

Palladium-catalysed direct cross-coupling of secondary alkylolithium reagents†

Cite this: *Chem. Sci.*, 2014, 5, 1361

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

Received 4th November 2013
Accepted 28th November 2013

DOI: 10.1039/c3sc53047g

www.rsc.org/chemicalscience

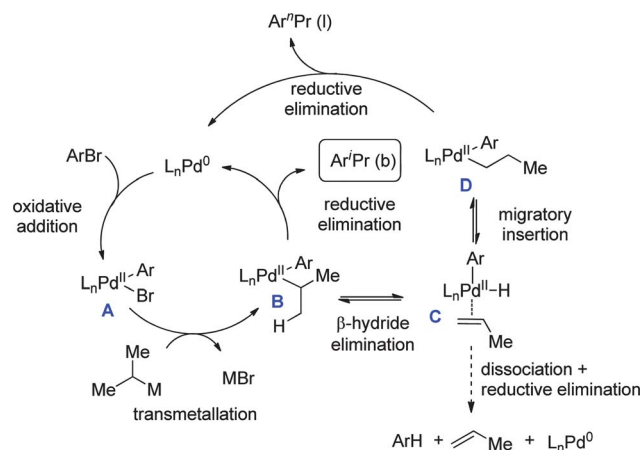
Palladium-catalysed cross-coupling of secondary C(sp³) organometallic reagents has been a long-standing challenge in organic synthesis, due to the problems associated with undesired isomerisation or the formation of reduction products. Based on our recently developed catalytic C–C bond formation with organolithium reagents, herein we present a Pd-catalysed cross-coupling of secondary alkylolithium reagents with aryl and alkenyl bromides. The reaction proceeds at room temperature and on short timescales with high selectivity and yields. This methodology is also applicable to hindered aryl bromides, which are a major challenge in the field of metal catalysed cross-coupling reactions.

Introduction

Transition metal catalysed cross-coupling reactions, and in particular palladium mediated couplings, have been extensively used for C–C bond formation in synthetic chemistry during the past three decades.¹ Among all these transformations, the coupling between C(sp²) and secondary C(sp³) partners is a challenging reaction. In this context, the coupling of secondary alkyl halides and C(sp²) nucleophiles² has been studied to a larger extent than the reverse cross-coupling of secondary C(sp³) organometallic nucleophiles with aryl halides.³ The use of secondary organometallic reagents in palladium-catalysed cross-coupling presents an additional problem as these organometallic moieties show a propensity for isomerisation of the alkyl chain, as illustrated in the mechanism depicted in Scheme 1.^{1a}

The oxidative addition of the aryl bromide to the Pd(0) complex generates Pd(II) species A, which by transmetalation of the secondary organometallic reagent affords the corresponding intermediate B. This intermediate can form the desired branched ⁱPr–Ar product (b) and regenerate the palladium catalyst *via* reductive elimination. As a competing reaction, B can undergo β-hydride elimination resulting in the formation of olefin-coordinated metal hydride C, which can afford D by migratory insertion leading to the undesired linear product (l) after reductive elimination. Also, the dissociation of the intermediate C can give rise to the corresponding olefin and formation of arene (Ar–H) upon reductive elimination. To suppress the isomerisation products, the rate of reductive elimination, relative to β-hydride elimination, should be

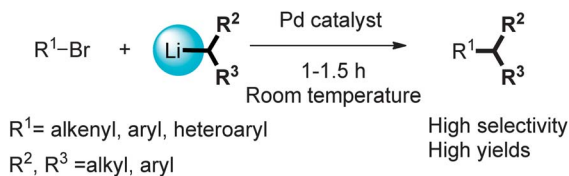
enhanced as much as possible. Successful examples of the use of palladium,^{4–16} nickel¹⁷ and other metal complexes¹⁸ as catalysts for the cross-coupling of secondary organometallic reagents have been described. For example, in the pioneering work of Hayashi,⁴ PdCl₂(dppf) was shown to efficiently catalyse the reaction between *sec*-butylmagnesium chloride with some aryl and alkenyl halides. Suzuki⁵ reported in 1989 the cross-coupling of secondary alkylboron compounds with iodo-benzene in moderate yields. Crudden⁶ in 2009 reported a palladium-catalysed cross-coupling of benzylic boronic esters and aryl iodides with retention of configuration. Molander⁷ and van den Hoogenband⁸ disclosed a Suzuki–Miyaura reaction with secondary alkyl trifluoroborates. In the case of Negishi cross-coupling, Knochel⁹ reported a stereoselective reaction between secondary diorganozinc reagents and (*E*)-1-iodohexene. Subsequently, several groups focused on secondary



Scheme 1 Proposed catalytic cycle for the Pd-catalysed cross-coupling of ⁱPrM with an aryl bromide.^{1a}

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands. E-mail: b.l.feringa@rug.nl; m.fananas.mastral@rug.nl; Fax: +31 50 363 4278; Tel: +31 50 3634296

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3sc53047g



Scheme 2 Palladium-catalysed direct cross-coupling of secondary alkyl organolithium reagents.

organozinc reagents. In order to avoid aryl iodides, Buchwald¹⁰ described an efficient catalytic system based on the bulky biarylphosphine ligand CPhos for the reaction of secondary alkylzinc reagents with common aryl bromides and chlorides. In 2010, Knochel¹¹ described a highly diastereoselective Negishi coupling with substituted five- and six-membered cycloalkylzinc reagents. Finally, Organ¹² disclosed a very effective system using *sec*-alkylZnBr reagents and Pd-PEPPSI-IPent^{Cl}, while Hiyama¹³ reported a cross-coupling with secondary alkylsilanes with very good selectivities. Recently, Biscoe¹⁴ described a successful Stille reaction between aryl halides and secondary alkyl azastannatranes.

Despite the great progress in cross-coupling of secondary alkyl organometallics, the toxicity, availability or preparation of these reagents represent a limitation in a number of cases. The design of alternative mild and selective catalytic procedures based on readily available reagents therefore continues to be a highly desirable goal.

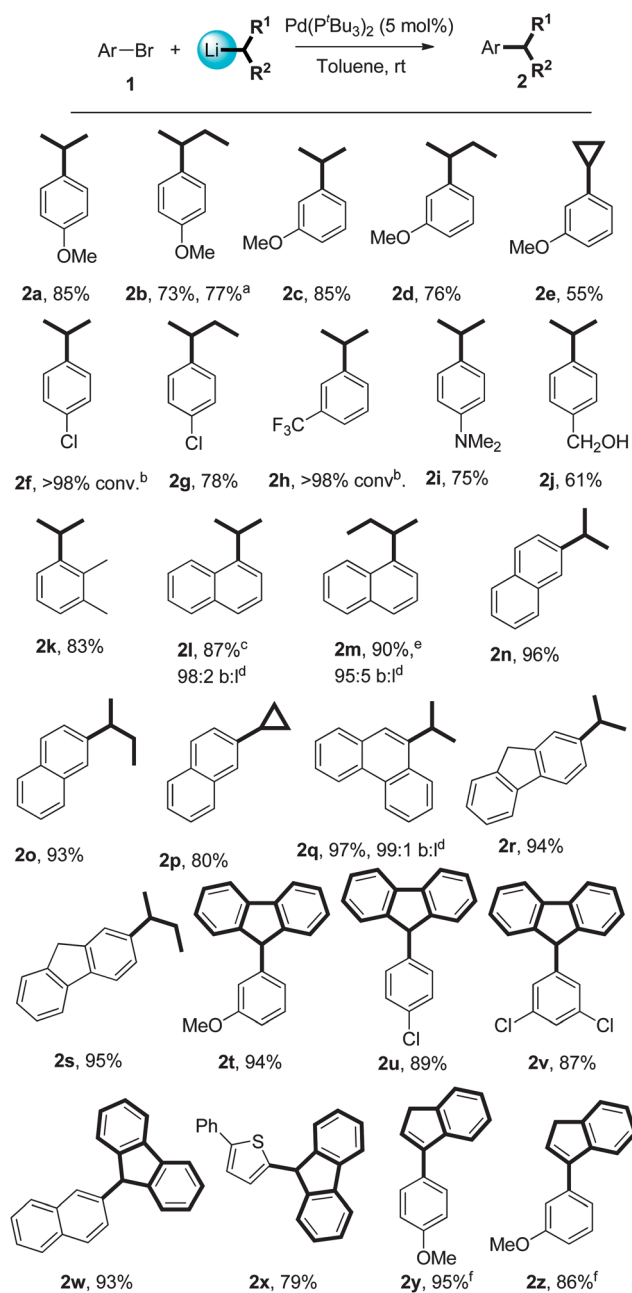
Organolithium reagents are commonly used reagents in chemical synthesis.¹⁹ Pioneering studies by Murahashi^{20a} of biaryl coupling using organolithium reagents also revealed the major limitations associated with the high reactivity of these organometallic compounds. As a consequence, the use of organolithium reagents has largely been neglected in the field of cross-coupling reactions.²⁰ In particular, secondary organolithium reagents represent a formidable challenge owing to their even higher reactivity and basicity. Very recently, our group described a direct catalytic cross-coupling of organolithium compounds with high selectivity and broad scope.²¹ The process proceeds quickly at room temperature and avoids the notorious lithium halogen exchange and homocoupling while the waste is simply LiBr.

Building on our recent findings, herein we present a highly efficient and selective catalytic cross-coupling of secondary alkyl lithium reagents with aryl and alkenyl bromides which proceeds quickly (1–1.5 h) at ambient temperature (Scheme 2). We also performed the reaction with hindered aryl bromides that have been rarely studied previously.³

Results and discussion

In order to establish a mild and general methodology for the coupling of secondary lithium reagents, a wide range of aromatic bromides were reacted with these lithium reagents, at room temperature in the presence of a catalytic amount of Pd(P^tBu₃)₂ (ref. 22) (Scheme 3). As shown in our previous work,²¹ the use of a non-polar solvent such as toluene and the slow

addition of the organolithium reagent were key factors in order to avoid lithium–halogen exchange.²³ Thus, the corresponding C(sp²)-C(sp³) cross-coupling products were obtained in high



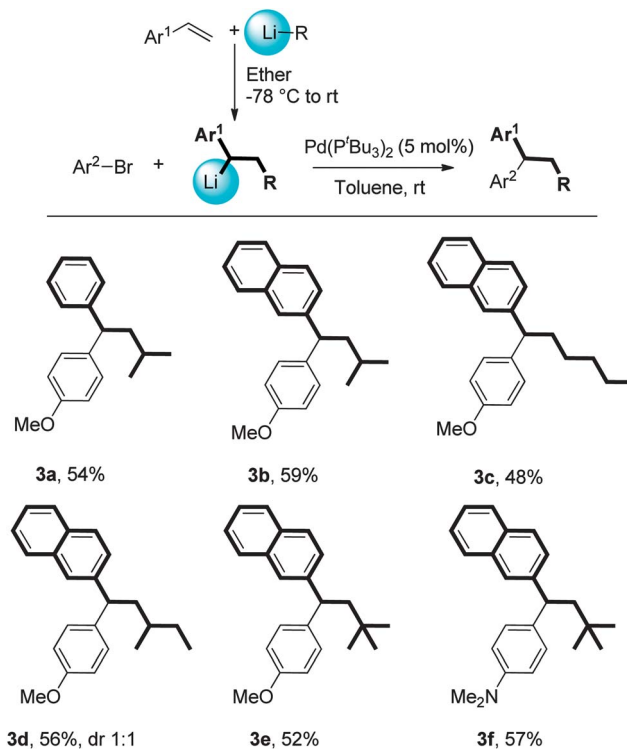
Scheme 3 Substrate scope for the palladium-catalysed cross-coupling of secondary alkyl lithium reagents and aryl bromides. Reaction conditions: RLi (0.36 mmol, diluted in toluene to reach 0.36 M) was added dropwise over 1 h to a stirred solution of ArBr (0.3 mmol) and Pd(P^tBu₃)₂ (0.015 mmol) in 2 mL of dry toluene at room temperature. Yield values refer to isolated yields after column chromatography. Branched : linear ratio >99 : 1 by ¹H NMR analysis unless otherwise noted. ^a 5.5 mmol (1.03 g) scale reaction using 2 mol% of catalyst. ^b 4% conversion, the product was not isolated due to volatility issues. ^c 4% dehalogenation (Ar–H) determined by GC and ¹H NMR analysis. ^d b : l refers to the branched : linear ratio of the product determined by ¹H NMR analysis. ^e 5% dehalogenation (Ar–H) determined by GC and ¹H NMR analysis. ^f RLi (0.4 mmol) was added dropwise over 2 h to a solution of substrate and catalyst warmed at 40 °C.

yields and with excellent selectivities. The reaction with ${}^t\text{PrLi}$ or *sec*-BuLi proceeds smoothly, independently of the electronic nature of the substituents in the aromatic ring (**2a–h**). For example, in the reaction with *p*-chloro-bromobenzene (**2f** and **2g**), only substitution of the bromide was observed, proving the high selectivity of this palladium-catalysed cross-coupling. In addition, (4-bromophenyl)methanol **1j**, bearing a free hydroxyl group, could be coupled with ${}^t\text{PrLi}$ (2.4 equiv.) in good yield. Polyaromatic compounds such as 1- and 2-bromonaphthalene were alkylated regioselectively at the position of the bromo-substituted carbon (**2l–q**), showing that the formation of benzyne intermediate *via* 1,2-elimination did not take place.

Interestingly, 2-bromofluorene could be alkylated (**2r** and **2s**) with only 1.2 equivalents of the corresponding organolithium reagent, despite the acidity of the benzylic protons ($\text{p}K_{\text{a}} = 22$). Cyclopropyllithium could also be coupled successfully and the corresponding products **2e** and **2p** were obtained in good yields. Additionally, to test the synthetic utility of the present methodology, **2b** was prepared on a gram scale (1.03 g, 5.5 mmol) with a similar yield and selectivity, using only 2 mol% of $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ in this case.

Taking into consideration the acidity of the benzylic protons of fluorene,²⁴ we decided to investigate the coupling of the corresponding fluorenyllithium reagent generated directly and easily by deprotonation of fluorene with ${}^n\text{BuLi}$.^{25,26} The resulting products would be of special synthetic interest as fluorene is an essential core structure in numerous materials science applications. For example, polyfluorenes are widely used in organic optoelectronic devices, such as organic light-emitting diodes or organic photovoltaic cells.²⁷ The palladium-catalysed cross-coupling of fluorenyllithium reagent with different substituted aryl bromides proceeded smoothly, and the corresponding products (**2t–x**) were isolated in excellent yields. Notably, the presence of MeO or Cl substituents in products **2t–x** allows for further functionalization of the aromatic ring. Finally, 2-bromo-5-phenylthiophene was successfully coupled with fluorenyllithium affording the corresponding product **2x** in 79% yield. Indenyllithium, prepared easily by deprotonation of indene with ${}^t\text{BuLi}$, was also examined as a lithium reagent. Due to the lower reactivity of this lithium reagent, the reaction had to be carried out at 40 °C to reach full conversion. The corresponding products **2y** and **2z** were isolated in excellent yields. Note that complete isomerisation of the double bond to the more substituted position was observed.

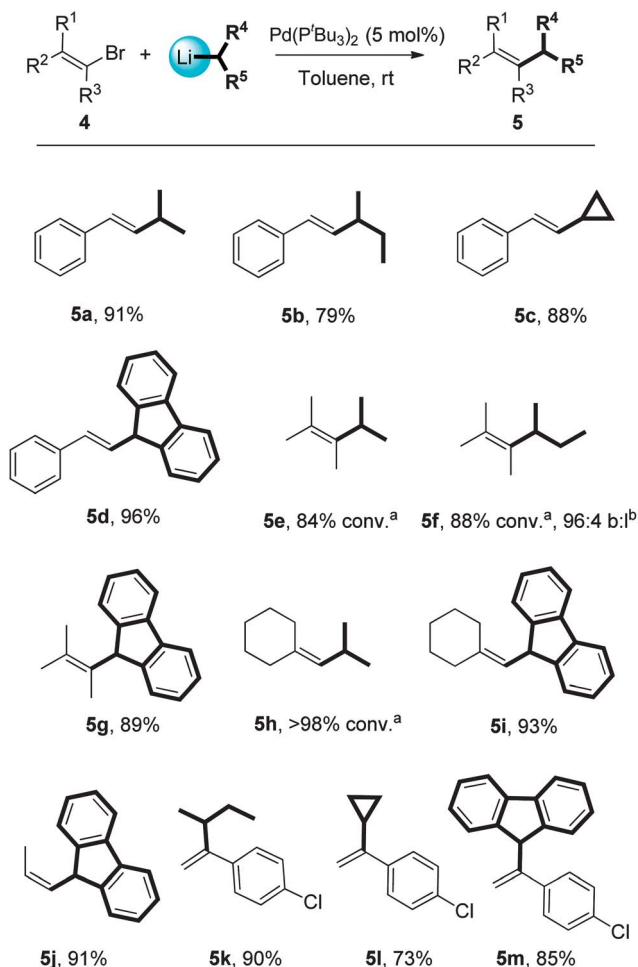
A particularly interesting method to generate secondary alkyl organolithium reagents involves direct alkene carbolithiation. This is an efficient and versatile procedure, which occurs with complete atom economy.²⁸ Consequently, we examined our palladium-catalysed cross-coupling methodology with the corresponding secondary alkyl organolithium reagents generated *in situ* from the carbolithiation of styrene and 2-vinylnaphthalene with commercially available alkylolithium reagents such as ${}^t\text{PrLi}$, ${}^n\text{BuLi}$, *sec*-BuLi or ${}^i\text{BuLi}$ (Scheme 4). Once we generated the corresponding benzylic organolithium reagents, the reaction with aryl bromides was tested under the optimised conditions and the corresponding 1,1-diaryllalkane products **3a–f** could be isolated in moderate yields.²⁹ It is important to note



Scheme 4 Three-component coupling involving olefin carbolithiation and alkyl–aryl cross coupling. Reaction conditions: RLi (0.36 mmol) was added dropwise over 1–1.5 h to a stirred solution of aryl bromide (0.3 mmol) and $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ (0.015 mmol) in 2 mL of dry toluene at room temperature.

that the 1,1-diaryllalkane core is present in many natural products and is a prominent structure in numerous pharmaceutical intermediates.³⁰ The present methodology represents a straightforward transformation to access these moieties. In addition, these results showed that a three component addition/cross-coupling is feasible. It should be noted that this carbometalation for the generation of secondary alkyl reagents in palladium-catalysed cross-coupling has, to the best of our knowledge, not been previously described.

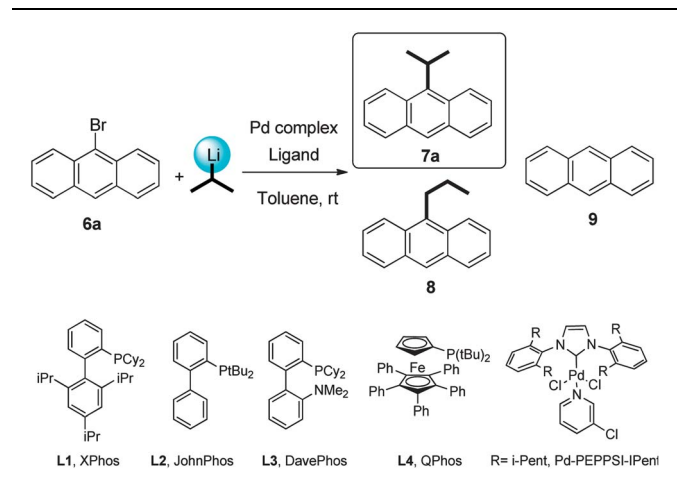
Having established this new coupling reaction with different aryl bromides, we turned our attention to the palladium-catalysed cross-coupling of secondary alkylolithium reagents with alkenyl bromides. This reaction would imply a selective synthesis of olefins branched at the alpha position which represents a cornerstone in organic chemistry. However, examples of palladium-catalysed cross-coupling of secondary alkyl organometallic reagents with alkenyl bromides are scarce. Following the early report of Hayashi,⁴ where the cross-coupling reaction of *sec*-BuMgCl with (*E*)- β -bromostyrene and 2-bromopropene was described for the first time, only Knochel⁹ has shown the reaction between secondary diorganozinc reagents and (*E*)-1-iodohexene catalysed by palladium. Therefore, the development of new cross-couplings of alkenyl bromides is highly desirable. To our delight, β -bromostyrene (commercially available as an 84/16 *trans*-*cis* mixture) reacted under the above mentioned conditions (1 h, rt) with isopropyl, *sec*-butyl, cyclopropyl, and 9-fluorenyllithium reagents, affording the



Scheme 5 Substrate scope for the palladium-catalysed cross-coupling of secondary alkylolithium reagents and alkenyl bromides. *Reaction conditions:* RLi (0.36 mmol, diluted in toluene to reach 0.36 M) was added dropwise over 1 h to a stirred solution of alkenyl bromide (0.3 mmol) and Pd(P^tBu₃)₂ (0.015 mmol) in 2 mL of dry toluene at room temperature. Yield values refer to isolated yields after column chromatography. Branched : linear ratio > 99 : 1 by ¹H NMR analysis unless otherwise noted. ^a Conversion determined by GC analysis; the product was not isolated due to volatility issues. ^b b : l refers to the branched : linear ratio determined by ¹H NMR analysis.

corresponding products (5a–d) in high yields (Scheme 5). In addition, 2-bromo-3-methylbutene and (bromomethylene)cyclohexane also underwent this palladium-catalysed cross-coupling affording the corresponding olefins with very good conversions (5e–g and 5h–i). It should be emphasized that the stereochemical integrity of the alkenyl bromide is preserved and no olefin isomerisation occurs in the course of the reaction. Thus, (*Z*)-1-bromopropene and 9-fluorenyllithium were successfully coupled, providing the product 5j as a pure *Z* isomer. Finally, the coupling of *sec*-butyl, cyclopropyl, and 9-fluorenyllithium reagents with 1-(1-bromovinyl)-4-chlorobenzene occurred exclusively at the Br-substituted carbon, and the corresponding olefins (5k–m) were selectively obtained in high yields, showing no dechlorination or coupling at the aromatic ring.

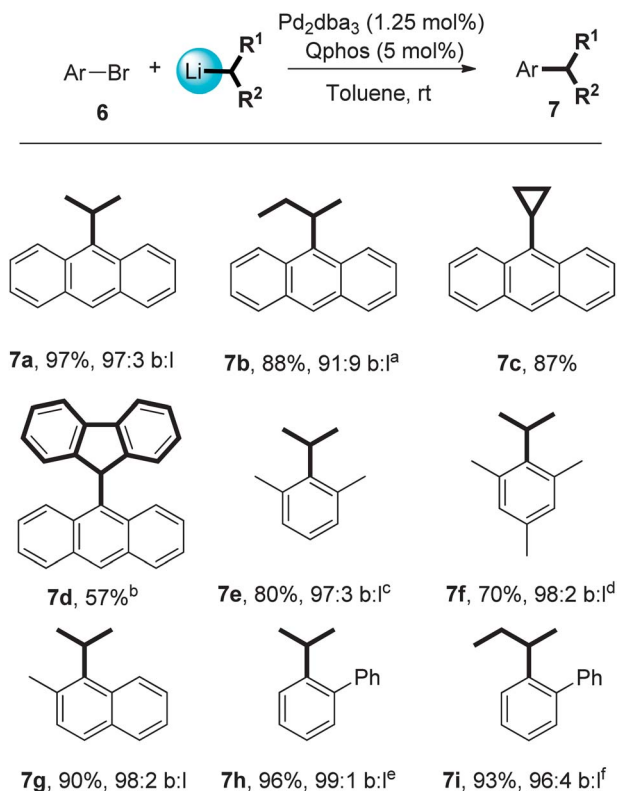
Table 1 Optimization of the reaction between hindered aryl bromide 6a and ^tPrLi^a



Entry	Pd complex (mol%)	Ligand (mol%)	Conv. ^b (yield) ^c	7a : 8 : 9 ^d
1	Pd(P ^t Bu ₃) ₂ (5)	—	Full (96)	48 : 52 : 0
2	Pd ₂ (dba) ₃ (2.5)	L1 (10)	Full	13 : 16 : 71
3	Pd ₂ (dba) ₃ (2.5)	L2 (10)	Full	5 : 5 : 90
4	Pd ₂ (dba) ₃ (2.5)	L3 (10)	Full	0 : 0 : >95
5	Pd-PEPPSI-IPent (5)	—	Full	57 : 28 : 15
6	Pd ₂ (dba) ₃ (2.5)	L4 (10)	Full (95)	97 : 3 : 0 ^e
7	Pd ₂ (dba) ₃ (1.25)	L4 (5)	Full (97)	97 : 3 : 0 ^e
8	Pd ₂ (dba) ₃ (0.63)	L4 (2.5)	Full (97)	88 : 3 : 9

^a *Reaction conditions:* ^tPrLi (0.36 mmol, diluted in toluene to reach 0.36 M) was added dropwise over 1 h to a stirred solution of 6a (0.3 mmol) and catalyst (5 mol%) in 2 mL of dry toluene at room temperature. ^b Conversions were determined by GC analysis. ^c Isolated yields after column chromatography. ^d Determined by GC analysis. ^e Determined by ¹H NMR analysis.

The cross-coupling of secondary alkylolithium reagents was also studied with hindered aryl bromides, such as 9-bromoanthracene (6a) (Table 1). This type of coupling has rarely been described, presumably due to reactivity, isomerisation or elimination issues. First we tried the optimised conditions of the palladium cross-coupling shown above for the reaction between 6a and ^tPrLi (Table 1, entry 1). The reaction proceeded with very high conversion, but unfortunately the ratio between branched and linear product was 1 : 1. This finding could be explained since the reductive elimination is presumably not fast enough and the rate of the β-hydride elimination and migratory insertion sequence is of a similar order to the rate of the reductive elimination (see Scheme 1). Other bulky phosphines were evaluated (Table 1) in order to increase the reductive elimination rate relative to the rate of β-hydride elimination. Biaryl based ligands³¹ L1, L2 and L3 gave unsatisfactory results, and the major reaction product was the reduced arene³² (anthracene, 9) (entries 2–4). Pd-PEPPSI-IPent¹² (entry 5) gave an improvement, reducing the isomerisation to afford a 2 : 1 b : l ratio, but showing far from satisfactory selectivity. Finally, when Hartwig's Qphos³³ (L4, entry 6), a very hindered ligand, was used, full conversion was achieved with a 96% isolated yield of



Scheme 6 Substrate scope for the palladium-catalysed cross-coupling of secondary alkyllithium reagents and hindered aryl bromides. *Reaction conditions:* RLi (0.36 mmol, diluted in toluene to reach 0.36 M) was added dropwise over 1 h to a stirred solution of ArBr (0.3 mmol), $\text{Pd}_2(\text{dba})_3$ (0.00375 mmol, 1.25 mol%) and QPhos (0.015 mmol, 5 mol%) in 2 mL of dry toluene at room temperature. Isolated yield after column chromatography. Branched : linear ratios determined by $^1\text{H-NMR}$ analysis. ^a 3% dehalogenation. ^b $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ (0.015 mmol) was used as a catalyst. ^c 8% dehalogenation. ^d 25% dehalogenation. ^e 3% homocoupling. ^f 4% homocoupling.

the desired product **7a**, with an excellent 97:3 b:l ratio. Therefore, when QPhos is used as a ligand, presumably a fast transmetallation–reductive elimination occurs, avoiding the other competitive pathways and leading to **7a** as the major product. Remarkably, the catalyst loading could be decreased to 2.5 mol% without erosion of the reactivity or selectivity, providing **7a** in a 97% isolated yield (entry 7). Furthermore, 0.63 mol% of $\text{Pd}_2(\text{dba})_3$ and 2.5 mol% of QPhos could be used (entry 8) whilst still obtaining a high branched : linear ratio, although a slight decrease in yield was observed and some reduction product (arene) was detected in this case.

With an efficient catalyst for the Pd-catalysed coupling of hindered aryl bromides established (entry 7, Table 1), the scope was studied using different secondary alkyllithium reagents and hindered aryl bromides (Scheme 6). *sec*-BuLi was reacted with **6a**, and the corresponding alkylated product **7b** was obtained after 1 h in 88% yield with a branched : linear ratio of 91 : 9. 9-Cyclopropylanthracene (**7c**) was also synthesised using the optimal conditions in very good yield (87%). Fluorenyllithium could be coupled, in this case using $\text{Pd}(\text{P}^t\text{Bu}_3)_2$, resulting in the corresponding alkylated product in 57% yield. In addition,

other hindered aryl bromides were reacted with $^t\text{PrLi}$ under the optimised conditions, and the corresponding products (**7e–i**) were obtained in excellent yields with almost no isomerisation (b : l = 96 : 4 to 99 : 1). One limitation of this cross-coupling is the use of 1-bromo-2-methoxybenzene as a coupling partner. In this case, the major product was the homocoupled biaryl (2,2'-dimethoxy-1,1'-biphenyl) resulting, most probably, from a Li–Br exchange and subsequent coupling. Probably, pre-complexation of the organolithium with the Lewis basic ether moiety might facilitate the metal–halogen exchange, as the high stabilisation by the methoxy group in the *ortho* position makes the corresponding lithium reagents the most stable lithium species. On the contrary, both alkyl and aryl substituents are tolerated in the *ortho* position of the aryl bromide (**7e–i**).

Conclusions

In conclusion, we have developed a highly efficient and selective catalytic system for the palladium-catalysed cross-coupling of secondary alkyllithium reagents with a wide range of aryl and alkenyl bromides. The reaction takes place under mild conditions and the products are obtained in good to excellent yields, with the undesired β -hydride elimination and isomerisation pathways being effectively suppressed in nearly all cases. In addition, different benzylic lithium reagents were prepared from direct carbolithiation of styrene or 2-vinylnaphthalene, and successfully coupled to provide different 1,1-diarylmethine compounds in moderate yields. This tandem carbometalation/cross-coupling involving secondary alkyl organometallic reagents has, as far as we know, not been reported for palladium-catalysed cross-coupling. Furthermore, a cross-coupling with hindered aryl bromides is described using $\text{Pd}_2(\text{dba})_3$ -QPhos as the catalyst providing the corresponding alkylated products in high yields and excellent selectivity. This new methodology shows the possibilities of using inexpensive and readily available secondary lithium reagents as complementary coupling partners. Moreover, the cross-coupling of the indenyl and fluorenyl moieties as nucleophilic partners is described showing excellent selectivity and reactivity, and opens new possibilities for the functionalization of the fluorene skeleton for optoelectronic materials. The results demonstrate that secondary alkyllithium reagents represent a valuable alternative for mild and selective C–C bond formation in an atom-economical manner.

Acknowledgements

Financial support from The Netherlands Organization for Scientific Research (NWO-CW), National Research School Catalysis (NRSC-Catalysis), the European Research Council (ERC advanced grant 227897), the Royal Netherland Academy of Arts and Sciences (KNAW) and the Ministry of Education Culture and Science (Gravity program 024.601035) is gratefully acknowledged. C.V. was supported by an Intra-European Marie Curie fellowship (FP7-PEOPLE-2011-IEF) (Contract number: 300826). We thank T. D. Tiemersma-Wegman for the HRMS analysis.

Notes and references

- 1 (a) *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2nd edn, 2004; (b) *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley-VCH Verlag GmbH, Weinheim, 2nd edn, 2004; (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-i. Negishi, John Wiley & Sons, New York, 2002; (d) M. R. Netherton and G. C. Fu, in *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*, ed. J. Tsuji, Springer, New York, 2005, pp. 85–108; (e) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442–4489; (f) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177–2250; (g) E. Negishi, *Angew. Chem., Int. Ed.*, 2011, **50**, 6738–6764; (h) C. C. C. Johanson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem., Int. Ed.*, 2011, **51**, 5062–5085.
- 2 A. Rudolph and M. Lautens, *Angew. Chem., Int. Ed.*, 2009, **48**, 2656–2670.
- 3 (a) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417–1492; (b) R. J. Lundgren and M. Stradiotto, *Chem.–Eur. J.*, 2012, **18**, 9758–9769.
- 4 T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.*, 1984, **106**, 158–163.
- 5 N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh and A. Suzuki, *J. Am. Chem. Soc.*, 1989, **111**, 314–321.
- 6 D. Imao, B. W. Glasspoole, V. S. Laberge and C. M. Crudden, *J. Am. Chem. Soc.*, 2009, **131**, 5024–5025.
- 7 (a) S. D. Dreher, P. G. Dormer, D. L. Sandrock and G. A. Molander, *J. Am. Chem. Soc.*, 2008, **130**, 9257–9259; (b) D. L. Sandrock, L. Jean-Gérard, C.-Y. Chen, S. D. Dreher and G. A. Molander, *J. Am. Chem. Soc.*, 2010, **132**, 17108–17110.
- 8 A. van den Hoogenband, J. H. M. Lange, J. W. Terpstra, M. Koch, G. M. Visser, M. Visser, T. J. Korstanje and J. T. B. H. Jastrzebski, *Tetrahedron Lett.*, 2008, **49**, 4122–4124.
- 9 A. Boudier and P. Knochel, *Tetrahedron Lett.*, 1999, **40**, 687–690.
- 10 C. Han and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 7532–7533.
- 11 T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer and P. Knochel, *Nat. Chem.*, 2010, **2**, 125–130.
- 12 (a) M. Pompeo, R. D. J. Froese, N. Hadei and M. G. Organ, *Angew. Chem., Int. Ed.*, 2012, **51**, 11354–11357; (b) S. Çalimsiz and M. G. Organ, *Chem. Commun.*, 2011, **47**, 5181–5183.
- 13 Y. Nakao, M. Takeda, T. Matsumoto and T. Hiyama, *Angew. Chem., Int. Ed.*, 2010, **49**, 4447–4450.
- 14 L. Li, C.-Y. Wang, R. Huang and M. R. Biscoe, *Nat. Chem.*, 2013, **5**, 607–612.
- 15 For reports using cyclic secondary organometallic reagents, see: (a) A. F. Littke, C. Dai and G. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020–4028; (b) X. Luo, H. Zhang, H. Duan, Q. Liu, L. Zhu, T. Zhang and A. Lei, *Org. Lett.*, 2007, **9**, 4571–4574; (c) E. G. Corey, K. Conrad, J. A. Murry, C. Savarin, J. Holko and G. Boice, *J. Org. Chem.*, 2004, **69**, 5120–5123.
- 16 For reports using α -functionalised secondary organometallic reagents, see: (a) T. Ohmura, T. Awano and M. Suginoe, *J. Am. Chem. Soc.*, 2010, **132**, 13191–13193; (b) M. Goli, A. He and J. R. Falck, *Org. Lett.*, 2011, **13**, 344–346; (c) T. Awano, T. Ohmura and M. Suginoe, *J. Am. Chem. Soc.*, 2011, **133**, 20738–20741; (d) G. A. Molander and S. R. Wisniewski, *J. Am. Chem. Soc.*, 2012, **134**, 16856–16868.
- 17 (a) K. Tamao, Y. Kiso, K. Sumitani and M. Kumada, *J. Am. Chem. Soc.*, 1972, **94**, 9268–9269; (b) L. Melzing, A. Gavryushin and P. Knochel, *Org. Lett.*, 2007, **9**, 5529–5532; (c) V. B. Phapale, M. Guisán-Ceinos, E. Buñuel and D. J. Cárdenas, *Chem.–Eur. J.*, 2009, **15**, 12681–12688; (d) A. Joshi-Pangu, M. Ganesh and M. R. Biscoe, *Org. Lett.*, 2011, **13**, 1218–1221.
- 18 For other metal-catalysed cross-coupling of secondary alkyl organometallic reagents, see: iron: (a) G. Cahiez and S. Marquais, *Tetrahedron Lett.*, 1996, **37**, 1773–1776; (b) G. Cahiez and H. Avedissian, *Synthesis*, 1998, 1199–1205; (c) A. Fürstner, A. Leitner, M. Mendez and H. Krause, *J. Am. Chem. Soc.*, 2002, **124**, 13856–13863; Cobalt: (d) G. Cahiez and H. Avedissian, *Tetrahedron Lett.*, 1998, **39**, 6159–6162.
- 19 *The Chemistry of Organolithium Compounds*, ed. Z. Rappoport and I. Marek, Wiley-VCH, 2004.
- 20 (a) S.-I. Murahashi, M. Yamamura, K.-I. Yanagisawa, N. Mita and K. Kondo, *J. Org. Chem.*, 1979, **44**, 2408–2417. For an application of Murahashi coupling in a flow microreactor, see: (b) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi and J.-I. Yoshida, *Angew. Chem., Int. Ed.*, 2009, **49**, 7543–7547. For the use of a silicon-based transfer agent, see: (c) A. B. Smith III, A. T. Hoye, D. Martinez-Solorio, W.-S. Kim and R. Tong, *J. Am. Chem. Soc.*, 2012, **134**, 4533–4536; (d) M. H. Nguyen and A. B. Smith III, *Org. Lett.*, 2013, **15**, 4258–4261.
- 21 (a) M. Giannerini, M. Fañanás-Mastral and B. L. Feringa, *Nat. Chem.*, 2013, **5**, 667–672; (b) V. Hornillos, M. Giannerini, C. Vila, M. Fañanás-Mastral and B. L. Feringa, *Org. Lett.*, 2013, **15**, 5114–5117; (c) M. Giannerini, V. Hornillos, C. Vila, M. Fañanás-Mastral and B. L. Feringa, *Angew. Chem. Int. Ed.*, 2013, **52**, 13329–13333.
- 22 Chelatingphosphine ligands such as DPEphos, which were used successfully in the palladium-catalysed cross-coupling of 2-butyilmagnesium chloride with bromobenzene (M. Kranenburg, P. C. J. Kamer and P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.*, 1998, 155–157), were not suitable for the cross-coupling with secondary alkyl lithium reagents (see ESI† for further details).
- 23 Control experiments, in which (4-methoxyphenyl)lithium was added slowly to a solution of 2-bromopropane and catalyst, were carried out in order to check whether (or not) the products coming from the lithium–halogen exchange could also couple under the reaction conditions. These experiments did not show positive results and only

- very little conversion to the cross-coupled product was observed (see ESI† for further details).
- 24 G. Rieveschl and F. E. Ray, *Chem. Rev.*, 1938, **23**, 287–389.
- 25 See ESI† for further details.
- 26 For a recent report on the synthesis of triarymethanes *via* deprotonative-cross-coupling processes, see: J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher and P. J. Walsh, *J. Am. Chem. Soc.*, 2012, **134**, 13765–13772.
- 27 (a) A. C. Grimsdale, K. L. Chan, R. E. Martin, P. G. Jokisz and A. B. Holmes, *Chem. Rev.*, 2009, **109**, 897–1091; (b) Y. Koyama, K. Nakazono, H. Hayashi and T. Tataka, *Chem. Lett.*, 2009, **39**, 2–9; (c) O. Inganäs, F. Zhang and M. R. Andersson, *Acc. Chem. Res.*, 2009, **42**, 1731–1739; (d) R. Abbel, A. P. H. J. Schenning and E. W. Meijer, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 4215–4233.
- 28 (a) X. Wei, P. Johnson and J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1109–1116. For a review see: (b) A.-M. L. Hogan and D. F. O'Shea, *Chem. Commun.*, 2008, 3839–3851.
- 29 A significant amount of the corresponding olefins was observed due to the β -hydride elimination of the corresponding benzyllithium reagents. Other palladium complexes were tried without improving the results achieved with Pd(P^tBu₃)₂. Also in the carbolithiation a competing pathway is the anionic polymerisation of styrene, see: (a) M. Merton, *Anionic Polymerisation: Principles and Practice*, Academic Press, New York, 1983; (b) R. Waack and M. A. Doran, *J. Org. Chem.*, 1967, **32**, 3395–3399.
- 30 (a) S. Messaoudi, A. Hamze, O. Provot, B. Treguier, D. L. J. Rodrigo, J. Bignon, J.-M. Liu, J. Wdzieczak-Bakala, S. Thoret, J. Dubois, J.-D. Brion and M. Alami, *ChemMedChem*, 2011, **6**, 488–497; (b) Q. Hu, L. Yin, C. Jagusch, U. E. Hille and R. W. Hartmann, *J. Med. Chem.*, 2010, **53**, 5049–5053; (c) K. Gligorich, R. Vaden, D. Shelton, G. Wang, C. Matsen, R. Looper, M. Sigman and B. Welm, *Breast Cancer Res.*, 2013, **15**, R58.
- 31 R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461–1473.
- 32 We cannot exclude the lithium–halogen exchange that would also afford the reduced arene after quenching.
- 33 N. Kataoka, Q. Shelby, J. P. Stambuli and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 5553–5566.