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Published in:
Angewandte Chemie - International Edition

DOI:
10.1002/anie.201700417

VIP Cross-Coupling Very Important Paper

International Edition: DOI: 10.1002/anie.201700417
German Edition: DOI: 10.1002/ange.201700417

Oxygen Activated, Palladium Nanoparticle Catalyzed, Ultrafast Cross-Coupling of Organolithium Reagents

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Abstract: *The discovery of an ultrafast cross-coupling of alkyl- and aryllithium reagents with a range of aryl bromides is presented. The essential role of molecular oxygen to form the active palladium catalyst was established; palladium nanoparticles that are highly active in cross-coupling reactions with reaction times ranging from 5 s to 5 min are thus generated in situ. High selectivities were observed for a range of heterocycles and functional groups as well as for an expanded scope of organolithium reagents. The applicability of this method was showcased by the synthesis of the [^{11}C]-labeled PET tracer celecoxib.*

Transition-metal-catalyzed cross-couplings of organometallic reagents have found widespread application in the synthesis of pharmaceutical products and organic materials, including the formation of important functionalized heterocycles.[1] Despite their prominent role in the modern synthetic repertoire, it remains of considerable interest to shorten reaction times, apply milder conditions, use less expensive starting materials, reduce catalyst loadings and trace residual metals in the desired product, and to minimize the amount of toxic waste. We have recently reported the direct cross-coupling of alkyl-, alkenyl-, and aryllithium reagents with a wide range of (pseudo)halogenated aryl and alkenyl electrophiles catalyzed by either palladium or nickel complexes.[2] These organolithium-based methods typically show cross-coupling with enhanced speed (<1 h), operate at mild temperatures (in most cases room temperature), and produce lighter and less toxic stoichiometric waste (LiX). Reactions with excellent chemoselectivity were initially achieved by slow addition of the highly reactive lithium reagent.[2] Typically, commercially available unaltered complexes were employed, including Pd/PEPPSI, Pd($P t Bu_3$)$_2$ (**C1**), or Pd/dba/XPhos, which are also prominent catalysts in closely related transformations, such as Negishi or Suzuki cross-coupling reactions.[3]

We envisioned that the exceptional reactivity and versatility of organolithium reagents could be taken advantage of in developing a fast cross-coupling that proceeds under ambient conditions, especially in light of the major current interest and important advances in fast cross-coupling reactions under mild conditions.[4] To the best of our knowledge, the very recently published procedure by the group of Schoenebeck, based on the use of Grignard and organozinc reagents (Figure 1), stands out in terms of short reaction times.[5]

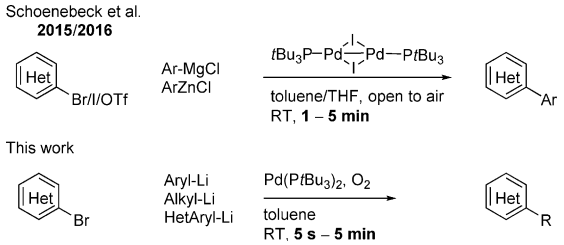

Figure 1. Recent fast cross-coupling reactions.

Herein, we present the discovery of an ultrafast cross-coupling with organolithium reagents. In stark contrast to the common practice of rigorously excluding oxygen when working with such extremely reactive organometallic reagents, we have found that molecular oxygen is essential to form the active catalyst. Under our conditions, rapid C–C bond formation occurs within seconds to minutes at room temperature while catalyst speciation studies point to the involvement of 2–3 nm large Pd nanoparticles. Using this new procedure, chemoselective cross-coupling reactions with organolithium reagents now include an expanded range of heterocycles, functional groups, and organolithium compounds. Furthermore, it provides a versatile method for isotope labeling, that is, for introducing CD_3 labels and short-lived ^{11}C radioisotopes ($t_{1/2}(^{11}C) = 20.3$ min) for PET imaging.

In preliminary experiments, we used the cross-coupling of methyllithium and 1-bromonaphthalene in the presence of Pd($P t Bu_3$)$_2$ (**C1**, 5 mol%) at room temperature to test

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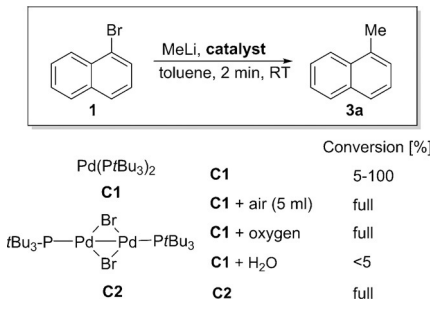
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201700417.

whether very short reaction times with full conversion would be possible (Scheme 1). Under presumably identical conditions, we were puzzled to observe greatly varying results.



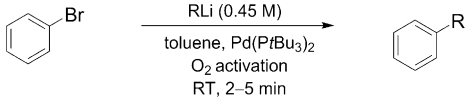
Scheme 1. Optimization of the fast cross-coupling.

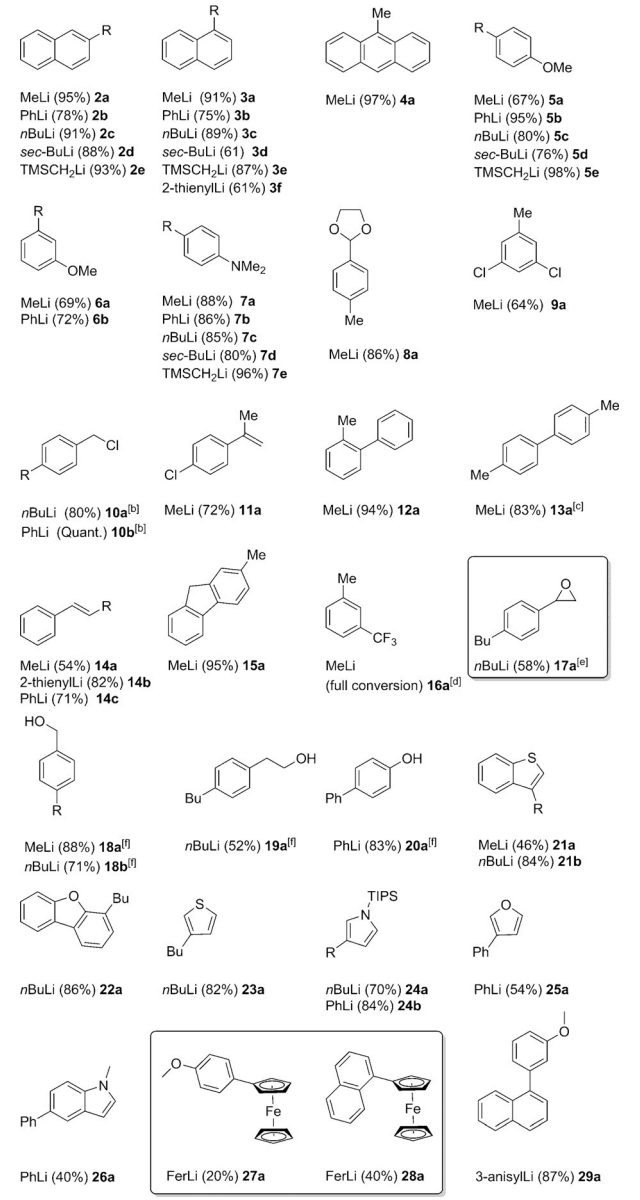
After eliminating many potential causes (variations in the concentration of the reagents, light, temperature, the presence of salts, water, or trace metal impurities), we established that minute traces of air were essential for catalyst activation. Samples briefly purged with dry oxygen prior to MeLi addition always gave complete and chemoselective conversion into 1-methylnaphthalene. The lack of reactivity observed after adding degassed water or when employing strictly oxygen-free conditions supported the notion that the presence of oxygen greatly enhanced the catalytic activity of the system.

Under the optimized conditions, an extended range of organolithium and aryl bromide reagents, compared to our previously reported method,[2] underwent highly selective coupling, providing excellent yields in 2–5 min at room temperature (Table 1). Substrates from the naphthalene (**2a**–**3f**) and anthracene families (**4a**) gave good yields with near-perfect selectivity when coupled with a variety of commercially available organolithium reagents. Gratifyingly, identical results were achieved with both electron-poor and electron-rich substrates (**5a**–**8a**). Unwanted side reactions were suppressed with near-perfect selectivity for C–Br over C–Cl in aromatic and aliphatic substrates with competitive coupling possibilities (**9a**–**11a**), while aryl bromides **12a**–**15a**, including CF_3-substituted analogue **16a**, gave selectivities similar to those of the naphthalene substrates.[6] Remarkably, the fast coupling of RLi can even be used when an epoxide functional group is present at a temperature as low as −10 °C, where the expected epoxide ring opening by the organolithium reagent is effectively suppressed, to provide the desired coupling product **17a**. Importantly, alcohols **18a**–**20a**, including an unprotected phenol, provided the corresponding products in good yields. Novel substrates were also found amongst heterocycles **21a**–**26a**.

The direct lithiation of inexpensive, commercially available ferrocene is well described in the literature,[7] and the corresponding nucleophile provides an alternative to the less available and costly boron or halide derivatives to yield **27a** and **28a**. Finally, aryllithium reagents synthesized via lithium–halogen exchange (e.g., 3-anisyllithium) also proved to be suitable coupling partners, providing biaryl **29a**.

Table 1: Fast cross-coupling of (hetero)aryl bromides with organolithium reagents.[a]

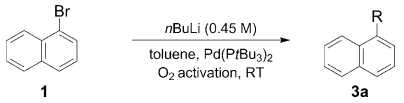




[a] Reaction conditions: 0.6 mmol substrate in 4 mL toluene, 5 mol% catalyst, 4 mL oxygen, 1.5 equiv (0.9 mmol) organolithium reagent. All reactions were carried out at room temperature. Yields of isolated products after column chromatography are given unless noted otherwise. [b] Reaction performed at 0 °C. [c] Performed with 2.5 equiv of the organolithium reagent at 40 °C. [d] Conversion determined by GCMS analysis. [e] Reaction performed with 1 equiv of *n*BuLi at −10 °C. [f] Reaction performed with 2.5 equiv of the organolithium reagent.

The reaction time of the coupling between *n*BuLi and 1-bromonaphthalene could be reduced to just 5 s at room temperature with 5 mol% of the precatalyst, giving full conversion and a turnover frequency of $14 \times 10^3\ h^{-1}$ (Table 2,

Table 2: Variation of the catalyst loading.[a]



Entry	**C1** [mol%]	Addition time	Conversion
1	5	5 s	full
2	0.5	2 min	full
3	0.05	10 min	full
4	0.025	10 min	40%
5	0.025	30 min	full
6[b]	0.05	30 min	full

[a] All experiments were conducted at room temperature in toluene (0.15 M initial substrate concentration); entries 1 and 2 were conducted on 0.3 mmol scale, entries 3–6 on 12 mmol (2.5 g) scale. Conversions were determined by GCMS analysis. [b] 4-Bromoanisole was used as the substrate.

entry 1), provided that an excess of oxygen was present with respect to Pd complex **C1**. With a catalyst loading of 0.05%, we were able to fully convert **1** on gram scale in just 10 min. On the other hand, by reducing the rate of addition of *n*BuLi, we were able to use a catalyst loading as low as 0.025 mol% (entry 2–5). A slightly higher catalyst loading was necessary for the coupling of 4-bromoanisole (entry 6).

Focusing on the crucial role of molecular oxygen, we observed that the catalyst solution turned red upon purging with O_2, suggesting that $Pd(PtBu_3)_2$ (**C1**) was converted into the active catalyst. Many d^{10} metal complexes are known to rapidly interact with O_2 to form stable η^2-peroxo complexes; however, **C1** has not been reported as one of them.[8] The reason for its stability towards O_2 was attributed to the extreme bulkiness of the ligands, which shield the Pd and hence hamper its oxidation. Therefore, the sterically hindered **C1** complex needs prolonged oxygen exposure at room temperature to ensure complete oxidation. To investigate whether known peroxo complexes could be excluded as possible catalysts, we tested the η^2-peroxo derivatives of $Pd(PCy_3)_2$ and $Pd(PPh_3)_2$,[5] which did not show any catalytic activity (see the Supporting Information). Extensive ^1H and ^{31}P NMR studies with catalytically inactive **C1** prior to and after exposure to oxygen revealed the formation of free $PtBu_3$ (see the Supporting Information), phosphine oxides, and (yet unidentified) oxidized Pd species (**C1^{ox}**) upon reaction with O_2.[9,10]

The hypothesis that the monoligated $[Pd(PtBu_3)]$ complex, arising from dissociation of one phosphine from the starting complex, acted as the active catalyst was excluded on the basis of the lack of reactivity with aryl chlorides and inhibition experiments by adding an excess of $PtBu_3$ (up to 10 equiv, see the Supporting Information), which had no effect on the outcome of the cross-coupling, suggesting a different active species.[5,11,12]

We were able to isolate the oxidized form (**C1^{ox}**) of **C1** by washing the residue of the oxidation step with acetonitrile (see the Supporting Information). Addition of 4-bromoanisole to **C1^{ox}** at room temperature showed no change at all by NMR analysis, which led to the conclusion that up until the addition of the organolithium reagent, no reaction is taking place.[13] Given the fast cross-coupling and the lack of any reaction between **C1** or **C1^{ox}** and the electrophile, we next tested whether the organolithium reagent initiates the catalytic cycle by generation of the active Pd species. Upon stoichiometric addition of *n*BuLi to a $[D_8]$toluene solution of **C1^{ox}**, some of the Pd species were reduced to form again catalytically inactive **C1** (^{31}P NMR analysis; see the Supporting Information), and stoichiometry indicates the formation of another Pd^0 species, presumably the active catalyst (see below). Important information came from independent experiments with the bridged dinuclear Pd^I complex **C2** (Scheme 1), which is also a catalyst precursor in our cross-coupling. Oxidation of **C2** occurs within seconds at room temperature, although we found that the product **C2^{ox}** arising from this reaction was not consistent with the one described in the literature (see the Supporting Information).[14] Both **C2** and **C2^{ox}** gave full conversion in cross-couplings with RLi reagents. The oxidation of **C2** and subsequent reduction of **C2^{ox}** by *n*BuLi was studied in detail by ^{31}P NMR spectroscopy (Figure 2), showing, much to our surprise, partial formation of mononuclear complex **C1**, which we knew to be catalytically inactive.

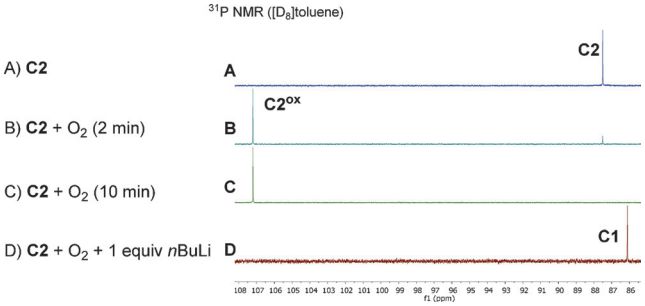
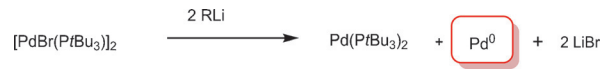


Figure 2. ^{31}P NMR spectra of **C2** in $[D_8]$toluene (a), after O_2 exposure (b, c), and *n*BuLi addition (d).

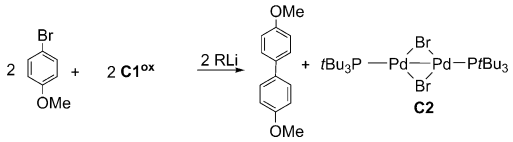
The lithium reagent promotes reduction from Pd^I to Pd^0 and the formation of both $Pd(PtBu_3)_2$ (**C1**) and apparently ligand-free Pd^0, which becomes evident from the observed stoichiometry (NMR analysis, see the Supporting Information) of the complexes and ligands (Scheme 2).



Scheme 2. Reduction of **C2** with RLi.

Following the cross-coupling reaction of 4-bromoanisole by NMR spectroscopy, we also observed the in situ formation of the bridged complex **C2** from **C1^{ox}** after RLi addition (in accordance with previous observations by Schoenebeck using Grignard reagents),[5] for which we suggest the stoichiometry shown in Scheme 3.

The combined results of the RLi addition experiments with **C1^{ox}**, **C2**, and **C2^{ox}**, which clearly showed reduction in all cases, led to the hypothesis that a common active species, that



Scheme 3. Schematic in situ formation of **C2** from **C1^{ox}**.

is, Pd nanoparticles (PdNPs), are formed in situ. TEM measurements were carried out to investigate the presence of nanoparticles in samples of **C1** and **C1^{ox}** prior to RLi addition, but in neither case, any PdNPs were observed. Studying the effect of the addition of the lithium reagent to **C1^{ox}**, we clearly observed PdNPs with dimensions of 2–3 nm (Figure 3).

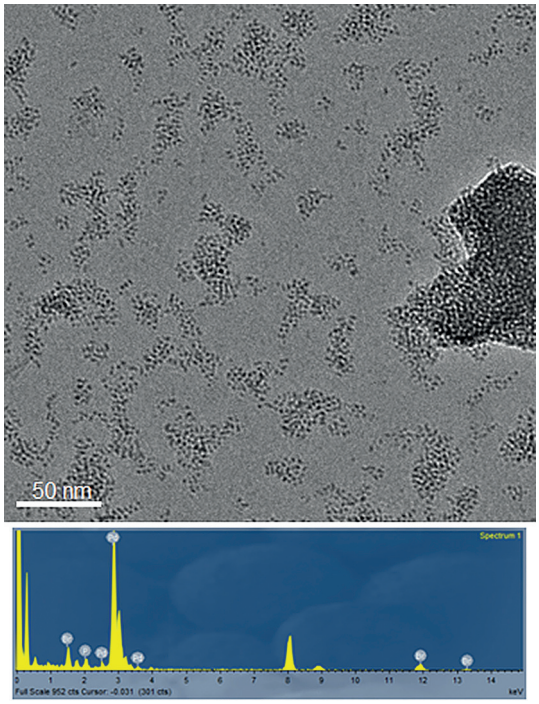
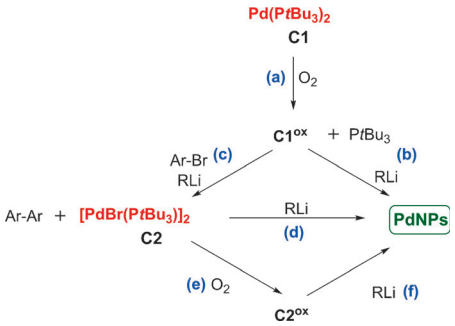


Figure 3. TEM image and corresponding EDX spectrum of the PdNPs.

In a highly informative set of experiments, under optimized cross-coupling conditions and with all previously mentioned precatalysts (**C1^{ox}**, **C2**, and **C2^{ox}**), samples were taken both during and at the end of the reaction, and analyzed by TEM for the in situ formation of nanoparticles (Figure 3 and the Supporting Information). We were pleased to see the formation of nanoparticles in all cases where product was formed. Energy-dispersive X-ray analysis (EDX)[15] revealed the elemental compositions of the samples, and clearly showed an increase in the Pd/P ratio with respect to catalytically inactive complexes, supporting the formation of PdNPs (see the Supporting Information). Isolation of these nanoparticles was successful by centrifugation and repeated washing with toluene, and the absence of homogeneous Pd complexes was confirmed by ^{1}H and ^{31}P NMR spectroscopy. Fast cross-coupling reactions of organolithium reagents with the isolated nanoparticles were successful, strongly supporting the involvement of PdNPs as the active catalyst.

Based on the experimental data, the catalyst activation pathway shown in Scheme 4 is proposed. PdNPs are known to be formed from Pd^{II} sources under reductive conditions.[16] In

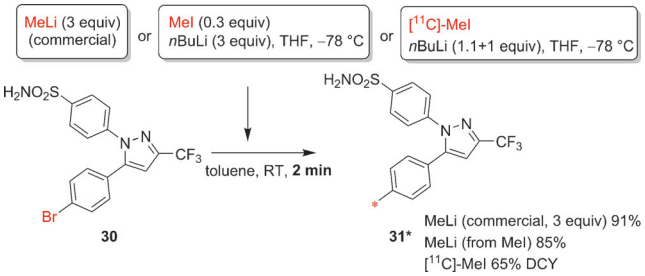


Scheme 4. Proposed catalyst activation pathway.

our system, O_2 reacts first with the Pd^{0} complex, thereby oxidizing it to **C1^{ox}** (Scheme 4 a), which is then in situ reduced to highly active Pd^{0} nanoparticles by means of the organolithium reagent, either directly (b) or via **C2**/**C2^{ox}** (c–f; for details, see the Supporting Information). The striking difference of the novel catalytic system presented here, compared to other PdNP-catalyzed cross-coupling reactions,[17] is the ultrafast cross-coupling of organolithium reagents, which can be explained by the in situ formation of numerous small (2–3 nm) Pd nanoparticles.

The benefits of the ultrafast coupling presented here can best be exploited in reactions where time restrictions are crucial. Therefore, we focused on the cross-coupling of [^{11}C]methyllithium ($t_{1/2}$(^{11}C) = 20 min) for PET labeling.[1,18,19] Such a method would be complementary to the more often used electrophilic quenching of a nucleophilic drug precursor with [^{11}C]iodomethane. The presence of several nucleophilic sites in specific precursors often results in undesired (over-alkylated) side products. We selected the synthesis of [^{11}C]celecoxib to illustrate the usefulness of our method (Scheme 5).[20,21]

Initially, we explored the reaction of commercially available MeLi and celecoxib precursor **30**. Having isolated the target **31** in excellent yield (91 %), we used in situ generated MeLi, prepared from MeI in both a stoichiometric and a substoichiometric (0.1 equiv) ratio with respect to *n*BuLi.[18] Gratifyingly, we were able to isolate the corre-

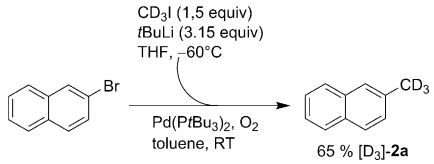


Scheme 5. Synthesis of radiolabeled celecoxib.

sponding product by preparative HPLC in good yield (85%) with respect to the MeI starting material.

With a representative result for the radiolabeling based on the use of substoichiometric MeI in hand, the synthesis of [^{11}C]celecoxib (**31***; coupling time 2 min, total preparation time including HPLC purification < 15 min) was pursued. The final decay-corrected radiochemical yield for **31*** was found to be 65% (average of three runs).

For further applications in isotope labeling, we considered the direct incorporation of the CD_3 moiety into organic compounds. The use of deuterated MeI is desirable from a cost perspective, and its use with a range of electrophiles has recently been shown by Hu and co-workers.[22] As the reported procedure requires a large excess of costly CD_3I (3.5 equiv), we anticipated that our method using in situ generated CD_3Li could provide a viable alternative (Scheme 6). As we had converted MeI into MeLi using



Scheme 6. Cross-coupling of [D_3]-MeLi.

*n*BuLi (see above), and successfully applied it in cross-coupling also with the ^{11}C analogue, an identical experimental setup for CD_3I was used. Much to our surprise, no CD_3 incorporation was observed in the cross-coupling reaction and in an electrophilic quench with benzaldehyde.[23,24] Switching to *t*BuLi gave the desired reagent CD_3Li, which readily coupled with 2-bromonaphthalene to provide [D_3]-**2a** in 65% yield, establishing a new method for the incorporation of the CD_3 moiety.

In conclusion, a novel procedure for the rapid palladium-catalyzed coupling of alkyl- and aryllithium reagents has been developed, with a crucial role for O_2 in generating the active catalyst. Systematic studies towards the active catalyst species revealed the formation of palladium nanoparticles for all three active precatalysts upon addition of the organolithium reagent, which facilitates rapid cross-couplings with a range of aryl bromides at room temperature. The application of this novel method was showcased in the coupling of [^{11}C]methyllithium in less than two minutes with a decay-corrected yield of 65% as a key step in the synthesis of the PET tracer celecoxib.

Acknowledgements

B.L.F. acknowledges financial support from The Netherlands Organisation for Scientific Research, 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 (Gravitation program 024.601035). C.V. was supported by an Intra-European Marie Curie Fellowship (FP7-PEOPLE-2011-IEF-300826).

Conflict of interest

The authors declare no conflict of interest.

Keywords: cross-coupling · isotope labeling · nanoparticles · organolithium regents · palladium

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 3354–3359
Angew. Chem. **2017**, *129*, 3402–3407

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Manuscript received: January 13, 2017
Final Article published: February 14, 2017

