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COMMUNICATION

Copper(I)/ketoABNO Catalysed Aerobic Alcohol Oxidation

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A Cu(I)/9-azabicyclo[3.3.1]nonan-3-one *N*-oxyl (ketoABNO) aerobic catalyst system is highly effective for the oxidation of secondary alcohols, including unactivated aliphatic substrates. The effects of pressure and gas composition on
10 catalyst performance are examined. The radical can be employed at low loadings and it is also amenable to immobilisation on to solid supports.

The selective oxidation of alcohols is an important reaction in organic chemistry. This fundamental reaction still poses problems
15 when carried out on a larger scale, as traditional methods often use toxic reagents and/or inefficient methods.[1] There has therefore been considerable interest in developing catalytic methods for alcohol oxidation,[2] and in our opinion one of the best aerobic catalytic systems available is the Cu/2,2,6,6-
20 tetramethylpiperidinyloxy (TEMPO) system.[3,4] The most active version of this catalyst system is composed of a Cu(I) salt, combined with 2,2′-bipyridine (bpy) as a ligand, *N*-methylimidazole (NMI) as a base and the stable radical TEMPO.[4a] This system has a number of attractive features. It can
25 oxidise a variety of alcohols including those possessing alkenes, alkynes and heteroatoms that cause significant problems for noble metal catalyst systems.[4a] The method is also very accessible to researchers, as all catalytic components are commercially available and on a small scale it is possible to employ an "open
30 flask" approach, using ambient air as the oxidant. One of the notable attributes of this system is the very high selectivity for primary alcohols over secondary alcohols.[4] However, this selectivity means this catalyst is not suitable for the oxidation of secondary alcohols to ketones, a synthetically useful
35 transformation. The poor performance of Cu/TEMPO systems for secondary alcohols is attributed to steric hindrance. The mechanism for alcohol oxidation involves the Cu complex and radical working in unison.[4,5] In order to efficiently oxidise secondary alcohols, replacing TEMPO with a radical that is less
40 sterically hindered should remove this limitation. Figure 1 shows the structures of TEMPO and some sterically unhindered stable nitroxyl radicals. Such unhindered radicals have been known since the 1960s and in fact ketoABNO was the first in this class to be reported.[6]

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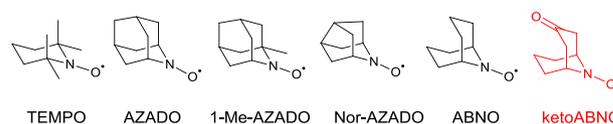
45 **Figure 1** Comparison of TEMPO with unhindered nitroxyl radicals.

To date TEMPO has undoubtedly been the most widely studied stable radical used in a number of alcohol oxidation systems,[3] for example, TEMPO/sodium hypochlorite type oxidations have
50 been applied on an industrial scale.[7] Although it was shown some time ago that such unhindered radicals are more reactive than TEMPO,[8] it is only recently that they have been explored in oxidation catalysis. Early studies used electrochemical or chemical (primarily sodium hypochlorite) oxidants to generate
55 the oxoammonium salt, which in turn acts as the catalyst.[9] There have also been reports of these systems being used with O_2 as the terminal oxidant, with initial reports using NO*x* type co-catalysts (*e.g.* sodium nitrite or nitric acid).[10] More recently, Cu/ketoABNO and Cu/ABNO aerobic systems have been used
60 for the oxidation of amines to imines[11] (and subsequent derivation) and the oxidation of amines to nitriles.[12]

Given the fundamental importance of alcohol oxidation we investigated the use of ketoABNO as a replacement for TEMPO. The synthesis of most unhindered radicals involves lengthy
65 synthetic procedures and in some cases undesirable steps.[13] ABNO can be prepared in three[9e] or four[10c] steps (depending on the route) and ketoABNO can be prepared in three steps.[11]

In this initial study we have focused on three model substrates to test the ability of Cu/ketoABNO to oxidise secondary alcohols
70 that Cu/TEMPO struggles to or indeed cannot oxidise (Figure 2). It is known from previous studies that Cu/TEMPO systems have excellent substrate scope tolerance (*e.g.* heteroatom and olefin containing molecules), so we wanted to focus on this limitation of secondary alcohols and examine the reactivity for such substrates.
75 The substrate 1-phenylethanol was included as an example of an activated secondary alcohol that the Cu(I)/TEMPO system can oxidise.[4a,14] The other model substrates are more challenging; 2-octanol is an aliphatic, unactivated alcohol and isoborneol is a sterically hindered, unactivated alcohol. In previous studies
80 isoborneol has been shown as an excellent test of steric hindrance using nitroxyl radicals under hypochlorite conditions.[9d]

1-Phenylethanol   2-Octanol   Isoborneol
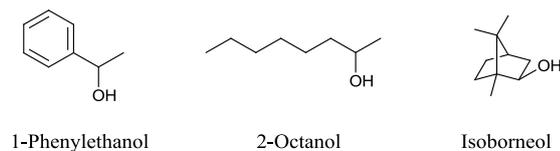
Figure 2 Secondary alcohols used as model substrates.

In Figure 3, we show a comparison in reactivity of ketoABNO, TEMPO and 4-oxoTEMPO for the three model substrates. Although TEMPO is commonly used, we have included 4-oxoTEMPO as perhaps this is more analogous to ketoABNO. In these reactions we used 7.5 mol% CuI, bpy and 10.5 mol% NMI with 1 mol% of the radical. In the case of TEMPO systems, typically the copper complex and radical are used at 5 mol% loadings.[4] We had anticipated that ketoABNO would be more reactive than TEMPO, allowing the use of lower catalyst loadings. However, when the copper complex and base were reduced to 1 and 1.4 mol% respectively, performance was poor (see SI). When the copper complex and base were kept at higher loadings excellent catalyst performance was observed with lower radical loadings. These results are in-line with previous mechanistic studies of Cu/TEMPO systems.[4b,5] The radical is significantly more expensive than the copper complex, therefore, from an economical and indeed a green point of view, emphasis should perhaps be on the optimal use of the radical.
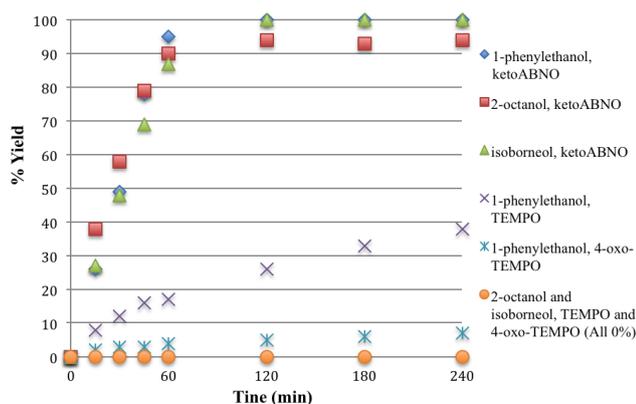
Figure 3 Comparison of ketoABNO, TEMPO and 4-oxoTEMPO for the oxidation of secondary alcohols. Reaction conditions: 1 mmol of substrate in acetonitrile (5 mL), nitroxyl radical (1 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, ambient air, stir rate = 340 RPM.

In Figure 3 it can be seen that there is a dramatic difference in performance of ketoABNO compared to TEMPO and 4-oxoTEMPO. The radicals TEMPO and 4-oxoTEMPO can only oxidise 1-phenylethanol and no oxidation products were obtained for the unactivated alcohols 2-octanol and isoborneol. As mentioned earlier, it is known that Cu(I)/TEMPO can oxidise some activated secondary alcohols[4a,14] and nearly 40% yield of acetophenone was obtained in four hours with this system. The yield was significantly decreased when 4-oxoTEMPO was used.

While this manuscript was in preparation, Steves and Stahl reported a study which focused on the use of Cu(I)/9-azabicyclo[3.3.1]nonane N-oxyl (ABNO) for aerobic alcohol oxidation.[15] In their initial screening, TEMPO, 4-methoxyTEMPO and 4-oxoTEMPO were compared against ABNO, ketoABNO and AZADO (2-azaadamantane N-oxyl).

They observed similar behaviour to that shown in Figure 3; where the sterically less hindered radicals delivered superior reactivity to TEMPO derivatives, particularly for secondary alcohols. Unhindered radicals were compared for the oxidation of cyclohexanemethanol at loadings of 5 mol% Cu complex and 5 mol% radical. It was found that all of the aforementioned unhindered radicals delivered similar reactivity under these conditions. Their study primarily focused on the use of ABNO and the catalyst system was further optimised to: 5 mol% Cu(MeCN)$_4$OTf, 5 mol% 4,4′-dimethoxy-2,2′-bipyridine (^{MeO}bpy), 10 mol% NMI and 1 mol% ABNO. This system was used to oxidise a wide range of primary and secondary alcohols at room temperature and at these loadings, most substrates were fully converted in 1 hr. This catalyst system was tolerant of a range of functionalities (*e.g.* heteroatoms, alkenes and alkynes) similar to that previously observed for Cu(I)/TEMPO.[4a] Substrates that could bind tightly or chelate with the Cu catalyst were found to be unreactive, again similar to that observed for Cu(I)/TEMPO.[4a]

In our studies we have not focused on a wide range of substrates. Rather, we wished to further examine the reactivity of our Cu(I)/ketoABNO system for the three representative substrates shown in Figure 2, as well as the development of a solid supported ABNO derivative.

In Figure 3 it can be seen that under these reaction conditions the ketoABNO enabled the oxidation of all three secondary alcohols at a very similar rate. This is unusual, as normally activated alcohols react much faster than aliphatic alcohols. This is arguably the case for all catalysts,[2] including Cu/TEMPO,[4] although Cu/TEMPO studies have been limited to primary alcohols. Given that the reactions shown in Figure 3 are carried out in "open flask" it was possible that, under these conditions, the reactions with ketoABNO were mass transfer limited in O$_2$. To test our theory we examined the influence of stir rate on the reaction. We examined stirrer speed effects with 1 mol% and 0.1 mol% loadings of ketoABNO for both 1-phenylethanol and 2-octanol. Different stirrer speeds were tested using a standard round bottom flask set-up, open to the air. There is arguably a limit to how much you can improve the efficiency of the gas-to-liquid mixing using such a set-up, therefore we also employed a mechanically stirred reactor / view cell with a constant flow of air supplied to avoid O$_2$ depletion (see SI for further details). This reactor meant we had to carry out reactions on a slightly larger scale; however, it is specifically designed for efficient mixing. It has a gas entrainment stirrer, which at high operating speeds (in this case 2400 RPM) delivers excellent dispersion of gases into the liquid phase. The reactor also has a viewing window that allows observation of the mixing, and we could see that at the high stir rate the mixture was very well mixed and highly aerated.

In Figure 4 we can see that for the reaction of 1-phenylethanol at 1 mol% ketoABNO loading the system is indeed mass transfer limited in O$_2$ under the conditions used in Figure 3. With improved mixing, the rate of reaction increases, with the best performance obtained in reactor with the gas entrainment stirrer. Consistent with these results, it is worth mentioning a relevant study by Mase *et al.*, which showed that using a "microbubble generator" to improve gas transport led to faster oxidation of activated alcohols with a Cu/TEMPO catalyst system.[16]
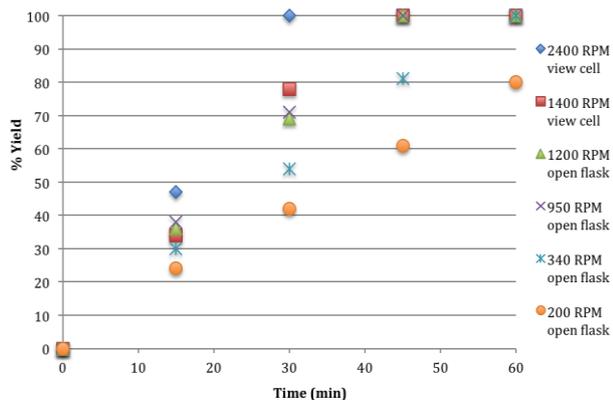
Figure 4 Stir rate effects on the oxidation of 1-phenylethanol. Reaction conditions: ketoABNO (1 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, ambient air. "open flask" = 1 mmol substrate scale, "view cell" = 7 mmol substrate scale.

When the loading of ketoABNO is dropped to 0.1 mol%, it can be seen in Figure 5 that there is less of an impact from stirrer speed, and it is possible to obtain similar reaction rates in both the flask and the reactor.
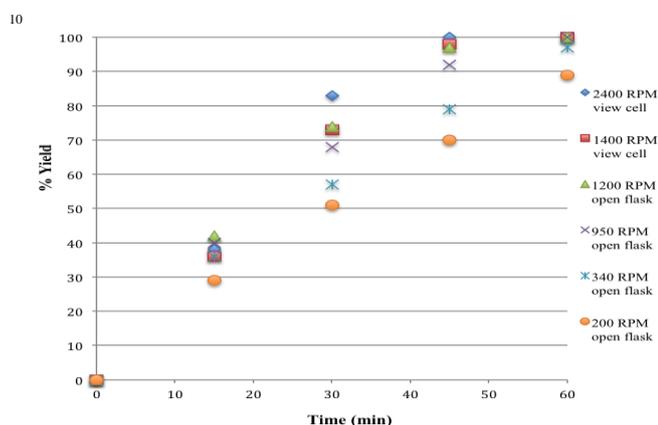
Figure 5 Stir rate effects on the oxidation of 1-phenylethanol. Reaction conditions: ketoABNO (0.1 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, ambient air. "open flask" = 1 mmol substrate scale, "view cell" = 7 mmol substrate scale.

Figure 6 shows the reaction course using 1 mol% ketoABNO for 2-octanol at a range of stirrer speeds and also isoborneol at the most efficient stirrer speed. Unlike that previously observed in Figure 3, when we compare the three model substrates with efficient mixing we now see that the reaction is significantly faster for the activated substrate 1-phenylethanol (*c.f.* Figures 4 and 6). It is clear that for these aliphatic substrates, even at 1 mol% it is possible to get out of the mass transfer limited regime using a round bottom flask.

Figure 7 shows stirring effects for the aliphatic substrates using the lower loading of 0.1 mol% ketoABNO. This figure once again highlights the difference between aliphatic substrates and activated substrates. With the less reactive substrates and lower loading of radical it is clear that stirring has essentially no effect on the reaction rate.
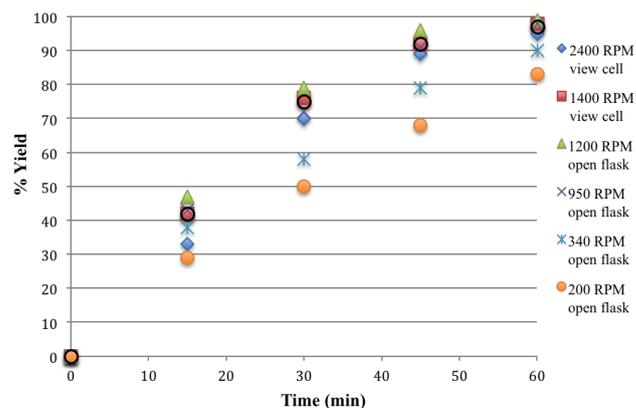
Figure 6 Stir rate effects on the oxidation of 2-octanol and isoborneol. Reaction conditions: ketoABNO (1 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, ambient air. "open flask" = 1 mmol substrate scale, "view cell" = 7 mmol substrate scale.
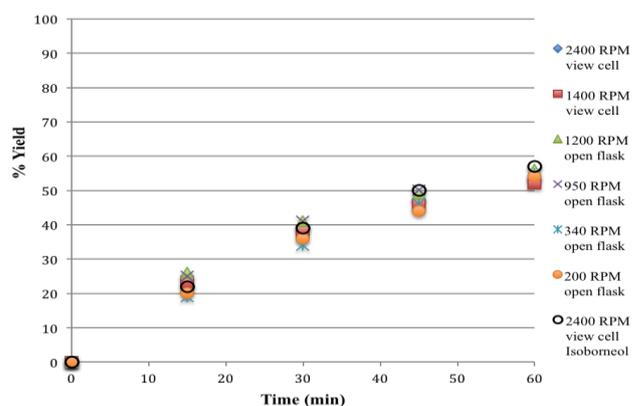
Figure 7 Stir rate effects on the oxidation of 2-octanol and isoborneol. Reaction conditions: ketoABNO (0.1 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, ambient air. "open flask" = 1 mmol substrate scale, "view cell" = 7 mmol substrate scale.

We also wanted to examine the effects of pressure on these reactions. The majority of studies on such metal/nitroxyl catalysts utilise ambient air or low pressures of O_2 (*e.g* 1 atm). Kinetic studies by Hoover and Stahl demonstrated that Cu(I)/TEMPO systems exhibited a first order dependence on O_2 pressure.[5] In those studies they utilised a pure O_2 atmosphere and the pressure was varied over quite a narrow range (up to 900 Torr (=1.2 bar)). In our studies we have utilised air and 8% O_2 (in N_2) at pressures of 40 bar and compared these to "open flask" conditions. This is relevant because dilute oxygen mixtures would most likely be employed if such systems were used in industry.[17] In fact a continuous flow system would probably be employed to further improve safety and scalability. Using dilute O_2 mixtures usually means higher pressures are required. For example, Stahl and co-workers have examined Cu(I)/TEMPO alcohol oxidation in a continuous flow system and they utilised 9% O_2 (in N_2) at a pressure of 35 bar.[18] Figure 8 shows the results from our studies examining the oxidation of 1-phenylethanol at different loadings of ketoABNO along with different pressures and O_2 compositions.
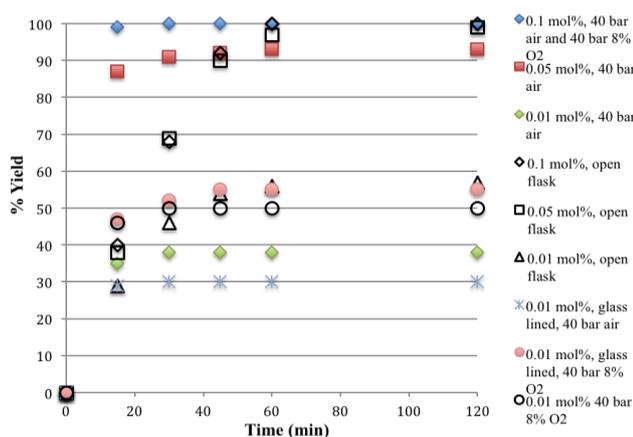
Figure 8 Influence of gas pressure and composition on the oxidation of 1-phenylethanol. Reaction conditions: 1 mmol of substrate in acetonitrile (5 mL), ketoABNO (X mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, stir rate = 950 RPM. "open flask" = ambient air, pressurised reactions carried out in small reactors (see SI).

The results in Figure 8 highlight a number of interesting features. It can be seen that applying a pressure of 40 bar of air or 8% O_2 (in N_2) enables a significant increase in rate with complete conversion of 1-phenylethanol in just 15 mins with only 0.1 mol% of ketoABNO. Such fast reaction rates make these reactions very suitable for continuous flow conditions. Impressively we can also obtain essentially complete conversion in 1 hr with just 0.05 mol% of ketoABNO. At this catalyst loading it can be seen that a very high conversion is obtained in just 15 minutes, however by 45 mins the same yield can be obtained with the open flask method. These results hinted that higher O_2 pressures may lead to faster catalyst decomposition and when we lowered the loadings of ketoABNO further this does indeed seem to be the case. A loading of 0.01 mol% ketoABNO gives better performance in the open flask than under 40 bar of air pressure. It is worth pointing out that mechanistic studies on Cu(I)/TEMPO indicate that the copper co-catalyst is involved in the re-oxidation/regeneration of the radical,[5] consequently at such low loadings of radical, the copper co-catalyst has to perform this task a greater number of times. We wondered if the stainless steel reactors were contributing to decomposition of the copper co-catalyst, as this has been observed previously.[18] However, we found that the performance with 40 bar of air in a glass-lined reactor was similar to that in a stainless steel reactor. A reaction was carried out in the glass lined reactor with 8% O_2 (40 bar) and it can be seen in Figure 8 that the performance improves. This supports the theory that higher O_2 concentrations can lead to increased catalyst decomposition. We believe that higher O_2 concentrations could be leading to decomposition of the copper co-catalyst. As mentioned earlier, to obtain good reaction rates we require high concentrations of the copper co-catalyst and poor performance is seen with loadings of just 1 mol% copper complex (see SI). A number of groups have previously discussed decomposition pathways for the copper co-catalyst in Cu/TEMPO systems,[4b,5] with insoluble/unreactive copper hydroxide or oxide species proposed as possible decomposition

products. Such decomposition is perhaps further accelerated at higher O_2 concentrations.

We also examined the oxidation of 2-octanol and isoborneol at lower ketoABNO loadings (0.1 and 0.01 mol%) with higher pressures of O_2 (Figure 9). In these experiments we once again found that the oxidation of the aliphatic substrates was significantly slower than 1-phenylethanol. Additionally, a similar effect of O_2 pressure was observed, albeit earlier in the reaction and at 0.1 mol% ketoABNO the open flask was superior to high pressure air.
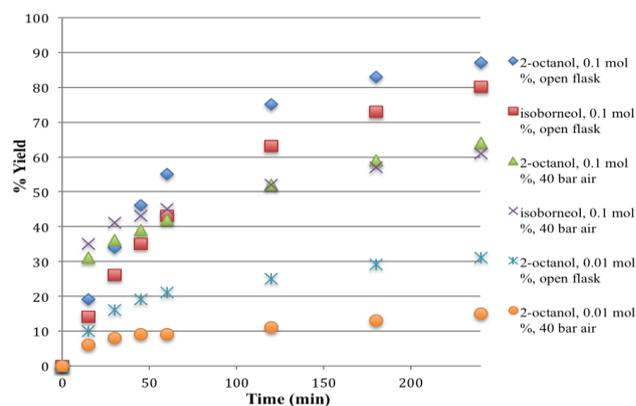
Figure 9 Influence of gas pressure and composition on the oxidation of 2-octanol and isoborneol. Reaction conditions: 1 mmol of substrate in acetonitrile (5 mL), ketoABNO (X mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, stir rate = 950 RPM. "open flask" = ambient air, pressurised reactions carried out in small reactors (see SI).

Although more detailed mechanistic studies are needed, the trends that we have observed for reactivity of activated versus unactivated substrates would suggest that the mechanism is the same as that previously determined for Cu(I)/TEMPO oxidation of primary alcohols.[5] With Cu(I)/TEMPO Hoover and Stahl determined that for activated alcohols, oxidation of the catalyst is the turnover limiting part of the catalyst cycle, while for less reactive aliphatic substrates, both substrate oxidation and catalyst oxidation contribute to the overall rate. For the Cu(I)/TEMPO system, a Cu^I resting state was observed for activated alcohols and a mixed Cu^I/Cu^{II} resting state for aliphatic substrates. These conclusions fit with the data obtained in our studies. It can be seen that higher concentrations of O_2 can lead to a dramatic improvement in the rate for 1-phenylethanol (Figure 8). In the case of aliphatic substrates we find that once outside the mass transfer regime, there are clear differences in reactivity between activated and unactivated substrates. We also found that using pressure to increase the O_2 concentration was not beneficial for aliphatic substrates (Figure 9). This indicates that for these alcohols the oxidation of the substrate is significantly slower. As has been discussed,[5] such substrates have a higher pK_a and stronger α-C-H bond, which contribute to slower substrate oxidation. For these aliphatic alcohols we found that better performance could be obtained using ambient air compared to higher pressures. We believe that this is a consequence of increased rates of copper co-catalyst decomposition due to a combination of higher O_2 and Cu^{II} concentrations.

As mentioned earlier, Steves and Stahl recently reported the

use of ABNO using Cu(MeCN)$_4$OTf as the copper source and ^{MeO}bpy as the ligand.[15] We examined this catalyst system for the oxidation of 1-phenylethanol and 2-octanol using 1 mol% and 0.1 mol% ABNO. We found (see SI for details) that at the lower catalyst loadings, once again the difference in reactivity between activated and unactivated alcohols became clear. In comparison to our system the ABNO system reported by Steves and Stahl[15] is somewhat faster. We also compared different combinations of ligands and copper salts for both ABNO and ketoABNO (see SI for details). We found that the ABNO CuOTf/^{MeO}bpy system was the fastest and ABNO was faster than ketoABNO when combined with CuI and bpy. However, it is worth noting that CuI and bpy are significantly less expensive than Cu(MeCN)$_4$OTf and ^{MeO}bpy. Furthermore, ketoABNO is arguably easier to prepare, as the synthesis of ABNO involves a Wolff-Kishner reduction.

Recovery of such radicals is desirable and the structure of ketoABNO means that it can be easily immobilised on to supports *via* a simple reductive amination (Figure 10). This is an approach that has been employed with 4-oxoTEMPO[19] and in fact silica tethered TEMPO is a commercial product.[7,19c]
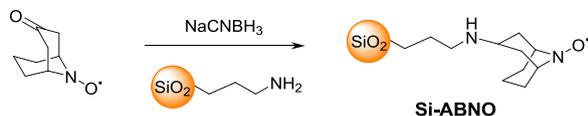
Figure 10 Preparation of Si-ABNO.

We prepared Si-ABNO and found that it could effectively oxidise alcohols aerobically when combined with the copper co-catalyst (see SI for more details). However, the performance of the Si-ABNO catalyst was significantly decreased upon attempted recycles of the radical. Further investigations are needed to examine the reasons behind deterioration of catalytic performance. Prior studies with Si-TEMPO have used sodium hypochlorite[19] or nitric acid[20] systems, therefore we need to assess if these problems are related to the copper system. Based on what we have observed with the homogeneous reactions, we believe that decomposition of the copper co-catalyst is likely to blame. As already mentioned, the copper co-catalyst is likely involved in the regeneration of the radical. Consequently, decomposition of the copper complex will lead to a reduction in the amount of radical. This may explain the decrease in performance with each successive run.

In summary, we have shown that a Cu(I)/ketoABNO system can effectively oxidise secondary alcohols, with the radical demonstrating high turnover numbers and turnover frequencies. Trends in reactivity for activated and unactivated alcohols suggest similar behaviour to the Cu(I)/TEMPO system. Preliminary results also demonstrate that ketoABNO can be easily tethered to silica gel and future work will be aimed at developing a recyclable solid supported ABNO catalyst system.

References

1. J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337.
2. Reviews on catalytic aerobic oxidation reactions: (a) T. Mallat and A. Baiker, *Chem. Rev*., 2004, **104**, 3037. (b) S. S. Stahl, *Angew. Chem. Int. Ed*. 2004, **43**, 3400. (c) C. P. Vinod, K. Wilson and A. F. Lee, *J. Chem. Technol. Biotechnol*., 2011, **86**, 161. (d) C. Parmeggiani and F. Cardona, *Green Chem*., 2012, **14**, 547. (e) J. Muzart, *Tetrahedron*, 2003, **59**, 5789. (f) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, and M. C. Kozlowski, *Chem. Rev*., 2013, **113**, 6234. (g) Book: J.-E. Backvall (Ed.) *Modern Oxidation Methods, 2nd Edition*, Wiley-VCH, Weinheim, 2010.
3. Reviews: (a) R. A. Sheldon and I. W. C. E. Arends, *Adv. Synth. Catal*., 2004, **346**, 1051. (b) R. A. Sheldon and I. W. C. E. Arends, *J. Mol. Catal. A: Chem.*, 2006, **251** 200. (c) L. Tebben and A. Studer, *Angew. Chem. Int. Ed*., 2011, **50**, 5034.
4. Leading references on Cu/TEMPO oxidation catalysis: (a) J. M. Hoover and S. S. Stahl, *J. Am. Chem. Soc*., 2011, **133**, 16901. (b) E. T. T. Kumpulainen, and A. M. P. Koskinen, *Chem. Eur. J.,* 2009, **15**, 10901. (c) P. Gamez, I. W. C. E. Arends, J. Reedijk and R. A. Sheldon, *Chem. Commun.*, 2003, 2414. (d) A. Dijksman, I. W. C. E. Arends and R. A. Sheldon, *Org. Biomol. Chem.*, 2003, **1**, 3232. (e) P. Gamez, I. W. C .E. Arends, R. A. Sheldon and J. Reedijk, *Adv. Synth. Catal*., 2004, **346**, 805. (f) N. Jiang and A. J. Ragauskas, *J. Org. Chem.*, 2006, **71**, 7087. (g) M. F. Semmelhack, C. R. Schmid, D. A. Cortes and S. Chou, *J. Am. Chem. Soc.,* 1984, **106**, 3374.
5. (a) J. M. Hoover, B. L. Ryland, and S. S. Stahl, *ACS Catal.,* 2013, **3**, 2599. (b) J. M. Hoover, B. L. Ryland and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 2357.
6. R. M. Dupeyre and A. Rassat, *J. Am. Chem. Soc*., 1966, **88**, 3180.
7. R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev*., 2010, **14**, 245.
8. For examples of fundamental studies examining the trapping of carbon centred radicals (a) V. W. Bowry and K. U. Ingold, *J. Am. Chem. Soc*., 1992, **114**, 4992. (b) A. L. J. Beckwith, V. W. Bowry and K. U. Ingold, *J. Am. Chem. Soc.,* 1992, **114**, 4983.
9. (a) Y. Demizu, H. Shiigi, T. Oda, Y. Matsumura and O. Onomura, *Tetrahedron Lett*., 2008, **49**, 48. (b) H. Shiigi, H. Mori, T. Tanaka, Y. Demizu and O. Onomura, *Tetrahedron Lett*., 2008, **49**, 5247. (c) M. Tomizawa, M. Shibuya and Y. Iwabuchi, *Org. Lett.,* 2009, **11**, 1829. (d) M. Shibuya, M. Tomizawa, I. Suzuki, and Y. Iwabuchi, *J. Am. Chem. Soc*., 2006, **128**, 8412. (e) M. Shibuya, M. Tomizawa, Y. Sasano and Y. Iwabuchi *J. Org. Chem*., 2009, **74**, 4619. (f) M. Shibuya, T. Sato, M. Tomizawa and Y. Iwabuchi, *Chem. Commun*., 2009, 1739. (g) M. Hayashi, Y. Sasano, S. Nagasawa, M. Shibuya and Y. Iwabuchi, *Chem. Pharm. Bull*., 2011, **59**, 1570.
10. (a) M. Shibuya, Y. Osada, Y. Sasano, M. Tomizawa and Y. Iwabuchi, *J. Am. Chem. Soc*., 2011, **133**, 6497. (b) Y. Kuang, Y. Nabae, T. Hayakawa and M. Kakimoto, *Green Chem.*, 2011, **13**, 1659. (c) M. B. Lauber and S. S. Stahl, *ACS Catal*., 2013, **3**, 2612.
11. T. Sonobe, K. Oisaki and M. Kanai, *Chem. Sci.,* 2012, **3**, 3249.
12. J. Kim and S. S. Stahl, *ACS Catal.*, 2013, **3**, 1652.
13. The synthesis of nor-AZADO has a step which involves refluxing NaH in DMF, a reaction that can result in thermal runaway: For examples see: G. DeWall,. *Chem. Eng. News*, 1982, **60**, 5 and 43.
14. G. Zhang, X. Han, Y. Luan, Y. Wang, X. Wen and C. Ding, *Chem. Commun*., 2013, **49**, 7908.
15. J. E. Steves and S. S. Stahl, *J. Am. Chem. Soc.,* 2013, **135**, 15742.
16. N. Mase, T. Mizumori and Y. Tatemoto, *Chem. Commun.*, 2011, **47**, 2086.
17. E. Brandes, W. Möller Safety Characteristic Data Vol. 1: Flammable Liquids and Gases, Wirtschaftsverlag NW, Bremerhaven, 2008.
18. J. F. Greene, J. M. Hoover, D. S. Mannel, T. W. Root, and S. S. Stahl, *Org. Process Res. Dev*., 2013, **17**, 1247.
19. (a) C. Bolm and T. Fey, *Chem. Commun.*, 1999, 1795. (b) C. Bolm, A. S. Magnus and J. P. Hildebrand, *Org. Lett*., 2000, **2**, 1173. (c) A. Michaud, G. Gingras, M. Morin, F. Béland , R. Ciriminna, D. Avnir, and M. Pagliaro, *Org. Process Res. Dev*., 2007, **11**, 766.
20. C. Aellig, D. Scholz, S. Conrada and I. Hermans, *Green Chem*., 2013, **15**, 1975.