Murahashi Cross-Coupling at −78 °C

Sinha, Narayan; Heijnen, Dorus; Feringa, Ben L.; Organ, Michael G.

Published in:
Chemistry

DOI:
10.1002/chem.201901678

Publication date:
2019

ChemPubSoc Europe

DOI: 10.1002/chem.201901678

CHEMISTRY
A European Journal
Communication

Synthetic Methods

Murahashi Cross-Coupling at −78 °C: 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

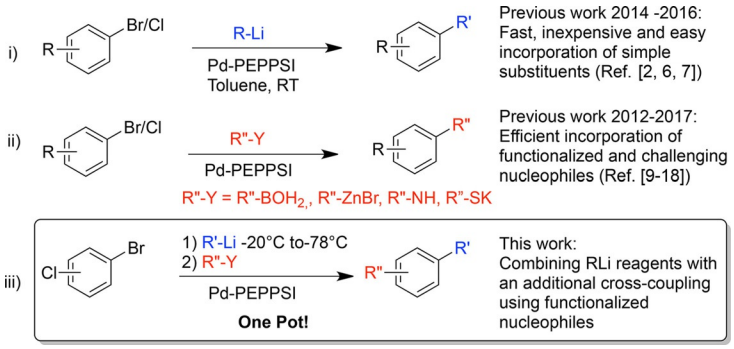
Narayan Sinha,[a, c] Dorus Heijnen,[a, b] Ben L. Feringa,*[b] and Michael G. Organ*[a, c]

Abstract: The coupling of organolithium reagents, including strongly hindered examples, at cryogenic temperatures (as low as −78 °C) has been achieved with high-reactivity Pd-NHC catalysts. A temperature-dependent chemoselectivity trigger has been developed for the selective coupling of aryl bromides in the presence of chlorides. Building on this, a one-pot, sequential coupling strategy is presented for the rapid construction of advanced building blocks. Importantly, one-shot addition of alkyllithium compounds to Pd cross-coupling reactions has been achieved, eliminating the need for slow addition by syringe pump.

Recent advancements in the cross-coupling of hard organometallic nucleophiles have been accelerated by the design of reactive catalysts with very high turnover frequencies.[1–6] Published work on the coupling of organolithium reagents offers new insights into the active palladium catalyst. For example, high-reactivity catalysts allow for cross-coupling of alkyllithium reagents with aryl bromides and iodides in which lithium–halogen exchange at these positions occurs rapidly with high efficiency. The use of organolithium reagents offer advantages in their ready commercial availability and ease of synthesis, but also in the reduction of (stoichiometric) waste generated because they can be prepared in situ and coupled directly.[7]

Aryl–phosphine Pd complexes have been used for Kumada coupling[8] to couple Knochel-type aryl Grignard reagents and aryl iodide at temperatures below 0 °C, but require several hours to reach full conversion.[8a] For electrophiles with a strong electron-withdrawing group, Fe-catalyzed reactions with Grignard reagents have also been reported.[8b] Very recently, Fe-catalyzed Csp^2–Csp^3 Kumada coupling of chlorobenzamides have been reported at 0 °C.[8c] An interesting article for the biaryl synthesis by homo- and hetero-Kumada couplings in water has also been reported.[8d] Feringa and co-workers have reported the use of Pd-phosphine catalysts for the coupling of organolithium reagents and found that, despite high turnover frequencies, coupling below −10 °C was not feasible.[2]

The Pd-NHC (N-heterocyclic carbene) catalyst family has also shown great stability and reactivity in the presence of aryl- and alkyllithium nucleophiles (Scheme 1 i) and has simultaneously proven to be a particularly active catalyst system for the cross-coupling of a variety of functionalized and challenging nucleophiles [R-ZnBr, R-$B(OR)_2$, R-SnR_3] in batch or flow (Scheme 1 ii).[9–18] Compared to simple NHC complexes, the design of Pd-PEPPSI catalysts with increased bulk on the flanking aryl groups increases turnover numbers[16] while decreasing competing side reactions arising from rearrangements, such as is seen in the coupling of secondary alkyl substrates by mitigating migratory insertion.[12a,b] These same catalysts also facilitate the coupling of profoundly hindered starting materials to make structurally complex products (e.g., tetra *ortho*-substituted biaryls).[7c,9,16] The fact that these challenging coupling procedures can be conducted routinely at room temperature[7c,9,12,15,17] paves the way for applications in the synthesis of natural products, biologically active compounds and complex ligands for metal catalysis.



Scheme 1. Overview of coupling reactions using Pd-PEPPSI catalysts.

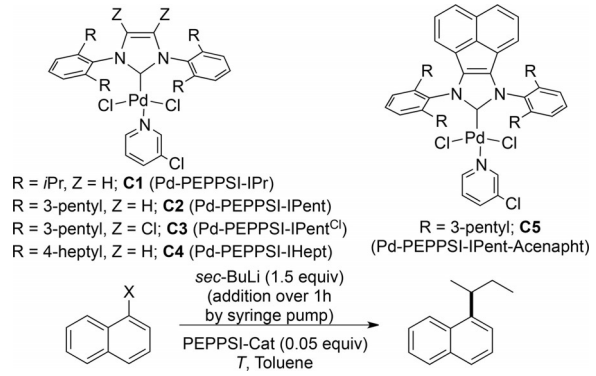
[a] Dr. N. Sinha, Dr. D. Heijnen, Prof. M. G. Organ
Department of Chemistry, York University
4700 Keele Street, Toronto, Ontario, M3J1P3 (Canada)
E-mail: organ@uottawa.ca

[b] Dr. D. Heijnen, Prof. B. L. Feringa
Stratingh Institute for Chemistry, University of Groningen
Nijenborgh 4, 9747 AG, Groningen (The Netherlands)
E-mail: b.f.feringa@rug.nl

[c] Dr. N. Sinha, Prof. M. G. Organ
Centre for Catalysis Research and Innovation (CCRI) and Department of Chemistry and Biomolecular Sciences, University of Ottawa
Ottawa, Ontario, K1N6N5 (Canada)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/chem.201901678.

Table 1. Structure–activity relationship (SAR) assessment of Pd-PEPPSI complexes with *sec*-BuLi.



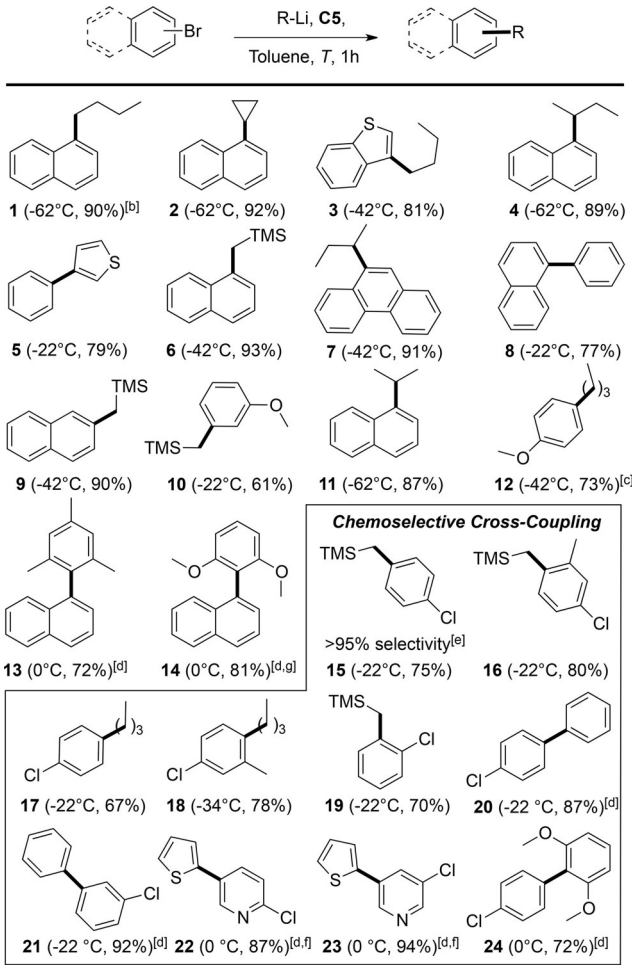
Entry	X	Catalyst	T [°C][a]	Conversion [%][b]
1	Br	**C1**	−78	0
2	Br	**C2**	−78	0
3	Br	**C4**	−78	10
4	Br	**C3**	−78	22
5	Br	**C5**	−78	37
6	Br	**C1**	−62	0
7	Br	**C2**	−62	88
8	Br	**C4**	−62	80
9	Br	**C3**	−62	91
10	Br	**C5**	−62	99
11	I	**C5**	−78	75[c]
12	Br	**C3**	−62	98[d]
13	Br	none	−62	0

[a] Reaction temperature was never allowed to rise and transformations were quenched at this temperature. [b] Percent conversion of 1-bromonaphthalene to 1-*sec*-butylnaphthalene, as determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] *n*BuLi was used. [d] 0.1 mol% catalyst was used and the reaction mixture was warmed to 23 °C.

The discovery (Scheme 1, Table 1) that naphthalene electrophiles could be coupled to alkyl lithium reagents by using Pd-NHC complexes at temperatures far below conventional cross-coupling temperatures (e.g., ≤ -20 °C) offers unique opportunities for organic synthesis.[7] To explore the potential of this observation, we embarked on a structure–activity relationship (SAR) study on the NHC ligand to determine its impact on reactivity at low temperatures. We systematically varied the flexible aliphatic groups on the N-aryl substituents, while at the same time assessing the electronic and steric effect of substituents on the NHC backbone (see Table 1).

We evaluated Pd-PEPPSI complexes by using the dropwise addition methodology developed in our laboratories[2,6] for the coupling of organolithium reagents at two temperatures, −62 and −78 °C, a temperature at which a successful cross-coupling method has yet to be reported. Changing the size of the N-aryl alkyl substituents (entries 1–5) had a noticeable impact on the coupling at −78 °C, with a similar trend observed at −62 °C (entry 6–10). Placing chlorides on the NHC core similarly improved reactivity at −78 °C (entry 2 vs. 4). Changing the core substituents from chlorides to a fused acenaphthaquinone system also yielded a high-performing catalyst, both at −78 °C (entry 5) and −62 °C (entry 10). Changing the oxidative addition (OA) partner to the corresponding iodide (entry 11) saw conversion at −78 °C jump to 75%, which represents the first such high-level conversion in a cross-coupling by using Pd catalysis below −65 °C. As the lower temperatures help to suppress catalyst deactivation, we were able to perform this reaction at very low catalyst loading (0.1 mol%, entry 12).

Substrate scope was evaluated and both naphthyl and (hetero)aryl halides proved to be excellent substrates (Scheme 2). When the nucleophile was changed from butyllithium to other organolithium reagents, we observed a trend between the strength of the nucleophile and the temperature cutoff (BuLi, −62 °C > TMS-CH_2Li, −42 °C > PhLi, −22 °C), suggesting a possible role for the nucleophile in the rate-determining step. Impressive reactivity was seen in the coupling of very hindered substrates (**13**, **14**, **24**) with **C3** and **C5**, relative to other cata-



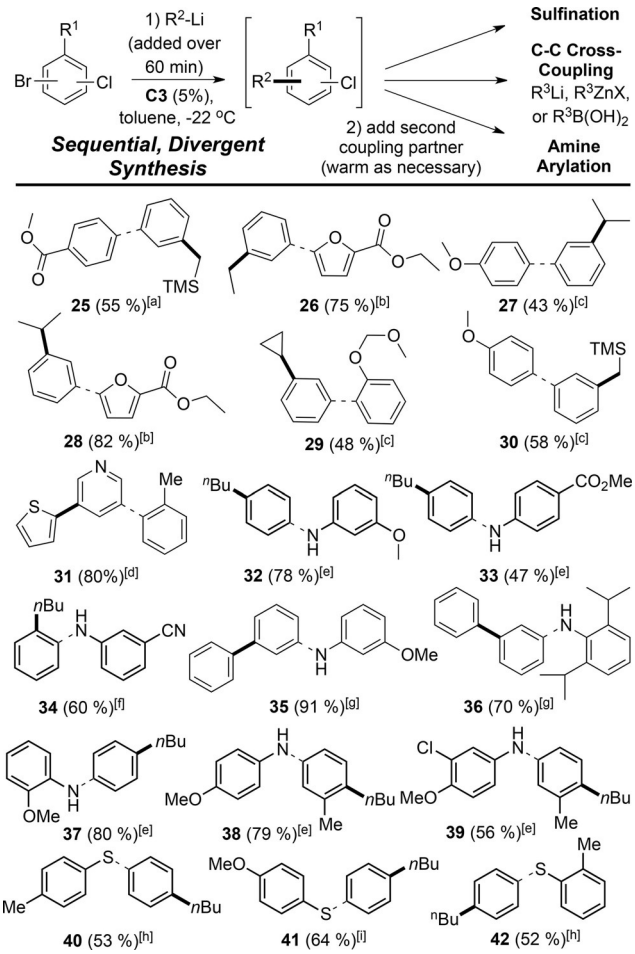
Scheme 2. Substrate scope for organolithium cross-coupling by using **C5**. Reaction conditions: (hetero)aryl bromide, **C5** (5 mol%), organolithium reagent (1.5 equiv), toluene, 1 h addition of organolithium reagent by syringe pump. The temperature of the reaction was never allowed to rise and the transformation was quenched at this temperature. Yields of isolated products following column chromatography. Additional reactions are reported in the Supporting Information. [b] 89% isolated yield at −42 °C after 10 min of reaction. [c] 4-Iodoanisole was used. [d] Pd-PEPPSI-IPent^{Cl} (**C3**) was used. [e] See the Supporting Information for details. [f] 1.2 equiv of 2-thienyllithium was used. [g] When 2.5 mol% of $Pd_2(I)_2(PtBu_3)_2$[1,3,4] was used, 7% conversion of naphthyl bromide was observed.

lysts of note. Further, byproducts arising from benzyne formation, a common side reaction,[19] were not observed with *ortho*-chloro substrates (**19**).

In an important observation, near perfect bromide/chloride chemoselectivity at −22 °C (**15** to **24**) was obtained with dihalogenated OA partners (see optimization table in the Supporting Information). Even when the bromide was sterically hindered (**16**, **18**), it was coupled preferentially over the chloride. Previously, the chemoselective[1,4,20] and sequential[21] couplings of bromo-chloro-arenes were achieved by changing solvent polarity, rate of transmetallation (TM) of the nucleophiles, or simply by using less reactive catalysts. For example, Watson and co-workers reported two interesting articles on the one-pot sequential Suzuki–Miyaura couplings of bromo-chloro-arenes controlling the rate of TM of the organoboron reagents.[21a,b] Very recently, Schoenebeck and co-workers presented the one-pot sequential Negishi couplings of bromo-chloro-arenes by sequential addition of aryl/alkyl zinc reagents and changing the solvent polarity.[21c] The catalytic turnover from **C3** at −62 °C shows that it is one of the most reactive catalysts yet reported for this transformation.

With this in mind, we envisioned a one-pot methodology in which a single catalyst would be capable of coupling multiple nucleophiles in a chemoselective fashion by using temperature as the selectivity trigger. This methodology would allow divergent synthesis to be achieved in an efficient manner, providing a powerful tool for synthesis. Methodology for the sequential coupling of two sp^2 hybridized organometallic reagents with a dihalide electrophile is known, but a general cross-coupling procedure in which one of the coupling partners is a sp^3 hybridized nucleophile is less prevalent.[21d,f] Small alkyl fragments, and in particular secondary (branched) centers, are crucial for the development of potent biomedically active compounds that bind with high selectivity to their protein targets.[22] The importance of such motifs in the structure of electronic materials is also well demonstrated.[23] Therefore, the development of an operationally simple, one-pot procedure to readily install such alkyl substituents on (hetero)aromatic core structures is highly desirable. Organolithium reagents coupled smoothly at −22 °C with bromo/chloro aromatics providing intermediates to which were added the reactants for Suzuki–Miyaura (**25**), Negishi (**26**, **28**), Murahashi[24] (**27**, **29**, **30**) and Kumada–Tamao–Corriu (**31**) cross-coupling procedures (Scheme 3). Not limited to carbon nucleophiles, amine arylation (**32**–**39**) and sulfination (**40**–**42**) reactions also proceeded well to give highly functionalized, advanced building blocks.

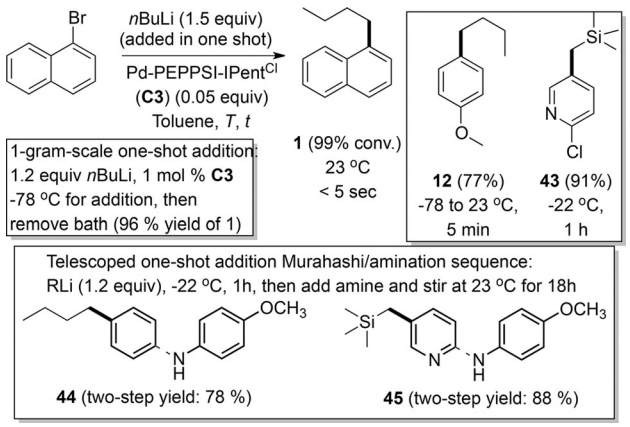
Although the methodology developed above represents an advancement for cross-coupling, Murahashi coupling,[24a] it is still thwarted by the perceived drawback for the necessity of syringe-pump addition.[7] Gradual charging of the reagent mitigates fast organolithium-related catalyst decomposition. What would be required to make the more-desirable, single-shot injection of the nucleophile possible is for catalysis to be so rapid that decomposition (presuming that it occurs) cannot complete with the desired pathway.[24b] Key would be a catalyst system capable of undergoing OA at near diffusion-limiting rates.



Scheme 3. One-pot sequential approach to divergent synthesis of functionalized molecules. Overall yield of isolated products following two-step process after column chromatography are reported in brackets. Additional reactions are reported in the Supporting Information. Conditions for second coupling: [a] $ArB(OH)_2$ (1.5 equiv), NaOMe (3 equiv), THF (3 mL), 75 °C, 18 h. [b] ArZnBr (1.5 equiv) 23 °C, 18 h. [c] ArLi (1.5 equiv) dropwise, 1 h, 40 °C. [d] First step at 0 °C; second step 1.5 equiv ArMgCl, 23 °C, 18 h. [e] Ar-NH_2 or Ar-NHMe (1.2 equiv), KO*t*Bu (1.5 equiv), 23 °C, 18 h. [f] Ar-NH_2 (1.2 equiv), Cs_2CO_3 (3 equiv), 80 °C, 18 h. [g] 1.5 equiv KO*t*Bu, 1.5 equiv $ArNH_2$, 60 °C, 18 h. [h] Ar-SH (1.2 equiv), KO*t*Bu (2 equiv), 80 °C, 18 h. [i] Ar-SH (1.2 equiv), KO*t*Bu (2 equiv), 23 °C, 18 h.

It has been proposed by Larrosa et al. that following one catalytic cycle with dihaloarenes that electron-rich Pd-PEPPSI-IPr (**C1**) undergoes OA with the remaining halide site faster than the catalyst can diffuse away from the mono cross-coupling product, which accounts for why they observed only di-coupling.[25] Indeed, rapid addition of *n*BuLi to naphthyl bromide and **C3** followed by the addition of methanol as quickly as possible thereafter saw full conversion to **1**, which worked equally well on a 1-gram scale (Scheme 4). The process seems general as deactivated OA partners (to give **12**) and heterocycles (**43**) also work fine. Finally, a telescoped, Murahashi/amination sequence like those in Scheme 3 worked perfectly well by using the one-shot alkyl-lithium addition method producing **44** and **45** in excellent yield.

In conclusion, the unprecedented coupling of organolithium reagents at cryogenic temperatures (as low as −78 °C) has



Scheme 4. One-shot addition of alkyllithium reagents in Murahashi coupling.

been attained by using highly reactive Pd-NHC catalysts. Alkyllithium reagents can be added in one-shot, rather than being added slowly by syringe pump. This is due to the ability of Pd-PEPPSI-IPent^{Cl} (**C3**) to conduct this coupling at near diffusion-limiting rates, which mitigates the typical catalyst destruction by these highly basic nucleophiles. A "thermal trigger" was used for the two-step, one-pot sequential coupling of alkyl- and aryl-lithium reagents and more functionalized nucleophiles. This methodology allows for rapid, sequential, yet divergent preparation of highly functionalized molecules and building blocks for applications in the research programs of drug discovery and materials science, as well as offering opportunities for telescoped synthesis at large scale in process chemistry and fine-chemical manufacturing.

Acknowledgements

B.L.F. acknowledges the NWO-CW, National Research School Catalysis (NRSC-Catalysis), the European Research Council (ERC Advanced Grant 227897), and the Ministry of Education, Culture and Science (Gravitation program 024.601035). M.G.O. is grateful to the NSERC (Canada) for a Discovery Grant.

Conflict of interest

M.G.O. and members of his team receive royalty payments from some of the catalysts used in this manuscript.

Keywords: Murahashi coupling · organolithium · Pd catalysis · PEPPSI · sequential cross-coupling

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Manuscript received: April 10, 2019
Revised manuscript received: May 2, 2019
Version of record online: June 24, 2019