An isocyanide ligand for the rapid quenching and efficient removal of copper residues after Cu/TEMPO-catalyzed aerobic alcohol oxidation and atom transfer radical polymerization

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Supplementary Information

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Experimental Details

General Remarks

The Cu^{I}/TEMPO alcohol aerobic oxidation (Table 1 and S1, Figure 2 and 3) were carried out under air. The atom transfer radical polymerizations (Figure 7 and 9, Table 2) were performed out under nitrogen using Schlenk techniques. All chemicals were purchased from commercial sources and used as received unless otherwise noted. 1,4-bis(3-isocyanopropyl)piperazine (**QA**) was purchased from *Strem Chemicals, Inc.* Tris(2-pyridylmethyl)amine (**TPMA**) was purchased from *AmBeed*. 4,4′-Dinonyl-2,2′-dipyridyl (**dNbpy**) was purchased from *Alfa Aesar*. 2,2′-Bipyridyl (**bpy**), *N*,*N*,*N*′,*N*′,*N*′-pentamethyldiethylenetriamine (**PMDETA**) ware purchased from *Sigma Aldrich*, tris[2-(dimethylamino)ethyl]amine (**Me_6TREN**) was received from *Koei Chemical Co., Ltd.* Tris(3,5-dimethyl4-methoxy-2-pyridylmethyl)amine (**TPMA**^{*3}) was synthesized according to previously published procedure.[1] 4-(Dimethylamino)pyridine (**DMAP**), 2,2,6,6-tetramethylpiperidine *N*-oxyl (**TEMPO**), 9-azabicyclo[3.3.1]nonane N-oxyl (**ABNO**), copper(I) iodide (≥99.5%), ethyl α-bromoisobutyrate (**EBiB**), 2-bromopropionate (**MBP**), propargyl 2-bromoisobutyrate (**PgBiB**) ware purchased from *Sigma Aldrich*. Methyl acrylate (**MA**, *Sigma Aldrich*, 99%), butyl acrylate (***n*BA**, *Sigma Aldrich*, ≥99%), *tert*-butyl acrylate (***t*BA**, *Sigma Aldrich*, ≥98%) were passed through a column of basic alumina to remove inhibitor prior to use. Filtration after Stahl oxidation was performed using *Merck Millipore* silica gel (60, particle size 0.043–0.063 mm) and syringe filter (1–2 μm). Filtration after ATRP was performed using syringe filter (0.2 μm).

Nuclear Magnetic Resonance (NMR)

NMR (^{1}H and ^{13}C) spectra were recorded on *Agilent* Mercury 400 MHz or *Bruker* Avance III 500 MHz spectrometers with $CDCl_3$ used as the solvent. Chemical shifts (δ) are given in ppm, with the solvent peak of $CDCl_3$ used as a point of reference. Coupling constants (J) are reported in hertz (Hz).

Gas Chromatography (GC)

GC measurements were done on *PerkinElmer* Clarus 580 with InertCap 5MS-Sil column.

UV-vis-NIR

The evolution of [Br–Cu^{II}/L] was monitored using a *Varian Cary* 5000 UV/Vis/NIR spectrometer.

Electrochemical Instrumentation

Electrochemical investigations were conducted in a 6-neck electrochemical cell connected to a potentiostat (Gamry Ref-600 or Autolab PGSTAT100N, *Metrohm* USA) through a three-electrode system

[1] Schröder, K.; Mathers, R. T.; Buback, J.; Konkolewicz, D.; Magenau, A. J. D.; Matyjaszewski, K. Substituted Tris(2-pyridylmethyl)amine Ligands for Highly Active ATRP Catalysts. *ACS Macro Lett.* **2012**, *1*, 1037– 1040.

composed of a Glassy Carbon (GC) disk as working electrode, a platinum wire as counter electrode and Ag|AgI|0.1 M *n*-Bu_4NI in DMF as reference electrode. The latter was calibrated after each experiment against the ferrocenium/ferrocene couple (Fc^+/Fc), which allowed for referring all potentials to the aqueous saturated calomel electrode (SCE) scale ($E^{o}_{Fc^+/Fc}$ = 0.449 V *vs.* SCE in DMSO). Before each experiment the GC disk was cleaned by polishing with a 0.25-µm diamond paste, followed by ultrasonic rinsing in ethanol for 5 minutes. The cell was thermostated at 25 °C, and maintained under N_2 atmosphere. For the chronoamperometry experiment, the GC tip was attached to a rotating disk electrode (RDE, *Metrohm* USA).

Size Exclusion Chromatography (SEC)

SEC was conducted using a *Waters* 515 HPLC Pump and *Waters* 2412 Refractive Index Detector using PSS columns (Styrogel 102, 103, 104, 105 Å) with THF as an eluent at 35 °C a flow rate of 1 mL/min at 35 °C. Linear poly(methyl methacrylate) standards were used for calibration.

Photoinduced ATRP

For *p*ATRP UV lamp (*MelodySusie® UV*) emitting light at 365 nm with the light intensity of 4.2 mW cm^{-2} was used.

Cytotoxicity Assay

Human embryonic kidney cell line (HEK293; ATCC®CRL-1573™) and murine embryonic fibroblasts cell line (NIH3T3; ATCC®CRL-1658™) were grown and maintained in Dulbecco's modified eagle media (DMEM; *Gibco*, Gaithersburg, MD) supplemented with 10% fetal bovine serum (*Thermo Fisher Scientific*, Waltham, MA) and 1% Penicillin-streptomycin (*Gibco*, Gaithersburg, MD).

Statistics

For statistical analysis of cytotoxicity assay, all data was subjected to Analysis of Variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons between treatment groups and the untreated control group using GraphPad Prism 8 software. Statistical significance was defined as $p<0.05$.

Inductively Coupled Plasma Mass Spectrometry (ICP-MS)

Copper content was determined by IPC-MS (NexION 300D, *Perkin Elmer*, USA) equipped with a traditional sample introduction system, which requires samples to be in solution in order to be analyzed.

Quenching of Stahl Oxidation of 1a by QA (Figure 1A)

A 25 mL round-bottomed flask equipped with magnetic stir bar was charged with substrate **1a** (154 mg, 1.0 mmol), copper(I) iodide (2.0 mL, 25.0 mM in MeCN, 9.6 mg, 0.05 mmol, 5.0 mol%), 2,2′-bipyridine (7.9 mg, 0.05 mmol, 5.0 mol%) and 4-dimethylaminopyridine (2.0 mL, 50.0 mM in MeCN, 12.3 mg, 0.1 mmol, 10 mol%). The scavenger **QA** (48.4 mg, 0.22 mmol, 4.4 equiv with respect to the copper) was added, followed by TEMPO (1.0 mL, 25.0 mM in MeCN, 8.0 mg, 0.05 mmol, 5.0 mol%). The reaction mixture was stirred (600 rpm) at rt for 24 h under ambient atmosphere in an open flask. The conversion of **1a** was determined by GC analysis and is based on the ratio of product/(product + starting material).

Control experiment

A 25 mL round-bottomed flask equipped with magnetic stir bar was charged with substrate **1a** (154 mg, 1.0 mmol), copper(I) iodide (2.0 mL, 25.0 mM in MeCN, 9.6 mg, 0.05 mmol, 5.0 mol%), 2,2′-bipyridine (7.9 mg, 0.05 mmol, 5.0 mol%) and 4-dimethylaminopyridine (2.0 mL, 50.0 mM in MeCN, 12.3 mg, 0.1 mmol, 10 mol%), followed by TEMPO (1.0 mL, 25.0 M in MeCN, 8.0 mg, 0.05 mmol, 5.0 mol%). The reaction mixture was stirred (600 rpm) at rt for 24 h under ambient atmosphere in an open flask. The conversion of **1a** was determined by GC analysis and is based on the ratio of product/(product + starting material).

Evaluation of the Performance of QA as a Quenching Agent (Figure 1B)

A 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with substrate **1a** (154 mg, 1.0 mmol), copper(I) iodide (2.0 mL, 25.0 mM in MeCN, 9.6 mg, 0.05 mmol, 5.0 mol%), 2,2′-bipyridine (7.9 mg, 0.05 mmol, 5.0 mol%) and 4-dimethylaminopyridine (2.0 mL, 50.0 mM in MeCN, 12.3 mg, 0.1 mmol, 10 mol%), followed by TEMPO (1.0 mL, 25.0 mM in MeCN, 8.0 mg, 0.05 mmol, 5.0 mol%). At the same time, a handheld stopwatch was started. The reaction mixture was stirred (600 rpm) at rt for 2 h under ambient atmosphere in an open flask. At regular time intervals, the reaction mixture (0.2 mL) was sampled by using a syringe and added to a solution of the scavenger **QA** (1 mL, 1 mg/mL) in dichloromethane. Sampling time was recorded at the moment of injection of the sample into the solution of the scavenger. The solutions obtained in this manner were analyzed by GC.

Evaluation of the Activity of Various Copper Catalytic Systems Utilizing QA (Figure S1)

A 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with substrate **1a** (154 mg, 1.0 mmol), copper(I) iodide (2.0 mL, 25.0 mM in MeCN, 9.6 mg, 0.05 mmol, 5.0 mol%), ligand (0.05 mmol, 5.0 mol%) and 4-dimethylaminopyridine (2.0 mL, 50.0 mM in MeCN, 12.3 mg, 0.1 mmol, 10 mol%), followed by TEMPO (1.0 mL, 25.0 mM in MeCN, 8.0 mg, 0.05 mmol, 5.0 mol%). At the same time, a handheld stopwatch was started. The reaction mixture was stirred (600 rpm) at rt for 2 h under ambient atmosphere in an open flask. At regular time intervals, the reaction mixture (0.2 mL) was sampled by using a syringe and added to a solution of the scavenger **QA** (1 mL, 1 mg/mL) in dichloromethane. Sampling time was recorded at the moment of injection of the sample into the solution of the scavenger. The solutions obtained in this manner were analyzed by GC.

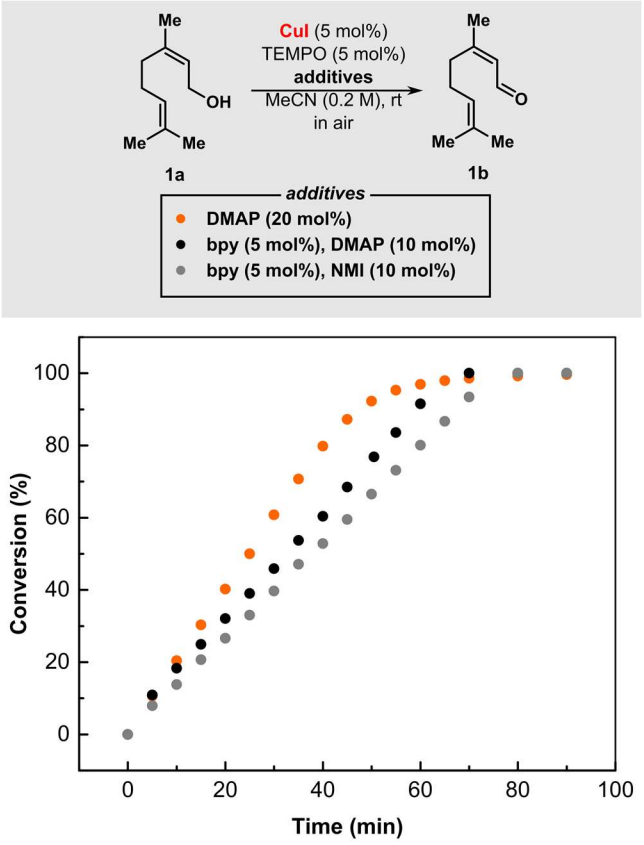


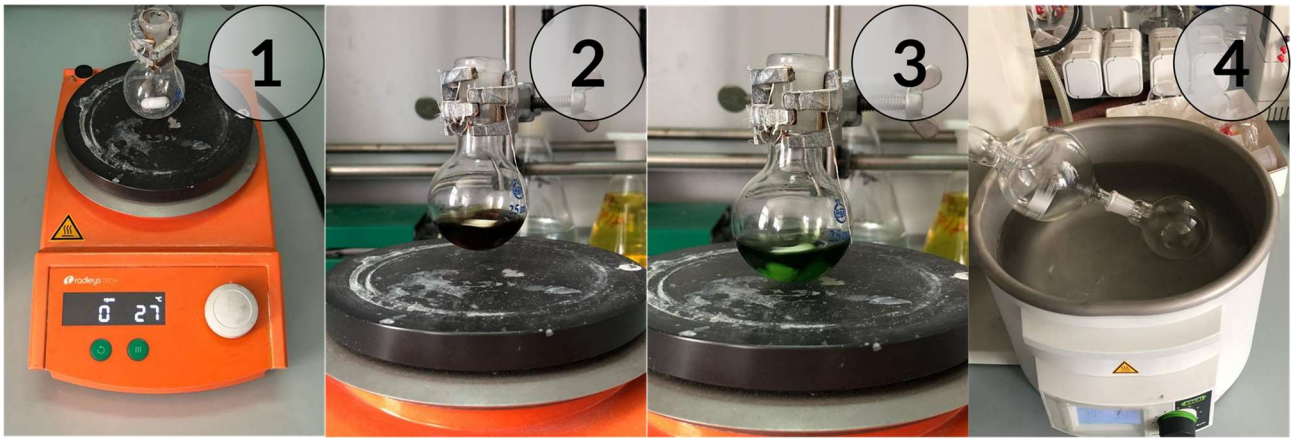
Figure S1. Evaluation of the activity of various copper catalytic systems utilizing **QA**, reaction conditions: **1a** (1 mmol), CuI (5 mol%), TEMPO (5 mol%), ligand (10 or 20 mol%), base (0 or 10 mol%), NMI = *N*-methylimidazole.

Removal of Cu Residues after Stahl Oxidation (Table 1)

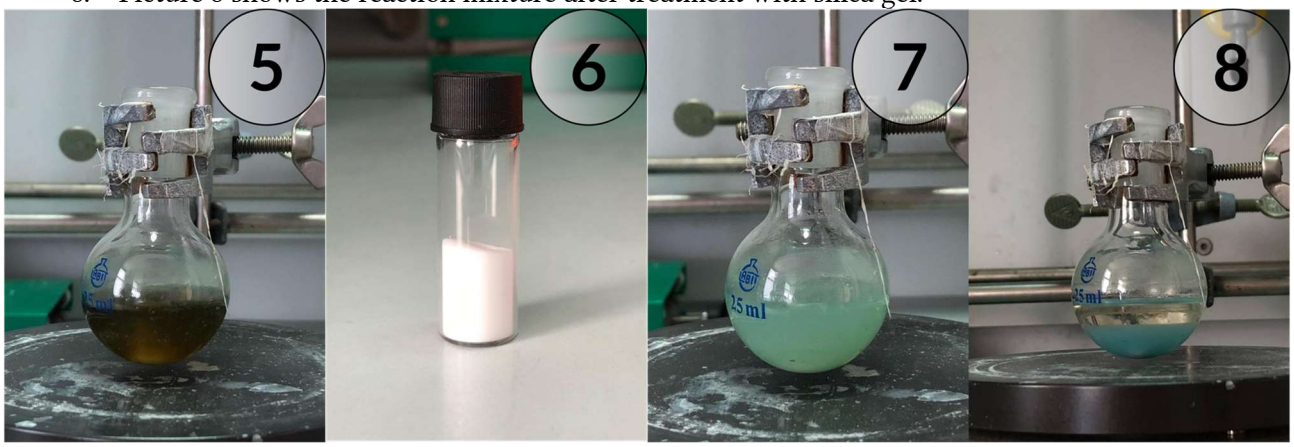
A 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with substrate (**1–6a)** (1.0 mmol), copper(I) iodide (2.0 mL, 25.0 mM in MeCN, 9.6 mg, 0.05 mmol, 5.0 mol%), 2,2′-bipyridine (7.9 mg, 0.05 mmol, 5.0 mol%) and 4-dimethylaminopyridine (2.0 mL, 50.0 mM in MeCN, 12.3 mg, 0.1 mmol, 10 mol%), followed by TEMPO (1.0 mL, 25.0 mM in MeCN, 8.0 mg, 0.05 mmol, 5.0 mol%). The reaction mixture was stirred (600 rpm) at rt for 2 h under ambient atmosphere in an open flask. Then MeCN was removed under reduced pressure. DCM (10 mL) was added. The stirrer was set to 600 rpm, silica gel (1.0 g, 100 mg of gel for every 0.005 mmol of the Cu-catalyst) was added and the resulting mixture was stirred for 30 min. Subsequently, scavenger **QA** (1.0 mL, 0.22 M in DCM, 48.4 mg, 0.22 mmol, 4.4 equiv with respect to the copper) was added and stirring continued for 30 min. Finally, the reaction mixture was filtered through a syringe filter (1–2 μm) into a 100 mL round-bottomed flask and the solvent was removed under reduced pressure to give crude **1–6b**.

Example experiment (Table 1)

1. A 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with substrate **1a** (156 mg, 1.0 mmol).
2. Copper(I) iodide (2.0 mL, 25.0 mM in MeCN, 9.6 mg, 0.05 mmol, 5.0 mol%), 2,2′-bipyridine (7.9 mg, 0.05 mmol, 5.0 mol%), 4-dimethylaminopyridine (2.0 mL, 50.0 mM in MeCN, 12.3 mg, 0.1 mmol, 10 mol%), and TEMPO (1.0 mL, 25.0 mM in MeCN, 8.0 mg, 0.05 mmol, 5.0 mol%) were added.
3. The reaction mixture was stirred (600 rpm) at rt for 2 h under ambient atmosphere. Picture 3 shows the reaction mixture after 2 h.
4. MeCN was removed under reduced pressure.

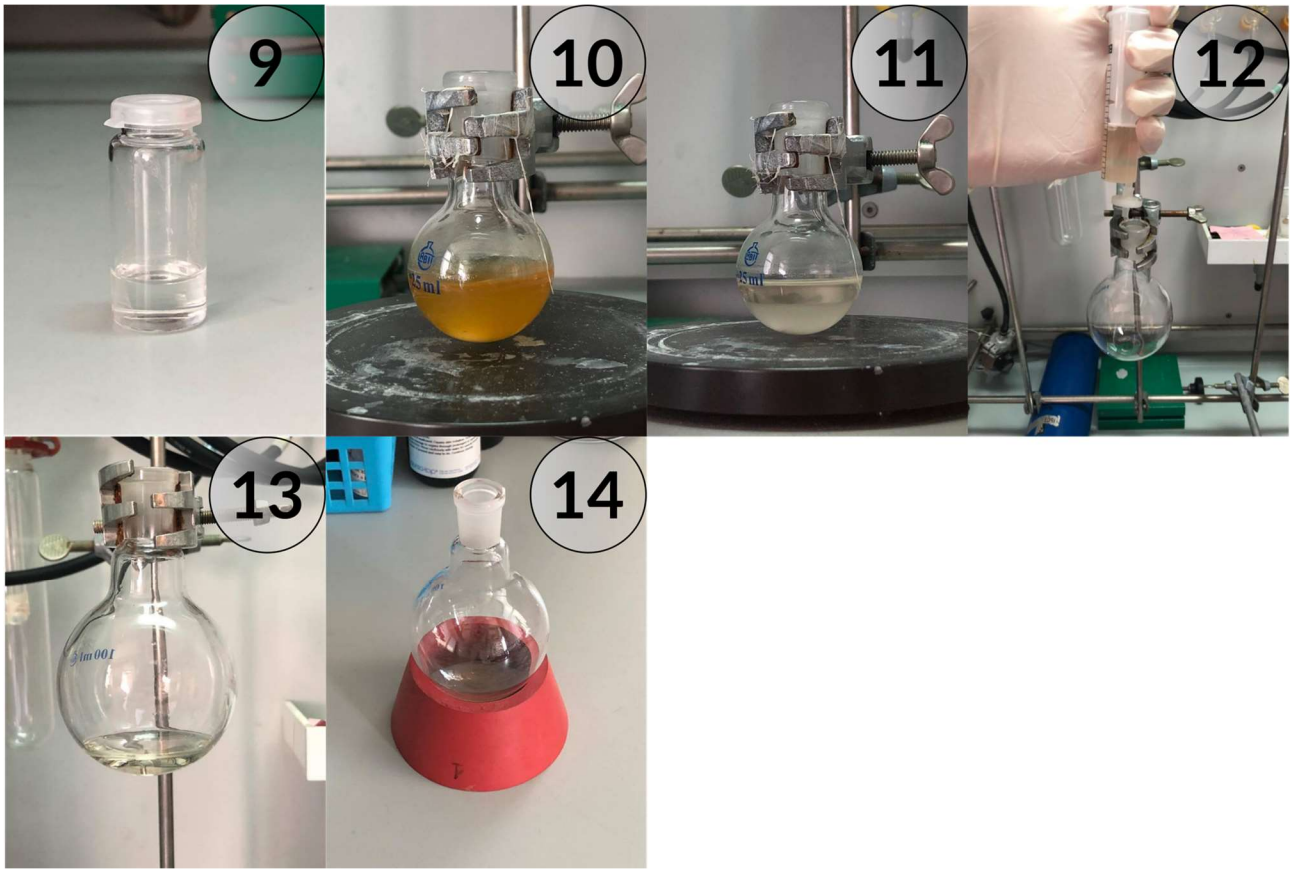


5. DCM (10 mL) was added.
6. Picture 6 shows the weighed silica gel (1.0 g)
7. The stirrer was set to 600 rpm, silica gel (1.0 g) was added and the resulting mixture was stirred for 30 min.
8. Picture 8 shows the reaction mixture after treatment with silica gel.



9. Picture 9 shows the solution of **QA** in DCM (0.22 M).
10. Scavenger **QA** (1.0 mL, 0.22 M in DCM, 48.4 mg, 0.22 mmol, 4.4 equiv with respect to the copper) was added and stirring continued for 30 min.

11. Picture 11 shows the reaction mixture after treatment with the scavenger.
12. The reaction mixture was filtered through a syringe filter into a 100 mL round-bottomed flask.
13. Picture 13 shows the reaction mixture after filtration.
14. The solvent was removed under reduced pressure to give crude 1b (99%,[a] 4.7 ppm Cu).

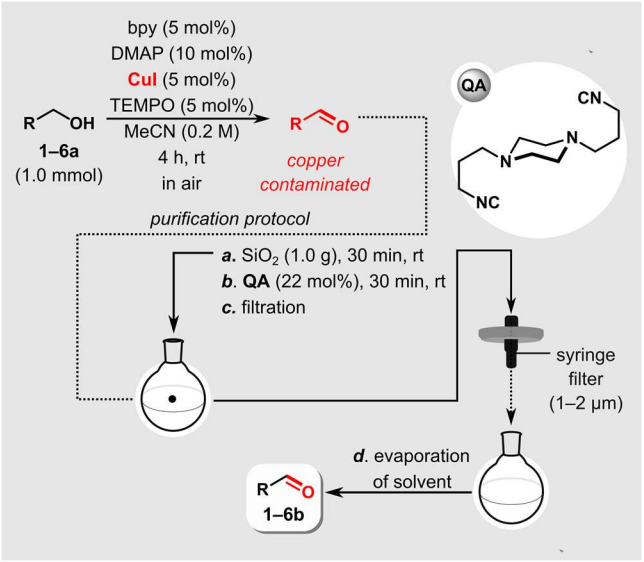


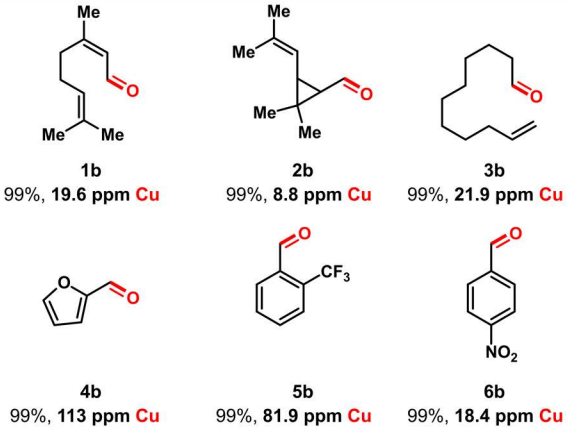
[a]Conversion was determined by GC analysis and is based on the ratio of product/(product + starting material)

Removal of Cu Residues after Stahl Oxidation without Evaporation of MeCN (Table 1S)

A 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with substrate (**1–6a)** (1.0 mmol), copper(I) iodide (2.0 mL, 25.0 mM in MeCN, 9.6 mg, 0.05 mmol, 5.0 mol%), 2,2′-bipyridine (7.9 mg, 0.05 mmol, 5.0 mol%) and 4-dimethylaminopyridine (2.0 mL, 50.0 mM in MeCN, 12.3 mg, 0.1 mmol, 10 mol%), followed by TEMPO (1.0 mL, 25.0 mM in MeCN, 8.0 mg, 0.05 mmol, 5.0 mol%). The reaction mixture was stirred (600 rpm) at rt for 4 h under ambient atmosphere in an open flask. Then the stirrer was set to 600 rpm, silica gel (1.0 g, 100 mg of gel for every 0.005 mmol of the Cu-catalyst) was added and the resulting mixture was stirred for 30 min. Subsequently, scavenger **QA** (5.0 mL, 0.044 M in THF, 48.4 mg, 0.22 mmol, 4.4 equiv with respect to the copper) was added and stirring continued for 30 min. Finally, the reaction mixture was filtered through a syringe filter (1–2 μm) into a 100 mL round-bottomed flask and the solvent was removed under reduced pressure to give crude **1–6b**.

Table S1. Removal of Cu Residues after Stahl Oxidation without Evaporation of MeCN





1b
99%, **19.6 ppm Cu**

2b
99%, **8.8 ppm Cu**

3b
99%, **21.9 ppm Cu**

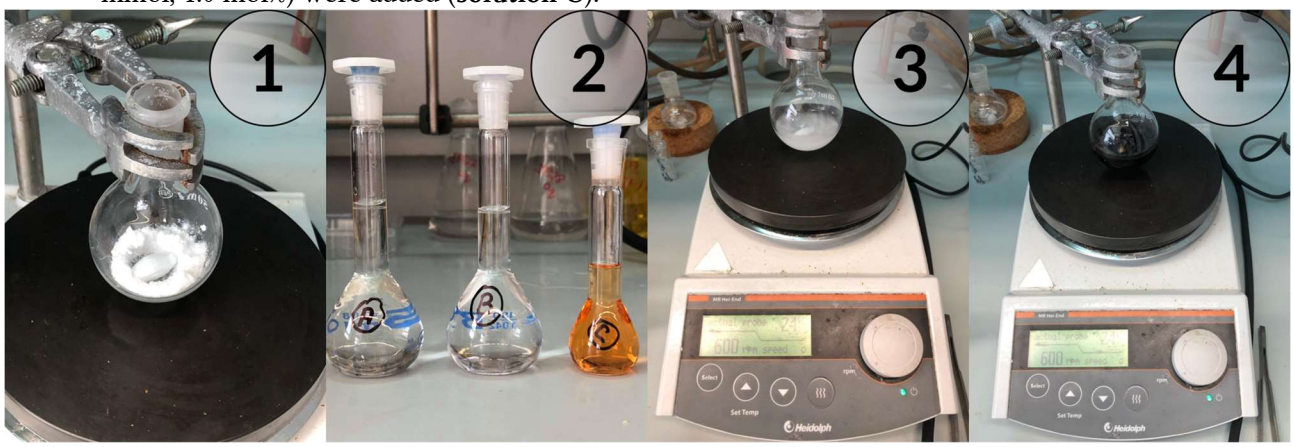
4b
99%, **113 ppm Cu**

5b
99%, **81.9 ppm Cu**

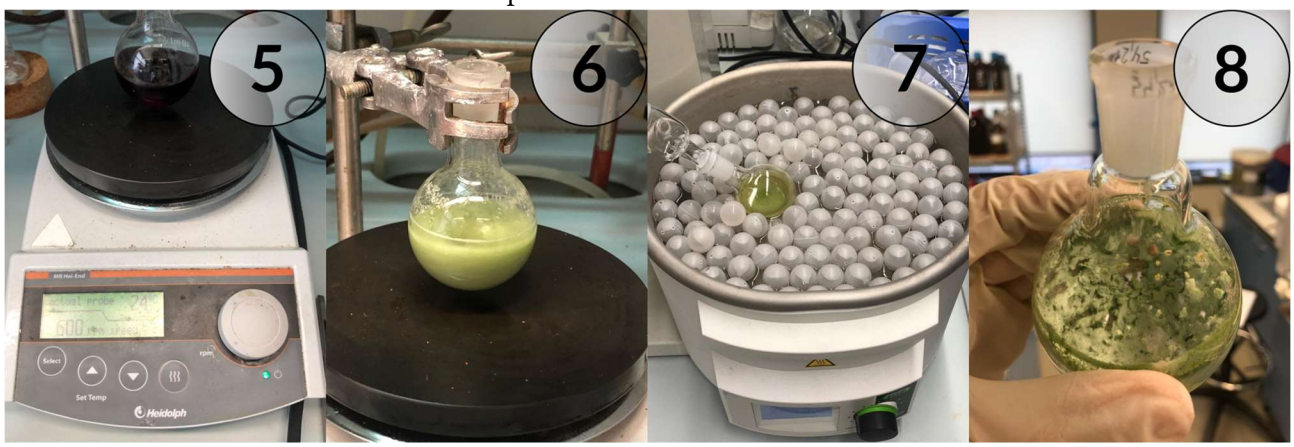
6b
99%, **18.4 ppm Cu**

Stahl Oxidation of the Rosuvastatin Precursor (7a) on a Gram Scale (Figure 2)

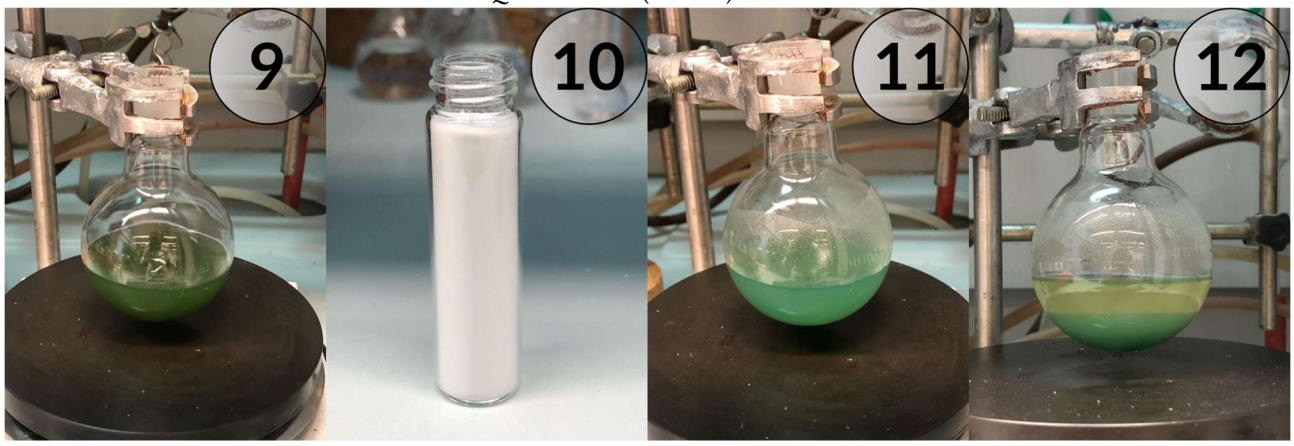
1. A 50 mL round-bottom flask equipped with a magnetic stir bar was charged with **7a** (1.41g, 4 mmol).
2. Solutions of the reagents in MeCN were prepared:
   - CuI (25.0 mM, 119.0 mg, 0.63 mmol) in 25 mL – **solution A**.
   - 2,2'-bipyridyne (25.0 mM, 97.6 mg, 0.625 mmol) and 4-dimethylaminopyridine (50.0 mM, 152.7 mg, 1.25 mmol) in 25 mL – **solution B**.
   - ABNO (10 mM, 7.0 mg, 0.05 mmol) in 5 mL – **solution C**.
3. Copper(I) iodide (8.0 mL, 25.0 mM in MeCN, 38.1 mg mg, 0.2 mmol, 5.0 mol%) was added (**solution A**).
4. 2,2'-bipyridyne (31.2 mg mg, 0.2 mmol, 5.0 mol%), 4-dimethylaminopyridine (48.9 mg, 0.2 mmol, 10 mol%) dissolved in 8 mL MeCN (**solution B**), and ABNO (4.0 mL, 10 mM in MeCN, 5.6 mg, 0.04 mmol, 1.0 mol%) were added (**solution C**).



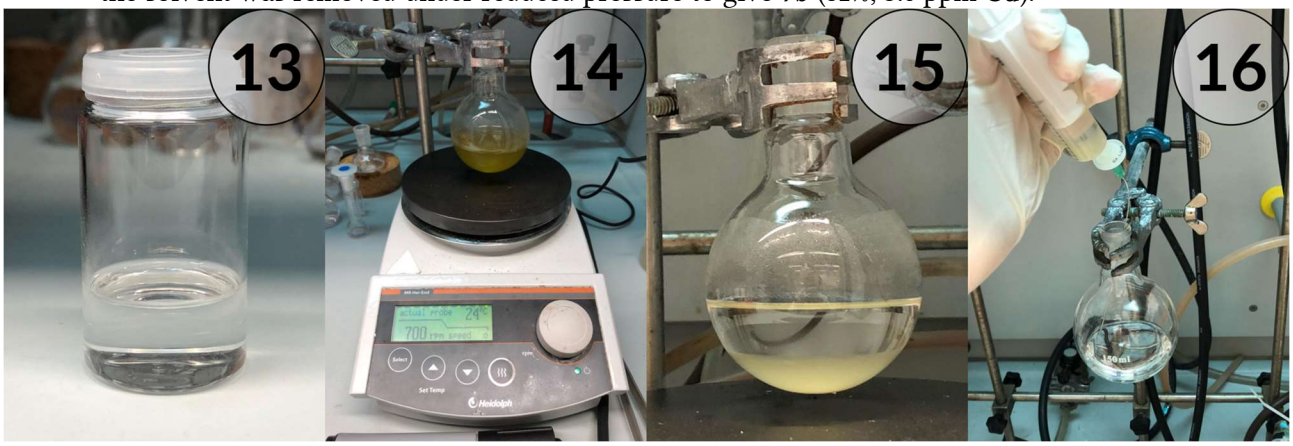
5. The reaction mixture was stirred (600 rpm) at rt for 2 h under ambient atmosphere.
6. Picture 6 shows the the reaction mixture after 2 h.
7. MeCN was removed under reduced pressure.
8. Picture 8 shows the flask after evaporation of MeCN.



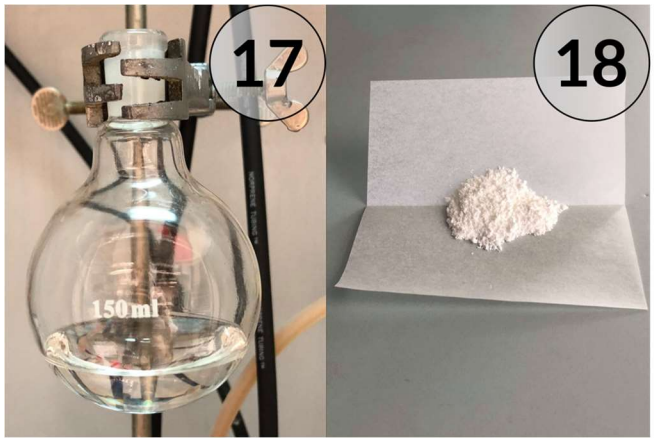
9. DCM (40 mL) was added.
10. Picture 10 shows the weighed silica gel (4.0 g).
11. The stirrer was set to 600 rpm, silica gel (4.0 g) was added and the resulting mixture was stirred for 30 min.
12. Picture 12 shows the reaction mixture after treatment with silica gel.
13. Picture 13 shows the solution of **QA** in DCM (0.22 M).



14. Scavenger **QA** (4.0 mL, 0.22 M in DCM, 194.0 mg, 0.88 mmol, 4.4 equiv with respect to the copper) was added and the resulting mixture was stirred for 30 min.
15. Picture 15 shows the reaction mixture after treatment with the scavenger.
16. The reaction mixture was filtered through a syringe filter into a 150 mL round-bottomed flask and the solvent was removed under reduced pressure to give **7b** (82%, 3.6 ppm **Cu**).

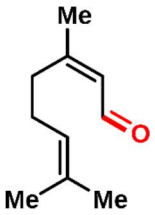


17. Picture 17 shows the reaction mixture after filtration.
18. Picture 18 shows the isolated product.



NMR Spectra of Stahl Oxidation Products

3,7-Dimethylocta-2,6-dienal (1b) mixture of isomers *E*/*Z* (1:9)

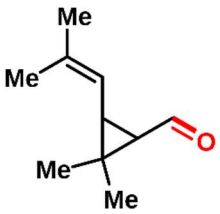


^{1}H NMR (400 MHz, $CDCl_3$):): δ 9.98 (d, J = 8.1 Hz, 1H, *E* isomer), 9.88 (d, J = 8.3 Hz, 1H, *Z* isomer), 5.89 – 5.84 (m, 1H), 5.12 – 5.02 (m, 1H), 2.57 (t, J = 7.5 Hz, 1H), 2.26 – 2.17 (q, J = 7.5 Hz, 2H), 1.95 (d, J = 1.3 Hz, 2H), 1.67 (s, 3H), 1.61 – 1.57 (m, 3H, *E* + *Z* isomer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 191.4 (*E* isomer), 190.9 (*Z* isomer), 164.0, 164.0, 133.7, 132.9, 128.6, 127.4, 122.5, 122.2,40.6, 32.6, 27.0, 25.7, 25.7, 25.7, 25.1, 17.7, 17.6.

Spectral data are in agreement with those reported in the literature.[2]

2,2-Dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carbaldehyde (2b)



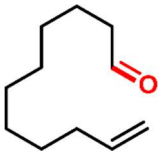
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (d, J = 5.4 Hz, 1H), 4.91 (d, J = 8.0 Hz, 1H), 4.91 (dd, J = 7.9 Hz, 5.1 Hz,1H), 1.72 (s, 3H), 1.70 (s, 3H), 1.63-1.59 (t, J = 5.2 Hz, 1H), 1.33 (s, 3H), 1.17 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.0, 136.2, 120.2, 45.1, 34.65, 31.5, 25.6, 22.2, 21.7, 18.5.

Spectral data are in agreement with those reported in the literature.[3]

[2] Han, L.; Xing, P.; Jiang, B; Selective Aerobic Oxidation of Alcohols to Aldehydes, Carboxylic Acids, and Imines Catalyzed by a Ag-NHC Complex. *Org. Lett.* **2014**, *16*, 3428–3431.
[3] Moore, P. W.; Read, C. D.; Bernhardt, P. V.; Williams, C. M. ATP3 and MTP3: Easily Prepared Stable Perruthenate Salts for Oxidation Applications in Synthesis. *Chem. Eur. J.*, **2018**, *24*, 4556–4561.

Undecenal (3b)

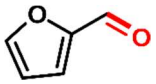


^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (t, J = 1.9 Hz, 1H), 5.87 – 5.75 (m, 2H), 5.03 – 4.91 (m, 2H), 2.42 (td, J = 7.3, 1.9Hz, 2H), 2.04 (q, J = 7.1 Hz, 2H), 1.67-1.58 (m, 2H), 1.41-1.25 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.0, 139.2, 114.2, 43.9, 33.8, 29.3, 29.3, 29.1, 29.0, 28.9, 22.1.

Spectral data are in agreement with those reported in the literature.[4]

Furfural (4b)

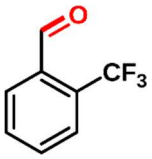


^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 7.70 (s, 1H), 7.26 (d, J = 3.2 Hz, 1H), 6.61 (dd, J = 3.5, 1.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.0, 153.0, 148.2, 121.1, 112.6.

Spectral data are in agreement with those reported in the literature.[5]

2-(Trifluoromethyl)benzaldehyde (5b)



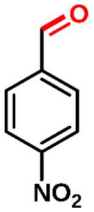
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.41 (q, J = 2.1 Hz, 1H), 8.17 – 8.12 (m, 1H), 7.83 – 7.77 (m, 1H), 7.75 – 7.70 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.1, 133.7, 132.4, 129.1, 126.1 (q, J_{C-F} = 5.8 Hz), 125.1, 122.3.

Spectral data are in agreement with those reported in the literature.[6]

[4] Xiao, P.; Tang, Z.; Wang, K.; Chen, H.; Guo, Q.; Chu, Y.; Gaoa, L.; Song, Z. Chemoselective Reduction of Sterically Demanding *N,N*-diisopropylamides to Aldehydes. *J. Org. Chem.*, **2018**, *83*, 1687–1700.
[5] Cheng, C.; Brookhart, M. Efficient Reduction of Esters to Aldehydes Through Iridium-Catalyzed Hydrosilylation. *Angew. Chem. Int. Ed.*, **2012**, *51*, 9422–9424.
[6] Liu, D.; Zhou, H.; Gu, X.; Shen, X.; Li, P. TEMPO-Mediated Oxidation of Primary Alcohols to Aldehydes Under Visible Light and Air. *Chin. J. Chem.* **2014**, *32*, 117–122.

4-Nitrobenzaldehyde (6b)

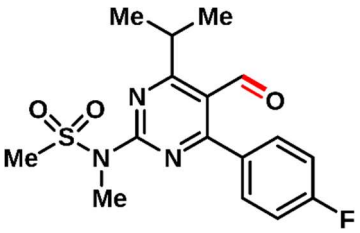


^{1}H NMR (400 MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.40 (d, J = 8.7 Hz, 2H), 8.08 (d, J = 8.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 190.3, 151.1, 140.0, 130.5, 124.3.

Spectral data are in agreement with those reported in the literature.[7]

***N*-(4-(4-Fluorophenyl)-5-formyl-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (7b)**



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.65 – 7.59 (m, 2H), 7.25 – s7.18 (m, 2H), 4.00 (hept, J = 6.7 Hz, 1H), 3.63 (s, 3H), 3.54 (s, 3H), 1.31 (d, J = 6.8 Hz 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 190.5, 179.1, 169.8, 164.5 (J_{C-F} = 252.6 Hz), 158.8, 132.7 (J_{C-F} = 8.8 Hz), 132.1 (J_{C-F} = 3.4 Hz), 119.5, 116.0 (J_{C-F} = 22.0 Hz), 42.5, 33.1, 32.0, 21.7.

Spectral data are in agreement with those reported in the literature.[8]

[7] Yu, B.; Zhao, Y.; Zhang, H.; Xu, J.; Hao,; Gao, X.; Liu, Z. Pd/C-Catalyzed Direct Formylation of Aromatic Iodides to Aryl Aldehydes Using Carbon Dioxide as a C1 Resource. *Chem. Commun.*, **2014**, *50*, 2330–2333.
[8] Steves, J. E.; Preger, Y.; Martinelli, J. R.; Welch, C. J.; Root, T. W.; Hawkins, J. M.; Stahl, S. S. Process Development of CuI/ABNO/NMI-Catalyzed Aerobic Alcohol Oxidation. *Org. Process Res. Dev.*, **2015**, *19*, 1548–1553.

QA Reactivity Towards $[Cu^{II}(TPMA)Br]^+$ (Figures 3)

A stock solution of $Cu^{II}Br_2$ (2.5 mM) and **TPMA** (2.5 mM) in DMSO was prepared in a 20 mL vial under an ambient atmosphere. 3.0 mL of $[Cu^{II}Br_2]$/[TPMA] stock solution was transferred to the cuvette. The UV-vis spectrum was recorded.[9] Subsequently, **QA** (6.6 mg, 0.03 mmol, 4 equiv with respect to $[Cu^{II}(TPMA)Br]^+$) was added. The UV-vis spectrum was recorded. Ascorbic acid (13.2 mg, 0.075 mmol, 10 equiv respect to $[Cu^{II}(TPMA)Br]^+$) was added followed by recording the UV-vis spectrum.

[9] The concentration of $[Cu^{II}(TPMA)Br]^+$ was monitored by following the absorption at 967 nm.

QA Reactivity Towards [Cu^{II}(Me$_6$TREN)Br]$^+$ (Figure S2)

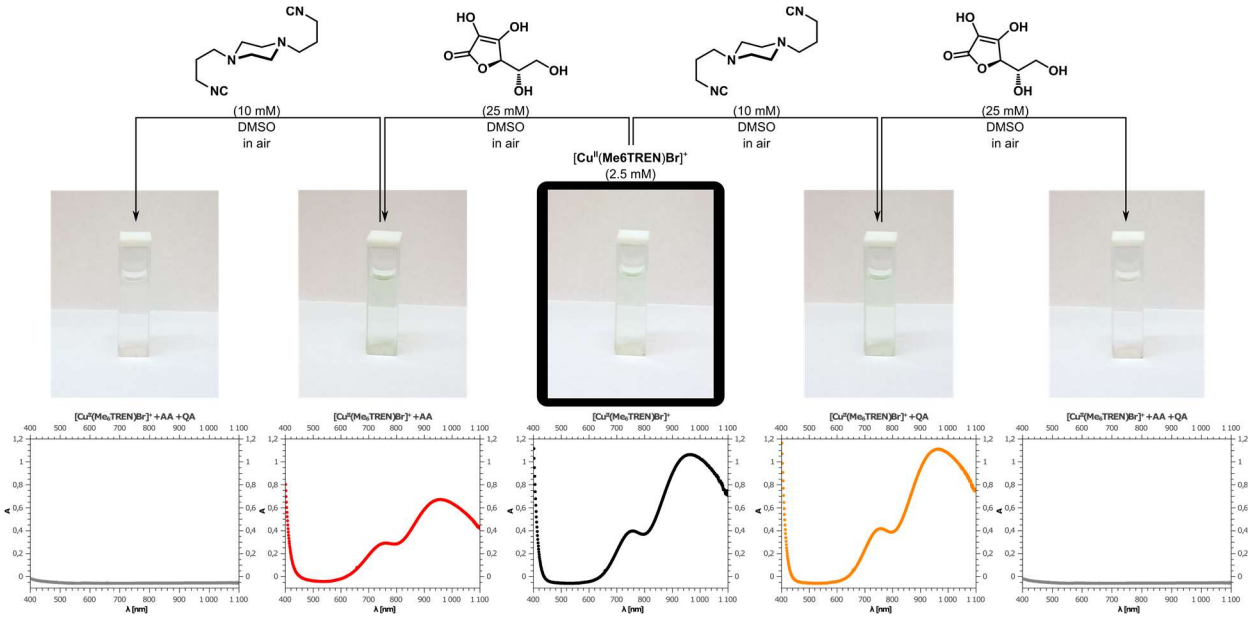


Figure S1. QA reactivity towards [Cu^{II}(Me$_6$TREN)Br]$^+$. UV–vis spectra of [Cu^{II}Br$_2$] = 2.5 mM; [Me$_6$TREN] = 2.5 mM; [AA] = 25 mM; [QA] = 10.0 mM in 3.0 mL DMSO at 22 °C in air.

QA Reactivity Towards [Cu^{II}(PMDETA)Br]$^+$ (Figure S3)

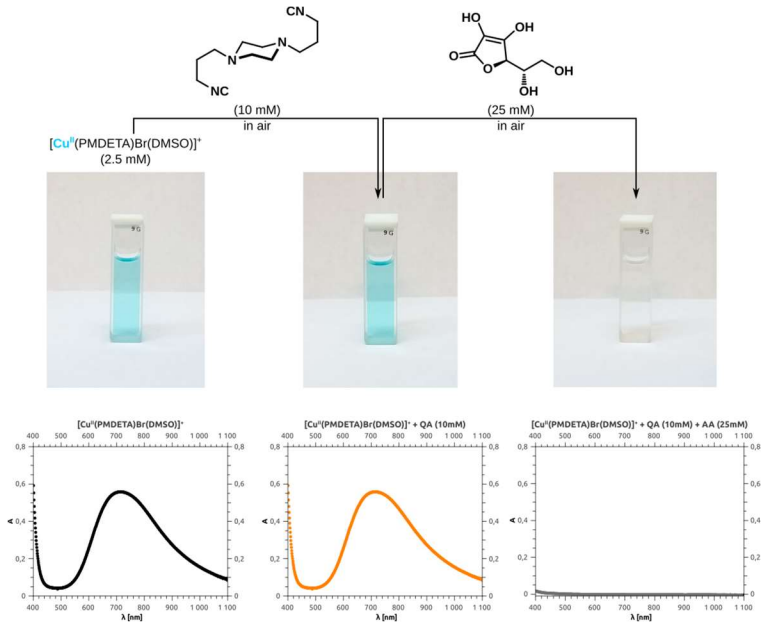


Figure 3. QA reactivity towards [Cu^{II}(PMDETA)Br]$^+$. UV–vis spectra of [Cu^{II}Br$_2$]$_0$ = 2.5 mM; [PMDETA]$_0$ = 2.5 mM; [AA]$_0$ = 25 mM; [QA]$_0$ = 10.0 mM in 3.0 mL DMSO at 22 °C in air.

AA Reactivity Towards $[Cu^{II}(TPMA)Br]^+$ (Figures S4)

A stock solution of $Cu^{II}Br_2$ (2.5 mM) and **TPMA** (2.5 mM) in DMSO was prepared in a 20 mL vial under an ambient atmosphere. 3.0 mL of $[Cu^{II}Br_2]$/[TPMA] stock solution was transferred to the cuvette. The UV-vis spectrum was recorded.[10] Subsequently, ascorbic acid (13.2 mg, 0.075 mmol, 10 equiv with respect to $[Cu^{II}(TPMA)Br]^+$) was added. The UV-vis spectrum was recorded. Then, **QA** (6.6 mg, 0.03 mmol, 4 equiv with respect to $[Cu^{II}(TPMA)Br]^+$) was added followed by recording the UV-vis spectrum.

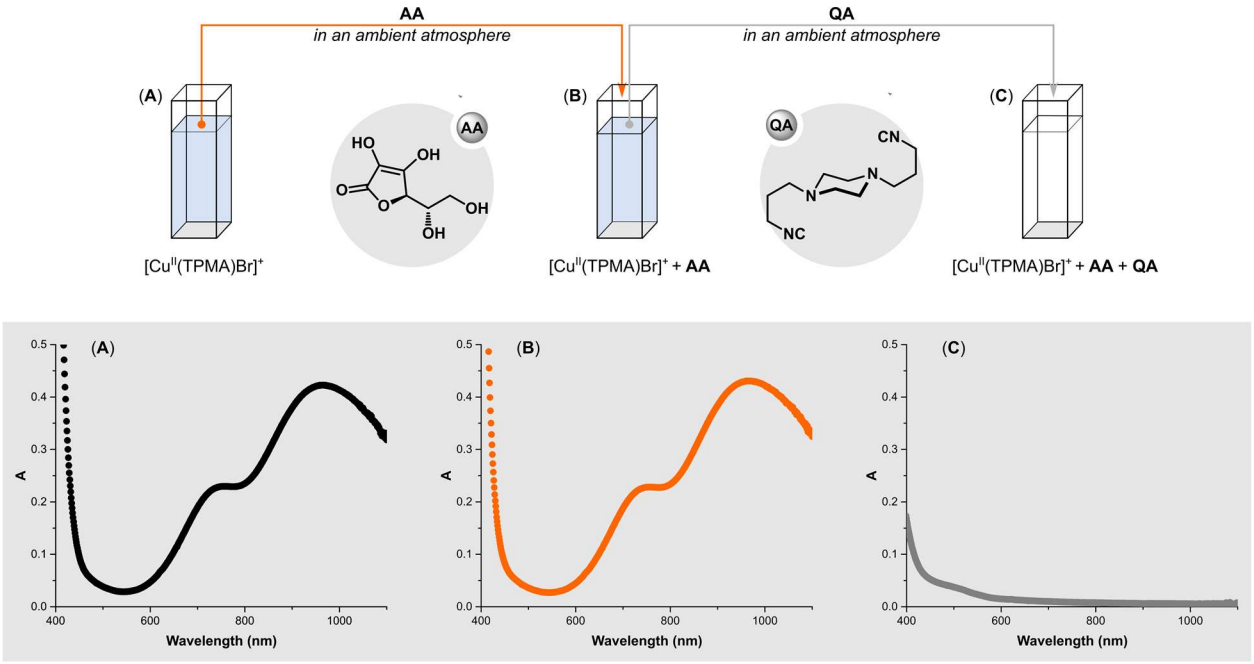


Figure S4. **AA** reactivity towards the $[Cu^{II}(TPMA)Br]^+$. (A) UV–Vis spectra of $[Cu^{II}Br_2]$ = 2.5 mM; [TPMA] = 2.5 mM in DMSO at 22 °C in air. (B) UV–Vis spectra of copper complex after additon of **AA** (4 equiv). (C) UV–vis spectra of copper complex after additon of **AA** (4 equiv) and **QA** (10 equiv).

[10] The concentration of $[Cu^{II}(TPMA)Br]^+$ was monitored by following the absorption at 967 nm.

Comproportionation of [Cu^{II}(TPMA)Br]$^+$ in the Presence of QA and Cu(0) Wire (Figures 4 and S5)

A stock solution of $Cu^{II}Br_2$ (2.5 mM), **TPMA** (5.25 mM) and **QA** (10.0 mM) in deoxygenated DMSO was prepared in the Schlenk flask (**1**) under an atmosphere of nitrogen gas. In the Schlenk flask (**2**) capped with an air-tight UV-Vis cuvette (path length = 1 cm) a stir bar was placed together with 4 cm Cu(0) wire (d =1 mm, S = 1.27 cm^2) which was pre-treated in a solution of HCl/MeOH = 1/2 for 5 minutes. This flask was placed under vacuum and purged with nitrogen gas five times. 4.5 mL of [$Cu^{II}Br_2$]/[TPMA]/[QA] stock solution was transferred to the Schlenk flask (**2**) by a nitrogen-purged syringe. The reaction mixture was magnetically stirred at 22 °C, and spectra were collected at specific time intervals (Figure 5). The decrease in the concentration of [Cu^{II}(TPMA)Br]$^+$ was monitored by following the absorption at 967 nm. After 18 hours, the reaction mixture was exposed to air and filtered through a syringe filter (0.2 μm). The spectrum was recorded after filtration (Figure S5A) and after 19 h of exposure to air (Figure S5B).

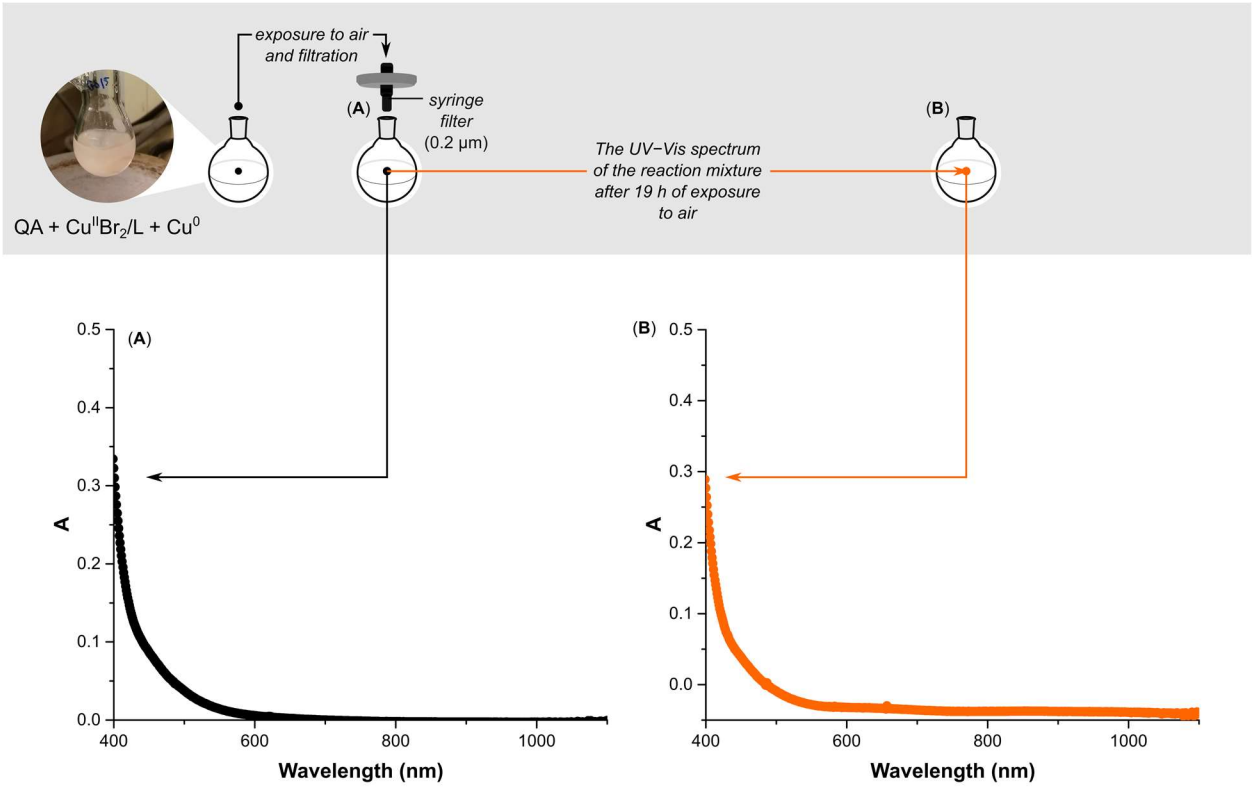


Figure S5. (A) UV–vis spectrum of the reaction mixture filtered through a syringe filter after 18 h. (B) UV-vis spectrum recorded after 19 h of exposure of the mixture to air. Initial conditions [$Cu^{II}Br_2$] = 2.5 mM; [TPMA] = 5.25 mM; [QA] = 10 mM; 4 cm Cu(0) wire (d =1 mm, S = 1.27 cm^2); in DMSO at 22 °C.

Comproportionation of $[Cu^{II}(TPMA)Br]^+$ in the Presence of Cu(0) Wire (Figure S6)

A stock solution of $Cu^{II}Br_2$ (2.5 mM) and **TPMA** (5.25 mM) in deoxygenated DMSO was prepared in the Schlenk flask (**1**) under an atmosphere of nitrogen gas. In the Schlenk flask (**2**) capped with an air-tight UV-Vis cuvette (path length = 1 cm) a stir bar was placed together with 4 cm Cu(0) wire (d =1 mm, S = 1.27 cm2) which was pre-treated in a solution of HCl/MeOH = 1/2 for 5 minutes. This flask was placed under vacuum and purged with nitrogen gas five times. 4.5 mL of $[Cu^{II}Br_2]$/[TPMA] stock solution was transferred to the Schlenk flask (**2**) by a nitrogen-purged syringe. The reaction mixture was magnetically stirred at 22 °C, and spectra were collected at specific time intervals (Figure 3SA). The decrease in the concentration of $[Cu^{II}(TPMA)Br]^+$ was monitored by following the absorption at 967 nm. After 18 hours, the reaction mixture was exposed to air, and spectra were collected at specific time intervals (Figure 3SB).

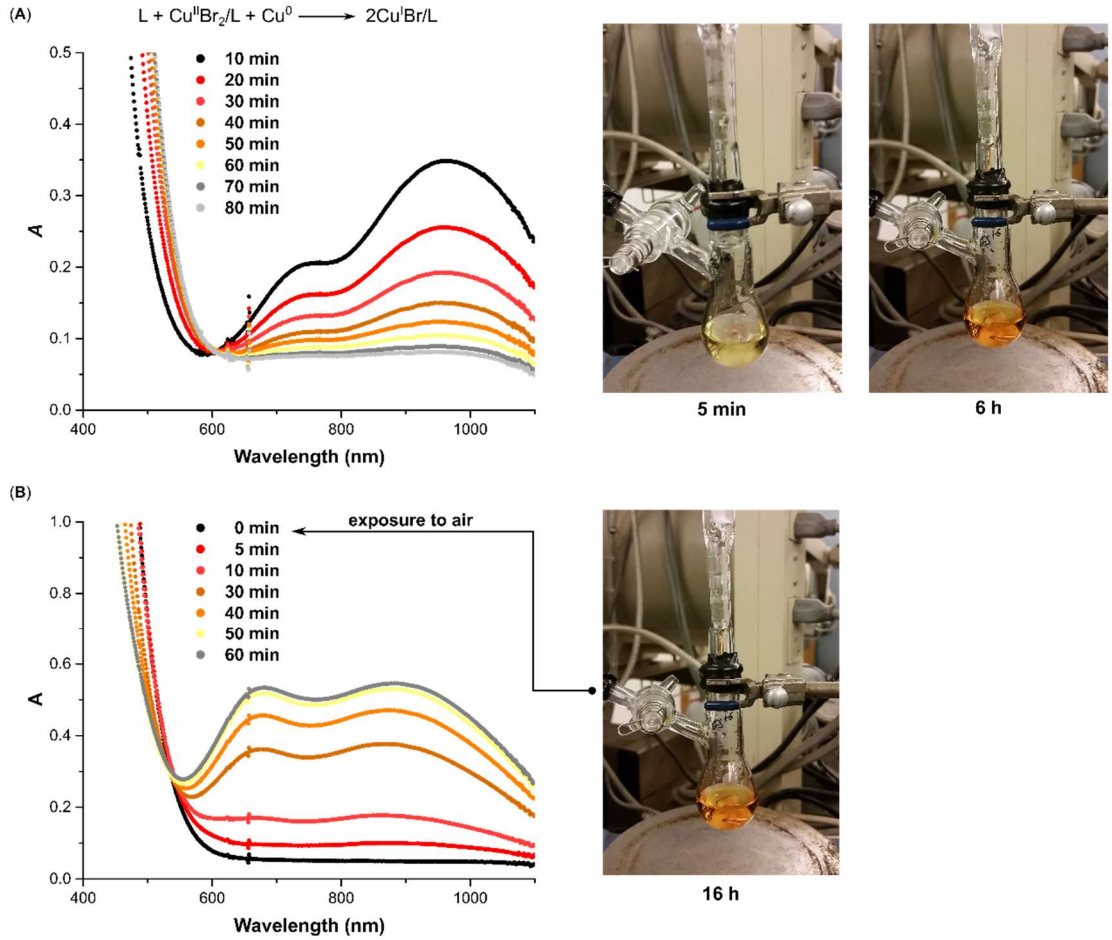


Figure 3S. Comproportionation of $[Cu^{II}Br_2]$ = 2.5 mM with [TPMA] = 5.25 mM in the presence of 4 cm Cu(0) wire (*d* =1 mm, *S* = 1.27 cm^2); in 4.5 mL DMSO at 22 °C (A), UV–vis spectra of the reaction mixture exposure to air (B).

Electrochemical Studies of QA

CV of $[Cu^{II}(TPMA)Br]^+$ in the absence and in the presence of QA (Figure 5 and S7)

In a typical CV experiment, Et_4NBF_4 (325.0 mg, 1.5 mmol) was put into the electrochemical cell together with a stir bar and anhydrous DMSO (15 mL), under N_2 flow. A CV was first recorded to verify the absence of oxygen and impurities. Then, $Cu^{II}Br_2$ (6.7 mg, 0.03 mmol), **TPMA** (9.0 mg, 0.031 mmol), and increasing amounts of **QA** were added in solution. A CV was recorded after each new addition.

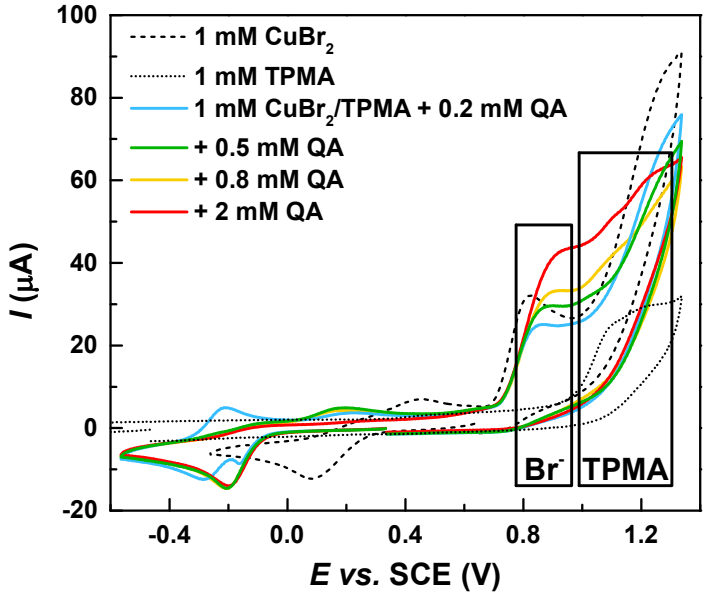


Figure S7. Cyclic voltammetry of 1 mM $[Cu^{II}(TPMA)Br]^+$ in DMSO + 0.1 M Et_4NBF_4, in the absence and presence of **QA**. Scan rate = 0.2 V s^{-1}, T = 25 °C. CVs of 1 mM $CuBr_2$ (dashed line) and TPMA (dotted line) in a similar system are also reported for comparison.

Chronoamperometry Experiments (Figure 6 and S8)

In a typical chronoamperometry experiment, Et_4NBF_4 (325.0 mg, 1.5 mmol) was put into the electrochemical cell together with a stir bar, anhydrous DMSO (15 mL), and **TPMA** (4.5 mg, 0.016 mmol) under N_2 flow. A CV was first recorded to verify the absence of oxygen and impurities. The RDE rotation was set at 4000 rpm, while a constant potential, E_{app}, was applied, and the resulting current was recorded. E_{app} values were selected such as to follow $[Cu^{I}(TPMA)]^{+}$ oxidation under mass transfer control in a potential range where no other processes occurred. The selected E_{app} value was 0.29 V vs. SCE. $Cu^{I}(OTf)$ (0.015 mmol) was withdrawn with a syringe from a stock solution, under inert atmosphere, and injected into the cell. The **QA** (0.064 mmol, 4 equiv) was withdrawn with a syringe from a stock solution, under inert atmosphere, and injected into the cell a few seconds after Cu^{I}.

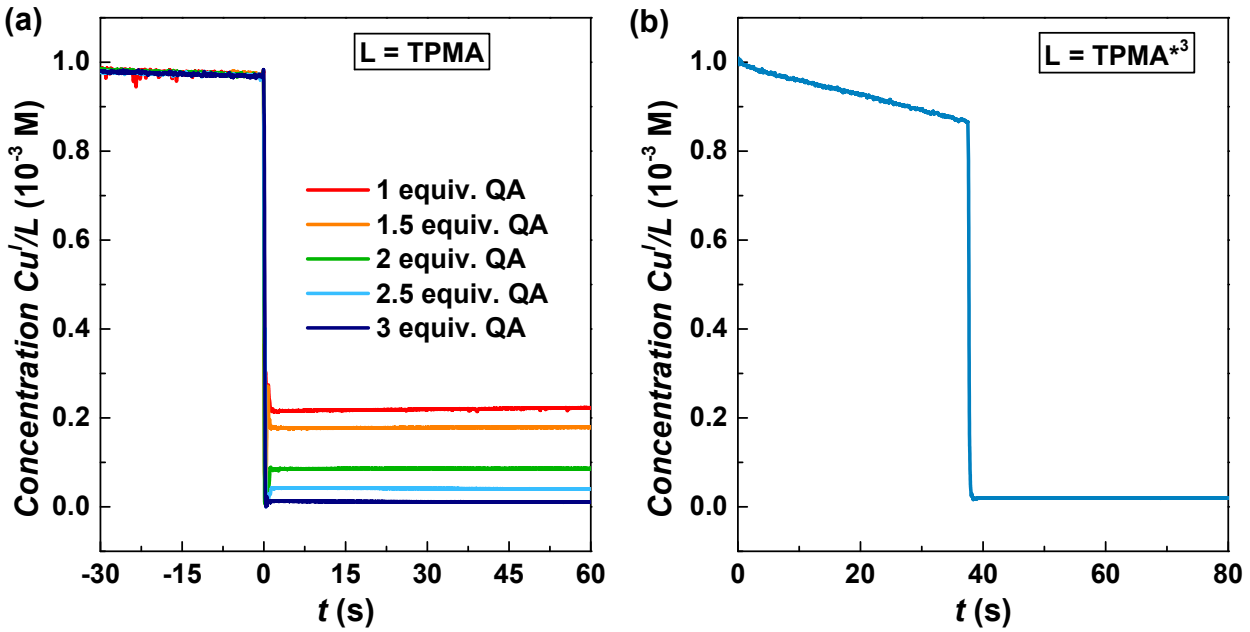


Figure S8. Variation of Cu^{I}/L concentration with the addition of **QA**, measured by chronoamperometry on a RDE (ω = 4000 rpm), in DMSO + 0.1 M Et_4NBF_4, T = 25 °C. 10^{-3} Cu^{I}/TPMA + 1-3 equiv of **QA** (the instant of **QA** injection was set as t = 0 for easier comparison) (A). Cu^{I}/TPMA*3 + 3 equiv of **QA** (B).

Quenching of SARA ATRP by QA (Figure 7)

In the Schlenk flask (**1**) a stir bar was placed together with 4 cm Cu(0) wire (d =1 mm, S = 1.27 cm^2) which was pre-treated in a solution of HCl/MeOH = 1/2 for 5 min. This flask was placed under vacuum and backfilled with nitrogen gas five times. The **MA** and DMSO were degassed separately for 40 min in 20 mL vials sealed with a rubber septum. The Schlenk flask (**2**) was charged with $Cu^{II}Br_2$ (4.9 mg, 0.022 mmol), **TPMA** (38.4 mg, 0.132 mmol), and was subjected to vacuum and backfilled with nitrogen gas five times. Deoxygenated DMSO (10 mL) was added via a nitrogen-purged syringe into the Schlenk flask (**2**). A stock solution of [$Cu^{II}Br_2$]/[TPMA] (1.5 mL, [$Cu^{II}Br_2$] = 2.2 mM, [TPMA] = 13.2 mM, dissolved in DMSO), deoxygenated **MA** (3.0 mL, 33.1 mmol), and **MBP** (18 μL, 0.166 mmol) were added using nitrogen-purged syringes into the Schlenk flask (**1**). The reaction mixture was stirred at 22 °C for 2 h. Samples were taken at various time intervals to monitor by ^{1}H NMR the decrease in [MA] *vs.* time.

Temporal control in ARGET ATRP using QA (Figure 8)[11]

A vial (8 mL) equipped with a magnetic stir bar was sealed with a rubber septum and deoxygenated by inert gas sparging for 5 min. A solution of **EBiB** (3.0 mL, 55.5 mM in **MA**, 32.5 mg, 0.167 mmol), $Cu^{II}Br_2$/Me_6TREN (0.5 mL, [$Cu^{II}Br_2$] = 16.6 mM, [Me_6TREN] = 50.0 mM, dissolved in DMSO), **AA** (1.0 mL, 41.6 mM in DMSO, 7.3 mg, 0.041 mmol) were added using syringes into the vial. The reaction mixture was stirred at 22 °C.

***Switch off* ATRP**. A solution of **QA** (0.2 mL, 166.6 mM in DMSO, 7.3 mg, 0.033 mmol) was added to polymerization solution. The sample was taken for ^{1}H NMR and SEC analyses.

***Switch on* ATRP**. A solution of $Cu^{II}Br_2$/Me_6TREN (0.2 mL, [$Cu^{II}Br_2$] = 41.6 mM, [Me6TREN] = 41.6 mM, dissolved in DMSO) was added to polymerization solution. The sample was taken for ^{1}H NMR and SEC analyses.

[11] ARGET ATRP in the presence of limited amounts of air (without degassing of DMSO and MA).

Removal of Cu Residues after ATRP (Table 2)

ARGET ATRP under anaerobic conditions

In a typical experiment, the Schlenk flask (**1**) equipped with a magnetic stir bar was charged with ascorbic acid (7.3 mg, 0.041 mmol, 0.25 equiv) and subjected to vacuum and backfilled with nitrogen gas five times. The monomer and MeCN were degassed separately for 40 min in 20 mL vials sealed with a rubber septum. The Schlenk flask (**2**) was charged with $Cu^{II}Br_2$ (12.3 mg, 0.055 mmol), **Me_6TREN** (63.6 mg, 0.28 mmol), and was subjected to vacuum and backfilled with nitrogen gas five times. Deoxygenated MeCN (10 mL) was added via a nitrogen-purged syringe into the Schlenk flask (**2**). A stock solution of [$Cu^{II}Br_2$]/[Me_6TREN] (1.5 mL, [$Cu^{II}Br_2$] = 5.5 mM, [Me_6TREN] = 28.0 mM, dissolved in MeCN), deoxygenated **MA** (3.0 mL, 33.1 mmol), and **EBiB** (24 μL, 0.166 mmol) were added using nitrogen-purged syringes into the Schlenk flask (**1**) placed in a water bath. The reaction mixture was stirred at 22 °C for 3 h.

SARA ATRP under anaerobic conditions

In the Schlenk flask (**1**) a stir bar was placed together with 4 cm Cu(0) wire (d =1 mm, S = 1.27 cm^2) which was pre-treated in a solution of HCl/MeOH = 1/2 for 5 min. This flask was placed under vacuum and backfilled with nitrogen gas five times. The **MA** and MeCN were degassed separately for 40 min in 20 mL vials sealed with a rubber septum. The Schlenk flask (**2**) was charged with $Cu^{II}Br_2$ (12.3 mg, 0.055 mmol), **Me_6TREN** (63.6 mg, 0.28 mmol), and was subjected to vacuum and backfilled with nitrogen gas five times. Deoxygenated MeCN (10 mL) was added via a nitrogen-purged syringe into the Schlenk flask (**2**). A stock solution of [$Cu^{II}Br_2$]/[Me_6TREN] (1.5 mL, [$Cu^{II}Br_2$] = 5.5 mM, [Me_6TREN] = 28.0 mM, dissolved in MeCN), deoxygenated **MA** (3.0 mL, 33.1 mmol), and **EBiB** (24 μL, 0.166 mmol) were added using nitrogen-purged syringes into the Schlenk flask (**1**) placed in a water bath. The reaction mixture was stirred at 22 °C for 3 h.

*p*ATRP under anaerobic conditions

The Schlenk flask (**1**) equipped with a magnetic stir bar was subjected to vacuum and backfilled with nitrogen gas five times. The **MA** and MeCN were degassed separately for 40 min in 20 mL vials sealed with a rubber septum. The Schlenk flask (**2**) was charged with $Cu^{II}Br_2$ (12.3 mg, 0.055 mmol), **Me_6TREN** (63.6 mg, 0.28 mmol), and was subjected to vacuum and backfilled with nitrogen gas five times. Deoxygenated MeCN (10 mL) was added via a nitrogen-purged syringe into the Schlenk flask (**2**). A stock solution of [$Cu^{II}Br_2$]/[Me_6TREN] (1.5 mL, [$Cu^{II}Br_2$] = 5.5 mM, [Me_6TREN] = 28.0 mM, dissolved in MeCN), deoxygenated **MA** (3.0 mL, 33.1 mmol), and **EBiB** (24 μL, 0.166 mmol) were added using nitrogen-purged syringes into the Schlenk flask (**1**). The reaction mixture was then irradiated under UV light at 365 nm for 3 h.

*p*ATRP in the presence of limited amounts of air (without degassing of MeCN and monomer)

The Schlenk flask equipped with a magnetic stir bar was subjected to vacuum and backfilled with nitrogen gas five times. A 20 mL vial was charged with $Cu^{II}Br_2$ (12.3 mg, 0.055 mmol), **Me_6TREN** (63.6 mg, 0.28 mmol), and MeCN (10 mL). A stock solution of [$Cu^{II}Br_2$]/[Me_6TREN] (1.5 mL, [$Cu^{II}Br_2$] = 5.5 mM, [Me_6TREN] = 28.0 mM, dissolved in MeCN), **MA** (3.0 mL, 33.1 mmol), and **EBiB** (24 μL, 0.166 mmol) were added using syringes into the Schlenk flask. the reaction mixture was then irradiated under UV light at 365 nm for 5 h.

Purification of polymers using QA[12]

A solution of **QA** (4 equiv with respect to $Cu^{II}Br_2$, dissolved in 5 mL of THF) was added into the Schlenk flask and the resulting mixture was stirred for 1 h. Afterwards, the reaction mixture was filtered through a syringe filter (0.2 μm) into a 20 mL vial.

Control experiments (purification of polymers without using QA)

THF (5 mL) was added into the Schlenk flask, and the resulting mixture was stirred for 1 h. From this point onwards, all manipulations were carried out under an ambient atmosphere. The reaction mixture was filtered through a syringe filter (0.2 μm) into a 20 mL vial.

[12] Purification in the presence of limited amounts of air (without degassing of THF).

Preventing Post-ATRP Glaser Coupling Using QA (Figure 9)

The Schlenk flask (**1**) equipped with a magnetic stir bar was charged with copper(I) bromide (48.7 mg, 0.34 mmol, 1 equiv), **dNbpy** (277.9 mg, 0.68 mmol, 2 equiv) and subjected to vacuum and backfilled with nitrogen gas five times. The styrene was degassed separately for 40 min in a 20 mL vial sealed with a rubber septum. Deoxygenated styrene (9.0 mL, 78.3 mmol, 230 equiv) was added via a nitrogen-purged syringe into the Schlenk flask (**1**). The flask (**1**) was placed in an oil bath held at 110 °C. After 15 min, **PgBiB** (69.7 mg, 0.34 mmol, 1 equiv) was added via a syringe *Hamilton* into the Schlenk flask (**1**). The reaction mixture was stirred at 110 °C for 1.5 h. Immediately after synthesis of the polymer, the Schlenk flask (**1**) was placed in a water bath for 5 min.

Purification without using QA.[13] The ATRP solution (4.5 mL) was then transferred via a nitrogen-purged syringe to the Schlenk flask (**2**) equipped with a magnetic stir bar and deoxygenated by vacuum and backfilled with nitrogen gas five times. THF (5 mL) was added via a syringe into the Schlenk flask (**2**), and the resulting mixture was stirred at rt for 1 h. From this point onwards, all manipulations were carried out under an ambient atmosphere. The reaction mixture was filtered through a syringe filter (0.2 μm) into the 20 mL vial (**I**). Once exposed to air, samples were collected at selected time intervals and instantly analyzed by GPC.

Purification using QA.[12] A solution of **QA** (5.0 mL, 34.0 mM in THF, 37.4 mg, 0.17 mmol, 4 equiv with respect to remainder $Cu^{II}Br_2$) was added into the Schlenk flask (**1**),[14] and the resulting mixture was stirred at rt for 1 h. From this point onwards, all manipulations were carried out under an ambient atmosphere. The reaction mixture was filtered through a syringe filter (0.2 μm) into the 20 mL vial (**II**). Once exposed to air, samples were collected at selected time intervals and instantly analyzed by GPC.

[13] Purification in the presence of limited amounts of air (without degassing of THF).
[14] The **QA** solution was added after 4.5 mL of reaction mixture was taken.

Cytotoxicity Study of QA (Figure 10 and S9)

Cytotoxicity was assessed using direct CyQUANT® nucleic acid-sensitive fluorescence assay (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. Briefly, 25×10^3 cells/well were plated in 48-well microplate (Corning Inc., Corning, NY, USA) and allowed to adhere overnight. Treatments with varying concentrations of the **QA** or **HQA** were added and co-incubated with cells for designated time-points. Next, cells were labeled with CyQUANT® Direct and fluorescence intensities were measured with TECAN spectrophotometer reader (TECAN, Männedorf, Switzerland). Cytotoxicity was assessed by normalizing fluorescence intensities to control group (no treatment) and plotted as percent viability.

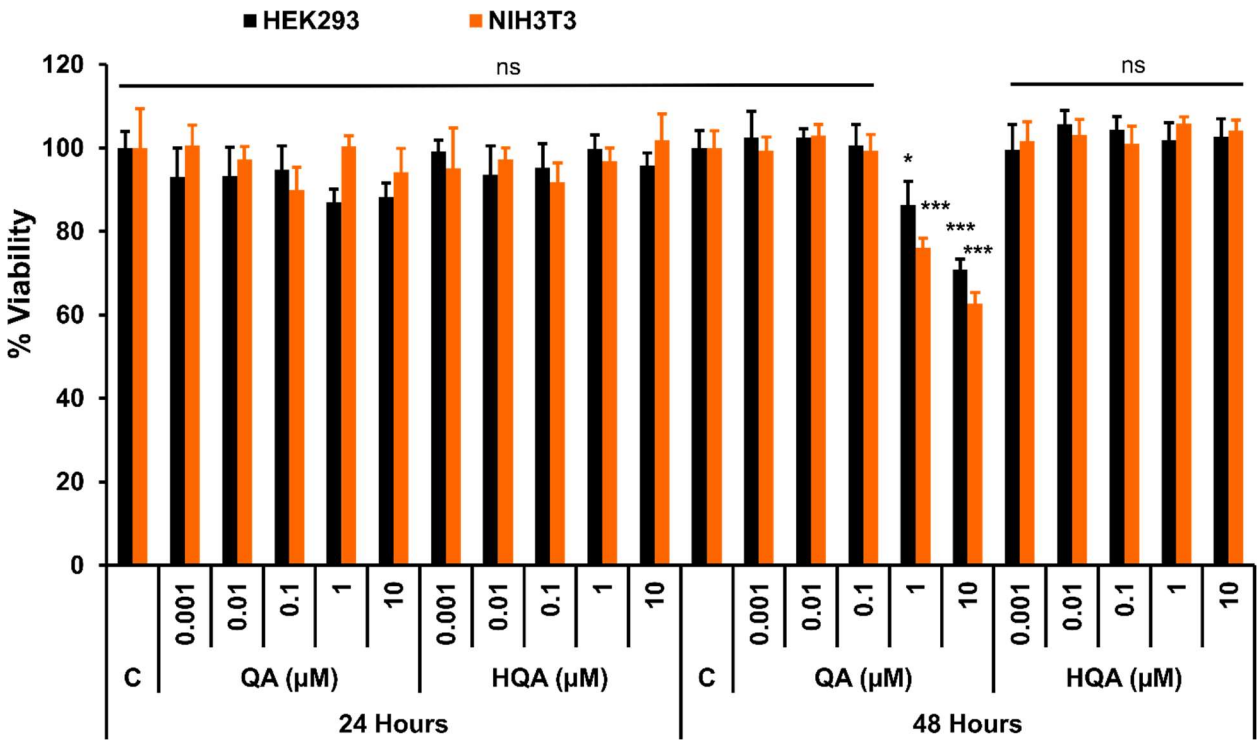


Figure S7. The cytotoxicity assay performed using HEK293 (black) and NIH3T3 cells (orange). Cells were treated with five concentrations of **QA** or HQA for 24/48 hours and compared to control group (no treatment). Bars indicate the mean percent viability ± SEM (n=3), ns: no significant difference, *p<0.5, ***p<0.001 (vs control group).

Analytic Determination of Copper Concentration

Copper content was determined by inductively coupled plasma mass spectrometry (IPC-MS, NexION 300D, *Perkin Elmer*, USA) equipped with a traditional sample introduction system, which requires samples to be in solution in order to be analyzed.

Mineralization

Samples ranging in mass from 20 to 100 mg were digested in capped PTFE vessels placed in a microwave assisted sample preparation system (single reaction cell - *UltraWAVE* system, *Milestone*, Italy) with 2 mL of 65% HNO_3 (*Suprapur*, *Merck*, Germany), 0.70 mL 35% of HCl (*Suprapur*, *Merck*, Germany) and 0.10 mL of 70% $HClO_4$ (ultra pure, *Chem-Lab NV*, Belgium). Different digestion methods, including different combination of acids and different digestion conditions, were tested on the chosen samples. Finally the microwave program was set to a 250 °C for 20 min after 25 min heat up period at 120 bar and 1500 W. All samples were pre-digested before microwaving by aging the sample mixed with acids for 12 h at room temperature. Final digests were diluted with deionized water and measured within 24 h.

ICP-MS

The ICP-MS apparatus was calibrated by measuring a series of reference solutions with concentrations ranging from 0.001 mg L^{-1} to 0.100 mg L^{-1} (obtained by diluting an ICP multi-element standard solution VI, *Merck*, Germany). The measurement was obtained as a count of ions with mass-to-charge ratio of 63 and 65. The apparatus was purged with a neutral solution for 60 s after each sample and was allowed to equilibrate for 40 s before the first measurement. Three measurements were obtained for each sample and averaged.