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Cross-Coupling

*t*BuLi-Mediated One-Pot Direct Highly Selective Cross-Coupling of Two Distinct Aryl Bromides

Carlos Vila,[a, b] Sara Cembellín,[a] Valentín Hornillos,[a] Massimo Giannerini,[a] Martín Fañanás-Mastral,[a, c] and Ben L. Feringa*[a]

Abstract: A Pd-catalyzed direct cross-coupling of two distinct aryl bromides mediated by *t*BuLi is described. The use of [Pd-PEPPSI-IPr] or [Pd-PEPPSI-IPent] as catalyst allows for the efficient one-pot synthesis of unsymmetrical biaryls at room temperature. The key for this selective cross-coupling is the use of an *ortho*-substituted bromide that undergoes lithium–halogen exchange preferentially.

Introduction

The development of synthetic methodologies for the preparation of unsymmetrical biaryls has attracted major interest over more than a century.[1,2] Biaryl compounds represent very important structures that have numerous applications in many fields of chemistry. For example, the biaryl structural motif is widely present in natural products[3] and a very common target in the pharmaceutical and agrochemical industry.[4] Furthermore, biaryls, especially chiral ones, play an important role in privileged ligands in catalysis.[5] Moreover, these compounds have proven essential in material science.[6] Transition metal-mediated coupling reactions, among the innumerable methods for the construction of biaryls, are arguably the leading strategies used.[7] In this context, palladium-catalyzed cross-coupling of arylmetal reagents and aryl (pseudo)halides to form biaryls is one of the most effective methods, which has fundamentally changed the chemist's approach to biaryl compounds during the past 40 years.[8] Many different aryl organometallic reagents have been used in Pd-catalyzed cross-couplings, including Grignard,[9] boron,[10] zinc,[11] tin[12] and silicon[13] reagents. In contrast, organolithium reagents[14] have found limited use in palladium-catalyzed cross-coupling reactions.[15] In 1979, following earlier stoichiometric approaches, Murahashi pioneered the use of organolithium reagents in catalytic cross-coupling reactions showing also the limitations associated with their high reactivity.[16] Approaches based on Si-transfer agents[16f–h] and flow chemistry[16d,e] have recently been introduced and our group described the direct catalytic cross-coupling of organolithium compounds using aryl bromides,[17] aryl chlorides[18] and aryl triflates.[19] However, these methods all require the separate preparation of a stoichiometric organometallic reagent,[20,21] being limited in some cases by the availability and stability of the reagent itself.

The one-pot direct cross-coupling of two different aryl halides, would provide a more straightforward method for the synthesis of unsymmetrical biaryls. There are some reports on the direct cross-coupling of distinct aryl halides involving Pd,[22] Ni[23] or Co[24] as the catalyst. These methodologies usually require additional reductive agents such as Zn, Mn, alcohols or amines and sometimes harsh conditions, while, in the case of nickel, electrochemical methods were employed. Normally, for an effective synthesis of unsymmetrical biaryls, different halides with significant differences in reactivity are used, such as cross-coupling of Ar–I with Ar–Br, Ar–I with Ar–Cl, or Ar–Br with Ar–Cl.[22–24] Therefore, the development of alternative strategies for the direct coupling of aryl halides for the synthesis of unsymmetrical biaryls is highly warranted. We questioned whether it would be possible to achieve the direct cross-coupling of two different aryl bromides selectively, generating in situ the organometallic reagent derived from one of these bromides. One easy and fast method to generate an organometallic compound in situ from an aryl bromide is the formation of the corresponding aryllithium reagent via lithium–halogen exchange.[14] The fundamental issue to solve is to achieve selective lithium–halogen exchange of one of the two aryl bromide coupling partners. For this purpose, we envisioned the use of 2-bromoanisole, which undergoes faster lithium–halogen exchange than other aryl bromides lacking an *ortho*-directing group (Scheme 1).

Recently, we developed a palladium-catalyzed cross-coupling of aryl bromides with aryllithium reagents.[17] These results prompted us to study the in situ formation of the organolithium reagent via lithium–halogen exchange. In this way, we could avoid the pre-formation of the organometallic reagent, providing fast, versatile and more straightforward methodolo-

[a] Dr. C. Vila, S. Cembellín, Dr. V. Hornillos, M. Giannerini, Dr. M. Fañanás-Mastral, Prof. Dr. B. L. Feringa
Stratingh Institute for Chemistry, University of Groningen
Nijenborgh 4, 9747 AG, Groningen (The Netherlands)
Fax: (+31) 50-363-4278
E-mail: b.l.feringa@rug.nl

[b] Dr. C. Vila
Present address: Departament de Química Orgànica, Facultat de Química
Universitat de València, Dr. Moliner 50, 46100 Burjassot, València (Spain)

[c] Dr. M. Fañanás-Mastral
Present address: Department of Organic Chemistry and Center for Research in Biological Chemistry and Molecular Materials (CIQUS)
University of Santiago de Compostela, 15782 Santiago de Compostela (Spain)

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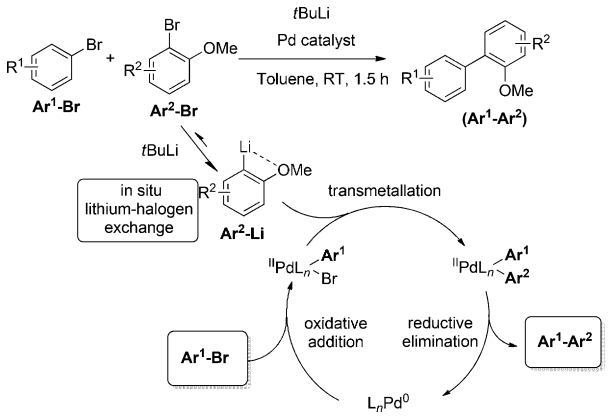


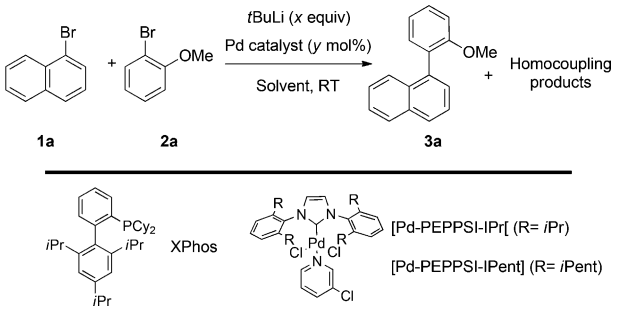
Scheme 1. Palladium-catalyzed cross-coupling with organolithium reagents.

gy. We reasoned that this protocol should be based on a lithium–halogen exchange being faster than the potential Pd-catalyzed alkylation reaction. Therefore, *t*BuLi was the lithiation agent of choice,[25] as *n*BuLi,[17a] *sec*-BuLi,[17c] and *i*PrLi[17c] can participate in palladium-catalyzed cross-coupling with aryl bromides, affording the corresponding alkylated products. Herein, we describe the direct synthesis of unsymmetrical biaryls in a one-pot procedure from two different aryl bromides in the presence of *t*BuLi catalyzed by palladium.

Results and Discussion

Our initial studies began with the cross-coupling reaction between 1-bromonaphthalene **1a** and 2-bromoanisole **2a** using $[Pd(P(tBu)_3)_2]$[26] as catalyst (Table 1, entry 1), and a solution of *t*BuLi in toluene was added slowly over 1 h. We were pleased to find that our hypothesis on the selective lithium–halogen exchange was correct, and the corresponding unsymmetrical biaryl **3a** was the major product isolated in 65% yield. When XPhos[5c] was used in combination with $[Pd_2(dba)_3]$ (Table 1, entry 2) the selectivity toward **3a** was lower. Recently, Organ and co-workers introduced highly effective [Pd-PEPPSI] pre-catalysts that are air stable and commercially available.[27] Both [Pd-PEPPSI-IPr] and [Pd-PEPPSI-IPent] were effective catalysts for this transformation, but with [Pd-PEPPSI-IPr],[28,29] biaryl **3a** was isolated in higher yield (80%; Table 1, entry 4). When diethyl ether was used as a solvent (Table 1, entry 5), a detrimental effect on the selectivity to the desired unsymmetrical biaryl was observed. The lack of selectivity could be attributed to the higher reactivity of *t*BuLi in coordinating solvents (due to the formation of lower order aggregates). Under these conditions, both halides undergo a fast lithiation, independently of the presence of the *ortho*-directing group. Based on these observations, we decided to use toluene as the preferred solvent. After tuning of the ratio of the aryl bromides (Table 1, entries 6–9), we found that when 2-bromoanisole was used in small excess, the product was isolated with slightly higher yields (Table 1, entries 7 and 9). Finally, the reaction was performed with 1 mmol of **1a** and 1.2 mmol of **2a**, using only 1 mol% of [Pd-PEPPSI-IPr], to afford the corresponding 1-(2-methoxyphenyl)naphthalene **3a** in 93% yield (Table 1, entry 10).[30]

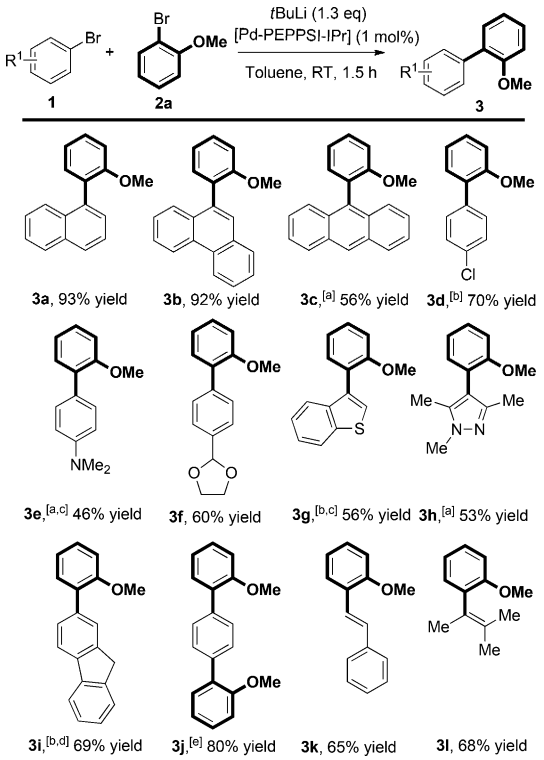
Table 1. Optimization of the direct cross-coupling.[a]



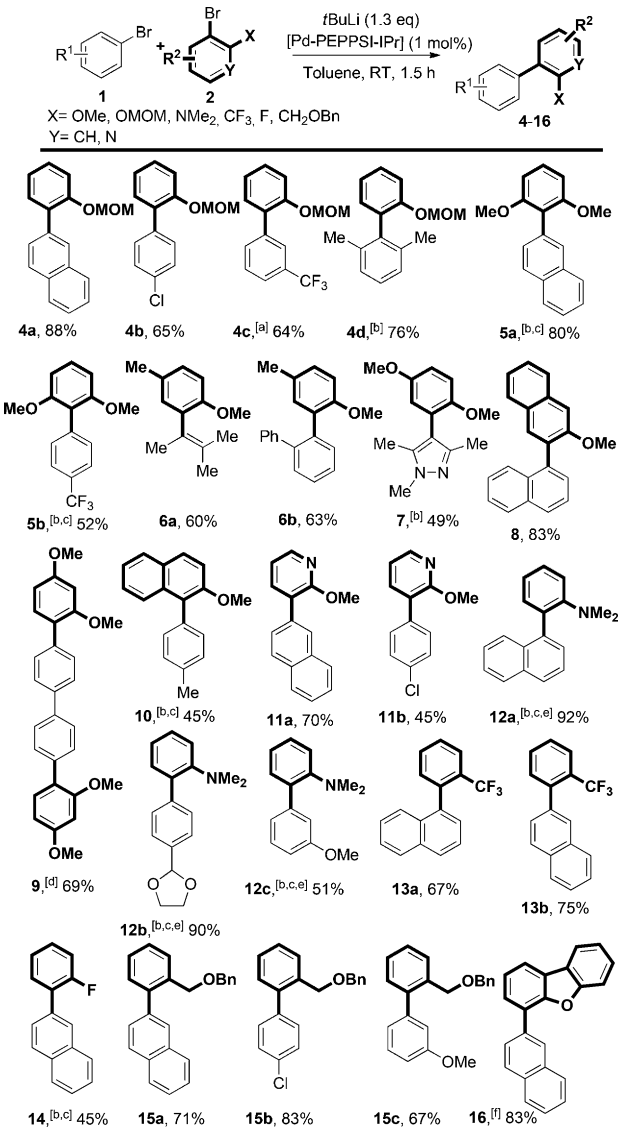
Entry	Pd source	*t*BuLi [equiv]	Yield [%][b]
1	$[Pd(PtBu_3)_2]$ (5 mol%)	1.1	65[c]
2	$[Pd_2(dba)_3]$(2.5 mol%) + XPhos (10 mol%)	1.1	52[d]
3	[Pd-PEPPSI-IPent] (2 mol%)	1.1	69[e]
4	[Pd-PEPPSI-IPr] (2 mol%)	1.1	80[f]
5[g]	[Pd-PEPPSI-IPr] (2 mol%)	1.1	39[h]
6[i]	[Pd-PEPPSI-IPr] (2 mol%)	1.5	88[j]
7[k]	[Pd-PEPPSI-IPr] (2 mol%)	1.5	91[j]
8[l]	[Pd-PEPPSI-IPr] (2 mol%)	1.25	89[j]
9[m]	[Pd-PEPPSI-IPr] (2 mol%)	1.25	91[j]
10[n]	[Pd-PEPPSI-IPr] (1 mol%)	1.3	93[j]

[a] Conditions, unless otherwise stated: **1a** (0.3 mmol), **2a** (0.3 mmol) and Pd catalyst were dissolved in toluene (2 mL). A solution of *t*BuLi (*x* equiv of commercially available 1.7 M solution in pentane, diluted to 1 mL with toluene) was added over 1 h; [b] isolated products; [c] 20% selectivity to the homocoupling products by GC analysis; [d] more than 20% selectivity to the homocoupling products by GC analysis; [e] 10% selectivity to the homocoupling products by GC analysis; [f] less than 10% selectivity to the homocoupling products by GC analysis; [g] Et_2O was used as solvent; [h] more than 30% selectivity to the homocoupling products by GC analysis; [i] 1.5 equiv of **1a** were used; [j] less than 5% selectivity to the homocoupling products by GC analysis; [k] 1.5 equiv of **2a** were used; [l] 1.25 equiv of **1a** were used; [m] 1.25 equiv of **2a** were used; [n] 1.0 mmol of **1a** and 1.2 mmol of **2a** was used, and *t*BuLi was added without dilution in toluene over 1.5 h.

Having established the optimized conditions and [Pd-PEPPSI-IPr] as an efficient catalyst for the cross-coupling of **1a** and **2a**, we studied the scope of the cross-coupling between different aryl bromides and 2-bromoanisole for the synthesis of unsymmetrical biaryls **3** (Scheme 2). For example, 9-bromophenanthrene reacted smoothly, affording the biaryl **3b** in 92% yield. However, with a more hindered bromide, such as 9-bromoanthracene, [Pd-PEPPSI-IPent] was necessary to obtain higher conversion to the tri-*ortho*-substituted biaryl **3b**, although full conversion was not achieved. Different substituents in the *para*-position of the aromatic ring, such as Cl, NMe_2 or an acetal-protected aldehyde, were tolerated and the corresponding biaryls **3d–f** were obtained in good yields. Bromo-substituted heterocycles, 3-bromobenzo[*b*]thiophene or 4-bromo-1,3,5-trimethyl-1*H*-pyrazole, were also tested, providing the corresponding products **3g** (56%) and **3h** (53%). Interestingly, 2-bromofluorene reacted smoothly with 2.2 equivalents of *t*BuLi, despite the acidity of the benzylic protons, and the product **3i** was obtained in good yield (69%). Furthermore, multiple coupling of **2a** took place in the twofold cross-cou-



Scheme 2. Scope of the reaction between different aryl bromides and **2a** in the presence of *t*BuLi catalyzed by Pd. Conditions, unless otherwise stated: to a solution of **1** (1 mmol), **2a** (1.2 mmol) and [Pd-PEPPSI-IPr] catalyst (1 mol%) in toluene (6 mL), *t*BuLi (1.3 equiv, 0.77 mL of a commercial 1.7 M solution in pentane) was added over 1.5 h. [a] 2 mol% of [Pd-PEPPSI-IPent] was used; [b] 2 mol% of [Pd-PEPPSI-IPr] was used; [c] the reaction was performed at 35 °C; [d] 2.2 equiv of *t*BuLi; [e] the reaction was performed with 1,4-dibromobenzene (0.5 mmol), **2a** (1.3 mmol), and [Pd-PEPPSI-IPr] catalyst (2 mol%) in toluene (6 mL), and *t*BuLi (2.8 equiv, 0.85 mL of a commercial 1.7 M solution in pentane) was added over 1.5 h; [f] yields refer to isolated products.



Scheme 3. Scope for the cross-coupling of aryl bromides catalyzed by Pd in the presence of *t*BuLi. Conditions, unless otherwise stated: to a solution of **1** (1 mmol), **2** (1.2 mmol) and [Pd-PEPPSI-IPr] catalyst (1 mol%) in toluene (6 mL), *t*BuLi (1.3 equiv, 0.77 mL of a commercial 1.7 M solution in pentane) was added over 1.5 h. [a] 2 mol% of [Pd-PEPPSI-IPr] was used; [b] 2 mol% of [Pd-PEPPSI-IPent] was used; [c] the reaction was performed at 40 °C; [d] the reaction was performed with 4,4′-dibromo-1,1′-biphenyl (0.5 mmol), 1-bromo-2,4-dimethoxybenzene (1.3 mmol) and [Pd-PEPPSI-IPr] catalyst (2 mol%) in toluene (6 mL), and *t*BuLi (2.8 equiv, 0.85 mL of a commercial 1.7 M solution in pentane) was added over 1.5 h; [e] 2.2 equiv of *t*BuLi; [f] reaction on 0.3 mmol scale; [g] yields refer to isolated products.

pling of 1,4-dibromobenzene, resulting in the terphenyl **3j**, isolated in 80% yield. Finally, the cross-coupling of 2-bromoanisole with alkenyl bromides was also feasible, illustrated by the formation of olefins **3k** and **3l**.

Having demonstrated the reaction between 2-bromoanisole and different aryl bromides, we decided to investigate aryl bromides with different *ortho* (directing) groups, such as -OMOM, -NMe_2, -CF_3, -F, or -CH_2OBn, as nucleophilic partners (Scheme 3). For example, methoxymethyl ether (MOM)-protected 2-bromophenol reacted efficiently with different aryl bromides, yielding the corresponding biaryl **4a**–**d**, including tri-*ortho*-substituted biaryl **4d** in 76% yield. When 2-bromo-1,3-dimethoxybenzene was used, it was necessary to perform the reaction at 40 °C to afford good conversions to the final products **5a** and **5b** in the presence of [Pd-PEPPSI-IPent] (2 mol%). The slightly diminished reactivity is probably due to the fact that the corresponding 2-lithium-1,3-dimethoxybenzene reagent is very hindered. Furthermore, more substituted 2-bromoanisole, 2-bromo-3-methoxynaphthalene and 1-bromo-2-methoxynaphthalene were tolerated for the reaction, and the corresponding products **6a**, **6b**, **7**, **8**, and **10** were obtained in moderate to good yields. Additionally, quaterphenyl **9** was successfully obtained in 69% yield by the multiple coupling of 1-bromo-2,4-dimethoxybenzene with 4,4′-dibromo-1,1′-biphenyl. Notably, although pyridines do not easily undergo cross-coupling reactions[31] and lithiated pyridines are not stable at non-cryogenic temperatures, 3-bromo-2-methoxypyridine was tolerated in the reaction and the corresponding biaryls with a pyridine moiety **11a** and **11b** could be isolated.

The methodology was also extended to the reaction of 2-bromo-*N*,*N*-dimethylaniline with different aryl bromides (**12a**–**c**), but in this case 2 mol% of [Pd-PEPPSI-IPent] and 2.2 equiv

of *t*BuLi were used and the reaction was performed at 40 °C. Fluorinated compounds are very important in the agrochemical and pharmaceutical industry, and frequently used in material science.[32] Exploring CF_3 and F as *ortho*-directing group, we were grateful that 1-bromo-2-(trifluoromethyl)benzene and 1-bromo-2-fluorobenzene could be used in cross-coupling reaction to allow the synthesis of fluorinated biaryls (**13a**, **13b** and **14**), without any traces of side products resulting from a nucleophilic aromatic substitution or benzyne formation. However, in the case of 1-bromo-2-fluorobenzene, the corresponding product **14** was isolated with moderate yield. Moreover, 1-((benzyloxy)methyl)-2-bromobenzene could be used for the coupling with various aryl bromides with electron-donating or electron-withdrawing groups, providing **15a**–**15c** in high yield. Finally, using 4-bromodibenzofuran and 2-bromonaphthalene the heterobiaryl **16** was obtained in 83% yield.

Conclusion

In summary, we have demonstrated the direct cross-coupling of two different aryl bromides by palladium catalysis mediated by *t*BuLi. The [Pd-PEPPSI-IPr] or [Pd-PEPPSI-IPent] complexes were shown to be efficient catalysts for the one-pot synthesis of unsymmetrical biaryls at room temperature. The reaction takes advantage of an *ortho*-substituted bromide to effect in situ preferred lithium–halogen exchange and to attain good selectivity toward the unsymmetrical biaryl. Several groups *ortho* to the bromide can be used, including -OMe, -OMOM, $-NMe_2$, $-CF_3$, -F, $-CH_2OBn$, or benzofuran. Furthermore, electrophilic partners, such as (hetero)aryl bromides with electron-donating or electron-withdrawing groups, were successfully used. Notably, we also showed that the cross-coupling with 3-bromo-2-methoxypyridine is possible. This new methodology provides a fast, highly versatile and straightforward one-pot protocol to access unsymmetrical biaryls under mild conditions.

Experimental Section

Synthesis of **3a**: In a dry Schlenk flask, PEPPSI-IPr (1 mol%, 0.01 mmol, 6.8 mg), 1-bromonaphthalene **1a** (1 mmol, 207.7 mg, 140 μL), and 2-bromoanisole (1.2 mmol, 224.4 mg, 150 μL) were dissolved in dry toluene (6 mL) and the mixture was stirred at room temperature. *t*BuLi (1.3 mmol, 0.77 mL of commercial 1.7 M solution in pentane) was slowly added over 1.5 h by syringe pump. When the addition was complete, the reaction was quenched with MeOH (2 mL). The solvent was evaporated under reduced pressure and the crude product purified by column chromatography on silica gel (*n*-pentane/ether 98:2) affording product **3a** as a white solid in 93% yield.

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Keywords: biaryls · cross-coupling · lithium · N-heterocyclic carbenes · palladium

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