2-Azaadamantane N-oxyls (AZADOs): The highly efficient organocatalyst for oxidation of alcohols

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Supporting Information

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**General experimental procedures:**

All reactions were carried out under an atmosphere of argon unless otherwise specified. Anhydrous solvents were transferred via syringe to flame-dried glassware, which had been cooled under a stream of dry nitrogen. Ethereal solvents and dichloromethane (anhydrous; Kanto Chemical Co., Inc) were used as received. All other solvents were dried and distilled by standard procedures. Yields refer to chromatographically and spectroscopically (\(^1\)H NMR) homogeneous materials unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification unless otherwise stated.

Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as visualizing agent and p-anisaldehyde in ethanol/aqueous H\(_2\)SO\(_4\)/CH\(_3\)CO\(_2\)H for staining. Column chromatography was performed using silica gel 60 particle size 0.063-0.210 mm. The eluents employed are reported as volume : volume percentages.

Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded using a JEOL JMN-AL400 (400 MHz), and a JEOL 500 (500 MHz) spectrometers. Chemical shift (\(\delta\)) is reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS). Coupling constants (\(J\)) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, Apparent. Carbon-13 nuclear magnetic resonance (\(^{13}\)C NMR) spectra were recorded using a JEOL JMN-AL400 spectrometer at 100 MHz. Chemical shift is reported in ppm relative to the center line of the triplet of CDCl\(_3\) (77.10 ppm).

Melting points were determined using Yazawa BY-2 melting point apparatus and are reported uncorrected. Infrared spectra were obtained on a JASCO FT-IR-410 at 4.0 cm\(^{-1}\) resolution and are reported in wavenumbers. High resolution mass spectra (HRMS) were recorded on a JMS-AX500 or JMS-700 using electron impact (EI). Low resolution mass spectra (MS) were recorded on JEOL JMS-DX303. Elemental analyses were performed using Yanaco CHN CORDER MT-6.
An improved synthesis of AZADO

Scheme S1. An improved synthetic route to AZADO starting from 1,3-adamantanediol

Reagents and conditions: (a) p-TsCl, pyridine/PhH, 75 °C, 81%; (b) OsO₄, NaIO₄, THF/H₂O, 54%; (c) HO(CH₂)₂OH, p-TsOH, PhMe, reflux, 94%; (d) HCl·NH₂OH, pyridine, quant; (e) NaBH₄, MoO₃, MeOH, 0 °C, then Et₃N, CbzCl, 75%; (f) 5% aq. HCl MeOH, quant; (g) H₂, Pd-C, MeOH; (h) SOCl₂, reflux; (i) LAH, DME, reflux; (j) UHP, Na₂WO₄·2H₂O, MeOH, 60% over four steps.

7-Methylene-bicyclo[3.3.1]nonan-3-one (6)

A mixture of 1,3-adamantanediol (5) (1 g, 5.95 mmol), p-TsCl (2.84 g, 14.9 mmol) in benzene-pyridine (40 ml, 1:1 v/v) was stirred at 75 °C for 12 h. After cooling to 0 °C, the reaction mixture was poured into H₂O and extracted with cold Et₂O. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO₂, 1:8 AcOEt: hexane) to give 6 (720 mg, 4.8 mmol, 81 %) as a white solid. a)
mp 158-159 °C (recrystallized from pet. ether), $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 4.78 (br s, 2H), 2.45-2.35 (m, 8H), 2.28 (d, $J = 13.7$ Hz, 2H), 1.97-1.88 (m, 1H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 211.1, 141.8, 114.6, 47.2, 41.3, 31.9, 30.7. IR (CHCl$_3$, cm$^{-1}$): 1716. MS m/z: 150 (M$^+$), 93 (100%). HRMS (EI): Calcd. for C$_{10}$H$_{15}$NO 150.1045 (M$^+$), found: 150.1061.

Bicyclo[3.3.1]nonane-3,7-dione (7)

To a solution of ketone 6 (1 g, 6.7 mmol) in THF- H$_2$O (34 ml, 5 : 1 v/v) at 0 °C was added NaIO$_4$ (3.6 g, 16.8 mmol), OsO$_4$ in THF (0.1967 M, 1.7 ml, 0.335 mmol). The mixture was allowed to stir at room temperature for 5 h and then quenched with a saturated aqueous solution of NaHCO$_3$ and a saturated aqueous solution of Na$_2$S$_2$O$_3$. The mixture was extracted ten times with AcOEt. The organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO$_2$, 4:1 AcOEt: hexane) to give 7 (550 mg, 3.6 mmol, 54 %) as a white solid.

mp 253-256 °C (recrystallized from pet. ether), $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 2.86 (br s, 2H), 2.60 (dd, $J = 15.4, 5.6$ Hz, 4H), 2.42 (br d, $J = 15.4$ Hz, 4H), 2.20 (br s, 2H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 208.3, 47.7, 32.6, 31.4. IR (neat, cm$^{-1}$): 1696.0. MS m/z: 152 (M$^+$), 152 (100%). HRMS (EI): Calcd. for C$_9$H$_{12}$O$_2$ 152.0837. (M$^+$), found: 152.0846.

7,7-Ethlenedioxybicyclo[3.3.1]nonan-3-one (8)

mp 158-159 °C (recrystallized from pet. ether), $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 4.78 (br s, 2H), 2.45-2.35 (m, 8H), 2.28 (d, $J = 13.7$ Hz, 2H), 1.97-1.88 (m, 1H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 211.1, 141.8, 114.6, 47.2, 41.3, 31.9, 30.7. IR (CHCl$_3$, cm$^{-1}$): 1716. MS m/z: 150 (M$^+$), 93 (100%). HRMS (EI): Calcd. for C$_{10}$H$_{15}$NO 150.1045 (M$^+$), found: 150.1061.
A solution of diketone 7 (300 mg, 1.97 mmol), HO(CH₂)₂OH (0.44 ml, 7.89 mmol) and p-TsOH·H₂O (37 mg, 0.197 mmol) in toluene (6.7 ml) was heated at reflux during 2 h under continuous removal of water by means of a Dean-Stark trap. After cooling to room temperature, the reaction was quenched with a saturated aqueous solution of NaHCO₃. The mixture was extracted with AcOEt. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 2:1 AcOEt: hexane) to give 8 (363 mg, 1.85 mmol, 94 %) as a white solid.

mp 79-80 °C (recrystallized from pet. ether), ¹H-NMR (400 MHz, CDCl₃): δ 3.93-3.91 (ddd, J = 7.2, 6.3, 1.5 Hz, 2H), 3.85-3.83 (ddd, J = 7.2, 6.3, 1.5 Hz, 2H), 2.52-2.46 (m, 4H), 2.37 (br d, J = 6.8 Hz, 1H), 2.33 (br d, J = 6.5 Hz, 1H), 1.87-1.75 (m, 6H). ¹³C-NMR (100 MHz, CDCl₃): δ 208.8, 107.3, 64.3, 63.3, 45.8, 40.0, 31.5, 29.1.  IR (neat, cm⁻¹): 1700.9.  MS m/z: 196 (M⁺), 139 (100%).  HRMS (EI): Calcd. for C₁₁H₁₆O₃ 196.1099 (M⁺), found: 196.1086. Anal: Calcd. for C₁₁H₁₆O₃ : C, 67.32; H, 8.22, found: C, 67.22; H, 8.10.

7, 7-Ethylendioxybicyclo[3.3.1]nonan-3-one oxime (9)

To a solution of ketone 8 (325 mg, 1.66 mmol) in pyridine (17 ml) was added HCl·NH₂OH (344 mg, 5 mmol) at room temperature. After stirring at 40 ºC for 4 h, pyridine was removed in vacuo. The residue was poured into H₂O and extracted with AcOEt. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 5:2 AcOEt: hexane) to give 9 (350 mg, 1.66 mmol, 100 %) as a white solid.

mp 135-138 °C (recrystallized from Et₂O-hexane), ¹H-NMR (400 MHz, CDCl₃): δ 3.96 (t, J = 6.4 Hz, 2H), 3.82 (t, J = 6.4 Hz, 2H), 3.09 (d, J = 17.9 Hz, 1H), 2.48 (br s, 1H), 2.44 (br dd, J = 17.9, 5.8 Hz, 1H), 2.34 (br s, 2H), 2.2 (br dd, J = 17.6, 5.8 Hz, 1H), 1.84 (d, J = 3.6, 2H), 1.78 (d, J = 3.6, 2H), 1.69 (s, 2H). ¹³C-NMR (100 MHz, CDCl₃): δ 157.1, 107.1, 64.2,
To a solution of oxime \(9\) (348 mg, 1.65 mmol), MoO\(_3\) \(^b\) (403 mg, 2.8 mmol) in MeOH (16 ml) at 0 ºC was added NaBH\(_4\) (187 mg, 4.95 mmol) portionwise. The mixture was then allowed to stir until the oxime was no longer detectable (TLC), and then it was added Et\(_3\)N (0.35 ml, 2.48 mmol), CbzCl (0.35 ml, 0.28 mmol) at 0 ºC. The mixture was stirred for an additional 1 h, and then filtered through Celite\(^\circledR\). The filtrate was concentrated under reduced pressure. The residue was poured into H\(_2\)O and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO\(_4\) and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO\(_2\), 1:3 AcOEt: hexane) to give \(10\) (410 mg, 1.24 mmol, 75 %) as a colorless oil.

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.36-7.29 (m, 5H), 5.07 (s, 2H), 4.64 (br d, \(J = 8.5\) Hz, 1H), 3.97 (t, \(J = 6.3\) Hz, 2H), 3.81 (t, \(J = 6.3\) Hz, 2H), 2.28 (br s, 2H), 2.16-2.07 (m, 2H), 1.84 (br d, \(J = 13.0\) Hz, 1H), 1.76 (br d, \(J = 13.0\) Hz, 2H), 1.73 (br d, \(J = 13.0\) Hz, 1H), 1.66-1.57 (m, 4H), 1.13 (d, \(J = 13.0\) Hz, 1H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 136.8, 128.5, 128.1, 128.0, 108.9, 66.4, 64.3, 62.6, 43.8, 41.8, 31.8, 27.6, 26.1. IR (neat, cm\(^{-1}\))): 3329.5, 1715.4, 1527.4. MS \(m/z\): 331 (M\(^+\)), 91 (100%). HRMS (EI): Calcd. for C\(_{19}\)H\(_{25}\)NO\(_4\) 331.1784 (M\(^+\)), found: 331.1784. Anal: Calcd. for C\(_{19}\)H\(_{25}\)NO\(_4\): C, 68.86; H, 7.60; N, 4.23, found: C, 68.71; H, 7.69; N, 4.16.
**N-Benzylxycarbonyl-2-azaadamantane-1-ol (11)**

To a solution of carbamate 10 (300 mg, 0.91 mmol) in MeOH (2.3 ml) at room temperature was added 5% aq. HCl (2.3 ml). The mixture was allowed to stir at room temperature for 2 h, and then quenched with a saturated aqueous solution of NaHCO₃. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:3 AcOEt: hexane) to give 11 (261 mg, 0.91 mmol, 100%) as a colorless oil.

**1H-NMR** (400 MHz, CDCl₃): δ 7.36-7.32 (m, 5H), 5.13 (s, 2H), 4.50 (br s, 1H), 2.24 (br s, 2H), 2.02 (br d, J = 12.7 Hz, 2H), 1.81 (br d, J = 15.4 Hz, 2H), 1.74 (br s, 2H), 1.72 (br d, J = 13.0 Hz, 1H), 1.62 (br d, J = 12.7 Hz, 1H), 1.55 (br d, J = 13.0, 1H).

**13C-NMR** (100 MHz, CDCl₃): δ 157.7, 136.2, 128.5, 128.1, 127.9, 83.9, 66.9, 51.0, 43.2, 35.0, 34.4, 29.0.

**IR** (neat, cm⁻¹): 3341.1, 1663.3, 1447.3. **MS m/z**: 287 (M⁺), 91 (100%). **HRMS (EI)**: Calcd. for C₁₇H₂₁NO₃ 287.1521 (M⁺), found: 287.1514.

1. H₂, Pd-C, MeOH
2. SOCl₂, reflux
3. LiAlH₄, DME, reflux
4. UHP, Na₂WO₄, MeOH

**2-Azaadamantane-N-oxyl (2)**

To a solution of carbamate 11 (130 mg, 0.457 mmol) in MeOH (4.6 ml) was added 10% Pd-C (12 mg) under Ar atmosphere. The reaction flask was evacuated and purged with H₂ three times and then the reaction was stirred at room temperature under H₂ atmosphere for 2h. The catalyst was removed by filtration through Celite®. The filtrate was concentrated under reduced pressure to give 12 as a white solid. Aminoalcohol 12 was used directory for further reaction. To a 10 ml flask charged with crude aminoalcohol 12 at 0 ºC was added dropwise SOCl₂ (0.4 ml, 5.7 mmol) over 10 min. The solution was heated to reflux for 1 h, and then the excess SOCl₂ was removed by distillation. The resulting solid was cooled, after which CH₂Cl₂ (3.8 ml) was added, followed by H₂O (7.6 ml). The two-phase mixture was rapidly stirred at 0 ºC for 30 min. A 10% aqueous
solution of NaOH was added dropwise until the aqueous phase became strongly basic. The layers were separated, and the aqueous phase was extracted with CHCl₃. The combined organic layers were dried over K₂CO₃ and concentrated under reduced pressure to give 13 as a white solid. Chloroamine 13 was used directly for further reaction. A solution of crude chloroamine 13 in dry dimethoxyethane (2.3 ml) at 0 ºC was added LiAlH₄ (28 mg, 0.74 mmol) portionwise. The mixture was allowed to heat at reflux for 1 h, then cooled to 0 ºC. To the mixture was diluted with Et₂O and added dropwise aq. NH₃. After stirring at room temperature for an additional 1h, the mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was poured into a saturated aqueous solution of Na₂CO₃ and extracted with CHCl₃. The organic layer was dried over K₂CO₃ and concentrated under reduced pressure to give 14 as a pale yellow oil. The crude product was not further purified. A mixture of crude amine 14 and Na₂WO₄·2H₂O (75 mg, 0.23 mmol) in MeOH (0.9 ml) was stirred at room temperature for 30 min. To the reaction mixture was added urea hydrogen peroxide 1) (172 mg, 1.83 mmol) at room temperature. After stirring for 3.5 h, the reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The mixture was extracted with CHCl₃, and the organic layer was dried over K₂CO₃ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:3 AcOEt: hexane) to give 2 (42 mg, 0.27 mmol, 60 %) as a red solid.

IR (neat, cm⁻¹): 1446.4, 1280.5. MS m/z: 152 (M⁺), 152 (100%). HRMS (EI): Calcd. for C₉H₁₄NO 152.1075 (M⁺), found: 152.1073. Anal: Calcd. for C₉H₁₄NO: C, 71.02; H, 9.27; N, 9.20; found: C, 70.68; H, 9.22; N, 8.88.
Synthesis of 1-Me-AZADO

Scheme S2.

Reagents and Conditions: (a) HCl·NH₂OH, pyridine, quant; (b) NaBH₄, MoO₃, MeOH, 0 °C; (c) I₂, MeCN, 48% over two steps; (d) LAH, THF, reflux; (e) 30% H₂O₂, Na₂WO₄·2H₂O, MeOH/H₂O, 39% over two steps; (f) H₂, Pd-C, MeOH, 34%; (g) O₂, Et₂O, 54%.

7-Methylene-bicyclo[3.3.1]nonan-3-one oxime (15)

To a solution of ketone 6 (3 g, 20 mmol) in pyridine (30 ml) was added HONH₂·HCl (2.8 g, 40 mmol). After stirring at room temperature for 4h, the solvent was removed in vacuo. The residue was diluted with AcOEt and then H₂O was added. The layers were separated and the aqueous layer was extracted with AcOEt. The organic layers were combined and washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO₂, 1:6 AcOEt: hexane) to give 15 (3.3 g, 20 mmol, 100 %) as a colorless solid.

mp 123-124 °C (recrystallized from pet. ether), ¹H-NMR (400 MHz, CDCl₃): δ 4.73 (s, 1H), 3.17 (d, J = 15.8 Hz, 1H), 2.43-2.23 (m, 8H), 1.96 (dd, J = 16.1, 5.4 Hz, 1H), 1.76 (s, 2H).
$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 158.4, 143.0, 111.6, 41.6, 40.6, 37.4, 33.2, 30.3, 29.7, 28.6.

IR (CHCl$_3$, cm$^{-1}$): 3590. MS $m/z$: 165 (M$^+$), 93 (100%). HRMS Calcd. for C$_{10}$H$_{15}$NO: 165.1154 (M$^+$), found: 165.1149. Anal: Calcd. for C$_{10}$H$_{15}$NO: C, 72.69; H, 9.15; N, 8.48, found: C, 72.61; H, 9.11; N, 8.48.

1-Iodomethyl-2-azaadamantane (18)

A mixture of oxime 15 (200 mg, 1.2 mmol), MoO$_3$ (240 mg, 1.7 mmol) in MeOH (12 ml) at 0 °C was added NaBH$_4$ (450 mg, 1.2 mmol) portionwise. After stirring at 0 °C for 2 h, the reaction was quenched with acetone and then filtered through Celite$^\circledR$. The filtrate was concentrated under reduced pressure. The resulting residue was poured into H$_2$O and extracted with AcOEt. The organic layer was dried over MgSO$_4$ and concentrated under reduced pressure to give 16 as a pale yellow oil. The crude product was not further purified. To a solution of crude amine 16 in CH$_3$CN (6 ml) at 0 °C was added I$_2$ (304 mg, 1.2 mmol). The mixture was allowed to stir at room temperature for 3 h and then quenched with a saturated aqueous solution of NaHCO$_3$ and a saturated aqueous solution of Na$_2$S$_2$O$_3$. The resulting mixture was extracted with CHCl$_3$, dried over K$_2$CO$_3$ and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO$_2$, 1:4 CHCl$_3$: MeOH) to give 17 (159 mg, 0.58 mmol, 48 %) as a yellow solid.

mp 48 °C (recrystallized from Et$_2$O-hexane), $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 3.25 (br, 1H), 3.15 (s, 2H), 2.10 (br s, 2H) 1.91 (br, 1H), 1.79-1.72 (m, 8H), 1.66 (br d, $J = 13.7$ Hz, 2H), 1.59 (br d, $J = 11.7$ Hz, 2H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 48.9, 48.0, 41.1, 36.2, 36.0, 27.9, 25.1. IR (CHCl$_3$, cm$^{-1}$): 3300. MS $m/z$: 277 (M$^+$), 93 (100%). HRMS (EI): Calcd. for C$_{10}$H$_{16}$I 277.0327 (M$^+$), found: 277.0323.
1-Methyl-2-azaadamantane-N-oxyl (3)

To a solution of amine 17 (3.35 g, 12 mmol) in THF (60 ml) at 0 °C was added LiAlH₄ (550 mg, 14.4 mmol) portionwise. After stirring at 70 °C for 30 min, the reaction was cooled to 0 °C and diluted with Et₂O and quenched with 30% aq. NH₃. The resulting mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was diluted with CHCl₃ and a saturated aqueous solution of Na₂CO₃ was added and extracted with CHCl₃. The organic layer was dried over K₂CO₃ and concentrated under reduced pressure to give 18 as a pale yellow oil. The crude product was not further purified. A mixture of crude amine 18 and Na₂WO₄·2H₂O (404 mg, 1.23 mmol) in H₂O-MeOH (20 ml, 1:4 v/v) was stirred at room temperature for 30 min. To the reaction mixture was added 30% H₂O₂ (5.6 ml, 51.2 mmol) at 0 °C and stirred for 30 min. After stirring at room temperature for 3 h, MeOH was removed by rotary evaporation. The residue was poured into a saturated aqueous solution of NaHCO₃ and extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:4 AcOEt: hexane) to give 3 (777 mg, 4.68 mmol, 39 %) as a red solid.

IR (CHCl₃, cm⁻¹): 3432. MS *m/z*: 166 (M⁺), 93 (100%). HRMS (EI): Calcd. for C₁₀H₁₆NO 166.1232 (M⁺), found: 166.1194. Anal: Calcd. for C₁₀H₁₆NO: C, 72.25; H, 9.70; N, 8.43, found: C, 72.55; H, 9.60; N, 8.28.
Synthesis of 1,3-dimethyl-AZADO

Scheme S3.

Reagents and conditions: (a) H₂, Pd-C, MeOH, quant; (b) NaCN, (NH₄)₂CO₃, aq. NH₃, 50 °C, 89%; (c) TfOH, CH₂Cl₂, 0 °C, quant; (d) Boc₂O, Et₃N, 4-DMAP, CH₂Cl₂, 0 °C, 98%; (e) 10N KOH/EtOH, reflux; (f) AcCl, MeOH, reflux, 74% over two steps; (g) p-TsCl, pyridine, reflux, 40%; (h) DIBAL, PhMe, 0 °C, 82%; (i) PPh₃, imidazole, I₂, CH₂Cl₂, 77%; (j) NaI, i-PrOH, reflux, 65%; (k) Na/NH₃, Et₂O, -78 °C, then EtOH/H₂O; (l) UHP, Na₂WO₄·2H₂O, MeOH, 41% over two steps.

7-Methyl-bicyclo[3.3.1]non-6-en-3-one (20)
To a solution of ketone 6 (2 g, 13.3 mmol) in MeOH (133 ml) was added 10% Pd-C (200 mg) under Ar atmosphere. The reaction flask was evacuated and purged with H₂ three times and then the reaction was stirred at room temperature under H₂ atmosphere for 3h. The catalyst was removed by filtration through Celite®. The filtrate was concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:8 AcOEt: hexane) to give 20 (2 g, 13.3 mmol, 100%) as a colorless oil.

\[
\begin{align*}
\delta & \quad 5.42 (\text{br d}, J = 5.6 \text{ Hz}, 2\text{H}), \\
& \quad 2.65 (\text{br s}, 1\text{H}), \\
& \quad 2.56 (\text{br s}, 1\text{H}), \\
& \quad 2.36-2.22 (\text{m}, 3\text{H}), \\
& \quad 2.00-1.90 (\text{m}, 2\text{H}), \\
& \quad 1.79 (\text{d}, J = 17.9 \text{ Hz}, 1\text{H}), \\
& \quad 1.58 (\text{s}, 3\text{H}).
\end{align*}
\]

\[
\begin{align*}
\delta & \quad 212.2, \\
& \quad 132.8, \\
& \quad 124.6, \\
& \quad 49.1, \\
& \quad 46.5, \\
& \quad 37.4, \\
& \quad 31.1, \\
& \quad 30.24, \\
& \quad 30.21, \\
& \quad 23.1.
\end{align*}
\]

IR (neat, cm⁻¹): 1714.4. MS m/z: 150 (M⁺), 93 (100%). HRMS (EI): Calcd. for C₁₀H₁₄O₁₅₀.1045 (M⁺), found: 150.1047.

7-Methyl-bicyclo[3.3.1]non-6-en-3-spiro-5'-hydantoin (21)

To a 100 ml sealed tube charged with NaCN (4.9 g, 100 mmol), (NH₄)₂CO₃ (22.4 g, 233 mmol) was added 30% aq. NH₃ (55 ml) at room temperature. The mixture was vigorously stirred for 10 min, and then ketone 20 (5 g, 33.3 mmol) was added. The solution was allowed to stir at 50 °C for 37 h. After cooling to room temperature, the mixture was diluted with H₂O and extracted with CHCl₃. The organic layer was dried over K₂CO₃ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:2 AcOEt: hexane) to give 21 (6.5 g, 29.6 mmol, 89%) as a white solid.

mp 205-207 °C (recrystallized from CHCl₃-hexane), ¹H-NMR (400 MHz, CDCl₃): \(\delta \) 8.79 (br s, 1H), 5.92 (br s, 1H), 5.68 (br d, \(J = 6.1 \text{ Hz}, 1\text{H}\)), 2.50 (br s, 1H), 2.43 (br dd, \(J = 18.1, 6.8 \text{ Hz}, 1\text{H}\)), 2.37 (br s, 1H), 2.24 (dd, \(J = 14.4, 4.9 \text{ Hz}, 1\text{H}\)), 2.07 (dd, \(J = 13.9, 3.7 \text{ Hz}, 1\text{H}\)).
1H), 1.94 (d, J = 18.1 Hz, 1H), 1.76-1.71 (m, 7H). 13C-NMR (100 MHz, CDCl₃): δ 178.8, 156.1, 135.8, 127.3, 62.9, 40.2, 37.3, 36.7, 30.2, 27.5, 25.8, 23.3. IR (neat, cm⁻¹): 3447.1, 3391.2, 3156.9, 3064.3, 1774.2, 1721.2, 1417.4. MS m/z: 220 (M⁺), 220 (100%). HRMS (EI): Calcd. for C₁₂H₁₆N₂O₂ 220.1212 (M⁺), found: 220.1201.

1,2-(1',3'-Diketoimidazo)-3-Methyl-2-azaadamantane (22)

To a solution of hydantoin 21 (835 mg, 3.8 mmol) in CH₂Cl₂ (38 ml) at 0 ºC was added TfOH (1 ml, 11.4 mmol). The mixture was allowed to stir at 0 ºC for 2h and then quenched with a saturated aqueous solution of Na₂CO₃ and extracted with CHCl₃. The organic layer was dried over K₂CO₃ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:2 AcOEt: hexane) to give 22 (830 mg, 3.8 mmol, 100 %) as a white solid.

mp 227-229 ºC (recrystallized from CHCl₃-hexane), ¹H-NMR (400 MHz, CDCl₃): δ 8.59 (br s, 1H), 2.30 (br s, 1H), 2.04 (d, J = 12.2 Hz, 2H), 1.86-1.73 (m, 6H), 1.66 (s, 3H), 1.59 (d, J = 12.7 Hz, 2H). ¹³C-NMR (100 MHz, CDCl₃): δ 176.3, 151.7, 61.8, 54.6, 43.2, 36.4, 33.8, 27.6, 26.3. IR (neat, cm⁻¹): 3163.7, 3047.9, 1763.6, 1698.0. MS m/z: 220 (M⁺), 220 (100%). HRMS (EI): Calcd. for C₁₂H₁₆N₂O₂ 220.1212 (M⁺), found: 220.1219.

1,2-(2'-t-Butoxycarbonyl-1',3'-diketoimidazo)-3-methyl-2-azaadamantane (23)

Hydantoin 22 (216 mg, 0.98 mmol) was dissolved in CH₂Cl₂ (5 ml) and cooled to 0 ºC. Et₃N (0.27 ml, 1.96 mmol), Boc₂O (430 mg, 1.96 mmol), 4-DMAP (12 mg, 0.1 mmol) was
added and the mixture was stirred at 0 °C for 10 min and then quenched with H₂O. The resulting biphasic mixture was extracted Et₂O. The combined organic layers were washed with brine and dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:2 AcOEt: hexane) to give 23 (313 mg, 0.97 mmol, 98 %) as a white solid.

\[ \text{\textsuperscript{1}H-NMR (400 MHz, CDCl₃): } \delta 2.39 \text{ (br s, 2H), 2.06 (br d, } J = 12.1 \text{ Hz, 2H), 1.84 (m, 3H), 1.76 (m, 3H), 1.69 (s, 3H), 1.60 (br d, } J = 11.6 \text{ Hz, 2H), 1.57 (s, 9H).} \]

\[ \text{\textsuperscript{13}C-NMR (100 MHz, CDCl₃): } \delta 172.1, 147.4, 146.8, 85.1, 59.9, 55.0, 43.0, 36.5, 33.7, 27.8, 27.4, 26.3. \]

IR (neat, cm⁻¹): 1800.2, 1767.4, 1721.2, 1454.1, 1385.6. MS \( m/z \): 320 (M⁺), 220 (100%). HRMS (EI): Calcd. for C₁₇H₂₄N₂O₄ 320.1736 (M⁺), found: 320.1756.

1. 10N KOH, EtOH, reflux
2. AcCl, MeOH, reflux

76%, 2 steps

Carbamate 23 (313 mg, 0.98 mmol) was dissolved in mixture of EtOH-10N \textit{aq.} KOH (5 ml, 1 : 1 v/v) and heated at reflux for 15 h. After cooling to room temperature, solvent was removed \textit{in vacuo}. The residue was poured into H₂O and extracted three times with CHCl₃. The aqueous layer was concentrated under reduced pressure to give amino acid 24. The crude product was not further purified. To a 20 ml flask charged with MeOH (2.5 ml) at 0 °C was added AcCl (0.33 ml, 4.7 mmol). The reaction mixture was allowed to stir at room temperature for 10 min, and then crude amino acid 24 was added. After stirring at 80 °C for 5 h, solvent was removed \textit{in vacuo}. The residue was poured into H₂O and extracted three times with CHCl₃. The aqueous layer was added a saturated aqueous solution of Na₂CO₃ until it became strongly basic. The aqueous phase was extracted with CHCl₃ and dried over K₂CO₃ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:4 MeOH:CHCl₃) to give 25 (156 mg, 0.76 mmol, 74 %) as a white solid.

3-Methyl-1-methoxycarbonyl-2-azaadamantane (25)

Carbamate 23 (313 mg, 0.98 mmol) was dissolved in mixture of EtOH-10N \textit{aq.} KOH (5 ml, 1 : 1 v/v) and heated at reflux for 15 h. After cooling to room temperature, solvent was removed \textit{in vacuo}. The residue was poured into H₂O and extracted three times with CHCl₃. The aqueous layer was concentrated under reduced pressure to give amino acid 24. The crude product was not further purified. To a 20 ml flask charged with MeOH (2.5 ml) at 0 °C was added AcCl (0.33 ml, 4.7 mmol). The reaction mixture was allowed to stir at room temperature for 10 min, and then crude amino acid 24 was added. After stirring at 80 °C for 5 h, solvent was removed \textit{in vacuo}. The residue was poured into H₂O and extracted three times with CHCl₃. The aqueous layer was added a saturated aqueous solution of Na₂CO₃ until it became strongly basic. The aqueous phase was extracted with CHCl₃ and dried over K₂CO₃ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:4 MeOH:CHCl₃) to give 25 (156 mg, 0.76 mmol, 74 %) as a white solid.
$^1$H-NMR (400 MHz, CDCl$_3$): δ 3.70 (s, 3H), 2.20 (br s, 1H), 1.97 (br d, $J = 12.1$ Hz, 2H), 1.81-1.69 (m, 4H), 1.57 (br s, 4H), 1.06 (s, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 175.4, 57.2, 51.9, 48.9, 42.4, 38.1, 35.0, 30.4, 27.9. IR (neat, cm$^{-1}$): 1735.6, 1435.7, 1245.8. MS m/z: 209 (M$^+$), 150 (100%). HRMS (EI): Calcd. for C$_{12}$H$_{19}$NO$_2$ 209.1416 (M$^+$), found: 209.1397.

\[ \text{p-TsCl, pyridine, reflux} \rightarrow \] 40%

\[ \text{CO}_2\text{Me} \quad \text{N} \quad \text{p-Ts} \quad \text{CO}_2\text{Me} \]

\[ \text{25} \rightarrow \text{26} \]

$N$-$p$-Toluenesulfonyl-3-methyl-1-methoxycarbonyl-2-azaadamantane (26)

To a solution of amine 25 (1g, 4.79 mmol) in pyridine (24 ml) at 0 ºC was added p-TsCl (4.6 g, 23.9 mmol). The mixture was heated at reflux for 19 h. After cooling to room temperature, the reaction mixture was poured into H$_2$O and extracted with CHCl$_3$. The organic layer was dried over K$_2$CO$_3$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO$_2$, 1:4 AcOEt: hexane) to give 26 (605 mg, 1.9 mmol, 40 %) as a white solid.

mp 198-199 ºC (recrystallized from AcOEt-hexane), $^1$H-NMR (400 MHz, CDCl$_3$): δ 7.96 (d, $J = 8.5$ Hz, 2H), 7.25 (d, $J = 8.5$ Hz, 2H), 3.71 (s, 3H), 2.33-2.04 (m, 6H), 1.99 (br d, $J = 12.3$ Hz, 1H), 1.96 (br d, $J = 12.3$ Hz, 1H), 1.75 (br d, $J = 12.7$ Hz, 1H), 1.70 (br d, $J = 12.7$ Hz, 1H), 1.45 (br d, $J = 13$ Hz, 1H), 1.42 (br d, $J = 13$ Hz, 1H), 1.15 (s, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 174.1, 142.7, 141.9, 129.2, 127.3, 77.2, 63.4, 59.1, 52.1, 34.2, 28.1, 27.0, 21.5. IR (neat, cm$^{-1}$): 1740.4, 1597.7, 1448.3, 1323.9, 1309.4. MS m/z: 363 (M$^+$), 363 (100%). HRMS (EI): Calcd. for C$_{19}$H$_{25}$NO$_4$S 363.1504 (M$^+$), found: 363.1503.

\[ \text{DIBAL, toluene, 0 ºC} \rightarrow \] 82%

\[ \text{CO}_2\text{Me} \quad \text{NTs} \quad \text{OH} \quad \text{NTs} \]

\[ \text{26} \rightarrow \text{27} \]

$N$-$p$-Toluenesulfonyl-1-hydroxymethyl-3-methyl-2-azaadamantane (27)
To a solution of sulfonamide 26 (605 mg, 1.9 mmol) in toluene (10 ml) at 0 °C was added DIBAL in toluene (7.5 ml, 7.5 mmol). The mixture was allowed to stir at 0 °C for 30 min, and then quenched with AcOEt, H2O. After stirring at room temperature for an additional 2 h, the mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO2, 1:5 AcOEt: hexane) to give 27 (520 mg, 1.56 mmol, 82 %) as a white solid.

mp 166-168 °C (recrystallized from CHCl3-Et2O), 1H-NMR (400 MHz, CDCl3): δ 7.79 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 3.88 (d, J = 7.8 Hz, 2H), 3.31 (t, J = 8.1 Hz, 1H), 2.41 (s, 3H), 2.25 (d, J = 12.5 Hz, 2H), 2.16 (br s, 2H), 2.04 (d, J = 8.3 Hz, 2H), 1.78-1.67 (m, 2H), 1.54 (br d, J = 13 Hz, 2H), 1.39 (br d, J = 13 Hz, 2H), 1.26 (s, 3H). 13C-NMR (100 MHz, CDCl3): δ 142.9, 142.3, 129.3, 129.1, 71.7, 65.0, 59.0, 43.2, 39.8, 34.4, 29.5, 26.5, 21.4. IR (neat, cm−1): 3575.4, 1596.8, 1445.4, 1321.0, 1302.7. MS m/z: 335 (M+), 180 (100%). HRMS (EI): Calcd. for C18H25NO3S 335.1555 (M+), found: 335.1526.

N-p-Toluenesulfonyl-1-iodomethyl-3-methyl-2-azaadamantane (28)

To a mixture of PPh3 (820 mg, 3.13 mmol) and imidazole (213 mg, 3.13 mmol) in CH2Cl2 (3 ml) at room temperature was added I2 (796 mg, 3.13 mmol). After stirring at room temperature for 30 min, sulfonamide 27 (350 mg, 1.05 mmol) in CH2Cl2 (2 ml) was cannulated into the reaction mixture. The reaction was stirred for an additional 2 h then quenched with a saturated aqueous solution of NaHCO3, which was extracted with AcOEt. The organic layer was washed with brine and dried over MgSO4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO2, 1:18 AcOEt: hexane) to give 28 (360 mg, 0.81 mmol, 77 %) as a white solid.

mp 128-130 °C (recrystallized from CHCl3-Et2O), 1H-NMR (400 MHz, CDCl3): δ 8.0 (d, J = 7.2 Hz, 2H), 7.23 (d, J = 7.2 Hz, 2H), 3.95 (s, 2H), 2.39 (s, 3H), 2.24 (br d, J = 12.6 Hz, 2H), 2.13 (br s, 2H), 1.70-1.61 (m, 4H), 1.37 (br d, J = 12.6 Hz, 2H), 1.09 (s, 3H). 13C-NMR (100 MHz, CDCl3): δ 143.2, 142.4, 129.1, 127.1, 61.0, 60.0, 43.1, 42.9, 34.3,
29.7, 27.1, 22.3, 21.4. IR (neat, cm⁻¹): 1586.2, 1457.9, 1323.9, 1311.4. MS m/z: 445 (M⁺), 319 (100%). HRMS (EI): Calcd. for C₁₈H₂₄I₄NO₂S 445.0572 (M⁺), found: 445.0564.

\[ \text{NaI, i-PrOH, reflux} \quad 65\% \]

\[ \begin{array}{c}
\text{28} \\
\text{NTs}
\end{array} \xrightarrow{\text{I}} 
\begin{array}{c}
\text{29} \\
\text{NTs}
\end{array} \]

**N-p-Toluenesulfonyl-1,3-dimethyl-2-azaadamantane (29)**

A mixture of sulfonamide 28 (200 mg, 0.45 mmol) and NaI (4.45 g, 22.5 mmol) in 2-propanol (2 ml) was heated at reflux until the starting material was no longer detectable (TLC, SM Rₜ = 0.3; 1:1 CHCl₃:benzene). The reaction was cooled to room temperature and then 2-propanol was removed in vacuo. The residue was poured into a saturated aqueous solution of NaHCO₃ and extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:18 AcOEt:hexane) to give 29 (93 mg, 0.29 mmol, 65 %) as a white solid.

mp 116-119 °C (recrystallized from CHCl₃-Et₂O), ¹H-NMR (400 MHz, CDCl₃): δ 7.72 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 2.39 (s, 3H), 2.11-2.09 (m, 6H), 1.68 (s, 2H), 1.51 (m, 4H), 1.43 (s, 6H). ¹³C-NMR (100 MHz, CDCl₃): δ 143.9, 141.8, 129.2, 126.2, 59.8, 44.2, 34.2, 30.8, 27.2, 21.3. IR (neat, cm⁻¹): 1598.7, 1439.6, 1347.0, 1308.5. MS m/z: 319 (M⁺), 164 (100%). HRMS (EI): Calcd. for C₁₈H₂₅NO₂S 319.1606 (M⁺), found: 319.1612.

\[ \begin{array}{c}
\text{29} \\
\text{NTs}
\end{array} \xrightarrow{\text{1. Na, liq.NH₃, -78 °C}} 
\begin{array}{c}
\text{29} \\
\text{O}
\end{array} \xrightarrow{\text{2. UHP, Na₂WO₄, MeOH}} 
\begin{array}{c}
\text{4} \\
\text{NO}.
\end{array} \]

**1,3-Dimethyl-2-azaadamantane N-oxyl (4)**

To a mixture of dry Et₂O (0.5 ml), liquid ammonia (2 ml) and sodium metal (excess amount) was added a dry Et₂O (2 ml) solution of sulfonamide 29 (70 mg, 0.22 mmol) at -78 °C, and the mixture was stirred for 1 h. To this was added EtOH-H₂O (5 ml, 1:4 v/v), and
the mixture was warmed to room temperature with evaporation of ammonia and stirred for 2 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl. The layers were separated, and the aqueous layer was extracted seven times with CHCl₃. The combined organic layers were dried over K₂CO₃ and concentrated under reduced pressure. The residue was dissolved in EtOH (1 ml) and added 7N EtOH solution of HCl (3 ml) at 0 ºC. The mixture was allowed to stir for 1 h and then solvent was removed under reduced pressure. The residue was poured into H₂O and extracted three times with CHCl₃. The aqueous layer was added 10% aq. NaOH until it became strongly basic, which was extracted with CHCl₃. The organic layer was dried over K₂CO₃ and concentrated under reduced pressure to give 30 as a colorless oil. Amine 30 was then used directly for further reaction. A mixture of amine 30 and Na₂WO₄·2H₂O (30 mg, 0.091 mmol) in MeOH (0.9 ml) was stirred at room temperature for 30 min. To the reaction mixture was added urea hydrogen peroxide (69 mg, 0.73 mmol) at room temperature. After stirring for 3 h, the reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The mixture was extracted with CHCl₃. The organic layer was dried over K₂CO₃ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:10 Et₂O: hexane) to give 4 (16.2 mg, 0.09 mmol, 41 %) as a red solid.

IR (neat, cm⁻¹): 1448.3, 1369.2, 1343.2. MS m/z: 180 (M⁺), 93 (100%). HRMS (EI): Calcd. for C₁₁H₁₈NO 180.1388 (M⁺), found 180.1380. Anal: Calcd. for C₁₁H₁₈NO: C, 73.29; H, 10.06; N, 7.77, found: C, 73.00; H, 9.92; N, 7.84.
General procedure A: Anelli’s oxidation conditions  

\[
\text{1-Me-AZADO (0.1 mol\%)}
\text{NaOCl (130 mol\%), KBr (10 mol\%)}
\text{n-Bu4NBr (5 mol\%)}
\]

\[
\text{CH2Cl2, aq. NaHCO3, 0 °C, 20 min.}
\]

A 20 ml flask was charged with a solution of 3-phenyl propanol (200 mg, 1.47 mmol), 1-Me-AZADO (3) (0.244 mg, 1.47 \( \mu \text{mol} \)) in CH\(_2\)Cl\(_2\) (3.9 ml) and a sat. aqueous solution of NaHCO\(_3\) (2 ml) containing KBr (17.5 mg, 0.074 M) and \( n-\text{Bu}_4\text{NBr} \) (23.7 mg, 0.037 M). To this cooled (0 °C, a water-ice bath) and well stirred mixture, a pre-mixed solution of aqueous NaOCl (8% Cl, purchased from Junsei Chemical Co.) and sat. aqueous solution of NaHCO\(_3\) (3.3 ml, 1:1.4 v/v) was added dropwise during 6 min. The reaction was stirred for 20 min at 0 °C, then quenched with a sat. aqueous solution of Na\(_2\)S\(_2\)O\(_3\) (4 ml). The aqueous layer was separated and extracted with Et\(_2\)O. The combined organic layers were washed with brine, dried over MgSO\(_4\) and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO\(_2\), 1:6 Et\(_2\)O: hexane) to give 3-phenyl propanal (177 mg, 1.32 mmol, 90 \%) as a colorless oil.

General procedure B: Margarita’s oxidation conditions  

\[
\text{1-Me-AZADO (1 mol\%)}
\text{Phl(OAc)\(_2\) (150 mol\%)}
\]

\[
\text{CH2Cl2 (1 M)}
\]

To a solution of cinnamyl alcohol (200 mg, 1.49 mmol) and 1-Me-AZADO (3) (2.47 mg, 14.9 \( \mu \text{mol} \)) in CH\(_2\)Cl\(_2\) (1.5 ml) was added Phl(OAc)\(_2\) (720 mg, 2.24 mmol) at one stroke. The reaction mixture was allowed to stir until the alcohol was no longer detectable (TLC), then it was diluted with Et\(_2\)O and quenched with a sat. aqueous solution of NaHCO\(_3\) (4 ml), followed by a sat. aqueous solution of Na\(_2\)S\(_2\)O\(_3\) (4 ml). The layer was separated and the aqueous layer was extracted with Et\(_2\)O. The combined organic layers were washed...
with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:9 Et₂O: hexane) to give cinnamaldehyde (183 mg, 1.39 mmol, 93 %) as a colorless oil.

<note> 1-Me-AZADO was added accurately as a CH₂Cl₂ solution.

**Catalytic efficiencies of 1,3-dimethyl-AZADO:**

Catalytic efficiencies of 1,3-dimethyl-AZADO (4) were evaluated by monitoring the oxidation of 3-phenylpropanol and l-menthol under Anelli’s condition. As shown in Table S1, 1, 3-dimethyl-AZADO (4) exhibited comparable catalytic activity towards the oxidation of 3-phenylpropanol to give 3-phenylpropanal in 92% yield after 20min. On the other hand, 1,3-dimethyl-AZADO (4) does not efficiently oxidize l-menthol similar to TEMPO (1), showing a remarkable difference from 1-Me-AZADO (3).

**Table S1**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Oxidation Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH₂CH₂OH</td>
<td>1-Me-AZADO (3)</td>
<td>3-phenylpropanal</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>1,3-dimethyl-AZADO (4)</td>
<td>3-phenylpropanal</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>TEMPO (1)</td>
<td>3-phenylpropanal</td>
<td>90%</td>
</tr>
<tr>
<td>l-menthol</td>
<td>1-Me-AZADO (3)</td>
<td>l-sabinene oxide</td>
<td>trace</td>
</tr>
<tr>
<td></td>
<td>1,3-dimethyl-AZADO (4)</td>
<td>l-sabinene oxide</td>
<td>trace</td>
</tr>
<tr>
<td></td>
<td>TEMPO (1)</td>
<td>l-sabinene oxide</td>
<td>trace</td>
</tr>
</tbody>
</table>
Procedure for the oxidation of 3-phenyl propanol

A 20 ml flask was charged with a solution of 3-phenyl propanol (200 mg, 1.47 mmol), 1,3-dimethyl-AZADO (4) (2.65 mg, 14.7 µmol) in CH₂Cl₂ (3.9 ml) and a sat. aqueous solution of NaHCO₃ (2 ml) containing KBr (17.5 mg, 0.074 M) and n-Bu₄NBr (23.7 mg, 0.037 M). To this cooled (0 ºC, a water-ice bath) and well stirred mixture, a pre-mixed solution of aqueous solution of NaOCl and sat. aqueous solution of NaHCO₃ (3.3 ml, 1:1.4 v/v) was added dropwise during 6 min. The reaction was stirred for 20 min at 0 ºC, then quenched with a sat. aqueous solution of Na₂S₂O₃ (4 ml). The aqueous layer was separated and extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, 1:6 Et₂O: hexane) to give 3-phenyl propanal (183 mg, 1.35 mmol, 92 %) as a colorless oil.

Procedure for the oxidation of l-menthol

A 20 ml flask was charged with a solution of l-menthol (200 mg, 1.28 mmol), 1,3-dimethyl-AZADO (4) (2.3 mg, 1.47 µmol) in CH₂Cl₂ (1.7 ml) and a sat. aqueous solution of NaHCO₃ (1.7 ml) containing KBr (15 mg, 0.074 M) and n-Bu₄NBr (20.3 mg, 0.037 M). To this cooled (0 ºC, a water-ice bath) and well stirred mixture, a pre-mixed solution of aqueous solution of NaOCl and sat. aqueous solution of NaHCO₃ (3.1 ml, 1:1.2
v/v) was added dropwise during 6 min. The reaction was stirred for 20 min at 0 °C, then quenched with a sat. aqueous solution of Na₂S₂O₃ (4 ml). The aqueous layer was separated and extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography to give trace amount of l-menthone and l-menthol (recovered yield: 49~56%).
Electrochemical measurements

We carried out cyclic voltammetric measurements to get insight into the electrochemical behaviors of the nitroxyl radicals used in this study. Although $E^{\circ}$ values of nitroxyl radicals have been summarized by Schukin and his coworkers (57 species) as well as by Bobbit, those of AZADO, 1-Me-AZADO, and 1,3-dimethyl-AZADO were unavailable. The cyclic voltammograms were measured on a Cypress CS-2010 electrochemical analyzer with a conventional three-electrode configuration at room temperature (approximately 23 °C). CH$_3$CN solutions of TEMPO, AZADO, 1-Me-AZADO, and 1,3-dimethyl-AZADO (2 mM) were used throughout the cyclic voltammetric measurements. Glassy carbon (BAS, 3 mm diameter), platinum wire, and Ag/Ag+ (BAS type RE-5) were used as working, auxiliary, and reference electrodes, respectively. Electric potential values reported herein referred to this reference electrode. NaClO$_4$ (0.1 M) was used as supporting electrolyte.

The cyclic voltammograms of TEMPO, AZADO, 1-Me-AZADO, and 1,3-dimethyl-AZADO are shown in Fig. S1, and the cyclic voltammograms obtained at various potential sweep rate ($\nu$) are independently given in Fig. S2 (TEMPO), Fig. S3 (AZADO), Fig. S4 (1-Me-AZADO), and Fig. S5 (1,3-dimethyl-AZADO). Obviously, these nitroxyl radicals showed cyclic voltammograms within $\nu = 200$ mV s$^{-1}$, with peak-to-peak separation ($\Delta E_p = E_{pa} - E_{pc}$; $E_{pa}$ and $E_{pc}$ denote anodic and cathodic peak potentials, respectively) being approximately 60 mV. These $\Delta E_p$ values establish that the electrochemical reactions of the nitroxyl radicals reversibly proceed by one-electron transfer. The $i_{pa}$ (electric current at $E_{pa}$) values of the nitroxyl radicals linearly correlate with $\nu^{1/2}$. This indicates that the electrochemical reactions of the nitroxyl radicals are of fusion-controlled. The highly reversible nature in electrochemical oxidation of the nitroxyl radicals implies that they can intrinsically function as catalysts for the oxidation of alcohols. It is noteworthy that such well-defined redox waves were retained after more than 100-cycle measurements with neither decreasing the $i_{pa}$ values nor shifting the $E_{pa}$ and $E_{pc}$ values. The observed marked durability of the nitroxyl radicals would result in the high turnover numbers prerequisite to efficient catalysts.
The $E''$ values of the nitroxy radicals, which were calculated by $(E_{pa} + E_{pa}) / 2$, are summarized in Table 1. The $E''$ values of the nitroxy radicals is in the order of 1,3-dimethyl-AZADO < 1-Me-AZADO < AZADO < TEMPO. However, the total efficiency of the nitroxy radicals as catalysts was in the order of 1,3-dimethyl-AZADO << TEMPO < 1-Me-AZADO. No obvious correlation between the two orders is found. Thus, we conclude that at least a part of the high efficiency of 1-Me-AZADO as an oxidative catalyst is due to kinetic factors, presumably decreased steric hindrance around the reaction center.

Fig. S1 Cyclic voltammograms of various nitroxy radicals (2 mM) at scan rate of 50 mV s$^{-1}$ (a; TEMPO, b; AZADO, c; 1-Methyl-AZADO, d; 1,3-dimethyl-AZADO)

Fig. S2 Cyclic voltammograms of TEMPO (2 mM) at varying scan rates. (a; 10 mV s$^{-1}$, b; 20 mV s$^{-1}$, c; 50 mV s$^{-1}$, d; 100 mV s$^{-1}$ e; 200 mV s$^{-1}$)

Fig. S3 Cyclic voltammograms of AZADO (2 mM) at varying scan rates. (a; 10 mV s$^{-1}$, b; 20 mV s$^{-1}$, c; 50 mV s$^{-1}$, d; 100 mV s$^{-1}$ e; 200 mV s$^{-1}$)
Fig. S4  Cyclic voltammograms of 1-Me-AZADO (2 mM) at varying scan rates. (a; 10 mV s$^{-1}$, b; 20 mV s$^{-1}$, c; 50 mV s$^{-1}$, d; 100 mV s$^{-1}$ e; 200 mV s$^{-1}$)

Fig. S5  Cyclic voltammograms of 1,3-dimethyl-AZADO (2 mM) at varying scan rates. (a; 10 mV s$^{-1}$, b; 20 mV s$^{-1}$, c; 50 mV s$^{-1}$, d; 100 mV s$^{-1}$ e; 200 mV s$^{-1}$)

Table S2  The formal potential of various nitroxy radicals

<table>
<thead>
<tr>
<th>Nitroxy radical</th>
<th>$E^{\text{ox}}$ vs Ag/Ag$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPO</td>
<td>+294 mV</td>
</tr>
<tr>
<td>AZADO</td>
<td>+236 mV</td>
</tr>
<tr>
<td>1-Me-AZADO</td>
<td>+186 mV</td>
</tr>
<tr>
<td>1,3-Dimethyl-AZADO</td>
<td>+136 mV</td>
</tr>
</tbody>
</table>
References and notes


(b) Ipaktschi, J. *Chem. Ber.* 1984, 117, 856-858.

(c) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* 1990, 533-535.


(g) Bobbit, J. M.; Flores, M. C. L. *Heterocycles* 1988, 27, 509-533.
