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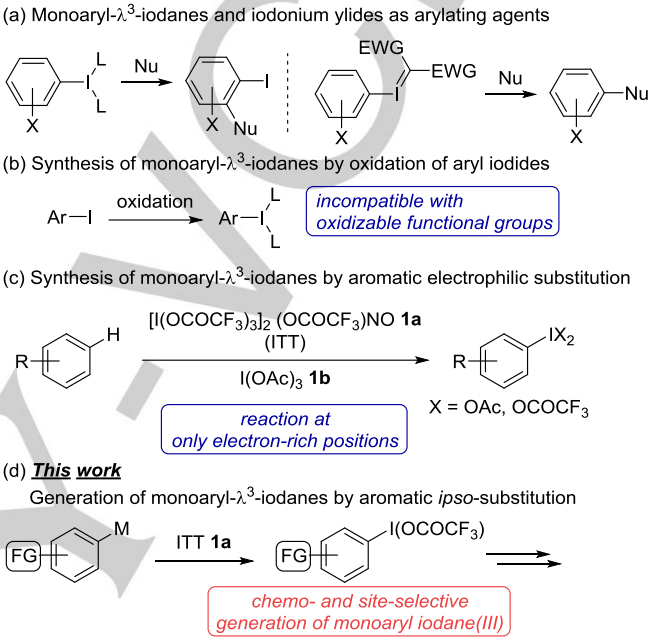
Synthesis of Functionalized Monoaryl-λ^3-iodanes via Chemo- and Site-selective *ipso*-Substitution Reactions

Narumi Komami,[†] Keitaro Matsuoka,[†] Ayako Nakano, Masahiro Kojima, Tatsuhiko Yoshino,* and Shigeki Matsunaga*

Abstract: Monoaryl-λ^3-iodanes are potentially attractive arylating agents. They are generally synthesized from aryl iodides via oxidation, which can cause functional group incompatibility, especially when polyfunctionalized derivatives are desired. Here we describe the direct synthesis of monoaryl-λ^3-iodanes via a chemoselective *ipso*-substitution reaction of arylgermanes and arylstannanes with iodine tris(trifluoroacetate). The generated iodanes were converted to iodonium ylides or used for further transformations in one pot. The presented method enables the preparation of polyfunctionalized monoaryl-λ^3-iodanes.

Hypervalent iodine compounds are widely studied in organic chemistry due to their unique reactivity and low toxicity.[1] Among the various I(III/V/VII) compounds reported, monoaryl-λ^3-iodane ($ArIL_2$) is one of the most popular classes of hypervalent iodines in terms of the versatile applications in oxidation reactions. Although these compounds are mainly used for oxidative transformations in which the aryl group is not involved in the products, some recent studies focused on their potential as arylating agents.[2-7] An interesting feature of most arylation reactions using a monoaryl-λ^3-iodane is that the C-I bond of the reagent is not cleaved, and a 2-iodoaryl group is introduced via sigmatropic rearrangement (Scheme 1a, left side).[2,3] Furthermore, monoaryl-λ^3-iodanes are easily converted to iodonium ylides, which also serve as arylating agents (Scheme 1a, right side).[5,6] The typical synthesis of monoaryl-λ^3-iodanes involves the introduction of I(I) to an aromatic ring and oxidation to I(III) (Scheme 1b).[1,8-13] The oxidation step can cause functional group incompatibility and limit the accessible structures. To further expand the applications of monoaryl-λ^3-iodanes as arylating agents, we considered that the development of efficient synthetic methods of monoaryl-λ^3-iodanes containing multiple functional groups is crucial.

Direct introduction of the -I(III)L_2 fragment to aromatic rings using iodine tricarboxylates[14] has been described in a few reports (Scheme 1c).[14-18] As early as 1974, Maletina and co-workers reported electrophilic aromatic substitution using iodine tris(trifluoroacetate) (ITT, **1a**),[15] followed by a report by Kurosawa and co-workers on the reactions between aryl ketones and ITT



Scheme 1. Synthesis of hypervalent iodine(III) reagents and their applications as arylating agents.

1a.[16] Recently, Wirth and co-workers reported that $I(OAc)_3$ **1b** or ITT **1a** reacts with several aromatic compounds to give (dicarboxyiodo)arenes.[17] The scope of these reactions, however, is limited to rather simple substrates, and the functional group compatibility was not well elucidated. Moreover, the site selectivity of these electrophilic substitution reactions depends on the electronic nature of the substrates, and the introduction of the -I(III)L_2 moiety at the less electron-rich position is difficult in principle.

Here we report the direct synthesis of monoaryl-λ^3-iodanes by chemo- and site-selective *ipso*-substitution reactions of stable arylmetal species (Ar-M, M = Si, Ge, Sn) with ITT **1a**.[19] Our method provides direct access to monoaryl-λ^3-iodanes containing several oxidizable functional groups, and the generated iodanes are converted to monoaryliodonium ylides or directly subjected to further transformation reactions in one pot (Scheme 1d).

ipso-Substitution reactions of arylsilanes[20] and their Ge[21] and Sn[22] analogues with halogen-based electrophiles are well-established methods for selectively introducing a halogen atom at the desired site. With this in mind, we began by seeking appropriate arylmetal compounds for *ipso*-substitution using ITT **1a** (Table 1).[23] To circumvent the decomposition of an I(III) species and facilitate the analysis, the reaction mixtures were treated with a basic aqueous solution of Meldrum's acid derivative

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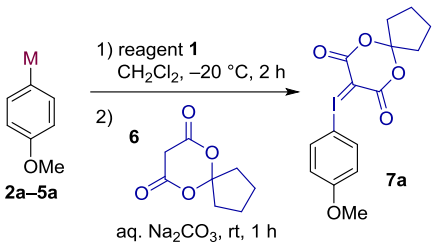
Table 1. *ipso*-Substitution of Arylmetal Compounds with **1**[a]

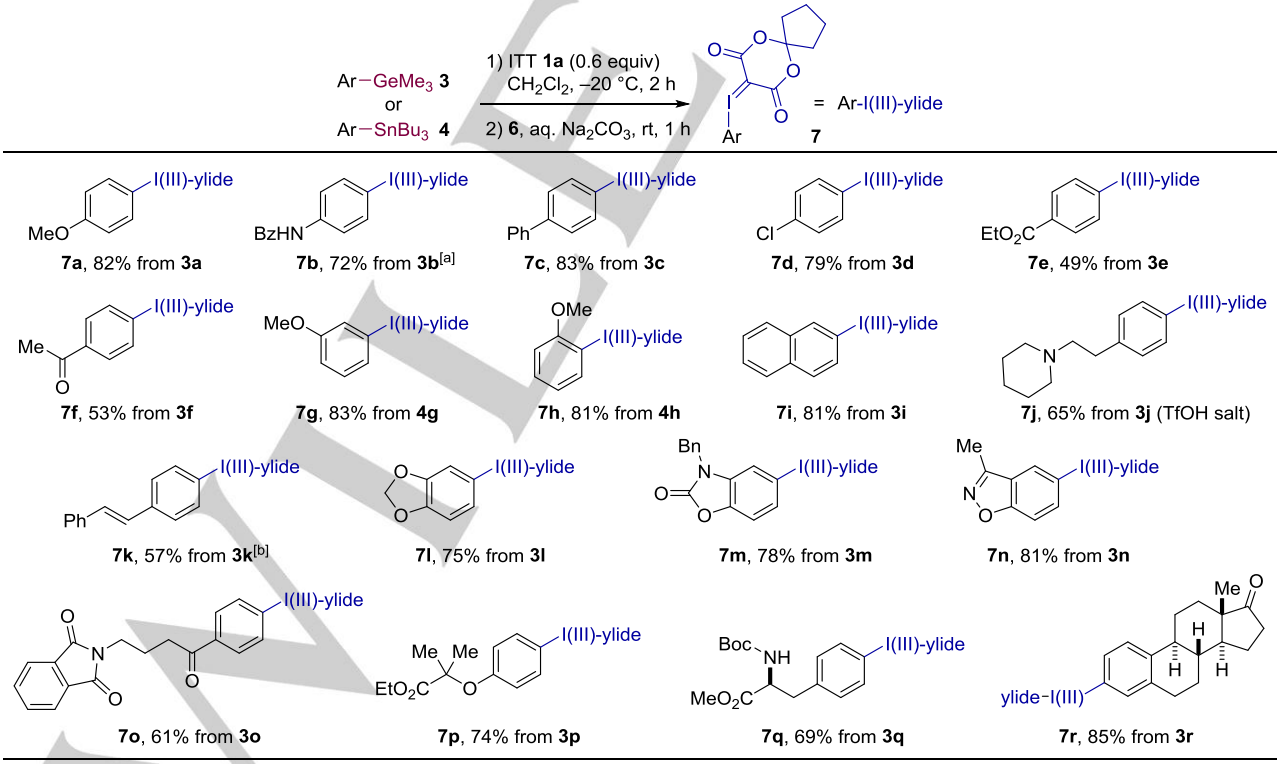


Entry	Arylmetal compounds (M)	Reagent (equiv)	Yield[b] (%)
1	**2a** ($SiMe_3$)	**1a** (0.6 equiv)	42
2	**3a** ($GeMe_3$)	**1a** (0.6 equiv)	82[c]
3	**4a** ($SnBu_3$)	**1a** (0.6 equiv)	77
4	**5a** (BPin)	**1a** (0.6 equiv)	complex mixture
5	**3a** ($GeMe_3$)	**1b** (1.2 equiv)	77

[a] Reaction conditions: 1) **2a–5a** (0.30 mmol) and reagent **1** [**1a** = $[I(OCOCF_3)_3]_2(NO)(OCOCF_3)$; **1b** = $I(OAc)_3$] in CH_2Cl_2 (3 mL) at –20 °C for 2 h; 2) aq. Na_2CO_3 (10% w/v, 0.9 mL) at rt for 1 h. [b] Determined by ^1H NMR analysis of crude mixtures using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield.

6 to convert the intermediate to a relatively stable iodonium ylide, **7a**.[6] Arylsilane **2a** reacted with ITT **1a** in CH_2Cl_2 at –20 °C, and the desired product **7a** was obtained in 42% yield after ylide formation (entry 1). Several byproducts, including trisubstituted benzenes, were observed in the crude mixture, probably due to the incomplete *ipso*-selectivity and competing electrophilic aromatic substitution reactions. We next examined other arylmetal compounds under similar reaction conditions (entries 2–4). Arylgermane **3a** and arylstannane **4a** exhibited higher reactivity and selectivity than arylsilane **2a**, providing **7a** in good yield (entries 2 and 3). In these cases, only **7a** and a small amount of 4-iodoanisole were detected, indicating improved *ipso*-selectivity. The improvement with **3a** and **4a** would be due to the stronger β-effects of Ge and Sn compared with Si to stabilize a cationic intermediate in the electrophilic aromatic *ipso*-substitution reaction.[24] Arylboronate **5a** was also examined as a substrate, but only a complex mixture was observed (entry 4). On the other hand, a reaction of arylgermane **3a** with $I(OAc)_3$ **1b** instead of ITT **1a** afforded a similar yield (entry 5). Although similar results were obtained in entries 2, 3, and 5, we decided to use arylgermanes **3**[25] and ITT **1a** (entry 2) as a standard combination for further studies due to the toxicity of organotin compounds and higher electrophilicity of ITT **1a**, which would be benefitial for *ipso*-substitution reactions using less reactive arylmetal substrates.

We applied the optimized protocol to various substrates bearing functional groups, and the results are summarized in Scheme 2. In all cases, the product was converted to the corresponding iodonium ylide **7** for isolation and characterization. Iodonium ylides of this type were not only stable and easy to isolate, but also served as efficient precursors for ^{18}F positron emission tomography probes.[6] *p*-Substituted arylgermanes underwent a selective *ipso*-substitution reaction to provide **7a–7f** regardless of the electronic properties and orientation toward electrophilic aromatic substitution of the substituent (**3a–3f**). When we use **3b**, with an amide substituent, the reaction in propionitrile instead of CH_2Cl_2 afforded cleaner conversion and



Scheme 2. Substrate scope of iodonium ylide synthesis via *ipso*-substitution of arylgermanes **3** and arylstannanes **4**. Reaction conditions: 1) **3** or **4** (0.30 mmol) and ITT **1a** (0.18 mmol) in CH_2Cl_2 (3 mL) at –20 °C for 2 h; 2) aq. Na_2CO_3 (10% w/v, 0.9 mL), rt, 1 h unless otherwise noted. [a] The reaction was run in propionitrile (3 mL) at –60 °C for 18 h. [b] –60 °C.

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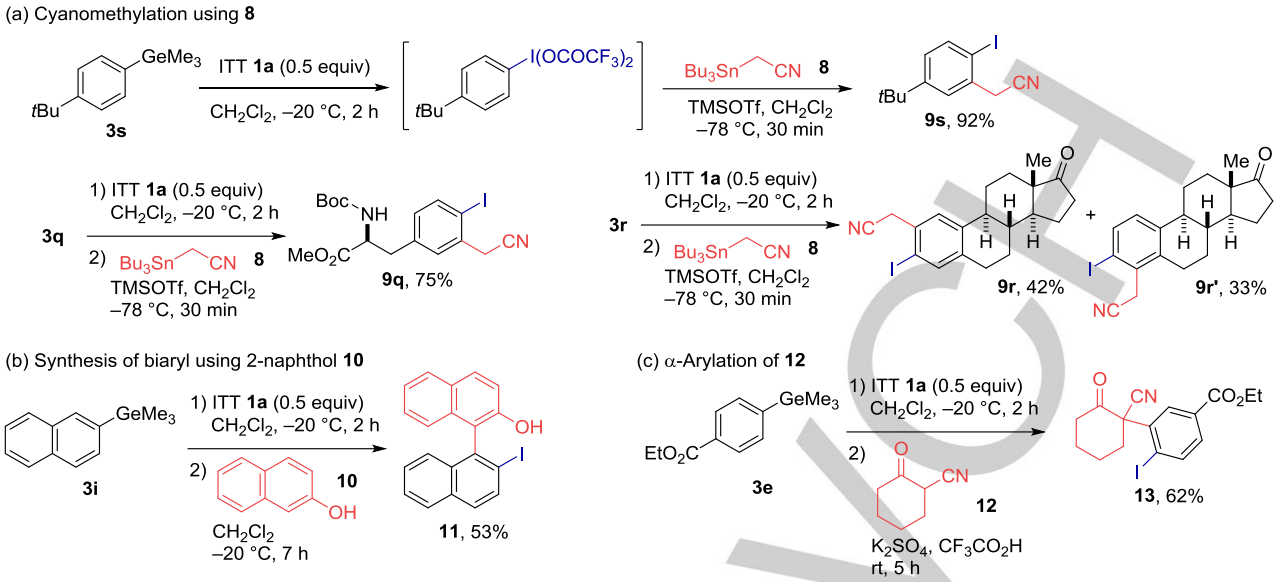

Scheme 3. One pot transformation of $ArI(OCOCF_3)_2$. See Supporting Information for detailed reaction conditions.

better yield (**7b**). Although arylgermanes with a *m*-methoxy or an *o*-methoxy substituent did not selectively afford the desired *ipso*-substitution product, the corresponding arylstannanes (**4g**, **4h**) were appropriate substrates, affording **7g** and **7h** in high yield. The results of **3e**, **3f**, **3i**, **4g**, and **4h** clearly demonstrate that *ipso*-selectivity of the arylmetals can override the intrinsic site-selectivity of the standard electrophilic aromatic substitution, and that our protocol effectively provides substitution patterns that are difficult to achieve by direct reactions of simple arenes and **1**.[15-17] *We successfully obtained an iodonium ylide containing an aliphatic amine moiety (**7j**) and an iodonium ylide containing an olefin conjugated with aromatic rings (**7k**), demonstrating the functional group compatibility of the developed conditions.* Arylgermanes containing an oxygen- and nitrogen-heterocycle were also tolerated to afford iodonium ylides **7l–7o** in good yield. Furthermore, an arylgermane with a fibrate-like structure (**3p**) and arylgermanes derived from tyrosine (**3q**) and estrone (**3r**) provided iodonium ylides **7p–7r** in 69%–85% yields, validating the applicability of our protocol for the synthesis of functionalized, biologically active molecules.

We next focused on one pot reactions of the generated monoaryl-λ^3-iodane(III) intermediates[26] to demonstrate the synthetic utility of the developed method (Scheme 3). Cyanomethylation reactions, reported by Huang, Wang, Peng, and co-workers,[3h] proceeded smoothly by the direct addition of α-stannylnitrile **8** to the reaction mixture of arylgermanes **3** and ITT **1a** to afford *o*-cyanomethyl iodoarenes **9** in good to excellent yields (Scheme 3a). A separable isomeric mixture was obtained from estrone derivative **3r**. Next, biaryl synthesis reported by Yorimitsu and co-workers[3g] was examined, and **11** was obtained in 53% yield from **3i**, ITT **1a**, and 2-naphthol **10** in one pot (Scheme 3b). An α-arylation protocol developed by Vallribera, Shafir, and co-workers[3c,f] was successfully applied to cyanoketone **12** and an iodane(III) intermediate generated in situ from **3e** and ITT **1a**, providing **13** in 62% yield (Scheme 3c).

In summary, chemoselective *ipso*-substitution reactions of arylgermanes **3** or arylstannanes **4** using ITT **1a** provided monoaryl-λ^3-iodanes, which were converted to iodonium ylides **7** or underwent further transformations in one pot. The presented method enables the preparation of polyfunctionalized monoaryl-λ^3-iodanes. The application to late-stage diversification of functionalized molecules and biological studies, including the synthesis of ^{18}F PET probes, are ongoing in our laboratory.

Acknowledgements

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Keywords: hypervalent iodine • iodonium ylide • *ipso*-substitution • arylation • germanium

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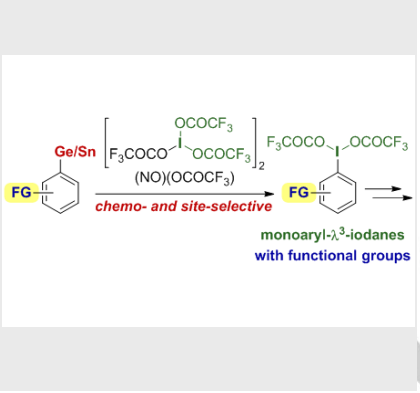

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