Catalytic Direct Cross-Coupling of Organolithium Compounds with Aryl Chlorides

ORGANIC LETTERS XXXX Vol. XX, No. XX 000–000

Valentín Hornillos, Massimo Giannerini, Carlos Vila, Martín Fañanás-Mastral,* and Ben L. Feringa*

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

b.l.feringa@rug.nl; m.fananas.mastral@rug.nl

Received September 4, 2013



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 Pd₂(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

(5) (a) Hiyama, T.; Nakao, Y. Chem. Soc. Rev. **2011**, 40, 4893. (b) Denmark, S. E.; Regens, C. S. Acc. Chem. Res. **2008**, 41, 1486.

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

 ^{(1) (}a) Negishi, E. Angew. Chem., Int. Ed. 2011, 50, 6738. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Angew. Chem., Int. Ed. 2005, 44, 4442. (c) Corbet, J.; Mignani, G. Chem. Rev. 2006, 106, 2651. (d) Dunetz, J. R. Chem. Rev. 2011, 111, 2177. (e) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Angew. Chem., Int. Ed. 2012, 51, 5062.

^{(2) (}a) Stille, J. K. Angew. Chem., Int. Ed. 1986, 25, 508. (b) Espinet, P.; Echavarren, A. M. Angew. Chem., Int. Ed. 2004, 43, 4704.

^{(3) (}a) Suzuki, A. Angew. Chem., Int. Ed. **2011**, *50*, 6723. (b) Miyaura, N. In *Metal Catalyzed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Vol. 1, pp 41–123.

^{(4) (}a) Negishi, E.; King, A. O.; Okukado, N. J. Org. Chem. 1977, 42, 1821. (b) King, A. O.; Okukado, N.; Negishi, E. J. Chem. Soc., Chem. Commun. 1977, 683. (c) Knochel, P.; Singer, R. D. Chem. Rev. 1993, 93, 2117. (d) Phapale, V. B.; Cárdenas, D. J. Chem. Soc. Rev. 2009, 38, 1598.

^{(6) (}a) Tamao, K.; Sumitani, K.; Kumada, M. J. Am. Chem. Soc. 1972, 94, 4374. (b) Knappe, C. E. I.; von Wangelin, A. J. Chem. Soc. Rev. 2011, 40, 4948. (c) Corriu, R. J. P.; Masse, J. P. Chem. Commun. 1972, 144.

⁽⁷⁾ Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Angew. Chem., Int. Ed. 2005, 44, 5384.

 ⁽⁸⁾ Rappoport, Z.; Marek, I. The Chemistry of Organolithium Compounds; Wiley-VCH: Chichester, 2004.

⁽⁹⁾ Anctil, E. J. Snieckus, V. In *Metal Catalyzed Cross-Coupling Reactions*, Vol. 1; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 761–813.

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 arvl and alkenvl bromides.¹¹ By the use of toluene as a solvent and P(^tBu)₃ as ligand and by finetuning of the reaction conditions, the high reactivity of the organolithium reagents was controlled, efficient transmetalation was achieved, and high selectivity and good vields 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 crosscoupling 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 crosscoupling methodology which combines both, cheap and easy accessible organolithium reagents and aryl chlorides is highly desirable. The anticipated process would

Chem. 2013, 5, 667.
(12) (a) Grushin, V. V.; Alper, H. Chem. Rev. 1994, 94, 1047. (b)
Grushin, V. V.; Alper, H. In Activation of Unactive Bonds and Organic Synthesis; Murai, S., Ed.; Springer: Berlin, 1999; p 203.

(13) (a) Littke, A. F.; Fu, G. C. Angew. Chem., Int. Ed. 1998, 37, 3387.
(b) Littke, A. F.; Dai, C.; Fu, G. C. J. Am. Chem. Soc. 2000, 122, 4020. (c) Dai, C.; Fu, G. C. J. Am. Chem. Soc. 2002, 124, 6343. (e) Littke, A. F.; Schwarz, L.; Fu, G. C. J. Am. Chem. Soc. 2002, 124, 6343. (e) Littke, A. F.; Fu, G. C. Angew. Chem., Int. Ed. 2002, 41, 4176. (f) Wolfe, J. P.; Buchwald, S. L. Angew. Chem., Int. Ed. 1999, 38, 2413. (g) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. J. Am. Chem. Soc. 1998, 120, 9722. (h) Buchwald, S. L.; Surrey, D. L. Angew. Chem., Int. Ed. 2008, 47, 6338. (i) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. J. Org. Chem. 2020, 67, 5553. (j) Herrmann, W. A. Angew. Chem., Int. Ed. 2002, 41, 1290. (k) Altenhoff, G.; Goddard, R.; Lehman, C. W.; Glorius, F. J. Am. Chem. Soc. 2004, 126, 15195.

(14) (a) Fu, G. C. Acc. Chem. Res. **2008**, 41, 1555. (b) Martin, R.; Buchwald, S. L. Acc. Chem. Res. **2008**, 41, 1461. (c) Nasielski, J.; Hadei, N.; Achonduh, G. E.; Kantchev, A. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. Chem.—Eur. J. **2010**, 16, 10844. (d) Valente, C.; Calimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. Angew. Chem., Int. Ed. **2012**, 51, 3314.

(15) (a) Navarro, O.; Kelly, R. A.; Nolan, S. P. J. Am. Chem. Soc.
2003, 125, 16194. (b) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.;
Scott, N. M.; Nolan, S. P. J. Am. Chem. Soc. 2006, 128, 4101. (c) Diebolt,
O; Braunstein, P.; Nolan, S. P.; Cazin, C. S. J. Chem. Commun. 2008,
3190. (d) Han, C.; Buchwald, S. L. J. Am. Chem. Soc. 2009, 131, 7532. (e)
Organ, M. G.; Çalimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. Angew.
Chem., Int. Ed. 2009, 48, 2383. (f) Sau, S. C.; Santra, S.; Sen, T. K.;
Mandal, S. K.; Koley, D. Chem. Commun. 2012, 48, 555.

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).





$entry^a$	[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 PCy₃ 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 Pd₂(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

^{(10) (}a) Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. J. Org. Chem. 1979, 44, 2408. (b) For an alternative approach using a flow microreactor: Nagaki, A.; Kenmoku, A.; Moriwaki, Y.; Hayashi, A.; Yoshida, J. Angew. Chem., Int. Ed. 2010, 49, 7543. For the use of a silicon-based transfer agent, see: (c) Smith, A. B., III; Hoye, A. T.; Martinez-Solorio, D.; Kim, W.; Tong, R. J. Am. Chem. Soc. 2012, 134, 4533. (d) Nguyen, M. H.; Smith, A. B., III. Org. Lett. 2013, 15, 4268. (11) Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. Nat.

⁽¹⁶⁾ Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. Adv. Synth. Catal. 2001, 343, 789.

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: Pd₂(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, arvl lithium reagents used in the preparation of biarvls 2g-2i were prepared via halogenmetal exchange, and the one used in the synthesis of 2j was prepared by direct metalation⁹ 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. I 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).





$entry^a$	[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	$3.5~\mathrm{h}^e$	full	93:1:6
4	Pd-PEPPSI- IPent	35	$3.5~\mathrm{h}^e$	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

⁽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 **10**, a reluctant chloride coupling partner, ¹⁸ using Pd₂(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 20 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-2,5dimethylbenzene, 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) Scheme 3. Selective Consecutive Cross-Coupling of 1-Bromo-4chlorobenzene with Different Aryl Lithium Reagents



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.

In our previous work, we described that the crosscoupling 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.

Acknowledgment. The Netherlands Organization for Scientific Research (NWO-CW), National Research School Catalysis (NRSC-C), European Research Council (ERC Advanced Grant 227897 to B.L.F.), Royal Netherland Academy of Arts and Sciences (KNAW), and Ministry of Education Culture and Science (Gravity program 024.601035) are acknowledged for financial support. C.V. was supported by an Intra-European Marie Curie fellowship (FP7-PEOPLE-2011-IEF) (Contract No. 300826).

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.

⁽¹⁸⁾ Denmark, S. E.; Smith, R. C.; Tau, W. T.; Muhuhi, J. M. J. Am. Chem. Soc. 2009, 131, 3104.

^{(19) (}a) Merlet, S.; Birau, M.; Wang, Z. Y. Org. Lett. 2002, 4, 2157.
(b) Lin, T.-C.; Hsu, C.-S.; Hu, C.-L.; Chen, Y.-F.; Huang, W.-J. Tetrahedron Lett. 2009, 50, 182.

The authors declare no competing financial interest.