Improved production of ^{76}Br, ^{77}Br and ^{80m}Br via CoSe cyclotron targets and vertical dry distillation

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Supplementary tables, figures and methods

	Isotopic composition (%)					
	^{74}Se	^{76}Se	^{77}Se	^{78}Se	^{80}Se	^{82}Se
^{76}Se	< 0.05	99.8 ± 0.1	0.2 ± 0.1	< 0.05	< 0.05	< 0.05
^{77}Se	0.02	0.14	99.66	0.09	0.05	0.04
^{80}Se	0.01	0.03	0.02	0.01	99.9	0.02

Table S1. Isotopic abundances of enriched selenium target material

Preparation and characterization of cobalt selenide cyclotron targets

Cobalt selenide was formed by weighing an equal molar ratio of cobalt (110 – 130 mg) and selenium (150 – 170 mg) into a quartz test tube. The tube was flushed by repeated evacuation to <100 Pa, back filled with argon, and sealed under vacuum. Over 100 minutes, the upright tube was heated from room temperature to 1200 °C where it was held for one hour, then removed from the furnace and rapidly cooled by immersion in water.

CoSe cyclotron targets were formed by hot pressing CoSe into a pocketed (⌀ = 9.5 mm, 1 mm deep) niobium disc (⌀ = 19 mm, 2 mm thick) using the vertical furnace assembly shown in Figure 1. The Nb disc, a ~250 mg CoSe pellet, and a boron nitride (BN) tamper were placed at the bottom of the flat-bottomed quartz tube (Fig 1, left) and flushed with argon through the assembly gas inlet. The assembled quartz tube was then lowered into a preheated vertical tube furnace at 1075 – 1100 °C for 5 minutes and flattened by loosening the outlet compression fitting and applying <0.1 MPa of pressure to the BN tamper with the bell-bottomed inner quartz tube. The CoSe target was rapidly cooled by lifting the assembly from inside the furnace and immediately immersing the water. This process was repeated using BN tampers of various configurations until CoSe was uniform and well adhered in the pocket of the niobium disc. CoSe that wetted the face of the niobium disc outside the pocket was removed using a razor blade and reclaimed. The niobium disc face was then polished using fine grit sandpaper, creating a suitable surface for an o-ring seal. Photographs depicting the stepwise process of CoSe cyclotron target formation are shown in Figure S1. This process resulted in 60 ± 10% of initial CoSe melting into the Nb pocket, with a 22 ± 4% of CoSe reclaimed as powder and a loss of 16 ± 4% CoSe (n=2). The bulk of this loss was due to removal via scraping and sanding of CoSe overflow from the pocket in the target disc.

Figure S1. Photographs of Co^{77}Se cyclotron target formation process. Top: before heating. Middle left: after 15 minutes at 1075 °C, flat BN press. Middle right: after 5 minutes at 1100 °C, tamped BN press. Bottom: after scraping and sanding.

The X-ray diffraction data collected on CoSe cyclotron targets includes peaks at 33.26°, 44.87°, 61.66°, 69.68°, 82.26° in good agreement with International Centre for Diffraction Data (ICDD) Powder Diffraction File (PDF) number 04-006-8806 for hexagonal Co$_{0.85}$Se [Zhan *et al.* Synthesis of nanocrystalline cobalt selenide in nonaqueous solvent *Solid State Chem* 2000;152:537–539], as shown in Figure S2. These data indicate successful formation of the desired CoSe intermetallic species.

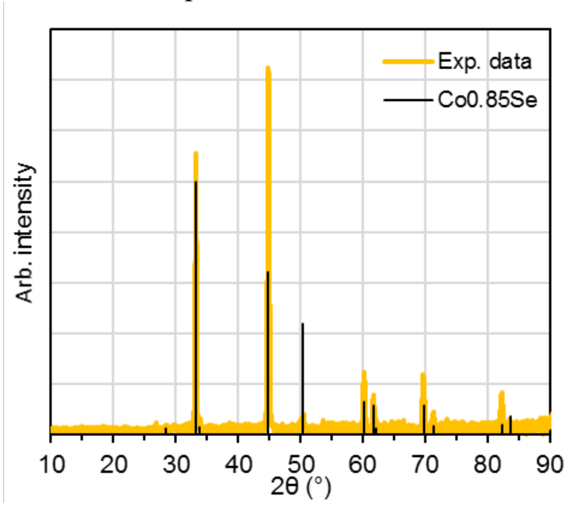

Figure S2. X-ray diffraction pattern of prepared CoSe cyclotron target (yellow) and hexagonal $Co_{0.85}Se$ standard (black).

Cyclotron irradiation of CoSe targets

To test the hypothesis that the proton beam spot was larger than the 9.5 mm $Co^{77}Se$ target diameter, stacks of thin (18 ± 3 µm) copper foils were masked using a 3-mm-thick aluminum disk with a 9.5 mm diameter aperture and irradiated with 1.5 µA·h of 12 MeV or 16 MeV protons. The HPGe quantified yields of ^{62}Zn, ^{63}Zn, and ^{65}Zn in the foils and measured cross sections [Hermanne A, Ignatyuk AV, Capote R *et al.* Reference Cross Sections for Charged-particle Monitor Reactions. *Nucl Data Sheets.* 2018;148:338–382.] were used to calculate the proton energy and intensity passing through the 9.5 mm aperture. This foil-measured proton intensity was compared with the nominal proton intensity recorded by the PETtrace control system, which includes stray beam impinging on the outer diameters of the target and degrader assembly. Results indicate a significant portion (~60% at 12 MeV and ~40% at 16 MeV) of the nominally measured proton intensity is *not* incident to the 9.5 mm diameter CoSe target (Table S2). Accounting for beam losses to degrader and target apertures, the measured ^{77}Br yields were in good agreement with theoretical yields calculated from measured cross sections [Hassan HE, Qaim SM, Shubin Yu, *et al.* Experimental studies and nuclear model calculations on proton-induced reactions on natSe, ^{76}Se and ^{77}Se with particular reference to the production of the medically interesting radionuclides ^{76}Br and ^{77}Br. *Appl Radiat Isot.* 2004;60:899–909.].

nominal E_p (MeV)	Measured E_p (MeV)	Percent nominal current
12	13 ± 1	40% ± 10%
16	16 ± 1	59% ± 8%

Table S2. Experimentally measured proton energy and percent of nominal proton current impinging upon 9.5 mm diameter CoSe targets.

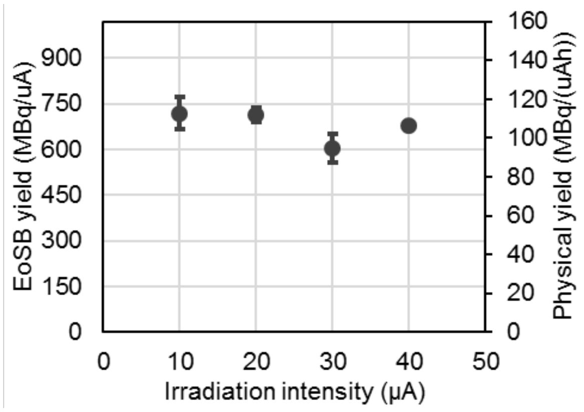

Figure S3. Bromine-80m production yield from 16 MeV proton irradiation of $Co^{80}Se$ at various intensities, reported both as end of saturated bombardment (EoSB, MBq/µA) and physical (MBq/(µA·h)) yields [Otuka and Takács Definitions of radioisotope thick target yields. *Radiochim Acta* 2015;103:1–6].

Radiochemical isolation of cyclotron produced radiobromine

Radiobromine was isolated from irradiated CoSe targets by thermochromatographic distillation using the furnace assembly shown in Figure 1. Following irradiation, the CoSe target was removed from the QIS transfer capsule, dried, placed in the flat-bottomed quartz tube, sealed inside the assembly, and flushed with 50 mL/min argon flow. The quartz tube was then lowered into the tube furnace preheated to 1050 °C. Collimated detectors monitored the radioactivity in the CoSe target and the initial H_2O trap. After 5 – 15 minutes of heating, the quartz tube was lifted from the furnace and immediately immersed in water, rapidly cooling the CoSe target. Argon flow continued while the assembly thermally cooled for 5 – 10 minutes. The assembly was allowed to come to atmospheric pressure and through manipulation of the 3-way valve, a total of 1 – 10 mL of warm water in five aliquots was used to rinse the top ~4 cm of the quartz outlet tube and the PTFE outlet line into the H_2O trap. Collected rinse and trap water was passed through a prepared QMA light cartridge, trapping the radiobromide, which was then eluted with 700 µL of 20 mM K_2SO_4 in 1:1::MeCN:H_2O.

Isolation of radiobromine from proton irradiated CoSe was readily accomplished by dry distillation at 1050 °C in the vertical furnace assembly shown in Figure 1. Typical traces of the detectors collimated on the CoSe target (Fig. 1, left) and H_2O trap (Fig. 1, right) are shown in Figure 4. Following the lowering of the assembly into the preheated furnace, radiobromine distilled from the CoSe in 5 – 6 minutes. Some non-bromine radioactivity remained in the CoSe target, including ^{93m}Mo and ^{58}Co, as shown in Fig. 4a, black line. The CoSe target, still encapsulated within the quartz tube, was then removed from the furnace and cooled in water for 10 – 15 minutes with Ar flow (Fig. 4b). During cooling, migration of radiobromine was observed through a continuous increase in H_2O trap detector radiation signal. After cooling, argon flow was halted, assembly vented, and quartz outlet tube and the PTFE outlet line rinsed with warm water into the initial H_2O trap, moving radiobromine into the H_2O trap (Fig. 4c). After rinsing, the water contained in the H_2O trap was passed through a prepared QMA light cartridge with Ar back pressure (Fig. 4d). Radiobromide was reclaimed from the QMA cartridge by slowly eluting with 700 µL of 20 mM K_2SO_4 or 0.1 M NH_4OH in 1:1::CH_3CN:H_2O.

Radiochemical labeling using ^{77}Br

Radiochemical quality of the [^{77}Br]bromide in 20 mM K_2SO_4 was evaluated through the reaction shown in Figure 3 by using 1 µmole pre-KX1-Bpin with varying solvent volume and composition, K_2SO_4 burden, and temperature. Reactions products were purified by diluting in 15 mL water, loading on a prepared C18 light cartridge, rinsing with 10 mL water, and eluting crude product in 700 µL ethanol. Following a 1:1 dilution with water, the product was purified by preparative HPLC (Kinetix XB-C18, 5 µm, 100 Å, 10x250 mm, 4 mL/min 40:60 :: MeCN:0.1 M ammonium formate, pH 4.5), followed by a final C18 light cartridge purification to obtain product in a small volume ethanol solution. Radiochemical conversion was determined by dose calibrator measurement of purified fractions. Stable iodinated KX1 was used as a standard to estimate the mass / 254 nm absorbance calibration curve for ^{77}Br-labeled compound.

	Reaction solvent		pre-KX1-Bpin (μmol)	Cu(py)$_4$(OTf)$_2$ (μmol)	Lig (μmol)	K$_2$SO$_4$ (μmol)	NH$_4$OH (μmol) *	Temp (℃)	Rxn time (min)	% lost in drydown	% of QMA elute	Time after distillation (d)	**RCC (%)**
	volume (μL)	composition											
{1}	70	11:2:1 ::: MeCN:MeOH:H$_2$O	1	0.5	0.5	0.2	0	20	60	n/a	2%	0	**95%**
{2}	110	7.5:1:2.5 ::: MeCN:MeOH:H$_2$O	1	0.5	0.5	1.0	0	20	90	n/a	12%	0	**16%**
{3}	160	10:1:50 ::: MeCN:MeOH:H$_2$O	1	0.5	0.5	1.9	0	20	110	n/a	24%	0	**4.7%**
{4}	65	8:2:1 ::: MeCN:MeOH:H$_2$O	1	0.5	0.5	1.0	0	20	45	<1%	12%	2	**26%**
{5}	140	30:1 :: DMSO:H$_2$O	1	0.5	0	1.5	0	80	45	n/a	19%	3	**31%**
{6}	115	3:1 :: MeOH:H$_2$O	1	0.5	0.5	0	11	45	20	n/a	27%	1	**37%**
{7}	85	MeOH	1	0.5	0.5	0	11	45	20	n/a	27%	3	**80%**
{8}	70	MeOH	1	0.5	0.5	0	15	20	60	7%	38%	0	**89%**
{9}	70	MeOH	1	0.5	0.5	0	25	20	60	6%	62%	8	**11%**
{10}	70	MeOH	1	0.5	0.5	0	40	20	60	11%	100%	0	**27%**
{11}	60	MeOH	1	0.5	0.5	0	25	20	65	4.3%	63%	1**	**47%**
{12}	60	MeOH	1	0.5	0.5	0	15	20	60	7.3%	37%	1**	**65%**

*Assuming no NH$_4$OH loss during drydown. **NH$_4{}^{77}$Br immediately dried down, then left as dry salts for 1 day.

Table S3. Radiochemical reaction conditions and radiochemical conversion (RCC) results of the reaction of [^{77}Br]bromide in a copper-mediated aryl boronic ester bromination.

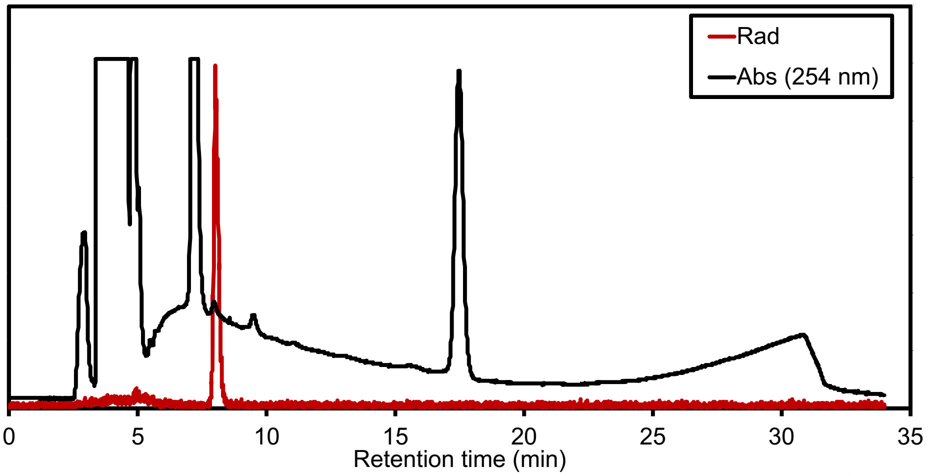

Figure S4. Preparative HPLC trace of ^{77}Br-PARPi using Kinetix XB-C18, 5 μm, 100 Å, 10x250 mm column and 4 mL/min 40:60 :: MeCN:0.1 M ammonium formate, pH 4.5.