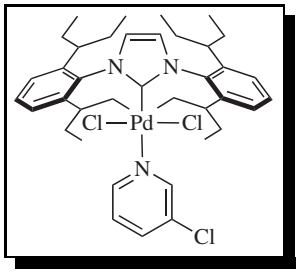
trans-[1,3-Bis(2,6-Di-3-pentylphenyl)-imidazol-2-ylidene](3-chloropyridyl)-palladium(II) Dichloride (*Pd-PEPPSI™-IPent*)[1]



[1158652-41-5] $C_{40}H_{56}Cl_3N_3Pd$ (MW 791.67)

InChI = 1S/C35H53N2.C5H4ClN.2ClH.Pd/c1-9-26(10-2)30-19-17-20-31(27(11-3)12-4)34(30)36-23-24-37(25-36)35-32(28(13-5)14-6)21-18-22-33(35)29(15-7)16-8;6-5-2-1-3-7-4-5;;;/h17-29H,9-16H2,1-8H3;1-4H;2*1H;/q;;;;+2/p-2

InChIKey = MSZBXTMQAMAAOX-UHFFFAOYSA-L

(precatalyst for Pd-mediated C–C, C–N, and C–S cross-coupling reactions)[2–14]

Physical Data: mp 195–201 °C.

Solubility: soluble in most organic solvents except for aliphatic hydrocarbons (e.g., pentane or hexanes); insoluble in water.

Form Supplied in: pale to dark yellow solid. Available from Sigma-Aldrich.

Analysis of Reagent Purity: NMR analysis.

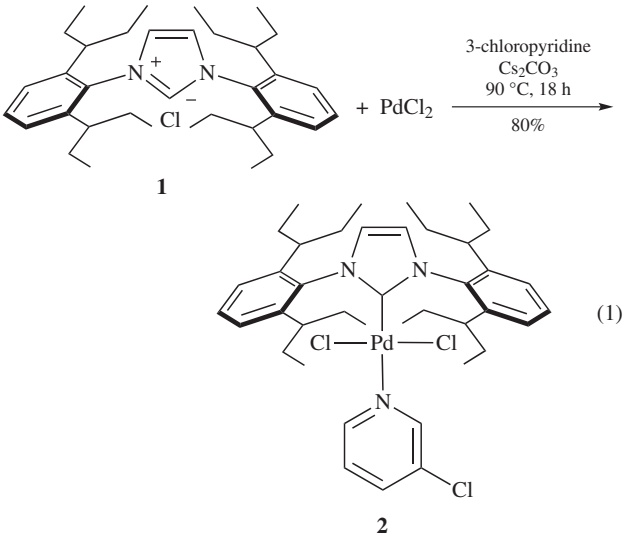
Preparative Methods: heating $PdCl_2$ (1.05 mmol), *N*,*N*-(2,6-di-pentylphenyl)imidazolium chloride (**1**; IPent·HCl; 1.0 mmol), and powdered Cs_2CO_3 (5.0 mmol) at 90 °C in neat 3-chloropyridine (5 mL) with vigorous stirring for 18 h (eq 1) afforded *Pd-PEPPSI™-IPent* (**2**; 80%) as a beige powder following filtration through a plug of silica gel/celite (CH_2Cl_2), vacuum distillation of excess 3-chloropyridine, a second filtration through a silica gel/celite plug, and trituration with pentane.

Purification: precipitation with pentane from concentrated ether or CH_2Cl_2 solution or flash chromatography on silica gel (pentane : CH_2Cl_2 = 1:2).

Handling, Storage, and Precautions: stable under ambient conditions in solid form or in solution. Incompatible with strong acids, bases, oxidizing, and reducing agents.

***Pd-PEPPSI™-IPent* Design and Use.** *N*-heterocyclic carbene ligands have gained in popularity for Pd-catalyzed cross-coupling reactions due to their favorable electronic and steric properties.[1,15–17] The combination of strong σ-electron donation and the projection of the bulky *ortho*-substituted aryl groups toward Pd contribute to the high catalytic activity.[18–20] These properties allow *Pd-PEPPSI™-IPent* to couple deactivated aryl chlorides and bromides in a wide range of reactions under mild conditions, which makes it a highly reactive and general-use catalyst.

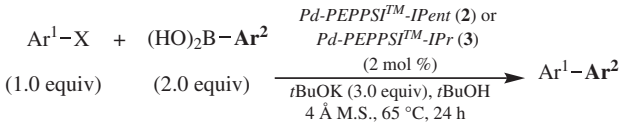
Pd-PEPPSI™-IPent is a bench-top stable Pd^{II} precatalyst that may be used in the solid state or as a stable stock solution. The 3-chloropyridine ligand stabilizes the monomeric Pd^{II} species and readily dissociates after catalyst activation. It is important to recognize that a low energy pathway to the active Pd^0 species must exist to ensure maximum conversion to the active catalyst from its' stable Pd^{II} precatalyst. The most facile pathways for activation are transmetalation of two organometallic species followed by reductive elimination or β-hydride elimination of alcohols and amines followed by reductive elimination. Fortunately, most cross-coupling reactions contain reagents that are sufficiently basic for low temperature precatalyst activation without the need for additives to assist the process.

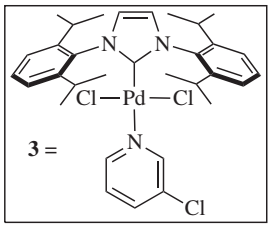


(1)

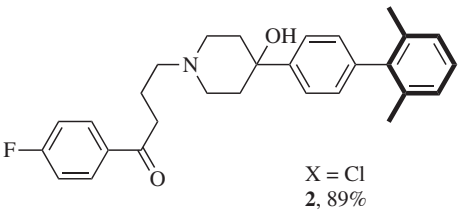
The Suzuki–Miyaura Reaction for the Synthesis of Tetra-*ortho*-Substituted Biaryls.[2] *Pd-PEPPSI™-IPent* is able to facilitate the cross-coupling of a wide range of sterically hindered aryl halides and boronic acids under mild conditions. To demonstrate the high level of reactivity of *Pd-PEPPSI™-IPent*, a study was undertaken to cross-couple two 2,6-di*ortho*-substituted aryl partners together to form tetra-*ortho* substituted biaryls, which represents perhaps the most sterically challenging coupling for a Pd catalyst. Reactions proceed well at 65 °C with KO*t*Bu in

*t*BuOH at 2 mol % precatalyst loading (eq 2). The increased reactivity from the additional bulk imparted by the longer alkyl chains is evident by comparison with *Pd-PEPPSI™-IPr* (**3**). See *Pd-PEPPSI™-IPr* for the cross-coupling of less sterically hindered (hetero)biaryl compounds.[21]

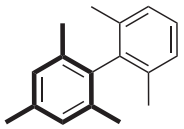




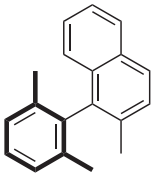
(2)



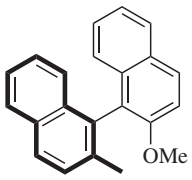
X = Cl
2, 89%



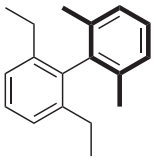
X = Br
3, 44%; **2**, 88%
X = Cl
3, 2%; **2**, 70%



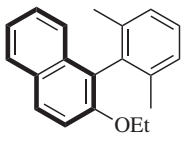
X = Cl
3, 47%; **2**, 95%



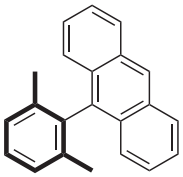
X = Br
3, 64%; **2**, 90%



X = Cl
3, 0%; **2**, 61%



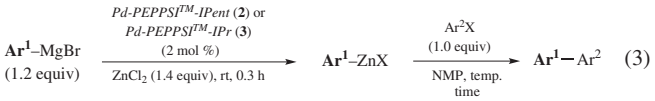
X = Br
3, 2%; **2**, 80%



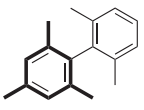
X = Cl
3, 0%; **2**, 95%

The Negishi Reaction for the Synthesis of Tetra-*ortho*-Substituted (Hetero)biaryls and Cross-coupling of Secondary Alkylzinc Halides with (Hetero)aryl Halides.[3,4] Analogous to the Suzuki–Miyaura reaction, *Pd-PEPPSI™-IPent* shows increased reactivity that allows for the preparation of highly sterically hindered (hetero)biaryls (eq 3). Owing to the ready transmetallation of organozinc reagents, relative to the corresponding organoborons, couplings can now be conducted at very mild temperatures (typically 23–60 °C as dictated by substrate sterics, but as low as 0 °C (see biaryl **4**)).

The coupling of a secondary alkylzinc with an aryl halide is challenging due to the propensity for β-hydride elimination to compete with reductive elimination.[4] Once β-hydride elimination has taken place the favored pathway is migratory insertion to the linear isomer followed by reductive elimination.[10] *Pd-PEPPSI™-IPent* is able to suppress the undesired β-hydride elimination and achieve good selectivity for the desired branched product (eq 4). Using a THF/toluene solvent system with 2 mol % *Pd-PEPPSI™-IPent* at room temperature a wide variety of cyclic and acylic secondary alkylzincs can be coupled with (hetero)aryl halides (eq 5) with minimal isomerization.

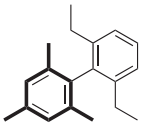


(3)

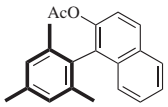


4

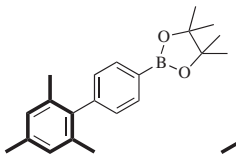
X = Cl
3, rt, 8 h, 3%
2, rt, 8 h, 99%
2, 0 °C, 8 h, 90%



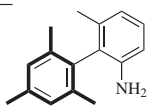
X = Br
3, 40 °C, 24 h, 1%
2, 40 °C, 24 h, 73%



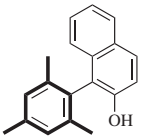
X = Br
3, rt, 16 h, 30%
2, rt, 16 h, 80%



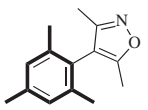
X = Br
3, 45 °C, 24 h, 90%
2, 45 °C, 24 h, 90%



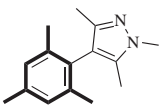
X = Br
Ar1-MgBr (2.6 equiv)
$ZnCl_2$ (3.0 equiv)
3, 50 °C, 24 h, 1%
2, 50 °C, 24 h, 57%



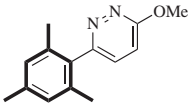
X = Br
NaH (1.0 equiv)
3, 50 °C, 24 h, 18%
2, 50 °C, 24 h, 95%



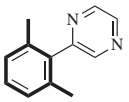
X = Br
2, rt, 24 h, 82%



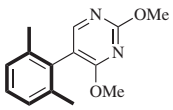
X = Br
2, rt, 24 h, 99%



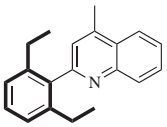
X = Cl
2, rt, 24 h, 99%



X = Cl
2, rt, 24 h, 99%

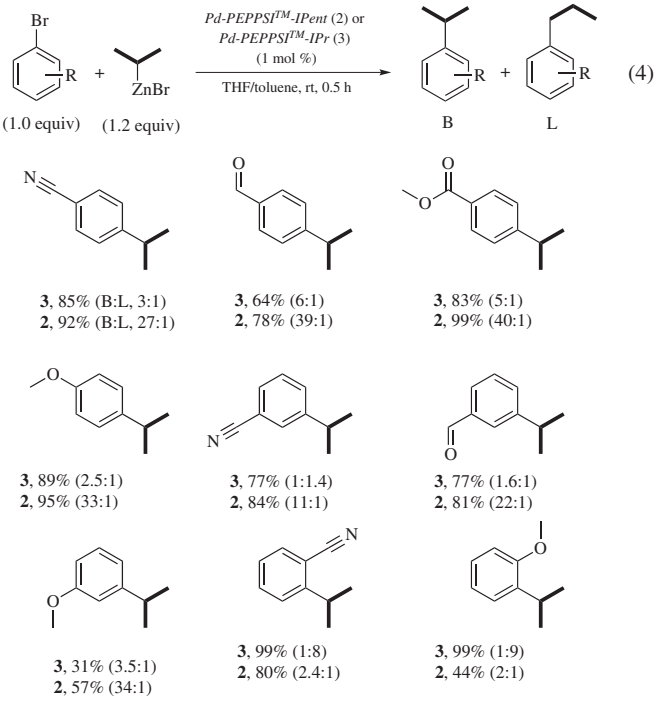


X = Br
2, rt, 24 h, 89%



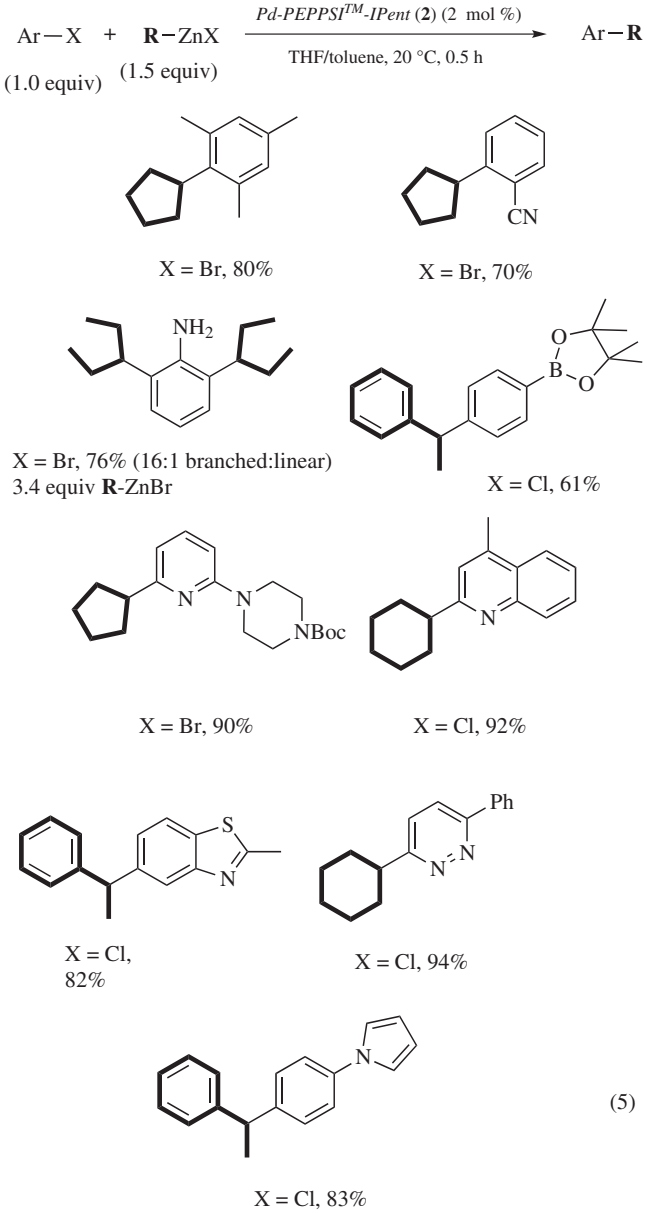
X = Cl
2, rt, 24 h, 95%

The Stille–Migita Cross-coupling for the Synthesis of Heterobiaryls.[5] Historically reluctant organometallic partners to undergo transmetallation, and thus cross-coupling, organostannanes typically require quite forcing conditions (e.g., >100 °C) in order to see any appreciable level of cross-coupling. However, *Pd-PEPPSI™-IPent* has demonstrated the ability to couple a variety of heteroaryl stannanes with heteroaryl chlorides and bromides at significantly lower temperatures than are typically required with other catalyst systems.[22–24] The mild conditions allow for the coupling of sensitive heterocycles such as benzothiazoles, furans, isooxazoles, and sulfonamides (eq 6).

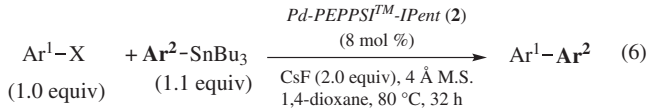


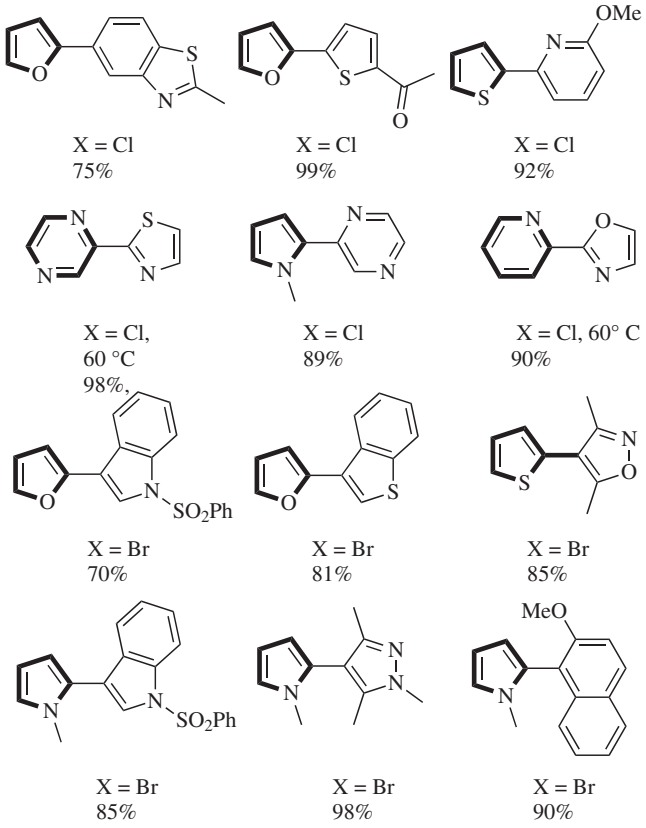
The Buchwald–Hartwig Amination Reaction.[6,7] The ability to couple an oxidative addition partner to a simple, unactivated amine is a major advance in cross-coupling and has become one of the most used reactions in the pharmaceutical sector.[25,26] *Pd-PEPPSI™-IPent* is able to couple secondary amines and arylamines with (hetero)aryl halides using the functional group tolerant Cs_2CO_3 as base. The ability to switch to Cs_2CO_3 from the ubiquitous *tert*-butoxides broadens the scope of coupling partners for *Pd-PEPPSI™-IPent* when compared with *Pd-PEPPSI™-IPr* (eq 7); with electronically deactivated (hetero)aryl halides, *Pd-PEPPSI™-IPent* provided consistently higher yields (eq 7 and 8).

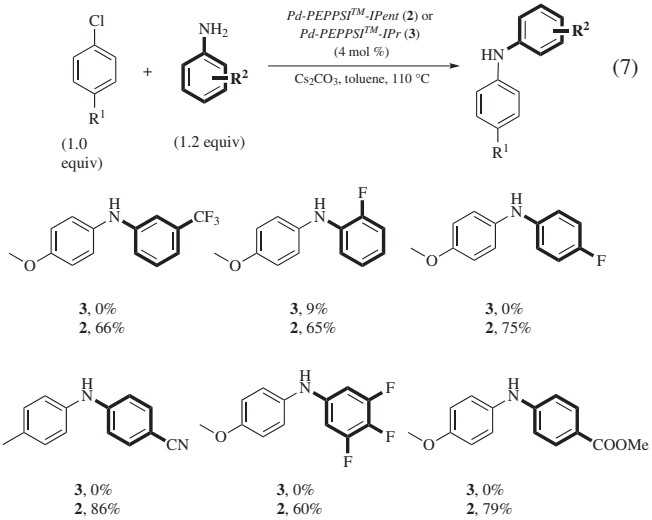
Sulfination of (Hetero)aryl Halides.[8] Sulfination of (hetero)aryl halides with primary, secondary, tertiary alkyl, and aryl thiols using 2 mol % of *Pd-PEPPSI™-IPent* proceeds smoothly at room temperature to 40 °C (eq 9). The temperatures required for electron rich (hetero)aryl chlorides and bromides are the lowest reported to date.



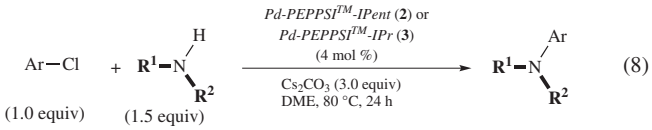
Organolithiums as Cross-coupling Partners with Aryl Halides[12–14] *Pd-PEPPSI™-IPent* is able to rapidly cross-couple bulky alkyl and aryl lithiums at room temperature to 40 °C with a wide variety of aryl halides (eq 10). Incorporation of a $TMSCH_2$ group allows for a diverse array of further functional group transformations.[13] Due to the high reactivity with *ortho*-substituted substrates, *Pd-PEPPSI™-IPent* works well in the synthesis of 3,3′-diaryl BINOL compounds that are useful for asymmetric catalysis.[14,27–29]

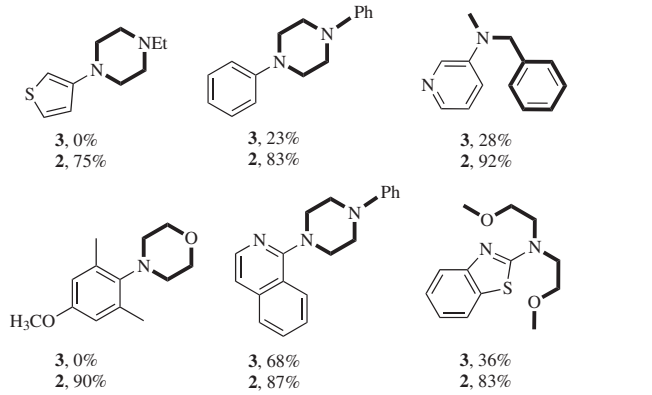


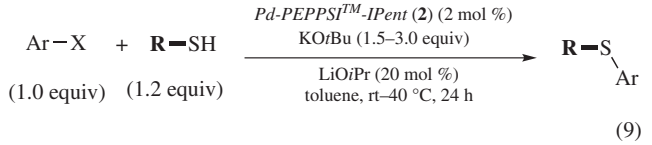


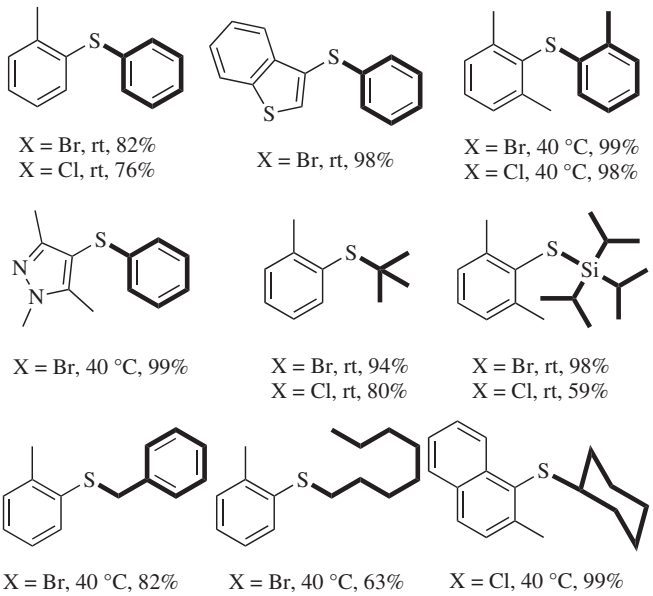


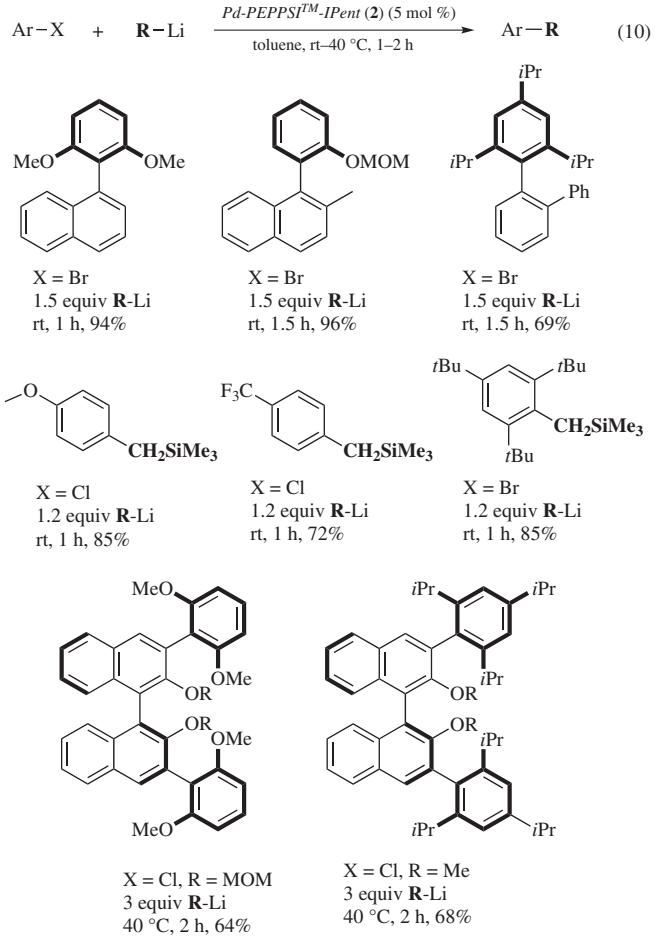
Summary. *Pd-PEPPSI™-IPent* is an air and moisture stable Pd-NHC precatalyst that is highly active across a broad range of cross-couplings using some of the mildest reaction conditions reported. The substrate scope includes heterocycles along with electronically and sterically deactivated cross-coupling partners. The success of *Pd-PEPPSI™-IPent* amongst Pd-NHC catalysts in these challenging reactions is attributed to the extra steric bulk around palladium imparted by the alkyl groups. Owing to these desirable properties, and its robust nature and ease of handling, the precatalyst has been claimed in 11 process patents and patent applications since being launched in 2009.[30]











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