Synthesis of New Chiral Diaryliodonium Salts

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Abstract A structurally diverse range of chiral diaryliodonium salts have been synthesised which have potential application in metal-free stereoselective arylation reactions.

Key words arylation, diaryliodonium salts, hypervalent iodine, stereoselective synthesis

Hypervalent iodine compounds have gained popularity in recent years as extremely versatile and environmentally benign reagents. Iodine(III) reagents with two heteroatom ligands are highly electrophilic and promote a range of selective oxidative transformations of organic molecules including the addition of heteroatom nucleophiles to unsaturated systems, oxidations of alcohols, and skeletal rearrangements of carbon systems.1

Diaryliodonium salts are iodine(III) compounds bearing two aryl ligands. They are potent electrophilic arylation reagents as reactions with these reagents are driven by the reductive elimination of an iodoarene.2 They have been employed extensively as aryl donors to copper and palladium centres in metal-catalysed cross-coupling reactions,3 notably for the α-arylation of carbonyls via copper(Ⅰ)-bisoxazoline catalysis,4 and for the α-arylation aldehydes in combination with chiral enamine catalysis.5 In combination with catalytic amounts of chiral Lewis acids, they have also recently been successfully employed for the asymmetric α-arylation of oxindoles.6

Of growing interest is the ability of diaryliodonium salts to take part in metal-free reactions. They have been successfully employed for biaryl synthesis,7 arylation of heteroatom nucleophiles such as phenols and more challenging substrates such as sulfonic and carboxylic acids;8 and in reactions with carbon nucleophiles including β-keto esters.9 Conditions have been established to predict which arene is transferred when unsymmetrical salts are employed and this has allowed the design of unsymmetrical salts as selective arene-transfer reagents. Transfer of the most electron-poor arene or those with ortho substituents can usually be predicted under metal-free conditions, thus allowing elaboration in the design of a non-transferable aryl ligand which often can be recycled as the iodoarene.10

Chiral diaryliodonium salts, where one substituent contains a stereogenic unit, have received very limited attention since the first derivative of that type, diphenyliodonium tartrate, was reported in 1907.11 Ochiai described the synthesis of 1,1′-binaphth-2-yl(phenyl)iodonium salts 1 (Figure 1) by a tin–iodine(Ⅲ) exchange with tetraphenyltin, and tested their efficacy in the arylation of a range of β-keto esters, achieving selective phenyl transfer in moderate yields and enantioselectivities (up to 53% ee).12 Zhdankin prepared amino acid derived benziodazoles 2 with an internal anion by a similar tin–iodine(Ⅲ) exchange.13 More recently, Olofsson described the metal-free synthesis of (phenyl)iodonium salts of type 3 via electrophilic aromatic substitution with [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser’s reagent), these salts bearing one, two, or three stereogenic centres derived from an enzymatic kinetic resolution of racemic 2-octanol.14

A theoretical study on the mechanism of α-arylation of carbonyl compounds with diaryliodonium salts revealed that asymmetric induction in this reaction could not be provided by chiral anions or chiral phase-transfer catalysts,15 therefore the design of iodonium salts bearing a chiral non-transferable aryl ligand is likely to be the most promising approach for enantiocontrol in metal-free reactions.

In recent years a number of chiral iodoarenes have emerged as highly efficient stereoselective reagents for cat-
alytic oxidation reactions. Conformationally flexible iodine reagents of type 4 (Figure 2) bearing stereogenic centres within coordinating side chains have been shown to provide excellent stereocontrol in stoichiometric alkene functionalisation reactions. In contrast, conformationally rigid iodoarenes such as 1,1-spiroindanone 5 have proven to be highly effective in spirocyclisation reactions. The recent interest in metal-free arylations prompted us to report our synthetic routes to chiral diaryliodonium salts 6–8, which bear non-transferable aryl ligands that are conformationally flexible (type 6), or possess a rigid chiral backbone (types 7 and 8). Wherever possible, the use of transition metals was avoided.

Inspired by the success of derivatives 4 in stereoselective syntheses, we devised a short synthetic route to iodonium salt 6a, where the reaction of the C3-symmetric arene 9 with [hydroxy(tosyloxy)iodo]benzene would avoid problems with unwanted regioisomers from the electrophilic aromatic substitution.

The required stereogenic centres were installed by trisalkylation of 1,3,5-trihydroxybenzene with activated methyl lactate. As previously observed in similar alkylation reactions, steric congestion resulted in a slow final alkylation and partial loss of stereochemical integrity. Chromatographic separation of the resultant diastereomeric mixture proved challenging, as did attempts at separation by crystallisation after hydrolysis of the methyl esters. Fortunately, after treatment with thionyl chloride and 2,4,6-trimethylaniline, amide 9 could be isolated as a single diastereomer after extensive chromatography. Subsequent electrophilic aromatic substitution with [hydroxy(tosyloxy)iodo]benzene gave diaryliodonium tosylate 6a as a single diastereomer in 90% yield. Trifluoroethanol has been used as it is known to be a versatile solvent in hypervalent iodine chemistry and in the synthesis of diaryliodonium(III) salts.

The need for chromatographic separation of diastereomers produced during the alkylation step and the low overall yield in the synthesis of 6a led us to consider a more direct route to iodonium salts of this type. Iodoarene 4a can be accessed with minimal racemisation via Mitsunobu reaction of 2-iodo-1,3,5-trihydroxybenzene with methyl lactate. Fortunately, direct oxidation of 4a with MCPBA and
BF₃·OEt₂ followed by boron–iodine(III) exchange with phenylboronic acid gave (phenyl)iodonium tetrafluoroborate efficiently in a single step (Scheme 2).

Chiral diaryliodonium salts of type 7 incorporating a binaphthyl backbone were first introduced by Ochiai (Figure 1). In contrast to conformationally flexible salts of type 6, binaphthyl systems 7 bearing a rigid, axially chiral backbone are anticipated to provide an asymmetric environment around the iodine which is less susceptible to interference from highly coordinating solvents or temperature effects. A synthetic route to chiral diaryliodonium salts of this type was envisaged, taking advantage of the known synthesis of iodonaphthyl derivatives from commercial sources of moisture and degassed solvents were routinely used. After installation of iodine in the 2-position, eclipsing interactions between the iodine and 2′-substituents provide a greatly increased barrier to racemisation. Indeed, no racemisation was observed after hydrolysis of the methoxymethyl ester (ee >99%, as determined by chiral HPLC). Arylation with diphenyliodonium triflate or alklylation with iodomethane provided model systems 12a and 12b to study the oxidation and salt forming steps.

Although a number of one-pot protocols have been developed for the direct synthesis of diaryliodonium salts from iodoarenes, electron-rich aryl ethers proved to be challenging substrates. A range of oxidants were tested under conditions typically employed for iodoarene oxidation. When MCPBA, peracetic acid, Oxone®, or potassium persulfate were used under ambient conditions, complex product mixtures resulted. At lower temperature (–78 °C to 0 °C), or when HTIB was used as an oxidant, polyaromatic products resulting from electrophilic substitution of the most electron-rich naphthalene ring could be tentatively assigned in the crude reaction mixture. Better results were obtained with sodium perborate in acetic acid (14b, 23% yield), and the use of Selectfluor in acetonitrile–acetic acid gave diacetates 14a and 14b in good yields (91% and 71%, respectively, Scheme 4).

Phenyl ether 14a was converted smoothly into the (phenyl)iodonium tetrafluoroborate (7a) by boron–iodine(III) exchange with phenyl boronic acid in the presence of BF₃·OEt₂. Methyl ether 7b proved to be much less stable, and activation with BF₃·OEt₂ or TsOH·H₂O during attempted reactions with phenylboronic acid or phenyl(trimethyl)silane led to complex reaction mixtures. Tetraphenyltin has been commonly used as a powerful arene donor to iodonium(III) vide supra. Wishing to avoid the use of transition metals where possible, we found that use of the boron analogue sodium tetraphenylborate in acetic acid provided diaryliodonium 7b albeit in low yield. Attempts at anion exchange with aqueous solutions of sodium tetrafluoroborate of the intermediate radical by hydrogen abstraction from solvent or from extraneous sources would result in reduced product 13, although all efforts were made to exclude sources of moisture and degassed solvents were routinely used. When MCPBA, peracetic acid, Oxone®, or potassium persulfate were used under ambient conditions, complex product mixtures resulted. At lower temperature (–78 °C to 0 °C), or when HTIB was used as an oxidant, polyaromatic products resulting from electrophilic substitution of the most electron-rich naphthalene ring could be tentatively assigned in the crude reaction mixture. Better results were obtained with sodium perborate in acetic acid (14b, 23% yield), and the use of Selectfluor in acetonitrile–acetic acid gave diacetates 14a and 14b in good yields (91% and 71%, respectively, Scheme 4).
conversion into diium nitrite in the presence of potassium iodide allowed loss of enantiomeric purity to 5). Hydrogenation with Raney nickel proceeded without sequence from (this backbone could be obtained via a short synthetic se-

The organic phase relative to water. relatively high affinity of the tetraphenylborate anion for or potassium triflate were unsuccessful, in part due to the relatively high affinity of the tetraphenylborate anion for the organic phase relative to water.

Chiral ligands based on partially hydrogenated 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthalene have shown greater efficiencies in several metal-catalysed asymmetric reactions than their parent 1,1′-binaphthalene systems due to the increased steric and electronic properties of the cy-

clohexene rings which also can provide increased solubility.29 We postulated that diaryliodonium salts of type 7b which was converted directly into (phenyl)iodonium tetrafluoroborate 8 with one equivalent of phenylboronic acid.32 Preliminary results suggest that the synthesised diaryliodonium salts 6–8 are selective phenylation reagents, and thus have potential application in metal-free arylation reactions or use as chiral phase-transfer catalysts. The ex-
tent of asymmetric induction provided by these new hyper-

valent iodine reagents is currently being investigated.

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**Supporting Information**

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**References and Notes**


under vacuum. Subsequent precipitation with MeOH-Et₂O yielded 7a (91 mg, 79%) as a light brown solid; mp 164.5–166 °C; [α]_D^20 74.0 (c 1.0, CHCl₃). IR (neat): 3061, 2933, 1489, 1235, 1053, 733 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 8.51 (1 H, d, J = 9 Hz), 8.20 (2 H, d, J = 9 Hz), 7.80 (1 H, d, J = 8 Hz), 8.00 (1 H, d, J = 8 Hz), 7.65 (1 H, t, J = 8 Hz), 7.45–7.32 (7 H, m), 7.22 (2 H, t, J = 8 Hz), 7.11 (2 H, t, J = 8 Hz), 7.04–6.98 (2 H, m), 6.83–6.80 (2 H, m), 6.46 (1 H, d, J = 9 Hz) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 150.1, 152.0, 141.8, 140.5, 135.1, 134.9, 133.2 (2 C), 130.2, 131.9 (2 C), 131.5, 131.1, 130.1, 129.5, 129.0, 128.3, 128.2, 128.1, 127.7, 127.1, 126.2, 125.1, 124.1, 124.0, 123.7, 118.8 (2 C), 118.2, 118.0, 112.6, 98.0 ppm. ¹⁹F NMR (282 MHz, CDCl₃): δ = –154.6 (4 F) ppm. MS (APCI⁺): m/z = 549 (100 [M⁺]). HRMS (ES⁺): m/z calcd for C₆₀H₄₀O₁₀ [M⁺]: 549.0710; found: 549.0699.


(R)-[(2′-(iodo-5,5′,6,6′,7,7′,8,8′-octahydro-1′,1′-binaphthyl-2-yl)phenyl)iodonium Tetrafluoroborate (8)] To a solution of (R)-2-(diacetoxy)iodo-2′-phenoxo-1′-binaphthyl (17, 210 mg, 0.41 mmol) in MeCN (6 mL) and AcOH (2 mL) was added Selectfluor (868 mg, 2.45 mmol). The reaction was stirred at rt for 9 h then concentrated under vacuum. H₂O (5 mL) was added, and the product extracted with CH₂Cl₂ (2 × 15 ml). Combined organic extracts were washed with H₂O (5 mL) and brine (5 mL) and concentrated under vacuum to give 18 (264 mg, 86%) as a yellow oil. ¹H NMR analysis showed the presence of a broad acetate signal (δ = 1.75 ppm) with integration consistent with 18. This crude material was immediately dissolved in CH₂Cl₂ (4 mL) and cooled to –78 °C. BF₃·OEt₂ (223 μL, 1.76 mmol) was added dropwise, followed after 2 min by PhOH (0.45 mg, 0.07 mmol) in one portion. The reaction was allowed to warm to rt and stirred for 15 min. The crude reaction mixture was applied to a short silica plug (2 g). Unreacted starting material and impurities were eluted with hexane–CH₂Cl₂ (0.10:1–0:1). The iodonium salt was eluted using with 10% MeOH in CH₂Cl₂ (10 ml). Subsequent precipitation with CH₂Cl₂–Et₂O yielded 19 (135 mg, 65%) as a colourless solid (mp 116–118 °C; [α]_D^19 +85.0 (c 1.0, CHCl₃). IR (neat): 2940, 1443, 1267, 1051, 729, 700 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 7.84 (2 H, d, J = 8 Hz), 7.70 (1 H, d, J = 8 Hz), 7.67 (1 H, d, J = 8 Hz), 7.59 (1 H, t, J = 7 Hz), 7.41 (2 H, t, J = 7 Hz), 7.19 (1 H, d, J = 8 Hz), 6.96 (1 H, d, J = 8 Hz), 2.92–2.76 (4 H, m), 2.34–2.26 (1 H, m), 2.13–2.00 (2 H, m), 1.92–1.84 (1 H, m), 1.80–1.67 (8 H, m) ppm. ¹³C NMR (125 MHz, MeOD-d₂): δ = 148.1, 146.3, 144.5, 140.6 (2 C), 138.8, 138.0, 137.4 (2 C), 135.7, 135.1, 133.7, 133.4, 133.2 (2 C), 115.3, 113.2, 98.2, 30.8, 30.4, 29.8, 29.6, 23.8 (2 C), 23.2, 23.1 ppm. ¹⁹F NMR (282 MHz, CDCl₃): δ = –149.0 (4 F) ppm. MS (El⁺): m/z = 591 (100 [M⁺]). HRMS (APCI⁺): m/z calcd for C₃₀H₂₉₂O₁₀ [M⁺]: 591.0006; found: 591.0005.