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Palladium-catalysed direct cross-coupling of secondary alkyllithium reagents

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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 isomerization 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 alkyllithium reagents with aryl and alkenyl bromides. The reaction proceeds at room temperature and in short times with high selectivity and yields. This methodology is also applicable to hindered aryl bromides and comprises a major challenge in the field of metal catalysed cross-coupling reactions.

Introduction

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Transition metal catalysed cross-coupling reactions, and in ¹⁵ 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 ²⁰ 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 crosscoupling presents an additional problem as these organometallics ²⁵ moieties show propensity to isomerise the alkyl chain as

illustrated in the mechanism depicted in Scheme 1.^{1a}



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

³⁰ The oxidative addition of the aryl bromide to the Pd(0) complex generates Pd(II) species **A**, which by transmetallation of

the secondary organometallic reagent affords the corresponding intermediate B. This intermediate can form the desired branched ¹Pr-Ar product (b) and regenerate the palladium catalyst via $_{35}$ reductive elimination. As a competing reaction, **B** can undergo β hydride elimination resulting in the formation of olefincoordinated metal hydride C, which can afford D by migratory insertion leading to the undesired linear product (1) after reductive elimination. Also, the dissociation of the intermediate C can give 40 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 ⁴⁵ 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 catalyse efficiently the reaction between sec-butylmagnesium chloride with some aryl and alkenyl halides. Suzuki⁵ reported in 1989 the 50 cross-coupling of secondary alkylboron compounds with iodobenzene 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 Hoogenband,⁸ disclosed a Suzuki-Miyaura reaction with 55 secondary alkyl trifluoroborates. In the case of Negishi crosscoupling, Knochel⁹ reported a stereoselective reaction between secondary diorganozinc reagents and (E)-1-iodohexene. Subsequently, several groups focused on secondary organozinc reagents. In order to avoid aryl iodides, Buchwald¹⁰ described an 60 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. 65 Finally, Organ¹² disclosed a very effective system using secalkylZnBr reagents and Pd-PEPPSI-IPent^{Cl} while Hiyama¹³

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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.

⁵ 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 continues therefore to be a highly ¹⁰ desirable goal.

Organolithium reagents are commonly used reagents in chemical synthesis.¹⁹ Pioneering studies by Murahashi^{20a} of biaryl coupling using organolithium reagents revealed also the major limitations associated with the high reactivity of these ¹⁵ 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 ²⁰ 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

- quickly at room temperature and avoids the notorious lithium halogen exchange and homocoupling while the waste is simply LiBr.
- ²⁵ Building on our recent findings, herein, we present a highly efficient and selective catalytic cross-coupling of secondary alkyllithium 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 ³⁰ have been rarely studied previously.³



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

Results and discussion

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- ³⁵ 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'Bu₃)₂²² (Scheme 3). As shown in our previous work,²¹ the use of a non-
- ⁴⁰ polar solvent such as toluene and the slow addition of the organolithium reagent were key factors in order to avoid the lithium-halogen exchange.²³ Thus, the corresponding $C(sp^2)$ - $C(sp^3)$ cross-coupling products were obtained in high yields and with excellent selectivities. The reaction with ^{*i*}PrLi or *sec*-BuLi
- ⁴⁵ 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 the substitution of the bromide was observed, proving the high selectivity of this palladium-catalysed cross-coupling. In addition,
- 50 (4-bromophenyl)methanol 1j, bearing a free hydroxyl group, could be coupled with ⁱPrLi (2.4 equiv) in good yield. Polyaromatic compounds such as 1- and 2-bromonaphthalene

were alkylated regioselectively at the position of the bromosubstituted carbon (**21-q**), showing that the formation of benzyne ⁵⁵ intermediate *via* 1,2-elimination did not take place.



Scheme 3 Substrate scope for the palladium catalyse cross-coupling of secondary alkyllithium reagents and aryl bromides. Reaction conditions:
60 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'Bu₃)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
65 reaction using 2 mol% of catalyst. ^b GC conversion, the product was not isolated due to volatility issues. ^c 4% dehalogenation (Ar-H) determined by GC and ¹H NMR analysis. ^d b:1 refers to the branched:linear ratio of the product determined by ¹H NMR analysis. ^c 5% dehalogenation (Ar-H) determined by GC and ¹H NMR analysis. ^f RLi (0.4 mmol) was added 70 dropwise over 2 h at 40 °C.

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 ($pK_a=22$). Cyclopropyllithium could also be coupled successfully and the

- s 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 similar yield and selectivity using only 2 mol% of $Pd(P'Bu_3)_2$ 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 "BuLi.^{25,26} The resulting products would be of special synthetic interest as fluorene is an 15 essential core structure in numerous material 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 crosscoupling of fluorenyllithium reagent with different substituted ²⁰ 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-5phenylthiophene was successfully coupled with fluorenyllithium ²⁵ affording the corresponding product **2x** in 79% yield. Indenyllithium, prepared easily by deprotonation of indene with
- ⁷BuLi, 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 ³⁰ **2y** and **2z** were isolated with excellent yields. Note that complete isomerization of the double bond to the more substituted position was observed.

A particular interesting method to generate secondary alkyl organolithium reagents involves the direct alkene carbolithiation. ³⁵ This is an efficient and versatile procedure, that 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 ⁴⁰ with commercially available alkyllithium reagents such as ^{*i*}PrLi, ^{*n*}BuLi, *sec*-BuLi or ^{*i*}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-diarylalkane products **3a-f** could be isolated in ⁴⁵ moderate yields.²⁹ It is important to note that the 1,1-diarylalkane 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
- ⁵⁰ 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.



3d, 56%, dr 1:1
 3e, 52%
 3f, 57%
 Scheme 4 Three-component coupling involving olefin carbolithiation and alkyl-aryl cross coupling Reaction conditions: RLi (0.36 mmol) was added dropwise over 1-1.5h to a stirred solution of aryl bromide (0.3 mmol) and Pd(P'Bu₃)₂ (0.015 mmol) in 2 mL of dry toluene at room temperature.

Having established this new coupling reaction with different aryl bromides, we turned our attention to the palladium-catalysed cross-coupling of secondary alkyllithium reagents with alkenyl bromides. This reaction would imply a selective synthesis of 65 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 70 reaction of sec-BuMgCl with (E)-β-bromostyrene and 2bromopropene was described for the first time, only Knochel⁹ had 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 75 highly desirable. To our delight, β -bromostyrene (commercially available as 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 corresponding products (5a-d) in high yields (Scheme 5). In 80 addition. 2-bromo-3-methylbutene and (bromomethylene)cyclohexane, also underwent this palladiumcatalysed 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

85 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 pure Z isomer. Finally, the coupling of *sec*-butyl, cyclopropyl, and 9fluorenyllithium reagents with 1-(1-bromovinyl)-4-chlorobenzene

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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.



Scheme 5 Substrate scope for the palladium catalysed cross-coupling of secondary alkyllithium reagents and alkenyl bromides. Reaction
 ¹⁰ 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'Bu₃)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
 ¹⁵ 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.

The cross-coupling of secondary alkyllithium reagents was also studied with hindered aryl bromides, such as 9-²⁰ bromoanthracene (**6a**) (Table 1). This type of coupling has been rarely 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 ^{*i*}PrLi (Table1, entry 1). The reaction proceeded with very ²⁵ high conversion, but unfortunately the ratio between branched

and linear product was 1:1. This finding could be explained because 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 as the rate of the reductive 30 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 arene 32 (anthracene, 9) 35 (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 96% isolated yield of the desired product 7a, 40 with an excellent 97:3 b:l ratio. Therefore, when QPhos is used as a ligand, probably, a fast transmetallation-reductive elimination occurs, that avoids the other competitive pathways leading to 7a as the major product. Remarkably, the catalyst loading could be decreased to 2.5 mol% without erosion in the reactivity or 45 selectivity providing 7a in 97% isolated yield (entry 7). Furthermore, 0.63 mol% of Pd₂(dba)₃ and 2.5 mol% of Qphos could be used (entry 8), still with a high branched:linear ratio although a slight decrease in yield was observed and some reduction product (arene) was detected in this case.





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
$7^{\rm f}$	$Pd_2(dba)_3(1.25)$	L4 (5)	Full (97)	97:3:0 ^e
8 ^g	$Pd_{2}(dba)_{3}(0.63)$	L4(2.5)	Full (97)	88:3:9

^a Reaction conditions: ⁱPrLi (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)
⁵⁵ and catalyst (5 mol%) in 2 mL of dry toluene at room temperature.
^bConversions were determined by GC analysis. ^c Isolated yields after column chromatography. ^d Determined by GC analysis. ^e Determined by ¹H NMR analysis. ^f 2.5 mol% of catalyst was used. ^g 1.25 mol% of catalyst was used.

With an efficient catalyst for the Pd-catalysed coupling of hindered aryl bromides established (entry 7, Table 1), the scope

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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. 9-5 cyclopropylanthracene (7c) was also synthesised using the optimal conditions in very good yield (87%). Fluorenyllithium could be coupled, using in this case $Pd(P'Bu_3)_2$, resulting in the corresponding alkylated product in 57% yield. In addition, other hindered aryl bromides were reacted with iPrLi under the 10 optimised conditions, and the corresponding products (7e-i) were obtained with 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-15 1,1'-biphenyl) resulting, most probably, from a Li-Br exchange and subsequent coupling. Probably, precomplexation 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 20 lithium reagents the most stable lithium species. On the contrary both alkyl and aryl substituents are tolerated in the ortho position



Scheme 6 Substrate scope for the palladium catalyse cross-coupling of 25 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 1h to a stirred solution of ArBr (0.3 mmol), Pd₂(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 30 chromatography. Branched:linear ratios determined by ¹H-NMR analysis.

^a 3% dehalogenation. ^b Pd(P'Bu₃)₂ (0.015 mmol) was used as a catalyst. ^c 8% dehalogenation. ^d 25% dehalogenation. ^e 3% homocoupling. ^f 4% homocoupling.

Conclusions

35 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 with good to excellent yields, with ⁴⁰ the undesired β-hydride elimination and isomerization pathways being effectively suppressed in nearly all the 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 with 45 moderate yields. This tandem carbometalation/cross-coupling involving secondary alkyl organometallic reagents has, as far as we know, not been reported for palladium-catalysed crosscoupling. Furthermore, a cross-coupling with hindered aryl bromides is described using Pd₂(dba)₃-Qphos as the catalyst 50 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 a 55 nucleophilic partner 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 a mild and selective 60 C-C bond formation in an atom-economic way.

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Notes and references

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