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Transition Metal-Free Selective Double sp^3 C−H Oxidation of Cyclic Amines to 3-Alkoxyamine Lactams

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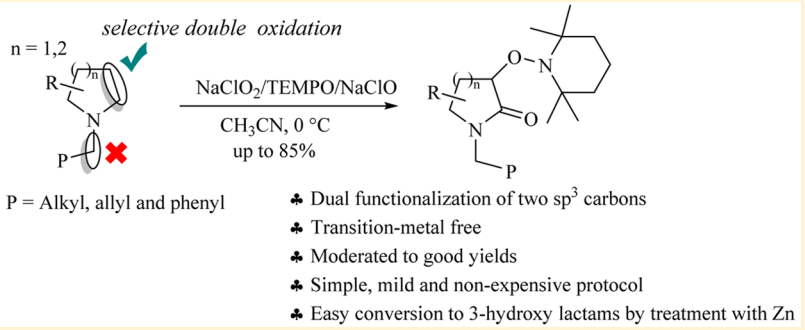
Supporting Information

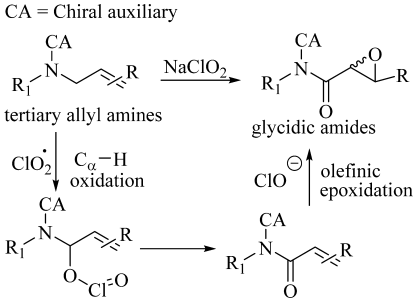


ABSTRACT: The first chemical method for selective dual sp^3 C−H functionalization at the alpha-and beta positions of cyclic amines to their corresponding 3-alkoxyamine lactams is reported. Unlike traditional C_α−H oxidation of amines to amides mediated by transition metals, the present protocol, which involves the use of $NaClO_2$/TEMPO/NaClO in either aqueous or organic solvent, not only allows the C_α−H oxidation but also the subsequent functionalization of the unreactive β-methylene group in an unprecedented tandem fashion and using environmentally friendly reactants.

The C_α−H oxidation reaction of cyclic amines mediated by transition-metals is becoming a powerful methodology for preparing lactams.[1] Since complex and expensive transition metal-catalysts are employed, direct C_α−H functionalization is frequently not attractive from an economic and environmental point of view, albeit dehydrogenation of cyclic amines in water mediated by ruthenium pincer complex might offer some green chemistry features.[1a] Because most of the oxidizing agents based on nontransition metals react at the nitrogen atom to furnish *N*-oxides rather than the desired C_α−H bond, one of the challenges is to evade the premature oxidation at the nitrogen atom.[2] Therefore, developing synthetic methodologies that could permit C_α−H functionalization of amines under transition-metal free conditions is imperative.

In 2012, a chemical method for the preparation of 2,3-epoxyamides (glycidic amides) from tertiary allyl amines was reported (Scheme 1).[3] Since the $NaClO_2$ was the sole oxidizing reagent used in the tandem C_α−H oxidation/olefinic epoxidation, this methodology represents an environmental-friendly and economic approach for the synthesis of highly oxygenated compounds.[4] Interestingly, $NaClO_2$, which is considered a strong oxidizing agent for organic materials,[5] does not oxidize the nitrogen atom. However, the synthesis of the glycidic amides was not diastereoselective even when employing chiral auxiliaries, such as the (*S*)-α-methylbenzylamine or the (*R*)-2-phenylglycinol.[3]

Scheme 1. Direct Chemical Method for the Synthesis of Glycidic Amides from Tertiary Amines



Searching for an efficient chiral auxiliary for this direct synthesis of glycidic amides, allyl amines derived from L-diphenylprolinol were thought to be suitable candidates. However, treatment of **1** with $NaClO_2$ under the previously established conditions did not afford the expected glycidic

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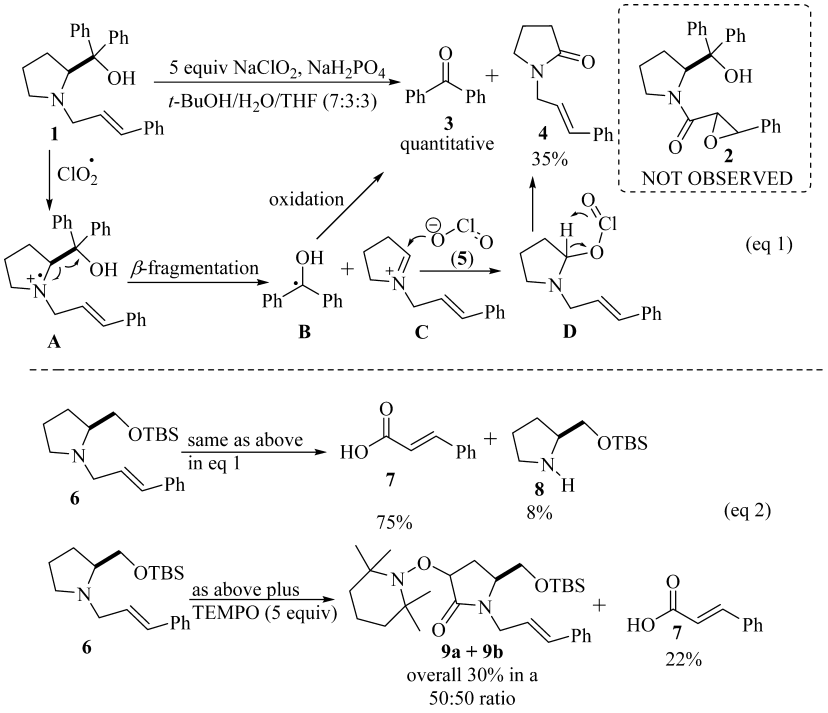
Scheme 2. Attempts for Diastereoselective Oxidation of Allyl Amine 1 to Glycidic Amide 2 in the Absence of TEMPO (eq 1), and in the Presence of TEMPO (eq 2)

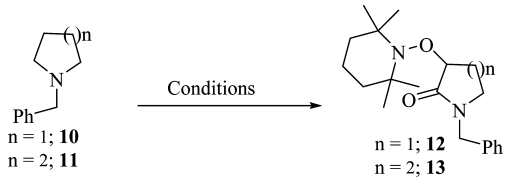


amide **2** but benzophenone **3** and γ-lactone **4** (eq 1, Scheme 2). The C−C bond cleavage of **1** can be explained by a β-fragmentation reaction of radical cation **A** to the resonance-stabilized radical **B** and the iminium cation **C**,[6] of which the former is further oxidized to benzophenone **3**, while the latter is transformed into γ-lactam **4** in two sequential steps: nucleophilic attack of a chlorite anion (**5**) to form **D** followed by elimination of hypochlorous acid.[7] Since the electronic effect of phenyl groups in **1** seems to provide the driving force for the C−C bond cleavage, the protected L-prolinol **6** was prepared and tested under the same reaction conditions as for **1**. But again, the formation of glycidic amide was not observed and now cinnamic acid **7** and the starting prolinol **8** were isolated, illustrating that the C−N bond cleavage is favored over C−C bond rupture.

In an attempt to evidence the presence of radicals, compound **6** was exposed to 5 equiv of TEMPO (radical scavenger), which inhibited the C−N bond cleavage (22% of **7**). Unexpectedly, diastereomeric 3-alkoxyamine pyrrolidinones **9a** and **9b** were obtained in 30% yield as an equimolar mixture (eq 2, Scheme 2). The accidental incorporation of TEMPO in the β-site of **6** to form **9a** and **9b** inspired the development of a new chemical reaction for the selective double C_α−H/C_β−H oxidation of pyrrolidines to 3-alkoxyamine pyrrolidinones under transition-metal-free conditions.

Benzyl pyrrolidine **10** and benzyl piperidine **11** represent suitable substrates for testing the apparent selectivity in the double C−H functionalization and were selected for screening a variety of reaction conditions (Table 1). Both benzyl amines **10** and **11** were treated under the same reaction conditions as for **6** (entries 1 and 2), but the expected 3-alkoxyamine lactams **12** and **13** were not observed. With the knowledge that in some cases the oxidative capacity of $NaClO_2$ and TEMPO is reinforced by the use of NaClO,[8] the reactions were performed also in the presence of 1.5 equiv of NaOCl. To our delight, the reaction now proceeded in good yield for 3-alkoxyamine-2-piperidone **13** (80%) and moderate yield (45%) for 3-

Table 1. Optimization for the Selective Double C_α−H/C_β−H Oxidation of *N*-Benzyl Piperidines and Pyrrolidines[a]



entry	cyclic amine	$NaClO_2$/TEMPO/NaOCl (equiv)	solvent (ratio v/v)	time (h)	product (yield %)[b]
1	**11**	5/5/0	THF/H_2O/*t*-BuOH (3/7/7)	4	**13** (0)[c]
2	**10**	5/5/0	THF/H_2O/*t*-BuOH (3/7/7)	4	**12** (0)[c]
3	**11**	5/5/1.5	THF/H_2O/*t*-BuOH (3/7/7)	1	**13** (80)
4	**10**	5/5/1.5	THF/H_2O/*t*-BuOH (3/7/7)	2	**12** (45)
5	**11**	3/5/1.5	THF/H_2O/*t*-BuOH (3/7/7)	1	**13** (85)
6	**10**	3/5/1.5	THF/H_2O/*t*-BuOH (3/7/7)	2	**12** (55)
7	**11**	0/3/1.5	THF/H_2O/*t*-BuOH (3/7/7)	2	**13** (0)[c]
8	**11**	5/5/1.5	MeCN	2	**13** (80)
9	**11**	3/3/4.5	MeCN	1	**13** (0)[c]
10	**11**	3/3/1.5	MeCN	2	**13** (85)
11	**11**	2/1.5/1.5	MeCN	4	**13** (85)
12	**10**	2/1.5/1.5	MeCN	4	**12** (60)

[a]Reactions were performed using 0.3 mmol of cyclic amine warming from 0 °C to room temperature and using 10 equiv of NaH_2PO_4 as buffer keeping a pH ∼5. [b]Unless noted, yields are reported after silica gel chromatography. [c]Starting material remains unchanged

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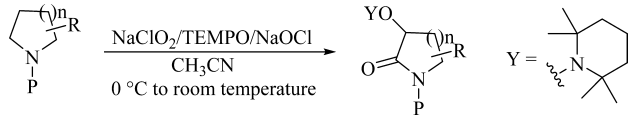
alkoxyamine-2-pyrrolidinone **12** (entries 3 and 4). By reducing the amount of $NaClO_2$ from 5 to 3 equiv, the yields of **13** and **12** were slightly increased (entries 5 and 6). As expected, in the absence of $NaClO_2$ the reaction did not proceed (entry 7). By using only MeCN as solvent, the yield of **13** was identical to that isolated from the THF/H_2O/*t*-BuOH mixture (entry 8). However, with an excess of NaOCl (4.5 equiv) the reaction did not proceed, and the starting materials remained almost unchanged (entry 9). These results establish that the use of 1.5 equiv of NaOCl is determinant for this unprecedented dual sp^3 C−H functionalization, and that at least 3 equiv of $NaClO_2$ and TEMPO are necessary to obtain **13** in good yield (entry 10). Finally, upon reduction of the stoichiometric amounts of $NaClO_2$ and TEMPO, the reaction conditions could be further optimized (2 equiv of $NaClO_2$, and 1.5 equiv of both NaOCl and TEMPO) to give **12** (60%) and **13** (85%), using MeCN as solvent (entries 11 and 12).

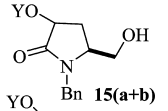
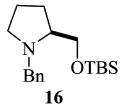
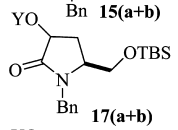
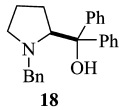
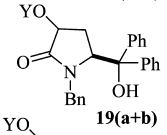
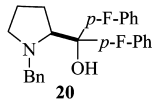
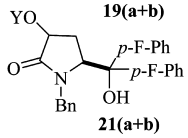
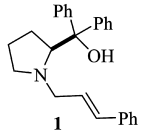
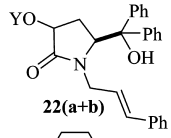
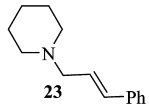
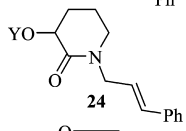
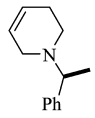
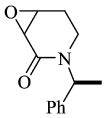
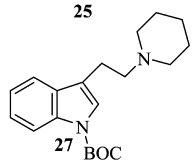
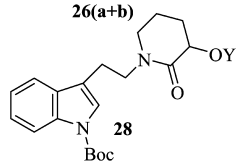
To explore the scope of the reaction, a series of substrates were selected in order to evaluate the selectivity of the double C−H oxidation that would allow to synthesize 3-alkoxyamine lactams of potential use in total synthesis. Thus, chiral tertiary pyrrolidines (**14**, **16**, **18**, and **20**) and tertiary piperidines (**23**, **25**,[4a] and **27**) were prepared from their corresponding L-prolinol derivatives and piperidine, respectively (Table 2). As determined after column chromatographic purification, pyrrolidinone **14** was transformed to an equimolar diastereomeric mixture of **15a** and **15b** in good yields, even though these oxidative reaction conditions are known to oxidize the hydroxyl groups to carboxylic acids (entry 1).[9] A slight reaction improvement was observed when the hydroxyl group was protected by the typical silyl group (**16** to **17a** and **17b**), illustrating the mildness of the reaction conditions (entry 2). As noted above for **1**, the presence of phenyl groups at the carbinol position of L-prolinol (**1**) favors dealkylation, and hence, only moderate yields were obtained for diastereomeric mixture of **19a−b** and **21a−b** (entries 3 and 4). With prolinol **1**, 66% of the corresponding diastereomeric mixture of the 3-alkoxyamine lactam **22a−b** were obtained (entry 5). For the *N*-alkyl substituted piperidine **23**, the reaction was less successful, giving **24** only in 14% yield (Table 2).

The chiral dihydropiperidine **25** was tested expecting to achieve C−H oxidation at both the C-5 and C-6 positions; however, the expected lactam was not observed, but instead the glycidic amide **26**[4a] (71%) was formed with good yield and with moderate diastereoselectivity (71:26) (entry 7). Since the reported direct method for the synthesis of glycidic amides occurs without any stereoselectivity,[3,4a] this result might provide a significant improvement for the stereocontrolled construction of the 3,4-epoxy-2-piperidone motif, which is a common skeleton encountered in numerous biologically active compounds.[10] A final remarkable result was obtained from the indole piperidine derivative **27** (entry 8), which not only features the high C−H oxidation selectivity and the compatibility of the Boc protecting group with the reaction conditions, but also the high stability of the indole ring against the inherent electrophilic species delivered from the oxidizing reagents employed. Thus, this later result represents a convenient way for the C−H functionalization of piperidines containing indole moiety, which is relevant for the total synthesis of indole alkaloids.[11]

Based on the α-aminoxylation of aldehydes[12] with enamines and $TEMPO^+X^-$, a mechanistic proposal for this double C−H oxidation is centered on the formation of enamine **E**, which might be generated by following the sequential transformation depicted in Scheme 3. TEMPO radical is first oxidized to oxammonium cation **F** that reacts with the cyclic amine[8,13] to give either **G** or **G′**, and after an elimination-like reaction, the iminium intermediate **H** is formed and rapidly transformed to enamine **E**. The reaction of enamine **E**[14] with oxammonium cation **F** (which the latter is probably regenerated by oxidation of TEMPOH[13]) allows the incorporation of TEMPO forming iminium **I** which is attacked by chlorite ion[7] to form **K**, and after elimination of HOCl provides the corresponding 3-alkoxyamine lactam (eq 3, Scheme 3). It is important to mention that the formation of enamine **E** (e. g., R = Ph) from radical cation **L** via an electron transfer reaction with ClO_2[6] might be not feasible because it would afford benzylic C−H

Table 2. Dual sp^3 C−H Oxidation of a Series of L-Prolinol and Piperidine Derivatives[a]



entry	substrate	time (h)	product	yield (%)[b]
1	 **14**	0.5	 **15(a+b)**	76[c,d]
2	 **16**	0.5	 **17(a+b)**	81[e]
3	 **18**	0.3	 **19(a+b)**	52[e]
4	 **20**	0.3	 **21(a+b)**	61[e]
5	 **1**	0.5	 **22(a+b)**	66[e]
6	 **23**	1	 **24**	14
7	 **25**	1	 **26(a+b)**	71[e]
8	 **27**	3	 **28**	78

[a]Reactions were carried out in 10 mL of CH_3CN using 2 equiv of $NaClO_2$, 1.5 equiv of TEMPO, 1.5 equiv of NaOCl, and 0.3 mmol of cyclic amines. [b]Yields were reported after silica gel chromatography. [c]Diastereomeric ratio (**a+b**) ~50:50. [d]Both diastereomers were structurally characterized by X-ray crystallographic studies. [e]Diastereomeric ratio (**a+b**) = 71:29.

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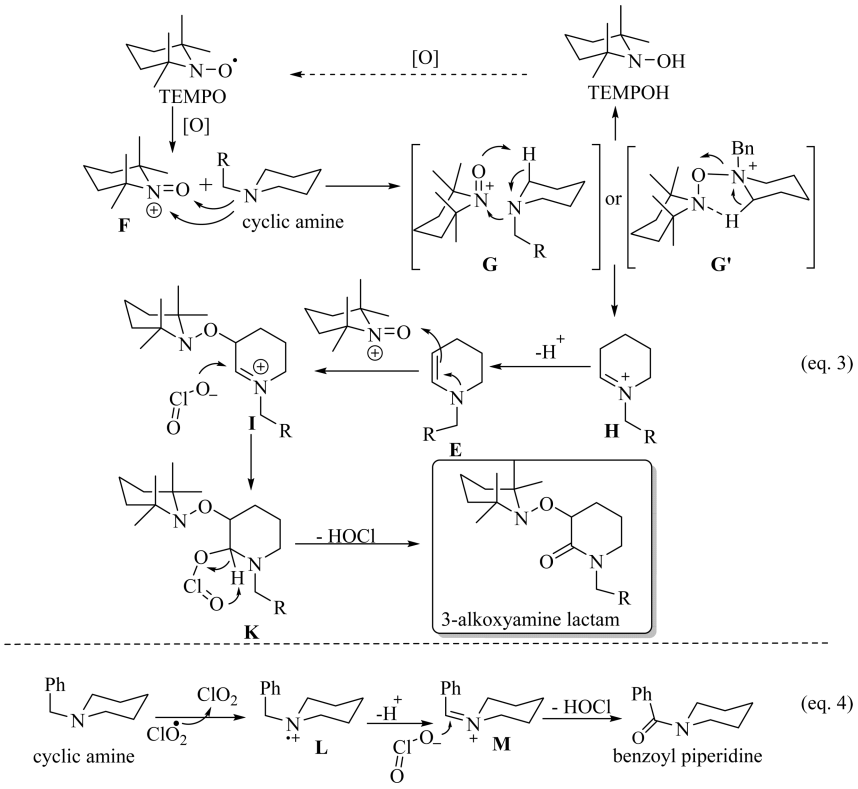
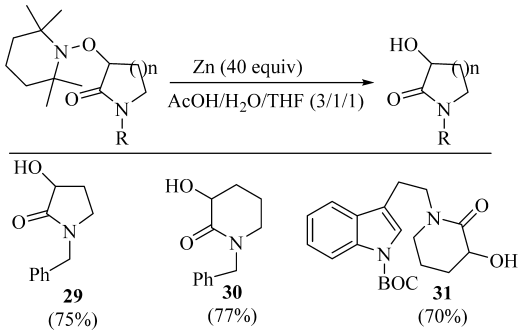
Scheme 3. Proposed Reaction Mechanism



oxidation (**M**), and after reacting with chlorite ion, benzoyl piperidine would be obtained as the major product (eq 4, Scheme 3).[3]

Finally, starting from the 3-alkoxylamine lactams, the respective 3-hydroxy lactams can be liberated by reduction with Zn.[15] This has been evidenced representatively for **13**, **12**, and **28** to give **29**, **30**, and **31**, respectively, in good yields (Scheme 4).

Scheme 4. Preparation of 3-Hydroxylactams



In summary, an unprecedented chemical method for the selective double C−H functionalization of cyclic amines to 3-alkoxyamine lactams is reported. Since this unprecedented dual sp^3 C−H functionalization is performed in the absence of a transition-metal catalyst, and cheap and nontoxic oxidizing reagents, such as $NaClO_2$ and NaOCl, are employed, this protocol represents a promising environmental-friendly method for the access to a number of pyrrolidine- and piperidine-derived alkaloids. Additionally, this new methodology represents a suitable methodology for α-oxygenation of lactams.[16]

EXPERIMENTAL SECTION

Commercially available reagents were used without further purification. Column chromatography (CC) was performed using silica gel (200−300 mesh) with solvents indicated in the text. Melting points were determined on an open capillary tube and were uncorrected. Optical rotations were measured in a digital polarimeter in the sodium D line (589 nm) and were reported as degrees at 20 °C and concentration was expressed as g/100 mL. Unless otherwise stated, ^{1}H NMR and ^{13}C NMR spectra were obtained in a 500 and 125 MHz spectrometer, respectively. All samples were analyzed in $CDCl_3$ with TMS as internal reference using a relative scale in parts per million (ppm) for the chemical shift (δ) and Hz for coupling constants (J). Splitting patterns are designated as follow: s, singlet; d, doublet; t, triplet; q, quartet; qu, quintet; m, multiple; and br, broad. High-resolution mass spectra (HRMS) were acquired in electron-impact (EI) mode using a TOF mass analyzer or in fast-atom-bombardment (FAB) mode using a QMS mass analyzer.

N-Cinnamyl-α,α-diphenyl-L-prolinol (1). To a solution of L-proline (2.0 g, 17.37 mmol) in CH_3OH (20 mL) at 0 °C was added dropwise $SOCl_2$ (2.53 mL, 4.13 g, 34.7 mmol). The reaction mixture was stirred over 5h at reflux temperature, and after the reaction was complete, the mixture was cooled and the solvent was removed under reduced pressure to obtain the corresponding methyl ester hydrochloride salt, which was dissolved in 30 mL of dry CH_2Cl_2 and treated with 4-dimethylaminopyridine (1.06 g, 8.68 mmol) and NEt_3 (3.512 g, 34.74 mmol). The reaction mixture was stirred for 15 min before the addition of cinnamyl bromide (4.10 g, 20.84 mmol) dissolved in CH_2Cl_2 (5 mL). The mixture was stirred under argon atmosphere at room temperature for 16 h, then 5 mL of concentrated aqueous solution of $NaHCO_3$ and 10 mL of H_2O were added. The organic phase was separated using an extraction funnel and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The organic portions were joined and concentrated just after passing on sodium sulfate to obtain methyl-*N*-cinnamyl-L-prolinate (4.018 g). The reaction crude was submitted to the next reaction without further purification. To a solution of methyl *N*-cinnamyl-L-prolinate (1.0 g, 4.06 mmol) in dry THF (30 mL) at 0 °C was added a 1.0 M solution in THF of

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phenylmagnesium bromide (10.15 mL, 10.15 mmol). The reaction mixture was stirred over 3 h in argon atmosphere at 0 °C and after the reaction was completed, a saturated solution of ammonium chloride was added dropwise until salt formation was observed. The solvent was removed by distillation at reduced pressure; the solids were washed with AcOEt (5 × 10 mL), then the liquids portions were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc, 6/1) to yield **1** (1.276 g, 85%) as a white crystalline solid. mp = 96−98 °C; $[\alpha]_D^{20}$ = +49.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.40−7.64 (m, 5H), 7.10−7.34 (m, 10H), 6.15 (d, *J* = 15.6 Hz, 1H), 6.00 (ddd, *J* = 15.6, 8.0, 5.2 Hz, 1H), 4.84 (s, 1H), 3.88 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.14−3.18 (m, 1H), 2.76 (ddd, *J* = 14.0, 5.2, 1.2 Hz, 1H), 2.64 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.51 (dt, *J* = 6.4, 9.2 Hz, 1H), 1.87−1.92 (m, 1H), 1.60−1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 148.0, 146.4, 131.7, 128.7, 128.5, 128.0, 128.0, 127.3, 127.2, 127.1, 126.9, 126.2, 126.2, 126.1, 125.6, 125.5, 77.7, 69.7, 57.5, 55.3, 29.8, 24.4; HRMS-ESI *m*/*z* 370.2075 (calcd. for $C_{26}H_{27}NO$, 369.2093).

***N*-Benzyl-*α*,*α*-diphenyl-L-prolinol (18).** Following the above procedure, but using methyl *N*-benzyl-L-prolinate (1.0 g, 4.56 mmol) and phenylmagnesium bromide (9.12 mL, 9.12 mmol) as substrate, prolinol **18**[17] (1.31 g, 84%) was obtained as white crystals. mp = 119−122 °C; $[\alpha]_D^{20}$ = +79.6 (*c* = 1.0, $CHCl_3$); lit[17] $[\alpha]_D^{22}$ = +91.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.72 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.31−7.14 (m, 8H), 7.09 (td, *J* = 7.0, 1.0 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 2H), 4.93 (br, 1H), 3.97 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.21 (d, *J* = 12.5 Hz, 1H), 3.02 (d, *J* = 13.0 Hz, 1H), 2.93−2.89 (m, 1H), 2.37−2.32 (m, 1H), 1.96 (dq, *J* = 13.0, 9.0 Hz, 1H), 1.78−1.73 (m, 1H), 1.66−1.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 147.9, 146.6, 139.6, 128.5, 128.1, 128.0, 128.0, 126.8, 126.3, 126.2, 125.5, 125.5, 77.9, 70.6, 60.5, 55.5, 29.7, 24.1.

***N*-Benzyl-*α*,*α*-bis(4-fluorophenyl)-L-prolinol (20).** Following the above procedure but using 4-fluorophenylmagnesium bromide (2.85 mL, 1.14 g, 5.7 mmol) as Grignard reagent, prolinol **20**[17] (0.679 g, 78.5%) was obtained as white crystals. mp = 150−152 °C; $[\alpha]_D^{20}$ = +71.4 (*c* = 1.0, $CHCl_3$); lit[17] $[\alpha]_D^{22}$ = +94.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.69−7.65 (m, 2H), 7.55−7.51 (m, 2H), 7.28−7.20 (m, 3H), 7.07−6.96 (m, 6H), 5.01 (br, 1H), 3.93 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.27 (d, *J* = 12.5 Hz, 1H), 3.09 (d, *J* = 12.5 Hz, 1H), 2.95 (ddd, *J* = 10.0, 6.0, 4.5 Hz, 1H), 2.39 (dt, *J* = 9.0, 8.0 Hz, 1H), 1.95 (apparent dq, *J* = 12.5, 9.0 Hz, 1H), 1.75−1.69 (m, 1H), 1.68−1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 161.4 (d, $^1J_{C-F}$ = 244.0 Hz), 161.2 (d, $^1J_{C-F}$ = 243.5 Hz), 143.7 (d, $^4J_{C-F}$ = 3.1 Hz), 142.4 (d, $^4J_{C-F}$ = 3.2 Hz), 139.3, 128.4, 128.2, 127.1 (d, $^3J_{C-F}$ = 7.7 Hz), 127.0 (d, $^3J_{C-F}$ = 7.7 Hz), 127.0, 115.1 (d, $^2J_{C-F}$ = 21.1 Hz), 114.9 (d, $^2J_{C-F}$ = 21.0 Hz), 77.3, 70.6, 60.6, 55.5, 29.7, 24.1.

***N*-Cinnamyl-*O*-ter-butyldimethylsilyl-L-prolinol (6).** To a suspension of $LiAlH_4$ (0.464 g, 12.22 mmol) in dry THF (20 mL) at 0 °C was added a solution of methyl *N*-cinnamyl-L-prolinate (2.0 g, 8.15 mmol) in dry THF (10 mL). The solution was allowed stirring over 3 h at 0 °C, after this time, aqueous solution of $NaHCO_3$ (5 mL) was dropwise aggregated until salt formation is observed. Then the resulting solids were filtered off, washed with AcOEt, and the organic phase was dried over Na_2SO_4, concentrated, and purified by flash chromatography on silica gel (eluent hexane/EtOAc: 1:2) to obtain the corresponding *N*-cinnamyl-L-prolinol (1.32 g, 75%) as a viscous liquid. $[\alpha]_D^{20}$ = −35.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.38−7.36 (m,2H), 7.32−7.29 (m, 2H), 7.23 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.28 (ddd, *J* = 16.0, 7.5, 6.0 Hz, 1H), 3.67 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.56 (ddd, *J* = 13.5, 6.0, 1.5 Hz, 1H), 3.43 (dd, *J* = 10.5, 2.5 Hz, 1H), 3.15 (apparent qu, *J* = 5.0 Hz, 1H), 3.09 (ddd, *J* = 13.5, 8.0, 1.5 Hz, 1H), 2.69 (dddd, *J* = 5.5, 3.5, 3.0, 2.5 Hz, 1H), 2.36 (apparent q, *J* = 8.5 Hz, 1H), 1.91 (ddt, *J* = 12.5, 9.0, 8.5 Hz 1H), 1.83- 1.77 (m, 1H), 1.76−1.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 136.9, 131.8, 128.5, 127.5, 127.4, 126.2, 63.8, 62.0, 56.4, 54.4, 27.8, 23.5. To a solution of *t*-Bu$(CH_3)_2$SiCl (0.754 g, 5.00 mmol) and imidazole (0.426 g, 6.26 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was dropwise added a solution of *N*-cinnamyl-L-prolinol (0.904 g, 4.17 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature over 3 h and then 5 mL of aqueous solution of $NaHCO_3$ was added. Both phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc: 9:1) to obtain **6**[18] (1.17 g, 85%) as a greenish yellow liquid. $[\alpha]_D^{20}$ = −45.8 (*c* = 1.0, $CHCl_3$); lit[18] $[\alpha]_D^{23}$ = −59.0 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.38−7.36 (m, 2H), 7.31−7.28 (m, 2H), 7.21 (tt, *J* = 7.0, 1.5 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.33 (ddd, *J* = 16.0, 8.0, 6.5 Hz, 1H), 3.73−3.69 (m, 2H), 3.47 (dd, *J* = 10.0, 7.0 Hz, 1H), 3.15−3.09 (m, 2H), 2.64 (qu, *J* = 6.5 Hz, 1H), 2.31 (dt, *J* = 9.0, 7.0 Hz, 1H), 1.91 (ddt, *J* = 12.5, 8.5, 8.0 Hz, 1H), 1.80−1.67 (m, 2H), 1.63−1.57 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 137.0, 131.8, 128.4, 127.8, 127.2, 126.2, 67.0, 64.8, 57.8, 54.8, 28.3, 25.9, 22.8, 18.2, −5.3, −5.3.

***N*-Benzyl-L-prolinol (14).** A solution of methyl *N*-benzylprolinate (2.0 g, 9.12 mmol) in dry THF (10 mL) was added to a suspension of $LiAlH_4$ (0.693 g, 18.25 mmol) in dry THF (20 mL). The mixture was stirred over 2 h before an aqueous solution of $NaHCO_3$ (5 mL) was added dropwise until salt formation was observed. Then the resulting solids were filtered off, washed with AcOEt, and the organic phase was dried over Na_2SO_4. Organic phase was concentrated under reduced pressure and purified by flash chromatography on silica gel (eluent hexane/EtOAc: 1:1) to give **14**[19] (1.517 g, 87%) as a yellow oil. $[\alpha]_D^{20}$ = −46.3 (*c* = 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.34−7.24 (m, 5H), 3.99 (d, *J* = 13.0 Hz, 1H), 3.66 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.44 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.38 (d, *J* = 13.0 Hz, 1H), 3.03−2.97 (m, 2H), 2.76 (ddd, *J* = 12.0, 6.0, 3.0 Hz, 1H), 2.31 (dt, *J* = 8.0, 9.5 Hz, 1H), 1.93 (apparent dq, *J* = 13.0, 9.0 Hz, 1H), 1.87−1.80 (m, 1H), 1.73−1.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 138.8, 128.7, 128.3, 127.1, 64.3, 61.6, 58.5, 54.3, 27.6, 23.4.

***N*-Benzyl-*O*-*tert*-Butyldimethylsilyl-L-prolinol (16).** To a solution of imidazole (0.408 g, 6.00 mmol) and *t*-Bu$(CH_3)_2$SiCl (0.723 g, 4.80 mmol) in 20 mL of dry CH_2Cl_2 was added a solution of **14** (0.765 g, 4.00 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature over 2 h and then 5 mL of aqueous solution of $NaHCO_3$ was added. Both phases were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc: 12:1) to obtain **16**[20] (1.03 g, 84%) as a greenish yellow liquid. $[\alpha]_D^{20}$ = −46.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.33−7.27 (m, 4H), 7.22 (tt, *J* = 7.5, 1.5 Hz, 1H), 4.11 (d, *J* = 13.0 Hz, 1H), 3.64 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.46 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.41 (d, *J* = 13.0 Hz, 1H), 2.90 (ddd, *J* = 9.0, 7.0, 2.5 Hz, 1H), 2.67 (ddd, *J* = 12.5, 8.5, 6.0 Hz, 1H), 2.21 (dt, *J* = 9.0, 7.5 Hz, 1H), 1.90 (dq, *J* = 12.5, 8.5 Hz, 1H), 1.74−1.63 (m, 2H), 1.62−1.56 (m, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 139.9, 128.9, 128.0, 126.6, 67.1, 65.0, 60.4, 54.8, 28.04, 25.9, 22.8, 18.2, −5.3, −5.3.

1-Cinnamylpiperidine (23). To a suspension of Na_2CO_3 (1.58 g, 15 mmol) in dry MeCN (20 mL) at room temperature was added piperidine (0.98 mL, 10. 0 mmol) and a solution of cinnamyl bromide (1.97 g, 10 mmol) in CH_2Cl_2 (10 mL). Then, the mixture was heated to reflux temperature over 4 h. After the reaction was completed, the solvent was removed under reduced pressure and the resulting solids were washed with EtOAc (5 × 10 mL). The organic portion was dried over Na_2SO_4, concentrated and purified by flash chromatography on silica gel (eluent hexane/EtOAc: 2/1) to obtain **23**[21] (1.12 g, 56%) as a black brownish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.38−7.36 (m, 2H), 7.31−7.28 (m, 2H), 7.21 (tt, *J* = 7.5, 1.5 Hz 1H), 6.49 (d, *J* = 15.5 Hz, 1H), 6.30 (dt, *J* = 16.0, 7.0 Hz, 1H), 3.11 (dd, *J* = 7.0, 1.5 Hz, 2H), 2.43 (br, 4H), 1.60 (qu, *J* = 6.0 Hz, 4H), 1.44 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 137.0, 132.5, 128.4, 127.3, 126.2, 61.8, 54.5, 25.9, 24.2.

***tert*-Butyl 3-[2-(piperidin-1-yl)ethyl]-1H-indole-1-carboxylate (27).** To a suspension of K_2CO_3 (0.704 g, 5.09 mmol) in dry MeCN (20 mL) at room temperature was added piperidine (0.325 g, 1.46 mmol) and *N*-Boc-2-bromoethylindole (0.826 g, 2.54 mmol).

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Then, the mixture was allowed to react over 4 h. After the reaction was completed, the solvent was removed under reduced pressure and the resulting solids were washed with EtOAc (5 × 10 mL). The organic portion was concentrated, dried over Na_2SO_4, and purified by flash chromatography on silica gel (eluent hexane/EtOAc: 1/1) to obtain **27** (1.20 g, 90%) as a light yellow oil. ^{1}H NRM (500 MHz, $CDCl_3$) δ: 8.11 (br, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.40 (br, 1H), 2.51 (br, 4H), 7.30 (ddd, J = 8.5, 7.5, 1.0 Hz, 1H), 7.23 (ddd, J = 8.5, 8.0, 1.0 Hz, 1H), 2.91−2.88 (m, 2H), 2.67−2.64 (m, 2H), 1.66 (s, 9H), 1.63 (m, 4H), 1.48 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 149.8, 135.3, 130.7, 124.2, 122.5, 122.2, 119.1, 118.9, 115.2, 83.2, 59.0, 54.5, 28.1, 25.9, 24.3, 22.5; HRMS-ESI m/z 328.2151 (calcd 328.2151 for $C_{20}H_{28}N_2O_2$).

Oxidation with TEMPO-$NaClO_2$−NaClO in a Mixture of *t*-butanol/H_2O/THF. To a solution of NaH_2PO_4 (3 mmol), $NaClO_2$ (0.9 mmol), and TEMPO (0.9 mmol) in 2 mL of a mixture of THF/H_2O/*t*-BuOH (3/7/7) at 0 °C was added 0.3 mmol of pyrrolidine or piperidine dissolved in 1.0 mL of THF. Immediately, 1.5 mL of a solution of NaClO (aq, 3%) was dropwise added. The mixture was allowed to stir until reaction was completed. Finally, the reaction was quenched by adding few drops of NaOH (aq) until the red-wine color was turned into a clear-red color. The resulting phases were separated; the organic layer was washed with brine (2 × 3 mL), whereas the aqueous phase was extracted with AcOEt (3 × 5 mL). Organic portions were concentrated and purified by flash chromatography on silica gel using hexanes/AcOEt as eluent.

Oxidation with TEMPO-$NaClO_2$−NaClO in MeCN. To a suspension of 3 mmol of NaH_2PO_4, 0.90 mmol of $NaClO_2$, and 0.60 mmol of TEMPO in 5 mL of MeCN was added 1.5 mL of a solution of NaClO (aq, 3%) at 0 °C, then 0.3 mmol of pyrrolidine or piperidine in 1.0 mL of MeCN was added. The mixture was stirred and monitored by TLC until the starting material reacted totally. Finally, 0.3 mL of NaOH (aq) was added dropwise to quench the reaction until the red-wine color was turned into a clear-red color. The resulting phases were separated in a separatory funnel, then solids were washed with AcOEt (3 × 5 mL) while the liquid was washed with brine (2 × 3 mL). The organic portions were concentrated at vacuum and purified by flash chromatography on silica gel using hexanes/AcOEt as eluent. Chiral pyrrolidines and piperidinas yielded diastereomeric equimolar mixture of 3-alkoxyamine lactams.

(5*S*,3*S)-5-[((*tert*-Butyldimethylsilyl)oxy)methyl)]-1-cinnamyl-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pirrolydin-2-one (9a).** Eluent hexanes/EtOAc: 19/1. Isolated 0.024 g (16%) as a greenish viscous liquid. $[\alpha]_D^{20}$ = +42.9 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33−7.31 (m, 2H), 7.28 (t, J = 7.0 Hz, 2H), 7.21 (tt, J = 7.5, 2.0 Hz, 1H), 6.49 (d, J = 16.0 Hz, 1H), 6.10 (ddd, J = 16.0, 8.0, 5.5 Hz, 1H), 4.80 (t, J = 9.0 Hz, 1H), 4.64 (ddd, J = 15.0, 5.5, 1.5 Hz, 1H), 3.69−3.65 (m, 2H), 3.58−3.55 (m, 1H), 3.52 (dd, J = 10.5, 3.5 Hz, 1H), 2.38 (dd, J = 12.5, 8.5 Hz, 1H), 2.10 (dt, J = 12.5, 9.5 Hz, 1H), 1.43−1.41 (m, 9H), 1.22 (br, 3H), 1.11 (br, 3H), 1.07 (br, 3H), 0.85 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.5, 136.2, 133.2, 128.4, 127.6, 126.2, 124.0, 82.5, 63.3, 60.8, 58.7, 54.8, 43.2, 40.4, 40.2, 34.3, 33.3, 32.3, 25.7, 20.2, 20.0, 18.0, 17.0, −5.6, −5.6; HRMS-ESI m/z 500.3432 (calcd. for $C_{29}H_{48}N_2O_3Si$, 500.3434).

(5*S*,3*R)-5-[((*tert*-Butyldimethylsilyl)oxy)methyl)]-1-cinnamyl-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pirrolydin-2-one (9b).** Isolated 0.021g (14%) as a greenish viscous liquid. $[\alpha]_D^{20}$ = +46.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35−7.21 (m, 5H), 6.53 (d, J = 16.0 Hz, 1H), 6.15 (dt, J = 15.5, 7.0 Hz, 1H), 4.57 (t, J = 8.5 Hz, 1H), 4.43 (dd, J = 15.0, 6.0 Hz, 1H), 3.88 (dd, J = 15.0, 7.5 Hz, 1H), 3.74 (dd, J = 10.5, 3.5 Hz, 1H), 3.69 (dd, J = 10.5, 5.0 Hz, 1H), 3.50- 3.46 (m, 1H), 2.46 (ddd, J = 12.5, 7.0, 6.0 Hz, 1H), 1.82 (dt, J = 12.5, 8.5 Hz, 1H), 1.47 (br, 4H), 1.43 (br, 3H), 1.31 (br, 2H), 1.24 (br, 3H), 1.16 (br, 3H), 1.10 (br, 3H), 0.90 (s, 9H), 0.70 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.3, 136.3, 132.7, 128.3, 127.4, 126.2, 124.2, 82.3, 64.4, 54.9, 43.2, 40.2, 40.1, 34.3, 32.4, 31.5, 25.6, 20.1, 20.0, 18.0, 16.9, −5.5, −5.6; HRMS-EI m/z 500.3433 (calcd. for $C_{29}H_{48}N_2O_3Si$, 500.3434).

1-Benzyl-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-pyrrolidin-2-one (12). Eluent hexanes/EtOAc: 2/1. Isolated 0.059 g (60%) as a yellow viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34−7.23 (m, 5H), 4.64 (dd, J = 9.5, 8.0 Hz, 1H), 4.55 (d, J = 14.5 Hz, 1H), 4.33 (d, J = 14.5 Hz, 1H), 3.13 (t, J = 9.5 Hz, 1H), 3.00 (dt, J = 9.5, 6.5 Hz, 1H), 2.46 (dt, J = 12.5, 6.5 Hz, 1H), 2.00 (tt, J = 12.5, 9.5 Hz, 1H), 1.57 (br, 1H), 1.46 (br, 4H), 1.44 (br, 3H), 1.32 (br, 1H), 1.28 (br, 3H), 1.15 (br, 3H), 1.11 (br, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.0, 136.0, 128.5, 128.2, 127.5, 83.1, 61.0, 59.0, 46.9, 41.9, 40.4, 40.2, 34.3, 32.4, 28.9, 20.3, 20.1, 17.11; HRMS-EI m/z 330.2306 (calcd. for $C_{20}H_{30}N_2O_2$, 330.2307).

1-Benzyl-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-piperidin-2-one (13). Eluent hexanes/EtOAc: 3/1. Isolated 0.087 g (85%) as a yellow and viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32−7.24 (m, 5H), 4.76 (d, J = 15.0 Hz, 1H), 4.40−4.38 (m, 1H), 4.38 (d, J = 15.0 Hz, 1H), 3.29 (ddd, J = 12.5, 6.5, 5.5 Hz, 1H), 3.11 (dt, J = 12.5, 6.5 Hz, 1H), 2.11−2.04 (m, 1H), 2.02−1.92 (m, 2H), 1.70−1.62 (m, 1H), 1.48 (br, 6H), 1.25 (br, 3H), 1.20 (s, 6H), 1.13 (br, 3H); ^{13}C NMR 125 (MHz, $CDCl_3$) δ: 169.3, 137.0, 128.4, 128.1, 127.1, 80.5, 60.5, 59.7, 49.9, 45.9, 40.1, 34.1, 33.0, 27.1, 20.4, 20.1, 18.7, 17.0. HRMS-EI m/z 344.2493 (calcd. for $C_{21}H_{32}N_2O_2$, 344.2464).

(3*S*,5*S*)-1-Benzyl-5-(hydroxymethyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrrolidin-2-one (15a). Eluent hexanes/EtOAc: 2/12. Isolated 0.041 g (38%) as a colorless crystal; mp =129−131 °C. $[\alpha]_D^{20}$ = +12.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35−7.26 (m, 5H), 4.64 (d, J = 8.5 Hz, 1H), 4.63 (d, J = 15.0 Hz, 1H) 4.43 (d, J = 15.0 Hz, 1H), 3.77 (ddd, J = 12.0, 4.5, 3.5 Hz, 1H), 3.50 (ddd, J = 12.0, 7.0, 3.0 Hz, 1H), 3.36 (ddt, J = 4.5, 3.5, 3.0 Hz, 1H), 2.43 (ddd, J = 13.0, 8.0, 6.5 Hz, 1H), 2.00 (dt, J = 13.0, 8.0 Hz, 1H), 1.62−1.60 (m, 2H), 1.48 (br, 6H), 4.40−1.33 (m, 2H), 1.24 (br, 3H), 1.19 (br, 3H), 1.12 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.2, 137.0, 128.8, 127.9, 127.7, 82.6, 62.1, 61.1, 59.3, 55.3, 45.3, 40.4, 34.4, 32.6, 30.9, 20.3, 20.2, 17.1; HRMS-EI m/z 360.2418 (calcd. for $C_{21}H_{32}N_2O_3$, 360.2413).

(3*R*,5*S*)-1-Benzyl-5-(hydroxymethyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrrolidin-2-one (15b). Isolated 0.040 g (38%) of a colorless crystal; mp =134−136 °C; $[\alpha]_D^{20}$ = +39.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34−7.26 (m, 5H), 4.87 (t, J = 9.0 Hz, 1H), 4.81 (dd, J = 15.0, 6.0 Hz, 1H), 4.24 (dd, J = 15.0, 12.0 Hz, 1H), 3.62 (dd, J = 11.0, 2.5 Hz, 1H), 3.49 (d, J = 11.0 Hz, 1H), 3.46−3.43 (m, 1H), 2.44 (ddd, J = 12.5, 8.5, 1.0 Hz, 1H), 2.17−2.10 (m, 1H), 1.89 (br, 1H), 1.71−1.58 (m, 1H), 1.46 (br, 7H), 1.32−1.27 (m, 4H), 1.14 (br, 3H), 1.11 (br, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.0, 136.5, 128.7, 128.1 127.6, 82.3, 62.6, 62.5, 61.1, 59.0, 55.1, 55.1, 45.2, 45.1, 40.4, 40.3, 34.3, 33.0, 32.3, 20.4, 20.2, 17.1; HRMS-EI m/z 360.2408 (calcd. for $C_{21}H_{32}N_2O_3$, 360.2413).

(5*S*,3*R*)-1-Benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrrolidin-2-one (17a). Absolute configuration at C-3 was determined by chemical correlation. Eluent hexanes/EtOAc: 19/1. Isolated 0.056 g (40%) as a yellow pale liquid; $[\alpha]_D^{20}$ = +54.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33−7.25 (m, 5H), 4.95 (d, J = 15.0 Hz, 1H), 4.87 (t, J = 9.0 Hz, 1H), 4.05 (d, J = 15.0 Hz, 1H), 3.61 (dd, J = 10.5, 3.5 Hz, 1H), 3.46 (dd, J = 11.0, 3.5 Hz, 1H), 3.38 (dt, J = 8.5, 3.5 Hz, 1H), 2.38 (dd, J = 8.0, 12.0 Hz, 1H), 2.07 (dt, J = 12.0, 9.0 Hz, 1H), 1.57 (br, 2H), 1.45 (br, 7H), 1.27 (br, 3H), 1.13 (br, 3H) 1.10 (br, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 136.2, 128.3, 128.0, 127.2, 82.4, 62.9, 60.7, 58.6, 54.5, 44.7, 40.3, 40.1, 34.2, 33.1, 32.2, 25.6, 20.1, 19.9, 17.9, 16.9, −5.7, −5.8; HRMS-EI m/z 474.3247 (calcd. for $C_{27}H_{46}N_2O_3Si$, 474.3278).

(5*S*,3*S*)-1-Benzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrrolidin-2-one (17b). Isolated 0.058 g (41%) as a yellow pale liquid. $[\alpha]_D^{20}$ = +40.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32−7.22 (m, 5H), 4.98 (d, J = 15 Hz, 1H), 4.59 (t, J = 8.5 Hz, 1H), 4.16 (d, J = 15 Hz, 1H), 3.66 (dd, J = 11.0, 4.0 Hz, 1H), 3.61 (dd, J = 11.0, 5.0 Hz, 1H), 3.34−3.30 (m, 1H), 2.39 (ddd, J = 12.5, 8.0, 6.5 Hz, 1H), 1.88 (dt, J = 12.5, 8.5 Hz, 1H), 1.77 (br, 1H), 1.57 (br, 1H), 1.47−1.45 (m, 7H), 1.25 (br, 3H), 1.17 (br, 3H), 1.11 (br, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s,

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3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.8, 136.9, 128.4, 128.0, 127.2, 82.5, 64.1, 61.0, 59.1, 54.5, 44.8, 40.3, 34.4, 32.6, 31.4, 25.8, 20.1, 18.2, 17.1, −5.4, −5.5; HRMS-EI m/z 474.3275 (calcd. for $C_{27}H_{46}N_2O_3Si$, 474.3278).

(5*S*,3*S- and 5*S*,3*R**)-1-Benzyl-5-(hydroxydiphenylmethyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrrolidin-2-one (19a and 19b).** Eluent hexanes/EtOAc: 19/1. Isolated 0.079 g (52%) as a yellow and very viscous liquid. Reported as a mixture of diastereoisomers. ^{1}RMN (500 MHz, $CDCl_3$) δ: 7.55 (br, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.36−7.19 (m, 23H), 7.16 (tt, J = 7.5, 1.0 Hz, 1H), 6.93 (d, J = 7.0 Hz, 2H), 6.70 (dd, J = 7.5, 3.5 Hz, 2H), 5.03 (d, J = 15.5 Hz, 1H), 4.82 (d, J = 15.0 Hz, 1H), 4.57 (dd, J = 8.0, 2.0 Hz, 1H), 4.52 (t, J = 9.0, 1H), 4.48 (dd, J = 8.0, 2.5 Hz, 1H), 4.39 (d, J = 9.0 Hz, 1H), 4.14 (s, 1H), 2.98 (d, J = 15.0 Hz, 1H), 2.96 (d, J = 15.0 Hz, 1H), 2.51 (dd, J = 13.0, 8.0 Hz, 1H), 2.45 (s, 1H), 2.20 (dt, J = 15.0, 8.0 Hz, 1H), 2.11−2.04 (m, 2H), 1.66 (br, 3H), 1.47−1.39 (m, 12H), 1.33 (br, 3H), 1.27−1.24 (m, 9H), 1.07 (br, 6H), 0.99 (br, 3H); ^{13}C RMN (125 MHz, $CDCl_3$) δ: 175.1, 173.0, 146.7, 145.0, 144.7, 144.3, 136.4, 136.1, 128.6, 128.4, 128.4, 128.4, 128.3, 127.8, 127.7, 127.5, 127.4, 127.2, 126.9, 126.8,, 126.0, 125.9, 125.6, 125.3, 81.9, 81.8, 80.0, 76.9, 61.9, 60.9, 60.0, 58.8, 45.7, 45.0, 40.5, 40.2, 34.3, 34.2, 32.3, 31.4, 29.6, 20.3, 20.1, 17.1, 17.0; HRMS-EI m/z 512.3049 (calcd. for $C_{33}H_{40}N_2O_3$, 512.3039).

(5*S*,3*R)-1-Benzyl-5-(bis(4-fluorophenyl) (hydroxy)methyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrrolidin-2-one (21a).** Eluent hexanes/EtOAc: 7/1. Isolated 0.053 g (32%) as a colorless viscous oil. $[\alpha]_D^{20}$ = +63.2 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32−7.24 (m, 7H), 6.96 (t, J = 8.5 Hz, 4H), 6.90 (d, J = 7.0 Hz, 2H), 4.98 (d, J = 15.0 Hz, 1H), 4.47 (t, J = 7.0 Hz, 1H), 4.35 (d, J = 9.0 Hz, 1H), 3.07 (d, J = 15.0 Hz, 1H), 3.01 (br, 1H), 2.42 (dd, J = 13.0, 8.0 Hz, 1H), 2.07 (dt, J = 12.5, 9.5 Hz, 1H), 1.53 (br, 1H), 1.42−1.40 (m, 5H), 1.32 (br, 3H), 1.23 (br, 4H), 1.08 (br, 3H), 1.00 (br, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.8, 161.8 (d, $^1J_{C-F}$ = 246.1 Hz), 161.6 (d, $^1J_{C-F}$ = 245.7 Hz), 140.2 (d, $^4J_{C-F}$ = 2.6 Hz), 140.0 (d, $^4J_{C-F}$ = 2.8 Hz), 135.6, 128.4, 127.6 (d, $^3J_{C-F}$ = 7.7 Hz), 127.6 (d, $^3J_{C-F}$ = 7.6 Hz), 127.4, 127.2, 115.2 (d, $^2J_{C-F}$ = 21.1 Hz), 115.1 (d, $^2J_{C-F}$ = 21.1 Hz), 81.4, 79.1, 60.8, 59.8, 58.7, 45.7, 40.2, 40.0, 34.1, 33.6, 32.2, 20.1, 20.0, 16.9; HRMS-FAB m/z [M + H]$^+$ 549.2919 (calcd. for $C_{33}H_{39}F_2N_2O_3$, 549.2929).

(5*S*,3*S)-1-Benzyl-5-(bis(4-fluorophenyl) (hydroxy)methyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrrolidin-2-one (21b).** Isolated 0.047 g (29%) as a colorless viscous oil. $[\alpha]_D^{20}$ = +78.6 (c = 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47−7.44 (m, 4H), 7.22 (br, 3H), 6.97 (dd, J = 12.5, 7.5 Hz, 4H), 6.71 (d, J = 3.0 Hz, 2H), 4.86 (d, J = 15.0 Hz, 1H), 4.53−4.49 (m, 2H), 4.30 (br, 1H), 2.99 (d, J = 15.0 Hz, 1H), 2.24−2.17 (m, 1H), 2.07 (d, J = 14.5 Hz, 1H), 1.49−1.47 (m, 8H), 1.27−1.22 (m, 4H), 1.08−1.05 (m, 3H), 0.91−0.87 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.3, 160.2 (d, $^1J_{C-F}$ = 245.0 Hz),159.9 (d, $^1J_{C-F}$ = 244.8 Hz), 141.0 (d, $^4J_{C-F}$ = 2.7 Hz), 139.2 (d, $^4J_{C-F}$ = 2.7 Hz), 134.5, 126.9, 126.0, 125.9, 125.8 (d, $^3J_{C-F}$ = 7.7 Hz), 125.4 (d, $^3J_{C-F}$ = 7.7 Hz), 113.7 (d, $^2J_{C-F}$ = 21.1 Hz), 113.6 (d, $^2J_{C-F}$ = 21.1 Hz), 80.2, 74.8, 60.2, 59.4, 58.6, 44.1, 38.9, 32.5, 31.5, 29.9, 18.9, 18.8, 15.4; HRMS-FAB m/z [M + H]$^+$ 549.2898 (calcd. for $C_{33}H_{39}F_2N_2O_3$, 549.2929).

(5*S*,3*R)-1-Cinnamyl-5-(hydroxydiphenylmethyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrrolidin-2-one (22a).** Eluent hexanes/EtOAc: 6/1. Isolated 0.056 g (36%) as a yellow viscous oil. $[\alpha]_D^{20}$ = +53.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.46−7.42 (m, 4H), 7.37−7.34 (m, 2H), 7.33−7.28 (m, 7H), 7.27−7.23 (m, 2H), 6.05 (dd, J = 16.0, 1.0 Hz, 1H), 5.89 (ddd, J = 16.0, 9.0, 4.5 Hz, 1H), 4.63 (d, J = 9.0 Hz, 1H), 4.52 (t, J = 9.0 Hz, 1H), 4.43 (dd, J = 14.5, 4.0, 2.0 Hz, 1H), 2.62 (dd, J = 15.0, 9.0 Hz, 1H), 2.55−2.50 (m, 2H), 2.16 (dt, J = 13.0, 9.5 Hz, 1H), 1.55−1.36 (m, 6H), 1.32 (br, 3H), 1.22 (br, 3H), 1.05 (br, 3H), 0.99 (br, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.7, 144.6, 144.3, 136.3, 133.9, 128.5, 128.4, 127.7, 127.5, 124.4, 126.3, 125.9, 123.8, 81.9, 79.8, 60.9, 60.4, 58.8, 44.7, 40.4, 40.1, 34.2, 34.2, 32.2, 20.3, 20.1, 17.0; HRMS-EI m/z 538.3166 (calcd. for $C_{35}H_{42}N_2O_3$, 538.3195).

(5*S*,3*R)-1-Cinnamyl-5-(hydroxydiphenylmethyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrrolidin-2-one (22b).** Isolated 0.048 g (30%) as a yellow and viscous oil. $[\alpha]_D^{20}$ = +45.0 (c = 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.68 (d, J = 7.0 Hz, 2H), 7.55 (dd, J = 9.0, 1.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.32−7.23 (m, 8H), 7.18 (tt, J = 7.5, 1.5 Hz, 1H), 5.82−5.73 (m, 2H), 4.75 (dd, J = 8.0, 3.0 Hz, 1H), 4.43 (dd, J = 7.5, 3.0 Hz, 1H), 4.23 (dd, J = 14.5, 3.5 Hz, 1H), 4.03 (s, 1H), 2.78 (dd, J = 14.5, 6.5 Hz, 1H), 2.24 (dt, 14.5, 8.0 Hz, 1H), 2.07 (dt, J = 15.0, 3.0 Hz, 1H), 1.45 (br, 8H), 1.23 (br, 4H), 1.05 (br, 3H), 0.88 (br, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.8, 146.5, 145.2, 136.2, 133.6, 128.5, 128.3, 128.2, 127.7, 127.0, 126.8, 126.3, 125.7, 125.2, 123.3, 81.9, 76.9, 61.8, 61.0, 59.9, 44.3, 40.4, 33.9, 33.0, 31.5, 20.5, 20.3, 16.9; HRMS-FAB m/z [M+H]$^+$ 539.3299 (calcd. for $C_{35}H_{43}N_2O_3$, 539.3274).

1-Cinnamyl-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-piperidin-2-one (24). Eluent hexanes/EtOAc: 10/1. Isolated 0.015 g (14%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 6.50 (d, J = 16 Hz, 1H), 6.17 (dt, J = 16.0, 7.0 Hz, 1H), 4.35 (dd, J = 5.5, 3.5 Hz, 1H), 4.15 (ddd, J = 14.5, 6.5, 1.0 Hz, 1H), 4.11 (ddd, J = 14.5, 8.0, 1.5 Hz, 1H), 3.37 (ddd, J = 12.0, 6.5, 5.5 Hz, 1H), 3.21 (ddd, J = 12.0, 6.5, 4.5 Hz, 1H), 2.08−1.97 (m, 3H), 1.77−1.70 (m, 1H), 1.47 (br, 6H), 1.25 (br, 3H), 1.20 (s, 6H), 1.13 (br, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.2, 136.5, 133.0, 128.5, 127.6, 126.3 124.3, 80.5, 60.6, 59.8, 48.8, 46.1, 40.2, 34.2, 33.0, 27.3, 20.5, 20.2, 18.9, 17.1; HRMS-EI m/z 370.2620 (calcd. for $C_{23}H_{34}N_2O_2$, 370.2620).

***tert*-Butyl-3-(2-(2-oxo-3-((2,2,6,6-tetramethylpiperidin-1-yl)-oxy)piperidin-1-yl)ethyl)-1H-indole-1-carboxylate (28).** Eluent hexanes/EtOAc: 4/1. Isolated 0.116 g (78%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.13 (br, 1H), 7.61 (d, 7.5 Hz), 7.41 (s, 1H), 7.31 (ddd, J = 8.5, 7.5, 1.0 Hz, 1H), 7.24 (ddd, J = 8.0, 7.5, 1.0 Hz, 1H), 4.33 (dd, J = 5.5, 4.0 Hz, 1H), 3.66 (ddd, J = 13.0, 9.0, 6.0 Hz, 1H), 3.55 (ddd, J = 13.0, 9.0, 6.0 Hz, 1H), 3.34 (ddd, J = 12.0, 7.0, 5.5 Hz, 1H), 3.12 (dt, J = 12.0, 6.0 Hz, 1H), 3.03−2.91 (m, 2H), 2.03−1.88 (m, 4H), 1.66 (s, 9H), 1.47 (br, 4H), 1.26 (m, 3H), 1.20 (s, 6H), 1.13 (br, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.3, 149.6, 130.4, 124.3, 123.0, 122.4, 119.0, 118.0, 115.1, 83.3, 80.4, 60.5, 59.7, 47.9, 47.6, 40.2, 34.1, 33.0, 28.1, 27.1, 22.7, 20.5, 20.2, 18.9, 17.1; HRMS-EI m/z 497.3263 (calcd. for $C_{29}H_{43}N_3O_4$, 497.3254).

General Procedure for Preparation of 3-Hydroxylactams. *1-Benzyl-3-hydroxypyrrolidin-2-one (**29**).* To a solution of **11** (0.055 g, 0.166 mmol) in acetic acid (2.0 mL), water (3.0 mL), and THF (2.0 mL) was added Zn powder (0.261 g), which was previously activated into an oven at 150 °C. The suspension was allowed to react for 1 h at 70 °C. Then the solution was cooled down to room temperature and quenched by adding a saturated solution of NaOH (3.0 mL). The organic component was extracted with AcOEt (5 × 5 mL) and concentrated at reduced pressure. Crude was purified by flash chromatography on silica gel (eluent hexane/EtOAc: 1/2) to obtain **29**[22,23] (0.0238 g, 75%) as a white solid. mp. 69−71 °C; lit[23] 69−70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35−7.22 (m, 5H), 4.50−4.42 (m, 3H), 3.25 (ddd, J = 9.5, 9.0, 2.0 Hz, 1H), 3.20−3.14 (m, 1H), 2.44−2.38 (m, 1H), 1.99−1.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.0, 135.6, 128.7, 128.0, 127.7, 69.9, 46.9, 43.0, 27.6.

*1-Benzyl-3-hydroxypiperidin-2-one (**30**).* Eluent hexane/EtOAc: 1/1. Isolated 0.207 g (78%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35−7.23 (m, 5H), 4.64 (d, J = 15.0 Hz, 1H), 4.52 (d, J = 15.0 Hz, 1H), 4.10 (dd, J = 10.5, 6.5 Hz, 1H), 3.90 (br, 1H), 3.26−3.19 (m, 2H), 2.31−2.25 (m, 1H), 1.93−1.87 (m, 1H), 1.86−1.78 (m, 1H), 1.73 (dtd, J = 12.5, 12.0, 4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.4, 136.3, 128.6, 128.0, 127.5, 68.0, 50.3, 47.0, 28.2, 19.8. HRMS-EI m/z 205.1087 (calcd. 205.1103 for $C_{12}H_{15}N_1O_2$).

*tert-Butyl-3-(2-(3-hydroxy-2-oxopiperidin-1-yl)ethyl)-1H-indole-1-carboxylate (**31**).* Eluent hexane/EtOAc: 1/1. Isolated 0.0211 g (70%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.13 (br, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.42 (s, 1H), 7.34 (ddd, J = 8.5, 7.5, 1.0 Hz, 1H), 7.28 (ddd, J = 8.5, 8.0, 1.0 Hz, 1H), 4.04 (dd, J = 11.0, 6.0 Hz, 1H), 3.82 (s, 1H), 3.72 (dt, J = 13.5, 7.5 Hz, 1H), 3.59 (dt, J = 13.5, 7.5 Hz, 1H), 3.28 (td, J = 12.0, 5.0 Hz, 1H), 3.21 (ddd, J = 11.0, 5.0, 3.5 Hz, 1H), 3.00 (t, J = 7.5 Hz, 2H), 2.27−2.23 (m, 1H), 1.88−1.84 (m, 1H), 1.79−1.70 (m, 2H), 1.68 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 149.7, 135.4, 130.3, 124.5, 123.1, 122.5, 118.9, 117.5,

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115.2, 83.5, 68.0, 48.5, 47.8, 28.2, 28.1, 22.7, 20.0; HRMS-FAB m/z $[M+H]^+$ 359.1975 (calcd. 359.1971 for $C_{20}H_{27}N_2O_4$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01566.

^1H and ^{13}C NMR spectra of new and relevant products (PDF)

X-ray crystallographic data for **15a** (CIF)

X-ray crystallographic data for **15b** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Jin, X.; Kataoka, K.; Yatabe, T.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 7212−7217. (b) Khusnutdinova, J. R.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2014**, *136*, 2998−3001. (c) Bechi, B.; Herter, S.; McKenna, S.; Riley, C.; Leimkühler, S.; Turner, N. J.; Carnell, A. J. *Green Chem.* **2014**, *16*, 4524−4529. (d) Klobukowski, E. R.; Mueller, M. L.; Angelici, R. J.; Woo, L. K. *ACS Catal.* **2011**, *1*, 703−708. (e) Preedasuriyachai, P.; Chavasiri, W.; Sakurai, H. *Synlett* **2011**, *2011*, 1121−1124. (f) A representative example of α-derivatization of secondary amines to imines: Sonobe, T.; Oisaki, K.; Kanai, M. *Chem. Sci.* **2012**, *3*, 3249−3255.

(2) (a) Howell, L. M.; Feng, K.; Clark, J. R.; Trzepkowski, L. J.; White, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 14590−14593. (b) Furthermore, hypervalent iodine has shown nitrogen tolerance in the C_α−H oxidation of cyclic amines. See: Moriarty, R. M.; Vaid, R. K.; Duncan, M. P.; Ochiai, M.; Inenaga, M.; Nagao, Y. *Tetrahedron Lett.* **1988**, *29*, 6913−6916.

(3) Fuentes, L.; Osorio, U.; Quintero, L.; Höpfl, H.; Vázquez-Cabrera, N.; Sartillo-Piscil, F. *J. Org. Chem.* **2012**, *77*, 5515−5524.

(4) (a) Romero-Ibañez, J.; Xochicale-Santana, L.; Quintero, L.; Fuentes, L.; Sartillo-Piscil, F. *J. Nat. Prod.* **2016**, *79*, 1174−1178. (b) Gómez-Fosado, C. G.; Quintero, L.; Fuentes, L.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2015**, *56*, 5607−5609. (c) Fuentes, L.; Hernández-Juárez, M.; Terán, J. L.; Quintero, L.; Sartillo-Piscil, F. *Synlett* **2013**, *24*, 878−882.

(5) *Riegel's Handbook of Industrial Chemistry*, 8th ed.; Kent, J.A., Ed.; Van Nostrand Reinhold Company: New York, 1983, pp 212−235.

(6) Hull, L. A.; Davis, G. T.; Rosenblatt, D. H.; Williams, H. K. R.; Weglein, R. C. *J. Am. Chem. Soc.* **1967**, *89*, 1163−1170.

(7) Mohamed, M. A.; Yamada, K.-i.; Tomioka, K. *Tetrahedron Lett.* **2009**, *50*, 3436−3438.

(8) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564−2566.

(9) (a) Tojo, G.; Fernández, M. *Oxidation of Alcohols to Aldehydes and Ketones*; Tojo, G., Ed.; Springer: New York, 2010. (b) Bobbitt, J. M.; Bruckner, C.; Merbouh, N. *Org. React.* **2009**, *74*, 103.

(10) Representative examples: (a) Cronan, J. M. L.; Cardellina, J. H., II *Nat. Prod. Lett.* **1994**, *5*, 85−88. (b) Capron, M. A.; Wiemer, D. F. *J. Nat. Prod.* **1996**, *59*, 794−795. (c) Kaou, A.M.; Mahiou-Leddet, V.; Canlet, C.; Debrauwer, L.; Hutter, S.; Azas, N.; Ollivier, E. *Fitoterapia* **2010**, *81*, 632−635.

(11) O'Connor, S. E.; Maresh, J. *Nat. Prod. Rep.* **2006**, *23*, 532−547.

(12) Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6638−6641.

(13) (a) Nucleophilic attack on nitrogen atom ($N{=}O^+$); see: Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (b) Nucleophilic attack on the oxygen atom ($N{=}O^+$) has been proposed by steric reasons; see: Bobbitt, J. M.; Bartelson, A. L.; Bailey, W. F.; Hamlin, T. A.; Kelly, C. B. *J. Org. Chem.* **2014**, *79*, 1055−1067. (c) Interaction between TEMPO−ClO_2 (CT complex) has been proposed as responsible for the strong dark red color. Furukawa, K.; Shibuya, M.; Yamamoto, Y. *Org. Lett.* **2015**, *17*, 2282−2285.

(14) Vicinal α,β-functionalization of amines via an enamine intermediate has been reported. Jiang, F.; Achard, M.; Bruneau, C. *Chem. - Eur. J.* **2015**, *21*, 14319−14323.

(15) Boger, D. L.; Garbaccio, R. M.; Jin, Q. *J. Org. Chem.* **1997**, *62*, 8875−8891.

(16) Representative reviews. (a) Jones, A. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon Press Ltd.: Oxford, 1991; Vol. 7, pp 151−191. (b) Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. In *Organic Reactions*; Overman, L. E., Ed.; John Wiley & Sons Inc.: New York, 2003; Vol. *62*, pp 1−356.

(17) Li, J.; Zhou, H.; Weng, J.; Wang, M.; Ge, C.; Tu, W. *Synlett* **2014**, *25*, 805−808.

(18) Laabs, S.; Münch, W.; Bats, J. B.; Nubbemeyer, U. *Tetrahedron* **2002**, *58*, 1317−1334.

(19) Sasano, Y.; Nagasawa, S.; Yamazaki, M.; Shibuya, M.; Park, J.; Iwabuchi, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 3236−3240.

(20) Murata, M.; Chiba, T. U.S. Patent 4, 923,857, 1990.

(21) Emayavaramban, B.; Roy, M.; Sundararaju, B. *Chem. - Eur. J.* **2016**, *22*, 3952−3955.

(22) Kamal, A.; Ramana, K. V.; Ramana, A. V.; Babu, A. H. *Tetrahedron: Asymmetry* **2003**, *14*, 2587−2594.

(23) Southwick, P. L.; Previc, E. P.; Casanova, J.; Carlson, E. H. *J. Org. Chem.* **1956**, *21*, 1087−1095.

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