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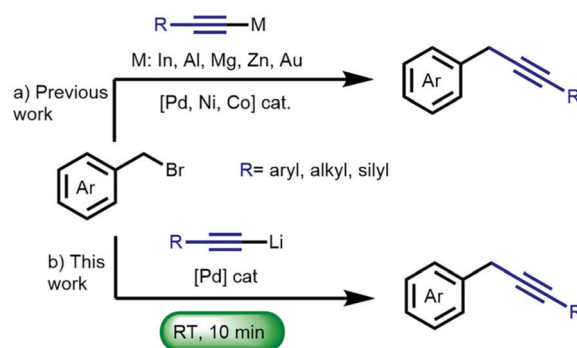
Pd-catalyzed $sp-sp^3$ cross-coupling of benzyl bromides using lithium acetylides†

 Anirban Mondal,^{ID} Paco Visser,^{ID} Anna M. Doze, Jeffrey Buter^{ID}* and Ben L. Feringa^{ID}*

Organolithium-based cross-coupling reactions have emerged as an indispensable method to construct C–C bonds. These transformations have proven particularly useful for the direct and fast coupling of various organolithium reagents (sp , sp^2 , and sp^3) with aromatic (pseudo) halides (sp^2). Here we present an efficient method for the cross-coupling of benzyl bromides (sp^3) with lithium acetylides (sp). The reaction proceeds within 10 min at room temperature and can be performed in the presence of organolithium-sensitive functional groups such as esters, nitriles, amides and boronic esters. The potential application of the methodology is demonstrated in the preparation of key intermediates used in pharmaceuticals, chemical biology and natural products.

Benzyl alkynes are versatile synthetic intermediates,¹ which are also found in several natural products,² pharmaceuticals, polymeric materials³ and applied in click chemistry.⁴ Although, at first sight, alkynylation at the benzylic position appears trivial, this transformation has proven to be surprisingly challenging as exemplified in previous reports showing the necessity of (i) transition metal-catalyzed cross-coupling of metal-alkynyls;⁵ (ii) Sonogashira-type coupling using terminal alkynes;⁶ and (iii) direct substitution of benzyl halides with an alkynyl lithium in the presence of the deaggregation agent *N,N*-dimethylpropyleneurea (DMPU).⁷ Despite the intrinsic reactivity of both the nucleophile and electrophile in the latter example, this ‘textbook’ S_N2 reaction required DMPU to proceed.⁸ This method can therefore not be applied in the presence of organolithium-sensitive functional groups due to the enhanced reactivity of organolithium reagents in the presence of *e.g.* DMPU, HMPA, TMEDA.⁹ Following pioneering work by Murahashi, on the early development of organolithium-based cross-coupling reactions,^{9,10} our group introduced a general methodology for the direct palladium-catalyzed cross-coupling of organolithium reagents with aryl- and alkenyl bromides to construct C–C bonds,¹¹ thereby avoiding transmetalation

to *e.g.* organozinc, –boron, –silicon, or –tin reagents. Having successfully tamed the extreme reactivity of organolithium compounds¹² in batch reactions, these palladium-catalyzed C–C bond formation reactions proceed fast (5–60 min) with high conversion and selectivity,¹³ and can be performed at room temperature,¹⁴ with a nickel catalyst,¹⁵ without solvent,¹⁶ under air,¹⁶ on ‘water’,¹⁷ at low temperature¹⁸ and have found application in stereoselective natural product synthesis.¹⁹ Recently, we reported a Sonogashira coupling employing lithium acetylides.²⁰ These reactions proceed at room temperature within 45 min, and display a remarkable functional group tolerance, including organolithium-sensitive functional groups such as esters, nitriles and boronic esters. Having demonstrated the cross-coupling of lithium acetylides with aryl bromides, we envisioned the development of fast and selective methodology for the functionalization of benzyl bromides (Scheme 1). Herein, we describe the cross-coupling of a variety of benzyl bromides with lithium acetylides, proceeding at room temperature in only ten minutes. Notably, the protocol shows high selectivity and an impressive tolerance towards functional groups such as esters, amides, nitriles, and a boronic ester. Furthermore, the versatility of the benzylic alkynes was displayed in the construction of key intermediates applied in the synthesis of pharmaceuticals and natural products.



Scheme 1 (a) Previous approaches towards the transition metal-catalyzed cross-coupling of organometallic acetylides with benzyl bromides. (b) This work.

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Our investigations started by reacting benzyl bromide, as well as its *p*-OMe and *p*-CF₃ derivatives, with trimethylsilyl- and tri(isopropyl)-silyl lithium acetylide, using different solvents, which in the absence of a transition-metal catalysts were affording only mediocre conversion to **3** (16%, THF after 2 h, see ESI† Table S1).

Moreover, performing the reaction in *N*-methyl-2-pyrrolidone (NMP), DMPU, or toluene also did not result in a productive reaction. These initial observations clearly demonstrated the necessity for the development of a catalytic method. Next the screening of a series of different Pd-catalysts and varying the addition time of the lithium acetylide **2a** (Table 1) was pursued. Satisfyingly, the use of 5 mol% of oxygen-activated Pd[P^tBu₃]₂,¹⁴ a catalyst we previously disclosed to be effective for the Sonogashira-type cross-coupling of lithium acetylides with aryl bromides,²⁰ resulted in 98% conversion into the desired product **3** (entry 1). Lowering the addition time from 30 to 15 min retained quantitative conversion, albeit with slightly lower selectivity (95%, entry 2). Moderate conversion of 44%, paired with a decreased selectivity, was observed when we lowered the addition time from 15 to 5 min (entries 2 vs. 3). Next, we investigated the use of [Pd(μ-I)P^tBu₃]₂, previously reported as an effective catalyst in Kumada-type cross-couplings by Schoenebeck and co-workers.²¹ Addition of the lithium acetylide over either 10 or 5 min in the presence of 5 mol% catalyst resulted in near-quantitative conversion with excellent selectivity (entries 4 and 5). Decreasing the catalyst loading to 2.5 mol% with an addition time of 5 min, however resulted in moderate conversion with decreased selectivity (entry 6). After optimizing the addition time, as well as the reaction conditions and organolithium-concentration, we found that optimal results were obtained using 3 mol% of the Pd-I dimer complex with toluene as solvent, and an

addition time of 10 min of the lithium acetylide (see ESI† Table S1). With a growing incentive to develop more sustainable chemical reactions, in which the amount of waste generated is minimized,²² we were also keen to explore whether this reaction could be performed without the use of additional solvents. Diminished solvent use could result in a transformation with a decreased *E*-factor.²³ Addition of **2a** to a mixture of **1** and Pd[P^tBu₃]₂ over 5 min under open-flask conditions provided the desired product **3** with 74% conversion (entry 8). Increasing the catalyst loading from 5 to 7.5% greatly improved both conversion and selectivity (entry 9).

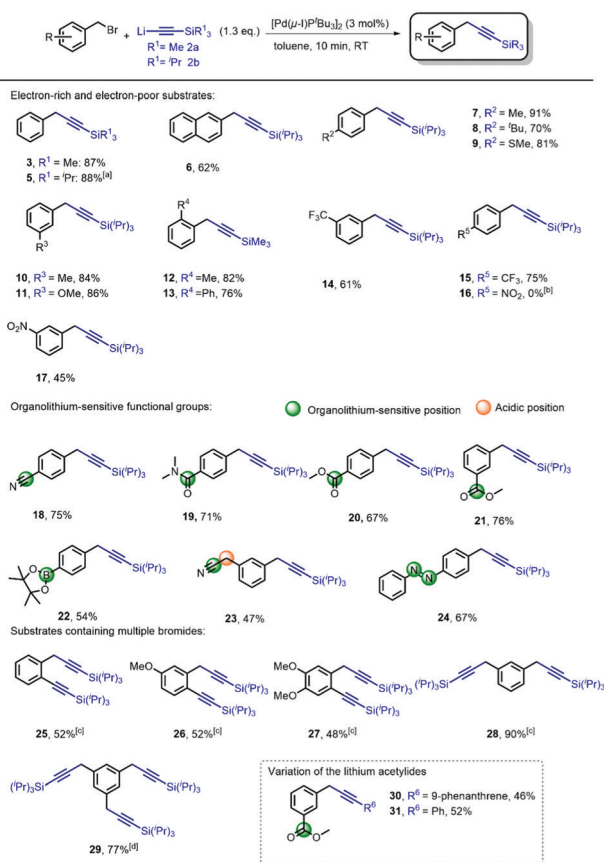
Although promising in terms of low *E*-factor, further screening showed that the general applicability was more troublesome, presumably due to the heterogenic nature of the reaction. With the optimized conditions obtained, using [Pd(μ-I)P^tBu₃]₂ (3 mol%) as the catalyst (see ESI† Fig. S1 for the proposed mechanism), we continued to investigate the general nature of the transformation by reacting benzyl bromides bearing different arene substituents (Scheme 2). During our initial studies, we found that chromatographic separation of the desired products from minor amounts of homo-coupling side-products proved to be challenging. However, we discovered that simply switching from lithium (trimethylsilyl) acetylide **2a** to lithium(triisopropylsilyl) acetylide **2b** circumvented this issue. Hence, we evaluated the generality of the reaction mainly using **2b**. Benzyl bromides with various arene substituents reacted smoothly towards the corresponding coupling products. Unsubstituted benzyl bromide was converted with both **2a** and **2b** to form **3** and **5** in excellent yield. Performing the synthesis of **5** on gram-scale afforded the desired product in similar yield (82%). The reaction of 2-(bromomethyl)-naphthalene also proceeded, providing **6** in 62% yield. Substrates bearing *p*-alkyl substituents readily underwent the cross-coupling reaction, to give **7** and **8** in 91% and 70% yield, respectively. The presence of electron-donating *para*-substituents was also tolerated *i.e.* *p*-thioanisole **9** (81%). Substituents in the *meta*-position also posed no problem since *m*-methoxy- and *m*-methyl-substituted benzyl bromides were efficiently converted to the corresponding products **10** (84%) and **11** (86%), respectively. Sterically demanding *o*-substituted methyl- and phenyl benzyl bromides remained challenging, resulting in non-productive reactions with lithium(triisopropylsilyl) acetylide **2b**. Reducing the steric bulk of the acetylide by using lithium (trimethylsilyl) acetylide (**2a**) proved crucial, and smoothly provided **12** and **13** (see ESI† Fig. S1 for detailed explanation). Next, we moved our attention towards electron-poor benzyl bromides. The reaction of both *m* and *p*-CF₃ benzyl bromide provided the desired product **14** and **15** in 61% and 75% yield, respectively. A significant difference in reactivity, however, was observed in the reactions of *p*- and *m*-nitrobenzyl bromide. The attempted cross-coupling with *p*-nitrobenzyl bromide proceeded with full conversion towards the homo-coupled 1,2-biarylethane. Due to the high acidity of the benzylic position (pK_a *p*-nitrotoluene = 20.4 vs. pK_a acetylene = 25),²⁴ lithium-halogen exchange results in the formation of a more stable *p*-nitrobenzyl anion, subsequently forming the 1,2-biarylethane side-product.²⁵ As expected, the homo-coupling product was not observed when we moved the nitro-substituent out of conjugation with respect to the benzylic position, which provided us with the desired product

Table 1 Screening of conditions^a for the direct cross-coupling using lithium acetylides

Entry	[Pd]	Mol%	Time (min)	Conversion of 1 (%)	3 : 4 ^b (%)
1	Pd(P ^t Bu ₃) ₂ /O ₂	5	30	> 99	98 : 2
2			15	> 99	95 : 5
3			5	44	82 : 18
4	[Pd(μ-I)P ^t Bu ₃] ₂	5	10	98	97 : 3
5			5	99	96 : 4
6	[Pd(μ-I)P ^t Bu ₃] ₂	2.5	5	59	88 : 12
7	[Pd(μ-I)P ^t Bu ₃] ₂ ^c	3	10	> 99	96 : 4
8	Pd(P ^t Bu ₃) ₂ /under air ^d	5	5	87	86 : 14
9	Pd(P ^t Bu ₃) ₂ /under air ^d	7.5	5	> 99	94 : 6

Reaction conditions. ^a RLi prepared from trimethylsilyl acetylene (0.65 mmol) and ⁿBuLi (1.6 M in hexanes; 1 equiv.) in THF (0.5 M) was added dropwise to a solution of [Pd] and **1** (0.5 mmol) in toluene (4 mL). ^b Conversion determined by GC-MS analysis. ^c RLi was prepared from trimethylsilyl acetylene (0.65 mmol) and ⁿBuLi (1.6 M in hexanes; 1 equiv.) in THF (0.6 M), and diluted with toluene (final concentration: 0.35 M). ^d The reaction was performed under air in the absence of additional solvent.





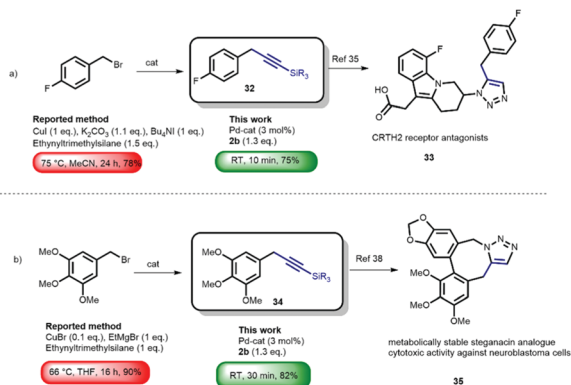
Scheme 2 Scope of the benzyl alkyne synthesis. Reaction conditions. Freshly prepared **2b** (1.3 equiv.; 0.35 M) was added to a solution of [Pd(μ -I)P^{*t*}Bu₃]₂ (3 mol%) and corresponding benzyl bromide (0.5 mmol) in toluene (2 mL), over 10 min. [a] The reaction was also performed on 1 gram scale with 82% yield [b] Quantitative formation to corresponding 1,2-biarylethane [c] Freshly prepared **2b** (2.6 equiv.) was added to a solution of [Pd(μ -I)P^{*t*}Bu₃]₂ (6 mol%) and **1** (0.5 mmol) in toluene (4 mL) over 20 min. [d] 3.9 equiv. of **2b** was used (also see ESI† for more information).

17 in 45% yield. Although organolithium reagents can be of great use, their inherent reactivity generally might limit their effectiveness as cross-coupling reagents in the presence of functional groups. In the case of lithium acetylides, due to their lower pK_a, and therefore diminished reactivity compared to alkyl- and alkenyllithium reagents, we anticipated that this transformation should be feasible in the presence of organolithium-sensitive functionalities. A nitrile-bearing substrate, which is prone to mono- or double addition reactions with organolithium reagents to form various imines and carbinamines,²⁶ could be efficiently transformed into coupled product **18** (75%). The presence of amides and esters are well tolerated and furnish **19–21** in high yields, despite their usual tendency to engage in undesired 1, 2-addition reactions with organolithium reagents to form ketones and alcohols. Furthermore, the presence of a boronic ester, a versatile functionality for Suzuki–Miyaura cross-coupling reactions, was well-tolerated, despite the fact that they easily react with organolithium compounds to form boronates.²⁷ Under our reaction conditions, bifunctional product **22** was readily synthesized (54%). A particularly challenging substrate is phenylacetonitrile-based benzyl bromide, containing, in addition to the reactive nitrile functionality, also an

acidic position (pK_a of phenylacetonitrile ~22).²⁴ Despite bearing these two reactive sites, our procedure afforded **23** in 47% yield. The use of the azobenzene moiety in photopharmacology²⁸ is of great interest due to its easy access and photo-switching behavior. The introduction of the benzylic alkyne functionality allows for facile attachment of the pharmacophore by means of Cu-catalyzed click-chemistry.^{4,29} Using our method, we successfully attached the ‘click handle’ to the azobenzene core in 67% yield (**24**). We also examined the reactions of benzyl bromides bearing both C(sp²)- and C(sp³)-bromides, as we previously observed that [Pd(μ -I)P^{*t*}Bu₃]₂ is also an effective catalyst for the cross-coupling of lithium acetylides with aryl bromides.²⁰ We were pleased to obtain the double coupling products **25–27** in 48–52% yield. These products are highly versatile synthons due to their application in various cycloaddition and cyclisation reactions.³⁰ Moreover, we were also able to synthesize di- (**28**) and tri- (**29**) substituted benzyl acetylenes in a one-pot procedure providing excellent yields of multiple coupled products. These compounds can fulfill roles as bridging/spacer units and dendrimer building blocks (*core* and *branching point*), respectively.³¹ Finally, we also performed the cross-coupling reactions by reacting two other substituted lithium acetylides with *m*-ester substituted benzyl bromide. As expected, the lithium acetylides generated from both phenylacetylene and 9-ethynylphenanthrene reacted smoothly and afforded **30–31** in 46% and 52% yield. In order to demonstrate the potential synthetic application of the methodology, we envisioned benzylic alkynes as versatile precursors for a wide array of products.³ There are numerous applications of the terminal alkynes³ which are directly accessible *via* our cross-coupling product using a TBAF-mediated deprotection.³² It should be noted that benzylic alkynes can undergo alkyne-allene isomerization under basic deprotection conditions. This can however be circumvented by carrying out the reaction with AgNO₃/KI.³³ Importantly however, allenes can also be very useful functional groups in view of their reactivity towards cycloaddition and cyclisation reaction.³⁴ We compared the use of our new acetylene coupling reaction to previously reported syntheses of important benzylic alkynes (Scheme 3). Fluorobenzyl alkyne **32** was used for the synthesis of CRTH2 receptor antagonists **33**.³⁵ The reported approach required stoichiometric amounts of CuI, and a reaction time of 24 h at 75 °C.³⁶ Our methodology provided **32** in merely 10 min at room temperature, in a comparable yield (75% vs. 78%). Furthermore, benzyl alkyne **34** is of particular interest since it is a common precursor used in the synthesis of lignans. These are plant-based natural products well-known for a wide variety of biological activities such as antitumor, antimitotic, and antiviral properties.³⁷ Interestingly, coupling product **34** has been used as a building block for the synthesis of metabolically stable steganacin analogue **35**.³⁸ This natural product derived compound exhibited cytotoxic activity against neuroblastoma cells. The reported procedure required a reaction time of 16 h at 66 °C, providing the desired product in 90% yield. Our method gave rise to the product in slightly reduced yield (82%), albeit using much milder (RT) and significantly more time-efficient (30 min) conditions.

In summary, we have developed a mild, fast and highly selective approach for the catalytic cross-coupling of benzyl bromides with lithium acetylides. The reaction proceeds in ten minutes at room temperature, offering an efficient pathway to a range of protected benzylic acetylenes in generally high yields





Scheme 3 Potential applications of the cross-coupling methodology. A comparison of the developed protocol with reported syntheses of different drugs.

under mild conditions. Due to the remarkable functional group tolerance of the transformation, the alkylation of benzyl bromides with lithium acetylides might likely find applications in the late-stage functionalization of (photo-)pharmacophores, natural products, materials and pharmaceuticals.

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Conflicts of interest

The authors declare no conflict of interest.

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