

PEPPSI™: Instructions for Use

Thank you for choosing the **PEPPSI™-IPr** (Generation 1) precatalytic system. If used correctly **PEPPSI™-IPr** will couple a wide range of partners in Negishi, Suzuki, Kumada, and Buchwald-Hartwig amination reactions. Please take a moment to familiarize yourself with its use by reading the suggested reaction conditions and notes below.

PEPPSI™-IPr is a **Pd(II)** precatalyst and like all precatalysts **it must be reduced to Pd(0)** in order to become an active cross-coupling catalyst. This is normally accomplished under the reaction conditions; however the user should be aware that there must be a mechanism of reduction available. This can be facilitated with an organometallic or β -hydride containing material (solvent or substrate) that can undergo a ligand exchange process with the complex.

The **PEPPSI™** precatalyst is remarkably stable and can be stored in air indefinitely; the complex will even tolerate an aqueous work up. However, once **PEPPSI™-IPr** has been activated, the Pd(0) center is extremely sensitive to oxidizing conditions (i.e. oxygen). The use of degassed solvent is preferred; however, anhydrous solvents are not essential to the success of the coupling reactions. It should be noted that Negishi or Kumada reactions require anhydrous conditions to avoid quenching of the basic organometallic reagents (organozinc or organomagnesium). In order to assist users, concise activation procedures for the use of **PEPPSI™-IPr** in the Suzuki, Negishi, Kumada and Buchwald-Hartwig reactions have been included below. Further development of the **PEPPSI™** precatalyst system continues and will provide valuable reaction protocols to meet the needs of discovery, process, and academic research programs. Therefore, please take the time to see if additional information has been included below, while exploring publications from the Organ lab[†] as well as updates on the Aldrich website at sigma-aldrich.com/pepsi.

Protocol Information

PEPPSI™-IPr in the Suzuki Reaction

There are 4 different protocols for this reaction dependent on the coupling partners. Robust functionality can be coupled at room temperature in isopropyl alcohol (IPA) using $\text{KO}t\text{-Bu}$ as base, while base-sensitive groups may be coupled utilizing K_2CO_3 at 60°C. For relatively hindered substrates sensitive to $\text{KO}t\text{-Bu}$ and where K_2CO_3 is ineffective, KOH may be used at room temperature. Central to the success is ensuring that the precatalyst is activated. When utilizing $\text{KO}t\text{-Bu}$, a change in reaction solution color, normally to orange or red, is observed. When utilizing K_2CO_3 or KOH, in the absence of strongly colored materials the reaction is generally complete when the solution is grey in color and contains noticeable precipitate.

Protocol 1 For Routine Coupling Partners. In air, a vial was charged with potassium *tert*-butoxide (154 mg, 1.30 mmol) and **PEPPSI™-IPr** (6.8 mg, 0.01 mmol) and the vial was sealed and purged under an inert atmosphere (3x). Technical grade isopropanol (1.0 mL) was added and the contents were stirred at room temperature until a color change from yellow to red/brown was observed (~10 min). Under an inert atmosphere, the boronic acid (1.20 mmol) was added, the vial was resealed with a septum and the organohalide (1.00 mmol) was injected via microlitre syringe. Alternatively, if the boronic acid is soluble in isopropanol, it can be added as a solution (1.0 mL). The solution was stirred at room temperature until the reaction was complete. The reaction was then diluted with diethyl ether (2 mL) and transferred to a round bottom flask. The reaction vial was rinsed with additional diethyl ether (2 mL) and combined with the previous dilution. The resulting solution was concentrated onto silica gel directly and purified by flash chromatography.

Protocol 2 for Base-Sensitive Functionality. In air, a vial was charged with **PEPPSI™-IPr** (6.8 mg, 0.01 mmol), potassium carbonate (207 mg, 1.50 mmol), the boronic acid (0.6 mmol) and the organohalide (0.5 mmol). The vial was sealed with a septum and purged under an inert atmosphere (3x). Dioxane (2.0 mL) was added and the contents were stirred at 60°C until the reaction was complete. The reaction was then diluted with diethyl ether (2 mL) and transferred to a round bottom flask. The reaction vial was rinsed with additional diethyl ether (2 mL) and combined with the previous dilution. The resulting solution were concentrated onto silica gel directly and purified by flash chromatography.



Protocol 3 for Trifluoroborates. In air, a vial was charged with **PEPPSI™-IPr** (6.8 mg, 0.01 mmol), potassium carbonate (207 mg, 1.50 mmol), the potassium trifluoroborate (0.55 mmol) and the organohalide (0.5 mmol). The vial was sealed with a septum and purged under an inert atmosphere (3x). Technical grade methanol (2.0 mL) was added and the contents stirred at 60°C until the reaction was complete. The reaction was then diluted with diethyl ether (2 mL) and transferred to a round bottom flask. The reaction vial was rinsed with additional diethyl ether (2 mL) and combined with the previous dilution. The resulting solution were concentrated onto silica gel directly and purified by flash chromatography.

Protocol 4 for Hindered Substrates. Protocol 2 was followed with the exception that solid KOH (84 mg, 1.50 mmol) was used in place of solid K_2CO_3 . The reaction should be attempted at room temperature and, if necessary, can be heated to 60°C.

PEPPSI™-IPr in the Negishi Reaction

There are 4 main protocols for this reaction dependant on organohalide and carbon hybridization present in the coupling partners. Whilst most reactions are carried out at room temperature, sterically encumbered partners require warming to 60-70 °C to ensure efficient cross-coupling. Furthermore, the addition of 2 equivalents (based on organozinc) of LiBr or LiCl (available from Aldrich as 1M anhydrous solutions in THF or DMI) is necessary to effect cross-coupling in some reaction types (see protocols). Efficient catalyst formation and reaction is normally indicated by a slow color change from pale yellow to a deep brown-colored solution when employing zinc made by the Hou protocol in DMI (*Org. Lett.* **2003**, *5*, 423). If this change is rapid, (1-2 seconds) this is indicative of a failed reaction and is normally the result of ineffective catalyst activation, which could be due to the steric and/or electronic properties of the organozinc reagent. Use of organozincs formed by Rieke zinc does not show the same color change. Additionally, the use of *n*-BuLi for formation of aryl zincs should be avoided as the generated butyl halide is a capable coupling partner for **PEPPSI™-IPr** due to its' high reactivity.

Cross-Coupling Procedures: All cross-coupling reactions were run with a final solvent volume of 2.4 mL.

Solvent ratios

Alkyl bromides: DMI/NMP: THF, 1:2

Alkyl chlorides, iodides, tosylates and mesylates: DMI/NMP: THF, 3:1

Aryl bromides: DMI/NMP: THF, 1:2

Aryl chlorides, triflates: DMI/NMP:THF, 3:1

(sp³X-sp³ZnX): A vial was charged with **PEPPSI™-IPr** (3.4 mg, 1 mol%), LiBr (139.0 mg, 1.6 mmol, transferred under a filter cone flowing with inert gas) and a stirbar, after which it was sealed with a septum and purged under an inert atmosphere. THF (X mL) and DMI (X mL) or NMP (X mL) were then added and the suspension stirred until the solids dissolved after which the organozinc (0.8 mL, 1.0 M in DMI or NMP, 0.8 mmol) and the organohalide or pseudo halide (0.5 mmol) were added. The septum was replaced with a Teflon®-lined screw cap under an inert atmosphere and the reaction stirred for 2h. After this time, the mixture was diluted with ether (15 mL) and washed successively with 1 M Na₃EDTA solution (prepared from EDTA and 3 equiv of NaOH), water and brine. After drying (anhydrous MgSO₄) the solution was filtered, the solvent removed in vacuo, and the residue purified by flash chromatography.

(sp³X-sp²ZnX): A vial was charged with **PEPPSI™-IPr** (3.4 mg, 1 mol%) and under an inert atmosphere ZnCl₂ (107 mg, 0.8 mmol, transferred under a filter cone flowing with inert gas) and a stirbar were added. The vial was then sealed with a septum and purged under an inert atmosphere. THF (0.8 mL) was added followed by the requisite Grignard reagent (0.8 mL, 1.0 M in THF, 0.8 mmol) and stirring continued for 15 minutes at which time a white precipitate formed. Under an inert atmosphere, LiBr (139.0 mg, 1.6 mmol), NMP (0.8 mL) or DMI (0.8 mL) and the organohalide or psuedo halide (0.5 mmol) were added. The septum was replaced with a Teflon®-lined screw cap under an inert atmosphere and the reaction stirred for 2h. After this time, the mixture was diluted with ether (15 mL) and washed successively with 1 M Na₃EDTA solution (prepared from EDTA and 3 equiv of NaOH), water and brine. After drying (anhydrous MgSO₄) the solution was filtered, the solvent removed in vacuo, and the residue purified by flash chromatography.

(sp²X-sp²ZnX): A vial was charged with **PEPPSI™-IPr** (3.4 mg, 1 mol%), LiBr (139.0 mg, 1.6 mmol, transferred under a filter cone flowing with inert gas) and a stirbar after which it was sealed with a septum and purged under an inert atmosphere. THF (X mL) and DMI (X mL) or NMP (X mL) were then added and the suspension stirred until the solids dissolved after which the organozinc (0.8 mL, 1.0 M in DMI or NMP, 0.8 mmol) and the organohalide or psuedo halide (0.5 mmol) were added. The septum was replaced with a Teflon®-lined screw cap under an inert atmosphere and the reaction stirred for 2h. After this time, the mixture was diluted with ether (15 mL) and washed successively with 1 M Na₃EDTA solution (prepared from EDTA and 3 equiv of NaOH), water and brine. After drying (anhydrous MgSO₄), the solution was filtered, the solvent removed in vacuo, and the residue purified by flash chromatography.



(sp^2X-sp^2ZnX): In air, a vial was charged with **PEPPSI™-IPr** (3.4 mg, 1 mol%) and $ZnCl_2$ (0.8 mmol, transferred under a filter cone flowing with inert gas) and a stirbar were added. The vial was then sealed with a septum and purged under an inert atmosphere. THF (X mL) was then added followed by the requisite Grignard reagent (0.8 mL, 1.0 M in THF, 0.8 mmol) and stirring continued for 15 minutes at which time a white precipitate formed. NMP (X mL) was then added followed by the organohalide or pseudo halide (0.5 mmol) and the septum was replaced with a Teflon®-lined screw cap under an inert atmosphere and the reaction stirred for 2h. After this time, the reaction mixture was diluted with ether (15 mL) and washed successively with 1 M Na_3EDTA solution (prepared from EDTA and 3 equiv of NaOH), water and brine. After drying (anhydrous $MgSO_4$) the solution was filtered, the solvent removed in vacuo, and the residue purified by flash chromatography.

PEPPSI™-IPr in the Kumada Reaction

There is one protocol for this reaction, however, additional heating or activation may be required for difficult partners. At the moment, we have only developed a protocol for the coupling of sp^2 carbon centers containing organomagnesium-tolerant functionality. Effective coupling partners are aryl chlorides and bromides. Simple couplings should be attempted at room temperature without the addition of LiCl; if this proves unproductive, heating at 60 or 70°C will normally facilitate the cross-coupling. If these conditions fail for challenging partners, 2 or 3 equivalents (based on organomagnesium reagent) of anhydrous LiCl should be added and the reaction temperature varied from RT to 70 °C. New conditions and an increased substrate range are presently under investigation and these results will be made available shortly, both on the Aldrich **PEPPSI™-IPr** website and in the published literature.

A vial was charged with **PEPPSI™-IPr** (7 mg, 2 mol%) and LiCl (67.0 mg, 1.6 mmol) as necessary followed by a stirbar under an inert atmosphere. The vial was then sealed with a septum and purged under an inert atmosphere after which DME (0.8 mL) was added and the suspension was stirred until **PEPPSI™-IPr** had dissolved. After this time, the organohalide (0.5 mmol) and the organomagnesium (0.8 mL, 1.0 M in THF or ether, 0.8 mmol) were added (active catalyst is indicated by the reaction solution turning orange). The septum was replaced with a Teflon®-lined screw cap under an inert atmosphere and the reaction stirred at RT or warmed to 60 or 70°C until complete. After this time, the mixture was diluted with a suitable organic solvent (15 mL) and washed successively with 1 M Na_3EDTA solution (prepared from EDTA and 3 equiv of NaOH), water and brine. After drying (anhydrous $MgSO_4$) the solution was filtered, the solvent removed in vacuo, and the residue purified by flash chromatography.

PEPPSI™-IPr in the Buchwald-Hartwig Reaction

At present, there is one protocol for this reaction. Activation of the complex is achieved by adding the amine neat to **PEPPSI™-IPr** and $KOt-Bu$ with rapid stirring followed by the organohalide and the solvent. For highly reactive amines the solvent is added before the amine. However, the user must ensure effective activation of **PEPPSI™-IPr** takes place. Best results are obtained when the amine contains a β -hydrogen with respect to the nitrogen atom. Effective coupling partners are aryl chlorides and bromides. Users should be conscious that amine-based products can be extremely air sensitive and isolation may not be trivial, thus care should be taken during isolation with workup steps performed rapidly. New conditions and an increased substrate range are presently under investigation and these results will be made available shortly, both on the Aldrich **PEPPSI™-IPr** website and in the published literature.

A vial was charged with **PEPPSI™-IPr** (14 mg, ~2 mol%), $KOt-Bu$ (135.0 mg, 1.2 mmol corrected for purity) and a stirbar were added after which it was sealed with a septum and purged with an inert atmosphere. The amine (1.1 mmol) and organohalide (1.0 mmol) were added and stirred rapidly for 1-2 min. When using 2,6-diisopropylaniline the reaction turns orange immediately; stirring should continue until the solution becomes dark orange to red (note: a green to dark green solution indicates a failure to form sufficient active catalyst). After this time, DME (1 mL) was added and the septum was replaced with a Teflon®-lined screw cap under an inert atmosphere and the reaction stirred at RT or 50°C until complete. After this time, the mixture was diluted with TBME (15 mL) and washed with water. After drying (anhydrous Na_2SO_4 , the use of $MgSO_4$ can be problematic), the solution was filtered, the solvent removed in vacuo, and the residue purified rapidly by flash chromatography and stored under an inert atmosphere. Pre-absorption of the crude amine product onto silica should be avoided as this practice has been found to lead to poor recovery.

† Lead references and information on the **PEPPSI™** technology can be found at:

- (1) Negishi reaction: O' Brien, C. J. et al. Chem. Eur. J. **2006**, ASAP.
- (2) Suzuki-Miyaura reaction: Organ, M. G. et al. Chem. Eur. J **2006**, ASAP.