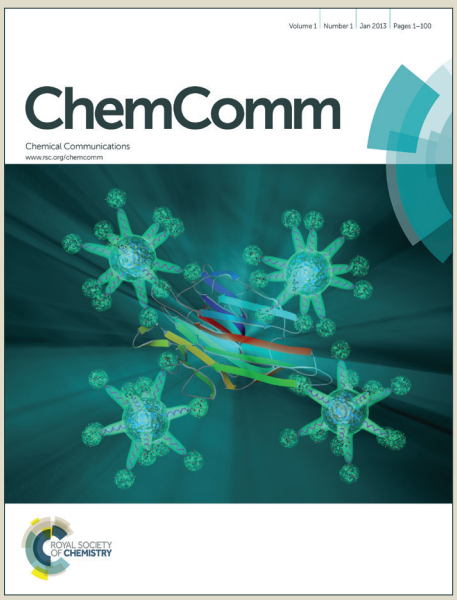
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

View Article Online
DOI: 10.1039/C5CC01519G

ChemComm

RSCPublishing

COMMUNICATION

Oxidations with air by ascorbate-driven quinone redox cycling†

Cite this: DOI: 10.1039/x0xx00000x

Gastón Silveira-Dorta,[a] Diego M. Monzón,[a] Fernando P. Crisóstomo,[a] Tomás Martín,[b] Víctor S. Martín,[a] and Romen Carrillo*[a]

Received 00th January 2012,
Accepted 00th January 2012

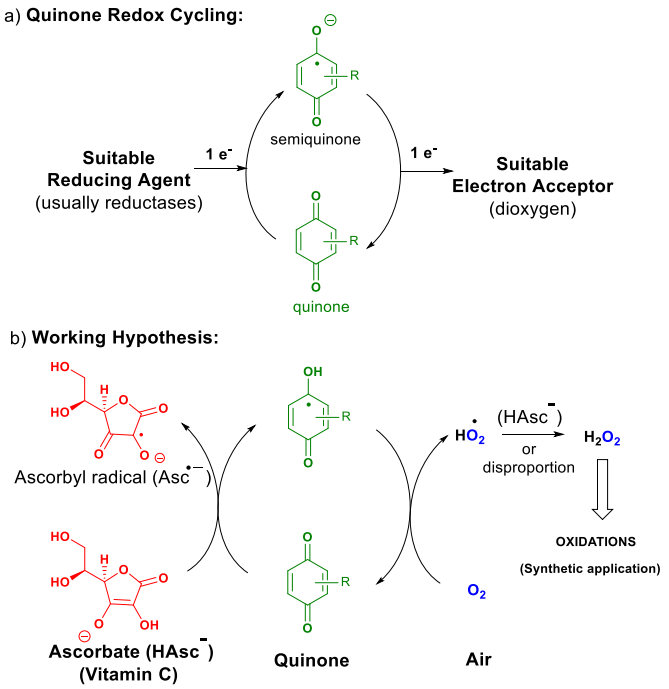
DOI: 10.1039/x0xx00000x

www.rsc.org/

Transition metal-free oxidations with air at room temperature have been achieved by simply using ascorbate (vitamin C) and catalytic amounts of menadione (vitamin K_3). A combination of the mentioned vitamins transforms atmospheric oxygen into hydrogen peroxide, which is able to oxidize arylboronic acids and other chemical moieties.

Oxidation is one of the most fundamental processes in chemistry. Conventional chemical oxidants, however, are usually toxic and there is an increasing academic and societal demand for environment friendly oxidation methods.[1] In this regard, molecular oxygen seems an ideal oxidant and oxygen-atom source for organic synthesis: it is abundant, environmentally benign and inexpensive, particularly if used directly from air.[2] However, the direct reaction of triplet dioxygen with singlet organic molecules is a spin-forbidden process.[3] As a consequence, oxidations with atmospheric oxygen display an extremely slow kinetics and they are usually accomplished only under transition metal catalysis,[4] and/or very high temperatures. Transition-metal-mediated reactions have raised several environmental and economic concerns,[5] which have motivated the development of plenty of transition-metal-free synthetic methods. However only some examples of transition metal-free oxidations by air has been previously reported,[6] and in some cases the reagents employed are toxic and/or too expensive.

With the aim of developing an efficient, economic and green way to activate oxygen from air, we took inspiration from biological systems. The biological activation of triplet dioxygen for controlled chemical synthesis occurs via electron transport chains by redox reactions. Particularly promising for our purposes is the redox performance of quinones.[7] In fact, several quinone-type natural molecules are efficient electron carriers, which are able to transfer one electron to dioxygen by the so-called quinone redox cycling (Scheme 1a): One-electron reduction of the quinone by a suitable reducing agent generates a semiquinone, which transfers one electron to dioxygen and reconverts itself into the original quinone.[8] Unfortunately, the single electron reduction of quinones is usually performed by reductases. A very appealing candidate as reducing agent to mimic the enzymatic quinone redox cycling is ascorbate.

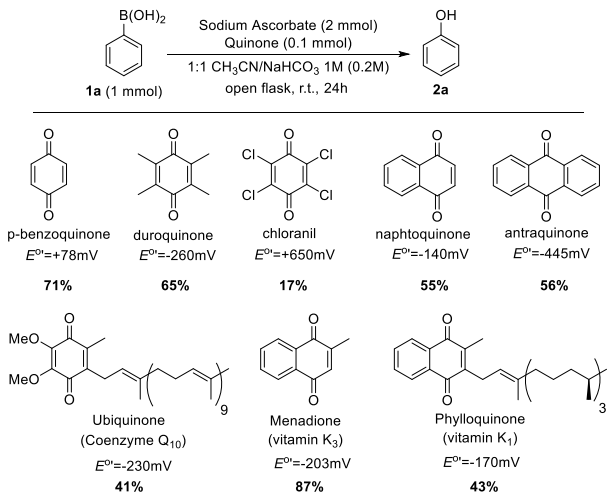


Scheme 1 a) General quinone redox cycling. b) Suggested activation of oxygen by ascorbate-driven quinone redox cycling through tandem proton-coupled electron transfer (PCET).

Indeed, vitamin C is a mild, inexpensive and non-toxic reducing agent which has been relatively underused in organic synthesis.[9] In this regard, it is known that ascorbate can promote quinone redox cycling.[10] Furthermore, it has been reported that a combination of ascorbate and menadione (2-methyl-1,4-naphtoquinone, also called

vitamin K_3) generates reactive oxygen species such as hydrogen peroxide in biological tissues.[11] It seems, therefore, a very interesting starting point to develop a transition metal-free oxidation method with air (Scheme 1b). Herein we have combined the pro-oxidant activity of ascorbate (vitamin C),[12] and the quinone redox cycling to develop an efficient and environment friendly method of oxidation by generating H_2O_2 from the air at room temperature.

Oxidative hydroxylation of arylboronic acids to phenols was chosen as an optimal example to test the effective generation of hydrogen peroxide from air. Additionally, mild, economical and green synthesis of phenols, particularly by using air, is increasingly attracting attention.[13] Oxidation of phenylboronic acid (**1a**) to phenol (**2a**) was evaluated in acetonitrile and $NaHCO_3$ solution (1M) stirring at room temperature under air, and protected from light to rule out any effect of irradiation. Several quinones were used to explore which one give the best results. Fortunately, the oxidation proceeded reasonably well with all the quinones. All yields are shown in Scheme 2 and correlated with the one-electron reduction potential of the corresponding quinone.

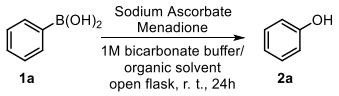


Scheme 2 *ipso*-Hydroxylation of phenylboronic acid with ascorbate and different quinones. Reducing potential values were taken from Ref. 8 and from Ref. 10 (measured in aqueous buffers around pH=7).

Although parameters such as solubility or chemical instability of quinones are important to explain these results, the reducing potential of the quinone is the most important factor. It is well-known that quinone redox cycling is involved in a delicate equilibrium: if the quinone is a very good oxidant, the first step (generation of semiquinone) will be favoured, but the second one (regeneration of quinone) not, and vice versa.[8,10] Menadione seems to fulfil perfectly the Goldilocks principle, carrying out oxidations with air and leading to the best yield.[14] Moreover, menadione is inexpensive, stable and displays low toxicity.

Encouraged by these results, a set of experiments were performed to optimize the reaction conditions (Table 1). Decreasing the amount of ascorbate lead to lower yields (Entries 2-3), which supports that hydrogen peroxide generation is enhanced by reduction of superoxide with another molecule of ascorbate (Scheme 1b).[15] Lower yield was also obtained when the amount of menadione was modified (Entries 4-5). The optimum pH range is 8-9.5, particularly pH=8.5 (Entries 6-9). Finally, the solvent does not play a key factor, even when it has been reported that acetonitrile can activate H_2O_2 (Entries 10-13).[16] Worth to mention, reaction with no organic co-solvent (entry 13) gave a good yield of phenol but led to lower yields in the oxidation of more lipophilic boronic acids, due to solubility problems. Thus, ethanol was chosen as organic co-solvent, not only because of the slightly higher yield but also because of its sustainability and low toxicity.[17]

Table 1 Optimization of the reaction conditions.

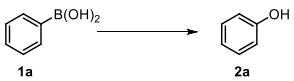


Entry	Sodium Ascorbate (mmol)	Menadione (mmol)	pH[a]	Organic Solvent[b]	Yield%[c]
1	2	0.1	8.5	CH_3CN	87
2	1	0.1	8.5	CH_3CN	65
3	0.5	0.1	8.5	CH_3CN	45
4	2	0.05	8.5	CH_3CN	54
5	2	0.2	8.5	CH_3CN	49
6	2	0.1	8	CH_3CN	83
7	2	0.1	9	CH_3CN	85
8	2	0.1	9.5	CH_3CN	85
9	2	0.1	10	CH_3CN	78
10	**2**	**0.1**	**8.5**	**EtOH**	**89**
11	2	0.1	8.5	*t*-BuOH	83
12	2	0.1	8.5	AcOEt	79
13	2	0.1	8.5	-	88

[a] Achieved by bicarbonate/carbonate buffer. [b] Reaction solvent is a 1:1 mixture of bicarbonate buffer solution and the organic solvent 0.2M. [c] Isolated yield.

Next, a series of control experiments were set in order to prove that all of the reagents employed are essential for the process. Under the optimized reaction conditions but in the absence of any one of the reagents, no conversion was observed (Table 2).

Table 2 Control experiments under optimized conditions.



Entry	Sodium Ascorbate	Menadione	Air	$NaHCO_3$	Yield%
1	+	+	+	+	**89**
2	-	+	+	+	n.r. [a]
3	+	-	+	+	trace
4	+	+	-	+	n.r.
5	+	+	+	-[b]	trace

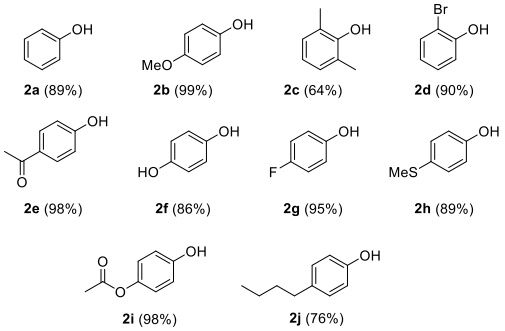
[a] n.r.=no reaction. [b] Experiment performed using either pure water or K_2HPO_4 (1M).

These control experiments also preclude any influence of adventitious metal traces. It is important to highlight that the bicarbonate requirement (entry 5) is not related with the pH value. Indeed the oxidation was unsuccessful when using 1M solution of K_2HPO_4 instead of bicarbonate, even though both salts provide comparable ionic strength and pH. The role of bicarbonate anion is to activate the peroxide generated, increasing the oxidative power of hydrogen peroxide,[18] which by itself is a relatively poor oxidizing agent. The optimum pH for the reaction (pH=8.5) supports the hypothesis of the

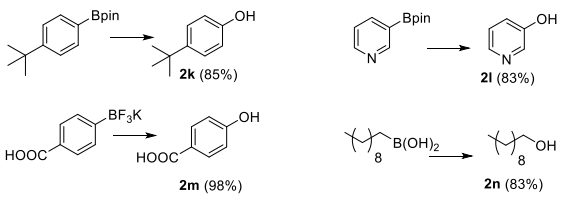
View Article Online
DOI: 10.1039/C5CC01519G
COMMUNICATION

bicarbonate-activated peroxide, which is experimentally proved below.

Once the optimal conditions were found, the scope of this procedure was evaluated. Different types of boronic acids were successfully oxidized with air by this methodology in good yield (Scheme 3). The nature of the substituents seem to have little effect on the outcome of the reaction. Only sterically crowded 2,6-dimethylphenylboronic acid led to moderate yields of phenol **2c**. Additionally, arylboronic esters, potassium trifluoroborate salts (Ar-BF_3K), and alkyl boronic acids can be also oxidized with this methodology (Scheme 4).[19]



Scheme 3 Scope of *ipso*-hydroxylation of arylboronic acids. Oxidations carried out under optimized conditions for 24h.

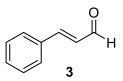
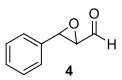
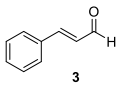
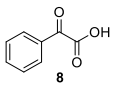
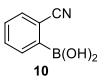
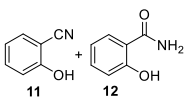


Scheme 4 *ipso*-Hydroxylation of arylboronic esters, potassium trifluoroborate salts and alkyl boronic acids, using the optimized conditions for 24h.

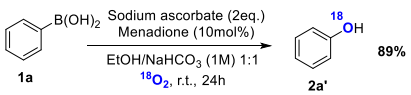
A few other reactions that reportedly occurs with H_2O_2 in the absence of metals were tested with this procedure.[20] As it can be seen in Table 3, ascorbate driven menadione redox-cycling is able to epoxidize cinnamaldehyde with air in similar yields as those reported in analogous conditions with hydrogen peroxide (Entry 1).[21] Noteworthy, epoxidation is only successful when a catalytic amount of pyrrolidine is present, in order to favour the nucleophilic addition of the peroxide.[22] Curiously, increasing the amount of ascorbate and menadione drives to over-oxidation of cinnamaldehyde yielding benzaldehyde in good yield (Entry 2).[23] Dakin oxidation was only achieved in poor yields, probably due to the lack of heating, and the mild basic conditions (Entry 3). Oxidative decarboxylation of phenyl glyoxylic acid was successful (Entry 4). And finally, concomitant ipso-hydroxylation and oxidative hydrolysis of nitrile 10 was also achieved (Entry 5). Unfortunately, oxidations of sulfides or tertiary amines were unsuccessful under these conditions.

While a precise reaction mechanism awaits further study, a few mechanistic experiments support the catalytic cycle depicted in Scheme 1b. When the oxidation of phenylboronic acid **1a** is carried out under $^{18}O_2$ atmosphere, incorporation of such heavier isotope of oxygen in the final compound is detected (Scheme 5). This fact proves that this methodology is indeed activating the atmospheric oxygen and incorporating it into the final products. The hypothesis of hydrogen peroxide production from the oxygen of air, was confirmed by detection of peroxymonocarbonate (HCO_4^-) by ^{13}CNMR (Figure S2): Indeed such anion is generated by reaction between H_2O_2 and bicarbonate, and therefore the presence of (HCO_4^-) in the reaction media necessarily implies that H_2O_2 has to be present.[24] Additionally, the bicarbonate activated peroxide mechanism is also confirmed by the formation of peroxymonocarbonate, which is a stronger oxidant than hydrogen peroxide.

Table 3 Miscellaneous oxidations.[a]

Entry	Reagent	Product	Time	Yield%
1	 3	 4	14h	62[b]
2	 3	 5	48h	66[b,c]
3	 6	 7	48h	32
4	 8	 9	24h	81
5	 10	 11 12	24h	94[d]

[a] Reactions conditions (unless otherwise stated): substrate (1mmol), sodium ascorbate (2mmol), menadione (0.1mmol), ethanol/sodium bicarbonate 1M (1:1), 0.2M, stirring under air at room temperature, protected from light. [b] Pyrrolidine (20 mol%) was added. [c] 4mmol of ascorbate and 0.4mmol of menadione were used. d Yield of 11: 50%, yield of 12: 44%.



Scheme 5 ^{18}O labelling experiment. Determined by E. I. mass analysis.

Conclusions

In summary, a novel and green method of oxidation with air is described herein. This procedure requires no transition metals but combines just two vitamins (ascorbate and menadione) at room temperature and atmospheric pressure. The hydrogen peroxide generated *in situ* by this method has proven to act efficiently as an oxidant of arylboronic acids and a few other organic moieties. These results can find several applications in many fields besides synthesis, such as water decontamination,[25] cosmetics,[26] or even powering nanomotors.[27] Further studies on combining this methodology with sustainable transition metals and chiral ligands are underway in our laboratory.

This research was supported by the European Commission (IMBRAIN project, FP7-REGPOT-2012-CT2012-31637-IMBRAIN), and the Spanish MECD CEI10/00018 and

MINECO, co-financed by the European Regional Development Fund (ERDF), CTQ2011-28417-C02-01, and CTQ2011-22653. G.S.-D. thanks EU Social Fund (FSE) and ACIISI for a pre-doctoral fellowship.

Dedicated in memoriam to Prof. Tsutomu Katsuki

Notes and references

[a] Departamento de Química Orgánica, Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO), Centro de Investigaciones Biomédicas de Canarias (CIBICAN), Universidad de La Laguna. Avda. Astrofísico Fco. Sánchez 2, Apdo. Correos 456, 38200 – La Laguna, S/C. de Tenerife (Spain).

[b] Instituto de Productos Naturales y Agrobiología, CSIC Avda. Astrofísico Fco. Sánchez, 3, 38206 La Laguna, S/C. de Tenerife (Spain).

†Electronic Supplementary Information (ESI) available: Full experimental details, spectroscopic data and copies of NMR spectra. See DOI: 10.1039/c000000x/

1 (a) *Modern Oxidation Methods* (Ed.: J. E. Bäckvall), VCH-Wiley, Weinheim, 2004; (b) R. A. Sheldon, I. W. C. E. Arends, G.-J. Ten Brink, A. Dijksman, *Acc. Chem. Res*., 2002, **35**, 774-781; (c) R. Noyori, M. Aoki, K. Sato, *Chem. Commun*., 2003, 1977-1983.

2 (a) J. Piera and J.-E- Bäckvall, *Angew. Chem. Int. Ed*., 2008, **47**, 3506-3523, and references therein; (b) A. Berkessel, *Adv. Inorg. Chem*., 2006, **58**, 1-28.

3 (a) B. F. Minaev, *Int. J. Quantum. Chem*., 1980, **17**, 367-374; (b) A. L. Buchchenko and V. L. Berdinsky, *J. Phys. Chem*., 1996, **100**, 18292-18299.

4 Paramagnetic metals can use the exchange interaction between the unpaired spin of the metal and the oxygen species for an effective intersystem crossing, which allows the triplet to singlet spin flip. See: R. Prabhakar, P. E. M. Siegbahn, B. F. Minaev and H. Ågren, *J. Phys Chem. B*, 2004, **108**, 13882-13892.

5 P. Anastas and N. Eghbali, *Chem. Soc. Rev*., 2010, **39**, 301-312.

6 (a) H. Kawai, S. Okusu, Z. Yuan, E. Tokunaga, A. Yamano, M. Shiro and N. Shibata, *Angew. Chem. Int. Ed*., 2013, **52**, 2221 –2225; (b) Y. Imada, H. Iida, S. Ono and S.-I. Murahashi, *J. Am. Chem. Soc*., 2003, **125**, 2868-2869; (c) F. Hollmann, A. Taglieber, F. Schulz and M. T. Reetz, *Angew. Chem. Int. Ed*., 2007, **46**, 2903-2906; (d) S. Chen and F. W. Foss Jr., *Org. Lett*., 2012, **14**, 5150-5153; (e) R. Liu, X. Liang, C. Dong and X. Hu, *J. Am. Chem. Soc*., 2004, **126**, 4112-4113; (f) R. Mu, Z. Liu, Z. Yang, Z. Liu, L. Wu and Z.-L. Liu, *Adv. Synth. Catal*., 2005, **347**, 1333-1336.

7 Industrial production of H_2O_2 relies almost exclusively in the anthraquinone oxidation method, which is catalyzed by transition metals. See: J. M. Campos-Martin, G. Blanco-Brieva, J. L. G. Fierro, *Angew. Chem. Int. Ed*., 2006, **45**, 6962-6984.

8 Y. Song, G. Buettner, *Free Radic. Biol. Med*., 2010, **49**, 919-962.

9 Usually ascorbate has only been used to reduce some metals, mainly Cu(II) to Cu(I), like in the CuCAAC "click" reaction. For other uses in synthesis, see: (a) F. P. Crisóstomo, T. Martín and R. Carrillo *Angew. Chem. Int. Ed*., 2014, **53**, 2181-2185; (b) D. L. Browne, I. R. Baxendale and S. V. Ley, *Tetrahedron*, 2011, **67**, 10296-10303.

10 V. Roginsky, T. Barsukova and H. B. Stegmann, *Chem. Biol. Interact*., 1999, **121**, 177–197.

11 (a) J. Verrax, R. Beck, N. Dejeans, C. Glorieux, B. Sid, R. C. Pedrosa, J. Benites, D. Vásquez, J. A. Valderrama and P. B. Calderon, *Anticancer Agents Med. Chem.*, 2011, **11**, 213-221; (b) R. Pethig, P. R. C. Gascoyne, J. A. Mclaughlin and A. Szent-Gyorgyi, *Proc. Natl. Acad. Sci*., 1983, **80**, 129-132; (c) J. Verrax, J. Cadrobbi, M. Delvaux, J. M. Jamison, J. Gilloteaux, J. L. Summers, H. S. Taper and P. B. Calderon, *Eur. J. Med. Chem*., 2003, **38**, 451-457; (d) R. Beck, J. Verrax, N. Dejeans, H. Taper and P. B. Calderon, *Int. J. Tox*., 2009, **28**, 33-42.

12 Q. Chen, M. G. Espey, A. Y. Sun, J.-H. Lee, M. C. Krishna, E. Shacter, P. L. Choyke, C. Pooput, K. L. Kirk, G. R. Buettner and M. Levine, *Proc. Natl. Acad. Sci*., 2007, **104**, 8749-8754.

13 (a) Z. He and T. F. Jamison, *Angew. Chem. Int. Ed*., 2014, **53**, 3353-3357; (b) Y.-Q. Zou, J.-R. Chen, X.-P. Liu, L.-Q. Lu, R. L. Davis, K. A. Jørgensen and W.-J. Xiao, *Angew. Chem. Int. Ed*., 2012, **51**, 784-788; (c) S. P. Pitre, C. D. McTiernan, H. Ismaili and J. C. Scaiano, *J. Am. Chem. Soc*., 2013, **135**, 13286−13289; (d) C. Zhu, R. Wang and J. R. Falck, *Org. Lett.*, 2012, **14**, 3494-3497; (e) Y. Zhong, L. Yuan, Z. Huang, W. Gu, Y. Shao and W. Han, *RSC Adv.*, 2014, **4**, 33164-33167; (f) H. Jiang, L. Lykke, S. U. Pedersen, W.-J. Xiao and K. A. Jørgensen, *Chem. Commun*., 2012, **48**, 7203-7205; (g) W. Ding, J.-R. Chen, Y.-Q. Zou, S.-W. Duan, L.- Q. Lu and W.-J. Xiao, *Org. Chem. Front*., 2014, **1**, 151-154; (h) P. Kaewmati, E. Somsook, R. N. Dhital and H. Sakurai, *Tetrahedron Lett*., 2012, **53**, 6104-6106.

14 J. N. Bull, C. W. West and J. R. Verlet, *Chem. Sci*., 2015, **6**, 1578-1589.

15 E. J. Nanni, Jr., M. D. Stallings and D. T. Sawyer, *J. Am. Chem. Soc*., 1980, **102**, 4481-4485.

16 G. B. Payne, P. H. Deming and P. H. Williams, *J. Org. Chem*., 1961, **26**, 659-663.

17 Reactions under pure O_2 led to similar yields. We chose open flask reactions because they are much more sustainable and affordable.

18 (a) H. Yao and D. E. Richardson, *J. Am. Chem. Soc*., 2000, **122**, 3220-3221; (b) D. E. Richardson, H. Yao, K. M. Frank and D. A. Bennett, *J. Am. Chem. Soc*., 2000, **122**, 1729-1739; (c) B. Balagam and D. E. Richardson, *Inorg. Chem*., 2008, **47**, 1173-1178.

19 Initial attempts to oxidize alkenyl boronic acids were unsuccessful.

20 We have chosen known transition metal free reactions in order to assure that metals have no influence in the generation of hydrogen peroxide or other reactive oxygen species.

21 W.Zhuang, M. Marigo and K. A. Jørgensen, *Org. Biomol. Chem*., 2005, **3**, 3883-3885.

22 Promising results with chiral prolinol derivatives will be reported elsewhere.

23 P. Wright and J. Abbot, *Int. J. Chem. Kinet.*, 1993, **25**, 901-911.

24 E. V. Bakhmutova-Albert, H. Yao, D. E. Denevan and D. E. Richardson, *Inorg. Chem*., 2010, **49**, 11287-11296.

25 (a) W. C. Ellis, C. T. Tran, R. Roy, M. Rusten, A. Fischer, A. D. Ryabov, B. Blumberg and T. J. Collins, *J. Am. Chem. Soc*., 2010, **132**, 9774-9781. (b) B. M. Smith, *Chem. Soc. Rev*., 2008, **37**, 470-478.

26 J. Marsh, R. M. Dahlgren, C. Clarke, J. Stonehouse and C. Nunn, *J. Cosmet. Sci*., 2009, **60**, 205-215.

27 S. Sánchez, L. Soler and J. Katuri, *Angew. Chem. Int. Ed*., 2015, **54**, 1414-1444, and references therein.