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High yield [^{125}I]iodide-labeling of iodinated carboranes by palladium-catalyzed isotopic exchange

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Dedicated to Professor M.F. Hawthorne on the occasion of his 75th birthday

Abstract

We have recently shown the feasibility of palladium-catalyzed isotopic exchange between [^{125}I]iodide and 2-iodo-*para*-carborane. In this work we have modified the methodology and extended its application to a wider range of iodinated carboranes. Thus, by using Herrmann's catalyst in toluene at 100 °C, 2-I-*p*-, 3-I-*o*-, 9-I-*o*-, 9-I-*m*-carborane, 1-phenyl-3-I-*o*-carborane and 1,2-diphenyl-3-I-*o*-carborane have been radiolabeled with ^{125}iodine in high to excellent yields.

Keywords: Isotopic exchange; Iodinated carboranes; [^{125}I]iodide; Labeling; Palladium; Catalyst

1. Introduction

There is a growing interest in the labeling of polyhedral boron compounds (PBC) such as carboranes and borate anions with halogens for biomedical applications such as in pharmacokinetic studies of boron compounds for boron neutron capture therapy. This area has recently been reviewed; see Tolmachev and Sjöberg and references therein [1]. Radio-halogenation of negatively charged PBC's using oxidative conditions is a well-known procedure. Unfortunately this method is less applicable to *closo*-carboranes.

Recently Grushin and co-workers [2] reported bromination of 9-I-*closo*-carborane by palladium-catalyzed nucleophilic substitution. We have previously demonstrated [3] that radioiodination of 2-I-*p*-carborane by a palladium-catalyzed isotopic exchange reaction is possible and that the labeling reaction proceeds cleanly and results in high yield.

In this study we describe a broadening of the scope of this labeling reaction and in order to create a more general reaction, some major experimental changes had to be implemented. The compounds investigated (Scheme 1) are 2-I-*p*-(**1**), 3-I-*o*-(**2**), 9-I-*o*-(**3**), 9-I-*m*-carborane (**4**), 1-phenyl-3-I-*o*-carborane (**5**) and 1,2-diphenyl-3-I-*o*-carborane (**6**).

Radioioidination of **1**, **3**, and **4**, via halogen exchange, has previously been reported by Stanko and Iroshnikova in a conference proceeding from 1970 [4].

2. Results and discussion

By using Herrmann's catalyst (HC) (Scheme 1) in toluene, we have found a very efficient and stable catalytic system. All experiments were performed at 100 °C under argon and the obtained radiolabeling yield for all non-C-substituted iodinated carboranes (**1**–**4**) exceeded 90% after 5 min (Fig. 1). Using the parent iodinated carboranes (**1**–**4**) as substrates the catalytic system is stable and no indication of palladium precipitation could be seen.

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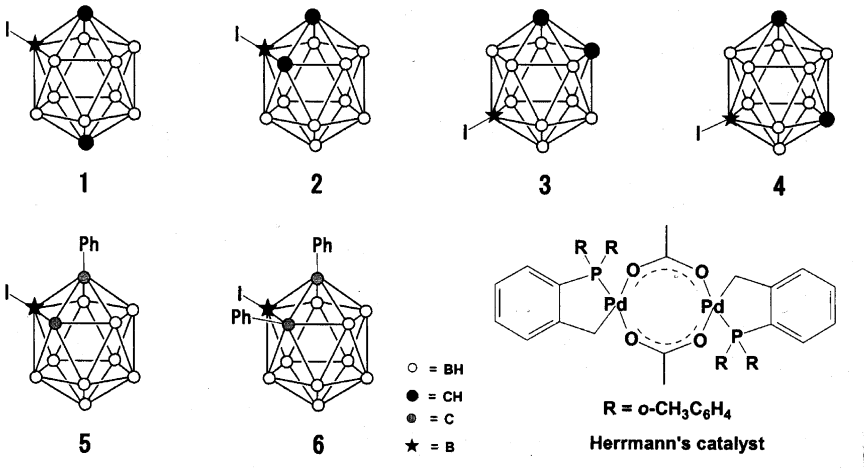


Scheme 1.

A representative TLC-chromatogram, showing the radiolabeling of 3-iodo-*ortho*-carborane (**2**) after 5 min, is shown in Fig. 2. The small peak at 0 ($R_f = 0.0$) corresponds to non-labeled [^{125}I]-iodide, and the peak at $R_f = 0.7$ corresponds to the labeled 3-[^{125}I]iodo-*o*-carborane.

In separate blank experiments, either the iodinated carborane or the HC was excluded. As expected, in those experiments no [^{125}I]-iodinated-carborane (*ortho*, *meta* or *para*) was detected.

Our previously reported [3] catalytic system [Pd(dba)$_3$/dppb; tris(dibenzylideneacetone)-dipalladium/1,4-*bis*-(diphenylphosphino)-butane] for this type of reaction required stabilization by a quaternary ammonium salt, tetra-*n*-butyl ammonium hydrogen sulphate (Q-HSO_4^-) for efficient labeling of the 2-I-*p*-carborane (**1**). However, under the present modified reaction conditions, no addition of Q-salt was needed. In none of the experiments did addition of Q-salt have any positive influence on the reaction outcome. On the contrary, in all experiments performed with the HC the radiolabeled yields decreased with the addition of Q-salt to the reactions.

In our attempts to optimize the labeling yield with regard to the concentration of the iodinated carborane, 2-iodo-*p*-carborane (**1**) was used as a model compound. Two different concentrations of **1**, 0.01 and 0.001 mg ml^{-1}, were compared with the standard concentration of 0.1 mg ml^{-1} (37 μmol ml^{-1}). The reactions were allowed to proceed for 5 min. Using 0.01 mg ml^{-1} of iodinated-carborane the radiolabeled yield decreased to 71%, and with 0.001 mg ml^{-1}, the radiolabeled yield decreased to 20%. These results indicate that a concentration around 0.1 mg ml^{-1} of iodinated carborane is necessary for maintaining the excellent radiolabeling yields.

In the first attempts to label *ortho*-carboranes, DMF was used as a solvent. Despite the short reaction time, degradation of the [^{125}I]-labeled carborane was found during the analysis. This was further investigated by running the same reaction without addition of [^{125}I]-iodide. The ^{11}B-NMR analysis of the reaction mixture

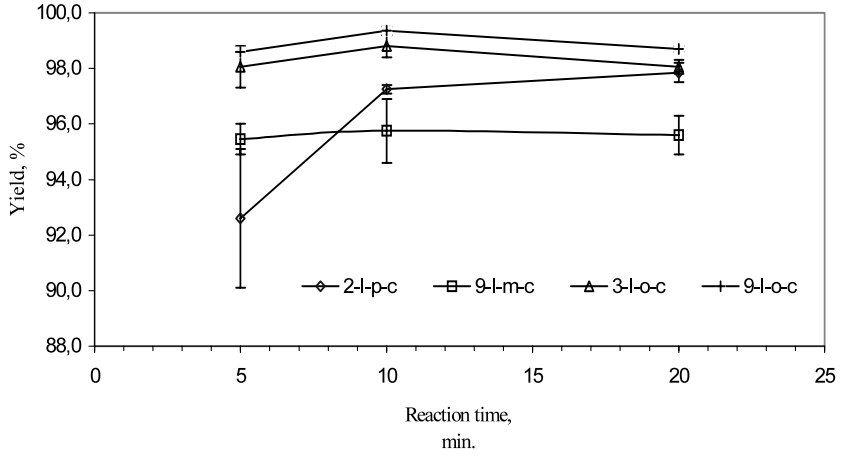


Fig. 1. [^{125}I] radiolabeled yield as a function of time for 2-I-*p*-(**1**), 9-I-*m*-(**4**), 3-I-*o*-(**2**), and 9-I-*o*-carborane (**3**), using the general labeling procedure.

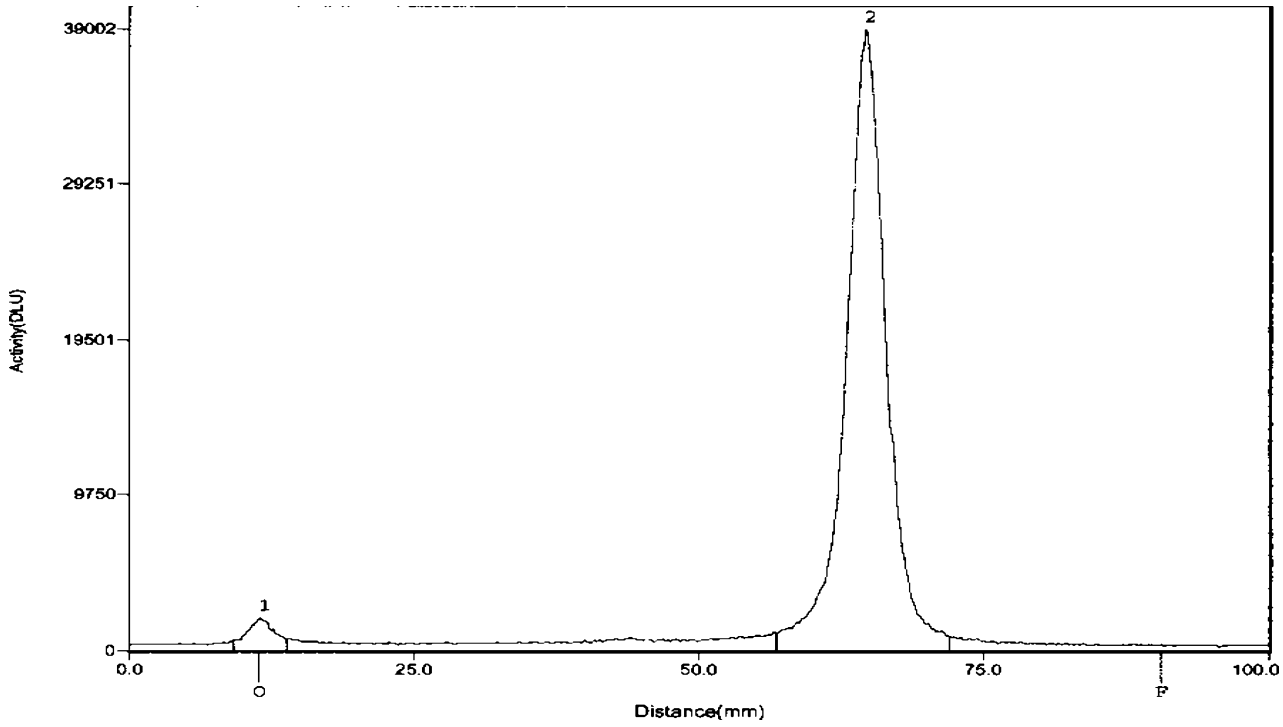


Fig. 2. Typical TLC-result of [^{125}I] radiolabeling of 3-I-*o*-carborane (**2**) using the general labeling procedure after 5 min.

using compound **2** as the substrate reveals the presence of the previously known 3-I-7,8-dicarba-*nido*-undecaborate [5] derived from **2**. To avoid this cluster partial degradation process from *closo* to the *nido*-analogue, DMF was replaced by toluene, a non-nucleophilic solvent. As a result no degradation of the *ortho*-carboranes **2** and **3** was observed.

By decreasing the amount of the HC, optimization of the catalytic loading was investigated. Again 2-I-*p*-carborane (**1**) was used as the model compound, and in addition to the initial loadings of 5 mol.%; 1, 0.1 and 0.01 mol.% of catalyst were evaluated. See Fig. 3.

These results show that the loading of catalyst can be decreased to 0.1 mol.% and still give a radiolabeling yield of over 90%. To confirm this further, the four non-arylated iodinated carboranes (**1**–**4**) were subjected to this lower catalyst loading. As shown in Table 1, this

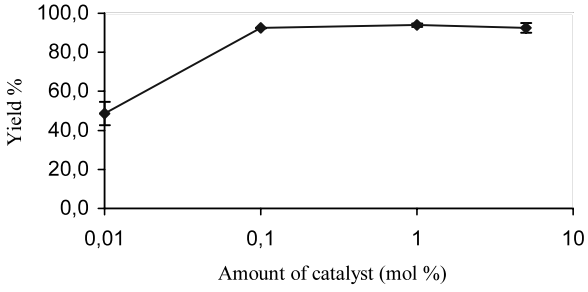


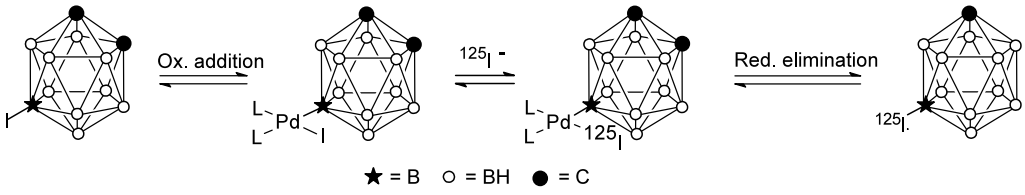
Fig. 3. Yield of [^{125}I] radiolabeling of 2-I-*p*-carborane (**1**) as a function of the amount of added catalyst. Five, 1, 0.1 and 0.01 mol.% of the HC was used (reaction time 5 min).

Table 1
Radiolabeling yields for the parent iodinated carboranes using 5 and 0.1 mol.% of HC at 5 min reaction time

Entry	Carborane	Yield: 5 mol.% HC	Yield: 0.1 mol.% HC
1	2-I-*p*-carborane (**1**)	92.6±2.5	92±0.1
2	3-I-*o*-carborane (**2**)	98.1±0.8	91±2.4
3	9-I-*o*-carborane (**3**)	98.6±0	90±1.6
4	9-I-*m*-carborane (**4**)	95.5±0.6	86±3.8

lower catalyst loading is quite feasible although the yields are somewhat lower.

To get an indication of the steric tolerance of the reaction, the two substituted carboranes, 1-phenyl-3-iodo-*ortho*-carborane (**5**) and 1,2-diphenyl-3-iodo-*ortho*-carborane (**6**) were labeled. In both cases, precipitation of palladium black could be seen. Despite the similarity of the compounds, the two compounds behave differently under these reaction conditions. The average radiolabeling yield for **5** was 83% after 5 min of reaction time. This yield decrease over time and after 20 min the radiolabeled yield dropped to 58%. This could be explained by the degradation of *ortho*-carborane to *nido*-carborate (as shown for 3-iodo-*ortho*-carborane in DMF). The initial radiolabeling yield for the di-substituted *ortho*-carborane **6** was lower, with an average value of 65% after 5 min. This yield increases with time and after 20 min the yield was 86%. By comparing the labeling yields of **5** and **6** with that for 3-I-*o*-caborane



Scheme 2.

(**2**) (98% after 5 min of reaction), the steric interactions seems to have an impact of the [^{125}I]iodide-labeling rate.

As discussed previously [3] a likely mechanism for this halogen exchange reaction is given in Scheme 2 for the radioiodination of 9-I-*o*-carborane (**3**).

3. Experimental

3.1. Materials

[^{125}I]-iodide was obtained from Amersham Pharmacia Biotech UK Limited, with a specific activity of 644 GBq mg^{-1}. HC (*trans*-di-μ-acetatobis[2-(di-*o*-tolylphosphino)benzyl]dipalladium) (II) and tetra-*n*-butyl ammonium hydrogen sulphate ($QHSO_4$) were purchased from Lancaster Ltd. Acetonitrile (HPLC grade) was purchased from Sigma-Aldrich Sweden AB and toluene was distilled from sodium and benzophenone. 9-I-*o*-carborane was prepared according to the procedure described by Jones and co-workers [6], and 2-I-*p*-carborane and 9-I-*m*-carborane in analogy with the procedure described by Hawthorne and co-workers [7] 3-I-*o*-carborane [6], 1-phenyl-3-I-*o*-carborane [8] and 1,2-diphenyl-3-I-*o*-carborane [9] were synthesized according to previously published procedures. All non-radioactive iodinated carborane was characterized by ^{1}H-, ^{13}C- and ^{11}B-NMR and spectral data were found to be consistent with those reported in the literature.

3.2. General ^{125}I-labeling procedure

The following stock solutions were prepared: iodinated carboranes (37 μmol ml^{-1}) in acetonitrile. HC (6.94 mg) was, prior to use, dissolved in 10 ml degassed toluene (0.74 μmol Pd (II) HC) under argon.

For a typical labeling experiment, 0.25 MBq or 3.9×10^{-7} mg (3.12×10^{-9} mol) of [^{125}I]iodide was used. Aqueous solution (5 μl) of sodium [^{125}I]iodide (stabilized with sodium hydroxide) and 100 μl of the acetonitrile solution of iodinated carborane were transferred to a 2-ml Eppendorf tube. The solvents were evaporated under a flow of argon at 100 °C. After complete evaporation, 200 μl of HC-stock solution was added, still under a flow of argon, and the reaction vial was sealed. The reaction proceeded at 100 °C for 5 min, and subsequently 200 μl of ethyl acetate was added to the reaction vial. After mixing, samples for TLC analysis (1–2 μl) were collected. Blank experiments were also performed, using exactly the same conditions, but neat toluene was used instead of the stock solution HC, or neat acetonitrile was used instead of the solution of iodinated carborane.

3.3. Analytical techniques and purification

Silica gel 60 F_{254} thin layer chromatography plates (E. Merck, Darmstadt, Germany) were used for analysis. The reaction mixture (1–2 μl) was applied on a TLC plate. R_f values for all reaction mixtures were determined by using non-labeled authentic samples. As an eluant, pentane was used for compounds **1** and **4** whereas ethylacetate/ether (1/1; v/v) was used for compounds **2**–**3** and **5**–**6**. Any *nido*-carborane used will stay on the base line of the chromatogram together with unreacted [^{125}I]-iodide ions. An eluted plate of non-labeled carborane and NaI was developed by dipping it into an acidified methanol solution of palladium (II) chloride followed by heating. Distribution of radioactivity along the TLC strips was measured on the Cyclone™ Storage Phosphor System (Packard Instruments Company Inc., Downers Grove, US) and analyzed using the OptiQuant™ Image Analysis Software. The labeled carboranes can easily be purified by chromatography using a small silica column with the same eluents as described for the TLC analysis.

4. Conclusion

We have demonstrated that by using HC in toluene, the catalyzed isotopic exchange between the iodide of iodinated carboranes and [^{125}I]iodide, [^{125}I]-labeled carboranes are provided under mild conditions in high to excellent radiolabeling yields. Further investigations of the isotopic exchange reaction using different radioactive isotopes and other substituted carboranes will be carried out.

Acknowledgements

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