 47.9, 46.3, 25.2, 20.9, 20.5, 20.2, 19.8; HRMS: calcd for $C_{22}H_{30}BrN_2O$ [M + H]: 417.1536. Found: 417.1539.

2-(4-Bromophenyl)-*N*,*N*-diisopropyl-2-(((*S*)-1-(4-methoxyphenyl)ethyl)amino)acetamide (5b). A flask was charged with **4b** (1.00 g, 3.14 mmol), *N*,*N*-diisopropylformamide (1.41 mL, 9.74 mmol), and toluene (20 mL). The solution was cooled to −78 °C and treated dropwise with LDA (4.71 mL, 9.43 mmol, 2.0 M solution in THF/heptane/ethylbenzene). After the LDA addition, the reaction mixture was stirred at −78 °C for 10 min and then warmed to 0 °C, at which point the reaction was quenched with water. The mixture was extracted with EtOAc, and the organic phase dried (Na_2SO_4), filtered, and concentrated. ^{1}H NMR analysis of the crude product mixture showed a reaction diastereoselectivity of 90:10. The crude product was purified by chromatography on SiO_2 (hexanes/MTBE, 75:25) to afford the pure major diastereomer of **5b** (1.18 g, 84%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.38 (m, 2 H), 7.31−7.27 (m, 2 H), 7.06−7.04 (m, 2 H), 6.91−6.87 (m, 2 H), 4.11 (s, 1 H), 3.82 (s, 3 H), 3.71 (q, J = 6.4 Hz, 1 H), 3.59−3.49 (m, 1 H), 3.39−3.28 (m, 1 H), 2.76 (br, 1 H), 1.53 (d, J = 6.8 Hz, 3 H), 1.43 (d, J = 6.8 Hz, 3 H), 1.33 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.65 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 158.8, 139.2, 137.3, 131.9, 129.4, 128.3, 121.5, 113.9, 60.5, 56.6, 55.3, 47.9, 46.3, 25.2, 20.9, 20.6, 20.2, 19.8; HRMS: calcd for $C_{23}H_{32}BrN_2O_2$ [M + H]: 447.1642. Found: 447.1646.

2-(4-Bromophenyl)-*N*,*N*-diisopropyl-2-(((*S*)-1-(naphthalen-1-yl)ethyl)amino)acetamide (5c). A flask was charged with **4c** (1.00 g, 2.96 mmol), *N*,*N*-diisopropylformamide (1.33 mL, 9.16 mmol), and toluene (20 mL). The solution was cooled to −78 °C and treated dropwise with LDA (4.43 mL, 8.87 mmol, 2.0 M solution in THF/heptane/ethylbenzene). After the LDA addition, the reaction mixture was stirred at −78 °C for 10 min and then warmed to 0 °C, at which point the reaction was quenched with water. The mixture was extracted with EtOAc, and the organic phase dried (Na_2SO_4), filtered, and concentrated. ^{1}H NMR analysis of the crude product mixture showed a reaction diastereoselectivity of 77:23. The crude product was purified by chromatography on SiO_2 (hexanes/MTBE, 75:25) to afford the pure major diastereomer of **5c** (967 mg, 70%) as a waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (br, 1 H), 7.88−7.76 (m, 3

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H), 7.52−7.40 (m, 5 H), 7.08−7.06 (m, 2 H), 4.66 (q, J = 6.4 Hz, 1 H), 4.11 (s, 1 H), 3.38−3.23 (m, 2 H), 2.87 (br, 1 H), 1.54 (d, J = 6.7 Hz, 3 H), 1.51 (d, J = 6.7 Hz, 3 H), 1.43 (d, J = 6.7 Hz, 3 H), 0.54 (d, J = 6.7 Hz, 3 H), 0.50 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 140.6, 139.1, 134.0, 131.9, 131.7, 129.4, 128.9, 127.5, 125.8, 125.7, 124.6, 123.4, 121.5, 60.8, 53.0, 47.8, 46.2, 24.3, 20.8, 20.2, 20.0, 19.7; HRMS: calcd for $C_{26}H_{32}BrN_2O$ [M + H]: 467.1693. Found: 467.1689.

(*Z*)-*N*-Benzyl-1-(4-bromophenyl)methanimine oxide (6). A flask was charged with benzyl hydroxylamine (2.95 g, 18.5 mmol, 1.0 equiv), 4-bromobenzaldehyde (3.42 g, 18.5 mmol, 1.0 equiv), sodium carbonate (1.96 g, 18.5 mmol, 1.0 equiv), and DCM (40 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, filtered through a thin layer of silica gel, and concentrated in vacuo to give **6** (3.95 g, 82%) as a white solid. mp 129−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.49−7.37 (m, 5H), 7.35 (s, 1H), 5.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 133.0, 131.7, 129.9, 129.3, 129.1 (2), 129.0, 124.3, 71.4; HRMS: calcd for $C_{14}H_{13}BrNO$ [M + H]: 290.0175. Found: 290.0160.

(*Z*)-1-(4-Bromophenyl)-*N*-(*tert*-butyl)methanimine oxide (7). A flask was charged with *tert*-butylhydroxylamine acetate (2.00 g, 13.4 mmol, 1.0 equiv), 4-bromobenzaldehyde (2.48 g, 13.4 mmol, 1.0 equiv), sodium carbonate (1.42 g, 13.4 mmol, 1.0 equiv), and DCM (20 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, filtered through a pad of Celite, and concentrated in vacuo. The crude material was purified by column chromatography (hexanes/MTBE) to give **7** (2.54 g, 74%) as a white solid. mp 62−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.6 Hz, 2H), 7.55−7.50 (m, 3H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6, 130.1, 129.9, 128.8, 123.7, 71.2, 28.3; HRMS: calcd for $C_{11}H_{15}BrNO$ [M + H]: 256.0332. Found: 256.0320.

2-(4-Bromophenyl)-2-(*tert*-butyl(hydroxy)amino)-*N*,*N*-diisopropylacetamide (8). A flask was charged with nitrone **7** (0.400 g, 1.56 mmol, 1.0 equiv), *N*,*N*-diisopropylformamide (1.38 mL, 9.53 mmol, 6.1 equiv), and toluene (4 mL), and the solution was cooled to 0 °C and treated dropwise with LDA (4.68 mL, 9.37 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at 0 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give **8** (430 mg, 72%) as a white solid. mp 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 4.76 (s, 1H), 3.86−3.70 (m, 1H), 3.44−3.29 (m, 1H), 1.46 (d, J = 6.8 Hz, 3H), 1.43 (d, J = 6.8 Hz, 3H), 1.24−1.18 (m, 12H), 0.79 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 136.9, 131.6, 130.8, 121.8, 59.8, 59.7, 48.9, 46.3, 27.4, 20.8, 20.4, 20.0, 19.9; HRMS: calcd for $C_{18}H_{30}BrN_2O_2$ [M + H]: 385.1485. Found: 385.1470.

2-(4-Bromophenyl)-2-(*tert*-butyl(hydroxy)amino)-*N*,*N*-dimethylacetamide (9). A flask was charged with nitrone **7** (0.300 g, 1.17 mmol, 1.0 equiv), *N*,*N*-dimethylformamide (0.550 mL, 7.14 mmol, 6.1 equiv), and toluene (3 mL), and the solution was cooled to 0 °C and treated dropwise with a solution of lithium 2,2,6,6-tetramethylpiperidide in THF (12.9 mL, 7.03 mmol, 0.54 M in THF, 6.0 equiv). The reaction mixture was stirred for 20 min at 0 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give **9** (260 mg, 67%) as a white solid. mp 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.88 (s, 1H), 2.97 (s, 3H), 2.94 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 135.8, 131.7, 130.9, 122.1, 60.1, 59.7, 37.2, 35.7, 27.0; HRMS: calcd for $C_{14}H_{22}BrN_2O_2$ [M + H]: 329.0860. Found: 329.0845.

2-(4-Bromophenyl)-2-(*tert*-butyl(hydroxy)amino)-*N*,*N*-dimethylacetamide Oxalic Acid Salt (9·HO_2CCO_2H). A flask was charged with nitrone **7** (0.350 g, 1.37 mmol, 1.0 equiv), *N*,*N*-dimethylformamide (0.650 mL, 8.34 mmol, 6.1 equiv), and toluene (3.5 mL), and the solution was cooled to −78 °C and treated dropwise with a solution of lithium 2,2,6,6-tetramethylpiperidide in THF (14.5 mL, 7.82 mmol, 0.54 M in THF, 6.0 equiv). The reaction mixture was stirred for 20 min at −78 °C. The reaction mixture was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. A solution of oxalic acid dihydrate (0.260 g, 2.05 mmol, 1.5 equiv) in methanol (5 mL) was added to the concentrate. The solution was diluted with MTBE (30 mL) and filtered to give the oxalic acid salt of **9** (490 mg, 79%) as light brown solid. mp 158−161 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.63 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 5.62 (s, 1H), 2.89 (s, 3H), 2.86 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, D_2O) 166.6, 132.7, 131.0, 127.0, 124.9, 71.1, 67.0, 36.7, 36.2, 23.5; HRMS: calcd for $C_{14}H_{22}BrN_2O_2$ [M + H − HO_2CCO_2H]: 329.0860. Found: 329.0851.

2-(4-Bromophenyl)-2-(*tert*-butyl(hydroxy)amino)-*N*,*N*-dimethylethanethioamide (10). A flask was charged with nitrone **7** (0.500 g, 1.95 mmol, 1.0 equiv), *N*,*N*-dimethylthioformamide (1.01 mL, 11.9 mmol, 6.1 equiv), and toluene (5 mL), and the solution was cooled to −78 °C and treated dropwise with LDA (11.7 mL, 11.7 mmol, 1.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at −78 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give **10** (400 mg, 59%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 7.42 (br s, 1H), 5.33 (s, 1H), 3.44 (s, 3H), 3.30 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 135.7, 131.9, 131.2, 122.2, 68.4, 60.2, 45.1, 42.2, 27.4; HRMS: calcd for $C_{14}H_{20}BrN_2S$ [M + H − H_2O]: 327.0525. Found: 327.0513.

2-(4-Bromophenyl)-2-(*tert*-butyl(hydroxy)amino)-1-morpholinoethan-1-one (11). A flask was charged with nitrone **7** (0.500 g, 1.95 mmol, 1.0 equiv), 4-formylmorpholine (1.19 mL, 11.9 mmol, 6.1 equiv), and toluene (5 mL), and the solution was cooled to −78 °C and treated dropwise with LDA (5.85 mL, 11.7 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at −78 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give **11** (500 mg, 70%) as a white solid. mp 123−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.88 (s, 1H), 3.82−3.65 (m, 2H), 3.63−3.41 (m, 4H), 3.35−3.20 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 135.8, 131.7, 130.9, 122.3, 66.6, 66.2, 60.7, 59.9, 46.1, 42.0, 27.0; HRMS: calcd for $C_{16}H_{24}BrN_2O_3$ [M + H]: 371.0965. Found: 371.0944.

2-(4-Bromophenyl)-2-(*tert*-butyl(hydroxy)amino)-*N*-methyl-*N*-phenylacetamide (12). A flask was charged with nitrone **7** (0.300 g, 1.17 mmol, 1.0 equiv), *N*-methyl formanilide (0.880 mL, 7.14 mmol, 6.1 equiv), and toluene (5 mL), and the solution was cooled to 0 °C and treated dropwise with LDA (3.51 mL, 7.02 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at 0 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give **12** (350 mg, 76%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.43−7.32 (m, 5H), 7.11 (d, J = 8.4 Hz, 2H), 6.99 (br s, 2H), 4.55 (s, 1H), 3.25 (s, 3H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 142.5, 136.7, 131.3, 131.1, 129.8, 128.6, 127.4, 122.0, 61.9, 59.9, 37.4, 26.6; HRMS: calcd for $C_{19}H_{24}BrN_2O_2$ [M + H]: 391.1016. Found: 391.0997.

(*Z*)-*N*-*tert*-Butyl-1-(*o*-tolyl)methanimine oxide (13). A flask was charged with *tert*-butyl-hydroxylamine acetate (2.00 g, 13.4 mmol, 1.0 equiv), *o*-tolualdehyde (1.55 mL, 13.4 mmol, 1.0 equiv), sodium carbonate (1.42 g, 13.4 mmol, 1.0 equiv), and DCM (20 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, filtered through a pad of Celite, and concentrated in vacuo. The crude material was purified by column chromatography to give **13** (1.95 g, 76%) as a white solid. mp 68−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18−9.13 (m, 1H), 7.73 (s, 1H), 7.29−7.25 (m, 2H), 7.22−7.17 (m, 1H), 2.39 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 130.1, 129.8, 129.3, 127.9, 126.6, 126.3, 71.2, 28.4, 19.9; HRMS: calcd for $C_{12}H_{18}NO$ [M + H]: 192.1383. Found: 192.1376.

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2-(*tert*-Butyl(hydroxy)amino)-*N*,*N*-diethyl-2-(*o*-tolyl)-acetamide (14). A flask was charged with nitrone **13** (0.500 g, 2.61 mmol, 1.0 equiv), *N*,*N*-diethylformamide (1.79 mL, 15.95 mmol, 6.1 equiv), and toluene (5 mL), and the solution was cooled to −78 °C and treated dropwise with LDA (7.84 mL, 15.68 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at −78 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give **14** (670 mg, 88%) as a white solid. mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.42 (d, J = 7.0 Hz, 1H), 7.22−7.12 (m, 3H), 4.96 (s, 1H), 3.47−3.36 (m, 1H), 3.36−3.25 (m, 1H), 3.11−3.00 (m, 1H), 3.00−2.89 (m, 1H) 2.44 (s, 3H), 1.27 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 136.3, 134.8, 131.1, 129.2, 128.1, 126.1, 60.6, 56.4, 41.8, 40.2, 27.3, 19.8, 14.0, 12.4; HRMS: calcd for $C_{17}H_{29}N_2O_2$ [M + H]: 293.2224. Found: 293.2211.

(*Z*)-*N*-*tert*-Butyl-1-(4-methoxyphenyl)methanimine Oxide (15). A flask was charged with *tert*-butyl-hydroxylamine acetate (2.00 g, 13.4 mmol, 1.0 equiv), 4-methoxybenzaldehyde (1.62 mL, 13.4 mmol, 1.0 equiv), sodium carbonate (1.42 g, 13.4 mmol, 1.0 equiv), and DCM (20 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, filtered through a pad of Celite, and concentrated in vacuo. The crude material was purified by column chromatography (MTBE/hexanes) to give **15** (2.44 g, 88%) as a white solid. mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 2H), 7.47 (s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 130.8, 129.6, 124.0, 113.8, 70.1, 55.3, 28.3; HRMS: calcd for $C_{12}H_{18}NO_2$ [M + H]: 208.1332. Found: 208.1324.

***N*-(*tert*-Butyl)-2-(*tert*-butyl(hydroxy)amino)-2-(4-methoxyphenyl)-*N*-methylacetamide (16).** A flask was charged with nitrone **15** (0.500 g, 2.41 mmol, 1.0 equiv), *N*-methyl-*N*-*tert*-butylformamide (1.69 g, 14.7 mmol, 6.1 equiv), and toluene (5 mL), and the solution was cooled to 0 °C and treated dropwise with LDA (7.23 mL, 14.5 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at 0 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give **16** (560 mg, 72%) as a white solid. mp 96−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.34 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.74 (s, 1H), 3.79 (s, 3H), 2.76 (s, 3H), 1.43 (s, 9H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 159.2, 130.3, 129.4, 114.0, 61.2, 59.5, 57.6, 55.3, 31.5, 28.0, 27.4; HRMS: calcd for $C_{18}H_{31}N_2O_3$ [M + H]: 323.2329. Found: 323.2312.

(*Z*)-*N*-*tert*-Butyl-1-(pyridin-2-yl)methanimine Oxide (17). A flask was charged with *tert*-butylhydroxylamine acetate (2.00 g, 13.4 mmol, 1.0 equiv), 2-pyridinecarboxaldehyde (1.27 mL, 13.4 mmol, 1.0 equiv), sodium carbonate (1.42 g, 13.4 mmol, 1.0 equiv), and DCM (20 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, filtered through a pad of Celite, and concentrated in vacuo. The crude material was purified by column chromatography to give **17** (1.70 g, 71%) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, J = 8.1 Hz, 1H), 8.65−8.61 (m, 1H), 7.92 (s, 1H), 7.79 (td, J = 1.5, 7.7 Hz, 1H), 7.30−7.26 (m, 1H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 149.4, 137.0, 131.6, 124.1, 123.7, 71.7, 28.3; HRMS: calcd for $C_{10}H_{15}N_2O$ [M + H]: 179.1179. Found: 179.1169.

***N*,*N*-Dibutyl-2-(*tert*-butyl(hydroxy)amino)-2-(pyridin-2-yl)-acetamide (18).** A flask was charged with nitrone **17** (0.270 g, 1.51 mmol, 1.0 equiv), *N*,*N*-dibutylformamide (1.68 mL, 9.24 mmol, 6.1 equiv), and toluene (2.7 mL), and the solution was cooled to −78 °C and treated dropwise with LDA (4.54 mL, 9.09 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at −78 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give **18** (240 mg, 53%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55−8.50 (m, 1H), 8.40 (s, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.66 (td, J = 1.8, 7.6 Hz, 1H), 7.19 (ddd, J = 1.2, 4.9 Hz, 1H), 5.16 (s, 1H), 3.44−3.35 (m, 2H), 3.26−3.17 (m, 1H), 3.15−3.05 (m, 1H), 1.55−1.45 (m, 3H), 1.34−1.22 (m, 5H), 1.14 (s, 9H), 0.93−0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 157.8, 148.8, 136.3, 124.5, 122.7, 64.2, 59.7, 47.6, 45.9, 30.9, 29.3, 26.8, 20.2, 20.1, 13.8; HRMS: calcd for $C_{19}H_{34}N_3O_2$ [M + H]: 336.2646. Found: 336.2634.

(*Z*)-*N*-*tert*-Butyl-1-(9-ethyl-9H-carbazol-3-yl)methanimine Oxide (19). A flask was charged with *tert*-butylhydroxylamine acetate (2.00 g, 13.4 mmol, 1.0 equiv), 9-ethyl-3-carbazole carboxaldehyde (2.99 g, 13.4 mmol, 1.0 equiv), sodium carbonate (1.42 g, 13.4 mmol, 1.0 equiv), and DCM (20 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, filtered through a pad of Celite, and concentrated in vacuo. The crude material was purified by column chromatography to give **19** (1.01 g, 26%) as an off-white solid. mp 123−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J = 1.5 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.05 (dd, J = 1.7, 8.7 Hz, 1H), 7.70 (s, 1H), 7.51−7.45 (m, 1H), 7.43−7.39 (m, 2H), 7.28−7.23 (m, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.67 (s, 9H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 140.4, 130.8, 127.8, 126.0, 123.4, 122.9, 122.3, 121.5, 121.0, 119.6, 108.7, 108.1, 69.9, 37.7, 28.4, 13.9; HRMS: calcd for $C_{19}H_{23}N_2O$ [M + H]: 295.1805. Found: 295.1790.

2-(*tert*-Butyl(hydroxy)amino)-2-(9-ethyl-9H-carbazol-3-yl)-*N*,*N*-diisopropylacetamide (20). A flask was charged with nitrone **19** (0.300 g, 1.02 mmol, 1.0 equiv), *N*,*N*-diisopropylformamide (0.900 mL, 6.22 mmol, 6.1 equiv), and toluene (3 mL), and the solution was cooled to −78 °C and treated dropwise with LDA (0.310 mL, 6.11 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at −78 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give **20** (260 mg, 60%) as a white solid. mp 165−167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.11 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H) 7.55 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.9 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 5.00 (s, 1H), 4.35 (q, J = 7.2 Hz, 2H), 4.01−3.90 (m, 1H), 3.39−3.29 (m, 1H), 1.50 (t, J = 7.1 Hz, 6H), 1.40 (t, J = 7.2 Hz, 3H), 1.27 (s, 9H), 1.20 (d, J = 6.5 Hz, 3H), 0.63 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 140.2, 139.6, 127.9, 127.0, 125.5, 123.0 (2), 121.1, 120.5, 118.7, 108.5, 108.4, 60.9, 59.6, 48.8, 46.2, 37.6, 27.5, 20.9, 20.6, 19.9, 19.8, 13.8; HRMS: calcd for $C_{26}H_{38}N_3O_2$ [M + H]: 424.2959. Found: 424.2940.

(*Z*)-*N*-(*tert*-Butyl)-2,2-dimethylpropan-1-imine Oxide (21). A flask was charged with *tert*-butylhydroxylamine acetate (2.00 g, 13.4 mmol, 1.0 equiv), trimethylacetaldehyde (1.45 mL, 13.4 mmol, 1.0 equiv), sodium carbonate (1.42 g, 13.4 mmol, 1.0 equiv), and DCM (20 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, filtered through a pad of Celite, and concentrated in vacuo. The crude material was purified by column chromatography to give **21** (1.84 g, 87%) as a white solid. mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (s,1H), 1.47 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 69.7, 32.6, 28.3, 26.2; HRMS: calcd for $C_9H_{20}NO$ [M + H]: 158.1539. Found: 158.1543.

2-(*tert*-Butyl(hydroxy)amino)-3,3-dimethyl-1-(pyrrolidin-1-yl)butan-1-one (22). A flask was charged with nitrone **21** (0.500 g, 3.18 mmol, 1.0 equiv), 1-formylpyrrolidine (1.85 mL, 19.4 mmol, 6.1 equiv), and toluene (5 mL), and the solution was cooled to −78 °C and treated dropwise with LDA (9.50 mL, 19.1 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at −78 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give **22** (460 mg, 56%) as a white solid. mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 3.57−3.44 (m, 4H), 3.34 (s, 1H), 2.01−1.85 (m, 4H), 1.11 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 63.4, 59.5, 47.5, 45.8, 36.0, 28.3, 26.6, 26.2, 23.9; HRMS: calcd for $C_{14}H_{29}N_2O_2$ [M + H]: 257.2224. Found: 257.2220.

(*Z*)-*N*-*tert*-Butyl-1-cyclohexylmethanimine Oxide (23). A flask was charged with *tert*-butylhydroxylamine acetate (3.0 g, 20.1 mmol, 1.0 equiv), cyclohexane carboxaldehyde (2.43 mL, 20.1 mmol, 1.0 equiv), sodium carbonate (2.13 g, 20.1 mmol, 1.0 equiv), and DCM

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(30 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, filtered through a pad of Celite, and concentrated in vacuo. The crude material was purified by column chromatography to give **23** (2.08 g, 57%) as a white solid. mp 60−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 7.2 Hz, 1H), 3.05−2.93 (m, 1H), 1.92−1.85 (m, 2H), 1.75−1.64 (m, 3H), 1.48 (s, 9H), 1.43−1.33 (m, 2H), 1.30−1.21 (m, 1H), 1.19−1.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 68.8, 35.2, 28.9, 28.0, 26.0, 25.4; HRMS: calcd for $C_{11}H_{22}NO$ [M + H]: 184.1696. Found: 184.1696.

2-(*tert*-Butyl(hydroxy)amino)-2-cyclohexyl-*N*,*N*-diisopropylacetamide (24). A flask was charged with nitrone (0.500 g, 2.73 mmol, 1.0 equiv), *N*,*N*-diisopropylformamide (2.42 mL, 16.6 mmol, 6.1 equiv), and toluene (5 mL), and the solution was cooled to −78 °C and treated dropwise with LDA (8.19 mL, 16.4 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at −78 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (MTBE/hexanes) to give the pure product (520 mg, 61%) as a white solid. mp 111−112.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 4.12−4.02 (m, 1H), 3.46 (d, J = 9.3 Hz, 1H), 3.43−3.34 (m, 1H), 2.38 (d, J = 13.1 Hz, 1H), 2.18−2.06 (m, 1H), 1.77−1.57 (m, 4H), 1.43 (d, J = 3.8 Hz, 3H), 1.41 (d, J = 3.8 Hz, 3H), 1.37−1.23 (m, 8H), 1.21−1.12 (m, 1H), 1.11 (s, 9H), 1.00−0.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 60.1, 58.5, 48.9, 46.5, 39.3, 31.3, 30.5, 26.8, 26.7, 26.6, 26.3, 20.9, 20.8, 20.3, 19.7; HRMS: calcd for $C_{18}H_{37}N_2O_2$ [M + H]: 313.2850. Found: 313.2860.

(*R*)-*O*-Benzoyl-*N*-(1-(benzyloxy)-3,3-dimethylbutan-2-yl)-hydroxylamine (26). *O*-Benzyl *R*-*tert*-leucinol (10.0 g, 48.3 mmol, 1.0 equiv) was added to a flask containing a mixed buffer solution (235 mL) of sodium bicarbonate (0.75 M) and sodium hydroxide (1.5 M). A solution of benzoyl peroxide (23.4 g, 96.5 mmol, 2.0 equiv) in water (220 mL) and DCM (60 mL) was then added, and the mixture was stirred 18 h at room temperature. The reaction mixture was extracted with DCM, and the organic layer was washed with brine and dried over Na_2SO_4. The crude product was concentrated in vacuo and purified by column chromatography with hexanes/MTBE to give **26** (7.09 g, 45%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.95 (m, 2H), 7.58−7.53 (m, 1H), 7.46−7.41 (m, 2H), 7.34−7.27 (m, 4H), 7.25−7.21 (m, 1H), 4.51 (dd, J = 12.0, 21.2 Hz, 2H), 3.67 (dd, J = 3.6, 10.0 Hz, 1H), 3.54 (dd, J = 8.1, 10.0 Hz, 1H), 3.01 (dd, J = 3.6, 8.1 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 137.9, 133.1, 129.3, 128.8, 128.5, 128.4, 127.7, 127.6, 73.3, 69.1, 66.9, 33.4, 27.7; HRMS: calcd for $C_{20}H_{26}NO_3$ [M + H]: 328.1907. Found: 328.1884.

(*R*)-*N*-(1-(Benzyloxy)-3,3-dimethylbutan-2-yl)hydroxylamine (27). A flask was charged with **26** (10.0 g, 48.3 mmol, 1.0 equiv) and methanol (7 mL). Ammonium hydroxide solution (28−30%, 5 mL) was added dropwise, and the solution was stirred for 18 h at room temperature. The reaction mixture was concentrated in vacuo, and the residue was dissolved in ethyl acetate, washed with brine, and dried over Na_2SO_4. The solution was concentrated in vacuo and purified by column chromatography to give **27** (1.03 g, 32%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 5.63 (br s, 1H), 4.55 (dd, J = 12.0, 15.8 Hz, 2H), 3.73 (dd, J = 3.6, 9.8 Hz, 1H), 3.59 (dd, J = 7.6, 9.7 Hz, 1H), 2.79 (dd, J = 3.7, 7.6 Hz, 1H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 128.4, 127.7, 127.6, 73.4, 69.6, 68.2, 33.0, 27.7; HRMS: calcd for $C_{13}H_{20}NO_2$ [M − H_2 + H]: 222.1489. Found: 222.1470.

(*R*,*Z*)-*N*-(1-(Benzyloxy)-3,3-dimethylbutan-2-yl)-1-(4-bromophenyl)methanimine oxide (28). A flask was charged with **27** (2.15 g, 9.63 mmol, 1.0 equiv), 4-bromobenzaldehyde (1.78 g, 9.63 mmol, 1.0 equiv), $MgSO_4$ (5.0 g), and DCM (21.5 mL), and the mixture was stirred for 18 h at room temperature. The reaction mixture was diluted with DCM, filtered through a pad of Celite, and concentrated in vacuo. The crude material was purified by column chromatography to give **28** (3.10 g, 83%) as a white solid. mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 7.34 (s, 1H), 7.30−7.27 (m, 1H), 7.25−7.21 (m, 3H), 4.58 (d, J = 11.9 Hz, 1H), 4.48 (d, J = 11.9 Hz, 1H), 4.26 (t, J = 10.0 Hz, 1H), 3.74 (dd, J = 2.3, 10.0 Hz, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 134.4, 131.6, 129.9, 129.5, 128.4, 127.7, 127.6, 123.7, 84.7, 73.6, 67.1, 33.3, 27.4; HRMS: calcd for $C_{20}H_{25}BrNO_2$ [M + H]: 390.1063. Found: 390.1043.

(*S*)-2-(((*R*)-1-(Benzyloxy)-3,3-dimethylbutan-2-yl)(hydroxy)-amino)-2-(4-bromo-phenyl)-*N*,*N*-dimethylacetamide (29). A flask was charged with nitrone **28** (0.270 g, 0.690 mmol, 1.0 equiv), *N*,*N*-dimethylformamide (0.330 mL, 4.22 mmol, 6.1 equiv), and toluene (2.7 mL), and the solution was cooled to 0 °C and treated dropwise with lithium 2,2,6,6-tetramethylpiperidide (6.10 mL, 4.15 mmol, 0.68 M, 6.0 equiv). The reaction mixture was stirred for 20 min at 0 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR analysis of the crude product showed a reaction diastereoselectivity of 80:20. The crude product was purified by flash chromatography (MTBE/hexanes) to give the major diastereomer of **29** (180 mg, 56%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.27 (m, 9H), 5.95 (s, 1H), 5.41 (s, 1H), 4.52 (s, 2H), 4.28 (dd, J = 8.0, 10.0 Hz, 1H), 3.57 (dd, J = 2.4, 9.9 Hz, 1H), 2.84 (s, 3H), 2.75 (s, 3H), 2.38 (dd, J = 2.4, 7.9 Hz, 1H), 0.84 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 138.8, 134.7, 131.4, 128.4, 127.8, 127.7, 122.2, 73.3, 69.2, 66.7 (2), 36.7, 36.1, 34.2, 28.3; HRMS: calcd for $C_{23}H_{32}BrN_2O_3$ [M + H]: 463.1591. Found: 463.1550.

(*S*)-2-(((*R*)-1-(Benzyloxy)-3,3-dimethylbutan-2-yl)(hydroxy)-amino)-2-(4-bromo-phenyl)-*N*,*N*-diisopropylacetamide (30). A flask was charged with nitrone (0.400 g, 1.02 mmol, 1.0 equiv), *N*,*N*-diisopropylformamide (0.910 mL, 6.25 mmol, 6.1 equiv), and toluene (4 mL), and the solution was cooled to 0 °C and treated dropwise with LDA (3.07 mL, 6.15 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at 0 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR analysis of the crude product showed a reaction diastereoselectivity of 88:12. The crude product was purified by flash chromatography (MTBE/hexanes) to give the major diastereomer of **30** (390 mg, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.31 (m, 7H), 7.23 (d, J 7.97 Hz, 2H), 6.09 (s, 1H), 5.36 (s, 1H), 4.53 (dd, J = 11.4, 15.6 Hz, 2H), 4.31 (t, J = 9.3 Hz, 1H), 4.02−3.91 (m, 1H), 3.57 (d, J = 9.8 Hz, 1H), 3.26−3.16 (m, 1H), 2.36 (d, J = 7.7 Hz, 1H), 1.42 (d, J = 6.6 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.5 Hz, 3H), 0.82 (s, 9H), 0.48 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 138.9, 135.4, 131.9, 131.4, 128.4, 127.8, 127.6, 121.9, 73.3, 70.4, 66.9, 66.0, 47.5, 46.1, 34.2, 28.3, 20.7, 20.5, 19.8, 19.5; HRMS: calcd for $C_{27}H_{40}BrN_2O_3$ [M + H]: 519.2217. Found: 519.2205.

(*S*)-2-(((*R*)-1-(Benzyloxy)-3,3-dimethylbutan-2-yl)(hydroxy)-amino)-2-(4-bromophenyl)-*N*-(*tert*-butyl)-*N*-methylacetamide (31). A flask was charged with nitrone **28** (0.400 g, 1.02 mmol, 1.0 equiv), *N*-methyl-*N*-*tert*-butylformamide (0.720 g, 6.25 mmol, 6.1 equiv), and toluene (4 mL), and the solution was cooled to 0 °C and treated dropwise with LDA (3.07 mL, 6.15 mmol, 2.0 M, 6.0 equiv). The reaction mixture was stirred for 20 min at 0 °C. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR analysis of the crude product showed a reaction diastereoselectivity of 89:11. The crude product was purified by flash chromatography (MTBE/hexanes) to give the major diastereomer of **31** (380 mg, 72%) as an off-white solid. mp 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.29 (m, 8H), 7.26−7.24 (m, 1H), 5.89 (s, 1H), 5.35 (s, 1H), 4.53 (dd, J = 11.5, 20.7 Hz, 2H), 4.29 (dd, J = 7.9, 10.0 Hz, 1H), 3.57 (dd, J = 2.6, 10.0 Hz, 1H), 2.64 (s, 3H), 2.35 (dd, J = 2.6, 7.8 Hz, 1H), 1.32 (s, 9H), 0.82 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 138.8, 134.9, 132.0, 131.3, 128.4, 127.8, 127.6, 122.0, 73.3, 71.4, 66.8, 66.2, 57.4, 34.2, 31.0, 28.2, 28.0; HRMS: calcd for $C_{26}H_{38}BrN_2O_3$ [M + H]: 505.2060. Found: 505.2030.

2-(4-Bromophenyl)-2-(hydroxyamino)-1-morpholinoethan-1-one (32). A flask was charged with (*N*-hydroxy)amino amide **11** (100 mg, 0.280 mmol) and methanesulfonic acid (2 mL), and the solution was stirred at 60 °C for 5 h. The reaction mixture was cooled to room temperature and then diluted with DCM. The solution was washed with saturated aqueous Na_2CO_3, and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by

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flash chromatography (MTBE/hexanes) gave **32** (60.0 mg, 68%) as a light brown film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.03 (br s, 1 H), 4.86 (s, 1H), 3.86−3.69 (m, 2H), 3.64−3.52 (m, 3H), 3.42−3.33 (m, 1H), 3.26−3.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 132.7, 132.5, 130.1, 123.3, 66.7, 66.6, 66.1, 45.5, 42.6; HRMS: calcd for $C_{12}H_{16}BrN_2O_3$ [M + H]: 315.0339. Found: 315.0320.

2-(4-Bromophenyl)-2-(*tert*-butylamino)-1-morpholinoethan-1-one (33). A flask was charged with (*N*-hydroxy)amino amide **11** (0.180 g, 0.470 mmol) and carbon disulfide (3 mL), and the solution was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (MTBE/hexanes) to give **33** (140 mg, 84%) as a waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 4.48 (s, 1H), 3.81−3.62 (m, 2H), 3.62−3.52 (m, 4H), 3.52−3.41 (m, 1H), 3.40−3.29 (m, 1H), 3.29−3.19 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 140.2, 132.2, 129.0, 121.5, 66.7, 66.2, 56.2, 51.2, 45.8, 42.8, 29.6; HRMS: calcd for $C_{16}H_{24}BrN_2O_2$ [M + H]: 355.1016. Found: 355.0997.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra, thermal ellipsoid plot, and CIF data for **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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