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

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Transition Metal Mediated Kumada Cross Coupling of $[^{11}C]$CH$_3$I and Aryl Grignard

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Objectives Radiolabeling of small molecules with carbon-11 has to date been largely based on the $S_N$2 reaction by amines or alkoxides on $[^{11}C]$CH$_3$I or $[^{11}C]$CH$_3$OTf. 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 $[^{11}C]$methyl moiety.

Methods A range of transition metals viz. Pd, Ni, Fe and Co and ligands DPPF, DPPP, PPh$_3$, P(”Tol”)$_2$, TMEDA were screened for their capability to mediate a model Kumada cross coupling between PhMgBr and $[^{11}C]$CH$_3$I in THF. The $[^{11}C]$CH$_3$I was prepared by standard gas phase reactions on the Tracerlab FXc Pro by extracting $[^{11}C]$CH$_3$I 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 N$_2$ for 2 minutes to discharge residual $[^{11}C]$CH$_3$I 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 $[^{11}C]$toluene to some extent. Of the different catalysts and ligands examined, only PdCl$_2$DPPF, PdCl$_2$(P(”Tol”)$_2$)$_2$ and CoCl$_2$ 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 $[^{11}C]$CH$_3$I was necessary in order to obtain a high yield. Increasing the reaction time from 2 minutes to 4 minutes with PdCl$_2$(P(”Tol”)$_2$)$_2$ 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 $[^{11}C]$CH$_3$I with PhMgBr. Palladium with phosphine ligands, DPPF and P(”Tol”)$_2$, was found to produce the $[^{11}C]$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


![Reaction Diagram](image)

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