# **Supporting Information**

# Copper(I)/ketoABNO Catalysed Aerobic Alcohol Oxidation

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# 1. General Considerations

Unless otherwise stated, all reagents were purchased from Sigma-Aldrich and used without any further purification. 4,4'-dimethoxy-2,2'-bipyridine ( $^{MeO}$ bpy) was obtained from CMS chemicals. An O<sub>2</sub>:N<sub>2</sub> (8:92) high pressure premixed gas cylinder ( $\beta$  standard) and high pressure air cylinder were obtained from BOC gases. All reactions were carried out in oven dried glassware. <sup>1</sup>H-NMR spectra were recorded on a Bruker AVX300 (300 MHz) spectrometer at room temperature.

For the synthesis of ketoABNO and ABNO, reactions were monitored by thin layer chromatography using Merck silica gel 60 sheets and visualised with UV light. Flash column chromatography was performed with 60Å silica gel as the stationary phase, and all solvents used were of analytical grade.

#### 2. Preparation of ketoABNO, ABNO and Si-ABNO

The radical syntheses were carried out according to the route previously reported in the literature.<sup>1,2</sup>

#### 2.1 Synthesis of 9-benzyl-9-azabicyclo[3.3.1]nonane-3-one



Benzylamine hydrochloride (8.62 g, 0.06 mol) and glutaraldehyde (18.9 mL, 0.05 mol) were added to a 500 mL round bottomed flask containing water (23 mL). The resulting orange solution was cooled to 0 °C in an ice bath and to this 1,3-acetonedicarboxylic acid (7.3 g, 0.05 mol) and 10 % NaOAc aq. (17 mL) were added. The ice bath was removed and the reaction mixture was left to stir at room temperature for 2 hours. After this time a reflux condenser was attached and the reaction mixture was heated to 50 °C and left overnight. The resulting dark brown solution containing a dark brown residue was left to cool to room temperature. Once cooled the solution was acidified to pH 2 *via* the slow addition of 10 % HCl solution. The solution was washed with 3 portions of diethyl ether and adjusted to pH 8 by the addition of saturated NaHCO<sub>3</sub> solution. The resulting cloudy orange solution was extracted with dichloromethane several times, combining the organic portions as a brown solution. The solution was concentrated under reduced pressure and the resulting oil was filtered over short pad silica gel using hexane/ ethyl acetate (3:2) as the eluent. Concentration of the filtrate resulted in a yellow solid in 45 % yield (5.15 g, 0.02 mol). The <sup>1</sup>H-NMR spectrum of the product was in accordance with the literature data.<sup>2</sup>

#### 2.2 Synthesis of 9-azabicyclo[3.3.1]nonane-3-one



The benzyl protecting group was removed using Pd/C under an  $H_2$  atmosphere. While others have carried out this step using glassware and a  $H_2$  balloon,<sup>1,2</sup> we employed a pressurised reactor system:

Into a Hasstelloy C276 100 mL Parr pressurised reactor body Pd/C (10 Wt%) (1.19 g) was carefully weighed and cooled to 0 °C. Degassed ethyl acetate (10 mL) was added into the reactor body to completely cover the potentially flammable catalyst. The reactor was sealed and left under a N<sub>2</sub> atmosphere. Starting material, 9-benzyl-9-azabicyclo[3.3.1]nonane-3-one (5.15 g, 0.02 mol), dissolved in degassed methanol (35 mL) was slowly added into the reactor body through an injection valve, under an atmosphere of N<sub>2</sub>. Once the solution had been added, the reactor was flushed with N<sub>2</sub> gas, followed by H<sub>2</sub> gas. Finally, the reactor was pressurised with hydrogen gas (30 bar) and left stirring overnight at 50 °C. The reactor can tolerate a maximum pressure of 200 bar, and has a safety release valve in the event of a pressure build up. At the end of the reaction, the reactor body was cooled in an ice bath and then slowly depressurised. The reaction solution was filtered through a celite plug with EtOAc/MeOH (3:1) as the eluent. After filtering the mixture, reduced catalyst was removed and stored in a sealed container under an aqueous environment to prevent the reduced catalyst drying out and igniting. The filtrate was concentrated under reduced pressure and collected as a yellow crystalline solid in 82 % yield (2.51 g, 0.018 mol). An <sup>1</sup>H-NMR spectrum of the product was in accordance with the literature data.<sup>2</sup>

#### 2.3 Synthesis of 9-azabicyclo[3.3.1]nonane-3-one N-oxyl (ketoABNO)



9-azabicyclo[3.3.1]nonane-3-one (2.51 g, 0.018 mol), Na<sub>2</sub>WO<sub>4</sub>.2H<sub>2</sub>O (0.60 g, 0.0018 mol) and acetonitrile (37 mL) were added to a round bottomed flask and cooled to 0 °C. Once cooled H<sub>2</sub>O<sub>2</sub>.urea (5.10 g, 0.05 mol) was slowly added. The ice bath was removed and reaction mixture left stirring at room temperature for 3 days. The reaction mixture was run through a short pad silica gel plug with hexane/EtOAc (1:2) as the eluent. The filtrate was collected and concentrated *en vacuo* and then purified by flash column chromatography (hexane/ethyl acetate (2:1)). The product 9-azabicyclo[3.3.1]nonane-3-one *N*-oxyl was collected as an orange crystalline solid in 44 % yield (1.21 g, 7.85 mmol).

CHN analysis: calculated (found) C; 62.32% (62.71%), H; 7.84% (7.69%), N; 9.08% (8.99%). HRMS (EI) [M<sup>+</sup>] /z calculated: 154.0868, measured: 154.0894.

### 2.4 Synthesis of 9-azabicyclo[3.3.1]nonane



To a 250 mL 3-necked round bottomed flask equipped with a stirrer bar was added 9azabicyclo[3.3.1]nonan-3-one (3 g, 21.5 mmol). Hydrazine hydrate (3.3 ml, 64.5 mmol) was slowly added and the reaction mixture was heated to 80 °C for 2 hours. The reaction mixture was cooled to room temperature and distillation apparatus attached. Potassium hydroxide (12 g, 215 mmol) was added followed by 31 mL of triethylene glycol. The mixture was heated to 220 °C for 30 minutes before 150 mL of water was added dropwise over a period of 3 hours. The water distillate was extracted with chloroform several times and dried with potassium carbonate to yield a yellow oil, 0.94g, 35%. The <sup>1</sup>H-NMR spectrum of the product was in accordance with the literature data.<sup>2</sup>

# 2.5 Synthesis of 9-azabicyclo[3.3.1]nonane N-oxyl (ABNO)



To a 250 mL round bottomed flask equipped with a stirrer bar was added 9-azabicyclo[3.3.1]nonane (1.33 g, 10.62 mmol) in 20 mL acetonitrile. Sodium tungstate dihydrate (0.351 g, 1 mmol) was added to the flask followed by slow addition of urea hydrogen peroxide (3 g, 32 mmol). The reaction mixture was stirred at room temperature for 48 hours, monitoring by TLC. The reaction mixture was diluted with water and extracted with chloroform. The organic layers were combined, dried with potassium carbonate and purified using flash column chromatography (ethyl acetate/hexane 1:1) to yield ABNO as a red solid in 29 % yield (0.434 g).

CHN analysis: calculated (found) C; 68.54% (68.08%), H; 9.99% (10.38%), N; 9.99% (9.85%). HRMS (EI) [M<sup>+</sup>] /z calculated: 140.1075, measured: 140.1075.

#### 2.6 Preparation of ABNO Functionalised Silica Gel

It is worth noting that end-capped amino functionalised silica gel is commercially available from a number of major suppliers (which would allow steps 1 and 2 to be avoided), however we prepared our own using the following procedure:

## Step 1: Preparation of amino functionalised silica gel



Silica gel (Davisil grade 646, 10 g) was weighed into a 500 mL two-neck round bottomed flask and dried under high vacuum at 130 °C overnight. The dry silica gel was cooled to room temperature and placed under a nitrogen atmosphere. Dry toluene (100 mL) was added to the flask followed by (3-aminopropyl)triethoxysilane (2.44 g, 11.0 mmol) and the mixture was left stirring at 80 °C under nitrogen overnight. CHN analysis of silica at this point indicates essentially quantitative attachment of the amine group. In general, we also end capped the silanol groups, using the following procedure:

Step 2: End-capping of the silanol groups



Under a nitrogen atmosphere the mixture (amino functionalised silica in toluene) was cooled to room temperature and then hexamethyldisilazane (10 mL), chlorotrimethylsilane (10 mL) and dry pyridine (50 mL) were added. The mixture was left stirring under nitrogen, at 115 °C overnight. Once cooled to room temperature the resulting functionalised silica gel was filtered under vacuum and washed with toluene, hexane and dichloromethane. Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy indicated that the majority of surface silanol groups were end-capped.

#### Step 3: Tethering of ketoABNO to amino functionalised silica



Amino-functionalised silica gel (5.0 g) was weighed into a 100 mL two-necked round bottom flask and dried under high vacuum. Under nitrogen flow, dry methanol (25 mL) and ketoABNO (0.96 g, 6.25 mmol) were added to the flask followed by the slow addition of sodium cyanoborohydride (3.14 g, 50 mmol). The mixture was left stirring under nitrogen, at room temperature for 3 days. The silica gel was filtered under vacuum and washed repeatedly with toluene, hexane and dichloromethane.

CHN and TGA analysis were in agreement and indicated a final loading of 0.35 mol% / gram.

#### 3. General Procedures for Catalytic Oxidation of Alcohols

The general procedures for the oxidation of alcohols are shown below for both heterogeneous and homogeneous systems. The quantities shown in these examples are for experiments with a 1 mol% radical loading in the case of homogeneous systems and 0.35 mol% loading in the case of supported ABNO. The example procedures give quantities for ketoABNO, bpy and CuI; however we also carried out comparisons with ABNO, <sup>MeO</sup>bpy and CuOTf (Section 6.1 of SI). For homogeneous experiments where lower loadings of ketoABNO and ABNO were employed, stock solutions of the radicals were prepared and the appropriate volume of stock solution was added to the flask or reactor using a micropipette. For all reactions a stock solution of *N*-methylimidazole was prepared by adding 0.086 g to a 10 mL volumetric flask, and making up the volume to 10 mL with acetonitrile. 1 mL portions of this stock solution were then used in the reaction.

## 3.1 Heterogeneous System

## 3.1.1 Open Air Method:

Into a round bottomed flask (50 mL), silica-ABNO (0.01 g, 0.35 mmol, 0.35 mol%), copper iodide (0.014 g, 0.075 mmol, 7.5 mol%), 2,2'-bipyridine (0.012 g, 0.075 mmol, 7.5 mol%), biphenyl (0.123 g, 0.8 mmol), *N*-methylimidazole (0.0086 g, 0.105 mmol, 10.5 mol%) and alcohol substrate (1 mmol) were added and dissolved in acetonitrile (5 mL). An elliptical magnetic stir bar (20 mm x 10 mm) was added, a reflux condenser was attached and the reaction was stirred (340 RPM) on a temperature-controlled hotplate at 25 °C. Reactions were sampled periodically and washed through a silica plug with diethyl ether to remove all catalyst components. The collected sample was submitted for GC analysis.





#### **3.1.2 Reactor Method:**

Into a stainless steel 16 mL reactor body silica-ABNO (0.01 g, 0.35 mmol, 0.35 mol%), copper iodide (0.014 g, 0.075 mmol, 7.5 mol%), 2,2-bipyridine (0.012 g, 0.075 mmol, 7.5 mol%), *N*-methylimidazole (0.0086 g, 0.105mmol, 10.5 mol%) and alcohol substrate (1 mmol) were added and dissolved in acetonitrile (5 mL). An elliptical magnetic stir bar (9 mm x 4 mm) was added and the reactor was sealed and pressurised with compressed air (40 bar) or  $O_2:N_2$  (8:92) (40 bar) and stirred (950 RPM) on a temperature-controlled hotplate at 25 °C. Reactions were sampled periodically by cooling the reactor body in an ice bath and slowly depressurising. The collected sample was washed through a silica plug with diethyl ether to remove all catalyst components. Filtrate was collected and submitted for GC analysis.







#### 3.2 Homogeneous System

#### 3.2.1 Open Air Method:

Into an oven dried round bottomed flask (50 mL) copper iodide (0.014 g, 0.075 mmol, 7.5 mol%), 2,2'-bipyridine (0.012 g, 0.075 mmol, 7.5 mol%) and biphenyl (0.123 g, 0.8 mmol) were added. *N*-methylimidazole (0.0086 g, 0.105 mmol, 10.5 mol%), ketoABNO (0.00154 g, 0.01 mmol, 1 mol%) and alcohol substrate (1 mmol) were then added and dissolved in acetonitrile (5 mL). An elliptical magnetic stir bar (20 mm x 10 mm) was added, a reflux condenser was attached and the reaction stirred at 25 °C on a temperature-controlled hotplate. Reactions were sampled periodically and washed through a silica plug with diethyl ether to remove all catalyst components. The collected sample was submitted for GC analysis.

#### **3.2.2 Reactor Method:**

Into a stainless steel 16 mL reactor body (see above for details) copper iodide (0.014 g, 0.075 mmol, 7.5 mol%), 2,2'-bipyridine (0.012 g, 0.075 mmol, 7.5 mol%) and biphenyl (0.123 g, 0.8 mmol) were added. *N*-methylimidazole (0.0086 g, 0.105 mmol, 10.5 mol%), ketoABNO (0.00154 g, 0.01 mmol, 1 mol%) and alcohol substrate (1 mmol) were then added and dissolved in acetonitrile (5 mL). An elliptical magnetic stir bar (9 mm x 4 mm) was added and the reactor was sealed and pressurised with compressed air (40 bar) or  $O_2:N_2$  (8:92) (40 bar) and stirred (950 RPM) at 25 °C on a temperature controlled hotplate. Reactions were sampled periodically by cooling the reactor body in an ice bath and slowly depressurising. The collected sample was washed through a silica plug with diethyl ether to remove all catalyst components. Filtrate was collected and submitted for GC analysis.

#### **3.2.3 Glass Liner Reactor Method:**

Into a stainless steel 50 mL reactor body fitted with a glass liner, copper iodide (0.014 g, 0.075 mmol, 7.5 mol%), 2,2'-bipyridine (0.012 g, 0.075 mmol, 7.5 mol%) and biphenyl (0.123 g, 0.8 mmol) were added. *N*-methylimidazole (0.0086 g, 0.105 mmol, 10.5 mol%), ketoABNO (0.00154 g, 0.01 mmol, 1 mol%) and alcohol substrate (1 mmol) were then added and dissolved in acetonitrile (5 mL). An elliptical magnetic stir bar (9 mm x 4 mm) was added and the reactor was sealed and pressurised with compressed air (40 bar) or  $O_2:N_2$  (8:92) (40 bar) and stirred (950 RPM) at 25 °C on a temperature controlled hotplate. Reactions were sampled periodically by cooling the reactor body in an ice bath and slowly depressurising. The collected sample was washed through a silica plug with diethyl ether to remove all catalyst components. Filtrate was collected and submitted for GC analysis.







## **3.2.4** View Cell Reactor Method:

Into a Hasstelloy C276 100 mL Parr pressurised reactor body copper iodide (0.10 g, 0.525 mmol, 7.5 mol%), 2,2'-bipyridine (0.082 g, 0.525 mmol, 7.5 mol%) and biphenyl (0.864 g, 5.6 mmol) were added. *N*-methylimidazole (0.06 g, 0.735 mmol, 10.5 mol%), ketoABNO (0.0108 g, 0.07 mmol, 1 mol%) and alcohol substrate (7 mmol) were then added and dissolved in acetonitrile (35 mL). The reactor was sealed and stirred at ambient temperature and compressed air was gently flowed through the reactor (*via* a dip pipe). Reactions were sampled periodically and the sample was washed through a silica plug with diethyl ether to remove all catalyst components. Filtrate was collected and submitted for GC analysis.







#### 4. Quantification of ketone product by GC

Analysis of catalytic reactions was carried out by gas chromatography, using an Agilent 6890N series gas chromatograph. Product yields were determined using biphenyl as an internal standard.

Samples were prepared by filtering through a silica plug with diethyl ether. The methods used are as reported under general considerations. Biphenyl was used as the internal standard (IS) and added prior to the reaction. In order to obtain an accurate yield, we carried out calibrations to obtain the relative response factors (RF) of the (commercially available) products and starting materials compared to the biphenyl internal standard.

Yields were calculated using the following equation:

*Moles of product* = (area of product peak  $\times$  moles of IS  $\times$  RF)/ area of IS

Reactions with 1-phenylethanol were analysed using a 30 m × 0.32 mm ID SOLGEL-WAX 0.5UM (SGE Analytical Science) column under the following conditions: initial column temperature, 50 °C; initial hold time, 1 min, next temperature, 200 °C; hold time, 0 min; rate of temperature ramp 1, 25 °C/min, final temperature 230 °C; hold time, 18 min; rate of temperature ramp 2, 3 °C/min; injection temperature, 250 °C; detection temperature, 250 °C. The effluent was combusted in an H<sub>2</sub>/ air flame and detected using a flame ionisation detector (FID).

2-Octanol and isoborneol reactions were analysed using an Agilent J&W HP-5, (30 m, 0.32 mm, 0.25  $\mu$ m) silica column, under the following conditions: initial column temperature, 40 °C; initial hold time, 0 min; rate of temperature ramp 1, 4 °C/min; next temperature, 100 °C; hold time, 0 min; rate of temperature ramp 2, 30 °C/min, final temperature 320 °C; hold time, 15 min; injection temperature, 250 °C; detection temperature, 250 °C. The effluent was combusted in a H<sub>2</sub>/air flame and detected using an FID.

# 5. NMR Spectra

<sup>1</sup>*H-NMR Spectrum 9-benzyl-9-azabicyclo*[3.3.1]*nonane-3-one (CDCl*<sub>3</sub>, 300 MHz)



<sup>1</sup>*H-NMR Spectrum 9-azabicyclo*[3.3.1]*nonane-3-one* (*CDCl*<sub>3</sub>, 300 *MHz*)





## 6. Additional Catalytic Results not Shown in the Manuscript

6.1 Additional homogeneous data:

Comparison of co-catalyst and loading (with ketoABNO at 1 mol%) for the oxidation of 2-octanol in a round bottom flask



Reaction Conditions: 1 mmol of substrate in acetonitrile (5 mL), nitroxyl radical (1 mol%), CuI (either 7.5 mol% or 1 mol%), bpy (either 7.5 mol% or 1 mol%), NMI (10.5 mol% or 1.4 mol%), 25 °C, ambient air, stir rate = 340 RPM





Reaction Conditions: 1 mmol of substrate in acetonitrile (5 mL), ABNO (X mol%), CuOTf (7.5 mol%), MeObpy (7.5 mol%) NMI (10.5 mol%), 25 °C, ambient air. Stir rate = 950 RPM. Note: This catalyst system was reported by Steves and Stahl<sup>3</sup> but in this case it is run under concentrations comparable to those we have used for our ketoABNO/bpy/CuI studies



# Comparison of catalyst and co-catalyst combinations for the oxidation of 2-octanol in a round bottom flask

Reaction Conditions: 1 mmol of substrate in acetonitrile (5 mL), nitroxyl radical (0.1 mol%), CuI or CuOTf (7.5 mol%), bpy or <sup>MeO</sup>bpy(7.5 mol%) NMI (10.5 mol%), 25 °C, ambient air. Stir rate = 950 RPM.

# 6.2 Additional Information and Data for Heterogeneous (Si-ABNO) Oxidation Reactions

The majority of experiments were carried out using Si-ABNO that was prepared as described above, where the silica surface was "end-capped". Multiple batches were prepared and different batches gave consistent results. The results shown below were carried out with such Si-ABNO; however, we also prepared Si-ABNO without carrying out the end-capping and preliminary experiments found that we could obtain similar performance for a single batch experiment using un-capped silica.



Oxidation of secondary alcohols using Si-ABNO (0.35 mol%)

Reaction Conditions: 1 mmol of substrate in acetonitrile (5 mL), Si-ABNO (0.35 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, "open flask" = ambient air, while "reactor" = 40 bar air pressure.

#### 6.3 Attempted Recycling of Si-ABNO

Previous batch reactions had been carried out on 1 mmol substrate, but to facilitate easier recycling of the Si-ABNO the reactions were scaled 10 fold, giving the following quantities: 2-octanol (10 mmol, 1.30 g), Si-ABNO (0.35 mol% or 0.7 mol% = 0.1 or 0.2 g), CuI (7.5 mol%, 0.75 mmol, 0.14 g), bpy (7.5 mol%, 0.75 mmol, 0.12 g), NMI (10.5 mol%, 1.05 mmol, 0.086 g), acetonitrile: 50 mL. Reactions were carried out in a 500 mL round bottom flask with a condenser attached, stirred at 340 RPM with elliptical sir bar (30 mm x 10 mm) at 25 °C on a hot plate for 4 h (without sampling). At the end of the reaction, the mixture was filtered through a sinter using a low vacuum and washed with acetonitrile. Biphenyl (0.5 g) was then added to the filtrate, and sampled for GC analysis. After washing with acetonitrile, the filtered silica catalyst was clearly coloured indicating that copper was adhered to it. Consequently we tried washing the Si-ABNO with different solvents: DMSO followed by acetonitrile and also aqueous ammonia, followed by water and then acetonitrile. These methods were better at removing the colour from the Si-ABNO (particularly the NH<sub>4</sub>OH approach), however the performance of the recovered Si-ABNO was not good when re-used (with fresh copper, ligand and base added). Results shown below:

2-octanol	Reaction 1	Reaction 2	Reaction 3
0.35 mol% Si-ABNO	96 %	60 %	5 %
0.7 mol% Si-ABNO	97 %	80 %	37 %

Recycling of Si-ABNO for the oxidation of 2-octanol washed with only acetonitrile:

# Recycling of Si-ABNO for the oxidation of 2-octanol and 1-phenylethanol washed with acetonitrile, then DMSO and then acetonitrile:

0.7 mol% Si-ABNO	Reaction 1	Reaction 2	Reaction 3	Reaction 4
2-octanol	93 %	80 %	41 %	27 %
1-phenylethanol	97 %	85 %	67 %	

# Recycling of Si-ABNO for the oxidation of 2-octanol washed with aqueous ammonia, then deionised water and then acetonitrile:

2-octanol	Reaction 1	Reaction 2
0.7 mol% Si-ABNO	98 %	50 %

# **References:**

<sup>&</sup>lt;sup>1</sup> T. Sonobe, K. Oisaki and M. Kanai, *Chem. Sci.*, 2012, **3**, 3249.

<sup>&</sup>lt;sup>2</sup> M. B. Lauber and S. S.Stahl, *ACS Catal.*, 2013, **3**, 2612.

<sup>&</sup>lt;sup>3</sup> J. E. Steves and S. S. Stahl, J. Am. Chem. Soc., 2013, 135, 15742.