Photooxidative Cleavage of Aromatic Alkenes into Aldehydes Using Catalytic Iodine and Molecular Oxygen under Visible Light Irradiation

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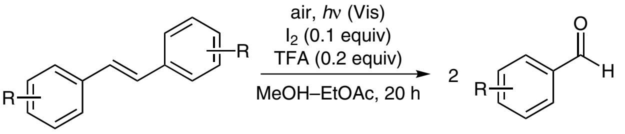
Abstract: We report a method for the photooxidative cleavage of aromatic alkenes to give aldehydes using molecular oxygen as the terminal oxidant, visible light, a catalytic amount of iodine and trifluoroacetic acid.

Key words: alkenes, aerobic, photooxidation, iodine, aldehydes

The carbon–carbon double bond is a key functional group for transformation in organic synthesis, and various reactions starting from alkenes have been developed. Among them, cleavage of alkenes to give carbonyl compounds is one of the most important examples.[1] Ozonolysis is probably the best known method for the cleavage of alkenes.[2] However, its utility is often limited by safety concerns; there have been some reports of serious accidents due to explosions.[3] Alternatively, transition metal catalysts such as osmium (Os), ruthenium (Ru), tungsten (W), iron (Fe), vanadium (V), and palladium (Pd), have been used to cleave carbon–carbon double bonds.[4] Since these catalysts have several drawbacks, such as high cost and detrimental environmental impact, the development of less expensive and more environmentally benign methods are very important. However, catalytic metal-free reactions, such as those using a triarylamine electrocatalyst,[5] *tert*-butyl nitrite/oxygen/compressed carbon dioxide,[6] and iodomesitylene/*m*-chloroperoxybenzoic acid (MCPBA), are limited.[7]

Light is an important factor in many reactions because it leaves no residue, has neither shape nor weight, and is an important component in the examination of environmentally friendly processes.[8] In addition, due to the increasing demand for more environmentally benign syntheses, molecular oxygen, which is inexpensive and has greater atom efficiency than other oxidants, has received considerable attention as the ultimate oxidant.[9] Thus, an aerobic photooxidative carbon–carbon bond cleavage reaction is attractive, and various reactions which use stoichiometric amounts of dimethoxybenzene,[10] catalytic amounts of 9,10-dicyanoanthracene (DCA),[11] 5,10,15-triphenyl-20-(4-hydroxyphenyl)-21*H*,23*H*-porphyrin (TPP-OH),[12] and metal catalysts (Pt,[13] Mn[14]), have been reported. However, these reactions require stoichiometric amounts of reagents and harmful UV light. In addition, they cannot be performed under an air atmosphere and the substituent scope of the substrates has not been investigated.

We have developed various aerobic photooxidation processes under an oxygen atmosphere using visible light irradiation and inexpensive iodine[15] or bromine sources as catalysts.[16] We previously reported the synthesis of the corresponding carboxylic acids through aerobic photooxidative cleavage of styrenes using molecular iodine–FSM-16[17] or carbon tetrabromide (CBr_4).[18] However, these methods also have some limitations, such as the use of harmful UV light and molecular oxygen rather than air. Furthermore, under these reaction conditions, carboxylic acids were obtained, and only low yields of aldehydes could be recovered.[19] In continuation of our efforts to develop an efficient protocol for the oxidative cleavage of alkenes, we report herein the molecular iodine catalyzed photooxidative cleavage of aromatic alkenes in the presence of air and visible light irradiation to give the corresponding aldehydes (Scheme 1).



Scheme 1 Photooxidative cleavage of aromatic alkenes into aldehydes

Table 1 shows the results of our investigation of the reaction conditions for the photooxidative cleavage reaction. The reaction conditions were examined with *trans*-4,4′-di-*tert*-butylstilbene (**1a**) as a test substrate in the presence of iodine sources and additives under air (open), with irradiation using four 22 W fluorescent lamps for 20 hours. In a preliminary experiment using methanol as the solvent, aldehyde **2a** (2%) and the corresponding dimethylacetal (63%) were obtained without an acidic work-up. Consequently, work-up using aqueous hydrochloric acid (2 M) extraction was employed, which resulted in the formation of aldehyde **2a** and its corresponding methyl ester. Among the iodine sources examined, molecular iodine gave good result (Table 1, entries 1–4). Of the solvents employed, methanol gave a low yield of **2a** because alkene **1a** was insoluble in this solvent (Table 1, entry 6). Thus, the combination of methanol and ethyl acetate, which dissolved substrate **1a**, was found to afford the de-

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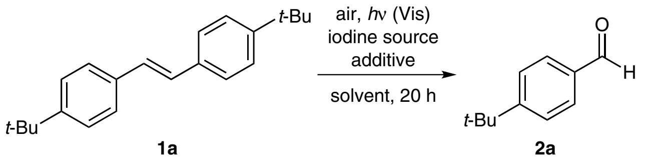
sired product most efficiently (Table 1, entries 4, 6 and 7). Subsequently, a series of additives were evaluated, and trifluoroacetic acid (TFA) (0.2 equiv) provided the best result (Table 1, entries 4 and 8–10). It was noted that iodine sources, trifluoroacetic acid, molecular oxygen, and visible light irradiation were necessary, otherwise unreacted substrates were recovered (Table 1, entries 5 and 11–13). When the reaction was carried out under an oxygen atmosphere, over-oxidation of the aldehyde proceeded to give methyl 4-*tert*-butylbenzoate (12%) and 4-*tert*-butylbenzoic acid (32%) (Table 1, entry 14).

Table 1 Optimization of the Reaction Conditions[a]



Entry	I_2 source (equiv)	Solvent (mL)	Additive (equiv)	Yield (%)[b]
1	CI_4 (0.1)	MeOH–EtOAc (1:2)	TFA (0.2)	trace
2	NaI (0.1)	MeOH–EtOAc (1:2)	TFA (0.2)	50
3	CaI_2 (0.1)	MeOH–EtOAc (1:2)	TFA (0.2)	76
4[c]	I_2 (0.1)	MeOH–EtOAc (1:2)	TFA (0.2)	84 (84)
5	–	MeOH–EtOAc (1:2)	TFA (0.2)	trace
6	I_2 (0.1)	MeOH (3)	TFA (0.2)	trace
7	I_2 (0.1)	EtOAc (3)	TFA (0.2)	29
8	I_2 (0.1)	MeOH–EtOAc (1:2)	TFA (0.1)	36
9	I_2 (0.1)	MeOH–EtOAc (1:2)	PTSA·H_2O (0.2)	65
10	I_2 (0.1)	MeOH–EtOAc (1:2)	AcOH (0.2)	8
11	I_2 (0.1)	MeOH–EtOAc (1:2)	–	0
12[d]	I_2 (0.1)	MeOH–EtOAc (1:2)	TFA (0.2)	0
13[e]	I_2 (0.1)	MeOH–EtOAc (1:2)	TFA (0.2)	0
14[f]	I_2 (0.1)	MeOH–EtOAc (1:2)	TFA (0.2)	36

[a] A solution of *trans*-4,4′-di-*tert*-butylstilbene (**1a**) (0.15 mmol), iodine source and additive in a dry solvent was stirred in a Pyrex test-tube under air (open), and externally irradiated with four 22 W fluorescent lamps for 20 h. Aqueous $Na_2S_2O_3$ was added to the mixture, which was extracted with EtOAc. The organic layer was washed with brine and aqueous HCl (2 M).

[b] Yields determined by ^{1}H NMR spectroscopy. Yield of isolated product is in parenthesis. The product yields were calculated based on 0.3 mmol of corresponding aldehydes.

[c] Methyl 4-*tert*-butylbenzoate (7%) was obtained as a by-product.

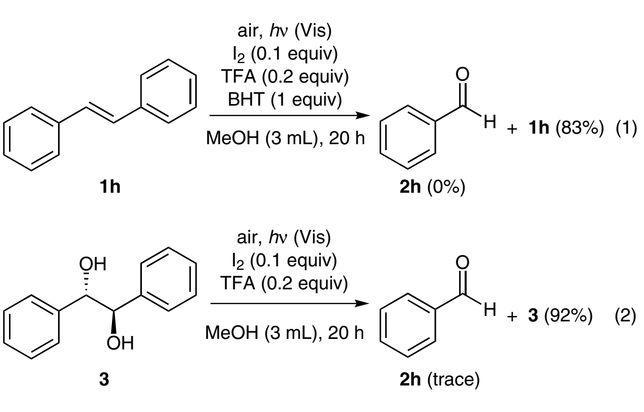
[d] The reaction was carried out under N_2.

[e] The reaction was carried out in the dark.

[f] The reaction was carried out under O_2. Methyl 4-*tert*-butylbenzoate (12%) and 4-*tert*-butylbenzoic acid (32%) were obtained as by-products.

Table 2 presents the scope and limitations of the photooxidative cleavage reactions under the optimized reaction conditions described above.[20] Electron-rich *trans*-stilbenes **1a**–**1g**, which have *t*-butyl, ethyl, and methyl groups on the benzene ring, and *trans*-stilbene (**1h**) gave good to high yields of the corresponding aldehydes (Table 2, entries 1–8). It should be noted that the presence of *ortho*-methyl groups was tolerated in this reaction (Table 2, entries 5–7). However, electron-rich *trans*-stilbene **1i** bearing methoxy groups on the benzene rings, electron-poor *trans*-stilbene **1j** with bromines on the aromatic rings, 4-*tert*-butylstyrene (**1k**), and cyclohexene (**1l**) were poor substrates in this reaction (Table 2, entries 9–12).

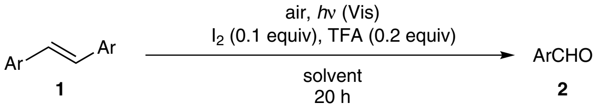
We performed control experiments in order to determine the reaction mechanism. 3,5-Di-*tert*-butyl-4-hydroxytoluene (BHT), which is a radical inhibitor, completely suppressed the reaction. This result suggests that the photooxidation proceeds via a radical mechanism (Scheme 2, equation 1). On the other hand, when *vicinal*-diol **3** was used as a substrate, only trace amounts of benzaldehyde were obtained and the majority of **3** was recovered (Scheme 2, equation 2).



Scheme 2 A study of the reaction mechanism

Scheme 3 shows a plausible mechanism for this oxidative cleavage reaction, which was proposed from the results presented above. Initially, the alkene is iodo-methoxylated in the presence of trifluoroacetic acid to give **4**, and subsequent homolytic cleavage of the C–I bond occurs under visible light irradiation to produce the benzyl radical species **5**. In contrast, when an aliphatic alkene was used as the substrate, the C–I bond probably cannot be cleaved to form an unstable alkyl radical. Intermediate **5** traps molecular oxygen from air to afford hydroperoxide **7** via peroxy radical **6**. Next, C–C bond cleavage occurs in the presence of H^+ to afford aldehyde **2** or acetal **10**.[21,22] Acetal **10** is relatively stable under these reaction conditions with iodine as the catalyst, in contrast to reactions with bromine sources. Finally, acetal **10** is transformed into aldehyde **2** during the acidic work-up with aqueous hydrochloric acid. Furthermore, in situ generated hydrogen iodide is reoxidized to iodine under aerobic photooxidation conditions.

Table 2 Scope and Limitations[a]



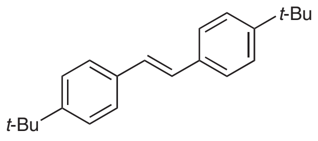
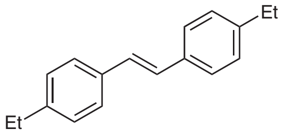
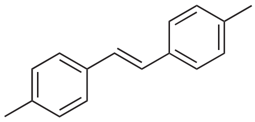
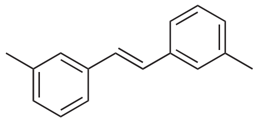
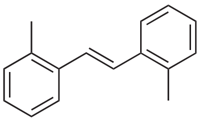
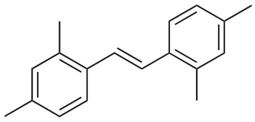
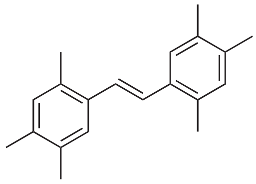
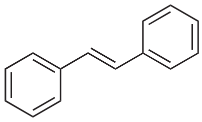
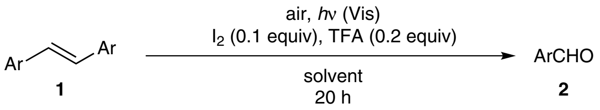
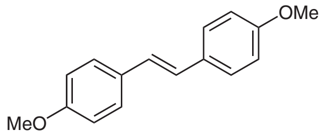
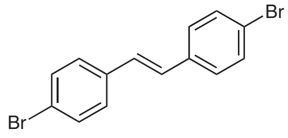
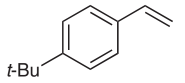
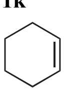
Entry	Substrate	Solvent (mL)	Yield (%)[b]
1	 **1a**	MeOH–EtOAc (1:2)	84
2	 **1b**	MeOH–EtOAc (2:1)	79
3[c]	 **1c**	MeOH–EtOAc (2:1)	79
4	 **1d**	MeOH (3)	30 (83)
5[c]	 **1e**	MeOH (3)	88
6	 **1f**	MeOH–EtOAc (1.5:1.5)	71
7	 **1g**	MeOH–EtOAc (4:6)	63
8	 **1h**	MeOH (3)	30 (67)

Table 2 Scope and Limitations[a] (continued)

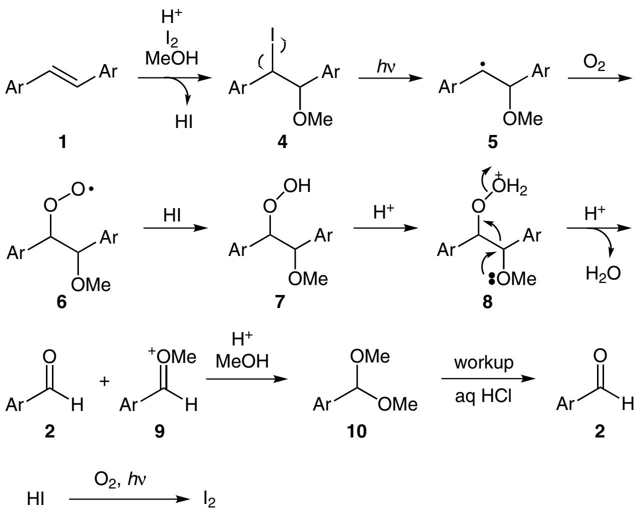


Entry	Substrate	Solvent (mL)	Yield (%)[b]
9	 **1i**	MeOH–EtOAc (1:2)	(12)
10	 **1j**	MeOH–EtOAc (1:2)	0
11	 **1k**	MeOH–EtOAc (1:2)	(2)
12	 **1l**	MeOH–EtOAc (1:2)	(0)

[a] A solution of substrate **1** (0.15 mmol), I_2 (0.1 equiv) and TFA (0.2 equiv) in a dry solvent was stirred in a Pyrex test-tube under air (open), and externally irradiated with four 22 W fluorescent lamps for 20 h. Aqueous $Na_2S_2O_3$ was added and the mixture extracted with EtOAc. The organic layer was washed with brine and aqueous HCl (2 M).

[b] Yields determined by ^{1}H NMR spectroscopy. Yields of isolated products are in parentheses. The product yields were calculated based on 0.3 mmol of the corresponding aldehydes.

[c] I_2 (0.05 equiv) was used.



Scheme 3 A plausible reaction mechanism

In conclusion, we have reported a photooxidative alkene cleavage reaction under an air atmosphere using catalytic molecular iodine, trifluoroacetic acid, and visible light irradiation. This novel reaction is valuable because it uses inexpensive and harmless molecular oxygen from air and visible light from general purpose fluorescent lamps. The application of this photooxidation to other reactions is now in progress in our laboratory.

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References and Notes

(1) *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; Larock, R. C., Ed.; Wiley-VCH: New York, **1999**, 2nd ed., 1213.
(2) Bailey, P. S. *Chem. Rev.* **1958**, *58*, 925.
(3) (a) Dorofeev, S. B.; Eletskii, A. V.; Smirnov, B. M. *Dokl. Akad. Nauk SSSR* **1981**, *257*, 592. (b) Koike, K.; Inoue, G.; Fukuda, T. J. *Chem. Eng. Jpn.* **1999**, *32*, 295. (c) Ogle, R. A.; Schumacher, J. L. *Process Saf. Prog.* **1998**, *17*, 127.
(4) For recent examples, see: (a) Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824. (b) Kumar, A. V.; Prakash, R. V.; Sridhar, R.; Srinivas, B.; Rama, R. K. *Synlett* **2009**, 739. (c) Kogan, V.; Quintal, M. M.; Neumann, R. *Org. Lett.* **2005**, *7*, 5039. (d) Ho, C.-M.; Yu, W.-Y.; Che, C.-M. *Angew. Chem. Int. Ed.* **2004**, *43*, 3303. (e) Sato, K.; Aoki, M.; Noyori, R. *Science* **1998**, *281*, 1646. (f) Rajabi, F.;

Karimi, N.; Saidi, M. R.; Primo, A.; Varma, R. S.; Luque, R. *Adv. Synth. Catal.* **2012**, *354*, 1707. (g) Anand, N.; Reddy, K. H. P.; Rao, K. S. R.; Burri, D. R. *Catal. Lett.* **2011**, *141*, 1355. (h) Wang, A.; Jiang, H. *J. Org. Chem.* **2010**, *75*, 2321.

(5) Wu, X.; Davis, A. P.; Fry, A. J. *Org. Lett.* **2007**, *9*, 5633.

(6) Miao, C.-X.; Yu, B.; He, L.-N. *Green Chem.* **2011**, *13*, 541.

(7) Miyamoto, K.; Sei, Y.; Yamaguchi, K.; Ochiai, M. *J. Am. Chem. Soc.* **2009**, *131*, 1382.

(8) (a) *Photochemistry of Organic Compounds: From Concepts to Practice*; Klán, P.; Wirz, J., Eds.; John Wiley & Sons: New York, **2009**. (b) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052.

(9) For recent reviews, see: (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (b) Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, *104*, 3037. (c) Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400. (d) Piera, J.; Backvall, J.-E. *Angew. Chem. Int. Ed.* **2008**, *47*, 3506.

(10) Bhalerao, U.; Sridhar, M. *Tetrahedron Lett.* **1993**, *34*, 4341.

(11) (a) Yuan, Z.; Zheng, S.; Zeng, Y.; Chen, J.; Han, Y.; Li, Y.; Li, Y. *New J. Chem.* **2010**, *34*, 718. (b) Fu, X.-G.; Zhang, L.-P.; Wu, L.-Z.; Tung, C.-H. *J. Photosci.* **2003**, *10*, 175. (c) Li, H.-R.; Wu, L.-Z.; Tung, C.-H. *Tetrahedron* **2000**, *56*, 7437.

(12) Murthy, R. S.; Bio, M.; You, Y. *Tetrahedron Lett.* **2009**, *50*, 1041.

(13) (a) Feng, K.; Peng, M.-L.; Wang, D.-H.; Zhang, L.-P.; Tung, C.-H.; Wu, L.-Z. *Dalton Trans.* **2009**, 9794. (b) Feng, K.; Zhang, R.-Y.; Wu, L.-Z.; Tu, B.; Peng, M.-L.; Zhang, L.-P.; Zhao, D.; Tung, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 14685.

(14) Baucherel, X.; Uziel, J.; Juge, S. *J. Org. Chem.* **2001**, *66*, 4504.

(15) (a) Nobuta, T.; Fujiya, A.; Tada, N.; Miura, T.; Itoh, A. *Synlett* **2012**, *23*, 2975. (b) Tada, N.; Ishigami, T.; Cui, L.; Ban, K.; Miura, T.; Itoh, A. *Tetrahedron Lett.* **2013**, *54*, 256. (c) Kanai, N.; Nakayama, H.; Tada, N.; Itoh, A. *Org. Lett.* **2010**, *12*, 1948. (d) Nobuta, T.; Hirashima, S.; Tada, N.; Miura, T.; Itoh, A. *Synlett* **2010**, 2335. (e) Nakayama, H.; Itoh, A. *Tetrahedron Lett.* **2007**, *48*, 1131. (f) Nakayama, H.; Itoh, A. *Chem. Pharm. Bull.* **2006**, *54*, 1620.

(16) (a) Nobuta, T.; Fujiya, A.; Hirashima, S.; Tada, N.; Miura, T.; Itoh, A. *Tetrahedron Lett.* **2012**, *53*, 5306. (b) Hirashima, S.; Nobuta, T.; Tada, N.; Miura, T.; Itoh, A. *Org. Lett.* **2011**, *13*, 2576.

(17) Itoh, A.; Kodama, T.; Masaki, Y.; Inagaki, S. *Synlett* **2002**, 522.

(18) Hirashima, S.; Kudo, Y.; Nobuta, T.; Tada, N.; Itoh, A. *Tetrahedron Lett.* **2009**, *50*, 4328.

(19) Conversions of alkenes into aldehydes in the presence of iodine under aerobic photooxidative conditions have been reported previously, see: (a) Hewgill, F. R. *Aust. J. Chem.* **1994**, *47*, 461. (b) Liu, L.; Yang, B.; Katz, T. J.; Poindexter, N. K. *J. Org. Chem.* **1991**, *56*, 3769.

(20) **Photooxidation; Typical Procedure**
A solution of trans-4,4′-di-tert-butylstilbene (**1a**) (0.15 mmol), I_2 (0.015 mmol), and TFA (0.03 mmol) in dry MeOH–EtOAc (1:2 mL) was stirred in a Pyrex test-tube under air (open), and externally irradiated with four 22 W fluorescent lamps for 20 h. The mixture was quenched with aq $Na_2S_2O_3$ solution and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine (20 mL) and aq HCl (2 M, 2 × 20 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude residue by column chromatography (hexane–EtOAc, 50:1) provided 4-tert-butylbenzaldehyde (**2a**) (41.1 mg, 84%).

(21) For heterolytic carbon–carbon bond cleavage reactions of hydroperoxides in methanol, see: Utaka, M.; Fujita, Y.; Takeda, A. *Chem. Lett.* **1982**, 1607.

(22) Homolytic carbon–carbon bond cleavage reactions of hydroperoxides cannot be ruled out, see: Gu, X.; Zhang, W.; Salomon, R. G. *J. Org. Chem.* **2012**, *77*, 1554.