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Iodine/water-mediated deprotective oxidation of allylic ethers to access α,β-unsaturated ketones and aldehydes†

Yuntian Xue,[a] Yaolong Yan,[a] Kezhi Jiang,[a] Weifeng Chen*[a] and Lei Yang *[ab]

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The first iodine/water-mediated deprotective oxidation of allylic ethers to access α,β-unsaturated ketones and aldehydes was achieved. The reaction tolerates a wide range of functionalities. Furthermore, this protocol was found to be applicable to the oxidative transformation of allylic acetates. The proposed mechanism involves an oxygen transfer from solvent water to the carbonyl products.

Introduction

The organic functional group transformation of allylic ethers into α,β-unsaturated ketones or aldehydes is a very useful tool in natural product synthesis and pharmaceutical synthesis and has attracted increasing interest from synthetic chemists and biochemists in recent years.[1–6] As a result, many useful methods, which can be summarized into two categories, have been developed to achieve this transformation. Traditionally, such transformation was achieved *via* a two-step method, *i.e.* deprotection of allylic ethers into allylic alcohols followed by oxidation in the presence of additional oxidants (Scheme 1a).[1,2] However, the decreased step economy of the process reduced the attractiveness of this approach. Another attractive method, which has been less explored to date, is the direct oxidative transformation of allylic ethers to their corresponding α,β-unsaturated ketones or aldehydes (Scheme 1b).[3–6] In this regard, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[3] oxo-ammonium salt,[4] *etc.*[5,6] could be used as the oxidants. Although significant improvements have been made in this research area, the use of toxic oxidants, the narrow substrate scope and the generation of stoichiometric amounts of organic waste restrict their further application. Moreover, most of these reported methods are not suitable for the simple allyl alkyl ethers. Thus, the development of new methods or nontoxic reagents for enabling such a functional group transformation is highly desirable. On the other hand, molecular iodine has been used extensively in various reactions as a green and environmentally benign reagent or catalyst,[7] because iodine is inexpensive, readily available, and nontoxic. Inspired by our ongoing research on the synthesis of (±)-cassumunin C and (±)-latifolin using iodine-mediated aromatic propargylation as the key step,[8] we herein report the first iodine-mediated direct transformation of allylic ethers to α,β-unsaturated ketones or aldehydes in a biphasic solvent system.

Results and discussion

The studies were initiated with (*E*)-(3-(benzyloxy)but-1-en-1-yl) benzene **1a** as a model substrate. As shown in Table 1, it was found that **1a** when heated with molecular iodine (1.6 eq.) in 1,4-dioxane/water (5 : 1)[9] at the refluxing temperature produced benzylideneacetone **2a** in 78% yield after 2 h (entry 1). Inspired by this result, we began to tune the reaction conditions to further improve the yield of **2a**. Knowing that the presence of water would be critical to the oxidative process, a variety of biphasic solvent systems was first screened (entries 2–7). A lower efficiency was observed when using other different biphasic solvents investigated, thus indicating the important role of the solvents in the reaction.

When the reaction was carried out under an argon instead of air atmosphere, the desired product was provided in 63% yield (entry 8). Temperature was also crucial to this transformation because the reaction could not occur at all when it was carried out at room temperature (entry 9). Control experiments demonstrated that the use of single 1,4-dioxane solvent did not give the desired product and the reaction could be performed in pure water, although this process becomes sluggish (entries 10 and 11). Furthermore, no product was observed in the absence of molecular iodine (entry 12). To our delight, we observed complete conversion to the desired ketone **2a** by extending the reaction time to 24 h (entry 13). In order to study the potential activity of iodine as a catalyst, the reaction was performed by using a lower loading of iodine. However, an obvious decreased yield of **2a** was obtained using 0.5 eq. of iodine (entry 14). In

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[a] *Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University, Hangzhou 311121, China. E-mail: lyang@hznu.edu.cn; chenwf@hznu.edu.cn*

[b] *Engineering Research Center of High Performance Polymer and Molding Technology, Ministry of Education, College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, China*

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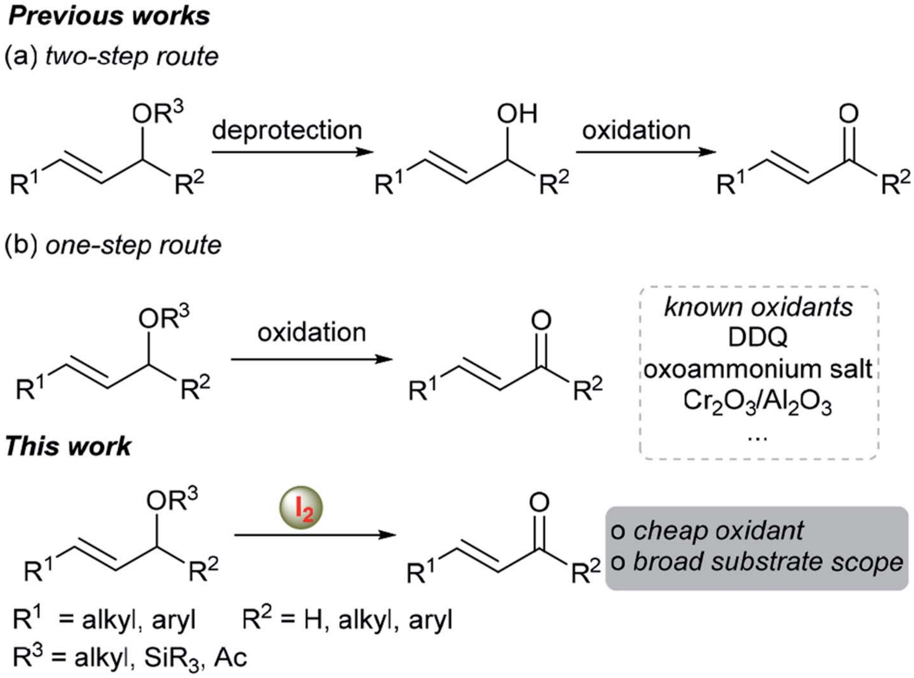
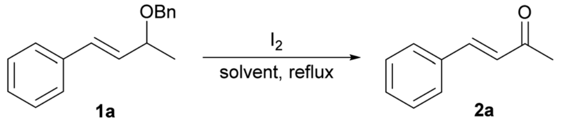


Scheme 1 Transformation of allylic ethers into α,β-unsaturated ketones or aldehydes.

addition, an increased amount of 2.0 eq. iodine also gave negative improvement on the yield of **2a** (entry 15). It is noteworthy that increasing the amount of 1,4-dioxane in the biphasic solvent system gave a positive effect on the product yield and the best ratio of 1,4-dioxane to water in current transformation is 5 : 1 (entries 16–18).

Table 1 Optimisation of reaction conditions[a]



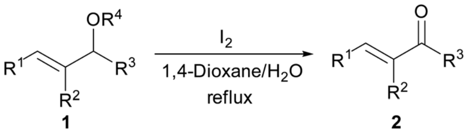
1a **2a**

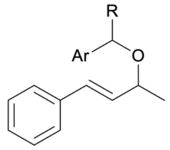
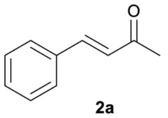
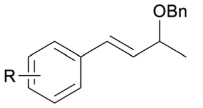
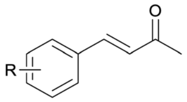
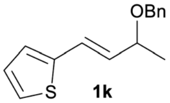
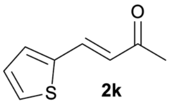
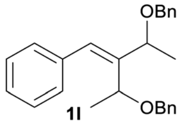
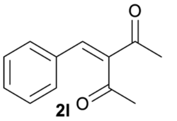
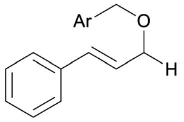
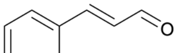
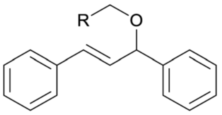
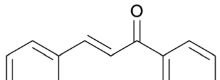
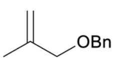
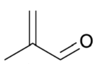
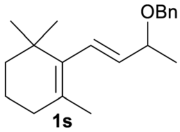
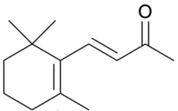
Entry	I_2 (eq.)	Solvent	Time (h)	Yield[b] (%)
1	1.6	1,4-Dioxane/H_2O (5 : 1)	2	78
2	1.6	Toluene/H_2O (5 : 1)	2	18
3	1.6	THF/H_2O (5 : 1)	2	40
4	1.6	MeOH/H_2O (5 : 1)	2	15
5	1.6	DMF/H_2O (5 : 1)	2	26
6	1.6	DMSO/H_2O (5 : 1)	2	51
7	1.6	DCM/H_2O (5 : 1)	2	12
8[c]	1.6	1,4-Dioxane/H_2O (5 : 1)	2	63
9[d]	1.6	1,4-Dioxane/H_2O (5 : 1)	2	0
10	1.6	1,4-Dioxane	2	0
11	1.6	H_2O	2	35
12	0	1,4-Dioxane/H_2O (5 : 1)	2	0
13	**1.6**	**1,4-Dioxane/H_2O (5 : 1)**	**24**	**91**
14	0.5	1,4-Dioxane/H_2O (5 : 1)	24	72
15	2.0	1,4-Dioxane/H_2O (5 : 1)	24	79
16	1.6	1,4-Dioxane/H_2O (1 : 1)	24	63
17	1.6	1,4-Dioxane/H_2O (2 : 1)	24	72
18	1.6	1,4-Dioxane/H_2O (10 : 1)	24	90

[a] General conditions: **1a** (0.1 mmol), I_2 (1.6 eq.), solvent (3.6 mL), at refluxing temperature, under air. [b] Isolated yields. [c] Under Ar. [d] At room temperature.

With the optimized reaction conditions in hand, we next explored the generality of this transformation on a range of allylic ethers (Tables 2 and 3). We initially scrutinized the effect of benzyl ether groups on the reaction. As shown in Table 2, allylic ethers bearing primary or secondary benzyl ether groups with either electron-donating or electron-withdrawing groups on phenyl ring of the benzyl ether groups were found to be suitable substrates for this transformation, affording ketone **2a** in 85–92% yields (entries 1–5). In addition, electronic and steric changes to the allyl ethers by introducing a substituent on the aromatic ring adjacent to olefin had little to no effect on the yields of ketone products (entries 6–10). Moreover, a heterocycle-containing allyl benzyl ether also proved amenable to deprotective oxidation under the standard reaction conditions (entry 11). Interestingly, allyl ethers bearing two benzyl ether groups proved to be a suitable substrate for this protocol and afforded the desired 1,3-diketone product **2l** in high yield (entry 12). In order to further demonstrate the generality of this methodology, other allylic ethers **1m–1q**, *e.g.* cinnamyl benzyl ethers **1m–1o**, which would be sterically different to **1a–1k**, were then investigated. To our delight, steric or electronic changes arisen from the allylic moiety had no dramatic effect on the success of this transformation. The desired products cinnamaldehyde **2m** (entries 13–15) and chalcone **2p** (entries 16 and 17) were produced in good yields. Finally, we found that our methodology was not limited to the aromatic allyl system. For instance, aliphatic allyl benzyl ethers **1r** and **1s** were also compatible with this protocol (entries 18 and 19), allowing

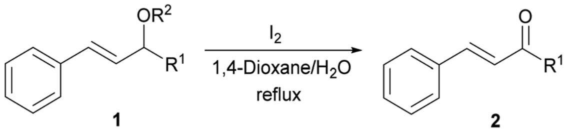
Table 2 Scope of I_2/H_2O-mediated oxidation of allyl benzyl ethers[a]



Entry	Substrate	Product	Yield[b]
		 2a	
1	**1a** R = H, Ar = Ph		91
2	**1b** R = H, Ar = 4-MeC_6H_4		91
3	**1c** R = H, Ar = 4-BrC_6H_4		92
4	**1d** R = H, Ar = 4-$OMeC_6H_4$		90
5	**1e** R = Me, Ar = Ph		85
			
6	**1f** R = 4-Me	**2f** R = 4-Me	92
7	**1g** R = 4-Br	**2g** R = 4-Br	91
8	**1h** R = 2-OMe	**2h** R = 2-OMe	88
9	**1i** R = 3-OMe	**2i** R = 3-OMe	89
10	**1j** R = 4-OMe	**2j** R = 4-OMe	90
11	 1k	 2k	51
12[c]	 1l	 2l	89
		 2m	
13[d]	**1m** Ar = Ph		92
14[d]	**1n** Ar = 4-BrC_6H_4		91
15[d]	**1o** Ar = 4-$OMeC_6H_4$		90
		 2p	
16	**1p** R = Ph		88
17	**1q** R = 2-naphthyl		89
18	 1r	 2r	91
19	 1s	 2s	87

[a] General conditions: **1** (0.1 mmol), I_2 (1.6 eq.), 1,4-dioxane/H_2O (5 : 1, 3.6 mL), at refluxing temperature, 24 h, under air. [b] Isolated yields. [c] I_2 (3.2 eq.). [d] I_2 (6.4 eq.).

Table 3 Scope of I_2/H_2O-mediated oxidation of other allyl ethers[a]



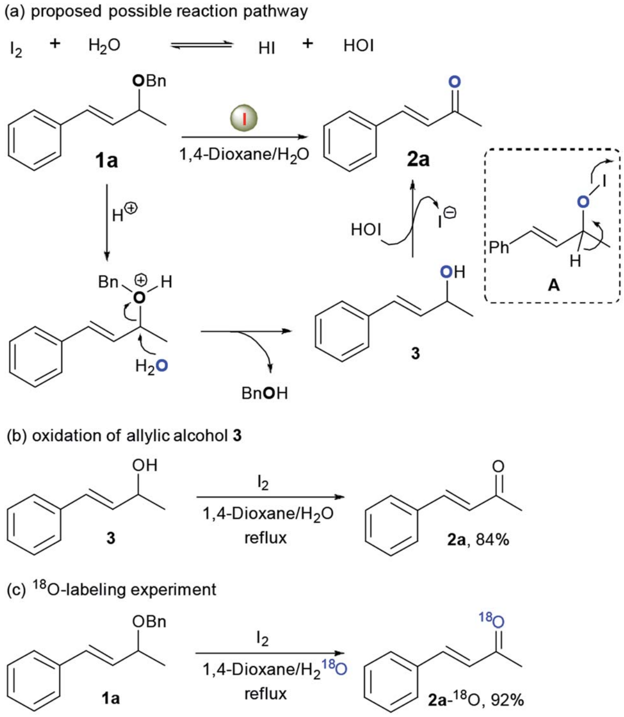
Entry	Ether	R^1	R^2	Product	Yield[b]
1	**1t**	Me	$SiEt_3$	**2a**	95
2	**1u**	Me	Si^iPr_3	**2a**	85
3	**1v**	Me	$SiMe_2{}^tBu$	**2a**	0
4	**1w**	Me	Ac	**2a**	47
5	**1x**	H	Ac	**2m**	56
6	**1y**	Me	Me	**2a**	61
7	**1z**	Me	Allyl	**2a**	52
8	**1aa′**	Ph	Me	**2p**	68
9	**1ab′**	Ph	Allyl	**2p**	64

[a] General conditions: **1** (0.1 mmol), I_2 (1.6 eq.), 1,4-dioxane/H_2O (5 : 1, 3.6 mL), at refluxing temperature, 24 h, under air. [b] Isolated yields.

access to 2-methylacrolein **2r** and ketone **2s** in 91% and 87% isolated yields, respectively.

Encouraged by the above results, we were interested in the possibility that other protective groups could serve as suitable replacements for benzylic groups of the allyl benzyl ethers. The results are summarized in Table 3. Considering its widely usage as a protective group and the required common conversion of allyl silyl ethers to enones[10] to organic and medicinal chemists, we first investigated the transformation of several allyl silyl ether compounds. The allyl silyl ethers with small trialkylsilyl groups (entries 1–2), *i.e.* $SiEt_3$ and $Si(^iPr)_3$, resulted in the desired product **2a** in high to excellent yields, whereas the allyl silyl ether bearing a $SiMe_2{}^tBu$ group resulted in no reaction (entry 3). This interesting effect of silyl protective groups in iodine/water-mediated oxidation of allyl silyl ethers would be useful in multistep organic synthesis. Notably, allyl esters, which are unreactive substrates under oxoammonium salt catalysis,[4a] were also valid substrates and delivered the corresponding ketone **2a** and cinnamaldehyde **2m** in 47% and 56% yields, respectively (entries 4 and 5). We next explored whether allyl ethers with other alkoxyl groups could be underwent oxidation under the reaction conditions (entries 6–9). Indeed, two methyl ethers (**1y** and **1aa′**) and two allyl ethers (**1z** and **1ab′**) were all proceeded smoothly and could be converted into **2a** and **2p**, albeit with moderate yields.

On the basis of our above results and the mechanistic understanding from the I_2-catalysed reaction,[7b,11] a possible reaction mechanism is proposed using **1a** as the substrate (Scheme 2). Initially, disproportionation of I_2 with water may generate an equilibrium mixture with hydroiodic acid (HI) and hydroiodous acid (HOI).[11,12] The protonation of benzylic ether group in **1a** with the generated HI provides an oxonium ion intermediate, which is subsequently attacked by water as a nucleophilic reagent, leading to the formation of allylic alcohol **3** and benzyl alcohol.[13,14] Finally, **3** is oxidized to afford



Scheme 2 Mechanistic considerations.

α,β-unsaturated ketone **2a** in the presence of electrophilic iodine species *via* intermediates such as **A**.[15] The proposed reaction mechanism was further convinced by following experiments.[14] First, to gain a better understanding of the possible reaction intermediates, we monitored the oxidation of **1a** under optimal conditions by GC-MS. Surprisingly, full conversion of **1a** was observed only after 30 min under the standard reaction conditions, yielding allylic alcohol **3** (65% GC yield), desired ketone **2a** (30% GC yield) and a large amount of benzyl alcohol. After 24 h, the allylic alcohol **3** was completely disappeared. These results clearly proved the possibility of above proposed deprotection/oxidation sequence, and also indicated that the deprotection step is faster than the following alcohol oxidation step under current reaction conditions. Moreover, the oxidation of **3** to **2a** (84% yield) could be effectively achieved under standard conditions. Finally, ^{18}O-labeling experiment revealed that the oxygen atom of ketone group in the formed α,β-unsaturated ketone originated from the ^{18}O-labeled water instead of the starting ether **1a**, thus giving a very facile method for the preparation of ^{18}O-labeled α,β-unsaturated ketones and aldehydes.

Conclusions

In summary, we have disclosed a protocol for the direct protective oxidation of a variety of allylic ethers to their corresponding aldehydes or ketones promoted by molecular iodine in the presence of water. Our protocol is practically simple and proceeds under ligand- and metal-free conditions. In addition, allylic esters can also undergo this oxidative process. The suggested mechanism involves an oxygen transfer from the solvent water to the carbonyl products. Further applications of this protocol are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) R. E. Ireland and M. G. Smith, *J. Am. Chem. Soc.*, 1988, **110**, 854–860; (*b*) J. Aleu, B. Bergamo, E. Brenna, C. Fuganti and S. Serra, *Eur. J. Org. Chem.*, 2000, 3031–3038; (*c*) A. B. Smith, Q. Lin, V. A. Doughty, L. Zhuang, M. D. McBriar, J. K. Kerns, A. M. Boldi, N. Murase, W. H. Moser, C. S. Brook, C. S. Bennett, K. Nakayama, M. Sobukawa and R. E. Lee Trout, *Tetrahedron*, 2009, **65**, 6470–6488.

2 (*a*) E. Brenna, C. Fuganti, S. Ronzani and S. Serra, *Helv. Chim. Acta*, 2001, **84**, 3650–3666; (*b*) P. A. Wender, M. F. T. Koehler and M. Sendzik, *Org. Lett.*, 2003, **5**, 4549–4552; (*c*) H. J. Schäfer, M. Harenbrock, E. Klocke, M. Plate and A. Weiper-Idelmann, *Pure Appl. Chem.*, 2007, **79**, 2047–2057; (*d*) S. I. Avramova, E. Galletti, M. L. Renzulli, G. Giorgi, G. Sgaragli, D. Alderighi, C. Ghiron, F. Corelli, M. Radi and M. Botta, *ChemMedChem*, 2008, **3**, 745–748; (*e*) T. Brodmann, D. Janssen, F. Sasse, H. Irschik, R. Jansen, R. Müller and M. Kalesse, *Eur. J. Org. Chem.*, 2010, 5155–5159; (*f*) H. Fuwa, S. Matsukida, T. Miyoshi, Y. Kawashima, T. Saito and M. Sasaki, *J. Org. Chem.*, 2016, **81**, 2213–2227.

3 (*a*) E. Lee-Ruff and F. J. Ablena, *Can. J. Chem.*, 1989, **67**, 699–702; (*b*) O. Piva, A. Amougay and J.-P. Pete, *Tetrahedron Lett.*, 1991, **32**, 3993–3996; (*c*) I. Paterson, C. J. Cowden, V. S. Rahn and M. D. Woodrow, *Synlett*, 1998, 915–917; (*d*) D. A. Evans, W. C. Trenkle, J. Zhang and J. D. Burch, *Org. Lett.*, 2005, **7**, 3335–3338; (*e*) R. K. Acharyya, P. Pal, S. Chatterjee and S. Nanda, *Org. Biomol. Chem.*, 2019, **17**, 3552–3566.

4 (*a*) C. B. Kelly, J. M. Ovian, R. M. Cywar, T. R. Gosselin, R. J. Wiles and N. E. Leadbeater, *Org. Biomol. Chem.*, 2015, **13**, 4255–4259; (*b*) T. A. Hamlin, C. B. Kelly, J. M. Ovian, R. J. Wiles, L. J. Tilley and N. E. Leadbeater, *J. Org. Chem.*, 2015, **80**, 8150–8167.

5 M. M. Heravi, D. Ajami and M. Ghassemzadeh, *Synthesis*, 1999, **3**, 393–394.

6 (*a*) T. Nishiguchi and M. Bougauchi, *J. Org. Chem.*, 1989, **54**, 3001–3002; (*b*) G. Deng, B. Xu and C. Liu, *Tetrahedron*, 2005, **61**, 5818–5821; (*c*) P. D. Lokhande and B. R. Nawghare, *Indian*

J. Chem., Sect. B: Org. Chem. Incl. Med. Chem., 2012, **51**, 328–333.

7 For a seminal report, see: (*a*) H. Hibbert, *J. Am. Chem. Soc.*, 1915, **37**, 1748–1763; for reviews, see: ; (*b*) H. Togo and S. Iida, *Synlett*, 2006, **14**, 2159–2175; (*c*) P. Finkbeiner and B. J. Nachtsheim, *Synthesis*, 2013, **45**, 979–999.

8 (*a*) Y. Dai, Y. He, Y. Wang, H. Jiang, Z. Li and W. Chen, *Synthesis*, 2014, **46**, 3041–3046; (*b*) Y. Dai, Q. Liu, Z. Li, W. Chen and Z. Liu, *Chin. J. Chem.*, 2015, **33**, 1287–1292.

9 H. Kikuchi, K. Kogure and M. Toyoda, *Chem. Lett.*, 1984, 341–344.

10 (*a*) H. Tanaka, T. Hasegawa, M. Iwashima, K. Iguchi and T. Takahashi, *Org. Lett.*, 2004, **6**, 1103–1106; (*b*) C. C. Sanchez and G. E. Keck, *Org. Lett.*, 2005, **7**, 3053–3056; (*c*) N. Itagaki and Y. Iwabuchi, *Chem. Commun.*, 2007, 1175–1176; (*d*) A.-R. Shareef, D. H. Sherman and J. Montgomery, *Chem. Sci.*, 2012, **3**, 892–895; (*e*) H. Yamada, M. Adachi, M. Isobe and T. Nishikawa, *Chem. - Asian J.*, 2013, **8**, 1428–1435.

11 For reviews, see: M. Breugst and D. von der Heiden, *Chem. Eur. J.*, 2018, **24**, 9187–9199.

12 In fact, the actual iodine-containing species in aqueous obtained are pH-dependent, see: (*a*) I. Lengyel, R. Epstein and K. Kustin, *Inorg. Chem.*, 1993, **32**, 5880–5882; (*b*) V. W. Truesdale, G. W. Luther and J. E. Greenwood, *Phys. Chem. Chem. Phys.*, 2003, **5**, 3428–3435. For the sake of simplicity, we proposed the formation of HOI was responsible for the final oxidation of **3** to **2a**.

13 The formation of benzyl alcohol was observed by GC-MS and TLC analysis at the early reaction stage.

14 See the ESI† for more details.

15 (*a*) J. Barluenga, M. Marco-Arias, F. González-Bobes, A. Ballesteros and J. M. González, *Chem. Commun.*, 2004, 2616–2617; (*b*) N. Mori and H. Togo, *Synlett*, 2005, 1456–1458.