

Enantioselective α -Oxytosylation of Ketones Catalysed by Iodoarenes

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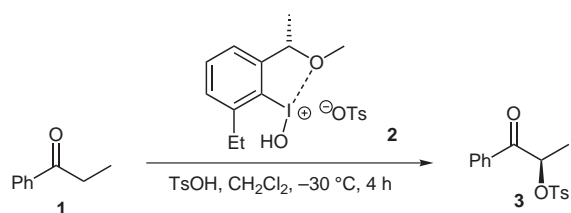
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Abstract: The α -oxytosylation of ketones catalysed by enantioenriched iodoarenes using mCPBA as stoichiometric oxidant is reported to give useful synthetic intermediates in good yield and modest enantioselectivity. We believe this to be the first report of an enantioselective catalytic reaction involving hypervalent iodine reagents which should open up a new field for enantioselective organocatalysis of oxidation reactions.

Key words: hypervalent iodine reagents, organocatalysis, oxidation, stereoselective synthesis

The use of enantioenriched hypervalent iodine reagents for asymmetric transformations has emerged as an interesting area of research in recent years.¹ These reagents are attractive because they can replace toxic heavy metal reagents.² One example is our report of the enantioselective α -oxytosylation of ketones **1** mediated by chiral Koser-type reagent **2** giving synthetically useful³ tosylates such as **3** in up to 40% ee (Scheme 1).^{1f,4} This reaction suffers the drawback that the λ^3 -iodane **2** must be present in stoichiometric quantities and that the preparation of this reagent requires two synthetic steps from the parent iodoarene. We have found the synthesis and isolation of many (especially electron-rich or sterically congested) aryl λ^3 -iodanes to be problematic. This includes many of the enantiopure iodoarenes that have been prepared in our laboratory for this purpose and, hence, the enantioinducing power of these reagents remains untested.



Scheme 1 Enantioselective oxytosylation of ketones

The use of hypervalent iodine reagents as catalysts in synthetic transformations has attracted recent attention.⁵ Indeed, during the course of this work, the racemic α -oxytosylation of acetophenone derivatives catalysed by iodo-benzene using *m*-chloroperbenzoic acid (mCPBA) as the

stoichiometric oxidant has been reported by Togo.⁶ It was thought that such catalytic use of iodoarenes should allow a much simplified procedure for the enantioselective α -oxytosylation of ketones and, hence, give a significant improvement on current methodology.

Initial studies towards identifying efficient iodoarene catalysts were performed using the reaction of 0.5 mmol of propiophenone (**1**) in acetonitrile with 10 mol% iodoarene **4–19**, 1.5 equivalents of commercial 70–77% wet mCPBA⁷ as the stoichiometric oxidant and *p*-toluenesulfonic acid monohydrate (TsOH·H₂O) as the source of the tosylate nucleophile. The reaction using stoichiometric iodane **2** is usually performed at –30 °C to maximise enantioselectivity,⁴ but at this temperature we find that the reactions employing catalytic amounts of iodobenzene or chiral iodide **4** and mCPBA as the stoichiometric oxidant proceed very slowly, consistent with the results of Togo.⁶ This suggests that the formation of the hydroxy(tosyloxy)iodoarene could be the rate-determining step in the catalytic cycle. To circumvent this problem, we performed our initial reactions at room temperature for two days using a range of iodoarenes (Table 1). In all cases, clean reactions to give tosylate **3** were observed.

The results in Table 1, entries 1–4 consist of those iodoarenes that have been previously tested as their hydroxy(tosyloxy)iodo derivatives. Of these, the 6-ethyl-substituted iodoarene **5** (entry 2) gives the highest enantioselectivity, a fact also observed in the stoichiometric reaction.^{1f,4} We find that the enantioselectivity obtained in this catalytic reaction is the same as that observed in the stoichiometric reaction performed at the same temperature in the same solvent. We have previously reported that methyl ethers give rise to the best selectivity^{1f} so we did not test any iodoarenes that did not possess the 1-aryl-1-methoxyethane function seen in **4–11**.

Iodoarenes **8–19** are those we could not previously test because they could not be converted into stable λ^3 -iodanes. Their activity as catalysts shown here highlights another important advantage of the catalytic procedure. As no reaction is observed in the absence of iodoarene, this suggests that our failure to isolate these iodanes is a result of their instability and not that the iodoarene cannot be oxidised. The naphthalene-based catalyst **19** fails to give any product and the unoxidised iodoarene is recovered at the end of the reaction, suggesting that this compound may be inert to mCPBA oxidation. Of those iodoarenes that could not be tested previously, the enantioselectivities obtained with iodoarene **11** (derived from

styrene oxide) or the binaphthyl derivative **16**⁸ are promising and further development of these catalysts may yield good results. Esters **12**–**15** offer a new class of λ^3 -iodanes that we are unable to prepare and give a promising lead

into potential new catalysts. Moving the chiral centre (and chelating group) in the simple ether **4** further from the iodoarene (entries 5, 6) diminishes the enantioselectivity of the catalysed reaction.

Table 1 Catalytic Reaction with a Range of Enantiopure Iodoarenes

Entry	Iodoarene	Conv. (%) ^a	ee of 3 (%) ^b	Yield of 3 (%) ^c
1		4 R = H 71	12 (<i>R</i>)	68
2		5 R = Et 62	27 (<i>R</i>)	59
3		6 R = OBn 50	25 (<i>R</i>)	48
4		7 R = <i>O</i> <i>t</i> -Bu 9	3 (<i>R</i>)	n.d.
5	 (–)- 8 ^d	76	3 (<i>R</i>)	n.d.
6	 (+)- 9 ^d	66	2 (<i>S</i>)	n.d.
7	 10	91	3 (<i>R</i>)	n.d.
8	 11	75	25 (<i>R</i>)	65
9	 (–)- 12 ^d R ¹ = H R ² = Me	95	24 (<i>S</i>)	72
10		(–)- 13 ^d R ¹ = H R ² = Et	23 (<i>S</i>)	83
11		(–)- 14 ^d R ¹ = H R ² = Bn	6 (<i>S</i>)	65
12		(–)- 15 ^d R ¹ = Me R ² = Pr	8 (<i>R</i>)	58
13	 16	82	12 (<i>S</i>)	79

Table 1 Catalytic Reaction with a Range of Enantiopure Iodoarenes (continued)

1 3

Entry	Iodoarene	Conv. (%) ^a	ee of 3 (%) ^b	Yield of 3 (%) ^c
14	<p>17</p>	33	5 (<i>R</i>)	n.d.
15	<p>(+)-18^d</p>	75	1 (<i>R</i>)	n.d.
16	<p>19</p>	<5	n.d.	n.d.

^a Determined by ¹H NMR analysis of the crude reaction product.^b Determined by HPLC.^c After purification by column chromatography of promising results or if HPLC trace not clean; n.d. = not determined.^d Absolute configuration of iodoarene unknown.

Iodoarene **5** (entry 2) is the catalyst giving rise to the highest enantioselectivity so this was used for further studies. Use of three equivalents of mCPBA and TsOH·H₂O resulted in an increase in the reaction rate without affecting the enantioselectivity, so this was used in further trials in order to obtain higher yields in the same reaction time. Further increases in the amount of these reagents resulted in insolubility and no beneficial effect on the yield or reaction rate. A solvent screen (Table 2) showed that the enantioselectivity is almost unaffected by the solvent (also observed in the stoichiometric reaction^{1f}) so acetonitrile was chosen for further studies as this resulted in the highest reaction rate and the cleanest product.⁹

Reducing the reaction temperature led to a very slow reaction. Other peracid oxidants were tried in an attempt to increase the rate. Peracetic acid led to no formation of the desired product and trifluoroperacetic acid¹⁰ gave only the products of Baeyer–Villiger oxidation not seen when using mCPBA.

Having optimised the reaction to use 10 mol% iodoarene **5**, three equivalents of mCPBA and TsOH·H₂O in acetonitrile at room temperature, this reaction was applied to a range of ketones (Table 3). The reactions were run for three days to maximise yield. Simple propiophenone derivatives (entries 1–4) generally gave good yields and

Table 2 Solvent Screen Using Catalyst **5**

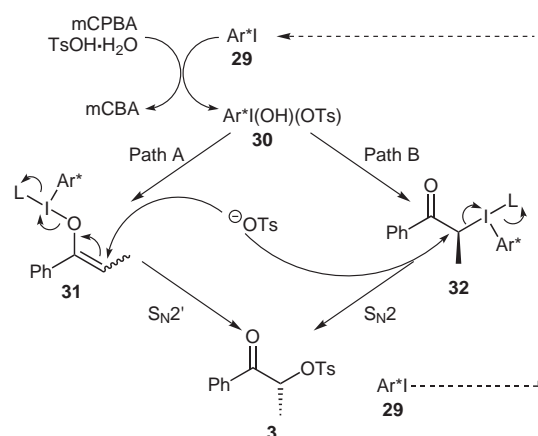
Entry	Solvent	Conv. (%) ^a	ee (%) ^b
1	MeCN	95	27
2	THF	40	27
3	CH ₂ Cl ₂	75	30
4	CHCl ₃	68	30
5	EtOAc	80	25
6	1,4-Dioxane	90	24

^a Determined by ¹H NMR analysis of the crude reaction product.^b Determined by HPLC.

reliable enantioselectivities. Electron-rich propiophenone (entry 5) underwent side reactions, possible owing to the anisole function,¹¹ and could not be purified. Increasing the steric congestion on the prochiral methylene group led to a slower reaction (entries 6, 7). The cyclic substrates (entries 8, 9) gave interesting results. Indanone (entry 8) gave a high yield and an enantioselectivity consistent with the acyclic propiophenone derivatives but tetralone (entry 9) underwent a very slow reaction giving almost racemic product. This slow reaction was also observed when preparing racemic material using Koser's reagent for HPLC

analysis and is probably a result of slow enolisation of the substrate. When the aryl group is removed from the ketone, the enantioselectivity is diminished (entry 10). Cyclopentanone and cyclohexanone underwent Baeyer–Villiger oxidation under these conditions.

During these trials it was noticed that if the reaction is quenched by addition of saturated aqueous sodium thiosulfate and sodium carbonate then extracted with ethyl acetate, the product (in the cases where the reaction proceeds to completion) is isolated cleanly with no contamination by the iodoarene. This can be recovered (85% yield) by reduction of the aqueous extracts (and the solid that remains after work-up) with potassium iodide and further extraction with ethyl acetate.



Scheme 2 Possible mechanisms for the α -oxytosylation

Two possible mechanisms can be proposed for this reaction (Scheme 2). After formation of the iodane **30**, the enol tautomer (unknown geometry) of propiophenone can react with **30** to give either enoxy iodane **31** (Path A) which can react with tosylate via an S_N2' reaction to displace the 'hyper-leaving group'¹³ generating the stereocentre. Alternatively, the reaction can proceed through alkyl iodane **32** (with the stereocentre already formed) followed by S_N2 substitution by tosylate (Path B, related to the mechanism proposed by Moriarty¹⁴). Given the enantio-induction observed in this reaction, it seems unlikely that Path A operates as the chiral aryl moiety is very distant from the reacting centre when the stereocentre is formed.

Three other points in this reaction are of interest. In our work and that of Togo,⁶ the product resulting from displacement of the hyper-leaving group by *m*-chlorobenzoate in place of tosylate is never observed. We were concerned that the enolisation of the substrate necessary for the reaction might also occur in the product **3**, leading to racemisation. This does not occur as the enantiomeric excess of the product does not change throughout the reaction and resubmission of the enriched product **3** to the reaction conditions does not diminish the enantioenrichment. The results in Table 1 show that a chelating group

Table 3 Scope of the α -Oxytosylation Catalysed by **5**¹²

Entry	Product	Yield (%) ^a	ee (%) ^b
1		78	27
2		66	24
3		86	27
4		70	28
5		35 ^c	n.d. ^c
6		<10	n.d.
7		55 ^c	n.d. ^c
8		79	21
9		15	1
10		67	3

^a After purification by column chromatography.

^b Determined by HPLC; n.d. = not determined

^c Reaction contained by-products that could not be separated – yield calculated from crude ¹H NMR analysis of the crude product against an internal standard.

^d Absolute stereochemistry of major enantiomer unknown.

is needed in the iodoarene in order to obtain high enantioselectivities. This is consistent with our earlier studies that suggest a pseudocyclic intermediate is formed in such iodanes.^{1f,4}

In conclusion, we have developed the first enantioselective oxidation catalysed by substoichiometric quantities of iodoarenes. Synthetically useful α -tosyloxyketones³ can be obtained in good yield and modest enantiomeric excess. In addition to this, many iodoarenes can be tested for enantio-induction that could not be investigated before and this will surely enhance understanding of the enantioselectivity observed in chiral hypervalent iodine chemistry as well as increase the range of chiral iodoarenes that can be evaluated. Studies into further enantioselective catalytic reactions, understanding the origin of selectivity and improved iodoarene catalysts are currently underway.

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- (12) **Representative Experimental Procedure**
A solution of propiophenone (**1**, 67 mg, 0.5 mmol) in MeCN (1 mL) was added to a solution of iodoarene **5** (15 mg, 0.05 mmol) TsOH·H₂O (285 mg, 1.5 mmol) and mCPBA (366 mg, 77% wet with H₂O, 1.5 mmol) in MeCN (2 mL) at r.t. The resulting solution was stirred at r.t. for 60 h then quenched by addition of sat. aq Na₂S₂O₃ (5 mL) and sat. aq Na₂CO₃ (5 mL). The mixture was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 80:20 hexane–EtOAc) to yield tosylate **3** (119 mg, 0.39 mmol, 78%) as a white powder. The ee was determined by HPLC on the crude and purified products: Chiracel OB-H column, 40:60 hexane–2-PrOH, 0.5 mL·min⁻¹, 40 °C, *t*_R = 18.1 min (*R*), 21.6 min (*S*).
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