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Synthesis of 5-alkyl-5-aryl-1-pyrroline *N*-oxides from 1-aryl-substituted nitroalkanes and acrolein via Michael addition and nitro reductive cyclization

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ABSTRACT

A general method for accessing 5-alkyl-5-aryl-1-pyrroline *N*-oxides (AAPOs) has been established using readily available aryl bromides, nitroalkanes, and acrolein as the starting materials. The palladium-catalyzed arylation of nitroalkanes gave the 1-aryl-substituted nitroalkanes, which underwent the Et_3N-catalyzed Michael addition with acrolein at room temperature to afford the 4-aryl-4-nitroaldehydes. The latter were then subjected to the nitro reductive cyclization using Zn–HOAc in EtOH at 0 °C followed by warming the reaction mixture to room temperature for 24 h, furnishing the 5-alkyl-5-aryl-1-pyrroline *N*-oxides in good overall yields. Selected examples of 1,3-dipolar cycloaddition of the cyclic nitrones with methyl methacrylate were also described.

1. Introduction

The 1-pyrroline *N*-oxide (3,4-dihydro-2*H*-pyrrole 1-oxide) is the core structure of a number of cyclic nitrone spin traps, such as DMPO (**1**),[1] MPPO (**2**),[2] EMPO (**3**),[3] AMPO (**4**),[4] and DEPMPO (**5**)[5] (Fig. 1). These cyclic nitrones and the well known acyclic congeners represented by (*Z*)-α-phenyl-*N*-*tert*-butylnitrone (PBN, **7**)[6] and disodium (*Z*)-4-[(*tert*-butylimino)methyl]benzene-1,3-disulfonate *N*-oxide (OKN-007, formerly referred to as NXY-059, **8**)[7] have been extensively studied as therapeutics for oxidative stress-related diseases, such as neurodegeneration, cardiovascular disease, and cancer.[8] Among them, the nitrone **8** has reached to clinical trials for treatment of acute stroke,[7a] and it delivers anticancer activity in animal glioma models[7b–d] and hepatocellular carcinoma.[7c,e] Over the years, acyclic nitrones represented by the general structure **I** (Ar=aryl or heteroaryl) have been synthesized for improved spin trap properties[9a–c] and for stroke treatment.[9d,e] Novel benzoxazinic nitrones **9**–**11**[10] and other cyclic nitrones[11] have also been reported for studying their reactivity toward oxygen- and carbon-centered radicals and as possible antioxidants in biological systems. Moreover, conjugates of acyclic and cyclic nitrones with cholesterol,[12a,e] β-cyclodextrin,[12b,c] and fluorinated amphiphilic carriers[12d,f] have been synthesized and evaluated for spin-trapping

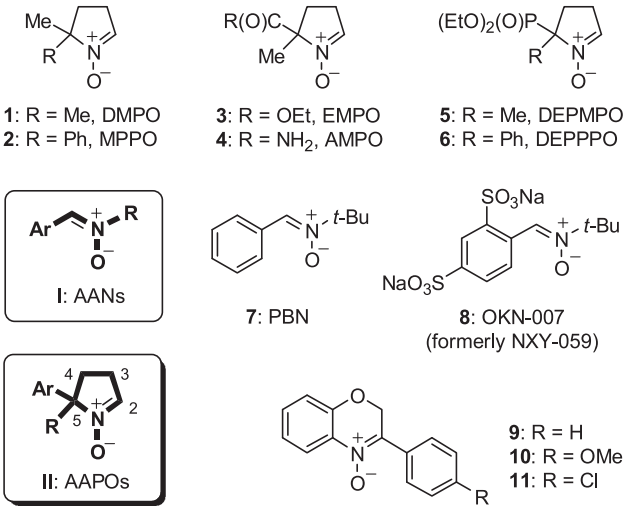

Fig. 1. Structures of cyclic and linear nitrone spin traps **1**–**11**.

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behavior[12a–d] and antioxidant properties in biomimetic membrances,[12f] and as antioxidants against light-induced retinal degeneration.[12e]

Substituent effect on the spin-trapping behavior of 1-pyrroline *N*-oxides has been examined. Replacement of one C5-methyl group in DMPO (**1**) by a phenyl group as in MPPO (**2**) improved its stability to have an excellent shelf life.[2a] Moreover, longer lifetimes of the spin adducts of MPPO were observed while similar spin-trapping rate constants as compared to those of DMPO were achieved. The unique stereochemistry of the spin adducts of MPPO rendered easy detection of the spin-adduct spectra. In some cases one major *trans* (with respect to the phenyl group) and one minor *cis* adducts were formed in addition reactions with the carbon-centered radicals while the reverse selectivity was observed for the superoxide/peroxyl radical adducts. For the hydroxyl radical adduct of MPPO, only one EPR spectrum was detected. In contrast, substitution of the C5-methyl group in DEPMPO (**5**) by a phenyl group gave DEPPPO (**6**)[13] with a significant decrease of the spin-trapping properties, such as non-stereoselective addition of free radicals on the nitronyl moiety due to less steric bias among the two substituents on the C5 position. It seems interesting to investigate the spin-trapping properties of the general structure **II** (Fig. 1) on the basis of MPPO (**2**).

There are two general methods for synthesis of nitrones, i.e., condensation of hydroxylamines with carbonyl compounds[14] and oxidation of hydroxylamines or secondary amines.[15] In the former cases, the hydroxylamines could be formed from reduction of nitro compounds, providing an efficient synthesis of cyclic nitrones from reductive cyclization of nitro carbonyl precursors.[16,17] Janzen and co-workers[2c] synthesized MPPO (**2**) by a four-step sequence (Fig. 2a), consisting of the Michael addition of nitromethane with methyl vinyl ketone,[16d,e] the nitro reductive cyclization, the Grignard addition with 2-methyl-1-pyrroline *N*-oxide, and finally the oxidation of the cyclic hydroxylamine. Merino and co-workers[18] prepared a similar nitrone **12** designed for studying neutral 2-aza-Cope rearrangement (Fig. 2b). Starting from the parent 1-pyrroline *N*-oxide, two iterative Grignard addition and hydroxylamine oxidation cycles were used and the overall yield of **12** was excellent. In our recent work, we established a general synthesis of 5-alkyl-5-aryl-γ-lactams from 1-aryl-substituted nitroalkanes.[19,20] We envisioned that 5-alkyl-5-aryl-1-pyrroline *N*-oxides (AAPOs) of the general structure **II** (Fig. 1) could be synthesized from the readily available 1-aryl-substituted nitroalkanes **13** via the Michael addition with acrolein followed by the reductive cyclization of the nitro aldehydes **14** to give the nitrones **15** (Fig. 2c).[16d–g] This synthetic sequence is advantageous not only for its generality but also for its tolerance of the functional groups, such as carboxylic esters, which could not survive under the Grignard addition conditions as employed in Janzen and Merino's preparations, respectively (Fig. 2a and b). The functional group X on the phenyl ring of **15** should enable formation of conjugates for achieving enhanced spin-trapping properties as demonstrated in the prior work mentioned above.[12]

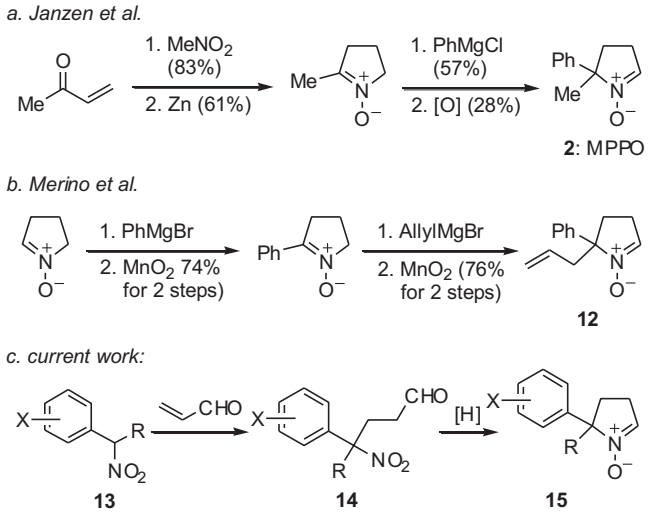
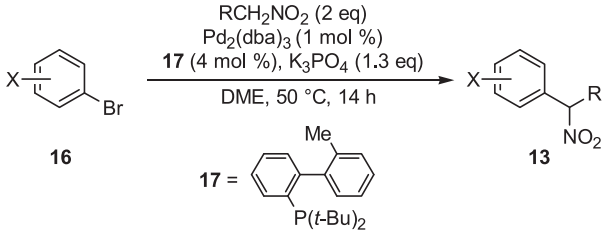


Fig. 2. Synthetic approaches toward 5-alkyl-5-aryl-1-pyrroline *N*-oxides.

2. Results and discussion

1-Aryl-substituted nitroalkanes **13a–g** and **13n** (entries 1–7 and 14, Table 1) were obtained by the Pd-catalyzed α-arylation of nitroalkanes under the optimized conditions in our previous work.[19] The compounds **13h–m** were newly synthesized by following the same procedure in good to excellent yields.

Table 1
Results of Pd-catalyzed arylation of nitroalkanes[a]



Entry	**16**: X	R	*t* (h)	**13**: Yield[b] (%)
1[c]	**16a**: 2-(1,3-Dioxolan-2-yl)	Me	24	**13a**: 71[d]
2	**16b**: 3-Me	Me	14	**13b**: 90[d]
3	**16c**: 4-Me	Me	14	**13c**: 78[d]
4[e]	**16d**: 2-MeO	Me	18	**13d**: 91[d]
5	**16e**: 4-MeO	Me	14	**13e**: 74[d]
6	**16f**: 4-Cl	Me	14	**13f**: 84[d]
7	**16g**: 4-MeO$_2$C	Me	14	**13g**: 88[d]
8	**16h**: 4-(1,3-Dioxolan-2-yl)	Et	14	**13h**: 75
9[e]	**16i**: 2-Me	Et	18	**13i**: 72
10	**16b**: 3-Me	Et	14	**13j**: 89
11	**16c**: 4-Me	Et	14	**13k**: 88
12[e]	**16d**: 2-MeO	Et	18	**13l**: 91
13	**16f**: 4-Cl	Et	14	**13m**: 80
14	**16g**: 4-MeO$_2$C	Et	14	**13n**: 87[d]

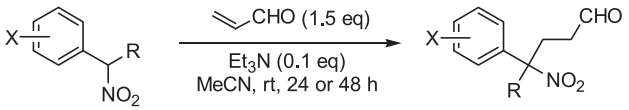
[a] Reaction conditions: 1 mol % $Pd_2(dba)_3$, 4 mol % **17**, 2 equiv of RCH_2NO_2, and 1.3 equiv of K_3PO_4, DME, 50 °C for 14 h.
[b] Isolated yields.
[c] Using 5 mol % $Pd_2(dba)_3$ and 20 mol % **17** in 1,4-dioxane at 110 °C.
[d] Data are taken from Ref. 19 for comparison.
[e] Using 5 mol % $Pd_2(dba)_3$ and 10 mol % **17** at 50 °C for 18 h.

In general, the *ortho*-substituent in the aryl bromides **16** rendered the arylation much more difficult to occur. For example, much higher temperature and catalyst loading should be applied for the arylation of **16a** as compared to **16h** (entry 1 vs entry 8, Table 1). Also, the reactions of **16d** and **16i** required higher catalyst loading and longer reaction time (entries 4, 9, and 12, Table 1). On the other hand, the R group in nitroalkanes, i.e., Me (entries 2–4, 6, and 7, Table 1) versus Et (entries 10–14, Table 1) did not show notable influence on the arylation results.

In our previous work on the Michael addition of the 1-aryl-substituted nitroalkanes **13** with methyl acrylate, it was found that Et_3N was not an efficient base to promote formation of the Michael adducts. Instead, DBU (0.5–1.0 equiv) should be used to facilitate the Michael addition in MeCN at room temperature for 2.5 h to furnish the adducts in excellent yields.[19] For the Michael addition of **13** with acrolein,[16f,g] we found that only 0.1 equiv of Et_3N was sufficient to catalyze the formation of the adducts **14** at room temperature. For the substrates **13b–d** and **13f** (R=Me) possessing

a methyl group at the α-carbon, their Michael adduct yields are generally higher than the corresponding Et analogues **13j**–**m** (entries 2–4 and 6 vs entries 10–13, Table 2). These results indicate that a bulky R group renders the Michael addition difficult to take place. When the acidity of the α-proton of the nitroalkanes **13g** and **13n** increases due to the presence of the *para*-carboxylic ester moiety on the benzene ring, the same yields are obtained (entry 7 vs entry 14, Table 2) regardless the bulkiness of the R group. The *ortho*-(1,3-dioxolan-2-yl) group in **13a** and *ortho*-methyl group in **13i** also affect the Michael addition to give diminished yields for **14a** (entry 1, Table 2) and **14i** (entry 9, Table 2), but the *ortho*-methoxy group in **13d**,**l** did not reduce the yields of the adducts **14d** (entry 4, Table 2) and **14l** (entry 12, Table 2). Moreover, the yields of some Michael adducts could be improved by extending the reaction times to 48 h (entries 2, 3, 5, and 10, Table 2).

Table 2
Results of Michael addition of **13** with acrolein[a]



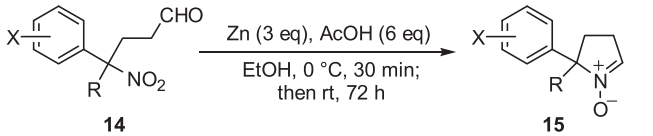
Entry	**13**: X	R	**14**: Yield[b] (%)
1	**13a**: 2-(1,3-Dioxolan-2-yl)	Me	**14a**: 66
2	**13b**: 3-Me	Me	**14b**: 80 (93)
3	**13c**: 4-Me	Me	**14c**: 84 (96)
4	**13d**: 2-MeO	Me	**14d**: 83 (83)
5	**13e**: 4-MeO	Me	**14e**: 84 (93)
6	**13f**: 4-Cl	Me	**14f**: 73
7	**13g**: 4-MeO_2C	Me	**14g**: 88 (88)
8	**13h**: 4-(1,3-Dioxolan-2-yl)	Et	**14h**: 71
9	**13i**: 2-Me	Et	**14i**: 57
10	**13j**: 3-Me	Et	**14j**: 64 (94)
11	**13k**: 4-Me	Et	**14k**: 70
12	**13l**: 2-MeO	Et	**14l**: 68 (69)
13	**13m**: 4-Cl	Et	**14m**: 67
14	**13n**: 4-MeO_2C	Et	**14n**: 87 (86)

[a] Reaction conditions: **13** (1 mmol), acrolein (1.5 mmol), and Et_3N (0.1 mmol) in MeCN (4 mL) at room temperature for 24 h.
[b] Isolated yields. The numbers given in the parentheses are the yields obtained after reaction for 2 days.

The reductive cyclization of the nitro aldehydes **14** went smoothly in the presence of zinc powder and AcOH in EtOH first at 0 °C for 30 min followed by warming up to room temperature for 72 h.[16] The yields of the 5-alkyl-5-aryl-1-pyrroline *N*-oxides **15a**–**n** are listed in Table 3. In general, yields ranging from 70 to 80% were obtained except for the nitrone **15c** (entry 3, Table 3). Some of the reductive cyclization experiments were repeated at room temperature for 24 h instead of 72 h and the nitrone yields were similar, suggesting that a longer reaction time might be not necessary. However, the yield and reaction time relationship for the two *ortho*-methoxy-substituted substrates is opposite and no explanation could be offered (entry 4 vs entry 12, Table 3).

Cyclic nitrones in chiral or achiral forms have been used in 1,3-dipolar cycloadditions with a variety of olefins.[21] Although DMPO (**1**) and similar cyclic nitrones were reported to undergo 1,3-dipolar cycloadditions,[22] to the best of our knowledge, unsymmetrical 5,5-disubstituted 1-pyrroline *N*-oxides **15** have not been investigated for this reaction type. It might be interesting to examine the regio- and stereoselectivity of **15** in 1,3-dipolar cycloaddition reactions. After preliminary screening of olefin substrates, it was found that cycloadditions of methyl acrylate and methyl crotonate with **15n**, for example, afforded good to excellent yields of the adducts but with low regio- and stereoselectivity. Fortunately, the cycloaddition of methyl methacrylate with **15c** at room temperature in MeCN for

Table 3
Results of formation of nitrones **15** via reductive cyclization of **14**[a]

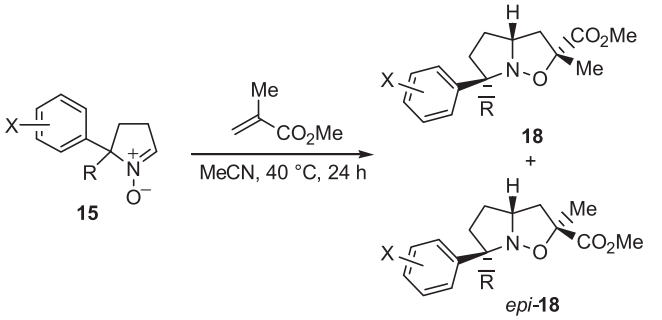


Entry	**14**: X	R	**15**: Yield[b] (%)
1	**14a**: 2-(1,3-Dioxolan-2-yl)	Me	**15a**: 70
2	**14b**: 3-Me	Me	**15b**: 83 (83)
3	**14c**: 4-Me	Me	**15c**: 63 (63)
4	**14d**: 2-MeO	Me	**15d**: 80 (60)
5	**14e**: 4-MeO	Me	**15e**: 77 (77)
6	**14f**: 4-Cl	Me	**15f**: 73
7	**14g**: 4-MeO_2C	Me	**15g**: 79 (71)
8	**14h**: 4-(1,3-Dioxolan-2-yl)	Et	**15h**: 78
9	**14i**: 2-Me	Et	**15i**: 71
10	**14j**: 3-Me	Et	**15j**: 86 (82)
11	**14k**: 4-Me	Et	**15k**: 73
12	**14l**: 2-MeO	Et	**15l**: 72 (83)
13	**14m**: 4-Cl	Et	**15m**: 77
14	**14n**: 4-MeO_2C	Et	**15n**: 74 (74)

[a] Reaction conditions: **14** (1.0 mmol), zinc powder (3.0 mmol), and AcOH (6.0 mmol) in EtOH (10 mL) at 0 °C fro 30 min and then at room temperature for 72 h.
[b] Isolated yields. The numbers given in the parentheses are the yields obtained after reaction for 24 h.

41.5 h furnished the adducts **18b** and *epi*-**186b** in 96:4 diastereomeric ratio and in 73% isolated yield of **18b** and *epi*-**18b** as an inseparable mixture (entry 2, Table 4). The other possible regioisomers were not detected by ^1H NMR analysis of the crude reaction mixture. The yield of the reaction of **15c** with methyl methacrylate could be improved to 78% by heating at 40 °C for 24 h with the same diastereoselectivity (entry 3, Table 4). Further increase of the reaction temperature to 80 °C in refluxing MeCN significantly shortened the reaction time to 5 h, providing the adducts in 80% combined yield but with slightly diminished diastereomeric ratio of 90:10 (entry 4, Table 4). By keeping the reaction temperature at 40 °C, other cyclic nitrones **15b**,**d**,**e**,**j** were

Table 4
Results of 1,3-dipolar cycloaddition of **15** with methyl methacrylate[a]



Entry	**15**: X	R	Yield[b] (%)	dr (**18**/*epi*-**18**)[c]
1	**15b**: 3-Me	Me	**18a**: 80	95:5
2[d]	**15c**: 4-Me	Me	**18b**: 73	96:4
3	**15c**: 4-Me	Me	**18b**: 78	95:5
4[e]	**15c**: 4-Me	Me	**18b**: 80	90:10
5	**15d**: 2-MeO	Me	**18c**: 82	94:6
6	**15e**: 4-MeO	Me	**18d**: 80	94:6
7	**15j**: 3-Me	Me	**18e**: 87	95:5

[a] Reaction conditions: **15** (1.0 mmol), methyl methacrylate (2.0 mmol) in MeCN (10 mL) in a closed process vial at 40 °C for 24 h.
[b] Isolated yields of both diastereomers **18** and *epi*-**18**.
[c] Determined by ^1H NMR spectroscopy analysis.
[d] Carried out at room temperature for 41.5 h.
[e] Carried out under refluxing for 5 h.

used for the same 1,3-dipolar cycloaddition with methyl methacrylate to afford the adducts **18a** and **18c**–**e** in 80–87% yields and with 94:6 to 95:5 diastereoselectivity (entries 1 and 5–7, Table 4). The structures of the major adducts **18** were assigned according to the preferred *endo* approach[23] assuming that the C5-aryl group in **15** (such as 2-methoxyphenyl in **15d**) is sterically more demanding than the C5-alkyl group (R=Me).

3. Conclusion

In summary, we have established a general and efficient synthesis of 5-alkyl-5-aryl-1-pyrroline *N*-oxides **15** by the Michael addition of 1-aryl-substituted nitroalkanes **13** with acrolein followed by the reductive cyclization of the nitro aldehydes **14**. Since the palladium-catalyzed α-arylation of nitroalkanes tolerates a variety of aryl bromides/chlorides, such as **16a**–**i**,[19,20] the above described synthetic protocol offers access to the diversely substituted 5-alkyl-5-aryl-1-pyrroline *N*-oxides **15** from the readily available nitro compounds **13**. The functional group, such as the carboxylic ester in **15g**,**n**, should provide a tethering point for formation of conjugates useful for application of these cyclic nitrone spin traps in biologically relevant systems. Moreover, these unique cyclic nitrones possessing 5,5-disubstituents have been examined for 1,3-dipolar cycloaddition with methyl methacrylate at 40 °C to furnish the adducts with only one regioisomer and in ≥94:6 diastereoselectivity.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone-d_6 (400 or 500 MHz for ^{1}H and 100 or 125 MHz for ^{13}C, respectively). IR spectra were taken on an FT-IR spectrophotometer. Mass spectra (MS) were measured by the ESI or EI method. Silica gel plates precoated on glass were used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Reagents were obtained commercially and used as received.

4.2. General procedure A for the arylation of nitroalkanes

A dried 10-mL process vial was charged with appropriate amounts of $Pd_2(dba)_3$ and 2-(di-*tert*-butylphosphinyl)-2′-methylbiphenyl (**17**), and 1.3 equiv of K_3PO_4. The vial was sealed with as cap containing a silicon septum. The loaded vial was evacuated and backfilled with nitrogen for three times. Then, aryl bromide **16** (1.0 mmol), nitroalkane (2.0 mmol), and degassed DME (5.0 mL) were added sequentially via a syringe. The resultant mixture was stirred vigorously for 1 min at room temperature, and then at 50 °C for 14 h. After cooling to ambient temperature the reaction mixture was diluted with EtOAc. The resulting solution was filtered off through a plug of Celite with washing by EtOAc. The combined filtrate was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and condensed under reduced pressure. The residue was purified by flash column chromatography over silica gel to give the product **13**. The results are found in Table 1. Characterization data for the compounds **13a**–**g**,**n** are found in our previous work.[19]

*4.2.1. 2-[4-(1-Nitropropyl)phenyl][1,3]dioxolane (**13h**).* Prepared according to the general procedure A in 75% yield as a colorless oil; R_f=0.41 (9% EtOAc in hexane); IR (film): 2976, 2938, 2884, 1704, 1552, 1368, 1085 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J*=8.4 Hz, 2H), 7.48 (d, *J*=8.0 Hz, 2H), 5.82 (s, 1H), 5.37 (dd, *J*=8.8, 6.8 Hz, 1H), 4.14–4.07 (m, 2H), 4.07–4.00 (m, 2H), 2.55–2.44 (m, 1H), 2.15–2.06 (m, 1H), 0.97 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 135.4, 127.9 (×2), 127.2 (×2), 103.1, 92.8, 65.5 (×2), 27.5, 10.7; HRMS (+EI) calcd for $C_{12}H_{15}O_2$ 191.1072 (M^+-NO_2), found 191.1070.

*4.2.2. 1-Methyl-2-(1-nitropropyl)benzene (**13i**).* Prepared according to the general procedure A in 72% yield as a colorless oil; R_f=0.43 (9% EtOAc in hexane); IR (film): 2976, 2935, 2875, 1552, 1463, 1366 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.51 (m, 1H), 7.32–7.22 (m, 3H), 5.72 (dd, *J*=8.8, 6.4 Hz, 1H), 2.62–2.50 (m, 1H), 2.48 (s, 3H), 2.17–2.06 (m, 1H), 1.03 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 133.2, 131.0, 129.6, 127.0, 126.4, 88.6, 27.2, 19.6, 10.8; HRMS (+EI) calcd for $C_{10}H_{13}$ 133.1017 (M^+-NO_2), found 133.1014.

*4.2.3. 1-Methyl-3-(1-nitropropyl)benzene (**13j**).* Prepared according to the general procedure A in 89% yield as a colorless oil; R_f=0.53 (9% EtOAc in hexane); IR (film): 2977, 2938, 2881, 1552, 1462, 1367 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 3H), 7.22 (d, *J*=6.8 Hz, 1H), 5.34 (dd, *J*=8.8, 6.8 Hz, 1H), 2.57–2.45 (m, 1H), 2.38 (s, 3H), 2.17–2.06 (m, 1H), 0.99 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 134.6, 130.6, 129.0, 128.4, 124.8, 93.2, 27.4, 21.5, 10.8; HRMS (+EI) calcd for $C_{10}H_{13}$ 133.1017 (M^+-NO_2), found 133.1020.

*4.2.4. 1-Methyl-4-(1-nitropropyl)benzene (**13k**).* Prepared according to the general procedure A in 88% yield as a colorless oil; R_f=0.54 (9% EtOAc in hexane); IR (film): 2977, 2938, 2881, 1550, 1516, 1462, 1367 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J*=8.0 Hz, 2H), 7.21 (d, *J*=8.0 Hz, 2H), 5.35 (dd, *J*=8.4, 6.4 Hz, 1H), 2.56–2.44 (m, 1H), 2.36 (s, 3H), 2.16–2.05 (m, 1H), 0.98 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 131.7, 129.7 (×2), 127.7 (×2), 92.9, 27.3, 21.3, 10.8; HRMS (+EI) calcd for $C_{10}H_{13}$ 133.1017 (M^+-NO_2), found 133.1019.

*4.2.5. 1-Methoxy-2-(1-nitropropyl)benzene (**13l**).*[20] Prepared according to the general procedure A in 91% yield as a colorless oil; R_f=0.45 (9% EtOAc in hexane); IR (film): 2974, 2941, 1549, 1494, 1464, 1368, 1250, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J*=7.6 Hz, 1H), 7.36 (t, *J*=8.0 Hz, 1H), 7.00 (t, *J*=8.0 Hz, 1H), 6.92 (d, *J*=8.4 Hz, 1H), 5.89 (dd, *J*=8.4, 6.8 Hz, 1H), 3.85 (s, 3H), 2.52–2.40 (m, 1H), 2.15–2.04 (m, 1H), 1.01 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 130.8, 127.7, 123.3, 121.0, 111.0, 85.8, 55.8, 26.7, 10.9.

*4.2.6. 1-Chloro-4-(1-nitropropyl)benzene (**13m**).* Prepared according to the general procedure A in 78% yield as a colorless oil; R_f=0.45 (9% EtOAc in hexane); IR (film): 2977, 2938, 1553, 1494, 1460, 1366, 1093, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J*=9.2 Hz, 2H), 7.38 (d, *J*=8.0 Hz, 2H), 5.34 (dd, *J*=8.8, 6.8 Hz, 1H), 2.54–2.43 (m, 1H), 2.14–2.03 (m, 1H), 0.98 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 133.0, 129.4 (×2), 129.3 (×2), 92.4, 27.5, 10.7; HRMS (+EI) calcd for $C_9H_{10}{}^{35}Cl$ 153.0471 (M^+-NO_2), found 153.0472.

4.3. General procedure B for the Michael addition of nitroalkanes 13 with acrolein

To a solution of **13** (1.0 mmol) and acrolein (1.5 mmol) in MeCN (4.0 mL) at room temperature under a nitrogen atmosphere was added Et_3N (0.1 mmol). The resultant mixture was stirred at room temperature for 24 h. The reaction mixture was condensed under reduced pressure and the residue was purified by flash column chromatography over silica gel to afford the nitro aldehyde **14**. The results are found in Table 2.

*4.3.1. 4-[2-(1,3-Dioxolan-2-yl)phenyl]-4-nitropentanal (**14a**).* Prepared according to the general procedure B in 66% yield as a pale yellow oil; R_f=0.41 (25% EtOAc in hexane); IR (film): 2953, 2893, 2730, 1723, 1538, 1450, 1388, 1342, 1212, 1134, 1096, 1066 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3) δ 9.66 (s, 1H), 7.76–7.74 (m, 1H), 7.54–7.52 (m, 1H), 7.49–7.47 (m, 2H), 5.65 (s, 1H), 4.15–4.10 (m, 2H), 3.98–3.93 (m, 2H), 2.79 (t, *J*=9.0 Hz, 2H), 2.50–2.43 (m, 1H), 2.26–2.19 (m, 1H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 200.7, 137.8, 137.6, 130.2, 129.8, 129.8, 127.7, 99.8, 93.7, 66.2, 66.1, 39.9, 33.0, 27.5; HRMS (+EI) calcd for $C_{14}H_{17}O_3$ 233.1178 (M^+-NO_2), found 233.1178.

*4.3.2. 4-Nitro-4-(3-tolyl)pentanal (**14b**).* Prepared according to the general procedure B (at room temperature for 2 days) in 93% yield as a colorless oil; R_f=0.35 (17% EtOAc in hexane); IR (film): 2988, 2946, 2873, 2834, 2730, 1724, 1539, 1456, 1386, 1343 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.28 (t, *J*=8.0 Hz, 1H), 7.19–7.13 (m, 3H), 2.78–2.70 (m, 1H), 2.67–2.59 (m, 1H), 2.46 (t, *J*=7.6 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 139.0, 138.9, 129.9, 128.9, 125.9, 122.3, 92.7, 39.5, 31.7, 24.3, 21.7; HRMS (+EI) calcd for $C_{12}H_{15}O$ 175.1123 (M^+-NO_2), found 175.1125.

*4.3.3. 4-Nitro-4-(4-tolyl)pentanal (**14c**).* Prepared according to the general procedure B (at room temperature for 2 days) in 96% yield as a colorless oil; R_f=0.32 (17% EtOAc in hexane); IR (film): 2991, 2953, 2920, 2863, 2727, 1723, 1538, 1515, 1386, 1343 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.25 (d, *J*=8.0 Hz, 2H), 7.20 (d, *J*=8.0 Hz, 2H), 2.77–2.69 (m, 1H), 2.69–2.61 (m, 1H), 2.46 (t, *J*=7.6 Hz, 2H), 2.35 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 139.2, 136.0, 129.7 (×2), 125.3 (×2), 92.5, 39.5, 31.7, 24.2, 21.1; HRMS (+EI) calcd for $C_{12}H_{15}O$ 175.1123 (M^+-NO_2), found 175.1123.

*4.3.4. 4-(2-Methoxyphenyl)-4-nitropentanal (**14d**).* Prepared according to the general procedure B in 83% yield as a colorless oil; R_f=0.30 (17% EtOAc in hexane); IR (film): 2945, 2841, 2727, 1715, 1544, 1494, 1462, 1250, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.35 (t, *J*=8.4 Hz, 1H), 7.25 (d, *J*=8.4 Hz, 1H), 6.99 (t, *J*=7.6 Hz, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 3.73 (s, 1H), 2.83–2.76 (m, 1H), 2.69–2.61 (m, 1H), 2.46–2.38 (m, 1H), 2.33–2.25 (m, 1H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 156.8, 130.6, 127.5, 126.9, 120.8, 112.0, 90.7, 55.5, 39.6, 29.7, 24.9; HRMS (+EI) calcd for $C_{12}H_{14}O_2$ 190.0994 (M^+-HNO_2), found 190.0996.

*4.3.5. 4-(4-Methoxyphenyl)-4-nitropentanal (**14e**).* Prepared according to the general procedure B (at room temperature for 2 days) in 93% yield as a colorless oil; R_f=0.34 (17% EtOAc in hexane); IR (film): 2976, 2935, 2839, 1730, 1515, 1253, 1182, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.31 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=8.8 Hz, 2H), 3.80 (s, 3H), 2.76–2.62 (m, 2H), 2.44 (dd, *J*=7.6, 6.8 Hz, 2H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 160.1, 130.71, 127.0 (×2), 114.3 (×2), 92.1, 55.5, 39.5, 31.6, 23.9; HRMS (+EI) calcd for $C_{12}H_{14}O_2$ 190.0994 (M^+-HNO_2), found 190.0998.

*4.3.6. 4-(4-Chlorophenyl)-4-nitropentanal (**14f**).* Prepared according to the general procedure B in 73% yield as a colorless oil; R_f=0.45 (25% EtOAc in hexane); IR (film): 2993, 2941, 2873, 2834, 2731, 1724, 1539, 1495, 1403, 1387, 1345, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.34 (d, *J*=7.2 Hz, 2H), 7.29 (d, *J*=7.2 Hz, 2H), 2.74–2.67 (m, 1H), 2.62–2.56 (m, 1H), 2.44 (t, *J*=6.4 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 137.4, 135.2, 129.2 (×2), 126.9 (×2), 92.0, 39.2, 31.5, 23.9; HRMS (+EI) calcd for $C_{11}H_{12}O^{35}Cl$ 195.0577 (M^+-NO_2), found 195.0578.

*4.3.7. Methyl 4-(2-nitro-5-oxopentan-2-yl)benzoate (**14g**).* Prepared according to the general procedure B in 88% yield as a colorless oil; R_f=0.38 (25% EtOAc in hexane); IR (film): 2999, 2954, 2840, 2732, 1727, 1542, 1436, 1410, 1345, 1284, 1195, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.05 (d, *J*=8.4 Hz, 2H), 7.41 (d, *J*=8.4 Hz, 2H), 3.92 (s, 3H), 2.80–2.72 (m, 1H), 2.67–2.59 (m, 1H), 2.48 (t, *J*=8.0 Hz, 2H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 166.3, 143.7, 131.0, 130.3 (×2), 125.5 (×2), 92.6, 52.5, 39.3, 31.6, 24.4; HRMS (+EI) calcd for $C_{13}H_{15}O_3$ 219.1021 (M^+-NO_2), found 219.1019.

*4.3.8. 4-[4-(1,3-Dioxolan-2-yl)phenyl]-4-nitrohexanal (**14h**).* Prepared according to the general procedure B in 71% yield as a colorless oil; R_f=0.38 (25% EtOAc in hexane); IR (film): 2978, 2887, 2733, 1723, 1538, 1391, 1350, 1086, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.49 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=8.5 Hz, 2H), 5.79 (s, 1H), 4.13–4.06 (m, 2H), 4.06–3.98 (m, 4H), 2.72–2.61 (m, 2H), 2.50–2.43 (m, 1H), 2.40–2.25 (m, 3H), 0.84 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 139.0, 138.9, 127.1 (×2), 125.9 (×2), 103.0, 96.5, 65.4 (×2), 38.9, 29.6, 27.5, 8.4; HRMS (+EI) calcd for $C_{15}H_{18}O_3$ 246.1256 (M^+-HNO_2), found 246.1258.

*4.3.9. 4-Nitro-4-(2-tolyl)hexanal (**14i**).* Prepared according to the general procedure B in 57% yield as a colorless oil; R_f=0.34 (17% EtOAc in hexane); IR (film): 2982, 2944, 2878, 2828, 2729, 1724, 1538, 1455, 1362 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.30–7.24 (m, 3H), 7.23–7.20 (m, 1H), 2.79–2.65 (m, 2H), 2.48–2.31 (m, 3H), 2.30–2.21 (m, 3H), 2.19 (s, 3H), 0.84 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 136.4, 136.0, 133.2, 128.8, 127.1, 126.1, 96.4, 39.3, 29.3, 26.9, 20.1, 8.7; HRMS (+EI) calcd for $C_{13}H_{16}O$ 188.1201 (M^+-HNO_2), found 188.1200.

*4.3.10. 4-Nitro-4-(3-tolyl)hexanal (**14j**).* Prepared according to the general procedure B (at room temperature for 2 days) in 94% yield as a colorless oil; R_f=0.41 (17% EtOAc in hexane); IR (film): 2978, 2947, 2923, 2881, 2724, 1725, 1538, 1455, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.28 (t, *J*=7.6 Hz, 1H), 7.18 (d, *J*=7.2 Hz, 1H), 7.09 (d, *J*=6.4 Hz, 1H), 7.06 (s, 1H), 2.75–2.63 (m, 2H), 2.54–2.43 (m, 1H), 2.41–2.27 (m, 3H), 2.36 (s, 3H), 0.87 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 138.8, 138.2, 129.8, 128.8, 126.3, 122.8, 96.7, 39.0, 29.5, 27.5, 21.7, 8.4; HRMS (+EI) calcd for $C_{13}H_{17}O$ 189.1279 (M^+-NO_2), found 189.1283.

*4.3.11. 4-Nitro-4-(4-tolyl)hexanal (**14k**).* Prepared according to the general procedure B in 70% yield as a colorless oil; R_f=0.35 (17% EtOAc in hexane); IR (film): 2979, 2944, 2923, 2884, 1714, 1538, 1455, 1412, 1348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.21–7.16 (m, 4H), 2.72–2.62 (m, 2H), 2.53–2.44 (m, 1H), 2.42–2.26 (m, 3H), 2.35 (s, 3H), 0.87 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 139.1, 135.3, 129.7 (×2), 125.7 (×2), 96.5, 39.1, 29.5, 27.5, 21.2, 8.5; HRMS (+EI) calcd for $C_{13}H_{17}O$ 189.1279 (M^+-NO_2), found 189.1275.

*4.3.12. 4-(2-Methoxyphenyl)-4-nitrohexanal (**14l**).* Prepared according to the general procedure B in 68% yield as a colorless oil; R_f=0.35 (17% EtOAc in hexane); IR (film): 2976, 2944, 2884, 2840, 2730, 1723, 1543, 1493, 1463, 1250, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.35 (t, *J*=7.6 Hz, 1H), 7.24 (d, *J*=7.6 Hz, 1H), 6.99 (t, *J*=7.6 Hz, 1H), 6.92 (d, *J*=8.0 Hz, 1H), 3.73 (s, 3H), 2.82–2.74 (m, 1H), 2.66–2.58 (m, 1H), 2.40–2.16 (m, 4H), 0.82 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 156.8, 130.4, 127.5, 126.8, 120.6, 112.1, 94.3, 55.5, 39.3, 28.3, 26.0, 8.5; HRMS (+EI) calcd for $C_{13}H_{17}O_2$ 205.1229 (M^+-NO_2), found 205.1229.

*4.3.13. 4-(4-Chlorophenyl)-4-nitrohexanal (**14m**).* Prepared according to the general procedure B in 67% yield as a colorless oil; R_f=0.51 (25% EtOAc in hexane); IR (film): 2979, 2941, 2884, 2834, 2727, 1724, 1539, 1496, 1352, 1097, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.37 (d, *J*=8.8 Hz, 2H), 7.23 (d, *J*=8.8 Hz, 2H), 2.67 (t,

J=7.6 Hz, 2H), 2.50–2.41 (m, 1H), 2.41–2.24 (m, 3H), 0.85 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 136.6, 135.2, 129.2 (×2), 127.4 (×2), 96.1, 38.8, 29.6, 27.3, 8.4; HRMS (+EI) calcd for $C_{12}H_{14}O^{35}Cl$ 209.0733 (M^+-NO_2), found 209.0731.

*4.3.14. Methyl 4-(3-nitro-6-oxohexan-3-yl)benzoate (**14n**).* Prepared according to the general procedure B in 87% yield as a colorless oil; R_f=0.43 (25% EtOAc in hexane); IR (film): 2980, 2953, 2881, 2843, 2730, 1727, 1542, 1436, 1284, 1194, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.04 (d, J=8.4 Hz, 2H), 7.34 (d, J=8.4 Hz, 2H), 3.90 (s, 3H), 2.68 (t, J=7.2 Hz, 2H), 2.51–2.26 (m, 4H), 0.85 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 166.2, 142.8, 130.8, 130.2 (×2), 126.0 (×2), 96.5, 52.4, 38.8, 29.8, 27.5, 8.3; HRMS (+EI) calcd for $C_{14}H_{17}O_3$ 233.1178 (M^+-NO_2), found 233.1176.

4.4. General procedure C for the synthesis of nitrones 15

To a solution of the nitro aldehydes **14** (1.0 mmol) and zinc powder (3.0 mmol) in EtOH (10 mL) cooled in an ice-water bath (0 °C) was added AcOH (6.0 mmol) slowly. The resultant mixture was stirred at 0 °C for 0.5 h followed by warming up to room temperature and stirring at the same temperature for 72 h. The reaction mixture was filtered off through a plug of Celite with washing by EtOAc. The combined filtrate was condensed under reduced pressure and the residue was purified by flash column chromatography over silica gel to give the nitrone **15**. The results are found in Table 3.

*4.4.1. 2-[2-(1,3-Dioxolan-2-yl)phenyl]-2-methyl-3,4-dihydro-2H-pyrrole 1-oxide (**15a**).* Prepared according to the general procedure C in 70% yield as a brown oil; R_f=0.24 (9% EtOH in EtOAc); IR (film): 2929, 2890, 1715, 1584, 1540, 1233, 1210, 1127, 1085, 1060 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, J=6.5, 2.5 Hz, 1H), 7.41 (dd, J=7.0, 2.0 Hz, 1H), 7.35–7.29 (m, 2H), 7.18 (s, 1H), 6.07 (s, 1H), 4.22–4.18 (m, 2H), 4.05–4.01 (m, 2H), 2.83–2.78 (m, 1H), 2.59–2.53 (m, 1H), 2.51–2.43 (m, 1H), 2.43–2.37 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 135.7, 134.4, 129.6, 128.5, 128.1, 126.1, 100.5, 80.6, 65.65, 65.60, 37.8, 27.4, 25.1; HRMS (+EI) calcd for $C_{14}H_{17}NO_3$ 247.1208 (M^+), found 247.1217.

*4.4.2. 2-Methyl-2-(3-tolyl)-3,4-dihydro-2H-pyrrole 1-oxide (**15b**).* Prepared according to the general procedure C in 83% yield as a brown oil; R_f=0.43 (9% EtOH in EtOAc); IR (film): 2982, 2932, 2857, 1682, 1580, 1489, 1454, 1240, 1210, 1191 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, J=7.6 Hz, 1H), 7.19–7.15 (m, 3H), 7.10 (d, J=7.6 Hz, 1H), 2.63–2.58 (m, 2H), 2.55–2.49 (m, 1H), 2.41–2.32 (m, 1H), 2.35 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 138.4, 134.9, 128.6, 128.5, 125.9, 122.4, 79.5, 37.2, 25.1, 25.0, 21.7; HRMS (+EI) calcd for $C_{12}H_{15}NO$ 189.1154 (M^+), found 189.1158.

*4.4.3. 2-Methyl-2-(4-tolyl)-3,4-dihydro-2H-pyrrole 1-oxide (**15c**).* Prepared according to the general procedure C in 63% yield as a brown oil; R_f=0.38 (9% EtOH in EtOAc); IR (film): 2978, 2936, 2859, 1707, 1574, 1515, 1454, 1274, 1239, 1195, 1081, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=7.6 Hz, 2H), 7.15 (d, J=8.0 Hz, 2H), 7.06 (s, 1H), 2.61–2.56 (m, 2H), 2.53–2.47 (m, 1H), 2.39–2.30 (m, 1H), 2.31 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 137.5, 134.2, 129.4 (×2), 125.3 (×2), 79.2, 37.1, 25.1, 25.0, 21.0; HRMS (+EI) calcd for $C_{12}H_{15}NO$ 189.1154 (M^+), found 189.1158.

*4.4.4. 2-(2-Methoxyphenyl)-2-methyl-3,4-dihydro-2H-pyrrole 1-oxide (**15d**).* Prepared according to the general procedure C in 80% yield as a brown oil; R_f=0.38 (9% EtOH in EtOAc); IR (film): 2977, 2938, 2838, 1698, 1593, 1582, 1493, 1463, 1436, 1244, 1193, 1070, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J=6.8 Hz, 1H), 7.23 (d, J=6.0 Hz, 1H), 7.10 (s, 1H), 6.92–6.85 (m, 2H), 3.81 (s, 3H), 2.74–2.67 (m, 1H), 2.60–2.44 (m, 2H), 2.23–2.15 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 135.8, 129.3, 128.8, 127.5, 120.8, 111.5, 79.1, 55.4, 34.6, 25.6, 24.5; HRMS (+EI) calcd for $C_{12}H_{15}NO_2$ 205.1103 (M^+), found 205.1111.

*4.4.5. 2-(4-Methoxyphenyl)-2-methyl-3,4-dihydro-2H-pyrrole 1-oxide (**15e**).* Prepared according to the general procedure C in 77% yield as a brown oil; R_f=0.35 (9% EtOH in EtOAc); IR (film): 2974, 2937, 2837, 1611, 1574, 1514, 1455, 1297, 1251, 1186, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J=8.8 Hz, 2H), 7.04 (s, 1H), 6.88 (d, J=8.8 Hz, 2H), 3.79 (s, 3H), 2.63–2.57 (m, 2H), 2.55–2.48 (m, 1H), 2.39–2.31 (m, 1H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 133.8, 133.6, 126.7 (×2), 114.1 (×2), 79.0, 55.4, 37.0, 25.2, 25.0; HRMS (+EI) calcd for $C_{12}H_{15}NO_2$ 205.1103 (M^+), found 205.1107.

*4.4.6. 2-(4-Chlorophenyl)-2-methyl-3,4-dihydro-2H-pyrrole 1-oxide (**15f**).* Prepared according to the general procedure C in 73% yield as a brown oil; R_f=0.37 (9% EtOH in EtOAc); IR (film): 2980, 2935, 1713, 1581, 1494, 1455, 1401, 1269, 1238, 1199, 1096, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H), 7.09 (s, 1H), 2.64–2.52 (m, 1H), 2.50–2.44 (m, 1H), 2.40–2.32 (m, 1H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 134.9, 133.9, 129.0 (×2), 127.1 (×2), 79.2, 37.0, 25.2, 25.1; HRMS (+EI) calcd for $C_{11}H_{12}ClNO$ 209.0607 (M^+), found 209.0609.

*4.4.7. 2-[4-(Methoxycarbonyl)phenyl]-2-methyl-3,4-dihydro-2H-pyrrole 1-oxide (**15g**).* Prepared according to the general procedure C in 79% yield as a brown oil; R_f=0.31 (9% EtOH in EtOAc); IR (film): 2983, 2952, 2850, 1722, 1580, 1436, 1283, 1240, 1194, 1113, 1019 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J=8.4 Hz, 2H), 7.43 (d, J=8.0 Hz, 2H), 7.09 (s, 1H), 3.88 (s, 3H), 2.66–2.54 (m, 2H), 2.53–2.45 (m, 1H), 2.44–2.34 (m, 1H), 1.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 146.6, 134.5, 130.0 (×2), 129.6, 125.5 (×2), 79.5, 52.2, 37.0, 25.1, 24.9; HRMS (+EI) calcd for $C_{13}H_{15}NO_3$ 233.1052 (M^+), found 233.1055.

*4.4.8. 2-[4-(1,3-Dioxolan-2-yl)phenyl]-2-ethyl-3,4-dihydro-2H-pyrrole 1-oxide (**15h**).* Prepared according to the general procedure C in 78% yield as a brown oil; R_f=0.29 (9% EtOH in EtOAc); IR (film): 2979, 2888, 1582, 1423, 1392, 1311, 1225, 1085, 1020 cm^{-1}; ^{1}H NMR 400 MHz, $CDCl_3$) δ 7.42 (s, 4H), 7.12 (s, 1H), 5.76 (s, 1H), 4.06–4.02 (m, 2H), 4.02–3.97 (m, 2H), 2.58–2.32 (m, 4H), 2.27–2.20 (m, 1H), 2.13–2.07 (m, 1H), 0.95 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 137.4, 136.1, 126.7 (×2), 125.6 (×2), 103.2, 82.4, 65.3, 31.9, 30.0, 25.2, 8.2; MS (+EI) m/z 205 (M^+, 14), 190 (M^+-Me, 100); HRMS (+EI) calcd for $C_{15}H_{19}NO_3$ 261.1365 (M^+), found 261.1362.

*4.4.9. 2-Ethyl-2-(2-tolyl)-3,4-dihydro-2H-pyrrole 1-oxide (**15i**).* Prepared according to the general procedure C in 71% yield as a brown oil; R_f=0.41 (9% EtOH in EtOAc); IR (film): 2966, 2935, 2879, 1583, 1489, 1463, 1225, 1194 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.44 (m, 1H), 7.27 (s, 1H), 7.18–7.12 (m, 3H), 2.66–2.54 (m, 2H), 2.52–2.41 (m, 3H), 2.40 (s, 3H), 2.22–2.13 (m, 1H), 1.02 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 137.3, 134.7, 132.7, 127.7, 126.6, 126.2, 84.0, 31.2, 29.3, 25.9, 21.4, 8.5; HRMS (+EI) calcd for $C_{13}H_{17}NO$ 203.1310 (M^+), found 203.1309.

*4.4.10. 2-Ethyl-2-(3-tolyl)-3,4-dihydro-2H-pyrrole 1-oxide (**15j**).* Prepared according to the general procedure C in 86% yield as a brown oil; R_f=0.46 (9% EtOH in EtOAc); IR (film): 2970, 2932, 2880, 1698, 1607, 1574, 1488, 1463, 1269, 1238, 1205, 1183 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.20 (m, 3H), 7.09 (d, J=6.8 Hz, 1H), 7.06 (t, J=2.8 Hz, 1H), 2.62–2.56 (m, 2H), 2.45 (dd, J=7.6, 6.4 Hz, 2H), 2.35 (s, 3H), 2.34–2.26 (m, 1H), 2.19–2.09 (m, 1H), 1.01 (t, J=7.2 Hz,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 138.2, 135.5, 128.5, 128.4, 126.1, 122.6, 82.5, 32.1, 29.9, 25.3, 21.7, 8.2; HRMS (+EI) calcd for $C_{13}H_{17}NO$ 203.1310 (M^+), found 203.1316.

*4.4.11. 2-Ethyl-2-(4-tolyl)-3,4-dihydro-2H-pyrrole 1-oxide (**15k**).* Prepared according to the general procedure C in 73% yield as a brown oil; R_f=0.43 (9% EtOH in EtOAc); IR (film): 2970, 2925, 2879, 2850, 1682, 1656, 1580, 1515, 1463, 1227, 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J=8.4 Hz, 2H), 7.16 (d, J=8.4 Hz, 2H), 7.10 (s, 1H), 2.61–2.54 (m, 2H), 2.47–2.41 (m, 2H), 2.36–2.23 (m, 1H), 2.32 (s, 3H), 2.20–2.10 (m, 1H), 0.99 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 137.6, 135.1, 129.4 (×2), 125.7 (×2), 82.4, 32.1, 30.2, 25.4, 21.1, 8.4; HRMS (+EI) calcd for $C_{13}H_{17}NO$ 203.1310 (M^+), found 203.1308.

*4.4.12. 2-Ethyl-2-(2-methoxyphenyl)-3,4-dihydro-2H-pyrrole 1-oxide (**15l**).* Prepared according to the general procedure C (at room temperature for 24 h) in 83% yield as a brown oil; R_f=0.41 (9% EtOH in EtOAc); IR (film): 2964, 2935, 2875, 2838, 1698, 1581, 1492, 1463, 1436, 1243, 1190, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J=7.6, 1.2 Hz, 1H), 7.27–7.22 (m, 1H), 7.17 (s, 1H), 6.93–6.87 (m, 2H), 3.81 (s, 3H), 2.56–2.49 (m, 3H), 2.41–2.29 (m, 2H), 2.26–2.17 (m, 1H), 0.97 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 137.0, 129.8, 129.0, 127.4, 120.7, 111.5, 82.2, 55.4, 30.4, 27.9, 26.0, 8.1; HRMS (+EI) calcd for $C_{13}H_{17}NO_2$ 219.1259 (M^+), found 219.1264.

*4.4.13. 2-(4-Chlorophenyl)-2-ethyl-3,4-dihydro-2H-pyrrole 1-oxide (**15m**).* Prepared according to the general procedure C in 77% yield as a brown oil; R_f=0.43 (9% EtOH in EtOAc); IR (film): 2972, 2937, 2880, 1688, 1581, 1494, 1464, 1401, 1223, 1095, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.4 Hz, 2H), 7.06 (s, 1H), 2.61–2.57 (m, 2H), 2.51–2.40 (m, 2H), 2.32–2.22 (m, 1H), 2.17–2.07 (m, 1H), 0.99 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 135.6, 133.8, 128.8 (×2), 127.3 (×2), 82.2, 31.9, 30.2, 25.3, 8.3; HRMS (+EI) calcd for $C_{12}H_{14}ClNO$ 223.0764 (M^+), found 223.0765.

*4.4.14. 2-Ethyl-2-[4-(methoxycarbonyl)phenyl]-3,4-dihydro-2H-pyrrole 1-oxide (**15n**).* Prepared according to the general procedure C in 74% yield as a brown oil; R_f=0.33 (9% EtOH in EtOAc); IR (film): 2971, 2953, 2881, 2850, 1722, 1611, 1580, 1435, 1281, 1230, 1193, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J=8.8 Hz, 2H), 7.50 (d, J=9.2 Hz, 2H), 7.07 (t, J=2.4 Hz, 1H), 3.88 (s, 3H), 2.60–2.54 (m, 2H), 2.52–2.38 (m, 2H), 2.34–2.24 (m, 1H), 2.17–2.08 (m, 1H), 0.99 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 146.8, 135.0, 130.0 (×2), 129.6, 125.8 (×2), 82.6, 52.2, 32.0, 30.1, 25.2, 8.2; HRMS (+EI) calcd for $C_{14}H_{17}NO_3$ 247.1208 (M^+), found 247.1210.

4.5. General procedure D for 1,3-dipolar cycloaddition of cyclic nitrones 15 with methyl methacrylate

A solution of the nitrone **15** (1.0 mmol) and methyl methacrylate (2.0 mmol) in MeCN (10 mL) was stirred at 40 °C for 24 h. The solution was evaporated under reduced pressure and the residue was purified by flash chromatography over silica gel to afford the adducts **18** and *epi*-**18**. The results are found in Table 4.

4.5.1. (2R,3aR*,6R*)-Methyl 2,6-dimethyl-6-(3-tolyl)hexahydropyrrolo[1,2-b]isoxazole-2-carboxylate (**18a**).* Prepared from **15b** according to the general procedure D in 80% combined yield as a 95:5 inseparable mixture of **18a** and *epi*-**18a**. A colorless oil; R_f=0.35 (9% EtOAc in PE); IR (film): 2985, 2952, 2873, 1755, 1732, 1605, 1486, 1455, 1369, 1301, 1212, 1163, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.30 (d, J=8.0 Hz, 1H), 7.18 (t, J=8.0 Hz, 1H), 7.02 (d, J=7.6 Hz, 1H), 3.78 (s, 3H), 3.67–3.61 (m, 1H), 2.62 (dd, J=12.8, 2.0 Hz, 1H), 2.48 (dd, J=12.8, 7.6 Hz, 1H), 2.34 (s, 3H), 2.31–2.27 (m, 1H), 2.19 (dt, J=12.8, 10.0 Hz, 1H), 1.83–1.73 (m, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.56–1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 145.8, 137.5, 127.9, 127.2, 126.4, 122.6, 82.2, 74.5, 63.9, 52.2, 47.0, 34.5, 31.0, 26.9, 25.3, 21.5; HRMS (+EI) calcd for $C_{17}H_{23}NO_3$ 289.1678 (M^+), found 289.1668.

4.5.2. (2R,3aR*,6R*)-Methyl 2,6-dimethyl-6-(4-tolyl)hexahydropyrrolo[1,2-b]isoxazole-2-carboxylate (**18b**).* Prepared from **15c** according to the general procedure D in 78% combined yield as a 95:5 inseparable mixture of **18b** and *epi*-**18b**. A colorless oil; R_f=0.35 (9% EtOAc in PE); IR (film): 2985, 2952, 2872, 1755, 1738, 1511, 1455, 1369, 1302, 1212, 1164, 1123 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J=8.4 Hz, 2H), 7.11 (d, J=8.0 Hz, 2H), 3.78 (s, 3H), 3.65–3.56 (m, 1H), 2.61 (dd, J=12.4, 2.4 Hz, 1H), 2.47 (dd, J=12.8, 8.0 Hz, 1H), 2.32 (s, 3H), 2.32–2.27 (m, 1H), 2.19 (dt, J=12.8, 10.0 Hz, 1H), 1.84–1.73 (m, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.57–1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 142.7, 136.2, 128.8 (×2), 125.7 (×2), 82.3, 74.6, 64.0, 52.3, 47.0, 34.4, 31.1, 27.0, 25.4, 20.9; HRMS (+EI) calcd for $C_{17}H_{23}NO_3$ 289.1678 (M^+), found 289.1677.

4.5.3. (2R,3aR*,6R*)-Methyl 6-(2-methoxyphenyl)-2,6-dimethylhexahydropyrrolo[1,2-b]isoxazole-2-carboxylate (**18c**).* Prepared from **15d** according to the general procedure D in 82% combined yield as a 94:6 inseparable mixture of **18c** and *epi*-**18c**. A colorless oil; R_f=0.24 (9% EtOAc in PE); IR (film): 2985, 2951, 2875, 1738, 1597, 1580, 1487, 1455, 1435, 1367, 1300, 1281, 1236, 1180, 1161, 1124, 1088, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J=8.0 Hz, 1H), 7.18 (t, J=8.0 Hz, 1H), 6.90 (t, J=7.6 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H), 3.96–3.90 (m, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 2.58–2.47 (m, 3H), 2.22 (dt, J=12.8, 8.8 Hz, 1H), 1.78–1.68 (m, 1H), 1.63 (s, 3H), 1.62 (s, 3H), 1.60–1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 156.4, 134.2, 127.6, 127.5, 120.4, 111.2, 83.0, 72.9, 63.4, 55.0, 52.3, 46.9, 35.4, 30.5, 25.1, 22.4; HRMS (+EI) calcd for $C_{17}H_{23}NO_4$ 305.1627 (M^+), found 305.1627.

4.5.4. (2R,3aR*,6R*)-Methyl 6-(4-methoxyphenyl)-2,6-dimethylhexahydropyrrolo[1,2-b]isoxazole-2-carboxylate (**18d**).* Prepared from **15e** according to the general procedure D in 80% combined yield as a 94:6 inseparable mixture of **18d** and *epi*-**18d**. A colorless oil; R_f=0.19 (9% EtOAc in PE); IR (film): 2985, 2952, 2836, 1747, 1731, 1608, 1581, 1505, 1455, 1369, 1297, 1247, 1212, 1124, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J=8.8 Hz, 2H), 6.83 (d, J=8.4 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.63–3.57 (m, 1H), 2.61 (dd, J=12.4, 2.0 Hz, 1H), 2.46 (dd, J=12.8, 7.6 Hz, 1H), 2.34–2.25 (m, 1H), 2.18 (dt, J=12.4, 10.0 Hz, 1H), 1.84–1.74 (m, 1H), 1.60 (s, 3H), 1.56 (s, 3H), 1.56–1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 158.2, 137.7, 126.9 (×2), 113.4 (×2), 82.3, 74.3, 64.0, 55.1, 52.3, 46.9, 34.4, 31.1, 27.0, 25.4; HRMS (+EI) calcd for $C_{17}H_{23}NO_4$ 305.1627 (M^+), found 305.1623.

4.5.5. (2R,3aR*,6R*)-Methyl 6-ethyl-2-methyl-6-(3-tolyl)hexahydropyrrolo[1,2-b]isoxazole-2-carboxylate (**18e**).* Prepared from **15j** according to the general procedure D in 87% combined yield as a 95:5 inseparable mixture of **18e** and *epi*-**18e**. A colorless oil; R_f=0.38 (9% EtOAc in PE); IR (film): 2973, 2876, 1751, 1738, 1605, 1487, 1455, 1367, 1300, 1211, 1160, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.26 (d, J=7.2 Hz, 1H), 7.17 (t, J=8.0 Hz, 1H), 7.02 (d, J=7.2 Hz, 1H), 3.78 (s, 3H), 3.60–3.54 (m, 1H), 2.61 (d, J=12.8 Hz, 1H), 2.47 (dd, J=12.8, 8.0 Hz, 1H), 2.34 (s, 3H), 2.32–2.28 (m, 1H), 2.16–2.06 (m, 2H), 1.97–1.88 (m, 1H), 1.79–1.69 (m, 1H), 1.61 (s, 3H), 1.44–1.52 (m, 1H), 0.68 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 143.2, 137.2, 127.6, 127.3, 127.2, 123.7, 81.6, 78.8, 63.6, 52.2, 46.9, 33.3, 32.3, 30.9, 25.3, 21.6,

9.3; HRMS (+EI) calcd for $C_{18}H_{25}NO_3$ 303.1834 (M^+), found 303.1831.

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Supplementary data

^1H and ^{13}C NMR spectra for compounds **13**–**15** and **18** are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.07.046.

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