The Resurrection of Murahashi Coupling After Four Decades

Susanta Hazra,[†] Carin C. C. Johansson Seechurn,[‡]* Sachin Handa,[†]* and Thomas J. Colacot[#]*

†2320 S. Brook St., Department of Chemistry University of Louisville, Louisville, KY 40292, USA

‡14b Warwick Road, Barnet, EN5 5EQ, UK

#MilliporeSigma (Business of Merck KGaA, Darmstadt), 6000 N. Teutonia Avenue, Milwaukee, WI, 53209, USA

ABSTRACT: Since the discovery of the pioneering cross-coupling name reactions in the 1970s, cross-coupling involving organo-lithium reagents (Murahashi coupling) was neglected for more than 30 years. It was considered to be a technically non-practical reaction based on the poor selectivity due to the high reactivity and low functional group tolerance of the organolithium coupling partner. In this review, we shall provide a comprehensive update on the renaissance of Murahashi coupling that enabled chemists to overcome many difficulties by using modern catalytic systems in conjunction with the development of appropriate reaction conditions.

1. Introduction

Both in academia and industry, palladium (Pd)-catalyzed carbon-carbon bond-forming reactions have become one of the most practiced methods in synthetic organic chemistry.[1-7] The pioneering named reactions developed during 1970-80, such as the Suzuki-Miyaura,[8,9] Negishi,[10-12] Kumada-Corriu,[13,14] Stille,[15-17] Heck-Mizoroki,[18,19] Hiyama-Denmark,[20] and Sonogashira couplings,[21] led to the 2010 Nobel Prize in Chemistry to Akira Suzuki, Ei-ichi Negishi, and Richard Heck.[1] The role of the organometallic coupling partners (nucleophilic reagent) and the selection of the catalysts under specific reaction conditions are vital in minimizing the byproducts formation, thereby improving the overall reaction efficiency and efficacy.[1-7] Despite the significant breakthroughs in cross-couplings over the last two decades, the Murahashi cross-coupling, *i.e.,* cross-coupling involving organolithium reagent, remains stagnated since its discovery.[22] A simple SciFinder search for "Murahashi Coupling" provided under 20 hits (Figure 1), while a search for "cross-coupling of organolithium" yielded ca. 400 references. Compared to the progress of other named reactions, the total references on Murahashi Coupling are far fewer than expected. This slow progress may be due to the well perceived low functional group tolerance coupled with the difficult handling of organolithium reagents in comparison to other nucleophiles, such as organoboron (Suzuki) and organozinc (Negishi) reagents. However, the synthesis of organoboron and organozinc reagents heavily involves organolithiums. The cross-couplings involving these reagents are far more popular as illustrated in Figure 1. For example, a SciFinder search on "Suzuki-Miyaura cross-coupling" and "Negishi cross-coupling" provided 29,407 and 2149 hits, respectively.

The Murahashi reaction has recently received renewed attention by many researchers,[23-40] in particular by Feringa and co-workers.[25-38] This has resulted in developing a relatively robust procedure with broader substrate scope and improved functional group tolerance by tweaking the reaction conditions. Notably, it took about 40 years for this critical development; hence, Murahashi coupling may be renamed as Murahashi-Feringa coupling, just as the Hiyama-Denmark or Mizoroki-Heck coupling.
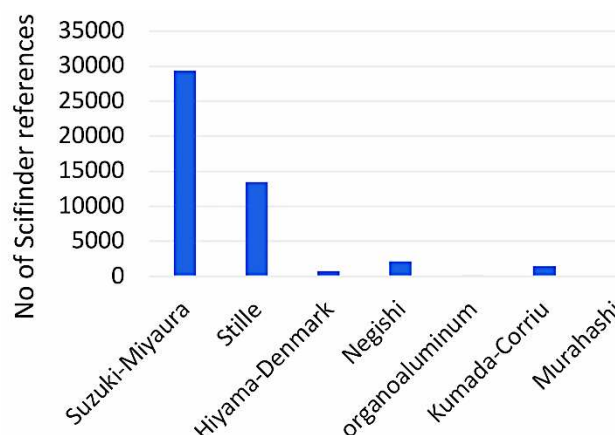

Figure 1. Number of references from SciFinder search for each cross-coupling.

The practicality and utility of organolithium reagents in cross-couplings have the potential to be far more valuable for organic synthesis, considering the low cost and ready availability of the lithium (Li) reagents. Therefore, in this review, we will highlight how this area of research has recently experienced significant progress as an emerging technology for metal-catalyzed C–C bond-forming reactions. While demonstrating the synthetic potential of this area, Feringa, et.al., followed by others have been able to overcome many of the enormous challenges by careful selection of catalysts and ingenious reactions design.[23-40] Since no comprehensive review is available on this topic, we hope this account will help organic chemists to further advance this area from a fundamental and applied chemistry perspective, so that this named reaction reaches a status comparable to the other named cross-couplings, especially in terms of its real-world applications.

1.1. Historical Notes

In 1974, Negishi reported a $C(sp^2)$-$C(sp^3)$ coupling of aryl bromides with alkyllithium reagents.[41] However, this reaction was not metal-catalyzed, but found to be promoted by THF solvent. Subsequently, in 1975, Murahashi discovered that organolithium reagents can be coupled with alkenyl halides in the presence of stoichiometric *tetrakis*(triphenylphosphine)palladium complex (Scheme 1).[42] Four years later, Murahashi reported its catalytic version.[43]

Scheme 1. Murahashi's seminal contributions
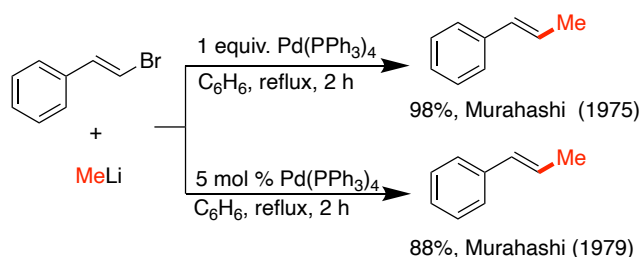
Three years later, Pd-catalyzed cross-coupling between aryl or vinyl iodides and allenyllithiums was reported by Linstrumelle (Scheme 2).[44] The next report on a Pd-catalyzed cross-coupling involving organolithium reagents came from the Pelter group in 1987.[45] The researchers demonstrated the coupling of 2-lithiofuran with benzyl bromides in THF as a solvent.

Besides the aforementioned four reports, there has been no mention of the Murahashi cross-coupling reaction[46] in the literature for the next 23 years, while other named reactions in the area of cross-coupling have been developing into practical methodologies in organic synthesis, leading to the 2010 Nobel Prize. However, a few literature reports document the high yielding catalyst-free reactions of organolithium reagents with aryl/alkyl halides via nucleophilic replacement pathway.[47-49]

Scheme 2. Post Murahashi reports on cross-coupling using organolithium reagents
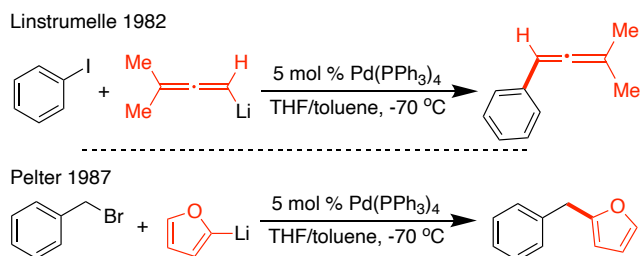
1.2. Why organolithiums are difficult coupling partners: Is there a correlation with electronegativity?

Murahashi already noted in his seminal work that organolithium reagents are highly reactive. However, there is always a risk involved for undesired side reactions to occur during elementary steps of their cross-coupling with aryl or vinyl halides, especially when one or more elementary steps in the catalytic cycle are slow (Figure 2).[1] Effective transmetallation seems to be a critical step in the catalytic cycle.
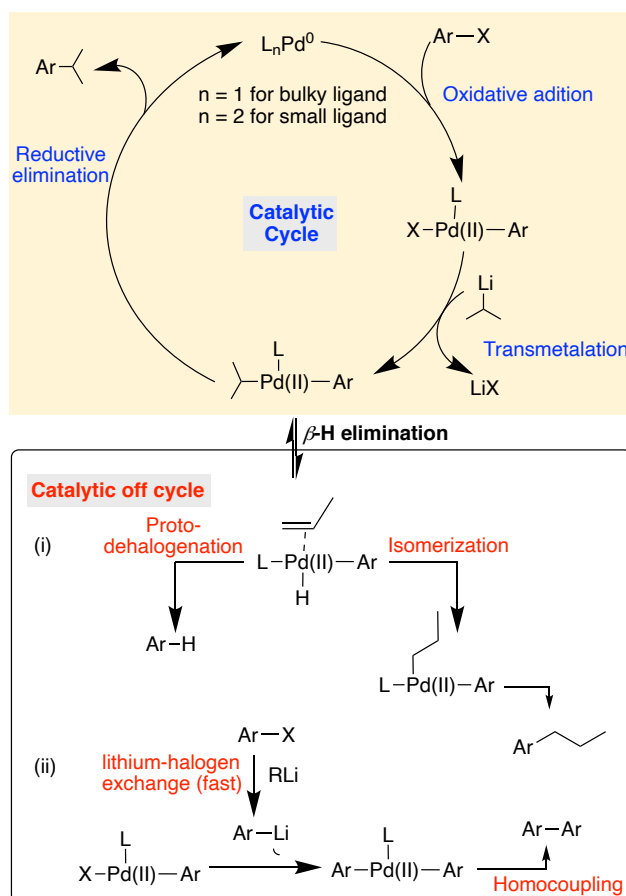

Figure 2: General catalytic cycle of Murahashi cross-coupling reaction with possible side-reactions (off cycle).

Table 1. Lithium-halogen interchange equilibria of various organolithiums

$$Ph\text{—}I + R\text{—}Li \underset{}{\overset{k_{obs}}{\rightleftharpoons}} Ph\text{—}Li + R\text{—}I$$

R	pK_a	k_{obs}
$\diagup\!\!\diagdown$ Li	36.5	0.004
PhLi	37	1
$\triangleright$—Li	39	9.5
Me $\diagdown\!\!\diagup$ Li	42	3200
Et $\diagdown\!\!\diagup$ Li	42	7600
$(H_3C)_2HC\diagdown\!\!\diagup$ Li	42	4×10^4
t-Bu $\diagdown\!\!\diagup$ Li	42	3×10^5
$\pentagon$—Li	44	8×10^7

Indeed, the major issues associated with the application of alkyllithium reagents in Pd-catalyzed cross-coupling reactions

are the competing homocoupling byproduct formation and isomerization due to β-hydrogen elimination (Figure 2). The formation of byproducts is due to fast lithium–halogen exchange on Pd(II) after oxidative addition; the resulting alkyl-Pd species generated after the transmetallation and the presence of excess organolithium reagent cause β-hydrogen elimination as an "off cycle" process *versus* the desired reductive elimination. Notably, the lithium-halogen exchange reaction of an aryl bromide or iodide with an organolithium is a high-yielding process, proceeding rapidly at low temperature and favors the more stable aryllithium at equilibrium.[50] The lithium-halogen exchange events are mainly dependent on the choice of halides, organolithiums, solvent, and reaction temperature. Rates of interchange decrease in the order: I > Br > Cl. Such trends are likely due to the more exothermic lattice energy formation of LiCl than that of LiBr and LiI.[50] Literature precedents reveal that aryl fluorides do not undergo exchange reactions due to stronger C–F bond.[51] In 1963, Brien and co-workers measured several halogen-lithium interchange equilibria to obtain the relative stabilities of various alkyl-, cycloalkyl, alkenyl- and aryllithium reagents which are shown in Table 1.[50] These data show that less stable or more basic alkyllithiums favor the equilibrium towards the right. Bailey and co-workers have performed detailed studies on the effect of solvents and temperature on the lithium-halogen exchange reactions using primary alkyl iodides and aryl bromides.[52,53] According to their studies, the exchange reactions are slow in pure hydrocarbon solvent but even small quantities of an ether as the co-solvent leads to an improvement in yield even at 0 °C. These results are likely related to the degree of association of organolithiums in the various solvents that were examined.[54-56] Furthermore, in the transmetallation step, the electronegativity of the metal in the nucleophile (organometallic reagent) may play a significant role. In theory, RLi should be a better nucleophile than the corresponding boron reagents for the transmetalation on Pd(II).

Table 2. Electronegativity values for selected elements[60]

Element	Cross-Coupling Reaction	Electronegativity[a][b]	
lithium	Murahashi	0.98	
magnesium	Kumada-Corriu	1.31	
aluminum	n/a	1.61	Increasing ease of sp²-sp² cross coupling
zinc	Negishi	1.65	
silicon	Hiyama-Denmark	1.90	
tin	Stille	1.96	
boron	Suzuki-Miyaura	2.04	

[a]Pauling scale; [b]carbon has an electronegativity of 2.55.

However, organoboron reagents are by far the most employed and versatile cross-coupling partners (nucleophiles) for sp²-sp² coupling, with boron being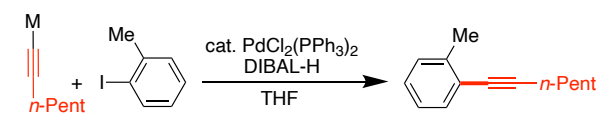 the most electronegative element (containing empty p_z orbital) out of the range of metals (Table 2). This is closely followed by tin. These organoboron reagents are usually air- and moisture-stable and have a broad functional group tolerance. Although organotin reagents are stable and can be readily synthesized via several methods, the toxicity of tin prevents Stille couplings to be a preferred reaction, especially in the industrial settings. Silicon (leading to Hiyama-Denmark cross-coupling) is the next element in line with an electronegativity value of 1.90 (Table 2). This is followed by zinc (Negishi cross-coupling). The organozinc (especially alkylzinc) reagents are generally more desirable than their tin counterparts. Thanks to their less toxic nature, good selectivity and reactivity, the Negishi reaction has found its niche in $C(sp^2)$-$C(sp^3)$ bond formation. Organoaluminum reagents (Al = 1.61 Pauling units) are less commonly used, possibly because they are more challenging to synthesize. Next metal down to the electronegativity is magnesium (Mg = 1.31 Pauling units); the organomagnesium is used in Kumada-Corriu cross-couplings. The latter are useful cross-couplings catalyzed by (*bis*)phosphine-bound Pd catalysts. They have, however, a lower functional group tolerance during cross-coupling than the organometallic reagents made with metals of higher electronegativity values. Working our way through the list of elements, we have then finally arrived at the focus metal of this review, lithium. Li being the most electropositive element (0.98), organolithium reagents are the most effective reagents in transmetallation. However, they produce dehalogenation byproduct along with cross-coupling product, in addition to its reactivity towards certain functional groups, thereby giving negative outcome.

These are the few reasons for the Murahashi couplings to receive the lowest attention in the cross-coupling family of reactions. However, organolithium reagents also have a few indisputable advantages over the other transmetallating agents.[57-59] These reagents are readily available in bulk and cheap (Table 3).

Table 3. Cost of organometallic reagents

R-M	Amount	Cost ($/mmol)[a]
n-BuLi	800 mL 2.5M	0.082
n-BuMgCl	800 mL 2.0M	0.18
n-BuAl	n/a	n/a
n-BuZnBr	50 mL 0.5M	8.76
n-Bu-SiMe₂OH	n/a	n/a
n-BuSnBu₃	100g	0.22
n-BuB(OH)₂	25g	0.74

[a] Cost for research quantities from MilliporeSigma as of April 2021.

Table 4. Negishi's evaluation of organometallic reagents

M	Temp (°C)	Time (h)	Product Yield (%)	Starting Material (%)
Li	25	24	3	80
MgBr	25	24	49	33
ZnCl	25	1	91	8
HgCl	reflux	6	trace	88
BBu$_3$Li	reflux	1	92	5
Al(i-Bu)$_2$	25	3	49	46
SnBu$_3$	25	6	83	6
ZrCp$_2$Cl	reflux	3	0	80

Unlike tin, they are relatively environmentally friendly. In fact, many of the other organometallic coupling partners (nucleophiles) are usually made from organolithiums. Hence, direct use of organolithiums will cut additional steps in an organic process from a sustainability point of view. It would therefore be ideal if the organolithium reagents themselves could be reliably used in the cross-coupling processes. When that happens, alongside the development of a process that can address the issue of low functional group tolerance, this coupling technology can potentially become one of the most industrially sought out reactions in cross-coupling. The idea of exploiting the properties of different organometallic reagents is not recent. In 1982, Negishi reported a comparative study of the organometallic reagents made from Li, Mg, Zn, Al, Hg, B, Sn and Zr for a C(sp)-C(sp^2) bond forming reaction (Table 4).[61] Having achieved the highest yield using the organozinc reagent, he simply chose to pursue the use of this metal in his studies, helping him to share the 2010 Nobel Prize in Chemistry. Notably, in his study, the organolithium reagent gave only 3% yield of the product in comparison to the 91% yield while using the corresponding organozinc reagent. Our literature search could not identify any relevant publications to directly correlate the electronegativity of the nucleophile to the ease of coupling. Hopefully this review will inspire theoretical chemists to come up with a rationale.

2. Recent Developments

As mentioned previously, 23 years after Pelter's report on a Pd-catalyzed Murahashi coupling reaction,[45] Yoshida and co-workers achieved selective cross-coupling reactions on a range of aryl bromides with aryl/heteroaryllithium reagents in a flow microreactor.[23] This was later expanded to include vinyl halides as the electrophiles.[24] Pd-PEPPSI-SIPr was found to be the best catalyst for the aryl bromide substrates, whereas ligand-free Pd(OAc)$_2$ was used for the coupling of vinyl bromides.[24]

2.1. Emergence of Murahashi cross-coupling by Feringa

A pioneering paper published by Feringa in 2013 was a breakthrough finding in this area, where he provided an ingenious solution to the use of challenging organolithium reagents in cross-coupling reactions (Scheme 3).[25] In the reported work,

chloro and benzylic alcohol functional groups remained intact. Notably, a substrate containing *N,N*-dimethylamine functional group cleanly participated in the desired reaction pathway. However, a substrate with methyl ester functional group provided only 43% yield, most likely due to side reaction between ester and organolithium reagent.

Scheme 3. Pioneering work of Feringa on Pd-catalyzed cross-coupling reactions using organolithiums with (*t*-Bu$_3$P)$_2$Pd catalyst[25]
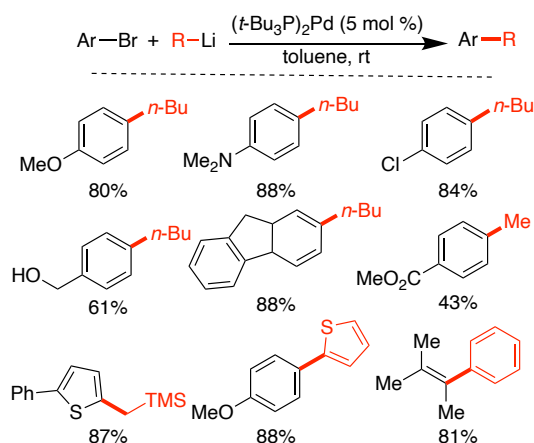
In this work, authors have used a catalyst containing bulky electron-rich ligand, such as *t*-Bu$_3$P,[62] which proved to be crucial in promoting faster reductive elimination to obtain the desired product, by minimizing the off-cycle processes, thereby speeding up the catalytic cycle. Besides, the electron-rich *t*-Bu$_3$P also enables the Pd as electron-rich center, thereby also promotes oxidative addition. The reactions take place under milder conditions with a broader substrate scope incorporating functional group tolerance. Examples includes ethers, amines, halides, alcohols, as well as substrates containing acidic protons (Scheme 3). The problem associated with the competing lithium-bromide exchange was cleverly solved by choosing an appropriate non-coordinating solvent (toluene), in combination with a fine-tuned Pd catalyst containing bulky electron-rich ligands (e.g., Pd/ *t*-Bu$_3$P, Buchwald's biaryl ligands or Pd-PEPPSI-IPent) and slow addition of the Li reagents (Figure 3).
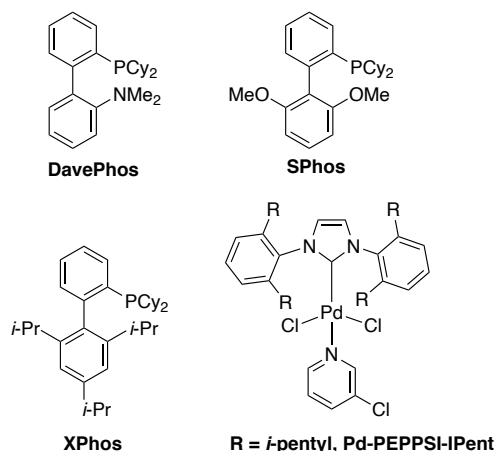

Figure 3. Ligands in conjunction with Pd and Pd based precatalyst used in the cross-coupling of organolithium reagents.

The solvent choice and slow addition might have helped to control the reactivity and aggregation state of the organolithium reagent, thereby preventing the lithium-bromide exchange; hence, facilitate an effective cross-coupling.[54] Moreover, milder conditions, such as lower concentration and ambient temperatures, were also important. Notably, the solvents of choice for the early reported Murahashi reactions were all ethereal solvents, such as THF or cyclopentyl methyl ether.

Scheme 4. Pd-catalyzed cross-coupling of aryl chlorides with aryllithiums[26]
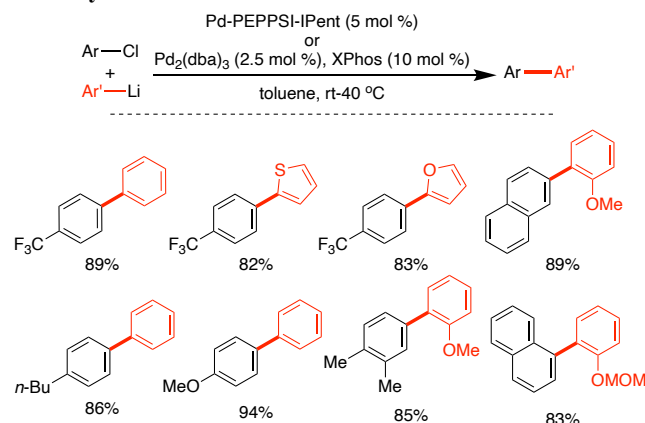

Although, Feringa's protocol is not suitable for functional groups such as ketones, and nitriles, it provides moderate yield for substrate containing ester functional group. In addition, this method is only applicable to aryl bromides. The substrate scope could be extended from the initially reported aryl bromides to typically more challenging aryl chlorides by changing the catalyst to either Pd-PEPPSI-IPent or Pd$_2$(dba)$_3$/XPhos system. In some cases, slightly elevated temperature was needed (40 °C) (Scheme 4).[26] Although this improvement meant that inexpensive aryl chlorides could be employed, this method has limited scope with respect to the aryllithium reagents.

Scheme 5. Pd-catalyzed sp^2-sp^3 cross-coupling of (hetero)aryl halides with TMSCH$_2$Li[27]
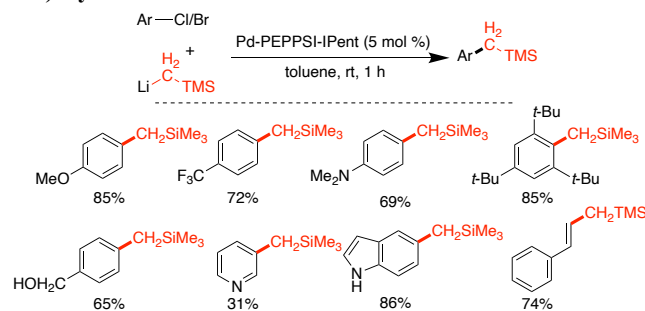

In 2015, Feringa and co-workers, further extended the scope of the reaction for the C(sp^2)-C(sp^3) cross-coupling using (trimethylsilyl)methyllithium as a bi-functional reagent (Scheme 5).[27] Among several Pd catalysts, the commercially available Pd-PEPPSI-IPent was found to be most effective for both aryl bromides and chlorides. The reactions took place under mild conditions and worked well with aryl/heteroaryl substrates with broad functional group tolerance, such as ether, amine, alcohol as well as presence of acidic proton. The nucleophile remained same in all examples.

Scheme 6. Pd-catalyzed arylation of trisubstituted allenes with aryl bromides[28]
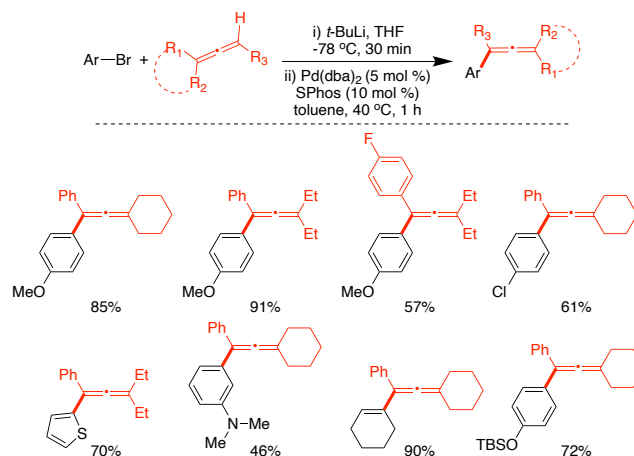
The same authors have also shown the feasibility of carrying out the direct lithiation and consecutive C(sp^2)-C(sp^2) cross-coupling reaction of allenes with ArBr.[28] The use of bulky biarylphosphine ligand, such as SPhos, is the key requirement for the reaction of allenes. This method provides the direct synthesis of tri- and tetra-substituted allenes in a single step, without using pre-functionalized substrates. This work has moderate substrate scope with respect to aryl bromides and is limited to allenes that are not prone to isomerization (Scheme 6).

Scheme 7. Pd-catalyzed sp^2-sp cross-coupling of aryl bromides with lithium acetylides[29]
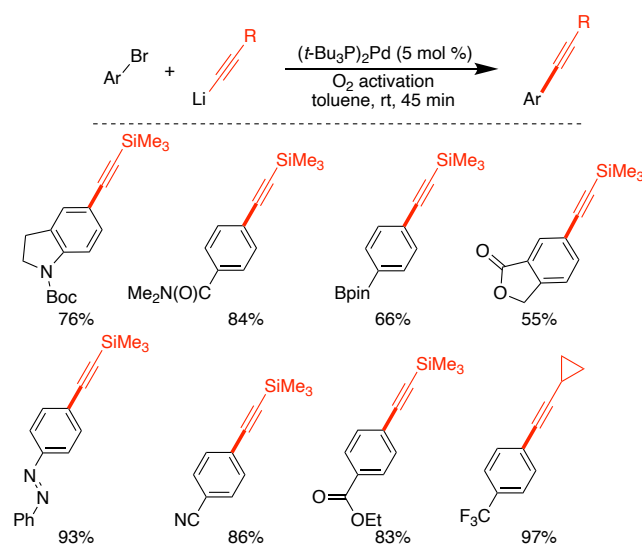

In 2020, the Feringa group has reported C(sp^2)-C(sp) cross-couplings using readily available aryl bromides and lithium acetylide under milder reaction conditions.[29] This method employed O$_2$-activated (t-Bu$_3$P)$_2$Pd as catalyst,[62] and reactions took place at ambient conditions in short reaction time. The substrate scope is broad with respect to both lithium acetylides and aryl bromides, having excellent functional group tolerance, such as, carbamates, amides, boronic esters, lactones, azobenzenes, nitriles, and esters (Scheme 7). This new protocol is also applicable for scalable synthesis, which opens avenues for the fast and

facile late-stage functionalization as complementary to the Sonogashira coupling.

However, the process safety risks arising from the use of a combination of alkynyllithium in organic solvent and oxygen can be a safety concern for large scale reactions. Nonetheless, the key feature is that aryl Bpin esters can be easily functionalized with alkynes. The high reaction yield in a substrate containing the acyclic ester functional group suggests that the nucleophilic replacement reaction under optimized conditions is inhibited or slow. The slower rate of nucleophilic replacement reaction is most likely due to the use of non-polar (toluene) solvent. Such side reaction may be dominant if the reaction solvent is dipolar-aprotic.

Biaryls are important structural units of many organic molecules, chiral ligands, natural products, and pharmaceuticals.[30] Nevertheless, the synthesis of sterically crowded tri- and tetra-ortho-substituted biaryls remains challenging. The major efforts have been focused on tuning the ligand systems to improve efficiency and selectivity using traditional approaches, such as Suzuki and Negishi cross-coupling. In 2013, Feringa and co-workers, for the first time, demonstrated the synthesis of sterically hindered biaryl systems by coupling of aryllithiums and aryl bromides using Pd-PEPPSI-IPent catalyst under mild conditions and short reaction time.[30] Various tri- and tetra-substituted biaryls can be easily obtained with this method (Scheme 8). However, the reactivity of heteroaromatics was missing in this study.

Scheme 8. Pd-catalyzed cross-coupling of hindered aryllithium reagents with substituted aryl bromides[30]
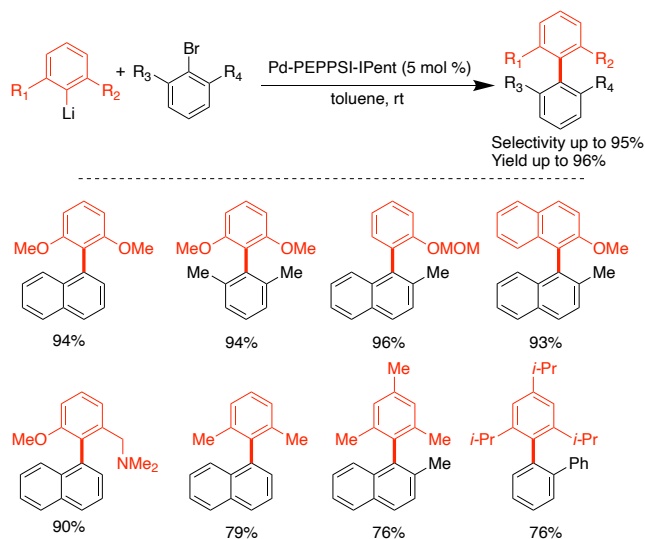
The major advantages of the abovementioned protocols are especially related to the use of lithium reagents. A variety of lithium reagents can be obtained from the corresponding bromide *via* Li-halogen exchange and can be used in subsequent cross-coupling in short reaction time without further purification. Simple aromatic compounds can be used for direct ortho metalation, which allows the direct formation of the organolithium reagents for cross-coupling. As expected, *o*-OMe group can stabilize the corresponding lithium reagents and provide high-efficiency to the desired cross-coupling.[53] In general, the organolithium compounds facilitate the transmetallation step due to

their higher reactivity. Besides, the reactions are completed within a short reaction time.[30] The 2-alkoxy-substituted aryl chlorides were also used as substrates amenable to cross-coupling with aryllithium reagents.[31] Using this methodology, the synthesis of several 3,3'-diaryl BINOLs was realized (Scheme 9). The reactions proceed under mild conditions in short reaction times to access chiral 3,3'-diaryl 1,1'-bi-2-naphthols. The resulting products are key synthons for asymmetric ligands. This methodology represents the first literature example for the synthesis of substituted binaphthyls from the corresponding enantiopure 3,3'-dichloro 1,1'-bi-2-naphthols.[31]

Scheme 9. Synthesis of 3,3'-diaryl BINOLs by Pd-catalyzed cross-coupling with aryllithiums[31]
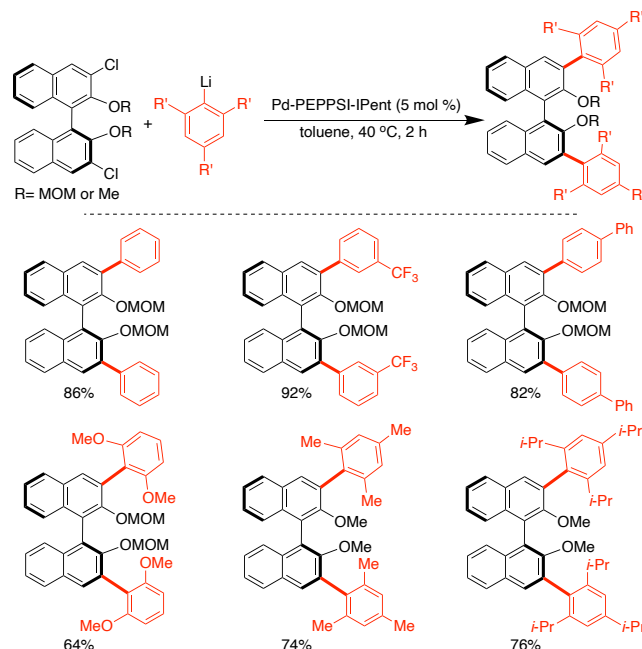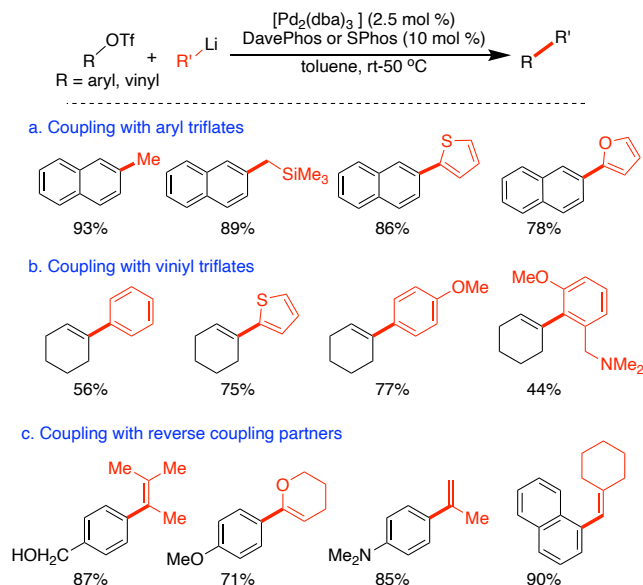

In addition to aryl halides, the use of triflates in metal-catalyzed cross-coupling reactions is particularly attractive as they are readily available from phenols and carbonyl enolates. Therefore, the scope of the work to include aryl and vinyl triflates was further undertaken by Feringa and co-workers.[32]

After screening a series of ligands and Pd pre-catalysts for the reactions, it was found that Pd$_2$(dba)$_3$/DavePhos system was the best catalyst for the aryl triflates and Pd$_2$(dba)$_3$/SPhos system provided the best results for vinyl triflates (Schemes 10a-b). Although the reaction proceeds at rt with aryl triflates in short reaction time, moderate heating is required (50 °C) to get the desired reactivity for vinyl triflates.
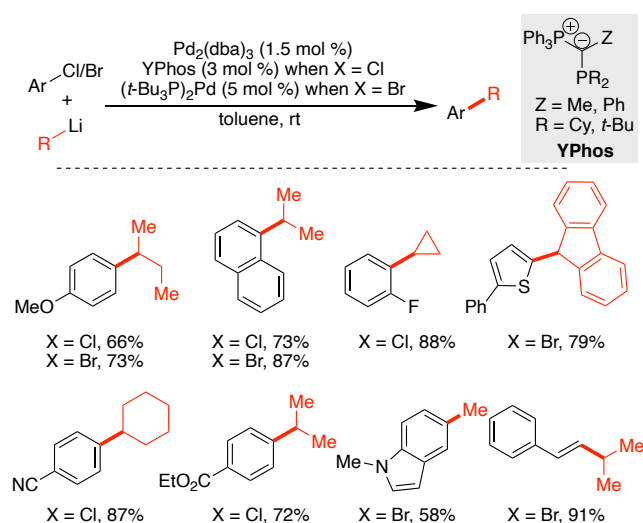
Subsequently, Feringa also demonstrated a cross-coupling reaction with reversed coupling partners, showcasing couplings of several vinyllithium reagents with aryl bromides or chlorides in the presence of Pd$_2$(dba)$_3$/SPhos catalyst (Scheme 10c).[33] However, these methods are only applicable for aryl or vinyllithiums. This may be due to the poor reactivity of triflates under mild conditions, and the side reactions associated with the use of alkyllithiums.

Scheme 10. Pd-catalyzed cross-coupling of organolithiums with aryl and vinyl triflates[32,33]

The presence of electron-rich ligands and mild conditions are the key factors to prevent undesired side reactions with secondary alkyllithiums. This method has a broad substrate scope, including aryl and heteroaryls. Functional groups, such as halogen, ether, nitrile, and ester are also compatible under optimized. However, there are formation of trace amounts of linear isomers (1-9%) in case of cross-coupling of aryl halides with secondary alkyllithiums.[35]

Another contribution that extends this methodology into the field of "green chemistry," was reported by the Feringa group in 2016. The solvent-free Murahashi reaction was demonstrated using Pd-PEPPSI-IPr or (*t*-Bu$_3$P)$_2$Pd as catalyst.[36,37] Feringa's publication in this area in 2017 describes an ultrafast cross-coupling reaction of organolithium reagents with aryl bromides, catalyzed by *in-situ* generated Pd nanoparticles (Scheme 12).[38] The nanoparticles are proposed to be generated by the reaction of molecular oxygen and (*t*-Bu$_3$P)$_2$Pd. This was proposed to occur *via* the formation of intermediate Pd(I) dimer [(*t*-Bu$_3$P)(Br)Pd]$_2$.

Notably, the cross-couplings between C(sp^2) and secondary C(sp^3) are generally very challenging. In this context, the coupling of secondary alkyl halides and C(sp^2) nucleophiles has received more attention than the reverse cross-coupling of secondary C(sp^3) organometallic nucleophiles with aryl halides. This is due to the inherent problems of β-hydrogen in secondary organometallic reagents, which leads to the formation of undesired olefins or isomerization of the alkyl chain in the presence of a Pd catalyst. However, Feringa and co-workers demonstrated the feasibility of the coupling of secondary alkyllithium reagents with (hetero)aryl bromides using Pd(P^{t}Bu$_3$)$_2$ as the catalyst (Scheme 11).[34]

Scheme 11. Pd-catalyzed cross-coupling of secondary alkyl organolithium reagents with aryl halides[34,35]
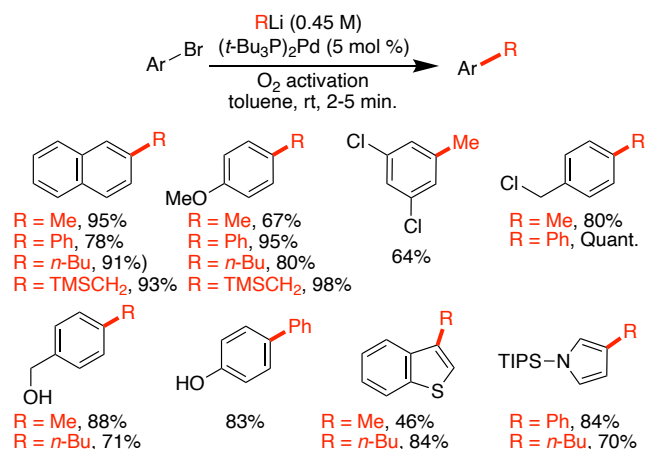
Very recently, in 2020, Gessner and co-workers have reported a Pd-catalyzed general protocol for the coupling of organolithium reagents with inexpensive aryl chlorides using an electron-rich ylide-substituted phosphine ligand, YPhos (Scheme 11).[35]

Scheme 12. Pd nanoparticle-catalyzed ultrafast cross-coupling of organolithium reagents[36,37]

Although this method has a broad substrate scope and functional group compatibility, one issue that may prevent this procedure from reaching its potential in industry, especially on large scale, is the safety aspect. By carrying out the reaction in an organic solvent under an oxygen atmosphere, two sides of the fire triangle are present (fuel and oxygen). If heat was to evolve, the risk of a fire would be considered very high. Hence this method might remain only in the academic settings under a safety-controlled environment.

Scheme 13. Low Pd-loading coupling reaction[38]
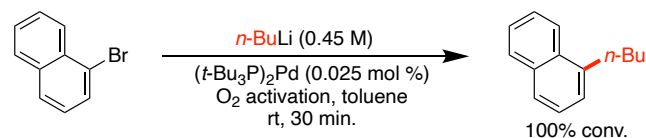
The coupling of 1-bromonaphthalene with *n*-BuLi has been achieved with full conversion using only 0.025 mol% (250 ppm) Pd catalyst (Scheme 13). However, claims on nanoparticle catalysis should be thoroughly evaluated, although the results are certainly interesting. Schoenebeck also observed

similar results on Kumada and Negishi couplings, although the couplings are not attributed to the "nano Pd".[39] Although, Feringa and co-workers reported solvent free Murahashi reaction in 2016,[36,37] the use of environmentally benign, bio-inspired protic solvents such as water, glycerol, and deep eutectic solvents (DESs) represent one of the most formidable challenges in the metal-catalyzed cross-coupling chemistry using organolithium reagents.[63-66] In 2019, Capriati and co-workers, for the first time, reported Pd-catalyzed cross-coupling reactions between organolithium reagents and (hetero)aryl halides in water using NaCl as an additive (Scheme 14).[40]

Scheme 14. Pd-catalyzed cross-coupling between (hetero)aryl halides and organolithium reagents on water at rt and under air[40]
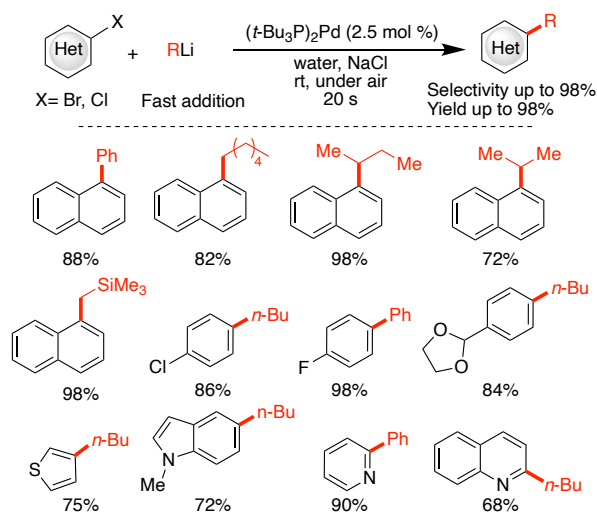

Notably, these reactions are carried out at rt, under air, and the reactions were completed within 20 seconds. This method has a broad substrate scope and moderate functional group tolerance showcasing the reactivity of substrates containing halogens, acetals, and ethers. Chloride ion seems to play a crucial role in the catalytic cycle by forming an anionic-complex while keeping a small P-Pd-P angle, which is a prerequisite for a low activation barrier for oxidative addition. The presence of electron-rich ligand, NaCl, oxygen, and the fast addition of lithium reagents on the surface of water with vigorous stirring are the key factors to obtain the best yields. The authors have also used other polar-protic solvents, such as MeOH, causing the formation of dehalogenated product. More detailed mechanistic investigations are required to find out the origin of the super reactivity of a known catalyst under these reaction conditions. Very recently, the same authors have reported Pd-catalyzed Negishi cross-couplings using either bulk water as a reaction medium or an environmentally responsible eutectic mixture under aerobic conditions.[67]

2.2 Murahashi cross-coupling using earth-abundant metal catalysts

Despite Murahashi's original claim that "nickel (Ni) catalysts are not applicable for the reaction with organolithium compounds,"[42] 21 years later, Ni catalyst was successfully used for this purpose. In 2000, Taillefer and co-workers reported a method for the Ni-catalyzed cross coupling of aryl halides with

aryllithiums using NiBr$_2$/ PPh$_3$ or NiBr$_2$/bpy catalytic system (4 mol %).[68] In 2011, an effective C(sp)-C(sp^3) bond formation was reported using [NiCl{C$_6$H$_3$-2,6-(OPPh$_2$)$_2$}] as a catalyst (Scheme 15).[69] Mori and co-workers subsequently reported the Murahashi reaction to polymerize thiophenes (Scheme 15).[70] Following Sun's Ni-catalyzed C(sp)-C(sp^2) Murahashi coupling,[69] Feringa has also reported C(sp^2)-C(sp^2) and C(sp^3)-C(sp^2) bond-forming reaction catalyzed by NiCl$_2$(PPh$_3$)IPr and NiCl$_2$(dppe), respectively.[71] Cross-coupling of organolithium with ethers has also been achieved using [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) as the pre-catalyst and SIMes as the ligand (Scheme 16).[72]

Scheme 15. Murahashi C(sp^2)-C(sp^2), C(sp)-C(sp^3) bond formation and polymerization using Ni catalysts[68-70]
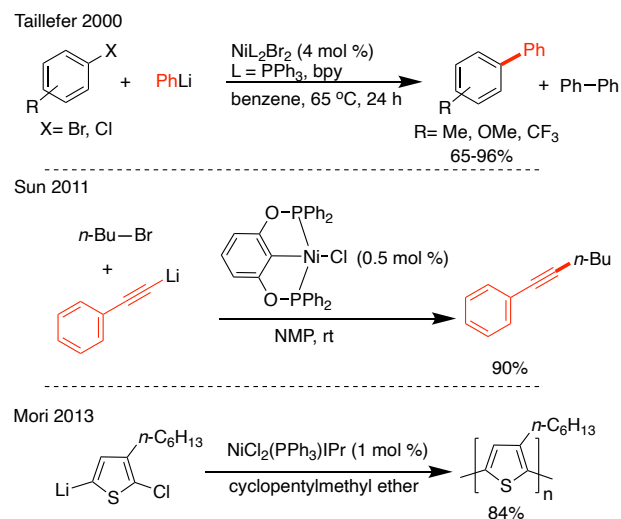

With due appreciations, the use of Ni(COD)$_2$ limits the practicality of this method considering its commercial production at an affordable price and handling of this highly air-sensitive Ni-complex. In 2019, Sawamura and co-workers reported cross-coupling between aryl chlorides and alkyllithiums using a heterogeneous Ni on polystyrene-based (bis)phosphine ligand.[73] The catalyst was found to be bench-stable and showed improved reactivity over previously reported Ni catalysts. The authors have demonstrated a 20 mmol scale reaction using the Ni-catalyst.

Scheme 16. Ni-catalyzed cross-coupling of organolithiums with ethers[72]
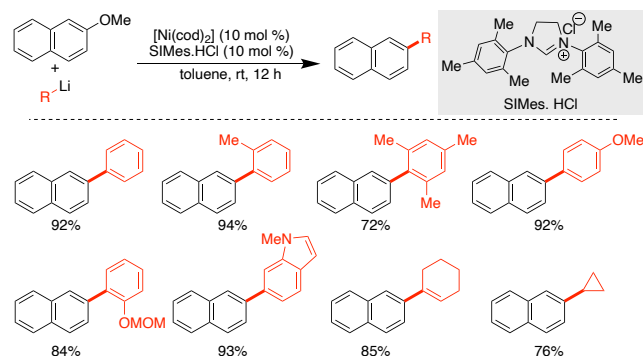
In 2016, Wang and co-workers reported a highly efficient method for the cross-coupling of aryllithium reagents with aryl or heteroaryl chlorides using Ni-NNP-pincer complexes. The method requires relatively low catalyst loadings, short reaction times, and mild reaction conditions, leading to good product yields in most cases (Scheme 17).[74] However, this method describes less functional group tolerance and is only suitable for electron-rich alkyl chlorides.

**Scheme 17. Ni-catalyzed cross-coupling of (hetero)aryl chlorides with aryllithiums[73]**
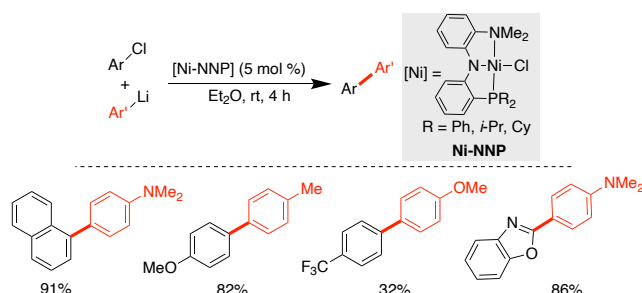
During the same year, Wong and co-workers reported iron (Fe)-catalyzed cross-coupling reactions of organolithiums with both aryl and alkyl halides (Scheme 18).[75] The authors also mentioned that TMEDA in a dipolar-aprotic solvent system with THF played a significance role to suppress the formation of homocoupling byproducts. Although it has broad substrate scope with respect to the lithium reagents, this protocol is very much substrate specific to aryl halides. This method works well only with electron-rich or -neutral substrates with moderate-to-good yields.

Scheme 18. Fe-catalyzed Murahashi coupling[75]
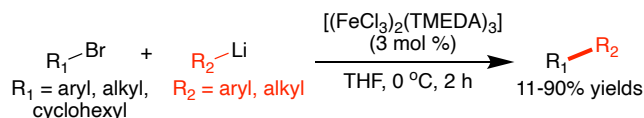
The methodology is demonstrated with a limited functional group tolerance, which limits its wide adoption for industrial applications, currently. Recently, the same authors reported ligand-free cross-coupling of alkenyllithium with vinyl halides to synthesize useful dienes in moderate-to-good yields using simple FeCl$_3$ as the catalyst (Scheme 19).[76]

Scheme 19. Fe-catalyzed cross-couplings of alkenyllithium with vinyl halides[76]
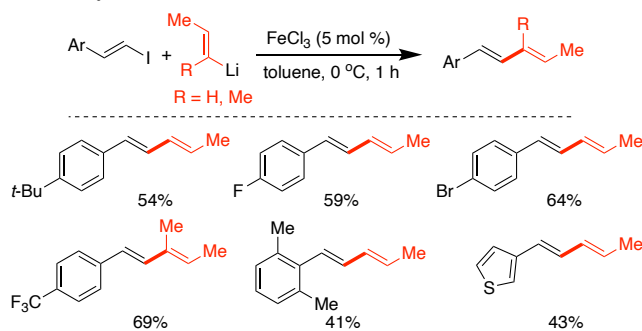
## 2.3 Murahashi cross-coupling in flow reactors: Direct cross-coupling of two different aryl bromides

Recently, continuous flow microreactors have emerged as a powerful tool in both discovery and process chemistry.[77,78] Microreactors provide several advantages over traditional batch reactors. It includes complete control on reaction and process safety, especially while using highly exothermic or explosive or toxic reagents and dealing with enhanced heat- and mass-transfer characteristics, precise control over reaction time, isolation of air- and water-sensitive products, the possibility of automation, and the ease of scale-up. Traditional cross-coupling reactions using flow reactors have also been recently reviewed by Buchwald and Yoshida.[77,78] In 2010, Yoshida and co-workers, for the first time, developed a microfluidic setup for the integration of an aryl halogen-lithium exchange and subsequent Murahashi coupling (Scheme 20).[23,24] The undesired side reactions, such as the reaction of Ar-Li with *in-situ* generated BuBr with another aryl bromide could be minimized. Therefore, cross-coupling of aryl bromide was accomplished in a continuous flow reactor with the residence time of a minute to form a new C-C bond.

Scheme 20. Murahashi cross-coupling in a flow reactor
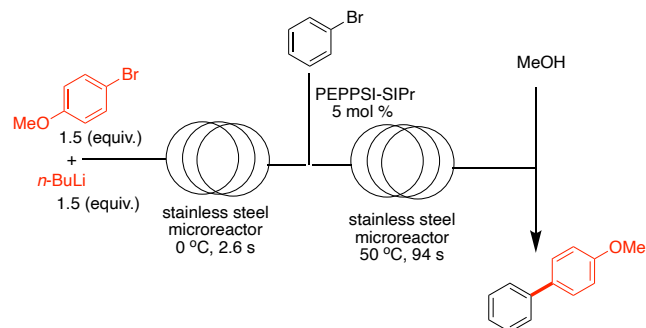
These methods still require the separate preparation of organolithium reagents. Therefore, direct tandem cross-coupling of two different aryl halides would be more attractive for the synthesis of unsymmetrical biaryls. A reported method for the direct cross-coupling of distinct aryl halides involves a Co-catalyst.[79] However, this method requires excessive amounts of a reducing reagent such as Mn. Electrochemical methods were also developed for cross-coupling of distinct aryl halides using a Ni-catalyst.[80]

Scheme 21. Highly selective direct cross-coupling of two different aryl bromides[81]
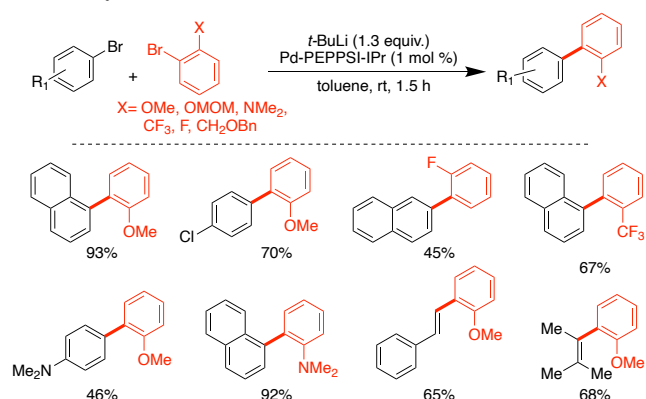
Interestingly, in 2015, Feringa and co-workers reported Pd-catalyzed highly selective cross-coupling of two distinct aryl bromides in a one pot fashion (Scheme 21).[81] The key point for this type of direct cross-coupling is the nature of orthogonal reactivity of the aryl bromides; one of them needs to undergo faster lithium–halogen exchange than the other aryl bromide. Therefore, this method is highly substrate specific. Following this approach, Feringa has also demonstrated the synthesis of intermediate of S_1P5 selective agonist, OLED synthesis for photovoltaic applications, and total synthesis of mastigophorene A (eight steps) in 27% yield over the final two steps as shown in Scheme 23.[82] The details are discussed in section 3.

**Scheme 22. Fe or Mn-catalyzed homo-couplings of alkenyllithium with aryl halides[83,84]**
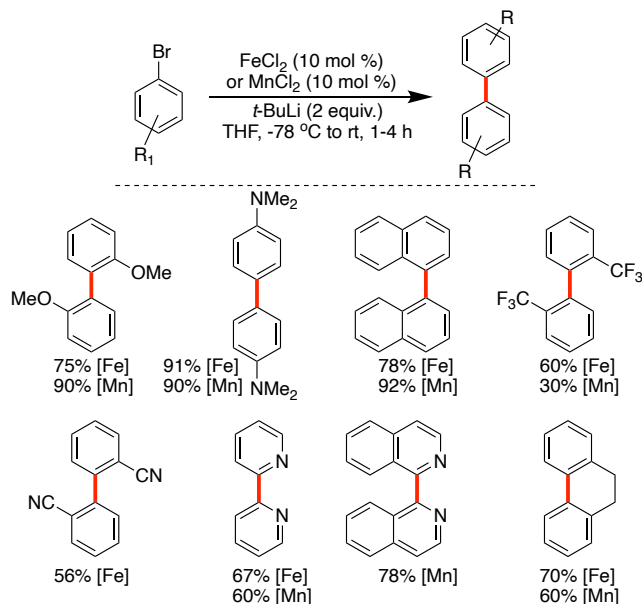
Iron and manganese-catalysts can also be used for the direct synthesis of symmetrical biaryl derivatives from aryl halides in very mild conditions.[83,84] The procedure, which proceeds via an *in-situ* quantitative aryl halide exchange with alkyllithiums (Scheme 22), allows for an excellent control of the reactivity for the further synthesis of the biaryl products. However, these protocols are only applicable for homocoupling products.

3. Synthetic applications of Murahashi-Feringa coupling

Finally, Feringa and co-workers have successfully demonstrated the utility of this new protocol for the synthesis of industrially relevant compounds, which were previously synthesized by other cross-coupling methods. Four examples are shown in Scheme 23, using the Murahashi-Feringa protocol, a $C(sp^2)$-$C(sp^3)$ cross-coupling reaction provided the product in up to 85% yield (Scheme 23a).[25] The previously reported method used a Pd-catalyzed Suzuki-Miyaura coupling at elevated temperature to obtain the product in 85% yield.[85] The product obtained is a key intermediate in the synthesis of a potential drug for the treatment of cognitive disorders (S_1P5 selective agonist). The second example involves the synthesis of a building block for OLED's.

The organolithium cross-coupling reaction provided the product in 85% yield (Scheme 23b), whereas the Pd-catalyzed Stille cross-coupling provides 73% yield under harsher reaction conditions.[86] The third example involves the synthesis of a functionally-enriched molecule, a first-generation light driven molecular motor in 85% yield (Scheme 23c).[87] Feringa's group also demonstrated the successful implementation of this protocol for the shortest atroposelective total synthesis of mastigophorene A (eight steps) in 27% yield over the final two steps (Scheme 23d). The previously reported methods require twenty steps to obtain the same product.[82] Besides, Murahashi cross-coupling can also be used for a one-pot procedure for sequential C-C/C-C, C-C/C-N, and C-C/C-S cross-coupling of bromo-chloro-arenes.[88]

Scheme 23. Applications of the Murahashi reaction in synthesis of bioactive molecule and OLED[25,82,85,87]

a. Synthesis of S_1P5 intermediate

b. Synthesis of OLED

c. Synthesis of molecular mottor

d. Synthesis of Mastigophorene A
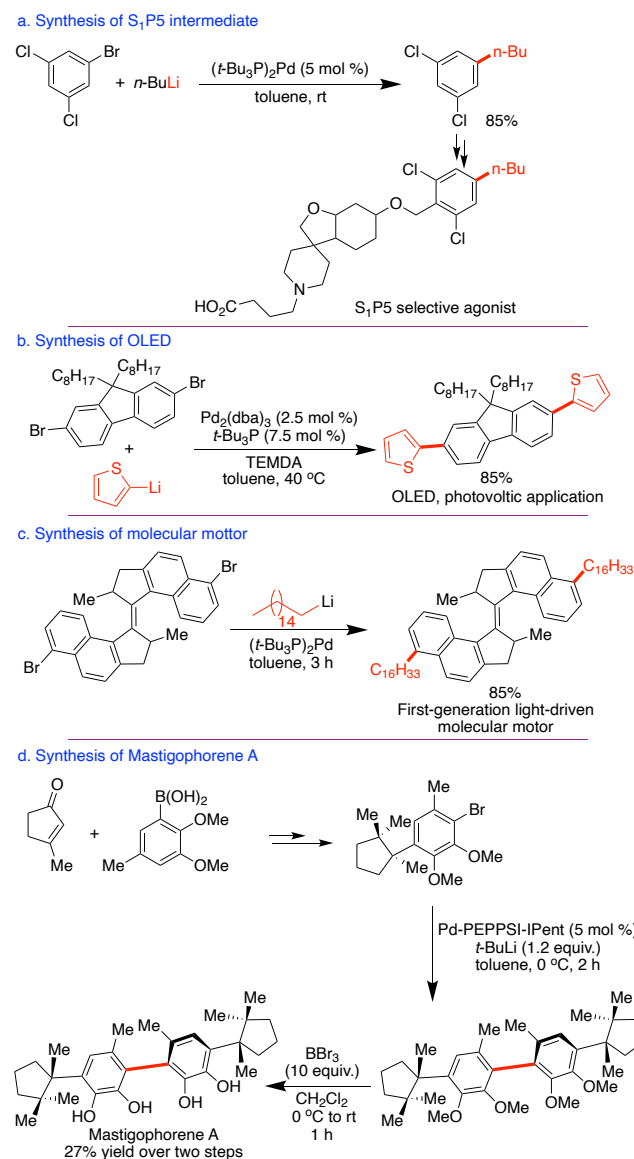
4. Prospects and Challenges

Almost 40 years after its discovery, the Murahashi reaction has been revived mainly due to the work of Feringa's group. This

technology has the potential to become a viable high-value synthetic methodology in organic synthesis because of the low cost and easy availability of organo-lithium reagents. As Mulvey has commented: "the recent reports of organolithium reactions taking place under aerobic and hydrous conditions represent one of the most remarkable breakthroughs in chemistry in recent times. We wait with eager anticipation to see how much this green chemistry will develop in the future."[89] Therefore, there are still many obstacles to overcome, such as poor functional group tolerance, and some limitations for the usage of heteroaryl halide coupling partners. Due to the inherent nature of these issues, creative solutions still need to be developed. Perhaps it will be required to investigate the chemical engineering aspect of this technology as much as the catalyst design and reaction optimizations. Flow chemistry could be a potential good approach to take this technology to the next phase. It is noteworthy that there are already examples of substrates with carbonyl groups, halides, and base-sensitive functionalities for the Murahashi coupling. The adoption of more environmentally responsible processes (e.g., recycling procedures with biodegradable solvents) as well as the use of stereodefined, more functionalized organolithium compounds are also highly desirable in the near future. The reaction also currently has limited scope. In fact, Murahashi reaction is facing challenges and trends similar to those previously faced by other well developed named cross-couplings, but we are optimistic that this emerging technology can become a viable methodology in cross-coupling. Recently, Aggarwal and coworkers demonstrated the direct coupling organolithium reagents with boronic esters to construct new C-C bonds.[90-98] In this case, boronic ester acts as Lewis acid (acceptor), and the reaction proceeds through a lithium boronate complex.
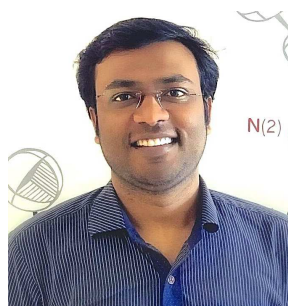
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AUTHOR INFORMATION

Corresponding Authors
*sachin.handa@louisville.edu
* johansson_carin@hotmail.com
*thomas.colacot@milliporesigma.com

Susanta Hazra received his M.Sc. degree in chemistry in 2015 and Ph.D. degree in 2020 from Indian Institute of Technology Delhi, India. He is currently a postdoctroal research associate at University of Louisville under the supervision of Prof. Sachin Handa. His research interests are mainly focused on sustainable asymmetric catalysis in aqueous micellar medium.

Sachin Handa was raised in Patti, a small town of Punjab (India), where he completed his undergraduate studies. He received a Ph.D. degree under the guidance of Prof. LeGrande Slaughter in the USA, where his research focus was the development of nonracemic acyclicdiaminocarbenes. Subsequently upon completing postdoctoral training under Prof. Bruce H. Lipshutz at UC Santa Barbara, he started his independent career as an assistant professor at the University of Louisville in August 2016. In July 2021, he was promoted to associate professor with tenure. His research laboratory focuses on the development of sustainable catalysts and reaction pathways. He is a recipient of the 2018 Ralph E. Powe Junior Faculty Enhancement Award by ORAU, the 2018 Peter J. Dunn Award for Green Chemistry and Engineering Impact in Industry by the American Chemical Society, and the NSF CAREER Award.

Carin Seechurn undertook her MChem with French studies at U.M.I.S.T (University of Manchester Institute of Science and Technology) and graduated in 2003. She subsequently moved to University of Cambridge for her Ph.D. studies in synthetic organic chemistry followed by a post-doctoral research associate position, both under supervision of Prof. Matthew Gaunt. After working 12 years in the homogeneous catalysis R & D at Johnson Matthey in developing many novel technologies, she joined Sinocompound as Technical Advisor in 2020. Using her extensive homogeneous catalysis knowledge, she is providing technical support to customers and is instrumental in executing technical marketing strategies. He is a recipient of Royal Society of Chemistry's 2020 Applied Catalysis Award.

Thomas J. Colacot joined as a R & D Fellow, Director - Global Technology Innovation, Life Science Chemistry at MilliporeSigma (Business of Merck KGaA, Darmstadt, Germany) in Milwaukee in 2018. He has extensive experience in developing new and innovative products and technology with very strong track record of commercialization globally is considered to be an industrial expert in cross coupling. His publication records with the generation of new IPs are significant. He is a recipient of many awards/honors including the prestigious 2021 Life Time Achievement Science Award from Merck (Merck KGaA, Darmstadt, Germany), 2018 Merck (Merck KGaA, Darmstadt, Germany) Outstanding Researcher, 2017Catalyis Club of Philadelphia Award for outstanding contributions in the field of catalysis, 2015 ACS Industry Chemistry Award, 2015 IPMI Henry Alfred Award, 2016 IIT Madras Distinguished Alumnus Award for Technology Innovation, 2016 Chemical Research Society of India CRSI Medal, 2012 RSC Applied Catalysis Award and medal, etc. Dr. Colacot was responsible for developing a very successful and sustainable homogeneous catalysis program at Johnson Matthey from 1995 to 2018. He has a MBA degree, from Penn State along with PhD and post-doctoral experiences. He is also a fellow of the Royal Society of Chemistry. He is coauthor of several books, peer- reviewed publications and patents.

Dedication. We dedicate this work to the loving memory of Prof. Victor Snieckus for his outstanding contributions in the area of organolithium chemistry.

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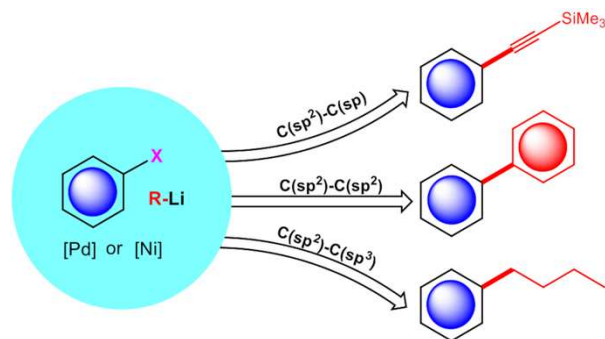
Since its discovery in the 1970's along with the other pioneering cross-coupling reactions, coupling involving organolithium reagents (Murahashi coupling) was neglected for more than 30 years. It was considered to be a technically impossible reaction in the area of cross-coupling by considering the poor selectivity, due to the high reactivity and low functional group tolerance of the organo-lithium species. In this Mini-Review, we shall provide a concise update on the revival of this coupling reaction, fueled largely by the research group of Feringa. Many of the difficulties associated with the Murahashi coupling have been overcome using modern catalytic systems in conjunction with the development of appropriate reaction conditions.