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Synthesis and Functionalization of Allenes by Direct Pd-Catalyzed Organolithium Cross-Coupling

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Abstract: A palladium-catalyzed cross-coupling between *in situ* generated allenyl/propargyl-lithium species and aryl bromides to yield highly functionalized allenes is reported. The direct and selective formation of allenic products preventing the corresponding isomeric propargylic product is accomplished by the choice of SPhos or XPhos based Pd catalysts. The methodology avoids the prior transmetalation to other transition metals or reverse approaches that required prefunctionalization of substrates with leaving groups, resulting in a fast and efficient approach for the synthesis of tri- and tetrasubstituted allenes. Experimental and theoretical studies on the mechanism show catalyst control of selectivity in this allene formation.

Introduction

Allenes^[1] represent a highly versatile functionality exhibiting two consecutive orthogonal double bonds with a central *sp* hybridized carbon atom. These structural features allow allenes to display axial chirality, arousing a growing interest in a variety of applications including chiroptical materials,^[2] chiral ligands^[3] and pharmaceutically active compounds.^[4] Furthermore, allenes exhibit fascinating reactivity in cyclization and cycloaddition reactions^[5] and act as a surrogate in allylic substitution transformations^[6] yielding complex chemical structures.

Such outstanding properties have encouraged chemists to develop more efficient methodologies that allow for convenient synthesis and functionalization of allenes.^[1,7] Traditional methods based on 1,2-elimination of functionalized alkenes^[8] or prototropic rearrangement of alkynes,^[9] that require specifically activated structures, have largely been displaced by the more straightforward metal catalyzed S_N2° reactions of electrophilic propargyl derivatives (R-CI, R-Br, R-OCO₂R', R-OPO(OR')₂, R-OSO₂R, etc.) with organometallic reagents.^[7b] Moreover, some examples based on Heck type couplings^[10] and other prominent enantiospecific and enantioselective approaches based on metal catalyzed transformations of alkynyl derivatives and enynes^[4b,11] have been recently reported.

Reverse approaches that involve the direct metalation of allenes^[12] or propargylic substrates^{[13],[14]}are highly attractive but

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Supporting information for this article is given via a link at the end of the document. their use as nucleophiles in cross-coupling transformations, avoiding prior substrate derivatization, have seen limited explorations (Scheme 1). Since the initial work of Vermeer,^[12a] the use of propargyl metal species in cross-coupling has been nearly restricted to the use of indium by Lee *et al.*^[13a,c] and the seminal works on propargyl/allenylzinc derivatives by Ma *et al.*^[14a,b,d,e] Albeit less explored, the use of allenylstannanes^[12b] and the elegant work on the use of allenylboranes by Fürstner^[12e], are to the best of our knowledge, the few cases in the direct application of both allenyl and propargylmetal species in cross-coupling reactions.

Recent advances in the use of organolithium compounds^[15] have revealed that these cheap and widely available reagents allow for fast and selective protocols in cross-coupling methodologies. In our efforts to exploit and extend the simplicity and versatility of organolithium reagents in cross-coupling transformations,^[16] we studied the feasibility of carrying out the direct lithiation and consecutive cross-coupling reaction of allenes and propargylic species with ArBr. In particular, we envisioned the direct synthesis of tri- and tetrasubstituted allenes in a single step, using substrates without any other prefunctionalization or avoiding the commonly required transmetalation step to other transition metals (Scheme 1c).





b) Direct arylation of propargylmetal species to yield allenes (Knochel, Ma, Lee)^{13,14}





Scheme 1. State of the art in the arylation of allenyl/propargylmetal species.

Results and Discussion

RESEARCH ARTICLE

First, we addressed the direct arylation of allene **1a**, which is not prone to isomerization, using 'BuLi as lithiation agent while screening different palladium catalysts for the subsequent crosscoupling with *p*-bromoanisole **2a** (Table 1). In toluene at 40°C (1h), the use of Pd(dba)₂ and various bulky biarylphosphine ligands (Table 1, entries 3-7) was shown to be more efficient in the formation of tetrasubstituted allene **3a** than Pd(PⁱBu₃)₂ or Pd-PEPPSI-iPent (Table 1, entry 1 and 2), in sharp contrast with the excellent performance demonstrated in other organolithium cross-coupling reactions.^[16a] The choice of SPhos as ligand (Table 1, entry 4) allowed the isolation of **3a** in 85% yield.

Table 1. Screening of conditions for the direct arylation of allenyllithium species.



Reaction conditions: **1a** (0.39 mmol) and 'BuLi (0.59 mmol), reacted in THF at -78 $^{\circ}$ C and then diluted at r.t. with toluene to a final concentration of 0.35 M. Slow addition of this solution for 1h to a solution of Pd catalyst (5 mol %) and **2a** (0.3 mmol) in toluene (0.5 mL). [a] Determined by ¹H-NMR using 1,1',2,2'-tetrachloroethane as internal standard. [b] Isolated yield.

Having established the optimal conditions, we evaluated the scope of the reaction with different trisubstituted allenes and aryl bromides (Scheme 2). The switch of the cyclic motif of allene **1a** to other aliphatic substituents (R^1 and R^2) did not affect the reactivity and selectivity, yielding products **3b** and **3c** in 91% and 74% respectively. Furthermore, different substituents were evaluated in the aromatic moiety at R^3 demonstrating also a remarkable performance under the reaction conditions even in the case of highly hindered allenes (**3d**), as well as bearing electron-donating (**3e**) or electron-withdrawing groups (**3f**). A series of aryl bromides were also tested with allenes **1a** and **1b**. Functionalities including heteroaryl, extended aromatic systems, *p*-Cl, *m*-NMe₂ or

p-OTBDMS were tolerated, furnishing the corresponding tetrasubstituted allenes **3h-3m** with good to high yields. Substrates substituted at the *ortho* and *meta* positions afforded the corresponding products **3n** and **3g** in moderate yields. Finally, the optimized conditions could also be extended to the use of alkenyl bromides, successfully obtaining product **3I** from the reaction with 1-bromocyclohexene in excellent yield (90%).



Scheme 2. Scope of the arylation of trisubstituted allenes with different aryl bromides. Reaction conditions: 1 (0.65 mmol) and 'BuLi (0.8 mmol), reacted in THF at -78 °C and then diluted at r.t. with toluene to a final concentration of 0.35 M. Slow addition of this solution for 1h to a solution of Pd(dba)₂ (5 mol%), SPhos (10 mol%) and 2 (0.5 mmol) in toluene (0.75 mL). [a]Reaction performed at 60 °C.

As indicated earlier, the use of propargyl derivatives (i.e. R-Br, R-Cl, R-OCO₂Me, -RPO(OR)₂, etc.) with organometallic reagents has been established as a general tool for the synthesis of allenes, in contrast to the few examples based on the reaction of alkynylmetal species with organic halides or pseudohalides. This latter approach, as proposed in Scheme 1c, may represent a more straightforward and atom efficient pathway since it implies the direct use of unfunctionalized allenes and propargylic starting materials. However, the control of reactivity and selectivity of this metalated species remains very challenging. The groups of Ma and Vermeer^[12a,14a,b,d,e] reported that it was not possible to directly react propargyllithium species with aryl bromides or iodides in the presence of Pd catalysts, requiring a transmetalation step to other transition metals to yield the corresponding allenes. These difficulties may be due to the interesting but complex chemistry of propargyllithium species: the presence of mono- and bislithiated

RESEARCH ARTICLE

species and coexistence of up to four different isomeric forms derived from the equilibrium and 1,3-H,Li rearrangement of propargyl/allenylmetal species (Figure 1).^[17] These features make extremely difficult to control and predict the reactivity and selectivity of these organometallic species, being highly dependent on the lithiation conditions,^[14b,d] temperature, nature of the solvent, presence of additives, nature of the electrophile^[18] or catalyst choice.^{[19],[20]} In a similar manner Knochel *et al.* reported the necessity of the use of mixed Li/Zn bases in order to control the selective formation of allenic product in silylated alkynes.^[13b]



Figure 1. Possible mono- and bislithiated species that can be identified in the equilibrium of propargyl- and allenyllithium species.

 Table 2.Screening of conditions for the direct synthesis of arylated allenes from alkynes.



Reaction conditions: **1a** (0.39 mmol) and 'BuLi (0.59 mmol), reacted in THF at -78 $^{\circ}$ C and then diluted at r.t. with toluene to a final concentration of 0.25 M. Slow addition of this solution for 1.5 h to a solution of Pd catalyst (5 mol %) and **2a** (0.3 mmol) in toluene (0.5 mL). [a] Determined by NMR using 1,1',2,2'-tetrachloroethane as internal standard.

Despite the major challenge associated with the use of these particular organolithium species, but encouraged by our recent

advances in the direct and fast coupling of organolithium reagents with novel Pd complexes, [16a-c, 16e-j] we attempted the direct coupling of propargyllithium species to yield trisubstituted allenes. Among the different lithiation conditions tested on 1-phenyl-1butyne 4a (Table 2), we found the use of 'BuLi or "BuLi at -78 °C to be the most efficient and reproducible.[21] A mixture of 4a-Li/4a'-Li in a 65/35 ratio was obtained^[22] and subsequently reacted with 2a in the presence of different Pd catalysts. Similar to the reaction of the formation of tetrasubstituted allenes (Table 1), biarylphosphines SPhos and XPhos exhibited a better performance (Table 2, entries 3 and 5), yielding the corresponding allenyl and propargyl products 5a and 6a in a similar ratio to the starting organolithium reagent mixture (2:1). Other ligands as CPhos and DavePhos furnished a complex mixture of byproducts derived from 4a as well as dehalogenation of 2a (entries 6 and 7). Much to our surprise, the moderate selectivity achieved by using Pd(dba)₂/XPhos as catalyst (62:38) was improved when XPhos-Pd-G2 precatalyst was used, affording product 5a (Table 2, entry 8) with excellent conversion (95%) and selectivity (>95:5). No isomers derived from the 1,3-H,Li rearrangement (Figure 1) were observed.[14b]



Scheme 3. Reaction conditions: 4 (0.65 mmol) and 'BuLi (0.8 mmol), reacted in THF at -78 °C and then diluted at r.t. with toluene to a final concentration of 0.25 M. Slow addition of this solution for 1.5h to a solution of XPhos-Pd-G2 (5 mol%)and 2 (0.5 mmol) in toluene (0.75 mL). [a]Reaction performed at 60 °C. [b]Combined yield for 5:6 mixture.

This remarkable selectivity led us to extend the conditions to different alkynes and aryl bromides in the synthesis of trisubstituted allenes from propargyllithium reagents. As depicted in Scheme 3, alkynes bearing different aliphatic chains or

RESEARCH ARTICLE

aromatic substituents were tolerated, preserving the selective formation of the allene derivative, providing products 5a-5i in good to high yields.^[23] Importantly, aryl bromides functionalized with electron-withdrawing, electron-donating groups or extended aromatic systems did not influence significantly the conversion or selectivity of the reaction (5a, 5d-5f). Protected alcohol and aldehyde functionalities were also tolerated under the optimized conditions with no observable cleavage of the protecting groups (5h and 5i). Curious about the softer nucleophilic character of 4-Li/4'-Li we wondered if pinacol boronic ester (Bpin), that is prone to react with organolithium reagents, [24] may remain unaltered during the reaction. We were rewarded with an excellent reactivity and chemoselectivity towards organolithium cross-coupling, without formation of any side product derived from Suzuki type coupling or reaction of the organolithium with the boronic ester. Moreover, the presence of Bpin induced a notably electronic effect, shifting the formation of products 51:61 to a 1:2.5 ratio. When the more hindered o-bromoanisole was examined at 40°C, it was found to be unreactive, requiring 60°C to reach full conversion. At this temperature, the product ratio 5j:6j drops to 1:1, revealing a significant influence of the enhanced steric hindrance of the ArBr 2 towards the selectivity of the reaction.[25] In the search for evidences indicating if the equilibrium between 4-Li and 4'-Li may affect the outcome of the reaction we evaluated the reactivity of the TMS-protected prop-2-yn-1ylbenzene, the lithiation of which was reported to not provide formation of allenyllithium species.[13b] Under the standard reaction conditions a remarkable 2:1 ratio of products 5k:6k was found, revealing the primordial role of the catalyst in governing the selectivity, with room for further improvement by careful selection of ligand.



Scheme 4. Proposed catalytic cycle for the Pd-catalyzed cross-coupling reaction of allenyl-/propargyllithium species with aryl bromides.

In the proposed catalytic cycle depicted in Scheme 4 the lithiated species **4a-Li** and **4a'-Li**, which are in equilibrium, transmetalate to ArPdLBr **II**, forming the corresponding allenyl-PdL-Ar **IIIA** and propargyl-PdL-Ar **IIIB**. These intermediates **III**, being also in

equilibrium, undergo the corresponding reductive elimination to yield products 5 or 6. According to this catalytic cycle, different hypothesis about the fundamental aspects that drive the selectivity of the reaction may be proposed. Our initial studies on the lithiation of substrate 4a revealed the formation of allenic 4-Li as major species at low temperature (-78 °C to -20 °C) and the equilibrium shifted at r.t. to a ratio (65:35) of 4-Li/4'-Li (Scheme 5). In view of the experimental results in the cross-coupling, that reveal a high selectivity in the formation of 5, an initial hypothesis considering that both species transmetalate to II, followed by a faster reductive elimination that yields products 5 or 6, with no effect of the Pd catalyst in the selectivity, might be discarded. In the same line, the possibility of an exclusive transmetalation of allenyllithium species 4-Li that push the equilibrium 4-Li/4'-Li seems also to be not feasible (vide infra) (Table 2, entry 5 and 8). To ensure that the initial ratio of the allenyl/propargyllithium reagent is not ruling the selectivity in this transformation and that the catalyst is mainly responsible for the selectivity, an experiment under stoichiometric conditions was performed, making the equilibrium mixture of 4-Li and 4'Li (65:35) to react with a slight excess of ArPd(XPhos)Br II (Scheme 5). Under these conditions, that allow both lithiated species 4-Li and 4'-Li to be immediately transmetalated and yield 5 or 6 after reductive elimination, only formation of the allenic product 5 was observed.



Scheme 5.Reaction of organolithium species with an excess of the oxidative additioncomplex.

To exclude that the fast equilibrium **4-Li/4'-Li** is not responsible for this result, via exclusive transmetallation of the allenic species, the analogous reaction using organozinc reagents, which exhibit a fixed **4-Zn/4'-Zn** ratio, was performed (Scheme 6). A mixture of **4-Zn/4'-Zn** (in a 45:55 ratio) was reacted with **2a** providing the formation of **5** and **6** in <u>82:18</u> (with Pd(dba)₂-XPhos) and <u>>95:5</u> (with XPhos-G2-Pd) ratios, respectively. These experiments accompanied by the results using silylated alkyne (Scheme 3, **5k**) highlights the key role of the catalyst, excluding the initial nature of the lithiated nucleophile as the determining factor governing the selectivity towards allene **5** or propargyl product **6**.

RESEARCH ARTICLE



Scheme 6. Comparison of the effect of catalyst in the reactivity and selectivity of the reaction of different propargylmetal (M: Li, Zn) species.

Intrigued by the remarkable influence of the use of the precatalyst XPhos-Pd-G2 instead of Pd(dba)₂/XPhos system on the selectivity for 5:6 (Table 2, entry 5 and 8), a model reaction was performed under the optimized conditions using a 10 mol% of (dba) as additive in order to find out its influence in the reaction outcome (See SI, S19). A significant effect was found in the presence of dba, observing a major decrease in the reactivity (from 95% to 45% conversion) and the selectivity (from 95:5 to 65:35).^[26] As indicated above, a similar effect in the selectivity was also found when using the corresponding 4-Zn/4'-Zn as nucleophile under the presence of dba. This result highlights again the importance of the Pd catalyst and the non-spectator role of dba. The effect of dba and other related ligands in Pd catalyzed transformations is well established, acting as a π ligand that diminishes the rate of oxidative addition to Pd complexes and may accelerate the reductive elimination.^[27] Our findings disclose not only an effect on the reactivity but also on the selectivity of the reaction, suggesting the presence of Pd(XPhos)(dba) or related species that may favor the formation of the propargylic product 6 by accelerating the reductive elimination in the formation of the Csp2-Csp3 and/or modifying the equilibrium IIIA-IIIB.[28] More comprehensive studies (beyond the scope of this work) to unveil the actual role of dba and species that can be formed in this specific reaction are warranted.

To corroborate these experimental findings and provide insight how the Pd catalyst determines the selectivity of the reaction, computational studies were performed. Calculations revealed close values for the corresponding energies of **IIIA** and **IIIB**, being **IIIA** slightly more stable than **IIIB**. The energy penalties for the evolution of these two intermediates through a reductive elimination is, as expected, significantly different. Thus, the formation of the allenic species **5** involves a barrier of only 8.22 kcal/mol whereas for the formation of **6** involves an energy penalty of more than 16 kcal/mol needs to be overcome (Figure 2). The energy profile found for the evolution of these two species (**IIIA** and **IIIB**) is in agreement with the experimental evidence previously described (for further details on the mechanistic exploration, see SI).



Figure 2. Energy profiles for the evolution of species IIIA and IIIB. The energies reported are relative Gibbs free energies, they have been obtained at the M06L/def2svp^[29] computational level, at 298 K and 1atm.

The described novel protocols offer a unique way for the synthesis of tri- and tetrasubstituted allenes without prior derivatization or transmetalation of starting materials, by means of the simple lithiation of unfunctionalized alkynes and allenes and consecutive Pd catalysed cross-coupling reaction with aryl bromides. To show the versatility of these new coupling methods, the two optimized reactions were performed sequentially even on a larger scale (4.0 mmol), allowing the synthesis of the tetrasubstituted allenes 7a-d endorsed with three different aryl moieties directly from simple alkynes 4a and 4b (Scheme 7a). In order to minimize risks, the sequential protocol was performed by using "BuLi, avoiding the use of large amounts 'BuLi. In addition diversification of the synthesized allenes was also carried out. Tetrasubstituted allenes 3b and 3e were converted into iodoindenes 8a-b in high yields (Scheme 7b),^[30] providing in this way an appealing scaffold present in intermediates and structures with potential biological activity.^[31] We also exploited the versatility of Cu catalyzed hydroboration of unsaturated bonds on trisubstituted allene 5b. While the hydroboration of mono and disubstituted allenes is well established,^[32] tri- and tetrasubstituted allenes are still unexplored, mainly because of selectivity issues due to the possible formation of vinylboronate and allylboronate products and their corresponding regio- and stereoisomers. By suitable choice of ligand, we were delighted to establish the regio- and stereoselective formation of the vinylboronate 9 in the presence of CuCl/PPh₃ as catalyst, representing a novel regio- and stereoselective hydroborylation of trisubstituted allenes. Finally, 9 was reacted with thienvllithium to furnish product **10** in high vields through an organoborate migratory insertion,^[33,34] providing an easy strategy for the synthesis of functionalized 1,1diarylmethanes.

RESEARCH ARTICLE

a) Sequential synthesis of tetrasubstituted from unfuctionalized alkynes









Scheme 7. a) Synthesis of tetrasubstituted allenes **7** from unfunctionalized alkyne **4**. b) and c) Synthetic application of tri- and tetra-substituted allenes prepared through the described Pd catalyzed organolithium cross-coupling.

Conclusion

In summary, a Pd-catalyzed methodology for the synthesis of triand tetrasubstituted allenes by direct lithiation/cross-coupling reaction is reported. The direct metalation of allenes allows its arylation with good to high yields with a broad range of aryl bromides. Lithiation of suitable alkynes at the propargylic position has also been exploited in order to accomplish the selective synthesis of trisubstituted allenes in a simple way, with no necessity of prior formation of transition metal reagents. The question on the determining factors governing the selectivity of this transformation with respect to the formation of allenic and propargylic products has also been addressed. Computational and experimental studies have been conducted, revealing a dynamic kinetic resolution process between the intermediates IIIA and IIIB with the formation of product 5 as the more favored pathway. In specific cases, when strong steric and electronic effects are involved, the selectivity is decreased. An interesting role of dba has been found, demonstrating to not be a spectator in the reaction, modifying both reactivity and selectivity of the transformation. The described protocols provide a new and efficient way of preparing tri- and tetrasubstituted allenes directly from readily available starting materials under mild conditions, allowing subsequent diversification to versatile building blocks as iodoindenes or vinylboronates.

Experimental Section

Preparation of allenyl lithium solution

In a dry Schlenk flask, under inert atmosphere, allene 1 or alkyne 4 (0.65 mmol) were dissolved in 0.5 mL of dry THF and cooled to -78 °C, followed by dropwise addition of 'BuLi (0.47 mL of a 1.7 M solution in pentane). The mixture was stirred at this temperature during 30 or 90 min., and subsequently the temperature was allowed to reach r.t. during another 30 min. The mixture was then diluted with toluene (0.6-0.7 mL) to provide a 0.35 M (for 1-Li) or 0.25 M (for 4-Li) solution of the freshly prepared organolithium reagent.

Synthesis of tri- and tetrasubstituted allenes

In a dry Schlenk flask, under inert atmosphere, Pd(dba)₂ (0.025 mmol, 14.4 mg) and SPhos (0.05 mmol, 20.5 mg) or XPhos-Pd G2 (0.025 mmol, 19.7 mg) were stirred in toluene (0.75 mL) at 40 °C for about 15 min. followed by the addition of the aryl bromide **2** (0.5 mmol). The solution of the prepared organolithium was then slowly added at 40 °C or 60 °C) during the indicated time using a syringe pump. After the addition was completed, a saturated aqueous solution of NH₄Cl was added and the mixture was extracted with AcOEt. The organic phase was collected, dry over Na₂SO₄ and the solvent evaporated under reduced pressure to yield the crude product **3** or **5** which were purified by column chromatography.

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RESEARCH ARTICLE

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- [22] As determined by 1H and 13C-NMR
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- [34] Regio- and stereochemistry of the products 9 and 10 was determined by 1D- and 2D NOESY NMR experiments (see Supporting Information) resulting in retention of the starting configuration of the double bond during the formation of 10.

RESEARCH ARTICLE

Entry for the Table of Contents (Please choose one layout)

Layout 2:

RESEARCH ARTICLE



Jaime Mateos-Gil,*Anirban Mondal* Marta Castiñeira Reis and Ben L. Feringa*

Page No. – Page No.

Synthesis and Functionalization of Allenes by Direct Pd-Catalyzed Organolithium Cross-Coupling

Selective formation of allenic product is achieved in the direct cross-coupling of allenyl- and propargyllithium species with aryl bromides. The fundamental role of ligand in the selectivity of the transformation is described, allowing the synthesis of tri- and tetrasubstituted allenes in good to excellent yields without any previous formation of transition metal species, resulting in a fast and efficient methodology. The determining factors that drive the selectivity and the critical role of dba in the selectivity have been discovered.