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Facile, One-Pot, and Gram-Scale Synthesis of 3,4,5-Triiodoanisole through a C–H Iodination/*ipso*-Iododecarboxylation Strategy: Potential Application towards 3,4,5-Trisubstituted Anisoles

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A facile, efficient, and gram-scale method for the conversion of *para*-anisic acid into 3,4,5-triiodoanisole through a one-pot C–H iodination/*ipso*-iododecarboxylation reaction was investigated. Commercially available benzoic acid was used, which allowed the reaction to be performed on a multigram scale in good yield. This report discloses a practical method for the one-pot synthesis of hitherto unknown 3,4,5-triiodoanisole that is catalytic, scalable, efficient, and easy to work up and purify. Potential application of the target compound as a precursor for novel site-selective metal–iodine exchange and Suzuki–Miyaura cross-coupling reactions were also explored. 3,4,5-Trisubstituted anisole derivatives were provided in a highly regioselective fashion; these compounds are useful building blocks in synthesis and indeed are hard to prepare by any other means.

Introduction

Halogenated anisoles and particularly iodinated motifs are ubiquitous and versatile intermediates in the synthesis of many biologically active targets and essential intermediates.[1] For instance, [3-(4-chloro-2-methylphenyl)-1-methyl-1*H*-pyrazol-5-yl](2-fluoro-6-iodo-4-methoxyphenyl)methanol (**1**; Figure 1) is a substituted pyrazole derivative that contains iodo and fluoro groups at the C6 and C2 atoms of the anisyl ring, respectively, and is found to have unique activity for controlling plant disease caused by a fungal pathogen.[2] Additionally, 9-iodo-7-methoxy-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (**2**) is a substituted benzodiazepinone derivative that contains an iodo group at the C9 atom of the aromatic ring and is found to increase abiotic stress tolerance in plants for strengthening plant growth and increasing plant yield.[3] Furthermore, 2-iodo-5-methoxy-1,1′-biphenyl (**3**) is a small iodinated anisole derivative that contains an iodo group at the C2 atom of the aromatic ring and is found to have antifungal activity against *Aspergillus niger*.[4] Lastly, (2-iodo-5-methoxyphenyl)boronic acid (MIBA, **4**; Figure 1), is an iodinated anisole boronic acid derivative that is reported to have unique room-temperature organocatalytic activity for green amide bond formation between amines and carboxylic acids.[1a,1d,1g]

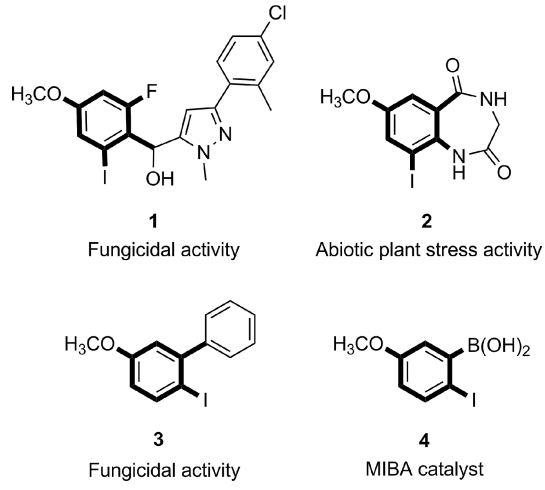

Figure 1. Some important iodinated anisole derivatives in medicine and industry.

A broad palette of synthetic protocols for aromatic iodination has been reported.[5] For instance, classical Friedel–Crafts halogenation reactions of aromatic and polycyclic aromatic compounds readily proceed with moderate regioselectivity in the presence of chloride and bromide derivatives, whereas the reaction with iodide derivatives fails. Alternatively, *ipso*-displacement reaction of amines, bromides, and carboxylic acids on an aromatic ring such as the diazo-

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tization of the corresponding amines, the conversion of aromatic bromides into aryllithium or arylmagnesium reagents followed by reaction with iodine or the iododecarboxylation of carboxylic acids provides exclusively one regioisomer.[6]

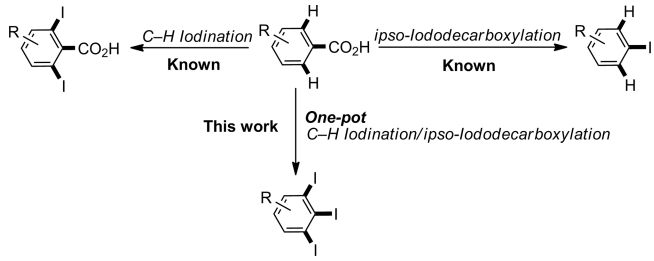
ipso-Iododecarboxylation and directed C–H iodination of aromatic carboxylic acids have recently emerged as alternative and effective methods for C–H transformations for which the position of the carboxylic acid group controls the regioselectivity of the iodination, whereas in common C–H activation reactions, regioselectivity is still a problem. Additionally, aromatic carboxylic acids are inexpensive substrates, broadly available, and easily removed from the product by a simple basic workup.[7]

1,2,3-Triiodoarenes are important substrates in both synthesis and biology. They exist in several biologically active compounds that show adrenoceptor activity[7f–7q] and analgesic activity,[8] they can be used as X-ray contrast agents,[9] and they additionally show pesticidal and fungicidal activities.[10] Owing to the relatively weak nature of the C–I bond, a particular use is found in different organic transformations such as transition-metal-catalyzed coupling reactions and nucleophilic displacement reactions.[11] Recently, we disclosed two practical methods for the synthesis of 1,2,3-triiodoarene compounds by two-step protocols from aromatic amines and aromatic carboxylic acids.[6a,6b] Remarkably, 1,2,3-triiodoarenes are crystalline and benchstable solids. Although these methods have proven successful in providing the desired 1,2,3-triiodoarenes in good yields, activated aromatic derivatives remain a challenging task. A general method allowing direct synthesis of 1,2,3-triiodoarenes from readily available activated benzoic acids would be highly useful.

Herein, we report the first synthesis of hitherto unknown 3,4,5-triiodoanisole in a tandem one-pot C–H iodination/*ipso*-iododecarboxylation from *para*-anisic acid that is catalytic, scalable, efficient, and easy to work up and purify. Potential application of the target compound as a precursor for novel site-selective metal–iodine exchange and Suzuki–Miyaura cross-coupling reactions is also demonstrated. 3,4,5-Trisubstituted anisole derivatives, which are useful building blocks in synthesis and hard to prepare by any other means, are provided in a highly regioselective manner.

Results and Discussion

Owing to our interest in the chemistry of 1,2,3-triiodoarenes, we sought to pursue new synthetic methodologies to expand the scope of these substrates and also their applications in synthesis and medicine. The ability to use effective and convenient protocols to quickly generate highly functionalized building blocks for the synthesis of complex molecules is of great interest to synthetic chemists. Our approach originated by screening the literature for an efficient method for the *ortho*-iodination and *ipso*-iododecarboxylation of benzoic acid. In spite of the number of reports on the iodination of aromatic compounds,[6f,12] aromatic carboxylic acids proved to be excellent directing groups for aromatic C–H and *ipso* functionalizations, as they provide one regioisomer at the *ortho* and *ipso* positions, respectively.[13] Accordingly, we envisioned that the sequence of C–H iodination/*ipso*-iododecarboxylation of benzoic acids could be achieved in a one-pot fashion to form the desired 1,2,3-triiodoarenes, as shown in Scheme 1.



Scheme 1. Synthetic approach to 1,2,3-triiodoarenes through a one-pot C–H iodination/*ipso*-iododecarboxylation strategy.

Multiple examples of carboxylate-directed *ortho*- or *ipso*-iodinations have been reported.[13,14] A very interesting *ortho*-iodination and -bromination approach was developed recently by Yu and co-workers. It involved the Pd^{II}-catalyzed activation of C–H bonds at 100 °C in the presence of iodine and (diacetoxy)iodobenzene (DAIB) to provide, as current state of the art, good substrate scope and yields.[13e] Other protocols for the *ortho*-halogenation and arylation of C–H bonds have been previously developed.[7g,7i–7q,13a,13f,13i,14a,15]

Alternatively, *ipso*-halodecarboxylation is a fundamental organic reaction that has received considerable attention in recent years as the heart of numerous C–X and C–C bond transformations.[7a–7c,7f,14f,14g,14i,14k,16] It is believed that extrusion of CO_2 to form the arylmetal species is the rate-determining step in these transformations. Several stoichiometric procedures have been developed by Hunsdiecker[17] and Borodine,[18] including the Cristol–Firth–Hunsdiecker modification,[19] Suárez modification,[7c,7d] Kochi modification,[20] Barton modification,[21] and Larrosa modification,[7b] in addition to the metal-free *ipso*-iododecarboxylation of aromatic carboxylic acids developed recently by Gandelman and co-workers.[7a] Notably, no catalytic method for the *ipso*-iododecarboxylation of aromatic acids have been reported to date.

The use of (diacetoxy)iodobenzene and iodine under UV photolysis (Suárez modification) is an interesting approach for the *ipso*-iododecarboxylation of aliphatic and aromatic carboxylic acids.[7c,7d] The reaction conditions are similar to those used by Yu (*ortho*-iodination) and Suárez (*ipso*-iododecarboxylation), and we envisioned that a combination of these two protocols under suitable conditions might be of intrinsic value to obtain a good and direct approach to access elusive 1,2,3-triiodoarenes quickly in a one-pot fashion. We were further encouraged by recent DFT studies on *ipso*-decarboxylation, which revealed that *ortho* substituents can significantly enhance the metal-catalyzed *ipso*-decarboxylation pathway.[22] According to these studies, doubly *ortho*-substituted benzoic acid is expected to be more reactive than the mono-*ortho*-substituted derivative. Conse-

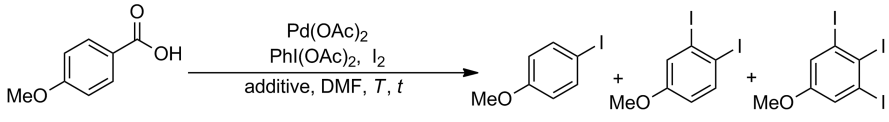
quently, it can be imagined that the Pd-catalyzed *ipso*-decarboxylation event is switched off and is only switched on after C–H iodination has occurred.

To examine this hypothesis, experiments were performed by using *para*-anisic acid under different reaction conditions. Three possible iodoarene products can be formed by this transformation. The results are summarized in Table 1. The C–H iodination/*ipso*-iododecarboxylation reaction by using palladium(II) acetate (5 mol-%), $PhI(OAc)_2$ (1.5 equiv.), and molecular iodine (1.5 equiv.) in DMF at 100 °C for 24 h (Yu conditions) afforded desired product **7** in only 4% yield along with 2% yield of diiodinated anisole **6** (Table 1, Entry 1). The formation of *para*-iodoanisole isomer **5** was not observed. Changing the reaction temperature and time slightly improved the yield (Table 1, Entries 2–4). Raising the catalyst loading appeared to be insignificant in promoting the extrusion of CO_2, as this resulted in only 15–19% conversion of product **7** (Table 1, Entries 5 and 6). The use of 2.0 equiv. of $PhI(OAc)_2$ improved the *ipso*-iododecarboxylation step and afforded desired product **7** in 27% yield (Table 1, Entry 7). These results led us to hypothesize that an excess amount of $PhI(OAc)_2$, which is a strong oxidant, resulted in oxidation of the aryl–Pd^{II} species to the Pd^{IV} species, and this allowed reductive elimination to take place in both the *ortho*- and *ipso*-iodinations. On the other hand, the use of an excess amount of $PhI(OAc)_2$ dramatically lowered the yield of *ipso*-iododecarboxylation and favored undesired processes (Table 1, Entries 8 and 9). The use of an excess amount of molecular iodine slightly improved the yield (Table 1, Entries 10 and 11). A longer reaction time was not beneficial, as the product was obtained in 38% yield in this case (Table 1, Entry 12). We then investigated whether irradiation (Suárez conditions) could further improve this transformation. The use of a 100 W bulb (tungsten lamp) improved the yield and afforded desired product **7** in 59% yield (Table 1, Entry 13). Other power sources such as 250 and 400 W bulbs dramatically lowered the yield of desired product **7** (Table 1, Entries 15 and 16). The best yield for the one-pot C–H iodination/*ipso*-iododecarboxylation reaction was obtained by using 10.0 mol-% $Pd(OAc)_2$, 2.0 equiv. $PhI(OAc)_2$, and 4.0 equiv. molecular iodine in DMF under 100 W irradiation at 120 °C (Table 1, Entry 17). Using these conditions, the reaction also worked well on a gram scale (Table 1, Entry 18).

The geometry of 3,4,5-triiodoanisole (**7**) is supported by X-ray crystallographic analysis (Figure 2),[23] which clearly shows the positions of the three iodo substituents. The molecular geometry indicates an intermolecular steric repulsion between the vicinal iodo substituents. This intermolecular repulsion is released by reducing the endocyclic angle (C3–C4–C5 117.1°) rather than by elongating the C–I bonds.[23]

Various approaches for the activation of C–H bonds and *ipso* bonds through the Pd^{II} carboxylate directed functionalization of benzoic acids have been previously employed and reported.[13b,13e,13n,24] Although our mechanism has not been fully studied, a plausible catalytic cycle for the one-pot C–H iodination/*ipso*-iododecarboxylation is proposed in Scheme 2. Ligand exchange/Pd^{II}-initiated C–H cleavage through coordination of the lone pair of electrons of the

Table 1. Conditions for the one-pot C–H iodination/*ipso*-iododecarboxylation reaction of *para*-anisic acid.[a]



5 **6** **7**

Entry	$Pd(OAc)_2$ [equiv.]	$PhI(OAc)_2$ [equiv.]	I_2 [equiv.]	Additive	*T* [°C, h]	Yield [%] of **5**[b] + **6**[b] + **7**[c]
1	5.0	1.5	1.5	–	100, 24	0 + 2 + 4
2	5.0	1.5	1.5	–	120, 24	0 + 3 + 8
3	5.0	1.5	1.5	–	140, 24	0 + 2 + 5
4	5.0	1.5	1.5	–	120, 48	0 + 2 + 6
5	10.0	1.5	1.5	–	120, 24	0 + 7 + 15
6	20.0	1.5	1.5	–	120, 24	0 + 9 + 19
7	10.0	2.0	1.5	–	120, 24	0 + 8 + 27
8	10.0	3.0	1.5	–	120, 24	0 + 10 + 22
9	10.0	4.0	1.5	–	120, 24	0 + 4 + 9
10	10.0	2.0	2.0	–	120, 24	0 + 7 + 35
11	10.0	2.0	3.0	–	120, 24	0 + 11 + 41
12	10.0	2.0	3.0	–	120, 48	0 + 9 + 38
13	10.0	2.0	3.0	100W[d]	120, 24	2 + 17 + 59
14	20.0	2.0	3.0	100W[d]	120, 24	2 + 22 + 63
15	10.0	2.0	3.0	250W[d]	120, 24	3 + 8 + 39
16	10.0	2.0	3.0	400W[d]	120, 24	3 + 7 + 21
17	***10.0***	***2.0***	***4.0***	***100W***[d]	***120, 24***	***2 + 18 + 64***
18[e]	10.0	2.0	4.0	100W[d]	120, 24	2 + 16 + 57

[a] All reactions were performed by using *para*-anisic acid (0.27 M, 3.29 mmol 1.0 equiv.) in DMF (12.0 mL). [b] Yield was determined by ^1H NMR spectroscopy. [c] Yield of isolated product. [d] Tungsten lamp. [e] 5 g scale (32.86 mmol).

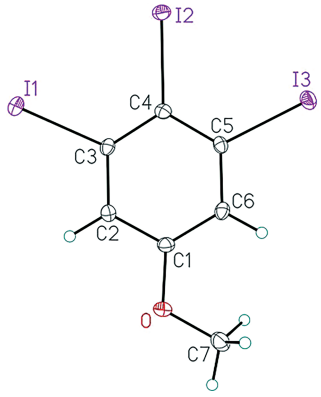


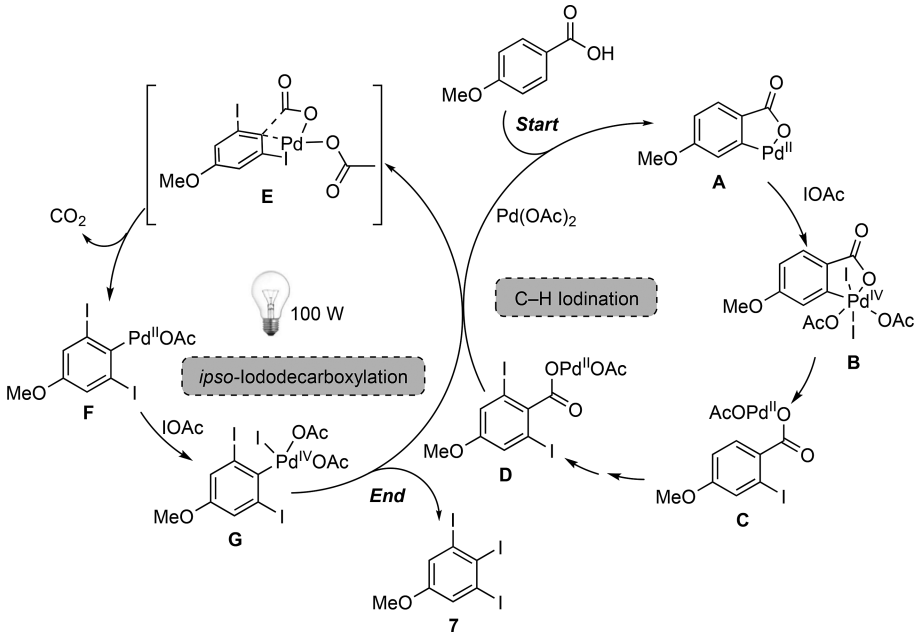
Figure 2. ORTEP view of 3,4,5-triiodoanisole (**7**). Thermal Gaussian ellipsoids at 30% probability level.

carboxyl group results in the formation of five-membered palladacycle **A**. Palladium(II) intermediate **A** is then oxidized by IOAc, which is generated in situ from $PhI(OAc)_2$ and molecular iodine,[25] to afford palladium(IV) intermediate **B**; this is followed by reductive elimination to form *ortho*-iodinated product **C**. The former steps are repeated to afford *ortho*-diiodinated species **D**, which enters into the next catalytic cycle. Irradiation-assisted decarboxylation is likely a process that follows a single-electron transfer mechanism via transition state **E**, followed by palladium transfer to form intermediate **F**. Palladium(II) intermediate **F** is then oxidized once more by IOAc to afford palladium(IV) intermediate **G**, which is followed by reductive elimination to form desired product **7** and to regenerate palladium(II) acetate so that it can once again enter the first catalytic cycle.

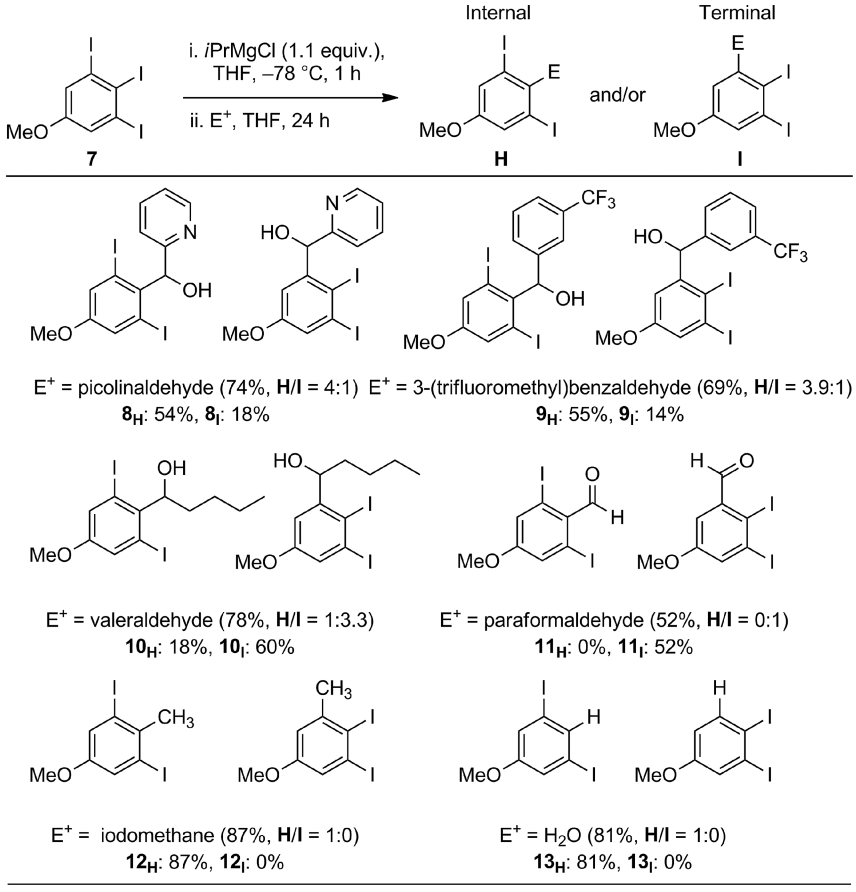
Having the optimized reaction conditions for this one-pot transformation in hand, we were encouraged to show the application of 3,4,5-triiodoanisole (**7**) as a useful intermediate in synthesis. Different synthetic transformations were performed by using Knochel's chemistry. The diiodoarene products were isolated in moderate to good yields, as shown in Scheme 3. Having only two regiochemically different sites occupied with iodine, the metal–iodine exchange/functionalization reaction sequence can afford no more than two possible regioisomers in this transformation, internal **H** and terminal **I**. As we previously observed in the metalation and reaction with 1,2,3-triiodobenzene and 3,4,5-triiodotoluene as electrophiles,[6a,6b,11a] the nature of the electrophile has a great influence on the regioselectivity of the reaction. For instance, the use of aldehydes as electrophiles provided a mixture of internal and terminal benzyl alcohol products (Scheme 3; see **8**–**10**). Interestingly, aromatic aldehydes were found to favor the formation of the internal benzyl alcohol product (see $\mathbf{8_H}$ and $\mathbf{9_H}$), whereas aliphatic aldehydes favored terminal products (see $\mathbf{10_I}$). Furthermore, the use of DMF as an electrophile afforded the terminal product as a sole regioisomer (Scheme 3; see $\mathbf{11_I}$). On the other hand, the use of iodomethane and water as electrophiles afforded exclusively the internal products (Scheme 3; see $\mathbf{12_H}$ and $\mathbf{13_H}$).

The ability to use inexpensive and readily available starting materials and intermediates to prepare highly functionalized molecules is crucial in synthesis. Screening the literature with respect to substitutions at C1, C2, and C3 as a core structure revealed that 1,2,3-trisubstituted arenes are a demanding class of compounds in synthesis and medicinal chemistry.[26] We decided to test whether our previous reports could be extended and used to quickly synthesize 3,4,5-trisubstituted anisoles in a regioselective manner.

The synthesis is described in Scheme 3. The internal iodo group was exchanged with excellent regioselectivity by using Knochel's chemistry and iodomethane as the electrophile to form diiodoarene $\mathbf{12_H}$. Suzuki–Miyaura cross-cou-

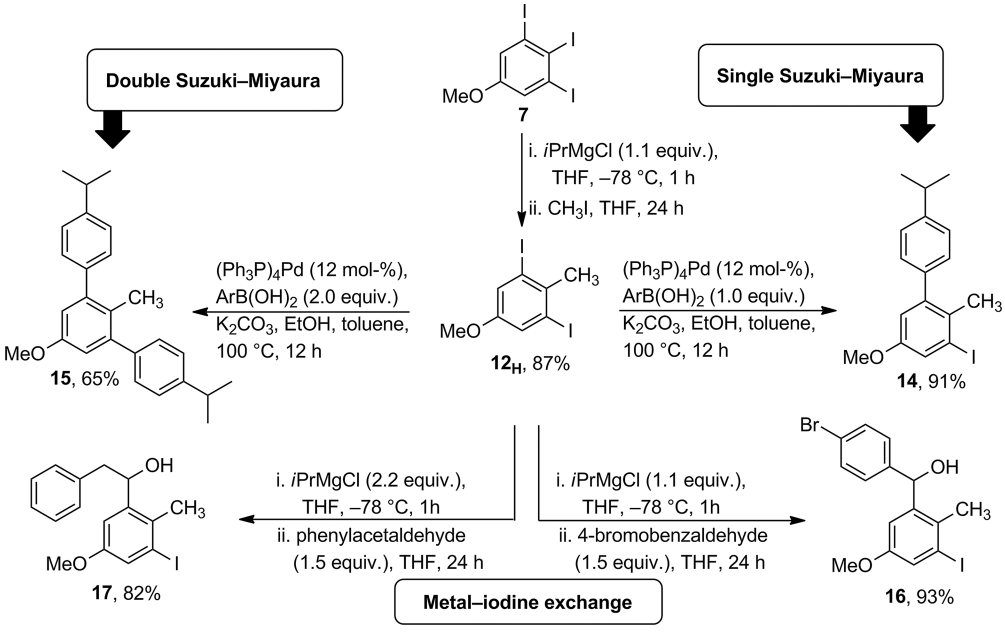


Scheme 2. Proposed mechanism for the one-pot Pd^{II}-catalyzed C–H iodination/*ipso*-iododecarboxylation of *para*-anisic acid.



Scheme 3. Terminal versus internal diiodinated anisole derivatives from metal–iodine exchange (MIE) of 3,4,5-triiodoanisole and different electrophiles.

pling of $\mathbf{12_H}$ provided the expected monocoupled product in 91% yield (Scheme 4; see **14**). Moreover, a one-pot double Suzuki–Miyaura cross-coupling reaction by using an arylboronic acid (2 equiv.) was also performed to afford the biscoupled product in moderate yield (Scheme 4; see **15**).[27] Consequently, diiodoarene $\mathbf{12_H}$ was followed by another



Scheme 4. Possible chemical transformations toward disubstituted and trisubstituted anisole derivatives from 3,4,5-triiodoanisole (**7**).

metal–iodine exchange by using two different aldehydes to provide the expected iodobenzyl alcohols in good yields (Scheme 4; see **16** and **17**).

Conclusions

We described the first one-pot synthesis of 3,4,5-triiodoanisole on a gram scale from *para*-anisic acid through a directed C–H iodination/*ipso*-iododecarboxylation strategy. This reaction is operationally simple, catalytic, scalable, and easy to work up and purify. 3,4,5-Triiodoanisole is a crystalline and remarkably bench-stable solid. The molecular geometry was assigned by X-ray crystallographic analysis. Utilizing 3,4,5-triiodoanisole as a useful intermediate in synthesis led to a versatile range of mono-, di-, and trisubstituted anisole derivatives in a series of regioselective metal–iodine exchange and Suzuki–Miyaura cross-coupling reactions. The products were isolated in moderate to good yields, are valuable building blocks, and are difficult to prepare by other means. With other iodo groups on the aryl ring, further elaboration can easily be explored.

Experimental Section

General: All commercial reagents and chromatography solvents, including diethyl ether, ethyl acetate, hexanes, palladium(II) acetate [$Pd(OAc)_2$], (diacetoxy)iodobenzene (DAIB), anhydrous sodium sulfate (Na_2SO_4, BDH), isopropylmagnesium chloride (*i*PrMgCl, 2 M in THF), and molecular iodine (I_2), were used as obtained unless otherwise stated. Anhydrous solvents were distilled from appropriate drying agents prior to use. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254. Merck silica gel 60 (0.063–0.2 mm) was used for column chromatography. Visualization of TLC was accomplished with UV light (254 nm). NMR spectra were recorded with a Bruker-Avance 400 MHz spectrometer. The residual solvent protons (^1H) or the solvent carbon atoms (^{13}C) were used as internal standards. Chemical shifts are given downfield from tetramethylsilane. High-resolution mass spectra were recorded by using chemical ionization (CI) and electrospray ionization (ESI) techniques.

Synthesis of 3,4,5-Triiodoanisole (7) through the One-Pot Directed C–H Iodination/*ipso*-Iododecarboxylation of *para*-Anisic Acid: A flame-dried, 100 mL round-bottomed flask was charged with *para*-anisic acid (3.29 mmol, 1.00 equiv.), palladium(II) acetate (0.33 mmol, 0.10 equiv.), (diacetoxy)iodobenzene (6.57 mmol, 2.0 equiv.), iodine (13.14 mmol, 4.00 equiv.), and anhydrous *N*,*N*-dimethylformamide (12.2 mL) in air. The flask was then sealed with a septum, and the mixture was stirred at 120 °C and irradiated (100 W bulb) for 24 h. The mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and filtered through a pad of Celite (545). The organic phase was washed with 0.5 N HCl (4 × 20 mL), brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100% hexanes) and washed with cold hexanes to yield the desired product as a white solid (64% yield). M.p. 79–81 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 2 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 138.5, 125.5, 110.0, 106.3, 55.9 ppm. IR (cast film): $\tilde{\nu}$ = 3054, 2986, 1583, 1426, 1394, 943 cm^{-1}. HRMS (CI): calcd. for $C_7H_5I_3O$ $[M]^+$ 485.7474; found 485.7468.

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[27] For other examples of the site-selective Suzuki–Miyaura cross-coupling reaction of 3,4,5-triiodoanisole (**7**) with different arylboronic acids, see ref.[11b]

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