318
Transition Metal Mediated Kumada Cross Coupling of $[^{11}]$C$\text{CH}_3$I 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 $[^{11}]$C$\text{CH}_3$I or $[^{11}]$C$\text{CH}_3$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 $[^{11}]$Cmethyl moiety.

Methods A range of transition metals viz. Pd, Ni, Fe and Co and ligands DPPF, DPPP, PPh$_3$, P(“Tol)$_3$, TMEDA were screened for their capability to mediate a model Kumada cross coupling between PhMgBr and $[^{11}]$C$\text{CH}_3$I in THF. The $[^{11}]$C$\text{CH}_3$I was prepared by standard gas phase reactions on the Tracerlab FXc Pro by extracting $[^{11}]$C$\text{CH}_3$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$\text{CH}_3$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 $[^{11}]$Ctoluene to some extent. Of the different catalysts and ligands examined, only PdCl$_2$DPPP, PdCl$_2$(P(“Tol)$_3$, 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$\text{CH}_3$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)$_3$, 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$\text{CH}_3$I with PhMgBr. Palladium with phoshine ligands, DPPP and P(“Tol)$_3$, was found to produce the $[^{11}]$Ctoluene 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


![Figure 1. Model system for radiolabeling by the Kumada cross coupling](image-url)