Transition Metal Mediated Kumada Cross Coupling of [11C]CH3I and Aryl Grignard

Dam, Johan Hygum

Published in:
Journal of Labelled Compounds and Radiopharmaceuticals

DOI:
10.1002/jlcr.3302_2

Publication date:
2015

Document version
Submitted manuscript

Citation for published version (APA):

Terms of use
This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk
318

**Transition Metal Mediated Kumada Cross Coupling of [11C]CH₃I and Aryl Grignard**

Johan H. Dam

Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark

**Objectives** Radiolabeling of small molecules with carbon-11 has to date been largely based on the S_N2 reaction by amines or alkoxides on [11C]CH₃I or [11C]CH₃OTf. The chemical space for labeling by cross coupling is still being developed within radiochemistry.[1] Herein, it was sought to explore the Kumada cross coupling for incorporation of the [11C]methyl moiety.

**Methods** A range of transition metals viz. Pd, Ni, Fe and Co and ligands DPPF, DPPP, PPh₃, P(Tol)₃, TMEDA were screened for their capability to mediate a model Kumada cross coupling between PhMgBr and [11C]CH₃I in THF. The [11C]CH₃I was prepared by standard gas phase reactions on the Tracerlab FXc Pro by extracting [11C]CH₃I from Valve 17 to an external glass vial with 0.35 mL THF, 4 μmol catalyst and 100 μmol of PhMgBr(in THF), cooled to -20 °C. The trapping was complete within 2 minutes and the vial was heated to 60 °C over 2 minutes, purged with N₂ for 2 minutes to discharge residual [11C]CH₃I and quenched with 1 mL 70% ethanol. The radiochemical purity was assessed by RP-HPLC on a Zorbax C18 Stablebond.

**Results** As a simple model system, many different combinations of transition metals and ligands produced the [11C]toluene to some extent. Of the different catalysts and ligands examined, only PdCl₂-DPPF, PdCl₂(P(Tol)₃)₂ and CoCl₂ with DPPP produced the carbon-11 labeled toluene in the higher yields of 67.9%, 67.0% and 66.5%, d.c., respectively. For the cobalt mediated cross coupling, addition of PhMgBr after trapping of the [11C]CH₃I was necessary in order to obtain a high yield. Increasing the reaction time from 2 minutes to 4 minutes with PdCl₂(P(Tol)₃)₂ did not increase the overall radiochemical yield. Lowering the reaction time to 1 minute reduced the radiochemical yield to 36.1% d.c.

**Conclusions** The Kumada cross coupling was examined for coupling of [11C]CH₃I with PhMgBr. Palladium with phoshine ligands, DPPF and P(Tol)₃, was found to produce the [11C]toluene in slightly better yields. As such, the palladium mediated Kumada cross coupling represent an attractive method for fast insertion of a metabolically more stable radiolabel into small molecules.

**Acknowledgements**


![Diagram](https://via.placeholder.com/150)

**Figure 1. Model system for radiolabeling by the Kumada cross coupling**