Synthesis of New Chiral Diaryliodonium Salts

Michael Brown* Marion Delorme Florence Malmedy Joel Malmgren Berit Olofsson Thomas Wirth*

School of Chemistry, Cardiff University, Park Place, Main Building, Cardiff CF10 3AT, UK wirth@cf.ac.uk
Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, 106 91 Stockholm, Sweden

Dedicated to Prof. Dr. Peter Vollhardt

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

Key words alkylation, 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.

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. They have been employed extensively as aryl donors to copper and palladium centres in metal-catalysed cross-coupling reactions, notably for the α-arylation of carbonyls via copper(I)-bisoxazoline catalysis, and for the α-arylation aldehydes in combination with chiral enamine catalysis. In combination with catalytic amounts of chiral Lewis acids, they have also recently been successfully employed for the asymmetric α-arylation of oxindoles.

Of growing interest is the ability of diaryliodonium salts to take part in metal-free reactions. They have been successfully employed for biaryl synthesis, arylation of heteroatom nucleophiles such as phenols and more challenging substrates such as sulfonic and carboxylic acids; and in reactions with carbon nucleophiles including β-keto esters. 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.

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. Ochiai described the synthesis of 1,1′-binaphth-2-yl(phenyl)iodonium salts (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). Zhdankin prepared amino acid derived benziodazoles with an internal anion by a similar tin–iodine(III) exchange. More recently, Olofsson described the metal-free synthesis of (phenyl)iodonium salts of type 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.

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, 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 iodoarenes 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 6b 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 synthetic iodonaphthyl derivatives from commercial availability (R)-1,1′-bi(2-naphthol) (Scheme 3). Alkylation or arylation of the naphthol oxygen would allow late-stage modification prior formation of the salt.

Initial attempts at radical cleavage and iodination of phosphate 10 with lithium naphthalenide (LiNAP) and iodine resulted in reduced naphthalene 13 as the major product in addition to the desired iodonaphthyl 11. The unwanted loss of chiral material in this step warranted further investigation. The product distribution was found to be highly dependent on the reaction time. Exposure of 10 to LiNAP for 2.5 h at –78 °C followed by addition of iodine led to an unfavourable product ratio of 11/13 (1:1.9), however, treatment with LiNAP for just 30 minutes at –78 °C resulted in much improved product ratio of 11/13 (5:1). Quenching 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. After installation of iodine in the 2-position, eclipsing interactions between the iodide 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 alkylation 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 12 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 iodine(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...
conversion into dium 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-
to the increased steric and electronic properties of the cy-
reactions than their parent 1,1′-binaphthalene. Chiral ligands based on partially hydrogenated,6,6′,7,7′-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-
ligands. We postulated that diaryliodonium salts of type 7a and 7b.

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 cyclohexene rings which also can provide increased solubility. We postulated that diaryliodonium salts of type 8 with this backbone could be obtained via a short synthetic sequence from (R)-1,1′-binaphthyl-2,2′-diamine 15 (Scheme 5). Hydrogenation with Raney nickel proceeded without loss of enantiomeric purity to 16,30 and oxidation with sodium nitrite in the presence of potassium iodide allowed conversion into 17.31 Selectfluor oxidation furnished the unstable tetraacetate 18 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 extent of asymmetric induction provided by these new hypervalent iodine reagents is currently being investigated.

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Supporting Information

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References and Notes


(9) Pribram, R. Justus Liebigs Ann. Chem. 1907, 351, 481. 


(20) Pribram, R. Justus Liebigs Ann. Chem. 1907, 351, 481.


(22) Zhdankin, V. V.; Kopyov, A. Y.; Su, L.; Boyarskikh, V. V.; Nettel, B. C.; Young, V. G. Org. Lett. 2003, 5, 1583.


(33) Zhdankin, V. V.; Kopyov, A. Y.; Su, L.; Boyarskikh, V. V.; Nettel, B. C.; Young, V. G. Org. Lett. 2003, 5, 1583.


(44) Zhdankin, V. V.; Kopyov, A. Y.; Su, L.; Boyarskikh, V. V.; Nettel, B. C.; Young, V. G. Org. Lett. 2003, 5, 1583.

