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## Fast and easy reactor-based production of copper-64 with high molar activities using recoil chemistry

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**Reactor-based production of medically relevant  $^{64}\text{Cu}$  is only possible using recoil chemistry. We report highly soluble *tert*-butyl copper(II) phthalocyanine as the target material. This enables efficient  $^{64}\text{Cu}$  recovery through liquid–liquid extraction after neutron capture. The automatable process allows reuse of the target material and achieves a molar activity of 950 MBq  $\mu\text{mol}^{-1}$ .**

The interest in copper-based radiopharmaceuticals has increased in the past years due to the variety of copper isotopes suitable for theranostic applications. Among the copper isotopes of interest,  $^{64}\text{Cu}$  has a medium half-life of 12.7 h and decays either by emission of a  $\beta^-$  particle (38.5%) to  $^{64}\text{Zn}$  or *via* electron capture (44%) or emission of a  $\beta^+$  particle (17.5%) to  $^{64}\text{Ni}$ . It finds application in both positron emission tomography (PET) and molecular radiotherapy.<sup>1,2</sup> Copper-64-based radiopharmaceuticals are regularly studied in clinical trials (*e.g.*, [ $^{64}\text{Cu}$ ]Cu-ATSM for hypoxia in tumor tissue) and have even found their place in routine clinical applications for neuroendocrine tumors (NETs) with the FDA approval of [ $^{64}\text{Cu}$ ]Cu-DOTATATE in 2020.<sup>3–6</sup> Moreover, [ $^{64}\text{Cu}$ ]CuCl<sub>2</sub> itself has been studied for imaging of different types of cancer.<sup>7</sup> Due to their prolonged half-life,  $^{64}\text{Cu}$ -labeled antibodies are studied as well.<sup>8</sup>

Copper-64 can be produced in cyclotrons *via* proton-induced reactions or in nuclear reactors *via* neutron capture. Currently, it is produced mostly *via* the  $^{64}\text{Ni}(\text{p},\text{n})^{64}\text{Cu}$  nuclear reaction in biomedical cyclotrons using enriched  $^{64}\text{Ni}$  electroplated on a gold or rhodium solid target.<sup>9–11</sup> This route is applied routinely in several countries<sup>10–13</sup> and yields non-carrier-added  $^{64}\text{Cu}$  in high quantity and radionuclidic purity.<sup>11,14</sup> Nevertheless, the use of highly enriched  $^{64}\text{Ni}$  (natural abundance: 0.9%) and limited availability of cyclo-

trons with adequate solid target systems restrict the production of  $^{64}\text{Cu}$ .

Neutron capture offers two possible production routes for  $^{64}\text{Cu}$  *via* the nuclear reactions of  $^{63}\text{Cu}(\text{n},\gamma)^{64}\text{Cu}$  or  $^{64}\text{Zn}(\text{n},\text{p})^{64}\text{Cu}$  using thermal or fast neutrons, respectively, whereas only the latter one offers access to non-carrier-added  $^{64}\text{Cu}$ . Non-carrier-added isotopes are characterized by high molar activities, an important factor in radiopharmaceutical sciences.<sup>15,16</sup> The production of  $^{64}\text{Cu}$  *via* the  $^{63}\text{Cu}(\text{n},\gamma)^{64}\text{Cu}$  route using thermal neutrons has its limitations due to the chemical identity of  $^{63}\text{Cu}$  and  $^{64}\text{Cu}$  and therefore the low molar activity of  $^{64}\text{Cu}$ .

Szilárd–Chalmers reactions are a possible way to increase the molar activity of  $^{64}\text{Cu}$  produced from  $^{63}\text{Cu}$ . The recoil energy of the emitted prompt gamma photon exceeds that of chemical bonds, causing the activated nucleus to be released in a chemically distinct form from the target material. This allows for chemical separation and enrichment of the product nucleus and, therefore, the achievement of higher molar activities. Key parameters in this process include the enrichment factor and extraction efficiency. The enrichment factor is defined as the ratio between the calculated molar activity before work-up and the molar activity achieved afterward, with values up to 1000 required for practical applications. Extraction efficiency, which represents the proportion of free radioisotope recovered, should exceed 50% to be considered viable.<sup>17</sup>

During neutron irradiation (typically close to or in the center of a nuclear reactor core), the target material is exposed to high  $\gamma$ -radiation and temperatures. This limits the choice of target materials mostly to inorganic salts or thermally highly stable complexes. Phthalocyanines have long been known as suitable targets due to their high stability and complexation with various metals.<sup>18</sup> Copper(II) phthalocyanine (CuPc) complexes are being investigated for the production of enriched  $^{64}\text{Cu}$ , but they lack in their cumbersome work-up, as CuPc is only soluble in concentrated sulfuric acid, making work-up based on liquid–liquid extraction impossible.<sup>19–21</sup> Ion

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exchange-based separation methods yield  $^{64}\text{Cu}$  with a molar activity of  $625 \text{ kBq } \mu\text{mol}^{-1}$ .<sup>19–22</sup> It was attempted to simplify the work-up using a water-soluble CuPc derivative, octacarboxyphthalocyanato copper(II), and separation of  $^{64}\text{Cu}$  by extraction with an oxine solution in chloroform. This, however, resulted in a very low molar activity of  $25 \text{ kBq } \mu\text{mol}^{-1}$ .<sup>23</sup>

We identified *tert*-butyl copper(II) phthalocyanine (*t*Bu-CuPc) as highly soluble in organic solvents, with a solubility of  $93 \text{ g L}^{-1}$  in toluene, enabling fast, easily automatable liquid-liquid extraction without the need for hazardous sulfuric acid. *t*Bu-CuPc is readily available from commercial suppliers or can be synthesized from inexpensive starting materials, 4-*tert*-butylphthalic anhydride and urea.<sup>24</sup> Its high solubility allows efficient extraction of free  $^{64}\text{Cu}$  from the target material using diluted acids, yielding  $[^{64}\text{Cu}]\text{CuCl}_2$  in a ready-to-use aqueous solution. Following neutron capture in a research reactor, the target was dissolved in toluene, and free  $^{64}\text{Cu}$  was extracted with diluted hydrochloric acid (see Fig. 1). To reduce radiation exposure and explore semi-automation, all steps were performed using interconnected vials. After toluene removal and flash chromatography purification, the target material *t*Bu-CuPc can be reused without performance loss.

Synthesis of the target material was straightforward from 4-*tert*-butylphthalic anhydride and urea under catalysis of ammonium heptamolybdate in a microwave reactor at  $180^\circ\text{C}$  for 10 minutes without solvent. Purification was performed using normal phase (NP) chromatography and ethyl acetate/petroleum ether after extraction with diluted hydrochloric acid

to remove unreacted inorganic copper. The purchased target material was used without further purification. The typical production process started from the preparation of the target by weighing *t*Bu-CuPc (25–35 mg) in a plastic vial or quartz glass tube. The latter one was sealed using a glass-blowing torch after careful removal of any remaining target material on the top edges. Irradiation experiments were carried out in a TRIGA Mark II research reactor at the lateral (plastic vial) or central (quartz glass tube) irradiation position for up to 8 h at 250 kW. The lateral irradiation position comprises a dry irradiation tube suitable for non-sealed plastic vials, whereas the central irradiation position requires samples sealed in quartz glass as the sample is placed directly in the reactor tank at a wet irradiation position. The irradiated samples were allowed to rest for at least one hour to minimize background radiation from the short-lived co-produced  $^{66}\text{Cu}$  ( $t_{1/2} = 5.1 \text{ min}$ ).

After decay of  $^{66}\text{Cu}$ , the target material was dissolved in toluene (25–40 mL) and transferred into a separation funnel equipped with two tubes, one for ventilation and one leading to a separate vial. The extraction medium (4–7 mL of 0.8% hydrochloric acid) was added and thoroughly mixed for 30 seconds. After separation of the layers, the aqueous layer containing extracted  $^{64}\text{Cu}$  was transferred to the connected empty vial under reduced pressure using a syringe connected to the vial. The extraction was repeated twice and samples from the organic and aqueous phases were taken after each extraction step. The total time from the end of irradiation until the first extraction took 1.5 hours.

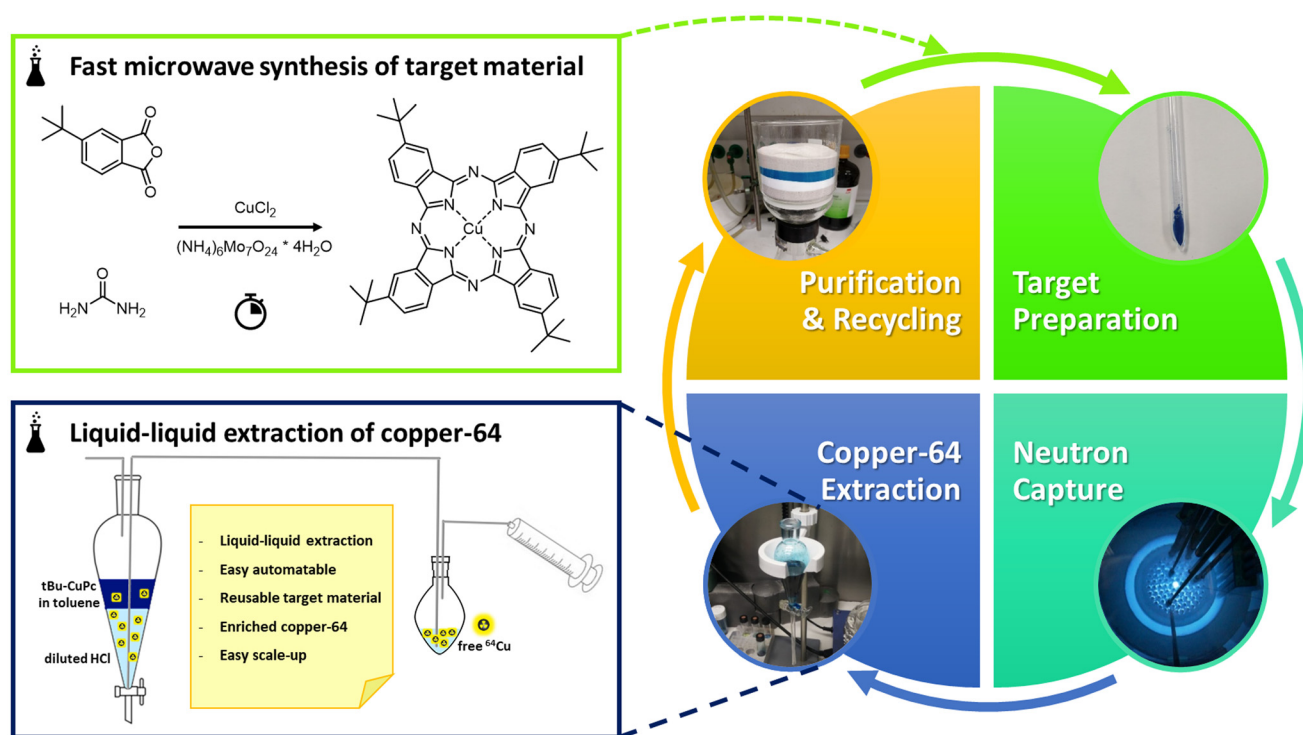


Fig. 1 Schematic representation of the  $^{64}\text{Cu}$  production cycle, including the fast and easy synthesis of the target material *t*Bu-CuPc and the setup of the extraction process.



The organic samples were analyzed using radio-thin layer chromatography (radio-TLC) for the determination of free  $^{64}\text{Cu}$  in the organic phase (see Fig. 2) before extraction. Aqueous samples were used to determine the activity and total copper content using a dose calibrator and inductively coupled plasma optical emission spectroscopy (ICP-OES) measurements, respectively. We investigated our approach towards parameters depending on the target material (purchased *vs.* synthesized), irradiation position (central *vs.* lateral) and recycling of the target material. Furthermore, we optimized the extraction process and analyzed the in-house synthesized target material towards the possible formation of the unwanted side product *tert*-butyl molybdenum(IV) oxophthalocyanine (*t*Bu-MoOPc).

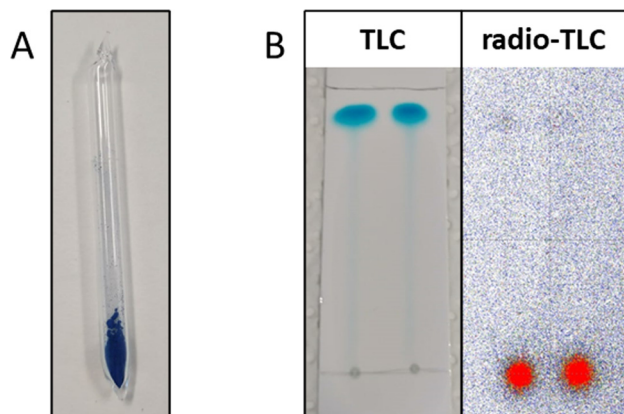
Due to the use of ammonium heptamolybdate as a catalyst in the synthesis of *t*Bu-CuPc, the formation of *t*Bu-MoOPc as a side product is possible. Neutron activation analysis of the in-house synthesized material showed no formation of *t*Bu-MoOPc during microwave synthesis, as no  $^{99}\text{Mo}$  ( $E_\gamma = 140$  keV) was detectable. Radio-TLC of the irradiated target material dissolved in toluene showed 97% of free copper-64 ( $R_f = 0$ ) and only 3% of  $^{64}\text{Cu}$  bound to the target material ( $R_f = 1$ ). This indicates a very low retention of  $^{64}\text{Cu}$ , which is favorable for high activity production of  $^{64}\text{Cu}$ .

A comparison between the purchased and in-house synthesized *t*Bu-CuPc revealed differences when the purchased material was used without purification prior to irradiation. The non-purified commercial *t*Bu-CuPc exhibited lower enrichment factors, extraction efficiency, and molar activity, likely due to its stated purity of only 97%. However, purification of the purchased material through extraction with hydrochloric acid and flash chromatography before irradiation resulted in performances comparable to those of the in-house synthesized material. Furthermore, the target material was reusable across several production cycles when purified *via* flash chromatography between cycles. The purification step in-between cycles guarantees no decrease in the enrichment factor, extraction efficiency or molar activity.

A comparison between the irradiation positions showed the central position resulting in higher activities for similar target sizes, due to its fivefold higher neutron flux compared to the lateral irradiation position. However, a higher enrichment factor ( $>1200$ ), extraction efficiency ( $>59\%$ ) and molar activity ( $>950$  MBq  $\mu\text{mol}^{-1}$ ) could be achieved at the lateral irradiation position, whereas at the central irradiation position, 276, 42.8% and 785 MBq  $\mu\text{mol}^{-1}$  of enrichment factor, extraction efficiency and molar activity, respectively, were obtained (see Table 1). This difference is most likely due to the increased radiolysis of the target material in the center of the reactor as the  $\gamma$ -radiation dose is higher at the lateral position.<sup>25</sup> The influence of the  $\gamma$ -radiation dose on the Szilárd–Chalmers production of  $^{64}\text{Cu}$  was investigated intensively recently, and a decrease in the molar activity was observed with a higher  $\gamma$ -radiation dose during neutron capture.<sup>22</sup> In the second extraction step, 28% of the total activity could be additionally extracted with lower molar activity, independent of the irradiation position. Furthermore, with higher extraction volumes, an increase in the extraction efficiency was observed.

We successfully developed a fast and efficient  $^{64}\text{Cu}$  production method based on the Szilárd–Chalmers effect, using highly soluble *tert*-butyl copper(II) phthalocyanine. Our process is easily automatable and the target material is reusable without losses. This makes our process highly suitable for routine  $^{64}\text{Cu}$  production, especially when there is no suitable cyclotron available. Enrichment factors up to 1200 and molar activities exceeding 950 MBq  $\mu\text{mol}^{-1}$  were achieved, both meeting practical requirements. With conventional cyclotron-based  $^{64}\text{Cu}$  production, higher activities with about an order of magnitude higher molar activities can be obtained. Both can be further improved by using enriched [ $^{63}\text{Cu}$ ]CuCl<sub>2</sub> for the synthesis of [ $^{63}\text{Cu}$ ] *t*Bu-CuPc and irradiation at high flux reactors, potentially achieving three orders of magnitude more copper-64 using similar target size and irradiation time.

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**Fig. 2** (A) Target material *t*Bu-CuPc sealed in a quartz glass tube before irradiation at the central irradiation position. (B) TLC (left) and radio-TLC (right) of the organic phase performed directly after irradiation of the target material showing 97% of free  $^{64}\text{Cu}$  in the origin and 3% of  $^{64}\text{Cu}$  activity remaining in the target material.

**Table 1** Comparison of the irradiation results at the lateral and central irradiation positions including the achieved enrichment factors, extraction efficiencies and molar activities of the first extracts. The achieved molar activity using the lateral irradiation position was higher, most likely due to the higher  $\gamma$ -radiation background in the centre of the reactor, leading to increased decomposition of the target material

Irradiation position	Lateral	Central
Neutron flux $\theta$ [ $\text{cm}^{-2} \text{s}^{-1}$ ]	$2 \times 10^{12}$	$10^{13}$
Target size [mg]	24	39
Capsule material	Plastic	Quartz glass
Irradiation time [hh:mm]	08:00	07:15
Activity @EOI [MBq]	25.1	405.0
$V$ (toluene) [mL]	25	40
$V$ (HCl) [mL]	4	7
Enrichment factor [%]	1202	276
Extraction efficiency [%]	59.6	42.8
Molar activity [MBq $\mu\text{mol}^{-1}$ ]	953	785



## Conflicts of interest

VR and CD hold IP (patent number AT525191) on parts of this work.

## Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information containing synthetic details, work-up and recycling procedure is available. See DOI: <https://doi.org/10.1039/d5dt02046h>.

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