

## Cross-Coupling

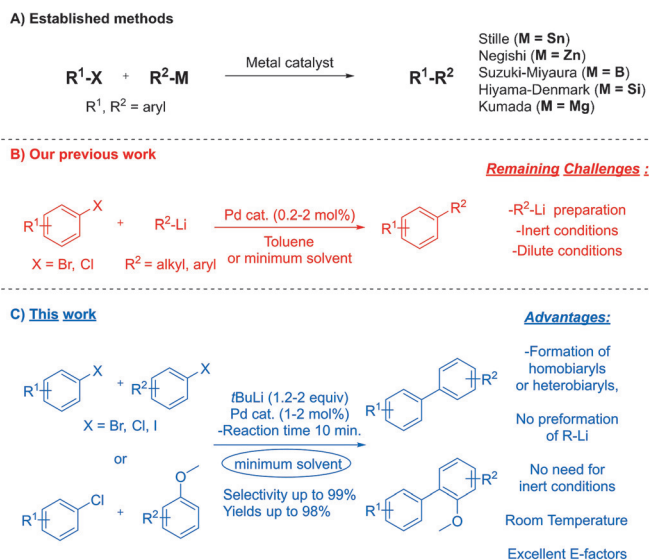
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## Fast, Efficient and Low E-Factor One-Pot Palladium-Catalyzed Cross-Coupling of (Hetero)Arenes

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**Abstract:** The homocoupling of aryl halides and the hetero-coupling of aryl halides with either aryl bromides or arenes bearing an ortho-lithiation directing group are presented. The use of a Pd catalyst, in combination with *t*-BuLi, allows for the rapid and efficient formation of a wide range of polyaromatic compounds in a one pot procedure bypassing the need for the separate preformation of an organometallic coupling partner. These polyaromatic structures are obtained in high yields, in 10 min at room temperature, with minimal waste generation (*E*-factors as low as 1.5) and without the need for strict inert conditions, making this process highly efficient and practical in comparison to classical methods. As illustration, several key intermediates of widely used BINOL-derived structures are readily prepared.

Biaryl structures are key components in catalysts, natural products, pharmaceuticals, polymers and many other important classes of chemicals.<sup>[1]</sup> The development of efficient syntheses of biaryls has therefore drawn major attention by the chemical community over the past decades.<sup>[2]</sup> Among the various methods explored, the transition metal catalyzed cross-coupling of two aryl groups (Figure 1 A) has proven to be among the most efficient and versatile strategies available and new developments continuously emerge expanding the scope of this approach.<sup>[3]</sup> One of the major remaining challenges is the development of complementary methods which are not only highly efficient but also economically viable and environmentally friendly. Indeed, many of the above mentioned well-established methods require the use of heat, stoichiometric amounts of additional reagents and/or additives as well as dilute conditions, which negatively impact the reaction outcome in terms of environmental cost while offering opportunities for low *E*-factor<sup>[4]</sup> alternatives. One of the solutions to overcome some of the above mentioned issues was the development of solvent free coupling reactions.<sup>[5]</sup> This resulted in significant improvements not only reducing the waste created but also, in many cases, of other parameters such as catalytic loading, reaction speed and scalability. Our group has been interested in the development of novel more sustainable cross-coupling methods which resulted in procedures for the palladium-catalyzed direct



**Figure 1.** A) Established methods for metal-catalyzed cross-coupling reactions. B) Catalytic cross-couplings with organolithium compounds. C) Fast and efficient one-pot Pd-catalyzed cross-coupling of distinct (hetero)arenes with low *E*-factors.

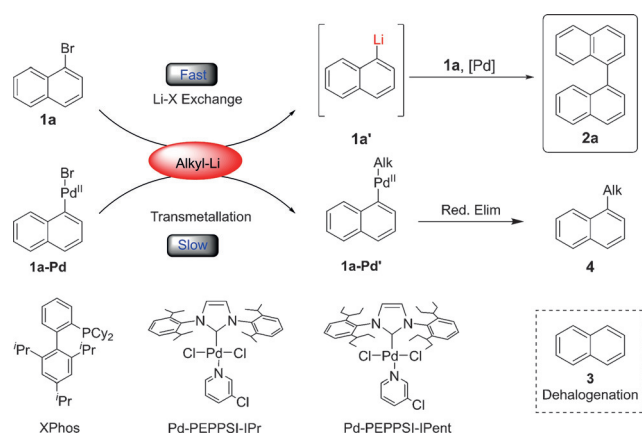
cross-coupling of highly reactive organolithium reagents with organic halides, ethers and triflates based on the pioneering work of Murahashi (Figure 1 B).<sup>[6]</sup> The use of organolithium reagents<sup>[7]</sup> instead of classical coupling partners such as Stille,<sup>[8]</sup> Kumada<sup>[9]</sup> or Suzuki-Miyaura<sup>[10]</sup> reagents resulted in a significant improvement in atom efficiency, employing mild conditions, while maintaining high yields. These methods have proven versatile alternatives and were recently applied to total synthesis of biologically active compounds.<sup>[11]</sup> In addition, these couplings often reach full conversion much faster than the previously mentioned methods, an improvement that has also been the focus of much research recently.<sup>[12]</sup> A second step towards higher efficiency was achieved very recently by our group by demonstrating that the direct coupling of organolithium compounds to aryl halides could also be performed solventless,<sup>[13]</sup> which reduced the overall waste of the reaction significantly with *E*-factors<sup>[14]</sup> up to tenfold lower than previously.<sup>[15]</sup> However remaining issues included the need to separately prepare the organolithium reagent, limited availability of coupling partners, and low functional group tolerance. The need to prepare separately the organolithium partner was considered the most important target. This two-step process was responsible for most of the generated waste, for lowering significantly the scope of substrates and also because the reactivity of the organolithium results in the degradation of several common functional groups. In order to address these issues, we furthered

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our investigation into the unique properties of these cross-coupling reactions and herein we report the development of a novel, solvent free, direct palladium catalyzed cross-coupling of a wide range of distinct (hetero)arenes mediated by organolithium reagents (Figure 1C). This simple and straightforward one-pot procedure affords a wide variety of biaryl products, including advanced intermediates, with excellent yields in record coupling times and featuring low E-factors. Moreover the need for inert conditions and the separate formation of the organolithium partner were eliminated.

In preliminary studies the Pd-catalyzed one pot homocoupling of 1-bromonaphthalene (**1a**) mediated by an alkyl lithium to obtain binaphthalene was examined (**2a**, Scheme 1). We reasoned it would be possible to bypass the



**Scheme 1.** Possible cross-coupling and lithium-halogen exchange reactions.

need for the separate formation of the aryl lithium partner due to the differences in kinetics between the various possible coupling and lithium-halogen exchange reactions. It was anticipated that with the use of either *t*-BuLi or *s*-BuLi the cross-coupling between an aryl bromide (**1a**) and in situ aryl lithium (**1a'**, leading to **2a**) would occur before side reactions that is, dehalogenation (leading to **3**) or cross-coupling between the aryl bromide and the alkyl lithium (leading to **4**). This meant that upon addition of the alkyl lithium to the aryl bromide, lithium halogen exchange would selectively occur to form an aryl lithium intermediate which is immediately consumed in the coupling step avoiding any buildup of the organolithium species (which would lead to **3** upon quenching) bypassing many of the issues in previous reported methods using organolithium reagents<sup>[6b]</sup> while retaining high levels of selectivity. In contrast *s*-BuLi with various catalyst (Table 1, entries 1–4), when *t*-BuLi<sup>[16]</sup> was added over a period of 10 min onto neat 1-bromonaphthalene in the presence of 1 mol % Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub> or Pd-PEPPSI-IPent<sup>[17]</sup> about 50 % conversion to **2a** occurred (entries 6 and 7). While no formation of **4** could be observed under these conditions, a significant amount of starting aryl bromide remained. Switching to cheaper Pd-PEPPSI-IPr as catalyst (entry 8) saw a slight increase in selectivity but no notable change in conversion which allowed to opt for the cheaper of the two.

**Table 1:** Optimization of the formation of **2a** over **3** and **4**.

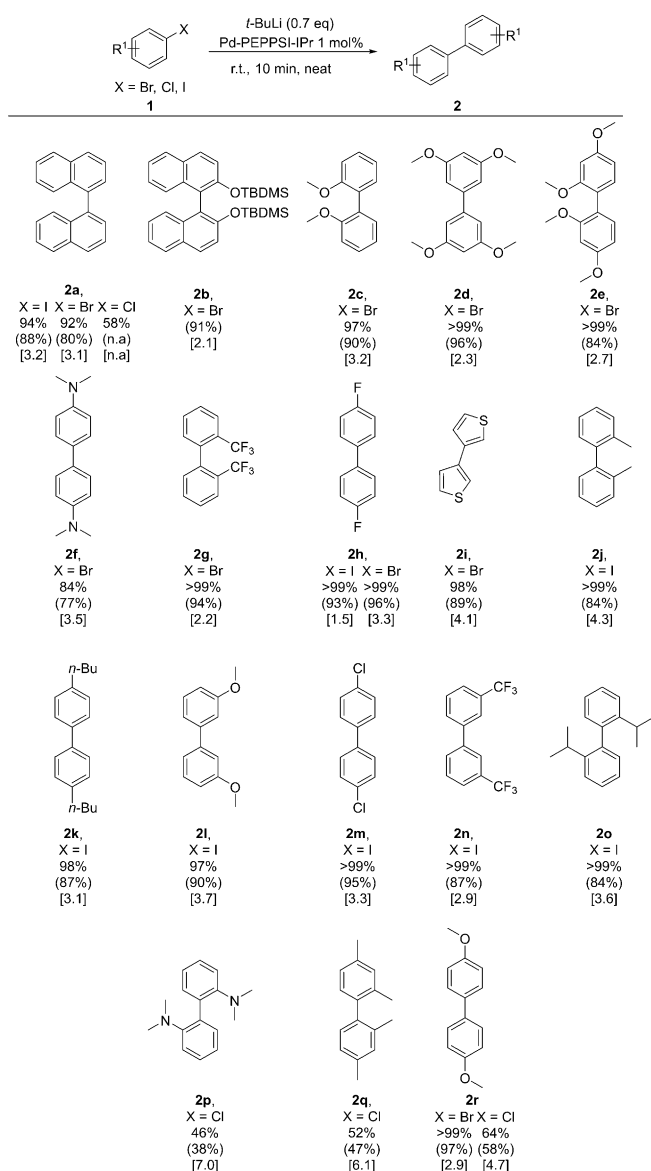
Entry	RLi (equiv)	[Pd] (x mol %)	<b>1a</b> : <b>2a</b> : <b>3</b> : <b>4</b> <sup>[a]</sup>
1	<i>s</i> -Bu (2)	Pd/C (5)	57:0:24:0
2	<i>s</i> -Bu (2)	Pd-PEPPSI-IPent (2)	57:14:13:15
3	<i>s</i> -Bu (2)	Pd-PEPPSI-IPr (2)	57:6:3:33
4	<i>s</i> -Bu (2)	Pd[P( <i>t</i> -Bu) <sub>3</sub> ] <sub>2</sub> (2)	54:17:4:25
5	<i>t</i> -Bu (2)	XPhos/Pd <sub>2</sub> dba <sub>3</sub> (1)	66:0:34:0
6	<i>t</i> -Bu (2)	Pd[P( <i>t</i> -Bu) <sub>3</sub> ] <sub>2</sub> (2)	36:47:18:0
7	<i>t</i> -Bu (2)	Pd-PEPPSI-IPent (2)	35:51:14:0
8	<i>t</i> -Bu (2)	Pd-PEPPSI-IPr (2)	32:55:13:0
9 <sup>[b]</sup>	<i>t</i> -Bu (2)	Pd-PEPPSI-IPr (2)	5:76:19:0
10 <sup>[b]</sup>	<i>t</i> -Bu (0.7)	Pd-PEPPSI-IPr (0.1)	8:81:11:0
11 <sup>[b]</sup>	<i>t</i> -Bu (0.7)	Pd-PEPPSI-IPr (1)	0:92:8:0

[a] Ratios determined by GC-MS. [b] Inert atmosphere was replaced by dry air. See the Supporting Information for experimental details.

The active form of the catalyst might be oxygen generated nanoparticles as we recently demonstrated to be the case in organolithium based transformations<sup>[6f]</sup> and that switching from an inert atmosphere to dry air might promote the formation of the active catalyst and enhance the conversion further. We were pleased to see that under these conditions, conversion to **2a** enhanced to 76 % (entry 9) with no proportional increase in side products. The amount of catalyst could be reduced to 1 mol % and of *t*-BuLi from two to 0.7 equiv (as 0.5 equiv are in theory needed, this actually represents a slight excess of *t*-BuLi, entry 11). Overall this resulted in an 80 % isolated yield of **2a** and an E-factor of 3.1 which is a significant drop in comparison to previous, similar, methods (for example 76<sup>[18]</sup>) towards the preparation of **2a**.

These conditions proved general, providing homocoupled products in high yields (Scheme 2). Sterically demanding substrates such as TBDMS protected 2-bromonaphthol (**1b**) and 2-bromoanisole (**1c**) similarly gave excellent yields (91 %, 90 %). Electron rich 3,5- and 2,4-dimethoxybromobenzene (**1d–e**), who might suffer from a loss in selectivity due to the added possibility of *ortho*lithiation, or 4-bromodimethylaniline (**1f**) also gave good to excellent yields of the homocoupled biphenyl products (**2d–f**, 77–96 %). Aryl bromides bearing electron withdrawing groups or heteroaryl bromides also function well (**2g–i**, 89–96 %). Employing aryl iodides instead of aryl bromides (**2a'**, **2h'**, **2j–m**) showed no significant difference in terms of conversion or selectivity, all giving excellent yields of the corresponding homocoupled biphenyl products (**2a**, **2h**, **2j–o**, 84–95 %). Compound **2m** especially was highly interesting as the reaction proved chemoselective for the iodine vs. the chloride. E-factors for these reactions vary from 1.6 to 4.3 remaining significantly lower than for reported methods. In the case of aryl chlorides (**2a'**, **2p–r**), however, lower conversions were obtained (46–64 %).

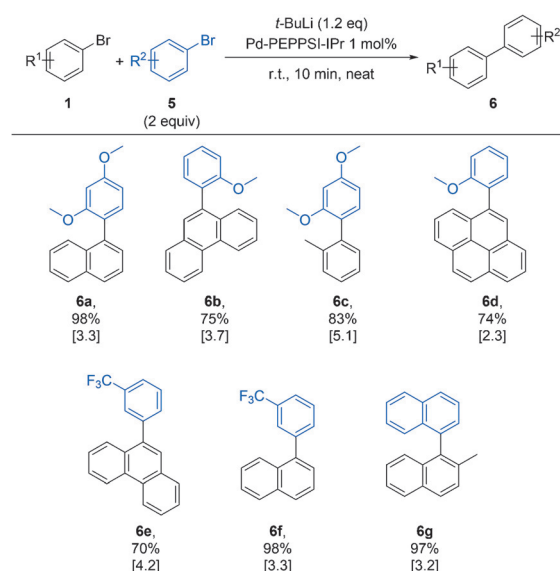
Subsequently the possibility of heterocoupling of two distinct aryl halides under the optimized conditions was explored (Scheme 3). We envisioned that even a slight difference in the rate of lithium-halogen exchange between both aryl halides would be sufficient to result in high selectivities for the heterocoupled product vs. the homocoupled product. Indeed when using 1-bromo-2,4-dimethoxybenzene (**5a**), in a coupling with **1a**, an approx 8:2 ratio in favor of the



**Scheme 2.** Scope of the homocoupling reaction. All experiments were carried out by stirring the starting material and catalyst under dry air, followed by the dropwise addition of the *t*-BuLi in heptanes over a period of 10 min at room temperature. Conversions determined by GCMS. Isolated yields indicated between parentheses. [E-factor].

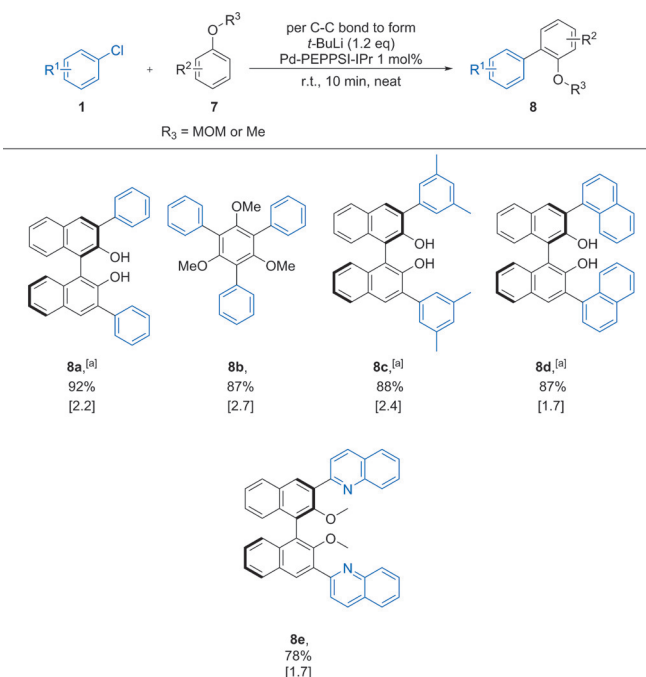
heterocoupled product was observed. Simply increasing the amount of **5a** and *t*-BuLi resulted in near full conversion of **1a** to the heterocoupled product **6a** with 98% isolated yield. The heterocoupling of various aryl bromides possessing *o*-methoxy directing groups with non-directed aryl bromides, including ones with extended  $\pi$ -systems and sterically encumbered substrates, also gave high yields of the desired heterocoupled products (**6b–d**, 74–98%). A directing group was not a strict requirement and substrates with different electronic (**6e,f**, 70–98%) or steric (**6g**, 97%) properties also resulted in very high selectivities.

Based on observations made during studies on the homocoupling that is, that *ortho*-lithiation<sup>[19]</sup> could occur faster than lithium–halogen exchange at aryl chlorides and



**Scheme 3.** Scope of the cross-coupling reaction of two distinct aryl halides. For experimental details, see the Supporting Information. [E-factor].

that steric hindrance was well tolerated, we further explored the heterocoupling between aryl chlorides and anisole derivatives (Scheme 4). Remarkably under the optimized conditions MOM-protected BINOL (**7a**) or 1,3,5-trimethoxybenzene react smoothly (10 min, RT, no additional solvent) with chlorobenzene in excellent yields and selectivities to form the corresponding multiple coupled polyaromatic com-



**Scheme 4.** Cross-coupling reaction of aryl chlorides to anisole derivatives. **1**, **7** and catalyst were stirred under dry air, followed by the dropwise addition of the *t*-BuLi in heptanes over a period of 10 min at room temperature. [a] Acidic workup to remove the MOM group and facilitate purification, see the Supporting Information. Indicated yields are after isolation. [E-factor].

pounds (**8a,b**, 87–92%) The formation of **8a** is particularly interesting as it opens the way for the efficient synthesis of various scaffolds often used in privileged chiral catalysts.<sup>[1b]</sup> Based on these results the scope was expanded to multiple other known, frequently used, chiral BINOL derivatives (**8c–e**) which were obtained in a highly efficient manner (78–88% yields).<sup>[20]</sup>

In summary, we have developed a highly efficient method for the homocoupling of aryl halides and the heterocoupling of aryl halides to either aryl bromides or arenes bearing a directing group for *ortho*-lithiation. Taking advantage of the remarkable affinity of Pd-PEPPSI-IPr for catalyzing the cross-coupling of aryl halides and organolithium reagents and carefully controlling the formation of the latter, we achieved high yields and selectivity for these reactions while eliminating the need for strict inert conditions, temperature control or for the separate formation of one of the coupling partners. This method provides a very fast, mild, highly selective, versatile and convenient way to access many important biaryl and polyaromatic structures. This is demonstrated by short reaction times, low waste generation and the capability of forming hindered biaryl systems.<sup>[21]</sup>

### Experimental Section

The corresponding aryl bromide (1 mmol, 1 equiv), the aryl bromine prone to lithium-halogen exchange (2 mmol, 2 equiv) and Pd-PEPPSI-IPr (7 mg, 1.0 mol%) were added to a Schlenk flask under a dry air atmosphere. *t*-BuLi solution (1.2 equiv, 2.2–3.2 M in heptane) was added at room temperature over a period of 10 min with a syringe pump. Standard aqueous workup and filtration over silica gel yielded the product, see the Supporting Information.

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### Conflict of interest

The authors declare no conflict of interest.

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[20] Comparison of the optical rotation of compound **8a** to literature values shows that no loss of optical activity occurs during the process.  
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