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Selective, Catalytic and Dual $C_{(sp3)}$–H Oxidation of Piperazines and Morpholines Under Transition Metal-Free Conditions

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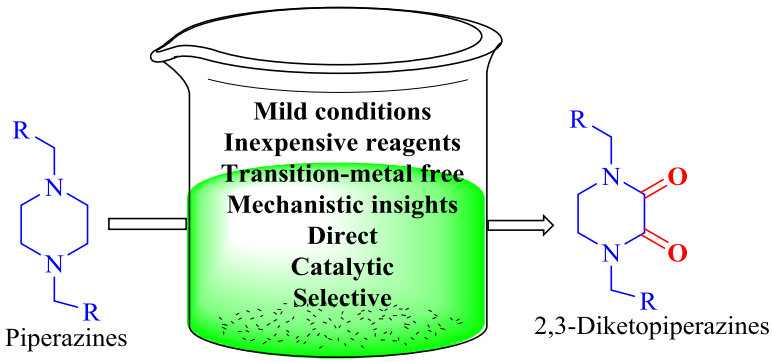
KEYWORDS C−H Oxidation, diketopiperazines, TEMPO, $NaClO_2$, NaOCl, environmentally friendly

Abstract: By using cheap and innocuous reagents, such as $NaClO_2$, NaOCl and catalytic amounts of TEMPO, a new environmentally friendly protocol for the selective and catalytic TEMPO $C_{(sp3)}$–H oxidation of piperazines and morpholines to 2,3-diketopiperazines (2,3-DKP) and 3-morpholinones (3-MPs), respectively, has been developed. This novel direct access to 2,3-DKP from piperazines provides significant advantages over the traditional N-monoacylation/intramolecular C–N cyclization procedure. Additionally, by modulating the amounts of TEMPO, 2-alkoxyamino-3-morpholinone can be prepared from morpholine derivatives, which would enable further functionalization at the C-2 position of the morpholine skeleton.

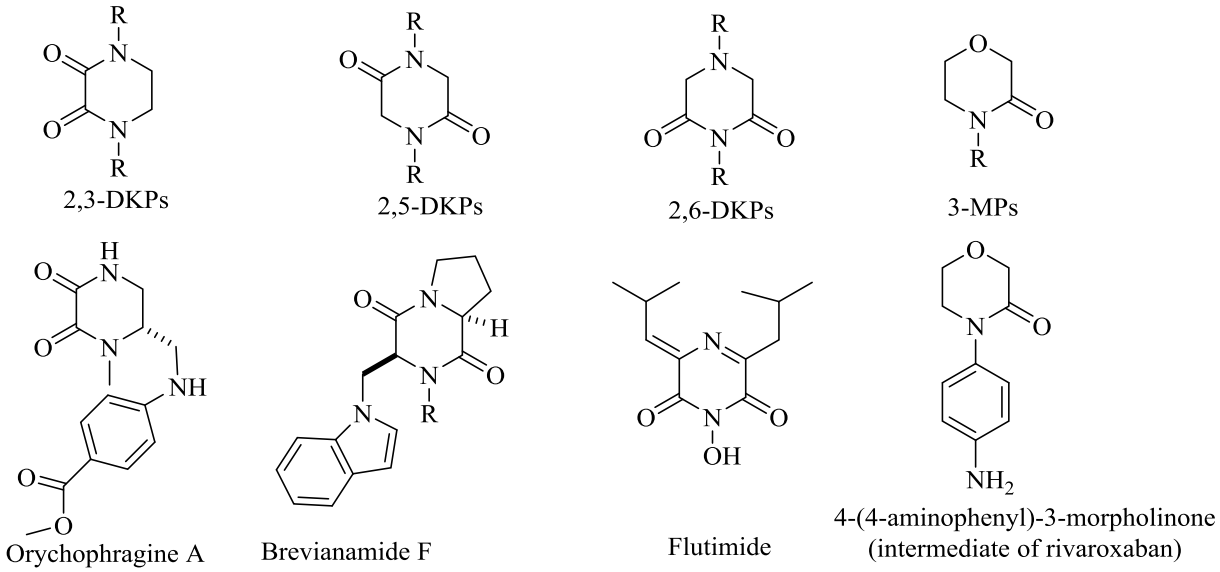


INTRODUCTION

Diketopiperazines (DKPs), in the three isomeric forms (2,3-DKP, 2,5-DKP and 2,6-DKP), belong to a privileged class of organic compounds, which due to their structural resemblance to peptides, have

attracted interest of chemists focused in drug discovery.[1] A numerous of naturally occurring bioactive products are DKP derivatives,[2] and another vast number of synthetic DKPs have been prepared for the purpose to mimic the conformational and biological properties of peptides.[3] On the other hand, although 3-morpholinones (3-MPs) are not common in nature,[4] they are frequently prepared in the laboratory as key precursors for pharmaceutical drugs.[5] A representative example of each KDPs and 3-MP is showcased in Figure 1. Orychophragine A is a 2,3-DKP derivative recently isolated from *Orychophragmus violaceus* which exhibited remarkable cytotoxicity against three cell lines.[6] Brevianamide F is a biosynthetic precursor of biologically active metabolites produced by the fungi *A. fumigates* and *Asperguillus* sp.[7] An inhibitor of the virus of influenza (virus A) is the 2,6-DKP derivative Flutimide.[8] On the other hand, an important 3-MP derivative is the 4-(4-aminophenyl)-3-morpholinone,[9] a key intermediate for the synthesis of rivaroxaban.[10]

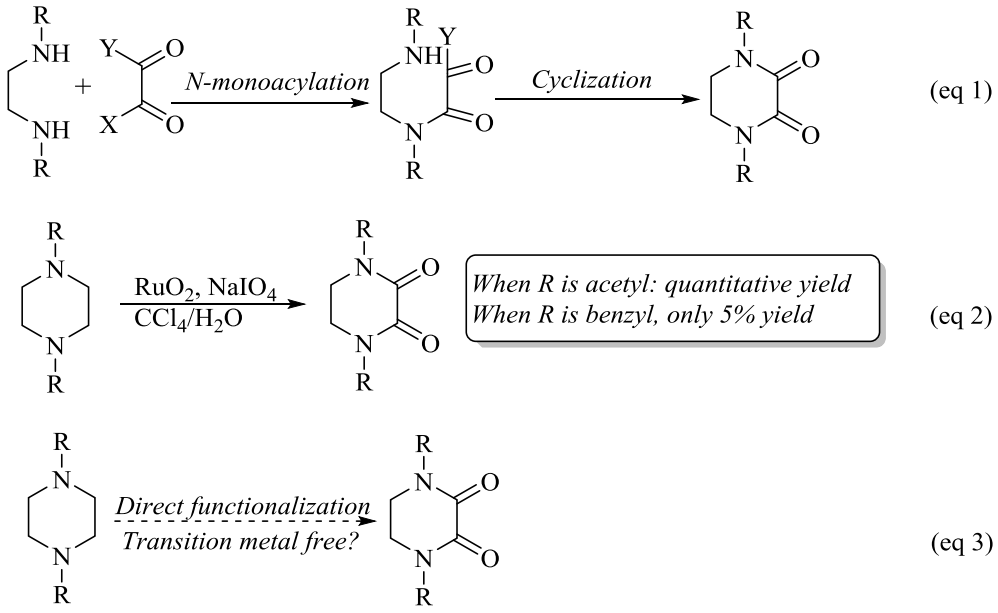
Figure 1. Isomeric DKPs and biologically important DKPs



In spite of the high importance of these organic compounds, there is, in fact, only one synthetic strategy for accessing to all of them.[1] For instance, the general strategy for preparing 2,3-DKPs includes the classical *N*-monoacylation followed by intramolecular amidation sequence process (eq 1, Scheme 1),[1,11] in which long and tedious activation processes of the carbonyl group are often required.[12]

Furthermore, an apparent solution to this synthesis problem might be the direct functionalization of preexisting heterocycle[13] via a direct C−H oxidation of piperazines to 2,3-DKPs or morpholines to 3-MPs. Unfortunately, the latter strategy does not provide consistent results when transition metals are employed (eq 2, Scheme 1).[14] Consequently, the current investigation offers a novel protocol for the direct functionalization of piperazines and morpholines to 2,3-diketopiperazines and 3-morpholinones, respectively, under transition-metal-free conditions, and using environmentally friendly reagents (eq 3, Scheme 1).

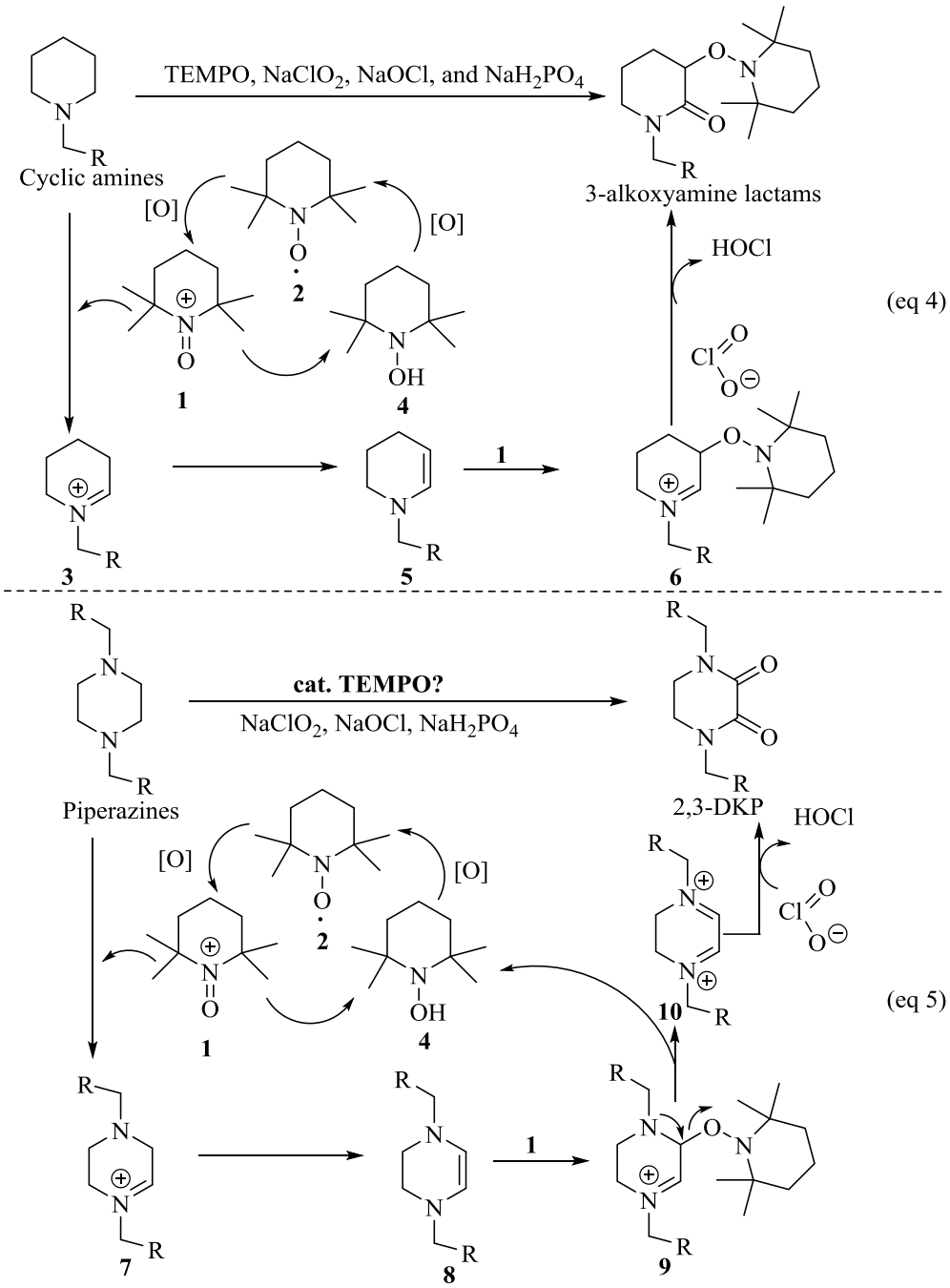
Scheme 1. Synthesis strategies to 2,3-diketopiperidines



RESULTS AND DISCUSSION

This novel dual C−H oxidation reaction of piperazines to 2,3-DKPs was inspired by a previous chemical reaction mechanism, in which piperidines and pirrolidines were directly transformed into their respective 3-alkoxyamino lactams via a selective and tandem C−H oxidation at the alpha and beta positions (eq 4, Scheme 2).[15]

Scheme 2. Mechanistic proposal for the selective and dual C−H oxidation of cyclic amines to 3-alkoxyamine lactams (eq 4). TEMPO-catalyzed mechanistic proposal for accessing to 2,3-DKP from piperazines (eq 5)



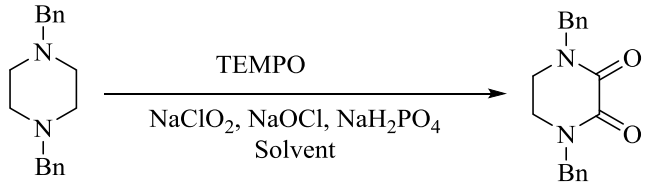
According to the proposed reaction mechanism, TEMPO oxammonium cation (**1**), which is generated *in situ* by oxidation of TEMPO radical (**2**) with $NaClO_2$ and NaOCl, enables selective alpha C−H activation of cyclic amines to iminium cation (**3**) plus TEMPOH (**4**), and the latter is re-oxidized to oxammonium cation **1**. Then, intermediate **3** is spontaneously transformed into enamine **5**. Nucleophilic attack of **5** to **1** engenders intermediate **6**,[16] which after oxidation with chlorite anion, produces the 3-alkoxyamine lactam (eq 4, Scheme 2). Assuming that TEMPO oxammonium cation **1** is regenerated during the reaction course, then we anticipated that substituted piperazine could follow similar

sequential reaction course as for the cyclic amines (**7** → **8** → **9**), albeit due to the presence of the second nitrogen atom at the C4 position, TEMPOH (**4**) would be expelled and incorporated into the catalytic cycle; finally, the formed diiminnium cation **10** would be oxidized to 2,3-DKP. Thus, a successful execution of this mechanistic proposal may open access to the development of a novel TEMPO-catalyzed dual C−H oxidation reaction of piperazines to 2,3-diketopiparazines in a very low economic and ecological cost (eq 5, Scheme 2).

Benzyl piperazine **11** was selected as a suitable substrate for testing the mechanistic proposal showcased in Scheme 2 (eq 2). Initial reaction conditions were taken from the original dual C−H oxidation reaction protocol,[15] in which TEMPO (1.5 equiv), $NaClO_2$ (3.0 equiv) NaOCl (1.5 equiv) and NaH_2PO_4 (10 equiv) were used, and after 2 h of reaction at room temperature in CH_3CN, piperazine **11** was transformed into 2,3-DKP **12** in 80% yield (Table 1, entry 1). Despite the dramatic decreasing of the amount of TEMPO from 3 equivalents to catalytic amount (0.1 equiv), and keeping the same quantities of the other reagents, the chemical yield of **12** was not affected (entry 2). Having promptly achieved this novel catalytic dual C−H oxidation mediated by TEMPO, further screening condition were explored with the intention to optimize other chemical reagents. When amounts of NaOCl and NaH_2PO_4 were reduced to more than fifty percent, the reaction gave a better chemical yield (entry 3). However, reducing only the amount of NaOCl to 0.1 equiv, chemical yield of **12** dropped to traces (entry 4). Similar behavior was observed when $NaClO_2$ was also reduced to less than 3 equivalents (entry 5). On the other hand, starting material **11** remained unchanged when buffer (NaH_2PO_4) was not employed (entry 6). The use of greener solvents such as MeOH (entry 7) or acetone (entry 8) did not provided the desired results, and further oxidized compounds like benzoic acid was obtained. And by reducing the amount of TEMPO to 5% mol, the chemical yield dropped to 65% (entry 9). Similar results were observed by reducing equivalents of TEMPO and co-oxidizing reagent NaOCl (entries 10 and 11). It is important to note that in the absence of TEMPO the benzylic C-H oxidation is a competitive reaction.[15] Therefore, this screening studies established that using only 10% mol of TEMPO, 3 equivalents of

$NaClO_2$ and NaH_2PO_4, and 0.7 equiv of NaOCl at 0 °C in acetonitrile as solvent, piperazine **11** can be transformed to diketopiperazine **12** in 95% yield (Table 1).

Table 1.[a,b] Screening conditions for TEMPO-catalyzed selective dual C−H oxidation of piperazine **11** to 2,3-diketopiparezine **12**



11 **12**

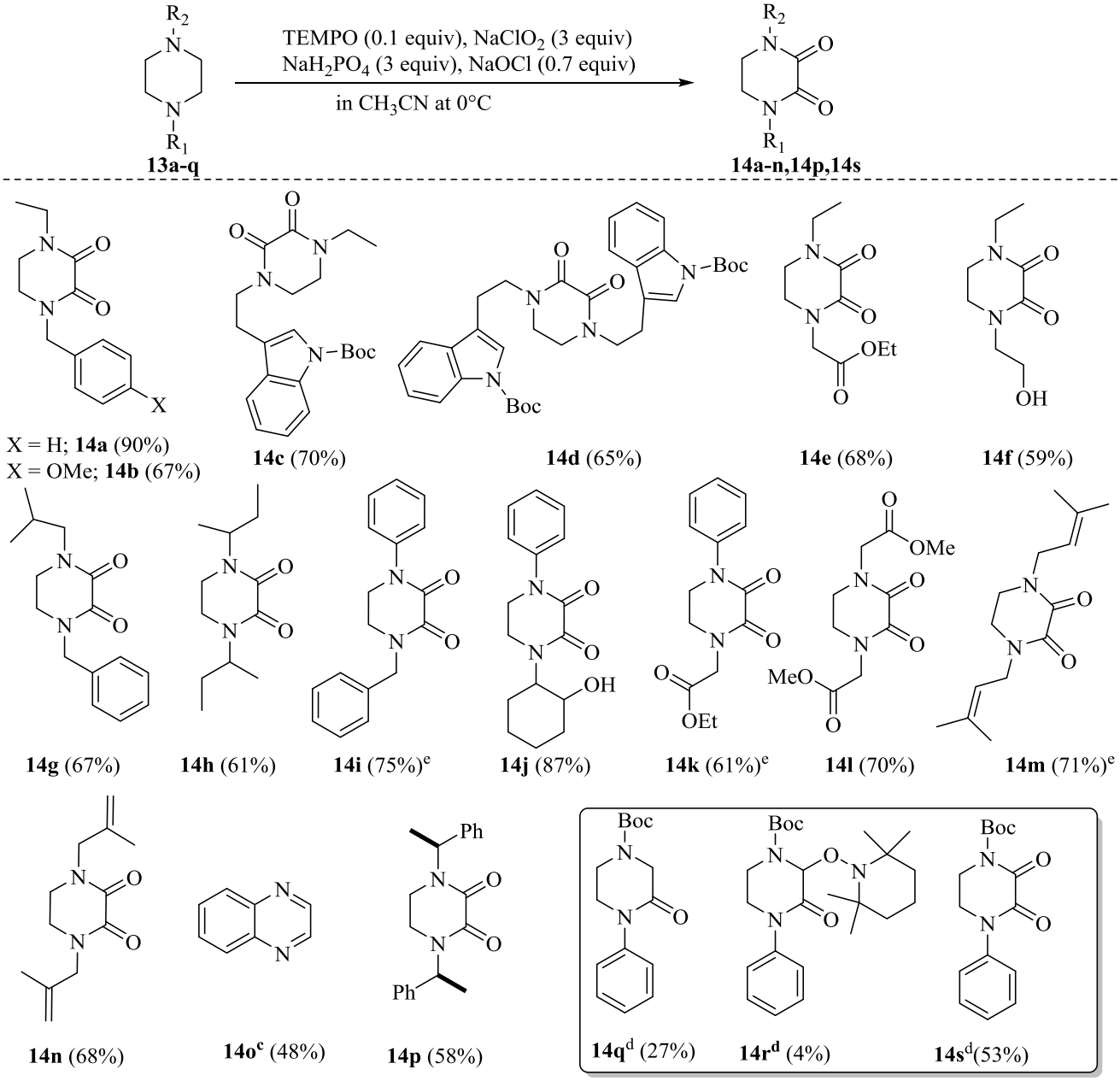
Entry	$NaClO_2$	NaH_2PO_4	TEMPO	NaOCl	Solvent	Time	Isolated yield
1	3	10	3	1.5	MeCN	2 h	80%
2	3	8	0.1	1.5	MeCN	2 h	88%
3	**3**	**3**	**0.1**	**0.7**	**MeCN**	**1 h**	**95%**
4	3	3	0.1	0.1	MeCN	10 h	traces
5	2	3	0.1	0.7	MeCN	10 h	45%
6	3	0	0.1	0.7	MeCN	24 h	a
7	3	3	0.1	0.7	MeOH	1 h	b
8	3	3	0.1	0.7	Acetone	1.5 h	45%
9	3	3	0.05	0.7	MeCN	2 h	65%[c]
10	3	3	0.03	0.7	MeCN	2 h	50%[c]
11	3	3	0.0	0.7	MeCN	2 h	48%

[a]Starting material remained unchanged. [b]Starting material is transformed into unwanted byproducts. [c]Benzoic acid is formed.

With optimized reaction conditions in hands, the scope of this novel catalytic reaction was evaluated. A series of symmetrical and non-symmetrical *N*-piperazines (**13a-q**) were selected with the idea of not only to prepare synthetic relevant precursors but also synthetic models that may provide mechanistic findings for this novel catalytic chemical reaction. Yields up to or more than 90% were obtained (Table 2, **13a-13p**). Because the *N*-ethyl-2,3-DKP molecular fragment is present in various pharmaceutical antibiotics such as piperacillin,[17] piperazines (**13a-c**, **13e** and **13f**) were prepared and tested for the catalytic dual oxidation giving good to high yields of 2,3-DKP (**14a-c**, **14e** and **14f**). By taking

advantage of this novel reaction, 1-benzyl-4-ethyl-2,3-DKP **14b** was obtained from its piperazine derivative **13b** in high yield, which after oxidative debenzylation with ceric ammonium nitrate (CAN), the relevant pharmacological intermediate ethyl-2,3-DKP was obtained.[18]

Table 2.[a,b] TEMPO-catalyzed selective dual C−H oxidation of piperazines to 2,3-diketopiparezines

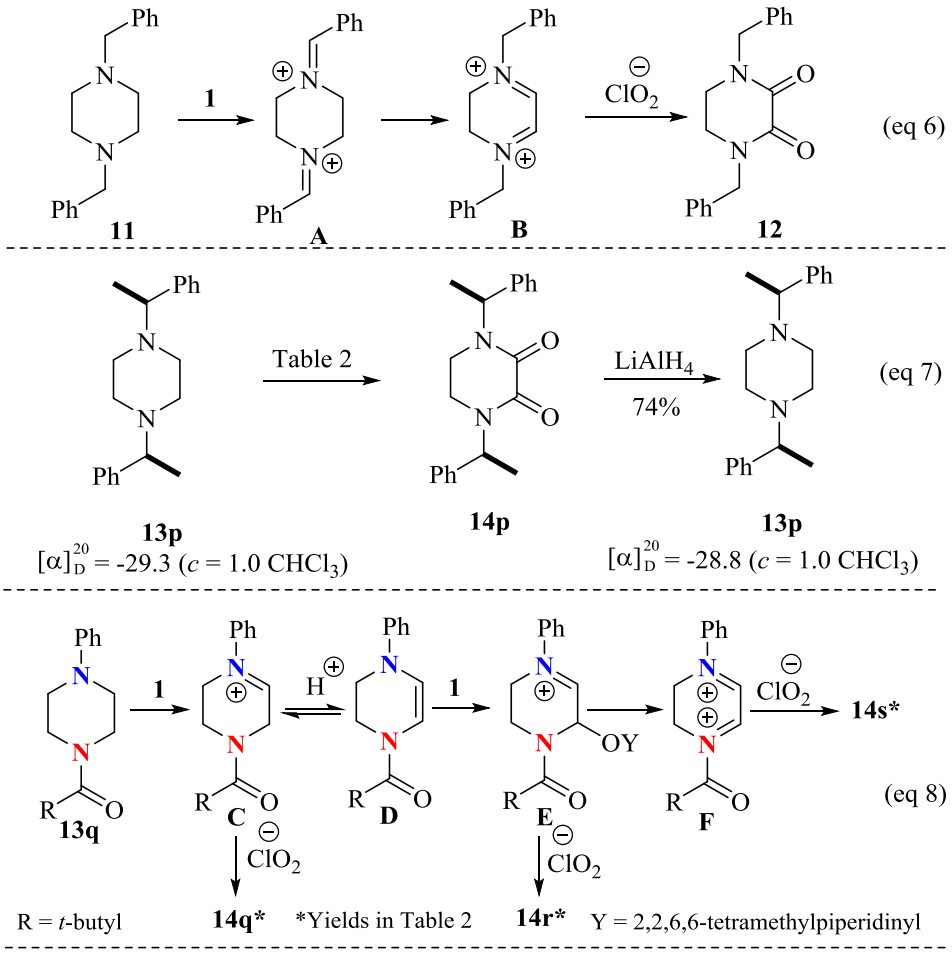


[a]Reaction performed on a 0.3 mmol scale. [b]Chemical yields after purification. [c]Obtained from *N*-allyltetrahydroquinoxaline [d]Obtained from the same *N*-Boc-piperazine derivative.[e]2-Methyl 2-butene was used as HOCl scavenger.

Because the presence of either indole moiety or phenyl group in 2,3-DKPs potentializes their biologically activity,[19] the respective piperazines **13c-d** and **13i-k** were prepared and subjected to

catalytic dual oxidation to obtain DKPs **14c**, **14d**, **14i**, **14j** and **14k**, respectively, in good to high yields. Similar results were observed with *N*-Alkyl and *N*-allyl-piperazines (**13g**, **13h**, **13m** and **13n**); however, when *N*-allyltetrahydroquinoxaline **13o** was tested, quinoxaline **14o** was obtained instead the expected *N*-allyl-2,3-DKP (not shown). It seems that the formation of the pyrazine ring is favored by aromatization via deallylation reaction.[20] For mechanistic purposes, optically pure piperazine **13p** was prepared. It is well-known that benzylic C−H bonds are weaker than most of alkylic C−H bonds, then benzylic C−H oxidation of piperazines, e. g., **11** in eq 6 to iminium **A**, could be a more favored process than the direct C−H oxidation of an endocyclic hydrogen to **B**; therefore, the likely formation of **B** from **A** was a chemical process that needed to be revised (Scheme 3, eqs 6 and 7).[21]

Scheme 3. Stereochemical proof for selective C−H oxidation of piperazines



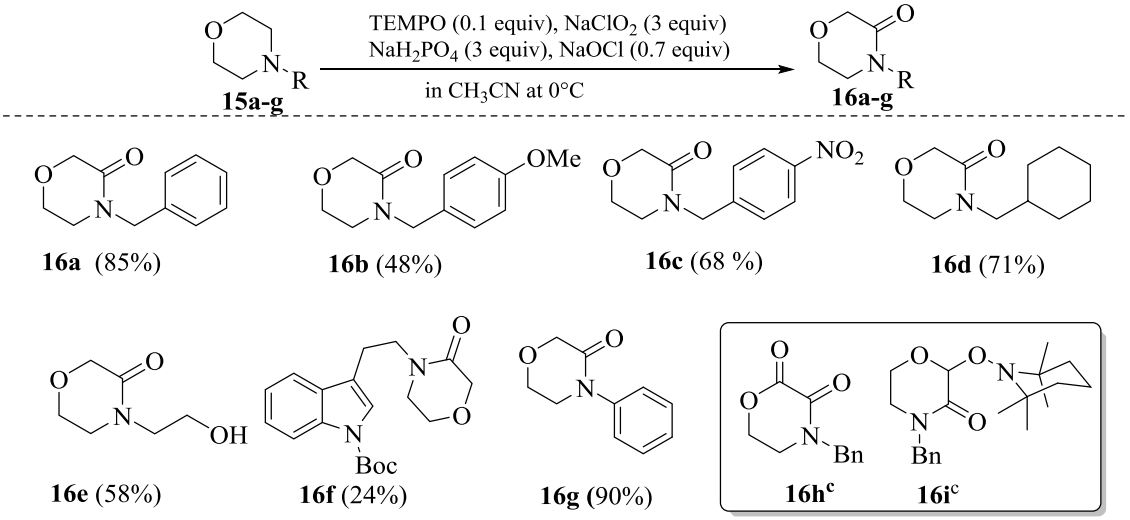
Thus, erosion of the optical purity in the chiral piperazine **13p** after reduction of **14p** would provide experimental evidence for the selective C−H oxidation of piperazines. Optically pure piperazine **13p**

was oxidized to chiral 2,3-DKP **14p** followed by reduction with $LiAlH_4$ to return to **13p**. Analysis of the optical rotation of the reduction product, which was identical to the initial piperazine **13p**, revealed a complete preservation of the optical purity (Scheme 3, eq 7). Additionally, *N*-boc-benzyl piperazine **13q** was prepared to gain further insights on the reaction mechanism (eq 8, Scheme 2). We hypothesized the following: if one nitrogen atom compromises its lone pair toward a carbonyl group (red atom), the first C−H oxidation would be highly selective upon the side where the nitrogen atom maintains the basic character (blue atom), and the catalytic cycle might be either interrupted or delayed preventing thus the dual oxidation. Accordingly, piperazine **13q** was tested under the same reaction conditions as for the other piperazines, and three oxidized compounds were obtained (**14q**, **14r** and **14s**). As expected, the first C−H oxidation occurred away from the amide nitrogen atom forming intermediate **C,** which produces **14q** after being attacked by ClO_2 anion.[22] Intermediate **E** is generated via a selective electrophilic attack of oxammonium cation **1** to intermediate **D**, which the latter is either oxidized to **14r** or transformed into intermediate **F** via TEMPOH elimination followed by chlorite anion attack to form **13s** (eq 8, Scheme 3). While the formation of **14q** can be explained in terms of an interrupted catalytic process, the formation of **14s** in low yield evidences the inefficient capacity of the amide nitrogen atom for restoring the catalytic TEMPO cycle by expelling the TEMPOH group.

With this mechanistic information in mind, which suggests that the C−H oxidation reaction of piperazines can be modulated by the electronic nature of the nitrogen atom; we thought that a more electronegative atom such as the oxygen atom could delay or interrupt the dual C−H oxidation reaction. Consequently, it was envisioned the possibility of transforming morpholines **15** into 3-morpholinones **16** under this novel environmentally friendly reaction conditions.[23] Consequently, benzyl, alkyl and phenyl morpholines underwent the expected C−H oxidation reaction alpha to the nitrogen atom giving 3-morpholinones in good to high yields (**16a**, **16c**, **16d** and **16g**); moderated or low yield when the aromatic ring in the benzyl group is found either activated (**16b**) or when the alkyl groups are susceptible to bond cleavage (**16e**). Interestingly, the free hydroxyl group in **16e** resulted to be unreactive under this reaction conditions, indicating that the amine group is more reactive with the

oxammonium cation **1** than the hydroxyl group.[15] Unfortunately, 3-morpholine derived from indole (**15f**) was not transformed to the respective 3-morpholinone**16f** in acceptable yield (Table 3).

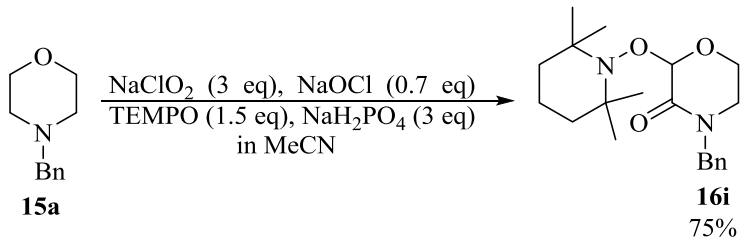
Table 3.[a,b] TEMPO-catalyzed selective C−H oxidation of morpholines to 3-morpholinones



[a]Reaction performed on a 0.3 mmol scale. [b]Yields after purification. [c]Obtained in traces from **15a**

The isolation, in traces, of byproducts **16h** and **16i** from *N*-benzyl morpholine (**15a**) suggests that morpholines can be selectively transformed into 2-alkoxyamino-3-morpholinones under non-catalytic TEMPO conditions. To proof this, *N*-benzyl morpholine **15a** was subjected to dual non-catalytic conditions (1.5 equivalents of TEMPO), and 2-aminoalkoxy-3-morpholinone **16i** was obtained in 75% yield (Scheme 4).

Scheme 4. Synthesis of 2-alkoxyamino-3-morpholinone **16j** from benzyl morpholine 15a



CONCLUSIONS

We have developed, in an unprecedented tandem-catalytic fashion and using environmentally friendly reagents, a new chemical reaction that allows the direct access to 2,3-diketopiperazines and 3-morpholinones from piperazines and morpholines, respectively. This novel methodology is highly competitive in efficiency and efficacy with the traditional N-monoacylation/intramolecular C−N cyclization procedure. Additionally, it was showed that under non-catalytic TEMPO conditions, morpholines can be transformed into 2-aminoalkoxy-3-morpholinones, which in turn, may offer a new way for functionalization of morpholinones. Thus, a new case of direct functionalization of preexisting heterocycle at low-economic and ecological cost was successfully achieved. Further application of this methodology to the synthesis of biologically relevant products is underway and will be reported soon.

EXPERIMENTAL SECTION

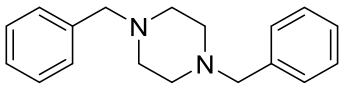
General considerations

C−H Oxidation reactions were carried out under air atmosphere at 0 °C, and the solvents used were non-anhydrous. Reactions sensitive to air or moisture were carried out under argon atmosphere in dry and freshly distilled solvents under anhydrous conditions. Reactions were monitored by thin layer chromatography (TLC), which were monitored by ultraviolet (UV). Purifications of products were performed by column chromatography using silica gel (230-400 mesh). NMR spectra were obtained in a 500 MHz spectrometer (500 MHz for ^{1}H and 125 MHz for $^{13}C\{^{1}H\}$). All samples were analyzed in $CDCl_3$ with TMS as internal reference using a relative scale in parts per millon (ppm) for the chemical shift (δ), Hz for coupling constants (J) and are calibrated using residual solvents signals (^{1}H NMR: $CHCl_3$ = 7.26 ppm; $^{13}C\{^{1}H\}$: $CHCl_3$ = 77.16 ppm). Splitting patterns are designated as follow: s, singlet; d, doublet; q, quartet; m, multiplet; dd, doublet doublet; br, broad; and their combinations. Optical rotation of the compounds was measured on a polarimeter on the D-line of sodium (589 nm) and expressed in degrees. The measurements were performed at a temperature of 20 °C and the concentration of the sample was expressed in g/100 mL. High resolution mass spectra (HRMS) were acquired in electron-impact (EI), electrospray ionization (ESI) mode using a TOF mass analyzer or in

fast-atom-bombardment (FAB) mode using a QMS mass analyzer. Melting points were determined with a fusiometer and are not corrected.

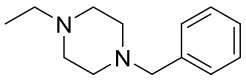
Preparation of piperazine derivatives

1,4-Dibenzylpiperazine (11)[24]



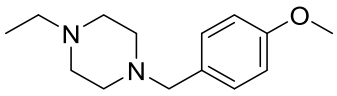
To a suspension of piperazine (1.00 g, 11.61 mmol) and K_2CO_3 (4.01 g, 29.02 mmol) in CH_3CN (28 mL) was added dropwise benzyl bromide (3.04 mL, 25.54 mmol). The reaction mixture was stirred at room temperature for 2 h. Then, the reaction mixture was cooled to room temperature and the resulting solids were filtered and washed with EtOAc (3 x 15 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 3:1) to give 2.79 g (90%) of **11** as a white solid. Mp = 88-90 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51 (br, 8H), 3.53 (s, 4H), 7.30 (m, 10H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 53.0, 63.1, 127.2, 128.3, 129.4, 138.9.

1-Benzyl-4-ethylpiperazine (13a)[25]



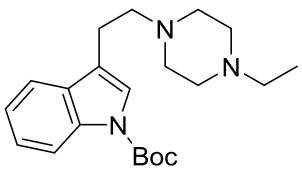
To a suspension of 1-ethylpiperazine (0.56 mL, 4.38 mmol) and K_2CO_3 (0.79 g, 5.69 mmol) in CH_3CN (10 mL) was added dropwise benzyl bromide (0.57 mL, 4.81 mmol). The resulting reaction mixture was stirred at room temperature for 2.5 h. Then, the reaction mixture was cooled to room temperature and the resulting solids were filtered and washed with EtOAc (3 x 10 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc/MeOH, 1:2:0.5) to give 0.74 g (83%) of **13a** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (t, J = 7.0 Hz, 3H), 2.41 (q, J = 7.0 Hz, 2H), 2.49 (br, 8H), 3.51 (s, 2H), 7.28 (m, 5H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.1, 52.4, 52.9, 53.1, 63.2, 127.1, 128.2, 129.3, 138.1.

1-(*p*-Methoxybenzyl)-4-ethylpiperazine (13b)[26]



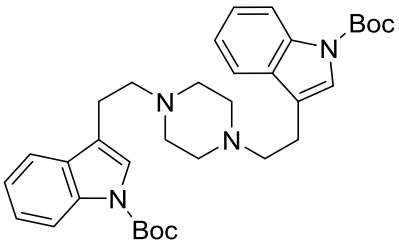
A mixture of 1-ethylpiperazine (1.27 mL, 10.00 mmol) and Na_2CO_3 (1.58 g, 15.00 mmol) in CH_3CN (20 mL) was added *p*-methoxybenzyl chloride (1.40 mL, 10.00 mmol). The reaction mixture was heated at reflux for 5 h. Then, the reaction mixture was cooled at room temperature and the resulting solids were filtered and washed with EtOAc (3 x 15 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 1:1) to give 1.58 g (68%) of **13b** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (t, J = 7.5 Hz, 3H), 2.40 (q, J = 7.5 Hz, 2H), 2.48 (br, 8H), 3.45 (s, 2H), 3.79 (s, 3H), 6.84 (m, 2H), 7.22 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.1, 52.4, 52.8, 53.0, 55.3, 62.5, 113.6, 130.1, 130.5, 158.7.

***tert*-Butyl 3-(2-(4-ethylpiperazin-1-yl)ethyl)-1*H*-indole-1-carboxylate (13c)**



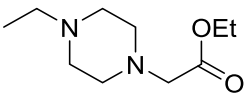
To a suspension of *N*-Boc-2-bromoethylindole (0.40 g, 1.23 mmol) and K_2CO_3 (0.25 g, 1.84 mmol) in CH_3CN (12 mL) was added 1-ethylpiperazine (0.18 mL, 1.47 mmol). The resulting reaction mixture was heated at reflux for 2 h. After this time, the mixture was cooled to room temperature and the resulting solids were filtered and washed with EtOAc (3 x 10 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:05) to give 0.41 g (93%) of **13c** as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, J = 7.0 Hz, 3H), 1.67 (s, 9H), 2.47 (q, J = 7.0 Hz, 2H), 2.61 (br, 8H), 2.73 (t, J = 8.0 Hz, 2H), 2.90 (app t, J = 8.0 Hz, 2H), 7.24 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.31 (ddd, J = 8.5, 7.5, 1.5 Hz, 1H), 7.41 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 8.11 (br, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.0, 22.7, 28.4, 52.5, 52.9, 53.2, 58.3, 83.5, 115.4, 119.0, 119.0, 122.5, 122.8, 124.4, 130.7, 135.5, 149.9. HRMS (ESI-TOF): calcd. for $C_{21}H_{32}N_3O_2$ $[M + H]^+$ 358.2494; found 358.2487.

di-*tert*-Butyl 3,3'-(piperazine-1,4-diylbis(ethane-2,1-diyl))bis(1*H*-indole-1-carboxylate) (13d)



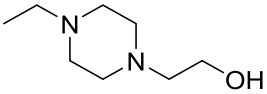
A suspension of piperazine (0.10 g, 1.16 mmol), *N*-Boc-2-bromoethylindole (0.82 g, 2.55 mmol) and K_2CO_3 (0.48 g, 3.48 mmol) in CH_3CN (10 mL) was heated at reflux for 6 h. After this time, the mixture was cooled at room temperature and the resulting solids were filtered and washed with EtOAc (3 x 10 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 1:5) to give 0.54 g (81%) of **13d** as a cream solid. Mp = 131-133 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (s, 18H), 2.68 (br, 8H), 2.74 (t, J = 7.5 Hz, 4H), 2.92 (t, J = 7.5 Hz, 4H), 7.24 (ddd, J = 8.0, 8.0, 1.0 Hz, 2H), 7.31 (ddd, J = 8.5, 7.5, 1.5 Hz, 2H), 7.43 (s, 2H), 7.54 (d, J = 8.0 Hz, 2H), 8.12 (br, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 22.8, 28.4, 53.4, 58.4, 83.5, 115.4, 119.0, 119.0, 122.5, 122.8, 124.4, 130.8, 135.5, 149.9. HRMS (FAB-QMS): calcd. for $C_{34}H_{45}N_4O_4$ $[M + H]^+$ 573.3441; found 573.3436.

Ethyl 2-(4-ethylpiperazin-1-yl)acetate (13e)



To a suspension of 1-ethylpiperazine (0.83 mL, 6.58 mmol) and K_2CO_3 (1.07 g, 7.78 mmol) in CH_3CN (12 mL) was added ethyl bromoacetate (0.66 mL, 5.98 mmol). The resulting reaction mixture was stirred at room temperature for 12 h. Then, the formed solids were filtered and washed with EtOAc (3 x 10 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/ MeOH, 4:1) to give 1.11 g (93%) of **13e** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 2.43 (q, J = 7.0 Hz, 2H), 2.58 (br, 8H), 3.21 (s, 2H), 4.19 (q, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.1, 14.3, 52.3, 52.6, 53.2, 59.7, 60.7, 170.4. HRMS (FAB-QMS): calcd. for $C_{10}H_{21}N_2O_2$ $[M + H]^+$ 201.1603; found 201.1612.

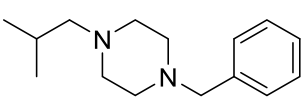
2-(4-Ethylpiperazin-1-yl)ethan-1-ol (13f)



To a suspension of 1-ethylpiperazine (0.88 mL, 7.00 mmol) and K_2CO_3 (1.25 g, 9.10 mmol) in CH_3CN (10 mL) was added 2-bromoethanol (0.54 mL, 7.69

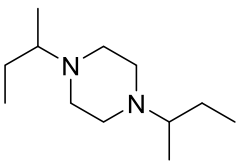
mmol). The resulting reaction mixture was stirred at room temperature overnight. Then, the formed solids were filtered and washed with EtOAc (3 x 10 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 8:1) to give 0.86 g (78%) of **13f** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (t, J = 7.0 Hz, 3H), 2.43 (q, J = 7.0 Hz, 2H), 2.56 (m, 10H), 2.94 (br, 1H), 3.63 (t, J = 5.5 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.0, 52.4, 52.8, 52.8, 57.8, 59.4. HRMS (ESI-TOF): calcd. for $C_8H_{19}N_2O_1$ $[M + H]^+$ 159.1497; found 159.1496.

1-Benzyl-4-isobutylpiperazine (13g)[27]



To a suspension of piperazine (0.20 g, 2.30 mmol) and Na_2CO_3 (0.40 g, 3.80 mmol) in CH_3CN (15 mL) was added *iso*-butyl bromide (0.2 mL, 1.92 mmol). The resulting reaction mixture was heated at reflux for 4 h. Then, the reaction mixture was cooled at room temperature and benzyl bromide (0.23 mL, 1.93 mmol) was added. The reaction mixture was stirred overnight at room temperature. Then, the resulting solids were filtered and washed with EtOAc (3 x 15 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 5:1) to give 0.16 g (30%) of **13g** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, J = 6.5 Hz, 6H), 1.76 (m, 1H), 2.07 (d, J = 6.0 Hz, 2H), 2.47 (m, 8H), 3.50 (s, 2H), 7.23 (m, 1H), 7.30 (m, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.1, 25.4, 53.2, 53.3, 53.6, 63.3, 127.0, 128.3, 129.4, 138.3.

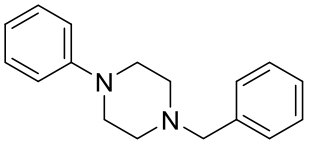
1,4-bis(*sec*-Butyl)piperazine (13h)[28]



To a suspension of piperazine (0.18 g, 2.00 mmol) and K_2CO_3 (0.70, 5.00 mmol) in CH_3CN (10 mL) was added *sec*-butyl bromide (0.49 mL, 4.40 mmol). The resulting reaction mixture was heated at reflux for 8h. Then, the resulting solids were filtered and washed with EtOAc (3 x 10 mL). The organic portion was concentrated under reduced pressure and

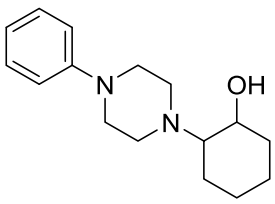
the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 2:1) to give 0.26 g (65%) of **13h** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 6H), 1.02 (d, J = 7.0 Hz, 6H), 1.28 (m, 2H), 1.62 (m, 2H), 2.43 (m, 2H), 2.58 (m, 8H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 11.3, 14.0, 25.9, 48.5, 60.7.

1-Benzyl-4-phenylpiperazine (13i)[29]



To a suspension of 1-phenylpiperazine (0.81 g, 5.00 mmol), Na_2CO_3 (0.79 g, 7.50 mmol) in CH_3CN (15 mL) was added benzyl bromide (0.71 mL, 6.00 mmol). The mixture was stirred at room temperature overnight. Then, the resulting solids were filtered and washed with EtOAc (3 x 15 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 5:1) to give 1.06 g (84 %) of **13i** as a white solid. Mp = 47-49 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61 (app t, J = 5.0 Hz, 4H), 3.20 (app t, J = 5.0 Hz, 4H), 3.57 (s, 2H), 6.84 (app tt, J = 7.5, 1.0 Hz, 1H), 6.92 (m, 2H), 7.26 (m, 3H), 7.34 (m, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 49.2, 53.2, 63.2, 116.1, 119.7, 127.2, 128.4, 129.2, 129.3, 138.0, 151.5.

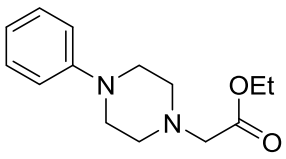
***rac–trans*-2-(4-Phenylpiperazin-1-yl)cyclohexanol (13j)**[30]



To a solution of cyclohexene oxide (0.62 mL, 6.11 mmol) in H_20 (2.5 mL) was added dropwise 1-phenylpiperazine (1.12 mL, 7.33 mmol). The resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with CH_2Cl_2 (5 x 8 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH, 1:0.3) to give 1.73 g (98%) of **13j** as a white solid. Mp = 132-134 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (m, 4H), 1.73 (m, 1H), 1.80 (m, 1H), 1.86 (m, 1H), 2.15 (m, 1H), 2.29 (ddd, J = 11.5, 9.5, 3.0 Hz, 1H), 2.59 (ddd, J = 11.5, 7.5, 3.5 Hz, 2H), 2.90 (ddd, J = 11.5, 8.0, 3.5 Hz, 2H), 3.20

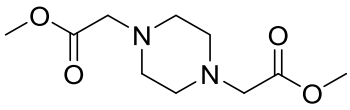
(m, 4H), 3.42 (ddd, *J* = 14.5, 10.0, 4.5 Hz, 1H), 4.02 (br, 1H), 6.87 (t, *J* = 7.25 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 22.3, 24.1, 25.6, 33.2, 48.3, 49.9, 68.7, 70.2, 116.3, 120.0, 129.2, 151.4.

Ethyl 2-(4-phenylpiperazin-1-yl)acetate (13k)[31]



A suspension of K_2CO_3 (0.45 g, 3.23 mmol) in CH_3CN (7 mL) was added 1-phenylpiperazine (0.33 mL, 2.16 mmol) and ethyl bromoacetate (0.26 mL, 2.37 mmol). The resulting reaction mixture stirred at room temperatura overnight. Then, the formed solids were filtered and washed with EtOAc (3 x 10 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 3:1) to give 0.40 g (75%) of **13k** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.0 Hz, 3H), 2.75 (t, *J* = 5.0 Hz, 3H), 3.26 (t, *J* = 5.0 Hz, 3H), 3.28 (s, 2H), 4.21 (q, *J* = 7.0 Hz, 2H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 2H), 7.27 (dd, *J* = 8.5, 7.0 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 14.3, 49.0, 53.1, 59.6, 60.8, 116.2, 119.9, 129.2, 151.2, 170.3. HRMS (ESI-TOF): calcd. for $C_{14}H_{21}N_2O_2$ $[M + H]^+$ 249.1603; found 249.1598.

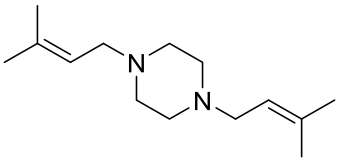
Dimethyl 2,2'-(piperazine-1,4-diyl)diacetate (13l)



To a suspension of piperazine (0.42 g, 5.01 mmol), Na_2CO_3 (1.32 g, 12.51 mmol) in CH_3CN (15 mL) was added methyl bromoacetate (1.04 mL, 11.03 mmol). The reaction mixture was stirred at room temperature overnight. Then, the resulting solids were filtered and washed with EtOAc (3 x 15 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 1:1) to give 0.69 g (60%) of **13l** as white solid. Mp = 59-61 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (br, 8H), 3.24 (s,

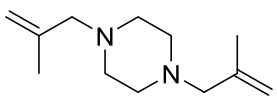
4H), 3.73 (s, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 51.9, 52.9, 54.4, 170.8. HRMS (FAB-QMS): calcd. for $C_{10}H_{19}N_2O_4$ $[M + H]^+$ 231.1345; found 231.1341.

1,4-bis(3-Methylbut-2-en-1-yl)piperazine (13m)



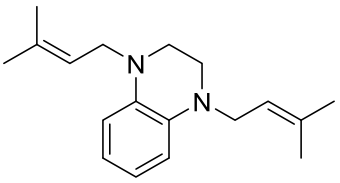
To a suspension of piperazine (0.3 g, 3.48 mmol) and NaH (0.27 g, 6.96 mmol, 60% dispersion in mineral oil) in THF (3 mL) at 0°C was added dropwise 3,3-dimethylallyl bromide (0.89 mL, 7.66 mmol). After 10 min, the reaction mixture was stirred at room temperature for 2 h. Then, the reaction mixture was cooled to room temperature, and H_2O (3 mL) was added. The reaction mixture was extracted with EtOAc (5 x 5 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 1:2) to give 0.66 g (86%) of **13m** as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (s, 6H), 1.72 (s, 6H), 2.43 (br, 8H), 2.96 (d, J = 7.5 Hz, 4H), 5.25 (app t, J = 7.5 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 18.1, 26.0, 53.1, 56.0, 120.8, 135.5. HRMS (EI-TOF): calcd. for $C_{14}H_{26}N_2$ $[M]^+$ 222.2096; found 222.2099.

1,4-bis(2-Methylallyl)piperazine (13n)



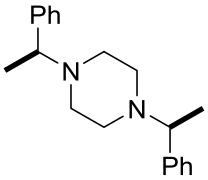
To a suspension of piperazine (0.5 g, 5.80 mmol) and NaH (0.46 g, 11.61 mmol, 60% dispersion in mineral oil) in THF (5 mL) at 0°C was added dropwise 3-bromo-2-methylpropene (0.89 mL, 7.66 mmol). After 10 min, the reaction mixture was stirred at room temperature overnight. Then, the mixture was cooled to room temperature, and H_2O (3 mL) was added. The mixture was extracted with EtOAc (5 x 8 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 5:1) to give 0.88 g (78%) of **13n** as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (s, 6H), 2.40 (br, 8H), 2.87 (s, 4H), 4.83 (s, 2H), 4.86 (s, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 21.1, 53.3, 65.5, 113.0, 142.8. HRMS (EI-TOF): calcd. for $C_{12}H_{22}N_2$ $[M]^+$ 194.1783; found 194.1789.

1,4-bis(3,3-Dimethylallyl)-1,2,3,4-tetrahydroquinoxaline (13o)



To a solution of phenylenediamine (0.50 g, 4.60 mmol) in THF (5 mL) was added glyoxal (0.63 mL, 40% sol. in water, 5.50 mmol). The resulting reaction was stirred for 2 h at room temperature. Then, the solvent was removed under reduced pressure. The crude product was used in the next reaction without further purification. To a solution of the crude product in THF (5 mL) at 0 °C was treated with $LiAlH_4$ (0.51 g, 13.50 mmol). The resulting reaction mixture was stirred overnight at room temperature. A brine solution was added, and the solution was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic phases were dried with Na_2SO_4 and the solvent was removed under reduced pressure to obtain 0.57 g (93%) of thetrahydroquinoxaline which was used without purification to the next reaction. To a mixture of $CaCO_3$ (0.28 g, 2.80 mmol) and tetrahydroquinoxaline (0.17 g, 1.40 mmol) in CH_3CN (3 mL) was added dropwise 3,3-dimethylallyl bromide (0.34 mL, 2.80 mmol) at room temperature. The mixture reaction was stirred for 4 h at room temperature until total consumption of starting material. The solvent was removed under reduced pressure and the solids were washed with CH_2Cl_2 (3 x 5 ml). The organic portion was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 9:1) to give 0.63 g (55 %) of **13o** as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (d, J = 7.5 Hz, 12H), 3.30 (s, 4H), 3.80 (d, J = 6.0 Hz, 4H), 5.26 (m, 2H), 6.56 (m, 2H), 6.63 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 18.1, 25.8, 47.1, 49.1, 111.5, 117.9, 120.5, 135.5, 135.9. HRMS (FAB-QMS): calcd. for $C_{18}H_{27}N_2$ $[M + H]^+$ 271.2174; found 271.2179.

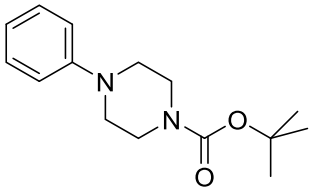
1,4-bis((*S*)-1-Phenylethyl)piperazine (13p)[32]



To a mixture of 1,4-bis((*S*)-1-phenylethyl))piperazin-2,5-dione[33] (0.63 g, 1.95 mmol) and $LiAlH_4$ (0.22 g, 5.85 mmol) at 0 °C, was added dropwise THF (6 mL). After 15 minutes, the reaction was stirred at room temperature for 1 h. Then, the mixture was cooled to 0 °C and H_2O was added dropwise until the formation of solids, which were washed with EtOAc (5 × 5 mL). The organic phase was dried with Na_2SO_4 and the solvent was removed under

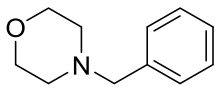
reduced pressure. The residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 3:1) to give 0.43 g (74 %) of **13p** as a white solid. Mp = 43-45 °C. $[\alpha]_D^{20}$ = –29.0 (c = 1.0, $CHCl_3$), $[\alpha]_D^{20}$ = –38.6 (c = 2.5, MeOH). Lit.[32] $[\alpha]_D^{20}$ = –34.2 (c = 2.54, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, J = 7.0 Hz, 6H), 2.39 (br, 8H), 3.32 (q, J = 7.0 Hz, 2H), 7.23 (m, 10H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 20.0, 50.9, 65.1, 126.9, 127.8, 128.3, 143.8. HRMS (FAB-QMS): calcd. for $C_{20}H_{27}N_2$ $[M + H]^+$ 295.2174; found 295.2180.

tert-Butyl 4-phenylpiperazine-1-carboxylate (13q)[34]



To a solution of di-*tert*-butyl dicarbonate (1.22 g, 5.59 mmol) and DMAP (0.11 g, 0.86 mmol) in CH_2Cl_2 (14 mL) were added drowise 1-phenylpiperazine (0.66 mL, 4.13 mmol) and Et_3N (0.64 mL, 4.30 mmol). The resulting reaction mixture was stirred for 2 h. After this time, H_2O (10 mL) was added. The mixture was extracted with CH_2Cl_2 (5 x 15 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 18:1) to give 1.11 g (98%) of **13q** as a white solid. Mp = 69-71 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 9H), 3.13 (t, J = 5.0 Hz, 4H), 3.58 (t, J = 5.0 Hz, 4H), 6.90 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 7.5 Hz, 2H), 7.28 (td, J = 7.0, 2.0 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 28.6, 43.1, 44.2, 49.6, 80.0, 116.8, 120.4, 129.3, 151.4, 154.9.

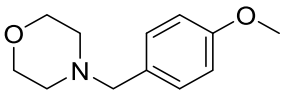
4-Benzylmorpholine (15a)[35]



To a suspension of morpholine (1.51 mL, 17.22 mmol) and K_2CO_3 (3.09 g, 22.38 mmol) in CH_3CN (20 mL) was added dropwise benzyl bromide (2.25 mL, 18.94 mmol). The mixture was stirred at room temperature for 2 h. Then, the resulting solids were filtered and washed with EtOAc (3 x 20 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 6:1) to give 2.87 g (94%) of

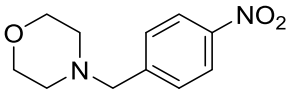
15a as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (t, J = 4.5 Hz, 4H), 3.47 (s, 2H), 3.68 (t, J = 4.5 Hz, 4H), 7.27 (m, 5H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 53.7, 63.6, 67.1, 127.3, 128.4, 129.4, 137.7.

4-(*p*-Methoxybenzyl)morpholine (15b)[35]



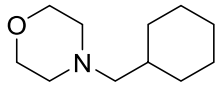
To a stirring mixture of morpholine (0.50 mL, 5.74 mmol) and NaH (0.17 g, 7.08 mmol, 60% dispersion in mineral oil) in THF (4 mL) was added dropwise to a solution of *p*-methoxybenzyl chloride (0.99 g, 6.32 mmol) in THF (6 mL). To mixture reaction was heated to reflux for 6 h. Then, the mixture was cooled at room temperature, and H_2O (3 mL) was added. The mixture was extracted with EtOAc (5 x 8 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 1:1) to give 1.13 g (98%) of **15b** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (br, 4H), 3.42 (s, 2H), 3.68 (t, J = 4.5 Hz, 4H), 3.78 (s, 3H), 6.84 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 53.5, 55.2, 62.8, 67.0, 113.6, 129.7, 130.4, 158.8.

4-(*p*-Nitrobenzyl)morpholine (15c)[35]



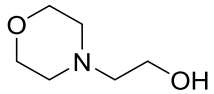
To a suspension of 1-(iodomethyl)-4-nitrobenzene (1.20 g, 4.56 mmol) and K_2CO_3 (0.82 g, 5.96 mmol) in CH_3CN (20 mL) was added dropwise morpholine (0.40 mL, 4.59 mmol). The reaction mixture was stirred at room temperature for 2 h. Then, the resulting solids were filtered and washed with EtOAc (3 x 20 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 5:1) to give 0.99 (98%) of **15c** as a yellow solid. Mp = 75-77 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (br, 4H), 3.60 (s, 2H), 3.73 (t, J = 4.5 Hz, 4H), 7.54 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 9.0 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 53.7, 62.6, 67.0, 123.7, 129.6, 146.0, 147.2.

4-(Cyclohexylmethyl)morpholine (15d)[36]



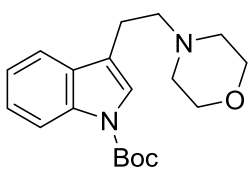
To a suspension of morpholine (1.00 mL, 11.48 mmol) and K_2CO_3 (1.90 g, 13.77 mmol) in CH_3CN (15 mL) was added dropwise (bromomethyl)cyclohexane (1.76 mL, 12.62 mmol). The reaction mixture was stirred at room temperature for 6 h. Then, the formed solids were filtered and washed with EtOAc (3 x 15 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 4:1) to give 1.34 g (62%) of **15d** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (m, 2H), 1.19 (m, 3H), 1.48 (m, 1H), 1.69 (m, 3H), 1.77 (m, 2H), 2.11 (d, J = 7.0 Hz, 2H), 2.38 (br, 4H), 3.70 (t, J = 5.0 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 26.2, 26.9, 32.0, 34.7, 54.3, 66.2, 67.1.

2-Morpholinoethan-1-ol (15e)



To a suspension of morpholine (0.50 mL, 5.73 mmol) and K_2CO_3 (1.03 g, 7.45 mmol) in CH_3CN (10 mL) was added 2-bromoethanol (0.48 mL, 6.88 mmol). The resulting reaction mixture was stirred at room temperature for 18 h. Then, the formed solids were filtered and washed with EtOAc (3 x 10 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/MeOH, 4:1) to give 0.56 g (75%) of **15e** as a pale red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 (br, 4H), 2.55 (t, J = 5.5 Hz, 2H), 2.99 (br, 1H), 3.64 (t, J = 5.5 Hz, 2H), 3.78 (t, J = 5.0 Hz, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 53.4, 57.6, 60.0, 70.0. HRMS (FAB-QMS): calcd. for $C_6H_{14}N_1O_2$ $[M + H]^+$ 132.1025; found 132.1033.

***tert*-Butyl 3-(2-morpholinoethyl)-1*H*-indole-1-carboxylate (15f)**



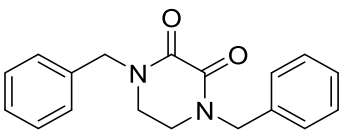
To a suspension of *N*-Boc-2-bromoethylindole (0.40 g, 1.23 mmol) and K_2CO_3 (0.22 g, 1.59 mmol) in CH_3CN (12 mL) was added morpholine (0.12 mL, 1.46 mmol). The reaction mixture was heated at reflux for 6 h. Then, the mixture was cooled to room temperature and the resulting solids were filtered and washed with EtOAc (3 x 10 mL). The organic portion was concentrated under reduced pressure and the residue was purified by flash

chromatography on silica gel (Hexane/EtOAc, 1:1) to give 0.39 g (94%) of **15f** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (s, 9H), 2.57 (br, 4H), 2.70 (app t, J = 8.5 Hz, 2H), 2.90 (t, J = 8.5 Hz, 2H), 3.77 (t, J = 4.5 Hz, 4H), 7.24 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 7.32 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.43 (s, 1H), 7.53 (d, J = 7.5 Hz, 1H), 8.12 (br, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 22.5, 28.4, 53.8, 58.7, 67.1, 83.6, 115.4, 118.8, 119.0, 122.5, 122.8, 124.5, 130.7, 135.5, 149.9. HRMS (FAB-QMS): calcd. for $C_{19}H_{27}N_2O_3$ $[M + H]^+$ 331.2022; found 331.1997.

General procedure for the selective and catalytic C-H oxidation

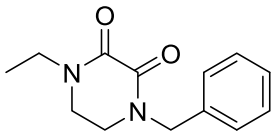
To a stirring mixture of NaH_2PO_4 (0.9 mmol) and TEMPO (0.03 mmol) in CH_3CN (4 mL) at 0 °C, was added a solution of piperazine or morpholine derivates (0.3 mmol) in CH_3CN (1 mL), and after stirring for 5 minutes, $NaClO_2$ (0.9 mmol) and NaOCl (0.7 mL of an aqueous solution of 3%) were added. When the reaction mixture turned from red to purple color the reaction is going well. The reaction course was monitored by TLC until the starting material is consumed. Then, a saturated solution of NaOH was added dropwise until the purple color disappeared. The phases were separated by funnel, the organic phase was washed with brine (2 x 3 mL) and the aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by flash chromatography on silica gel with mixtures of Hexane/EtOAc as mobile phase. It is important to note that in some cases is necessary to add 2-methyl-2-butene as a HOCl scavenger (see Table 2).

1,4-Dibenzylpiperazine-2,3-dione (12)[37]



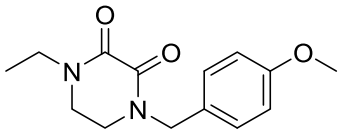
Eluent: hexane/EtOAc, 1:3. Isolated 0.5 g (95%) of **12** as a white solid. Mp = 199-201 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 (s, 4H), 4.67 (s, 4H), 7.31 (m, 10H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 43.4, 50.6, 128.1, 128.4, 128.9, 135.4, 157.4.

1-Benzyl-4-ethylpiperazine-2,3-dione (14a)



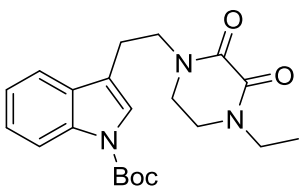
Eluent: CH_2Cl_2/EtOAc, 1:1. Isolated 0.10 g (90%) of **14a** as a white solid. Mp = 117-119 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, J = 7.0 Hz, 3H), 3.42 (m, 2H), 3.47 (m, 2H), 3.53 (q, J = 7.0 Hz, 2H), 4.68 (s, 2H), 7.32 (m, 5H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.3, 42.4, 43.6, 43.9, 50.6, 128.2, 128.5, 129.0, 135.6, 157.0, 157.7. HRMS (ESI-TOF): calcd. for $C_{13}H_{17}N_2O_2$ $[M + H]^+$ 233.1290; found 233.1293.

1-(*p*-Methoxybenzyl)-4-ethylpiperazine-2,3-dione (14b)



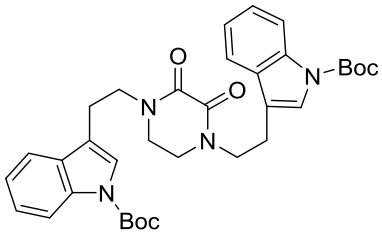
Eluent: hexane/EtOAc, 1:4. Isolated 0.18 g (70%) of **14b** as a colorless solid. Mp = 133-135 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, J = 7.0 Hz, 3H), 3.39 (m, 2H), 3.43 (m, 2H), 3.52 (q, J = 7.0 Hz, 2H), 3.80 (s, 3H), 4.61 (s, 2H), 6.86 (br, J = 8.5 Hz, 2H), 7.22 (br, J = 8.5 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.2, 42.3, 43.1, 43.7, 49.8, 55.2, 114.1, 127.5, 129.8, 157.0, 157.4, 159.3. HRMS (FAB-QMS): calcd. for $C_{14}H_{19}N_2O_3$ $[M + H]^+$ 263.1395; found 263.1397.

***tert*-Butyl 3-(2-(4-ethyl-2,3-dioxopiperazin-1-yl)ethyl)-1*H*-indole-1-carboxylate (14c)**



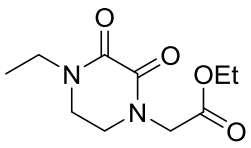
Eluent: CH_2Cl_2/MeOH, 97:03. Isolated 0.075 g (70%) of **14c** as a cream solid. Mp = 163-165 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, J = 7.0 Hz, 3H), 1.67 (s, 9H), 3.04 (t, J = 7.5 Hz, 2H), 3.30 (m, 2H), 3.35 (m, 2H), 3.49 (q, J = 7.0 Hz, 2H), 3.77 (t, J = 7.5 Hz, 2H), 7.25 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.33 (ddd, J = 8.5, 7.5, 1.5 Hz, 1H), 7.44 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 8.15 (br, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.3, 23.2, 28.3, 42.4, 43.8, 45.8, 48.6, 83.9, 115.4, 117.3, 119.0, 122.8, 123.4, 124.7, 130.2, 135.6, 149.7, 157.0, 157.6. HRMS (ESI-TOF): calcd. for $C_{21}H_{28}N_3O_4$ $[M + H]^+$ 386.2079; found 386.2068.

di-*tert*-Butyl 3,3'-((2,3-dioxopiperazine-1,4-diyl)bis(ethane-2,1-diyl))bis(1*H*-indole-1-carboxylate) (14d)



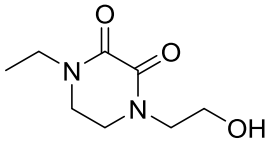
Eluent: hexane/EtOAc, 3:5. Isolated 0.10 g (65%) of **14d** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 18H), 3.00 (t, J = 7.5 Hz, 4H), 3.16 (s, 4H), 3.73 (app t, J = 7.5 Hz, 4H), 7.23 (ddd, J = 8.0, 8.0, 1.0 Hz, 2H), 7.32 (ddd, J = 8.5, 8.5, 1.5 Hz, 2H), 7.42 (s, 2H), 7.57 (d, J = 8.0 Hz, 2H), 8.12 (br, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 23.2, 28.3, 45.6, 48.5, 83.9, 115.5, 117.3, 119.0, 122.8, 123.4, 124.8, 130.3, 135.6, 149.7, 157.4. HRMS (FAB-QMS): calcd. for $C_{34}H_{41}N_4O_6$ $[M + H]^+$ 601.3021; found 601.3003.

Ethyl 2-(4-ethyl-2,3-dioxopiperazin-1-yl)acetate (14e)



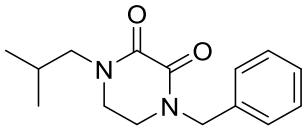
Eluent: CH_2Cl_2/EtOAc, 1:2. Isolated 0.11 g (68%) of **14e** as a white solid. Mp = 66-68 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H), 3.56 (q, J = 7.0 Hz, 2H), 3.62 (m, 2H), 3.66 (m, 2H), 4.21 (q, J = 7.0 Hz, 2H), 4.26 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.3, 14.2, 42.4, 43.9, 45.6, 48.4, 61.8, 156.5, 157.9, 168.2. HRMS (FAB-QMS): calcd. for $C_{10}H_{17}N_2O_4$ $[M + H]^+$ 229.1188; found 229.1165.

1-Ethyl-4-(2-hydroxyethyl)piperazine-2,3-dione (14f)



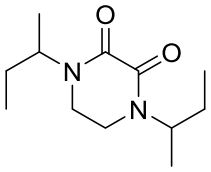
Eluent: CH_2Cl_2/MeOH, 93:07. Isolated 0.14 g (59%) of **14f** as a white solid. Mp = 117-119 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, J = 7.0 Hz, 3H), 2.39 (br, 1H), 3.52 (q, J = 7.0 Hz, 2H), 3.57 (app dd, J = 6.0, 4.0 Hz, 2H), 3.60 (t, J = 5.5 Hz, 2H), 3.73 (app dd, J = 6.0, 4.0 Hz, 2H), 3.83 (t, J = 5.5 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.3, 42.4, 44.0, 46.2, 50.6, 60.2, 157.3, 158.2. HRMS (FAB-QMS): calcd. for $C_8H_{15}N_2O_3$ $[M + H]^+$ 187.1083; found 187.1086.

1-Benzyl-4-isobutylpiperazine-2,3-dione (14g)



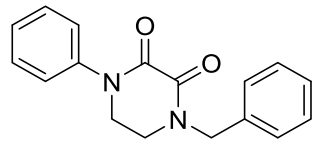
Eluent: hexane/EtOAc, 2:1. Isolated 0.044 g (67%) of **14g** as a colorless solid. Mp = 140-142 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, J = 6.5 Hz, 6H), 1.97 (m, 1H), 3.94 (d, J = 7.5 Hz, 2H), 3.41 (m, 2H), 3.44 (m, 2H), 4.69 (s, 2H), 7.30 (m, 5H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 20.1, 26.8, 43.5, 45.2, 50.6, 55.0, 128.2, 128.5, 129.0, 135.6, 157.5, 157.7. HRMS (FAB-QMS): calcd. for $C_{15}H_{21}N_2O_2$ $[M + H]^+$ 261.1603; found 261.1602.

1,4-bis(*sec*-Butyl)piperazine-2,3-dione (14h)



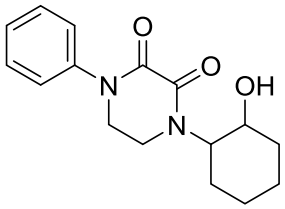
Eluent: EtOAc. Isolated (61%) of **14h** as a colorless solid. Mp = 183-186 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H), 1.15 (ddd, J = 7.0, 2.5, 1.0 Hz, 6H), 1.50 (m, 4H), 3.33 (m, 4H), 4.62 (st, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 11.1, 17.7, 26.4, 38.5, 50.7, 157.8. HRMS (FAB-QMS) calcd. for $C_{12}H_{23}N_2O_2$ $[M + H]^+$ 227.1760; found 227.1758.

4-Benzyl-1-phenylpiperazine-2,3-dione (14i)[37]



Eluent: hexane/EtOAc, 1:2. Isolated 0.063 g (75%) of **14i** as a white solid. Mp = 131-133 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.57 (ddd, J = 7.5, 5.5, 4.0 Hz, 2H), 3.89 (ddd, J = 7.5, 6.0, 4.0 Hz, 2H), 4.75 (s, 2H), 7.27 (m, 1H), 7.36 (m, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 43.8, 47.7, 50.8, 124.6, 127.3, 128.3, 128.6, 129.1, 129.3, 135.5, 140.8, 156.7, 157.7.

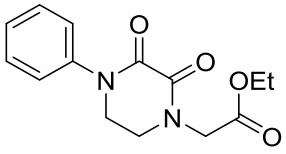
***rac*–*trans*-1-(2-Hydroxycyclohexyl)-4-phenylpiperazine-2,3-dione (14j)**



Eluent: hexane/EtOAc/MeOH, 3:2:0.5. Isolated 0.29 g (87%) of **14j** as a white solid. Mp = 245-247 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (m, 2H), 1.44 (m, 3H), 1.81 (m, 2H), 2.15 (m, 1H), 2.80 (br, 1H), 3.56 (br, 1H), 3.61 (ddd, J =

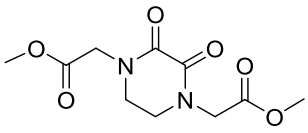
11.5, 8.0, 3.5 Hz, 1H), 3.73 (ddd, *J* = 11.0, 7.0, 3.5 Hz, 1H), 3.90 (ddd, *J* = 11.0, 7.5, 3.5 Hz, 1H), 4.07 (ddd, *J* = 11.5, 7.5, 3.5 Hz, 1H), 4.24 (td, *J* = 10.5, 4.0 Hz, 1H), 7.33 (m, 5H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 24.7, 24.9, 28.7, 35.1, 40.3, 48.0, 60.7, 70.3, 124.7, 127.2, 129.3, 141.0, 157.2, 158.8. HRMS (ESI-TOF): calcd. for $C_{16}H_{21}N_2O_3$ $[M + H]^+$ 289.1552; found 289.1547.

Ethyl 2-(2,3-dioxo-4-phenylpiperazin-1-yl)acetate (14k)



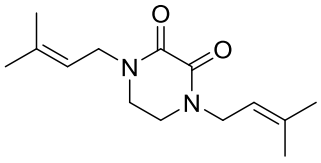
Eluent: hexane/EtOAc, 2:3. Isolated 0.085 g (55%) of **14k** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.0 Hz, 3H), 3.79 (m, 2H), 4.04 (m, 2H), 4.24 (q, *J* = 7.0 Hz, 2H), 4.32 (s, 2H), 7.30 (m, 2H), 7.35 (m, 2H), 7.42 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 14.3, 45.9, 47.8, 45.6, 61.9, 124.6, 127.4, 129.4, 140.8, 156.3, 158.0, 168.2. HRMS (ESI-TOF): calcd. for $C_{14}H_{17}N_2O_4$ $[M + H]^+$ 277.1188; found 277.1178.

Dimethyl 2,2'-(2,3-dioxopiperazine-1,4-diyl)diacetate (14l)



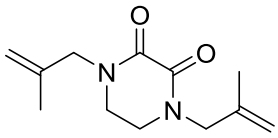
Eluent: EtOAc. Isolated 0.054 g (70%) of **14l** as a colorless crystal. Mp = 112-114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 4H), 3.76 (s, 6H), 4.28 (s, 4H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 45.6, 48.3, 52.6, 157.2, 168.5. HRMS (FAB-QMS): calcd. for $C_{10}H_{15}N_2O_6$ $[M + H]^+$ 259.0930; found 259.0924.

1,4-bis(3-Methylbut-2-en-1-yl)piperazine-2,3-dione (14m)



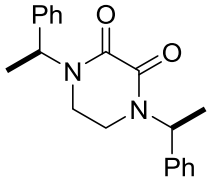
Eluent: hexane/EtOAc, 1:4. Isolated 0.053 g (71%) of **14m** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (s, 6H), 1.75 (s, 6H), 3.44 (s, 4H), 4.08 (d, *J* = 3.0 Hz, 4H), 5.15 (t, *J* = 3.0 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 17.9, 25.7, 43.1, 44.3, 117.5, 138.6, 157.2. HRMS (FAB-QMS): calcd. for $C_{14}H_{23}N_2O_2$ $[M + H]^+$ 251.1756; found 251.1751.

1,4-bis(2-Methylallyl)piperazine-2,3-dione (14n)



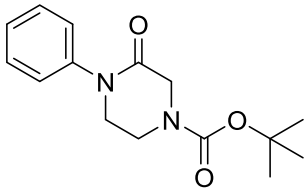
Eluent: hexane/EtOAc/MeOH, 2:4:1. Isolated 0.046 g (68%) of **14n** as a colorless solid. Mp = 111-113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 (s, 6H), 3.43 (s, 4H), 4.07 (s, 4H), 4.88 (s, 2H), 4.97 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 15.4, 39.2, 51.4, 127.5, 128.1, 128.9, 139.1, 157.4. HRMS (FAB-QMS): calcd. for $C_{12}H_{19}N_2O_2$ $[M + H]^+$ 223.1446; found 223.1440.

1,4-bis((*S*)-1-Phenylethyl)piperazine-2,3-dione (14p)



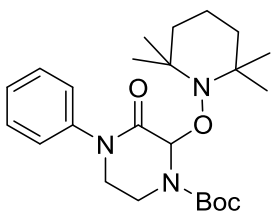
Eluent: hexane/EtOAc, 1:2. Isolated 0.063 g (58%) of **14p** as a white solid. Mp = 252-255 °C. $[\alpha]_D^{20}$ = –136.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (d, J = 7.0 Hz, 6H), 2.89 (m, 2H), 3.13 (m, 2H), 6.00 (q, J = 7.0 Hz, 2H), 7.32 (m, 10H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 15.2, 39.0, 51.2, 127.3, 127.9, 128.7, 138.9, 157.3. HRMS (EI-TOF): calcd. for $C_{20}H_{22}N_2O_2$ $[M]^+$ 322.1681; found 322.1689.

***tert*-Butyl 3-oxo-4-phenylpiperazine-1-carboxylate (14q)**



Eluent: hexane/EtOAc, 3:1. Isolated 0.047 g (27%) of **14q** as a cream solid. Mp = 155-157 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 3.74 (m, 2H), 3.78 (m, 2H), 4.26 (s, 2H), 7.29 (m, 3H), 7.41 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 28.4, 40.5, 48.4, 49.8, 81.0, 125.7, 127.3, 129.4, 141.8, 153.9, 165.8. HRMS (FAB-QMS): calcd. for $C_{15}H_{21}N_2O_3$ $[M + H]^+$ 277.1552; found 277.1549.

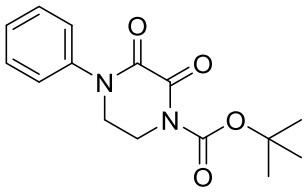
***tert*-Butyl 3-oxo-4-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperazine-1-carboxylate (14r)**



Eluent: hexane/EtOAc, 9:1. Isolated 0.010 g (4%) of **14r** as a cream solid. Mp = 146-148 °C. NMR data is reported as a mixture of *E*/*Z* rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (m), 1.46 (m), 1.55 (s), 3.60 (m), 3.68 (m), 3.75 (m), 4.21 (m), 4.27 (m), 6.14 (s), 6.19 (s), 7.26 (m), 7.34 (m), 7.41 (m). $^{13}C\{^1H\}$ NMR

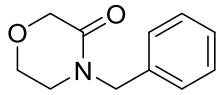
(125 MHz, $CDCl_3$) δ 17.1, 17.2, 20.0, 20.5, 20.5, 28.3, 28.5, 32.7, 33.0, 33.5, 40.0, 40.2, 40.5, 40.6, 41.2, 42.2, 46.2, 46.5, 59.4, 61.3, 61.4, 80.8, 81.2, 87.3, 87.5, 124.9, 124.9, 126.5, 126.7, 129.0, 129.1, 141.2, 141.3, 154.1, 154.4, 164.5. HRMS (FAB-QMS): calcd. for $C_{24}H_{38}N_3O_4$ $[M + H]^+$ 432.2862; found 432.2861.

***tert*-Butyl 2,3-dioxo-4-phenylpiperazine-1-carboxylate (14s)**



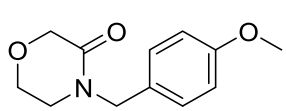
Eluent: hexane/EtOAc, 3:1. Isolated 0.097 g (53%) of **14s** as a white solid. Mp = 153-155 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (s, 9H), 3.98 (m, 2H), 4.10 (m, 2H), 7.29 (m, 1H), 7.35 (m, 2H), 7.42 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 28.0, 43.0, 47.4, 85.0, 124.3, 127.5, 129.4, 140.1, 151.1, 156.1, 156.2. HRMS (ESI-TOF): calcd. for $C_{15}H_{19}N_2O_4$ $[M + H]^+$ 291.1344; found 291.1356.

4-Benzylmorpholin-3-one (16a)[38]



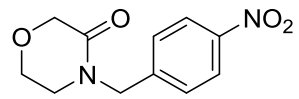
Eluent: hexane/EtOAc, 2:1. Isolated 0.091 g (85%) of **16a** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.26 (t, J = 5.0 Hz, 2H), 3.83 (t, J = 5.0 Hz, 2H), 4.24 (s, 2H), 4.62 (s, 2H), 7.30 (m, 5H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 45.5, 49.4, 63.9, 68.2, 127.7, 128.2, 128.8, 136.1, 166.8.

4-(*p*-Methoxybenzyl)morpholin-3-one (16b)



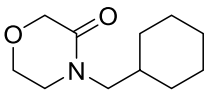
Eluent: hexane/EtOAc, 3:1. Isolated 0.056 g (48%) of **16b** as a white solid. Mp = 62-64 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.25 (t, J = 5.0 Hz, 2H), 3.80 (s, 3H), 3.82 (t, J = 5.0 Hz, 2H) 4.23 (s, 2H), 4.56 (s, 2H), 6.87 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 45.3, 48.9, 55.3, 64.0, 68.2, 114.1, 128.2, 129.8, 159.2, 166.7. HRMS (FAB-QMS): calcd. for $C_{12}H_{16}NO_3$ $[M + H]^+$ 222.1053; found 222.1049.

4-(*p*-Nitrobenzyl)morpholin-3-one (16c)[39]



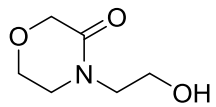
Eluent: hexane/EtOAc, 1:2. Isolated 0.066 g (62%) of **16c** as a white solid. Mp = 136-138 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.35 (app t, J = 5.0 Hz, 2H), 3.91 (app t, J = 5.0 Hz, 2H), 4.29 (s, 2H), 4.73 (s, 2H), 7.47 (d, J = 9.0 Hz, 2H), 8.22 (d, J = 8.5 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 46.2, 49.2, 63.9, 68.3, 124.1, 128.9, 143.8, 147.5, 167.2.

4-(Cyclohexylmethyl)morpholin-3-one (16d)



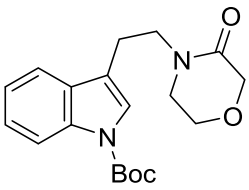
Eluent: hexane/EtOAc, 3:2. Isolated 0.090 g (71%) of **16d** as a colorless crystal. Mp = 48-51 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (m, 2H), 1.20 (m, 3H), 1.69 (m, 6H), 3.25 (d, J = 7.5 Hz, 2H), 3.36 (t, J = 5.0 Hz, 2H), 3.88 (app t, J = 5.0 Hz, 2H), 4.18 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 25.9, 26.5, 30.8, 35.7, 47.1, 52.8, 64.0, 68.2, 166.9. HRMS (FAB-QMS): calcd. for $C_{11}H_{20}NO_2$ $[M + H]^+$ 198.1419; found 198.1421.

4-(2-Hydroxyethyl)morpholin-3-one (16e)[40]



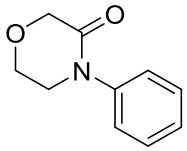
Eluent: hexane/EtOAc, 1:7. Isolated 0.035 g (58%) of **16e** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (br, 1H), 3.50 (t, J = 5.5 Hz, 2H), 3.58 (t, J = 5.0 Hz, 2H), 3.82 (t, J = 5.5 Hz, 2H), 3.91 (t, J = 5.0 Hz, 2H), 4.20 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 47.8, 50.2, 61.1, 63.8, 68.0, 168.6.

***tert*-Butyl 3-(2-(3-oxomorpholino)ethyl)-1*H*-indole-1-carboxylate (16f)**



Eluent: hexane/EtOAc, 3:1. Isolated 0.028 g (24%) of **16g** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (s, 9H), 3.01 (t, J = 7.5 Hz, 2H), 3.28 (t, J = 5.0 Hz, 2H), 3.70 (t, J = 7.5 Hz, 2H), 3.76 (t, J = 5.0 Hz, 2H), 4.19 (s, 2H), 7.26 (m, 1H), 7.33 (m, 1H), 7.44 (s, 1H), 7.60 (d, J = 7.5 Hz, 1H), 8.13 (br, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 23.0, 28.4, 47.3, 47.4, 63.9, 68.3, 83.8, 115.5, 117.6, 119.0, 122.7, 123.3, 124.7, 130.4, 135.6, 149.7, 167.1. HRMS (FAB-QMS): calcd. for $C_{19}H_{25}N_2O_4$ $[M + H]^+$ 345.1726; found 345.1724.

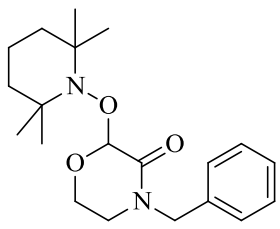
4-Phenylmorpholin-3-one (16g)[41]



Eluent: hexane/EtOAc, 3:1. Isolated 0.258 g (90%) of **16h** as a white solid. Mp = 113-115 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (app t, J = 5.0 Hz, 2H), 4.02 (app t, J = 5.0 Hz, 2H), 4.34 (s, 2H), 7.31 (m, 3H), 7.41 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 49.7, 64.2, 68.6, 125.6, 127.2, 129.4, 141.4, 166.7.

4-Benzyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)morpholin-3-one (16i)

To a stirring mixture of NaH_2PO_4 (0.70 g, 5.07 mmol), TEMPO (0.39 g, 2.54 mmol) and $NaClO_2$ (0.46 g, 5.08 mmol) in CH_3CN (27 mL) at 0 °C was added dropwise 0.99 mL of a solution of NaOCl (aq, 3%). The reaction mixture was turned from red to red-wine color. After 5 min, a solution of **15a** (0.30 g, 1.69 mmol) in CH_3CN (1 mL) was added dropwise. The resulting reaction mixture was stirred for 1 h. Then, a saturated solution of NaOH was added dropwise until the red-wine color disappeared. The phases were separated by funnel, organic phase washed with brine (2 x 10 mL) and the aqueous phase was extracted with EtOAc (3 x 15 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 (Hexane/EtOAc, 6:1) to give 0.44 g (75%) of **16i** as a colorless oil.



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (m, 10H), 1.53 (b, 8H), 3.08 (ddd, J = 12.0, 3.5, 1.5 Hz, 1H), 3.44 (td, J = 11.5, 4.5 Hz, 1H), 3.69 (ddd, J = 12.0, 5.0, 2.0 Hz, 1H), 4.20 (td, J = 11.5, 3.5 Hz, 1H), 4.56 (d, J = 14.5 Hz, 1H), 4.68 (d, J = 14.5 Hz, 1H), 5.40 (s, 1H), 7.28 (m, 3H), 7.34 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 17.1, 20.2, 20.9, 32.6, 34.0, 40.6, 40.7, 45.4, 49.9, 57.4, 59.4, 61.8, 100.7, 127.7, 128.3, 128.8, 136.1. HRMS (FAB-QMS): calcd. for $C_{20}H_{31}N_2O_3$ $[M + H]^+$ 347.2335; found 347.2330.

Reduction of 14p to 13p mediated by $LiAlH_4$

To a mixture of **14p** (0.080 g, 0.25 mmol) and $LiAlH_4$ (0.028 g, 0.74 mmol) at 0 °C, was added dropwise THF (2 mL). After 15 minutes, the reaction was stirred at room temperature for 1 h. Then, the

mixture was cooled to 0 °C and H_2O was added dropwise until the formation of solids. The resulting solids were washed with EtOAc (5 × 5 mL). The organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (Hexane/EtOAc, 3:1) to give 0.051 g (70 %) of **13p** as a white solid. Mp = 43-45 °C. $[\alpha]_D^{20}$ = –28.8 (c = 1.0, $CHCl_3$).

ASSOCIATED CONTENT

The supporting information is available free of charge on the ACS Publications website at: Copies of ^1H and ^{13}C NMR spectra of relevant products.

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CONFLICTS OF INTEREST

There are no conflicts to declare

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