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Catalyst-free aerobic oxidation of aldehydes into acids in water under mild conditions

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Yue Zhang,[a]† Yujia Cheng,[a]† Huizhuo Cai,[a] Shaopo He,[a] Qiheng Shan,[a] Hongwei Zhao,[b,c] Yiping Chen,[a] and Bo Wang*[a,b]

The first example of catalyst-free aerobic oxidation of aldehydes in water under respective acidic, neutral and alkaline conditions was developed. The sole oxidant is molecular oxygen of 1 atomosphric and reactions can proceed under extremely mild conditions. This procedure covers a wide range of aldehydes, and operated easily. No additives and catalyst were required for that purpose, and most of the aldehydes can be converted to their corresponding carboxylic acids with good to excellent yields, in addition, no side-product formation could be observed during or after reactions. To well illustrate why oxidation rate become fast firstly and then slows with increased temperatures, five control reactions were carried out and a Fe^{3+}/Fe^{2+} recycling system was introduced to facilitate aldehyde oxidation rate. The generality of this method offers the potential for industrial aldehyde-containing waste water treatment.

Introduction

Oxidation is one of the most fundamental reactions in nature, and the oxidation of aldehydes into their corresponding carboxylic acids is an important biological process for daily life activities.[1] One of the most representative examples is the oxidation of acetaldehyde into acetic acid in liver cells at 37°C in water using the sole oxidant oxygen and dehydrogenase as the catalyst under neutral pH conditions as some aldehydes, for instance, acetalhyde can cause damage to human DNA.[2] As has been illustrated(Route **a**, **Fig.1**),[3-6] most aldehydes are generally stable and inert towards autoxidation though being prone to oxidation as most of them need strong oxidizer such as $KMnO_4$, CrO_4, or KIO_4 to assist their transformation to carboxylic acids.[7] In addition, most procedures for aldehyde oxidation still rely on stoichiometric loadings of hazardous oxidants such as dichromate/permanganate,[8-9] oxone,[5] periodate reagent,[6] and *etc* promoted oxidation reactions, which usually proceeded in harmful organic solvents, and followed is the generation of large amounts of waste water stream usually containing heavy metals, which are wasteful and usually considered not environmentally benign.[10-12] Therefore, procedures with molecular oxygen as the terminal oxidant and proceed in aqueous phase remains scare for clean preparation of carboxylic acids from aldehydes.[13]

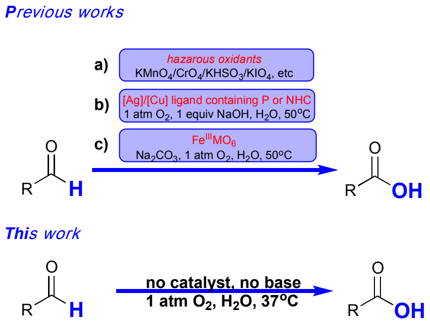

Fig.1 Representative examples and schematic profile of oxidation of aldehydes into carboxylic acids

In addition, in some draining waste water from chemical companies especially those from medicine chemical synthesis corporations, 'trace-less' aldehydes usually exist, which are difficult for natural biodegradation and may cause serious environmental problems,[13,14] for instance, diatoms can release toxic polyunsaturated aldehydes.[15] Therefore, before discarded, aldehydes must be removed or converted to their corresponding stable formats (carboxylic acids) that are not harmful to living creatures, one important principle is the removal process shouldn't introduce new chemical(s) that might be new pollution sources, and therefore base/acid or oxidants for waste water treatment are unsuitable as further downstream neutralization or reduction processes are required, usually followed is salt stream requiring a second salt removal treatment. Therefore, developing green and catalyst-

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[a] *Mr. Y. Zhang, Ms. Y.J. Cheng, Ms. H.Z. Cai, Mr. S.P. He, Mr. Q.H. Shan, Prof. Y.P. Chen, Prof. Dr. B. Wang.*
Key Laboratory of Advanced Materials of Tropical Island Resources (Hainan University), Ministry of Education,
No.58 Renmin AVE. Haikou 570228, PR China.
Email: wangbo@hainu.edu.cn, bo.wang@hainu.edu.cn (Prof. B. Wang)
[b] *Prof. Dr. B. Wang, Assoc. Prof. H.W. Zhao*
State Key Lab of Marine Resource Utilisation in South China Sea, Hainan University,
No. 58 Renmin AVE. Haikou 570228, PR China
Email: wangbo@hainu.edu.cn, bo.wang@hainu.edu.cn (Prof. B. Wang)
[c] *Assoc. Prof. H.W. Zhao*
Institute of Tropical Agriculture and Forestry, Hainan University
No. 58 Renmin AVE. Haikou 570228, PR China

† Both authors contributed equally to this work, and the order of authors was determined by coin toss.

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free protocols using molecular oxygen as the sole oxidant and proceeded smoothly at ambient temperatures covering a wide range of pH is highly desirable in both industry and academia, especially useful for aldehyde-containing waste water treatment processes.

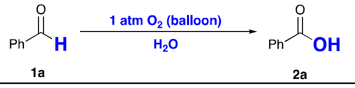
Compared to commonly used organic solvents, the natural abundance of water and its inherently greener characteristics makes it extremely attractive for developing eco-friendly reactions. Recently, aerobic oxidations of aldehydes using molecular oxygen have received a plethora of attentions.[7,16,17] Li *et al.* developed the first example of a homogeneous catalyst silver-/copper- ligand promoted aerobic oxidation in water,[7] an array of aldehydes was converted to acids with ideal yields under mild conditions (50°C, Route **b**, **Fig.1**). Wei *et al.* reported the first example using a recyclable homogeneous catalyst iron(III)-catalysed aerobic oxidation of aldehydes in water under mild conditions,[17] a wide range of functionalized aldehydes were transformed into carboxylic acids in good to excellent yields of up to 99% (50°C, Route **c**, **Fig.1**). Nevertheless, in both methods, metal catalysts were involved, and strong alkalinity of reaction media is relied on, which are incompatible with alkalinity sensitive substrates or substrate with alkalinity sensitive group(s). And when reactions were completed, an additional neutralization processes are required, leading to the formation of large amount of waste salt stream.

Herein, we present a catalyst-free aerobic oxidation process for treatment of trace-aldehyde-containing waste water through the way of converting aldehyde into carboxylic acids at extremely mild conditions, noted that here we use mimic waste water (dissolving aldehyde in water) instead of real-life one aims at easy and accurate detection of aldehyde and their related carboxylic acids, molecular oxygen of 1 atmospheric is used as the sole oxidant. For testing the generality of the protocol, acidic, neutral and alkaline conditions were assessed to expect for satisfactory results (**Table.2**). A wide range of aldehydes were evaluated and no additional additives (base or acid) were required for that purpose. And 37°C was chosen as the optimized temperature for reactions after optimization reactions, five control reactions were carried out with/without Fe^{3+} ions to investigate how and the effect of phase transfer on aldehyde conversions with increased temperatures. Most of the aldehydes can be converted to their corresponding carboxylic acids with good to excellent yields of up to 99%, and no side-product formation could be detected during or after reactions.

Results and discussion

Initial investigations were carried out using benzaldehyde as the model substrate under aqueous conditions, in order to meet some principles of green chemistry, H_2O_2 and molecular oxygen were selected as candidates for oxidation of aldehydes into carboxylic acids as the resulted sole by-product is water after reaction. Oxygen was simply flushed into a balloon and sealed along with the flask after substrate aldehyde and water as the solution were charged. Compared with those employing oxidant H_2O_2, reactions using molecular oxygen could offer better conversions at 25°C in 8h, as when using H_2O_2 under the same conditions, the conversion was 47%(Entry 1, **Table 1**), and a higher temperature when at 37°C, the yields declined sharply to 8% (Entry 2, **Table 1**). Nevertheless when use molecular oxygen as the oxidant at 37°C and the reaction time was prolonged to 24h, the yield was boosted to >99% (Entry 13, **Table 1**), indicating that oxygen is more suitable for aldehyde oxidative conversion compared to H_2O_2, and therefore in future evaluations, oxygen will be chosen as the oxidant and reaction time is 24h. Reaction temperatures varied from 25°C to 50°C were also evaluated for suitable oxidation conditions, when temperature was increased from 25°C to 37°C, and finally to 50°C, the yield of product benzoic acid **2a** was firstly boosted from 78% to a quantitative yield of 99%, and then declined to 94% at 50°C (Entry 6,9,13, **Table 1**), indicating that 37°C is more suitable among all tested temperatures for oxidation. Conventionally, those reactions proceed at a higher temperature give faster reaction rates compared to those at a lower temperature, and therefore, the conversion of aldehyde is supposed to increase before reaching a full conversion.

Table 1. Optimization of reaction conditions[a]



Entry	*C* (mM)	Oxidant	Temp. (°C)	Time (h)	Yield (%)
1	10	H_2O_2	25	8	47
2	10	H_2O_2	37	8	8
3	10	O_2	37	8	35
4	5	O_2	25	8	35
5	5	O_2	25	12	62
6	5	O_2	25	24	78
7	5	O_2	50	8	32
8	5	O_2	50	12	77
9	5	O_2	50	24	94
10	5	O_2	37	8	37
11[b]	5	O_2	37	8	99
12	5	O_2	37	12	81
13	5	O_2	37	24	>99
14	10	O_2	37	24	90
15	2	O_2	37	24	99

[a]Conditions: all reactions were carried out at a 5ml scale at varied temperatures under pH = 5.0, after all substances were charged in closed vessels. Yields were determined by HPLC analysis using a SHIMADZU LC-16 instrument equipped with a C18-WR column at the wavelength of 254 nm; [b] Reaction was performed with conditions as in footnote a, except that the pH of the reaction medium was made at 3.0 using Fe^{3+} of 0.5%mol.

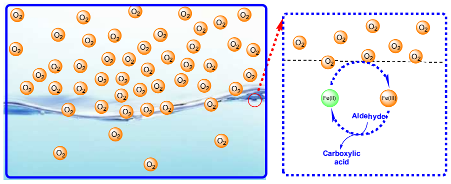


Fig.2 Oxygen on/below the surface of reaction medium and Fe^{3+}/Fe^{2+} recycling system

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With increased temperatures from 25°C to 50°C, a promotion in the reaction rate was observed, however, the solubility of molecular oxygen in water shows a reverse tendency, reaction rate slowed. The decline in the yield (94%) of product **2a** at 50°C may possibly attribute to mass transfer resistance of oxygen from oxygen gas on liquid surface down to liquid solution. Larger mass transfer resistance of oxygen makes the concentration of oxygen lower, and as a consequence, fewer benzaldehyde molecular will be successfully transformed to benzoic acids though oxidation reaction rate maybe accelerated at a higher temperature.

To well address increased mass transfer resistance of oxygen with increased temperatures and whose effects on the oxidation of aldehydes in water, five control reactions **A, B, C, D, E** (**Fig. 3**) under different conditions were carried out and evaluated. A Fe^{3+}/Fe^{2+} recycling system was introduced and functioned as a shuttle moving up and down from the surface of solution down to inside it (**Fig. 2**), Fe^{3+} ion can oxidize benzaldehyde into benzoic acid easily and very fast, which was then converted to a reduced format Fe^{2+}(**Scheme A**) after oxidizing aldehyde into acid, and when ion Fe^{2+} moves to the surface of reaction medium, it was converted back to Fe^{3+} the moment when meeting with oxygen, and again back to solution ready for oxidation in a following round. In reaction **A,** ion Fe^{3+} of 0.5mol% was dissolved in water, and the solution was set at pH3.0, after 8h, an almost full conversion of >99% was achieved. However, in reaction **B**, with no Fe^{3+} ions, in the same time 8h, only a poorer conversion of 38% was obtained. Based on these results, it is indicated that the oxygen transfer from on the solution surface down to inside the solution was greatly accelerated. By prolonging the reaction time to 24h, we found that a quantitative yield could also be afforded, indicating that under pH 3.0, ion Fe^{3+} could greatly enhance oxidation rate and reduce reaction time. In addition, the results also indicated that with enough oxygen gradually dissolving in solution, the conversion can also be very close to that using a Fe^{3+}/Fe^{2+} recycling system, a conclusion can thus be drawn that with increasing temperatures, lower conversions were associated before full conversions, a longer reaction time was necessary for theoretically ideal conversions. In reaction **C**, we used N_2 instead of O_2 and ion Fe^{3+} of 0.5mol% to test the oxidation capacity of Fe^{3+}, and as expected, about 0.5% of aldehyde was successfully converted to benzoic acid, even when reaction was prolonged to 24h. After reaction, the volume of N_2 after reaction remains the same as before, proved that the airtightness of reaction vessel was quite good. As is known, ion Fe^{3+} will precipitate when pH of the solution turns to be >3.2. And in order to test whether oxidation reaction can still proceed well when pH of the reaction medium was made at 9.0 (in such case, the majority portion of Fe^{3+} will become precipitate, leading to a very small portion of metal ion dissolved and remained in the reaction system, and the left Fe^{3+} ions were supposed to loss their capability for oxidation of aldehyde). After 8h, the conversion was measured by HPLC to be 40%, a slight increase compared to that proceeded under pH 3.0, it was proposed that stronger alkaline can make positive contributions to oxidative transformation, and also similar results were provided by Li *et al*. and Wei *et al*. as in whose reported procedures, NaOH/Na_2CO_3 was essential for such transformation. By prolonging the reaction time to 24h, the results made basically no difference in both reactions as both could provide yields of up to 99%. Replacing ion Fe^{3+} in reaction **E** and compared with reaction **D**, similar results can still be obtained, indicating that when with no assistance of ion Fe^{3+} after a prolonged time, the conversions can still approach theoretical conversions.

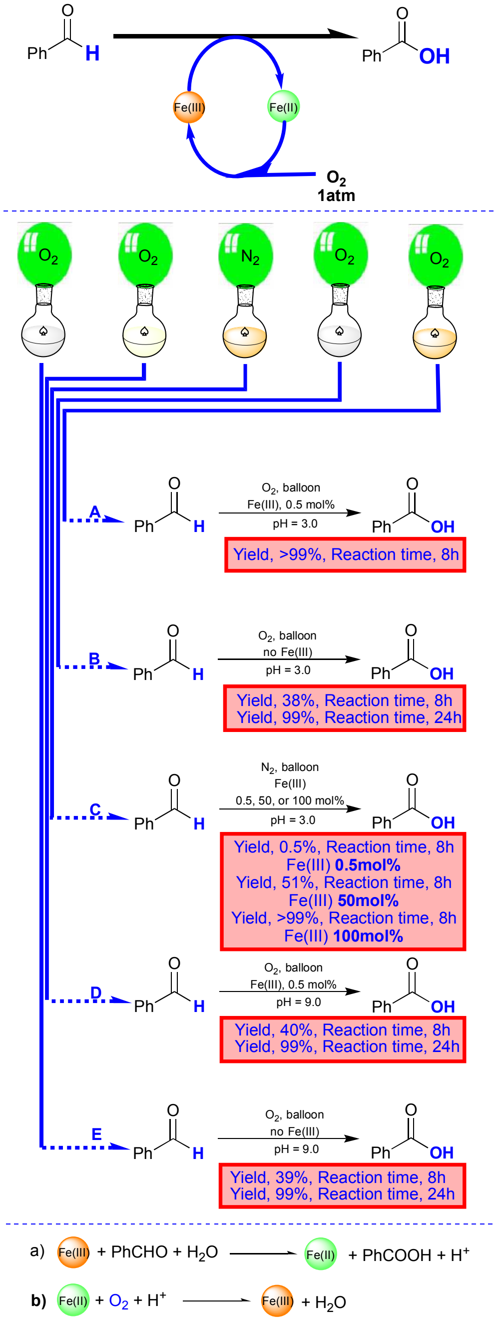

Fig. 3 Control experiments for exploring possible effects on aldehyde oxidation caused by mass transfer resistance of oxygen

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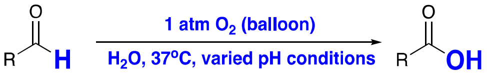
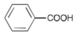
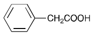
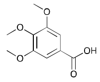
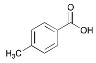
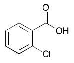
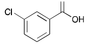
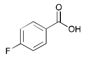
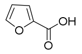
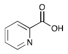
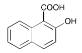
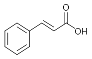
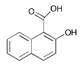
The concentration of benzaldehyde can also have some effects on conversion of benzaldehyde during oxidation process, as has been addressed that the bottleneck in this reaction is continuous dissolving oxidant oxygen in reaction solution. When concentration of benzaldehyde **1a** was made at 10mM, after reacted for 24h, the yield of product **2a** was 90% (Entry 14, Table 1), nevertheless, when substrate **1a** was set at a lower concentration 5mM under the same conditions, almost full conversion (99%) was achieved (Entry 13, Table 1), indicating that either by increasing the concentration of molecular oxygen or lowering aldehyde's concentration, the yields of product **2a** can be theoretically obtained to be quantitative, however it is quite tough to increase the concentration of oxygen at a higher temperature with 1 atmospheric oxygen. Therefore, a lower aldehyde concentration of 5.0mM will be chosen in future investigations.

Table 2 Results of oxidation under acidic, neutral and alkaline conditions



Aldehyde	Product	Entry	*C* (mM)	pH	Time (h)	Yield (%)	Entry	*C* (mM)	pH	Time (h)	Yield (%)	Entry	*C* (mM)	pH	Time (h)	Yield (%)
1a		1	10	5.0	24	90	16	10	7.0	24	92	31	10	9.0	24	96
		2	5	5.0	24	96	17	5	7.0	24	99	32	5	9.0	24	>99
		3[b]	5	3.0	8	99	18[d]	5	7.0	8	39	33[f]	5	9.0	8	41
1b		4	5	5.0	24	74	19	5	7.0	24	83	34	5	9.0	24	90
1c		5	5	5.0	24	84	20	5	7.0	24	84	35	5	9.0	24	86
1d		6	5	5.0	24	87	21	5	7.0	24	97	36	5	9.0	24	93
1e		7	5	5.0	24	98	22	5	7.0	24	>99	37	5	9.0	24	99
1f		8	5	5.0	24	99	23	5	7.0	24	96	38	5	9.0	24	99
1g		9	5	5.0	24	99	24	5	7.0	24	>99	39	5	9.0	24	89
1h		10	5	5.0	12	95	25	5	7.0	24	95	40[g]	5	9.0	36	99
1i		11	5	5.0	24	63	26	5	7.0	24	65	41	5	9.0	24	85
1j		12	5	5.0	24	99	27	5	7.0	24	>99	42	5	9.0	24	99
1k		13	5	5.0	24	75	28	5	7.0	24	78	43	5	9.0	24	89
1l		14[c]	5	3.0	8	99	29[e]	5	7.0	8	47	44[h]	5	9.0	8	51
		15	5	5.0	24	99	30	5	7.0	24	99	45	5	9.0	24	>99

[a] Conditions: Unless otherwise stated, all reactions were carried out at a 5ml scale at 37°C under varied pH conditions with oxygen of 1 atmospheric, after all substances were charged in closed vessels and oxygen was flushed in a balloon and sealed, which was stirred in a shaker incubator for 24 h. Yields were determined by HPLC analysis using a SHIMADZU LC-16 instrument equipped with a C18-WR column (4.6 mm×250 mm,5μm) at the wavelength of 254 nm; [b,c] Reaction was performed with conditions as in footnote a, except that the pH of the reaction medium was made at 3.0 when using Fe^{3+} of 0.5%mol, and when at pH = 5.0, and 9.0, no Fe^{3+} ions were employed herein, reaction time, 8h; [d,e,f,h] Reaction time, 8h; [g] Reaction time, 36h.

With all optimized reaction conditions in hand, the scope of substrates and functional-group compatibility of this procedure were further evaluated (Table 2) under varied pH conditions (pH = 3.0, 5.0, 7.0, and 9.0). An array of aldehydes was then conducted and some of them bear various functional groups (electron- donating/withdrawing group(s)), all reactions were proceeded smoothly and the results were summarized in Table 2. To our satisfied, most of the reactions could afford good to excellent yields of up to 99% except aldehyde **1i**, the yields were 65%, 63%, and 85% respectively when carried out under pH 5.0, 7.0 and 9.0 (Entry 11, 26, 41, **Table 2**). It was supposed that in the molecular structure of **1i**, the aromatic heterocyclic ring as a functional group functioned as withdrawing electron to the aldehyde moiety, making the aldehyde moiety less inactive for oxidation compared with conventional aromatic rings with no substituent(s). In most conditions, reactions proceeded under pH 9.0 could provide better yields than those under pH 5.0, indicating that better conversions can benefit from the addition of base (Entry 1-3,16-18,31-33, **Table 2**), which correlated well with the reported procedures by Li *et al*. and Wei *et al*. However, using base for assisting oxidation process by molecular oxygen might be unpractical especially for aldehydes bearing alkaline sensitive functional groups, and also for consideration of green and sustainable development for industrial purpose as in the following downstream treatment process, large amounts of

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waste water were usually generated. As to the aliphatic aldehyde *n*-butyl aldehyde, this aerobic oxidation seems to be not compatible well as poor conversion of 32% was obtained. Further optimisation of the conditions for aliphatic aldehydes so that these substrates can be utilized is underway.

In conclusion, we have, for the first time developed a catalyst-free aerobic oxidation of an array of aldehydes proceeding in aqueous solution. During oxidation reactions, ultra-green molecular oxygen is used as the sole oxidant, the generality of the procedure under acidic, neutral and alkaline conditions were evaluated and most of them gave satisfactory conversions. To illustrate why the conversions became lower at a higher temperature 50^{o}C, five control reactions were carried out, and some were introduced with a Fe^{3+}/Fe^{2+} recycling system to facilitate fast oxidation. It was found that the solubility of molecular oxygen plays an essential role in increased mass transfer resistance of oxygen. A wide array of aldehydes was subject and most of the reactions offer the corresponding carboxylic acids with good to excellent yields of up to 99%, no side-product formation reactions were observed. Offering potentials for sustainable and clean synthesis of carboxylic acids from aldehydes, especially for 'trace-less' aldehyde waste processing in chemical industry.

Acknowledgements

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Notes and references

1 a) J. March, *Advanced Organic Chemistry*: *Reactions, Mechanisms, and Structure*, 4th ed., Wiley, New York, 1992; b) T.J. Collins, *Acc. Chem. Res*. 1994, **27**, 279; c) M. B. Smith, J. March, *March's Advanced Organic Chemistry*: *Reactions, Mechanisms, and Structure*, 6th ed., Wiley, Hoboken, 2007; d) G. Tojo, M. Fernández, *Oxidation of Primary Alcohols to Carboxylic Acids,* Springer, New York, 2010; e) P.Y. Ruce, *Organic Chemistry*, Prentice Hall, Englewood Cliffs, NJ, 2012.

2 a) D. W. Crabb, M. Matsumoto, D. Chang, M. You, *Proc. Nutr. Soc.* 2004, **63**, 49; b) E. MC. Tacconi, X. N. Lai, C. Folio, M. Porru, G. Zonderland, S. Badie, J. Michl, I. Sechi, M. Rogier, V. M. García, A. S. Batra, O. M. Rueda, P. Bouwman, J. Jonkers, A. Ryan, B. Reina-San-Martin, J. Hui, N. Tang, A. Bruna, A. Biroccio, M. Tarsounas, *EMBO Molecular Medicine*, 2017, 1-17. DOI: 10.15252/emmm.201607446

3 A. Mahmood, G. E. Robinson, L. Powell, *Org. Process Res. Dev.*
1999, **3***,* 363.

4 J.K. Thottathil, J.L. Moniot, R.H. Mueller, M.K.Y. Wong, P.T. Kissick, *J. Org. Chem.* 1986, **51***,* 3140.

5 B.R. Travis, M.G. Sivakumar, O. Hollist, B. Borhan, *Org. Lett.* 2003, **5***,* 1031.

6 M. Hunsen, *Synthesis* 2005, **15**, 2487.

7 M. Liu, C.-J. Li, *Angew. Chem. Int. Ed.* 2016, **128**, 10964.

8 a) R.L. Shriner, E.C. Kleiderer, *Org. Synth*. 1930, **2**, 538; 6) J.R. Ruhoff, *Org. Synth*. 1936, **2**, 315.

9 L.T. Sandborn, *Org. Synth*. 1921, **1**, 340.

10 M. Yoshida, Y. Katagiri, W.-B. Zhu, K. Shishido, *Org. Biomol. Chem*. 2009, **7**, 4062.

11 L. Han, P. Xing, B. Jiang, *Org. Lett.* 2014, **16**, 3428.

12 P. de Frémont, N. M. Scott, E.D. Stevens, T. Ramnial, O.C. Lightbody, C.L.B. Macdonald, J. Clyburne, A.C.C.D. Abernethy, S.P. Nolan, *Organometallics* 2005, **24**, 6301.

13 S.S. Stahl, *Science* 2005, **309**, 1824.

14 I. Arends, U. Hanefeld, Green Chemistry and Catalysis, ed. R. A. Sheldon, Wiley-VCH, Weinheim, 2007.

15 M. Pepi, H. J. Heipieper, C. Balestra, M. Borra, E. Biffali, R. Casotti, *Chemosphere*, 2017, **177**, 258.

16 M. Liu, H. Wang, H. Zeng, C.-J. Li, *Sci. Adv.* 2015, 1, e1500020

17 H. Yu, S. Ru, G. Dai, Y. Zhai, H. Lin, S. Han, Y. Wei, *Angew. Chem. Int. Ed.* 2017, **56**, 3867.