Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. R. Bathula, S. Pochampalli, R. Owk and P. R. Muktapuram, *Org. Biomol. Chem.*, 2015, DOI: 10.1039/C5OB01569C.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C5OB01569C

Journal Name

Copper Catalyzed Oxygen Assisted C(CNOH)-C(alkyl) Bond Cleavage: A Facile Conversion of Aryl/Aralkyl/Vinyl Ketones to Aromatic Acids

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

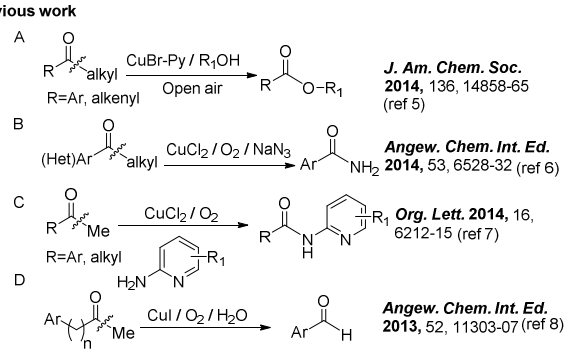
Pochampalli Sathyanarayana,[a] Owk Ravi,[a] Prathap Reddy Muktapuram,[a] and Surendar Reddy Bathula*[a]

A novel copper-catalyzed aerobic oxidative C(NOH)-C(alkyl) bond cleavage reaction of aryl/aralkyl/vinyl ketones for the synthesis of aromatic/acrylic acids is described. A series of ketones having aryl/aralkyl/vinyl at one end and methyl to any higher alkyl at the other end can be selectively cleaved and converted into the corresponding acids via oxime intermediates.

Cleavage of C-C single bonds, which are ubiquitous in nature, is an emerging interest in the field of organic chemistry because of its use in functionalization, biodegradation and industrial applications.[1a-i] Given the high activation energy, achieving such selective cleavages without effecting other starting materials and functional groups has been a challenging task.[1a-i] In addition to some well known methods such as, the use of strained skeletons[2a-h] or chelation assisted strategies,[3a-i] recently emerged Cu-catalyzed aerobic oxidative cleavage of alkyl groups adjacent to a keto functional group has become promising means for such hitherto formidable processes.[4] Jiao et al. have reported Cu-catalyzed aerobic oxidative C-C bond cleavage reactions from ketones to esters[5] and to amides[6] (Scheme 1A-B). Kaliappan et al. have demonstrated a one-pot oxidation reaction of methyl ketones to N-heterocyclic amides[7](Scheme 1C). Bi et al. have developed a copper-catalyzed aerobic oxidative C(CO)-C(methyl)bond cleavage reaction for the synthesis of aldehydes[8] (Scheme 1D). Here we report the synthesis of aryl/vinyl carboxylic acids using copper catalyzed C(CO)-C bond cleavage reaction under an oxygen atmosphere (Scheme 1E).

Aromatic acids are prevalent in nature and they are prominently used in both industry and academia.[9] In addition, most of the non-steroid antiphlogistic drugs such as Aspirin, Diflunisal, Mefenamic acid, Meclofenamic, Niflumic acid and Tolfenamic acid etc. are aromatic carboxylic acids. Arenes are major precursors of aromatic carboxylic acids and this conversion require strong oxidants and harsh reaction conditions.[10] Moreover, aryl methyl ketones are the best alternative precursors because they are readily available if not they can be easily prepared by acylation reactions. However, oxidation of these ketones is possible only by the cleavage of the α C-C single bond. Among the available methods, haloform reaction[11] using sodium hypochlorite is superior for the conversion of acyl arenes to aromatic acids. But, it requires an extra acidification step and also this reaction is not applicable for the higher alkyl aryl ketones and sensitive vinyl methyl ketones. Hence, an efficient C-C bond cleavage strategy which can convert the above mentioned substrates to their corresponding acids is highly desirable.

Scheme 1. Copper mediated cleavage of C-C bond adjacent to carbonyl group.



Based on the recent publications on the oxidative C-C bond cleavage of acetophenones,[5-8] and inspired by a report by Chiba et al for the cleavage of α-keto imino copper intermediates[12] we aimed for the C-C bond cleavage that is adjacent to oxime. This may lead to the formation of corresponding nitriles.

Thus, we treated 4-methoxyacetophenone (**1a**, 1 mmol) with 2 eq of hydroxylamine and 30 mol% CuI in DMSO under oxygen atmosphere (table 1). When the contents were stirred at rt for 12 h we obtained only oxime **2a** in 55% yield. Increase of hydroxyl amine to 4 equivalents at rt improved the yield of **2a** to 70% along with the surprising formation of acid **3a** in 12%. When the temperature

[a]Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad-500007, India. E-mail: bsreddy@iict.res.in

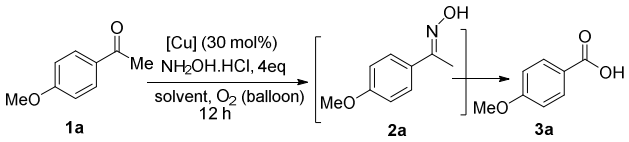
Electronic Supplementary Information (ESI) available: Experimental procedures and compound characterization data.. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C5OB01569C

was raised to 50 °C the yield of **3a** was improved to 43%. Interestingly, at 100 °C, the above reaction exclusively produced carboxilic acid (**3a**) with excellent yield (95%, entry 4, table 1). Of note is that the use of anhydrous DMSO led to the sluggish and incomplete conversion, demonstrating that the presence of water is necessary for the reaction. However, the reaction did not occur in the absence of Cu-catalyst or hydroxyl amine (entry 12 and 13, table 1). On the other hand, when conducted in the open air, the reaction ended up with the intermediate oxime even after 24 h.

Among the tested copper salts copper (I) chloride, bromide and iodide are all equally effective in promoting reaction and we got best result with CuI (entry 4-6). Copper (II) acetate gave mixture of products (entry 7) and, with Copper Oxide only starting material was recovered (entry 8). In agreement with the earlier reports,[8] DMSO was found to be the appropriate solvent and no product formation was observed in solvents such as DMF, DCE and EtOH. Effectiveness of DMSO in aerobic oxidations may be attributed to its efficient metal-coordinating and catalyst stabilizing properties.

Table 1. Optimization of hydroxyl amine mediated carbon-carbon bond cleavage reaction conditions[a].

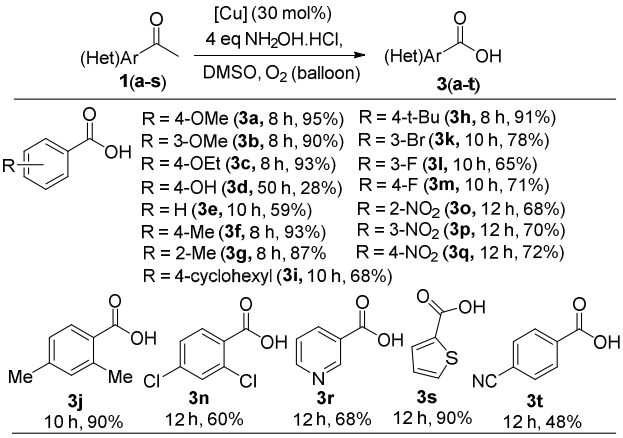


entry	[Cu]	$NH_2OH.HCl$	solvent	temp (°C)	Yields%[b] 2a	3a
1	CuI	2eq	DMSO	rt	55	--[c]
2	CuI	4eq	DMSO	rt	70	12
3	CuI	4eq	DMSO	50	45	43
4	**CuI**	**4eq**	**DMSO**	100	--	**95**
5	CuCl	4eq	DMSO	100	--	92
6	CuBr	4eq	DMSO	100	--	90
7	$Cu(OAc)_2$	4eq	DMSO	100	56	15[c]
8	CuO	4eq	DMSO	100	--	--[c]
9	CuI	4eq	DMF	100	12	--[c]
10	CuI	4eq	DCE	100	--	--[c]
11	CuI	4eq	EtOH	70	--	--[c]
12	CuI	--	DMSO	100	--	--[c]
13	--	4eq	DMSO	100	--	--[c]

[a] Reaction conditions: **1a** (1.0 mmol), $NH_2OH.HCl$ (4.0 mmol), copper catalyst (0.03 mmol), heated in DMSO at 100 °C for 12 h under O_2 balloon. [b] Isolated yields. [c] Starting material recovered.

Having the optimized conditions (entry 4 in table 1) in hand, we first planned to investigate the scope of (hetero)aryl methyl ketones in above reaction conditions. As depicted in table 2, a broad variety of acids could be readily obtained under the optimized conditions. Aromatic methyl ketones with electron-donating groups at either Ortho, Meta or Para-positions of the aryl ring all furnished the corresponding products (**3a**-**3c**) in good to excellent yields (90-95%). The presence of an electron-withdrawing group on the aromatic methyl ketones was also tolerated (**3k**-**3q**). However, the products were obtained in moderate to good yields (60-78%). Furthermore, heteroaromatic methyl ketones also offered the corresponding acids (**3r**-**3s**) in good to excellent yields (68-90%). But, in the case of 4-acetylbenzaldehyde we didn't observed 4-formylbenzoic acid. Instead of the above said compound, we observed 4-cyanobenzoic acid (**3t**) in moderate yield (48%).

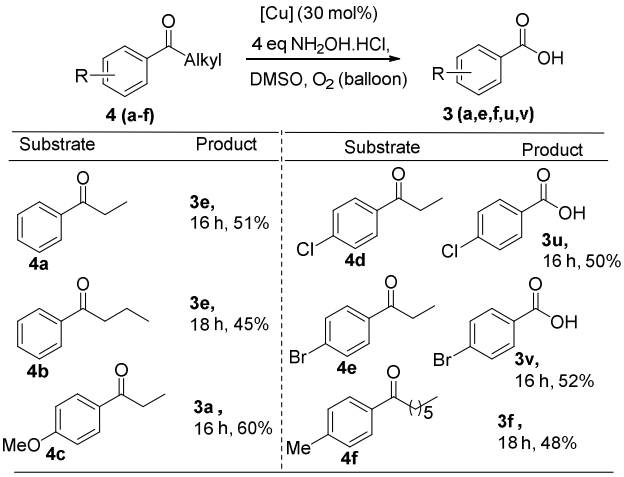
Table 2. Synthesis of aromatic acids from aryl methyl ketones.



Reaction conditions: **1** (1.0 mmol), $NH_2OH.HCl$ (4.0 mmol), copper catalyst (0.03 mmol), heated in DMSO at 100 °C, under O_2 balloon. Yields are based on Isolated products.

Encouraged by the above results, we turned our attention towards the more challenging aryl higher alkyl (other than methyl) ketones (**4a**-**4f**) as our next substrates (table 3). To our delight, these substrates reacted well under the standard reaction conditions with the scission of entire alkyl group irrespective of its length to produce corresponding benzoic acids (**3a**, **3e**, **3f**, **3u**, **3v**) in moderate yields (45 to 60%). Such an erosion of any length of alkyl group was also demonstrated by Jiao et al[6] during the synthesis of amides. Of note is that the classical alternative, the haloform reaction, cannot be extended to such higher alkyl ketones.

Table 3. Synthesis of benzoic acids from aryl alkyl ketones.



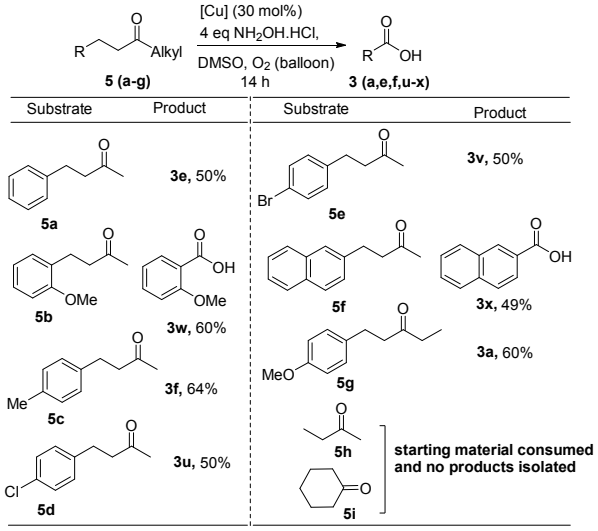
Reaction conditions: **4** (1.0 mmol), $NH_2OH.HCl$ (4.0 mmol), copper catalyst (0.03 mmol), heated in DMSO at 100 °C, under O_2 balloon. Yields are based on Isolated products.

View Article Online
DOI: 10.1039/C5OB01569C

Next, we became curious about the fate of the reaction of aralkyl alkyl ketones. Thus, we reacted **5a** under the standard conditions. Interestingly, this led to the formation of **3a** through oxidative scission of both the methyl and the methylene groups on either side of keto group, with an ending of oxidation process at the aromatic terminal (table 4). Recently, Bi et al[8] and Jiao et al[5] also observed a similar cleavage process during the conversion of aralkyl methyl ketones to aromatic aldehydes and aromatic esters respectively. Noteworthy is that this is in contrast to the productivity of haloform pathway where the similar substrate undergoes the oxidation of only methyl group to afford aralkyl acids. Next, the scope of the reaction was evaluated (table 4). Thus, various aralkyl methyl ketones (**5a**-**5g**) yielded corresponding benzoic acids (**3a**, **3e**, **3f** and **3u**-**3x**) in good yields (49-64%). Aralkyl ethyl ketone (**5g**, example with other than methyl group) also gave benzoic acid (**3a**) in 60% yield.

Our curiosity next turned to test the fate of dialkyl ketone which lacks aromatic ring at either terminals of ketone to abort the oxidation process. Towards this, butanone (**5h**) and cyclohexanone (**5i**) were employed in the reaction (table 4). Surprisingly, the substrates were completely consumed and no products were detected on TLC. We did not pursue it further as the desired product was not obtained.

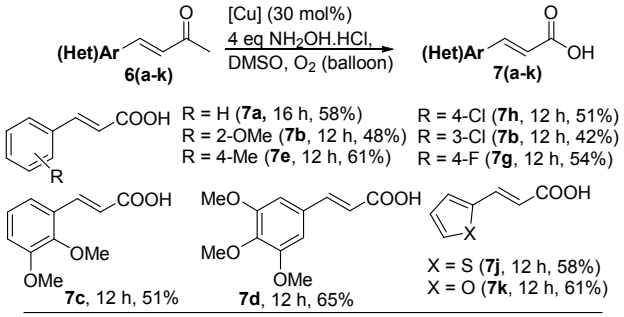
Table 4. Degradation of aralkyl or alkyl methyl ketones.



Reaction conditions: **5** (1.0 mmol), $NH_2OH.HCl$ (4.0 mmol), copper catalyst (0.03 mmol), heated in DMSO at 100 °C, under O_2 balloon. Yields are based on Isolated products.

The above results prompted us to check the reactivity of the vinyl methyl ketones to find whether an alkenyl group can act as a terminator to the above oxidation process. If so, it should deliver the interesting acrylic/cinnamic acids. Accordingly benzylideneacetone **6a** was selected for the initial screening. When subjected under the standard reactions, remarkably, it did not undergo vinyl degradation to produce benzoic acid but we isolated cinnamic acid after selective C(CO)-C(methyl) bond cleavage. Cinnamic acids and their derivatives are promising pharmaceuticals.[13] Similarly, **6a**-**6k** were employed as substrates and the results are summarized in table 5. The electron withdrawing (**6g**-**6h**) or donating groups (**6b**-**6d**) present on aromatic ring of benzylideneacetones were well tolerated to produce **7g**-**7h** and **7b**-**7d** in moderate yields (table 5). Heteoaromatic vinyl ketones (**6j**-**6k**) also smoothly reacted to produce corresponding heteroaromatic vinyl acids (**7j**, 58% and **7k**, 61%).

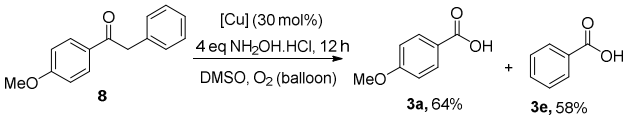
Table 5. Chemo selective C(CO)-C(methyl) bond cleavage of vinyl methyl ketones.



Reaction conditions: **6** (1.0 mmol), $NH_2OH.HCl$ (4.0 mmol), copper catalyst (0.03 mmol), heated in DMSO at 100 °C, under O_2 balloon.Yields are based on Isolated products.

Next, when we subjected **8**, having aryl groups at either side of ketone (scheme 2), to standard reaction conditions, interestingly, the both ends of the substrate was converted to corresponding acids.

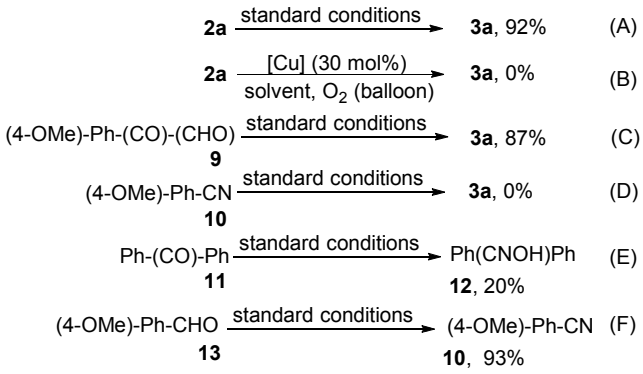
Scheme 2. Oxidative cleavage of Phenylacetophenone.



Before proposing the mechanism, we have conducted some control experiments (Scheme 3). First, we separately synthesized the oxime **2a** and subjected this to the standard reaction conditions. As expected, the reaction smoothly occurred to produce the corresponding product **3a** in 92% yield. However, without hydroxylamine oxime **2a** could not offered acid **3a** (scheme 3B). This indicate the requirement of more than one equivalent of hydroxyl amine in the reaction. Since Bi et al[8] have reported the formation of glyoxal intermediate from the acetophenone under the same reaction conditions, we have employed glyoxal **9** to verify its formation. Interestingly, **9** was smoothly transformed to the corresponding acid **3a** in 87% yield (scheme 3C) suggesting the possible formation of α-oxo intermediates. Furthermore, nitrile **10** did not react under the standard conditions (scheme 3D), implying that nitrile was not a possible intermediate in this process. Moreover benzophenone **11** could not yield corresponding acid under standard reaction conditions but formation of oxime (**12**) was observed (scheme 3E). Moreover, under the standard reaction conditions aldehyde (**13**) offered nitrile (**10**) via dehydration of oxime.

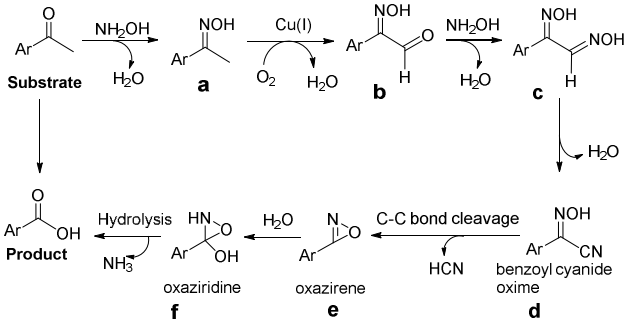
View Article Online
DOI: 10.1039/C5OB01569C

Scheme 3. Control experiments.



Based on these results, we propose a mechanistic possibility of this Cu-catalyzed reaction under an O_2 atmosphere as shown in scheme 3. Reaction starts with the oxime (**a**) formation and its subsequent Cu(I)-mediated oxidation provides corresponding α-oxo oxime **b**[8]. This intermediate reacts further with hydroxylamine to produce di-oxime **c**. Subsequent dehydration of aldoxime (**c**) generates benzoyl cyanide oxime **d.** This further produce intermediate oxazirene **e** along with the release of hydrogen cyanide (HCN) via C-C bond cleavage. Next, It reacts with water to generate oxaziridine **f**. Finally, oxaziridine undergo hydrolysis[14] to deliver the desired acid**.** In case of higher alkyl groups the entire chain has decomposes to HCN.

Scheme 3. Proposed mechanism



In conclusion, a novel and efficient copper-catalyzed aerobic oxidative C-C bond cleavage of ketones to corresponding acids via unprecedented cleavage of alkyl groups adjacent to oxime has been developed. Readily available and inexpensive copper catalyst, and use of molecular oxygen as oxidant make this transformation green and practical. Wide array of ketones having aryl/aralkyl/vinyl at one end and methyl to any higher alkyl at the other end can be efficiently cleaved and converted in to their corresponding acids in fair to excellent yields. Preliminary mechanistic experiments have disclosed the formation of oxime intermediate. Further investigations to clearly understand the reaction mechanism and the synthetic applications are currently underway.

This work was supported by CSIR-ORIGIN (CSC0108), New Delhi. We are thankful to NMR, Mass divisions of CSIR-IICT, for providing the analytical facilities. P.S.N, O.R and P.R.M. thank UGC and CSIR for the Ph.D. fellowships.

Notes and references

1 (a) R. H. Crabtree, *Chem. Rev.,* 1985, **85,** 245-269; (b) M. Miura and T. Satoh. In *Palladium in organic synthesis*, Springer: 2005; pp 1-20. (c) B. Rybtchinski and D. Milstein, *Angew. Chem. Int. Ed.,* 1999, **38,** 870-883; (d) C. -H. Jun, *Chem. Soc. Rev.,* 2004**, 33**, 610-618; (e) M. Tobisu and N. Chatani, *Chem. Soc. Rev.,* 2008**, 37**, 300-307; (f) A. Masarwa and I. Marek, *Chem. Eur. J.,* 2010, **16**, 9712-9721; (g) M. Murakami and T. Matsuda, *Chem. Commun.,* 2011, **47**, 1100-1105; (h) S. Murai, *Activation of unreactive bonds and organic synthesis*. Springer Science & Business Media: 1999; Vol. **3** pp. 97-129. (i) Y. Yang, F. Ni, W-M. Shu and A-X. Wu, *Chem. Eur. J.*, 2014, **20**, 11776 – 11782.

2 (a) M. Murakami, H.Amii, K.Shigeto and Y. Ito, *J. Am. Chem. Soc.,* 1996, **118**, 8285-8290; (b) O. G. Kulinkovich, *Chem. Rev.,* 2003, **103,** 2597-2632; (c) S. C. Bart and P. J. Chirik, *J. Am. Chem. Soc.,* 2003, **125,** 886-887; (d) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.,* 2007, **107,** 3117-3179; (e) T. Seiser and N. Cramer, *Org. Biomol. Chem.,* 2009, **7,** 2835-2840; (f) T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew. Chem. Int. Ed.,* 2011, **50,** 7740-7752; (g) T. Seiser and N. Cramer, *J. Am. Chem. Soc.,* 2010, **132,** 5340-5341; (h) I. Marek, A. Masarwa, P. O. Delaye and M. Leibeling, *Angew. Chem. Int. Ed.,* 2015, **54,** 414-429.

3 (a) C. -H. Jun and H. Lee, *J. Am. Chem. Soc.,* 1999, **121,** 880-881; (b) N. Chatani, Y. Ie, F. Kakiuchi and S. Murai, *J. Am. Chem. Soc.,* 1999, **121,** 8645-8646; (c) M. Gandelman and D. Milstein, *Chem. Commun.,* 2000, 1603-1604; (d) C. H. Jun, D. Y. Lee, H. Lee and J. B. Hong, *Angew. Chem. Int. Ed.,* 2000, **39,** 3070-3072; (e) N. Zhang and J. Vozzolo, *J. Org. Chem.,* 2002, **67,** 1703-1704; (f) A. M. Dreis and C. J. Douglas, *J. Am. Chem. Soc.,* 2008, **131,** 412-413; (g) J. Wang, W. Chen, S. Zuo, L. Liu, X. Zhang and J. Wang, *Angew. Chem. Int. Ed.,* 2012, **51,** 12334-12338; (h) Z. Q. Lei, H. Li, Y. Li, X. S. Zhang, K. Chen, X. Wang, J. Sun and Z. J. Shi, *Angew. Chem. Int. Ed.,* 2012, **51,** 2690-2694; (i) J. Cornella, E. P. Jackson and R. Martin, *Angew. Chem.,* 2015, **127,** 4147-4150.

4 (a) W. Zhou, Y. Yang, Y. Liu and G. –J. Deng, *Green Chem.,* 2013, **15,** 76-80; (b) C. Zhang, P. Feng and N. Jiao, *J. Am. Chem. Soc.,* 2013, **135,** 15257-15262.

5 X. Huang, X. Li, M. Zou, S. Song, C. Tang, Y. Yuan and N. Jiao, *J. Am. Chem. Soc.,* 2014, **136,** 14858-14865.

6 C. Tang and N. Jiao, *Angew. Chem.,* 2014, **126,** 6646-6650.

7 P. Subramanian, S.Indu and K. P. Kaliappan, *Org. Lett.* 2014, **16,** 6212-6215.

8 L. Zhang, X. Bi, X. Guan, X. Li, Q. Liu, B. D. Barry and P. Liao, *Angew. Chem.,* 2013, **125,** 11513-11517.

9 (a) D. Yang, H. Yang and H. Fu, *Chem. Commun.,* 2011, **47,** 2348-2350; (b) B. Beyersdorf-Radeck, U. Karlson and R. Schmid, *Anal. Lett.,* 1994, **27,** 285-298; (c) P. Palade and R. Barchi, *J. Gen. Physiol.,* 1977, **69,** 879.

10 (a) E. L. Larghi, M. A. Operto, R. Torres and T. S. Kaufman, *Bioorg. Med. Chem. Lett.,* 2009, **19,** 6172-6175; (b) I. Navarro, C. Pöverlein, G. Schlingmann and A. G. Barrett, *J. Org. Chem.,* 2009, **74,** 8139-8142; (c) J. Fraga-Dubreuil, E. Garcia-Verdugo, P. A. Hamley, E. M. Vaquero, L. M. Dudd, I. Pearson, D. Housley, W. Partenheimer, W. B. Thomas, K. Whiston, *Green Chem.,* 2007, **9,** 1238-1245; (d) G. Barak, J. Dakka, Y. Sasson, *J. Org. Chem.,* 1988, **53,** 3553-3555; (e) D. Könning, T. Olbrisch, F. D. Sypaseuth, C. Tzschucke and M. Christmann, *Chem. Commun.,* 2014, **50,** 5014-5016; (f) Y.

View Article Online
DOI: 10.1039/C5OB01569C

Hirai, T. Kojima, Y. Mizutani, Y. Shiota, K. Yoshizawa and S. Fukuzumi, *Angew. Chem.,* 2008, **120,** 5856-5860; (g) K. Miyamoto, Y. Sei, K. Yamaguchi and M. Ochiai, *J. Am. Chem. Soc.,* 2009, **131,** 1382-1383; (h) J. Mecinović, R. B. Hamed and C. J. Schofield, *Angew. Chem. Int. Ed.,* 2009, **48,** 2796-2800.

11 (a) S. K. Chakarbatty, In oxidation in organic chemistry, Part. C (Eds.: W. S. Trahanovsky), Academic Press, Newyork, 1978, pp. 348-351. (b) M. J. Taschner and A. Shahripour, *J. Am. Chem. Soc.,* 1985, **107,** 5570-5572.

12 S. Chiba, L. Zhang, G. Y. Ang and B. W. –Q. Hui, *Org. Lett.,* 2010, **12,** 2052-2055.

13 (a) J. A. Hoskins, *J. Appl. Toxicol.,* 1984, ***4,*** 283-292; (b) K. V. Thimann, in Physiology of plant growth and development, (Eds.: M. B. Son), McGrew-Hill, London, **1969**, pp. 2-45.

14 A. R. Butler, B. C. Challis and A. M. Lobo, *J. chem. Soc., Perkin Trans. II.,* 1979, 1035-1038.