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# Catalytic Direct Cross-Coupling of Organolithium Compounds with Aryl Chlorides

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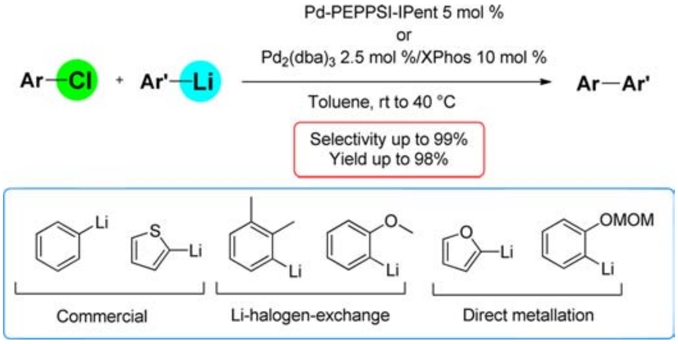
## ABSTRACT



**Palladium-catalyzed direct cross-coupling of aryl chlorides with a wide range of (hetero)aryl lithium compounds is reported. The use of Pd-PEPPSI-IPent or $Pd_2(dba)_3$/XPhos as the catalyst allows for the preparation of biaryl and heterobiaryl compounds in high yields under mild conditions (room temperature to 40 °C) with short reaction times.**

The development of new catalytic methodologies for C–C bond formation continues to be a major challenge in organic synthesis.[1] Cross-coupling reactions, in particular Pd-catalyzed processes, are among the most important current methods for C–C bond formation.[1e] The well-established Stille (with organotin as the nucleophile),[2] Suzuki–Miyaura (organoboron),[3] Negishi (organozinc),[4] Hiyama–Denmark (organosilicon),[5] or Kumada (organomagnesium)[6] reactions are widely employed for this transformation with numerous applications in disciplines varying from material science to natural products synthesis, asymmetric catalysis, and medicinal chemistry.[1,7]

Organolithium compounds are among the most versatile and widely used reagents in organic synthesis.[8] Their use is also well documented for the preparation of softer organometallic nucleophiles including Sn, Si, or B reagents.[9] However, their direct use in catalytic cross-couplings, which would eliminate this additional transformation, has been largely prohibited due to the high reactivity

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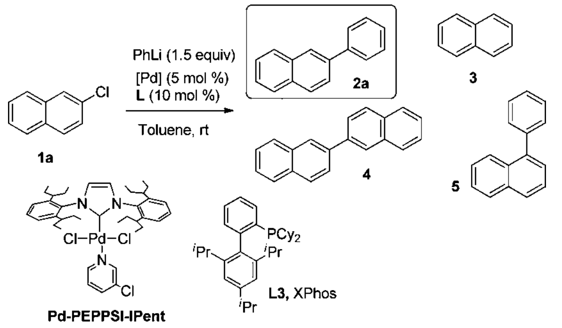
usually accompanied by the lack of selectivity.[10] Our group has recently described the direct use of organolithium reagents in the Pd-catalyzed cross-coupling of a wide variety of aryl and alkenyl bromides.[11] By the use of toluene as a solvent and $P(^tBu)_3$ as ligand and by fine-tuning of the reaction conditions, the high reactivity of the organolithium reagents was controlled, efficient transmetalation was achieved, and high selectivity and good yields were obtained, avoiding the notorious lithium halogen exchange and homocoupling side reactions. Nonetheless, the coupling of organolithium reagents with the corresponding aryl chlorides remains challenging. Aryl chlorides are generally more desirable substrates than their corresponding bromide and iodide counterparts taking advantage of low cost and availability.[12] However, their low reactivity has traditionally made these substrates reluctant coupling partners in these reactions, usually requiring high temperatures and long reaction times.[13] Major efforts have been made in the past decade toward the development of highly active Pd catalysts for the cross-coupling of aryl chlorides and organometallic reagents under mild reaction conditions.[14] In general, sterically hindered dialkylbiaryl phosphines and *N*-heterocyclic carbenes (NHCs) have proved to be useful in effecting these transformations with organoboron, organozinc, organotin, or organomagnesium reagents.[15]

We surmised that the development of new cross-coupling methodology which combines both, cheap and easy accessible organolithium reagents and aryl chlorides is highly desirable. The anticipated process would drastically reduce the amount of byproducts, the light and nontoxic LiCl being the only stoichiometric reaction waste. Herein, we report that the use of the commercially available Pd-PEPPSI-IPent or $Pd_2(dba)_3$/XPhos catalysts allows the selective cross-coupling of (hetero)aryllithium compounds with aryl chlorides in high yields under mild conditions (rt to 40 °C) and short reaction times (40 min to 4 h).

We started this study with the reaction between phenyllithium and 2-chloronaphthalene **1a**. Under the optimized conditions for the cross-coupling of organolithium reagents with aryl bromides ($Pd_2(dba)_3/P(^tBu)_3$),[11] the desired product **2a** was obtained in the presence of a large amount of homocoupling side product **4** (Table 1, entry 1).

**Table 1.** Screening of Different Ligands (see also Supporting Information, Table S1)



| entry[a] | [Pd] | ligand | conv (%) | **2a**:**3**:**4**:**5**[b] |
|---|---|---|---|---|
| 1 | **$Pd_2(dba)_3$** | **L1**, $P(tBu)_3$[c] | 78 | 46:3:26:2 |
| 2 | **$Pd_2(dba)_3$** | **L2**, $P(Cy)_3$[c] | 90 | 49:2:20:19 |
| 3 | **$Pd_2(dba)_3$** | **L3**, XPhos | full | 99:<1:<1:0 |
| 4 | **Pd-PEPPSI-IPent** | | full | 94:3:2:0 |
| 5[d] | **Pd-PEPPSI-IPent** | | full | 97:3:<1:0 |

[a] Conditions: PhLi (0.45 mmol, 1.8 M solution in dibutyl ether diluted with THF to a final concentration of 0.6 M) was added (1 mL/h) to a solution of 2-chloronaphthalene (0.3 mmol) in toluene (2 mL unless otherwise noted). [b] **2a**:**3**:**4**:**5** ratios determined by GC analysis. [c] 7.5 mol % was used. [d] In 1 mL of toluene. dba = dibenzylideneacetone.

The use of $PCy_3$ was detrimental for the selectivity and 1-phenylnaphthalene **5** was also formed indicating the formation of a benzyne intermediate via 1,2-elimination promoted by the organolithium reagent (entry 2).[16] To our delight, when XPhos (**L3**) was used in combination with $Pd_2(dba)_3$ (2.5 mol %) the cross-coupled product **2a** was obtained with excellent selectivity ( > 99%), avoiding dehalogenation ( < 1%) and inhibiting the formation of the homocoupling or isomerized side products ( < 1%, entry 3). The use of other sterically hindered phosphines resulted in lower selectivity with incomplete conversion (see Supporting Information (SI), Table S1). We also evaluated catalysts based on NHC ligands and observed that the air stable Pd-PEPPSI-IPent, introduced by Organ,[15e] also displayed high reactivity and selectivity (entry 4). In this

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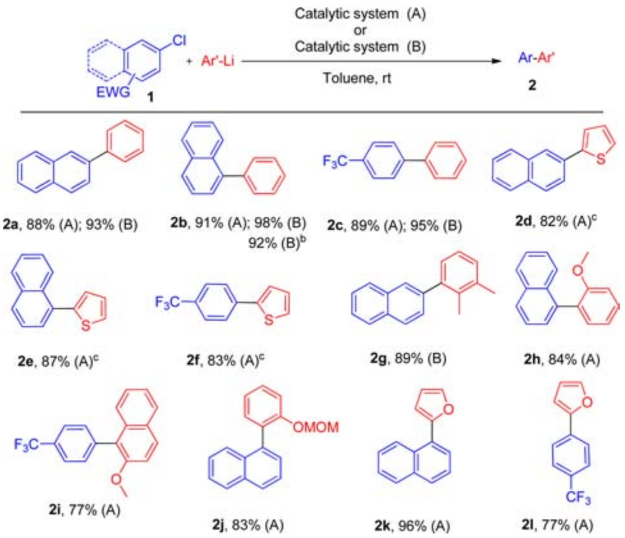
case, slower addition of PhLi (0.5 mL/h) and a higher concentration were found to be beneficial for an increase of the selectivity (entry 5). It should be noted that, for both catalytic systems, the reaction proceeds at rt and is finished once the addition of the lithium reagent is completed (40 min to 1 h) providing **2a** in 88% and 93% yield, respectively.

Having in hand these two optimized catalytic systems (A based on Pd-PEPPSI-IPent and B using $Pd_2(dba)_3$/XPhos), we examined the cross-coupling between different organolithium reagents and aryl chlorides (Scheme 1).

**Scheme 1.** Pd-Catalyzed Cross-Coupling of Aryl Lithium Reagents with Activated Aryl Chlorides[a]

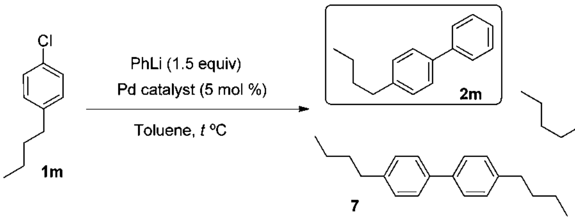


[a] Aryl chloride (0.3 mmol), ArLi (0.45 mmol, diluted with THF to reach 0.60 M concentration, unless otherwise noted). Catalytic system A: Pd-PEPPSI-IPent (5 mol %). Toluene (1 mL), flow rate = 0.5 mL/h. Catalytic system B: $Pd_2(dba)_3$ (2.5 mol %)/XPhos (10 mol %). Toluene (2 mL), flow rate = 1.0 mL/h. [b] 10 mmol (1.63 g) scale reaction using 2 mol % of catalyst. [c] TMEDA (1.2 equiv) was added to a thienyllithium solution (0.45 mmol, diluted with toluene to reach 0.60 M concentration), and the reaction was performed at 40 °C. Selectivity > 95% in all cases. Yield values refer to isolated yields after purification. EWG = electron withdrawing group.

1-Chloronaphthalene (**1b**) was selectively coupled with phenyllithium in high yield (91–98%), with no formation of the regioisomer **2a**. Notably, when this reaction is performed on gram scale (10 mmol, 1.63 g) employing 2 mol % of catalyst B, product **2b** is still obtained, after 6 h at rt, with similar selectivity and yield. The electron deficient 1-chloro-4-(trifluoromethyl)benzene **1c** also underwent clean coupling with phenyllithium giving high isolated yields (catalyst A: 89% and catalyst B: 95%) of the trifluoromethylated biaryl scaffold **2c**. Heteroaryl lithium compounds were also successful coupling partners. Thus, commercially available thienyllithium was shown to allow the cross-coupling with **1d**, **1e**, **1f** giving rise to compounds **2d**, **2e**, and **2f** with high yields and excellent selectivity (Scheme 1). In this case, the use of tetramethylethylenediamine (TMEDA) as an activating agent and a slightly higher temperature (40 °C) was necessary due to the reduced reactivity of this organometallic reagent.[11] Highly gratifying were the results observed with sterically hindered *ortho*-substituted organolithium reagents as in the preparation of compounds **2g**, **2h**, **2i**, and **2j** where in all cases the cross-coupling reaction proceeded at rt, in high yield and without loss of selectivity. It should be emphasized that this new methodology is compatible with currently available procedures to access organolithium species. For example, aryl lithium reagents used in the preparation of biaryls **2g**–**2i** were prepared via halogen–metal exchange, and the one used in the synthesis of **2j** was prepared by direct metalation[9] of methoxymethyl (MOM)-protected phenol (see SI for details). In addition, direct lithiation of furan led to furyllithium which was used for the reaction with chlorides **1k,l** to give the corresponding cross-coupling products in good yields and high selectivity.

To explore the effectiveness of this cross-coupling with respect to the reactivity of the aryl chloride, we examined a more electron-rich aryl chloride such as 1-butyl-4-chlorobenzene **1m** (Table 2).

**Table 2.** Optimization of the Cross-Coupling of PhLi with Electron-Rich Aryl Chloride **1m** (see also SI, Table S2)



| entry[a] | [Pd] | $t$ (°C) | reaction time | conv (%) | **2m:6:7**[b] |
|---|---|---|---|---|---|
| 1[c] | $Pd_2(dba)_3$/**L3** | rt | 40 min[d] | <1 | <1:0:0 |
| 2 | Pd-PEPPSI-IPent | rt | 40 min[d] | 61 | 57:4:0 |
| 3 | $Pd_2(dba)_3$/**L3** | 40 | 3.5 h[e] | full | 93:1:6 |
| 4 | Pd-PEPPSI-IPent | 35 | 3.5 h[e] | full | 92:4:4 |

[a] Conditions: PhLi (1.8 M solution in dibutyl ether diluted with THF to a final concentration of 0.6 M) was added to a solution of 1-butyl-4-chlorobenzene (0.3 mmol) in toluene (1 mL unless otherwise noted). [b] **2m**:**6**:**7** ratios determined by GC analysis. [c] In 2 mL of toluene. [d] Flow rate = 1 mL/h. [e] Flow rate = 0.2 mL/h. dba: dibenzylideneacetone.

No conversion was found when $Pd_2(dba)_3$/Xphos was used as a catalyst, and incomplete conversion was observed in the case of Pd-PEPPSI-IPent at rt (Table 2, entries 1 and 2). Further optimization of the reaction conditions (entries 3 and 4, and SI, Table S2) showed that slightly higher temperatures (35 or 40 °C) and longer addition times (3 h) of the organolithium reagent were key factors to reach full conversion with high selectivity. Interestingly, as electron-rich aryl chlorides do not react at rt in the presence of the $Pd_2(dba)_3$/Xphos catalytic system (B) while electron-poor aryl chlorides are coupled

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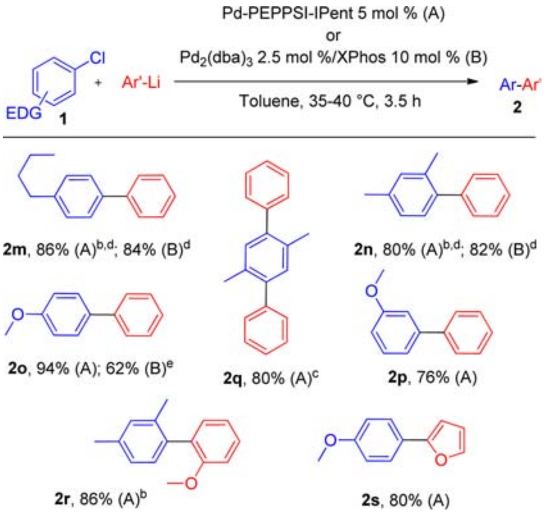
(17) For illustrative examples on the substrate scope limitations, see Supporting Information, Scheme S1.

efficiently at this temperature, the difference could be exploited for selective cross-coupling with different chlorides present in the same molecule.

A range of deactivated aryl chlorides could be coupled with different organolithium reagents using these optimized conditions (Scheme 2).[17]

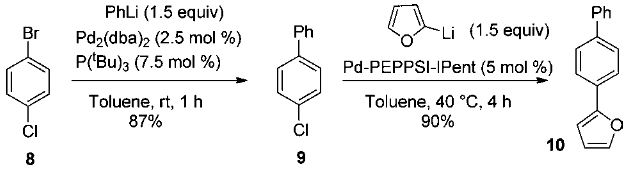
**Scheme 2.** Pd-Catalyzed Cross-Coupling of Aryl Lithium Reagents with Deactivated Aryl Chlorides[a]



[a] Aryl chloride (0.3 mmol), ArLi (0.45 mmol, diluted with THF to reach 0.60 M concentration and added at 0.2 mL/h flow rate). Toluene (1 mL) at 40 °C. Selectivity > 95% unless otherwise noted. [b] Reaction performed at 35 °C. [c] PhLi (0.9 mmol). [d] Selectivity > 90%. [e] Selectivity > 85%. Yield values refer to isolated yields after purification. EDG = electron donating group.

Sterically hindered *ortho*-substituded aryl chloride **1n** reacted in high selectivity with phenyllithium providing biaryl **2n** in good yield using both optimized catalytic systems. The cross-coupling of PhLi with 4-methoxychlorobenzene **1o**, a reluctant chloride coupling partner,[18] using $Pd_2(dba)_3$/XPhos gave rise to a large amount of homocoupling side product. Nonetheless, we could reduce the formation of this side product to < 2% by the use of Pd-PEPPSI-IPent as a catalyst which afforded product **2o** in excellent yield (94%). Similarly 1-chloro-3-methoxybenzene **1p** was readily arylated in good yield employing catalytic system A. Twofold arylation of 1,4-dichloro-2,5-dimethylbenzene, to form **2q**, was achieved in high selectivity and good yield exemplifying the applications of this catalytic system in multiple couplings. Triaryl compound **2q** is a precursor for a variety of indenofluorene derivates with application in electronic (e.g., thin film transistor) and optoelectronic materials (e.g., organic light emitting diodes, OLED).[19] A remarkable result is that the very hindered bis-*ortho*-substituted biaryl **2r** was readily formed under mild conditions and high yield by reaction between aryl chloride **1r** and 2-methoxyphenyllithium, employing catalytic system A. Finally, highly selective and fast coupling was also obtained in the reaction between furyllithium and 4-methoxy-chlorobenzene using the same catalytic system.

**Scheme 3.** Selective Consecutive Cross-Coupling of 1-Bromo-4-chlorobenzene with Different Aryl Lithium Reagents



In our previous work, we described that the cross-coupling of 1-bromo-4-chlorobenzene **8** with PhLi using the $Pd_2(dba)_3/P(tBu)_3$ catalyst system proceeds selectively, leaving the chloride untouched.[11] To demonstrate the complementarity of our new methodology, we further converted chloride **9**, in a subsequent cross-coupling, into heterotriaryl **10** in high yield by reaction with 2-furyllithium in the presence of the Pd-PEPPSI-IPent catalyst (Scheme 3).

In summary, we have shown the direct cross-coupling of aryl-lithium reagents with aryl chlorides in high yields and excellent selectivity. The methodology is based on the use of commercially available catalytic systems, $Pd_2(dba)_3$/XPhos or air stable Pd-PEPPSI-IPent. The reactions take place under mild conditions and feature short reaction times. The low cost and availability of both aryllithium reagents and aryl chlorides, together with the selectivity of this new methodology, make it a valuable alternative for well-established cross-coupling procedures.

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**Supporting Information Available.** Optimization tables, experimental procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.