Oxidation of secondary alcohols using solid-supported hypervalent iodine catalysts†

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It is shown how secondary alcohols are oxidized to provide the corresponding ketones by use of Ozone® and solid-supported hypervalent iodine catalysts. Under experimentally simple conditions with acetonitrile at elevated temperatures, excellent conversions were achieved with low catalyst loadings (0.2–5 mol%) when employing the conjugates 5 and 6 derived from IBX and IBS. The catalysts are broadly applicable to a range of alcohol substrates. Of primary importance with respect to sustainability issues, the metal-free catalysts are easily removed from the reaction mixture through filtration, and they can be re-used in oxidation processes for multiple times, without loss of catalytic activity.

Introduction

The formation of carbonyls through alcohol oxidation is one of the most fundamental reactions in contemporary chemistry. A great plethora of methods already exist to fulfill this task, and hypervalent iodine reagents belong to the most applied oxidation agents.1–5 For example, the Dess–Martin periodiane (DMP) became the standard textbook reagent for all kinds of alcohol oxidation, after its invention in 1983.6 Its parent compound, 2-iodoxybenzoic acid (IBX, 1),7–9 is even older and was reported first in 1893 by Hartmann and Meyer (Scheme 1).10 Since then, IBX was mainly forgotten over more than half a century before it experienced a renaissance with the breakthrough reports by Frigerio and Santagostino in 1994: IBX was shown to be a moisture-stable and easy-to-handle reagent for the mild oxidation of alcohols in DMSO at room temperature.11,12 The IBX oxidation of alcohols then emerged as a standard transformation in organic synthesis with numerous applications in complex molecule synthesis.13 Nowadays IBX is considered one of the most versatile oxidizing agents, with an extraordinary array of reactivities beyond alcohol oxidation, including phenol oxidation,14,15 functional group transfer onto activated methylene compounds,16–22 and dehydrogenations.23,24

Despite the many advantages IBX offers, several issues are unattractive to practitioners: (i) similar to many other beloved oxidation agents, stoichiometric amounts of the hypervalent iodine compound are required for alcohol oxidation. This is particularly problematic since IBX is reported to be shock- and heat-sensitive,25,26 at least under certain conditions, thus weakening its routine for large-scale applications. (ii) The regeneration of the IBX species from the 2-iodosobenzoic acid (IBA) formed during the oxidative process is typically avoided, resulting in significant amounts of “organic waste”.27 (iii) DMSO is the preferred solvent for all variants of IBX oxidations,28,29 requiring sophisticated work-up protocols to remove the remainder of the hypervalent iodine reagent, for...
example by addition of chlorinated solvents. It is therefore reasonable to summarize that IBX and its derivatives are not the ideal reagents with respect to the principles of Green Chemistry\textsuperscript{10,11} since they are mostly used as stoichiometric and non-recyclable reagents.

Several strategies were developed to tackle those issues. For example, modified IBX reagents\textsuperscript{32–37} for the use in common solvents other than DMSO and safer formulations\textsuperscript{38,39} of IBX with reduced explosive properties were described. Experimental procedures that aimed at the effective recovery of the reduced form of the hypervalent iodine compounds using biphasic protocols or fluorous techniques led to further improvements.\textsuperscript{40–44} Polymer-supported IBX reagents were also reported, with the goal to ease work-up protocols and to improve recyclability,\textsuperscript{45} including polymer-supported variants of IBX\textsuperscript{46–48} IBX-amides,\textsuperscript{51–56} IBX-esters,\textsuperscript{57} and 2-iodophenol ethers.\textsuperscript{58} In addition, the oxidation with catalytic amounts of IBX\textsuperscript{59–61} and particularly 2-iodoxybenzenesulfonic acid (IBS, 2)\textsuperscript{62–65} was shown to be highly efficient.\textsuperscript{66} Those catalytic methods typically rely on Oxone® as the stoichiometrically used co-oxidant,\textsuperscript{67} a reagent that is considered environmentally safe, non-toxic and non-explosive.\textsuperscript{75} To facilitate the recovery of the hypervalent iodine organocatalyst, fluorous IBX was recently introduced.\textsuperscript{76} However, the catalytic use of hypervalent iodine oxidants bound to a polymer support was not reported, until now. This is despite the fact that there would be obvious advantages: the iodine-based catalysts are an environmentally sustainable alternative to transition metals, relatively inexpensive and easily recoverable.\textsuperscript{77}

In this paper, we present two new solid-supported hypervalent iodine reagents for the oxidation of secondary alcohols, derived from readily available starting materials: one is based on IBX, and the other is an IBS derivative. In the presence of Oxone®, the two reagents are shown to be highly effective catalysts when using a water-acetonitrile solvent mixture, with catalyst loadings as low as 1 mol%. We also demonstrate that the two metal-free organocatalysts are easily reusable, and work-up protocols consist of simple filtrations. Therefore, our hypervalent iodine compounds may become attractive ‘green catalysts’ in the ever-evolving fields of alcohol oxidations and other challenging oxidative processes.\textsuperscript{70,71,78–81}

Results and discussion

We recently presented the use of solid-supported DMAP–peptide conjugates 3 for the highly regioselective acylation of polyhydroxylated small molecules (Scheme 1).\textsuperscript{82,83} We now expanded this concept to connect hypervalent iodine precursor units with peptide-modified resins. Our initial plan was to study conjugates 4 consisting of the glycine-modified Merrifield resin and a (poly)alanine linker, the N-terminus of which was connected to the iodine-containing catalyst. For reasons detailed below, we also generated the conjugates 5 and 6 where the (poly)alanine linker was attached to an aminomethyl polystyrene resin. While 5 is based on the same IBX-derived catalytically active unit used for 4, the solid-supported catalyst 6 was designed as a variant of IBS.

### Synthesis of the solid-supported precatalysts 4, 5 and 6

We started the synthesis of the precatalyst 4 as summarized in Scheme 2A, using 2-iodobenzoic acid as the commercially available and cheap starting material. Nitration of the aromatic core gave the 5-nitro analogue in 65% yield, as pure substance after simple recrystallization. Subsequent conversion into the
tert-butyI ester furnished 7 in excellent yields. Reduction of the
nitro group with palladium on charcoal and H₂ pressure (8
bar) led to the desired aniline derivative 8 in 82% yield. The
iodobenzoic acid variant was coupled to a protected glutamic
acid with classical conditions providing the unnatural amino
acid 9 in 90% yield. The methyl ester was then saponified
while the tert-butyI ester remained untouched: this step was
accomplished using lithium hydroxide in aqueous THF in 73% yield.

With the Fmoc-protected amino acid 10 in hand, the immo-
ibilization on glycin-modified Merrifield resin was accom-
plished using standard solid-phase peptide synthesis (see ESI†
for details). Of note, alanine was chosen as the linker amino
acid because of the ease of its introduction with SPPS tech-
niques, its lack of functional groups, and its stability toward
oxidative conditions (particularly in comparison to glycine).
We decided to start with the conjugate 4 having four alanines
as linker unit since, at the outset of our studies, we expected
that the use of an elongated and flexible linker that provides a
spatial separation of the catalytically active part from the
polymer body will be advantageous.51 The loading of the resin
was determined to be around 0.46 mmol g⁻¹ via UV-VIS
measurements (see ESI†). The amino acid 10 was also linked
to the aminooethyl polystyrene resin giving conjugates 5. We
constructed those conjugates with several linker lengths for
further tests, with 5a having no alanine unit (n = 0), 5b having
two alanines (n = 2) and 5e having four alanines (n = 4). In all
cases, a loading between 0.3 and 0.4 mmol g⁻¹ was achieved.

We next focused on the synthesis of the solid-supported precatalyst 6 (Scheme 2B), relying on our previous synthetic
approach to the oxidant IBX-SO₃K.37,84,85 We began with 4-amino-
ethyl polystyrene resin 1,3-diphenylpropan-2-ol and 2,2-dimethyl-1-phenylpropan-1-ol
were easily oxidized by use of catalyst 4. The formation of by-
products was not detected via ¹H NMR or GC-FID analysis of
the crude reaction mixture. Hence, the performance of the oxida-
tion reactions was easily screened by determining the ratio
of starting substrate 13 and oxidation product 14 with GC-FID
in a standardized way. In the absence of precatalyst 4, 8% con-
version of the starting substrate were observed after 18 h, thus
indicating a minor background reaction with no synthetic use
(entry 1). However, it was truly disappointing that the poly-
meric system 4 lacked a main asset: it was not reusable. A loss
of activity was already found in the second cycle when reusing
after simple filtration for the borneol oxidation (entry 3). A
markedly lowered conversion of 82% was observed after 18 h,
under otherwise identical conditions. This trend continued,
and the fifth reaction with the same batch of catalyst gave only
15% conversion, demonstrating that resin-supported catalyst 4
had no recyclability of value.

The failure of 4 was attributed to the weakness of the ester
bond between the Merrifield resin and the glycine linker
which lead to hydrolysis under the reaction conditions. Indeed,
control experiments showed that esters were partly hydrolysed
in aqueous acetonitrile at 70 °C in the presence of OxoOne®
while amide bonds remained fully stable. As a result, column
chromatography was required to obtain analytically pure oxida-
tion products when employing precatalyst 4. Simple fil-
tration, on the other hand, gave the ketones with traces of
impurities that were not unequivocally identified, but may cer-
tainly stem from the partial hydrolysis of 4. The design error of
4 then led us to carefully study the systems 5 and 6 where the
hypervalent iodine precursor units were connected to the
aminooethyl polystyrene resin via more stable amide bonds.

### Table 1 Recycling tests with precatalyst 4, 5, 6

| Entry | Catalyst (mol%) | Cycle no. | 13a/14a a |
|-------|-----------------|-----------|-----------|
| 1     | —               | 1 (initial) | 92/8      |
| 2     | 4 (4)           | 1 (initial) | 2/100     |
| 3     | 4 (4)           | 2 (1st reuse) | 18/82    |
| 4     | 4 (4)           | 3 (2nd reuse) | 64/36    |
| 5     | 4 (4)           | 4 (3rd reuse) | 82/18    |
| 6     | 4 (4)           | 5 (4th reuse) | 85/15    |
| 7     | 5e (5)          | 1 (initial) | 0/100     |
| 8     | 5e (5)          | 2 (1st reuse) | 0/100    |
| 9     | 5e (5)          | 3 (2nd reuse) | 0/100    |
| 10    | 5e (5)          | 4 (3rd reuse) | 0/100    |
| 11    | 5e (5)          | 5 (4th reuse) | 19/81    |
| 12α   | 6 (1)           | 1 (initial) | 21/79     |
| 13α   | 6 (1)           | 2 (1st reuse) | 14/86    |
| 14α   | 6 (1)           | 3 (2nd reuse) | 12/88    |
| 15α   | 6 (1)           | 4 (3rd reuse) | 14/86    |
| 16α   | 6 (1)           | 5 (4th reuse) | 19/81    |
| 17α   | 6 (1)           | 6 (5th reuse) | 22/78    |

a Recycling and reuse of catalyst by filtration. b Ratio 13a/14a was determined via GC-FID (calibrated with stock solutions of 13a and 14a) after 18 h. With 40 mol% of Bu₄NHSO₄, 2 h, MeCN.
 Gratifyingly, it was easily possible to reuse the catalysts 5 and 6 for multiple times, after recycling of the resins through simple filtration. As shown in Table 1 (entries 7–11), the IBX-derived system 5c kept its activity over five cycles, and complete oxidation of borneol was achieved using 5 mol% of the catalyst with 1.6 equivalents of Oxone® at 70 °C in aqueous acetonitrile. Lower catalyst loadings (<2.5 mol%) were shown to provide incomplete conversions, even after elongated reaction times. The IBS variant 6 was effectively reused for five times (Table 1, entries 12–17), accomplishing a constant conversion between 78% and 88%, albeit with lowered catalyst loading (1 mol%) and reduced reaction times (2 h). As a result of the recycling tests, we decided that both systems 5 and 6 based on the aminoethyl polystyrene resin qualify well for catalyzing the oxidation of secondary hydroxy groups under the premise that they deliver easy work-up and multiple reuses.

Our optimization attempts with catalyst 5c then showed that a broad range of reaction conditions is feasible, and the oxidation proceeds equally well in water-free MeNO2, aqueous MeCN (5–30% water), and aqueous conditions (method B). In the presence of 0.4 equivalents of NBu4NHSO4, it was easily possible to use 6 with extremely low catalyst loadings of 1 mol% and 0.2 mol% to accomplish useful conversions (entries 8 and 9). Under the conditions, a TON up to 455 was reached with regard to each catalytic center (with a TOF of around 5.3 × 10⁻³ s⁻¹).

The scope of the catalyzed oxidation of secondary alcohols with Oxone® was then explored, using the solid-supported compounds 5c and 6 under standardized conditions. As summarized in Table 4, various structurally diverse secondary alcohols 13 were examined as substrates using method A [5c (5 mol%), Oxone® (1.6 equiv.), 18 h, 70 °C, MeCN–H₂O (7:3)] and method B [6 (5 mol%), Oxone® (1.6 equiv.), NBu4NHSO4 (0.4 equiv.), 18 h, 70 °C, MeCN]. We point out that the addition of the phase transfer agent was only required when using nonaqueous conditions (method B); aqueous solvent mixtures (method A) do not require the additive since Oxone® is easily dissolved under the conditions. A general trend was that the performance of the IBS-derived catalyst 6 was superior. In par-

Table 2 Effect of the linker length of precatalysts 5a, 5b, 5c

| Entry | Catalyst | 13b/14b  |
|-------|----------|----------|
| 1     | 5a       | 1/99     |
| 2     | 5b       | 3/97     |
| 3     | 5c       | 3/97     |

α Ratio 13b/14b was determined via GC-FID (calibrated with stock solutions of 13b and 14b) after 18 h.

Table 3 Optimization of the oxidations with IBS-derived catalysts 6 and 6′

| Entry | Catalyst (mol%) | Additive | Solvent | 13b/14b  |
|-------|-----------------|----------|---------|----------|
| 1     | 6′ (3)          | —        | MeCN–H₂O (7:3) | 5/95     |
| 2     | 6 (3)           | —        | MeCN–H₂O (7:3) | 3/97     |
| 3     | 6 (2.5)         | —        | MeCN    | 94/6     |
| 4     | 6 (2.5)         | —        | MeNO2   | 91/9     |
| 5     | 6 (2.5)         | NBu₄NHSO₄ (10 mol%) | MeCN    | 43/57    |
| 6     | 6 (2.5)         | NBu₄NHSO₄ (10 mol%) | MeNO2  | 63/37    |
| 7     | 6 (2.5)         | NBu₄NHSO₄ (20 mol%) | MeCN    | 3/97     |
| 8     | 6 (1)           | NBu₄NHSO₄ (40 mol%) | MeCN   | 2/98     |
| 9     | 6 (0.2)         | NBu₄NHSO₄ (40 mol%) | MeCN   | 9/91     |
| 10    | —               | NBu₄NHSO₄ (40 mol%) | MeCN   | 94/6     |

α Ratio 13b/14b was determined via GC-FID (calibrated with stock solutions of 13b and 14b). b 6 h. c 2 h. d 4 h. e 24 h.
ticular, sterically demanding secondary alcohols (e.g., 13a, 13d, 13f and 13k) were easier oxidized to the corresponding ketones using method B. The reaction times until full conversion of the starting substrate were also markedly shorter with catalyst 6, compared to 5c (method A). Another advantage of catalyst 6 was that it was employed in a combination with tBu4NHSO4 under non-aqueous conditions, allowing to use other solvents than acetonitrile if required due to solubility issues of the sub-

### Table 4 Scope of the oxidations with catalysts 6 and 5c

| Entry | Alcohol 13 | # Ketone 14 | Yield [%] | Entry | Alcohol 13 | # Ketone 14 | Yield [%] |
|-------|------------|-------------|-----------|-------|------------|-------------|-----------|
|       |            |             | A         |       |            |             | B         |
| 1     |            | a           | 79        | 11    | k          |             | 76        |
| 2     |            | b           | 70        | 12    | l          |             | 82        |
| 3     |            | c           | 80        | 13    | m          |             | 71        |
| 4     |            | d           | 32        | 14    | n          | n.r.        | 89        |
| 5     |            | e           | 71        | 15    | o          |             | 0         |
| 6     |            | f           | 0         | 16    | p          |             | 0         |
| 7     |            | g           | 82        | 17    | q          |             | 95        |
| 8     |            | h           | 84        | 18    | r          |             | 0         |
| 9     |            | i           | n.r.      | 19    | s          |             | 0         |
| 10    |            | j           | 75/58/69/82/63 | 20    | t          | n.r.        | 75 |

| Yield [%] | A | B |
|-----------|---|---|
| a Isolated yield.     | b n.r. = experiment was not run.     | c 3 h. d 24 h. e 72 h in acetone. f 90% from benzoin. g 18 h in toluene. h Determined via GC-FID (calibrated with stock solutions of 13t/14t). |
strate. For example, 5α-cholestan-3β-ol 13s was successfully oxidized with Oxone® and 6 in toluene under otherwise identical conditions (entry 19). The main advantage of method A (with 5c) was the simple work-up protocol consisting only of filtration to remove 5c and subsequent extraction of the aqueous layer. If the starting material was completely converted, further purification by column chromatography was typically not necessary. In the case of method B (with 6), an additional filtration over silica for the removal of the tetrabutylammonium salts was required to obtain analytically pure compounds; the phase transfer agent was not recovered.

We point out that primary alcohols also provide oxidation products under the conditions of method B. However, aldehydes were produced in markedly reduced yields and mixed with various products of over-oxidation, thus limiting the use of the catalytic system tremendously. In the case of primary allylic alcohols 15, it was possible to isolate the corresponding aldehydes in pure form and moderate yields, as outlined for 16a and 16b in Scheme 3. Two other limitations of our catalyst system for the oxidation of secondary alcohols were identified in the course of our studies: (1) phenols are not stable under the conditions,14,15 and (2) amines are not tolerated due to various competing condensation and oxidation reactions that were not further analyzed.

Method B using IBS-derived polymer 6 is also easily applicable to larger scales, as demonstrated in Scheme 4 for the conversion of secondary alcohol 13b into ketone 14b: 50 mmol of 13b led to the isolation of the desired ketone with 80% yield after 5 h, using only 1 mol% of catalyst 6. Of note, 95% of the supported catalyst were recovered for re-uses.

**Conclusions**

We have presented two new catalytic systems 5c (based on IBX) and 6 (based on IBS) that are outstanding tools for the oxidation of secondary alcohols with Oxone® under ketone formation. The catalysts, derived from hypervalent iodine reagents linked to a polymer support, are highly active, and a broad scope is demonstrated for both catalysts. However, the catalytic oxidation with 6 proceeded more rapidly and cleanly. After completion of the reaction, the catalysts were recovered through simple filtration, and it was possible to reuse them for multiple times, thus rendering them highly attractive for the objectives of Green Chemistry: recoverable and prepared from readily available starting materials consisting of abundant chemical elements.

Our future studies will make use of the catalyst systems for chemoselective oxidations, by varying the linker units. We will also show in due course how the immobilized catalysts are of use in flow chemical oxidation processes.

**Conflicts of interest**

There are no conflicts to declare.

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