ChemPubSoc Europe

DOI: 10.1002/cctc.201300774

Oxidative Breakdown of Iodoalkanes to Catalytically Active Iodine Species: A Case Study in the α-Tosyloxylation of Ketones

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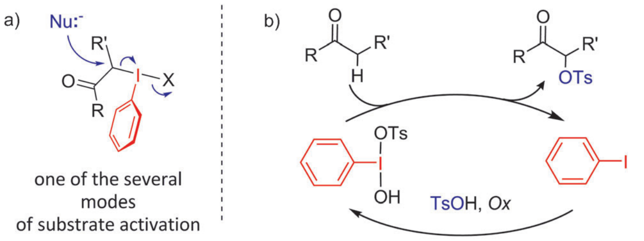
Catalysis of the oxidative processes by iodoarenes has become a promising direction in synthesis. The mechanism, involving the well-known isolable hypervalent iodine species, is generally limited to aromatic iodides, since the corresponding aliphatic species are normally highly unstable. Nevertheless, in this work catalytic amount of several primary, secondary or tertiary iodoalkanes were found to promotes the α-tosyloxylation of a range of ketones with RSO_3H, including aliphatic sulfonates. The process, was found to proceed through the oxidative breakdown of the iodoalkane to an inorganic catalytic species (likely IO^- or IO_2^-), thus falling within the previously described catalysis using molecular iodine or inorganic iodides. The catalyst eventually becomes deactivated through the precipitation of an iodine overoxidation product, the structure of which was solved ab initio from the powder diffraction data as a hitherto unreported phase of the iodic acid (HIO_3).



Scheme 1. Hypervalent iodine in the α-tosyloxylation of ketones. Ox = oxidant.

Iodoarenes are known to undergo oxidation at iodine to give the corresponding hypervalent iodine reagents. In particular, partial oxidation of ArI gives rise to highly reactive T-shaped ArIXX′ species, exemplified by $PhI(OAc)_2$ and PhI(OH)(OTs) (Koser reagent, Ts = *para*-toluenesulfonyl).[1] In synthesis, such a reagent may act as an oxidant capable of delivering one of the X^- fragments to the product, such as in the oxidative α-tosyloxylation of aliphatic ketones, which usually proceeds via an iodonium enolate intermediate (Scheme 1 a for a mechanism proceeding through a C-enolate; alternative paths involving iodonium O-enolates have also been invoked).[2] This kind of oxidative C–H functionalization provides rapid access to valuable building blocks for the construction of thiazoles, oxazoles, selenazoles, and imidazoles, among others.[3] Given that, in principle, ArI can be recovered and reused, variants of such processes have been developed (including asymmetric versions) following the early reports[4] by the groups of Ochiai and Kita, whereby ArI was used as a catalyst in the presence of a cheaper terminal oxidant.[5] In these cases, the catalytic cycle involves the in situ regeneration of the organoiodine(III) reagent (Scheme 1 b). The burgeoning field of hypervalent iodine catalysis was recently the subject of two Minireviews.[5d,e]

In light of the close relationship between hypervalent iodine catalysis and classical stoichiometric applications, it is not surprising that the field has been limited to iodoarenes. After all, with the exception of some very bulky or heavily fluorinated derivatives, hypervalent iodoalkanes are notoriously unstable,[1b] which makes their use in stoichiometric applications unfeasible. Indeed, upon generation, the $-IX_2$ moiety in such species has a leaving group ability that is orders of magnitude higher than that of an iodide.[6] During the course of our own investigations into immobilized organoarenes,[7] we observed that the products of the oxidative breakdown of certain iodoalkanes were still catalytically active. We wondered whether such activity paralleled the catalysis by simple molecular iodine and inorganic iodides that was reported recently.[8] We also became interested in the catalyst deactivation pathways frequently suffered by such systems.

To confirm the catalytic activity of the species obtained upon the in situ oxidative decomposition of iodoalkanes, the performance of 2-iodobutane was compared to that of iodobenzene in the tosyloxylation of propiophenone by following a process reported by Togo et al. that involved the employment of *meta*-chloroperbenzoic acid (*m*CPBA) as the terminal oxidant.[5b] Indeed, the use of a catalytic amount of PhI (10 mol %) gave, as expected, a 75 % yield of the α-tosyloxylated product after 10 h at 65 °C. Under the same conditions, a 10 mol % loading of *s*BuI also proved active, and it afforded a respectable 65 % yield of the product (Scheme 2), albeit with

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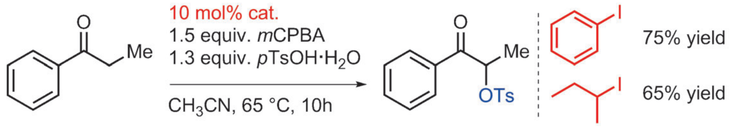
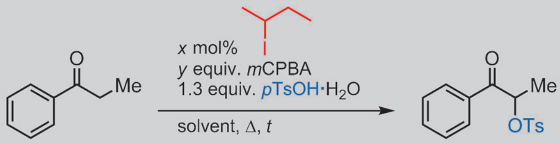
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201300774.



Scheme 2. Tosyloxylation of propiophenone by PhI and *s*BuI.

no improvement at longer reaction times. As discussed below, the loss of catalytic activity after approximately 10 h was accompanied by the precipitation of a white solid that was found to be ^{1}H NMR spectroscopy silent.

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	*m*CPBA [equiv.]	2-BuI [mol %]	*T* [°C]	*t*[b] [h]	Yield[c] [%]
1	CH_3CN	1.0	10	65	10	50
2	CH_3CN	1.1	10	65	10	58
3	CH_3CN	1.3	10	65	10	65
4	CH_3CN	1.5	10	65	10	74
5	CH_3CN	2.0	10	65	10	69
6	CH_3CN	1.5	10	50	22	77
7	CH_3CN	1.5	10	40	22	73
8	CH_3CN	1.5	10	75	10	45
9	toluene	1.5	10	50	22	34
10	EtOAc	1.5	10	50	22	21
11	$CHCl_3$	1.5	10	50	22	59
12	CH_3CN	1.5	5	50	22	65
13	CH_3CN	1.5	20	50	22	69

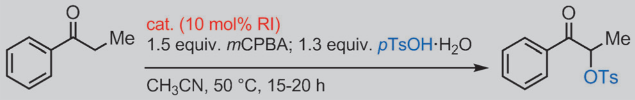
[a] [Substrate] = 0.2 м. [b] Reaction was stopped when no further evolution was detected by GC. [c] Corrected GC yield (PhCl used as an internal standard).

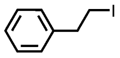
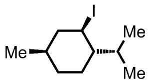
To gain further insight into the catalyst stability, the performance of *s*BuI was examined under a range of reaction conditions (Table 1). Thus, an *m*CPBA loading of 1.5 equivalent was found to be optimal (Table 1, entries 1–5),[9] and the best yields were achieved at 50 °C, albeit at the cost of a somewhat slower reaction (Table 1, compare entries 4 and 6–8). However, no further improvement could be achieved either by changing the solvent (Table 1, entries 6 and 9–11) or by varying the catalyst loading (Table 1, entries 12 and 13). In all cases, the formation of a white solid was observed towards the end of the reaction. These results indicated that although the oxidative breakdown of *s*BuI gave a catalytically active iodine species, further evolution of such species into a white insoluble material resulted in catalyst deactivation.

The formation of an active tosyloxylation catalyst was found to be quite general for a range of iodoalkanes tested (Table 2). Long-, medium-, and short-chain primary iodoalkanes (Table 2, entries 1–3) all performed quite well, but a somewhat diminished yield was obtained for $C_{12}H_{25}I$ (Table 2, entry 1) likely owing to its poor miscibility with CH_3CN. All three iodobutane isomers as well as 2-iodopropane proved active (Table 2, entries 3–6); the use of simple iodomethane (Table 2, entry 7) also gave a product that was isolated in 75 % yield. The formation of the catalyst was unaffected by the presence of an aromatic group (Table 2, entry 8). The similarity of the catalytic behavior of such a wide range of iodoalkanes is also strong evidence that, unlike aryl iodides, the catalytic cycle does not involve a hypervalent organoiodane, but rather proceeds through a common inorganic iodine species.

Additional control experiments were consistent with this hypothesis. Thus, an enantioenriched menthol-derived iodocyclohexane (Table 2, entry 9), although catalytically active, afforded a racemic product (see the Supporting Information).

Table 2. Screening of iodoalkanes as potential tosyloxylation precatalysts.[a]



Entry[a]	RI	Yield[b] [%]
1	*n*-iodododecane	69
2	*n*-iodohexane	78
3	*n*-iodobutane	78
4	*sec*-iodobutane	75
5	*tert*-iodobutane	78
6	2-iodopropane	79
7	MeI	75
8		79
9		69
10	C_4F_9I	< 5
11	CF_3CH_2I	< 5
12	$I(CF_2)_6I$	< 5
13	I_2	69/61[c]
14	NaI	77
15	KI	73

[a] [Substrate] = 0.2 м. [b] Yield of isolated product. [c] 5 and 2.5 mol % I_2.

Interestingly, fluorinated iodoalkanes (Table 2, entries 10–12), which presumably could give a reasonably stable hypervalent species and, thus, operate through an organoiodane-based catalytic cycle (such as that depicted in Scheme 1 b), proved inactive under the catalytic conditions tested. Additional experiments established that a reaction between C_4F_9I and *m*CPBA did not lead to oxidative breakdown.[10a] As suggested by a referee, a stable Koser-type iodane $C_4F_9I(OH)OTs$ was prepared following a method developed by Zhdankin et al.;[10b] a reaction between propiophenone and a stoichiometric amount of this reagent, however, proved sluggish, and only a trace amount of the corresponding tosyloxylated product was delivered after 24 h at 50 °C. It would appear, therefore, that this resistance to oxidative breakdown of the fluorinated iodoalkanes, coupled to the peculiar reactivity of the corresponding hydroxytosylate reagents (and, perhaps, their low solubility in CH_3CN) would all contribute to the lack of catalytic activity of such reagents under our conditions.

In contrast, molecular iodine and inorganic iodides, as previously reported,[8] also proved catalytically active (Table 2, entries 13–15). In addition, the systems obtained from *n*BuI, *s*BuI, and *t*BuI showed similar kinetic profiles (Figure 1), although with some differences likely resulting from different rates of iodoalkane breakdown. Interestingly, the reaction rates were found to be only slightly lower than those obtained with a more-studied PhI catalyst (Figure 1).

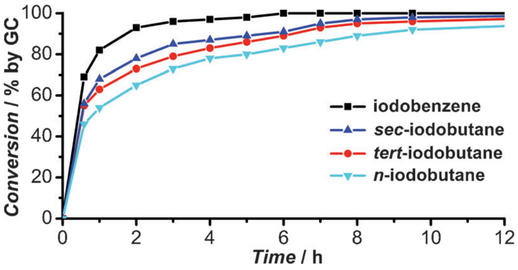


Figure 1. Kinetic profiles of *n*BuI, *s*BuI, and *t*BuI versus that of PhI. The conversion of propiophenone according to GC is shown and was corrected by using PhCl as an internal standard with conditions as in Table 2.

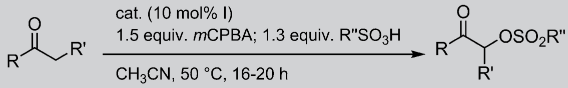
In addition to its mechanistic implications, the oxidative α-tosyloxylation of ketones with the use of iodoalkanes as catalyst precursors might offer, under certain conditions, an attractive synthetic procedure. Thus, before delving into the nature of the catalytic species, we briefly tested the performance, as catalyst precursors, of the iodobutanes along with KI and I_2, in the α-tosyloxylation of additional substrates. As seen in Table 3, all five catalysts performed quite well with propiophenone and the *para*-substituted propiophenones, including those with a halide or a nitro substituent (Table 3, entries 1–5). However, with the exception of KI, only a 30–36% yield could be achieved for 3-pentanone (Table 3, entry 6). Interestingly, the catalytic activity of I_2 in this reaction was previously found to proceed through the in situ decomposition of TsOH to *p*-iodotoluene, which would act as the true catalyst [Eq. (1)].[8a] It was argued, therefore, that an aromatic sulfonic acid was required if I_2 were to be used as a precatalyst. A related proposal by a different group suggested that a catalytic iodobenzene was formed through the iodination of the benzene solvent employed:

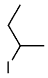
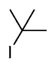
$$p\text{-}MeC_6H_4S(O)_2OH + I_2 \rightarrow p\text{-}MeC_6H_4I \qquad (1)$$

However, in our hands, even the simplest aliphatic sulfonic acid, $MeSO_2OH$, was coupled in good yields, by using either iodobutane or molecular iodine as the precatalyst (10 mol% I; Table 3, entry 7); no aromatic solvent was used. The result suggests that a species other than an aromatic iodide may act as the catalyst in this process. In fact, even 10-camphorsulfonic acid gave a modest yield (22%) of the product; the results were somewhat improved by using *s*BuI (40%; Table 3, entry 8). Control tests in the absence of any iodine source (Table S1, Supporting Information)[11] failed to produce the desired product.

During the course of the model α-tosyloxylation reactions, the GC peak for the iodoalkane disappeared immediately and, as mentioned above, a white solid appeared gradually.[9b] Given that the nature of the white solid might shed some light on the mode of catalyst deactivation, the solid obtained in entry 4 of Table 1 (denoted **M1**) was separated and examined. The material was found to be insoluble in organic solvents and soluble in water, and its ^1H NMR spectrum in D_2O was void of signals. To our surprise, the powder X-ray diffraction (PXRD) pattern of **M1** (Figure S1) produced a pattern identical to that of a substance identified in an earlier publication[12a] as a mixed iodine oxide I_4O_9, formulated as $I(IO_3)_3$, and described as a yellow, air-sensitive solid obtained through the ozonation of I_2 or MeI.[12,13] Our surprise stemmed from the fact that, despite the coincidence of the diffraction patterns, product **M1** was white and showed no sign of decomposition in air. Incidentally, a material with the same diffraction pattern, denoted as **M2**, could be prepared in the absence of the two substrates (ketone and *p*TsOH) simply by oxidizing RI (or I_2) with *m*CPBA (Table S2).[12b] The structure of **M1** was solved from powder data[14] by using the cluster-based direct methods implemented in XLENS_pd6[14a] and refined with RIBOLS[14b] by applying an unrestrained Rietveld refinement. The crystal structure of

Table 3. α-Tosyloxylation of ketones with iodine sources as catalysts[a]



Product				Yield[b] [%]				
Entry	R	R′	R″				KI	I_2
1	*p*-CH_3Ph	H	*p*-CH_3Ph	64	65	68	59	55
2	Ph	H		70	76	70	80	64
3	*p*-BrPh	H		82	86	81	81	73
4	*p*-ClPh	H		73	72	75	70	66
5	*p*-NO_2Ph	H		66	58	65	63	56
6	Et	Me		36	32	31	66	30
7	Ph	H	Me	64	76	80	72	61
8	Ph	H	10-camphor	29	40	33	27	22

[a] [Substrate] = 0.2 M. [b] Yield of isolated product.

this solid,[14c] combined with thermogravimetric analysis, X-ray photoelectron spectroscopy, and elemental analysis data,[14d,e] showed it to be a hitherto unreported crystal form of iodic acid, HIO_3.[15] The iodine atoms form hexagonal layers parallel to the crystalline *bc* planes, and each iodine is surrounded by oxygen atoms in a distorted octahedral coordination (Figure 2); each HIO_3 molecule is connected to neighbor molecules through three weak I⋯O interactions and a (probable) O2⋯O3′ hydrogen bond [2.62(3) Å]. In spite of the different crystal packing, bond lengths are similar to those reported in other HIO_3 structures.[15b–d]

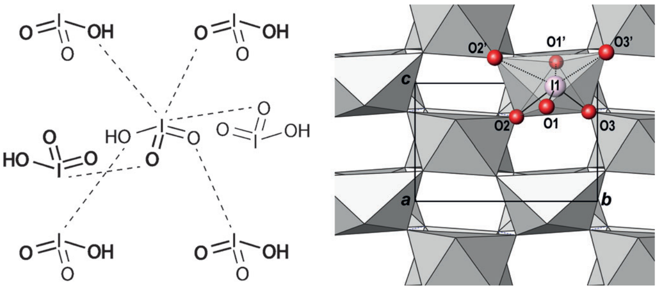
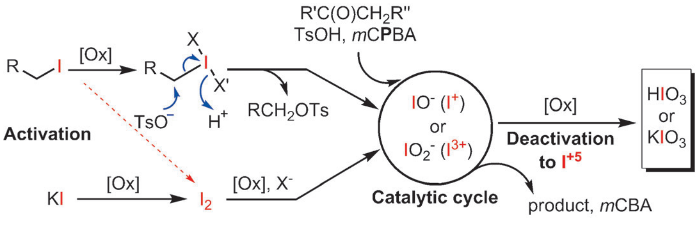


Figure 2. Crystal structure of **M1**. Left: Molecular scheme of the I–O weak interactions (-----, 2.5 to 2.8 Å); right: packing of the distorted iodine octahedra. Iodine centers form hexagonal layers normal to *a*.

Consistent with the notion that the precipitation of the white solid is symptomatic of catalyst deactivation, neither isolated **M1** nor the commercially available sample of HIO_3 or its anhydride, I_2O_5, showed any activity in the α-tosyloxylation of propiophenone (Table S3). It was also found that although an analogous overoxidation process did take place in the case of KI, the diffraction pattern obtained for the corresponding white solid corresponded to that of KIO_3 rather than the acid.

On the basis of these results and previous research[16] on related processes, we propose that an inorganic iodine (+1) and/or (+3) intermediate might be the true catalyst for cases in which alkyl iodides are used (Scheme 3). As previously proposed,[16] the specific species corresponding to these oxidation states might be hypoiodite IO^- and iodite IO_2^-. Attack of the tosylate on a transient hypervalent iodine species[17] derived from the alkyl iodide would give rise to the catalytically active I^{+1} (or I^{+3}) intermediate.[18] Here, the I^{+3} (e.g., hypoiodite) species could also form through disproportionation of I^+ to I^{+3} and I^- species. Further oxidation might then lead to the inactive I^{+5} products (i.e., **M1** or KIO_3); this explains the drop in the catalytic activity over time. The I^{+5} (specifically IO_3^-) species might also form as a result of the known propensity of hypoiodite IO^- to disproportionate into iodide and iodate. The same active species may be obtained from the oxidation of iodide or molecular iodine (the initial brown color observed with RI also indicates the formation of at least some I_2).



Scheme 3. Proposed evolution of the I species throughout the reaction.

In summary, we have shown that, in addition to ArI, simple iodoalkanes can also serve as precursors to species that are active in the catalytic oxidative α-tosyloxylation of aliphatic ketones with sulfonic acids. However, unlike ArI, the catalytic activity of which is based on the intermediacy of $PhIX_2$ species, the iodoalkanes appear to quickly degrade into catalytically active inorganic iodites (and/or hypoiodites). Overoxidation and/or disproportionation of such species leads to catalyst deactivation through the formation of a white solid that was identified as a previously unreported polymorph of HIO_3 (observed as a white precipitate, i.e., **M1**), or, in some cases, as KIO_3.

Acknowledgements

Financial support from the Ministerio de Ciencia e Innovación (MICINN) of Spain [Projects CTQ2009-07881 and CTQ2011-22649 and Consolider Ingenio 2010 (CSD2007-00006)]. A Ramón y Cajal scholarship to A.S. [Ministerio de Educación y Ciencia (MEC), Spain, RYC-2006-001425], Departament d'Universitats, Recerca i Societat de la Informació (DURSI)-Generalitat de Catalunya (SGR2009-1441), and China Scholarship Council (CSC scholarship to W.G.) are gratefully acknowledged.

Keywords: hypervalent compounds · iodine · iodoalkanes · powder diffraction · tosyloxylation

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[9] a) As suggested by Ochiai (Ref. [4a]), *m*CPBA was dried under reduced pressure for at least 1 h prior to its use; b) the color of all mixtures turned from brown to beige, followed by the appearance of a white solid.

[10] a) The fluorinated iodane thus obtained was fully insoluble in CH_3CN, which might further explain the lack of catalytic activity; b) For the preparation of hypervalent fluorinated iodoalkanes, see: A. A. Zagulyaeva, M. S. Yusubov, V. V. Zhdankin, *J. Org. Chem.* **2010**, *75*, 2119–2122.

[11] Tables S1–7 and Figures S1–4 can be found in the Supporting Information. No reaction occurred if using H_2O_2 as an oxidant and propiophenone as a substrate in the presence of a catalytic amount of iodobutane (Table S1).

[12] ICDD card references of XRD spectra: a) I_4O_9, 00-045-0872; b) all XRD spectra of the products in Table S2 can be found in Figure S1.

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[17] Alkyl tosylates have been detected by GC–MS in some cases.

[18] For a related mechanism for the oxidation of methyl iodide to the hypoiodous acid, see G. Asensio, C. Andreu, C. Boix-Bernardini, R. Mello, M. E. González-Núñez, *Org. Lett.* **1999**, *1*, 2125–2128.

Received: September 14, 2013