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RESEARCH ARTICLE

Base-Mediated Radio-Iodination of Arenes by using Organosilane and Organogermane as Radiolabelling Precursors

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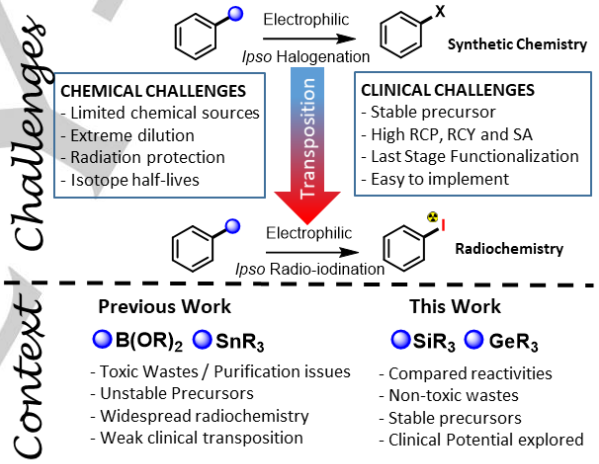
Abstract: The radio-iodination of arenes is investigated from organosilane and organogermane precursors using *ipso*-electrophilic halogenation (IEH). Discovery of a mild base mediated process allows radio-iodination in HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) of either aryl silane or germane, with germanes being more reactive. Clinical potential of arylgermanes as radio-iodination precursors is demonstrated through the labelling of **[^{125}I]IMTO** (iodometomidate) and **[^{125}I]MIBG** (*meta*-iodobenzylguanidine) thus offering an alternative to radio-iododestannylation processes using non-toxic precursors.

Introduction

Radio-halogens are prevalent species in nuclear medicine due to their wide field of applications in molecular imaging and radiotherapy.[1–6] Thus, covalent bond formation between radio-halogens and relevant molecular substrates is a major topic in radiochemistry generally, achieved through transfer of standard halogenation reactions to radio-halogenation reactions. Several challenges arise when it comes to performing halogenation in a radiosynthetic context, such as limited chemical sources, extreme dilution of the radio-isotope, large excess of substrate and reagents, radiation protection and isotope half-lives (Scheme 1).[5] Other challenges occur regarding the use of radio-labelled molecules in clinical applications: radiochemical precursors must be stable and high radiochemical purity (RCP)/ radiochemical yield (RCY)/ specific activity (SA) are expected. Moreover, the radiochemical process needs to be facile to implement, and the radio-isotope ideally introduced during the last step of the synthesis. Following these challenging requirements and using radio-iodination reactions, single-photon emission computed tomography (SPECT) tracers with iodine-123,[7,8] positron emission tomography (PET) tracers with iodine-124,[9–11] radiolabelled molecules for radioimmunoassay or binding experiments with iodine-125[12–15] or radiotherapeutics with iodine-131[16] can be prepared efficiently from sodium iodide as the sole available radiochemical source.



Scheme 1. Radio-iodination through IEH: challenges and context.

One of the most prevalent strategies to access aryl halides is electrophilic halogenation (EH) where direct replacement of a hydrogen atom by a halogen is performed using halogenation reagents.[17–20] However, the EH strategy suffers generally from a lack of selectivity and most reaction conditions limit functional tolerance. *Ipso*-electrophilic halogenation (IEH) of prefunctionalized arenes offers a much more defined synthetic alternative that delivers positional selectivity, and efficient iodinations have been described using boron[21–26], silicon[27–33] or recently germanium-based[34,35] leaving groups. In the context of IEH-mediated radio-iodination, the most prominent example is the widespread radio-iododestannylation reaction.[36] However, despite its efficacy and popularity, this reaction is notoriously hampered by the difficult organostannane isolation/purification[37], the toxicity of organotin precursors[38] and the production of tin wastes during the radiosynthetic step. So far, these important constraints have limited the use of this radio-iodination approach

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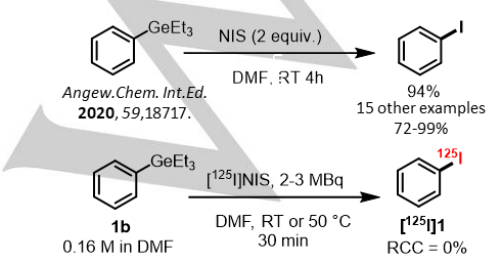
for human applications and restricted it to almost exclusively to research using animal models. The use of arylboronic acids and esters have also been investigated to promote radio-iododeboronation reactions and simple adaption of standard iododeboronation reactions[39–42] with limited scopes were first described. The recent discovery of an efficient base-catalyzed radio-iododeboronation from boronic acids[25] offers great radiochemical perspectives, however, its transfer to the clinic is not achieved yet. The choice of unstable and/or difficult to access boronic acid precursors may hamper this transfer. Taking advantage of widely described iododesilylation reactions, some radio-iododesilylation reactions have been investigated. The reaction generally requires the use of strongly acidic media with heating, oxidant or toxic additives such as TFA (trifluoroacetic acid),[43] *tert*-butylhypochlorite[44–46] or $Tl(OCOCF_3)_3$.[47] Even if the reaction has been applied to label some investigational radiotracers,[43,48–55] this approach remains scarcely used. Radio-iododegermylation reactions have seen limited studies. So far, this process is only known from phenyltrimethylgermane and six *para*-substituted arylgermanes using the strong oxidizing agent dichloramine-T in AcOH.[56,57] Despite these precedents, to date arylsilanes and germanes have not replaced arylstannanes as radio-iodination precursors.

This is likely due to the relatively harsh reaction conditions employed in prior protocols that likely prevent applications in more functionalized molecules, which so far made them a poor alternative to toxic stannanes to label clinically relevant molecules. However, arylsilanes and germanes present several advantages as radio-labelling precursors in clinical applications such as low-toxicity, preparation ease from metal-halogen exchange or transition metal-catalyzed routes and an enhanced stability compared to stannane or borane.[58] Considering the possibilities and limitations offered by both radio-iododestannylation and radio-iododeboronation, we reasoned that an in-depth exploration of radio-iodination from organosilane and organogermane could result in the development of a valuable radio-iodination methodology with clinical potential.

Results and Discussion

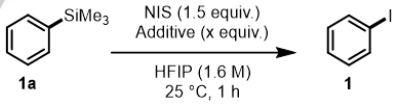
Initiating this study, we thought that the recently described mild iododegermylation reaction conditions[34] will be straightforwardly transferable to radio-iodination. However, to our surprise, there was not even a trace of iodinated material detected (Scheme 2) when reacting organogermane **1b** with [^{125}I]NIS (*N*-iodosuccinimide) in DMF (*N*,*N*-dimethylformamide) at room temperature or 50 °C. We hypothesize that the extremely low molar amount of iodine-125 (~20 to 40 pmol) used in the radiosynthetic step is the limiting factor that dramatically lowers the reaction rate.



Scheme 2. Preliminary results of radio-iodination using organogermane as radiolabelling precursors.

We hence embarked on an exploration of suitable reaction conditions and tested HFIP as solvent as well as basic additives. The use of HFIP has led to rate accelerations in several prior transformations that involve an electrophilic substitution,[59] and basic additives have been highlighted as promotors in ipso substitution.[25] To our delight, when we reacted phenyltrimethylsilane **1a** with NIS and 2,6-lutidine in HFIP, iodobenzene **1** was obtained in 30% at room temperature in relatively short reaction time (1h) (Table 1, entry 1). Other pyridine-based additives were screened (see SI for complete reaction set-up) and a slight yield improvement was observed in the presence 2,3-dibromo-5-methylpyridine (Table 1, entry 2). Aliphatic amines were then evaluated as additives and **1** was obtained in 61% NMR yield (nuclear magnetic resonance) with TMP (2,2,6,6-tetramethylpiperidine) (Table 1, entry 3). Fluorine based additives were then evaluated, and the conversion was found to be nearly complete using CsF with a 92% NMR yield (Table 1, entry 4). Acetates were also evaluated and a NMR yield of 89% was observed with NaOAc (Table 1, entry 5). A control experiment without additives was performed (Table 1, entry 6) revealing the crucial role of the latter in these iododesilylation reactions. Considering the slight yield differences between CsF and NaOAc and the less hygroscopic nature of NaOAc, the rest of this study was conducted with NaOAc.

Table 1. Iododesilylation reaction set-up



1a 1

Entry	Additive (Equiv.)	**1** ^{1}H NMR yield[a]
1	2,6-Lutidine (1.25)	30%
2	2,3-DiBr-5-Me-pyridine (1.25)	43%
3	TMP (1)	61%
4	CsF (1)	92%
5	NaOAc (1)	89%
6	-	1%

[a] ^{1}H NMR yields are reported using MTBE as an internal standard.

With a rapid iodination protocol established, we next attempted to apply this protocol in radio-iodination. To this end, [^{125}I]NIS was pre-formed *in situ* by reacting NCS (*N*-chlorosuccinimide) and [^{125}I]NaI (Scheme 3, Conditions A) in HFIP. After 15 min, phenyltrimethylsilane **1a** and a large excess of NaOAc were added. The formation of **[^{125}I]1** was observed with a radio-chemical conversion (RCC) of 20%. A direct impact on the RCC was observed by changing the addition order without pre-formation of [^{125}I]NIS (Scheme 3, Conditions B). Thus, a RCC of 62% was obtained with the following reagent addition order: substrate, NaOAc, NCS and finally [^{125}I]NaI.

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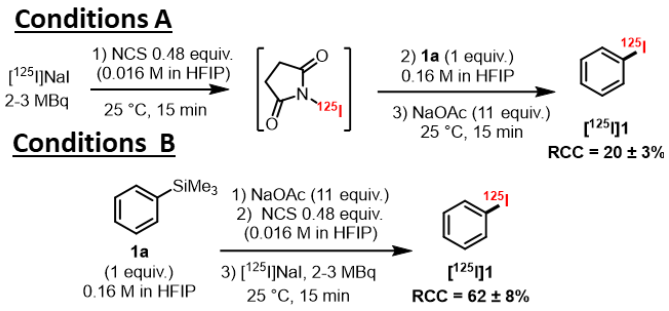
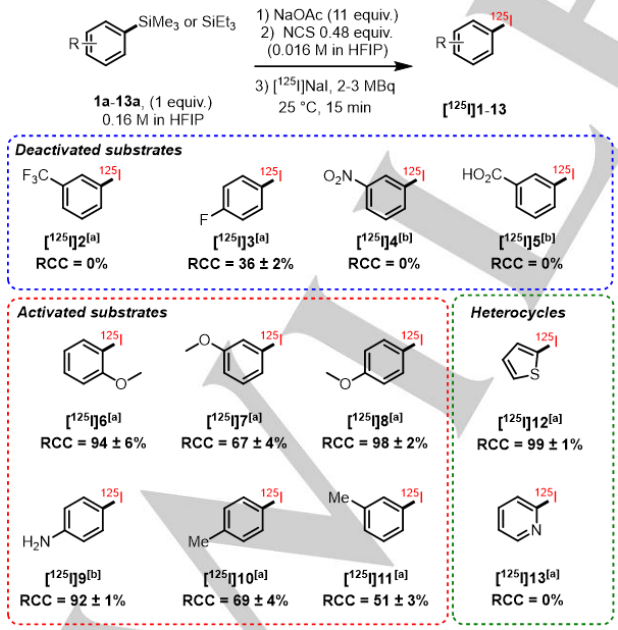


Scheme 3. Radio-iododesilylation set-up. Radiochemical conversions (RCC) are given n = 2 and were determined by HPLC (high pressure liquid chromatography) analysis using a radiodetector; **1a** = trimethylphenylsilane.

The radio-iodination scope was then evaluated from various organosilicon precursors (Scheme 4). Concerning the deactivated substrates, a RCC of 36% was found with trimethyl(4-fluorophenyl)silane **3a**. However, no radio-iodination was observed with substrates bearing strong deactivating groups such as trifluoromethyl, carboxylic acid or nitro. As expected, electron-rich substrates were found to be very reactive using these conditions. Indeed, with substrates bearing methoxy groups (**6a-8a),** nearly complete conversions were observed for the *ortho*- and *para*-isomers with 94% and 98% respectively. A RCC of 67% was detected with the *meta*-methoxy isomer and a RCC of 92% was found with the aniline derivative **9a**. With methyl groups in *para*- and *meta*- positions, **10** and **11** were formed with RCC of 69% and 51%. Investigation of heterocyclic substrates was performed from trimethyl(thiophen-2-yl)silane **12a** and 2-(trimethylsilyl)pyridine **13a**. 2-Iodothiophene **[^{125}I]12** was formed with a 99% RCC and no conversion was observed with 2-(trimethylsilyl)pyridine **13a**.



Scheme 4. Radio-iodination scope from organosilicon precursors. Radiochemical conversions (RCC) are given n = 2 and were determined by HPLC analysis using a radiodetector. [a] Starting from a trimethylsilane. [b] Starting from a triethylsilane.

The reaction was then investigated with organogermanium precursors (Scheme 5). Compared to silanes **1a** and **3a**, using phenyltriethylgermane **1b** and triethyl(4-fluorophenyl)germane **3b**, improved RCC of 97% and 98% were observed. RCCs of 58%, 28% and 66% respectively were obtained from arenes substituted in the *para* position with a chlorine **14b**, a bromine **15b** or an iodine **16b** atom. No conversion was observed starting from triethyl(2,6-dichlorophenyl)germane **17b**, probably due to steric hindrance, and nitro and trifluoromethyl derivatives **18b** and **19b** behaved as their silicon analogues affording no reaction. Almost full conversion was measured with the substrates bearing a methoxy group in **6b** and **8b** in *ortho*- and *para*-position giving a RCC of 96% and 99% respectively. Aniline derivative **9b** afforded **[^{125}I]9** with a RCC of 92%. The methyl substituted derivative **10b** was evaluated and gave a RCC of 93% while 3- and 4-*t*-butyl derivatives **20b** and **21b** showed RCCs of 90% and 97% respectively. Germane **22b** was also reactive with a RCC of 89% thus revealing the compatibility of carbon-carbon double bonds with this process. Polycyclic derivatives were also submitted to the radio-iodination and RCCs of 96%, 94% and 83%, were observed, respectively, from naphthalene **23b**, phenanthrene **24b** and 2-methoxynaphthalene **25b**. Concerning heterocycles, a 95% RCC was obtained from thiophene **12b** and no conversion was detected starting from pyridines **13b** and **26b**. Overall, the obtained RCCs were generally higher using organogermanes as radiolabelling precursors, the scope of the reaction is also larger with these latter. Moreover, comparison of the obtained radiochromatograms for similar compounds revealed a systematic difference between the reaction from organosilanes or -germanes (See SI for details). As opposed to the arylgermanes, where clean radiochromatograms were observed, radiochemical impurities were frequently seen for radio-iodination of aryl silanes.

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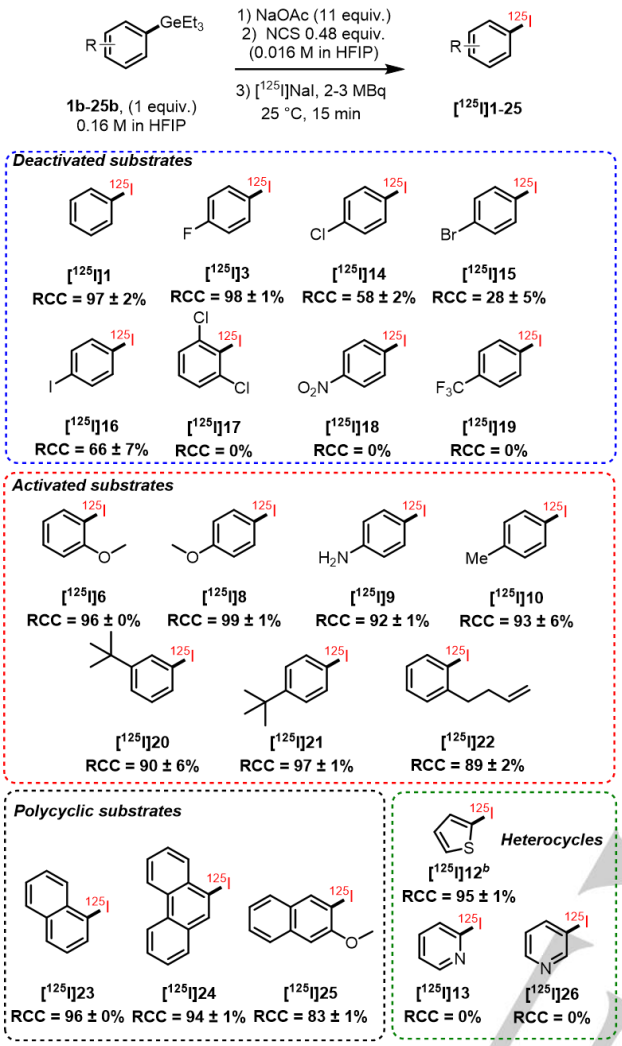
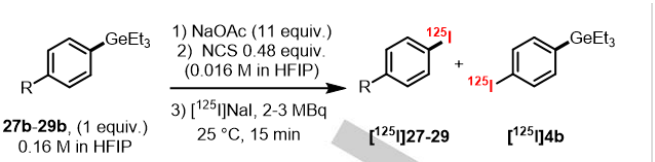


Scheme 5. Radio-iodination scope from organogermanium precursors. Radiochemical conversions (RCC) are given n = 2 and were determined by HPLC analysis using a radiodetector.

Further investigations to assess the selectivity of the labelling with arylgermane through an intramolecular competition with $SiMe_3$, $SnBu_3$ and Bpin groups were designed (Table 2). First a reaction starting from trimethyl[4-(triethylgermyl)phenyl]silane **27b** was performed and afforded radio-iodination almost exclusively at the germanium site. The formation of **[^{125}I]27** was observed with a RCC of 87%. However, a slight conversion into **[^{125}I]4b** was recorded with 3.5% RCC. Concerning triethyl[4-(tributylstannyl)phenyl]germane **28b**, the conversion into **[^{125}I]4b** was nearly complete and no trace of iododergermylation was observed. Finally, a reaction was performed to compare the reaction of germane and Bpin groups under these conditions as arylboronic esters are known to promote radio-iodination under similar conditions.[25] Interestingly, the radio-iodination occurred exclusively at the germanium site along with hydrolysis of the ester to give boronic acid **[^{125}I]29** in 98 % RCC.

Table 2. Radio-iodination selectivity

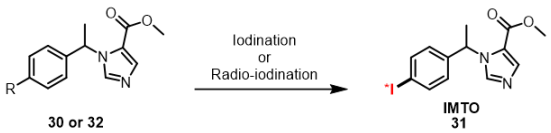


Starting material	[^{125}I]27-29 RCC[a]	[^{125}I]4b RCC[a]
27b R = $Si(Me)_3$	**[^{125}I]27** 87 ± 8%	3.5 ± 0.5%
28b R = $Sn(Bu)_3$	**[^{125}I]28** 0%	93 ± 0%
29b R = Bpin	**[^{125}I]29** 98 ± 1%[b]	0%

[a] Radiochemical conversions (RCC) are given n = 2 and were determined by HPLC analysis using a radiodetector.
[b] **[^{125}I]29** was integrally recovered as the 4-iodophenylboronic acid due to hydrolysis of the pinacol ester during the work-up. Bpin = pinacolborane

The potential for both organosilanes and organogermanes to become valuable radiochemical precursors in radio-iodination through IEH was then assessed (Table 3). To do so, iodination and radio-iodination of **IMTO 31**[60,61], an investigational radiotherapeutic and imaging agent, was evaluated from the corresponding organosilane **30** and organogermane **32**. Using **30**, the reaction was found to be efficient for iodination but inefficient for radio-iodination. Using **32**, both iodination and radio-iodination occurred. Key radiochemical efficiency indicators were determined through isolation and a RCY of 31% along with a RCP of 90% and a molar activity (A_m) greater than 0.68 GBq.µmol^{-1} were found (See SI for details). Beyond demonstrating that organogermane are valuable radiochemical precursors, these results show also that the latter can serve as a source of UV reference for radio-iodination, thus increasing synthetic convergence when it comes to labelling complex molecular substrates.

Table 3. (Radio-)iodination of IMTO through (radio-)iododesilylation and (radio-)iododegermylation.



Isotope	R = $SiMe_3$	R = $GeMe_3$
^{127}I (Yield)	56%[a]	73%[b]
^{125}I (RCC)	0%[c]	80% ± 8%[d]

[a] Performed by reacting **30** (0.16 M in HFIP) with NaOAC (1equiv.) and NIS (1.5 equiv.) at RT for 1 h.
[b] Performed by reacting **32** (0.16 M in HFIP) with NaOAC (1equiv.) and NIS (1.5 equiv.) at RT for 1 h.
[c] Performed from **30** using reactions conditions depicted in scheme 3 at 25 or 50 °C.
[d] Performed from **32** using reactions conditions depicted in scheme 4 at 50 °C. Radiochemical conversion (RCC) is given n = 2 and were determined by HPLC analysis using a radiodetector.

Radio-iododegermylation was evaluated in a clinically relevant context in an attempt to produce **MIBG 34**,[62,63] a radiotracer used daily in nuclear medicine facilities to detect or treat endocrine tumors (Scheme 6). After radioiodination,

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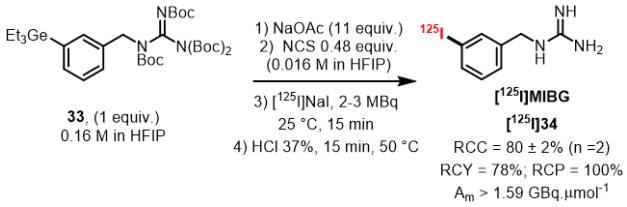
deprotection and isolation, a RCY of 78%, a RCP of 100% and a A_m greater than 1.59 GBq.μmol^{-1} were found (See SI for details). These results are in accordance with what is expected for a clinical application.



Scheme 6. (Radio-)iodination of MIBG through radio-iododegermylation.

Conclusion

We herein present a mild and operationally simple radio-iodination protocol for aryl silanes and germanes. The arylgermanes display greater reactivity and superiority in delivering the radio-iodinated products in terms of robustness, scope and radio-chemical yield as compared to the corresponding silanes. More importantly, when applied to molecular tracers, the base-mediated iodo-degermylation is a reliable tool, able to provide both the UV standard and the radio-iodinated scaffold with high radiochemical yield and molar activity. Combined with the low toxicity of arylgermanes and their straightforward access, from metalation, palladium catalyzed- or photoredox mediated-germylation,[64–70] we anticipate that the base-mediated radio-iododegermylation has the potential to be an alternative to radio-iododestannylation under clinical applications.

Experimental Section

General (chemistry)

All solvent and chemicals were used as purchased unless stated otherwise. All NMR spectra were recorded on a Bruker Avance III 400 spectrometer, a Varian V-NMRS 600 or a Varian V-NMRS 400 spectrometer. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in part per million (ppm). Coupling constants (*J*) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplets: s (singulet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). High resolution mass spectra (HRMS, m/z) were recorded on a Waters Acquity UPLC H-ClassXevo G2-XS Spectrometer (ESI), a Thermo Scientific LTQ Orbitrap XL (ESI) or an Finnigan MAT 95 (EI, 70 eV). Melting points of solids were measured on a Stuart Automatic Melting point SMP-50 apparatus. IR spectra were recorded on a Spectrum 100 spectrometer with an UATR Diamond/KRS-5 crystal with attenuated total reflectance (ATR) or on KBr Discs with a Perkin Elmer BX FT-IR. Flash column chromatography was performed over silica gel C60 (40-60 µm) or Rp-18 (50 µm) using eluent systems as described for each experiment. Unless otherwise described specified, all reagent were obtained from commercial suppliers. For the synthesis of arylgermane, Anhydrous and degassed THF (tetrahydrofurane), DCM (dichloromethane) and Et_2O were obtained using an Innovative Technology PS-MD-5 solvent purification system and solvents used in work-up and purification were distilled prior to use. Previously described compounds were obtained using known procedures (see SI for details).

Triethyl(3-nitrophenyl)silane (4a)

To a solution of 1-iodo-3-nitrobenzene (2.49 g, 10 mmol), LiCl (1.7 g, 40 mmol) and $Pd(OAc)_2$ (50 mg, 0.22 mmol) in dry NMP (1-methylpyrrolidin-2-one) (30 mL) under nitrogen, were added pyridine (2 mL, 25 mmol) and triethylsilane (4 mL, 25 mmol). After stirring 18 h at room temperature, the solution was quenched with water. The organic layer was extracted with EtOAc and the organic layer was washed with brine. The combined organic layer was dried under $MgSO_4$ and solvents were removed under *vacuum*. The crude was purified by SiO_2 column chromatography using cyclohexane/EtOAc (95:5) as eluent. The title product (470 mg, 1.98 mmol) was obtained as a colorless oil in 19% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31(dd, *J* = 2.5, 1.0 Hz, 1H), 8.19 (ddd, *J* = 8.2, 2.4, 1.1 Hz, 1 H), 7.79 (dt, *J* = 7.2, 1.1 Hz, 1 H), 7.52 (t, *J* = 7.7 Hz, 1 H) 1.04 – 0.93 (m, 9 H), 0.91 – 0.79 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.0, 140.6, 140.4, 128.8, 128.7, 123.8, 7.4 (3C), 3.3 (3C). HRMS/ESI calcd for $C_{12}H_{19}NO_2NaSi$ $[M+Na]^+$ 260.10773, found 260.s10728. IR (KBr, cm^{-1}) = 3063, 2956, 2913, 2876, 1604, 1525, 1463, 1416, 1380, 1347, 1266, 1238, 1011, 872, 720, 689.

3-Triethylsilylbenzoic acid (5a)

To a solution of 3-iodobenzoic acid (2.10 g, 8.5 mmol), LiCl (1.44 g, 32 mmol) and $Pd(OAc)_2$ (55 mg, 0.24 mmol) in dry NMP (342 mL) under nitrogen, were added pyridine (1.7 mL, 21.3 mmol) and triethylsilane (3.4 mL, 21.3 mmol). After stirring 18 h at room temperature, the solution was quenched with water. The organic layer was extracted with EtOAc and the organic layer was washed with brine. The combined organic layer was dried under $MgSO_4$ and solvents were removed under *vacuum*. The crude was purified by SiO_2 column chromatography using cyclohexane/EtOAc (98:2) as eluent. The title product (583 mg, 2.46 mmol) was obtained as a colorless oil in 29% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 8.10 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.73 (dt, *J* = 7.3 Hz, 1.3 Hz, 1H), 7.47 (dt *J* = 7.3, 1.3 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 1.02 – 0.93 (m, 9H), 0.89-0.79 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.5, 139.7, 138.4, 136.0, 130.7, 128.6, 127.9, 7.5 (3C), 3.4 (3C). HRMS (ESI) calcd for $C_{13}H_{19}O_2Si$ $[M-H]^-$ 235.1154, found 235.1157. IR (KBr, cm^{-1}) = 3438, 2955, 2937, 2911, 2875, 2731, 2658, 2549, 1693, 1573, 1458, 1262, 1107, 942, 846, 720, 689.

General procedure for the preparation of aryltriethylgermane

Triethylgermanium chloride (1.05 equiv.) and the corresponding aryl iodide or aryl bromide (3.0 mmol, 1.0 equiv.) were dissolved in anhydrous and degassed THF (0.2 M) under argon, *i*PrMgCl (1.2 equiv.) was added slowly and the reaction was stirred for 3 h at room temperature (ArI) or for 12 h at 60 °C (ArBr). The reaction was quenched by addition of aqueous solution of NH_4Cl (sat.), the organic phase was separated, and the aqueous phase was extracted with DCM (3x). The combined organic phases were dried with $MgSO_4$, the solvent was removed under reduced pressure and the crude product mixture was purified by silica column chromatography.

4-(Triethylgermyl)aniline (9b)

Triethylgermanium chloride (1001 µL, 6.0 mmol, 2.0 equiv.) and 4-iodoaniline (657 mg, 3.0 mmol, 1.0 equiv.) were dissolved in anhydrous and degassed THF (0.2 M) under argon, *i*PrMgCl (12.0 mmol, 4.0 equiv.) was added slowly and the reaction was stirred for 12 h at 60 °C. The reaction was quenched by addition of aqueous solution of NH_4Cl (sat.), the organic phase was separated, and the aqueous phase was extracted with DCM (3x). The combined organic phases were dried with $MgSO_4$, the solvent was removed under reduced pressure. The crude was purified by SiO_2 column chromatography using pentane/EtOAc 10:1 as eluents. The title product (456 mg, 1.80 mmol) was obtained as a colorless oil in 60% yield. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.22 (d, *J* = 7.9 Hz, 2H), 6.69 (d, *J* = 7.9 Hz, 2H), 3.64 (s, 2H), 1.05 (t, *J* = 7.8 Hz, 9H), 0.94 (q, *J* = 7.9 Hz, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 146.6, 135.1, 127.7, 115.1, 9.1, 4.4. HRMS (ESI) calculated for $C_{12}H_{22}{}^{74}GeN$: 254.0958 $[M+H]^+$, found:

254.0953. IR (neat, cm^{-1}) = 3455, 3355, 2951, 2872, 1601, 1499, 1460, 1424, 1274, 1182, 1089, 1016, 966, 816, 750, 691.

(2,6-Dichlorophenyl)triethylgermane (17b)

Starting from 1,3-dichloro-2-iodobenzene, using the general procedure for the preparation of aryltriethylgermane. The crude was purified by SiO_2 column chromatography using pentane as eluent. The title product (716 mg, 2.34 mmol) was obtained as a colorless oil in 78% yield. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.24 – 7.21 (m, 2H), 7.13 (dd, *J* = 8.5, 7.3 Hz, 1H), 1.27 (q, *J* = 7.8 Hz, 6H), 1.07 (t, *J* = 7.9 Hz, 9H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 142.2, 138.5, 130.3, 128.3, 9.3, 8.3. HRMS (APCI) calcluated for $C_{10}H_{13}{}^{74}GeCl_2$: 276.9606 $[M-Et]^+$, found: 276.9596. IR (neat, cm^{-1}) = 2952, 2872, 1551, 1459, 1410, 1379, 1240, 1175, 1137, 1009, 970, 767, 708.

Triethyl(4-nitrophenyl)germane (18b)

1-iodo-4-nitrobenzene (249 mg, 1.0 mmol, 1.0 equiv.) was added to a round bottom flask and dissolved in anhydrous and degassed THF (2 mL) under argon. PhLi (1.1 mmol, 1.1 equiv.) was added dropwise at -78 °C and the reaction was stirred for 30 min. Triethylgermanium chloride (184 µL, 1.1 mmol, 1.1 equiv.) was added and the mixture was stirred while warming to room temperature for 2 h. The reaction was quenched by addition of aqueous solution of NH_4Cl (sat.), the organic phase was separated and the aqueous phase was extracted with DCM (3x). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by SiO_2 column chromatography using pentane/EtOAc 20:1 as eluents. The title product (184 mg, 0.65 mmol) was obtained as a yellow oil in 65% yield. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 1.08 – 1.03 (m, 15H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 150.4, 148.4, 134.9, 122.4, 9.0, 4.3. HRMS (EI) calculated for $C_{12}H_{19}{}^{74}GeNO_2Na$: 306.0519 $[M+Na]^+$, found: 306.0514. IR (neat, cm^{-1}) = 2952, 2872, 2329, 2087, 1804, 1594, 1516, 1460, 1428, 1382, 1346, 1312, 1228, 1106, 1080, 1014, 967, 844, 737, 702.

(3-(Tert-butyl)phenyl)triethylgermane (20b)

Starting from 1-iodo-4-(tert-butyl)benzene, using the general procedure for the preparation of aryltriethylgermane. The crude was purified by SiO_2 column chromatography using hexane as eluent. The title product (963 mg, 2.2.65 mmol) was obtained as a colorless oil in 88% yield. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.47 (s, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.26 (m, 2H), 1.35 (s, 9H), 1.09 (t, *J* = 7.5 Hz, 9H), 1.00 (q, *J* = 7.7 Hz, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 150.2, 139.5, 131.2, 130.9, 127.6, 125.2, 34.8, 31.5, 9.1, 4.4. HRMS (APCI) calcluated for $C_{14}H_{23}{}^{74}Ge$: 265.1012 $[M-Et]^+$, found: 265.1006. IR (neat, cm^{-1}) = 2953, 2871, 1586, 1460, 1393, 1263, 1126, 1015, 966, 788, 701.

(4-(Tert-butyl)phenyl)triethylgermane (21b)

Starting from 1-iodo-4-(trifluoromethyl)benzene, using the general procedure for the preparation of aryltriethylgermane. The crude was purified by SiO_2 column chromatography using pentane as eluent. The title product (651 mg, 2.22 mmol) was obtained as a colorless oil in 74% yield. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.42 – 7.35 (m, 4H), 1.33 (s, 9H), 1.07 (t, J = 8.2 Hz, 9H), 1.01 – 0.96 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 51.0, 136.4, 133.9, 124.9, 34.7, 31.5, 9.1, 4.3. HRMS (EI) calculated for $C_{16}H_{28}{}^{74}Ge$: 294.1397 $[M]^+$, found: 294.1397. IR (neat, cm^{-1}) = 3016, 2946, 2328, 2897, 1456, 1384, 1088, 1014, 965, 794, 697.

3-(Triethylgermyl)pyridine (26b)

Triethylgermanium chloride was added to a solution of 3-bromopyridine (482 µL, 5.00 mmol, 1.0 equiv.) in anhydrous THF (0.3 m). After that under argon *i*PrMgCl·LiCl (4.6 ml, 6.00 mmol, 1.2 equiv.) was added dropwise and the obtained solution was stirred at room temperature for 40 min. Then the mixture was placed in preheated oil bath and stirred at 60 °C for 2 h. The reaction mixture was quenched with addition of water. The organic layer was separated and the aqueous layer was extracted with DCM (3x). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure. The title product was obtained after purification by column chromatography (20:1 *n*-pentane/EtOAc with 1% Et_3N) as a light brown oil (490.1 mg, 2.06 mmol, 41%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61-8.58 (m, 1H), 8.55-8.52 (m, 1H), 7.73-7.69 (m, 1H), 7.27-7.21 (m, 1H), 1.09-0.98 (m, 15H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.3, 149.4, 141.9, 135.0, 123.6, 8.9, 4.2. HRMS (ESI) calculated for $C_{11}H_{20}N^{74}Ge$: 240.0808 $[M+H]^+$, found: 240.0801. IR (KBr, cm^{-1}) = 2951, 2872, 1566, 1461, 1427, 1394, 1331, 1223, 1193, 1108, 1017, 968, 792, 707.

1-[4-(Trimethylgermyl)phenyl]ethan-1-ol

To a solution of 1-(4-bromophenyl)ethan-1-ol (194 mg, 1.00 mmol, 1.0 equiv.) in dry THF (5 mL) at -78 °C was added dropwise *n*-BuLi (2.4 M in hexanes, 0.83 mL, 2.00 mmol, 2.0 equiv.) under N_2. The resulting solution was stirred 1 h at -78 °C and Me_3GeCl (0.33 mL, 2.00 mmol, 2.0 equiv.) was added dropwise at -78 °C. The reaction mixture was allowed to warm up to 25 °C for 18 h. The solution was quenched with water. The aqueous layer was extracted with Et_2O and the organic layer was washed with brine. The combined organic layer was dried under $MgSO_4$ and solvents were removed under *vacuum*. The crude was purified by SiO_2 column chromatography using cyclohexane/EtOAc 95:5 with a gradient to 85:15 as eluents. The title product (122 mg, 0.51 mmol) was obtained as a colorless oil in 51% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 4.87 (q, *J* = 6.5 Hz, 1H), 1.51 (d, *J* = 6.5 Hz, 3H), 0.45 (s, 9H), signal corresponding to -OH is missing. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.0, 141.6, 133.2 (2C), 125.1 (2C), 70.3, 25.1, -1.7 (3C). HRMS (ESI) calcd for $C_{11}H_{17}{}^{74}Ge$ $[M-H_2O+H]^+$ 223.0542, found 223.0550.

Methyl 1-{1-[4-(trimethylgermyl)phenyl]ethyl}-1H-imidazole-5-carboxylate (32)

To a stirred solution of methyl *1H*-imidazole-5-carboxylate (339 mg, 1.42 mmol, 1 equiv.) and triphenylphosphine (163 mg, 1.29 mmol, 0.9 equiv.) in dry THF (3 mL) was added dropwise a solution of 1-[4-(trimethylgerman)phenyl]ethan-1-ol (441 mg, 1.68 mmol, 1.18 equiv.) in dry THF (3 mL) at -30 °C under N_2. Then a solution of DEAD (40% in toluene, 706 µL, 1.55 mmol, 1.1 equiv.) was added dropwise to the reaction mixture at -30 °C and the solution was allowed to warm up to 25 °C and was stirred for 30 min. Solvent was removed under *vacuum* and the residue was dissolved with Et_2O 1 h. The resulting solution was filtered through a pad of Celite with Et_2O. The filtrate was concentrated under *vacuum*. The crude was purified by SiO_2 column chromatography using cyclohexane/Et_2O 80:20 as eluent with a gradient to 75:25. The title product (143 mg, 0.41 mmol) was obtained as a yellow solid in 29% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (dd, *J* = 14.4, 1.1 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.34 (q, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 1.85 (d, *J* = 7.1 Hz, 3H), 0.36 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.7, 142.5, 141.0, 139.9, 138.2, 133.5 (2C), 125.8 (2C), 122.3, 55.3, 51.4, 22.2, -1.9 (3C). Melting point 119-121 °C**.** HRMS (ESI) calcd for $C_{16}H_{23}N_2O_2{}^{74}Ge$ $[M+H]^+$ 349.0971, found 349.0981. IR (KBr, cm^{-1}) = 3139, 3040, 2988, 2946, 2923, 2852, 1702, 1535, 1436, 1362, 1222, 1135, 820, 600.

1-Tert-butyl-3-iodobenzene (20)

To a solution of $NaNO_2$ (76 mg, 1.10 mmol) in H_2O (0.25 mL) was added dropwise a mixture of 3-tert-butylaniline (158 µL, 1.00 mmol) in H_2O (1.6 mL) and 12 N HCl (0.4 mL) below 5 °C. The mixture was stirred for 10 min. Then a solution of KI (250 mg, 1.50 mmol) in H_2O (0.4 mL) was added. The mixture was stirred at 50 °C for 1 h and at room temperature for 5 h. The aqueous solution was extracted with Et_2O twice and the organic layer was washed with brine. The combined organic layer was dried under

$MgSO_4$ and solvents were removed under *vacuum*. The crude was purified by SiO_2 column chromatography using pentane as eluent. The title product (143 mg, 0.55 mmol) was obtained as a colourless oil in 55% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.72 (t, *J* = 1.8 Hz, 1H), 7.52 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 7.35 (ddd, *J* = 7.9, 1.9, 1.0 Hz, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.9, 134.8, 134.7, 130.0, 124.8, 94.8, 34.9, 31.3 (3C). HRMS (ESI) calcd for $C_{10}H_{13}I$ $[M]^+$ 260.0062, found 260.0066.

General (radiochemistry)

Sodium [^{125}I]iodide was purchased from Perkin Elmer as non-carrier added [^{125}I]sodium iodide in 1x10^{-5}M NaOH. In each case, this was diluted in MeOH prior to use. HPLC analysis were performed with a Waters Alliance HPLC system equipped with an autosampler, a Water 2996 Photodiode Array UV-detector and LB 500 HERM GAMMA radiodetector. Radiochemical conversions are determined by integration of the observed peaks on the radio-chromatogramm. Identity of the radio-iodinated molecules was assessed by comparison of rentention times of standards on the UV-detector. The activities of [^{125}I]radiolabelled samples were determined using a radioisotope dose calibrator CRC-15R (Capintec) and standardized with a calibration source of ^{133}Ba (9.402 MBq from Eckert & Ziegler). All experiments involving radio-elements were performed in IMOGERE facilities.

General procedure for the radio-iodination of organo-silane or -germane precursors:

In a V-vial equipped with a stir bar were succesively added NaOAc (3 mg), a solution of organo-silane or -germane substrate (20 µL, 0.16 M in HFIP), *N*-chlorosuccinimide (95 µL, 0.016 M in HFIP) and an methanolic solution of [^{125}I]sodium iodide (5µL, 2-3 MBq). The reaction mixture was stirred for 15 minutes at 25 °C and quenched with a solution of sodium thiosulfate (200 µL, 0.05 M in water) and diluted with methanol (1100 µL). An aliquot was removed for analysis by radio-HPLC to assess the radiochemical conversion.

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RESEARCH ARTICLE

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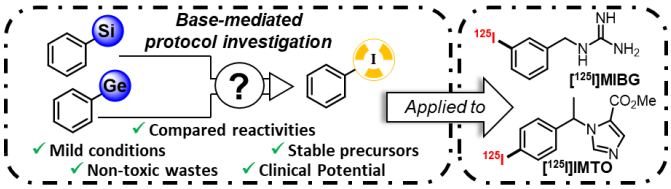

Discovery of a mild base mediated process allows radio-iodination to take place from either silane or germane. Comparison of the results shows that arylgermanes offers clinical potential as radio-iodination precursors. Proof of concept is demonstrated through the labelling of **[^{125}I]IMTO** and **[^{125}I]MIBG** thus offering an alternative to radio-iododestannylation processes using non-toxic precursors.

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