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Aerobic oxidative α-iodination of carbonyl compounds using molecular iodine activated by a nitrate-based catalytic system

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ABSTRACT

The novel reaction system comprising air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$ is introduced as a simple, safe, cheap, efficient, and regioselective mediator for direct aerobic oxidative α-iodination of aryl, heteroaryl, alkyl, and cycloalkyl methyl ketones. The reaction system enabled the moderate to quantitative regioselective iodination of a large range of different methyl ketone derivatives including those bearing oxidizable heteroatom (S, N) substituents. Several activated aromatic compounds were also efficiently and selectively iodinated. The practical applicability of the presented reaction system was shown on 20 mmol scale under ambient pressure and 100% conversion of substrate was achieved.

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Iodo-substituted organic compounds, particularly α-iodo methyl ketones and iodoaromatics, are among the most versatile intermediates and valuable synthons or precursors for carbon—carbon, carbon—nitrogen, or carbon—oxygen bond formation in combinatorial synthesis.[1] Due to their useful properties, iodinated organic compounds have found widespread use in medicine, particularly in medical diagnostics as contrast agents or radioactively labeled markers, pharmacology, agricultural chemistry, and biochemistry.[2] Moreover iodomethyl ketones are usually prepared indirectly by oxidative iodination of olefins,[3] electrophilic iodination of ketone derivatives (enol ethers and acetates),[4] or by halogen interchange of bromo compounds with sodium iodide.[5] Because of the difficulties in the synthesis and purification of enol silyl ethers and acetals, one-step α-iodination would be the most preferred choice and has lately received much attention.

The standard sources, molecular iodine (I_2) and the iodide anion (I^-), have often been used for the preparation of iodinated organic compounds, but since I_2 is often poorly reactive and the iodide anion is a weak nucleophile, electrophilic iodination has long been recognized as the most convenient approach for selective iodination.[6] Generally, the direct conversion of methyl ketone derivatives into α-iodo compounds is usually achieved using I_2-$Ce(NO_3)_4$,[7] I_2-$HgCl_2$,[8] and I_2-SeO_2,[9] while in the last few years substantial efforts have been directed toward the invention and development of alternative strategies. For the α-iodination of methyl ketone derivatives, iodonium donating systems, such as NIS-PTSA,[10] I_2-DME,[11] HIO_4-Al_2O_3,[12] I_2-F-TEDA-BF_4,[13] NIS-Lewis acid[14] have been employed. These latter methods are useful for the introduction of iodine into organic compounds, however, because of the high chemical- and energy-consuming protocols for the production of the reagents, these are low atom economy processes producing large excesses of waste, representing just some of the limitations for their use on industrial scale.

On the other hand, it is well known that in nature electrophilic halogenations mainly occur by enzymatically supported oxidative halogenation processes, in conjunction with vanadium, iron, or flavin co-catalysis, using hydrogen peroxide (H_2O_2) or molecular oxygen (O_2) as natural oxidants for the transformation of inactive iodide into the active iodonium species necessary for carbon—iodine bond formation.[15]

In spite of some well-known drawbacks of hydrogen peroxide and its variants, such as high cost and its undesirable decomposition into H_2O and ½O_2 during reactions influenced by higher temperatures and/or impurities and traces of metallic catalysts, which are often used to activate it, Oxone®[16] and urea–H_2O_2[17] have been successfully employed for aerobic oxidative iodination of organic compounds. On the other hand, molecular oxygen, as the most abundant oxidant, providing high atom economy for transformations of organic compounds is still an attractive and challenging research subject from the viewpoint of green approaches to organic synthesis and for industrial use. Transformations of organic

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compounds using molecular oxygen usually need transition metal catalysis to promote the reaction rate and selectivity to partial oxidation products. For this purpose, organometallic complexes [$(NH_4)_2Ce(NO_3)_6$,[18] $H_5PV_2Mo_{10}O_{40}$[19], and $Bi(NO_3){\cdot}5H_2O\text{-}BiCl_3$[20]] or nanoparticles[21] are often used, while nitrites [$NaNO_2$,[22] NO_2 gas[23]], nitrates [$Mg(NO_3)_2$,[24] NH_4NO_3[25]] or nitric acid (HNO_3)[26] as transition metal-free catalysts for aerobic transformations of organic compounds have recently been used. Nitrogen oxides (NO/NO_2), as highly oxidative species, also play an important role as reactive compounds which are useful in several chemical[27] and biological applications.[28] Over the last two decades, many articles have reported efficient and selective iodinations of organic compounds under aerobic oxidative conditions exploiting the NO/NO_2 oxidative catalytic redox cycle in combination with molecular oxygen as the oxidant. For this purpose nitrites ($NaNO_2$) in combination with acids, as a good source of nitrogen oxides,[29] were mainly used, while nitrate-based reaction systems were researched less extensively, mostly for iodination of aromatic compounds.[30] To the best of our knowledge, no data are available on the direct aerobic α-iodination of aryl and alkyl methyl ketones using molecular iodine activated by a full metal-free nitrate-based reaction system.

In the context of our projects focusing on aerobic oxidative halogenation under environmentally friendly conditions,[29] we now report the discovery and development of a novel full metal-free nitrate-based reaction system for the efficient and chemoselective aerobic oxidative iodination of methyl ketone derivatives, alpha to the carbonyl group and aromatic compounds, in high yields, using ammonium nitrate (NH_4NO_3) as a cheap and readily accessible source of nitrogen oxides (NO/NO_2) under acidic conditions.

In our recently published paper we reported an efficient and regioselective reaction system consisting of air/$NH_4NO_{3(cat.)}$/$I_{2(cat.)}$/HCl for the α-chlorination of aryl and alkyl methyl ketones under aerobic oxidative conditions.[31] The use of a catalytic amount of molecular iodine enabled moderate to quantitative and regioselective α-chlorination, while using 50 mol % of I_2 and HCl as the catalyst, 2-iodo-1-(4-methoxyphenyl)ethanone **2b** as the main and 2-chloro-1-(4-methoxyphenyl)ethanone as the side product were formed. Because of the increasing worldwide demand for such iodomethyl ketone derivatives, synthesized in direct one-step reactions under environmentally friendly conditions, optimization of the air/$NH_4NO_{3(cat.)}$/I_2/H^+ reaction system for aerobic oxidative iodination of methyl ketones has been undertaken.

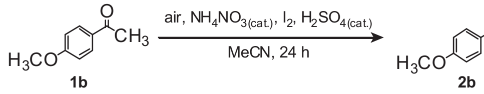
Optimization studies were executed on a model compound, 1-(4-methoxyphenyl)ethanone (**1b**). The best acid to support the process quantitatively was found to be H_2SO_4 (aqueous 96% solution) [see Table S1 in Supporting information (SI)]. Hence the air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$ reaction system was studied further.

The use of organic solvents in chemical processes is one of the most conflicting issues from the green chemistry point of view.[32] Solvent losses are a major contributor to high E (environmental) factors. In order to establish an environmentally friendly reaction process, different solvents were tested. Unfortunately low to moderate conversions were achieved for aerobic oxidative iodination in cyclopentyl methyl ether, 2-methyltetrahydrofuran, a mixture of MeCN and H_2O, (4:1) and pure H_2O. The highest conversion was achieved, in the environmentally acceptable, MeCN (see Table S2 in SI).

We also wanted to optimize the reaction system (air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$) further in order to achieve quantitative conversion of the model compound into the desired α-iodinated product in MeCN. Different parameters such as the reaction temperature and amount of added catalyst were investigated (Table 1). Firstly, the efficiency of the reaction system at different reaction temperatures (20, 40, and 60 °C) using NH_4NO_3 (20 mol %) and H_2SO_4 (10 mol %) (aqueous 96% solution) in solvent (2 mL) was studied and 60 °C was found to be the best choice (entry 6). Next, varying the amount of added catalyst NH_4NO_3 and acid H_2SO_4 in MeCN (2 mL) at different temperatures was studied (entries 2, 4, and 5), and after analysis of the ^1H NMR spectra of the crude reaction mixture, the optimal conditions were found (Table 1, entries 5 and 6).

Table 1

Effect of temperature and amounts of added catalysts on the efficiency of the air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$ reaction system for the α-iodination of 1-(4-methoxyphenyl)ethanone (**1b**)[a,b]



Entry	NH_4NO_3 (mol %)	H_2SO_4 (mol %)	Temp (°C)	Conversion[b] (%)
1	20	10	20	45
2	20	20	20	65
3	20	10	40	67
4	20	20	40	88
5	10	5	60	92
6	20	10	60	95

[a] Reaction conditions: 1-(4-methoxyphenyl)ethanone (**1b**) (1 mmol), NH_4NO_3 (10–20 mol %), I_2 (50 mol %), H_2SO_4 (10–20 mol %), MeCN (2 mL), balloon filled with 1 L of air, 60 °C, 24 h.

[b] Conversions of **1b** into **2b** were determined from the ^1H NMR spectra of the crude reaction mixtures.

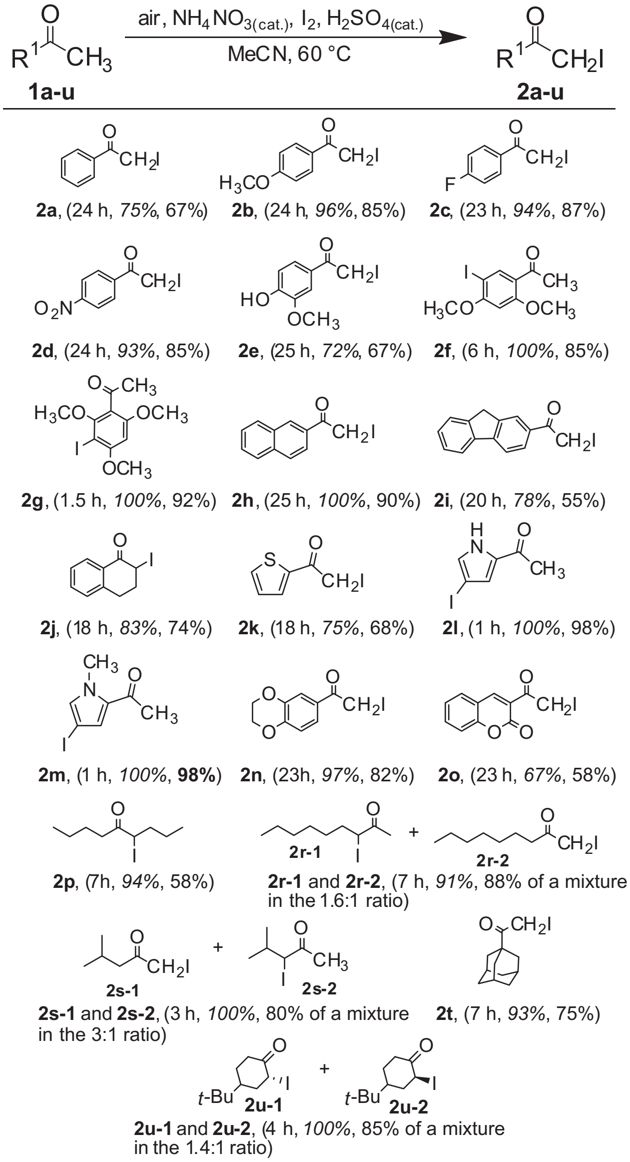
Control experiments highlighting the essential role of each member of the described reaction system, that is, aerial oxygen, NH_4NO_3 as the catalyst, and H_2SO_4 as the activator were performed. All the control experiments gave negative results under argon or under air. In the absence of any of the components of the reaction system, 1-(4-methoxyphenyl)ethanone (**1b**) was not converted into α-iodo derivative (**2b**). These data are summarized in SI (Table S3).

Encouraged by these preliminary results, we applied the air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$ reaction system under the optimized conditions for the α-iodination of a series of aryl and alkyl methyl ketones. As can be seen from Table 2, a variety of aryl, heteroaryl, and alkyl methyl ketones could be efficiently and selectively converted into their corresponding α-iodo derivatives in high yields in 1–25 h.[33] In general, we found that electron-withdrawing and electron-donating substituents on the phenyl ring supported the transformation of substrates **1a**–**e** into their iodomethyl derivatives **2a**–**e** efficiently and regioselectively (alpha to carbonyl position). On the other hand, in the case of strongly activated aromatic rings **1f** and **1g**, substituted with two or three methoxy substituents, regioselective iodination of only the aromatic ring occurred, producing mono iodinated aromatic derivatives **2f** and **2g**. Next, the efficiency and selectivity of the present reaction system was examined on two additional aromatic methyl ketones, 1-(naphthalen-2-yl)ethanone (**1h**) and 1-(9*H*-fluoren-2-yl)ethanone (**1i**). After ^1H NMR spectral analysis of the crude reaction mixtures, we found that only α-iodination had occured, producing 2-iodo-1-(naphthalen-2-yl)ethanone (**2h**) and 1-(9*H*-fluoren-2-yl)-2-iodoethanone (**2i**). 3,4-Dihydronaphthalen-1(2*H*)-one **1j** was also iodinated alpha to the carbonyl group in good yield.

The presence of functional groups bearing oxidizable or acid-sensitive heteroatoms such as sulfur or nitrogen in the target molecules could represent additional reaction centers for side reactions. As can be seen from Table 2, we examined the efficiency and selectivity of the air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$ reaction system for heteroaryl methyl ketones in order to make the methodology more general. 1-(Thien-2-yl)ethanone (**1k**) was efficiently and selectively converted into the corresponding iodomethyl ketone derivative **2k**. Nitrogen-containing 1-(1*H*-pyrrol-2-yl)ethanone (**1l**) and 1-(1-

Table 2

Aerobic oxidative α-iodination of aryl, heteroaryl, and alkyl methyl ketones using the air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$ reaction system[a,b,c,d]



2a, (24 h, *75%*, 67%) **2b**, (24 h, *96%*, 85%) **2c**, (23 h, *94%*, 87%)

2d, (24 h, *93%*, 85%) **2e**, (25 h, *72%*, 67%) **2f**, (6 h, *100%*, 85%)

2g, (1.5 h, *100%*, 92%) **2h**, (25 h, *100%*, 90%) **2i**, (20 h, *78%*, 55%)

2j, (18 h, *83%*, 74%) **2k**, (18 h, *75%*, 68%) **2l**, (1 h, *100%*, 98%)

2m, (1 h, *100%*, **98%**) **2n**, (23h, *97%*, 82%) **2o**, (23 h, *67%*, 58%)

2p, (7h, *94%*, 58%) **2r-1** and **2r-2**, (7 h, *91%*, 88% of a mixture in the 1.6:1 ratio)

2s-1 and **2s-2**, (3 h, *100%*, 80% of a mixture in the 3:1 ratio) **2t**, (7 h, *93%*, 75%)

2u-1 and **2u-2**, (4 h, *100%*, 85% of a mixture in the 1.4:1 ratio)

[a] Reaction conditions: substrate (1 mmol), NH_4NO_3 (10–25 mol %), I_2 (50 mol %), H_2SO_4 (5–12.5 mol %), MeCN (2 mL), balloon filled with 1 L of air, 60 °C, 1–25 h; exact reaction conditions for each product are given in SI.

[b] Conversions were determined from the ^1H NMR spectra of the crude reaction mixtures.

[c] Yields were determined from the ^1H NMR spectra after purification of the crude reaction mixtures by column or preparative chromatography.

[d] Values in brackets: (reaction time, *conversion*, yield).

methyl-1*H*-pyrrol-2-yl)ethanone (**1m**) underwent 100% regioselective iodination of the aromatic ring at position 4, thus producing 1-(4-iodo-1*H*-pyrrol-2-yl)ethanone (**2l**) and 1-(4-iodo-1-methyl-1*H*-pyrrol-2-yl)ethanone (**2m**) in yields of 98%. The oxygen-containing heterocyclic methyl ketone derivative 1-(2,3-dihydrobenzo[*b*] [1,4]dioxin-6-yl)ethanone (**1n**) was efficiently converted into the corresponding iodomethyl derivative **2n**. Acetyl-substituted coumarins often possess bioactivity of pharmaceutical interest,[34] and we thus chose 3-acetyl-2*H*-chromen-2-one (**1o**) as a substrate, which underwent selective conversion into 3-(2-iodoacetyl)-2*H*-chromen-2-one **2o** in moderate yield.

The reactivity, efficiency, and regioselectivity of the air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$ reaction system was further examined, using different alkyl and cycloalkyl methyl ketones. We found that for successful transformation of the starting substrate into the desired product, slightly higher amounts of the catalyst (NH_4NO_3) and acid (H_2SO_4) were needed in order to obtain high yields. Firstly, nonan-5-one (**1p**) and nonan-2-one (**1r**) were tested. Iodination of **1p** occurred efficiently and regioselectively alpha to the carbonyl group, while in the case of **1r**, a mixture of 3-iodononan-2-one (**2r-1**) and 1-iodononan-2-one (**2r-2**) was isolated in the ratio 1.6:1. The regioselectivity of the reaction system was further studied on 4-methylpentan-2-one (**1s**) and again a mixture of two products was obtained, 1-iodo-4-methylpentan-2-one (**2s-1**) and 3-iodo-4-methylpentan-2-one (**2s-2**) in a 3:1 ratio. Also, 1-acetyladamantane (**1t**), a common structural type in pharmaceutical compounds, was efficiently and selectively α-iodinated in up to 75% yield. As a representative of cycloalkyl methyl ketones, 4-*tert*-butylcyclohexanone was successfully converted into a mixture of *trans*-2-iodo-4-*tert*-butylcyclohexanone (**2u-1**) and *cis*-2-iodo-4-*tert*-butylcyclohexanone (**2u-2**) in a 1.4:1 ratio.

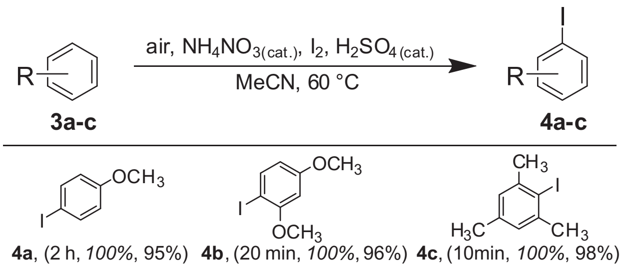
After selective ring iodination of polysubstituted aryl methyl ketones **2f** and **2g** (see Table 2) using air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$ in acetonitrile, we extended the range of tested poly alkyl and alkoxy group substituted aromatics **3a**–**c**. As is evident from the results collected in Table 3, quantitative conversions were achieved for all the tested substrates. In the case of anisole (**3a**), iodination occurred selectively only at the *para* position and 1-iodo-4-methoxybenzene (**4a**) was isolated in up to 95% yield. 1-Iodo-2,4-dimethoxybenzene (**4b**), and 2-iodo-1,3,5-trimethylbenzene (**4c**) were also obtained in good yields.

We additionally checked the practical applicability of our new procedure for large scale use.[35] Thus we treated 3 g (20 mmol) of 1-(4-methoxyphenyl)ethanone (**1b**) in MeCN (50 mL) with NH_4NO_3 (20 mol %, 320 mg), I_2 (50 mol %, 2.54 g) and H_2SO_4 (aqueous 96% solution, 10 mol %, 222.7 µL) in a 100 mL glass reactor equipped with a glass condenser open to the air at 60 °C. After 25 h, the reaction was complete; a white solid was filtered off and identified as ammonium sulfate. The solvent was distilled off under reduced pressure, and the crude reaction mixture was extracted with ethyl acetate (3 × 10 mL) and analyzed by ^1H NMR spectroscopy. Spectroscopic data of the crude reaction mixture showed 100% iodination of the starting substrate alpha to the carbonyl group, and 2-iodo-1-(4-methoxyphenyl)ethanone (**2b**) was isolated without the need for further purification.

Oxidative iodination[29b–d] and bromination[22e] of organic compounds catalyzed with nitrogen oxides (NO/NO_2) using air as

Table 3

Aerobic oxidative iodination of activated aromatic compounds using air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$ in MeCN[a,b,c,d]



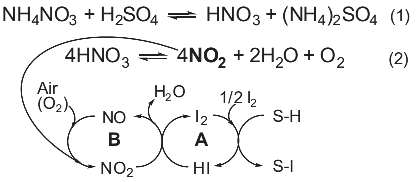
4a, (2 h, *100%*, 95%) **4b**, (20 min, *100%*, 96%) **4c**, (10min, *100%*, 98%)

[a] Reaction conditions: substrate (1 mmol), NH_4NO_3 (20 mol %), I_2 (50 mol %), H_2SO_4 (aqueous 96% solution, 10 mol %), balloon filled with 1 L of air, 60 °C, 10–120 min; exact reaction conditions for each product are given in SI.

[b] Conversions were determined from the ^1H NMR spectra of the crude reaction mixtures.

[c] Yields were determined from the ^1H NMR spectra after purification of the crude reaction mixtures by column or preparative chromatography.

[d] Values in brackets: (reaction time, *conversion*, yield).



Scheme 1. Proposed reaction path for the aerobic oxidative iodination of organic compounds using air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$.

the terminal oxidant with accompanying mechanistic elucidation has been elaborated several times.

The reported novel and optimized reaction system (air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$) was successfully used for highly efficient and regioselective iodination of several aromatic compounds and the direct one-step α-iodination of methyl ketone derivatives. The mechanism is shown in Scheme 1. In cycle A, iodination of the enol form of the ketone with I_2 at the alpha position with respect to the carbonyl occurs and I_2 is reduced to HI. The re-oxidation of iodide to I_2 by NO_2 is illustrated as cycle B. NO_2 is reduced to NO when it completes the oxidation of iodide, while the oxidation of NO to NO_2 is a process accomplished with the aerial oxygen.

Acidic conditions are essential and have two main roles: the first role is to convert ammonium nitrate into HNO_3 [Eq. 1], which is a thermally accelerated decomposing equilibrium with NO_2 [Eq. 2] and the second is in tuning the reactivity by increasing enolization of the ketone.

In conclusion, we have developed a four-component air/$NH_4NO_{3(cat.)}$/I_2/$H_2SO_{4(cat.)}$ reaction system for the efficient and selective α-iodination of aryl, heteroaryl, alkyl, and cycloalkyl methyl ketones, while in the case of strongly activated aryl methyl ketones, regioselective iodination on the aromatic ring was observed. In addition, efficient and selective iodination of activated aromatic compounds was achieved and will be elaborated in more detail along with an increased variety of substrates. It was shown that each member of the reaction system had an essential role. The use of NH_4NO_3 as a simple, inexpensive, and metal-free catalyst is possible in open-air instead of higher-pressure oxygen-conditions (autoclave or balloon technique). The generation of minimum amounts of waste and the possibility of process scale-up, including recovery of some possible hazardous solvents and the reactants, make the methodology useful and interesting from both environmental and economic points of view.

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Supplementary data

Supplementary data (full experimental details and characterization data for all products can be found in the supplementary data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.055.

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33. *General procedure for the aerobic oxidative iodination of methyl ketones and aromatic compounds:* A 10 mL glass flask equipped with a magnetic stir bar was charged with a methyl ketone (1 mmol) and dissolved in MeCN (2 mL). To the thermostated solution NH_4NO_3 (10–25 mol %), I_2 (50 mol %) and H_2SO_4 (aqueous 96% solution, 10–20 mol %) were added and the flask was further equipped with a balloon filled with air (1 L) and magnetically stirred at 60 °C. The consumption of starting material was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, diluted with EtOAc (10 mL), and insoluble material identified as ammonium sulfate was filtered off. The filtrate neutralized with $NaHCO_3$ (aqueous 10% solution, 2 mL) and $Na_2S_2O_3$ (aqueous 10% solution, 2 mL) and phase was separated. The water phase was washed with EtOAc additionally two times (2 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and the solvent distilled under reduced pressure. The crude product obtained was analyzed by ^1H NMR. Finally the crude product was purified using column chromatography (SiO_2, *n*-hexane/CH_2Cl_2 elution) and preparative thin layer chromatography to afford pure material, which was compared to authentic samples. Detailed data, concerning catalyst loading, reaction times, yields of pure products and their spectroscopic and other identification data are given in SI in the chapter *Characterization data of isolated final products*. Characterization, for example, *1-(9H-fluoren-2-yl)-2-iodoethanone (**2i**):* 1-(9*H*-Fluoren-2-yl)ethanone (1 mmol, 208.3 mg), NH_4NO_3 (0.15 mmol, 12 mg), I_2 (0.50 mmol, 126.7 mg), H_2SO_4 (aqueous 96% solution, 0.10 mmol, 5.56 μL), 2 mL MeCN, balloon filled with 1 L of air, 60 °C, 20 h were

used; crystallization from acetone; yield: 187.2 mg (55%) yellow solid, mp 163–164 °C. ^{1}H NMR (303 MHz, $CDCl_3$+two drops of DMSO, 25 °C, TMS): δ (ppm) 3.92 (s, 2H), 4.41 (s, 2H), 7.32–7.44 (m, 2H), 7.54–7.59 (m, 1H), 7.77–7.84 (m, 2H), 7.96–8.02 (m, 1H), 8.13 (s, 1H); ^{13}C NMR (76.2 MHz, $CDCl_3$+two drops of DMSO, 25 °C): δ (ppm) 2.3, 36.6, 119.6, 120.7, 125.0, 125.3, 126.9, 128.1, 128.1, 131.5, 139.9, 143.2, 144.3, 146.8, 192.4; MS (ESI): *m*/*z* 335 ((M+H)$^+$, 100%); HR-MS (ESI): *m*/*z* = 334.9925, calcd for $C_{15}H_{12}IO$: 334.9933; Anal. calcd for $C_{15}H_{11}IO$: C, 53.92; H, 3.32; found: C, 54.39; H, 3.05. *3-(2-Iodoacetyl)-2H-chromen-2-one (**2o**):* 3-Acetyl-2*H*-chromen-2-one (1 mmol, 188.2 mg), NH_4NO_3 (0.20 mmol, 16 mg), I_2 (0.50 mmol, 126.7 mg), H_2SO_4 (aqueous 96% solution, 0.1 mmol, 5.56 μL), 2 mL MeCN, balloon filled with 1 L of air, 60 °C, 23 h were used; column chromatography (SiO_2, CH_2Cl_2); yield: 182.2 mg (58%), yellow solid; mp 135–138 °C. ^{1}H NMR (303.0 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) 4.68 (s, 2H), 7.34–7.46 (m, 2H), 7.64–7.76 (m, 2H), 8.66 (s, 1H); ^{13}C NMR (76.2 MHz, $CDCl_3$, 25 °C): δ (ppm) 6.8, 116.7, 118.1, 121.4, 125.1, 130.2, 134.9, 149.5, 155.3, 158.6, 190.1; MS (ESI): *m*/*z* 314.9 ((M+H)$^+$, 100%); HR-MS (ESI): *m*/*z* = 314.9523, calcd for $C_{11}H_8IO_3$: 314.9518.

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35. *Scale-up procedure for the aerobic oxidative α-iodination of 1-(4-methoxyphenyl)ethanone:* A 100 mL glass reactor equipped with a magnetic stir bar was charged with 1-(4-methoxyphenyl)ethanone (20 mmol, 3 g) and dissolved in MeCN (50 mL). To a thermostated solution (thermostated for 30 min at 60 °C), NH_4NO_3 (10–25 mol %), I_2 (50 mol %) and H_2SO_4 (aqueous 96% solution, 10–20 mol %) were added in 2 min intervals and the reactor equipped with a condenser open to the air. The mixture was magnetically stirred (500 rpm) at 60 °C for 25 h. The consumption of starting material was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and insoluble material identified as ammonium sulfate was filtered off and washed with fresh MeCN. After evaporation of the filtrate, the mixture was dissolved in fresh EtOAc, quantitatively transferred into a separation funnel and the organic phase neutralized with $NaHCO_3$ (aqueous 10% solution, 5 mL), $Na_2S_2O_3$ (aqueous 10% solution, 5 mL) and the solvent distilled under reduced pressure. The water phase was washed with EtOAc additionally two times (2×10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and the solvent distilled under reduced pressure. The crude product obtained was analyzed by ^{1}H NMR.