A Practical, Large-Scale Synthesis of *p*-(Difluoroiodo)toluene (*p*-TolIF$_2$)

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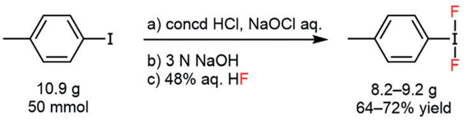

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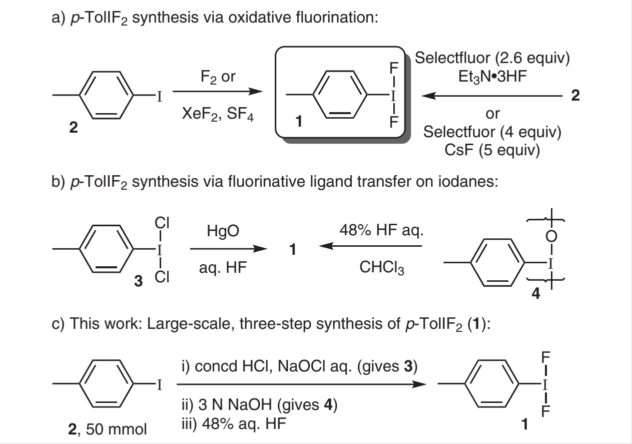
Abstract *p*-(Difluoroiodo)toluene (*p*-TolIF$_2$) is a versatile fluorinating agent that acts as both a surrogate for elemental fluorine, and as a source of 'electrophilic' fluorine. Described here is a detailed three-step synthesis of *p*-TolIF$_2$, carried out on a 50 mmol scale, that consistently provides high-quality product that is suitable for long-term storage. The reactions employ inexpensive, readily available starting materials and reagents, and uses the commodity chemical 48% aqueous HF as the source of fluorine atoms.

Key words hypervalent iodine, *p*-(difluoroiodo)toluene, fluorination, synthetic methodology, oxidation

The organic chemistry of hypervalent iodine (HVI) has been known for over 130 years, and in addition to their common use as oxidising agents, these species also serve as 'electrophilic' sources of a variety of functional groups.[1] This latter reactivity derives from the 3c-4e bonding within the hypervalent ligand sphere of aryl-λ^3-iodanes, which renders the iodine atom electrophilic and susceptible to nucleophilic attack. Exploitation of this reactivity has led to tremendous growth in the field of hypervalent iodine chemistry over the past two decades. This is due to the new reactivity patterns offered by these reagents, to the typically mild reaction conditions and to the environmentally benign, recyclable reaction by-products.

The hypervalent iodine reagent *p*-TolIF$_2$ (**1**) was among the first hypervalent iodine reagents reported,[2] and it serves as a stable, solid surrogate for elemental fluorine. It has found great success as a source of 'electrophilic' fluorine or as a fluorine transfer agent,[3] and its many uses include the synthesis of α-fluoro carbonyl compounds,[4] desulfurative fluorinations[5] and fluorinative rearrangements of styrenes and related compounds.[6] In 2013, we reported the reaction between *p*-TolIF$_2$ and phenyldiazoacetates, which resulted in a *gem*-difluoride synthesis via the denitrogenation of diazo compounds.[7] This strategy was expanded by Gouverneur and co-workers to include α-trifluoromethyl diazo compounds,[8] and by Wang and co-workers to include α-diazophosphonates.[9] In all three reports, the synthesis of *p*-TolIF$_2$ was accomplished by titrating *p*-iodosotoluene with aqueous HF, and in each instance the product was described as a pale-yellow or off-white solid. Given that a significant part of our research program is devoted to developing new HVI-mediated fluorination reactions,[6b,10] developing a scalable, detailed and reproducible synthesis of *p*-TolIF$_2$ was essential.

Previously reported syntheses of **1** include the direct oxidative fluorination of *p*-iodotoluene (**2**) using fluorine gas (Scheme 1a).[11] Working with fluorine gas, however, requires a specialised laboratory setup, and the administrative barriers to securing fluorine in an academic lab can be onerous. Variations on this strategy include using XeF$_2$[12] or SF$_4$[13] as fluorine sources, but these have drawbacks related to cost or hazardousness of the reagents. Shreeve and co-workers reported a related synthesis of **1** from *p*-iodotoluene (**2**), using Selectfluor® (electrophilic fluorine) and Et$_3$N·3HF (Scheme 1a).[14] They further developed a tandem iodination/oxidative fluorination reaction, and Gilmour and co-workers showed that CsF was also an effective fluoride source.[15] The weakness in these strategies is the use of 2.6–4 equivalents of Selectfluor to deliver a single fluorine atom which, as the costliest reagent, is at significant expense. Hara reported the electrochemical oxidation of *p*-iodotoluene (1.5 V vs. Ag/Ag$^+$), using Et$_3$N·5HF as the source of fluoride,[16] but such electrochemical methods are not widely employed. An alternate approach to **1** involves displacing ligands on an existing iodine(III) compound by fluoride, such as treating *p*-TolICl$_2$ (**3**) with yellow mercuric oxide and aqueous HF (Scheme 1b).[6a,17] At scale, however, this would be discouraged due to environmental concerns. The original synthesis of **1** by Weinland and Stille was accomplished by treating *p*-iodosotoluene (**4**) with aqueous HF,[2] and this remains the main method for preparing **1**.[4c,18]



Scheme 1 Synthetic strategies towards *p*-(difluoroiodo)toluene

We set the goal of developing a reproducible, large-scale and expeditious synthesis of high-quality *p*-TolIF$_2$ that can be accomplished by a single individual in one day. Our plan was to optimise a large-scale process involving the chlorination of *p*-iodotoluene (**2**) to give **3**, hydrolyzing this to **4**, and then treating with aqueous HF to give **1** (Scheme 1c). We tested the need for isolating and purifying intermediates **3** and **4**, and we used repeated experimentation and detailed observation to develop a precise purification sequence for **1**. The result is a three-step procedure using inexpensive, commodity chemicals, that gives high-quality *p*-TolIF$_2$ that can be stored long-term. Using aqueous HF as our fluorine source offers a significant financial advantage over other direct syntheses, but as this is highly corrosive and a contact poison, appropriate care must certainly be taken when working with this reagent.

The synthesis begins with the oxidation of *p*-iodotoluene (**2**). This reagent is obtained in varying degrees of colouration from commercial suppliers, and it should be purified to a white crystalline state prior to use. We decolorized it by dissolving in hexanes, treating with aqueous sodium thiosulfate solution until colourless, and then concentrating the organic layer under vacuum. We observed that if this pre-purification is omitted, the contaminant will be carried through the synthesis and the resulting *p*-(difluoroiodo)toluene will be faint yellow in colour. The oxidation of *p*-iodotoluene is commonly accomplished by two methods: oxidation to *p*-TolI(OAc)$_2$ or oxidation to TolICl$_2$, both of which are viable in this synthesis. We found that the latter oxidation could be rapidly and reproducibly accomplished by the Zhang protocol of treating **2** with chlorine gas generated in situ by the addition of concd HCl to 5.25% aqueous NaOCl and acetonitrile (Figure 1).[19] Other than cooling, this required no stringent reaction conditions, and was generally accomplished on a 50 mmol scale within 2 hours. The resulting wet filter cake could be carried on without purification or characterization, thus minimising the potential for decomposition due to instability or light/heat sensitivity. If desired, intermediate **3** can be dried by the procedure described for the synthesis of (dichloroiodo)benzene.[20] The chlorination procedure is a significant improvement over synthesis involving *p*-TolI(OAc)$_2$, which requires strict temperature control over a longer period of time; however, if one wishes to store an intermediate at this stage of the synthesis, *p*-TolI(OAc)$_2$ is recommended over *p*-TolICl$_2$.

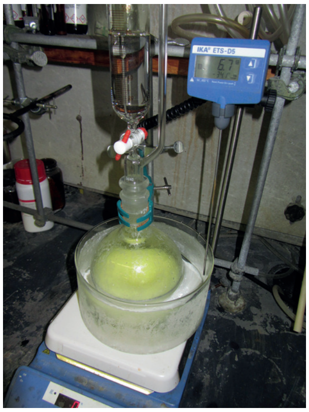


Figure 1 Chlorination of *p*-iodotoluene by adding concd HCl to aqueous NaOCl and acetonitrile

The conversion of *p*-TolICl$_2$ (**3**) to *p*-iodosotoluene (**4**) was readily accomplished using a simplified variant of a previously reported procedure.[18] Dropwise addition of 3 N NaOH to **3** in THF leads to the iodoso compound **4**. This reaction is exothermic, and slow addition of NaOH is needed so that the resulting exotherm can be suppressed by the cooling bath. After various modifications to this procedure were tested, we found that effective cooling of the large-scale reaction could be achieved by pre-suspending the wet filter cake of **3** in THF (Figure 2a).[18] So long as the reaction mixture is adequately cooled in a –10 °C ice-saltwater bath, this obviates the need for ice within the reaction vessel.

The resulting precipitate is very fine, and removal of THF and water via filtration could be very laborious. The following steps were developed to expedite the filtration process, while minimising the need for specialised lab equipment and transfers between vessels: the filtration flask is supported at ca. 40° angle, and the reaction mixture is poured such that a small portion of the sintered glass surface remained dry (and thus unplugged).[22] Filtration yielded a wet cake of **4** that was again carried forward without purification or characterization, so as to minimise the potential for decomposition by disproportionation or explosion upon drying. If desired, *p*-iodosotoluene can be isolated by using a procedure described for the related compound iodo-

Figure 2 (a) Reaction setup for hydrolysis of **3** and (b) filter flask setup that minimises the time required for filtration of **4** as fine particulates.

sobenzene,[21] and although we did not experience any difficulties using **4** as a wet paste, iodosoarenes are known to detonate when heated and especially when dried.

The procedure for converting **4** into *p*-TolIF$_2$ uses 48% aqueous HF, and is adapted from various syntheses reported in the literature. The wet *p*-iodosotoluene filter cake is immediately slurried in chloroform in a Teflon vessel, cooled, and treated with aqueous HF. A large excess of HF was needed to drive the reaction to completion, and we found that using less HF led to an incomplete reaction, even with prolonged stirring. As this is an inexpensive reagent, the cost associated with this is minimal. Earlier reports suggested that if the HF is added in one portion, the yield of the final transformation is reduced,[4c] so we employed continuous dropwise addition of aqueous HF in this step (Figure 3a). Once the suspended solid had been consumed, the two resulting phases were separated by removal of the top, aqueous layer. One must ensure that all the aqueous droplets are removed, or else the subsequent purification will be compromised (Figure 3b).[23] Concentrating the mixture to a reduced volume, instead of to dryness,[7] was critical to recovering high quality product. Also, the use of a mild heating bath helped keep the temperature stable, giving more consistent reaction outcomes. When following purification protocols that involved concentrating to dryness and recrystallising from hexanes,[18] the product rapidly yellowed in colour upon storage, consistent with the many reports of **1** being an off-white or pale-yellow solid. By following our new purification sequence, in which direct crystallisation of **1** is achieved from the reaction solvent, we can recover 8.2–9.2 grams (64–72% yield over three steps) of *p*-TolIF$_2$. The white, crystalline solid could be stored in a –20 °C freezer under inert atmosphere for a year without discoloration or a notable loss of reactivity.

In conclusion, we have developed an optimised procedure for conducting a three-step synthesis of *p*-TolIF$_2$ (**1**) on a 50 mmol scale. The reactions involve the use of inexpensive and readily available starting materials, and the complete synthesis can be accomplished in a single day by one experimentalist. This detailed synthesis provides high purity, crystalline product that is stable to prolonged storage, and we believe that this procedure will be of interest to practitioners of hypervalent iodine mediated fluorination.

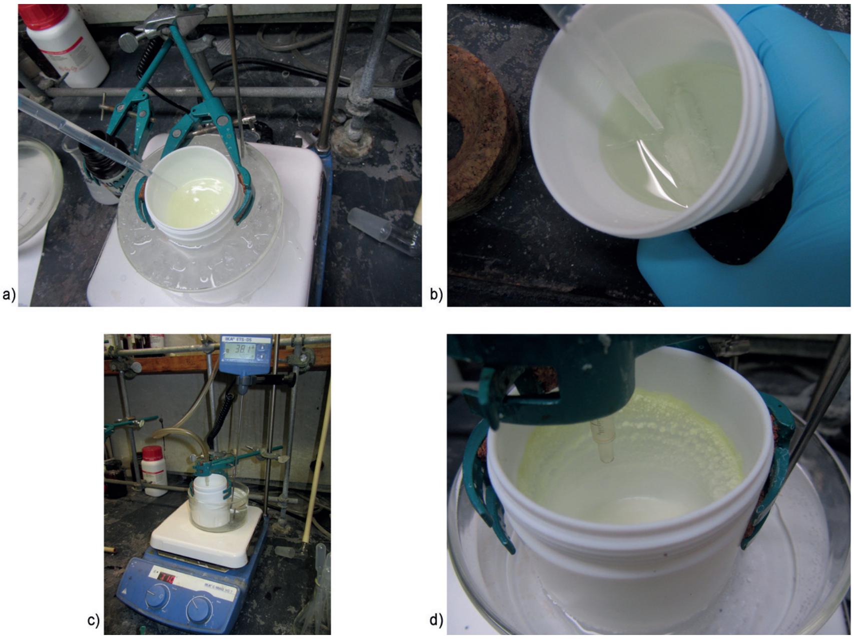


Figure 3 (a) Setup for dropwise addition of 48% aq. HF to **4**; (b) removal of the aqueous layer by transfer pipette; (c) setup for concentrating the organic phase under a stream of nitrogen gas; and (d) a view inside the reaction vessel while partially concentrating the crude product.

Reactions were carried out using borosilicate glassware or in a 250 mL Teflon beaker. *p*-Iodotoluene [CAS Reg. No. 624-31-7] was purchased from Aldrich Chemical Company, Inc., Oakwood Products, Inc., or Matrix Scientific. Acetonitrile (>99.5%), hexanes (98.5%), THF (>99.5%), chloroform (>99.8%, stabilised with amylene), hydrochloric acid (37%), NaOH pellets (97%), and hydrofluoric acid (48%) were purchased from Aldrich Chemical Co., Inc. and were used as received. The 5.25% aq. NaOCl [CAS Reg. No. 7681-52-9] solution used was common household bleach, specifically without hydroxide additives.

Melting points were recorded with a MEL-TEMP II instrument and are uncorrected. Infrared spectra were recorded with a Perkin Elmer FT-IR Spectrum Two with ATR Two. Proton NMR spectra (^{1}H NMR) were recorded at 500 MHz, and are reported (ppm) relative to the residual chloroform peak (7.26 ppm), and coupling constants (*J*) are reported in hertz (Hz). Carbon NMR spectra (^{13}C NMR) were recorded at 125 MHz, and are reported (ppm) relative to the centre line of the triplet from $CDCl_3$ (77.16 ppm). ^{19}F NMR spectra were recorded at 282 MHz, and are reported relative to TFA. TGA Analysis was performed with a TGA Q500 V20.13 Build 39.

CAUTION! Mixing hydrochloric acid and aqueous NaOCl (bleach) generates toxic chlorine gas. The chlorination of *p*-iodotoluene should be performed in a well-ventilated fumehood.

CAUTION! The intermediate compound *p*-iodosotoluene **4** is explosive. The related compound iodosobenzene is known to detonate when isolated, dried and heated to ca. 200 °C. This intermediate is carried forward wet in this synthesis, and there have been no adverse events.

CAUTION! Hydrofluoric acid is extremely toxic. Consult standard operating procedures before handling, use only in a well ventilated fumehood and ensure that proper PPE is worn when using this reagent. Consult institutional HF handling SOPs and ensure suitable training prior to carrying out this synthesis.

Step 1a: Synthesis of *p*-TolICl$_2$ (3)

In ambient atmosphere, a 1 L round-bottomed flask with a 29/34 ground glass joint was charged with a 6 cm long Teflon-coated, ellipsoidal magnetic stir bar and *p*-iodotoluene (**2**, 10.9 g, 50 mmol, 1 equiv). The flask was then charged with acetonitrile (100 mL) and the mixture was stirred to give a colourless solution. The flask was then cooled in a 5 °C ice-water bath and charged with 5.25% aq. NaOCl (300 mL, 211 mmol, 4.2 equiv). The flask was then equipped with a 125 mL pressure-equilibrating addition funnel charged with concentrated HCl (100 mL, 1.2 mol, 24.8 equiv). The reaction mixture was stirred vigorously and the HCl was then added dropwise over 30 minutes. The pale-yellow solution became dark-yellow during the first half of the addition, and the solution became less intensely coloured as the addition neared completion and *p*-iodotoluene dichloride was observed as a yellow solid suspended in a faintly yellow solution.

After the addition of HCl was complete, the reaction mixture was stirred for an additional 30 minutes. The mixture was then filtered through a 350 mL medium porosity sintered glass funnel (pore size: 10–15 microns, 9 cm diameter) and the filtrate was discarded. The filter cake was washed with deionised water (3 × 200 mL), followed by hexanes (3 × 50 mL), to give a wet filter cake of **3**, usually weighing 15.35–16.10 g, that was used without further purification.

Step 1b: Synthesis of *p*-TolIO (4)

The wet filter cake of **3** was immediately transferred into a 300 mL, single-neck round-bottomed flask with a 24/40 joint, using THF (100 mL) to assist with the transfer. To this was further added a 4 cm long Teflon-coated ellipsoidal magnetic stir bar and the flask was maintained at ambient temperature. The flask was cooled to <–10 °C in an ice-salt-water bath and equipped with a 125 mL pressure-equilibrating addition funnel charged with 3 N NaOH (50 mL, 150 mmol, 3 equiv). The NaOH was added to the flask dropwise over 5 minutes, and then stirred for an additional 30 min, yielding an off-white solid suspended in a colourless solution. Dichloromethane (100 mL) was added to the reaction flask and the resulting suspension was stirred for an additional 2 minutes prior to being filtered through a 350 mL medium porosity sintered glass funnel (pore size: 10–15 microns, 9 cm diameter). The off-white filter cake was washed with water (5 × 30 mL), then dichloromethane (3 × 30 mL), which resulted in a wet, pale-yellow paste of *p*-TolIO **4** that was carried forward without purification or weighing.

Step 1c: Synthesis of *p*-TolIF$_2$ (1)

The wet filter cake of *p*-TolIO (**4**) was transferred to a 250 mL Teflon beaker (6 cm diameter) equipped with 5 cm long magnetic stir bar. The beaker was charged with chloroform (80 mL) and the resulting suspension was stirred. The reaction vessel was cooled in a 0 °C an ice-water bath and six portions of concentrated hydrofluoric acid (6 × 2.5 mL, 6 × 69 mmol, 6 × 1.4 equiv) were continuously added (dropwise) to the beaker using a 3 mL polypropylene graduated pipette. After the addition of HF, the mixture was stirred for 30 minutes, after which the solid *p*-iodosotoluene was no longer visible and the reaction mixture consisted of two colourless phases. The reaction vessel was then removed from the cooling bath and the top layer of the biphasic mixture was removed by using a 3 mL polypropylene pipette. *Ensuring complete removal of all the aqueous droplets was critical to the success of this reaction.* The beaker was then placed in a preheated to 40 °C water bath and stirred while being concentrated to approximately 25% of its original volume by using a gentle stream of nitrogen gas.

Crystallisation of the crude *p*-iodotoluene difluoride was induced by slowly adding hexanes (100 mL) from a graduated cylinder to the Teflon beaker at 40 °C over 1 minute. The resulting mixture was concentrated to approximately 25% of its original volume with a gentle stream of nitrogen gas. The resulting slurry was cooled to 0 °C and decanted, ensuring that the white solid adhering to the side of the Teflon beaker was quickly scraped down into the bulk solid by using a metal spatula. (*If desired, a polypropylene funnel equipped with filter paper can be used to collect any lost p-iodotoluene difluoride during decantation.*) This bulk solid was washed twice with hexanes (50 mL), decanting between washes. The resulting white solid was transferred to a 10 dram Teflon or polypropylene vial, placed into a 40 °C water bath, and the excess hexanes was evaporated by concentration under a gentle stream of nitrogen gas. The vial containing the solid was deposited into a vacuum chamber and dried under high vacuum (<0.1 torr) until a constant weight of 8.2–9.2 g (64–72% yield over three steps) of *p*-iodotoluene difluoride (**1**) was achieved. The resulting solid, white needles (mp 99–101 °C), were stored in a –20 °C freezer under an atmosphere of nitrogen gas. The purity of the product was determined by quantitative ^{1}H NMR analysis using hexamethyldisiloxane (HMDSO) as internal standard.

IR (ATR): 1478 (m), 1380 (w), 1208 (w), 1001 (m), 789 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.6 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 2.46 (s, 3 H).

^{13}C (125 MHz, $CDCl_3$): δ = 142.3, 132.1, 130.2, 120.8 (t, ^2J = 11 Hz), 21.1.

^{19}F (282 MHz, $CDCl_3$): δ = –177.22.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611526.

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(22) We maintained the angled filtration setup while adding solvents for washing, and then slowly rotated it more upright such that the filtrate could be drained through the unclogged portion of the filter funnel.

(23) This aqueous layer contains extremely toxic hydrofluoric acid. Appropriate protective equipment and handling procedures for safe HF use should be adhered to. This aqueous hydrofluoric acid was quenched using a dilute solution of calcium or magnesium hydroxide.